Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients
Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

- **Versions 2002–2020:**
  Bauerfeind / Dall / Diel / Fersis / Fehm / Friedrichs / Gerber / Göring /
  Hanf / Harbeck / Huober / Jackisch / Lisboa / Lück / Lux / Maass / von
  Minckwitz / Möbus / Müller / Nitz / Oberhoff / Schaller / Scharl /
  Schneeweiss / Schütz / Solomeyer / Stickeler / Thomssen /

- **Version 2021:**
  Fasching / Loibl
Endocrine responsiveness:

In case of ER negative / PR positive (>10% positive 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 receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early breast


8. Furlanetto J, Nekljudova V: Impact of chemotherapy-induced ovarian failure (CIOF) on disease–fee survival (dfs) and overall survival (osI in young women with early breast cancer, ESMO 2019 180 PD


8. Regan MM, Walley BA, Francis PA et al. Concurrent and sequential initiation of ovarian function suppression with chemotherapy in

### Adjuvant Endocrine Therapy

<table>
<thead>
<tr>
<th>Endocrine therapy</th>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine responsive</td>
<td>1a A</td>
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<tr>
<td>Endocrine doubtful responsiveness</td>
<td>3b D</td>
<td>+</td>
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<tr>
<td>Endocrine therapy sequentially after CT</td>
<td>5 D</td>
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<tr>
<td>Endocrine therapy concurrent with T-DM1/anti-HER2 therapy (w/o chemotherapy)</td>
<td>5 D</td>
<td>+</td>
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<tr>
<td>Non-responsive: No endocrine therapy</td>
<td>1a A</td>
<td>++</td>
<td></td>
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</tbody>
</table>

9. Villegas S, Lederer B: Similarities between low hormone receptor positive and hormone receptor negative breast cancer: an analysis of 4366 patients from multicenter clinical trials, SABCS 2018 P2-08-10


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, 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.


NEU:
- CTS-5
- BCI (H/I)
Premenopausal Patients

Initial Adjuvant Endocrine Therapy (Year 1-5)

- Tamoxifen 5 years (low risk of relapse)
- Tamoxifen + OFS 2-5 years (intermediate risk of relapse)*
- AI + OFS* for 5 years (high risk of relapse)*
- GnRH alone
  (only, if relevant contraindication for Tam vs. no therapy at all)

OFS: ovarian function suppression
* as long as tolerated and the patient is clearly premenopausal
after chemotherapy if ovarian function resumes within 24 months
Applicaiton of chemotherapy in the trials served as a surrogate for high recurrence risk
# In premenopausal women AI only in combination with OFS

Tamoxifen 5-10 yrs:
GnRH as monotherapy:

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


Postmenopausal Patients
Initial Adjuvant Endocrine Therapy (Years 1-5)

- 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**

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<th>Oxford</th>
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</table>

* 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

AI for first 5 years:
3. FACE Studie?
   - Especially in case of lobular cancer
4. 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:
**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:**
Patient care/ adherence and side effects


### Adjuvant therapy with CDK 4/6 inhibitors

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<td>C</td>
<td>−</td>
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<tr>
<td>1b</td>
<td>B</td>
<td>−</td>
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</table>

In patients at high-risk of relapse according to trial 1,2,3

- Abemaciclib for 2 years + standard endocrine therapy
- Palbociclib for 2 years + standard endocrine therapy
- Palbociclib for 1 year + standard endocrine therapy


### Premenopausal Patients

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

<table>
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<th>Oxford</th>
<th>LoE</th>
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<td>1a</td>
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<td>1b</td>
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#### In case of high risk of recurrence

- 5 years Tamoxifen after 5 years Tamoxifen
- 2–5 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

#### 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)**

<table>
<thead>
<tr>
<th>In case of high risk of recurrence</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
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</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 for 2–5 years*</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>High-risk and good tolerability of AI</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

### 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 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 Al containing therapy (upfront or switch) further prolongation of endocrine therapy with Al 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 (EBCTCG)
## Extended adjuvant treatment, overview

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Time to Diagnosis (Years)</th>
<th>DFS Comparison</th>
<th>AI Therapy (%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLAS</td>
<td>Tamoxifen</td>
<td>5 vs 10</td>
<td>0.75 vs 0.80</td>
<td>0</td>
</tr>
<tr>
<td>ATTOM</td>
<td>Tamoxifen</td>
<td>5 vs 10</td>
<td>0.75 vs 0.80</td>
<td>0</td>
</tr>
<tr>
<td>MA17</td>
<td>Tamoxifen</td>
<td>5 vs 10</td>
<td>0.57 vs 0.60</td>
<td>0</td>
</tr>
<tr>
<td>NCCTC</td>
<td>TAMOXIFEN</td>
<td>5 vs 10</td>
<td>0.63 vs 0.68</td>
<td>0</td>
</tr>
<tr>
<td>ADJUVANT</td>
<td>Tamoxifen</td>
<td>5 vs 8</td>
<td>0.62 vs 0.68</td>
<td>0</td>
</tr>
<tr>
<td>DATA</td>
<td>Alendronate</td>
<td>6 vs 9</td>
<td>0.79 vs 1.00</td>
<td>100</td>
</tr>
<tr>
<td>HER2NEG</td>
<td>Tamoxifen</td>
<td>10 vs 15</td>
<td>0.66 vs 1.00</td>
<td>100</td>
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<tr>
<td>MA17R</td>
<td>Tamoxifen</td>
<td>10 vs 15</td>
<td>0.66 vs 1.00</td>
<td>100</td>
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<tr>
<td>NRGOC</td>
<td>DOCO-05</td>
<td>7.5 vs 10</td>
<td>0.82 vs 0.88</td>
<td>0</td>
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<tr>
<td>ADJUVANT</td>
<td>Tamoxifen</td>
<td>7 vs 10</td>
<td>1.07 vs 0.84</td>
<td>40</td>
</tr>
<tr>
<td>GALE</td>
<td>Tamoxifen</td>
<td>10 vs 10</td>
<td>1.09 vs 0.91</td>
<td>01</td>
</tr>
</tbody>
</table>

- **brown**: Tamoxifen
- **green**: Tamoxifen or AI
- **blue**: AI

- **p**-value: Zeit der randomisierten Intervention vs keine Therapie od. Plazebo
- ***:** randomisation

§: MA17R after 5 years AI with / w/o Tam before


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 function protection


7. Lambertini M, Moore HCF, Leonard RCF et al.: Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of


Pregnancy rates

Fertility preservation counselling

Fertility preservation with assisted reproduction therapy

