GERMLINE MUTATIONS AS A THERAPEUTIC TARGET IN CANCER

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DISCLOSURE OF INTEREST

Advisory board: Astra Zeneca, Pfizer, Bristol Myers
QUESTION TO THE AUDIENCE

Which of the following germline genetic alterations might be used to guide/personalize cancer therapy?

1. TP53
2. MLH1, MSH2, MSH6, PMS2 causing MSI
3. BRCA1 and BRCA2
4. PTEN deficiency
5. All of them
CONSULTATION IN APRIL 2010

A 36-year-old woman with a family history of breast cancer, a known mutation in BRCA2, and a high desire for immediate pregnancy:

Newly diagnosed of breast lobular carcinoma, grade 2, RH +, HER2-, Ki67 12% (35% in biopsy), cT1bN0M0.

Her consultation is about:

- Preservation of fertility and reproductive options
- Type of surgery: therapeutic and prophylactic
- Need for adjuvant treatment and type
- When to undergo prophylactic bilateral salpingo-oophorectomy
OS did not differ according to BRCA status, but these tumors were detected more advanced than the ones screen-detected.

**BRCA+**: 36% Node +
From 678 deaths:
- 651 (96%) were due to BC
- *6 of 201 (3%) new primary tumors in BRCA1 mutation carriers*: 3 ovarian cancer, 1 primary peritoneal, 1 esophageal, 1 pancreatic cancer
- No deaths attributed to second primary tumors in **BRCA2** carriers

POSH Study, Lancet Oncology 2018
Contradictory data on the ovarian reserve in mutation carriers BRCA1 / 2 versus control population

Increased frequency of chemo-induced amenorrhea in mutation carriers in BRCA2, especially if tamoxifen

Pregnancy post BC in women with mutation in BRCA1/2 has not shown negative impact on survival

Valentini 2013; Phillips 2016; Wang 2014; Johnson 2017; Lambertini, ASCO 2019
CONTRALATERAL BC RISK

Van der Broek, JCO 2015
BC<41 + BRCA1/2 mutation+ family history: **38% risk at 10 years** (95% CI 25-52%)
BC AND OV CANCER RISK IN BRCA1/2 CARRIERS

Figure 2. Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation Carriers

A Cumulative risk of first breast cancer among BRCA1 and BRCA2 mutation carriers

B Cumulative risk of ovarian cancer among BRCA1 and BRCA2 mutation carriers

Kuchenbaecker K. JAMA 2017
**EndoPredict®** is a gene expression assay for patients with ER+, HER2- early-stage breast cancer. From this genomic analysis, a 12-Gene Molecular Score is assigned. This score, combined with tumor size and nodal status, contributes to the **EPclin Risk Score**, from which the risks of distant recurrence (10-year and 5 to 15-years) with 5 years of adjuvant endocrine therapy alone and the estimated absolute benefit of chemotherapy (at 10 years) are determined.

### Initial Treatment Planning

<table>
<thead>
<tr>
<th>0-10 Year Likelihood of Distant Recurrence</th>
<th>7.4%</th>
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</thead>
<tbody>
<tr>
<td>(For patients treated with 5 years of endocrine therapy alone)</td>
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</table>

<table>
<thead>
<tr>
<th>Estimated Absolute Chemotherapy Benefit at 10 years</th>
<th>1.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(For patients treated with 5 years of endocrine therapy alone)</td>
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</table>

### Long-Term Treatment Planning

<table>
<thead>
<tr>
<th>Likelihood of Late Distant Recurrence Years 5-15</th>
<th>5.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(For patients with no recurrence after 5 years of endocrine therapy and no chemotherapy administered)</td>
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</tbody>
</table>
**BRCA1 AND BRCA2**

BRCA1 and BRCA2 are essential genes for DNA repair by homologous recombination.

PROGNOSIS AND SURVIVAL

Breast cancer

Ovarian cancer

Copson ER, et al. Lancet Oncology 2018;
PLATINUMS IN BRCA-METASTATIC BREAST CANCER

**TNT study**

Advanced TNBC or gBRCA1/BRCA2m with Breast Cancer

[Diagram showing the study design with arrows indicating progression between Carboplatin AUC 6 q3w x 6 cycles and Docetaxel 100 mg/m² q3w x 6 cycles.]

**Primary endpoint**
- ORR by RECIST

**Key secondary efficacy endpoints**
- TTP
- PFS
- ORR 2nd line
- Toxicity
- OS

**Phase 3, 74 centers in the United Kingdom**

### Unselected population

<table>
<thead>
<tr>
<th></th>
<th>Carboplatin</th>
<th>Docetaxel</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>31.4</td>
<td>34.0</td>
<td>0.66</td>
</tr>
<tr>
<td>Absolute difference (95% CI)</td>
<td>-2.6 (-12.1–6.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mPFS, months (95% CI)</td>
<td>3.1 (2.5–4.2)</td>
<td>4.5 (4.1–5.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>mOS, months (95% CI)</td>
<td>12.4 (10.4–15.3)</td>
<td>12.3 (10.5–13.6)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

### gBRCAm population

<table>
<thead>
<tr>
<th></th>
<th>Carboplatin</th>
<th>Docetaxel</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>68%</td>
<td>33.3%</td>
<td>0.03</td>
</tr>
<tr>
<td>Absolute difference (95% CI)</td>
<td>34.7 (6.3–63.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mPFS, months</td>
<td>6.8</td>
<td>4.4</td>
<td></td>
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</tbody>
</table>

Tutt A et al, Nat Medicine 2018
PLATINUMS IN BRCA-OVARIAN CANCER

Treatment-free interval in BRCA mutation carriers vs. patients with sporadic OvC

Platinum-based chemotherapy

Non platinum-based chemotherapy

BRCA1/2 DEFICIENCY AND TARGETED THERAPIES

Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase

Helen E. Bryant¹, Niklas Schultz², Huw D. Thomas³, Kayan M. Parker¹, Dan Flower¹, Elena Lopez¹, Suzanne Kyle³, Mark Meuth¹, Nicola J. Curtin² & Thomas Helleday¹,²

NATURE VOL 434 | 14 APRIL 2005

Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy

Hannah Farmer¹,², Nuala McCabe¹,², Christopher J. Lord²,³, Andrew N. J. Tutt²,³, Damian A. Johnson², Tobias B. Richardson², Manuela Santarosa²,³, Krystyna J. Dillon², Ian Hickson¹, Charlotte Knights⁴, Niall M. B. Martin⁴, Stephen P. Jackson¹,², Graeme C. M. Smith¹ & Alan Ashworth¹,²

NATURE VOL 434 | 14 APRIL 2005
MECHANISM OF ACTION PARPI
Olaparib, rucaparib, niraparib, talazoparib, veliparib

PARP1 functions in BER
DNA damage
Single-strand break
Double-strand break
Base excision pair
PARP1
PARPi
DNA damage
Cell death

PARP1 inhibits NHEJ
DNA damage
Double-strand break
Ku 70/80
DNA PKc
HR defect
PARP1
PARPi
NHEJ
PARP1
DNA damage
Error-prone DNA repair
Genomic instability
Cell death

PARP1 trapping on DNA damage
DNA damage
PARPi
PARP1 trapping
DNA damage
DNA damage
Cell death

PHASE II STUDY OF OLAPARIB

In patients with advanced cancer and a germline BRCA1/2 mutation (study 42)

<table>
<thead>
<tr>
<th></th>
<th>Ovarian (n=193)</th>
<th>Breast (n=62)</th>
<th>Pancreas (n=23)</th>
<th>Prostate (n=8)</th>
<th>Other (n=12)</th>
<th>Total (N=298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>31%</td>
<td>13%</td>
<td>22%</td>
<td>50%</td>
<td>8%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Treatment with olaparib 400 mg bid was associated with clinical responses in heavily pre-treated patients with BRCA1/2 mutations and recurrent, treatment-refractory cancer.
PARPI IN MONOTHERAPY FOR OVARIAN CANCER

- Olaparib (germline BRCA1/2, three or more previous therapies, n=193):
  - Response rate 31% (24.6-38.1)
  - PFS:
    - All patients: 6.7 months (5.5-7-6)
    - Platinum- sensitive: 9.4 months (6.7-11.4)
    - Platinum- resistant: 5.5 months (4.2-6.7)

- Rucaparib (germline or somatic BRCA1/2, platinum-sensitive high grade, two or more previous therapies, n=106):
  - Response rate 54% (43.8 – 63.5)
  - PFS (Ariel 2): 12.8 months (9.0-14.7)

PLATINUM-BASED CHEMO FOLLOWED BY PARPI
Phase III study designs

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Response</th>
<th>Eligibility</th>
<th>Prognosis</th>
<th>Follow-up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOVA</td>
<td>Niraparib</td>
<td>CR/PR (&lt;2 cm) after platinum</td>
<td>BRCA and non-BRCA</td>
<td>PFS (central review)</td>
<td>553 (203 BRCA +)</td>
<td></td>
</tr>
<tr>
<td>SOLO 2</td>
<td>Olaparib</td>
<td>CR/PR after platinum</td>
<td>Only BRCA</td>
<td>PFS (investigator-assessed)</td>
<td>295 (gBRCA+)</td>
<td></td>
</tr>
<tr>
<td>ARIEL 3</td>
<td>Rucaparib</td>
<td>CR/PR after platinum</td>
<td>BRCA and non-BRCA</td>
<td>PFS (investigator-assessed)</td>
<td>594 (196 gBRCA+)</td>
<td></td>
</tr>
</tbody>
</table>
PLATINUM-BASED CHEMO FOLLOWED BY PARPI

NOVA trial, niraparib

PLATINUM-BASED CHEMO FOLLOWED BY PARPI

SOLO 2 trial, olaparib

**g/s BRCA1/2**

HR = 0.30 (0.22-0.41)

19.1 m vs. 5.5 m
PLATINUM-BASED CHEMO FOLLOWED BY PARPI

ARIEL 3, rucaparib

SOLO 1: STUDY DESIGN

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic BRCA mutation
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

2:1 randomisation

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

Primary endpoint
- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints
- PFS using BICR
- PFS2
- Overall survival
- Time from randomisation to first subsequent therapy or death
- Time from randomisation to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

2 years' treatment if no evidence of disease

Moore et al, NEJM 2018
SOLO 1 RESULTS: PFS

B  Progression-free Survival as Assessed by Blinded Independent Central Review

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.20–0.39)
P<0.001

Moore et al, NEJM 2018
PHASE III TRIAL DESIGNS FOR ADVANCED GBRC\(\textit{A}\) MUTATED BREAST CANCER PATIENTS

- *gBRCA1 / BRCA2* carriers with advanced cancer
  - Anthracycline and/or taxane pre-treated

- PARP inhibitor
  - Physician’s choice within SOC options
    - Capecitabine
    - Vinorelbine
    - Eribulin
    - (Gemcitabine)

- Primary endpoint: PFS

**Trial Designs**
- Olaparib – OlympiAD
- BMN 673 – EMBRACA
- Niraparib – BRAVO Trial
OLYMPIAD PHASE III: OLAPARIB

Primary endpoint: PFS by BICR

- Progression/deaths, n (%): Olaparib 300 mg bd: 163 (79.5); Chemotherapy TPC: 71 (73.2)
- Median PFS, months: Olaparib 300 mg bd: 7.0; Chemotherapy TPC: 4.2
- HR: 0.58
- 95% CI: 0.43 to 0.80; P=0.0009

Primary endpoint: PFS by blinded central review

<table>
<thead>
<tr>
<th></th>
<th>TALA (n = 287)</th>
<th>Overall PCT (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, no. (%)</td>
<td>186 (65%)</td>
<td>83 (58%)</td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>8.6 (7.2, 9.3)</td>
<td>5.6 (4.2, 6.7)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.54, 95% CI</td>
<td>0.41, 0.71</td>
</tr>
<tr>
<td>P</td>
<td>&lt; .0001</td>
<td></td>
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Litton J, et al. NEJM 2018
Time to Deterioration in QoL

Statistically significant delay in the time to clinically meaningful deterioration* in GHS/QoL favoring TALAZOPARIB

<table>
<thead>
<tr>
<th></th>
<th>TALA 1 mg PO daily (n = 262)</th>
<th>PCT (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, no. (%)</td>
<td>76 (29%)</td>
<td>48 (42%)</td>
</tr>
<tr>
<td>Median, mo (95% CI)</td>
<td>24.3 (13.8, NR)</td>
<td>6.3 (4.9, 12.2)</td>
</tr>
<tr>
<td>Hazard ratio, 0.38</td>
<td>95% CI, 0.26, 0.55</td>
<td>P &lt; .0001</td>
</tr>
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</table>

Abbreviation: NR, not reached. *≥ 10-point decrease and no subsequent observation with a < 10-point decrease from baseline.
PHASE III ADJUVANT TRIAL

Olaparib vs. placebo in gBRCA and high risk HER2 negative primary breast cancer

- PARP inhibition has strong proof of concept in BRCA1/2 carriers
- Treatment early in disease minimises therapy-induced resistance
- TNBC has few other targets
- Mechanism and expectation of effect is the same in ER+

Study population:
- Post neoadjuvant: TNBC with non-pCR; HR+/HER2- with non-pCR and CPS&EG score ≥3
- Post adjuvant: TNBC >2 cm or LN+; HR+/HER2- >4LN+

Olaparib vs. placebo after standard therapy

Primary objective: Invasive Disease Free Survival

NCT02032823
Neoadjuvant Talazoparib for Early Stage Breast Cancer Patients with a BRCA Mutation

Study Design

N=20*

Talazoparib
1 mg orally daily

Biopsy
Ultrasound

Ultrasound

(0-2-4-6)
(Cycles**)

Surgery

Residual Tissue Correlatives

Systemic Therapy of
Physician’s Choice

Eligibility

• Tumors > 1 cm
• Clinical Stage I-III
• Germline BRCA mutation
• No previous therapy for invasive breast cancer

Exclusion

• HER2 positive

Primary Objectives

• pCR (ypT0/is ypN0)
• RCB-0 + RCB-I

Secondary Objective

• Evaluate toxicity

*1 patient took 5 months of talazoparib and then refused biopsy and surgery and proceeded to chemotherapy
** 1 cycle=28 days
Pathologic Results

Number of Patients

<table>
<thead>
<tr>
<th>RCB-0</th>
<th>RCB-I</th>
<th>RCB-II</th>
<th>RCB 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

pCR (RCB-0): $\frac{10}{19} = 53\%$, 95% CI = 32%, 73%

RCB-0+I: $\frac{12}{19} = 63\%$, 95% CI = 41%, 81%
PARPI IN BRCA-PANCREATIC CANCER TRIALS ONGOING

PARPi maintenance in pancreatic cancer

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Setting under investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>III</td>
<td>Germline \textit{BRCA}1/2 mutated pancreatic cancer patients who have received platinum-based chemotherapy and have not progressed</td>
</tr>
<tr>
<td>NCT02184195</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rucaparib</td>
<td>II</td>
<td>Germline or somatic \textit{BRCA}1/2 or PALB2 mutated pancreatic cancer who have received platinum-based chemotherapy and have not progressed</td>
</tr>
<tr>
<td>NCT03140670</td>
<td></td>
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TOPARP-A

Olaparib in metastatic, castration-resistant prostate cancer

CURRENT INVESTIGATIONAL STATUS OF PARP INHIBITORS IN PROSTATE CANCER

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Setting under investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib</td>
<td>II</td>
<td>Open label study of olaparib 400 mg bid in patients with <em>BRCA1/2</em> mutations</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Monotherapy vs. combination treatment (with abiraterone/prednisone) in patients with mCRPC and DNA repair defects</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Combination therapy (olaparib 200 or 300 mg bid + abiraterone 1000 mg) in patients with mCRPC</td>
</tr>
<tr>
<td>Niraparib</td>
<td>II</td>
<td>Monotherapy in patients with mCRPC and DNA repair anomalies</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>Combination therapy (with enzalutamide) in patients with mCRPC</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>III</td>
<td>Monotherapy (administered orally) vs. abiraterone acetate or enzalutamide or docetaxel in patients with mCRPC and HR gene deficiency</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Monotherapy (administered orally) in patients with mCRPC and HR gene deficiency</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>I</td>
<td>Monotherapy (administered orally) in patients with recurrent solid tumours (including prostate cancer)</td>
</tr>
</tbody>
</table>
TAKE HOME MESSAGES

- *BRCA1/2* mutations may cause homologous recombination deficiency and be a predictive biomarker for targeted therapies, i.e. platinums and PARPi.

- Several PARPi have been approved by FDA or EMA for ovarian, breast, or prostate cancer (breakthrough designation) with a germline or somatic BRCA mutation.

- Mainstream genetic testing for therapeutic indications will likely increase the number of mutation carriers identified and it will be an opportunity for cascade testing in relatives who may benefit from individualised surveillance and prevention options.
THANK YOU!