Endocrine and “Targeted” Therapy in Metastatic Breast Cancer
Endocrine Therapy of Metastatic Breast Cancer

- **Version 2002:** Gerber / Friedrichs

- **Versions 2003–2015:** Albert / Bischoff / Dall / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Liedtke / Loibl / Lück / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Schneeweiß / Schütz / Stickeler

- **Version 2016:** Hanf / Mundhenke
## Indication

**Endocrine Therapy in Metastatic Breast Cancer**

Endocrine therapy represents the first choice for metastatic breast cancer with positive (or unknown) hormone receptor (HR) status.

- **Exception:** acute life-threatening disease
- **Caveat:** HR might change during the course of disease. Histology of recurrent site should be obtained whenever possible.
Comparison ER/PR and HER2 Metastasis vs. Primary Tumor

Meta-analysis based on 48 (mostly retrospective) analyses:

Pooled discordance proportions were
- 20% (95%CI 16-35%) for ER
- 33% (95%CI 29-38%) for PR
- 8% (95% CI 6-10%) for HER2

Pooled proportions of tumors shifting from positive to negative and negative to positive were
- 4% and 14% for ER
- 46% and 15% for PR
- 13% and 5% for HER2
Endocrine Therapy
General considerations

Within all lines of treatment, treatment options should take previous endocrine therapies, age and comorbidities into consideration as well as respective approval status.
# Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRHa + tamoxifen (vs. OFS or Tam)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Ovarian function suppression (OFS)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>GnRHa + AI (first or second line)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>GnRHa + Fulvestrant</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>GnRHa + Fulvestrant + Palbociclib</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Aromatase inhibitors without OFS</td>
<td>3</td>
<td>D</td>
<td>--</td>
</tr>
</tbody>
</table>
Endocrine Therapy in Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

*There is no evidence for superiority of a single aromatase inhibitor. As everolimus plus exemestane is indicated after AI treatment, a non-steroidal AI should be preferred in first line. MA$: Megestrole-acetate, ** steroidal or non-steroidal resp. depending on previous AI

- Fulvestrant 500 mg
- Aromatase inhibitors (3rd gen) **
- Tamoxifen
- Letrozole + Palbociclib
- Fulvestrant 500 mg plus Palbociclib
- Exemestane + Everolimus
- Tamoxifen + Everolimus
- MPA/MA $§$
- Fulvestrant 250 mg + Anastrozol
- Estradiol valerate 2-6 mg daily
- Repeat prior treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
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<tbody>
<tr>
<td>Fulvestrant 500 mg</td>
<td>1b B ++</td>
<td>1a A ++</td>
</tr>
<tr>
<td>Aromatase inhibitors (3rd gen) **</td>
<td>1a A ++</td>
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<td>1a A ++</td>
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</tr>
<tr>
<td>Fulvestrant 500 mg plus Palbociclib</td>
<td>1b B ++</td>
<td>1b B +</td>
</tr>
<tr>
<td>Exemestane + Everolimus</td>
<td>1b A +</td>
<td>1b A +</td>
</tr>
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<td>Tamoxifen + Everolimus</td>
<td>2b B +</td>
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<tr>
<td>MPA/MA $§$</td>
<td>1a A +/-</td>
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</tr>
<tr>
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<td>1b B +/-</td>
<td>1b B +/-</td>
</tr>
<tr>
<td>Estradiol valerate 2-6 mg daily</td>
<td>2b C +/-</td>
<td>2b C +/-</td>
</tr>
<tr>
<td>Repeat prior treatments</td>
<td>5 D +/-</td>
<td>5 D +/-</td>
</tr>
</tbody>
</table>
Therapy Algorithm After Adjuvant Tamoxifen

Fulvestrant 500 mg or Non-steroidal AI 3rd generation or Tamoxifen*

Exemestane + everolimus

Fulvestrant 500 mg +/- Palbociclib

Tamoxifen

Fulvestrant 500 mg +/− Palbociclib

Exemestane + everolimus

Tamoxifen

*(after long recurrence-free interval)
Therapy Algorithm After Adjuvant AI

Short treatment free interval ≤12 months

- Exemestane + everolimus

Fulvestrant 500 mg +/- Palbociclib

Tamoxifen

Long treatment free interval >12 months

- Fulvestrant 500 mg

- Tamoxifen

- Exemestane + everolimus

Tamoxifen

Fulvestrant 500 mg + Palbociclib
Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer Patients in Combination with Bevacizumab

- Maintenance bevacizumab plus endocrine therapy after remission with chemotherapy and bevacizumab
  
- Bevacizumab plus endocrine treatment as first line therapy for advanced disease

Oxford / AGO
LoE / GR

2b B +

1b B -
HER2 Positive and HR-Positive Metastatic Breast Cancer
Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients

- Anastrozole plus trastuzumab 1b B +/-
- Letrozole plus trastuzumab 2b B +/-
- Letrozole plus lapatinib 1b B +/-
- Fulvestrant plus lapatinib 1b B +/-

Poor efficacy of endocrine therapy alone.

Consider induction chemotherapy + anti-HER2-therapy!
### Combination of Endocrine Treatment with Anti-HER2-Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS (months)</th>
<th>Response rate (CBR)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + anastrozole vs. anastrozole (n=207)</td>
<td>4.8 vs. 2.4 (5.6 vs. 3.8 with centrally confirmed receptor status)</td>
<td>42.7% vs. 27.9%</td>
<td>28.5 vs. 23.9 mo; n.s.</td>
</tr>
<tr>
<td>Trastuzumab + letrozole vs. letrozole (n=57)</td>
<td>14.1 vs. 3.3</td>
<td>27% vs. 13%</td>
<td>not reported</td>
</tr>
<tr>
<td>Lapatinib + letrozole vs. letrozole (n=219/1286)</td>
<td>8.2 vs. 3.0</td>
<td>48% vs 29%</td>
<td>33.3 vs. 32.3 mo</td>
</tr>
<tr>
<td>Lapatinib + fulvestrant vs. fulvestrant (n=146/145)</td>
<td>4.1 vs. 3.8 (HER2-) p: 0,25  5.9 vs. 3.3 (HER2+) p: 0,53</td>
<td>(CR +PR) 20 vs. 9% p: 0,048</td>
<td>30 vs. 26.4 mo (all), n.s.</td>
</tr>
</tbody>
</table>
Concomitant or Sequential Endocrine-Cytostatic Treatment

- **Concomitant endocrine-cytotoxic treatment**
  - May increase response rate and progression free interval but **not** overall survival
    - May increase toxicity
  - **Maintenance endocrine therapy after chemotherapy induced response**
    - Increases progression free interval

**Oxford / AGO LoE / GR**

1b A -

2b B ++
Endocrine and “Targeted” Therapy in Metastatic Breast Cancer (2/14)

No further information

No references
Endocrine and “Targeted” Therapy in Metastatic Breast Cancer (3/14)

No further information

References:

**Comparison ER/PR and HER2 Metastasis vs. Primary Tumor (4/14)**

No further information

References:

Endocrine Therapy General Considerations (5/14)

No further information

References:

"Aromatase inhibitors (3rd gen) (> non-AI*)"


4. Thuerlimann, B, Robertson, JFR, Nabholtz, JM, Buzdar, A, Bonneterre, J, Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women European Journal of Cancer 2003 39

5. Bonneterre, J, Buzdar, A, Nabholtz, JA, Robertson, JFR, Thuerlimann, B, von Euler, M, Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92


**Fulvestran 250 mg (=AI)**

1. Howell, A, Robertson, JFR, Quaresma Albano, J, Ascgermannova, A, Mauriac, L, Kleeberg, UR, Fulvestrant, formerly ICI 182, 780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment Journal of Clinical Oncology 2002 20
2. Mauriac, L, Pippen, JE, Quaresma Albano, J, Gertler, SZ, Osborne, CK, Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials European Journal of Cancer 2003 39
fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol. 2008 Apr 1;26(10):1664-70.


Fulvestrant 500 mg


MPA/MA inferior to AI)

5. Goss, PE, Winer, EP, Tannock, IF, Schwarz, LH, Randomized phase III trial comparing the new potent and selective third generation aromatase inhibitor vorozole with megestrol acetate in postmenopausal advanced breast cancer patients Journal of Clinical Oncology 1999 17

Comparison of different AI


**Fulvestrant and anastrozol (vs. AI)**


**Letrozole and Palbociclib (vs. Letrozol)**

Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer (6/14)

No further information

References:

GnRHa plus Tamoxifen (vs. OFS or Tam)


**Ovarian function suppression (OFS), Tamoxifen**


**GnRHa plus AI (first or second line)**


**GnRHa plus Fulvestrant**


**GnRHa+ Fulvestrant +/- Palbociclib**

Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer (7/14)

No further information

References:

“...Aromatase inhibitors (3rd gen) (> non-AI*)“

4. Thuerlimann, B, Robertson, JFR, Nabholtz, JM, Buzdar, A, Bonneterre, J, Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women European Journal of Cancer 2003 39
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Kaufmann, M, Bajetta, E, Dirix, LY, Fein, LE, Jones, SE, Zilembo, N, Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomised double-blind trial Journal of Clinical Oncology 2000 18

**Comparison of different AI**


**Fulvestrant and anastrozol (vs. AI)**


**Letrozole and Palbociclib (vs. Letrozol)**

Fulvestrant and Palbociclib

**Therapy Algorithm after Adjuvant Tamoxifen (8/14)**

*No further information*

*No references*
Therapy Algorithm after Adjuvant AI (9/14)

No further information

No references
Endocrine Therapy in Premenopausal HER2-Negative Metastatic Breast Cancer Patients in Combination with Bevacizumab (10/14)

No further information

References:


2. Bevacizumab plus endocrine treatment as first line therapy for advanced diseasePhase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer: the letrozole/fulvestrant and avastin (LEA) study.

Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients (12/14)

No further information

References

Anastrozole and trastuzumab


Letrozole and trastuzumab


Letrozole and lapatinib

Fulvestrant and lapatinib

Combination of Endocrine Treatment with Anti-HER2-Treatment (13/14)

No further information

References:


Concomitant or Sequential Endocrine-Cytostatic Treatment (14/14)

No further information

References:

Concomitant endocrine-cytotoxic treatment


Maintenance endocrine therapy after chemotherapy induced response