Endocrine based and targeted Therapy of Metastatic Breast Cancer
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- **Versions 2002–2022:**
  - Albert / Bischoff / Dall / Fasching / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Kolberg-Liedtke / Loibl / Lüftner / Lück / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Schmidt / Schneeweiß / Schütz / Stickeler / Thill / Untch / Witzel / Wöckel

- **Version 2023:**
  - Banys-Paluchowski / Lux / Untch
Endocrine-based and targeted Therapy of Metastatic Breast Cancer

Indication

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

Endocrine-based therapy is the first treatment option in patients with hormone receptor (HR) positive / HER2-negative metastatic breast cancer.

Impending organ failure and/or symptomatic visceral metastases do not necessarily represent an indication for chemotherapy, and endocrine-based therapy can be used individually for endocrine-sensitive disease.

Caveat: Receptor status—may change during the course of disease. Histology of recurrent site should be obtained whenever possible.

1. Lu YS, Mahidin EIBN, Azim H. Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician’s Choice Combination Chemotherapy. SABCS 2022; GS1-10.


**Comparison ER / PR and HER2**

**Metastasis vs. Primary Tumor (n = 5.521)**

Meta-analysis based on 39 (mostly retrospective) analyses, exclusively comparing primary tumor and metastasis (no lymph nodes):

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Discordance Proportions</th>
<th>Positive to Negative</th>
<th>Negative to Positive</th>
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<tbody>
<tr>
<td>ER</td>
<td>19.3% (95% CI: 15.8% to 23.4%)</td>
<td>22.5% (95% CI: 16.4% to 30.0%)</td>
<td>21.5% (95% CI: 18.1% to 25.3%)</td>
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<tr>
<td>PR</td>
<td>30.9% (95% CI: 26.6% to 35.6%)</td>
<td>49.4% (95% CI: 40.5% to 58.2%)</td>
<td>15.9% (95% CI: 11.3% to 22.0%)</td>
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<tr>
<td>HER2</td>
<td>10.3% (95% CI: 7.8% to 13.6%)</td>
<td>21.3% (95% CI: 13.1% to 30.5%)</td>
<td>9.5% (95% CI: 7.4% to 12.1%)</td>
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**Meta-analysis:**

Endocrine Therapy
General Considerations

- Within all lines of treatment, treatment options should consider prior endocrine therapies, age and comorbidities as well as the respective approval status.

- Premenopausal patients treated with GnRH analogues or after ovariectomy can be treated like postmenopausal patients.

- In this chapter, the recommendations refer to pre- and postmenopausal women, unless menopausal status is explicitly mentioned (in premenopausal patients, the combination with GnRH analogues is usually carried out).

Endocrine Resistance in Metastatic Breast Cancer

Primary endocrine resistance:
- Relapse within 2 years of adjuvant endocrine treatment (ETx)
- Progressive disease within first 6 months of first-line ETx for MBC

Secondary (required) endocrine resistance:
- Relapse while on adjuvant ETx but after the first 2 years or a relapse within 12 months after completing adjuvant ETx
- PD ≥ 6 months after initiation of ET for MBC

International consensus
Guidelines


GnRHa plus fulvestrant plus palbociclib


GnRHa plus AI plus ribociclib


GnRHa plus AI plus palbociclib

GnRH plus Fulvestrant + Abemaciclib


GnRHa plus tamoxifen (vs. OFS or tam)


Ovarian function suppression (OFS), tamoxifen


GnRHa plus AI (first or second line)


GnRHa plus fulvestrant

## Endocrine-Based Therapy with CDK4/-Inhibitor for Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer

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<tr>
<td></td>
<td>LoE</td>
</tr>
<tr>
<td>Ribociclib</td>
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<tr>
<td>Abemaciclib</td>
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<tr>
<td>Palbociclib</td>
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### Guidelines

### Meta-analysis CDK4/6 inhibitors

### Endokrin vs. Chemotherapie
CDK4/6 inhibitor management


Letrozole and palbociclib (vs. letrozole alone)


**Fulvestrant 500 mg plus Palbociclib (vs. Fulvestrant alone)**


Letrozole plus palbociclib vs. Fulvestrant plus palbociclib

Letrozol plus Ribociclib (vs. Letrozol alone)
3. Hortobagyi GN, Stemmer SM, Burris HA et al. Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2—) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741

Fulvestrant plus Ribociclib (vs. Fulvestrant alone)


**Biomarker in MONALEESA**


**Fulvestrant plus Abemaciclib (vs. Fulvestrant alone)**


**Non-steroidal AI plus Abemaciclib (vs. AI alone)**


as initial therapy in patients with HR+, HER2- advanced breast cancer. ESMO, 2022
Endocrine-Based Therapy with CDK4-/Inhibitor for Patients with HER2-Negative Metastatic Breast Cancer

- Abemaciclib monotherapy
- CDK4/6-Inhibitor beyond progression (with change of the endocrine therapy partner)
- CDK4/6-Inhibitor switch based on toxicity

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</table>

Combination with GnRH agonists recommended in the premenopause.

CDK4/6 inhibitor management

Abemaciclib Monotherapy

CDK4/6i after CDK4/6i
2. Kalinsky K, Accordino MK, Chiuza C, et al. A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after
Progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastatic hormone receptor positive, HER negative breast cancer: MAINTAIN Trial. ASCO, 2022
CDK4/6 Inhibitors in First-line Studies

<table>
<thead>
<tr>
<th>Study name</th>
<th>Paloma-2</th>
<th>Monarch-3</th>
<th>Monaleesa-2</th>
<th>Monaleesa-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment arms</td>
<td>Palbociclib / placebo with letrozole</td>
<td>Abemaciclib / placebo with nonsteroidal AI</td>
<td>Ribociclib / placebo with letrozole</td>
<td>Ribociclib / placebo with tamoxifen or non-steroidal aromatase inhibitor, all with goserelin</td>
</tr>
<tr>
<td>Patients</td>
<td>666</td>
<td>493</td>
<td>668</td>
<td>672</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>postmenopausal</td>
<td>postmenopausal</td>
<td>postmenopausal</td>
<td>premenopausal</td>
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<tr>
<td>Progression-free survival (months, m)</td>
<td>27.6 vs. 14.5 m (+ 13.1 m) (HR 0.563)</td>
<td>29.0 vs. 14.8 m (+ 14.2 m) (HR 0.518)</td>
<td>25.3 vs. 16.0 m (+ 9.3 m) (HR 0.568)</td>
<td>23.8 vs. 13.0 m (+ 10.8 m) (HR 0.55)</td>
</tr>
<tr>
<td>Overall survival (months, m)</td>
<td>53.9 vs. 51.2 m (+ 2.7 m) (HR 0.956, n.s.)</td>
<td>67.1 vs. 54.5 m (+ 12.6 m) (HR 0.754, n.s.)</td>
<td>63.9 vs. 51.4 m (+ 12.5 m) (HR 0.76)</td>
<td>58.7 vs. 48.0 m (+ 10.7 m) (HR 0.76)</td>
</tr>
</tbody>
</table>

4. Hortobagyi GN, Stemmer SM, Burris HA et al. Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741
6. Lu YS, Im SA, Colleoni M et al. Updated Overall Survival of Ribociclib Plus Endocrine Therapy vs Endocrine Therapy Alone in Pre-


### Further Endocrine-Based Treatment Options for Patients with HER2-Negative Metastatic Breast Cancer

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<tr>
<td>Alpelisib + Fulvestrant (PIK3CA mutated)</td>
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<tr>
<td>Everolimus</td>
<td></td>
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<tr>
<td>+ Exemestane</td>
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<td>A</td>
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<tr>
<td>+ Tamoxifen</td>
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<tr>
<td>+ Letrozole</td>
<td>2b</td>
<td>B</td>
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<tr>
<td>+ Fulvestrant</td>
<td>2b</td>
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Combination with GnRH agonists recommended in the premenopause.

### Guidelines


### Endokrin vs. Chemotherapie


### Exemestane and everolimus (vs. exemestane alone)


or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). Ann Oncol. 2016;27(9):1719-25

**Tamoxifen and everolimus**


**Fulvestrant and everolimus**


**Letrozole and everolimus**

Guidelines


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


Endokrine Monotherapie (AI/ Fulvestrant) nach CDK4/6-Vortherapie:

1. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the

2. Kalinsky K, Accordino MK, Chiuzan C, et al. A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after rporgession on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastastic hormone receptor positive, HER negative breast cancer: MAINTAIN Trial. ASCO, 2022

Elacestrant
1. Bardia A. et al., SABCS, 2021
2. Kaklamani V. et al., SABCS, 2022
### Endocrine Therapy in Patients with HER2-Negative Metastatic Breast Cancer in Combination with Bevacizumab

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Combination with GnRH agonists recommended in the premenopause.

**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

<table>
<thead>
<tr>
<th>PARP Inhibitor</th>
<th>Oxford LoE</th>
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<tbody>
<tr>
<td>Olaparib</td>
<td>1b</td>
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<tr>
<td>Talazoparib</td>
<td>1b</td>
<td>A</td>
<td>++</td>
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</tbody>
</table>

#### Guidelines

#### Olaparib
2. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of...


Talazoparib


HR-positive and HER2-positive Metastatic Breast Cancer
Endocrine-based Therapy in HER2-Positive Metastatic Breast Cancer Patients

- Abemaciclib + Fulvestrant + Trastuzumab (≥3rd line, after T-DM1)  
  Oxford LoE 2b, GR B, AGO +
- Aromatase inhibitor + Trastuzumab + Pertuzumab  
  Oxford LoE 2b, GR B, AGO +
- Aromatase inhibitor + Trastuzumab  
  Oxford LoE 1b, GR B, AGO +/−
- Aromatase inhibitor + Lapatinib  
  Oxford LoE 1b, GR B, AGO +/−
- Fulvestrant + Lapatinib  
  Oxford LoE 1b, GR B, AGO +/−

Poor efficacy of endocrine therapy alone.
Consider induction chemotherapy + anti-HER2-therapy (followed by endocrine + anti-HER2-therapy as maintenance therapy)!
Combination with GnRH agonists recommended in the premenopause.

Guidelines

Anastrozole and trastuzumab
Letrozole and trastuzumab

Letrozole and lapatinib

Fulvestrant and lapatinib

Abemaciclib plus Fulvestrant plus Trastuzumab
3. André F, Nadal JC, Denys H et al. Final overall survival (OS) for abemaciclib plus trastuzumab +/- fulvestrant versus trastuzumab plus
chemotherapy in patients with HR+, HER2+ advanced breast cancer (monarcHER): a randomized, open-label, phase 2 trial. ESMO Congress 2022, Abstract 2806 LBA2806

Endocrine therapy and trastuzumab/pertuzumab


### Concomitant or Sequential Endocrine-Cytostatic Treatment

<table>
<thead>
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- **Concomitant endocrine-cytotoxic treatment**
  - May increase response rate and progression free interval but not overall survival
  - May increase toxicity

- **Endocrine maintenance therapy after chemotherapy +/- anti-HER2 therapy-induced response +/- anti HER2 therapy**
  - Increases progression free interval

### Guidelines

### Concomitant endocrine-cytotoxic treatment

### Maintenance endocrine therapy after chemotherapy induced response