Adjuvant Endocrine-based Therapy in pre- and postmenopausal Patients
Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

- **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
Assessment of Steroid Hormone Receptor Status

Endocrine responsive – hormone receptor positive

<table>
<thead>
<tr>
<th>Immunohistology (ER and/or PgR)</th>
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<tbody>
<tr>
<td>0% pos. cells:</td>
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<tr>
<td>1–10% pos. cells:</td>
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<tr>
<td>&gt; 10% pos. cells:</td>
</tr>
<tr>
<td>Unknown hormone receptor status:</td>
</tr>
</tbody>
</table>

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

Endocrine responsiveness:

In case of ER negative / PR positive (>10% cells): consider immunohistochemical re-evaluation:
1. Viale G, Regan MM, Maiorano E et al. Prognostic and predictive value of centrally reviewed expression of estrogen and progesterone...


Adjuvant Endocrine Therapy

- **Endocrine responsive**
- **Endocrine doubtful responsiveness**
- **Endocrine therapy sequentially after CT**
- **Endocrine therapy simultaneous to anti-HER2 therapy (w/o chemotherapy)**
- **Not sensitiv to endocrine therapy**

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<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
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<tbody>
<tr>
<td>Endocrine responsive</td>
<td>1a</td>
<td>A</td>
<td>++</td>
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<tr>
<td>Endocrine doubtful responsiveness</td>
<td>3b</td>
<td>D</td>
<td>+</td>
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<tr>
<td>Endocrine therapy sequentially after CT</td>
<td>2a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Endocrine therapy simultaneous to anti-HER2 therapy (w/o chemotherapy)</td>
<td>2b</td>
<td>B</td>
<td>+</td>
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<tr>
<td>Not sensitiv to endocrine therapy</td>
<td>1a</td>
<td>A</td>
<td>--</td>
</tr>
</tbody>
</table>

11. Loibl S, H Chiun-Sheng, Mano MS, Adjuvant trastuzumab emtansine (T-DM1) vs trastuzumab (T) in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: subgroup analysis from KATHERINE. ESMO Breast 2020
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.

18. Hortobagyi G, Stroyakovsky D, Yardley D, et al. Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2– early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial. SABCS, 2023, GS03-03
20. De Censi A. et al., 10 Year Results of Phase 3 Trial of low-dose Tamoxifen in noninvasive Breast Cancer, SABCS, 2022, GS408
Tamoxifen 5-10 yrs:

GnRH as monotherapy:
1. Cuzick J, Ambroisine L, Davidson N et al: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in

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**Premenopausal Patients**

**Initial Adjuvant Endocrine Therapy (Year 1-5)**

<table>
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<tr>
<th>Oxford</th>
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<tr>
<td>Low recurrence risk:</td>
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<tr>
<td>Tamoxifen for 5 years</td>
<td>1a</td>
<td>A</td>
<td>++</td>
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<tr>
<td>Increased recurrence risk:</td>
<td></td>
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<tr>
<td>OFS 2-5 years* + tamoxifen for 5 years</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>OFS* + AI for 5 years</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>GnRHa monotherapie (If severe contraindications for Tam exist, compared to no therapy)</td>
<td>1a</td>
<td>B</td>
<td>+</td>
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</table>

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 premenopausal women AI only in combination with OFS

**Ovarian function suppression (OFS) with Tam/Al and Tam with or without OFS:**


4. Regan MM, Walley BA, Fleming GF et al. Randomized comparisons of adjuvant exemestane + ovarian function suppression versus Tamoxifen + OFS versus tamoxifen in premenopausal women with HR + early breast: update of the TEXT and SOFT trials. SABCS 2021, GS2-05.


### Postmenopausal Patients

**Initial Adjuvant Endocrine Therapy (Years 1-5)**

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<td>1a</td>
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**Aromatase inhibitor (AI) for first 5 years**
- Non steroidal-AI in lobular cancer
- High risk of recurrence

**Sequential therapy for first 5 years** *
- Tam (2-3 yrs.) followed by AI to complete 5 years
- AI (2-3 yrs.) followed by tamoxifen to complete 5 years

**Tamoxifen 20 mg/d for 5 years** **

* ** 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

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**AI for first 5 years:**
3. FACE Studie?

**Especially in case of lobular cancer**
1. Strasser-Weippl K et al. Outcomes in women with invasive ductal or invasive lobular early stage breast cancer treated with anastrozole or exemestane in CCTG (NCIC CTG) MA.27. Eur J Cancer 2018;90:19-25. doi: 10.1016/j.ejca.2017.11.014

**High risk of recurrence:**
1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Aromatase inhibitors versus tamoxifen in early breast cancer: patient-
Sequential therapy for first 5 years:
Tam (2-3 yrs.) followed by AI to complete 5 years
AI (2-3 yrs.) followed by Tam to complete 5 years


Tamoxifen 20 mg/d for first 5 yrs:
3. Rydén L, Heibert Arnlind M, Vitols S et al. Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal
early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. Breast. 2016;26:106-14.

**Patient care/ adherence and side effects**


8. Hortobagyi G, Stroyakovsky D, Yardley D, et al. Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2− early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial. SABCS, 2023, GS03-03


5. Johnston et al. SABCS 2022

6. Hortobagyi GN, Stroyakovskiy D, Yardley DA et al. (GS03-03) Ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) as adjuvant treatment in patients with HR+/HER2- early breast cancer: final invasive disease–free survival (iDFS) analysis from the NATALEE trial SABCS 2023 (GS03-03)
**Premenopausal Patients**

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

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<td>5</td>
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**In case of high risk of recurrence**

- 5 years tamoxifen after 5 years tamoxifen
- 2.5 – 5 years AI after 5 years tamoxifen in initially premenopausal patients who obtain validated postmenopausal status during course of therapy
- 5 years tamoxifen after 5 years of endocrine therapy + OFS

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**5 years Tamoxifen after 5 years Tamoxifen:**


2. Gray RG, Rea D, Handley K et al. ATTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6953 women with early breast cancer. J Clin Oncol 2013; 31 (18 suppl):S.


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**2–5 years AI after 5 years Tamoxifen in initially premenopausal patients with validated postmenopausal status in the course of therapy:**

### Postmenopausal Patients

**Extended Adjuvant Endocrine Therapy (EAT) (Years 6–10)**

<table>
<thead>
<tr>
<th>In case of high risk of recurrence</th>
<th>Oxford</th>
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<tbody>
<tr>
<td><strong>5 years tamoxifen after 5 years tamoxifen</strong></td>
<td>1a A +</td>
</tr>
<tr>
<td><strong>2–5 years AI after 5 years tamoxifen</strong></td>
<td>1a A ++</td>
</tr>
<tr>
<td><strong>After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI in total for 7-8 years</strong></td>
<td></td>
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<tr>
<td>- High-risk of recurrence and good tolerability of AI, good bone health</td>
<td>1a A +</td>
</tr>
<tr>
<td>- Low-risk, poor tolerability of AI</td>
<td>1a A -</td>
</tr>
<tr>
<td><strong>Interruption of endocrine treatment up to 3 months during EAT with AI</strong></td>
<td>1b B +/-</td>
</tr>
</tbody>
</table>

* Up to date, no impact on OS

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**5 years Tamoxifen after 5 years Tamoxifen:**

2–5 years AI after 5 years Tamoxifen
7. Gray R (EBCTCG ) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials. SABCS 2018;GS3-03
10. Del Mastro L, Masutti M, Bisagni G: Extended therapy with letrozole as adjuvant treatment of postmenopausal patients with early-

11. Mamounas EP, Bandos H: Ten year results from NRG/NSABP – B42: a randomized, double blinded placebo controlled clinical trial of extended adjuvant endocrine therapy with letrozole in postmenopausal women with hormone receptor + breast cancer who have completed previous adjuvant therapy with an aromatase inhibitor after initial AI containing therapy (upfront or switch) further prolongation of endocrine therapy with AI 2-5years. SABCS 2019, GS4-01


**low risk, poor tolerability of the AI**


6. Gray R (EBCTCG ) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials. SABCS 2018;GS3-03


Interruption of endocrine treatment up to 3 months during EAT:

1. Gray R (EBCTCG ) et al. Extended aromatase inhibitor treatment following 5 or more years of endocrine therapy: a metaanalysis of 22192 women in 11 randomised trials. SABCS 2018;GS3-03


10. Bartlett J, Sgroi D: Trans-aTTom: Breast Cancer Index predicts benefit of extended endocrine therapy in HR+ breast cancers treated in the adjuvant tamoxifen-to offer more (aTTom) trial Abstract 505 ASCO 2019


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

- **CTx + GnRHa** (preservation of ovarian function) (GnRHa application > 2 weeks prior to chemotherapy, independent of hormone receptor status)
- **CTx + GnRHa** (preservation of fertility)
- **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](https://fertiprotekt.com/english))

**Oxford**

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<tr>
<td>1a</td>
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<td>+</td>
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<tr>
<td>2a</td>
<td>B</td>
<td>+/-</td>
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Fertility preservation counselling

5. [https://register.awmf.org/assets/guidelines/015-082l_S2k_Fertilitaetserhaltung-bei-onkologischen-Therapien_2017-12-verlaengert.pdf](https://register.awmf.org/assets/guidelines/015-082l_S2k_Fertilitaetserhaltung-bei-onkologischen-Therapien_2017-12-verlaengert.pdf)

Fertility preservation with assisted reproduction therapy


Prognosis is not influenced by fertility preservation and ART:

Ovarian function protection
6. Zong X, Yu Y, Yang H, Chen W et al. Effects of Gonadotropin-Releasing Hormone Analogs on Ovarian Function Against Chemotherapy-
Induced Gonadotoxic Effects in Premenopausal Women With Breast Cancer in China: A Randomized Clinical Trial. JAMA Oncol. 2022;8(2):252-258


Pregnancy rates


## Fertility Preservation and Assisted Reproductive Therapy (ART) - Oncologic safety

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### Pretreatment approaches to preserve fertility

- **GnRHa**
  - 1a A ++

- **Cryopreservation of ovarian tissue with subsequent transplantation**
  - 4 D +

- **Cryopreservation of oocytes (unfertilized / fertilized) after ovarian stimulation**
  - 2a C +

### ART after breast diagnosis of breast cancer

- 4 C +/-

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### GnRH-Analogue:


### Cryopreservation of ovarian tissue:


2. Rosendahl M, Greve T, Andersen CY. The safety of transplanting cryopreserved ovarian tissue in cancer patients: a review of the
Cryoconservation of oocytes after ovarian stimulation:

ART after treatment:
2. Azim H, Niman S, Patridge A et al. Fertility preservation and assisted reproductive technologies in breast cancer patients interrupting adjuvant endocrine therapy to attempt pregnancy. Results from the positive trial. SABCS 2023
Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

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 +

1. Partridge, A. on behalf of the POSITIVE Consortium: Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive breast cancer Initial Results from the POSITIVE Trial (IBCSG 48-14 / BIG 8-13 / Alliance A221405), SABCS 2022
Adjuvant endocrine therapy in premenopausal patients with the desire to get pregnant

Study design

**GO +**

- 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.

5. Partridge, A. on behalf of the POSITIVE Consortium: Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive breast cancer Initial Results from the POSITIVE Trial (IBCSG 48-14 / BIG 8-13 / Alliance A221405), SABCS 2022
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1. Azim H, Niman S, Patridge A, et al. Fertility preservation and assisted reproductive technologies (ART) in breast cancer (BC) patients (pts) interrupting endocrine therapy (ET) to attempt pregnancy. SABCS 2023, GS02-11
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