Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Guidelines Breast
Version 2022.1D

FORSCHEN
LEHREN
HEILEN

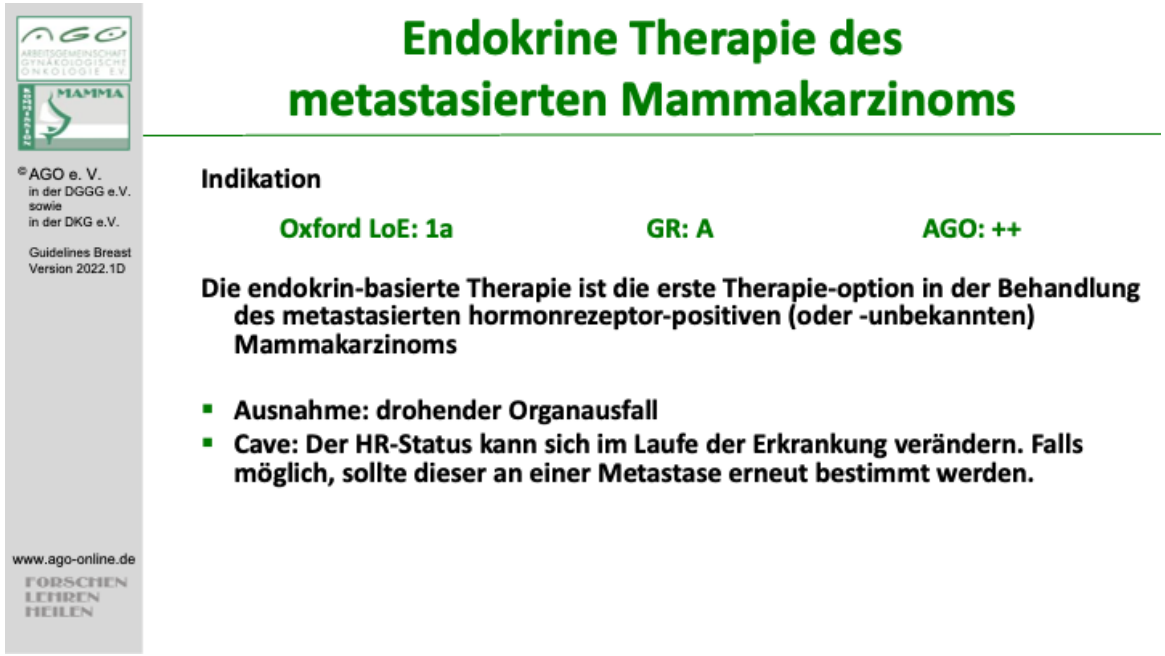
Endokrin-basierte und zielgerichtete Therapie des metastasierten Mammakarzinoms

Endokrine Therapie des metastasierten Mammakarzinoms

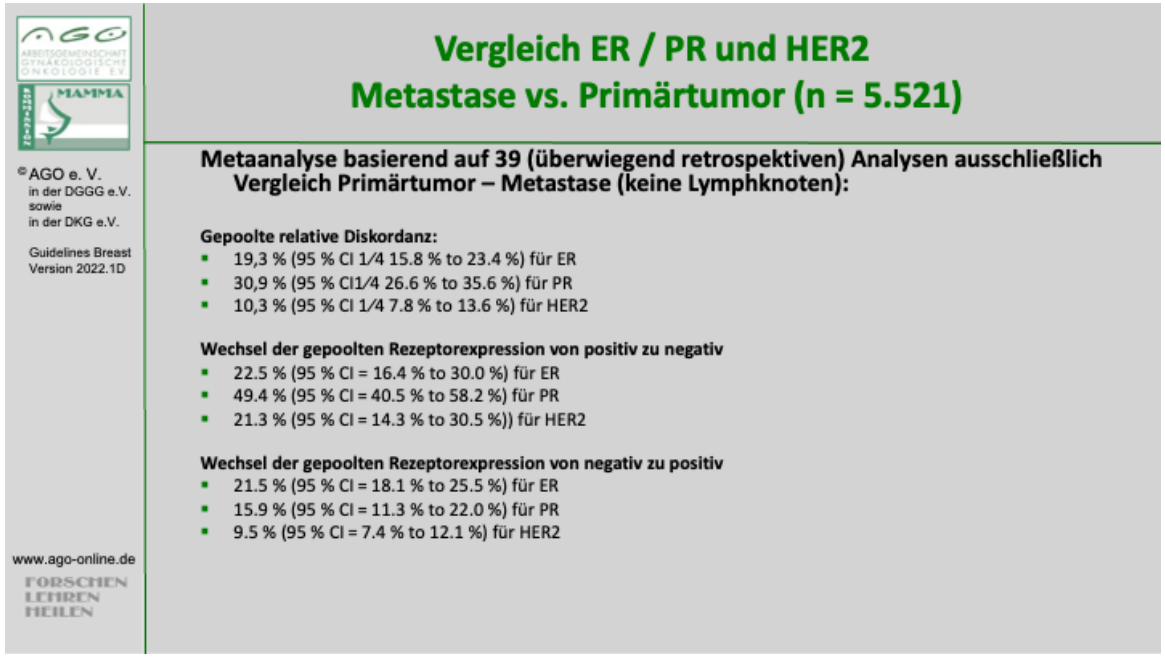
Guidelines Breast
Version 2022.1D

- **Versionen 2002–2021:**
  Albert / Bischoff / Dall / Fasching / Fersis / Friedrich / Gerber / Huober / Janni / Jonat / Kaufmann / Kolberg-Liedtke / Loibl / Lüftner/ Lück / von Minckwitz / Möbus / Müller / Mundhenke / Nitz / Schmidt / Schneeweiß / Schütz / Stickeler / Thill / Untch / Wöckel
- **Version 2022:**
  Schmidt / Witzel

www.ago-online.de
FORSCHEN
LEHREN
HEILEN

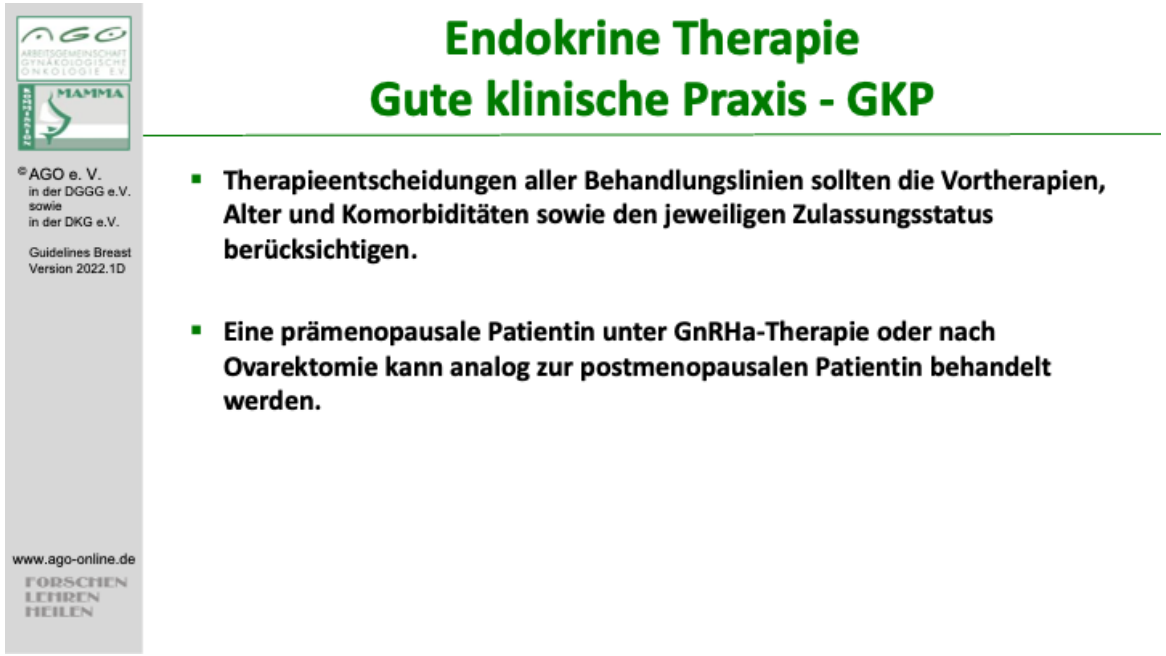


1. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623-1649. doi:10.1016/j.annonc.2020.09.010
2. Lee CI, Goodwin A, Wilcken N. Fulvestrant for hormone-sensitive metastatic breast cancer. Cochrane Database Syst Rev. 2017;1:CD011093. doi:10.1002/14651858.CD011093.pub2.
3. 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.
4. Wilcken N, Hornbuckle J, Ghersi D Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev. 2003;(2):CD002747.

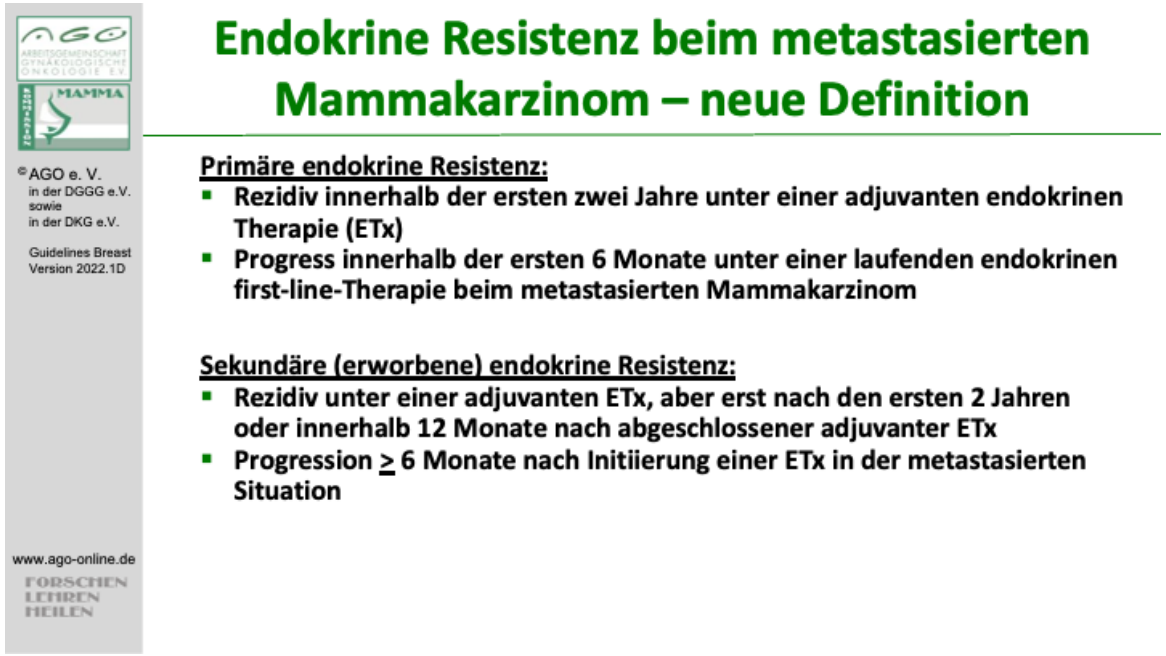


<u>Meta-analysis:</u>

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

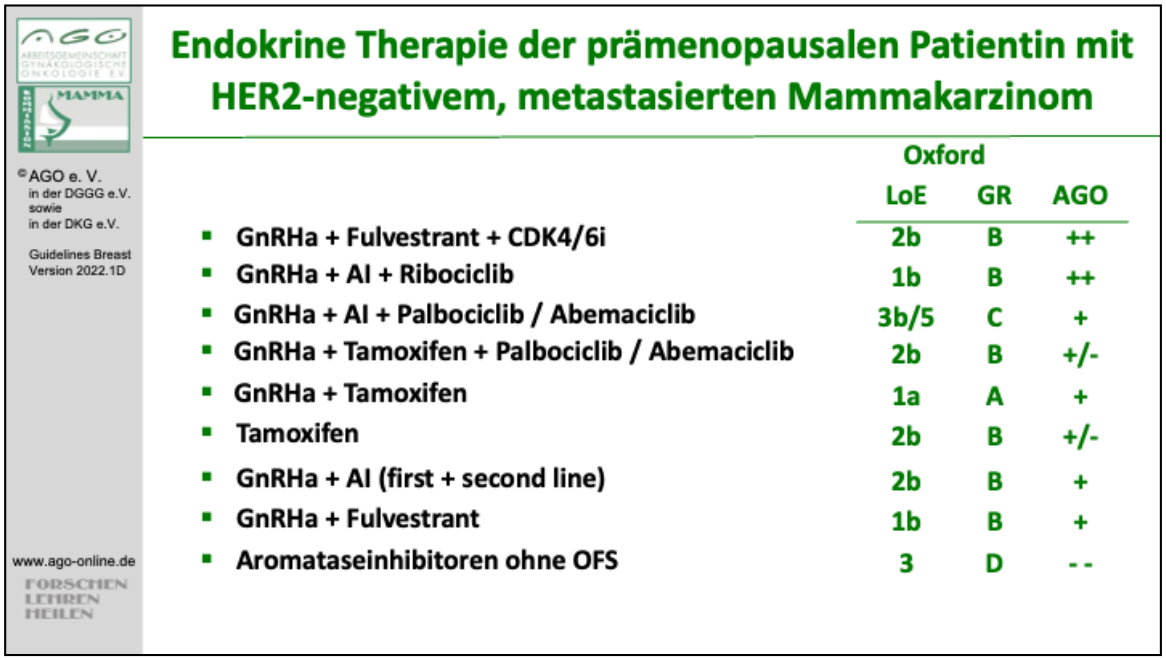


1. Cardoso F, Paluch-Shimon S, Senkus E, et al. (2020) 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 31:1623–1649. https://doi.org/10.1016/j.annonc.2020.09.010
2. Gibson L, Lawrence D, Dawson C, et al. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev. 2009 ;(4):CD003370. doi: 10.1002/14651858.CD003370.pub3.
3. 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.
4. 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.



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



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

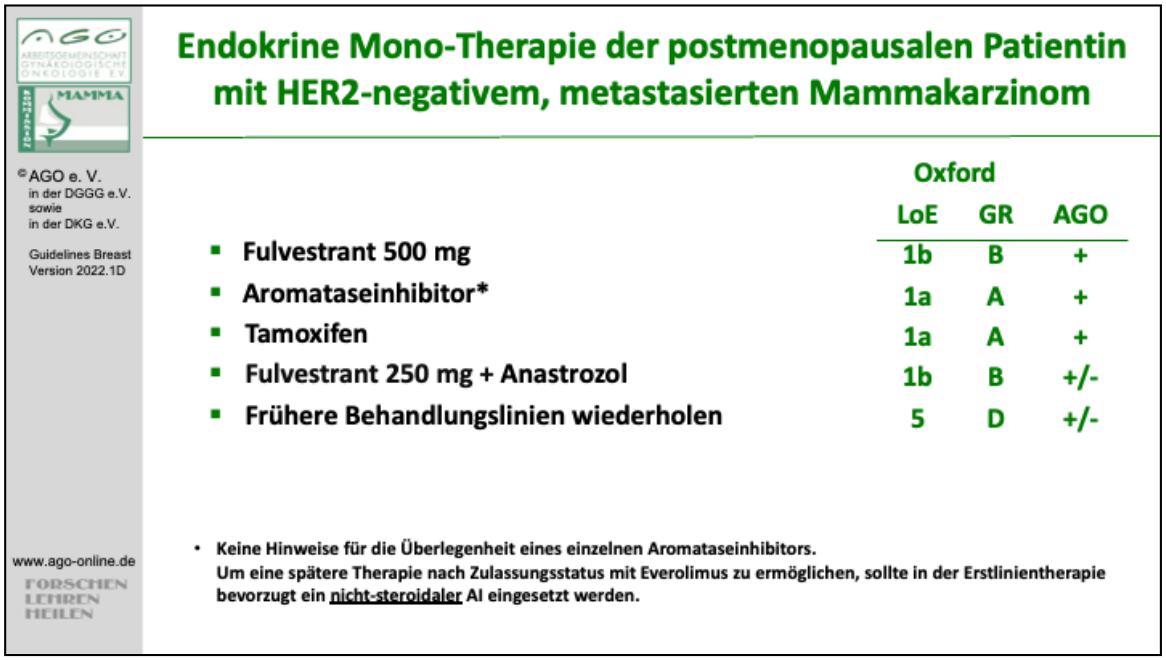
patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol 1998;16:994-999.
2. Osborne CK: Tamoxifen in the treatment of breast cancer. N Engl J Med 1998;339
3. Crump M, Sawka CA, DeBoer G, et al: An individual patient-based meta-analysis of tamoxifen versus ovarian ablation 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



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

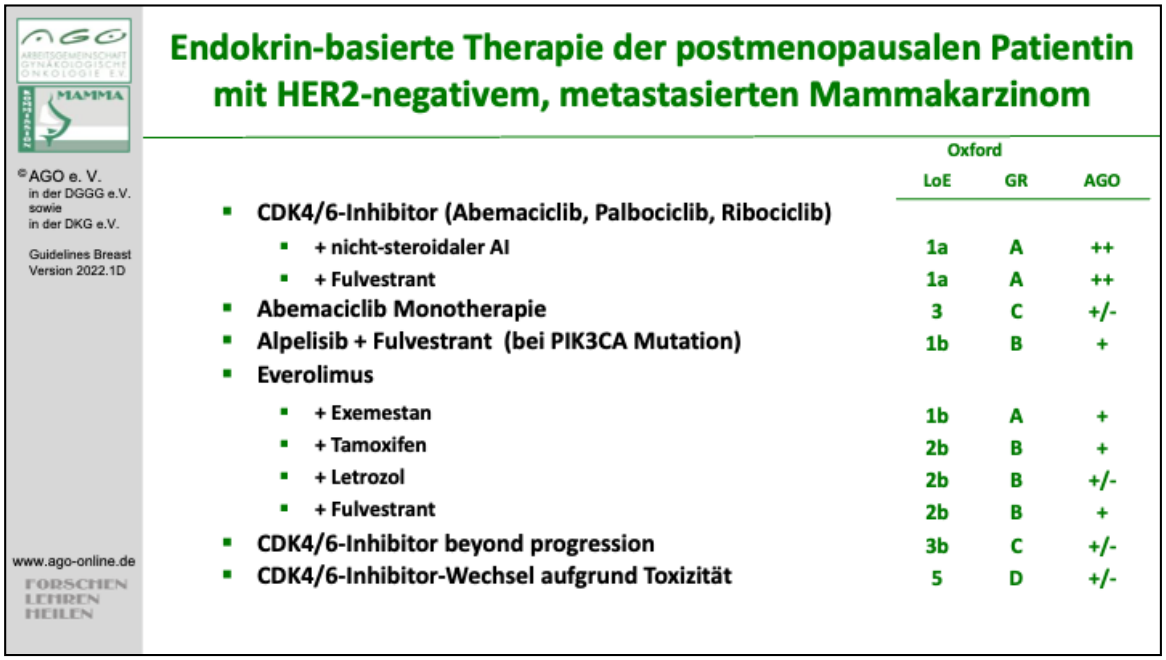
Aromatase inhibitors (3rd generation) (>non-AI)

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.

Estrogentherapie nach Aromatase inhibitors / fortgeschrittene MaCa

1. Ellis MJ et al: Lower-dose vs high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced

breast cancer: a phase 2 randomized study. JAMA . 2009 Aug 19;302(7):774-80. doi: 10.1001/jama.2009.1204.
2. Schmidt, M et al: Tumor suppression, dose-limiting toxicity and wellbeing with the fetal estrogen estetrol in patients with advanced breast cancer. Journal of Cancer Research and Clinical Oncology https://doi.org/10.1007/s00432-020-03472-8



Endokrin-basierte Therapie der postmenopausalen Patientin mit HER2-negativem, metastasierten Mammakarzinom

	Oxford LoE	GR	AGO
▪ CDK4/6-Inhibitor (Abemaciclib, Palbociclib, Ribociclib)			
▪ + nicht-steroidaler AI	1a	A	++
▪ + Fulvestrant	1a	A	++
▪ Abemaciclib Monotherapie	3	C	+/-
▪ Alpelisib + Fulvestrant (bei PIK3CA Mutation)	1b	B	+
▪ Everolimus			
▪ + Exemestan	1b	A	+
▪ + Tamoxifen	2b	B	+
▪ + Letrozol	2b	B	+/-
▪ + Fulvestrant	2b	B	+
▪ CDK4/6-Inhibitor beyond progression	3b	C	+/-
▪ CDK4/6-Inhibitor-Wechsel aufgrund Toxizität	5	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

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

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

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
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

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.

<u>Fulvestrant plus Ribociclib (vs. Fulvestrant alone)</u>

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

<u>Biomarker in MONALEESA</u>

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.

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.

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

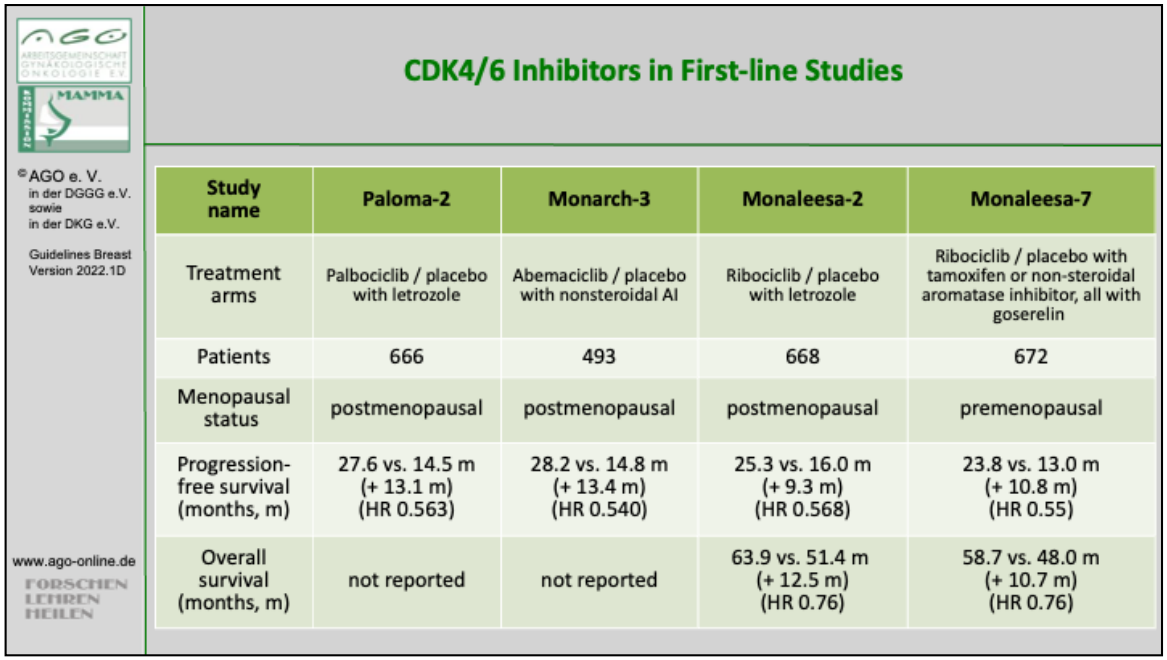
1. Kornblum N, Zhao F, Manola J, et al. Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women With Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102. 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.

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



CDK4/6 Inhibitors in First-line Studies

Study name	Paloma-2	Monarch-3	Monaleesa-2	Monaleesa-7
Treatment arms	Palbociclib / placebo with letrozole	Abemaciclib / placebo with nonsteroidal AI	Ribociclib / placebo with letrozole	Ribociclib / placebo with tamoxifen or non-steroidal aromatase inhibitor, all with goserelin
Patients	666	493	668	672
Menopausal status	postmenopausal	postmenopausal	postmenopausal	premenopausal
Progression-free survival (months, m)	27.6 vs. 14.5 m (+ 13.1 m) (HR 0.563)	28.2 vs. 14.8 m (+ 13.4 m) (HR 0.540)	25.3 vs. 16.0 m (+ 9.3 m) (HR 0.568)	23.8 vs. 13.0 m (+ 10.8 m) (HR 0.55)
Overall survival (months, m)	not reported	not reported	63.9 vs. 51.4 m (+ 12.5 m) (HR 0.76)	58.7 vs. 48.0 m (+ 10.7 m) (HR 0.76)

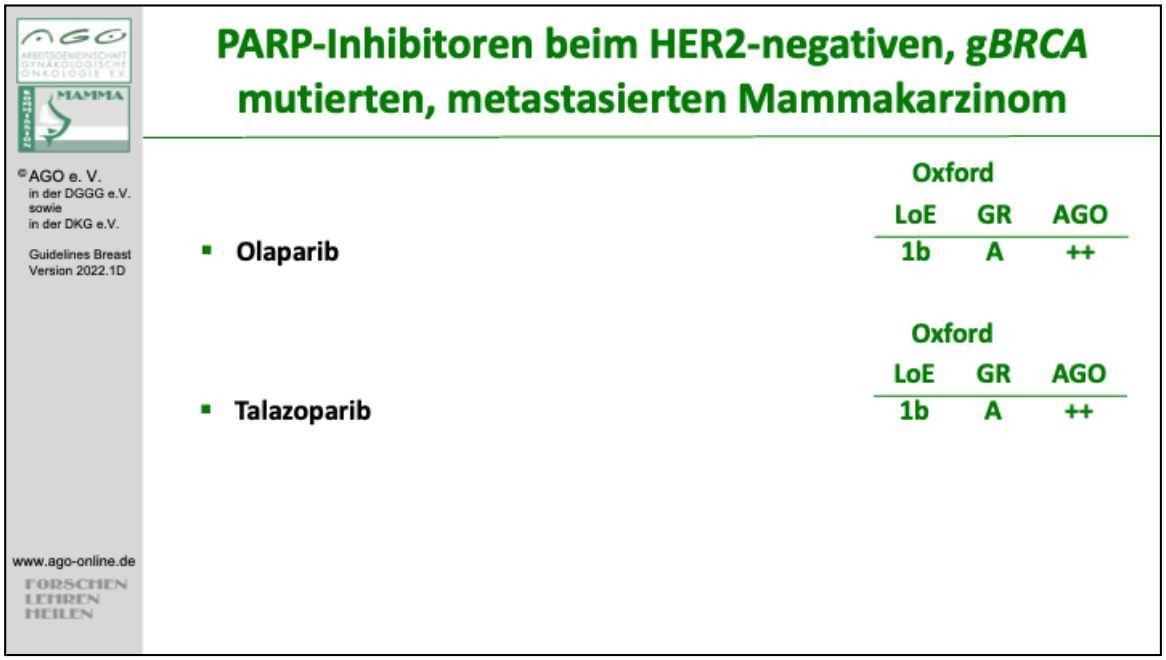
1. Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. Breast Cancer Res Treat. 2019 Apr;174(3):719-729. doi: 10.1007/s10549-018-05125-4. PMID:30632023
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.

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.



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

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

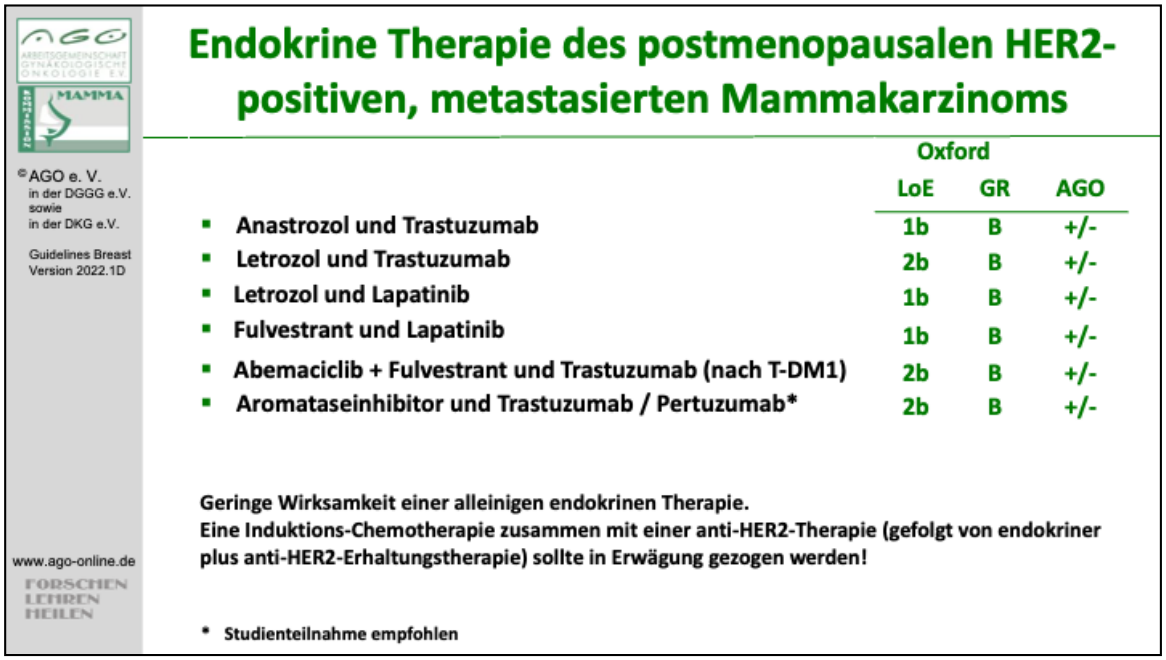
1. Ettl J, Quek RGW, Lee KH, et al., Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial. Ann Oncol. 2018 Sep 1;29(9):1939-1947. doi: 10.1093/annonc/mdy257. PMID:30124753
2. 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.
3. 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
4. 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

Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

Guidelines Breast
Version 2022.1D

FORSCHEN
LEHREN
HEILEN

HER2-positives und HR-positives metastasiertes Mammakarzinom



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

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. Giordano SH, et al. American Society of Clinical Oncology. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jul 1;32(19):2078-99.
3. 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. Giordano SH, et al. American Society of Clinical Oncology. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jul 1;32(19):2078-99.
3. 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.
3. Grassadonia A, Caporale M, Tinari N, et al. Effect of targeted agents on the endocrine response of breast cancer in the neoadjuvant setting: a systematic review. J Cancer. 2015 May 12;6(6):575-82.

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)

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

Abemaciclib plus Fulvestrant plus Trastuzumab

1. 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
2. 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.

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.