A six month progress report prepared for

The Gynaecological Cancer Fund

February 2017

Gynaecological Cancer Research – Dr Susana Banerjee

Update

Dr McLachlan and Dr Dumas both went on maternity leave and we have appointed two new fellows in their place, Dr Cecilia Orbegoso and Dr Clare Pate.

Over the last few months the team have been testing samples for a specific mutation that has the potential to identify which women will benefit from a novel, targeted drug. We are really pleased with the initial results. The results demonstrate that there are women with gynaecological cancers who have the mutation and therefore might respond well to this drug. We are delighted that we are now developing plans to take this to a national clinical trial, with the view to improve treatment for this patient group. This important research would not have been possible without your support, and we could not be more grateful to you.

We are proud that Dr McLachlan achieved a Consultant position, specialising in gynaecological cancers, on her return to her home to New Zealand – thereby taking her experience gained at The Royal Marsden to women in her home country. Dr Dumas is expected to return to The Royal Marsden Gynaecological Cancer Research team in June 2017 and will continue working on improving outcomes for older women with gynaecological cancers.

Dr Cecilia Orbegoso

We are thrilled to have welcomed Cecilia Orbegoso as a Gynaecological Cancer Fund Research Fellow replacing Dr McLachlan. Dr Orbegoso joined The Royal Marsden in November 2016 having been a consultant oncologist and researcher in Spain. Her previous experience ignited her interest in the diagnosis and treatment of rarer types of gynaecological cancer. In addition to working on clinical trials for patients with gynaecological cancers she will be working on projects including:

- lynch syndrome (a genetic condition linked to cancer) and its connection with endometrial cancer
- carcinosarcomas (rare tumours) in patients with ovarian and endometrial cancer
- testing BRCA genes to guide treatments for ovarian cancer patients

Dr Clare Pate

Clare joined the team in December 2016. She completed medical training the UK and has recently been furthering her oncology training in New Zealand. In addition to working on clinical trials for patients with gynaecological cancers, Dr Pate will be working on a specific project to understand more about ovarian cancer patients who have the BRCA mutation, in particular those who have had breast cancer.

Key developments: July 2016 - December 2016

ARID1A gene mutations: a biomarker for gynaecological cancer?

Colleagues at the Institute of Cancer Research have identified that cancers with mutations in a gene called ARID1A are more susceptible to a new type of targeted drug called ATR inhibitors. Dr Banerjee and her team have therefore taken the opportunity to apply this science to gynaecological cancers with the hope that it could provide a new treatment option for patients.

50 tumour samples collected from patients with ovarian, endometrial and cervical cancers have been tested for the gene mutation ARID1A. The cancer samples underwent a process called 'staining', which enables cellular structures and their distinguishing characteristics to be viewed

under a microscope. We successfully identified some patients with the mutation, which is an important step towards being able to select the most effective treatments for patients. We now plan to test the drug in patients both with and without the mutation, to see if there is a good response in either group.

Dr Banerjee presented the results of this research at the National Cancer Research Institute Gynaecological Cancers Group (UK) and received over whelming support from fellow experts in the industry. Dr Banerjee and her team are now in discussions with a pharmaceutical company to expand this research into a clinical trial, so that patients can benefit from this new understanding of their cancer's genetic make-up. It will be the first trial in the world testing if ATR inhibitors have a better response in patients with a certain molecular abnormality.

It is thanks to funding from the Gynaecological Cancer Fund that the team has been able to take on this project and move quickly to identify potential new treatments for women with gynaecological cancers. This research fits very well into the portfolio of the Gynaecological Cancer Fund's research as it is an excellent example of how we could potentially personalise treatment for patients with a mutation of the ARID1A gene.

Discussions with the pharmaceutical company will continue and the team are carrying out further validation tests to collect the relevant data before moving forwards to a clinical trial. The intention is to publish the tumour sample testing work in a peer-reviewed journal later this year. We will keep you updated about the progress of this project and success in collaborating with the pharmaceutical company so that this research can be translated into the clinic for the benefit of patients sooner.

Creating a platform of genetic and molecular tests to be utilised for women with gynaecological cancers

The purpose of this work is to establish a test that will look for a number of molecular or genetic abnormalities that could help select the best treatment for patients with gynaecological cancer. Using a method called 'gene sequencing' it is possible to test for lots of different abnormalities all at once. This is an incredibly challenging area of work because decisions must be made about which are the potentially most promising genes that could impact on treatment decisions for women with gynaecological cancers. The team has so far identified 120 samples for testing, in order to improve our understanding as to which genes will be most valuable and effective for future sequencing .

Publishing research supported by the Gynaecological Cancer Fund

The Gynaecological Cancer Fund has been acknowledged in the following three publications for their support in making the following research possible.

The impact of systemic therapy beyond first-line treatment for advanced cervical cancer. *McLachlan J, Boussios S, Okines A, Glaessgen D, Bodlar S, Kalaitzaki R, Taylor A, Lalondrelle S, Gore M, Kaye S, Banerjee S. Clin Oncol (R Coll Radiol). 2017 March (3): 153-160*

http://www.sciencedirect.com/science/article/pii/S0936655516303259

This research analysed the impact of systemic therapy (i.e. drugs that go everywhere in the body such as chemotherapy) in patients with advanced cervical cancer when the first line

(standard or normal) treatment had not been successful. The study found that currently there is no typical standard of care if first line treatment does not work for patients; the options vary and the response rate to second line treatment is generally less than 15%. The publication made the case that more patients should be considered for clinical trials to access novel targeted agents and immunotherapy. Only by more patients accessing these trials will patients potentially benefit and lives might be saved.

The current status of PARP inhibitors in ovarian cancer. *McLachlan J, George A, Banerjee S. Tumori, 2016 Oct 13;102(5):433-440*

Abstract available at https://www.ncbi.nlm.nih.gov/pubmed/27716873

This review focuses on the current evidence for PARP inhibitors in ovarian cancer. This class of drug (eg. olaparib, niraparib) is having a significant impact on the management of women with ovarian cancer, in particular those with a BRCA mutation. These drugs are also being tested in other cancers such as breast and prostate cancer. This article discusses on-going clinical trials and future research directions in this rapidly evolving area.

Targeting the mitogen-activated protein kinase pathway in low-grade serous carcinoma of the ovary. *McLachlan J, Gore M, Banerjee S. Pharmacogenomics. 2016 Aug;17(12):1353-63*

Abstract available at https://www.ncbi.nlm.nih.gov/pubmed/27469379

Until recently there has been little difference in the way that women with certain ovarian cancers are treated, despite them having very different subtypes of the cancer. Low grade serous carcinoma is a rare form of ovarian cancer making up 6-8% of all ovarian cancers. This review article outlines the promising potential of a particular enzyme that plays an important role in the development of low-grade serous carcinoma and a class of targeted drugs called MEK inhibitors. Dr McLachlan emphasises the importance for translational research to identify suitable biomarkers to personalise medicine for this specific group of patients.

Research into the management of treatments, outcomes and care for women over 65 years old

This research project will continue after the return of Dr Dumas from June 2017.

CORAL

In the last report we outlined the results of the CORAL study that had trialled abiraterone in ovarian cancer. Abiraterone is used very successfully in men with prostate cancer but did not have the same response for patients with ovarian cancer. Dr Banerjee presented these findings at the European Society of Medical Oncology Congress in Copenhagen in October 2016. The team plan to publish the trial in a peer-reviewed journal later this year.

Important global news about gynaecological cancer research

Rucaparib approved for ovarian cancer treatment (US only)
Rucaparib is a PARP inhibitor that has been tested in women with breast and ovarian cancer that have the BRCA gene. Dr Banerjee was involved in the recruitment of patients for a clinical trial, which led to the being approved in the US. It is approved for use in women with advanced ovarian cancer and an associated BRCA mutation, who have been treated with two or more chemotherapies. It is possible that European and UK approval will follow. This will mean that patients with BRCA associated advanced ovarian cancer, who have tried the standard chemotherapy routes with no success, will have another option of treatment.

The NOVA trial, niraparib
The NOVA trial investigated an oral PARP inhibitor drug called niraparib. This large, international trial showed that niraparib substantially slowed down disease progression, and thereby prolonging survival, in ovarian cancer patients with a BRCA mutation. Excitingly, this benefit also extended to other patients who do not have a BRCA mutation. Dr Banerjee contributed to this pivotal study and recruited most of the UK patients to the trial. Applications for approvals are underway so that the drug might be licensed and therefore accessible to patients.

Dr Banerjee
Dr Banerjee has been selected to serve on the European Society of Medical Oncology Executive Board for two years. This is a very prestigious position, which will give Dr Banerjee further opportunities to improve cancer care globally.

Key expected outcomes: January - June 2017

Over the next six months the team will be progressing the outlined research projects.

Key expected outcomes:

1. *Complete ARID1A mutation research and work towards the development of a national, multi-centre clinical trial for women with ovarian, endometrial and cervical cancer*
2. *Via a new collaboration with Dr Yin Yin Yuan, team leader at the ICR, Dr Orbegosowill focus on a new area of research looking at the how the immediate environment of a tumour influences cancer cells. This includes looking at immune cells. The project will use a technique called digital automated analysis to analyse patients' tumour samples.*
3. *Progress the work on understanding the disease characteristics and behaviour of ovarian cancer in relation to BRCA mutations and those who have had breast cancer. We aim to submit preliminary results to the European Congress.*
4. *Submit publications in peer-reviewed journals on carcinosarcoma, drugs targeting angiogenesis inhibitors (blocking the formation of blood vessels related to cancer), and the CORAL study.*

Future plans

Dr Banerjee is leading a national clinical trial called OCTOPUS in women with ovarian cancer that has returned. The trial adds a cancer growth blocker (AZD2014) to a weekly chemotherapy treatment called paclitaxel to understand if this improves treatment for ovarian cancer, what the side effects are and how it might impact a patient's quality of life. If the combination is successful, it will benefit many patients with ovarian cancer.

The aim is to recruit 140 women from over 12 sites. Over 50 women have entered so far. Once the trial has been completed, it will be critical to analyse the tumour samples obtained from biopsies to help identify why some patients responded better than others. Support from the Gynaecological Cancer Fund will enable us to analyse these samples to inform the development of more personalised treatment for women in the future.

Thank you

Your funding has led to a very exciting six months in gynaecological research. We are so thrilled that tests showed some women with gynaecological cancer do have specific mutations in ARID1A, as we know that ATR inhibitor drugs can be very effective in targeting this mutation, and that patients respond well. Without your funding the research to gather preliminary data would never have happened, and the knowledge that this mutation could be driving some women's cancers would not yet be known. We now plan to move to a clinical trial, which if successful could lead to an entirely new treatment option to a group of patients with ovarian, endometrial and cervical cancers.

Furthermore, the team has successfully published review articles outlining the current status of research in certain areas and making an evidence-based call for more patients with gynaecological cancers to access clinical trials. Thank you so much for your continued support and fundraising for The Royal Marsden Cancer Charity.

The Gynaecological Cancer Fund has many exciting events planned over the next six months and Dr Banerjee and staff at The Royal Marsden Cancer Charity are very much looking forward to supporting you. We also look forward to seeing on May 2nd when you visit for an update from Dr Banerjee and to see some of this exciting research in action.