When CT is needed for Luminal ABC

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ESMO Board of Directors & Director of Membership
Chair, ABC Global Alliance and ABC Guidelines
ESO Breast Cancer Program Coordinator
DISCLOSURES SLIDE

Financial disclosures:

*Personal financial interest in form of consultancy role for:* Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Seattle Genetics, Teva.

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Non-Financial disclosures:

Chair ABC Global Alliance and ABC Consensus Conference and Guidelines.
Member/Committee Member of ESMO, ESO, EORTC-BCG, IBCSG, SOLTI, ASCO, AACR, EACR, SIS, ASPIC
The ABC Global Alliance
Continuing the work of the ABC Consensus Conference and Guidelines

The power of lobbying!

Members as of 20 May 2019
177 members from 84 countries
ABC Global Alliance

Who We Are:

- A multi-stakeholder platform for all those interested in collaborating in common projects relating to advanced breast cancer (ABC) around the world
- Continuation of the work developed through the ABC International Consensus Conference and Guidelines
- Launched during the World Cancer Congress in Paris on 3 November 2016

Our Vision/Mission:

- To improve and extend the lives of women and men living with ABC in all countries worldwide and to fight for a cure
- To raise awareness of advanced breast cancer and lobby worldwide for the improvement of the lives of ABC patients

Website www.abcglobalalliance.org

Email ABCGlobalAlliance@eso.net

Social media @ABCGlobalAll
5 year survival rates for mBC still around 25%


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

Quality of life in patients with mBC as assessed by EQ-5D, 2004-2012, Generic (non-Cancer Specific) Health Utility Score²

- An analysis of the trends in quality of life for mBC* indicates that there has been **not been significant improvement** over the past decade²
- In fact, there has been a **slight decrease** in quality of life²

*Analysis was based on a review of 132 articles, of which a quantitative analysis was conducted of 14 studies reporting QoL measures 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.

ABC Global Charter
10 goals for the next 10 years

COMPREHENSIVE NEEDS ASSESSMENT
DEFINES MOST URGENT AND ACTIONABLE GOALS
Done with (almost) all different stakeholders involved in ABC

1. HELP PATIENTS WITH ABC LIVE LONGER BY DOUBLING ABC MEDIAN OVERALL SURVIVAL BY 2025

2. ENHANCE OUR UNDERSTANDING ABOUT ABC BY INCREASING THE COLLECTION OF HIGH QUALITY DATA

3. IMPROVE THE QUALITY OF LIFE (QOL) OF PATIENTS WITH ABC

4. ENSURE THAT ALL PATIENTS WITH ABC RECEIVE THE BEST POSSIBLE TREATMENT AND CARE BY INCREASING AVAILABILITY OF ACCESS TO CARE FROM A MULTIDISCIPLINARY TEAM

5. IMPROVE COMMUNICATION BETWEEN HEALTHCARE PROFESSIONALS (HCP) AND PATIENTS WITH ABC THROUGH THE PROVISION OF COMMUNICATION SKILLS TRAINING FOR HCPS

6. MEET THE INFORMATIONAL NEEDS OF PATIENTS WITH ABC BY USING EASY TO UNDERSTAND, ACCURATE AND UP-TO-DATE INFORMATION MATERIALS AND RESOURCES

7. ENSURE THAT PATIENTS WITH ABC ARE MADE AWARE OF AND ARE REFERRED TO NON-CLINICAL SUPPORT SERVICES

8. COUNTERACT THE STIGMA AND ISOLATION ASSOCIATED WITH LIVING WITH ABC BY INCREASING PUBLIC UNDERSTANDING OF THE CONDITION

9. ENSURE THAT PATIENTS WITH ABC HAVE ACCESS TO TREATMENT REGARDLESS OF THEIR ABILITY TO PAY

10. HELP PATIENTS WITH ABC CONTINUE TO WORK BY IMPLEMENTING LEGISLATION THAT PROTECTS THEIR RIGHTS TO WORK AND ENSURE FLEXIBLE AND ACCOMMODATING WORKPLACE ENVIRONMENTS
HELP PATIENTS WITH ABC LIVE LONGER BY DOUBLING ABC MEDIAN OVERALL SURVIVAL BY 2025

1. STOP ACCEPTING PFS BENEFIT ALONE AS THE MAIN GOAL
2. OS MUST BE AT LEAST A CO-PRIMARY
3. INVEST IN LESS BUT “BIGGER” (SUFFICIENTLY POWERED) TRIALS
4. COLLECT POST-PROGRESSION DATA
5. USE REAL WORLD AND BIG DATA
• STOP PRESCRIBING SO MUCH UNECESSARY CT
• NOT ALL PATIENTS NEED COMBINATION OF ET + TARGETED
• ADEQUATE SYMPTOM CONTROL (Access to opioids)
NEED FOR CHANGE IN REIMBURSEMENT RULES
In many countries, current rules do not facilitate oral, less toxic treatments, nor shorter treatments of radiotherapy
• STOP PRESCRIBING SO MUCH UNECESSARY CT
• NOT ALL PATIENTS NEED COMBINATION OF ET + TARGETED
• ADEQUATE SYMPTOM CONTROL (Access to opioids)

• DEVELOP BETTER AND SPECIFIC QoL TOOLS
• ASK EXPERTS FOR HELP WHEN CHOOSING QoL TOOLS AND ENDPOINTS
<table>
<thead>
<tr>
<th>Title</th>
<th>Improving health-related quality of life in metastatic breast cancer: taking stock of achievements and delivering better measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal investigator(s) &amp; contact details</td>
<td>Galina Velikova – University of Leeds, UK and EORTC QLG Fatima Cardoso – Champalimaud Clinical Center Lisbon, Portugal and chair of Breast Cancer Group</td>
</tr>
<tr>
<td>Group Membership of Principal investigator(s)</td>
<td>EORTC Quality of Life Group, EORTC Breast Cancer Group, and members of the EORTC Breast Cancer Group.</td>
</tr>
</tbody>
</table>

**Ongoing project:**

**Development of a QoL tool specific for ABC**

**Ongoing project:**

**Development of Quality Indicators for ABC/MBC**
In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium

D. J. A. Lobbezoo1,2, R. J. W. van Kampen1, A. C. Voogd1,3, M. W. Dercksen2, F. van den Berkmortel4, T. J. Smilde5, A. J. van de Wouw6, F. P. J. Peters7, J. M. G. H. van Riel8, N. A. J. B. Peters9, M. de Boer1, P. G. M. Peer10 & V. C. G. Tjan-Heijnen11

1 GROW—School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht; 2Department of Internal Medicine, Maastricht Medical Centre, Veldhoven; 3Netherlands Comprehensive Cancer Organisation, Utrecht; 4Department of Internal Medicine, Ahern-Orbis Heerlen, Heerlen; 5Department of Medical Oncology, Jeroen Bosch Hospital, Den Bosch; 6Department of Internal Medicine, VU University Medical Center, Amsterdam; 7Department of Internal Medicine, Ahern-Orbis Sittard, Sittard; 8Department of Internal Medicine, St Elisabeth Hospital, Tilburg; 9Department of Internal Medicine, St Jans-Hospital, Weert; 10Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands

Received 24 May 2015; revised 28 August 2015 and 14 October 2015; accepted 26 October 2015

Starting with ET vs. Starting with CT

PFS

OS

Patients with initial chemotherapy, median PFS 5.3 months (95% CI 4.2–6.2)

Patients with initial endocrine therapy, median PFS 13.3 months (95% CI 11.3–15.5)

Patients with initial chemotherapy, median OS 16.1 months (95% CI 13.7–19.7)

Patients with initial endocrine therapy, median OS 36.9 months (95% CI 30.6–43.9)
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/GoR: I/A) (96%)
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>Beslja 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><strong>678</strong></td>
<td><strong>886</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.16 [1.03, 1.31]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 9.41$, df = 7 ($P = 0.22$); $I^2 = 26$
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>Beslja 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>
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</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><strong>807</strong></td>
<td><strong>979</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.04 [0.93, 1.16]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 10.54$, df = 8 ($P = 0.23$); $I^2 = 24$
Test for overall effect: $Z = 0.76$ ($P = 0.45$)

Dear RF et al. Combination vs. sequential single agent CT for MBC (Review) 2013
Duration of each regimen and number of regimens should be tailored to each individual patient. (LoE/GoR: Expert opinion/A) (96%)

Usually each regimen (except anthracyclines) should be given until progression of disease or unacceptable toxicity. What is considered unacceptable should be defined together with the patient. (LoE/GoR: I/B) (72%)

✓ A meta-analysis of published trials (Gennari et al) concluded that longer 1st line CT duration is associated with a marginally longer OS and a substantially longer PFS.
**Optimal Duration of Chemotherapy?**

- **Longer CT duration associated with:**
  - significant 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)

### Results: Progression Free Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Longer better</th>
<th>Shorter better</th>
<th>%Weight</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coates 1987</td>
<td>13</td>
<td>0.56</td>
<td>0.44-0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris 1990</td>
<td>2</td>
<td>1.18</td>
<td>0.65-2.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muss 1991</td>
<td>3</td>
<td>0.26</td>
<td>0.16-0.43</td>
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<td></td>
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<tr>
<td>Ejertsen 1993</td>
<td>28</td>
<td>0.71</td>
<td>0.61-0.83</td>
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<tr>
<td>Gregory 1997</td>
<td>10</td>
<td>0.70</td>
<td>0.53-0.92</td>
<td></td>
<td></td>
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<tr>
<td>Falkson 1998</td>
<td>5</td>
<td>0.46</td>
<td>0.31-0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bastit 2000</td>
<td>11</td>
<td>0.65</td>
<td>0.50-0.84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nooj 2003</td>
<td>8</td>
<td>0.67</td>
<td>0.50-0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gennari 2006</td>
<td>6</td>
<td>1.01</td>
<td>0.71-1.43</td>
<td></td>
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<tr>
<td>Majordomo 2009</td>
<td>8</td>
<td>0.77</td>
<td>0.57-1.05</td>
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<td></td>
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<tr>
<td>Alba 2010</td>
<td>6</td>
<td>0.53</td>
<td>0.37-0.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>100</td>
<td>0.64</td>
<td>0.55-0.76</td>
<td></td>
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</tbody>
</table>

Test for heterogeneity, p=0.001  
Test for treatment effect, p<0.001

### Results: Overall Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Longer better</th>
<th>Shorter better</th>
<th>%Weight</th>
<th>HR</th>
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<tr>
<td>Coates 1987</td>
<td>13</td>
<td>0.79</td>
<td>0.62-1.01</td>
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<tr>
<td>Harris 1990</td>
<td>2</td>
<td>1.06</td>
<td>0.57-1.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muss 1991</td>
<td>5</td>
<td>1.11</td>
<td>0.74-1.67</td>
<td></td>
<td></td>
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<tr>
<td>Ejertsen 1993</td>
<td>17</td>
<td>0.78</td>
<td>0.63-0.97</td>
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<td>Gregory 1997</td>
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<td>0.81</td>
<td>0.54-1.21</td>
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<td>0.94</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nooj 2003</td>
<td>17</td>
<td>1.03</td>
<td>0.83-1.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gennari 2006</td>
<td>4</td>
<td>1.12</td>
<td>0.73-1.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Majordomo 2009</td>
<td>7</td>
<td>0.94</td>
<td>0.67-1.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alba 2010</td>
<td>5</td>
<td>0.86</td>
<td>0.58-1.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>100</td>
<td>0.91</td>
<td>0.84-0.99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity, p=0.69  
Test for treatment effect, p=0.044

![Diagram](attachment:image.png)

**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 !?!!**

Gennari et al, J Clin Oncol 2011
Duration (ASCO Guidelines)

- Chemotherapy should be continued until progression of disease as tolerated because it modestly improves overall survival and substantially improves progression-free survival, but this has to be balanced against toxicity and quality of life.

- Short breaks, flexibility in scheduling, or a switch to endocrine therapy (in patients with hormone receptor-positive disease) may be offered to selected patients.

Then:

- **TOXICITY PROFILE** is crucial
- **DOSE REDUCTIONS** are acceptable and often needed (and better than interruptions)
- **ORAL** vs IV (convenient, cost-effective, maintain work responsibilities...)
- **PATIENT PREFERENCES** (oral treatment approaches and time saving drug delivery strategies are usually preferred by the patients)

**GOAL in ABC:**
to treat for as long as possible with a good QoL
Taxonomy of the burden of treatment

From "Taxonomy of the burden of treatment: a multi-country web-based qualitative study of patients with chronic conditions." Tran VT et al., BMC Med, 2015

Factors that exacerbate the burden of treatment

Healthcare tasks

Consequences of healthcare tasks imposed on patients

Does being a patient have to be a full-time job?

Most doctors believe in holistic care, yet the clinical guidelines they use, and the way they discuss and deliver care, rarely take into account the demands that a given treatment option will make on the patient and their daily life. Anna Wagstaff reports on calls for this to change. Additional reporting by Peter McIntyre.
Strengths and Weaknesses of Oral CT

• Surveys have shown that most patients prefer oral to IV treatments\(^1\)

• A minority prefer IV due to possible less effectiveness of oral therapies (last resort)\(^2\)

• Convenient, less visits to the Hospital,

• Keep work schedules (patients and careers), less financial burden

• No need for iv administration (veins...)


Reviewed in Cardoso F et al. Cancer Treatment Communications 6S1 (2016) S1–S10
Strengths and Weaknesses of Oral CT

- Adherence

- Not free from potentially dangerous side-effects

- Dosing mistakes such as forgetting the treatment breaks commonly used with some therapies (i.e., 2 weeks on, 1 week off for capecitabine) or taking the wrong number of pills can negatively affect both efficacy and tolerability.

- Improper handling or storage of oral medications

CRUCIAL ROLE OF CONTINUOUS PATIENT EDUCATION & SIMPLE DOSING SCHEDULES

Reviewed in Cardoso F et al. Cancer Treatment Communications 6S1 (2016) S1–S10
Factors Associated With Nonadherence to Prescribed Oral Chemotherapy

- Complex treatment regimen
- Substantial behavioral change required
- Inconvenient or inefficient clinics
- Inadequate supervision
- Poor communication with healthcare providers
- Inadequate social support
- History of nonadherence
- History of mental illness

But: this is a problem mainly in the early setting, not so much in the metastatic setting.

Courtesy M. Colleoni & Prime Oncology

## Oral Therapy From the Perspective of Patients, Healthcare Professionals, and Funders

<table>
<thead>
<tr>
<th>Needs</th>
<th>Healthcare Funders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Needs</td>
<td>• Reimbursement reform in some countries</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefits</td>
<td>• Cost savings</td>
</tr>
<tr>
<td></td>
<td>• Staffing savings</td>
</tr>
</tbody>
</table>


IV, intravenous
Which agents?
In the absence of medical contraindications or patient concerns, anthracycline or taxane based regimens, preferably as single agents, would usually be considered as first line CT for HER-2 negative MBC, in those patients who have not received these regimens as (neo)adjuvant treatment and for whom chemotherapy is appropriate.

Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient (LoE: 1 A) (71%).
In patients with taxane-naive and anthracycline-resistant MBC or with anthracycline cumulative dose or toxicity (i.e. cardiac) who are being considered for further CT, taxane-based therapy, preferably as single agents, would usually be considered as treatment of choice.

Other options are, however, available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient.

(LoE: 1 A) (59%).
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%)
Capecitabine

5 Fluoro-5'-deoxycytidine

5 Fluoro-5'-deoxyuridine

TEGAFUR

TEGAFUR

+ uracil = UFT

+ inhibitor 1* = S1

Eniluracil

5-FU

5-FU

PRPP

5FUMP → 5FUDP → 5FUTP → RNA

Anti-RNA pathway

5FUDR → 5FdUMP → 5FdUDP → 5FdUTP → DNA

Anti-DNA pathway

DHFU

dThdPase (tumor)

Carboxylesterase (liver)

Cytidine deaminase (liver + tumor)

dThdPase (tumor)

5FU

*Eniluracil

5FUMP → 5FUDP → 5FUTP → RNA

Anti-RNA pathway

5FUDR → 5FdUMP → 5FdUDP → 5FdUTP → DNA

Anti-DNA pathway

5,10-me THF

dihydrofolate
Efficacy of Capecitabine in MBC: A Systematic Review


<table>
<thead>
<tr>
<th>Study Phase and Design</th>
<th>Dosing Scheme</th>
<th>Inclusion Period</th>
<th>No. of Pts</th>
<th>Median Age (Range), Years</th>
<th>WHO Performance Status, n (%)</th>
<th>Pretreated With Anthracyclines, n (%)</th>
<th>Pretreated With Taxanes, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III, randomized</td>
<td>1250 mg/m² twice daily for 14 days every 3 weeks</td>
<td>2004-2006</td>
<td>201</td>
<td>51 (28-83)</td>
<td>118 (59)</td>
<td>83 (41)</td>
<td>0</td>
</tr>
<tr>
<td>II, randomized</td>
<td>1250 mg/m² twice daily for 14 days every 3 weeks</td>
<td>2002-2004</td>
<td>23</td>
<td>50 (31-70)</td>
<td>23 (100)</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>III, randomized</td>
<td>1250 mg/m² twice daily for 14 days every 3 weeks</td>
<td>2003-2006</td>
<td>377</td>
<td>52 (25-79)</td>
<td>237 (63)</td>
<td>136 (36)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>II, single arm</td>
<td>1250 mg/m² twice daily for 14 days every 3 weeks</td>
<td>2001-2003</td>
<td>37</td>
<td>52 (34-84)</td>
<td>22 (60)</td>
<td>13 (35)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>III, randomized</td>
<td>1250 mg/m² twice daily for 14 days every 3 weeks</td>
<td>2000-2002</td>
<td>230</td>
<td>Mean 52 (30-77)</td>
<td>115 (50)</td>
<td>115 (50)</td>
<td>0</td>
</tr>
<tr>
<td>II, single arm</td>
<td>1250 mg/m² twice daily for 14 days every 3 weeks</td>
<td>1998-2001</td>
<td>126</td>
<td>54 (30-80)</td>
<td>55 (44)</td>
<td>61 (49)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>II, single arm</td>
<td>1250 mg/m² twice daily for 14 days every 3 weeks</td>
<td>1999-2002</td>
<td>38</td>
<td>48 (31-66)</td>
<td>21 (55)</td>
<td>--</td>
<td>17 (45)</td>
</tr>
<tr>
<td>II, single arm</td>
<td>1255 mg/m² twice daily for 14 days every 3 weeks</td>
<td>1997-1999</td>
<td>74</td>
<td>Mean 52 (29-77)</td>
<td>74 (100)</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>II, single arm</td>
<td>1255 mg/m² twice daily for 14 days every 3 weeks</td>
<td>1996-1996</td>
<td>162</td>
<td>Mean 56 (26-78)</td>
<td>162 (100)</td>
<td>--</td>
<td>0</td>
</tr>
</tbody>
</table>

**SUMMARY EFFICACY:**

- Mean disease control rate (9 studies, 1174 pts): 55%
- Mean TTP (6 studies; 737 pts): 3.9 months
- Mean PFS (4 studies; 667 pts): 4.2 months
- Median OS (9 studies; 1027 pts) 13.5 months

**MAIN SIDE EFFECTS:** HFS: 16% and diarrhea: 10%
Capecitabine Versus Classical CMF As First-Line Chemotherapy for Advanced Breast Cancer: PFS and OS

The average duration of chemotherapy was longer in those assigned capecitabine than in those assigned CMF.

CI, confidence interval
TRIAL 303: Eribuline vs. Capecitabine in 1st, 2nd and 3rd line

- Global, randomized, open-label Phase III trial (Study 301)

Patients (N=1102)
Locally advanced or MBC
- ≤3 prior chemotherapy regimens (≤2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Eribuline mesylate
1.4 mg/m²† 2- to 5-min IV
Day 1 & 8 q21 days

Capecitabine
1250 mg/m² BID orally
Days 1-14, q21 days

Co-primary endpoint
- OS and PFS

Secondary endpoints
- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribuline arm only)

Stratification:
- Geographical region, HER2 status

†Equivalent to 1.23 mg/m² eribuline
Overall Survival

- **No significant differences in outcomes (PFS nor OS)**

- **Different toxicity profile (PATIENT PREFERENCES)** (neuropathy & neutropenia vs. HFS)

**Median OS (months)**
- Eribulin (n=554): 15.9
- Capecitabine (n=548): 14.5

HR: 0.879 (95% CI 0.770, 1.003)  
* p value: 0.056

**Median (months)**
- Progression-free Survival
  - Independent Review: Eribulin (n=554): 4.1, Capecitabine (n=548): 4.2
  - Investigator Review: Eribulin (n=554): 4.2, Capecitabine (n=548): 4.1

HR: 1.079 (95% CI 0.932, 1.250)  
* p value: 0.305

**Survival probability**

**Time (months)**
0 4 8 12 16 20 24 28 32 36 40 44

**San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center – December 4-8, 2012**

This presentation is the intellectual property of the author.

*ITT population; †HR Cox model including geographic region and HER2 status as strata
‡p value from stratified log-rank test based on clinical database*
Vinorelbine

Inhibition of tubulin polymerization with a differential affinity

- Selective affinity for mitotic spindle microtubules
- Low affinity for axonal microtubules

- Potent anti-tumoral activity
- Low neurotoxicity

Binet, Sem.Onc 1989
PHARMACOKINETIC DATA: ORAL VS IV

Equivalent AUCs:

<table>
<thead>
<tr>
<th>I.V.</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg/m²</td>
<td>80 mg/m²</td>
</tr>
<tr>
<td>25 mg/m²</td>
<td>60 mg/m²</td>
</tr>
</tbody>
</table>

Marty, Ann. Oncol. 2001
## Efficacy of Vinorelbine in MBC: A Systematic Review

### Study Phase and Design

<table>
<thead>
<tr>
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<th>Pretreated With Taxanes, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II, single arm</td>
<td>25 mg/m² weekly</td>
<td>2004-2009</td>
<td>26</td>
<td>47 (37-71)</td>
<td>21 (81)</td>
<td>5 (19)</td>
<td>24 (92)</td>
</tr>
<tr>
<td>II, randomized</td>
<td>30 mg/m² days 1 and 8 every 3 weeks</td>
<td>2002-2004</td>
<td>24</td>
<td>54 (31-71)</td>
<td>24 (100)</td>
<td>24 (100)</td>
<td></td>
</tr>
<tr>
<td>III, randomized</td>
<td>30 mg/m² days 1 and 8 every 3 weeks</td>
<td>2001-2005</td>
<td>126</td>
<td>57 (35-80)</td>
<td>45 (36)</td>
<td>58 (46)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>II, dual arm</td>
<td>25 mg/m² weekly</td>
<td>2000-2004</td>
<td>33</td>
<td>57 (35-74)</td>
<td>29 (88)</td>
<td>3 (9)</td>
<td>33 (100)</td>
</tr>
<tr>
<td>II, single arm</td>
<td>25 mg/m² days 1 and 8 every 3 weeks</td>
<td>2001-2003</td>
<td>50</td>
<td>55 (37-71)</td>
<td>38 (76)</td>
<td>7 (14)</td>
<td>50 (100)</td>
</tr>
<tr>
<td>II, single arm</td>
<td>8 mg/m² bolus, followed by 8 mg/m² days 1-4, every 3 weeks</td>
<td>1996-1999</td>
<td>47</td>
<td>54 (34-78)</td>
<td>47 (100)</td>
<td>--</td>
<td>44 (94)</td>
</tr>
<tr>
<td>II, single arm</td>
<td>30 mg/m² weekly</td>
<td>1997-1999</td>
<td>40</td>
<td>49 (39-69)</td>
<td>40 (100)</td>
<td>--</td>
<td>40 (100)</td>
</tr>
<tr>
<td>II, single arm</td>
<td>25 mg/m² every 2 weeks</td>
<td>1997-1998</td>
<td>20</td>
<td>47 (23-71)</td>
<td>3 (15)</td>
<td>2 (10)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>I-II, single arm</td>
<td>30 mg/m² weekly, dose escalation 35 mg/m²</td>
<td>1993-1995</td>
<td>40</td>
<td>Median 48 (33-73)</td>
<td>40 (100)</td>
<td>--</td>
<td>40 (100)</td>
</tr>
</tbody>
</table>

### SUMMARY EFFICACY:

- Mean disease control rate (8 studies; 366 pts): 49%
- Mean TTP (5 studies; 190 pts): 3.6 months
- Mean PFS (3 studies; 176 pts): 3.8 months
- Median OS (7 studies; 336 pts) 12.6 months

### MAIN SIDE EFFECTS: Fatigue: 13%
Oral Vinorelbine As a Single Agent in MBC

Table 2
Oral vinorelbine as a single agent in metastatic breast cancer [27,41–46]

<table>
<thead>
<tr>
<th>Reference</th>
<th>Oral vinorelbine schedule</th>
<th>N</th>
<th>Line of treatment</th>
<th>ORR, %</th>
<th>CBR, %</th>
<th>PFS/TTP, months</th>
<th>OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freyer et al. J Clin Oncol 2003 [41]</td>
<td>80 mg/m² weekly (after 3 administrations at 60 mg/m²)</td>
<td>58</td>
<td>1st</td>
<td>31</td>
<td>62</td>
<td>4.2</td>
<td>Not reached</td>
</tr>
<tr>
<td>Amadori et al. ECCO 2001 [27,42]</td>
<td>80 mg/m² weekly (after 3 administrations at 60 mg/m²)</td>
<td>63</td>
<td>1st</td>
<td>27</td>
<td>NR</td>
<td>4.6</td>
<td>21</td>
</tr>
<tr>
<td>Bartsch et al. ESMO 2008 [27,43]</td>
<td>60 mg/m² d1,8 q3w</td>
<td>100</td>
<td>1st–4th Post anthra</td>
<td>25</td>
<td>51</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Blancas et al. ASCO 2010 [27,44]</td>
<td>60 mg/m² weekly</td>
<td>45</td>
<td>1st or 2nd</td>
<td>29.5</td>
<td>59</td>
<td>4</td>
<td>NR</td>
</tr>
<tr>
<td>Mansour et al. IACT 2010 [27,45]</td>
<td>80 mg/m² d1,8 q3w (after 1 cycle at 60 mg/m²)</td>
<td>26</td>
<td>1st Post anthra and/or txn</td>
<td>42</td>
<td>NR</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>Steger et al. ESMO 2014 [46]</td>
<td>80 mg/m² weekly (after 4 administrations at 60 mg/m²)</td>
<td>70</td>
<td>1st (bone mets)</td>
<td>NR</td>
<td>55.7</td>
<td>8.2</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: anthra, anthracycline; CBR, clinical benefit rate; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; TTP, time to progression; txn, taxane

ORR about 30%
Median PFS or TTP of 4.0 months to 8.2 months
LIPOSOMAL TECHNOLOGY
“Old” agents with new technology

Doxorubicin  Liposomal Doxorubicin  Pegylated Liposomal Doxorubicin
Metronomic Delivery of Chemotherapy

Lower dose on a daily basis
Lower doses on a weekly basis
MTD every 3 weeks

“Metronomic Chemotherapy is the minimum biologically effective dose of a chemotherapeutic agent, which, when given at a continuous dosing regimen with no prolonged drug-free breaks leads to anti-tumor activity.”

(Klement & Kamen JPHO 2011)
Metronomic Scheduling and Inhibition of Tumor Growth: In Vivo Models


Drug-Resistant EMT-6 Breast Cancer

Conventional schedule

Antiangiogenic schedule

Metronomic Chemotherapy

Most frequently agents used in BC:

- **CM** (cyclophosphamide + methotrexate)
- Vinorelbine
- Capecitabine
- Vino + Cape

**Fig. 1.** Potential mechanisms of action of metronomic chemotherapy [61]. Reprinted by permission from Macmillan Publishers Ltd: Nat Rev Clin Oncol 2014;11:413-31. Copyright 2014. Abbreviations: CECs, circulating endothelial cells; DC, dendritic cell; EPC, endothelial progenitor cell; HIF-1α, hypoxia inducible factor 1 alpha; MDSC, myeloid-derived suppressor cell; THBS-1, thrombospondin 1; T_{REG}, regulatory T cell.
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.
Which Chemotherapy Regimen?

- No single agent has demonstrated superiority in the treatment of patients with advanced breast cancer, and there are several active agents appropriate for first-line chemotherapy. The evidence for efficacy is strongest for taxanes and anthracyclines. Other options include capecitabine, gemcitabine, platinum-based compounds, vinorelbine, and ixabepilone.

- Second- and later-line therapy may be of clinical benefit and should be offered as determined by previous treatments, toxicity, coexisting medical conditions, and patient choice. As with first-line treatment, no clear evidence exists for the superiority of one specific drug or regimen. Active agents include those active in first-line treatment. The most convincing data are for eribulin based on survival superiority against best standard treatment.

Clinical Efficacy of Cytotoxic Agents

Research question: BEST SEQUENCE!?
Chemotherapy for Recurrent MBC

Likelihood of response by **extent of prior treatment**

![Bar graph showing % Response by Number of Prior Regimens](Image)

Personal communication, A. Seidman; Courtesy A. Gennari
Advanced Breast Cancer

Fifth ESO-ESMO International Consensus Conference

14-16 November 2019 | Lisbon, Portugal
Coordinating Chair: F. Cardoso, PT
Co-Chairs: G. Curigliano, IT - S.A. Mertz, US
Scientific Committee Members: K. Gelmon, CA
F. Penault-Llorca, FR - E. Senkus, PL - C. Thomssen, DE

The ABC5 guidelines will be developed by ESO and ESMO
The ABC5 conference and guidelines are endorsed by

The ABC5 conference is held under the auspices of

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