Individualised Ovarian Cancer Treatment through Integration of Genomic Pathology into Multidisciplinary Care – An Analysis of Initial Recruitment to the INOVATe Study

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Background

Precision Medicine aims to improve patient outcome by moving treatment from the traditional "one-size-fits-all" approach to one that takes individual differences into account.

INOVATe (Individualised Ovarian Cancer Treatment Through Integration of Genomic Pathology into Multidisciplinary Care) is a research program that has been established to develop strategies to better define ovarian cancer patient subsets, based on tumour genomic profiling in conjunction with conventional histological subtyping, to optimise the selection of patients for novel molecularly-targeted clinical trials and ultimately to individualise treatment.

Aim

Our aim is to establish the mechanisms to implement a personalised approach to the management of women with ovarian cancer based on molecular tumour profiling.

Methods

INOVATe is a multi-centre, collaborative research program being conducted in the major Gynaecological Oncology treatment and research centres across Sydney.

Women with ovarian, fallopian tube and primary peritoneal cancers are eligible for inclusion. An overview of the INOVATe clinical workflow is presented in **Figure 1** and an overview of the INOVATe program is presented in **Figure 2**. Patients consented to the study receive standard-of-care primary treatment, specialised molecular testing is undertaken, with results available for allocation of patients to biomarker-based clinical trials at disease progression or relapse.

•Next generation multi-gene mutation testing and whole genome copy number profiling are conducted (Qiagen Human Ovarian Cancer Panel, Illumina MiSeq (AGRF); Colorectal and Solid Somatic Mutation panels (Australian Clinical Labs); Illumina Infinium Human OmniExpress-24 BeadChip arrays (AGRF)).

•A predictive logistic regression model is used to determine homologous recombination repair deficiency (HRD) status based on three genomic lesion scores (HRD score) obtained from SNP array data.

•*CCNE1* copy number is measured by droplet digital PCR (ddPCR) (Bio-Rad).

•Immunohistochemistry for protein biomarkers of interest including CCNE1, EpCAM and Mesothelin, is conducted using standard techniques.

Results

Recruitment commenced in March 2016 and 100 eligible patients have been consented as of 24 August 2017 (**Figure 3**). Molecular testing has been undertaken on 52 cases to date, with examples of molecular results summarised in **Figure 4**.

Clinically significant mutations have been identified in *TP53* (n=14), *KRAS* (n=5), *PIK3CA* (n=4), *BRAF* (n=3), *BRCA2* (n=3), *BRCA1* (n=2), *ARID1A* (n=2) and *PTEN* (n=2). Mutations identified to date are consistent with the histological subtypes of the cases.

Eleven cases have undergone copy number profiling, with HRD scores calculated for six cases. Four cases were classified as HR-intact and two as HR-deficient, predictive of response to PARP inhibitors and platinum chemotherapy.

CCNE1 copy number has been measured in 45 cases with *CCNE1* gained (copy number >4) in four cases and amplified (copy number >8) in three cases, indicating eligibility for a CCNE1-targetted clinical trial.

A local instance of cBioPortal has been developed to aide in the visualisation and analysis of the complex genomic data. A multi-site Molecular Tumour Board has been established for the return of the molecular results to the multidisciplinary clinical team and to enhance the team's ability to interpret the molecular data.

Three patients have been entered onto early phase clinical trials thus far, three are pending, and five have alterations that could be targeted if the patients relapse with progressive disease.

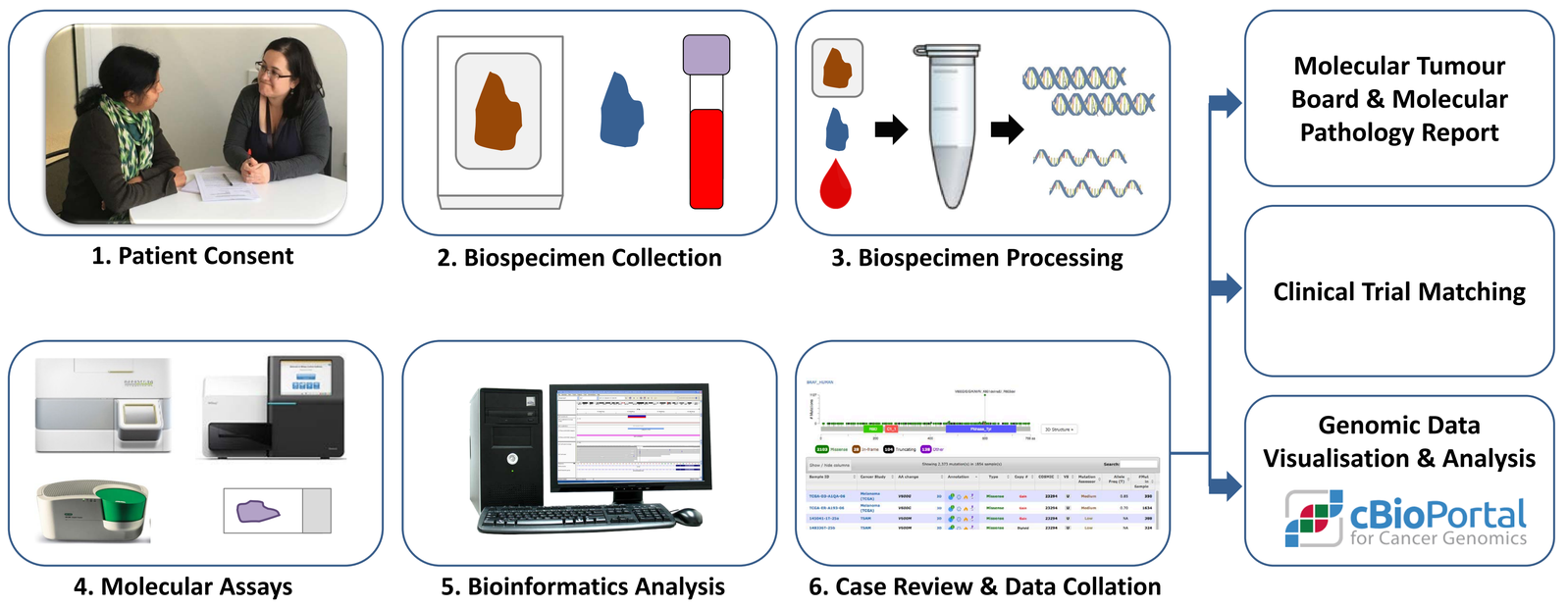


Figure 1: Overview of the INOVATe clinical workflow.

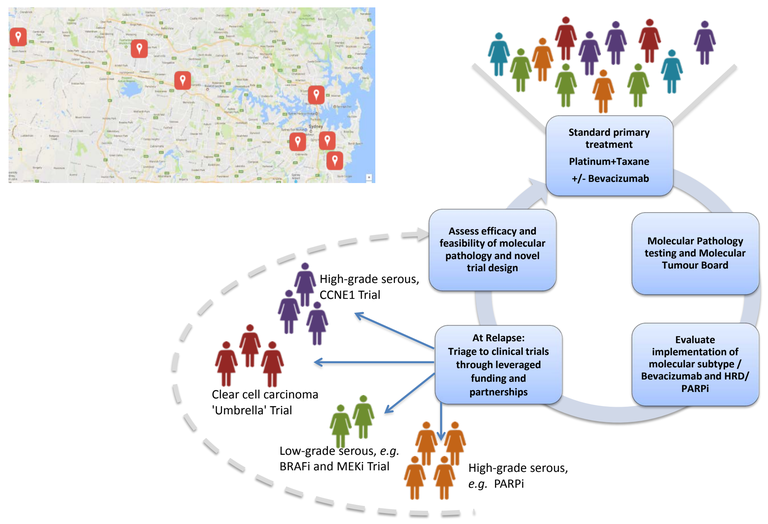


Figure 2: Overview of the INOVATe program and study sites.

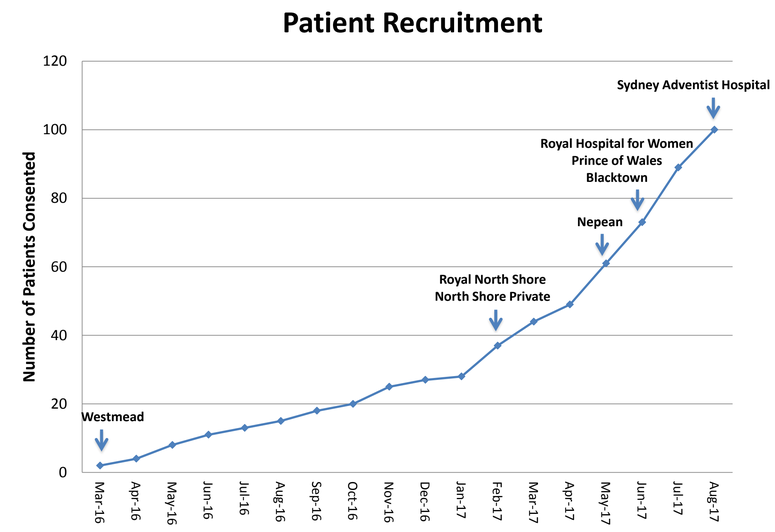
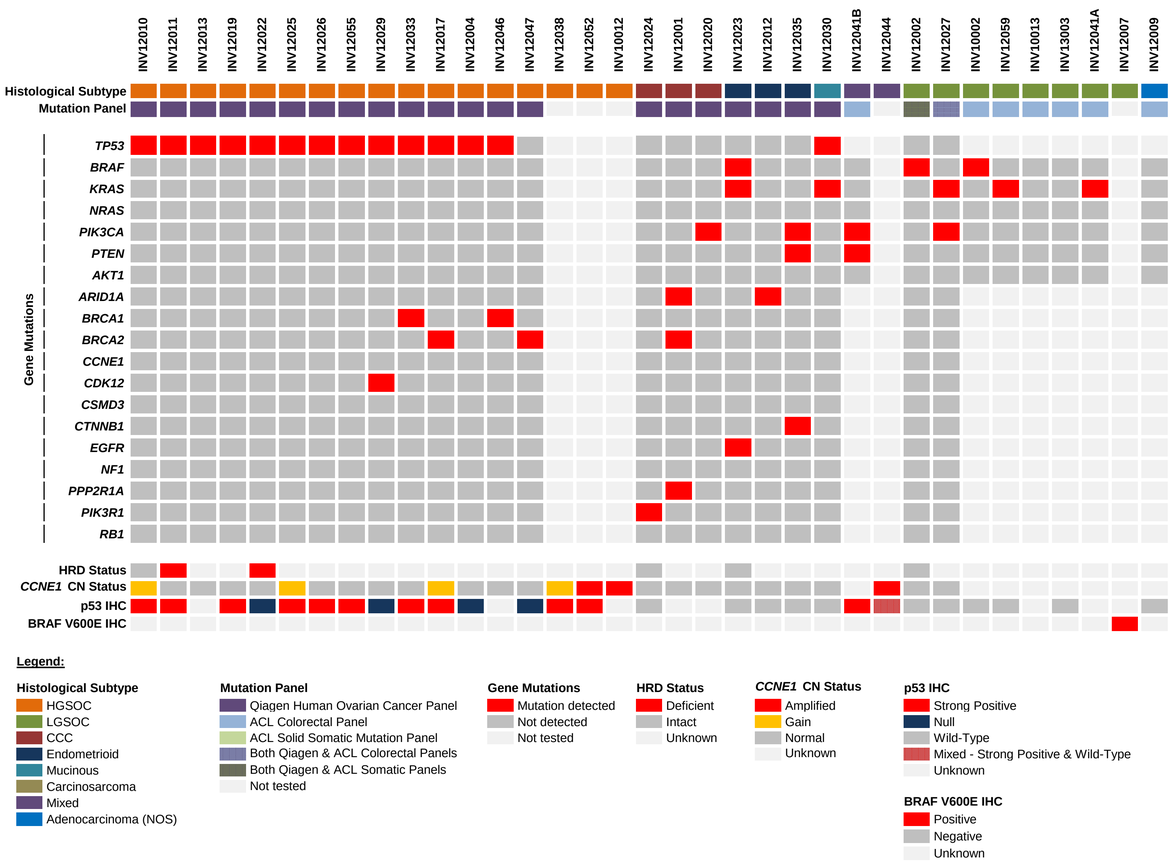


Figure 3: Recruitment to the INOVATe program.



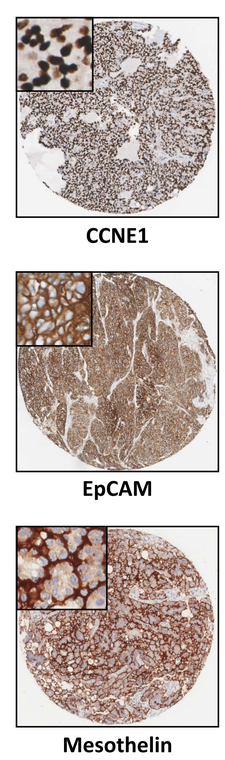


Figure 4: Examples of molecular alterations identified in the INOVATe cohort.

Conclusions

The INOVATe study is developing a framework for integration of molecular pathology into current models of multidisciplinary care and implementation of precision medicine that is applicable not only to ovarian cancer, but to patients with a range of cancer types.

Acknowledgements

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Participating Hospitals and Research Institutes