Guidelines Breast
Version 2023.1D

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# Endokrin-basierte und zielgerichtete Therapie des metastasierten Mammakarzinoms

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Version 2023.1D



# Endokrin-basierte und zielgerichtete Therapie des metastasierten Mammakarzinoms

- **Versionen 2002–2022:**
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# Endokrin-basierte und zielgerichtete Therapie des metastasierten Mammakarzinoms

**Indikation**

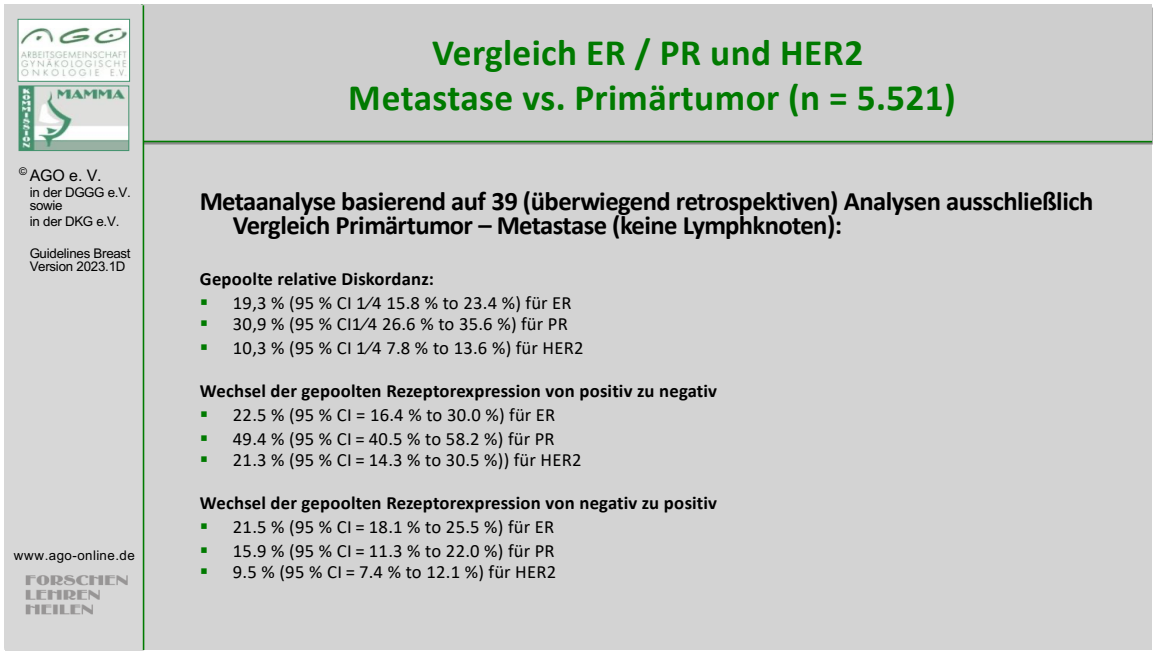
**Oxford LoE: 1a** **GR: A** **AGO: ++**

**Die endokrin-basierte Therapie ist die erste Therapieoption in der Behandlung des metastasierten hormonrezeptor-positiven HER2-negativen Mammakarzinoms**

**Auch drohender Organausfall und/oder symptomatische viszerale Metastasierung stellen nicht zwingend eine Indikation zur Chemotherapie dar und eine endokrin-basierte Therapie kann bei endokrin-sensitiver Erkrankung individuell eingesetzt werden.**

- **Cave: Der Rezeptor-Status kann sich im Laufe der Erkrankung verändern. Falls möglich, sollte dieser an einer Metastase erneut bestimmt werden.**

1. Lu YS, Mahidin EIBN, Azim H. Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy. SABCS 2022; GS1-10.
2. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
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. Mouabbi JA, Osborne CK, Schiff R, et al. Management of hormone receptor-positive, human epidermal growth factor 2-negative metastatic breast cancer. Breast Cancer Res Treat. 2021 Nov;190(2):189-201. doi: 10.1007/s10549-021-06383-5. Epub 2021 Sep 13. PMID: 34515904.
5. Wilcken N, Hornbuckle J, Ghersi D Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev. 2003;(2):CD002747.
6. Lu YS, Bin Mohd Mahidin EI, Azim H, Eralp Y, Yap YS, Im SA, Rihani J, Bowles J, Delgar Alfaro T, Wu J, Gao M, Slimane K, El Saghir N. Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy




<u>Meta-analysis:</u>

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

# Endokrine Therapie
# Gute klinische Praxis - GKP

- **Therapieentscheidungen aller Behandlungslinien sollten die Vortherapien, Alter und Komorbiditäten sowie den jeweiligen Zulassungsstatus berücksichtigen.**
- **Eine prämenopausale Patientin unter GnRHa-Therapie oder nach Ovarektomie kann analog zur postmenopausalen Patientin behandelt werden.**
- **In dem vorliegenden Kapitel beziehen sich die Empfehlungen auf prä- und postmenopausale Frauen, es sei denn, der Menopausenstatus wird explizit erwähnt (bei prämenopausalen Patientinnen erfolgt i.d.R. die Kombination mit GnRH-Agonisten).**

1. Burstein HJ, Somerfield MR, Barton DL et al. Endocrine Treatment and Targeted Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 39:3959-3977. 2021
2. Cardoso F, Paluch-Shimon S, Senkus E, et al. (2020) 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 31:1623–1649. https://doi.org/10.1016/j.annonc.2020.09.010
3. 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.

# Endokrine Resistenz beim metastasierten Mammakarzinom

**Primäre endokrine Resistenz:**

- **Rezidiv innerhalb der ersten zwei Jahre unter einer adjuvanten endokrinen Therapie (ETx)**
- **Progress innerhalb der ersten 6 Monate unter einer laufenden endokrinen first-line-Therapie beim metastasierten Mammakarzinom**

**Sekundäre (erworbene) endokrine Resistenz:**

- **Rezidiv unter einer adjuvanten ETx, aber erst nach den ersten 2 Jahren oder innerhalb 12 Monate nach abgeschlossener adjuvanter ETx**
- **Progression ≥ 6 Monate nach Initiierung einer ETx in der metastasierten Situation**

International consensus

1. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010

## Endokrine Therapie der prämenopausalen Patientin mit HER2-negativem, metastasierten Mammakarzinom

| | 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 | + |
| ▪ Aromataseinhibitoren ohne OFS | 3 | D | - - |

Guidelines

1. Burstein HJ, Somerfield MR, Barton DL, et al. (2021) Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 39:3959–3977. https://doi.org/10.1200/JCO.21.0139
2. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010

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.
3. Finn RS et al: Treatment effect of palbociclib plus endocrine therapy by prognostic and intrinsic subtype and biomarker analysis in patients with bone-only disease: a joint analysis of PALOMA-2 and PALOMA-3 clinical trials. Breast Cancer Res Treat 2020 Nov;184(1):23-35. doi: 10.1007/s10549-020-05782-4. Epub 2020 Aug 11.

GnRHa plus AI plus ribociclib

1. Tripathy D, Im SA, Colleoni M et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018 Jul;19(7):904-915. doi: 10.1016/S1470-2045(18)30292-4. Epub 2018 May 24. PMID: 29804902.
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

GnRHa plus AI plus palbociclib

1. DeMichele A, Cristofanilli M, Brufsky A et al. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2- metastatic breast cancer in US real-world clinical practice. Breast Cancer Res. 2021 Mar 24;23(1):37. doi: 10.1186/s13058-021-01409-8. PMID: 33761995; PMCID: PMC7989035.

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
2. Neven P, Rugo HS, Tolaney SM, et al. Abemaciclib plus fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in premenopausal women: subgroup analysis from the MONARCH 2 trial. Breast Cancer Res. 2021;23(1):87. Published 2021 Aug 23. doi:10.1186/s13058-021-01463-2

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


## Endokrin-basierte Therapie mit CDK4/6-Inhibitor der postmenopausalen Patientin mit HER2-negativem, metastasierten Mammakarzinom

| | Oxford LoE | Oxford GR | AGO |
|---|---|---|---|
| **Ribociclib** | | | |
| + nicht-steroidaler AI | 1b | A | ++ |
| + Fulvestrant | 1b | A | ++ |
| **Abemaciclib** | | | |
| + nicht-steroidaler AI | 1b | A | + |
| + Fulvestrant | 1b | A | ++ |
| **Palbociclib** | | | |
| + nicht-steroidaler AI | 1b | A | + |
| + Fulvestrant | 1b | A | + |


Guidelines

1. Burstein HJ, Somerfield MR, Barton DL, et al. (2021) Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 39:3959–3977. https://doi.org/10.1200/JCO.21.0139
2. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010

Meta-analysis CDK4/6 inhibitors

1. Li Y, Li L, Du Q, et al. (2021) Efficacy and Safety of CDK4/6 Inhibitors Combined with Endocrine Therapy in HR+/HER-2- ABC Patients: A Systematic Review and Meta-Analysis. Cancer Invest 39:369–378. https://doi.org/10.1080/07357907.2021.1910705
2. Schettini F, Giudici F, Giuliano M et al. Overall Survival of CDK4/6-Inhibitor–Based Treatments in Clinically Relevant Subgroups of Metastatic Breast Cancer: Systematic Review and Meta-Analysis. JNCI J Natl Cancer Inst (2020) 112(11): djaa071

Endokrin vs. Chemotherapie

1. Giuliano M, Schettini F, Rognoni C, et al. (2019) Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. Lancet Oncol 20:1360–

1369. https://doi.org/10.1016/S1470-2045(19)30420-6

CDK4/6i 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. 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
3. 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.
4. 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. Schmidt M. et al. 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. 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
3. 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

4. DeMichele A, Cristofanilli M, Brufsky A, et al. (2021) Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2- metastatic breast cancer in US real-world clinical practice. Breast Cancer Res 23:37. https://doi.org/10.1186/s13058-021-01409-8
5. Finn RS, Rugo HS, Gelmon KA, Cristofanilli M, et al. (2021) Long-Term Pooled Safety Analysis of Palbociclib in Combination with Endocrine Therapy for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Updated Analysis with up to 5 Years of Follow-Up. Oncologist 26:e749-e755. https://doi.org/10.1002/onco.13684
6. Finn RS, Rugo HS, Dieras VC, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2− ABC): Analyses from PALOMA-2. J Clin Oncol 40, 2022 (suppl 17; abstr LBA1003).
7. Rugo HS, Brufsky A, Liu X, et al. Overall Survival With First-Line Palbociclib Plus an Aromatase Inhibitor (AI) vs AI in Metastatic Breast Cancer: A Large Real-World Database Analysis. European Society for Medical Oncology (ESMO) Breast Cancer, 169P, 2022.

<u>Fulvestrant 500 mg plus Palbociclib (vs. Fulvestrant alone</u>)

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
3. Finn RS, Cristofanilli M, Ettl J, et al.(2020) Treatment effect of palbociclib plus endocrine therapy by prognostic and intrinsic subtype and biomarker analysis in patients with bone-only disease: a joint analysis of PALOMA-2 and PALOMA-3 clinical trials. Breast Cancer Res Treat 184:23–35. https://doi.org/10.1007/s10549-020-05782-4
4. Rugo HS, Cristofanilli M, Loibl S, et al. (2021) Prognostic Factors for Overall Survival in Patients with Hormone Receptor-Positive Advanced Breast Cancer: Analyses From PALOMA-3. Oncologist 26:e1339-e1346. https://doi.org/10.1002/onco.13833
5. Cristofanilli M, Rugo HS, Im SA, Slamon DJ, Harbeck N, Bondarenko I, Masuda N, Colleoni M, DeMichele A, Loi S, Iwata H, O'Leary B, André F, Loibl S, Bananis E, Liu Y, Huang X, Kim S, Lechuga Frean MJ, Turner NC. Overall Survival with Palbociclib and Fulvestrant in Women with HR+/HER2- ABC: Updated Exploratory Analyses of PALOMA-3, a Double-blind, Phase III Randomized Study. Clin Cancer

Res. 2022 Aug 15;28(16):3433-3442. doi: 10.1158/1078-0432.CCR-22-0305

Letrozole plus palbociclib vs. Fulvestrant plus palbociclib

1. Llombart-Cussac A, Pérez-García JM, Bellet Met al. (2021) Fulvestrant-Palbociclib vs Letrozole-Palbociclib as Initial Therapy for Endocrine-Sensitive, Hormone Receptor-Positive, ERBB2-Negative Advanced Breast Cancer: A Randomized Clinical Trial. JAMA Oncol 7:1791–1799. https://doi.org/10.1001/jamaoncol.2021.4301

Letrozol plus Ribociclib (vs. Letrozol alone)

1. 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.
2. Hortobagyi GN, Stemmer SM, Burris HA et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol. 2018 Jul 1;29(7):1541-1547. doi: 10.1093/annonc/mdy155. Erratum in: Ann Oncol. 2019 Nov 1;30(11):1842. PMID: 29718092.
3. Hortobagyi GN, Stemmer SM, Burris HA et al. Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741
4. Tripathy D, Im SA, Colleoni M et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018 Jul;19(7):904-915. doi: 10.1016/S1470-2045(18)30292-4. Epub 2018 May 24. PMID: 29804902.
5. Lu YS, Im SA, Colleoni M et al. Updated Overall Survival of Ribociclib Plus Endocrine Therapy vs Endocrine Therapy Alone in Pre- and Perimenopausal Patients With HR+/HER2- Advanced Breast Cancer in MONALEESA-7: A Phase III Randomized Clinical Trial. Clin Cancer Res. 2021 Dec 29:clincanres.3032.2021. doi: 10.1158/1078-0432.CCR-21-3032. Epub ahead of print. PMID: 34965945.

Fulvestrant plus Ribociclib (vs. Fulvestrant alone)

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]
3. Slamon DJ, Neven P, Chia S, et al. (2021) Ribociclib plus fulvestrant for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase III randomized MONALEESA-3 trial: updated overall survival. Ann Oncol 32:1015–1024. https://doi.org/10.1016/j.annonc.2021.05.353

Biomarker in MONALEESA

1. Prat A, Chaudhury A, Solovieff N, et al. (2021) Correlative Biomarker Analysis of Intrinsic Subtypes and Efficacy Across the MONALEESA Phase III Studies. J Clin Oncol 39:1458–1467. https://doi.org/10.1200/JCO.20.0297

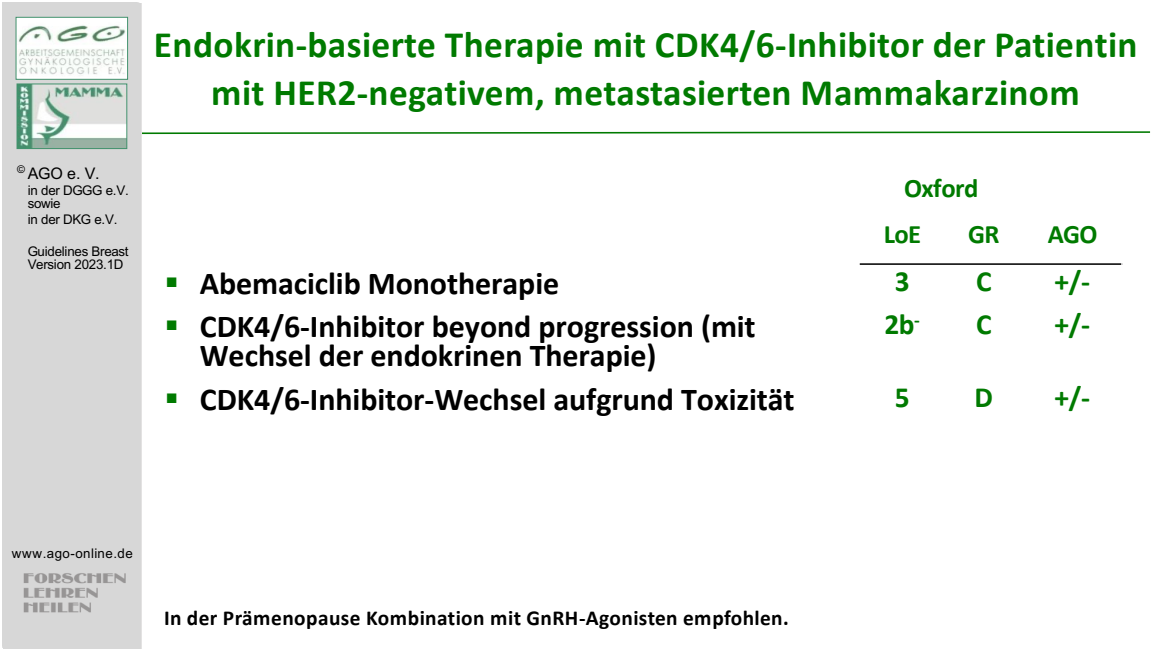
Fulvestrant plus Abemaciclib (vs. Fulvestrant alone)

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 (vs. AI alone)

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
3. Johnston S, O'Shaughnessy J, Martin M, et al. Abemaciclib as initial therapy for advanced breast cancer: MONARCH 3 updated results in prognostic subgroups. NPJ Breast Cancer. 2021 Jun 22;7(1):80. doi: 10.1038/s41523-021-00289-7. PMID: 34158513; PMCID: PMC8219718.
4. Goetz MP, Toi M, Huober J, et al. MONARCH 3: Interim overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor

as initial therapy in patients with HR+, HER2- advanced breast cancer. ESMO, 2022





CDK4/6 inhibitor management

1. Schmidt M. et al. 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

Abemaciclib Monotherapy

1. Dickler MN, Tolaney SM, Rugo HS 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 Sep 1;23(17):5218-5224. doi: 10.1158/1078-0432.CCR-17-0754. Epub 2017 May 22. Erratum in: Clin Cancer Res. 2018 Nov 1;24(21):5485. PMID: 28533223; PMCID: PMC5581697.

CDK4/6i after CDK4/6i

1. Wander SA, Zangardi M, Niemierko A et a. A multicenter analysis of abemaciclib after progression on palbociclib in patients (pts) with hormone receptor-positive (HR+)/HER2- metastatic breast cancer (MBC). J Natl Compr Canc Netw. 2021 Mar 24;1-8. doi: 10.6004/jnccn.2020.7662
2. Kalinsky K, Accordino MK, Chiuzan C, et al. A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after

rporgession on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastastic hormone receptor positive, HER negative breast cancer: MAINTAIN Trial. ASCO, 2022

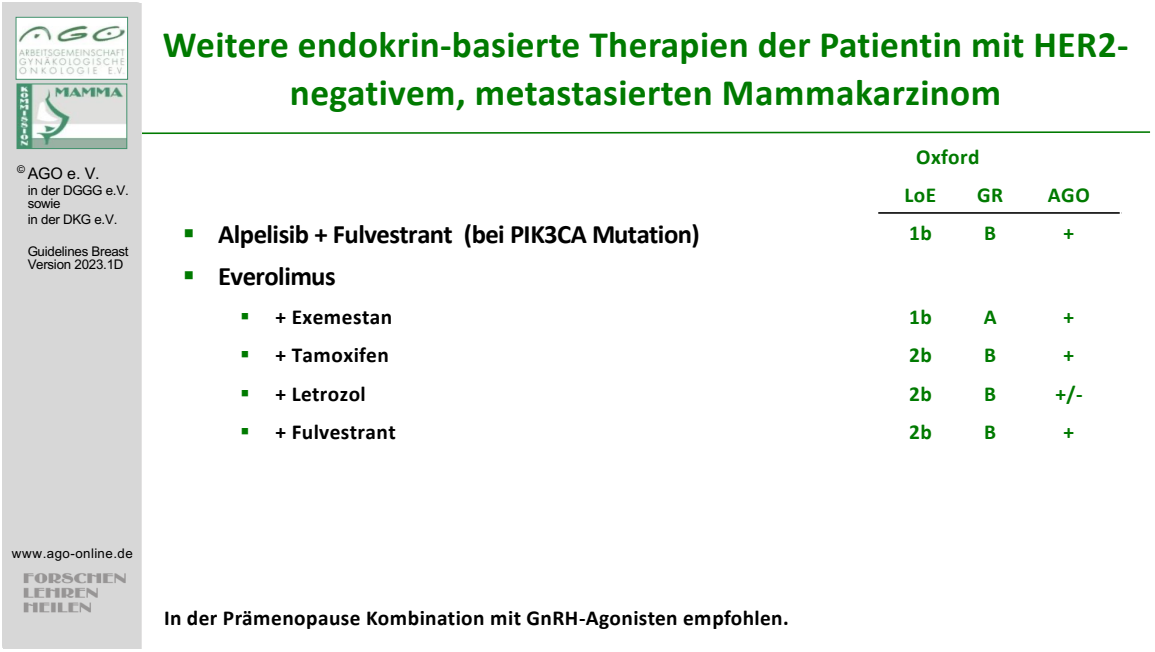
## CDK4/6 Inhibitors in First-line Studies

| 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) | 29.0 vs. 14.8 m (+ 14.2 m) (HR 0.518) | 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.) | 67.1 vs. 54.5 m (+ 12.6 m) (HR 0.754, 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) |

1. 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
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
3. Johnston S, O'Shaughnessy J, Martin M, et al. Abemaciclib as initial therapy for advanced breast cancer: MONARCH 3 updated results in prognostic subgroups. NPJ Breast Cancer. 2021 Jun 22;7(1):80. doi: 10.1038/s41523-021-00289-7. PMID: 34158513; PMCID: PMC8219718.
4. Hortobagyi GN, Stemmer SM, Burris HA et al. Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB). Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741
5. Tripathy D, Im SA, Colleoni M et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018 Jul;19(7):904-915. doi: 10.1016/S1470-2045(18)30292-4. Epub 2018 May 24. PMID: 29804902.
6. Lu YS, Im SA, Colleoni M et al. Updated Overall Survival of Ribociclib Plus Endocrine Therapy vs Endocrine Therapy Alone in Pre-

and Perimenopausal Patients With HR+/HER2- Advanced Breast Cancer in MONALEESA-7: A Phase III Randomized Clinical Trial. Clin Cancer Res. 2021 Dec 29:clincanres.3032.2021. doi: 10.1158/1078-0432.CCR-21-3032. Epub ahead of print. PMID: 34965945.

7. Goetz MP, Toi M, Huober J, et al. MONARCH 3: Interim overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy in patients with HR+, HER2- advanced breast cancer. ESMO, 2022
8. Finn RS, Rugo HS, Dieras VC, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2− ABC): Analyses from PALOMA-2. J Clin Oncol 40, 2022 (suppl 17; abstr LBA1003).




## Weitere endokrin-basierte Therapien der Patientin mit HER2-negativem, metastasierten Mammakarzinom

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ **Alpelisib + Fulvestrant (bei PIK3CA Mutation)** | 1b | B | + |
| ▪ **Everolimus** | | | |
| ▪ **+ Exemestan** | 1b | A | + |
| ▪ **+ Tamoxifen** | 2b | B | + |
| ▪ **+ Letrozol** | 2b | B | +/- |
| ▪ **+ Fulvestrant** | 2b | B | + |

**In der Prämenopause Kombination mit GnRH-Agonisten empfohlen.**


Guidelines

1. Burstein HJ, Somerfield MR, Barton DL, et al. (2021) Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 39:3959–3977. https://doi.org/10.1200/JCO.21.0139
2. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010

Endokrin vs. Chemotherapie

1. Giuliano M, Schettini F, Rognoni C, et al. (2019) Endocrine treatment versus chemotherapy in postmenopausal women with hormone receptor-positive, HER2-negative, metastatic breast cancer: a systematic review and network meta-analysis. Lancet Oncol 20:1360–1369. https://doi.org/10.1016/S1470-2045(19)30420-6

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

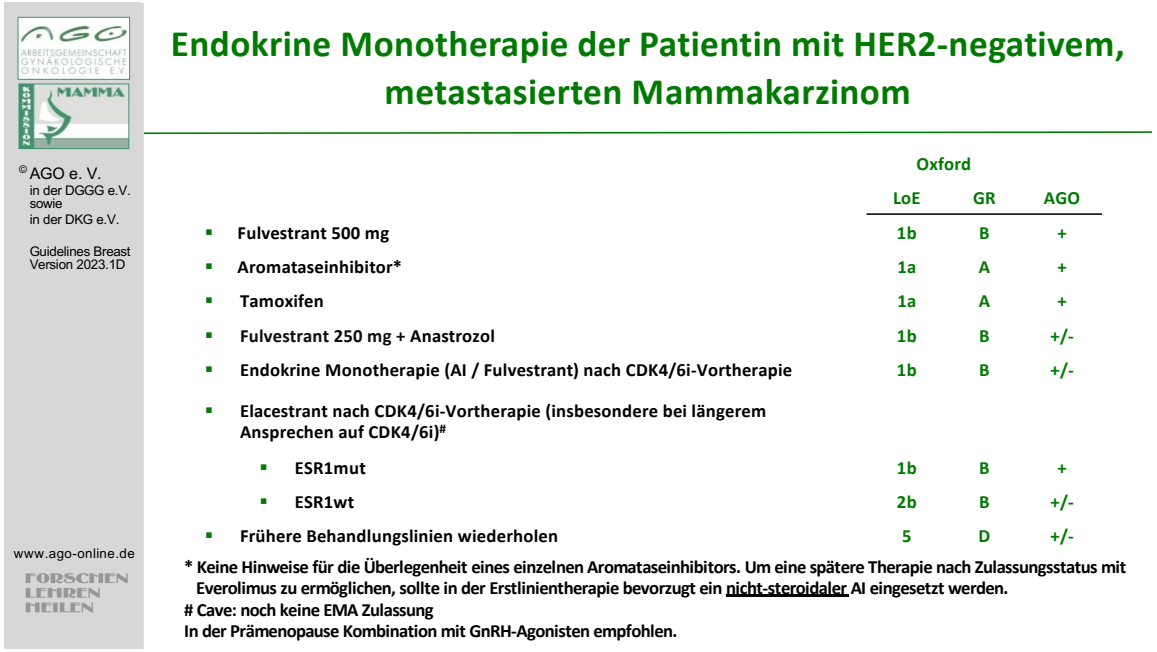
1. Bachelot T, et al. Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study. J Clin Oncol 2012; 30: 2718-2724.

Fulvestrant and everolimus

1. Kornblum N, Zhao F, Manola J, et al. Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102. J Clin Oncol. 2018 Jun 1;36(16):1556-1563. doi: 10.1200/JCO.2017.76.9331. Epub 2018 Apr 17. PMID: 29664714; PMCID: PMC7186582.

Letrozole and everolimus

1. Royce M, Bachelot T, Villanueva C, Özgüroglu M, Azevedo SJ, Cruz FM, Debled M, Hegg R, Toyama T, Falkson C, Jeong J, Srimuninnimit V, Gradishar WJ, Arce C, Ridolfi A, Lin C, Cardoso F. Everolimus Plus Endocrine Therapy for Postmenopausal Women With Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: A Clinical Trial. JAMA Oncol. 2018 Jul 1;4(7):977-984. doi: 10.1001/jamaoncol.2018.0060. PMID: 29566104; PMCID: PMC5885212.




## Endokrine Monotherapie der Patientin mit HER2-negativem, metastasierten Mammakarzinom

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Fulvestrant 500 mg | 1b | B | + |
| ▪ Aromataseinhibitor* | 1a | A | + |
| ▪ Tamoxifen | 1a | A | + |
| ▪ Fulvestrant 250 mg + Anastrozol | 1b | B | +/- |
| ▪ Endokrine Monotherapie (AI / Fulvestrant) nach CDK4/6i-Vortherapie | 1b | B | +/- |
| ▪ Elacestrant nach CDK4/6i-Vortherapie (insbesondere bei längerem Ansprechen auf CDK4/6i)# | | | |
| ▪ ESR1mut | 1b | B | + |
| ▪ ESR1wt | 2b | 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.
# Cave: noch keine EMA Zulassung
In der Prämenopause Kombination mit GnRH-Agonisten empfohlen.


Guidelines

1. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
2. Burstein HJ, Somerfield MR, Barton DL, et al. (2021) Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 39:3959–3977. https://doi.org/10.1200/JCO.21.0139

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. Bonneterre 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. Bonneterre, J, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92
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.
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.

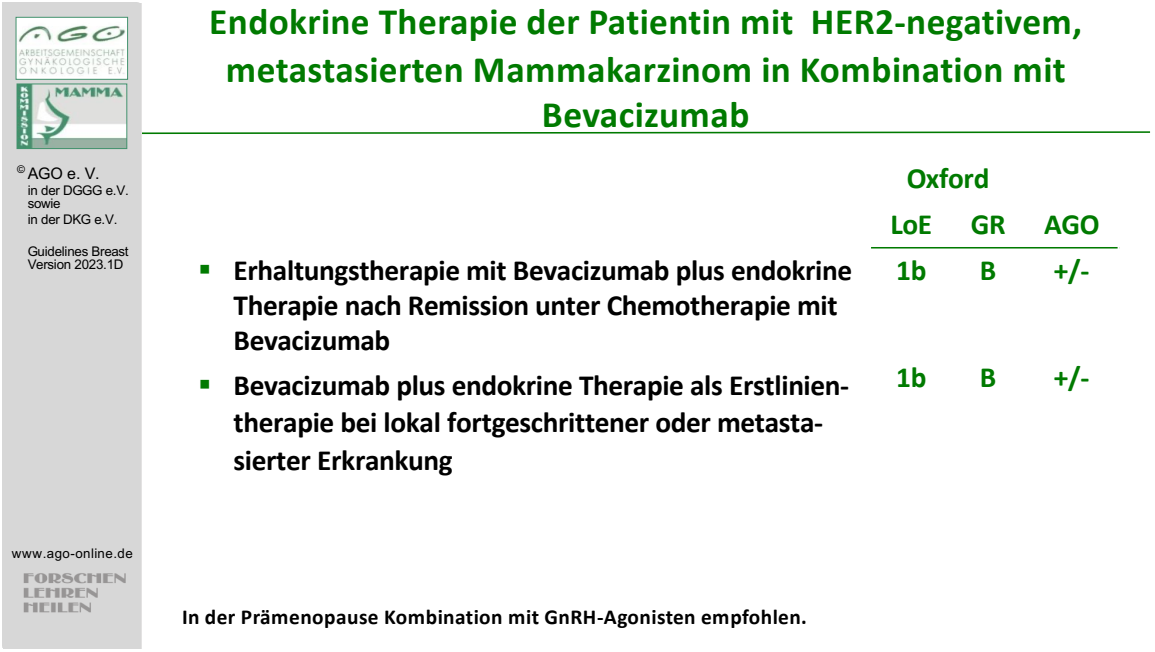
Endokrine Monotherapie (AI/ Fulvestrant) nach CDK4/6-Vortherapie:

1. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the

Randomized Phase III EMERALD Trial. Clin Oncol. 2022 Oct 1;40(28):3246-3256. doi: 10.1200/JCO.22.00338. Epub 2022 May 18.
2. Kalinsky K, Accordino MK, Chiuzan C, et al. A randomized phase II trial of fulvestrant or exemestane with or without ribociclib after rporgession on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition in patients with unresectable or metastastic hormone receptor positive, HER negative breast cancer: MAINTAIN Trial. ASCO, 2022

Elacestrant

1. Bardia A. et al., SABCS, 2021
2. Kaklamani V. et al., SABCS, 2022
3. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. Clin Oncol. 2022 Oct 1;40(28):3246-3256. doi: 10.1200/JCO.22.00338. Epub 2022 May 18.




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.


# PARP-Inhibitoren beim HER2-negativen, g*BRCA* mutierten, metastasierten Mammakarzinom

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ **Olaparib** | 1b | A | ++ |

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ **Talazoparib** | 1b | A | ++ |


Guidelines

1. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
2. Gennari A, Andre F, Barrios CH et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-1495, doi: 10.1016/j.annonc.2021.09.019
3. Miglietta F, Cinquini M, Dieci MV et al. PARP-inhibitors for BRCA1/2-related advanced HER2-negative breast cancer: A meta-analysis and GRADE recommendations by the Italian Association of Medical Oncology. Breast. 2022;66:293-304. doi: 10.1016/j.breast.2022.10.014
4. Burstein HJ, Somerfield MR, Barton DL, et al. (2021) Endocrine Treatment and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 39:3959–3977. https://doi.org/10.1200/JCO.21.0139

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

1. Litton JK, Hurvitz SA, Mina LA et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol. 2020;31(11):1526-1535. doi: 10.1016/j.annonc.2020.08.2098
2. Ettl J, Quek RGW, Lee KH, et al., Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial. Ann Oncol. 2018 Sep 1;29(9):1939-1947. doi: 10.1093/annonc/mdy257. PMID:30124753
3. Hurvitz SA, Gonçalves A, Rugo HS, et al., Talazoparib in Patients with a Germline *BRCA*-Mutated Advanced Breast Cancer: Detailed Safety Analyses from the Phase III EMBRACA Trial. Oncologist. 2020 Mar;25(3):e439-e450. doi: 10.1634/theoncologist.2019-0493. Epub 2019 Nov 25.
4. Litton J. et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med 2018; 379:753-763 DOI: 10.1056/NEJMoa1802905
5. Turner NC, Telli ML, Rugo HS, et al.; ABRAZO Study Group. A Phase II Study of Talazoparib after Platinum or Cytotoxic Nonplatinum Regimens in Patients with Advanced Breast Cancer and Germline *BRCA1/2* Mutations (ABRAZO). Clin Cancer Res. 2019 May 1;25(9):2717-2724. doi: 10.1158/1078-0432.CCR-18-1891. PMID:30563931

Guidelines Breast
Version 2023.1D

FORSCHEN
LEHREN
HEILEN

# HR-positives und HER2-positives metastasiertes Mammakarzinom



Guidelines Breast
Version 2023.1D

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FORSCHEN
LEHREN
HEILEN

# Endokrin-basierte Therapie des HR-positiven HER2-positiven, metastasierten Mammakarzinoms

| | Oxford | | |
|---|---|---|---|
| | LoE | GR | AGO |
| ▪ Abemaciclib + Fulvestrant + Trastuzumab (≥3rd line, nach T-DM1) | 2b | B | + |
| ▪ Aromatase-Inhibitor + Trastuzumab + Pertuzumab | 2b | B | + |
| ▪ Aromatase-Inhibitor + Trastuzumab | 1b | B | +/- |
| ▪ Aromatase-Inhibitor + Lapatinib | 1b | B | +/- |
| ▪ Fulvestrant + Lapatinib | 1b | 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!**
**In der Prämenopause Kombination mit GnRH-Agonisten empfohlen.**

Guidelines

1. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
2. Gennari A, Andre F, Barrios CH et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-1495, doi: 10.1016/j.annonc.2021.09.019
3. Giordano SH, Temin S, Chandarlapaty S, et al. (2018) Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 36:2736–2740. https://doi.org/10.1200/JCO.2018.79.2697

Anastrozole and trastuzumab

1. Kaufman B, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol. 2009 Nov 20;27(33):5529-37.
2. Riemsma R, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). Curr Med Res Opin. 2012 Aug;28(8):1263-79.

Letrozole and trastuzumab


1. Huober J, et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer - results of the eLEcTRA trial. Breast. 2012 ;21(1):27-33.
2. Riemsma R, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). Curr Med Res Opin. 2012 Aug;28(8):1263-79.


Letrozole and lapatinib


1. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol. 2009 Nov 20;27(33):5538-46.
2. Riemsma R, Forbes CA, Amonkar MM, et al. Systematic review of lapatinib in combination with letrozole compared with other first-line treatments for hormone receptor positive(HR+) and HER2+ advanced or metastatic breast cancer(MBC). Curr Med Res Opin. 2012 Aug;28(8):1263-79.


Fulvestrant and lapatinib


1. Burstein HJ, Cirrincione CT, Barry WT et al: Endocrine Therapy With or Without Inhibition of Epidermal Growth Factor Receptor and Human Epidermal Growth Factor Receptor 2: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Fulvestrant With or Without Lapatinib for Postmenopausal Women With Hormone Receptor-Positive Advanced Breast Cancer-CALGB 40302 (Alliance). J Clin Oncol 32:3959-3966 (2014)


Abemaciclib plus Fulvestrant plus Trastuzumab


1. Tolaney SM, Wardley AM, Zambelli S, et al. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial. Lancet Oncol. 2020 Jun;21(6):763-775. doi: 10.1016/S1470-2045(20)30112-1. Epub 2020 Apr 27. Erratum in: Lancet Oncol. 2021 Mar;22(3):e92. Erratum in: Lancet Oncol. 2021 Nov;22(11):e472. PMID: 32353342
2. Tolaney S, Wardley AM, Zambelli S et al., monarcHER: A randomized Phase 2 study of abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with HR+, HER2+ advanced breast cancer (ABC). Ann Oncol 2019, 30 (suppl_5): v851-v934. 10.1093/annonc/mdz394
3. André F, Nadal JC, Denys H et al. Final overall survival (OS) for abemaciclib plus trastuzumab +/- fulvestrant versus trastuzumab plus

chemotherapy in patients with HR+, HER2+ advanced breast cancer (monarcHER): a randomized, open-label, phase 2 trial. ESMO Congress 2022, Abstract 2806 LBA2806

Endocrine therapy 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
2. Arpino G, de la Haba-Rodriguez J, Ferrero JM et al. Final analysis of PERTAIN: A randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of first-line pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in patients with HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer [abstract]. In: Proceedings of the 2020 San Antonio Breast Cancer Virtual Symposium; 2020 Dec 8-11; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2021;81(4 Suppl):Abstract nr PD3-02
3. Janni W, Fehm T, Müller V et al. Omission of chemotherapy in the treatment of HER2-positive and hormone-receptor positive metastatic breast cancer –interim results from the randomized phase 3 DETECT V trial. SABCS 2022 PD 18-07
4. Krause S, Friedl T, Fehm T et al. DETECT V/CHEVENDO – Comparison of dual HER2-targeted therapy with trastuzumab plus pertuzumab in combination with chemo- or endocrine therapy in addition with CDK4/6 inhibition in patients with HER2-positive and hormone-receptor positive metastatic breast cancer. SABCS 2018 Volume 79, Issue 4 Supplement, pp. OT2-07-01

# Simultane oder sequenzielle endokrin-zytostatische Behandlung

| | Oxford LoE | Oxford GR | Oxford AGO |
|---|---|---|---|
| ▪ **Simultane endokrin-zytotoxische Therapie** | 1b | A | - |
| ▪ **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** | 2b | B | + |
| ▪ **Verlängert das progressionsfreie Überleben** | | | |

Guidelines

1. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
2. Giordano SH, Temin S, Chandarlapaty S, et al. (2018) Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 36:2736–2740. https://doi.org/10.1200/JCO.2018.79.2697

Concomitant endocrine-cytotoxic treatment

1. Sledge GW, Hu P, Falkson G, et al. Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic, hormone-sensitive breast cancer: An eastern cooperative oncology group study. J Clin Oncol 18, 262-266, 2000.
2. Partridge AH, Burstein HJ, Winer EP. Side effects of chemotherapy and combined chemohormonal therapy in women with early-stage breast cancer. J Natl Cancer Inst Monogr. 2001;(30):135-42.

Maintenance endocrine therapy after chemotherapy induced response

1. Rossi S, Schinzari G, Basso M, et al. Maintenance hormonal and chemotherapy treatment in metastatic breast cancer: a systematic review. Future Oncol. 2016 May;12(10):1299-307

2. Sutherland S, Miles D, Makris A. Use of maintenance endocrine therapy after chemotherapy in metastatic breast cancer. Eur J Cancer. 2016 Dec;69:216-222.