Expression of Interest for CRUK/Wellcome Trust Clinical PhD fellowship

Project Title:

Understanding the role of therapeutic pressure on Ki67 changes in ER+HER2+ tumour evolution and response to therapy

Primary Supervisor: Maggie Chon U Cheang (Division of Clinical Studies, Genomic Analysis in Clinical Trials, ICR-CTSU)

Supervisory Team: Judith Bliss (ICR), Mitch Dowsett (Royal Marsden), Stephen Johnston (Royal Marsden), Alistair Ring (Royal Marsden)

The Genomic Analysis – Clinical Trial team at the ICR focuses on computational analyses of the ever-growing rich datasets of multi-analyte measurements (genomic, genetic, proteomic, metabolites, imaging etc.). More specifically, we lead the integrated analysis of molecular data with demographic, pathologic and outcome data to identify predictive and prognostic biomarkers for selective therapeutic agents. Dr Cheang is a biostatistician and molecular pathology trained scientist with expertise in clinical trials analysis particularly with 16 years of experience in molecular characterisation of breast cancer subtypes and gene expression profiling of various platforms including RNA-sequencing. She is recognised as a world expert in developing robust and reproducible genomic signatures, and she is the steering committee member of the CM-PATH Clinical Trial Pathology Advisory group.

Professor Dowsett (Royal Marsden and ICR) is the biological lead for the POETIC trial, providing clinical molecular pathology expertise and responsible for the translational research aspects of the trial. He is the co-chairman of the International Ki67 in Breast Cancer Working Group and is a well-recognised expert on the use of Ki67 for multiple purposes in breast cancer research and management.

Professor Bliss, the Director & Lead for Breast Trials at The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU), is the POETIC trial's research methodology lead and has been responsible for overseeing the statistical design, management and analysis of the trial and together with the clinical leads has joint responsibility for the efficient and effective delivery of the POETIC trial and will advise on the interpretation and presentation of results for this pilot project.

Prof Stephen Johnston and Dr Alistair Ring of The Royal Marsden Hospital NHS Foundation Trust are world renowned breast cancer oncologists, and experienced clinical trialists and who will provide clinical leadership, and responsible for overseeing the project objectives related to the pressing scientific questions needed to be addressed to improve the clinical management of this subgroup of patients.

Project Summary

Hormone receptor positive (HR+) breast cancer is the most common type of breast cancer accounting for about 60-70% of the whole breast cancer population. Approximately 15-20% of HR+ cases are also classified as positive and/or over-expressed for human epidermal growth factor (HER2+). Mechanisms of resistance to aromatase inhibitors (AIs) vary between patients; a rational application of the emerging large number of targeted agents against resistance mechanisms that are present in individual tumours requires novel clinical

approaches. We propose to analyse data from the POETIC (Peri-Operative Endocrine Therapy – Individualising Care) Phase III randomised controlled trial. POETIC was the world's largest perioperative window-of-opportunity trial (and the UK's largest trial devoted to patients with ER+ early breast cancer) which explored the benefits of peri-operative therapy (vs. no perioperative treatment control [randomised allocation ratio 2:1]) in postmenopausal women. The recruitment of almost 4500 patients from 130 UK centres raised the profile of WOP studies and established a network of sties committed to, and capable of, recruitment of patients in the perioperative setting where multiple research biopsies are required.

In this cohort, they found that KI67 levels and changes in the levels after perioperative AI treatment was associated with time to recurrence (TTR) and overall survival (OS). Interestingly, when they looked within the ER+HER2+ cohort, these samples were more likely to have KI67 at 2 weeks ($Ki67_{2wk}$) values >10 which retained high even after AI treatment more so than in the HR+HER2- subset. Identification of the mechanisms underlying endocrine resistance within HR+HER2+ tumours has been one of the most important mandates for this clinical subgroup as it is still unclear whether this ability is inherent to the primary tumour or results in gained alterations such as those seen in HR+HER2- cancers.

Project objectives and plan: Our objective is to characterize the resistance mechanisms to endocrine therapy in ER+HER2+ breast cancer to determine if they are driven by baseline genomic signatures or genomic alterations that lead to KI67 changes occurring in response to therapy. By defining the key genomic changes in tumours at baseline and post-therapy and correlating these alterations to patient response and clinical outcome, we seek to develop predictive signatures and address the clinical challenge of identifying patients who are likely to benefit from each of the specific therapies as an ultimate goal.

We will analyse the molecular data from the HER2+ tumour samples from POETIC trial. Formalin-fixed paraffin-embedded (FFPE) tumour tissues have been obtained from 402 unique patients with HR+HER2+ disease (before treatment and after 2-weeks of endocrine at surgery). We will perform total RNA sequencing on pre and post treatment samples and whole genome sequencing on the subgroup of patients demonstrating extra-ordinary responses. Applying various machine learning methodologies on analysing these molecular with data with patient outcome, we aim to study the underlying biology of the tumours and to identify molecular features that may assist to predict sensitivity and resistant tumours.

Specific clinical specialties and areas of interest: Clinical or medical oncologist or pathologist who are interested in molecular characterisation, bioinformatics, clinical trials and biostatistics.