Current Management of Breast Cancer

F. Cardoso, MD
Director, Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal
ESMO Board of Directors & NR Committee Chair
ESO Breast Cancer Program Coordinator
EORTC Breast Group Chair
DISCLOSURES

Consultant/Ad Board:

Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Teva
BREAST CANCER: A GLOBAL HEALTH ISSUE

1 out of 8 to 10 women will have BC during their lifespan

In Europe:
There will be an estimated **561,334 deaths** worldwide in 2015 and an estimated **805,116 by 2030**, representing a 43% increase in absolute number of deaths from BC.

About 1/3 EBC will relapse
ABC at diagnosis: 10-15% developed to 50-60% developing countries

Most prevalent cancer by country – females

1. **Breast** 145 countries worldwide
2. **Cervix** 37 countries in South & Central America, West & Southern Africa, Asia
3. **Thyroid** South Korea, Vanuatu

HOW MANY ABC PATIENTS EXIST?

Incidences
- 1,924,710 (28.9%)
- 228,082 (3.4%)
- 229,923 (3.5%)
- 238,719 (3.6%)
- 319,605 (4.8%)
- 320,301 (4.8%)

- 1,676,633 (25.2%)
- 614,304 (9.2%)
- 583,100 (8.8%)
- 527,624 (7.9%)

5-Year PREVALENCE
- 3,730,161 (21.6%)
- 1,216,504 (7.1%)
- 507,340 (3.0%)
- 1,547,161 (9.0%)

If 1 third would be MBC: about 2 million MBC patients
BUT it is just a very rough estimation

Mortality
- 1,215,200 (34.3%)
- 320,250 (9.0%)
- 491,194 (13.8%)
- 265,653 (7.5%)
- 254,096 (7.2%)

- 224,486 (6.3%)
- 27,142 (0.8%)
- 151,905 (4.3%)
- 76,155 (2.1%)
Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer

Aleix Prat¹,²,³, Joel S Parker¹,², Olga Karginova¹,²,³, Cheng Fan¹, Chad Livasy¹,³, Jason I Herschkowitz⁴, Xiaping He¹,²,³, Charles M Perou¹,²,³*
<table>
<thead>
<tr>
<th>ER/PR</th>
<th>HER2</th>
<th>PCAD</th>
<th>CK5</th>
<th>EGFR</th>
<th>CK14</th>
</tr>
</thead>
</table>

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

*Courtesy of MJ Brito*
A Breast-Cancer-Specific Survival According to Immunohistochemical Subtype

Breast-Cancer-Specific Survival

Years after Diagnosis

ER+ or PR+/HER2-
ER+/HER2+
ER-/PR-/HER2-/basal marker-
ER-/PR-/HER2-/basal marker+
ER-/PR-/HER2+

Overall survival and sequential treatment of patients with MBC

- 134 sites, 298 oncologists, all over Germany
- > 3,700 pts/1409 ABC pts
- (goal: 4,500 BC pts/2250 ABC pts by end 2015)

- 59% HR pos HER2 neg
- 19% HR pos HER2 pos
- 10% HR neg HER2 pos
- 13% triple neg
Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

E. Senkus¹, S. Kyrriakides², S. Ohno³, F. Penault-Llorca⁴,⁵, P. Poortmans⁶, E. Rutgers⁷, S. Zackrisson⁸ & F. Cardoso⁹, on behalf of the ESMO Guidelines Committee*

¹Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; ²Europa Donna Cyprus, Nicosia, Cyprus; ³Breast Oncology Center, Cancer Institute Hospital, Tokyo, Japan; ⁴Department of Pathology, Centre Jean Perrin, Clermont-Ferrand; ⁵EA 4677 Université d’Auvergne, Clermont-Ferrand, France; ⁶Radboud University Medical Center, Nijmegen, The Netherlands; ⁷Department of Surgery, Netherlands Cancer Institute, Amsterdam, The Netherlands; ⁸Department of Diagnostic Radiology, Lund University, Malmö, Sweden; ⁹Breast Unit, Champalimaud Clinical Center, Lisbon, Portugal

St. Gallen 2015
Tailoring Therapy: Towards Precision Treatment of Patients with Early Breast Cancer

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) (“Oxford Overview”)
EARLY BREAST CANCER

MAIN MESSAGES:

SCREENING & EARLY DETECTION saves lives
MORE IS NOT ALWAYS BETTER

MAIN GOALS:
Detect early
Maintain efficacy and reduce toxicity
EBC OUTCOME EVOLUTION

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
### Table 1.1: Chronological history of operations related to total mastectomy

<table>
<thead>
<tr>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halsted</td>
</tr>
<tr>
<td>Patey</td>
</tr>
<tr>
<td>McWhirter</td>
</tr>
<tr>
<td>Toth</td>
</tr>
<tr>
<td>Noguchi</td>
</tr>
<tr>
<td>VerHeyden</td>
</tr>
</tbody>
</table>

### Table 1.2: Chronological history of operations related to breast reconstruction

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berson</td>
<td>1944</td>
<td>Derma-fat grafts</td>
</tr>
<tr>
<td>Longacre</td>
<td>1953</td>
<td>Local flaps</td>
</tr>
<tr>
<td>Snyderman</td>
<td>1969</td>
<td>Prosthetic devices</td>
</tr>
<tr>
<td>Arnold</td>
<td>1976</td>
<td>Omentum and prosthetics</td>
</tr>
<tr>
<td>Schneider</td>
<td>1977</td>
<td>Latissimus dorsi</td>
</tr>
<tr>
<td>Hartrampf</td>
<td>1982</td>
<td>TRAM flap</td>
</tr>
<tr>
<td>Argenta</td>
<td>1984</td>
<td>Tissue expansion</td>
</tr>
<tr>
<td>Grotting</td>
<td>1989</td>
<td>Free TRAM flap</td>
</tr>
<tr>
<td>Allen</td>
<td>1994</td>
<td>Perforator flaps</td>
</tr>
</tbody>
</table>

### Table 1.3: Chronological history of operations related to partial mastectomy

<table>
<thead>
<tr>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crile</td>
</tr>
<tr>
<td>Montague</td>
</tr>
<tr>
<td>Veronesi</td>
</tr>
<tr>
<td>Gabka</td>
</tr>
<tr>
<td>Clough</td>
</tr>
<tr>
<td>Amanti</td>
</tr>
<tr>
<td>Anderson</td>
</tr>
</tbody>
</table>

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In M. Nahabedian in Oncoplastic Surgery of the Breast, Elsevier 2009

Courtesy of MJ Cardoso
EVOLUTION RADIOTHERAPY

Calypso Beacon System

"GPS for the Body"
Improves accuracy by tracking a tumor's location continuously during treatment.

Cobalt

Linear accelerator

Tridimensional RT

Internal Radiation Therapy (Brachytherapy)

Internal radiation therapy or brachytherapy treats cancer by placing tiny radioactive sources or seeds into the body either directly into or next to the area requiring treatment. This enables clinicians to deliver a high dose of radiation with minimal impact on surrounding healthy tissues.
EARLY BREAST CANCER: WHO CAN AVOID ADJUVANT CT?

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

**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.

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
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

C-low/G-low

No Chemotherapy

F. Cardoso et al, NEJM 2016
Conclusions (2)

• Mindact results provide level 1A evidence of the clinical utility of MammaPrint® for assessing the lack of a clinically relevant chemotherapy benefit in the clinically high risk (c-High) population.

• c-High/g-Low patients, including 48% Node positive, had a 5-year DMFS rate in excess of 94%, whether randomized to adjuvant CT or no CT.

• Among the c-High risk patients, the clinical use of MammaPrint® is associated with a 46% reduction in chemotherapy prescription.
PREOPERATIVE CHEMOTHERAPY IN BC
HISTORICAL PERSPECTIVE


**GOAL**

- **DISEASE**
  - Locally advanced
  - Early
  - Early
  - Early

- **GOAL**
  - Local control
  - Rate of breast conservation
  - Survival
  - Treatment tailoring

- **ACHIEVED**
- **ACHIEVED**
- **NO DIFFERENCE**
- **ONGOING**

Adapted from M. Piccart
Neoadjuvant therapy compared with adjuvant therapy for breast cancer

A. Death
- Avril/Mauriac
- Danforth
- Gazet
- Makris
- NSABP B18
- Scholl
- Scholl/Broet
- Semiglazov
- Van der Hage
- ALL

Risk ratio (95% CI) for neo-adjuvant vs. adjuvant treatment

B. Disease progression
- Avril/Mauriac
- Danforth
- Makris
- NSABP B18
- Scholl
- Scholl/Broet
- Semiglazov
- Van der Hage
- ALL

Risk ratio (95% CI) for neo-adjuvant vs. adjuvant treatment

C. Distant recurrence
- Avril/Mauriac
- Danforth
- Gazet
- Makris
- NSABP B18
- Scholl
- Scholl/Broet
- Semiglazov
- Van der Hage
- ALL

Risk ratio (95% CI) for neo-adjuvant vs. adjuvant treatment

D. Loco-regional recurrence
- Avril/Mauriac
- Danforth
- Gazet
- Makris
- NSABP B18
- Scholl
- Scholl/Broet
- Semiglazov
- Van der Hage
- ALL

Risk ratio (95% CI) for neo-adjuvant vs. adjuvant treatment

Association between pCR and EFS by BC subtype

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

### 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>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>RR 0.97 [SE 0.10] years 10–14</td>
<td>RR 0.68 [SE 0.08] years 10–14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2p&lt;0.00001</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

Switch AI after TAM vs. TAM

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

EBCTCG, Lancet. 2005
Trial Designs Extended Adjuvant Therapy

MA-17
NSABP-B33
ABCSG-6a
NSABP-B42
MA-17R
ABCSG-16
DATA
IDEAL
SOLE

Tam
Tam
Tam
Tam
Tam
Tam
Tam
Tam
Tam

Al
Al
Al
Al
Al
Al
Al
Al
Al

Let
Placebo
Exe
Placebo
Let
Placebo
Let
Let
Let

Let
Placebo
Ana
nil
Ana
Ana
Ana
Ana
Ana

HR DFS
0.57
0.68
0.62
0.85
0.80
0.79
0.88

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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)</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>0.66</td>
<td>2.7%*</td>
<td>0.0115</td>
<td>2</td>
<td>Smith 2007</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>1.27</td>
<td>−1.5%</td>
<td>n.s.</td>
<td>4</td>
<td>Spielmann 2007</td>
</tr>
</tbody>
</table>

Reduction in mortality risk of 34% to 59%

*Benefit at 3y

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

bCombined US: Joint analysis of NSABP B-31 and NCCTG N9831
5 year survival rates for mBC still around 25%

5-year Survival Rates by Stage at Diagnosis (Female Breast Cancer, US SEER), 1992-1999 Compared with 2005-2011\(^1,2\)

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Changes in 5 year survival after diagnosis of *de novo* Stage IV BC

US SEER Data

Forbes 2015, by Dr Elaine Schattner

Analysis suggests **limited improvement in quality of life** for patients with mBC over the last decade.

An analysis of the trends in quality of life for mBC* indicates that there has not been **significant improvement** over the past decade.2

In fact, there has been a **slight decrease in quality of life**.

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*Analysis was based on a review of 132 articles, of which a quantitative analysis was conducted of 14 studies reporting QoL measure values for mBC. Values are weighted based on sample size. This analysis indicates a numerical decrease over time. It does not intend to demonstrate statistical significance.

---

ADVANCES HAVE BEEN DIFFERENT IN DIFFERENT MBC SUBTYPES

**Prognosis in MBC by HER-2 Status and by Therapy with Trastuzumab**

<table>
<thead>
<tr>
<th>Patients (n = 2,091) (median f/u = 16.9 mo)</th>
<th>1 y survival (95% CI)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2-pos</strong></td>
<td>118 (5.6%)</td>
<td>70.2% (60.3%, 78.1%)</td>
</tr>
<tr>
<td><strong>HER2-neg</strong></td>
<td>1,782 (85.3%)</td>
<td>75.1% (72.9%, 77.2%)</td>
</tr>
<tr>
<td>HER2-pos treated with trastuzumab</td>
<td>191 (9.1%)</td>
<td>86.6% (80.8%, 90.8%)</td>
</tr>
</tbody>
</table>

Dawood et al, ASCO abstract 1018, 2008

**ER and/or PR positive tumours**

The median survival was 22 months & has not increase over time since the 90’s (introduction of AIs)

**Trends in survival in metastatic breast cancer. Sundquist et al. EBCC 2010, abst # 453**

- HER-2+ BC: the one with the major advances
- TNBC: the one with less advances
- ER+ BC: advances until the 90’s and then stalled...
Balancing treatment efficacy and toxicity is the main objective.

**Goals of treatment:**
- Improve survival (*very few agents achieve it!*)
- Delay disease progression
- Prolong duration of response
- Palliate symptoms
- Improve or maintain quality of life
- Transform into a chronic disease
The management of ABC is complex and, therefore, involvement of all appropriate specialties in a multidisciplinary team (including but not restricted to medical, radiation, surgical oncologists, imaging experts, pathologists, gynecologists, psycho-oncologists, social workers, nurses and palliative care specialists), is crucial (LoE: Expert opinion). (100%)
96% of HCPs agree that a multidisciplinary team approach improves the level of care for patients with ABC\textsuperscript{10}.

But...

Over a quarter (26%) of the HCPs surveyed do not work as part of a multidisciplinary team\textsuperscript{10}.
Following a thorough assessment and confirmation of MBC, the potential treatment goals of care should be discussed. Patients should be told that MBC is incurable but treatable, and that some patients can live with MBC for extended periods of time (many years in some circumstances).

This conversation should be conducted in accessible language, respecting patient privacy and cultural differences, and whenever possible, written information should be provided.

(LoE: Expert opinion) (97%)
From the time of diagnosis of ABC, patients should be offered appropriate psychosocial care, supportive care, and symptom-related interventions as a routine part of their care. The approach must be personalized to meet the needs of the individual patient. (LoE: Expert opinion) (100%).
PATIENT-CENTERED MEDICINE

QUALITY OF LIFE
SYMPTOMS’ CONTROL
LESS AGGRESSIVE TREATMENTS
KNOW WHEN TO STOP...
48–76% of the general public believe that advanced/metastatic breast cancer is curable

The Challenges of Extreme Societal Opinions about mBC

<table>
<thead>
<tr>
<th>Death sentence</th>
<th>mBC Attitudes</th>
<th>Curable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some believe people with mBC will die very soon</td>
<td>Others overly positive, thinking people can “beat” mBC</td>
<td></td>
</tr>
<tr>
<td>Driven by perception that all cancer is terrible / imminently fatal</td>
<td>Typically driven by visibility of success stories in eBC</td>
<td></td>
</tr>
<tr>
<td>Or by perception that once cancer spreads, end of life must be close</td>
<td>Patients themselves may believe their mBC can be cured – in some cases, the medical team appears to have painted an overly positive picture</td>
<td></td>
</tr>
</tbody>
</table>

FIGHT STIGMA!
Minimal staging workup for MBC includes a history and physical examination, hematology and biochemistry tests, and imaging of chest, abdomen and bone (LoE: 2 C). (67%)

Notes:
✓ Biochemistry tests including liver function tests, renal function, electrolytes, calcium, total proteins and albumin
✓ In many cases a chest X-ray, an abdominal ultrasound and a bone scan are sufficient (lot of discussion about the optimal imaging modality- LoE 2C)
✓ Consensus that a PET-scan should NOT be part of the minimal staging workup but should be reserved for specific situations
9) **Brain imaging should NOT be routinely** performed in asymptomatic patients. This approach is applicable to all patients with MBC including those patients with HER-2+ and/or TNBC MBC *(LoE: Expert opinion) (94%)*

**BUT**

- **Careful evaluation of signs and symptoms** is needed since clinical manifestations of brain metastases may sometimes be quite *subtle*, particularly among patients with HER-2+ or TN MBC.

- In the setting of suggestive signs or symptoms, a **lower threshold to image** such patients should be considered given the higher pre-test probability for CNS involvement.
The clinical value of tumor markers is not well established for diagnosis or follow-up after adjuvant therapy, but their use (if elevated) as an aid to evaluate response to treatment, particularly in patients with non-measurable metastatic disease, is reasonable. **A change in tumor markers alone should not be used to initiate a change in treatment.**

(LoE: 2 C) (84%)
Treatment choice should take into account at least these factors:

HR & HER-2 status,
previous therapies and their toxicities, disease-free interval,
tumor burden (defined as number and site of metastases),
biological age, performance status, co-morbidities (including organ dysfunctions),
menopausal status (for ET),
need for a rapid disease/symptom control,
socio-economic and psychological factors,
available therapies in the patient’s country and patient preference.

(LoE: Expert opinion) (100%)
A biopsy (preferably providing histology) of a metastatic lesion should be performed, if easily accessible, to confirm diagnosis particularly when metastasis is diagnosed for the first time. (LoE: 1 B) (98%)

Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible. (LoE: 1 B) (98%)

Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist.
Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance. (LoE: 1 A) (93%)
ESMO Guidelines for the Use of First-Line Endocrine Therapy in Postmenopausal HR+ ABC

ENDOCRINE TREATMENT STRATEGY

\[ \text{ET}_1 \xrightarrow{\text{response}} \text{ET}_2 \xrightarrow{\text{response}} \text{ET}_3 \xrightarrow{\text{response}} \text{ET} \ldots \]

CT

ER POSITIVE / HER-2 NEGATIVE MBC

For **pre-menopausal** women, for whom ET was decided, ovarian suppression/ablation combined with additional endocrine therapy is the preferred choice. *(LoE: 1 B) (93%)*

For **pre-menopausal** women, the additional endocrine agent can be **AI** or **tamoxifen**, according to type and duration of prior adjuvant endocrine therapy but AI absolutely mandates the use of ovarian suppression/ablation. *(LoE: 1 B) (95%)*

**Fulvestrant** is also a valuable option, but for the moment also mandates the use of ovarian suppression/ablation. *(LoE: 1 C) (95%)*
The preferred 1st line ET for postmenopausal patients depends on type and duration of adjuvant ET as well as time elapsed from the end of adjuvant ET; it can be an aromatase inhibitor, tamoxifen or fulvestrant. (LoE: 1 A) (84%)
Combining Targeted and Antiestrogen Therapies in HR-Positive Breast Cancer

mTOR Inhibitors
- Everolimus
- Sirolimus
- Temsirolimus

CDK4/6 Inhibitors
- Palbociclib
- Abemaciclib
- Ribociclib

HDAC Inhibitor
- Entinostat

Aromatase Inhibitor
Nonsteroidal AIs:
- Anastrozole
- Letrozole
Steroidal AI:
- Exemestane

ER Downregulator
- Fulvestrant

Selective ER Modulators
- Tamoxifen
- Toremifene

ER target gene transcription

Cell Cycle
Transcription Silencing


Slide credit: clinicaloptions.com
The **optimal sequence** of endocrine agents after 1\textsuperscript{st} line ET is uncertain. It depends on which agents were used in the (neo)adjuvant and 1\textsuperscript{st} line ABC settings.

**Available options** include AI, tamoxifen, fulvestrant + palbociclib, AI + everolimus, tamoxifen + everolimus, fulvestrant, megestrol acetate and estradiol.

*(LoE: 1 A) (93%)*

It is currently unknown how the different combinations of endocrine + biological agents compare with each other, and with single agent CT. Several trials are ongoing.
WHEN CHEMOTHERAPY IS NEEDED . . .
Both combination and sequential single agent CT are reasonable options. Based on the available data, we recommend sequential monotherapy as the preferred choice for MBC.

Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases, or need for rapid symptom and/or disease control.

(LoE: 1 B). (96%)

Please see also Cardoso et al, JNCI 2009; 101: 1174–1181
Cochrane meta-analysis of Combination vs. Sequential monoCT for ABC

### Progression-free survival (all trials)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Combination Total</th>
<th>Sequential Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba 2004</td>
<td>0.0296</td>
<td>0.1827</td>
<td>69</td>
<td>75</td>
<td>10.7%</td>
<td>1.03 [0.72, 1.47]</td>
<td></td>
</tr>
<tr>
<td>Baker 1974</td>
<td>0.239</td>
<td>0.2295</td>
<td>46</td>
<td>30</td>
<td>6.8%</td>
<td>1.27 [0.81, 1.99]</td>
<td></td>
</tr>
<tr>
<td>Beslaja 2006</td>
<td>-0.6033</td>
<td>0.2865</td>
<td>50</td>
<td>50</td>
<td>4.3%</td>
<td>0.55 [0.31, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Conte 2004</td>
<td>0.0862</td>
<td>0.139</td>
<td>106</td>
<td>92</td>
<td>18.5%</td>
<td>1.09 [0.83, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Fountzilas 2001</td>
<td>0.2151</td>
<td>0.1579</td>
<td>90</td>
<td>93</td>
<td>14.3%</td>
<td>1.24 [0.91, 1.69]</td>
<td></td>
</tr>
<tr>
<td>Park 2010</td>
<td>0.2776</td>
<td>0.2429</td>
<td>41</td>
<td>40</td>
<td>6.0%</td>
<td>1.32 [0.82, 2.12]</td>
<td></td>
</tr>
<tr>
<td>Sledge 2003</td>
<td>0.2469</td>
<td>0.0962</td>
<td>230</td>
<td>453</td>
<td>38.5%</td>
<td>1.28 [1.06, 1.55]</td>
<td></td>
</tr>
<tr>
<td>Tomova 2010</td>
<td>-0.1625</td>
<td>0.6415</td>
<td>46</td>
<td>53</td>
<td>0.9%</td>
<td>0.85 [0.24, 2.99]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>678</td>
<td>886</td>
<td>100.0%</td>
<td>1.16 [1.03, 1.31]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 9.41, df = 7 (P = 0.22); I² = 26%
Test for overall effect: Z = 2.52 (P = 0.01)

### Overall survival (all trials)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Combination Total</th>
<th>Sequential Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
<th>Hazard Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alba 2004</td>
<td>0.2151</td>
<td>0.2634</td>
<td>69</td>
<td>75</td>
<td>4.5%</td>
<td>1.24 [0.74, 2.08]</td>
<td></td>
</tr>
<tr>
<td>Baker 1974</td>
<td>0.3716</td>
<td>0.2606</td>
<td>46</td>
<td>30</td>
<td>4.6%</td>
<td>1.45 [0.87, 2.42]</td>
<td></td>
</tr>
<tr>
<td>Beslaja 2006</td>
<td>-0.6387</td>
<td>0.3182</td>
<td>50</td>
<td>50</td>
<td>3.1%</td>
<td>0.53 [0.28, 0.99]</td>
<td></td>
</tr>
<tr>
<td>Chlebowski 1989</td>
<td>-0.1054</td>
<td>0.1282</td>
<td>129</td>
<td>93</td>
<td>19.2%</td>
<td>0.90 [0.70, 1.16]</td>
<td></td>
</tr>
<tr>
<td>Conte 2004</td>
<td>0.174</td>
<td>0.2355</td>
<td>106</td>
<td>92</td>
<td>5.7%</td>
<td>1.19 [0.75, 1.89]</td>
<td></td>
</tr>
<tr>
<td>Fountzilas 2001</td>
<td>0.1989</td>
<td>0.1667</td>
<td>90</td>
<td>93</td>
<td>11.3%</td>
<td>1.22 [0.88, 1.69]</td>
<td></td>
</tr>
<tr>
<td>Park 2010</td>
<td>-0.1744</td>
<td>0.235</td>
<td>41</td>
<td>40</td>
<td>5.7%</td>
<td>0.84 [0.53, 1.33]</td>
<td></td>
</tr>
<tr>
<td>Sledge 2003</td>
<td>0.0488</td>
<td>0.0901</td>
<td>230</td>
<td>453</td>
<td>38.8%</td>
<td>1.05 [0.88, 1.25]</td>
<td></td>
</tr>
<tr>
<td>Tomova 2010</td>
<td>0.1989</td>
<td>0.211</td>
<td>46</td>
<td>53</td>
<td>7.1%</td>
<td>1.22 [0.81, 1.84]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>807</td>
<td>979</td>
<td>100.0%</td>
<td>1.04 [0.93, 1.16]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 10.54, df = 8 (P = 0.23); I² = 24%
Test for overall effect: Z = 0.76 (P = 0.45)
**Metronomic chemotherapy** is an reasonable treatment option, for patients not requiring rapid tumor response. 
*(LoE: 1 B) (88%)*

The better studied regimen is CM (low dose oral cyclophosphamide and methotrexate); other regimens are being evaluated (including capecitabine and vinorelbine).

Randomized trials are needed to accurately compare metronomic CT with standard dosing regimens.
Anti-HER-2 therapy should be offered early to all HER-2+ MetaBC patients, except in the presence of contra-indications for use of such therapy (LoE: 1 A). (91%)
Chemotherapy ± trastuzumab in the first-line treatment of ErbB2+ metastatic breast cancer

H0648g trial

- Longer OS: 25.1 vs. 20.3 ms (p=0.046)
- Longer TTP: 7.4 vs. 4.6 ms (p<0.001)
- Higher RR: 50 vs. 32% (p<0.001)
- Longer duration: 9.1 vs. 6.1 ms (p<0.001)
All patients with HER-2+ MBC who relapse after adjuvant anti-HER-2 therapy should be considered for further anti-HER-2 therapy, except in the presence of contraindications (LoE: 1 B) (97%)
CAUTION!!!!
Only 21% - 26% pts had previously received (neo)adjuvant trastuzumab

HR 0.62
p < 0.0001

Δ = 6.1 mo.

Ptz+T+D: 18.5 mo.
Pla+T+D: 12.4 mo.

Ptz+T+D: 56.5 mo.
Pla+T+D: 40.8 mo.

Δ = 15.7 mo.

HR 0.68
p = 0.0002

Unstratified HR=0.66 (P<0.0001).

\(~5\) MS BENEFIT IN OS

Probably a new standard of care!

EMILIA Study
T-DM1 vs Cap+Lap
TRIPLE NEGATIVE ABC

Selected messages
Heterogeneity of TRIPLE NEGATIVE BC: TNBC Classification

Mesenchymal-like TNBC (ML-TNBC)

Immune-associated (IM) TNBC

Basal-like (BL) TNBC

Immune-signature (IM) TNBC

Luminal/apocrine (LA) TNBC

HER2-enriched (HER2e) TNBC

Lehmann's classification

PAM50/claudin-low classification

Le Du F. Oncotarget. 2015;6:12890-12908. This work is licensed under a Creative Commons Attribution 3.0 Unreported License.
For **non-BRCA**-associated triple negative ABC, there are **no data supporting different or specific CT recommendations**. Therefore, all CT recommendations for HER-2 negative disease also apply for triple negative ABC.

(LoE: 1 A) (98%)

The role of **PLATINUM** in BRCA-related and non-BRCA-related...
For the purpose of these recommendations, LABC means INOPERABLE, LOCALLY ADVANCED BREAST CANCER THAT HAS NOT SPREAD TO DISTANT SITES
MISSION

The ABC Global Alliance, established by the European School of Oncology (ESO), is a multi-stakeholder platform for all those interested in collaborating in common projects relating to ABC. Its goal is to improve and extend the lives of women and men living with ABC in all countries worldwide and to fight for a cure. It will also raise awareness and lobby worldwide for the improvement of the lives of ABC patients.

ABCglobalalliance@eso.net
Advanced Breast Cancer

Fourth ESO-ESMO International Consensus Conference

2-4 November 2017 | Lisbon, Portugal
Coordinating Chair: F. Cardoso, PT
Co-Chairs: E. Senkus, PL - E. Papadopoulos, CY
Scientific Committee Members: M.S. Aapro, CH - F. André, FR
N. Harbeck, DE

The ABC4 guidelines will be developed by ESO and ESMO
The ABC4 conference and guidelines are endorsed by
and will be submitted for endorsement to

The ABC4 conference is held
with support from
under the auspices of
and with official representatives of

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