Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients
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- **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
Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1   GR: A   AGO: ++

endocrine responsive – hormone receptor positive

Immunhistology (ER and/or PgR)

<table>
<thead>
<tr>
<th></th>
<th>pos. cells:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td></td>
<td>endocrine resistant</td>
</tr>
<tr>
<td>1–10%</td>
<td></td>
<td>possibly endocrine sensitive</td>
</tr>
<tr>
<td>&gt; 10%</td>
<td></td>
<td>endocrine sensitive</td>
</tr>
</tbody>
</table>

Unknown hormone receptor status: endocrine sensitive

IF ER negative / PR positive (> 10% positive cells): reassess IHC status
<table>
<thead>
<tr>
<th>Assessment of menopausal status:</th>
<th>Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Menstruation history</td>
<td>++</td>
</tr>
<tr>
<td>▪ FSH, E2</td>
<td>++</td>
</tr>
</tbody>
</table>
## Adjuvant Endocrine Therapy

### Endocrine therapy:

- **Endocrine responsive**
  - Oxford: 1a A ++

- **endocrine doubtful responsiveness**
  - Oxford: 3b D +

- **Endocrine therapy sequentially after CT**
  - Oxford: 5 D +

- **Endocrine therapy concurrent with T-DM1/anti-HER2 therapy (w/o chemotherapy)**
  - Oxford: 5 D +

- **Non-responsive: No endocrine therapy**
  - Oxford: 1a A ++
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.
## Premenopausal Patients

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

<table>
<thead>
<tr>
<th>Therapy Description</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen 5 years (low risk of relapse)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Tamoxifen + OFS 2-5 years (intermediate risk of relapse)*</td>
<td>2b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>AI + OFS# for 5 years (high risk of relapse)*</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>GnRH alone (only, if relevant contraindication for Tam vs. no therapy at all)</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

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

**TEXT**

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

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

**SOFT**

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

- Tamoxifen 20 mg/day + OFS* (n = 1332)
- 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
GnRH Analogue every 3 months

Leuprolide 3M depot 11.25 mg

<table>
<thead>
<tr>
<th>Sample interval (post operation month)</th>
<th>Mean E2 level (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>63.7 (33.8)</td>
</tr>
<tr>
<td>3</td>
<td>4.1 (0.5)</td>
</tr>
<tr>
<td>6</td>
<td>4.8 (2.5)</td>
</tr>
<tr>
<td>12</td>
<td>4.8 (1.7)</td>
</tr>
<tr>
<td>18</td>
<td>6.1 (5.1)</td>
</tr>
<tr>
<td>24</td>
<td>4.9 (2.3)</td>
</tr>
</tbody>
</table>

Mean pg/mL (SD)
Number

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

### Table: Oxford LoE, GR, AGO

<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>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>1b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
</tbody>
</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
Aromatase Inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials.

Adjuvant therapy with CDK 4/6 inhibitors

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

- Abemaciclib for 2 years + standard endocrine therapy\(^1\)
  
- Palbociclib for 2 years + standard endocrine therapy\(^2\)
  
- Palbociclib for 1 year + standard endocrine therapy\(^3\)

\(^1\)MonarchE; \(^2\)Pallas; \(^3\)PenelopeB
### CDK4/6 Inhibitoren zusätzlich zu einer standardmäßigen endokrinen Therapie in der adjuvanten Situation

<table>
<thead>
<tr>
<th>Tabelle</th>
<th>PALLAS</th>
<th>MonarchE</th>
<th>Penelope</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapie</strong></td>
<td>Palbociclib for 2 years</td>
<td>Abemaciclib for 2 years</td>
<td>Palbociclib for 1 year</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>5600</td>
<td>5637</td>
<td>1250</td>
</tr>
</tbody>
</table>
| **Main Inclusion Criteria** | AJCC Stage II:  
- T0/T1 N1  
- T2 N0  
- T2 N1  
- T3 N0  
or AJCC Stage III  
- T0/T1 N2  
- T2 N2  
- T3 N1/N2 | T1-T4 and N1 with one of the following criteria  
- ≥4 ipsilateral pos. axillary lymph nodes  
- 1-3 ipsilateral pos. axillary lymph nodes and one of the following criteria  
  - G3  
  - Tumor size ≥5 cm  
  - Ki-67 ≥20% | ≥ypT1 or  
≥ypN1  
CPS-EG score ≥3 pr 2 ypN+  
Neoadjuvant Chemotherapy of at least 16 weeks |
| **Early discontinuation of therapy** | 43% | 27% | 20% |
| **Median follow up** | 24 months | 15 months | 43 months |
| **Results (iDFS)** | HR: 0.93 (95%CI: 0.76-1.15)  
3 year iDFS: 88.2% vs 88.5% | HR = 0.713 (0.583-0.871)  
2 year iDFS: 92.3% vs 89.3% | HR=0.93 (95%CI: 0.74-1.17)  
3 year iDFS: 81.2% vs 77.7% |
### Premenopausal Patients

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

In case of high risk of recurrence

- 5 years Tamoxifen after 5 years Tamoxifen
  - Oxford: 1a A ++
- 2–5 years AI after 5 years Tamoxifen in initially premenopausal patients who obtain validated postmenopausal status during course of therapy
  - Oxford: 1b B +
- 5 years Tamoxifen after 5 years of endocrine therapy + OFS
  - Oxford: 5 D +
## Postmenopausal Patients

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

<table>
<thead>
<tr>
<th>In case of high risk of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years Tamoxifen after 5 years Tamoxifen</td>
</tr>
<tr>
<td>2–5 years AI after 5 years Tamoxifen</td>
</tr>
<tr>
<td>After initial AI-containing therapy (upfront or switch), prolongation of endocrine therapy with AI for 2–5 years*</td>
</tr>
<tr>
<td>High-risk and good tolerability of AI</td>
</tr>
<tr>
<td>Low-risk, poor tolerability of AI</td>
</tr>
<tr>
<td>Interruption of endocrine treatment up to 3 months during EAT with AI</td>
</tr>
</tbody>
</table>

* 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)

Absolute risk reduction (in %) of extended Al therapy differs after 10 years by type of prior endocrine therapy

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

Gray R et al. SABCS 2018 (GS3-03)
## Extended adjuvant treatment, overview

<table>
<thead>
<tr>
<th>Studie</th>
<th>Therapien</th>
<th>De-facto-Vergleiche (Jahre)</th>
<th>HR für DFS</th>
<th>AI-Therapie Jahre 0-5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jahre nach Diagnose</strong></td>
<td>1 2 3 4 5 6 7 8 9 10 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Studien mit Tamoxifen nach 5 Jahren Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATLAS</td>
<td></td>
<td>5 vs 10</td>
<td>0,75 – 0,99 t</td>
<td>0</td>
</tr>
<tr>
<td>ATTOM</td>
<td></td>
<td>5 vs 10</td>
<td>0,75 – 0,99 t</td>
<td>0</td>
</tr>
<tr>
<td><strong>Studien mit AI nach 5 Jahren Tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA.17</td>
<td></td>
<td>5 vs 10</td>
<td>0,57</td>
<td>0</td>
</tr>
<tr>
<td>NSABPB-33</td>
<td></td>
<td>5 vs 10</td>
<td>0,68</td>
<td>0</td>
</tr>
<tr>
<td>ABCSG 6a</td>
<td></td>
<td>5 vs 8</td>
<td>0,62</td>
<td>0</td>
</tr>
<tr>
<td><strong>Studien mit erweiterter AI-Th. nach 5 Jahren endokrin inkl. AI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DATA</td>
<td></td>
<td>6 vs 9</td>
<td>0,79</td>
<td>100</td>
</tr>
<tr>
<td>NSABPB-42</td>
<td></td>
<td>5 vs 10</td>
<td>0,85</td>
<td>100</td>
</tr>
<tr>
<td>MA.17R</td>
<td></td>
<td>10 vs 15</td>
<td>0,66</td>
<td>100</td>
</tr>
<tr>
<td><strong>Studien bzgl. optimaler Dauer in Jahr 5-10</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOOG 2006-05 IDEAL</td>
<td></td>
<td>7,5 vs 10</td>
<td>0,92</td>
<td>88</td>
</tr>
<tr>
<td>ABCSG 16</td>
<td></td>
<td>7 vs 10</td>
<td>1,007</td>
<td>49</td>
</tr>
<tr>
<td>SOLE</td>
<td></td>
<td>Cont vs unterbr</td>
<td>1,08</td>
<td>81</td>
</tr>
</tbody>
</table>

* brown: Tamoxifen  
* green: Tamoxifen or AI  
* blue: AI  
* stripes: Zeit der randomisierten Intervention vs keine Therapie od. Plazebo  
* §: randomisation

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

Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients
Decision criteria for extended therapy

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

- Fertility preservation counselling including referral of all potential patients to appropriate reproductive specialists ++

- CTx + GnRHa
  - (preservation of ovarian function)
  - (GnRHa application > 2 weeks prior to chemotherapy, independent of hormone receptor status)
  - 1a A +

- CTx + GnRHa
  - (preservation of fertility)
  - 1b A +/-
Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient–Level Data

N= 837 patients from 5 trial, median follow-up time 5.0 years (IQR, 3.0-6.3 years)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>GnRH</th>
<th>HR (95%-CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>POI&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>30.9%</td>
<td>14.1%</td>
<td>0.38; 0.26 to 0.57</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<sup>1</sup> premature ovarian insufficiency, <sup>2</sup> different definitions and time points were used
<sup>3</sup> in most trials POI and not pregnancy was defined as the primary endpoint

No significant differences in disease-free survival and overall survival were observed between groups.

Lambertini M et al. J Clin Oncol 2018