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Guidelines Breast  
Version 2025.1D

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# Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome

## Endokrin-basierte und zielgerichtete Therapie des metastasierten Mammakarzinoms



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## Endokrin-basierte und zielgerichtete Therapie des metastasierten Mammakarzinoms

### ■ Versionen 2002–2024:

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### ■ Version 2025:

**Dall / Mundhenke**

## Endokrin-basierte und zielgerichtete Therapie des metastasierten Mammakarzinoms

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

**Oxford LoE: 1a**

**GR: A**

**AGO: ++**

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

**Oxford LoE: 2b**

**GR: B**

**AGO: ++**

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

### Guidelines:

1. A. Gennari, F. André, C. H. Barrios, 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.
2. H. S. Rugo, R. B. Rumble, E. Macrae etl al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol 2016;34(25):3069-103.

### Meta-analysis chemotherapy versus endocrine therapy:

1. Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev. 2003;(2):CD002747.
2. Sledge GW Jr, Hu P, Falkson G, et al: Comparison of chemotherapy with chemohormonaltherapy as first-line therapy for metastatic, hormone-sensitive breast cancer: An Eastern Cooperative Oncology Group study. J Clin Oncol. 2000;18:262-266.
3. 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.2019;20:1360–1369.

### Chemotherapy versus endocrine-based therapy:

1. Z.Zielinski, M. Ruiz-Borrego, et al. Palbociclib in combination with endocrine therapy versus capecitabine in hormonal receptor-positive, human epidermal growth factor 2-negative, aromatase inhibitor-resistant metastatic breast cancer: a phase III randomised controlled trial-PEARL. M. Maftin,. *Ann Oncol.* 2020;32(4):488-499.
2. Y. H. Park, T.-Y. Kim, G. M. Kim, et al. Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15-10): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol.* 2019 Dec;20(12):1750-1759.
3. 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.*
4. De la Haba Rodriguez, J, Cortes J et al. Abigail: Randomized phase II study of abemaciclib plus endocrine therapy with or without a short course of induction paclitaxel in patients with previously untreated HR-positive/Her2-negative advanced breast cancer with aggressive disease criteria. *Annals of Oncology* 2024, 35: 1-72.
5. Loibl, S et al. Primary results of the randomized phase III trial comparing first-line ET plus palbociclib vs standard mono-chemotherapy in women with high risk Her2-/HR+ metastatic breast cancer and indication for chemotherapy. *SABCS 2024,Abstract SESS-3616, LB1-03*



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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**

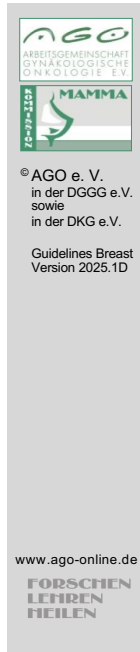
- 22.5 % (95 % CI = 16.4 % to 30.0 %) für ER
- 49.4 % (95 % CI = 40.5 % to 58.2 %) für PR
- 21.3 % (95 % CI = 14.3 % to 30.5 %) für HER2

**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



## Endokrine Therapie (ET) 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 Ovariectomie 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).

### Guidelines:

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. 2021;39:3959-3977.
2. A. Gennari, F. André, C. H. Barrios, 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.

## Endokrine Resistenz beim metastasierten Mammakarzinom

### Primäre endokrine Resistenz:

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

### Sekundäre (erworbene) endokrine Resistenz:

- Rezidiv unter einer adjuvanten ET, aber erst nach den ersten 2 Jahren oder innerhalb von 12 Monaten nach abgeschlossener adjuvanter ET
- Progression  $\geq$  6 Monate nach Initiierung einer ET in der metastasierten Situation

### Guidelines:

1. A. Gennari, F. André, C. H. Barrios, 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.

## Endokrine Therapie der prämenopausalen Patientin mit HER2-negativem, metastasiertem 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. 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. 2021;39:3959–3977.
2. A. Gennari, F. André, C. H. Barrios, 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.

### GnRHa plus Fulvestrant plus palbociclib

1. Turner NC, Ro J, André F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2015;373(3):209-19.
2. Turner NC, Slamon DJ, Ro I, 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. 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.

### GnRH plus Fulvestrant + Abemaciclib / Ribociclib

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.

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.

#### 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;19(7):904-915.
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.

#### 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.* 2024;23(1):37

#### 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*. 2012;48:1932–1938.
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, metastasiertem Mammakarzinom

	Oxford		
	LoE	GR	AGO
▪ <b>Ribociclib</b>			
▪ + nicht-steroidaler AI	1b	A	++
▪ + Fulvestrant	1b	A	++
▪ <b>Abemaciclib</b>			
▪ + nicht-steroidaler AI	1b	A	+
▪ + Fulvestrant	1b	A	++
▪ <b>Palbociclib</b>			
▪ + nicht-steroidaler AI	1b	A	+
▪ + Fulvestrant	1b	A	+
▪ + Fulvestrant + Inavolisib*	1b	A	+

\* Bei primärer endokriner Resistenz und PIK3CA-Mutation

### Guidelines

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.* 2021;39:3959–3977.
2. A. Gennari, F. André, C. H. Barrios, 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.

### Meta-analysis

1. Y. Liu, J. Wu, Z. Ji, et al. Comparative efficacy and safety of different combinations of three CDK4/6 inhibitors with endocrine therapies in HR+/HER-2 – metastatic or advanced breast cancer patients: a network meta-analysis. *BMC Cancer.* 2023;23:816.
2. Li Y, Li L, Du Q, et al. 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.* 2021;39:369–378.
3. 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)+
4. 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.*

2019;20:1360–1369.

5. 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.
6. 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;174(3):597-604.
7. Rossi V, Berchiolla 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;11(11).
8. 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.

#### Letrozole plus Ribociclib (vs. Letrozole 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;29(7):1541-1547.
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).
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;19(7):904-915.
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.

#### 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;36(24):2465-2472.
2. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. *N Engl J Med.* 2019.
3. Slamon DJ, Neven P, Chia S, et al. 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.*2021;32:1015–1024.

#### 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;5:5.
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;7(1):80.
4. M. P. Goetz, M. Toi, J. Huober, et al. MONARCH 3: Final overall survival results of abemaciclib plus a non-steroidal aromatase inhibitor as first-line therapy for HR+, HER- advanced breast cancer. *SABCS 2023.*

#### 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

#### Letrozole plus 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;5:1-19.

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;174(3):719-729.
4. 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;23:37.
5. 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.* 2022 (suppl 17; abstr LBA1003).
6. H.S. Rugo, A. Brufsky, X. Liu, et al. Real-world study of overall survival with palbociclib plus aromatase inhibitor in HR+/HER2- metastatic breast cancer. *NPJ Breast Cancer.* 2022;8(1):114.

#### 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
3. Rugo HS, Cristofanilli M, Loibl S, et al. Prognostic Factors for Overall Survival in Patients with Hormone Receptor-Positive Advanced Breast Cancer: Analyses From PALOMA-3. *Oncologis.* 2021;26:e1339-e1346.
4. 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;28(16):3433-3442.


#### Letrozole plus palbociclib vs. Fulvestrant plus palbociclib

1. Llombart-Cussac A, Pérez-García JM, Bellet Met al. 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.* 2021;7:1791–1799.

#### Palbociclib plus Fulvestrant plus Inavolisib

1. Turner, N. et al, Inavolisib-based therapy in PIK3CA-mutated advanced breast cancer. *N Engl J Med* 2024, 391: 1584-1596

	Paloma-2	Monarch-3	Monaleesa-2	Monaleesa-7
Treatment arms	Letrozole +/- palbociclib	Nonsteroidal AI +/- abemaciclib	Letrozole +/- ribociclib	Goserelin + nonsteroidal AI or tamoxifen +/- ribociclib
Patients	666	493	668	672
Randomization	2:1	2:1	1:1	1:1
Primary endpoint	PFS	PFS	PFS	PFS
Menopausal status	post	post	post	pre
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 0.53)	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.)	66,8 vs. 53,7 m (+ 13,1 m) (HR 0,804 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)



  
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## CDK4/6 Inhibitors in First-line Studies

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;174(3):719-729.
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;5:5.
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;7(1):80.
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).
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;19(7):904-915.
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.
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(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.* 2022 (suppl 17; abstr LBA1003).

8. Goetz M, Toi M, Huober J et al. MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy for HR+, HER2- advanced breast cancer. *SABCS 2023*;GS01-12.

 <h2 style="text-align: center; color: green;">CDK4/6 Inhibitors beyond Progression</h2>				
	postMONARCH (Phase III)	MAINTAIN (Phase II)	PACE (Phase II)	PALMIRA (Phase II)
N	368	119	166	198
CDK4/6i	Palbo→Abema (59%) Ribo→Abema (33%) Abema→Abema (8%)	Palbo → Ribo (86%) Ribo → Ribo (14%)	Palbo → Palbo (93%) Ribo → Palbo (4%) Abema → Palbo (3%)	Palbo → Palbo (100%)
Endocrine therapy	AI→Fulvestrant (100%)	AI → Fulvestrant (83%) Fulvestrant → AI (27%)	AI → Fulvestrant (100%)	AI → Fulvestrant (88%) Fulvestrant → AI (12%)
initial treatment duration ≥12 months	71%	67%	78%	85%
Median PFS ET alone	5.3 (3.7-5.6) mo	2.76 (2.66-3.25) mo	4.8 (2.1-8.2) mo	3.6 (2.7-4.2) mo
Median PFS ET + CDK4/6i beyond progression	6.0 (5.6-8.6) mo	5.29 (3.02-8.12) mo	4.6 (3.6-5.9) mo	4.2 (3.5-5.8) mo
HR	0.73 (0.57-0.96)	0.57 (0.39-0.95)	1.11 (0.74-1.66)	0.8 (0.6-1.1)
p-value	0.02	0.006	0.62 (ns)	0.206 (ns)

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in der DKG e.V.

Guidelines Breast  
Version 2025.1D

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FORSCHEN  
LEHREN  
HEILEN

1. Kalinsky K, Accordino MK, Chiuzan C, et al. Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. *J Clin Oncol.* 2023;20;41(24):4004-4013.
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4. Kalinsky K et al.: postMONARCH: A phase 3 study of abemaciclib plus fulvestrant versus placebo plus fulvestrant in patients with HR+, HER2-, metastatic breast cancer following progression on a CDK4 & 6 inhibitor and endocrine therapy.. *JCO* 40, TPS1117-TPS1117(2022).

## Endokrin-basierte Therapien 2nd Line und höher beim HER2-negativen, metastasierten Mammakarzinom (unabhängig vom Nachweis therapierelevanter Mutationen)

	Oxford		
	LoE	GR	AGO
▪ <b>CDK4/6i + ET*</b>	<b>1A</b>	<b>A</b>	<b>++</b>
▪ <b>Everolimus</b>			
▪ + Exemestan	1b	A	+
▪ + Tamoxifen / Fulvestrant	2b	B	+
▪ + Letrozol	2b	B	+/-
▪ <b>CDK4/6-Inhibitor beyond progression im met. Setting (jeweils mit Wechsel des CDK4/6i und der endokrinen Therapie)</b>	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>Endokrine Monotherapie (AI / Fulvestrant) nach CDK4/6i-Vorthherapie</b>	<b>1b</b>	<b>B</b>	<b>+/-</b>

\* falls nicht in der 1st-line erfolgt

### 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

### CDK4/6i + ET

1. Sonke G, van Ommen A, Wortelboer N et al. Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC). J Clin Oncol. 2023;41, 17S. LBA1000
2. Slamon DJ, Neven P, Chia S, et al. 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, 2021
3. 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

6(1):116-124, 2020

4. Cristofanilli M, Rugo HS, Im SA, et al. 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

#### 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

#### Tamoxifen / Fulvestrant and everolimus

1. Bachelot T, Bourcier C, Cropet C 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.
2. 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.

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#### CDK4/6i beyond progression

1. Kalinsky K, Accordino MK, Chiuzan C, et al. Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. J Clin Oncol 20;41(24):4004-4013, 2023K.L.

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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* 40(28):3246-3256, 2022
2. Kalinsky K, Accordino MK, Chiuzan C, et al. Randomized Phase II Trial of Endocrine Therapy With or Without Ribociclib After Progression on Cyclin-Dependent Kinase 4/6 Inhibition in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: MAINTAIN Trial. *J Clin Oncol* 20;41(24):4004-4013, 2023

## Therapien 2nd Line und höher beim HR+ / HER2-negativen, metastasierten Mammakarzinom

*(Nachweis von therapierelevanten Mutationen / Alterationen notwendig)*

	Oxford		
	LoE	GR	AGO
▪ <b>ESR1-mutiert und Z. n. CDK 4/6i-Therapie:</b> <b>Elacestrant*</b>	1b	B	+
▪ <b>PIK3CA-mutiert</b> <b>Alpelisib + Fulvestrant</b>	1b	B	+
▪ <b>Nachweis von PIK3CA/AKT1 oder PTEN-Alterationen</b> <b>Capivasertib + Fulvestrant</b>	1b	B	+
▪ <b>gBRCA-mutiert</b> <b>Olaparib</b>	1b	A	++
<b>Talazoparib</b>	1b	A	++
▪ <b>Olaparib bei sBRCA- oder gPALB2-Mutation</b>	2b	B	+

\* bevorzugt bei längerem Ansprechen auf vorheriger CDK 4/6i-Therapie

### 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

### ESR-1 mutated and previous CDK 4/6i therapy

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. J Clin Oncol. 40(28):3246-3256, 2022
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### PIK3CA mutated:

1. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med* 16;380(20):1929-1940, 2019

#### PIK3CA/AKT1 or PTEN alterations:

1. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med* 388(22):2058-2070, 2023
2. Oliveira M, Rugo HS, Howell SJ, Capivasertib and fulvestrant for patients with hormone receptor-positive, HER2-negative advanced breast cancer (CAPitello-291): patient-reported outcomes from a phase 3, randomised, double-blind, placebo-controlled trial, *Lancet Oncol* 2024; 25: 1231–44

#### gBRCA mutated:

##### Olaparib

1. Robson M, Im SA, Senkus E, 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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##### 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
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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 JK, Rugo HS, Ettl 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

## Weitere endokrine Therapieoptionen beim HER2-negativen, metastasierten Mammakarzinom 1st-Line oder höher (wenn keine zielgerichtete oder Kombinationstherapie möglich)

	Oxford		
	LoE	GR	AGO
▪ <b>Fulvestrant 500 mg</b>	<b>1b</b>	<b>B</b>	<b>+</b>
▪ <b>Aromataseinhibitor*</b>	<b>1a</b>	<b>A</b>	<b>+</b>
▪ <b>Tamoxifen</b>	<b>1a</b>	<b>A</b>	<b>+</b>
▪ <b>Fulvestrant 250 mg + Anastrozol</b>	<b>1b</b>	<b>B</b>	<b>+/-</b>
▪ <b>ET + Bevacizumab als 1st-line Therapie</b>	<b>1b</b>	<b>B</b>	<b>+/-</b>
▪ <b>Frühere endokrine Behandlungslinien wiederholen</b>	<b>5</b>	<b>D</b>	<b>+/-</b>

\* Keine Hinweise für die Überlegenheit eines einzelnen Aromataseinhibitors

### 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
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### Fulvestrant 500 mg (vs. anastrozole)

1. Ellis MJ, Llombart-Cussac A, Feltl D, 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
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### Aromatase inhibitors (3rd generation)\*

1. 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.
2. 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.

#### Bevacizumab plus endocrine treatment as first line

1. Martín M, Loibl S, von Minckwitz G et al. Bevacizumab plus endocrine treatment as first line therapy for advanced disease Phase 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, Barry WT, Cirrincione CT 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.

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

	Oxford		
	LoE	GR	AGO
▪ <b>Abemaciclib + Fulvestrant + Trastuzumab (≥ 3rd line, nach T-DM1)</b>	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>Aromatase-Inhibitor + Trastuzumab + Pertuzumab</b>	<b>2b</b>	<b>B</b>	<b>+</b>
▪ <b>Aromatase-Inhibitor + Trastuzumab</b>	<b>1b</b>	<b>B</b>	<b>+/-</b>
▪ <b>Aromatase-Inhibitor + Lapatinib</b>	<b>1b</b>	<b>B</b>	<b>+/-</b>
▪ <b>Fulvestrant + Lapatinib</b>	<b>1b</b>	<b>B</b>	<b>+/-</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. 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.

### 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;763-775.
2. 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.

### AI and trastuzumab/pertuzumab

1. Arpino G, de la Haba Rodríguez J, Ferrero JM et al. Pertuzumab, Trastuzumab, and an Aromatase Inhibitor for HER2-Positive and Hormone Receptor-Positive Metastatic or Locally Advanced Breast Cancer: PERTAIN Final Analysis. Clin Cancer Res. 2023;29(8):1468-1476.

2. 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;36(28):2826-2835.
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*;PD18-07.

#### AI 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;27(33):5529-37.
2. 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.

#### AI and lapatinib

1. Johnston S, Pippin 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;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;28(8):1263-79.

#### Fulvestrant and lapatinib

1. Burstein HJ, Cirincione 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*. 2014; 32:3959-3966.

## Simultane oder sequenzielle endokrin-zytostatische Behandlung

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

### 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
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### 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.

Maintenance of bevacizumab plus endocrine therapy:

1. Trédan O, Follana P, Moullet I, 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.

## mBC HER2-negativ / HR-positiv nach Vorbehandlung\*

	Oxford		
	LoE	GR	AGO
▪ Trastuzumab Deruxtecan			
- nach Chemotherapievorbehandlung und HER2-low	1b	A	++
- ohne Chemotherapievorbehandlung und nicht für weitere endokrin-basierte Therapie geeignet und HER2-low	1b	B	+
- nicht für weitere endokrin-basierte Therapie geeignet und HER2-ultralow	2b	B	+/-
▪ Sacituzumab Govitecan	1b	A	++
▪ Capecitabin	2b	B	+
▪ Eribulin	1b	B	+
▪ Vinorelbin	2b	B	+
▪ (Peg)-liposomales Doxorubicin	2b	B	+
▪ Taxan Re-Challenge**	2b	B	+
▪ Anthrazyklin Re-Challenge**	3b	C	+
▪ Metronomische Therapie (z. B. Cyclophos. und MTX)	2b	B	+

\* Siehe entsprechenden Zulassungstext hinsichtlich der Vorbehandlung

\*\* Mindestens 1 Jahr rezidivfrei nach adjuvanter Gabe

### 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.

### Trastuzumab Deruxtecan

1. Cortés J, Kim S-B, Chung W-P, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022 Mar 23;386(12):1143-1154. doi: 10.1056/NEJMoa2115022.
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### Sacituzumab Govitecan

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<b>mBC - HER2-Negative / HR-Positive*</b>			
	<b>Trastuzumab Deruxtecan</b>		<b>Sacituzumab-Govitecan</b>
<b>Trial</b>	<b>Destiny-Breast 06</b> HR+/HER2-low: n=359 HR+/HER2-ultralow: n=76	<b>Destiny-Breast 04</b> HR+/HER2-low: n=331	<b>Tropics 02</b> HR+/HER2-negative: n=272
<b>Previous CTX for mBC</b>	no previous CTX for mBC	60%: 1 prior line of CTX 40%: > 1 prior line of CTX	2%: 1 prior line of CTX 41%: 2 prior lines of CTX 57%: > 2 prior lines of CTX
<b>Median PFS (months)</b>	13.2 (HER2-low) 13.2 (ITT) 13.2 (HER2-ultralow)	9.6	5.5
<b>Hazard ratio for PFS</b>	0.62 (HER2-low) 0.64 (ITT)	0.37	0.66
<b>Median OS (months)</b>		23.9	14.4
<b>Hazard ratio for OS</b>	0.83 (n.s.)	0.69	0.79

• Data from different phase 3 studies with differently pretreated patients  
 • ITT: intention-to-treat population; n.s.: not significant, PFS: Progression free survival, OS: Overall survival



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