Response and Resistance to PARP inhibitors: Beyond BRCA1/2

Presenter: Clare Scott, Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia

Summary: Maintenance treatment with Poly (ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, have been shown to extend progression-free survival in a subset of patients with ovarian cancer. PARPi target cancers with defective DNA-damage repair capability, including BRCA1 and BRCA2 mutation-associated breast and ovarian cancers. Despite its efficacy in some patients, may women achieve a non-durable benefit of less than 2 years. This research focuses on identification of biomarkers of defective DNA repair as potential targets of therapeutics and predicts PARPi resistance in a pre-clinical model.

Comment (Dr. Rachel Delahunty): Associate Professor Clare discussed her laboratory work in Response and Resistance to PARPi: Beyond BRCA1/2.

PARPi inhibitors (PARPi) are promising new therapeutic agents being utilised in homologous recombination (a DNA repair pathway) deficient (HRD) cancers such as high grade serious extra-uterine cancers. Exciting results for PARPi as maintenance therapy in the relapsed platinum sensitive ovarian cancer has led to the recent PBS listing of olaparib in Australia, with other listings expected in the future. Despite the promising efficacy of PARPi in treating HRD cancers, less than 50% of BRCA1/2 defective cancers have sustained response, and thus investigation of resistance mechanisms is required.

A/Prof Clare Scott discussed her work with patient-derived xenografts (PDXs) to investigate potential therapeutic agents and resistance mechanisms in ovarian cancer. A/Prof Scott has shown that BRCA1 methylation is associated with PARPi response and of great interest, she confirmed that RAD 51C knockout confers sensitivity to PARPi, and that these HRD genes pose potential targets for future trials.

Her work has also explored mechanisms of PARPi resistance and demonstrated secondary mutations that correct primary homologous recombination defects. She has shown for the first time that secondary mutations in Rad 51 C/D in addition to BRCA 1/2 restore the function of the HRD genes and thus are a key mechanism in PARPi resistance.

Session: Pure Science Symposium 1 (Abstract 3943)
Exploring the genomic landscape of mucinous ovarian tumours

**Presenter:** Kylie Gorringe, Peter MacCallum Cancer Centre, East Melbourne, Australia

**Summary:** These researchers performed a genomic analysis of 120 mucinous ovarian carcinoma (MOC) cases and one autopsy case including RNAseq (n=85), exome sequencing (n=45), SNP arrays (n=67) and whole genome sequencing (WGS) (n=5) with the aim of gaining a better understanding of the genomics of these rare tumours. MOC had more copy number (CN) changes than benign (MBT) or borderline (MBOT) tumours (p>0.001), including 17p loss and 8q gain with higher grade tumours correlating to more CN changes than low grade. ERBB2 amplification was found in 18% of MOC and all MOC with ERBB2 amplification were TP53 mutant (p=0.002). TP53 mutations were associated with more CN changes (p<0.01), were common in MOC only and increased with grade (G1 39%, G2 47%, G3 100%, p=0.03). Whole genome sequencing of a stage 1 MOC primary and four G3 metastases sites from an autopsy case showed key drivers of KRAS and TP53, chr7 and chr19 CN events and p16 loss at all sites but extensive diversification of metastases from the primary.

**Comment (Dr Ali Freimund):** Mucinous ovarian cancers (MOC) account for < 5% of ovarian epithelial neoplasms and advanced disease is associated with poor prognosis and decreased responses to chemotherapy. Little is known about their genomic profile in contrast to high-grade serous carcinomas which have been extensively studied. The Genomic Analysis of Mucinous Tumours (GAMuT) study is an international collaboration to better understand the genomics of these rare tumours and to identify novel targets for therapy. Dr Gorringe presented preliminary data on 120 MOC cases and one autopsy case. ERBB2 amplification was found in nearly 20% of MOC and may suggest a potential response to treatment with antiHER2 therapy. Other potential therapies derived from this research that could be evaluated in future studies include: BRAF inhibitors for V600E mutations, hormone therapy in ER+ MOC, Wnt inhibitors in RNF43 mutations, PI3K inhibitors in cases with PTEN or PIK3CA mutations, and immunotherapy in high grade MOC with high level copy number change.

**Session:** Pure Science Symposium 2 (Abstract 3702)

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A Framework for Personalised Approaches to Ovarian Cancer

**Presenter:** Anil Sood, MD Anderson Cancer Center, Houston, Texas, United States

**Summary/Comment (Dr Rachel Delahunt):** There has been an abundance of recent data demonstrating the prognostic link between the degree of postoperative residual disease and patient outcome in ovarian cancer. Additionally, studies from the GOG have demonstrated that the maximal diameter of residual disease is an independent predictor of overall survival. In view of this evidence, Dr Anil Sood described a quality improvement program that his group at MD Anderson have introduced, aimed to improve the proportion of patients with advanced-stage high grade serous ovarian cancer (HGSOC) undergoing complete cytoreduction to R0. The algorithm aims to personalise the approach to surgery and forms part of the Women’s Cancer Moon Shot Program, a comprehensive multidisciplinary research effort at MD Anderson to improve patient outcomes.

The algorithm has some key features including the requirement that all patients presenting with advanced-stage (stage III or IV) disease be considered for a two-surgeon laparoscopic tumour evaluation with utilisation of a validated scoring system to determine the ability to resect the tumour to R0. It also involves a consensus recommendation to offer neoadjuvant chemotherapy to those patients in whom a R0 resection is unlikely to be achieved. Following three cycles of neoadjuvant chemotherapy, interval cytoreduction is undertaken in all patients who exhibit partial response to induction chemotherapy. There is also a requirement for the collection of tumour samples and weekly quality improvement meetings, to ensure adherence to pre-set guidelines and reporting of morbidity and patient outcome. In addition to improving R0 rates, this approach allows the collection of tumour specimens and facilitates translation research.

Through the use of this algorithm Dr Sood and the MD Anderson group have significantly improved rates of complete resection from 20% pre-implementation to 84% post-implementation; P < 0.01, in addition to other benefits including improved BRCA testing rates, to an impressive 90%. These patients will be followed to evaluate whether improvement in R0 resection translates into improved PFS and OS, but this is a promising personalised approach that warrants ongoing investigation.

**Session:** Making a Difference for Women with Gynaecological Cancer (Abstract 3889)

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Ovarian Clear Cell Carcinomas: Challenges and opportunities

**Presenter:** David Tan, National University Cancer Institute, Singapore

**Summary/Comment (Dr Ali Freimund):** Ovarian clear cell carcinomas (OCCCa) account for 5-10% of epithelial ovarian carcinoma in Western populations with overall response rates in recurrent disease <10%. Dr Tan presented data that the incidence in Asia is as high as 25% and may represent a molecularly distinct entity. With a median OS from first relapse of 40 weeks, and a PFS of 11 weeks, OCCCs present a clinical management challenge. Dr Tan highlighted data on the molecular pathogenesis of OCCCs including mutations in ARID1A (46% of OCCCa) and PIK3CA (33% of OCCCa), inactivation of PTEN (44%), increased angiogenic pathways with high IL-6 expression (49%), and mismatch repair defects (7-14%). As research into these diverse molecular pathways continues, novel therapeutic approaches must be included studying including PARP, ATR, mTOR, VEGF receptor, and PD-L1 inhibitors. Dr Tan emphasised that there is currently insufficient evidence to recommend specific treatments for OCCCs however the ultimate aim from this research would be to offer individualised treatment for patients.

**Session:** Making a Difference for Women with Gynaecological Cancer (Abstract 3853)

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Immunotherapy-promise, potential and pitfalls

**Presenter:** George Au-Yeung

**Summary/Comment (Dr Rachel Delahunt):** Dr Au-Yeung described the role of immunotherapy in endometrial, cervical and ovarian cancers highlighting that immunotherapy is likely to have a role in treatment of gynaecological cancers, but patient selection via molecular sub classification is pivotal.

The most promising role for immunotherapy in gynaecological cancers currently is checkpoint inhibitors in endometrial cancer. The link between mutational burden and response to checkpoint inhibitors has been well described. Recent work by the TCGA has defined 4 molecular subgroups of endometrial cancer. Two of these groups, the MSI hypermutated and POLE ultramutated group, are associated with a high mutational load and a good prognosis. These characteristics provide much hope for future treatment including the potential role of immunotherapy. It is hypothesised that similar to MSI high (MMRd) colorectal cancer, MSI high endometrial cancers will respond well to checkpoint inhibitors. To investigate this hypothesis, ANZGOG has opened ‘PHAEORA’ a randomised Phase 2 study of Durvalumab in advanced endometrial cancer stratified by MSI/MMR status.

Cervical cancer has been known for many years to be an immunogenic cancer however surprisingly, in a Phase 1 study, the results of checkpoint inhibitors were underwhelming, with response rates of 13% (KEYNOTE-028). A promising agent on the horizon is AXAL, a live, highly attenuated Listeria monocytogenes targeted immunotherapy that targets HPV-transformed cells, inducing antitumor T-cell immunity and breaking immune tolerance in the tumour microenvironment.

AXAL is being investigated in cervical cancer. In ovarian cancer, early phase studies of checkpoint inhibitors have been generally disappointing with response rates of 10-15% across studies and notably PD-L1 has no predictive benefit. It is hoped that in future, studies with a more personalised patient selection criteria may facilitate a more meaningful response to checkpoint inhibitors.

**Session:** Improving Clinical Practice for Women with Cancer
Reducing the cervical cancer burden among Aboriginal and Torres Strait Islander Women

**Presenter:** Lisa Whop, Menzies School of Health Research, Brisbane, QLD, Australia

**Summary/Comment (Dr Ali Freimund):** Cervical cancer incidence and mortality in Australia is amongst the lowest in the world with a 50% reduction in both outcomes because of the effectiveness of the National Cervical Screening Program (NCSP). Dr Whop presented research into the effectiveness of the NCSP, highlighting the increased incidence and mortality rates for Aboriginal and Torres Strait Islander women than non-Indigenous Australian women. Important gaps in understanding these clinical differences include an absence of national data on both Indigenous status on women participating in NCSP and on the prevalence of abnormalities and time to follow-up after a diagnosis of an abnormality by Indigenous and non-Indigenous women. The National Indigenous Cervical Screening Project is working to link Pap Test Registers to hospital data to obtain Indigenous status and cervical cancer registration data. The aim of this research is to generate an evidence base to make the NCSP more effective for Indigenous women.

**Session:** Reducing the Cancer Burden (Abstract 3938)

Leading the cervical cancer prevention revolution: Australia’s new cervical screening approach in the HPV vaccine era

**Presenter:** Julia Brotherton

**Summary/Comment (Dr Ali Freimund):** Given the high level of women covered by the quadrivalent HPV vaccine in Australia, the declining prevalence of HPV and high grade CIN, and the fact that the majority of high grade cervical lesions are detected in the first screening round with fewer cancers diagnosed at subsequent rounds, the Australian national cervical screening program is currently undergoing reform. Dr Brotheron outlined the upcoming changes to the screening program whereby HPV testing will be every 5 years for women aged 25-74 with the option of self-sampling for women who would otherwise not participate (no prior Pap smear or lapsed smear). It is estimated that these changes will result in 20% fewer cervical cancer occurrences with increased sensitivity. Dr Brotheron also described the expected change in vaccine policy to move to a two dose schedule, nine-valent HPV vaccine to further reduced HPV-related disease in the future.

**Session:** Reducing the Cancer Burden

Lifestyle, side-effects and chemotherapy completion; results from the Ovarian Cancer Prognosis and Lifestyle (OPAL) Study

**Presenter:** Penelope Webb et al., QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

**Summary:** The National OPAL prospective study is an ongoing investigation designed to identify epithelial ovarian cancer patients most likely to experience side effects from standard chemotherapy and lifestyle factors associated with reduced presence or severity of side-effects. This update gives preliminary results from the comparison of medical records to self-reported lifestyle data from 659 women during first line chemotherapy treatment and 157 women at the end of treatment. Preliminary results indicate that 50% of women most likely to experience severe treatment related side-effects and lifestyle factors associated with reduced presence or severity of side effects. The principal investigator of OPAL, Dr Penny Webb, presented an update on the findings from self-reported lifestyle data from 659 women whom completed questionnaires during first-line chemotherapy and 157 women at the end of treatment. Preliminary results indicate that half of women experience moderate side effects including neuropathy, myelosuppression, and fatigue. Early data also suggests that women who were more physically active early during their treatment reported significantly less fatigue (p=0.002) and neurotoxicity (p<0.001) at the end of treatment.

**Comment (Dr Ali Freimund):** The ongoing OPAL study has prospectively recruited 958 women diagnosed with primary epithelial ovarian cancer since 2012 to identify women most likely to experience severe treatment related side-effects and lifestyle factors associated with reduced presence or severity of side effects. The principal investigator of OPAL, Dr Penny Webb, presented an update on the findings from self-reported lifestyle data from 659 women whom completed questionnaires during first-line chemotherapy and 157 women at the end of treatment. Preliminary results indicate that half of women experience moderate side effects including neuropathy, myelosuppression, and fatigue. Early data also suggests that women who were more physically active early during their treatment reported significantly less fatigue and neurotoxicity at the end of treatment. When analysis is finalised it is likely that there will be important implications on adjuvant treatment recommendations such as targeted exercise interventions during chemotherapy for ovarian cancer patients.

**Session:** Improving Quality of Life (Abstract 3901)

Gene expression molecular subtypes in ovarian cancer: the next stop for precision medicine?

**Presenter:** David Tan, National University Cancer Institute, Singapore

**Summary/Comment (Dr Rachel Delahunty):** It has been recognised for some time that ovarian cancer is not one disease, but many diseases with the same geographic distribution. The high grade tumours fall in to 4 molecular subgroups: C1, C2, C4, and C5. C2 tumours are the immunoreactive subtype and display high amounts of intratumoural T-cell infiltration and are associated with the best prognosis. C1 tumours are associated with enhanced expression of stromal genes and tissue desmoplasia and have a poor prognosis. C5 is defined by genes expressed in mesenchymal development and is associated with increased WNT/beta-catenin signalling and are also associated with a poor outcome. The C4 (differentiated) subtype shares gene expression features with borderline tumours and are seen as intermediate subtype with an intermediate prognosis. Due to the variability across ovarian cancer subtypes, Dr Tan emphasised the importance of developing a personalised approach to therapy.

**Session:** New Horizons- Bench to Bedside (Abstract 3854)

Introducing molecular prognostic factors for endometrial cancer into clinical practice- the PORTEC4a experience

**Presenter:** Remi Nout, Leiden University Medical Centre, Netherlands

**Summary/Comment (Dr Rachel Delahunty):** Dr Remi Nout presented the two pivotal PORTEC studies that have helped define our management of early stage endometrial cancer (EO). PORTEC-1, which assessed the role of postoperative pelvic radiotherapy, demonstrated improved locoregional (LR) control but demonstrated a non-statistically significant difference in overall survival (OS). PORTEC 2 compared vaginal brachytherapy and pelvic external beam radiation and demonstrated non-inferiority for brachytherapy for vaginal recurrence rates and OS with improved toxicity but higher pelvic recurrence. PORTEC 3, a trial to assess the role of chemotherapy in addition to radiation, is closed to recruitment and the results are due to be reported at ASCO this year. To date, no early stage adjuvant therapy study has shown a survival advantage. Traditionally EC has been seen as two types; Type 1 and 2, but it is well recognised that there is much heterogeneity amongst EC which may explain some of the results of these clinical trials. In view of this, there has been work done by the TRANSPORTEC group aiming to molecularly subclassify patients from PORTEC 1/2. The results of this work support data from the TCGA demonstrating 4 unique subgroups, with simplified technique for sub-classification. These results give further weight to the need for a more personalized approach to treatment and which provides the platform for PORTEC-4. PORTEC-4 is a randomised Phase III Trial of molecular profile-based versus standard recommendations for adjuvant radiotherapy for women with early stage EC. The PORTEC-4a trial has been approved as an ANZGOG study, it aims to answer the critical question of whether we can improve patient outcomes by personalised therapy based on molecular features.

**Session:** New Horizons- Bench to Bedside (Abstract 3927)

Breast Cancer Research Review

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for BRCAm

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*as maintenance therapy for PSR disease, in response after platinum-based chemotherapy (must have ≥2 courses)¹

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MBS item 73295: Detection of germline BRCA1 or BRCA2 gene mutations, in a patient with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer with high grade serous features or a high grade serous component, and who has responded to subsequent platinum-based chemotherapy, requested by a specialist or consultant physician, to determine whether the eligibility criteria for olaparib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Explanatory note: Patients who are found to have a germline BRCA1 or BRCA2 mutation should be referred for post-test genetic counselling, as there may be implications for other family members. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral.

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Practical guidance on the use of OLAPEARIB in women with Platinum-Sensitive Relapsed BRCA-mutated HGSOC

Presenter: Michael Friedlander

Summary/Comment (Dr Christopher Steer): The PARP inhibitor olaparib is now subsidised by the PBS for the maintenance treatment of patients with platinum-sensitive, relapsed BRCA-mutated, high grade serous ovarian cancer (HGSOC) who have received at least two platinum-containing regimens and gained a partial or complete response to the most recent regimen.

This complication will restrict the use of this olaparib to a relatively small percentage of patients with ovarian cancer in Australia however it has been shown to significantly improve progression free survival in this patient population.

Olaparib has been approved as monotherapy at an initial dose of 400mg twice daily. This translates to 8 x 50mg capsules twice a day taken on an empty stomach. A more potent tablet formulation is rumoured to be in development. The most common adverse events are nausea, vomiting, fatigue and anaemia. Most patients find that nausea occurs early in the treatment and then settles with time. Nausea can be successfully managed with antiemetics and proton pump inhibitors, treatment pauses and, ultimately, dose reduction.

Although olaparib will ultimately be only used in a small number of patients in Australia it represents a key advance in the care of women with HGSOC. The toxicity profile is manageable and most side effects tend to improve over time.

Session: ANZGOG Evening Session

Associate Professor Alison Brand is a gynaecological oncology surgeon, Director of Gynaecological Oncology at Westmead Hospital, Sydney, NSW and Clinical Associate Professor at the University of Sydney. She is currently Chair of the Australia New Zealand Gynaecological Oncology Group (ANZGOG) and has held key positions within the group. She has been a member of several working parties for the development of national gynaecological cancer guidelines, the latest being the new Cervical Screening Guidelines. She is Senior Editor for the International Journal of Gynaecological Cancer. She is passionate about participation in clinical trials as a way to improve the lives of women with gynaecological cancers, now and in the future.

Dr Ali Freimund is a consultant medical oncologist at the Peter MacCallum Cancer Centre and has a particular interest in the treatment of gynaecological cancers. She is a sub-investigator on multiple clinical trials at Peter MacCallum in the field of gynaecological cancers and is working to open a pilot study investigating the benefits of exercise for endometrial cancer patients. She has also recently commenced a PhD in the Cancer Genetics and Genomics Laboratory at the Peter MacCallum Cancer Centre and the University of Melbourne and is investigating the mechanisms driving poor response to therapy in a cohort of patients with germline BRCA1/2 ovarian cancer. Dr Freimund is a member of the Australia New Zealand Gynaecological Oncology Group (ANZGOG).

Dr Rachel Delahunty is an early career medical oncologist with a special interest in gynaecological oncology and translational and clinical research.

She graduated from Monash University before completing advanced training in medical oncology in Melbourne and was awarded Fellowship to The Royal Australian College of Physicians in January 2016. Following this she worked as The Clinical Trials Fellow at Eastern Health, overseeing the conduct of phase 1-phase 3 clinical trials and in 2017, commenced a Masters of Philosophy (Research) in the Bowtell laboratory at The Peter MacCallum Cancer Centre.

Dr Delahunty will be running ‘TRACEBACK’, a clinical trial aimed to improve the detection of pathogenic BRCA mutations in patients with a history of ovarian cancer with the aim of reducing the number of BRCA related cancers in Australia.

In addition she will lead a pilot translational research project of ctDNA in endometrial cancer which she will run alongside ongoing clinical work in medical oncology.

Dr Delahunty is a member of the Australia New Zealand Gynaecological Oncology Group (ANZGOG).

Dr Christopher Steer is a medical oncologist working at Border Medical Oncology in the recently completed Albury Wodonga Regional Cancer Centre. Christopher was the inaugural chair of the geriatric oncology interest group of the Clinical Oncological Society of Australia (COSA). He is actively involved in the International Society of Geriatric Oncology (SIGOG) and was chair of the scientific committee of the annual scientific meeting in Prague in November 2015. He is an editorial board member of the Journal of Geriatric Oncology and the European Journal of Surgical Oncology. Christopher is chair of the geriatric oncology interest group of the Multinational Association for Supportive Care in Cancer (MASCC).

Christopher is the current president of the Private Cancer Physicians of Australia (PCPA) and is a member of the MOGA/PCPA cancer drugs working group.

Christopher is a principle investigator at the Border Medical Oncology research unit (BMORU) and a member of the Research Advisory Committee of the Australia New Zealand Gynaecological Oncology Group (ANZGOG). BMORU has been recognized for innovation in clinical research particularly in delivering care to a rural/regional population. Christopher is active on Twitter as @drcbsteer.