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
Chemotherapy ± Targeted Drugs in Metastatic Breast Cancer

- **Versions 2002–2020:**
  Albert / Bischoff / Dall / Fehm / Fersis / Friedrichs / Harbeck /
  Jackisch / Janni / Kolberg-Liedtke / Lüftner / Lux / von Minckwitz /
  Möbus / Müller / Rody / Schaller / Scharl / Schmutzler / Schneeweiss /
  Schütz / Stickeler / Thill / Thomssen / Untch

- **Version 2021:**
  Jackisch / Schmidt
Metastatic Breast Cancer (mBC) 
Disease-Free and Overall Survival

- In mBC, an increase in survival over time has been shown in clinical trials 

- Multiple lines of sequential therapy are beneficial 
(at least similar efficacy, less toxicity) 

- Targeted drugs in combination with chemotherapy can induce substantial survival benefits 

International consensus

Increase

Multiple lines
Metastatic Breast Cancer
Endocrine Resistance

**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 (required) 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**
### Endocrine therapy


### Endocrine therapy - ESR1:


### Alpelisib

Chemotherapy


Anti-HER2-Therapy


Checkpoint-Inhibitors


PARP-Inhibitors


Bone modifying drugs


**CTC monitoring (any therapy)**


**Metastatic Breast Cancer Treatment Rationale**

<table>
<thead>
<tr>
<th>Oxford LoE: 1b</th>
<th>GR: A</th>
<th>AGO: ++</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mono-Chemotherapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Favorable therapeutic index*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Indicated in case of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Slow, not life-threatening progression</td>
<td></td>
<td></td>
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<tr>
<td>• Insensitivity to or progression during endocrine therapy</td>
<td></td>
<td></td>
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<tr>
<td><strong>Poly-Chemotherapy:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Unfavorable therapeutic index</td>
<td></td>
<td></td>
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<tr>
<td>• Indicated to achieve rapid remission in the case of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Extensive symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Visceral crisis (ABC-5 definition)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Survival benefit in comparison to sequential single-agent therapies with the same compounds not proven</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Therapeutic index evaluates overall efficacy, toxicity, and impact on quality of life</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**International consensus**


**Combination vs single agent**

Cochrane analysis
International consensus


**Definition of visceral crisis (ABC 5)**

- **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 organ compromise leading to a clinical indication for the most rapidly efficacious therapy.
International consensus
International consensus

Treatment until progression
3. Park YH, Jung KH, Im SA, et al. Phase III, multicenter, randomized trial of maintenance chemotherapy versus observation in patients
Chemotherapy in mBC
General Considerations - Drug Selection

AGO: ++
- Participation in clinical trials is recommended
- The choice of systemic therapy depends on:
  - ER / PR, HER2, PD-L1 status, gBRCA status, PIK3CA, e.g. MSI, NTRK (clinical actionability of molecular targets)
  - Prior therapies (and their toxicities)
  - Disease-free interval after end of adjuvant treatment
  - Progression-free interval achieved by the previous line of therapy
  - Disease aggressiveness and localization of metastases
  - Estimated life expectancy
  - Co-morbidities (including organ dysfunction)
  - Patient preferences and expectations

International consensus

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

Limitations of palliative chemotherapy

**PD-L1-Status**

**PIK3CA**

**MSI/NTRAK**

Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer
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...


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-positive:
Chemotherapy after Anthracycline Treatment*

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

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

**International consensus**

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

**Nab-paclitaxel**

**Erubulin**
International consensus


Capecitabine


Eribulin

4. Pivot X, Im SA, Guo M, Marmé F. Subgroup analysis of patients with HER2-negative metastatic breast cancer in the second-line setting.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LoE</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b</td>
</tr>
<tr>
<td>Eribulin</td>
<td>1b</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2b</td>
</tr>
<tr>
<td>(Peg)-liposomal Doxorubicin</td>
<td>2b</td>
</tr>
<tr>
<td>Taxane re-challenge*</td>
<td>2b</td>
</tr>
<tr>
<td>Anthracycline re-challenge*</td>
<td>3b</td>
</tr>
<tr>
<td>Metronomic therapy (e.g. cyclophos. + MTX)</td>
<td>2b</td>
</tr>
<tr>
<td>Gemcitabine + Cisplatin / Carboplatin</td>
<td>2b</td>
</tr>
</tbody>
</table>

**Taxane re-challenge**

**Anthracycline re challenge**

**Metronomic chemotherapy**

**Gemcitabine + cisplatin / carboplatinum**
1. Li HC, Russell CA Gemcitabine and platinum-based chemotherapy in metastatic breast cancer. Oncology (Williston Park). 2004

**Gemcitabine + capecitabine**

**Gemcitabine + Vinorelbine**
International consensus


Checkpoint-inhibitoren:


2. Cortes J, Cescon DW, Rugo HS et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic
International consensus

Bevacizumab as first-line therapy
**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
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
Metastatic Breast Cancer
Bevacizumab Treatment in HER2-neg. Disease

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
### HER2-positive mBC

**After Trastuzumab or w/o Pretreatment (+ Chemotherapy)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + Trastuzumab + Pertuzumab</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Paclitaxel (weekly) + Trastuzumab + Pertuzumab</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Nab-Paclitaxel + Trastuzumab + Pertuzumab</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Vinorelbine + Trastuzumab + Pertuzumab</td>
<td>3b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>1st line Chemotherapy* + Trastuzumab</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>TBP: 2nd line Capecitabine + Trastuzumab</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Capecitabine + Lapatinib</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Taxane + Lapatinib</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Taxane + Trastuzumab + Everolimus</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>

* Taxane; Vinorelbine; Paclitaxel/Carboplatin; Capecitabine/Docetaxel,

---

**International consensus**


**ASCO recommendation**


**Nab-Paclitaxel + trastuzumab + pertuzumab**


**Vinorelbine + trastuzumab + pertuzumab**


**1st line chemotherapy + trastuzumab**


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

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

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
2. Yardley D, Hurvitz S, Jiang Z-f, et al. Everolimus plus trastuzumab and paclitaxel as first-line therapy in women with HER2+ advanced breast cancer: Overall survival results from BOLERO-1. SABCS 2016, Poster Session 4 - Treatment: Advanced Therapy - Targeted,
Abstract No. P4-22-13

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

**Lapatinib + aromatase inhibitors (if ER+)**
**HER2-positive mBC**

**Further Therapy Options after Trastuzumab**

<table>
<thead>
<tr>
<th>Therapy Options</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
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</thead>
<tbody>
<tr>
<td>T-DM 1 (Recurrence after 6 months and after taxanes and trastuzumab)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Trastuzumab + Lapatinib (HR-negative tumor)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Trastuzumab mono</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Trastuzumab + Aromatase-Inhibitors (ER+)</td>
<td>2b</td>
<td>B</td>
<td>+/-*</td>
</tr>
<tr>
<td>Lapatinib + Aromatase-Inhibitors (ER+)</td>
<td>2b</td>
<td>B</td>
<td>+/-*</td>
</tr>
<tr>
<td>AI + Trastuzumab + Pertuzumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abemaciclib + Trastuzumab + Fulvestrant</td>
<td>2b</td>
<td>B</td>
<td>+/-*</td>
</tr>
<tr>
<td>Trastuzumab + Pertuzumab</td>
<td></td>
<td></td>
<td>+/-</td>
</tr>
</tbody>
</table>

* See Chapter „endocrine +/- targeted Therapy“

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**International consensus**

**ASCO recommendation**

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**Metaanalyse post Trastuzumab**

Trastuzumab mono

Trastuzumab + aromatase inhibitors (if ER+)

Lapatinib + aromatase inhibitors (if ER+)

AI + Trastuzumab + Pertuzumab

Abemaciclib + Trastuzumab + Fulvestrant
1. Tolaney SM, Wardley AM, Zambelli S et al. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a

Trastuzumab + Pertuzumab
# HER2-positive mBC

## Therapy after Trastuzumab/Pertuzumab

<table>
<thead>
<tr>
<th>Oxford</th>
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<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM 1</td>
<td>1b</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>TBP: 2nd line Chemotherapy + Trastuzumab</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>2nd line Chemotherapy* + Trastuzumab + Pertuzumab</td>
<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>* Taxane + Trastuzumab + Pertuzumab</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>* Capecitabine + Trastuzumab + Pertuzumab</td>
<td>1b*</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>* Capecitabine + Lapatinib</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* e.g. Vinorelbine; Taxane/Carboplatin; Capecitabine/Docetaxel (*Toxicity!*)

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**International consensus**


**ASCO recommendation**

Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer


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

**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.
**HER2-positive mBC**

**Therapy after T-DM 1**

<table>
<thead>
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<th>Oxford</th>
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<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tucatinib + Trastuzumab + Capecitabine</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Neratinib + Capecitabine</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Capecitabine + Lapatinib</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Capecitabine + Trastuzumab + Pertuzumab</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Trastuzumab Deruxtecan</td>
<td>2b</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Experimental anti-HER2 regimes</td>
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<td>D</td>
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</table>

**International consensus**

**ASCO recommendation**

Neratinib + Capecitabine

Capecitabine + Lapatinib

Capecitabine + Trastuzumab + Pertuzumab

Trastuzumab-Deruxtecan
382 (7): 610–621.
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>Oxford</th>
<th>LoE</th>
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</tbody>
</table>

#### Immundiagnostik
- Tumor tissue: PD-L1 IC status in TNBC
- Blood: Immunological parameters

#### Systemic Immunotherapies
- Atezolizumab + Nab-Paclitaxel first-line TNBC, PD-L1 IC ≥1
- Atezolizumab + Paclitaxel first line TNBC, PD-L1 IC ≥1
- Pembrolizumab + Chemo* in TNBC & PD-L1 CPS ≥10
- Pembrolizumab-Monotherapy (after chemotherapy without Immun oncology pretreatment) if CPS ≥20

# (see chapter „Pathology“)
* nab-Paclitaxel or Paclitaxel or Carboplatin/Gemcitabine
1 CAVE: no label

---

**Checkpoint-inhibitoren:**


3. Cortes J, Cescon DW, Rugo HS et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-