Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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

- **Versions 2002–2019:**
  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

- **Version 2020:**
  Thill / Untch
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

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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):

Pooled discordance proportions were:
- 19.3% (95% CI 1/4 15.8% to 23.4%) for ER
- 30.9% (95% CI 1/4 26.6% to 35.6%) for PR
- 10.3% (95% CI 1/4 7.8% to 13.6%) for HER2

Pooled proportions of tumors shifting from positive to negative
- 22.5% (95% CI = 16.4% to 30.0%) for ER
- 49.4% (95% CI = 40.5% to 58.2%) for PR
- 21.3% (95% CI = 14.3% to 30.5%) for HER2

Pooled proportions of tumors shifting from negative to positive
- 21.5% (95% CI = 18.1% to 25.5%) for ER
- 15.9% (95% CI = 11.3% to 22.0%) for PR
- 9.5% (95% CI = 7.4% to 12.1%) for HER2

Meta-analysis:

Additional literature:


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.


**Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th>Therapeutic Regimen</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH-A + Fulvestrant + Palbociclib</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>GnRH-A + AI + Palbociclib*</td>
<td>3b*</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>GnRH-A + AI + Ribociclib</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>GnRH-A + Fulvestrant + Abemaciclib</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>GnRH-A + Tamoxifen (vs. OFS or Tam)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Ovarial 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>GnRH-A + AI (first + second line)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>GnRH-A + Fulvestrant</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>

* Extrapolated from data of postmenopausal patients (with AI)

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**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

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**


Fulvestrant 500 mg (vs. anastrozole)


Fulvestrant 500 mg >> 250 mg


Aromatase inhibitors (3rd generation)*


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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant 500 mg</td>
<td>1b B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aromatase inhibitor*</td>
<td>1a A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1a A</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant 250 mg + Anastrozole</td>
<td>1b B +/-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat prior treatments</td>
<td>5 D</td>
<td>+/-</td>
<td></td>
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</tbody>
</table>

* 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 used in first line.

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
**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 al. 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 post-menopausal 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
Maintenance of bevacizumab plus endocrine therapy


Bevacizumab plus endocrine treatment as first line


Olaparib


Talazoparib


Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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

<table>
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<tr>
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<td>AGO</td>
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</table>

- Anastrozole plus trastuzumab
- Letrozole plus trastuzumab
- Letrozole plus lapatinib
- Fulvestrant plus lapatinib
- Abemaciclib plus fulvestrant plus trastuzumab (after T-DM1)
- Aromatase inhibitors plus trastuzumab / pertuzumab*

* Poor efficacy of endocrine therapy alone.
Consider induction chemotherapy + anti-HER2-therapy (followed by endocrine + anti-HER2-therapy as maintenance therapy)!

* Study participation recommended

Anastrozole and trastuzumab

Letrozole and trastuzumab


**Letrozole and lapatinib**


**Fulvestrant and lapatinib**

AI and trastuzumab/pertuzumab


Abemaciclib plus Fulvestrant plus Trastuzumab

**Concomitant or Sequential Endocrine-Cytostatic Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
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<tbody>
<tr>
<td>Concomitant endocrine-cytotoxic treatment</td>
<td>1b</td>
<td>A</td>
<td>-</td>
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<tr>
<td>- May increase response rate and progression free interval but not overall survival</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- May increase toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine maintenance therapy after chemotherapy +/- anti-HER2 therapy-induced response +/- anti HER2 therapy</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>- Increases progression free interval</td>
<td></td>
<td></td>
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**Concomitant endocrine-cytotoxic treatment**


**Maintenance endocrine therapy after chemotherapy induced response**