Clinical Study Protocol	
Study Intervention	Olaparib (AZD2281) and Durvalumab (MEDI4736)
Study Code	D931CC00001
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A Phase II, Multicentre, Open-Label Study to Assess the Efficacy and Safety of Olaparib Monotherapy and Olaparib Plus Durvalumab Combination as Neoadjuvant Therapy in Patients with *BRCA* Mutations and Early Stage HER2-Negative Breast Cancer (OlympiaN)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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This CSP has been subject to a peer review according to AstraZeneca Standard procedures. The CSP 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 Number: D931CC00001

Amendment Number: 4

Study Intervention: Olaparib (AZD2281) and Durvalumab (MEDI4736)

Study Phase: II

Short Title: Efficacy and Safety of Neoadjuvant Olaparib Monotherapy and Olaparib Plus Durvalumab Combination in HER2-Negative *BRCA*m Breast Cancer

Acronym: OlympiaN

Medical Monitor Name and Contact Information will be provided separately

International co-ordinating investigators: PPD, Beth Israel Deaconess Medical Center, Boston, USA; and PPD Vall d'Hebron University Hospital, Barcelona, Spain.

Redacted for Public Disclosure

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	*22 March 2024*
Amendment 3	*01 June 2023*
Amendment 2	*10 June 2022*
Amendment 1	*09 March 2022*
Original Protocol	*13 January 2022*

Amendment 4 (22-March-2024)

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.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to clarify details regarding the schedule of assessments and study procedures that resulted from many questions from investigative sites when they attempted to conduct the study and to add missing procedures and tests into the End of Treatment Visit and the mandatory collection of CCI samples at definitive surgery. These and other changes incorporated in this amendment are described in the following table. In addition, minor text clarifications, administrative changes, corrections of minor errors, and changes for consistency across the study-related documents and within the protocol have been made; as these changes were minor, they are not listed in detail in the table.

List of Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 6.1.1 Investigational Products, Section 7.1 Temporary Discontinuation of Study Intervention at Completion of Neoadjuvant Therapy for Definitive Surgery	Added statement that definitive surgery will be performed within 6 weeks following final dose of neoadjuvant olaparib therapy (or per local standard of care). Removed statement that surgery may be scheduled earlier than Cycle 4 in some cases based on clinical response.	To clarify the permitted timing for definitive surgery and prevent protocol deviations for surgery after <4 cycles of treatment, as these participants are not evaluable for pCR.
Section 1.1 Synopsis, Section 4.1 Overall Design	Removed statement that participants whose *BRCA*m has been detected on the basis of a tumour test may be eligible to enrol.	To correct error as participants are tested locally and may have documented *BRCAm* by blood or tumour test. There is no requirement for only blood test results to be eligible prior to treatment allocation.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Added serum or urine pregnancy test, clinical safety laboratory assessments, vital signs, study intervention returned/compliance check, and concomitant medications at End of Treatment Visit. Added targeted physical examination, weight collection, and ECOG performance status during Post-Neoadjuvant Safety assessment and at End of Treatment Visit.	To correct error, as the required safety procedures and tests were missing from the End of Treatment Visit.
Section 1.3 Schedule of Activities (including Footnote "t")	Added row and associated footnote for mandatory CCI sample for central pathology review of residual disease and pCR assessment.	To correct error, as the required CCI sample was missing. Added to align with Pathology Manual and ensure collection to support primary endpoint.
Section 1.3 Schedule of Activities (Footnote "hh" and "ii")	Details added regarding monitoring of participants during durvalumab infusions for Cohort B participants.	To align with main body of the protocol, which specifies special monitoring required when administering durvalumab.
Section 5.1 Inclusion Criteria (#2)	Added statement that participants unable to have MRIs performed are not eligible for the study.	For clarity, based on questions from site since MRI is the only allowed method to calculate CCI volume, which supports secondary end point.

List of Non-Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 1.2 Schema, Section 4.1 Overall Design, Section 6.1.1 Investigational Products, Section 7.1 Temporary Discontinuation of Study Intervention at Completion of Neoadjuvant Therapy for Definitive Surgery	Revised language to state that total duration of olaparib therapy in the neoadjuvant and adjuvant setting must not exceed 12 cycles.	To clarify that there is no flexibility in the total duration of olaparib treatment.
Section 1.1 Synopsis, Section 4.1 Overall Design, Section 8.6.1 Collection of Samples for Biomarker Analysis	Updated language regarding baseline research CCI .	To provide clarity and align with laboratory manual.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 4.1 Overall Design	Removed statement that all CCI CCI will be utilised for CCI research.	To correct error, as CCI CCI will also be used for central pathology assessment (primary endpoint).
Section 1.1 Synopsis, Section 1.3 Schedule of Activities	Revised statement that End of Treatment Visit should be conducted within 7 days of permanent discontinuation of study intervention.	To clarify timing of visit.
Section 1.3 Schedule of Activities	Revised survival status collection so that survival status is only collected during survival follow-up visits.	To correct error, as survival status collection incorrectly appeared in all on-study visits.
Section 1.3 Schedule of Activities (Footnote "b")	Revised statement to clarify that participants may discontinue study treatment early (<4 cycles) based upon disease progression.	Administrative change for clarity.
Section 1.3 Schedule of Activities, Section 7.2.1 Safety Follow-up of Participants Post Discontinuation of Study Intervention	Revised window of Post-Neoadjuvant Safety Assessment and Safety Follow-up assessment to +7 days following last dose of the respective treatments. Removed "-7 days".	To ensure safety follow-up at required amount of time post the last dose of study intervention for safety assessments (ie 30 days after last dose of olaparib or 90 days after last dose of durvalumab).
Section 1.3 Schedule of Activities, Section 8.1.4 Radiological Assessments	Removed "other radiological assessments" that were not used for secondary endpoint.	For clarity, based on questions and concerns from sites. These radiological assessments are done as standard of care for staging at initial diagnosis, which is recorded in the eCRF. These radiological assessments were not collected in the eCRF.
Section 1.3 Schedule of Activities (including Footnote "g"), Section 8.2.1 Physical Examinations, Section 8.2.2.2 Vital Signs at Subsequent Infusions of Durvalumab (Cohort B Only)	Revised details for weight, blood pressure, and pulse recording by cohort.	To align with main body of the protocol, which specifies special monitoring required when administering durvalumab.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (Footnote "o")	Corrected statement that CCI will be submitted to the Central Laboratory instead of AstraZeneca.	To correct error.
Section 1.3 Schedule of Activities (Footnote "u")	Added footnote that only one set of blood sample collection for CCI is required in cases where the Post-Neoadjuvant Safety Assessment Visit 30 days after the last dose of olaparib is on the same date as the as Pre-Definitive Surgery Visit.	To clarify blood collection for CCI research, based upon questions from investigative sites. Added flexibility to reduce blood draws in cases where visit schedule overlaps.
Section 1.3 Schedule of Activities (Footnote "w"), Section 8.6.2 Blood Samples for Biomarker Analysis (Mandatory)	Revised statement regarding timing of CCI sample collection.	To align with main body of the protocol and provide clarity in response to questions from investigative sites.
Section 1.3 Schedule of Activities (including Footnote "x")	Clarified details and timing of CCI testing for participants in Cohort B.	To correct error in SOA and provide clarity with schedule, and to align with the CCI standard CCI testing.
Section 1.3 Schedule of Activities (column associated Footnote "aa")	Removed from Safety Follow-Up Visit that investigators will ask if the participant has developed MDS/AML or a new primary malignancy. It is only required during the survival follow-up.	To correct error and align with footnote.
Section 1.3 Schedule of Activities (Footnote "dd")	Revised statement regarding anticancer treatments to be collected to include radiation and endocrine therapy. Removed erroneous eCRF completion instructions and transfusions which are not considered anti-cancer therapy.	To correct errors and align with main body of the protocol.
Section 1.3 Schedule of Activities (Footnote "ee")	Removed additional tumour volume imaging at discretion of investigator to assess disease response more frequently, as additional MRIs should only be performed if disease progression is suspected.	To correct error and ensure consistent frequency of MRIs across study.
Section 4.1 Overall Design	Revised statement regarding additional non-protocol therapy in the context of timing of definitive surgery.	For clarity, as non-protocol therapy is not allowed prior to definitive surgery.

Section # and Name	Description of Change	Brief Rationale
Section 4.1 Overall Design, Section 7.2 Permanent Discontinuation of Study Intervention	Revised statement regarding what happens when a participant discontinues from study intervention to specify that participants will continue study participation in the survival follow-up phase of the study. Added to Section 7.2 for consistency.	For clarity to ensure participant retention after discontinuing study intervention and starting subsequent treatment.
Section 5.1 Inclusion Criteria (#2)	Added that participants with invasive breast cancer or concurrent ipsilateral/contralateral ductal carcinoma in situ are eligible, as long as each cancer displays required characteristics.	For clarity based on questions from site.
Section 5.1 Inclusion Criteria (#3)	Removed statement detailing the type of laboratory where tumour test must have been performed.	To allow for flexibility and alignment across the olaparib clinical trial program.
Section 5.1 Inclusion Criteria (#6)	Removed statement excluding participants if there is not written confirmation of availability of CCI prior to start of study intervention. Note regarding documentation of archival CCI CCI shifted from Inclusion Criteria #7.	For clarity.
Section 5.1 Inclusion Criteria (#2)	Added that participants with invasive breast cancer or concurrent ipsilateral/contralateral ductal carcinoma in situ are eligible, as long as each cancer displays required characteristics.	For clarity based on questions from site.
Section 5.4 Screen Failures	Statement regarding documentation of screen failures revised.	Corrected error and aligned with CRF Completion Guidelines.
Section 6.4.2 Durvalumab Compliance (Cohort B)	Revised statement regarding confirmation of dose of durvalumab and study participant identification.	To add flexibility to the investigative site and align with standard compliance monitoring.
Section 7.2 Permanent Discontinuation of Study Intervention	Removed statement that crossover within the study will not be permitted.	To align with protocol template and reduce redundancy.
	Removed requirement for resolution to Grade 2 or less of olaparib-related toxicity for Cohort B participants who discontinue olaparib due to treatment-related toxicities and wish to continue durvalumab in the neoadjuvant setting.	To align across olaparib program.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 Surgical Assessment	Removed statement regarding decision on intended surgery following completion of study intervention.	To clarify because this is not requirement for surgery that must be documented or collected in CRF.
Section 8.1.2 Definitive Surgery	Removed statement that sponsor should be informed of a delay in definitive surgery beyond 6 weeks.	To clarify this is not a requirement for the study (ie, would not be a protocol deviation and delay does not require approval) and the site is allowed to extend the time to surgery due to local practice.
	Shifted paragraph regarding decision to proceed to definitive surgery if disease progression occurs prior to completion of planned neoadjuvant therapy from Section 8.1.1 (Surgical Assessment), and revised recording/processing procedure for these participants.	To correct misplacement of the information and move it to the relevant section.
Section 8.1.2.3 Collection and Storage of Definitive Surgery Tissue Specimens for Central Pathology Review (Mandatory)	Shifted placement of previous Section 8.1.4.1 and revised text relating to surgical specimen tissue collection and pCR analysis.	For clarity to improve site compliance with surgical tissue specimen submission to Central Pathology.
Section 8.1.3 Imaging Tumour Assessments	Added statement that details regarding post-surgery MRIs will not be recorded in the eCRF.	For clarity due to questions from investigative site.
	Removed note regarding percent change in tumour volume calculation.	Corrected misplacement of information that is not applicable for site. Information describes how data will be interpreted by Sponsor instead.
Section 8.2.2 Vital Signs	Added statement respiratory rate will not be recorded in the eCRF after Screening.	To align with eCRF template.
Section 8.2.3 Electrocardiograms (Cohort B Only)	Noted that this subsection applies to Cohort B only.	For clarity and consistency with the SoA.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.4 Clinical Safety Laboratory Assessments (Table 9: Laboratory Safety Variables)	Removed bicarbonate from list of assessments; added erythrocytes to list of assessments.	To align with current best safety practices, eCRF template, and olaparib protocol template.
	Removed PTT from list of assessments and added footnote that INR is only required in participants receiving warfarin.	To correct inconsistency with the main body text.
	Revised Footnote "a" to state that if absolute neutrophil or absolute lymphocyte counts are not available, percentage results (not differential counts) should be recorded.	Corrected error.
	Expanded Footnote "b" to include additional details regarding reticulocyte count collection for Cohort B participants.	Added for consistency with main body text.
Section 8.2.5.3 Bone Marrow or Blood Cytogenetic Samples	Added to statement that bone marrow and blood cytogenetic analysis reports are to be anonymised.	To align with privacy requirements for participant documents sent into Sponsor.
Section 8.3.12 Reporting of Serious Adverse Events	Removed statement that investigators or other site personnel send relevant eCRF modules by fax to the designated AstraZeneca representative.	Corrected error in text. SAEs for the study are reported directly into eCRF and sites do not fax in SAEs.
Section 8.3.13.1 Maternal Exposure	Removed instructions regarding PREGOUT as form used to report outcomes of pregnancy in eCRF and added that outcomes should be reported to AstraZeneca.	To correct error and provide clarity, as the PREGOUT eCRF module does not exist, but the outcome must still be reported to Sponsor representative.
Section 8.6.1 Collection of Samples for Biomarker Analysis	Removed "if clinically appropriate" from statement regarding optional CCI taken at the time of disease recurrence.	For consistency with SoA.

Section # and Name	Description of Change	Brief Rationale
Section 8.6.2 Blood Samples for Biomarker Analysis (Mandatory)	Revised statement that blood samples for biomarker analysis are collected at the 30-day Post-Neoadjuvant Safety Assessment visit (not the Safety Follow-up visit).	For consistency with SoA.
	Removed "via central laboratory" from statement regarding serum samples for assessment of CCI [redacted].	Corrected error since the blood is drawn (obtained) locally instead of at a central laboratory.
Section 9.4.2.2.3 Change from Baseline in Tumour Volume	Moved statement from Appendix I regarding analysis of percentage reduction in tumour volume to the correct section.	Corrected misplacement of information that is not applicable for site. Information describes how data will be interpreted by Sponsor instead.
Appendix I Guidelines for Acquisition and Evaluation of MRI for Lesion Assessments	Removed statement that changes from the baseline in tumour volume will be assessed by the investigator.	Corrected misplacement of information that is not applicable for site. Information describes how data will be interpreted by Sponsor instead.
	Included instructions for sites regarding cases where breast lesion is too small to measure.	For clarity and to ensure eCRF completed correctly for the secondary endpoint.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

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

Short Title:

Efficacy and Safety of Neoadjuvant Olaparib Monotherapy and Olaparib plus Durvalumab Combination in HER2-Negative *BRCA*m Breast Cancer

Rationale:

Triple negative breast cancer (TNBC), characterised by a lack of the expression of oestrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2), has a poor prognosis and is difficult to treat. HER2-negative, low ER expression (ER ≤10%) breast cancers are biologically similar to TNBC. Historically, the systemic treatment of TNBC has been mainly based on traditional chemotherapy, although the antibody-drug conjugate sacituzumab govitecan recently gained regulatory approval for metastatic TNBC. In the early disease setting (operable and without known distant metastases), neoadjuvant therapy is followed by definitive surgery. If pathological complete response (pCR) is achieved, there is a significant correlation of pCR after neoadjuvant chemotherapy in patients with TNBC with long-term clinical benefit such as event-free survival (EFS) and overall survival (OS) (Liedtke et al. 2008; Cortazar et al. 2014; Yee et al. 2020). Patients with early stage disease who receive neoadjuvant chemotherapy but who do not achieve a pCR at surgery have the option of further therapy with capecitabine (Masuda et al. 2017). Even though TNBC is considered relatively more chemo-sensitive than other breast cancer subtypes, the disease recurrence rate with currently available therapies is high, and patients who develop recurrent disease have a very poor outcome. Therefore, TNBC remains a disease with high unmet medical need.

There are emerging data to demonstrate that patients with breast cancer with a low expression of ER derive limited benefit from endocrine therapy (ET) and are biologically similar to TNBC (Landmann et al. 2018). The American Society of Clinical Oncology (ASCO)/College of American Pathologists guidelines were recently updated to create a new category of ER-low (ie, 1% to 10% staining) breast cancer (Allison et al. 2020). Some authors have suggested using this new cut-off of 10% ER, rather than <1%, to define TNBC (Dieci et al. 2021). Additionally, there is controversy about the very existence of breast cancers with ER-negative/PgR-positive receptor status (De Maeyer L et al. 2008). A series of 5993 cases of breast cancer found no ER-negative/PgR-positive tumours (Nadji M. et al. 2005). In a cross neoadjuvant clinical trial comparison of HER2-negative breast cancer patients with negative, low, or strong hormone receptor (HR) expression, low HR-positive, HER2-negative tumours had a similar clinical behaviour to TNBC showing high pCR rates and poor survival and also a basal-like gene expression signature, suggesting that patients with low HR-positive tumours should be regarded as candidates for therapy strategies that target TNBC (Villegas SL, 2021). Thus, this study will enrol patients with ER-negative or

ER-low disease and will not select participants on the basis of PgR status, although the expectation is that the vast majority of participants enrolled will be PgR negative. Additionally, recently reported data suggest that only a small minority (approximately 6%) of the eligible patient population are likely to be those who fulfil the definition of HR-low (Tung N et al. 2020).

The tumour-suppressor genes *BRCA1* and *BRCA2* are associated with deoxyribonucleic acid (DNA) damage repair. Mutations of these genes, especially *BRCA1*, are known to increase the risk of developing breast cancer. Patients with a *BRCA1* mutation are predisposed to developing TNBC, whereas patients with a *BRCA2* mutation most often have tumours that are ER+ (Antoniou AC et al. 2012; Mavaddat N et al. 2012). While only 10% to 20% of all TNBC occurs in women with a g*BRCA*m, approximately 70% of the breast cancers that develop in women with a g*BRCA1*m are TNBC (Metzger-Filho et al 2012).

The use of polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors in patients with g*BRCA*m and HER2-negative breast cancer offers a molecularly targeted treatment approach, via a mechanism termed synthetic lethality (Farmer et al. 2005).

The PARP inhibitor olaparib is registered for use in the United States, European Union, and other countries for treatment of advanced/metastatic breast cancer in patients with g*BRCA*m, HER2-negative breast cancer, based on signals of efficacy observed in the OlympiAD trial in patients with metastatic HER2-negative (triple-negative or HR-positive), g*BRCA*m breast cancers (Robson et al. 2019). In the recently reported Phase 3 randomised trial OlympiA, patients with HER2-negative early breast cancer with *BRCA1* or *BRCA2* germline variants and high-risk clinical/pathological features who had completed (neo)adjuvant therapy were randomised to 1 year of oral olaparib or placebo. At a median follow-up of 2.5 years, the 3-year invasive disease-free survival was 85.9% in the olaparib group versus 77.1% in the placebo group (hazard ratio 0.58; 99.5% confidence interval [CI], 0.41 to 0.82; P<0.001) (Tutt et al. 2021).

The immune checkpoint inhibitor (ICI) pembrolizumab has been approved by the Food and Drug Administration for use in combination with chemotherapy as neoadjuvant treatment followed by monotherapy adjuvant treatment for patients with high-risk early stage TNBC. This approval was based on the results of the KEYNOTE-522 study which, despite showing only a modest improvement in pCR, demonstrated that the addition of pembrolizumab to neoadjuvant chemotherapy followed by adjuvant pembrolizumab improved EFS in high-risk early-stage TNBC compared to chemotherapy alone (Schmid et al. 2021a) in patients both with and without the presence of lymph nodes (Schmid et al. 2021b).

Additionally, the programmed death-ligand 1 inhibitor durvalumab has been tested in the neoadjuvant setting in 174 patients with TNBC in the Phase II GeparNuevo trial. Patients were randomized to nab-neoadjuvant paclitaxel followed by standard chemotherapy plus either durvalumab or placebo, followed by definitive surgery. The pCR rates were 53.4% (95% CI 42.5% to 61.4%) and 44.2% (95% CI 33.5% to 55.3%) in the durvalumab and placebo arms, respectively, and the difference was not statistically significant (Loibl et al. 2019). Overall, a total of 34 events occurred in 174 patients at a median follow-up of 42.2 months; the 3-year invasive disease-free survival in pCR versus non-pCR patients was 92.0% versus 71.9%. Therefore, this study demonstrated that despite only a modest improvement in pCR, durvalumab significantly improved long-term outcome in this

population (Loibl et al. 2021a).

Historically, neoadjuvant chemotherapy alone in patients with TNBC has shown that pCR is relatively well-correlated with longer-term outcomes such as EFS (Liedtke et al. 2008, Cortazar et al. 2014). However, this correlation between pCR and EFS in patients with TNBC is less clear in the recent studies, such as KEYNOTE-522 and GeparNuevo, where ICIs were added to chemotherapy, perhaps due to an apparent late benefit of the ICI after completion of definitive treatment. Moreover, there are limited data related to the correlation between pCR and EFS or OS when other classes of anticancer agents, such as PARP inhibitors, are used either as monotherapy or in combination with ICIs as neoadjuvant treatments. Therefore, while pCR is a standard and accepted primary endpoint in neoadjuvant breast cancer studies, it requires the additional data provided by long-term follow-up endpoints such as EFS as per standard of care.

Talazoparib is a PARP inhibitor approved as monotherapy treatment for adult patients with g*BRCA1/2*-mutated HER2-negative locally advanced or metastatic breast cancer. A Phase II, non-randomised, single-arm, open-label study (NCT03499353; NEOTALA) evaluated the efficacy and safety of talazoparib in the neoadjuvant setting for patients with early g*BRCA1/2*-mutated HER2-negative breast cancer. The primary endpoint was pCR. The evaluable population consisted of 48 patients with TNBC. Of 45 patients, 22 patients achieved a pCR (45.8%; 95% CI 32.0, 60.6). As long-term outcomes were not reported (Litton et al. 2021), it is not known whether the use of a monotherapy PARP inhibitor as neoadjuvant treatment might be a de-escalation strategy for selected patients in whom traditional chemotherapeutic agents can be omitted altogether.

A growing body of evidence has shown a relationship between PARP inhibitor-induced DNA damage and the immune system, and suggests that PARP inhibitors may trigger an antitumour immune response. It has been demonstrated that olaparib induces in vivo cluster of differentiation (CD)8+ T-cell infiltration and activation, mediated via the cyclic GMP-AMP synthase-stimulator of interferon gene pathway, thus providing a scientific rationale for combining olaparib with immuno-oncology agents for the treatment of TNBC (Pantelidou et al. 2019). Moreover, in a recent Phase I/II study involving patients with advanced g*BRCA*m breast cancer, the administration of durvalumab in combination with olaparib demonstrated encouraging antitumour activity and was well tolerated (Domchek et al. 2020).

The investigation of olaparib as monotherapy or olaparib in combination with durvalumab in patients with early stage *BRCA*m, ER-negative or ER-low, HER2-negative breast cancer who are candidates for neoadjuvant therapy supports the ongoing effort to identify novel agents and new drug combinations that can improve pCR rates and EFS. In patients at a lower risk (T1b-c/N0) of disease recurrence and a higher chance for cure, monotherapy olaparib may provide adequate neoadjuvant treatment. In contrast, monotherapy olaparib may be inadequate neoadjuvant treatment for those patients at a higher risk (T1/N1 or T2/N0) of recurrence, and the addition of an ICI to the neoadjuvant regimen may improve pCR rates and long-term outcomes as was seen in KEYNOTE-522 and GeparNuevo. The risk of irreversible immune-mediated adverse events (AEs) of the endocrine system due to ICI use (Yoest JM 2017) supports the use of ICIs only in the cohort of patients at higher risk for disease recurrence. For both the lower (Cohort A: T1b-c/N0) and higher risk (Cohort B: T1/N1 or T2/N0) groups, the

study intervention has the potential for the development of de-escalation strategies in this disease setting where traditional chemotherapy regimens may be decreased or avoided altogether.

In summary, the investigation proposed in this Phase II study is supported by the following key rationale: (1) pCR rates from the monotherapy talazoparib study that are similar to the pCR rates seen with traditional chemotherapy, (2) the longer term improvements in EFS relative to pCR rates from the KEYNOTE-522 and GeparNuevo studies with the addition of ICIs to neoadjuvant therapy for patients with early stage high-risk breast cancer, and (3) the evidence that PARP inhibitors may trigger an antitumour immune response that render the tumour vulnerable to the combination of a PARP inhibitor with an ICI.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy, measured by pCR rate, of olaparib monotherapy and olaparib plus durvalumab combination therapy, as assessed by central pathology review.	pCR is defined as ypT0/Tis ypN0 (ie, no invasive residual in breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes) following completion of neoadjuvant systemic therapy.
Secondary	
To evaluate the efficacy, measured by pCR rate, of olaparib monotherapy and olaparib plus durvalumab combination therapy as assessed by local pathology review.	pCR is defined as ypT0/Tis ypN0 (ie, no invasive residual in breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes) following completion of neoadjuvant systemic therapy.
To evaluate the efficacy, measured by RCB, of olaparib monotherapy and olaparib plus durvalumab combination therapy as assessed by central pathology review.	RCB is an index value using 6 variables to categorize response in 1 of 4 classes: RCB 0 (pCR), I (minimal RCB), II (moderate RCB), and III (extensive RCB).
To evaluate the efficacy, measured by RCB, of olaparib monotherapy and olaparib plus durvalumab combination therapy as assessed by local pathology review.	RCB is an index value using 6 variables to categorize response in 1 of 4 classes: RCB 0 (pCR), I (minimal RCB), II (moderate RCB), and III (extensive RCB).
To evaluate the efficacy of olaparib monotherapy and olaparib plus durvalumab combination therapy in terms of change from baseline tumour volume. Tumour volume will be assessed by local radiology review.	Percentage change in tumour volume from baseline after 3 and 6 cycles of treatment will be measured using MRI. Baseline is defined as the most recent measurement prior to the first administration of study intervention. Percent change from baseline is defined as: (Difference in value between post-baseline volume and baseline volume) divided by baseline volume and multiplied by 100.

Objectives	Endpoints
To evaluate the efficacy of olaparib monotherapy and olaparib plus durvalumab combination therapy by assessment of EFS.	EFS is defined as time from the first dose of study intervention administration to any of the following events: progression of disease that precludes surgery, local or distant recurrence after surgery, second primary malignancy (breast or other invasive cancers), or death due to any cause.
Safety	
To assess the safety and tolerability profile of olaparib monotherapy and olaparib plus durvalumab combination therapy.	Safety and tolerability will be evaluated in terms of AEs/SAEs, physical examination, vital signs including blood pressure, pulse, heart rate, body temperature, body weight, and height, clinical laboratory assessments including clinical chemistry/haematology parameters, and ECGs. Assessments related to AEs cover: • Occurrence/frequency • Relationship to study intervention as assessed by investigator • CTCAE grade • Seriousness • Death • Discontinuation of study intervention • AESIs • Other significant AEs • Exposure
To assess the safety and tolerability profile of olaparib monotherapy when given as adjuvant therapy to participants who achieve pCR.	

Abbreviations: CCI [redacted]; AE = adverse event; AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Event; ECG = electrocardiogram; EFS = event-free survival; MRI = magnetic resonance imaging; pCR = pathological complete response; RCB = residual cancer burden; SAE = serious adverse event.
Note: Pathological staging following neoadjuvant systemic therapy is recorded using the 'yp' designation.

For tertiary/exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

This is a Phase II multicentre, open-label study to determine the efficacy and safety of olaparib monotherapy and olaparib plus durvalumab combination therapy in participants with primary, operable, ER-negative or ER-low, HER2-negative breast cancer with documented *BRCA*m who are candidates for neoadjuvant therapy. All participants must have a known deleterious or suspected deleterious *BRCA*m determined prior to treatment allocation. Confirmation of eligibility criteria for treatment allocation (see Sections 5.1 and 5.2 for inclusion and exclusion criteria that must be met) will take place within 28 days prior to treatment allocation. Every effort should be made to minimise the time between study intervention allocation and the start of study intervention (ie, within 3 calendar days, maximum of 7 calendar days).

Participants' disease will be defined per the American Joint Committee of Cancer (AJCC) manual for breast cancer (8th edition): primary tumour (T) size of T1 or T2; lymph node (N) status of N0 or N1; and metastasis (M) status of M0 or MX. Throughout this protocol, TNM stages refer to clinical (and not pathological) staging, unless specified otherwise.

The target population of interest in this study is participants with known *BRCA*m, HER2-negative, ER-negative or ER-low, non-metastatic breast cancer. Eligible participants will have small volume disease (T1b-c/N0, T1/N1, or T2/N0). The size of the primary tumour should be >1 mm for participants with N1 status and >5 mm for participants with N0 status.

Cohort	Clinical Disease Staging
A (Lower Risk)	T1b (>5 mm but ≤10 mm), N0 **OR** T1c (>10 mm but ≤20 mm), N0
B (Higher Risk)	T1 (>1 mm but ≤20 mm), N1 **OR** T2 (>20 mm but ≤50 mm), N0.

Participants with primary, early stage, operable, non-metastatic ER-negative or ER-low, HER2-negative breast cancer are required to provide their archival/diagnostic formalin CCI CCI sample, if available. CCI A participant's tumour receptor status for eligibility at screening will be based on local laboratory results. Mandatory CCI will also be collected at definitive surgery. In addition, the collection of optional CCI is strongly recommended at Cycle 2 or Cycle 3 and an optional CCI will be collected at disease recurrence following definitive surgery. Mandatory whole blood samples to extract plasma will be collected for CCI analysis and for other biomarker analysis. CCI will include assessment of the presence of and changes in CCI and its association with measures of pathologic response and clinical outcomes.

Participants will be separated into 2 cohorts (lower risk and higher risk) based on the size of the tumour and the absence or presence of lymph nodes.

The study will enrol the following cohorts:

- **Cohort A** will consist of a **lower-risk** population of participants with HER2-negative, ER-negative or ER-low non-metastatic breast cancer defined as having a tumour size >5 mm and ≤20 mm and N0 (T1b-c/N0). Approximately 25 participants will be enrolled into Cohort A and treated with neoadjuvant olaparib monotherapy for 4 to 6 cycles of 28 days each. Participants will then undergo definitive surgery within 6 weeks following the final dose of neoadjuvant olaparib therapy (or per local standard of care) followed by standard treatment (radiation therapy, systemic therapy per institutional standards). Participants who achieve pCR at surgery, as determined by local pathology assessment, will be allowed to continue treatment with olaparib in the adjuvant setting in lieu of standard adjuvant systemic therapy, per physician choice. If the physician chooses adjuvant olaparib, then the total duration of olaparib therapy in the neoadjuvant and adjuvant setting must not exceed 12 cycles. Adjuvant ET may be co-administered with olaparib in participants with pCR who are ER-low and who continue receiving olaparib in the adjuvant setting, per physician's choice.
- **Cohort B** will consist of a **higher-risk** population of participants with HER2-negative, ER-negative or ER-low non-metastatic breast cancer defined as having a tumour size

of >20 mm but ≤50 mm and N0 (T2/N0), or having a tumour size of >1 mm but ≤20 mm and N1 (T1/N1). Approximately 25 participants will be enrolled into Cohort B and treated with olaparib plus durvalumab combination therapy for 4 to 6 cycles of 28 days each. Participants will then undergo definitive surgery within 6 weeks following the final dose of neodjuvant olaparib therapy (per local standard of care) followed by standard treatment (radiation therapy, systemic therapy per institutional standards). Participants who achieve pCR at surgery, as determined by local pathology assessment, will be allowed to continue treatment with olaparib monotherapy in the adjuvant setting in lieu of standard adjuvant systemic therapy, per physician's choice. If the physician chooses adjuvant olaparib, then the total duration of olaparib therapy in the neoadjuvant and adjuvant setting must not exceed 12 cycles. Adjuvant ET may be co-administered with olaparib in participants with pCR who are ER-low and who continue receiving olaparib in the adjuvant setting, per physician's choice.

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

Without pausing enrolment, data will be assessed for each of Cohorts A and B once [redacted] participants complete neoadjuvant therapy or discontinue treatment for any reason. The review will focus on participants with clinical progression of disease (cPD) defined as "the clear worsening of the patient's clinical status or prognosis in the opinion of the treating clinician, taking into consideration clinical findings, imaging (including, but not limited to, objective imaging response criteria) and laboratory test results" (Saini and Twelves 2021), and including the investigator's decision to change neoadjuvant therapy or proceed to definitive surgery prior to completion of neoadjuvant therapy as a rescue intervention or deaths that occur in the neoadjuvant treatment period. The first [redacted] participants in each cohort who complete neoadjuvant therapy or discontinue treatment for any reason will be included in this assessment.

- If no more than [redacted] of these initial [redacted] participants experience cPD/death, then enrolment in that cohort will continue to ensure a total of approximately 25 participants in that cohort.
- If [redacted] of these initial [redacted] participants experience cPD/death, then enrolment in that cohort will be paused, while data are reviewed for further enrolment.

Definitive surgery, such as breast conservation surgery or mastectomy with or without axillary lymph node dissection, will be performed after a minimum of 4 and up to a maximum of six 28-day cycles.

Disclosure Statement:

This is a Phase II, multicentre, open-label study assessing the efficacy and safety of neoadjuvant olaparib monotherapy and olaparib plus durvalumab combination therapy in participants with ER-negative or ER-low, HER2-negative breast cancer and documented *BRCA*m.

Participant Population:

The target population of interest in this study is participants with documented *BRCA*m, HER2-negative, ER-negative or ER-low, primary, operable, early stage, non-metastatic breast cancer. Participants' disease will be defined per the AJCC manual for breast cancer (8th edition): primary tumour (T) size >5 mm and ≤50 mm; lymph node (N) status of N0 or N1; and metastasis (M) status of M0 or MX. Participants will be separated into the following cohorts: Cohort A consisting of a lower-risk population defined as having a tumour size of >5 mm and ≤20 mm and TNM nodal status of N0 (T1b-c/N0); and Cohort B consisting of a higher-risk population defined as having a tumour size of >20 mm but ≤50 mm and a TNM nodal status of N0 (T2/N0) or having a tumour size of >1 mm but ≤20 mm and a TNM nodal status of N1 (T1/N1).

Number of Participants:

Participants will be recruited from approximately 65 sites in 10 countries.

In Cohort A, approximately 25 lower-risk (based on tumour size and lymph node status as defined above) participants with documented *BRCA*m, ER-negative/ER-low, and HER2-negative early breast cancer will be recruited in the study and be allocated to receive treatment with olaparib monotherapy for 4 to 6 cycles of 28 days each.

In Cohort B, approximately 25 higher-risk (based on tumour size and lymph node status as defined above) participants with documented *BRCA*m, ER-negative/ER-low, and HER2-negative early breast cancer will be recruited in the study and be allocated to receive treatment with olaparib plus durvalumab combination therapy for 4 to 6 cycles of 28 days each.

Additional participants may be enrolled to ensure approximately 25 participants evaluable for pCR analysis are obtained in both Cohorts A and B.

The redacted *BRCA* status report from the local laboratory will be reviewed by the study physician prior to enrolment of the participant to confirm the presence of a deleterious or suspected deleterious mutation.

Intervention Groups and Duration:

Participants will be allocated to receive [redacted] mg oral olaparib twice daily as monotherapy or in combination with durvalumab 1500 mg via intravenous infusion every 4 weeks for a minimum of 4 and a maximum of six 28-day cycles before undergoing definitive surgery. Each participant will undergo definitive surgery within 6 weeks after receiving the final dose of neoadjuvant olaparib therapy (or per local standard of care), followed by standard treatment (radiation therapy, systemic therapy per institutional standards). Participants who achieve pCR at surgery, as determined by local pathology assessment, will be allowed to continue on treatment with olaparib in the adjuvant setting in lieu of standard adjuvant systemic therapy, per physician's choice. If the physician chooses adjuvant olaparib, then the total duration of olaparib therapy in the neoadjuvant and adjuvant setting must not exceed 12 cycles. Adjuvant ET may be co-administered with olaparib in participants with pCR who are ER-low and who continue receiving olaparib in the adjuvant setting, per physician's choice.

Follow-up of Participants after Discontinuation of Study Intervention:

After study intervention discontinuation, all participants will undergo an End of Treatment Visit (within 7 days of permanent discontinuation of study intervention) and will be followed up for safety assessments 30 days (+7 days) after their last dose of olaparib. Participants receiving olaparib and durvalumab in combination will also undergo an additional safety follow-up visit 90 days (+7 days) after their last dose of durvalumab.

After the safety follow-up period, participants will be followed for disease recurrence and survival, per the Schedule of Activities (Table 1). Where feasible, blood samples for CCI analyses will be collected at disease recurrence and during survival follow-up.

See Section 6.7 for a description of assessments following study data cutoff.

Independent Data Monitoring Committee:

This study will not use an Independent Data Monitoring Committee. A steering committee comprised of Principal Investigators for Study D931CC00001 and members of the AstraZeneca olaparib and durvalumab development programs will convene to review efficacy and safety data at time point(s) to be defined in a separate charter.

Statistical Methods:

In Cohort A, approximately 25 lower-risk participants will receive olaparib monotherapy. In Cohort B, approximately 25 higher-risk participants will receive olaparib plus durvalumab combination therapy.

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

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

The primary statistical analysis in the FAS will assess pCR rate according to central pathology assessment. A sample size of approximately 25 participants was chosen for each cohort to ensure adequate precision in the estimate of pCR rate by assessing the width of the 95% CI. An estimate of the pCR rate and its 95% exact CI will be calculated in the FAS for Cohorts A and B, separately.

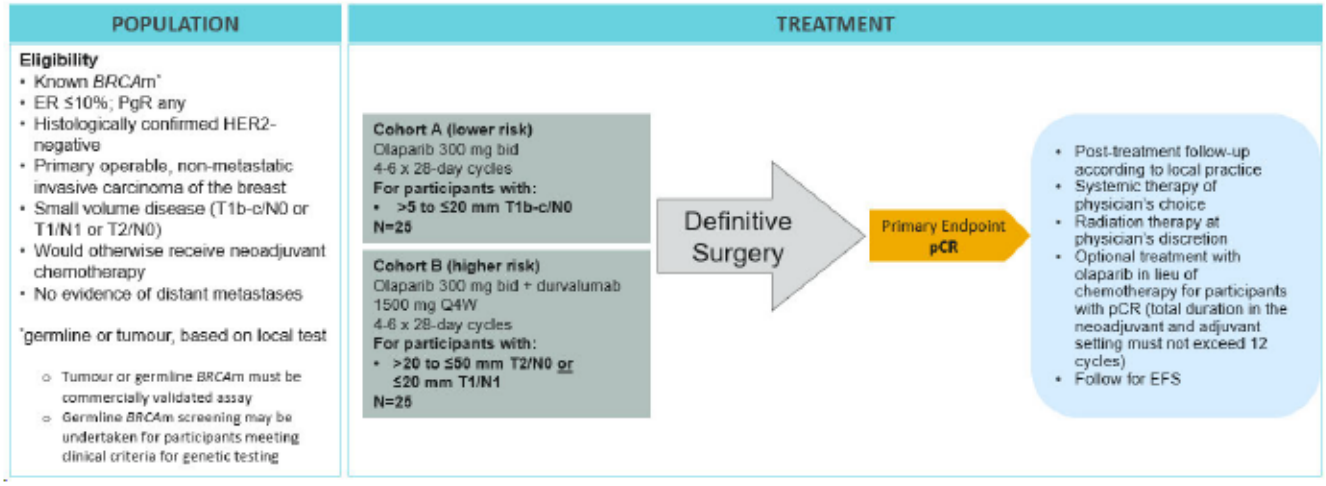
Secondary analysis of pCR will be assessed locally and will be analysed using the same methodology specified for the primary endpoint. Residual cancer burden (evaluated via central and local pathology assessment) and tumour volume change from baseline will be summarised for each cohort. Event-free survival (defined as the time from the date of first dose of study intervention administration to the date of progression of disease that precludes surgery, local or distant recurrence, second primary malignancy [breast or other invasive cancers], or death due to any cause) will also be assessed.

When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all participants who received at least one dose of study intervention (olaparib or durvalumab). The safety data will be summarised descriptively and will not be formally tested unless otherwise specified.

Appropriate summaries of exploratory outcome variables (including biomarkers) will be produced, and data listings will be presented for each cohort. Graphical methods will be widely used in exploring the characteristics and relationships of outcome variables.

1.2 Schema

Figure 1 Study Design



Abbreviations: BID = twice daily; EFS = event-free survival; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; pCR = pathological complete response; PgR = progesterone receptor; Q4W = every 4 weeks.

1.3 Schedule of Activities

The procedures for this study are presented in the SoA (Table 1).

Table 1 Schedule of Activities

Procedure	Screening	Neoadjuvant Intervention Period (treatment visits every 4 weeks)[a]						Post-Neoadjuvant Safety Assessment[c]		Definitive Surgery		Adjuvant Olaparib Intervention Period (for participants achieving pCR)[a]	EOT Visit	Post-intervention Follow-up Period			Details in CSP Section or Appendix
														Safety Follow-up	Survival Follow-up		
															Up to 2 Years	Year 3	
		C1	C2	C3	C4[b]	C5[b]	C6[b]			Pre-	Post-						
Visit	1	2	3	4	5	6	7	30 days after last dose of olaparib	90 days after last dose of durvalumab			Every 28 days up to a total of 12 cycles	At permanent discontinuation of study intervention	30 days after last dose of olaparib	Every 3 months from EOT Visit	Every 6 months from EOT Visit	
Day	-28 to -1	1	Every 28 days														
Window (Days)	NA	+3	±3	±3	±3	±3	±3	+7	+7	-7		±7	+ 7	+7	±14	±14	
Informed consent: main study and mandatory exploratory biomarker[d] *(All participants)*	X																Section 5.1 and Appendix A 3
Informed consent: [redacted] sample and analysis (optional)	X																Sections 5.1, 8.7, and Appendix A 3
Inclusion and exclusion criteria	X	X															Sections 5.1 and 5.2
Demography	X																Section 5.1
Full physical examination	X	X[e]															Section 8.2.1

Procedure	Screening	Neoadjuvant Intervention Period (treatment visits every 4 weeks)[a]						Post-Neoadjuvant Safety Assessment[c]		Definitive Surgery		Adjuvant Olaparib Intervention Period (for participants achieving pCR)[a]	EOT Visit	Post-intervention Follow-up Period			Details in CSP Section or Appendix
														Safety Follow-up	Survival Follow-up		
															Up to 2 Years	Year 3	
		C1	C2	C3	C4[b]	C5[b]	C6[b]			Pre-	Post-						
Visit	1	2	3	4	5	6	7	30 days after last dose of olaparib	90 days after last dose of durvalumab			Every 28 days up to a total of 12 cycles	At permanent discontinuation of study intervention	30 days after last dose of olaparib	Every 3 months from EOT Visit	Every 6 months from EOT Visit	
Day	-28 to -1	1	Every 28 days														
Window (Days)	NA	+3	±3	±3	±3	±3	±3	+7	+7	-7		±7	+ 7	+7	±14	±14	
Targeted physical examination[f]			X	X	X	X	X	X	X			X	X	X			Section 8.2.1
Height	X																Section 8.2.1
Weight	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]			X[e]	X[e]	X[e]			Section 8.2.1
Family history of cancer	X																
Past and current medical conditions	X	X[h]															Sections 5.1 and 5.2
CCI status (if local testing results available)	X																Section 8.6.1
ECOG performance status	X	X[a]	X	X	X	X	X	X	X			X	X	X			Section 8.2.5.4
Serum or urine pregnancy test (WOCBP only)	X	X	X	X	X	X	X	X	X			X	X	X			Sections 5.1, 5.2, and 8.2.4

Procedure	Screening	Neoadjuvant Intervention Period (treatment visits every 4 weeks)[a]						Post-Neoadjuvant Safety Assessment[c]		Definitive Surgery		Adjuvant Olaparib Intervention Period (for participants achieving pCR)[a]	EOT Visit	Post-intervention Follow-up Period			Details in CSP Section or Appendix
														Safety Follow-up	Survival Follow-up		
															Up to 2 Years	Year 3	
		C1	C2	C3	C4[b]	C5[b]	C6[b]			Pre-	Post-						
Visit	1	2	3	4	5	6	7	30 days after last dose of olaparib	90 days after last dose of durvalumab			Every 28 days up to a total of 12 cycles	At permanent discontinuation of study intervention	30 days after last dose of olaparib	Every 3 months from EOT Visit	Every 6 months from EOT Visit	
Day	-28 to -1	1	Every 28 days														
Window (Days)	NA	+3	±3	±3	±3	±3	±3	+7	+7	-7		±7	+ 7	+7	±14	±14	
Hepatitis B and C screening (only if previously had hepatitis B or C positive test or suspect hepatitis at screening) and HIV screening	X																Section 5.2
Clinical safety laboratory assessments (clinical chemistry, haematology, urinalysis, INR)[j]	X[j]	X[e]	X	X	X	X	X	X	X			X[k]	X	X			Sections 6.6.1.1, 8.2.4, and 8.2.5.1
12-lead ECG (durvalumab participants only)[l]	X	As clinically indicated						X	X								Section 8.2.3
Vital signs (temperature, blood pressure, respiratory rate, and pulse)	X	X[m]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]	X[z]			X[z]	X[z]	X[z]			Section 8.2.2
Surgical Assessment	X																Section 8.1.1
Treatment allocation		X[a]															Section 6.3
[redacted] sample[o]	X																Section 8.6.1

Procedure	Screening	Neoadjuvant Intervention Period (treatment visits every 4 weeks)[a]						Post-Neoadjuvant Safety Assessment[c]		Definitive Surgery		Adjuvant Olaparib Intervention Period (for participants achieving pCR)[a]	EOT Visit	Post-intervention Follow-up Period			Details in CSP Section or Appendix
														Safety Follow-up	Survival Follow-up		
															Up to 2 Years	Year 3	
		C1	C2	C3	C4[b]	C5[b]	C6[b]			Pre-	Post-						
Visit	1	2	3	4	5	6	7	30 days after last dose of olaparib	90 days after last dose of durvalumab			Every 28 days up to a total of 12 cycles	At permanent discontinuation of study intervention	30 days after last dose of olaparib	Every 3 months from EOT Visit	Every 6 months from EOT Visit	
Day	-28 to -1	1	Every 28 days														
Window (Days)	NA	+3	±3	±3	±3	±3	±3	+7	+7	-7		±7	+ 7	+7	±14	±14	
Mandatory pre-treatment [redacted]	X																Section 8.6.1
Mandatory [redacted] sample for [redacted] analysis[q]										X							Section 8.6.1
Mandatory [redacted] for residual disease[r]		←═══════════→															Section 8.6.1
Optional [redacted] on-treatment[s]			X														Section 8.6.1
Mandatory [redacted] sample for central pathology review of residual disease and pCR assessment[t]										X							Sections 8.1.2.1, 8.1.2.2, and 8.1.2.3
Optional [redacted] at disease recurrence[s]												←═══════════→					Section 8.6.1
Blood sample for retrospective *BRCA*m confirmation		X															Section 8.6.1

Procedure	Screening	Neoadjuvant Intervention Period (treatment visits every 4 weeks)[a]						Post-Neoadjuvant Safety Assessment[c]		Definitive Surgery		Adjuvant Olaparib Intervention Period (for participants achieving pCR)[a]	EOT Visit	Post-intervention Follow-up Period			Details in CSP Section or Appendix
														Safety Follow-up	Survival Follow-up		
															Up to 2 Years	Year 3	
		C1	C2	C3	C4[b]	C5[b]	C6[b]			Pre-	Post-						
Visit	1	2	3	4	5	6	7	30 days after last dose of olaparib	90 days after last dose of durvalumab			Every 28 days up to a total of 12 cycles	At permanent discontinuation of study intervention	30 days after last dose of olaparib	Every 3 months from EOT Visit	Every 6 months from EOT Visit	
Day	-28 to -1	1	Every 28 days														
Window (Days)	NA	+3	±3	±3	±3	±3	±3	+7	+7	-7		±7	+ 7	+7	±14	±14	
Blood samples for CCI CCI analysis	X	X (pre-dose)	X	X	X	X	X	X[n]	X	X[n]							Section 8.6.2
CCI samples and completion of CCI CCI (WOCBP only)[v]	X							X							X (only at 2 years)		Section 8.6.2
Blood samples for CCI CCI	X	X (pre-dose)	X	X	X	X	X	X[n]	X	X[n]							Section 8.6.2
Blood sample for CCI CCI (collect on Day 1 of each cycle)[w]	X	X (pre-dose)	X	X	X	X	X			X	X[w]	X			X	X	Section 8.6.2
Blood for CCI CCI	X	X (pre-dose)	X	X	X	X	X	X[n]	X	X[n]							Section 8.6.2
Blood sample for CCI CCI testing– Cohort B[x]		X (pre-dose)	X	X					X				X				Section 8.5.2

Procedure	Screening	Neoadjuvant Intervention Period (treatment visits every 4 weeks)[a]						Post-Neoadjuvant Safety Assessment[c]		Definitive Surgery		Adjuvant Olaparib Intervention Period (for participants achieving pCR)[a]	EOT Visit	Post-intervention Follow-up Period			Details in CSP Section or Appendix
														Safety Follow-up	Survival Follow-up		
															Up to 2 Years	Year 3	
		C1	C2	C3	C4[b]	C5[b]	C6[b]			Pre-	Post-						
Visit	1	2	3	4	5	6	7	30 days after last dose of olaparib	90 days after last dose of durvalumab			Every 28 days up to a total of 12 cycles	At permanent discontinuation of study intervention	30 days after last dose of olaparib	Every 3 months from EOT Visit	Every 6 months from EOT Visit	
Day	-28 to -1	1	Every 28 days														
Window (Days)	NA	+3	±3	±3	±3	±3	±3	+7	+7	-7		±7	+ 7	+7	±14	±14	
CCI CCI exploratory CCI sample[y]		X															Section 8.7 and Appendix D
AE	X	←——											→[z]	X[z]	X[aa]		Section 8.3
Concomitant medications (including blood transfusions)	X[bb]	←——						X	X			X	X	X			Section 6.5
Definitive surgery										X							Section 8.1.2
Local pathologic assessment										X[cc]							Section 8.1.2
Documentation of subsequent anticancer therapy following discontinuation of study intervention and/or surgery (systemic/radiation/endocrine therapy)[dd]								X	X					X	X	X	

Procedure	Screening	Neoadjuvant Intervention Period (treatment visits every 4 weeks)[a]						Post-Neoadjuvant Safety Assessment[c]		Definitive Surgery		Adjuvant Olaparib Intervention Period (for participants achieving pCR)[a]	EOT Visit	Post-intervention Follow-up Period			Details in CSP Section or Appendix
														Safety Follow-up	Survival Follow-up		
															Up to 2 Years	Year 3	
		C1	C2	C3	C4[b]	C5[b]	C6[b]			Pre-	Post-						
Visit	1	2	3	4	5	6	7	30 days after last dose of olaparib	90 days after last dose of durvalumab			Every 28 days up to a total of 12 cycles	At permanent discontinuation of study intervention	30 days after last dose of olaparib	Every 3 months from EOT Visit	Every 6 months from EOT Visit	
Day	-28 to -1	1	Every 28 days														
Window (Days)	NA	+3	±3	±3	±3	±3	±3	+7	+7	-7		±7	+ 7	+7	±14	±14	
Tumour size imaging (MRI of breast)[ee]	X				X					X (pre-operative)[ff]							Section 8.1.3
Olaparib dispensed (daily dosing)[gg]		X	X	X	X	X	X					X					Section 6.2
Durvalumab administered (IV infusion)		X[hh]	X[ii]	X[ii]	X[ii]	X[ii]	X[ii]										Sections 6.2.2, 8.2.2.1, 8.2.2.2
Study intervention returned/compliance check			X	X	X	X	X	X				X	X				Section 6.4
EFS/RFI															X	X	Sections 8.1.5, 8.1.6
Survival status															X	X	Sections 8.1.5, 8.1.6

Abbreviations: AE = adverse event; AML = acute myeloid leukaemia; BID = twice daily; C = cycle; CRF = Case Report Form; CSP = clinical study protocol; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EFS = event-free survival; EOT = End of Treatment; CCI [redacted]; HIV = human immunodeficiency virus; INR = international normalised ratio; IV = intravenous; MDS = myelodysplastic syndrome; MRI = magnetic resonance imaging; pCR = pathological complete response; CCI [redacted] RFI = recurrence-free interval; SAE = serious adverse event; WOCBP = women of childbearing potential.

Note: If there is a dosing delay during the treatment schedule, the subsequent time between 2 consecutive doses of durvalumab cannot be less than 21 days (olaparib administration may continue as scheduled if durvalumab is delayed).

[a] All assessments on treatment days are to be performed prior to study intervention administration, unless otherwise indicated.

[b] Participants will receive four to six 28-day cycles prior to definitive surgery. A decision for earlier study intervention discontinuation may be made by the investigator based on disease progression.

[c] For participants in Cohort A, the Post-Neoadjuvant Safety Assessment will be conducted 30 days (+7 days) after the last dose of olaparib. For participants in Cohort B, the Post-Neoadjuvant Safety Assessment will be conducted 30 days (+7 days) after the last dose of olaparib and 90 days (+7 days) after the last dose of durvalumab.

[d] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. Exploratory biomarker research is a mandatory element of the study and is discussed within the main informed consent form.

[e] If screening assessments have been performed within 7 days prior to starting study intervention, they do not have to be repeated at C1D1 if the participant's condition has not changed. Please refer to Sections 6.2.2, 8.2.2.1, and 8.2.2.2 for further details.

[f] Targeted physical examination – clinically directed based on signs and symptoms. The examination will include, at a minimum, assessments of the breast, skin, lungs, cardiovascular system, and abdomen (liver and spleen). If clinically significant changes are found, they should be recorded as AEs.

[g] **For Cohort A:** Weight, blood pressure, and pulse measurements will not be recorded in the eCRF after C1D1. If a change in any of those values are clinically significant, it should be entered as an AE in the AE eCRF. Only body temperature will be recorded in the Vital Signs CRF after C1D1. **For Cohort B:** Starting at C2D1, blood pressure, pulse, and weight should be measured, collected/recorded in the eCRF prior to the start of the infusion. If no infusion reaction occurred with the initial infusion of durvalumab, and at the discretion of the investigator, the 1-hour observation period may be shortened or eliminated. Weight, blood pressure, and pulse measurements will not be recorded thereafter in the Vital Signs CRF during olaparib adjuvant treatment, if applicable, for Cohort B.

[h] Ensure that all medical conditions present up until just prior to the participant starting study intervention on C1D1 are entered into the Medical History eCRF.

[i] For a list of all required laboratory tests, please refer to Section 8.2.4. ONLY for participants who are taking warfarin–- INR test should be performed at screening and if clinically indicated. See Section 8.2.5.1.

[j] Cohort B participants must have reticulocyte count performed at screening and as clinically indicated if participant experiences CTCAE grade ≥ 3 anaemia and requires a transfusion (reticulocyte count must be performed PRIOR to the transfusion). Please refer to Table 6.

[k] Clinical chemistry and haematology at start of Adjuvant Olaparib Intervention Period must meet Inclusion Criterion #5, as specified in Section 5.1.

[l] Whenever ECG, vital signs, and blood draws are scheduled on the same day, the assessments should occur in the following order: ECG, vital signs, and then blood draws.

[m] For participants receiving durvalumab (Cohort B), a 1-hour observation period is recommended where blood pressure and pulse must be taken (lying or standing) before, during (ie, after 30 minutes of infusion), and after the first infusion.

[n] Every effort should be made to minimise the time between study intervention allocation and the start of study intervention (ie, within 3 calendar days, maximum of 7 calendar days).

[o] CCI should be provided if available. Sample required only for participants allocated to receive treatment. Confirmation required in clinical notes regarding availability of sample during the screening period; however, sample will only be submitted to the Central Laboratory once the participant has been assigned treatment. CCI are preferred but slides will be accepted.

[p] Pre-treatment CCI samples should be collected as CCI (Section 8.6.1; details provided in the Laboratory Manual). For participants with T1b/N0 disease who have insufficient CCI, the CCI may be omitted but provision of their CCI sample will be mandated. When collection of the CCI is deemed not medically feasible, please consult the sponsor. *Note: A clip should be placed in the* CCI. *If a clip was not placed at the time of the* CCI, *then one should be placed at the time of the Cycle 2 or Cycle 3 optional* CCI.

[q] Mandatory post-neoadjuvant treatment CCI sample will be collected at time of definitive surgery for biomarker analysis. CCI samples should be collected as CCI (Section 8.6.1; details provided in the Laboratory Manual).

[r] If, after exposure to olaparib monotherapy therapy (in Cohort A) or olaparib plus durvalumab combination therapy (in Cohort B), the participant does not undergo surgery because the investigator believes (on the basis of clinical and/or imaging findings) that there is the likelihood of residual disease and plans to give additional non-protocol therapy (eg, chemotherapy), an additional on-treatment CCI must be performed and assessed to confirm the presence or absence of residual disease. This is a clinical diagnostic CCI (not a research CCI and must be read by the local pathologist. Blocks from this CCI will be submitted as CCI for research purposes after being used for clinical decision-making.

[s] On-treatment CCI collection is strongly recommended at Cycle 2 or Cycle 3. An optional CCI may be collected at CCI samples should be collected as CCI (Section 8.6.1; details provided in the Laboratory Manual).

[t] Mandatory post-neoadjuvant treatment CCI sample will be collected at time of definitive surgery for central pathology review and pCR assessment. CCI samples should be provided as H & E-stained slides, including margins, lymph nodes, and breast tumour (Section 8.6.1; additional details provided in the Manual for Processing Tissue Specimens for Central Pathology and CCI Research).

[u] In cases where the Post-Neoadjuvant Safety Assessment Visit 30 days after the last dose of olaparib is the same date as the Pre-Definitive Surgery Visit, only 1 set of blood samples for the tests indicated by this footnote is needed and the tubes should be labelled using the applicable labels for the Pre-Definitive Surgery Visit.

[v] CCI samples are to be collected and the CCI eCRF is to be completed in premenopausal women at screening, after completion of the Neoadjuvant Treatment Period but prior to definitive surgery (ie, at the 30-day safety follow-up), and at the 2-year survival follow-up visit.

[w] For each visit at baseline and the first 3 cycles, 4 samples will be collected for CCI (total volume of 40 mL). For each of the following visits prior to surgery, 2 samples (total volume of 20 mL) will be collected. Samples for CCI should be also collected prior to surgery, at the first post-surgical visit (approximately 2 to 4 weeks after surgery), at Day 1 of all adjuvant treatment cycles (if applicable), at disease progression or recurrence at any time, and during survival follow-up.

[x] CCI samples are collected pre-dose at Cycle 1 (+3 days), Cycle 2 (±3 days), and Cycle 3 (±3 days), 90 days (3 months) (+7 days) after treatment with CCI ends, and at the End of Treatment visit (+7 days). If the blood is drawn on the day of a CCI, the blood draw should occur within 60 minutes prior to the CCI.

[y] The sample for CCI will be obtained at Day 1 pre-dose. If, for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per participant for CCI during the study.

[z] All ongoing AEs/SAEs and any new AEs/SAEs identified during the 30 calendar days (olaparib) or 90 calendar days (durvalumab) follow-up period after the last dose of study medication must be followed to resolution unless the event is considered by the investigator to be unlikely to resolve, or the participant is lost to follow-up.

[aa] Any SAE of MDS/AML or new primary malignancy occurring after the 30-day (olaparib) or 90-day (durvalumab) safety follow-up period should be reported to AstraZeneca Patient Safety regardless of the investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked if the participant has developed MDS/AML or a new primary malignancy during the survival follow-up and prompted to report any such cases.

[bb] Record blood transfusions within 120 days prior to start of study treatment and the reasons for the transfusions (eg, bleeding or myelosuppression).

[cc] Parameters required to determine residual cancer burden should be included on the pathology report (Appendix J).

[dd] Include all anticancer treatments (including, but not limited to, surgery, chemotherapy, radiation, endocrine therapy, and targeted agents) and the investigator's opinion of response to them.

[ee] Breast MRI must be performed at baseline, prior to the start of Cycle 4 (Week 12 [±7 days]), and pre-operatively (Week 24 [±7 days]). Additional tumour volume imaging (MRI or ultrasound) may be performed if disease progression is suspected. If any suspicious nodes are seen on breast MRI, then axillary ultrasound must be done. *Note: Sentinel nodes confirmed as suspicious by ultrasound at baseline should be clipped (only 1 node is recommended if several are identified). If a clip is not placed at this time, use dual tracers (radioisotope and blue dye) to identify sentinel nodes at the time of surgery.*

[ff] If MRI has been performed at Week 12 (ie, start of Cycle 4) and the participant proceeds to definitive surgery following Cycle 4 or Cycle 5, the MRI scan does not need to be repeated for the pre-operative assessment (Week 24), unless clinically indicated. Participants who discontinue neoadjuvant study intervention to receive additional non-protocol treatment prior to definitive surgery do not need to undergo subsequent MRIs (Section 8.1.3).

[gg] Sufficient study treatment should be dispensed for at least each treatment cycle plus overage.

[hh] Participants will be monitored and vital signs collected/recorded in the eCRF prior to, during, and after infusion of durvalumab, as per Section 8.2.2.1, within approximately 30 minutes prior to the infusion start, at approximately 30 minutes after the start of infusion, and at end of infusion (approximately 60 minutes ±10 minutes).

[ii] Participants should be carefully monitored. Blood pressure, pulse, and other vital signs should be measured during and after infusions, as per institution standards and as clinically indicated. If no infusion reaction occurred with the C1D1 infusion, and at the discretion of the investigator, the 1-hour observation period may be shortened or eliminated. For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

2 INTRODUCTION

2.1 Study Rationale

The investigation of olaparib as monotherapy or olaparib in combination with durvalumab in patients with early stage *BRCA*m, oestrogen receptor (ER)-negative or ER-low, human epidermal growth factor receptor 2 (HER2)-negative breast cancer who are candidates for neoadjuvant therapy supports the ongoing effort to identify novel agents and new drug combinations that can improve pathological complete response (pCR) rates and event-free survival (EFS). In patients at a lower risk (T1b-c/N0) of disease recurrence and a higher chance for cure, monotherapy olaparib may provide adequate neoadjuvant treatment. In contrast, monotherapy olaparib may be inadequate neoadjuvant treatment for those patients at a higher risk (T2/N0 or T1/N1) of recurrence, and the addition of an immune checkpoint inhibitor (ICI) to the neoadjuvant regimen may improve long-term outcomes, as was seen in KEYNOTE-522 (Schmid et al. 2021a, Schmid et al. 2021b) and GeparNuevo (Loibl et al. 2021a). However, the risk of irreversible immune-mediated adverse events (AEs) of the endocrine system due to ICI use (Yoest JM 2017) supports the use of ICIs only in the cohort of patients at higher risk for disease recurrence. For both the lower and higher risk groups, the study treatments have the potential for the development of deescalation strategies in this disease setting where traditional chemotherapy regimens may be avoided altogether.

2.2 Background

A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of olaparib and durvalumab is provided in the respective Investigator's Brochure (IB) for each compound.

2.2.1 Breast Cancer

Among women, breast cancer is the most commonly diagnosed malignancy and the second leading cause of cancer death. In 2020, an estimated 279,100 new cases of invasive breast cancer were expected to be diagnosed among United States (US) women, and approximately 42,690 women were expected to die from breast cancer (American Cancer Society 2020). In the European Union (EU), a total of 409,920 new female breast cancer cases was estimated to occur in 2018 (Dafni et al. 2019).

Approximately 3% of breast cancers are associated with a mutation in the *BRCA1* gene and approximately 2% are associated with the *BRCA2* gene. In breast cancer, there are differences between *BRCA1* and *BRCA2* mutation carriers in terms of ER/progesterone receptor (PgR)/HER2 expression. Approximately 70% of breast cancer patients with *BRCA1* mutations present with triple negative breast cancer (TNBC). In contrast, patients carrying mutations in the *BRCA2* gene are more likely to have ER-positive breast cancer, with only about 20% developing TNBC (Mavaddat et al. 2012).

Although there are phenotypic differences in breast cancers resulting from *BRCA1* or *BRCA2* mutations, their important commonality is that mutations in either gene result in tumours that are deficient in homologous recombination, making both appropriate for treatment with polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors whereby the process of synthetic lethality can be exploited. In a previous AstraZeneca

sponsored Phase II proof of concept study (Study D0810C00008) in patients with breast cancer carrying *BRCA* mutations, approximately 60% of participants had *BRCA*1 mutations, while the remaining 40% had *BRCA*2 mutations; overall, 55% of participants had TNBC. Anti-tumour activity with olaparib was seen in patients with either *BRCA1* or *BRCA2* mutations (Tutt et al. 2010).

Given the small size of the *BRCA*-mutated subpopulation in breast cancer, information comparing the outcome from this subpopulation with the overall breast cancer population is based on reports from a number of small studies (Robson et al. 2004, Rennert et al. 2007, Bordeleau et al. 2011, Goodwin et al. 2012) and firm conclusions cannot be drawn. The overall body of evidence suggests that once baseline prognostic factors (such as hormone receptor [HR] and HER2 status) and treatment are taken into account, patients with *BRCA* mutations have a similar outcome to their counterparts with *BRCA* wild type status (Huzarski et al. 2013). This is in contrast to patients with *BRCA1*/*BRCA2*-related ovarian cancer who have an improved survival compared with non-carriers, particularly if they receive platinum-based therapy.

2.2.2 Triple Negative and ER-low Breast Cancer and Neoadjuvant Treatment

TNBC is a particular subset of breast cancer defined by lack of immunohistochemical expression of ER, PgR, and HER2 (immunohistochemistry [IHC] 0, 1+ or 2+ /fluorescent in situ hybridization non-amplified) and represents approximately 12% to 17% of breast cancers overall (Foulkes et al. 2010). Although it is a heterogeneous group, patients with TNBC have generally poor prognosis (Metzger-Filho et al. 2012). The fundamental clinical characteristic of TNBC is early recurrence with likely early visceral metastases, as well as a shorter period from time to recurrence to death as compared with other breast cancer types (Dent et al. 2007). Chemotherapy remains the ultimate treatment option for these patients, with varied impact on long-term prognosis. The use of endocrine treatment and anti-HER2 treatments has significantly improved the clinical outcomes in ER/PgR-positive and HER2-positive breast cancer patients, respectively, but patients with TNBC do not benefit from these therapies due to lacking the relevant therapy targets. A Trop-2 targeting antibody drug conjugate has recently been approved for use in patients with advanced TNBC (Bardia et al. 2019). The standard clinical practice for early stage TNBC following completion of definitive local and systemic chemotherapy treatment is observation. Patients with TNBC have a poor prognosis and limited treatment options, and they represent an unmet need for targeted treatment development.

It is assumed that approximately a third to half of the patients with TNBC will receive chemotherapy in the neoadjuvant setting. The key prognostic information following neoadjuvant chemotherapy is whether patients have residual disease or have had a pCR (defined by the absence of any residual invasive cancer on haematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes [including isolated tumour cells found in axillary nodes by haematoxylin and eosin or IHC staining if performed]). Patients who achieve pCR following neoadjuvant chemotherapy have significant improvement in both disease-free survival (hazard ratio 0.48, 95% confidence interval [CI]: 0.37-0.63) and overall survival (hazard ratio 0.48, 95% CI: 0.33-0.69) compared with patients with residual invasive disease (Mieog et al. 2007). An M.D. Anderson, single institution

experience reported 46% pCR rate achieved in a small number of *BRCA1*-mutated (n=57) breast cancer patients following anthracycline/taxane neoadjuvant chemotherapy (Arun et al. 2011). In TNBC, the prognosis of patients who experience pCR is very similar to that for patients with other breast cancer subtypes, with less than 10% developing a distant recurrence at 5 years. However, those patients with TNBC who do not experience pCR have a much poorer prognosis (Liedtke et al. 2008, Cortazar et al. 2014). A meta-analysis of anthracycline and taxane containing neoadjuvant chemotherapy trials showed that of 911 patients with TNBC, 282 patients (31%) experienced a pCR (Von Minckwitz 2012). Compared with these patients, patients who did not experience a pCR were at higher risk of earlier recurrence over time (hazard ratio 6.02, 95% CI: 3.92-9.25) and at higher risk of earlier death over time (hazard ratio 12.41, 95% CI: 5.82-26.49). The findings that the pCR is correlated with survival have led to increased efforts in identifying new drugs and drug combinations that can deliver higher pCR in TNBC. While neoadjuvant chemotherapy alone in patients with TNBC has historically shown that, on an individual patient level, pCR is relatively well-correlated with longer-term outcomes such as EFS (Liedtke et al. 2008, Cortazar et al. 2014), this correlation between pCR and EFS in patients with TNBC has been less clear in recent studies, such as KEYNOTE-522 (Schmid et al. 2021a) and GeparNuevo (Loibl et al. 2021a). In these studies, the addition of ICIs to chemotherapy seemed to demonstrate a greater improvement in long-term outcomes independent of the improvement in pCR, perhaps due to an apparent late benefit of the ICI after completion of definitive treatment. Moreover, there are limited data related to the correlation between pCR and EFS or overall survival (OS) when other classes of anticancer agents, such as PARP inhibitors, are used either as monotherapy or in combination with ICIs as neoadjuvant treatments. A Phase II, non-randomised, single-arm, open-label study evaluated the efficacy and safety of the PARP inhibitor talazoparib in the neoadjuvant setting for patients with early g*BRCA1/2*m HER2-negative breast cancer. The evaluable population for the primary endpoint of pCR consisted of 48 patients with TNBC. Of 45 patients, 22 achieved a pCR (45.8%; 95% CI 32.0, 60.6). Long-term outcomes were not reported and, therefore, it is not yet known whether the use of a monotherapy PARP inhibitor as neoadjuvant treatment might be a de-escalation strategy for selected patients (Litton et al. 2021).

There are emerging data to demonstrate that patients with breast cancer that have a low expression of ER derive limited benefit from endocrine therapy (ET) and are biologically similar to TNBC (Landmann et al. 2018). The American Society of Clinical Oncology (ASCO)-College of American Pathologists (CAP) guidelines were recently updated to create a new category of ER-low (ie, 1% to 10% staining) breast cancer (Allison et al. 2020). Additionally, there is controversy about the very existence of breast cancers with ER-negative/PgR-positive receptor status (De Maeyer et al. 2008). A series of 5993 cases of breast cancer found no ER-negative/PgR-positive tumours (Nadji et al. 2005). In a cross neoadjuvant clinical trial comparison of HER2-negative breast cancer patients with negative, low, or strong HR expression, low HR-positive, HER2-negative tumours had a similar clinical behaviour to TNBC showing high pCR rates and poor survival and also a basal-like gene expression signature, suggesting that patients with low HR-positive tumours should be regarded as candidates for therapy strategies that target TNBC (Villegas SL et al. 2021). Another population-based 15-year study of a cohort of 38,560 women diagnosed with early invasive breast cancer compared patient characteristics and outcomes of HR-low positive

tumours with HR-negative and HR-strongly positive tumours. The study concluded that patients with HR-low positive/HER2-negative tumours and HR-negative/HER2-negative tumours showed a similar prognosis and, as such, patients with HR-low positive/HER2-negative tumours could be regarded as and treated similarly to patients with TNBC (Schrodi S et al. 2021). However, recently available data suggest that HR-low patients constitute only a small minority of the g*BRCA*m, HER2-negative, newly diagnosed early breast cancer population. The randomised Phase II study of neoadjuvant cisplatin versus doxorubicin and cyclophosphamide in patients with g*BRCA*m HER2-negative breast cancer (INFORM; NCT01670500) reported that of the of the 118 g*BRCA*m carriers with breast cancer, only 7 (5.9% of patients) had ER or PR 1-10% (Tung N et al. 2020).

2.2.3 PARP Inhibition as a Therapeutic Strategy Target for *BRCA* Mutated Breast Cancer

PARP inhibition is a novel approach to targeting tumours with deficiencies in deoxyribonucleic acid (DNA) repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HRR). Tumours with homologous recombination deficiencies (HRD), such as ovarian or breast cancers in patients with g*BRCA1/2*m, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates.

2.2.3.1 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP-1, -2, and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anticancer agents.

BRCA1 and *BRCA2* defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo (Rottenberg et al. 2008, Hay et al. 2009) and in the clinic (Fong et al. 2009).

The mechanism of action for olaparib results from the trapping of inactive PARP onto the SSBs preventing their repair (Helleday 2011; Murai et al. 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by homologous recombination. *BRCA*-mutated tumours with HRD cannot accurately repair DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib offers an efficacious and less toxic cancer treatment than chemotherapy.

Olaparib demonstrated a statistically significant improvement in progression free survival in Study D0819C00003 (OlympiAD; 205 patients received olaparib), a randomised Phase III study comparing olaparib ([redacted] mg twice daily [BID] tablets) with treatment of physician's choice (TPC) in the treatment of patients with g*BRCA*m HER-2 negative metastatic breast cancer. At 77.5% maturity, progression free survival by Blinded Independent Central Review was significantly longer in patients treated with olaparib versus TPC (hazard ratio 0.58; 95% CI 0.43-0.80; p=0.0009; 7.0 versus 4.2 months, respectively). Objective response rate was 59.9% and 28.8% in the olaparib and TPC arms, respectively (Robson et al. 2017). Final analysis of OS at 64% maturity revealed a median OS of 19.3 months for olaparib versus

17.1 months for TPC (hazard ratio 0.90; 95% CI 0.66-1.23; Robson et al. 2019).

LUCY was a Phase IIIb, single-arm, open-label multicentre study of olaparib CCI mg BID (tablet formulation) monotherapy in the treatment of HER2-negative metastatic breast cancer patients with *gBRCA1/2m*. A total of 255 patients with *gBRCAm* were enrolled and received at least one dose of olaparib. At the time of the DCO (01 September 2021) the median PFS was 8.18 months after 208 events (81.6% maturity) with a 95% CI from 6.97 to 9.17 months (Gelmon et al 2021).In the Phase III, double-blind, randomised trial OlympiA, 1836 patients with HER2-negative early breast cancer with g*BRCA1*m or g*BRCA2*m and high-risk clinical features who had received local treatment and neoadjuvant or adjuvant chemotherapy were randomised 1:1 to 1 year of oral olaparib or placebo. The 3-year invasive disease-free survival was 85.9% in the olaparib group and 77.1% in the placebo group (95% CI, 4.5 to 13.0; hazard ratio for invasive disease or death, 0.58; 99.5% CI, 0.41 to 0.82; P<0.001) (Tutt et al. 2021).

As of November 2020, olaparib has been approved by the Food and Drug Administration (FDA) in the following indications:

- Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy
- Treatment of patients with deleterious or suspected deleterious g*BRCA*m HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting
- Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy
- Maintenance treatment of adult patients with deleterious or suspected deleterious g*BRCA*m metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen
- 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 HRD-positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability
- Treatment of adult patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer who have progressed following prior therapy with new hormonal agent.

Olaparib is approved in the EU for the following indications:

- Treatment of adult patients with g*BRCA*m, HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor-positive breast cancer should also have progressed on or after prior ET, or be considered unsuitable for ET
- Monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed *BRCA*m germline and/or (dependent on country) somatic high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy
- Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy
- Maintenance treatment of adult patients with advanced (Fédération Internationale de Gynécologie et d'Obstétrique Stages III and IV) *BRCA*1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy
- Maintenance treatment of adult patients with advanced (Fédération Internationale de Gynécologie et d'Obstétrique Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD positive status defined by either a *BRCA1/2* mutation and/or genomic instability
- Maintenance treatment of adult patients with germline *BRCA1/2* mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen
- Treatment of adult patients with metastatic castration resistant prostate cancer and *BRCA1/2*-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent.

2.2.4 Targeting PD-1 Immune Checkpoints for Cancer Treatment

The ability of human cancer to evade destruction by the immune system has been recognized as an emerging hallmark of cancer (Hanahan and Weinberg, 2011).

CCI is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-1 and CCI belong to a family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T-cell response. When CCI binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumour cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

TNBCs are characterised by CCI positivity and the presence of tumour infiltrating lymphocytes (TILs), which suggests that PD-1 immune checkpoint inhibition is a therapeutic strategy worthy of further investigation for the treatment of this aggressive breast cancer subtype (Saini et al. 2021).

2.2.4.1 Durvalumab

Durvalumab is a human monoclonal antibody of the immunoglobulin G 1 kappa subclass that blocks the interaction of CCI (but not CCI) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca). The proposed mechanism of action for durvalumab is interference in the interaction of CCI with PD-1 and CD80 (B7.1). Blockade of CCI /PD-1 and CCI /CD80 interactions releases the inhibition of immune responses, including those that may result in tumour elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of CCI on primary human T cells resulting in the restored proliferation of interferon (IFN)-γ (Stewart et al. 2015). In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T-cell-dependent mechanism (Stewart et al. 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumour immune response by binding to CCI and shifting the balance toward an antitumour response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

Durvalumab was approved in the US in February 2018 for the treatment of patients with non-small cell lung cancer (NSCLC) who have not progressed following concurrent platinum-based chemotherapy and radiation therapy. In the EU, durvalumab was approved in September 2018 for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express CCI on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. In March 2020, durvalumab was approved in the US for use in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer.

As of 12 July 2022, durvalumab has been given to more than CCI patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab are summarised in Section 4.3.2 and Section 8.3.10.2.

Refer to the current durvalumab IB for a complete summary of preclinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

2.2.5 Olaparib in Combination with Durvalumab

The potential synergistic activity of combining a PARP inhibitor with a CCI inhibitor is based on the hypothesis that pharmacological inhibition of PARP by olaparib will result in enhanced immunogenicity which can be further enhanced with an ICI, such as durvalumab. This could occur through several mechanisms:

- Olaparib has been shown to activate the CCI pathway in preclinical models, leading to increased production of cytokines and chemokines (such as CXCL10 and CCL5), which may have the potential to promote antitumour immunity (Shen et al. 2019).
- Accumulating DNA damage induced through PARP inhibition has the potential to

modify the immunogenicity of tumours through triggering several intracellular signalling events that result in the activation of transcription factors, such as nuclear factor kappa B, IFN regulatory factor 3, and 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, Reisländer et al. 2019).

- PARP inhibitors can complement immune checkpoint blockade by increasing cell death, which may help to promote antigen release and subsequent immune priming (Kroemer et al. 2013).
- Increased DNA damage can also lead to upregulation of surface receptors such as major histocompatibility complex class I, ligands for natural-killer group 2, member D, and inducible T-cell costimulatory ligand, and could make tumour cells more visible and sensitive to killing by cytotoxic T-cells and natural killer cells (Tang et al. 2014, Gasser et al. 2005).
- PARP inhibition demonstrated increased activity in combination with anti-CCI in preclinical models (Jiao et al. 2017, Shen et al. 2019).

Given the promising preclinical data which support the combination hypothesis, PARP inhibitors and ICIs are now being studied in combination in the clinical setting. Safety and efficacy of the combination of olaparib and durvalumab are being assessed across multiple tumour types and settings in several ongoing studies:

- Ovarian Cancer (MEDI-O, Phase I National Cancer Institute Study ESR-14-10366 [Lee et al. 2017] and DUO-O, Phase III; NCT03737643)
- Breast cancer, small cell lung cancer, ovarian cancer, and gastric cancer (MEDIOLA, Phase 1/II [NCT02734004; Bang et al. 2019; Domchek et al. 2019; Domchek et al. 2018; Drew et al. 2018; Krebs et al. 2017]). Over 200 patients have been treated in this study with the combination of olaparib and durvalumab to date.
- Bladder cancer (BISCAY, Phase IB; NCT02546661)
- Urothelial cancer (BAYOU, Phase II; NCT03459846)
- NSCLC (ORION, Phase II; NCT03775486)
- NSCLC (HUDSON, Phase II; NCT03334617)

While assessment of the efficacy of the combination of olaparib and durvalumab is ongoing, there are sufficient safety data available to develop a safety and tolerability profile for the combination. Safety data from the ongoing MEDIOLA study (Bang et al. 2019; Domchek et al. 2019; Domchek et al. 2018; Drew et al. 2018; Krebs et al. 2017) and completed MEDI-O study (Lee et al. 2017), both investigating the combination of durvalumab and olaparib, have been consistent across multiple tumour types. Observed safety and tolerability have been similar to that expected for either drug alone, with no unexpected safety signals identified to date.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of olaparib and durvalumab may be found in the respective IB for each compound.

2.3.1 Risk Assessment

2.3.1.1 Olaparib

From the available data to date in patients with solid tumours, olaparib is generally well tolerated at monotherapy doses up to CCI mg BID (tablet formulation). Adverse laboratory findings and/or clinical diagnoses considered to be causally associated with administration of olaparib monotherapy include haematological effects (anaemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, mean cell volume elevation), decreased appetite, nausea and vomiting, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, hypersensitivity, rash, dermatitis, cough, dyspnoea, angioedema, myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML), erythema nodosum, and venous thromboembolism.

In a relatively small number of patients, pneumonitis and new primary malignancies have been observed.

2.3.1.1.1 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies (eg, dog cardiovascular and respiratory function tests), and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic, or motor effects in the rat at the doses studied.

Rodent and dog toxicology studies have indicated that the primary target organ of toxicity is the bone marrow with recovery seen following withdrawal of olaparib. Ex vivo studies have confirmed that olaparib is cytotoxic to human bone marrow cells.

Olaparib was not mutagenic in the Ames test but was clastogenic in the Chinese hamster ovary chromosome aberration test in vitro. When dosed orally, olaparib also induced micronuclei in the bone marrow of rats. This profile is consistent with the potential for genotoxicity in man.

Reproductive toxicology data indicate that olaparib can have adverse effects on embryo-foetal survival and development at dose levels that do not induce significant maternal toxicity.

Further information can be found in the current version of the olaparib IB.

2.3.1.2 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyperthyroidism and hypothyroidism, and Type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, encephalitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain Barre syndrome, myasthenia gravis).

In monotherapy clinical studies, AEs at an incidence of ≥ 20% include events such as fatigue and decreased appetite. Approximately 10% of patients discontinued the drug due to an AE.

The majority of treatment-related AEs were manageable, with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 6.6.2).

Please refer to "Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy or in Combination with Other Products" as provided to the investigative site as an Annex document, which is maintained within the Site Master File.

2.3.1.3 Olaparib plus Durvalumab Combination Therapy

Encouraging clinical activity, combined with acceptable and manageable safety, has been seen to date with olaparib in combination with durvalumab. In general, the toxicity profiles of durvalumab and olaparib are non-overlapping. Pneumonitis is considered to be a potential risk for olaparib and an identified risk for durvalumab. Presentations of pneumonitis can range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia (Teply and Lipson 2014). Early consideration of pneumonitis should be realised when patients present with new onset or worsening of respiratory symptoms such as dyspnoea or cough. Additional information about the frequency and risk of pneumonitis can be found in the current durvalumab and olaparib IBs.

Clinical data on the safety and efficacy of durvalumab plus olaparib combination therapy are emerging. The open-label, Phase 1/2, basket trial of durvalumab and olaparib in solid tumours (MEDIOLA) recruited a cohort of 34 patients with germline *BRCA*m, metastatic breast cancer, among whom the most common Grade 3 or worse AEs were anaemia (4 [12%]), neutropenia (3 [9%]), and pancreatitis (2 [6%]). Twenty-four (80%; 90% CI 64·3–90·9) of 30 patients eligible for activity analysis had disease control at 12 weeks (Domchek et al. 2020).

The combination of olaparib and durvalumab has also shown acceptable safety and encouraging activity in men with metastatic castrate-resistant prostate cancer, especially those with DNA damage repair (DDR) (Karzai et al. 2018). Nine of 17 (53%) patients had a radiographic and/or prostate-specific antigen response: median radiographic progression-free survival for all patients was 16.1 months (95% CI: 4.5-16.1 months); nausea was the only nonhematologic Grade 3 or 4 toxicity occurring in > 1 patient (2/17).

Patients (n=28) with cT2-T4a muscle-invasive bladder cancer aimed for cystectomy were treated during 6 to 8 weeks pre-cystectomy with the combination of durvalumab plus olaparib (NEODURVARIB Trial); and the pCR rate observed was 44.5%; Grade 3 to 4 AEs were seen in 8.3% of cases (Rodriguez-Moreno et al. 2020).

Multiple other studies are ongoing, including in endometrial cancer (NCT04269200), ovarian cancer (NCT03737643), and other cancer types.

2.3.2 Benefit Assessment

2.3.2.1 Olaparib

As of 15 December 2022, approximately CCI patients were estimated to have received olaparib in the clinical program. An estimated CCI patients with ovarian, breast, pancreatic, prostate and a variety of other solid tumours were estimated to have received treatment with

olaparib. Since 2013, most new clinical studies have utilised the tablet formulation, which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. In the AstraZeneca and AstraZeneca-Merck Alliance sponsored, interventional studies, olaparib was given either as monotherapy (CCI patients) or in combination with chemotherapy or other anticancer agents, including studies where patients received monotherapy and combination therapy sequentially (3623 patients).

As presented in Section 2.2.3.1, olaparib is US FDA approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy; for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*m advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy; in patients with deleterious or suspected deleterious g*BRCA*m, HER2-negative metastatic breast cancer who have previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. (Patients with HR-positive breast cancer should have been treated with a prior ET or be considered inappropriate for endocrine treatment). Moreover (as described in Section 2.2.3), there is nonclinical evidence demonstrating a strong correlation between platinum and olaparib responsiveness in multiple tumour types (including *BRCA*m cancers), as well as evidence showing PARP inhibition having the potential to modify the immunogenicity of tumours, leading to enhanced susceptibility to immune checkpoint inhibition.

These findings suggest that olaparib may be a neoadjuvant treatment option as monotherapy or in combination with durvalumab for patients with known *BRCA*m ER-negative or ER-low, HER2-negative breast cancer.

2.3.2.2 Durvalumab

As of 12 July 2022, an estimated CCI patients have received durvalumab in the clinical program. An estimated CCI patients have been randomised and treated. Of these, CCI patients received durvalumab monotherapy, CCI patients received durvalumab in combination with tremelimumab, and CCI patients received durvalumab or durvalumab plus tremelimumab in combination with an investigational and/or an approved product. Clinical benefit was observed regardless of CCI status with generally greater clinical activity in CCI high patients.

In the Phase II randomised GeparNuevo trial, 174 patients with TNBC received durvalumab or placebo given every 4 weeks (Q4W) in addition to nab-paclitaxel followed by standard chemotherapy. Of these, 117 participated in the window-phase where durvalumab/placebo alone was given 2weeks before start of nab-paclitaxel. Randomisation was stratified by stromal TILs. The observed pCR rate with durvalumab was 53.4% (95% CI 42.5% to 61.4%) versus placebo 44.2% (95% CI 33.5% to 55.3%). Significant effect of durvalumab was observed only in the window cohort (pCR 61.0% versus 41.4%, OR = 2.22, 95% CI 1.06-4.64, P = 0.035; interaction P = 0.048); and in both arms, a significantly higher pCR (P < 0.01) was observed in patients with higher stromal TILs (Loibl et al. 2019).

2.3.2.3 Olaparib plus Durvalumab Combination Therapy

Encouraging clinical activity has been seen to date with durvalumab in combination with olaparib outside of NSCLC (Lee et al. 2017, Karzai et al. 2018). In a recent study of patients with g*BRCA*m breast cancer (progressive, locally advanced, or metastatic) treated with

olaparib and durvalumab, promising antitumour activity was observed, with an objective response rate of 63% and disease control in 80% of patients at 12 weeks (Domchek et al. 2020).

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

The emergence of the novel coronavirus disease 2019 (SARS CoV-2 / COVID-19) pandemic presents a potential safety risk for participants, and therefore several risk mitigation factors have been implemented in this study (Appendix K).

2.3.3 Overall Benefit: Risk Conclusion

Both olaparib and durvalumab have regulatory approvals and well characterised safety profiles (see Sections 2.2.3.1 and 2.2.4.1, respectively).

Treatment with olaparib in combination with durvalumab has shown clinical activity in several tumour types with a subset of patients deriving meaningful and durable responses with an acceptable safety profile. The molecular targeting of olaparib or olaparib in combination with durvalumab to *BRCA*m tumours may provide a further opportunity for an effective and tolerable treatment regimen for selected patients.

Based upon the available clinical efficacy and safety data for olaparib monotherapy and olaparib and durvalumab combination, and the mitigations designed for this study through participant selection and close clinical monitoring during treatment, the investigation of the potential therapeutic efficacy of neoadjuvant olaparib and of the combination of olaparib plus durvalumab in participants with *BRCA*m ER-negative or ER-low, HER2-negative breast cancer is acceptable, and the overall benefit/risk assessment supports the proposed study design.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

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

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

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

Objectives	Endpoints/Estimands
CCI To characterise CCI in tumour and blood samples.	treatment: CCI and other CCI CCI and their zygosity, CCI origin, CCI and other CCI other CCI status; CCI CCI burden; CCI profiles (eg, CCI ; the expression and activity of CCI and/or CCI (eg, CCI), secreted CCI (eg, CCI or protein and CCI ; presence of CCI ; the number, phenotype, and expression profile of CCI CCI .
To explore whether CCI to olaparib monotherapy or olaparib plus durvalumab combination therapy can be CCI	Evaluation of CCI and CCI samples collected before CCI mentioned above.
Exploratory research into CCI and/or CCI or CCI may be performed on the CCI CCI that were collected during the course of the study.	Analysis and outcome CCI CCI
To collect and store CCI according to each country's local and ethical procedures for CCI that may CCI to study treatments and/or CCI (optional).	CCI for the CCI CCI measured by the CCI CCI from an CCI sample.
To explore the impact of olaparib monotherapy and olaparib plus durvalumab combination therapy on CCI in women who C CI	Evaluation of CCI and CCI CCI collected CCI CCI fo CCI

Abbreviations: CCI ; AE = adverse event; AESI = adverse event of special interest; CCI ; CTCAE = Common Terminology Criteria for Adverse Event; CCI ; ECG = electrocardiogram; EFS = event-free survival; CCI ; MoA = mechanism of action; CCI MRI = magnetic resonance imaging; pCR = pathological complete response; CCI RCB = residual cancer burden; CCI SAE = serious adverse event; CCI .

Note: Pathological staging following neoadjuvant systemic therapy is recorded using the 'yp' designation.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase II multicentre, open-label study to determine the efficacy and safety of neoadjuvant olaparib monotherapy and olaparib plus durvalumab combination therapy in participants with primary, operable, ER-negative or ER-low, HER2-negative breast cancer with documented *BRCA*m who are candidates for neoadjuvant therapy. A participant's HR and HER2 status for eligibility at screening will be based on local test results.

There will be approximately 65 sites in 10 countries in the study and participants will be enrolled into the following cohorts:

- In Cohort A, approximately 25 lower-risk participants (defined as having a tumour size >5 mm and ≤20 mm and Tumour, Node, Metastasis [TNM] nodal status of N0 [T1b-c/N0]) will be allocated to receive treatment with olaparib monotherapy CCI mg BID continuously in 28-day cycles.
- In Cohort B, approximately 25 higher-risk participants (defined as having a tumour size of >20 mm but ≤50 mm and N0 [T2/N0] or having a tumour size of >1 mm but ≤20 mm and N1 [T1/N1]) will receive olaparib plus durvalumab combination therapy in 28-day cycles.

Participants eligible for the trial are those with known deleterious or suspected deleterious *BRCA*m identified by either a germline or tumour test.

The redacted *BRCA* status report from the local laboratory will be reviewed by the study physician prior to enrolment of the participant to confirm the presence of a deleterious or suspected deleterious mutation.

Enrolment into each cohort will occur simultaneously. Without pausing enrolment, data will be assessed separately for each of Cohorts A and B once CCI participants complete neoadjuvant treatment or discontinue treatment for any reason. The review will focus on participants with clinical progression of disease (cPD), defined as "the clear worsening of the patient's clinical status or prognosis in the opinion of the treating clinician, taking into consideration clinical findings, imaging (including, but not limited to, objective imaging response criteria) and laboratory test results" (Saini and Twelves 2021), and including the investigator's decision to change neoadjuvant therapy or proceed to definitive surgery prior to completion of neoadjuvant therapy as a rescue intervention or deaths that occur in the neoadjuvant treatment period. The first CCI participants in each cohort who complete neoadjuvant therapy or discontinue treatment for any reason will be included in this assessment.

- If CCI of these initial CCI participants experience cPD/death, then enrolment in that cohort will continue to ensure a total of approximately 25 participants in that cohort
- If CCI of these initial CCI participants experience cPD/death, then enrolment in that cohort will be paused, while data are reviewed for further enrolment.

The study will not use randomisation. Study intervention allocation will be determined by tumour size and TNM nodal status (see Section 6.3).

All participants will receive four to six 28-day cycles of study intervention. Confirmation of eligibility criteria (see Sections 5.1 and 5.2) will take place within 28 days prior to allocation of study intervention. Every effort should be made to minimise the time between study intervention allocation and the start of study intervention (ie, within 3 calendar days, maximum of 7 calendar days).

Participants with primary, early stage, operable, non-metastatic ER-negative or ER-low, HER2-negative breast cancer with *BRCA*m are required to provide their archival/diagnostic CCI sample, if available. CCI In addition, while not mandatory, the collection of CCI samples is strongly recommended at any point during Cycle 2 or 3. CCI samples will also be collected at definitive surgery.

Breast magnetic resonance imaging (MRI) will be used as a noninvasive serial measurement of response during the course of treatment. The MRI longest diameter and tumour volume will be measured and recorded at each time point, as per the Schedule of Activities (SoA) (Table 1 and Appendix I).

Definitive surgery, such as breast conservation surgery or mastectomy with or without axillary lymph node dissection, will be performed as part of the local standard of care after completion of four to six 28-day cycles of neoadjuvant study treatment. Each participant will undergo definitive surgery within 6 weeks following the final dose of neoadjuvant olaparib therapy (or per local standard of care). The participant will have an MRI and blood draw prior to surgery, and tumour tissue will be collected at surgery from the surgical specimen.

Thorough evaluation of breast cancer status, pathological staging per American Joint Committee of Cancer (AJCC) Breast Cancer Staging (8th edition), and assessment of surgical margins will be performed by the local pathologist on all the tissues removed during the surgery. The primary endpoint is pCR (defined as absence of invasive tumour in breast or lymph nodes at the completion of all neoadjuvant study intervention) by central pathology review. Residual cancer burden (RCB) will be used to evaluate surgical specimens. RCB is estimated from routine pathologic sections of the primary breast tumour site and the regional lymph nodes after completion of neoadjuvant therapy. Six variables are required to calculate RCB following neoadjuvant treatment (see Section 8.1.2.2). If, after exposure to olaparib monotherapy therapy (in Cohort A) or olaparib plus durvalumab combination therapy (in Cohort B), the participant does not undergo surgery because the investigator believes (on the basis of clinical and/or imaging findings) that there is the likelihood of residual disease and plans to give additional non-protocol therapy (eg, chemotherapy), an additional on-treatment CCI must be performed to confirm the presence or absence of residual disease. This is a clinical diagnostic CCI (not a research CCI and must be read by the local pathologist. Blocks from this CCI will be submitted as CCI for research purposes after being used for clinical decision-making.

Participants who achieve pCR will be allowed to continue treatment with olaparib monotherapy in the adjuvant setting, in lieu of standard adjuvant systemic therapy, per physician's choice. If the physician chooses adjuvant olaparib, then the total duration of olaparib therapy in the neoadjuvant and adjuvant settings must not exceed 12 cycles. Adjuvant ET may be co-administered with olaparib in participants with pCR who continue receiving

olaparib in the adjuvant setting. In those participants who did not achieve pCR at the definitive surgery or who achieved pCR and choose not to receive adjuvant olaparib, post-operative systemic and radiation therapy will be administered in accordance with local standard of care, as applicable. The development of local or distant recurrence and start and stop dates of subsequent anticancer treatment will be collected until death, loss to follow-up, or withdrawal of consent.

In the event a participant discontinues from study intervention, subsequent treatment options will be at the discretion of the investigator as the participant continues in the survival follow-up phase of the study.

There will be a primary pCR analysis data cutoff (DCO) approximately 6 months after the last participant has enrolled (ie, once all participants have been assessed for pCR following surgery or earlier if no surgery is performed). There will also be a final DCO defined as 3 years after last participant dosed or once all participants have had an EFS event, or have withdrawn consent, whichever occurs first. At this time point, the clinical study database will close to new data. Please see Section 6.7 for cases where participants are permitted to continue to receive study intervention beyond the closure of the database. Collection and reporting of AEs and serious adverse events (SAEs) after the final DCO is described in Section 8.3.11.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Efficacy Endpoints

The primary objective of the study is to assess the efficacy of olaparib monotherapy and of olaparib plus durvalumab combination therapy in terms of pCR via central pathology review. Following neoadjuvant therapy for breast cancer, participants who achieved pCR have demonstrated sustained clinical benefit regardless of breast cancer subtypes. Large, pooled analyses have demonstrated strong association of pCR (when defined as ypT0 ypN0 – no invasive or noninvasive residual tumour in both breast and lymph nodes) with improved long-term benefit as measured by EFS and OS (Carey LA et al. 2007; Liedtke C et al. 2008).

A secondary objective of the study is to assess the efficacy of olaparib monotherapy and of olaparib plus durvalumab combination therapy in terms of RCB via both central and local pathology review. RCB has been proposed as a determinant of the extent of residual disease in the post-treatment surgical resection specimen in patients with breast cancer who receive neoadjuvant therapy. The RCB score reports pCR as a score of zero and combines findings in the primary tumour bed and the regional lymph nodes to quantify increasing amounts of residual disease as an increasing continuous RCB score (see Section 8.1.2.2). RCB after neoadjuvant therapy has shown strong, long-term prognostic value in several independent cohorts, including patients with HER2-negative breast cancer (Symmans et al. 2013).

Event-free survival as an endpoint has been commonly used in recent/contemporary TNBC studies, such as GeparNeuvo (Loibl et al. 2021a), BrighTNess (Loibl et al. 2021b), and KEYNOTE-522 (Schmid et al. 2021a). In this present study, a follow-up of up to 3 years was deemed to be adequate to capture most events, given that recurrences in TNBC tend to occur early. However, the study is not powered to assess long-term survival outcomes.

Breast MRI is sometimes used for evaluation of response to neoadjuvant therapy, especially in patients with TNBC. Such evaluation may also be part of clinical surveillance in many

institutions and may be considered to be clinically relevant. MRI is considered to be among the most accurate imaging modalities to demonstrate response to therapy and to assist with accurate presurgical planning (Reig et al. 2021). MRI volume (not length, breadth, height), calculated by local site using software or manually, will be collected (see Section 8.1.3 and Appendix I).

4.2.2 Rationale for Safety Endpoints

Safety parameters such as incidence of AE/SAEs (including fatal SAEs) and laboratory abnormalities, rates of dose interruption and discontinuation due to AEs, and AEs of special interest (AESIs) are important endpoints for safety and tolerability evaluations.

4.2.3 Rationale for Other Study Endpoints

Cancer immunotherapies represent an important and novel class of antitumour agents. However, the mechanism of action of these new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the [CCI] [CCI] as well as determinants of AEs in the course of clinical trials. These efforts will [CCI] and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify [CCI], we will collect [CCI] etc.) to support analyses of [CCI] (eg, [CCI]) and other [CCI]. Investigations may include but are not limited to:

Genetic (DNA) Analyses

The application of new technologies, such as next [CCI], has provided scientists the opportunity to identify [CCI] [CCI] Key [CCI] of interest to immune-oncology drug development include the [CCI] which could be [CCI] to treatment. [CCI] (sometimes referred to as a [CCI]) may generate [CCI]. To conduct this type of research, it is important to identify [CCI] that occur [CCI] [CCI]. Thus, [CCI] may be used for this effort. Note that in order to understand tumour-specific mutations, it is necessary to compare the [CCI] with the [CCI].

[CCI] **Research**

[CCI] is mandatory for all participants in the study as per tertiary/exploratory objectives. The [CCI] and [CCI] and other [CCI] in the [CCI] will be explored pre-treatment and on treatment, at surgery, and at progression to identify [CCI] and to [CCI] [CCI] of olaparib monotherapy and olaparib plus durvalumab combination therapy. Research on [CCI] in the [CCI] might be key in identifying [CCI] [CCI] to olaparib. [CCI] will include assessment of the presence of and changes in [CCI] at screening, on treatment, and following

treatment and/or progression. Correlation of [CCI redacted], to [CCI redacted] at screening and after treatment may be evaluated to identify [CCI redacted], to characterise [CCI redacted], to identify [CCI redacted] of efficacy, and/or to develop [CCI redacted]

[CCI redacted] Research

The sponsor may conduct optional [CCI redacted] on specimens from appropriately consented participants. This research may include [CCI redacted] depending on which specimens are consented for [CCI redacted]. These samples may be used for future [CCI redacted]

Such research is for [CCI redacted] to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for [CCI redacted] is to explore and identify [CCI redacted] The overarching goal is to use such information to develop [CCI redacted], and/or to ensure that participants receive the correct [CCI redacted] at the [CCI redacted].

4.3 Justification for Dose

4.3.1 Olaparib Dose Rationale

The dose of olaparib to be used as monotherapy in the study ([CCI redacted] mg BID) is consistent with the approved dose across a range of tumour types, including ovarian and breast cancer.

For combination dosing with durvalumab, olaparib dose selection is based on the results from the National Cancer Institute Study ESR-14-10366 and AstraZeneca Study D081KC00001, a Phase I/II study of durvalumab in combination with olaparib in patients with advanced solid tumours. In Study ESR-14-10366 (Lee et al. 2017), olaparib was administered at 200 or 300mg BID, and durvalumab was studied at a fixed dose of 10 mg/kg every 2 weeks (Q2W) for the first 2 cohorts. Later in the study, the durvalumab dosing schedule was changed to a dose schedule of Q4W. Administration of the durvalumab plus olaparib combination was well tolerated, with no instances of dose-limiting toxicity observed. Data from this study formed the basis for the dose selection in Study D081KC00001. Based on these data, the dose of olaparib to be used in this study in combination with durvalumab will be the recommended monotherapy dose of [CCI redacted] mg BID.

Dose reductions may be required in participants experiencing toxicities related to olaparib treatment.

4.3.2 Rationale for Fixed Dosing of Durvalumab

A population PK model was developed for durvalumab using monotherapy data from Study 1108 (N=292; doses=0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks; solid tumours). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab

(coefficient of 0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady-state PK concentrations (5th, median, and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of approximately 75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady-state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

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 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 therapeutic proteins and peptides in terms of reducing the between-patient variability in PK/pharmacodynamic 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, it was considered feasible to switch to fixed dosing regimens. Based on median body weight of approximately 75 kg, a fixed dose of durvalumab 1500 mg (equivalent to [redacted] mg/kg) is included in the current study.

A fixed dose of 1500 mg durvalumab administered Q4W is to be used for all participants in Cohort B with a body weight greater than 30 kg in combination with [redacted] mg olaparib BID. Currently, the use of a fixed dose of 1500 mg durvalumab, administered both in combination with chemotherapy and as monotherapy, is approved for treatment of extensive stage small cell lung cancer; additionally, the 1500 mg fixed dose is approved in some countries as monotherapy for unresectable Stage III NSCLC. Refer to the package insert (or label) for the current approved dosing regimens for your specific country, as applicable.

4.3.3 Rationale for Proposed Study Dose and Schedule

The proposed dosing schedule is aligned with the standard dosing for olaparib monotherapy and olaparib plus durvalumab combination therapy, which is supported by efficacy and safety as well as tolerability across multiple studies.

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

- European Union requirements define study completion as the last visit of the last subject for any protocol-related activity.
- Food and Drug Administration requirements define 2 completion dates:
  - Primary Completion Date – the date that the final participant is examined or receives an intervention for the purpose of final collection of data for the primary outcome measure, whether the clinical study concluded according to

the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

– Study Completion Date – is defined as the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled assessment as shown in the SoA (Table 1).

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

The end of the study is defined as the date of last scheduled assessment as shown in the SoA (Table 1) for the last participant in the study globally.

See Section 6.7 for details on participant management following the final DCO as well as following study completion.

4.5 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 study 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 participants 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 participant's ability to conduct the study. The investigator or designee should contact AstraZeneca/Contract Research Organisation (CRO) 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 participants, maintain compliance with Good Clinical Practice (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 consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the informed consent form [ICF] should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study may be performed in previously screened participants.

The investigator should confirm this with the sponsor/CRO's designated Medical Monitor. If rescreening takes place more than 30 days after the initial screen, participants must have repeat serum or urine pregnancy test, if woman of child-bearing potential.

- 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 participants using telecommunication technology including phone calls, virtual or video visits, and mobile health devices.
- At-home study intervention administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the participant or the participant's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

5 STUDY POPULATION

The target population of interest in this study is participants with known *BRCA*m, HER2-negative, ER-negative or ER-low, non-metastatic breast cancer. Eligible participants will have small volume disease (T1b-c/N0; T1/N1; T2/N0). The size of the primary tumour should be >1 mm for participants with N1 status, and >5 mm for participants with N0 status (Table 3).

Table 3 Clinical Disease Staging of Target Population

Cohort	Clinical Disease Staging
A (Lower Risk)	T1b (>5 mm but ≤10 mm), N0 **OR** T1c (>10 mm but ≤20 mm), N0
B (Higher Risk)	T1 (>1 mm but ≤20 mm), N1 **OR** T2 (>20 mm but ≤50 mm), N0

Participants eligible for the trial are those with known deleterious or suspected deleterious *BRCA*m identified by either a germline or tumour test. Prior to performing the *BRCA* testing, an investigator's judgement of a participant's potential eligibility for the study should be made according to the National Comprehensive Cancer Network (NCCN) Hereditary Cancer Testing Criteria (Version 1.2021; Appendix F) and by reviewing the inclusion/exclusion criteria. All inclusion criteria will then be assessed following confirmation that they harbour an eligible deleterious or suspected deleterious *BRCA* mutation.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. Each participant should meet all of the inclusion criteria and none of the exclusion criteria for this study. Participants who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.4.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1) Participants must be males or females ≥18 years at the time of screening.

Type of Participant and Disease Characteristics

2) Histologically confirmed, newly diagnosed, primary, operable, non-metastatic invasive breast cancer with the following characteristics:

   - ER-negative or ER-low defined as IHC nuclear staining ≤10%

   HER2-negative (not eligible for anti-HER2 therapy) defined as:

   - IHC 0, 1+ without in situ hybridization **OR**
   - In situ hybridization non-amplified with ratio less than 2.0 **OR**
   - In situ hybridization average HER2 copy number < 6 signals/cells

   Clinical TNM staging (per AJCC 8th Edition) as follows:

   - T1b (>5 mm but ≤10 mm), N0, no known metastases (M0 or MX); **OR**
   - T1c (>10 mm but ≤20 mm), N0, no known metastases (M0 or MX); **OR**
   - T1 (>1 mm but ≤20 mm), N1, no known metastases (M0 or MX); **OR**
   - T2 (>20 mm but ≤50 mm), N0, no known metastases (M0 or MX).

   Note: Participants with tumour size >5 mm and ≤20 mm and nodal status of N0 (T1b-c/N0) will be allocated to receive olaparib monotherapy (**lower risk, Cohort A**). Participants with tumour size of >20 mm but ≤50 mm and N0 (T2/N0) or with tumour size of >1 mm but ≤20 mm and N1 (T1/N1) will receive olaparib plus durvalumab in combination (**higher risk, Cohort B**).

   Note: In addition to unifocal lesions, multi-focal and/or multi-centric and/or bilateral invasive breast cancer or concurrent ipsilateral/contralateral ductal carcinoma in situ (DCIS) are allowed, as long as each discrete cancer displays the above characteristics. Per AJCC 8th Edition, the maximum dimension of the largest tumour will be used to define the tumour size.

   Note: tumour size (T) will be determined by breast MRI. If participants are unable to have MRIs performed, they will not be eligible for study participation.

   Note: axillary nodes that are abnormal on clinical examination or by imaging and are confirmed as suspicious by axillary ultrasound must be CCI

3) Documented deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2* from local *BRCA* testing using either a germline or tumour test. If local *BRCA* testing results are not available at the time of consent, local *BRCA* testing may be performed during screening, according to local guidelines (see NCCN Guidelines Version 1.2021; Appendix F), if the results are expected to be available within the protocol-specified screening period. (Note: the redacted *BRCA* status report from the local laboratory will be

reviewed by the study physician prior to enrolment of the participant to confirm that the *BRCA* mutation is deleterious or suspected deleterious).

4) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Section 8.2.5.4).

5) Participants must have adequate organ and bone marrow function as follows:

- Haemoglobin ≥ 10.0 g/dL with no blood transfusion within the past 28 days.
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
- Platelet count ≥ 100 x 10^9/L.
- Total bilirubin (TBL) ≤1.5×the upper limit of normal (ULN) or ≤3×ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia).
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5×ULN.
- Calculated creatinine clearance (CrCL) of ≥51 mL/min, as determined by Cockcroft-Gault (using actual body weight) or based upon a 24-hour urine test or another validated test as per local practice:

  For Males:

  $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

  For Females:

  $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

6) Participant must be willing to undergo a [CCI] prior to start of study treatment. This baseline [CCI] **must** be performed at screening, with [CCI] collected and [CCI] for central testing. Refer to Section 8.6.1 ([CCI] Samples at Diagnosis and at Baseline [Mandatory]).

Note: for participants with T1b/N0 disease who have insufficient tissue for the required baseline [CCI], the [CCI] may be omitted but provision of their [CCI] sample will be mandated.

7) Participant must be willing to have any leftover [CCI] from the [CCI] submitted for research purposes, if available.

Weight

8) Minimum body weight of 30 kg.

Sex

9) Female and male participants.

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Reproduction

10) Negative pregnancy test (urine or serum) for women of childbearing potential.

11) Female participants must be 1 year post-menopausal, surgically sterile, or using one highly effective form of birth control prior to planned study intervention allocation via interactive voice response system (IVRS)/interactive web response system (IWRS) (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). See Appendix G for definition of postmenopausal. Female participants of childbearing potential must use one highly effective form of contraception from enrolment (defined as study intervention allocation via IVRS/IWRS) throughout the study and until at least 6 months after the last dose of olaparib and for at least 3 months after the last dose of durvalumab (for participants who have continued on monotherapy neoadjuvant durvalumab as described in Section 6.6.1), whichever is longer (see Appendix G for complete list of highly effective birth control methods). Additionally, nonsterilised 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.

12) Non-sterilised male participants, who intend to be sexually active with a female partner of childbearing potential or a pregnant woman, must be surgically sterile or using an acceptable method of contraception (see Appendix G) from enrolment (defined as study intervention allocation via IVRS/IWRS) until the latest time point that is 3 months after the last dose of olaparib and/or durvalumab to prevent pregnancy in a partner. Male participants must not donate or bank sperm during this same time period. Female partners of male participants should also use a highly effective form of contraception (as described in Appendix G) if they are of childbearing potential.

Informed Consent

13) Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this CSP. Additional country-specific requirements are noted in Appendix L.

14) The main consent form also includes a consent to mandatory exploratory CCI research. All participants in the study must agree to provide samples and consent for exploratory research, which is part of the study (ie, exploratory objectives). There is also a separate consent question for the optional CCI component of the study. If the participant gives consent for the collection of optional CCI, CCI research on these samples is mandatory. If a participant declines to participate in the optional exploratory CCI research, there will be no penalty or loss of benefit to the participant and the participant will not be excluded from other aspects of the study. Provision of signed and dated written Optional CCI Research Information informed consent prior to collection of the sample for optional genetic research that supports the CCI.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1) As judged by the investigator, any evidence of other diseases (such as severe or uncontrolled systemic diseases or active, uncontrolled infections, including but not limited to, uncontrolled ventricular arrhythmia, uncontrolled hypertension, recent [within 3 months] myocardial infarction, uncontrolled major seizure disorder, renal transplant, active bleeding diseases, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography scan that, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the protocol.
2) Participants may not have had prior ipsilateral invasive breast cancer, unless the only treatment was excision without any radiation or systemic therapy (including ET). Prior ipsilateral DCIS is permitted if treated only with excision.
3) Refractory nausea and vomiting, chronic gastrointestinal disease likely to interfere with absorption of the study medication, inability to swallow the formulated product, or that would preclude adequate absorption, distribution, metabolism, or excretion of olaparib.
4) History of another primary malignancy except for malignancy treated with curative intent with no known active disease for ≥5 years before the first dose of study intervention and of low potential risk for recurrence. Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that has undergone potentially curative therapy, curatively treated in situ cancer of the cervix, DCIS, and Stage 1, Grade 1 endometrial carcinoma.
5) Participants with MDS or AML or with features suggestive of MDS or AML.
6) For **higher risk (Cohort B)** participants only: Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, sarcoidosis, granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc), autoimmune pneumonitis, and autoimmune myocarditis. The following are exceptions to this criterion:
    - Participants with vitiligo or alopecia.
    - Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
    - Any chronic skin condition that does not require systemic therapy.
    - Participants without active disease in the last 5 years may be included but only after consultation with the study clinical lead.
    - Participants with coeliac disease controlled by diet alone.
7) Known active hepatitis infection, positive hepatitis C antibody, hepatitis B virus surface antigen or hepatitis B virus core antibody at screening. Testing is not required at screening unless there was a prior known positive hepatitis B or C test or hepatitis is suspected at screening.

- Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. For participants with evidence of chronic HBV infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
- Participants with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

8) Known to have tested positive for human immunodeficiency virus unless currently on effective anti-retroviral therapy with an undetectable viral load within 6 months. (Please verify that anti-retroviral treatment being taken is not prohibited. See exclusion criterion #21 to determine if any change in anti-retroviral treatment should be considered).
9) Known history of drug or alcohol abuse within 6 months of screening.
10) History of arrhythmia (multifocal premature ventricular contractions, bigeminy, trigeminy, ventricular tachycardia), which is symptomatic or requires treatment (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3), symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation controlled by medication or arrhythmias controlled by pacemakers may be permitted based upon Investigator judgement with cardiologist consultation recommended.
11) Failure to comply with all required screening procedures due to circumstances related to pandemic or public health emergency.

Prior/Concomitant Therapy

12) Participant must not have had any prior treatment for the current breast cancer, including surgery, chemotherapy, hormonal therapy, radiation, or experimental therapy.
13) Prior exposure to a PARP inhibitor, including olaparib.
14) For **higher risk (Cohort B)** participants only: Prior exposure to [redacted] or anti-CTLA4 agents (ICIs); OR an agent directed to other co-inhibitory or co-stimulatory T-cell receptors.
15) Receipt of previous anticancer therapy, targeted therapy, and radiation therapy within 12 months prior to the first dose of study intervention.
16) Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab (see Appendix H 2).
17) Exposure to an investigational product within 30 days or 5 half-lives (whichever is longer) prior to receiving the first dose of study intervention.
18) Any concurrent anticancer treatment. Concurrent use of hormonal therapy for noncancer related conditions (eg, hormone replacement therapy) is allowed.
19) Major surgical procedure (excluding placement of vascular access, local surgery of isolated lesions, or diagnostic staging) within 2 weeks of the first dose of study intervention and participants must have recovered from any effects of any major surgery

or an anticipated need for major surgery during the study. Significant traumatic injury within 4 weeks of the first dose of study intervention.

20) For **higher risk (Cohort B)** participants only: Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
    - Systemic corticosteroids (that are not excluded according to exclusion criterion #18) at physiologic doses not exceeding 10 mg/day of prednisone or its equivalent
    - Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication)
21) Concomitant use of:
    - Known strong cytochrome P450 (CYP3A) inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) within 2 weeks prior to first dose of study intervention (see Appendix H 1).
    - Known strong CYP3A inducers (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg, bosentan, efavirenz, modafinil). The required washout period prior to starting study therapy is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents (see Appendix H 1).
22) Whole blood transfusions within 120 days prior to *BRCA* testing sample collection at screening (Note: packed red blood cells and platelet transfusions are acceptable).
23) Previous allogenic bone marrow transplant or double umbilical cord blood transplantation.

Prior/Concurrent Clinical Study Experience

24) Previously assigned treatment in the present study.
25) Participants with a known hypersensitivity to any of the agents included in the study intervention, including olaparib and durvalumab, and to any of the excipients of olaparib or durvalumab.

Other Exclusions

26) Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
27) Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

28) For women only: Currently pregnant (confirmed with positive pregnancy test) or breastfeeding.

5.3 Lifestyle Considerations

The following restrictions apply while the participant is receiving study intervention and for the specified times before and after:

1. Participants must follow the contraception requirements outlined in Appendix G. Female participants of childbearing potential should be informed prior to receiving study intervention about the options that may preserve their ability to have children.
2. Participants should not donate blood or blood components while participating in this study and through 30 days after the last dose of olaparib or 90 days after the last dose of durvalumab.
3. During study intervention and for 4 weeks after the last dose of study intervention, participants should be advised to avoid prolonged exposure to the sun, wear protective clothing including a hat, and seek shade from the sun as much as possible; in addition, SP30+ sunscreen should be used. Exposure to other sources of ultraviolet light including sun beds and tanning booths, etc, should be avoided.

Restrictions relating to concomitant therapies are described in Appendix H 2.

5.3.1 Meals and Dietary Restrictions

Participants must refrain from consumption of Seville oranges and grapefruit or grapefruit juice during treatment with olaparib.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. Rescreened participants should be assigned the same participant number (ie, E-code) as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed. All assessments must be repeated for rescreening unless they are within 28 days of treatment allocation.

These participants should have the reason for study discontinuation recorded in the Disposition electronic Case Report Form (eCRF) as "screen failure" (ie, participant does not meet the required inclusion/exclusion criteria). This reason for study discontinuation is only valid for screen failures (ie, participants who are not allocated to receive study intervention).

Participant enrolment and treatment allocation are described in Section 6.3.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the CSP. Study intervention in this study refers to olaparib and durvalumab.

6.1 Study Interventions Administered

6.1.1 Investigational Products

AstraZeneca will supply olaparib and durvalumab. Dose modifications are described in Section 6.6.

Table 4 Investigational Products

Intervention Name	Olaparib	Durvalumab
Type	Synthetic drug	Biologic
Dose Formulation	Tablet	Concentrate for solution for infusion
Unit Dose Strength(s)	CC mg tablet CC mg tablet (available if dose reductions are required)	500 mg vial containing C mg/mL solution for IV infusion after dilution
Dosage Level(s)	CC mg olaparib CCI mg tablets) twice daily	1500 mg Q4W or C mg/kg Q4W in participants who weigh ≤ 30 kg
Route of Administration	Oral	IV infusion
Use	Experimental	Experimental
IMP and NIMP	IMP and NIMP	IMP and NIMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labelling	Study intervention will be provided in high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle will contain sufficient medication for at least 28 days plus overage. Each bottle will be labelled in accordance with GMP Annex 13 and per country requirements.	Study intervention will be provided in a 500 mg vial for infusion after dilution. The solution contains C mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% w/v polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume for durvalumab is 10.0 mL Investigational product vials are stored at [redacted]°C to [redacted]°C ([redacted]°F to [redacted]°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure. Each vial will be labelled in accordance with GMP Annex 13 and per country requirements.
Aliases	Lynparza®; AZD2281	Imfinzi®; MEDI4736

Abbreviations: IV = intravenous; GMP = Good Manufacturing Practice; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; Q4W = every 4 weeks.

Olaparib

Before commencing treatment, participants must first meet the haematology/clinical chemistry requirements specified in Section 5.1.

Participants in the olaparib monotherapy group (Cohort A) and the olaparib plus durvalumab combination therapy group (Cohort B) will take CCI mg olaparib orally BID. Olaparib should be taken at the same time each day, approximately 12 hours apart with a glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib tablets can be taken with or without food. If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any participant enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the participant 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 participant should take their allotted dose at the next scheduled time.

Durvalumab

Durvalumab is a sterile, clear to opalescent, colourless to slightly yellow solution, free from visible particles.

Durvalumab will be administered as 1500 mg IV Q4W, on Day 1 of each cycle, to participants in the combination therapy arm (Cohort B) for four to six 28-day cycles per the SoA (Table 1) prior to receiving definitive surgery, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Duration of Treatment

Cohort A

- Neoadjuvant olaparib monotherapy taken daily for four to six 28-day cycles.
- Participants will then undergo definitive surgery within 6 weeks following the final dose of neoadjuvant olaparib therapy (or per local standard of care) followed by standard treatment (radiation therapy, systemic therapy per institutional standards).
- Participants who achieve pCR at surgery, as determined by local pathology assessment, will be allowed to receive adjuvant olaparib monotherapy in lieu of standard adjuvant systemic therapy, per physician choice. If the physician chooses adjuvant olaparib:
    - Adjuvant ET may be co-administered with olaparib in participants with pCR who are ER-low and who continue receiving olaparib in the adjuvant setting, per physician's choice.
    - Participants who receive post-surgical radiotherapy should start adjuvant olaparib monotherapy ideally within 8 weeks after last treatment (surgery or radiotherapy) but in no case longer than 12 weeks after the last treatment.

- **Adjuvant olaparib monotherapy must not start until the participant demonstrates adequate marrow and organ function (as described in Inclusion Criterion #5).**
- The total duration of olaparib therapy in the neoadjuvant and adjuvant setting must not exceed 12 cycles.

Cohort B

- Neoadjuvant combination therapy with olaparib ([redacted] mg BID) plus durvalumab (1500 mg IV Q4W) for four to six 28-day cycles.
- Participants will then undergo definitive surgery within 6 weeks following the final dose of neoadjuvant olaparib therapy (or per local standard of care) followed by standard treatment (radiation therapy, systemic therapy per institutional standards).
- Participants who achieve pCR at surgery, as determined by local pathology assessment, will be allowed to receive adjuvant olaparib monotherapy in lieu of standard adjuvant systemic therapy, per physician choice. If the physician chooses adjuvant olaparib:
  - Adjuvant ET may be co-administered with olaparib in participants with pCR who are ER-low and who continue receiving olaparib in the adjuvant setting, per physician's choice.
  - Participants who receive post-surgical radiotherapy should start adjuvant olaparib monotherapy ideally within 8 weeks after last treatment (surgery or radiotherapy) but in no case longer than 12 weeks after the last treatment.
  - **Adjuvant olaparib monotherapy must not start until the participant demonstrates adequate marrow and organ function (as described in Inclusion Criterion #5).**
  - The total duration of olaparib therapy in the neoadjuvant and adjuvant setting must not exceed 12 cycles.

Participants with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, or spinal cord compression) must discontinue olaparib and durvalumab.

Crossover within the study will not be permitted.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1) The investigator or designee (eg, pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study intervention received at the site and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area at the site, in accordance with the labelled storage conditions and with access limited to the investigator and authorised site staff.

3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.2.1 Storage of Study Interventions: Durvalumab

Durvalumab vials are stored at refrigerated temperatures ([redacted]°C to [redacted]°C [[redacted]°F to [redacted]°F]) and must not be frozen. 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.

Study intervention must be kept in original packaging until time of preparation to prevent prolonged light exposure.

6.2.2 Durvalumab Infusion Preparation and Administration

6.2.2.1 Preparation

The dose of durvalumab must be prepared by the investigator or designee (eg, pharmacist) using aseptic technique. A dose of 1500 mg for participants > 30 kg in weight will be prepared using an intravenous (IV) bag containing[redacted] for injection, with a final durvalumab concentration ranging from [redacted] mg/mL. Add [redacted] mL (ie, 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within [redacted] mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If participant weight falls to ≤ 30 kg, weight-based dosing at [redacted] mg/kg will be prepared using an IV bag size selected such that the final concentration is within [redacted] mg/mL.

Total time from needle puncture of the study intervention vial to the start of administration must not exceed:

- [redacted] hours at [redacted]°C to [redacted]°C ([redacted]°F to [redacted]°F)
- [redacted] hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials. Durvalumab vials do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

6.2.2.2 Administration

Durvalumab infusions are to be administered through an IV administration set with a 0.2 or 0.22 µm filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

The durvalumab infusion time is [redacted] hour ± [redacted] minutes; however, if there are interruptions, the total allowed time must not exceed [redacted] hours with the infusion bag maintained at room

temperature, otherwise a new dose must be prepared from new vials.

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

The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

6.3 Measures to Minimise Bias

Participant Enrolment and Treatment Allocation

All participants will be centrally assigned to receive study intervention using an IVRS/IWRS. In Cohort A (classified as lower risk), all participants will be allocated to receive neoadjuvant olaparib monotherapy. In Cohort B, all participants (classified as higher risk) will be allocated to receive neoadjuvant olaparib plus durvalumab combination therapy. Before the study is initiated, the call/log-in directions and user guides for the IVRS/IWRS will be provided to each site.

Study intervention will be dispensed at the study visits summarised in SoA (Table 1).

Returned study intervention should not be re-dispensed to the participants.

If a participant withdraws from the study, then his/her enrolment code cannot be reused. Additional participants may be enrolled to ensure approximately 25 participants are evaluable for pCR analysis in both Cohorts A and B.

Investigators should keep a record (ie, the participant screening log) of participants who entered screening.

At screening/baseline (Days -28 to -1), the investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the participant. However, all screening laboratory and imaging results must have been obtained within 28 days of the first dose of study intervention.
- Participants will be identified to the IVRS/IWRS per country regulations. Obtain a unique PPD enrolment number (E-code) through the IVRS/IWRS in the following format PPD . This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
- Determine participant eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for genetic research study (optional). Participants who decide not to sign the specific genetic ICF, but the general study ICF, are eligible for study enrolment and all other study procedures.
- Once the participant is confirmed to be eligible, the investigator or suitably trained delegate will assign a treatment group via the IVRS/IWRS, based upon the participant's baseline risk category (ie, lower risk or higher risk).

If the participant is ineligible and not assigned a study intervention, the IVRS/IWRS should be accessed to terminate the participant in the system.

Participants must not be assigned a treatment and treated unless all eligibility criteria have been met. Participants will begin treatment on Day 1. Every effort should be made to minimise the time between study intervention allocation and the start of study intervention (ie, within 3 calendar days, maximum of 7 calendar days).

Procedures for Handling Incorrectly Enrolled Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, receive study intervention. There can be no exceptions to this rule. Participants who are enrolled but subsequently found not to meet all the eligibility criteria must not be started on study intervention and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is incorrectly started on treatment in error, 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 participant from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

Methods for Assigning Treatment Groups

Participants will be allocated treatment on the basis of their assigned risk category (ie, lower risk or higher risk).

Methods for Ensuring Blinding

This is an open-label study; rigorous methodology will be employed to ensure robustness of the primary endpoint assessment with a primary analysis of pCR based on central pathology assessment to minimise potential imaging reader bias.

6.4 Study Intervention Compliance

Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

The Investigational Product Storage Manager is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention.

6.4.1 Olaparib Compliance (Cohorts A and B)

When participants self-administer olaparib at home, participants should be given clear instructions on how and when to take their study treatment and compliance with olaparib will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documenting in the source documents and eCRF. All participants must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Participants will be instructed to notify study site personnel of missed doses.

A record of the number of olaparib tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the eCRF.

6.4.2 Durvalumab Compliance (Cohort B)

When participants are dosed at the site with durvalumab, durvalumab will be prepared, dispensed, and administered directly from the investigator or designee, under medical supervision. The date of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of durvalumab and study participant identification will be confirmed at the time of dosing in accordance with local treatment practices.

6.5 Concomitant Therapy

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

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. If any concomitant therapy is administered due to new or unresolved AE, it should be recorded. Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix H 2. Guidance regarding potential interactions with concomitant medications is provided in Appendix H 1.

Drug-drug Interactions

Olaparib

Guidance regarding potential interactions with concomitant medications is provided in Appendix H 1.

Durvalumab

There is no information to date on drug-drug interactions with durvalumab either preclinically or in patients.

As durvalumab is a monoclonal antibody that will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that durvalumab will induce or inhibit the major drug metabolizing CYP pathways. The mechanism of action of durvalumab involves binding to CCI As a result, there are no expected drug-drug interactions.

6.5.1 Rescue Medicine

As a result of immune-related AEs (imAE) that could potentially be experienced by participants on durvalumab, steroids and other immunosuppressant rescue medication have to be made available to the Cohort B participant population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for hepatitis).

Under certain circumstances when local sourcing by the study site is not feasible or local regulations prevent the use of infliximab or mycophenolate for this use (as they are considered off-label for management of immunotherapy related toxicities), AstraZeneca will centrally supply the required rescue medications, which will be labelled and accompanied by Prescribing Information with local language translated text in accordance with regulatory guidelines. Accountability and storage requirements, as specified in Section 6.2, apply for any study intervention supplied by AstraZeneca.

The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Management of Study Intervention Related Toxicities and Dose Modifications

6.6.1 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.

In case a dose reduction is necessary, olaparib will be administered according to Table 5 below. Once the dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Appendix H 1 for the dose modifications associated with concomitant treatment with CYP3A4/5 inhibitors). If the reduced dose of CCI mg BID is not tolerable, no further dose reduction is allowed and study intervention should be discontinued. Participants in Cohort B who discontinue olaparib may continue durvalumab monotherapy in the neoadjuvant treatment period at the discretion of the Investigator.

Table 5 Olaparib Dose Levels and Reductions to Manage Adverse Events[a]

Initial Dose	Dose Reduction 1	Dose Reduction 2
CC mg twice daily	CC mg CCI	CC mg CCI

[a] See Section 6.6.1.7 for dose modifications for renal impairment.

6.6.1.1 Management of Anaemia

Common treatable causes of anaemia (eg, iron, vitamin B12, or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anaemia may require blood transfusions.

For cases where participants develop prolonged haematological toxicity (≥2-week interruption/delay in olaparib due to CTCAE Grade 3 or 4 anaemia and/or development of

blood transfusion dependence), refer to Section 6.6.1.3. See Table 6 below for olaparib dose modifications to manage anaemia.

Table 6 Olaparib Dose Modifications for Anaemia

Haemoglobin	Action to be taken
Hb < 10 *but* ≥ 8 g/dL (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (eg, transfusion) *or* interrupt dose for a maximum of 4 weeks. Olaparib can be restarted if Hb has recovered to > 9g/dL. **Subsequent occurrences:** If Hb< **10** *but* ≥ **9 g/dL**, investigator judgement to continue olaparib with supportive treatment (eg, transfusion) *or* dose interrupt (for max of 4 weeks) and upon recovery, a dose reduction may be considered (to CCI as a first step and to CCI as a second step). If Hb< **9** *but* ≥ **8 g/dL**, dose interrupt[a] (for max of 4 weeks) until Hb ≥ 9 g/dL and upon recovery dose reduction may be considered (to CCI as a first step and to CCI as a second step).
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 CCI as a first step and to CCI CCI as a second step in the case Hb decrease recurs. Additional actions for participants in Cohort B (olaparib + durvalumab): **Prior to any transfusions, perform**: • Direct Coombs test • Reticulocyte count • Haptoglobin • Lactate deyhdrogenase

[a] Dose interruption is recommended as described in the setting of recurrent anaemia with Hb <9 but ≥ 8 g/dL; however, a dose interruption is not required if, in the investigator's clinical judgment, it is considered to be in the participant's best interest to continue treatment uninterrupted. Dose reduction(s) should be considered but are not required. In the absence of a dose interruption and/or dose reduction(s), haemoglobin levels should be assessed at least bi-weekly in order to detect the development of CTCAE Grade ≥3 anaemia. If CTCAE Grade ≥3 anaemia develops, the participant should be managed according to Table 6.

6.6.1.2 Management of Neutropenia, Leukopenia, and Thrombocytopenia

Prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended. However, if a participant develops febrile neutropenia, olaparib 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 24 hours (7 days for pegylated G-CSF) of the last dose of olaparib unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines. See Table 7 below for olaparib dose modifications to manage neutropenia, leukopenia, and thrombocytopenia.

Table 7 Olaparib Dose Modifications for Neutropenia, Leukopenia, and Thrombocytopenia

Toxicity	Olaparib Dose Adjustment
CTCAE Grade 1-2	Investigator judgement to continue olaparib or interrupt dosing (for a maximum of 4 weeks); give appropriate supportive treatment and investigate causality.
CTCAE Grade 3-4	Dose interruption (for a maximum of 4 weeks) until recovered to CTCAE Grade 1 or resolved. If CTCAE Grades 3 or 4 reoccurs, dose reduce to CC **mg twice daily** as a first step and CC **mg twice daily** as a second step.

6.6.1.3 Management of Prolonged Haematological Toxicity

If a participant develops prolonged haematological toxicity (≥2 weeks interruption/delay in study treatment due to CTCAE Grade 3 or 4 anaemia, neutropenia [ANC < 1 x 10^9/L], or thrombocytopenia [platelets < 50 x 10^9/L]) and/or development of blood transfusion dependence:

- Check weekly differential blood counts, including reticulocytes and perform a peripheral blood smear.
- If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the participant should be referred to a haematologist for further investigations.
- Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage, according to standard haematological practice.
- Olaparib should be discontinued if blood counts do not recover to CTCAE Grade 1 or resolve within 4 weeks of dose interruption.

6.6.1.3.1 Myelodysplastic Syndrome, Acute Myeloid Leukaemia, or Other Clonal Blood Disorders

Development of a confirmed MDS, AML, 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 should be discontinued if participant's diagnosis of MDS and/or AML is confirmed.

6.6.1.4 Management of Non-Haematological Toxicity

Dose interruptions are allowed, as required, for a maximum of 4 weeks on each occasion. If the interruption is > 4 weeks, the study monitor must be informed. Where toxicity recurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then the participant should be considered for dose reduction or must permanently discontinue olaparib.

Olaparib can be dose reduced to CCI mg BID as a first step and to CCI mg BID as a second step. Olaparib must be interrupted if at the discretion of the investigator, if any CTCAE Grade 3 or 4 AE occurs which the investigator considers to be related to administration of olaparib.

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

6.6.1.5 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 olaparib 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 olaparib can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca study physician.

6.6.1.6 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 severity (CTCAE Grade 1 or 2), 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 approximately 9 months, and for vomiting at approximately 6 to 7 months.

No prophylactic antiemetic treatment is required at the start of olaparib treatment; however, participants 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 food.

As per international guidance on antiemetic use in cancer patients (European Society for Medical Oncology, NCCN), a single agent antiemetic should be considered (eg, dopamine receptor antagonist, antihistamines, or dexamethasone).

6.6.1.7 Management of Renal Impairment

If subsequent to study entry and while on olaparib therapy, a participant's estimated CrCl falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly to calculate creatinine clearance by Cockcroft-Gault equation or based on a 24-hour urine test. See Table 8 below for olaparib dose modifications to manage renal impairment.

Table 8 Olaparib Dose Modifications for Renal Impairment

Renal Impairment	Olaparib Dose Adjustment
Moderate (CrCl 31 - 50 mL/min)	Recommend dose reduction to CCI [redacted]. The investigator should use his or her discretion in determining whether a dose change or discontinuation of olaparib is warranted since CrCl is only an estimate of renal function.
Severe (CrCl ≤ 30 mL/min)	Recommend that olaparib be **discontinued**. Olaparib has not been studied in patients with severe renal impairment or end-stage renal disease.

6.6.1.8 Interruptions for Intercurrent Non-Toxicity Related Events

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

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

Olaparib should be stopped at least 3 days prior to planned surgery. After surgery, olaparib can be restarted when the wound has healed. No stoppage of olaparib is required for any needle CCI procedure.

Olaparib should be discontinued for a minimum of 3 days before a participant undergoes radiation treatment. Participants with pCR who receive post-surgical radiotherapy and who plan to receive adjuvant olaparib monotherapy should resume olaparib therapy ideally within 8 weeks after last treatment (surgery or radiotherapy) but in no case longer than 12 weeks after completion of last treatment.

6.6.2 Durvalumab

Dose delays (interruptions) are permitted for immune-oncology therapy; however, dose reductions are **not permitted** (see Dosing Modification and TMG in the Annex document to this CSP).

Participants may delay dosing under certain circumstances.

- Dosing may be delayed per the Dosing Modification and TMG, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
- Dosing intervals of a subsequent cycle may be shortened as clinically feasible in order to gradually align treatment cycles with the breast MRI for volumetric assessment. Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-lives of durvalumab (see current IB for durvalumab).

6.6.2.1 Management of Toxicities

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 study intervention 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.

If a participant in Cohort B discontinues treatment with durvalumab due to toxicity, they may continue with olaparib in monotherapy as long as they are continuing to show clinical benefit, as judged by the investigator in consultation with the study physician, and in the absence of discontinuation criteria. If olaparib is discontinued due to treatment-related toxicity in Cohort

B, durvalumab may continue at the discretion of the investigator and participant when toxicity resolves to Grade 2 or less.

6.6.2.2 Durvalumab Guidelines

Comprehensive TMGs have been developed to assist investigators with the recognition and management of toxicities associated with the use of durvalumab [redacted] inhibitor). These guidelines are applicable when durvalumab is used in combination with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially 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 (TMGs) for Durvalumab Monotherapy or in Combination with Other Products" is provided to the investigative site as an Annex document and is maintained within the Site Master File.

Participants should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other aetiologic causes of the AE. Serologic, immunologic, and histologic ([redacted] data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative aetiology, events should be considered potentially immune related. In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 of this CSP and the Dosing Modification and TMGs). Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and TMGs. 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 durvalumab regimen by the reporting investigator.

6.7 Intervention after the End of the Study

As described in Section 4.4, the study will remain open until all participants have discontinued study intervention and completed their last expected visit/contact.

After the final DCO for this study, AstraZeneca will continue to supply olaparib to participants who achieved pCR at surgery, as determined by local pathology assessment, and are receiving adjuvant olaparib monotherapy in lieu of standard adjuvant systemic therapy, per physician choice, until the participant reaches a maximum of 12 cycles total duration of olaparib therapy in the neoadjuvant and adjuvant setting or until meeting any other discontinuation criteria, as defined in Section 7.2, whichever occurs first. Participants should be followed according to the institution's standard of care assessments. No further data collection is required, except for reporting of SAEs.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by

AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the participant(s) to alternative supply, where possible.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participant(s) currently receiving treatment with olaparib may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be eligible to move to such a study would be given a new informed consent, as applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Upon completion of neoadjuvant therapy, all participants will discontinue study intervention either temporarily (Section 7.1) or permanently (Section 7.2) depending the outcome of definitive surgery and the investigator's plans for further therapy after definitive surgery. Participants who opt to withdraw early from protocol-specified neoadjuvant therapy will be considered to have permanently discontinued study intervention (Section 7.2). Participants receiving olaparib monotherapy in the adjuvant setting will be permanently discontinued from study intervention upon completion of adjuvant olaparib monotherapy (Section 7.2).

7.1 Temporary Discontinuation of Study Intervention at Completion of Neoadjuvant Therapy for Definitive Surgery

Participants will temporarily discontinue study intervention at the completion of the neoadjuvant therapy to undergo definitive surgery within 6 weeks following the final dose of neoadjuvant olaparib therapy (or per local standard of care) and will be followed up for safety in Post-Neoadjuvant Safety Assessments at 30 days (+7 days) after the last dose of olaparib (Cohort A and B) and 90 days (+7 days) after the last dose of durvalumab (Cohort B), per GCP. Additional assessments to be performed at the time of the 30-day and 90-day Post-Neoadjuvant Safety Assessment visits are detailed in the SoA (Table 1).

Participants who achieve a pCR at surgery, as determined by local pathology assessment, will be allowed to resume study intervention with adjuvant olaparib monotherapy in lieu of standard adjuvant systemic therapy, per physician choice. If the physician chooses adjuvant olaparib, then the total duration of olaparib therapy in the neoadjuvant and adjuvant setting must not exceed 12 cycles. Adjuvant ET may be co-administered with olaparib in participants with pCR who are ER-low and who continue receiving olaparib in the adjuvant setting, per physician's choice. **Adjuvant olaparib monotherapy must not start until the participant demonstrates adequate marrow and organ function (as described in Inclusion Criterion #5).**

7.2 Permanent Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention either due to early discontinuation or completion of the protocol-specified neoadjuvant or adjuvant therapy (ie, completion of study intervention).

The investigator should instruct the participant to contact the site before or at the time that study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention will need to be discontinued from the IVRS/IWRS. All olaparib should be returned by the participant at their next on-site study visit or unscheduled visit.

Participants may be discontinued from study intervention in the following situations.

- Clinical progression.
- Investigator determination that the participant is no longer benefiting from study intervention.
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing, including any AE that meets criteria for discontinuation defined in the dose modification guidelines (Section 6.6).
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- Severe non-compliance with the CSP as judged by the investigator or AstraZeneca.
- Pregnancy or intent to become pregnant.
- Incorrectly enrolled participants (ie, the participant does not meet the required inclusion/exclusion criteria for the study, and, in the opinion of AstraZeneca, it would not be safe for the participant to continue the study intervention).
- Completion of study treatment.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study. In the event a participant discontinues from study intervention, subsequent treatment options will be at the discretion of the investigator as the participant continues in the survival follow-up phase of the study.

If a participant in Cohort B discontinues treatment with durvalumab due to toxicity, they may continue with olaparib in monotherapy as long as they are continuing to show clinical benefit, as judged by the investigator in consultation with the study physician, and in the absence of discontinuation criteria.

If olaparib is discontinued due to treatment-related toxicity for participants in Cohort B, durvalumab may continue in the neoadjuvant setting at the discretion of the investigator.

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation (ie, the End of Treatment Visit) and follow-up and for any further evaluations that need to be completed.

7.2.1 Safety Follow-up of Participants Post Discontinuation of Study Intervention

If neoadjuvant study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety in the post-neoadjuvant safety follow-up period (30 days after last dose [+7 days] for Cohort A and at 30 days after last dose of olaparib [+7 days] and 90 days after last dose of durvalumab [+7 days] for Cohort B,), as per the SoA (Table 1). All participants who permanently discontinue adjuvant monotherapy olaparib will be followed up for post-intervention safety assessments at 30 days (+7 days) after the last dose of olaparib, per GCP. Additional assessments to be performed at the time of the 30-day Post-Intervention Safety Follow-up visit are detailed in the SoA (Table 1).

7.2.2 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA (Table 1) until death, withdrawal of consent, or the end of the study. The status of ongoing, withdrawn (from the study), and "lost to follow-up" participants at the time of an EFS analysis should be obtained by the site personnel by checking the participant notes and hospital records, via telephone contact with the participant or the participant's family, by contact with the participant's current physician, or by checking publicly available death registries. In the event that the participant has actively withdrawn consent to the processing of their personal data, the vital status of the participant can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

For participants with cPD, CCI sample and optional CCI should be collected where medically feasible. Additional assessments to be performed at the time of survival follow-up visits are detailed in the SoA (Table 1).

7.3 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at 30 days [+7 days] after discontinuing olaparib and at 90 days [+7 days] for those participants who received durvalumab after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records).

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If the participant requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.4 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the participant's status at that time.

Participants who decline 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 participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the protocol.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered to have been lost to follow-up from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant during survival follow-up within legal and ethical boundaries for all participants randomised. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

In order to support the efficacy endpoint of EFS assessment, the survival status of all participants in the Full Analysis and the Safety Analysis Sets should be re-checked; this includes those participants who withdrew consent or are classified as "lost to follow-up."

- Lost to follow-up – Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the participant's current physician, to obtain a current survival status (the applicable eCRF modules will be updated).
- In the event that the participant has actively withdrawn consent to the processing of their personal data, the survival status of the participant can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1). Data collection following study analysis until the end of the study is described below.

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

Data Collection Following Final Study Analysis until the End of the Study

For SAE and AE reporting and laboratory assessment collection after final analysis, see Section 8.3.11.

After the final DCO and database closure, only SAEs including MDS, AML, and new primary malignancies will be reported for the purposes of this study (see Section 8.3.11).

8.1 Efficacy Assessments

8.1.1 Surgical Assessment

All participants will be evaluated (at a minimum) or examined (ideally) by the treating surgeon at screening and must be evaluated and examined by the treating surgeon at a pre-surgery visit. Visits will include a clinical breast and lymph node examination and review of the imaging studies (MRI) of the breast and axilla. After evaluating the participant and reviewing the pertinent radiographic studies at the screening visit, the surgeon will determine whether the participant is a candidate for potentially curative surgery. Surgery must be planned to occur at completion of the protocol-stated four to six 28-day cycles of study intervention.

8.1.2 Definitive Surgery

Participants will undergo definitive surgery per local standard of care within 6 weeks following the final dose of neodjuvant olaparib therapy.

Details regarding date of definitive surgery, type of definitive surgery, tumour resectability, etc. will be recorded in the appropriate pages of the eCRF. Detailed pathological staging per AJCC and assessment of surgical margins will be performed by the local pathologist on all the tissues removed during the surgery. Pathology information from the definitive breast surgery will be entered into the eCRF when the pathology report is available.

If disease progression occurs prior to completion of planned neoadjuvant therapy, participants will permanently discontinue study intervention, have an End of Treatment Visit, and may proceed to definitive surgery, at the discretion of the responsible study physician. However, the participant's surgery information would not be entered into the eCRF and their surgical CCI samples should not be sent to central pathology. The participant would then enter the Survival Follow-up phase of the study.

8.1.2.1 Pathological Response

The primary analysis (pCR) for this study will be based on the central pathology review of histopathology slides from the participants' definitive surgeries. The local site pathologist will also assess pCR based upon examination of surgical specimens per local institutional standards and procedures. Further details will be provided in the Pathology Manual.

8.1.2.2 Residual Cancer Burden

The key secondary analysis will involve central and local pathology review of RCB.

The following 6 variables are required for the calculation of RCB after neoadjuvant treatment (http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3):

1) The largest 2 dimensions of the residual tumour bed in the breast.
2) Submission of the entire largest cross-sectional area of the residual tumour bed for histologic mapping, with specific identification of those slides in the pathology report.

3) Histologic assessment of the percentage of the tumour bed area that contains carcinoma (all carcinoma [ie, invasive and in situ]).
4) Histologic estimate of the percentage of the carcinoma in the tumour bed that is in situ.
5) The number of positive (metastatic) lymph nodes.
6) The largest diameter (mm) of the largest nodal metastasis.

Additional pathology documentation guidelines are provided in Appendix J.

8.1.2.3 Collection and Storage of Definitive Surgery Tissue Specimens for Central Pathology Review (Mandatory)

Tissue obtained during definitive surgery following neoadjuvant study intervention will be assessed using standard histopathologic parameters and the RCB technique to evaluate the extent of residual disease by the site pathologist (see Appendix J for pathology features required to be collected and reported for RCB determination).

Stained slides or a tissue block will be prepared as per the Pathology Manual and collected on an ongoing basis to be sent to a central laboratory for quality control, storage, and to perform the central pathology review to determine the primary endpoint, pCR. A complete copy of the local pathology report must be provided with the samples and maintained at the investigator site as source documents. Please refer to the Pathology Manual for complete instructions on specimen requirements, processing, and shipment.

8.1.3 Imaging Tumour Assessments

Tumour assessments will use volume images from MRI with IV contrast of the breast (bilateral) collected during screening/baseline and at Week 12 (Cycle 4) and at Week 24 (prior to definitive surgery, if applicable), and will be assessed locally. If MRI has been performed at Week 12 (ie, start of Cycle 4) and the participant proceeds to definitive surgery following Cycle 4 or Cycle 5, the MRI scan does not need to be repeated prior to definitive surgery, unless clinically indicated.

If, after exposure to olaparib monotherapy therapy (in Cohort A) or olaparib plus durvalumab combination therapy (in Cohort B), the participant does not undergo definitive surgery because the investigator believes (on the basis of clinical and/or imaging findings) that there is the likelihood of residual disease and plans to give additional non-protocol therapy (eg, chemotherapy), subsequent MRIs do not need to be performed.

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

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

It is important to follow the tumour assessment schedule as closely as possible (refer to the SoA [Table 1) relative to start of study intervention.

Screening/baseline imaging should be performed no more than 28 days before start of study

intervention and ideally should be performed as close as possible to and prior to the start of study intervention. *Note: If any suspicious nodes are identified in the screening MRI, an axillary ultrasound must be done. Sentinel nodes confirmed by ultrasound should be clipped (only 1 node is recommended if several are identified). If a clip is not placed at this time, the investigator should use dual tracers (radio-isotope and blue dye) to identify sentinel nodes at the time of surgery.*

Any further imaging following surgery will be at the discretion of the investigator and details regarding any post-surgery MRIs will not be recorded in the eCRF.

Neoadjuvant treatment continues for a maximum of 6 cycles and scanning/tumour assessments continue throughout neoadjuvant treatment until definitive surgery, as per the SoA (Table 1). Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit.

The tumour volume as calculated by the site's MRI software should be recorded in the participant's eCRF. Individual dimensions used in the volume calculation do not need to be recorded. If the tumour volume must be calculated by hand it should be calculated as follows:

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

The guidelines describing the acquisition and analysis of tumour volume measurements are provided in Appendix I.

8.1.4 Post-Surgery Follow-up

Participants should receive post-operative systemic and radiation therapy per standard of care. Refer to Section 6.1.1 for participants receiving olaparib in the adjuvant setting.

8.1.5 Event-Free Survival (EFS)

A participant's EFS status is defined as progression of disease that precludes surgery, local or distant recurrence, second primary malignancy (breast or other invasive cancers), or death due to any cause. Scans and other clinical assessments will be performed according to the local practice. EFS status will be determined every 3 months (±14 days) for the first 2 years post End of Treatment Visit and then every 6 months (±14 days) thereafter. The date of EFS assessment and investigator opinion of progression status will be recorded in the source documents and the eCRF.

8.1.6 Recurrence Free Interval (RFI)

Participants who achieve pCR will have their RFI status recorded per local standard clinical practice. A participant's RFI status is defined as the time from date of surgery at which pCR is identified to local or distant recurrence of breast cancer, or death due to breast cancer, whichever occurs first. RFI status will be determined every 3 months (±14 days) for the first 2 years post End of Treatment Visit and then every 6 months (±14 days) thereafter. The date of RFI assessment and investigator opinion of recurrence status will be recorded in the source documents and the eCRF.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Physical Examinations

- A full physical examination will be performed according to the SoA (Table 1) and will include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, hematologic/lymphatic, and neurological systems.
- A targeted physical examination will be performed according to the SoA (Table 1) and will include, at a minimum, assessments of the breast, skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Physical examinations, as well as assessments of height and weight, will be performed at time points specified in the SoA (Table 1). For Cohort A, weight will not be recorded in the eCRF after Cycle 1 Day 1. However, weight must be recorded in the eCRF for Cohort B during the entire neoadjuvant combination treatment. If a participant's weight change is clinically significant, it should be entered as an AE in the Adverse Events eCRF. Investigators should pay special attention to clinical signs related to previous serious illnesses, as new or worsening abnormalities may qualify as AEs; see Section 8.3.5 for details.

8.2.2 Vital Signs

Vital signs will be performed at time points specified in the SoA.

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed at Screening. Respiratory rate will not be recorded in the eCRF after Screening.

The date of collection and measurement of vital signs will be recorded on the appropriate eCRF. For Cohort A, blood pressure and pulse measurements will not be recorded in the eCRF after Cycle 1 Day 1; only body temperature will be recorded in the eCRF after Cycle 1 Day 1. However, see Section 8.2.2.1 for instructions regarding vital signs collection for Cohort B. For participants who receive olaparib adjuvant treatment, blood pressure and pulse measurements will not be recorded in the eCRF; only body temperature will be recorded in the eCRF.If a participant's vital signs are clinically significant, the medical term for the abnormality should be entered as an AE in the Adverse Events eCRF.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5.

8.2.2.1 Vital Signs at First Infusion of Durvalumab (Cohort B Only)

On the first infusion day, participants in the olaparib plus durvalumab combination therapy arm will be monitored and vital signs collected/recorded in the eCRF prior to, during, and after infusion of durvalumab, as presented in the bulleted list below.

Blood pressure and pulse will be collected from participants 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 the infusion up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes after starting the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ±10 minutes)

If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab.

8.2.2.2 Vital Signs at Subsequent Infusions of Durvalumab (Cohort B Only)

On subsequent infusion days starting at Cycle 2 Day 1, blood pressure, pulse, and weight should be measured, collected/recorded in the eCRF prior to the start of the infusion. Participants should be carefully monitored, and blood pressure and pulse should be measured during and after infusions, as per institution standards and as clinically indicated. If no infusion reaction occurred with the initial infusion, and at the discretion of the investigator, the 1-hour observation period may be shortened or eliminated.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5. For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

8.2.3 Electrocardiograms (Cohort B Only)

Single 12-lead electrocardiograms (ECGs) will be performed at time points as specified in the SoA (Table 1) after the participant has been resting semi-supine for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT interval corrected by Fridericia's formula intervals.

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

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 participant's medical record as source data.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Table 1).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry and haematology will be performed at a local laboratory at or near to the investigator site. Other safety laboratory tests include assessment for pregnancy (serum or urine) in women of child-bearing potential at the time points shown in the SoA (Table 1). 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). The following laboratory variables will be measured.

Table 9 Laboratory Safety Variables

Haematology/Haemostasis (Whole Blood)	Clinical Chemistry (Serum or Plasma)
Haemoglobin (Hb)	Albumin
Leukocyte count (total white cell count)	Alkaline phosphatase
Absolute[a] or differential lymphocyte count	ALT
Absolute[a] or differential neutrophil count	Amylase
Platelet count	AST
Reticulocyte count[b]	Bilirubin, total
	Calcium, total
Coagulation	Chloride
INR[c]	Creatinine
	Gamma-glutamyl transferase
Urinalysis	Glucose
Colour and appearance	Lactate dehydrogenase
pH and specific gravity	Lipase
Erythrocytes	Magnesium
Blood	Potassium
Bilirubin	Protein, total
Glucose	Sodium
Ketone bodies	TSH
	T3 free (reflex)
	T4 free (reflex)
	Urea or blood urea nitrogen (BUN), depending on local practice

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic Case Report Form; INR = international normalised ratio; PTT = partial thromboplastin time; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.
Note: See Section 8.2.5.1 for details regarding coagulation tests. ONLY required for participants taking warfarin.
a Absolute neutrophil count and absolute lymphocyte count results are preferred. If a laboratory reports both the absolute values and a percentage (%), only the absolute values should be entered into the eCRF. If absolute values are not available, percentage results should be entered into the eCRF.
b For Cohort B participants only. Performed at screening and as clinically indicated if participant experiences CTCAE grade ≥ 3 anaemia and requires a transfusion (reticulocyte count must be performed PRIOR to the transfusion). Please refer to Table 6 in Section 6.6.1.1.
c Only required if the participant is receiving warfarin.
For further details, please refer to the Schedule of Assessments (Table 1).

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. 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 8.3.5.

All participants with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study intervention must be followed and 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.

NB. In case a participant shows an AST **or** ALT ≥3×ULN together with TBL ≥2×ULN, please refer to Appendix E "Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law" for further instructions.

8.2.5 Other Safety Assessments

8.2.5.1 Coagulation Tests

Coagulation assessments are only required if the participant is receiving warfarin.

International normalised ratio (INR) will be performed at screening and if clinically indicated.

For participants taking warfarin, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Each coagulation test result will be recorded in the eCRF.

8.2.5.2 Pneumonitis (ILD) Investigation

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the durvalumab Dosing Modification and TMG (see the Annex document to this CSP) will be applied. The results of the full diagnostic workup (including high-resolution CT, blood and sputum culture, haematological 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 oedema, or pulmonary haemorrhage. In the presence of confirmatory high-resolution CT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the durvalumab Dosing Modification and TMGs (see the Annex document to this CSP) should be followed.

In addition, see Section 6.6.1.5 for management of new or worsening pulmonary symptoms

(eg, dyspnoea) in regard to olaparib dosing and toxicity management.

8.2.5.3 Bone Marrow or Blood Cytogenetic Samples

Bone marrow and/or blood cytogenetic samples may be collected for participants with prolonged haematological toxicities as defined in Section 6.6.1.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis, and flow cytometry, and a core [redacted] 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 anonymised reports must be provided by the investigator for documentation in the Patient Safety database. These data are not required to be entered into the eCRF.

8.2.5.4 ECOG Performance Status

ECOG performance status will be assessed at the times specified in the SoA (Table 1) based on the following:

0. Fully active; able to carry out all usual activities without restrictions.
1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work).
2. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.
3. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4. Completely disabled; unable to carry out any self-care and totally confined to bed or chair.
5. Dead.

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

8.3 Adverse Events and Serious Adverse Events

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

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, recording, and reporting events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from the time of signature of the ICF, throughout the treatment period, and until the safety follow-up period is completed. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.12.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or

her, the investigator shall, without undue delay, report the SAE to the sponsor.

For pharmacovigilance purposes and characterisation, any SAE of MDS/AML or new primary malignancy occurring after the 30-day safety follow-up period should be reported to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. Investigators will be asked if the participant has developed MDS/AML or a new primary malignancy during the survival follow-up and prompted to report any such cases.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event 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 (Appendix B).
- Investigator causality rating against the study interventions (yes or no).
- Action taken with regard to study interventions.
- Administration of treatment for the AE.
- Outcome.

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

- Date AE met criteria for SAE.
- Date investigator became aware of SAE.
- Seriousness criteria.
- Date of hospitalisation.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment to other medication.

The grading scales found in the National Cancer Institute CTCAE version 5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE

grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.3 Causality Collection

The investigator should assess causal relationship between study interventions 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 study intervention?"

For SAEs, causal relationship should 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 B of the CSP.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant 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.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests, vital signs, physical examinations, and ECGs will be summarised in the clinical study report (CSR).

Deterioration as compared with baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention [eg, dose adjustment or study intervention interruption]).

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, anaemia versus low haemoglobin 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 progressive disease (PD), 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 unless unequivocally related to the disease under study.

8.3.6 Hy's Law

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

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the study intervention 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 metastases or the progression of existing primary tumours or metastasis to the primary cancer under study should be considered as PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study.

8.3.8 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New primary cancers are those that are not the primary reason for the administration of study intervention and are identified after the participant's inclusion in this study. They do not include recurrence of the original cancer.

8.3.9 Deaths

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

- Death clearly resulting from PD should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to PD under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of study intervention should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

8.3.10 Adverse Events of Special Interest (AESIs)

AESIs are events of scientific and medical interest specific to the further understanding of the olaparib and durvalumab safety profiles and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.3.12.

8.3.10.1 Adverse Events of Special Interest for Olaparib

AESIs for olaparib are the important identified risk of MDS/AML and the important potential risks of new primary malignancy (other than MDS/AML) and the potential risk of pneumonitis.

Any event of MDS/AML, new primary malignancy, or pneumonitis should be reported to AstraZeneca Patient Safety whether it is considered a non-serious AE (eg, non-melanoma skin cancer) or SAE, and regardless of investigator assessment of causality. These AEs must be reported according to the timelines for reporting an SAE (see Section 8.3.1) to allow timely safety monitoring.

Additional detailed information regarding the AESI will be requested from any investigator reporting an AESI. During the study, there may be other events identified as AESIs that require the investigators to provide additional detailed information to help characterise the event and gain a better understanding regarding the relationship between the event and study intervention.

8.3.10.2 Adverse Events of Special Interest for Durvalumab

AESIs for durvalumab 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. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology.

If the investigator has any questions in regard to an event being an imAE, the investigator should promptly contact the study physician.

AESI/imAEs observed with anti PD-L/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhoea/colitis, intestinal perforation, endocrinopathies (hypo- and hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism, and Type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis, encephalitis, and rare/less frequent events (including, but not limited to, haematological events [such as immune-mediated neutropenia], neuromuscular toxicities [such as myasthenia gravis and Guillain-Barré syndrome], non-infectious meningitis, pericarditis, rheumatological events, sarcoidosis, skin events, uveitis, cholangitis sclerosing, immune-mediated cystitis [and other events involving the eye], and vasculitis).

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

More detailed guidelines for their evaluation and treatment are described in detail in the Dose Modification and TMGs (see the Annex document to this CSP). 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 intervention/study regimen by the reporting investigator.

8.3.11 Safety Data to be Collected Following the Final Data Cut-Off of the Study

For participants continuing to receive study intervention after the final DCO, AEs and SAEs will be collected, but only SAEs, including MDS, AML, and new primary malignancies, will be reported. In addition, it is recommended that investigators monitor the participant's safety laboratory results periodically during treatment in order to manage AEs, consistent with the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6). All data after the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving olaparib (or within the 30 days following the last dose) and/or durvalumab (or within 90 days following the last dose) after the final DCO must be reported as detailed in Section 8.3.12.

8.3.12 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, 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.

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 electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone followed by completion of a paper SAE form.

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

For further guidance on the definition of an SAE, see Appendix B of the CSP.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drugs (olaparib and durvalumab).

8.3.13 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partner of male participants, should be reported to AstraZeneca.

8.3.13.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention 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 participant 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 hour**s 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 8.3.12) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and subsequently the outcome of the pregnancy should be reported to AstraZeneca.

8.3.13.2 Paternal Exposure

Non-sterilised male participants who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or donating or banking sperm for the duration of the study (from the time of screening) and for 3 months after the last dose of study intervention.

Pregnancy of the participant'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 of study intervention until 3 months after the last dose of study intervention should be followed up and documented in the medical record and provided to the AstraZeneca Patient Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the participant's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and

submit it to the relevant Regulatory Authority/Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) prior to use.

8.3.14 Medication Error, Drug Abuse, and Drug Misuse

8.3.14.1 Timelines

In an event of medication error, drug abuse **or** drug misuse during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one day**, ie, immediately but no later than 24 hours of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (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, drug abuse, or misuse (see Section 8.3.12) and **within 30 days** for all other events.

8.3.14.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for a study intervention or AstraZeneca non-investigational medicinal product that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of a medication error can be found in Appendix B 4.

8.3.14.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of study intervention or AstraZeneca non-investigational medicinal product for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.14.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of study intervention or AstraZeneca non-investigational medicinal product for medicinal purposes outside of the authorised product information, or for unauthorised study intervention(s), outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4 Overdose

Use of olaparib or durvalumab in doses exceeding that specified in the protocol (ie, olaparib >CCI mg BID or durvalumab >1500 mg Q4W) is considered to be an overdose. There is currently no specific treatment in the event of overdose of olaparib or durvalumab, and possible symptoms of overdose are not established.

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 intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives 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 overdoses associated with an SAE (see Section 8.3.12) and within 30 days for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection, handling, storage, and shipping of biological samples will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality.

Samples will be stored for a maximum of 15 years from the end of the study (as defined in the CSP) in line with consent and local requirements, after which they will be destroyed/repatriated.

- Samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years from the end of the study (as defined in the CSP). Additional use includes but is not limited to further characterisation of any CCI [redacted] CCI confirmation and/or requalification of the assay as well as additional assay development work and diagnostic development. The results from future analysis will not be reported in the CSR.

For further details on Handling of Human Biological Samples, see Appendix C.

8.5.1 Pharmacokinetics

PK parameters are not evaluated in this study.

8.5.2 CCI [redacted] Assessments (Cohort B Only)

Only applicable to participants treated with durvalumab: Blood samples for determination of CCI [redacted] and CCI [redacted] in serum will be assayed by bioanalytical test sites

operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

CCI may also be further tested for characterisation of the CCI.

8.5.3 Pharmacodynamics

8.5.3.1 Collection of Samples

Whole blood samples and whole blood soluble biomarkers are pharmacodynamics parameters in this study.

Pharmacodynamics data and samples collected as part of the study may be used for development of current or future diagnostic tests, as required.

8.6 Human Biological Sample Biomarkers

CCI



8.6.1 Collection of Samples for Biomarker Analysis

Participant consent to the study includes participation in the mandatory biomarker assessment components of the study.

Samples for biomarker assessment are required and will be collected from all participants in this study as specified in the SoA (Table 1) and as described below.

CCI **Samples**

CCI *Status*

CCI status will be evaluated retrospectively via central testing for all participants using

their diagnostic or baseline [CCI] samples. Both [CCI] may be performed to assess [CCI] expression. In addition, information from local [CCI] testing will be collected if available, including information regarding the assay, cut-off used, and positive/negative status. [CCI] may be explored. The association between [CCI] status and other biomarkers, and [CCI] will be explored.

[CCI] *Samples at Diagnosis*

All participants will be required to provide a [CCI] sample from the [CCI] if available (per SoA [Table 1]: [CCI] sample").

[CCI] *Samples at Baseline (Mandatory)*

A [CCI] of the [CCI] must be performed during screening to provide a [CCI] for [CCI] research (details in the Laboratory Manual) (per SoA [Table 1]: "Mandatory pre-treatment [CCI] This mandatory pre-treatment [CCI] must not be taken from a previously [CCI] . *Note: Ideally, a clip should be placed in the [CCI] at the [CCI] . If a clip was not placed at the time of the initial [CCI] then one should be placed at the time of the Cycle 2 or Cycle 3 optional [CCI] , if performed.*

For participants with T1b/N0 disease who have insufficient [CCI] for the required baseline [CCI] the [CCI] may be omitted but provision of their [CCI] [CCI] sample will be mandated.

When performing the pre-treatment [CCI] is deemed not medically feasible, please consult the sponsor.

[CCI] *Collected at Surgery (Mandatory)*

[CCI] collection from surgical resection is mandatory for all participants (per SoA [Table 1]: Mandatory [CCI] sample for biomarker analysis"). [CCI] [CCI] will be used for [CCI] research, as detailed above.

Tumour Tissue Collected for Residual Disease in the Setting of Discontinuation of Neoadjuvant Study Treatment to Receive Additional Non-Protocol Therapy (Mandatory)

If, after exposure to olaparib monotherapy therapy (in Cohort A) or olaparib plus durvalumab combination therapy (in Cohort B), the participant does not undergo surgery because the investigator believes (on the basis of clinical and/or imaging findings) that there is the likelihood of residual disease and plans to give additional non-protocol therapy (eg, chemotherapy), a [CCI] must be performed and assessed to confirm the presence or absence of residual disease (per SoA [Table 1]: "Mandatory tumour [CCI] for residual disease"). This is a clinical diagnostic [CCI] (not a research [CCI] and must be read by the local pathologist. [CCI] from this [CCI] will be submitted as [CCI] purposes after being used for clinical decision-making.

On-Treatment and Recurrence [CCI] *(Optional)*

Additional [CCI] samples will be collected during the study. The on-treatment [CCI] is strongly recommended if medically feasible and can be collected at any time during Cycle 2 or Cycle 3 (per SoA [Table 1]: "Optional [CCI] on-treatment").

CCI taken at the time of disease recurrence following definitive surgery are optional, as described below (per SoA [Table 1]: "Optional CCI at disease recurrence").

For collection of the Cycle 2 or Cycle 3 CCI or the CCI, participants will undergo a CCI to collect CCI for CCI research. Details for CCI collection, processing, storage, and shipment are provided in the Laboratory Manual.

CCI

CCI samples collected at baseline, on-treatment, at surgical resection (CCI only), and at progression will be used for exploratory objectives in the study, including but not limited to:

CCI

Results of the exploratory biomarker analysis may be reported separately to the CSR.

8.6.2 Blood Samples for Biomarker Analysis (Mandatory)

All consenting participants will provide blood samples at screening and on Day 1 prior to first dose of study treatment, at Day 1 of each cycle on-study, and at the 30-day Post-Neoadjuvant Safety Assessment Visit per the SoA (Table 1) for exploratory biomarker research. Blood samples may include but not limited to analysis of CCI, CCI CCI, confirmation of CCI status, and CCI.

Baseline measures and changes in CCI will be correlated with CCI as detailed in exploratory objectives. Note that samples will be obtained from participants allocated to each treatment arm. Comparisons will be made between CCI CCI and CCI to determine if CCI are CCI associated with olaparib monotherapy and olaparib plus durvalumab combination therapy and to inform on CCI

Results of the exploratory biomarker analysis may be reported separately in the CSR. The

exploratory biomarkers that will be investigated are described below.

CCI Status

All participants must have a known deleterious or suspected deleterious *BRCA*m to be allocated treatment; this may have been determined by local genetic testing on blood or CCI prior to study entry. The specific *BRCA* alteration on which eligibility is based must be entered into the trial database.

CCI sample collected on Day 1 prior to first dose of study treatment will be used for CCI status and to evaluate future CCI CCI. These samples may also be used for additional exploratory work, to CCI, understand the CCI, and improve the understanding of CCI CCI

Whole blood for CCI

Whole blood (approximately 40 mL at baseline and first 3 cycles and approximately 20 mL at Day 1 of all additional cycles until surgery, at the pre-surgery collection timepoint, and at the first post-surgical visit [approximately 2 to 4 weeks after surgery]) will be collected (please see all time points as described in the SoA [Table 1]). In addition, CCI samples will also be collected at Day 1 of all adjuvant cycles (if applicable), disease progression or recurrence at any time, and during survival follow-up. CCI will be extracted for CCI and CCI of CCI analysis.

Determining the molecular CCI has numerous advantages over relying on CCI, not least because these features may be tracked over time and CCI may inform CCI CCI. In addition, quantification of CCI from CCI in the blood is being explored as a useful CCI in numerous disease types, as early drops in CCI may be predictive of treatment benefit, whereas CCI CCI as measured by presence of CCI has been associated with CCI CCI Detection of CCI in CCI requires a complex multi-step assay, and may require whole exome sequencing of participants' CCI and whole blood to develop personalized CCI panel. Other highly sensitive CCI may be employed. Baseline CCI levels, longitudinal changes in CCI and CCI will be associated with CCI. Samples may be used for complete CCI and for comparison of different CCI assays. Baseline samples will be processed into CCI and CCI or a separate CCI will be analysed for CCI CCI to inform interpretation of CCI data.

All samples submitted for CCI analysis will be coded to prevent participant identification. CCI data and CCI from CCI analysis will be stored in a secure system at designated organizations and/or at AstraZeneca to analyse the sample.

Whole blood for CCI

Whole blood samples will be collected from all participants as described in the SoA (Table 1).

CCI diversity and tumour loss of CCI CCI have both been demonstrated to influence clinical response to ICIs

(Chowell et al. 2018). The [CCI] contains a high proportion of [CCI]. DNA extracted from this sample may be used specifically to enable determination of [CCI] and [CCI] of the [CCI] in the [CCI] as well as [CCI].

Whole blood [CCI]

Whole blood samples will be obtained from all participants as described in the SoA (Table 1). [CCI] will be prepared for quantification of [CCI] and/or [CCI] using [CCI] technology.

Focus is likely to be given to the [CCI] of [CCI] previously found to be [CCI] to olaparib and/or durvalumab (eg, [CCI]). This battery of genes is likely to be similarly [CCI] combination therapy. Moreover, [CCI] may indicate active [CCI] that may be augmented by [CCI]; correlations with [CCI] will be completed on select candidate, [CCI] with the aim of identifying [CCI]

Blood sample for [CCI]

Whole blood to extract [CCI] will be obtained from all participants at time points described in the SoA (Table 1).

Changes in the levels of [CCI] and [CCI] in the blood after treatment with [CCI] have been shown to be associated with [CCI] (Socinski et al. 2018). Please refer to the Laboratory Manual for specific instruction on sample collection. [CCI] Comparisons will be made between [CCI] and with treatment, to determine if [CCI] ith olaparib or olaparib plus durvalumab therapy.

Serum samples and [CCI]

Serum will be obtained from all participants at time points described in the SoA (Table 1).

[CCI] will be analysed in [CCI] and entered into the eCRF based on serial assessments of [CCI] [CCI] Comparisons will be made between baseline results and changes in concentrations over time to determine if [CCI] associated with olaparib monotherapy or olaparib plus durvalumab combination therapy in the neoadjuvant setting.

8.6.3 Collection of Optional [CCI] Samples

Collection of optional samples for [CCI] assessment is also part of this study as specified in the SoA (Table 1) and is subject to agreement in optional consent.

Optional [CCI] for [CCI] Research are recommended to be taken on-treatment and at recurrence for investigation of [CCI] for olaparib and

durvalumab and of [redacted] to olaparib or olaparib in combination with durvalumab.

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to Appendix C and the Laboratory Manual.

8.6.4 Other Study-Related [redacted] Assessments

Already collected samples may be analysed on different [redacted] including, but not limited to [redacted] to evaluate their association with observed [redacted] to olaparib or olaparib plus durvalumab.

Additional mandatory exploratory analyses may be undertaken on participants' samples to identify other [redacted]

For further details on Handling of Human Biological Samples, including storage, re-use and destruction, refer to Appendix C and the Laboratory Manual.

8.7 Optional Exploratory [redacted]

Collection of optional samples for [redacted] research is also part of this study as specified in the SoA (Table 1) and is subject to agreement in the ICF addendum.

Blood samples for [redacted] will be collected from participants who have consented to participate in the [redacted] component of the study. Participation is optional. Participants who do not wish to participate in the [redacted] research may still participate in the study.

See Appendix D for information regarding the storage and destruction of the [redacted] sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

8.8 Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

9.1 Statistical Hypotheses

There is no formal statistical hypothesis. The primary objective of this study is to obtain an estimate with adequate precision of the pCR rate as determined by central pathology review in 2 study intervention arms: olaparib monotherapy for lower risk participants (Cohort A) and olaparib plus durvalumab combination therapy for higher risk participants (Cohort B).

9.2 Sample Size Determination

The study is sized to characterise the pCR benefit of neoadjuvant olaparib monotherapy and

olaparib plus durvalumab combination therapy in participants with known *BRCA*m, HER2-negative, ER-negative or ER-low, non-metastatic breast cancer. In Cohort A, approximately 25 lower-risk participants will receive olaparib monotherapy treatment. In Cohort B, approximately 25 higher-risk participants will receive olaparib plus durvalumab combination therapy. Additional participants may be enrolled to ensure approximately 25 participants evaluable for pCR analysis are obtained in each cohort.

The primary endpoint is pCR (ypT0/Tis ypN0) rate. No formal comparison of the study intervention arms will be carried out. A sample size of 25 participants in each cohort was chosen to ensure adequate precision in the estimated pCR rate by assessing the width of the exact 95% CIs. With 25 participants, the precision of the estimation of pCR rate will be within ±21% (eg, pCR 48.0%, 95% CI 27.8%, 68.7%). Table 10 provides a set of Clopper-Pearson exact 95% CIs generated for different estimated pCR rates with a sample size of 25 participants.

Table 10 Exact Confidence Intervals of the Estimated Pathological Complete Response (pCR) Rate

Estimated pCR Rate (n=25)	95% Confidence Interval (n=25)
48.0% (12/25)	27.8%-68.7%
60.0% (15/25)	38.7%-78.9%
72.0% (18/25)	50.6%-87.9%
84.0% (21/25)	63.9%-95.5%

9.3 Populations for Analyses

The following populations are defined:

Table 11 Populations for Analysis

Population/Analysis Set	Description
Enrolled	All participants who sign the ICF.
Full Analysis Set (FAS)	All enrolled participants who received at least 1 dose of study intervention. Treatment groups will be assessed on the study intervention assigned (olaparib monotherapy in Cohort A or olaparib plus durvalumab combination therapy in Cohort B), regardless of the study intervention received.
pCR evaluable set	The pCR evaluable set will include all participants in the FAS from Cohorts A and B that underwent surgery and had an evaluable pCR assessment. Analyses on the pCR evaluable set will be performed according to the study intervention assigned (olaparib monotherapy in Cohort A or olaparib plus durvalumab combination therapy in Cohort B), regardless of the study intervention received.
Safety analysis set	All enrolled participants who have received at least 1 dose of study intervention. Safety Analysis Set participants are analysed according to the actual study intervention received.

CCI [redacted]

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

9.4 Statistical Analyses

The Statistical Analysis Plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Table 12 gives a summary of outcome variables and analysis populations.

Table 12 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
Pathological Complete Response (pCR)	Full Analysis Set + pCR evaluable set
Residual Cancer Burden (RCB)	Full Analysis Set + pCR evaluable set
Change in tumour volume from baseline	Full Analysis Set
Event-Free Survival (EFS)	Full Analysis Set
Demographic Data/Baseline Characteristics	
Demography	Full Analysis Set
Baseline and disease characteristics	Full Analysis Set
Protocol deviations (protocol deviations and important protocol deviations)	Full Analysis Set
Medical/surgical history	Full Analysis Set
Previous anticancer therapy	Full Analysis Set
Concomitant/previous medications/procedures	Full Analysis Set
Subsequent anticancer therapy	Full Analysis Set
CCI	
Safety Data	
Exposure	Safety Analysis Set
Adverse events	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital signs	Safety Analysis Set
Physical examination	Safety Analysis Set
Electrocardiogram (ECG; durvalumab only)	Safety Analysis Set

9.4.1 General Considerations

Participants will be analysed according to 2 study intervention arms in all efficacy analyses: olaparib monotherapy lower risk (Cohort A) and olaparib plus durvalumab combination therapy higher risk (Cohort B). The statistical analyses of efficacy will summarise the treatment groups on the basis of allocated study intervention. When assessing safety and tolerability, summaries will be produced based on the actual treatment received. This will include all participants who receive at least one dose of study intervention (olaparib or olaparib plus durvalumab). The safety data will be summarised descriptively and presented separately by cohort. No formal statistical testing will be performed.

Depending on the extent of any impact, summaries of data relating to participants diagnosed with COVID-19 and the impact of COVID-19 on study conduct (in particular missed visits, delayed or discontinued study intervention, and other protocol deviations) may be generated. More detail will be provided in the SAP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

9.4.2.1.1 Pathological Complete Response (pCR) Rate (ypT0/Tis ypN0)

The pCR rate (ypT0/Tis ypN0) is defined as the proportion of participants without residual invasive cancer in breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy per current AJCC staging criteria assessed by central pathology review at the time of definitive surgery. The analysis will be performed on all participants who received at least one dose of study intervention according to study intervention assigned. The measure of interest is the overall pCR rate.

Analysis Methods

The primary analysis will be based on the central pathology review of pCR and will be performed using the Full Analysis Set (FAS). Definitions of participants who will be considered responders or non-responders for the primary analysis of pCR are presented in Table 13.

Table 13 Definitions of Responders vs. Non-responders for pCR Assessments

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

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

An estimate of the pCR rate and its 2-sided exact Clopper-Pearson 95% CI will be calculated for each of the study intervention arms in Cohorts A and B in the FAS.

A supplementary analysis will be performed using the FAS, accounting for all responders regardless of whether the participants receive any subsequent therapy. A supplementary analysis of pCR as described above will also be performed in the pCR evaluable set.

If applicable, a further sensitivity analysis may be performed for the primary efficacy endpoint (pCR) using the same method as described above but based on all participants confirmed to have *BRCA*m by the retrospective central test. Additional supplementary and sensitivity

analyses may be explored to assess the robustness of treatment effects for the primary efficacy endpoint and will be specified in the SAP.

9.4.2.2 Secondary Endpoints

9.4.2.2.1 Pathological Complete Response (pCR) Rate (ypT0/Tis ypN0) – Local Pathology Review

pCR is defined as ypT0/Tis ypN0 (ie, no invasive residual in breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes) following completion of neoadjuvant systemic therapy, as assessed by the local pathologist. pCR rates will be analysed in the same way as the primary efficacy endpoint.

9.4.2.2.2 Residual Cancer Burden – Central and Local Pathology Review

The RCB is a numerical index of 4 classes to measure residual disease in either the breast or lymph node at the time of definitive surgery as assessed by both central and local pathology review by combining histopathologic components of residual disease (cellularity, overall diameter, number, and extent of nodal involvement). This evaluation is performed after the completion of neoadjuvant systemic therapy. The 4 classes are RCB 0 (pCR), RCB-I, RCB-II, and RCB-III.

The number and percentage of participants in each class will be presented. Percentage of participants with low residual disease (pCR and RCB-I) with exact Clopper-Pearson 95% CI will be calculated for each treatment arm, where possible.

9.4.2.2.3 Change from Baseline in Tumour Volume

Percentage change in tumour volume from baseline at Week 12 (Cycle 4) and Week 24 (prior to definitive surgery, if applicable) will be measured using MRI. Baseline is defined as the most recent measurement prior to the first administration of study intervention. Tumour volume at each assessment time point will be calculated locally at site and reported on the eCRF. Percentage change from baseline is defined as the value of post baseline minus baseline value, divided by baseline value, and multiplied by 100. The percentage reduction in tumour volume will be considered as 99% if the tumour becomes too small to measure at a post-baseline visit.

Percentage change from baseline will be summarised by treatment group and time point using descriptive statistics. In addition, percentage change in tumour volume will be presented graphically using waterfall plots for each treatment group, to present each participant's best percentage change in tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease.

9.4.2.2.4 Event-Free Survival

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

For participants who reached the time point of analysis without a known record of death or recurrence, the EFS will be censored at the date of last evaluable assessment.

No formal analysis of EFS data will be carried out. The number of events will be summarised

and the EFS data will be listed and may be presented in a swimmer plot, where appropriate.

9.4.2.3 Other Efficacy Endpoints

9.4.2.3.1 Recurrence-Free Interval

RFI may also be derived in participants who achieve pCR. Details will be given in the SAP.

9.4.2.3.2 ECOG performance status

ECOG performance status will be summarised by visit and by treatment group.

9.4.3 Safety

Safety data will be summarised descriptively and listed only. No formal statistical comparisons will be performed on the safety data. All safety data will be summarised based on the actual treatment received (olaparib monotherapy or olaparib plus durvalumab) in the Safety Analysis Set. The safety data will be summarised for Cohorts A and B separately.

Methods/Definitions

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities.

Adverse events occurring prior to start of study intervention, treatment-emergent AEs, and post-treatment AEs will be presented separately.

Treatment-emergent AEs are those events with an onset date (or worsening) on or after the first dose of study intervention and within 30 days following discontinuation with olaparib or 90 days following discontinuation with durvalumab, whichever is longer.

Adverse event summary tables will include treatment-emergent AEs observed overall and will be summarised by phase: neo-adjuvant intervention period (ie, up to surgery) and adjuvant intervention period (ie, from first dose of olaparib after surgery up to 30 days after discontinuation of olaparib). The Neoadjuvant Intervention Period (ie, up to surgery) will more accurately depict AEs attributable to study intervention only as a number of AEs following discontinuation of the study intervention are likely to be attributable to subsequent therapy.

Adverse events of special interest

AESIs are events of scientific and medical interest specific to the further understanding of the safety profiles of olaparib and durvalumab and may require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI may be serious or non-serious.

Other significant adverse events

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

9.4.3.1 Adverse Events

An overview of AEs will present for each treatment group the number and percentage of participants with any AE, AEs with outcome of death, SAEs, AEs causally related to study treatment, and AEs leading to discontinuation of study intervention, as well as AEs leading to study intervention dose interruptions and AEs leading to study intervention dose reduction, as well as the number of individual occurrences in those categories.

All AEs, both in terms of Medical Dictionary for Regulatory Activities preferred term and CTCAE grade, will be listed and summarised descriptively by count (n) and percentage (%) for each treatment arm. AEs will be presented for each treatment group by system organ class, high level term, and/or preferred term covering number and percentage of participants reporting at least one event and number of events where appropriate.

Separate AE tables will be provided, taking into consideration the relationship as assessed by the investigator, CTCAE grading, seriousness, death, and events leading to discontinuation of study intervention as well as other action taken related to study intervention, events of special interest, and other significant AEs.

An additional table may present the number and percentage of participants with the most common AEs. Most common (eg, frequency ≥%) will be defined in the SAP.

Key participant information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention.

An AE listing for the Safety Analysis Set will cover details for each individual AE.

Other safety data will be assessed in terms of physical examination, clinical chemistry, haematology, urinalysis, vital signs, and ECGs using descriptive statistics.

Full details of all safety analyses will be provided in the SAP.

9.4.4 Other Analyses

9.4.4.1 CCI

CCI status will be assessed for participants in each cohort according to prespecified criteria that may be detailed in the SAP. The relationship of exploratory CCI CCI may be presented. Biomarker exploratory analyses may be described in a separate analysis plan and may be reported outside the CSR in a separate report. The results of this CCI assessment will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this CCI assessment may be pooled with CCI data from other studies with the study intervention to generate hypotheses to be tested in future research. The results of this CCI assessment may be used for development of current or future diagnostic tests, as required.

9.4.4.2 Optional Exploratory CCI

Data will be reported outside the CSR (please see Appendix D).

9.4.4.3 CCI Data (Cohort B only)

CCI results will be listed by participant, and a summary will be provided by the

number and percentage of participants who develop [redacted] following study intervention. The [redacted] will be listed for samples confirmed positive for the presence of [redacted].

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

9.4.4.4 Demographic and Baseline Characteristics Data

The following will be listed and/or summarised by allocated treatment group: olaparib monotherapy lower risk (Cohort A) and olaparib plus durvalumab combination therapy higher risk (Cohort B).

- Participant disposition (including screening failures and reason for screening failure)
- Important deviations
- Inclusion in analysis populations
- Demographics (age, age group, sex, race and ethnicity)
- Participant characteristics at baseline (height, weight, and weight group)
- Participant recruitment by country and centre
- Disease characteristics at baseline (ECOG performance status, *BRCA* mutation status at screening [*BRCA*1, *BRCA*2 or *BRCA1/2*], primary tumour location, histology type, tumour grade, and AJCC stage)
- Evidence for family history of cancer, including *BRCA* related cancers
- Disease-related medical history, such as history of prior breast or ovarian cancer
- Relevant surgical history
- Physical examination at baseline

9.4.4.5 Treatment Exposure

Exposure will be calculated per participant and summarised descriptively. The duration of exposure in weeks will be summarised by means of descriptive statistics in the Safety Analysis Set. The number of cycles received will also be described.

The number of participants with permanent discontinuation of study treatment and the reasons will be summarized by cohort. All dosing data will be listed.

9.5 Interim Assessment

An interim assessment of efficacy will be performed in Cohort A and Cohort B and will include the first [redacted] participants in each cohort who have completed neoadjuvant therapy or discontinue study intervention for any reason. Within each cohort, if no more than [redacted] participant experiences cPD/death, enrolment will continue in that same cohort until approximately 25 participants are enrolled. If more than [redacted] of the initial [redacted] participants experience cPD/death, enrolment will be paused for additional review.

The SAP will describe the interim assessment in greater detail.

9.6 Data Monitoring Committee

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

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences International Ethical Guidelines (CIOMS)
  - Applicable International Council for Harmonisation (ICH) GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR) 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

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 an 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.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency Clinical Trials Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

A 2 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.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre. Note: In Germany, only participants who can provide informed consent will be eligible. Consent by a legally authorised representative is not allowed.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be re-consented and, if so, this must be to the most current version of the ICF(s) during their participation in the study.
- Participants who are rescreened are required to sign a new ICF.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants 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.

A 4 Data Protection

- 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.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The GDPR defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Unless previously specified, the biomarker data will have unknown clinical significance and AstraZeneca will not provide biomarker assessment results to participants, their family members, any insurance company, any employer, a clinical study investigator, a general physician, or any other third party, unless required to do so by law.

The participant's samples will not be used for any purpose other than those described in the study protocol.

A 5 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 CSP and letters to investigators.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRF 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 eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and Regulatory Authority inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined in the Integrated Quality Risk Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the quality tolerance limits and remedial actions taken will be summarised in the CSR.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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 a minimum of 25 years after study archiving as required by local regulations, according to the AstraZeneca GRAD schedule. 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.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF 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).

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 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 multicentre 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.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

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

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 intervention has been administered.

B 2 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up) that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as Non-Serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the study intervention under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of

B cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

B 2.1 Life threatening

"Life-threatening" means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the participant's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 2.2 Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 2.3 Important medical event or medical treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability, or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation\Development of drug dependency or drug abuse

B 2.4 Intensity rating scale

The grading scales found in the revised National Cancer Institute CTCAE version 5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

For each episode of an AE, all changes to the CTCAE grade attained should be reported.

It is important to distinguish between serious and severe AEs. Severity is a measure of

intensity whereas seriousness is defined by the criteria in Appendix B 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 Appendix B 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 a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as "not related".

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a study intervention or AstraZeneca non-investigational medicinal product that either causes harm to the participant or has the potential to cause harm to the participant.

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 participant.

Medication error includes situations where an error:

- occurred.
- was identified and intercepted before the participant received the drug.
- did not occur, but circumstances were recognised 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 participant).
- Drug not administered as indicated (eg, wrong route, dose error [greater than ±10%], 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 participant received the medication (excluding IVRS/IWRS errors).
- Wrong drug administered to participant (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 one of the above listed events that would otherwise have been a medication error.
- Participant accidentally missed drug dose(s) (eg, forgot to take medication).
- Accidental overdose (will be captured as an overdose).
- Participant failed to return unused medication or empty packaging.

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of study intervention or AstraZeneca non-investigational medicinal products for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of study intervention or AstraZeneca non-investigational medicinal products for medicinal purposes outside of the authorised product information, or for unauthorised study intervention(s) outside the intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that they were feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca team during the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent specifically to the subsequent use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of or repatriated. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used as per protocol.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.

- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

IATA (https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx) classifies infectious substances into 3 categories: Category A, Category B, or Exempt.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening, or fatal disease in otherwise healthy humans or animals.

Category A pathogens are, for example, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, for example, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry-ice require additional dangerous goods specification for the dry-ice content.

Appendix D Optional CCI Initiative Sample

D 1 CCI

CCI

D 2 Genetic Research Plan and Procedures

Selection of genetic research population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and provide informed consent for the CCI Initiative sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant or double umbilical cord blood transplantation.

- Whole blood transfusions in the last 120 days prior to *BRCA* testing sample collection at screening (packed red blood cells and platelet transfusions are acceptable; for timing refer to Inclusion Criterion #22).
- Healthy volunteers and paediatric participant samples will not be collected for the CCI Initiative.

Withdrawal of consent for genetic research

Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.3 of the main CSP.

Collection of samples for genetic research

The blood sample for this genetic research will be obtained from the participants pre-dose at the first dosing visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at the first dosing visit, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and storage of DNA samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples may be stored for a maximum of 15 years from the end of the study (as defined in the protocol), after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed consent

The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study, the participant must sign and date both the consent form for the main study and the addendum for the [redacted] Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant data protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.

- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods

The number of participants that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A SAP may be prepared where appropriate.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the study intervention.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

PHL

AST or ALT ≥3×ULN **together with** TBL ≥2×ULN at any point during the study following the start of study intervention irrespective of an increase in alkaline phosphatase.

HL

AST or ALT ≥3×ULN **together with** TBL ≥2×ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases (eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug).

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the

elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3×ULN.
- AST ≥3×ULN.
- TBL ≥2×ULN.

Local laboratories being used

The investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative.
- Determine whether the participant meets PHL criteria (see Section E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criterion "Important medical event" and causality assessment "yes/related" according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change in the participant's condition.

- The AstraZeneca study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the AstraZeneca study physician.
- Complete the 3 Liver eCRF Modules as information becomes available.

A "significant" change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the AstraZeneca study physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the AstraZeneca study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study intervention:

- Send updated SAE (report term "Hy's Law") according to AstraZeneca standard processes.
  - The "Medically Important" serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL (report term now "Hy's Law case") ensuring causality assessment is related to study intervention and seriousness criterion is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on-study intervention visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease)?

If **No**: follow the process described in Section E 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the participant's condition

compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Section E 4.2 for reporting PHL as an SAE.

E 7 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89(6):806-15.

FDA Guidance 2009
Food and Drug Administration. Guidance for industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009. Available from: URL: https://www.fda.gov/downloads/guidances/UCM174090.pdf. Accessed 08 October 2019.

Appendix F National Comprehensive Cancer Network Guidelines: Genetic/Familial High-Risk Assessment

Please note that this text has been adapted from NCCN Guidelines Version 1.2021. Further details regarding testing criteria are provided on the NCCN website (NCCN.org) which is updated periodically. Investigators should follow institutional guidelines for the genetic risk assessment and should refer to the most current version of the NCCN Guidelines as necessary.

Testing criteria for high-penetrance breast and/or ovarian cancer susceptibility genes (this can include *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, *TP53* among others).[a,b,c,d]

Testing is clinically indicated in the following scenarios:

1. Individuals with any blood relative with a known pathogenic/likely pathogenic[e] variant in a cancer susceptibility gene.

2. Individuals meeting the criteria below but tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing.

3. Personal history of cancer

    - Breast cancer with at least one of the following:

        i) Diagnosed at age ≤45 years; or

        ii) Diagnosed at age 46-50 years with:

            a) Unknown or limited family history[f]; or

            b) A second breast cancer diagnosed at any age; or

            c) ≥1 close blood relative[g] with breast, ovarian, pancreatic, or prostate cancer at any age.

        iii) Diagnosed at age ≤60 years with triple-negative breast cancer;

        iv) Diagnosed at any age with:

            a) Ashkenazi Jewish ancestry; or

            b) ≥1 close blood relative[g] with breast cancer at age ≤50 years or ovarian, metastatic, intraductal/cribriform histology, or high- or very-high risk group prostate cancer at any age; or

            c) ≥3 total diagnoses of breast cancer in participant and/or close blood relatives[f]

v) Diagnosed at any age with male breast cancer.

6. Family history of cancer

- An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision-making).[h]

  i) If the affected relative has pancreatic cancer or prostate cancer (metastatic, intraductal/cribriform, or NCCN Guidelines for Prostate Cancer "High" or "Very-High" Risk Group), only first-degree relatives should be offered testing unless indicated for other relatives based on additional family history.

- An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[i]

Testing may be considered in the following scenarios (with appropriate pre-test education and access to post-test management):

1. Multiple primary breast cancers, first diagnosed between the ages of 50 and 65 years.

2. An Ashkenazi Jewish individual.[j]

3. An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%-5% probability of *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).[b]

There is a low probability (<2.5%) that testing will have findings of document clinical utility in the following scenarios:

1. Women diagnosed with breast cancer at age >65 years, with no close relative[g] with breast, ovarian, pancreatic, or prostate cancer.

2. Men diagnosed with localized prostate cancer with Gleason Score <7 and no close relative[g] with breast, ovarian, pancreatic, or prostate cancer.

Source: Adapted from National Cancer Comprehensive Network Guidelines, Version 1.2021 (09/08/20).

[a] For further details regarding nuances of genetic counselling and testing, see the current NCCN guidelines (NCCN.org).

[b] Testing for pathogenic variants in other genes should take into consideration factors such as patient preferences, turnaround time, and insurance restrictions to particular laboratories (and thus particular panels). The prevalence of VUS increases with testing of additional genes. Individuals should have pre-test education on the challenges in managing pathogenic variants in genes associated with specific syndromes (eg, *CDH1* and *TP53* given their expanding clinical phenotypes) in the absence of a family history typical of such syndromes (does not apply for de novo pathogenic variants). Participants should also have pre-test education regarding the uncertain clinical utility of identifying certain pathogenic variants (eg, monoalellic *MUTYH*).

[c] Meeting one or more of these criteria warrants further personalized risk assessment, genetic counselling, and often genetic testing and management.

[d] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

[e] Equivalent to deleterious/suspected deleterious as referenced in the protocol body.

[f] Weitzel J, et al. JAMA 2007; 297:2587-2595.

[g] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family (see the current NCCN guidelines [NCCN.org] for further details).

[h] This may be extended to an affected third-degree relative if related through 2 male relatives (eg, paternal grandfather's mother or sister). If the affected first-degree relative underwent genetic testing and is negative for detectable mutations and there is no other family history of cancer, there is a low probability that any finding will have documented clinical utility.

[i] The approximate 5% threshold for probability of carrying *BRCA1/2* pathogenic variants is utilized because of availability of prior probability models; however, it is recognized that current model estimates vary substantially, and that different thresholds may be appropriate if other genes are included in the model utilized. If genes other than *BRCA1* and *BRCA2* are to be included in models evaluating the threshold for testing, the penetrance, clinical actionability, and phenotypic features of cancers associated with mutations in these genes should be considered. The panel encourages the development of validated models that include these parameters to determine eligibility and appropriateness for gene panel testing for inherited cancer risk. These models are only validated for *BRCA1/2*.

[j] Testing for 3 founder mutations of *BRCA1/2* may be offered to men and women as early as age 18-25 years who have one grandparent identified as of Ashkenazi Jewish ancestry, irrespective of cancer history in the family, as part of longitudinal studies. For those without access to longitudinal research studies, testing may be provided if there is access to pre-test education along with post-test counselling, additional genetic testing if indicated, and high-risk management. Testing should not be offered outside of a medical framework or clinical trial.

Appendix G Contraception Requirements

Olaparib and durvalumab are regarded as compounds with medium/high foetal risk.

Contraception requirements for this study are as follows.

G 1 Female Participants

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

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months prior to planned study intervention allocation via IVRS/IWRS 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 prior to study intervention allocation via IVRS/IWRS following cessation of exogenous hormonal treatment and if they have and follicle-stimulating hormone levels in the post-menopausal range.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more prior to study intervention assignement via IVRS/IWRS following cessation of exogenous hormonal treatment, or had radiation-induced menopause with last menses >1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago.

Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a nonsterilised male partner must use at least 1 highly effective method of contraception (Table 14) from enrolment throughout the study and until at least 6 months after the last dose of olaparib and 3 months after the last dose of durvalumab (for participants who have continued on monotherapy neoadjuvant durvalumab as described in Section 6.6.1), whichever is longer. A highly effective contraception is defined as one that has a failure rate of <1% per year when used consistently and correctly. Cessation of contraception after this time should be discussed with a responsible physician.

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for females of child-bearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to randomisation/study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use

of HRT during the study without use of a contraceptive method.

Non-sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of enrolment of their female partner, throughout their participation in the study, and until the latest timepoint that is 3 months after their female partner's last dose of olaparib and/or durvalumab. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments). Female participants should refrain from breastfeeding throughout this period.

G 2 Male Participants with a Female Partner of Childbearing Potential

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 male condom plus spermicide (condom alone in countries where spermicides are not approved) from enrolment until the latest time point that is 3 months after the last dose of olaparib and/or durvalumab to prevent pregnancy in a partner.

Periodic abstinence, (eg, calendar, ovulation symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study intervention, and withdrawal method (coitus interruptus), spermicides only, and lactational amenorrhoea are not acceptable methods of contraception. Female condom and male condom should not be used together. Male participants should refrain from sperm donation or banking throughout this period.

Vasectomised (ie, sterile) males are considered fertile if there was no medical assessment of the surgical success and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception from the time of study enrolment of their male partner until the latest time point that is at least 3 months after the last dose of olaparib and/or durvalumab (Table 14).

G 3 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 Table 14. 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).

Table 14 Highly Effective Methods of Contraception (<1% Failure Rate)

Non-Hormonal Methods	Hormonal Methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant; and must continue for at least 3 months after the last dose of olaparib and/or durvalumab for male participants) • Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Bilateral tubal occlusion[b] • Intrauterine device (provided coils are copperbanded)[b]	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®)[a,b] • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a,b] • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®)[b] • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®)[b] • Combined pill: Normal and low dose combined oral contraceptive pill[b] • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Xulane)[b] • Mini pill: Progesterone based oral contraceptive pill using desogestrel. (Cerazette® is currently the only highly effective progesterone-based pill)[b]

a. Hormonal methods not prone to drug-drug interactions.

b. Additionally, non-sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide. A condom alone may be used in countries where spermicides are not approved.

Appendix H Concomitant Medications

H 1 Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

DRUGS INDUCING OR INHIBITING CYP3A4/5 METABOLISM THAT ASTRAZENECA STRONGLY RECOMMENDS ARE NOT COMBINED WITH STUDY INTERVENTION

Olaparib is metabolised by CYP3A4 and CYP3A5 enzymes. Therefore, inhibitors or inducers of CYP3A4/5 may increase or decrease exposure, respectively, to olaparib.

A drug-drug interaction study of olaparib evaluated in participants showed that there is potential for olaparib to be a victim when coadministered with strong inducers of CYP3A4/5. Olaparib concentrations are decreased when co-dosed with strong CYP3A4/5 inducers (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, and St John's Wort).

A drug-drug interaction study of olaparib evaluated in participants showed that there is potential for olaparib to be a victim when coadministered with strong inhibitors of CYP3A4/5. Olaparib concentrations are increased when co-dosed with strong CYP3A4/5 inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir).

Strong and moderate inducers of CYP3A4/5 should not be combined with olaparib. Inducers of CYP3A4/5 should be stopped at least 3 weeks before the first dose of olaparib, with the exception of enzalutamide or phenobarbital which should be stopped at least 5 weeks prior to olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the participant's safety and welfare, this could diminish the clinical efficacy of olaparib. If a participant requires use of a strong or moderate CYP3A inducer, then they must be monitored carefully for any change in efficacy of olaparib.

The following are examples of drugs known to be inducers of CYP3A4/5 (Table 15). This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4/5 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Table 15 Examples of Drugs Known to be Inducers of CYP3A4/5

Strong CYP3A4/5 inducers *(should not be combined)*	**Moderate CYP3A4/5 inducers** *(permitted with caution)*
avasimibe	semagacestat[a]
carbamazepine	talviraline[a]
enzalutamide	bosentan
mitotane	efavirenz
nevirapine	etravirine
phenobarbital	genistein
phenytoin	lersivirine
rifabutin	lopinavir
rifampin	modafinil
rifapentine	nafcillin
St John's Wort	thioridazine
	tipranavir and ritonavir[b]

a. Not available on the United States market.

b. Ritonavir has dual effects of simultaneous CYP3A inhibition and induction; the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity.

Strong and moderate inhibitors of CYP3A4/5 (see Table 16) should not be combined with olaparib. Inhibitors of CYP3A4/5 should be stopped at least 2 weeks before the first dose of olaparib (3 weeks for St John's Wort). If there is no suitable alternative concomitant medication for the strong or moderate inhibitor of CYP3A4/5, then the dose of olaparib should be reduced as follows:

- **Strong CYP3A inhibitors:** Reduce the dose of olaparib to CCI mg BID 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 CCI mg BID 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.
- The dose reduction of olaparib should be recorded in the eCRF with the reason documented as concomitant CYP3A inhibitor use.

The following are drugs known to be inhibitors of CYP3A4/5 (Table 16). This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4/5 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue.

Table 16 Examples of Drugs Known to be Inhibitors of CYP3A4/5

Strong CYP3A4/5 inhibitors *(should not be combined)*	**Moderate CYP3A4/5 inhibitors** *(permitted with caution)*
boceprevir	amprenavir
clarithromycin	aprepitant
conivaptan	atazanavir
elvitegravir/ritonavir	casopitant
fluconazole	cimetidine
grapefruit juice[a,b]	ciprofloxacin
indinavir	crizotinib
itraconazole	cyclosporine
ketoconazole	darunavir
lopinavir/RIT	diltiazem
mibefradil	dronedarone
nefazodone	erythromycin
nelfinavir	grapefruit juice[b]
posaconazole	imatinib
ritonavir	schisandra sphenanthera
saquinavir	tofisopam
telaprevir	verapamil
telithromycin	
tipranavir/ritonavir	
troleandomycin	
voriconazole	

a. Double-strength grapefruit juice

b. Participants should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice [120 mL] or half a grapefruit or 1 to 2 teaspoons [15 g] of Seville orange marmalade daily).

MEDICINES WHOSE EXPOSURES MAY BE AFFECTED BY OLAPARIB THAT ASTRAZENECA CONSIDERS MAY BE ALLOWED WITH APPROPRIATE CLINICAL MONITORING OR WITH CAUTION

Based upon limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, breast cancer resistance protein (BCRP), P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, and MATE2K (Table 17).

Table 17 Drugs whose Exposure, Pharmacological Action, and Toxicity May be Increased by Olaparib

Medication/Class of Drugs with Warning of Possible Interaction	Advice
• CYP3A substrates with narrow therapeutic margin: cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, and tacrolimus • P-gp substrates	Drugs are permitted but appropriate clinical monitoring is recommended. Please refer to the full Prescribing Information for all drugs prior to co-administration with olaparib.
• Sensitive CYP3A substrates • BCRP substrates • OAT1B1 substrates: bosetan, glibenclamide, repaglinide, statins, and valsartan	Drugs are permitted but caution should be exercised. Please refer to the full Prescribing Information for all drugs prior to co-administration with olaparib.
• OCT1, MATE1, and MATE2K substrates: metformin • OCT2 substrates: serum creatinine • OAT3 substrates: furosemide, methotrexate	Drugs are permitted. Please refer to the full Prescribing Information for all drugs prior to co-administration with study intervention.

Based on limited in vitro data, olaparib may reduce the exposure to substrates of CYP2B6 (and potentially substrates of CYP2C9, CYP2C19, and P-gp) (Table 18). Olaparib may decrease the exposure to CYP2B6 substrates and some hormonal contraceptives.

Table 18 Drugs whose Exposure, Pharmacological Action, and Toxicity May be Decreased by Olaparib

Medication/Class of Drugs with Warning of Possible Interaction	Advice
• CYP2B6 substrates: bupropion and efavirenz • Hormonal contraceptives	Drugs are permitted but their efficacy may be reduced. Please refer to the full Prescribing Information for all drugs prior to co-administration with study intervention.

H 2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted, prohibited, and permitted concomitant medications/therapies are described in Table 19, Table 20, and Table 21. Refer also to the dose modification guidelines for management of study intervention-related toxicities in Section 6.6.

Table 19 Restricted Medications/Therapies

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which it is allowed)
Hormonal therapy	For non-cancer-related conditions (eg, hormone replacement therapy) only.

Medication/class of drug/therapy	Usage (including limits for duration permitted and special situations in which it is allowed)
Corticosteroids and/or bisphosphonates (including denosumab)	For the treatment of bone metastases and for the treatment of specific adverse drug reactions (refer to Toxicity Management Guidelines document). 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 intervention.
Foods or medications that are moderate inducers or inhibitors of CYP3A4/5	See Appendix H 1
Anticoagulant therapy	Participants who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (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. Each coagulation test result will be recorded in the eCRF.

CYP3A4/5=Cytochrome P450 3A4/5.

Table 20 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	Usage
Any anticancer therapy other than those under investigation in this study (including curative radiotherapy, chemotherapy, immunotherapy, hormonal therapy[a], biological therapy, other novel agents)	Must not be given concomitantly while the participant is on study intervention.
Herbal and natural remedies that may interfere with interpretation of study results	Must not be given concomitantly unless agreed by the sponsor.
Foods or medications that are strong inducers or inhibitors of CYP3A4/5, which are deemed to impact the pharmacokinetics of study medications	Must not be given concomitantly unless agreed by the sponsor (See Appendix H 1).
Live virus vaccines Live bacterial vaccines	Not permitted while the participant is receiving study medication and during the 30-day safety 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 olaparib are unknown.

CYP3A4/5=Cytochrome P450 3A4/5.

a Hormone replacement therapy is acceptable.

Table 21 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate adverse event management, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table 20
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management) except for those medications identified as "prohibited," as listed above	Should be used, when necessary, for all participants except for those medications identified as "prohibited," as listed in Table 20
Inactivated viruses, such as those in the influenza vaccine	Permitted
Required for management of other medical conditions	As required except for those identified as "prohibited," as listed in Table 20
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 intervention should be discontinued for a minimum of 3 days before a participant undergoes therapeutic palliative radiation treatment. Study intervention should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Appendix I Guidelines for Acquisition and Evaluation of MRI for Lesion Assessments

Imaging modalities and acquisition specifications

A tumour assessment via breast MRI with IV contrast must be performed at baseline, Week12, and Week 24 visits. If MRI has been performed at Week 12 and the participant proceeds to definitive surgery following Cycle 4 or Cycle 5, the MRI scan does not need to be repeated unless clinically indicated.

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

Table 22 shows the recommended acquisition parameters, and it is required to use parameters as close as possible to those listed. Once settings have been selected at baseline, they shall remain consistent throughout this examination and study follow-up examinations.

Table 22 Recommended MRI Acquisition Parameters for Lesion Assessments

Scanner Field Strength	Minimum 1.5 Tesla
Participant Orientation	Head first supine - Head pointing towards the magnet Position the participant with breasts inside the breast coil and center the laser localizer over the mid chest
Scan Locations/Coverage	A 3 plane localizer must be taken initially to localize/plan the sequences. Ensure a sufficient number of image slices to cover the whole breast. To avoid artefacts from the chest and heart motion, the phase encoding direction should be right to left for axial planes.
Plane Angulation	Plan the axial slices on the sagittal plane. Angle the position block parallel to breast. Check the positioning in the axial and coronal plane. An appropriate angle should be given in coronal plane (ie, perpendicular to right and left nipple).
Coil	Breast coil
Scan FOV	Large enough to cover all the required anatomy and consistent throughout the study. Typically, 350 mm or close.
Slice Thickness	Axial T2 FSE/TSE: ≤ 3mm Axial T2 STIR: ≤ 3 mm Axial DWI: ≤ 5 mm Axial 3DT1 Dynamic FLASH: 1 mm
Skip/Gap (Slice Spacing)	No Gap preferred. Up to 10% gap accepted.
Sequences Pre-contrast	Axial T2 FSE/TSE

	Axial T2 STIR[a, b] DWI (optional)
Sequence Post-contrast	Axial 3DT1 Dynamic FLASH[c]
IV Contrast	IV contrast dose = 0.1 mmoL/kg of gadolinium-based agent Alternative gadolinium-based agents can be used at a comparable dose (Gd-EOB-DTPA).

[a] STIR sequence is preferably used for fat suppression for participant with breast implants because the resonance frequencies of fat and silicone are very close. Thus, the method involving selective suppression of the fat peak may fail. Consequently, it is important to suppress only the fat signal without affecting the silicon signal.

[b] For STIR sequences, the inversion time should be chosen with caution, typically 140-170 ms at 1.5T and 190-210 ms at 3T to ensure efficient fat attenuation/suppression.

[c] Dynamic Flash 3D fat sat sequence consists of 6 flash 3D scans. First scan is the pre-contrast scans (used as a mask for the post contrast scans) and 2nd to sixth are post contrast scans.

Lesion evaluation

The MRI longest diameter and tumour volume will be measured at each time point, as per the SoA (Table 1) and will be used for early evaluation of response. The longest diameter must be measured in mm and recorded at all visits. The tumour volume as calculated by the site's MRI software should be recorded in the participant's eCRF in mm^3. Individual dimensions used in the calculation do not need to be recorded. If the tumour volume must be calculated by hand it should be calculated as follows:

$$\text{Volume} = (\text{length} \times \text{width} \times \text{height} \times \pi)/6$$

In cases where the breast lesion is to small to measure, the longest diameter should be entered as "1 mm" and the tumour volume should be entered as "0.01 mm^3" in order to allow for quantitative analysis.

Appendix J Residual Cancer Burden Pathology Report

FOR REFERENCE ONLY: ALL INFORMATION TO BE INCLUDED ON ORIGINAL PATHOLOGY REPORT

The following form should be given ahead of time to the pathologist responsible for the pathology assessment of the tumour excised at the time of definitive surgery upon completion of neoadjuvant therapy.

This document is meant to be used to help facilitate collection of all of the required pathology information, and to help the research staff identify information that must be entered on the eCRFs. Only the official pathology report including this information is considered source documentation.

Pathology Documentation Guidelines

These guidelines are meant to help the research staff identify and document required information for the study and will help future assessment of Residual Cancer Burden. All requested information should be in the original pathology report as per CAP protocol Invasive Breast Cancer: https://documents.cap.org/protocols/cp-breast-invasive-18protocol-4100.pdf

Pathology Primary Tumour Bed (if bilateral tumours, report each breast individually)

- It is highly recommended that the pathology report of the primary tumour in the breast includes identification of the original tumour through notation of treatment response in the tumour bed and/or identification of the CCI clip.
- If more than one invasive cancer was identified before neoadjuvant therapy, please report the pathologic response for each invasive lesion.
- If residual cancer is found in the primary tumour bed, please include the following information in the pathology report:
    - Primary Tumour Bed Area, defined as the largest 2 dimensions in mm of the residual tumour bed (please choose the largest tumour bed if multicentric disease)
        - Dimension 1: _____ (mm)
        - Dimension 2: _____ (mm)
        - Overall Cancer Cellularity (all cancer, invasive & in situ, as percentage of the primary tumour bed area)
            - Percentage: _____ (%)
        - Amount of residual cancer that is DCIS
            - Percentage: _____ (%)

Axillary Lymph Nodes

- Immunohistochemical staining is not required for routine evaluation of sentinel nodes found to be negative by haematoxylin and eosin. However, if the routine haematoxylin and eosin section is indeterminate, IHC for cytokeratins of a section from each of the lymph node slices is then strongly encouraged.
- Pathologic reporting of axillary nodes should include the following information:
    - Number of positive lymph nodes (combined total if sentinel lymph node CCI and axillary lymph node dissection performed): _____
    - **The largest diameter (mm) of largest nodal metastasis**: _____ (mm)
- If the sentinel nodes were negative, was IHC for cytokeratins performed: Y/N
    - If Yes, was cancer found? Y/N

Appendix K Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak

Changes below should be implemented only during study disruptions due to any of or a combination 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 participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits These changes should only be implemented if allowable by local/regional guidelines and following agreement from the AZ.

Note: In Germany, the changes should only be implemented during the COVID-19 pandemic (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. In Germany, changes are not applicable to study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis. These changes should only be implemented if allowable by local/regional guidelines and following agreement from AZ.

K 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary (eg, remote visits). Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections K 2 to K 5. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

K 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study clinical lead.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in Section 1.3 the participant will need to be rescreened to reconfirm eligibility before commencing study

procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 5.4 must be undertaken to confirm eligibility using the same randomisation number as for the participant.

K 3 Home or Remote Visit to Replace On-site Visit (Where Applicable)

A qualified HCP from the study site or TPV service may visit the participant's home/or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

K 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication to be reported and documented.

K 5 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

K 6 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for participant management in an event of COVID-19, and actions to be taken on study treatment (see Section K 9). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritise trial participant

safety and data validity; in case these 2 conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

K 7 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section K 10 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with olaparib and durvalumab. The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

K 8 New Participant Enrolment

Study sites may continue to recruit new participants into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new participants effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

K 9 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participant's treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

AEs, SAEs, cycle delays, and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed.

K 10 Ongoing Participants

Participants receiving study intervention should continue to undergo safety assessments prior

to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

K 10.1 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing, and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, study intervention may be resumed per the CSP.
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

K 10.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab/tremelimumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

K 10.3 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, laboratory testing, and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

K 10.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally,

administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

K 11 Durvalumab: Product-specific guidance in relation to the ongoing and emerging novel coronavirus (COVID-19) pandemic

K 11.1 Ongoing participants receiving durvalumab

Participants receiving treatment with durvalumab should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, treatment with durvalumab should be interrupted until such assessments can be completed.

K 11.2 Participants with an event suspected to be COVID-19

Delay or omit treatment with durvalumab as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing, and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, treatment with durvalumab may be resumed per the CSP. If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

K 11.3 Participants with confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have treatment with durvalumab withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation.

K 11.4 Restarting treatment with durvalumab

Treatment with durvalumab must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, laboratory testing, and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

K 12 Olaparib: Product-specific guidance in relation to the ongoing and emerging novel coronavirus (COVID-19) pandemic

For ongoing participants:

- Participants must continue to have safety blood tests as per protocol schedule. Alternative methods for safety assessments include using local laboratories and follow-up by phone contact, virtual visits can be used.
- If it becomes unfeasible to perform the required safety blood tests for a participant, then study treatment should be interrupted until this can be resumed and the reason clearly documented, with reference to COVID-19.
- If a participant tests positive for the COVID-19 virus, interrupting olaparib treatment for 14 days or until symptoms resolve should be considered. Factors that should be taken into consideration might include:
  - Severity of COVID-19 symptoms
  - Status of safety blood results, particularly haemoglobin, neutrophils, and lymphocytes
  - Benefit risk for the individual participants, including intent of treatment and response to olaparib
- If participants present with new or worsening respiratory symptoms such as dyspnoea, cough and fever, or an abnormal chest radiologic finding is observed, olaparib treatment should be interrupted, and prompt investigation initiated to determine whether symptoms are due to COVID-19 or potentially drug-induced pneumonitis.
- Olaparib is cleared by metabolism, predominantly by the CYP3A4/5 isozymes. Therefore, the use of olaparib with the concomitant use of strong inhibitors of these isoenzymes including some antibiotics and antivirals (eg, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, and telaprevir) is not recommended.

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Appendix L Country-Specific Requirements

Country	Requirement
Germany	**Section 5.1 Inclusion Criteria (#13)** Only participants who can provide informed consent will be eligible. Consent by a legally authorised representative is not allowed.

Appendix M Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

Amendment 3 (01-June-2023)

Overall Rationale for the Amendment:

The primary purpose of this amendment was to modify safety monitoring for patients in Cohort B who experience anaemia or prolonged haematological toxicity in alignment with the updated olaparib Investigator's Brochure and to incorporate recent changes for contraception requirements for patients being treated with olaparib. These and other changes incorporated in this amendment are described in the following table. In addition, minor text clarifications, administrative changes, and changes for consistency across the clinical program have been made; as these changes were minor, they are not listed in detail in the table.

List of Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria (#11 and #12) Appendix G Contraception Requirements	Revised details/timing of contraceptive use requirement in female and male participants.	To align across clinical program.

List of Non-Substantial Modifications

Section # and Name	Description of Change	Brief Rationale
Title Page	The EU CT study number was added.	To provide the appropriate regulatory identification for the study.
Section 1.3 Schedule of Activities Section 8.2.4 Clinical Laboratory Assessments (Table 9)	Added requirement for participants in Cohort B to have reticulocyte count testing performed at screening.	To aid evaluation of the cause of severe anaemia in olaparib/durvalumab combination studies.

Section # and Name	Description of Change	Brief Rationale
Section 6.6.1.1 Management of Anaemia (Table 6)	Added new testing requirements for participants in Cohort B with anaemia (Hb < 8 g/dL) to undergo prior to any transfusions.	To aid evaluation of the cause of severe anaemia in olaparib/durvalumab combination studies
Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 5.1 Inclusion Criteria (#7) Section 8.6.1 Collection of Samples for Biomarker Analysis	Added note that if the pre-treatment CCI is not medically feasible, AstraZeneca should be contacted.	To allow flexibility in the current CCI collection plan.
Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 8.6.2 Blood Samples for Biomarker Analysis (Mandatory)	Clarified timing for collection of blood samples for CCI analysis.	For alignment with current study plan.
Section 1.3 Schedule of Activities	Removed requirement for hepatitis B, C, and HIV testing during Post-Neoadjuvant Safety Assessment.	For alignment with current best safety practices.
	Indicated that blood samples for CCI will be collected within 7 days prior to surgery.	To correct for previously missing collection window.
	Removed AE collection during Survival follow-up and shifted footnote regarding SAEs of MDS/AML or new primary malignancy after Safety Follow-up.	For clarity as not all AEs are to be reported during Survival Follow-up.
Section 1.3 Schedule of Activities Section 3 Objectives and Endpoints Section 8.6.2 Blood Sample Collection for Biomarker Analysis (Mandatory)	Noted that assessment of CCI CCI includes a CCI	To align with current study plan.
Section 1.3 Schedule of Activities Section 8.7 Optional Exploratory CCI Initiative Sample	Clarified that the CCI CCI sample is exploratory.	To align across clinical program.

Section # and Name	Description of Change	Brief Rationale
Section 2.2.3.1 PARP Inhibition as a Therapeutic Strategy Target for BRCA Mutated Breast Cancer (Olaparib)	Included results of LUCY study.	To provide further justification for the use of PARP inhibition in *BRCA*-mutated breast cancer
	Removed indication of olaparib for treatment of deleterious or suspected deleterious *gBRCA*m advanced ovarian cancer in patients treated with 3 or more prior lines of chemotherapy.	This indication has been withdrawn by the FDA.
Section 2.3.2.2 Benefit Assessment (Durvalumab)	Updated cumulative exposure data for olaparib and durvalumab.	To align across clinical program.
Section 4.1 Overall Design Section 6.7 Intervention after the End of the Study	Added reference to Section 6.7 in Section 4.1 and expanded description of End of Study intervention details for olaparib.	To align across the clinical program.
Section 4.4 End of Study Definition	Expanded End of Study definition for EU and FDA.	To align with Clinical Trial Transparency guidelines and EU/FDA requirements.
Section 5.1 Inclusion Criteria (#2)	Added clarification that participants with unifocal lesions are allowed (as long as each discrete cancer displays noted histological characteristics).	For clarity.
Section 5.1 Inclusion Criteria (#13) Appendix A3 Informed Consent Process Appendix L Country-Specific Requirement	Updated text and added country-specific requirement appendix to clarify that signing of informed consent by legally authorised representative is not allowed in Germany.	To align with German Regulatory Authority request.
Section 5.2 Exclusion Criteria (#10)	Revised process for permission of participants with atrial fibrillation or arrhythmias.	To align across clinical program.
Section 6.6.1 Management of Study Intervention Related Toxicities and Dose Modifications (Olaparib)	Added statement that participants in Cohort B who discontinue olaparib may continue durvalumab monotherapy.	For clarity.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.14 Medication Error, Drug Abuse, and Drug Misuse Appendix B4, Medication Error, Drug Abuse, and Drug Misuse	Clarified definition of medication error and added definitions and descriptions for drug abuse and drug misuse.	To align across clinical program.
Appendix A1 Regulatory and Ethical Considerations	Added details regarding investigator oversight of study conduct and reporting of serious breaches.	To align across clinical program.
Appendix A3 Informed Consent Process	Added flexibility to statement requiring reconsent in case of ICF updates.	To align across clinical program.
Appendix A4 Data Protection	Added details regarding use of personal data.	To align across clinical program.
Appendix A6 Dissemination of Clinical Study Data	Added statement regarding reporting of technical and lay summaries results.	To align across clinical program.
Appendix A7 Data Quality Assurance	Expanded data monitoring details, including quality tolerance limits, and updated requirements for record retention.	To align across clinical program.

Amendment 2 (10-June-2022)

Overall Rationale for the Amendment:

The primary purpose of this amendment was to modify inclusion criteria related to reproduction and fertility in alignment with olaparib safety guidelines. These and other changes incorporated in this amendment are described in the following table. In addition, minor text clarifications, administrative changes, and changes for consistency across the clinical program have been made; as these changes were minor, they are not listed in detail in the table.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9.4.4.4 Demographic and Baseline Characteristic Data	Removed BMI as safety endpoint.	For alignment with the olaparib clinical program.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 8.6.1 Collection of Samples for Biomarkers Analysis Section 8.6.3 Collection of Optional CCI Samples	Clarified that the optional CCI is performed at CCI (not progression) following definitive surgery.	As there is no known disease after definitive surgery, any disease that occurs after this point is more appropriately called recurrence rather than progression.	Non-substantial
Section 1.3 Schedule of Assessments Section 8.2.5.4 Echocardiogram/Multigated Acquisition Scan (Cohort B Only) Section 8.3.5 Adverse Events Based on Examinations and Tests	Removed echocardiogram/MUGA as safety assessment.	The echocardiogram/MUGA assessement is no longer a safety requirement for the durvalumab clinical program.	Substantial
Section 1.3 Schedule of Assessments Section 8.6.1 Collection of Samples for Biomarkers Analysis	Clarified that the optional CCI will be performed after definitive surgery.	To avoid ambiguity.	Non-substantial
Section 1.3 Schedule of Assessments Section 4.1 Study Design Section 8.1.1 Surgical Assessment Section 8.6.1 Collection of Samples for Biomarkers Analysis	Clarified that the mandatory on-treatment CCI will be performed to confirm presence or absence of residual disease in participants that do not proceed to definitive surgery after any exposure to protocol-specified neoadjuvant treatment.	To analyse the biosample after any exposure to study intervention.	Substantial
Section 1.3 Schedule of Assessments Section 8.1.3 Imaging Tumour Assessments	Added statement that participants who discontinue neoadjuvant study intervention to receive additional non-protocol treatment prior to definitive surgery do not need subsequent MRIs.	MRI including volumetric measurements are being performed in the study as surrogate measures of efficacy of study intervention. For participants who receive non-protocol treatment, MRI is no longer required.	Non-substantial
Section 4.1 Study Design	Replaced reference to early discontinuation with reference to additional non-protocol	For clarity as residual tumour tissue will also be collected if the participant	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.6.1 Collection of Samples for Biomarker Analysis	therapy in the context of proceeding to definitive surgery.	discontinues after completion of neoadjuvant period.	
Section 5.1 Inclusion Criteria Appendix G Contraception Requirements	Added modification that female participants must use two effective forms of birth control for at least 30 days after the last dose of olaparib.	For alignment with current olaparib safety guidelines.	Substantial
	Added statement that female partners of male participants should also use a highly effective form of contraception if they are of childbearing potential.		
Section 5.3 Lifestyle Considerations	Added statement that female participants of childbearing potential should be informed prior to receiving study intervention about the options that may preserve their ability to have children.	For alignment with current olaparib safety guidelines for premenopausal patients when no prior chemotherapy has been received.	Substantial
Section 8.2.4 Clinical Safety Laboratory Assessments (Table 9)	Revised to include differential lymphocyte and neutrophil counts as acceptable measurements, and footnote added to specify that absolute counts are preferred.	For alignment with clinical safety laboratory collection practices.	Non-substantial
Section 8.6.1 Collection of Samples for Biomarker Analysis	Clarified that for CCI participants will undergo at least CCI	To align collection of CCI throughout the protocol.	Non-substantial
	Removed statement specifying that CCI will be collected as CCI	To remove redundancy.	Non-substantial

Amendment 1 (09-March-2022)

Overall Rationale for the Amendment:

The amendment was made to expand the eligible participant population based on current literature supporting the use of neoadjuvant immuno-oncology therapy in participants with smaller volume, high-risk breast cancer.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis Section 2.1 Study Rationale Section 11 References	Added language and citation reflecting results from the KEYNOTE-522 study that patients with and without the presence of lymph nodes benefit from the addition of IO to chemotherapy.	Text added to justify modification of Cohort B.	Substantial
Section 1.1 Synopsis Section 4.1 Overall Design Section 5 Study Population Section 5.1 Inclusion Criteria	Expanded the list of eligible participants to include those with the T1b/N0 disease staging classification.	To expand the population eligible for Cohort A.	Substantial
Section 1.1 Synopsis Section 1.3 Schedule of Assessments (footnote "p") Section 4.1 Overall Design Seciton 8.6.1 Collection of Samples for Biomarker Analysis	Added language to mandate the submission of remaining CCI for participants with T1b disease who have CCI for the required baseline CCI CCI	To ensure pre-treatment CCI is available for all participants for CCI objectives.	Substantial
Section 1.2 Schema	Presentation of cohorts updated in study design figure.	To reflect changes in participant populations.	Substantial
Section 1.3 Schedule of Activities	Added clarification that mandatory CCI is collected for CCI analysis	To avoid ambiguity	Non-substantial
Section 1.3 Schedule of Activities	Modified timing of blood sample collection for retrospective *BRCA*m confirmation from screening to C1D1.	To avoid testing participants who are not enrolled into the study.	Non-substantial
Seciton 2.3.1.1 Olaparib (Risk Assessment)	Add venous thromboembolism as a new ADR.	To align with the the most current olaparib IB (V21, January 2022)	Substantial
Section 8.3.10.1 Adverse Events of Special Interest for Olaparib	Pneumonitis was demoted from an important potential risk to a potential risk.	To align with the most current olaparib IB (V21, January 2022)	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.6.1 Collection of Samples for Biomarker Analysis	Added text and link to SoA for each [redacted] to be collected.	To align with SoA listing and avoid ambiguity.	Non-substantial
Appendix J Residual Cancer Burden Pathology Report	Language not applicable to the study removed.	To clarify the appendix and remove incorrect language.	Non-substantial
Appendix K Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, Including COVID-19 Outbreak	Revised text to specify that template language applies in Germany only during the COVID-19 pandemic.	To align with German Health Authority requirements.	Non-substantial

Appendix N Abbreviations

Abbreviation or Special Term	Explanation
CCI [redacted]	
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee of Cancer
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BCRP	breast cancer resistance protein
BID	twice daily
BRCA	breast cancer susceptibility gene
CAP	College of American Pathologists
CD	cluster of differentiation
CHIP	clonal haematopoiesis of indeterminate potential
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences International Ethical Guidelines
COVID-19	coronavirus disease 2019
cPD	Clinical progression of disease (a clear worsening of the patient's clinical status or prognosis in the opinion of the treating clinician, taking into consideration clinical findings, imaging [including, but not limited to, objective imaging response criteria] and laboratory test results).
CrCL	calculated creatinine clearance
CRO	Contract Research Organisation
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	
CTIS	Clinical Trials Information System
CYP	cytochrome P450
DCIS	ductal carcinoma in situ
DCO	data cutoff

Abbreviation or Special Term	Explanation
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DDR	DNA damage repair
DSB	double strand break
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group: a performance status using scales and criteria to assess how a patient's disease is progressing
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
ER	oestrogen receptor
ET	endocrine therapy
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
CCI	[redacted]
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCP	Health Care Professional
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HL	Hy's Law
CCI	[redacted]
HR	hormone receptor
HRD	homologous recombination deficiency
HRR	homologous recombination repair
HRT	hormone replacement therapy
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
IEC	Independent Ethics Committee
IFN	interferon

Abbreviation or Special Term	Explanation
IHC	immunohistochemistry
ILD	interstitial lung disease
imAE	immune-related adverse event
International co-ordinating investigator	If a study is conducted in several countries the international co-ordinating investigator is the investigator co-ordinating the investigators and/or activities internationally.
INR	international normalised ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
MDS	myelodysplastic syndrome
CCI [redacted]	
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
OS	overall survival
PARP	polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerase
pCR	pathological complete response
PD	progressive disease
CCI [redacted]	
PgR	progesterone receptor
PHL	Potential Hy's Law
PK	pharmacokinetic
Q2W	every 2 weeks
Q4W	every 4 weeks
RCB	residual cancer burden
RFI	recurrence-free interval
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SSB	single strand break
CCI [redacted]	
TBL	total bilirubin

Abbreviation or Special Term	Explanation
TIL	tumour infiltrating lymphocyte
TMG	Toxicity Management Guideline
TNBC	triple negative breast cancer
TNM	Tumour, Node, Metastasis
TPC	treatment of physician's choice
TPV	third-party vendor
ULN	upper limit of normal
US	United States
WOCBP	Women of child-bearing potential

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