Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

* Substances without published evidence based on at least one phase III/IIb trial were omitted
Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **Versions 2002–2017:**
  Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck /
  Jackisch / Janni / von Minckwitz / Möbus / Müller /
  Rody / Schaller / Scharl / Schmutzler / Schneeweiss / Schütz /
  Stickeler / Thill / Thomssen / Untch

- **Version 2018:**
  Liedtke / Möbus

**International consensus**

Disease-Free and Overall Survival in Metastatic Breast Cancer

- An increase in survival over time in MBC has been shown in some retrospective analyses
- Patients with MBC today have received more adjuvant treatment and in this regard can be considered more drug resistant
- Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity)
- Targeted drugs in combination with chemotherapy can induce substantial survival benefits

International consensus

Increase

Multiple lines
Endocrine Resistance in Metastatic Breast Cancer

**Primary endocrine resistance:**
- Relapse within 2 years of adjuvant endocrine treatment (ET)
- Progressive disease within first 6 months of first-line ET for MBC

**Secondary endocrine resistance:**
- Relapse while on adjuvant ET but after the first 2 years or a relapse within 12 months after completing adjuvant ET
- PD ≥ 6 months after initiation of ET for MBC

International consensus
CTC monitoring


Cytotoxic Therapy Goals

Oxford LoE: 1b GR: A AGO: ++

- **Mono-Chemotherapy:**
  - Favorable therapeutic index
  - Indicated in case of
    - Slow, not life-threatening progression
    - Insensitivity to or progression during endocrine therapy

- **Poly-Chemotherapy:**
  - Unfavorable therapeutic index
  - Indicated to achieve rapid remission in the case of
    - Extensive symptoms
    - Imminent life-threatening metastasis
  - Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven

Therapeutic index evaluates overall efficacy, toxicity and impact on quality of life

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International consensus


Combination vs single agent


Cochrane analysis

### Cytotoxic and Targeted Therapy

<table>
<thead>
<tr>
<th>GR: A</th>
<th>AGO: ++</th>
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<tbody>
<tr>
<td>- Evaluate compliance before and during therapy (especially in patients of older age, with reduced performance status, or significant co-morbidities)</td>
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<tr>
<td>- Assess subjective and objective toxicities, symptoms, and performance status repeatedly</td>
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<tr>
<td>- Use dosages according to published protocols</td>
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<tr>
<td>- Assess tumor burden at baseline and approx. every 2 months, i.e. every 2-4 cycles. Assessment of a target lesion may be sufficient. In slowly growing disease, longer intervals are acceptable.</td>
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3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017

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**International consensus**

Cytotoxic Therapy Duration

- **As long as therapeutic index remains positive**
  - Treatment until progression
  - Treatment until best response
  - Change to alternative regimen before progression

- **Stop therapy in case of**
  - Progression
  - Non tolerable toxicity

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<td></td>
<td>1c</td>
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</table>

**International consensus**


**Change to alternative regimen before progression:**


**Treatment until progression**


Chemotherapy for MBC – General Considerations: Drug Selection

International consensus


Quality of life: Paclitaxel/gemcitabine vs paclitaxel-mono. Combination tends to be better


Limitations of palliative chemotherapy


The choice of cytotoxic drugs to be used is dependent on:

- ER / PR, HER2; combination with biologicals
- Previous treatments (and their toxicities)
- Disease-free interval after end of adjuvant treatment
- Aggressiveness of disease and localization of metastases
- Estimated life expectancy
- Co-morbidities (including organ dysfunction)
- Patient preferences and expectations
International consensus


Single Agents


5. Gradishar WJ, Krasnojon D, Cheporov S, et al. Phase II trial of nab-paclitaxel compared with docetaxel as first-line chemotherapy in patients with metastatic breast cancer:


**Polychemotherapy**

**Metaanalysis:**


**Cochrane analysis containing taxane based regimens**


After anthracycline treatment two studies could show a survival benefit:


**Doxorubicin/docetaxel vs. Doxorubincin/paclitaxel as first line treatment in metastatic breast cancer (ERASME3-study) did not show any significant differences in terms of efficacy and overall QoL:**


**Other combinations:**


International consensus


Cochrane analysis taxane-containing regimens for metastatic breast cancer


Nab-paclitaxel


Eribulin


MBC HER2-negative/HR-positive: Cytotoxic Therapy after adjuvant Taxane and Anthracycline Treatment

<table>
<thead>
<tr>
<th>Therapy</th>
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<tbody>
<tr>
<td>Experimental therapies within studies</td>
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<tr>
<td>Capecitabine</td>
<td>2b</td>
<td>B</td>
<td>++</td>
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<tr>
<td>Eribulin</td>
<td>1b</td>
<td>B</td>
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<tr>
<td>Vinorelbine</td>
<td>2b</td>
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<td>++</td>
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<tr>
<td>(Peg)-liposomal Doxorubicin</td>
<td>2b</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Taxane re-challenge*</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Anthracycline re-challenge*</td>
<td>3b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Metronomic therapy (eg. cyclophos. + MTX)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Gemcitabine + Cisplatin / Carboplatin</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Gemcitabine + Capecitabine</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Gemcitabine + Vinorelbine</td>
<td>1b</td>
<td>B</td>
<td>-</td>
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</tbody>
</table>

* At least one year disease-free after adjuvant treatment

International consensus


Capecitabine:


Eribulin


Taxane re-challenge

Anthracycline re challenge

Metronomic chemotherapy

Gemcitabine + cisplatin / carboplatin

Gemcitabine + capecitabine
1. Park JS, Jeung HC, Rha SY, et al. Phase II gemcitabine and capecitabine combination therapy in recurrent or metastatic breast cancer patients pretreated with anthracycline and taxane.
Gemcitabine + Vinorelbine:


Triple Negative mBC Independent of Genomic BRCA 1/2 Mutation

Oxford

| Experimental therapies within studies | ++ |
| Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC | +/- |
| Carboplatin (vs. Docetaxel) | 1b | B | +/- |
| Gemcitabine/Cisplatin (vs. Gem/Pac) | 1b | A | + |
| Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem) | 2b | B | + |
| Bevacizumab added to first line cytotoxic therapy | 1b | B | + |

International consensus


Carboplatin (vs. Docetaxel) / Carboplatin in gBRCA mutation:

1. The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012) Tutt A, Ellis P, Kilburn L, Gilett C, et al. San Antonio Breast Cancer Symposium 2014; S3-01.

Gemcitabine/Cisplatin (vs. Gem/Pac)


Nab-Paclitaxel / Carboplatin:

1. Yardley D, Coleman R, Conte P, et al. nab-paclitaxel + carboplatin or gemcitabine vs gemcitabine/carboplatin as first-line treatment for patients with triple-negative metastatic breast cancer: Results from the randomized phase 2 portion of the tnAcity trial. SABCS 2016 Abstract #P5-15-03
Bevacizumab as first-line therapy

International consensus


Carboplatin (vs. Docetaxel) / Carboplatin in gBRCA mutation:

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PARP Inhibitoren bei triple negativ und BRCA 1/2 Mutation


- Experimental therapies within studies
- Carboplatin (vs. Docetaxel) (if Platinum-naive)
- PARP inhibitors
  - Olaparib (HER2-negative)
  - Olaparib (HER2-positive)
**Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th>1st line in combination with:</th>
<th>Oxford</th>
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<tbody>
<tr>
<td>Paclitaxel (q1w)</td>
<td>1b</td>
<td>B</td>
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<tr>
<td>Capecitabine</td>
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<td>Anthracyclines</td>
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<td>Nab-Pac</td>
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<td>Docetaxel (q3w)</td>
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<td>2nd line in combination with:</td>
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<td>Taxanes</td>
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<tr>
<td>Capecitabine</td>
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<tr>
<td>Gemcitabine or vinorelbine</td>
<td>1b</td>
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</table>

2nd line as treatment through multiple lines:  

| 1b     | B   | -  |     |

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**International consensus**


**First-line chemotherapy and bevacizumab:**


**Taxane and bevacizumab first-line**


**Nab-Paclitaxel and bevacizumab first-line:**

1. Rugo HS, Barry WT, Moreno-Aspitia A, et al. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per

Capecitabine and bevacizumab first-line

Cap+Bev as maintenance after Doc+Bev:

Second-line chemotherapy and bevacizumab:

2nd line as treatment through multiple lines:
International consensus


ASCO recommendation:


Docetaxel + trastuzumab + pertuzumab


Paclitaxel weekly + trastuzumab + pertuzumab


**Nab-Paclitaxel + trastuzumab + pertuzumab**


**Vinorelbine + trastuzumab + pertuzumab**


**T-DM1 after rapid progress**


**1st line chemotherapy + trastuzumab**


5. Wardley AM, Pivot X, Morales-Vasquez F et al.: Randomized Phase II Trial of First-


Trastuzumab mono

Taxanes+ lapatinib

Taxane + trastuzumab + everolimus
1. Hurvitz SA et al., Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial, Lancet Oncol. 2015;16(7):816-29

Trastuzumab + aromatase inhibitors (if ER+)
Lapatinib + aromatase inhibitors (if ER+)

2\textsuperscript{nd} line Therapy of HER2-positive mBC (If Pretreatment with Trastuzumab)

- **T-DM 1**
- **TBP: 2\textsuperscript{nd} line chemotherapy + trastuzumab**
- **BP: 2\textsuperscript{nd} line chemotherapy + trastuzumab + pertuzumab**
- **Any other 2\textsuperscript{nd} line chemotherapy* + trastuzumab + pertuzumab**
  - Taxane + trastuzumab + pertuzumab
  - Capecitabine + trastuzumab + pertuzumab
- **Capecitabine + lapatinib**
- **Trastuzumab + lapatinib (HR neg. disease)**

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<th>LoE</th>
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* e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)

International consensus
1. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO\textsuperscript{int}ernational consensus guidelines for Advanced Breast Cancer (ABC 3). Breast 2017;31:244-259;

ASCO recommendation:

**T-DM1**

**TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression)**
1. von Minckwitz G, Schwedler K, Schmidt M, et al; GBG 26/BIG 03-05 study group and participating investigators. Trastuzumab beyond progression: overall survival analysis of

TBP: 2nd-Line chemotherapy + Trastuzumab + pertuzumab (Treatment beyond progression)

Any other 2nd-Line chemotherapy + trastuzumab + pertuzumab

Taxane + trastuzumab + pertuzumab

Capecitabine + Trastuzumab + Pertuzumab

Capecitabine + lapatinib
3. When compared against capecitabine alone, the addition of lapatinib has a cost-effectiveness ratio exceeding the threshold normally used by NICE.

Trastuzumab + lapatinib vs lapatinib
### Further Lines of Therapy of HER2-Positive Metastatic Breast Cancer

#### Pretreatment with Trastuzumab

- **T-DM 1**
- Capecitabine + lapatinib
- Vinorelbine + lapatinib
- Trastuzumab + lapatinib (HR neg. disease)
- Chemotherapy + trastuzumab (*treatment beyond progression*)
- Trastuzumab + pertuzumab
- Vinorelbine + trastuzumab + everolimus (*trastuzumab resistant, taxane pretreated*)

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#### Neither data for patients pretreated with trastuzumab and pertuzumab nor data for treatment beyond progression available.

- Experimental anti-HER2-regimen
- For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above.

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**International consensus**


**ASCO recommendation:**


**T-DM1**


**Capecitabine + Lapatinib**


Vinorelbine + Lapatinib:


Trastuzumab + lapatinib vs lapatinib


TBP: 2nd-line chemotherapy + trastuzumab


Trastuzumab + pertuzumab


Vinorelbine + Trastuzumab + Everolimus

**Lapatinib in HER2-positive Metastatic Breast Cancer**

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<tr>
<td>In combination with</td>
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<tr>
<td>Trastuzumab for heavily pre-treated pts (HR negative)</td>
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<tr>
<td>Pacitaxel in 1st line</td>
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<tr>
<td>Capecitabine in &gt; 2nd line</td>
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<tr>
<td>Vinorelbine</td>
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<tr>
<td>AI in ER positive disease</td>
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<tr>
<td>In patients with brain metastasis (radioresistance) in combination with capecitabine</td>
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**Trastuzumab + lapatinib vs lapatinib**


**Taxanes + lapatinib**


**Capecitabine + Lapatinib**

that has progressed on trastuzumab: updated efficacy and biomarker analyses. 


**Vinorelbine + Lapatinib:**

**Lapatinib + aromatase inhibitors (if ER+)**

**Brain metastases (radioresistance)**
**Immunodiagnostic Tests and Immunotherapy**

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- **Immunodiagnostic tests:**
  - Immunological parameters in peripheral blood

- **Local immunotherapy**
  - Imiquimod topically for skin metastasis

- **Systemic immunotherapy - including items below – only within clinical trials:**
  - HER2-vaccination in high risk population
  - Immunomodulation (e.g. addition of Nov-2 to AC –T)
  - Dendritic cell intradermal vaccination
  - Active vaccination
  - Passive vaccination
  - Therapy with oncolytic viruses
  - Cytokines
  - Checkpoint inhibitors (PD1; PDL-1; ...)

* Study participation recommended