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 2003–2015:**
Bischoff / Dall / Fersis / Friedrichs / Harbeck / Jackisch / Janni / Möbus / Müller / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thomssen / von Minckwitz

➤ **Version 2016:**
Thill / Rody
Disease-Free and Overall Survival in Metastatic Breast Cancer

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

Oxford / AGO LoE / GR

2a
1b
Endocrine Resistance in Metastatic Breast Cancer

Primary endocrine resistance:
Relapse while on the first 2 years of adjuvant ET,
Or PD within first 6 months of first-line ET for MBC, while on ET

Secondary endocrine resistance:
Relapse while on adjuvant ET but after the first 2 years, or a relapse within 12 months of completing adjuvant ET, or PD $\geq$ 6 months after initiating ET for MBC, while on ET
## 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>Endocrine therapy</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>Chemotherapy</td>
<td>previous response</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Anti-HER2-drugs</td>
<td>HER2 (primary tumor, better metastasis)</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>bone metastasis</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Bone modifying drugs</td>
<td>bone metastasis</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Any therapy</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

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

LoE: 1c    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.
# 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

<table>
<thead>
<tr>
<th>Oxford / AGO LoE GR</th>
<th>1a A ++</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b B +</td>
<td></td>
</tr>
<tr>
<td>2b B +/-</td>
<td></td>
</tr>
<tr>
<td>2b B +/-</td>
<td></td>
</tr>
<tr>
<td>1c A ++</td>
<td></td>
</tr>
</tbody>
</table>
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
MBC HER2-negative/HR-positive Cytotoxic 1\textsuperscript{st}-Line Therapy*  

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

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

*In ER pos. disease only if endocrine therapy is not or not anymore indicated*
Taxane-containing Regimens for Metastatic Breast Cancer


See: Forest plot of comparison: I Overall survival, outcome: I.I Overall effect: Taxane-containing regimes vs. not
MBC HER2-negative/HR-pos: Cytotoxic Therapy after Anthracycline Treatment*

- Paclitaxel q1w  
- Docetaxel q3w  
- Capecitabine  
- Nab-paclitaxel  
- Peg-liposomal doxorubicin  
- Eribulin  
- Vinorelbine  
- Docetaxel + Peg-liposomal Doxo

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

*Independent whether anthracyclines were used in adjuvant or 1st line metastatic situation
MBC HER2-negative/HR-positive: Cytotoxic Therapy after adjuvant Taxane and Anthracycline Treatment

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

- Bevacizumab added to first line cytotoxic therapy

Oxford / AGO LoE / GR

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

1st line in combination with:
- Paclitaxel (q1w)
- Capecitabine
- Anthracyclines
- Nab-Pac
- Docetaxel (q3w)

Cap+Bev as maintenance after Doc+Bev

2nd line as treatment through multiple lines

2nd line in combination with:
- Taxanes
- Capecitabine
- Gemcitabine or vinorelbine

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford</th>
<th>AGO</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (q1w)</td>
<td>1b</td>
<td>B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1b</td>
<td>B</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Nab-Pac</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Docetaxel (q3w)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Cap+Bev as maintenance after Doc+Bev</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>2nd line as treatment through multiple lines</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine or vinorelbine</td>
<td>1b</td>
<td>B</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
### First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LoE</th>
<th>AGO LoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + trastuzumab + pertuzumab</td>
<td>1b A ++</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (wk) + trastuzumab + pertuzumab</td>
<td>2b B +</td>
<td></td>
</tr>
<tr>
<td>Vinorelbine + Trastuzumab + Pertuzumab</td>
<td>3b&lt;sup&gt;a&lt;/sup&gt; B +/-</td>
<td></td>
</tr>
<tr>
<td>T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)</td>
<td>2b B +</td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line chemotherapy* + trastuzumab</td>
<td>1b B +</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab mono</td>
<td>2b B +/-</td>
<td></td>
</tr>
<tr>
<td>Taxanes + lapatinib</td>
<td>1b B +/-</td>
<td></td>
</tr>
<tr>
<td>Taxanes + trastuzumab + everolimus</td>
<td>1b B -</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab + aromatase inhibitors (if ER+)</td>
<td>2b B +/-**</td>
<td></td>
</tr>
<tr>
<td>Lapatinib + aromatase inhibitors (if ER+)</td>
<td>2b B +/-**</td>
<td></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)

- T-DM 1
- TBP: 2nd line chemotherapy + trastuzumab
- Capecitabine + lapatinib
- Trastuzumab + lapatinib (HR neg. disease)
- Taxane + trastuzumab + pertuzumab
- Any other 2nd line chemotherapy* + trastuzumab + pertuzumab
- Trastuzumab + aromatase inhibitors (if ER+)
- Lapatinib + aromatase inhibitors (if ER+)

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

Oxford / AGO
LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>Grade</th>
<th>Notes</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>D+</td>
<td></td>
</tr>
<tr>
<td>Capecitabine + lapatinib</td>
<td>1b</td>
<td>B+</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab + lapatinib (HR neg. disease)</td>
<td>2b</td>
<td>B+</td>
<td></td>
</tr>
<tr>
<td>Taxane + trastuzumab + pertuzumab</td>
<td>5</td>
<td>D+/-</td>
<td></td>
</tr>
<tr>
<td>Any other 2nd line chemotherapy* + trastuzumab</td>
<td>5</td>
<td>D+/-</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab + aromatase inhibitors (if ER+)</td>
<td>3b</td>
<td>B+</td>
<td></td>
</tr>
<tr>
<td>Lapatinib + aromatase inhibitors (if ER+)</td>
<td>3b</td>
<td>B+</td>
<td></td>
</tr>
</tbody>
</table>
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)

There is no data for patients pretreated with trastuzumab and pertuzumab

- Experimental anti-HER2-regimen

For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above. There is no data for treatment beyond progression for pertuzumab.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM 1</td>
<td>1b A ++</td>
</tr>
<tr>
<td>Capecitabine + lapatinib</td>
<td>1b B +</td>
</tr>
<tr>
<td>Vinorelbine + lapatinib</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Trastuzumab + lapatinib (HR neg. disease)</td>
<td>2b B +</td>
</tr>
<tr>
<td>Chemotherapy + trastuzumab + (“treatment beyond progression“)</td>
<td>2b B +</td>
</tr>
<tr>
<td>Trastuzumab + pertuzumab</td>
<td>2b B +</td>
</tr>
<tr>
<td>Vinorelbine + trastuzumab + everolimus (trastuzumab resistant, taxane pretreated)</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Experimental anti-HER2-regimen</td>
<td>5 D +</td>
</tr>
</tbody>
</table>
### Lapatinib in HER2-positive Metastatic Breast Cancer

**In combination with**

- Trastuzumab for heavily pre-treated pts  
  - Oxford / AGO LoE / GR: 2b B +
- Paclitaxel in 1\textsuperscript{st} line  
  - Oxford / AGO LoE / GR: 2b B -
- Capecitabine in > 2\textsuperscript{nd} line  
  - Oxford / AGO LoE / GR: 1b B +
- Vinorelbine  
  - Oxford / AGO LoE / GR: 2b B +/-
- AI in ER positive disease  
  - Oxford / AGO LoE / GR: 2b B +/-
- In patients with brain metastases (radioresistance) in combination with capecitabine  
  - Oxford / AGO LoE / GR: 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

5 D --

4 C +/-

*Study participation recommended
Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer (2/20)

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 Metastastic Breast Cancer (3/20)

No further information

References:


Multiple lines

Endocrine resistance in metastatic breast cancer (4/20)

No further information

References:

International consensus
Treatment of Metastatic Breast Cancer - Predictive Factors (5/20)

No further information

References:

CTC monitoring


**Cytotoxic Therapy Goals (6/20)**

*No further information*

**References:**

2. (Sledge et al, 2003).

**Combination vs single agent**


**Metaanalysis**

Docetaxel alone or in combination
Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.

Cochrane analysis


Single trials:

Combination not superior compared to single agent regimen.


Tailored therapy in MBC

Toxicity-adjusted treatment with ET and TEX showed similar efficacy in terms of PFS, OS, and OR. In this trial with limited power, the addition of capecitabine to epirubicin and paclitaxel as first-line treatment did not translate into clinically relevant improvement of the outcome.

Cytotoxic and Targeted Therapy (7/20)

No further information

References:

Cytotoxic Therapy Duration (8/20)

Further information:

Consent:
Treatment until progression  6++, 18+, 2+/-,1-
Treatment until best response 1++, 3+, 23+/-,1-
Change to alternative regimen before progression 1++, 0+, 25+/-, 5-

References:

Change to alternative regimen before progression:


Treatment until progression


Chemotherapy for MBC – General Considerations: Drug Selection (9/20)

No further information

References:

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


Limitations of palliative chemotherapy


Metaanalyses

HRQOL is one of the key indicators of treatment benefit in advanced breast cancer, but contemporary systemic therapies in this setting do not appear to affect HRQOL differentially.
MBC HER2 negative Cytotoxic 1st-Line Therapy (10/20)

No further information

References:


Liposomal doxorubicin is equally effective to doxorubicin but has less cardio and myelotoxicity but more skin toxicity (O’Brien et al, 2004).
Polychemotherapy with anthracyclines and taxanes induce high remission rates but are more toxic then anthracycline or taxane free combinations.
After anthracycline treatment two studies could show a survival benefit with gemcitabine paclitaxel or with Docetaxel/Capecitabine (O’Shaughnessy et al, 2002 and Albain, 2004).
Retrospective date show that patients who respond to first line therapy with a complete response have a survival benefit compared to patients without CR (Greenberg et al, 1996).
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. Cassier et al., Breast Cancer Research and Treatment (electronic publication 2007).
Individual trials

NabPaclitaxel vs Ixabepilone vs paclitaxel +/- bevacizumab


Nab-Paclitaxel


Ixabepilone + capecitabine vs capecitabine alone


Metaanalyses

Docetaxel alone or in combination

Metaanalysis; MBC
Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC.


Cochrane analysis taxane-containing regimens for metastatic breast cancer

Taxane-containing Regimens for Metastatic Breast Cancer (11/20)

No further information

No references
MBC HER2 negative: Cytotoxic Therapy after Anthracycline Treatment* (12/20)

Further information and references:

Consent: Eribulin: 5++, 21+, 4+/-


Suggested after anthracyclines (in alphabetical order): Capecitabine, Docetaxel, study-integrated experimental therapies, Gemcitabine, Pegliposomales Doxorubicin, Paclitaxel and Vinorelbine.

As monotherapy after anthracyclin-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 Pegliposomal Doxorubicin was superior to docetaxel alone in a randomised phase III trial by Sparano et al. It is one of the largest trials in this setting with 751 pts and demonstrated a clear PFS advantag from 9.8 vs 7 months without improving the OS. QoL was not different. Hand foot syndrome and mucositis were more common with the combination.
Nab-paclitaxel


Metaanalysis

1. Cochrane analysis taxane-containing regimens for metastatic breast cancer
MBC HER2 negative: Cytotoxic Therapy After Taxane and Anthracycline Treatment (13/20)

Further information:

Consent:

Capecitabine/Vinorelbine:  ++: 16; +: 2; +/-: 0; -: 0; --: 0
Taxane/anthracycline re-challenge:  ++: 1; +: 20; +/-: 6; -: 0; --: 0
Metronomic therapy:  ++: 0; +: 13; +/-: 9; -: 0; --: 0

References:

Ixabepilone:

**Gemcitabine/vinorelbine**


**Systematic review**


**Eribulin**

**Meta-analysis and evaluation**

Phase III trials


Taxane re-challenge


Anthracycline re challenge


Metronomic chemotherapy


Gemcitabine + cisplatin / carboplatinum


Review

Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-) (14/20)

Further information and references:

Consent:

Carboplatin (vs. Docetaxel): 2++, 11+, 19+/-
Carboplatin in gBRCA mutation: 1++, 26+
Gemcitabin/Cisplatin (vs. GemPac): 1++, 18+, 10+/-

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


Gemcitabin/Cisplatin (vs. GemPac)

Triple negative patients

**Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (15/20)**

*Further information and references:*

**Consent 2014:**
Cap+Bev as maintenance after Doc+Bev: 1++, 3+, 22+-, 4-
2nd line as treatment through multiple lines: 19+-, 4-

**Cap+Bev as maintenance after Doc+Bev:**


**2nd line as treatment through multiple lines:**


Individual trials

Taxanes +/- Bevacizumab
NabPaclitaxel vs Ixabepilone vs paclitaxel

Review and opinion


Side effects

Metaanalysis:

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (16/20)

Further information:

Consent:

Paclitaxel + trastuzumab + pertuzumab: ++: 12; +: 13; +/-: 0; -: 0; --: 0
Vinorelbine + trastuzumab – pertuzumab: ++: 0; +: 5; +/-: 17; -: 0; --: 0
Taxanes + lapatinib: ++: 1; +: 3; +/-: 9; -: 4; --: 0
Taxanes + trastuzumab + everolimus: ++: 0; +: 2; +/-: 9; -: 14; --: 0

References:


Docetaxel + trastuzumab + pertuzumab

Pertuzumab side effects


Paclitaxel weekly + trastuzumab + pertuzumab


Vinorelbine + trastuzumab + pertuzumab

1. Michael Andersson, José Manuel López-Vega, Thierry Petit, Claudio Zamagni, Margarita Donica, Julia Kamber, Edith A. Perez. The co-administration of pertuzumab (P) and trastuzumab (T) as a single infusion, followed by vinorelbine (V), in first-line (1L) treatment of HER2-positive locally advanced or metastatic breast cancer (MBC) patients (pts): VELVET study interim analysis. J Clin Oncol 33, 2015 (suppl; abstr 586)

1st line chemotherapy + trastuzumab

2. Valero V., Forbes J., Pegramet M. D. et al.: Multicenter Phase III Randomized Trial Comparing Docetaxel and Trastuzumab With Docetaxel, Carboplatin, and Trastuzumab As First-Line Chemotherapy for Patients With HER2-
Gene-Amplified Metastatic Breast Cancer (BCIRG 007 Study): Two Highly Active Therapeutic Regimens. DOI: 10.1200/JCO.2010.28.6450


6. Dang C et al., Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer, J Clin Oncol. 2015 Feb 10;33(5):442-7

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 Jul;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) (17/20)

Further information:

Consent:

Paclitaxel + trastuzumab + pertuzumab: ++: 12; +: 13; +/-: 0; -: 0; --: 0

References:

T-DM1


Capecitabine + lapatinib


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


**Trastuzumab + lapatinib (if CT not possible)**

**Trastuzumab + lapatinib vs lapatinib**


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


**Taxane + trastuzumab + pertuzumab**

Any other 2nd-Line chemotherapy* + trastuzumab + pertuzumab

**Trastuzumab mono**

2nd line:


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


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

Letrozole Versus Letrozole and Placebo As First-Line Therapy for Postmenopausal Hormone Receptor–Positive Metastatic Breast Cancer. DOI: 10.1200/JCO.2009.23.3734
Further Lines of Therapy of HER2 Overexpressing Metastatic Breast Cancer (18/20)

Further information:

Consent:

Vinorelbine + lapatinib: ++: 0; +: 4; +/-: 21, -: 1; --: 0

References:

TBP: 2nd-line chemotherapy + trastuzumab + pertuzumab („treatment beyond progression“; with taxanes, vinorelbine, paclitaxel/carboplatin, or capecitabine/docetaxel)


Review
“Emerging evidence from randomized controlled trials supports the potential clinical utility of continuing trastuzumab-based therapy beyond progression and supports the National Comprehensive Cancer Network recommendation to consider this treatment approach. Future treatment of HER2-positive MBC may involve trastuzumab being used in successive regimens in combination with other targeted therapies.”


Capecitabine + lapatinib


Vinorelbine + lapatinib

Trastuzumab + lapatinib (if CT not possible)


Experimental anti-HER2-regimen (including trastuzumab-Emtansine, T-DM1)

1. Blackwell K. et al. (2012) Primary Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated With Trastuzumab and a Taxane. ASCO 2012
Lapatinib in HER2-positive Metastatic Breast Cancer (19/20)

No further information

References:

Anthraclycline and Taxane and Trastuzumab pre-treatment


Trastuzumab naive patients: first line therapy


Brain metastases (radioresistance)

Immunodiagnostic Tests and Immunotherapy (20/20)

No further information

No references