Management of (breast) cancer in young women

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ESMO Board of Directors & Director of Membership
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ESO Breast Cancer Program Coordinator
DISCLOSURES SLIDE

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Original article

ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3)

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BCY4 Manuscript in preparation
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, MPH\(^1\); Stacey A. Fedewa, MPH\(^2\); Ann Goding Sauer, MPhSH\(^3\); Joan L. Kramer, MD\(^4\); Robert A. Smith, PhD\(^5\); Ahmedin Jemal, DVM, PhD\(^6\)

<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</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>28,220</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

Elsaghir N et al; BMC Cancer 2006
Anders C et al; JCO 2008
Cancello G et al; Ann Oncol 2010

Whole population (n=2901)

Time (years)
RFS (%) 0 2 4 6 8 10
0
20
40
60
80
100
≤ 40 (n=339)
41-52 (n=968)
53-64 (n=732)
≥ 65 (n=862)
Log-Rank: p<0.0001
Log-Rank test for trend: p=0.0003

ER-HER2- (n=615)

Time (years)
RFS (%) 0 2 4 6 8 10
0
20
40
60
80
100
≤ 40 (n=110)
41-52 (n=229)
53-64 (n=137)
≥ 65 (n=139)
Log-Rank: p=0.69
Log-Rank test for trend: p=0.5

HER2+ (n=432)

Time (years)
RFS (%) 0 2 4 6 8 10
0
20
40
60
80
100
≤ 40 (n=69)
41-52 (n=167)
53-64 (n=103)
≥ 65 (n=93)
Log-Rank: p=0.42
Log-Rank test for trend: p=0.4

Luminal A (n=975)

Time (years)
RFS (%) 0 2 4 6 8 10
0
20
40
60
80
100
≤ 40 (n=61)
41-52 (n=325)
53-64 (n=273)
≥ 65 (n=316)
Log-Rank: p=0.07
Log-Rank test for trend: p=0.42

Luminal B (n=879)

Time (years)
RFS (%) 0 2 4 6 8 10
0
20
40
60
80
100
≤ 40 (n=99)
41-52 (n=247)
53-64 (n=219)
≥ 65 (n=314)
Log-Rank: p=0.03
Log-Rank test for trend: p=0.006
Elucidating Prognosis and Biology of Breast Cancer Arising in Young Women Using Gene Expression Profiling

Hatem A. Azim Jr, Stefan Michiels, Philippe L. Bedard, Sandeep K. Singhal, Carmen Criscitiello, Michail Ignatiadis, Benjamin Haibe-Kains, Martine J. Piccart, Christos Sotiriou, and Sherene Loi

Basal  Luminal-A  Luminal-B  HER2

Chi-square: p<0.0001
More aggressive tumor features in BC arising at a young age

Colleoni M et al; Ann Oncol 2002

<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
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

5th ESO-ESMO Latin American Masterclass in Clinical Oncology

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</td>
<td>down</td>
</tr>
<tr>
<td></td>
<td>CASP3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BAD</td>
<td></td>
</tr>
<tr>
<td>MAP kinase –related</td>
<td>MAPK</td>
<td>up</td>
</tr>
<tr>
<td>mTOR/PI3K –related</td>
<td>PDPk1</td>
<td>up</td>
</tr>
<tr>
<td></td>
<td>PIK3CA-GS</td>
<td></td>
</tr>
<tr>
<td>BRCA-related</td>
<td>BRCA1</td>
<td>down</td>
</tr>
<tr>
<td></td>
<td>BRCA1</td>
<td>up</td>
</tr>
<tr>
<td>Stem cell-related</td>
<td>RANKL</td>
<td>up</td>
</tr>
<tr>
<td></td>
<td>MaSC</td>
<td>up</td>
</tr>
<tr>
<td>Luminal progenitor</td>
<td>c-kit</td>
<td>up</td>
</tr>
<tr>
<td></td>
<td>Luminal progenitor</td>
<td>up</td>
</tr>
</tbody>
</table>
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, gene expression), tumor stage, menopausal status, genetic status (if available) and patient’s comorbidities and preferences.

(LoE: Expert opinion) (100%)
BIOLOGY AND PROGNOSIS

Systematic research into age-specific host-tumor characteristics is needed.
In particular, the identification of age-specific molecular, biological, radiomics-based and/or genomic aberrations with prognostic and predictive significance could open the door for tailored therapeutic interventions.

(LoE: Expert opinion) (100%)
BIOLOGY AND PROGNOSIS

A number of factors including patient and tumor characteristics and gene expression, should be considered when deciding whether to administer adjuvant chemotherapy in young women with HR+ early breast cancer. Further research on this subject is needed, in particular in N+ patients.

Commercially available gene expression tests have not been widely studied in young women. Increasing data are available in premenopausal women which might support their role in predicting the additional benefit of chemotherapy over endocrine therapy alone in HR+ early breast cancer in women <40 years at diagnosis.

(LoE: Expert opinion) (100%)
MammaPrint “MINDACT”

- **High clinical risk / low genomic risk**
- 5 year freedom from distant mets = 95%

MammaPrint provides similar prognostic info even in young patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low Clinical Risk</th>
<th>High Clinical Risk</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>24 (0.9)</td>
<td>13 (2.2)</td>
<td>122 (1.8)</td>
</tr>
<tr>
<td>35 to &lt;50</td>
<td>774 (28.2)</td>
<td>165 (27.9)</td>
<td>2104 (31.4)</td>
</tr>
</tbody>
</table>
Table 1. Characteristics of the Patients at Baseline, According to Recurrence-Score Cohort.:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recurrence Score, 0–10 (N = 1626)</th>
<th>Recurrence Score, 11–25 (N = 6897)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of all enrolled patients</td>
<td>15.9</td>
<td>67.3</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>Median (interquartile range) — yr</td>
<td>58 (50–64)</td>
<td>55 (48–62)</td>
</tr>
<tr>
<td></td>
<td>Mean — yr</td>
<td>57±9</td>
<td>55±9</td>
</tr>
<tr>
<td>Distribution — no. (%)</td>
<td>≤40 yr</td>
<td>58 (4)</td>
<td>319 (5)</td>
</tr>
<tr>
<td></td>
<td>41–50 yr</td>
<td>372 (23)</td>
<td>1964 (28)</td>
</tr>
<tr>
<td></td>
<td>51–60 yr</td>
<td>566 (35)</td>
<td>2502 (36)</td>
</tr>
<tr>
<td></td>
<td>61–70 yr</td>
<td>519 (32)</td>
<td>160 (26)</td>
</tr>
<tr>
<td></td>
<td>&gt;70 yr</td>
<td>111 (7)</td>
<td>300 (4)</td>
</tr>
<tr>
<td>Menopausal status — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1143/1623 (70)</td>
<td>4396/6873 (64)</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>480/1623 (30)</td>
<td>2477/6873 (36)</td>
<td></td>
</tr>
</tbody>
</table>

Sparano et al, NEJM, 2015
### TAILORx Results - ITT Population: Exploratory Analysis of Chemotherapy Treatment Interactions in RS 11-25 Arms

<table>
<thead>
<tr>
<th>No statistically significant chemo treatment interactions</th>
<th>Statistically significant chemo treatment interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• RS</td>
<td>• Age (≤ 50, 51-65, &gt; 65) and chemo benefit</td>
</tr>
<tr>
<td>• 11-15 vs. 16-20 vs. 21-25</td>
<td>• IDFS (p=0.003)</td>
</tr>
<tr>
<td>• 11-17 vs. 18-25</td>
<td>• RFI (p=0.02)</td>
</tr>
<tr>
<td>• Tumor size (&lt;2 cm vs. &gt;2 cm)</td>
<td>• Age (or menopause), RS (11-15, 16-20, 21-25), and chemo benefit</td>
</tr>
<tr>
<td>• Grade (low vs. int. vs. high)</td>
<td>• IDFS - Age-RS (p=0.004)</td>
</tr>
<tr>
<td>• Menopausal status (pre vs. post)</td>
<td>• IDFS - Menopause-RS (p=0.02)</td>
</tr>
<tr>
<td>• Clinical risk category (high vs. low)</td>
<td></td>
</tr>
</tbody>
</table>

### BE VERY CAREFUL!!
- Exploratory analysis!
- Very few pts had OFS (therefore CT effect probably through OFS induction)

### TAKE HOME MESSAGE
CT should not be a substitute for a sub-optimal ET!

### TAILORx Results - ITT Population: Potential Chemotherapy Benefit in Women < 50 Years (N=2216) in RS 11-25 Arms

- **RS 16-25 - some chemo benefit**
  - RS 16-20: 9% fewer IDFS events, including 2% fewer distant recurrences
  - RS 21-25: 6% fewer IDFS events, mainly consisting of fewer distant recurrences

- **RS 0-15 - good prognosis with endocrine therapy**
  - 3% distant recurrence with ET alone
  - no evidence for chemo benefit in RS 11-15

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Sparano et al, ASCO 2018, NEJM 2018

Joseph A. Sparano, MD

5th ESO-ESMO Latin American Masterclass in Clinical Oncology
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).

<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>Onco brain</td>
<td>Long term effects more worrying: bone, cardiovascular…</td>
</tr>
</tbody>
</table>
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 or young-adulthood 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%
ADJUVANT RADIOTHERAPY

Indications and schedules of hypo-fractionation are in principle the same as in other age groups, despite no long-term toxicity data available.

Indications and extension of nodal irradiation are the same as in other age groups.

PBI or accelerated PBI, have not been sufficiently studied in young patients and should not be performed in this age group.

Indications of adjuvant RT are independent of BRCA status. Limited and discordant evidence is available in presence of pathogenic gene variants in other predisposing genes (e.g. p53, CHEK2, ATM): in these patients the risk-benefit ratio needs to be individually discussed.
Accumulating data suggests that a discussion of omitting adjuvant chemotherapy in very young women (≤35 years at diagnosis) is appropriate in selected cases with favorable clinical and pathological features including low-risk gene expression profiles.

(LoE: Expert opinion) (95%)
Neo/adjuvant systemic treatment
CHEMOTHERAPY

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.
Neo/adjuvant systemic treatment
CHEMOTHERAPY

Standard duration of treatment (minimum of 4 and maximum of 8 cycles) should also be prescribed.

Sequential regimens have at least equal or superior efficacy over combinations and are better tolerated.

Young age by itself should not be an indication to prescribe a more intense combination of cytotoxic agents.

The indication for dose-dense chemotherapy is independent of age.

(LoE: IA) (100%)
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
CHEMOTHERAPY

For patients with HER2-negative disease not achieving a pCR after standard preoperative regimens, six-eight cycles of post-surgical capecitabine should be discussed in selected patients, as in other age groups.

(LoE: IB) (79%)

There are no data on the use of platinum derivatives in the adjuvant setting and therefore these can not be recommended.
Neo/adjuvant systemic treatment
ENDOCRINE THERAPY

Previous talk
Neo/adjuvant systemic treatment
ANTI-HER2 THERAPY

Nothing different depending on age
ADVANCED BREAST CANCER (ABC) (i.e. metastatic disease diagnosed before the age of 40)

The BCY panel **endorses the ESO-ESMO ABC 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.**
Many trials in ER+ ABC have not included pre-menopausal women. Despite this, we recommend that young women with ER+ ABC should have adequate ovarian suppression or ablation (OFS/OFA) and then be treated in the same way as post-menopausal women with endocrine agents with or without targeted therapies. (LoE/GoR: Expert Opinion/A) (95%)

Future trials exploring new endocrine-based strategies should be designed to allow for enrollment of both pre- and post-menopausal women, and men. (LoE/GoR: Expert Opinion/A) (92%)
ADEQUATE OVARIAN FUNCTION SUPPRESSION (OFS) IN THE CONTEXT OF ABC

Adequate OFS for ABC premenopausal patients can be obtained through bilateral ovariectomy, continuous use of LHRH agonists or ovarian function ablation through pelvic radiotherapy (this latter is not always effective and therefore is the least preferred option). (LoE/GoR: I/A) (85%)

If a LHRH agonist is used in this age group, it should usually be given on a q4w basis to optimize OFS. (LoE/GoR: II/B) (85%)

Efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, specially if an AI is administered. (LoE/GoR: Expert Opinion/B)

As all endocrine interventions for premenopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires balance of patient’s wish for potentially preserving fertility, compliance with frequent injections over along period of time, and cost.
Adding OS to tamoxifen improves survival in premenopausal women with advanced disease

(Klijn, et al. JNCI 2000)
Premature menopause and/or treatment related amenorrhea increase the risk of osteopenia and osteoporosis and patients should be counseled, monitored and treated following national/international guidelines, as in other age groups.

(LoE: Expert opinion)
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.
All young women should be informed about approved fertility preservation options and referred for specialist counseling/consultation if interested in fertility preservation prior to commencement of any therapy.

(LoE: Expert opinion)