Management of (breast) cancer in young women

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ESMO Board of Directors & NR Committee Chair
EORTC Breast Group Past-Chair
DISCLOSURES

Consultant/Ad Board:

Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, MacroGenics, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Seattle Genetics, Teva
ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3)

Shani Paluch-Shimon a,1, Olivia Pagani b,1, Ann H. Partridge c, Omalkhair Abulkhair d, Maria-João Cardoso e, Rebecca Alexandra Dent f, Karen Gelmon g, Oreste Gentilini h, Nadia Harbeck i, Anita Margulies i, Dror Meirow a, Giancarlo Pruneri j, Elzbieta Senkus m, Tanja Spanic n, Medha Sutliff o, Luzia Travado e, Fedro Peccatori k,2, Fatima Cardoso e,2

Inside Track Conference

3RD ESO-ESMO BReast Cancer in Young Women International Conference

10-12 November 2016 - Lugano, Switzerland

Chair:
O. Pagani, CH

Scientific Committee:
H.A. Azim Jr, BE - F. Cardoso, PT - R. Dent, SG - S. Loibl, DE

FURTHER INFORMATION
WWW.ESO.NET
#BCYlugano
INTRODUCTION

DEFINITION OF YOUNG: < 40 years
(for the purpose of these guidelines, because they have specific issues related to FERTILITY PRESERVATION, PREGNANCY, AND LACTATION that deserve a different approach and management from slightly older pre- and peri-menopausal women)

• The risk BC is age-dependent
(30-39 y: 0.04% until >10% in > 80 y)

• Dramatic increase of BC in pre-menopausal women in several countries
(5.5% in US <40 y; 1 in 40 is very young (< 35 years)

<table>
<thead>
<tr>
<th>Age</th>
<th>Annual incidence/100 000 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0.1</td>
</tr>
<tr>
<td>20-24</td>
<td>1.4</td>
</tr>
<tr>
<td>25-29</td>
<td>8.1</td>
</tr>
<tr>
<td>30-34</td>
<td>24.8</td>
</tr>
<tr>
<td>35-39</td>
<td>58.4</td>
</tr>
<tr>
<td>40-44</td>
<td>116.1</td>
</tr>
<tr>
<td>45-49</td>
<td>198.5</td>
</tr>
</tbody>
</table>
Breast Cancer Statistics, 2015

Carol E. DeSantis, MPH¹⁺; Stacey A. Fedewa, MPH²; Ann Goding Sauer, MPSH³; Joan L. Kramer, MD⁴; Robert A. Smith, PhD⁵; Ahmedin Jemal, DVM, PhD⁶

<table>
<thead>
<tr>
<th>AGE</th>
<th>IN SITU CASES</th>
<th>INVASIVE CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>1,900</td>
<td>10,980 (4.7%)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>15,650</td>
<td>48,910</td>
</tr>
<tr>
<td>50-64</td>
<td>26,770</td>
<td>84,210</td>
</tr>
<tr>
<td>65+</td>
<td>22,220</td>
<td>99,220</td>
</tr>
<tr>
<td>All ages</td>
<td>64,640</td>
<td>232,340</td>
</tr>
</tbody>
</table>

BC accounts for more than 40% of all cancers in this age group

Courtesy Dr Azim, BCY3
Breast cancer is the leading cause of cancer-related deaths in young women

<table>
<thead>
<tr>
<th>Age at diagnosis, years</th>
<th>5-year relative survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>82%</td>
</tr>
<tr>
<td>40-74</td>
<td>89%</td>
</tr>
<tr>
<td>75 and older</td>
<td>88%</td>
</tr>
</tbody>
</table>

(ACS Research, SEER 2005)
Incidence

✓ Possible absolute increase, at least in some countries

✓ Probable relative increase in countries with high percentage of young women

✓ Relative increase in countries where HRT dependent postmenopausal breast cancer is decreasing (e.g. US)
AGE and BIOLOGY

- **AGE IS AN INDEPENDENT PROGNOSTIC FACTOR:** continuous linear effect, with a 4% decrease in distant recurrence and 6% in local recurrence for every additional year of age.

- Some data suggest a different distribution of BC biological subtypes in young women (higher prevalence of TNBC & HER-2+) BUT a clear molecular characterization in these pts is lacking and is a RESEARCH PRIORITY.

- **AGE IS NOT A PREDICTIVE FACTOR:** When ER status is taken into account, age disappears as an independent factor for the benefit of CT.
BC in the young associated with poor(er) prognosis

Elucidating Prognosis and Biology of Breast Cancer Arising in Young Women Using Gene Expression Profiling

Hatem A. Azim Jr¹, Stefan Michiels³, Philippe L. Bedard², Sandeep K. Singhal¹, Carmen Criscitiello¹, Michail Ignatiadis¹, Benjamin Haibe-Kains³, Martine J. Piccart⁴, Christos Sotiriou¹, and Sherene Loi¹

Chi-square: p<0.0001

<table>
<thead>
<tr>
<th></th>
<th>&lt; 40 (n=15,548)</th>
<th>&gt; 40 (n=227,464)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T &gt; 2cm</td>
<td>61.4%</td>
<td>48.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Node-positive</td>
<td>45.4%</td>
<td>33.6%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ER-negative</td>
<td>28%</td>
<td>14.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PgR-negative</td>
<td>30.1%</td>
<td>20.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 3</td>
<td>42.6%</td>
<td>25.9%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Courtesy Dr Azim, BCY3
More aggressive tumor features in BC arising at a young age

Colleoni M et al; Ann Oncol 2002
Prognosis of BC in young women
Particularly poorer outcome in ER+ tumors

Whole population (n = 2909)

Relapse-free survival (%)

Time (days)

<= 40 (n = 341)

41-52 (n = 973)

53-64 (n = 733)

>= 65 (n = 862)

p < 0.0001

Luminal A (n = 975)

p = 0.07

Luminal B (n = 878)

p = 0.03

Basal-like (n = 615)

p = 0.69

Azim HA Jr et al; Clin Cancer Res 2012

Courtesy Dr Azim, BCY3
Both early discontinuation and non-adherence to HT were common and associated with increased mortality. Interventions to improve continuation of and adherence to HT may be critical to improve BC survival.
BC in young women is biologically unique and not just a surrogate of aggressive BC subtypes

<table>
<thead>
<tr>
<th>Genes</th>
<th>Gene sets</th>
<th>Direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptosis-related</td>
<td>FAS, CASP3, BAD</td>
<td>down</td>
</tr>
<tr>
<td>MAP kinase-related</td>
<td>MAPK</td>
<td>up</td>
</tr>
<tr>
<td>mTOR/PI3K-related</td>
<td>PDPk1, PIK3CA-GS</td>
<td>up</td>
</tr>
<tr>
<td>BRCA-related</td>
<td>BRCA1</td>
<td>down, up</td>
</tr>
<tr>
<td>Stem cell-related</td>
<td>RANKL, MaSC</td>
<td>up, up</td>
</tr>
<tr>
<td>Luminal progenitor</td>
<td>c-kit, Luminal progenitor</td>
<td>up, up</td>
</tr>
</tbody>
</table>

Zhang B Cancer Res 2008;68:9570-9573
Prognosis and biology

✓ Prognosis remains worse in very young women with breast cancer, compared to their older counterpart.

✓ No screening, more advanced cases, “too young to be cancer”

✓ Higher percentage of HER2+, Luminal B and triple negative (race/ethnicity)

✓ Intrinsic genomic differences (genetics, hormonal milieu, recent pregnancy)

Courtesy F. Peccatori
Young age by itself should **not be the reason to prescribe more aggressive therapy** than general recommendations.

Choice of treatment should include but not be limited to the complete **biological characteristics** of the tumor (ER/PR, HER-2, proliferation markers (e.g. Ki-67), histological grade), tumor **stage**, **menopausal status**, **genetic status** (if available) and patient’s **comorbidities** and **preferences**.
Systematic research into age-specific tumor characteristics is needed.
In particular, the prognostic and predictive impact of **multitargeted gene expression and mutational status** to identify specific genomic aberrations that could open the door for tailored therapeutic interventions.

(LoE: Expert opinion) (94%)
MammaPrint “MINDACT”

High clinical risk / low genomic risk

5 year freedom from distant mets = 95%

MammaPrint provides similar prognostic info even in young

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
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<tbody>
<tr>
<td>≥ 65</td>
</tr>
<tr>
<td>53-54</td>
</tr>
<tr>
<td>41-52</td>
</tr>
<tr>
<td>≤ 40</td>
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</tbody>
</table>
All

<table>
<thead>
<tr>
<th>Number (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
</tr>
<tr>
<td>24 (0.9)</td>
</tr>
<tr>
<td>13 (2.2)</td>
</tr>
<tr>
<td>20 (1.3)</td>
</tr>
<tr>
<td>65 (3.6)</td>
</tr>
<tr>
<td>122 (1.8)</td>
</tr>
<tr>
<td>35 to &lt;50</td>
</tr>
<tr>
<td>774 (28.2)</td>
</tr>
<tr>
<td>165 (27.9)</td>
</tr>
<tr>
<td>514 (33.2)</td>
</tr>
<tr>
<td>651 (36.0)</td>
</tr>
<tr>
<td>2104 (31.4)</td>
</tr>
</tbody>
</table>

Cardoso F et al; NEJM 2016
TAILORx RS ≤ 10

Sparano et al, NEJM, 2015
General recommendations

In view of the many specific aspects related to young age, personalized psychosocial support, counseling on genetic predisposition, fertility, sexual health, & socio-economic impact are highly recommended as part of the individual treatment planning.

Patients’ and support groups should be developed and promoted. Open discussion and shared-decision making should be promoted in a clear, culturally appropriate form, encouraging patients to be proactive in their cancer care.

(LoE: Expert opinion) (100%)
In view of the long potential life expectancy, **particular attention should be paid to possible long-term toxicities of adjuvant treatments** (e.g. secondary cancers, cardiovascular toxicity, irreversible ovarian failure, weight gain, cognitive function, bone health).

### EARLY BREAST CANCER: General

<table>
<thead>
<tr>
<th>Secondary tumours</th>
<th>More life-time = more secondary tumours (many descriptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psycho-social impacts and survivorship</td>
<td>Familial and social adverse events: divorce, unemployment, children care...</td>
</tr>
<tr>
<td>Decreased fertility</td>
<td>Major concern, specific to young pts</td>
</tr>
<tr>
<td>Early menopause</td>
<td>More symptoms if early menopause</td>
</tr>
<tr>
<td></td>
<td>Long term effects more worrying: bone, cardiovascular...</td>
</tr>
</tbody>
</table>

**Onco brain**
DIAGNOSIS AND IMAGING FOR STAGING AND FOLLOW-UP

Diagnosis, imaging and staging in young women should follow standard algorithms consistent with older women.

Additional consideration may be given to ultrasound and breast MRI in young women particular in the setting of very dense breast tissue or consideration of a genetic predisposition or other high risk individuals (i.e. radiotherapy for childhood malignancy) for the disease.
It is not an emergency! Time to discuss!

Should in general not differ from that of older patients despite young age is associated with increased local recurrence

BCS → RT, first option whenever suitable.

Importance of skin-sparing/nipple-sparing mastectomy and oncoplastic techniques

SLNB: no evidence of increased false negative rate or worse outcome in young pts. Indications as in older pts.
Forest plot analysis of survival outcomes in young patients (age ≤ 40) comparing BCS and mastectomy

Voogd, 2001
Kroman, 2004 (age < 35 y)
Kroman, 2004 (age 35-39 y)
Bantema-Joppe, 2011 (N+)
Bantema-Joppe, 2011 (N0)
Van der Sangen, 2011
Mahmood, 2012
Won Jeon, 2013 (N+)
Won Jeon, 2013 (N0)

SHR excluding DMFS: 0.88 (95% CI: 0.78, 1.01)

Summary Hazard Ratio: 0.90 (95% CI: 0.81, 1.00)

I² = 34%

BCS Better
Indications and schedules of hypo-fractionation are in principle the same as in other age groups, despite no long-term toxicity data available. (LoE: 1 B) (77%)

Indications and extension of nodal irradiation are the same as in other age groups. (LoE: 1 B) (82%)

PBI has not been sufficiently studied in young patients and should not be performed in this age group. (LoE: Expert opinion) (82%)

Indications of adjuvant RT are independent of BRCA status. (LoE: Expert opinion) (82%)

Data are stronger for benefits of post-mastectomy RT for young women.
Adjuvant systemic treatment

There are minimal data on recommending adjuvant ET alone in very young women (≤35 years at diagnosis) with low risk ER+ disease.

Available data suggest that a discussion of omitting adjuvant chemotherapy in this age group is appropriate in selected cases with favorable clinical and pathological features including low gene expression profiles where available.

(LoE: Expert opinion) (88%)
No age-specific neo/adjuvant CT regimen regarding efficacy and long-term tolerance is currently known. As for all stage I-III breast cancer patients, the preferred regimens are standard anthracycline, alkylating, and taxane based regimens.
Neoadjuvant systemic treatment

In patients with **TNBC** or **BRCA-associated** tumors the incorporation of **platinum agents** increases pCR rates and may be considered when neoadjuvant chemotherapy is indicated. Data on the impact of incremental increases in pCR on long term outcome are not conclusive.

*(LoE: 2A) (77%)*

The use of platinum has **potential additional impact on fertility and increased toxicity** that may compromise standard duration and dosing of standard systemic treatment, and this needs to be clearly communicated to patients.
(Neo)adjuvant systemic treatment

For patients with **TNBC not achieving a pCR** after standard neoadjuvant regimens, the routine addition of adjuvant chemotherapy (such as capecitabine or metronomic CM) is not recommended; however, may be considered in highly selected patients, as in other age groups.

(LoE: Expert opinion) (65%)  

There are **no data on the use of platinum derivatives in the adjuvant setting** and therefore these can not be recommended.
EARLY BREAST CANCER: Endocrine Therapy

Previous talk
ADVANCED BREAST CANCER (ABC)
(i.e. metastatic disease diagnosed before the age of 40)

The BCY3 panel endorses the ESO-ESMO ABC 3 guidelines for the management of ABC in pre-menopausal women.

MAIN MESSAGE!

Also in the metastatic setting, age alone is not a reason to prescribe more aggressive therapy.
Advanced breast cancer

Many trials in ER+ ABC have not included pre-menopausal women. Despite this, we recommend that young women with ER+ ABC have adequate ovarian suppression or ablation and then be treated in the same way as post-menopausal women with endocrine agents and targeted therapies such as an aromatase inhibitor or fulvestrant plus a CDK 4/6 inhibitor or exemestane with everolimus. (LoE: Expert Opinion) (91%)

Future trials exploring new endocrine/endocrine-biological strategies should be designed to allow for enrollment of both pre- and post-menopausal women.
Adding OS to tamoxifen improves survival in premenopausal women with advanced disease.
Exogenous hormonal contraception is generally contraindicated in young cancer survivors and alternative strategies should be considered.

Patients should be informed of the possibility of getting pregnant while on systemic therapies, despite developing long-term amenorrhea, and of the need for adequate non-hormonal contraception.
SUPPORTIVE CARE

Premature menopause and/or treatment related amenorrhea increase the risk of bone thinning and patients should be counseled, monitored and treated accordingly.
SUMMARY STATEMENT ON BEHALF OF THE YOUNG WOMEN ADVOCATES

Medha Sutliff, USA; YSC
Tanja Spanic, SI; ED Slovenia
Our voice

1. Quality of life for young BC patients
2. Survivorship – long term side effects and economic impact on young BC patients
3. Fertility Preservation
4. Clinical trials for young BC patients
5. Research and legislative advocacy training opportunities for young BC patients
4th ESO-ESMO Breast Cancer in Young Women International Conference

6-8 October 2018
Lugano, Switzerland

Chair: O. Pagani, CH
Scientific committee: F. Cardoso, PT - N. Harbeck, DE
S. Paluch-Shimon, IL - F. Peccatori, IT - A. Partridge, US
E. Senkus, PL - Y. Wengström, SE

Important Deadlines
- Abstracts and travel grants: 6 May 2018
- Early registration: by 17 June 2018
- Late registration: by 23 September 2018
- Onsite registration: from 24 September 2018

Organising Secretariat: European School of Oncology (ESO) | Via Turali, 2g | 20121 Milan | Italy | Francesca Marangoni | fmarangoni@eso.net | ph +39 02 85464 525

Further information available at www.eso.net | Follow us on facebook | twitter | #BCYlugano

Inside Track Conference