Diagnosis and Treatment of Patients with early and advanced Breast Cancer

Guidelines Breast
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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

- **Versions 2002–2018:**
  Bauerfeind / Dall / Diel / Fersis / Friedrichs / Gerber / Göring / Hanf / Harbeck / Huober / Jackisch / Lisboa / Lück / Lux / Maass / von Minckwitz / Möbus / Müller / Oberhoff / Schaller / Scharl / Schneeweiss /Schütz / Solomeyer / Stickeler / Thomssen / Untch

- **Version 2019:**
  Fehm / Gerber

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Assessment of Steroid Hormone Receptor Status

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

Endocrine responsiveness: formerly known as receptor negativ

Immunohistochemistry (ER and / or PgR)

0%	**pos. cells:**	**endocrine non responsive**
1–9%	**pos. cells:**	**endocrine doubtfully responsive**
≥ 10%	**pos. cells:**	**endocrine responsive**
Hormon Receptor Status unknown:		**endocrine responsive**

In case of ER negative / PR positive (> = 10% cells):
consider immunohistochemical re-evaluation

Adjuvant Endocrine Therapy
Assessment of Menopausal Status

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

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Adjuvant Endocrine Therapy

- **Endocrine responsive & doubtfull responsive**
  Endocrine therapy
- **Endocrine therapy**
  Sequentially after CT
- **Non-responsive:**
  No endocrine therapy

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

General Principles in Adjuvant Endocrine Therapy AGO ++

- **Adjuvant endocrine therapy is divided into initial therapy (years 0-5) and extended adjuvant therapy (EAT, years 6-15).**
- **Standard treatment duration is 5 years.**
- **Extended treatment should be considered based on individual benefits and risks.**
- **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 to stop.**
- **AI should be used as first treatment in postmenopausal patients especially in cases of lobular cancers and high risk of recurrence.**
- **To date, there is no sufficiently validated biomarker that identifies patients for early versus late recurrence.**

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Premenopausal Patients
Initial Adjuvant Endocrine Therapy (Year 0-5)

	Oxford LoE	Oxford GR	AGO
Tamoxifen* 5–10 years	1a	A	++
GnRH alone (only, if relevant contraindication for Tam)	1a	B	+
Without indication for neo-/adjuvant chemotherapy and preserved ovarian function			
Tamoxifen	1b	B	++
Tamoxifen + OFS**	1b	B	+/-
AI + OFS**	1b	B	+/-
Following neo-/adjuvant chemotherapy and preserved ovarian function (≤ 8 months EOC)			
Tamoxifen + OFS 5 years**	1b	B	+
➔ in patients < 35 years	1b	B	++
AI + OFS**	1b	B	+/-
➔ in patients < 35 years	1b	B	+

OFS: ovarian Function-Suppression; EOC: end of chemotherapy treatment as long as tolerable and the pat. is clearly premenopausal
**** only limited data on OS available**

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

Incomplete Ovarian Suppression within SOFT – Study (SOFT-EST-Substudy)

- **In Soft-EST: Exe + OFS: E2, E1, E1-Sulfate - levels were significantly lower than in pats. with Tam + OS**
- **66% of premenopausal pats. on Exe + OFS had profound persistent suppression of E2 etc. for 12 months.**
- **However, 34% had an E2 level greater than menopausal threshold at least once, 17% at all time-points:**
  - **These patients were more likely younger than 35 y; chemo-naïve; had higher BMI**
  - **Importantly:** Combining ABCSG-12, SOFT, and TEXT studies, **showed 65 fewer DFS events** (HR 0.89, 95% CI 0.57–1.39) **but 30 more deaths** for ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen (HR 1.31, 95% CI 0.93–1.84, P = 0.12, s = 0.03, heterogeneity, P = 0.18).
- **Hence the question arises, whether incomplete ovarian suppression led to this discrepancy**

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Postmenopausal Patients
Initial Adjuvant Endocrine Therapy (Years 0-5)

	Oxford LoE	Oxford GR	AGO
▪ **Aromatase Inhibitor (AI) for first 5 years**	1a	A	++
▪ Non steroidal-AI in lobular cancer	2b	B	+
▪ High risk of recurrence			
▪ **Sequential therapy for first 5 years ***			++
▪ 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 at some point

** Tamoxifen might be offered to very old patients or in patients with very low rik of recurrence or if contraindications for AI ar present

Aromatase Inhibitor vs. Tamoxifen vs. Sequentiell Therapy – 5 Years Upfront Therapie

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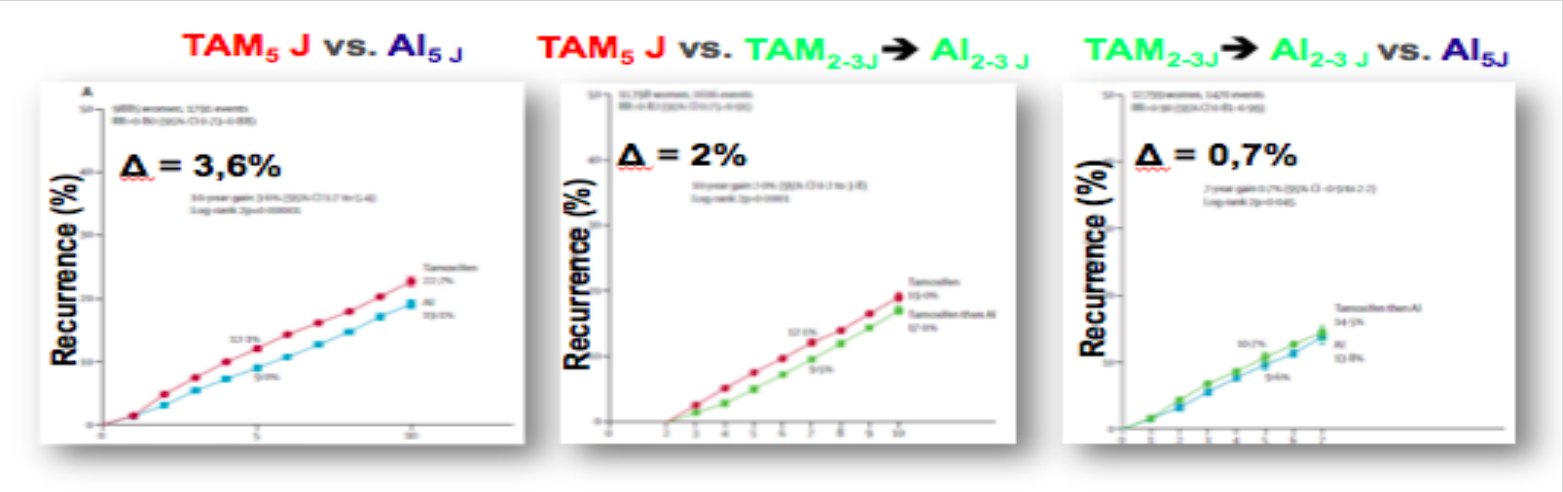

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

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

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	Oxford LoE	Oxford 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 with validated postmenopausal status in the course of therapy	1b	B	+
▪ 5 years Tamoxifen after 5 years of endocrine therapy + OFS	5	D	+

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

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	Oxford LoE	Oxford 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 the AI	1a	A	+
▪ low risk, poor tolerabilty of the AI	1a	A	-
▪ Interruption of endocrine treatment up to 3 months during EAT	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)

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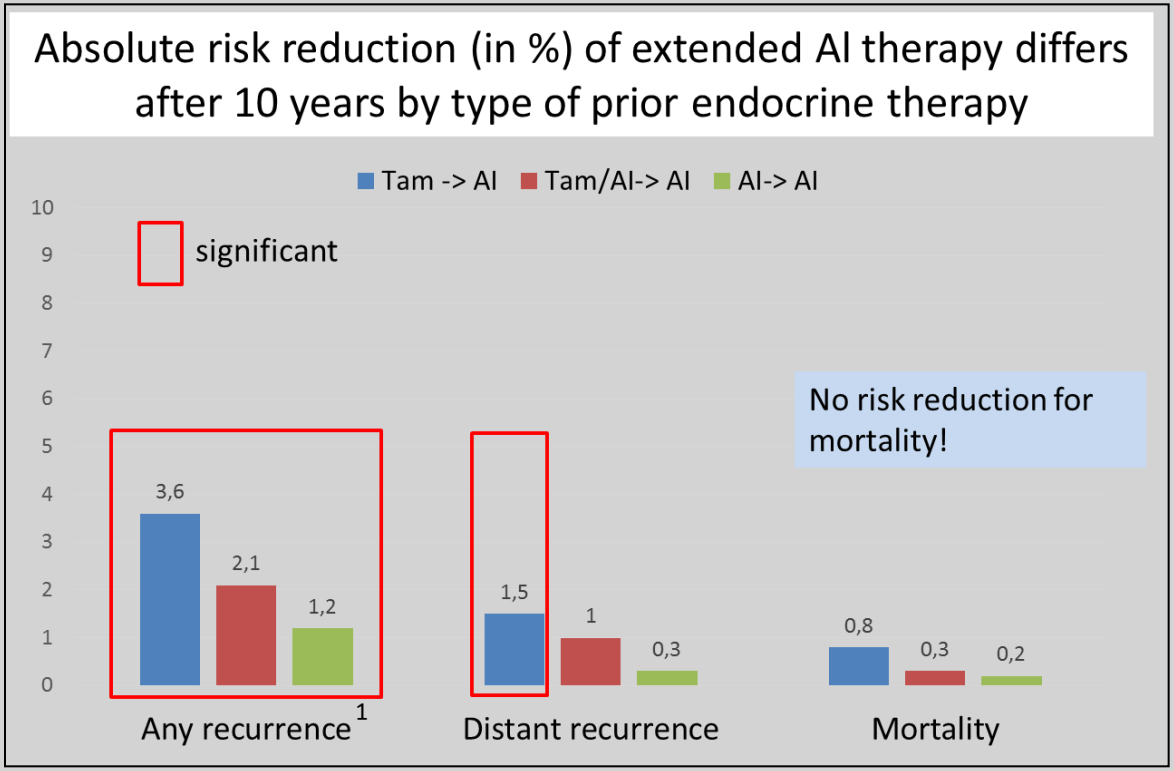

[1] *(new primary breast cancer, local and distant recurrence)*

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

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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**

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)

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	Oxford LoE	GR	AGO
▪ CT + GnRHa (preserve ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independently of hormone receptor status)	1a	A	+
▪ CHT + GnRHa (preserve fertility)	1b	A	+/-
▪ Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information www.fertiprotect.de)			++

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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
Pregnancy[3]	5.5%	10.3%	1.83; 1.06 to 3.15;	0.03

[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

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