Guidelines Breast
Version 2024.1E

Endocrine based and targeted Therapy of Metastatic Breast Cancer

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- **Versions 2002–2023:**

  Albert / Banys-Paluchowski / Bischoff / Dall / Fasching / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Kolberg-Liedtke / Loibl / Lüftner/ Lück / Lux / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Schmidt / Schneeweiß / Schütz / Stickeler / Thill / Untch / Witzel / Wöckel

Version 2024:

Fehm / Hartkopf

Endocrine-based and targeted Therapy of Metastatic Breast Cancer

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

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

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.

Oxford LoE: 2b **GR: B** **AGO: +**

Caveat: Receptor status-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% 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 (ET)
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 ovarectomy 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 (ET)**
- **Progressive disease within first 6 months of first-line ETx 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/5	C	+
▪ GnRHa + Tamoxifen + Palbociclib / Abemaciclib	2b	B	+/-
▪ GnRHa + Tamoxifen	1a	A	+
▪ Tamoxifen	2b	B	+/-
▪ GnRHa + AI (first + second line)	2b	B	+
▪ GnRHa + Fulvestrant	1b	B	+
▪ Aromataseinhibitors without OFS	3	D	- -

Endocrine-Based Therapy with CDK4/6-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	+

CDK4/6 Inhibitors in First-line Studies

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	Paloma-2	Monarch-3	Monaleesa-2	Monaleesa-7
Treatment arms	Letrozole +/- palbociclib	Nonsteroidal AI +/- abemaciclib	Letrozole+/- ribociclib	Goserelin + nonsteroidal AI or tamoxifen +/- ribociclib
Patients	666	493	668	672
Randomization	2:1	2:1	1:1	1:1
Primary endpoint	PFS	PFS	PFS	PFS
Menopausal status	post	post	post	pre
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 0.53)	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.**)	66,8 vs. 53,7 m (+ 13,1 m) (HR 0,804 **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)

Endocrine-Based Therapy with CDK4/6-Inhibitor for Patients with HER2-Negative Metastatic Breast Cancer

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	Oxford		
	LoE	GR	AGO
■ Abemaciclib monotherapy*	3	C	+/-
■ CDK4/6-Inhibitor beyond progression in the metastatic situation (with change of the endocrine therapy partner)	2b^{-}	B	+/-
■ CDK4/6-Inhibitor switch based on toxicity	5	D	+/-

- Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting (according to study inclusion criteria)

CDK4/6 Inhibitors beyond Progression

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	MAINTAIN (Phase II)	PACE (Phase II)	PALMIRA (Phase II)
N	119	166	198
CDK4/6i	**Palbo → Ribo (86%)** Ribo → Ribo (14%)	**Palbo → Palbo (93%)** Ribo → Palbo (4%) Abema → Palbo (3%)	**Palbo → Palbo (100%)**
Endocine therapy	**AI → Fulvestrant (83%)** Fulvestrant → AI (27%)	**AI → Fulvestrant (100%)**	**AI → Fulvestrant (88%)** Fulvestrant → AI (12%)
initial treatment duration ≥12 months	67%	78%	85%
Median PFS ET alone	2.76 (2.66-3.25) mo	4.8 (2.1-8.2) mo	3.6 (2.7-4.2) mo
Median PFS ET + CDK4/6i beyond progression	5.29 (3.02-8.12) mo	4.6 (3.6-5.9) mo	4.2 (3.5-5.8) mo
HR	0.57 (0.39-0.95)	1.11 (0.74-1.66)	0.8 (0.6-1.1)
p-value	0.006	0.62 (ns)	0.206 (ns)

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Second- and Subsequent-Line Endocrine-based Therapies for HR Pos. / HER2-Neg. Metastatic Breast Cancer

(No mutations / alterations required)

	Oxford		
	LoE	GR	AGO
▪ **CDK4/6i + ET***	1A	A	++
▪ **Everolimus**			
▪ + Exemestane	1b	A	+
▪ + Tamoxifen / Fulvestrant	2b	B	+
▪ + Letrozole	2b	B	+/-
▪ **CDK4/6i beyond progression**	2b	B	+/-
▪ **Endocrine monotherapy (AI / Fulvestrant) after CDK4/6i-therapy**	1b	B	+/-

*** if not given in 1st line setting**

Second- and Subsequent-Line Therapies for HR Pos. / HER2 Neg. Metastatic Breast Cancer

(Specific mutations / alterations required)

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	Oxford		
	LoE	GR	AGO
▪ ***ESR1*-mutated and CDK4/6i-pretreatment**			
Elacestrant*	**1b**	**B**	**+**
▪ ***PIK3CA*-mutated**			
Alpelisib + Fulvestrant	**1b**	**B**	**+**
▪ **Alterations in *PIK3CA, AKT1, or PTEN***			
Capivasertib + Fulvestrant**	**1b**	**B**	**+**
▪ ***gBRCA*-mutated**			
Olaparib	**1b**	**A**	**++**
Talazoparib	**1b**	**A**	**++**

* *particularly in patients who experienced prolonged PFS on the prior lines of ET and CDK 4/6 inhibitors*

** *no EMA approval yet (01/2024)*

Further Endocrine Treatment Options for HR Pos. / HER2 Neg. Metastatic Breast Cancer: First and Subsequent Lines

(in case no combination or targeted therapies are possible)

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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	+/-
▪ ET + Bevacizumab as 1st-line treatment	1b	B	+/-
▪ Repeat prior endocrine treatments	5	D	+/-

*** There is no evidence for superiority of a single aromatase inhibitor**

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

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

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	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	+
▪ Bevacizumab maintenance plus endocrine therapy after remission with chemotherapy and bevacizumab	1b	B	+/-