Luminal *early* breast cancer: (neo-) adjuvant chemotherapy

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Disclosures

Honoraria for lectures and/or consulting:
Agendia, Amgen, Astra Zeneca, Celgene, Daiichi-Sankyo, Genomic Health, Lilly, MSD, Nanostring, Novartis, Odonate, Pfizer, Roche, Sandoz/Hexal, Seattle Genetics
Luminal EBC: (Neo-)adjuvant chemotherapy

- Treatment concepts in luminal EBC
- Indication for chemotherapy
- Standard regimens
  - Additional agents
  - Dose-dense options
- Standard duration
- Open questions
- YOUR Questions
Therapy strategies in early breast cancer

Luminal-like (ER or PgR positive, or both; HER2 negative)

Lymph node involvement; grade; Ki67; multigene signature or uPA/PAI-1 test

Luminal A or low risk (only in pN0–1)

Endocrine therapy

Luminal B or high risk (always in pN2–3)

Chemotherapy → endocrine therapy
EC-DOC Trial (1-3 LN): EFS

EC-Doc vs. FEC

Survival Functions

Luminal A

Survival Functions

LUMINAL B

Nitz et al, SABCS 2009; Huober et al, SABCS 2010
## Multigene assays in *early* breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Oncotype DX</th>
<th>Endopredict</th>
<th>Mammaprint</th>
<th>Prosigna</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Genomic Health</td>
<td>Sividon (distribution by Myriad)</td>
<td>Agendia</td>
<td>NanoString Technologies</td>
</tr>
<tr>
<td>Assay</td>
<td>21 gene recurrence score</td>
<td>11 gene assay</td>
<td>70 gene assay</td>
<td>50 gene assay (PAM 50, ROR score)</td>
</tr>
<tr>
<td>Tissue</td>
<td>FFPE</td>
<td>FFPE</td>
<td>FFPE (technical validation of original fresh-frozen tissue assay)</td>
<td>FFPE</td>
</tr>
<tr>
<td>Method</td>
<td>Quantitative RT-PCR</td>
<td>Quantitative RT-PCR</td>
<td>RNA microarray</td>
<td>nCounterTechnology</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Centralised (USA)</td>
<td>Decentralised</td>
<td>Centralised (Netherlands)</td>
<td>Decentralised</td>
</tr>
<tr>
<td>Registration or accreditation</td>
<td>Clinical Laboratory Improvement Amendment, College of American Pathologists</td>
<td>CE-Mark</td>
<td>FDA (In Vitro Diagnostic Multivariate Index Assay)</td>
<td>FDA (510k), CE-Mark</td>
</tr>
<tr>
<td>Determination of molecular subtype</td>
<td>No</td>
<td>No</td>
<td>Yes (using Blueprint)</td>
<td>Yes (not reported in USA)</td>
</tr>
<tr>
<td>Prognostic information (outcome)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Risk groups</td>
<td>Low, intermediate, high</td>
<td>Low vs high</td>
<td>Low vs high</td>
<td>Low, intermediate, high</td>
</tr>
<tr>
<td>Predictive information (response to adjuvant chemotherapy)</td>
<td>Yes</td>
<td>No data so far</td>
<td>Yes</td>
<td>No data so far</td>
</tr>
<tr>
<td>Evidence-based test indication</td>
<td>pN0-1, ER-positive, endocrine therapy</td>
<td>pN0-1, ER-positive, HER2-negative, endocrine therapy</td>
<td>pN0-1</td>
<td>pN0-1, ER-positive, HER2-negative, endocrine therapy, postmenopausal</td>
</tr>
<tr>
<td>Retrospective clinical validation*</td>
<td>NSABP B14 and B20; TransATAC; ECOG 9127; SWOG B814</td>
<td>ABCSG 6 and 8; TransATAC</td>
<td>Multicentre</td>
<td>ABCSG 8; TransATAC; MA.21</td>
</tr>
<tr>
<td>Prospective clinical trials</td>
<td>WSG-Plan B (3198 patients); WSG ADAPT (around 5000 patients); TAILORx (pNO; 10 253 patients); RxPONDER (pN1; around 9000 patients)</td>
<td>TUM (DI unicentre study, 167 patients)</td>
<td>MINDACT (BIG; WSG for Germany; 6693 patients); WSG PRIME (DI study, 34 centres; 452 patients)</td>
<td>Several European DI studies: WSG (11 centres, 200 patients); GEICAM; French multicentre study</td>
</tr>
</tbody>
</table>

FFPE=formalin-fixed, paraffin-embedded. FDA=Food and Drug Administration. ER=oestrogen receptor. DI=decision impact. *Cohort for translational research only, a subgroup of total study collective.

**Table 1: Commonly used multigene assays for risk assessment in early breast cancer**
MINDACT: Primary Endpoint

Clinical outcome of the MINDACT population at 5y median follow-up

B) DISCORDANT RISK GROUPS: PRIMARY TEST

The primary analysis population

Discordant risks

c-Low / g-High

RANDOMIZATION

No chemotherapy
N = 748

No change in risk post enrolment and no CT received
N = 644

c-High/g-Low

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% !!!

Piccart et al, AACR 2016
**Substantial 34.1% discordance** between clinical and molecular luminal subtypes

**MammaPrint and the corresponding molecular subtype BluePrint** strongly impacted clinical therapy decisions (**28.4% switch**) in EBC with up to 3 involved LN.

**Table 3: Reclassification by BluePrint**

<table>
<thead>
<tr>
<th>Clinical subtype</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>Basal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>luminal A-like</td>
<td>193</td>
<td>61</td>
<td>2</td>
<td>256</td>
</tr>
<tr>
<td>luminal B-like</td>
<td>79</td>
<td>90</td>
<td>4</td>
<td>173</td>
</tr>
<tr>
<td>Her2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>272</td>
<td>152</td>
<td>6</td>
<td>430</td>
</tr>
</tbody>
</table>

**Table 4: CT decision based on BluePrint/MammaPrint**

<table>
<thead>
<tr>
<th>Post test recommendation</th>
<th>BluePrint/MammaPrint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Luminal A</td>
</tr>
<tr>
<td>CT</td>
<td>25 (9.2%)</td>
</tr>
<tr>
<td>no CT</td>
<td>247 (90.8%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>272</td>
</tr>
</tbody>
</table>
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
**TransATAC:** For Any Recurrence Score the Rate of Distant Recurrence Increases with the Number of Positive Nodes

Dowsett et al, SABCS 2008, Abstract # 53
planB trial: Design
HER2-negative breast cancer

- pT1-4
- R0
- pN+ (pN0 high risk)
  - pT>2cm
  - G2-3
  - uPA/PAI-1↑
  - HR-
  - age ≤35y

- pT1-4
- R0
- pN0 high risk

**Randomization**

- HR-:
  - 0-3 LK and RS>11 or ≥ 4 LK
- HR+:
  - 0-3 LK and RS≤11

- T_{75}C_{600} \times 6^*
- E_{90}C_{600} \times 4 \rightarrow Doc_{100} \times 4^*
- Endocrine therapy*

* endocrine therapy and radiotherapy according to national guidelines
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>336 (45.1%)</td>
</tr>
</tbody>
</table>

Overall agreement in HR+ disease 66%
PlanB: Recurrence Score by (central) Ki-67

Good Correlation:
RS and Ki67 (if <10% or if >40%)
PlanB: Excellent distant DFS in RS low-risk group with endocrine therapy alone
(5-y DFS in pp population, n=2160, no chemotherapy in pN0-1 RS 0-11)
Luminal B EBC: Aggressive disease - Therapy optimization urgently needed (PlanB trial, 5y DFS)

Nitz U, Gluz O, ... Harbeck N. BCRT 2017
Luminal EBC: (Neo-)adjuvant chemotherapy

- Which are standard regimens?
**Luminal early breast cancer | Prof. Harbeck**

**OXFORD OVERVIEW 2011:**
**TAXANE + ANTHRACYCLINE VS. ANTHRACYCLINE (N=44,000)**

![Graphs and data showing survival benefit from adjuvant taxanes in all settings.](image)

**Survival benefit from adjuvant taxanes in all settings**

Risk reduction independent of age, T, N, G or HR status
Adjuvant chemotherapy standards: weekly paclitaxel and docetaxel q3w
Particular benefit for weekly paclitaxel in TNBC

Sparano et al, SABCS 2014
GEPARSEPTO: Does the taxane matter?

Δ pCR 9%  
p<0.001

3 yrs Δ 6.4%  
Log rank p=0.0044

- Paclitaxel
- Nab-paclitaxel

Untch et al, Lancet Oncology 2016; Schneeweiss et al, SABCS 2017
PlanB/SuccessC meta-analysis for 6x DOC/CYC (TC) in EBC (n=5923; median follow-up 62 months)

- Luminal A
- Luminal B
- TNBC
- pN2-3
PlanB: Disease-free survival (DFS) according to Recurrence Score (HR+)*

RS < 25

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

RS > 25

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

*ITT patients with RS measured; after early amendment
EBCTCG: Dose-dense chemotherapy

Pooled analysis of all 25 dose-dense and sequential trials

Recurrent

34122 women

RR 0.85 (0.81-0.89)
Logrank 2p < 0.00001
10-y gain 3.6% (CI 2.3-4.9)
Stnd 32.0%
Dose dense 28.4%

Breast Cancer Mortality

34122 women

RR 0.87 (0.82-0.92)
Logrank 2p < 0.00001
10-y gain 2.7% (CI 1.5-3.9)
Stnd 22.2%
Dose dense 19.5%

Gray et al, SABCS 2017
EBCTCG: Dose-dense chemotherapy

Pooled Analysis: recurrence by ER status

**ER- Negative**
- 9209 women
- RR 0.82 (0.76–0.88)
- Logrank 2p < 0.00001
- 10-y gain 4.7% (CI 2.3 – 7.1)
- Stnd 38.3%
- Dose dense 33.6%

**ER- Positive**
- 23495 women
- RR 0.86 (0.81–0.91)
- Logrank 2p < 0.00001
- 10-y gain 3.1% (CI 1.5 – 4.7)
- Stnd 29.4%
- Dose dense 26.3%

Gray et al, SABCS 2017
EBCTCG: Dose-dense chemotherapy

Pooled Analysis

Death without recurrence

RR 0.85 (0.74–0.98)
Logrank 2p = 0.02
10-y gain 0.5% (CI -0.3 – 1.2)

All cause mortality

RR 0.87 (0.82–0.91)
Logrank 2p < 0.00001
10-y gain 3.0% (CI 1.7 – 4.2)

Gray et al, SABCS 2017
Luminal EBC: (Neo-)adjuvant chemotherapy

- Is there a role for additional agents?
Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial

Lucia Del Mastro, Sabino De Placido, Paolo Bruzzi, Michele De Laurentiis, Corrado Boni, Giovanna Cavazzini, Antonio Durando, Anna Turletti, Cecilia Nistico, Enrichetta Valle, Onella Garrone, Fabio Pugliesi, Filippo Montemurro, Sandro Barni, Andrea Ardizzoni, Teresa Gamucci, Giuseppe Colantuoni, Mario Giuliano, Adriano Gravina, Paolo Papaldo, Claudia Bighin, Giancarlo Bisogni, Valeria Forestieri, Francesco Cognetti, for the Gruppo Italiano Mammella (GIM) investigators

- 5 FU
- Dose dense
**NSABP B-38 TRIAL: NO BENEFIT VS. TAC GAINED BY ADDING GEMCITABINE TO DD-AC-P IN NODE-POSITIVE BREAST CANCER**

<table>
<thead>
<tr>
<th></th>
<th>DD AC → P G (n = 1630)</th>
<th>DD AC → P (n = 1634)</th>
<th>TAC (n = 1630)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year DFS</td>
<td>80.6 %</td>
<td>82.2 %</td>
<td>80.1%</td>
</tr>
<tr>
<td>5 year OS</td>
<td>90.8 %</td>
<td>89.1 %</td>
<td>89.6%</td>
</tr>
<tr>
<td>HR DFS</td>
<td></td>
<td>HR 0.89 p= 0.14</td>
<td></td>
</tr>
<tr>
<td>HR OS</td>
<td></td>
<td>HR 1.01 p= 0.92</td>
<td></td>
</tr>
<tr>
<td>Toxicity (significant)</td>
<td>More febrile neutropenia and diarrhea</td>
<td>More sensory neuropathy. More anemia (increased use of ESA and transfusions)</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>13</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>AML/MDS</td>
<td>5</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>
Capecitabine in Addition to Anthracycline- and Taxane-Based Neoadjuvant Treatment in Patients With Primary Breast Cancer: Phase III GeparQuattro Study

Gunter von Minckwitz, Mahdi Rezai, Sibylle Loibl, Peter A. Fasching, Jens Huober, Hans Tesch, Ingo Bauerfeind, Jörn Hilfrich, Holger Eidtmann, Bernd Gerber, Claus Hanusch, Thorsten Kühn, Andreas du Bois, Jens-Uwe Blommer, Christoph Thomssen, Serban Dan Costa, Christian Jackisch, Manfred Kaufmann, Keyur Mehta, and Michael Untch

See accompanying editorial doi: 10.1200/JCO.2009.23.8451

<table>
<thead>
<tr>
<th>End Point Variable by Histologic RG</th>
<th>Treatment Arm</th>
<th>Analysis P</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>patients</td>
<td>A: EC + Docetaxel</td>
<td>B: EC + TX</td>
<td>C: EC + T-X</td>
</tr>
<tr>
<td>Total No.</td>
<td>471</td>
<td>471</td>
<td>479</td>
</tr>
<tr>
<td>RG 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>89</td>
<td>80</td>
<td>97</td>
</tr>
<tr>
<td>%</td>
<td>18.9</td>
<td>17</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Conclusion
Adding capecitabine to or prolonging duration of neoadjuvant EC plus docetaxel does not result in higher efficacy at surgery.

*J Clin Oncol* 28. © 2010 by American Society of Clinical Oncology
NSABP B40 TRIAL: PARTICULAR BENEFIT FROM BEVACIZUMAB IN LUMINAL DISEASE

- similar pCR with additional drugs (X, G)

- pCR higher with bevacizumab

Additional impact of bevacizumab
NSABP B40 and GEPARQUINTO: Inconsistent results regarding benefit from bevacizumab in subgroups

Figure 2. Pathological Complete Response (pCR), According to Subgroup.
The analyses of subgroups according to tumor and node stage and hormone-receptor status were prespecified and stratified.
Luminal EBC: (Neo-)adjuvant chemotherapy

- Chemotherapy before or after surgery?
Luminal EBC: Neoadjuvant chemotherapy

Neoadjuvant Systemic Chemotherapy - Indications

- Inflammatory breast cancer
- Inoperable breast cancer
- Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory breast cancer</td>
<td>2b</td>
<td>B</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Inoperable breast cancer</td>
<td>1c</td>
<td>A</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Large operable breast cancer requiring mastectomy and adjuvant chemotherapy with the goal of breast conservation</td>
<td>1b</td>
<td>B</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>If similar postoperative adjuvant chemotherapy is indicated</td>
<td>1b</td>
<td>A</td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>
pCR Rates by Tumor Subtypes

- **HR+**
  - Grade 1-2: 7
  - Grade 3: 16

- **HER2+ HR+**
  - No Tras: 18
  - Yes Tras: 30

- **HER2+ HR-**
  - No Tras: 31
  - Yes Tras: 50

- **TRIPLE NEG**: 34
Neoadjuvant chemotherapy: Subtype matters even within luminal disease

Luminal early breast cancer | Prof. Harbeck

Luminal EBC: Neoadjuvant chemotherapy does not necessarily render high pCR rates

In patients with no Ki-67 decrease, pCR is only 5.6%: CTx may not be the optimal solution

Ellis et al, JCO
Luminal EBC: (Neo-)adjuvant chemotherapy

- Future developments
Luminal EBC: Combination of static risk and dynamic early endocrine response assessment

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

- G3 with Ki-67 ≥40% in tumors >1cm
- N2/3
- N0 or N1
- RS ≥26
- RS 12-25
- RS ≤11
- Ki-67post ≥10%
- Ki-67post ≤10%

- Paclitaxel 175mg/m² q2w, 8w → Epirubicin 90mg/m² Cyclophosphamide 600mg/m² q2w, 8w
- Nao-Pac. 125mg/m² q1w, 8w → Epirubicin 90mg/m² Cyclophosphamide 600mg/m² q2w, 8w

Surgery
In case of neo-adjuvant treatment

- High risk
- Intermediate risk
- Low risk

*with or without prior endocrine "test" treatment

Interim analysis for efficacy (pCR)

Studiendesign ADAPT HR+/HER2-

Robertson et al, SABCS 2017
So, Where are we exactly?
Luminal *early* breast cancer: Chemotherapy

✓ Adjuvant CTx reduces the relative risk of relapse by ~25%

✓ **Luminal EBC**: main question (in pN0-1) is “who needs CTx” in addition to endocrine therapy:

✓ Luminal B or patients with *high-risk* luminal disease – Multigene assays can aid in decision making

✓ If CTx is indicated, (neo-)/adjuvant administration feasible

✓ Standards: Duration: 18-24 weeks

✓ Regimen: Anthracycline *and* taxane (sequence / combination) (eg. TAC; EC/AC - paclitaxel q7/docetaxel q21)

✓ 6x Doc/Cyclo (TC) evidence-based option for intermediate clinical risk (pN0-1)

✓ Dose-dense CTx seems more effective (EBCTCG), particularly in patients at high-risk/high tumor burden (pN2-3)
EVIDENCE-BASED, PATIENT-ORIENTED BREAST CANCER THERAPY

BreastCare
Multidisciplinary Journal for Research, Diagnosis and Therapy

www.karger.com/brc

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