(Neo)Adjuvant Chemotherapy for ER+/HER2 neg EBC

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DISCLOSURES SLIDE

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Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

F. Cardoso, S. Kyriakides, S. Ohno, F. Penault-Llorca, P. Poortmans, I. T. Rubio, S. Zackrisson and E. Senkus, on behalf of the ESMO Guidelines Committee

ESMO Early Breast Cancer Guidelines 2019

St. Gallen 2019
Escalating and de-escalating treatment in Early Breast Cancer across subtypes and treatment modalities

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) (“Oxford Overview”)
1st QUESTION: Is CT needed?
EARLY BREAST CANCER: WHO NEEDS ADJUVANT CT?

- CLINICAL/PATHOLOGICAL/GENOMIC FACTORS ARE BEST USED IN COMBINATION.
- Responsiveness is a continuum.
- PATIENT PREFERENCE!

In favor of adjuvant chemotherapy
- ER negative
- Ductal histology
- Grade 3
- High proliferation
- High uPA and PAI1
- Basal and HER2 positive
- High MammaPrint® or Oncotype DX® or GGI

Against adjuvant chemotherapy
- ER positive
- Lobular histology
- Grade 1
- Low proliferation
- Low uPA and PAI1
- Luminal A
- Low MammaPrint® or Oncotype DX® or GGI

Figure 2 | The chemosensitivity of a breast tumor depends on many factors. In individual treatment-decision making all these factors should be taken into consideration as well as the patient’s risk of recurrence and risk of adverse effects, the likely benefit of adjuvant systemic therapy, and the patient’s preferences. Abbreviations: ER, estrogen receptor; GGI, genomic grade index.
CLINICOPATHOLOGICAL PROGNOSTIC FACTORS IN EBC

- Tumor size
- Lymph node status
- Grade
- ER, PR and HER-2 receptor expression
- Presence of lymphovascular invasion
PROGNOSTIC ALGORITHMS FOR TREATMENT DECISION MAKING

- Predict Plus
- Adjuvant! Online
- Nottingham Prognostic Index

INTERNATIONAL TREATMENT GUIDELINES

- ESMO, St. Gallen, NCCN, ASCO, AGO, Cancer Care Ontario Clinical Practice Guidelines, and others...
PROGNOSTIC VALUE OF BC MOLECULAR SUBTYPES

Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer

- Luminal
- HER2
- Basal
- Immune
- Cell Adhesion
- Mesenchymal/ECM
- Proliferation

Relapse Free S

- Basal-like
- Claudin-low
- HER2-enriched
- Luminal A
- Luminal B

p=7.67e-06

Months

Courtesy of MJ Brito
PROGNOSTIC VALUE OF SUBTYPES IHC SURROGATES

CRUCIAL ROLE OF HIGH QUALITY PATHOLOGY (and also cost-effective!)

8th Edition AJCC: ANATOMIC and PROGNOSTIC STAGGING

7th Edition Stage

Tumor Size
Metastasis
Nodal Involvement

7th Edition Stage

2010-2017

8th Edition

Tumor Size
Low risk GES
Tumor Grade
8th Edition Prognostic Stage Group
Nodal Involvement
Metastasis
ER/PR/HER2

2018 and beyond
MINDACT TRIAL DESIGN

Registration & Screening Surgery

N= 6600

Clinical-Pathological (C) risk (Adjuvant! Online)
Genomic (G) risk (70-gene signature)

C-high/ G-high

Discordant cases
C-high/G-low or C-low/G-high

1st randomization to treatment
use Clinical vs. Genomic risk

Chemotherapy

2nd randomization
Anthracycline –based vs. Capecitabine-Docetaxel

Endocrine therapy

3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

No Chemotherapy

C-low/G-low

HR+
MINDACT population at 5y median follow-up
DMFS IN ALL 4 RISK GROUPS

Distant Metastasis Free Survival

% at 5 year
- cL/gL 97.6 (96.9, 98.1)
- cL/gH 94.8 (92.4, 96.4)
- cH/gL 95.1 (93.8, 96.2)
- cH/gH 90.6 (89.0, 92.0)

Number of patients at risk:

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk:</th>
<th>corrected risk</th>
</tr>
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<tbody>
<tr>
<td>77</td>
<td>2745</td>
<td>2628</td>
<td>2331</td>
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<tr>
<td>32</td>
<td>592</td>
<td>550</td>
<td>484</td>
</tr>
<tr>
<td>82</td>
<td>1550</td>
<td>1457</td>
<td>1317</td>
</tr>
<tr>
<td>171</td>
<td>1806</td>
<td>1689</td>
<td>1462</td>
</tr>
</tbody>
</table>
MINDACT population at 5y median follow-up

DISCORDANT RISK GROUPS: PRIMARY TEST

The primary statistical test
(DMFS at 5Y)

Distant Metastasis Free Survival
cHgL no ACT

Null Hypothesis: set at 92%

Observed 5Y DMFS = 94.7%

95% CI ≈ 92.5 – 96.2% excludes 92% !!!
### Efficacy: CT vs no CT in discordant risk groups

#### Intent-to-treat analysis

<table>
<thead>
<tr>
<th>Allocated Treatment strategy</th>
<th>% at 5 Year(s) (95% CI)</th>
<th>Hazard Ratio (adjusted Cox model) (95% CI)</th>
<th>p-value (adjusted logrank)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT</strong></td>
<td>95.9 (94.0, 97.2)</td>
<td>0.78 (0.50, 1.21)</td>
<td>0.267</td>
</tr>
<tr>
<td><strong>no CT</strong></td>
<td>94.4 (92.3, 95.9)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

### Distant Metastasis Free Survival

**c-High/g-Low**

- **CT**: 95.8 (92.9, 97.6)
- **no CT**: 95.0 (91.8, 97.0)

**c-Low/g-High**

- **CT**: 95.0 (92.9, 97.6)
- **no CT**: 95.0 (91.8, 97.0)
Practical use of Mammaprint® in the clinic based on evidence from the MINDACT trial

HR+ tumor: Define clinical risk

Clinical “low” risk*
- Treatment according to guidelines

Clinical “high” risk
- Discuss with patient if she would value a 1.5% gain in DMFS with adjuvant chemotherapy
  - No
    - Order Mammaprint
  - Yes
    - Proceed with chemotherapy

* Courtesy M. Piccart
TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010

Preregister – Oncotype DX RS (N=11,232) → Register (N=10,273)

ARM A: Low RS 0-10 (N=1629 evaluable)
ASSIGN Endocrine Therapy (ET)

Mid-Range RS 11-25 (N=6711 evaluable)
RANDOMIZE
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM B: Experimental Arm (N=3399)
ET Alone

ARM D: High RS 26-100 (N=1389 evaluable)
ASSIGN Chemo and ET

ARM C: Standard Arm (N=3312)
Chemo and ET

Joseph A. Sparano, MD
Results LOW RISK ARM (ET alone)

No. of events: 88 iDFS events and 30 deaths within 5 years of registration, including 18 recurrences (10 distant as first event), 15 second primary breast cancers, 43 other second primary cancers, 12 deaths without another event

5 year iDFS Rate
93.8%
(95% CI 92.4%, 94.9%)

5 year DRFI Rate
99.3%
(95% CI 98.7%, 99.6%)

5 year RFI Rate
98.7%
(95% CI 97.9%, 99.2%)

5 year OS Rate
98.0%
(95% CI 97.0%, 98.6%)
TAILORx Results – ITT Population: RS 11-25 (Arms B & C)

836 IDFS events (after median of 7.5 years), including 338 (40.3%) with recurrence as first event, of which 199 (23.8%) were distant.

**Primary Endpoint**
Invasive Disease-Free Survival

- **CHEMO + ET**
- **ET Alone**

**Secondary Endpoint**
Distant Relapse-Free Interval

- **CHEMO + ET**
- **ET Alone**

**Other Secondary Endpoints**

- **Relapse-Free Interval**
- **Overall Survival**
TAILORx Results - ITT Population: All Arms (A,B,C & D)

9-Year Event Rates

- **RS 0-10 (Arm A)**
  - 3% distant recurrence with ET alone

- **RS 11-25 (Arms B & C)**
  - 5% distant recurrence rate overall
  - ≤ 1% difference for all endpoints
    - IDFS (83.3 vs. 84.3%)
    - DRFI (94.5 vs. 95.0%)
    - RFI (92.2 vs. 92.9%)
    - OS (93.9 vs. 93.8%)

- **RS 26-100 (Arm D)**
  - 13% distant recurrence despite chemo + ET
• The **choice of treatment strategy** should be based on the **tumour burden/location** (size and location of primary tumour, number of lesions, extent of lymph node involvement) and **biology** (pathology, including biomarkers and gene expression), as well as the **age, menopausal status, general health status and preferences** of the patient [V, A].

• **Age** should be taken into consideration in conjunction with other factors and should not be the sole determinant for withholding or recommending a treatment [V, A].

• **Validated gene expression profiles** may be used to gain additional prognostic and/or predictive information to complement pathology assessment and help in adjuvant ChT decision-making [I, A].
• Most **luminal A-like tumours** do not require ChT, except those with high disease burden [I, A].

• ChT use in **luminal B-like HER2-negative** patients depends on individual risk of recurrence, presumed responsiveness to ET and patient preferences [V, A].

• In cases of **uncertainty regarding indications for adjuvant ChT** (after consideration of all clinical and pathological factors), expression of **uPA-PAI1** [I, A] or gene expression assays, such as MammaPrint, Oncotype DX, Prosigna, Endopredict or Breast Cancer Index, can be used [I, A for the first two tests].
GENOMIC TESTS IN ALL OR ONLY SELECTED BREAST CANCER CASES?

TRIPLE NEGATIVE
(ER-, PR-, HER-2 neg)

CT indispensable

LUMINAL
ER+ HER-2 neg

CT → HT

HER-2 POSITIVE

CT + anti-HER indispensable

“Clear” indication from classical factors

All LOW risk: high levels
ER, PR, grade 1, node negative, low proliferation

All HIGH risk: low levels
ER, PR, grade 3, node positive, high proliferation

“No Clear” indication from classical factors; some high & some low risk

CRUCIAL IMPORTANCE OF HIGH QUALITY PATHOLOGY

HT alone

GENOMIC TEST
2nd QUESTION: Neoadjuvant versus Adjuvant

In my opinion: if CT is needed, then do it as neoadjuvant IF you are working in a multidisciplinary setting with experienced Radiologists, Pathologists, Surgeons and Radiation Oncologists
NEoadjuvant Setting

**15 days**

**Systemic therapy**

**4 - 6 months**
PREOPERATIVE CHEMOTHERAPY IN BC
HISTORICAL PERSPECTIVE

1970

Locally advanced

1980

Early

GOAL

Local control

↑

Achieved

Adapted from M. Piccart

1990

Early

Rate of breast conservation

↑

Achieved

2000

Early

Survival

↑

No difference

Early

Treatment tailoring

↑

Ongoing
NEoadjuvant CT is safe & efficient

- Facilitates less invasive loco-regional treatment
- No difference in DFS and OS between neoadj & adjuvant CT
- Slight difference in locoregional recurrence rate

Dose dense specially useful for high proliferative and/or ER neg tumors

Incorporation of taxanes
- Increase in RR; not consistent benefit in long term outcome
- Responders to A-based seem to derive greater benefit from switching to taxane-based than from continuing A-based
- Weekly paclitaxel superior to 3-weekly
**Table 1:** Trials of neoadjuvant versus adjuvant chemotherapy that began by 2005

<table>
<thead>
<tr>
<th></th>
<th>Trials (n)</th>
<th>Women (n)</th>
<th>Deaths (n)</th>
<th>Median years per woman (IQR)</th>
<th>Woman-years by years since entry (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;10</td>
</tr>
<tr>
<td>No anthracycline or taxane⁸,¹¹,¹³,¹⁷,₂₅</td>
<td>4</td>
<td>918</td>
<td>315</td>
<td>7.0 (4.2–9.3)</td>
<td>6.0</td>
</tr>
<tr>
<td>Anthracyline, no taxane⁸,¹⁰,¹⁴–¹⁶</td>
<td>5</td>
<td>2936</td>
<td>1163</td>
<td>10.2 (4.9–15.4)</td>
<td>22.1</td>
</tr>
<tr>
<td>Anthracyline and taxane¹³</td>
<td>1</td>
<td>902</td>
<td>126</td>
<td>7.9 (5.0–10.7)</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10</strong></td>
<td><strong>4756</strong></td>
<td><strong>1604</strong></td>
<td><strong>8.6 (4.8–13.7)</strong></td>
<td><strong>34.6</strong></td>
</tr>
</tbody>
</table>

*Data are missing for six small trials that randomised about 500 women, so they were not included in this analysis (appendix p 17). †Includes 1356 deaths with recurrence, 72 of unknown cause, without recurrence, and 176 of known cause without recurrence. ‡In these trials, women allocated to the neoadjuvant group completed their chemotherapy after surgery.
Substantially higher frequency of BCS with neoadjuvant
NEOADJUVANT CT - Clinical trials: Take home messages

Strong correlation between pCR and outcome

MD Anderson experience (Kuerer et al, JCO 1999)
272 LABC pts treated by anthracycline-based NAC; pCR= 12%
Association between pCR and EFS by BC subtype

The magnitude of improvement in pCR rate did not predict EFS and OS effect.

Overall survival as a function of response to neoadjuvant PCT

Liedtke C et al, J Clin Oncol, 2008, 26:1275
3rd QUESTION: Which agents?
## CHEMOTHERAPY REGIMENS FOR BREAST CANCER

<table>
<thead>
<tr>
<th>1st Generation HD 15-20%</th>
<th>2nd Generation +HD 15-20%</th>
<th>3rd Generation +HD 15-20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF X6</td>
<td>FAC X6</td>
<td>TAC X6</td>
</tr>
<tr>
<td>FEC50 X4</td>
<td>FEC50/100 X6; CEF can X6</td>
<td>FEC100 X3- DX3</td>
</tr>
<tr>
<td>AC X4</td>
<td>FAC4- TX4</td>
<td>ddAC/ECX4-TX4</td>
</tr>
<tr>
<td></td>
<td>FECX4-DX4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACX4-TX4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DCX4</td>
<td></td>
</tr>
</tbody>
</table>

C (cyclophosphamide) M (metotrexate) F(5-FU)  
F E(epirubicine) C  
A (doxorubicine) C  
T (paclitaxel)  
D (docetaxel)  

Courtesy B. Sousa
WHICH TYPE OF CHEMOTHERAPY?

Messages from the EBCTCG overview & individual trials

✓ Efficacy of adjuvant CT compared with no CT

<table>
<thead>
<tr>
<th></th>
<th>Risk of recurrence</th>
<th>Breast cancer mortality</th>
<th>Overall mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthracycline based regimen vs no CT</strong></td>
<td>RR:0.73, 95%CI</td>
<td>RR:0.79, 95%CI</td>
<td>RR:0.84, 95%CI</td>
</tr>
<tr>
<td></td>
<td>Absolute gain: 8%</td>
<td>Absolute gain: 6.5%</td>
<td>Absolute gain: 5%</td>
</tr>
<tr>
<td><strong>CMF regimen vs no CT</strong></td>
<td>RR:0.70, 95%CI</td>
<td>RR:0.76, 95%CI</td>
<td>RR:0.84, 95%CI</td>
</tr>
<tr>
<td></td>
<td>Absolute gain: 10.2%</td>
<td>Absolute gain: 6.2%</td>
<td>Absolute gain: 4.7%</td>
</tr>
</tbody>
</table>

Ribeiro, Sousa and Cardoso, ECCO-ESMO 2013 Educational Book
WHICH TYPE OF CHEMOTHERAPY?

Taxanes > Anthra > CMF > No Chemo

Control 36.4%
CMF 32.2%
Anthra 27.0%
Taxane 25.9%

EBCTCG 2005-06 Overview Peto SABCS 2007
EBCTCG conclusions

100,000 women, 123 randomized trials

*Lancet, 2012*

- CMF equivalent to ACx4 (↓20-25% death)
- 6 cycles better than ACx4 (6 ciclos, FEC/CEF/FAC, or plus taxane) (↓15-20%)
- Taxanes plus anthracyclines (A) better than A based regimens
- Best regimens achieve ↓36% death relative risk
- Benefit independent of age, T, Nodal status, estrogen receptor
ONGOING CONTROVERSY ABOUT ANTHRACYCLINES
2017: ABC Trials, MINDACT CT-question, PLAN-B

MY TAKE-HOME MESSAGES:

• For **TNBC and HER-2+** Anthracyclines and Taxanes, in a sequential regimen, are the standard.
• For **Luminal A with high burden of disease** justifying CT, probably it does not matter which regimen is chosen
• For **Luminal B**, depends on burden of disease: high burden: Anthracyclines and Taxanes: Low burden: probably ok to omit A

- **Important to consider:**
  • Long term toxicity of only 3 to 4 cycles of A is lower than the “old” 6 cycles of FEC/FAC
  • Are we sure that the risk of leukemia is A-related (or C-related?)
Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37,298 women with early breast cancer in 26 randomised trials

The Lancet, 2019

**PROBLEM:**
COST OF GROWTH FACTORS

**POTENTIAL SOLUTION:**
Biosimilars
• **Sequential anthracycline/taxane-based regimen** is the standard for the majority of patients [I, A].

• In selected **lower risk patients** four cycles of anthracycline- or taxane-based ChT or CMF may be used [II, B].

• **Non-anthracycline regimens** may be used in **patients at risk of cardiac complications** [I, A].

• Anthracycline-based regimens should not include 5-FU (EC or AC is standard) [I, A].

• Platinum compounds should not be used routinely in the adjuvant setting [V, E].

• The use of dose-dense schedules [with granulocyte colony-stimulating factor (G-CSF) support] should be considered, particularly in highly proliferative tumours [I, A] [158, 159].
There is nothing more fulfilling in your job than working with the best team in the world!