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

- **Versions 2002–2017:**
  Bauerfeind / Dall / Diel / Fersis / Friedrichs / Gerber /
  Göring / Hanf / Harbeck / Huober / Jackisch / Lisboa / Lück / Lux
  Maass / von Minckwitz / Möbus / Müller / Oberhoff /
  Schaller / Scharl / Schneeweiss /Schütz / Solomeyer /
  Stickeler / Thomssen / Untch

- **Version 2018:**
  Jackisch / Lück
Assessment of Steroid Hormone Receptor Status

Oxford LoE: 1  GR: A  AGO: ++

Endocrine responsiveness: formerly known as receptor negativ
Immunohistochemistry (ER and / or PgR)

0% pos. cells: endocrine non responsive
1-9% pos. cells: endocrine doubtfully responsive
≥ 10% pos. cells: endocrine responsive

Hormon Receptor Status
unknown: endocrine responsive
Adjuvant Endocrine Therapy
Assessment of Menopausal Status

Assessment of menopausal status:

- Menstruation history
- FSH, E2

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
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<tr>
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</table>
Adjuvant Endocrine Therapy

Standard therapy for responsive / doubtfull endocrine responsive tumors:

- **Endocrine therapy**
- **Chemotherapy followed by endocrine therapy**
  (dependent on individual risk and tumor biology)

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<tbody>
<tr>
<td><strong>1a</strong></td>
<td>A</td>
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<tr>
<td><strong>1a</strong></td>
<td>A</td>
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</tbody>
</table>
Adjuvant Endocrine Therapy

- Endocrine responsive & doubtfull responsive Endocrine therapy

- Endocrine therapy
  Sequentially after CT

- Non-responsive:
  No endocrine therapy

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
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<th>AGO</th>
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<tbody>
<tr>
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<td>1a</td>
<td>A</td>
<td>++</td>
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<tr>
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<td>2b</td>
<td>C</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
</tbody>
</table>
Adjuvant endocrine therapy is divided into initial therapy (years 0-5) and extended adjuvant therapy (EAT, years 6-15).

Standard treatment duration is 5 years.

Extended treatment should be considered based on individual benefits and risks.

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 to stop.

AI should be used as first treatment in postmenopausal patients especially in cases of lobular cancers and high risk of recurrence.

To date, there is no validated biomarker that identifies patients for early versus late recurrence.
**Premenopausal Patients**

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

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Tamoxifen* 5 -10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GnRH alone</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>(only, if relevant contraindication for Tam)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without indication for neo-/adjuvant chemotherapy and preserved ovarian function</td>
<td></td>
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<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>++</td>
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<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tamoxifen + OFS**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AI + OFS**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Following neo-/adjuvant chemotherapy and preserved ovarian function (≤ 8 months EOC)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>+</td>
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<td></td>
<td>1b</td>
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<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>AI + OFS**</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>in patients &lt; 35 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>OFS: ovarian Function-Suppression; EOC: end of chemotherapy treatment as long as tolerable and the pat. is clearly premenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>** only limited data on OS available</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Postmenopausal Patients
Initial Adjuvant Endocrine Therapy (Years 0-5)

- **Aromatase Inhibitor (AI) for first 5 years**
  - 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 at some point

** Tamoxifen might be offered to very old patients or in patients with very low risk of recurrence or if contraindications for AI are present
Pre- and Postmenopausal Patients
Extended Adjuvant Endocrine Therapy (EAT) (Years 6-10)

Premenopause:
- 2.5 - 5 years AI after 5 years Tamoxifen premenopausal in patients with validated postmenopausal status in the course of therapy
- 5 years Tamoxifen after 5 years Tamoxifen (in case of high risk of recurrence)

Postmenopause:
- After 2 - 5 years Tamoxifen AI for 2.5 - 5 years
- After initial therapy with AI further prolongation of endocrine therapy with AI*
  - high risk and good tolerability of the AI
  - low risk, poor tolerability of the AI

* Up to date, no impact on OS
Ovarian Protection and Fertility Preservation in Premenopausal Patients Receiving (Neo)-Adjuvant Chemotherapy (CT)

- **CT + GnRHa**  
  (preserve ovarian function)  
  (GnRHa application > 2 weeks prior to chemotherapy, independently of hormone receptor status )  
  Oxford:  
  LoE: 1a  
  GR: B  
  AGO: +

- **CHT + GnRHa**  
  (preserve fertility)  
  Oxford:  
  LoE: 2a  
  GR: B  
  AGO: +/-

- **Fertility preservation counselling**  
  Oxford:  
  LoE: 4  
  GR: C  
  AGO: ++

- **Fertility preservation using assisted reproduction therapy (ART)**  
  (further information www.fertiprotect.de)  
  Oxford:  
  LoE: 4  
  GR: C  
  AGO: +
TEXT

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

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 = 1328)

Exemestane 25 mg/day + OFS* (n = 1332)

Exemestane 25 mg/day + OFS* (n = 1014)

Tamoxifen 20 mg/day + OFS* (n = 1016)

Median follow-up: 5.7 yrs

Joint Analysis

Tamoxifen + OFS* (n = 2344)

Exemestane + OFS* (n = 2346)

*OF S

- TEXT: triptorelin 3.75 mg IM every 28 days for 6 mos, then optional bilateral oophorectomy or irradiation
- SOFT: choice of method

In Soft-EST: Exe + OFS: E2, E1, E1-Sulfate - levels were significantly lower than in pats. with Tam + OS

66% of premenopausal pats. on Exe + OFS had profound persistent suppression of E2 etc. for 12 months.

However, 34% had an E2 level greater than menopausal threshold at least once, 17% at all time-points:

- These patients were more likely younger than 35 y; chemo-naïve; had higher BMI
- Importantly: Combining ABCSG-12, SOFT, and TEXT studies, showed 65 fewer DFS events (HR 0.89, 95% CI 0.57–1.39) but 30 more deaths for ovarian suppression plus aromatase inhibitor compared to ovarian suppression plus tamoxifen (HR 1.31, 95% CI 0.93–1.84, P = 0.12, s = 0.03, heterogeneity, P = 0.18).

Hence the question arises, whether incomplete ovarian suppression led to this discrepancy.
### 10 yrs versus 5 yrs Breast Cancer Mortality in ER+ Rate ratio per period in aTTom and ATLAS 5 yrs. vs. 10 yrs Tamoxifen

<table>
<thead>
<tr>
<th></th>
<th>10 yrs. vs. 5 yrs. Tam aTTom Trial (n=6934 ER+)</th>
<th>10 yrs. vs. 5 yrs. Tam Atlas Trial (n=10543 ER+)</th>
<th>10 yrs. vs. 5 yrs. Tam aTTom + Atlas combined (n=17477 ER+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Years 5-9</strong></td>
<td>1.08 (0.85-1.38)</td>
<td>0.92 (0.77-1.09)</td>
<td>0.97 (0.84-1.15)</td>
</tr>
<tr>
<td><strong>Years 10+</strong></td>
<td>0.75 (0.63-0.90)</td>
<td>0.75 (0.63-0.90)</td>
<td>0.75 (0.65-0.86)</td>
</tr>
<tr>
<td></td>
<td>p = 0.07</td>
<td>p = 0.002</td>
<td>p = 0.00004</td>
</tr>
<tr>
<td><strong>All years</strong></td>
<td>0.88 (0.74-1.03)</td>
<td>0.83 (0.73-0.86)</td>
<td>0.85 (0.77-0.94)</td>
</tr>
<tr>
<td></td>
<td>p = 0.1</td>
<td>p = 0.004</td>
<td>P= 0.001</td>
</tr>
</tbody>
</table>
# Aromatase Inhibitors in Adjuvant Therapy

## Overview over Published Trials: Initial Therapy (years 1-5)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>AI</th>
<th>Indication</th>
<th>Pts</th>
<th>DFS/BCFS/TTR/TTDR/CBC</th>
<th>OS</th>
<th>Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>ATAC Trialists’ Group 2010</td>
<td>A</td>
<td>upfront vs T</td>
<td>6241</td>
<td>HR + patients: DFS HR 0.86, p=0.003 TTR 0.79, p=0.0002 TTDR 0.85, p=0.02</td>
<td>HR 0.87 p=0.4</td>
<td>SAE T&gt;A gyn AE T&gt;A VE T&gt;A SE A&gt;T</td>
<td>only anastrozole vs tamoxifen, combination arm stopped after first analysis; ER+PR=ER+PR+ (Cuzick 2010) QoL→ (Cella 2006)</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>BIG 1-98 Collaborative Group 2011</td>
<td>L</td>
<td>upfront² vs T</td>
<td>4922</td>
<td>DFS = 0.86 P = 0.007</td>
<td>P = 0.048</td>
<td>SAE T=L gyn AE T&gt;L TE T=L CE L&gt;T SE L&gt;T</td>
<td>L&gt;T in particular in case of N+</td>
</tr>
<tr>
<td>NCIC CTG MA.27</td>
<td>Goss 2010</td>
<td>E</td>
<td>upfront vs A</td>
<td>7576</td>
<td>EFS HR 1.02 DDFS HR 0.95</td>
<td>ns</td>
<td>Osteoporosis A&gt;E El. liver enzymes E&gt;A Hyperlypidaemia A&gt;E</td>
<td>Randomization for Celecoxib cancelled</td>
</tr>
<tr>
<td>Meta-analysis EBCTCG</td>
<td>EBCTCG 2015</td>
<td></td>
<td>5 y. Al vs. 2-3 y. tam → Al to y. 5 vs. 5 y. Tam</td>
<td>31920</td>
<td>10 y. gain recurrence rate 5 y. Al vs. 5 y. Tam 3.6%, p&lt;0.0001</td>
<td>10 y. gain OS 5 y. Al vs. 5 y. Tam 2.1%, p&lt;0.009</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10 y. gain recurrence rate 5 y. Al vs. 2-3 y. Tam → Al to y. 5 0.7%, p&lt;0.045</td>
<td>10 y. gain OS 5 y. Al vs. 2-3 y. Tam → Al to y. 5 1.1%, p&lt;0.011</td>
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<tr>
<td></td>
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<td></td>
<td>10 y. gain recurrence rate 2-3 y. Tam → Al to y. 5 vs. 5 y. Tam 2.0%, p&lt;0.0001</td>
<td>10 y. gain OS 2-3 y. Tam → Al to y. 5 vs. 5 y. Tam 1.5%, p&lt;0.01</td>
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</tbody>
</table>

A anastrozole; gyn AE, gynecological adverse event; BCFS, breast cancer-free survival; CBC, contralateral breast cancer; CE, cardiac events; CVE, cardiovascular events; Cx, chemotherapy; DFS, disease-free survival; RFS relapse-free survival; E, exemestane; ER, estrogen receptor; HR, hazard ratio; L, letrozole; OS, overall survival; P, placebo; PR, progesterone receptor; QoL, quality of life; Rx, radiotherapy; SAE, serious adverse adverse event; SE, skeletal event; T, tamoxifen; TE, thromboembolism; TTR, time-to-recurrence; TTDR, time-to-distant-recurrence; VE, vascular event; (?) according to retrospective analysis. * only HR positive population
Upfront Therapies
Overview

Rydén L, Heibert Arnlind M, Vitols S, Höistad M, Ahlgren J.

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.

Extended Endocrine Therapies

MA-17
- TAM for 4 years
- Letrozole (Let) for 6 years
- Placebo for 10 years

NSABP-B33
- TAM for 4 years
- Exemestane (Exe) for 6 years
- Placebo for 10 years

ABCSG-6a
- TAM for 4 years
- Anastrozole (Ana) for 6 years

NSABP-B42
- TAM and AI for 4 years
- Letrozole (Let) for 6 years
- Placebo for 10 years

MA-17R
- TAM for 4 years
- AI for 6 years
- Letrozole (Let) for 10 years

ABCSG-16
- AI for 4 years
- Tamoxifen (Tam) for 6 years
- Anastrozole (Ana) for 10 years

DATA
- Tamoxifen (Tam) for 4 years
- Anastrozole (Ana) for 6 years
- Letrozole (Let) for 10 years

IDEAL
- AI for 4 years
- Tamoxifen (Tam) for 6 years
- Anastrozole (Ana) for 10 years

SOLE
- AI for 4 years
- Tamoxifen (Tam) for 6 years
- Anastrozole (Ana) for 10 years

Gnant M. et al., SABCS, 2016 (S1-06, Discussion)
### Aromatase Inhibitors in Adjuvant Therapy

**Overview over Published Trials:**

**Extended Therapy I**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Patient number</th>
<th>Population</th>
<th>Upfront therapy</th>
<th>Trial Arms</th>
<th>Reported outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG</td>
<td>Tomey 1996</td>
<td>193</td>
<td>Prem./postm.</td>
<td>Tamoxifen</td>
<td>Tamoxifen vs. no therapy</td>
<td>RFS: 85% vs. 73% (p=0.10) OS: 86% vs. 89% (p=0.52)</td>
</tr>
<tr>
<td>Scottish</td>
<td>Stewart 1996</td>
<td>342</td>
<td>Prem./postm.</td>
<td>Tamoxifen</td>
<td>Tamoxifen vs. no therapy</td>
<td>Events: 60 vs. 49 EFS HR: 1.27 (0.87-1.85)</td>
</tr>
<tr>
<td>NSABP B-14</td>
<td>Fisher 2001</td>
<td>1142</td>
<td>Prem./postm.</td>
<td>Tamoxifen</td>
<td>Tamoxifen vs. placebo</td>
<td>DFS: 78% vs. 82% (p=0.03) OS: 91% vs. 94% (p=0.07)</td>
</tr>
<tr>
<td>ATLAS</td>
<td>Davies 2013</td>
<td>6846</td>
<td>Prem./postm.</td>
<td>Tamoxifen</td>
<td>Tamoxifen vs. placebo</td>
<td>Recurrence: 617 vs. 711 (p=0.01) OM: 639 vs. 722 (p=0.01)</td>
</tr>
<tr>
<td>aTTOM</td>
<td>Gray 2013</td>
<td>6953</td>
<td>Prem./postm.</td>
<td>Tamoxifen</td>
<td>Tamoxifen vs. no therapy</td>
<td>Recurrence: 580 vs. 672 (p=0.003) OM: 849 vs. 910 (p=0.1)</td>
</tr>
<tr>
<td>MA.17</td>
<td>Goss 2005</td>
<td>5187</td>
<td>Postm.</td>
<td>Tamoxifen</td>
<td>Letrozole vs. placebo</td>
<td>DFS: HR 0.68 (0.55-0.83; p=0.001) OS: HR 0.98 (0.78-1.22; p=0.85)</td>
</tr>
<tr>
<td>NSABP B-33</td>
<td>Mamounas 2008</td>
<td>1598</td>
<td>Postm.</td>
<td>Tamoxifen</td>
<td>Exemestane vs. placebo</td>
<td>DFS: 91% vs. 89% (p=0.07) RFS: 96% vs. 94% (p=0.004)</td>
</tr>
<tr>
<td>ABCSG-6a</td>
<td>Jakesz 2007</td>
<td>856</td>
<td>Postm.</td>
<td>Tamoxifen</td>
<td>Anastrozole vs. placebo</td>
<td>Recurrence: 30 vs. 56, HR 0.64 (0.41-0.99; p=0.047)</td>
</tr>
<tr>
<td>Meta-</td>
<td>Petrelli 2013</td>
<td>29138</td>
<td>Prem./postm.</td>
<td>Tamoxifen</td>
<td>Fixed duration (5 years) with an extended course of endocrine therapy vs. no therapy</td>
<td>RFS OR: 0.72 (0.56-0.92; p=0.01) BCSS OR: 0.78 (0.69-0.9; p=0.0003) OS OR: 0.89 (0.80-0.99; p=0.03)</td>
</tr>
</tbody>
</table>

**AI = aromatase inhibitor; BCSS = breast cancer specific survival; DFS = disease-free survival; EFS = event free survival; HR = hazard ratio; OM = overall mortality; OS = overall survival; prem. = premenopausal; postm. = postmenopausal; RFS = relapse-free survival**
## Aromatase Inhibitors in Adjuvant Therapy
### Overview over Published Trials: Extended Therapy II

<table>
<thead>
<tr>
<th>Trial</th>
<th>Source</th>
<th>Patient number</th>
<th>Population</th>
<th>Upfront therapy</th>
<th>Trial Arms</th>
<th>Reported outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATER</td>
<td>Zdenkowski 2016</td>
<td>360</td>
<td>Postm.</td>
<td>≥ 4 years of endocrine therapy (11.7% AI, 50.3% Tam, 38.0% other)</td>
<td>5 y. letrozole vs. observation</td>
<td>Breast cancer recurrence difference: 8.4% (3.8%-13.0%), p=0.0004</td>
</tr>
<tr>
<td>MA17R</td>
<td>Goss 2016</td>
<td>1918</td>
<td>Postm.</td>
<td>5 years of any other AI with or without prior tamoxifen</td>
<td>Letrozole vs. placebo</td>
<td>DFS: 95% vs. 91% (HR for disease recurrence or occurrence of contralateral breast cancer: 0.66; p=0.01) OS: 93% vs. 94% (HR: 0.97; p=0.83)</td>
</tr>
<tr>
<td>IDEAL</td>
<td>Blok 2016</td>
<td>1824</td>
<td>Postm.</td>
<td>5 years of tamoxifen, AI or tamoxifen → AI</td>
<td>Letrozole 2.5 vs. 5 years</td>
<td>DFS HR: 0.88 (0.64-1.21; p=0.43) 5-year DFS: 88.4 vs. 87.9% OS HR: 1.09 (0.70-1.70)</td>
</tr>
<tr>
<td>DATA</td>
<td>Tjan-Heijnen 2016</td>
<td>1912</td>
<td>Postm.</td>
<td>Tamoxifen 2-3 years</td>
<td>Anastrozole 6 vs. 3 years</td>
<td>DFS HR: 0.79 (0.62-1.02; p=0.07) 5-year DFS: 83.1 vs. 79.4 OS HR: 0.91 (0.65-1.29)</td>
</tr>
<tr>
<td>NSABP B-42</td>
<td>Mamounas 2016</td>
<td>3923</td>
<td>Postm.</td>
<td>AI or tamoxifen → AI 5 years</td>
<td>Letrozole vs. placebo</td>
<td>DFS HR: 0.85 (0.73-0.999; p=0.048*) * did not reach statistical significance level of 0.0418</td>
</tr>
</tbody>
</table>

AI = aromatase inhibitor; BCSS = breast cancer specific survival; DFS = disease-free survival; EFS = event free survival; HR = hazard ratio; OM = overall mortality; OS = overall survival; prem. = premenopausal; postm. = postmenopausal; RFS = relapse-free survival
Conclusion for Possible Therapy Decision

Extended Endocrine Therapy

- After 2 - 5 years tamoxifen
  → add aromatase inhibitor for 2,5 to 5 years.

- After initial aromatase inhibitor therapy consider carefully:
  - further AI therapy:
    - up to now well tolerated AI therapy,
    - good bone health,
    - younger age,
    - high risk by clinopathological factors,
    - node positive disease.

Gnant M. et al., SABCS, 2016 (S1-06, Discussion)
Adjuvant Endocrine Therapy in Pre- and Postmenopausal Patients

- **Premenopause**
  - Adjuvant year 0-5: Tamoxifen
  - EAT year 6-10: Tamoxifen, Letrozol (MA.17)

- **Postmenopause**
  - Adjuvant year 0-5: Tamoxifen, Exemestan, Tam + GnRH
  - EAT year 6-10: Tamoxifen, Letrozol (MA.17)
  - Carry over effect > 10: Letrozol (MA.17R)