Chemotherapy With or Without Targeted Drugs* in Metastatic Breast Cancer

* Substances without published evidence based on at least one phase III/II b trial were omitted
International consensus

International consensus


Increase


Multiple lines

International consensus

**Anti-HER2-zielgerichtete Therapie**

1. Swain S M, Miles D, Kim S B. End-of-study analysis from the phase III, randomized, double-blind, placebo (Pla)-controlled CLEOPATRA study of first-line (1L) pertuzumab (P), trastuzumab (H), and docetaxel (D) in patients (pts) with HER2-positive metastatic breast cancer (MBC) J Clin Oncol. 2019 doi: 10.1200/JCO.2019.37.15


**CTC monitoring**


PARP-Inhibitoren


Checkpoint-Inhibitoren

International consensus


Combination vs single agent


Cochrane analysis

Definition of visceral crisis (ABC 4)

- 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.

Metastatic Breast Cancer
Cytotoxic and Targeted Therapy

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

International consensus
## Metastatic Breast Cancer

### Duration of Cytotoxic Therapy

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
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<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
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<td>2b</td>
<td>B</td>
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<tr>
<td>2b</td>
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<td>+/-</td>
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<tr>
<td>2b</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td>1c</td>
<td>A</td>
<td>++</td>
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</table>

- **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

### International consensus


### Change to alternative regimen before progression


### Treatment until progression


International consensus


Change to alternative regimen before progression


Treatment until progression


**Monotherapy:**
- Paclitaxel (q1w), Docetaxel (q3w)
- Doxorubicin, epirubicin, Peg-liposomal doxorubicin (A_{1p})
- Vinorelbine
- Capecitabine
- Nab-paclitaxel

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<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
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<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
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</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
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<tr>
<td>3b</td>
<td>B</td>
<td>+</td>
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<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
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<table>
<thead>
<tr>
<th>Polychemotherapy:</th>
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<tbody>
<tr>
<td>A + T</td>
</tr>
<tr>
<td>Paclitaxel + capecitabine</td>
</tr>
<tr>
<td>Docetaxel + capecitabine after adj. A</td>
</tr>
<tr>
<td>T + gemcitabine after adj. A</td>
</tr>
<tr>
<td>A + C or A_{1p} + C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>LoE</th>
<th>GR</th>
<th>AGO</th>
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<tbody>
<tr>
<td>1b</td>
<td>A</td>
<td>++</td>
<td></td>
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<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
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</tr>
<tr>
<td>1b</td>
<td>A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>B</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

* In ER pos. patients only if endocrine therapy is not indicated or should be discontinued

**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


### MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel q1w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Docetaxel q3w</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Peg-liposomal doxorubicin</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Erubulin</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Docetaxel + Peg-liposomal doxorubicin</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Independent whether anthracyclines were used in adjuvant or 1st line metastatic situation

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**International consensus**


**Cochrane analysis taxane-containing regimens for metastatic breast cancer**


**Nab-paclitaxel**


**Erubilin**

International consensus


Capecitabine


Eribulin


**Taxane re-challenge**


**Anthracycline re-challenge**


**Metronomic chemotherapy**


Gemcitabine + cisplatin / carboplatin


Gemcitabine + capecitabine


Gemcitabine + Vinorelbine


International consensus


Checkpoint-inhibitoren:


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


Gemcitabin/Cisplatin (vs. GemPac)

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

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, et al. San Antonio Breast Cancer Symposium 2014; S3-01.

PARP Inhibitoren bei triple negativ und BRCA 1/2 Mutation


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

1. Brufsky et al., RIBBON-2: A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating the Efficacy and Safety of

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


**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+)

**2nd line Therapy in HER2-positive MBC (Trastuzumab-Pretreated)**

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

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

**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 vs lapatinib


## International consensus


## ASCO recommendation


### T-DM1


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### Further Lines of Therapy in HER2-Positive Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Pretreatment with Trastuzumab</th>
<th>Oxford LoE</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM 1</td>
<td>1b</td>
<td>+</td>
</tr>
<tr>
<td>Capecitabine + lapatinib</td>
<td>1b</td>
<td>+</td>
</tr>
<tr>
<td>Vinorelbine + lapatinib</td>
<td>2b</td>
<td>+/-</td>
</tr>
<tr>
<td>Trastuzumab + lapatinib (HR-neg. disease)</td>
<td>2b</td>
<td>+</td>
</tr>
<tr>
<td>Chemotherapy + trastuzumab (&quot;treatment beyond progression&quot;)</td>
<td>2b</td>
<td>+</td>
</tr>
<tr>
<td>Trastuzumab + pertuzumab</td>
<td>2b</td>
<td>+</td>
</tr>
<tr>
<td>Vinorelbine + trastuzumab + everolimus (trastuzumab resistant, taxane pretreated)</td>
<td>1b</td>
<td>+/-</td>
</tr>
<tr>
<td>Abemaciclib + Trastuzumab + Fulvestrant</td>
<td>2b*</td>
<td>+/</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data for patients pretreated with trastuzumab and pertuzumab or for treatment beyond progression with pertuzumab are not available.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab-Deruxtecan</td>
</tr>
<tr>
<td>Experimental anti-HER2-regimen</td>
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<td>For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above.</td>
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</tbody>
</table>

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**Notes:**
- LoE: Level of Evidence
- AGO: German Association of Breast Surgeons
- GR: Grade of Recommendation

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**Further Lines of Therapy in HER2-Positive Metastatic Breast Cancer**

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<td>1b</td>
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</tr>
<tr>
<td>Capecitabine + lapatinib</td>
<td>1b</td>
<td>+</td>
</tr>
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<td>+</td>
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<td>Vinorelbine + trastuzumab + everolimus (trastuzumab resistant, taxane pretreated)</td>
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</tr>
</tbody>
</table>
study collaborators.

**Capecitabine + Lapatinib**


**Vinorelbine + Lapatinib**


**Trastuzumab + lapatinib vs lapatinib**


**TBP: 2nd-line chemotherapy + trastuzumab**

**Trastuzumab + Pertuzumab**


**Vinorelbine + Trastuzumab + Everolimus**


**Abemaciclib + Trastuzumab + Fulvestrant**

1. SanAN2019 abstract

**Trastuzumab-Deruxtecan**

**Tucatinib + Trastuzumab + Capecitabine**

San An 2019 Abstract

**Trastuzumab + lapatinib vs lapatinib**


**Taxanes+ lapatinib**


Capecitabine + Lapatinib

Vinorelbine + Lapatinib

Lapatinib + aromatase inhibitors (if ER+)

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

<table>
<thead>
<tr>
<th>Category</th>
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<tr>
<td><strong>Immunodiagnostic tests:</strong></td>
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</tr>
<tr>
<td>Tumor tissue: PD-L1 IC status in TNBC</td>
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<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Blood: Immunological parameters</td>
<td>5</td>
<td>D</td>
<td>--</td>
</tr>
<tr>
<td><strong>Systemic immunotherapy:</strong></td>
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</tr>
<tr>
<td>Atezolizumab and nab-paclitaxel in PD-L1 IC positive TNBC first line</td>
<td>1b</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Other immunotherapies in clinical trials, only</td>
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<td></td>
<td></td>
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<tr>
<td>HER2-vaccination in high-risk population</td>
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<tr>
<td>Immunomodulation (e.g., addition of Nov-2 to AC–T)</td>
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<tr>
<td>Dendritic cell intradermal vaccination</td>
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<td>Active vaccination</td>
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<td>Passive vaccination</td>
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<td>Therapy with oncolytic viruses</td>
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<tr>
<td>Cytokines</td>
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<tr>
<td><strong>Local immunotherapy</strong></td>
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<tr>
<td>Imiquimod topically for skin metastasis</td>
<td>4</td>
<td>C</td>
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</table>

**Checkpoint-Inhibitoren**