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Version 2023.1E

# Adjuvant Endocrine-based Therapy in pre- and postmenopausal Patients

# Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients



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- **Versions 2002–2022:**
  **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 2023:**
  **Gerber / Jackisch**

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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**

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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 | 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) 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, 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.**

# TEXT / SOFT Joint Analysis

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

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

*5 yrs*

- **Tamoxifen 20 mg/day + OFS*** (n = 1328)
- **Exemestane 25 mg/day + OFS*** (n = 1332)
- **Tamoxifen 20 mg/day + OFS*** (n = 1016)
- **Exemestane 25 mg/day + OFS*** (n = 1014)
- **Tamoxifen 20 mg/day**

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

| | Oxford | | |
|---|---|---|---|
| | LoE | 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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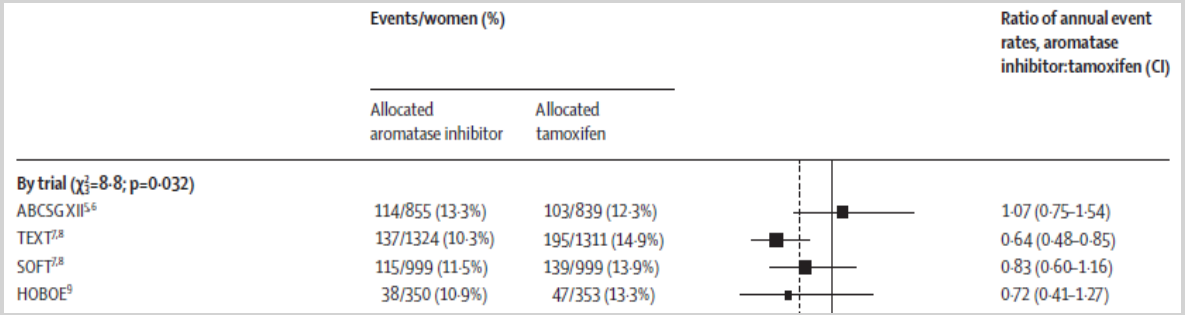
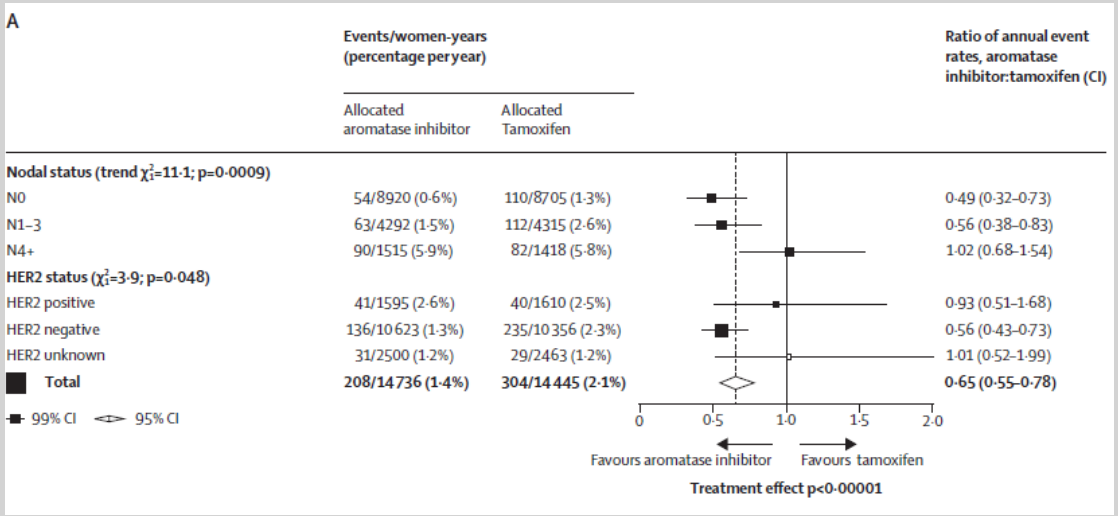


| | Events/women (%) | | Ratio of annual event rates, aromatase inhibitor:tamoxifen (CI) |
|---|---|---|---|
| | Allocated aromatase inhibitor | Allocated tamoxifen | |
| **By trial ($\chi^2_3$=8·8; p=0·032)** | | | |
| ABCSG XII[5,6] | 114/855 (13·3%) | 103/839 (12·3%) | 1·07 (0·75–1·54) |
| TEXT[7,8] | 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 $\chi^2_1$=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 ($\chi^2_1$=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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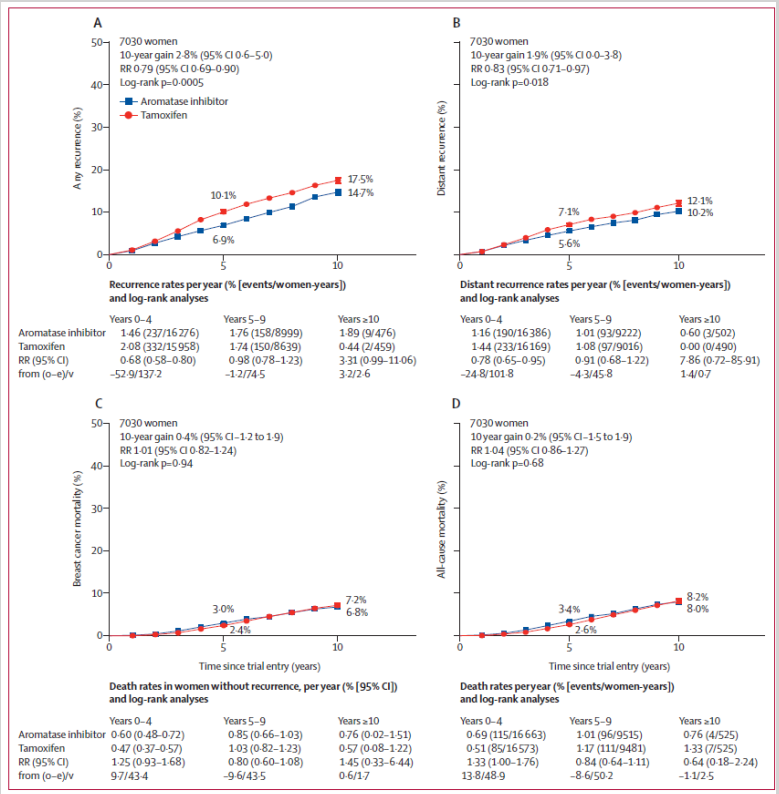
**Any recurrence**




**Distant recurrence**

**Breast cancer mortality**

**All-case mortality**

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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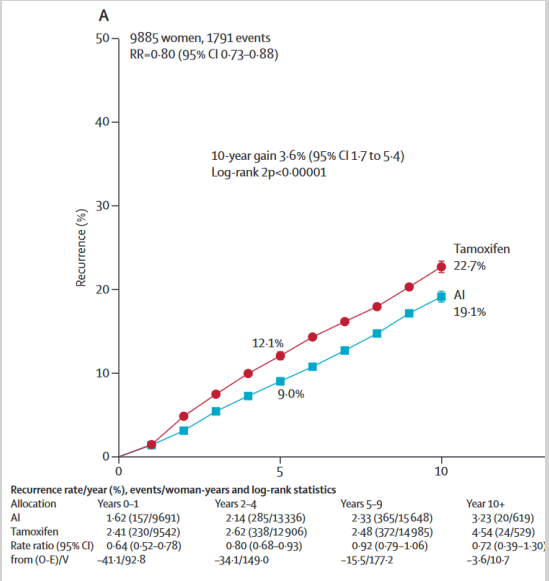


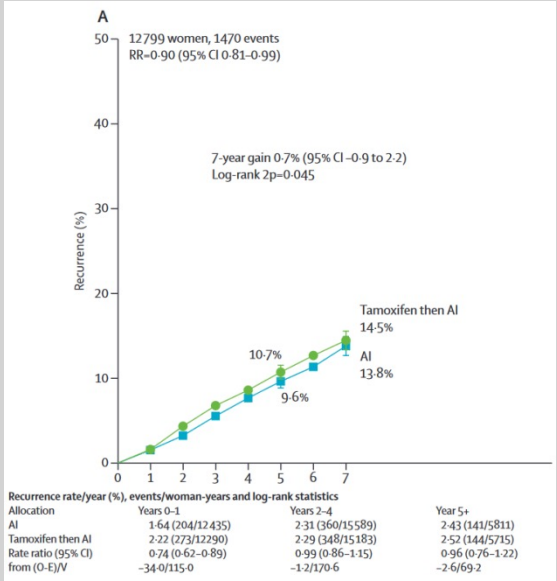


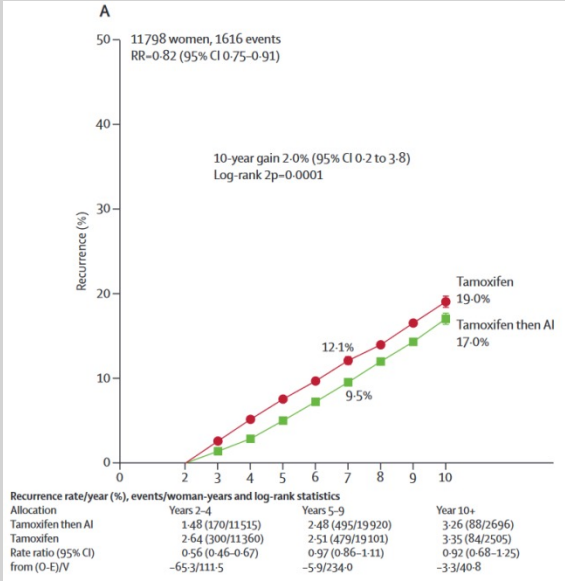


**Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet. 2015 Oct 3;386(10001):1341-52.**

# 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 and characteristics 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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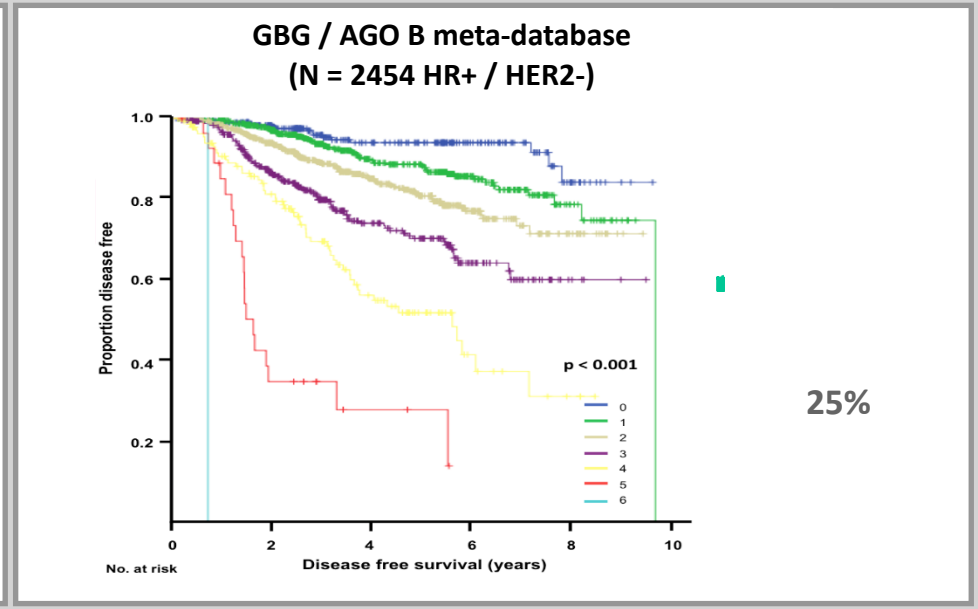
**Point assignment for CPS+EG score**

| | | |
|---|---|---|
| **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 | |




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

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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 – 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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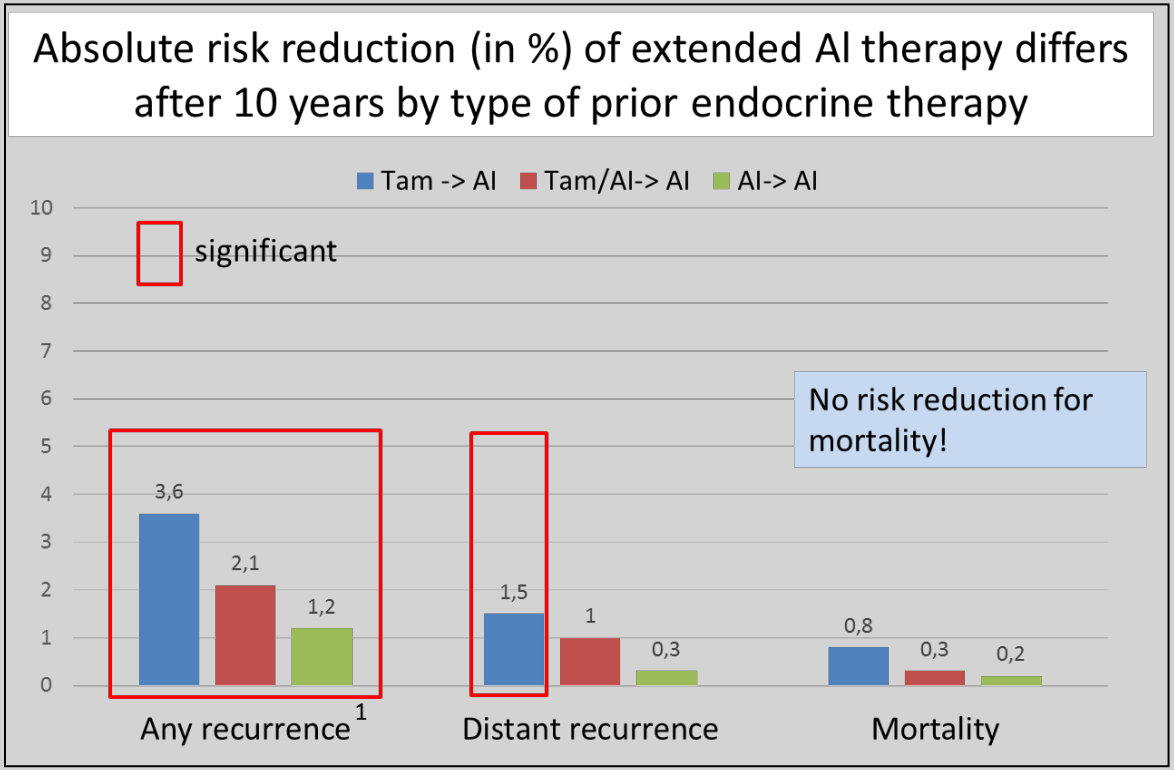


[1] *(new primary breast cancer, local and distant recurrence)*

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

# 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 |
| GIM 4 | | | | | | | | | | | | 5 vs 7 | 0,78 | 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 |

**Braun:** Tamoxifen

**Grün:** Tamoxifen oder AI

**Blau:** AI

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

*: Rando-misierungs-zeitpunkt

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



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FORSCHEN
LEHREN
HEILEN

# 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 (neo-)adjuvant systemic treatment** | 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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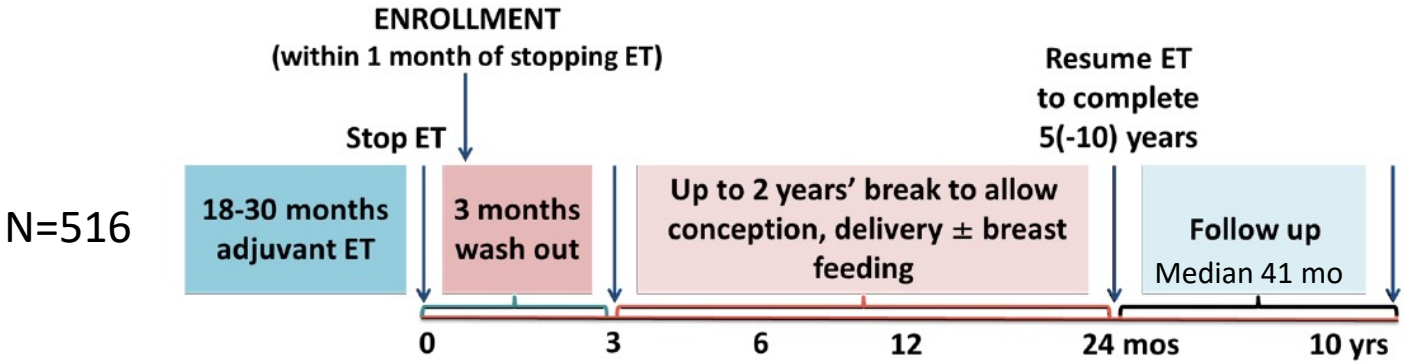
## Study design

**AGO +**




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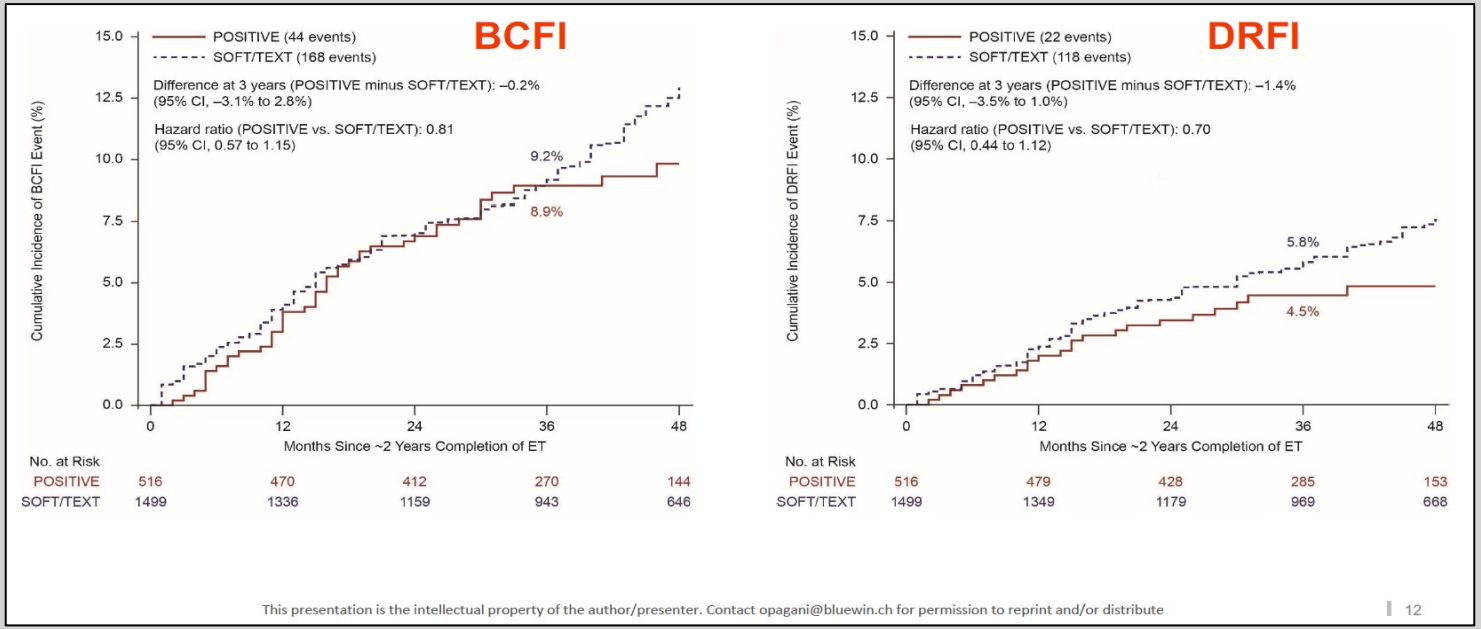
Pregnancies outcome: 317 (64% of all women) had at least one live birth, 62% reported breast feeding, 2% showed birth defects

**BREAST CANCER OUTCOMES – POSITIVE & SOFT/TEXT**



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



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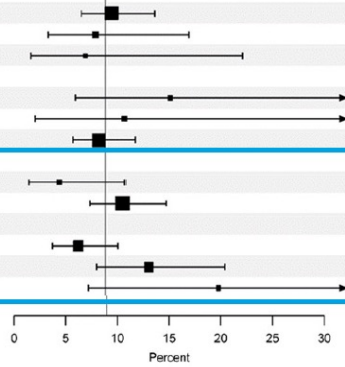
## 3- YEAR BCFI CUMULATIVE INCIDENCE – POSITIVE only

- 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) |