Guidelines Breast
Version 2021.1E

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

Guidelines Breast
Version 2021.1E

- **Versions 2002–2020:**
  Bauerfeind / Dall / Diel / Fersis / Fehm / Friedrichs / Gerber / Göring / Hanf/ Harbeck / Huober / Jackisch / Lisboa / Lück / Lux / Maass / von Minckwitz / Möbus / Müller / Nitz / Oberhoff / Schaller / Scharl / Schneeweiss / Schütz / Solomeyer / Stickeler / Thomssen /
- **Version 2021:**
  Fasching / Loibl

Guidelines Breast
Version 2021.1E

Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1 GR: A AGO: ++

endocrine responsive – hormone receptor positive
Immunhistology (ER and/or PgR)

0%	pos. cells:	endocrine resistant
1–10%	pos. cells:	possibly endocrine sensitive
> 10%	pos. Zellen:	endocrine sensitive
Unknown hormone receptor status:		endocrine sensitive

IF ER negative / PR positive (> 10% positive cells): reassess IHC status

Adjuvant Endocrine Therapy
Assessment of Menopausal Status

Guidelines Breast
Version 2021.1E

	Oxford		
	LoE	GR	AGO
Assessment of menopausal status:			
▪ **Menstruation history**			++
▪ **FSH, E2**			++

Adjuvant Endocrine Therapy

Guidelines Breast
Version 2021.1E

	Oxford		
	LoE	GR	AGO
Endocrine therapy:			
▪ Endocrine responsive	1a	A	++
▪ endocrine doubtful responsiveness	3b	D	+
▪ Endocrine therapy sequentially after CT	5	D	+
▪ Endocrine therapy concurrent with T-DM1/anti-HER2 therapy (w/o chemotherapy)	5	D	+
▪ Non-responsive: No endocrine therapy	1a	A	++

Guidelines Breast
Version 2021.1E

General Principles in Adjuvant Endocrine Therapy AGO ++

- **Adjuvant endocrine therapy is divided into initial therapy (years 1-5) and extended adjuvant therapy (EAT, years 6-10+).**
- **Standard treatment duration is 5 years.**
- **Extended therapy should be considered based on individual risks and benefits.**
- **Duration, choice & sequence of AI or Tam mainly depend on menopausal status, tolerability, and risk of recurrence.**
- **Switch to another better tolerated endocrine treatment (Tam or AI) is better than stopping endocrine therapy altogether.**
- **AI should be used as first treatment in patients, especially in case of lobular cancers and/or high risk of recurrence.**
- **To date, there is no sufficiently validated biomarker for identification of patients at risk for early versus late recurrence.**

Premenopausal Patients
Initial Adjuvant Endocrine Therapy (Year 1-5)

	Oxford		
	LoE	GR	AGO
▪ Tamoxifen 5 years (low risk of relapse)	1a	A	++
▪ Tamoxifen + OFS 2-5 years (intermediate risk of relapse)*	2b	C	++
▪ AI +OFS# for 5 years (high risk of relapse)*	1b	B	+
▪ GnRH alone (only, if relevant contraindication for Tam vs. no therapy at all)	1a	B	+

OFS: ovarian function suppression;

* as long as tolerated and the patient is clearly premenopausal
after chemotherapy if ovarian function resumes within 24 months
Application of chemotherapy in the trials served as a surrogate for high recurrence risk

\# in premenopausal women AI only in combination with OFS

TEXT /SOFT Joint Analysis

TEXT

Premenopausal Patients with HR+ BC ≤ 12 wks after surgery (N = 2672)

- **Tamoxifen 20 mg/day + OFS*** (n = 1328)
- **Exemestane 25 mg/day + OFS*** (n = 1332)

SOFT

Premenopausal patients with HR+ BC ≤ 12 wks after surgery (if no chemo) *or* ≤ 8 mos after chemo (N = 3066)

- **Tamoxifen 20 mg/day + OFS*** (n = 1016)
- **Exemestane 25 mg/day + OFS*** (n = 1014)
- **Tamoxifen 20 mg/day**

5 yrs

Median follow-up: 5.7 yrs

Joint Analysis

- **Tamoxifen + OFS*** (n = 2344)
- **Exemestane + OFS*** (n = 2346)

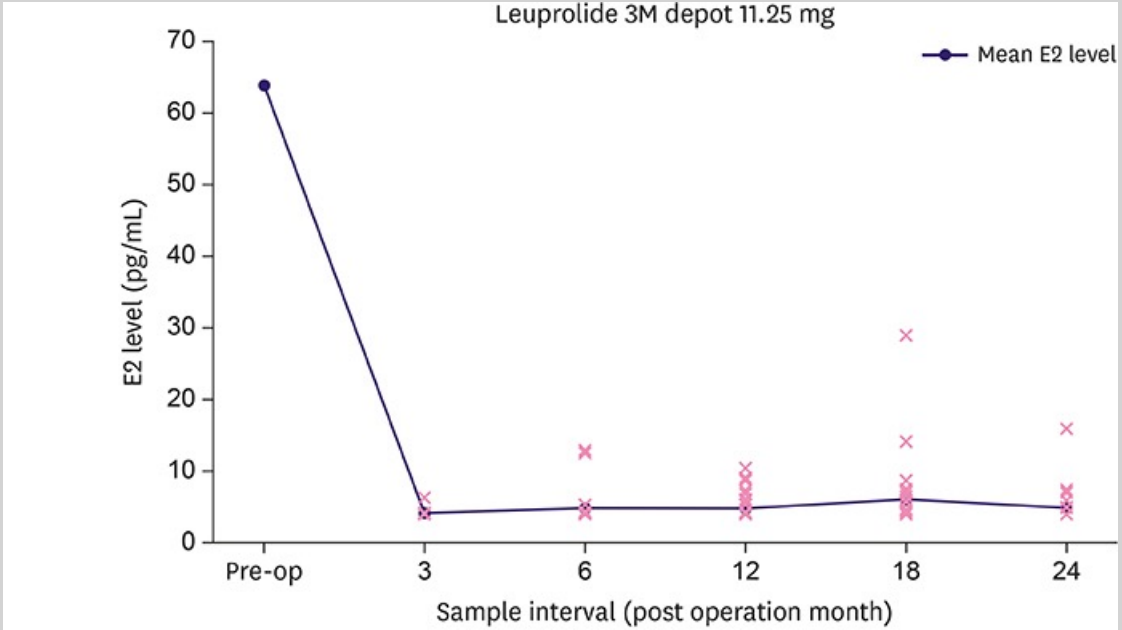
*OFS

- TEXT: triptorelin 3.75 mg IM every 28 days for 6 mos, then optional bilateral oophorectomy or irradiation
- SOFT: choice of method

Nach Pagani O, et al. N Eng J Med, 371(2) 2014

GnRH Analogue every 3 months

Guidelines Breast
Version 2021.1E



Mean pg/mL (SD)	63.7 (93.8)	4.1 (0.5)	4.8 (2.5)	4.8 (1.7)	6.1 (5.1)	4.9 (2.3)
Number	318	19	23	35	27	30

Postmenopausal Patients
Initial Adjuvant Endocrine Therapy (Years 1-5)

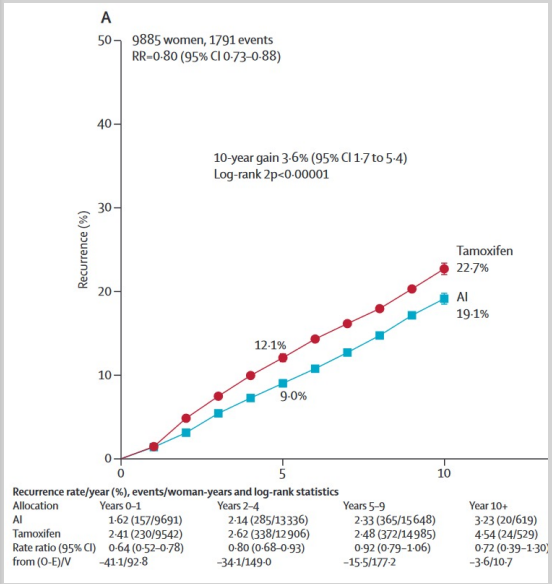
	Oxford		
	LoE	GR	AGO
▪ Aromatase Inhibitor (AI) for first 5 years	1a	A	++
▪ Non steroidal-AI in lobular cancer	2b	B	+
▪ High risk of recurrence	2b	B	+
▪ Sequential therapy for first 5 years *	1a	A	++
▪ Tam (2-3 yrs.) followed by AI to complete 5 years	1a	A	++
▪ AI (2-3 yrs.) followed by Tamoxifen to complete 5 years	1b	C	++
▪ Tamoxifen 20 mg/d for 5 years**	1a	A	+

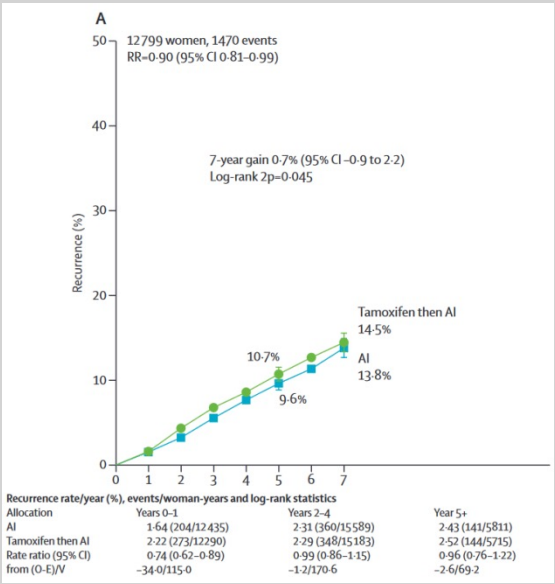
* in postmenopausal patients, AI should be integrated in the first five years

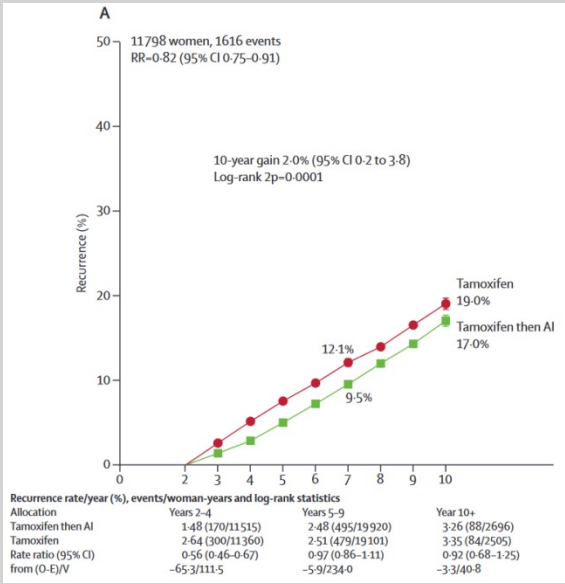
** Tamoxifen may be offered to individual patients with very low risk of recurrence or if contraindications for AI are present

Aromatase Inhibitor vs. Tamoxifen vs. Sequentieller Therapie - 5 Jahre Upfront Therapie

Guidelines Breast
Version 2021.1E







Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

Guidelines Breast
Version 2021.1E

Adjuvant therapy with CDK 4/6 inhibitors

	Oxford		
	LoE	GR	AGO
In patients at high-risk of relapse according to trial [1,2,3]			
▪ **Abemaciclib for 2 years + standard endocrine therapy[1]**	2b	C	+/-
▪ **Palbociclib for 2 years + standard endocrine therapy[2]**	2b	C	-
▪ **Palbociclib for 1 year + standard endocrine therapy[3]**	1b	B	-

[1]MonarchE; [2]Pallas [3]PenelopeB

CDK4/6 Inhibitoren zusätzlich zu einer standardmäßigen endokrinen Therapie in der adjuvanten Situation

Guidelines Breast
Version 2021.1E

	PALLAS	MonarchE	Penelope
Therapie	Palbociclib for 2 years	Abemaciclib for 2 years	Palbociclib for 1 year
N	5600	5637	1250
Main Inclusion Criteria	AJCC Stage II: • T0/T1 N1 • T2 N0 • T2 N1 • T3 N0 or AJCC Stage III • T0/T1 N2 • T2 N2 • T3 N1/N2	T1-T4 and N1 with one of the following criteria • ≥4 ipsilateral pos. axillary lymph nodes • 1-3 ipsilateral pos. axillary lymph nodes and one of the following criteria - G3 - Tumor size ≥5 cm - Ki-67 ≥20%	• ≥ypT1 or • ≥ypN1 • CPS-EG score >=3 pr 2 ypN+ • Neoadjuvant Chemotherapy of at least 16 weeks
Early discontinuation of therapy	43%	27%	20%
Median follow up	24 months	15 months	43 months
Results (iDFS)	HR: 0,93 (95%CI: 0,76-1,15) 3 year iDFS: 88.2% vs 88.5%	HR = 0,713 (0.583-0.871) 2 year iDFS: 92.3% vs 89.3%	HR=0,93 (95%KI: 0,74-1,17) 3year iDFS: 81.2% vs 77.7%

Premenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years Tamoxifen after 5 years Tamoxifen	1a	A	++
▪ 2–5 years AI after 5 years Tamoxifen in initially premenopausal patients who obtain validated postmenopausal status during course of therapy	1b	B	+
▪ 5 years Tamoxifen after 5 years of endocrine therapy + OFS	5	D	+

Guidelines Breast
Version 2021.1E

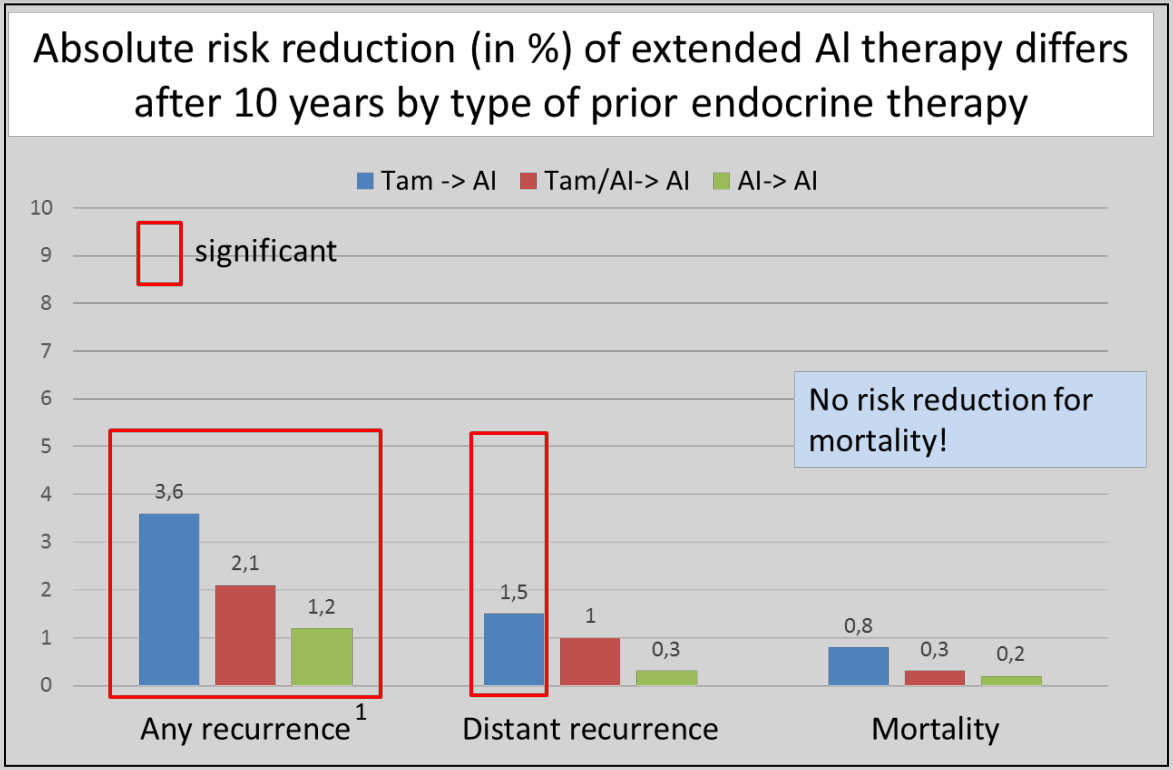
Postmenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)

	Oxford		
	LoE	GR	AGO
In case of high risk of recurrence			
▪ 5 years Tamoxifen after 5 years Tamoxifen	1a	A	+
▪ 2–5 years AI after 5 years Tamoxifen	1a	A	++
▪ After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI for 2–5 years*			
▪ High-risk and good tolerabilty of AI	1a	A	+
▪ Low-risk, poor tolerabilty of AI	1a	A	-
▪ Interruption of endocrine treatment up to 3 months during EAT with AI	1b	B	+/-

* Up to date, no impact on OS

Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials (EBCTCG)

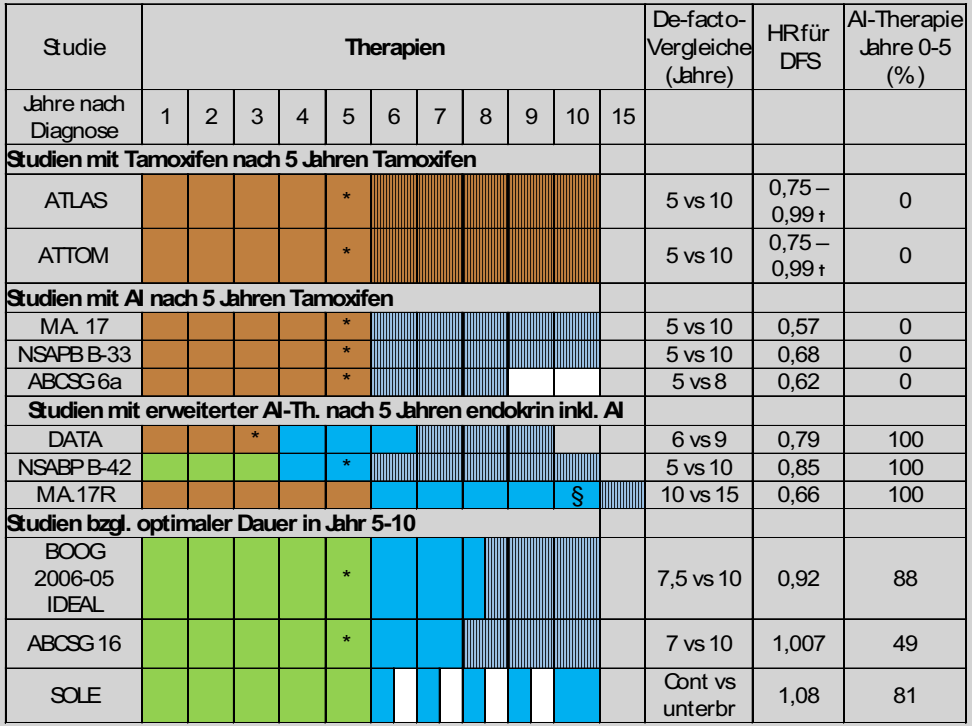
Guidelines Breast
Version 2021.1E



[1] *(new primary breast cancer, local and distant recurrence)*

Gray R et al. SABCS 2018 (GS3-03)

Extended adjuvant treatment, overiew



Studie	Therapien											De-facto-Vergleiche (Jahre)	HR für DFS	AI-Therapie Jahre 0-5 (%)
Jahre nach Diagnose	1	2	3	4	5	6	7	8	9	10	15			
Studien mit Tamoxifen nach 5 Jahren Tamoxifen														
ATLAS					*							5 vs 10	0,75 – 0,99 †	0
ATTOM					*							5 vs 10	0,75 – 0,99 †	0
Studien mit AI nach 5 Jahren Tamoxifen														
MA. 17					*							5 vs 10	0,57	0
NSAPB B-33					*							5 vs 10	0,68	0
ABCSG 6a					*							5 vs 8	0,62	0
Studien mit erweiterter AI-Th. nach 5 Jahren endokrin inkl. AI														
DATA			*									6 vs 9	0,79	100
NSABP B-42					*							5 vs 10	0,85	100
MA.17R										§		10 vs 15	0,66	100
Studien bzgl. optimaler Dauer in Jahr 5-10														
BOOG 2006-05 IDEAL					*							7,5 vs 10	0,92	88
ABCSG 16					*							7 vs 10	1,007	49
SOLE												Cont vs unterbr	1,08	81

brown: Tamoxifen

green: Tamoxifen or AI

blue: AI

stripes: Zeit der randomisierten Intervention vs keine Therapie od. Plazebo

*: randomisation

§ : MA17R after 5 years AI with / w/o Tam before

Guidelines Breast
Version 2021.1E

Guidelines Breast
Version 2021.1E

Decision criteria for extended therapy

Factors indicating a clinical benefit from EAT:

- Adjuvant tamoxifen therapy only
- Condition after chemotherapy (indicating high risk)
- Positive lymph node status and /or T2/T3 tumors
- Elevated risk of recurrence based on immunohistochemical criteria or based on multi-gene expression assays
- High CTS5-score
- BCI (H/I) (Breast Cancer Index)

Further decision criteria:

- Wish of patient
- up to now well tolerated AI therapy,
- good bone health
- younger age
- adherence

Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

	Oxford LoE	Oxford GR	AGO
▪ **Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists**			++
▪ **CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemotherapy, independent of hormone receptor status)**	1a	A	+
▪ **CTx + GnRHa (preservation of fertility)**	1b	A	+/-

Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient–Level Data

N= 837 patients from 5 trial, median follow-up time 5.0 years (IQR, 3.0-6.3 years)

	Control	GnRH	HR (95%-CI)	P-value
POI[1,2]	30.9%	14.1%	0.38; 0.26 to 0.57	< 0.001

[1]premature ovarian insufficiency, [2] different definitions and time points were used
[3] i n most trials POI and not pregnancy was defined as the primary endpoint

No significant differences in disease-free survival and overall survival were observed between groups.

Lambertini M et al. J Clin Oncol 2018