

# ***BRCA-Associated Ovarian Cancer: How to Personalize First-Line and Subsequent Therapies?***

**Susana Banerjee, MBBS, MA, MRCP, PhD**  
Consultant Medical Oncologist and  
Research Lead Gynaecology Unit  
The Royal Marsden Hospital  
London, United Kingdom

# Why Should *BRCA*-Associated Ovarian Cancer Be Treated Differently?

*BRCA* mutation carriers – distinct clinical behaviour:

- **Age at diagnosis:** *BRCA1* lower
  - Mean *BRCA1* 53.4 yrs, *BRCA2* 59.8 yrs, noncarrier 60.5yrs<sup>1</sup>
- **Improved overall survival<sup>2,3</sup>**
- **High grade serous/endometrioid<sup>1</sup>**
- **Disease distribution**
  - visceral metastases (liver, lung, splenic)<sup>4</sup>

| Mutation Status          | 5-yr OS <sup>2</sup> %; HR  | 5-yr OS <sup>3</sup> %; HR  |
|--------------------------|-----------------------------|-----------------------------|
| <i>BRCA1</i>             | 44; 0.73<br><i>P</i> <.001  | 44; 0.76<br><i>P</i> = .35  |
| <i>BRCA2</i>             | 52; 0.49<br><i>P</i> <.001) | 61; 0.33<br><i>P</i> = .003 |
| <i>BRCA</i> non-carriers | 36                          | 25                          |

1. Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663; 2. Bolton KL, et al. *JAMA.* 2012;307(4):382-390; 3. Yang D, et al. *JAMA.* 2011;306(14):1557-1565; 4. Gourley C, et al. *J Clin Oncol.* 2010;28(15):2505-2511.

# Why Should *BRCA*-Associated Ovarian Cancer Be Treated Differently?

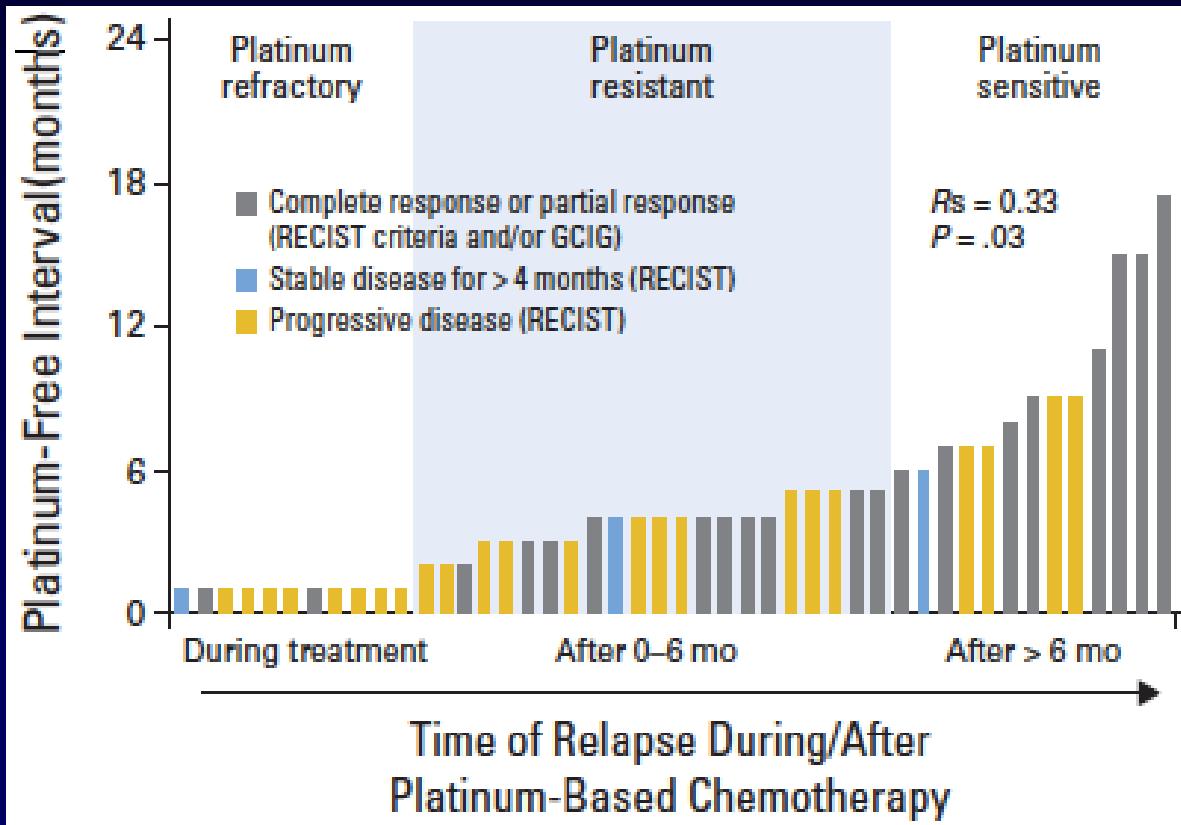
*BRCA* mutation carriers – distinct clinical behaviour:

- Improved response to chemotherapy
  - platinum and non-platinum agents<sup>1,3</sup>
- Retain platinum sensitivity<sup>1,2,3</sup>
- PARP inhibitors effective<sup>4</sup>

17% high-grade serous ovarian cancer patients have a *BRCA* mutation<sup>1,5</sup>

1. Alsop K, et al. *J Clin Oncol.* 2012;30(21):2654-2663; 2. Yang D, et al. *JAMA.* 2011;306(14):1557-1565; 3. Tan DS, et al. *J Clin Oncol.* 2008;26(34):5530-5536; 4. Fong PC, et al. *J Clin Oncol.* 2010;28(15):2512-2519; 5. George A, et al. *Ann Oncol.* 2010;21(Suppl 8): Abstract 881PD.

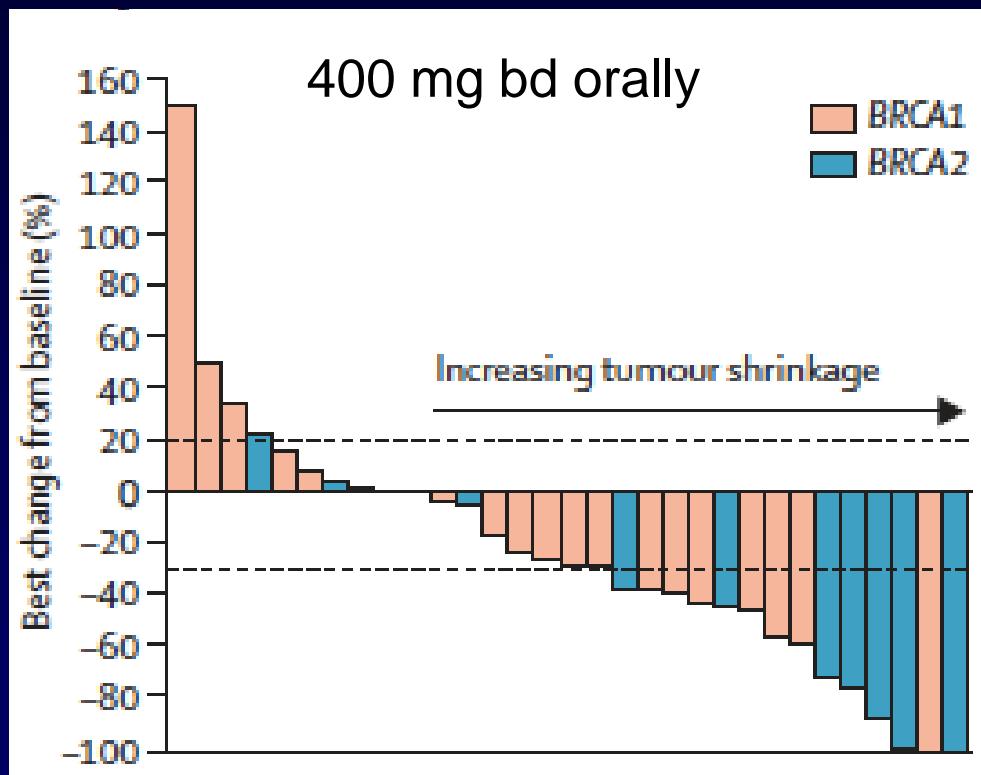
# PARP Inhibitor: Olaparib Phase I



- **40% combined response rate**
- **46% clinical benefit rate:**

Platinum-sensitive 69%    platinum-resistant 45%    platinum-refractory 23%

# Oral PARP Inhibitor, Olaparib in *BRCA*-Mutated Recurrent Ovarian Cancer Phase II



- Clear evidence of beneficial tumour response in heavily pretreated cancer patients with *BRCA* mutations
- Well tolerated and not associated with the typical toxicities of chemotherapy (nausea, fatigue, anaemia mostly grade 1 or 2)

- 61% combined response rate
- 33% overall response
- Progression-free survival 5.8 months
- Duration of response 9.5 months

# **When Should *BRCA*-Associated Ovarian Cancer Be Treated Differently?**

## Clinical Scenarios:

- **1<sup>st</sup>-line**
- **Relapse**
- **2<sup>nd</sup>-line treatment – platinum-sensitive**
- **Subsequent lines:**
  - Platinum-sensitive
  - Platinum-resistant/refractory

# Scenario #1: First-Line Treatment for *BRCA*-Associated Ovarian Cancer

- 45-year-old presents with high-grade serous ovarian carcinoma stage IV (pleural effusion)
  - performance status 2
  - albumin 26
  - *BRCA* unknown at diagnosis

**Treatment Options?**

# First-Line Treatment for *BRCA*-Associated Ovarian Cancer: Standard Options

Primary debulking surgery



Carboplatin and paclitaxel

Neoadjuvant carboplatin and paclitaxel



Interval debulking surgery followed by carboplatin and paclitaxel

+ bevacizumab concurrent and maintenance

Can we identify molecular subsets that derive more benefit than others?

(Winterhoff BJ, et al. *J Clin Oncol.* 2014;32(5S): Abstract 5509; Gourley C, et al. *J Clin Oncol.* 2014;32(5S): Abstract 5502.)

Outcomes of *BRCA* carriers following first-line bevacizumab treatment?

Samples from GOG218 and ICON7 help address these important questions.

# First-Line Treatment for *BRCA*-Associated Ovarian Cancer: Trial Options

- Dose-dense delivery of carboplatin and paclitaxel?
  - ICON8 trial
- Intraperitoneal Chemotherapy?
  - GOG-172 retrospective *BRCA* IHC expression analysis  
(Lesnock JL, et al. *Br J Cancer*. 2013;108(6):1231-1237.)
  - aberrant *BRCA1* expression:  
median OS: 84 vs 47 months in the IP vs IV group ( $P = .0002$ )
  - Needs prospective validation
- PARP inhibitors? Phase III SOLO1 *BRCA* mutation maintenance

Newly diagnosed, III/IV

High-grade serous,

High-grade endometrioid 2:1 ratio

*BRCA* (germline or somatic)

Olaparib 300 mg BD continuously

Treat up to 2 years or disease progression

# Scenario #2: 1<sup>st</sup> Platinum-Sensitive Relapse

- 52-year-old *BRCA2* carrier stage IIIc
  - Primary debulking surgery, no residual disease
  - Adjuvant carboplatin and paclitaxel 3 x weekly, 6 cycles
  - CA125 normalised
- Rising CA125, mild abdominal discomfort, performance status 1
  - Platinum-free interval 2 years
  - CT confirms abdominal recurrence (para-aortic nodes, several peritoneal nodules)

**Treatment Options?**

# **1<sup>st</sup> Platinum-Sensitive Relapse Treatment Options**

- **Surgery**
  - DESKTOP III trial
- **Platinum-based combination chemotherapy**
  - Carboplatin/paclitaxel
  - Carboplatin/liposomal doxorubicin
  - Carboplatin/gemcitabine
- **Maintenance Therapy:**
  - Carboplatin/gemcitabine + bevacizumab → maintenance bevacizumab
  - Platinum-based chemotherapy → maintenance PARP inhibitor in clinical trial
  - Other maintenance trials: PankoMab-GEX anti-MUC1, dendritic cell immunotherapy
- **PARP inhibitor non-maintenance trial**

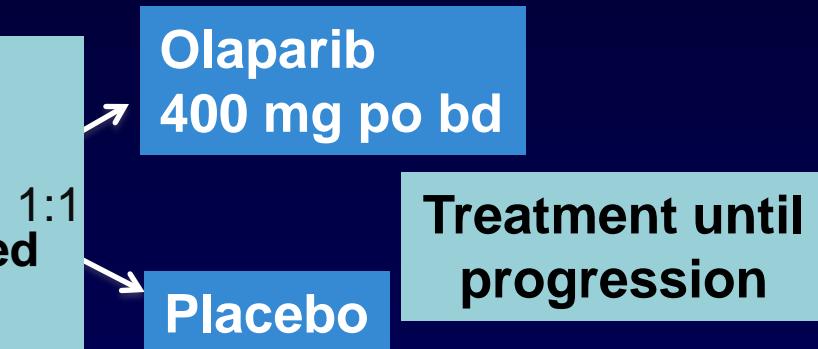
# 1<sup>st</sup> Platinum-Sensitive Relapse: Antiangiogenic Agents

- **Maintenance Therapy– Antiangiogenics:**
  - Licensed: Carboplatin/gemcitabine + bevacizumab followed by maintenance bevacizumab
    - OCEANS<sup>1</sup>:
      - Median PFS improvement 4 months, HR 0.48
      - No overall survival benefit seen
  - Other options: cedirinib?
    - ICON6<sup>2</sup>:
      - Median PFS improvement 3.1 months, HR 0.57
      - Overall survival benefit 2.7 months, HR 0.7

1. Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045; 2. Lederman J, et al. *Eur J Cancer.* 2013;49(Suppl2) Abstract LBA10..

# Randomized Trial of Maintenance Olaparib in Platinum-Sensitive Relapsed Ovarian Cancer

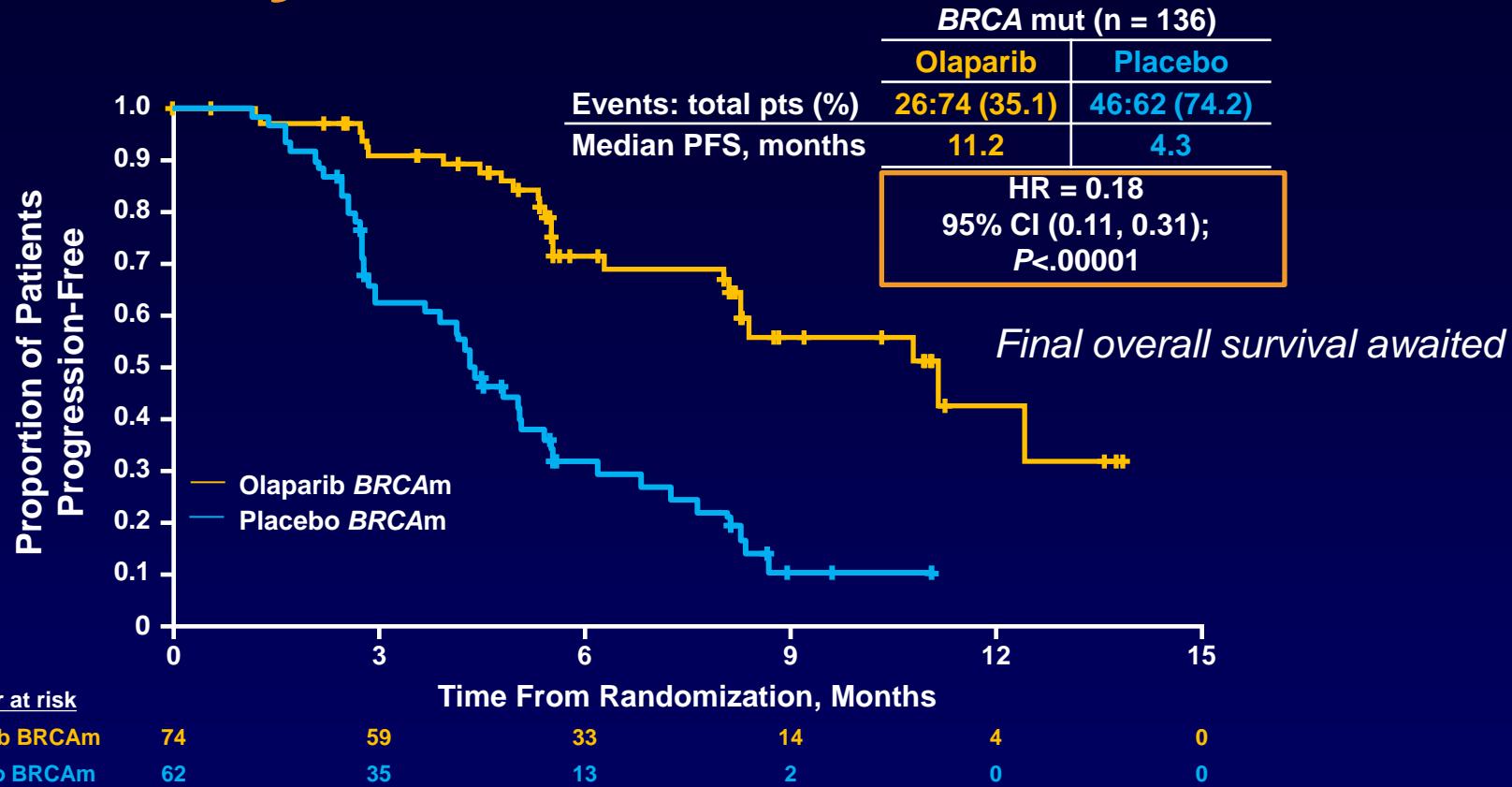
- Platinum-sensitive high-grade serous
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based to which maintained PR or CR was achieved prior to enrolment
- Stable CA125



|                                      | Olaparib | Placebo |
|--------------------------------------|----------|---------|
| <b>Median PFS (months)</b>           | 8.4      | 4.8     |
| <b>HR = 0.35; <i>P</i>&lt;.00001</b> |          |         |

Updated analysis (265 patients):  
 51.3% *BRCA* mutated  
 (germline/somatic)  
 44.5% *BRCA* wild type  
 4.2% *BRCA* not available

# PFS by *BRCA* Mutation Status



136 (51.3%) patients had a known deleterious *BRCA*m (germline or somatic)

- 82% reduction in risk of disease progression or death with olaparib

EMA Marketing Authorisation Application for olaparib submitted  
Potential to be the first PARP inhibitor approved

# Maintenance PARP Inhibitors: Current Trials

| RECURRENT                          | Agent     | Patient group   |
|------------------------------------|-----------|---|
| <b>SOLO-2</b><br><b>Phase III</b>  | Olaparib  | <i>BRCA</i> mutation only<br>High-grade serous<br>High-grade endometrioid<br>Platinum-sensitive<br>≥2 prior platinum                  |
| <b>ARIEL-3</b><br><b>Phase III</b> | Rucaparib | <i>gBRCA</i> mutation and non- <i>BRCA</i><br>Platinum-sensitive<br>High-grade serous<br>High-grade endometrioid<br>≥2 prior platinum |
| <b>NOVA</b><br><b>Phase III</b>    | Niraparib | <i>gBRCA</i> mutation and non- <i>BRCA</i><br>high- grade serous or known<br><i>BRCA</i><br>Platinum-sensitive<br>≥2 prior platinum   |

# PARP Inhibitor Non-Maintenance Trials

## ARIEL2: Rucaparib in Relapsed, Platinum-Sensitive, High-Grade Ovarian Cancer

### Key Eligibility:

- High-grade ovarian (serous or endometrioid), fallopian tube or primary peritoneal cancer
- ≥1 prior platinum
- Last tx = platinum based; must have sensitive disease
- Documented radiologic relapse
- Adequate screening tumor tissue
- No prior PARPi

N = 180

*BRCA* and non-*BRCA* included

600 mg BID rucaparib continuously until disease progression by RECIST

- CA-125 every 4 wks
- CT scans every 8 wks

### Primary EP:

- ORR by RECIST and GCIG CA-125 criteria in HRD subgroups

### Secondary EPs:

- DOR
- PFS
- Safety
- Steady-state PK

# Platinum-Sensitive Relapse: Cediranib + Olaparib

Preclinical data potential synergy between PARPi and antiangiogenics



- Phase II open-label randomised study
  - 1:1 randomisation to cediranib/olaparib combination or single-agent olaparib
  - Platinum-sensitive recurrent ovarian, fallopian tube, or primary peritoneal cancer

- Plat-sensitive, recurrent OC
- High grade serous/endometrioid
- No prior PARPi
- No prior AA for recurrence
- No platinum limit

Randomise  
1:1

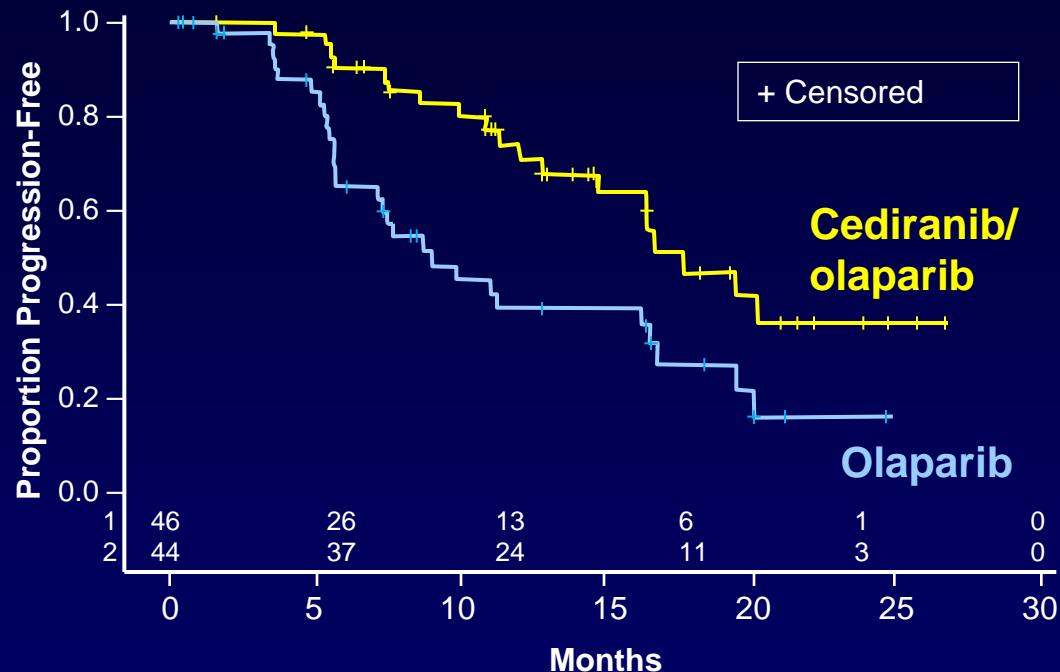
Olaparib  
capsules  
400mg BID

Cediranib  
30mg daily +  
Olaparib  
capsules  
200mg BID

Disease  
progression  
by RECIST  
v1.1 criteria

# Primary Outcome: Cediranib/Olaparib Significantly Increased PFS Compared to Olaparib Alone

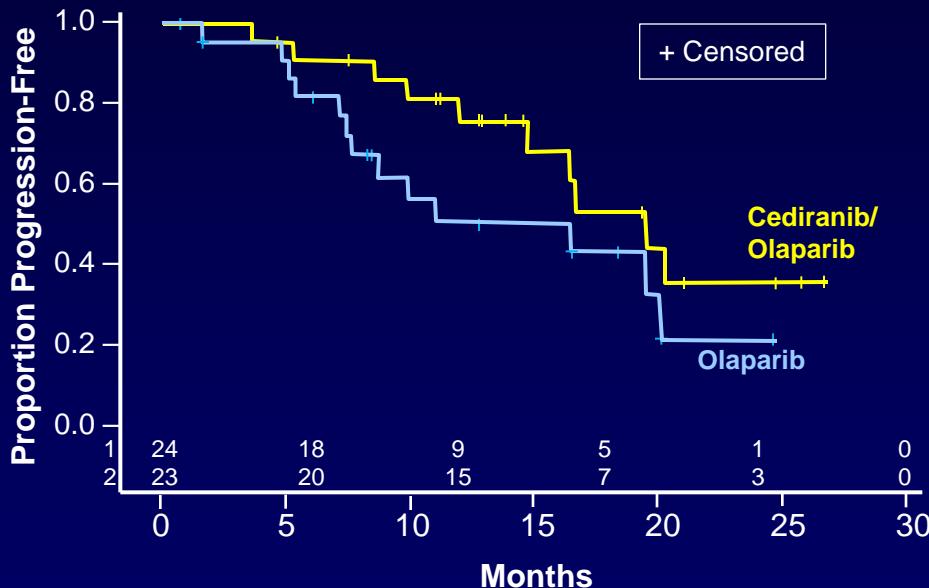
|                             | Olaparib | Ced/Olap |
|-----------------------------|----------|----------|
| PFS events                  | 28       | 19       |
| Median PFS                  | 9.0 mo   | 17.7 mo  |
| $P = .005$                  |          |          |
| HR 0.42 (95% CI: 0.23-0.76) |          |          |



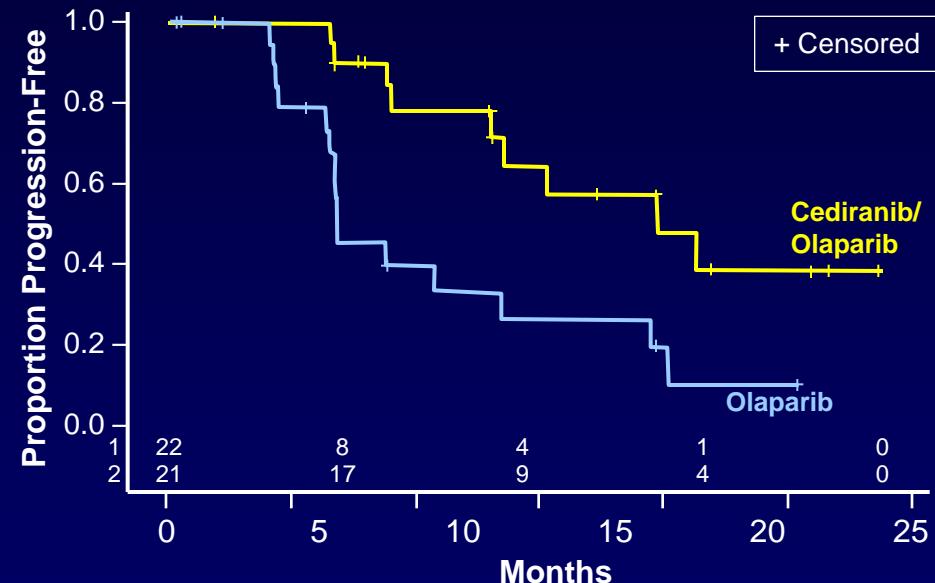
| Arm                | ORR |      |
|--------------------|-----|------|
|                    | N   | %    |
| Olaparib alone     | 22  | 47.8 |
| Cediranib/olaparib | 35  | 79.6 |
| $P = .002$         |     |      |

# Cediranib/Olaparib Significantly Increased PFS in Patients Without a *BRCA* Mutation

*BRCA* Mutation Carrier



*BRCA* Noncarrier/Unknown



|            | <i>BRCA</i> Mutation Carrier<br>Olaparib | <i>BRCA</i> Mutation Carrier<br>Ced/Olap | <i>BRCA</i> Noncarrier/Unknown<br>Olaparib | <i>BRCA</i> Noncarrier/Unknown<br>Ced/Olap |
|------------|--|--|--|--|
| PFS events | 13                                       | 10                                       | 15   | 9  |
| Median PFS | 16.5 mo                                  | 19.4 mo                                  | 5.7 mo                                     | 16.5 mo                                    |
|            | $P = .16$                                |  | $P = .008$                                 |  |
|            | HR 0.55 (95% CI: 0.24-1.27)              |  | HR 0.32 (95% CI: 0.14-0.74)                |  |

# **Platinum-Sensitive Relapse Treatment Options**

## **Maintenance antiangiogenic agents or PARP inhibitors?**

Issue is 1<sup>st</sup> platinum-sensitive relapse

- may be in situation where patients can either have bevacizumab or PARP inhibitor
- If patient does not receive bevacizumab for 1<sup>st</sup> platinum-sensitive relapse, may not be able to access bevacizumab in subsequent relapse (eg, too many lines by time platinum-resistant)

# Platinum-Sensitive Relapse Treatment Options

## Maintenance antiangiogenic agents or PARP inhibitors?

Issue is 1<sup>st</sup> platinum-sensitive relapse

- may be in situation where patients can either have bevacizumab or PARP inhibitor
- If patient does not receive bevacizumab for 1<sup>st</sup> platinum-sensitive relapse, may not be able to access bevacizumab in subsequent relapse (eg, too many lines by time platinum-resistant)
- Do *BRCA* carriers derive the same benefit from antiangiogenic agents as non-*BRCA* carriers?
- Is response to PARP inhibitor affected by prior antiangiogenic agent?

## URGENT NEED FOR BIOMARKER

Potential for molecular subgroups within high-grade serous predicting outcome with bevacizumab (Gourley C, et al. *J Clin Oncol.* 2014;32(5S): Abstract 5502.)

# **Scenario #3: 2<sup>nd</sup>-Line and Subsequent Platinum-Sensitive Relapse in *BRCA* Ovarian Cancer**

- **Platinum-based combination chemotherapy**
  - Carboplatin/paclitaxel
  - Carboplatin/liposomal doxorubicin
  - Carboplatin/gemcitabine
- **Maintenance therapy**
  - Platinum-based chemotherapy → maintenance PARP inhibitor in clinical trial
  - Other maintenance trials: PankoMab-GEX anti-MUC1
  - ICON6-cediranib?
- **PARP inhibitor non-maintenance trial**
  - eg, ARIEL2, combination

# Scenario #4: Platinum-Resistant/Refractory *BRCA*-Associated Ovarian Cancer: Treatment Options

- **Standard Chemotherapy**

- **Liposomal doxorubicin, weekly paclitaxel**

Evidence of efficacy in *BRCA* mutation carriers is equivalent or superior<sup>1,2</sup>

- **PARP inhibitors alone**

- Phase I: CBR platinum resistant 45%, refractory 23%

- **or in combination** (with chemotherapy, antiangiogenics)

*PI3K-AKT pathway inhibitors*<sup>3,4</sup> PI3Ki → HR → PARPi sensitivity

- Phase I BKM120 (oral PI3kinase inhibitor) and olaparib
  - Phase I AZD5363(oral AKT inhibitor) and olaparib
  - Phase I AZD2014(oral mTORC1/2 inhibitor) or AZD5363 and olaparib

- **Other clinical trials**

- phase II 6MP BRCA: 6-mercaptopurine/methotrexate
  - Phase II Chk1/2 Inhibitor (LY2606368)

1. Kaye SB, et al. *J Clin Oncol.* 2012;30(4):372-379; 2. Tan DS, et al. *Eur J Cancer.* 2013;49(6):1246-1253; 3. Juvekar A, et al. *Cancer Discov.* 2012;2(11):1048-1063; 4. Ibrahim YH, et al. *Cancer Discov.* 2012;2(11):1036-1047.

# Others PARP Inhibitors in Development

In addition to olaparib, rucaparib, niraparib

- Veliparib
- E7449
- BMN 673

## BMN 673, a Novel and Highly Potent PARP1/2 Inhibitor for the Treatment of Human Cancers with DNA Repair Deficiency

Clinical Cancer Research

Shen Y, et al. *Clin Cancer Res.* 2013;19(18):5003-5015.

### PARP 1 Enzyme Inhibition

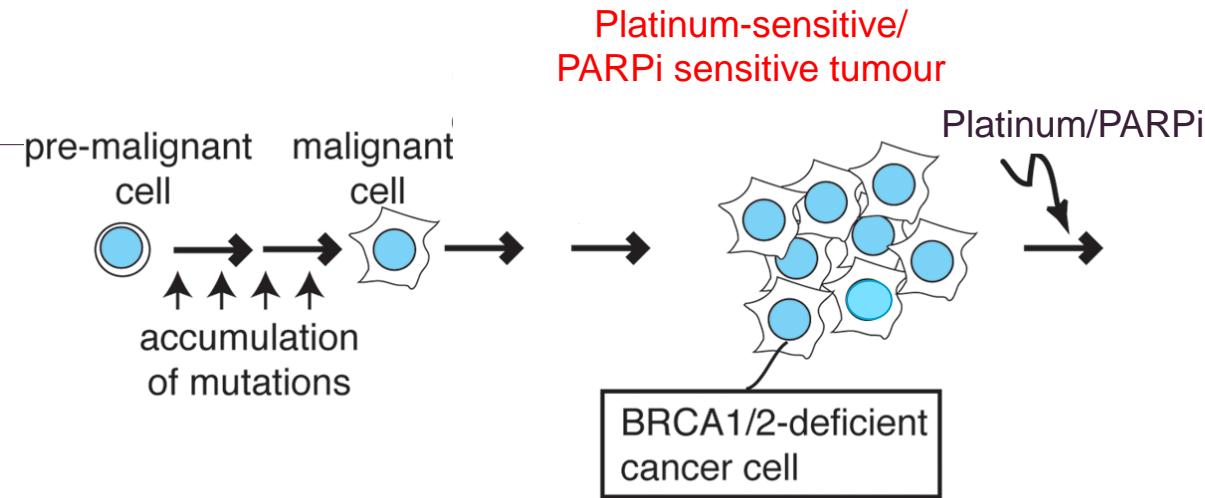
IC<sub>50</sub>, nmol/L

|                |             |
|----------------|-------------|
| Veliparib      | 4.73        |
| Rucaparib      | 1.98        |
| Olaparib       | 1.94        |
| LT-00628       | 1.82        |
| <b>BMN 673</b> | <b>0.57</b> |

BMN 673 in ovarian cancer  
Phase I: ASCO 2013<sup>1</sup>; ECC 2013<sup>2</sup>  
*BRCA* mutated: RECIST 44% (11/25)  
(platinum-resistant 20%; sensitive 50%)

1. De Bono JS, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 2580; 2. Ramanathan R, et al. *Ann Oncol.* 2013;49(Suppl 3): Abstract LBA29.

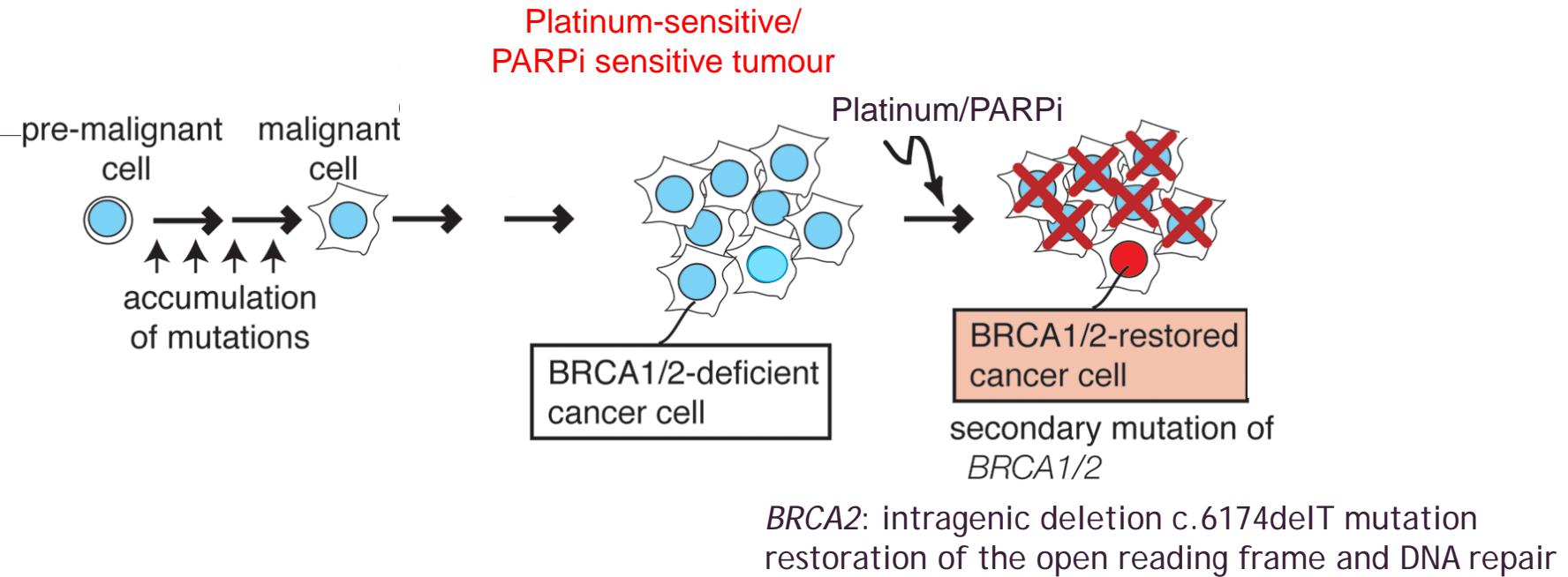
# A Model of PARP Inhibitor Resistance



- We exploit the disease-causing *BRCA1/2* mutations as weak points of cancer cells for chemotherapy (platinum) or PARP inhibitors (synthetic lethality)



# A Model of PARP Inhibitor Resistance



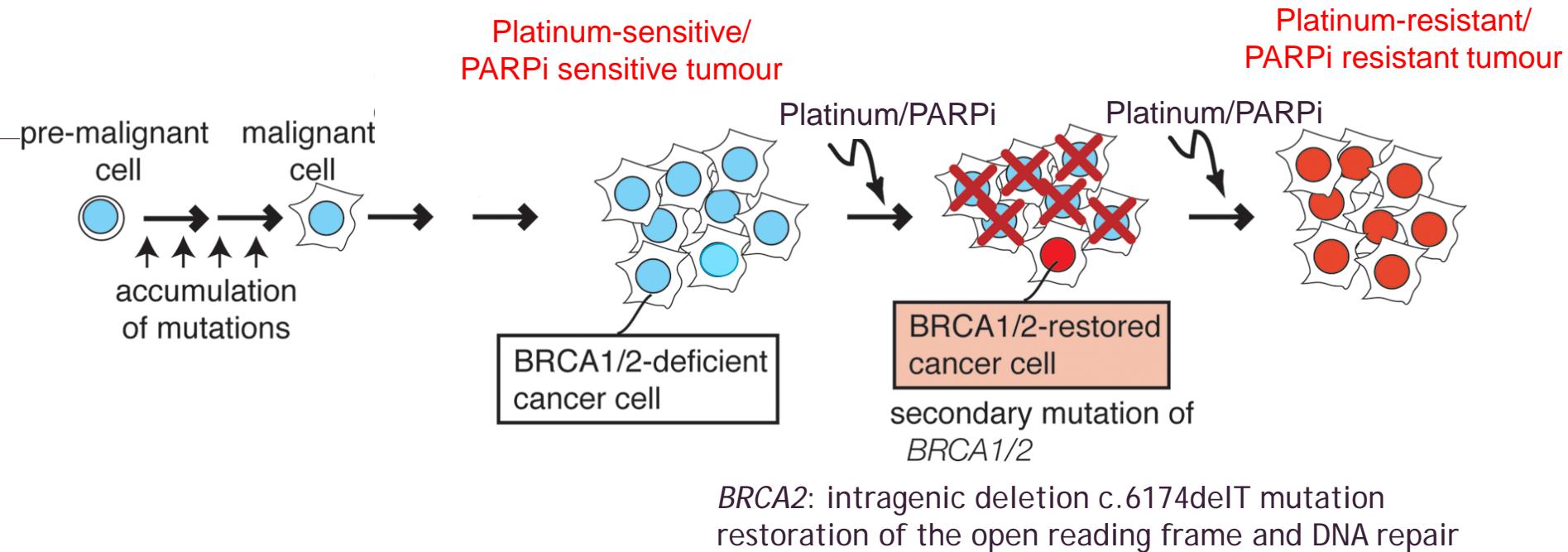
- We exploit the disease-causing *BRCA1/2* mutations as weak points of cancer cells for chemotherapy (platinum) or PARP inhibitors (synthetic lethality)
- Cancer cells evolve during the course of drug treatment by further mutating the tumour suppressor genes, resulting in development of resistance



Edwards SL, et al. *Nature*. 2008;451(7182):1111-1115; Sakai W, et al. *Nature*. 2008;451(7182):1116-1120.

Adapted from Taniguchi

# A Model of PARP Inhibitor Resistance

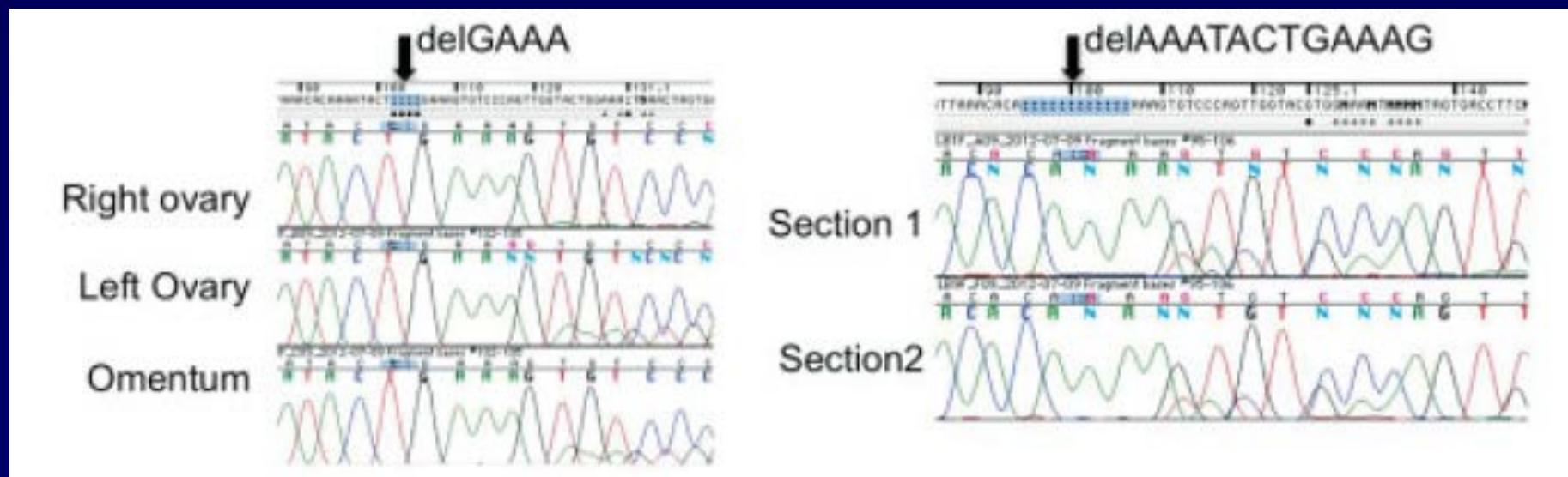
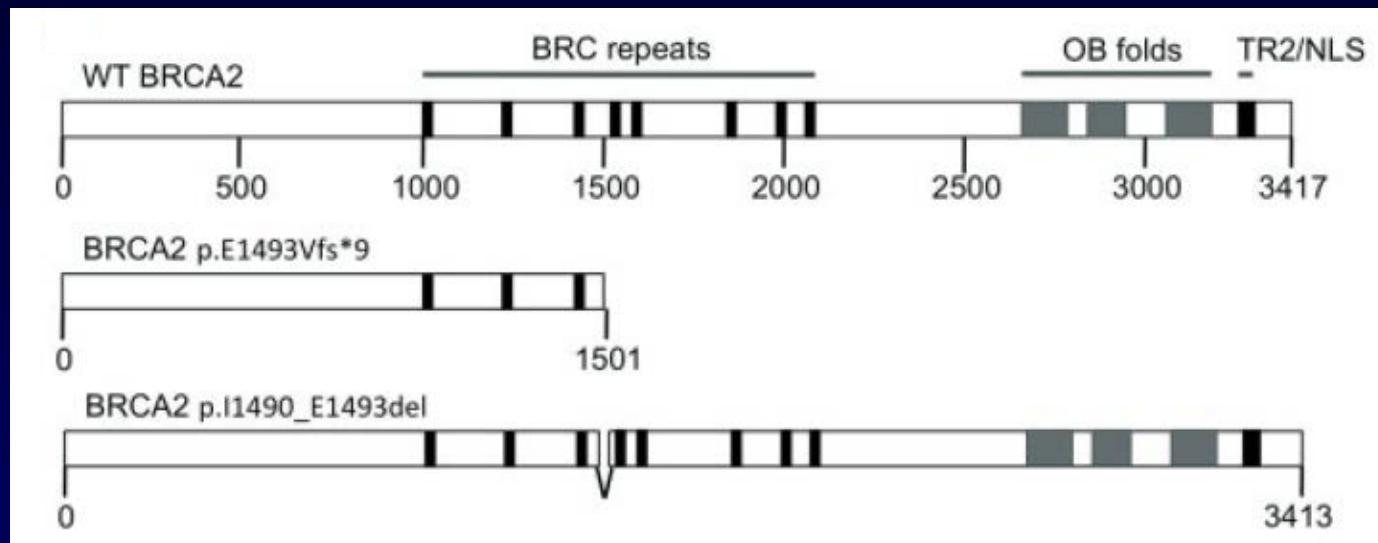


Cancer cells evolve during the course of drug treatment by further mutating the tumour suppressor genes, resulting in development of resistance

*This is one mechanism of PARPi resistance:  
It is complex and other mechanisms are involved*



# Clinical Evidence in Ovarian Cancer of a Secondary Mutation in *BRCA2* After Resistance to Olaparib



# **Response to Chemotherapy Post PARP Inhibitors in *BRCA*-Carrier Ovarian Cancer- Retrospective Study**

**78 patients (median 3 lines chemotherapy pre-olaparib)**

- Response rate RECIST 36%, PFS 17 weeks; OS 34 weeks

**Responses to platinum post olaparib**

- Response rate RECIST 40%, PFS 22 weeks, OS 45 weeks

**In 6 cases tested, secondary mutations not observed**

**Responses observed regardless of pre-PARP  
platinum-sensitivity**

**Platinum-to-platinum interval associated with  
response to post-PARP platinum**

# Mechanisms of PARP Inhibitor Resistance

Restoration  
of HR

*BRCA* Reversion  
or P53BP1 loss

Drug  
Efflux

Upregulation of  
P-glycoprotein

PARP1  
Loss

Mechanism  
Unknown

PARPi  
Resistance

NEED BIOPSIES TO CLARIFY CLINICAL SIGNIFICANCE

- Represents over 15% of epithelial ovarian cancer
  - Clinical characteristics (better prognosis, platinum sensitivity)
- PARP inhibitors may be effective in multiple clinical scenarios in a patient's cancer pathway
- Ongoing clinical trials will help define how best to personalise therapy

# Questions to Be Answered: Treatment of *BRCA*-Associated Ovarian Cancer

**URGENT!!!** We need to gain approval for what is a new effective therapy for germline *BRCA* mutation carriers with ovarian cancer

- When to treat with PARP inhibitors?  
Platinum-sensitive, platinum-resistant, maintenance? First line?
- How best to integrate with other treatments? eg, IP chemotherapy-targeted agents, eg antiangiogenics?
- Who to treat? Biomarkers for *BRCA*ness. Germline and somatic *BRCA* mutations. Biopsy studies to understand resistance - trial entry criteria
- After PARPi? - Another PARPi, combinations, cycling treatment chemotherapy followed by PARP again?

# Acknowledgements

Gynaecology Unit Royal Marsden

Stan Kaye, Martin Gore

Toshiyasu Taniguchi

Joyce Liu

Alan Ashworth



NIHR RM/ICR Biomedical Research  
Centre



# Shaping the Future of Personalized Therapy in Ovarian Cancer: A Focus on *BRCA* Biomarkers