(Neo) Adjuvant Chemotherapy in early luminal BC

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ESMO Breast Cancer Preceptorship – October 2019
Disclosures

Roche: Speakers bureau, honoraria, consultancy
Astra Zeneca: Speakers bureau, honoraria, consultancy
Novartis: Speakers bureau, honoraria, consultancy
Pfizer: Speakers bureau, honoraria, consultancy
Nanostring: Speakers bureau, honoraria
Teva: Speakers bureau, honoraria
Background - Luminal Cancers
"Intrinsic" gene set on 78 single tumor samples

Survival analysis was done on the set of 51 doxorubicin treated patients only (if all 76 patients are used, then the "basal" and "ERBB2+" groups are significant predictors in a multivariate analysis versus ER, grade, tumor size and node status).

Sorlie et al, PNAS, 2001
Surrogate Definitions of Intrinsic Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>ER+ &amp; PR+</td>
</tr>
<tr>
<td></td>
<td>HER2-</td>
</tr>
<tr>
<td></td>
<td>Low Ki67</td>
</tr>
<tr>
<td>Luminal B</td>
<td>ER+ and/or PR+</td>
</tr>
<tr>
<td></td>
<td>HER2+</td>
</tr>
<tr>
<td></td>
<td>or HER2- with high Ki67</td>
</tr>
<tr>
<td>HER2</td>
<td>ER- and PR-</td>
</tr>
<tr>
<td></td>
<td>HER2+</td>
</tr>
<tr>
<td>Basal-like*</td>
<td>Triple negative</td>
</tr>
<tr>
<td></td>
<td>ER- and PR-</td>
</tr>
<tr>
<td></td>
<td>HER2-</td>
</tr>
</tbody>
</table>

*Approximately 80% overlap between ‘triple negative’ and intrinsic ‘basal-like’ subtype but ‘triple negative’ also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence. Staining for basal keratins although shown to aid selection of true basal-like tumors, is considered insufficiently reproducible for general use.

*Need good pathology!!!*

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Is Luminal BC the “friendliest” BC?

- NEJM 2017, EBCTCG
High risk breast cancer?

Hormone Positive

HER2+

Triple Negative
Treatment approaches in Luminal EBC

- who needs chemotherapy?
How to decide if and when chemotherapy indicated?

Cardoso et al, Ann Oncol, 2019
EBCTCG – everyone benefits from chemotherapy

EBCTCG, Lancet, 2005
NA-CTX - pCR as a surrogate for outcome

Cortazar et al, Lancet, 2014
NA-CTX= pCR & outcome by subtype

Luminal A
Luminal B - ER+/HER2-neg
Luminal B - ER+/HER2-pos

Von Minckwitz et al, JCO, 2012
Do Luminal A & Luminal B behave differently?

EC-DOC vs FEC Trial (1-3 LN): EFS

Nitz et al, SABCS 2009; Huober et al, SABCS 2010
Biological features & Genomic features determine risk that aid & decision making

- Classic clinical-pathological information
  - Genomic tests
Classic features – Grade

**PlanB**: Grade assessment by local and central pathology lab

<table>
<thead>
<tr>
<th>Histologic grade by local lab</th>
<th>Grade 1 (n = 164)</th>
<th>Grade 2 (n = 1602)</th>
<th>Grade 3 (n = 521)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (n = 120)</td>
<td>46 (38.3%)</td>
<td>70 (58.3%)</td>
<td>4 (3.3%)</td>
</tr>
<tr>
<td>Grade 2 (n = 1422)</td>
<td>106 (7.5%)</td>
<td>1135 (79.8%)</td>
<td>181 (12.7%)</td>
</tr>
<tr>
<td>Grade 3 (n = 745)</td>
<td>12 (1.6%)</td>
<td>397 (53.3%)</td>
<td><strong>336 (45.1%)</strong></td>
</tr>
</tbody>
</table>

Overall agreement in HR+ disease 66%

Gluz O, Nitz U, … Harbeck N. JCO 2016
PEPI (Pre-operative Endocrine Prognostic Index) score

Validated for use in studies of neo-adjuvant endocrine therapy

Patients with a low PEPI score following NA ET – will do exceptionally well with endocrine therapy alone

Table 4. The preoperative endocrine prognostic index*

<table>
<thead>
<tr>
<th>Pathology, biomarker status</th>
<th>RFS HR</th>
<th>RFS Points</th>
<th>BCSS HR</th>
<th>BCSS Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological tumor size</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td></td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>T3/4</td>
<td>2.8</td>
<td>3</td>
<td>4.4</td>
<td>3</td>
</tr>
<tr>
<td>Node status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>3.2</td>
<td>3</td>
<td>3.9</td>
<td>3</td>
</tr>
<tr>
<td>Ki67 level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%-2.7% (0-1t)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2.7%-7.3% (1-2t)</td>
<td>1.3</td>
<td>1</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>&gt;7.3%-19.7% (2-3t)</td>
<td>1.7</td>
<td>1</td>
<td>2.0</td>
<td>2</td>
</tr>
<tr>
<td>&gt;19.7%-63.1% (3-4t)</td>
<td>2.2</td>
<td>2</td>
<td>2.7</td>
<td>3</td>
</tr>
<tr>
<td>&gt;53.1% (&gt;4t)</td>
<td>2.9</td>
<td>3</td>
<td>3.8</td>
<td>3</td>
</tr>
<tr>
<td>ER status, Allred score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>2.8</td>
<td>3</td>
<td>7.0</td>
<td>3</td>
</tr>
<tr>
<td>3-8</td>
<td></td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

* To obtain the preoperative endocrine prognostic index (PEPI) score, risk points for relapse-free survival (RFS) and breast cancer-specific survival (BCSS) were assigned depending on the hazard ratio (HR) given in Table 3.

Ellis et al, JNCI, 2008
PEPI score & Ki67 changes as predictors of outcome to help select for continued NA ET

Outcome for NA chemotherapy in AI-poorly responsive tumors – based on Ki67 after 2-4 weeks of NET

Goncalves et al, BCRT, 2017
Ellis et al, JCO, 2017
Recurrence Score/Oncotype DX®

- A RT-PCR-based gene signature that measures the expression of 21 genes (16 cancer-related genes and 5 reference genes)
- *It uses the Recurrence score (RS) to predict the risk of distant relapse within 10 years*
- Developed in ER+, under tamoxifen treatment
- Extensive retrospective validation; ongoing prospective validation

Paik, NEJM 2004
Trial Assigning Individualized Options for Treatment (Rx), or TAILORx

- Designed to determine whether adjuvant endocrine therapy alone is as effective as adjuvant endocrine therapy in combination with chemotherapy for certain women with breast cancer (ER+, HER2-, node-neg ESBC, 1.1-5.0 cm or 0.6-1.0 cm and grade 2 or 3)

Enrolled 10,071 pts (2006-2010) 900 sites, 6 countries

Study arm presented at ECC / ESMO 2015

Enrolled 10,071 pts (2006-2010) 900 sites, 6 countries

Oncotype DX® assay

Secondary study group
Recurrence Score® result
<11 ~29% of population

Secondary study group
Recurrence Score® result
>25 ~27% of population

Primary study group
Recurrence Score® result
11–25 ~44% of population

RANDOMISE

ARM A: endocrine therapy alone
N=1626 (15.9%)

ARM B: endocrine therapy alone
Recurrence Score = 11
- 7.3% distant recurrence rate at 10 years
- 95% CI 5%, 10%

ARM C: chemotherapy plus endocrine therapy

Recurrence Score = 25
- 16.1% distant recurrence rate at 10 years
- 95% CI 13%, 20%

Study arms for primary analysis To be reported at a later date (2017)

TAILORx Patients with Recurrence Score Results 0-10 on Endocrine Therapy: Less Than 1% Risk of Distant Recurrence at 5 Years

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

n=1626
Median follow-up 69 months

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
TAILORX: IMPLICATIONS FOR CLINICAL PRACTICE

How Does This Affect Practice Tomorrow? (for node-negative patients appropriate for chemo)

**Recurrence Score: Postmenopausal**
- ET alone: 11
- ET alone: 18
- ET alone: 25
- ET + chemo (who knows?): 31
- Chemotherapy + ET

**Recurrence Score: Premenopausal**
- ET alone: 11
- ET alone: 16/18
- ET alone: 25
- Chemotherapy + ET (omitting chemo not tested but consistent): 31
- Chemotherapy + ET

Presented By Lisa Carey at 2018 ASCO Annual Meeting
Results - DRFI: Comparison of Actual Outcomes For Patients Treated with Chemotherapy plus Endocrine Therapy (N=1300) vs. Expected Outcomes with Endocrine Therapy Alone

Chemo + ET (Actual) vs. ET Alone (Expected**)

** based on treatment effect of chemo in B20

5-Year Estimate

<table>
<thead>
<tr>
<th>DRFI Rate</th>
<th>Chemo + ET (Actual)</th>
<th>ET Alone (Expected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95.0%</td>
<td>93.0% (±0.8%)</td>
<td>86.8% (±1.7%)</td>
</tr>
<tr>
<td>90.0%</td>
<td>78.8% (±14.0%)</td>
<td>65.4% (±10.4%)</td>
</tr>
</tbody>
</table>

* Standard error (SE)
**TransATAC:** For Any Recurrence Score the Rate of Distant Recurrence Increases with the Number of Positive Nodes

Dowsett et al, SABCS 2008, Abstract # 53
MINDACT TRIAL DESIGN

Registration & Screening Surgery

N = 6694

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
C-low/G-low

1st randomization to treatment
use Clinical vs. Genomic risk

Chemotherapy

2nd randomization
Anthraclycline –based vs. Capecitabine-Docetaxel

Endocrine therapy

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

No Chemotherapy

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)

Discordant risk groups

F. Cardoso, NEJM 2016
MINDACT population at 5y median follow-up
DISCORDANT RISK GROUPS: PRIMARY TEST

The primary statistical test
(DMFS at 5Y)

Null Hypothesis: set at 92%
Observed 5Y DMFS = 94.7%
95% CI ≈ 92.5 – 96.2% excludes 92% !!!

F. Cardoso, NEJM 2016
Efficacy: CT vs no CT in discordant risk groups
Intent-to-treat analysis

Distant Metastasis Free Survival
c-High/g-Low

<table>
<thead>
<tr>
<th>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>CT</td>
<td>95.9 (94.0, 97.2)</td>
<td>0.78</td>
<td>0.267</td>
</tr>
<tr>
<td>no CT</td>
<td>94.4 (92.3, 95.9)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Distant Metastasis Free Survival
c-Low/g-High

<table>
<thead>
<tr>
<th>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>CT</td>
<td>95.8 (92.9, 97.6)</td>
<td>1.17</td>
<td>0.657</td>
</tr>
<tr>
<td>no CT</td>
<td>95.0 (91.8, 97.0)</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>
The MINDACT population: CT assignment according to a “Clinical” vs a “Genomic” strategy

Whole population $N = 6,693$

«Clinical» strategy
- CT to $1550 + 1806 = 3,356$ pts
- $50\%$

«Genomic» strategy
- CT to $592 + 1806 = 2,398$ pts
- $36\%$

14% reduction

F. Cardoso, NEJM 2016
Proposed future clinical use of MammaPrint®

Clinical risk (c)
Adjuvant Online!

Genomic risk (g)
70-gene signature or
MammaPrint®

- **c-Low/g-Low**
- **c-Low/g-High**
- **c-High/g-High**
- **c-High/g-Low**

**Discordant**

Clinical «Low risk» patients
No proven added value of MammaPrint®

Clinical «High risk» patients
Proven added value of MammaPrint®
with a \(46\%[1550/(1550+1806)]\) reduction in CT prescription (depends on baseline CT prescription rate!)

F. Cardoso, NEJM 2016
These results are similar to those reported by Gnant et al, who used the PAM50-based ROR score to analyze tissue samples from patients with **node-positive** disease who participated in the ABCSG-8 trial and the TransATAC trial.
The Danish Breast Cancer Group

Who?

ALL postmenopausal patients in Denmark who, by nationwide guidelines, in January 2000 through December 2003 were allocated to 5 years of endocrine treatment as the ONLY systemic treatment after a first diagnosis of ER+ breast cancer.

Eligible patients were ≥ 50 years and met at least one of the following risk criteria:

- a tumor size ≥ 20 mm (any histologic subtype)
- ductal histology with malignancy grade 2 or 3
- or one to three positive nodes (any histologic subtype)
Major findings from this study – with regards to distant recurrence risk at 10 years after 5 years of endocrine therapy alone

<table>
<thead>
<tr>
<th></th>
<th>Node Negative (n=1163)</th>
<th>Node Positive (n=1395)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>5% (95% CI, 2.9% to 8.0%)</td>
<td>3.5% (95% CI, 1.9% to 6.1%)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>7.3% (95% CI, 4.8% to 10.5%)</td>
<td>11.5% (95% CI, 8.0% to 15.6%)</td>
</tr>
<tr>
<td>High risk</td>
<td>17.8% (95% CI, 14.9% to 22.4%)</td>
<td>22.1% (95% CI, 18.6% to 25.8%)</td>
</tr>
</tbody>
</table>

All patients categorized as low risk regardless of nodal involvement status had DR absolute risk below or equal to 5%
Conclusions - DBCG Study

• Confirmation in a large nationwide clinical practice setting of Prosigna Clinical Validation data results (ABC5G8 and TransATAC)

• ALL patients in LOW RISK (N- or N+) had DR risk $\leq$ 5%.

• Prosigna could identify 26% of the N+ as low-risk with a 10yr risk of DR of just 3.5%

• By tailoring risk categorization by number of positive nodes
  - 37% of patients with 1 positive lymph node $\rightarrow$ Low risk
  - 15% of patients with 2 positive nodes $\rightarrow$ Low risk

• Outcome in high- and low-risk patients differed significantly in both the N0 and N+ subgroups (P<0.001)

• Luminal B tumors had a significantly worse outcome than Luminal A tumors
### Level of Evidence for applying Genomic tests?

<table>
<thead>
<tr>
<th>First-generation signatures (Mamma Print, Oncotype DX)</th>
<th>Gene expression profile, RT-PCR</th>
<th>For ER-positive, HER2-negative tumours</th>
<th>Prognostic</th>
<th>(Neo)Adjuvant ChT is indicated if high risk or high score</th>
<th>I</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation signatures (Prosigna®, Endopredict®)</td>
<td>N-Counter™ technology, RT-PCR</td>
<td>Can be carried out in biopsy or surgical specimen</td>
<td>For ER-positive, HER2-negative tumours, include T size and N status in their final score</td>
<td>Prognostic</td>
<td>(Neo)Adjuvant ChT is indicated if high risk or high score</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Can be carried out in biopsy or surgical specimen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(Neo)Adjuvant chemotherapy in Luminal EBC:
- timing
- type
- scheduling
Timing - Neo-adjuvant vs adjuvant

- Neo-adjuvant CTX is safe & efficient
  - Facilitates less invasive loco-regional treatment
  - No difference in DFS and OS between neo-adjuvant & adjuvant CTX
  - Slight difference in loco-regional recurrence rate
  - May facilitate tailoring of therapy
Can genomic scores be used to guide decisions about whether to give neo-adjuvant chemotherapy?

• Possibly!
• If the genomic score = High risk → chemotherapy
• If the genomic score = Low/intermediate risk – validity of making a final decision on chemotherapy will depend on extent of nodal involvement
WHICH TYPE OF CHEMOTHERAPY?

Taxanes > Anthra > CMF > No Chemo

Control 36.4%  4.2%
CMF 32.2%

CMF 31.3%  4.3%

Anthra 31.0%

Taxane 25.9%  5.1%

Years

EBCTCG 2005-06 Overview Peto SABCS 2007

Courtesy Fatima Cardoso
Taxanes beneficial for all sub-groups
### Results - Arm D: KM Estimates of Distant Relapse-Free Interval (DRFI) by Chemotherapy Regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>5-Year Rate</th>
<th>SE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>92.7%</td>
<td>+1.2%</td>
</tr>
<tr>
<td>A without T</td>
<td>92.3%</td>
<td>+1.6%</td>
</tr>
<tr>
<td>A and T</td>
<td>95.1%</td>
<td>+1.5%</td>
</tr>
<tr>
<td>CMF</td>
<td>88.5%</td>
<td>+4.8%</td>
</tr>
<tr>
<td>Other</td>
<td>95.5%</td>
<td>+2.5%</td>
</tr>
</tbody>
</table>

Cox model: any chemo regimen (N=1300) versus none (N=89)
- Adjustment for tumor size (>2 vs. <=2 cm), grade, RS, and age (>65 vs. 51-65 vs.<=50 years)
- Estimated hazard ratios 0.74  (95% CI 0.32, 1.69) for administration of any chemotherapy vs. none

* Standard error (SE)
ABC Trials Schema

Node+ or High Risk Node-Negative Stratification Variables
Number of + Nodes (0, 1-3, 4-9, 10+); Hormone Receptor (ER or PgR+, Both Negative)

ARM 1 (TaxAC Options)

A  TAC q 3 wk

B  AC q 3 wk  →  PTX q 1 wk

C  AC q 2 wk  →  PTX q 1 wk

D  AC q 2 wk  →  PTX q 2 wk

ARM 2 (TC)

TC q 3 wk

Arm 1 Options Per Study
• USOR 06-090 - 1A only
• NSABP B-46l/USOR 07132 - 1A only
• NSABP B-49 - investigator choice 1A-1D

Endocrine therapy for ER+ or PgR+ patients for minimum of 5 years

Presented By Joanne Blum at 2016 ASCO Annual Meeting
### Forest Plot of IDFS By Hormone and Nodal Status

<table>
<thead>
<tr>
<th>Nodes(+) ER/PgR Neg</th>
<th>HR</th>
<th>95% CI</th>
<th>Int.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.31</td>
<td>0.86-1.99</td>
<td></td>
</tr>
<tr>
<td>1-3</td>
<td>1.58</td>
<td>0.90-2.79</td>
<td>0.71</td>
</tr>
<tr>
<td>4+</td>
<td>1.34</td>
<td>0.62-2.91</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodes(+) ER or PgR (+)</th>
<th>HR</th>
<th>95% CI</th>
<th>Int.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.69</td>
<td>0.39-1.19</td>
<td>0.026</td>
</tr>
<tr>
<td>1-3</td>
<td>1.14</td>
<td>0.77-1.69</td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>1.46</td>
<td>0.95-2.26</td>
<td></td>
</tr>
</tbody>
</table>

**Overall**

HR = Hazard Ratio

HR Favors TC  HR Favors TaxAC
# ABC Trials: IDFS by Hormone and Nodal Status

## Exploratory Analysis

<table>
<thead>
<tr>
<th>ER/PgR (-)</th>
<th>Pts TaxAC</th>
<th>Events TaxAC</th>
<th>4 yr IDFS TaxAC</th>
<th>4 yr IDFS TC</th>
<th>Delta</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-</td>
<td>459</td>
<td>37</td>
<td>89.5</td>
<td>87.0</td>
<td>2.5%</td>
<td>1.31 (0.86-1.99)</td>
</tr>
<tr>
<td>1-3 N+</td>
<td>153</td>
<td>21</td>
<td>85.5</td>
<td>74.6</td>
<td>10.9%</td>
<td>1.58 (0.90-2.79)</td>
</tr>
<tr>
<td>4+ N+</td>
<td>42</td>
<td>11</td>
<td>71.8</td>
<td>60.8</td>
<td>11.0%</td>
<td>1.34 (0.62-2.91)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ER or PgR (+)</th>
<th>Pts TaxAC</th>
<th>Events TaxAC</th>
<th>4 yr IDFS TaxAC</th>
<th>4 yr IDFS TC</th>
<th>Delta</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-</td>
<td>358</td>
<td>29</td>
<td>91.5</td>
<td>94.2</td>
<td>-2.7%</td>
<td>0.69 (0.39-1.19)</td>
</tr>
<tr>
<td>1-3 N+</td>
<td>771</td>
<td>46</td>
<td>94.3</td>
<td>92.3</td>
<td>2.0%</td>
<td>1.14 (0.77-1.69)</td>
</tr>
<tr>
<td>4+ N+</td>
<td>279</td>
<td>35</td>
<td>87.2</td>
<td>81.4</td>
<td>5.8%</td>
<td>1.46 (0.95-2.26)</td>
</tr>
</tbody>
</table>
Prospective WSG Phase III PlanB trial: Final analysis on adjuvant 4xEC→4xDoc vs. 6xDocetaxel/Cyclophosphamide in high clinical and intermediate/high genomic risk HER2-negative early breast cancer

Nadia Harbeck, Oleg Gluz, Michael Clemens, Wolfram Malter, Toralf Reimer, Benno Nuding, Bahriye Aktas, Andrea Stefek, Anke Pollmanns, Fatemeh Lorenz-Salehi, Christoph Uleer, Petra Krabisch, Sherko Kuemmel, Cornelia Liedtke, Steven Shak, Rachel Wuerstlein, Matthias Christgen, Ronald E. Kates, Hans H. Kreipe, and Ulrike Nitz, on behalf of the WSG PlanB investigators
PlanB: Design
HER2-negative early breast cancer

- Age < 75 years
- cM0
- free margins
- pN+
- pN0 high risk

HR-
- pT > 2
- G2-3
- uPA/PAI-1↑
- HR-
- age < 35 years

HR+
- 0-3 LN and RS > 11
- 0-3 LN and RS ≤ 11

Doc75C600 x 6*
E90C600x4 → Doc100 x4*

Endocrine therapy*

* Endocrine Therapy and RT according to national guidelines
E: Epirubicin; Doc: Docetaxel; C: Cyclophosphamide

Recurrence Score: after early amendment

Presented by: Nadia Harbeck, MD

Courtesy of Nadia Harbeck
PlanB: Translational subprotocol
5-year DFS in per-protocol population
(no chemotherapy in pN0-1 and Recurrence Score 0-11)

Gluz et al, EBCC 2016, plenary lecture

Presented by: Nadia Harbeck, MD
PlanB: Disease-free survival (DFS) according to Recurrence Score (HR+)*

RS<25

- 5y DFS: TC: 95%, EC-Doc: 94%

RS>25

- 5y DFS: TC: 85%, EC-Doc: 86%

*ITT patients with RS measured; after early amendment

Presented by: Nadia Harbeck, MD
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

Figure 6: 10-year recurrence (A) and breast cancer mortality (B) by estrogen receptor status.

Poshla data from all trials of dose intense versus standard schedule chemotherapy. Of the 10,000 women who are estrogen receptor (ER) negative, 66% are ER-; and of the 25,052 women who are ER positive, 54% are ER+.
Other strategies
Phase 2 Randomized Trial of Primary Endocrine Therapy Versus Chemotherapy in Postmenopausal Patients With Estrogen Receptor-Positive Breast Cancer

To be presented by Dr Cardoso

Semiglazov et al, Cancer, 2007
Further studies?

ADAPT HR+/HER2-
Chemotherapy trial (neo-adjuvant)

- Prognosis Estimation
  - Ki-67
  - RS

- Efficacy Estimation
  - N2/3
  - R

- Surgery
  - Ki-67
  - RS

- Interim analysis for efficacy (pCR)
  - 3w

- Treatment
  - 16w
  - Paclitaxel 175mg/m² q2w, 8w
  - Epirubicin 90mg/m² Cyclophosphamide 600mg/m² q2w, 8w
  - Nab-Paclitaxel 125mg/m² q1w, 8w
  - Epirubicin 90mg/m² Cytophosphamide 600mg/m² q2w, 8w
  - Ki-67pos
    - >10%
  - Ki-67neg
    - ≤10%

- Surgery (in case of neoadjuvant treatment)
- High risk
- Intermediate risk
- Low risk

Robertson et al, SABCS 2017
Further studies?

- Waiting for RxPONDER results: Role of CT for RS low (<25) in N1 (1-3) ER[+] HER2[-]

<table>
<thead>
<tr>
<th>Study (ClinicalTrials.gov Identifier)</th>
<th>Description</th>
<th>Estimated Enrollment</th>
<th>Phase, Estimated Primary Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALLAS (NCT02513394)</td>
<td>Palbociclib for 2 years + standard ET for ≥5 years vs standard ET for ≥5 years in HR+/HER2- stage II or III early invasive breast cancer</td>
<td>5600</td>
<td>III September 2020</td>
</tr>
<tr>
<td>NATALEE (NCT03701334)*</td>
<td>Ribociclib + ET or ET alone in patients with stage II or III HR+/HER2- early breast cancer</td>
<td>4000</td>
<td>III November 2025</td>
</tr>
<tr>
<td>monarchE (NCT03155997)</td>
<td>Abemaciclib + ET or ET alone in patients with resected node-positive, early stage HR+, HER2- invasive breast cancer</td>
<td>4580</td>
<td>III April 2021</td>
</tr>
</tbody>
</table>
Conclusions

• Chemotherapy beneficial in Luminal B or high-risk Luminal A/B
• Selecting who needs chemotherapy in N0-N1?
  - Genomic risk score, tumor burden
  - Ki67 and PEPI scores validated for neo-adjuvant ET
• What?
  - Anthracycline-Taxane or TCx4-6
  - In high risk (N2+) – **Anthracycline+Taxane**
    [no other agents (5FU, Capecitabine, Gemcitabine, Bevacizumab) demonstrated to give additional benefit]
• When? Benefits of NA – downgrading axilla, ↑BCS
• How? Dose-dense beneficial, especially for higher risk
Other key issues in systemic treatment in Luminal EBC

- Results of studies of genomic score driven therapy in node positive
- Escalation/de-escalation of chemotherapy
- Studies “adjuvant” CDKi in high risk patients
- NA ET
- NA ET+ CDKi
- Adaptive, bio-marker/genomic driven clinical trials

International Guidelines:
ESMO, St. Gallen, NCCN, ASCO, AGO, Cancer Care Ontario Clinical Practice Guidelines, and others...
Advanced Breast Cancer

Fifth ESO-ESMO International Consensus Conference

14-16 November 2019 | Lisbon, Portugal

Coordinating Chair: F. Cardoso, PT
Co-Chairs: G. Curigliano, IT - S.A. Mertz, US

The ABC5 guidelines will be developed by ESO and ESMO.

The ABC5 conference and guidelines are endorsed by:

The ABC5 conference is held under the auspices of with official representatives of and is endorsed by:

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