Diagnosis and Treatment of Patients with early and advanced Breast Cancer

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Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

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- **Versions 2002–2019:**
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- **Version 2020:**
  Nitz / Huober

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Assessment of Steroid Hormone Receptor Status

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

Endocrine responsiveness: formerly known as hormone receptor positive

Immunohistochemistry (ER and / or PgR)

0%	**pos. cells:**	**endocrine non responsive**
1–9%	**pos. cells:**	**doubtful endocrine responsiveness**
≥ 10%	**pos. cells:**	**endocrine responsive**
Hormone receptor status unknown:		**endocrine responsive**

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

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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

	Oxford LoE	Oxford GR	AGO
Endocrine therapy:			
▪ Endocrine responsive	1a	A	++
▪ endocrine doubtful responsiveness	3b	D	+
▪ Endocrine therapy Sequentially after CT	1a	A	++
▪ Non-responsive: No endocrine therapy	1a	A	++

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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 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 postmenopausal 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 0-5)

	Oxford LoE	Oxford GR	Oxford AGO
Tamoxifen* 5–10 years	1a	A	++
GnRH alone (only, if relevant contraindication for Tam vs. no therapy at all)	1a	B	+
No 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 **			
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; * as long as tolerated and the patient is clearly premenopausal
**** If ovarian function resumes during 24 months**

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

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

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

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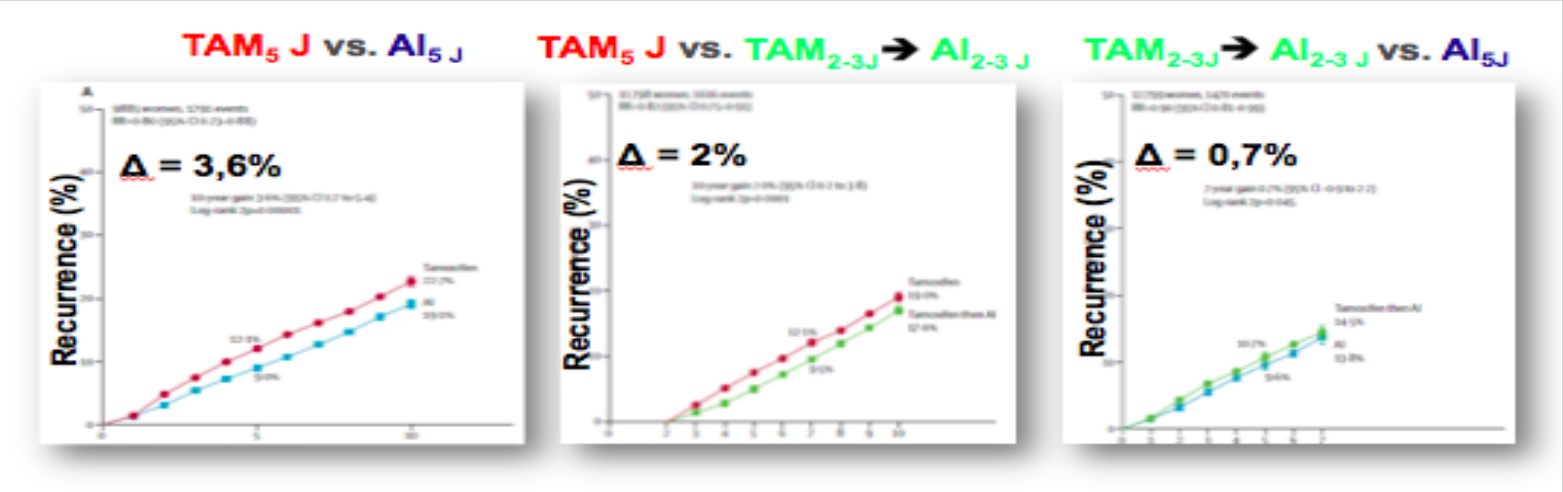

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

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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	+

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

	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 AI	1a	A	+
▪ Low-risk, poor tolerabilty of 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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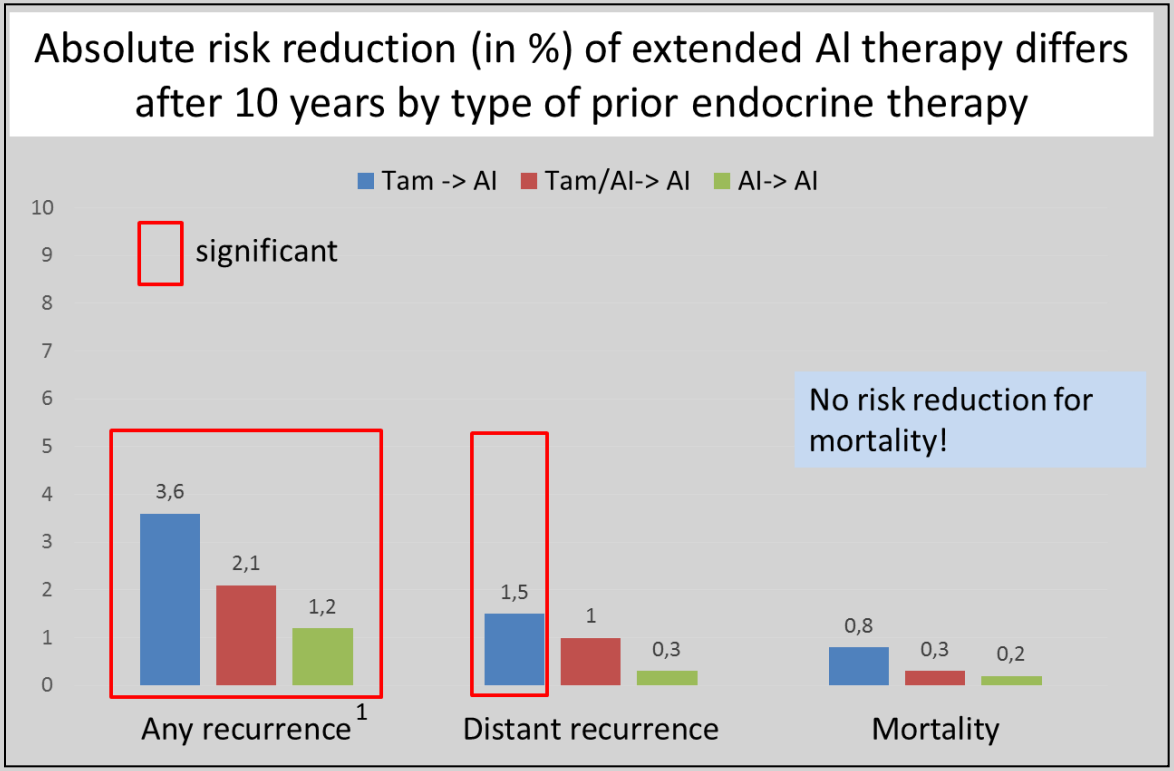

[1] *(new primary breast cancer, local and distant recurrence)*

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
▪ Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (further information www.fertiprotekt.com)			++
▪ CT + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)	1a	A	+
▪ CHT + 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
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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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

Braun: Tamoxifen,

Grün: Tamoxifen oder AI,

Blau: AI

Gestreift: Zeit der randomisierten Intervention vs keine Therapie od. Plazebo,

*: Randomisierungs-zeitpunkt,

§ : MA17R nach 5 Jahren AI mit /ohne Tam zuvor

www.ago-online.de

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HEILEN