

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Guidelines Breast
Version 2023.1E

Endocrine based and targeted Therapy of Metastatic Breast Cancer

Endocrine-based and targeted Therapy of Metastatic Breast Cancer

- **Versions 2002–2022:**

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- **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.

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

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

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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 \geq 6 months after initiation of ET for MBC

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

Oxford

LoE	GR	AGO
2b	B	++
1b	B	++
3b/5	C	+
2b	B	+/-
1a	A	+
2b	B	+/-
2b	B	+
1b	B	+
3	D	--

- GnRHa + Fulvestrant + CDK4/6i
- GnRHa + AI + Ribociclib
- GnRHa + AI + Palbociclib / Abemaciclib
- GnRHa + Tamoxifen + Palbociclib / Abemaciclib
- GnRHa + Tamoxifen
- Tamoxifen
- GnRHa + AI (first + second line)
- GnRHa + Fulvestrant
- Aromataseinhibitors without OFS

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



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	Oxford		
	LoE	GR	AGO
■ Ribociclib			
■ + non-steroidal AI	1b	A	++
■ + Fulvestrant	1b	A	++
■ Abemaciclib			
■ + non-steroidal AI	1b	A	+
■ + Fulvestrant	1b	A	++
■ Palbociclib			
■ + non-steroidal AI	1b	A	+
■ + Fulvestrant	1b	A	+

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

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

Oxford		
LoE	GR	AGO
3	C	+/-
2b ⁻	C	+/-
5	D	+/-

CDK4/6 Inhibitors in First-line Studies

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

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

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- **Alpelisib + Fulvestrant (PIK3CA mutated)**
- **Everolimus**
 - + Exemestane
 - + Tamoxifen
 - + Letrozole
 - + Fulvestrant

Oxford		
LoE	GR	AGO
1b	B	+
1b	A	+
2b	B	+
2b	B	+/-
2b	B	+

Endocrine Monotherapy in Patients with HER2-Negative Metastatic Breast Cancer

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	LoE	GR	AGO
▪ Fulvestrant 500 mg	1b	B	+
▪ Aromatase inhibitor*	1a	A	+
▪ Tamoxifen	1a	A	+
▪ Fulvestrant 250 mg + Anastrozole	1b	B	+/-
▪ Endocrine monotherapy (AI / Fulvestrant) after prior CDK4/6i therapy	1b	B	+/-
▪ Elacestrant after prior CDK4/6i therapy (especially in case of prolonged response to CDK4/6i) [#]			
▪ ESR1mut	1b	B	+
▪ ESR1wt	2b	B	+/-
▪ Repeat prior treatments	5	D	+/-

* 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.

Cave: no EMA approval yet
Combination with GnRH agonists recommended in the premenopause.



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

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

Oxford		
LoE	GR	AGO
1b	B	+/-
1b	B	+/-

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



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- **Olaparib**

Oxford		
LoE	GR	AGO
1b	A	++

- **Talazoparib**

Oxford		
LoE	GR	AGO
1b	A	++

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HR-positive and HER2-positive Metastatic Breast Cancer

Endocrine-based Therapy in HER2-Positive Metastatic Breast Cancer Patients

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- **Abemaciclib + Fulvestrant + Trastuzumab (≥3rd line, after T-DM1)**
- **Aromatase inhibitor + Trastuzumab + Pertuzumab**
- **Aromatase inhibitor + Trastuzumab**
- **Aromatase inhibitor + Lapatinib**
- **Fulvestrant + Lapatinib**

LoE	GR	AGO
2b	B	+
2b	B	+
1b	B	+/-
1b	B	+/-
1b	B	+/-

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.

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