WHAT'S NEW IN THE MANAGEMENT OF BRCA POSITIVE OVARIAN AND BREAST CANCER PATIENTS -
2ND CONFERENCE

Grand Hotel Union Ljubljana, Slovenia
- Thursday, 19th of October 2017 -
SPEAKERS:
Judith Balmaña, Vall D’Hebron Institute of Oncology, Barcelona, Spain
Kathleen Claes, Ghent University, Belgium
Srdjan Novaković, Division of Molecular Diagnostics, Institute of Oncology Ljubljana, Slovenia
Mateja Krajc, Division of Cancer Genetic Counselling, Institute of Oncology Ljubljana, Slovenia
Ana Blatnik, Division of Cancer Genetic Counselling, Institute of Oncology Ljubljana, Slovenia
Ksenija Strojnik, Division of Cancer Genetic Counselling, Institute of Oncology Ljubljana, Slovenia
Erik Škof, Division of Medical Oncology, Institute of Oncology Ljubljana, Slovenia
Maja Ravnik, Division of Medical Oncology, University Medical Centre Maribor, Slovenia
Simona Borštnar, Division of Medical Oncology, Institute of Oncology Ljubljana, Slovenia
Janez Žgajnar, Division of Surgery, Institute of Oncology Ljubljana, Slovenia

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ORGANIZERS AND PUBLISHERS:
Institute of Oncology Ljubljana
Slovenian Senologic Society

SPONSORS OF THE MEETING:
AstraZeneca
Roche
Ljubljana, 19th October 2017
PROGRAM:
15:30 - 16:00  Participants gathering

16:00 - 16:10  INTRODUCTION, Mateja Krajc
16:10 - 16:50  Cancer genetic counselling and testing in view of new treatment options/establishing new clinical pathways (Spanish experiences)
               PARP inhibitors in breast cancer: a look back and a look forward (OlympiAD trial), Judith Balmana
16:50 - 17:40  Cancer genetic counselling and testing in view of new treatment options/establishing new clinical pathways (Belgian experiences)
               Tumor testing – where is its position in clinical pathways, Kathleen Claes
17:40 - 18:00  DISCUSSION

18:00 - 18:15  Coffee Break

18:15 - 19:15  HEREDITARY BREAST AND OVARIAN CANCER – SLOVENIAN EXPERIENCES
               • HBOC – germline/ somatic genetic testing – laboratory experiences (latest updates), Srdjan Novaković
               • Cancer genetic counselling – new clinical pathways in view of treatment options, Ana Blatnik, Mateja Krajc and Ksenija Strojnik
               • Slovenian experiences with olaparib in ovarian cancer treatment, Erik Škof and Maja Ravnik
               • PARP inhibitors in breast cancer – current and future perspectives in Slovenia, Simona Borštner
               • Surgical treatment of BRCA positive breast cancer patients – current practice and Slovenian results, Janez Žgajnar
19: 15 - 19:30  DISCUSSION

19:30 -  Dinner
Cancer genetic counseling and testing in view of new treatment options/establishing new clinical pathways

Judith Balmaña
Clinical cancer genetics
Medical Oncology Department
Hospital Vall d’Hebron

New paradigms

Teaching model: Directive
Disease-Based, Doctor-Centered Medicine

Counseling model: Non-directive
Patient-centered Medicine

Walsh, PNAS 2011
**BRCA-targeted approved therapies**
- Olaparib (Lynparza™, AstraZeneca)
  - EMA (Dec2014): Monotherapy maintenance treatment of platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous ovarian cancer patients
  - FDA (Dec2014): Monotherapy for germline BRCA1/2 mutated advanced ovarian cancer patients who have been treated with minimum three prior lines of chemotherapy. Aug 2017: FDA approved olaparib as maintenance treatment of patients with recurrent epithelial ovarian cancer who are in a response to platinum-based chemotherapy.
- Rucaparib (Rubraca™, Clovis Oncology)
  - FDA (Dec2016): Monotherapy for patients with advanced ovarian cancer and deleterious BRCA mutation (germline and/or somatic) who have been treated minimum two chemotherapies.
- Niraparib (Zejula™, Tesaro)
  - FDA (Mar2017): Monotherapy for maintenance treatment of patients with recurrent epithelial ovarian cancer, whose tumours have a response to platinum-based chemotherapy.

**BRCA1/2 testing**

**Treatment implications**

![Chart showing increased workload and faster turnaround times required for genetic counselling and testing models.]

**Ovarian Cancer Patients tested**

![Graph showing the increase in ovarian cancer patients tested from 2015 to 2017.]

Zhang et al. Gynecologic Oncology (2011)

M. De la Hoya
Personal communication, 2017
Treatment implication  New Genetic Counselling models

The 'DNA-direct' model (The Netherlands)

- **Processing time is reduced. Similar psychological outcomes, but patients were not randomised.**
- **Telephone pretest GC**
- **BRCA testing**
- **Face-to-face postest GC**

Telephone-based counselling model (USA)

- **Lower uptake. Not recommended for newly diagnosed or metastatic cancer patients.**
- **Telephone pretest GC**
- **BRCA testing**
- **Telephone postest GC**

Royal Marsden testing model (UK)

- **Cancer distress reduction Genetic Counseling helpful**

Clinical validity for cancer risk assessment BRIP1, RAD51C, RAD51D

<table>
<thead>
<tr>
<th>GENES</th>
<th>CASES</th>
<th>CONTROLS</th>
<th>MEAN AGE</th>
<th>RELATIVE RISK (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIP1</td>
<td>0.9%</td>
<td>0.09%</td>
<td>63.8y(93%&gt;50y)</td>
<td>5.8% at 80y cc. 11.2 (3-34)</td>
</tr>
<tr>
<td>BARD1</td>
<td>0.12%</td>
<td>0.06% (p=.39)</td>
<td>55.5 y (53-60)</td>
<td>-</td>
</tr>
<tr>
<td>PALB2</td>
<td>0.28%</td>
<td>0.09% (p=.08)</td>
<td>56 y (49-65)</td>
<td>-</td>
</tr>
<tr>
<td>NBN</td>
<td>0.28%</td>
<td>0.23% (p=.61)</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>RAD51C</td>
<td>0.41%</td>
<td>0.07%</td>
<td>70% &gt;50y</td>
<td>5.2 (1.1-24)</td>
</tr>
<tr>
<td>RAD51D</td>
<td>0.35%</td>
<td>0.04%</td>
<td>92% &gt;50y</td>
<td>12 (1.5-90)</td>
</tr>
</tbody>
</table>

VUS and cancer distress

<table>
<thead>
<tr>
<th>BRCA UN</th>
<th>BRCA VUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=714</td>
<td>n=71</td>
</tr>
<tr>
<td>35.80%</td>
<td>94.10%</td>
</tr>
<tr>
<td>23%</td>
<td>92.50%</td>
</tr>
</tbody>
</table>

**Cancer distress reduction Genetic Counseling helpful**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mammography (clinical breast examination and/or breast MRI)</th>
<th>RR SO</th>
<th>Colonoscopy</th>
<th>Pancreatic screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Annual starting at 40*</td>
<td>Family history*</td>
<td>Family history*</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>CHEK2 (truncating)</td>
<td>Annual starting at 40**</td>
<td>Family history*</td>
<td>Family history*</td>
<td>NA</td>
</tr>
<tr>
<td>NBN</td>
<td>Annual starting at 40*</td>
<td>Family history*</td>
<td>Family history*</td>
<td>NA</td>
</tr>
<tr>
<td>PALB2</td>
<td>Annual starting at 30</td>
<td>Family history*</td>
<td>Family history*</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>BRIP1/RAD51C/RAD51D</td>
<td>Family history*</td>
<td>50-55 years</td>
<td>Family history*</td>
<td>NA</td>
</tr>
</tbody>
</table>

Challenges of panel testing

Ovarian Cancer Patient tested

51% and 30% of breast cancer patients at average risk and with a VUS or no-BRCA mutation underwent bilateral mastectomy

Kurian, JCO 2017

NGS → Change in genetic counseling model

BRCA germline testing first for urgent therapeutics
PARP inhibitors in breast cancer - a look back and a look forward

Phase II/III studies with PARPi & biomarker analysis in breast cancer

1. Phase II: ABRAZO - talazoparib, mBC, gBRCA
   Cohort 1: platinum-treated (ORR 71%)
   Cohort 2: platinum-naïve, but heavily pre-treated (ORR 37%)

2. Phase III: OlympiaAD - olaparib, mBC, gBRCA
3. Phase III: BRAVO - niraparib, mBC, gBRCA
4. Phase III: EMBRACA - talazoparib, mBC, gBRCA
Background

- Cancers arising in women with deleterious germine mutations in breast cancer susceptibility genes 1 or 2 (BRCA1 and BRCA2) are deficient in DNA double-strand break repair and repair of stalled replication forks.\(^1\) - These cells depend on poly (ADP-ribose) polymerase (PARP) for DNA repair
- PARP inhibitors
  - Inhibit PARP catalytic activity\(^1\)
  - Trap PARP at sites of DNA damage\(^1\)
  - Prevent DNA damage repair, resulting in cell death in BRCA1/2-mutated cancer cells

Phase 2 Clinical Trial – Key Eligibility Criteria

- Patients with advanced breast cancer who carry a deleterious or suspected deleterious germine BRCA1/2 mutation (by central laboratory or a local report approved by the sponsor)
  - Cohort 1: PR or CR to last platinum-containing regimen for metastatic disease with disease progression > 8 weeks following the last dose of platinum
  - Cohort 2: 3 or more prior cytotoxic regimens for metastatic disease; no prior platinum for metastatic disease
- Measurable disease by RECIST v1.1
- ECOG performance status 0 or 1
- Adequate organ and bone marrow function
- CNS metastases permitted, provided stable following local therapy
- HER2+ breast cancer permitted, provided the patient’s disease is refractory to HER2-targeted therapy
- Washout from prior therapy (systemic therapy, RT, surgery): 14 days

Background – Talazoparib

Talazoparib is a highly potent inhibitor of PARP.\(^1\)

Study Design

Objectives

- Primary endpoint: confirmed ORR by central independent radiology facility (IRF) using RECIST v1.1
- Secondary endpoints:
  - DOR, CBR lasting ≥ 24 weeks, PFS, OS
  - Safety

Abbreviations: CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; RT, radiation therapy


### Select Baseline Characteristics

**ITT Population**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>50 (31-74)</td>
<td>52 (33-75)</td>
<td>50 (31-75)</td>
</tr>
<tr>
<td>ECOG = 0, No. (%)</td>
<td>34 (69)</td>
<td>15 (43)</td>
<td>49 (58)</td>
</tr>
<tr>
<td>History of CNS metastasis, No.(%)</td>
<td>8 (16)</td>
<td>1 (2)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Visceral disease, No.(%)</td>
<td>38 (76)</td>
<td>23 (69)</td>
<td>61 (73)</td>
</tr>
<tr>
<td>Hormone receptor status, No.(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2+</td>
<td>1 (2)</td>
<td>5 (14)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>29 (59)</td>
<td>6 (17)</td>
<td>35 (42)</td>
</tr>
<tr>
<td>ER+ or PR+</td>
<td>20 (41)</td>
<td>29 (83)</td>
<td>49 (58)</td>
</tr>
<tr>
<td>BRCA status, No.(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1+</td>
<td>26 (53)</td>
<td>15 (43)</td>
<td>41 (49)</td>
</tr>
<tr>
<td>BRCA2+</td>
<td>22 (45)</td>
<td>20 (57)</td>
<td>42 (50)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>6</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

### Maximal Percent Change in Sum of Diameters of Target Lesions by BRCA Mutation Status

**Cohort 1**

BRCA1+ | BRCA2+ | Unknown/missing

**Cohort 2**

BRCA1+ | BRCA2+ | Unknown/missing

### Maximal Percent Change in Sum of Diameters of Target Lesions by Hormone Receptor Status

**Cohort 1**

TNBC (ER- and PR- and HER2+), Hormone ER/PR positive (ER+ or PR+)

**Cohort 2**

TNBC (ER- and PR- and HER2+), Hormone ER/PR positive (ER+ or PR+)

### Primary Efficacy Endpoint - ORR by Independent Radiologist Facility

**Cohort 1**

Prior Platinum (n = 48)

<table>
<thead>
<tr>
<th>Objective response rate, % (95% CI)</th>
<th>21 (19-35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response, % (No.)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Complete response</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Partial response</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>38 (18)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>38 (18)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

**Cohort 2**

3L+, No Prior Platinum (n = 36)

<table>
<thead>
<tr>
<th>Objective response rate, % (95% CI)</th>
<th>37 (22-55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response, % (No.)</td>
<td>0</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>37 (13)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>51 (18)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

**Total**

<table>
<thead>
<tr>
<th>Objective response rate, % (95% CI)</th>
<th>28 (19-39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response, % (No.)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Partial response</td>
<td>25 (21)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>43 (36)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>27 (22)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>
Safety - Hematologic
All TEAEs in ≥15% of patients and G3+ TEAEs in ≥5% of patients

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 Prior Platinum (n = 48)</th>
<th>Cohort 2 3L+, No Prior Platinum (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients ≥ 1 TEAE, No. (%)</td>
<td>All Grade 3 Grade 4 All Grade 3 Grade 4</td>
<td>All Grade 3 Grade 4</td>
</tr>
<tr>
<td>Anemia</td>
<td>31 (64.4) 23 (47.9) 2 (4.2)</td>
<td>23 (85.7) 15 (42.9) 2 (5.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>18 (37.5) 8 (16.7) 2 (4.2)</td>
<td>9 (25.7) 4 (11.4) 2 (5.7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (20.8) 6 (12.5) 0</td>
<td>12 (34.3) 6 (17.1) 0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7 (14.6) 1 (2.1) 0</td>
<td>6 (17.1) 2 (5.7) 0</td>
</tr>
</tbody>
</table>

No grade 5 TEAEs were observed.

Safety - Nonhematologic
All TEAEs in ≥20% of patients and G3+ TEAEs in ≥5% of patients

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 Prior Platinum (n = 48)</th>
<th>Cohort 2 3L+, No Prior Platinum (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients ≥ 1 TEAE, No. (%)</td>
<td>All Grade 3 Grade 4 All Grade 3 Grade 4</td>
<td>All Grade 3 Grade 4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (86.1) 16 (56.9) 2 (6.7)</td>
<td>8 (22.9) 0 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (69.0) 2 (6.7) 0</td>
<td>15 (42.9) 0 0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (55.4) 1 (2.1) 0</td>
<td>10 (28.6) 0 0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11 (22.9) 1 (2.1) 0</td>
<td>9 (25.7) 0 0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11 (22.9) 1 (2.1) 1 (2.1)</td>
<td>9 (25.7) 2 (5.7) 0</td>
</tr>
<tr>
<td>Alopecia (grade 1)</td>
<td>11 (22.9) 0 0</td>
<td>7 (20.0) 0 0</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (22.9) 0 0</td>
<td>7 (20.0) 0 0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (20.8) 0 0</td>
<td>7 (20.0) 0 0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>4 (8.3) 3 (8.3) 0</td>
<td>4 (11.4) 2 (5.7) 0</td>
</tr>
</tbody>
</table>

No grade 5 TEAEs were observed.

Safety - Hematologic
All TEAEs in ≥15% of patients and G3+ TEAEs in ≥5% of patients

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<thead>
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<td>7 (14.6) 1 (2.1) 0</td>
<td>6 (17.1) 2 (5.7) 0</td>
</tr>
</tbody>
</table>

No grade 5 TEAEs were observed.
Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 300 mg bd (N=205)</th>
<th>Chemotherapy TPC (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median, range)</td>
<td>44 (22-76)</td>
<td>45 (24-68)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>5 (2)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>134 (65)</td>
<td>63 (65)</td>
</tr>
<tr>
<td>BRCA mutation status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>117 (57)</td>
<td>51 (53)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>84 (41)</td>
<td>46 (47)</td>
</tr>
<tr>
<td>Both</td>
<td>4 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Hormonal receptor status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ and/or PR+ TNBC</td>
<td>103 (50)</td>
<td>49 (51)</td>
</tr>
<tr>
<td></td>
<td>102 (50)</td>
<td>48 (49)</td>
</tr>
<tr>
<td>Prior chemotherapy for metastasis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>146 (71)</td>
<td>69 (71)</td>
</tr>
<tr>
<td>Prior platinum treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 (29)</td>
<td>26 (27)</td>
</tr>
</tbody>
</table>

Primary endpoint: progression-free survival by BICR

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 300 mg bd</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression/death, n (%)</td>
<td>163 (79.5)</td>
<td>71 (73.2)</td>
</tr>
<tr>
<td>HR</td>
<td>0.58</td>
<td>4.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.43 to 0.80</td>
<td>0.38 to 0.53</td>
</tr>
</tbody>
</table>

Objective response by BICR

<table>
<thead>
<tr>
<th></th>
<th>Olaparib 300 mg bd</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>60%</td>
<td>29%</td>
</tr>
<tr>
<td>Complete response</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Median time to response, days</td>
<td>6.2 (4.6-7.2)</td>
<td>7.1 (2.9-12.2)</td>
</tr>
<tr>
<td>Median duration of response, months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Subgroup analyses: PFS by BICR

- **ER+ and/or PR+**
  - Olaparib
    - Progression or death:
      - 82 (79.6%)
      - 31 (93.3%)
      - HR: 0.82
      - 95% CI: 0.55 to 1.26
  - TPC
    - Progression or death:
      - 81 (79.4%)
      - 49 (83.3%)
      - HR: 0.83
      - 95% CI: 0.52 to 1.33

- **TNBC**
  - Olaparib
    - Progression or death:
      - 50 (83.3%)
      - 21 (80.6%)
      - HR: 0.67
      - 95% CI: 0.41 to 1.14
  - TPC
    - Progression or death:
      - 113 (77.9%)
      - 50 (70.6%)
      - HR: 0.80
      - 95% CI: 0.40 to 0.84

Safety summary: adverse events and exposure

- **n (%)**
- **Olaparib 300 mg bid (N=205)**
- **Chemotherapy TPC (N=91)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Olaparib 300 mg bid</th>
<th>Chemotherapy TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1–2</td>
<td>124 (60.5)</td>
<td>42 (46.2)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>75 (36.6)</td>
<td>46 (50.5)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.5)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>AEs leading to drug discontinuations</td>
<td>10 (4.9)</td>
<td>7 (7.7)</td>
</tr>
<tr>
<td>AEs leading to dose reductions</td>
<td>52 (25.4)</td>
<td>28 (30.8)</td>
</tr>
<tr>
<td>AEs leading to dose interruptions/delay</td>
<td>72 (35.1)</td>
<td>25 (27.5)</td>
</tr>
<tr>
<td>Median duration of treatment, months</td>
<td>8.2 (0.5–28.7)</td>
<td>3.4 (0.7–23.3)</td>
</tr>
</tbody>
</table>

Adverse events (any grade) in ≥15% of patients

- **Nausea**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)

- **Anorexia**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)

- **Vomiting**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)

- **Fatigue**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)

- **Nausea**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)

- **Anemia**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)

- **Constitutional**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)

- **Hematologic**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)

- **Nonhematologic**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)

- **Other**
  - Olaparib 300 mg bid (N=205)
  - Chemotherapy TPC (N=91)
Conclusions

- Olaparib tablet monotherapy provided a statistically significant and clinically meaningful PFS benefit versus standard-of-care chemotherapy for patients with HER2-negative metastatic breast cancer and a gBRCAm.
- Olaparib was generally well tolerated with <5% discontinuing treatment for toxicity and a lower rate of Grade ≥3 AEs compared with chemotherapy.
- OlympiAD is the first Phase III study in metastatic breast cancer patients demonstrating benefit for a PARP inhibitor over an active comparator.
2 hit hypothesis

**BRCA1/2 germline mutations lead to increased ovarian cancer risk**

**BRCA1/2 somatic mutations are restricted to the neoplastic cells and may drive ovarian tumorigenesis in individuals without a germline mutation**
BeSHG guidelines for HBOC testing

- Woman with breast cancer and one or more of the following:
  - diagnosed ≤ 35 yrs
  - diagnosed ≤ 40 yrs and one relative with bilateral or ovarian, or breast ≤ 50, or male breast cancer
  - bilateral breast cancer and both diagnosed ≤ 50 yrs
  - ovarian cancer, any age
  - triple negative breast cancer ≤ 50 yrs
  - three individuals with breast cancer, one is a first degree relative (FDR) of the other two (excluding male transmitters) and one diagnosed ≥ 50 years
  - individual with breast cancer and higher frequency of specific mutations (e.g. 6th characteristic allele for founder mutation testing)
  - other family situations (e.g. multiple pancreatic cancer) with a prior chance of mutation ≤ 14% according to BRCAPRO or >2 FDR male or female carriers
  - test more than one affected relative of a certain positive after excluding the8nier or case at a phenocopy

- Woman with high grade serous or papillary epithelial ovarian cancer at any age (excludes borderline, low grade and mucinous ovarian cancer)

- Male with breast cancer

- Individual with pancreatic cancer at any age with ≥ 2 FDR excluding male transmitters with breast where one diagnosed

- Family history
  - first degree unaffected relative of any of the above on a case by case basis
  - testing of unaffected family members should only be considered when no affected family member is available and then the unaffected family member with the highest probability of mutation should be tested
tBRCA testing - workflow

1. >20% tumor cells
   Time between resection and fixation: <1h
   Fixation time: 6-72h

2. 4-6 slides 10 µM

3. DNA

4. tumor region: 5x5 mm

5. Multiplex PCR

6. Library preparation

7. sequencing

8. data analysis

9. report

FFPE: caveats

1. Fragmentation of DNA

2. artificial C>G > T>A SNVs

3. Cytosine deamination

4. ONA repair

5. UDG repair
Genetic architecture of HBOC

Missing heritability in complex diseases

There is more to repair than BRCA1/2
Homologous recombination deficiency

Not HR deficient

HR deficient

Variant classification

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Type of variant (source of DNA)</th>
<th>Classification recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer risk assessment of a person + relatives; PGD/PND</td>
<td>Germline (blood)</td>
<td>5-tier IARC/ACMG (1)</td>
</tr>
<tr>
<td>Clinical actionability: diagnosis, prognosis, treatment</td>
<td>Somatic (tumor)</td>
<td>5-tier (2, 3, 4) vs. 4-tier (5)</td>
</tr>
</tbody>
</table>

Variant classification – genetics: 5 classes

- **Class 5**
  - Predicted to be pathogenic; this result therefore confirms the diagnosis
  - Predictive testing
  - Prenatal testing
  - PGD

- **Class 4**
  - Likely pathogenic; consistent with the diagnosis

- **Class 3**
  - Uncertain pathogenicity; does not confirm or exclude diagnosis
  - Unsure about the pathogenicity and offer further work before offering further diagnostic or cancer testing

- **Class 2**
  - Likely to be pathogenic; diagnosis not confirmed molecularly
  - No evidence suggesting pathogenicity but not at a high enough frequency to say it's not pathogenic?

- **Class 1**
  - Not pathogenic
  - "Common" polymorphism
  - No evidence suggesting pathogenicity and at "high" frequency

Classes 3, 4, 5 are reported

Variant classification – precision medicine: 4 tier system

Tier I: Variants of Strong Clinical Significance (hereditary, prognostic & diagnostic)

Tier II: Variants of Potential Clinical Significance (therapeutic, prophylactic & diagnostic)

Tier III: Variants of Unknown Clinical Significance

Tier IV: Benign or Likely Benign Variants

Tiers I to III must be reported; it is NOT recommended to include tier IV variants/alterations in the report

Statistical and Genetic Methods for the Characterization and Reporting of Variants in Cancer

Variant classification - precision medicine: 4 tier system

Tier I: Variants of Strong Clinical Significance (hereditary, prognostic & diagnostic)

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Tier III: Variants of Unknown Clinical Significance

Tier IV: Benign or Likely Benign Variants

Tiers I to III must be reported; it is NOT recommended to include tier IV variants/alterations in the report
Variant classification – precision medicine: 5 tier system

<table>
<thead>
<tr>
<th>Classification methods for somatic cancer variants</th>
<th>BWH/OFIC method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1. Clinically actionable for therapeutic,</td>
<td></td>
</tr>
<tr>
<td>prognostic, or diagnostic purposes for same</td>
<td></td>
</tr>
<tr>
<td>tumor type</td>
<td></td>
</tr>
<tr>
<td>Class 2. Limited evidence of therapeutic,</td>
<td></td>
</tr>
<tr>
<td>prognostic, or diagnostic implications for same</td>
<td></td>
</tr>
<tr>
<td>tumor type</td>
<td></td>
</tr>
<tr>
<td>Class 3. Clinical evidence of therapeutic response</td>
<td></td>
</tr>
<tr>
<td>from another tumor type</td>
<td></td>
</tr>
<tr>
<td>Class 4. Preclinical association to therapeutic</td>
<td></td>
</tr>
<tr>
<td>response</td>
<td></td>
</tr>
<tr>
<td>Class 5. Established as benign</td>
<td></td>
</tr>
</tbody>
</table>

BWH/OFIC = Brigham Women's Institute/Draper-Harriet Cancer Institute

Haskins et al., Current Opinion in Genetics and Development, 2017

Tumor first? Germline first?

- Discuss advantages and disadvantages

Illustrative examples
KORAK NAPREJ
pri zdravljenju
onkoloških bolnikov.
HBOC – germline/somatic genetic testing – laboratory experiences (latest updates)

Srdjan Novaković

Hereditary breast and ovarian cancer - HBOC

- Five to ten percent of all breast/ovarian cancers (HBOC) are inherited, primarily due to mutations in BRCA1 or BRCA2 genes.
- The rest of HBOC hereditary cancers are a result of mutations in other genes such as TP53, STK11, PTEN, CDH1, MSH2, MLH1, MSH6, PMS2, EPCAM, CHEK2, PALB2, ATM, RAD51c, BLM, BRIP1, RAD51D, NBN, NF1, BARD1, MRE11A, XRCC2, ABRAXAS, CYP1A1, CYP17, GSTP or others.

BRCA1 and BRCA2

Since the identification and cloning of BRCA1/2 genes, according to ClinVar data base, more than 5000 different pathogenic or likely pathogenic mutations have been discovered, most of them in only one or few families.
Results of BRCA1/2 mutation screening 1999 - december 2016

3071 tested individuals from 2095 Slovene breast and/or ovarian cancer families

Ratio of healthy and diseased probands among the first tested family members

- 452 BRCA1/2 positive families
  - BRCA1 – 318
  - BRCA2 – 134

Mutation detection rate: 21.6% (452/2095)
94 different deleterious mutations:

43 in BRCA1:
- Missense mutations affecting the 5'RING domain
- Nonsense mutations
- Frame-shift mutations
- Deletions of whole exons
- Splice site mutations

51 in BRCA2:
- Missense mutations
- Nonsense mutations
- Frame-shift mutations

The most common mutation found in the BRCA1 gene was missense mutation c.181T > G (p.Cys61Gly). It was detected in 82 families.

The most common mutation in the BRCA2 gene was a splice site mutation c.7806-2A > G. It was detected in 33 families.

Novel mutations - pathogenic variants in BRCA1 and BRCA2

In the period from 1999 to 2016

New BRCAl and BRCA2 mutations

Novel BRCA1 and BRCA2 mutations

% patients harbouring VUS in BRCA1 and BRCA2

% novel BRCA1 and BRCA2 VUS
NGS - genes tested in breast and ovarian cancer patients in 2015 - 2016

NGS panel 2015:
ATM, BRCA1, BRCA2, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, STK11, TP53

NGS panel 2016:
ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTPN11, RAD51C, RAD51D, STK11, TP53

Number of patients with different mutations detected with NGS in 2015 - 2016

<table>
<thead>
<tr>
<th>GENE</th>
<th>No. of patients with mutation</th>
<th>%</th>
<th>No. of different mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>16</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>BRCA1</td>
<td>30</td>
<td>75.17%</td>
<td>28</td>
</tr>
<tr>
<td>BRCA2</td>
<td>20</td>
<td>70.83%</td>
<td>16</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>56</td>
<td>100%</td>
<td>44</td>
</tr>
</tbody>
</table>

* In a single patient, mutations in both BRCA1 and BRCA2 were detected simultaneously.

Reported incidental findings

<table>
<thead>
<tr>
<th>GENE</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>CDH1</th>
<th>CHEK2</th>
<th>EPCAM</th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
<th>NBN</th>
<th>PALB2</th>
<th>PMS2</th>
<th>PTPN11</th>
<th>RAD51C</th>
<th>RAD51D</th>
<th>STK11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inc</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>14</td>
<td>11</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Distribution of mutations detected with NGS in breast and ovarian cancer patients in 2015 - 2016

Mutation detection rate in 2015 - 2016: 28.70%

Conclusion

Even though the testing focus in HBOC families is on detection of BRCA mutations, other highly penetrant, but less frequently mutated genes, have been recommended for testing.

Genetic testing of BRCA genes provides the key to:
- Accurate cancer risk assessment
- Effective genetic counseling
- Appropriate medical follow-up
- Appropriate treatment
  - DNA quality from FFPE tissue is a major obstacle
  - Improve analysis and interpretation by:
    - Running in duplicate
    - Being careful with assay design and minimum coverage
  - Additional steps (e.g., Uracil-DNA Glycosylase (UDG) treatment) can help minimise deamination artefacts
Cancer genetic counselling – new clinical pathways in view of treatment options
Ana Iliatnik, Mateja Kraje, Ksenija Strojnik

HBOC at the Institute of Oncology
• 1999 - genetic testing for BRCA genes available - in collaboration with Vrije Universiteit Brussel
• 2008 - all tests performed at the Institute of Oncology Ljubljana, state insurance covers the costs of counseling and testing when indicated
• 2010 – management of individuals at high risk for breast/ovarian cancer at our institution
• 2011 – clinical pathways established
• 2014/2015 – genetic testing performed using an NGS based approach (multi-gene panel)
• 2014 – priority assessment for therapeutical purposes introduced
Olaparib as a game changer!

PARP inhibitor olaparib approved for BRCA mutation carriers as maintenance therapy in recurrent platinum sensitive OC in October 2014 we started offering BRCA tests to all ovarian cancer, fallopian tube and primary peritoneal serous carcinoma patients with high grade serous histology need for fast-tracking - how to manage the additional workload?

Increase in number of counselling sessions

1999-2017:
- ~900 BRCA positive families
- ~additional 2-3 family members tested from each family
- loose testing criteria, yet a high mutation detection rate!
Simplifying the clinical pathway

Referral by the treating physician (usually a medical oncologist)

Patient contacts the cancer genetic clinic for appointment within 1-2 months, family data verification unnecessary.

Post-test counselling, discussion of findings and cancer prevention strategies appropriate for the patient.

Pre-test counselling – testing done with an NGS panel – possibility of secondary findings and VUS.

Genetic testing (with a HBOC core panel) – results within 1-2 months, sooner if necessary.

Genetic testing made available to relatives if indicated.

BRCA mutation detection rate

<table>
<thead>
<tr>
<th>Mutation status</th>
<th>No of pts (258)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None identified</td>
<td>150</td>
<td>58.1%</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>93</td>
<td>36.0%</td>
</tr>
<tr>
<td>other*</td>
<td>15</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

BRCA1 (n=71), BRCA2 (n=22).

Other findings

<table>
<thead>
<tr>
<th>Mutation identified</th>
<th>No of pts (258)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>150</td>
<td>58.1%</td>
</tr>
<tr>
<td>BRCA1/2</td>
<td>93</td>
<td>36.0%</td>
</tr>
<tr>
<td>other*</td>
<td>15</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

*Other gene mutations identified from the panel:

- ATM
- RAD51C
- RAD51D
- MUTYH
- CHECK2
- MSH2
- PALB2
- CDH1
- STK11

Attendance rate

- 13% no contact (39 pts)
- 0.7% declined testing (2 pts)
Mutation detection rate depending on family history

- **Positive family history:** 165 pts (64%)
  - BRCA 1/2 mutation detection rate: 44.8% (74/165 pts)

- **Negative family history:** 93 pts (36%)
  - BRCA 1/2 mutation detection rate: 18.3% (17/93 pts)

Conclusions

- Testing all high-grade serous OC yielded an unusually high mutation detection rate – a higher prevalence of mutation carriers in the Slovene population or a selection bias?
- Panel testing (VUS, secondary findings, mutations in OC genes with no therapeutic implications)
- Adopting a modified strategy of germline testing with patients attending a cancer genetics clinic feasible for OC, but with breast cancer...
- Tumor tissue genetic testing – pros and cons (detecting somatic mutations vs more limited panels)?
- Testing for defective homologous repair?

Mutation rate in patients tested when diagnosed with ovarian cancer

- BRCA 1/2 mutation detection rate in 134 pts tested at the time of OC diagnosis
  - Excluding patients with recurrent OC or a long disease-free interval
  - 33.6% (45/134 pts)
Slovenian experiences with olaparib in ovarian cancer treatment

Maja Ravnik, Erik Škof
What's new in the management of BRCA positive ovarian and breast cancer patients - 2nd conference
19th of October 2017

Ovarian cancer: Slovenija

- Study 19
  - showed 7 months PFS benefit of maintenance therapy with olaparib in patients with relapsed BRCA+ ovarian cancer.
  - Olaparib prolonged overall survival for 4.7 months compared to placebo (the difference was not statistically significant).
  - EMA approval of olaparib for relapsed BRCA+ ovarian cancer on 16/12/2014
  - Since 5th of February 2016 olaparib therapy is reimbursed by ZZZS (Health Insurance Institute of Slovenia) for patients with relapsed BRCA+ ovarian cancer in Slovenia

Ovarian cancer: Slovenija

- Incidence - 177*
- Median age - 60 years
- Stage of disease:
  - 75% advanced (FIGO IIIC/IV)
- Histology
  - "High-grade" serous (75%)
- Frequent relapses (80%)
- 5 y OS in SLO 43%*

* Cancer in Slovenia 2013
Olaparib experience in Slovenija

- Systemic therapy is applied in two institutions:
  - Institute of Oncology Ljubljana
  - University Medical centre Maribor
- No clinical trial with olaparib in Slovenia
- First 2 pts received olaparib through „Early-access programme“ in November 2015.
- Label for olaparib is the same as in Study 19.

Overall 48 pts recieved therapy with olaparib
- At the moment: 25 pts on treatment
- Duration of th: range 1-23 months (median 5 months)
- AE – mild nausea, fatigue, anemia (G1)
- 12 pts. had progression of the disease
- 4 pts SAE – G3 anemia
  - 2pts continue th with reduced dose (50% dose)
  - 2 pts declined th without evidence of AE

Ovarian cancer: Slovenija

- Current recommendations:
  - The „need for speed“ of gBRCA testing results:
    - Medical oncologist
    - Geneticist
    - Molecular lab.
    - Medical oncologist
    - Therapy with olaparib
  - Waiting list for genetic counseling
    - „Highest priority“ patient with relapsed HGS ovarian cancer
    - „High priority“ patient with HGS of diagnosis

Near future – upfront tBRCA* testing?
- Faster results
- Complete results – tBRCA = sBRCA+gBRCA
- No need for genetic counselling in majority (pts. and relatives)

BRCA* – BRCA mutation in Luminal HGS

BRCA1 – high-grade serous

Median age - 60 years
- BRCA 1 – 56 years
- BRCA 2 – 63 years
- BRCA 1 – 70%
Olaparib experience in Slovenija
(data from Institute of Oncology Ljubljana)

Number of patients prior to first line therapy

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Olaparib experience in Slovenija
(data from Institute of Oncology Ljubljana)

Adverse events of olaparib:

- Nausea
  - usually first month (metoclopramide p.o.)
- Fatigue
  - in majority first month (KT)
- Anemia
  - in majority G1 (no transfusion needed)
  - G3 (Hb < 50 g/l) - 4 patients

<table>
<thead>
<tr>
<th>Phase</th>
<th>Cycles</th>
<th>Patients</th>
<th>Total Doses</th>
<th>Cumulative Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>6</td>
<td>4</td>
<td>24.5</td>
<td>49%</td>
</tr>
<tr>
<td>G2</td>
<td>6</td>
<td>4</td>
<td>24.5</td>
<td>49%</td>
</tr>
<tr>
<td>G3</td>
<td>0</td>
<td>1</td>
<td>7.0</td>
<td>57%</td>
</tr>
<tr>
<td>G4</td>
<td>0</td>
<td>1</td>
<td>7.0</td>
<td>57%</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>10</td>
<td>162.0</td>
<td>162.0</td>
</tr>
</tbody>
</table>

2 patients continue with dose reduction (50%) - G1 anemia - old on therapy
1 patient with dose reduction (50%) had disease progression - end of therapy
1 patient despite dose reduction (50%) transient G3 anemia - end of therapy due to SAE

Genetic counseling – information for patients

1/71 patients with 1. relapse are still on therapy
SAE - G3 anemia (discontinue dose reduction)

UKC:

UKC:

UKC:

UKC:

UKC:
PARP inhibitors in breast cancer – current and future perspectives in Slovenia
Simona Borštnar
Division of Medical Oncology
Institute of oncology Ljubljana

Clinical Breast Cancer Subsets Defined by IHC in metastatic disease

Questions

- What is the proportion of metastatic breast cancer patients suitable for treatment with PARP inhibitors?
- What is current approach in the treatment of BRCA mutation carriers?
- When PARP inhibitors will be available for the treatment of patients with breast cancer in Slovenia?
- Are we ready to use PARP inhibitors in breast cancer?

Overall survival of patients with metastatic breast cancer (2008–2013)

<table>
<thead>
<tr>
<th>Breast cancer subtype</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+/HER2- (n = 4926)</td>
<td>43.7</td>
<td>42.0</td>
<td>40.9</td>
<td>42.0</td>
<td>44.5</td>
<td>40.3</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(40.2–46.6)</td>
<td>(38.9–44.6)</td>
<td>(38.0–43.4)</td>
<td>(39.2–45.04)</td>
<td>(41.0–47.3)</td>
<td>(37.8–NR)</td>
</tr>
<tr>
<td>HR+/HER2+ (n = 2861)</td>
<td>38.7</td>
<td>42.3</td>
<td>40.1</td>
<td>42.3</td>
<td>50.5</td>
<td>MedNR</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(33.6–44.6)</td>
<td>(38.3–50.8)</td>
<td>(35.2–45.6)</td>
<td>(36.5–49.8)</td>
<td>(46.5–NR)</td>
<td>MedNR</td>
</tr>
<tr>
<td>HR-/HER2- (n = 2317)</td>
<td>13.3</td>
<td>14.9</td>
<td>13.9</td>
<td>13.9</td>
<td>14.1</td>
<td>14.1</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(11.0–16.6)</td>
<td>(11.2–17.0)</td>
<td>(10.2–17.0)</td>
<td>(11.4–15.9)</td>
<td>(11.4–25.9)</td>
<td>(12.5–15.5)</td>
</tr>
</tbody>
</table>

HR, hormone receptor; NR = not reached. Delaloge S, et al. ASCO 2017 (Abstract 1074).
Estimated number of metastatic breast cancer (mBC) patients according to different subtypes in Slovenia

- ER+/HER2- >250
- HER2 positive mBC
- TNBC <5

5-10% mBC pts are BRCA 1/2 positive

N=30**

Estimated number of new mBC per year: primary metastatic (N = 90) and secondary metastatic (N = 300-320)

** estimated number of BRCA positive mBC per year

Current treatment in BRCA positive breast cancer patients

- Traditionally, BRCA carriers have received conventional systemic chemotherapy based on their baseline tumor characteristics.
- Tumors arising in patients with BRCA mutations were shown to be particularly sensitive to platinum compounds or inhibitors of PARPs.
- BRCA1-mutation carriers seem to benefit from anthracycline-taxane-containing regimens as much as sporadic triple-negative breast cancers do.


Characteristics of TNBC

- Most TNBC are invasive ductal, minority represent medullary, metaplastic or adenoid cystic carcinoma.
- By gene expression profiling TNBC are classified in two basal-like (BL1 and BL2), immunomodulatory (IM) and luminal androgen receptor (LAR) subtype.
- Distant metastatic recurrences tend to occur within the first 2 to 5 years after diagnosis, late recurrences are rare.

BRCA 1/2 mutation carriers = 30% (N = 20]

50-80% of all BRCA 1 and 30-50% of all BRCA 2 mutation carriers

Narod SA. Nat Rev Clin Oncol 2010

Clinical studies with PARPs in BRCA1/2 positive advanced breast cancer

- OlympiAD
- BROCADE
- NCT02163694
- EMBRACA
- ABRAXO
- BRAVO
- NCT00664781

Livraghi L and Garber JE. MC Medicine 2015: 13:188
When PARP inhibitors will be available for the treatment of patients with breast cancer in Slovenia?

- Expected approval by FDA:
  - Few months?

- Expected approval by EMA:
  - March 2018?

- Reimbursement by national health insurance company (ZZS):
  - 2019?

- Compassionate use program in 2018?

Are we ready to use PARP inhibitors for breast cancer in Slovenia?

Genetic testing is available to all breast cancer patients who meet the criteria:
- A family member with BRCA mutation
- Diagnosis of BC under the age of 45
- Diagnosis of TNBC under the age of 60
- Diagnosis of two separate breast cancers (one of which was diagnosed under the age of 50)
- Diagnosis of breast cancer and ovarian cancer in same person
- Diagnosis of ovarian cancer
- Man with breast cancer
- One or more close blood relatives with breast cancer that was diagnosed under the age of 50

It is very likely that we will have information about the BRCA mutation in majority of patients at the time of relapse.
Surgical treatment of BRCA positive breast cancer patients – current practice and Slovenian results

Janez Zgajnar
Institute of Oncology Ljubljana

Strategies in BRCA1/2 mutation carriers

- Intensive follow up
- Chemoprevention – (tamoxifen)
- Prophylactic surgery
  - Oophorectomy
  - Mastectomy

All data presented are unpublished
---

**Table 2. Reported Rates of Uptake of RRS in the BRCA-Positive Population in Current Literature**

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Sample size</th>
<th>% RRSO</th>
<th>% Surveillance</th>
<th>% RAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uyey et al.</td>
<td>2006</td>
<td>37</td>
<td>24</td>
<td>57</td>
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<tr>
<td>Kiyler et al.</td>
<td>2006</td>
<td>43</td>
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<td>NRI</td>
<td>78</td>
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<tr>
<td>Frieb et al.</td>
<td>2007</td>
<td>537</td>
<td>23</td>
<td>38</td>
<td>55</td>
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<tr>
<td>Metcalfe et al.</td>
<td>2008</td>
<td>1,383</td>
<td>NA</td>
<td>49</td>
<td></td>
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<tr>
<td>Bauc et al.</td>
<td>2009</td>
<td>272</td>
<td>23</td>
<td>NRI</td>
<td>51</td>
</tr>
<tr>
<td>Kwong et al.</td>
<td>2010</td>
<td>31</td>
<td>18</td>
<td>NRI</td>
<td>19</td>
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<tr>
<td>Slyde et al.</td>
<td>2010</td>
<td>306</td>
<td>50</td>
<td>NRI</td>
<td>75</td>
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<tr>
<td>Schwartz et al.</td>
<td>2012</td>
<td>144</td>
<td>37</td>
<td>NRI</td>
<td>65</td>
</tr>
<tr>
<td>Garcia et al.</td>
<td>2013</td>
<td>305</td>
<td>44</td>
<td>NRI</td>
<td>74</td>
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<tr>
<td>Fippo et al.</td>
<td>2014</td>
<td>87</td>
<td>44</td>
<td>41</td>
<td>46</td>
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</table>

**Note:** RR, risk-reducing surgery; NRI, risk-reducing induction; RAM, risk-reducing mastectomy.

---
RESULTS OF THE INSTITUTE OF ONCOLOGY LJUBLJANA

- Evaluate the uptake of the risk reducing surgery in BRCA 1 and BRCA 2 mutation carriers in Slovenia
- Analyze the breast reconstruction rate in patients with risk reducing mastectomy
- Comparison of two periods
  - Until end of 2015
  - Year 2016

PATIENTS INCLUDED

- FEMALE, BRCA 1 AND BRCA 2 MUTATION POSITIVE
- DATA AVAILABLE
- NO CANCER HISTORY (n=174)
  OR
- BREAST CANCER AT ANY TIME (n=232)
- PATIENTS WITH OTHER CANCER TYPES WERE EXCLUDED

PATIENTS INCLUDED

- FEMALE, BRCA 1 AND BRCA 2 MUTATION POSITIVE
- DATA AVAILABLE
- NO CANCER HISTORY (n=174)
  OR
- BREAST CANCER AT ANY TIME (n=232)
- PATIENTS WITH OTHER CANCER TYPES WERE EXCLUDED
PATIENTS WITH BREAST CANCER

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>232</td>
<td>100</td>
</tr>
</tbody>
</table>

NO RR SURGERY

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>35</td>
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RROO

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>35</td>
<td>15</td>
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RRM

<table>
<thead>
<tr>
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<th>%</th>
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</thead>
<tbody>
<tr>
<td>33</td>
<td>14</td>
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RROOM

<table>
<thead>
<tr>
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<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>83</td>
<td>36</td>
</tr>
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</table>

RRM 116/232 - 50%

~ 65% RISK REDUCING SURGERY

PATIENTS WITH BC

<table>
<thead>
<tr>
<th>BREAST RECONSTRUCTION TYPE</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIEP</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>COMBINATION</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>RROOM</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>RROO</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>NO RR SURGERY</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

PATIENTS WITHOUT ANY CANCER

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>174</td>
<td>100</td>
</tr>
</tbody>
</table>

NO RR SURGERY

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>57</td>
</tr>
</tbody>
</table>

RROO

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>21</td>
</tr>
</tbody>
</table>

RRM

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>6</td>
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RROOM

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>16</td>
</tr>
</tbody>
</table>

RRM 38/174 - 22%

22/38 - 2013-15

~ 40% RISK REDUCING SURGERY

PATIENTS WITHOUT ANY CANCER

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>100</td>
</tr>
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</table>

NO RECONSTRUCTION

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
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<tbody>
<tr>
<td>7</td>
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IMPLANT

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>58</td>
</tr>
</tbody>
</table>

DIEP

<table>
<thead>
<tr>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>24</td>
</tr>
</tbody>
</table>

BREAST RECONSTRUCTION TYPE

<table>
<thead>
<tr>
<th>BREAST RECONSTRUCTION TYPE</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPLANT</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>DIEP</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

~ 80% BREAST RECONSTRUCTION RATE

~ 80% BREAST RECONSTRUCTION RATE
PATIENTS INCLUDED

- 102 patients
- NO CANCER HISTORY (n=52)
  OR
- BREAST CANCER AT ANY TIME (n=50)
- EXCLUDED 97 carriers
  - 26 male patients
  - 39 ovarian cancer patients
  - 7 Bilateral BC patients
  - 22 missing data
  - 4 others

Risk reducing surgery of any type

RRM

- 72% patients with breast cancer
- 15% patients without breast cancer

RROO

- 78% patients with breast cancer
- 33% patients without breast cancer

- 22/35 age > 40
Breast Reconstruction rate

- Patients with BC
  - 33/36 92%
- Patients without BC
  - 8/52 15%

Conclusion

- Patients with a history of BC have a higher uptake of risk reducing surgeries compared to patients without cancer
- The overall risk reducing surgery uptake is becoming higher
- Patients at hereditary risk performing PM have a higher rate of immediate breast reconstruction compared to patients with sporadic BC

Comparison

<table>
<thead>
<tr>
<th></th>
<th>until 2015</th>
<th>2016</th>
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<tbody>
<tr>
<td>any RRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with BC</td>
<td>65%</td>
<td>92%</td>
</tr>
<tr>
<td>without BC</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>RRM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with BC</td>
<td>50%</td>
<td>72%</td>
</tr>
<tr>
<td>without BC</td>
<td>22%</td>
<td>15%</td>
</tr>
<tr>
<td>RROO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with BC</td>
<td>51%</td>
<td>78%</td>
</tr>
<tr>
<td>without BC</td>
<td>37%</td>
<td>33%</td>
</tr>
</tbody>
</table>
Za boljše življenje.
Že vse od 1896.

Tradicija napredka znanosti in medicine. Včeraj, danes in jutri.