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 negative
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

7. Su HI et al.. Antral follicle count provides additive information to hormone measures for determining ovarian function in breast cancer survivors. Fertil Steril. 2011 Apr;95(5):1857-9
Adjuvant Endocrine Therapy

Standard therapy for responsive / doubtful endocrine responsive tumors:

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

<table>
<thead>
<tr>
<th>Oxford</th>
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<td>1a</td>
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General Principles in Adjuvant Endocrine Therapy
AGO ++

- 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.

9. Rydén L 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 Apr;26:106-140


Premenopausal Patients
Initial Adjuvant Endocrine Therapy (Year 0-5)

- **Tamoxifen** 5 -10 years
  (only, if relevant contraindication for Tam)
- **Without indication for neo-/adjuvant chemotherapy and preserved ovarian function**
  - Tamoxifen
  - Tamoxifen + OFS**
  - AI + OFS**
- **Following neo-/adjuvant chemotherapy and preserved ovarian function (≤ 8 months EOC)**
  - Tamoxifen + OFS 5 years**
    - in patients < 35 years
  - AI + OFS**
    - in patients < 35 years

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<thead>
<tr>
<th>Oxford</th>
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</thead>
<tbody>
<tr>
<td>Tamoxifen* 5 -10 years</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>GnRH alone</td>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Without indication for neo-/adjuvant chemotherapy and preserved ovarian function</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>Following neo-/adjuvant chemotherapy and preserved ovarian function (≤ 8 months EOC)</td>
<td>1b</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td>Following neo-/adjuvant chemotherapy and preserved ovarian function (≤ 8 months EOC)</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Following neo-/adjuvant chemotherapy and preserved ovarian function (≤ 8 months EOC)</td>
<td>1b</td>
<td>B</td>
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OFS: ovarian Function-Suppression; EOC: end of chemotherapy treatment as long as tolerable and the pat. is clearly premenopausal
** only limited data on OS available

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**Tamoxifen 5-10 yrs.**

In patients with ovarian function (within 8 mon.) after adjuvant chemotherapy:
OFS (ovarian function suppression) 5 years + Tam 5 years - OFS 5 years + AI 5 years in patients < 35 y.

8. Shiba E et al. A randomized controlled study evaluating safety and efficacy of leuprorelin acetate every-3-months depot for 2 versus 3 or more years with tamoxifen for 5 years as adjuvant treatment in premenopausal patients with endocrine-responsive breast cancer. Breast Cancer. 2016 May;23(3):499-509.
10. Kim HA et al. The role of the addition of ovarian suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or regain menstruation after chemotherapy (ASTRRA): study protocol for a randomized controlled trial and progress. BMC Cancer. 2016 May 19;16:319.
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**

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<tr>
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</tr>
<tr>
<td></td>
<td>1a</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>C</td>
<td></td>
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</table>

* 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

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**AI for first 5 years**

*Especially in case of lobular cancer*

**High risk of recurrence**

3. Rydén L 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 Apr;26:106-14

**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

2. Rydén L 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 Apr;26:106-14


Tamoxifen 20 mg/d for first 5 yrs.


Patient care/ adherence and side effects


### Pre- and Postmenopausal Patients

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

<table>
<thead>
<tr>
<th>Premenopause:</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
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</thead>
<tbody>
<tr>
<td>2.5 - 5 years AI after 5 years Tamoxifen premenopausal in patients with validated postmenopausal status in the course of therapy</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>5 years Tamoxifen after 5 years Tamoxifen (in case of high risk of recurrence)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Postmenopause:</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 2 - 5 years Tamoxifen AI for 2.5 - 5 years</td>
<td>1a</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>After initial therapy with AI further prolongation of endocrine therapy with AI*</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>high risk and good tolerability of the AI</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td>low risk, poor tolerability of the AI</td>
<td>1b</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>

* Up to date, no impact on OS

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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 increased risk of relaps)


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**After 2 - 5 years Tamoxifen AI for 2.5 - 5 years**

1. Goss PE et al. Randomized trial of letrozole following tamoxifen as extended adjuvant...


After initial therapy with AI further prolongation of endocrine therapy with Al*

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**high risk and good tolerability of the AI**

**low risk, poor tolerability of the AI**


5. Mamounas EP et al. NRG Oncology/NSABP. A randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy (tx) with letrozole (L) in postmenopausal women with hormone-receptor (+) breast cancer (BC) who have completed previous adjuvant tx with an aromatase inhibitor (AI): Results from NRG Oncology/NSABP B-42. 2016 San Antonio Breast Cancer Symposium, Publication Number: S1-05


9. Tjan-Heijnen VC C et al. First results from the multicenter phase III DATA study comparing 3 versus 6 years of anastrozole after 2-3 years of tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer. 2016 San Antonio Breast Cancer Symposium, Publication Number: S1-03

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** | **GR** | **AGO**  
  --- | --- | ---  
  1a | B | +  

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

- Fertility preservation counselling  
  **LoE** | **GR** | **AGO**  
  --- | --- | ---  
  4 | C | ++  

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


Incomplete Ovarian Suppression within SOFT – Study (SOFT-EST-Substudy)

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

- 66% of premenopausal pts. 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>Years 5-9</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>Years 10+</td>
<td>0.75 (0.63-0.90) p = 0.07</td>
<td>0.75 (0.63-0.90) p = 0.002</td>
<td>0.75 (0.65-0.86) p = 0.00004</td>
</tr>
<tr>
<td>All years</td>
<td>0.88 (0.74-1.03) p = 0.1</td>
<td>0.83 (0.73-0.86) p = 0.004</td>
<td>0.85 (0.77-0.94) P= 0.001</td>
</tr>
</tbody>
</table>

1. Gray RG et al., et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6953 women with early breast cancer J Clin Oncol 31, 2013(suppl; abstract 5)


6. Duffy S. Gynecological adverse events including hysterectomy with anastrozole tamoxifen: Data from the ATAC (‘Arimidex’, Tamoxifen, Alone or in Combination) trial. J Clin Oncol 2005;23(Suppl.):585, Abs 723.


Rydén L, Heibert Arnliand 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.


1. Gnant M. et al., SABCS, 2016 (S1-06, Discussion)


8. Mamounas EP et a. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical


12. Tjan-Heijnen VC C, First results from the multicenter phase III DATA study comparing 3 versus 6 years of anastrozole after 2-3 years of tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer. 2016 San Antonio Breast Cancer Symposium, Publication Number: S1-03

13. Mamounas EP et al. NRG Oncology/NSABP. A randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy (tx) with letrozole (L) in postmenopausal women with hormone-receptor (+) breast cancer (BC) who have completed previous adjuvant tx with an aromatase inhibitor (AI): Results from NRG Oncology/NSABP B-42. 2016 San Antonio Breast Cancer Symposium, Publication Number: S1-05


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>2denkowski 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% (3.3%-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>Bick 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 2 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.

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

PREMENOPAUSE
- Tamoxifen
- Letrozol (MA.17)

POSTMENOPAUSE
- Tamoxifen
- Letrozol (MA.17)
- AI

Adjuvant year 0-5
- Tamoxifen
- Exemestan, Tam + GnRH

EAT year 6-10
- Tamoxifen
- AI

carry over effect > 10
- Letrozol (MA.17)
- AI
- Letrozol (MA.17R)