PHOENIX DDR/Anti-PD-L1 Trial:

A pre-surgical window of opportunity and post-surgical adjuvant biomarker study of DNA damage response inhibition with or without anti-PD-L1 immunotherapy in patients with neoadjuvant treatment resistant residual triple negative breast cancer

PROTOCOL

Version: 10.0

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Sponsor:	The Institute of Cancer Research
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	The Institute of Cancer Research
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The PHOENIX DDR/Anti-PD-L1 trial has been endorsed by Cancer Research UK's Clinical Research Committee (CRC) and is part of the National Institute for Health Research Clinical Research Network Trial Portfolio

ICR The Institute of Cancer Research

CANCER RESEARCH UK

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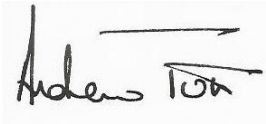
Prof Andrew Tutt (Chief Investigator)		23 April 2025

This protocol describes the PHOENIX DDR/Anti-PD-L1 Trial and provides information about procedures for entering participants into this trial. The protocol should not be used as a guide for the treatment of patients outside of this trial.

Every care was taken in the preparation of this protocol, but corrections or amendments may be necessary. Protocol amendments will be circulated to participating sites as they occur, but sites entering patients for the first time are advised to contact ICR-CTSU to confirm they have the most recent version.

HISTORY OF CHANGES

PROTOCOL VERSION AND DATE	**SUMMARY OF CHANGES**
Version 1.0, 05 December 2018	Original version
Version 1.1, 20 February 2019	• Eligibility update • Trial Registration eligibility criteria updated to exclude patients with a history of non-infectious pneumonitis • Other updates • Interim analyses and stopping rules section updated to clarify that the trial may be stopped at any time if emerging safety issues arise • Update to trial co-ordination contact details
Version 1.2 3 April 2019	• Addition of text for clarity confirming that biopsy cores can be taken on the day of surgery or taken by the surgeon intraoperatively when an image-guided biopsy on Day 14 of the pre-operative window of opportunity is not feasible. • Correction of error in wording of primary endpoints: surgical resection sample corrected to post-treatment biopsy **Administrative updates** Correction of minor typographical errors throughout
Version 2.0 08 May 2019	• Addition of 3 new AESI for cohort D following update to Durvalumab Investigator Brochure to Edition 13 dated 27Nov2018. • Addition of new Trial Manager name and telephone number to Administration section. • Amended wording regarding AEs of Special Interest (AESI) for cohort D Durvalumab to specify that these AESI can be classified as either serious or non-serious.
Version 3.0 16 January 2020	• Addition of ISRCTN number to protocol cover page • Addition of new trial team members to “Protocol Development Group” table • Addition of wording to sections 3.1 and Appendix 2 to clarify that baseline and pre-operative biopsy collection may be guided by ultrasound imaging or, where tumours

	are not readily visible on ultrasound, stereotactic or digital breast tomosynthesis (DBT) guidance may be used. • Amendment to wording throughout to replace "ultrasound-guided" with "image-guided" • Clarification of wording in Appendix 2 and section 5.3.1 Inclusion criteria 9 confirming that if it is deemed unsafe to proceed with biopsy upon Trial Entry the patient will not be eligible for participation in the trial • Amendment to wording in section 10 to clarify that participating sites are required to keep a log of patients with mid-NACT resistant residual TNBC who are identified as potentially eligible, and not patients identified post-NACT. • Removal of wording in sections 11.1, B1.1.1 and PART 1 schedule of Assessments as requirement for cohort B patients to receive their first dose of AZD6738 in hospital followed by blood pressure monitoring is no longer necessary • Amendment to section 11.2 and part 1 schedule of assessments to remove cohort C specific WOP day 7 visit • Removal of requirement for hepatitis serology testing at every visit for cohort D patients only, and addition of hepatitis serology testing as a trial entry screening assessment for all patients (wording changed throughout protocol) • Minor revision to text throughout protocol to clarify that Trial entry MRI should be performed at least 1 week following day 1 of the final cycle of NACT • Addition of wording to section 11.3 (PART 1 Surgery), 11.7 (PART 1 Schedule of Assessments) and Appendix 2 to detail requirements and instructions for calculating residual cancer burden (RCB) for surgical resection tissue • Addition of text to section 11.6, Schedule of Assessments, 15.6, 16.2 and Appendix 2 to confirm provision of recurrence tumour tissue samples for each patient who has tissue available from biopsy/surgery performed as part of routine care • Amendment to wording in section 12.1 and Appendix 2 to update timelines for mutation analysis from 4 weeks to 6-8 weeks • Amendment to timeframe for completion of baseline assessments in section 11.1 (to be completed within 3 days prior to commencing trial treatment in the WOP) • Addition of visit windows in Part 1 schedule of assessments and clarification of wording in footnote 1 • Addition of wording to sections 12, B4,C4,D4,B5,C5,D5 & C6 to clarify that patients may receive radiotherapy following surgery in PART 1 and prior to commencement of trial treatment in PART 2 • Clarification of PART 2 visit window wording in sections 15.2 and 15.3 to state that assessments should be performed prior to treatment administration • Amendment to visit windows in Part 2 schedule of assessments and amendment of wording in footnotes to clarify that assessments should be performed within 3 days prior to treatment administration • Addition of text to section 15.7 Discontinuation of Treatment to include withdrawal of consent and serious non-attendance/non-compliance • Amendment of wording in section 17.1 subsection "Adverse Events of Special Interest (AESI) in Cohort D" to state that If an AESI is defined as serious, sites should follow the SAE reporting procedure detailed in section 17.3 • Clarification of seriousness criteria for reporting of pregnancies in section 17.9 to include stillbirth or spontaneous abortion/miscarriage • Addition of wording to sections 18.1.1, B1.1.2, C1.1.2 and D1.1.2 to clarify that patients who miss >20% doses/infusion during PART 1 or any doses on Day 14 of the WOP (applicable for cohorts B&C only) will be considered non-evaluable and will be replaced.

	• Clarification throughout that archival diagnostic tissue or surgical resection tissue must include primary breast with or without involved lymph node tissue • Amendment to wording in section 22.6 to clarify that a patient withdrawal form (and not a deviation form) should be completed in MACRO • Removal of guidance for management of cardiovascular toxicities in olaparib non-haematological toxicity table (table C3 section C1.2.4) • Amendment to PBMC blood collection volume in Appendix 2 from 16ml to 20ml • Removal of duplicate wording in appendix 8 table 2 • Addition of intestinal perforation as an AESI for cohort D to section 17.1 • Replacement of durvalumab toxicity management guidelines (appendix 9) with October 2019 version
Version 4.0 26 November 2020	• Amendment to wording throughout for the Cohort D CD8+ primary endpoint definition of response. This has been amended from an increase in frequency of CD8 counts to an absolute increase in the percentage CD8+ stromal tumour infiltrating lymphocytes (sTILs) • Amendment to Trial Summary section to extend the trial recruitment duration from 24 to 36 months • Addition of information throughout the protocol relating to national guidance on self-isolation prior to surgery during the COVID-19 pandemic. Wording added throughout to state that surgery may be delayed by up to 3 days due to self-isolation requirements and that in these cases, the last dose of drug taken on D14 would therefore not be taken within 24 hours of surgery • Addition of information throughout the protocol relating to the requirement for COVID-19 testing. Testing should be considered at the point of Trial Entry and at D14 WOP if required pre-surgery according to national guidance or local hospital policy during the COVID-19 pandemic • Correction of error in table in section 15.8 (PART 2 SCHEDULE OF ASSESSMENTS – ctDNA POSITIVE GROUP) addition of crosses to disease recurrence row to denote that recurrence tissue should be collected at every time point (except for ctDNA Screening) throughout PART 2 • Addition of wording to Central Data Monitoring section 21.4 to state that ICR-CTSU will request from sites redacted copies of each patient's trial-specific MRI scan report and surgical pathology report for central monitoring purposes. • Minor amendment to wording in section 5.4 to clarify that two highly effective forms of contraception includes a condom and one other method from the list outlined. • Replacement of durvalumab toxicity management guidelines (appendix 9) with November 2020 version
Version 5.0 21 May 2021	• Removal of data management contacts from administration section of the protocol • Amendment to wording throughout to change imaging modality mandated at the mid-NACT assessment. MRI is no longer mandated at this time point and any imaging modality can be used to assess residual disease size. • Amendment throughout to clarify that any imaging modality can be used for collection of the trial specific pre-operative image guided biopsies • Amendment to wording throughout to change the requirement for residual disease size at trial entry from ≥2cm to ≥1cm • Addition of wording throughout to clarify that patients whose clinical management includes adjuvant Capecitabine will not be invited to participate in PART 2 of the trial • Amendment to Trial Rationale section to update "**COHORT C Known Risks and Benefits of Olaparib"** and **"COHORT D Known Risks and Benefits of Durvalumab"** sections to bring these in line with information within the most recent investigator brochures for olaparib and Durvalumab.

	• Amendment to inclusion criteria for trial registration section 5.3.1 and lifestyle guidance section 5.4 to clarify that patients must use a condom and one highly effective form of contraception in combination • Amendments to section 6 and section 9 to sign post site teams to the trial guidance notes for the procedure to follow for patient registration and randomisation • Removal of duplicated wording (intestinal perforation) from section 17.1 **Adverse Events of Special Interest (AESI) in Cohort D** • Addition of text to section 9 and section 18.2 to clarify that an additional balancing factor of residual disease size following completion of neoadjuvant chemotherapy will be used at the time of trial entry • Amendment to section 18.5 to state that the IDSMC will monitor RCB rate at surgery to ensure the trial is recruiting sufficiently high risk patients • Addition of text to section B5 and appendix 5 to include reference to CYP1A2 inhibitors or inducers to bring the protocol in line with information in the most recent investigator brochure for AZD6738 **Administrative updates** • Correction of minor typographical errors throughout
Version 6.0 24 Nov 2021	• Addition of new data management contacts from administration section of the protocol • Amendments throughout to clarify that the patient information sheets for part 2 can be provided to patients at the 30 day post-surgery visit if trackable mutation status has been confirmed • Amendments throughout to permit treatment with durvalumab during Part 2 for patients allocated to Cohort A (reference cohort) at Trial Entry • Amendment to exploratory endpoints 3 & 4 to clarify that these refer to cohorts B-D only • Clarification of the trial patient population to include moderate to significant viable residual disease as per RCB requirements • Amendment to exclusion criteria for trial entry number 8 for clarification only • Clarification that archival diagnostic tissue samples should be sent to the PHOENIX central laboratory immediately following trial entry • Clarification throughout that pregnancy testing in part 1 is required for cohorts B-D only • Replacement of durvalumab toxicity management guidelines (appendix 9) with October 2021 version
Version 7.0 08 Aug 2022	• Minor edits to job titles within administration section • Clarification that the PIS for PART 2 can be provided at any point during PART 1 of the trial, and that patients should be asked to consent to PART 2 at the 30-day post-surgery visit • Amendments to timing of ctDNA screening to include screening at the 30- day post-surgery visit and/or 3-month post-surgery visit (dependent on detection of trackable mutations and development of the trackable mutation assay) • Amendment to the visit schedule to allow for patients who consent to PART 2 and screen ctDNA positive at the 30-day post-surgery visit to skip the 3-month post-surgery visit and proceed straight to the PART 2 pre-screening assessments • Amendment to the PART 2 pre-treatment assessments to include assessment for surgical complications (for patients screened positive at 30 days post-surgery) • Clarification that all patients will be followed up for a total of 24 months from the 3 month-post surgery visit or from the 30-day post-surgery visit for those screened ctDNA positive at 30 days post-surgery

	• Changes to timing for provision of primary archival diagnostic tissue block to request that this is sent to the trial central laboratory at the time of trial registration • Amendment to the anticipated % of patients continuing to PART 2 from 30% to 20% • Amendment to exploratory endpoint 4 to include patients screened ctDNA positive at both 30 days and 3 months post-surgery • Updates to **Cohort B Known Risks and Benefits of AZD6738** section to bring in line with updated AZD6738 investigator brochure Edition 10 • Updates to section B6 to bring in line with updated AZD6738 investigator brochure Edition 10 • Updates to **Cohort C Known Risks and Benefits of Olaparib** section to bring in line with updated Olaparib investigator brochure Edition 21 • Updates to **COHORT D (Part 1) and Cohorts A and D (Part 2) Known Risks and Benefits of Durvalumab** section and **Adverse Events of Special Interest (AESI) in patients who receive durvalumab (cohort D in Part 1, and Cohorts A and D in Part 2)** section to bring in line with updated Durvalumab investigator brochure Edition 17 • Amendment to text to confirm that a minimum of 4 and up to a maximum of 8 core biopsies should be collected at each biopsy time point (WOP Day 1 and WOP Day 14) • Amendment to outline that PBMC samples should be collected for patients in all cohorts at those sites designated for PBMC collection (not just patients in cohorts A&D) • Amendment to section 17.3 **Reporting of SAE's to ICR-CTSU** to clarify that completed SAE forms should be emailed to the ICR specific SAE email account • Addition of a new reference #45 (Olaparib IB Ed 21)
Version 8.0 05 May 2023	• Addition of new trial management contact from administration section of the protocol • Updates to **Cohort B Known Risks and Benefits of AZD6738** section to bring in line with updated AZD6738 investigator brochure Edition 11 • Updates to **COHORT D (Part 1) and Cohorts A and D (Part 2) Known Risks and Benefits of Durvalumab** section to bring in line with updated Durvalumab investigator brochure Edition 18 • Replacement of durvalumab toxicity management guidelines (appendix 9) with October 2022 version
Version 9.0 16 April 2024	• Closure of cohorts A-D • Addition of new cohorts E-G • Addition of HRD and BRCA1/2m testing for treatment cohort allocation for cohorts E-G • Change to trial registration and trial entry eligibility to allow inclusion of patients that receive pembrolizumab as standard of care. • Removal of AZD6738- and durvalumab-specific eligibility criteria at Trial Registration and Trial Entry following closure of Cohorts B and D. Revisions to other eligibility based on current guidelines associated with trial IMPs. • Modification to informed consent process with patients being asked to consent to both Part 1 (WOP) and Part 2 (post-surgery) at Trial Entry. • Removal of ctDNA screening post-surgery and removal of requirement to have a ctDNA positive result to receive trial treatment in Part 2 (post-surgery) • Change in adjuvant treatment: (i) escalation using olaparib and durvalumab combination therapy for patients allocated to Cohorts F and G and (ii) treatment

	of Physician's choice for patients allocated to cohort E. Addition of Part 2 trial treatment eligibility criteria for Cohorts F and G. • Addition of co-primary endpoint of change in ctDNA (cohorts E-G only) • Addition of secondary and exploratory endpoints relating to HR deficiency • Addition of 'screening only' centres • Replacement of durvalumab toxicity management guidelines (appendix 7) with 21 September 2023 version
Version 10.0 23 April 2025	• Minor updated to trial management contacts in administration section of the protocol • Updates to **COHORTS F & G (Part 2) Known Risks and Benefits of Durvalumab** section to bring in line with updated Durvalumab investigator brochure Edition 20.0 • Minor corrections to section **12.1.2 Exclusion Criteria for durvalumab treatment in Part 2** • Updates to **Adverse Events of Special Interest (AESI) in patients who receive durvalumab (Part 2)** in section 16.1 of the protocol to bring in line with updated Durvalumab investigator brochure Edition 20.0 • Minor clarifications throughout section 16 of the protocol relating to pharmacovigilance reporting procedures • Replacement of durvalumab toxicity management guidelines (appendix 7) with 06 August 2024 version

CONTENTS

TRIAL SUMMARY

PROTOCOL TITLE	**PHOENIX DDR/Anti-PD-L1 Trial:** A pre-surgical window of opportunity and post-surgical adjuvant biomarker study of DNA damage response inhibition with or without anti-PD-L1 immunotherapy in patients with neoadjuvant treatment resistant residual triple negative breast cancer
PROTOCOL CONTEXT	This trial is part of the PHOENIX Platform: A post-neoadjuvant treatment resistant residual triple negative breast cancer, phase IIa novel therapy window of opportunity platform (WOP) aiming to identify biomarker response signals of biological activity to inform phase II and/or efficacy endpoint trials The platform design has enabled amendment and extension to the platform, from version 9.0 of the protocol, with addition of new treatment cohorts within the WOP to accommodate changes of standard of care to pembrolizumab containing NACT-IO in NHS practice for early stage II/III TNBC, and post surgery olaparib for gBRCA1/2m patients with residual invasive breast cancer disease after NACT or NACT-IO. The platform WOP and post-surgery trial treatment design remains the same, incorporating trial treatments included in previous versions of the protocol.
TARGET DISEASE	Neoadjuvant treatment resistant residual early triple negative breast cancer (TNBC) with high risk of metastatic relapse
TRIAL HYPOTHESIS	In patients with TNBC with molecular alterations and/or mutational signature associated with homologous recombination deficiency (HRD) beyond gBRCA1/2 mutation, and who have moderate to significant residual disease following neoadjuvant treatment, will show a signal of biological activity in residual disease tissue following short exposure to the PARP inhibitor olaparib in a post-neoadjuvant treatment preoperative window of opportunity (WOP) setting.
PRIMARY OBJECTIVE	**Cohorts A-D**: To assess whether short exposure to a DDR inhibitor or anti-PD-L1 immunotherapy in a preoperative WOP in patients with post-NACT high risk residual disease, generates a signal of anti-tumour biological activity within residual disease tissue. **Cohorts F & G:** To assess whether short exposure to the DDR inhibitor olaparib with or without anti-PD-1 immunotherapy in a preoperative WOP in patients with HRD associated TNBC and post-neoadjuvant treatment high risk residual disease, generates a signal of anti-tumour biological activity within residual disease tissue.
SECONDARY OBJECTIVES	1. **Cohort E:** To assess whether short exposure to a DDR inhibitor with or without anti-PD-1 immunotherapy in a preoperative WOP in patients with non-HRD associated TNBC and post-neoadjuvant treatment high risk residual disease, generates a signal of anti-tumour biological activity within residual disease tissue. 2. To characterise the safety of designated IMPs in a WOP trial context.

3. To examine levels of methylation of BRCA1 and RAD51C at diagnosis, pre- and post-WOP in tumour tissue and changes in the level of methylation between timepoints

EXPLORATORY OBJECTIVES

1. To examine the overall effect on the growth index (calculated as Ki67/ apoptosis %) of the residual tumour.
2. Explore within patient associations between responses seen in PART 1 and circulating tumour DNA (ctDNA) dynamics in PART 2.
3. Explore associations between ctDNA dynamics and disease related outcomes in PART 2.
4. To evaluate RAD51 foci as a functional marker of HR deficiency and predictor of response to olaparib.
5. To examine levels of methylation of other HRD genes (including but not limited to BRCA2 and XRCC3) in diagnosis, pre- and post-WOP tumour tissue and changes in the level of methylation between timepoints
6. To examine biomarkers of the DNA damage response and cancer or stroma pathway reprogramming/ signalling following trial treatment.
7. To examine levels at baseline and changes in the level of methylation of BRCA1 or RAD51C in cfDNA at all sampling time points
8. To examine the frequency of BRCA1 and BRCA2 “reversion mutations” in treatment naïve archival tumour material, pre-WOP biopsy and post WOP biopsy and definitive surgical material.
9. To examine the frequency of other known platinum or PARP inhibitor resistance mechanisms in treatment naïve archival tumour material, pre-WOP biopsy and post WOP biopsy and definitive surgical material.
10. To examine changes in the cellular Tumour Micro-Environment (TME) between treatment naïve archival tumour material, pre-WOP biopsy and post WOP biopsy and definitive surgical material.
11. Evaluate concordance between HRD status by Myriad MyChoice assay and Genomics England testing.

TRIAL DESIGN

WOP, open-label, multi-centre, phase IIa trial comprising multiple non-comparative treatment cohorts with patient allocation via minimisation (cohorts A-D) or allocation according to HRD and germline *BRCA1/2* mutation status (cohorts E-G).

The trial consists of two parts: a post-neoadjuvant treatment preoperative WOP component (PART 1); and a post-operative component (PART 2).

TRIAL POPULATION

Patients with early TNBC who are poor responders to neoadjuvant treatment with residual disease, as defined by imaging, and for whom definitive complete surgical excision of disease is planned.

PART 1 – WINDOW OF OPPORTUNITY COMPONENT

In PART 1 patients identified as poor responders to neoadjuvant treatment during mid-assessment scan as per standard imaging guideline (i.e. predicted to have ≥1cm residual disease at the end of NACT) will be approached to consent for Trial Registration. Registered patients with confirmed residual disease ≥1cm on the trial-specific imaging performed at least 1 week following day 1 of the final cycle of NACT will be approached to consent for Trial Entry.

The trial will comprise multiple non-comparative treatment cohorts with patient allocation via minimisation (cohorts A-D) or allocation according to HRD and germline *BRCA1/2* mutation status (cohorts E-G).

Eligible patients will commence trial treatment, as applicable as indicated below, within the WOP defined as the 2-week time period starting at least 3 weeks after the first day of the final cycle of NACT and 2 weeks prior to the patient's scheduled surgical intervention. The WOP is referred to as Day 1 – Day 14.

Cohort A: Standard care reference cohort (no trial treatment during Part 1). Cohort closed from protocol Version 9.0.

Cohort B: pre-operative exposure to AZD6738. Cohort closed from protocol Version 9.0.

- 160mg AZD6738 to be administered orally twice daily on **Days 5-14** of the WOP.

Cohort C: pre-operative exposure to olaparib. Cohort closed from protocol Version 9.0.

- 300mg of olaparib to be administered orally twice daily on **Days 1-14** of the WOP.

Cohort D: pre-operative exposure to durvalumab. Cohort closed from protocol Version 9.0.

- 1,500mg durvalumab to be administered via intravenous (IV) infusion on **Day 1 only** of the WOP*

** If there is an absence of a response signal in Cohort D co-primary endpoints, consideration will be given to protocol amendment to add a new durvalumab cohort starting durvalumab 6 weeks prior to surgery with or immediately following the final cycle of NACT supported by associated safety data given the possible latency of T-cell response after anti-PDL1 therapy [2].*

Cohort E (non-HRD and g*BRCA1*g*BRCA1/2* wildtype confirmed at HRD screening): pre-operative exposure to olaparib.

- 300mg of olaparib to be administered orally twice daily on **Days 1-14** of the WOP.

Cohort F (g*BRCA1/2* mutation confirmed at HRD screening): pre-operative exposure to olaparib.

- 300mg of olaparib to be administered orally twice daily on **Days 1-14** of the WOP.

Cohort G (HRD & g*BRCA1/2* wildtype confirmed at HRD screening): pre-operative exposure to olaparib.

- 300mg of olaparib to be administered orally twice daily on **Days 1-14** of the WOP.

Potential future cohorts:
Potential future cohorts, including if appropriate treatment combinations, may be added to the PHOENIX platform via future amendment as new targeted treatments become available and/or new therapeutic targets are identified.
Research blood and tissue samples will be collected from all patients at the beginning and end of the WOP to allow pre- and post-treatment comparison.

All patients will be followed up with a visit at 30 days post-surgery (including collection of research blood samples), at 3 months post-surgery (this will incorporate the PART 2 Pre-Treatment Assessments visit for patients in Cohorts F & G and eligible for adjuvant trial treatment and will undergo a further 24 months follow-up post-surgery at the following frequency:

- every 3 months (Cohort E and/or non-consenting to adjuvant trial treatment). Or,
- Every 4 weeks for up to 12 months of adjuvant trial treatment followed by every 3 months (Cohorts F & G)

At Trial Registration patients will be required to provide consent for transfer of their primary archival diagnostic tissue and collection and transfer of a blood sample for HRD testing at the central laboratory. For those patients who go on to consent to Trial Entry, this tissue sample will also be used to perform sequencing at the central laboratory for the development of a tumour-informed ctDNA assay for assessment of ctDNA in Parts 1 and 2.

PART 2 – POST-OPERATIVE COMPONENT

All patients will be followed up for 24-months post-surgery as detailed above. Patients allocated to cohort E and patients allocated to Cohorts F or G who are not eligible or who do not consent to trial treatment in Part 2 will receive SOC treatment of Physician's choice and followed up for 24 months.

Patients allocated to cohorts F and G will be provided with further information about trial treatment in Part 2 as soon as possible following confirmation of HRD

status and cohort allocation during Part 1 and invited to consent at the 30 day post-surgery visit. In all cases trial treatment can only commence provided that the pre-treatment assessments confirm suitability to receive trial treatment in PART 2. Part 2 trial treatment includes olaparib and durvalumab combination therapy:

Durvalumab dosing schedule:

- 1,500mg durvalumab to be administered via intravenous (IV) infusion on Day 1 only of each 28 day cycle.

Olaparib dosing schedule:

- 300mg olaparib (2 x 150mg tablets) to be administered orally twice daily on a continuous schedule Day 1-28 of each 28 day cycle.

For Part 2 trial treatment a cycle consists of 28 days and the planned trial treatment duration is 12 months (13 cycles). Patients will continue on trial treatment for up to a maximum of 12 months with serial ctDNA blood samples collected every 4 weeks. Subsequently patients will be followed up every 3 months with serial ctDNA blood sample collection for up to 24 months from the Part 2 pre-treatment assessment visit (anticipated to be approximately 3 months post-surgery).

RECRUITMENT TARGET

A maximum of 119 evaluable patients will be recruited into the trial as outlined below:
Cohort A – max. 9 patients (closed)
Cohort B – max. 24 patients (closed)
Cohort C – max. 24 patients (closed)
Cohort D – max. 24 patients (closed)
Cohort E – max. 15 patients
Cohort F – max. 8 patients
Cohort G – max. 15 patients

PRIMARY ENDPOINTS

The primary endpoint is specific to each treatment cohort based on the nature of the target and the biological effect being targeted.

The co-primary endpoints for Cohorts B, C and D are as outlined below:

Cohort B and C:

1. **Change in mean proliferation index** (as measured by tumour cell Ki67 staining) post-WOP intervention within post-treatment biopsy compared to pre-treatment baseline biopsy.
   A patient will be defined as being a Ki67 responder if they experience a relative decrease in Ki67 positive cells of ≥33% in the post-treatment biopsy sample

AND/OR

2. **Changes in the proliferation gene expression signature** post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.
   A patient will be defined as being a responder if there is a ≥1.5-fold decrease in the proliferation gene expression score in the post-treatment biopsy sample

Cohort D:

1. **Change in CD8$^+$ stromal tumour infiltrating lymphocytes (sTILs)** post anti-PD-L1 immunotherapy within the post-treatment biopsy compared to pre-treatment baseline biopsy.
   A patient will be defined as being a responder if they experience an absolute increase of ≥ 10% in the percentage CD8+ sTILs within the post-treatment biopsy sample

AND/OR

2. **Changes in the interferon gamma-positive (IFNγ$^+$) signature** post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.
   A patient will be defined as being a responder if there is a ≥2-fold increase in the IFNγ+ gene expression in the post-treatment biopsy sample

Cohort A (standard care reference cohort) will allow some characterization of any (artefactual) biopsy effects on the co-primary endpoints assessed in treatment Cohorts B, C and D.

Cohorts F-G:

1. **Change in mean proliferation index** (as measured by tumour cell Ki67 staining) post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

AND/OR

2. **Changes in the proliferation gene expression signature** post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

AND/OR

3. **Changes in the plasma ctDNA** (D0-D14) post WOP intervention compared to pre-treatment.

SECONDARY ENDPOINTS

1. Cohort E: Change in proliferation index and/or changes in proliferation gene expression signature and/or change in plasma ctDNA defined as per the primary endpoint for cohorts F-G.
2. Incidence of adverse events (AEs) during trial treatment (including surgical complications) by treatment cohort at 1 month post-surgery.
3. Methylation status of BRCA1 and RAD51C on diagnostic and pre- and post-WOP tumour samples and changes in methylation levels between these timepoints.

EXPLORATORY ENDPOINTS

1. Assess the ratio change in apoptosis and tumour cell proliferation in the post-treatment biopsy compared with pre-treatment baseline biopsy.
2. Relationship between the primary and secondary endpoints with the mutational landscape of the treated tumour as assessed by deep sequencing of the primary and residual disease and any subsequent metastatic relapse tumour genome and of tumour ctDNA in plasma.
3. Descriptive relationship between changes in ctDNA in Part 2 (post surgery) compared to biomarkers response to PART 1 in all patients from cohorts B-G.
4. Descriptive relationship between response status in PART 1 and changes in ctDNA in PART 2 within patients from cohorts B-G identified as ctDNA positive 30 days/3 months post-surgery who receive trial treatment in PART 2.
5. Descriptive relationship between ctDNA mutational profile in mutated genes in ctDNA pre-treatment and post-treatment ctDNA profiles in patients in both PART 1 and PART 2.
6. Descriptive differences in time between ctDNA detection and time to recurrence by 2 years in both the treated groups and observation group in PART 2.
7. RAD51 foci and geminin scoring on pre-wop biopsy samples
8. Methylation status of other HRD genes (including but not limited to BRCA2 and XRCC3) on diagnostic and pre- and post-WOP tumour samples, and the changes in methylation status between these timepoints.
9. Changes in phosphorylation of ataxia telangiectasia and Rad3-related protein (ATR) and its downstream effectors (including but not limited to Chk1, γH2AX, pKAP1, TAO upon drug exposure: including but not limited to levels of phosphorylation of p53, p38, p21/p27, cyclin dependent kinases (CDC25)).
10. Changes in biomarkers of DDR and adaptive and innate response, including but not limited to 53BP1, RAD51, RAD51C, RPA, RPA32, pRPA, BRCA1/2, PARP proteins, Shieldin complex components expression and immune checkpoint ligands and receptors and adaptive and innate immune response markers (IFNγ, cGAS-STING pathway, NKG2D receptors, ligands and cell markers) in the post-treatment biopsy compared to pre-treatment baseline biopsy using gene expression profiling.
11. Changes in biomarkers of DDR and adaptive and innate response, including but not limited to 53BP1, RAD51, RAD51C, RPA, RPA32, pRPA, BRCA1/2, PARP proteins, Shieldin complex components expression and immune checkpoint ligands and receptors and adaptive and innate immune response markers (IFNγ, cGAS-STING pathway, NKG2D receptors, ligands and cell markers) in the post treatment biopsy compared to pre-treatment baseline biopsy using reverse phase protein array (RPPA) and other proteome profiling.
12. Assessment of associated expression of co-inhibitory immune checkpoint receptors and ligands and frequency and function of TILs and myeloid cells subsets using immune cell markers and high content image de-convolution.
13. Changes in the levels of Th1/IFNγ response as measured by transcriptional and proteomic profiling.
14. Immune cell population sub-set characterisation using appropriate and T and B cell receptor DNA sequencing methodologies.

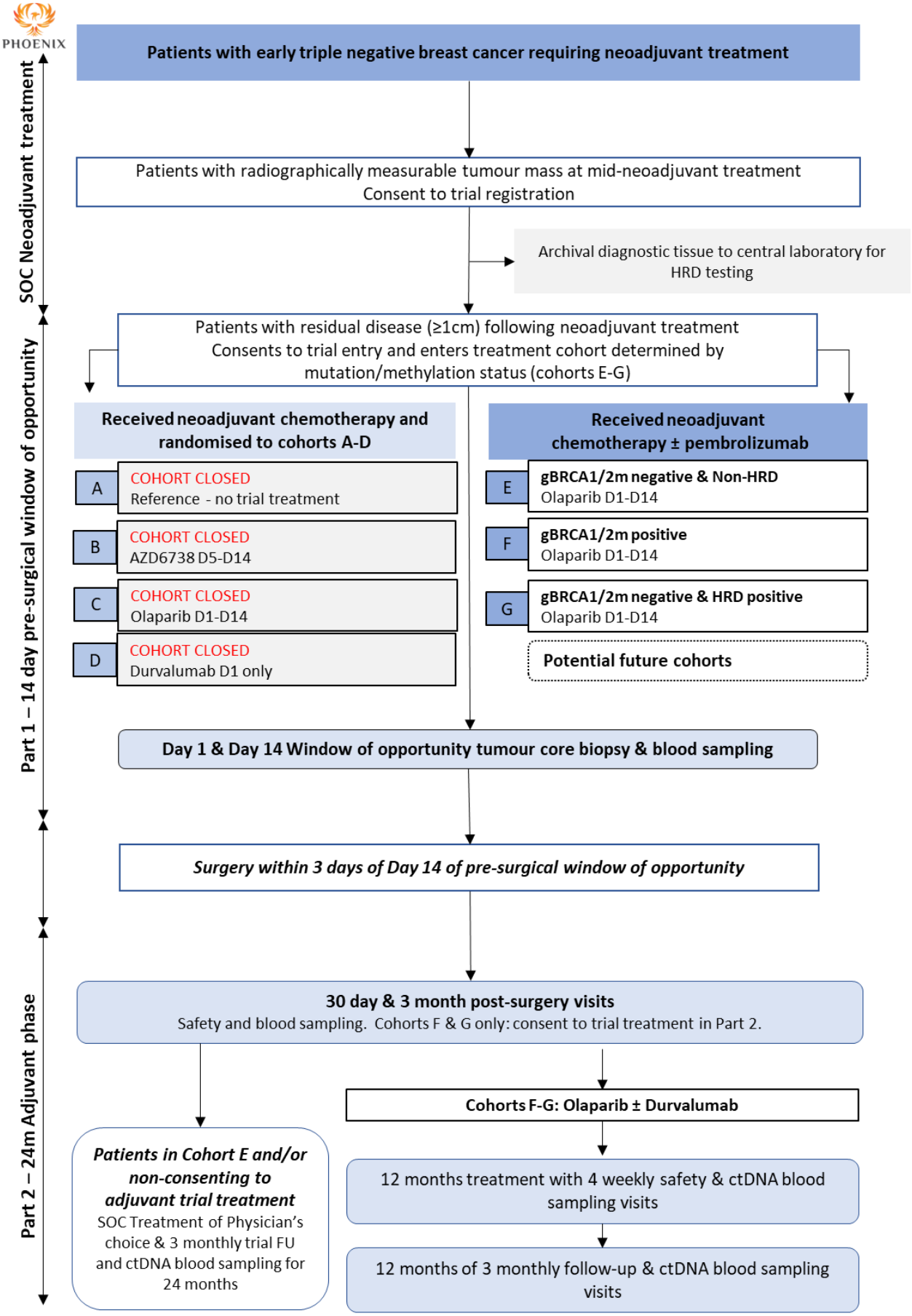
15. Assess change in the Ki67:CD8+ ratio within the post-treatment biopsy compared to pre-treatment baseline biopsy.
16. HRD status according to Myriad MyChoice and Genomics England testing.

TRIAL DURATION AND FOLLOW UP

It is anticipated that recruitment to Cohorts E-G will take approximately 24 months to complete.

All patients will be followed up for a total of 24 months post-surgery/Part 2 pre-treatment assessment visit.

TRIAL SCHEMA



1. INTRODUCTION

1.1. Background

Triple-negative breast cancers (TNBC), characterised by failure of tumour cells to express hormone receptors (oestrogen receptor (ER) or progesterone receptor (PR)) or be human epidermal growth factor receptor 2 (HER2) amplified, account for approximately 15-20% of all breast cancer diagnoses. TNBC is characterised by its clinically aggressive nature, younger age at presentation, distinct metastatic patterns and lack of effective targeted therapies, thus representing an important clinical challenge. TNBC relapse rates are particularly high during the first few years following surgery with a peak recurrence risk 3 years post-surgery [3]. Prognosis for patients with TNBC suffering metastatic relapse is significantly poorer than for patients with other subtypes of breast cancer.

Many TNBC patients are treated with neoadjuvant chemotherapy (NACT) before proceeding to definitive excisional breast surgery. Since publication of the BrighTNess and Keynote 522 studies [4,5] many patients now receive carboplatin based chemotherapy with the anti-PD1 antibody pembrolizumab (NACT-IO). While those TNBC patients who achieve a pathological complete response (pCR) or minimal residual cancer burden (RCB)-I [1] at surgery following NACT-IO have an excellent long-term outcome, the majority of patients who have moderate (RCB-II) or extensive (RCB-III) residual disease suffer a much poorer outcome [4, 5] (Figure 1).

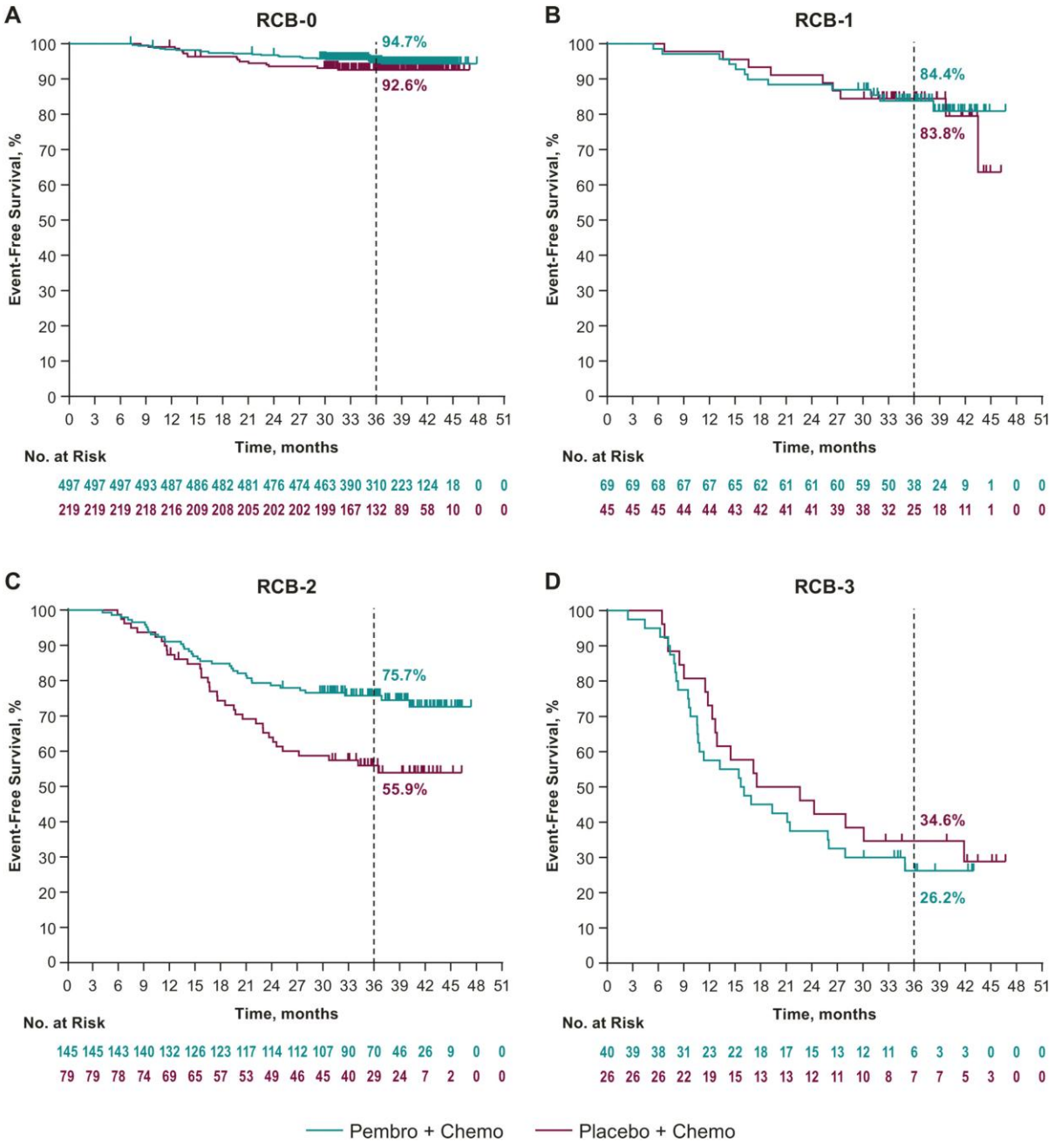


Figure 1: Event-free survival by RCB category in the KEYNOTE-522 trial [5]

Residual cancer remaining after NACT or NACT-IO is likely to represent the cancer cell population intrinsically resistant to chemotherapy (and if NACT-IO immunotherapy) at distant organ sites that leads to subsequent presentation with less readily biologically assessable clinically evident metastatic disease. Currently, this resistant residual disease will remain in situ for a minimum of 4 weeks after the final cycle of NACT prior to surgical excision. Outside the setting of patients with germline mutation in BRCA1 or BRCA2 genes there is a lack of effective additional adjuvant targeted therapies available and there is no current approved systemic therapy standard of care except continuation of adjuvant anti-PD1 therapy for patients with TNBC who have residual disease after NACT-IO following surgery. Current guideline and NHS approved management is adjuvant pembrolizumab alone although the role of the adjuvant component of pembrolizumab anti-PD1 treatment is subject to an ongoing clinical trial. Although a single study has reported survival endpoint benefits from a further use of 6 months of capecitabine chemotherapy as a second adjuvant therapy this was

conducted in an East Asian population following non-intensified standard non-platinum NACT [6]. Intensification of NACT with addition of a platinum and pembrolizumab in NACT +/- IO is now considered standard of care in the UK and so there remains divergent practice in the UK with regard to the use of capecitabine as second adjuvant therapy after NACT with or without anti-PDL1 therapy and definitive surgery.

1.2. Trial Rationale

Whole genome sequencing studies in TNBC have indicated that 60% of early TNBCs have deficiency in the homologous recombination DNA repair pathway (HRD) [7]. Only 15-20% of this 60% HRD group being due to germline mutation BRCA1 or BRCA2 (gBRCA1/2m) and the remaining 40% due to BRCA1/RAD51C methylation, germline PALB2 or somatic BRCA1/2 mutation. One year of treatment with the PARP inhibitor olaparib after chemotherapy and definitive surgery has been shown to improve both invasive disease-free survival and overall survival without detrimental side effects [8-10] leading to global marketing approval for patients with gBRCA1/2m including those with residual disease after NACT or NACT-IO. This provides a strong rationale to seek biomarker trial evidence for efficacy of olaparib in early TNBC with HRD beyond the gBRCA1/2m group.

The PHOENIX DDR/Anti-PD-L1 trial is a pre-surgical WOP, phase IIa trial aiming to identify signals of biological activity of DNA damage response (DDR) targeted therapy with or without anti-programmed death ligand 1 (PD-L1) immunotherapy in patients with post-neoadjuvant resistant residual TNBC at high risk of metastatic relapse. The design has the opportunity to test proof of concept for effect of PARPi therapy with olaparib in HRD TNBC beyond the gBRCA1/2m context (Cohort G) but using this group and a comparator positive control for biomarker endpoint assessment in a population (Cohort F) proven in the OlympiA trial to gain survival benefit from 12 months of adjuvant Olaparib therapy. The trial has been amended to account for the change of standard of care to pembrolizumab containing NACT-IO in NHS practice for early stage II/III TNBC, and post surgery olaparib for gBRCA1/2m patients with residual invasive breast cancer disease after NACT or NACT-IO. It also allows flexibility for physician choice to use post-surgery adjuvant capecitabine after surgery in PART 2 for non-HRD TNBC patients in Cohort E if this is local protocol or for gBRCA1/2m HRD TNBC in Cohort F who decline to receive 12 months of post-surgery adjuvant Olaparib, if this is local protocol.

COHORT A (Part 1 Standard Care) – Closed to recruitment

Presurgical WOP trials envision a short course treatment in the time window between baseline biopsy and biopsy at time of surgical resection of the tumour. This approach allows testing therapeutics when pre- and post-treatment tumour tissues are available for comprehensive molecular analyses; thereby defining the target patient population for subsequent larger studies. An important consideration in designing a “signal finding” biomarker endpoint WOP trial is the biological effects of the wound healing process, which is activated upon biopsy, and the correlated changes in gene expression profile may be confounding and should not be underestimated, especially when applying high-throughput technologies [11]. Cohort A therefore comprises of a standard care (chemotherapy only) reference cohort (Cohort A). The intention of the reference group within PART 1 is to characterise the existence of any biopsy effect, if any; and thus avoid misinterpretation of treatments effect in Cohorts B–D. Patients allocated to Cohort A will be invited to participate in Part 2 of the trial and so will have the opportunity to receive trial treatment with durvalumab in Part 2 if they are shown to be eligible. **This cohort was closed to recruitment on approval of version 9 of the protocol.** This follows agreement that further recruitment to this cohort would not add substantially to the reference data collected to date prior to approval of version 9 of the protocol.

COHORT B - AZD6738 – Closed to recruitment

AZD6738 is a potent, selective inhibitor of the serine/threonine-specific protein kinase, ataxia telangiectasia and Rad3-related protein (ATR), with good selectivity against other phosphatidylinositol 3-kinase-related kinase (PIKK) family members. ATR is a serine/threonine protein kinase and member of the PIKK family. During normal replication, ATR is recruited at stalled replication forks which can progress to double strand breaks if left unrepaired. ATR is also recruited to single strand DNA coated with Replication Protein A (RPA) following single strand DNA damage or the resection of double strand breaks. Recruitment and activation of ATR leads to cell cycle arrest in the S phase while the DNA is repaired and the stalled replication fork resolved, or nuclear fragmentation and entry into programmed cell death (apoptosis). In the clinic, ATR inhibitors are expected to cause growth inhibition in tumour cells dependent upon ATR for DNA repair e.g. ATM-deficient tumours. In addition to monotherapy activity, ATR inhibitors are also predicted to potentiate the activity of cytotoxic DNA damaging agents and radiotherapy (through inhibition of ATR-dependent DNA repair processes) when used in combination. There is also a rationale for combining with anti-PD1/PD-L1 agents as ATR inhibition may stimulate the production of tumour neo-antigens and directly affect the tumour immune microenvironment. Preclinical *in vitro* and *in vivo* data have demonstrated anti-tumour activity of AZD6738 in multiple ATM-deficient cell lines. AZD6738 shows a good margin of selectivity against other kinases in broad *in vitro* assay screens (0/442 kinases show >50% inhibition at 1µM) and no significant inhibition of other PI3K-like kinases DNA-PK, ATM, mTOR or AKT with IC50 >5µM in cells [12]. When used in combination with either DNA damaging chemotherapy agents or ionizing radiation, AZD6738 demonstrates synergistic cell killing activity across multiple cell lines in vitro and in xenograft studies [10, 11]. AZD6738 when combined with cisplatin in HER2-positive breast cancer cells demonstrates synergistic anti-tumour activity [13]. **This cohort was closed to recruitment on approval of Version 9 of the protocol.** This follows confirmation that any further data would not contribute to future clinical development of AZD6738 as a monotherapy for treatment of TNBC and so unlikely to impact clinical care.

COHORT B Rationale for AZD6738 Dosing

In a head and neck squamous cell carcinoma (HNSCC) window-of-opportunity study (NCT03022409: A Study to Investigate Biomarker Effects of Pre-Surgical Treatment With DDR Agents in Patients With HNSCC), patients are dosed for a minimum of 10 days with the investigational agent (olaparib or AZD6738) and a maximum of 3 weeks [14]. Surgery occurs within 24 hours immediately following three consecutive regularly scheduled days of administration of Investigational Medicinal Products (IMPs) and it is permitted to dose on the day of surgery. In PHOENIX patients will receive the last dose of AZD6738 the day before surgery (D14)***** as an extra precaution. Additionally, review of the haematological data in response to dosing of AZD6738 at 320 mg daily for 14 days (either 320 mg od or 160 mg bd), suggests there is an associated decrease in blood counts in ≈20% of patients. This is not the case with daily dosing for less than 10 days. Taking this data into account, patients will receive 160mg bd of AZD6738 for a total of 10 days, starting at Day 5 of the WOP with 160mg AZD6738 to be administered twice daily on **Days 5-14** of the WOP and the final dose of AZD6738 taken on the evening before surgery***** to minimize any risk of delaying the planned surgery at the end of the WOP.

COHORTS C and E-G - Olaparib - – Cohort C closed to recruitment

Olaparib (AZD2281, KU-0059436) is a potent inhibitor of PARP developed as a monotherapy as well as for combination with chemotherapy, ionising radiation and other anti-cancer agents including novel agents and immunotherapy. 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 the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair. Tumours with HR deficiencies, such as cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo [15, 16] and in the clinic [17]. The mechanism of action for olaparib results from the trapping of inactive PARP onto the SSBs preventing their repair [18, 19]. Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by homologous recombination repair.

Cohort C was closed to recruitment on approval of Version 9 of the protocol as the results of the OlympiA Trial in a post NACT second adjuvant setting showed a significant improvement in overall survival in gBRCA1/2m breast cancer patients including those with residual disease after NACT and so Olaparib has now become part of standard of care for gBRCA1/2m carriers in this setting [8,9].

COHORTS E-G Known Risks and Benefits of Olaparib

As of 15 December 2023, 11222 patients with ovarian, breast, pancreatic, gastric, prostate and a variety of other solid tumours are estimated to have received treatment with olaparib in clinical studies as either monotherapy or in combination with other chemotherapy/anti-cancer agents[20]. Olaparib monotherapy is generally well tolerated at monotherapy doses up to 400mg twice daily (capsule formulation) and 300mg twice daily (tablet formulation) in patients with solid tumours. The capsule formulation of olaparib was approved in December 2014 by the European Commission and United States (US) Food and Drug Administration (FDA). The majority of completed studies have been performed with the capsule formulation of olaparib but most new studies, including the Phase III registration studies, use the tablet formulation. The tablet formulation was subsequently registered in the US in August 2017 and Japan in January 2018. The recommended olaparib monotherapy tablet dose under investigation is 300 mg bd with an approved dose of 4 tablets daily (300 mg bd). The registration studies of olaparib in both advanced [21] and early breast cancer breast cancer [8] have used this formulation. The adverse event profile of 1 year of adjuvant olaparib at this dose has been considered mild and any adverse quality of life impacts minimal and not clinically significant [10].

Across all studies reported in the smPC adverse event (AE) reports considered to be associated with administration of olaparib are generally mild or moderate (NCI CTCAE Grade 1 or 2) haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia), decreased appetite, nausea and vomiting, diarrhoea, rash, hypersensitivity, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, venous thromboembolism and a small number of reported events of myelodysplastic syndromes (MDS)/acute myeloid leukaemia (AML) and new primary malignancies. In a small number of patients, pneumonitis has been reported, however data from the development programme does not support a conclusion that there is a causal relationship between olaparib and these events. This potential risk for olaparib is being kept under close pharmacosurveillance. No excess second malignancy or adverse event of special interest events were noted with 1 year of adjuvant olaparib use in the OlympiA trial [9].

COHORT D (Part 1), COHORTS A and D (Part 2) and COHORTS F & G (Part 2) - Durvalumab - Cohorts A and D closed to recruitment

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1 with PD-1 and CD80.

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumours [22]. PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor [23] and to CD80 [24]. PD-L1 expression is an adaptive response that helps tumours evade detection and elimination by the immune system. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g., IFNγ) and can be found on both tumour cells and tumour-infiltrating immune cells. The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target tumour cells and protecting the tumour from immune elimination [25]. PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated [24] [26].

The inhibitory mechanism described above is co-opted by tumours that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumour immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28. In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T cell-dependent mechanism [27]. PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumour immune responses in patients with cancer. Results of non-clinical and clinical studies of mAbs targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumour immune response in cancer patients [28-33] ; with responses that tend to be more pronounced in patients with tumours that express PD-L1[34-36]. In addition, high mutational burden [37] may contribute to the responses seen with immune therapy.

Cohorts A and D were closed to recruitment on approval of Version 9 of the protocol as immune checkpoint inhibitor therapy is now standard of care in NACT-IO in TNBC in those without contraindication to IO.

COHORTS F & G (Part 2) Known Risks and Benefits of Durvalumab

As of 30 April 2024, an estimated 18553 patients have received durvalumab in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumour types, stages of disease and lines of therapy [38]. Of these, 6242 patients received durvalumab monotherapy, 4487 patients received durvalumab in combination with tremelimumab, and 7824 patients received durvalumab or durvalumab plus tremelimumab in combination with an investigational and/or an approved product. No study has been terminated prematurely due to toxicity. Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus (which may present with diabetic

ketoacidosis), and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, psoriasis, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, non-infective encephalitis, subcutaneous injection site reaction, immune-mediated arthritis, uveitis, lung inflammation and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g. Guillain-Barré syndrome, myasthenia gravis). For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies, AEs at an incidence of ≥ 20% include events such as fatigue and decreased appetite. Approximately 10% of participants discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 5 events reported across the durvalumab program.

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 reactions (Appendix 7).

Efficacy data are available for 16 monotherapy studies or studies with a monotherapy arm, with a further 26 studies when durvalumab was given in combination with tremelimumab, chemotherapy agents or other anti-cancer agents. Durvalumab monotherapy and its combinations have demonstrated significant clinical benefit in multiple indications, particularly in PD-L1 high NSCLC, SCLC, and HCC. While the combination with tremelimumab and chemotherapy has yielded strong efficacy results, combinations with olaparib and other targeted therapies require further investigation. Durvalumab is approved in some countries as monotherapy for unresectable Stage III NSCLC (following chemoradiation therapy), and in combination with chemotherapy for extensive-stage small cell lung cancer and for locally advanced or metastatic biliary tract cancer. Durvalumab is approved as monotherapy in unresectable hepatocellular carcinoma in Japan. Durvalumab is also approved when administered in combination with tremelimumab for unresectable hepatocellular carcinoma, and also in combination with tremelimumab plus chemotherapy for participants with metastatic NSCLC without EGFR or ALK mutations. Refer to the current durvalumab IB for a complete summary of preclinical and clinical information including safety, efficacy and PK. .

COHORT D (Part 1), COHORTS A and D (Part 2) and COHORTS F & G (Part 2) Rationale for Durvalumab Fixed Dosing

A population pharmacokinetic (PK) model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; 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 ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40–120 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. 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[39]. In addition, they investigated 18 therapeutic proteins and peptides and showed

that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters. A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the PHOENIX trial.

1.3. Trial Hypotheses

Cohorts A-D

In patients with TNBC who have moderate to significant residual disease following NACT, short exposure to a DDR inhibitor and/or anti-PD-L1 immunotherapy in the post-NACT, preoperative WOP will show a signal of biological activity in residual disease tissue and for those patients who have post-operative evidence of presence of micro-metastatic relapse exposure to the same therapy will show a signal of anti-tumour activity.

Cohorts E-G

In patients with TNBC with molecular alterations associated with HRD beyond g*BRCA1/2* mutation, and who have moderate to significant residual disease following neoadjuvant treatment, will show a signal of biological activity following short exposure to the PARP inhibitor olaparib with or without anti-PD-L1 immunotherapy in residual disease tissue in a post-neoadjuvant treatment preoperative WOP setting. As PARP inhibition could potentially have effects on the trials biomarker endpoints outside the setting of HRD inclusion of patients with non-HRD associated TNBC (cohort E) will also enable detection of any effect beyond the know synthetic lethal interaction between PARP inhibition and germline mutation in BRCA1/2 and also the evaluation of the HRD specific effects of the PARP inhibitor olaparib in those with non-gBRCA1/2m forms of HRD.

1.4. Description of Population

Patients with early TNBC who are identified as poor responders to neoadjuvant treatment (with or without pembrolizumab) with moderate to significant residual disease, as defined by imaging and for whom definitive complete surgical excision of disease is planned.

2. TRIAL OBJECTIVES

2.1. Primary Objectives

Cohorts A-D

To assess whether short exposure to a DDR inhibitor or anti-PD-L1 immunotherapy in a preoperative WOP in patients with post-NACT high risk residual disease, generates a signal of anti-tumour biological activity within residual disease tissue.

Cohorts F & G

To assess whether short exposure to the DDR inhibitor olaparib with or without anti-PD-1 immunotherapy in a preoperative WOP in patients with HRD associated TNBC and post-neoadjuvant treatment high risk residual disease, generates a signal of anti-tumour biological activity within residual disease tissue.

2.2. Secondary Objectives

1. **Cohort E:** To assess whether short exposure to a DDR inhibitor with or without anti-PD-1 immunotherapy in a preoperative WOP in patients with non-HRD associated TNBC and post-neoadjuvant treatment high risk residual disease, generates a signal of anti-tumour biological activity within residual disease tissue.
2. To characterise safety of designated IMPs in a WOP trial context.
3. To examine levels of methylation of BRCA1 and RAD51C at diagnosis, pre- and post-WOP in tumour tissue and changes in the level of methylation between timepoints

2.3. Exploratory Objectives

1. To examine the overall effect on the growth index (calculated as Ki67/apoptosis %) of the residual tumour.
2. Explore within patient associations between responses seen in PART 1 and circulating tumour DNA (ctDNA) dynamics in PART 2.
3. Explore associations between ctDNA dynamics and disease related outcomes in PART 2.
4. To evaluate RAD51 foci as a functional marker of HR deficiency and predictor of response to olaparib.
5. To examine levels of methylation of other HRD genes (including but not limited to BRCA2 and XRCC3) in diagnosis, pre- and post-WOP tumour tissue and changes in the level of methylation
6. To examine biomarkers of the DNA damage response and cancer or stroma pathway reprogramming/ signalling following trial treatment.
7. To examine changes in the level of methylation of BRCA1 or RAD51C in cfDNA at all sampling time points
8. To examine the frequency of BRCA1 and BRCA2 “reversion mutations” in treatment naïve archival tumour material, pre-WOP biopsy and post WOP biopsy and definitive surgical material.
9. To examine the frequency of other known platinum or PARP inhibitor resistance mechanisms in treatment naïve archival tumour material, pre-WOP biopsy and post WOP biopsy and definitive surgical material.
10. To examine changes in the cellular Tumour Micro-Environment (TME) between treatment naïve archival tumour material, pre-WOP biopsy and post WOP biopsy and definitive surgical material.
11. Evaluate concordance between HRD status by Myriad MyChoice assay and Genomics England testing.

3. TRIAL DESIGN

The PHOENIX DDR/Anti-PD-L1 trial is a WOP, open-label, multi-centre, phase IIa trial comprising multiple non-comparative treatment cohorts with patient allocation via minimisation (cohorts A-D) or allocation according to HRD and germline *BRCA1/2* mutation status (cohorts E-G). The trial consists of two parts: a post-neoadjuvant treatment preoperative WOP component (PART 1); and a post-surgery component (PART 2).

Part 1 – Preoperative Window of Opportunity

The trial initially comprised of 4 non-comparative cohorts allocated via minimisation to avoid selection bias in cohort populations; a standard care reference cohort in whom all endpoints are measured (Cohort A); two DDR treatment cohorts (Cohort B: ATR inhibitor, AZD6738 and Cohort C: PARP inhibitor, olaparib); and an anti-PD-L1 immunotherapy treatment cohort (Cohort D: mAB durvalumab) administered as single agents in high-risk patients with NACT resistant residual early TNBC.

From protocol Version 9.0 Cohorts A-D will close to recruitment and a further 3 non-comparative cohorts E-G have been added to the PHOENIX platform with allocation according to HRD and germline *BRCA1/2* mutation status, with all patients receiving the PARP inhibitor olaparib as for Cohort C:

Cohort E: patients without germline *BRCA1/2* mutations or other HR deficiency. This provides a non-HR deficient "reference" cohort of patients and will enable assessment of biological activity in this subset of TNBC patients.

Cohort F: patients with germline *BRCA1/2* mutation. This represents the marketing authorisation approved population of patients with TNBC and post NACT residual disease and forms a positive reference population.

Cohort G: patients with evidence of HRD beyond the presence of a germline *BRCA1/2* mutation. This tests the PARP inhibition effects in a defined HRD population outside the current olaparib indication and may inform the potential development strategy for novel highly potent PARP1 selective PARP inhibitors outside the olaparib indication or application for extension of the olaparib label.

Intermediate biomarker co-primary endpoints of response in malignant cells, change in tumour cell proliferation by Ki67 immunohistochemistry (IHC) and/or proliferation gene expression (Cohorts B, C, E-G), change in proliferation of effector T-cells by IHC or T-cell activation by gene expression (Cohort D) and change in ctDNA (Cohorts E-G), are used as indicators of drug activity in the neoadjuvant treatment resistant residual disease and can be associated with pre-exposure tumour biomarker characteristics and drug induced changes in secondary biomarkers.

Provided adequate safety data are available, there is potential for further treatment cohorts to be added to the PHOENIX platform via future amendment, including either single or combination therapies associated with DDR inhibition and/or PD-1/PD-L1 immune checkpoint inhibition.

In PART 1 a two-stage design will be used, with any treatment cohorts showing no evidence of activity on pre-defined biomarker co-primary endpoints being stopped after the first stage and accrual focused on remaining cohorts in the second stage.
For all cohorts, patients are followed every 3 months for 24 months post-surgery.

Part 2 – Post-surgery component

Cohorts A-D

Cohorts A-D were closed to recruitment on approval of Version 9.0 of the protocol. For these cohorts, patients
were screened for the presence of ctDNA at 30 days post-surgery and 3 months post-surgery (for those patients who screened negative at 30 days post-surgery). Subsequent trial pathway was dependent on whether a patient was screened negative or positive for ctDNA. At the time of approval of Version 9.0 of the protocol all recruited patients in Cohorts A-D had either screened negative for ctDNA or were screened positive for ctDNA but were found not to be eligible for continued trial treatment. Therefore, all patients allocated to Cohorts A-D and who consented to Part 2 are being followed up every 3 months, with optional ctDNA blood sampling for a total duration of 24 months from the 3 month post-surgery /30 day post-surgery visit (for those screened ctDNA positive at 30 days post-surgery)).

Full details of the Part 2 trial pathways for patients allocated to Cohorts A-D can be found in Version 8.0 of the protocol. Patients in Cohorts A-D that remain in follow-up on approval of Version 9.0 of the protocol should continue in follow-up for a total duration of 24-months as described in 14.

Cohorts E-G
Patients allocated to Cohorts F & G will be invited to consent to further trial treatment in Part 2 at the 30 day visit. Eligible and consenting patients will receive trial olaparib and durvalumab combination therapy for a maximum of 12 months with 4 weekly follow-up and (optional) ctDNA blood sampling for 24 months. Patients that are not eligible for durvalumab will receive olaparib monotherapy.

Patients allocated to Cohort E, or those allocated to Cohorts F or G and non-consenting or not eligible for trial treatment in part 2, will receive (SOC) treatment of physician's choice with 3-monthly follow-up with (optional) ctDNA blood sampling for 24 months.

3.1. PART 1 – Window of Opportunity Component

Eligible patients with early TNBC who are identified as poor responders to neoadjuvant treatment at the mid-assessment scan as per standard imaging guidelines (i.e. predicted to have ≥1cm residual disease at the end of NACT) will be invited to register for the trial. On completion of neoadjuvant treatment, trial-specific imaging will be performed at least 1 week following the day 1 of the final cycle of NACT to confirm residual disease ≥1cm and patients will be approached to consent for Trial Entry. Tumours of this size are most likely to also be amenable to at least 4 core biopsies and multiple studies specifically show that imaging determinants of larger residual tumours are highly correlated with that found in histopathological measurements supporting that a high percentage of these patients will correspond to moderate to extensive residual disease [40-42].

At Trial Registration, patients will consent to transfer of their primary archival diagnostic tumour tissue (must include primary breast with or without involved lymph node tissue) and collection and transfer of a blood sample to the central laboratory. Sections of this tumour tissue sample will be used to determine HRD status and for development of a tumour-informed assay for assessment of ctDNA as described in the Investigator Laboratory Manual.
Patients meeting the eligibility criteria for Trial Entry will be allocated according to HRD and germline *BRCA1/2* mutation status:

Cohort E: patients without germline *BRCA1/2* mutations and without other HR deficiency.

Cohort F: patients with germline *BRCA1/2* mutation.

Cohort G: patients with evidence of HRD beyond the presence of a germline *BRCA1/2* mutation.

It is anticipated that in the majority of cases the results of HRD testing will be available prior to or shortly after Trial Entry to determine cohort allocation. However, retrospective allocation to Cohorts E-G is permitted during the pre-surgical window since all patients, regardless of cohort allocation, receive trial treatment with olaparib within the WOP as described below.

In PART 1 eligible patients **in Cohorts E-G will** commence trial treatment with olaparib within the WOP as indicated below:

Cohorts E-G: pre-operative exposure to olaparib

- 300mg of olaparib to be administered orally twice daily on Days 1-14 of the WOP – with the final dose taken on the evening before surgery*.

***The final dose should be taken on the evening of D14 of the WOP. In most cases this will be on the evening before surgery but may be up to 3 days prior to surgery if required.

The WOP is defined as the 2-week time period starting at least 3 weeks after the first day of the final cycle of NACT and 2 weeks prior to the patient's scheduled surgical intervention). The WOP period is referred to as Day 1 – Day 14. At the beginning of the WOP (and prior to commencing trial treatment) a mandatory image-guided core biopsy of the residual tumour with new distinct radio-opaque marker insertion will be performed together with the collection of research blood samples from all patients. Patients will then commence trial treatment within the WOP. At the time of the biopsy collection, a minimum of 4 and up to a maximum of 8 core biopsies should be collected. The number of cores to be collected should be decided on a case-by-case basis by the radiologist at the time of collection, with the aim of ensuring that at least 4 high quality tissue cores are obtained.

A second trial-specific pre-operative image-(radio-opaque marker) guided core biopsy will be performed on Day 14 together with the collection of research blood samples from all patients. Patients will undergo surgical resection of the residual tumour breast conserving surgery or mastectomy plus axillary surgery according to local protocol. In exceptional cases, image guided research biopsy cores can be taken on the day of surgery, either before surgery or taken by the surgeon intraoperatively (e.g. where radiologically guided biopsy of the post-window residual disease on Day 14 is not feasible) with the time from D14 WOP to biopsy minimised and recorded. In most cases it is anticipated that the collection of the baseline and pre-operative biopsies will be completed via ultrasound-guidance, however, any other imaging modalities may be used (including stereotaxis, digital breast tomosynthesis, contrast enhanced mammography and MRI) as deemed suitable by the local centre depending on expertise and availability, may be used to target biopsy sites.

All patients will be followed up with a visit at 30 days post-surgery (including collection of research blood samples), at approximately 3 months post-surgery. Patients allocated to Cohort E, or those patients allocated to Cohorts F or G who do not consent to and/or are not eligible to receive further trial treatment in Part 2 will be followed up every 3 months for 24 months post-surgery.

3.2. PART 2 – Post-Surgery Component

Patients allocated to Cohorts F and G

Patients allocated to Cohorts F and G during Part 1 will be provided with information relating to further trial treatment in Part 2 for discussion and at the 30-day post-surgery visit. Eligible and consenting patients will receive trial treatment for 12 months (13 cycles) in Part 2 with 4 weekly follow-up visits and serial ctDNA blood sampling.

In all cases treatment can only commence provided that the Part 2 pre-treatment assessments confirm suitability to receive trial treatment in PART 2. Trial treatment will include olaparib and durvalumab combination therapy:

Olaparib: 300mg of olaparib to be administered orally twice daily on a continuous schedule Day 1-28 of each 28 days cycle.

Durvalumab: 1,500mg durvalumab to be administered via intravenous (IV) infusion on Day 1 only of each 28 day cycle.

For each treatment cohort a cycle consists of 28 days and planned trial treatment duration is 12 months (13 cycles) unless there is evidence of unacceptable toxicity, withdrawal of consent or if the investigator decides it is not in the best interest of the patient to continue.

Patient follow-up post-discontinuation of trial treatment

Following end of trial treatment (on completion of 13 cycles or at treatment discontinuation) all patients will undergo an end of treatment visit. Safety follow-up visits will be performed 30 days (±7 days) and 90 days (±7 days) after the last dose of trial treatment. All patients will be followed up after trial treatment every 3 months (±14 days) for survival status and serial ctDNA blood sampling for up to 24 months from the Part 2 pre-treatment assessment visit.

Patients allocated to Cohort E, and those allocated to Cohorts F and G non-consenting or ineligible for Part 2 trial treatment

Patients allocated to Cohort E during Part 1, or for those allocated to Cohorts F and G and non-consenting or ineligible for Part 2 trial treatment, will not receive any further trial treatment in Part 2. Patients will receive standard of care adjuvant treatment of physician's choice according to local practice and as clinically indicated. Treatment of physician's choice should be limited to only currently approved, and NHS available, therapies given as SOC in the target trial population. There are no protocol restrictions for treatment of physician's choice in terms of dose reductions permitted or treatment discontinuation, which will be based on Investigator's judgment. Details of treatment of physician's choice will be recorded in the trial database.

All patients will be followed up every 3 months (±14 days) for survival status and serial ctDNA blood sampling for 24 months.

3.3. Future Planned Cohorts

Potential future cohorts, including if appropriate treatment combinations, may be added to the PHOENIX platform via future amendment as new targeted treatments become available and/or new therapeutic targets are identified.

Treatment allocation was performed via minimisation into the initial 4 cohorts A-D as a mechanism to ensure balanced patient subtype heterogeneity and unbiased populations across all 4 treatment cohorts. Cohorts E-G, added to the trial via protocol amendment from Version 9.0 onwards, will be biomarker stratified.

4. TRIAL ENDPOINTS

4.1. Primary Endpoints

The primary endpoint is treatment cohort specific based on the nature of the target and the biological effect being targeted.

The co-primary endpoints for each cohort are as outlined below:

Cohorts B and C:

1. **Change in mean proliferation index** (as measured by tumour cell Ki67 staining) post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

AND/OR

2. **Changes in the proliferation gene expression signature** post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

Cohort D:

1. **Change in $CD8^+$ stromal tumour infiltrating lymphocyte (sTIL) frequency** post anti-PD-L1 immunotherapy within the post-treatment biopsy compared to pre-treatment baseline biopsy.

AND/OR

2. **Changes in the Interferon Gamma-positive ($IFN\gamma^+$) signature** post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

Cohort A (standard care reference cohort) will allow assessment of any biopsy effect on all co-primary endpoints assessed in treatment cohorts B, C and D.

Cohorts F-G:

1. **Change in mean proliferation index** (as measured by tumour cell Ki67 staining) post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

AND/OR

2. **Changes in the proliferation gene expression signature** post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

AND/OR

3. **Changes in the plasma ctDNA** (D0-D14) post WOP intervention compared to pre-treatment.

4.2. Secondary Endpoints

1. Cohort E: Change in proliferation index and/or changes in proliferation gene expression signature and/or change in plasma ctDNA defined as per the primary endpoint for cohorts F-G.
2. Incidence of adverse events (AEs) during trial treatment (including surgical complications) by treatment cohort at 1 month post-surgery.
3. Methylation status of BRCA1 and RAD51C on diagnostic and pre- and post-WOP tumour samples and changes in methylation levels between these timepoints.

4.3. Exploratory Endpoints

1. Assess the ratio change in apoptosis and tumour cell proliferation in the post-treatment biopsy compared with pre-treatment baseline biopsy.
2. Relationship between the primary and secondary endpoints with the mutational landscape of the treated tumour as assessed by deep sequencing of the primary and residual disease and any subsequent metastatic relapse tumour genome and of tumour ctDNA in plasma.
3. Descriptive relationship between changes in ctDNA in Part 2 (post surgery) compared to biomarkers response to PART 1 in all patients from cohorts B-G.
4. Descriptive relationship between response status in PART 1 and changes in ctDNA in PART 2 within patients from cohorts B-G identified as ctDNA positive 30 days/3 months post-surgery who receive trial treatment in PART 2.
5. Descriptive relationship between ctDNA mutational profile in mutated genes in ctDNA pre-treatment and post-treatment ctDNA profiles in patients in both PART 1 and PART 2.
6. Descriptive differences in time between ctDNA detection and time to recurrence by 2 years in both the treated groups and observation group in PART 2.
7. RAD51 foci and geminin scoring on pre-wop biopsy samples
8. Methylation status of other HRD genes (including but not limited to BRCA2 and XRCC3) on diagnostic and pre- and post-WOP tumour samples, and the changes in methylation status between these timepoints.
9. Changes in phosphorylation of ataxia telangiectasia and Rad3-related protein (ATR) and its downstream effectors (including but not limited to Chk1, γH2AX, pKAP1, TAO upon drug exposure: including but not limited to levels of phosphorylation of p53, p38, p21/p27, cyclin dependent kinases (CDC25)).
10. Changes in biomarkers of DDR and adaptive and innate response, including but not limited to 53BP1, RAD51, RAD51C, RPA, RPA32, pRPA, BRCA1/2, PARP proteins, Shieldin complex components expression and immune checkpoint ligands and receptors and adaptive and innate immune response markers (IFNγ, cGAS-STING pathway, NKG2D receptors, ligands and cell markers) in the post-treatment biopsy compared to pre-treatment baseline biopsy using gene expression profiling.
11. Changes in biomarkers of DDR and adaptive and innate response, including but not limited to 53BP1, RAD51, RAD51C, RPA, RPA32, pRPA, BRCA1/2, PARP proteins, Shieldin complex components expression and immune checkpoint ligands and receptors and adaptive and innate immune response markers (IFNγ, cGAS-STING pathway, NKG2D receptors, ligands and cell markers) in the post treatment biopsy compared to pre-treatment baseline biopsy using reverse phase protein array (RPPA) and other proteome profiling.
12. Assessment of associated expression of co-inhibitory immune checkpoint receptors and ligands and frequency and function of TILs and myeloid cells subsets using immune cell markers and high content image de-convolution.
13. Changes in the levels of Th1/IFNγ response as measured by transcriptional and proteomic profiling.
14. Immune cell population sub-set characterisation using appropriate and T and B cell receptor DNA sequencing methodologies.
15. Assess change in the Ki67:CD8+ ratio within the post-treatment biopsy compared to pre-treatment baseline biopsy.
16. HRD status according to Myriad MyChoice and Genomics England testing.

5. SELECTION OF PARTICIPANTS FOR TRIAL REGISTRATION

5.1. Number of Participants

A maximum of 81 evaluable patients will be recruited into cohorts A-D of the trial and 38 recruited into cohorts E-G.

PART 1:
Cohort A – 9 patients (closed)
Cohort B – max. 24 patients (closed)
Cohort C – max. 24 patients (closed)
Cohort D – max. 24 patients (closed)

Cohort E – max. 15 patients
Cohort F – max. 8 patients
Cohort G – max. 15 patients

PART 2:
Cohorts A-D (cohorts closed from protocol Version 9.0)
Any patients with a ctDNA positive result at ctDNA screening at 30 days post-surgery or 3 months post-surgery will be given the opportunity to receive trial treatment in PART 2 provided they are confirmed suitable to commence treatment. Therefore a maximum of 81 patients may receive trial treatment within PART 2 cohorts A-D, however it is anticipated that the number of patients identified as ctDNA positive at this time point will be substantially lower (approx. 20%).

Cohorts E-G
All patients in cohorts F and G will be given the opportunity to receive trial treatment in PART 2 provided they are confirmed suitable to commence trial treatment. Patients in cohort E will not be eligible for trial treatment in PART 2. Therefore, a maximum of 23 patients may receive trial treatment within PART 2.

5.2. Source of Participants

Participants will be recruited from approximately 20 participating sites in the UK. This will include a network of screening only and treatment delivery sites as described in Section 20. Potential participants will be identified in oncology clinics and discussed at Multi-Disciplinary Team (MDT) meetings.

Patients identified as poor responders to NACT and likely to have ≥1cm residual disease after NACT following mid-assessment imaging as per standard imaging guidelines will be approached to consent for Trial Registration. Registered patients with confirmed residual disease ≥1 cm on trial-specific imaging performed at least 1 week following day 1 of the final cycle of NACT will be invited to consent for Trial Entry.

5.3. Eligibility Criteria for Trial Registration

Patients will be considered eligible for Trial Registration if they fulfil all eligibility criteria listed below. Additional eligibility criteria for Trial Entry apply and must be confirmed prior entering a patient into the trial, please refer to Section 8.1.

Patients who have participated in previous clinical trials (for this episode of breast cancer) may still enter PHOENIX, provided they meet all the eligibility criteria and participation in multiple trials will not compromise endpoint evaluation in either.

5.3.1. Inclusion Criteria for Trial Registration

1. Signed Informed Consent Form (ICF) for Trial Registration;
2. Aged ≥18 years old;
3. Histologically confirmed invasive triple negative breast cancer (TNBC). *TNBC defined as ER negative, PgR negative (ER and PgR negative as defined by Allred score 0/8, 1/8 or 2/8 or stain in <1% of cancer cells) or PgR unavailable, and HER2 negative (immunohistochemistry 0/1+ or negative in situ hybridization) as determined by local laboratory and recorded in the patients notes;*
4. Planned definitive surgical treatment after at least 6 cycles of neoadjuvant chemotherapy (NACT) *Patients currently receiving SOC pembrolizumab, or having previously received SOC pembrolizumab but subsequently discontinued treatment, in combination with NACT are eligible for Trial Registration*;
5. Radiographically measurable tumour mass assessable for new distinct radio-opaque marker insertion and repeated biopsies on the NACT mid-assessment standard of care imaging modality;
6. Eastern Oncology Cooperative Group (ECOG) performance status 0-1;
7. Considered fit enough to have breast cancer surgery with curative intent;
8. Considered fit to complete at least 2 weeks of pre-operative trial treatment in the WOP;
9. Patients must be suitable for a mandatory pre-treatment baseline biopsy performed Day -1 or 1 of the window of opportunity (WOP) and a post-treatment biopsy performed on Day 14 of the WOP. Registered patients who are approached for Trial Entry will be required to consent to the pre- and post- WOP treatment biopsy. If it is deemed unsafe to proceed with biopsy upon Trial Entry the patient will not be eligible for participation in the trial.
10. Patients with clinical stage II or III disease or clinical suspicion of metastatic disease must have staging studies to exclude metastatic disease if this is standard of care, and staging methods should be used as per standard of care (axillary lymph nodes or internal mammary node involvement will not be regarded as evidence of metastatic disease);
11. Patients with previous invasive cancers (including breast cancer) are eligible if the treatment was completed >5 years prior to Trial Registration, and there is no evidence of recurrent disease;
12. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the trial protocol and follow-up schedule; those conditions should be discussed with the patient before Trial Registration;
13. Patients must be a) surgically sterile (*i.e. if female have undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy; if male have undergone a bilateral orchidectomy*); b) have a sterilised sole partner; or c) be post-menopausal; or d) must agree to practice total/true abstinence; or e) use a condom and one highly effective form of contraception in combination during the period

of trial treatment and be willing to do so for a period of at least 6 months following the end of trial treatment. *Please refer to Section 5.4 Lifestyle Guidance for the definition of total/true abstinence and a list of the permitted highly effective forms of contraception.*

Post-menopausal is defined by at least one of the following criteria:

a. Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments

b. Luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range for the institution for women < 50 years of age not using hormonal contraception or hormonal replacement therapy. *Please note: in absence of amenorrhea for 1 year, a single LH and/or FSH measurement is insufficient.*

c. Radiation-induced oophorectomy with last menses >1 year ago

d. Chemotherapy-induced menopause with >1 year interval since last menses

e. Surgical sterilisation (hysterectomy, bilateral salpingectomy or bilateral oophorectomy)

5.3.2. Exclusion Criteria for Trial Registration

1. Definitive evidence of metastatic disease (axillary lymph nodes or internal mammary node involvement will not be regarded as evidence of metastatic disease) ;
2. Patients with bilateral tumours.
3. History of another primary malignancy within the last 5 years prior to Trial Registration, except for:
    a. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease;
    b. Adequately treated carcinoma in situ without evidence of disease;
4. Patients with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML) or with features suggestive of MDS/AML;
5. Severe concurrent disease, infection or co-morbidity that, in the judgment of the local Investigator, would make the patient inappropriate for Trial Registration;
6. Resting ECG indicating uncontrolled, potentially irreversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >470 msec, electrolyte disturbances, etc.), or patients with congenital long QT syndrome;
7. Patients unable to swallow orally administered medication;
8. Patients receiving therapeutic anti-coagulation treatment (including warfarin and novel oral anti-coagulants).
9. Patients with gastrointestinal disorder affecting absorption (e.g. gastrectomy, active peptic ulcer disease within last 3 months);

10. History of seizure or any condition that may predispose to seizure.

11. Other non-malignant systemic disease that would preclude trial treatment or would prevent required follow-up;

12. Pregnant or breast-feeding;

13. Prior exposure to PARP inhibitor, including olaparib, anti-PD-1 or anti-PDL1 immunotherapy (including durvalumab) except for pembrolizumab if received as standard of care in combination with neoadjuvant chemotherapy;

14. Any other disease(s), psychiatric condition, metabolic dysfunction, or findings from a physical examination or clinical laboratory test result that in the investigators opinion would cause reasonable suspicion of a disease or condition, that contraindicates the use of trial treatment, that may increase the risk associated with trial participation, that may affect the interpretation of the results, or that would make this trial inappropriate for the patient;

15. Patients with a known hypersensitivity to pembrolizumab, durvalumab or olaparib or any excipients of the products;

16. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT);

17. Active infection including **tuberculosis** (TB) (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (HBV; known positive HBV surface antigen (HBsAg) result), **hepatitis C** (HCV), or **human immunodeficiency virus** (HIV; positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA;

Please note, the following exclusion criteria will apply prior to Trial Entry. These criteria should be considered prior to Trial Registration with the expectation that the patient would not be excluded from Trial Entry based on these points:

1. History of clinically significant or uncontrolled cardiovascular disease including:
    - Myocardial infarction within 6 months prior to Trial Entry;
    - Uncontrolled angina within 3 months prior to Trial Entry;
    - Congestive heart failure New York Heart Association (NYHA) class III or IV, or patients with history of congestive heart failure NYHA class III or IV in the past, unless an echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan performed within 3 months prior to Trial Entry results in a left ventricular ejection fraction that is 45%;
    - History of clinically significant ventricular arrhythmias (e.g. ventricular tachycardia, ventricular fibrillation, torsades de pointes);
    - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place;
    - Consistent evidence of hypotension as indicated by systolic blood pressure < 90 millimeters of mercury (mm Hg) prior to Trial Entry;
    - Consistent evidence of bradycardia as indicated by a heart rate of < 50 beats per minute on the ECG prior to Trial Entry;

- Consistent evidence of uncontrolled hypertension as indicated by systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg prior to Trial Entry.

2. History of loss of consciousness or transient ischemic attack within 12 months prior to Trial Entry;

3. Patients with Grade ≥2 neuropathy, as defined by the National Cancer Institute (NCI)'s Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) will be evaluated on a case-by-case basis after consultation with the CI or Coordinating Investigator;

4. Major surgery (excluding minor procedures, e.g. placement of vascular access) within 2 weeks prior to Trial Entry. *Patients must have recovered from any effects of any major surgery prior to commencing trial treatment.*

5. Use of any investigational agent within 30 days prior to commencing trial treatment.

6. Concomitant use of known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) within 2 weeks prior to first dose of trial treatment. *The required washout period prior to commencing trial treatment is 2 weeks;*

7. Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate (e.g. bosentan, efavirenz, modafinil) CYP3A inducers. *The required washout period prior to commencing trial treatment is 5* weeks;

8. Whole blood infusion or erythropoietin within 28 days prior to trial entry (packed red blood cells and platelet transfusions are acceptable).

9. Receipt of live attenuated vaccine within 30 days prior to commencing trial treatment.

5.4. Lifestyle Guidance

Participants must be surgically sterile (*i.e. if female have undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy; if male have undergone a bilateral orchidectomy*), or have a sterilised sole partner, or be post-menopausal (*as defined in the Trial Registration Inclusion Criteria Section 5.3.1*), or must agree to practice total/true abstinence or use a condom and one highly effective form of contraception in combination as defined below.

Women of childbearing potential and their partners, who are sexually active, must agree to the use of a condom and **ONE highly effective** form of contraception in combination as listed below. This should be started from the signing of the ICF for Trial Entry and continue throughout the period of trial treatment and for at least 6 months after last dose of trial treatment, or they must totally/truly abstain from any form of sexual intercourse (see definition of total/true abstinence below).

Male participants must use a condom during trial treatment and for 6 months after the last dose of trial treatment when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male participants should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Male participants should not donate sperm throughout the period of trial treatment and for 6 months following the last dose of trial treatment.

Birth control methods used must include a condom and ONE of the following highly effective methods:

- Vasectomised sexual partner. With participant assurance that the vasectomised partner has received post-vasectomy medical confirmation of surgical success (azoospermia).
- Bilateral tubal occlusion.
- Intrauterine device (IUD). Provided coils are copper-banded.
- Combined (oestrogen and progestogen containing) oral hormonal contraception pill associated with inhibition of ovulation.
- Cerazette (desogestrel). *Cerazette is currently the only highly efficacious progestogen-only oral hormonal contraception based pill associated with inhibition of ovulation.*
- Hormonal injection (e.g. Depo-Provera).
- Etonogestrel implants (e.g. Implanon, Norplant).
- Norelgestromin / ethinyl estradiol (EE) transdermal system.
- Intrauterine system (IUS) device (e.g. levonorgestrel releasing IUS -Mirena®).
- Intravaginal device (e.g. EE and etonogestrel).

Definition of Total/True abstinence:
When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 6 months after the last dose of trial treatment. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not highly effective methods of contraception.

5.5. Procedure for Obtaining Informed Consent for Trial Registration

The Principal Investigator (PI) (or delegated individual) must ensure that each trial patient is fully informed about the nature and objectives of the trial and possible risks associated with participation. Participants should be given the current ethics approved **PHOENIX Patient Information Sheet (PIS) for Trial Registration** for their consideration. Patients should only be asked to consent for registration after they have had sufficient time to consider their participation, and had the opportunity to ask any further questions.

No protocol required assessments, other than those required as part of standard patient care, should be conducted until the **PHOENIX Informed Consent Form (ICF) for Trial Registration** has been signed and dated by both the patient and the PI (or delegated individual).

Confirmation that the patient meets all eligibility criteria should be documented in the patient's medical notes by the PI (or delegated individual), along with confirmation of the patient's consent for registration.

One copy of the signed ICF should be provided to the patient, one copy should be filed in the patient's medical records and the original should be retained in the Site Investigator file (SIF), which must be available for verification by ICR-CTSU trial staff or for regulatory inspection at any time.

5.6. Trial Registration Screening Assessments

Only those procedures required as part of standard patient care should be conducted prior to obtaining written informed consent from the patient for registration as detailed in Section 5.5.

The following assessments should be conducted within 14 days prior to Trial Registration:

- Written informed consent for Trial Registration
- Complete medical history to confirm suitability for Trial Registration
- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Review of concomitant medication

6. TRIAL REGISTRATION PROCEDURE

The **Trial Registration Eligibility Checklist** (signed by the PI or delegated Co-investigator) must be completed prior to completing the **Trial Registration Form**, and both must be completed prior to registration. Written confirmation that eligibility has been checked by an Investigator should also be documented in the patient's medical notes.

Participants must be registered centrally with the trials unit (ICR-CTSU) before protocol required activities commence. Please refer to the **PHOENIX Trial Guidance Notes** for the procedure to follow for patient registration.

Patients can be registered by ICR-CTSU from **09.00-17.00 (UK time) Monday to Friday**.

The following information will be required at registration:

- Name of hospital, Investigator and person registering patient
- Confirmation that patient has given written informed consent for Trial Registration
- Confirmation that the patient is eligible for Trial Registration by completion of the Registration Eligibility Checklist
- Patient's initials and date of birth

At the time of registration, the ICR-CTSU staff will give the caller the patient's unique Trial Registration Number and confirmation will be sent to the site contact for the trial (Research Nurse/Trial Coordinator).

6.1. Procedure for assessment of HRD status

Once trial registration is confirmed, the patient's archival diagnostic tumour tissue sample (must include primary breast with or without involved lymph node tissue) and collected blood sample should be sent to the PHOENIX Central Laboratory immediately. Laboratory testing will be co-ordinated centrally and results will not be required to determine eligibility. The provision of the patient's archival tumour tissue and blood

sample is required in order to allocate patients to the appropriate cohort based on their HRD and germline *BRCA1/2* mutation status.

If following Trial Registration it is determined that the patient's archival diagnostic tissue sample is unavailable for transfer this should be discussed with the trial team and the patient should not be invited to consent to Trial Entry. Please refer to the **PHOENIX Investigator Laboratory Manual** for tissue sample requirements.

7. CONFIRMATION OF RESIDUAL DISEASE FOLLOWING END OF NACT

For all patients registered to PHOENIX, trial-specific imaging should be performed at least 1 week following day 1 of the final cycle of NACT. The imaging modality used should be according to local practice. Please refer to the Radiology Guidance Document detailing recommended use of MRI and summary of associated MRI scan acquisition protocol. This imaging will be used to confirm that residual disease is ≥ 1cm to determine eligibility for Trial Entry.

Patients who do not have confirmed residual disease ≥ 1cm by imaging should not be approached for Trial Entry but should be treated outside of the trial as per standard care.

8. SELECTION OF PATIENTS FOR TRIAL ENTRY

In order to proceed to Trial Entry the patient must meet all trial entry eligibility criteria provided below.

8.1. Eligibility Criteria for Trial Entry

Patients will be considered eligible for Trial Entry if they fulfil all Trial Entry eligibility criteria listed below.

8.1.1. Inclusion Criteria for Trial Entry

1. Signed Informed Consent Form (ICF) for Trial Entry;

2. Residual disease is confirmed as at least one viable disease focus ≥1cm on trial-specific imaging performed at least 1 week following day 1 of the final cycle of NACT.

3. Provision of acceptable archival diagnostic tumour tissue sample prior to Trial Entry as defined in the Investigator Laboratory Manual.

4. Recovery from all acute adverse events of prior NACT or pembrolizumab to baseline or NCI CTCAE Grade ≤1, except for alopecia. *Patients with irreversible toxicity not reasonably expected to be exacerbated by trial treatment may be included only after consultation with the CI or Coordinating Investigator.*

5. Patients must have adequate haematological, renal and hepatic function as defined by:
   - Haemoglobin (Hb) ≥ 10 g/dL (≥ 100 g/L) with no blood transfusion in the past 28 days
   - Absolute neutrophil count (ANC) ≥ 1500/mm^3 (≥ 1.5 x 10^9/L)
   - Platelet count ≥100,000/mm^3 (≥ 100 x 10^9/L)

- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional ULN
- Calculated creatinine clearance ≥51 mL/min using the Cockcroft-Gault equation (please refer to Appendix 4) or based on a 24 hour urine test or another validated test as per local practice

6. Women of childbearing potential must have a confirmed menstrual period and a negative urinary or serum pregnancy test prior to Trial Entry. *This should be repeated as applicable to ensure a negative pregnancy test is performed on the day of planned trial treatment.*

7. Confirmation that all Trial Registration inclusion criteria listed in Section 5.3.1 remain satisfied.

8.1.2. Exclusion Criteria for Trial Entry

1. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or any psychiatric disorder that prohibits obtaining informed consent.

2. Major surgery (excluding minor procedures, e.g. placement of vascular access) within 2 weeks prior to Trial Entry. *Patients must have recovered from any effects of any major surgery prior to commencing trial treatment.*

3. Use of any investigational agent within 30 days prior to commencing trial treatment.

4. Concomitant use of known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). *The required washout period prior to commencing trial treatment is 5 weeks;*

5. Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate (e.g. bosentan, efavirenz, modafinil) CYP3A inducers. The required washout period prior to commencing trial treatment is 5 weeks;

6. Whole blood infusion within 28 days prior to trial entry (packed red blood cells and platelet transfusions are acceptable).

7. Receipt of live attenuated vaccine within 30 days prior to commencing trial treatment.

8. Confirmation that none of the Trial Registration exclusion criteria listed in Section 5.3.2 are met.

8.2. Procedure for Obtaining Informed Consent for Trial Entry

The PI (or delegated Co-investigator) must ensure that each trial participant is fully informed about the nature and objectives of the trial and possible risks associated with participation. Patients should be given the

current ethics approved **PHOENIX Patient Information Sheet for Trial Entry** for their consideration. Patients should only be asked to consent to Trial Entry after they have had sufficient time to consider their participation, and had the opportunity to ask any further questions.

No further protocol required assessments, other than those required as part of standard patient care, should be conducted until the **PHOENIX Informed Consent Form for Trial Entry** has been signed and dated by both the patient and the PI (or delegated Co-investigator).

Confirmation that the patient meets all eligibility criteria must be documented in the patient's medical notes by the PI (or delegated Co-investigator), along with confirmation of the patient's consent and the informed consent process for Trial Entry. One copy of the signed consent form should be provided to the patient, one copy should be filed in the patient's medical records and the original should be retained in the SIF, which must be available for verification by the trial team at the ICR-CTSU or for regulatory inspection at any time.

8.3. Registered Patients Who Do Not Consent to Trial Entry

Patients may be registered for PHOENIX but then decide not to consent for Trial Entry even though they may meet the eligibility criteria for Trial Entry. The reason for declining Trial Entry will be documented within the trial database.

8.4. Trial Entry Screening Assessments

Only those procedures required as part of standard patient care should be conducted prior to obtaining written informed consent from the patient for Trial Entry as detailed in Section 8.2.

- Written informed consent for Trial Entry
- Medical history
- Physical examination and vital signs (including height, weight, blood pressure (BP), heart rate, temperature)
- ECOG performance status
- Review of concomitant medication
- Safety bloods to confirm adequate haematological, renal and hepatic function as per inclusion criteria for Trial Entry, and assessment of hepatitis serologies (hepatitis B and C mandatory, hepatitis A as per local practice)
- Pregnancy test for women of childbearing potential
- ECG

9. TRIAL ENTRY PROCEDURE

The **Trial Entry Eligibility Checklist** (signed by the PI or delegated Co-investigator) must be completed prior to completing the **Trial Entry Form**, and both must be completed prior to entry. Written confirmation that eligibility has been checked by an Investigator should also be documented in the patient's medical notes.

Patients must be entered into the trial centrally by the trials unit (ICR-CTSU) before protocol trial treatment can commence. Please refer to the **PHOENIX Trial Guidance Notes** for the procedure to follow for patient randomisation.

Patients can be entered into the trial by ICR-CTSU from **09.00-17.00 (UK time) Monday to Friday**.

The following information will be required at trial entry:

- Patient's unique Trial Registration Number
- Patient's full name, date of birth, hospital number, postcode and NHS/CHI number
- Name of hospital, Investigator and person entering the patient
- Residual tumour size assessed on imaging following completion of neoadjuvant chemotherapy
- Confirmation that patient has given written informed consent Trial Entry;
- Confirmation that patient is eligible for the trial by completion of the Trial Entry Eligibility Checklist

At the time of trial entry, the ICR-CTSU staff will give the caller the patient's unique Trial Identification Number (Trial ID), and confirmation will be sent to the trial contact (Research Nurse/Trial Coordinator) and pharmacist to enable dispensing of the trial treatment. Cohort allocation for cohorts E-G will be confirmed by the ICR-CTSU trial team as soon as possible following Trial Entry.

10.SCREENING LOG

All participating sites will be required to keep a log of all patients with mid-NACT resistant residual TNBC who are identified as potentially eligible for this trial. The information collected on the log will include:

- Date patient identified at MDT
- Registration screening outcome (i.e. patient approached/accepted participation/declined participation)
- Reasons for not approaching / declining participation (if available)
- Date of PHOENIX Trial Registration and unique Trial Registration Number (if applicable)

This information will be used by the Trial Management Group (TMG) to monitor recruitment activity. No patient identifiable data from the screening log should be sent to ICR-CTSU.

11.PART 1 TRIAL ASSESSMENTS

11.1. PART 1 Baseline Assessments WOP (All Cohorts)

The following assessments should be performed within 3 days prior to commencing trial treatment in the WOP defined as the 2-week time period (Day 1 – Day 14) starting at least 3 weeks after the first day of the final cycle of NACT and 2 weeks prior to the patients scheduled surgical intervention (taking into account any pre-surgical self-isolation period required according to national COVID-19 guidance):

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Assessment of baseline conditions
- Review of concomitant medications

- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea.
- ECG
- Pregnancy test should be performed for women of child bearing potential on Day 1 prior to commencing trial treatment

Research tissue and blood sample collection pre-treatment on either Day -1 or 1:

- Research tissue collection:
  - Mandatory pre-treatment image-guided baseline biopsy – guided by a new distinct radio-opaque marker insertion into residual disease
  - Collection of a minimum of four and up to a maximum of eight core biopsies for research purposes. (The number of cores should be decided on a case-by-case basis by the radiologist at the time of collection, with the aim of ensuring that at least 4 high quality tissue cores are obtained).
- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

Please refer to Appendix 2 for further details on the sample collection requirements.

FOR DETAILS ON PART 1 OLAPARIB TREATMENT INCLUDING DOSE SCHEDULE, DOSE MODIFICATIONS, PERMITTED AND CONTRAINDICATED CONCOMITANT MEDICATIONS AND TOXICITY MANAGEMENT, PLEASE REFER TO SECTION 24: THE PART 1 OLAPARIB TRIAL TREATMENT .

11.2. PART 1 WOP Day 14 Assessments (All Cohorts)

The following procedures should be performed on D14 of the WOP:

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea.
- Assessment of AEs
- Dosing compliance
- Review of **Appendix 6: Olaparib DDI with anaesthetics** prior to surgery.
- **Cohorts F & G only: Provision of Patient Information Sheet for PART 2 Trial Treatment to the patient for those allocated to <u>Cohorts F and G</u> if confirmed by the ICR-CTSU trial team prior to this trial visit. If cohort allocation has not been confirmed at the time of this visit the Patient Information Sheet should be shared as soon as possible and ahead of the 30-day post surgery visit but only once cohort allocation has been confirmed.**

Research tissue and blood sample collection:

- Research tissue collection:
  - Mandatory post-treatment image-guided core biopsy – taken from the same site as the pre-treatment biopsy guided by the distinct radio-opaque marker inserted pre-treatment
  - Collection of a minimum of four and up to a maximum of eight core biopsies for research purposes. (The number of cores should be decided on a case-by-case basis by the radiologist at the time of collection, with the aim of ensuring that at least 4 high quality tissue cores are obtained).
  - *In exceptional cases when the collection of the biopsy on Day 14 is not feasible then image-guided research biopsy cores can be collected on the day of surgery or taken by the surgeon intraoperatively, with the time from the Day 14 assessments to biopsy minimised and recorded.*

- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

Please refer to Appendix 2 for further details on the sample collection requirements.

11.3. PART 1 Surgery (All Cohorts)

Research tissue collection:

- Provision of Surgical Resection blocks (must include primary breast with or without involved lymph node tissue).

Residual Cancer Burden (RCB) should be assessed from surgical resection tissue for each PHOENIX patient. **For instructions on how to calculate RCB, the parameters required and for further details on sample collection requirements, please refer to Appendix 2.**

11.4. PART 1 - 30 Day Post-Surgery Follow-up Assessments (All Cohorts)

The following assessments should be performed 30 days (±5 days) post-surgical resection:

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea.
- Pregnancy test for women of childbearing potential
- ECG
- Assessment of AEs
- Assessment for any surgical complications including wound healing assessment.
- **Cohorts F & G only**: patient invited to consent to further trial treatment in Part 2 using the Part 2

Trial Treatment Patient Information sheet and consent form (See Section 12 for details).

Research blood sample collection:

- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

Please refer to Appendix 2 for further details on the sample collection requirements.

Please refer to Section 13 for further details relating to treatment and follow-up in PART 2.

11.5. PART 1 SCHEDULE OF ASSESSMENTS

PART 1 Procedures & Assessments	Prior to Trial Registration	Prior to Trial Entry	Window of Opportunity Visits		Surgery	Post-Surgery Safety follow-up visit
Time point	**Post NACT SOC mid-assessment (MRI/US)**	**Post completion of NACT**	**Baseline assessments (Pre-treatment)[1]**	**D14 (Post-treatment)**	**Post-WOP[12]**	**30 days (±5 days) post-surgical resection**
TRIAL ASSESSMENTS						
Informed Consent	X (Trial Registration)	X (Trial Entry)				X[13] (Part 2 Trial treatment)
Medical History	X	X				
Physical examination and vital signs[2]	X	X	X	X		X
ECOG Performance Status	X	X	X	X		X
Assessment Baseline Conditions			X			
Review of Concomitant Medication	X	X	X	X		X
Safety bloods[3]		X	X	X		X
Pregnancy Test (urine or serum)[4]		X	On Day 1 pre-treatment			X
ECG		X	X			X
Trial imaging[5]		X				

Assessment of Adverse Events[6]				X		X
Review of potential DDI with anaesthetics				X[7]		
Wound Healing Assessment						X
TRIAL TREATMENT						
Cohorts E-G			Olaparib Taken Days 1-14 (refer to Section 24)			
Dosing compliance				X		
RESEARCH BLOOD AND TISSUE SAMPLE COLLECTION						
Image-Guided New Distinct Radio-Opaque Marker Insertion			X			
Research Core Biopsy[8]			X	X		
Research Blood Samples (for biomarkers and ctDNA analysis)[9]	X		X	X		X
Research Blood Samples (for PBMC isolation)[10]			X	X		X
Obtain Archival Diagnostic Block and research blood sample	X					
Surgical Resection FFPE Block[11]					X	

Footnotes:

1. **Baseline assessments (including physical examination and vital signs, ECOG performance status, assessment of baseline conditions, review of concomitant medications, safety bloods, ECG):** may be performed within 3 days prior to commencing trial treatment within the WOP (with the exception of Research tissue and blood samples which should be collected pre-treatment on either Day -1 or 1.
2. **Physical examination and vital signs:** To include height at prior Trial Entry only, and weight, blood pressure (BP), heart rate and temperature at all time points.
3. Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea. Hepatitis serologies (hepatitis B and C mandatory, hepatitis A as per local practice) should be performed as part of the Trial Entry screening assessments only
4. **Pregnancy Test:** Women of childbearing potential should have a negative serum or urine pregnancy test within 3 days prior to commencing trial treatment and this test should be repeated prior to trial treatment on Day 1 of the WOP and at the 30 day post-surgery visit.
5. Trial-specific imaging: should be performed at least 1 week following day 1 of the final cycle of NACT and will be used to confirm that the residual disease is ≥ 1cm in order to confirm eligibility for Trial Entry.
6. **Assessment of Adverse Events:** SAEs should be followed up until resolution.
7. **Review of potential Drug–Drug Interactions (DDI) with anaesthetics:** Please refer to Appendix 6.
8. **Research Core Biopsy:** A minimum of four and up to a maximum of 8 core biopsies should be collected. The number of cores to be collected should be decided on a case-by-case basis by the radiologist at the time of collection, with the aim of ensuring that at least 4 high quality tissue cores are obtained. Please refer to the PHOENIX Investigator Laboratory Manual for further instruction. *In exceptional cases when the collection of the biopsy on Day 14 is not feasible then image-guided research biopsy cores can be collected on the day of surgery or taken by the surgeon intraoperatively, with the time from the Day 14 assessments to biopsy minimised and recorded.*
9. **Research Blood Sample Collection:** Please refer to the PHOENIX Investigator Laboratory Manual for further instruction.
10. **Peripheral Blood Mononuclear Cell (PBMC) Isolation Blood Sample Collection:** Sites geographically located in order for the sample to be couriered to the PHOENIX Central Laboratory for same day processing will be required to collect PBMC isolation blood samples from all patients. Where possible, blood for PBMC isolation should be collected in the morning to allow for prompt shipment and processing within the required time-frame. Please refer to the PHOENIX Investigator Laboratory Manual for further instruction.
11. **Surgical Resection:** Residual Cancer Burden (RCB) should be assessed from surgical resection tissue for each PHOENIX patient. For instructions on how to calculate RCB and the parameters required, please refer to Appendix 2.
12. **Timing of Surgery in relation to WOP:** The optimal trial schedule is for surgery to take place within 24 hours of the D14 WOP visit. However, surgery can take place up to 3 days following the D14 WOP visit to allow patients to self-isolate prior to surgery if required as part of national or local guidelines.
13. **Trial treatment in Part 2:** Eligible patients allocated to Cohorts F and G will be invited to receive further trial treatment in Part 2. Provision of the Part 2 Trial Treatment Patient Information Sheet to the patient should be as soon as possible following confirmation of cohort allocation with patients being invited to consent at the 30-day post-surgical resection visit.

12.SELECTION OF PATIENTS FOR TRIAL TREATMENT IN PART 2

All patients consent to follow-up after surgery at the time of Trial Entry. Trial pathway in Part 2 is dependent on cohort allocation i.e. HRD and g*BRCA1/2* mutation status, and whether a patient is eligible and consents to further trial treatment in Part 2:

- Patients allocated to Cohort E (g*BRCA1/2m* negative and non-HRD), and patients allocated to either Cohort F or G who are ineligible for or non-consenting to further trial treatment, will receive SOC adjuvant treatment of Physician's Choice with 3 monthly follow-up and ctDNA blood sampling visits (Section 14)
- Patients allocated to either Cohort F or Cohort G, who consent to and are eligible for trial treatment in Part 2 will receive olaparib and durvalumab in combination for 12 months with 4 weekly safety and ctDNA blood sampling visits. This will be followed by a further 12 months of 3 monthly follow-up and ctDNA blood sampling visits (Section 13). Patients who are found to be ineligible for durvalumab treatment will receive olaparib only.

Patients may be offered adjuvant radiotherapy following surgery if clinically indicated. Radiotherapy should be delivered according to local practice and must be completed at least three weeks prior to commencement of any trial treatment in PART 2. If a patient receives radiotherapy as SOC, this information must be recorded in the patient's notes, as well as in the appropriate eCRF pages within the PHOENIX database.

Patients who are receiving SOC pembrolizumab will be required to discontinue this treatment following consent to Part 2 Trial Treatment and prior to commencing trial treatment, and details relating to this are included in the Part 2 Trial Treatment Patient Information Sheet. The washout period required between discontinuation of pembrolizumab and day 1 cycle 1 of durvalumab is 30 days and further details are included in Section 12.3 below. Patients who are unwilling to discontinue pembrolizumab should not be invited to consent to Trial Treatment in Part 2 and instead receive SOC treatment of Physician's Choice (including continued pembrolizumab) and followed up as detailed in Section 14.
Patients whose clinical management includes the use of adjuvant capecitabine will not be invited to receive further trial treatment in PART 2 of the trial, but will be followed up every 3 months with ctDNA blood sampling for a total of 24 months as detailed in Section 14.

In order to receive trial treatment in Part 2 the patient must meet all trial entry eligibility criteria provided below.

12.1. Eligibility Criteria for Trial Treatment in Part 2 - Cohorts F & G only

As all patients receive olaparib during the post-neoadjuvant treatment and pre-surgical 14-day WOP, fulfilment of eligibility criteria for olaparib treatment is confirmed at the time of Trial Entry. To determine eligibility for further olaparib trial treatment in Part 2, pre-treatment assessments will include repeat physical examination and assessments of vital signs, ECOG performance status, and safety bloods as detailed in Section 13.1. These pre-treatment assessments should be used to determine fulfilment of the eligibility criteria for further olaparib treatment in Part 2 included in Section 12.1.1 below. **Any patients who experienced unacceptable toxicity as judged by the investigator and/or discontinued olaparib treatment during the WOP should not be invited to consent to further trial treatment in Part 2, and should receive SOC treatment of Physician's Choice and followed up as described in Section 14.**

Patients who remain eligible for further olaparib treatment in Part 2, must fulfil the exclusion criteria for durvalumab listed below (Section 12.1.2) to receive olaparib and durvalumab combination therapy otherwise they will receive olaparib alone (Section 12.1.3):

12.1.1. Inclusion Criteria for trial treatment in Part 2

1. Eastern Oncology Cooperative Group (ECOG) performance status 0-1;

2. Confirmation of residual disease following primary surgery as per local pathology reporting;

3. Patients must have adequate haematological, renal and hepatic function as defined by:

    - Haemoglobin (Hb) ≥ 10 g/dL (≥ 100 g/L)
    - Absolute neutrophil count (ANC) ≥ 1500/mm^3 (≥ 1.5 x 10^9/L)
    - Platelet count ≥100,000/mm^3 (≥ 100 x 10^9/L)
    - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) ≤ 2.5 x institutional ULN
    - Calculated creatinine clearance ≥51 mL/min using the Cockcroft-Gault equation (please refer to Appendix 4) or based on a 24 hour urine test or another validated test as per local practice

12.1.2. Exclusion Criteria for durvalumab treatment in Part 2

1. Body weight ≤ 30kg.
2. Patients who have received prior pembrolizumab:
    a) Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.
    b) All immunotherapy-related AEs while receiving prior pembrolizumab must have completely resolved or resolved to baseline prior to screening *for eligibility for Part 2 durvalumab treatment*.
    c) Must not have experienced a ≥Grade 3 immune related AE or an immune related neurologic or ocular AE of any grade while receiving prior immunotherapy. NOTE: Patients with endocrine AE of ≤Grade 2 are eligible for durvalumab if they are stably maintained on appropriate replacement therapy and are asymptomatic.
    d) Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.
3. Patients receiving, or having received pembrolizumab must have a minimum washout period of 30 days from last dose of pembrolizumab and Day 1 Cycle 1 of durvalumab trial treatment (see Section 12.3 for details).
4. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of durvalumab
5. History of allogenic organ transplantation.
6. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis,

Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

a. Patients with vitiligo or alopecia
b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
c. Any chronic skin condition that does not require systemic therapy
d. Patients without active disease in the last 5 years may be included but only after consultation with the Chief Investigator or Coordinating Investigator
e. Patients with celiac disease controlled by diet alone

7. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

8. Receipt of live attenuated vaccine within 30 days prior to the first dose of durvalumab. Note: Patients who commence durvalumab therapy in Part 2 should not receive live vaccine whilst receiving durvalumab and up to 90 days after the last dose of durvalumab.

9. Known allergy or hypersensitivity to durvalumab or any excipient.

12.1.3. Part 2 trial treatment for patients ineligible for durvalumab treatment

Patients who do not fulfil eligibility criteria above for durvalumab treatment, and who remain eligible for olaparib, should receive olaparib monotherapy for 12 months (13 cycles) during Part 2.

12.2. Obtaining Informed Consent for Trial Treatment in Part 2 - Cohorts F & G only

Patients allocated to Cohorts F and G should be invited to consent for PART 2 Trial Treatment using the Part 2 Trial Treatment Patient Information Sheet (PISs) and Informed Consent Form.
The PI (or delegated Co-investigator) must ensure that each trial participant is fully informed about trial treatment in Part 2 and possible risks involved.

At the WOP D14 visit, or sooner if preferred and only if Cohort allocation has been confirmed, the patient should be given the current ethics approved **PHOENIX Patient Information Sheet for PART 2 Trial Treatment** for their consideration and for subsequent discussion at the 30 day post-surgery visit.

Patients should only be asked to consent to PART 2 Trial Treatment at the 30 day post-surgical visit once they have had sufficient time to consider their participation, and had the opportunity to ask any further questions. For those patients who do go on to consent please refer to Section 13 for details of trial treatment and assessments.

Confirmation that the patient meets all Part 2 trial treatment eligibility criteria must be documented in the patient's medical notes by the PI (or delegated Co-investigator), along with confirmation of the patient's consent and the informed consent process for Part 2 trial treatment. One copy of the signed consent form

should be provided to the patient, one copy should be filed in the patient's medical records and the original should be retained in the SIF, which must be available for verification by the trial team at the ICR-CTSU or for regulatory inspection at any time.

Upon patient consent for trial treatment in PART 2 the **PART 2 Trial Treatment Form** must be completed. consent. Written confirmation that the patient has consented to trial treatment in PART 2 should also be documented in the patient's medical notes.

Patients must be logged centrally by the trials unit (ICR-CTSU) following consent to Part 2 trial treatment before trial treatment can commence. Please refer to the **PHOENIX Trial Guidance Notes** for the procedure to follow.

Patients can be logged for Part 2 trial treatment by ICR-CTSU from **09.00-17.00 (UK time) Monday to Friday**.

The following information will be required at confirmation of trial treatment in PART 2:

- Name of hospital, Investigator and person providing confirmation
- Confirmation that patient has given written informed consent for PART 2 trial treatment
- Patient's initials, date of birth and Trial ID

The ICR-CTSU Trial Team will send notification of confirmation of trial treatment in PART 2 to the site contact for the trial (Research Nurse/Trial Coordinator).

12.2.1. Non-consenting Patients from Cohorts F & G

Patients who do not consent to, or who are ineligible for, trial treatment in Part 2 should receive adjuvant treatment of Physician's Choice and followed up as described in Section 14.

12.3. Pembrolizumab treatment washout period requirement for patients eligible to receive durvalumab treatment in Part 2

Patients who are receiving pembrolizumab as part of standard of care, and who fulfil the eligibility criteria for durvalumab treatment in Part 2, should be asked to discontinue pembrolizumab only once consent to trial treatment in Part 2 has been obtained. The minimum washout period between last dose of pembrolizumab and Cycle 1 Day 1 of durvalumab is 30 days. Details relating to treatment with pembrolizumab, including date of last dose, will be captured in on the appropriate eCRF within the clinical database.

13. PART 2 TRIAL ASSESSMENTS: COHORTS F & G

13.1. Only patients allocated to Cohorts F and G who have consented to trial treatment in Part 2 can commence trial treatment post-surgery. PART 2 Pre-Treatment Assessments

The following pre-treatment assessments should be conducted once a patient has consented to trial treatment in Part 2.

The pre-treatment assessments should be performed prior to commencing trial treatment in PART 2 as indicated below:

13.1.1. Assessments to be conducted within 28 days prior to commencing treatment:

- ECG
- Pre-treatment conditions
- Assessment for any surgical complications including wound healing assessment

13.1.2. Assessments to be conducted within 3 days prior to Cycle 1 Day 1:

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea.
- Pregnancy test for women of childbearing potential

For patients who received pembrolizumab as SOC, and who discontinued this following consent to trial treatment in Part 2, the above assessments required within 3 days of Cycle 1 Day 1 should only be conducted once the required washout period of 30 days has been completed (see Section 12.3).

Research blood sample collection:

- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

Please refer to Appendix 2 for further details on the sample collection requirements.

FOR DETAILS ON PART 2 TRIAL TREATMENT INCLUDING DOSE SCHEDULE, DOSE MODIFICATIONS, PERMISSIVE AND CONTRAINDICATED CONCOMITANT MEDICATIONS AND TOXICITY MANAGEMENT PLEASE REFER TO SECTION 25: PART 2 OLAPARIB & DURVALUMAB COMBINATION THERAPY.

13.2. PART 2 On-Treatment Assessments Cycle 2, Day 1 Pre-Treatment

The following assessments should be performed as close to as possible and within 3 days prior to treatment administration:

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Dosing compliance
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea. **In addition for patients receiving durvalumab:** TSH
- ECG
- Review of AEs
- Pregnancy test for women of childbearing potential

Research blood sample collection:

- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual (taken pre-dose for each cycle).

Please refer to Appendix 2 for further details on the sample collection requirements.

13.3. PART 2 On-Treatment Assessments Cycle 3 Onwards, Day 1 Pre-Treatment

The following assessments should be performed as close to as possible and within 3 days prior to treatment administration:

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Dosing compliance
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea**. In addition for patients receiving durvalumab:** TSH
- ECG
- Review of AEs
- Pregnancy test for women of childbearing potential

Research blood sample collection:

- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual (taken pre-dose for each cycle).

Please refer to Appendix 2 for further details on the sample collection requirements.

13.4. PART 2 Treatment Discontinuation Assessments

The following assessments should be performed at the time of discontinuation of trial treatment for any reason:

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Dosing compliance
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea. **In addition for patients receiving durvalumab:** TSH
- ECG
- Review of AEs

Research blood sample collection:

- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

Please refer to Appendix 2 for further details on the sample collection requirements.

13.5. PART 2 30 Days (and 90 Days for patients receiving durvalumab) Post-Treatment Discontinuation Assessments

The following assessments should be performed 30 (± 7) days (and 90 [± 7] days for **patients receiving durvalumab**) post-treatment discontinuation:

- Physical examination and vital signs (including weight, blood pressure, heart rate, temperature)
- ECOG performance status
- Review of concomitant medications
- Safety bloods: Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea. **In addition for patients receiving durvalumab:** TSH
- ECG
- Review of AEs
- Pregnancy test for women of childbearing potential (30 day post-treatment discontinuation visit only)

13.6. PART 2 Post-Treatment Follow Up Assessments

All patients should be followed up at 3 monthly intervals (+/-2 weeks) from the end of trial treatment for 12 months or for a total of 24 months from the Part 2 pre-treatment assessment visit in case trial treatment is stopped earlier than 12 months; assessment should be in line with standard practice and should include:

- Survival and disease recurrence
- Further treatment

Research blood sample collection:

- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

A recurrence tumour tissue sample should be provided at relapse for each patient who has tissue available from a biopsy or from surgery performed routinely as part of standard patient care.

Please refer to Appendix 2 for further details on the sample collection requirements.

13.7. PART 2 Discontinuation from Treatment

Participants may discontinue from trial treatment at any time at their own request, or they may be discontinued at the discretion of the Principal Investigator (or delegated Co-Investigator). Reasons for discontinuation will include:

- Disease progression or recurrence
- Unacceptable toxicity
- Pregnancy
- Withdrawal of consent
- Serious non-attendance and/or persistent non-compliance with procedures defined in the trial protocol

Participants who discontinue treatment should continue to be followed up.

13.8. PART 2 SCHEDULE OF ASSESSMENTS: COHORTS F & G

PART 2 TRIAL ASSESSMENTS – COHORTS F & G	Pre-treatment		Trial Treatment Cycles								End of Treatment	Post-Treatment	Follow up
			C1	C2	C3	C4	C5	C6	C7	C8 – C13	Discontinuation (max. 13 cycles)	Safety Follow-up	Follow Up Visits
	Day -28 to Day -1	**Day -3 to Day -1**	D1	D1[1]	D1[2]	D1[2]	D1[2]	D1[2]	D1[2]	D1[2]	At time of treatment discontinuation	30 (±7) days (and 90 [±7] days for patients receiving durvalumab) post treatment discontinuation	Every 3 months (± 2 weeks) post discontinuation for 12 months
Pre-Treatment Conditions Assessment	X												
ECG	X			X	X	X	X	X	X	X	X	X	
Physical examination and vital signs[3]		X		X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X		X	X	X	X	X	X	X	X	X	
Review of Concomitant Medication		X		X	X	X	X	X	X	X	X	X	
Safety bloods[4]		X		X	X	X	X	X	X	X	X	X	
Pregnancy test (urine or serum)[5]		X		X	X	X	X	X	X	X		X (30 days only)	
Review Adverse Events				X	X	X	X	X	X	X	X	X[6]	
Assessment for any surgical complications including wound healing assessment	X												
Olaparib Administration (refer to Section 25: Part 2 Olaparib & Durvalumab Combination Therapy)			X D1-28	X D1-28	X D1-28	X D1-28	X D1-28	X D1-28	X D1-28	X D1-28			
Durvalumab Administration (refer to Section 25: Part 2			X D1	X D1	X D1	X D1	X D1	X D1	X D1	X D1			

	Pre-treatment		Trial Treatment Cycles								End of Treatment	Post-Treatment	Follow up
			C1	C2	C3	C4	C5	C6	C7	C8 – C13	Discontinuation (max. 13 cycles)	Safety Follow-up	Follow Up Visits
PART 2 TRIAL ASSESSMENTS – COHORTS F & G	**Day -28 to Day -1**	**Day -3 to Day -1**	D1	D1[1]	D1[2]	D1[2]	D1[2]	D1[2]	D1[2]	D1[2]	At time of treatment discontinuation	30 (±7) days (and 90 [±7] days for patients receiving durvalumab) post treatment discontinuation	Every 3 months (± 2 weeks) post discontinuation for 12 months
Olaparib & Durvalumab Combination Therapy)													
Dosing Compliance (Olaparib only)				X	X	X	X	X	X	X	X		
Research Blood Samples for ctDNA analysis		X		X	X	X	X	X	X	X	X		X[7]
Survival and further treatment follow up													X
Disease recurrence[8]	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes:

1. **Cycle 2 Day 1**: Assessments should be performed as close as possible and within 3 days prior to treatment administration; trial treatment should be administered as per the above schedule, however if not possible due to unavoidable circumstances treatment may be administered 1 day prior to or delayed for up to 3 days after the due date.
2. **Cycle 3 Day 1 onwards:** Assessments should be performed as close as possible and within 3 days prior to treatment administration; trial treatment should be administered as per the above schedule, however if not possible due to unavoidable circumstances treatment may be administered 1 day prior to or delayed for up to 7 days after the due date.
3. **Physical Examination and Vital Signs:** To include weight, blood pressure, heart rate and temperature.
4. **Safety bloods:** Haematology – full blood count, white cell count with differential and ANC, prothrombin time and international normalised ratio (INR); Biochemistry – sodium, potassium, calcium, magnesium, ALT, gamma-glutamyl transferase (GGT), bilirubin, albumin, creatinine, alkaline phosphatase, glucose, urea. In addition for patients receiving durvalumab: TSH
5. **Pregnancy Test:** Women of childbearing potential should have a negative serum or urine pregnancy test within 3 days prior to commencing trial treatment within PART 2, prior to trial treatment on Day 1 of each treatment cycle and at Day 30 after last dose of trial treatment.
6. **Review of Adverse Events:** SAEs should be followed up until resolution.
7. **Research Blood Sample Collection:** Research blood samples to be collected in ctDNA preservation tubes every 3 months (+/- 2 weeks) for up to 2 years from Cycle 1 Day 1 of trial treatment in Part 2 . Please refer to the PHOENIX Investigator Laboratory Manual for further instruction.
8. **Disease recurrence**: A recurrence tumour tissue sample should be obtained for each patient who has tissue available from a biopsy or from surgery, performed routinely as part of standard patient care

14. PART 2 TRIAL ASSESSMENTS: Cohort E (and patients from Cohorts F & G who do not consent trial treatment in Part 2)

All patients allocated to Cohort E, and patients allocated to Cohorts F & G who did not consent to trial treatment in Part 2, should receive adjuvant treatment of physician's choice and follow-up as described in the sections below.

14.1. Part 2 Treatment of Physician's Choice

Patients should receive adjuvant treatment of physician's choice as clinically indicated and according to national and local guidance for dosing schedule, preparation, handling, warnings, precautions and contraindications. Treatment of physician's choice should be limited to only currently approved, and NHS available, therapies given as SOC in the trial eligible population. There are no protocol restrictions for treatment of physician's choice in terms of dose reductions permitted or treatment discontinuation, which will be based on Investigator's judgment. Details of treatment received should be documented on the appropriate eCRF within the trial database.

14.2. PART 2 Follow Up

All patients should be followed up as per standard guidelines, including any investigation that is deemed clinically indicated, every 3 months (+/-2 weeks), with ctDNA blood sampling, for a total of 24 months post-surgery visit.

Assessment should be in line with standard practice and should include:

- Survival and disease recurrence
- Further treatment

An assessment for any surgical complications including wound healing assessment should be performed at the 3-month post-surgery visit only.

A recurrence tumour tissue sample should be provided at relapse for each patient who has tissue available from a biopsy or from surgery, performed routinely as part of standard patient care.

Research blood sample collection:

- Research blood sample collection as specified in the PHOENIX Investigator Laboratory Manual.

Please refer to Appendix 2 for further details on the sample collection requirements.

Please refer to Section 14 PART 2 Schedule of Assessments - Cohort E (and patients from Cohorts F & G who do not consent trial treatment in Part 2)

14.3. PART 2 SCHEDULE OF ASSESSMENTS : Cohort E (and patients from Cohorts F & G who do not consent trial treatment in Part 2)

PART 2 Cohort E (and patients from Cohorts F & G who do not consent trial treatment in Part 2)	PART 2 Follow-up Assessments Months from surgery							
	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
Assessments & Procedures	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks
Blood sample for ctDNA analysis[1]	X	X	X	X	X	X	X	X
Assessment for any surgical complications including wound healing assessment	X							
Survival and further treatment follow up	X	X	X	X	X	X	X	X
Disease recurrence[2]	X	X	X	X	X	X	X	X

Footnotes:

1. Research Blood Sample Collection: Research blood samples to be collected in ctDNA preservation tubes every 3 months (+/- 2 weeks) for up to 2 years from 3 month post-surgery. Please refer to the PHOENIX Investigator Laboratory Manual for further details.
2. Disease recurrence: A recurrence tumour tissue sample should be obtained for each patient who has tissue available from a biopsy or from surgery, performed routinely as part of standard patient care

15.TRIAL TREATMENT

Olaparib and durvalumab are the investigational medical products (IMPs) within PHOENIX (protocol version 9.0 onwards).

FOR DETAILS ON TRIAL TREATMENT INCLUDING DOSE SCHEDULE, DOSE MODIFICATIONS, PERMITTED AND CONTRAINDICATED CONCOMITANT MEDICATIONS AND TOXICITY MANAGEMENT PLEASE REFER TO SECTIONS 24 and 25.

Part 1 Olaparib monotherapy – Section 24

Part 2 – Olaparib and durvalumab combination therapy – Section 25

16.PHARMACOVIGILANCE

16.1. Definitions

Adverse Event (AE)
An AE is any untoward medical occurrence in a patient or clinical trial subject; the event does not necessarily have a causal relationship with the treatment or usage.

Serious Adverse Event (SAE)
An SAE is any untoward medical occurrence that occurs after the patient has provided written informed consent for Trial Entry and within 30 days after surgery or 30 days (or 90 days for durvalumab) after the last administration of trial treatment for patients who commence trial treatment in PART 2 or patient withdrawal from the trial and:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious.

According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, Grade 4 events are life threatening events. Any Grade 4 event should therefore be considered an SAE.

Progression of the indicated disease, death due to progression of the indicated disease and planned hospital admissions (e.g. for surgery) are not considered SAEs and do not need to be reported as such but should be reported on the appropriate electronic case report form (eCRF) within the clinical database.

Pregnancy or aid in the conception of a child whilst participating in a trial is not itself considered an SAE but should be followed up for congenital anomalies or birth defects (see Section 16.9 for further information).

Serious Adverse Reaction (SAR)
A SAR is an SAE that is suspected as having a causal relationship to the IMP, as assessed by the investigator responsible for the care of the patient. A suspected causal relationship is defined as possibly, probably or definitely related (see definitions of causality table).

Definitions of causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship with the trial drug
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial treatment). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment)
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
A SUSAR is a SAR, the nature or severity of which is not consistent with the information set out in the Reference Safety Information (RSI).

Reference Safety Information (RSI)
A list of medical events that defines which reactions are expected for the IMP within a given trial and thus determining which Serious Adverse Reactions (SARs) require expedited reporting. The RSI for PHOENIX is contained in a clearly identified section of the Investigator's Brochure (IB) for each IMP.

Adverse Events of Special Interest (AESI) in patients receiving olaparib (Part 1 and Part 2)
In addition, selected AEs experienced by any patient who has commenced olaparib treatment meeting any of the criteria listed below are AESI, and are reportable to the ICR-CTSU in the same timeframe as SAEs as detailed in Section 16.3. **Therefore for the purposes of pharmacovigilance reporting the below events should be considered serious**:

- Any event of pneumonitis
- Any event of myelodysplastic syndromes (MDS)/acute myeloid leukaemia (AML)
- Any new primary malignancy

Adverse Events of Special Interest (AESI) in patients who receive durvalumab (Part 2)
In addition, selected AEs experienced by any patient who has commenced treatment with durvalumab meeting any of the criteria listed below are AESI. **These AESI may be serious or non-serious.** If an AESI is

defined as serious, sites should follow the SAE reporting procedure detailed in section 16.3. If an AESI is defined as non-serious, sites should report the event in the clinical trial database. If the Investigator has any questions in regards to an event being an Important Medical (adverse) Event, the Investigator should promptly contact the ICR-CTSU Trial Team. AESIs observed with durvalumab include:

- Diarrhoea / Colitis and intestinal perforation
- Pneumonitis / Interstitial lung disease (ILD)
- Hepatic events (please refer to section 16.8 for evaluation and reporting of Potential Hy's Law (PHL) cases)
- Intestinal perforations
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyperthyroid events, hypothyroid events, thyroiditis, type I diabetes mellitus (which may present with diabetic ketoacidosis) and diabetes insipidus))
- Guillain-Barré syndrome
- Myasthenia gravis
- Rash / Dermatitis (including pemphigoid)
- Nephritis
- Pancreatic events
- Renal events
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, immune thrombocytopenia, subcutaneous injection site reaction, Immune-mediated neutropenia, immune-mediated cystitis, immune-mediated lung disease, sclerosing cholangitis pericarditis, sarcoidosis, uveitis, vasculitis, non-infectious meningitis and non-infectious encephalitis, other events involving the eye and skin, haematological and rheumatological events.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 7). These guidelines have been prepared 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 trial treatment/trial regimen by the reporting investigator.

16.2. Reporting AEs to ICR-CTSU

Any toxicity, sign or symptom that occurs after the patient has provided written informed consent for Trial Entry and within 30 days after surgery in PART 1 or up to 30 days (or 90 days for durvalumab) of the last administration of trial treatment for patients who commence trial treatment in PART 2, which is not unequivocally due to progression of disease, should be considered an AE.

All AEs must be reported on the relevant eCRF and submitted to ICR-CTSU.

The severity of AEs should be graded according to the NCI CTCAE v5.0. For each AE, the highest grade observed since the last visit should be reported.

Abnormal laboratory findings that meet the criteria for Grade 2 or above toxicity as defined by NCI CTCAE v5.0 are considered to be clinically significant and should be reported as AEs.

Whenever one or more toxicity/sign/symptom corresponds to a disease or a well-defined syndrome only the main disease/syndrome should be reported.

16.3. Reporting of SAEs to ICR-CTSU

Any SAE that occurs after the patient has provided written informed consent for Trial Entry and within 30 days after surgery in PART 1 or up to 30 days (or 90 days for durvalumab) following the last administration of trial treatment for patients who commence trial treatment in PART 2 or up to 30 days (or 90 days for durvalumab) after patient has withdrawn from the trial must be reported.

Any SAEs that occur more than 30 days (or 90 days for durvalumab) after the last dose of trial treatment that, in the opinion of the Principal Investigator, are related to the trial treatment should be reported to ICR-CTSU if the Principal Investigator becomes aware of them.

Any case of MDS/AML or a new primary malignancy occurring after the 30 day (or 90 days for durvalumab) follow up period should be reported to ICR-CTSU, whether or not it is considered an SAE, and regardless of the investigator's assessment of causality.

All SAEs should be reported to ICR-CTSU within 24 hours of the Principal Investigator (or delegated Co-investigator) becoming aware of the event, by completing the PHOENIX SAE form and emailing to:

sae-icr@icr.ac.uk
For the attention of the **PHOENIX Trial Team**

As much information as possible, including the Investigator's assessment of causality, must be reported to ICR-CTSU in the first instance. Additional follow up information including final diagnosis and outcome should be reported as soon as it is available.

All SAE forms must be completed, signed and dated by the Principal Investigator or delegated Co-investigator.

All reported SAEs and follow up information will be forwarded to AstraZeneca (AZ) upon receipt at ICR-CTSU.

16.4. Review of SAEs

The Chief Investigator (or designated representative) will assess all reported SAEs for causality. SAEs assessed as having a causal relationship to trial treatment will be evaluated for expectedness based on the RSI

contained in the relevant Investigator Brochure. (NB. The Chief Investigator cannot downgrade the Principal Investigator's assessment of causality.)

SAEs assessed as having a causal relationship to trial treatment and as being unexpected (SUSARs) will undergo expedited reporting to the relevant authorities and all other interested parties by ICR-CTSU (see Section 16.5).

Sites should respond as soon as possible to requests from the Chief Investigator or designated representative (via ICR-CTSU) for further information that may be required for final assessment of an SAE as soon as possible.

16.5. Expedited Reporting of SUSARs

If an SAE is identified as being a SUSAR by the Chief Investigator, and is fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, the Research Ethics Committee (REC), AZ and all other interested parties within 7 days of being notified of the event.

If an SAE is identified as a SUSAR by the Chief Investigator, and is not fatal or life threatening, it will be reported by ICR-CTSU to the MHRA, REC and AZ within 15 days of ICR-CTSU being notified of the event.

ICR-CTSU will report any additional relevant information to the MHRA, REC and AZ as soon as possible, or within 8 days of the initial report of a fatal/life threatening SUSAR.

The Principal Investigators at all actively recruiting sites will be informed of any SUSARs occurring within the trial at appropriate intervals.

16.6. Follow up of Serious Adverse Events

SAEs should be followed up until clinical recovery is complete or until disease has stabilised. SAE outcomes should be reported to ICR-CTSU using the relevant section of the SAE form as soon as the Principal Investigator or designee becomes aware of the outcome.

16.7. Annual Reporting of Serious Adverse Reactions

An annual report will be provided to the MHRA and REC by ICR-CTSU at the end of the reporting year.

16.8. Liver Dysfunction (Hy's Law)

Hy's Law is based on the observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. A diagnosis of potential drug-induced liver injury caused by a trial treatment can only be determined/inferred by excluding other potential causes of liver injury (e.g., other drugs or viral hepatitis) and by ruling out an obstructive cause for the elevated bilirubin (e.g., alkaline phosphatase should not be substantially elevated).

16.8.1. Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the trial following the start of trial treatment irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than trial treatment, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

16.8.2. Evaluation of Potential Hy's Law (PHL) Cases

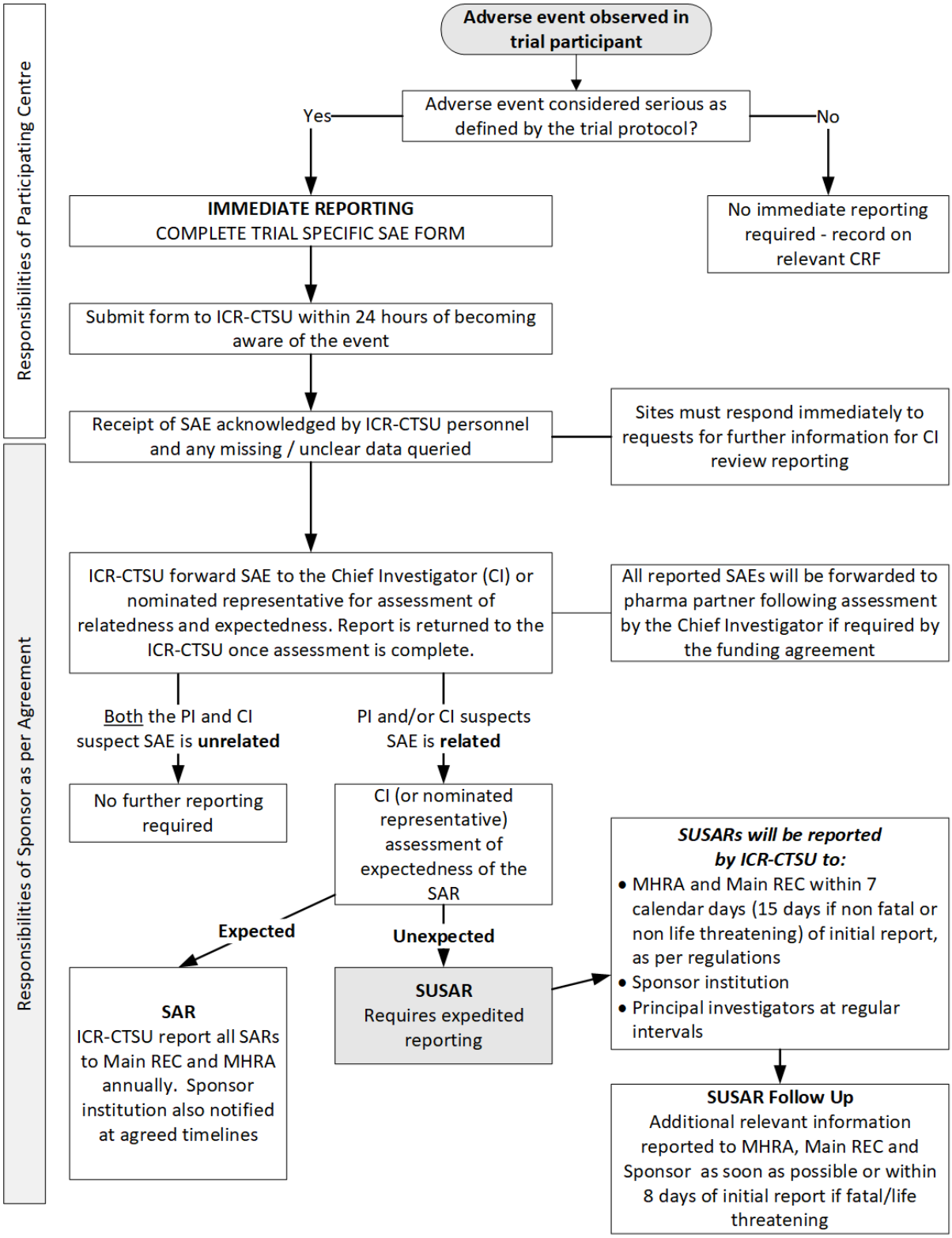
The patient should return to the participating site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g. biliary tract) may be warranted. The possibility of progressive disease should be considered.

Potential Hy's Law (PHL) cases should be reported as SAEs (see Section 16.3).

16.9. Reporting Pregnancies

If any trial participant or a trial participants' partner becomes pregnant while receiving trial treatment or up to 6 months after receiving trial treatment, this should be reported to ICR-CTSU using the pregnancy reporting form. Participants who become pregnant should discontinue from trial treatment immediately. Pregnancies should be followed up until conclusion and all follow-up information should be reported to ICR-CTSU. If the outcome of the pregnancy meets the definition of serious (i.e. congenital abnormality, stillbirth or spontaneous abortion/miscarriage) this should be reported to ICR-CTSU following the serious adverse event reporting procedures described above.

Figure 3: Flow diagram for SAE reporting, and action following report



All SAEs should be followed up until resolution.

17.STATISTICAL CONSIDERATIONS

17.1. Statistical Design and Sample Size Justification

17.1.1. PART 1: Window of opportunity component

For the purposes of statistical analysis, a patient will be defined as having a response in PART 1 if they meet either of the treatment cohort specific response criteria defined in Section 17.3. For example, a patient allocated to Cohort B to receive AZD6738 will be said to have a response if they have either a drop in Ki67 of 33% or ≥1.5-fold drop in the proliferation gene expression.

A Simon two-stage optimal design will be used within treatment cohorts B, C and D to assess activity according to the pre-specified response criteria defined in Section 17.3. Given a power of 90%, alpha of 10%, response probabilities of inactive trial treatment p_0=0.05 and of active trial treatment p_1=0.25, 9 patients will be recruited in the first stage, Stage 1. If 0 responses out of 9 patients are observed, the trial treatment will be declared inactive and no further patients entered to this treatment cohort. Recruitment will be suspended between stage 1 and 2 unless prior indication to continue directly is given by the Independent Data and Safety Monitoring Committee (IDSMC). For all cohorts successfully reaching the second stage (1 or more responses observed) a further 15 patients will be entered in the second stage, Stage 2. A treatment cohort can be declared active if 3 or more responses are observed in a total of 24 patients. Patients who miss >20% of doses during PART 1 or any doses on Day 14 (applicable to cohorts B and C only) and/or for whom the primary endpoint is not evaluable (i.e. if paired samples are not available) will be considered non-evaluable and will be replaced.

9 patients will be entered concurrently into a standard care reference cohort within the first stage. Although direct comparisons will not be made between the cohorts, this standard care reference cohort will not receive trial treatment in the WOP and will allow responses seen in the treatment cohorts to be presented in context of natural and artefactual variation seen in untreated patients.

A Simon two-stage minimax design will be used within cohort G to assess activity. Given a power of 90%, alpha of 10%, response probabilities of inactive trial treatment p_0=0.1 and of active trial treatment p_1=0.4, 8 patients will be recruited in the first stage, Stage 1. If <1 responses out of 8 patients are observed, the trial treatment will be declared inactive and no further patients entered. If 1 or more responses are observed a further 7 patients will be entered in the second stage, Stage 2. Treatment can be declared active if 4 or more responses are observed in a total of 15 patients.

Patients will be entered concurrently into cohort E in parallel with recruitment to cohort G to enable the activity of olaparib to be estimated in patients with non-HRD associated TNBC. A futility analysis will be performed after the first 8 patients have completed the WOP and if no responses are observed in these 8 patients this cohort will be closed to further recruitment. If at least 1 response is observed recruitment will continue to this cohort until recruitment to cohort G is complete (up to a maximum of 15 patients).

Patients will also be entered concurrently into cohort F up to a total of 8 patients within the first stage. Although direct comparisons will not be made between the cohorts because comparisons would be confounded by differing disease characteristics between cohorts, this cohort will act as a positive reference cohort and will allow responses seen in cohorts E and G to be presented in context against the activity observed in g*BRCA1/2+* patients where olaparib is known to be active.

Due to differing proportions of patients in each of the cohorts, recruitment to cohort F may take longer than cohorts E & G (recruitment to these two cohorts likely to occur at a similar rate). If this is the case, advice will be sought from the IDMC on the continuation of recruitment to cohort F (and E if applicable) once recruitment to cohort G is completed.

17.1.2. PART 2: Post-operative treatment component

Patients from PART 1 will be followed up with ctDNA mutation tracking at 30 days following surgical resection. For patients allocated to Cohorts B-D, a positive ctDNA result at ctDNA screening will trigger repeat intervention of their PART 1 trial treatment for up to 12 months in PART 2. For patients allocated to Cohort A, a positive ctDNA result will trigger trial treatment with durvalumab for up to 12 months in Part 2.

Patients in cohorts A-D with a negative ctDNA result at 30 days post-surgery and 3 months post-surgery will be followed up with ctDNA mutation tracking in PART 2 of the trial for 24 months.

Patients in cohorts F and G will have the opportunity to receive treatment in PART 2 regardless of their ctDNA status.

PART 2 is exploratory and descriptive in nature.

17.2. Treatment Allocation

PHOENIX is a non-comparative, multiple parallel cohort platform trial. In cohorts A-D, patients meeting the eligibility criteria will be allocated via minimisation to either the standard care reference cohort (Cohort A) or one of three treatment cohorts (Cohort B: AZD6738, Cohort C: Olaparib, Cohort D: Durvalumab).

Treatment allocation is by minimisation with a random element; balancing factors will be residual tumour size following completion of neoadjuvant chemotherapy (1-2cm vs. ≥2cm) and *BRCA1/2* mutation status combined with use of platinum containing treatment prior to Trial Entry (*BRCA1/2* mutated/ not known *BRCA1/2* mutated with prior platinum use/ not known *BRCA1/2* mutated with no prior platinum use).

Patients will be allocated in a 1:1:1:1 ratio into Cohorts A-D until 9 patients have been recruited into cohort A. Following this, patients will be allocated in a 1:1:1 ratio to Cohorts B-D.

Patients in cohorts E-G will be allocated to a cohort based on the HRD status of their tumour and germline *BRCA1/2* mutation status. Patients who are negative for HRD and germline *BRCA1/2* mutations will be allocated to cohort E. Those with a germline *BRCA1/2* mutation will be allocated to cohort F and those who are germline *BRCA1/2* wildtype but positive for HRD will be assigned to cohort G. All patients will receive olaparib.

17.3. Endpoint Definitions

17.3.1. Primary Endpoints Definitions

The primary endpoint is treatment cohort specific based on the nature of the target and the biological effect of targeting.

The primary endpoint for each of the cohorts are as outlined below:

Cohorts B and C:

1. **Change in mean proliferation index** (as measured by tumour cell Ki67 staining) post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.
   A patient will be defined as being a Ki67 responder if they experience a relative decrease in Ki67 positive cells of ≥33% in the post-treatment biopsy sample. This represents a characterised threshold that we do not believe would be exceeded by chance in this patient population.

AND/OR

2. **Changes in the proliferation gene expression signature** post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.
   A patient will be defined as being a responder if there is a ≥1.5-fold drop in the proliferation gene expression in the post-treatment biopsy sample.

   The proliferation gene signature will be based on this list of 11 highly correlated proliferation genes shown in multiple studies including those published by The Cancer Genome Atlas and they also contribute to the calculation of the proliferation score in the publicly available PAM50 classifier [43-45]. The list consists of : CCNB1","UBE2C","BIRC5","NDC80","CDC20","PTTG1","RRM2","MKI67","TYMS","CEP55",”NUF2"

   For each sample, a proliferation gene module score will be calculated according to the expression of the relevant genes as described below:

$$\text{Proliferation score} = \sum_{i=1}^{n} W_i X_i / \sum |W_i|$$

   where *n* is the number of genes in a module, X_i represents the normalized gene expression in the new sample, and gene-specific weights W_i are equal to their associated weights according to the direction (+/-) of their association with the phenotype. In this case, they are all +1.

The proportion with objective response (by either Ki67 response or gene expression signature response) will be presented along with the corresponding exact two-sided 95% confidence interval separately for each cohort. Response for each component of the endpoint will also be reported separately.

Cohort D:

1. **Change in frequency of CD8$^+$ sTILs** post anti-PD-L1 immunotherapy within the post-treatment biopsy compared to pre-treatment baseline biopsy.

A patient will be defined as being a responder if they experience an absolute increase of ≥ 10% in the percentage CD8+ sTILs within the post-treatment biopsy sample.

The % CD8+ sTILs value denotes the area occupied by CD8+ sTILs over total intratumoural stromal area.

AND/OR

2. **Changes in the Interferon Gamma-positive (IFNγ$^+$) signature** post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

A patient will be defined as being a responder if there is a ≥2-fold increase in the IFNγ+ *gene expression in the post-treatment biopsy sample*

The four-gene IFNγ+ score [46], comprising of IFNγ, CD274, LAG3, and CXCL9 will be calculated as the mean of the four gene using the formula as below:

$$\text{Inteferon gamma score} = \sum_{i=1}^{n} W_i X_i / \sum |W_i|$$

where *n* is the number of genes in a module, X_i represents the normalized gene expression in the new sample, and gene-specific weights W_i are equal to their associated weights according to the direction (+/-) of their association with the phenotype. In this case, they are all +1.

The proportion with objective response (by either CD8+ sTILs response or IFNγ$^+$ signature response) will be presented along with the corresponding exact two-sided 95% confidence interval. Response for each component of the endpoint will also be reported separately.

Cohort A (standard care reference cohort) will allow assessment of any biopsy effect on the primary endpoints assessed in treatment cohorts B, C and D.

Cohorts F-G:

1. **Change in mean proliferation index** (as measured by tumour cell Ki67 staining) post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

A patient will be defined as being a Ki67 responder if they experience a relative decrease in Ki67 positive cells of ≥33% in the post-treatment biopsy sample. This represents a characterised threshold that we do not believe would be exceeded by chance in this patient population.

AND/OR

2. **Changes in the proliferation gene expression signature** post WOP intervention within the post-treatment biopsy compared to pre-treatment baseline biopsy.

A patient will be defined as being a responder if there is a ≥1.5-fold drop in the proliferation gene expression in the post-treatment biopsy sample.

The proliferation gene signature will be based on this list of 11 highly correlated proliferation genes shown in multiple studies including those published by The Cancer Genome Atlas and they also contribute to the calculation of the proliferation score in the publicly available PAM50 classifier [41-43]. The list consists of : CCNB1","UBE2C","BIRC5","NDC80","CDC20","PTTG1","RRM2","MKI67","TYMS","CEP55","NUF2"

For each sample, a proliferation gene module score will be calculated according to the expression of the relevant genes as described below:

$$\text{Proliferation score} = \sum_{i=1}^{n} W_i X_i / \sum |W_i|$$

where *n* is the number of genes in a module, X_i represents the normalized gene expression in the new sample, and gene-specific weights W_i are equal to their associated weights according to the direction (+/-) of their association with the phenotype. In this case, they are all +1.

AND/OR

3. **Changes in the plasma ctDNA** (D0-D14) post WOP intervention compared to pre-treatment.

A patient will be defined as being a responder if the ratio of ctDNA post-WOP compared to pre-WOP is <0.25. This cut-off has been selected in line with other studies of PARP inhibitors in TNBC [47].

The proportion with objective response (by either Ki67 response or gene expression signature response or ctDNA) will be presented along with the corresponding exact two-sided 95% confidence interval separately for each cohort. Response for each component of the endpoint will also be reported separately.In addition, within cohort G, the proportion of objective responses will be presented by subgroups further defined by i. BRCA1meth+, ii. RAD51cMeth+, iii. Somatic BRCA1 or BRCA2+, iv. gPALB2m or sPALB2m +ve, v. HRD other. This analysis will be descriptive due to the likely small number of observations within each subgroup.

17.3.2. Secondary Endpoints Definitions

1. Response in Cohort E, defined as per the primary endpoint for cohorts F-G.
2. Incidence of adverse events during trial treatment (including surgical complications) by treatment cohort at 1 month post-surgery. The proportions of patients experiencing adverse events of any grade, and of grade ≥3 during trial treatment will be listed.

   Safety will be assessed using NCI CTCAE v5.0 and summarised in tabular format for each cohort. Reported toxicities will be coded using MedDRA (current version at the time of first coding).
3. Methylation status (methylated vs. non-methylated and level of methylation) of BRCA1 and RAD51C on diagnostic and pre- and post-WOP tumour samples and changes in methylation levels between these timepoints.

Secondary endpoint 1 will be analysed within cohort E as per the primary endpojnt for cohorts F-G. For secondary endpoints3-4, association between each marker/change in marker and response (response as defined for the co-primary endpoint) will be assessed via logistic regression models. Response (yes/no) will be used as the outcome variable and the marker/change in marker as the explanatory variable or interest. Further details will be provided in the statistical analysis plan.

17.3.3. Exploratory Endpoints Definitions

1. Assess the ratio change in apoptosis and tumour cell proliferation in the post-treatment biopsy compared with pre-treatment baseline biopsy.
2. Relationship between the primary and secondary endpoints with the mutational landscape of the treated tumour as assessed by deep sequencing of the primary and residual disease and any subsequent metastatic relapse tumour genome and of tumour ctDNA in plasma.
3. Descriptive relationship between changes in ctDNA in Part 2 (post surgery) compared to biomarkers response to PART 1 in all patients from cohorts B-G.
4. Descriptive relationship between response status in PART 1 and changes in ctDNA in PART 2 within patients from cohorts B-G identified as ctDNA positive 30 days/3 months post-surgery who receive trial treatment in PART 2.
5. Descriptive relationship between ctDNA mutational profile in mutated genes in ctDNA pre-treatment and post-treatment ctDNA profiles in patients in both PART 1 and PART 2.
6. Descriptive differences in time between ctDNA detection and time to recurrence by 2 years in both the treated groups and observation group in PART 2.
7. RAD51 foci and geminin scoring on pre-WOP biopsy samples
8. Methylation status of other HRD genes (including but not limited to BRCA2 and XRCC3) on diagnosis and pre- and post-WOP tumour samples and changes between these timepoints
9. Changes in phosphorylation of ataxia telangiectasia and Rad3-related protein (ATR) and its downstream effectors (including but not limited to Chk1, γH2AX, pKAP1, TAO upon drug exposure: including but not limited to levels of phosphorylation of p53, p38, p21/p27, cyclin dependent kinases (CDC25)).
10. Changes in biomarkers of DDR and adaptive and innate response, including but not limited to 53BP1, RAD51, RAD51C, RPA, RPA32, pRPA, BRCA1/2, PARP proteins, Shieldin complex components expression and immune checkpoint ligands and receptors and adaptive and innate immune response markers (IFNγ, cGAS-STING pathway, NKG2D receptors, ligands and cell markers) in the post-treatment biopsy compared to pre-treatment baseline biopsy using gene expression profiling.
11. Changes in biomarkers of DDR and adaptive and innate response, including but not limited to 53BP1, RAD51, RAD51C, RPA, RPA32, pRPA, BRCA1/2, PARP proteins, Shieldin complex components expression and immune checkpoint ligands and receptors and adaptive and innate immune response markers (IFNγ, cGAS-STING pathway, NKG2D receptors, ligands and cell markers) in the post treatment biopsy compared to pre-treatment baseline biopsy using reverse phase protein array (RPPA) and other proteome profiling.
12. Assessment of associated expression of co-inhibitory immune checkpoint receptors and ligands and frequency and function of TILs and myeloid cells subsets using immune cell markers and high content image de-convolution.
13. Changes in the levels of Th1/IFNγ response as measured by transcriptional and proteomic profiling.
14. Immune cell population sub-set characterisation using appropriate and T and B cell receptor DNA sequencing methodologies.
15. Assess change in the Ki67:CD8+ ratio within the post-treatment biopsy compared to pre-treatment baseline biopsy.
16. HRD status according to Myriad MyChoice and Genomics ENgland testing.

Analysis methods for additional exploratory endpoints will be defined in the statistical analysis plan.

17.4. Statistical Analysis Plan

Further details of analysis methods will be specified in a Statistical Analysis Plan in accordance with ICR-CTSU Standard Operating Procedures.

17.5. Interim Analyses and Stopping Rules

As described in Section 17.1 a Simon two-stage optimal design will be used within treatment cohorts B, C and D which includes a stopping rule if 0 response is observed out of the 9 patients, per cohort, in the PART 1 Stage 1.

A Simon two-stage minimax design will be used within cohort G which includes a stopping rule if 0 response is observed out of the 8 patients in the PART 1 Stage 1. A similar futility analysis will be carried out in cohort E after the first 8 patients are recruited and recruitment to this cohort will be stopped if 0 responses are observed,

An Independent Data and Safety Monitoring Committee (IDSMC) will meet regularly to review emerging safety and activity data from all cohorts. The IDSMC will also specifically monitor RCB rates at surgery and emerging evidence from other studies regarding prognosis by RCB classification to ensure the trial is recruiting sufficiently high risk patients.

The trial may be stopped at any time if emerging safety issues arise, either during the conduct of the trial or from external sources. In such an event the IDSMC will be convened on an ad hoc basis to review the safety issue and the trial stopped as appropriate.

18.TRIAL MANAGEMENT

18.1. Trial Management Group (TMG)

The Trial Management Group (TMG) will be constituted from members of the Protocol Development Group (PDG) and will include the Chief Investigator (CI), Coordinating Investigator, ICR-CTSU Scientific & Trials Methodology Lead, Trial Biomarker Bioinformatics Lead, Co-investigators and identified collaborators (to include AZ coordinating representative), key ICR-CTSU staff and a lay representative. Principal Investigators (PIs) and key trial personnel will be invited to join the TMG as appropriate to ensure representation from a range of sites and professional groups. A copy of the current membership of the TMG can be obtained from the PHOENIX Trial Manager at ICR-CTSU.

The TMG will meet at regular intervals, and at least annually. Notwithstanding the legal obligations of the sponsor and Chief Investigator, the TMG have operational responsibility for the conduct of the trial. The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

18.2. Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be set up and will comprise an independent Chair and at least two further independent members with clinical or statistical expertise (at least one member must be a statistician). The TSC will meet at regular intervals, and at least annually. The TSC will provide expert

independent oversight of the trial on behalf of sponsor and funder. The Committee's terms of reference, roles and responsibilities will be defined in charter issued by ICR-CTSU.

18.3. Independent Data and Safety Monitoring Committee (IDSMC)

An Independent Data and Safety Monitoring Committee (IDSMC) will be set up to monitor the progress of the trial and will comprise a Chair and at least two further members with clinical or statistical expertise (at least one member must be a statistician).

The IDSMC will meet in confidence at regular intervals, and at least annually. A summary of findings and any recommendations will be produced following each meeting. This summary will be submitted to the TMG and TSC, and if required, the main REC and the MHRA.

The IDSMC will reserve the right to release any data on outcomes or side-effects through the TSC to the TMG (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

The Committee's terms of reference, roles and responsibilities will be defined in a charter issued by ICR-CTSU.

19.RESEARCH GOVERNANCE

19.1. Sponsor Responsibilities

The sponsor, as defined by The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, of the PHOENIX trial is The Institute of Cancer Research (ICR).

19.2. Participating Site Responsibilities

Responsibilities delegated to participating sites are defined in an agreement between the Sponsor and the individual site. The Principal Investigator is responsible for trial conduct at the participating site.

19.3. AstraZeneca Responsibilities

AZ is responsible on behalf of the Sponsor for the manufacture, packing, labelling and distributing of trial drug to participating sites in accordance with Good Manufacturing Practice and all applicable local legislation. Responsibilities are defined in an agreement between AZ and the Sponsor.

20.TRIAL ADMINISTRATION & LOGISTICS

20.1. PHOENIX Participating Sites

PHOENIX will be opened across a network of approximately 20 Screening only and Treatment sites. It is the expectation that Screening Only Sites will identify and register patients with radiographically measurable tumour mass on standard of care imaging performed at the mid-assessment timepoint of SOC neoadjuvant treatment. Registered patients will then undergo protocol mandated end of neoadjuvant chemotherapy imaging, with patients eligible for Trial Entry (including residual disease ≥1cm) referred to an appropriate

Treatment site for Trial Entry. After completion of trial follow-up the patient can be transferred back to the Screening Only Site for continued follow up according to standard and local practice.

20.1.1. Screening Only Sites

Screening Only Site selection will be based on proximity to and natural referral into an open Treatment Site. The pairing of Screening Only and Treatment Sites will be determined at the time of site activation of the Screening Only Site.

Screening Only Centres will perform the following tasks:

- Approach patients and obtain consent for Trial Registration
- Transfer of patient's archival diagnostic tissue to the central laboratory for analysis
- Arrange and complete protocol-mandated imaging at the end of standard of care neoadjuvant chemotherapy
- Initiate the consent process for Trial Entry by providing the PHOENIX Trial Entry patient information sheet to potentially eligible patients in order to confirm that the patient is willing to be referred for consent at the Treatment Site
- Referral of patients to the Treatment Site for consent to Trial Entry as per local practice
- If applicable and appropriate, follow up once patient care is transferred back from the Treatment Site, upon completion of trial follow-up or on withdrawal from the trial.

Please note: Screening Only Sites should not consent patients for Trial Entry. This task should **only** be performed by the Treatment Site who will be responsible for consenting the patient to Trial Entry, cohort allocation and administration of trial treatment.

20.1.2. Treatment Sites

Treatment Site selection will be based on experience in the delivery of early phase breast cancer trials and the ability to receive referrals from the Screening Only Sites.

Treatment Sites will perform the following tasks:

- Approach patients and obtain consent for Trial Registration
- Transfer of patient's archival diagnostic tissue to the central laboratory for analysis
- Arrange and complete protocol-mandated imaging at the end of standard of care neoadjuvant chemotherapy
- Obtain consent from potentially eligible patients for Trial Entry, including those patients referred from a Screening Only site
- Trial treatment administration in Part 1 (pre-surgical WOP) and Part 2 (post-surgery)
- Follow up of all patients for up to 24 months from the Part 2 pre- treatment assessment/ 3-month post-surgery visit, after which point standard of care follow up can be continued either at the Treatment Site or at the original referring Screening Only site.

20.2. Site Activation

Before recruitment can commence at a site, the site agreement must have been signed by all required signatories, the required trial documentation (as specified by ICR-CTSU) must be in place and a site initiation must have taken place. Site initiation may be by teleconference or by on site visit if requested by the Principal

Investigator or if deemed appropriate by ICR-CTSU. ICR-CTSU will provide the final confirmation that recruitment can commence at a site. This confirmation should be filed in the Site Investigator File. No patients should be registered until the site has received activation confirmation from ICR-CTSU.

20.3. Investigator Training

Training in the scoring of residual cancer burden (RCB) will be provided by a named site lead pathologist. Additionally, given as in exceptional cases, research biopsy cores may be taken by the surgeon intraoperatively (e.g. where radiologically guided biopsy of the post-window residual disease is not feasible), training will need to be provided by the site lead radiologist or surgeon.

20.4. Data Acquisition

Electronic (e) Case Report Forms (CRFs) will be used for the collection of trial data and data should be entered into the clinical trial database in a timely manner. ICR-CTSU will provide guidance to sites to aid the completion of the eCRFs. The Trial Management Group reserves the right to amend or add to the eCRF template as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by sites in accordance with the guidelines provided by ICR-CTSU.

20.5. Central Data Monitoring

Once data has been entered on the eCRF by the site personnel, ICR-CTSU will review it for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be identified, queries will be raised for resolution by the site.

Any systematic inconsistencies identified through central data monitoring may trigger an on-site monitoring visit.

ICR-CTSU will also request from sites redacted copies of each patient's trial-specific imaging report and surgical pathology report for central monitoring purposes.

20.6. On-Site Monitoring

If a monitoring visit is required, ICR-CTSU will contact the site to arrange the visit. Once a date has been confirmed, the site should ensure that full patient notes of participants selected for source data verification are available for monitoring.

ICR-CTSU staff conducting on-site monitoring will review essential documentation and carry out source data verification to confirm compliance with the protocol. If any problems are detected during the course of the monitoring visit, ICR-CTSU will work with the Principal Investigator or delegated individual to resolve issues and determine appropriate action.

20.7. Completion of the Trial and Definition of Trial End Date

The trial end date is deemed to be the date of last data capture expected to be once all patients have completed 24 months of follow up in Part 2.

20.8. Archiving

Essential trial documents should be retained according to local policy and for a sufficient period for possible inspection by the regulatory authorities (at least 5 years after the date of last data capture). Documents should be securely stored and access restricted to authorised personnel.

21. PATIENT PROTECTION AND ETHICAL CONSIDERATIONS

21.1. Sponsor Risk Assessment and Approvals

This trial has been formally assessed for risk and approved by the sponsor's Committee for Clinical Research (CCR).

ICR-CTSU, on behalf of the sponsor, will ensure that the trial has received ethics approval from a research ethics committee (REC) for multi-centre trials, regulatory approval from the MHRA and relevant NHS Permissions. Before recruiting patients, the Principal Investigator at each site is responsible for obtaining local approvals.

21.2. Public and Patient Involvement

Patient advocate members were involved in protocol design including methodology, sample collection, patient information and consent forms and are represented on the TMG.

21.3. Ethics and Regulatory Approvals

The trial will not commence at any participating site until the required approvals are in place. The ICR-CTSU, on behalf of the Sponsor, will ensure that the trial has received ethics approval from a research ethics committee (REC) for multi-centre trials, regulatory approval from the MHRA and relevant NHS Permissions. Before recruiting patients, the Principal Investigator at each site is responsible for obtaining local approvals.

21.4. Trial Conduct

This trial will be conducted according to the approved protocol and its amendments, supplementary guidance and manuals supplied by the ICR-CTSU and in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 as amended, the Research Governance Framework for Health and Social Care and the principles of GCP and relevant data protection legislation.

21.5. Informed Consent

Patients should be asked to provide consent for a trial in a three-step process. Patients should be asked to sign the current ethics approved **PHOENIX ICF for Trial Registration** prior to Trial Registration. Patients who subsequently meet the eligibility criteria for Trial Entry should be asked to sign the current ethics approved **PHOENIX ICF for Trial Entry** prior to Trial Entry. Patients who are suitable for trial treatment in PART 2 should be asked to sign the current ethics approved **PHOENIX ICF forPART 2 Trial Treatment** prior to further trial treatment post-surgery.

Consent should only be taken after receiving both verbal and written information about the trial, having been given sufficient time to consider this information. All consent forms must be countersigned by the Principal Investigator or a delegated individual. A signature log of delegated responsibilities, listing the designated individuals and the circumstances under which they may countersign consent forms, must be maintained at the participating site. This log, together with original copies of all signed patient consent forms, should be retained in the Site Investigator File and must be available for inspection. The current ethics approved PHOENIX patient information sheets should be provided in addition to any standard patient information sheets that are provided by the site and used in routine practice. The consent process including the version of PIS and consent form used should be documented in the patient's notes.

21.6. Discontinuation from Follow-up

If a patient withdraws from further follow-up a patient withdrawal form should be completed in the MACRO database stating whether the patient simply no longer wishes to attend trial follow up visits or whether the patient has withdrawn consent for any further information to be sent to the ICR-CTSU.

21.7. Patient Confidentiality

Patients will be asked to consent to their full name being collected at Trial Entry in addition to their date of birth, hospital number, postcode and NHS number or equivalent to allow linkage with routinely collected NHS data and ensure accuracy in handling biological samples.

Each investigator should keep a separate log of all participants' Registration Numbers, Trial IDs, names, addresses and hospital numbers. The investigator must retain trial documents (e.g. participants' written consent forms) in strict confidence. The investigator must ensure the participants' confidentiality is maintained at all times.

Representatives of ICR-CTSU and the regulatory authorities will require access to participants' hospital notes for quality assurance purposes. ICR-CTSU will maintain the confidentiality of participants at all times and will not reproduce or disclose any information by which participants could be identified.

21.8. Data Protection

All parties must comply with all applicable data protection laws.

21.9. Insurance and Liability

The sponsor holds clinical trials insurance. Indemnity to meet the potential legal liability of investigators participating in this trial is provided by the usual NHS indemnity arrangements.

22. FINANCIAL MATTERS

This trial is investigator designed and led, has been endorsed by Clinical Research Committee (CRC) of Cancer Research UK, and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

The trial is part of the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio by virtue of its endorsement by CRC. NIHR CRN resources should therefore be made available for the trial to cover UK specific research costs.

The sponsor has received an Investigator Initiated Research (IIR) grant from AZ for the conduct of this trial.

23.PUBLICATION POLICY

The main trial results for each cohort will be published either separately or together in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, consisting of members of the TMG. Participating clinicians may be selected to join the writing group on the basis of intellectual and time input. All participating clinicians will be acknowledged in the publication.

Any presentations and publications relating to the trial must be authorised by the TMG. Authorship of any secondary publications e.g. those relating to sub-studies, will reflect intellectual and time input into these studies.

No investigator may present or attempt to publish data relating to the PHOENIX trial without prior permission from the TMG.

Section 24
PART 1: OLAPARIB MONOTHERAPY TRIAL TREATMENT INFORMATION COHORTS E-G

24. PART 1 OLAPARIB MONOTHERAPY: TRIAL TREATMENT INFORMATION COHORTS E-G

24.1. Part 1 Trial Treatment

Olaparib is the IMP for Cohorts E-G in Part 1.

24.1.1. Part 1 Olaparib: Dose and Schedule

Olaparib 300mg (2 x 150mg tablets) twice daily should be administered orally on Days 1–14 of the WOP.

Olaparib should be taken at the same time each day, approximately 12 hours apart with one glass of water. Olaparib tablets can be taken with or without food.

Trial treatment should be swallowed whole and not chewed, crushed, dissolved or divided.

It is prohibited to consume grapefruit juice while taking olaparib. In addition it is recommended that patients avoid the consumption of grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of any of these (such as marmalade) during treatment and preferably 7 days before the first dose of trial treatment.

24.1.2. Part 1 Olaparib: Duration of Trial Treatment

Patients will receive trial treatment for 14 days during the WOP from Day 1 to Day 14.

A patient is considered evaluable if they receive ≥80% of expected doses **and** receive both doses of olaparib on WOP D14.

24.1.3. Part 1 Olaparib: Dose Modifications

No dose modifications will apply in the WOP.

24.1.4. Part 1 Olaparib: Discontinuation of Trial Treatment

Trial treatment should continue as instructed in the WOP unless the patient experiences unacceptable toxicity or withdraws consent.

24.2. Part 1 Olaparib: Prescription and Dispensing

Olaparib tablets will be provided in non-patient-specific bottles. The patient's Trial ID should be recorded on the bottle label prior to dispensing. Patients should be instructed to keep their trial treatment in the bottles provided and not transfer it to any other container.

All efforts should be made to ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply and unused trial treatment and/or empty bottles should be returned at the appropriate time points. Returned unused trial treatment must not be re-dispensed to any patient and should only be destroyed with prior approval from ICR-CTSU according to local destruction policy.

Olaparib should be prescribed by the PI or Co-investigator and dispensed by the hospital pharmacy from trial stock supplied specifically for use within PHOENIX only.

24.3. Part 1 Olaparib: Patient Cards and Treatment Diary Cards

A small wallet sized patient card template will be provided by ICR-CTSU for completion by the participating site. Each card will state:

- The name of the participating site
- That the patient is participating in the PHOENIX trial
- That the patient is taking olaparib
- An emergency site contact number

Patients should be advised to keep their patient card in their possession at all times.

A treatment diary card will be provided by ICR-CTSU for completion by the patient, in order to record the number of tablets taken on each day of the WOP.

24.4. Part 1 Olaparib: Permitted Concomitant Therapy

Patients who are receiving neoadjuvant pembrolizumab as SOC can continue this treatment during Part 1 of the trial. All other medication considered necessary for the participants' welfare and which is not expected to interfere with the evaluation of the trial treatment may be given at the discretion of the investigator. All concomitant medications must be recorded in the patient's notes, as well as the appropriate eCRF pages within the clinical database.

The use of any natural/herbal products or other traditional 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.

Bisphosphonates, RANK ligand antagonists (e.g. denosumab) and blood transfusions should be given as required at the discretion of the Investigator.

Patients may take corticosteroids but increased vigilance is recommended on electrolyte and glucose levels.

Patients who require anti-coagulation during trial treatment should start on LMWH.

24.5. Part 1 Olaparib: Non-permissible Medications/Therapies

With the exception of pembrolizumab (as indicated in the section above) no other anti-cancer therapy (chemotherapy, immunotherapy other than pembrolizumab, hormonal therapy (Hormone replacement therapy is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving trial treatment during the 14-day pre-surgical WOP.

Live virus and live bacterial vaccines should not be administered whilst the patient is receiving trial treatment and during a period of 30 days following the last dose of trial treatment. 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.

PLEASE REFER TO APPENDIX 6 FOR PROHIBITED CONCURRENT MEDICATIONS FOR OLAPARIB.

It is recommended that known potent inhibitors/inducers of CYP3A are not co-administered with olaparib. Please see Appendix 6 for details. The required washout period prior to commencing trial treatment is 5 weeks for known strong or moderate CYP3A inhibitors or inducers. Please refer to Section 8.1.2 Trial Entry Exclusion Criteria for further information.

Caution should be exercised when substrates of CYP3A4 or UGT1A1 are combined with olaparib, in particular those with a narrow therapeutic margin. Caution should be exercise if olaparib is administered in combination with P-gp inhibitors which may increase exposure to olaparib. Caution should be exercised if olaparib is administered in combination with any statin. **Please see Appendix 6 for additional guidance.**

Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp. **Please see Appendix 6 for examples of substrates.**

The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.

Anticoagulant Therapy

Patients 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. Subcutaneous heparin and low molecular weight heparin are permitted.

Anti-emetics/Anti-diarrhoeals

If a patient develops nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs (see Section 16) and appropriate treatment of the event given.

Administration of other anti-cancer agents

With the exception of pembrolizumab, if being received as part of SOC, patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on trial treatment during Part 1.

24.6. Part 1 Olaparib: Additional Cautions

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

Olaparib is regarded as a compound with medium/high foetal risk. Please refer to Section 5.4 Lifestyle Guidance for guidance on the contraception requirements for participants within the PHOENIX trial.

24.7. Part 1 Olaparib: Missed Doses

The scheduled trial treatment dose can be taken up to 2 hours after the scheduled dose time. If greater than 2 hours has passed, the missed dose should not be taken. If a dose is missed, trial treatment should be

resumed at the next scheduled dose. Missed doses should not be made up. If the patient vomits after taking a dose of trial treatment they should be advised to resume treatment at the next scheduled dose.

24.8. Part 1 Olaparib: Overdoses

There is currently no specific treatment in the event of an overdose with olaparib and possible symptoms of overdose are not established. If overdose occurs, this should be managed symptomatically. Please contact the ICR-CTSU Trial Team for advice.

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mg twice daily (tablet).

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

24.9. Part 1 Olaparib: Compliance

Patients must be asked to bring all their trial treatment and diary card when they attend the clinic for WOP D14 assessments for the purposes of treatment compliance assessment and drug accountability. Every effort should be made to encourage patients to return the unused trial treatment and empty bottles. The unused tablets should be collected by the Investigator/Research Nurse and counted to ascertain patient compliance, trial treatment will then be returned to pharmacy for drug accountability. Drug destruction should only be carried out with prior approval from ICR-CTSU and according to local destruction policy.

24.10. Part 1 Olaparib: Supply and Distribution of Olaparib

Olaparib is manufactured and provided free of charge by AZ to participating sites.

No trial treatment will be distributed to participating sites unless ICR-CTSU is satisfied that the required approvals and agreements and initiation procedures are complete.

24.11. Part 1 Olaparib: Formulation, Packaging, Storage Conditions and Labelling

Olaparib will be supplied as oval film-coated tablets supplied in HDPE bottles containing desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence. Olaparib tablets should be stored below 30°C. Tablets should be stored in the bottles provided and taken according to the instructions on the label.

The drug distribution company is responsible for labelling olaparib in accordance with the MHRA approved trial label. Pharmacies may add their own hospital dispensing label to the trial treatment but should not obscure the existing label on the trial treatment packaging.

24.12. Part 1 Olaparib: Pharmacy Responsibilities and Drug Accountability

Olaparib supplied for the trial must not be used outside the context of the protocol. Records must be kept of all deliveries, dispensing and destruction in accordance with the trial Pharmacy Guidance Notes. These

records may be requested by ICR-CTSU during the trial to monitor supply and usage of stock. Account must be given of any discrepancies, and certificates of delivery and destruction must be signed and dated.

SECTION 25 PART 2: OLAPARIB AND DURVALUMAB COMBINATION THERAPY TRIAL TREATMENT INFORMATION COHORTS F & G

25. PART 2 OLAPARIB AND DURVALUMAB COMBINATION THERAPY: TRIAL TREATMENT INFORMATION COHORTS F & G

25.1. Part 2 Trial Treatment

Olaparib and durvalumab are the IMP for Cohorts F & G in Part 2 of the trial. Eligible patients will receive olaparib and durvalumab combination therapy. Patients who are not eligible for durvalumab treatment can receive olaparib monotherapy.

For patients that are receiving pembrolizumab as SOC the washout period from last dose of pembrolizumab and start of durvalumab is 30 days. Further details can be found in Section 12.3.

Trial treatment details for olaparib and durvalumab are shown separately below. The Investigator should use clinical judgement when attributing a toxicity to olaparib or durvalumab when given in combination. The choice of toxicity management guidelines should be based on the investigator's assessment of the causal role of the individual IMPs. In situations where the assessment qualifies both IMP toxicity management guidelines for a particular toxicity, the more conservative dose modification and/or dose interruption should be applied.

25.1.1. Part 2 Duration of Trial Treatment

Patients will remain on trial treatment for 12 months (13 cycles) in PART 2.

25.1.2. Part 2 Discontinuation of Trial Treatment

Patients may discontinue olaparib and/or durvalumab early if they experience unacceptable toxicity or if the investigator believes further treatment with one or both IMPs is no longer appropriate or at the patient's request. Protocol-specified reasons for discontinuation include:

- Disease progression or recurrence
- Unacceptable toxicity
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML), pure red cell aplasia (PRCA) or auto-immune haemolytic anaemia (AIHA))
  Note: if PRCA or AIHA are observed in patients with germline BRCA1/2 mutation (cohort F), olaparib may be restarted outside of the protocol as part of standard of care treatment on haematological recovery according to investigator discretion.
- Pregnancy
- Withdrawal of consent
- Serious non-attendance and/or persistent non-compliance with procedures defined in the trial protocol

Patients can continue on monotherapy trial treatment if one IMP is discontinued. All patients who discontinue both olaparib and durvalumab should continue to be followed up. Patients should be asked for consent for future linkage with routinely collected health data (via national registries) to trace their eventual vital status and assess subsequent unexpected co-morbidities.

25.2. Part 2 Olaparib: Trial Treatment

25.2.1. Part 2 Olaparib: Dose and Schedule

Olaparib 300mg (2 x 150mg tablets) twice daily should be administered orally on a continuous schedule Days 1-28 of each 28 day treatment cycle.

Olaparib should be taken at the same time each day, approximately 12 hours apart with one glass of water. Olaparib tablets can be taken with or without food.

Olaparib should be swallowed whole and not chewed, crushed, dissolved or divided. The scheduled dose of olaparib can be taken up to 2 hours after the scheduled dose time. If greater than 2 hours has passed, the missed dose should not be taken and patient should continue with next dose at allotted time.

It is prohibited to consume grapefruit juice while taking olaparib. In addition it is recommended that patients avoid the consumption of grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of any of these (such as marmalade) during trial treatment and preferably 7 days before the first dose of olaparib.

Olaparib should be administered as per the above schedule, however if this is not possible due to unavoidable circumstances (i.e. bank holidays) from Cycle 2 onwards Day 1 of trial treatment may be delayed for up to 3 days after the due date for Cycle 2, or delayed for up to 7 days after the due date for Cycle 3 onwards.

For further guidance on trial treatment delay due to toxicity please refer to Sections 25.2.3, 25.2.4 and 25.2.5.

25.2.2. Part 2 Olaparib: Dose Modifications

Every effort should be made to administer olaparib at the planned dose and schedule. Any toxicity observed during the course of the trial treatment should be managed by interruption of olaparib, as deemed appropriate by the Investigator. Patients experiencing toxicities related to the olaparib may have their dose modified as outlined in this section. Further guidance on specific toxicities requiring dose modifications are described in Sections 25.2.2.

Any dose reductions should be applied to subsequent cycles unless a further dose reduction is required. Once a reduction is made the patient should not increase back to a higher dose level.

Table. Olaparib dose reductions guidelines

Dose Level	**Olaparib**
Starting dose	300mg BD Days 1-28
First dose reduction	
For haematological toxicity	250mg BD Days 1-28
For non-haematological toxicity	250mg BD Days 1-28
Second dose reduction	200mg BD Days 1-28
Third dose reduction	Discontinue trial treatment

The haematological criteria for initiation of a treatment cycle are blood counts on Day 1 of any cycle (within 72 hours pre-treatment):

- ANC ≥1500/mm^3 (≥1.5 x 10^9/L)
- Platelet count ≥75,000/mm^3 (≥75x 10^9/L)
- Haemoglobin (Hb) ≥8g/dL (≥80g/L) (with the exception of Cycle 1 where Hb must be >10g/dL (100g/L)).

25.2.3. Part 2 Olaparib: Specific Toxicities Requiring Dose Modifications

Haematological toxicity

Table. Olaparib haematological toxicity management guidelines

Toxicity	Action
Any Grade 3 haematological toxicity	**First occurrence** • Withhold dose for up to 28 days until recovery to Grade ≤1 then resume olaparib at the same dose level. • If symptoms do not recover to Grade ≤1 within 28 days, discontinue olaparib. **Second occurrence** • Withhold dose for up to 28 days until recovery to Grade ≤1 then reduce olaparib to the first dose reduction level for haematological toxicity. • If symptoms do not recover to Grade ≤1 within 28 days, discontinue olaparib. **Third occurrence** • Withhold dose for up to 28 days until recovery to Grade ≤1 then reduce olaparib to the second dose reduction level for haematological toxicity. • If symptoms do not recover to Grade ≤1 within 28 days, discontinue olaparib. **Fourth occurrence** • Discontinue olaparib.
Any Grade 4 haematological toxicity	**First occurrence** • Withhold dose for up to 28 days until recovery to Grade ≤1 then reduce olaparib to the first dose reduction level for haematological toxicity. • If symptoms do not recover to Grade ≤1 within 28 days, discontinue olaparib **Second occurrence** • Withhold dose for up to 28 days until recovery to Grade ≤1 then reduce olaparib to the second dose reduction level for haematological toxicity. • If symptoms do not recover to Grade ≤1 within 28 days, discontinue olaparib **Third occurrence** • Discontinue olaparib
Anaemia	• Common treatable causes of anaemia (e.g. iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. The use of erythropoietin is not allowed at any stage.

Toxicity	Action
Haemoglobin (Hb) <10g/dL but ≥8g/dL (Grade 2)	**General management** • Give appropriate supportive treatment and investigate causality. • Investigator judgement to continue trial treatment with supportive treatment (e.g. transfusion) or interrupt dose for a maximum of 28 days, for investigations and supportive treatment. • Before initiation of any treatment cycle (Day 1) the Hb must be >8g/dL (80g/L) (with the exception of Cycle 1, where Hb must be >10g/dL (100g/L)). **First occurrence** • General management as above, and resume olaparib at the same dose level. **Subsequent occurrences** • **If Hb <10g/dL but ≥9g/dL**: General management as above. Upon recovery dose reduction may be considered to reduce olaparib to the first dose reduction level for haematological toxicity as a first step and to second dose reduction as a second step. • **If Hb <9g/dL but ≥8g/dL**: Interrupt dose for a maximum of 28 days until Hb ≥9g/dL and upon recovery dose reduction may be considered to reduce olaparib to the first dose reduction level for haematological toxicity as a first step and to second dose reduction as a second step.
Hb <8g/dL (Grade ≥3)	**General management** • Appropriate supportive treatment should be given (e.g. transfusion) and causality investigated. • Interrupt olaparib for a maximum of 28 days until Hb≥8g/dL (i.e., Grade ≤2). **First occurrence** • General management as above, and reduce olaparib to the first dose reduction level for haematological toxicity. **Second occurrence** • General management as above, and reduce olaparib to the second dose reduction level for haematological toxicity. **Third occurrence** • Discontinue olaparib.
Neutropenia, leukopenia and thrombocytopenia	• Neutropenia, leukopenia and thrombocytopenia should be managed as deemed appropriate by the Investigator with close follow up. • For toxicity of Grades 1-2, appropriate supportive treatment should be given and causality investigated. Trial treatment can be interrupted for a maximum of 28 days at the Investigator's discretion. • If Grade ≥3 neutropenia occurs interrupt trial treatment and follow the instructions for any haematological toxicity above as appropriate. • Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, trial treatment should be interrupted for a maximum of 28 days and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for pegylated G-CSF) of the last dose of trial treatment unless absolutely necessary. • Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Toxicity	Action
Prolonged haematological toxicity such as ≥2 week interruption/delay in trial treatment due to Grade ≥3: • Anaemia and/or development of blood transfusion dependence • Neutropaenia (ANC <1 x 10^9/L) • Thrombocytopaenia and/or development of platelet transfusion dependence (platelet count <50 x 10^9/L)	• Check weekly differential blood counts (including reticulocytes and peripheral blood smear). • If any blood parameters remain clinically abnormal after 28 days of dose interruption, the patient 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 local haematological practice. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, trial treatment should be discontinued and a full description of findings should be submitted in an SAE report. • Trial treatment should be discontinued if blood counts do not recover to Grade ≤1 within 28 days of dose interruption. • Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE, please refer to Section 16. • Trial treatment should be discontinued if the diagnosis of MDS and/or AML, or PRCA or AIHA is confirmed. Note: if PRCA or AIHA are observed in patients with germline BRCA1/2 mutation (cohort F), olaparib may be restarted outside of the protocol as part of standard of care treatment on haematological recovery according to investigator discretion.

Non-haematological toxicity

Table. Olaparib non-haematological toxicity management guidelines

Toxicity	Action
Any non-haematological toxicity Grade ≥3	**First occurrence** • Withhold dose for up to 28 days until recovery to Grade ≤1. For Grade 3 toxicity olaparib may be resumed at the same dose level at the discretion of the Investigator. In the case of Grade 4 toxicity olaparib should be reduced to the first dose reduction level for non-haematological toxicity. • If symptoms do not recover to Grade ≤1 (or recover to baseline level if baseline was Grade 2) within 28 days, discontinue olaparib. Patients with alopecia may continue on trial treatment. **Second occurrence** • Withhold dose for up to 28 days until recovery to Grade ≤1 then reduce olaparib to the next dose reduction level for non-haematological toxicity. • If symptoms do not recover to Grade ≤1 (or recover to baseline level if baseline was Grade 2) within 28 days, discontinue olaparib. Patients with alopecia may continue on therapy. **Third occurrence** • Withhold dose for up to 28 days until recovery to Grade ≤1 then reduce olaparib to the second dose reduction level for non-haematological toxicity. Patients who are currently receiving the second dose reduction level should discontinue olaparib.

Toxicity	Action
	• If symptoms do not recover to Grade ≤1 (or recover to baseline level if baseline was Grade 2) within 28 days, discontinue olaparib. Patients with alopecia may continue on therapy. **<u>Fourth occurrence</u>** • Discontinue olaparib.
New or worsening pulmonary symptoms **NB. Pneumonitis is an important potential risk for olaparib**	• If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in trial treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed to exclude pneumonitis. • The following assessments, and additional assessments if required, should be performed to enhance the investigation and diagnosis of potential cases of pneumonitis: o Physical examination and signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field. o Saturation of peripheral oxygen (SpO_2) o The following markers should be measured where possible: ILD markers (KL-6, SP-D) and β-D-glucan; tumour markers related to disease progression. • Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then trial treatment can be restarted, if deemed appropriate by the Investigator. • If significant pulmonary abnormalities are identified, these should be raised with the PHOENIX Trial Team in the first instance for discussion with the Chief or Coordinating Investigator. • If Grade ≥2 pneumonitis is confirmed, olaparib treatment should be discontinued and the patient treated appropriately. • Any event of pneumonitis should be reported as an AESI, please refer to Section 16 for further information.
Nausea and vomiting	• Events of nausea and vomiting are known to be associated with olaparib treatment. They are generally mild to moderate (Grade ≤2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months. • If the patient vomits after taking a dose of trial treatment they should be advised to resume treatment at the next scheduled dose • No routine prophylactic anti-emetic treatment is required at the start of trial treatment, however patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (i.e. 2 pieces of toast or a couple of biscuits). As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered (e.g. dopamine receptor antagonist, antihistamines or dexamethasone).
Diarrhoea	• Loperamide 4mg should be administered at the first onset of diarrhoea and then 2mg every 2 hours until diarrhoea-free for at least 12 hours. The first dose of loperamide could be lowered to 2mg if the diarrhoea is recurrent and if, in the opinion of the Investigator, the diarrhoea is not severe.

Toxicity	Action
	• Patients should be instructed to notify the Investigator or research staff of the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhoea within 24 hours of using loperamide or other prescribed anti diarrhoeal medications. • If diarrhoea is severe (i.e., requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhoea or any diarrhoea associated with severe nausea or vomiting should be hospitalised for intravenous hydration and correction of electrolyte imbalances.
Myelodysplastic syndrome (MDS)/Acute Myeloid Leukaemia (AML) **NB. MDS/AML are important potential risks for olaparib**	• Olaparib treatment should be discontinued if the diagnosis of MDS and/or AML is confirmed and the patient should be treated appropriately. • Development of a confirmed MDS and/or AML whilst on trial treatment with olaparib or following treatment discontinuation should be reported as an AESI, please refer to Section 16 for further information.
Renal impairment	• If creatinine increases to Grade ≥2, creatinine clearance should be calculated by Cockcroft and Gault equation (see Appendix 4). If calculated creatinine clearance is >51 ml/min treatment should be continued at the current dose. • A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation of between 31 and 50 ml/min) for any reason during trial treatment. The dose of olaparib should be reduced to 200mg BD. • Because the creatinine clearance determination is only an estimate of renal function, in instances where the creatinine clearance falls to between 31 and 50 ml/min, the Investigator should use their discretion in determining whether a dose change or discontinuation of trial treatment is warranted. • Caution should be used in patients with a creatinine clearance less than 30ml/min as safety and efficacy have not been evaluated in this population. • The safety and efficacy of trial treatment has not been evaluated in patients with severe renal impairment (creatinine clearance ≤30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease it is recommended that all trial treatment be discontinued.
Hepatic toxicity	• Please refer to Table C4 for hepatic toxicity management guidelines.

Hepatic toxicity

Table C4. Cohort C hepatic toxicity management guidelines

Event	Actions
• Grade 3 ALT/AST or Grade 3 bilirubin	• Withhold olaparib for up to 28 days until recovery to Grade ≤1 (or Grade ≤2 in patients with Grade 2 ALT at baseline). • Look for alternative causes. • Reduce olaparib to the next dose reduction level. • If symptoms do not recover to Grade ≤1 (or Grade ≤2 in patients with Grade 2 ALT at baseline) within 28 days, discontinue olaparib.
• Grade 4 ALT/AST or Grade 4 bilirubin	• Permanently discontinue olaparib. • Evaluate alternative cause.

• AST or ALT >3 x ULN AND • Total bilirubin >2 x ULN	• Withhold olaparib. Please refer to Section 16.8 for further information on evaluation and reporting requirements for potential Hy's Law cases. • Evaluate the patient as soon as possible (within 48 hours if possible). All cases confirmed on repeat testing with no alternative explanation for abnormal liver function should be considered potential Hy's Law cases. • Report as an SAE. • Discontinue trial treatment if Hy's Law confirmed. • If the criteria for Hy's Law are not met, follow the guidance above for Grade 3/4 ALT/AST or bilirubin.

25.2.4. Part 2 Olaparib: Dose interruptions

In addition to the specific toxicity management guidelines within Section 25.2.3 olaparib treatment should be interrupted if patients experience any Grade ≥3 toxicity.

Following an interruption for Grade ≥3 toxicity, olaparib should be delayed for up to 28 days until these toxicities have resolved to Grade ≤1 or returned to baseline.

Repeat dose interruptions are allowed as required, for a maximum of 28 days on each occasion. If a patient remains off olaparib for >28 days, olaparib should be permanently discontinued.

25.2.5. Part 2 Olaparib: Prescription and Dispensing

Olaparib tablets will be provided in non-patient-specific bottles. The patient's Trial ID should be recorded on the bottle label prior to dispensing. Patients should be instructed to keep their trial treatment in the bottles provided and not transfer it to any other container.

All efforts should be made to ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply and unused trial treatment and/or empty bottles should be returned at the appropriate time points. Returned unused trial treatment must not be re-dispensed to any patient and should only be destroyed with prior approval from ICR-CTSU according to local destruction policy.

Olaparib should be prescribed by the PI or Co-investigator and dispensed by the hospital pharmacy from trial stock supplied specifically for use within PHOENIX only.

25.2.6. Part 2 Olaparib: Patient Cards and Treatment Diary Cards

A small wallet sized patient card template will be provided by ICR-CTSU for completion by the participating site. Each card will state:

- The name of the participating site
- That the patient is participating in the PHOENIX trial
- That the patient is taking olaparib (and durvalumab if applicable)
- An emergency site contact number

Patients should be advised to keep their patient card in their possession at all times.

A treatment diary card will be provided by ICR-CTSU for completion by the patient, in order to record the number of olaparib tablets taken on each day of trial treatment.

25.2.7. Part 2 Olaparib: Permitted Concomitant Therapy

All medication considered necessary for the participants' welfare and which is not expected to interfere with the evaluation of the trial treatment may be given at the discretion of the investigator. All concomitant medications must be recorded in the patient's notes, as well as the appropriate eCRF pages within the clinical database.

The use of any natural/herbal products or other traditional 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.

Bisphosphonates, RANK ligand antagonists (e.g. denosumab) and blood transfusions should be given as required at the discretion of the Investigator.

Patients may take corticosteroids but increased vigilance is recommended on electrolyte and glucose levels.

Patients who require anti-coagulation during trial treatment should start on LMWH.

25.2.8. Part 2 Olaparib: Non-permissible Medications/Therapies

No other anti-cancer therapy (chemotherapy, immunotherapy, radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving trial treatment with olaparib ± durvalumab. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. **Please note:** patients may receive adjuvant radiotherapy as per SOC post-operatively during PART 1 but this must be completed at least three weeks prior to commencement of any trial treatment in PART 2.

Live virus and live bacterial vaccines should not be administered whilst the patient is receiving trial treatment and during a period of 30 days following the last dose of trial treatment. 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.

PLEASE REFER TO APPENDIX 5 FOR PROHIBITED CONCURRENT MEDICATIONS FOR OLAPARIB .

It is recommended that known potent inhibitors/inducers of CYP3A are not co-administered with olaparib. Please see Appendix 5 for details. The required washout period prior to commencing trial treatment is 5 weeks for known strong or moderate CYP3A inhibitors or inducers. Please refer to Section 8.1.2 Trial Entry Exclusion Criteria for further information.

Caution should be exercised when substrates of CYP3A4 or UGT1A1 are combined with olaparib, in particular those with a narrow therapeutic margin. Caution should be exercise if olaparib is administered in

combination with P-gp inhibitors which may increase exposure to olaparib. Caution should be exercised if olaparib is administered in combination with any statin. **Please see Appendix 5 for additional guidance.**

Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp. **Please see Appendix 5 for examples of substrates.**

The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.

Anticoagulant Therapy

Patients 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. Subcutaneous heparin and low molecular weight heparin are permitted.

Anti-emetics/Anti-diarrhoeals

If a patient develops nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs (see Section 16) and appropriate treatment of the event given.

Administration of other anti-cancer agents

With the exception of pembrolizumab, if being received as part of SOC, patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on trial treatment during Part 1.

25.2.9. Part 2 Olaparib: Additional Cautions

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

Olaparib is regarded as a compound with medium/high foetal risk. Please refer to Section 5.4 Lifestyle Guidance for guidance on the contraception requirements for participants within the PHOENIX trial.

25.2.10. Part 2 Olaparib: Missed Doses

The scheduled olaparib dose can be taken up to 2 hours after the scheduled dose time. If greater than 2 hours has passed, the missed dose should not be taken. If a dose is missed, olaparib should be resumed at the next scheduled dose. Missed doses should not be made up. If the patient vomits after taking a dose of olaparib they should be advised to resume treatment at the next scheduled dose.

25.2.11. Part 2 Olaparib: Overdoses

There is currently no specific treatment in the event of an overdose with olaparib and possible symptoms of overdose are not established. If overdose occurs, this should be managed symptomatically. Please contact the ICR-CTSU Trial Team for advice.

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mg twice daily (tablet).

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

25.2.12. Part 2 Olaparib: Compliance

Patients must be asked to bring all their trial treatment and diary card when they attend the clinic for the purposes of treatment compliance assessment and drug accountability. Every effort should be made to encourage patients to return the unused trial treatment and empty bottles. The unused tablets should be collected by the Investigator/Research Nurse and counted to ascertain patient compliance, trial treatment will then be returned to pharmacy for drug accountability. Drug destruction should only be carried out with prior approval from ICR-CTSU and according to local destruction policy.

25.2.13. Part 2 Olaparib: Supply and Distribution of Olaparib

Olaparib is manufactured and provided free of charge by AZ to participating sites.

No trial treatment will be distributed to participating sites unless ICR-CTSU is satisfied that the required approvals and agreements and initiation procedures are complete.

25.2.14. Part 2 Olaparib: Formulation, Packaging, Storage Conditions and Labelling

Olaparib will be supplied as oval film-coated tablets supplied in HDPE bottles containing desiccant. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence. Olaparib tablets should be stored below 30°C. Tablets should be stored in the bottles provided and taken according to the instructions on the label.

The drug distribution company is responsible for labelling olaparib in accordance with the MHRA approved trial label. Pharmacies may add their own hospital dispensing label to the trial treatment but should not obscure the existing label on the trial treatment packaging.

25.3. Part 2 Durvalumab: Trial Treatment

25.3.1. Part 2 Durvalumab: Dose and Schedule

Based on average body WT of 75 kg, a fixed dose of 1,500mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) should be administered via IV infusion on Day 1 of each 28 day treatment cycle.

First infusion of durvalumab:
On the first infusion day, patients should be monitored and vital signs collected/recorded prior to, during and after infusion of durvalumab. BP and pulse will be collected from patients before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

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

Trial treatment should be administered as per the above schedule, however if this is not possible due to unavoidable circumstances (i.e. bank holidays) from Cycle 2 onwards Day 1 of trial treatment may be delayed for up to 3 days after the due date for Cycle 2, or delayed for up to 7 days after the due date for Cycle 3 onwards.

For further guidance on trial treatment delay due to toxicity please refer to Sections 25.3.2, 25.3.3 and 25.3.4.

Subsequent infusions of durvalumab
Blood pressure, pulse and other vital signs should be measured, collected/recorded prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated.

25.3.2. Part 2 Durvalumab: Dose Modifications

Every effort should be made to administer durvalumab as per the planned schedule. Any toxicity observed during the course of the trial treatment should be managed by interruption of durvalumab, as deemed appropriate by the Investigator. Patients experiencing toxicities related to durvalumab may have their dose modified as outlined in this section. Further guidance on specific toxicities requiring dose modifications are described in Section 25.3.3 and Appendix 7.

25.3.3. Part 2 Durvalumab: Specific Toxicities Requiring Dose Modifications

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy are provided in the **Dosing Modification and Toxicity Management Guidelines at Appendix 7**. Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

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 durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.

- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE, v5.0.

Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed, as described in the **Dosing Modification and Toxicity Management Guidelines** at Appendix 9.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the ICR-CTSU Trial Team.

Eyes
For signs and symptoms suggestive of keratitis or uveitis (such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and /or red eye), subjects should be advised to seek medical advice promptly, and, if required, referred promptly to an ophthalmologist. AEs related to the eye may be immune related and should be managed according to local practice. Please also refer to the Dosing Modification and Toxicity Management Guidelines at Appendix 9.

25.3.4. Part 2 Durvalumab: Dose interruptions

As directed in Section 25.3.3 and the **Dosing Modification and Toxicity Management Guidelines** at Appendix 7, durvalumab treatment should be interrupted if patients experience any Grade ≥2 toxicity.

Following an interruption for Grade ≥2 toxicity, trial treatment may be delayed for up to 12 weeks until these toxicities have resolved to Grade ≤1 or returned to baseline.

Repeat dose interruptions are allowed as required, for a maximum of 12 weeks on each occasion. If a patient remains off trial treatment for >12 weeks, trial treatment should be permanently discontinued.

25.3.5. Part 2 Durvalumab: Prescription and Dispensing

Durvalumab should be prescribed by the PI or delegated Co-investigator and dispensed by the hospital pharmacy from trial stock supplied specifically for use within the PHOENIX trial only.

25.3.6. Part 2 Durvalumab: Patient Cards

A small wallet sized patient card template will be provided by ICR-CTSU for completion by the participating site. Each card will state:

- The name of the participating site
- That the patient is participating in the PHOENIX trial
- That the patient is receiving treatment with olaparib ± durvalumab
- An emergency site contact number

Patients should be advised to keep their patient card in their possession at all times.

25.3.7. Part 2 Durvalumab: Permitted Concomitant Therapy

All medication considered necessary for the participants' welfare and which is not expected to interfere with the evaluation of the trial treatment may be given at the discretion of the investigator. All concomitant

medications must be recorded in the patient's notes, as well as the appropriate eCRF pages within the clinical database.

Patients may receive adjuvant radiotherapy as per SOC post-operatively during PART 1 but this must be completed at least three weeks prior to commencement of any trial treatment in PART 2.

The use of any natural/herbal products or other traditional 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.

Patients should not donate blood whilst receiving trial treatment, or for at least 90 days following the last infusion of durvalumab.

Concomitant medications or treatments (e.g. paracetamol or antihistamines) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "non-permissible" in Section 25.3.8 may be given as required at the discretion of the Investigator.

Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management) should be used when necessary.

Inactivated viruses, such as those in the influenza vaccine are permitted excluding the nasal vaccine as this is a live vaccine.

Bisphosphonates, RANK ligand antagonists (e.g. denosumab) and blood transfusions should be given as required at the discretion of the Investigator.

Patients who require anti-coagulation during trial treatment should start on LMWH.

Please refer to Appendix 7 for Durvalumab Toxicity Management Guidelines for further information on toxicity management and permitted concomitant therapy.

25.3.8. Part 2 Durvalumab: Non-permissible Medications/Therapies

Other investigational agents (including monoclonal antibodies against CTLA-4, PD-1 or PD-L1) must not be given while the patient is on trial treatment.

No other anti-cancer therapy (chemotherapy, immunotherapy, radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving trial treatment olaparib ± durvalumab. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. **Please note:** patients may receive adjuvant radiotherapy as per SOC post-operatively during PART 1 but this must be completed at least three weeks prior to commencement of any trial treatment in PART 2.

Herbal and natural remedies which may have immune-modulating effects should not be given concomitantly unless agreed by the CI or Coordinating Investigator.

Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisolone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers should not be given concomitantly, or used for premedication prior to durvalumab infusions.

The following are allowed exceptions:

- Use of immunosuppressive medications for the management of IMP-related AEs.
- Use in patients with contrast allergies.
- In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.

A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.), however trial treatment should be held if the patient is receiving greater than 10mg/day of prednisolone or equivalent.

Please refer to Appendix 7 for Durvalumab Toxicity Management Guidelines for further information on toxicity management, permitted concomitant therapy and non-permissible medications.
Drugs with laxative properties and herbal or natural remedies for constipation should be used with caution through to 90 days after the last dose of durvalumab trial treatment.

EGFR Tyrosine Kinase Inhibitors (TKIs) should not be given concomitantly and should be used with caution in the 90 day period post the last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.

Live virus and live bacterial vaccines should not be administered whilst the patient is receiving trial treatment and during a period of 30 days following the last dose of trial treatment..

25.3.9. Part 2 Durvalumab: Additional Cautions

Please refer to Section 5.4 Lifestyle Guidance for guidance on the contraception requirements for participants within the PHOENIX trial.

25.3.10. Part 2 Durvalumab: Overdoses

There is currently no specific treatment in the event of an overdose with durvalumab and possible symptoms of overdose are not established. If overdose occurs, this should be managed symptomatically. Please contact the ICR-CTSU Trial Team for advice.

25.3.11. Part 2 Durvalumab: Supply and Distribution

Durvalumab is manufactured and provided free of charge by AZ to participating sites. No trial treatment will be distributed to participating sites unless ICR-CTSU is satisfied that the required approvals and agreements and initiation procedures are complete.

25.3.12. Part 2 Durvalumab: Formulation, Packaging, Storage Conditions and Labelling

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

The drug distribution company is responsible for labelling durvalumab in accordance with the MHRA approved trial label. Pharmacies may add their own hospital dispensing label to the trial treatment but should not obscure the existing label on the trial treatment packaging.

25.4. Part 2 Pharmacy Responsibilities and Drug Accountability

Olaparib and durvalumab supplied for the trial must not be used outside the context of the protocol. Records must be kept of all deliveries, dispensing and destruction in accordance with the trial Pharmacy Guidance Notes. These records may be requested by ICR-CTSU during the trial to monitor supply and usage of stock. Account must be given of any discrepancies, and certificates of delivery and destruction must be signed and dated.

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APPENDIX 1: GLOSSARY

AE	Adverse Event
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukaemia
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATR	Ataxia telangiectasia and Rad3-related protein
AUC	Area Under Curve
BP	Blood pressure
CI	Chief Investigator
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EE	Ethinyl estradiol
ctDNA	Circulating tumour DNA
CTU	Clinical Trials Unit
DDI	Drug–drug interaction
DSB	Double-stranded break
DDI	Drug-Drug Interaction
DDR	DNA Damage Response
DILI	Drug-induced Liver Injury
ER	Oestrogen receptor
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
G-CSF	Growth Colony-Stimulating Factors
GGT	Gamma-glutamyl transferase
Hb	Haemoglobin
HBsAg	HBV surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIE	Health Institution Exemption
HIV	Human immunodeficiency virus
HL	Hy's Law
HNSCC	Head and neck squamous cell carcinoma
IB	Investigator's Brochure
ICR	The Institute Of Cancer Research
IDSMC	Independent Data and Safety Monitoring Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IMP	Investigational Medicinal Product
INR	International Normalised Ratio

IV	Intravenous
LFT	Liver Function Test
mAb	Monoclonal antibody
MDS	Myelodysplastic syndrome
MDT	Multi-disciplinary team
MRD	Minimal residual disease
MRI	Magnetic Resonance Imaging
MUGA	Multi-gated acquisition
NACT	Neoadjuvant chemotherapy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
PBMC	Peripheral Blood Mononuclear Cell
pCR	Pathological complete response
PDG	Protocol development group
PD-L1	Programmed death ligand 1
PHL	Potential Hy's Law
PI	Principal Investigator
PIKK	Phosphatidylinositol 3-kinase-related kinase
PIS	Patient Information Sheet
PK	Pharmacokinetic
PR	Progesterone receptor
R&D	Research and Development
RCB	Residual cancer burden
RP2D	Recommended phase 2 dose
RPA	Replication protein A
RPPA	Reverse phase protein array
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvate Transaminase
SIF	Site Investigator File
SSB	Single stranded break
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TBL	Total bilirubin
TIL	Tumour-infiltrating lymphocyte
TMG	Trial Management Group
TNBC	Triple Negative Breast Cancer
TSC	Trial Steering Committee
TSH	Thyroid stimulating hormone
ULN	Upper Limit of Normal
US	Ultrasound
WOP	Window of opportunity

APPENDIX 2: SAMPLE COLLECTION AND TRANSLATIONAL RESEARCH

All PHOENIX trial samples should be collected, processed, stored and shipped as detailed in the **PHOENIX Investigator Laboratory Manual**.

All samples must be labelled with the unique patient Trial ID, initials, date of birth and date of sample collection to enable cross referencing.

All PHOENIX trial samples will be sent to the PHOENIX Central Laboratory at The Institute of Cancer Research and Royal Marsden Hospital NHS Trust.

PART 1 SAMPLE COLLECTION

PART 1 Tumour Tissue Sample Collection

Research Biopsies
Please refer to the **PHOENIX Investigator Laboratory Manual** for details on the collection, handling, labelling, storage, tracking and shipment of tumour samples.

Research tissue samples should be collected at two time-points within PART 1:

- **Baseline image-guided biopsy of the residual tumour** – performed at the beginning of the WOP (Day -1 or 1) prior to commencing trial treatment and guided by a new radio-opaque marker insertion into viable residual disease. *As per the eligibility criteria patients must be suitable for a pre-treatment baseline biopsy on Trial Entry. Patients who are approached for entry into the trial are requested to consent to a baseline biopsy. If it is deemed unsafe to proceed with a baseline biopsy on Trial Entry the patient will not be eligible for participation in the trial.*

- **Pre-operative image-guided biopsy of the residual tumour** – performed at the end of the WOP on Day 14 and guided by the radio-opaque marker inserted at the baseline biopsy in order to collect the cores from the same site. *In exceptional cases when the collection of the biopsy on Day 14 is not feasible then image-guided research biopsy cores can be collected on the day of surgery or taken by the surgeon intraoperatively, with the time from the Day 14 assessments to biopsy minimised and recorded.*

In most cases it is anticipated that the tumour bed will be visible on ultrasound, allowing for the collection of the baseline and pre-operative biopsies via ultrasound-guidance, however, any other imaging modalities may be used (including stereotaxis, digital breast tomosynthesis, contrast enhanced mammography and MRI) as deemed suitable by the local centre depending on expertise and availability, may be used to target biopsy sites.

At each biopsy intervention a minimum of 4 and up to a maximum of 8 core biopsies should be collected from different coil referenced locations of radiologically assessed viable disease as detailed in the PHOENIX Investigator Laboratory Manual. The number of cores to be collected should be

decided on a case-by-case basis by the radiologist at the time of collection, with the aim of ensuring that at least 4 high quality tissue cores are obtained.

Archival Tumour Tissue Sample Collection

At Trial Registration the patient's archival diagnostic tumour tissue sample (must include primary breast with or without involved lymph node tissue) should be sent to the PHOENIX Central Laboratory. If following Trial Registration it is determined that a patient's archival diagnostic tumour tissue sample is unavailable or inadequate for assessment of HRD following assessment by the central laboratory the patient should not be invited to consent to Trial Entry. Please refer to the **PHOENIX Investigator Laboratory Manual** for tissue sample requirements.

Surgical Resection Tumour Tissue Sample Collection

Following surgery the patient's surgical resection tissue sample (must include primary breast with or without involved lymph node tissue) should be sent to the PHOENIX Central Laboratory. Please refer to the **PHOENIX Investigator Laboratory Manual** for tissue sample requirements.

Assessment of Residual Cancer Burden (RCB)

Residual Cancer Burden (RCB) should be assessed from surgical resection tissue for each PHOENIX patient. In order to assess RCB, the following parameters are required:

- Primary tumour bed area (in millimetres)
- Overall cancer cellularity (as percentage of area)
- Percentage of cancer that is *in situ* disease
- Number of positive lymph nodes
- Diameter of largest nodal metastasis in millimetres (this score can be '0' if no positive nodes)

Residual cancer burden can be calculated with these parameters using the MD Anderson RCB calculator which can be found online at the following link along with examples of percentage cellularity and methodology:

http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

Tumour Tissue Mutation Analysis to Determine Cohort Allocation and Development of a Tumour-informed ctDNA Assay

The archival diagnostic tumour tissue block will be analysed at the Central Laboratory for assessment of mutations associated with HR deficiency, including BRCA1/2 status, for cohort allocation. Sites will be notified of cohort allocation once results have been received from the Central Laboratory. Whole exome sequencing will also be performed to allow development of a tumour-informed ctDNA assay for assessment in ctDNA at multiple timepoints in both Part 1 and Part 2. Assessment of ctDNA will be performed via batch analysis and per patient test results will not be shared with sites. The tissue samples provided will be stored at the PHOENIX Central Laboratory and may also be used for associated exploratory analyses as per the protocol.

Disease Recurrence

A recurrence tumour tissue sample should be provided for each patient who relapses and has tissue available from a biopsy or from surgery performed routinely as part of standard patient care. The tissue sample should be sent to the central laboratory as soon as it is available.

PART 1 Research Blood Sample Collection

All samples should be labelled with the unique patient Trial ID, initials, date of birth and date of sample collection to enable cross referencing. The **PHOENIX Investigator Laboratory Manual** should be referred to for further instruction regarding packing and shipment of samples.

Research blood samples should be collected as per the schedules shown below:

PART 1 RESEARCH BLOOD SAMPLE COLLECTION (All Cohorts)

Visit	Blood samples
Trial Registration	• **10 ml blood collected for BRCA1/2 mutation analysis**
Pre-Treatment Baseline (Day -1 or 1)	• 20 ml blood collected for ctDNA analysis • 10ml blood collection for RNA analysis • 20ml blood collected for PBMC isolation
Post-Treatment (WOP Day 14)	• 20 ml blood collected for ctDNA analysis • 10ml blood collection for RNA analysis • 20ml blood collected for PBMC isolation
30 Day Post-Surgery Follow-up	• 20 ml blood collected for ctDNA analysis • 10ml blood collection for RNA analysis • 20ml blood collected for PBMC isolation •

PART 1 Blood Sample Collection for PBMC isolation (All cohorts)

Patients at designated recruiting centres will be asked to provide blood for Peripheral Blood Mononuclear Cell (PBMC) isolation. The PBMC sites will be geographically determined in order for the sample to be couriered to the PHOENIX Central laboratory for same day processing. Where possible, blood for PBMC isolation should be collected in the morning to allow for prompt shipment and processing within the required timeframe.

Patients at the designated PBMC sites will have blood samples for PBMC isolation collected pre-treatment on Day -1 or 1 and post-treatment on Day 14 of the WOP and at the 30 Day post-surgery follow up visit as indicated in the above table.

PART 2 SAMPLE COLLECTION

PART 2 Research Blood Sample Collection

All samples should be labelled with the unique patient Trial ID, initials, date of birth and date of sample collection to enable cross referencing. The PHOENIX Investigator Laboratory Manual should be referred to for further instruction regarding packing and shipment of samples.

PART 2 RESEARCH BLOOD SAMPLE COLLECTION

Visit	Blood samples
3 Month Post-Surgery Follow-up	• 20ml blood collected for ctDNA analysis
Patients from Cohorts F & G Commencing Trial Treatment in PART 2:	
Within 3 days prior to Cycle 1 Day 1 Pre-Treatment	• 20ml blood collected for ctDNA analysis
On Treatment Cycle 2 Onwards Day 1 Pre-Treatment (4 weekly)	• 20ml blood collected for ctDNA analysis
Treatment Discontinuation	• 20ml blood collected for ctDNA analysis
12 months Post-Treatment 3-monthly Follow Up (for a total of 24 months from 3 month post-surgery visit)	• 20ml blood collected for ctDNA analysis
Patients from Cohort E (and patients not eligible for trial treatment in Part 2 from Cohorts F & G)	
3-monthly Follow Up for a total of 24 months post-surgery visit	• 20ml blood collected for ctDNA analysis

APPENDIX 3: ECOG PERFORMANCE STATUS

Appendix 3, Table 1. ECOG performance status

Score	Activity performance description
0	Fully active, able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work
2	Ambulatory and capable of all 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; cannot carry on any self-care; totally confined to bed or chair

APPENDIX 4: CREATININE CLEARANCE CALCULATION

Cockcroft & Gault calculation:

Men:

$$\text{Creatinine Clearance (ml/min)} = \frac{(140\text{-age}) \times \text{mass(kg)} \times 1.23}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

Women:

$$\text{Creatinine Clearance (ml/min)} = \frac{(140\text{-age}) \times \text{mass(kg)} \times 1.04}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

APPENDIX 5: OLAPARIB CONCOMITANT TREATMENT CAUTIONS AND RESTRICTIONS

STRONG OR MODERATE CYP3A INHIBITORS

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib. If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration.

Strong CYP3A inhibitors – reduce the dose of olaparib to 100mg BD 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 150mg BD 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.

STRONG OR MODERATE CYP3A INDUCERS

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (e.g. bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib. If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib. If a patient requires use of a strong or moderate CYP3A inducer or inhibitor then they must be monitored carefully for any change in efficacy of olaparib.

P-gp INHIBITORS

It is possible that co-administration of P-gp inhibitors (e.g. amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

EFFECT OF OLAPARIB ON OTHER DRUGS

Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K. Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp.

The efficacy of hormonal contraceptives may be reduced if co administered with olaparib.

Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered. Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin
- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 – lansoprazole, omeprazole, S-mephenytoin
- P-gp – simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 – bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 – serum creatinine
- OAT3 – furosemide, methotrexate

APPENDIX 6: OLAPARIB POTENTIAL DDI WITH ANAESTHETICS

See also "the Flockhart Table": http://medicine.iupui.edu/clinpharm/ddis/main-table/
Olaparib
FROM IB:
4.2.5 Drug interaction potential
Investigations in human in vitro systems indicated metabolism of olaparib was **CYP mediated and that CYP3A4 and 3A5 were the dominant metabolic enzymes.** Similar studies indicated flavin mono-oxygenase-3 was not able to metabolise olaparib.

In in vitro direct inhibition assays, **olaparib (0.1 to 500 µM) was a weak inhibitor of CYP3A** (IC50 119 µM). Olaparib (0.1 to 100 µM) was also tested against CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1. At 100 µM olaparib, no significant direct inhibitory effect on CYPs 1A2, 2A6, 2B6, 2C8, 2D6 or 2E1 was observed although **more limited inhibition of CYP2C9 (22%) and CYP2C19 (26%) was observed**. Regulatory guidance suggested clinically meaningful drug interaction due to olaparib directly inhibiting hepatic and GI tract CYP3A4/5 cannot be excluded.

In time dependant inhibition assays, **olaparib had a minor effect against CYP3A** (Kinact 0.0675 min-1 and KI 72.2 µM) and no effect against other CYPs. Regulatory guidance suggested clinically meaningful time dependent inhibition of hepatic or GI tract CYP3A4/5 is unlikely. The CYP induction potential of olaparib (up to 133 µM) was investigated in cultures of human hepatocytes. Using messenger RNA as a marker of induction potential, **olaparib had a limited effect on CYP1A2, a more notable effect on CYP2B6 and a marked effect on CYP3A4.**

Application of **regulatory guidance suggested a clinical effect on CYPs 1A2, 2B6 and 3A4 in the liver, as well as CYP3A4 in the GI tract**, cannot be excluded.

In vitro investigations indicated that **olaparib (0.243 to 100 µM) was able to inhibit the Phase II metabolism enzyme UGT1A1 (IC50 96.7 µM) but had no appreciable effect against UGT2B7**. Application of regulatory guidance suggested a clinical effect on UGT1A1 in the liver cannot be excluded.

Using isolated human hepatocytes, olaparib was actively transported into the cells and this was probably by organic anion transport proteins. In studies using human embryonic kidney 293 cells transfected with hepatic uptake transporters OATP1B1, OATP1B3 and OCT1, olaparib was shown not to be a substrate of these proteins. In studies using Madin-Darby Canine Kidney (MDCK) II cells transfected with MDR1 (Pgp), BCRP (hepatic and GI tract drug efflux transporters) or MRP-2 (hepatic drug efflux transporter), olaparib was shown to be a substrate of MDR1 but not BCRP or MRP-2.

The possibility that olaparib may be an inhibitor of the hepatic uptake transporters OATP1B1, OATP1B3, OCT1 or NTCP was investigated. **Olaparib was an inhibitor of OATP1B1** and the IC50 (20.3 µM and 27.1 µM) was dependent on the substrate used. **Olaparib was an inhibitor of OCT1** (IC50 37.9 µM), **it caused no significant inhibition of OATP1B3** and was **a very weak inhibitor of NTCP** (IC50 >100 µM). Regulatory criteria indicate **olaparib has the potential to cause clinically significant inhibition of hepatic OATP1B1 and OCT1.**

The capacity for olaparib to inhibit MDR1 (Pgp), BCRP and MRP-2 was investigated. MDR1 and BCRP were expressed in MDCKII cells while MRP-2 was prepared in isolated membrane vesicles. **Olaparib was shown to inhibit MDR1 (IC50 76.0 µM) and very weakly inhibit BCRP. Olaparib did not inhibit MRP-2**. Regulatory criteria indicate olaparib has the potential to cause clinically significant inhibition of biliary and GI tract MDR1.

These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal (GI) tract. **Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (eg, irinotecan, nintedanib, ezetimibe, raltegravir and buprenorphine).**

The likelihood that olaparib would inhibit the renal uptake and efflux transporters OCT2, OAT1, OAT3, MATE1 and MATE2K was investigated. **Olaparib was able to inhibit OCT2 (IC50 19.9 µM), OAT3 (IC50 18.4 µM), MATE1 (IC50 5.50 µM) and MATE2K (IC50 47.1 µM). Olaparib had no significant effect on OAT1.** Regulatory criteria indicate olaparib has the potential to cause clinically significant inhibition of renal OCT2, OAT3, MATE1 and MATE2K.

Table 2: Commonly used drugs used during anaesthesia (pre-operative, during surgery and post-operative)

Drug	**Indication**	**Metabolic Summary**	**AZ opinion on likelihood of clinically important interaction with Olaparib**	**Interaction Summary**
Cyclizine	Anti-emetic	Limited information is available on metabolism and excretion. Drug not recommended for patients with liver failure. Drug interactions identified with cyclizine are mainly pharmacodynamic in nature. Listed as a substrate of CYP2D6 which shows a 33% increase in concentration in poor metabolisers compared to extensive CYP2D6 metabolisers. No treatment restrictions based on the CYP2D6 phenotype of patients identified.	Low	
Dexamethasone	Anti-emetic (steroid)	Dexamethasone is a moderate inducer of CYP3A4 and is sensitive to strong inhibitors of CYP3A4. P-glycoprotein inducer	Moderate	Dexamethasone may induce metabolism of Olaparib. Olaparib is a weak inhibitor of CYP3A4 and may inhibit dexamethasone metabolism.

				Olaparib is a P-glycoprotein inhibitor
Granisetron	Anti-emetic (5-HT3 antagonist)	Not identified as a sensitive CYP3A4 or 2D6 substrate. However, no interaction studies have been performed	Low	
Ondansetron	Anti-emetic (5-HT3 antagonist)	CYP3A4 and 2D6 substrate – inhibitors known to reduce clearance of ondansetron	Moderate	Olaparib is a weak inhibitor of CYP3A4
cefuroxime	Anti-infective	These anti-infective agents are primarily cleared by excretion of unchanged drug in urine. At this time no likelihood of interactions has been identified	Low	
Co-amoxiclav	Anti-infective		Low	
flucloxacillin	Anti-infective		Low	
gentamycin	Anti-infective		Low	
teicoplanin	Anti-infective		Low	
vancomycin	Anti-infective		Low	
erythromycin	Anti-infective	Has the potential for interaction as it is an inhibitor of CYP3A4 and also a substrate of CYP3A4 affected by strong inhibitors. Inhibits OATP1B1 Inhibits P-glycoprotein	Moderate	Erythromycin may inhibit Olaparib metabolism Olaparib may inhibit erythromycin metabolism Olaparib inhibits OATP1B1 Olaparib is a P-glycoprotein substrate and inhibitor Current studies recommend combined use with caution
propofol	Induction agent	PK does not appear to be affected by renal and hepatic impairment – no potential for interaction identified.	Low	
atracurium	NMJ block	Metabolised by non-specific plasma cholinesterases and chemical instability (Hofmann elimination) – no potential for interaction identified.	Low	
suxamethonium	NMJ block	Metabolised by plasma cholinesterases – no potential for interaction identified.	Low	

rocuronium	NMJ block	Hepatic clearance. Uncertain Which cytochrome P450's (CYPs) are involved.	Moderate	Uncertain – avoid if possible
vecuronium	NMJ block	Longer recovery times in patients with hepatic impairment. Uncertain routes of metabolism.	Moderate	Uncertain – avoid if possible
neostigmine	NMJ block reversal	Renal clearance unchanged drug and hepatic metabolism; cholinesterases – no potential for interaction identified.	Low	
isoflurane	Maintenance agent	CYP2E1 metabolism	Low	
sevoflurane	Maintenance agent	CYP2E1 metabolism	Low	
bupivacaine	Local nerve block	Primarily metabolised by hepatic glucuronidation	Low	Olaparib may inhibit UGT1A1 but this is unlikely to have an effect on bupivacaine
Ketamine	Induction and Maintenance agent	CYP3A4, CYP2B6 and CYP2C9 metabolism OCT3 substrate	Moderate	Olaparib is a CYP3A4 inhibitor
alfentanil	Analgesia	CYP3A4 and CYP3A5 metabolism	Moderate	Olaparib is a CYP3A4 inhibitor
Codeine	Analgesic	Not identified as a sensitive CYP3A4 substrate. Label states that caution is required with inhibitors of CYP3A4 and 2D6 as they may produce altered responses. The results will be 'opposite' as CYP3A4 inhibition will reduce metabolism to an inactive Ndemethylation metabolite, whereas CYP2D6 inhibition will reduce metabolism to the active O-demethyl metabolite.	Moderate	Olaparib is a CYP3A4 inhibitor
dyhydrocodeine	Analgesic	Metabolised through CYP2D6 to dihydromorphine and morphine. Inhibition of CYP2D6 not identified as likely to cause drug-drug interaction.	Low	
fentanyl	Analgesia	Boxed warning – use with CYP3A4 inhibitors may cause fatal respiratory depression	Moderate	Olaparib is a CYP3A4 inhibitor
Morphine	Analgesia	Glucuronication P-glycoprotein substrate	Moderate	Olaparib may inhibit UGT1A1 but this is unlikely to

				have an effect on morphine Olaparib is a P-Glycoprotein substrate and inhibitor
NSAIDs, (ibuprofen, diclofenac, celecoxib, parecoxib) analgesic	Analgesia	Metabolised to some extent by CYP2C9. None identified as a sensitive CYP3A4 or 2D6 substrate.	Moderate	Olaparib is a limited CYP2C9 inhibitor (22%)
Oxycodone	Analgesia	Not identified as a sensitive CYP3A4 or 2D6 substrate. Metabolised by CYP3A4 and CYP2D6, but inhibitors of CYP3A4 or CYP2D6 are not considered to be of clinical significance	Low	Olaparib is a CYP3A4 inhibitor
paracetamol	Analgesia	Main metabolism by conjugation formation of the hepatotoxic NAPQI metabolite to some extent involves CYP2D6 metabolism (theoretically CYP2D6 inhibition would reduce production of this metabolite)	Low	
Pethidine	Analgesia	Not identified as a sensitive CYP3A4 substrate. Label states use with caution with strong 3A4 inhibitors.	Moderate	Olaparib is a CYP3A4 inhibitor
Remifentanil	Analgesia	Cleared by esterase activity in blood – PK unaffected by renal / hepatic impairment – no likelihood of interaction identified	Low	
tramadol	Analgesia	30% of dose excreted unchanged in urine. 60% metabolised mainly through CYP3A4 and 2D6.	Low	Olaparib is a CYP3A4 inhibitor

APPENDIX 7: Durvalumab Dosing Modification and Toxicity Management Guidelines

Toxicity Management Guidelines (TMGs)

Drug Substance	Durvalumab and Tremelimumab
TMG Version	06 August 2024

ANNEX TO PROTOCOL

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

Note: Annex is to be used in any clinical trial protocol within which patients are treated with Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

VERSION HISTORY

August 2024

The Toxicity Management Guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either durvalumab or tremelimumab or a combination of these two immune checkpoint inhibitors (ICI) is used in combination with other anti-cancer drugs (e.g., antineoplastic chemotherapy, targeted agents). These other anticancer drugs can be 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 monotherapy or combination ICI regimens, with specific instructions for ICI dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

Dosing modification and toxicity management for immune-mediated, infusion-related, and non-immune–mediated reactions associated with the use of a checkpoint inhibitor or checkpoint inhibitors in clinical study protocol (CSP) – whether that is durvalumab alone, tremelimumab alone, or durvalumab + tremelimumab in combination, or durvalumab +/- tremelimumab in combination with other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially – should therefore be performed in accordance with this Annex to CSP, which for the purposes of submission and approval of substantial updates is maintained as a standalone document. TMG updates are iterated by date, and should be used in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version specified in the CSP.

Although the TMG versioning is independent of the protocol, the TMG Annex to Protocol should be read in conjunction with the Clinical Study Protocol, where if applicable additional references for the management of toxicities observed with other anti-cancer treatment are included in the specific section of the Clinical Study Protocol.

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy –August 2024

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.

Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressivetreatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and re levant guidelines. With long-term steroid and other immunosuppressive use, consider the need for glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

Considerations for Prophylaxis for Long Term use of Steroids for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

- **Infection Prophylaxis: Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation**
- **Gastritis: Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid therapy**
- **Osteoporosis: Consider measures for prevention and mitigation of osteoporosis .**

Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Please note, these were the current versions of these guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines.

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021, version 1.2;9:e002435
2. Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology (ASCO) Guideline Update. J Clin Oncol 2021;39(36):4073-4126.
3. Haanen J, et al. Management of toxicities from immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guideline for diagnosis, treatment, and follow-up. Annals Oncol 2022;33(12):1217-1238.
4. Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72(2):320-341.
5. Thompson JA, et al. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 1.2024. Published December 7, 2023.

4.

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.	− All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. − The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. − The recommendations for intravenous immunoglobulin (IVIG) and plasmapheresis use provided for adult patients may be considered for pediatric patients. − The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. − For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist. − With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definingthe CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g. infection, progressive disease). − Monitor patients for signs (e.g. tachypnoea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. − Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as described below. − Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up (including clinically relevant culture specimens to rule out infection), and high- resolution computed tomography (CT) scan. − Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** − Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.	**For Grade 2** − Monitor symptoms daily and

		If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper (≤10 mg prednisone or equivalent).	consider hospitalization, as clinically indicated. − Consider Pulmonary and Infectious Diseases Consults; − Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). Consider HRCT or chest CT with contrast, Repeat imaging study as clinically indicated − If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. − If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy. such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Consider discussing with Clinical Study Lead.

	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Hospitalize the patient – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treatingprovider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression,

	study protocol for defining the CTCAE grade/severity)		other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Consider further evaluation with imaging study with contrast. – Consult a gastrointestinal (GI) specialist for consideration of further workup. – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolytereplacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin and/or calprotectin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.

	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 – If toxicity improves to Grade ≤1, then study drug/study regimen can be	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes

		resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	(e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Consider further evaluation with imaging study with contrast. – Consider consult of a gastrointestinal (GI) specialist for consideration of further workup. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 days despite therapy with 1 to 2 mg/kg IV methylprednisolone, reconsult GI specialist and, if indicated, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.** – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** – For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (≤10 mg prednisone per day, or equivalent). – For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study	**For Grade 3 or 4** – Urgent GI consult and imaging and/or colonoscopy as appropriate. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

		investigator, in discussion with AstraZeneca Clinical Study Lead. **<u>For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy:</u>** **<u>A.</u> <u>Permanently discontinue tremelimumab for Grade 3 diarrhea/colitis. HOLD durvalumab until resolution to Grade ≤ 1; durvalumab alone can be resumed after completion of steroid taper (<10 mg prednisone per day or equivalent)</u>** **<u>B.</u> Permanently discontinue both durvalumab and tremelimumab for 1) Grade 4 diarrhea/colitis or 2) Any grade of intestinal perforation** **Grade 4** Permanently discontinue study drug/study regimen.	– **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis ***Infliximab should not be used for management of immune-related hepatitis.*** **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin .
	ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN	– No dose modifications. – If it worsens, then consider holding therapy.	– Continue transaminase andtotalbilirubin monitoring per protocol.

CON TMGs		12 (36)

(HCC) patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])	ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN	– Hold study drug/study regimen dose until ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent). – Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT >3 × ULN AND	– Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve. - Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis) – If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed.

		bilirubin ≥2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	– If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	ALT or AST > 5- ≤ 10 x ULN	– Hold study drug/study regimen. Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN after completion of steroid taper (<10 mg prednisone, or equivalent). – **If in combination with tremelimumab, do not restart tremelimumab.**	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. - Check CPK and aldolase (to rule out myositis) – Perform Hepatology Consult, abdominal workup, and imaging as appropriate. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN	Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Hepatitis **(elevated transaminases and total bilirubin)** ***Infliximab should not be used for*** ***management of immune-related hepatitis.***	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate AST, ALT, ALP, and T. Bili.

			– For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg).

THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])			– For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.
See instructions at bottom of shadedarea if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	Isolated AST or ALT >ULN and ≤2.5×BLV,	– No dose modifications. – If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. – For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	ALT or AST > 2.5- ≤ 5X BLV and ≤ 20xULN	– Hold study drug/study regimen dose until resolution to AST or ALT ≤2.5×BLV . – If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤2.5×BLV , resume	– Regular and frequent checking of Transaminases and total bilirubin (e.g., every 1 to 3 days) until elevations of these are improving or resolved. - Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis) – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead.

	study drug/study regimen after completion	

	of steroid taper (<10 mg prednisone, or equivalent).	– If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULN	- Withhold durvalumab and permanently discontinue tremelimumab – Resume study drug/study regimen if elevations downgrade to AST or ALT ≤2.5×BLV and after completion of steroid taper (<10 mg prednisone, or equivalent). – Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤2.5×BLV within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. - Check CPK and aldolase (to rule out myositis) – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Study Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used.**

	ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue study drug/study regimen.	**Same as above (except recommend obtaining liver biopsy early)**
Nephritis and/or renal dysfunction	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider Consulting a nephrologist. – Consider imaging studies to rule out any alternative etiology – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). Follow urine protein/creatinine ratio every 3-7 days
	Grade 1	No dose modifications.	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. – Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion	**For Grade 2** – Consider including hydration, electrolyte replacement, and diuretics as clinically indicated – Follow urine protein/creatinine ratio every 3-7 days – Carefully monitor serum creatinine as clinically warranted.

		of steroid taper (<10 mg prednisone, or equivalent).	– Consult nephrologist and consider renal biopsy if clinically indicated. – Start prednisone 1 to 2 mg/kg/day if other causes are ruled out – If event is persistent beyond 5 days or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – Follow urine protein/creatinine ratio every 3-7 days – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days of steroids or worsens despite prednisoneat 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant
Dermatologic Adverse Events (Including Pemphigoid)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). **HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)[1] IS SUSPECTED.**

			– **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPIGOID IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** – Consider dermatology consult and skin biopsy, as indicated. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3	**For Grade 3** – Hold study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. – Consider, as necessary, discussing with Clinical Study Lead.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 4** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.

			– Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Consider consulting an endocrinologist for endocrine events. – Consider discussing with Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)). If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibodytesting. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoringand treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide

			assessment of early morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropinstimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	– For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>, consider holding study drug/study regimen dose until acute symptoms resolve. – Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. – **Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.** – **Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.</u>** – For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression,

	study protocol for defining the CTCAE grade/severity)		viral infection, concomitant medications, substance abuse). − For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. − Assess for signs/symptoms of pancreatitis − Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) − If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase − If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology. − Consider Gastroenterology referral
	Grade 2	**Consider holding study drug/regimen**	**Grade 2** − Consider IV hydration − Consider Gastroenterology referral

	Grade 3, or 4	**For Grade 3** Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Nervous System Disorders			
Aseptic Meningitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis. – Patients may be febrile. – Mental status should be normal	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) - Consider antibiotic for bacterial coverage until cultures/panel results are back – Consider IV acyclovir until polymerase chain reactions are available
	Any Grade	Permanently discontinue study drug/study regimen	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available – Consider, as necessary, discussing with Clinical Study Lead.

			– Consider hospitalization.

			– Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.
Encephalitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. –	**For Any Grade** – Consider neurology consult – Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. – Exclude bacterial and viral infections. (i.e. HSV)Consider IV acyclovir until polymerase chain reactions are available. – Add bacterial coverage
	Grade 2	**For Grade 2** Permanently discontinue study drug/study regimen.	**For Grade 2** – Consider, as necessary, discussing with the Clinical Study Lead. – Once infection has been ruled out methylprednisolone 1–2 mg/kg/day – For progressive symptoms or if oligoclonal bands are present consider methylprednisolone 1 g IV daily for 3–5 days plus IVIG or plasmapheresis
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with Clinical Study Lead. – Consider hospitalization. – Once infection is ruled out, start methylprednisolone 1 g IV daily for 3–5 days for progressive symptoms consider adding IVIG or plasmapheresis

Demyelinating Disease (optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis (ADEM))	**Any Grade**	**General Guidance** – Permanently discontinue immunotherapy – Consider MRI of the spine and brain	**For Any Grade** – Consider neurology consult – Inpatient care – Consider prompt initiation of high methylprednisolone pulse dosing – Strongly consider IVIG or plasmapheresis

		– Once imaging is complete, consider lumbar puncture Consider testing to rule out additional aetiologies: B12, copper, HIV, rapid plasma reagin (RPR), ANA, anti- Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel	
Peripheral neuropathy	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology for neuropathy (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
	Grade 1	No dose modifications.	**For Grade 1** – Consider discussingwith the Clinical Study Lead, as needed. – Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2** – Consult a neurologist. – Consider EMG/NCS

			– Consider discussing with the Clinical Study Lead, as needed. – Observation for additional symptoms or consider initiating prednisone 0.5–1 mg/kg orally – If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider discussing with Clinical Study Lead, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. – **Treat per Guillain-Barré Syndrome recommendations**
Guillain-Barré Syndrome (GBS)		General Guidance	– Recommend hospitalization – Obtain neurology consult – Obtain MRI of spine to rule out compression lesion – Obtain lumbar puncture – Antibody tests for GBS variants – Pulmonary function tests – Obtain electromyography (EMG) and nerve conduction studies – Frequently monitor pulmonaryfunction tests and neurologic evaluations – Monitor for concurrent autonomic dysfunction – Initiate medication as needed for neuropathic pain
	Grade 2-4	Grade 2-4 Permanently discontinue	**Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis		General Guidance	– Obtain neurology consult – Recommend hospitalization – Obtain pulmonary function tests

			− Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies − Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis − Obtain electromyography (EMG) and nerve conduction studies − Consider MRI of brain/spine to rule out CNS involvement by disease − Avoid medications that might exacerbate MG (e.g. beta blockers, some antibiotics, IV magnesium)
	Grade 2	Permanently discontinue	− Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily) − Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)
	Grade 3-4	Permanently discontinue	− Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement − Start plasmapheresis or IVIG − Consider rituximab if refractory to plasmapheresis or IVIG − Frequent PFT assessments − Daily neurologic evaluations
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** − Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with

			baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
	Grade 2, 3 or 4	– If Grade 2-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Consider cardiology consultation and a prompt start of high-dose/pulse corticosteroid therapy – Supportive care (e.g., oxygen). – If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant r or relevant practice guidelines. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

	defining the CTCAE grade/severity)		– Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, and; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the Clinical Study Lead. - **Consider that patients may present with or progress to rhabdomyolysis. Treat signs and symptoms as per institutional protocol or local clinical practice.** – Initial work-up should include clinical evaluation, **creatine kinase, aldolase**, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.

Grade 1	– No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult.

		– Consider, as necessary, discussing with the Clinical Study Lead.
Grade 2	– Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Consider Rheumatology or Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 days, consider additional – immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3	**For Grade 3** – Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30	**For Grade 3** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussingwith the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant.

		days or if there are signs of respiratory insufficiency.	– If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**Grade 4** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussingwith the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

[1] SCAR terms include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Drug-induced hypersensitivity syndrome.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	– Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. – Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).
Grade 3	Hold study drug/study regimen until resolution to Grade ≤1 or baseline	
Grade 4	Permanently discontinue study drug/study regimen	

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushingand/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** − The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. − Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedicationper institutional standard or study protocol prior to subsequent doses. − Consider steroids for patients who have previously experienced infusion reaction; use of steroid premedication may be permitted in these situations
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** − Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines, and society guidelines.

Non-Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2-3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

List of Abbreviations

AChE	Acetylcholinesterase	ILD	Interstitial lung disease
ACTH	Adrenocorticotropic hormone	imAE(s)	Immune-mediated adverse event(s)
ALT	Alanine aminotransferase	INR	International normalized ratio
ASCO	American Society of Clinical Oncology	IU	International units
AST	Aspartate aminotransferase	IV	Intravenous
(T) Bili	(Total) Bilirubin	IVIG	Intravenous immunoglobulin
BNP	B-type natriuretic peptide	LDH	Lactate dehydrogenase
BUN	Blood urea nitrogen	LFTs	Liver function tests
CRP	C-reactive protein	LLN	Lower limit of normal
CSP	Clinical Study Protocol	MRCP	Magnetic resonance cholangiopancreatography
CT	Computed tomography	MRI	Magnetic resonance imaging
CTCAE	Common Terminology Criteria for Adverse Events	NCCN	National Comprehensive Cancer Network
CTLA-4	Cytotoxic T-lymphocyte antigen-4	NCI	National Cancer Institute
DILI	Drug-induced liver injury	PD-L1	Programmed cell death ligand-1
ECG	Electrocardiogram	PJP	Pneumocystis jirovecii pneumonia
ECHO	Echocardiogram	PO	By mouth
ESMO	European Society of Medical Oncology	SCAR	Severe cutaneous adverse reaction
GI	Gastrointestinal	SITC	Society for Immunotherapy of Cancer
HBcAb	Hepatitis B core antibody	SJS	Stephen Johnson Syndrome
HBeAg	Hepatitis B envelope antigen	T1DM	Type 1 diabetes mellitus
HBsAg	Hepatitis B surface antigen	T3	Triiodothyronine
HBV	Hepatitis B virus	T4	Thyroxine
HCC	Hepatocellular cancer	TEN	Toxic Epidermal Necrolysis
HCV	Hepatitis C virus	TMG(s)	Toxicity management guideline(s)
HgA1c	Hemoglobin A1C	TSH	Thyroid stimulating hormone
ICI(s)	Immune checkpoint inhibitor(s)	ULN	Upper limit of normal

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