Guidelines Breast
Version 2024.1E

Adjuvant Endocrine-based Therapy in pre- and postmenopausal Patients

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

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- **Versions 2002–2023:**
  Bauerfeind / Dall / Diel / Fasching / Fersis / Fehm / Friedrich / Friedrichs / Gerber / Göring / Hanf/ Harbeck / Huober / Jackisch / Lisboa / Loibl / Lück / Lux / Maass / von Minckwitz / Möbus / Müller / Nitz / Oberhoff / Schaller / Scharl / Schneeweiss / Schütz / Solomeyer / Stickeler / Thomssen / Untch

- **Version 2024:**
  Lux / Wöckel

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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. cells:	endocrine sensitive
Unknown hormone receptor status:		endocrine sensitive

If ER negative / PR positive (> 10% positive cells): reassess IHC status
If ER low (1-10%): Implications for therapy should be recommended in the pathology report

Adjuvant Endocrine Therapy
Assessment of Menopausal Status

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

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Adjuvant Endocrine Therapy

	Oxford		
	LoE	GR	AGO
▪ Endocrine responsive	1a	A	++
▪ Endocrine doubtful responsiveness	3b	D	+
▪ Endocrine therapy sequentially after CT	2a	B	+
▪ Endocrine therapy simultaneous to anti-HER2 therapy (w/o chemotherapy)	2b	B	+
▪ Not sensitiv to endocrine therapy	1a	A	--

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General Principles in Adjuvant Endocrine Therapy AGO ++

- **Adjuvant endocrine therapy is divided into initial therapy (years 1-5), extended adjuvant therapy (EAT, years 6-10+) and adjuvant endocrine-based treatment (years 1-2).**
- **Standard treatment duration is 5 years.**
- **Extended therapy and initial adjuvant endocrine-based therapy should be considered based on individual risks and benefits.**
- **Duration, choice & sequence of AI or Tam or the combination with GnRHa mainly depend on menopausal status, tolerability, and risk of recurrence.**
- **Switch to another better tolerated endocrine treatment (Tam or AI) or Tam low dose is better than stopping endocrine therapy altogether.**
- **AI should be used as first treatment in patients, 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.**

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

	Oxford LoE	Oxford GR	AGO
▪ **Low recurrence risk:**			
▪ **Tamoxifen for 5 years**	1a	A	++
▪ **Increased recurrence risk:**			
▪ **OFS 2-5 years* + tamoxifen for 5 years**	1a	A	++
▪ **OFS# + AI for 5 years**	1a	A	++
▪ **GnRHa monotherapie** (If severe contraindications for Tam exist, compared to no therapy)	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. The application of chemotherapy in the trials served as surrogate for high recurrence risk

\# in premopausal women AI only in combination with OFS

Adjuvant endocrine therapy in premenopausal patients (OFS + TAM / AI)

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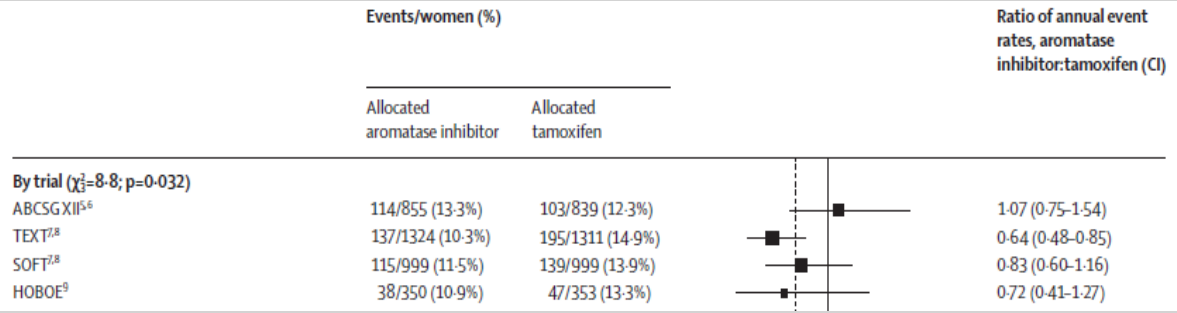
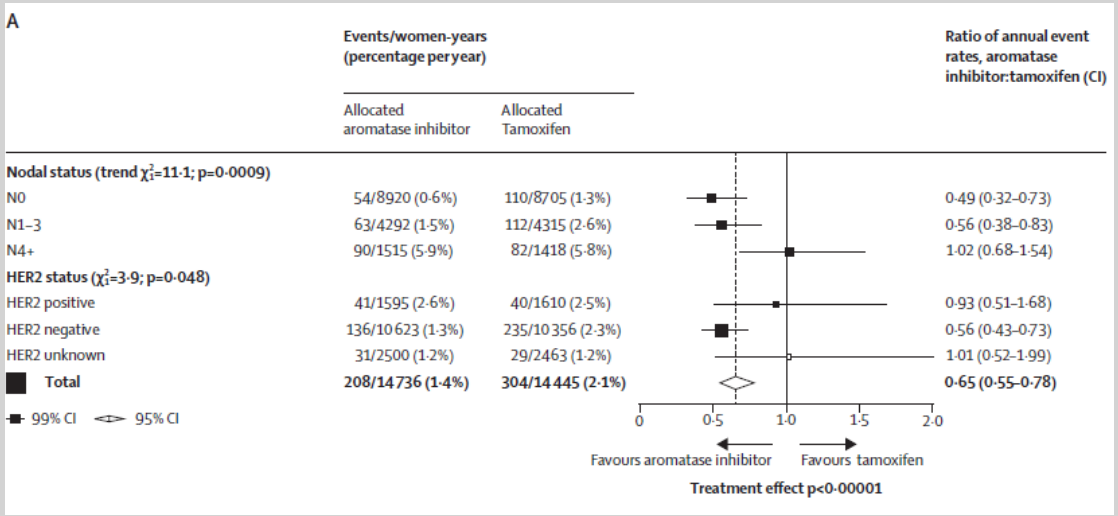


	Events/women (%)		Ratio of annual event rates, aromatase inhibitor:tamoxifen (CI)
	Allocated aromatase inhibitor	Allocated tamoxifen	
By trial (χ^2_3=8·8; p=0·032)			
ABCSG XII[5,6]	114/855 (13·3%)	103/839 (12·3%)	1·07 (0·75–1·54)
TEXT[7,8]	137/1324 (10·3%)	195/1311 (14·9%)	0·64 (0·48–0·85)
SOFT[7,8]	115/999 (11·5%)	139/999 (13·9%)	0·83 (0·60–1·16)
HOBOE[9]	38/350 (10·9%)	47/353 (13·3%)	0·72 (0·41–1·27)



A

	Events/women-years (percentage per year)		Ratio of annual event rates, aromatase inhibitor:tamoxifen (CI)
	Allocated aromatase inhibitor	Allocated Tamoxifen	
Nodal status (trend χ^2_1=11·1; p=0·0009)			
N0	54/8920 (0·6%)	110/8705 (1·3%)	0·49 (0·32–0·73)
N1–3	63/4292 (1·5%)	112/4315 (2·6%)	0·56 (0·38–0·83)
N4+	90/1515 (5·9%)	82/1418 (5·8%)	1·02 (0·68–1·54)
HER2 status (χ^2_1=3·9; p=0·048)			
HER2 positive	41/1595 (2·6%)	40/1610 (2·5%)	0·93 (0·51–1·68)
HER2 negative	136/10623 (1·3%)	235/10356 (2·3%)	0·56 (0·43–0·73)
HER2 unknown	31/2500 (1·2%)	29/2463 (1·2%)	1·01 (0·52–1·99)
Total	**208/14736 (1·4%)**	**304/14445 (2·1%)**	**0·65 (0·55–0·78)**

99% CI 95% CI

0 0·5 1·0 1·5 2·0

Favours aromatase inhibitor Favours tamoxifen

Treatment effect p<0·00001

EBCTCG: Lancet Oncol. 2022;23:382-392

Adjuvant endocrine therapy in premenopausal patients (OFS + TAM / AI)

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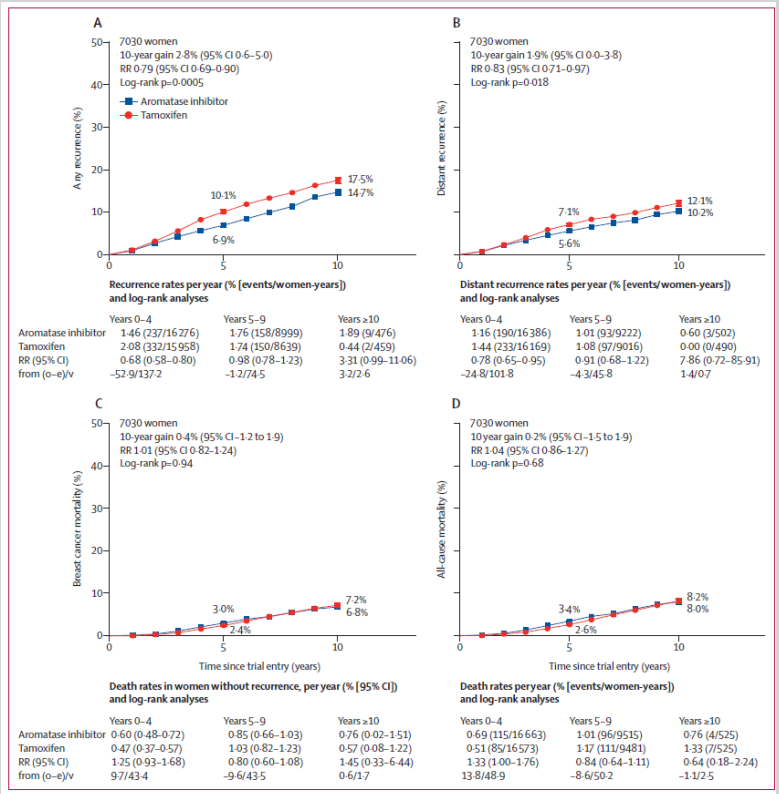
Any recurrence



Distant recurrence

Breast cancer mortality

All-case mortality

www.ago-online.de

FORSCHEN
LEHREN
HEILEN

EBCTCG: Lancet Oncol. 2022;23:382-392

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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. Sequential Therapy - 5 years up-front Therapy

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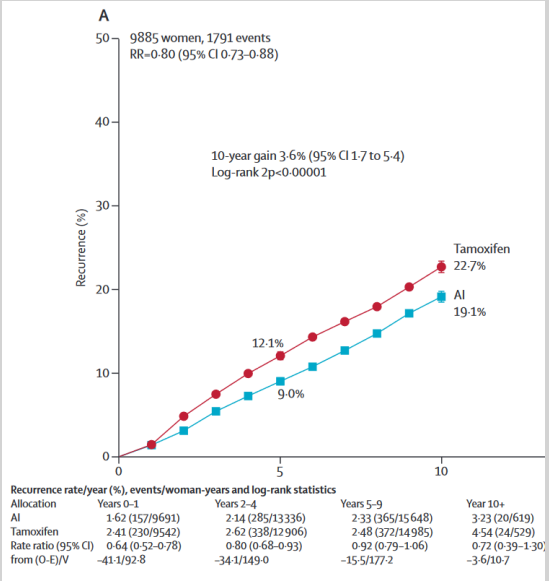

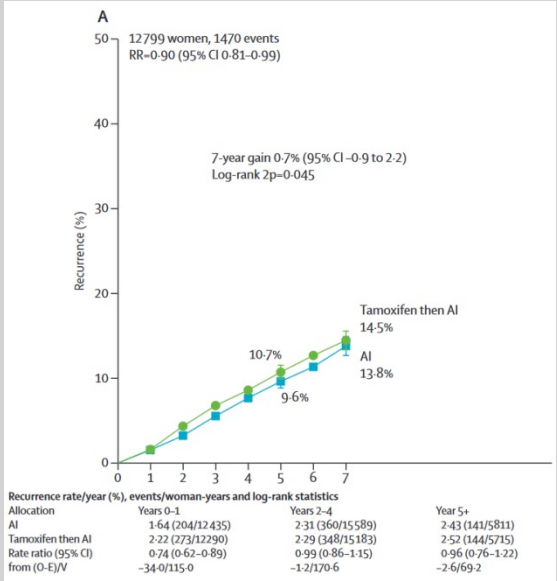

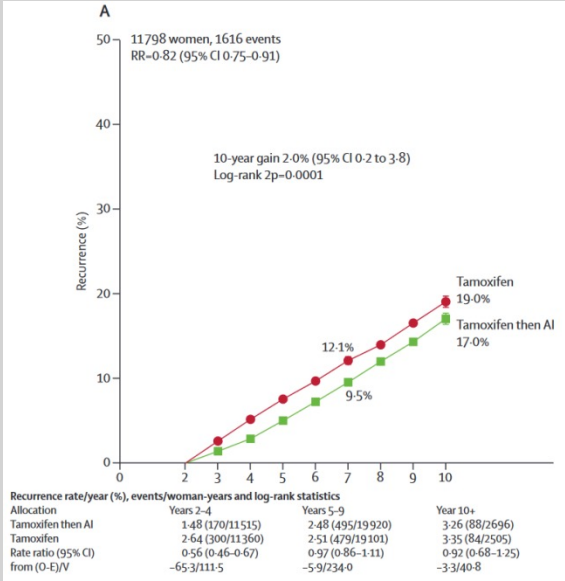

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.

Adjuvante Endocrine-Based Therapy with CDK4/6 Inhibitors and PARP Inhibitors

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	Oxford		
	LoE	GR	AGO
In patients with increased risk of recurrence, characteristics and drug doses corresponding to study criteria			
▪ **Abemaciclib for 2 years***	1b	B	+
▪ **Olaparib for 1 year in patients with *gBRCA1/2* mutations****	1b	B	++

* corresponding to MonarchE-Study
** corresponding to OlympiA-Study

How to calculate CPS+EG Score?

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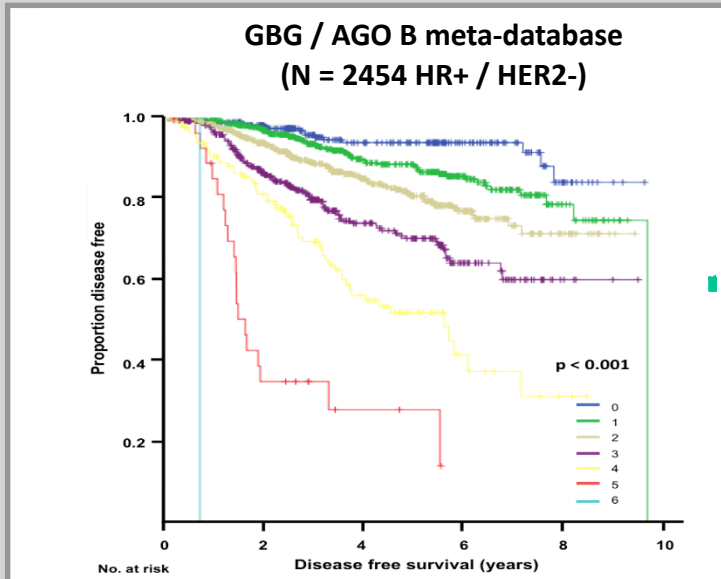
Point assignment for CPS+EG score

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	



25%

Mittendorf EA, J Clin Oncol 2011;29:1956-1962
Marmé F, et al. Eur J Cancer 2021;153:203-212

Adjuvant / Post-Neoadjuvant Treatment with CDK4/6i

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	monarchE	PALLAS	PENELOPE[B]	NATALEE
N	5,637	5,600	1,250	5,101
CDK4/6i	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
% of pts. with NACT	37%	n.r.	100%	n.a.
Duration of CDK4/6i treatment	24 months	24 months	12 months	36 months
Follow-up	42.0 months	24 months	43 months	33.3 months
Discontinuation rate	30.6%	42%	20%	35.5%
Discontinuation rate due to AE_{CDKi}	18.5%	27%	5%	19.5%
IDFS-HR (95%-CI)	0.664 (0.578-0.762) p < 0.0001	0.96 (0.81-1.14) p = 0.65	0.93 (0.74-1.16) p = 0.525	0.749(0,628-0.892) P=0.0006
2-yrs IDFS	92.7% vs. 89.9%	n.r.	88% vs. 78%	93.5% vs. 92.0%
3-yrs IDFS	89.2% vs. 84.4%	88% vs. 89%	81% vs. 78%	90.7% vs. 87.6%
4-yrs IDFS	85.8% vs. 79.4%	84.2% vs. 84.5%	73% vs. 72%	

IDFS: invasive disease-free survival

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Version 2024.1E

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 – 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	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 in total for 7-8 years*			
▪ High-risk of recurrence and good tolerability of AI, good bone health	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)

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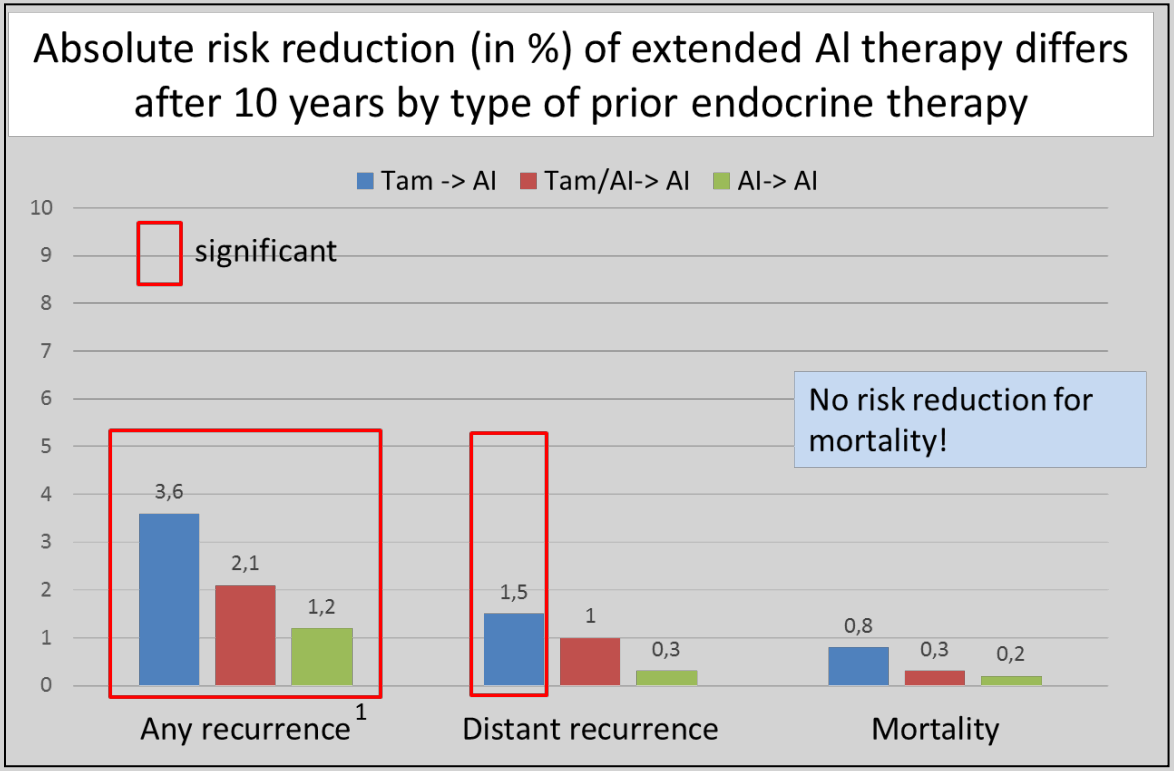

[1] *(new primary breast cancer, local and distant recurrence)*

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

Decision Criteria for Extended Adjuvant Therapy

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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 with GnRHa and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

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	Oxford		
	LoE	GR	AGO
▪ **CTx + GnRHa (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemo-therapy, independent of hormone receptor status)**	1a	A	+
▪ **CTx + GnRHa (preservation of fertility)**	2a	B	+/-
▪ **Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists (ART; further information *https://fertiprotekt.com/english; S2k guideline Fertility protection in patients with malignancies*)**			++

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Fertility Preservation and Assisted Reproductive Therapy (ART)

- Oncologic safety[1] -

	Oxford LoE	Oxford GR	AGO
▪ **Pretreatment approaches to preserve fertility**			
GnRHa	1a	A	++
Cryopreservation of ovarian tissue with subsequent transplantation[2]	4	D	+
Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation	2a	C	+
▪ **ART after breast diagnosis of breast cancer**	4	C	+/-

[1] Evidence is limited due to studies with poor quality e.g. (prospective randomized trials are not feasible)
[2] Risk of relapse caused by transplantation of ovarian tissue containing tumor cells from the original malignancy; removal of transplanted ovarian tissue is necessary in patients with BRCA1/2 mutations due to increased risk of ovarian cancer

Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

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Temporary interruption of adjuvant endocrine treatment (ET) after 18-30 month of ET, allowing a wash out period of 3 months, the attempt to get pregnant in a period of up to 2 years for those women with the desire to get pregnant does not impact short-term breast cancer outcome.

AGO +

Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

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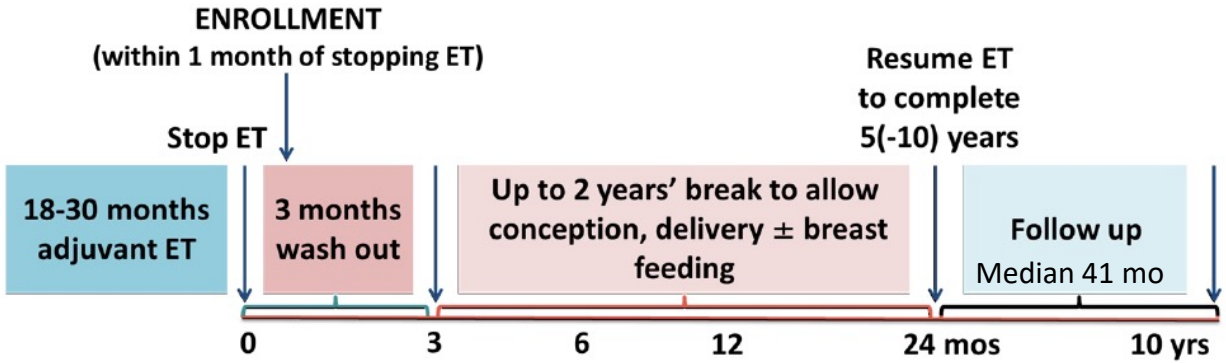
Study design

AGO +

N=516



- Premenopausal women (≤42 years at study entry) wishing to get pregnant
- At least 18 months and no more than 30 months of prior adjuvant ET for stage I-III HR+ BC
- Up to 2 years to attempt pregnancy, conceive, deliver, and breastfeed, including
- 3-months washout period
- If no pregnancy by 1 y., fertility assessment recommended
- ET resumption strongly recommended after pregnancy to complete planned 5-10 yrs.

Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

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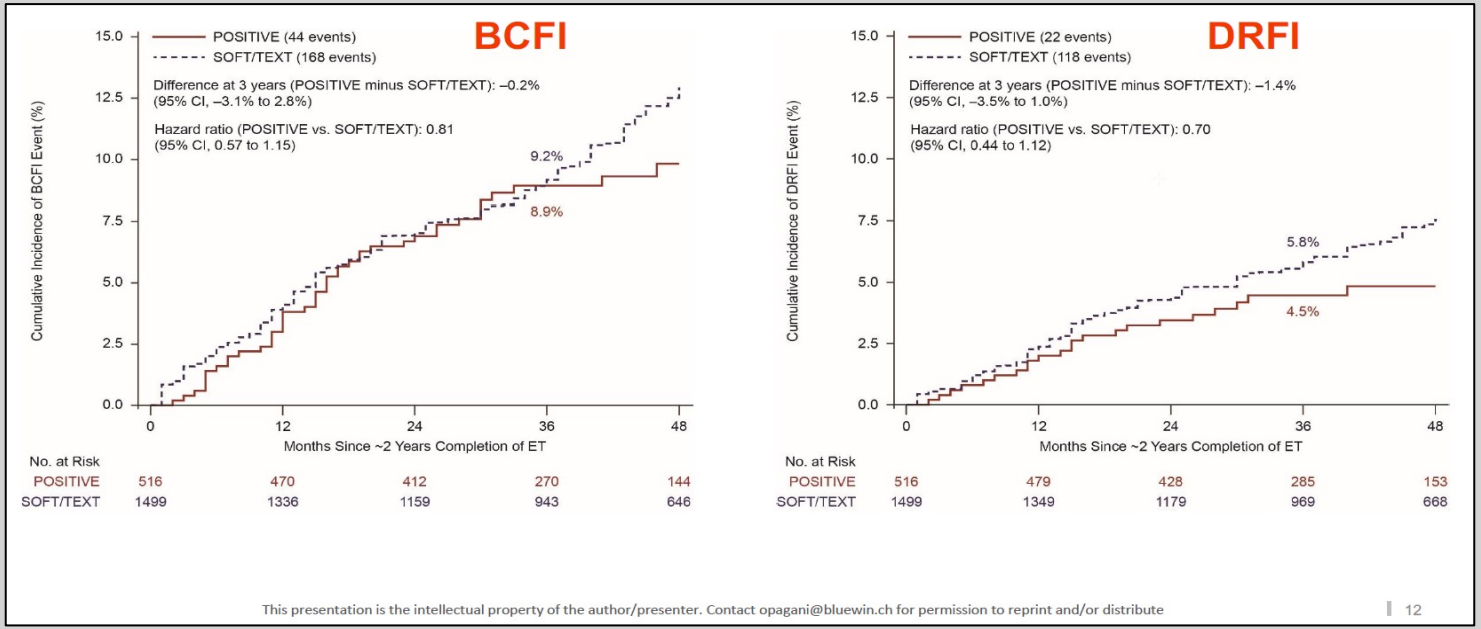
Pregnancies outcome: 317 (64% of all women) had at least one live birth, 62% reported breast feeding, 2% showed birth defects

BREAST CANCER OUTCOMES – POSITIVE & SOFT/TEXT



Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

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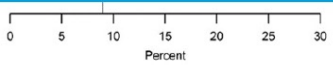
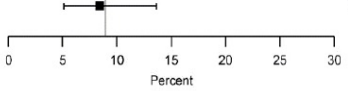
3- YEAR BCFI CUMULATIVE INCIDENCE – POSITIVE only

- 3-year BCFI varied according to clinical-pathological characteristics

Subgroup	No. Events / Total No. Patients	3-Year BCFI Cumulative Incidence Percent (95% CI)
Overall	44/516	8.9 (6.7–11.9)
Age at enrollment (years)		
<35	14/177	9.1 (5.4–14.9)
35–39	18/221	7.7 (4.8–12.3)
40–42	12/118	11.2 (6.5–18.9)
BMI at enrollment (kg/m²)*		
<25	34/371	9.5 (6.8–13.2)
25 to <30	7/90	8.0 (3.9–16.1)
≥30	3/49	7.2 (2.4–20.9)
BRCA status		
BRCA Positive	5/38	14.5 (6.3–31.6)
Other mutation	4/21	10.5 (2.7–35.9)
No documented mutation†	35/457	8.4 (6.1–11.5)
HER2 status		
Positive	6/134	4.9 (2.2–10.6)
Negative	38/382	10.4 (7.6–14.1)
Nodal status		
pN0	21/342	6.6 (4.3–10.0)
pN+ 1–3	18/151	12.6 (8.1–19.3)
pN+ 4–9	5/23	18.7 (7.4–42.6)



Subgroup	No. Events / Total No. Patients	3-Year BCFI Cumulative Incidence Percent (95% CI)
Tumor size (cm)‡		
≤2	24/331	7.6 (5.1–11.2)
>2 to ≤5	16/161	10.3 (6.3–16.5)
>5	4/21	21.1 (8.3–47.6)
Tumor grade‡		
1 (BRE 3–5)	5/89	6.4 (2.7–14.8)
2 (BRE 6–7)	21/252	8.9 (5.8–13.6)
3 (BRE 8–9)	18/172	10.4 (6.6–16.2)
Breast surgery		
Mastectomy	29/233	12.7 (8.9–17.9)
Breast conservation	15/283	5.7 (3.4–9.5)
Prior endocrine therapy		
SERM alone	20/215	9.9 (6.4–15.1)
SERM+OFS	20/184	11.4 (7.4–17.4)
AI+OFS	1/82	1.2 (0.2–8.4)
Other	3/35	8.8 (2.9–24.9)
Prior chemotherapy		
Anthracycline (A) based	8/36	19.4 (9.8–36.5)
Taxane (T) based	4/66	6.7 (2.5–16.9)
Both A and T based	16/215	8.4 (5.2–13.4)
Neither A or T based	0/3	
None	16/196	8.4 (5.1–13.6)



Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

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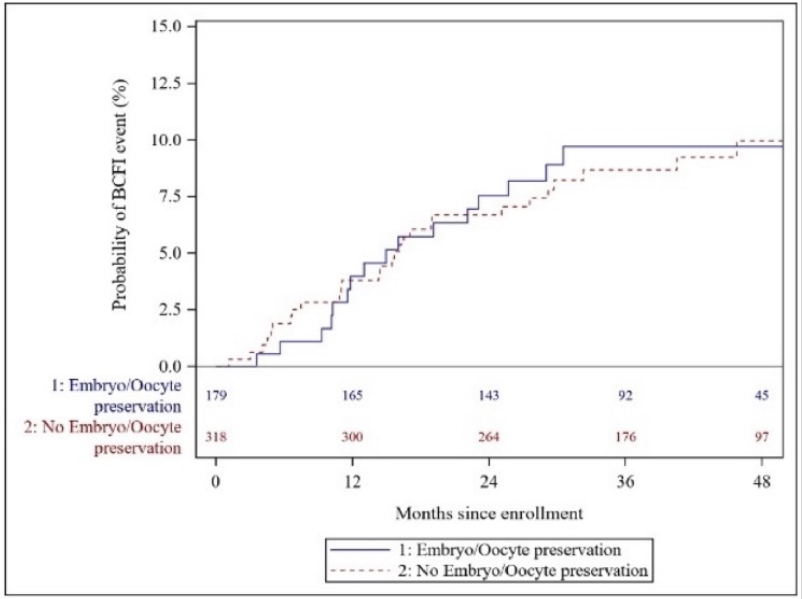
Version 2024.1E

Ovarian stimulation and breast cancer outcome – results from the POSITIVE trial

1) As part of embryo/oocyte cryopreservation - after BC diagnosis

At 3-years, BCFI-events cumulative incidence

- **9.7%** (95% CI: 6.0% to 15.4%) for the 179 patients who underwent ovarian stimulation
- **8.7%** (95% CI: 6.0% to 12.5%) for the 318 patients who did not



Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

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Ovarian stimulation and breast cancer outcome – results from the POSITIVE trial

2) As part of ART - after enrollment

- **397 patients alive and BC free at 24-months (landmark analysis)**
  - 2 BC events amongst 71 patients in the ovarian stimulation group
  - 8 BC events amongst 326 patients in the non-ovarian stimulation group