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

- **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
Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1  GR: A  AGO: ++

Endocrine responsive – hormone receptor positive

<table>
<thead>
<tr>
<th>Immunohistology (ER and/or PgR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% pos. cells:</td>
</tr>
<tr>
<td>1–10% pos. cells:</td>
</tr>
<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

Endocrine responsiveness:

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


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

NEU:
• CTS-5
• BCI (H/I)


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

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low recurrence risk:</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Tamoxifen for 5 years</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Increased recurrence risk:</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<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 monotherapy*</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* 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

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...

Ovarian function suppression (OFS) with Tam/AI and Tam with or without OFS:
3. 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)

### Oxford

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

- **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** **

* \[ \text{in postmenopausal patients, AI should be integrated in the first five years} \]

** \[ \text{Tamoxifen may be offered to individual patients with very low risk of recurrence or if contraindications for AI are present} \]

---

### 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**


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

In patients with increased risk of recurrence and characteristics corresponding to study criteria
- Abemaciclib for 2 years*
- Olaparib for 1 year in patients with gBRCA1/2 mutations**

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>

* corresponding to MonarchE-Study
** corresponding to Olympia-Study


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  +

5 years Tamoxifen after 5 years Tamoxifen:

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)**

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**In case of high risk of recurrence**

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


11. Mamounas EP, Bandos H: Ten year results from NRG/NSABP – B42: a randomized , double blinded placebo controlle clinical trial of extended adjuvant endocrine therapy with letrozole in postmenopausal women with hormone receptor + breast cancer who have completed previoius 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
ow 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
## Extended Adjuvant Treatment, Overview

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>Duration</th>
<th>HR for DFS 0-5 years</th>
<th>Duration</th>
<th>HR for DFS 5-10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLAS*</td>
<td>5 vs 10</td>
<td></td>
<td>0.75 – 0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTOM*</td>
<td>5 vs 10</td>
<td></td>
<td>0.75 – 0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA.17*</td>
<td>5 vs 10</td>
<td></td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP B-33*</td>
<td>5 vs 10</td>
<td></td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCSG 6a*</td>
<td>5 vs 8</td>
<td></td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DATA*</td>
<td>6 vs 9</td>
<td></td>
<td>0.79</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>NSABP B-42*</td>
<td>5 vs 10</td>
<td></td>
<td>0.85</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>GIM 4</td>
<td>5 vs 7</td>
<td></td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA.17R §</td>
<td>10 vs 15</td>
<td>100</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: Randomised intervention vs no therapy or placebo

§: MA17R after 5 years AI with/without Tam previous

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* Tamoxifen
* Alendronate
* AI: aromatase inhibitors

**Guidelines Breast Version 2023.1E**

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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

Fertility preservation counselling

Fertility preservation with assisted reproduction therapy


Prognosis is not influenced by fertility preservation and ART:

Ovarian function protection


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

- Pretreatment approaches to preserve fertility
  - GnRH agonists
    - LoE: 1a, Grade: A, Evidence: ++
  - Cryopreservation of ovarian tissue with subsequent transplantation
    - LoE: 4, Grade: D, Evidence: +
  - Cryopreservation of oocytes (unfertilized/fertilized) after ovarian stimulation
    - LoE: 2a, Grade: C, Evidence: +
  - ART after (neo-)adjuvant systemic treatment
    - LoE: 4, Grade: C, Evidence: +


Cryopreservation of ovarian tissue:


Cryoconservation of oocytes after ovarian stimulation:


ART after treatment:

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

<table>
<thead>
<tr>
<th>ENROLLMENT (within 1 month of stopping ET)</th>
<th>Resume ET to complete 5-10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop ET</td>
<td>Follow up Median 41 mo</td>
</tr>
<tr>
<td>18-30 months adjuvant ET</td>
<td>Up to 2 years’ break to allow conception, delivery &amp; breast feeding</td>
</tr>
<tr>
<td>3 months wash out</td>
<td></td>
</tr>
<tr>
<td>0 3 6 12 24 mos</td>
<td></td>
</tr>
<tr>
<td>N=516</td>
<td></td>
</tr>
</tbody>
</table>

- 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.

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

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**

1. Ann Partridge 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
1. Ann Partridge 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