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# Endocrine-based and targeted Therapy of Metastatic Breast Cancer

# Endocrine Therapy of Metastatic Breast Cancer



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- **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 / Schneeweiß / Schütz / Stickeler / Thill / Untch**

- **Version 2021:**
  **Gerber / Wöckel**

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# 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**

# 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% CI1⁄4 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

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# Endocrine Therapy
# General Considerations

- **In all lines of treatment, treatment options should consider prior endocrine therapies, age, and comorbidities as well as the respective approval status.**
- **Premenopausal patients receiving GnRH analogues or after ovariectomy can be treated like postmenopausal patients.**

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# 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**

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

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ GnRHa + Fulvestrant + CDK4/6i | 2b | B | ++ |
| ▪ GnRHa + AI + Ribociclib | 1b | B | ++ |
| ▪ GnRHa + AI + Palbociclib / Abemaciclib | 3b[a]/5 | C | + |
| ▪ GnRHa + Tamoxifen + Palbociclib / Abemaciclib | 2b | B | +/- |
| ▪ GnRHa + Tamoxifen | 1a | A | + |
| ▪ Ovarian Function Suppression(OFS) | 2b | B | + |
| ▪ Tamoxifen | 2b | B | +/- |
| ▪ GnRHa + AI (first + second line) | 2b | B | + |
| ▪ GnRHa + Fulvestrant | 1b | B | + |
| ▪ Aromataseinhibitors without OFS | 3 | D | - - |

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



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| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Fulvestrant 500 mg | 1b | B | + |
| ▪ Aromatase inhibitor* | 1a | A | + |
| ▪ Tamoxifen | 1a | A | + |
| ▪ Fulvestrant 250 mg + Anastrozole | 1b | B | +/- |
| ▪ Repeat prior treatments | 5 | D | +/- |

* 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.

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



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| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ CDK4/6-Inhibitor (Abemaciclib, Palbociclib, Ribociclib) | | | |
| ▪ + non-steroidal AI | 1b | B | ++ |
| ▪ + Fulvestrant | 1b | B | ++ |
| ▪ Abemaciclib monotherapy | 3 | C | +/- |
| ▪ Alpelisib + Fulvestrant (PIK3CA mutated) | 1b | B | + |
| ▪ Everolimus | | | |
| ▪ + Exemestane | 1b | A | + |
| ▪ + Tamoxifen | 2b | B | + |
| ▪ + Letrozole | 2b | B | +/- |
| ▪ + Fulvestrant | 2b[a] | B | + |
| ▪ CDK4/6-Inhibitor beyond progression | 5 | D | - |
| ▪ CDK4/6-Inhibitor switch based on toxicity | 5 | D | +/- |

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# Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer in Combination with Bevacizumab

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Maintenance bevacizumab plus endocrine therapy after remission with chemotherapy and bevacizumab | 1b | B | +/- |
| ▪ Bevacizumab plus endocrine treatment as first line therapy for advanced disease | 1b | B | +/- |

# PARP Inhibitors in Patients with HER2-negative, gBRCA-Mutant, Metastatic Breast Cancer



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| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ **Olaparib** | 1b | A | ++ |

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ **Talazoparib** | 1b | B | ++ |

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# HER2-Positive and HR-Positive Metastatic Breast Cancer

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



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| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Anastrozole + trastuzumab | 1b | B | +/- |
| ▪ Letrozole + trastuzumab | 2b | B | +/- |
| ▪ Letrozole + lapatinib | 1b | B | +/- |
| ▪ Fulvestrant + lapatinib | 1b | B | +/- |
| ▪ Abemaciclib + fulvestrant + trastuzumab (after T-DM1) | 2b[a] | B | +/- |
| ▪ Aromatase inhibitors + trastuzumab / pertuzumab* | 2b | B | +/- |

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

* **Study participation recommended**

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# Concomitant or Sequential Endocrine-Cytostatic Treatment

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ **Concomitant endocrine-cytotoxic treatment** | 1b | A | - |
| ▪ 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** | 2b | B | + |
| ▪ Increases progression-free interval | | | |