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Young early breast cancer patient with PALB2 mutation
None
Young BC patient with PALB2 germline mutation

- BC patient:
- diagnosed at age of 27
- CNB of the right breast was done
  - HP ductal invasive carcinoma, GR2
- clinically she was staged as T1N0M0

- 10.08.2009. subcutaneous mastectomy with primary reconstruction of the right breast was done with SLNB of the right axila due to the multifocality on MRI of breasts.

- HP: invasive ductal carcinoma, grade 2, 4 TU:
  - TU1-10x8mm, T2-7x7mm, TU3-5x3mm, TU4-1x1mm;
  - Inn 0/3
  - IHC was done on TU1:
    - ER 6(60%), PR 7(50%), HER2:1+, Ki-67 45%
Young BC patient with PALB2 germline mutation

- Adjuvant therapy:
  - chemotherapy FAC 6 cycles up to JAN 2010.
  - continued with hormonotherapy:
  - LHRH analog plus tamoxifen for 5 years up to JAN 2015.
Q 1

Is this optimal therapy today?
-the risk of relapse-
Optimal adjuvant therapy

| Age at diagnosis | – | 27 | + |
| Age must be between 25 and 85 |

| Post Menopausal? | Yes | No | Unknown |
| Tumour size (mm) | – | 10 | + |
| Tumour grade | 1 | 2 | 3 |
| Detected by | Screening | Symptoms | Unknown |
| Positive nodes | – | 0 | + |
| Micrometastases only | Yes | No | Unknown |

Positive means more than 10%
Optimal adjuvant therapy

**Treatment Options**

- **Hormone Therapy**
  - No
  - Yes
  - Hormone (endocrine) therapy
  - Available when ER-status is positive

- **Chemotherapy**
  - None
  - 2nd gen
  - 3rd gen

- **Trastuzumab**
  - No
  - Yes
  - Available with chemotherapy when HER2 status is positive

- **Bisphosphonates**
  - No
  - Yes
  - Available for post-menopausal women

**Results**

These results are for women who have already had surgery. This display shows the outcomes for 100 women based on the inputs and treatments you have selected.

- 5 years after surgery: 2 extra survivors due to chemotherapy
- 10 years after surgery: 5 extra survivors due to hormone therapy
- 15 years after surgery: 83 survivors with surgery alone

- 1 death due to other causes
- 9 breast cancer related deaths
## Optimal adjuvant therapy

### Treatment Options

<table>
<thead>
<tr>
<th>Option</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definition</td>
<td>Hormone (endocrine) therapy Available when ER-status is positive</td>
<td></td>
</tr>
<tr>
<td>Available</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definition</td>
<td>None 2nd gen 3rd gen</td>
<td></td>
</tr>
<tr>
<td>Available</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trastuzumab</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definition</td>
<td>No Yes</td>
<td></td>
</tr>
<tr>
<td>Available</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bisphosphonates</strong></td>
<td>No Yes</td>
<td></td>
</tr>
<tr>
<td>Definition</td>
<td>Available for post-menopausal women</td>
<td></td>
</tr>
</tbody>
</table>

### Results

These results are for women who have already had surgery. This display shows the outcomes for 100 women based on the inputs and treatments you have selected.

- 5 10 15 years after surgery.

- 1 death due to other causes
- 7 breast cancer related deaths
- 4 extra survivors due to chemotherapy
- 5 extra survivors due to hormone therapy
- 83 survivors with surgery alone
Family history

- GF
- GM
- UNCLE
- Father
- Brother
- PATIENT
- Sister
- AUNT
- GM
- Lung Ca at age 65
- Mother
- Breast cancer at age 44
- Breast cancer at age 27
Young BC patient with PALB2 germline mutation

- DEC 2015 blood sample was taken
- JAN 2017 Next generation sequencing on germline DNA blood sample was done
  - PALB2 germline mutation was detected
PALB2 biallelic germline loss-of-function mutations cause Fanconi’s anemia,
- PALB2 monoallelic loss-of-function mutations are associated with an increased risk of breast cancer and pancreatic cancer.
- PALB2 is critical for the function of BRCA2 in DNA repair and tumor suppression.
- It was also shown to interact with BRCA1.
- PALB2 loss-of-function mutations have now been observed in **0.6 to 3.9% of families with a history of breast cancer**, depending on the population.
Q2

What is her risk of relapse, second primary BC and secondary malignancies?
Optimal follow up?
Breast-Cancer Risk in Families with Mutations in PALB2

- Analyzed the risk of breast cancer among 362 members of 154 families who had deleterious mutations in PALB2 (311 W with PALB2 mutations, of whom 229 had BC, and 51 M with PALB2 mutations, of whom 7 had BC).

- The estimated cumulative risk of breast cancer among female mutation carriers was:
  - 14% (95% CI, 9 to 20) by 50 years of age and
  - 35% (95% CI, 26 to 46) by 70 years of age.

- The absolute breast-cancer risk for PALB2 female mutation carriers by 70 years of age ranged from 33% (95% CI, 25 to 44) for those with no family history of breast cancer to 58% (95% CI, 50 to 66) for those with two or more first-degree relatives with breast cancer at 50 years of age.

NEJM 2014 Antoniou et al.
Breast-Cancer Risk in Families with Mutations in PALB2


Table 1. Breast and Ovarian cancer among Female PALB2 Mutation Carriers and Noncarriers and Untested Females, According to Age at Diagnosis or Data Censoring.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>PALB2 Mutation Carriers</th>
<th>Tested Noncarriers</th>
<th>Untested</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unaffected</td>
<td>Breast Cancer</td>
<td>Ovarian Cancer*</td>
</tr>
<tr>
<td>&lt;20 yr</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20–29 yr</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>30–39 yr</td>
<td>2</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>40–49 yr</td>
<td>15</td>
<td>84</td>
<td>1</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>23</td>
<td>55</td>
<td>4</td>
</tr>
<tr>
<td>60–69 yr</td>
<td>14</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>70–79 yr</td>
<td>12</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>≥80 yr</td>
<td>11</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>229</td>
<td>8</td>
</tr>
</tbody>
</table>

* This category includes all diagnosed cases of ovarian cancer (including those diagnosed after a breast-cancer diagnosis).
17 900 w with BC of whom 12 529 were genotyped successfully.
A PALB2 mutation was present in 116 of 12 529 patients and in 10 of 4702 controls.

10-year survival for women with BC and a PALB2 mutation was 48·0% (95% CI 36·5–63·2), compared with 74·7% (73·5–75·8) for with BC without a mutation (adjusted hazard ratio for death 2·27, 95% CI 1·64–3·15; p<0·0001).
clinical practice guidelines

Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening†

S. Paluch-Shimon¹, F. Cardoso², C. Sessa³, J. Balmana⁴, M. J. Cardoso², F. Gilbert⁵ & E. Senkus⁶, on behalf of the ESMO Guidelines Committee*
Table 1. Prevention and screening strategies for specific mutations

<table>
<thead>
<tr>
<th>PALB2 mutation</th>
<th>Screening</th>
<th>Prevention/risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1) Clinical breast examination every 6–12 months starting from age 20–25 [V]</td>
<td>1) Consider risk-reducing mastectomy</td>
</tr>
<tr>
<td></td>
<td>2) Annual breast MRI from age 20–29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) Annual breast MRI and/or mammogram at age 30–75 [V]</td>
<td></td>
</tr>
</tbody>
</table>

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Footnotes on GENE-5
### BOADICEA

**Computed results for the Target: JM(1)**

#### Mutation carrier probability

<table>
<thead>
<tr>
<th>Age</th>
<th>Contralateral Breast Cancer Risks (Percent)</th>
<th>Ovarian Cancer Risks (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>2.3</td>
<td>0.0</td>
</tr>
<tr>
<td>39</td>
<td>4.8</td>
<td>0.0</td>
</tr>
<tr>
<td>40</td>
<td>7.6</td>
<td>0.0</td>
</tr>
<tr>
<td>41</td>
<td>10.5</td>
<td>0.0</td>
</tr>
<tr>
<td>42</td>
<td>13.5</td>
<td>0.1</td>
</tr>
<tr>
<td>45</td>
<td>23.8</td>
<td>0.1</td>
</tr>
<tr>
<td>47</td>
<td>30.4</td>
<td>0.1</td>
</tr>
<tr>
<td>50</td>
<td>40.0</td>
<td>0.2</td>
</tr>
<tr>
<td>55</td>
<td>51.9</td>
<td>0.3</td>
</tr>
<tr>
<td>60</td>
<td>60.1</td>
<td>0.5</td>
</tr>
<tr>
<td>65</td>
<td>66.3</td>
<td>0.7</td>
</tr>
<tr>
<td>70</td>
<td>70.8</td>
<td>1.0</td>
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<tr>
<td>75</td>
<td>73.6</td>
<td>1.3</td>
</tr>
<tr>
<td>80</td>
<td>75.4</td>
<td>1.7</td>
</tr>
</tbody>
</table>

#### Model Parameters

- **Target Family Member**: JM
- **Mutation Frequencies**: UK
  - BRCA1: 6.394d-4
  - BRCA2: 0.00102
  - PALB2: 0.000575
  - ATM: 0.001921
  - CHEK2: 0.002614
- **Cancer Incidence Rates**
Young BC patient with PALB2 germline mutation

CONSULTATION with tumour board members:

- 16.10.2017. subcutaneous mastectomy of the left breast was done with primary reconstruction in private hospital
- She is on regular follow up and without evidence of relapse.
- She is planning to have family now.
Q3

What fertility preservation options you would recommend at your centre?
On the basis of estimates, the breast-cancer risk for a \textit{PALB2} mutation carrier, even in the absence of a family history of breast cancer, would be classified as high according to various guidelines. This level of risk may justify adding \textit{PALB2} to genetic testing for \textit{BRCA1} and \textit{BRCA2} (Taylor et al JMG 2018, Singer et al EJC 2019).

The information currently available on prognosis of breast cancer in \textit{PALB2} carriers does not seem mature enough to prompt specific prevention and treatment recommendations, particularly with respect to preventive surgery.

Careful breast surveillance should, however, be recommended, using currently available techniques.
Thank you for your attention!