IQWiG Reports – Commission No. A18-72

Abemaciclib (breast cancer; combination with an aromatase inhibitor) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of the executive summary of the dossier assessment *Abemaciclib (Mammakarzinom; Kombination mit einem Aromatasehemmer) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 January 2019). Please note: This document was translated by an external translator and 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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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug abemaciclib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 October 2018.

Research question

The aim of this report was to assess the added benefit of abemaciclib in combination with an aromatase inhibitor in comparison with the appropriate comparator therapy (ACT) in women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, locally advanced or metastatic breast cancer.

Depending on the therapy line and the patients' menopausal status, the G-BA distinguished between 4 different treatment situations and specified different ACTs for each of them. This results in 4 research questions for this benefit assessment, which are presented in Table 2.

Table 2[2]: Research questions of the benefit assessment of abemaciclib in combination with an aromatase inhibitor

Research question	Indication	ACT[a]
Women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer[b]		
A1	Postmenopausal women, initial endocrine therapy	Anastrozole or letrozole or fulvestrant or, if aromatase inhibitors are not suitable, tamoxifen
A2	Premenopausal and perimenopausal women, initial endocrine therapy	Tamoxifen in combination with ovarian suppression
B1	Postmenopausal women who received prior endocrine therapy	Depending on prior therapy: ▪ Tamoxifen or ▪ Anastrozole or ▪ Fulvestrant, only for patients with relapse or disease progression following antioestrogen treatment[c] or ▪ Letrozole, only for patients with relapse or disease progression following antioestrogen treatment or ▪ Exemestane, only for patients with disease progression following antioestrogen treatment or ▪ Everolimus in combination with exemestane, only for patients without symptomatic visceral metastasis after disease progression following nonsteroidal aromatase inhibitor therapy
B2	Premenopausal and perimenopausal women who received prior endocrine therapy	Endocrine therapy upon the physician's discretion, in accordance with the respective approval[d].

a: Presentation of the respective ACT specified by the G-BA.
b: For the therapeutic indications in question, it is assumed that (potentially further) endocrine therapy is indicated for patients and that no indication exists for chemotherapy or (secondary) resection or radiation therapy with curative intent.
c: The approval of fulvestrant requires prior antioestrogen treatment. This diverges from the use of fulvestrant as recommended in the guidelines and as established in patient care, including after prior aromatase inhibitor therapy. In this special treatment and care situation, the G-BA sees an objective medical reason which – in this exceptional case – would justify including fulvestrant, which is also used following aromatase inhibitor treatment, as a comparator.
d: It is assumed that ovarian suppression with a GnRH analogue is being continued. Tamoxifen, letrozole, exemestane, megestrol acetate, and medroxyprogesterone acetate are approved for this therapeutic indication. However, the available evidence on megestrol acetate and medroxyprogesterone acetate with regard to this therapeutic indication is considered insufficient for making a concrete recommendation. In addition, progestogens are explicitly approved only for the palliative treatment of breast cancer.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor-2; HR: hormone receptor

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

In Module 3A, the company explicitly specified an ACT only for research question A1. For this research question, the company chose anastrozole or letrozole. In the criteria for study inclusion, however, the company followed the G-BA and listed ACTs for research questions A2, B1, and B2 as well.

This benefit assessment was conducted for all 4 research questions in comparison with the ACT specified for each of them by the G-BA. For research question A1, the company's choice of ACT was accepted. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for deriving an added benefit.

Results

Research question A1: Postmenopausal women, initial endocrine therapy

Study pool and study characteristics

For research question A1, the MONARCH 3 study was included in the benefit assessment.

The study is a double-blind RCT in which abemaciclib in combination with anastrozole or letrozole was directly compared with anastrozole or letrozole. The study included 493 postmenopausal women with locally advanced or metastatic HR-positive and HER2-negative breast cancer who did not receive prior chemotherapy or endocrine therapy in the locally advanced or metastatic stage. Patients had to have a Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1 at the time they joined the study. Randomization into the two study arms of abemaciclib + anastrozole or letrozole and placebo + anastrozole or letrozole was conducted in a 2:1 ratio. Treatment with the study drugs abemaciclib, letrozole, and anastrozole was largely in accordance with the respective Summary of Product Characteristics.

Risk of bias

The risk of bias at study and outcome levels for the outcomes of overall survival and discontinuation due to AEs was rated as low. There was a high risk of bias for the results of further outcomes (symptoms, health status, and health-related quality of life as well as the outcomes on adverse events).

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment arms was found. Consequently, there is no hint of added benefit of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. An added benefit is therefore not proven.

Symptoms

Symptoms were surveyed through the symptom scales of fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea of the European Organisation for

Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the symptom scales of side effects of systemic treatment, breast symptoms, arm symptoms, and upset by hair loss of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23 (EORTC QLQ-BR23). For this benefit assessment, the results of the prescheduled analyses were used by means of a mixed-effect model repeated measures (MMRM).

In each of the symptom scales for fatigue, nausea and vomiting, appetite loss, diarrhoea, and adverse effects of systemic treatment, there were statistically significant effects to the disadvantage of abemaciclib. However, of all effects, only the one found on the diarrhoea scale had a confidence interval of Hedges' g outside the irrelevance range [−0.2; 0.2]. Said effect was interpreted as a relevant effect; for the remaining scales, it cannot be concluded that the effects are relevant. For the scales of pain, dyspnoea, insomnia, constipation, breast symptoms, and arm symptoms, no statistically significant differences between study arms were found.

All things considered, for the outcome of diarrhoea, there is a hint of added benefit of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For all other outcomes, there is no hint of added benefit of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Health status

Health status was surveyed using the visual analogue scale (VAS) of the European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L) questionnaire. For this benefit assessment, the results of the prescheduled analyses were used by means of an MMRM. For the VAS of EQ-5D-5L, no statistically significant difference between treatment arms was found. Consequently, there is no hint of added benefit of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was surveyed through the scale of global health status and the functional scales of physical functioning, role functioning, and emotional, cognitive, and social functioning of the EORTC QLQ-C30 questionnaire as well as the functional scales of body image, sexual function, sexual enjoyment, and future perspective of the EORTC QLQ-BR23. For this benefit assessment, the results of the prescheduled analyses were used through an MMRM.

For global health status, role functioning, social functioning, and body image, there are statistically significant differences to the disadvantage of abemaciclib, but none of them have a confidence interval of Hedges' g outside the irrelevance range [−0.2; 0.2]. Hence, the effect cannot be rated as relevant for any of these scales. For each of the scales of physical functioning, emotional functioning, cognitive functioning, sexual functioning, and future perspective, no statistically significant differences between study arms were found.

All things considered, for health-related quality of life, there is no hint of added benefit of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

SAEs

For the outcome of SAEs, the event time analysis shows a statistically significant effect to the disadvantage of abemaciclib.

An effect modification by the attribute of age was found. For women ≥ 65 years of age, this results in a hint of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole, while for women < 65 years of age, there is no proof of greater or lesser harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Severe AEs (CTCAE grade ≥ 3)

For the outcome of severe AEs (CTCAE grade ≥ 3), the event time analysis showed a statistically significant effect to the disadvantage of abemaciclib.

An effect modification by the attribute of age was found. For women < 65 years of age, there is a hint of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For the result for women ≥ 65 years of age, high certainty of results is assumed due to the effect size and the fact that the events occurred early in the follow-up period, despite the high risk of bias on the outcome level. For women ≥ 65 years of age, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Discontinuation due to AEs

The outcome of discontinuation due to AEs examines the discontinuation of one or both drugs. For the outcome of discontinuation due to AEs, there is a statistically significant effect to the disadvantage of abemaciclib. For this outcome, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Neutropenia (CTCAE grade ≥ 3)

For the specific AE of neutropenia, the relative risk (RR) shows a statistically significant effect to the disadvantage of abemaciclib. Despite the high risk of bias at outcome level, high certainty of results is assumed due to the effect size. For this outcome, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Research questions A2 (premenopausal and perimenopausal women, initial endocrine therapy), B1 (postmenopausal women who received prior endocrine therapy), and B2 (premenopausal and perimenopausal women who received prior endocrine therapy)

The company did not present any data on research questions A2, B1, and B2. For these outcomes, this results in no hint of added benefit of abemaciclib in comparison with the ACT. An added benefit is not proven for these research questions.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug abemaciclib in combination with an aromatase inhibitor in comparison with the ACT are assessed as follows:

All things considered, the results on research question A1 show no positive effects of abemaciclib in combination with anastrozole or letrozole in comparison with anastrozole or letrozole. Rather, for several outcomes, hints and indications of lesser benefit or greater harm from abemaciclib in combination with anastrozole or letrozole in comparison with anastrozole or letrozole were found, ranging up to a considerable extent.

In summary, for postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer, there is an indication of lesser benefit of abemaciclib in combination with an aromatase inhibitor as the initial endocrine therapy in comparison with anastrozole or letrozole.

No data were available for research questions A2, B1, and B2.

Table 3 presents a summary of the probability and extent of the added benefit of abemaciclib in combination with an aromatase inhibitor.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Abemaciclib in combination with an aromatase inhibitor – probability and extent of added benefit

Research question	**Indication**	**ACT**[a]	**Probability and extent of added benefit**
Women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer[b]			
A1	Postmenopausal women, initial endocrine therapy	**Anastrozole** or **letrozole** or fulvestrant or, if aromatase inhibitors are not suitable, tamoxifen	Indication of lesser benefit[c]
A2[d]	Premenopausal and perimenopausal women, initial endocrine therapy	Tamoxifen in combination with ovarian suppression	Added benefit not proven
B1[d]	Postmenopausal women who received prior endocrine therapy	Depending on prior therapy: ▪ Tamoxifen or ▪ Anastrozole or ▪ Fulvestrant, only for patients with relapse or progression following antioestrogen treatment[e] or ▪ Letrozole, only for patients with relapse or disease progression following antioestrogen treatment or ▪ Exemestane, only for patients with disease progression following antioestrogen treatment or ▪ Everolimus in combination with exemestane, only for patients without symptomatic visceral metastasis after disease progression following nonsteroidal aromatase inhibitor therapy	Added benefit not proven
B2[d]	Premenopausal and perimenopausal women who received prior endocrine therapy	Endocrine therapy upon the physician's discretion, in consideration of the respective approval[f].	Added benefit not proven

(continued)

Table 3: Abemaciclib in combination with an aromatase inhibitor – probability and extent of added benefit (continued)

a: Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice by the company is printed in bold.
b: For the therapeutic indications in question, it is assumed that (potentially further) endocrine therapy is indicated for patients and that no indication exists for chemotherapy or (secondary) resection or radiation therapy with curative intent.
c: Only patients with an ECOG-PS of 0 or 1 were included in the relevant study. It remains unclear whether the observed effects translate to patients with an ECOG-PS ≥ 2.
d: The company did not explicitly choose an ACT for these research questions.
e: The approval of fulvestrant requires prior antioestrogen treatment. This diverges from the use of fulvestrant as recommended in the guidelines and as established in patient care, including after prior aromatase inhibitor therapy. In this special treatment and care situation, the G-BA sees an objective medical reason which – in this exceptional case – would justify including fulvestrant, which is also used following aromatase inhibitor treatment, as a comparator.
f: It is assumed that ovarian suppression with a GnRH analogue is being continued. Tamoxifen, letrozole, exemestane, megestrol acetate, and medroxyprogesterone acetate are approved for this therapeutic indication. However, the available evidence on megestrol acetate and medroxyprogesterone acetate with regard to this therapeutic indication is considered insufficient for making a concrete recommendation. In addition, progestogens are explicitly approved only for the palliative treatment of breast cancer.
ACT: appropriate comparator therapy; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor-2; HR: hormone receptor

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

Note:

An addendum (A19-24) to dossier assessment A18-72 has been published.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-72-abemaciclib-in-combination-with-an-aromatase-inhibitor-breast-cancer-benefit-assessment-according-to-35a-social-code-book-v.10908.html.