The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL

PROJECT DETAILS	
Project Title:	Identification of biomarkers to predict response for emerging therapeutic agents for triple negative breast cancer
Short Project Title:	Identification of response biomarkers for emerging therapeutic agents

SUPERVISORY TEAM	
Primary Supervisor(s):	Dr Maggie Chon U Cheang
Other supervisory team members:	Professor Andrew Tutt Professor Judith Bliss

DIVISIONAL AFFILIATION	
Primary Division:	Clinical Studies
Primary Team:	Genomics Analysis –Clinical Trial
Other Division:	Breast Cancer Division

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

Lacking effective targeted therapies, patients with triple negative breast cancer (TNBC) have relatively poorer prognosis with higher likelihood of distant recurrence within 5 years of diagnosis. Approximately 34% of TNBC achieve a pathological complete response (pCR) to surgery after the use of neoadjuvant (i.e. prior surgery) multi-agent chemotherapy, and are associated with improved outcomes. The poor prognosis of TNBC is, therefore, derived largely from the fraction of patients with significant residual disease in the breast after neoadjuvant chemotherapy (NACT).

There is a range of emerging therapeutic options for advanced TNBC recurring after anthracycline and taxane therapy, including carboplatin, cisplatin and eribulin and novel therapies such as, immunotherapy, Poly(ADP-ribose) polymerases (PARP) inhibitors and other DNA damage response inhibitors with varying levels of efficacy. Platinum-based chemotherapy is a common treatment option for patients with metastatic TNBC (mTNBC). Studies had shown that patients who have inherited breast cancer with germline *BRCA1/2* mutations, they may actually do better longer with platinum drugs first. Results from our TNT trial (a randomized Phase III trial of carboplatin compared to docetaxel for patients with metastatic or recurrent locally advanced ER–, PR– and HER2– breast cancer) have also suggested that mTNBC with *BRCA1/2* mutation may have greater benefit from carboplatin than standard of care. On the other hand, the OlympiAD (Phase III) trial showed that olaparib, one kind of PARP inhibitor, delayed progression of HER2-negative *BRCA*-mutation advanced breast cancer, compared to chemotherapy.

PROJECT AIMS

AIM#1. To determine the expression patterns of the transcriptional signatures of BRCAness and DNA-repair deficiency in metastatic triple negative breast cancer

AIM#2. To evaluate the ability of the transcriptional signatures of BRCAness and DNA-repair deficiency to predict objective tumour response for carboplatin in triple negative breast cancer at metastatic setting (TNT Trial).

AIM#3. To identify transcriptional biomarkers associated with defects in *BRCA1* or *BRCA2* and other genes involved in hormologous recombination repair (TNT Trial).

AIM#4. To identify changes in expression of the transcriptional aberrant signatures between treatment naïve disease and post neoadjuvant chemotherapy, in relation to Day 0 to Day 14 response to treatment of olaparib in patients with chemotherapy resistant TNBC with aim to engage investigators to examine their relation to therapy response to platinum and emerging data on PARPi in neoadjuvant therapy studies (PHOENIX).

AIM#5. To evaluate the predictive ability of integrative model of genome HR deficiency scars and transcriptional measures of *BRCA1/2* loss of function and wider HRD deficiency as defined by mutation signatures by whole genome sequencing and RNA-sequencing in relation to response to carboplatin (TNT) and for surrogates of response to olaparib (PHOENIX).

RESEARCH PROPOSAL

Developing predictive biomarkers for patient response to additional therapeutic targets is critical in metastatic setting. The aim of this proposal is to understand the key genetic content make up as well as the expression changes of BRCAness transcriptional signatures in tumours after 2-week exposure to olaparib. Using the genomic data collected in TNT trial, we aim to develop accurate transcriptional measure of aberrant DNA repair deficiency. We would also evaluate the expression patterns of these transcriptional BRCAness signatures in our newly developed trial, PHOENIX, of high-risk metastatic risk TNBC. PHOENIX is a post neoadjuvant pre-surgical disease profiling and novel therapy biomarker endpoint trial can provide an opportunity to answer key biological hypotheses and more rapidly inform combination therapy treatment approaches in a biologically assessable chemotherapy resistant treatment site within a subgroup of TNBC patients who are at high risk of metastatic relapse. In particular, we plan to study the underlying biology of tumours treated with olaparib in PHOENIX. The clinical impact of this proposed study is **to develop predictive biomarkers and address the clinical challenge of identifying patients who are likely to benefit from standard and emerging therapies for mTNBC.**

TNT clinical trial design: TNT was a phase III, parallel group, randomised controlled trial conducted in 74 UK centres (ISRCTN97330959, NCT00532727) (Chief Investigator: Professor Andrew Tutt). For details of trial protocol, ethics review, trial management, governance and funding please see supplementary materials. Patients provided written informed consent. 376 patients with advanced germline BRCA1/2 mutation or TNBC suitable for taxanes were randomly assigned to docetaxel or carboplatin. The primary endpoint was objective response (ORR). Secondary endpoints included progression-free survival (PFS), overall survival, and safety.

"**PHOENIX**" is a peer reviewed and Cancer Research UK endorsed clinical trial platform initiative involving post neoadjuvant pre-surgical disease profiling and novel therapy "window of opportunity" (WOP) biomarker endpoint trial. This WOP trial provides an opportunity to answer key biological hypotheses and more rapidly inform and refine combination therapy treatment approaches in a biologically assessable

chemotherapy resistant treatment site within a subgroup of TNBC patients who are at high risk of metastatic relapse. In this project, the focus will be to study the underlying biology of tumours treated with the PARP trapping PARPi, olaparib, in PHOENIX, and to investigate the expression pattern and changes of the transcriptional aberrant signatures between treatment naive disease and post neoadjuvant chemotherapy, and in relation to Day 0 to Day 14 response to treatment of olaparib in patients with chemotherapy resistant TNBC.

To accomplish AIMS#1-3, we would complete the statistical and bioinformatics analysis of total-RNA sequencing data from the formalin-fixed paraffin embedded (FFPE) tumour tissues of TNT trial in a retrospective manner. To accomplish AIMS#4-5, we will start and complete the PHOENIX clinical trial (Chief Investigator: Professor Andrew Tutt) with Professor Judith Bliss and Clinical Trials and Statistics Unit at ICR (ICR-CTSU) team. Dr. Maggie Cheang is the Biomarker and Translational Study Lead for PHOENIX trial, so her Genomic Analysis team will analyze all the biological data, including whole genome and RNA-sequencing data from tumour samples in a prospective manner.

The clinical impact of this proposed study is to develop predictive biomarkers and address the clinical challenge of identifying patients who are likely to benefit from standard and emerging therapies for metastatic TNBC. More recently, studies have indicated that combination strategies such as PARPi and platinum are making progress in clinic. Germline *BRCA1/2* mutation is a validated diagnostic marker of an HR defect that is targetable, but an important issue we face today is how can we identify more patients who may benefit from these targets on HR defects. The biological data generated from tumours in cohort of olaparib treatment in patients with chemotherapy resistant TNBC provide a means to engage investigators to examine their relation to therapy response to platinum and emerging data on PARPi in neoadjuvant therapy studies.

LITERATURE REFERENCES

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CANDIDATE PROFILE

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1)

Pre-requisite qualifications of applicants: e.g. BSc or equivalent in specific subject area(s)	Master of Science in statistics, computer science, computational biology or bioinformatics

Intended learning outcomes:

1. Bioinformatics – data analysis of RNA-sequencing and whole genome sequencing
2. Biostatistics – machine learning to develop biomarker response classifier
3. Clinical trial statistics analysis
4. Breast cancer biology with focus on triple negative breast cancer and *BRCA1/2* mutation
5. Molecular classification of breast cancer subtypes using genomic data
6. "Big Data" analysis