Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

*Substances are only discussed if there is at least published evidence based on one phase III / IIb study available
Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **Version 2002:**
  von Minckwitz / Schaller / Untch

- **Versions 2003–2016:**
  Bischoff / Dall / Fersis / Friedrichs / Harbeck /
  Jackisch / Janni / von Minckwitz / Möbus / Müller /
  Rody / Scharl / Schmutzler / Schneeweiss /
  Schütz / Stickeler / Thill / Thomssen

- **Version 2017:**
  Fehm / Jackisch
Disease-Free and Overall Survival in Metastatic Breast Cancer

- An increase in survival over time in MBC has been shown in some retrospective analyses (2a)
- However, patients with MBC today have received more adjuvant treatment and have therefore to be considered more drug resistant (2a)
- Multiple lines of sequential therapy are beneficial (at least same efficacy, less toxicity) (1b)
- Especially targeted drugs in combination with chemotherapy can induce substantial survival benefits (1b)
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 initiating ET for MBC
## Treatment of Metastatic Breast Cancer

### Predictive Factors

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Factor</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine therapy</strong></td>
<td>ER / PR (primary tumor, metastasis)</td>
<td>1a A ++</td>
</tr>
<tr>
<td></td>
<td>previous response</td>
<td>2b B ++</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>previous response</td>
<td>1b A ++</td>
</tr>
<tr>
<td><strong>Anti-HER2-drugs</strong></td>
<td>HER2 (primary tumor, better metastasis)</td>
<td>1a A ++</td>
</tr>
<tr>
<td><strong>Bone modifying drugs</strong></td>
<td>bone metastasis</td>
<td>1a A ++</td>
</tr>
<tr>
<td><strong>Any therapy</strong></td>
<td>CTC monitoring</td>
<td>1b A +*</td>
</tr>
</tbody>
</table>

*(other potentially biological factors see chapter „Predictive factors“)*

*Within clinical trials*
Cytotoxic Therapy Goals

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

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

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

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

GR: A  AGO: ++

- Evaluate compliance before and during therapy (especially in patients of older age, with reduced performance status, or significant co-morbidities)
- Assess subjective and objective toxicities, symptoms, and performance status repeatedly
- Use dosages according to published protocols
- Assess tumor burden at baseline and approx. every 2 months, i.e. every 2-4 cycles. Assessment of a target lesion might be sufficient. In slowly growing disease, longer intervals are acceptable.

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017
Cytotoxic Therapy

Duration

As long as therapeutic index remains positive

- Treatment until progression
  - 1a A ++

- Treatment until best response
  - 2b B +

- Change to alternative regimen before progression
  - 2b B +/-

- Stop therapy in case of
  - Progression
    - 1c A ++
  - Non tolerable toxicity
Chemotherapy for MBC – General Considerations: Drug Selection

AGO: ++

The choice of cytotoxic drugs to be used depends 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 dysfunctions)
- Patients preference and expectations

3rd ESO–ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3) 2017
MBC HER2-negative/HR-positive
Cytotoxic 1\textsuperscript{st}-Line Therapy\* 

**Monotherapy:**
- Paclitaxel (q1w), Docetaxel (q3w)
- Doxorubicin, epirubicin, mitoxantrone (A) 
  Peg. liposomal doxorubicin ($A_{\text{lip}}$)
- Vinorelbin
- Capecitabine
- Nab-paclitaxel

**Polychemotherapy:**
- A + T
- Paclitaxel + capecitabine
- Docetaxel + capecitabine after adj. A
- $T + \text{gemcitabine after adj. A}$
- A + C or $A_{\text{lip}} + C$

*In ER pos. disease only if endocrine therapy is not or not anymore indicated*
**MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment**

- Paclitaxel q1w 1a A ++
- Docetaxel q3w 1a A ++
- Capecitabine 2b B ++
- Nab-paclitaxel 2b B ++
- Peg-liposomal doxorubicin 2b B +
- Eribulin 1b B +
- Vinorelbine 2b B +
- Docetaxel + Peg-liposomal Doxo 1b B +/-

*Independent whether anthracyclines were used in adjuvant or 1st line metastatic situation*
<table>
<thead>
<tr>
<th>Experimental therapies within studies</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>2b B ++</td>
</tr>
<tr>
<td>Eribulin</td>
<td>1b B ++</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2b B ++</td>
</tr>
<tr>
<td>(Peg)-liposomal Doxorubicin</td>
<td>2b B +</td>
</tr>
<tr>
<td>Taxane re-challenge*</td>
<td>2b B +</td>
</tr>
<tr>
<td>Anthracycline re-challenge*</td>
<td>3b C +</td>
</tr>
<tr>
<td>Metronomic therapy (eg. cyclophos. + MTX)</td>
<td>2b B +</td>
</tr>
<tr>
<td>Gemcitabine + Cisplatin / Carboplatin</td>
<td>2b B +/−</td>
</tr>
<tr>
<td>Gemcitabine + Capecitabine</td>
<td>2b B +/−</td>
</tr>
<tr>
<td>Gemcitabine + Vinorelbine</td>
<td>1b B -</td>
</tr>
</tbody>
</table>

*At least one year disease-free after adjuvant treatment
Triple Negative Metastatic Breast Cancer

- Experimental therapies within studies  
  
- Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC
  - Carboplatin (vs. Docetaxel)
    - in gBRCA mutation
  - Gemcitabine/Cisplatin (vs. Gem/Pac)
  - Nab-Paclitaxel/Carboplatin (vs. Carbo/Gem)
  - Bevacizumab added to first line cytotoxic therapy

Oxford / AGO LoE / GR

- ++
- +
- 1b\(^a\) B +/-
- 1b\(^a\) B +
- 1b A +
- 2b\(^a\) B +
- 1b B +
### Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>1st line in combination with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (q1w)</td>
</tr>
<tr>
<td>Capecitabine</td>
</tr>
<tr>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Nab-Pac</td>
</tr>
<tr>
<td>Docetaxel (q3w)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cap+Bev as maintenance after Doc+Bev</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b(^a) B +/-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd line in combination with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxanes</td>
</tr>
<tr>
<td>Capecitabine</td>
</tr>
<tr>
<td>Gemcitabine or vinorelbine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2nd line as treatment through multiple lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b B -</td>
</tr>
</tbody>
</table>
First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

- Docetaxel + trastuzumab + pertuzumab
- Paclitaxel (wk) + trastuzumab + pertuzumab
- Nab-Paclitaxel + trastuzumab + pertuzumab
- Vinorelbine + Trastuzumab + Pertuzumab
- T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)
- 1st line chemotherapy* + trastuzumab
- Trastuzumab mono
- Taxanes + lapatinib
- Taxanes + trastuzumab + everolimus
- Trastuzumab + aromatase inhibitors (if ER+)
- Lapatinib + aromatase inhibitors (if ER+)

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
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</thead>
<tbody>
<tr>
<td>1b        A        ++</td>
</tr>
<tr>
<td>2b        B        ++</td>
</tr>
<tr>
<td>3b(^a) C        +</td>
</tr>
<tr>
<td>3b        B        +</td>
</tr>
<tr>
<td>2b        B        +</td>
</tr>
<tr>
<td>1b        B        +</td>
</tr>
<tr>
<td>2b        B        +/-</td>
</tr>
<tr>
<td>1b        B        +/-</td>
</tr>
<tr>
<td>1b        B        -</td>
</tr>
<tr>
<td>2b        B        +/-**</td>
</tr>
<tr>
<td>2b        B        +/-**</td>
</tr>
</tbody>
</table>

*Taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel
**see chapter Endocrine +/- targeted
### 2nd line Therapy of HER2-positive mBC
(If Pretreatment with Trastuzumab)

<table>
<thead>
<tr>
<th>Option</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T-DM 1</strong></td>
<td>1b A ++</td>
</tr>
<tr>
<td><strong>TBP: 2nd line chemotherapy + trastuzumab</strong></td>
<td>2b B +</td>
</tr>
<tr>
<td><strong>TBP: 2nd line chemotherapy + trastuzumab + pertuzumab</strong></td>
<td>5 D +/-</td>
</tr>
<tr>
<td><em><em>Any other 2nd line chemotherapy</em> + trastuzumab + pertuzumab</em>*</td>
<td>5 D +/-</td>
</tr>
<tr>
<td>- Taxane + trastuzumab + pertuzumab</td>
<td>5 D +</td>
</tr>
<tr>
<td>- Capecitabine + trastuzumab + pertuzumab</td>
<td>1b B +/-</td>
</tr>
<tr>
<td><strong>Capecitabine + lapatinib</strong></td>
<td>1b B +</td>
</tr>
<tr>
<td><strong>Trastuzumab + lapatinib (HR neg. disease)</strong></td>
<td>2b B +</td>
</tr>
</tbody>
</table>

*e.g. vinorelbine; taxane/carboplatin; capecitabine/docetaxel (toxicity!)*
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*)

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>1b</th>
<th>A</th>
<th>++</th>
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<tbody>
<tr>
<td>1b</td>
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<tr>
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</tbody>
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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.

<table>
<thead>
<tr>
<th>5</th>
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<td>+</td>
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</tbody>
</table>
Lapatinib in HER2-positive Metastatic Breast Cancer

In combination with

- Trastuzumab for heavily pre-treated pts (HR negative)  
  2b B +
- Paclitaxel in 1\textsuperscript{st} line  
  1b B +/−
- Capecitabine in > 2\textsuperscript{nd} line  
  1b B +
- Vinorelbine  
  2b B +/−
- AI in ER positive disease  
  2b B +/−
- In patients with brain metastases (radioresistance) in combination with capecitabine  
  2b B +/−
Immunodiagnostic Tests and Immunotherapy*

Immunodiagnostic tests: Immunological parameters in peripheral blood

Local immunotherapy

- Imiquimod topically for skin metastases

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;...)

Oxford / AGO LoE / GR

- Immunodiagnostic tests: Immunological parameters in peripheral blood
- Local immunotherapy
- Systemic immunotherapy - including items below – only within clinical trials:

<table>
<thead>
<tr>
<th>Study participation recommended</th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Oxford / AGO LoE / GR</td>
<td>5</td>
<td>D</td>
<td>--</td>
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<tr>
<td>4 C +/-</td>
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<td></td>
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<tr>
<td>++</td>
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<td></td>
</tr>
</tbody>
</table>
Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer (2/19)

No further information

References:

International consensus

Update since 2013 based on versions 2012.1 E (fusion of Chapter 21, Cytotoxic Therapy in Metastatic Breast Cancer, and Chapter 25, Targeted Agents).
Disease-Free and Overall Survival in Metastatic Breast Cancer (3/19)

No further information

References:

International consensus


Increase


Multiple lines

**Endocrine resistance in metastatic breast cancer (4/19)**

No further information

**References:**

International consensus

Treatment of Metastatic Breast Cancer - Predictive Factors (5/19)

No further information

References:

CTC monitoring


Cytotoxic Therapy Goals (6/19)

No further information

References:

International consensus


Combination vs single agent


Cochrane analysis
Cytotoxic and Targeted Therapy (7/19)

No further information

References:

International consensus

Cytotoxic Therapy Duration (8/19)

No further information

References:

International consensus


Change to alternative regimen before progression:


Treatment until progression


Chemotherapy for MBC – General Considerations: Drug Selection (9/19)

No further information

References:

International consensus


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


Limitations of palliative chemotherapy


MBC HER2 negative Cytotoxic 1<sup>st</sup>-Line Therapy (10/19)

No further information

References:

International consensus


Single Agents


**Polychemotherapy**

**Metaanalysis:**


Cochrane analysis containing taxane based regimens


After anthracycline treatment two studies could show a survival benefit:


Doxorubicin/docetaxel vs. Doxorubicin/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:


Further information and references:

International consensus


Cochrane analysis taxane-containing regimens for metastatic breast cancer


Nab-paclitaxel


Erubilin


Suggested after anthracyclines (in alphabetical order): Capecitabine, docetaxel, study-integrated experimental therapies, pegylated doxorubicin, paclitaxel and vinorelbine. As monotherapy after anthracyclins-pretreatment only docetaxel improved OAS as compared to a standard treatment arm in a prospective randomized trial in metastatic breast cancer (Nabholtz et al, 1999).

A Cochrane-metaanalysis of taxane treatment in metastatic breasts cancer (Ghersi et al, 2015) shows a significant survival advantage as compared to non-taxane-based therapies. There was no significant difference in QoL or treatment related deaths. Final analysis of further end points was difficult due to significant heterogeneity of the single studies. Indirect and direct comparisons of docetaxel and paclitaxel show a trend towards higher efficacy of docetaxel (Ghersi et al, 2015; Ravdin et al, 2003). Due to different toxicity profiles of each substance individual indication is needed.

Docetaxel in combination with pegylated doxorubicin was superior to docetaxel alone in a randomised phase III trial (Sparano et al. 2009). It is one of the largest trials in this setting with 751 pts and demonstrated a clear PFS advantag fro m 9.8 vs 7 months without improving the OS. QoL was not different. Hand foot syndrome and mucositis were more common with the combination.
**MBC HER2 negative: Cytotoxic Therapy After Taxane and Anthracycline Treatment (12/19)**

No further information

**References**

International consensus


**Capecitabine:**


**Eribulin**


**Taxane re-challenge**


**Anthracycline re-challenge**


**Metronomic chemotherapy**


Gemcitabine + cisplatin / carboplatin


Gemcitabine + capecitabine


Gemcitabine + Vinorelbine:

Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-) (13/19)

Further information and references:

International consensus


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


Gemcitabine/Cisplatin (vs. GemPac)

Nab-Paclitaxel / Carboplatin:


Bevacizumab as first-line therapy

**Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (14/19)**

**Further information and references:**

International consensus


**First-line chemotherapy and bevacizumab:**


**Taxane and bevacizumab first-line**

Nab-Paclitaxel and bevacizumab first-line:


Capecitabine and bevacizumab first-line


Cap+Bev as maintenance after Doc+Bev:


Second-line chemotherapy and bevacizumab:


2nd line as treatment through multiple lines:

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (15/19)

No further information

References:

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


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+)

Second Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment with Trastuzumab)  
(16/19)

No further information

References:

International consensus


ASCO recommendation:

T-DM1


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


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**


Further Lines of Therapy of HER2 Overexpressing Metastatic Breast Cancer (17/19)

No further information

References:

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 (18/19)

No further information

References:

Trastuzumab + lapatinib vs lapatinib


Taxanes + lapatinib


Capecitabine + Lapatinib


Vinorelbine + Lapatinib:


Lapatinib + aromatase inhibitors (if ER+)

Brain metastases (radioresistance)

No further information

No references