Progress in the treatment of ovarian cancer. Lessons from homologous recombination deficiency – the first 10 years

Professor Stan Kaye
Royal Marsden Hospital
London

Valencia
March
2015
Conflict of Interest

Advisory boards and continued discussion over several years with:

• AstraZeneca/Kudos
• Merck/Tesaro
• Pfizer/Clovis
• Biomarin
Homologous recombination deficiency – implications for the treatment of ovarian cancer – the first 10 years.

First preclinical evidence of exquisite sensitivity of BRCAm cells to PARPi

Start of Phase 1

June

2005

2010

2015

First clinical proof-of-concept in Phase I trials of olaparib

Genomic and clinical data indicating potential Beyond BRCAm

Positive randomised trial of maintenance therapy in relapsed BMOC patients in remission

Randomised trial of olaparib vs chemo in pts with recurrent BMOC

International confirmation of efficacy

In BMOC: Approval (EU) for maintenance treatment. Approval (US) for advanced disease.

First preclinical evidence of exquisite sensitivity of BRCAm cells to PARPi

But what causes PARPi resistance and are there rational targeted combination strategies?

BMOC – BRCA mutation associated ovarian cancer

April

Farmer et al, Nature 2005
Bryant et al, Nature 2005

Fong et al NEJM 2009

Audeh et al Lancet 2010

Fong et al JCO 2010

GCA Network Nature 2011

Kaye et al JCO 2012

Gelman et al Lancet Oncology 2011

Ledermann et al NEJM 2012 
& Lancet Oncology 2014

Ibrahim et al Cancer Discovery 2012

Jaspers et al Cancer Discovery 2013

Liu et al Lancet Oncology 2014
What is homologous recombination?

• Type of genetic recombination in which nucleotide sequences are exchanged between 2 similar /identical strands of DNA – first described 100 years ago.

• Universal biological mechanism, an essential process whereby cells accurately repair potentially harmful double strand breaks in DNA during cell division.

• Decreased rate, i.e. homologous recombination deficiency (HRD) causes inefficient DNA repair and increased susceptibility to cancer

• HRD also provides opportunity to treat cancer by targeting that weakness

Morgan T. 1916, Critique of the theory of evolution.
Intracellular proteins involved in homologous recombination deficiency

……..include loss of function of......

Key proteins whose dysfunction is closely linked to ovarian and breast cancer predisposition

Provides opportunity for selective treatment using PARP inhibitors


BRCA 1
BRCA 2
RAD 51
RAD 54
DSS 1
RPA 1
NBS 1
ATR
ATM
CHK 1
CHK 2
FAN CD 2
FANC A
FANC C
etc.
Poly(ADP-Ribose) Polymerase (PARP)

Key enzyme in normal cellular process of single strand DNA repair – occurring many thousand times/cell/day

DNA damage

PARP

Binds directly to single strand breaks

NAD+

nicotinamide + pADPr

Once bound to damaged DNA, PARP modifies itself producing large branched chains of Poly(ADP-ribose)

repair enzymes

repaired DNA
PARP inhibition and tumor-selective synthetic lethality

DNA damage (SSBs)
DNA replication (accumulation of DNA DSBs)

PARP inhibition

Normal cell with functional HR pathway

HR-mediated DNA repair
Cell survival

HR-deficient tumor cell (e.g. BRCA 1/2−/−)

Impaired HR-mediated DNA repair (NHEJ etc.)
Cell death

Tumor-selective cytotoxicity

DSB, double-strand break;
HR, homologous recombination
SSB, single-strand break
NHEJ, non-homologous end joining

PS PARP inhibitors can also trap cytotoxic PARP-DNA complexes; clinical relevance unclear.

The incidence of BRCA mutations in high grade serous ovarian cancer

- BRCA 1/2 germline mutation 14%
- BRCA 1/2 somatic mutation 6%
- Total 20%

Olaparib, Chapter 1, 2005-9

Pre-clinical

Exquisite preclinical efficacy of PARPi in BRCA deficient ES cells

Clonogenic survival curves with inc. concentration of KU 58948

<table>
<thead>
<tr>
<th>KU-0058948 IC&lt;sub&gt;50&lt;/sub&gt; = 3.4nM</th>
</tr>
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<tbody>
<tr>
<td>1250 fold difference in SF50 between BRCA2 +/- and +/+</td>
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</table>

Lesson 2 – listen to the patient
“this is nothing like chemotherapy”

Early clinical trials (Phase I incl. IB)

Phase I trial of KU59436 (olaparib) indicated excellent tolerance and expansion in 50 BRCA patients showed 46% response.


Farmer et al, Nature 434 917-921 2005
also Bryant et al, Nature 434 922-926 2005
Olaparib, a novel, orally active and well tolerated PARP inhibitor

- Olaparib (AZD2281; KU-0059436) 400 mg bd is the maximum tolerated dose\(^1\) with maximum PARP inhibition at 100mg bd, and tumour response at 100–400 mg bd
- **Most common toxicities:** CTCAE grade 1 and 2 nausea and fatigue; rare toxicity – neuro-cognitive.

46% (23/50 pts) combined response rate (RECIST and CA125) in BMOC\(^2\) in cohort expansion at 200 mg bd, with median response duration of 8 months.

### Correlation with platinum-free interval

<table>
<thead>
<tr>
<th>PFI</th>
<th>&lt; 0</th>
<th>0-6m</th>
<th>&gt;6m</th>
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<tbody>
<tr>
<td><strong>Patient number total</strong></td>
<td>13</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Response RECIST and/or CA125 or SD&gt; 4m</strong></td>
<td>3</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>percentage</td>
<td>23%</td>
<td>46%</td>
<td>69%</td>
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</table>

International Phase II trial of olaparib in BRCAm-associated ovarian cancer

57 pts (BRCA 1 39; BRCA 2 18) received either 400 mg bd or 100 mg bd in two sequential cohorts – (med. 3 prior CT)

Audeh MW et al., 2010, Lancet 376: 245-51

<table>
<thead>
<tr>
<th>33 pts at 400 mg bd</th>
<th>RECIST response</th>
<th>Clinical benefit (incl. CA125 response)</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>11 (33%)</td>
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<td></td>
<td>22 (66%)</td>
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<table>
<thead>
<tr>
<th>24 pts at 100 mg bd</th>
<th>RECIST response</th>
<th>Clinical benefit (incl. CA125 response)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 (13%)</td>
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<tr>
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<td>10 (42%)</td>
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Conclusion:
- Level of efficacy confirmed, med. response duration 9.5 m
- Favorable toxicity profile confirmed
- 400 mg bd appears to be more active than 100 mg bd

Key issues for olaparib in BRCA-mutated ovarian cancer:
- What is the optimal dose of capsule (200mg bd or 400mg bd)?
  - A - Probably 400mg
- As prelude to registration/approval, how does this compare with standard therapy, e.g. liposomal doxorubicin (Caelyx)?
What is the optimal dose of olaparib, and how does it compare with caelyx?

- Efficacy of olaparib (400 mg bd) was as predicted, with response (RECIST/CA125) in 59% and median PFS of 8.8 m.
- Caelyx was more effective than anticipated (response 39%; median PFS 7.1 m), thus no significant difference in primary end-point.
- HR 0.88  p = 0.66
- Overall, both treatments well tolerated (<10% discontinuation)

**Primary objective:** compare efficacy of 2 dose levels of olaparib (300 mg and 400 mg bd) with liposomal doxorubicin (Caelyx)

**Patients:**
Advanced BRCA1- or BRCA2-mutated ovarian cancer who had progressive or recurrent disease <12 months after previous platinum-based chemotherapy.

**Sample size:**
total 90 (30 per arm)

- Olaparib 200 mg bid in 28-day cycles
- Olaparib 400 mg bid in 28-day cycles
- Caelyx 50 mg/m² iv every 4 weeks

Lesson 3:
Beware assumptions about control arm chemo in BRCA patients

**Clinical development strategy changed:**
- Maintenance therapy in BRCAm patients
- Evaluation in sporadic ovarian cancer

Randomized trial of maintenance olaparib in platinum-sensitive relapsed ovarian cancer

Study aim and design

Patients:
- Platinum-sensitive high-grade serous ovarian cancer
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based to which they had a maintained PR or CR prior to enrolment
- Stable CA-125

<table>
<thead>
<tr>
<th>Treatment until disease Progression</th>
</tr>
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<tbody>
<tr>
<td>Olaparib 400 mg po bid</td>
</tr>
<tr>
<td>Randomized 1:1</td>
</tr>
<tr>
<td>Placebo po bid</td>
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</tbody>
</table>

Primary end point: PFS

Total of 265 recruited:
- Initially BRCA status known for only 36%
- Subsequent analysis increased this to 96%

Lesson 4: In PARP inhibitor trials ensure BRCA status can be assessed

Ledermann et al, NEJM 2012 366 1382-192
As maintenance treatment, gBRCAm patients derive most PFS benefit: 7.1 months median PFS improvement

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (N=53)</th>
<th>Placebo (N=43)</th>
</tr>
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<tr>
<td>Median (95%CI)</td>
<td>11.2 mo (8.3, NC)</td>
<td>4.1 mo (2.9, 5.1)</td>
</tr>
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</table>

**J Ledermann et al. Lancet Oncology 2014 15 852-861**
Overall Survival in Patients With BRCA Mutation

- 14/62 (22.6%) placebo patients switched to a PARP inhibitor
- OS in BRCA WT patients: HR = 0.98; 95% CI, 0.62–1.55; P = .946
  - Median OS: olaparib, 24.5 months; placebo, 26.2 months

Randomized Trial of Olaparib as Maintenance Therapy in Platinum-Sensitive Sporadic Ovarian Cancer

Trial positive for primary endpoint (PFS). But overall survival impact less clear.

Does this reflect cross-over (23%), or too early analysis, or is there an impact of olaparib on subsequent response to chemo, and will this depend on BRCA mutation status?

What do we know about PARPi (and platinum) resistance?
Does PARPi resistance = platinum resistance?

- Preclinical data in BRCA mutated cells indicate that resistance to both PARPi and platinum can result from secondary mutations in BRCA 1/2 gene, causing reversion to functional BRCA gene, and return of DNA DSB repair capacity.

Barber et al J Path. 2013 229 422-429
- Demonstrate 2 clinical examples of secondary mutations linked to resistance to olaparib.
  - Male patient with BRCAm breast cancer
  - Female patient with BRCAm ovarian cancer

So, is this the answer? When patients become resistant to olaparib, are they resistant to platinum?
Chemosensitivity Post Olaparib in BRCA-Mutated Ovarian Cancer

- In 78 evaluable olaparib-treated patients, response to subsequent chemotherapy seen in 36% (24/67) by RECIST and in 45% (35/78) by CA125 and/or RECIST

- For platinum-based treatment:
  - RECIST response in 19/48 (40%)
  - RECIST and/or CA-125 response in 26/53 (50%)
  - Median PFS: 22 weeks
  - Median OS: 45 weeks

- ORR/OS significantly associated with interval since last (pre-olaparib) platinum

- Molecular analysis of tumour resected post-olaparib: No evidence of secondary mutations in 6 cases

What other mechanisms of PARPi resistance may apply?

Resistance to PARP inhibitors

- Is likely to be multifactorial; factors to consider include:
  - Secondary BRCA mutation
  - P-glycoprotein-based enhanced drug efflux
  - Reduced 53BP1, partially restoring HR
  - NER pathway alterations
  - And what is the relevance of PARPi trapping as alternative mechanism of action?
    - And why do a minority of cases (up to 20%) stay in remission long-term?
    - Is this all due to tumour heterogeneity?

Lesson 5 – take every opportunity to collect tumour at relapse/progression

Fojo T, and Bates S, Cancer Discovery 2013 3 20 – 23
Ceccaldi R et al. Canc res. 2015 75 628
Jaspers et al Cancer Discovery 2013 3 68-81
Long-term responders to olaparib

Pooled analysis from 13 studies – 1489 patients received olaparib 400mg bd (including Phase I/II and maintenance trials).

Of these,
- 137 patients continued for > 2 years
- 84 patients for > 3 years
- 46 patients for > 4 years
- 9 patients for > 5 years
- 4 patients for > 6 years

(including Mrs J.B.)

L’Heureux et al. JCO 32 5S abt 5534, 2014
Mrs J B, aged 59

BRCA 2 mutation positive ovarian cancer

April 2002
- Presented with stage IV disease – pelvic mass, positive pleural effusion
- Surgery then carbo/taxol to August 2002

- Four episodes of multi-site peritoneal recurrence
- Treated with carboplatin-based chemo

June 2007
- 5th relapse (peritoneal, rising CA125)
- i.e., 5 months after last carboplatin (platinum resistant)
- Began KU59436 (olaparib) in Phase I trial – 200mg bd
- Complete remission and remained in CR until 2014

June 2014
- Isolated liver recurrence, 2cm, segment V

September 2014
- Complete resection, no disease elsewhere

February 2015
- Continues on olaparib 200mg bd
- Molecular analysis ongoing
Why isn’t PARP inhibitor treatment just another form of platinum-based therapy?

- Fundamentally different mechanism of action
- Efficacy in patients with platinum-resistant disease
- Efficacy of platinum in patients progressing on PARP inhibitor.
- Different pace of disease when PARPi resistance develops
- Some very long-term responders
Olaparib in BMOC

• The paths to registration

a) Maintenance therapy (Europe)

b) Advanced, recurrent disease (USA)
Olaparib in BRCA mutation associated advanced recurrent ovarian cancer
Kaufman et al, J. Clin Onc 33 244-250, 2015

- non-randomised all-comers (BRCAm) trial of olaparib 400mg bd.
  - n=298, inc. 193 ovarian cancer patients
  - all BMOC patients platinum resistant or “not suitable for further platinum therapy”
  - 77% BRCA1 : 23% BRCA 2

  - RECIST response in 60 (31%)
  - Median PFS = 7.0m; median OS = 16.6m
  - Treatment well tolerated, although 3 patients treated for 6-10m died (2acute leukaemia, 1 MDS)
  - No difference in response between BRCA1 and 2
Olaparib in advanced recurrent BRCAm ovarian cancer

Total of 300 patients treated in 6 trials including:

- Initial phase I/II trials
- Randomised trial vs Caelyx
  - Kaye et al, JCO 2012
- Bioavailability and scheduling studies
  - Capsule » tablet, cont. v intermittent, Mateo et al, EJC 2013
- Non-randomised, multiple BRCAm disease
  - Kaufman et al JCO 2015
- Total of 273 patients had measurable disease
Olaparib for recurrent BRCAm ovarian cancer - recent developments

- From the ongoing pooled analysis of 300 patients, data on subgroup of 137 patients who received ≥ 3 lines of chemo presented to FDA for accelerated approval.
  - response rate 34%; response duration 7.9m.

**FDA News Release**

FDA approves Lynparza to treat advanced ovarian cancer

First LDT companion diagnostic test also approved to identify appropriate patients

For Immediate Release

December 19, 2014
Status of olaparib/Lynparza – January 2015

Europe – approved as maintenance treatment for platinum sensitive relapsed BRCA m ovarian cancer – patients in remission following platinum-based therapy.

USA – approved as monotherapy for patients who have received $\geq 3$ lines of chemotherapy
- Not approved as maintenance therapy
- Approval also for companion diagnostic (Myriad Genetics BRCA analysis CDx)
PARP Inhibitors – what are the next steps?

- Define activity in sporadic ovarian cancer and other cancers, e.g. prostate
- Develop robust predictive biomarker
- Assess PARP inhibitors other than olaparib (rucaparib, niraparib, BMN-673)
- Test novel combinations (with P13K or angiogenesis inhibitors, etc.)
- Monitor long-term toxicity
- Understand mechanisms of PARPi resistance
Potential of PARP inhibitors in sporadic ovarian cancer

The Cancer Genome Atlas, Molecular profiling of serous ovarian cancer, D. Levine 2011

- approximately 50% of patients with high grade serous ovarian cancer predicted to be candidates for PARPi therapy
- what are the clinical data (4 PARP inhibitors)?
- What alternative predictive biomarkers are available, apart from BRCA mutation analysis?
Analysis of Efficacy in maintenance study including BRCA WT

Forest Plot of PFS Hazard Ratios by subgroups – FDA analysis (ODAC briefing book)

<table>
<thead>
<tr>
<th>AstraZeneca subgroup denomination</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>Overall</td>
<td>265</td>
</tr>
<tr>
<td>gBRCAm</td>
<td>96</td>
</tr>
<tr>
<td>gBRCA1m</td>
<td>70</td>
</tr>
<tr>
<td>gBRCA2m</td>
<td>26</td>
</tr>
<tr>
<td>sBRCAm</td>
<td>18</td>
</tr>
<tr>
<td>gBRCAwt</td>
<td>114</td>
</tr>
<tr>
<td>wtBRCA</td>
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</table>
# Single agent activity for PARP inhibitors in ovarian cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>BRCA Mutation positive</th>
<th>BRCA wild type and unknown</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>% resp</td>
<td>% resp</td>
</tr>
<tr>
<td></td>
<td>resp. duration</td>
<td>resp. duration</td>
</tr>
<tr>
<td>Olaparib</td>
<td>&gt;100 (most plat resist)</td>
<td>30-60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rucaparib</td>
<td>23 (all plat sens)</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niraparib</td>
<td>20 (9 plat sens)</td>
<td>45%</td>
</tr>
<tr>
<td>BMN 673</td>
<td>28 (22 plat sens)</td>
<td>68%</td>
</tr>
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</table>
Treatment of sporadic ovarian cancer with PARP inhibitors. How close are we to predicting who will benefit?

Predictive biomarker: possibilities include:

• functional test for loss of HR (RAD 51 foci-formation)\(^1,2\)
• molecular signature (gene array) \(^3\)
• immunohistochemistry for BRCA 1 protein\(^4\)

Circumstantially:

• repeated response to platinum-based chemotherapy
• prolonged survival (>5 yrs)
• high grade serous histology

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1 Mukhopadhay et al, Clin Cancer Res, 2010, 16, 2344-51
2 Graeser et al, Clin Cancer Res, 2010; epub
3 Konstantinopoulos et al, J Clin Oncol, 2010, 28, 3555-41
Homologous recombination deficiency (HRD) assay - Do we have one?

Swisher et al EORTC/NCI/AACR 2014 (EJC 50 supp 6 abst 215)

- HRD causes genome wide loss of heterozygosity (LOH), which can be measured by genome profiling using NGS
- Developed algorithm for LOH score (high/low), i.e. BRCA-like signature, and confirmed correlation with overall survival (309 patients)
- Provided preliminary evidence of correlation between BRCA-like signature and response to rucaparib in 38 patients in Phase II trial.

...and differential rucaparib activity seen in patients with/without BRCA-like signature

- Clinical activity observed in BRCA<sup>wt</sup> patients with BRCA-like signature (n=25)
  - 32% ORR (RECIST)
  - 40% ORR (RECIST & CA-125)
  - 52% of patients continuing on treatment (+)
- Few responses observed in BRCA<sup>wt</sup> patients without BRCA-like signature (n=13)
  - 8% ORR (RECIST)
  - 8% ORR (RECIST & CA-125)
  - 38% of patients continuing on treatment (+)
Homologous recombination deficiency (HRD) assay - Do we have one?

Haluska P et al, NCI/EORTC/AACR 2014 (EJC 50 supp 6 abst 214 page 72)

Developed HRD score incorporating 3 components:

- Loss of heterozygosity (LOH)
- Telomeric allelic imbalance (TAI)
- Large-scale state transitions (LST)

HRD score is sum of LOH + TAI + LST scores

- Presented evidence of correlation between HRD score and in vitro/in vivo response to niraparib in 106 tumour samples
  – clinical data in ovarian cancer awaited.

Thus:

- Two assays under further evaluation, as key elements in 2 ongoing randomised maintenance trials, with niraparib and rucaparib in sporadic and BRCAm associated ovarian cancer.
PARP inhibitor – combination strategies

Aim: enhance activity of PARPi by increasing HRD in treated cells

Pre-clinical data with:

• Antiangiogenic agents
• P13K/AKT pathway inhibitors
Antiangiogenic agents/PARP inhibitors

Hypoxia-induced HR defects sensitise tumour cells to DNA damaging agents

- Complementary targets/mechanisms of action
- Potential enhancement of sensitivity to PARPi by increasing HRD through changes in oxygenation caused by antiangiogenic agent.
- Bevacizumab/olaparib – Phase I trials confirmed feasibility and randomised trial planned.
- Cediranib/olaparib – randomised trial presented at ASCO 2014

Chan N and Bristow RG, Clin Can Res 16 4553-4560, 2010

Dean et al. BJC 2012 106 468-474
Liu et al. Lancet Oncology 2014 15 1207-1214
olaparib /cediranib in ovarian cancer

Liu et al, Lancet Oncology 2014

Randomise

Platinum sensitive relapsed patients n =90
(BRCA mut 47
BRCA wild type 23
BRCA unknown 20

Olaparib 400mg bd n=46
(BRCA m 24)

Olaparib 200mg bd+ cediranib 30mg od
n=44
(BRCA m 23)

Main toxicity: h/t, diarrhoea, fatigue,
leading to dose reduction n 34/44
(77%) and 4 pts discontinued treatment
on olaparib/cediranib.

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>Med PFS</th>
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<tr>
<td>22 (48%) Including 2 CR</td>
<td>9m (BRCAmut 16.5m BRCA other 5.7m)</td>
</tr>
<tr>
<td>35 (80%) Including 5 CR</td>
<td>17.7m (BRCAmut 19.4m BRCA other 16.5m)</td>
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<table>
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<tr>
<th>P value for PFS difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCAmut</td>
</tr>
<tr>
<td>BRCA other</td>
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</table>
Conclusions / concerns

- An open label study with no placebo may lead to bias.
- Nevertheless, most likely a significantly superior efficacy is seen for combination compared to olaparib alone, particularly in BRCA “other group”.
- At dose of 30mg od cediranib toxicity was considerable.
- Further studies of this combination are warranted both as maintenance therapy and for recurrent disease.
PARP inhibitor plus PI3K inhibitor

- Preclinical data in TNBC cells demonstrate that PI3K inhibition suppresses BRCA 1/2 expression and enhances sensitivity to PARP inhibition, partly through activation of ERK and transcription factor ETS1.

- Phase I trials now underway, including olaparib plus AZD5363
  - Initial data encouraging with no overlapping toxicity

Ibrahim et al, Cancer Discovery 2012 2 1036-1047

Juvekar et al. Cancer Discovery 2012 2 1036-1047
Rehman et al. Cancer Discovery 2012 2 982-984
Emerging questions – the next 10 years

a) Should BRCA mutation testing become routine in oncology clinics?
   – If so, should this include somatic (tumour) as well as germ line analysis?
   – But what do we know about tumour heterogeneity?
     **Note:** germline: somatic mutation frequency is 3-5 : 1

b) Should chemotherapy for BRCAm carriers be the same as or different to BRCA WT patients?
   – Clinical data indicate enhanced efficacy for Caelyx and perhaps Trabectadain as well as platinum

c) How should a BMOC patient with platinum-sensitive relapse be treated?
   – olaparib?
   – bevacizumab?
   Will it vary according to individual patient history?

d) How will PARPi resistance be circumvented?
   – novel inhibitors?
   – new combinations, e.g. with ATR inhibitors?
Summary

The last decade –

• Therapeutic targeting of HRD becomes a reality
• First PARP inhibitor – olaparib – approved for treatment of BRCA mutation-associated ovarian cancer.

The next decade –

• Other applications
• HRD assay
• Combination approaches
• PARPi resistance and its circumvention

Is in safe hands
Acknowledgements

ICR/RMH

- Johann de Bono
- Tim Yap
- Joo Ern Ang
- Peter Fong
- Craig Carden
- Martin Gore
- Susie Banerjee
- Chris Lord
- Alan Ashworth

- Clinical collaborators in Europe, USA, Australia
- Colleagues at AZ, Clovis, Tesaro, Biomarin

Lesson 6 – it’s the team stupid!

- All the research nurses, clinical fellows and data managers in the DDU
- Support from CRUK, ICR and Biomedical Research Centre at RMH