IQWiG Reports – Commission No. A18-73

Abemaciclib (breast cancer; combination with fulvestrant) –

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 Fulvestrant) – 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 in combination with fulvestrant. 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 fulvestrant 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 fulvestrant

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. In this regard, there is a discrepancy with 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.

For the assessment of the combination of abemaciclib with fulvestrant, the company specifies fulvestrant as the ACT for all research questions.

For research questions A1 and B1, the company's choice of ACT (fulvestrant) was accepted. For research question A2 and B2, the company's deviation from the G-BA's ACT was rejected. This benefit assessment was conducted separately for 4 research questions, each in comparison with the ACT specified by the G-BA.

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 any added benefit.

Results on added benefit

Research question A1 (postmenopausal women, initial endocrine therapy) and research question B1 (postmenopausal women who received prior endocrine therapy)

Study pool and study characteristics

For assessing research questions A1 and B1, a subpopulation of the MONARCH 2 study was included.

The study is a double-blind RCT in which abemaciclib in combination with fulvestrant was directly compared with fulvestrant. The study initially included women with locally advanced or metastatic HR-positive and HER2-negative breast cancer, regardless of menopausal status, who either had or had not received prior endocrine therapy. Patients had to have a Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1 at the time they joined the study.

In the further course of the study, as a result of the protocol change dated 30 March 2015, patients who had not received endocrine therapy at any prior time, not even (neo)adjuvantly, (endocrine-naïve patients) were no longer included. A total of 669 patients were included in the study (+ 44 endocrine-naïve patients) and randomized in a 2:1 ratio to the two study arms of abemaciclib + fulvestrant and placebo + fulvestrant.

From among these patients, 338 patients of the MONARCH 2 study (+ 36 endocrine-naïve patients) are generally relevant for research question A1 due to their menopausal and prior treatment status. However, instead of analysing the endocrine-naïve patients as part of the MONARCH 2 study population, the company provided a separate analysis despite the fact that these patients were part of the population of research question A1. The available separate analyses done by the company on endocrine-naïve patients are not suitable for the benefit assessment. It can be assumed though that these postmenopausal, endocrine-naïve patients who were not included in the analysis of the MONARCH 2 study would not have changed the available results for research question A1 to a relevant extent.

For research question B1, a different subpopulation of the MONARCH 2 study was included, namely postmenopausal patients who received prior endocrine therapy in the advanced or

metastatic stage. Fulvestrant, which was administered as comparator therapy in the study, was specified by the G-BA as one of the ACT options, but (due to fulvestrant approval) only for patients with relapse or disease progression after antioestrogen treatment. In accordance with the G-BA's note on the ACT, however, studies in which patients with prior aromatase inhibitor treatment used fulvestrant were included as well. In the study's subpopulation of patients with prior endocrine treatment, only a few, if any, women did not receive prior antioestrogen or aromatase inhibitor therapy; therefore, the entire corresponding subpopulation (213 patients) was used in the assessment.

The use of the study drugs abemaciclib and fulvestrant in the MONARCH 2 study was largely in accordance with the respective Summary of Product Characteristics, with the exception of the starting dose of 200 mg abemaciclib specified in the initial study protocol.

Starting dose of 200 mg abemaciclib

In accordance with the initial MONARCH 2 study protocol, a starting dose of 200 mg abemaciclib every 12 hours was required. However, the dose of 200 mg is higher than the ultimately approved abemaciclib dose of 150 mg. With the protocol change dated 12 January 2015, the starting dose and maximum dose were reduced to the later approved dosage of 150 mg every 12 hours. All patients who received 200 mg abemaciclib at that time reduced their dose to 150 mg. At the time of the protocol change, 101 (27%) postmenopausal patients had already been included in the abemaciclib arm, and 47 (26%) postmenopausal patients had been included in the placebo arm. No data are available on the relevant subpopulations for research questions A1 and B1.

The company submitted analyses on treatment duration and dose intensity on 200 mg and 150 mg for the overall population as well as subgroup analyses broken down by starting dose for postmenopausal women. While these analyses are missing for the relevant subpopulations, the high starting dose (200 mg instead of 150 mg) is not assumed to entirely negate the study results for subpopulations A1 and B1. The available results on the A1 and B1 subpopulations of the MONARCH 2 study were therefore used in the benefit assessment. The high starting dose was, however, taken into account when deriving the reliability of the study results (see below).

Risk of bias and reliability of results for research questions A1 and B1

The risk of bias at study level as well as the risk of bias for the results of both research questions regarding the outcomes of overall survival and discontinuation due to adverse events (AEs) was rated as low.

For the outcomes of symptoms, pain, health status, health-related quality of life, and neutropenia (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), no (usable) data were available for subpopulations A1 and B1; therefore, the risk of bias of these results was not rated. For the outcomes of serious AEs (SAEs) and severe AEs (CTCAE grade ≥ 3), there is a high risk of bias for the results for both research questions.

Overall, it must be borne in mind that a high percentage of postmenopausal patients received an off-label, higher dose of abemaciclib (200 mg instead of 150 mg) at the start of the study. A relevant influence of this high dose on the results of all outcomes of the respective research question cannot be ruled out. An influence of the high starting dose on the observed effect is particularly conceivable when looking at the event time analyses and the outcomes of the adverse events category. However, effect modifications in the categories of morbidity and health-related quality of life are conceivable as well. Adverse events can lead to treatment discontinuation or other severe consequences, even death, and also have negative effects on overall survival, while greater effectiveness due to a higher dose might have positively influenced overall survival.

Therefore, the reliability of results is low even for outcomes with a low risk of bias. Consequently, on the basis of the MONARCH 2 study, at most hints can be derived for all outcomes.

Results for research question A1 (postmenopausal women, initial endocrine therapy)

- Overall survival

For the outcome of overall survival, no statistically significant difference between treatment arms was found. This results in no hint of added benefit of abemaciclib + fulvestrant in comparison with fulvestrant. An added benefit is therefore not proven.

- Morbidity and health-related quality of life

In the study, morbidity was surveyed on the symptom scales of the instruments European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORCT QLQ-C30) as well as European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23 (EORTC QLQ-BR23) for symptoms, the Modified Brief Pain Inventory-Short Form (mBPI-SFI) questionnaire for pain as well as the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions, 5-level version (EQ-5D-5L) questionnaire for health status. The study surveyed health-related quality of life using the corresponding scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.

For the relevant subpopulation, usable data on morbidity and health-related quality of life were not available for any of the mentioned instruments. For the outcomes of symptoms, pain, and health status, this results in no hint of added benefit of abemaciclib + fulvestrant in comparison with fulvestrant. An added benefit is therefore not proven.

- SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs

For each of the outcomes of SAEs, severe AEs, and discontinuation due to AEs (discontinuation of one or both drugs), a statistically significant effect to the disadvantage of abemaciclib was found. Due to the low reliability of results, for each of these outcomes, there is a hint of greater harm from abemaciclib + fulvestrant in comparison with fulvestrant as initial endocrine therapy in postmenopausal patients.

- Neutropenia (CTCAE grade ≥ 3)

For the relevant subpopulation A1, no analyses on severe neutropenia were available.

- Further specific AEs

It was not possible to select further specific AEs on the basis of their frequency and differences between treatment arms on the level of the system organ class (SOC) and preferred term (PT), because no corresponding analyses of common AEs were available for subpopulation A1.

Results for research question B1 (postmenopausal women who received prior endocrine therapy)

- Overall survival

For the outcome of overall survival, no statistically significant difference between treatment arms was found. This results in no hint of added benefit of abemaciclib + fulvestrant in comparison with fulvestrant. An added benefit is therefore not proven.

- Morbidity and health-related quality of life

In the study, morbidity was surveyed through the symptom scales of the instruments EORTC QLQ-C30 as well as EORTC QLQ-BR23 for symptoms, the mBPI-SFI questionnaire for pain as well as the VAS of the EQ-5D-5L questionnaire for health status. The study surveyed health-related quality of life using the corresponding scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 instruments.

For the relevant subpopulation, usable data on morbidity and health-related quality of life were not available for any of the mentioned instruments. For the outcomes of symptoms, pain, and health status, this results in no hint of added benefit of abemaciclib + fulvestrant in comparison with fulvestrant. An added benefit is therefore not proven.

- SAEs

For the outcome of SAEs, no statistically significant effect between treatment arms was found. This results in no hint of greater or lesser harm from abemaciclib + fulvestrant in comparison with fulvestrant for postmenopausal patients who received prior endocrine therapy. Greater or lesser harm is therefore not proven.

- SAEs, severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs

For each of the outcomes of severe AEs and discontinuation due to AEs (discontinuation of one or both drugs), a statistically significant effect to the disadvantage of abemaciclib was found. Due to the low reliability of results, for each of these outcomes, there is a hint of greater harm from abemaciclib + fulvestrant in comparison with fulvestrant for postmenopausal patients who received prior endocrine therapy.

- Neutropenia (CTCAE grade ≥ 3)

No analyses were available on severe neutropenia in the relevant subpopulation for research question B1.

- Further specific AEs

It was not possible to select further specific AEs on the basis of frequency and differences between the treatment arms on the level of the SOC and PT because no corresponding analyses of common AEs were available for subpopulation B1.

Research question A2 (premenopausal and perimenopausal women, initial endocrine therapy) and research question B2 (premenopausal and perimenopausal women who received prior endocrine therapy)

The company did not present any suitable data on research questions A2 and B2. For these research questions, 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 fulvestrant in comparison with the ACT are assessed as follows:

All things considered, for research questions A1 and B1, there are no positive effects of abemaciclib in combination with fulvestrant in comparison with fulvestrant. However, for both research questions, there are several hints of greater harm from abemaciclib + fulvestrant in comparison with fulvestrant for the outcome category of adverse events.

In summary, for postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer who received their initial endocrine therapy (research question A1) or who had received prior endocrine therapy (research question B1), there is a hint of lesser benefit of abemaciclib in combination with fulvestrant in comparison with fulvestrant.

The company did not present any suitable data to assess the added benefit of abemaciclib in combination with fulvestrant in premenopausal and perimenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer who received their initial

[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].

endocrine therapy (research question A2) or in women who had received prior endocrine therapy (research question B2). An added benefit is not proven for these patients.

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

Table 3: Abemaciclib in combination with fulvestrant – 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/metastatic breast cancer[b]			
A1	Postmenopausal women, initial endocrine therapy	Anastrozole or letrozole or fulvestrant or, if aromatase inhibitors are not suitable, tamoxifen	Hint of lesser benefit[c]
A2	Premenopausal and perimenopausal women, initial endocrine therapy	Tamoxifen in combination with ovarian suppression	Added benefit not proven
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[d] 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	Hint of lesser benefit[c]
B2	Premenopausal and perimenopausal women who received prior endocrine therapy	Endocrine therapy upon the physician's discretion, in accordance with the respective approval[d].	Added benefit not proven

(continued)

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

a: Presentation of the respective ACT specified by the G-BA.
b: For the therapeutic indications in question, it is assumed that 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 approval of fulvestrant requires prior antioestrogen treatment. In this regard, there is a discrepancy with 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.
e: 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 (A19-25) to dossier assessment A18-73 has been published.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-73-abemaciclib-in-combination-with-fulvestrant-breast-cancer-benefit-assessment-according-to-35a-social-code-book-v.10909.html.