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Guidelines Breast
Version 2022.1E

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

Endocrine based and targeted Therapy of Metastatic Breast Cancer



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Endocrine Therapy of Metastatic Breast Cancer

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Endocrine Therapy of Metastatic Breast Cancer

Indication

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


Endocrine-based therapy is first line treatment in patients with metastatic breast cancer and positive (or unknown) hormone receptor (HR) status.

Exception: imminent organ failure

Caveat: HR may change during the course of disease.

Histology of recurrent site should be obtained whenever possible

1. 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, Ghera D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev. 2003;(2):CD002747.



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Comparison ER / PR and HER2 Metastasis vs. Primary Tumor (n = 5.521)

Meta-analysis based on 39 (mostly retrospective) analyses, exclusively comparing primary tumor and metastasis (no lymph nodes):

Pooled discordance proportions were:

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

Pooled proportions of tumors shifting from positive to negative


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

Pooled proportions of tumors shifting from negative to positive


- 21.5% (95% CI = 18.1% to 25.5%) for ER
- 15.9% (95% CI = 11.3% to 22.0%) for PR
- 9.5% (95% CI = 7.4% to 12.1%) for HER2

Meta-analysis:

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



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Endocrine Therapy

General Considerations

- **Within all lines of treatment, treatment options should consider prior endocrine therapies, age and comorbidities as well as the respective approval status.**

- **Premenopausal patients treated with GnRH analogues or after ovariectomy can be treated like postmenopausal patients.**

1. 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> 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.
2. 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.
3. Rugo HS, et al. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol 2016;34(25):3069-103.



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Metastatic Breast Cancer Endocrine Resistance

Primary endocrine resistance:

- Relapse within 2 years of adjuvant endocrine treatment (ETx)
- Progressive disease within first 6 months of first-line ETx for MBC

Secondary (required) endocrine resistance:

- Relapse while on adjuvant ETx but after the first 2 years or a relapse within 12 months after completing adjuvant ETx
- PD ≥ 6 months after initiation of ET for MBC

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

Endocrine Therapy in Premenopausal Patients with HER2-Negative Metastatic Breast Cancer			
	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	+
▪ Aromataseinhibitors without OFS	3	D	--

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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



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

	Oxford		
	LoE	GR	AGO
■ Fulvestrant 500 mg	1b	B	+
■ Aromatase inhibitor*	1a	A	+
■ Tamoxifen	1a	A	+
■ Fulvestrant 250 mg + Anastrozole	1b	B	+/-
■ Repeat prior treatments	5	D	+/-

* There is no evidence for superiority of a single aromatase inhibitor. As everolimus plus exemestane is indicated after AI treatment, a non-steroidal AI should be used in first line.

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- 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
- 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)

- 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
- 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

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

Aromatase inhibitors (3rd generation)*

1. Bonnetterre J, et al: Anastrozole versus Tamoxifen as First-Line Therapy for Advanced Breast Cancer in 668 Postmenopausal Women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and tolerability Study. J Clin Oncol 2000;18:3748-3757
2. Thürlimann B, et al: Anastrozole (Arimidex) versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind cross-over SAKK trial 21/95 – a substudy of the TARGET (Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability) trial. Breast Cancer Res Treat 2004;85:247-254

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

1. Bonnetterre, J, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma Cancer 2001 92
2. 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>

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

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- 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>
- 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

- 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

- 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](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.

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)

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Fulvestrant and everolimus

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CDK4/6i after CDK4/6i

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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)

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Endocrine Therapy in Postmenopausal HER2-Negative Metastatic Breast Cancer in Combination with Bevacizumab			
	Oxford		
	LoE	GR	AGO
■ Maintenance bevacizumab plus endocrine therapy after remission with chemotherapy and bevacizumab	1b	B	+/-
■ Bevacizumab plus endocrine treatment as first line therapy for advanced disease	1b	B	+/-

Maintenance of bevacizumab plus endocrine therapy

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

Bevacizumab plus endocrine treatment as first line

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Diagnosis and Treatment of Patients with early and advanced Breast Cancer

HER2-Positive and HR-Positive Metastatic Breast Cancer



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Endocrine Therapy in Postmenopausal HER2-Positive Metastatic Breast Cancer Patients

	Oxford		
	LoE	GR	AGO
▪ Anastrozole + trastuzumab	1b	B	+/-
▪ Letrozole + trastuzumab	2b	B	+/-
▪ Letrozole + lapatinib	1b	B	+/-
▪ Fulvestrant + lapatinib	1b	B	+/-
▪ Abemaciclib + fulvestrant + trastuzumab (after T-DM1)	2b	B	+/-
▪ Aromatase inhibitors + trastuzumab / pertuzumab*	2b	B	+/-

Poor efficacy of endocrine therapy alone.
Consider induction chemotherapy + anti-HER2-therapy (followed by endocrine + anti-HER2-therapy as maintenance therapy)!

* Study participation recommended

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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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.
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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 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

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

Guidelines

- 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

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Maintenance endocrine therapy after chemotherapy induced response

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