Endocrine-based and targeted Therapy of Metastatic Breast Cancer
Endocrine Therapy of Metastatic Breast Cancer

▪ Versions 2002–2020:
  Albert / Bischoff / Dall / Fasching / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Kolberg-Liedtke / Loibl / Lüftner / Lück / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Schmidt / Schneeweß / Schütz / Stickeler / Thill / Untch

▪ Version 2021:
  Gerber / Wöckel
Endocrine Therapy in Metastatic Breast Cancer

**Indication**

- **Oxford LoE:** 1a
- **GR:** A
- **AGO:** ++

Endocrine-based therapy is first line treatment in patients with metastatic breast cancer and positive (or unknown) hormone receptor (HR) status.

**Exception:** imminent organ failure

**Caveat:** HR may change during the course of disease.

Histology of recurrent site should be obtained whenever possible.

Meta-analysis:


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
### GnRHa plus fulvestrant plus palbociclib

### GnRHa plus AI plus palbociclib
1. Layman RM et al. Comparative effectiveness of palbociclib plus letrozole vs. letrozole for metastatic breast cancer in US-real world clinical practises, ESMO 2019, #329P

### GnRHa plus AI/Tamoxifen plus ribociclib
1. Tripathy D et al. First-line ribociclib vs placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized phase III MONALEESA-7 trial. SABCS 2017, GS-2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LoE</th>
<th>GR</th>
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</thead>
<tbody>
<tr>
<td>GnRHa + Fulvestrant + CDK4/6i</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>GnRHa + AI + Ribociclib</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>GnRHa + AI + Palbociclib / Abemaciclib</td>
<td>3b/5</td>
<td>C</td>
<td>+</td>
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<tr>
<td>GnRHa + Tamoxifen + Palbociclib / Abemaciclib</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td>GnRHa + Tamoxifen</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 + 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>Aromatase inhibitors without OFS</td>
<td>3</td>
<td>D</td>
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</table>

**GnRH plus Fulvestrant + Abemaciclib**

**GnRHa plus tamoxifen (vs. OFS or tam)**

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

**GnRHa plus AI (first or second line)**
3. Carlson RW, et al. Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of...

**GnRHa plus fulvestrant**

Endocrine Mono-Therapy in Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

- Fulvestrant 500 mg
- Aromatase inhibitor*
- Tamoxifen
- Fulvestrant 250 mg + Anastrozole
- Repeat prior treatments

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<td>1b</td>
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<td>1a</td>
<td>A</td>
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<td></td>
<td>5</td>
<td>D</td>
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* There is no evidence for superiority of any specific aromatase inhibitor. As everolimus plus exemestane is indicated after AI treatment, a non-steroidal AI should be used in first line.

**Fulvestrant 500 mg (vs. anastrozole)**

**Fulvestrant 500 mg >> 250 mg**

**Aromatase inhibitors (3rd generation)**
Aromatase inhibitors (3rd generation) (>non-AI)
1. Bonneterre, J, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92

Estrogentherapie nach Aromatase inhibitors / fortgeschrittene MaCa
CDK4/6 metaanalysis


CDK4/6 inhibitor management


Letrozole and palbociclib (vs. letrozole alone)

Fulvestrant 500 mg plus Palbociclib (vs. Fulvestrant alone)

Letrozol plus Ribociclib

Fulvestrant plus Ribociclib

Fulvestrant plus Abemaciclib

Non-steroidal AI plus Abemaciclib

CDK4/6i metaanalysis

CDK4/6i after CDK4/6i
1. Wander SA, Zangardi M, Niemierko A et a. A multicenter analysis of abemaciclib after progression on palbociclib in patients (pts) with hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC). DOI: 10.1200/JCO.2019.37.15_suppl.1057, JCO 37
Exemestane and everolimus (vs. exemestane alone)

Tamoxifen and everolimus

Fulvestrant and everolimus
1. Kornblum NS, et al. PrECOG 0102: A randomized, double-blind, phase II trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC) resistant to aromatase inhibitor (AI) therapy. SABCS 2016,#S1-02

Letrozole and everolimus

Abemaciclib Monotherapy
1. Dickler MN, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR<sup></sup>+<sub></sub>/HER2<sup></sup>-<sub></sub> Metastatic Breast Cancer. Clin Cancer Res. 2017;23(17):5218-5224.
Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer 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

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<tr>
<td></td>
<td>1b</td>
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<tr>
<td></td>
<td>1b</td>
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Maintenance of bevacizumab plus endocrine therapy

Bevacizumab plus endocrine treatment as first line
PARP Inhibitors in Patients with HER2-negative, gBRCA-Mutant, Metastatic Breast Cancer

### Olaparib


### Talazoparib


HER2-Positive and HR-Positive Metastatic Breast Cancer
## Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients

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<tbody>
<tr>
<td>Anastrozole + trastuzumab</td>
<td>1b</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Letrozole + trastuzumab</td>
<td>2b</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>Letrozole + lapatinib</td>
<td>1b</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Fulvestrant + lapatinib</td>
<td>1b</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Abemaciclib + fulvestrant + trastuzumab (after T-DM1)</td>
<td>2b*</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>Aromatase inhibitors + trastuzumab / pertuzumab*</td>
<td>2b</td>
<td></td>
<td>+/-</td>
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*Poor efficacy of endocrine therapy alone. Consider induction chemotherapy + anti-HER2-therapy (followed by endocrine + anti-HER2-therapy as maintenance therapy)!

### Anastrozole and trastuzumab


### Letrozole and trastuzumab


**Letrozole and lapatinib**


**Fulvestrant and lapatinib**


**AI and trastuzumab/pertuzumab**

Abemaciclib plus Fulvestrant plus Trastuzumab

Concomitant endocrine-cytotoxic treatment

Maintenance endocrine therapy after chemotherapy induced response