Revised Clinical Study Protocol	
Drug Substance	Olaparib and MEDI4736
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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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VERSION HISTORY

Revised Protocol edition 7, 17 December 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The primary change to the protocol has been the removal of the 3 Third Stage Cohorts from the study to reflect the current development strategy for the olaparib + MEDI4736 combination: the BRCAm breast cancer expansion cohort (Module 8; previously detailed in Appendix P), the HRRm breast cancer cohort (Module 9; previously detailed in Appendix Q), and the triple negative breast cancer triplet cohort (Module 10; previously detailed in Appendix R). As a result, all text referring to these cohorts, including text in the Core Protocol and Appendices P to S has been removed.

The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. The study mitigation changes described below will only be initiated at a time of study disruption. Study mitigation language is presented in new Section 1.5.1 of the Core Protocol, and in the newly-added Appendix P (Changes related to mitigation of study disruptions due to cases of civil crisis, natural disaster, or public health crisis). Additionally, Section 1.3.5 (Impact on Benefit/Risk from Study Disruptions due to Coronavirus Disease 2019) has been added in the context of the COVID-19 pandemic.

Text has been included throughout the Clinical Study Protocol stating that enrollment into the *BRCAm* ovarian cancer expansion cohort has been terminated after 51 patients had been enrolled, and will not continue until the originally planned 80 patients have been enrolled. As PARP inhibitors have become standard of care in the first line setting for *gBRCAm* patients, the high unmet clinical need in this patient population has reduced. In addition, as a result of the success of PARP inhibitors in this setting, there are limited numbers of PARP inhibitor-naïve patients eligible for inclusion in the *BRCAm* ovarian cancer expansion cohort. Therefore, despite high response rates in this patient population with olaparib and MEDI4736 combination treatment as shown in the initial stage *gBRCAm* ovarian cancer cohort, recruitment for the *BRCAm* ovarian cancer expansion cohort was closed early. Additionally, planned interim analyses for the cohort have been removed.

Due to slow recruitment of the *gBRCAm* expansion cohort and removal of the Third Stage breast cancer cohorts, the final data cut-off has been updated in Section 9.3, and is anticipated to occur in 2021. Updated text on the final data cut-offs and the closure of the clinical database is updated based on current data maturity in Section 9.3 of the Core Protocol, and referenced accordingly in Section 9 of each cohort-specific appendix. Additional language has been added to Section 9.3 defining the end of study.

The use of blinded independent central review (BICR) for tumor assessments in select

cohorts is being removed from the protocol, as there is no intent to use data from any cohorts as pivotal data for regulatory filings for new indications and these additional independent reviews are not required for the scientific evaluation of the study. This update provides consistency between the protocol and the analyses performed on the study for both the Initial Stage Cohorts and Second Stage Cohorts (in the *gBRCAm* ovarian cancer and *gBRCAm* breast cancer cohorts). As a result, all mention of BICR has been removed from the protocol, including the endpoints based on BICR assessments and the requirement for an additional scan to confirm Investigator-assessed disease progression, which was performed in order to minimize bias in the BICR assessment.

The status of the study and the clinical development of the study drugs has been updated throughout the protocol as appropriate, including: the benefit/risk language for MEDI4736 and how many patients have received MEDI4736 in clinical studies; the approval status of olaparib for different indications and territories, the enrollment status of the study (all cohorts have completed enrollment); and a brief summary of the results from Initial Stage Cohorts.

Section 6.8.4 (Specific toxicity management and dose modification information - MEDI4736) and Section 6.8.5 (MEDI4736 adverse events of special interest) have been updated to ensure consistency with current MEDI4736 standards. Additionally, the toxicity management guidelines portal for MEDI4736 was decommissioned at the end of September 2020, and therefore reference to this website has been removed; this document is provided to sites as an annex to the protocol. Finally, to ensure that the toxicity management guidelines are the sole source for the most current information, individual subsections describing the management of each MEDI4736 AESI have been deleted as they are duplicative to the toxicity management guidelines.

In Section 7.7 of the Core Protocol, the list of prohibited and restricted medications has been updated for consistency with the latest guidance for olaparib and MEDI4736. Table 8 (Supportive medications) has also been added to give further details of permitted medications.

Updated text on cohort-specific data cut-offs and the closure of the clinical database has been modified in Section 9.3 of the Core Protocol and in Section 9 of each cohort appendix. The expected date of final cut-off (in 2021) has also been added.

Clarification on order of administration of bevacizumab and MEDI4736 has been implemented in Appendix M (Module 6; ovarian cancer triplet cohort), Section 4 Table 3 (study schedule for the combination therapy treatment period). A statement on the order of infusions for MEDI4736 and bevacizumab has also been repeated in Section 4.2 and Section 7.2.1 of Appendix M, and Section 7.2.3 of the Core Protocol.

Descriptions of myelodysplastic syndrome/acute myeloid leukaemia, an adverse event of special interest for olaparib, have been updated to reflect the fact it is now an identified risk, and not a potential risk per the latest Olaparib Investigator Brochure. Changes have been

made in Section 1.3.1 and Section 6.8 of the Core Protocol.

Throughout the Core Protocol and Appendices B and D, minor language updates and additions have been made to align with current AstraZeneca standards for clinical study protocols and to provide additional clarity. The updates do not mandate changes in the procedures of the study. Sections affected include: Section 3.8(Restrictions), to clarify contraception guidance; Section 5.2.1 (Laboratory safety assessments) and Appendix D (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law), for reporting of liver abnormalities; Section 5.2.4.1 (Pulse and blood pressure); addition of Section 5.2.5.3 (Pneumonitis/interstitial lung disease), to provide details of management and reporting of pneumonitis/interstitial lung disease; Section 6.3.3 (Adverse events after the 90-day follow-up period); Section 6.3.12 (Deaths); Section 6.7 (Medication error); Section 7.1.1 (MEDI4736), to add language on administration of MEDI4736 to patients with body weight ≤ 30 kg; Section 7.2.2 (Olaparib); Section 7.8 (Post study access to study treatment); Section 10 (Ethical and regulatory requirements); and Appendix B (International Airline Transportation Association 6.2 Guidance Document).

Further minor changes to the protocol include:

- Updates to references in the Core Protocol (Section 11) and Module 5 (Section 11 of Appendix L) including their epub status, and to remove some citations no longer referenced.

- In Section 4.1 of the Core Protocol text was added stating that ovarian cancer patients in the Second Stage Cohorts are exempt from provision of a new biopsy sample even when/even if the archival tumor sample is more than 3 years old for consistency with other parts of the protocol.

Text referring to HRR testing has been removed from the Core Protocol as this applied only to the Third Stage Cohorts (primarily Section 5.6 of the Core Protocol).

- Minor typographical corrections and update of paragraph formatting for consistency with current AstraZeneca document standards.

Revised Protocol edition 6, 29 November 2019

The primary change to the protocol has been the removal of Toxicity Management Guidelines (TMGs) relating to MEDI4736 from the body of the core protocol (Section 6.8), to be replaced by references to the standalone TMG Annex document available on a website and in the Site Master File. This document contains the latest guidance for dosing modification and toxicity management to be followed by Investigators.

In addition, ADA analysis for bevacizumab has been removed. Due to an oversight, the

sample collection and analysis for this has not been done thus far and the decision was made that this testing is not critical to the study and could be removed as a secondary outcome measure for 2 cohorts (the ovarian cancer triplet cohort and the triple negative breast cancer triplet cohort).

Changes in each section are summarized below, in addition minor editorial changes to clarify language and to correct typos, cross-references, and formatting have also been made and are not described in the version history.

Protocol synopsis (Objectives and outcome measure for all cohorts) and Section 2.2 (Secondary objectives):

- For secondary objective relating to PK, immunogenicity and pharmacodynamics of bevacizumab, reference in objective to immunogenicity and outcome measures referring to ADAs for bevacizumab have been removed (applies to triplet cohorts only).

Section 1.4 (Study design):

- In Section 1.4.1, for participants of Review Committee, requirement that the study physician will chair the meeting has been removed.

Section 3.8 (Restrictions):

- Clarification has been added that use of 2 acceptable methods of contraception by females of childbearing potential must be started from the time of signature of the first informed consent.

Section 5.2.1 (Laboratory safety assessments) and Section 6.3.8 (Elevations in liver biochemistry parameters):

- Clarification has been added that cases of elevated liver biochemistry parameters must be reported as SAEs if the criteria for Potential Hy's Law are met and no alternative explanation can be identified.

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- Sampling for bevacizumab ADA analysis has been removed.

Section 6.3.1 (Time period for collection of adverse events):

- Clarification has been added that AEs will be collected from the time of signature of first informed consent.

Section 6.8 (Management of IP-related toxicities):

- In Sections 6.8.1 (General comments) and 6.8.4 (formerly entitled "MEDI4736"),

guidance has been updated in line with the latest AstraZeneca standard template language and refers to a standalone TMG Annex maintained within the site master file and on a specified website.

- Tables 6, 7, 8, and 9, that included dosing modification and toxicity management guidelines and followed Section 6.8.6, have been removed. References to these tables have been removed and replaced by references to the TMG Annex in all relevant subsections within Section 6.8.

All cohort specific appendices, Section 3.2 (Exclusion criteria):

- In exclusion criterion 12, blood malignancy has been additionally specified as an exclusion in this criterion.

- In exclusion criterion 22, irritable bowel disease has been corrected to inflammatory bowel disease.

Appendix M (Module 6: Ovarian cancer triplet cohort):

- In Section 5.2 (Safety assessments), number of samples and corresponding total volume for olaparib PK samples in Table 5 have been corrected per Table 6 (total of 5 samples).

Appendix R (Module 10: Triple negative breast cancer triplet cohort):

- In Section 5.2 (Safety assessments), number of samples and corresponding total volumes for olaparib PK samples and ADA samples in Table 6 have been corrected per Table 7 (total of 5 olaparib PK samples) and Table 8 (total of 4 ADA samples), respectively.

Revised Protocol edition 5, 16 August 2018

The primary change to the protocol has been the addition of 3 breast cancer cohorts, based on the preliminary results from this study, 1 of which is an expansion of the current (*gBRCAm*) breast cancer cohort, 1 of which assesses the olaparib+MEDI4736 combination in HER2-negative, non *BRCAm*, HRRm breast cancer patients, and 1 of which assesses the olaparib+MEDI4736+bevacizumab combination in triple-negative non *BRCAm*, non HRRm breast cancer patients.

These cohorts have been added as Appendix P (*BRCAm* breast cancer expansion cohort; Module 8), Appendix Q (HRRm breast cancer cohort; Module 9), and Appendix R (triple negative breast cancer triplet cohort; Module 10). In addition, Appendix S has been added; Appendix S describes the screening processes for the 3 new cohorts.

Throughout the whole protocol, the following changes have been made and are applicable to the **whole study** (including cohort-specific appendices):

- In the Core Protocol, information and cross-references for the 3 new Third Stage Cohorts have been added as appropriate.
- The Initial Stage breast cancer cohort is now referred to as the *gBRCAm* breast cancer cohort for clarity as new breast cancer cohorts have been added.
- Reference to "modified" RECIST has been removed throughout the protocol, as RECIST 1.1 is no longer being modified to require confirmatory scans at progression.
- "Quintiles" has been replaced with "IQVIA" to reflect the change in company name of the Contract Research Organization.
- A Statement that "Imaging assessments every 8 weeks are required for patients who continue receiving the study drug combination beyond disease progression" has been added where appropriate to clarify the imaging requirements of patients who have progressed but remain on study treatment.
- In addition to the final data cut-off at the end of the study, details have been added on when the cut-off for each cohort will occur, and what data may be collected after the cohort data cut-off (survival, investigational product dispensing/accountability, subsequent anticancer treatment, and selected safety data).
- Text stating that details of pregnancy tests must be recorded in the patient's medical records has been added for consistency with current AstraZeneca procedures.
- For consistency with current AstraZeneca templates and procedures, Section 5.4 (Pharmacogenetics) in the Core Protocol and all cohort-specific appendices has been re-titled "Genetics", references to pharmacogenetics have been similarly altered. A new Appendix (Appendix C Genetic Research) has been added and details of the optional genetics assessments moved to the Appendix. Addition of the Appendix has resulted in re-lettering of all subsequent Appendices. In Section 10.2, ethics information for genetics samples and data have been removed and are now in Appendix C.
- Increase in the size of visit windows for visits with previous window of ±2 days to ±3 days at the suggestion of study centers, to allow patients and centers to accommodate weekends and national holidays.
- A requirement for completion of a specific eCRF page in the event of nausea/vomiting during the study treatment period has been removed, as data on olaparib and nausea/vomiting are no longer required.

- Text to introduce the optional taking of tumor biopsies at disease progression (where patients consent and biopsy is clinically feasible) has been added for all cohorts (Core Protocol and cohort-specific appendices).

- In treatment period flow charts the following text was added in all cohorts: If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit. Imaging assessments are required for patients who continue receiving the study drug, including those who continue beyond progressive disease.

- In post-treatment flow charts details on the optional taking of tumor biopsies at disease progression were added for all cohorts, and it was clarified in the footnotes that RECIST 1.1 assessments continue until objective disease progression (ie, should continue after clinical progression until objective progression is determined).

- Dexamethasone has been added as a moderate CYP3A inducer to be considered in exclusion criteria and concomitant medications.

- Throughout the protocol it has been clarified that study treatment will continue until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria.

- It has been clarified that screening (and all) T3 and T4 assessments will only be made if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

- Specified that both urine and serum pregnancy tests (previously just serum) are suitable for screening and subsequent pregnancy testing (eligibility criteria and schedules of assessment).

- Update in QTc prolongation exclusion criterion from exclusion of >470 msec to >500 msec, consistent with current olaparib guidance, text in the rest of the protocol has been made consistent with this change.

- Change of exclusion criteria "previous enrollment in the present study" to "previous treatment in the present study", to allow rescreening.

- In the screening flow chart in all cohorts, it is no longer required to wait until eligibility is confirmed before any blood samples are taken at screening/baseline (eg plasma for circulating soluble factors).

Changes in each section are summarized below, in addition minor editorial changes to clarify language and to correct typos, cross-references, and formatting have also been made and are not described in the version history.

Protocol synopsis:

- Content was adapted and added to incorporate and describe the 3 new breast cancer cohorts (Modules 8 to 10).
- Minor changes were also made to update the synopsis according to the most recent AstraZeneca protocol template (including removal of table showing start and projected end times of study cohorts).
- The tables for primary, secondary, and exploratory objectives were modified to increase the clarity of the objectives and endpoints.
- Data cut-offs for each cohort are detailed, in addition to the original overall final data cut-off.
- Details on the sourcing, labeling and storage of bevacizumab have been added to the synopsis for information.

Section 1 (Introduction):

- Details of regulatory approvals have been updated to the most current information.
- A rationale for the addition of the 3 Third Stage Cohorts has been added (new subsection: Section 1.2.3).
- In Section 1.4 (Study design), diagrams have been updated for clarity and accuracy.
- In Section 1.4 (Study design), subsection 1.4.3 (Third Stage Cohorts) has been added which details the study design of the Third Stage Cohorts and illustrates the *BRCA* and HRR testing process.
- In Section 1.4 (Study design), subsection 1.4.4 (Summary of breast and ovarian cancer cohort characteristics) has been added to provide a single summary of cohort characteristics for ovarian and breast cancer patients (eg, molecular markers, previous treatment lines)
- Section 1.5 (Study governance and oversight): information has been moved from Section 6.8 to here for consistency with other recent AstraZeneca protocols. In addition, information on study monitoring and review committees has been added.

Section 2 (Study objectives):

- The tables for primary, secondary, and exploratory objectives were modified to increase the clarity of the objectives and endpoints.

Section 3 (Patient selection, enrollment, randomization, restrictions, discontinuation and

withdrawal)

- In Section 3 a reference has been added to Section 3.10.1 to highlight new information on rescreening of patients.
- Section 3.1 and 3.2 (inclusion and exclusion criteria): To improve readability and navigation of the protocol, specific cross-references to the inclusion and exclusion criteria for each module have been provided, instead of general references to module-specific appendices.
- In Section 3.3 (Patient enrollment), text has been added stating that patients re-enrolled after rescreening will be assigned a new E-code.
- Section 3.5.3 (Third Stage Cohorts, new section) has been added and describes methods for assigning Third Stage Cohort patients to the different Third Stage breast cancer cohorts.
- Section 3.8.1 (Olaparib and CYP3A4): the recommendation not to consume grapefruit juice while on olaparib treatment was updated to a prohibition, in line with the most recent guidance on olaparib.
- Section 3.9.1 (Procedures for discontinuation of a patient from investigational product): a sentence stating that data on subsequent anticancer treatment after study treatment discontinuation would be collected was added.
- In Section 3.10.1 (Screen failures), text has been added describing in what circumstances patients can be rescreened.

Section 4 (Study plan and timing of procedures):

- Cross-references to all the schedules of assessments across the study have been added to enable faster and easier navigation of the protocol.
- Section 4.1 (Enrollment/screening period): Text has been added stating that the screening period for the Third Stage Cohorts can be up to 40 days (to allow for Myriad laboratory testing of greater complexity in these cohorts). Text confirming that baseline tumor assessment and pregnancy tests should still occur within 28 days prior to study treatment has been added, as well as a statement that if screening activities take less than the full time available, patients can start study treatment.

Section 5.1.3 (Central reading of scans)

- Text has been added stating that, in the *BRCAm* ovarian cancer expansion and *BRCAm* breast cancer expansion cohorts, patients who are determined to have progressed according to RECIST 1.1 criteria by the Investigator will have 1 additional RECIST assessment at the next scheduled RECIST visit in order to

minimize bias in the blinded independent central review (BICR) assessment in the event the Investigator declares objective progression. This change has also been made in the relevant cohort-specific appendices.

Section 5.5.2.3 (Third Stage Cohorts):

- Text on mandatory archival tumor samples from breast cancer patients in the 3 new Third Stage Cohorts has been added.

Section 5.5.4.1 (Pharmacodynamics: paired tumor biopsies):

- CCI [redacted]

Section 5.5.4.11 (Pharmacodynamics: tumor biopsy at disease progression):

- CCI [redacted]

Section 5.5.5 (Biomarker sample and data management):

- CCI [redacted]

Section 5.6 (BRCA status) and Section 5.6.3 (Third Stage Cohorts)

- The title and content have been modified to reflect the additional (HRR) screening tests required for the Third Stage Cohorts.

Sections 6.1 and 6.2 (Definition of adverse events, Definitions of serious adverse events):

- Text has been updated to reflect current AstraZeneca standards.

Section 6.3.3 (Adverse events after the 90-day follow-up period):

- Text has been updated to reflect current AstraZeneca standards.

Section 6.3.10 (New cancers):

- Text has been updated to reflect current AstraZeneca standards.

Section 6.6 (Pregnancy):

- A statement that pregnancies discovered before study treatment starts do not need to be reported to AstraZeneca, in line with current AstraZeneca standards.

Section 6.7 (Medication error; new section)

- This section added for consistency with current AstraZeneca templates and standards, to define a medication error and detail the actions to be taken in the event of a medication error. Subsequent sections were renumbered accordingly.

Section 6.8.2 (Olaparib, previously Section 6.7.2):

- Minor updates were made in the management of anemia for consistency with current olaparib guidance.

- Updates were made to the management of nausea and vomiting for consistency with current olaparib guidance.

Section 6.8.3 (Olaparib adverse events of special interest, previously Section 6.7.3):

- Text on the expedited reporting of olaparib adverse events of special interest has been removed, for consistency with current AstraZeneca standards.

Section 6.7.8 (Bevacizumab adverse events of special interest)

- Section deleted, as there are no adverse events of special interest for bevacizumab.

Section 6.8 (Study governance and oversight)

- Information in this section was moved to Section 1.5, and deleted here.

Section 7.1 (Identity of investigation products)

- An error regarding the dosage form and strength of bevacizumab was corrected in Table 8 (now Table 10) – the value was changed from 10 mg/kg to 25 mg/mL.

Section 7.2.1 (Olaparib)

- Olaparib dose reduction guidance for patients has been updated in line with current olaparib guidelines.

Section 7.5 (Compliance):

- Text has been updated to reflect current AstraZeneca standards.

Section 7.7 (Concomitant and other treatment) and Appendix G (Medications to be Avoided with Olaparib):

- Section 7.7 has been updated and reformatted for consistency with other olaparib protocols and current guidance on olaparib. Information in Appendix G has been

moved to Section 7.7, and replaced with a cross-reference to Section 7.7.

- Guidance on olaparib dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided has been added in a new table (Table 13).

Section 7.7.3 (Rescue medication, new section)

- A new section with guidance on rescue medication for immune-mediated adverse events potentially experienced by patients receiving MEDI4736 has been added.

Section 8.3.1 (Full analysis set):

- Text cross-referencing the full analysis set definition for the *BRCAm* ovarian cancer expansion cohort has been deleted, as the definition is the same as for other cohorts.

Sections 8.4.2.5 (Objective response) 8.4.2.6 (Best objective response), 8.4.2.7 (Duration of response):

- Information on objective response and duration of response were split into 2 sections (8.4.2.5 and 8.4.2.7, respectively) for consistency with the Statistical Analysis Plan.

- Section 8.4.2.6 (Best objective response) was added to define the calculation and analysis of best objective response.

Section 9.3 (Study timetable and end of study):

- Information has been added to define data cut-offs for each cohort. In line with expected recruitment, clinical response, and reporting, cohorts have been grouped into 3 data cut-offs.

Appendix C (Genetic Research, new appendix)

- The appendix has been added to hold all information on the optional genetics assessments in one place, in accordance with current AZ standard and templates.

Appendix E (Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria; previously Appendix D)

- Updates were made to reflect the removal of the requirement for confirmatory scans.

Appendix F (Monitoring Plan for Futility and Efficacy; previously Appendix E)

- Details of the monitoring plan for futility and efficacy in the 3 new Third Stage Cohorts have been added.

Appendix G (Medications to be Avoided with Olaparib; previously Appendix F)

- Information has been removed from this appendix to Section 7.7 (concomitant medications) for clarity, and for consistency with current AZ templates. To ensure Investigators are alerted to the new location, a cross-reference has been placed in the appendix.

In the Initial Stage cohorts, the following changes were made:

- Retrospective BICR analysis of scans in the *gBRCAm* breast cancer cohort were added to Cohort 2.
- Cohort schemas have been updated to more clearly represent the cohort design.
- Update exclusion criterion relating to previous malignancies for consistency with olaparib standards.

In the Second Stage Cohorts, the following changes were made:

- Cohort schemas have been updated to more clearly represent the cohort design.
- Updated, and clearer, definitions in inclusion/exclusion criteria for prior treatment lines.
- Updated the creatinine clearance inclusion criterion in line with current olaparib standards.
- Update exclusion criterion relating to previous malignancies for consistency with olaparib standards.
- Update (relaxation) of QTc prolongation exclusion criterion in line with current olaparib standards.
- Modified NOTE 1 in the screening schedules of assessment footnotes to state that waivers may be granted to extend the 28 day screening period in order to allow for tumor biopsy sample acquisition, scan scheduling, and other screening procedures.
- Removal of the Cycle 1, Day 1 RECIST assessment, which was included in error.
- (*BRCAm* ovarian cancer expansion cohort only): text was added indicating that patients who are determined to have progressed according to RECIST 1.1 criteria by the Investigator will have 1 final RECIST assessment at the next scheduled RECIST visit in order to minimize bias in the BICR assessment in the event the Investigator declares objective progression.
- Details on the tissue requirements for paired biopsies have been added. Four cores

(2 for processing as FFPE blocks and 2 for immediate freezing) should be taken where possible.

- (Ovarian cancer triplet cohort only): new information on bevacizumab approvals and clinical data has been added to Sections 1.1.1.1, 1.1.1.2, and 1.2.3.1.
- (Ovarian cancer triplet cohort only): the specification of a bevacizumab vial size of 400 mg was removed to allow for different local packaging.
- Appendix O (*BRCA* screening process; previously Appendix N): minor updates have been made around the use of the Myriad central laboratory and *BRCA* testing. No changes to the screening/testing process have been made.
- Section 8.2 of the *BRCAm* ovarian cancer expansion cohort (definition of full analysis set; Module 5) has been deleted as it is not required (definition is the same as all other cohorts, and described in Core Protocol).
- Section 1.4 of the ovarian cancer triplet cohort (Module 6; Study Design) and Section 1.3 of the ovarian cancer doublet cohort (Module 7; Study Design), the point at which DCR is assessed as reported in Figure 1 of each section has been corrected from 12 to 24 weeks.

Three new Third Stage Cohorts enrolling breast cancer patients have been added. These are:

- The *BRCAm* breast cancer expansion cohort – Module 8. Detailed in Appendix P. Please see the introduction to Appendix P for background information and rationale for the cohort.
- The HRR breast cancer cohort – Module 9. Detailed in Appendix Q. Please see the introduction to Appendix Q for background information and rationale for the cohort.
- The triple negative breast cancer triplet cohort – Module 10. Detailed in Appendix R. Please see the introduction to Appendix R for background information and rationale for the cohort.
- The BRCA and HRR screening processes for the Third Stage Cohorts are detailed in Appendix S.

Revised Protocol edition 4, 12 April 2018
Section 3.8 of the Core Protocol and Section 3.8 of Appendix L (Module 6) were updated to include the guidance for duration of use of effective contraception after bevacizumab treatment.

Revised Protocol edition 3, 31 January 2018
In this amendment of the protocol, 3 new ovarian cohorts have been added based on preliminary results from this study, 1 of which is an expansion of the current *gBRCAm* ovarian cohort. The 2 other new cohorts will explore the olaparib+MEDI4736 combination in non *BRCAm* ovarian cancer patients with or without the addition of bevacizumab to the combination, which is based on recent findings that suggest vascular endothelial growth factor (VEGF) therapy can enhance the activity of polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerization (PARP) inhibitors in non *BRCAm* ovarian patients. In order to keep the overall protocol organized and easy to reference with the additional 3 cohorts, the protocol has been restructured so that information specific to each cohort in individual "Modules". Information applicable across the study is contained in the "Core Protocol". Within the Core Protocol, the four initial cohorts are now referred to as the "Initial Stage Cohorts", whereas the 3 new ovarian cohorts are referred to as "Second Stage Cohorts". This change has been made to simplify the protocol for Investigators, placing information specific to each in 1 section or module of the protocol. Specific details for the "Initial Stage" cohorts (Modules 1 to 4; Appendices G to J) and the "Second Stage Cohorts" (Module 5 to 7; Appendices K to M) have been organized into the same basic structure as the Core Protocol to improve ease of reference for sites. Whole document: Cohort-specific information has typically been removed from the "Core Protocol" and moved to the cohorts-specific Modules. This includes - • Section 1 (Introduction): – Introductory text (background, rationales, study design) from the previous protocol version has been maintained in the Core Protocol, and referred to in the cohort-specific Modules as appropriate. – Information on the clinical experience with olaparib and MEDI4736 has been updated. – Benefit-risk text for olaparib and MEDI4736 alone and in combination has been updated. – The structure of the introduction has been updated to reflect the focus on

olaparib+MEDI4736.

- Additional introductory text for the Second Stage Cohorts has been included in Section 1 of each Module (Appendices K to M).

- Section 2 (Study objectives): All study objectives for all cohorts of the study are presented in Section 2 of the Core Protocol. The following changes and additions have been made:
  - For the Initial Stage *gBRCAm* ovarian cancer cohort, endpoints assessed by retrospective independent central review of scans (in addition to Investigator assessment) have been added. Independent central review will be used to retrospectively assess the efficacy endpoints for this cohort, which are dependent on medical imaging, to verify the results.
  - Dose-limiting toxicities are not being collected, so have been removed as safety endpoints.
  - Where time points or endpoints differ for Second Stage Cohorts, these have been added in, and subheadings added to indicate which endpoints apply to which cohorts.
  - Pharmacokinetic (PK) endpoints have been updated to reflect that olaparib PK samples are plasma, not serum (this has been corrected throughout the document).
  - PK endpoints that are not planned to be reported in the Clinical Study Report have been removed; they will be reported separately.
  - CCI [redacted]
  - Exploratory objectives to be described separately from the Clinical Study Report have been removed.

- Section 3 (Patient selection, enrollment, randomization, restrictions, discontinuation and withdrawal):
  - All inclusion and exclusion criteria have been moved to the cohort-specific Modules to provide a single source for each cohort. Furthermore, within each Initial Stage Cohort Module, the text not relevant to the cohort has been removed (eg, information on *BRCA* status for gastric cancer cohort). This has not resulted in any changes to the

eligibility criteria for the Initial Stage Cohorts.

  - In Section 3.8 (Restrictions), all information has been maintained in the Core Protocol, however information on pregnancy and contraception has been updated consistent with the most current appropriate guidelines for olaparib

- Section 4 (Study plan and timing of procedures): The study flowcharts in the Core Protocol have been removed, and cohort-specific flowcharts have been added to Section 4 of each Module. Common information remains in Sections 4.1 to 4.3 of the Core Protocol, cohort-specific information regarding the screening (with or without olaparib run-in), treatment and follow-up periods is included in Sections 4.1 to 4.3 of each Module.

- Section 5.1 (Efficacy assessments): The majority of information has been retained in the Core Protocol, limited cohort-specific information has been included in Section 5.1 of cohort-specific Modules.

- Section 5.2 (Safety assessments):

  - All safety assessment information remains in Section 5.2 of the Core Protocol, with the exception of bevacizumab-specific urinalysis assessments, which are described in Module 6 of the protocol.

  - Tables detailing the blood volumes taken in the study have been separated out into the cohort-specific Modules (Table 5 in each Module). Note: the *gBRCAm* ovarian cancer cohort blood sample volumes have been updated based on the 52-week extension of the follow-up period. Where appropriate, blood volume samples not relevant to a specific cohort have been removed (eg, CA-125 in gastric cancer cohort).

  - Information on pregnancy testing has been updated according to the most recent guidelines for olaparib. These changes have been reflected in updates to the study schedule table footnotes in the cohort-specific appendices (see Table 2 and Table 3 in each Module).

- Section 5.3 (Pharmacokinetics), Section 5.4 (Pharmacogenetics), and Section 5.5 (Biomarker analysis):

  - Sampling schedules are presented in the cohort-specific Modules and have been removed from the Core Protocol.

  - Information on sample collection, storage, labeling etc has been retained in the Core Protocol, as has other information common to all cohorts.

  - CCI [redacted]

CCI [redacted]

  - In Section 5.5.2 (Mandatory archival tumor sample), information on the requirements for mandatory tumor samples in the Initial Stage Cohorts have been retained in the Core Protocol in new subsection 5.5.2.1. Additionally, requirements for these samples for the Second Stage Cohorts have been added into the Core Protocol (subsection 5.5.2.2).

- Section 5.6 (*BRCA* status):
  - Details on whether *BRCA* status assessment is required has been added to each cohort-specific Module. The information on *BRCA* testing for the breast cancer and *gBRCAm* ovarian cancer has been retained in the Core Protocol (new subsection 5.6.1).
  - *BRCA* status testing for the second stage cohorts is referred to in new Core Protocol subsection 5.6.2. The majority of information is presented in Appendix N for clarity.
- Section 6 (Safety reporting and medical management): All text remains in the Core Protocol, additional text specific to bevacizumab is presented in Section 6 of Module 6.
  - Text on olaparib safety monitoring and management has been updated in Section 6.7.2 (Olaparib).
  - Text on MEDI4736 safety monitoring and management has been updated in Sections 6.7.5 (MEDI4736 AESI) and 6.7.6 (Immune-related adverse events). Section 6.7.6 contains the most recent toxicity management guidelines, as well as a link for Investigators to access current information as it is updated.
- Section 7 (Investigational Product and other treatments):
  - All information on olaparib and MEDI4736 has been retained in Section 7 of the Core Protocol. Information specific to bevacizumab is presented in Section 7 of Module 6.
  - In Section 7.1.2 (Olaparib), information on dose management for olaparib in renal impairment has been updated with the most recent guidance.
- Section 8 (Statistical analyses): The majority of information has been retained in Section 8 of the Core Protocol. Additional information regarding the analysis of the Second Stage Cohorts has also been included in the Core Protocol. Sample size

calculation information for each cohort has been moved to Section 8.1 in Modules 1 to 7. Appendix E (futility and efficacy for Bayesian design) has been updated with values for the ovarian cancer triplet and doublet cohorts.

- Section 9: (Study and data management by AstraZeneca): Section 9 of the Core Protocol has been modified to accurately describe all cohorts. In Section 9 of each Module, information relevant to the start and end of cohorts has been added (eg, the fact that Modules 1 to 4 have, at the time of this amendment, been fully enrolled).

- Section 10 (Ethical and regulatory requirements): All information has been retained in Section 10 of the Core Protocol as it is relevant to all cohorts

- Section 11 (List of references): References in the Core Protocol are referenced here. Each Module also has a standalone reference list.

Whole document: Formatting, grammatical and minor editorial changes have been made throughout the document. In addition, changes have been made to section heading numbers and table cross-references, where necessary, due to amendments detailed in this document.

Whole document: Three new ovarian cancer cohorts have been added to the study (Modules 5 to 7; Appendices K to M). These are:

- A *BRCAm* ovarian cancer "expansion" cohort (referred to as "*BRCAm* ovarian cancer expansion cohort" in the protocol [Module 5; details in Appendix K]). Preliminary results in the initial stage *gBRCA* mutated ovarian cohort showed a 12-week disease control rate (DCR) that was in the superiority region. Based on this observation, validation of these results is necessary in a larger number of patients. Expansion of the current cohort will be the most efficient way to confirm these results and improve the confidence in the objective response rate (ORR). The objective for expanding this cohort is to achieve an equal or improved ORR with olaparib and MEDI4736 combination compared to that observed in the standard chemotherapy setting. This could provide a potentially more tolerable, non-chemotherapy option for patients with platinum-sensitive recurrent (PSR) *gBRCAm* ovarian cancer. In contrast to other cohorts in this study, the tumor assessments for the *BRCAm* ovarian cancer expansion cohort will undergo BICR in addition to review by Investigators (BICR will also be performed on the Initial Stage *gBRCAm* ovarian cancer cohort).

- Two non *BRCAm* ovarian cancer cohorts, 1 of which will receive olaparib+MEDI4736+bevacizumab (referred to as "ovarian cancer triplet cohort" in the protocol [Module 6; Details in Appendix L]), and 1 of which will receive olaparib+MEDI4736 (referred to as "ovarian cancer doublet cohort" in the protocol [Module 7; Details in Appendix M]).

  – The "triplet" cohort will assess the combination of olaparib+MEDI4736+bevacizumab in treatment of non *BRCAm* ovarian

cancer. Bevacizumab is approved in ovarian cancer. Additionally, there is clinical evidence that combination treatment with PARP inhibitors, such as olaparib, and VEGF inhibitors, such as bevacizumab, is efficacious and tolerable in ovarian cancer. Furthermore, preclinical evidence shows potential synergistic, antitumor activity with the combination CCI [redacted] and VEGF inhibition. Please see the Introduction of Appendix M for further details.

– The "doublet" cohort is of value in assessing the combination of MEDI4736+olaparib for the treatment of non *BRCAm* ovarian cancer patients. Olaparib monotherapy has shown clinical efficacy in the non *BRCAm* population, therefore it is likely that the addition of MEDI4736 will enhance the efficacy in this patient population in a similar fashion. Additionally, this cohort will serve to evaluate the contribution of bevacizumab when comparing the "doublet" combination to the "triplet".

Minimal changes to the design of the Initial Stage Cohorts have been made in this amendment (with the exception of extending the duration of follow-up, and adding independent central review of scans, for the *gBRCAm* ovarian cancer cohort, see below). The design of the Second Stage Cohorts differs from that of the Initial Stage Cohorts in the following ways:

- The Second Stage Cohorts, including the *BRCAm* ovarian cancer expansion cohort, have no olaparib monotherapy run-in period; all study treatments (olaparib+MEDI4736 ± bevacizumab) will start at the same time. The hypothesis that PARP inhibition induces changes in the tumor microenvironment was tested by taking paired biopsies before and after the olaparib monotherapy 4-week run-in period in the Initial Stage Cohorts. Since this question is currently being addressed in the data collected from the Initial Stage Cohorts, the Second Stage Cohorts will no longer include the olaparib monotherapy 4 week run-in. By starting the combination of olaparib and MEDI4736 together, the efficacy of the combination treatment in platinum-sensitive relapsed ovarian cancer can be evaluated. In addition, this dosing schedule more closely represents the intended clinical use under investigation.

- The *BRCAm* ovarian cancer expansion cohort has ORR as the primary endpoint. A high ORR was seen in the initial *gBRCAm* ovarian cancer cohort. To confirm this observation, ORR was chosen as the primary endpoint for the expansion cohort.

- The follow-up for the Second Stage Cohorts is 104 weeks (versus 52 for original cohorts) after the final patient has started treatment. This change has been made to capture the progression events in the majority of the patients.

- In Section 6 of Module 6 (Appendix L; ovarian cancer triplet cohort), additional

information on adverse events of special interest and measures required for events associated with bevacizumab treatment have been added. Urinalysis assessments specific to bevacizumab treatment have also been added.

- In Section 5.5.3 of Modules 6 and 7 (Appendices L & M; ovarian cancer triplet and doublet cohorts), information has been added on assessment of free VEGF in this module to assess the activity of bevacizumab on this parameter.

In addition to the new cohorts, and the restructuring of the document to a modular presentation, the following changes have been made:

- Introductory text (Section 1 and subsections) has been updated with new information on the approval status and clinical data available for olaparib and MEDI4736.

- An additional exclusion criterion has been added for consistency with current AstraZeneca standards: Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

- An additional exclusion criterion has been added to all cohorts for consistency with the most recent MEDI4736 information: Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of study treatment. Additionally, pregnancy testing has been added to all cohorts for female patients at the 2- and 3-month follow-up visits.

- In the breast cancer cohort inclusion criteria (Module 2; Section 3.2), "eligibility of breast cancer with bone only disease is a Principal Investigator (PI) decision on an individual patient basis" has been deleted, as it conflicts with other information in the protocol.

- To capture the majority of the disease progression events in the Initial Stage ovarian cancer cohort, the follow-up period in this cohort has been extended from 52 to 104 weeks.

- Retrospective independent central review of radiographic scans has been added in the Initial Stage *gBRCAm* ovarian cancer cohort. This is in addition to the Investigator assessment.

- In Section 3.8, definitions of childbearing and post-menopausal women have been updated based on most recent AstraZeneca standards for the investigational products. The list of acceptable forms of contraception have been updated for the same reason.

- Section 5.5.5 (Mechanisms of resistance) has been deleted, as tumors at progression

are not being taken in the study.

- In Section 7.1 of the Core Protocol, the final column (Manufacturer and supplier) of Table 5 has been removed. This information is kept current in different study documents, and has therefore been removed from the protocol.

- The frequency of the safety monitoring informal meetings ("Investigator Calls") has been changed from every 4 to 6 weeks to "as necessary", based on the experience of the safety profile of olaparib+MEDI4736 accumulated to date.

- Guidance on olaparib administration with food has been updated from "with a light meal/snack" to "with or without food". The effect of food on olaparib tablet has been investigated. Co-administration with food slowed the rate of absorption, however food did not significantly affect the extent of absorption. Therefore, olaparib tablets can be given without regard to food.

- As a result of updates to the MEDI4736 Investigator's Brochure, changes were made to the Core Protocol. The details are:

  – Section 6.7.5 (MEDI4736 adverse events of special interest): Myocarditis and myositis/polymyositis were added as adverse events of special interest for MEDI4736.

  – Section 6.7.6 (Immune-related adverse events): Myocarditis was added to the list of possible immune-related adverse events. Text was also added regarding the close monitoring and prompt evaluation of patients with pre-existing cardiac disorders in cases of suspected myocarditis.

  – Table 4 (Dosing modification and toxicity management guidelines for immune-mediated, infusion-related and non-immune-mediated reactions [MEDI4736]): Details on the dose modifications and toxicity management recommended for suspected and biopsy-confirmed immune-mediated myocarditis were added.

- Section 6.7.5.2 (Diarrhea/Colitis and Intestinal Perforation): This section has been added to provide information on observation and management of diarrhea/colitis and intestinal perforation.

Revised Protocol edition 2, 06 September 2016

Changes to the protocol are summarized below:

Whole document: The protocol template was updated for consistency with other AstraZeneca studies. Protocol appendices are now included within the same document as the main protocol

text, and Appendix A (signatures) was removed according to the new template, with other Appendices re-lettered accordingly. Appendices have been formatted for consistency with the new template.

Whole document: Formatting, grammatical and minor editorial changes have been made throughout the document. In addition, changes have been made to section heading numbers and table cross-references, where necessary, due to amendments detailed in this document.

Protocol synopsis (Study sites and number of patients planned): The number of countries and sites the study is being performed at were updated for consistency with the current status of the study. Additionally, the number of patients expected to be enrolled overall in each cohort was updated based on the changes to the Bayesian design of the study; the numbers of additional and total patients have also been updated accordingly.

Whole document: The definition of the gastric cancer cohort as "ATM-negative" was removed throughout the protocol, as the target patient population in this cohort was widened to include gastric cancer patients irrespective of ataxia-telangiectasia-mutated (ATM) status (for rationale of this change, see changes to Section 1.3.1).

CCI [redacted]

Protocol synopsis (Study design); Protocol synopsis (Duration of treatment); Section 3.9 (Discontinuation of investigational product); Section 4.2.4 (previously Section 4.2.5; Duration of therapy); Section 5.1.1 (Tumor assessments by CT or MRI scans): Text was added stating that clinically stable patients with disease progression identified after olaparib monotherapy has started but before receiving combination therapy are permitted to start combination therapy if the Investigator believes they may derive benefit from study therapy. The text was added to clarify the status of patients progressing prior to starting combination therapy. Where appropriate, text has also been added indicating these patients should be scanned at Week 12 (8 weeks after start of combination therapy).

CCI [redacted]

Protocol synopsis (Target patient population): Text was added to clarify the resolution of toxicities of prior therapy to Common Terminology Criteria for Adverse Events (CTCAE) grade ≤1 (except alopecia) is required prior to the start of treatment.

Section 1.2.1 (Rationale for the study design):

- Text was updated with information on the effects of olaparib in ovarian and gastric

cancers from recent studies to provide updated information in the protocol, and to support the widening of the gastric cancer cohort from patients with ATM-negative tumors to patients who are ATM-positive or -negative.

- To improve patient accrual in the ovarian cancer cohort, second-line ovarian cancer patients are now included in the target population as well as third-line ovarian cancer patients. The text has been updated to reflect this.

Section 1.3.1 (Olaparib benefit/risk in monotherapy and combination therapy): The section was updated to include the recently-reported effects of olaparib in gastric cancer (GOLD study) that support the widening of the gastric cancer cohort from patients with ATM-negative tumors to patients who are ATM-positive or -negative. Updated information on the numbers of patients to receive olaparib in different settings was also added.

Section 1.3.2 (MEDI4736 benefit/risk): CCI [redacted] Updated information on the numbers of patients to receive MEDI4736 in different settings was also added.

Figure 1 (Study design: Bayesian predictive probability design – Initial Stage Cohorts), Appendix E: The Bayesian design and maximum numbers of patients per cohort have been modified. These changes are to amend the study design to demonstrate superiority, rather than parity, with standard of care and olaparib monotherapy, and to reflect new learning on progression-free survival rates from recent studies.

Section 3.1 (Inclusion criteria for ovarian cancer patients):

- Text was updated to clarify the requirement for *gBRCAm* ovarian cancer patients with recurrent disease to have relapsed at least 24 weeks after the administration of their last platinum treatment.

- The requirement for ovarian cancer patients to have received at least two previous courses of platinum-based therapy has been altered to at least one previous course of platinum-based therapy. This change is intended to improve patient accrual in the ovarian cancer cohort.

Section 3.1 (Inclusion criteria for gastric cancer patients):

- The requirement that patients be ATM-negative was removed. This is because a recent study (the GOLD study) indicated there was a trend towards a survival advantage in the overall gastric cancer population, and so there is no need to select patients based on ATM status.

- Due to the removal of ATM-negative status as an inclusion criterion, the requirement for prospective ATM testing was also removed.

- The prohibition of triplet chemo regimens as acceptable first-line treatment for gastric cancer patients was removed as this is a common regimen used in clinical practice for this patient population. Text for the same criterion was updated to clarify that the first-line treatment regimen much have contained **at least** a doublet 5-fluoropyrimidine and platinum based regimen.

Section 3.1 (Inclusion criteria, criterion 2): Text was updated to clarify the relationship between the baseline scan and the start of olaparib monotherapy.

Section 3.1 (Inclusion criteria, criterion 6):

- The minimum measured creatinine clearance for inclusion was updated from >60 mL/min/1.73m^2 to ≥51 mL/min/1.73m^2. This change was made to reflect updated guidance on olaparib and MEDI4736 with regards to renal function.

- The required laboratory values for alanine aminotransferase (serum glutamic-oxalo-acetic transaminase) and aspartate aminotransferase (serum glutamate pyruvate transaminase) in patients with liver metastases was updated from ≤2.5×upper limit of normal (ULN) to ≤5.0 ULN to reflect this population's increased likelihood of impaired liver function.

Section 3.1 (Inclusion criteria, criterion 10): The definition of female patients of non-childbearing potential was removed and a reference to Section 3.8 added, where an updated definition was added.

Section 3.1 (Inclusion criteria, criterion 11; Table 3): As a result of ATM-negative status being removed as an inclusion criterion for gastric cancer patients, reference to ATM status and resultant sampling requirements were removed, and sample requirements for gastric cancer patients were aligned with other cohorts.

Section 3.2 (Exclusion criteria, criteria 1 and 7): The criterion was modified to state that estrogen receptor positive or progesterone receptor positive breast cancer patients are allowed anti-hormonal treatment for estrogen receptor positive or progesterone receptor positive breast cancer until 7 days prior to treatment with olaparib. This was amended for consistency with the prohibition against these treatments in Section 7.7 (Concomitant medications).

Section 3.2 (Exclusion criteria, criterion 1):

- The prohibition on exposure to investigational agents within 30 days or 5 half-lives prior to enrollment was changed to 30 days or 5 half-lives prior to starting olaparib treatment for consistency with language elsewhere in the criterion.

- It was clarified that prior receipt of PD-L2 inhibitors is permitted.

Section 3.2 (Exclusion criteria, criterion 6), Section 7.7.1 (Medications that may NOT be administered): The exclusion criterion was updated with new requirements for CYP3A

inhibitors and inducers. In both sections, text was added to clarify the required washout periods for CYP3A inducers enzalutamide and phenobarbital (5 weeks).

Section 3.2 (Exclusion criteria, criterion 8): This criterion excluding patients requiring long acting narcotic analgesics was removed for consistency with other, similar AstraZeneca studies. Subsequent criteria have been renumbered accordingly.

Section 3.2 (Exclusion criteria): A new exclusion criterion (number 14) was added excluding patients with a history of active primary immunodeficiency. This change was made for consistency with other MEDI4736 studies.

Section 3.2 (Exclusion criteria, criterion 15): The criterion was updated to allow patients with controlled brain metastases and clarify the status of patients with spinal cord compression. This change was made after discussion with Investigators, and for consistency with other olaparib studies.

Section 3.2 (Exclusion criteria, criterion 16): The criterion was rephrased for greater clarity.

Section 3.2 (Exclusion criteria, criterion 21):

- The criterion was modified to allow inclusion of patients with a past or resolved hepatitis B infection, and patients positive for hepatitis C virus (HCV) antibody but who are negative for HCV RNA as assessed by polymerase chain reaction. This change was made at the request of Investigators.

- It was clarified that active tuberculosis infection is not permitted.

Section 3.2 (Exclusion criteria, criterion 22): The wording of the criterion was updated to clarify that stable hypothyroidism treated with hormone replacement, and chronic skin conditions that do not require systemic treatment, are not criteria for exclusion.

Section 3.2 (Exclusion criteria, additional criteria for *BRCAm* HER2-negative breast cancer patients): The combination of an aromatase inhibitor and palbociclib was added as a treatment regimen not considered cytotoxic chemotherapy. This change was made to clarify that palbociclib is not a cytotoxic chemotherapy.

Section 3.5 (Methods for assigning treatment groups): The maximum cohort sample sizes were updated, for consistency with the changes to the Bayesian design changes described above.

Section 3.8 (Restrictions): The text regarding restrictions for female patients of childbearing potential and males with a female partner of childbearing potential was updated to be consistent with other MEDI4736 and olaparib studies. This includes acceptable methods of contraception, which are now presented as a list, with Table 4 deleted. The definitions of females of childbearing/non-childbearing potential have also been updated.

Section 3.8.1 (Restrictions related to olaparib and CYP3A4): A restriction on consumption of grapefruit juice whilst receiving olaparib was added for consistency with other olaparib studies.

Section 4 (Study plan and timing of procedures): Text was added to clarify that patients can continue to receive olaparib+MEDI4736 treatment beyond the 12-month period described in Table 5 (previously Table 6).

Section 4 (Study plan and timing of procedures, Table 4 [previously Table 5]):

- The Table and footnotes were updated to reflect the removal of prospective ATM testing and the need for written consent for ATM assessment.
- Text was added to footnote "c" (previously "d") clarifying that the scan performed during screening/baseline acts as baseline for disease control rate (DCR) assessments. Text was also added clarifying the timing between baseline assessments and the start of olaparib treatment.
- A footnote ("i") was added stating that patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. This change was made for consistency with the change in exclusion criterion 21.
- Reference to footnote "k" for "Mandatory whole blood for immunophenotyping by flow cytometry (CytoChex and ACD-B tubes)" was removed as the reference was not correct.
- Text was added to indicate that ovarian cancer patients who have an archival tumor sample >3 years old no longer have to provide a new biopsy sample. A higher proportion of ovarian cancer patients have older archival biopsies. This change is to increase patient accrual in this population.
- Text was deleted regarding ATM testing in gastric cancer patients, as the requirement for these patients to be ATM-negative was removed.
- Footnote "p" was added to clarify olaparib dosing and the duration of the monotherapy treatment period.

Whole document (first mention: Section 4, Table 4 [previously 5]): Where central diagnostic testing by Myriad is mentioned, text was added to state "a central laboratory, such as Myriad", to allow central testing to be performed by other certified vendors.

Section 4 (Study plan and timing of procedures, Table 5 [previously Table 6]):

- Table 6 was re-titled to reflect treatment can continue beyond 12 months.

- The MEDI4736 PK sample at C1D15 was removed, it was previously included in error.

- Text was added to footnote "m" clarifying that the scan performed during screening/baseline acts as baseline for DCR assessments.

Section 4 (Study plan and timing of procedures, Table 6 [previously Table 7]): The time window for the first follow-up visit after discontinuation of investigational product was changed from 3 days to 1 week to balance the requirements for follow-up with patient quality of life.

Section 4.2.1 (Dosing regimen): Text was added to clarify olaparib dosing and the duration of the monotherapy treatment period.

Section 4.2.2 (Definition of dose-limiting toxicity): This section was deleted as the dose-finding phase of the olaparib clinical program is completed. Events previously captured as dose-limiting toxicities (DLTs) will be captured as appropriately-graded AEs, and there is now no need to define DLTs. Subsequent subsections in Section 4.2 have been renumbered.

Section 5.2 (Safety assessments, Table 7 [previously Table 8]):

- The timepoint of first "Whole blood for gene expression (PAXgene-RNA tube)" sample was corrected from Screening to Week 1, Day 1 for consistency with the study schedule.

- The number of blood samples for MEDI4736 PK was updated according to changes made in Table 8 (previously Table 9). The total volume of these samples and the total blood volume overall have been updated accordingly.

Section 5.2.1 (Laboratory safety assessments):

- Text was added to clarify that local laboratory results can be used by Investigators for clinical decision making.

- Text was added stating hepatitis C viral load is to be performed (patients with history of hepatitis C only).

Section 5.2.2 (Physical examination): Text was added to state that urogenital examination is not required for breast, gastric or small cell lung cancer cohort patients, as this is not an assessment typically performed for these patients.

Section 5.3.1 (Collection of samples and the determination of olaparib concentrations; Table 8 [previously Table 9]):

- Changes were made to the format of the table to improve clarity.

- The pre-dose MEDI4736 sample on Day 15 was deleted, it was previously included in error.

- The reference to Day 29 was corrected to Day 22 (Week 4 Day 1).

Section 5.3.4.3 (Pharmacodynamic samples): This section was deleted as it repeats information already provided in Section 5.3.4.2.

Section 5.5.1 (Data and samples for patient selection and eligibility): The requirements for prospective ATM testing were removed, consistent with the removal of the requirement for gastric cancer patients to be ATM-negative.

Section 5.5.2 (Mandatory tumor sample):

- Text was added confirming that tissue blocks may be repatriated on request.

- Text was added to indicate that ovarian cancer patients who have an archival tumor sample >3 years old no longer have to provide a new biopsy sample. A higher proportion of ovarian cancer patients have older archival biopsies, this change is to increase patient accrual in this population.

- Text on gastric tumor samples for ATM testing was removed, consistent with the removal of the requirement for gastric cancer patients to be ATM-negative.

Section 5.5.4.1 (Pharmacodynamics: paired tumor biopsies): CCI [redacted]

Section 6.3.3 (Adverse events after the 90-day follow-up period), Section 6.7.3 (Olaparib adverse events of special interest) Section 9.3 (Study timetable and end of study): Text was removed relating to Investigator's knowledge of treatment arm, as this is an open-label study.

Section 6.5 (Overdose): Text was added to further clarify that an overdose should be reported if 1 or more doses are found to be missing during tablet counts.

Section 6.7.2.1 (Management of hematological toxicity): In Table 11 (previously Table 12), the option for patients with an on-study hemoglobin value of <10 but ≥8 g/dL was added to the protocol to allow Investigators greater discretion in the best way to manage cases of anemia.

Section 6.7.4 (MEDI4736): Repeat text was deleted to improve clarity.

Section 6.7.5 (MEDI4736 adverse events of special interest): Text was updated based on the

most recent knowledge on MEDI4736.

Section 6.7.6 (Immune-related adverse events): Table 13 (previously 14) was updated with up-to-date information on MEDI4736 dose modifications and toxicity management guidelines for immune-mediated, infusion-related and non-immune-mediated reactions.

Section 7.1.1 (MEDI4736): The text was updated to remove reference to the 1.125 g dose of MEDI4736, as dose reduction for MEDI4736 was removed from the study.

Section 7.2.1 (Olaparib): Text was added giving guidance on olaparib dose reductions for patients who develop renal insufficiency (determined by creatinine clearance). This text was added for consistency with other current olaparib studies.

Section 7.7 (Concomitant and other treatments); Appendix F: Text was updated to reflect the most up-to-date knowledge on the interactions between olaparib and other drugs.

Section 7.7.1 (Medications that may NOT be administered):

- A reference to palliative radiotherapy was added in the text to highlight to readers where further information can be found on when it is permitted.
- Text was updated to reflect the most up-to-date knowledge on the interactions between olaparib and other drugs.
- Text was added to describe an olaparib dose reduction strategy for patients who require strong CYP3A inhibitors to allow them to remain on olaparib treatment where possible.

Sections 8.2.1 to 8.2.4 (Sample size estimate and cohort expansion criteria): Median progression-free survival estimates, proportions of patients anticipated to be progression-free at 12 weeks, target DCR and DCR value considered undesirable have been updated to reflect emerging evidence of the latest efficacy associated with the four cancer cohorts.

Section 8.3.3 (Pharmacokinetic analysis set): A new section (Section 8.3.3) was added that defines the pharmacokinetic analysis set.

Section 8.6 (Methods for statistical analysis): The 28-week analysis of DCR was identified as a result to be presented without 95% CIs.

Section 9.4 (Data management by Quintiles): text on the AstraZeneca genotyping LIMS database was updated to reflect current AstraZeneca processes.

Section 11 (References): Ledermann et al 2014 and Ledermann et al 2016 were added to the list of references to support changes made elsewhere in the protocol. Kim et al 2014 and Le et al 2015 were deleted as they are no longer cited in the text.

Appendix D (previously E; Guidelines for Evaluation of Objective Tumor Response Using

RECIST 1.1 Criteria [Response Evaluation Criteria in Solid Tumors]): This appendix was updated to the most recent text appropriate for RECIST 1.1 criteria. Appendix E (previously F; Monitoring Plan for Futility and Efficacy): This appendix was updated with values consistent with the amended Bayesian design.

Revised Protocol edition 1, 23 November 2015
Refer to the separate Clinical Study Protocol Amendment document dated 23 November 2015 for the changes made in Protocol Amendment Number 1.

Edition 1, 9 September 2015
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

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

International Co-ordinating Investigator

PPD

USA

and

PPD Philadelphia, PA 19104, USA

Study sites and number of patients planned

This modular study will initially be conducted in approximately 7 countries world-wide.

This study comprises 2 groups ("stages") of cohorts:

- **Initial Stage Cohorts**: a total of CCI have enrolled approximately 30 patients in each of 4 exploratory Initial Stage Cohorts (Modules 1 to 4). These cohorts (Modules 1 to 4) include patients with relapsed small cell lung cancer (SCLC), germline *BRCA* mutated (*gBRCAm*) metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer, *gBRCAm* platinum-sensitive relapsed ovarian cancer, and gastric cancer. Enrollment for these cohorts has been completed and data reported in a Clinical Study Report (CSR).
- **Second Stage Cohorts**: a total of CCI (including some centers that enrolled patients in the Initial Stage Cohorts) enrolled patients into 3 exploratory Second Stage Cohorts (Modules 5 to 7) that were originally planned to include a total of approximately 140 ovarian cancer patients overall. These Second Stage Cohorts (Modules 5 to 7) were planned to include patients with *BRCAm* platinum-sensitive relapsed ovarian cancer (n=80), and non *BRCAm* platinum-sensitive relapsed ovarian cancer (n=30 for each of 2 cohorts). Enrollment for these cohorts has been completed; enrollment for the cohort of *BRCAm* platinum-sensitive relapsed ovarian cancer patients was terminated when 51 of 80 planned patients had been enrolled; see Study Design below for further details.

Each cohort has its own dedicated Module with cohort-specific information. The Figure below illustrates the location of each cohort-specific Module in the protocol.

Phase of development: I/II

Location of cohort modules in the protocol

	Patient population	Cohort	Location in Protocol
Initial Stage Cohorts Solid tumors	Relapsed SCLC	SCLC cohort; **Module 1**	Appendix H
	gBRCAm HER2-negative breast cancer	*gBRCAm* breast cancer cohort; **Module 2**	Appendix I
	gBRCAm platinum-sensitive relapsed ovarian cancer	*gBRCAm* ovarian cancer cohort; **Module 3**	Appendix J
	Gastric cancer	Gastric cancer cohort; **Module 4**	Appendix K
Second Stage Cohorts Ovarian cancer	*BRCAm* platinum-sensitive relapsed ovarian cancer	*BRCAm* ovarian cancer expansion cohort; **Module 5**	Appendix L
	Non *BRCAm* platinum-sensitive relapsed ovarian cancer	Ovarian cancer triplet cohort; **Module 6**	Appendix M
		Ovarian cancer doublet cohort; **Module 7**	Appendix N

Patients in the ovarian cancer triplet cohort (Module 6) will receive olaparib+MEDI4736+bevacizumab treatment. Patients in all other cohorts will receive olaparib+MEDI4736.
BRCAm=BRCA mutated; *gBRCAm*=germline BRCA mutated; SCLC=small cell lung cancer.

Study design

This is a Phase I/II open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics (PK) and antitumor activity of MEDI4736 in combination with olaparib in patients with advanced solid tumors, selected based on a rationale for response to olaparib. Patients in the Initial Stage Cohorts have selected solid tumors and patients in the Second Stage Cohorts have ovarian cancer. Ovarian cancer patients enrolled into Module 6 (ovarian cancer triplet cohort; Appendix M) will receive bevacizumab treatment in combination with MEDI4736+olaparib treatment.

Patients will be poly (adenosine diphosphate-ribose) polymerase (PARP)-inhibitor and immunotherapy (IMT)-naïve (defined as no prior exposure to PARP inhibitors or IMT, including, but not limited to, other anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], anti-programmed cell death 1 [PD-1], CCI monoclonal antibodies, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

In all cohorts, patients should continue to receive study treatment (ie, MEDI4736+olaparib±bevaciumab) until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by the Investigator, or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria.

Each cohort will have a specific data cut-off. The clinical database will close once the doublet and triplet Second Stage Cohorts have reached a median value for overall survival. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database 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. At routine clinic visits, patients will return used medication packaging and unused medication, and a thorough drug accountability assessment will be performed. However, where local regulations allow, patients may be switched from clinical trial supplies to marketed IP in those territories where IP is approved for the disease under study. For these patients, any SAEs which occur on treatment or within 90 days of treatment discontinuation will be reported to Patient Safety. However, and furthermore, SAEs in patients continuing on olaparib after the end of combination treatment, and which occur **after** the 90-day window has passed, will be reported if they fall within 30 days of this latter timepoint (ie, up to 120 days after discontinuation).

Olaparib dose selection was based on the results of an independent study, the National Cancer Institute (NCI) Study ESR-14-10366 (hereafter referred to as the "NCI study"; Lee et al 2017). On the basis of these data, the dose of olaparib to be used in this study will be the recommended monotherapy dose of 300 mg twice daily (bid).

The safety and tolerability of olaparib 300 mg bid/MEDI4736 1.5 g every 4 weeks (Q4W) (hereafter referred to as "Full Dose") was convincingly supported by the NCI study. During the study a Review Committee will be convened and review pre-specified safety and efficacy data at the times specified in the cohort-specific appendices, where applicable. 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.

Initial Stage Cohorts

Initially, patients were enrolled concurrently into 4 exploratory cohorts (**Initial Stage Cohorts**, Modules 1 to 4), which include:

- Patients with relapsed SCLC ("SCLC cohort") (**Module 1**; see Appendix H)
- Patients with *gBRCAm* metastatic HER2-negative breast cancer ("*gBRCAm* breast cancer cohort") (**Module 2**; see Appendix I)
- Patients with *gBRCAm* platinum-sensitive relapsed ovarian cancer ("*gBRCAm* ovarian cohort") (**Module 3**; see Appendix J)
- Patients with relapsed gastric cancer ("gastric cancer cohort") (**Module 4**; see Appendix K)

Patients in Modules 1 to 4 are receiving study treatment of MEDI4736+olaparib.

In the Initial Stage Cohorts, after evaluating disease control rate (DCR) (defined for the Initial Stage Cohorts as: complete response [CR]+partial response [PR]+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.

To ensure uniform decision making, a Bayesian predictive probability design will be consistently employed in the Initial Stage Cohorts.

There will be an initial period of 4 weeks monotherapy treatment with olaparib 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. A proportion of patients (minimum of 5 evaluable pairs per cohort) will undergo pre- and post-olaparib treatment tumor biopsies to evaluate the tumor microenvironment changes and to identify potential biomarkers predictive of activity of the combination. 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. These patients should be scanned at 12 weeks (8 weeks after start of combination therapy).

In the final analysis of the Initial Stage Cohorts, patients will be evaluated for DCR at 12 weeks and 28 weeks, objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), percentage change from baseline in tumor size at 12 and 28 weeks, best percentage change from baseline in tumor size, time to study treatment discontinuation (TDT), and overall survival (OS) following objective radiological disease progression according to RECIST 1.1 as assessed by the Investigator. Because of the 4-week initial run-in period, the counting of weeks is different when referring to dosing and when referring to assessment.

Data from the Initial Stage Cohorts have been reported in a CSR. In all 4 Initial Stage Cohorts, the olaparib + MEDI4736 combination was well-tolerated, and AEs were consistent with those seen in olaparib and MEDI4736 monotherapy studies. In the breast and ovarian cancer cohorts, the combination of olaparib and MEDI4736 showed promising antitumor activity. In the SCLC and gastric cancer cohorts the 12-week disease control rate was below the pre-specified target, however durable responses were observed in a minority of patients in these cohorts.

Second Stage Cohorts

In the second stage of the study (**Second Stage Cohorts**), additional patients will be enrolled in the following cohorts:

- Patients with *BRCAm* platinum-sensitive relapsed ovarian cancer, who will receive study treatment with a combination of MEDI4736+olaparib ("*BRCAm* ovarian cancer expansion cohort") (**Module 5**; see Appendix L)

- Patients with non *BRCAm* platinum-sensitive relapsed ovarian cancer, who will receive study treatment with "triplet" therapy (MEDI4736+olaparib+bevacizumab; "ovarian cancer triplet cohort") (**Module 6**; see Appendix M)
- Patients with non *BRCAm* platinum-sensitive relapsed ovarian cancer, who will receive study treatment with "doublet" therapy (MEDI4736+olaparib; "ovarian cancer doublet cohort") (**Module 7**; see Appendix N)

Enrollment into the ovarian cancer doublet cohort will only occur after enrollment for the ovarian cancer triplet cohort has been completed. The *BRCAm* ovarian cancer expansion cohort and the ovarian cancer triplet cohort will enroll concurrently. In the Second Stage Cohorts, no olaparib run-in period will be included, and all study treatment will start concurrently (olaparib+MEDI4736±bevacizumab).

Patients should continue to receive study treatment (ie, MEDI4736+olaparib±bevaciumab) until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria.

Enrollment in the Second Stage Cohorts has completed.

BRCAm ovarian cancer expansion cohort

A cohort of *BRCAm* ovarian cancer patients will be enrolled in order to confirm the high response rate seen in the Initial Stage *gRBCAm* ovarian cancer cohort, with ORR as the primary endpoint. These patients will also be assessed for disease control rate (assessed at 24 and 56 weeks), PFS, and DoR to get a better understanding of the longer-term efficacy of the combination. Additionally, percentage change from baseline in tumor size (at 24 and 56 weeks), TDT, and OS following objective radiological disease progression according to RECIST 1.1 as assessed by the Investigator will be assessed.

Enrollment into the *BRCAm* ovarian cancer expansion cohort was terminated when 51 of 80 planned patients had been enrolled. As PARP inhibitors have become standard of care in the first line setting for *gBRCAm* patients, the high unmet clinical need in this patient population has reduced. In addition, as a result of the success of PARP inhibitors in this setting, there are limited numbers of PARP inhibitior-naïve patients eligible for inclusion in the *BRCAm* ovarian cancer expansion cohort. Therefore, despite high response rates in this patient population with olaparib and MEDI4736 combination treatment as shown in the initial stage *gBRCAm* ovarian cancer cohort, recruitment for the *BRCAm* ovarian cancer expansion cohort was closed early.

Non BRCAm ovarian cancer triplet and doublet cohorts

The safety of the "triplet" treatment regimen will be evaluated in 10 patients after 4 weeks of treatment in the ovarian cancer triplet cohort.

In the ovarian cancer triplet and doublet cohorts, DCR (defined as: CR+PR+SD, evaluated at 24 weeks) and selected safety data will be reviewed after data from 15 evaluable patients from each cohort are available, and then again at the maximum sample size (n=30). 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.

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 as 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.

Objectives and outcome measure for all cohorts

Primary Objectives	Outcome Measures		
	Initial Stage Cohorts	Second Stage Cohorts	
		***BRCAm* ovarian cancer expansion cohort**	**Ovarian cancer triplet and doublet cohorts**
To assess the effect of MEDI4736 in combination with olaparib±bevacizumab in patients with selected advanced solid tumors	DCR (CR+PR+SD) based on RECIST 1.1 at 12 weeks	ORR (CR+PR) based on RECIST 1.1 assessed by the Investigator	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	• AEs, vital signs including blood pressure, pulse, ECG and laboratory findings including clinical chemistry and hematology. • 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. • Dose interruptions, dose reductions. • Causes of olaparib and MEDI4736 discontinuation.		
	NA	NA	**Triplet cohort only:** Causes of bevacizumab discontinuation.

AE=adverse event; *BRCAm*=Mutated breast cancer susceptibility gene; CR=complete response; DCR=disease control rate; ECG=electrocardiogram; irAE=immune-related adverse event; NA=not applicable; ORR=objective response rate; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

Secondary Objectives	Outcome Measures		
	Initial Stage Cohorts	Second Stage Cohorts	
		***BRCAm* ovarian cancer expansion cohort**	**Ovarian cancer triplet and doublet cohorts**
To investigate the preliminary antitumor activity of MEDI4736 in combination with olaparib±bevacizumab in patients with selected advanced solid tumors	• DCR at 28 weeks • ORR (CR+PR) based on RECIST 1.1 • DoR based on RECIST 1.1 • PFS based on RECIST 1.1 • Percentage change from baseline in tumor size at 12 weeks and	• DCR at 24 weeks and 56 weeks • DoR based on RECIST 1.1 • PFS based on RECIST 1.1 • Percentage change from baseline in tumor size at 24 weeks and 56 weeks • Best percentage change from	• DCR at 56 weeks • DoR based on RECIST 1.1 • PFS based on RECIST 1.1 • ORR (CR+PR) based on RECIST 1.1 assessed by the Investigator • Percentage change from baseline in tumor size at 24 weeks and

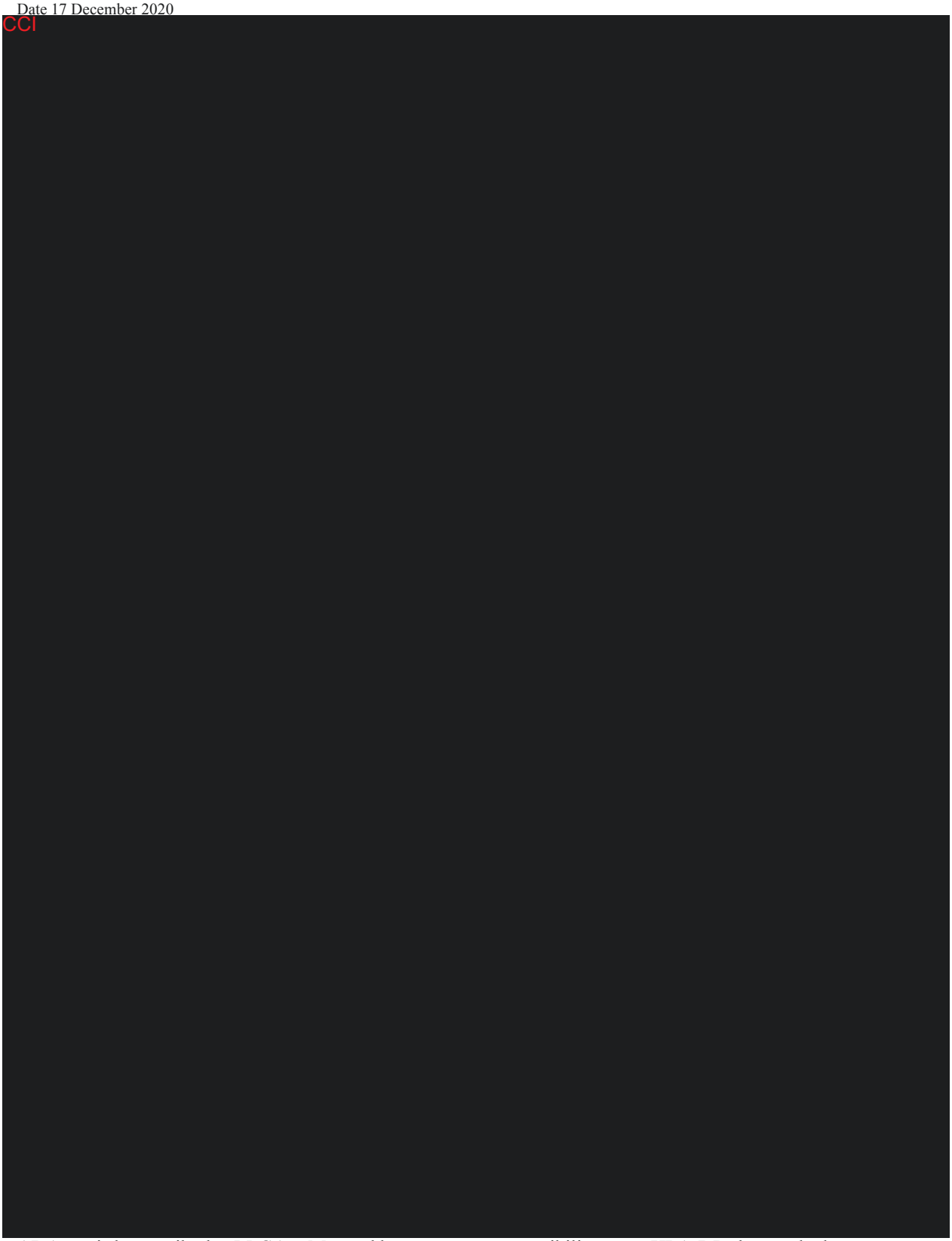
Secondary Objectives	Outcome Measures		
	Initial Stage Cohorts	Second Stage Cohorts	
		***BRCAm* ovarian cancer expansion cohort**	**Ovarian cancer triplet and doublet cohorts**
	28 weeks • Best percentage change from baseline in tumor size • TDT • Overall survival	baseline in tumor size • TDT • Overall survival	56 weeks • Best percentage change from baseline in tumor size • TDT • 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	• Serum concentrations of MEDI4736, MEDI4736 anti-drug antibody (ADA). Plasma concentrations of olaparib • Presence of ADAs for MEDI4736 • CCI	• Serum concentrations of MEDI4736, MEDI4736 anti-drug antibody (ADA). Plasma concentrations of olaparib • Presence of ADAs for MEDI4736	• Serum concentrations of MEDI4736, MEDI4736 anti-drug antibody (ADA). Plasma concentrations of olaparib • Presence of ADAs for MEDI4736
To characterize the PK and pharmacodynamics of bevacizumab after single dosing and multiple dosing when given intravenously to patients in combination with MEDI4736 and olaparib	NA	NA	**Triplet cohort only:** • Serum concentrations of bevacizumab
CCI [redacted]	[redacted]		

ADA=anti-drug antibody; *BRCAm*=Mutated breast cancer susceptibility gene; CR=complete response; DCR=disease control rate; DoR=duration of response; NA=not applicable; ORR=objective response rate; CCI [redacted]; PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; CCI [redacted] TDT=time to study treatment discontinuation.

CCI

[redacted]

CCI



ADA=anti-drug antibody; *BRCAm*=Mutated breast cancer susceptibility gene; HLA-DR=human leukocyte antigen – antigen D related; NA=not applicable; Pd=pharmacodynamic; PD-1=programmed cell death-1;

CCI PK=pharmacokinetic; CCI
VEGF=vascular endothelial growth factor.

Target patient population

Males and females aged 18 years and over (19 years or over in South Korea) with histologically or cytologically confirmed progressive metastatic or recurrent solid tumor.

To be enrolled in 1 of the Initial Stage Cohorts of the study, only the following tumor types were allowed:

- *gBRCAm* ovarian cancer
- *gBRCAm* HER2-negative metastatic breast cancer
- Relapsed SCLC
- Gastric cancer.

To be enrolled in 1 of the ovarian cancer Second Stage Cohorts of the study, only the following tumor types were allowed:

- *BRCAm* ovarian cancer (*BRCAm* ovarian cancer expansion cohort)
- non *BRCAm* ovarian cancer (ovarian cancer triplet and doublet cohorts).

Details of how *BRCA* status will be determined to enable enrollment into the Second Stage Cohorts are presented in Appendix O.

All patients must have at least 1 measurable lesion that can be *accurately* assessed by baseline computed tomography (CT), or by magnetic resonance imaging where CT is contraindicated, and which is suitable for repeated assessment as per RECIST 1.1. Patients must have adequate organ and marrow function. Toxicities of prior therapy (excepting alopecia) should be resolved to less than or equal to grade 1 per Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 prior to the start of olaparib treatment.

Duration of treatment

In the Initial Stage Cohorts there will be a 4-week olaparib only run-in period (SCLC, gastric cancer, *gBRCAm* breast cancer, and *gBRCAm* ovarian cancer cohorts; Modules 1 to 4). In contrast, in the Second Stage Cohorts the study drugs will initiate concurrently.

Patients should continue to receive study treatment until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria. Clinically stable patients in the Initial Stage Cohorts, 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.

After discontinuation of study treatment, the Investigator will be at liberty to define further the most appropriate anticancer treatment. All patients will be followed for disease progression and survival until the cohort data cut-off, and may be followed for survival, selected safety, investigational product dispensing/accountability, and subsequent anticancer treatment data after the cohort data cut-off.

Investigational product, dosage, and mode of administration

Olaparib is available as a film-coated tablet containing 150 mg or 100 mg of olaparib. Patients will be administered study treatment orally at a dose of 300 mg bid. The initial dose of 300 mg bid will be made up of 2×150 mg tablets bid. The 100 mg and 150 mg tablets will be used to manage dose reductions.

MEDI4736 will be supplied by AstraZeneca as a 500-mg vial for solution for infusion. The solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. Total in-use storage time from needle puncture of MEDI4736 vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the in-use storage time exceeds these limits, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives and any unused portion must be discarded.

Patients will receive MEDI4736 1.5 g Q4W ±3 days via intravenous (IV) infusion.

In the ovarian cancer triplet cohort (Module 6), bevacizumab will be started at a dose of 10 mg/kg Q2W via IV infusion. Bevacizumab will be sourced locally or centrally supplied by AstraZeneca if local sourcing is not feasible. Bevacizumab should be administered according to local prescribing information, including any treatment restrictions, and should be stored according to the local label.

For patients in the Initial Stage Cohorts: Treatment with MEDI4736 will commence on Cycle 1, Day 1 following the completion of the 4-week olaparib-only run-in period and will continue on a Q4W schedule until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria.

For patients in Second Stage Cohorts: All study drugs will commence on Cycle 1, Day 1 and will continue on a 28-day (or 4-week) cycle until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria.

Statistical methods

Sample size

All cohorts except *BRCAm* ovarian cancer expansion cohort

Progression-free survival is the most relevant endpoint for decision making but is difficult to determine accurately in a small cohort. However, there is an approximate relationship between PFS and DCR at specified timepoints because patients whose disease has responded or is stable cannot have had a disease progression. For example, if the median PFS of interest is 6 months this would suggest that 70% of patients will be progression-free at 3 months, assuming an exponential distribution of progression times. For this reason, the primary efficacy endpoint of these cohorts is DCR and this endpoint has been used to define the sample size.

Each cohort, excluding the *BRCAm* ovarian cancer expansion cohort, will be considered as individual predictive probability designs as described by Lee & Liu (2008). These designs are based on Bayesian predictive probability and the minimax criterion. Taking this approach, in each cohort, we assume that the response (DCR) has a prior distribution of beta (0.5, 0.5) – a Jeffrey's non-informative prior. A predictive probability threshold for futility and efficacy is set at 10% and 90%, respectively.

For example, in the Initial Stage Cohorts, the selection of a DCR of 70% at 3 months (ie, at 12 weeks, using the timing conventions used throughout this protocol) to drive decision making will give some assurance that a level of PFS of interest is realistic without having to wait to actually observe the PFS times. After evaluating the DCR of the first 10 patients at 12 weeks it will be monitored after every 5 patients until the maximum sample size is reached. 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.

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).

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. Additionally, if the DCR is such that the null hypothesis will not be able to be rejected at the end of the trial the cohort may be stopped for futility at any of the interim looks defined above.

Expansion cohort

To confirm the promising results in the Initial Stage *gBRCAm* ovarian cancer cohort, patients will be evaluated for ORR as the primary endpoint in the *BRCAm* ovarian cancer expansion cohort.

In the *BRCAm* ovarian cancer expansion cohort, when the sample size is n=80, a 2-sided 95.0% confidence interval 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.

Outcome measures for analysis

The primary efficacy variable for the Initial Stage Cohorts and the Second Stage triplet and doublet ovarian cancer cohorts is DCR. The DCR is defined as the percentage of patients who have at least 1 visit response of CR or PR or have demonstrated SD which is maintained until the RECIST 1.1 assessment at 12 weeks (Initial Stage Cohorts) and 24 weeks (ovarian cancer triplet and doublet cohorts).

The primary efficacy variable for the *BRCAm* ovarian cancer expansion cohort is ORR as assessed by the Investigator.

Other efficacy endpoints include DCR at 24, 28, and 56 weeks, PFS, OS, TDT, ORR, DoR, percentage change from baseline in tumor size, and best percentage change from baseline in tumor size. All tumor assessment-related endpoints will be based on radiological response as assessed by the Investigator using RECIST 1.1.

All patients who receive at least 1 dose of 1 study drug (olaparib in the Initial Stage Cohorts, or any constituent of the combination treatment in the Second Stage Cohorts) and have not been excluded from the study for administrative reasons, eg, failing important inclusion

criteria (a full list will be predefined in the statistical analysis plan), will be included in efficacy analyses. All patients who received at least 1 dose of study drug will be included in safety analyses.

Methods for statistical analysis

The DCR will be summarized (ie, number of patients, %) in each tumor group. Patients who do not complete the DCR assessment at the timepoint of interest (for example, due to drop out prior to the assessment) will be considered as a treatment failure. For all cohorts except the *BRCAm* ovarian cancer expansion cohort, 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% CI and 1-sided p-value will also be presented.

Safety and tolerability will be assessed within each tumor type in terms of AEs, deaths, laboratory data, vital signs and ECGs. These will be collected for all patients. Appropriate descriptive summaries of these data will be presented.

Pharmacokinetic analysis

The PK of olaparib and MEDI4736 will be assessed in all cohorts. Additionally, the PK of bevacizumab will be assessed in the ovarian cancer triplet cohort.

The plasma concentration-time data will be analyzed by non-linear mixed effects modeling in order to evaluate the PK characteristics of olaparib alone and in combination with MEDI4736, quantify variability in the PK, identify demographic or pathophysiological covariates which may explain the observed variability and explore exposure-response relationships. The relationship between exposure to olaparib and MEDI4736 and pharmacodynamics response (safety and/or efficacy) will be investigated if deemed appropriate. Population PK/pharmacodynamic results will be reported separately from the CSR.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Core Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADL	Activities of daily living
ADP	Adenosine diphosphate
AE	Adverse event
AESI	Adverse event(s) of special interest
ALT (SGOT)	Alanine aminotransferase (serum glutamic-oxalo-acetic transaminase)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST (SGPT)	Aspartate aminotransferase (serum glutamate pyruvate transaminase)
ATM	Ataxia telangiectasia mutated (gene or protein)
bid	Twice daily
BICR	Blinded independent central review
BP	Blood pressure
BOR	Best objective response
BRCA	Breast cancer susceptibility gene, ie, *BRCA1* and *BRCA2*
BRCAm	Mutated breast cancer susceptibility gene
BUN	Blood urea nitrogen
CA-125	Cancer antigen 125
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CR	Complete response
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4

Abbreviation or special term	Explanation
CXCL	C-X-C motif ligand
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EU	European Union
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
gBRCAm	Germline mutated breast cancer susceptibility gene
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
Hb	Hemoglobin
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HLA-DR	Human leukocyte antigen – antigen D related
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
IFN	Interferon
IHC	Immunohistochemistry
IL	Interleukin
INR	International normalized ratio
imAE	Immune-mediated AE
IMT	Immunotherapy

Abbreviation or special term	Explanation
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally.
IP	Investigational product
irAE	Immune-related adverse events
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFT	Liver function test
LLN	Lower limit of normal
LPFV	Last patient first visit
mAb	Monoclonal antibody
MATE	Multidrug and toxin extrusion
MDS	Myelodysplastic syndrome
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NED	No evidence of disease
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
P	P interval on the ECG
PARP	polyadenosine 5’diphosphoribose (poly [ADP ribose]) polymerization
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Anti-programmed cell death 1

Abbreviation or special term	Explanation
PD-L1	Anti-programmed death-ligand 1
Pgp	P-glycoprotein
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial response
PSR	Platinum-sensitive recurrent
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QRS	QRS interval on the ECG
QTc	Heart rate corrected QT interval
QTcF	Heart rate corrected QT interval (Fridericia's formula)
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
sPD-L1	Soluble PD-L1
T_3	Tri-iodothyronine
T_4	Thyroxine
TBL	Total bilirubin
TDT	Time to study treatment discontinuation
TL	Target lesion
TMGs	Toxicity Management Guidelines
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
Treg	Regulatory T-cells
ULN	Upper limit of normal
US	United States of America
VEGF	Vascular endothelial growth factor
WBDC	Web Based Data Capture

Abbreviation or special term	Explanation
WT	Weight

1. INTRODUCTION

Further introductory information can be found in Section 1 of each of the cohort-specific Modules (Appendix H to Appendix N).

1.1 Background and rationale for conducting this study

1.1.1 Background

1.1.1.1 Tumor immunotherapy and programmed cell death-ligand 1

Immune responses directed against tumors are 1 of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T-cells. CCI [redacted] which is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some indications. In a number of these cancers, including lung (Mu et al 2011), renal (Krambeck et al 2007; Thompson et al 2005; Thompson et al 2006), pancreatic (Loos et al 2008; Nomi et al 2007; Wang et al 2010), and ovarian cancer (Hamanishi et al 2007), CCI [redacted]

Anti-programmed death-ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. CCI [redacted] This results in reduced T-cell activation and fewer activated T-cells in circulation. CCI [redacted] This delivers an inhibitory signal to those T-cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zou and Chen 2008).

Based on in vitro studies, an antibody that blocks the interaction between CCI [redacted] and enhance the cytotoxic

activity of antitumor T-cells (Blank et al 2006). The levels of tumor-infiltrating lymphocytes, and more specifically cytotoxic T-cells, have been correlated with improved prognosis in a number of cancers including colorectal, melanoma, and lung (Pages et al 2010), suggesting that an antitumor immune response is beneficial to patients. CCI [redacted] Results of several pre-clinical studies using mouse tumor models support this hypothesis (Hirano et al 2005; Iwai et al 2002; Okudaira et al 2009; Zhang et al 2008). CCI [redacted]

Stimulating an antitumor immune response is a mechanism employed successfully by a number of approved cancer therapies. For example, aldesleukin (Proleukin®), a recombinant human interleukin (IL)-2, in renal cancer (Schmidinger et al 2004) and sipuleucel-T (Provenge®) in prostate cancer (Madan and Gulley 2011) both directly stimulate immune activation. Ipilimumab (Yervoy®) also stimulates the immune response, but does so by blocking the T-cell co-inhibitory molecule, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), thereby removing an immunosuppressive signal.

Blocking CCI [redacted] is an approach similar to CTLA-4 inhibition, but with some distinct differences. First, the expression of CTLA-4 and its ligands is restricted to the hematopoietic system and thus, the site of action for molecules targeting CTLA-4 is solely the peripheral lymphoid organs. In contrast, CCI [redacted] is expressed on cells of the hematopoietic system and on a range of tumor types. Therefore, targeting CCI [redacted] should have additional effects within the tumor microenvironment. Second, CTLA-4 plays an early and critical role in controlling T-cell activation. This is reflected in the phenotype of CTLA-4 knockout mice, which die between 3 and 4 weeks of age due to lymphoproliferative disease and tissue destruction. In contrast, CCI [redacted] acts later in the process of T-cell activation (Fife and Bluestone 2008) and is considered less critical to the control of initial T-cell activation. This is reflected in the phenotype of CCI [redacted] knockout mice, which are viable and have normal T-cell numbers and activation levels but show increased T-cell activation in response to antigen and increased susceptibility in certain autoimmune models (Dong et al 2002; Latchman et al 2004). Similarly, mice lacking PD-1, a CCI [redacted] receptor, show strain-specific phenotypes that are milder than those seen in CTLA-4 knockouts (Nishimura et al 1998; Nishimura et al 2001). Therefore, inhibition of the CCI [redacted] /PD-1 pathway might be expected to result in less toxicity relative to CTLA-4 inhibition. In support of these findings, recent Phase I clinical studies assessing the tolerability of agents targeting PD-1 have demonstrated a toxicity profile that is

more favorable than that of CTLA-4 (Brahmer et al 2010; Berger et al 2008; Wolchok et al 2010; Topalian et al 2012).

1.1.1.2 Rationale for combination of MEDI4736+olaparib in solid tumors

Treatment options for the broad patient populations eligible for enrollment in this study (see below for full details), ie, second-line (or later) ovarian cancer, human epidermal growth factor receptor 2 (HER2)-negative breast cancer who have already received standard therapies, small cell lung cancer (SCLC) who have already received platinum-based chemotherapy, and second-line gastric cancer, are limited and frequently require consideration of investigational agents. Molecular selection criteria with the use of an approved cancer therapy (olaparib) targeting deoxyribonucleic acid (DNA) damage repair mechanisms will be used to provide a rational therapeutic option for the ovarian, breast, and gastric cancer cohorts, and this agent will be combined with an immunotherapeutic agent to broaden the therapeutic effect of this regimen, based in part on the separate nonoverlapping mechanisms of action of the component agents and on the considerations outlined below.

Inhibition of PARP in sensitive tumor cells, for example those carrying mutations in the *BRCA1* or *BRCA2* genes, results in accumulating levels of DNA damage and genomic instability, ultimately resulting in cell death (Farmer et al 2005). Accumulating DNA damage has the potential to modify the immunogenicity of tumors through a number of key mechanisms:

- Triggering of intracellular signaling events that result in the activation of nuclear factor kappa B (NFκB) and interferon (IFN) regulatory factor 7 (IRF7). These transcriptional regulators result in the increased production of cytokines and chemokines that have the potential to promote antitumor immunity, such as type I IFNs (Chatzinikolaou et al 2014).
- Upregulation of surface receptors such as major histocompatibility complex, ligands for natural-killer group 2, member D (NKG2D) and inducible T-cell costimulatory ligand (ICOSL), which render tumor cells more visible to detection by cytotoxic T-cells (Tang et al 2014).
- Death of tumor cells and release of antigen, which may help to promote antigen presentation and immune priming (Kroemer et al 2012).

In agreement with this hypothesis, olaparib was associated with a significant improvement in progression-free survival (PFS) as a maintenance treatment in ovarian cancer (Ledermann et al 2014), and recent analyses suggests this may translate into a survival advantage (Ledermann et al 2016).

These effects would be expected to help promote an effective antitumor immune response. In keeping with this hypothesis, several tumor types with genetic defects expected to lead to

increased DNA damage show evidence of enhanced immune recognition. For example, *BRCAm* tumor cells are associated with higher levels of tumor infiltrating lymphocytes and secreting lymphocyte attractants (eg, C-X-C motif ligand [CXCL] 10) and immune suppressive ligands such as CCI (Mulligan et al 2014). The GOLD Phase III study did not meet the primary endpoint of overall survival (OS) in advanced gastric cancer patients, in either the overall population or patients whose tumor tested negative for ataxia telangiectasia mutated (ATM) protein. While there was a numerical survival trend in the olaparib plus paclitaxel arm, it did not meet statistical significance.

Based on this basic biology, the hypothesis to be tested in this study is that increased DNA damage triggered through PARP inhibition will result in enhanced antitumor immunity that can be further enhanced through combination with an immune checkpoint inhibitor in advanced cancers. This hypothesis is supported by published studies in mouse models of cancer, demonstrating that administration of a PARPi to sensitive tumor types results in increased T-cell infiltration and activation within tumors (Higuchi et al 2015; Huang et al 2015). In order to test this hypothesis clinically, patients will receive olaparib monotherapy for a period of 4 weeks prior to commencing combination treatment. It is also anticipated that MEDI4736 will prolong the duration of response (DoR) to olaparib in patients with DNA repair deficient cancers.

The rationale for combining bevacizumab and MEDI4736 with olaparib in the current study is discussed in Section 1.1.2 of Module 6 (ovarian cancer triplet cohort).

1.1.2 Background on individual investigational products

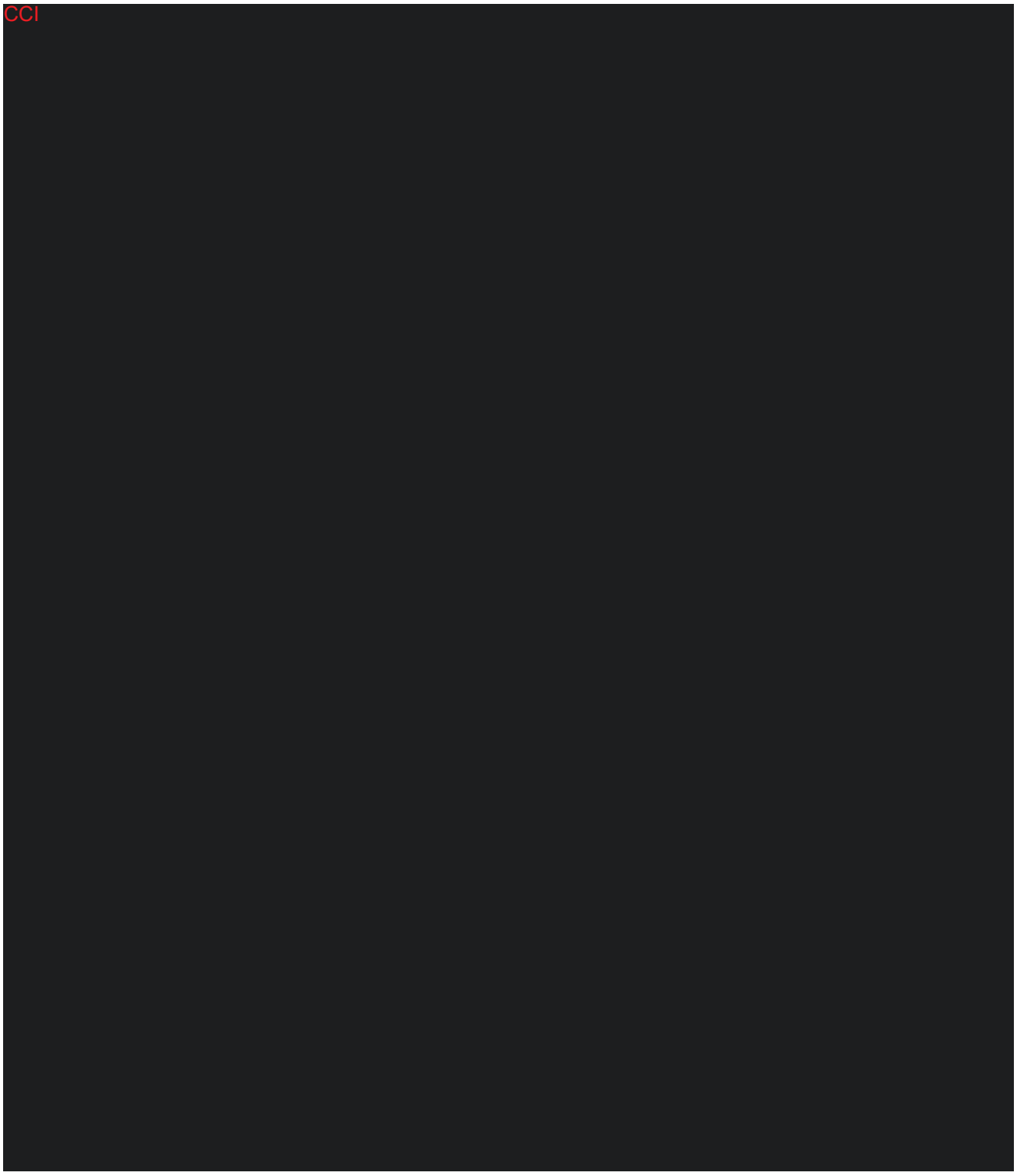
1.1.2.1 Olaparib

Olaparib (AZD2281, KU-0059436, Lynparza™) is a potent polyadenosine 5' diphosphoribose [poly (ADP ribose)] polymerization (PARP) inhibitor (PARPi; PARP-1, -2, and -3), the capsule formation of which was initially approved by Food and Drug Administration (FDA) as monotherapy in patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (*BRCA*) mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy.

The initial FDA approval for olaparib was mainly based on data from Study CCI (Study 42) (Kaufman et al 2015); a Phase II non-comparative study in *gBRCAm* advanced tumors, including ovarian cancer using olaparib capsule formulation, 400 mg bd.

In Study CCI (Study 19; a Phase II, randomized, double-blind, placebo controlled multicenter study using olaparib capsule formulation, 400 mg bd), CCI

CCI



In Europe, based on the Study 19 data, olaparib capsules was approved on 16 December 2014 as a maintenance treatment for patients with PSR *BRCAm* high grade serous epithelial

ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial response) to platinum-based chemotherapy (capsule formulation).

In the EU, the tablet formulation of olaparib for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response [CR] or partial response [PR]) to platinum-based chemotherapy has now been approved.

As of November 2020, olaparib has been granted several more additional approvals in ovarian cancer:

- By the FDA and European Medicines Agency (EMA) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (*gBRCAm* or *sBRCAm*) advanced epithelial ovarian, fallopian tube or primary peritoneal canacer who are in complete or partial response to first line platinum-based chemotherapy.
- By the FDA for treatment of adult patients with *gBRCA*-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy
- By the FDA and EMA for treatment in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:

    - A deleterious or suspected deleterious BRCA mutation, and/or
    - Genomic instability

Besides ovarian cancer, olaparib has been studied in other disease indications. The Phase III study GOLD did not meet the primary endpoint of OS in advanced gastric cancer patients, in either the overall population or patients whose tumor tested negative for ATM protein. While there was a numerical survival trend in the olaparib plus paclitaxel arm, it did not meet statistical significance (Bang et al 2017).

A Phase III trial (OlympiAD) in patients with metastatic germline *BRCA* mutated breast cancer showed a median progression-free survival significantly longer in the olaparib group than that in the standard-therapy group (7.0 months versus 4.2 months; hazard ratio for disease progression or death, 0.58; 95% CI: 0.43 to 0.80; $p<0.001$). The response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy group (Robson et al 2017). In the United States of America (US), an efficacy supplement seeking licensure of the tablets in the treatment of HER2-negative metastatic breast cancer, based on the OlympiAD study, was approved in 2018; it has also been approved by the EMA.

As of August 2020, olaparib has also been approved by the FDA and EMA for the maintenance treatment of adult patients with deleterious or suspected deleterious *gBRCAm* metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen, and by the FDA for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer who have progressed following prior treatment with enzalutamide or abiraterone, and also approved by the EMA for the BRCA 1/2 population.

Olaparib is being evaluated in combination with other anticancer agents, including immune-oncology agents.

1.1.2.2 MEDI4736

MEDI4736 (durvalumab, Imfinzi®) is a mAb of the immunoglobulin G1 kappa subclass that inhibits binding of CCI to PD-1 and CD80. It has shown preliminary activity in advanced solid tumors. The mechanism of action of MEDI4736 suggests the potential to combine it with a number of targeted anticancer treatments, resulting in either synergistic or additive activity in different tumor types. MEDI4736 was FDA-approved for the treatment of advanced urothelial cancer in 2017.

In 2017, MEDI4736 was approved for the treatment of advanced or metastatic urothelial carcinoma. Approval was based on 1 single-arm trial of 182 patients with locally advanced or metastatic urothelial carcinoma whose disease progressed after prior platinum-containing chemotherapy. MEDI4736, 10 mg/kg intravenously, was administered every 2 weeks. Confirmed objective response rate (ORR) as assessed by BICR per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, was 17.0% (95% CI: 11.9 to 23.3). At the data cut-off for the ORR analysis, median response duration was not reached (range: 0.9+ to 19.9+ months). CCI

CCI

CCI [redacted]

A recent Phase III trial (PACIFIC) showed a positive result for MEDI4736 after chemoradiotherapy in stage III NSCLC. The median progression-free survival from randomization was 16.8 months (95% CI: 13.0 to 18.1) with MEDI4736 versus 5.6 months (95% CI: 4.6 to 7.8) with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI: 0.42 to 0.65; p<0.001); the 12-month progression-free survival rate was 55.9% versus 35.3%, and the 18-month progression-free survival rate was 44.2% versus 27.0%. The response rate was higher with MEDI4736 than with placebo (28.4% versus 16.0%; p<0.001), and the median duration of response was longer (72.8% versus 46.8% of the patients had an ongoing response at 18 months). The median time to death or distant metastasis was longer with MEDI4736 than with placebo (23.2 months versus 14.6 months; p<0.001) (Antonia et al 2017). Based on the results of the PACIFIC trial, MEDI4736 was approved by the FDA for the treatment of stage III non-small cell lung cancer.

CCI [redacted] Details on the safety profile of MEDI4736 monotherapy are summarized in Section 1.3.2. Refer to the current MEDI4736 Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics (PK).

1.1.2.3 Bevacizumab

See Section 1.1.3.1 in Module 6 for background information on bevacizumab.

1.1.3 Pre-clinical experience with investigational products

The pre-clinical experience with olaparib and MEDI4736 is fully described in the respective current versions of the olaparib and MEDI4736 IBs.

1.1.4 Clinical experience with investigational products

Clinical experience with olaparib and MEDI4736 is described in the current respective versions of the olaparib and MEDI4736 IBs.

Clinical experience with bevacizumab can be found in the FDA label.

1.2 Rationale for study design, doses, and control groups

This open-label, multicenter, Phase I/II study will evaluate the safety, tolerability, PK and antitumor activity of MEDI4736 in combination with olaparib (±bevacizumab), in patients with metastatic or recurrent solid malignancies with DNA damage repair deficiencies, in which there is a rationale for olaparib to be effective and the potential for the combination to be more effective than olaparib alone.

1.2.1 Rationale for the study design: Initial Stage Cohorts

While most signal seeking studies utilize a study design focused on using overall response rate as a measure of activity, this endpoint does not capture the depth of response which is especially important for assessing immunotherapy containing regimens. For these regimens, PFS is a more relevant endpoint for decision making but is difficult to determine accurately in a small cohort without a comparator control. Since PFS is driven by progression events it is possible to define a relationship between PFS and disease control rate (which is based on the absence of progression) at a given timepoint. This study has utilized this strategy to define target DCR based on historical PFS targets (for standard of care therapy) for each cohort.

The study uses a Bayesian predictive design for each individual cohort which allows for the assessment at multiple intervals of the probability that the trial will show a conclusive result at the end of the study, given the current information (see Section 8.2 for more details on the statistical design). This design, therefore, allows an assessment of the activity and durability of response with relatively small cohort size and even the ability to stop early if futility or efficacy.

1.2.2 Rationale for the study design: Second Stage Cohorts

The rationales for the design of the platinum-sensitive ovarian mutated breast cancer susceptibility gene (*BRCAm*) cohort ("*BRCAm* ovarian cancer expansion cohort"), the

platinum-sensitive ovarian non *BRCAm* cohort treated with MEDI4736+olaparib+bevacizumab ("ovarian cancer triplet cohort"), and the platinum-sensitive ovarian non *BRCAm* treated with MEDI4736+olaparib ("ovarian cancer doublet cohort"), are described in Section 1.1 of Module 5, Section 1.2 of Module 6, and Section 1.1 of Module 7, respectively.

1.2.3 Selection of doses

1.2.3.1 Olaparib

Use in monotherapy

The approved olaparib tablet dose is 300 mg twice daily (bid).

Use in combination

Dose selection for this study is based on the results of an independent study, the National Cancer Institute (NCI) Study CCI [redacted] (Lee et al 2017). On the basis of data from this study, the dose of olaparib to be used in this study will be the recommended monotherapy dose of 300 mg bid.

1.2.3.2 MEDI4736

CCI [redacted]

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

better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on an average body WT of 75 kg, it is planned that a fixed dose of 1.5 g Q4W ±3 days MEDI4736 (equivalent to 20 mg/kg Q4W) will be administered via intravenous (IV) infusion, in combination with olaparib.

1.2.3.3 Bevacizumab

The rationale for selection of the bevacizumab dose in the ovarian cancer triplet cohort is presented in Section 1.2 of Module 6.

1.2.4 Patient population

All patients must have at least 1 measurable lesion at baseline that can be accurately measured at follow-up assessments. The primary and secondary efficacy outcome measures will use the RECIST 1.1 as assessed by the Investigator, which is a standard tool for measuring response in oncology study in solid tumors.

Molecular testing data from an appropriately accredited laboratory will be documented prior to a patient commencing treatment in the study.

1.2.4.1 Initial Stage Cohorts

The 4 exploratory Initial Stage Cohorts comprise patients with relapsed SCLC (Module 1, Appendix H), germline *BRCA* mutated (*gBRCAm*), metastatic HER2-negative breast cancer (Module 2, Appendix I), *gBRCAm* platinum-sensitive relapsed ovarian cancer (Module 3, Appendix J), and gastric cancer (Module 4, Appendix K).

The scientific rationale for the choice of tumors is discussed in Section 1.1.1.2.

1.2.4.2 Second Stage Cohorts

The 3 exploratory Second Stage Cohorts are comprised of patients with PSR *BRCAm* ovarian cancer (*BRCAm* ovarian cancer expansion cohort, Module 5, Appendix L), or with PSR non *BRCAm* ovarian cancer (ovarian cancer triplet cohort, Module 6, Appendix M; and ovarian cancer doublet cohort, Module 7, Appendix N).

1.3 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with MEDI4736 monotherapy, olaparib monotherapy, and MEDI4736+olaparib combination therapy, respectively, prior to the overall benefit/risk assessment.

The benefit/risk and ethical assessment for the non *BRCAm* ovarian cancer triplet cohort is described in Section 1.3 of Module 6.

1.3.1 Olaparib benefit/risk in monotherapy and combination therapy

Olaparib was first studied in ovarian cancer where it is now approved as a second-line maintenance treatment in an all-comer population, as well as in fourth line treatment in the *gBRCAm* ovarian cancer population. Clinical trials are ongoing to explore its role in the earlier line setting. A positive phase III trial in breast cancer also lead to FDA approval in the *gBRCA*m patient population. It is clear that olaparib has some activity also in gastric cancer. However, the Phase III trial did not show significant superiority in the olaparib arm - likely due to the low dose of olaparib that was limited by use of chemotherapy. Combination studies in non-chemotherapy setting are being conducted in gastric cancer to explore the olaparib activity seen in Phase II and III trials. Phase III trials are ongoing in prostate and pancreatic cancers in biomarker selected patient populations. Phase II trials using olaparib as a monotherapy and in combination with immunotherapies are ongoing in SCLC.

Regarding toxicity, olaparib has proven to be better tolerated compared with chemotherapy. Most adverse events can be managed. The main toxicities are anemia and gastrointestinal symptoms, such as nausea and vomiting. Anemia can be managed by dose reductions and occasional blood transfusions. The available evidence from across the olaparib clinical development programme supports a conclusion that there is reasonable possibility of a causal relationship between olaparib and the AE of special interest of myelodysplastic syndrome/ acute myeloid leukemia (MDS/AML). Therefore, should anemia become chronic and severe, a rare possibility of these conditions must be ruled out. Gastrointestinal toxicities should be managed by aggressive treatment of nausea with commonly used antiemetics. For information on all identified and potential risks with olaparib refer to the current version of the olaparib IB.

Overall, the studies conducted in olaparib show clinical activity in multiple indications and in populations beyond the germline *BRCA*-mutated population in ovarian cancer. Given the clinical activity and tolerable toxicity profile, olaparib may represent an alternative therapeutic option for some indications that may challenge the standard of care chemotherapy. Olaparib

provides a less toxic alternative treatment option for patients, possibly making the quality of life better for the patients, while maintaining the efficacy.

1.3.2 MEDI4736 benefit/risk

MEDI4736 is joining the increasing number of immune checkpoint inhibitors being studied in the treatment of cancer. It is FDA-approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma and in stage III NSCLC.

MEDI4736 is being studied extensively in multiple indications as a monotherapy and in combination with other immunotherapies, as well as with chemotherapy and targeted agents, such as olaparib. It is hypothesized that the antitumor effects of MEDI4736 are durable and sometimes occur long after the administration of the immunotherapy has already been stopped, making it a desirable partner to combine with agents that have activity upfront.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune-mediated effects can occur in nearly any organ system.

Risks with MEDI4736 include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, Type 1 diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, myasthenia gravis).

For information on all identified and potential risks with MEDI4736, please always refer to the current version of the MEDI4736 IB.

The overall advantage of MEDI4736 treatment is its tolerable toxicity profile compared with that of chemotherapy. While the immune-related adverse events can potentially be severe, they are rare and can be managed with the use of steroids and other immunosuppressants. It is possible that immunotherapies, such as MEDI4736, will become alternative treatment options to chemotherapy in many indications, making the quality of life better for the patients with incurable cancer.

1.3.3 Olaparib and MEDI4736 benefit/risk

Despite the many advances in oncology treatment in recent years, chemotherapy remains the primary systemic therapy for many advanced cancers. The toxicities associated with chemotherapy can be challenging for patients to tolerate and difficult for physicians to manage. The toxicity associated with chemotherapy limits how long patients can be treated and ultimately most patients eventually progress while on these therapies.

PARP inhibitors like olaparib have been shown to be effective for patients with *BRCA* mutation both as maintenance therapy following chemotherapy (Pujade-Lauraine et al 2017) and as a standalone treatment option without chemotherapy (Robson et al 2017). It has been hypothesized that the PARP inhibitor olaparib could be used with immune checkpoint inhibition (MEDI4736) as a new potential combination therapy where the increased DNA damage caused by PARP inhibition may stimulate the immune microenvironment, which could complement and enhance the antitumor activity of an immune checkpoint inhibitor in advanced cancers. If this hypothesis is correct, this combination could bring together the activity of PARP inhibitors with the increased durability of responses associated with immune checkpoint inhibition which could lead to greater benefit for patients compared with current treatment options.

Based on the known toxicity profiles of olaparib and MEDI4736, the combination should be significantly more tolerable than most chemotherapies and preliminary data supports this prediction. In the Phase I part of the MEDI-O trial, the combination has been shown to be tolerable with promising activity in treating women's cancers with no dose-limiting toxicities observed (Lee et al 2017). Preliminary data from the prostate cancer cohort of the MEDI-O study also supports that this combination is well tolerated with encouraging signs of preliminary activity (Karzai et al 2017). These results suggest that the olaparib+MEDI4736 combination is tolerable with significantly less toxicity than what would be expected with conventional chemotherapy.

The combination of olaparib and MEDI4736 is now being studied extensively across several tumor types with almost 250 patients treated in 2 clinical studies (MEDI-O and MEDIOLA). While the efficacy results are still pending, preliminary safety data suggests that the combination is tolerable. Given the potential for the combination in multiple advanced tumors and the predicted tolerability of the combination, participation in this study should present an acceptable benefit:risk consideration for patients with advanced cancers.

1.3.4 Bevacizumab benefit/risk

See Section 1.3 of Module 6 for the benefit/risk of bevacizumab discussed in the context of treatment in combination with olaparib+MEDI4736.

1.3.5 Impact on Benefit/Risk from Study Disruptions due to Coronavirus Disease 2019

The emergence of the coronavirus 2019-nCoV (COVID-19) pandemic presents a potential safety risk for patients and therefore several risk mitigation factors have been implemented in this study (see Section 1.5.1 and Appendix P).

1.4 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 in patients with advanced solid tumors, selected based on a rationale for response to olaparib.

Patients will be PARP-inhibitor and immunotherapy (IMT)-naïve (defined as no prior exposure to PARP inhibitors or IMT, including, but not limited to, other anti-CTLA-4, PD-1, CCI or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

Safety measures for all cohorts of the study include routine safety monitoring on an ongoing basis conducted by AstraZeneca and a formal Review Committee mechanism as described in the cohort-specific appendices.

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 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).

Patients should continue to receive study treatment until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting 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.

Patients who remain on study treatment after the final data cut-off will be monitored according to routine clinical practice as defined by the Investigator (see Section 9.3 for details of safety data collection after the final data cut-off).

1.4.1 Initial Stage Cohorts

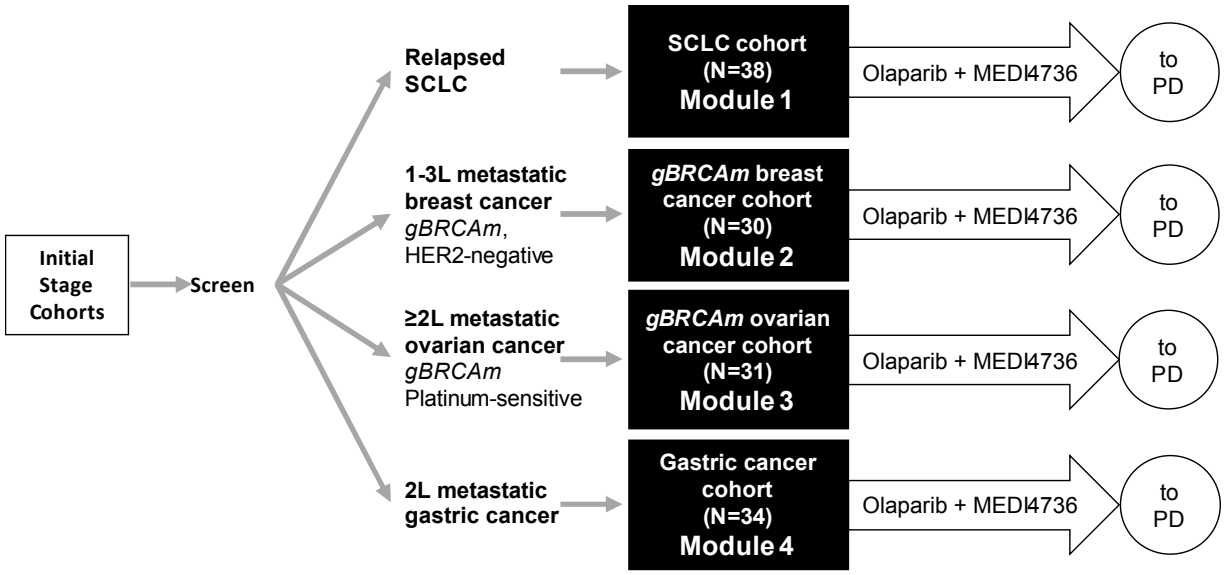
Enrollment in the Initial Stage Cohorts has completed. Data from the Initial Stage Cohorts have been reported in a Clinical Study Report (CSR). In all 4 Initial Stage Cohorts, the olaparib + MEDI4736 combination was well-tolerated, and AEs were consistent with those seen in olaparib and MEDI4736 monotherapy studies (Bang et al 2019, Domchek et al 2020, Drew et al 2018, Krebs et al 2017, Drew et al 2019). In the breast and ovarian cancer cohorts, the combination of olaparib and MEDI4736 showed promising antitumor activity (Domchek et al 2020, Drew et al 2018, Drew et al 2019). In the SCLC and gastric cancer cohorts the 12-week disease control rate was below the pre-specified target, however durable responses were observed in a minority of patients in these cohorts (Bang et al 2019, Krebs et al 2017).

In the initial stage of the study, patients were enrolled concurrently into 4 exploratory Initial Stage Cohorts, which include patients with:

- Relapsed SCLC
- *gBRCAm* metastatic HER2-negative breast cancer
- Relapsed *gBRCAm* platinum-sensitive ovarian cancer
- Relapsed gastric cancer

The Initial Stage Cohorts are illustrated in Figure 1.

Figure 1 Initial Stage Cohorts



1L, 2L, 3L=first, second, third-line; *gBRCAm*=germline *BRCA* mutation; HER2=human epidermal growth factor receptor 2; PD=progressive disease; SCLC=small cell lung cancer.

Based on the results of the NCI study (see Section 1.2.3.1; Lee et al 2017), the current study will start at a dose of olaparib 300 mg bid/MEDI4736 1.5 g Q4W (hereafter referred to as "Full Dose"). Within each cohort, a Review Committee 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. 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 SAEs, AESI, discontinuations, dose reductions and dose interruptions will be reviewed, as well as any lesser-grade 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 in the first 10 patients, and other data from external sources as indicated).

Participants of the Review Committee discussed above will consist of the Principal Investigators (PIs) and/or their delegates, other relevant clinical staff from the sites, a study physician and a clinical scientist. Ad hoc members, such as the Study Pharmacokineticist, Study Statistician, Global Safety Physician (or delegate), Study Delivery Leader, NCI study team members, a IQVIA representative, and others may also be invited as appropriate. Attendance of the Global Safety Physician (or delegate) is required if safety data are discussed. Safety data and pertinent tumor assessment data collected to date (including scans

and other data eg, physical examinations if available) will be considered, as will relevant data from the NCI study (and efficacy data as appropriate).

Further specific operating procedures will be described in a separate document.

Additional safety measures include informal meetings ("Investigator Calls"), which will be held as necessary while patients are on treatment, with the AstraZeneca study team, the PIs (or their delegates), and a representative from IQVIA to provide an ongoing forum in which to exchange and update information and to discuss the progress and data from the study. The meetings will focus on the safety and tolerability data, but will not exclude other topics, such as efficacy and operational issues, as needed.

To ensure uniform decision making, a Bayesian predictive probability design will be consistently employed across the Initial Stage Cohorts (Lee and Liu 2008).

For the Initial Stage Cohorts, after evaluating DCR (defined as: CR+partial response [PR]+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 2 summarizes, in graphical form, the Bayesian predictive probability design for the Initial Stage Cohorts. For full details, please refer to Section 8.2.

Figure 2 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; RECIST=Response Evaluation Criteria in Solid Tumors; SCLC=small cell lung cancer.

[a] Per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting 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 complete response (CR)+partial response (PR)+stable disease (SD), evaluated at 12 weeks.

There will be an initial 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. A proportion of patients (minimum of 5 evaluable pairs per cohort) will undergo pre- and post-olaparib treatment tumor biopsies to evaluate the tumor microenvironment changes and to identify potential biomarkers predictive of activity of the combination.

Details on the analysis of DCR, the closing of the clinical database, and the treatment plan schematic for the Initial Stage Cohorts are provided in Section 1.1 of Module 1, Section 1.1 of Module 2, Section 1.1 of Module 3 and Section 1.1 of Module 4.

1.4.2 Second Stage Cohorts

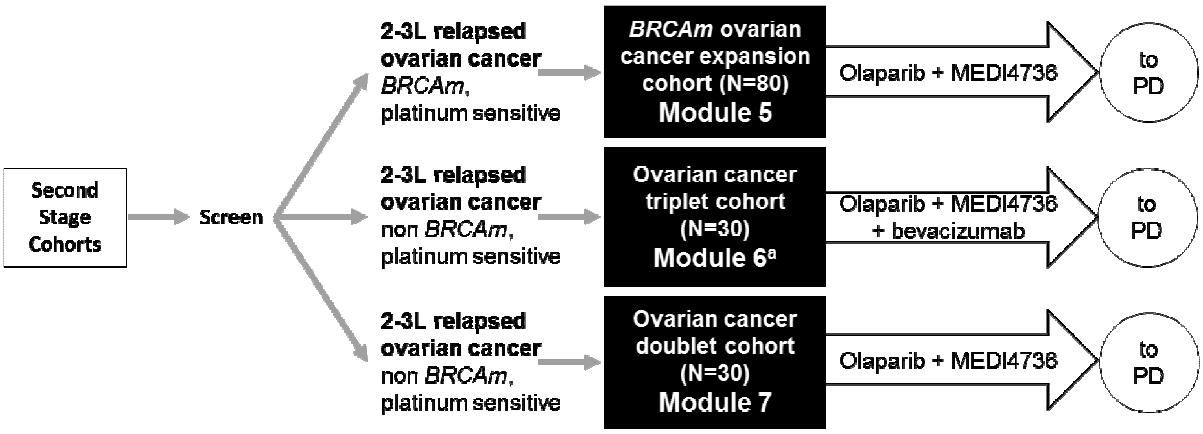
Enrollment for the Second Stage Cohorts has been completed. Enrollment of the *BRCAm* ovarian cancer expansion cohort was terminated when 51 of 80 planned patients had been enrolled. As PARP inhibitors have become standard of care in the first line setting for *gBRCAm* patients, the high unmet clinical need in this patient population has reduced. In addition, as a result of the success of PARP inhibitors in this setting, there are limited numbers of PARP inhibitior-naïve patients eligible for inclusion in the *BRCAm* ovarian cancer expansion cohort. Therefore, despite high response rates in this patient population with olaparib and MEDI4736 combination treatment as shown in the initial stage *gBRCAm* ovarian cancer cohort (Drew et al 2019, Drew et al 2018), recruitment for the *BRCAm* ovarian cancer expansion cohort was closed early.

In the second stage of the study, patients were enrolled into 1 of 3 exploratory Second Stage Cohorts, which include patients with:

- *BRCAm* PSR ovarian cancer ("*BRCAm* ovarian cancer expansion cohort") - Module 5 (Appendix L)
- Non *BRCAm* PSR ovarian cancer ("ovarian cancer triplet cohort") - Module 6 (Appendix M)
- Non *BRCAm* PSR ovarian cancer ("ovarian cancer doublet cohort") - Module 7 (Appendix N)

The Second Stage Cohorts are illustrated in Figure 3.

Figure 3 Second Stage ovarian cancer cohorts



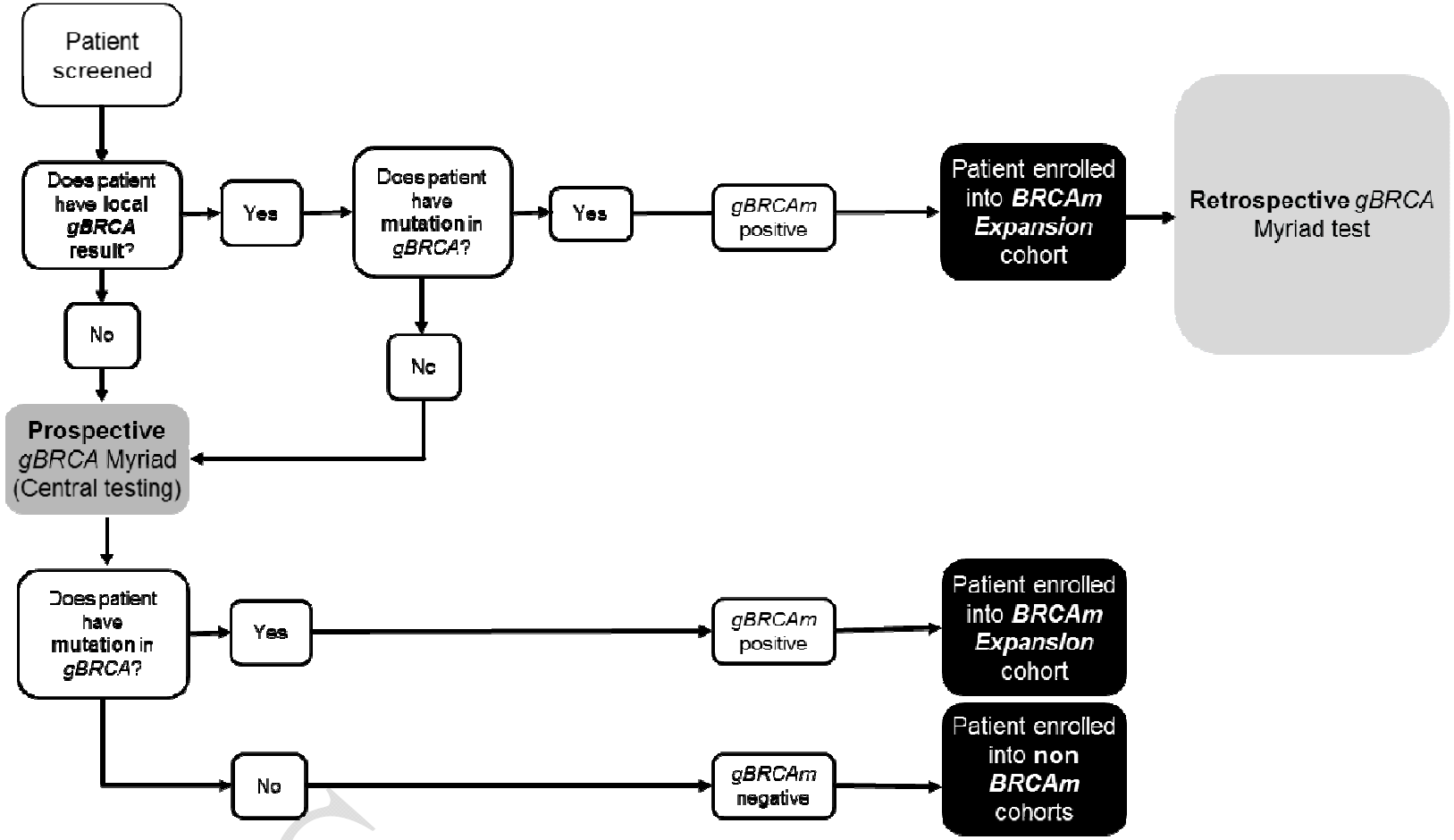
[a] Doublet cohort will be enrolled once triplet cohort enrollment has been completed.
There will be no olaparib run-in treatment period in the Second Stage Cohorts.
2L, 3L=second, third-line; *gBRCAm*=germline *BRCA* mutation; HER2=human epidermal growth factor receptor 2; PD=progressive disease; SCLC=small cell lung cancer.

In addition to other eligibility criteria specified in each Module, assignment to the 3 Second Stage Cohorts will depend on the *BRCA* status of ovarian cancer patients. For inclusion in the *BRCAm* ovarian cancer expansion cohort, patients must have documented evidence 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) from either a prior local test or Myriad central testing. For inclusion in the ovarian cancer triplet or doublet cohorts, patients must have documented evidence from the Myriad central laboratory indicating 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).

Enrollment into the *BRCAm* ovarian cancer expansion and ovarian cancer triplet cohorts will be concurrent, enrollment into the ovarian cancer doublet cohort will only commence once enrollment into the ovarian cancer triplet cohort has been completed. Full details of *BRCA* testing for ovarian cancer patients prior to assignment to 1 of the Second Stage Cohorts are presented in Appendix O.

Figure 4 illustrates the *BRCA* testing steps for the Second Stage Cohorts.

Figure 4 Diagnostic *BRCA* testing for Second Stage ovarian cancer cohorts



Testing is shown in grey boxes. Black boxes indicate how patient is assigned to a cohort as a result of testing/prior knowledge of *BRCA* status.
Non *BRCAm* cohort=ovarian cancer triplet or doublet cohorts. Enrollment to triplet cohort will be completed before enrollment into the doublet cohort commences.

gBRCA=germline *BRCA*; *gBRCAm*=germline *BRCA* mutation; *BRCAm=BRCA* mutation.

Details for the dosing and review of safety data for each of the Second Stage Cohorts are specified in their corresponding Module.

1.4.3 Summary of ovarian cancer cohort characteristics

The ovarian cancer cohorts in this study have a range of defining molecular markers, numbers of previous cycles of treatment, and treatment regimens. For clarity, this information is summarized below in Table 1.

Table 1 Summary of ovarian cancer cohort characteristics

	Initial Stage Cohort	**Second Stage Cohorts**		
	***gBRCAm* ovarian cancer cohort**	***BRCAm* ovarian cancer expansion cohort**	**Ovarian cancer triplet cancer cohort**	**Ovarian cancer doublet cohort**
Module	Module 3 (Appendix J)	Module 5 (Appendix L)	Module 6 (Appendix M)	Module 7 (Appendix N)
Study treatment	Olaparib + MEDI4736 (with 4-week olaparib run-in)	Olaparib + MEDI4736 (no run-in)	Olaparib + MEDI4736 + bevacizumab (no run-in)	Olaparib + MEDI4736 (no run-in)
***BRCA* status**	*gBRCAm*	*gBRCAm*[a]	Non *gBRCAm*	Non *gBRCAm*
Platinum classification	Platinum sensitive[b]	Platinum sensitive[b]	Platinum sensitive[b]	Platinum sensitive[b]
Other eligibility	≥1 prior lines of chemotherapy	1 or 2 prior lines of chemotherapy	1 or 2 prior lines of chemotherapy	1 or 2 prior lines of chemotherapy

[a] A **local test result demonstrating that the patient has *gBRCAm*** will allow only those patients to bypass prospective testing. All other patients must undergo prospective testing. See Appendix O.
[b] Defined as at least 24 weeks from completion of last (most recent) platinum treatment to next relapse.
gBRCAm=germline BRCA mutation.

1.5 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

In this Phase I/II open-label study, a data monitoring committee was not considered necessary.

In the Initial Stage Cohorts:

Within each Initial Stage Cohort, a Review Committee 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, as described in Section 1.4.1.

Informal meetings ("Investigator Calls"), which will be held as necessary and focus on the safety and tolerability data, but will not exclude other topics, such as efficacy and operational issues, as needed (see Section 1.4.1).

In the Second Stage Cohorts:

The cohorts with a Bayesian design (ovarian cancer triplet cohort, ovarian cancer doublet cohort) have the same Review Committee approach to review interim safety and efficacy data described in Section 1.4.1 for the Initial Stage Cohorts.

In addition, a review committee will review the ongoing safety and efficacy data of patients in the *BRCAm* ovarian cancer expansion cohort (Module 5).

1.5.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this Clinical Stusy Protocol (CSP) and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The Investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with GCP, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining reconsent for the mitigation procedures (note, where allowable in the case of verbal reconsent), the Informed Consent Form (ICF) should be signed at the patient's next contact with the study site.

- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home or Remote Location Investigational Product (IP) administration: Performed by a site-qualified HCP, HCP provided by a TPV, or by the patients or the patient caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.
- At-home or Remote Delivery of olaparib.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix P.

2. STUDY OBJECTIVES

2.1 Primary objectives

Primary Objectives	**Outcome Measures**		
	Initial Stage Cohorts	**Second Stage Cohorts**	
		***BRCAm* ovarian cancer expansion cohort**	**Ovarian cancer triplet and doublet cohorts**
To assess the effect of MEDI4736 in combination with olaparib±bevacizumab in patients with selected advanced solid tumors	DCR (CR+PR+SD) based on RECIST 1.1 at 12 weeks	ORR (CR+PR) based on RECIST 1.1 assessed by the Investigator	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	• AEs, vital signs including blood pressure, pulse, ECG and laboratory findings including clinical chemistry and hematology. • 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. • Dose interruptions, dose reductions. • Causes of olaparib and MEDI4736 discontinuation.		
	NA	NA	**Triplet cohort only:** Causes of bevacizumab discontinuation.

AE=adverse event; *BRCAm*=Mutated breast cancer susceptibility gene; CR=complete response; DCR=disease control rate; ECG=electrocardiogram; irAE=immune-related adverse event; NA=not applicable; ORR=objective response rate; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

2.2 Secondary objectives

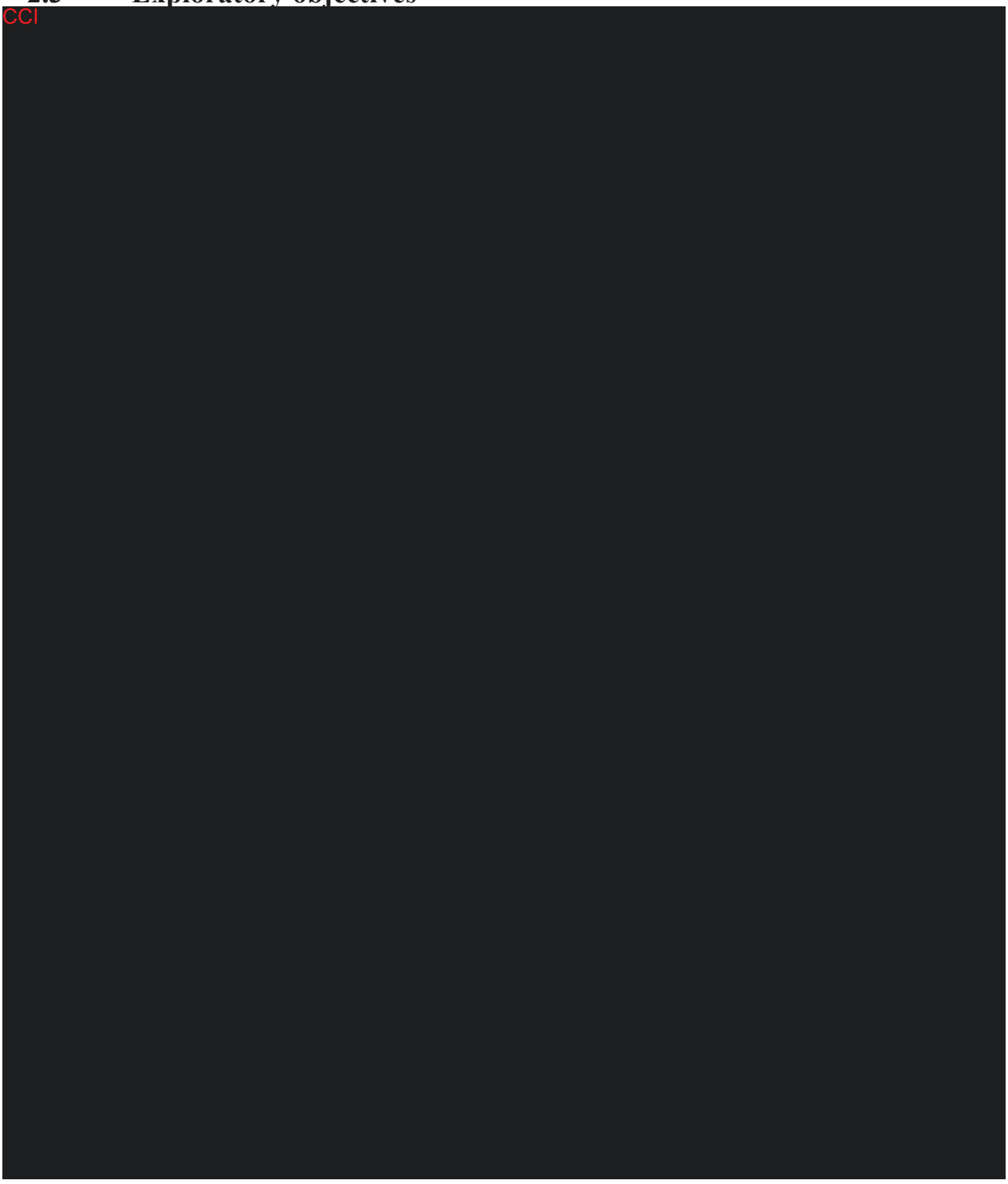
Secondary Objectives	Outcome Measures		
	Initial Stage Cohorts	Second Stage Cohorts	
		***BRCAm* ovarian cancer expansion cohort**	**Ovarian cancer triplet and doublet cohorts**
To investigate the preliminary antitumor activity of MEDI4736 in combination with olaparib±bevacizumab in patients with selected advanced solid tumors	• DCR at 28 weeks • ORR (CR+PR) based on RECIST 1.1 • DoR based on RECIST 1.1 • PFS based on RECIST 1.1 • Percentage change from baseline in tumor size at 12 weeks and 28 weeks • Best percentage change from baseline in tumor size • TDT • Overall survival	• DCR at 24 weeks and 56 weeks • DoR based on RECIST 1.1 • PFS based on RECIST 1.1 • Percentage change from baseline in tumor size at 24 weeks and 56 weeks • Best percentage change from baseline in tumor size • TDT • Overall survival	• DCR at 56 weeks • DoR based on RECIST 1.1 • PFS based on RECIST 1.1 • 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 • TDT • 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	• Serum concentrations of MEDI4736, MEDI4736 anti-drug antibody (ADA). Plasma concentrations of olaparib • Presence of ADAs for MEDI4736 • CCI	• Serum concentrations of MEDI4736, MEDI4736 anti-drug antibody (ADA). Plasma concentrations of olaparib • Presence of ADAs for MEDI4736	• Serum concentrations of MEDI4736, MEDI4736 anti-drug antibody (ADA). Plasma concentrations of olaparib • Presence of ADAs for MEDI4736

Secondary Objectives	Outcome Measures		
	Initial Stage Cohorts	Second Stage Cohorts	
		BRCAm ovarian cancer expansion cohort	Ovarian cancer triplet and doublet cohorts
To characterize the PK and pharmacodynamics of bevacizumab after single dosing and multiple dosing when given intravenously to patients in combination with MEDI4736 and olaparib	NA	NA	**Triplet cohort only:** • Serum concentrations of bevacizumab
CCI [redacted]	[redacted]		

ADA=anti-drug antibody; *BRCAm*=Mutated breast cancer susceptibility gene; CR=complete response; DCR=disease control rate; DoR=duration of response; NA=not applicable; ORR=objective response rate; CCI [redacted] PFS=progression-free survival; PK=pharmacokinetic; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; CCI [redacted]; TDT=time to study treatment discontinuation.

2.3 Exploratory objectives

CCI



CCI

[redacted]

ADA=anti-drug antibody; *BRCAm*=Mutated breast cancer susceptibility gene; HLA-DR=human leukocyte antigen – antigen D related; NA=not applicable; Pd=pharmacodynamic; PD-1=programmed cell death-1; CCI PK=pharmacokinetic; CCI ; VEGF=vascular endothelial growth factor.

3. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient enrolled should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. Patients can be rescreened once as described in Section 3.10.1.

3.1 Inclusion criteria

Inclusion criteria are presented separately for each cohort in:

- **Initial Stage Cohorts** (enrollment is complete): Module 1 (SCLC cohort), Module 2 (*gBRCAm* breast cancer cohort), Module 3 (*gBRCAm* ovarian cancer cohort), and Module 4 (gastric cancer cohort)
- **Second Stage Cohorts**: Module 5 (*BRCAm* ovarian cancer expansion cohort), Module 6 (ovarian cancer triplet cohort), and Module 7 (ovarian cancer doublet cohort)

3.2 Exclusion criteria

Exclusion criteria are presented separately for each cohort in:

- **Initial Stage Cohorts** (enrollment is complete): Module 1 (SCLC cohort), Module 2 (*gBRCAm* breast cancer cohort), Module 3 (*gBRCAm* ovarian cancer cohort), and Module 4 (gastric cancer cohort)
- **Second Stage Cohorts**: Module 5 (*BRCAm* ovarian cancer expansion cohort), Module 6 (ovarian cancer triplet cohort), and Module 7 (ovarian cancer doublet cohort)

For details on the procedures for withdrawal of incorrectly enrolled patients see Section 3.4 of the Core Protocol.

3.3 Patient enrollment

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Obtain a unique 7-digit enrollment code (E-code), through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).
3. Determine patient eligibility. See Sections 3.1 and 3.2 of each Module (Appendix H to Appendix N).
4. Obtain signed informed consent if patient is participating in the genetic research study.

Patient eligibility will be established before treatment. If a patient discontinues participation in the study, then their E-code cannot be reused. Patients re-enrolled after rescreening will be assigned a new E-code (see Section 3.10.1).

3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment and must be withdrawn from the study as screen failures.

Where a patient does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

3.5.1 Initial Stage Cohorts

The 4 exploratory Initial Stage Cohorts will include patients with metastatic or recurrent solid tumors, selected based on a rationale for response to olaparib.

Each cohort (tumor types for each cohort are defined in the cohort-specific Inclusion Criteria in Modules 1 to 4 [Appendix H to Appendix K]) has 10 patients to be enrolled in the initial exploratory phase and a possible maximum size as follows:

- *gBRCAm* ovarian cancer: maximum sample size of 31 patients
- *gBRCAm* metastatic HER2-negative breast cancer: maximum sample size of 30 patients
- Relapsed SCLC: maximum sample size of 38 patients
- Gastric cancer: maximum sample size of 34 patients

These cohorts are also depicted in Figure 2.

3.5.2 Second Stage Cohorts

The 3 Second Stage Cohorts will include patients with metastatic or recurrent solid tumors (tumor types for each cohort are defined in the cohort-specific Inclusion Criteria in Section 3.1 of Module 5 [*BRCAm* ovarian cancer expansion cohort], Section 3.1 of Module 6 [ovarian cancer triplet cohort], and Section 3.1 of Module 7 [ovarian cancer doublet cohort]), selected based on a rationale for response to olaparib in combination with MEDI4736.

Appendix O shows how patients will be assigned to the 3 Second Stage Cohorts based on prior knowledge and on-study testing of their *BRCA* status. Section 4.1 describes the Screening process for the Second Stage Cohorts.

Each cohort will have a target sample size as follows:

- *BRCAm* PSR ovarian cancer (*BRCAm* ovarian cancer expansion cohort): 80 patients
- Non *BRCAm* PSR ovarian cancer (ovarian cancer triplet cohort): 30 patients
- Non *BRCAm* PSR ovarian cancer (ovarian cancer doublet cohort): 30 patients

Enrollment in the doublet cohort did not start until enrollment in the triplet cohort was completed. Enrollment in the Second Stage Cohorts has been completed; enrollment of the *BRCAm* ovarian cancer expansion cohort was terminated when 51 of 80 planned patients had been enrolled as described in Section 1.4.2.

3.6 Methods for ensuring blinding

Not applicable. This is an open-label, unblinded study.

3.7 Methods for unblinding

Not applicable. This is an open-label, unblinded study.

3.8 Restrictions

The following restrictions apply while the patient is receiving study treatment (both combination treatment and during olaparib monotherapy) and for the specified times before and after:

1. Female patients of childbearing potential:

   – Females of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 highly effective form of birth control (see list below) and their partners must use a male condom. ***This should be started from the screening period and continuing throughout the period of taking study treatment***

and for at least 90 days months after last dose of MEDI4736 and/or olaparib (for at least 6 months after last dose of bevacizumab, whichever is longer [Module 6 only]).

- Non-sterilized male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant. Female patients should refrain from breastfeeding throughout this period.

2. Male patients:

- Non-sterilised male participants (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with a female partner of childbearing potential must be using an acceptable method of contraception such as a male condom plus spermicide (or a condom alone in countries where spermicides are not approved) ***from the screening period and continuing throughout the period of taking study treatment and for at least 90 days after last dose of MEDI4736 and/or olaparib*** (for at least 6 months after last dose of bevacizumab, whichever is longer [Module 6 only]) to prevent pregnancy in a partner.

- Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

- Vasectomised (ie, sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

- Male patients must use a condom plus spermicide (where approved) throughout this period when having sexual intercourse with a pregnant woman or with a woman of childbearing potential.

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception (see list below) throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

- Women < 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses > 1 year ago, or had chemotherapy-induced menopause with last menses > 1 year ago.

Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in the list below. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Non-hormonal Highly Effective Methods of Contraception (< 1% failure rate):

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 3 months after last dose of MEDI4736 and/or olaparib (for at least 6 months after last dose of bevacizumab [Module 6 only]).
- Vasectomized sexual partner PLUS male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia).
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded

Hormonal Highly Effective Methods of Contraception (< 1% failure rate):

- Combined pill PLUS male condom: Normal and low dose combined oral pills.
- Mini pill PLUS male condom: Progesterone based oral contraceptive pill using desogestrel: Cerazette (Merck Sharp & Dohme) is currently the only highly efficacious progesterone based pill available.
- Hormonal shot or injection PLUS male condom: Medroxyprogesterone injection (eg, Depo-Provera, Pfizer).

- Implants PLUS male condom: Etonogestrel-releasing implants (eg, Nexplanon, Merck Sharp & Dohme)
- Patch PLUS male condom: Norelgestromin / ethinyl estradiol transdermal system (eg, Xulane)
- Levonorgestrel-releasing Intrauterine system PLUS male condom (eg, Mirena, Bayer])
- Intravaginal devices PLUS male condom: (eg, ethinyl estradiol/etonogestrel-releasing intravaginal devices such as NuvaRing, Merck Sharp & Dohme)

In addition, the following conditions apply from screening through 90 days after receipt of the final dose of IP:

- All patients: Patients should not donate blood while participating in this study and for 90 days following the last dose of study treatment.

Restrictions relating to concomitant medications are described in Section 7.7.

3.8.1 Olaparib and CYP3A4

- Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate Cytochrome P450 (CYP)3A4 enzyme activity (see Section 7.7) from the time they enter the screening period until 30 days after the last dose of study medication.
- It is prohibited to consume grapefruit juice while on olaparib therapy.

3.9 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Withdrawal of consent from further treatment with IP: The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 3.10.2).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in Section 6.
- Pregnancy or the intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from study treatment (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Bone marrow findings consistent with MDS/acute myeloid leukemia (AML)
- Objective radiological disease progression according to RECIST 1.1 (unless in the Investigator's opinion the patient is benefitting from the treatment and does not meet any other discontinuation criteria as outlined in this section).

NOTE (for Initial Stage Cohorts only): 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. These patients should be scanned at 12 weeks (8 weeks after start of combination therapy).

- Patient is determined to have met 1 or more of the exclusion criteria for study participation at study entry and continuing the IP might constitute a safety risk.
- An AE related to IP that is ≥Grade 3, with the exception of toxicities that do not meet criteria for discontinuation, as defined in Section 6.8.
- ≥Grade 3 infusion reaction.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (ie, IP and assessments – see Section 3.10), without prejudice to further treatment. When a patient discontinues treatment for reasons other than disease progression, the AstraZeneca study physician should be informed immediately. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). All AEs will be followed up (see Section 6); all IP should be returned by the patient.

By discontinuing from treatment, the patient is not withdrawing from the study. Patients should be followed for progression (if discontinuation in the absence of progression), OS, and subsequent anticancer treatment following treatment discontinuation as per the protocol schedule. If a patient is withdrawn from study, see Section 3.10.

Any patient discontinuing IP should be seen at 30 days post-discontinuation for the evaluations outlined in the study schedule (see Section 4 of each cohort: SCLC cohort [Module 1], *gBRCAm* breast cancer cohort [Module 2], *gBRCAm* ovarian cancer cohort [Module 3], gastric cancer cohort [Module 4], *BRCAm* ovarian cancer expansion cohort [Module 5], ovarian cancer triplet cohort [Module 6], and ovarian cancer doublet cohort [Module 7]).

The patient's tumor status should be assessed clinically. After discontinuation of IP, the PI/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the eCRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If patients discontinue IP, the AstraZeneca monitor must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all IP.

After discontinuation of the IP at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow-up (see Section 6.3.2). All new AEs and SAEs occurring during the 90 calendar days after the last dose of IP must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.4) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing IP to collect and/or complete AE information. For guidance on reporting AEs after the 90-day follow-up period see Section 6.3.3.

Any patient who has not yet shown objective radiological disease progression at withdrawal from IP should continue to be followed as per RECIST 1.1 as detailed in Section 5.1.2.

Patients who are permanently discontinued from receipt of IP should also be discontinued in IVRS/IWRS.

All patients will be followed for disease progression and survival until the cohort data cut-off, and may be followed for survival, selected safety, investigational product dispensing/accountability, and subsequent anticancer treatment data after the cohort data cut-off (see Section 9.3 for full details).

3.10 Criteria for withdrawal

Reasons for withdrawal of a patient from the study include:

- Voluntary withdrawal by the patient (all patients are free at any time to discontinue their participation in the study, without prejudice to further treatment)
- Incorrectly enrolled patients, ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient is lost to follow-up
- Death

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

- further participation in the study including any further follow-up (eg, survival calls)
- the use of their study-generated data
- withdrawal to the use of any samples (see Section 5.5.7)

3.10.1 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study and therefore must not be assigned to treatment. These patients should have the reason for study withdrawal

recorded as 'Incorrect Enrollment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not enrolled patients).

Patients who were enrolled, screened but not dosed (ie, withdrew from the study prior to dosing) may be re-enrolled and re-screened once if, in the opinion of the Investigator, and with the agreement of the Study Physician, the reason(s) for earlier withdrawal no longer applies. Patients cannot re-enter the study if dosed and subsequently withdrawn from the study. Patients re-enrolled after rescreening will be assigned a new E-code.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn his or her consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

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

If a patient withdraws from participation in the study, then his or her patient identification number cannot be reused. Withdrawn patients will not be replaced.

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

The vital status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final analysis for each cohort should be obtained by the site personnel by checking the patient 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.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening period (and the 4-week run-in treatment period with olaparib [Initial Stage Cohorts only]), the combination therapy treatment period, and after a patient has completed combination therapy or is discontinued early from treatment are presented in Section 4 of each Module (Appendix H to Appendix N).

Links to the schedules of assessments for Screening (with run-in for Initial Stage Cohorts), combination treatment, and after treatment completion/early discontinuation are presented below for each Module to allow easy navigation of the document.

Initial Stage Cohorts (advanced solid tumors)			
SCLC cohort (Module 1)	Screening and run-in: Table 2	Combination therapy treatment period: Table 3	After treatment[a]: Table 4
***gBRCAm* breast cancer cohort (Module 2)**	Screening and run-in: Table 2	Combination therapy treatment period: Table 3	After treatment[a]: Table 4
***gBRCAm* ovarian cancer cohort (Module 3)**	Screening and run-in: Table 2	Combination therapy treatment period: Table 3	After treatment[a]: Table 4
Gastric cancer cohort (Module 4)	Screening and run-in: Table 2	Combination therapy treatment period: Table 3	After treatment[a]: Table 4

Second Stage Cohorts (ovarian cancer)			
***BRCAm* ovarian cancer expansion cohort (Module 5)**	Screening: Table 2	Combination therapy treatment period: Table 3	After treatment[a]: Table 4
Ovarian cancer triplet cohort (Module 6)	Screening: Table 2	Combination therapy treatment period: Table 3	After treatment[a]: Table 4
Ovarian cancer doublet cohort (Module 7)	Screening: Table 2	Combination therapy treatment period: Table 3	After treatment[a]: Table 4

[a] Completed combination therapy or is discontinued early from treatment.

Patients can continue to receive study treatment beyond the period specified in each Module, as described in Section 4.2.4.

4.1 Enrollment/screening period

The screening period will be up to 28 days for the Initial and Second Stage cohorts. For all cohorts, if all screening procedures are completed and eligibility confirmed earlier than this, the screening period can be concluded early as appropriate. Note that in **all cohorts** the baseline tumor assessment scan should **always** be within 28 days prior to Cycle 1 Day 1, independent of the duration of screening. Similarly, for female patients of childbearing potential, a pregnancy test should be taken within 28 days prior to Cycle 1 Day in **all cohorts**.

All screening and enrollment procedures will be performed according to the assessment schedule presented in Section 4 of each of the Modules (SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort). Demographic data and other characteristics will be recorded including date of birth or age, gender, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained. For gastric cancer patients, the history must include whether they have had partial or full gastrectomy.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be required to provide consent to supply an archival tumor sample (not more than 3 years old) for entry into this study. This consent is included in the main patient ICF. Ovarian cancer patients in the Second Stage Cohorts are exempt from provision of a new biopsy sample even when/even if the archival tumor sample is more than 3 years old.

All patients should be consented to the study within 28 days prior to Day 1 of the first dose of study drug therapy.

Screening/baseline evaluations may be performed over more than 1 visit.

For Second Stage Cohorts, the process by which *BRCA* testing should be performed to allocate patients to the correct cohort according to their *BRCA* status is described in Appendix O. Note that enrollment for the ovarian cancer doublet cohort will commence after enrollment is filled for the ovarian cancer triplet cohort. Enrollment for the *BRCAm* ovarian cancer expansion and ovarian cancer triplet cohorts will be concurrent.

The timing of vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Section 5.3 of each of the Modules (Appendix H to Appendix N).

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

4.2 Treatment period

All procedures to be conducted during the treatment period will be performed according to the assessment schedule presented in Section 4 of each of the Modules (SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort).

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in in Section 5.3 of each of the Modules (SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort).

4.2.1 Dosing regimen

In the Initial Stage Cohorts, there will be an initial 4-week period of monotherapy treatment with olaparib beginning on Week 1, Day 1 (monotherapy) before starting MEDI4736 on Cycle 1 Day 1 (combination therapy), 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. This 4-week period (28 days) represents a set period and the planned visit schedule must not be adjusted regardless of the number of missed olaparib doses.

In the Second Stage Cohorts, the study drugs (MEDI4736+olaparib, or MEDI4736+olaparib+bevacizumab) will initiate concurrently on Cycle 1, Day 1 without the 4-week period of olaparib monotherapy.

Patients will be administered study olaparib treatment orally at a dose of 300 mg bid. The initial dose of 300 mg bid will be made up of 2×150 mg tablets bid. The 100 mg and 150 mg tablets will be used to manage dose reductions.

MEDI4736 dose selection is discussed in Section 1.2.3.2. Patients will receive MEDI4736 1.5 g via IV infusion Q4W ±3 days. Treatment with MEDI4736 will commence on Cycle 1 Day 1 concurrently with olaparib and will continue on a Q4W schedule until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria.

In the ovarian cancer triplet cohort (Module 6; Appendix M), patients will be administered bevacizumab in line with normal clinical practice, with a dose and schedule of 10 mg/kg of body weight Q2W ±3 days. Treatment with bevacizumab will commence on Cycle 1, Day 1 following administration of olaparib and MEDI4736 therapy. Bevacizumab will continue on a Q2W schedule until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria.

Refer to Section 7.2 of the Core Protocol for additional details on IP administration.

4.2.2 Definition of evaluable patient

An evaluable patient is defined as a patient who has received at least 1 dose of study treatment and has not been excluded from the study for administrative reasons, eg, failing important inclusion criteria (a full list will be predefined in the Statistical Analysis Plan).

4.2.3 Dose modifications

Please refer to Section 6.8 for details on dose modifications during the treatment period in the event of IP-related toxicities.

4.2.4 Duration of therapy

There is no maximum duration for taking study treatment with olaparib. Patients should continue to receive combination treatment until objective radiological disease progression per

RECIST 1.1, as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria.

In the Initial Stage Cohorts, 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.

After discontinuation of study treatment, the Investigator will be at liberty to define further most appropriate anticancer treatment. All patients will be followed for disease progression and survival until the cohort data cut-off, and may be followed for survival, selected safety, investigational product dispensing/accountability, and subsequent anticancer treatment data after the cohort data cut-off (see Section 9.3 for full details).

4.3 Follow-up period

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule presented in Section 4 of each of the Modules (Appendix H to Appendix N).

Whenever vital signs, electrocardiograms (ECGs), and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Section 5.3 of each of the Modules (SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort).

5. STUDY ASSESSMENTS

The Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Tumor assessments by CT or MRI scans

At baseline, the imaging modalities used for assessment should be contrast enhanced computed tomography (CT) (magnetic resonance imaging [MRI] where CT is contraindicated) scans of the chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease. Follow-up CT or MRI assessments will cover chest (in those patients with disease in the chest or upper abdomen lymphadenopathy at baseline), abdomen and pelvis with any other regions imaged at baseline where disease was present. Any other sites at which new disease is suspected should also be appropriately imaged.

Radiological examinations performed in the conduct of this study should be retained at site as source data.

All treatment decisions will be based on site assessment of scans.

In the Initial Stage Cohorts, the baseline scan must be performed at screening unless obtained within 28 days prior to first dose of olaparib. Following the baseline tumor assessment, the next tumor assessment will be 4 weeks after the first olaparib monotherapy dose and prior to the start if the combination therapy and then all subsequent tumor assessments should be performed every 8 weeks (±1 week) relative to the date of start of combination therapy, up to objective radiological disease progression as defined by RECIST 1.1, and as determined by the Investigator. Patients with objective radiological disease progression identified after olaparib monotherapy has started but before receiving combination therapy, who start combination therapy (see Section 3.9) should be scanned at 12 weeks (8 weeks after start of combination therapy).

In the Second Stage Cohorts, the baseline scan must be performed at screening unless obtained within 28 days prior to first dose of study treatment. Following the baseline tumor assessment, the next tumor assessment will be 8 weeks after the first study treatment dose and then all subsequent tumor assessments should be performed every 8 weeks (±1 week) relative to the date of start of study treatment, up to objective radiological disease progression as defined by RECIST 1.1, and as determined by the Investigator.

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. Imaging assessments are required for patients who continue receiving the study drug combination beyond disease progression.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of scheduled visit ±1-week window interval and the patient has not experienced disease progression, every attempt should be made to perform the subsequent scans at their scheduled timepoints.

5.1.2 Tumor evaluation

RECIST 1.1 will be used to assess patient response to treatment, as assessed by the Investigator. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions (TL and NTL) and the objective tumor response criteria (CR, PR, SD or PD) are presented in Appendix E (Eisenhauer et al 2009).

Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTL or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

5.2 Safety assessments

The total volume of blood that will be drawn from each patient is summarized in Section 5.2 of Modules 1 to 7 (Appendix H to Appendix N).

5.2.1 Laboratory safety assessments

Blood samples for determination of clinical chemistry and hematology will be taken at the times indicated in the assessment schedules and as clinically indicated (see Section 4 of each cohort: SCLC cohort [Module 1], *gBRCAm* breast cancer cohort [Module 2], *gBRCAm*

ovarian cancer cohort [Module 3], gastric cancer cohort [Module 4], *BRCAm* ovarian cancer expansion cohort [Module 5], ovarian cancer triplet cohort [Module 6], and ovarian cancer doublet cohort [Module 7]). Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units, levels, and reference ranges) will be recorded on the appropriate eCRF.

All clinical laboratory safety tests, including serum pregnancy tests, will be performed at a local laboratory at or near the investigational site. Local laboratory results can be used for clinical decision making. Should these results be contradicted by central laboratory results (when obtained), relevant sampling and tests should be repeated. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix D for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 6.3.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum β-hCG) samples will be performed for pre-menopausal women of childbearing potential as specified in the assessment schedule (see Section 4 of each cohort: SCLC cohort [Module 1], *gBRCAm* breast cancer cohort [Module 2], *gBRCAm* ovarian cancer cohort [Module 3], gastric cancer cohort [Module 4], *BRCAm* ovarian cancer expansion cohort [Module 5], ovarian cancer triplet cohort [Module 6], and ovarian cancer doublet cohort [Module 7]). Tests will be performed by the hospital's local laboratory. If results are positive, the patient must not start

or continue treatment. In the event of a suspected pregnancy during the study, the test should be repeated. Details of the pregnancy tests must be recorded in the patient's medical records.

Other safety tests to be performed include assessment for hepatitis B surface antigen, hepatitis C antibodies, hepatitis C viral load (for patients with history of hepatitis C only), HIV antibodies, thyroid-stimulating hormone (TSH), free tri-iodothyronine (T_3), and free thyroxine (T_4). Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

The laboratory variables to be measured are presented in Sections 5.2.1.1 (hematology), 5.2.1.2 (coagulation), and 5.2.1.3 (clinical chemistry).

5.2.1.1 Hematology

The following hematology variables will be measured:

Hb	Mean cell hemoglobin
Hematocrit	White blood cell count
Platelets	Absolute differential white cell count
Mean cell volume	Neutrophils, lymphocytes, monocytes, eosinophils and basophils and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials are not available % differentials should be provided.

5.2.1.2 Coagulation

The following coagulation variables will be measured:

- Activated partial thromboplastin time (APTT) will be performed at screening and if clinically indicated
- International normalized ratio (INR) will be performed at screening and if clinically indicated, unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

All coagulation test results will be recorded in the eCRF.

5.2.1.3 Clinical chemistry

The following clinical chemistry parameters will be measured:

Sodium	Lipase
Potassium	Alkaline phosphatase
Calcium	Bicarbonate
Chloride	AST
Magnesium	ALT
Creatinine	Amylase
Total bilirubin [a]	Urea or blood urea nitrogen
Gamma glutamyltransferase [b]	Uric acid
Glucose	Total protein
Lactate dehydrogenase	Albumin

[a] If total bilirubin is ≥2×ULN (and evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

[b] At baseline and as clinically indicated

5.2.1.4 Disease specific tumor marker samples (CA-125)

As part of the routine safety blood samples, cancer antigen-125 (CA-125) will be measured in the ovarian cancer cohorts only (see Module 3 [Appendix J], Module 5 [Appendix L], Module 6 [Appendix M], and Module 7 [Appendix N]). Patients in this cohort will supply a 2-mL blood sample for the assessment of CA-125 status at the beginning of each 28-day period prior to the patient receiving study treatment (see Section 4 of each of the cohorts specific Modules [*gBRCAm* ovarian cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort]).

It is important to follow the assessment schedule as closely as possible. If CA-125 assessment is performed outside of scheduled visit ±1-week window interval, every attempt should be made to assess the CA-125 at the scheduled timepoints. Patients will be evaluated until objective disease progression, based on progressive serial elevation of serum CA-125 according to the modified Gynecologic Cancer InterGroup (GCIG) criteria. (NOTE: GCIG criteria is not validated for this study population).

Further assessment of CA-125 post-serological progression will be at the discretion of the Investigator according to local clinical practice.

5.2.1.5 Urinalysis

Urinalysis will be performed in the ovarian cancer triplet cohort as described in Module 6.

5.2.1.6 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in Section 6.8.2.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the Investigator for documentation on the Patient Safety database. These data are not required to be entered into eCRF.

5.2.2 Physical examination

Physical examinations will be performed according to the assessment schedules (see Section 4 in each cohort-specific Module [SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, gastrointestinal (GI), breast, urogenital (**not** required for breast, gastric and small cell lung cancer cohort patients), musculoskeletal (including spine and extremities), neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 6.3.7.

5.2.3 ECG

Resting 12-lead ECGs will be recorded at screening and on Day 1, and as clinically indicated throughout the study (see Section 4 in each cohort-specific Module [SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort). All ECGs should be performed once the patient has rested in the supine position for at least 5 minutes in each case. ECGs will be recorded at 25 mm/sec.

At screening, ECGs will be obtained in triplicate (all 3 within a 5-minute time period, at least 1 minute apart) on which the Fridericia's-corrected QT interval (QTcF) must be <500 msec.

On Study Day 1, and at other timepoints as clinically indicated, a single ECG will be performed.

Heart rate, P and QRS durations, PR, QT and QTc intervals will be recorded from standard lead of the computerized quantitative 12-lead ECG.

In case of clinically significant ECG abnormalities, including a QTcF value >500 msec, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

All ECGs should 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 eCRF. The original ECG traces must be stored in the patient medical record as source data.

Situations in which ECG results should be reported as AEs are described in Section 6.3.7.

5.2.4 Vital signs

Height will be assessed at screening only.

Weight will be assessed according to the Study Schedule (see Section 4 in each cohort-specific Module [SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort) and as clinically indicated at any other time.

Any changes in vital signs should be recorded as an AE, if applicable. For information on how AEs based on changes in vital signs should be recorded and reported, see Section 6.3.7.

5.2.4.1 Pulse and blood pressure

Vital signs (blood pressure [BP], pulse, temperature, and respiratory rate) will be evaluated according to the assessment schedules (see Section 4 in each cohort-specific Module [SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort]).

On infusion days, patients will be monitored during and after infusion of IP as presented in the bulleted list below.

Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 to 10 minutes. BP and pulse will be collected from patients before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)
- A 1-hour observation period is recommended after the first infusion of MEDI4736. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each MEDI4736 infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF page.

5.2.4.2 Body temperature

Body temperature will be measured in degrees Celsius according to local practice at the times indicated in the Study Schedule (see Section 4 in each cohort-specific Module [SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort).

The date of collection and measurement will be recorded on the appropriate eCRF.

5.2.5 Other safety assessments

5.2.5.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment and on Day 1 of the study prior to commencing treatment, at the time points shown in the assessment tables during study treatment and at the 30-day follow-up visit. Tests will be performed by the hospital's local

laboratory. Urine pregnancy tests will be performed at schedule visits as presented in Section 4 of each cohort-specific Module (SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort) during treatment and the 90-day follow-up period. If results are positive the patient is ineligible/must be discontinued from study treatment immediately.

5.2.5.2 Performance status

The patient's performance status will be assessed at screening using the upper limit of normal (ECOG) performance status scale (see Section 4 in each cohort-specific Module [SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort); patients must have an ECOG performance status 0-1 to be eligible for enrollment.

During the study, the performance status will be assessed at the timepoints in Section 4 of each cohort-specific Module, using the ECOG performance status scales.

5.2.5.3 Pneumonitis/interstitial lung disease

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 6.8.2.2 and Section 6.8.4) will be applied. If pneumonitis/ILD is suspected, olaparib treatment should be interrupted and prompt investigation initiated. If pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately, and for MEDI4736 the guidance in the toxicity management guidelines (TMGs) should be followed. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    - (ii) Tumor markers: Particular tumor markers which are related to disease progression.
    - (iii) Additional Clinical chemistry: CRP, LDH

5.3 Pharmacokinetics

5.3.1 Collection of samples and the determination of olaparib concentrations

Blood samples (2.0 mL) will be taken for the determination of olaparib in plasma. The study plans in Section 4 of Modules 1 to 7 (SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort) present the days on which olaparib PK samples will be taken for each cohort. The details of the sampling times are presented in Section 5.3.1 of each Module. The total volume of blood taken during the study for olaparib concentration measures is presented in Section 5.2 of each cohort-specific Module (Appendix H to Appendix N).

Samples for determination of olaparib in plasma will be analyzed by Covance on behalf of the Clinical Bioanalysis Alliance, AstraZeneca, using an appropriate bioanalytical method.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

5.3.2 Collection of samples and the determination of MEDI4736 concentrations

Blood samples (3.5 mL) will be taken for the determination of MEDI4736 in serum. The study plans in Section 4 of Modules 1 to 7 (SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort) present the days on which samples will be taken for each cohort. The details of the sampling times are presented in Section 5.3.1 of each Module. The total volume of blood taken during the study for MEDI4736 concentration measures is presented in Section 5.2 of each cohort-specific Module (Appendix H to Appendix N).

Samples for determination of MEDI4736 concentrations in serum will be analyzed by a designated third party on behalf AstraZeneca/MedImmune, using a validated immunoassay using a Meso Scale Discovery platform.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

5.3.3 Collection of samples and the determination of bevacizumab concentrations

Assessment of bevacizumab PK will only be performed in the ovarian cancer triplet cohort (Module 6; Appendix M).

Blood samples (3.5 mL) will be taken for the determination of bevacizumab in serum. The study plans in Section 4 of Module 6 (Appendix M) present the days on which samples will be taken in the ovarian cancer triplet cohort. The details of the sampling times are presented in Section 5.3.1 of Module 6 (Appendix M). The total volume of blood taken during the study for bevacizumab concentration measures is presented in Section 5.2 of Module 6 (Appendix M).

Samples for determination of bevacizumab concentrations in serum will be analyzed by a designated third party on behalf AstraZeneca/MedImmune, using a validated immunoassay.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

5.3.4 Collection of samples to measure the presence of ADAs CCI

The study plans in Section 4 of Modules 1 to 7 (SCLC cohort, *gBRCAm* breast cancer cohort, *gBRCAm* ovarian cancer cohort, gastric cancer cohort, *BRCAm* ovarian cancer expansion cohort, ovarian cancer triplet cohort, and ovarian cancer doublet cohort) present the days on which samples will be taken for each of the Initial Stage Cohorts. The details of the sampling times are presented in Section 5.3.2 of each Module. At each timepoint, approximately 3.5 mL blood will be drawn for detection of MEDI4736 ADAs CCI

Samples will be measured for the presence of MEDI4736 ADAs using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive negative cut points previously statistically determined from drug-naïve validation samples will be employed.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

5.3.5 Storage and destruction of pharmacokinetic, ADA and CCI

5.3.5.1 Olaparib samples

Olaparib PK samples will be disposed of or destroyed and anonymized by pooling after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in an Assay Validation Report as an Addendum.

CCI [redacted]

5.3.5.2 MEDI4736 samples

Samples will be archived and then disposed of after a minimum of 5 years from the Biologic License Application filing.

For sample processing, handling and shipment refer to the Investigators Laboratory Manual.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in an Assay Validation Report as an Addendum.

CCI [redacted]

5.3.5.3 Bevacizumab samples

Bevacizumab PK samples will be disposed of or destroyed and anonymized by pooling after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in an Assay Validation Report as an Addendum.

CCI [redacted]

5.4 Genetics

5.4.1 Collection of genetic samples

The decision by the patient to participate in the genetic research components of the study is entirely optional.

NOTE: This section refers to the *optional* genetic blood sample. The *mandatory* *BRCA* gene testing on blood samples required for determining eligibility is discussed in Section 5.6.

See Appendix C.

5.4.2 Storage, re-use and destruction of genetic samples

See Appendix C.

5.5 Biomarker analysis

CCI [redacted]

[redacted]

[redacted]

5.5.1 Data and samples for patient selection and eligibility

The molecular testing data from an appropriately accredited laboratory that must be documented prior to a patient commencing treatment in the study is defined for each cohort in Section 5.5.1 of each cohort-specific Module (Appendix H to Appendix N).

5.5.2 Mandatory tumor sample

5.5.2.1 Initial Stage Cohorts

All patients must provide an archival tumor sample (formalin-fixed paraffin-embedded; [FFPE]); a tumor tissue block is preferred. If a tissue block is unavailable, unstained freshly cut sections from the tissue block may be submitted. Specific instructions and guidelines regarding sections are provided in the laboratory manual. Tissue blocks may be repatriated on request.

Where taken expressly for the study, tumor samples should be collected via an image-guided core needle (18 gauge or larger) or be collected as an excisional or incisional tumor biopsy sample.

Tumor lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy. If a RECIST 1.1 target lesion is used for biopsy, the lesion must be ≥ 2 cm in the longest diameter and must be biopsied outside of the screening period.

When fresh tissue is obtained, effort should be made to maximize material for downstream analyses. CCI [redacted] These should be placed in formalin and processed to a single paraffin embedded block. That written, and as a guidance, it is anticipated that 4 passes of a core needle will provide sufficient tissue for establishing eligibility and for delivering protocol defined exploratory objectives. Whenever feasible, additional cores CCI [redacted] should be obtained and immediately frozen as described in the Laboratory Manual. Please consult the Laboratory Manual for additional information and guidance regarding how to split excisional biopsies for downstream purposes.

CCI [redacted]

5.5.2.2 Second Stage Cohorts

Ovarian cancer patients in the Second Stage Cohorts are exempt from provision of a new biopsy sample even when/even if the archival tumor sample is more than 3 years old.

All patients must provide a FFPE archival tumor sample at the screening visit, after other eligibility criteria are confirmed (see Sections 3.1 and 3.2). Formalin fixed and embedded in paraffin tumor tissue blocks are required, but if not available, tissue sections are accepted. At least forty (40) unstained sections without cover slips must be submitted to ensure sufficient material. Samples must meet the minimum tumor content and tissue volume as specified in the laboratory manual.

If an archival sample is not available a new biopsy may be provided. Consideration should be given to the potential benefit to the patient (should they be eligible for the study) in the context of the risk posed by the biopsy procedure. Tissue biopsy sampling should be conducted in accordance with expert guidelines, only by Investigators experiences in performing these sampling methods in appropriate clinical settings. Four cores (2 for processing as FFPE blocks and 2 for immediate freezing) should be taken where possible.

Further details can be found in Section 5.5.2.1 of the Core Protocol and the Laboratory Manual.

Residual tumor and blood (or its derivatives) may be used to evaluate future BRCA/HRR gene companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease recurrence (including gene mutation status and its role in response).

5.5.3 Candidate predictive biomarker analyses on mandatory tumor tissue

CCI [redacted]

5.5.4 Investigational, immunomodulatory biomarker analyses

CCI [redacted]

CCI [redacted]

Additional sample collections and analyses may be completed at select study sites by site-specific amendment. All samples collected for such exploratory analyses will be stored at site, a reference laboratory, or at AstraZeneca's facilities and may be used for subsequent research relevant to evaluating response to IMT.

5.5.4.1 Pharmacodynamics: paired tumor biopsies

CCI [redacted]

5.5.4.2 Pharmacodynamics: sPD-L1 analyses

Please refer to Section 5.3.4.

5.5.4.3 Pharmacodynamics: whole blood for gene expression (PAXgene-RNA)

CCI [redacted]

CCI [redacted]

5.5.4.4 Pharmacodynamics: ctDNA in the plasma (Second Stage Cohorts only)

CCI [redacted]

5.5.4.5 Pharmacodynamics: circulating soluble factors in the plasma

CCI [redacted]

CCI [redacted]

5.5.4.6 Pharmacodynamics: anti-drug antibodies

Please refer to Section 5.3.4.

5.5.4.7 Pharmacodynamics: whole blood for immunophenotyping

CCI [redacted]

5.5.4.8 Pharmacodynamics: peripheral blood mononuclear cells

CCI [redacted]

5.5.4.9 Pharmacodynamics: Plasma for free vascular endothelial growth factor (ovarian cancer triplet and ovarian cancer doublet cohorts only)

CCI [redacted]

5.5.4.10 Pharmacodynamics: Serum for eg angiogenic evaluation (ovarian cancer triplet and ovarian cancer doublet cohorts only)

CCI [redacted]

5.5.4.11 Pharmacodynamics: tumor biopsy at disease progression

CCI

[redacted]

[redacted]

5.5.5 Biomarker sample and data management

CCI

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

5.5.6 Labeling and shipment of biological samples

The PI will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix B "IATA 6.2 Guidance Document."

Any samples identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

5.5.6.1 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The PI at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate).

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use will be registered by the AstraZeneca Biobank team during the entire life cycle.

5.5.7 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

The PI will ensure that

- AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples
- Biological samples from that patient, if stored at the study site, are immediately identified, disposed of or destroyed and the action documented
- The laboratory(ies) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the signed document is returned to the study site
- The patient and AstraZeneca are informed about the sample disposal

5.6 *BRCA* status

Mandatory blood samples are collected to determine *BRCA* gene mutation status (ovarian cancer patients).

5.6.1 Initial Stage Cohorts: *gBRCAm* breast cancer cohort and *gBRCAm* ovarian cancer cohort

BRCA gene testing for study inclusion purposes in the *gBRCAm* breast cancer and *gBRCAm* ovarian cancer cohorts will be performed on a blood sample taken specifically for that purpose and all local guidelines for such genetic testing must be followed. Patients must have a known deleterious or suspected deleterious *BRCA* mutation to be enrolled into the study; this can be either a local laboratory result or a Sponsor-designated central laboratory (such as Myriad) test result. Patients with a suspected (ie, unconfirmed *BRCA* mutation) will have the blood sample taken at the screening visit, after other eligibility criteria are confirmed. Patients for whom *BRCA* status is already known, should be consented to the study within 28 days prior to Day 1 of the first dose of olaparib monotherapy and have a blood sample taken for confirmation of *BRCA* status at the Week 1/Day 1 visit. All patients must provide samples and consent to study-related Sponsor-designated central laboratory (such as Myriad) *gBRCA* status testing, and must also have a blood sample taken at the same time for the purpose of developing and validating a diagnostic test for *BRCA* mutations.

5.6.2 Second Stage Cohorts

Patients in the 3 ovarian cancer Second Stage Cohorts will either have *BRCAm* ovarian cancer (*BRCAm* ovarian cancer expansion cohort; Appendix L), or non *BRCAm* ovarian cancer (ovarian cancer triplet and doublet cohorts; Appendix M and Appendix N, respectively). Information on *BRCA* testing for the Second Stage Cohorts is provided in Appendix O.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent 1 of the outcomes listed above.

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events, including SAEs, will be collected from the time of signature of first informed consent throughout the treatment period up to and including the 90-day follow-up period. All ongoing and any new AEs/SAEs identified during the 90 calendar days' follow-up period, after the last dose of study medication must be followed to resolution. After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

6.3.2 Follow-up of unresolved adverse events

Any SAEs or non-serious AEs that are unresolved at the time of the 90-day follow-up period must be followed up to resolution unless the event is considered by the Investigators as unlikely to resolve or the patient is lost to follow-up. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Adverse events after the 90-day follow-up period

For Pharmacovigilance purposes and characterization of SAE, any case of MDS/AML or new primary malignancy occurring after the 90-day follow-up period should be reported to AstraZeneca, Patient Safety, **regardless of Investigator's assessment of causality**. Investigators will be asked during the regular follow-up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases.

At any time after a patient has completed the study, if an Investigator learns of any SAE including death, and he/she considers there is a reasonable possibility that the event is causally related to the IP, the Investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post-data cut-off and/or post-study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

Otherwise, after study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow-up period (90 days).

All ongoing AEs/SAEs and any new AEs/SAEs identified during the 90 calendar days follow-up period after last dose of study medication must be followed to resolution unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow-up. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.4 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no) / combination drug (Yes/No)
- Action taken with regard to IP/combination drug
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge from hospital
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medications
- Description of AE

Severity of the adverse event

For each episode of an AE, all changes to the CTCAE grade attained, as well as the highest CTC grade, are to be reported.

It is important to distinguish between seriousness and severity. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.2.

The grading scales found in the NCI CTCAE v 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is that the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation program website (http://ctep.cancer.gov).

6.3.5 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP/comparator/combination drug?'

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

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

6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECGs should therefore only be reported as AEs if 1 of the following is met:

- Any criterion for an SAE is fulfilled
- Causes discontinuation of study treatment
- Causes interruption of study treatment
- Causes a dose reduction of study treatment
- The Investigator believes that the abnormality should be reported as an AE.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low Hb value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.8 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.3.10 New cancers

The development of a new primary cancer should be reported as an AE (see Section 6.8.3) and would in most cases meet seriousness criteria (with the exception of some non-melanoma skin cancers). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

6.3.11 Lack of efficacy

In this study, lack of efficacy (ie, deterioration in the cancer, for which the study treatment(s) is being used) is not to be reported as an AE.

6.3.12 Deaths

All deaths that occur during the study, or within the protocol defined 90-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death that is clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the DEATH eCRF, but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the cause of death must be reported as an SAE with a fatal outcome within 24 hours (see Section 6.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information must be captured in the 'death eCRF'.

If the death occurred as a result of an event that started post the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug then it should also be reported as an SAE.

Deaths with an unknown cause should always be reported as a SAE. If performed, a copy of the post mortem results should be forwarded to AstraZeneca within 24 hours.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca, Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs, **and within 5 calendar days** for follow-up information.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the IB for MEDI4736 and olaparib, the EU Summary of Product Characteristics for olaparib, and the FDA bevacizumab label.

6.5 Overdose

6.5.1 Overdose of olaparib and/or MEDI4736

Use of IP in doses in excess of that specified in the protocol is considered to be an overdose. Olaparib compliance will be assessed by tablet count (see Section 7.5). An overdose should be reported if 1 or more doses are found to be missing during the tablet count.

There is currently no specific treatment in the event of overdose with olaparib or/and MEDI4736 and possible symptoms of overdose are not established.

Olaparib/ MEDI4736 must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.5.2 Overdose of bevacizumab

See Appendix M for the overdose instruction for bevacizumab.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca, except for:

- If the pregnancy is discovered before the study patient has received any study drug

Should pregnancy occur, the physician should discuss with the patient the potential hazard to the fetus or potential risk of loss of the pregnancy.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately.

The outcomes of any conception occurring from the date of the first dose of study medication until 90 days after the last dose of study medication must be followed up and documented.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca, Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days following the last dose of IP (refer to Section 3.8).

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

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

6.7 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to 1 of the above listed events that would otherwise have been a medication error

- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Management of IP-related toxicities

In general, the toxicity profiles of MEDI4736 and of olaparib are nonoverlapping, therefore, management of toxicities will be per the individual guidelines of the respective agents. Pneumonitis is considered to be the most important potential exception. The management guidelines for pneumonitis (see Section 5.2.5.3, Section 6.8.2.2, and Section 6.8.4) integrate the guidance provided for these 2 agents.

6.8.1 General comments

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE, Version 4.03.

6.8.2 Olaparib

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed, as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step (Table 2). If the reduced dose of 200 mg bid is not tolerable, no further dose reduction is allowed and study treatment should be discontinued.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 7.7).

Table 2 Dose reductions for study treatment

Initial dose	Following re-challenge post-interruption: dose reduction 1	Dose reduction 2
300 mg twice daily	250 mg twice daily	200 mg twice daily

6.8.2.1 Management of hematological toxicity

Management of anemia

The management of anemia is presented in Table 3.

Table 3 Management of anemia

Hemoglobin	Action to be taken
Hb <10 *but* ≥8 g/dL (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgment to continue olaparib with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to >9 g/dL. **Subsequent occurrences:** If Hb **<10 *but* ≥9 g/dL** Investigator judgment to continue with supportive treatment (eg transfusion) *or* dose interrupt (for max of 4 weeks) and upon recovery dose reduction to may be considered (**250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). If Hb<**9** *but* ≥**8** g/dl, dose interrupt (for max of 4 weeks) until Hb ≥9 g/dl and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).

Hemoglobin	Action to be taken
Hb <8 g/dL (CTCAE Grade 3)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥9 g/dl. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

CTCAE=Common Terminology Criteria for Adverse Event; Hb=hemoglobin

Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases where patients develop prolonged hematological toxicity (≥2-week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence), refer to the dedicated section below ("Management of prolonged hematological toxicities while on study treatment") for the management of these cases.

Management of neutropenia, leukopenia and thrombocytopenia

The management of neutropenia, leucopenia, and thrombocytopenia is presented in Table 4.

Table 4 Management of neutropenia, leukopenia, and thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgment to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

bid=twice daily; CTCAE=Common Terminology Criteria for Adverse Events

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the Investigator with close follow-up and interruption of study drug if CTC grade 3 or worse neutropenia occurs.

Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local

hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged hematological toxicity (≥2-week interruption/delay in study treatment due to CTC grade 3 or worse), refer to guidance later in this section for the management of this.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC $<1\times10^9$/L)
- ≥2-week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets $<50\times10^9$/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTC grade 1 or better within 4 weeks of dose interruption.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

6.8.2.2 Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of study treatment.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

As pneumonitis is an AESI for MEDI4736, please refer to Section 6.8.4.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic antiemetic treatment is required at the start of study treatment, however, patients should receive appropriate antiemetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie, 2 pieces of toast or a couple of biscuits).

As per international guidance on antiemetic use in cancer patients (European Society for Medical Oncology, NCCN), generally a single agent antiemetic should be considered eg, serotonin receptor antagonists or dopamine receptor antagonists. For persistent nausea, combination therapy is recommended.

Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AstraZeneca study physician.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

6.8.3 Olaparib adverse events of special interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the Investigators to AstraZeneca. Adverse events of special interest for olaparib are the Important Identified Risk of MDS/AML, and the Important Potential Risks of new primary malignancy (other than MDS/AML) and pneumonitis.

A questionnaire will be sent to any Investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study, there may be other events identified as AESIs that require the use of a questionnaire to help characterize the event and gain a better understanding regarding the relationship between the event and study treatment.

6.8.4 Specific toxicity management and dose modification information - MEDI4736

Comprehensive toxicity management guidelines (TMG) have been developed to assist Investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitor MEDI4736 CCI [redacted] These guidelines are applicable when MEDI4736 is used alone or is administered concurrently or sequentially with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents), as part of a protocol

specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment. The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is maintained within the Site Master File.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related. In addition, there are certain circumstances in which MEDI4736 should be permanently discontinued (see Section 3.9 of this protocol and the Dosing Modification and Toxicity Management Guidelines). Following the first dose of IP, subsequent administration of MEDI4736 can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the MEDI4736 therapy regimen by the reporting Investigator.

Dose reductions for MEDI4736 are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

6.8.5 MEDI4736 adverse events of special interest

An AESI is an AE of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Adverse events of special interest for MEDI4736 include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or

hormone replacement therapy. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP. These AESIs are being closely monitored in clinical studies with MEDI4736 monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an AE being an irAE, the Investigator should promptly contact the Study Physician.

AESIs observed with MEDI4736 include:

- Diarrhea/colitis
- Intestinal perforations
- Pneumonitis
- Hepatitis
- Endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus)
- Rash/dermatitis
- Nephritis
- Pancreatitis
- Myocarditis
- Myositis/polymyositis
- Neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the MEDI4736 Investigator Brochure (IB). More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities.

These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

6.8.6 Bevacizumab

For information on management of bevacizumab-related toxicities, please see Appendix M.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational products

The AstraZeneca Pharmaceutical Technology and Development R&D Supply Chain will supply the investigational sites with MEDI4736 and olaparib. Bevacizumab will be sourced locally or centrally and should be administered according to local prescribing information, including any treatment restrictions (Table 5).

In this study protocol, the term "IP" refers to the treatment regimen (including MEDI4736+olaparib, MEDI4736+olaparib+bevacizumab, and olaparib monotherapy).

Table 5 All investigational products for this study

Investigational product[a]	Dosage form and strength
MEDI4736[b]	50 mg/mL, solution for infusion
Olaparib[b]	150 mg and 100 mg tablet
Bevacizumab	25 mg/mL, solution for infusion

[a] May be cohort-dependent, please see each cohort-specific appendix.
[b] Descriptive information for olaparib and MEDI4736 can be found in the respective olaparib and MEDI4736 Investigator's Brochures.

7.1.1 MEDI4736

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

Preparation of MEDI4736 doses for administration with an IV bag

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

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

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 1.5 g will be administered using an IV bag containing 0.9% (weight/volume) saline or 5% (weight/volume) dextrose, with a final MEDI4736 concentration ranging from 1 mg/mL to 20 mg/mL and delivered through an IV administration set with a 0.2-µm or 0.22-µm in-line filter. Remove a volume of IV solution equivalent to the dose volume of MEDI4736 (30.0 mL) from the IV bag prior to addition of MEDI4736. Next, the 30.0 mL dose of MEDI4736 is added to the IV bag such that the final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Please note, if a patient's weight is 30 kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of MEDI4736 once every 4 weeks after consultation between Investigator and Study Physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of MEDI4736 1500 mg once every 4 weeks.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

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

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

In the event that either preparation time or infusion time exceeds the time limits outlined, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives and any unused portion must be discarded.

No incompatibilities between MEDI4736 and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed.

Preparations are to be in accordance with the study-specific drug handling instructions.

7.1.2 Olaparib

Olaparib is available as a film-coated tablet containing 150 mg or 100 mg of olaparib.

7.1.3 Bevacizumab

For bevacizumab preparation, see Appendix M.

7.2 Dose and treatment regimens

There is no maximum duration of treatment with study treatment. Patients should continue to receive study treatment until objective radiological disease progression as per RECIST 1.1 as assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria. Treatment will be supplied as open labeled drug via manual supply once the IVRS/IWRS has been closed.

7.2.1 Olaparib

For all centers, olaparib will be packed in high-density polyethylene bottles with child-resistant closures. The olaparib study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for at least each treatment period plus overage. Multiple bottles of study treatment may be required for dispensing in order to make up the desired dose.

Patients will be administered olaparib study treatment tablets orally at a dose of 300 mg bid. The initial dose of 300 mg bid will be made up of 2×150 mg tablets bid. The 100 mg and 150 mg tablets will be used to manage dose reductions.

All doses of study treatment should be taken at the same times each day approximately 12 hours apart and with approximately 240 mL of water. The olaparib treatment tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Study tablets can be taken with or without food. On the PK sampling day patients should fast from 1 hour before taking the olaparib dose to 2 hours after.

If vomiting occurs shortly after the study treatment tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the

scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Dose Reductions

For guidance on dose reductions for management of AEs refer to Section 6.8.2. For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see Section 7.7.

Renal Impairment

If subsequent to study entry and while still on study therapy, a patient's estimated creatinine clearance falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance [CrCl] by Cockcroft-Gault equation or based on a 24-hour urine test of between 31 and 50 mL/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg twice daily.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the Investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

7.2.2 MEDI4736

MEDI4736 should be given at least 1 hour after the patient has taken their olaparib morning dose. Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

Following preparation of MEDI4736 (see Section 7.1.1), the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes). MEDI4736 (1.5 g) will be administered via IV infusion Q4W ±3 days. Treatment with MEDI4736 will commence on Day 1 following confirmation of eligibility and will continue on a Q4W schedule until objective radiological disease progression as per RECIST 1.1 as

assessed by the Investigator or as long as, in the Investigator's opinion, they are benefitting from treatment and they do not meet any other discontinuation criteria.

A 1-hour observation period is recommended after the first infusion of MEDI4736. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each MEDI4736 infusion).

7.2.3 Bevacizumab

For bevacizumab dosing, see Appendix M. Bevacizumab should be administered after the MEDI4736 observation period at visits where both drugs are administered.

7.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language.

Specific dosing instructions will not be included on the label; the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing.

The patient emergency contact details will not be on the label, but can be found in the informed consent and the 'Patient Dispensing Card'. For emergency purposes the patient must be in possession of the emergency contact details at all times.

7.4 Storage

7.4.1 Olaparib

Olaparib should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage. Storage is also described in the IB.

7.4.2 MEDI4736

The Investigator, or an approved representative (eg, pharmacist), will ensure that all MEDI4736 is stored in a secured area, in refrigerated temperatures (2°C to 8°C) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label

storage. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

7.4.3 Bevacizumab

For storage of bevacizumab, see Appendix M.

7.5 Compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF.

Treatment compliance will be assured by reconciliation of site drug accountability logs.

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer olaparib. Study site staff will make tablet counts at regular intervals during treatment. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the eCRF.

Patients must return all containers and any remaining tablets at the end of the study.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study site staff will account for all study drugs dispensed to and returned from the patient, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return (as applicable for particular study drug) should be signed.

7.7 Concomitant and other treatments

The use of any natural/herbal products or other traditional remedies should be discouraged, but use of these products, as well as any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

Table 6 and Table 7 show prohibited and restricted medications, respectively. Table 7 also shows guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided. Table 8 details permitted supportive medications. Refer to Section 6.8 for guidance on management of IP-related toxicities.

From screening onwards, should a patient develop nausea, vomiting and/or diarrhea, then these symptoms should be reported as AEs (see Section 6.3) and appropriate treatment of the event given.

Table 6 Prohibited medications

Prohibited medication/class of drug:	
Anticancer therapy: Chemotherapy Immunotherapy Hormonal therapy[a] Radiotherapy (except palliative) Biological therapy Other novel agents Any investigational anticancer therapy other than those under investigation in this study	Not permitted while the patient is receiving study medication.
mAbs against CTLA-4, PD-1, or CCI other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment.
Live attenuated vaccines Live bacterial vaccines	Not permitted while the patient is receiving study medication and during the 30 day follow□up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with study medications are unknown.

Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the MEDI4736 infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of MEDI4736. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with first generation EGFR TKIs) has been reported when MEDI4736 has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

[a] Hormone Replacement Therapy (HRT) is acceptable.
AE, adverse event; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; IP, Investigational Product; PD-1, anti programmed cell death 1; CCI [redacted]

Table 7 Restricted concomitant medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which the medication is allowed):
Strong CYP3A inhibitors: eg, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, and telaprevir **Moderate CYP3A inhibitors**: eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, and verapamil	Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use. • Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg twice daily for the duration of concomitant therapy with the strong inhibitor and for 5 half lives afterwards. • Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg twice daily for the duration of concomitant therapy with the moderate inhibitor and for 3 half lives afterwards. • After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which the medication is allowed):
Strong CYP3A inducers: eg, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide, and St John's Wort **Moderate CYP3A inducers**: eg, bosentan, efavirenz, and modafinil	Strong or moderate CYP3A inducers should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers is considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer then they must be monitored carefully for any change in efficacy of olaparib.
CYP3A4 substrates with narrow therapeutic margin: eg, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and warfarin **Sensitive CYP3A4 substrates**: eg, buspirone, felodipine, fluticasone, lovastatin, quetiapine, saquinavir, sildenafil and simvastatin **CYP2B6 substrates**: eg, bupropion and efavirenz **OATP1B1 substrates**: eg, bosentan, glibenclamide, repaglinide, statins and valsartan **OCT1, MATE1 and MATE2K substrates**: eg, metformin **OCT2 substrates**: eg, cimetidine and metformin **OAT3 substrates**: eg, furosemide and methotrexate **BCRP substrates**: eg, methotrexate and rosuvastatin P-**gp substrates**: eg, simvastatin, pravastatin, dabigatran, digoxin and colchicine	Effect of olaparib on other drugs: Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited in vitro data, olaparib may reduce the exposure to substrates of 2B6 (and potentially substrates of CYP2C9, CYP2C19 and P-gp). The efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Caution should be observed if statins or sensitive CYP3A4 substrates are co-administered. Appropriate clinical monitoring is recommended for patients receiving P-gp substrates or CYP3A substrates with a narrow therapeutic margin concomitantly with olaparib.
Anticoagulant therapy	Patients who are taking warfarin may participate in this trial; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with olaparib and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (eg, apixaban and rivaroxaban) if possible.
Palliative radiotherapy	Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which the medication is allowed):
Administration of other anticancer agents	Patients must not receive any other concurrent anticancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

CYP=cytochrome P450; CRF= case report form; INR=international normalized ratio; MATE=Multidrug and toxin extrusion; OAT=organic anion transporter; OCT=organic cation transporter.

Table 8 Supportive medications

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

Subsequent therapies for cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. CCI [redacted]

7.7.1 Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.7.2 Bevacizumab-specific guidelines for concomitant treatments

Details of bevacizumab-specific guidelines and restrictions on concomitant treatments for patients in the ovarian cancer triplet cohort can be found in Appendix M.

7.7.3 Rescue medication

As a result of immune mediated adverse events (imAEs) that could potentially be experienced by patients on MEDI4736, steroids and other immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for hepatitis). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for management of immunotherapy related toxicities. These rescue medications must be receipted, controlled, and administered by the pharmacist and stored according to the labeled storage conditions, with temperature excursions reported accordingly by the pharmacist.

Infliximab will be locally sourced by the market where possible. Where not possible, central sourced material will be provided.

Mycophenolate will be locally sourced by the market where possible. Where not possible, central sourced material will be provided.

7.8 Post study access to study treatment

Patients receiving study treatment at the time of study completion (ie, after final data cut-off date) may continue to receive study treatment if, in the opinion of the Investigator, they are continuing to receive benefit from treatment.

The provision of study drug at study completion may include, but is not limited to, transition to a roll-over study, continuous supply within this trial (for example in countries where regulatory approval is not obtained for a roll-over study) or switching to commercial drug as permitted by local regulations.

After discontinuation of study treatment, the Investigator will be at liberty to define further most appropriate anticancer treatment.

Subsequent anticancer treatment is expected to be initiated following the cancer recurrence or development of a new cancer. Information on subsequent PARP inhibitors or other cancer therapies should be recorded on the clinical database.

Please refer to the "AstraZeneca Global Standard: Providing Study Drug to Patients Following Completion of a Clinical Study." (http://portalapps.is.astrazeneca.net/azgard-

components/ldms-documents/Global_Compliance/Effective/Global%20Standard/LDMS_001_00108183.pdf).

8. STATISTICAL ANALYSES

8.1 Statistical considerations

All statistical analyses will be performed by IQVIA.

A comprehensive statistical analysis plan will be prepared. The primary aim of the study is to assess the safety, tolerability and antitumor activity of MEDI4736 in combination with olaparib (±bevacizumab) in patients with selected advanced solid tumors.

8.2 Sample size estimate and cohort expansion criteria

Progression-free survival is the most relevant endpoint for decision making but is difficult to determine accurately in a small cohort. However, there is an approximate relationship between PFS and DCR at specified timepoints because patients whose disease has responded or is stable cannot have had a disease progression. For example, if the median PFS of interest is 6 months this would suggest that 70% of patients will be progression-free at 3 months, assuming an exponential distribution of progression times. Therefore, the selection of a DCR of 70% at 3 months (ie, at 12 weeks, using the timing conventions used throughout this protocol) for the Initial Stage Cohorts to drive decision making would also give some assurance that a level of PFS of interest is realistic without having to wait to actually observe the PFS times.

For this reason, the primary efficacy endpoint of the study in 6 of the 7 cohorts (ie, except the *BRCAm* ovarian cancer expansion cohort) is DCR, assessed at the following timepoints:

- At 12 weeks for the Initial Stage Cohorts
- At 24 weeks for the Second Stage ovarian cancer triplet and doublet cohorts

Disease control rate as an endpoint has been used to define the sample size in these cohorts.

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 stopped for efficacy. If neither threshold is crossed the study continues. 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, we assume 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 below with the monitoring plans summarized in Figure 2 of the Core Protocol, Figure 1 of Appendix M, and Figure 1 of Appendix N, and details in Appendix F.

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/) (first accessed 07 August 2015).

The details of the sample size estimate for each cohort can be found in Section 8.1 of the relevant Module (Appendix H to Appendix N).

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The full analysis set 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 (a full list will be predefined in the Statistical Analysis Plan). The full analysis set will be used for all efficacy analyses.

8.3.2 Safety analysis set

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

8.3.3 Pharmacokinetic analysis set

For the Initial Stage Cohorts, the PK analysis set will include all patients who receive at least 1 dose of olaparib and provide evaluable PK profiles for at least 1 treatment period (olaparib run-in or olaparib+MEDI4736 combination period).

For the Second Stage Cohorts, the PK analysis set will include all patients who receive at least 1 dose of any study treatment (olaparib, MEDI4736, bevacizumab) and provide evaluable PK profiles for at least 1 treatment period.

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.

8.4 Outcome measures for analyses

At each visit when a tumor evaluation takes place the patient will be assigned a RECIST 1.1 visit response of CR, PR, SD, PD, not evaluable (NE), no evidence of disease (NED) depending on the status of their disease compared to baseline and previous assessments.

8.4.1 Primary efficacy endpoint

The primary efficacy endpoints for the study cohorts are 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 or have demonstrated SD which is maintained until the RECIST 1.1 assessment at 12 weeks.
- **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 or have demonstrated SD which is maintained until the RECIST 1.1 assessment at 24 weeks.

- ***BRCAm* ovarian cancer expansion cohort**: ORR

  – Objective response rate is defined as the number (%) of patients with at least 1 visit response of CR or PR, as assessed by the Investigator (see Section 8.4.2.5 for further details).

8.4.2 Secondary efficacy endpoints

8.4.2.1 Disease control rate at 24, 28, and 56 weeks

DCR as defined in Section 8.4.1, but reported at 24, 28, or 56 weeks.

8.4.2.2 Progression-free survival

Progression-free survival based on RECIST 1.1 as assessed by the Investigator is a secondary endpoint for all cohorts.

PFS 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. 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 has disease progression 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 of olaparib treatment unless they die within 2 tumor assessment visits of treatment start.

The PFS time will always be derived based on scan/assessment dates not visit dates. All scans, not only those planned at weeks 12, 24, 28, and 56 for the DCR analysis, 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) 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

(b) 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 target lesions (compared to previous minimum sum) and an absolute increase of >5 mm, or an overall NTL assessment of progression or a new lesion.

8.4.2.3 Overall survival

Overall survival 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. 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 for the methods to be used to obtain vital status for patients who are no longer in the study.

8.4.2.4 Time to study treatment discontinuation or death

The TDT will be assessed. 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. 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.

8.4.2.5 Objective response rate

Objective response rate based on RECIST 1.1 as assessed by the Investigator is a secondary endpoint in all cohorts, except for the *BRCAm* ovarian cancer expansion cohort. Objective response rate is defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of response rate. Patients who discontinue study treatment without progression, receive a subsequent anticancer therapy and then respond will not be included as responders in the ORR. 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.

8.4.2.6 Best objective response

Best objective response (BOR) is calculated based on the overall visit responses from each RECIST assessment, described in Section 4.6 of Appendix E. It is the best response a patient

has had following enrollment, 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. Categorization 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. Patients who discontinue treatment without progression, receive a subsequent anticancer 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. For patients who die in the absence of progression and have no evaluable visit responses prior to death, BOR will be set to PD.

8.4.2.7 Duration of response

Duration of Response (DoR) based on RECIST 1.1 as assessed by the Investigator is a secondary endpoint for all cohorts. Duration of Response will be 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. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

8.4.2.8 Percentage change in tumor size

The percentage change from baseline in tumor size at 12 and 28 weeks (Initial Stage Cohorts) and the percentage change from baseline in tumor size at 24 and 56 weeks (Second Stage Cohorts) are based on RECIST 1.1 target lesion measurements taken at baseline and either 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 target lesions. Target lesions are measurable tumor lesions. Baseline for RECIST 1.1 is defined to be the last evaluable assessment prior to starting olaparib treatment. The percentage change in target lesion tumor size at each timepoint will be obtained for each patient taking the difference between the sum of the target lesions at each timepoint and the sum of the target lesions at baseline divided by the sum of the target lesions at baseline times 100; eg, for Week 12 (Week 12 - baseline) / baseline * 100).

8.4.2.9 Best overall percentage change from baseline in tumor size

The best percentage change from baseline in tumor size is based on RECIST 1.1 target lesion 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.

8.5 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed within each tumor type in terms of AEs, deaths, laboratory data, vital signs and ECGs. These will be collected for all patients. Appropriate summaries of these data, to be described in the Statistical Analysis Plan, will be presented.

8.6 Methods for statistical analyses

For the Initial Stage Cohorts and the Second Stage ovarian cancer triplet and doublet cohorts, the primary endpoint is DCR in patients using Investigator assessments per RECIST 1.1. In the *BRCAm* ovarian cancer expansion cohort, ORR is the primary endpoint. Each cohort, with the exception of the *BRCAm* ovarian cancer expansion cohort, has been sized to characterize the DCR of MEDI4736+olaparib (or MEDI4736+olaparib+bevacizumab, for the ovarian cancer triplet cohort). All formal statistical analysis will be performed on a per cohort basis, to test the main hypotheses that the DCR is above the threshold of interest defined for each cohort, or in the case of the *BRCAm* ovarian cancer expansion cohort, test the main hypothesis that the ORR is above the threshold of interest.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by cohort. Continuous variables will be summarized by the number of observations, mean, standard deviation, 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 for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of olaparib for Initial Stage Cohorts, or Cycle 1 Day 1 for Second Stage Cohorts.

All data collected will be listed. Efficacy and safety data will be summarized on the Efficacy and Safety Analysis Sets.

With the exception of DCR at 12, 24, 28, and 56 weeks (which will be presented with 90% CIs; see Section 8.6.1.1), results will be presented with 95% CIs, unless otherwise stated.

8.6.1 Analysis of the primary variable(s)

8.6.1.1 Disease control rate (Initial Stage, ovarian cancer triplet, and ovarian cancer doublet cohorts)

The DCR will be summarized (ie, number of patients, %) in each tumor group. Patients who do not complete the DCR assessment at the timepoint of interest (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% CI and 1-sided p-value will also be presented.

8.6.1.2 Objective response rate (*BRCAm* ovarian cancer expansion cohort)

Objective response rate will be analyzed when all 80 patients have been followed for a minimum of 24, 40, 56, 80, and 104 weeks. For the *BRCAm* ovarian expansion cohort, at n=80, a 2-sided 95% 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 (eg, 95% CI: 69.5% to 87.5%).

8.6.2 Analysis of the secondary variables

8.6.2.1 Progression-free survival, overall survival and time to study treatment discontinuation or death

A Kaplan-Meier plot 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.

The estimated PFS rates at specific timepoints (every 6 months to a maximum of 24 months) will also be presented.

The analysis will be based on the overall visit assessments (ie, individual tumor measurements will not be used) and using all scans regardless of whether they were scheduled or not.

The analysis will be repeated for OS and TDT.

8.6.2.2 Summary of objective response rate

The ORR will be summarized (ie, number of patients, %) in each tumor group.

8.6.2.3 Percentage change in tumor size and best percentage

These endpoints will be reported by cohort using summary statistics.

8.6.3 Subgroup analysis

Not applicable.

8.6.4 Interim analysis

8.6.4.1 Safety review

A formal Safety Review process will be put in place throughout this study. Please refer to Section 1.4 of the Core Protocol and to the cohort-specific Modules for further for details.

8.6.4.2 Continuous monitoring

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. 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 10 patients, the DCR will be monitored after every 5 patients become evaluable.

In the 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 addition, 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.

Full details of these analyses will be included in the statistical analysis plan.

8.6.5 Sensitivity analysis

Not applicable.

8.6.6 Exploratory analysis

Not applicable; these endpoints will not be reported in the CSR.

8.7 Calculation or derivation of pharmacokinetic variables

The PK analysis of the plasma concentration data for olaparib will be performed at AstraZeneca Research & Development or by a clinical research organization identified by AstraZeneca Research & Development. The actual sampling times will be used in the PK calculations. For each patient providing a complete set of PK samples, non-linear mixed

effects modeling will be used to estimate steady state maximum observed plasma concentration, area under the curve, and minimum observed plasma concentration.

8.7.1 Olaparib and MEDI4736

CCI [redacted]

Bevacizumab

Bevacizumab serum concentrations will be listed and summarized by timepoint.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in

accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each/the center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as the date of the last visit of the last patient occurring when all patients have completed study therapy.

In the event that a roll-over or safety extension study is available at the time of the final data cut-off and database closure, patients currently receiving MEDI4736 and/or olaparib treatment may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient proposed to move to such a study would be given a new ICF.

There will be a data cut-off for each cohort, after which only survival, subsequent anticancer treatment, and specific safety data (see below) may be collected in the clinical study database (see Section 9 of each cohort for cohort-specific details). The data cut-offs will be as follows:

- For the Initial Stage SCLC, gastric cancer, *gBRCAm* breast cancer, and *gBRCAm* ovarian cancer cohorts, the data cut-off occurred once all 4 cohorts had reached last patient first visit (LPFV) + 2 years **and** all 4 cohorts had observed a median value for PFS. For the Initial Stage *gBRCAm* ovarian cancer cohort **only**, once the data cut-off occurred, only survival, subsequent anticancer treatment, and safety data will continue to be collected in the clinical study database, until the final data cut-off is reached.
- For the Second Stage Cohorts, the final data cut-off will be once the doublet and triplet ovarian cancer cohorts have observed a median value for overall survival. The expansion cohort will be analyzed once this data cut-off has occurred. At this timepoint, the clinical study database will close to new data.

9.3.1 Post final data cut off

Patients are permitted to continue to receive study treatment beyond the closure of the database 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. At routine clinic visits, patients will return used medication packaging and unused medication, and a thorough drug accountability assessment will be performed. CCI [redacted]

For patients who do continue to receive treatment beyond the time of the data cut-off, Investigators will continue to report all SAEs to AstraZeneca Patient Safety until 90 days after study treatment is discontinued, in accordance with Core Protocol Section 6.4 (Reporting of Serious Adverse Events).

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the IP, the Investigator should notify AstraZeneca, Patient Safety. Additionally, as stated in Core Protocol Section 6.3 (Recording of AEs), any SAE or non-serious AE that is ongoing at the time of this data cut-off, must be followed up by the Investigator for as long as medically indicated.

The study started in Q2 2016; the final data cut-off is expected to occur in 2021.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with olaparib and MEDI4736. AstraZeneca reserves the right to close the study site or terminate the study at any time for any reason.

9.4 Data management by IQVIA

Data management will be performed by IQVIA, according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities. Medications will be classified according to the World Health Organisation (WHO) Drug Dictionary. Classification coding will be performed by IQVIA.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

SAE Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data Management of genotype data

See Appendix C.

Data associated with human biological samples

CCI [redacted]

Management of external data

Data from external providers (eg, central laboratories) will be validated as appropriate to ensure they are consistent with the clinical data and this data will be included in the final database.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilising medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Refer to Appendix C for details of data protection for genetic samples and information.

10.3 Financial Disclosure

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

10.4 Ethics and regulatory review

An EC/IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, EC/IRB and PIs with safety updates/reports according to local requirements.

10.5 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient’s legally authorized representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

If a patient’s partner becomes pregnant during or within 90 days after the last dose of study treatment, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

10.6 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the PI and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant EC/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the Clinical Study Protocol to each PI(s). For distribution to EC/IRB see Section 10.4.

If a change to a Clinical Study Protocol requires a change to a center's ICF, AstraZeneca and the center's EC/IRB are to approve the revised ICF before the revised form is used.

10.7 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

10.8 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

10.9 Dissemination of clinical study data

A description of this clinical study will be available on *http://astrazenecaclinicaltrials.com* a*nd http://www.clinicaltrials.gov* as will the summary of the *main* study results when they are available. The clinical study and/or summary of *main* study results may also be available on

other websites according to the regulations of the countries in which the *main* study is conducted.

10.10 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.11 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

10.12 Publication policy

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

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

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

11. LIST OF REFERENCES

Antonia et al 2017
Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(20):1919-29.

Bang et al 2019
Bang YJ, Kaufman B, Geva R, Stemmer S, Hong SH, Lee JS, et al. An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in patients with relapsed gastric cancer. J Clin Oncol 2019;37:140.

Bang et al 2017
Bang YJ, Xu RH, Chin K, Lee KW, Park SH, Rha SY, et al. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(12):1637-51.

Berger et al 2008
Berger R, Rotem-Yehudar R, Slama G, Landes S, Kneller A, Leiba M, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. Clin Cancer Res. 2008;14(10):3044-51.

Blank et al 2006
Blank C, Kuball J, Voelkl S, Wiendl H, Becker B, Walter B, et al. Blockade of PD-L1 (B7-H1) augments human tumor-specific T-cell responses in vitro. Int J Cancer. 2006;119(2):317-27.

Brahmer et al 2010
Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167-75.

Chatzinikolaou et al 2014
Chatzinikolaou G, Karakasilioti I, Garinis GA. DNA damage and innate immunity: links and trade-offs. Trends Immunol. 2014;35(9):429-35.

Domchek et al 2020
Domchek SM, Postel-Vinay S, Im SA, Park YH, Delord JP, Italiano A, et al. Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study. Lancet Oncol. 2020;21(9):1155-1164.

Dong et al 2002
Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002;8(8):793-800.

Drew et al 2019
Drew Y, Kaufman B, Banerjee S, Lortholary A, Hong SH, Park YH, et al. 1190PD - Phase II study of olaparib + durvalumab (MEDIOLA): Updated results in germline BRCA-mutated platinum-sensitive relapsed (PSR) ovarian cancer (OC). Ann. Oncol. 2019;30(supplement 5):v485-486.

Drew et al 2018
Drew Y, de Jonge M, Hong SH, Park YH, Wolfer A, Brown J, et al. An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): Results in germline BRCA -mutated (gBRCA m) platinum-sensitive relapsed (PSR) ovarian cancer (OC). Gynecologic Oncology. 2018;149:246-247.

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

Farmer et al 2005
Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in *BRCA* mutanT-cells as a therapeutic strategy. Nature. 2005;434(7035):917-21.

FDA bevacizumab label
Avastin® (bevacizumab). Solution for intravenous infusion. 2004. Genentech, Inc

Fife and Bluestone 2008
Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev. 2008;224:166-82.

Hamanishi et al 2007
Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Nat Acad Sci U S A. 2007;104(9):3360-5.

Higuchi et al 2015
Higuchi T, Flies DB, Marjon NA, Mantia-Smaldone G, Ronner L, Gimotty PA, et al. CTLA-4 Blockade Synergizes Therapeutically with PARP Inhibition in *BRCA1*-Deficient Ovarian Cancer. Cancer Immunol Res. 2015;3(11):1257-68.

Hirano et al 2005
Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by Monoclonal Antibodies Potentiates Cancer Therapeutic Immunity. Cancer Res. 2005;65(3):1089-96.

Huang et al 2015
Huang J, Wang L, Cong Z, Amoozgar Z, Kiner E, Xing D, et al. The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer. Biochem Biophys Res Commun. 2015;463(4):551-6.

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A. 2002;99(19):12293-7.

Karzai et al 2017
Karzai F, Madan RA, Owens H, Hankin A, Couvillon A, Houston ND, et al. A phase II study of the anti-programmed death ligand-1 antibody durvalumab (D; MEDI4736) in combination with PARP inhibitor, olaparib (O), in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2017;35:6(suppl) 162-162.

Kaufman et al 2015
Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015 Jan 20;33(3):244-50.

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

Krambeck et al 2007
Krambeck AE, Dong H, Thompson RH, Kuntz SM, Lohse CM, Leibovich BC, et al. Survivin and B7-H1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. Clin Cancer Res. 2007;13(6):1749-56.

Krebs et al 2017
Krebs M, Ross K, Kim S, De Jonge M, Barlesi F, Postel-Vinay S, et al. P1.15-004 An open-label, multitumor phase II basket study of olaparib and durvalumab (MEDIOLA):Results in patients with relapsed SCLC. J Thorac Oncol 2017;12: S2044-S2045.

Kroemer et al 2012
Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol. 2013;31:51-72.

Latchman et al 2004
Latchman YE, Liang SC, Wu Y, Chernova T, Sobel RA, Klemm M, et al. PD-L1-deficient mice show that PD-L1 on T-cells, antigen-presenting cells, and host tissues negatively regulates T-cells. Proc Natl Acad Sci U S A. 2004;101(29):10691-6.

Ledermann et al 2012
Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382-92.

Ledermann et al 2014
Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by *BRCA* status in a randomised phase 2 trial. Lancet Oncol. 2014;15(8):852-61.

Ledermann et al 2016
Ledermann JA, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Overall survival (OS) in patients (pts) with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) receiving olaparib maintenance monotherapy: An interim analysis. J Clin Oncol. 2016;34 (suppl; abstr 5501).

Lee et al 2017
Lee JM, Cimino-Mathews A, Peer CJ, Zimmer A, Lipkowitz S, Annunziata CM, et al. Safety and Clinical Activity of the Programmed Death-Ligand 1 Inhibitor Durvalumab in Combination With Poly (ADP-Ribose) Polymerase Inhibitor Olaparib or Vascular Endothelial Growth Factor Receptor 1-3 Inhibitor Cediranib in Women's Cancers: A Dose-Escalation, Phase I Study. J Clin Oncol. 2017;35(19):2193-2202.

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.

Loos et al 2008
Loos M, Giese NA, Kleeff J, Giese T, Gaida MM, Bergmann F, et al. Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic cancer. Cancer Lett. 2008;268(1):98-109.

Madan and Gulley 2011
Madan RA, Gulley JL. Sipuleucel-T: harbinger of a new age of therapeutics for prostate cancer. Expert Rev Vaccines. 2011;10(2):141-50.

Mu et al 2011
Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol. 2011;28(3):682-8.

Mulligan et al 2014
Mulligan JM, Hill LA, Deharo S, Irwin G, Boyle D, Keating KE, et al. Identification and validation of an anthracycline/cyclophosphamide-based chemotherapy response assay in breast cancer. J Natl Cancer Inst. 2014;106(1):djt335.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet. 2013;52(11):1017–27.

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

Nishimura et al 1998
Nishimura H, Minato N, Nakano T, Honjo T. Immunological studies on PD-1 deficient mice: implication of PD-1 as a negative regulator for B cell responses. Int Immunol. 1998;10(10):1563-72.

Nishimura et al 2001
Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001;291(5502):319-22.

Nomi et al 2007
Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res. 2007;13(7):2151-7.

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

Pages et al 2010
Pages F, Galon J, Dieu-Nosjean MC, Tartour E, Sautès-Fridman C, Fridman WH. Immune infiltration in human tumors: a prognostic factor that should not be ignored. Oncogene. 2010;29(8):1093-1102.

Park et al 2010
Park J, Omiya R, Matsumura Y, Sakoda Y, Kuramasu A, Augustine MM, et al. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. Blood. 2010;116(8):1291-8.

Powles et al 2017
Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, et al. Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma: Updated Results From a Phase 1/2 Open-label Study. JAMA Oncol. 2017;3(9):e172411.

Pujade-Lauraine et al 2017
Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT5, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA*1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18(9):1274-84.

Robson et al 2017
Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation. N Engl J Med. 2017;377(6):523-33.

Schmidinger et al 2004
Schmidinger M, Hejna M, Zielinski CC. Aldesleukin in advanced renal cell carcinoma. Expert Rev Anticancer Ther. 2004;4(6):957-80.

Tang et al 2014
Tang ML, Khan MK, Croxford JL, Tan KW, Angeli V, Gasser S. The DNA damage response induces antigen presenting cell-like functions in fibroblasts. Eur J Immunol. 2014;44(4):1108-18.

Tarhini 2013
Tarhini A. Immune-Mediated Adverse Events Associated with Ipilimumab CTLA-4 Blockade Therapy: The Underlying Mechanisms and Clinical Management. Scientifica (Cairo). 2013;2013:857519.

Thompson et al 2005
Thompson RH, Gillett MD, Chevillem JC, Lohsem CM, Dongm H, Webster WS, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer. 2005;104(10):2084-91.

Thompson et al 2006
Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res. 2006;66(7):3381-5.

Topalian et al 2012
Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-54.

Wang et al 2010
Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M. Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma. World J Surg. 2010;34(5):1059-65.

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

Wolchok et al 2010
Wolchok JD, Weber JS, Hamid O, Lebbé C, Maio M, Schadendorf D, et al. Ipilimumab efficacy and safety in patients with advanced melanoma: a retrospective analysis of HLA subtype from four trials. Cancer Immun. 2010;10:9.

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

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

Zou and Chen 2008
Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol. 2008;8(6):467-77.

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