Current standards and practice changing studies in Early Breast Cancer in 2019

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Chair, ABC Global Alliance and ABC Guidelines
ESMO Guidelines and Public Policy Steering Committees
ESO Scientific Committee
DISCLOSURES SLIDE

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CANCER AS A CAUSE OF DEATH

70% OF CANCER DEATHS OCCURS

FIGURE 1. Global Map Presenting the National Ranking of Cancer as a Cause of Death at Ages Below 70 Years in 2015. The numbers of countries represented in each ranking group are included in the legend. Source: World Health Organization.

Bray et al, CA Cancer J Clin 2018;0:9–31; Globocan 2018
Africa is witnessing a double burden as most countries are faced with both Communicable and non communicable diseases.
PUBLIC HEALTH EXPENDITURE AND OUT OF POCKET PERCENTAGES

BIGGEST INCREASE IN INCIDENCE EXPECTED

ECONOMIC CATASTROPHE both at PATIENT LEVEL and at COUNTRY LEVEL

(Courtesy Prof R. Sullivan)
CANCER IN THE WORLD – WOMEN - INCIDENCE

Bray et al, CA Cancer J Clin 2018;0:9–31
Globcan 2018
BREAST CANCER IN AFRICA

Incidence

GLOBOCAN 2018*

Mortality

Breast Cancer

Despite ↑ incidence - ↓ mortality

* Screening & early diagnosis
* Education & advocacy
  but also
* Better treatment options
* Better treatment strategies

UK and USA 1950–2003/2: Females
Breast cancer mortality at ages 35–69

Death rate / 100 000 women, age standardised

*Mean of annual rates in the seven component 5-year age groups
Source: WHO mortality & UN population estimates
Estimating the magnitude of clinical benefit of systemic and local therapies in patients with EBC

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) ("Oxford Overview")

St. Gallen 2019

ESMO EBC Guidelines 2019
2 MAIN QUESTIONS TO BE ANSWERED

WHO NEEDS TREATMENT?

WHICH TREATMENT IS BEST?

TREATMENT CHOICES

AVOID UNDER AND OVER TREATMENT

INDIVIDUALIZE TREATMENT

New/better PROGNOSTIC FACTORS

New/better PREDICTIVE FACTORS
8th Edition AJCC: ANATOMIC and PROGNOSTIC STAGGING

7th Edition Stage

- Tumor Size
- Nodal Involvement
- Metastasis

8th Edition Prognostic Stage Group

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

2010-2017

2018 and beyond
CLINICOPATHOLOGICAL PROGNOSTIC FACTORS IN EBC

- Tumor size
- Lymph node status
- Grade
- ER, PR and HER-2 receptor expression
- Presence of lymphovascular invasion
PROGNOSTIC VALUE OF BC MOLECULAR SUBTYPES

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

A

B

Relapse Free Survival

0.0 0.2 0.4 0.6 0.8 1.0

0 20 40 60 80 100 120 140

Months

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

p=7.67e-06

Courtesy of MJ Brito
PROGNOSTIC VALUE OF SUBTYPES IHC SURROGATES

IHC TRANSLATION OF MOLECULAR CLASSIFICATION

ER/PR    HER2    PCAD    CK5    EGFR    CK14

LUMINAL A
LUMINAL B
HER 2 OE
BASAL

Courtesy of MJ Brito

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


Breast-Cancer-Specific Survival According to Immunohistochemical Subtype

VALIDATED PREDICTIVE MARKERS

Breast Cancer

HER2

Negative predictive value

HIGH 95%

(<5% chance to respond to anti-estrogens or trastuzumab)

ER/PGR

Positive predictive value

30-50%

Cut off 1%

Courtesy F. Penault-Llorca
**St Gallen 2019 Consensus**

- **TIL’s (tumor-infiltrating lymphocytes):**
  - Panel (66%) recommend routine characterization and reporting
  - 90% would not decide upon indication for or de-escalation (79%) of chemotherapy based on high TILs

Prognostic value of tumor infiltrating lymphocytes (TILs) in patients with early-stage triple negative breast cancers (TNBC) in the absence of chemotherapy: A pooled analysis of 4 individual cohorts. J Park @ESMO 2019

![Survival outcomes in patients with sTILs ≥30%](Image)

![Further Excellent Outcomes In pStage I tumors](Image)

Courtesy J. Ribeiro
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...
SOURCES OF VARIATION IN BIOMARKERS TESTING

IHC, ISH testing variables

Pre-analytical

- Time to slicing and fixation
- Method of tissue processing
- Time of fixation
- Type of fixation
- Assay validation
- Equipment calibration
- Laboratory procedures

Analytical

- Assay conditions
- Control materials
- Test reagents
- Staff competence
- Type of antigen retrieval

Post-analytical

- Reporting elements
- Scoring system
- Interpretation criteria
- Use of image analysis
- Post-analytical variables

Pre-analytical variables

- Wolff et al 2007
- Courtesy F. Penault-Llorca
Variable Specimen Handling Affects Hormone Receptor Test Results in Women With Breast Cancer

A Large Multihospital Retrospective Study

Flory L. Nkoy, MD, MS, MPH; M. Elizabeth H. Hammond, MD; William Rees, MD; Tom Belnap, MS; Braden Rowley, BS; Steve Catmull, BS; William Sause, MD

Figure 2. Frequency of estrogen receptor (ER) and progesterone receptor (PR) negative test results by day of surgery.
When to question a Pathology report

... according to Frédérique Penault-Llorca

- PgR+, ER-
- Lobular, tubular carcinoma HER2+
- Grade 1, ER++, PgR++, HER2+
- Grade 3, ER-, ki67 <5%
- Grade 3 ER++, PgR++
- Medullary carcinoma is extremely rare and has been removed from WHO classification

➤ May redo HER2 (and ER) on surgical specimen if grade 3, ER- or ER+
➤ If ER and/or PgR is negative on a biopsy redo on surgical specimen

MULTIDISCIPLINARY CARE IS CRUCIAL!
MINDACT TRIAL DESIGN

C-List/G-low

PAM 50 (Prosigna Breast Cancer Assay)

Breast Cancer Index (BCI)

Endopredict / Endopredict Clin

TAILORx Method: Treatment Assignment & Randomization
Accrued between April 2006 - October 2010

ARM A: Low RS 0-10
(N=11,232 evaluable)
ASSIGN
Endocrine Therapy (ET)

ARM B: Experimental Arm
(N=3,399)
ET Alone

ARM C: Standard Arm
(N=3,312)
Chemo and ET

ARM D: High RS 26-100
(N=1,389 evaluable)
ASSIGN
Chemo and ET

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

Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM: Low RS 0-10
Mid Range RS 11-25
High RS 26-100

Register

No Chemotherapy

HR+ HR+
N= 6600

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ARM: Low RS 0-10
Mid Range RS 11-25
High RS 26-100

Register

No Chemotherapy

HR+ HR+
N= 6600
MINDACT population at 5y median follow-up

**DISCORDANT RISK GROUPS: PRIMARY TEST**

Null Hypothesis: set at 92%

Observed 5Y DMFS = 94.7%

95% CI = 92.5 – 96.2% excludes 92% !!!

**The primary statistical test (DMFS at 5Y)**

Efficacy: CT vs no CT in discordant risk groups

Intent-to-treat analysis

Implementation problems:

Cost of the test, lack of reimbursement, logistics, time

The use of MammaPrint allows to spare chemotherapy in about 46% of patients traditionally considered at high risk
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
GENOMIC TESTS IN ALL OR ONLY SELECTED BREAST CANCER CASES?

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

LUMINAL
ER+ HER-2 neg
“Clear” indication from classical factors
All LOW risk: high levels ER, PR, grade 1, node negative, low proliferation
HT alone

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

HER-2 POSITIVE
CT + anti-HER indispensable

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

CRUCIAL IMPORTANCE OF HIGH QUALITY PATHOLOGY
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.

PREOPERATIVE CHEMOTHERAPY IN BC
HISTORICAL PERSPECTIVE

1970
1980
1990
2000

DISEASE
Locally advanced  Early  Early  Early

GOAL
↑ Local control  ↑ Rate of breast conservation  ↑ Survival  ↑ Treatment tailoring

ACHEIVED  ACHIEVED  NO DIFFERENCE  ONGOING

Adapted from M. Piccart
Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials

EBCTCG Neoadjuvant vs Adjuvant CT. Lancet Oncology 2017

Substantially higher frequency of BCS with neoadjuvant
Association between pCR and EFS by BC subtype

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

ESMO EBC Guidelines.
Cardoso F et al, Annals of Oncology 2019
IMPORTANT TAKE-HOME MESSAGES

• Neoadjuvant approach only works if management is TRULY MULTIDISCIPLINARY
  • Patient case must be discussed BEFORE any therapeutic decision and at least surgeon, medical oncologist, radiologist, pathologist and radiation oncologist must be present
  • Surgeon must see the patient before/around the start of neoadjuvant systemic therapy
  • LESION(S) MUST ALL BE BIOPSED AND MARKED
  • PATHOLOGY is crucial (histology, grade, ER, (PR), HER2, proliferation)
  • Imaging must be performed before starting, preferable in the middle of, and at the end of therapy
THE ROLE OF EXPERIENCE AND EXPERTISE

CRUCIAL IMPORTANCE OF EXPERIENCE

Effect of hospital volume on processes of care and 5-year survival after breast cancer: A population-based study on 25,000 women

France Verinaer, Sabine St Verdoux, Joos Belsens, Stephane Devereux, Elizabeth Van Eyck, Jan Vlayenc

< 50 bcp  vs  > 150 bcp
75%  vs  84% survival at 5 years

Conclusion: Survival benefits reported in high-volume hospitals suggest a better application of recommended processes of care, justifying the centralization of breast cancer care in such hospitals.
Surgical Treatment after NACT in EBC

Operable breast cancer, T1-T3, stage I-IIIA invasive ductal carcinoma (all biologic subtypes) with clinical complete response by physical exam and radiologic complete or near complete response by imaging after neoadjuvant systemic treatment.

ENROLLMENT IN THE TRIAL

IMAGE-GUIDED CORE BIOPSY

SURGERY
(Breast conserving surgery or Mastectomy)

RESPONDER
MICRA TRIAL
NRG-BR005
MI Pooled Anal*

Assess the accuracy of post-NAC image-guided breast biopsy to predict residual cancer (FNR* for residual cancer)

* FNR – False Negative Rate

Courtesy J. Ribeiro
## Surgical Treatment after NACT in EBC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample size (n)</th>
<th>Biologic Subtypes</th>
<th>1(^\text{st}) End-point FNR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPONDER</td>
<td>398</td>
<td>TN: 33% HER2: 34% HR+ve:33%</td>
<td>17.8% (12.8 – 23.7)</td>
</tr>
<tr>
<td>MI Pooled Analysis</td>
<td>166</td>
<td>TN: 36% HER2: 45% HR+ve:19%</td>
<td>17.4% (8.4 – 25.4)</td>
</tr>
<tr>
<td>MICRA</td>
<td>167</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>NRGA-BR005</td>
<td>98</td>
<td>TN: 32% HER2: 45.8% HR+ve:22%</td>
<td>*NPV = 77.5% (66.8 – 86.1)</td>
</tr>
</tbody>
</table>

- **Findings at this time do not support omitting surgery**
  - False negative rates between 17% - 37%
  - Negative predictive value well bellow 90%
  - Residual disease is missed in 2/3 of patients

Courtesy J. Ribeiro
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>
WHICH TYPE OF CHEMOTHERAPY?

Taxanes > Anthra > CMF > No Chemo
TAKE-HOME MESSAGES REGARDING TYPE OF (NEO)ADJUVANT CT

• For **TNBC and HER-2+** Anthracyclines and Taxanes, in a sequential regimen, are the standard.
• For **Luminal A-like with high burden of disease** justifying CT, probably it does not matter which regimen is chosen
• For **Luminal B-like**, 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
  • No need to use 5-FU (LoE 1A)
WHICH TYPE OF ENDOCRINE THERAPY?

Messages from the EBCTCG overview & individual trials

✓ Efficacy of 5 years Tam 9% ABSOLUTE BENEFIT

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms/Population (n)</th>
<th>Median FU</th>
<th>Recurrence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tamoxifen 5 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overview 2011[76]</td>
<td>TAM 5 y vs no TAM 10 645 ER+</td>
<td>15 y</td>
<td>RR 0.53 [SE 0.03] years 0–4</td>
<td>RR 0.71 [SE 0.05] years 0–4,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR 0.68 [SE 0.06] years 5–9</td>
<td>RR 0.66 [SE 0.05] years 5–9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2p&lt;0.00001</td>
<td>RR 0.68 [SE 0.08] years 10–14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR 0.97 [SE 0.10] years 10–14</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

CARRY-OVER EFFECT

MCBS: A

Ribeiro, Sousa and Cardoso, ECCO-ESMO 2013 Educational Book
Adjuvant Aromatase Inhibitors: A meta-analysis

Dowsett M et al., J Clin Oncol 2010
More than Half of all Breast Cancer Recurrences and Deaths Occur Post-5y Tamoxifen

Recurrences

- 15% Tamoxifen
- 17% Control

Breast cancer deaths

- 9% Tamoxifen
- 18% Control

EBCTCG, Lancet. 2005
Trial Designs Extended Adjuvant Therapy

- MA-17: Tam, R
- NSABP-B33: Tam, R
- ABCSG-6a: Tam, R
- NSABP-B42: Tam, Al, R
- MA-17R: Tam, Al, R
- ABCSG-16: Tam, Al
- DATA: Tam, R, Ana
- IDEAL: Tam, Al
- SOLE: Tam, Al

HR DFS:
- MA-17: 0.57
- NSABP-B33: 0.68
- ABCSG-6a: 0.62
- NSABP-B42: 0.85
- MA-17R: 0.80
- ABCSG-16: 0.79
- IDEAL: 0.88

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2019: POTENTIAL NEW UTILITY OF GENOMIC SIGNATURES
Breast Cancer index (BCI)

- a second-generation gene signature that is prognostic for pts with ER+ EBC who have/have not received TAM
- a qRT-PCR method that measures expression of 2 genes, HOXB13 and IL17BR and classifies pts into low, intermediate and high-risk group
- Validation: the Stockholm study, n=317 pts, ER+, N0, TAM

BCI was the only significant prognostic factor for risk of both, early and late distant recurrence (apart from OncotypeDx RS and IHC4, which predicted only early distant recurrence).

Sgroi DC et al., Lancet Oncol 2013.
aTTom Parent Study

- 6956 early stage patients who completed at least 4 years of tamoxifen randomized to either stop or continue tamoxifen for an additional 5 years.
- Demonstrated benefit from 10 years tamoxifen in disease-free interval (DFI) at a median 8.9 years of follow-up.
  - HR: 0.86, 95% CI 0.77-0.96, (p=0.006)
- Extended tamoxifen treatment was associated with a significant increase in endometrial cancer (p<0.0001)
- Data available to 12.6 years median follow-up (2017)

Gray R et al. J Clin Oncol 2013; 31 (suppl; abstr 5).

78% ≥ 55 years old, 50% T1, 38% T2, 31% node-positive

8863 enrolled
7324 randomized after 4+ years of tamoxifen
1539 <4 years prior tamoxifen
3656 CONTINUE
3668 STOP
3470 CONTINUE
3486 STOP
84 DCIS/LCIS
102 ER-negative
87 DCIS/LCIS
95 ER-negative
N=6956

John Bartlett, PhD <John.Bartlett@oicr.on.ca>

Centralized testing of HR status
- Blinded to clinical outcome
- ER, PR, HER2
Trans-aTTom
- Planned ~2500 cases
- N0 and N+
- Confirmed HR+
- HER2- or HER2+

Trans-aTTom Study Design

BCI testing
- Blinded to clinical outcome

Interim Analysis
- Planned analysis N=1200 HR+
- Prespecified p value stopping boundary: 0.0334

Final Analysis
- Planned analysis N = ~1800 HR+
- Final p value stopping boundary: 0.0336

aTTom trial
6956 patients
12.6 years FU
Relative Benefit of Extended Tamoxifen by BCI (H/I) Status: Trans-aTTom N+ cases

<table>
<thead>
<tr>
<th>Hazard Ratio (mean 95% CI)</th>
<th>Relative Benefit</th>
<th>Favors 10-year</th>
<th>Favors 5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>All N+ Patients</td>
<td>0.88 (0.65 - 1.18)</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>BCI (H/I)-Low</td>
<td>1.07 (0.69 - 1.65)</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>BCI (H/I)-High</td>
<td>0.35 (0.15 - 0.86)</td>
<td>0.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

N=583

N=296 (51%)

N=287 (49%)

John Bartlett, PhD <John.Bartlett@oicr.on.ca>

Absolute Benefit of Extended Tamoxifen by BCI (H/I) Status

<table>
<thead>
<tr>
<th>Reduction in Risk of Recurrence</th>
<th>All N+ Patients</th>
<th>BCI (H/I)-Low</th>
<th>BCI (H/I)-High</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>4.7%</td>
<td>-0.2%</td>
<td>10.2%</td>
</tr>
<tr>
<td>5%</td>
<td>p=0.388</td>
<td>p=0.768</td>
<td>p=0.027</td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

John Bartlett, PhD <John.Bartlett@oicr.on.ca>

Bartlett et al, ASCO 2019
Outcomes from Premenopausal Adjuvant Chemotherapy Trials with no Hormonal Rx

Goldhirsch A et al. JNCI Monogr 2001;30:44-51

Hazard Ratio of Relapse

0.5 1 1.5 2

ER+, 35+
ER-, 35+
ER+, <35
ER-, <35

Hazard Ratio of Relapse

0.5 1 1.5 2

ER+, 35+
ER-, 35+
ER+, <35
ER-, <35
TEXT and SOFT Trials: Comparison of Tamoxifen or Exemestane With OFS

**TEXT**
- Premenopausal Patients with HR+ BC ≤ 12 wks after surgery (N = 2672)
- Joint Analysis
- Tamoxifen 20 mg/day + OFS* (n = 1328)
- Exemestane 25 mg/day + OFS* (n = 1332)
- Tamoxifen 20 mg/day + OFS* (n = 1016)
- Exemestane 25 mg/day + OFS* (n = 1014)
- Tamoxifen 20 mg/day

**SOFT**
- Premenopausal patients with HR+ BC ≤ 12 wks after surgery (if no chemo) or ≤ 8 mos after chemo (N = 3066)
- Joint Analysis
- Tamoxifen + OFS* (n = 2344)
- Exemestane + OFS* (n = 2346)

*OFS: triptorelin 3.75 mg IM every 28 days for 6 mos, then optional bilateral oophorectomy or irradiation
- TEXT: choice of method

**Joint Analysis**
- 5 yrs


---

**SOFT: SUPPRESSION of OVARIAN FUNCTION TRIAL**

Premenopausal ER+ve and/or PR+ve Breast Cancer

3047 Patients Randomized in ITT, Dec 2003 - Jan 2011

- Primary Analyses (n=2033)
- Median follow-up 5.6 years

Two Patient Cohorts (stratified)

- No Chemotherapy (47%)
  - Premenopausal, within 12 weeks of surgery
  - (Median time since surgery = 1.8 months)
- Prior Chemotherapy (53%)
  - Premenopausal after completing chemotherapy;
  - Randomization within 8 months of completion
  - (Median time since surgery = 8.0 months)

Randomize

- Tamoxifen x 5y (n=1018)
- Tamoxifen+OFS x 5y (n=1015)
- Exemestane+OFS x 5y (n=1014)

OFS=ovarian function suppression
( GnRH triptorelin, oophorectomy or irradiation)

*According to locally-determined fsh level in premenopausal range

**Francis et al, N Engl J Med, 2015**
TAKE HOME MESSAGES and OPEN QUESTIONS, regarding ADJUVANT ET

• TAMOXIFEN is essential. AIs provide a small additional benefit and different toxicity profile
  • No predictive markers to discriminate between Tam & AI

• 5 years is the minimal duration for all patients. In pts with “sufficiently high risk” consider extended adjuvant

• Optimal duration for the individual patient is unknown; Best strategy for extended adjuvant (10 y Tam; 10 y AI, sequence, “sandwich”, ...) is unknown

• Ovarian suppression/ablation is indicated in pts with high risk of recurrence needing CT and recovering menses after CT. Reserve AI+OFS to very high risk only (toxicity!)
  • Decision for the individual patient still difficult; optimal duration unknown
TAILORx Results AT MEDIAN FU OF 9 YEARS: Summary

• Primary conclusions
  • RS 11-25: ET was non-inferior to chemotherapy + ET (primary endpoint - ITT)
  • RS 0-10: Distant recurrence rates very low (2-3%) with ET alone at 9 years
  • RS 26-100: Significantly higher event rates, driven by more recurrences despite adjuvant chemo plus ET

• Other observations
  • Age – RS – Chemo treatment interaction:
    • Some chemo benefit in women 50 or younger with a RS 15-25
    • Greatest impact on distant recurrence with RS 21-25

Joseph A. Sparano, MD

CONCLUSIONS

1. This unplanned and underpowered subgroup analysis of MINDACT was initiated following the observation in TailorX of heterogenous clinical outcomes according to age in women at “high clinical risk” using MINDACT’s definition.

2. Although cautious interpretation is needed (see large confidence intervals), the present analysis suggests that in women younger than 50, in the cH/gl group, tamoxifen alone might not be the optimal treatment, though the difference seen between CT and no-CT groups is small (<3%).

3. It is possible that this age-dependent effect is due to chemotherapy-induced ovarian function suppression. Neither MINDACT nor TailorX are able to answer this question.
## Summary recommendations for ER positive, HER2 negative BC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Ovarian Suppression</th>
<th>Duration of Endocrine Therapy</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1ab</td>
<td>No OFS</td>
<td>AI or tam (5yrs)</td>
<td>No</td>
</tr>
<tr>
<td>T1c</td>
<td>No OFS</td>
<td>AI or tam (5yrs)</td>
<td>Individualized decision based on T size, N status, histological subtype, LVI, grade, proliferation assays, quantitative hormone receptor expression, proliferation, and preferably, genomic signatures; and patient preferences</td>
</tr>
<tr>
<td><strong>Stage 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node-negative</td>
<td>OFS and AI/tam for high risk (large T; warranting chemo, Age &lt; 35; high grade; adverse gene signature)</td>
<td>AI preferred as initial therapy (especially with lobular histology); extended favored (especially after initial 5 yrs Tam)</td>
<td></td>
</tr>
<tr>
<td>Node-positive</td>
<td>OFS and AI/tam</td>
<td>Extended</td>
<td></td>
</tr>
<tr>
<td><strong>Stage 3</strong></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
Adjuvant chemotherapy ± trastuzumab trials: overall survival

<table>
<thead>
<tr>
<th>Study</th>
<th>HR</th>
<th>Difference at 4y/3y</th>
<th>p</th>
<th>Median FU yrs</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined US (n=3969)b</td>
<td>0.63</td>
<td>3.2%</td>
<td>0.0004</td>
<td>3</td>
<td>Perez 2007</td>
</tr>
<tr>
<td>HERA (n=3401)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCIRG AC-DT (n=1074)</td>
<td>0.59</td>
<td>6%</td>
<td>0.004</td>
<td>3</td>
<td>Slamon 2006</td>
</tr>
<tr>
<td>BCIRG DCarboT (n=1075)</td>
<td>0.66</td>
<td>5%</td>
<td>0.017</td>
<td>3</td>
<td>Slamon 2006</td>
</tr>
<tr>
<td>FinHER (n=232)</td>
<td>0.41</td>
<td>6.6%*</td>
<td>0.07</td>
<td>3</td>
<td>Joensuu 2006</td>
</tr>
<tr>
<td>PACS-04 (n=528)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**REDUCTION IN MORTALITY RISK: 34%-59% IN EBC**

**COST TRASTUZUMAB: ~ 2.300 €/cycle (s.c T)**

*Benefit at 3y

*Absolute difference in percentage of patients with OS at 4 or 3 years

*Combined US: Joint analysis of NSABP B-31 and NCCTG N9831

**MCBS: A**
TRIALS EVALUATING ADJUVANT TRASTUZUMAB DURATION

1 vs. 2 years: HERA

9 weeks: FinHER (Finland)

1 year vs. 3 ms: E 2198 (US)

1 year vs. 9 weeks: ShortHER

1 year vs. 9 weeks: SOLD

1 year vs. 6 ms: PHARE (France)

1 year vs. 6 ms: HeCOG (Greece)

1 year vs. 6 ms: Persephone (UK)
Treatment delay due to cardiotoxicity: 6% (12m) vs 4% (6m), p=0.01
Treatment stopped due to cardiotoxicity: 8% (12m) vs 4% (6m), p<0.0001
Cardiac function recovers pós trastuzumab; 6m patients had a faster recovery (p=0.02)
TAKE HOME MESSAGES – DURATION anti-HER2+

Duration of adjuvant trastuzumab: **1 YEAR IS STILL THE STANDARD**

**BUT:**

PHERSEPHONE results demand discussion of shorter duration in “low risk” patients

**Open questions:**
De-escalate anti-HER2 therapy or CT or both?
How to define “low risk HER2+ BC”?
Can we find a biomarker to help with the decision?

**In total about 15.000 pts enrolled to answer duration question!**
Really needed? Can we be smarter in trial design?
If we had done 1 trial but sufficiently powered?
TRIALS EVALUATING DUAL HER2 BLOCKADE

Advanced Disease

Strategies:

**STRATEGY A**
- EGF104900
- NeoALTTO
  - Cherlob
  - LPT 109096
  - NSABP B-41
  - CALGB 40601
- ALTTO

**STRATEGY B**
- Cleopatra
  - PERUSE
  - PHEREXA
- NeoSPHERE
  - TRYPHAENA
  - WSG-ADAPT
  - KRISTINE
- APHINITY

Settings:
- Neoadjuvant setting
- Adjuvant setting

Alvaro Moreno-Aspitia et al, ASCO 2017
**APHINITY: Trial Design**

- **Central confirmation of HER2 status** (N = 4805)
- Randomisation and treatment within 8 weeks of surgery
- **Anti-HER2 therapy for a total of 1 year (52 weeks)** (concurrent with start of taxane)
- Radiotherapy and/or endocrine therapy may be started at the end of adjuvant chemotherapy

**Randomisation and Treatment**

- Chemotherapy* + trastuzumab + pertuzumab
- Chemotherapy* + trastuzumab + placebo

**COST PERTUZUMAB:** ~ 4.100 €/cycle

**DUAL BLOCKADE COST:** ~ 6.400 €/cycle

**MCBS:** A for Node+ or ER neg

**Expected Survival**

- Absolute difference: 2%
- Number needed to treat: 112
- Expected: 89.2%

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*G. von Minckwitz et al, ASCO 2017, NEJM 2017*
APHINITY: Node-positive Subgroup

Absolute difference: 3%

APHINITY: Hormone Receptor-negative Subgroup

Absolute difference: 3%
APHINITY: 2nd INTERIM OS ANALYSIS - SABCS 2019
Median FU: 74.1 months

Primary endpoint IDFS (ITT population)

OS (ITT population)
In the node positive cohort absolute benefit 4.5%
APHINITY: Updated results, SABCS 2019
By ER status, Median FU: 74.1 months

The effect of pertuzumab is now seen in the HR neg and in the HR+ve cohort (absolute benefit 2.5% to 3.0%)
**KATHERINE Study Design**

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

**Stratification factors:**
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

**THE ROLE OF T-DM1 IN EBC**
(post-neoadjuvant)

- **T-DM1**
  - 3.6 mg/kg IV Q3W
  - 14 cycles

- **Trastuzumab**
  - 6 mg/kg IV Q3W
  - 14 cycles

Radiation and endocrine therapy per protocol and local guidelines

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### Invasive Disease-Free Survival

![Graph showing invasive disease-free survival rates between Trastuzumab and T-DM1](image)

**Main Problem:**
COST!!

**Absolute difference: 11% in iDFS**

### Distant Recurrence

![Graph showing distant recurrence rates between Trastuzumab and T-DM1](image)

**Unstratified HR = 0.60 (95% CI, 0.45–0.79)**

3-year event-free rate: 83.0% for Trastuzumab vs. 89.7% for T-DM1

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**THE ROLE OF T-DM1 IN EBC**

(post-neoadjuvant)

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HER-2+ EBC: Anti-HER2 therapies

ESMO EBC Guidelines.
Cardoso F et al, Annals of Oncology 2019
Timing of Distant Recurrences in relation to Adjuvant Trastuzumab

< 2% of patients relapse on adjuvant trastuzumab and < 5% in the year following


Courtesy G. Curigliano
ExteNET: 5-year analysis: iDFS

ExteNET: Side Effects

<table>
<thead>
<tr>
<th>N %</th>
<th>Neratinib (n=14080)</th>
<th>Placebo (n=1408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>G3-4</td>
<td>All grades</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1343 (95.4)</td>
<td>562 (39.9)</td>
</tr>
<tr>
<td>Dose reduction:</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Tx termination:</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

What does G3 diarrhea mean?
- > 7 stools daily
- incontinence;
- hospitalization indicated
- limiting self care ADL

Courtesy of Dr Aleksandra Łacko
7 years FU results (only 23 events):

**DFS**: 93% (95% CI, 90.4 to 96.2)

(only 4 (1.0%) distant recurrences)

**OS**: 95% (95% CI, 92.4 to 97.7)
Major message: NOT PRACTICE CHANGING

Results not comparative
Only T1, 75% ER+
Higher toxicity and discontinuation with T-DM1

Tolaney S et al, SABCS 2019
TAKE HOME MESSAGES regarding HER2+ EBC

• **Trastuzumab** is life-saving and has changed the natural history of HER2+ EBC! *(should be the focus of lobbying/pressure for access)*

• **Dual blockage with Pertuzumab** adds some benefit in **Node+** *(but expensive!)*

• **Lapatinib not useful. Neratinib too toxic and small benefit.**

• **T-DM1 role is post-neoadjuvant is interesting** *(but expensive!)*

• **USE (approved and high quality) BIOSIMILARS**

• **Open questions:**
  • Role of 2 anti-HER-2 agents alone *(with no CT)*?
  • Resistance
  • Biomarkers to decide for dual-blockade
KEYNOTE-522: Study Design

- Current analysis of pCR rates in key patient subgroups, by treatment exposure, residual cancer burden, and immune-mediate adverse events

**Primary endpoints:** pCR (ypT0/Tis ypN0) AND EFS by LR

Pathological Complete Response at IA1

**Primary Endpoint:** ypT0/Tis ypN0

- pCR: 64.8% (56.4-21.0)%
- pCR%: 93.2% (85.3-100.0)%

**Secondary Endpoints:** Other pCR Definitions

- Δ 13.5 (5.4-21.0)%
- Δ 14.5 (6.2-22.7)%
- Δ 14.8 (6.8-23.0)%

**KEYNOTE-522: Results EFS**

- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

**One word about Triple Negative EBC**

EBC: Systemic Therapy Summary

ESMO EBC Guidelines.
Cardoso F et al, Annals of Oncology 2019
• Expensive medicines are not the priority! Except TRASTUZUMAB, which is an WHO essential medicine

• FOCUS ON:
  • EARLY DETECTION / EDUCATION / AWARENESS
  • MULTIDISCIPLINARY CARE
  • QUALITY PATHOLOGY
  • ACCESS TO RADIOTHERAPY (no RT – BCS very, very difficult)
  • BIOSIMILARS and GENERICS (if approved and high-quality)
  • FIGHT FOR TRASTUZUMAB
  • FOCUS ON TAMOXIFEN, ANTHRACYCLINES, TAXANES
  • DON’T WASTE RESOURCES on “fashionable things”
THANK YOU! OBRIGADA!

Breast Unit

Champalimaud Foundation