IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A10-03

# Aromatase inhibitors for female breast cancer[1]

## Executive Summary

[1] Translation of the executive summary of the final report *Aromatasehemmer beim Mammakarzinom der Frau* (Version 1.0; Status: 20 September 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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The responsibility for the contents of the report lies solely with IQWiG.

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## Executive summary

With its letter of 15 July 2010, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess aromatase inhibitors for female breast cancer. IQWiG started working on the report in July 2011.

### *Research question*

The aims of the present investigation are:

- the benefit assessment of treatment with aromatase inhibitors in comparison with a different treatment option, in particular treatment with tamoxifen, under consideration of the different treatment regimens for aromatase inhibitors
- the benefit assessment of treatment with aromatase inhibitors in comparison with each other
- the benefit assessment of treatment with aromatase inhibitors in comparison with placebo or no treatment

in each case in patients with early and advanced breast cancer with regard to patient-relevant outcomes.

### *Methods*

The assessment was conducted on the basis of randomized controlled trials (RCTs) on the research question defined above. For this purpose, a systematic literature search was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for relevant systematic reviews was conducted in MEDLINE and Embase parallel to the search for relevant primary studies, as well as by means of searches in the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The last search was conducted on 23 June 2015.

In addition, systematic reviews were searched for additional studies, as were publicly available trial registries. Publicly available regulatory documents and the study publications and study information provided in the hearing procedure on the preliminary report plan (protocol) were screened. Moreover, the manufacturers of the drugs approved in Germany (anastrozole, exemestane and letrozole) were contacted and asked to provide relevant published and unpublished studies and these manufacturers, as well as the authors of publications on relevant studies, were asked to provide clinical study reports and clarify important questions.

The selection of relevant studies was performed by 2 reviewers independently of one another for the results of the searches in bibliographic databases and publicly available trial registries as well as for the results of the screening of potentially relevant studies from systematic

reviews. The selection of relevant studies from the other information sources was performed by one reviewer and checked by another.

The following outcomes were considered in the assessment: overall survival; symptomatic tumour progression; morbidity: progression-free survival (PFS) and disease-free survival (DFS), insofar as the operationalization of these outcomes indicated patient relevance; morbidity: symptoms; health-related quality of life; as well as adverse events (AEs). AEs were investigated by means of general and specific AEs. For general AEs, the outcomes of severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grades 3 and 4), serious AEs (SAEs), and treatment or study discontinuations due to AEs were assessed. The specific AEs were operationalized by means of fractures (as AEs), neoplasms (as SAEs), cerebrovascular events (as SAEs), cardiovascular events (as SAEs), general thromboembolic events (as SAEs), and endocrine AEs.

Data were extracted into standardized tables. To evaluate the certainty of results, the risk of bias at study and outcome level was assessed and in each case rated as low or high. The results of the individual studies were organized by outcomes and described. If the studies were comparable regarding the research question and relevant characteristics, the individual results were pooled quantitatively by means of meta-analyses. In addition, meta-analyses across drugs were performed, insofar as studies with different aromatase inhibitor interventions but the same control intervention were available within a research question. The meta-analyses were performed under the assumption that the effects of the different aromatase inhibitors within this drug class are similar and that thus, even in the case of different aromatase inhibitors, similar effects are shown in comparison with the control intervention.

***Results***

A total of 19 studies were included for the benefit assessment (12 on early and 7 on advanced breast cancer). The overview in Table 1 shows which studies were assessed in the present benefit assessment. Data on several comparisons/strategies were available from one study (BIG 1-98).

Table 1: Summarizing overview of studies assessed and number of patients included (early and advanced breast cancer)

| **Stage**<br>**Treatment strategy**<br>**Comparison** | **Number of studies** | **Number of studies published** | **Number of patients** |
|---|---|---|---|
| **Early breast cancer** | | | |
| **Upfront therapy** | | | |
| Anastrozole vs. tamoxifen | 1 (ATAC) | 1 | 6241[a] |
| Letrozole vs. tamoxifen | 1 (BIG 1-98) | 1 | Primary core analysis[b]: 8010<br>Monotherapy arm analysis[c]: 4922 |
| Letrozole vs. anastrozole | 1 (FACE) | 0 | 4172 |
| **Sequential therapy** | | | |
| Anastrozole vs. sequential (Tam.→Exe.) | 1 (TEAM-Japan) | 1 | 111 |
| Sequential (Let.→Tam.) vs. tamoxifen | 1 (BIG 1-98) | 1 | 3088 |
| Sequential (Let.→Tam.) vs. letrozole | 1 (BIG 1-98) | 1 | 3086 |
| **Switch therapy** | | | |
| Anastrozole (switch) vs. tamoxifen (continuation) | 5 (ABCSG 08, ARNO 95, ITA, NSAS BC 03, Van Calster 2011) | 5 | 4845 |
| Exemestane (switch) vs. tamoxifen (continuation) | 2 (Francini 2006, IES) | 2 | 4784 |
| **Extended therapy** | | | |
| Letrozole vs. placebo | 1 (MA-17) | 1 | 5170[d] |
| **Neoadjuvant therapy** | | | |
| Letrozole vs. placebo | 0 | 0 | 0 |
| **Advanced breast cancer** | | | |
| **First-line therapy** | | | |
| Anastrozole vs. tamoxifen | 4 (1033IL/0030, Milla Santos 2003, TARGET, TARGET-Japan) | 3 | 1290 |
| Letrozole vs. tamoxifen | 1 (P025) | 1 | 916 |

(continued)

Table 1: Summarizing overview of studies assessed and number of patients included (early and advanced breast cancer) (continued)

| | | | |
|---|---|---|---|
| **Second-line therapy after pretreatment with anti-oestrogens** | | | |
| Exemestane vs. anastrozole | 1 (A5991021) | 1 | 130 |
| Letrozole vs. anastrozole | 1 (Rose 2003) | 1 | 713 |
| **Third-line therapy** | | | |
| AI vs. placebo | 0 | 0 | 0 |

a: Number of patients who participated in the subprotocol on quality of life, n = 732.
b: The primary core analysis included all treatment arms of randomization options 1 and 2 in which patients were allocated to treatment with letrozole or tamoxifen at the start of the study (monotherapy arms or sequential therapy arms).
c: The monotherapy arms from randomizations options 1 and 2 are included.
d: Number of patients who participated in the subprotocol on quality of life, n = 3618.
Exe.: exemestane; Let.: letrozole; Tam.: tamoxifen; vs.: versus

For the studies on early breast cancer, the risk of bias at the study and outcome level was mainly low. No evaluable results on individual outcomes were available for some studies, in particular on specific AEs. The reason for this was usually that an analysis was available only on the level of the Preferred Term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA), by means of which the proportion of patients with at least one event could not be calculated due to potential double counting.

For the studies on advanced breast cancer, the risk of bias at study level was low for half of the studies assessed. The results at outcome level mainly showed a high risk of bias. For some studies, no results or no evaluable results were available on all or on several harm outcomes.

The 2 following tables show an overview of the results of the assessment on early (Table 2) and advanced (Table 3) breast cancer.

Table 2: Evidence map of all drugs, early breast cancer

| **Stage**<br>**Treatment regimen**<br>**Comparison** | | | | | **General adverse events** | | | | **Specific adverse events** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Overall survival** | **Morbidity: DFS** | **Morbidity: symptoms** | **Health-related quality of life** | **Severe AEs (CTCAE Grade 3)** | **Severe AEs (CTCAE Grade 4)** | **SAEs** | **Discontinuations due to AEs** | **Fractures** | **Neoplasms** | **Cerebrovascular events** | **Cardiovascular events** | **Thromboembolic events** | **Endocrine events** |
| **Upfront therapy** | | | | | | | | | | | | | | |
| Results of the meta-analysis across drugs | | | | | | | | | | | | | | |
| AI vs. Tam. | ↑ | n. i.[a] | - | - | - | - | ↑[b] | ↑↓ | n. i.[c] | n. i.[d] | n. i.[e] | ↑↓ | ↑ | - |
| Results of the comparisons on the basis of individual drugs | | | | | | | | | | | | | | |
| Ana. vs. Tam. | ⇗ | ⇑ | - | ⇔ | - | - | ⇑[b]/ ⇔[f] | ⇑ | ⇓[b, f] | ↔[d] | ⇔ | ⇔ | ⇑ | ⇔ |
| Let. vs. Tam. | ⇑ | ⇑ | - | - | ⇔[g] | | ⇗ | ⇔ | ⇓[b]/⇘[f] | ↔[d] | ⇔ | ⇔ | ⇗ | - |
| Let. vs. Ana. | ⇔ | ⇔ | - | - | ⇔[g] | | ⇔ | ⇔ | ⇔ | ↔[d] | ⇔ | ⇓ | ⇔ | - |
| **Sequential therapy** | | | | | | | | | | | | | | |
| Results of the meta-analysis across drugs | | | | | | | | | | | | | | |
| Insufficient data for a meta-analysis across drugs | | | | | | | | | | | | | | |
| Results of the comparisons on the basis of individual drugs | | | | | | | | | | | | | | |
| Ana vs. sequential (Tam.→Exe.) | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Sequential (Let.→Tam.) vs. Tam. | ⇔ | ⇔[h]/ ⇗[i] | - | - | ⇔[g] | | ⇔ | ⇔ | ⇔ | ↔[d] | ⇔ | ⇔ | ⇔ | - |
| Sequential (Let.→Tam.) vs. Let. | ⇔ | ⇔ | - | - | ⇔[g] | | ⇔ | ⇔ | ⇑ | ↔[d] | ⇔ | ⇔ | ⇓ | - |
| **Switch therapy** | | | | | | | | | | | | | | |
| Results of the meta-analysis across drugs | | | | | | | | | | | | | | |
| AI vs. Tam. | ↑[j] | n. i.[a] | - | - | - | - | ↑[j] | n. i.[e] | ↓ | n. i.[d] | - | - | - | ↔ |
| Results of the comparisons on the basis of individual drugs | | | | | | | | | | | | | | |
| Ana. vs. Tam. | ⇗ | ⇑ | - | ⇔ | - | - | ⇑⇑ | ⇑⇓ | ⇘ | ↔[d] | (⇔) | (⇔) | (⇔) | (⇔) |
| Exe. vs. Tam. | ⇗ | ⇑ | - | ⇔ | ⇔ | ⇔ | ⇗ | ⇔ | ⇓ | ↑[d] | - | - | - | ⇔ |

(continued)

Table 2: Evidence map of all drugs, early breast cancer (continued)

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Extended therapy** | | | | | | | | | | | | | | | |
| Let. vs. placebo | ⇔ | ⇗ | - | - | ⇔[g] | - | ⇓ | ⇔[k] | - | - | - | - | - | | |
| **Neoadjuvant therapy** | | | | | | | | | | | | | | | |
| Let. vs. placebo | No relevant studies identified | | | | | | | | | | | | | | |

⇑⇑: Proof of a(n) (added) benefit or lesser harm.
⇑: Indication of a(n) (added) benefit or lesser harm.
⇗: Hint of a greater (added) benefit or lesser harm.
⇔: No hint, homogeneous result.
(⇔): No hint, homogeneous result, but data insufficient (e.g. only one study with a few patients).
⇑⇓: No hint; heterogeneous result.
⇓: Indication of a lesser benefit or greater harm.
⇘: Hint of a lesser benefit or greater harm.
↑: Statistically significant difference in favour of the intervention.
↓: Statistically significant disadvantage of AI.
↑↓: Heterogeneous result.
↔: No statistically significant difference.
-: No data reported, therefore no hint of a(n) (added) benefit.

a: No meta-analysis across drugs, as significant advantage (in the same direction) on the basis of the individual drugs.
b: Events during treatment.
c: No meta-analysis across drugs, as significant disadvantage (in the same direction) on the basis of the individual drugs.
d: Patient relevance of individual events cannot be evaluated.
e: No meta-analysis across drugs, as contrary results on the basis of the individual drugs.
f: Results during the whole observation period.
g: Pooled analysis of severe AEs (CTCAE Grades 3 and 4).
h: No hint of an added benefit in the subgroup of patients who did not receive adjuvant or neoadjuvant chemotherapy.
i: Hint of an added benefit in the subgroup of patients who received adjuvant or neoadjuvant chemotherapy.
j: Meta-analysis across drugs of studies with a high or moderate certainty of results.
k: Statistically significant difference in favour of control; however, substantially biased effect. The results are interpretable only in a qualitative manner. Greater harm from letrozole is not excluded.

AE: adverse event; AI: aromatase inhibitor; Ana.: anastrozole; CTCAE: Common Terminology Criteria for Adverse Events; DFS: disease-free survival; Exe.: exemestane; Let.: letrozole; n. i.: not investigated; SAE: serious adverse event; Tam.: tamoxifen; vs.: versus

Table 3: Evidence map of all drugs, advanced breast cancer

| Stage<br>Treatment regimen<br>Comparison | Overall survival | Morbidity: symptoms | Health-related quality of life | General adverse events: Severe AEs (CTCAE Grade 3) | Severe AEs (CTCAE Grade 4) | SAEs | Discontinuation due to AEs | Specific adverse events: Fractures | Neoplasms | Cerebrovascular events | Cardiovascular events | Thromboembolic events | Endocrine events |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **First-line therapy** | | | | | | | | | | | | | |
| Results of the meta-analysis across drugs | | | | | | | | | | | | | |
| AI vs Tam. | - | - | - | - | - | n. i.[a] | ↔ | n. i.[a] | n. i.[b] | - | ↔ | - | - |
| Results of the comparisons on the basis of individual drugs | | | | | | | | | | | | | |
| Ana. vs. Tam. | ⇑⇓ | - | - | - | - | ⇔ | ⇔ | ⇔ | ⇔ | (⇔) | ⇔ | (⇔) | - |
| Let. vs. Tam. | ⇔ | - | - | - | - | ⇔[c] | ⇔[c] | ⇔[c] | ↔[b, c] | ⇔[c] | ⇔[c] | ⇔[c] | - |
| **Second-line therapy after pretreatment with anti-oestrogens** | | | | | | | | | | | | | |
| Results of the meta-analysis across drugs | | | | | | | | | | | | | |
| AI vs. Tam. | No data for the meta-analysis across drugs for the comparison of AI vs. Tam. | | | | | | | | | | | | |
| Results of the comparisons on the basis of individual drugs | | | | | | | | | | | | | |
| Exe. vs. Ana. | ⇔ | - | - | ⇔ | ⇔ | ⇔ | ⇔ | - | ⇔ | ⇔ | ⇔ | ⇔ | - |
| Let. vs. Ana. | ⇔ | - | - | ⇔ | ⇔ | ⇔ | ⇔ | ⇔ | ↓[b] | ⇔ | ⇔ | ⇔ | - |
| **Third-line therapy** | | | | | | | | | | | | | |
| AI vs. placebo | No relevant studies identified | | | | | | | | | | | | |

⇑⇑: Proof of a(n) (added) benefit or lesser harm.
⇑: Indication of a(n) (added) benefit or lesser harm.
⇗: Hint of a greater (added) benefit or lesser harm.
⇔: No hint, homogeneous result.
(⇔): No hint, homogeneous result, but data insufficient (e.g. only one study with a few patients).
⇑⇓: No hint; heterogeneous result.
⇓: Indication of a lesser benefit or greater harm.
⇘: Hint of a lesser benefit or greater harm.
↑: Statistically significant difference in favour of the intervention.
↔: No statistically significant difference.
↓: Statistically significant effect in favour of the control.
-: No data reported, therefore no hint of a(n) (added) benefit.

a: No meta-analysis across drugs, as contrary results on the basis of the individual drugs.
b: Patient relevance of individual events cannot be evaluated.
c: The results are interpretable only in a qualitative manner.

AE: adverse event; Ana.: anastrozole; CTCAE: Common Terminology Criteria for Adverse Events; Exe.: exemestane; Let.: letrozole; n. i.: not investigated; SAE: serious adverse event; Tam.: tamoxifen; vs.: versus

**Conclusions**

In the following text the conclusions of the present benefit assessment are presented separately for early and advanced breast cancer.

***Early breast cancer***

*Treatment start with an aromatase inhibitor after surgery without pretreatment with anti-oestrogens (upfront therapy)*

Only anastrozole und letrozole are approved for therapy without pretreatment with anti-oestrogens (upfront therapy): for both drugs studies were mainly available in which continuous treatment was compared versus tamoxifen over 5 years.

For upfront therapy, the studies available show an added benefit of aromatase inhibitors over tamoxifen for the outcome of **overall survival**. In this context, the certainty of results differed between the 2 drugs approved for this treatment strategy: the data provide a hint of an added benefit for anastrozole and an indication of added benefit for letrozole. However, the direct comparison of the 2 drugs (one study) shows no advantage or disadvantage for either aromatase inhibitor for the outcome of overall survival.

In addition, for both anastrozole and letrozole the data provide an indication of an added benefit over tamoxifen for the outcome of **DFS**.

No data were available for the outcome of **symptoms**, so that no hint of an added benefit of aromatase inhibitors over tamoxifen can be inferred.

Data on the outcome of **health-related quality of life** were only available for anastrozole; they do not provide a hint of an added benefit of anastrozole over tamoxifen. Due to a lack of data, the same applies to letrozole.

In summary, an advantage of aromatase inhibitors over tamoxifen is shown for the complex of **AEs**. This is based on an indication of lesser harm versus tamoxifen for overall SAEs. For discontinuations due to AEs, the data provide a hint of lesser harm versus tamoxifen only for anastrozole; they do not provide a hint of greater or lesser harm for letrozole. For specific AEs there are both advantages and disadvantages of aromatase inhibitors versus tamoxifen: Fractures occurred more often (for both drugs an indication of greater harm) and thromboembolic events occurred less often (for anastrozole an indication of, for letrozole a hint of lesser harm). Finally, the direct comparison between the 2 aromatase inhibitors provides an indication of greater harm of letrozole versus anastrozole for the outcome of cardiovascular events.

*Studies on sequential therapy (treatment start with an aromatase inhibitor with a subsequent switch to an anti-oestrogen)*

Furthermore, results were available on aromatase inhibitor therapy shortened to 2 to 3 years with a subsequent switch to tamoxifen, namely, from a sequential study on letrozole. It can be

assumed that, in clinical practice, the treatment decision to switch from aromatase inhibitor therapy to an anti-oestrogen (in this case tamoxifen) is always made under consideration of the findings from pretreatment (e.g. occurrence of adverse events or recurrences of the disease). Studies on sequential therapy in which these findings are not considered are thus of subordinate practical relevance. In particular, it cannot be inferred from the results of the available sequential study on letrozole that a treatment period shortened to 2 to 3 years is equivalent to a 5-year treatment period with letrozole. The results of the sequential study are therefore not presented here.

*Treatment switch to an aromatase inhibitor after 2 to 3 years of pretreatment with an anti-oestrogen (switch therapy)*

Only anastrozole and exemestane are approved for switch therapy. Studies on both drugs were available comparing a switch to an aromatase inhibitor therapy after pretreatment with tamoxifen versus the continuation of tamoxifen treatment.

For **overall survival**, the data provide a hint of an added benefit over tamoxifen for both anastrozole and exemestane.

For **DFS**, the data provide an indication of an added benefit over tamoxifen for both anastrozole and exemestane.

No data were available for **symptoms**, so that there is no hint of an added benefit of aromatase inhibitors over tamoxifen.

For **health-related quality of life**, the studies available show no hint of an added benefit of aromatase inhibitors over tamoxifen.

For the complex of **AEs**, in summary the data show an advantage of both anastrozole and exemestane over tamoxifen. This is based on lesser harm with regard to overall SAEs (anastrozole: proof; exemestane: indication). Discontinuations due to AEs did not occur more often or less often under anastrozole or exemestane than under tamoxifen. For the specific AE "fractures" the data provide an indication of greater harm from both anastrozole and exemestane versus tamoxifen. No hint of greater or lesser harm from aromatase inhibitors versus tamoxifen is shown for other specific AEs.

*Extended therapy with an aromatase inhibitor after completion of 5-year tamoxifen therapy*

Only letrozole is approved for extended therapy.

The data available on letrozole provide no hint of a benefit for overall survival. They provide a hint of a benefit for DFS. This is opposed by an indication of harm for discontinuations due to AEs. No harm from letrozole is shown for severe AEs; data on SAEs are lacking. An unfavourable effect of letrozole is shown for fractures. However, the data show a high risk of bias; overall, harm from letrozole cannot be excluded. Corresponding data on further specific AEs are lacking.

*Neoadjuvant therapy*

Only letrozole is approved for neoadjuvant therapy.

No relevant study on neoadjuvant therapy with letrozole was identified. There is therefore no hint of a benefit of neoadjuvant therapy with letrozole.

*Summary*

Overall, in patients with early breast cancer an added benefit of aromatase inhibitors over tamoxifen can be inferred both for upfront therapy and for switch therapy. In this context, the results between the different drugs differ with regard to individual outcomes and the certainty of results. However, informative studies directly comparing aromatase inhibitors are not available.

Overall, for extended therapy there is no hint of a benefit of aromatase inhibitors in comparison with placebo.

Due to a lack of data, there is no hint of a benefit of aromatase inhibitors for neoadjuvant therapy either.

***Advanced breast cancer***

*First-line therapy*

Anastrozole and letrozole are approved for first-line therapy of advanced breast cancer. The data available show no hint of an added benefit of either drug over tamoxifen.

*Second-line therapy after pretreatment with anti-oestrogens*

Anastrozole, exemestane and letrozole are all approved for second-line therapy of advanced breast cancer after pretreatment with anti-oestrogens.

No relevant studies on the benefit of such a therapy are available for any of the 3 drugs. There is thus no hint of a benefit of aromatase inhibitors as second-line therapy for advanced breast cancer.

As the benefit of second-line therapy is not proven, the results of studies directly comparing aromatase inhibitors are of only subordinate relevance. However, the data available do not show a hint of an added benefit or greater harm from any aromatase inhibitor compared with the other ones.

*Third-line therapy*

No relevant study on third-line therapy was identified. There is thus no hint of a benefit of an aromatase inhibitor as third-line therapy for advanced breast cancer.

**Keywords:** aromatase inhibitors, anastrozole, letrozole, exemestane, breast neoplasms, benefit assessment, systematic review

*The full report (German version) is published under*

*https://www.iqwig.de/en/projects-results/projects/drug-assessment/a10-03-aromatase-inhibitors-in-female-breast-cancer.1311.html*