ABC2 Guidelines for the treatment of LABC and MBC

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ESMO Board of Directors
EORTC Secretary General & Board
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Goals in the Treatment of MBC

- 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
More than half a million deaths worldwide every year

In Europe:
1 diagnosis every 2.5 minutes
1 death every 6.5 minutes

Median OS: 2 to 3 years!
Advances have been different in different MBC subtypes

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

<table>
<thead>
<tr>
<th>HER2 status</th>
<th>Patients (%)</th>
<th>1 y survival (95% CI)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-pos</td>
<td>118 (5.6%)</td>
<td>70.2% (60.3%, 78.1%)</td>
<td>--</td>
</tr>
<tr>
<td>HER2-neg</td>
<td>1,782 (85.3%)</td>
<td>75.1% (72.9%, 77.2%)</td>
<td>0.56 (0.45-0.69, p = 0.0001)</td>
</tr>
</tbody>
</table>

HER2-pos treated with trastuzumab:

- 191 (9.1%)
- 86.6% (80.8%, 90.8%)

Dawood et al, ASCO abstract 1018, 2008

**ER and/or PR positive tumours**

The median survival was 22 months & has not increased 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...
Conclusion

Treatment according to consensus recommendations is associated with improved survival of women with breast cancer in the community. Promoting the adoption of guidelines for treatment is an effective strategy for disease control.
MAIN PRINCIPLES OF ABC RECOMMENDATIONS

✔ Apply the main principles of modern oncology:
  ✔ Multidisciplinary treatment
  ✔ Specialized breast cancer units
  ✔ Evidence-based medicine
    (please STOP “eminence-based” medicine!!)
  ✔ Individualized (tailored) therapy

✔ Remember the specificities of ABC setting

✔ Patient’s preferences & active participation

✔ Identify areas of UNMET NEEDS & RESEARCH PRIORITIES
INTERNATIONAL CONSENSUS GUIDELINES NOW EXIST IT IS OUR RESPONSIBILITY TO IMPLEMENT THEM!

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Original article

1st International consensus guidelines for advanced breast cancer (ABC 1)

F. Cardoso a,*, A. Costa b, L. Norton c, D. Cameron d, T. Cufer e, L. Fallowfield f, P. Francis g, J. Gligorov h, S. Kyriakides i, N. Lin j, O. Pagani k, E. Senkus l, C. Thomssen m, M. Aapro n, J. Bergh o, A. Di Leo p, N. El Saghir q, P.A. Ganz r, K. Gelmon s, A. Goldhirsch t, N. Harbeck u, N. Houssami v, C. Hudis w, B. Kaufman x, M. Leadbeater y, M. Mayer z, A. Rodger aa, H. Rugo bb, V. Sacchini cc, G. Sledge dd, L. van’t Veer ee, G. Viale ff, I. Krop gg, E. Winer gg

www.abc-lisbon.org
ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2)†

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%)
The age of the patient should not be the sole reason to withhold effective therapy (in elderly patients) nor to overtreat (in young patients). Age alone should not determine the intensity of treatment. (LoE: 1 B) (100%)

First international consensus guidelines for breast cancer in young women (BCY1)

Ann H. Partridge, Olivia Pagani, Omalkhair Abulkhair, Stefan Aebi, Frédéric Amant, Hatem A. Azim Jr., Alberto Costa, Suzette Delaloge, Gloria Freilich, Oreste Davide Gentilini, Nadia Harbeck, Catherine M. Kelly, Sibylle Loibl, Dror Meirow, Fedro Peccatori, Bella Kaufmann, Fatima Cardoso

Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA)

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: 2 C) (96%)

Biological markers (especially HR and HER-2) should be reassessed at least once in the metastatic setting, if clinically feasible (LoE: 2 C) (90%)

If the results of tumour biology in the metastatic lesion differ from the primary tumour, it is currently unknown which result should be used for treatment-decision making. Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of targeted therapy (ET and/or anti-HER-2 therapy) when receptors are positive in at least one biopsy, regardless of timing (LoE: Expert opinion) (87%)
CAN WE MANAGE PROPERLY WHAT WE CAN’T MEASURE?

• What is the prevalence of ABC? (most cancer registries capture diagnosis and mortality but not relapse!)

• What is the best endpoint for advanced cancer?
1 out of 8 to 10 women will have BC during their lifespan.

In Europe:
1 diagnosis every 2.5 minutes
1 death every 6.5 minutes

Almost half of the ABC patients will relapse.

ABC at diagnosis: 10-15% developed to 50-60% in developing countries.

More than half a million deaths worldwide every year.
HOW MANY ABC PATIENTS EXIST?

Incidence

- 1,924,710 (28.9%)
- 1,676,633 (25.2%)
- 614,304 (9.2%)
- 583,100 (8.8%)
- 527,824 (7.9%)
- 320,301 (4.8%)
- 238,719 (3.6%)
- 229,923 (3.5%)
- 228,082 (3.4%)

GLOBOCAN 2012 data

5-Year PREVALENCE

- 3,730,161 (21.6%)
- 6,255,391 (36.4%)
- 1,590,151 (9.3%)

Mortality

- 1,215,200 (34.3%)
- 521,817 (14.7%)
- 320,250 (9.0%)
- 265,653 (7.5%)
- 254,096 (7.2%)
- 224,486 (6.3%)
- 27,142 (0.8%)
- 151,905 (4.3%)
- 76,155 (2.1%)

- 491,194 (13.8%)
- 566,624 (3.4%)
- 934,805 (5.4%)
- 179,925 (1.0%)

- Breast
- Colorectum
- Lung
- Cervix uteri
- Stomach
- Corpus uteri
- Ovary
- Thyroid
- Liver
- Other and unspecified
HOW MANY ABC PATIENTS EXIST?

About 1/3 EBC will relapse

ABC at diagnosis: 10-15% developed to 50-60% developing countries

More than half a million deaths worldwide every year

5-year prevalence: 6,255,391 patients

If 1 third would be MBC: about 2 million MBC patients
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)

ER+ ABC: 60% 3 lines, 35% 4 lines ; ER- ABC: 40% 3 lines, 22% 4 lines

Lung: 39% 2 lines, 19% 3 lines, 5% 4 lines
Colorectal: 68% 2 lines, 45% 3 lines, 25% 4 lines
Renal: 51% 2 lines, 27% 3 lines, 12% 4 lines
Which is/are best endpoint(s) for MBC?

**OS**

**Pros:**
1) The most objective endpoint
2) The most desired endpoint (both for patients & physician)

**Cons:**
1) May be influenced by subsequent therapies
2) Needs longer follow-up
3) More subjective endpoint (especially when response assessment is difficult (e.g. bone disease))

**COMPOSITE ENDPOINTS**

**Pros:**
1) Is not a good surrogate for OS benefit
2) Obtained faster

**Cons:**
1) Is not a good surrogate for OS benefit
2) Not always associated with clinically meaningful benefit (only when associated with symptom control and/or low toxicity)
3) More subjective endpoint (specially in situations where response assessment is difficult (e.g. bone disease))
Which is/are best endpoint(s) for advanced cancer?

DOES PFS BENEFIT MATTER IF NOT ASSOCIATED WITH OS BENEFIT?

Depends!
- on the type of disease:
  - PD not always linked to symptoms (ovarian ≠ breast)
  - Available therapies
- on the type of drug:
  - Toxicity / QoL
  - Affordability

ESMO Magnitude of Clinical Benefit Scale
Strong consideration should be given to the use of validated instruments for patients to report the symptoms of disease and side effects of treatment they experience as a regular part of their clinical care.

These PRO (patient-reported outcomes) instruments should be simple, and user-friendly to facilitate their use in clinical practice.

This systematic monitoring will serve to facilitate communication between patients and their treatment teams, allow optimal quality of life, and may better characterize the toxicities of all anticancer therapies.

(LoE: I C) (89%)

UNMET NEED: Define the best endpoint(s) in ABC
The true value of the removal of the primary tumor in patients with stage IV breast cancer is currently unknown. However, it can be considered in selected patients. Of note, some studies suggest that surgery is only valuable if performed with the same attention to detail (e.g. attaining clear margins and addressing disease in the axilla) as in patients with early stage disease (LoE: 2 B). (100%)

Prospective clinical trials to confirm the value of this approach, the best candidates and timing are currently ongoing.

Please see also Pagani, Senkus et al. JNCI 2010; 102: 1–8
SELF-SEEDING HYPOTHESIS

- Primary cancer should be controlled
- Metastatic foci should be controlled, when possible (i.e. when limited)

RESEARCH PRIORITIES:

- Prospective (randomized) data (local therapy primary/mets)
- Revisit the value of detecting limited metastatic disease (if local therapy proven valid)
SURGERY OF THE PRIMARY TUMOR IN BC STAGE IV AT DIAGNOSIS

• Meta-analysis of 15 studies (all retrospective case series) for a total of 15,378 patients.

• Surgery of the primary breast cancer appeared to be an independent factor for an improved survival in the multivariate analyses from the individual studies, with an **HR of 0.69 (p < 0.00001)**.

• Survival benefit was independent of age, extend of the disease but directly proportional to systemic therapies and RT and inversely correlated to ER+ status.

• Surgery reduces the risk of death by **30%;** this results are particular significant if surgery is associated with RT and systemic therapy (multimodality strategy).

Petrelli F et al. abstr 368 P ESMO 2012
Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer: a Turkish Study

In the Soran et al. study, no statistically different difference in OS at early follow-up was seen but benefit was seen in selected subgroups of pts (age <55, bone-only metastatic disease).

- Patients with multiple pulmonary or liver metastases have worse prognosis with initial surgery.
- Loco-regional relapse was 5 times higher in the arm of no local control.
- Longer FU is necessary.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Death</th>
<th>Median (months)</th>
<th>HR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>140</td>
<td>38</td>
<td>46</td>
<td>.76 (0.49-1.16)</td>
<td>.20</td>
</tr>
<tr>
<td>ST</td>
<td>138</td>
<td>48</td>
<td>42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Surgical Removal of primary tumor and axillary lymph nodes in women with metastatic breast cancer at first presentation.

In the Badwe et al. study, surgical removal of primary tumor did not result in OS benefit.

The result of decreased distant PFS in the group of patients with locoregional control is counter-intuitive and against previous available evidence.

Patient stratification:
- Site of metastasis (visceral, bone, both)
- Number of metastases (<3 or >3)
- ER/PgR (positive or negative)

*Breast-conserving therapy or modified radical mastectomy plus axillary lymph node dissection followed by radiation therapy (standard adjuvant guidelines).

Badwe R, et al. SABCS 2013. Abstract S2-02

Badwe R, et al. SABCS 2013. Abstract S2-02
Conclusions for surgical removal of primary tumour in women with MBC at first presentation

- Previous retrospective data (including a meta-analysis of 15 studies) showed important OS benefit (+/- 30%) for surgical removal of primary tumour.

- Both are small studies, the timing of surgery and selection of patients are crucial.

- More studies, better patient selection and longer follow-up are necessary.

- Although the possible survival advantage for removal of the primary remains unproven, it is unlikely that it will provide a large benefit as it was suggested by retrospective series (up to 30% in the meta-analysis).

- Several prospective randomized trials are ongoing. Until these results are available, it can not be offered as a routine practice but only discussed on a case-by-case basis.
ABC IMPORTANT DEFINITIONS

IMPACT:
Clinical practice
Clinical Trials
VISCERAL CRISIS is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.

Visceral crisis is not the mere presence of visceral metastases but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.

(LoE: Expert opinion) (95%)
PRIMARY ENDOCRINE RESISTANCE is defined as:
Relapse while on the first 2 years of adjuvant ET, or
PD within first 6 months of 1st line ET for MBC, while on ET

SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE is defined as:
Relapse while on adjuvant ET but after the first 2 years, or
Relapse within 12 months of completing adjuvant ET, or
PD ≥ 6 months after initiating ET for MBC, while on ET

(LoE: Expert opinion) (67%)

Note: resistance is a continuum and these definitions help mainly clinical trials and not necessarily clinical practice
For the purpose of these recommendations, LABC means INOPERABLE, LOCALLY ADVANCED BREAST CANCER THAT HAS NOT SPREAD TO DISTANT SITES
INOPERABLE LABC

BEFORE starting any therapy, a core biopsy providing histology and biomarker (ER, PR, HER-2, proliferation/grade) expression is indispensable to guide treatment decisions. *(LoE: I B) (97%)*

Since LABC patients have a significant risk of metastatic disease, a full staging workup, including a complete history, physical examination, lab tests and imaging of chest and abdomen (preferably CT) and bone, prior to initiation of systemic therapy is highly recommended. *(LoE: I B) (100%)*

PET-CT, if available, may be used (instead of and not on top of CTs & bone scan). *(LoE: II B) (100%)*
INOPERABLE LABC

Systemic therapy (not surgery or RT) should be the initial treatment.

If LABC remains inoperable after systemic therapy and eventual radiation, “palliative” mastectomy should not be done, unless the surgery is likely to result in an overall improvement in quality of life.

(LoE: Expert opinion) (100%)

A combined treatment modality based on a multidisciplinary approach (systemic therapy, surgery and radiotherapy) is strongly indicated in the vast majority of cases. (LoE: I A) (100%)
LABC TNBC
Anthracycline- and-taxane-based chemotherapy is recommended as initial treatment. (LoE: I A) (85%)

LABC HER-2+
Concurrent taxane and anti-HER-2 therapy is recommended since it increases the rate of pCR. (LoE: I A) (92%)
Anthracycline-based chemotherapy should be incorporated in the treatment regimen. (LoE: I A) (72%). When an anthracycline is given, it should be administered sequentially with the anti-HER-2 therapy. (LoE: I A) (87%)

LABC HR+
Options for HR+ LABC include an anthracycline- and taxane-based chemotherapy regimen, or endocrine therapy. (LoE: I A) (85%)
The choice of CT versus ET, as initial treatment, will depend on tumor (grade, biomarker expression) and patient (menopausal status, performance status, comorbidities, preference) considerations. (85%)
Following effective neoadjuvant systemic therapy with or without radiotherapy, surgery will be possible in many patients.

This will consist of mastectomy with axillary dissection in the vast majority of cases, but in selected patients with a good response, breast conserving surgery may be possible. (LoE: II B) (98%)
For inflammatory LABC, overall treatment recommendations are similar to those for non-inflammatory LABC, with systemic therapy as first treatment. *(LoE: I B) (93%)*

Mastectomy with axillary dissection is recommended in almost all cases, even when there is good response to primary systemic therapy. *(LoE: I B) (95%)*

Immediate reconstruction is generally not recommended in patients with inflammatory LABC *(LoE: Expert opinion) (95%)*

Loco-regional radiotherapy (chest wall and lymph nodes) is required, even when a pCR is achieved with systemic therapy. *(LoE: I B) (98%)*
Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or or there is disease needing a fast response (LoE: 1 A). (100%)
For pre-menopausal women, ovarian suppression/ablation combined with additional endocrine therapy is the first choice (LoE: 1 A) (97%).

The additional endocrine agent should be tamoxifen unless tamoxifen resistance is proven. An AI is also a viable option, but absolutely mandates the use of ovarian suppression/ablation (LoE: 1 B) (97%).

Fulvestrant has not been adequately studied in premenopausal women.

RESEARCH PRIORITY
The preferred 1st line ET for postmenopausal patients is an aromatase inhibitor or tamoxifen, depending on type and duration of adjuvant ET. (LoE: 1 A) (83%)

Fulvestrant HD is also an option. (LoE: 1 B) (83%)

Optimal post-aromatase inhibitor treatment is uncertain.

Available options include, but are not limited to, tamoxifen, another AI (with a different mechanism of action), fulvestrant HD, megestrol acetate and everolimus + AI. (LoE: 1 A) (97%)
The addition of everolimus to an AI is a valid option for some post-menopausal patients with disease progression after a non-steroidal AI, since it significantly prolongs PFS by a median interval of 5 months. There is a survival prolongation of similar magnitude (4.4 months) although this difference is not statistically significant. The decision to treat must take into account the relevant toxicities associated with this combination and should be made on a case by case basis. (LoE: 1 B) (100%)

At present, no predictive biomarker exists to identify those patients who will benefit from this approach.
PD 0332991 (Palbociclib) + Letrozole vs Letrozole: PFS

<table>
<thead>
<tr>
<th></th>
<th>PD 0332991 + Letrozole (n = 84)</th>
<th>Letrozole (n = 81)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>21 (25)</td>
<td>40 (49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>26.1 (12.7-26.1)</td>
<td>7.5 (5.6-12.6)</td>
<td>0.37 (0.21-0.63)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Finn RS, et al. SABCS 2012. Abstract S1-6

Exemestane +/- HDAC inhibitor Entinostat

and RESEARCH continues...

Fig 2. Kaplan-Meier estimates of (A) progression-free survival (PFS) and (B) overall survival (OS). (A) Vertical tick marks represent the PFS time of patients without progressive disease. (B) Vertical tick marks represent the survival time of patients alive or lost to follow-up as of the last contact.

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>Beslila 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>
</tbody>
</table>

Total (95% CI) 678 886 100.0% 1.16 [1.03, 1.31]

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>
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<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>Beslila 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>
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<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>
</tbody>
</table>

Total (95% CI) 807 979 100.0% 1.04 [0.93, 1.16]

Heterogeneity: Chi² = 10.54, df = 8 (P = 0.23); I² = 24%
Test for overall effect: Z = 0.76 (P = 0.45)
In patients pre-treated (in the adjuvant or metastatic setting) with an anthracycline and a taxane, and who do not need combination CT, single agent capecitabine, vinorelbine or eribulin are the preferred choices. Additional choices include gemcitabine, platinum agents, taxanes, and liposomal anthracyclines. The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.

(LoE: 1 B) (77%)
**Single-agent T** significantly worse than single-agent A in PFS but not in RR nor OS.

**T-based** significantly better than A-based combinations in RR and PFS, but not in OS.

**PATIENTS IN THESE TRIALS WERE TAXANE-NAÏVE** (Dogma even less valid for today’s 1st line population)
HERNATA Trial of Docetaxel/Trastuzumab vs Vinorelbine/Trastuzumab

Median PFS (months) D+T: 12.4 V+T: 15.3
P=0.67 HR 0.94 (95% CI 0.71-1.25)

Anderssen et al EBCC 2010
In press J Clin Oncol
N=284
Docetaxel + trastuzumab
Vinorelbine + trastuzumab

First-line MBC
No prior trastuzumab
Measurable Disease
N=81
Paclitaxel or Docetaxel + Trastuzumab
Vinorelbine + Trastuzumab

TRAVIOTA:
Taxane + Trastuzumab vs. Vinorelbine + Trastuzumab
p=0.09

Vinorelbine & Capecitabine:
Consistent efficacy results & NO ALOPECIA

Extrapolating from HER-2+ disease:
Vinorelbine seems at least as good as taxane and significantly less toxic
Optimal Duration of Chemotherapy?

- **Longer CT duration associated with:**
  - significant and clinically meaningful improvement in PFS (HR 0.64; 95% CI 0.55 – 0.76)
  - significant improvement in OS (HR 0.91; 95% CI 0.84-0.99)

These results provide support to the clinical approach of prolonging 1st line CT in the absence of significant toxicity and disease progression (when CT is the only option...)

Role of biologics, HT, metronomic CT !?!
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%)
WHY ARE GUIDELINES IMPORTANT?

• Unfortunately not all medical decisions can be based on level 1 evidence.

• There is a wealth of (new) data in oncology that needs to be “digested”, put into perspective and applied to clinical practice.

• Patients in routine clinical practice are often very different from a clinical trial population.

• Many cancer patients are still treated totally outside the recommendations and available data!

• If all cancer patients would be treated according to the current knowledge, mortality would substantially decrease!
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Chairs:
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