IQWiG Reports – Commission No. A18-63

Palbociclib (breast cancer) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of the executive summary of the dossier assessment *Palbociclib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 20 December 2018). 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 palbociclib. 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 28 September 2018.

Research question

The aim of this report is to assess the added benefit of palbociclib in combination with fulvestrant (hereinafter palbociclib + fulvestrant) in comparison with the appropriate comparator therapy (ACT) in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer who received prior endocrine therapy.

On the basis of menopausal status, 2 research questions, for which the G-BA specified different appropriate comparator therapies (ACTs), result for this benefit assessment. The research questions are presented in Table 2.

Table 2[2]: Research questions of the benefit assessment of palbociclib

Research question	Indication[a]	ACT[b]
Women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression after endocrine therapy		
B1	Postmenopausal women	Depending on prior therapy, further endocrine therapy using ▪ tamoxifen or ▪ anastrozol or ▪ **fulvestrant**; only for patients with relapse or disease progression following anti-oestrogen treatment, or ▪ letrozol; only for patients with relapse or disease progression following anti-oestrogen treatment, or ▪ exemestan; only for patients with disease progression following anti-oestrogen treatment, or ▪ everolimus in combination with exemestan; only for patients without symptomatic visceral metastasis after disease progression following nonsteroidal aromatase inhibitor therapy
B2	Premenopausal and perimenopausal women	Endocrine therapy upon the physician's discretion in consideration of the respective approval[c]: For this therapeutic indication, tamoxifen, letrozol, exemestan, megestrol acetate, and medroxyprogesterone acetate are approved.[d]

a: For this therapeutic indication, it is assumed that chemotherapy or (secondary) resection or radiotherapy with curative intention are not indicated.
b: 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**.
c: Ovarian suppression with a GnRH analogue is assumed to be continued.
d: The available evidence on megestrol acetate and medroxyprogesterone acetate is considered insufficient for making a concrete recommendation.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; HR: hormone receptor

This assessment covers exclusively the combination of palbociclib + fulvestrant for the therapeutic indication of advanced or metastatic breast cancer following prior endocrine therapy. The additional research questions (A1 and A2) covered by the initial assessment of palbociclib for patients on first-line therapy as well as the combination of palbociclib with aromatase inhibitors following endocrine therapy are not part of this benefit assessment in accordance with the G-BA's commission and the validity time limits imposed by G-BA's justification paper.

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

This assessment was conducted using the appropriate comparator therapy (ACT) specified by the G-BA. The company deviated from the ACT specified by the G-BA in both research questions. For research question B1, it chose fulvestrant without restricting this choice to patients with relapse or disease progression following antioestrogen therapy. For research question B2, the company chose fulvestrant monotherapy although the G-BA specified endocrine therapy upon the physician's discretion as the ACT.

The assessment was conducted using patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Relevance of the study used by the company

As in the initial assessment, the company used the PALOMA-3 study for assessing the added benefit of palbociclib for both research questions. Due to the inadequate implementation of the ACT for both research questions, this study continues to be unsuitable for deriving an added benefit of palbociclib. Hereinbelow, this is being justified in more detail for the individual research questions.

Research question B1: postmenopausal women following endocrine therapy

For postmenopausal women, fulvestrant monotherapy is approved only after anti-oestrogen therapy. However, one inclusion criterion of the PALOMA-3 study specified that postmenopausal women had to have received prior therapy with an aromatase inhibitor. Therefore, fulvestrant is not an approved therapy for postmenopausal women pretreated with aromatase inhibitor in the comparator arm of the PALOMA-3 study and hence is not an ACT. On 29 May 2017 – hence after the decision on the previous assessment, which was taken on 18 May 2017 – the European Medicines Agency (EMA), citing insufficient evidence, for the 2nd time rejected an application for extending the marketing authorisation for fulvestrant to patients pretreated with aromatase inhibitors. Therefore, fulvestrant continues to deviate from the ACT specified by the G-BA.

Research question B2: premenopausal/perimenopausal women following endocrine therapy

The ACT specified by the G-BA for premenopausal/perimenopausal patients – endocrine therapy upon the physician's discretion – offers a choice between several treatment options. This choice is not available in the PALOMA-3 study due to the selection of fulvestrant as the only ACT. In addition, fulvestrant monotherapy is approved only for postmenopausal women pretreated with anti-oestrogen therapy, but not for premenopausal or perimenopausal women. All things considered, fulvestrant monotherapy therefore is not an ACT for the patient population presented by the company.

Validity time limits imposed by the G-BA and handling of the PALOMA-3 study in this assessment

Regardless of fulvestrant's approval, the G-BA considered the PALOMA-3 study in its justification paper on the decision on palbociclib dated 18 May 2017 and limited the validity period of the decision. For benefit re-assessment after expiry, the final study results from the PALOMA-3 study were to be presented.

In accordance with validity time limits imposed by the G-BA, this assessment presents and assesses the company's newly submitted results of the PALOMA-3, regardless of their relevance to the benefit assessment of palbociclib. Adopting the G-BA's approach in the justification paper dated 18 May 2017, the results of the total population of the PALOMA-3 study were examined.

Study pool and study characteristics

The PALOMA-3 study is a randomized, controlled, blind study comparing palbociclib + fulvestrant with placebo + fulvestrant. The study included patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer. Prior to being included in the study, participants had to have experienced disease progression during or after endocrine therapy.

Postmenopausal women were included in the study only if they had undergone prior therapy with an aromatase inhibitor. Premenopausal/perimenopausal women were included only after prior tamoxifen therapy (as adjuvant therapy) or endocrine therapy (in advanced/metastatic stage). In addition to endocrine therapy, it was permissible for patients to have received a maximum of 1 round of chemotherapy in the advanced or metastatic stage before they were included in the study. Only patients in good general health (Eastern Cooperative Oncology Group Performance Status [ECOG-PS] of 0 or 1) were included in the study.

A total of 521 patients were allocated in a 2:1 ratio to either treatment with palbociclib + fulvestrant (N = 347) or placebo + fulvestrant (N = 174). Randomization was stratified according to the factors of menopause status, sensitivity to prior hormone therapy, and the presence of visceral metastases. The study included about one quarter more patients than originally planned; therefore, the number of events required for the final analysis on overall survival was later adjusted.

Palbociclib treatment was administered largely in accordance with the Summary of Product Characteristics (SPC). In the comparator arm of the PALOMA-3 study, the administration of fulvestrant was not in conformance with the approval (see discussion on the relevance of the study).

In both study arms, treatment was continued until objective disease progression, deterioration of symptoms, need for new or additional anticancer therapy, unacceptable toxicity, or the investigator's or patient's decision to discontinue treatment. Provided no follow-up therapy was started, it was possible to continue treatment beyond disease progression upon the physician's

discretion. The study protocol did not allow switching to the treatment of the other study arm. Nevertheless, at the data cut-off date of 13 April 2018, some 17% of patients in the study's comparator arm received palbociclib as follow-up therapy.

The primary outcome of the study was progression-free survival (PFS). Secondary outcomes comprised overall survival as well as outcomes on symptoms, health status, health-related quality of life, and adverse events.

This assessment is based on results presented by the company on the final data cut-off date of 13 April 2018 on the outcome of overall survival. The number of events required to reach the final data cut-off are based not on the original planning, but on a change in the statistical analysis plan dated 10 January 2018. This change was implemented after the final data cut-off was supposed to have already taken place according to the original plan, when initial results of the study were already known.

Risk of bias

The risk of bias at study level of the PALOMA-3 study is low. At the outcome level, the risk of bias is rated as high for all outcomes examined in the benefit assessment, except for discontinuation due to AEs.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. The analysis also reveals a strikingly high rate of lost-to-follow-up cases (> 10% in both treatment arms) and is based on a subsequent, disproportionate change in the event ratio required for final analysis after some results of the PALOMA-3 study had become known. In addition, this change was made after the time the final analysis was supposed to have already been carried out according to the original plan.

Morbidity – Symptoms

Pain measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core30 (QLQ-C30)

For the outcome of pain, as surveyed using the EORTC QLQ-C30 questionnaire, a statistically significant difference in favour of palbociclib + fulvestrant was found.

Health-related quality of life

Emotional functioning (EORTC QLQ-C30)

For the outcome of emotional functioning, as surveyed using the EORTC QLQ-C30 questionnaire, a statistically significant difference in favour of palbociclib + fulvestrant was found.

Adverse events

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

For the outcome of severe AEs (CTCAE grade ≥ 3), a statistically significant difference to the disadvantage of palbociclib + fulvestrant was found.

Injury, poisoning, and procedural complications (CTCAE grade ≥ 3)

For the outcome of injury, poisoning, and procedural complications (CTCAE grade ≥ 3), a statistically significant difference in favour of palbociclib + fulvestrant was found.

Leukopenia, neutropenia, low neutrophil count, low leukocyte count (all CTCAE grade ≥ 3)

For each of the outcomes of leukopenia, low leukocyte count, neutropenia, and low neutrophil count (all CTCAE grade ≥ 3), there was a statistically significant difference to the disadvantage of palbociclib + fulvestrant.

Other (non-serious) specific AEs

The data presented by the company on non-serious specific AEs are incomplete.

Other outcomes

For all other outcomes regarding the categories of morbidity, health-related quality of life, and adverse events, no statistically significant differences were found.

Overall evaluation of results

Overall, the PALOMA-3 study revealed neither an advantage nor a disadvantage of palbociclib + fulvestrant in comparison with placebo + fulvestrant.

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 palbociclib in comparison with the ACT is assessed as follows:

Due to the inadequate implementation of the ACT in the PALOMA-3 study, no conclusions can be drawn on the added benefit of palbociclib in comparison with the ACT on the basis of the available results. Notwithstanding the above, the overall analysis of the PALOMA-3 study

[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].

reveals neither an advantage nor a disadvantage of palbociclib + fulvestrant in comparison with placebo + fulvestrant.

All things considered, this results in no hint of added benefit of palbociclib in comparison with the ACT for either of the two research questions. An added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of added benefit of palbociclib.

Table 3: Palbociclib – probability and extent of added benefit

Research question	**Indication**[a]	**ACT**[b]	**Probability and extent of added benefit**
Women with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression after endocrine therapy			
B1	Postmenopausal women	Depending on prior therapy, further endocrine therapy using ▪ tamoxifen or ▪ anastrozol or ▪ **fulvestrant**; only for patients with relapse or disease progression following anti-oestrogen treatment, or ▪ letrozol; only for patients with relapse or disease progression following anti-oestrogen treatment, or ▪ exemestan; only for patients with disease progression following anti-oestrogen treatment, or ▪ everolimus in combination with exemestan; only for patients without symptomatic visceral metastasis after disease progression following nonsteroidal aromatase inhibitor therapy	Added benefit not proven
B2	Premenopausal and perimenopausal women	Endocrine therapy upon the physician's discretion in consideration of the respective approval[c]: Tamoxifen, letrozol, exemestan, megestrol acetate, and medroxyprogesterone acetate are approved for this therapeutic indication.[d]	Added benefit not proven

a: For this therapeutic indication, it is assumed that chemotherapy or (secondary) resection or radiotherapy with curative intention are not indicated.
b: 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**.
c: Ovarian suppression with a GnRH analogue is assumed to be continued.
d: The available evidence on megestrol acetate and medroxyprogesterone acetate is considered insufficient for making a concrete recommendation.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; HR: hormone receptor

The G-BA decides on the added benefit.

Note:

An addendum (A19-14) to dossier assessment A18-63 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.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-63-palbociclib-breast-cancer-benefit-assessment-according-to-35a-social-code-book-v-expiry-of-the-decision.10624.html.