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 2003–2014:**
  Bischoff / Dall / Fersis / Friedrichs / Harbeck / Jackisch / Janni / Möbus / Rody / Scharl / Schmutzler / Schneeweiss / Schütz / Stickeler / Thomssen

- **Version 2015:**
  von Minckwitz / Müller
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

ENG 2a
ENG 2a
ENG 1b
ENG 1b
## 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>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

- 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment until progression</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Treatment until best response</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Change to alternative regimen before progression</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Stop therapy in case of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non tolerable toxicity</td>
<td>1c</td>
<td>A</td>
</tr>
</tbody>
</table>

Oxford / AGO LoE GR

1a A ++

2b B +

2b B +/-

2b B +/-

1c A ++
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 1st-Line Therapy*

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

### Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel, Docetaxel</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Doxorubicin, epirubicin, mitoxantrone</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Peg. liposomal doxorubicin</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>3b</td>
<td>B</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>

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

### Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A + T</td>
<td>1b</td>
<td>A</td>
</tr>
<tr>
<td>T + gemcitabine after adj. A</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>A + C or $A_{\text{lip}}$ + C</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Paclitaxel + capecitabine</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Docetaxel + capecitabine after adj. A</td>
<td>1b</td>
<td>A</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford LoE</th>
<th>AGO LoE</th>
<th>GR</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>Eribulin</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 Doxo</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

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

- Experimental therapies within studies  
- Capecitabine  
- Eribulin  
- Vinorelbine  
- (Peg)-liposomal Doxorubicin  
- Gemcitabine + Cisplatin / Carboplatin  
- Gemcitabine + Capecitabine  
- Gemcitabine + Vinorelbine*

* Cave neutropenia / therapeutic index!

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford</th>
<th>AGO LoE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental therapies within studies</td>
<td>++</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>++</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Eribulin</td>
<td>++</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>++</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>(Peg)-liposomal Doxorubicin</td>
<td>+</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Gemcitabine + Cisplatin / Carboplatin</td>
<td>+/-</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Gemcitabine + Capecitabine</td>
<td>+/-</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Gemcitabine + Vinorelbine*</td>
<td>-</td>
<td>1b</td>
<td>B</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

- Experimental therapies within studies: ++
- Cytotoxic therapy as for patients with HR pos / HER2 neg. mBC: +
- Carboplatin (vs. Docetaxel): 1b\(^a\) B +/-
- in gBRCA mutation: 1b\(^a\) B +
- Gemcitabine/Cisplatin (vs. GemPac): 1b\(^a\) A +
- Bevacizumab added to first line cytotoxic therapy: 2b 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
First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + trastuzumab + pertuzumab</td>
<td>1b A ++</td>
</tr>
<tr>
<td>(nab)Paclitaxel + trastuzumab + pertuzumab</td>
<td>2b B +</td>
</tr>
<tr>
<td>T-DM 1 (relapse within 6 months after taxane and trastuzumab-pretreatment)</td>
<td>2b B +</td>
</tr>
<tr>
<td>1\textsuperscript{st} line chemotherapy* + trastuzumab</td>
<td>1b B +</td>
</tr>
<tr>
<td>Trastuzumab mono</td>
<td>2b B +/-</td>
</tr>
<tr>
<td>Taxanes + lapatinib</td>
<td>1b\textsuperscript{a} B -</td>
</tr>
<tr>
<td>Taxanes + trastuzumab + everolimus</td>
<td>1b\textsuperscript{a} B -</td>
</tr>
<tr>
<td>Trastuzumab + aromatase inhibitors (if ER+)</td>
<td>2b B +/-**</td>
</tr>
<tr>
<td>Lapatinib + aromatase inhibitors (if ER+)</td>
<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>Treatment Options</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ T-DM 1</td>
<td>1b A ++</td>
</tr>
<tr>
<td>➢ TBP: 2nd line chemotherapy + trastuzumab</td>
<td>2b D +</td>
</tr>
<tr>
<td>➢ Capecitabine + lapatinib</td>
<td>1b B +</td>
</tr>
<tr>
<td>➢ Trastuzumab + lapatinib (HR neg. disease)</td>
<td>2b B +</td>
</tr>
<tr>
<td>➢ Taxane + trastuzumab + pertuzumab</td>
<td>5 D +</td>
</tr>
<tr>
<td>➢ Any other 2nd line chemotherapy* + trastuzumab + pertuzumab</td>
<td>5 D +/-</td>
</tr>
<tr>
<td>➢ Trastuzumab + aromatase inhibitors (if ER+)</td>
<td>3b B +</td>
</tr>
<tr>
<td>➢ Lapatinib + aromatase inhibitors (if ER+)</td>
<td>3b 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
- Trastuzumab + lapatinib (HR neg. disease)
- Chemotherapy + trastuzumab + (“treatment beyond progression“)
  - Trastuzumab + pertuzumab
  - Vinorelbine + trastuzumab + everolimus

<table>
<thead>
<tr>
<th>Pretreatment</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>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</td>
<td>1b B +/-</td>
</tr>
</tbody>
</table>

There is no data for patients pretreated with trastuzumab and pertuzumab

- Experimental anti-HER2-regimen

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental anti-HER2-regimen</td>
<td>5 D +</td>
</tr>
</tbody>
</table>

For patients pretreated with trastuzumab and pertuzumab treatment according to the recommendations above. There is no data for treatment beyond progression for pertuzumab.
Lapatinib in HER2-positive Metastatic Breast Cancer

In combination with

- Trastuzumab for heavily pre-treated pts
- Paclitaxel in 1\textsuperscript{st} line
- Capecitabine in > 2\textsuperscript{nd} line
- AI in ER positive disease

- In patients with brain metastases (radioresistance) in combination with capecitabine

Oxford / AGO LoE / GR

<table>
<thead>
<tr>
<th>Drug</th>
<th>LoE</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td>AI</td>
<td>2b</td>
<td>B</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>2b</td>
<td>B</td>
</tr>
</tbody>
</table>
# 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;…)

<table>
<thead>
<tr>
<th>Oxford / AGO LoE / GR</th>
<th>5 D --</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 C +/-</td>
<td>++</td>
</tr>
</tbody>
</table>
Chemotherapy With or Without Targeted Drugs in Metastatic Breast Cancer (2/18)

Further information and 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 (3/18)

No further information

References:

Increase


More adjuvant..

Multiple lines

References:

CTC monitoring


(Hilner et al. 2003 JCO)
Cytotoxic Therapy Goals (5/18)

Further information and references:

(Sledge et al, 2003).
(S Carrick et al, The Cochrane Database of Systematic Reviews 2005)

2013

Combination vs single agent


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.

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 (6/18)

No further information

References:

Cytotoxic Therapy Duration (7/18)

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
3. Park et al. JCO 2013
Chemotherapy for MBC – General Considerations: Drug Selection (8/18)

Further information:

The selection of the drugs and drug combinations should take into account patients expectations, general health conditions, aggressiveness of the disease, localisation of metastases and previous therapies.

References:

2013
Quaylty of life: Paclitaxel/gemcitabie 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 (9/18)

Further information and 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’Shaugnessy 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).

2013
Individual trials

1. Taxanes +/- Bevacizumab
2. NabPaclitaxel vs Ixabepilone vs paclitaxel

weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-paclitaxel (NP) or ixabepilone (Ix) with or without bevacizumab (B) as first-line therapy for locally recurrent or metastatic breast cancer (MBC). J Clin Oncol 30, 2012 (suppl; abstr CRA1002)

Nab-Paclitaxel
1st line MBC, rand Phase II (n=302)
Treatment with nab-paclitaxel 150 mg/m(2) qw 3/4 resulted in a median overall survival (OS) of 33.8 months compared with 22.2, 27.7, and 26.6 months for nab-paclitaxel 100 mg/m(2) qw 3/4, nab-paclitaxel 300 mg/m(2) q3w, and docetaxel, respectively (overall P = .047).
A trend toward a longer OS was noted in the 150 mg/m(2)nab-paclitaxel arm versus docetaxel arm (hazard ratio, 0.688). Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in all nab-paclitaxel arms compared with docetaxel.


Ixabepilone + capecitabine vs capecitabine alone in 1st line MBC


Results: In 293 patients, ixabepilone plus capecitabine, as compared to capecitabine alone, increased PFS (median: 5.6 months vs. 2.8 months; hazard ratio, 0.58; p < 0.0001), ORR (46% vs. 24%) and OS (median: 15.1 months vs. 12.5 months; hazard ratio, 0.84; p = 0.208). Major toxicities of this regimen included neuropathy, neutropenia and hand-foot syndrome, but were manageable.
Metaanlyses
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.

MBC HER2 negative: Cytotoxic Therapy after Anthracycline Treatment* (10/18)

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 breast cancer (Ghersi et al, 2003) 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, 2003; 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 advantage 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
**MBC HER2 negative: Cytotoxic Therapy After Taxane and Anthracycline Treatment (11/18)**

*Further information and references:*


Nab Paclitaxel (100-150mg/m² d1,8,15,q28) has been tested in different populations. Not all pts received an anthracycline and a taxane. It seems that a weekly dosing is superior to a 3 weekly dosing in terms of efficacy and side effects.

Suggested after anthracycline and taxane treatment (alphabetical order): capecitabine, study-integrated experimental therapies, pegliposomal doxorubicin and vinorelbin.

Studies with more than 100 patients showed overall remissions of 9% and 20% using vinorelbine and pegylated liposomal doxorubicin vs. capecitabine, respectively and a median survival of 9 months and 13 months.

Ixabepilone/Capecitabine vs. Capecitabine after anthracycline and taxane treatment in metastatic breast cancer is a phase III randomised trial showing a significant improvement in PFS for the combination with a higher toxicity especially in neurotoxicity. Ixabepilone is not licensed in Germany; Thomas et al., JCO 25:5210-7 (2007)

Gemcitabine/vinorelbin vs. vinorelbin after anthracycline/taxane treatment in metastatic breast cancer; Martin et al., Lancet Oncol 8:219-25 (2007)

-38 pts treated with Gemcitabine/Cisplatin after anthracycline and taxane pretreatment as (neo)adjuvant, or 1st line met therapy demonstrated a TTP of 5.2 months CI 3.6-6.8 and an OS of 19.5months CI 11.2-27.8 months. Kim JH; Cancer Res Treat 2008; 40: 101-105

2013

Meta-analysis and evaluation

Eribulin mesylate (E7389): review of efficacy and tolerability in breast, pancreatic, head and neck, and non-small cell lung cancer. Scarpace SL.

New microtubule-targeting agents.
Review
Triple Negative Metastatic Breast Cancer (TNBC: ER-, PR-, HER2-) (12/18)

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)

1. Gemcitabine with cisplatin or paclitaxel in metastatic triple-negative breast cancer. Xichun Hu, Binghe Xu, Li Cai, Zhonghua Wang, Biyun Wang, Jian Zhang, Yuee Teng, Zhongsheng Tong, Yueyin Pan, Yongmei Yin, Changping Wu, Zefei Jiang, Xiaojia Wang, Guyin Lou, Donggeng Liu, Jifeng Feng, Jianfeng Luo, Jiong
2. Wu, Zhimin Shao and Joseph Ragaz San Antonio Breast Cancer Symposium 2014; P3-10-02
Triple negative patients

J Clin Oncol 26: 2008 (May 20 suppl; abstr 1051)
Author(s):
B. Sirohi, M. Arnedos, S. Popat, S. Ashley, A. Nerurkar, G. Walsh, S. Johnston, I. E. Smith
Citation:
Author(s):
J. W. Chia, P. Ang, H. See, Z. Wong, L. Soh, Y. Yap, N. Wong

2013
Met-TNBC Phase II (n=40; RR 35%, med OS 12 m, med TTP 6 m; 27% neutropenia °3/4)

Bevacizumab Treatment in HER2-neg. Metastatic Breast Cancer (13/18)

Further information and references:

Consent:
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:


2013

Individual trials

1. Taxanes +/- Bevacizumab
2. NabPaclitaxel vs Ixabepilone vs Paclitaxel

Review and opinion


Side effects
Metaanalysis:

First Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (14/18)

Further information and references:

Consent:
Taxanes + trastuzumab + everolimus: 4+/-, 21-, 5—


2013

Docetaxel + trastuzumab + pertuzumab (LoE 1bA AGO++)
Baselga et al., December 7, NEJM 2011

Side effects Pertuzumab
Skin rash
Pertuzumab is associated with a significant risk of rash, and the incidence varies among different tumor types. Prevention, early recognition, and appropriate treatment of this rash may lead to improvement in patient quality of life, adherence to therapy, and possibly optimize clinical outcomes.

Paclitaxel + trastuzumab + pertuzumab (LoE 5D AGO+/−)
1st-Line chemotherapy* + trastuzumab (LoE 1bB AGO+)
(*taxanes; vinorelbine; paclitaxel/carboplatin; capecitabine/docetaxel)


Trastuzumab mono (LoE 2bB AGO+/−)

Taxanes + lapatinib (LoE 1b A AGO +/-)


Trastuzumab + aromatase inhibitors (if ER+) (LoE 2b B AGO +/-)


Lapatinib + aromatase inhibitors (if ER+) (LoE 2bB AGO +/-)

Second Line Therapy of HER2 Overexpressing Metastatic Breast Cancer (If Pretreatment with Trastuzumab) (15/18)

Further information and references:

T-DM1

2. Baselga et al., December 7, NEJM 2011

2013
Capecitabine + lapatinib (LoE 1b B AGO+)


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) (LoE 3b B AGO+)
Trastuzumab plus lapatinib vs lapatinib
Met-HER2posBC phase iii (2nd and further lines; n=291, HR-PFS =0.74, p=0.011; HR OS =0.74, p=0.026)


TBP: 2nd-Line chemotherapy + trastuzumab (Treatment beyond progression) (LoE 2b D AGO +)


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.”

Taxane + trastuzumab + pertuzumab (LoE 5 D AGO +)
Any other 2nd-Line chemotherapy* + trastuzumab + pertuzumab (LoE 5 D AGO +/-)
Trastuzumab mono (DATEN?) (LoE 2b B AGO +/-)

2nd line:


1st line:


Trastuzumab + aromatase inhibitors (if ER+)(LoE 3b B AGO +)


Lapatinib + aromatase inhibitors (if ER+)(LoE 3b B AGO +)

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 (16/18)

Further information and references:

2013

TBP: 2nd-line chemotherapy + trastuzumab + pertuzumab ("treatment beyond progression"; with taxanes, vinorelbine, paclitaxel/carboplatin, or capecitabine/docetaxel) (LoE 5 D AGO +/-)


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 (LoE 2b B AGO +)


Trastuzumab + lapatinib (if CT not possible) (LoE 3bb AGO +)


Experimental anti-HER2-regimen (including trastuzumab-Emtansine, T-DM1) (LoE 5D AGO +)

EMILIA

1. Blackwell K. et al. (2012) Primary Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in

2. HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated With Trastuzumab and a Taxane. ASCO 2012


4. Baselga et al., Dec
Lapatinib in HER2-positive Metastatic Breast Cancer (17/18)

Further information and references:

Anthracycline and Taxane and Trastuzumab pre-treatment


Trastuzumab naive patients: first line therapy


Brain metastases (radioresistance)

No further information

No references