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Management of Breast Cancer: Early disease

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ESMO Council Member
Chair of the Fellowship Committee
Disclosure information

- Advisory board from Roche/GNE
- Research grant (to my institute) from Roche/GNE, Servier, Astra Zeneca and GSK/Novartis
- Travel grants from Roche/GNE
Breast cancer is the most common cancer affecting women in both the developed and developing world.

- 2.08 millions new cases diagnosed in 2018
- 12% of all new cancer cases
- Fifth cause of death from cancer overall (6.6%)
- Second cause of death from cancer in women in developed countries
Epidemiology of Breast Cancer

LA & Caribbean
199,734 new cases
52,558 deaths
Epidemiology of Breast Cancer

C.E. DeSantis, CA Cancer J Clin (2016)
Breast Cancer PHENOTYPE

LUMINAL EPITHELIAL/ER gene cluster
- Luminal A (low proliferation)
- Luminal B (high proliferation)

HR Positive
- Erb-B2 overexpression cluster
- HER2 Positive

Basal cluster
- TNBC

Not routinely performed in clinical practice in most countries

The molecular profile do not always correspond to the intrinsic phenotype.

The breast cancer phenotype is most commonly used in clinical practice for therapeutic decision making.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER+, HER2-, Low proliferation</td>
</tr>
<tr>
<td>Luminal B HER2-</td>
<td>ER+, HER2-, High proliferation</td>
</tr>
<tr>
<td>Luminal B HER2+</td>
<td>ER+, HER2+</td>
</tr>
<tr>
<td>HER2</td>
<td>ER-, PgR-, HER2+</td>
</tr>
<tr>
<td>Basal-like</td>
<td>ER-, PgR-, HER2-</td>
</tr>
</tbody>
</table>

*Sorlie et al. PNAS (2003)*
*Sotirou et al. PNAS (2003)*
Early breast cancer treatments

Senkus E et al, ESMO guidelines 2015
HOW TO TREAT SYSTEMICALLY BREAST CANCER?
GENERAL RECOMMENDATIONS
Systemic treatment recommendations

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Recommended therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A-like</td>
<td>ET alone in the majority of cases</td>
<td>Consider ChT if: high tumour burden (four or more positive LN, T3 or higher) grade 3</td>
</tr>
<tr>
<td>Luminal B-like (HER2-negative)</td>
<td>ET + ChT for the majority of cases</td>
<td></td>
</tr>
<tr>
<td>Luminal B-like (HER2-positive)</td>
<td>ChT + anti-HER2 + ET for all patients</td>
<td>If contraindications for the use of ChT, one may consider ET + anti-HER2 therapy, although no randomised data exist.</td>
</tr>
<tr>
<td>HER2-positive (non-luminal)</td>
<td>ChT + anti-HER2</td>
<td></td>
</tr>
<tr>
<td>Triple-negative (ductal)</td>
<td>ChT</td>
<td></td>
</tr>
</tbody>
</table>

For special histological types, we recommend following the St Gallen 2013 recommendations [23] that propose ET for endocrine responsive histologies (cribriform, tubular and mucinous), ChT for high-risk endocrine nonresponsive (medullary, metaplastic) and no systemic therapy for low-risk endocrine nonresponsive (secretory juvenile, adenoid cystic and apocrine).

ET, endocrine therapy; ChT, chemotherapy; LN, lymph node; HER2, human epidermal growth factor 2 receptor.

*Senkus E et al, ESMO guidelines 2015*
Dose-dense is superior to conventional chemotherapy

EBCTCG group, Lancet 2019
Benefit independently of HR status

**ER-**

- Any recurrence, ER-negative (10,900 women)

- Dose-intense
- Standard schedule

- RR 0.85 (95% CI 0.80–0.92)
- Log-rank p<0.0001
- 10-year gain 3.7% (95% CI 1.7 to 5.8)

**ER+**

- Any recurrence, ER-positive (25,029 women)

- RR 0.86 (95% CI 0.81–0.91)
- Log-rank p<0.0001
- 10-year gain 3.1% (95% CI 1.6 to 4.6)

*EBCTCG group, Lancet 2019*
Adjuvant biphosphonate

- 38 trials; 18,776 patients
### Benefit per subgroup

#### (b) Menopausal status (trend $\chi^2 = 3.5; \ 2p = 0.06$)

<table>
<thead>
<tr>
<th>Status</th>
<th>Patients (Risk%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal</td>
<td>217/3296 (6.6%)</td>
<td>0.92 (0.71-1.20)</td>
</tr>
<tr>
<td>Perimenopausal</td>
<td>28/461 (6.1%)</td>
<td>0.72 (0.57-0.90)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>252/6099 (4.1%)</td>
<td></td>
</tr>
</tbody>
</table>

#### (c) ER status ($\chi^2 = 0.6; \ 2p = 0.4$)

<table>
<thead>
<tr>
<th>Status</th>
<th>Patients (Risk%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER negative</td>
<td>107/1964 (5.4%)</td>
<td>0.76 (0.54-1.07)</td>
</tr>
<tr>
<td>ER unknown</td>
<td>42/637 (6.6%)</td>
<td>1.06 (0.60-1.85)</td>
</tr>
<tr>
<td>ER positive</td>
<td>348/7255 (4.8%)</td>
<td></td>
</tr>
</tbody>
</table>

#### (j) Chemotherapy ($\chi^2 = 0.3; \ 2p = 0.6$)

<table>
<thead>
<tr>
<th>Status</th>
<th>Patients (Risk%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence</td>
<td>39/1616 (2.4%)</td>
<td>0.74 (0.48-1.14)</td>
</tr>
<tr>
<td>Presence</td>
<td>458/8240 (5.6%)</td>
<td></td>
</tr>
</tbody>
</table>

**EBCTCG, Lancet 2015. [https://doi.org/10.1016/S0140-6736(15)60908-4](https://doi.org/10.1016/S0140-6736(15)60908-4)**
Benefit according to menopausal status

Postmenopausal was defined as “natural or induced, either potentially reversibly, using LHRH, or permanently by oophorectomy.”

Prophylactic use of bisphosphonates may be discussed in women with a low-oestrogen status (undergoing ovarian suppression or postmenopausal) [1B].

**Recommendation 1**
- It is recommended that administration of bisphosphonates as adjuvant therapy be considered for postmenopausal patients with breast cancer (including patients premenopausal before treatment who have menopause induced by ovarian suppression as detailed in Recommendation 5) deemed candidates for adjuvant systemic therapy.

**Recommendation 2**
- Zoledronic acid and clodronate are the recommended bisphosphonates for adjuvant therapy in breast cancer.

**Recommendation 4**
- For patients who will receive adjuvant bisphosphonates (Recommendation 1), zoledronic acid at 4 mg intravenously over 15 min (or longer) every 6 months for 3 to 5 years or clodronate orally at 1,600 mg/d for 2 to 3 years are recommended. Different durations may be considered.
HER2 POSITIVE BREAST CANCER
Better DFS with 1 year adjuvant trastuzumab

Sustained improvement in OS as well

HERA (3,399)
B31 / N9831 (4,046)
BCIRG AC→TH (2,147)
BCIRG TCH

<table>
<thead>
<tr>
<th></th>
<th>Rate</th>
<th>Median FU yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>6.8%</td>
<td>10</td>
</tr>
<tr>
<td>B31 / N9831</td>
<td>11.5%</td>
<td>8.4</td>
</tr>
<tr>
<td>BCIRG AC→TH</td>
<td>6.7%</td>
<td>10.3</td>
</tr>
<tr>
<td>BCIRG TCH</td>
<td>5.1%</td>
<td>10.3</td>
</tr>
</tbody>
</table>

Adapted from I. Smith
Small tumors, node negative, <3cm: APT trial

Disease-Free Survival

<table>
<thead>
<tr>
<th>Stratum</th>
<th>No. of events</th>
<th>7-yr DFS</th>
<th>95% Conf. Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR Negative</td>
<td>10</td>
<td>90.7%</td>
<td>84.6% to 97.2%</td>
</tr>
<tr>
<td>HR Positive</td>
<td>13</td>
<td>94.6%</td>
<td>91.8% to 97.5%</td>
</tr>
</tbody>
</table>

Tolaney S, ASCO, 2017
Extenet trial

- HER2+ breast cancer
  - IHC 3+ or ISH amplified (locally determined)
  - Prior adjuvant trastuzumab + chemotherapy
  - Lymph node +/-, or residual invasive disease after neoadjuvant therapy
- Stratified by: nodal status, hormone receptor status, concurrent vs sequential trastuzumab

**Randomization (1:1)**

- N=2840
- Neratinib x 1 year
  - 240 mg/day
- Placebo x 1 year

**Part A**
- 2-year follow-up for iDFS

**Part B**
- 5-year follow-up for iDFS

**Part C**
- Overall survival

**Primary endpoint:** invasive disease-free survival (iDFS)

**Secondary endpoints:** DFS-DCIS, time to distant recurrence, distant DFS, CNS recurrences, OS, safety

**Other analyses:** biomarkers, health outcome assessments (FACT-B, EQ-5D)

Endocrine adjuvant therapy given to patients with HR-positive tumors according to local practice
5-year analysis: iDFS : ExteNET Trial

HR (95% CI) = 0.73 (0.57–0.92)  
Two-sided P = 0.008

No. at risk
Neratinib 1420 1316 1272 1225 1106 978 965 949 938 920 885
Placebo 1420 1354 1298 1248 1142 1029 1011 991 978 958 927

Intention-to-treat population. Cut-off date: March 1, 2017

Martins et al, ESMO 2017
ExteNET: iDFS by hormone receptor status

**HR-positive subgroup**
- HR (95% CI) = 0.60 (0.43-0.83)
- Two-sided P = 0.002

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Months after randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neratinib</td>
<td>816 757 731 705 642 571 565 558 554 544 523</td>
</tr>
<tr>
<td>Placebo</td>
<td>815 779 750 719 647 581 567 556 551 542 525</td>
</tr>
</tbody>
</table>

Intention-to-treat population. Cut-off date: March 1, 2017

**HR-negative subgroup**
- HR (95% CI) = 0.95 (0.66-1.35)
- Two-sided P = 0.762

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Months after randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neratinib</td>
<td>604 559 541 520 464 407 400 391 384 376 362</td>
</tr>
<tr>
<td>Placebo</td>
<td>605 575 548 529 495 448 444 435 427 416 402</td>
</tr>
</tbody>
</table>

Martins et al, ESMO 2017
Aphinity trial

Invasive disease free survival

Median follow-up 45.4 months

IDFS: node positive

Median follow-up 44.5 months

Post-neoadjuvant therapy: KATHERINE

- HER2+ patients with residual disease after neoadjuvant chemo + anti-HER2 therapy
- (N = 1486)
- 14 cycles of TDM1 versus trastuzumab
- Primary endpoint iDFS

von Minckwitz et al, NEJM 2018
Post-neoadjuvant therapy: KATHERINE

DDFS Δ 6.7%: HR 0.60 (95% CI 0.45-0.79)

von Minckwitz et al, NEJM 2018
### Post-neoadjuvant therapy: KATHERINE

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>T-DM1</th>
<th>Trastuzumab</th>
<th>Hazard Ratio for Invasive-Disease Event (95% CI)</th>
<th>3-Yr Invasive Disease–free Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>91/743</td>
<td>165/743</td>
<td>0.50 (0.39–0.64)</td>
<td>88.3% vs 77.0%</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 yr</td>
<td>20/143</td>
<td>37/153</td>
<td>0.50 (0.29–0.86)</td>
<td>86.5% vs 74.9%</td>
</tr>
<tr>
<td>40–64 yr</td>
<td>64/542</td>
<td>113/522</td>
<td>0.49 (0.36–0.67)</td>
<td>88.8% vs 77.1%</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>7/58</td>
<td>15/68</td>
<td>0.55 (0.22–1.34)</td>
<td>87.4% vs 81.1%</td>
</tr>
<tr>
<td>Clinical stage at presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inoperable breast cancer</td>
<td>42/185</td>
<td>70/190</td>
<td>0.54 (0.37–0.80)</td>
<td>76.0% vs 60.2%</td>
</tr>
<tr>
<td>Operable breast cancer</td>
<td>49/553</td>
<td>95/553</td>
<td>0.47 (0.33–0.66)</td>
<td>92.3% vs 82.8%</td>
</tr>
<tr>
<td>Hormone-receptor status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative (ER-negative and progesterone-receptor–negative or unknown)</td>
<td>38/209</td>
<td>61/203</td>
<td>0.50 (0.33–0.74)</td>
<td>82.1% vs 66.9%</td>
</tr>
<tr>
<td>Positive (ER-positive, progesterone-receptor–positive, or both)</td>
<td>53/534</td>
<td>104/540</td>
<td>0.48 (0.35–0.67)</td>
<td>90.7% vs 80.7%</td>
</tr>
<tr>
<td>Preoperative HER2-directed therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab alone</td>
<td>78/600</td>
<td>141/596</td>
<td>0.49 (0.37–0.65)</td>
<td>87.7% vs 75.9%</td>
</tr>
<tr>
<td>Trastuzumab plus additional HER2-directed agent or agents</td>
<td>13/143</td>
<td>24/147</td>
<td>0.54 (0.27–1.06)</td>
<td>90.9% vs 81.8%</td>
</tr>
<tr>
<td>Pathological nodal status after preoperative therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node-positive</td>
<td>62/343</td>
<td>103/346</td>
<td>0.52 (0.38–0.71)</td>
<td>83.0% vs 67.7%</td>
</tr>
<tr>
<td>Node-negative or NE</td>
<td>29/400</td>
<td>62/397</td>
<td>0.44 (0.28–0.68)</td>
<td>92.8% vs 84.6%</td>
</tr>
<tr>
<td>Primary tumor stage at definitive surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT0, ypT1a, ypT1b, ypT1mic, ypTis</td>
<td>40/331</td>
<td>52/306</td>
<td>0.66 (0.44–1.00)</td>
<td>88.3% vs 83.6%</td>
</tr>
<tr>
<td>ypT1b</td>
<td>14/175</td>
<td>42/184</td>
<td>0.34 (0.19–0.62)</td>
<td>91.9% vs 75.9%</td>
</tr>
<tr>
<td>ypT2</td>
<td>25/174</td>
<td>44/185</td>
<td>0.50 (0.31–0.82)</td>
<td>88.3% vs 74.3%</td>
</tr>
<tr>
<td>ypT3</td>
<td>9/51</td>
<td>21/57</td>
<td>0.40 (0.18–0.88)</td>
<td>79.8% vs 61.1%</td>
</tr>
<tr>
<td>ypT4</td>
<td>3/12</td>
<td>6/11</td>
<td>0.29 (0.07–1.17)</td>
<td>70.0% vs 30.0%</td>
</tr>
<tr>
<td>Regional lymph-node stage at definitive surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypNX</td>
<td>28/344</td>
<td>56/335</td>
<td>0.46 (0.30–0.73)</td>
<td>91.9% vs 83.9%</td>
</tr>
<tr>
<td>ypN1</td>
<td>29/220</td>
<td>50/213</td>
<td>0.49 (0.31–0.78)</td>
<td>88.9% vs 75.8%</td>
</tr>
<tr>
<td>ypN2</td>
<td>16/86</td>
<td>38/103</td>
<td>0.43 (0.24–0.77)</td>
<td>81.1% vs 58.2%</td>
</tr>
<tr>
<td>ypN3</td>
<td>17/37</td>
<td>15/30</td>
<td>0.71 (0.35–1.42)</td>
<td>52.0% vs 40.6%</td>
</tr>
<tr>
<td>ypNX</td>
<td>1/56</td>
<td>6/62</td>
<td>0.17 (0.02–1.38)</td>
<td>98.1% vs 88.7%</td>
</tr>
</tbody>
</table>

von Minckwitz et al, NEJM 2018
HER2 positive algorithm (Expert opinion)

< 2cm N0 → Surgery

≤ 0.5 cm → No CT/antiHER2
ET si ER+

0.6-1.0 cm → Consider adjuvant paclitaxel + trastuzumab
ET si ER+

1.1-2.0cm → ER+: adjuvant paclitaxel + trastuzumab + ET
ER-: discuss Anthracycline use based on risk

≥ 2cm or Cytology confirmed N+ → NEOADJUVANT THERAPY
4EC → 12 paclitaxel
trastuzumab ± pertuzumab or 6 TCH±P

If pCR
14 x Trastuzumab ± Pertuzumab
ET si ER+

If NO pCR
14 x TDM1
ET si ER+
LUMINAL BREAST CANCER: CHOICE OF ENDOCRINE THERAPY
Adjuvant endocrine trials comparing tamoxifen with AI

Gingras I, Rossari J, de Azambuja E, Piccart-Gebhart M. Medical Treatments in Breast Cancer, ESGO 2016, chapter 203
Type of endocrine therapy

Premenopausal
Tamoxifen ± LHRH
Tam → AI (LHRH)
AI + LHRH

Postmenopausal
Tamoxifen
Tam → AI
AI

The choice of endocrine therapy is based on relapse risk, but most of postmenopausal patients will be treated with AI at same point.
Premenopausal patients

Figure 1  Algorithm for the adjuvant endocrine therapy in premenopausal patients with breast cancer. AI, aromatase inhibitor; OFS, ovarian function suppression; Tam, tamoxifen.

Lambertini M, et al. ESMO OPEN 2018
WHO ARE THE PATIENTS WITH LUMINAL BREAST CANCER WHO DO NOT REQUIRE CHEMOTHERAPY?
Mindact trial

MINDACT
n=6,693

c-Low/g-Low
N=2,745 (41.0%)
c-Low/g-High
N=592 (8.8%)
c-High/g-Low
N=1,550 (23.2%)
c-High/g-High
N=1,806 (27.0%)

Discordance Rate=32%

R1

NO CHEMOTHERAPY

CHEMOTHERAPY

Sparing of chemotherapy in patients HC/LG (DMFS)

**Figure 3. Survival without Distant Metastasis in the Four Risk Groups.**
The analysis includes all enrolled patients, and the risk groups are based on corrected risk. The time-to-event curves were estimated by means of the Kaplan–Meier method.

Low Clinical /Low Genomic = 97.6%

Underpowered!
Tailorx trial

Oncotype DX testing →

Registration and specimen banking →

RS<11 → RS 11-25 → RS>25

N=10,254 pts

Arm A
Hormonal therapy alone

N=1626 (15.9%)

Arm B
Hormonal therapy alone

N=6897 (67.3%)

Randomize
Stratification factors:
tumor size, menopausal status, planned chemotherapy, planned radiation

Arm C
Chemotherapy plus hormonal therapy

Arm D
Chemotherapy plus hormonal therapy

N=1736 (16.9%)

Sparano JA et al., N Engl J Med 2018
Chemo and ET: similar benefit in midrange 21-gene RS

Most of patients were clinical low risk as per MINDACT definition

Benefit of chemotherapy in the young population (50 years or younger)
International guidelines

Inclusion of Oncotype DX and Mammaprint in the 8th TNM edition for BC:

<table>
<thead>
<tr>
<th>CHANGE</th>
<th>DETAILS OF CHANGE</th>
<th>LEVEL OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction of multigene panels (when available) as stage modifiers—21-gene recurrence score (Oncotype Dx)</td>
<td>For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a 21-gene (Oncotype Dx) recurrence score less than 11, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0, and the tumor is staged using the AJCC prognostic stage group table as stage I.</td>
<td>I</td>
</tr>
<tr>
<td>Induction of multigene panels (when available) as stage modifiers—Mammaprint</td>
<td>For patients with hormone receptor-positive, HER2-negative, and lymph node-negative tumors, a Mammaprint low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a-T1b N0 M0.</td>
<td>II</td>
</tr>
</tbody>
</table>

Both tests are recommended by: ASCO, ESMO, European Group on Tumor Markers, St. Gallen Panel

NCCN guidelines: recommends Oncotype DX, but considers Mammaprint as an alternative
Can we forgot GEP in some cases?

ER-positive tumor: Define clinical risk

- Clinical “low” risk
  - Treatment according to guidelines
  - ≈50% will be spared CT

- Clinical “high” risk
  - Discuss with patient if she would value a 1.9% gain in DMFS with adjuvant chemotherapy
  - No
    - Order Mammaprint™
  - Yes
    - Proceed with chemotherapy

≈50% of the cases do not need Mammaprint

Adapted from Brandão M et al, Future Oncol 2018
TRIPLE NEGATIVE BREAST CANCER
### Biological heterogeneity of TNBC

<table>
<thead>
<tr>
<th>Subtype</th>
<th>&quot;Driver pathways&quot;</th>
<th>Possible sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like 1</td>
<td>high Ki-67; DNA damage response</td>
<td>PARP-I and Cisplatin</td>
</tr>
<tr>
<td>Basal-like 2</td>
<td>GF pathways</td>
<td>Anti-EGFR</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>Immune genes</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>Cell motility</td>
<td>PI3K-mTOR Inh</td>
</tr>
<tr>
<td>Mesenchymal stem-like</td>
<td>Cell motility; claudin-low</td>
<td>Anti-angiogenetic</td>
</tr>
<tr>
<td>Luminal androgen receptor</td>
<td>Steroid pathways</td>
<td>AR antagonist</td>
</tr>
</tbody>
</table>

Platinum-based NACT: meta-analysis of randomized trials

- 9 RCTs (N=2109) on platinum-based vs platinum-free neoadjuvant CT in TNBC
- Neoadjuvant carboplatin improves pCR from 37.0% to 52.1%:

If Anthracyclines and taxanes in both arms: OR 1.85 (1.31-2.61)

Poggio F et al, Ann Oncol 2018

<table>
<thead>
<tr>
<th>Subtypes according to clinical-pathologic and genomic risk assessment</th>
<th>Treatment recommendation</th>
<th>De-escalation</th>
<th>Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal triple negative Higher T and N stage</td>
<td>Neoadjuvant therapy for stage II or III is suggested as initial treatment approach. Chemotherapy should include anthracycline and taxanes</td>
<td>Dose-dense adjuvant chemotherapy preferred by only a minority of the consensus panel.</td>
<td>No consensus on post-neoadjuvant treatment in case of residual disease.</td>
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<td>In BRCA1/2 associated cancers, the Panel was evenly split on whether to recommend (neo)adjuvant platinum chemotherapy though agreed that such patients should receive alkylating chemotherapy.</td>
</tr>
</tbody>
</table>

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

General recommendations

68. 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 IIA
Figure 2. Kaplan–Meier Estimates of Disease-free Survival and Overall Survival.

Panels A and B show disease-free survival and overall survival, respectively, in the full analysis set (primary analysis). Tick marks indicate censored data. Panels C and D show disease-free survival and overall survival, respectively, in the subgroup of patients with triple-negative breast cancer (i.e., breast cancer that was negative for estrogen receptors, progesterone receptors, and HER2).

International guidelines

**ASCO**

Patients with early-stage, HER2-negative breast cancer with pathologic invasive residual disease after surgery following standard anthracycline- and taxane-based preoperative therapy may be offered up to six to eight cycles of adjuvant capecitabine.

Qualifying Statements: If clinicians decide to use capecitabine, then the Expert Panel preferentially supports the use of adjuvant capecitabine in patients with hormone receptor-negative, HER2-negative breast cancer. The capecitabine dosage used in the CREATE-X study (1,250 mg/m² twice daily) is associated with higher toxicity in patients ≥ 65 years old.

Type: evidence-based, benefits outweigh harms

Evidence quality: intermediate

Strength of recommendation: moderate

**NCCN**

- “Consider adjuvant capecitabine in patients with TNBC and residual invasive disease after neoadjuvant treatment.”

**BSMO**

- In TNBC, in case of incomplete partial response after neoadjuvant chemotherapy, adjuvant capecitabine could be considered.
Post-neoadjuvant TNBC
Expert opinion

TNBC after NACT → No pCR

- RCB I → Follow-up*
- RCB II/III → Capecitabine x 8**

* Capecitabine could be coonsidered in selected patients
** Capecitabine 2000 mg/m² D1-14 or 1500 BID as flat dose (France experience)
- RT to be given prior to capecitabine
Take home messages

- Treatment modalities of breast cancer patients differ according to molecular subtypes and relapse risk
- Genomic signatures may help identifying luminal breast cancer patients who do not require chemotherapy
- HER2 positive
  - dual anti-HER2 blockade in high risk patients
  - more neoadjuvant approach: TDM1 if no pCR
- TNBC
  - the addition of platinum salts increases pCR rates
  - post-neoadjuvant capecitabine improves outcomes