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# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## Endocrine and targeted Therapy of Metastatic Breast Cancer


# Endocrine Therapy of Metastatic Breast Cancer

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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**

1. Wilcken N, Hornbuckle J, Gheri D Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev. 2003;(2):CD002747.
2. Gibson L, Lawrence D, Dawson C, et al. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev. 2009 ;(4):CD003370. doi: 10.1002/14651858.CD003370.pub3.
3. Lee CI, Goodwin A, Wilcken N. Fulvestrant for hormone-sensitive metastatic breast cancer. Cochrane Database Syst Rev. 2017;1:CD011093. doi:10.1002/14651858.CD011093.pub2.
4. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC4)<sup>†</sup>. Ann Oncol. 2018 ;29(8):1634-1657. doi: 10.1093/annonc/mdy192. No abstract available. PMID: 30032243



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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% 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


### Meta-analysis:

1. Schrijver WAME, Suijkerbuijk KPM, van Gils CH, et al. Receptor Conversion in Distant Breast Cancer Metastases: A Systematic Review and Meta-analysis. J Natl Cancer Inst. 2018 Jun 1;110(6):568-580. doi: 10.1093/jnci/djx273. PMID: 29315431

### Additional literature:

1. Amir E, Miller N, et al. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol 2012; 30(6):587-92.
2. Amir E, et al. Tissue confirmation of disease recurrence in breast cancer patients: pooled analysis of multi-centre, multi-disciplinary prospective studies. Cancer Treat Rev. 2012 Oct;38(6):708-14.
3. Chan A, Morey A, Brown B, et al. A retrospective study investigating the rate of HER2 discordance between primary breast carcinoma and locoregional or metastatic disease. BMC Cancer. 2012;12:555.
4. Lindström LS, Karlsson E et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol ;30:2601-8, 2012.

5. Lower EE, Glass EL, Bradley DA, et al. Impact of metastatic estrogen receptor and progesterone receptor status on survival. *Breast Cancer Res Treat*. 2005;90(1):65-70.
6. Macfarlane R, Seal M, Speers C, et al. Molecular alterations between the primary breast cancer and the subsequent locoregional/metastatic tumor. *Oncologist*. 2012;17(2):172-8.
7. Niikura N, Liu J, et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. *J Clin Oncol*;30(6):593-9, 2012.
8. Thompson AM, Jordan LB, Quinlan P, et al; Breast Recurrence in Tissues Study Group. Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the Breast Recurrence In Tissues Study (BRITS). *Breast Cancer Res*. 2010;12(6):R92
9. Sighoko D, Liu J, Hou N, et al. Discordance in hormone receptor status among primary, metastatic, and second primary breast cancers: biological difference or misclassification? *Oncologist*. 2014;19(6):592-601.
10. Curtit E, et al. Discordances in estrogen receptor status, progesterone receptor status, and HER2 status between primary breast cancer and metastasis. *Oncologist*. 2013 Jun;18(6):667-74.
11. Niikura N et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. *J Clin Oncol*. 2012;30(6):593-9.



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## 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.**

1. Partridge AH, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2014;32(29):3307-29.
2. Rugo HS, et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol 2016;34(25):3069-103.



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

	Oxford		
	LoE	GR	AGO
■ GnRH-A + Fulvestrant + Palbociclib	2b	B	++
■ GnRH-A + AI + Palbociclib*	3b <sup>a</sup>	C	++
■ GnRH-A + AI + Ribociclib	1b	B	++
■ GnRH-A + Fulvestrant + Abemaciclib	2b	B	++
■ GnRH-A + Tamoxifen (vs. OFS or Tam)	1a	A	++
■ Ovarial function suppression (OFS)	2b	B	+
■ Tamoxifen	2b	B	+
■ GnRH-A + AI (first + second line)	2b	B	+
■ GnRH-A + Fulvestrant	1b	B	+
■ Aromatase inhibitors without OFS	3	D	--

\* Extrapolated from data of postmenopausal patients (with AI)

### GnRHa plus fulvestrant plus palbociclib

1. Turner N et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med 2015; 373:209-219
2. Loibl S, et al. Palbociclib Combined with Fulvestrant in Premenopausal Women with Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results. Oncologist. 2017;22(9):1028-1038.

### GnRHa plus AI plus palbociclib

1. Layman RM et al. Comparative effectiveness of palbociclib plus letrozole vs. letrozole for metastatic breast cancer in US-real world clinical practises, ESMO 2019, #329P

### GnRHa plus AI/Tamoxifen plus ribociclib

1. Tripathy D et al. First-line ribociclib vs placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized phase III MONALEESA-7 trial. SABCs 2017, GS-2

2. Im SA, Lu YS, Bardia A, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med. 2019 Jul 25;381(4):307-316. doi: 10.1056/NEJMoa1903765. PMID:31166679

#### GnRH plus Fulvestrant + Abemaciclib

1. Sledge GW Jr, Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol. 2019 Sep 29. doi: 10.1001/jamaoncol.2019.4782. [Epub ahead of print] PMID:31563959

#### GnRHa plus tamoxifen (vs. OFS or tam)

1. Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol. 2001;19(2):343-53.
2. Rugo HS, et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol. 2016; 34(25):3069-103.

#### Ovarian function suppression (OFS), tamoxifen

1. Taylor CW, Green S, Dalton WS, et al: Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol 1998;16:994-999.
2. Osborne CK: Tamoxifen in the treatment of breast cancer. N Engl J Med 1998;339
3. Crump M, Sawka CA, DeBoer G, et al: An individual patient-based meta-analysis of tamoxifen versus ovarian ablation as first line endocrine therapy for premenopausal women with metastatic breast cancer. Breast Cancer Res Treat 1997;44:201-210.

#### GnRHa plus AI (first or second line)


1. Forward DP, Cheung KL, Jackson L, et al. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. Br J Cancer. 2004 ;90(3):590-4.



2. Park IH, Ro J, Lee KS, et al. Phase II parallel group study showing comparable efficacy between premenopausal metastatic breast cancer patients treated with letrozole plus goserelin and postmenopausal patients treated with letrozole alone as first-line hormone therapy. J Clin Oncol. 2010;28(16):2705-11.
3. Carlson RW, et al. Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of the breast in premenopausal women. J Clin Oncol. 2010;28(25):3917-21.

#### GnRHa plus fulvestrant

1. Bartsch R, Bago-Horvath Z, et al. Ovarian function suppression and fulvestrant as endocrine therapy in premenopausal women with metastatic breast cancer. European Journal of Cancer 48: 1932–1938, 2012.
2. Turner M et al. Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer. N Engl J Med 2015; 373:209-219
3. Loibl S, et al. Palbociclib Combined with Fulvestrant in Premenopausal Women with Advanced Breast Cancer and Prior Progression on Endocrine Therapy: PALOMA-3 Results. Oncologist. 2017;22(9):1028-1038.



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

	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.

### Fulvestrant 500 mg (vs. anastrozole)

1. Ellis MJ, et al. Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. J Clin Oncol. 2015;33(32):3781-7
2. Robertson JF, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet. 2016 ;388(10063):2997-3005.

### Fulvestrant 500 mg >> 250 mg

1. Di Leo A, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst. 2014;106(1):djt337.

### Aromatase inhibitors (3rd generation)\*

1. Bonnetterre J, et al: Anastrozole versus Tamoxifen as First-Line Therapy for Advanced Breast Cancer in 668 Postmenopausal Women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and tolerability Study. J Clin Oncol 2000;18:3748-3757

2. Thürlimann B, et al: Anastrozole (Arimidex) versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind cross-over SAKK trial 21/95 – a substudy of the TARGET (Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability) trial. Breast Cancer Res Treat 2004;85:247-254

#### Aromatase inhibitors (3rd generation) (>non-AI)

1. Bonnetterre, J, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92
2. Mouridsen, H, et al, Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group Journal of Clinical Oncology. J Clin Oncol. 2003;21(11):2101-9.
3. Paridaens R, et al; European Organization for the Research and Treatment of Cancer (EORTC)- Investigational Drug Branch for Breast Cancer (IDBBC). Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. Ann Oncol. 2003 Sep;14(9):1391-8.
4. Gibson L, Lawrence D, Dawson C, et al. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev. 2009;(4):CD003370.
5. Xu HB, Liu YJ, Li L. Aromatase inhibitor versus tamoxifen in postmenopausal woman with advanced breast cancer: a literature-based meta-analysis. Clin Breast Cancer. 2011;11(4):246-51.
6. Rugo HS, et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol. 2016 ;34(25):3069-103.
7. Sini V, et al. Endocrine therapy in post-menopausal women with metastatic breast cancer: From literature and guidelines to clinical practice. Crit Rev Oncol Hematol. 2016;100:57-68.

Endocrine-Based Treatment Options for Postmenopausal Patients with HER2-Negative Metastatic Breast Cancer			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>CDK4/6-Inhibitor (Abemaciclib, Palbociclib, Ribociclib) <ul style="list-style-type: none"> <li>+ non-steroidal AI</li> <li>+ Fulvestrant</li> </ul> </li> <li>Abemaciclib Monotherapie</li> <li>Alpelisib + Fulvestrant (PIK3CA mutated)</li> <li>Everolimus <ul style="list-style-type: none"> <li>+ Exemestane</li> <li>+ Tamoxifen</li> <li>+ Letrozole</li> <li>+ Fulvestrant</li> </ul> </li> <li>CDK4/6i beyond progression</li> <li>CDK4/6i switch based on toxicity</li> </ul>	 1b 1b 3 1b  1b 2b 2b 2b <sup>a</sup> 5 5	 B B C B  A B B B D D	 ++ ++ +/- +  + + +/- + - +/-

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### CDK4/6 metaanalysis

1. Gao JJ, Cheng J, Bloomquist E, et al. CDK4/6 inhibitor treatment for patients with hormone receptor-positive, HER2-negative, advanced or metastatic breast cancer: a US Food and Drug Administration pooled analysis. Lancet Oncol. 2019 Dec 16. pii: S1470-2045(19)30804-6. doi: 10.1016/S1470-2045(19)30804-6. [Epub ahead of print] PMID: 31859246
2. Wang L, Gao S, Li D, et al. CDK4/6 inhibitors plus endocrine therapy improve overall survival in advanced HR+/HER2- breast cancer: A meta-analysis of randomized controlled trials. Breast J. 2019 Dec 11. doi: 10.1111/tbj.13703. [Epub ahead of print] No abstract available. PMID: 31828901

### CDK4/6 inhibitor management

1. Thill M, Schmidt M. Management of adverse events during cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based treatment in breast cancer. Ther Adv Med Oncol. 2018 Sep 3;10:1758835918793326. doi: 10.1177/1758835918793326. eCollection 2018. Review. Erratum in: Ther Adv Med Oncol. 2018 Dec 03;10:1758835918810116. PMID: 30202447

### Letrozole and palbociclib (vs. letrozole alone)

1. Finn RS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016;375(20):1925-1936.
2. Finn RS, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2015;16(1):25-35.
3. Im SA, Mukai H, Park IH, et al. Palbociclib Plus Letrozole as First-Line Therapy in Postmenopausal Asian Women With Metastatic Breast Cancer: Results From the Phase III, Randomized PALOMA-2 Study. J Glob Oncol. 2019 May;5:1-19. doi: 10.1200/JGO.18.00173. PMID:31125276
4. Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. Breast Cancer Res Treat. 2019 Apr;174(3):719-729. doi: 10.1007/s10549-018-05125-4. PMID:30632023

#### Fulvestrant 500 mg plus Palbociclib (vs. Fulvestrant alone)

1. Turner NC, Ro J, André F, et al; PALOMA3 Study Group. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015 Jul 16;373(3):209-19.
2. Turner NC et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer N Engl J Med 2018; 379:1926-1936 DOI: 10.1056/NEJMoa1810527

#### Letrozol plus Ribociclib

1. Hortobagyi GN, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016;375(18):1738-1748.
2. Yardley DA, Hart L, Favret A, et al. Efficacy and Safety of Ribociclib With Letrozole in US Patients Enrolled in the MONALEESA-2 Study. Clin Breast Cancer. 2019 Aug;19(4):268-277.e1. doi: 10.1016/j.clbc.2019.02.007.

#### Fulvestrant plus Ribociclib

1. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018 Aug 20;36(24):2465-2472. doi: 10.1200/JCO.2018.78.9909. PMID:29860922
2. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2019 Dec 11. doi: 10.1056/NEJMoa1911149. [Epub ahead of print]

#### Fulvestrant plus Abemaciclib

1. Sledge GW Jr, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017;35(25):2875-2884.
2. Sledge GW Jr, Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol. 2019 Sep 29. doi: 10.1001/jamaoncol.2019.4782. [Epub ahead of print] PMID:31563959

#### Non-steroidal AI plus Abemaciclib

1. Goetz MP, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol. 2017 ;35(32):3638-3646.
2. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019 Jan 17;5:5. doi: 10.1038/s41523-018-0097-z. eCollection 2019. PMID:30675515

#### CDK4/6i metaanalysis

1. Petrelli F, Ghidini A, Pedersini R, et al. Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials. Breast Cancer Res Treat. 2019 Apr;174(3):597-604. doi:

10.1007/s10549-019-05133-y. PMID:30659432

2. Rossi V, Berchialla P, Giannarelli D, et al. Should All Patients With HR-Positive HER2-Negative Metastatic Breast Cancer Receive CDK 4/6 Inhibitor As First-Line Based Therapy? A Network Meta-Analysis of Data from the PALOMA 2, MONALEESA 2, MONALEESA 7, MONARCH 3, FALCON, SWOG and FACT Trials. *Cancers (Basel)*. 2019 Oct 26;11(11). pii: E1661. doi: 10.3390/cancers11111661.

#### CDK4/6i after CDK4/6i

1. Wander SA, Zangardi M, Niemierko A et al. A multicenter analysis of abemaciclib after progression on palbociclib in patients (pts) with hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC). DOI: 10.1200/JCO.2019.37.15\_suppl.1057, JCO 37

#### Exemestane and everolimus (vs. exemestane alone)

1. Baselga J, Campone M et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*;366(6):520-9. 2012
2. Jerusalem G, et al. Safety of everolimus plus exemestane in patients with hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer progressing on prior non-steroidal aromatase inhibitors: primary results of a phase IIIb, open-label, single-arm, expanded-access multicenter trial (BALLET). *Ann Oncol*. 2016;27(9):1719-25

#### Tamoxifen and everolimus

1. Bachelot T, et al. Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study. *J Clin Oncol* 2012; 30: 2718-2724.

#### Fulvestrant and everolimus

1. Kornblum NS, et al. PrECOG 0102: A randomized, double-blind, phase II trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC) resistant to aromatase

inhibitor (AI) therapy. SABCS 2016,#S1-02



#### Letrozole and everolimus

1. Gradishar WJ, et al. BOLERO-4: Multicenter, open-label, phase II study of everolimus plus letrozole as first-line therapy in ER+, HER2-metastatic breast cancer. J Clin Oncol 31, 2013 (suppl; abstr TPS661)

#### Abemaciclib Monotherapy

1. Dickler MN, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR<sup>+</sup>/HER2<sup>-</sup> Metastatic Breast Cancer. Clin Cancer Res. 2017;23(17):5218-5224.




Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer in Combination with Bevacizumab			
	Oxford		
	LoE	GR	AGO
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<div> <div>  <p>© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.  Guidelines Breast Version 2020.1</p> <p>www.ago-online.de</p> <p>FORSCHEN LEHREN HEILEN</p> </div> <div> <p>■ <b>Bevacizumab plus endocrine treatment as first line therapy for advanced disease</b></p> </div> </div>	1b	B	+/-

### Maintenance of bevacizumab plus endocrine therapy

1. Tredan O, et al. A phase III trial of exemestane plus bevacizumab maintenance therapy in patients with metastatic breast cancer after first-line taxane and bevacizumab: a GINECO group study. Ann Oncol 2016; 27(6):1020–1029.

### Bevacizumab plus endocrine treatment as first line

1. Martín M, Loibl S, et al. Bevacizumab plus endocrine treatment as first line therapy for advanced diseasePhase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer: the letrozole/fulvestrant and avastin (LEA) study. J Clin Oncol. 2015 ;33(9):1045-52.
2. Dickler MN, et al. Phase III Trial Evaluating Letrozole As First-Line Endocrine Therapy With or Without Bevacizumab for the Treatment of Postmenopausal Women With Hormone Receptor-Positive Advanced-Stage Breast Cancer: CALGB 40503 (Alliance). J Clin Oncol. 2016;34(22):2602-9.



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

Oxford		
LoE	GR	AGO
1b	A	++

Oxford		
LoE	GR	AGO
1b	B	+

- **Olaparib**
  
- **Talazoparib**

### Olaparib

1. Robson M, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-533.
2. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. 2019 Apr 1;30(4):558-566. doi: 10.1093/annonc/mdz012. PMID:30689707
3. Robson M, Ruddy KJ, Im SA, et al. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial. Eur J Cancer. 2019 Oct;120:20-30. doi: 10.1016/j.ejca.2019.06.023. PMID:31446213


### Talazoparib

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# Diagnosis and Treatment of Patients with early and advanced Breast Cancer

## HER2-Positive and HR-Positive Metastatic Breast Cancer



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

	Oxford		
	LoE	GR	AGO
■ Anastrozole plus trastuzumab	1b	B	+/-
■ Letrozole plus trastuzumab	2b	B	+/-
■ Letrozole plus lapatinib	1b	B	+/-
■ Fulvestrant plus lapatinib	1b	B	+/-
■ Abemaciclib plus fulvestrant plus trastuzumab (after T-DM1)	2b <sup>a</sup>	B	+/-
■ Aromatase inhibitors plus 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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#### AI and trastuzumab/pertuzumab

1. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al.; PERTAIN Study Group. First-Line Trastuzumab Plus an Aromatase Inhibitor, With or Without Pertuzumab, in Human Epidermal Growth Factor Receptor 2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. J Clin Oncol. 2018 Oct 1;36(28):2826-2835. doi: 10.1200/JCO.2017.76.7863. PMID:30106636

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Concomitant or Sequential Endocrine-Cytostatic Treatment			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> <li>Concomitant endocrine-cytotoxic treatment           <ul style="list-style-type: none"> <li>May increase response rate and progression free interval but not overall survival</li> <li>May increase toxicity</li> </ul> </li> <li>Endocrine maintenance therapy after chemotherapy +/- anti-HER2 therapy-induced response +/- anti HER2 therapy           <ul style="list-style-type: none"> <li>Increases progression free interval</li> </ul> </li> </ul>	1b	A	-
	2b	B	+



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