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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Endokrine und zielgerichtete Therapie des metastasierten Mammakarzinoms



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Endokrine Therapie des metastasierten Mammakarzinoms

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Endokrine Therapie des metastasierten Mammakarzinoms


Indikation

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

Die endokrin-basierte Therapie ist die erste Therapie-option in der Behandlung des metastasierten hormonrezeptor-positiven (oder - unbekannten) Mammakarzinoms

- Ausnahme: drohender Organausfall
- Cave: Der HR-Status kann sich im Laufe der Erkrankung verändern. Falls möglich, sollte eine Histologie aus einer der neuen Metastasen gewonnen werden

1. Wilcken N, Hornbuckle J, Gherzi 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)[†]. Ann Oncol. 2018 ;29(8):1634-1657. doi: 10.1093/annonc/mdy192. No abstract available. PMID: 30032243



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Vergleich ER/PR und HER2 Metastase vs. Primärtumor (N=5.521)

**Metaanalyse basierend auf 39 (überwiegend retrospektiven) Analysen
ausschließlich Vergleich Primärtumor – Metastase (keine Lymphknoten):**

Gepoolte relative Diskordanz:

- 19,3% (95% CI 1/4 15.8% to 23.4%) für ER
- 30,9% (95% CI 1/4 26.6% to 35.6%) für PR
- 10,3% (95% CI 1/4 7.8% to 13.6%) für HER2

Wechsel der gepoolten Rezeptorexpression von positiv zu negativ

- 22.5% (95% CI = 16.4% to 30.0%) für ER
- 49.4% (95% CI = 40.5% to 58.2%) für PR
- 21.3% (95% CI = 14.3% to 30.5%) für HER2

Wechsel der gepoolten Rezeptorexpression von negativ zu positiv

- 21.5% (95% CI = 18.1% to 25.5%) für ER
- 15.9% (95% CI = 11.3% to 22.0%) für PR
- 9.5% (95% CI = 7.4% to 12.1%) für 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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Endokrine Therapie

Allgemeine Überlegungen

- Therapieentscheidungen aller Behandlungslinien sollten die Vortherapien, Alter und Komorbiditäten sowie den jeweiligen Zulassungsstatus berücksichtigen.
- Eine prämenopausale Patientin unter GnRH-A-Therapie oder nach Ovariectomie kann analog zur postmenopausalen Patientin behandelt werden.

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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Endokrine Therapie der prämenopausalen Patientin mit HER2-negativem metastasiertem Mammakarzinom

Oxford

	LoE	GR	AGO
▪ GnRH-A + Fulvestrant + Palbociclib	2b	B	++
▪ GnRH-A + AI + Palbociclib*	3b ^a	C	++
▪ GnRH-A + AI + Ribociclib	1b	B	++
▪ GnRH-A + Fulvestrant + Abemaciclib	2b	B	++
▪ GnRH-A + Tamoxifen (vs. OFS od. Tam)	1a	A	++
▪ Unterdrückung der Ovarialfunktion (OFS)	2b	B	+
▪ Tamoxifen	2b	B	+
▪ GnRH-A + AI (first + second line)	2b	B	+
▪ GnRH-A + Fulvestrant	1b	B	+
▪ Aromataseinhibitoren ohne OFS	3	D	--

* Extrapoliert aus Daten postmenopausaler Patientinnen (mit 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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Endokrine Mono-Therapie der postmenopausalen Patientin mit HER2-negativem, metastasiertem Mammakarzinom

	Oxford		
	LoE	GR	AGO
▪ Fulvestrant 500 mg	1b	B	+
▪ Aromataseinhibitor*	1a	A	+
▪ Tamoxifen	1a	A	+
▪ Fulvestrant 250 mg + Anastrozol	1b	B	+/-
▪ Frühere Behandlungslinien wiederholen	5	D	+/-

* Keine Hinweise für die Überlegenheit eines einzelnen Aromataseinhibitors.
Um eine spätere Therapie nach Zulassungsstatus mit Everolimus zu ermöglichen, sollte in der Erstlinientherapie bevorzugt ein nicht-steroidaler AI eingesetzt werden.

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.

Endokrin-basierte Therapie der postmenopausalen Patientin mit HER2-negativem metastasiertem Mammakarzinom			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> CDK4/6-Inhibitor (Abemaciclib, Palbociclib, Ribociclib) <ul style="list-style-type: none"> + nicht-steroidaler AI + Fulvestrant Abemaciclib Monotherapie Alpelisib + Fulvestrant (bei PIK3CA Mutation) Everolimus <ul style="list-style-type: none"> + Exemestan + Tamoxifen + Letrozol + Fulvestrant CDK4/6i beyond progression CDK4/6i-Wechsel aufgrund Toxizität 	1b 1b 3 1b 1b 2b 2b 2b ^a 5 5	B B C B A B B B D D	++ ++ +/- + + + +/- + - +/-

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CDK4/6 metaanalysis

- 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
- 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

- 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⁺/HER2⁻ Metastatic Breast Cancer. Clin Cancer Res. 2017;23(17):5218-5224.

Endokrine Therapie der postmenopausalen Patientin mit HER2-negativem metastasiertem Mammakarzinom in Kombination mit Bevacizumab			
	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> Erhaltungstherapie mit Bevacizumab plus endokrine Therapie nach Remission unter Chemotherapie mit Bevacizumab 	1b	B	+/-
<ul style="list-style-type: none"> Bevacizumab plus endokrine Therapie als Erstlinientherapie bei lokal fortgeschrittener oder metastasierter Erkrankung 	1b	B	+/-



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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-Inhibitoren beim HER2-negativen, gBRCA mutierten, metastasiertem Mammakarzinom

- **Olaparib**

- **Talazoparib**

Oxford		
LoE	GR	AGO
1b	A	++

Oxford		
LoE	GR	AGO
1b	B	+

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.
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Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

HER2-positives und HR-positives metastasiertes Mammakarzinom



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Endokrine Therapie der postmenopausalen HER2-positiven metastasierten Mammakarzinompatientin

	Oxford		
	LoE	GR	AGO
▪ Anastrozol und Trastuzumab	1b	B	+/-
▪ Letrozol und Trastuzumab	2b	B	+/-
▪ Letrozol und Lapatinib	1b	B	+/-
▪ Fulvestrant und Lapatinib	1b	B	+/-
▪ Abemaciclib + Fulvestrant und Trastuzumab (nach T-DM1)	2b ^a	B	+/-
▪ Aromataseinhibitor und Trastuzumab / Pertuzumab*	2b	B	+/-

Geringe Wirksamkeit einer alleinigen endokrinen Therapie.
Eine Induktions-Chemotherapie zusammen mit einer anti-HER2-Therapie (gefolgt von endokriner plus anti-HER2-Erhaltungstherapie) sollte in Erwägung gezogen werden!

* Studienteilnahme empfohlen

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AI and trastuzumab/pertuzumab

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Simultane oder sequenzielle endokrin-zytostatische Behandlung

	Oxford		
	LoE	GR	AGO
<ul style="list-style-type: none"> ■ Simultane endokrin-zytotoxische Therapie <ul style="list-style-type: none"> ■ Höhere Ansprechraten und progressionsfreies ÜL möglich, keine Verbesserung des Gesamtüberlebens ■ Kann Nebenwirkungsrate/Toxizität erhöhen ■ Endokrine Erhaltungstherapie +/- Anti HER2 Therapie nach Ansprechen auf eine Chemotherapie +/- Anti-HER2 Therapie <ul style="list-style-type: none"> ■ Verlängert das progressionsfreie Überleben 	1b	A	-
	2b	B	+

Concomitant endocrine-cytotoxic treatment

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