Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients
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- **Versions 2002–2019:**
  Bauerfeind / Dall / Diel / Fersis / Fehm / Friedrichs / Gerber / Göring / Hanf / Harbeck / Huober / Jackisch / Lisboa / Lück / Lux / Maass / von Minckwitz / Möbus / Müller / Oberhoff / Schaller / Scharl / Schneeweiss / Schütz / Solomeyer / Stickeler / Thomssen / Untch / Fehm / Gerber

- **Version 2020:**
  Nitz / Huober
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 receptors in a randomized trial comparing letrozole and tamoxifen adjuvant therapy for postmenopausal early


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### Adjuvant Endocrine Therapy

<table>
<thead>
<tr>
<th>Endocrine therapy:</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Endocrine responsive</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>- endocrine doubtful responsiveness</td>
<td>3b</td>
<td>D</td>
<td>+</td>
</tr>
<tr>
<td>- Endocrine therapy</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>- Sequentially after CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Non-responsive: No endocrine therapy</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
</tbody>
</table>


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

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
### Premenopausal Patients

#### Initial Adjuvant Endocrine Therapy (Year 0-5)

<table>
<thead>
<tr>
<th>Tamoxifen* 5–10 years</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH alone</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>(only, if relevant contraindication for Tam vs. no therapy at all)</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>No indication for neo-/adjuvant chemotherapy and preserved ovarian function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Tamoxifen + OFS</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>AI + OFS</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>Following neo-/adjuvant chemotherapy and preserved ovarian function</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Tamoxifen + OFS 5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in patients &lt; 35 years</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>AI + OFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in patients &lt; 35 years</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
</tbody>
</table>

OFS: ovarian function suppression; * as long as tolerated and the patient is clearly premenopausal
** If ovarian function resumes during 24 months

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**Tamoxifen 5-10 yrs:**

GnRH as monotherapy:

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

AI for first 5 years:

*Especially in case of lobular cancer*
3. 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 Al to complete 5 years
Al (2-3 yrs.) followed by Tam to complete 5 years


Tamoxifen 20 mg/d for first 5 yrs:

Patient care/ adherence and side effects


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

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

<table>
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<tr>
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<th>LoE</th>
<th>GR</th>
<th>AGO</th>
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<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 in initially premenopausal patients who obtain validated postmenopausal status during course of therapy</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>5 years Tamoxifen after 5 years of endocrine therapy + OFS</td>
<td>5</td>
<td>D</td>
<td>+</td>
</tr>
</tbody>
</table>

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:


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: Benefit from letrozole as extended adjuvant therapy after sequential endocrine therapy: a randomized phase III trial of the Gruppo Italiano Mammella, ASCO 2019, abstract 505

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 prevoius 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
Ovarian function protection


Pregnancy rates


Fertility preservation counselling


Fertility preservation with assisted reproduction therapy


# Adjuvant Endocrine Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
<th>Dose (years)</th>
<th>HR for DFS</th>
<th>AI-Therapy (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years after Diagnosis</strong></td>
<td>1 2 3 4 5 6 7 8 9 10 15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies with Tamoxifen only 5 years Tamoxifen</td>
<td>ATLAS</td>
<td>5 vs 10</td>
<td>0.75</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ATOM</td>
<td>5 vs 10</td>
<td>0.75</td>
<td>0</td>
</tr>
<tr>
<td>Studies with AI only 5 years Tamoxifen</td>
<td>MA 17</td>
<td>5 vs 10</td>
<td>0.17</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>NSABP B31</td>
<td>5 vs 10</td>
<td>0.68</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ABCG5a</td>
<td>5 vs 8</td>
<td>0.62</td>
<td>0</td>
</tr>
<tr>
<td>Studies with sequential AI + 5 years endocrine AI</td>
<td>DATA</td>
<td>4 vs 9</td>
<td>0.79</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>NSABP B-49</td>
<td>5 vs 10</td>
<td>0.45</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>MA 17R</td>
<td>10 vs 15</td>
<td>0.66</td>
<td>100</td>
</tr>
<tr>
<td>Studies with optimal dose in 5-10 yrs</td>
<td>BOCG 2006-05</td>
<td>7.5 vs 10</td>
<td>0.92</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>ABCG5-16</td>
<td>7 vs 10</td>
<td>1.007</td>
<td>49</td>
</tr>
</tbody>
</table>

- **Brown:** Tamoxifen,
- **Green:** Tamoxifen or AI,
- **Blue:** AI

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

*: Randomisierungszeitpunkt,

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