



Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Version 2025.1E

Endocrine based and targeted Therapy of Metastatic Breast Cancer

Endocrine-based and targeted Therapy of Metastatic Breast Cancer

- **Versions 2002–2024:**

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- **Version 2025:**

Dall / Mundhenke



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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 endocrine-sensitive disease preferentially.

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.**

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 (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 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).**

Metastatic Breast Cancer

Endocrine resistance

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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 \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 CDK4/6-Inhibitor for Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer



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	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Ribociclib <ul style="list-style-type: none"> ■ + non-steroidal AI ■ + Fulvestrant ■ Abemaciclib <ul style="list-style-type: none"> ■ + non-steroidal AI ■ + Fulvestrant ■ Palbociclib <ul style="list-style-type: none"> ■ + non-steroidal AI ■ + Fulvestrant ■ + Fulvestrant + Inavolisib* 	<p>1b</p> <p>1b</p> <p>1b</p> <p>1b</p> <p>1b</p> <p>1b</p> <p>1b</p>	<p>A</p> <p>A</p> <p>A</p> <p>A</p> <p>A</p> <p>A</p> <p>A</p>	<p>++</p> <p>++</p> <p>+</p> <p>++</p> <p>+</p> <p>+</p> <p>+</p>

* In primary endocrine resistance and PIK3CA mutation

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)

CDK4/6 Inhibitors beyond Progression

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	postMONARCH (Phase III)	MAINTAIN (Phase II)	PACE (Phase II)	PALMIRA (Phase II)
N	368	119	166	198
CDK4/6i	Palbo→Abema (59%) Ribo→Abema (33%) Abema→Abema (8%)	Palbo → Ribo (86%) Ribo → Ribo (14%)	Palbo → Palbo (93%) Ribo → Palbo (4%) Abema → Palbo (3%)	Palbo → Palbo (100%)
Endocrine therapy	AI→Fulvestrant (100%)	AI → Fulvestrant (83%) Fulvestrant → AI (27%)	AI → Fulvestrant (100%)	AI → Fulvestrant (88%) Fulvestrant → AI (12%)
initial treatment duration ≥12 months	71%	67%	78%	85%
Median PFS ET alone	5.3 (3.7-5.6) mo	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	6.0 (5.6-8.6) mo	5.29 (3.02-8.12) mo	4.6 (3.6-5.9) mo	4.2 (3.5-5.8) mo
HR	0.73 (0.57-0.96)	0.57 (0.39-0.95)	1.11 (0.74-1.66)	0.8 (0.6-1.1)
p-value	0.02	0.006	0.62 (ns)	0.206 (ns)

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 in metastatic disease (change of CDK4/6i and endocrine therapy)	2b	B	+
■ Endocrine monotherapy (AI / Fulvestrant) after CDK4/6i-therapy	1b	B	+/-

* if not given in 1st line setting

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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
<ul style="list-style-type: none"> ESR1-mutated and CDK4/6i-pretreatment Elacestrant* 	1b	B	+
<ul style="list-style-type: none"> PIK3CA-mutated Alpelisib + Fulvestrant 	1b	B	+
<ul style="list-style-type: none"> Alterations in PIK3CA, AKT1, or PTEN Capivasertib + Fulvestrant 	1b	B	+
<ul style="list-style-type: none"> gBRCA-mutated Olaparib 	1b	A	++
<ul style="list-style-type: none"> Talazoparib 	1b	A	++
<ul style="list-style-type: none"> Olaparib (sBRCA- oder gPALB2-mutation) 	2b	B	+

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

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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

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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- **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**
- **Bevacizumab maintenance plus endocrine therapy after remission with chemotherapy and bevacizumab**

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

mBC - HER2-negative / HR-positive: Chemotherapy after pretreatment *

Oxford

LoE GR AGO

	LoE	GR	AGO
<ul style="list-style-type: none"> ▪ Trastuzumab-Deruxtecan - after prior chemotherapy with HER2-low - without prior chemotherapy and not suitable for further endocrine therapy, with HER2-low - not suitable for further endocrine therapy, with HER2-ultralow 	1b 1b	A B	++ +
▪ Sacituzumab Govitecan	1b	A	++
▪ Capecitabin	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbine	2b	B	+
▪ (Peg)-liposomal Doxorubicin	2b	B	+
▪ Taxane re-challenge**	2b	B	+
▪ Anthracycline re-challenge**	3b	C	+
▪ Metronomic therapy (e.g. cyclophos. + MTX)	2b	B	+

* See approval details for previous therapy

** at least 1 year recurrence free after adjuvant therapy

mBC - HER2-negative / HR-positive*

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	Trastuzumab Deruxtecan		Sacituzumab-Govitecan
Trial	Destiny-Breast 06 HR+/HER2-low: n=359 HR+/HER2-ultralow: n=76	Destiny-Breast 04 HR+/HER2-low: n=331	Tropics 02 HR+/HER2-negative: n=272
Previous CTX for mBC	no previous CTX for mBC	60%: 1 prior line of CTX 40%: > 1 prior line of CTX	2%: 1 prior line of CTX 41%: 2 prior lines of CTX 57%: > 2 prior lines of CTX
Median PFS (months)	13.2 (HER2-low) 13.2 (ITT) 13.2 (HER2-ultralow)	9.6	5.5
Hazard ratio for PFS	0.62 (HER2-low) 0.64 (ITT)	0.37	0.66
Median OS (months)		23.9	14.4
Hazard ratio for OS	0.83 (n.s.)	0.69	0.79

- Data from different phase 3 studies with differently pretreated patients
- ITT: intentio-to-treat population; n.s.: not significant, PFS: progression free survival, OS: overall survival