eha Sf(PM)

# Therapeutic response and resistance:

## Informed by preclinical models of rare gynaecological cancers

27th Sept 2024 Prof Clare L Scott
Walter and Eliza Hall Institute of Medical Research
Peter MacCallum Cancer Centre

# Disclosure Information

*Clare L Scott*

**I have the following financial relationships to disclose:**

**Advisory Boards:**
**AstraZeneca, Clovis Oncology, Eisai inc, Sierra Oncology, Roche, Takeda, MSD**

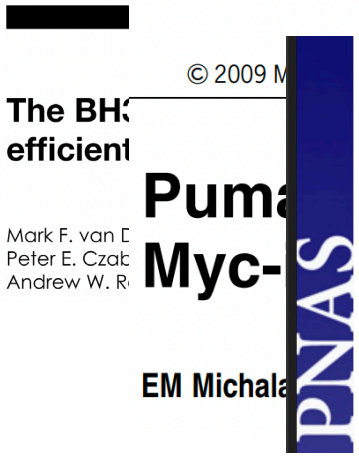
**Grant/Research support from:**
**AstraZeneca, Eisai Inc, Sierra Oncology, Boehringer Ingelheim, , Ideaya, Clovis Oncology, Roche, Beigene**

**Travel support**
**AstraZeneca, Illumina, Takeda, Roche, MSD**

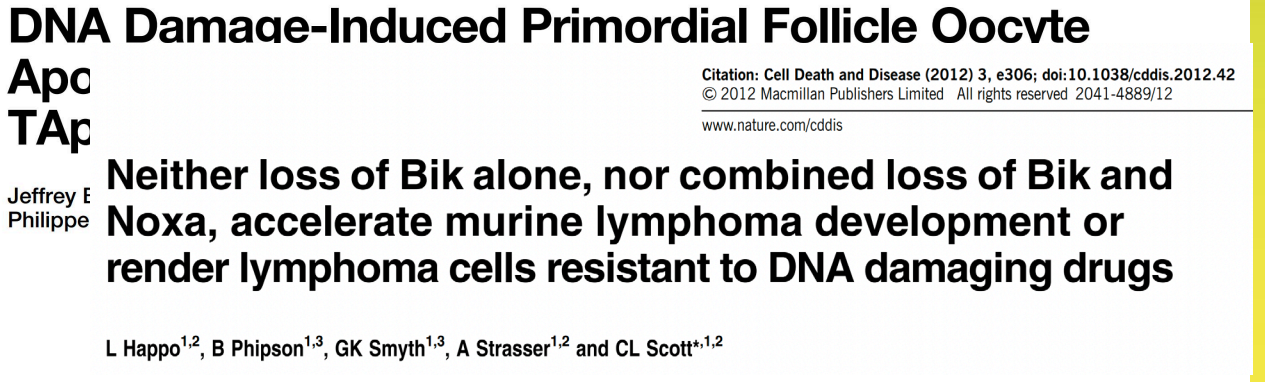
# Contents

# Prior track record in BH3-only and Pro-survival biology: the hidden side of making a drug (venetoclax)

WEHI
brighter together







# Background of rare gynaecological cancers

WEHI
brighter together

Stafford Fox Medical Research Foundation

# Rare Cancer definition

BioGrid
Connecting health information

- **Rare cancer: incidence < 6/100,000 population pa***
- **Collectively: 22% of all cancer diagnoses**
  **30% of all cancer deaths**
- **Often the precise cell of origin and etiology is unknown**
- **Treatment is according to closest histopathology/tumour stream**
- Lack of preclinical models and evidence-based treatment data
- Lack of appropriate clinical trials and/or drug approval and/or funding

(RARECARE: Surveillance of rare cancers in Europe; Gatta et al, Eur J Canc, 2011)

AUSTRALIAN RARE CANCER PORTAL

Outcomes are inferior to those for common cancers
(5-year survival of 47% compared to 65% for common cancers)

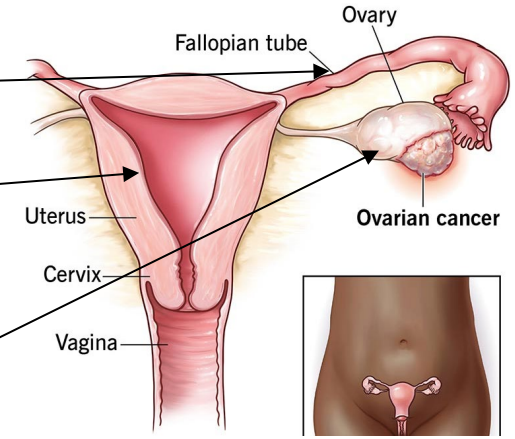
>50% of gynaecological cancers are classified as rare cancers

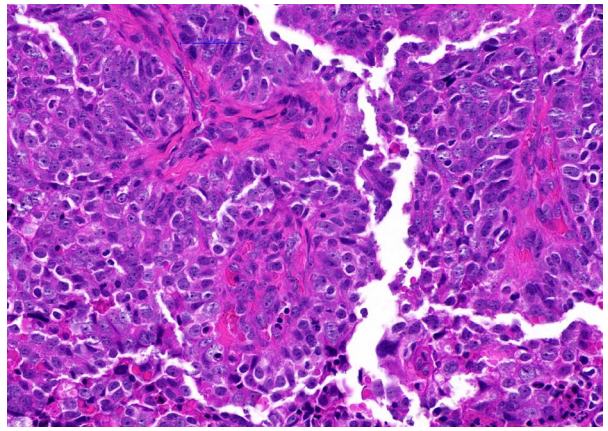
rare cancers AUSTRALIA

# Ovarian Cancer

- 2020, a total of 313,959 cases diagnosed globally
- 5-year overall survival ~49%
- Histological classifications

i. High-grade serous
ii. Low-grade serous
iii. Clear cell
iv. Endometrioid
v. Mucinous
vi. Sex cord-stromal tumours
vii. Carcinosarcoma
viii. Other very rare subtypes (i.e. malignant Brenner, sarcoma, germ cell tumours)

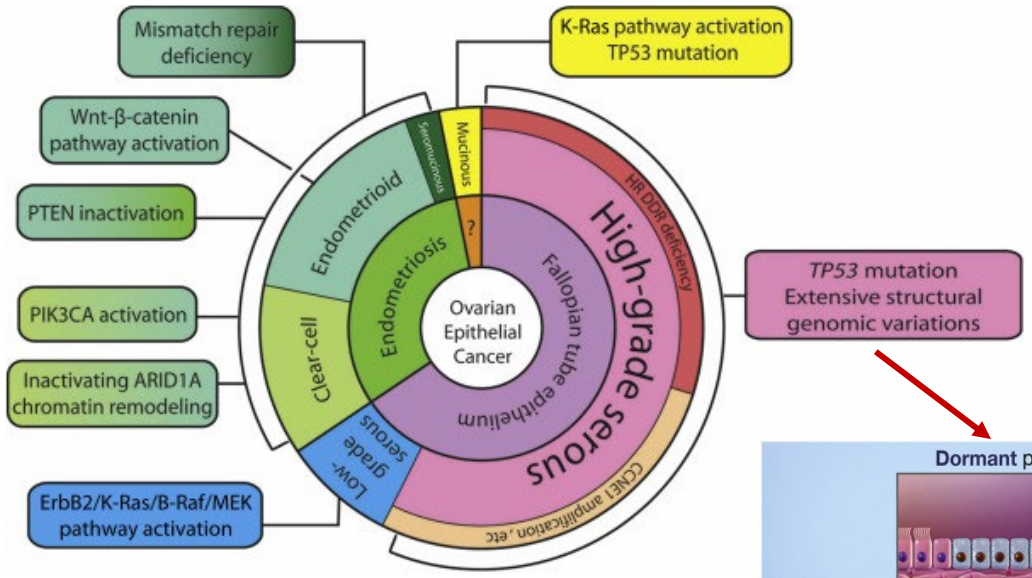




High grade serous ovarian carcinoma (#095)

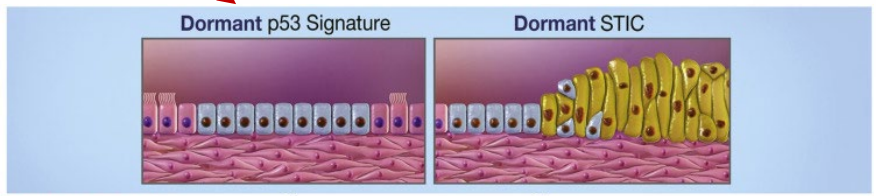
| Subtype | 5-year survival | *TP53*mut freq |
|---|---|---|
| High-grade serous | 32-84% | >95% |
| Low-grade serous | 54-93% | ~8% |
| Carcinosarcoma | 15-70% | >60% |
| Mucinous | 14-83% | ~64% |
| Endometrioid | 45-87% | ~30% |
| Clear cell | 22-82% | ~10% |
| Sex cord-stromal | 59-95% | ~5%* |

*mostly granulosa cell tumours (GCT), single case reports in Sertoli-Leydig and gynandroblastoma

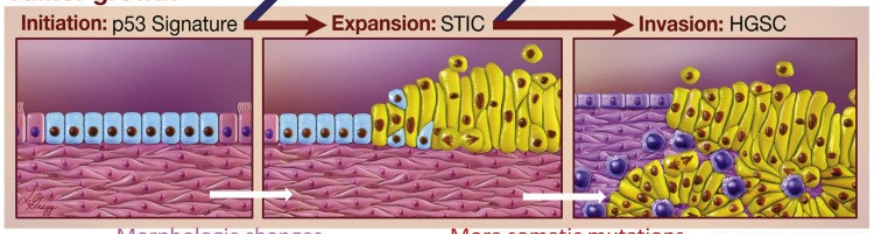
# Molecular characteristics of ovarian cancer subtypes and outcomes




*TP53* mutation
Extensive structural genomic variations



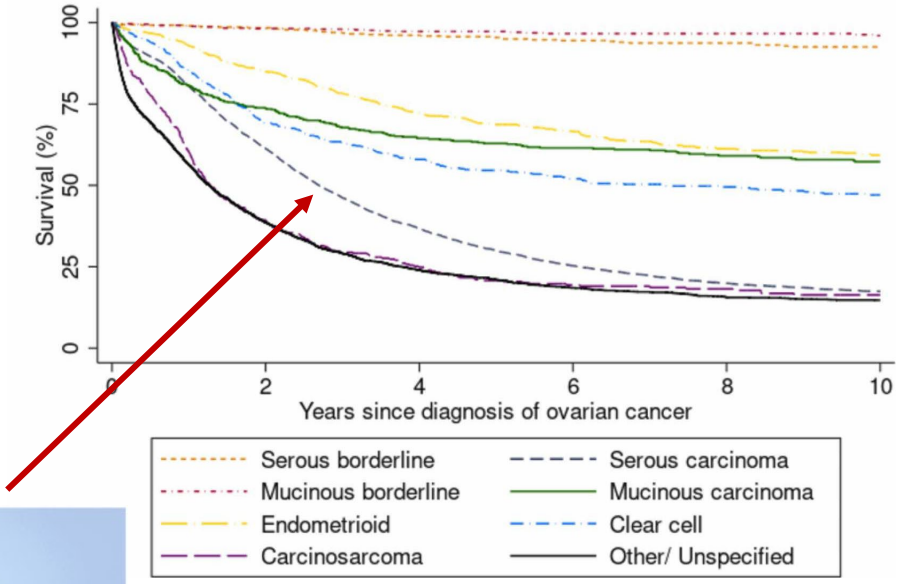

**Tumor growth**




Morphologic changes
More somatic mutations
Methylation change
LINE-1 activation
*CCNE1* amplification
Telomere shortening

More somatic mutations
More LOH events
Centrosome amplification
Telomere stops shortening
Immune cell infiltration

Genomic instability



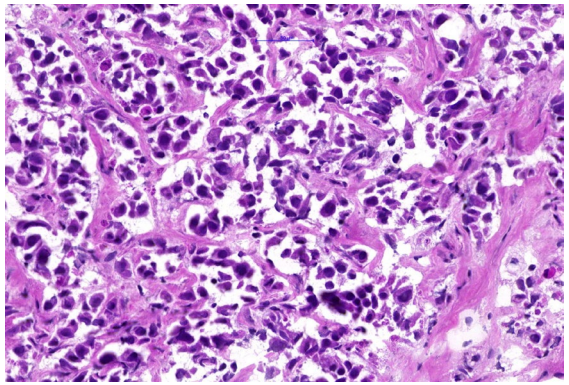

Shih, Wang and Wang, Amer J Path, 2021; Gaitskell et al, Canc Epid, 2022

# Cervical/vulvar/vaginal Cancer

- **Worldwide**, cervical cancer is the 4th most commonly diagnosed cancer in women
- **Worldwide**, cervical cancer is responsible for the most gynae cancer-related deaths
- HPV incidence varies according to geographic location
- Incidence is reducing in some countries due to vaccination programs

5-year survival rates:

- Cervical cancer (~75% SCC): 55-66%
  - adenocarcinoma a challenge
- Vulvar cancer (mostly SCC): 41-90%
- Vaginal cancer (mostly SCC): 57-84%



Vulvar Paget's disease (#333)

| Subtype | 5-year survival | *TP53*mut freq |
|---|---|---|
| Squamous cell carcinoma (SCC) | 55-65% | 5-6% |
| Adenocarcinoma (incl. mucinous, clear cell and serous) | 55-65% | 4-18% |
| Other (i.e. adenosquamous, small/large cell neuroendocrine) | 34% (adeno), 27%(NET) | 6-13% |
| SCC HPV+ | 70-90% | 0-50% |
| **SCC HPV- (p53wt; p53mut)** | **49-76%; 41-55%** | **41-92%** |
| Melanoma | 15% | 18-22% |
| Other very rare subtypes include basal cell, verrucous, adenocarcinoma including **extra-mammary Paget's disease (20-38%),** Bartholin gland and sarcoma | | |
| Squamous cell carcinoma (HPV+) | 57-84% | ~29% (~17%) |
| Adenocarcinoma (inc. clear cell) | ND | ND |
| Melanoma | 15% | 28-33% |
| Other very rare subtypes include sarcoma and lymphoma | | |

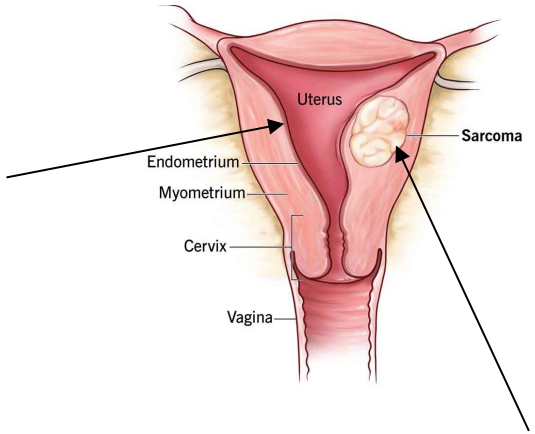
# Uterine Cancer

- 5th most common cancer in women
- 2019, 435,041 new diagnoses with **91,641 deaths globally**
- Rising incidence globally

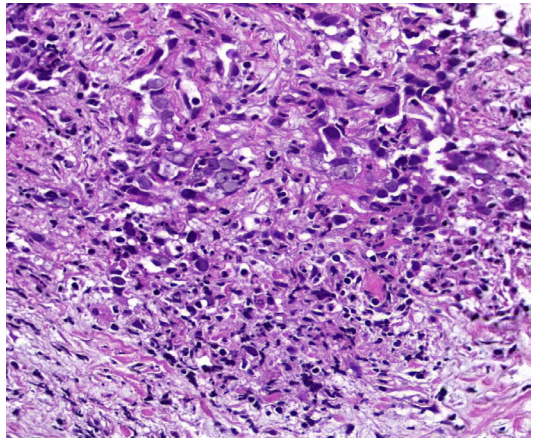
- 5-year overall survival ~83%
  Non-endometrioid have a worse prognosis

- 4 histological classifications for carcinomas (5-year survival)

i. Endometrioid (~85%)
ii. Clear cell
iii. Carcinosarcoma
iv. Serous



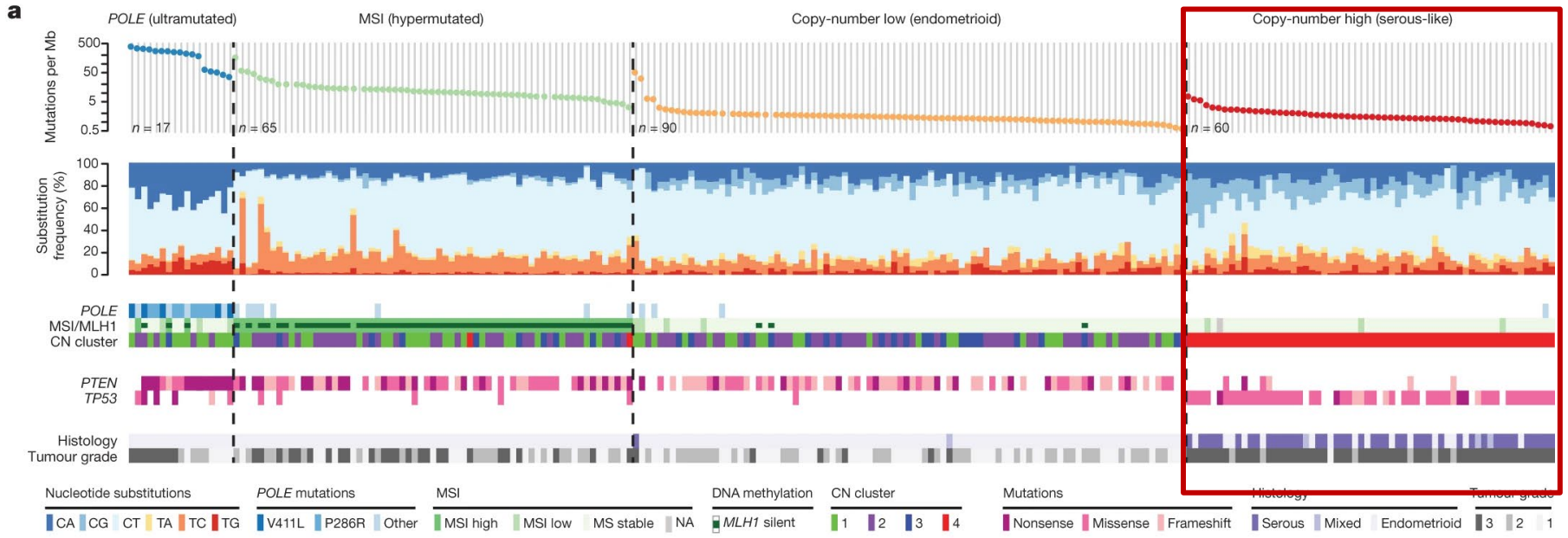

- Uterine sarcomas account for 3-7% of uterine malignancies

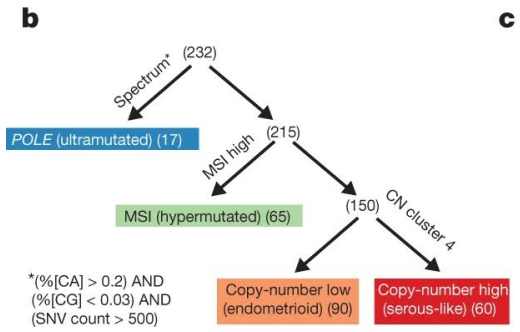


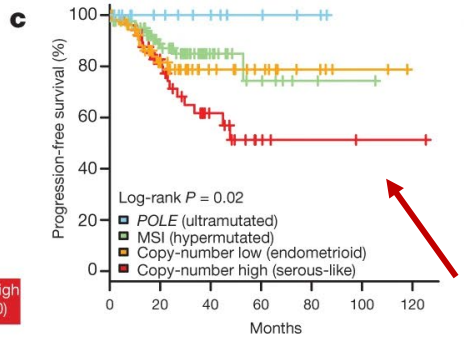
High grade serous endometrial carcinoma (#116)

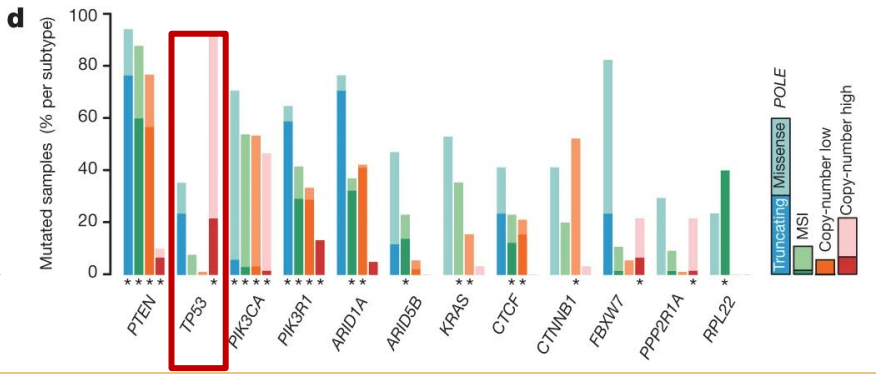
| Subtype | 5-year survival |
|---|---|
| Endometrioid | ~86% |
| Uterine serous cancer | 0-50% |
| Clear cell | 46-62% |
| Carcinosarcoma | 15-70% |
| uLMS | 14-63% |
| Adenosarcoma | 23-70% |
| Low-grade stromal sarcoma | 80-90% |
| High-grade stromal sarcoma | 15-40% |
| PEComa | ND |

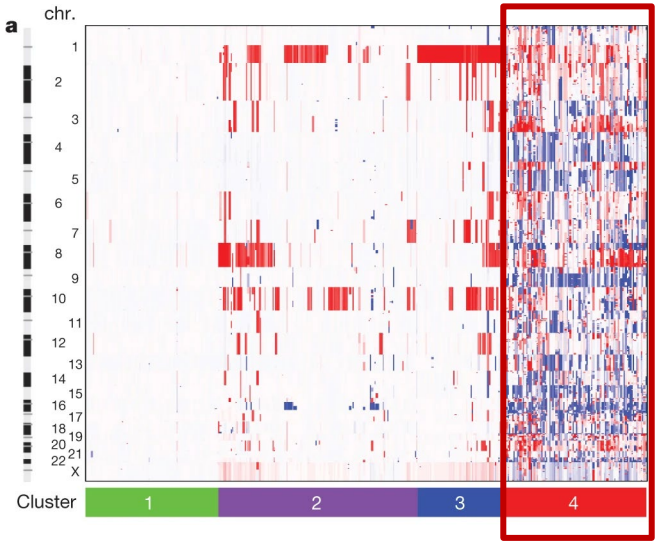
# Molecular landscape of uterine cancer and survival outcomes




Levine and TCGA, Nature, 2013

RAINBO Research Consortium, Int J Gynecol Cancer. doi:10.1136/ijgc-2022-004039

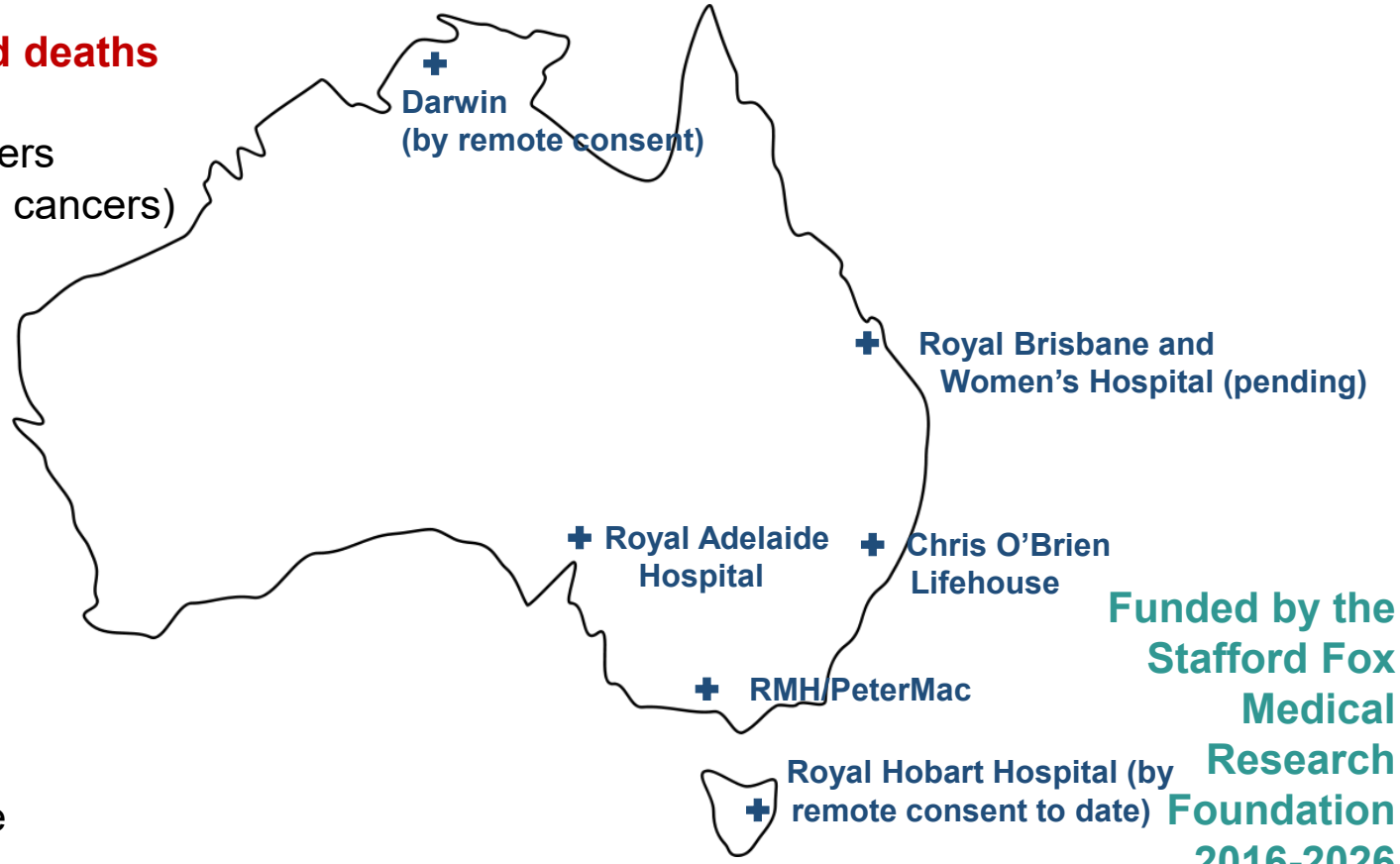
# WEHI Stafford Fox Rare Cancer Program:
## National – PIs Clare Scott and Tony Papenfuss

- National study of rare cancer cases (patients to be able to provide consent in each capital city)
- Patients can consent via **remote option OR via the ARC Portal**
- Collection of clinical data and tissue (eg FFPE, fresh tissue from surgery or biopsy, blood incl cfDNA, PBMCs, plasma)

**AIM: To build a national rare cancer resource to underpin rare cancer research**

Rare cancers account for **~30% of all cancer-related deaths**

**Inferior** outcomes for individuals with rare cancers
(5-year survival of **47%** compared to 65% for common cancers)



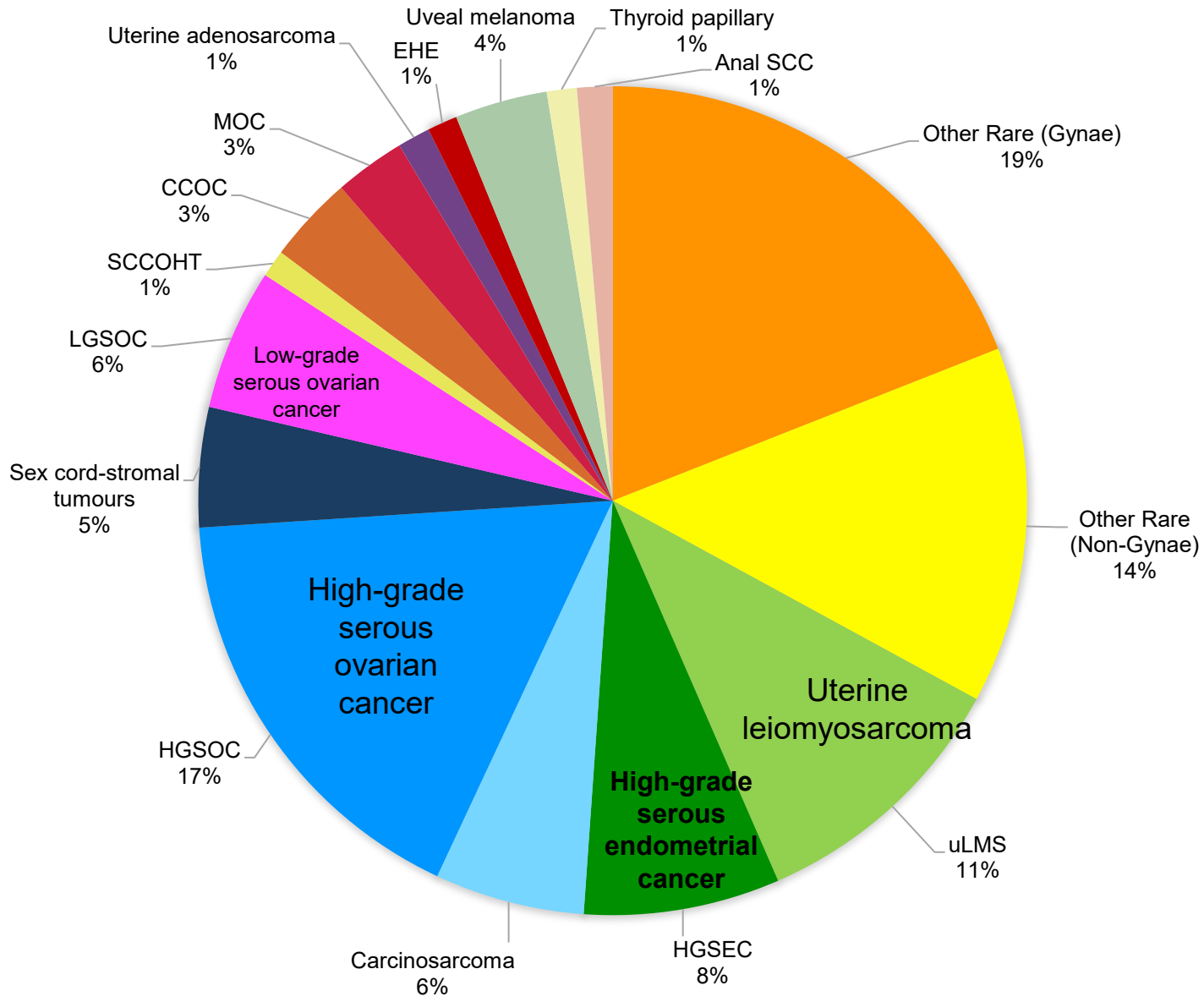

**We offered sequencing for RC patients nationally**
WGS if fresh tissue of sufficient purity
WES if FFPE / and sufficient purity
TSO500 if low tumor purity/germline DNA unavailable

Funded by the Stafford Fox Medical Research Foundation 2016-2026

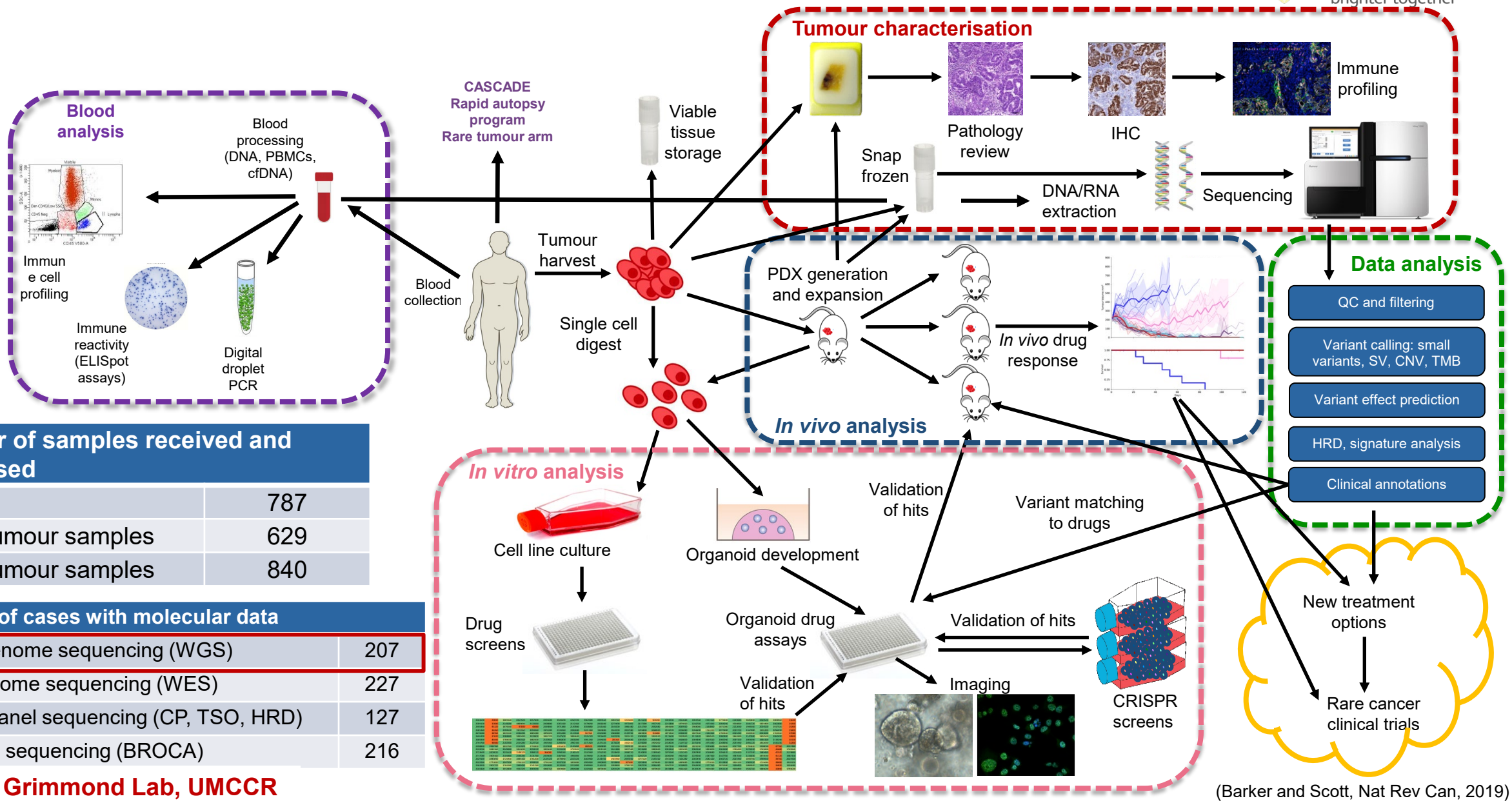
# WEHI- SFRCP

| Accrual to Date (since end of 2016) | |
|---|---|
| Patients | 924 |
| Tumours (gynae) | 1090 (724) |
| Rare tumour subtypes (gynae) | 213 (103) |

| Projects | # |
|---|---|
| HGSOC | 160 |
| HGSEC | 72 |
| uLMS | 99 |
| Carcinosarcoma | 55 |
| Sex cord-stromal tumours | 44 |
| LGSOC | 52 |
| SCCOHT | 10 |
| CCOC (clear cell) | 32 |
| MOC (mucinous) | 26 |
| Uterine adenosarcoma | 12 |
| EHE | 11 |
| Uveal melanoma | 34 |
| Thyroid papillary | 11 |
| Anal SCC | 13 |
| Other Rare (Gynae) | 179 |
| Other Rare (Non-gynae) | 131 |



# WEHI-Stafford Fox Rare Cancer Program




| Number of samples received and processed | |
|---|---|
| Bloods | 787 |
| Fresh tumour samples | 629 |
| FFPE tumour samples | 840 |

| Number of cases with molecular data | |
|---|---|
| Whole genome sequencing (WGS) | 207 |
| Whole exome sequencing (WES) | 227 |
| Cancer panel sequencing (CP, TSO, HRD) | 127 |
| HR panel sequencing (BROCA) | 216 |

**Grimmond Lab, UMCCR**

(Barker and Scott, Nat Rev Can, 2019)

# PDX models

| | Tumour type | # PDX | *TP53*mut | Cell lines (*TP53*mut) | Organoids (*TP53* mut) |
|---|---|---|---|---|---|
| Ovarian | HGSOC / HGS FT | 44 | 44 | 5/5 | 17/17 |
| | Carcinosarcoma | 8 | 7 | 1/1 | 4/3 |
| | Clear cell carcinoma | 6 | 2 | 1/0 | 3/2 |
| | Large cell NET | 1 | 1 | 0 | 1/1 |
| | Yolk sac tumour | 1 | 0 | 0 | 0 |
| | Mucinous | 1 | 1 | 0 | 0 |
| | Endometrioid | 1 | 0 | 0 | 0 |
| Endometrial | HGSEC | 12 | 12 | 9/9 | 5/5 |
| | Carcinosarcoma | 8 | 8 | 0 | 1/1 |
| | uLMS | 12 | 12 | 0 | 1/1 |
| | Clear cell carcinoma | 1 | 1 | 0 | 0 |
| | Adenosarcoma | 1 | 0 | 1/0 | 0 |
| | Low grade endometrial stromal sarcoma | 1 | 0 | 0 | 0 |
| | Undifferentiated carcinoma and sarcoma | 1 | 0 | 0 | 0 |
| Cervical | Adenocarcinoma (AC) | 2 | 1 | 0 | 0 |
| | Squamous cell carcinoma | 1 | 1 | 0 | 0 |
| | Poorly differentiated AC with sarcomatoid differentiation | 1 | 0 | 0 | 0 |
| | Mucinous adenocarcinoma | 1 | 1 | 0 | 0 |
| | CNS embryonal tumour with multi-layered rosettes | 1 | 0 | 0 | 0 |
| Vulval | Squamous cell carcinoma | 1 | 1 | 0 | 0 |
| | Adenocarcinoma (possibly from HGSEC) | 1 | 1 | 0 | 0 |
| | Adenocarcinoma arising from Paget's disease | 1 | 1 | 0 | 1/1 |
| Vaginal | Adenocarcinoma (possibly from HGSEC) | 1 | 1 | 0 | 0 |
| | Adenocarcinoma of mucinous/GI type/non-HPV | 1 | 1 | 0 | 0 |
| | Periurethral adenocarcinoma | 1 | 1 | 0 | 0 |

**To date:**

**109 PDX models** of rare gynaecological cancers (from 103 individuals)

**4 PDX models** of non-gynae rare cancer (incl. mantle cell lymphoma, pseudomyxoma peritonei)

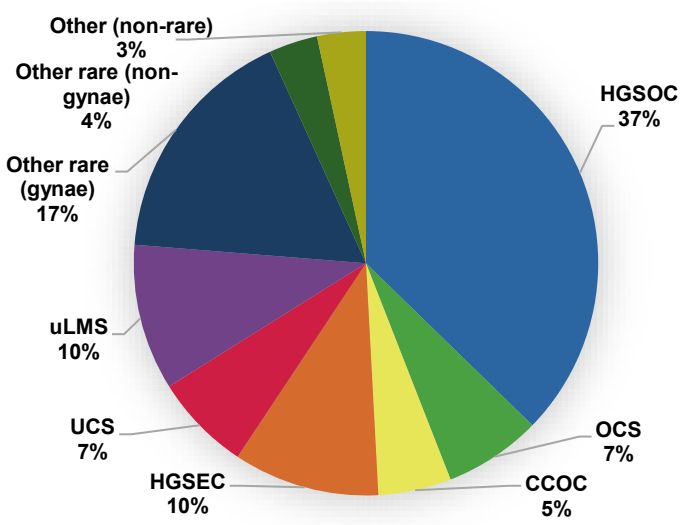
**4 PDX models** of non-rare gynaecological cancer (endometrioid endometrial cancer)

**Dr Cassandra Vandenberg**

**PDX verified and characterised by:**

IHC and expert gynae pathologist review

Most have WGS, WES or BROCA, STR profiling, cisplatin and taxol response




**Cass Vandenberg**, Silvia Stoev, Kathy Barber, Ratana Lim, Chloe Neagle, Andrew Farrell, Rachael Taylor, Joe Polidano, Liz Kyran, Gayanie Ratnayake

# PDX models of rare gynaecological cancers

| | Tumour type | # PDX | Potentially Targetable Molecular Aberrations* |
|---|---|---|---|
| Ovarian | HGSOC * | 34 | ***BRCA1/BRCA2* mutations; *BRIP1,* *ARID1A*, *PIK3CA* mutation; *RAD51C* methylation, *CCNE1* amp** |
| | Carcinosarcoma * | 10 | ***AKT2*, *CCNE1*, *FGFR3* amplification; *FBXW7* mutation; Signature 3** |
| | HGSFT* | 2 | ***ERBB2* amp** |
| | Clear cell carcinoma | 3 | ***PIK3CA* mutation** |
| | Large cell NET | 1 | ***BRCA2* rearrangement; Signature 3** |
| | Yolk sac tumour | 1 | pending |
| | SCTAT | 1 | *TERT* promoter |
| | Mucinous | 1 | ***NRAS* mutation** |
| | Endometrioid | 1 | ***PIK3CA* mutation**, *ATM, ESR1, gALK* VUS, *CDKN2A* del |
| Endometrial | HGSEC * | 12 | ***AKT1* mutation**; ***CCNE1*, *ERBB2* amp; Signature 3** |
| | Carcinosarcoma * | 6 | ***PIK3CA, PTEN* mutation**; ***CCNE1* amp**; *MYCN* amp; **Signature 3** |
| | uLMS * | 11 | ***BRCA2*, *RB1* deletion; *NTRK2* amp; Signature 3** |
| | HG Clear cell carcinoma | 2 | *EZH2, MSH6* mutations |
| | Adenosarcoma* | 1 | ***KRAS* mutation**; *CDKN2A* and *CDKN1B* del |
| Cervical | Adenocarcinoma | 3 | **Signature 3** |
| | Squamous cell carcinoma | 1 | *FBXW7* mutation |
| | Poorly differentiated adenocarcinoma with sarcomatoid diff | 1 | *FANCD2* mutation |
| | Mucinous adenocarcinoma | 2 | *MSH2* mut, *ARID1A* mut, *ATR* mut, ***PIK3CA* mut**, *ARAF* mut |
| | CNS embryonal tumour with multilayered rosettes | 1 | *CTNNB1* mutation (x2) |
| Vulval | Squamous cell carcinoma | 1 | *CDKN2A*, *NTRK3* mutations, *EGFR* amp |
| | Adenocarcinoma arising from Paget's disease* | 1 | High TMB, ***PIK3CA* mutation**, *ARID1B* rearrangement, ***ERBB2* amp** |
| Vaginal | Adenocarcinoma | 1 | ***ERBB2* amp**, *CDKN2A* mut, *SRC* amp, *NF1* rearrangement |
| | Adenocarcinoma of mucinous/GI type/non-HPV | 1 | ***CCNE1*, *ERBB2***, *ERBB3*, *CDK4*, ***KRAS***, *MTOR* amplifications |

**To date:**

**100 PDX models** of rare gynaecological cancer subtypes from 85 patients (samples collected from different sites or time points in clinical history)

**4 PDX models** of non-rare gynaecological cancer (endometrioid endometrial cancer)

**3 PDX models** of non-gynae rare cancer (mantle cell lymphoma and pseudomyxoma peritonei)

* Successful cell lines and organoids developed from some models

**RED – potential PARPi sensitivity**

**PURPLE – *PIK3CA/AKT/PTEN* mut/amp; potential alpelisib sensitivity**

**GREEN – ERBB2 amp; potential trastuzumab sensitivity**

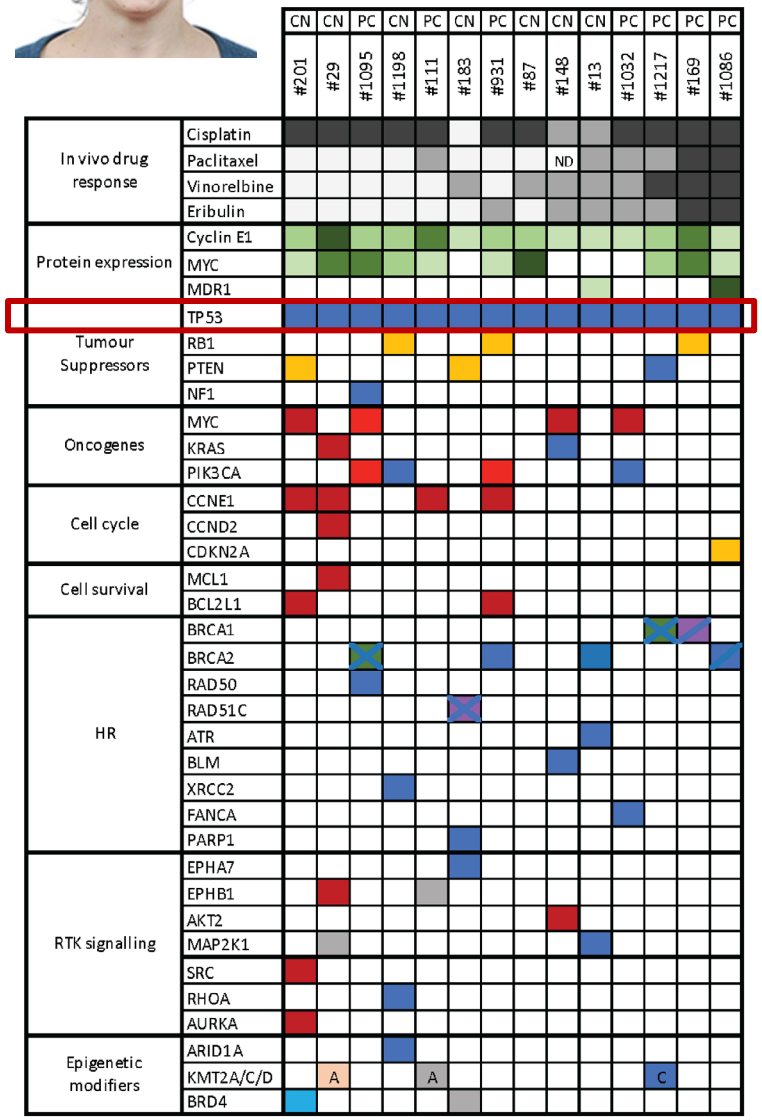
**ORANGE – *KRAS/NRAS* mut/amp; RAS/RAF inhibitor**

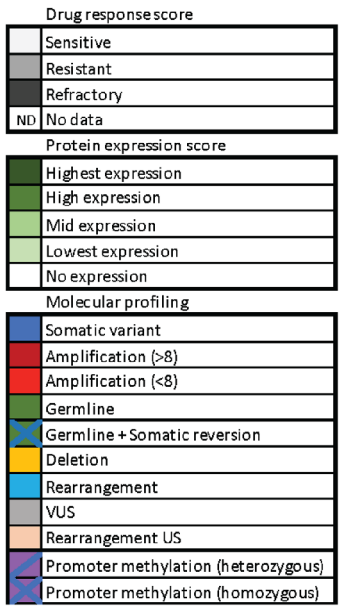
**BLUE – *CCNE1* amp; cell cycle checkpoint inhibitors**

Dr Holly Barker

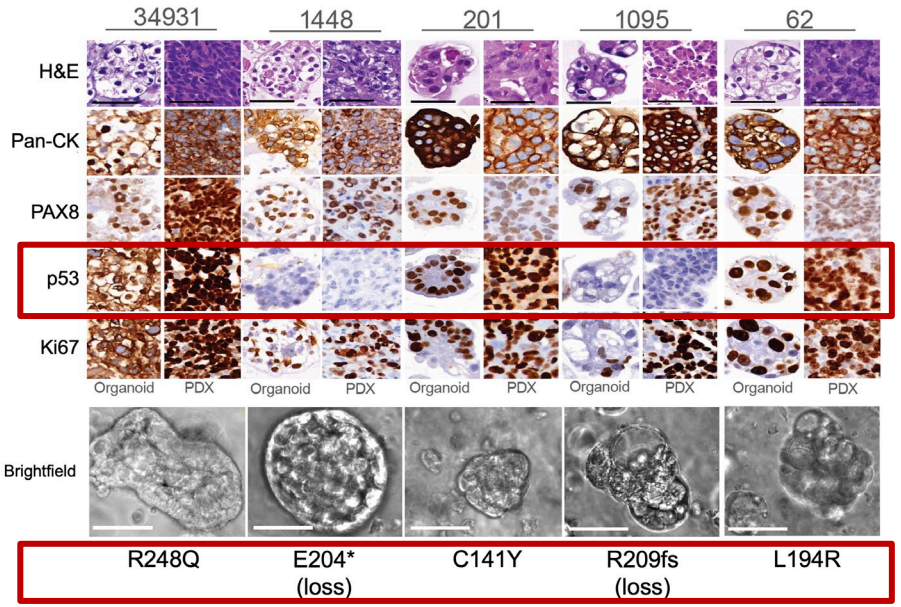
# Preclinical models of HGSOC

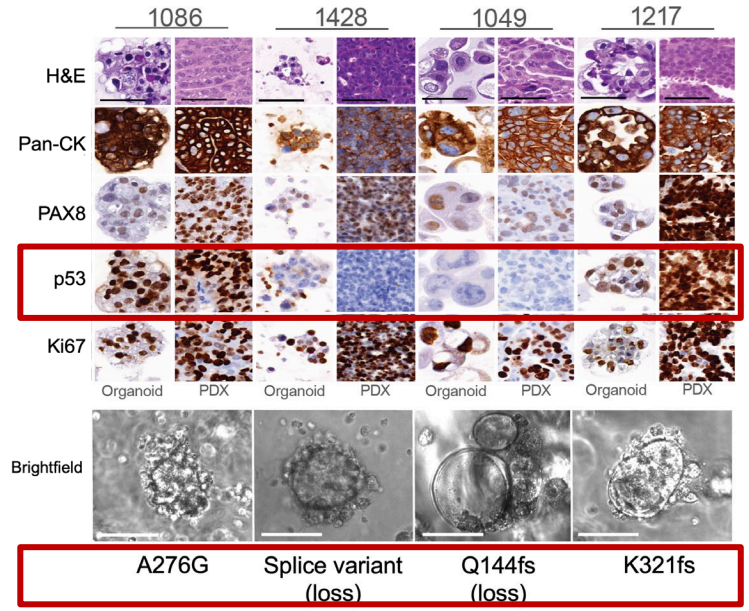
WEHI brighter together



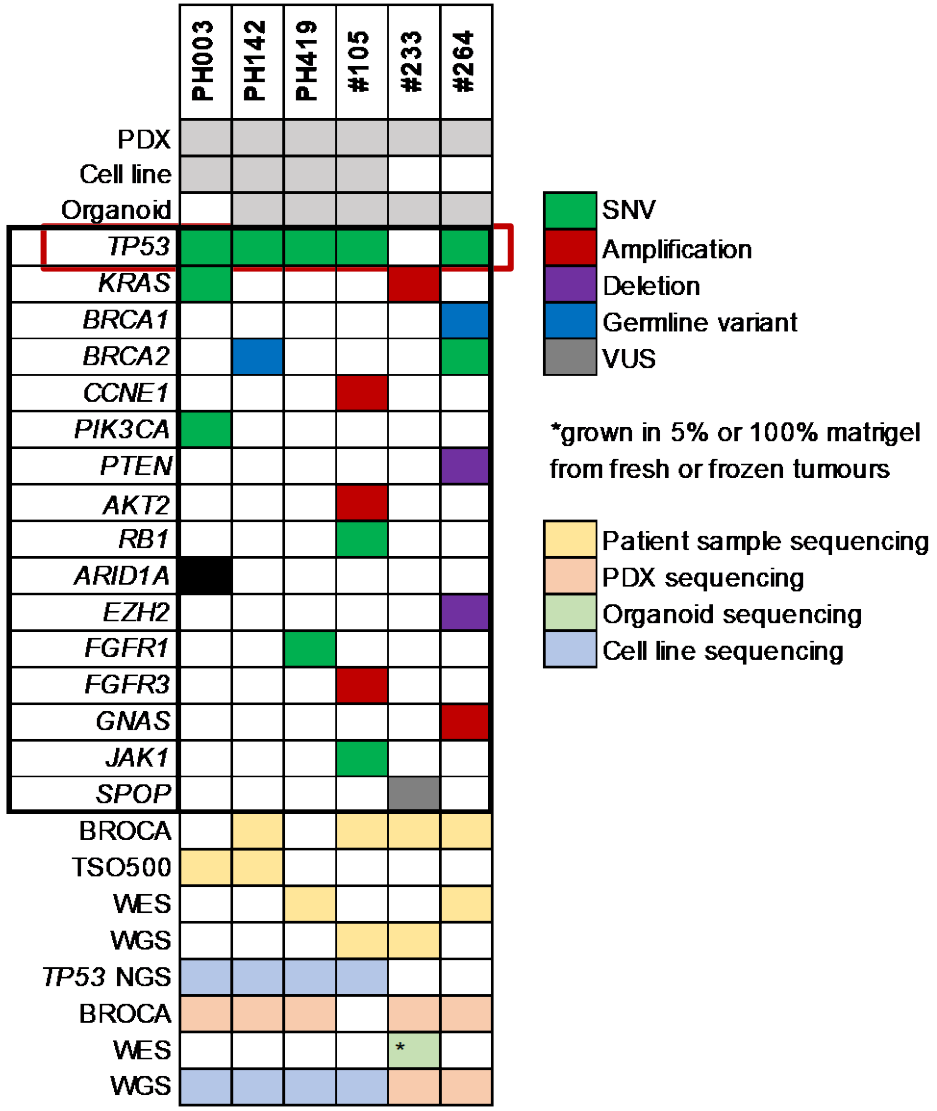

- Most cell lines and organoid models have been generated from PDX tissue
- All models are validated by at least 3 methods:
  - Human PCR
  - STR profiling
  - *TP53* sequencing
  - IHC
  - More in-depth sequencing (WES or WGS) if possible




Ho et al, Ther Adv Med Oncol, 2023; Liz Kyran, Cass Vandenberg

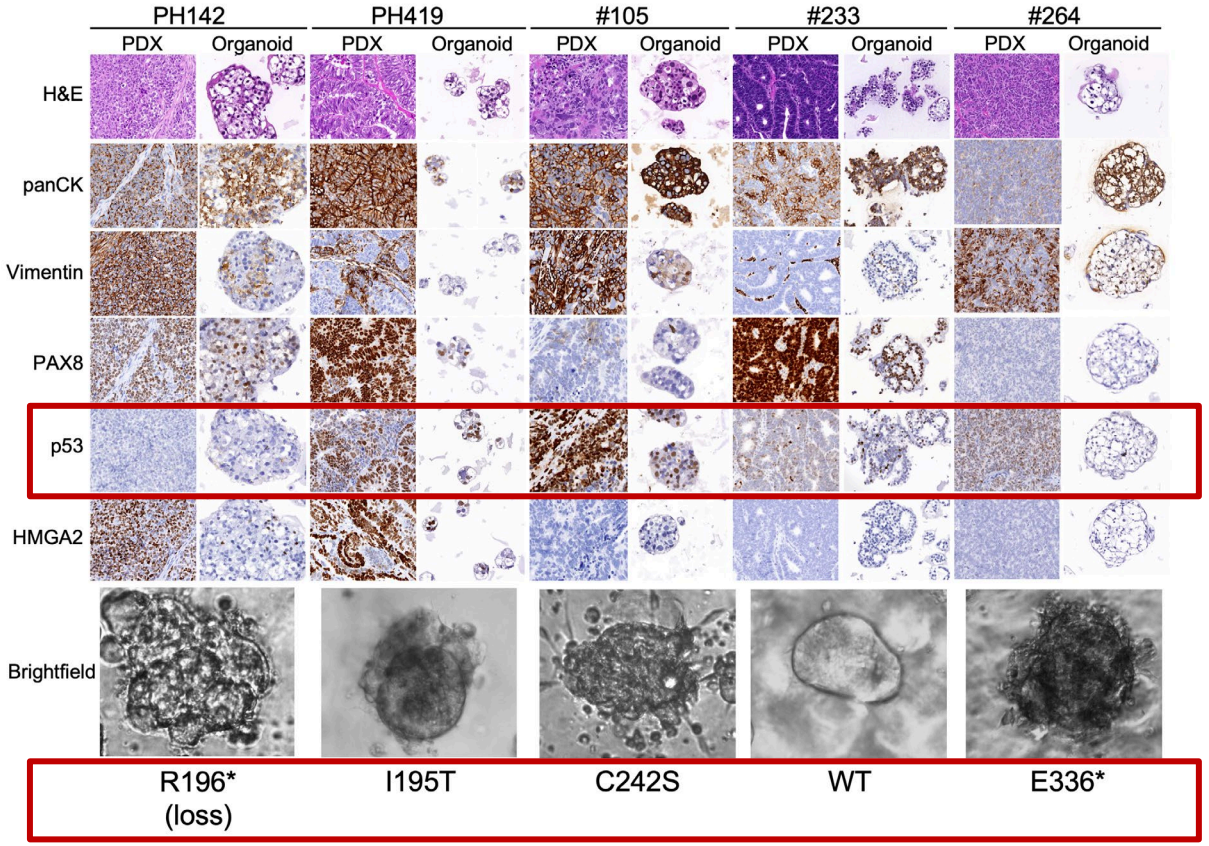
# Preclinical models of OCS




SNV
Amplification
Deletion
Germline variant
VUS

*grown in 5% or 100% matrigel from fresh or frozen tumours

Patient sample sequencing
PDX sequencing
Organoid sequencing
Cell line sequencing

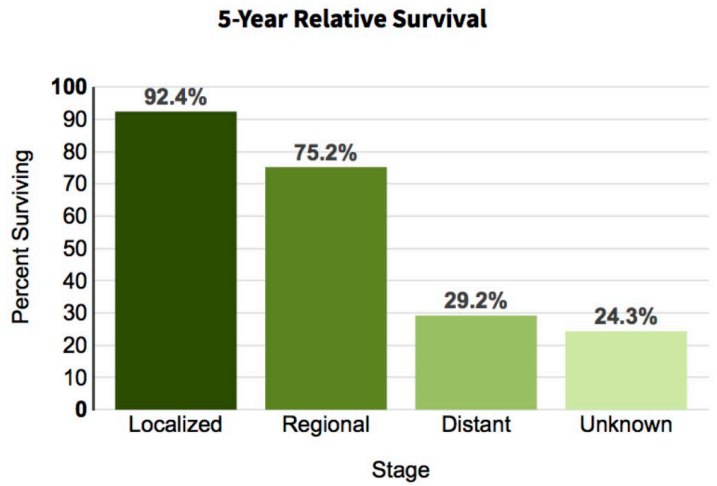



Ho et al, Can Res, 2022; Andrew Farrell, Rachael Taylor, Cass Vandenberg

# Pre-clinical models to aid delivery of PARPi in HGSOC

# High-grade serous ovarian carcinoma (HGSOC)

- Most common epithelial ovarian cancer subtype (~75% cases)
- Aggressive, often diagnosed at advanced stage
- Poor survival outcomes




## Molecular characteristics:

- Ubiquitous ***TP53*** mutations
- Homologous recombination (HR) DNA repair pathway defects
  - *e.g* ***BRCA1*** **and** ***RAD51C***
- High degree of genomic instability

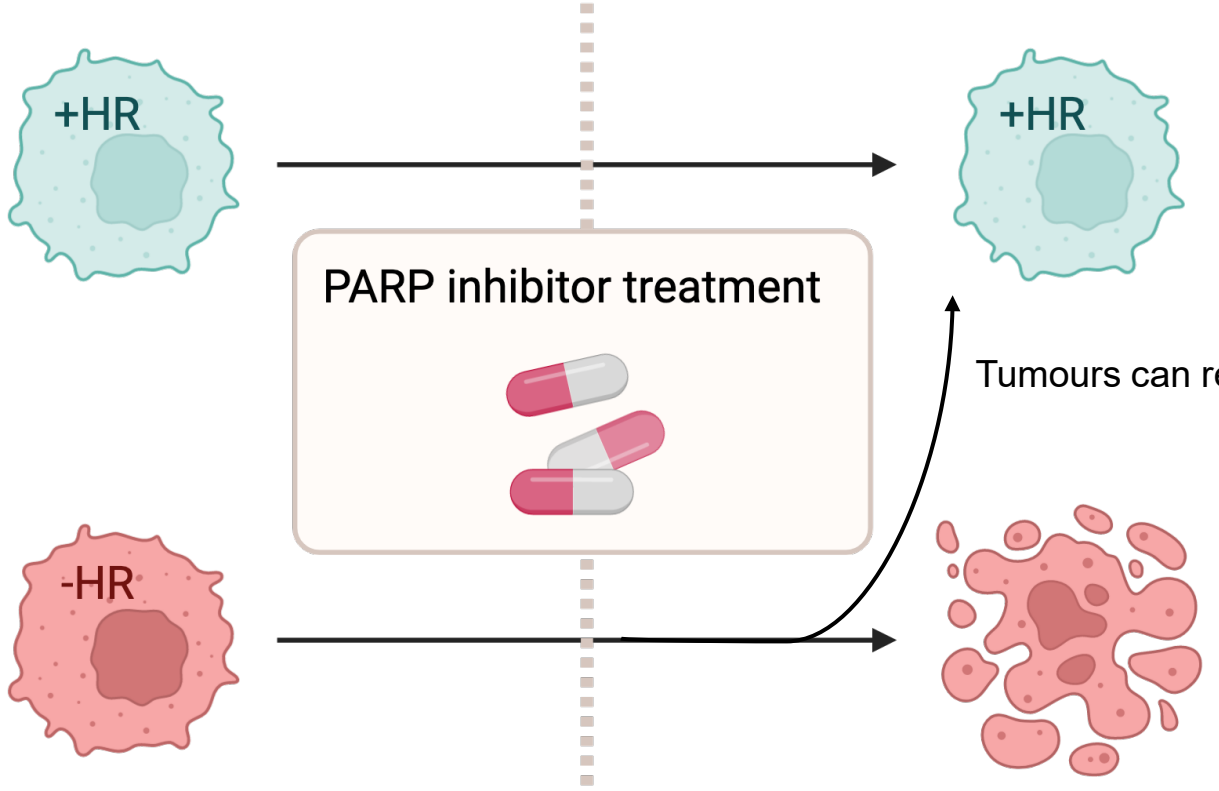
Susceptible to treatment with:

- **Platinum agents**
- **PARP inhibitors**

SEER 2009-2018 data; Bowtell et al., Nat Rev Cancer, 2015

# PARP inhibitors (PARPi)

- Despite their great success in the clinic, **many patients on PARPi eventually relapse**
- Multiple PARPi resistance mechanisms have been described, many rely on restored HR DNA repair
    - *e.g.* secondary HR gene mutations, loss of HR gene methylation, alternative splicing

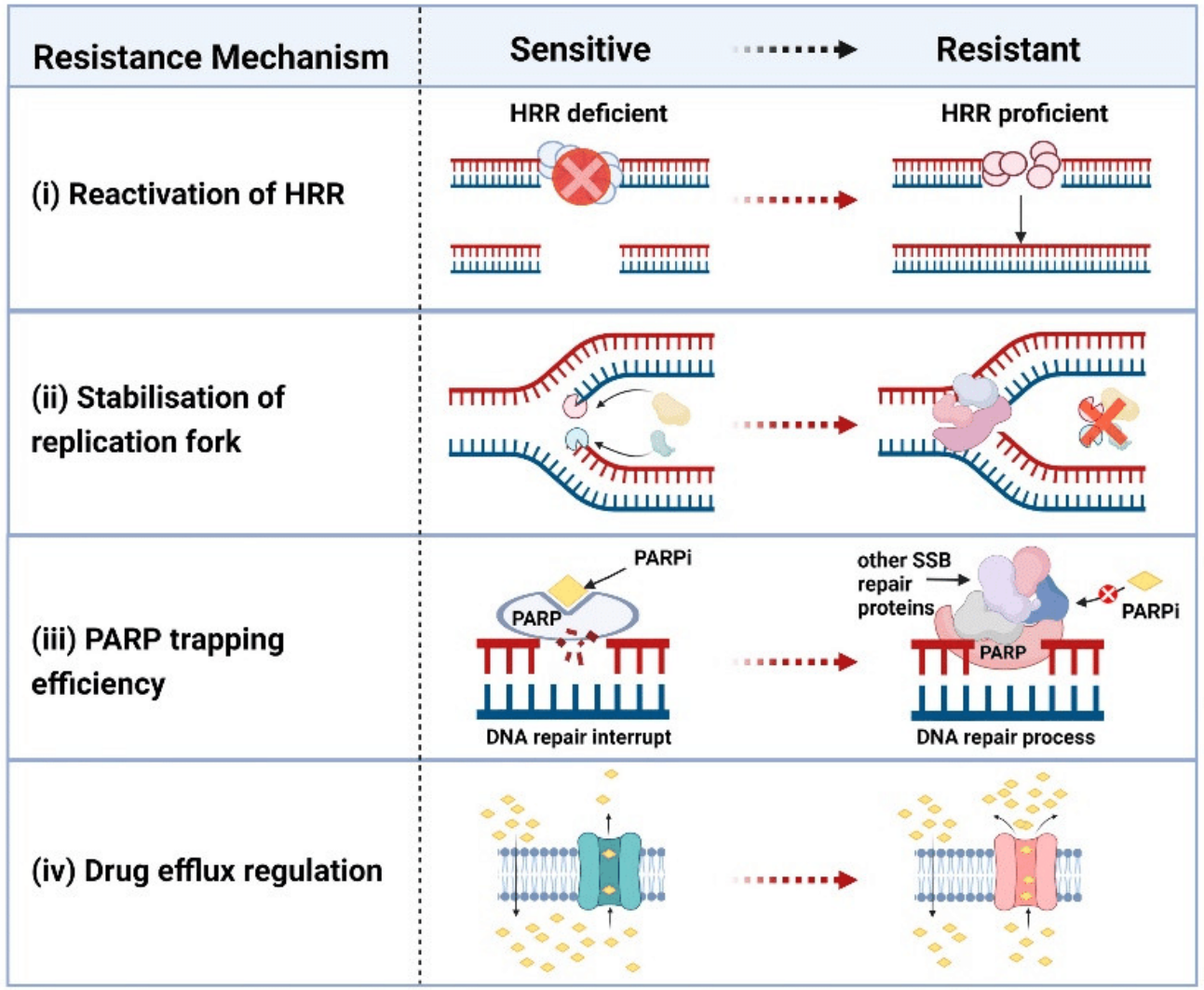



Tumours can restore HR under treatment pressure
➔ PARPi resistance

Commonly used PARPi:
Rucaparib, Olaparib and Niraparib

Figure made in BioRender

# Diversity of PARPi resistance mechanisms




- **Correcting reversion mutations in HR genes *RAD51C, RAD51D*** Kondrashova et al Can Discov 2017

- **Loss of *BRCA1* or *RAD51C* methylation with gene silencing**
  Kondrashova et al Nat Communs 2018;
  Nesic et al Cancer Res 2021;
  Hurley et al NAR Cancer, 2021 (Kaufmann Lab, MAYO)
  Xu et al NAR Cancer 2024 (Kondrashova Lab, QIMR)

- **Secondary splice site mutations of *BRCA1* + 2**
  Nesic et al Molecular Cancer 2024

- PARP1 mutations: PARP1 DMS (Matthew Wakefield, Scott Lab, WEHI)

Olga Kondrashova

Ksenjia Nesic

Matthew Wakefield

Figure from Xie et al., Cancers, 2022

# Diversity of PARPi resistance mechanisms

Published OnlineFirst June 6, 2017; DOI: 10.1158/2159-8290.CD-17-0419

RESEARCH

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*RAD51C*
Acquire
Rucapar

Olga Kondrashova
Nelson N.H. Teng[5]
Maria Jasin[9], Rohi
Kara A. Bernstein
Ganessan Kichena
Lara Maloney[3], Da
Matthew J. Wakef
Mitch Raponi[3], Iai

nature COMMUNICATIONS

ARTICLE

DOI: 10.1

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Olga Ko

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Research Article

Acquired RAD51C pr
grade serous ovarian

Ksenija Nesic, Olga Kondrashova, Rachel M
Kristy Shield-Artin, Marc Radke, Ashan Mus
Nadia Traficante, Australian Ovarian Cance
Alexander Dobrovic, Matthew J. Wakefield,

HGSOC (ARIEL2 Part 1 trial) confirmed that homozyg
predicts rucaparib clinical response, and that methyl
chemotherapy. Accordingly, quantitative *BRCA1* me
biopsy could allow identification of patients most lik
PARPi therapy.

*Published online 9 July 2021*

*NAR Cancer, 2021, Vol. 3, No. 3 1*
*https://doi.org/10.1093/narcan/zcab028*

**Characterization of a *RAD51C*-silenced high-grade serous ova**
**PARP inhib**

*NAR Cancer*, 2024, **6**, zcae033
https://doi.org/10.1093/narcan/zcae033
Advance access publication date: 25 J

**Cancer Gene Regulation, Chromatin, a**

Rachel M. Hurley[1]
Taylor M. Weiskitt
Nicholas M. Patho
Paula A. Schneide
Ee Ming Wong[7,8],
Thomas C. Hardin
Matthew J. Wakefi
Andrea E. Wahner
S. John Weroha[5,‡]

**High-level tum**
**required for ho**
**cancers**

Lijun Xu[1,2], Brett Liddell
Matthew J. Wakefield[3,4]

[1]Cancer Research Program, QIMR
[2]The University of Queensland, Bri
[3]The Walter and Eliza Hall Institute
[4]Department of Obstetrics and Gyr

Nesic *et al. Molecular Cancer* (2024) 23:158
https://doi.org/10.1186/s12943-024-02048-1

Molecular Cancer

**CORRESPONDENCE** **Open Access**

Check for updates

## *BRCA1* secondary splice-site mutations drive exon-skipping and PARP inhibitor resistance

Ksenija Nesic[1,2†], John J. Krais[3,4†], Yifan Wang[3], Cassandra J. Vandenberg[1,2], Pooja Patel[3], Kathy Q. Cai[3], Tanya Kwan[5], Elizabeth Lieschke[1,2], Gwo-Yaw Ho[6], Holly E. Barker[1,2], Justin Bedo[1,2], Silvia Casadei[7], Andrew Farrell[1,2], Marc Radke[7], Kristy Shield-Artin[1,2], Jocelyn S. Penington[1,2], Franziska Geissler[1,2], Elizabeth Kyran[1,2], Robert Betsch[3], Lijun Xu[8,9], Fan Zhang[10], Alexander Dobrovic[10], Inger Olesen[11], Rebecca Kristeleit[12,13], Amit Oza[14], Iain McNeish[15], Gayanie Ratnayake[16], Nadia Traficante[17,18], Australian Ovarian Cancer Study, Anna DeFazio[19,20,21], David D. L. Bowtell[17,18], Thomas C. Harding[5], Kevin Lin[5], Elizabeth M. Swisher[7], Olga Kondrashova[1,8,9], Clare L. Scott[1,2,16,17,18,22*†], Neil Johnson[3*†] and Matthew J. Wakefield[1,2,22*†]

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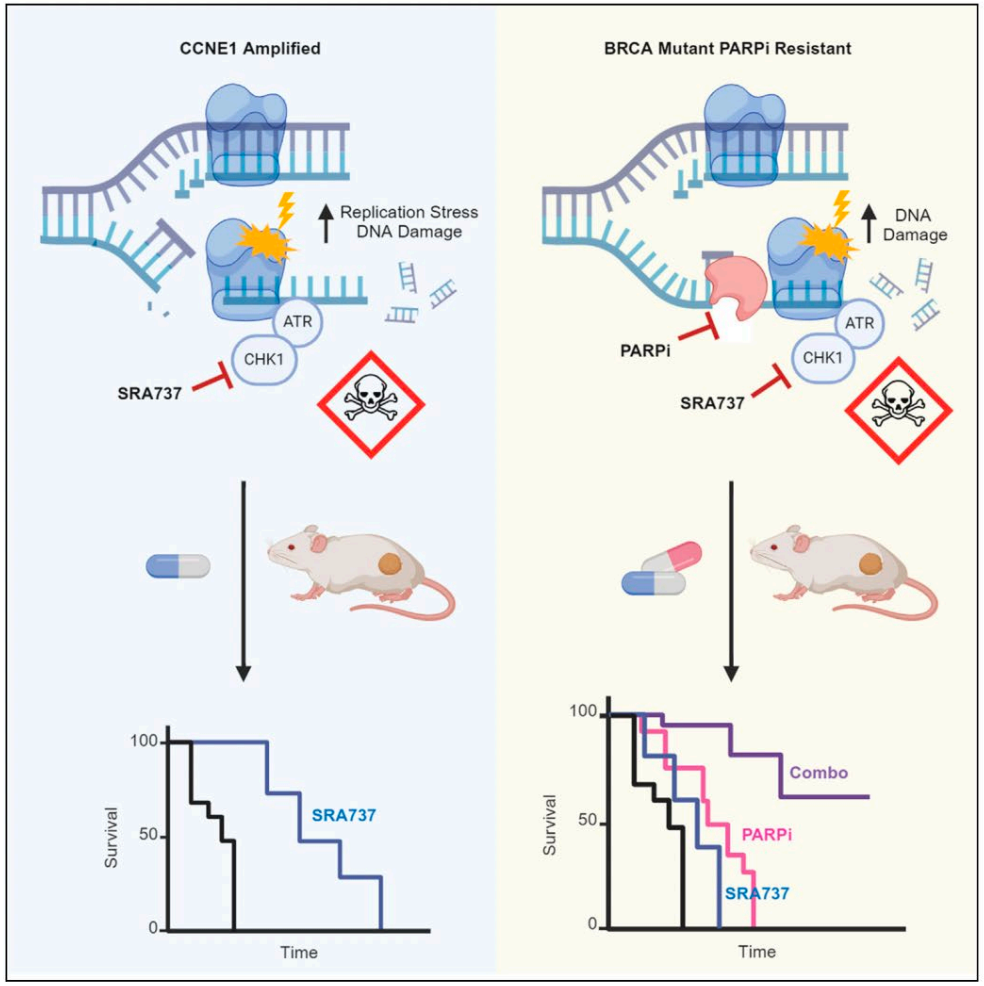
# PARPi DDRi combination therapy

WEHI
brighter together

## 1st example

Article

## CHK1 inhibitor SRA737 is active in PARP inhibitor resistant and *CCNE1* amplified ovarian cancer




Haineng Xu, Sarah B. Gitto, Gwo-Yaw Ho, ..., Cassandra J. Vandenberg, Clare L. Scott, Fiona Simpkins

scottc@wehi.edu.au (C.L.S.)
fiona.simpkins@pennmedicine.edu (F.S.)

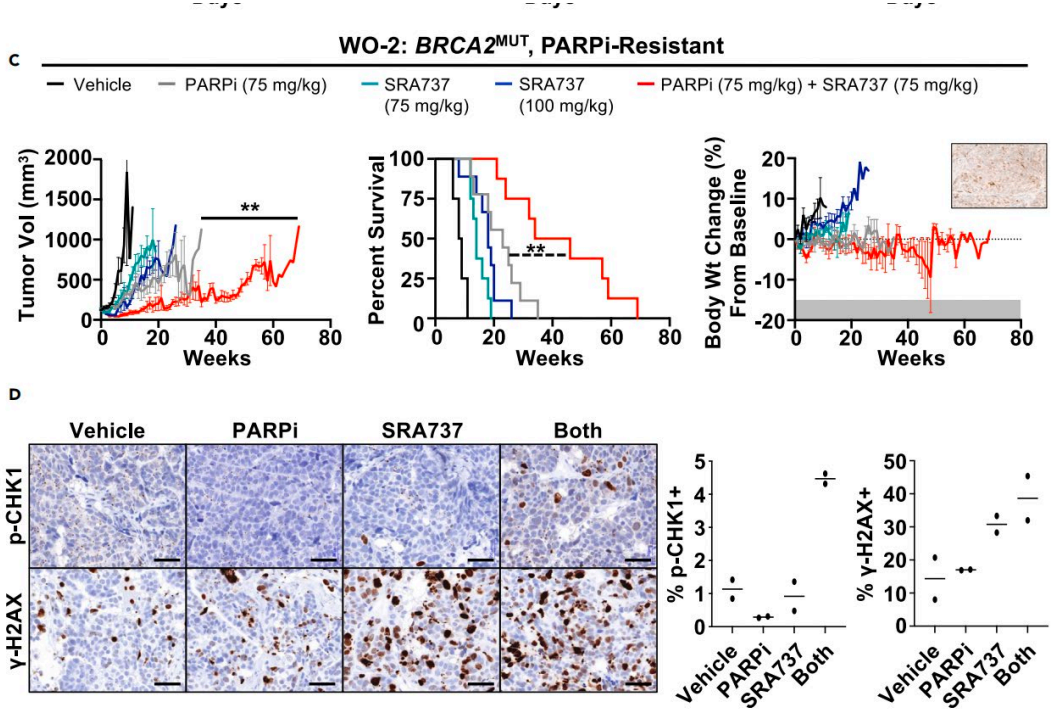
### Highlights

Selective oral CHK1 inhibitor SRA737 alone is active in CCNE1 amplified models

SRA737 combined with PARP inhibitor shows synergy in multi-drug resistant cells

Combination treatment increases replication stress and apoptosis

Combination shows significant activity in PARPi-resistant BRCA mutant PDX models



# ESMO2024: Novel prognostic blood immune biomarker for PARPi response

## #747P: SOLACE2 (ANZGOG 1723): A Phase 2 randomized trial of Olaparib (O) and Durvalumab (D) with or without low dose cyclophosphamide (LDCy) in platinum-sensitive recurrent ovarian cancer


Clare L. Scott[1,5], Michael Friedlander[2], Katherine E. Francis[3], Apriliana E.R. Kartikasari[4], Katrina Diamante[3], Nirashaa Bound[1], Claire Davies[5], Rachel O'Connell[3], Yeh Chen Lee[2,3], Janine Lombard[6], Sally Baron-Hay[7], Yoland Antill[8], Catherine Shannon[9], Sudarsha Selva-Nayagam[10], Philip Beale[11], Kristy Shield-Artin[1], Matthew Wakefield[1], Cassandra Vandenberg[1], Magdalena Plebanski[4], Chee Khoon Lee[3,12]

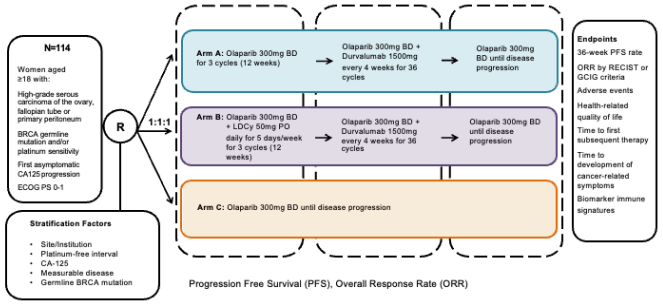
[1] Walter and Eliza Hall Institute of Medical Research (WEHI), VIC, Australia [2] Prince of Wales Hospital, NSW, Australia [3] NHMRC Clinical Trials Centre, The University of Sydney, NSW, Australia [4] Royal Melbourne Institute of Technology (RMIT), VIC, Australia [5] Australia New Zealand Gynaecological Oncology Group (ANZGOG), NSW, Australia [6] Newcastle Private Hospital, NSW, Australia [7] Royal North Shore Hospital, NSW, Australia [8] Frankston Hospital, VIC, Australia [9] Mater Cancer Care Centre, QLD, Australia [10] Royal Adelaide Hospital, SA, Australia [11] Chris O'Brien Lifehouse, NSW, Australia [12] St George Hospital, NSW, Australia


## Background:

- Priming of immune cells in epithelial ovarian cancer (EOC) could improve response to immune checkpoint inhibitor.
- We hypothesized priming with olaparib or olaparib with LDCy will enhance the effect of the subsequent combination olaparib and durvalumab.
- We hypothesized an immune signature in blood could have prognostic utility.

## Methods:

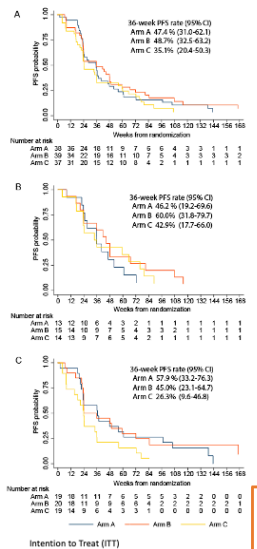
- We conducted a multi-centre, non-comparative, phase 2 randomized controlled trial




Progression Free Survival (PFS), Overall Response Rate (ORR)

## Progression-free survival by randomized arms:

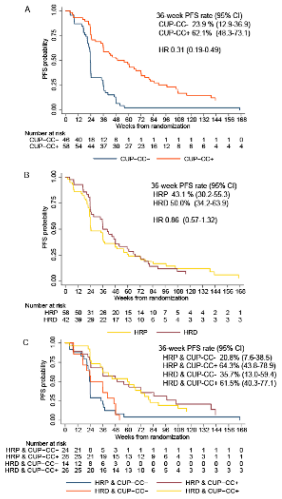
(A) ITT population (B) HRD population (C) HRP population




Intention to Treat (ITT)
Homologous Recombination Defective (HRD)
Homologous Recombination Proficient (HRP)

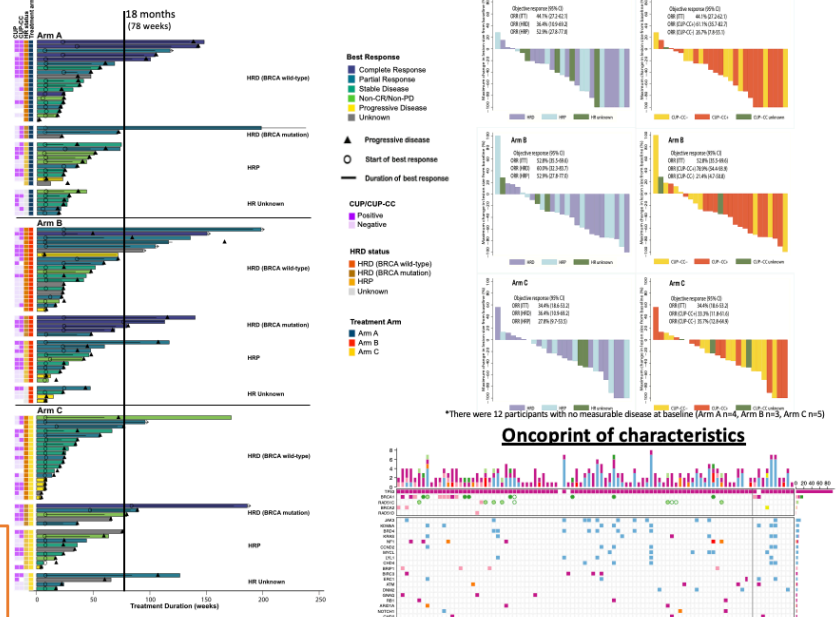
## Progression-free survival by:

(A) CUP-CC status (B) HR-status
(C) Combination HR and CUP-CC status




**Immune signature: CUP-CC**
**CUP: CCR4 upregulation (CUP)** proportion of effector CD4 and CD8 T cells post *in vitro* MAF treatment.
**CC: levels of four cytokines/chemokines (CC)**: We explored combining these cytokines and chemokines (CC) to further enhance the prognostic utility of CUP, generating a CUP-CC signature.
**HR status:** HRD or HRP (details in oncoprint).
**Combined immune and HR status:** CUP-CC status and PFS separated by HRP/HRD.

## Swimmer plot: outcome by treatment arms according to HR status

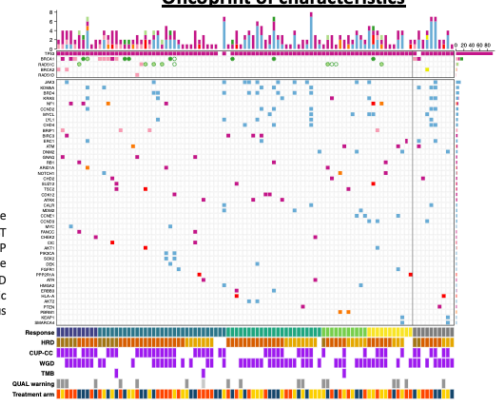



## Objective response rate by randomized arms according to HR or immune status*




*There were 12 participants with no measurable disease at baseline (Arm A n=4, Arm B n=3, Arm C n=5)

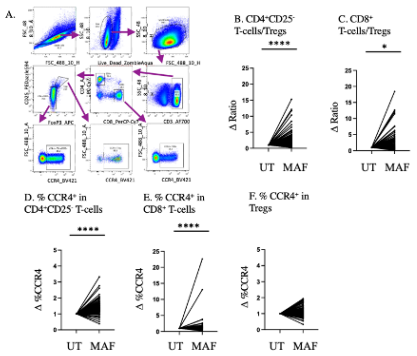
## Oncoprint of characteristics




## Baseline characteristics

| | Arm A N=38 (%) | Arm B N=39 (%) | Arm C N=37 (%) |
|---|---|---|---|
| Median Age (range) | 65 (42-83) | 63 (44-81) | 72 (46-87) |
| ECOG PS 0 | 31 (81.6) | 32 (82.1) | 27 (73.0) |
| Measurable disease | 27 (71.1) | 28 (71.8) | 26 (70.3) |
| PFI >12 months | 25 (65.8) | 24 (61.5) | 24 (64.9) |
| CA125>100 | 23 (60.5) | 24 (61.5) | 22 (59.5) |
| HRP BRCA wild-type | 19 (50.0) | 20 (51.3) | 19 (51.4) |
| HRD BRCA mutation | 3 (7.9) | 5 (12.8) | 5 (13.5) |
| HRD BRCA wild-type | 10 (26.3) | 10 (25.6) | 9 (24.3) |
| CUP-CC- | 15 (42.9) | 16 (44.4) | 15 (45.4) |
| CUP-CC+ | 20 (57.1) | 20 (55.6) | 18 (54.6) |

## Development of the CUP assay




**CCR4-upregulation (CUP) ASSAY.**
**Mafosfamide (bioactive cyclophosphamide derivative) increases *in vitro* the CD4$^+$CD25$^-$ T cells/Treg and CD8$^+$ T cells/Treg ratio, and the expression of CCR4 on the surface of CD4$^+$CD25$^-$ T cells and CD8$^+$ T cells, but not Treg in SOLACE2 participants at baseline.** T-cell subsets and percentages of CCR4$^+$ expressing cells were measured following 72 hrs incubation of peripheral blood mononuclear cells (PBMC) with or without Mafosfamide (MAF), using flow cytometry (N=106). A) Gating strategy. B) Ratio of CD4$^+$CD25$^-$ T cells/Treg and C) CD8$^+$ T cells/Treg increased following MAF culture. Mafosfamide increased the proportion of CCR4+ cells within D) CD4$^+$CD25$^-$ T cells, E) CD8$^+$ T cells, but not F) Treg. Untreated (UT). Non-parametric Wilcoxon matched-pairs signed-rank test. **** P<0.0001, *** P<0.001, ** P<0.01 * P<0.05.

## Conclusion

- Priming with either olaparib alone or olaparib with LDCy, followed by olaparib+durvalumab resulted in numerically greater 36-week PFS rates than did olaparib continuous monotherapy
  - however, this trial failed to meet the prespecified threshold.
- CUP-CC+ immune signature was prognostic for greater PFS for olaparib-based treatments.
- By contrast, increased T effector/Treg ratios were not prognostic of PFS (data not shown).
- CUP-CC has prognostic utility across both HRD and HRP EOC.
- Future studies need to investigate the utility of CUP-CC as a biomarker to supplement or replace tissue-based HRD testing for EOC.

**Oncoprint:** Whole Exome Sequencing analysis (TWIST Exome 2.0 with 1Mb SNP backbone and IDT UMI for single molecule normalization); HRD status determined by Genomic Instability Score, mutation status and manual review.

**Promoter methylation analysis of *BRCA1* and *RAD51C***

| #Cases | meBRCA1 | meRAD51 |
|---|---|---|
| Total tested | 105 | 105 |
| Methylation positive | 14 | 11 |
| High adjusted methylation (>70%) | 9 | 0 |
| Low adjusted methylation (<70%) | 2 | 7 |
| Unadjusted positive | 2 | 1 |
| Low confidence | 1 | 3 |

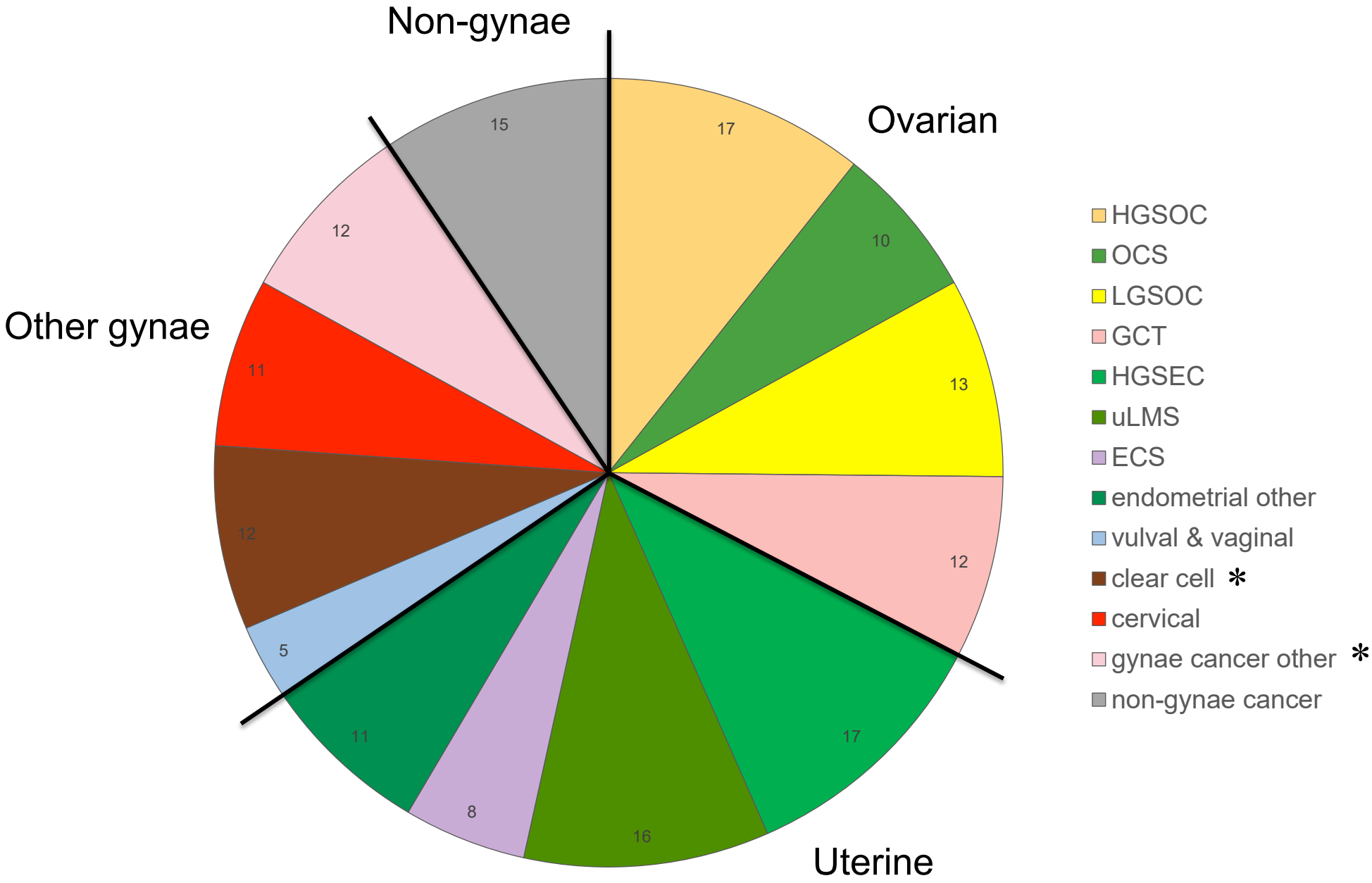

**Presenting Author**: Professor Clare Scott
**Contact:** solace2.study@sydney.edu.au


*Prof. Scott reports grant and research support from AstraZeneca, Clovis Oncology, Eisai Inc, Sierra Oncology; membership on Advisory boards: AstraZeneca, Clovis Oncology, Eisai, Sierra Oncology, Takeda, MSD.*


***Acknowledgements:*** We acknowledge all the trial participants, their families and carers.
*This research was conducted with support from AstraZeneca, ANZGOG and NHMRC CTC.*

# Whole Genome Sequencing of Rare Gynaecological Cancers

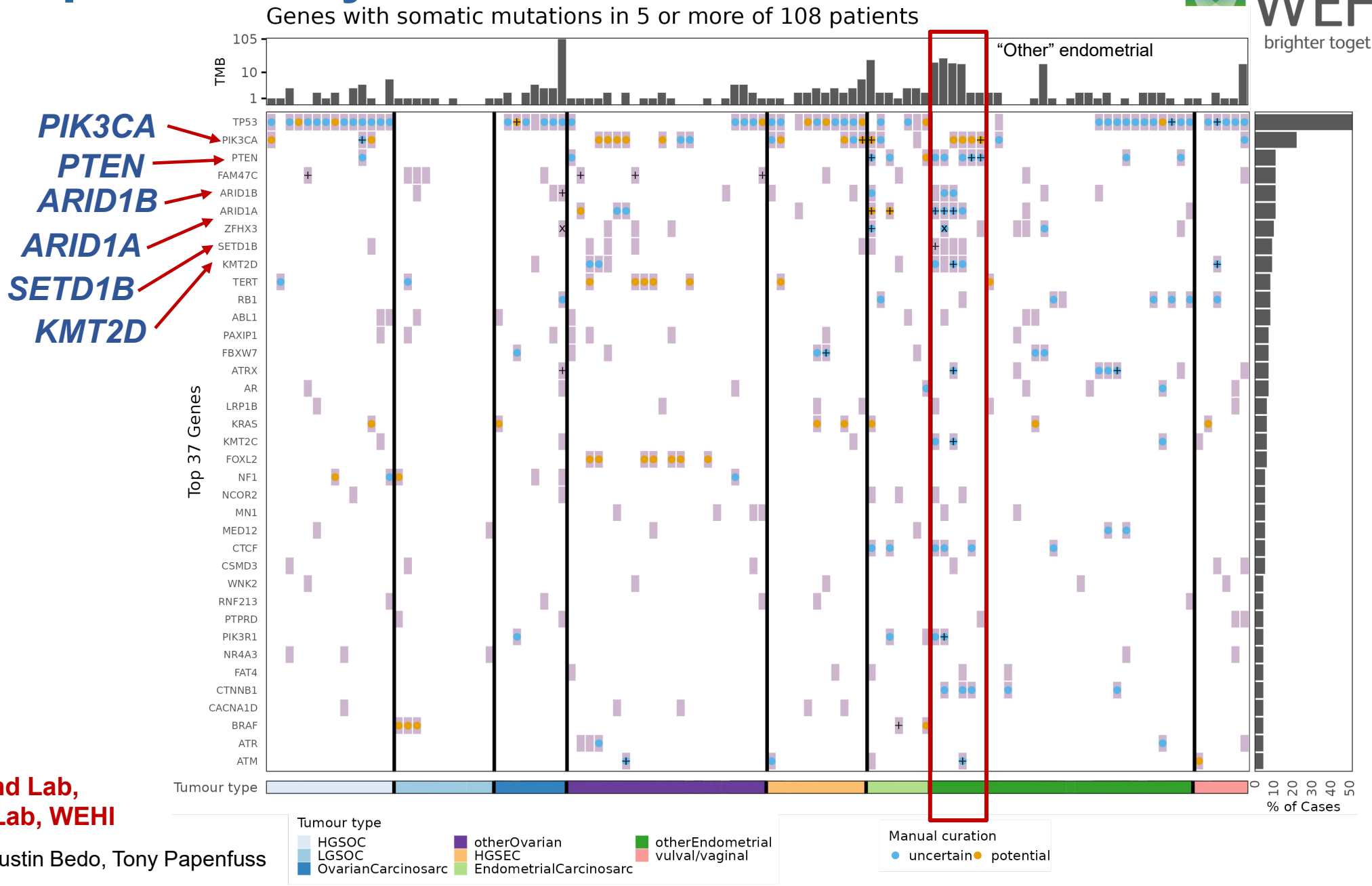
# WGS of rare cancer subtypes




- HGSOC
- OCS
- LGSOC
- GCT
- HGSEC
- uLMS
- ECS
- endometrial other
- vulval & vaginal
- clear cell *
- cervical
- gynae cancer other *
- non-gynae cancer

Samples for WGS
164 samples
159 patients

# WGS preliminary results - somatic variants

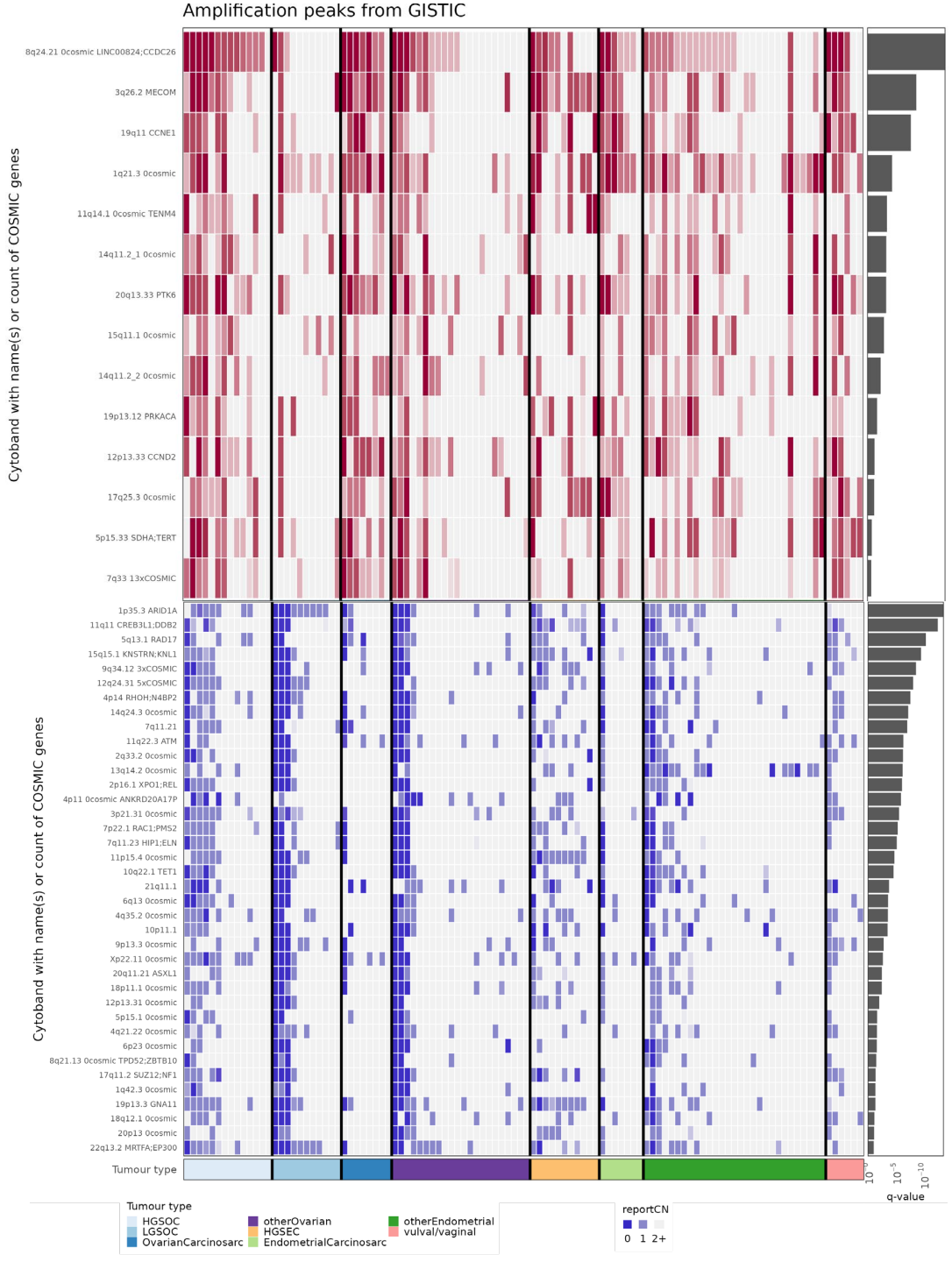




**Grimmond Lab, Papenfuss Lab, WEHI**

Jocelyn Penington, Justin Bedo, Tony Papenfuss

# WGS preliminary results - CNV

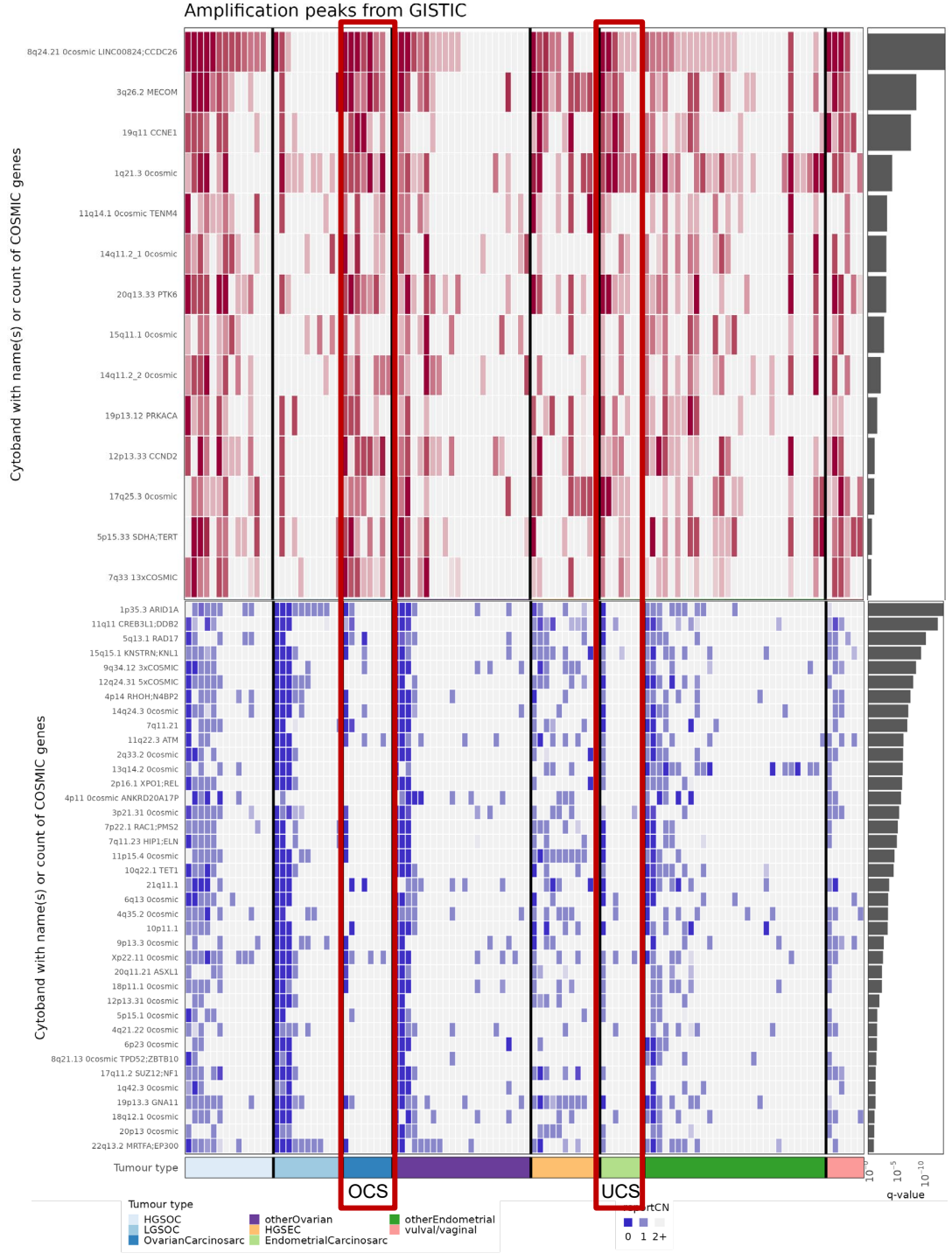




**Grimmond Lab,**
**Papenfuss Lab, WEHI**

Jocelyn Penington, Justin Bedo, Tony Papenfuss

# WGS preliminary results - CNV





**Grimmond Lab,**
**Papenfuss Lab, WEHI**

Jocelyn Penington, Justin Bedo, Tony Papenfuss

# WGS – actionable aberrations identified



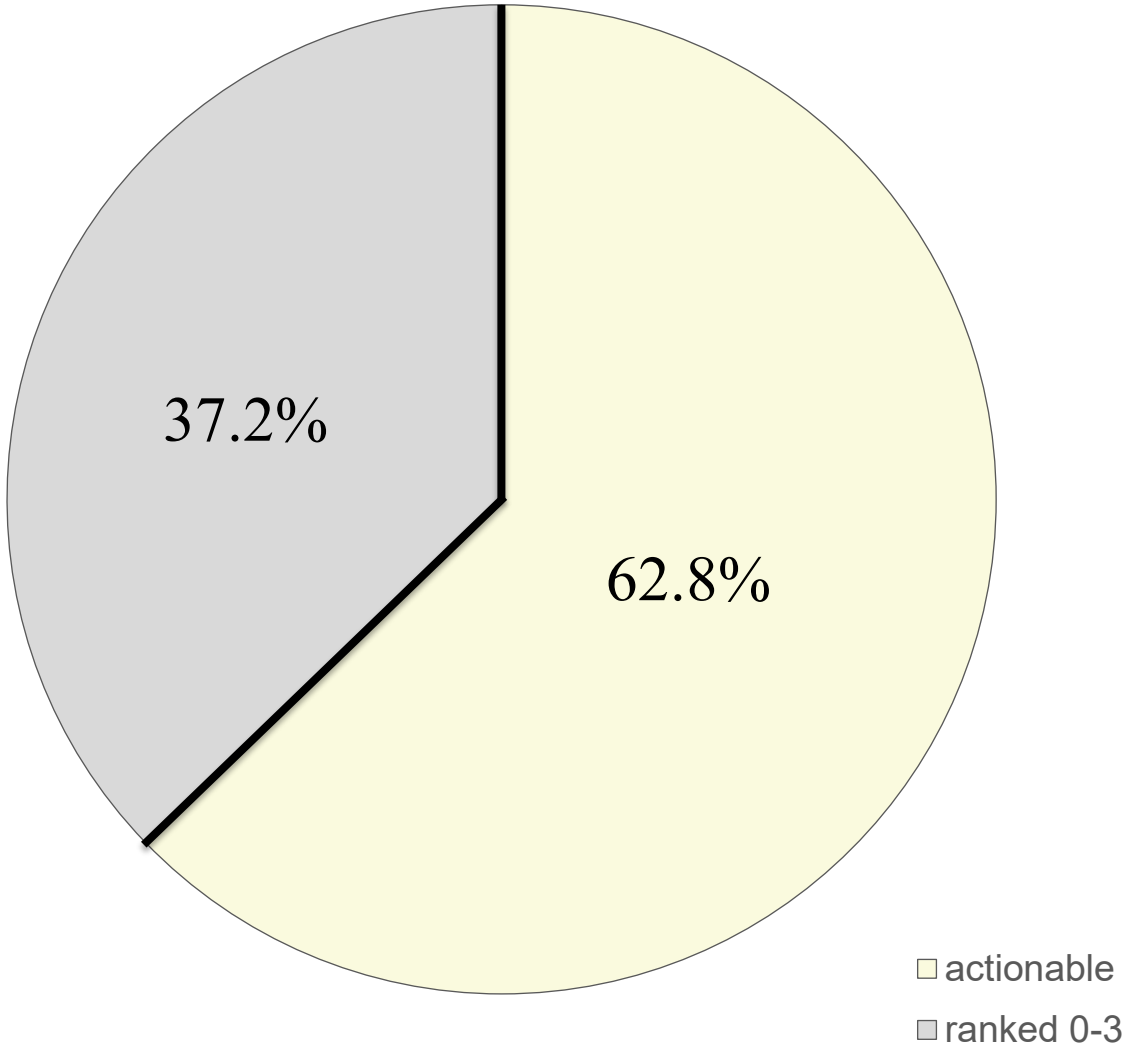
To date:

- Total WGS = 164 cases (10 failed)
- Rare gynae WGS = 147 (fresh and successful = 122)

- Actionable aberrations detected in 93/122 cases (76%)
- Highly actionable aberrations detected in 70/122 (57%)

| | PARP inhibitor therapy | RAF dimer + MEK inhibition | Immune checkpoint inhibitor therapy | HER2 targeted therapy | Moderate impact aberrations |
|---|---|---|---|---|---|
| | e.g. HRD due to *BRCA1/2* mutations **(12)** or Cosmic mut signature 3<br><br>**21/122 cases (17%)** | e.g. *KRAS, NRAS* mutations<br><br>**27/122 cases (22%)** | High tumour mutational burden (TMB), over 15 mut/Mb<br><br>**9/122 cases (7%)** | Amplification or mutation of *ERBB2*<br><br>**4/122 cases (3%)** | Some *CCNE1* amplifications, *ARID1A, AKT* and *PIK3CA* mutations<br>**27/122 cases (22%)** |
| Ovary | HGSOC **(11),** OCS, OvNET, OvCCC | HGSOC, OCS, LGSOC, GrCT, OvMucAdCa | OvCCC | | HGSOC, OCS, LGSOC, OvMucCa, GrCT, OvCCC |
| Endo | HGSEC, UCS, uLMS | HGSEC, UCS, uLMS, AdSarcUt, EndoCa | HGSEC, UCS, EndoCa | | HGSEC, UCS, EndoCa, uLMS |
| Cervix | CxSCC | CxAdCa | CxSCC | CxAdCa, CxMucAdCa | CxNET, CxSCC, CxMucAdCa |
| Other | | Vaginal Ca | Vaginal Ca<br>Vulval AdCa | Vaginal Ca<br>Vulval AdCa | Vaginal MucCa |

# WGS in all cases - actionable aberrations identified




**Ranking**

10 - change in diagnosis to PBS therapy with CR
9 - change in diagnosis to PBS therapy with prolonged SD, PR or CR

8 - accessed therapy - CR (includes treatment on PBS)
7 - accessed therapy - PR or prolonged SD >6mo

6 - accessed therapy - potential benefit (includes trials)
5 - clinical trial available in Australia

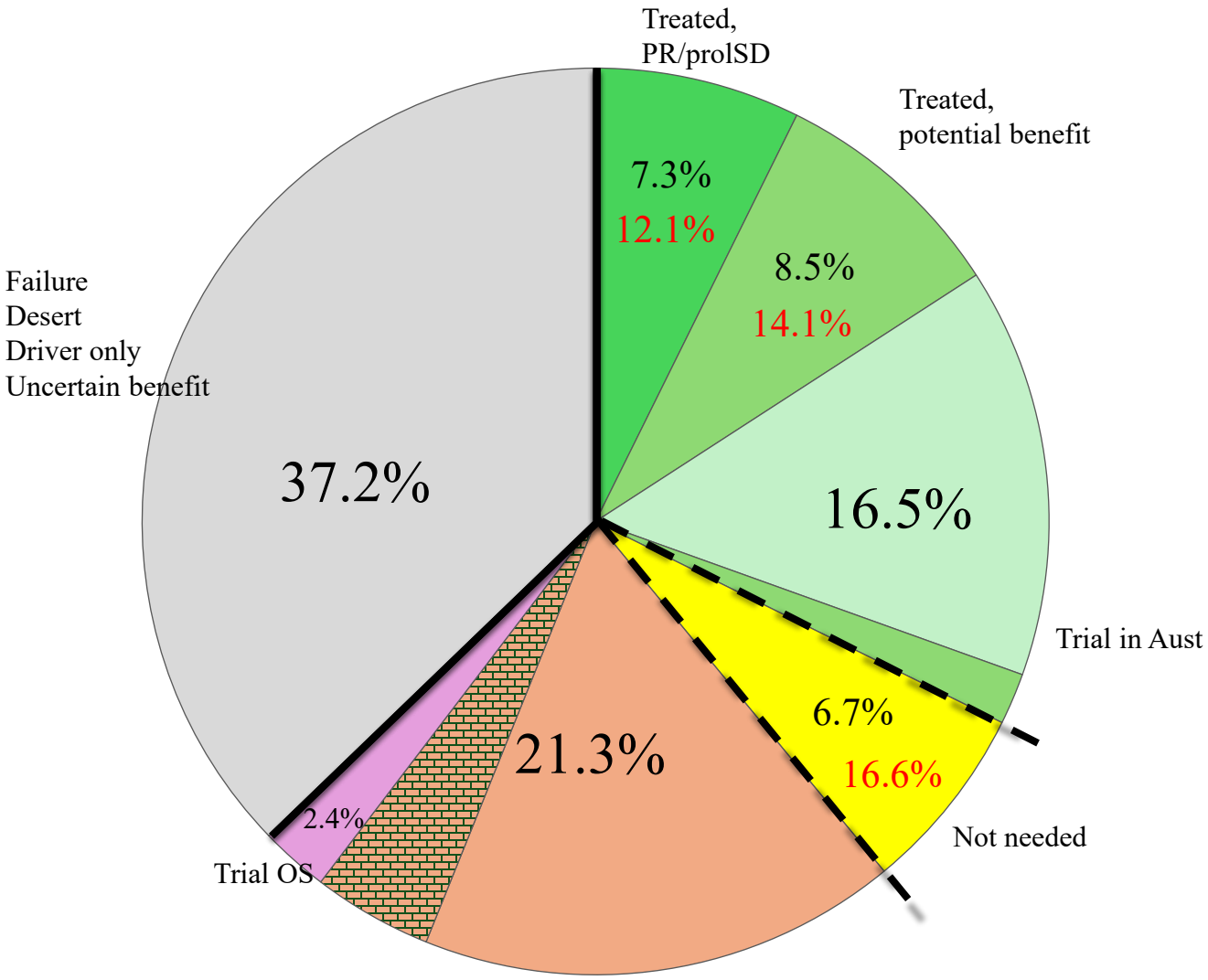
4 - clinical trial available outside Australia

3 - matched treatment questionable eg PIK3CAi

2 - nothing actionable, has a known driver
1 - nothing actionable, no driver = desert
0 - nothing actionable due to technical/sample failure

Dr Ratana Lim, SFRCP Team

# WGS in all cases – treatment access and eligibility




ranked 7
ranked 6
ranked 5
5 - accessed
5 - not needed
5 - too late
PDX (4-5)
ranked 4
ranked 0-3

8 - access to therapy with CR (PBS funded therapy or not)

7 - access to therapy with PR, or prolonged stable disease >6 months

6 - accessed therapy with potential benefit, including clinical trials

5 - potentially eligible for clinical trial in Aust

% of all 164 samples

% of actionable findings

- Samples tested too late in the patient's journey
- Could not access/ drug not available in Aust
- Single agent therapies not enough?

Patient data still ongoing

Dr Ratana Lim, SFRCP Team

# WGS – actionable aberrations identified



To date:

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|---|---|---|---|---|---|
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| Endo | HGSEC, UCS, uLMS | HGSEC, UCS, uLMS, AdSarcUt, EndoCa | HGSEC, UCS, EndoCa | | HGSEC, UCS, EndoCa, uLMS |
| Cervix | CxSCC | CxAdCa | CxSCC | CxAdCa, CxMucAdCa | CxNET, CxSCC, CxMucAdCa |
| Other | | Vaginal Ca | Vaginal Ca<br>Vulval AdCa | Vaginal Ca<br>Vulval AdCa | Vaginal MucCa |

# HER2 amplified rare gynaecological cancers

# HER2 amplifications occur throughout gynae tract, predominantly in rare adenocarcinoma subtypes

| Tumor Type | HER2 amplification rate per tumour histologic subtype | | | |
|---|---|---|---|---|
| Ovarian | 0/53 HGSOC | 1/11 HGFTC (panel) | 0/6 PPC | 0/41 other OC |
| Endometrial | 18/54 USC* | 1/1 HG EEC | | |
| Cervical | 0/11 SCC | 1/20 adenoca incl 1/7 GAS# | | 0/6 clear cell, 1 other CC |
| Vulval | 0/5 SCC | 1/1 Paget's-derived adenoca | | |
| Vaginal | 0/1 vaginal | 1/1 Vaginal adenoca | 2/2 mucinous adenoca | 0/1 SCC vag/periurethral |

**25 cases HER2-amp rare gynae cancer:**
**WGS, WES, panel, IHC**

**Encourage HER2 IHC/ISH of all rare gynae adenocarcinoma histologies**

* Reflects referrals to HGSEC HER2 project (VCA Fellowship) – agrees with current estimate of 30% HGSEC being HER2+

# GAS endocervical adenocarcinoma - Mucinous adenocarcinoma of gastric type of the uterine cervix
- patient benefited from T-DM1 (trastuzumab emtansine) on MoST trial
- 7-14% HER2+ previously seen in other GAS studies, with one study also identifying activating mutations in 7% cases

- Additional cases with equivocal HER2 staining (2+) – T-DXd (trastuzumab deruxtecan) effective in low-HER2 cases

**HER2 therapies should be considered for more rare-gynae subtypes (not just UCS)**

Ratana Lim, Gayanie Ratnayake, SFRCP Team and Grimmond Lab

(Nakamura et al, 2019, Med Mol Morph; Shi et al, 2021, J Path; Selenica et al, 2021, Mod Path)

# PDX models of rare gynaecological cancers

| | Tumour type | # PDX | Potentially Targetable Molecular Aberrations* |
|---|---|---|---|
| Ovarian | HGSOC * | 34 | *BRCA1/BRCA2* mutations; *BRIP1, ARID1A, PIK3CA* mutation; *RAD51C* methylation, *CCNE1* overexpression |
| | Carcinosarcoma * | 10 | *AKT2, CCNE1, FGFR3* amplification; *FBXW7* mutation; Signature 3 |
| | HGSFT* | 2 | ***ERBB2* amp** |
| | Clear cell carcinoma | 3 | *PIK3CA* mutation |
| | Large cell NET | 1 | *BRCA2* rearrangement; Signature 3 |
| | Yolk sac tumour | 1 | pending |
| | SCTAT | 1 | *TERT* promoter |
| | Mucinous | 1 | *NRAS* mut |
| | Endometrioid | 1 | *PIK3CA* mutation, *ATM, ESR1, gALK* VUS, *CDKN2A* del |
| Endometrial | HGSEC * | 12 | *AKT1* mutation; *CCNE1*, ***ERBB2* amp**; Signature 3 |
| | Carcinosarcoma * | 6 | *PIK3CA, PTEN* mutation; *CCNE1* amp; *MYCN* amp; Signature 3 |
| | uLMS * | 11 | *BRCA2, RB1* deletion; *NTRK2* amp; Signature 3 |
| | HG Clear cell carcinoma | 2 | *EZH2, MSH6* mutations |
| | Adenosarcoma* | 1 | *KRAS* mutation; *CDKN2A* and *CDKN1B* del |
| Cervical | Adenocarcinoma | 3 | Signature 3 |
| | Squamous cell carcinoma | 1 | *FBXW7* mutation |
| | Poorly differentiated adenocarcinoma with sarcomatoid diff | 1 | *FANCD2* mutation |
| | Mucinous adenocarcinoma | 2 | *MSH2* mut, *ARID1A* mut, *ATR* mut, *PIK3CA* mut, *ARAF* mut |
| | CNS embryonal tumour with multilayered rosettes | 1 | *CTNNB1* mutation (x2) |
| Vulval | Squamous cell carcinoma | 1 | *CDKN2A*, *NTRK3* mutations, *EGFR* amp |
| | Adenocarcinoma arising from Paget's disease* | 1 | High TMB, *PIK3CA* mutation, *ARID1B* rearrangement, ***ERBB2* amp** |
| Vaginal | Adenocarcinoma | 1 | ***ERBB2* amp**, *CDKN2A* mut, *SRC* amp, *NF1* rearrangement |
| | Adenocarcinoma of mucinous/GI type/non-HPV | 1 | *CCNE1*, ***ERBB2***, *ERBB3*, *CDK4*, *KRAS*, *MTOR* **amplifications** |

WEHI
brighter together

**To date:**

**100 PDX models** of rare gynaecological cancer subtypes from 85 patients (samples collected from different sites or time points in clinical history)

**4 PDX models** of non-rare gynaecological cancer (endometrioid endometrial cancer)

**3 PDX models** of non-gynae rare cancer (mantle cell lymphoma and pseudomyxoma peritonei)

* Successful cell lines and organoids developed from some models

**GREEN – ERBB2 amp; potential trastuzumab sensitivity**

# PDX models of rare gynaecological cancers

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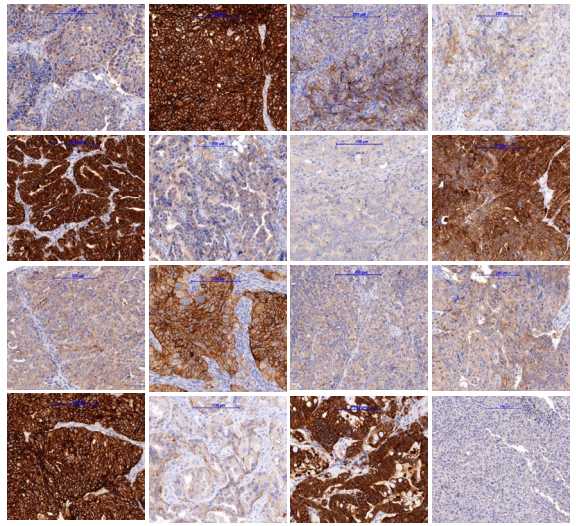
| | Adenocarcinoma of mucinous/GI type/non-HPV | 1 | *CCNE1*, ***ERBB2***, *ERBB3*, *CDK4*, *KRAS*, *MTOR* **amplifications** |

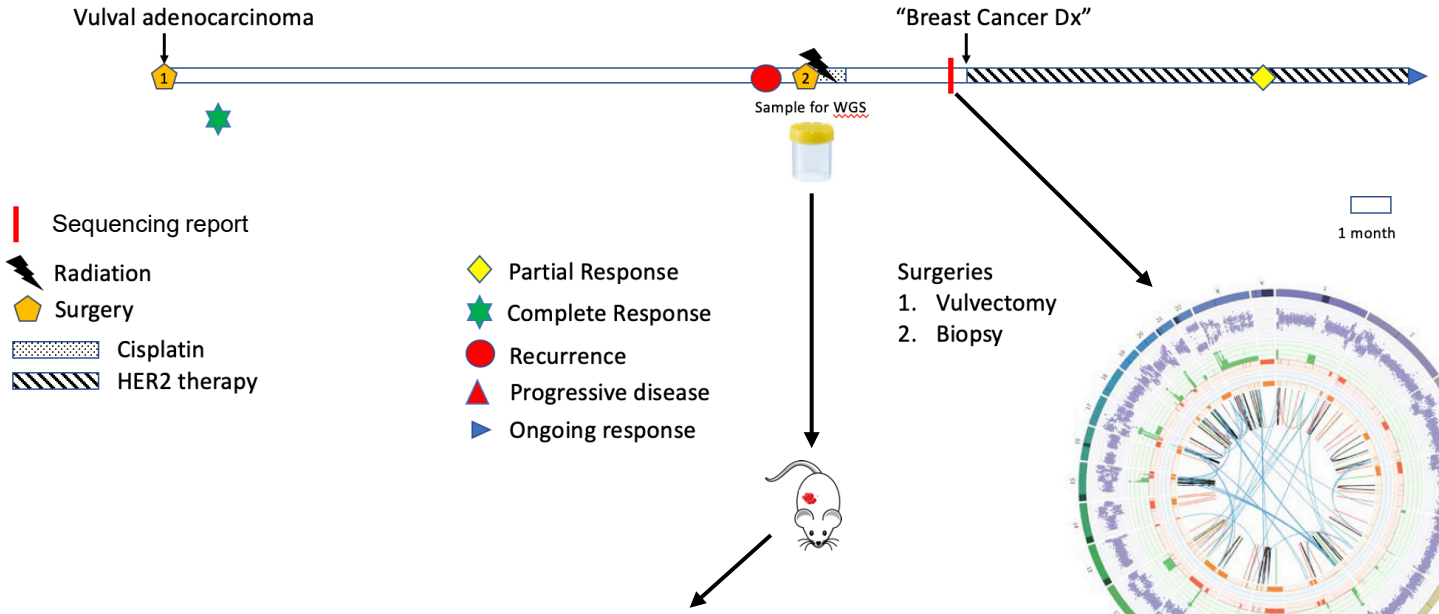
WEHI
brighter together

**+ multiple models with HER2 2+ for testing with ADCs**



**vulval adenca HER2 amp PDX**

# #333 – HER2 amplified vulval adenocarcinoma

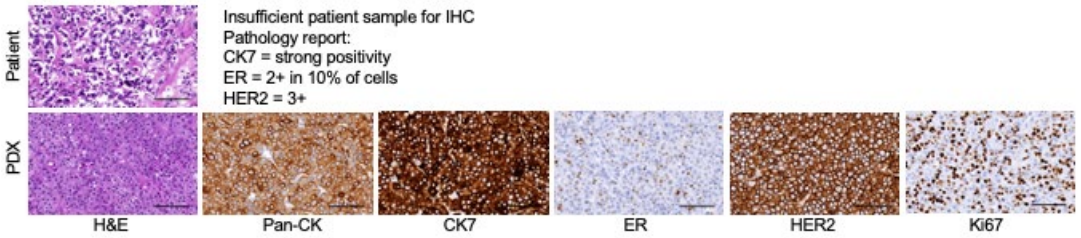





**WGS CIRCOS plot**
(outside -> in: BAF, CNV, MAF, SV events)

| Somatic mutations of potential clinical significance | Effect | AF |
|---|---|---|
| *TP53*; c.853G>A; p.E285K | LoF | 34% |
| **Somatic mutations of uncertain clinical significance** | | **AF** |
| ***PIK3CA***; c.1735G>A; p.E579K | | 32% |
| **Focally amplified Genes** | | **Copies** |
| ***ERBB2*** *(WTS = 99th % cf TCGA pan-cancer cohort)* | | **24-25** |
| ***CCND1*** *(WTS = 80th % cf TCGA pan-cancer cohort)* | | **11** |
| **Rearranged Cancer Genes (LoF)** | | **AF** |
| *ARID1B* | | 40% |
| **Dominant Somatic Signatures** | | **% assigned** |
| Signature 13; APOBEC/AID activity | | 52% |
| Signature 2; APOBEC/AID activity | | 44% |
| **TMB > 20 mut/Mb** | | |

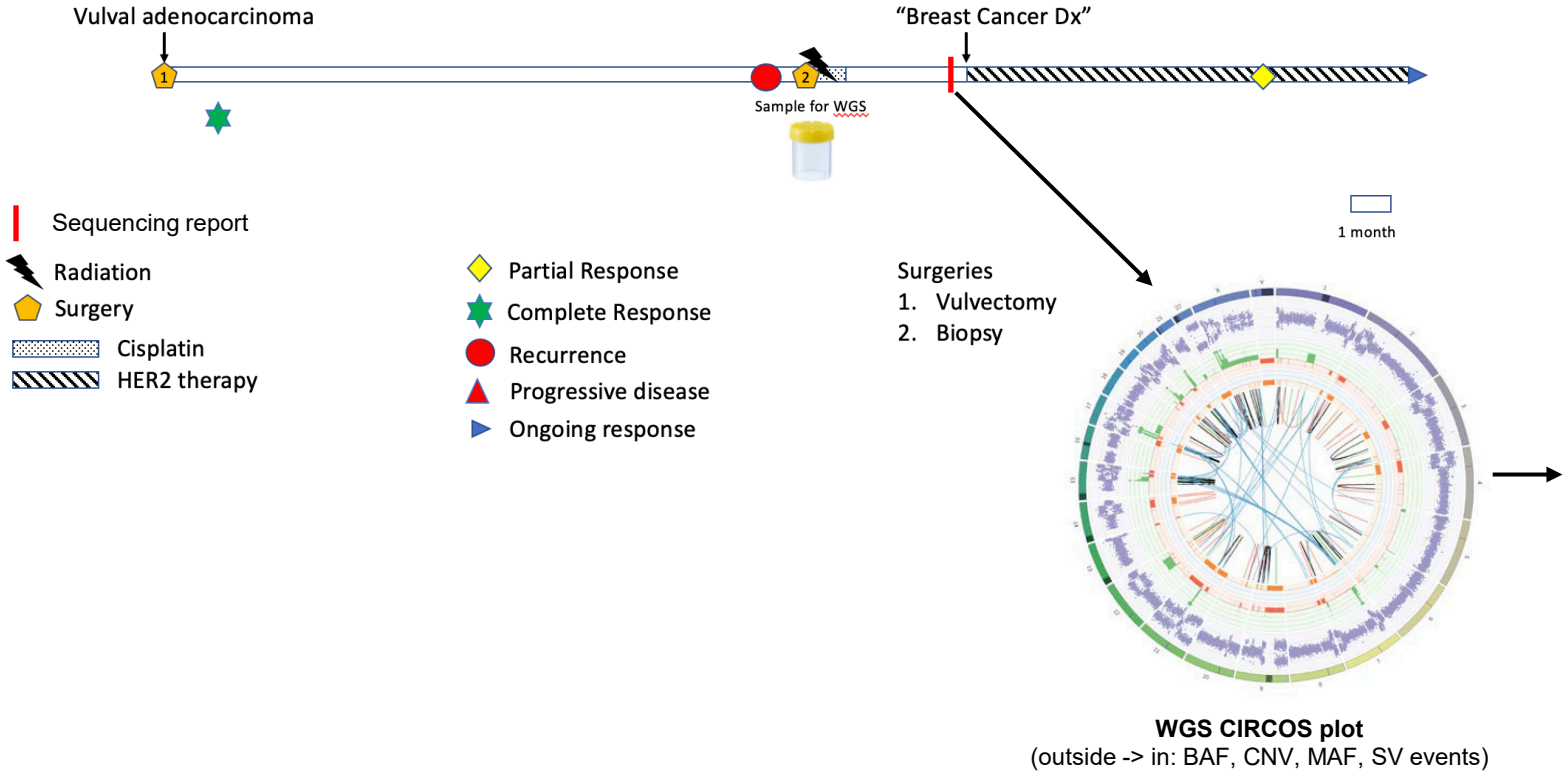
## PDX histology




- Vulval adenocarcinoma rising from Paget's disease
- Age at diagnosis: late 50s
- Recurrence in LN (sample for WGS) and explosion of disease into liver and bones (similarities with breast cancer)
- **Molecular + clinical picture = milk line breast / mammary tissue in vulva = change in diagnosis**
- Access to Govt funded combination HER2 targeted therapy

Orla McNally, David Bernshaw, Marisa Grossi, Gayanie Ratnayake, Cass Vandenberg, Grimmond Team, SFRC Team

# #333 – HER2 amplified vulval adenocarcinoma

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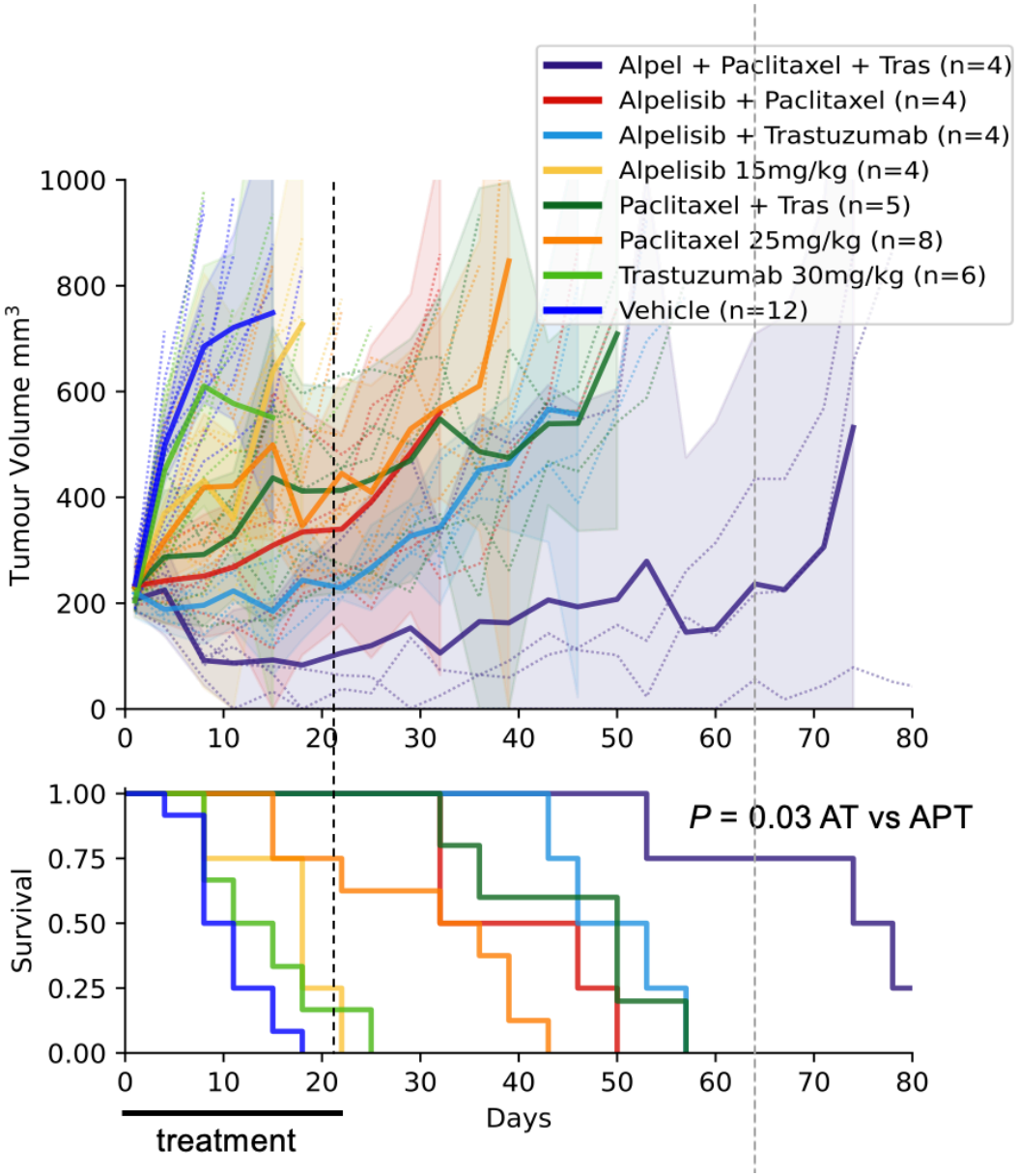
## Access to Govt funded combination HER2 targeted therapy

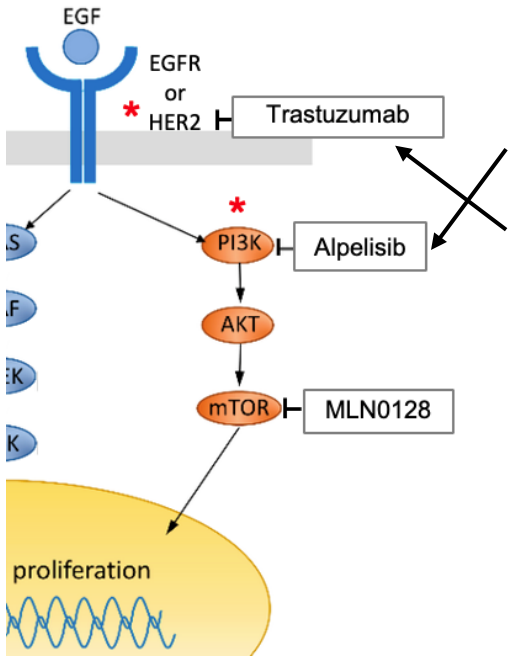
## Chemotherapy followed by PBS-funded Trastuzumab/Pertuzumab

## Prognosis was 6 months:  1 Yr later, PR, near CR

Orla McNally, David Bernshaw,  Marisa Grossi, Gayanie Ratnayake, Cass Vandenberg, Grimmond Team, SFRC Team

# #333 – HER2 amplified vulval adenocarcinoma

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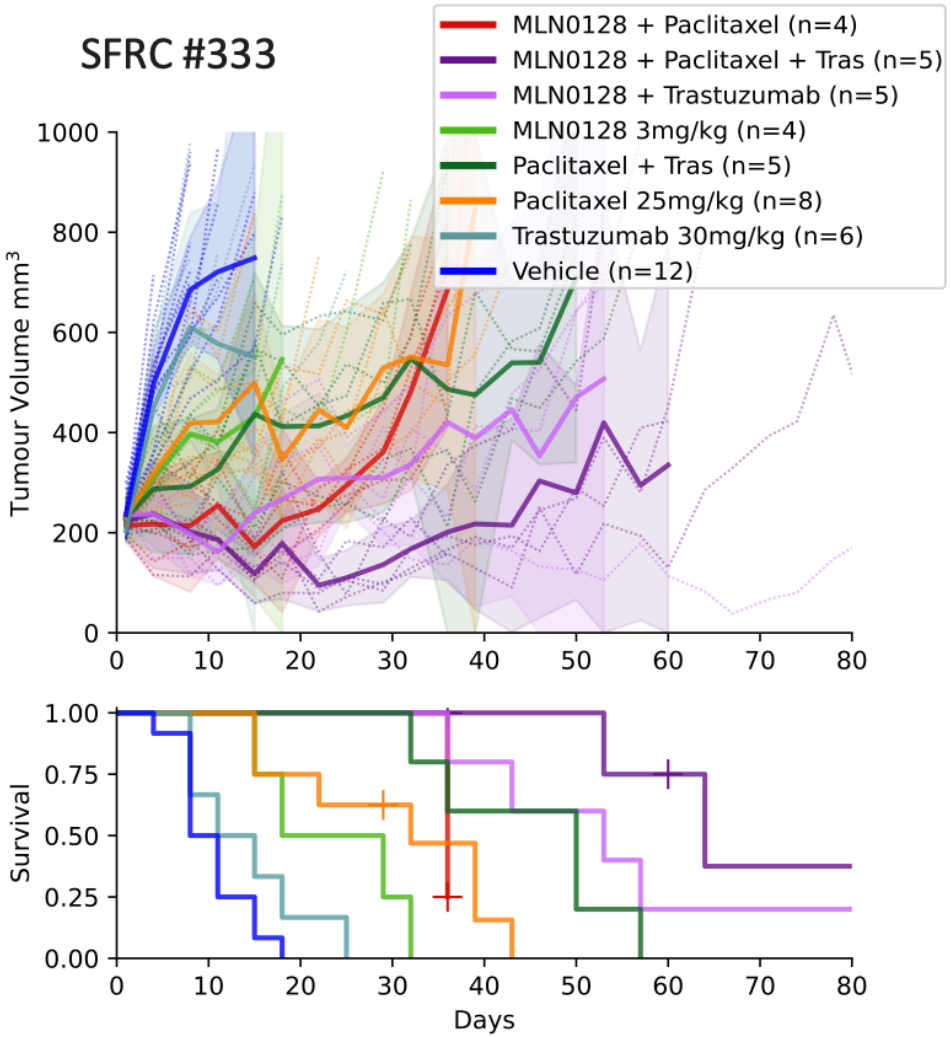
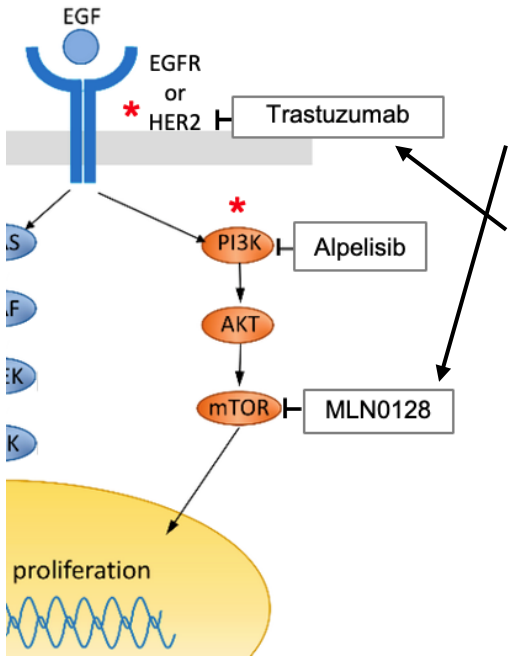
- What other triple combination therapy might help?

Paclitaxel
Trastuzumab, HER2 inhibitory mAb
**Alpelisib, a PI3K kinase inhibitor**

Orla McNally, David Bernshaw, Marisa Grossi, Gayanie Ratnayake, Cass Vandenberg, Grimmond Team, SFRC Team

# #333 – HER2 amplified vulval adenocarcinoma

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- What other triple combination therapy might help?

- Paclitaxel
- Trastuzumab, HER2 inhibitory mAb
- **MLN0128 an mTORC1/2 kinase inhibitor**

Orla McNally, David Bernshaw, Marisa Grossi, Gayanie Ratnayake, Cass Vandenberg, Grimmond Team, SFRC Team

# How best to match targets identified in a rare cancer

# How often will one matched therapeutic reveal true potential?

- **What is the aim of molecular sequencing – especially in rare cancers?**

- To identify potential therapeutic targets eg the top one, two or three targets in a tumour
- Most new therapies are evaluated as single agents - very few agents are impressive
- Rational targeting of two aberrations +/- a third treatment: a triple combination
- What should the third drug be?

  Chemotherapy? Immunotherapy? RT? ADC? A third targeted therapy?

- The majority of rare cancers are treated with single agent therapy following molecular sequencing,
- as combination therapy is more expensive, difficult to access, unproven (ComboMATCH underway)
- **Results may be misleading**

# How often will one matched therapeutic reveal potential in a generic combination?

- We need to trial combination therapies

British Journal of Cancer

ARTICLE OPEN

## A signal-seeking Phase 2 study of olaparib advanced solid cancers with homologous r gene alterations

Subotheni Thavaneswaran[1,2,3,4,13]✉, Maya Kansara[3,4,13], Frank Lin[1,3,4,5], David Espinoza[1], Mandy L. Ballinger[3,4], Lucille Sebastian[1], Theresa Corpuz[3,4], Min Ru Qiu[3,6], Piyushkumar Mu Ulf Schmitz[8,9,10,11], John Simes[1], Anthony M. Joshua[2,3,4] and David M. Thomas[2,4,12]



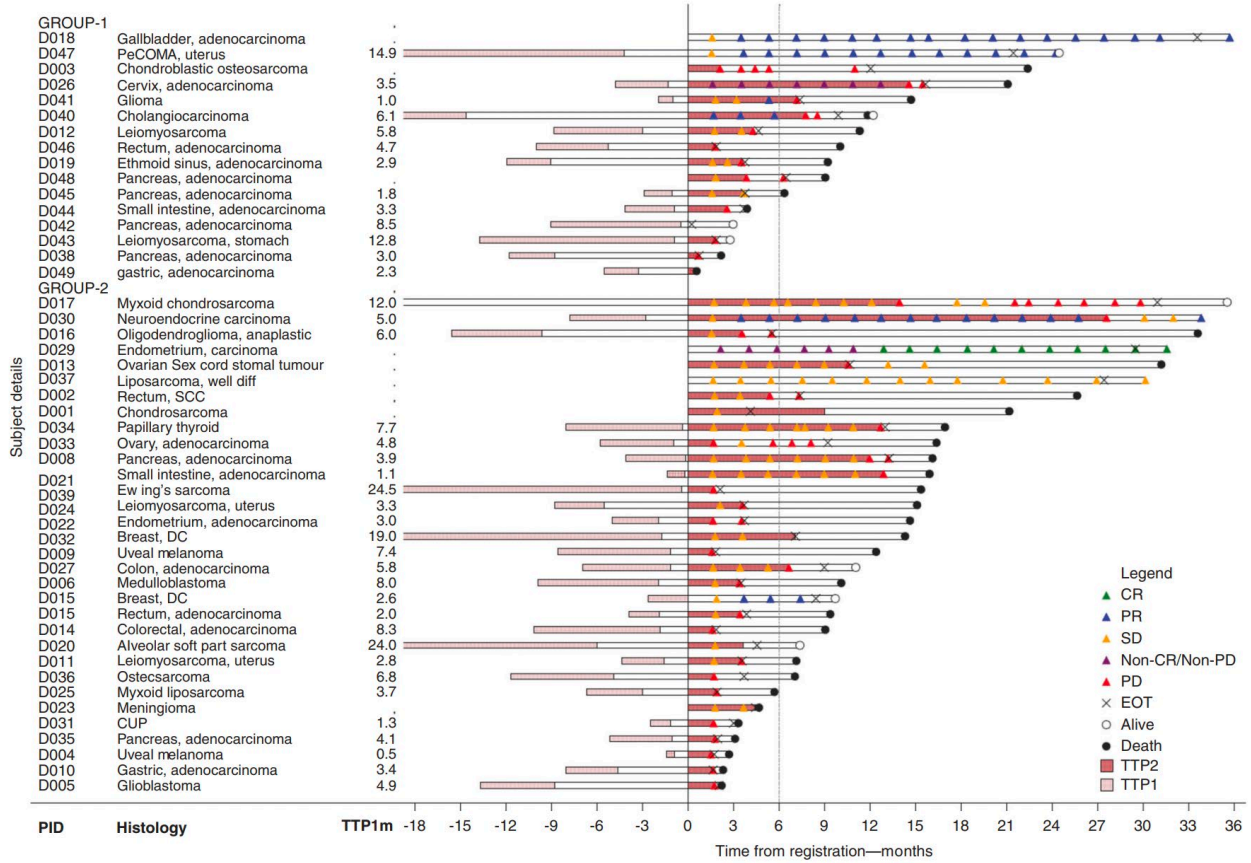



**Fig. 2 Swimmer plot characterising secondary trial endpoints by the individual patients within each group.** Group 1: *BRCA1/2* alterations and Group 2: other homologous recombination repair alterations. TTP1—time to progression prior to trial, with the bar left of 0 depicting duration of therapy and timing of prior therapy in relation to commencing on trial. PID patient ID, CR complete response, PR partial response, SD stable disease, PD progressive disease, EOT end of treatment, TTP2 time to progression on trial.

# How often will one matched therapeutic reveal true potential?

- We need to trial combination therapies targeting multiple aberrations (Kato et al, Nat Comms, 2020)

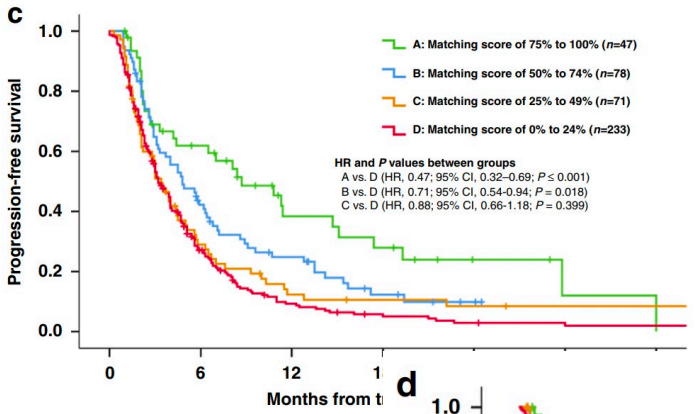
nature COMMUNICATIONS

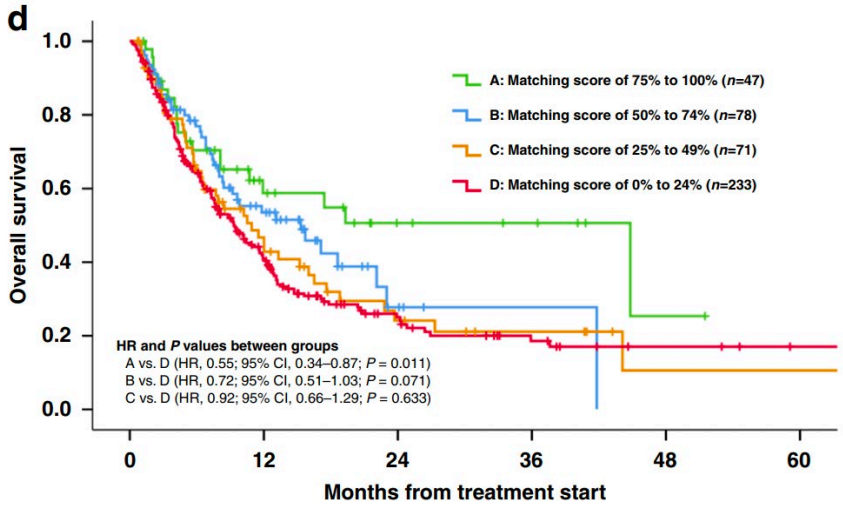
ARTICLE

https://doi.org/10.1038/s41467-020-18613-3 OPEN

## Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy

Shumei Kato et al.#



# Using preclinical models to study therapeutic efficacy and resistance in rare uterine malignancies

# Uterine Cancer

- 5th most common cancer in women

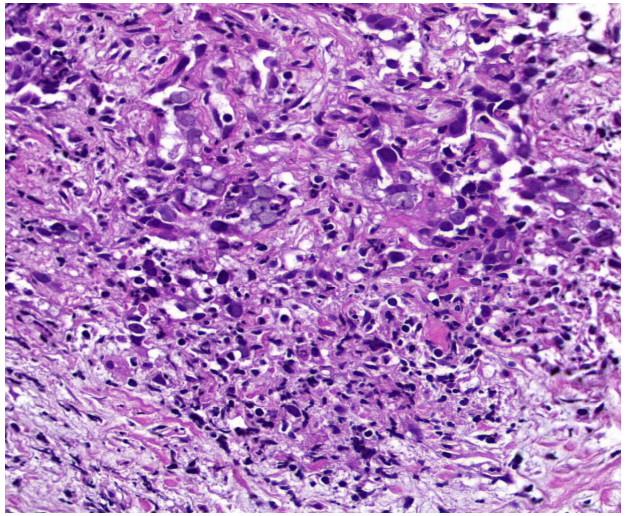
- Rising incidence globally

- 5-year overall survival ranges ~83% (common subtypes have good prognosis)

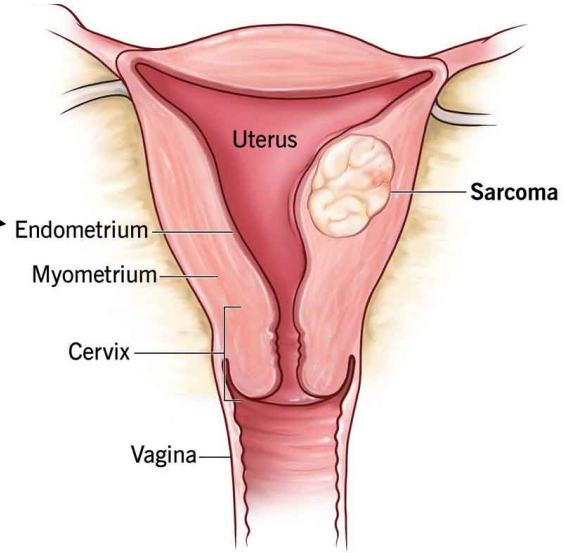
- 4 histological classifications for carcinomas (5-year survival)

  i. Endometrioid (common; 86%)
  ii. Clear cell (rare; 46-62%)
  **iii. Carcinosarcoma (rare; 30-40%)**
  **iv. Serous (rare; 0-50%)**

- **Uterine sarcomas account for 3-7% of uterine cancers**



High grade serous endometrial carcinoma



# Rare and aggressive subtypes of uterine cancer

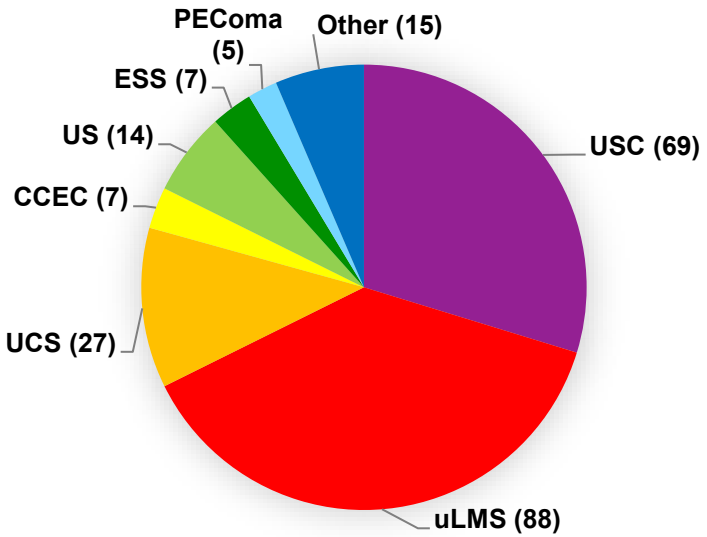
**Standard treatments:**

- Platinum- and taxane-based chemotherapy (carcinoma and mixed subtypes)
- Gemcitabine and doxorubicin chemotherapy (sarcoma)

**Rare subtypes have a much worse prognosis:**

- Initial treatment failure, or
- Recurrence with chemoresistance due to:
    - DNA repair mechanisms increased
    - Drug efflux pumps increased
    - Survival pathways increased
    - Suppression of immune responses

**Stafford Fox Rare Cancer Program**




**Subtypes (5-year survival)**
uLMS = uterine leiomyosarcoma (~30-42%)
USC = uterine serous carcinoma (0-50%)
UCS = uterine carcinosarcoma (30-40%)
US = uterine sarcoma (~43%)
ESS = endometrial stromal sarcoma (~10%)
CCEC = clear cell endometrial cancer (42-62%)

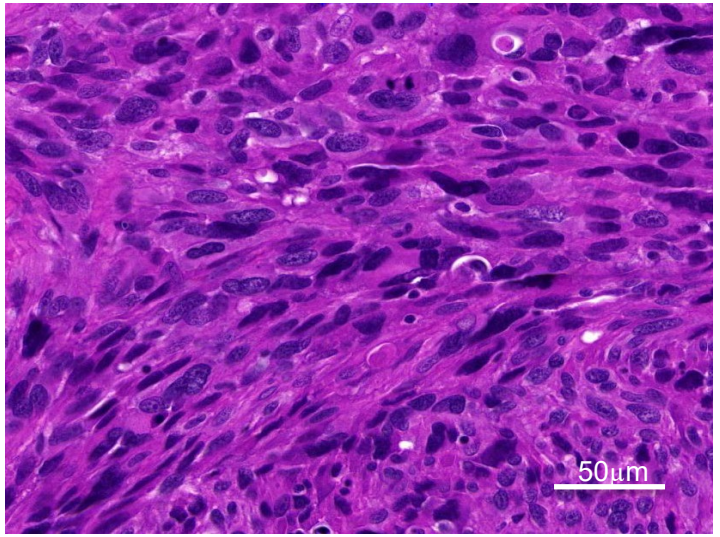
Dr Holly Barker

# Uterine Leiomyosarcoma (uLMS)

Dr Gen Dall

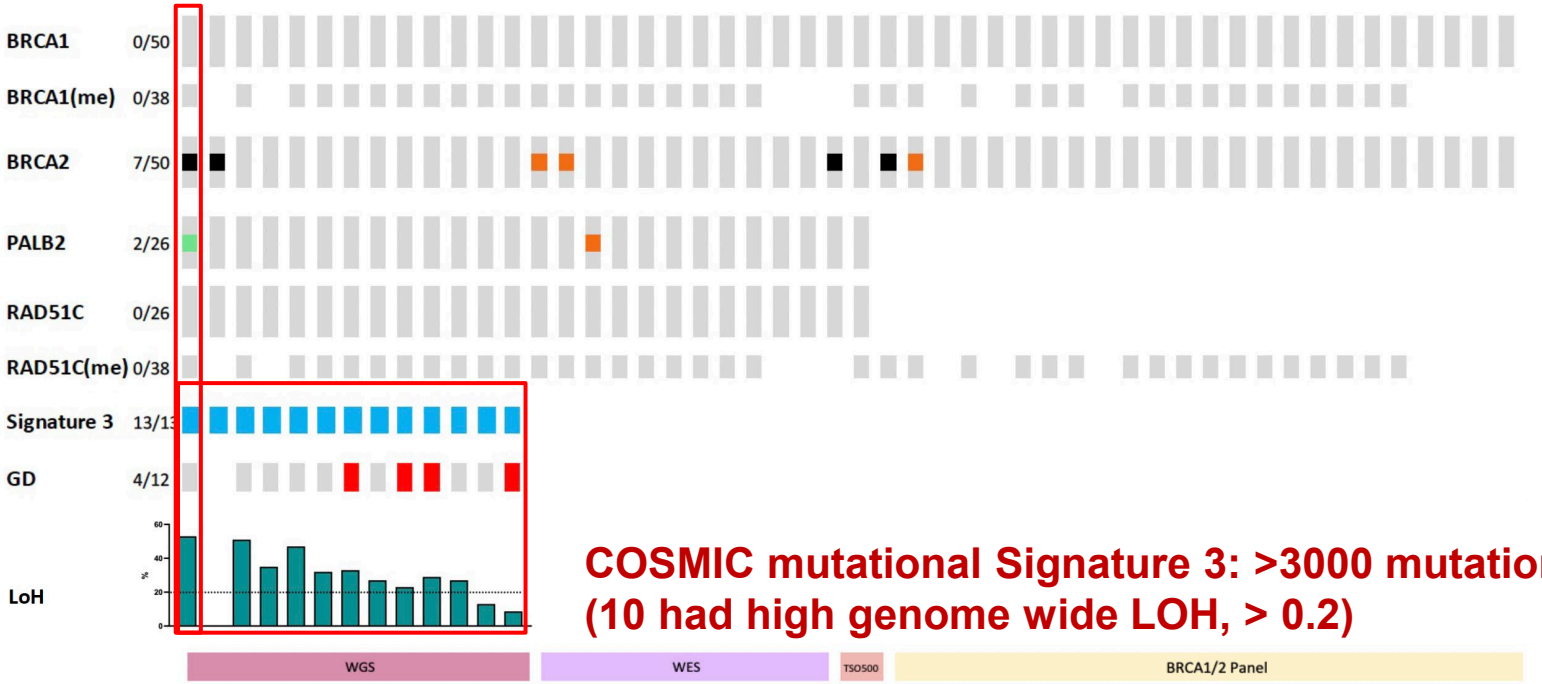
- Smooth muscle tumour arising from the muscular wall of the uterus
- Incidence rate ~0.8/100,000 women (1-2% of all uterine malignancies)
- 5-year survival:
  - up to 75% for early stage disease
  - 10-15% for metastatic uLMS

#1227



# Measuring HR abnormalities in uLMS

SFRCP recruited 88 patients (incl. remote consent via ARC portal)
HR screened (**67 to date**): WGS (fresh tissue; n=22)
WES (low tumour purity fresh tissue or high tumour purity FFPE; n=25)
Panel tests (FFPE) (TSO500 or HR BROCA panel (EM Swisher) or BRCA1/2 only; n=55)




Stafford Fox Medical Research Foundation

Overall:
**4/50 (8%) pathogenic aberrations**

8/50 (16%) any variants

**13/13 (WGS) COSMIC mutational Signature 3**

**COSMIC mutational Signature 3: >3000 mutations, in top 3 signatures (10 had high genome wide LOH, > 0.2)**

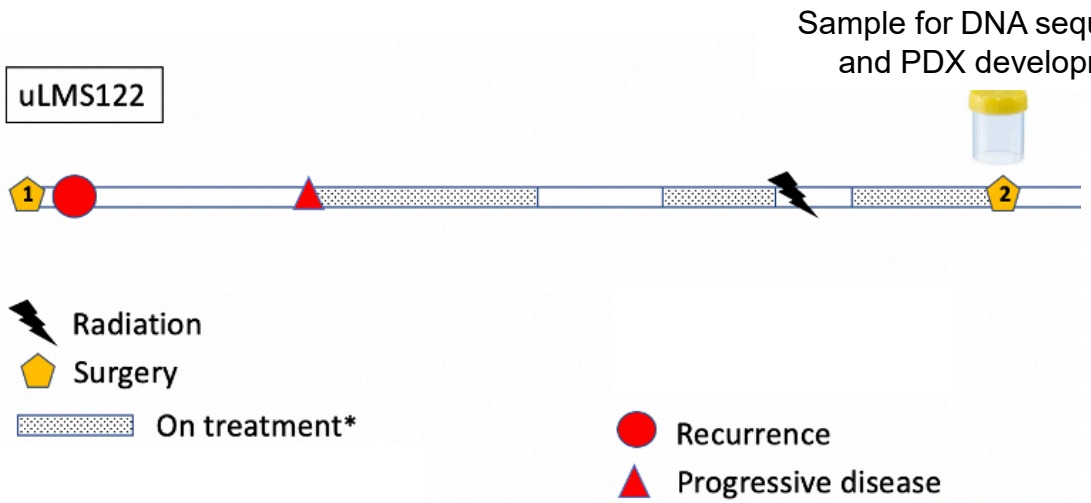
| Test | BRCA1/2 | Other HR genes | COSMIC Signature 3 | LoH signature |
|---|---|---|---|---|
| WGS | ✅ | ✅ | ✅✅ | ✅✅ |
| WES | ✅ | ✅ | ✅ | ✅ |
| TSO500 | ✅ | ✅ | X | X |
| BRCA1/2 panel | ✅ | X | X | X |

WGS = Whole genome sequencing
WES = Whole exome sequencing
LoH = Loss of Heterozygosity

Seligson ND, Kautto EA, Passen EN, Stets C, Toland AE, Millis SZ, et al. Oncologist. 2019;24(7):973–9.

Fox lab

# uLMS #122 – *BRCA2* deleted: WGS sample #1

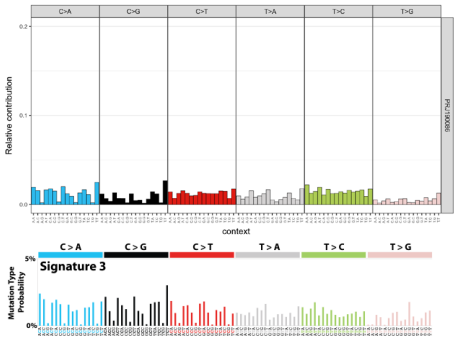



*standard uLMS treatments (chemotherapy, endocrine therapy)

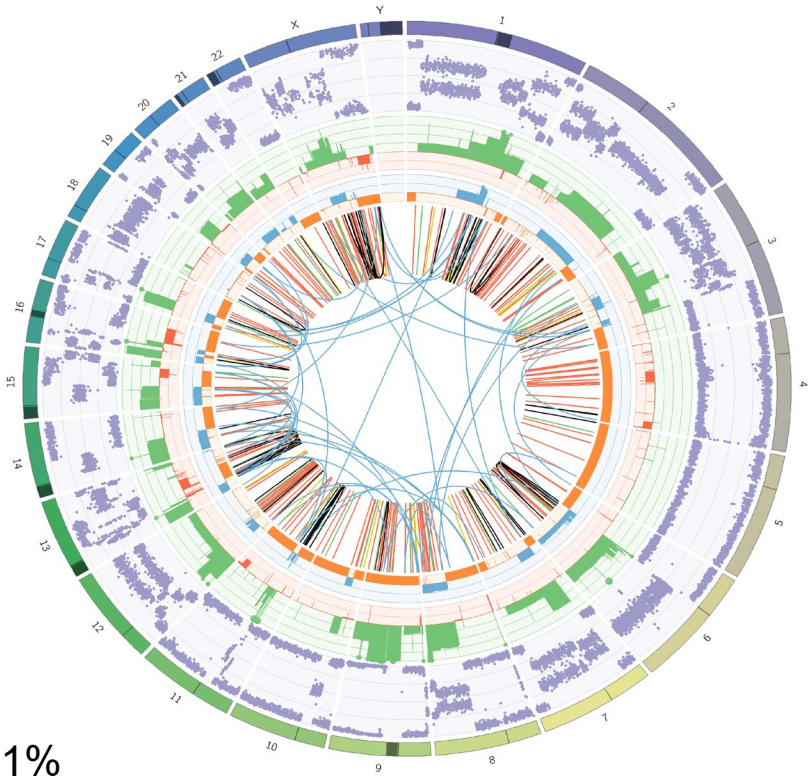
## Compassionate access to PARPi (olaparib)

- **Whole Genome Sequencing #1** performed on heavily pre-treated sample:
  - *TP53* near-splice site deletion and loss of heterozygosity
  - *ATRX* frameshift mutation
  - Homozygous deletion *RB1*

  - **Homozygous deletion *BRCA2***
  - COSMIC Mutation Signature 3 dominant



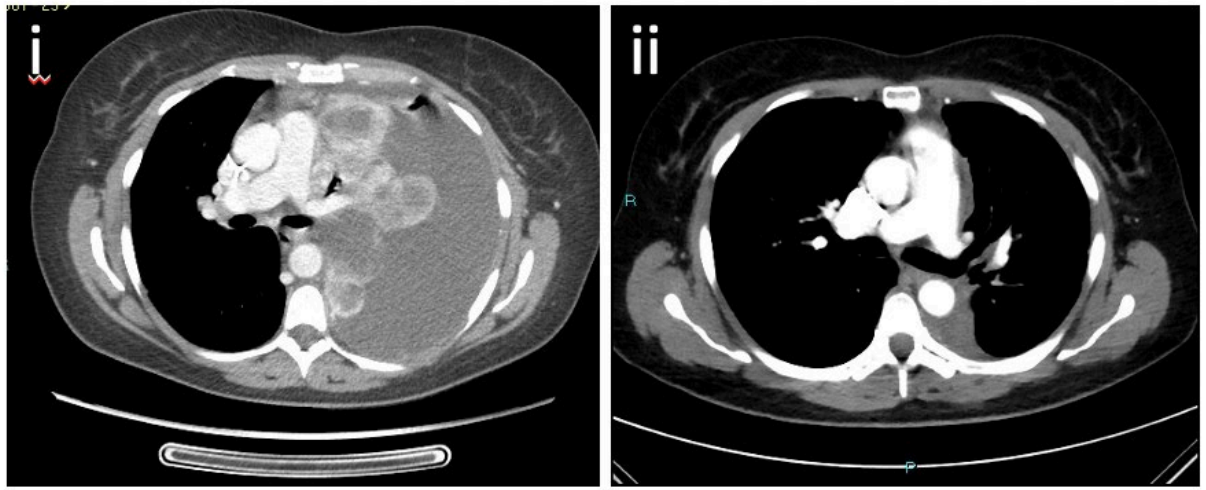

31%



**Circos Plot**

Gen Dall, Cassandra Vandenberg, Kathy Barber, Silvia Stoev, Sean Grimmond, Joep Vissers, Jocelyn Penington, Justin Bedo, Tony Papenfuss, Gayanie Ratnayake

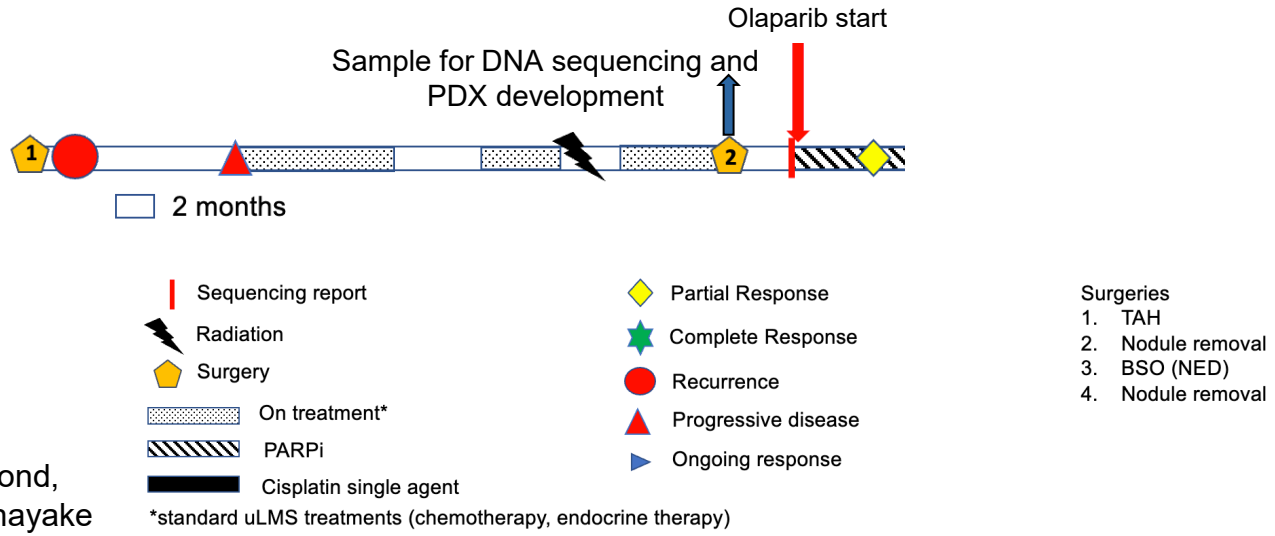
# uLMS #122 – *BRCA2* deleted: olaparib response




**At SFRCP enrollment**

**Partial Response following PARPi (4mo)**

Dr Teng Han Tan,
Radiologist

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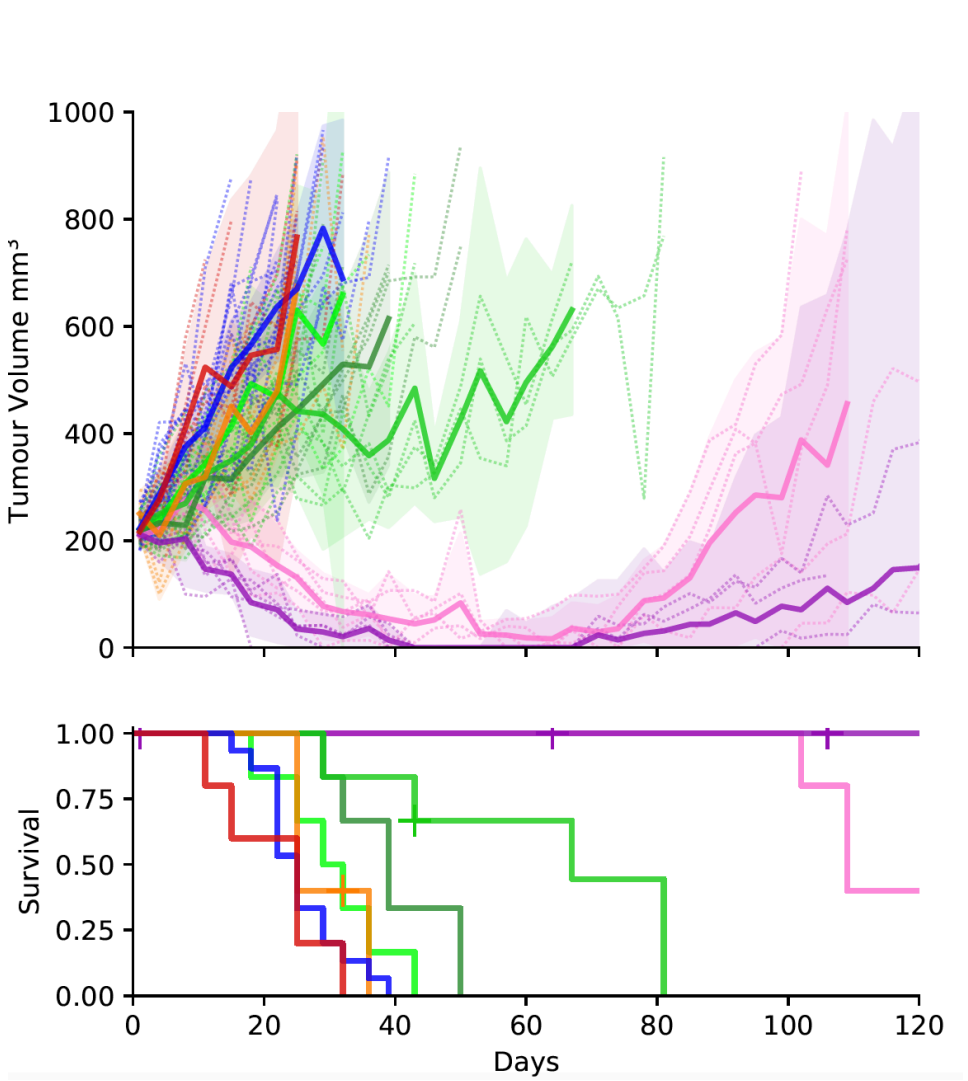
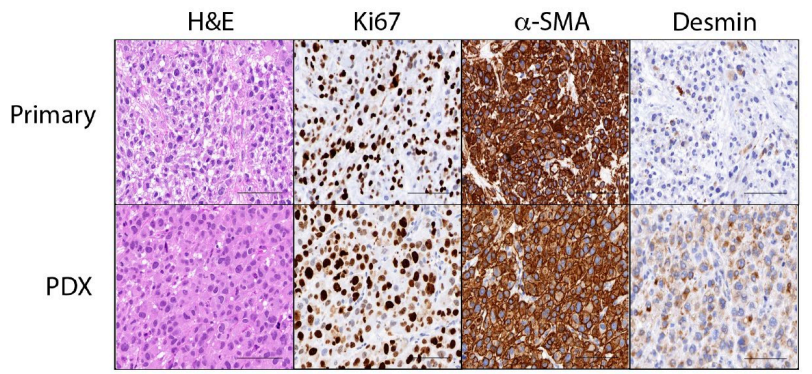
# uLMS #122 – *BRCA2* deleted PDX #1




PDX generated from patient tissue

- Responsive to highest dose of PARPi Olaparib (150mg/kg) 6wks
- Regression + CR (compete response) with Cisplatin
- **Regression + longer CR with Cisplatin + PARPi**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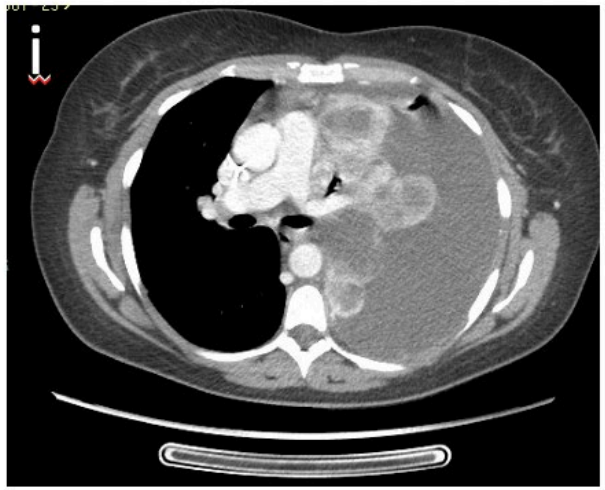
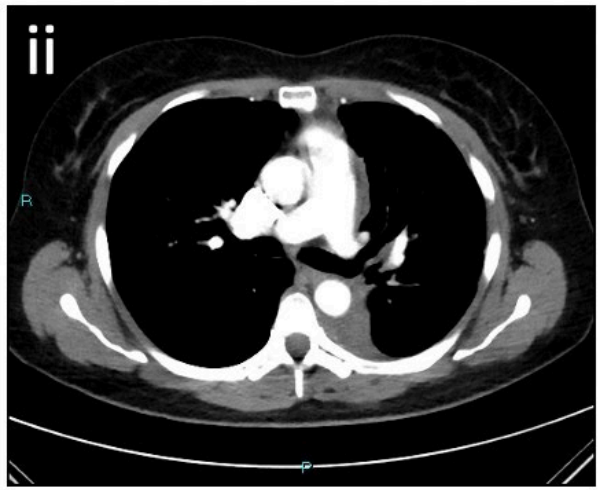
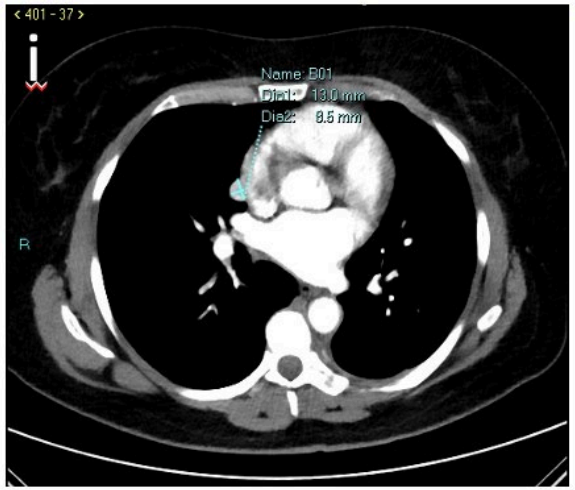
# uLMS #122 – *BRCA2* deleted: addition of cisplatin to olaparib with additional response



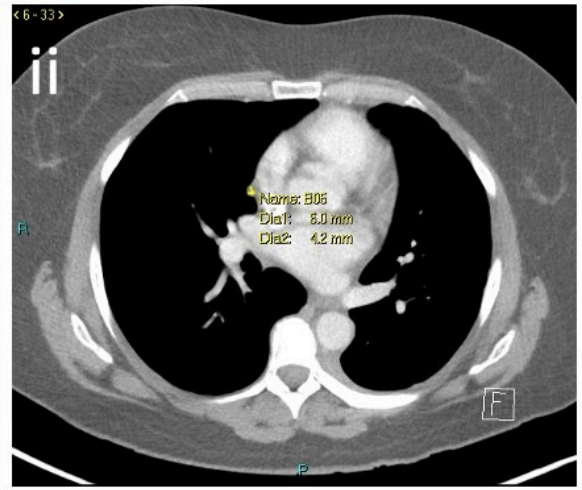

**At SFRCP enrollment**




**Partial Response following PARPi (4mo)**

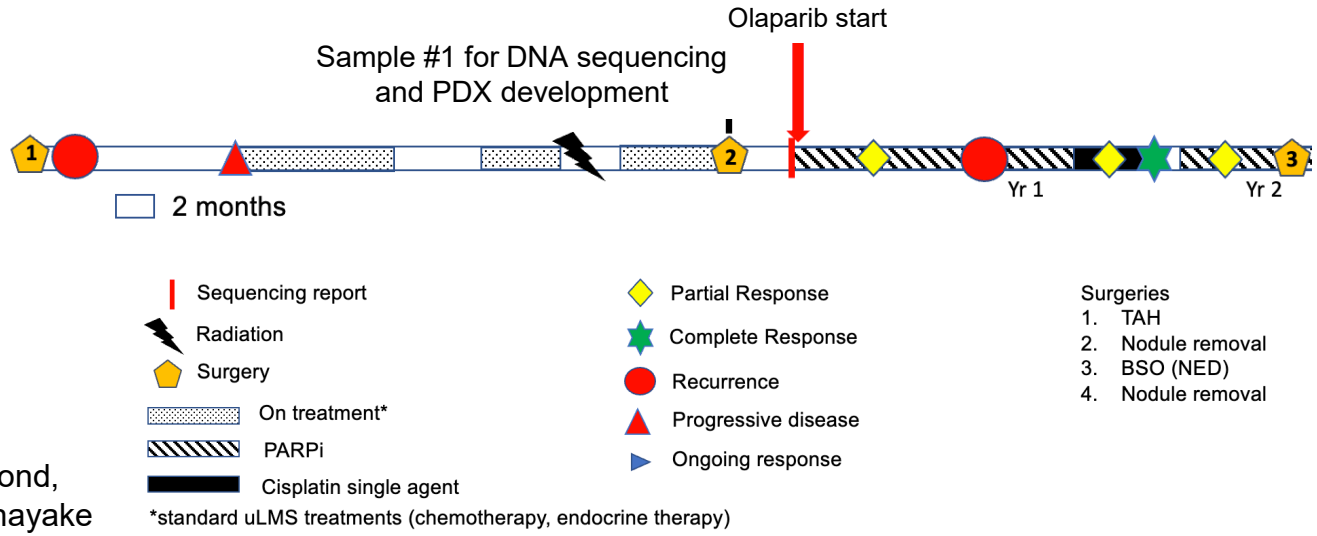



**Post-Olaparib, minor PD**




**Partial Response following PARPi + cisplatin**

Dr Teng Han Tan,
Radiologist

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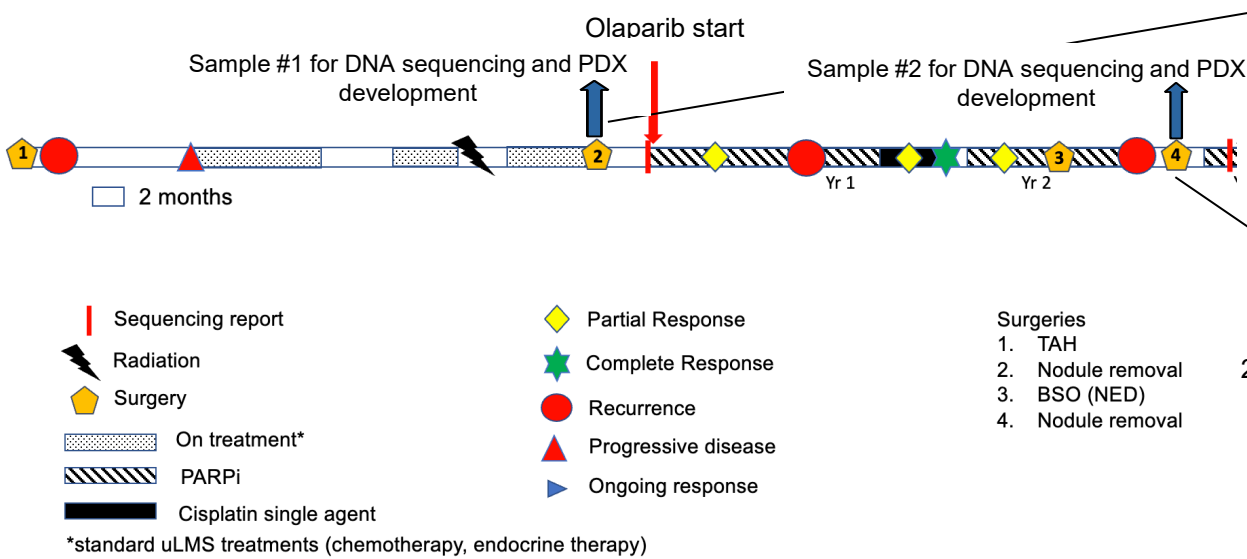
# uLMS #122 – *BRCA2* deleted
# Progression post cisplatin + olaparib: WGS sample #2

Minor PD 4 mo post BSO; lung nodule excised



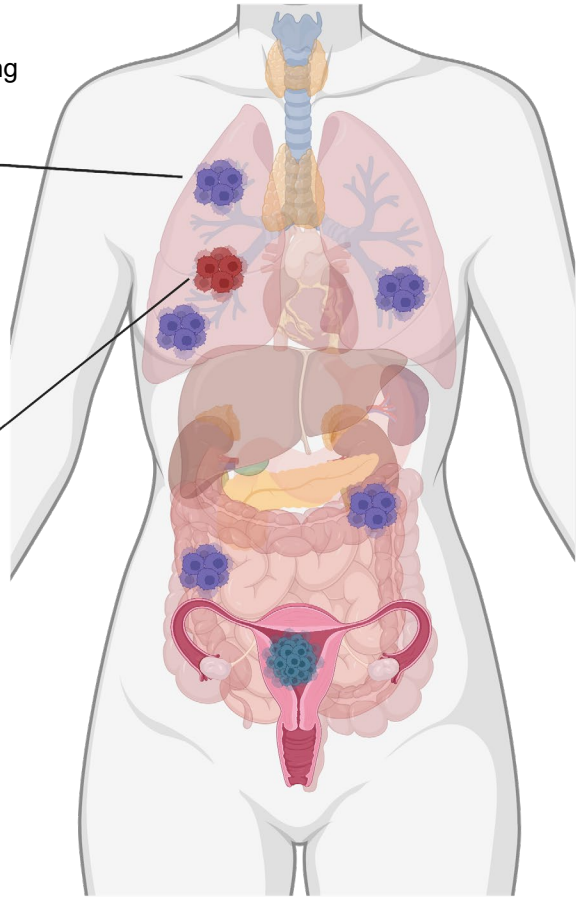

Surgeries
1. TAH
2. Nodule removal
3. BSO (NED)
4. Nodule removal

1st sample for sequencing

Post
- chemotherapy
- hormone therapy
- targeted therapy

*BRCA2* del
COSMIC Signature 3

2nd sample for sequencing



Primary Tumour

Progressive metastases

Progressive metastasis

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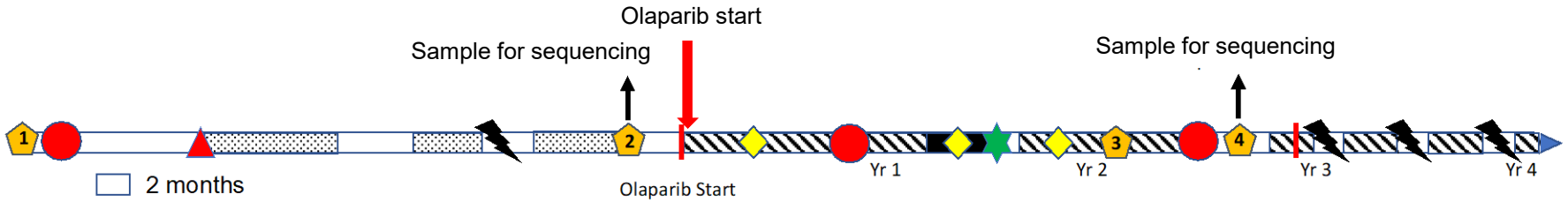
# uLMS #122 – *BRCA2* deleted with *PRKDC* variants




Radiation
Surgery
On treatment*
PARPi
Platinum + PARPi

Partial Response
Complete Response
Recurrence
Progressive disease
Ongoing response

Surgeries
1. TAH
2. Nodule removal
3. BSO (NED)
4. Nodule removal

## Sensitivity to radiation?

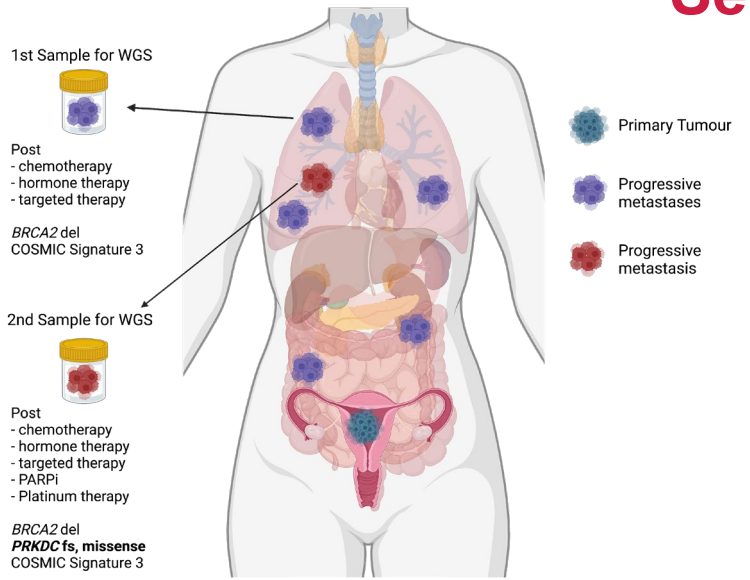
**Whole genome sequencing #2 performed:**

- Previous findings confirmed (*TP53, ATRX, RB1, BRCA2*, Mutation Signature 3)
- New:

*PRKDC* mutations (2x)

Missense and frameshift

(encodes DNA-PKcs – core NHEJ factor)




Olaparib continued

3 month scan = minor PD

**ECOG 0 (well, no restrictions)**

**Radiotherapy (SABR) to 2 sites then continued Olaparib**

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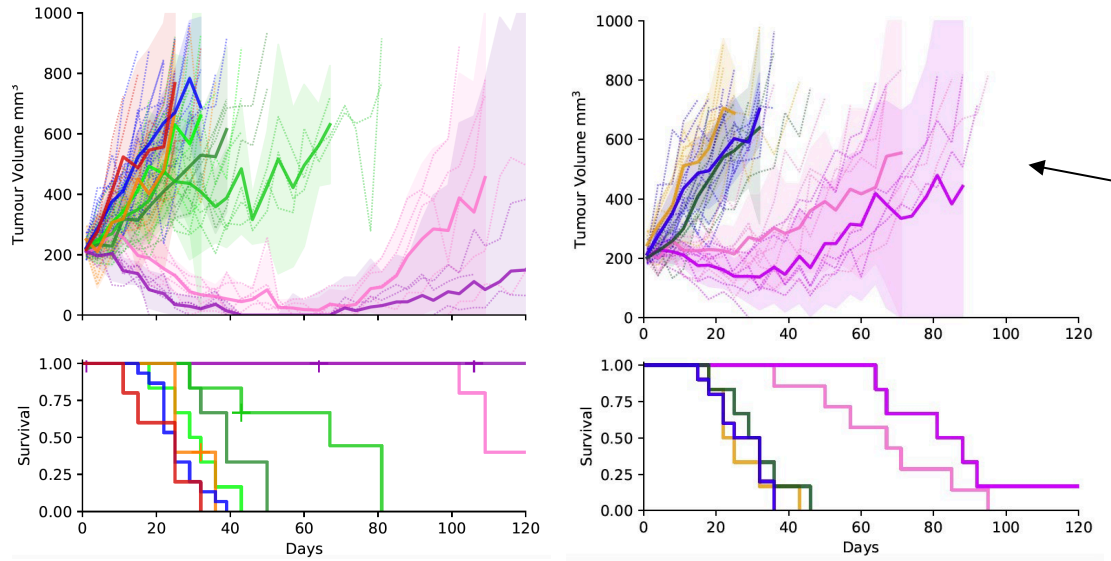
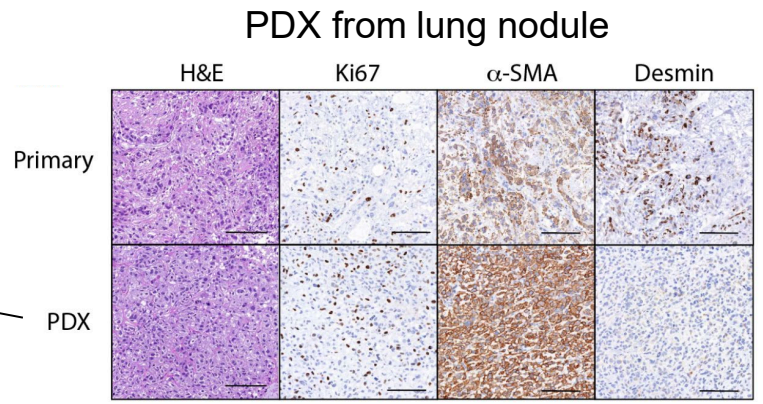
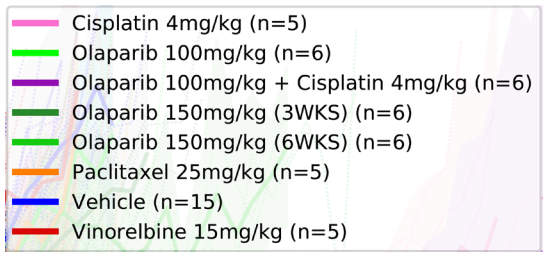
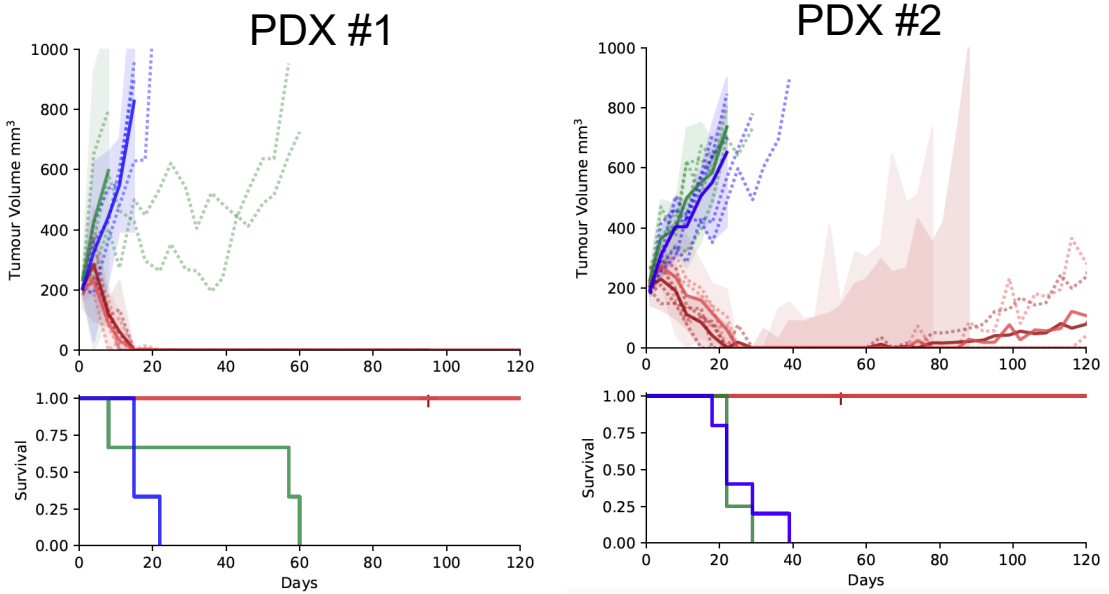
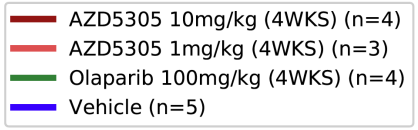
# uLMS #122 PDX #2 PRKDC variants resistant to olaparib but responsive to selective PARP1i AZD5305 (Pt Rx with RT)

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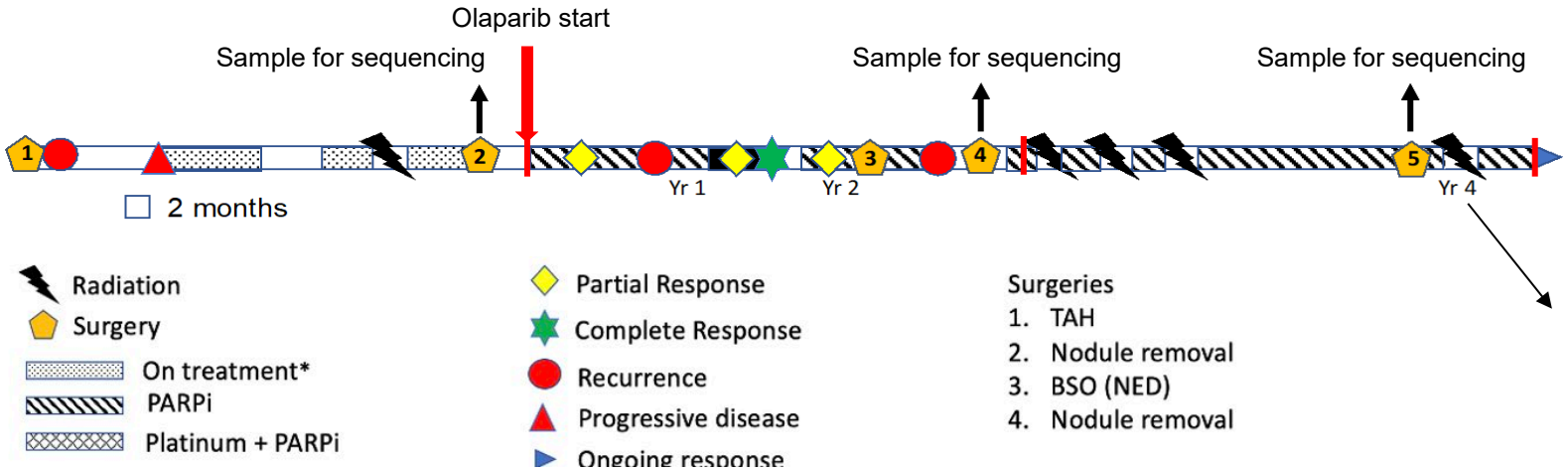
# Progression post cisplatin + olaparib: WGS sample #3 *PARG* rearrangement




Olaparib continued

4 brain mets, lung mets, new kidney met

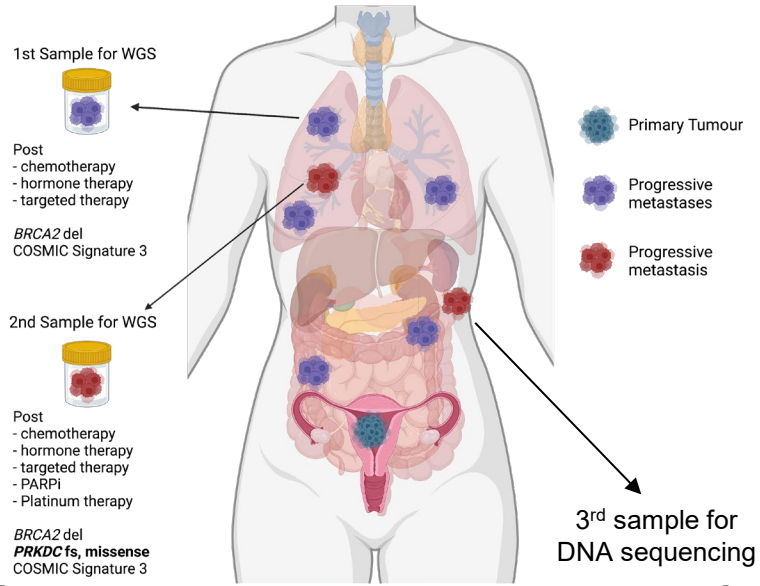
**ECOG 0-1**

**Radiotherapy (SABR) to kidney, brain**

**HAD BEEN ON OLAPARIB +/- cisplatin for > FOUR YEARS**

**Whole genome sequencing #3 performed:**

- Previous findings confirmed (*TP53, RB1, BRCA2*, Mutation Signature 3)
- New:
- *PRKDC* mutations (2x) NOT PRESENT
- *ATRX* rearrangement, c/w clonal heterogeneity
- ***PARG* rearrangements**




**Considering ATRi trial:**

**Gogola et al, Cancer Cell, 2018:**
Loss of PARG = resistance to PARPi in mouse mammary tumours – inc radiosensitivity

**da Costa et al, Nat Rev Can, 2023:**
Cells that become PARPi resistant through PARG down-regulation exhibit high replication stress and dependence on ATR-CHK1-WEE1 pathway

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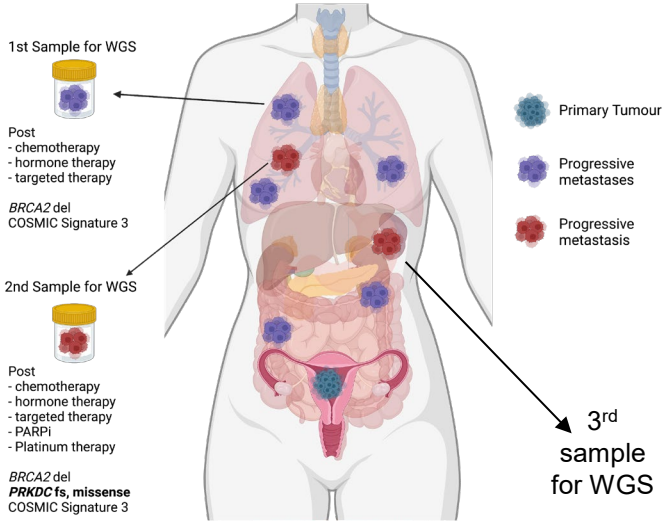
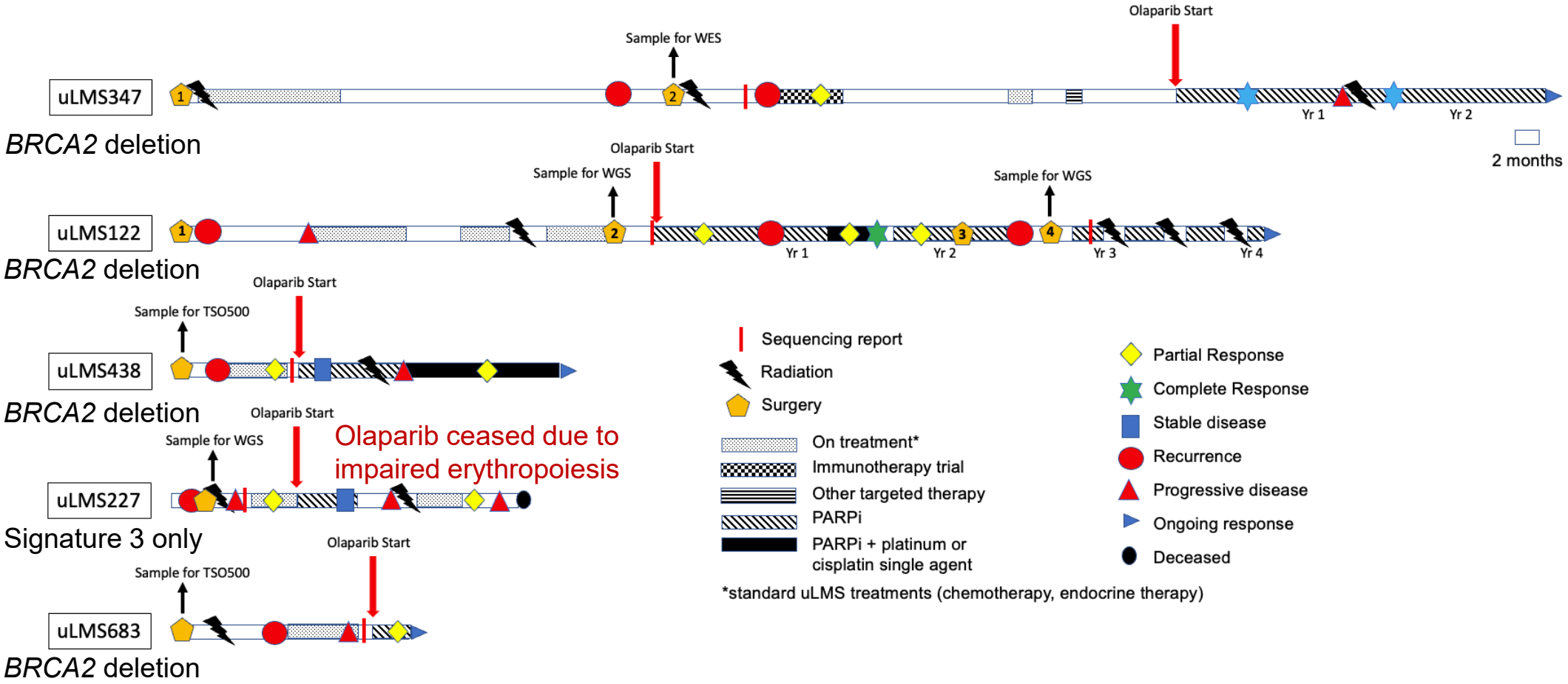
# uLMS #1122 – WGS reports

| Aberration | WGS#1 | WGS#2 | WGS#3 |
|---|---|---|---|
| **Germline mutation of clinical significance** | **AF** | **AF** | **AF** |
| *POT1*; c.1071dup; p.Q358fs | ? (SFRC 67%) | 38% (SFRC 66%) | 36% |
| **Homozygous deletion of cancer genes** | **Deleted** | | |
| *BRCA2* | ✅ | ✅ 53% | 65% |
| *RB1 (x2)* | ✅ | ✅ 73% + 60% | 75% + 86% |
| **Mutations of uncertain clinical significance** | **AF** | **AF** | **AF** |
| *CTNNB1*; c.1877A>G; p.E626G | 30% | ❌ | ❌ |
| *FOXP1*; c.1444G>C; p.E482Q | 41% | ❌ | ❌ |
| *ATRX*; c.4698del; p.D1566fs | 59% | 52% | N/A (see SV) |
| *TP53*; c.560-25_560-5delinsGCTT | ❌ | 61% | 78% |
| *PRKDC*; c.2476_2503del; p.F826fs | ❌ | 39% | ❌ |
| *PRKDC*; c.4778T>C; p.V1593A | ❌ | 32% | ❌ |
| *CHEK1*; c.66-3_69del | ❌ | 31% | ❌ |
| **Focally amplified cancer genes** | **Copies** | **Copies** | **Copies** |
| *NTRK2* | 10 (not in SFRC) | ❌ | ❌ |
| *GNAQ* | 12 | ❌ | ❌ |
| **SV inactivation of cancer genes** | **AF** | **AF** | **AF** |
| *PALB2* (large deletion - predicted inactivation) | 40% (LOH) | No SV but LOH | ❌ |
| *ATRX* (interchromosomal translocation – predicted inactivation) | ❌ | ❌ | ✅ |
| *ATRX* (interchromosomal translocation – predicted inactivation) | ❌ | ❌ | ✅ |
| *PARG* (Breakpoint between exons 12+13 - predicted inactivation) | ❌ | ❌ | ✅ |
| *PARG* (Multiple breakpoints between exons 10+12 - uncertain effect) | ❌ | ❌ | ✅ |
| **Dominant Somatic Signatures** | **% assigned** | **% assigned** | **% assigned** |
| Signature 3; BRCA deficiency signature | 32% | 27% | 28% |
| Signature 8; Aetiology unknown | 26% | 22% | |
| **Likelihood of HR deficiency prediction score** | **Score** | **Score** | **Score** |
| CHORD/HRDetect | ? | 80%/0.979 | 73%/0.88 |
| **Microsatellite instability** | **Score** | **Score** | **Score** |
| MSI-status | ? | High (MSI) | MSS |



# PARPi response in other individuals with uLMS




Cassandra Vandenberg, Kathy Barber, Silvia Stoev, Sean Grimmond, Joep Vissers, Layla Zhu, Wing-Yee Lo, Oliver Hofmann, Jocelyn Penington, Justin Bedo, Tony Papenfuss, Gayanie Ratnayake, Teng Tan, Ian Collins, Steve Barnett, Matt Wakefield

# PARPi response in other individuals with uLMS

Dall *et al. J Exp Clin Cancer Res* (2023) 42:112
https://doi.org/10.1186/s13046-023-02687-0

RESEARCH Open Access

# uLMS Future Directions

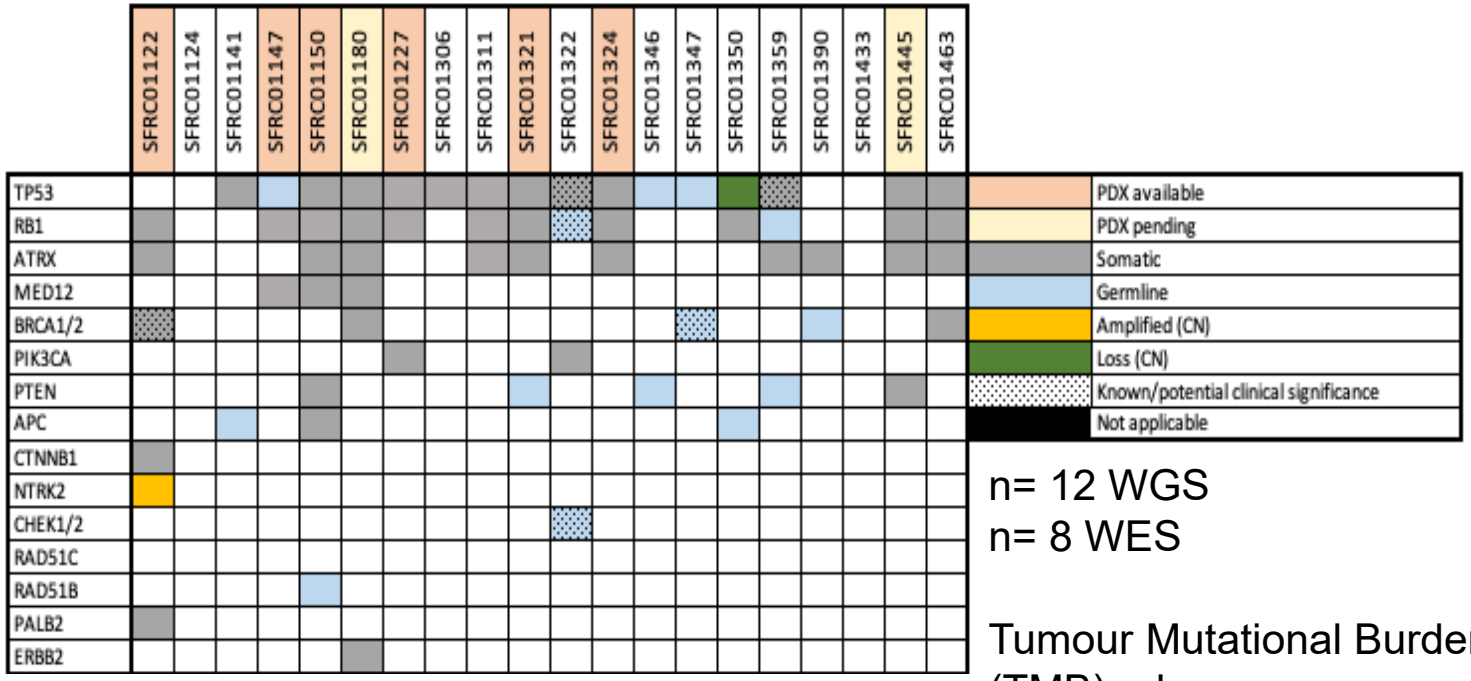
WEHI brighter together

**Dr Holly Barker**

- **HRD Screening of uLMS is required**
- **~10% of our uLMS cohort are HRD**
- **Clinical and pre-clinical evidence of PARPi benefit in HRD patients**
- **Demonstration of efficacy for PARPi combinations with platinum or RT**
- New interpretation of COSMIC signature 3
  – combine with HRDetect/CHORD and LoH scores
- 20 uLMS PDX models: explore uLMS biology - HRD and non-HRD
- Collaboration with Prof Roger Reddel and Dr Liz Connolly, Proteomics of uLMS

**ESMO 2024 1727MO - Can proteomics predict metastatic relapse in leiomyosarcoma (LMS)? Development of an 8 protein signature in a >350 sample study including a validation cohort**

## Most uLMS have nothing clinically actionable on WGS: need research urgently




n= 12 WGS
n= 8 WES

Tumour Mutational Burden (TMB) ~ low

# New targeted therapy combinations for USC

USC comprises 10% of endometrial cancer cases but is responsible for at least **40% of endometrial cancer-related deaths** (and is also increasing with rising obesity)

Overall survival rate is just 18-27%

Total number of cases in SFRCP: **69**

(46 with molecular data)

**Potentially HRD = 15/46 (32.6%)**

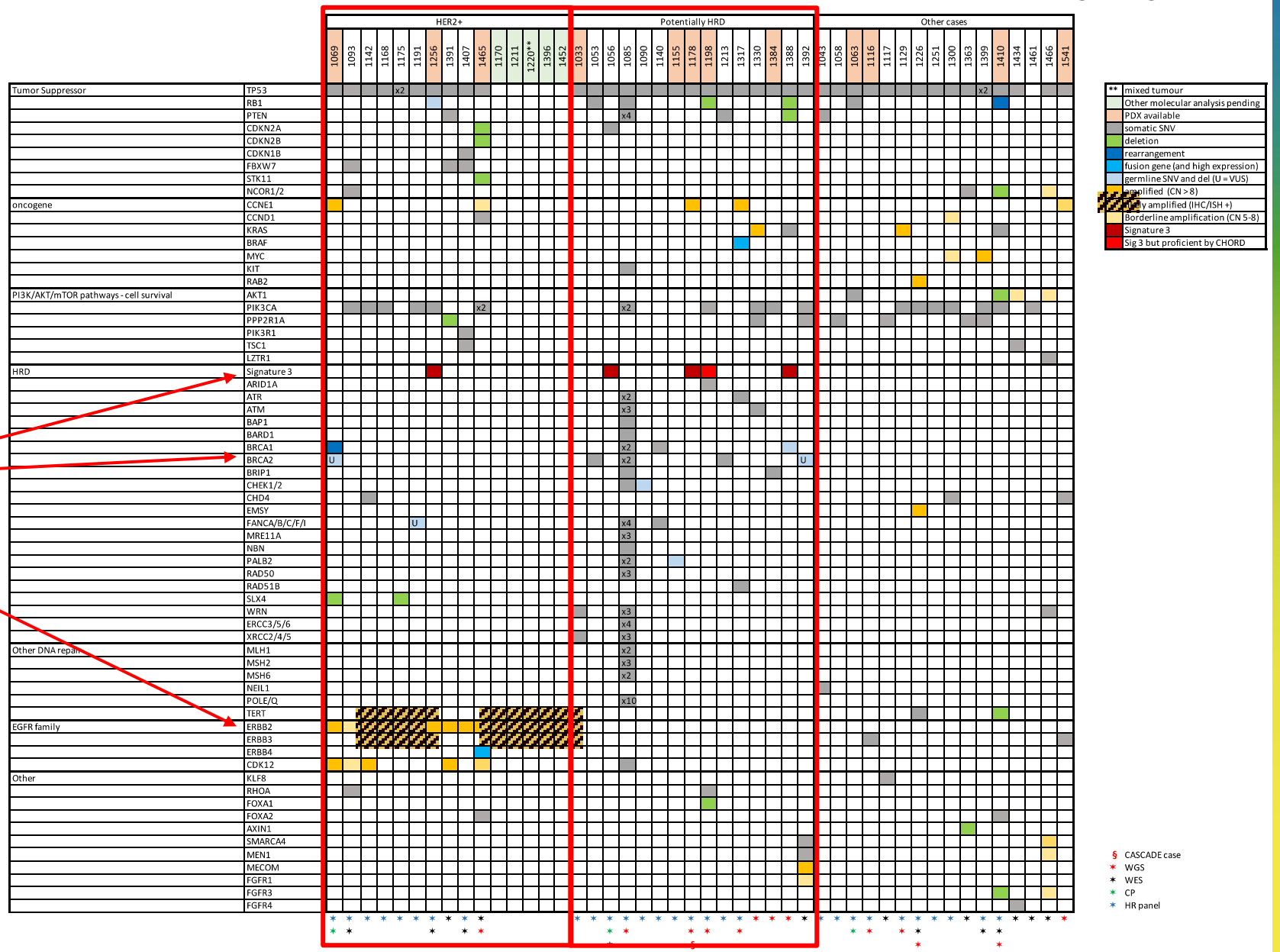
**HER2+ = 15/46 (32.6%)**

HRD;

Homologous Recombination Deficient = potentially sensitive to PARP inhibitors (PARPi)

<u>Aim:</u>

Develop cell lines and organoid models in which to test response to combinations involving PARPi and other therapies



# New targeted therapy combinations for USC

Dr Holly Barker

## Cell lines

#1256 – *ERBB2* amplification

#1116 – *ERBB3* mutation

#1178 – Sig 3 and *CCNE1* amplification

## Plan:

Initial drug screening for potential combinations involving:

- PARPi
- HER2i (i.e. T-Dxd)
- RT

| | | HER2+ | | | Potentially HRD | | | | Other cases | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1069 | 1256 | 1465 | 1033 | 1178 | 1198 | 1384 | 1063 | 1116 | 1155 | 1410 | 1541 |
| Tumor Suppressor | TP53 | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV |
| | RB1 | | germline SNV and del (U = VUS) | | | | deletion | | somatic SNV | | | rearrangement | |
| | CDKN2A | | | deletion | | | | | | | | | |
| | CDKN2B | | | deletion | | | | | | | | | |
| | FBXW7 | | | | | x2 | | | | | | | |
| | STK11 | | | deletion | | | | | | | | | |
| | NCOR1/2 | | | | | | | | | | x2 | deletion | |
| oncogene | CCNE1 | amplified (CN > 8) | | Borderline amplification (CN 5-8) | | amplified (CN > 8) | | | | | | | Borderline amplification (CN 5-8) |
| | CCND1 | | | somatic SNV | | | | | | | | | |
| | KRAS | | | | | | | | | | | somatic SNV | |
| PI3K/AKT/mTOR pathways - cell survival | AKT1 | | | | | | | | somatic SNV | | | deletion | |
| | PIK3CA | | somatic SNV | x2 | | | somatic SNV | somatic SNV | | | | somatic SNV | |
| HRD | Signature 3 | | Signature 3 | | | Sig 3 but proficient by CHORD | Sig 3 but proficient by CHORD | | | | | | |
| | ARID1A | | | | | | somatic SNV | | | | | | |
| | BRCA1 | rearrangement | | | | | | | | | | | |
| | BRCA2 | U | | | | | | | | | | | |
| | BRIP1 | | | | | | | somatic SNV | | | | | |
| | CHD4 | | | | | | | | | | | | somatic SNV |
| | SLX4 | deletion | | | | | | | | | | | |
| | WRN | | | | somatic SNV | | | | | | | | |
| | XRCC2/4/5 | | | | somatic SNV | | | | | | | | |
| Other DNA repair | TERT | | | | | | | | | | | deletion | |
| EGFR family | ERBB2 | amplified (CN > 8) | amplified (CN > 8) | amplified (CN > 8) | | | | | | | | | |
| | ERBB3 | | | | | | | | | somatic SNV | | | somatic SNV |
| | ERBB4 | | | fusion gene (and high expression) | | | | | | | | | |
| | CDK12 | amplified (CN > 8) | | amplified (CN > 8) | | | | | | | | | |
| Other | RHOA | | | | | | somatic SNV | | | | | | |
| | CTNNB1 | | | | | | somatic SNV | | | | somatic SNV | | |
| | BRD4 | | | | | | somatic SNV | | | | U | | |
| | FOXA1 | | | | | | deletion | | | | | | |
| | FOXA2 | | | somatic SNV | | | | | | | | somatic SNV | |
| | FGFR3 | | | | | | | | | | | deletion | |
| | | ✶ ✶ | ✶ ✶ ✶ | ✶ ✶ | ✶ | ✶ ✶ § | ✶ ✶ ✶ | ✶ | ✶ ✶ | ✶ ✶ ✶ | ✶ | ✶ ✶ ✶ ✶ | ✶ |

| | |
|---|---|
| somatic SNV | |
| deletion | |
| rearrangement | |
| fusion gene (and high expression) | |
| germline SNV and del (U = VUS) | |
| amplified (CN > 8) | |
| Borderline amplification (CN 5-8) | |
| Signature 3 | |
| Sig 3 but proficient by CHORD | |

§ CASCADE case

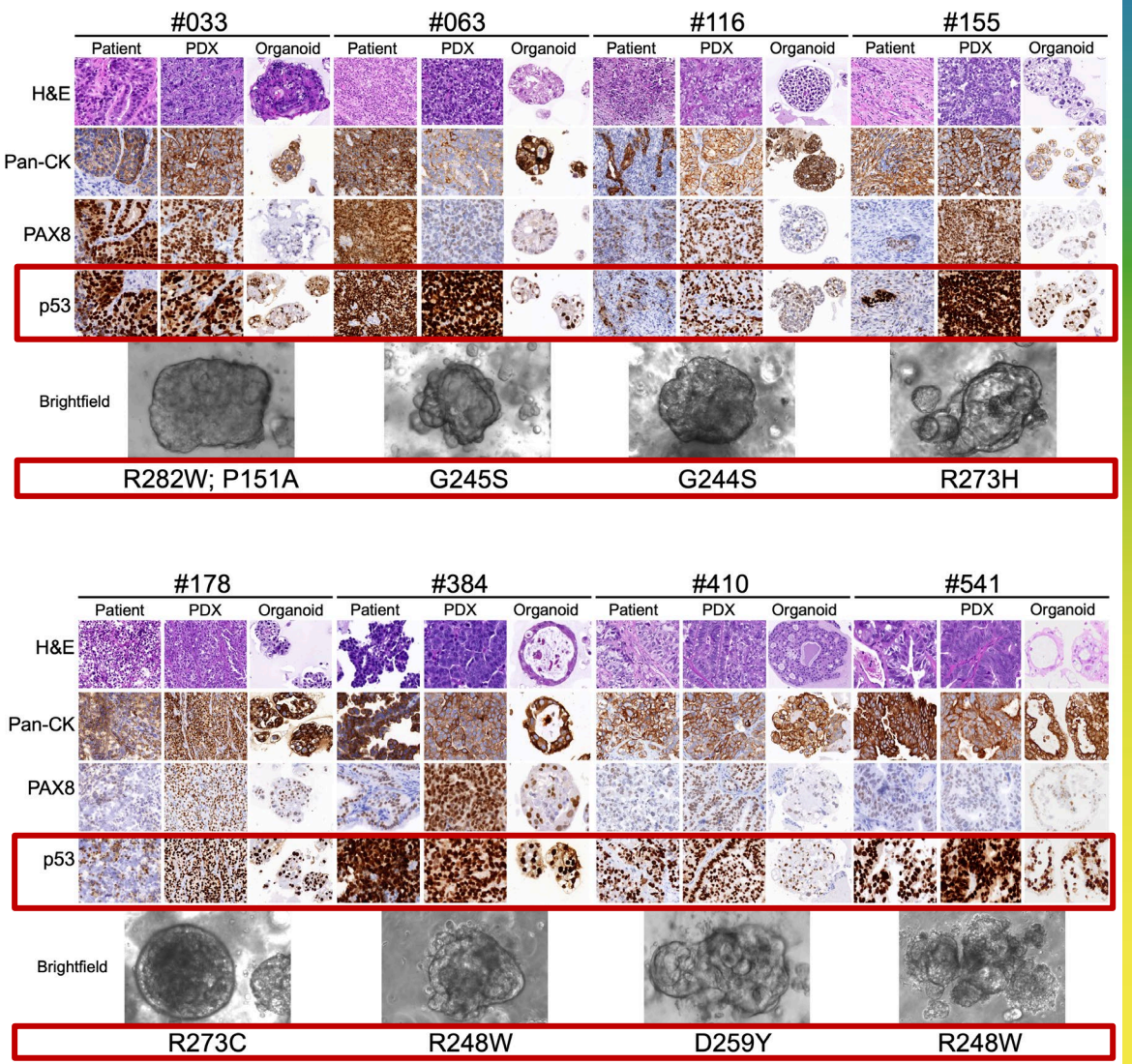
✶ WGS

✶ WES

✶ CP

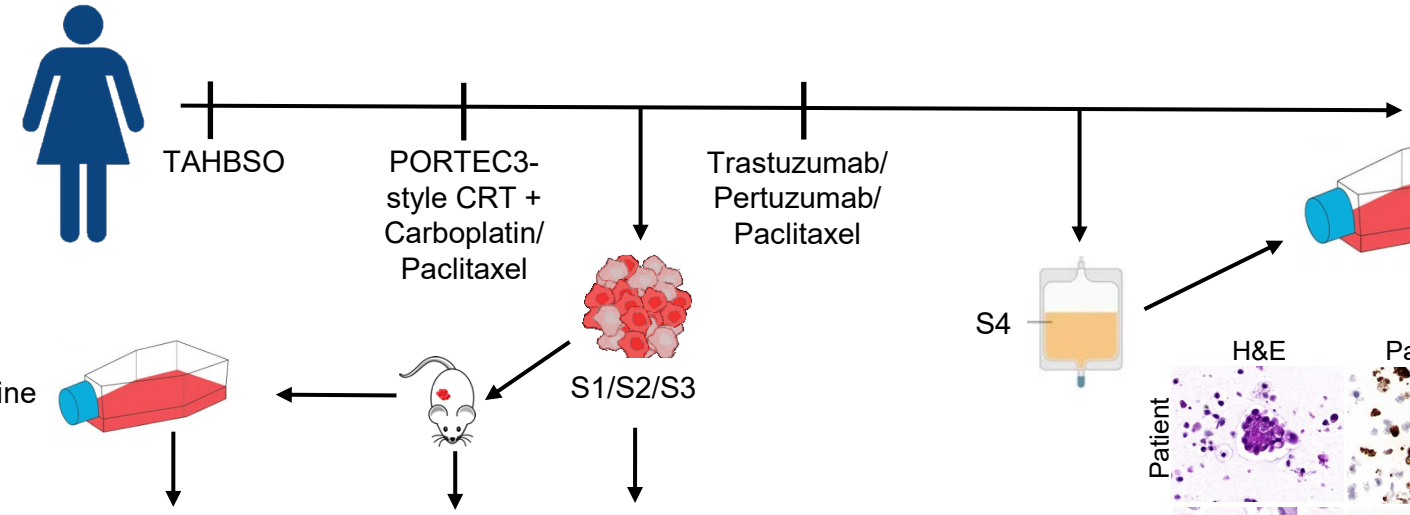
✶ HR panel

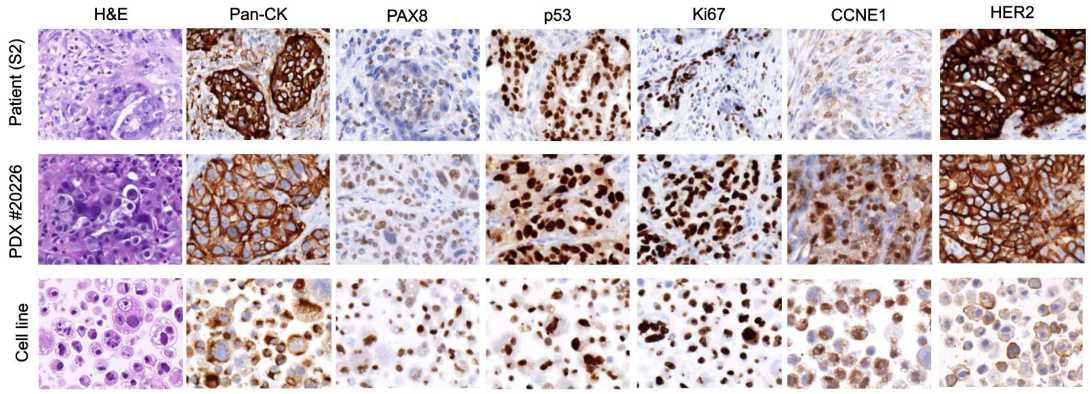
# Preclinical models of Uterine Serous Cancer

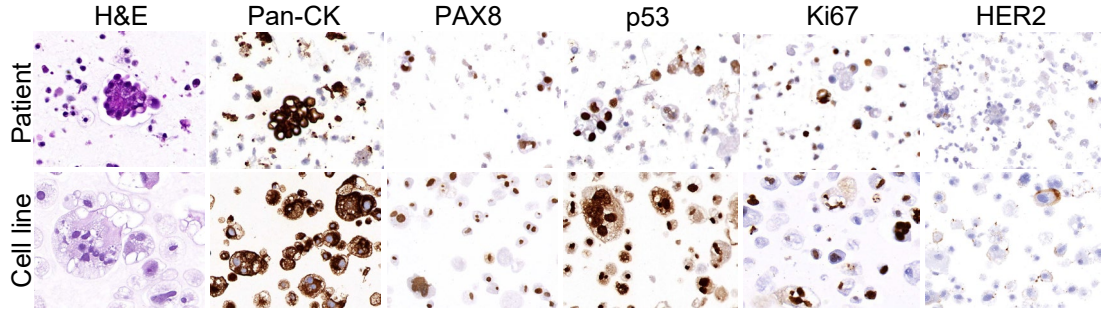



Andrew Farrell, Rachael Taylor, Cass Vandenberg

# #1256 – HER2 amplified USC




WES

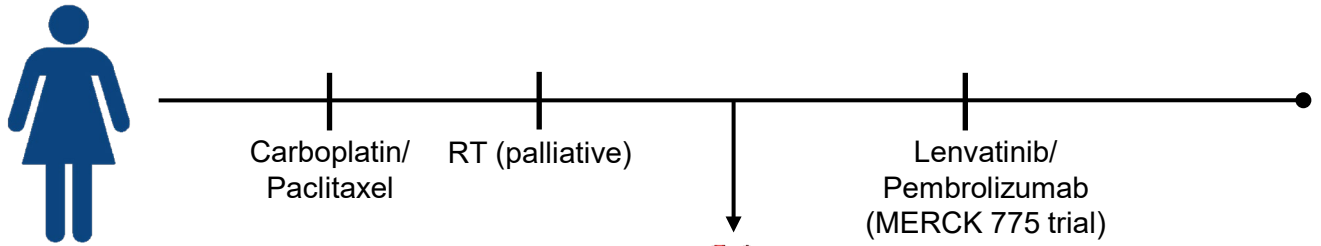
WGS

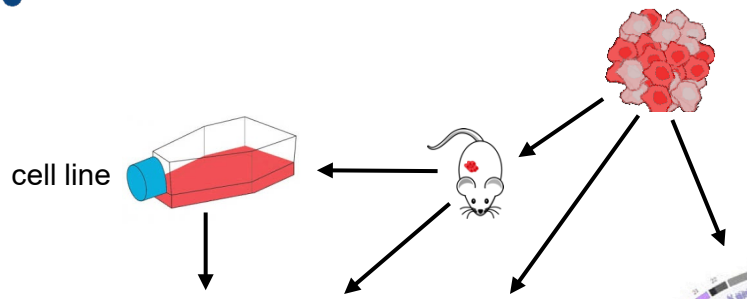
| Mutations of potential clinical significance | Effect | AF |
|---|---|---|
| *TP53*; c.437G>A; p.W146* | LoF | 86% |
| *TP53*; c.817C>T; p.R273C | LoF | 51% |
| *PIK3CA*; c.1636C>G; p.Q546E | GoF | 92% |
| **Focally amplified Genes** | | **Copies** |
| *FBLN2* | | 54 |
| *CDK12, IKZF3, **ERBB2*** | | **19** |
| **Deleted Genes** | | |
| *ERBB4, GATA3* | | |
| **Dominant Somatic Signatures** | | **% assigned** |
| Signature 3; **BRCA deficiency** (HRD) signature | | 26% |
| Signature 6; Mismatch repair deficiency | | 16% |

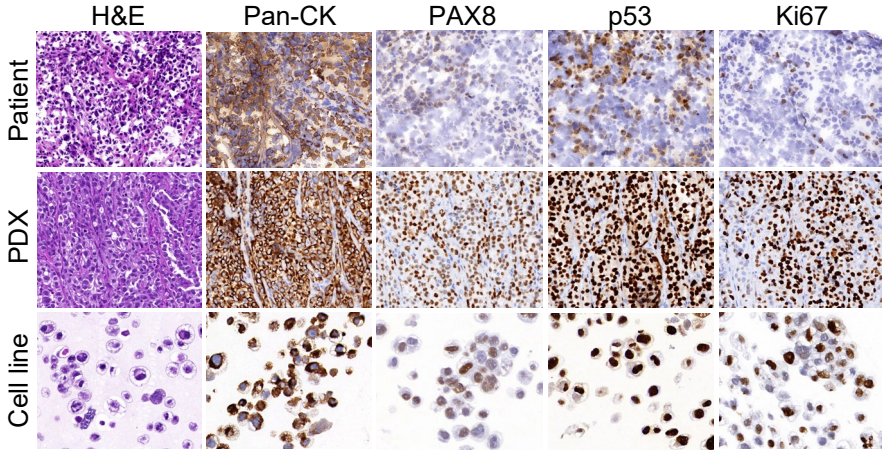
WES; Whole exome sequencing
WGS; Whole genome sequencing
HRD; Homologous recombination deficiency

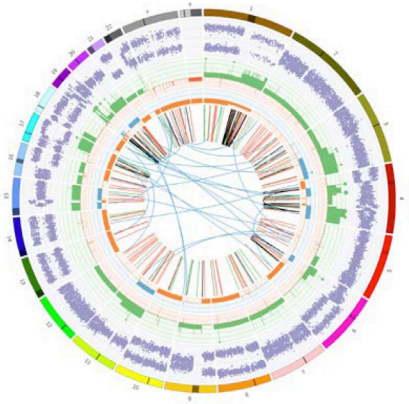
Cassandra Vandenberg, Kathy Barber, Silvia Stoev, Gayanie Ratnayake

# #1178 – Cyclin E amplified USC
# Paired samples pre len/pem and at warm autopsy



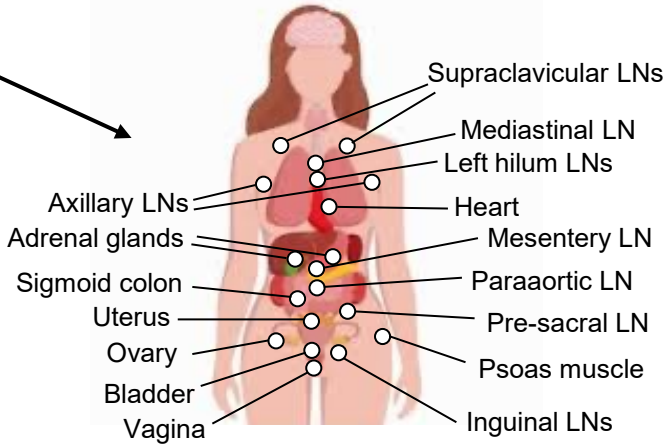



**WGS CIRCOS plot**
(outside -> in: BAF, CNV, MAF, SV events)

Unstable genome
with features of HRD

WGS

CASCADE program – Cancer tissue
Collection After Death




| **Mutations of potential clinical significance** | **Effect** | **AF** |
|---|---|---|
| *TP53*; c.817C>T; p.R273C | LoF | 37% |
| **Mutations of uncertain clinical significance** | **Effect** | **AF** |
| *FBXW7*; c.1598_1599del; p.C533fs | LoF | 53% |
| *FBXW7*; c.1145C>T; p.S382F | LoF | 21% |
| **Focally amplified Genes** | | **Copies** |
| *CCNE1* | | >25 |
| **Dominant Somatic Signatures** | | **% assigned** |
| Signature 3; **BRCA deficiency** (HRD) signature | | 19% |
| Signature 1; Deamination signature (all cancers) | | 14% |
| **Likelihood of HRD prediction score** | | |
| CHORD/HRdetect | | ? |

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Dr Holly Barker

# Validation of combinations in USC organoid models

WEHI brighter together

**USC models**

#1069 – doesn't form organoids
#1256 – organoids ✓
#1465 – organoids ✓
#1033 – organoids ✓
#1178 – Rastrum organoids ✓
#1198 – organoids ✓
#1384 – organoids ✓
#1063 – organoids ✓
#1116 – organoids ✓
#1155 – organoids ✓
#1410 – organoids ✓
#1541 – organoids ✓

| | | HER2+ | | | Potentially HRD | | | | Other cases | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1069 | 1256 | 1465 | 1033 | 1178 | 1198 | 1384 | 1063 | 1116 | 1155 | 1410 | 1541 |
| Tumor Suppressor | TP53 | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV | somatic SNV |
| | RB1 | | germline SNV and del (U = VUS) | | | | deletion | | somatic SNV | | | rearrangement | |
| | CDKN2A | | | deletion | | | | | | | | | |
| | CDKN2B | | | deletion | | | | | | | | | |
| | FBXW7 | | | | | x2 | | | | | | | |
| | STK11 | | | deletion | | | | | | | | | |
| | NCOR1/2 | | | | | | | | | | x2 | deletion | |
| oncogene | CCNE1 | amplified (CN > 8) | | Borderline amplification (CN 5-8) | | amplified (CN > 8) | | | | | | | Borderline amplification (CN 5-8) |
| | CCND1 | | | somatic SNV | | | | | | | | | |
| | KRAS | | | | | | | | | | | somatic SNV | |
| PI3K/AKT/mTOR pathways - cell survival | AKT1 | | | | | | | | somatic SNV | | | deletion | |
| | PIK3CA | | somatic SNV | x2 | | | somatic SNV | somatic SNV | | | | somatic SNV | |
| HRD | Signature 3 | | Signature 3 | | | Sig 3 but proficient by CHORD | Sig 3 but proficient by CHORD | | | | | | |
| | ARID1A | | | | | | somatic SNV | | | | | | |
| | BRCA1 | rearrangement | | | | | | | | | | | |
| | BRCA2 | U | | | | | | | | | | | |
| | BRIP1 | | | | | | | somatic SNV | | | | | |
| | CHD4 | | | | | | | | | | | | somatic SNV |
| | SLX4 | deletion | | | | | | | | | | | |
| | WRN | | | | somatic SNV | | | | | | | | |
| | XRCC2/4/5 | | | | somatic SNV | | | | | | | | |
| Other DNA repair | TERT | | | | | | | | | | | deletion | |
| EGFR family | ERBB2 | amplified (CN > 8) | amplified (CN > 8) | amplified (CN > 8) | | | | | | | | | |
| | ERBB3 | | | | | | | | | somatic SNV | | | somatic SNV |
| | ERBB4 | | | fusion gene (and high expression) | | | | | | | | | |
| | CDK12 | amplified (CN > 8) | | Borderline amplification (CN 5-8) | | | | | | | | | |
| Other | RHOA | | | | | | somatic SNV | | | | | | |
| | CTNNB1 | | | | | | somatic SNV | | | | somatic SNV | | |
| | BRD4 | | | | | | somatic SNV | | | | U | | |
| | FOXA1 | | | | | | deletion | | | | | | |
| | FOXA2 | | | somatic SNV | | | | | | | | somatic SNV | |
| | FGFR3 | | | | | | | | | | | deletion | |
| | | ✶ ✶ ✶ ✶ | ✶ ✶ ✶ | ✶ ✶ ✶ | ✶ ✶ ✶ ✶ | ✶ ✶ ✶ § | ✶ ✶ ✶ | ✶ | ✶ ✶ ✶ | ✶ ✶ ✶ | ✶ | ✶ ✶ ✶ ✶ | ✶ |

§ CASCADE case
✶ WGS
✶ WES
✶ CP
✶ HR panel

Potential PARPi response
Potential HER2i response
Other drug response
?

# Therapeutic response and resistance informed by preclinical models of rare gynaecological cancers

- **Include rare gynaecological cancers in research planning**

- Molecular sequencing and other characterization is essential
- Preclinical models – PDX, PDX-derived organoids, PDX-derived cell lines, cell lines all have unique utility, depending on the context, add value
- The study of drug resistance must occur at the same time as studying drug response
- Value is cumulative and worthwhile: PDX provide very pure populations of tumour cells for analysis, allowing analyses which could not otherwise be performed

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People with rare cancers and their families and friends


Stafford Fox Medical Research Foundation

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Royal Melbourne Hospital

AOCS
australian ovarian cancer study