Management of BRCA mutation carriers

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ESMO Breast Cancer Preceptorship - November 2018
Disclosures

Roche: Speakers bureau, honoraria, consultancy
Astra Zeneca: Speakers bureau, honoraria, consultancy
Novartis: Speakers bureau, honoraria, consultancy
Pfizer: Speakers bureau, honoraria, consultancy
Background

• Germline mutations in BRCA1/2 account for majority of hereditary breast cancer (BC) & ~5-10% of all BC

• BRCA1/2 mutations - ↑ prevalence in younger women with BC, TNBC, FHx of BC or Ovarian cancer (+ other malignancies) and in certain ethnic groups (Ashkenazi Jewish)

• A mutation in BRCA1/2 confers a lifetime risk of 35-90% of BC

• In most studies, similar prognosis for BRCA1/2+ & sporadic BC

BC=Breast Cancer   TNBC=Triple Negative Breast Cancer

Tung et al JCO 2016
Kuchenbacker et al JAMA 2017
Goodwin et al 2012
Copson E et al, Lancet Oncology, 2018
# BRCA-associated Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Earlier</td>
<td>Slightly older than with BRCA1</td>
</tr>
<tr>
<td><strong>Subtype</strong></td>
<td>Most often “triple negative”</td>
<td>Most often hormone positive</td>
</tr>
<tr>
<td><strong>Risk of other malignancies</strong></td>
<td>Ovarian cancer</td>
<td>Ovarian cancer, Pancreatic cancer, Melanoma (and in males – breast cancer, prostate cancer)</td>
</tr>
<tr>
<td><strong>Other features</strong></td>
<td>High grade, medullary subtype, pushing margins, lymphocytic infiltrate</td>
<td>Sensitivity to DNA damage</td>
</tr>
</tbody>
</table>

*Many similarities, but they are distinct entities and BRCA1 and BRCA2 cancers may not respond identically to treatment*
IMAGING FOR SCREENING AND DIAGNOSIS IN BRCA1/2
Screening & Diagnosis:
MRI in women with high risk of breast cancer

American Cancer Society Guidelines, 2007
**Screening & Diagnosis:**
**MRI in women with high risk of breast cancer**

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>Mammography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The Netherlands</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Positives</td>
<td>13.7%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Recalls</td>
<td>10.84%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Biopsies</td>
<td>2.93%</td>
<td>3.08%</td>
</tr>
<tr>
<td>Cancers</td>
<td>1.04%</td>
<td>1.44%</td>
</tr>
<tr>
<td>False negatives</td>
<td>0.23%</td>
<td>0.43%</td>
</tr>
</tbody>
</table>

American Cancer Society Guidelines, 2007
Why is MRI superior to mammography in BRCA+?

- BRCA+ breast tumors are:
  - often in younger women with dense breasts – sensitivity of mammography inversely related to breast density
  - with “pushing margins” rather then scirrhouos, irregular margins, giving a more “benign” appearance on mammography
  - Less-often associated with DCIS (which often have micro-calcifications that are detected on mammography) – especially true for BRCA1
Impact of a BRCA1/2 mutation on treatment decisions

- **Local management**
  - Lumpectomy vs mastectomy
  - Bilateral mastectomy?
- **Systemic therapy**
  - No EBM to change adjuvant chemotherapy, conflicting evidence re: NAST
  - Evidence to support use of DNA cross-linking agents & alkylating agents:
    - Platinum agents, Mitomycin, CMF (Cyclophosphamide/MTX/5FU)
    - PARPi
- **Reproductive considerations**
- **Ongoing follow-up**
LOCAL THERAPY CONSIDERATIONS
BCS vs Mastectomy

• BCS is a legitimate and safe choice
• Therapeutic radiation is safe:
  - Reduces local ipsilateral recurrence
  - Does not increase contra-lateral disease
• Contralateral mastectomy – some studies suggest that there may be a long term survival benefit
• Decision must be tailored to individual’s needs
Does CRRM improve survival?

Stage 1 & 2 at Dx
Most were <50 at Dx

Metcalfe, BMJ, 2014

Greatest benefit in <40 & low risk/favorable features

Heemskerk-Gerritsen, Int J Cancer, 2015
WHY DOES PRESENCE OF A BRCA1/2 MUTATION HAVE AN IMPACT ON SYSTEMIC THERAPY?
DNA REPAIR IS MORE ERROR-PRONE WHEN BRCA1 OR BRCA2 PROTEINS ARE DEFICIENT

**DNA Damage**

- **Single-Strand Breaks (SSBs)**
- **Double-Strand Breaks (DSBs)**

**Repair Mechanism**

- **BER**
- **HRR**
- **NHEJ**

**Proteins**

- **PARP1**
- **XRCC1**
- **LIGASE 3**
- **BRCA1**
- **BRCA2**
- **PALB2**
- **CHEK1**
- **CHEK2**
- **RAD51**
- **KU70/80**
- **CAN-PK**
- **ATM**

**Two Major Mechanisms for the Repair of DNA Double-Stranded Breaks**

1. **Homologous Recombination Repair (HRR)**
   - Non-functioning HRR may be due to BRCA 1 or BRCA 2 deficiency
   - Less precise, more error-prone

2. **Non-Homologous End-Joining (NHEJ)**
   - Less precise, more error-prone

**Non-functioning HRR results in:**

- Accumulation of additional mutations
- Chromosomal instability
- Increased risk for malignant transformation

**BER** = base excision repair; **HRR** = homologous recombination repair; **NHEJ** = non-homologous end-joining.

SYSTEMIC THERAPIES IN \textit{BRCA1/2+} BREAST CANCER
Chemotherapy
Chemotherapy in BRCA1/2+ Breast Cancer

• Pre-clinical studies - ↑ sensitivity to DNA damaging agents that interferes with DNA replication forks & subsequently require DNA repair by homologous recombination:
  - DNA cross-linking agents (carboplatin, cisplatin, mitomycin)
• Early clinical data in neo-adjuvant setting - platinum sensitivity
• ↑sensitivity to chemotherapy doesn’t necessarily prognosticate for BRCA1/2 associated BC

Silver et al JCO
Bysrki et al JCO 2014
Paluch-Shimon et al BCRT 2016
Fasching et al JCO 2018
Platinum in the neo-adjuvant setting for BRCA+

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol</th>
<th>pCR</th>
<th>DFS (med f/u – 35 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeparSixto</td>
<td>Liposomal Doxorubicin + Paclitaxel +/-Carboplatin*</td>
<td>wtBRCA (n=241) 36.4% vs 55% p=0.004</td>
<td>73.5% vs 85.3% p=0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA+ (n=50) 66.7% vs 65.4% p=0.92</td>
<td>82.5% vs 86% NS</td>
</tr>
</tbody>
</table>

* Also randomization to bevacizumab

Hahnen et al, JAMA Oncology, 2017

BrighT Ness
Paclitaxel +/-Carboplatin +/-Veliparib → ACx4

No outcome data

Loibl et al, Lancet Oncology, 2018
# Platinum in BRCA+ in ABC

<table>
<thead>
<tr>
<th>Phase</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNT III</td>
<td>Carboplatin vs Docetaxel in BRCA-wt Carboplatin vs Docetaxel in BRCA+</td>
<td>28% vs 36% (p=0.16) 68% vs 33% (p=0.03)</td>
</tr>
<tr>
<td>TBCRC009 II</td>
<td>Platinum in TNBC BRCA+ vs BRCA-wt</td>
<td>55% vs 20% (p=0.02)</td>
</tr>
</tbody>
</table>

Tutt A, et al. Nat Med, 2018
PARP Inhibitors
PARP Inhibitors

Dual Activity – Catalytic and Trapping

• Work by catalytic enzyme activity and by trapping where they lock PARP onto the DNA

• Different PARP inhibitors with equal catalytic inhibition potency show markedly different PARP trapping ability which affects their potency

• Clinical PARP inhibitors can be ranked by their ability to trap PARP (from the most to the least potent): *talazoparib >> niraparib > olaparib = rucaparib >> veliparib*
# Proof of concept studies - Olaparib in BRCA+ BC

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tutt et al</td>
<td>41%</td>
<td>At least 1 previous line of chemotherapy</td>
</tr>
<tr>
<td>Kaufman et al</td>
<td>13%</td>
<td>Heavily pre-treated</td>
</tr>
</tbody>
</table>

Tutt et al, Lancet, 2010  
Kaufman et al, JCO 2015
How does PARP inhibition compare with SOC chemotherapy in ABC?

- gBRCA1 / BRCA2 Carriers
  - Advanced anthracycline taxane resistant breast cancer

- Niraparib – BRAVO Trial EORTC / BIG
- Talazoparib – EMBRACA - NCT01945775
- Olaparib - OLYMPIAD NCT02000622

- Potent PARP inhibitor at MTD as continuous exposure
- Physician Choice within SOC options
  - Capecitabine
  - Vinorelbine
  - Eribulin
  - Gemcitabine

Primary endpoint PFS

## PARP inhibitors in BRCA+ ABC

<table>
<thead>
<tr>
<th>Phase</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLYMPIAD III Olaparib vs TPC</td>
<td>60% vs 29%</td>
<td>7 vs 4.2</td>
</tr>
<tr>
<td>ABRAZO II Talazoparib after platinum Talazoparib after 3+ lines of Rx (&amp; no platinum)</td>
<td>21% 37%</td>
<td>4 5.6</td>
</tr>
<tr>
<td>EMBRACA III Talazoparib vs TPC</td>
<td>63% vs 27%</td>
<td>8.6 vs 5.6</td>
</tr>
<tr>
<td>BROCADE2 II Palclitaxel/Carboplatin + Veliparib/Placebo</td>
<td>78% vs 61% (p=0.027)</td>
<td>14.1 vs 12.3 (NS)</td>
</tr>
</tbody>
</table>

Robson et al, New Engl J Med 2017
Turner et al, ASCO, 2017
Litton et al, SABCS, 2017
Han et al Annals of Oncology, 2018
Olaparib versus physicians’ choice: the phase III OLYMPIAD study

- HER2-negative metastatic breast cancer
  - ER and/or PR positive (HR+) or
  - TNBC
- Deleterious or suspected deleterious gBRCAm
- \( \leq 2 \) prior chemotherapy lines in metastatic setting
- Prior anthracycline and taxane
- HR+ disease progressed on \( \geq 1 \) endocrine therapy, or not suitable
- If prior platinum use
  - No evidence of progression adjuvant treatment
  - \( \geq 12 \) months since (neo)adjuvant treatment

Olaparib
300 mg tablets bd

2:1 randomization

Primary endpoint
- Progression-free survival (RECIST 1.1, BICR)

Secondary endpoints
- Overall survival
- Time to second progression or death
- Objective response rate
- Global HRQoL (EORTC-QLQ-C30)
- Safety and tolerability

Treat until progression

Robson et al, New Engl J Med 2017

Chemotherapy treatment of physician’s choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine
Primary end point: centrally-evaluated PFS

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 300 mg bd</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (%)</td>
<td>163 (79.5)</td>
<td>71 (73.2)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>7.0</td>
<td>4.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.43 to 0.80</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.0009</td>
<td></td>
</tr>
</tbody>
</table>

Robson et al, New Engl J Med 2017
Overall survival in prespecified subgroups

No prior chemotherapy for mBC (1L)

Olaparib TPC
Deaths, n (%) 30 (50.8) 21 (75.0)
Median OS, mo 22.6 14.7
HR 0.51 (95%CI 0.29–0.90; P=0.02)
Alive at 6 mo, % 93.2 88.5
Alive at 18 mo, % 62.1 46.2
Median follow-up, mo 25.5 26.9

Prior chemotherapy for mBC (2/3L)

Olaparib TPC
Deaths, n (%) 100 (68.5) 41 (59.4)
Median OS, mo 18.8 17.2
HR 1.13 (95%CI 0.79–1.64; P=NS)
Alive at 6 mo, % 93.1 84.9
Alive at 18 mo, % 50.8 48.8
Median follow-up, mo 25.2 26.0

Nominal P values calculated using a likelihood ratio test; OS stratification factors were prespecified but not alpha controlled

1L, first line; 2/3L, second or third line; NS, not significant

Courtesy of Mark Robson
OLYMPIAD: additional efficacy data

ORR was 60% vs 29% favoring the Olaparib monotherapy
Median onset to response:
Olaparib – 47 days
Chemotherapy TPC – 45 days

Delaloge et al, ESMO 2017 poster-discussion#243 PD
At 18 months 19% in the olaparib arm remained on treatment

*Data are cumulative and patients are included if their total duration (including dose interruptions) on study treatment is greater than or equal to that month

Data Cutoff: 25th September 2017

1. AZ data on file (2018); 2. Robson et al. AACR, 2018
**Study Design: EMBRACA**

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation*†*

**Stratification factors:**
- Number of prior chemo regimens (0 or ≥ 1)
- TNBC or hormone receptor positive (HR+)
- History of CNS mets or no CNS mets

**Primary endpoint**
- Progression-free survival by RECIST by blinded central review

**Key secondary efficacy endpoints**
- Overall survival (OS)
- ORR by investigator
- Safety

**Exploratory endpoints**
- Duration of response (DOR) for objective responders
- Quality of life (QoL; EORTC QLQ-C30, QLQ-BR23)

**Phase 3, international, open-label study randomized**
- 431 patients in 16 countries and 145 sites

**Abbreviations:**
- CNS, central nervous system
- EORTC, European Organisation for Research and Treatment of Cancer
- HER2, human epidermal growth factor receptor 2
- mets, metastases
- PO, orally (per os)
- QLQ-BR23, Quality of Life Questionnaire breast cancer module
- QLQ-C30, Quality of Life Questionnaire Core 30
- R, randomized
- RECIST, Response Evaluation Criteria In Solid Tumors version 1.1
- TNBC, triple-negative breast cancer

*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or anthracycline unless medically contraindicated.
†HER2-positive disease is excluded.
‡Physician’s choice of therapy must be determined prior to randomization.

www.clinicaltrials.gov (NCT01945775)
Primary Endpoint: PFS by Blinded Central Review

<table>
<thead>
<tr>
<th></th>
<th>TALA</th>
<th>Overall PCT</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 0.41, 0.71</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&lt; .0001</td>
<td></td>
</tr>
</tbody>
</table>

1-Year PFS 37% vs 20%    Median follow-up time: 11.2 months
PFS: Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients, no. (%)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All randomized patients (ITT)</td>
<td>431 (100)</td>
<td>0.54 (0.41-0.71)</td>
</tr>
<tr>
<td>Patients with central testing available</td>
<td>408 (94.7)</td>
<td>0.53 (0.40-0.70)</td>
</tr>
<tr>
<td><strong>BRCA</strong> status by central testing**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>183 (42.5)</td>
<td>0.59 (0.39-0.90)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>225 (52.2)</td>
<td>0.47 (0.32-0.70)</td>
</tr>
<tr>
<td>Hormone receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNBC based on most recent biopsy</td>
<td>190 (44.1)</td>
<td>0.60 (0.41-0.87)</td>
</tr>
<tr>
<td>HR+ based on most recent biopsy</td>
<td>241 (55.9)</td>
<td>0.47 (0.32-0.71)</td>
</tr>
<tr>
<td>History of CNS metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63 (14.6)</td>
<td>0.32 (0.15-0.68)</td>
</tr>
<tr>
<td>No</td>
<td>368 (85.4)</td>
<td>0.58 (0.43-0.78)</td>
</tr>
<tr>
<td>Prior platinum treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76 (17.6)</td>
<td>0.76 (0.40-1.45)</td>
</tr>
<tr>
<td>No</td>
<td>355 (82.4)</td>
<td>0.52 (0.39-0.71)</td>
</tr>
<tr>
<td>Prior regimens of cytotoxic chemo for aBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>165 (38.3)</td>
<td>0.57 (0.34-0.95)</td>
</tr>
<tr>
<td>1</td>
<td>161 (37.4)</td>
<td>0.51 (0.33-0.80)</td>
</tr>
<tr>
<td>≥ 2</td>
<td>105 (24.4)</td>
<td>0.56 (0.34-0.95)</td>
</tr>
</tbody>
</table>
PARP Inhibitors – in EBC
Study Design

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
# Baseline Characteristics

**N = 20**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Median=38 (Range 23-58)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7</td>
</tr>
<tr>
<td>Black</td>
<td>5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
</tr>
<tr>
<td><strong>Clinical Stage</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td>12</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>18</td>
</tr>
<tr>
<td>Lobular</td>
<td>1</td>
</tr>
<tr>
<td>Metaplastic-chondrosarcomatous</td>
<td>1</td>
</tr>
</tbody>
</table>
Pathologic Results

- **pCR (RCB-0):** \(\frac{10}{19} = 53\%,\ 95\%\ CI = 32\%,\ 73\%\)
- **RCB-0+I:** \(\frac{12}{19} = 63\%,\ 95\%\ CI = 41\%,\ 81\%\)

Courtesy of Jennifer Litton
Platinum vs PARPi in the neo-adjuvant setting

<table>
<thead>
<tr>
<th></th>
<th>Talazoparib</th>
<th>Cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>107</td>
</tr>
<tr>
<td>BRCA1</td>
<td>85%</td>
<td>100%</td>
</tr>
<tr>
<td>pCR</td>
<td>53%</td>
<td>61%</td>
</tr>
</tbody>
</table>

Litton et al, ASCO 2018
Byrski et al, BCRT 2014
Randomise 1:1
Double blind
N=1500

Post neoadjuvant gBRCA
HR+, TNBC,
Non-PathCR pts

Restricted to Germline
Mutation carriers

Post adjuvant gBRCA
HR+, TNBC
T2 or N+

Olaparib
300 mg bd
12 month
duration

Placebo
12 month
duration

IDFS

Distant DFS, OS

Olaparib in Adjuvant
BRCAm breast cancer

IDFS

Distant DFS, OS

Post adjuvant gBRCA
HR+, TNBC
T2 or N+

AstraZeneca
## Long term safety of PARPi: hematological malignancies

Long term incidence of AML, MDS, CMML in germline mutant carriers in phase III studies:

<table>
<thead>
<tr>
<th>Trial</th>
<th>Context</th>
<th>Treatment arm</th>
<th>Placebo arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOL02</strong></td>
<td>• Maintenance olaparib vs placebo, <strong>ovarian</strong> cancer&lt;br&gt;• Germline BRCA1/2 mutation</td>
<td>2% (med FU 22.2 months, med treatment duration 19.1 months)</td>
<td>4% (med FU 22.1 months, med treatment duration 5.5 months)</td>
</tr>
<tr>
<td><strong>NOVA</strong></td>
<td>• Maintenance niraparib vs placebo, <strong>ovarian</strong> cancer&lt;br&gt;• Both sporadic and Germline BRCA1/2 mutation</td>
<td>1.4% (med FU 16.9 months)</td>
<td>1.1% (med FU 16.9 months)</td>
</tr>
<tr>
<td><strong>OLYMPIAD</strong></td>
<td>• Olaparib vs placebo, <strong>breast</strong> cancer&lt;br&gt;• Germline BRCA1/2 mutation</td>
<td>0% (med FU 14.5 months)</td>
<td>0% (med FU 14.1 months)</td>
</tr>
</tbody>
</table>

FU: follow-up, med: median; AML: acute myeloblastic leukaemia, MDS: myelodysplastic syndrome, CMML: chronic myelomonocytic leukaemia

## Genomic Profiling – 21 Gene Recurrence Score

<table>
<thead>
<tr>
<th>Oncotype-Dx Recurrence Score</th>
<th>General Population</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N=1,019)</td>
<td>Node+ (N=195)</td>
<td>Node- (N=824)</td>
</tr>
<tr>
<td>Low risk (&lt;18)</td>
<td>539 (52.9%)</td>
<td>98 (50.3%)</td>
<td>441 (53.5%)</td>
</tr>
<tr>
<td>Intermediate risk (18-30)</td>
<td>387 (37.9%)</td>
<td>78 (40%)</td>
<td>309 (37.5%)</td>
</tr>
<tr>
<td>High risk (≥31)</td>
<td>93 (9.1%)</td>
<td>19 (9.7%)</td>
<td>74 (9%)</td>
</tr>
</tbody>
</table>

*Courtesy of Rinat Yerushalmi*
Genomic Profiling – 21 Gene Recurrence Score

• *BRCA1/2* - independent predictor for RS on MVA

• 45 months median follow-up - 6.9% developed recurrent disease

• Oncotype-DX scores of patients with disease recurrence were in the intermediate and low ranges - *None of these patients had received adjuvant chemotherapy*

Lewin et al BCRT 2016
What next?
Targeting Resistance to PARP inhibitors

• Restoration of HR function:
  - BRCA reversion mutations
  - Loss of TP53BP1
  - Reversal of epigenetic BRCA silencing

• ↑ P glycoprotein efflux pumps

• ↓ levels of PARP-1 expression/activity
Other compounds under investigation in BRCA+ BC

<table>
<thead>
<tr>
<th>Compounds</th>
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<tbody>
<tr>
<td>PARPi +</td>
<td>Immunotherapy</td>
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<td></td>
<td>Chemotherapy</td>
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<tr>
<td></td>
<td>Radiotherapy</td>
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<tr>
<td>Novel Agents +/- PARPi</td>
<td>ATR inhibitors, ATM inhibitors, WEE1 inhibitors, PI3Ki, VEGFi, HSP90, G-quadruplex interacting compounds</td>
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<tr>
<td>Novel chemotherapeutic agents</td>
<td>BTP-114, a novel platinum product</td>
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<tr>
<td>Other</td>
<td>Lurbinectedin/Trabectedin - covalent DNA minor groove binder</td>
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<td>Sacituzumab govitecan (IMMU-132) - anti-Trop-2-SN-38 Antibody-Drug Conjugate with topoisomerase I (Topo I)- inhibitory activity</td>
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</tbody>
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Conclusions
Ongoing challenges

• Sequencing treatment in BRCA+ ABC
• Resistance & cross-resistance to platinum & PARPi
• Clinical significance/application of:
  - Differences in BRCA1 & BRCA2
  - somatic BRCA mutations
  - loss-of-heterozygosity in BRCA-associated tumors
  - Homologous Recombination Defect (HRD) scoring
• Cost of new therapies!
Summary

• **Germline testing has therapeutic implications in the setting of ABC**

• Platinum agents superior in triple negative *BRCA*+ ABC

• PARPi superior to TPC

• Future studies – immunotherapy, overcoming PARPi resistance, novel agents

• Reproductive issues & tailoring risk reducing measures → further study

• **All BRCA+ patients should be offered participation in clinical trials!!!**
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Fifth ESO-ESMO International Consensus Conference

14-16 November 2019 | Lisbon, Portugal

Coordinating Chair: F. Cardoso, PT
Co-Chairs: G. Curigliano, IT - S.A. Mertz, US
Scientific Committee Members: K. Gelmon, CA - F. Penault-Llorca, FR - E. Senkus, PL
C. Thomassen, DE

The ABC5 guidelines will be developed by ESO and ESMO.

The ABC5 conference and guidelines are endorsed by:

The ABC5 conference is held under the auspices of
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