PHOENIX

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ICR The Institute of Cancer Research

CANCER RESEARCH UK

Trial Organisation

Sponsor: The Institute of Cancer Research

Funder: AstraZeneca (with Cancer Research UK endorsement)

Chief Investigator: Professor Andrew Tutt

Coordinating Investigator & Translational Research Group Chair: Dr Sheeba Irshad

Scientific Lead: Professor Judith Bliss

Trial Biomarker Bioinformatics Lead: Dr Maggie Cheang

Clinical Trial Programme Manager: Michelle Frost

Trial Manager: Hannah Johnson

Statistician: Holly Tovey

Data Managers: Katy Jarman & Solomon Brown

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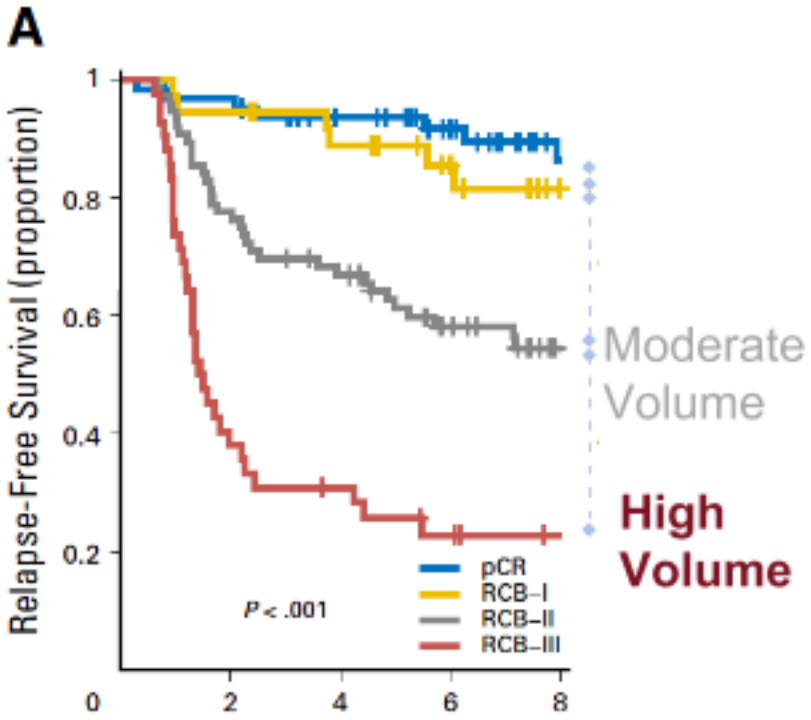
PHOENIX DDR/Anti-PD-L1 Trial:

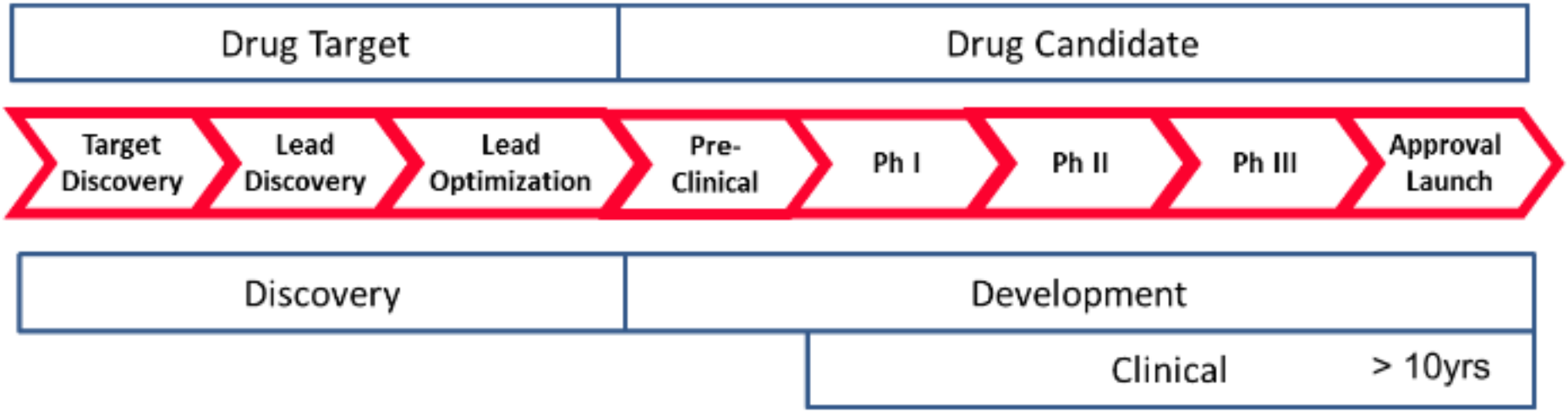
A pre-surgical **window of opportunity** and post-surgical adjuvant biomarker study of DNA damage response inhibition and/or anti-PD-L1 immunotherapy **in patients with neoadjuvant chemotherapy resistant residual triple negative breast cancer**

Triple Negative Breast Cancer – An important clinical challenge



- TNBC accounts for approx. **10-15%** of all breast cancer diagnoses
- TNBC **relapse rate is high** with peak recurrence rate 3 years post-surgery
- Patients with **moderate residual cancer burden** (RCB)-II or extensive RCB-III sufferer much **poorer outcome**
- TNBC population at high risk of relapse remain of **clinical interest** and **unmet need**

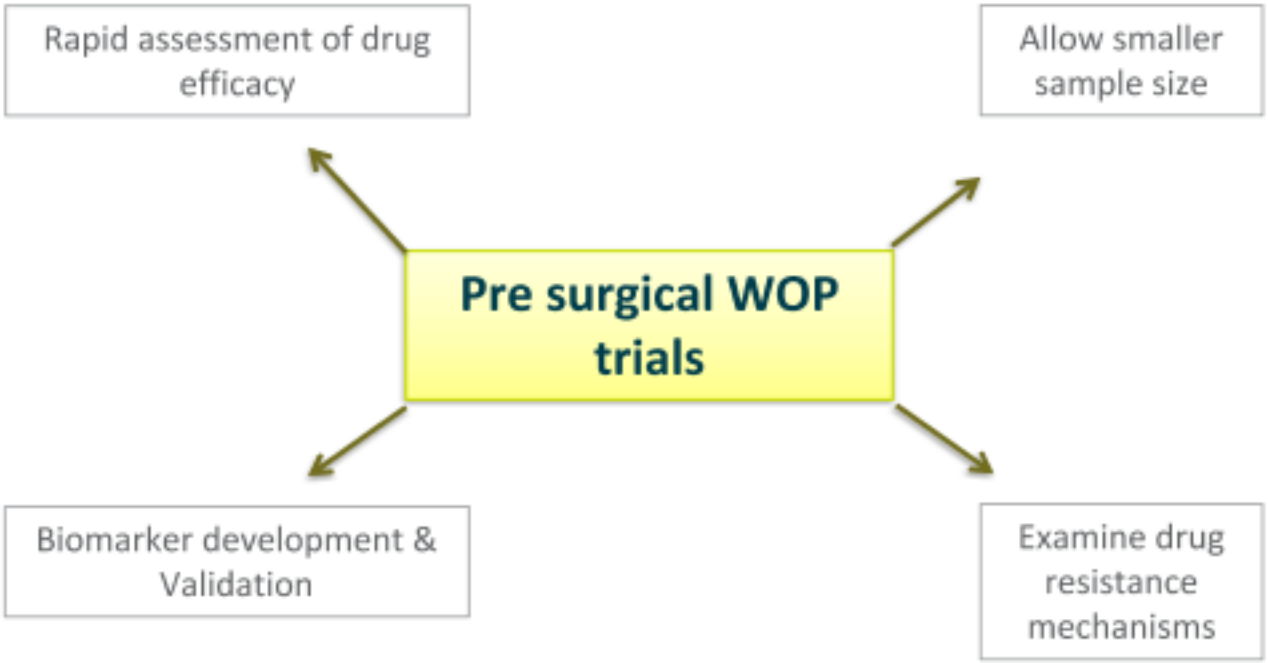
Drug Development Pipeline



- *Slow, expensive, significant patient resource*

Utilising the “window of opportunity” trial design

WOP trials – i.e. pre-surgical trials provide a platform to understand and overcome drug resistance

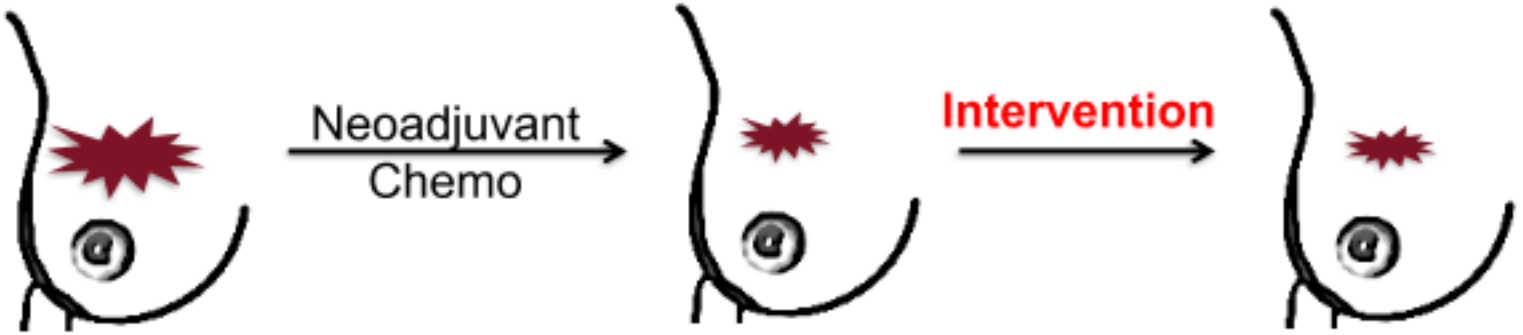


Pre-surgical Window of Opportunity trials

Surgery

UK experience in delivering Window Trials within pre-surgical patient pathway

Improve Patient Selection – a Post Neo-adjuvant Umbrella Trial Platform



Surgery

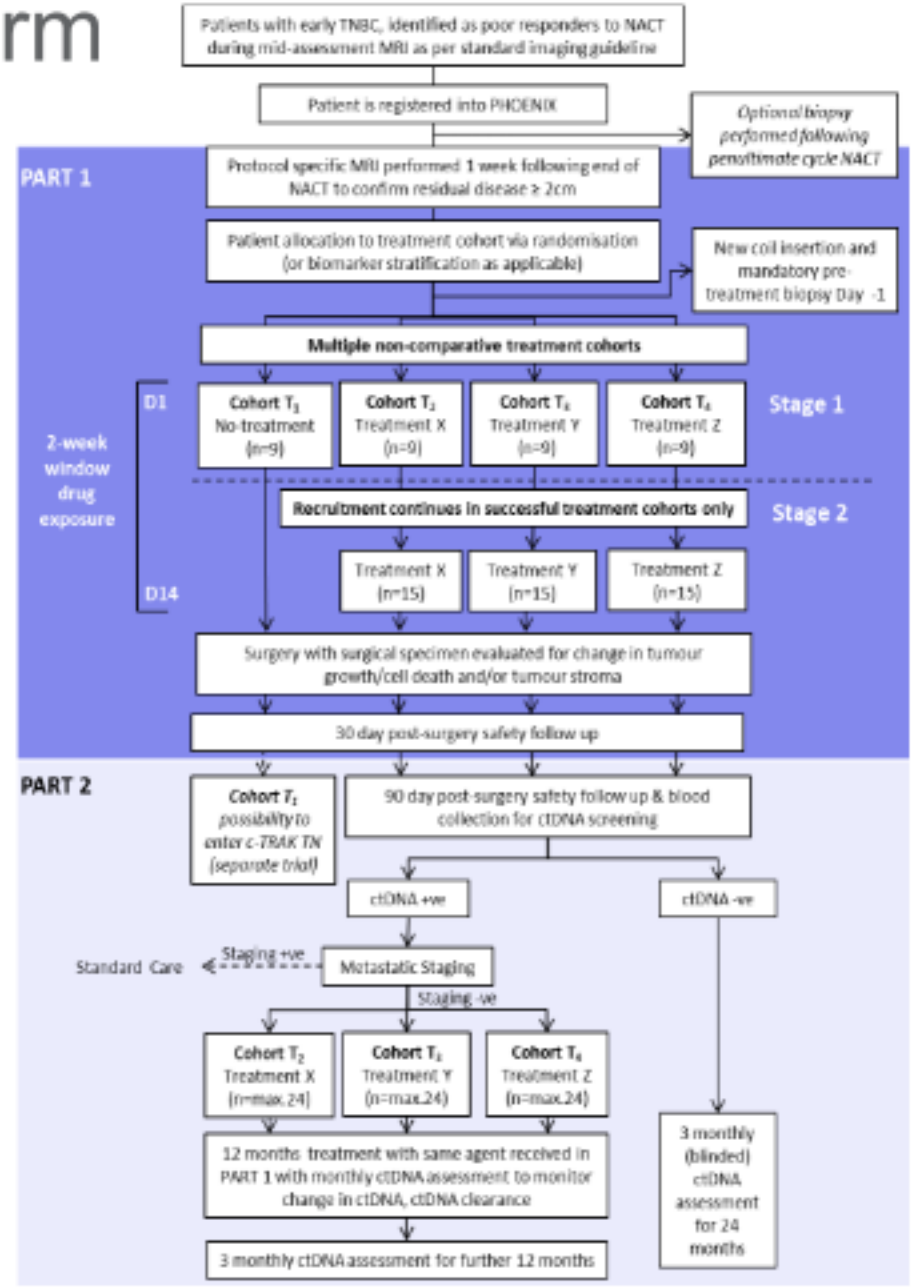
PHOENIX WOP is a 2 week window starting at least 3 weeks after the first day of final cycle of NACT, and 2 weeks before planned surgery

PHOENIX Trial Platform

Patient population: early TNBC, poor responders to NACT with significant viable residual disease, as defined by MRI imaging, and for whom definitive complete surgical excision of disease is planned

PART 1: Post-NACT pre-surgical disease WOP profiling and novel therapy biomarker endpoint study in biologically assessable NACT resistant residual primary tumour

PART 2: Post-operative exploratory micrometastatic disease biological response signal-finding study in patients who are at high risk of developing clinical metastatic disease



Trial Objectives

PRIMARY OBJECTIVE

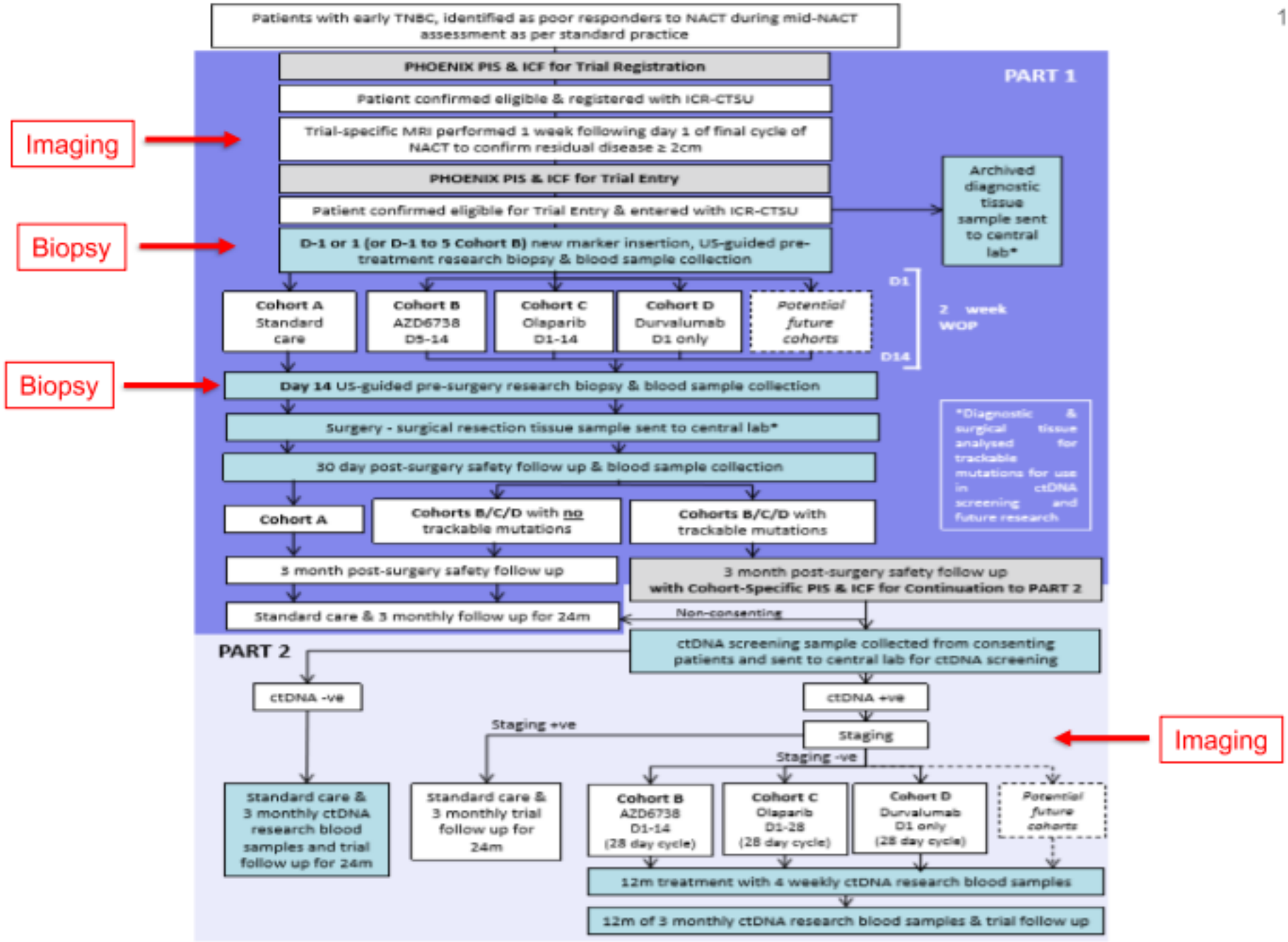
To assess whether **short exposure to a DDR inhibitor and/or anti-PD-L1 immunotherapy** in a pre-op WOP in patients with post-NACT high risk residual disease, **generates a signal of anti-tumour biological activity** within residual disease tissue.

SECONDARY OBJECTIVES

- To characterise the **safety** of designated IMPs in a WOP trial context
- To **examine biomarkers** of cancer or stroma pathway reprogramming/ signalling following trial treatment.

EXPLORATORY OBJECTIVES

- To examine the overall effect on the growth index (calculated as Ki67/ apoptosis %) of the residual tumour.
- Explore within patient associations between responses seen in PART 1 and changes in circulating tumour DNA (ctDNA) in PART 2.
- Explore associations between ctDNA detection and disease related outcomes in PART 2.


Patients with early TNBC, identified as poor responders to NACT during mid-NACT assessment as per standard practice
PART 1
PHOENIX PIS & ICF for Trial Registration
Patient confirmed eligible & registered with ICR-CTSU
Imaging
Trial-specific MRI performed 1 week following day 1 of final cycle of NACT to confirm residual disease ≥ 2cm
PHOENIX PIS & ICF for Trial Entry
Patient confirmed eligible for Trial Entry & entered with ICR-CTSU
Archived diagnostic tissue sample sent to central lab*
Biopsy
D-1 or 1 (or D-1 to 5 Cohort B) new marker insertion, US-guided pre-treatment research biopsy & blood sample collection
D1
2 week WOP
D14
Cohort A Standard care
Cohort B AZD6738 D5-14
Cohort C Olaparib D1-14
Cohort D Durvalumab D1 only
Potential future cohorts
Biopsy
Day 14 US-guided pre-surgery research biopsy & blood sample collection
*Diagnostic & surgical tissue analysed for trackable mutations for use in ctDNA screening and future research
Surgery - surgical resection tissue sample sent to central lab*
30 day post-surgery safety follow up & blood sample collection
Cohort A
Cohorts B/C/D with no trackable mutations
Cohorts B/C/D with trackable mutations
3 month post-surgery safety follow up
3 month post-surgery safety follow up with Cohort-Specific PIS & ICF for Continuation to PART 2
Standard care & 3 monthly follow up for 24m
Non-consenting
PART 2
ctDNA screening sample collected from consenting patients and sent to central lab for ctDNA screening
ctDNA -ve
ctDNA +ve
Staging +ve
Staging
Staging -ve
Imaging
standard care & 3 monthly ctDNA research blood samples and trial follow up for 24m
standard care & 3 monthly trial follow up for 24m
Cohort B AZD6738 D1-14 (28 day cycle)
Cohort C Olaparib D1-28 (28 day cycle)
Cohort D Durvalumab D1 only (28 day cycle)
Potential future cohorts
12m treatment with 4 weekly ctDNA research blood samples
12m of 3 monthly ctDNA research blood samples & trial follow up

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Radiology Procedures

Research biopsies as a trial endpoint

- PHOENIX research biopsies will be used to assess the **PRIMARY ENDPOINT**
- **High quality biopsy samples are essential**
- Radio-opaque marker must be placed in residual tumour bed so that the **most active, viable** and **non-necrotic part of the tumour** is biopsied
- The person taking the biopsies should be appropriately qualified/experienced to ensure high quality samples.
- Each participating site has a **named** PHOENIX radiology lead
- Steering Group Committee members have representation from radiology
- Individual(s) responsible for collection of biopsy samples should be recorded on PHOENIX **delegation log** (held by the main site contact).

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RADIOLOGY GUIDANCE MANUAL

EudraCT Number:	2018-002077-21
IRAS Project ID:	249774
ICR-CTSU Protocol Number:	ICR-CTSU/2017/10065
Sponsor Number:	CCR4706

- This document must be kept within the Site Investigator File
- Updates will be sent to sites from ICR-CTSU periodically
- Please keep a copy of previous versions on file

Radiology Guidance Document:	Version 1.0
Effective Date:	XX/XXX/2019
Supersedes:	N/A

Contents

Developed with **Prof Iain Lyburn**

Scanning Requirements

PART 1

- Dynamic contrast enhanced MRI **to confirm eligibility for trial entry** (at least **1 week following day 1 of final NACT cycle)** viable residual disease must be ≥ 2cm

Scanning Requirements

PART 2

Following a **positive ctDNA** screening result and prior to commencing PART 2 treatment

- **Staging scans** to confirm **no evidence of macroscopic disease** (same imaging modality as used for diagnosis)

Research Core Biopsies - *imaging and biopsy guidance available*

WOP **Baseline** (pre-treatment) (WOP Day -1 or 1, or WOP Day -1 to 5 for cohort B)

WOP **Day 14** (post-treatment) (WOP Day 14 only)

Four cores should be obtained at each visit with a **14G core biopsy needle**

- **Three** cores for formalin fixation and standard paraffin embedding at site
- **One** core in RNAlater solution

If four cores cannot be collected, please prioritise:

- If only **one** core - should be FFPE
- If only **two** cores - one FFPE one RNAlater
- If only **three** cores - two FFPE one RNAlater

Research Core Biopsies - *imaging and biopsy guidance available*

Ultrasound guided biopsies of residual tumour with new distinct radio-opaque marker insertion

Baseline WOP (pre-treatment) new marker insertion

A new radio-opaque marker should be inserted into the residual tumour identified on the trial MRI scan performed on completion of NACT. It is important that this marker is placed in the residual tumour bed so that the most active, viable and non-necrotic part of the tumour can be referenced from the coil for biopsy collection. It is anticipated that in most cases a new marker will need to be inserted to maximise sampling of viable tumour and re-sampling on D14 WOP. However in some cases the marker placed prior to NACT may be in the optimal position for sampling viable tissue meaning that a new marker insertion may not be required, although this should be verified by ultrasound. In all cases the location of the biopsies taken in reference to this marker should be noted.

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Post-treatment WOP biopsy

The post window of opportunity biopsies should be undertaken utilising the same technique. As much as is possible, these biopsies should be taken from similar locations noted for the pre-treatment biopsies.

In case of multifocal tumour, biopsies should be taken from one lesion; the post-treatment research biopsy should be performed in the same site.

Research Core Biopsies cont.

In exceptional cases, where biopsy collection on Day 14 is not possible, biopsy cores can be taken by the surgeon intraoperatively at time of surgery

If taken intraoperatively:

- Ensure cores placed in formalin or RNA **within 30 minutes of biopsy collection**
- **Time taken** to collect the biopsy from surgically resected tissue should be minimised and **recorded**

Please refer to radiology guidance for more info

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Questions?