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Version 2022.1E

Endocrine based and targeted Therapy of Metastatic Breast Cancer

Endocrine Therapy of Metastatic Breast Cancer

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- **Versions 2002–2021:**

  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 / Wöckel

- **Version 2022:**

  Schmidt / Witzel

Endocrine Therapy of Metastatic Breast Cancer

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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)

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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

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 ovarectomy 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 (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 ≥ 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 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 a single 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	1a	A	++
▪ + Fulvestrant	1a	A	++
▪ Abemaciclib monotherapy	3	C	+/-
▪ Alpelisib + Fulvestrant (PIK3CA mutated)	1b	B	+
▪ Everolimus			
▪ + Exemestane	1b	A	+
▪ + Tamoxifen	2b	B	+
▪ + Letrozole	2b	B	+/-
▪ + Fulvestrant	2b	B	+
▪ CDK4/6-Inhibitor beyond progression	3b	C	+/-
▪ CDK4/6-Inhibitor switch based on toxicity	5	D	+/-

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CDK4/6 Inhibitors in First-line Studies

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)	28.2 vs. 14.8 m (+ 13.4 m) (HR 0.540)	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)	not reported	not reported	63.9 vs. 51.4 m (+ 12.5 m) (HR 0.76)	58.7 vs. 48.0 m (+ 10.7 m) (HR, 0.76)

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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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- **Olaparib**

Oxford		
LoE	GR	AGO
1b	A	++

- **Talazoparib**

Oxford		
LoE	GR	AGO
1b	A	++

Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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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	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			