IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Palbociclib (breast cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Palbociclib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 23 February 2017). 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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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BCS	Breast Cancer Subscale
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life-5 Dimensions
ER	oestrogen receptor
FACT-B	Functional Assessment of Cancer Therapy-Breast Cancer
FACT-G	Functional Assessment of Cancer Therapy-General
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LHRH	luteinizing hormone-releasing hormone
MMRM	mixed-effects model repeated measures
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
STE	surrogate threshold effect
TOI	Trial Outcome Index
TTP	time to progression
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) 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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 23 November 2016.

Research question

The aim of the present report was to assess the added benefit of palbociclib 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:

- in combination with an aromatase inhibitor
- in combination with fulvestrant in women who have received prior endocrine therapy

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

Research question

Table 2: Research questions of the benefit assessment of palbociclib

Research question	Subindication[a]	ACT[b]
Women with HR-positive, HER2-negative advanced/metastatic breast cancer		
A1	Postmenopausal women, initial endocrine therapy (first-line treatment)	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable
A2	Pre- and perimenopausal women, initial endocrine therapy (first-line treatment)	Tamoxifen in combination with suppression of the ovarian function
B1	Postmenopausal women who have progressed after endocrine therapy (second and subsequent line of treatment)	Depending on the prior therapy: ▪ tamoxifen or ▪ anastrozole or ▪ **fulvestrant**; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ exemestane; only for patients with progression following anti-oestrogen therapy or ▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor
B2	Pre- and perimenopausal women who have progressed after endocrine therapy (second and subsequent line of treatment)	Endocrine therapy specified by the physician under consideration of the respective approval[c]

a: It is assumed for the present therapeutic indication that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
b: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
c: It is assumed that ovarian suppression with a GnRH analogue is continued.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; GnRH: gonadotropin-releasing hormone

According to the approval, palbociclib should be administered either in combination with an aromatase inhibitor or in combination with fulvestrant (in women who have received prior endocrine therapy). According to information provided by the Federal Institute for Drugs and Medical Devices (BfArM), the approval for the combination with fulvestrant includes both women who have received endocrine therapy in the metastatic setting and women who have already received adjuvant endocrine therapy.

The present assessment was conducted in comparison with the ACT specified by the G-BA. For research questions A1 and B1, this concurs with the choice of the company, which chose letrozole (research question A1) and fulvestrant (research question B1) from the options cited by the G-BA. The company did not investigate research question A2. Deviating from the G-BA, the company chose fulvestrant as only ACT for research question B2. This approach of the company was not followed.

The company presented data only for part of the research questions and possible drug combinations. An overview of the data presented by the company is shown in Table 3.

Table 3: Data presented by the company on the individual research questions

Research question	Subindication	Data presented by the company
Women with HR-positive, HER2-negative advanced/metastatic breast cancer		
A1	Postmenopausal women, initial endocrine therapy	
	▪ in combination with aromatase inhibitor	▪ RCTs (for the combination with letrozole; PALOMA-1 und PALOMA-2)
	▪ in combination with fulvestrant[a]	▪ no data
A2	Pre- and perimenopausal women, initial endocrine therapy	
	▪ in combination with aromatase inhibitor	▪ no data
	▪ in combination with fulvestrant[a]	▪ no data
B1	Postmenopausal women who have progressed after endocrine therapy	
	▪ in combination with aromatase inhibitor	▪ no data
	▪ in combination with fulvestrant	▪ RCT (PALOMA-3)
B2	Pre- and perimenopausal women who have progressed after endocrine therapy	
	▪ in combination with aromatase inhibitor	▪ no data
	▪ in combination with fulvestrant	▪ RCT (PALOMA-3)

a: In women who have already received adjuvant endocrine therapy.
HER2: human epidermal growth factor receptor 2; HR: hormone receptor; RCT: randomized controlled trial

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

Results

Research question A1: first-line treatment in postmenopausal women

Study pool and study characteristics

For the present research question, the studies PALOMA-1 and PALOMA-2 were included in the benefit assessment. Both studies compared a combination of palbociclib + letrozole with letrozole monotherapy. According to the approval, a combination of palbociclib with fulvestrant is also an option for the first-line treatment in postmenopausal women if these

patients have already received endocrine therapy at an earlier stage of the disease. The company did not present studies investigating a combination of palbociclib and fulvestrant versus the ACT for research question A1, however.

The PALOMA-1 study included postmenopausal women with oestrogen receptor (ER)-positive and HER2-negative locally recurrent or metastatic breast cancer. The study was randomized and unblinded and compared the drug combination palbociclib + letrozole with letrozole monotherapy. The patients had not yet received endocrine therapy for the advanced stage of the disease. A total of 165 patients were randomly assigned to treatment with palbociclib + letrozole (N = 84) or letrozole (N = 81).

The PALOMA-2 study was a randomized blinded study comparing the drug combination of palbociclib + letrozole with letrozole + placebo. This study included patients with ER-positive and HER2-negative locoregionally recurrent or metastatic breast cancer. The patients had not yet received systemic treatment for the advanced stage of the disease. A total of 666 patients were randomly allocated in a ratio of 2:1 to treatment with palbociclib + letrozole (N = 444) or letrozole + placebo (N = 222).

In both studies, treatment of the patients in the intervention and comparator arm concurred with the Summaries of Product Characteristics (SPCs) of palbociclib and letrozole. In both study arms, treatment was to be continued until disease progression, symptomatic deterioration, necessity of additional anticancer therapy or unacceptable toxicity.

Risk of bias at study level and outcome level

For the PALOMA-1 study, the risk of bias at study level was rated as high. Consequently, the risk of bias at outcome level was rated as high for all patient-relevant outcomes. In addition, there was a large proportion of potentially informative censorings for the outcomes “serious adverse events (SAEs)” and “severe adverse events (AEs)”.

For the PALOMA-2 study, the risk of bias at study level was rated as low. There was a high risk of bias for the outcomes “health status”, “health-related quality of life”, “SAEs” and “severe AEs” due to the large proportion of potentially informative censoring.

The PALOMA-2 study was the main study for the interpretation of the results and the derivation of the added benefit of palbociclib. The results of PALOMA-2 cannot be called into question or supported by the PALOMA-1 study because of its low certainty of conclusions and sample size. An overall consideration of both studies was only conducted if the effects in the PALOMA-1 study were so clear that the respective effect was not questioned despite the high risk of bias. This only applied to the outcome “severe AEs”.

On the basis of the available data on the studies PALOMA-1 and PALOMA-2, at most hints, e.g. of an added benefit, can be determined for the outcomes “health status”, “health-related

quality of life" and "SAEs" and at most indications for "overall survival", "severe AEs" and "discontinuation due to AEs".

Results

Overall survival

The PALOMA-2 study showed no statistically significant difference between the treatment arms for the outcome "overall survival". The difference between the treatment arms was not statistically significant also in the PALOMA-1 study.

Overall, no hint of an added benefit of palbociclib + letrozole versus letrozole was shown for the outcome "overall survival"; an added benefit is therefore not proven.

- Progression-free survival as surrogate for overall survival

In the assessment of the added benefit for the outcome "overall survival", the company included the findings of an investigation it had conducted on the validation of the outcome "progression-free survival (PFS)" as surrogate for overall survival.

The company aimed to validate the outcome "PFS" as surrogate for overall survival using a correlation-based method. A conclusion on the effect of the treatment on overall survival was to be derived using a surrogate threshold effect (STE) calculation from the effect estimate for PFS.

This method is generally suitable for surrogate validation. However, the company's approach, on the one hand, showed an error in the information retrieval, the effects of which on the result of the validation cannot be estimated. On the other, the company's selection of the studies was inadequate. First, the company included studies with comparisons of 2 monotherapies, which does not concur with the therapeutic strategy under palbociclib treatment. Second, the company used studies that considered the time to progression (TTP) instead of PFS. Third, the company excluded studies with palbociclib. This is inadequate because the company conducted no drug-related validation for palbociclib, but a validation in the therapeutic indication. Finally, its calculation of the STE was methodologically flawed, resulting in an overestimation of the STE. If a study pool adjusted correspondingly is used for the surrogate validation, no sufficiently large correlation is notable and an STE cannot be determined. As a consequence, PFS is no valid surrogate for overall survival in the present case.

Morbidity – health status using the EQ-5D VAS

The outcome "health status" was only recorded in the PALOMA-2 study. No statistically significant difference between the treatment arms was shown in the change in comparison with the start of the study. As a result, there was no hint of an added benefit of palbociclib + letrozole versus letrozole for this outcome; an added benefit is therefore not proven.

Health-related quality of life using the FACT-B

Health-related quality of life was only recorded in the PALOMA-2 study. There were both responder analyses regarding the time to deterioration and analyses on the change in comparison with the start of the study based on continuous data. No statistically significant difference between the treatment arms was shown for any of the two types of analysis. This applied both to the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) total score and to the subscales of the Functional Assessment of Cancer Therapy-General (FACT-G) (including its 4 dimensions), the Breast Cancer Subscale (BCS) and the Trial Outcome Index (TOI). As a result, there was no hint of an added benefit of palbociclib + letrozole versus letrozole for this outcome; an added benefit is therefore not proven.

Side effects – serious adverse events

Only the PALOMA-2 study provided interpretable data for the outcome "SAEs". There was a statistically significant difference in favour of letrozole. This resulted in a hint of greater harm of palbociclib for the outcome "SAEs".

Side effects – severe adverse events (CTCAE grade 3 or 4)

A statistically significant difference in favour of letrozole was shown for the outcome "severe AEs" both for the individual studies and in the meta-analysis. In the overall consideration of both studies, this resulted in an indication of greater harm of palbociclib for the outcome "severe AEs".

Side effects – treatment discontinuation due to adverse events

In the PALOMA-2 study, there was no statistically significant difference between the treatment arms for the outcome "discontinuation of both study medications due to AEs". The difference between the treatment arms was not statistically significant also in the PALOMA-1 study.

Hence for this outcome, there was no hint of greater or lesser harm from palbociclib + letrozole in comparison with letrozole; greater or lesser harm is therefore not proven.

In the PALOMA-2 study, there was no statistically significant difference between the treatment arms for the outcome "discontinuation of palbociclib or placebo due to AEs". Hence for this outcome, there was no hint of greater or lesser harm from palbociclib + letrozole in comparison with letrozole; greater or lesser harm is therefore not proven.

Side effects – specific adverse events

There were no usable data for specific AEs.

Research question A2: first-line treatment in pre-/perimenopausal women

The company presented no relevant studies for research question A2.

Overall, there was no hint of an added benefit of palbociclib in comparison with the ACT for research question A2. An added benefit of palbociclib is not proven for this research question.

Research question B1: second and subsequent line of treatment in postmenopausal women

The company included the PALOMA-3 study for the assessment of the added benefit of palbociclib for research question B1. This study was unsuitable to derive conclusions on the added benefit of palbociclib for the present research question because the comparator therapy did not concur with the ACT specified by the G-BA.

Hence no relevant studies were available for this research question.

Overall, there was no hint of an added benefit of palbociclib in comparison with the ACT for research question B1. An added benefit of palbociclib is not proven for this research question.

Research question B2: second and subsequent line of treatment in pre-/perimenopausal women

The company included the PALOMA-3 study for the assessment of the added benefit of palbociclib for research question B2. This study was unsuitable to derive conclusions on the added benefit of palbociclib for the present research question because the comparator therapy did not concur with the ACT specified by the G-BA.

Hence no relevant studies were available for this research question.

Overall, there was no hint of an added benefit of palbociclib in comparison with the ACT for research question B2. An added benefit of palbociclib is therefore not proven for this research question.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug palbociclib compared with the ACT is assessed as follows.

Research question A1: first-line treatment in postmenopausal women

There were 2 relevant studies for the drug combination of palbociclib + letrozole. None of the 2 studies showed positive effects for palbociclib. However, the overall consideration of both

[4] 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, no added benefit, or less benefit). For further details see [1,2].

studies showed a hint of greater harm with the extent “minor” for the outcome “SAEs” and an indication of greater harm with the extent “major” for the outcome “severe AEs”.

In summary, there is an indication of a lesser benefit of palbociclib + letrozole as initial endocrine therapy versus the ACT letrozole for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

Research questions A2 (first-line treatment in pre-/perimenopausal women), B1 (second and subsequent line of treatment in postmenopausal women) and B2 (second and subsequent line of treatment in pre-/perimenopausal women)

No relevant data were available for the research questions A2, B1 and B2. The added benefit of palbociclib versus the ACT is therefore not proven for any of the research questions.

Summary

Table 4 presents a summary of the extent and probability of the added benefit of palbociclib.

Table 4: Palbociclib – extent and probability of added benefit

Research question	Subindication[a]	ACT[b]	Extent and probability of added benefit
Women with HR-positive, HER2-negative advanced/metastatic breast cancer			
A1	Postmenopausal women, initial endocrine therapy (first-line treatment)	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	*For palbociclib in combination with letrozole:* indication of lesser benefit *For palbociclib in combination with fulvestrant[c]:* added benefit not proven
A2	Pre- and perimenopausal women, initial endocrine therapy (first-line treatment)	Tamoxifen in combination with suppression of the ovarian function	Added benefit not proven
B1	Postmenopausal women who have progressed after endocrine therapy (second and subsequent line of treatment)	Depending on the prior therapy: ▪ tamoxifen or ▪ anastrozole or ▪ **fulvestrant**; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ exemestane; only for patients with progression following anti-oestrogen therapy or everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor	Added benefit not proven
B2	Pre- and perimenopausal women who have progressed after endocrine therapy (second and subsequent line of treatment)	Endocrine therapy specified by the physician under consideration of the respective approval[d]	Added benefit not proven

(continued)

Table 4: Palbociclib – extent and probability of added benefit (continued)

a: It is assumed for the present therapeutic indication that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
b: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
c: In women who have already received adjuvant endocrine therapy.
d: It is assumed that ovarian suppression with a GnRH analogue is continued.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; GnRH: gonadotropin-releasing hormone

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of palbociclib in comparison with the ACT in patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor
- in combination with fulvestrant in women who have received prior endocrine therapy

In pre- and perimenopausal women, the therapy was to be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

Depending on the line of treatment and the menopausal status of the patients, the G-BA distinguished between 4 different treatment situations and specified different ACTs for them. This resulted in 4 research questions for the present benefit assessment, which are presented in Table 5.

Table 5: Research questions of the benefit assessment of palbociclib

Research question	Subindication[a]	ACT[b]
Women with HR-positive, HER2-negative advanced/metastatic breast cancer		
A1	Postmenopausal women, initial endocrine therapy (first-line treatment)	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable
A2	Pre- and perimenopausal women, initial endocrine therapy (first-line treatment)	Tamoxifen in combination with suppression of the ovarian function
B1	Postmenopausal women who have progressed after endocrine therapy (second and subsequent line of treatment)	Depending on the prior therapy: ▪ tamoxifen or ▪ anastrozole or ▪ **fulvestrant**; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ exemestane; only for patients with progression following anti-oestrogen therapy or ▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor
B2	Pre- and perimenopausal women who have progressed after endocrine therapy (second and subsequent line of treatment)	Endocrine therapy specified by the physician under consideration of the respective approval[c]

a: It is assumed for the present therapeutic indication that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
b: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
c: It is assumed that ovarian suppression with a GnRH analogue is continued.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; GnRH: gonadotropin-releasing hormone

Hereinafter, the treatment line of research questions A1 and A2 is referred to as "first-line treatment for advanced or metastatic breast cancer", the treatment line of research questions B1 and B2 as "second and subsequent line of treatment". According to the approval, palbociclib should be administered either in combination with an aromatase inhibitor or in combination with fulvestrant (in women who have received prior endocrine therapy). According to information provided by the BfArM, the approval for the combination with fulvestrant includes both women who have received endocrine therapy in the metastatic setting and women who have already received adjuvant endocrine therapy [3].

The present assessment was conducted in comparison with the ACT specified by the G-BA (see Section 2.8.1 of the full dossier assessment). For research questions A1 and B1, this concurs with the choice of the company, which chose letrozole (research question A1) and fulvestrant (research question B1) from the options cited by the G-BA. The company did not investigate research question A2. Deviating from the G-BA, the company chose fulvestrant as only ACT for research question B2. This approach of the company was not followed (see Section 2.8.1 of the full dossier assessment).

The company presented data only for part of the research questions and possible drug combinations. An overview of the data presented by the company is shown in Table 6.

Table 6: Data presented by the company on the individual research questions

Research question	Subindication	Data presented by the company
Women with HR-positive, HER2-negative advanced/metastatic breast cancer		
A1	Postmenopausal women, initial endocrine therapy	
	▪ in combination with aromatase inhibitor	▪ RCTs (for the combination with letrozole; PALOMA-1 und PALOMA-2)
	▪ in combination with fulvestrant[a]	▪ no data
A2	Pre- and perimenopausal women, initial endocrine therapy	
	▪ in combination with aromatase inhibitor	▪ no data
	▪ in combination with fulvestrant[a]	▪ no data
B1	Postmenopausal women who have progressed after endocrine therapy	
	▪ in combination with aromatase inhibitor	▪ no data
	▪ in combination with fulvestrant	▪ RCT (PALOMA-3)
B2	Pre- and perimenopausal women who have progressed after endocrine therapy	
	▪ in combination with aromatase inhibitor	▪ no data
	▪ in combination with fulvestrant	▪ RCT (PALOMA-3)

a: In women who have already received adjuvant endocrine therapy.
HER2: human epidermal growth factor receptor 2; HR: hormone receptor; RCT: randomized controlled trial

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

2.3 Research question A1: first-line treatment in postmenopausal women

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on palbociclib (status: 8 September 2016)
- bibliographical literature search on palbociclib (last search on 7 September 2016)
- search in trial registries for studies on palbociclib (last search on 8 September 2016)

To check the completeness of the study pool:

- search in trial registries for studies on palbociclib (last search on 9 December 2016)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 7: Study pool – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
A5481003 (PALOMA-1[b])	Yes	Yes	No
A5481008 (PALOMA-2[b])	Yes	Yes	No

a: Study for which the company was sponsor.
b: Hereinafter, the study is referred to with this abbreviated form.
RCT: randomized controlled trial; vs.: versus

For the present research question, the studies PALOMA-1 and PALOMA-2 were included in the benefit assessment. Both studies compared a combination of palbociclib + letrozole with letrozole monotherapy. According to the approval, a combination of palbociclib with fulvestrant is also an option for the first-line treatment in postmenopausal women if these patients have already received endocrine therapy at an earlier stage of the disease. The company did not present studies investigating a combination of palbociclib and fulvestrant versus the ACT for research question A1, however.

Postmenopausal patients in first-line treatment were also included in the PALOMA-3 study [4-7]. This study is not relevant for research question A1, however, because the comparator therapy did not concur with the ACT specified by the G-BA. Further information on this can be found in Section 2.8.2.3.2 of the full dossier assessment.

The evidence provided by the company therefore only allowed conclusions on the added benefit of palbociclib + letrozole for postmenopausal women in first-line treatment. No usable data were available for patients treated with palbociclib + fulvestrant.

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Table 8 and Table 9 describe the studies used for the benefit assessment.

Table 8: Characteristics of the studies included – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PALOMA-1	RCT, open-label, parallel	Postmenopausal women with ER-positive, HER2-negative[b], locally recurrent/metastatic[c] breast cancer without prior endocrine therapy for the advanced stage	Phase 2[d]: palbociclib + letrozole[e] (N = 84) letrozole[e] (N = 81)	Screening: up to 28 days Treatment: until disease progression, symptomatic deterioration, necessity of additional anticancer therapy, unacceptable toxicity, decision by the physician or the patient to discontinue, loss to follow-up, or withdrawal of consent Follow-up: outcome-specific, at most until death or withdrawal of consent	50 centres in Canada, France, Germany, Hungary, Ireland, Italy, Russia, South Africa, South Korea, Spain, Ukraine and USA 9/2008–ongoing Data cut-off: 29 Nov 2013	Primary: PFS Secondary: overall survival, AEs

(continued)

Table 8: Characteristics of the studies included – RCT, direct comparison: palbociclib + letrozole vs. letrozole (continued)

PALOMA-2	RCT, double-blind, parallel	Postmenopausal women with ER-positive, HER2-negative[f], locoregionally recurrent/ metastatic[g] breast cancer without prior systemic treatment for the advanced stage	Palbociclib + letrozole (N = 444) placebo + letrozole (N = 222)	Screening: up to 28 days Treatment: until disease progression, symptomatic deterioration, necessity of additional anticancer therapy, unacceptable toxicity, decision by the patient or the investigator to discontinue, loss to follow-up, death, or withdrawal of consent Follow-up: outcome-specific, at most until death or withdrawal of consent or final survival time analysis[i]	186 centres in Australia, Belgium, Canada, France, Germany, Hungary, Ireland, Italy, Japan, Poland, Russia, South Korea, Spain, Taiwan, Ukraine, United Kingdom, USA 2/2013–ongoing Data cut-off: 26 Feb 2016	Primary: PFS Secondary: overall survival, health status, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: HER2 status was determined with FISH or ICH; a positive ER status was defined as ≥ 10 fmol of H^3-oestrogen binding per mg of cytosol protein for dextran-coated charcoal and sucrose density methods, or ≥ 0.10 fmol of H3-oestrogen binding per mg of DNA for IF/EIA technique.
c: Patients with brain metastases were excluded.
d: The study consisted of phase 1 and phase 2; the one-arm phase 1 is not relevant for the benefit assessment and is not described further.
e: Patients were randomized in 2 separate cohorts by biomarker status (cohort 2 includes patients with CCND1 gene amplification and/or loss of the p16 gene); according to the study protocol, these were analysed both separately and together.
f: HER2 status was determined with FISH, CISH, dual ISH or ICH; a positive ER status was determined histologically or cytologically based on laboratory results.
g: Patients with advanced symptomatic visceral or uncontrolled or symptomatic CNS metastases were excluded.
h: Patients could continue treatment with the study medication beyond progression at the investigator's discretion if this was in the patients' interest.
i: Planned after 390 deaths.

AE: adverse event; CCND: cyclin D1; CNS: central nervous system; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 9: Characteristics of the interventions – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study	Intervention	Comparison	Pretreatment and concomitant treatment
PALOMA-1	Palbociclib 125 mg/day, orally in weeks 1–3 of a 28-day cycle + letrozole 2.5 mg/day, orally for palbociclib dose reduction (to 100 mg/day or 75 mg/day) or interruption possible in case of toxicity no dose adjustment possible for letrozole; interruption allowed	Letrozole 2.5 mg/day, orally no dose adjustment possible for letrozole; interruption allowed	**Non-permitted pretreatment:** ▪ pretreatment for advanced cancer disease, with the exception of radiation therapy to at most 25% of bone marrow at least 2 weeks prior to study treatment initiation ▪ (neo)adjuvant pretreatment with letrozole during or within 12 months after treatment **Non-permitted concomitant treatment:** ▪ other anticancer therapies ▪ strong CYP3A inhibitors **Non-recommended concomitant treatment:** ▪ strong CYP3A inducers
PALOMA-2	Palbociclib 125 mg/day, orally in weeks 1–3 of a 28-day cycle + letrozole 2.5 mg/day, orally for palbociclib dose reduction (to 100 mg/day or 75 mg/day) or interruption possible in case of toxicity no dose adjustment possible for letrozole; interruption allowed	Placebo + letrozole 2.5 mg/day, orally dose reduction (to 100 mg/day or 75 mg/day) or interruption possible for placebo in case of toxicity no dose adjustment possible for letrozole; interruption allowed	**Non-permitted pretreatment:** ▪ systemic pretreatment for locoregionally recurrent or metastatic ER-positive disease ▪ (neo)adjuvant pretreatment with aromatase inhibitors (e.g. anastrozole, letrozole) with recurrence during or within 12 months after this treatment ▪ CDK4/6 inhibitors ▪ CYP3A inhibitors and inducers and drugs that prolong the QT interval within 7 days before the start of the study **Non-permitted concomitant treatment:** ▪ other anticancer therapies ▪ strong/moderate CYP3A inhibitors or inducers ▪ drugs that prolong the QT interval ▪ hormone replacement therapy ▪ proton pump inhibitors **Non-recommended concomitant treatment:** ▪ dexamethasone, herbal drugs, chronic immunosuppressant therapy including systemic corticosteroids

CDK4/6: cyclin-dependent kinase; CYP3A: cytochrome P450 liver enzymes; ER: oestrogen receptor; RCT: randomized controlled trial; vs.: versus

Two studies relevant for research question A1 were included in the present benefit assessment: PALOMA-1 and PALOMA-2.

The PALOMA-1 study consisted of a one-arm non-randomized phase 1 substudy and a randomized phase 2 substudy. The one-arm phase 1 substudy is not relevant for the benefit assessment and is not described further. The phase 2 substudy relevant for the assessment was randomized and unblinded and compared the drug combination palbociclib + letrozole with letrozole monotherapy. Hereinafter, this substudy is referred to as "PALOMA-1". The study included women with ER-positive and HER2-negative locally recurrent or metastatic breast cancer. The patients had not yet received endocrine therapy for the advanced stage of the disease. A total of 165 patients were randomly assigned to treatment with palbociclib + letrozole (N = 84) or letrozole (N = 81). Randomization was stratified by metastatic site (bone metastases only versus other non-visceral metastases versus visceral metastases) and disease-free interval from the end of the (neo)adjuvant treatment to recurrence of the disease (> 12 months versus ≤ 12 months).

The PALOMA-2 study was a randomized blinded study comparing the drug combination of palbociclib + letrozole with letrozole + placebo. This study included patients with ER-positive and HER2-negative locoregionally recurrent or metastatic breast cancer. The patients had not yet received systemic treatment for the advanced stage of the disease. A total of 666 patients were randomly allocated in a ratio of 2:1 to treatment with palbociclib + letrozole (N = 444) or letrozole + placebo (N = 222). Randomization was stratified by visceral metastases (yes versus no), disease-free interval from the end of the (neo)adjuvant treatment to recurrence of the disease (de-novo metastatic disease versus > 12 months versus ≤ 12 months) and by type of prior (neo)adjuvant anticancer therapy (hormonal therapy versus no prior hormonal therapy).

In both studies, treatment of the patients in the intervention and comparator arm concurred with the SPCs of palbociclib and letrozole [8,9]. In both study arms, treatment was to be continued until disease progression, symptomatic deterioration, necessity of additional anticancer therapy or unacceptable toxicity.

In both studies, the patients could start subsequent therapy after discontinuation of the study medication. Treatment switching from the comparator intervention placebo to the experimental intervention palbociclib was not allowed in either of the 2 studies. In the PALOMA-2 study, about 42% of the patients in the palbociclib + letrozole arm and about 61% of the patients in the letrozole + placebo arm were receiving subsequent therapy at the time point of the available data cut-off. No data on this were available for the PALOMA-1 study.

Planned duration of follow-up

Table 10 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 10: Planned duration of follow-up – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study **Outcome category** **Outcome**	**Planned follow-up**
PALOMA-1	
Mortality	
Overall survival	Every 2 months after treatment discontinuation until death, withdrawal of consent or loss to follow-up
Morbidity	No usable data available
Health-related quality of life	Not recorded
Side effects	
All outcomes in the category "side effects"	28 days after treatment discontinuation
PALOMA-2	
Mortality	
Overall survival	Every 6 months after treatment discontinuation until death, study discontinuation or final survival time analysis[a]
Morbidity	
Health status (EQ-5D VAS)	Until treatment discontinuation
Health-related quality of life (FACT-B)	Every 6 months after treatment discontinuation until study discontinuation or final survival time analysis[a]
Side effects	
All outcomes in the category "side effects"	28 days after treatment discontinuation

a: Planned after 390 deaths.

EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Only overall survival and health-related quality of life (in the PALOMA-2 study) were to be recorded until the end of study participation. It is unclear, however, whether data on health-related quality of life beyond the end of the treatment duration were included in the company's analyses.

The observation periods for the outcomes "side effects" and "morbidity" were systematically shortened because they were only recorded for the time period of treatment (plus 28 days for side effects). To be able to draw a reliable conclusion on side effects and morbidity over the total study period or the time until death of the patients, it would be necessary to record these outcomes over the total period of time, as was the case for survival.

Patient characteristics

Table 11 shows the characteristics of the patients in the studies included.

Table 11: Characteristics of the study populations – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study Characteristics Category	PALOMA-1		PALOMA-2	
	Palbociclib + letrozole	Letrozole	Palbociclib + letrozole	Placebo + letrozole
	N[a] = 84	N[a] = 81	N[a] = 444	N[a] = 222
Age [years], mean (SD)	63 (10)	63 (9)	62 (11)	61 (11)
Ethnicity, n (%)				
White	76 (90.5)	72 (88.9)	344 (77.5)	172 (77.5)
Black	1 (1.2)	1 (1.2)	8 (1.8)	3 (1.4)
Asian	6 (7.1)	4 (4.9)	65 (14.6)	30 (13.5)
Other	1 (1.2)	4 (4.9)	27 (6.1)	17 (7.7)
Region, n (%)				
Europe	67 (79.8)	56 (69.1)	212 (47.8)	95 (42.8)
North America	14 (16.7)	22 (27.2)	168 (37.8)	99 (44.6)
Other	3 (3.6)[b]	3 (3.7)[b]	64 (14.4)[c]	28 (12.6)[c]
ECOG PS, n (%)				
0	46 (54.8)	45 (55.6)	257 (57.9)	102 (45.9)
1	38 (45.2)	36 (44.4)	178 (40.1)	117 (52.7)
2	0 (0)	0 (0)	9 (2.0)	2 (1.4)
Disease-free interval from the end of the (neo)adjuvant treatment to recurrence of the disease (based on randomization), n (%)				
De-novo metastatic	44 (52.4)[d]	37 (45.7)[d]	148 (33.3)	74 (33.3)
≤ 12 months	12 (14.3)[d]	11 (13.6)[d]	89 (20.0)	44 (19.8)
> 12 months	28 (33.3)[d]	33 (40.7)[d]	207 (46.6)	104 (46.8)
Type of prior anticancer therapy in the (neo)adjuvant setting (at randomization), n (%)				
Hormonal therapy	27 (32.1)	28 (34.6)	253 (57.0)	127 (57.2)
No prior hormonal therapy	57 (67.9)	53 (65.4)	191 (43.0)	95 (42.8)
Prior chemotherapy in the adjuvant setting, n (%)				
Yes	34 (40.5)	37 (45.7)	213 (48.0)	109 (49.1)
No	50 (59.5)	44 (54.3)	231 (52.0)	113 (50.9)
Current disease stage, n (%)				
IIIB	2 (2.4)	1 (1.2)	ND	ND
IV	82 (97.6)	80 (98.8)	ND	ND

(continued)

Table 11: Characteristics of the study populations – RCT, direct comparison: palbociclib + letrozole vs. letrozole (continued)

Study Characteristics Category	PALOMA-1		PALOMA-2	
	Palbociclib + letrozole	Letrozole	Palbociclib + letrozole	Placebo + letrozole
	N[a] = 84	N[a] = 81	N[a] = 444	N[a] = 222
Type of recurrence, n (%)				
Locoregional	ND	ND	2 (0.5)	2 (0.9)
Local	ND	ND	6 (1.4)	3 (1.4)
Regional	ND	ND	3 (0.7)	1 (0.5)
Distant metastasis	ND	ND	294 (66.2)	145 (65.3)
Newly diagnosed	ND	ND	139 (31.3)	71 (32.0)
Site of metastases[e], n (%)				
Breast	29 (34.5)	27 (33.3)	137 (30.9)	74 (33.3)
Bone	61 (72.6)	62 (76.5)	325 (73.2)	162 (73.0)
Liver	19 (22.6)	23 (28.4)	75 (16.9)	46 (20.7)
Lungs	31 (36.9)	30 (37.0)	150 (33.8)	71 (32.0)
Lymph nodes	53 (63.1)	51 (63.0)	212 (47.7)	110 (49.5)
Treatment discontinuation, n (%)	64 (76.2)	69 (85.2)	239 (53.8)[f]	161 (72.5)[f]
Study discontinuation, n (%)	35 (41.7)	39 (48.1)	120 (27.0)	58 (26.1)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: "Other" summarizes Asian countries and South Africa.
c: "Other" summarizes Australia and Asian countries.
d: According to the information provided by the company in Module 4 A; calculated according to the definition in the PALOMA-2 study (the PALOMA-1 study distinguished between the categories > 12 months and ≤ 12 months or de-novo metastatic).
e: Sites that applied to > 20% of the patients in at least one study arm.
f: Treatment discontinuation of all drugs. Number of patients who only discontinued palbociclib or placebo: n = 245 (55.2%) and n = 161 (72.5%).
ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The studies PALOMA-1 and PALOMA-2 are comparable regarding the composition of their patient populations. The mean age of the women in both studies was about 60 years; most patients were white (> 77%). Almost all patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1; the proportion of patients with ECOG PS 2 was below 2%.

The PALOMA-1 study had a slightly larger proportion of women with de-novo metastatic disease than PaLOMA-2 (53–46% versus 33%). There were also differences regarding prior hormonal therapy of the patients. This proportion was about 33% in PALOMA-1 compared with 57% in PALOMA-2. About half of the patients in both studies had already received chemotherapy.

Information on the disease stage was only available for the PALOMA-1 study; according to this information, almost all patients had distant metastases (stage IV). The PALOMA-2 study, in contrast, had information on the type of recurrence, with distant metastases also constituting the largest proportion (over 65%). There were differences between the studies in the rates of treatment and study discontinuations. Overall, more patients discontinued treatment in the PALOMA-1 study than in PALOMA-2, with notable differences between the study arms in both studies (PALOMA-1: 76% versus 85%; PALOMA-2: 54% versus 73%). The number of study discontinuations was also higher in PALOMA-1 than in PALOMA-2 (42–48% versus 27%).

Course of the study

Table 12 shows the median treatment duration of the patients and the observation period for individual outcomes.

Table 12: Information on the course of the study – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study **Outcome category**	**Palbociclib + letrozole**	**Letrozole**
PALOMA-1 (data cut-off 29 Nov 2013)	N = 83	N = 77
Treatment duration [months][a, b]		
Median [min; max]	14.1 [0.2; 40.9]	7.6 [0.9; 39.3]
Mean (SD)	16.6 (11.0)	11.1 (9.7)
Observation period [months]		
Overall survival		
Median [95% CI]	29.6 [27.9; 36]	27.9 [25.5; 31.1]
Mean (SD)	ND	ND
Health-related quality of life	Not recorded	
Morbidity, side effects	ND	ND
PALOMA-2 (data cut-off 26 Feb 2016)	N = 444	N = 222
Treatment duration [months][a, c]		
Median [min; max]	20.3 [0; 34.1]	13.8 [0.3; 35.4]
Mean (SD)	17.0 (8.4)	14.0 (8.9)
Observation period [months]		
Overall survival		
Median [95% CI]	23.0 [22.6; 23.4]	22.3 [21.9; 22.9]
Mean (SD)	ND	ND
Morbidity, health-related quality of life, side effects	ND	ND

a: Institute's calculation from days.
b: Duration of treatment with at least one drug. Letrozole treatment could be continued after discontinuation of palbociclib. Duration of treatment with palbociclib (months, Institute's calculation from days): median [min; max]: 13.8 [0.2; 40.9]; mean (SD): 16.4 (11.1).
c: Duration of treatment with at least one drug. Letrozole treatment could be continued after discontinuation of palbociclib/placebo. Duration of treatment (months, Institute's calculation from days) with palbociclib: median [min; max]: 19.8 [0; 34.1]; mean (SD): 16.5 (8.6), duration of treatment with placebo: median [min; max]: 13.6 [0.3; 35.2], mean (SD): 13.8 (9.0).
CI: confidence interval; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In the PALOMA-1 study, the median treatment duration was almost twice as long in the palbociclib + letrozole arm as in the letrozole arm (14 versus 8 months). The median observation period for the outcome "overall survival" was comparable in both arms (30 versus 28 months). There was no information on the observation period for the outcomes on morbidity and side effects; according to the study protocol, however, they were only recorded until the end of the treatment (side effects + 28 days). It can be inferred from this that the median observation period for these outcomes was also about twice as high in the palbociclib arm as in the letrozole arm.

The treatment durations differed notably between the treatment arms also in the PALOMA-2 study (20 months in the palbociclib + letrozole arm versus 14 months in the letrozole arm). The median observation period for the outcome "overall survival" was comparable in both arms (about 23 months), however. There was no information on the observation period for the outcomes on morbidity, health-related quality of life and side effects. Since, according to the study protocol, morbidity and side effects were only recorded until the end of the treatment (side effects + 28 days), it can be concluded that the median observation period for these outcomes was 1.5 times as long in the palbociclib + letrozole arm as in the letrozole arm.

Risk of bias at study level

Table 13 shows the risk of bias at study level.

Table 13: Risk of bias at study level – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
PALOMA-1	Yes	Yes	No[a]	No[a]	Yes	No[b]	High[c]
PALOMA-2	Yes	Yes	Yes	Yes	Yes	Yes	Low

a: Open-label study design.
b: Unblinded assessment of progression by the investigators resulted in a high risk of bias in comparison with blinded assessment (see Section 2.8.2.4.2 of the full dossier assessment).
c: Due to additional aspects.
RCT: randomized controlled trial; vs.: versus

The PALOMA-1 study had a high risk of bias. This is mainly due to the fact that the assessment of progression conducted by the investigators differed notably from a blinded, independent and central assessment conducted retrospectively. In comparison with the assessment by the investigators, the independent assessment confirmed 12% fewer events (10 of 83 patients) in the palbociclib + letrozole arm and 34% fewer events (26 of 77 patients) in the letrozole arm. Since the decision on the continuation of treatment was based on the assessment of progression by the investigators, it can be assumed that this resulted in an increased risk of bias for all outcomes. See Section 2.8.2.4.2 of the full dossier assessment for more details. This deviates from the assessment of the company, which rated the risk of bias at study level as low.

Limitations resulting from the open-label study design are described in Section 2.3.2 with the outcome-specific risk of bias.

For the PALOMA-2 study, the risk of bias at study level was rated as low. This is in accordance with the assessment of the company.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.8.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms
  - health status, measured with the European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS)
- Health-related quality of life
  - FACT-B
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4)
  - Treatment discontinuations due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.8.2.4.3 of the full dossier assessment).

The company additionally tried to validate the outcome “PFS” as surrogate for the outcome “overall survival”. For this purpose, it presented comprehensive data in its dossier. However, it cannot be derived from the data presented by the company that PFS constitutes a valid surrogate for overall survival (see Sections 2.8.2.4.3 and 2.8.2.9.4 of the full dossier assessment).

Table 14 shows for which outcomes data were available in the studies included.

Table 14: Matrix of outcomes – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study	Outcomes						
	Overall survival	Symptoms	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3 or 4)
PALOMA-1	Yes	No[a]	No[a]	No[a]	Yes	Yes	Yes
PALOMA-2	Yes[b]	No[a]	Yes	Yes	Yes	Yes	Yes

a: Outcome not recorded.
b: No survival time analysis of overall survival available; only naive rates available.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.3.2.2 Risk of bias

Table 15 shows the risk of bias for the relevant outcomes.

Table 15: Risk of bias at study and outcome level – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study	Study level	Outcomes						
		Overall survival	Symptoms	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3 or 4)
PALOMA-1	H	H[b]	-[a]	-[a]	-[a]	H[b,c]	H[b]	H[b,c]
PALOMA-2	L	L	-[a]	H[c, d]	H[c, d]	H[c]	L	H[c]

a: Outcome not recorded.
b: High risk of bias at study level.
c: Large proportion of potentially informative censoring.
d: Unclear proportion of missing values.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

PALOMA-1

In the PALOMA-1 study, all patient-relevant outcomes had a high risk of bias. On the one hand, this was due to the high risk of bias at study level (see Section 2.3.1.2). On the other,

there was a large proportion of potentially informative censorings for the outcomes “SAEs” and “severe AEs” (see Section 2.8.2.4.2 of the full dossier assessment). For overall survival, this assessment deviates from the approach of the company, which rated the risk of bias for this outcome as low. For side effects, the company assumed a high risk of bias overall based on the open-label study design, but did not additionally mention the potentially informative censoring as a reason.

Overall, the risk of bias of the results for the outcome “SAEs” was so high because of the possibly premature treatment discontinuations and the potentially informative censoring that these results are not usable. Due to the effect size and the early occurrence of the events in the course of the study, it is unlikely for the outcome “severe AEs” (CTCAE grade 3–4) that the potentially biasing factors raise fundamental doubts about the treatment effect. Hence a quantitative assessment of this outcome is possible.

PALOMA-2

For the PALOMA-2 study, the risk of bias for the outcome “overall survival” was rated as low. This deviates from the assessment of the company, which did not assess this outcome at all (see Section 2.3.2.3).

There was a high risk of bias for the outcomes “health status”, “health-related quality of life”, “SAEs” and “severe AEs” due to the large proportion of potentially informative censoring. For the outcomes “health status” and “health-related quality of life”, it was also unclear how large the proportion of missing values was at the respective documentation times (see Section 2.8.2.4.2 of the full dossier assessment). This approach deviates from that of the company, which assumed a low risk of bias for all mentioned outcomes in the PALOMA-2 study.

There was a low risk of bias for the outcome “discontinuation due to AEs”. This concurs with the company’s assessment.

Overall certainty of conclusions

The PALOMA-2 study was the main study for the interpretation of the results and the derivation of the added benefit of palbociclib. The results of PALOMA-2 cannot be called into question or supported by the PALOMA-1 study because of its low certainty of conclusions and sample size. An overall consideration of both studies was only conducted if the effects in the PALOMA-1 study were so clear that the respective effect was not questioned despite the high risk of bias. This only applied to the outcome “severe AEs”.

2.3.2.3 Results

The results on the comparison of palbociclib + letrozole with letrozole in postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who received palbociclib as initial endocrine therapy are summarized in Table 16 and Table 17. Where necessary, the data from the company’s dossier were supplemented with calculations conducted by the Institute.

Table 16: Results (mortality, health-related quality of life, side effects – time to first event) – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Outcome category Outcome Study	Palbociclib + letrozole N	Palbociclib + letrozole Median survival time in months [95% CI] Patients with event n (%)	Letrozole N	Letrozole Median survival time in months [95% CI] Patients with event n (%)	Palbociclib + letrozole vs. letrozole HR [95% CI]; p-value
Mortality					
Overall survival					
PALOMA-1	84	37.5 [28.4; NA] 30 (35.7)	81	33.3 [26.4; NA] 31 (38.3)	0.81 [0.49; 1.35]; 0.421[a]
PALOMA-2	444	ND 95 (21.4)[b]	222	ND 38 (17.1)[b]	RR 1.25 [0.89; 1.76]; 0.198[c]
Health-related quality of life – time to deterioration					
FACT-B (PALOMA-2 only)					
FACT-B[d] (decrease by ≥ 7 points)	439[e]	7.6 [5.6; 11.0] 262 (59.7)	218[e]	9.2 [5.6; 12.9] 118 (54.1)	1.06 [0.85; 1.31]; 0.601[f]
FACT-G (decrease by ≥ 5 points)	439[e]	5.5 [3.7; 8.1] 276 (62.9)	218[e]	5.6 [3.7; 9.3] 130 (59.6)	0.98 [0.80; 1.21]; 0.919[f]
BCS (decrease by ≥ 2 points)	439[e]	5.6 [3.9; 7.5] 279 (63.6)	218[e]	7.5 [5.5; 12.9] 120 (55.0)	1.18 [0.95; 1.46]; 0.121[f]
TOI (decrease by ≥ 5 points)	439[e]	7.4 [5.6; 11.0] 265 (60.4)	218[e]	9.2 [3.7; 11.3] 126 (57.8)	0.98 [0.79; 1.21]; 0.917[f]
FACT-G subscales (decrease by ≥ 2 points)					
Physical well-being	439[e]	4.1 [3.7; 5.6] 302 (68.8)	218[e]	3.7 [2.0; 5.6] 150 (68.8)	0.92 [0.76; 1.12] 0.448[f]
Social well-being	439[e]	5.5 [3.7; 6.2] 284 (64.7)	218[e]	3.7 [1.9; 5.5] 139 (63.8)	0.86 [0.70; 1.06]; 0.173[f]
Emotional well-being	439[e]	8.5 [6.5; 11.2] 260 (59.2)	218[e]	11.1 [5.7; 16.7] 120 (55.0)	1.03 [0.83; 1.28]; 0.741[f]
Functional well-being	439[e]	5.6 [3.8; 7.6] 284 (64.7)	218[e]	3.7 [2.6; 7.3] 139 (63.8)	0.91 [0.74; 1.11]; 0.365[f]
Side effects					
AEs (supplementary information)					
PALOMA-1	83	ND 83 (100)	77	ND 65 (84.4)	–
PALOMA-2	444	ND 439 (98.9)	222	ND 212 (95.5)	–

(continued)

Table 16: Results (mortality, health-related quality of life, side effects – time to first event) – RCT, direct comparison: palbociclib + letrozole vs. letrozole (continued)

Outcome category Outcome Study	Palbociclib + letrozole N	Palbociclib + letrozole Median survival time in months [95% CI] Patients with event n (%)	Letrozole N	Letrozole Median survival time in months [95% CI] Patients with event n (%)	Palbociclib + letrozole vs. letrozole HR [95% CI]; p-value
SAEs					
PALOMA-1	83	NA [NA; NA] 18 (21.7)	77	NA [23.7; NA] 5 (6.5)	–[g]
PALOMA-2	444	NA [NA; NA] 87 (19.6)	222	NA [NA; NA] 28 (12.6)	1.63 [1.06; 2.49]; 0.023[f]
Severe AEs (CTCAE grade 3 or 4)					
PALOMA-1	83	1.4 [1.0; 2.3] 64 (77.1)	77	NA [15.5; NA] 16 (20.8)	5.47 [3.15; 9.51]; < 0.001[a]
PALOMA-2	444	1.0 [1.0; 1.4] 344 (77.5)	222	NA [NA; NA] 56 (25.2)	5.50 [4.14; 7.31]; < 0.001[f]
Total[h]					5.49 [4.26; 7.08]; < 0.001
Severe AEs (CTCAE grade 3 or 4), without laboratory results					
PALOMA-1	*83*	*20.8 [16.0; NA]* *36 (43.4)*	*77*	*NA [22.6; NA]* *15 (19.5)*	*1.72 [0.94; 3.15]; 0.078[a]*
PALOMA-2	*444*	*NA [NA; NA]* *156 (35.1)*	*222*	*NA [NA; NA]* *56 (25.2)*	*1.47 [1.08; 1.99]; 0.013[f]*
Total[h]					*1.52 [1.16; 2.00]; 0.002[b]*
Discontinuation due to AEs					
PALOMA-1 (discontinuation of all drug components)[i]	83	NA [NA; NA] 12 (14.5)	77	NA [NA; NA] 2 (2.6)	3.90 [0.86; 17.60]; 0.057[a]
PALOMA-2					
Discontinuation of palbociclib or placebo	444	NA [NA; NA] 41 (9.2)	222	NA [NA; NA] 12 (5.4)	1.74 [0.92; 3.32]; 0.087[f]
Discontinuation of all drug components	444	ND 27 (6.1)	222	ND 11 (5.0)	RR 1.23 [0.62; 2.43]; 0.617[c]

(continued)

Table 16: Results (mortality, health-related quality of life, side effects – time to first event) – RCT, direct comparison: palbociclib + letrozole vs. letrozole (continued)

a: Effect and 95% CI: Cox proportional hazards model, stratified by cohort within the phase 2 part of the PALOMA-1 study (distribution by biomarker status); p-value: 2-sided log-rank test.
b: Institute's calculation.
c: Institute's calculation; p-value: unconditional exact test (CSZ method according to [10]).
d: The FACT-B total score is calculated as sum of the general questionnaire FACT-G and the breast-cancer-specific subscale BCS.
e: Patients who have answered at least 80% of the questions.
f: Effect and 95% CI: Cox proportional hazards model, stratified by visceral metastases; p-value: 2-sided log-rank test.
g: Results not meaningfully interpretable (see Section 2.8.2.4.2 of the full dossier assessment).
h: Meta-analysis with random effects according to DerSimonian and Laird.
i: No patient discontinued only one of both drug components.

AE: adverse event; BCS: Breast Cancer Subscale; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; FACT-G: Functional Assessment of Cancer Therapy-General; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TOI: Trial Outcome Index; vs.: versus

Table 17: Results (morbidity, health-related quality of life – continuous data) – RCT, direct comparison: palbociclib + letrozole vs. letrozole

Study Outcome category Outcome	Palbociclib + letrozole			Letrozole			Palbociclib + letrozole vs. letrozole
	N[a]	Values at start of study mean (SD)	Change at end of treatment mean (SD)	N[a]	Values at start of study mean (SD)	Change at end of treatment mean (SD)	MD [95% CI][b]; p-value
PALOMA-2							
Morbidity							
Health status (EQ-5D VAS)	437	71.3 (21.2)	-3.4 (21.2)	218	72.3 (19.8)	-0.6 (17.9)	-0.18 [-2.29; 1.93]; 0.869
Health-related quality of life							
FACT-B[c]	439	101.5 (19.1)	-4.8 (17.8)	218	103.2 (18.7)	-2.3 (16.6)	-0.33 [-2.63; 1.98]; 0.782
FACT-G	439	77.7 (15.5)	-4.4 (15.4)	218	79.1 (15.4)	-2.8 (13.3)	0.14 [-1.74; 2.03]; 0.883
BCS	439	24.0 (5.6)	-0.7 (5.1)	218	24.2 (5.5)	0.4 (5.3)	-0.64 [-1.29; 0.01]; 0.055
TOI	439	63.4 (13.6)	-3.2 (12.5)	218	64.3 (13.3)	-0.5 (12.5)	-0.80 [-2.40; 0.79]; 0.325
FACT-G subscales							
Physical well-being	439	21.9 (5.5)	-1.7 (6.1)	218	21.8 (5.4)	-0.4 (5.7)	-0.30 [-0.89; 0.37]; 0.414
Social well-being	439	21.8 (5.9)	-0.5 (5.7)	218	22.2 (5.6)	-0.9 (5.7)	0.10 [-0.56; 0.77]; 0.762
Emotional well-being	439	16.3 (4.7)	-1.3 (4.7)	218	16.6 (4.7)	-0.9 (4.9)	0.20 [-0.37; 0.70]; 0.538
Functional well-being	439	17.5 (6.0)	-1.2 (6.2)	218	18.3 (6.0)	-0.5 (5.4)	-0.10 [-0.81; 0.55]; 0.707

a: Number of patients considered in the analysis for the calculation of the effect estimate. Number of patients with measurement at the end of treatment: palbociclib + letrozole N = 179 and letrozole N = 131. The values at the start of the study are based on other patient numbers.
b: Effect, 95% CI and p-value: MMRM with an intercept term, the factors treatment, time, and an interaction term treatment*time and baseline as covariables.
c: FACT-B and all components: A positive change at the end of study in comparison with the start of the study indicates improvement.

BCS: Breast Cancer Subscale; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; FACT-G: Functional Assessment of Cancer Therapy-General; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; TOI: Trial Outcome Index; VAS: visual analogue scale; vs.: versus

On the basis of the available data on the studies PALOMA-1 and PALOMA-2, at most hints, e.g. of an added benefit, can be determined for the outcomes “health status”, “health-related quality of life” and “SAEs” and at most indications for “overall survival”, “severe AEs” and

"discontinuation due to AEs". This is largely due to the partly high risk of bias for individual outcomes in the PALOMA-2 study and the overall high risk of bias for the PALOMA-1 study (see Section 2.3.2.2).

Mortality

Overall survival

For overall survival, the company only presented results of the PALOMA-1 study in Module 4 A. According to the company, the data on overall survival for the PALOMA-2 study were only available to an external data monitoring committee, but were not yet available in the framework of the dossier. This statement is not comprehensible. The clinical study report (CSR) contains information on the number of patients who had died in each treatment arm until the data cut-off. Since the observation period in both treatment arms was almost equal (median duration of about 23 months), the relative risk can be used as an approximation.

The PALOMA-2 study showed no statistically significant difference between the treatment arms for the outcome "overall survival". The difference between the treatment arms was not statistically significant also in the PALOMA-1 study.

Overall, there was no hint of an added benefit of palbociclib + letrozole versus letrozole for this outcome; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived a hint of an added benefit for overall survival on the basis of the data on PFS from the studies PALOMA-1 and PALOMA-2 (see Section 2.8.2.9.4 of the full dossier assessment for information on the validation of PFS as surrogate for overall survival).

Morbidity

Health status using the EQ-5D VAS

The outcome "health status" was only recorded in the PALOMA-2 study. No statistically significant difference between the treatment arms was shown in the change in comparison with the start of the study. As a result, there was no hint of an added benefit of palbociclib + letrozole versus letrozole for this outcome; an added benefit is therefore not proven.

This is in accordance with the assessment of the company.

Health-related quality of life

FACT-B

Health-related quality of life was only recorded in the PALOMA-2 study. There were both responder analyses regarding the time to deterioration and analyses on the change in comparison with the start of the study based on continuous data (mixed-effects model repeated measures [MMRM] analysis). No statistically significant difference between the treatment arms was shown for any of the two types of analysis. This applied both to the

FACT-B total score and to the subscales FACT-G) (including its 4 dimensions), BCS and TOI. As a result, there was no hint of an added benefit of palbociclib + letrozole versus letrozole for this outcome; an added benefit is therefore not proven.

This is in accordance with the assessment of the company.

Side effects

Serious adverse events

Only the PALOMA-2 study provided interpretable data for the outcome "SAEs" (see Section 2.3.2.2).

A statistically significant difference in favour of letrozole was shown for the outcome "SAEs". This resulted in a hint of greater harm of palbociclib for the outcome "SAEs".

This partly deviates from the assessment of the company, which, instead of a hint, derived an indication of lesser benefit of palbociclib.

Severe adverse events (CTCAE grade 3 or 4 adverse events)

A statistically significant difference in favour of letrozole was shown for the outcome "severe AEs" both for the individual studies and in the meta-analysis. In the overall consideration of both studies, this resulted in an indication of greater harm of palbociclib for the outcome "severe AEs".

This is in accordance with the assessment of the company.

Table 29 and Table 30 of the full dossier assessment show that the effect observed in both studies was largely determined by blood and lymphatic system disorders (mainly neutropenia). The effect in favour of letrozole also remains when AEs that are only based on laboratory parameters are excluded from the analysis, however. The company presented such analyses in Module 5, but presented them only in Section 4.4.2 of the dossier and only for the PALOMA-2 study. A figure showing the meta-analysis of these results can be found in Appendix C of the full dossier assessment.

Treatment discontinuation due to adverse events

In Module 4 A of the dossier, the company showed the number of AEs that had resulted in discontinuation of palbociclib or placebo, but not the number of AEs that had resulted in discontinuation of all drug components. The CSR of the PALOMA-1 study showed that no patient in the palbociclib + letrozole arm of the study had discontinued only one of both study medications. Hence the 2 operationalizations for this study agree with each other. This does not apply to the PALOMA-2 study.

Discontinuation of all drug components (palbociclib + letrozole or letrozole)

In the PALOMA-2 study, there was no statistically significant difference between the treatment arms for the outcome "discontinuation of both study medications due to AEs". The difference between the treatment arms was not statistically significant also in the PALOMA-1 study. Hence for this outcome, there was no hint of greater or lesser harm from palbociclib + letrozole in comparison with letrozole; greater or lesser harm is therefore not proven.

Discontinuation of palbociclib or placebo

The PALOMA-2 study showed no statistically significant difference between the treatment arms for this outcome. Hence for this outcome, there was no hint of greater or lesser harm from palbociclib + letrozole in comparison with letrozole; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which, based on the results of its meta-analysis, derived an indication of lesser benefit of palbociclib.

Specific adverse events

There were no usable data for specific AEs (see Section 2.8.2.4.3 of the full dossier assessment).

This deviates from the assessment of the company, which derived an indication of lesser benefit of palbociclib for the following AEs of particular interest: neutropenia, anaemia, leukopenia, thrombocytopenia, fatigue, stomatitis, increased aspartate aminotransferase, alopecia, decreased appetite, infections and influenza. The company derived a hint of lesser benefit of palbociclib for the AE "white blood cell count decreased".

2.3.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the benefit assessment:

- age (< 65 years, ≥ 65 years)
- region (North America, Europe, other)
- metastatic site (visceral, bone only, other)
- visceral metastases (yes, no)
- prior hormonal therapy (yes, no)
- disease-free interval from the end of the (neo)adjuvant treatment to recurrence of the disease (de-novo metastatic, ≤ 12 months, > 12 months)

For all outcomes with high risk of bias, only the results are presented below for which there was proof of an interaction between treatment and subgroup characteristic. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. In addition, subgroup results are only presented if there is a statistically

significant and relevant effect in at least one subgroup. The outcomes “overall survival” and “discontinuation due to AEs” in the PALOMA-2 study are exceptions. Due to the high certainty of conclusions, subgroups can also be considered for these outcomes when there are indications of an effect modification (p-value < 0.2).

The company presented no subgroup analyses for the outcome “overall survival” in the PALOMA-2 study. For the outcome “discontinuation due to AEs”, the company’s subgroup analyses for the PALOMA-2 study were incomplete because there were no analyses on treatment discontinuation of all drug components. Hence no potential effect modifiers can be determined for these outcomes.

A relevant effect modification (according to the definition provided above) was only present for the PALOMA-1 study for the factor “age” in the outcome “severe AEs”. Since for this factor, there was no proof of an effect modification in the PALOMA-2 study, these results are not presented.

2.3.3 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.3.2 resulted in indications and hints of lesser benefit of palbociclib. The extent of the respective added benefit at outcome level was estimated from these results (see Table 18).

Table 18: Extent of added benefit at outcome level: palbociclib vs. letrozole

Outcome category **Outcome**	**Palbociclib + letrozole vs. letrozole** **Median time to event** **Proportion of events or MD** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	37.5 vs. 33.3 months[c] 21.4-35.7% vs. 17.1-38.3%[d] Heterogeneous results[e] There was no statistically significant effect in any of the 2 relevant studies.	Lesser benefit/added benefit not proven
Morbidity		
Health status (EQ-5D VAS)[f]	Change at end of treatment versus start of the study: -3.4 (21.2) vs. -0.6 (17.9) MD: -0.18 [-2.29; 1.93] p = 0.869	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-B[f]	Time to deterioration (decrease by ≥ 7 points): 7.6 vs. 9.2 months 59.7% vs. 54.1% p = 0.601	Lesser benefit/added benefit not proven
	Change at end of treatment versus start of the study: -4.8 (17.8) vs. -2.3 (16.6) MD: -0.33 [-2.63; 1.98] p = 0.869	Lesser benefit/added benefit not proven
Side effects		
SAEs[f]	Median time to event: NA 19.6% vs. 12.6%[d] HR: 1.63 [1.06; 2.49] HR: 0.61 [0.40; 0.94][g] p = 0.023 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”
Severe AEs (CTCAE grade 3 or 4)	1.0–1.4 months vs. NA[i] 77.1-77.5% vs. 20.8-25.2%[d] HR: 5.49 [4.26; 7.08] HR: 0.18 [0.14; 0.23][g] p < 0.001 probability: “indication”	Outcome category: serious/severe side effects $CI_u < 0.75$ greater harm, extent: “major”

(continued)

Table 18: Extent of added benefit at outcome level: palbociclib vs. letrozole (continued)

Outcome category **Outcome**	**Palbociclib + letrozole vs. letrozole** **Median time to event** **Proportion of events or MD** **Effect estimate [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Discontinuation due to AEs (discontinuation of all drug components)	Median time to event: NA 6.1-14.5% vs. 2.6-5.0%[d] There was no statistically significant effect in any of the 2 relevant studies.	Greater/lesser harm not proven
Discontinuation due to AEs (discontinuation of palbociclib or placebo)[h]	Median time to event: NA 9.2% vs. 5.4% HR: 1.74 [0.92; 3.32] p = 0.087	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Information of the median time to event only available for the PALOMA-1 study.
d: Minimum and maximum proportions of events in the included studies.
e: No common effect estimate can be provided due to heterogeneous data.
f: Usable data are only available from the PALOMA-2 study.
g: Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
h: Information from the PALOMA-2 study for patients who discontinued only treatment with palbociclib or placebo, but continued treatment with letrozole.
i: Minimum and maximum medians of the time to event in the studies included.
CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; HR: hazard ratio; MD: mean difference; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.3.3.2 Overall conclusion on added benefit

Table 19 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of palbociclib + letrozole in comparison with letrozole

Positive effects	**Negative effects**
–	Hint of greater harm – extent: "minor" (outcome category: serious/severe side effects: SAEs)
	Indication of greater harm – extent: "major" (outcome category: serious/severe side effects: severe CTCAE grade 3 or 4 AEs)

AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event

There were 2 relevant studies for the drug combination of palbociclib + letrozole. None of the 2 studies showed positive effects for palbociclib. However, the overall consideration of both studies showed a hint of greater harm with the extent "minor" for the outcome "SAEs" and an indication of greater harm with the extent "major" for the outcome "severe AEs".

In summary, there is an indication of a lesser benefit of palbociclib + letrozole as initial endocrine therapy versus the ACT letrozole for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

The result of the assessment of the added benefit of palbociclib in comparison with the ACT is summarized in Table 20.

Table 20: Palbociclib – extent and probability of added benefit (research question A1)

Subindication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
In postmenopausal women with HR-positive, HER2-negative advanced/metastatic breast cancer as initial endocrine therapy (first-line treatment)	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	*For palbociclib in combination with letrozole:* indication of lesser benefit *For palbociclib in combination with fulvestrant*[b]*:* added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: In women who have already received adjuvant endocrine therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor		

Overall, there is an indication of lesser benefit of palbociclib in combination with letrozole in comparison with letrozole in the present research question. This deviates from the approach of the company, which derived major added benefit for the combination of palbociclib with an aromatase inhibitor, irrespective of the patients' menopausal status.

2.3.4 List of included studies

PALOMA-1

Bell T, Crown JP, Lang I, Bhattacharyya H, Zanotti G, Randolph S et al. Impact of palbociclib plus letrozole on pain severity and pain interference with daily activities in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer as first-line treatment. Curr Med Res Opin 2016; 32(5): 959-956.

Finn RS, Crown JP, Ettl J, Schmidt M, Bondarenko IM, Lang I et al. Efficacy and safety of palbociclib in combination with letrozole as first-line treatment of ER-positive, HER2-negative, advanced breast cancer: expanded analyses of subgroups from the randomized pivotal trial PALOMA-1/TRIO-18. Breast Cancer Res 2016; 18: 67.

Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 2014; 16(1): 25-35.

Pfizer. Phase 1/2, open-label, randomized study of the safety, efficacy, and pharmacokinetics of letrozole plus PD 0332991 (oral CDK 4/6 inhibitor) and letrozole single agent for the first-line treatment of ER positive, HER2 negative advanced breast cancer in postmenopausal women [online]. In: EU Clinical Trials Register. [Accessed: 15.12.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-002392-27.

Pfizer. Phase 1/2, open-label, randomized study of the safety, efficacy, and pharmacokinetics of letrozole plus PD 0332991 (oral CDK 4/6 inhibitor) and letrozole single agent for the first-line treatment of ER-positive, HER2-negative advanced breast cancer in postmenopausal women; study A5481003; clinical study report [unpublished]. 2015.

Pfizer. Phase 1/2, open-label, randomized study of the safety, efficacy, and pharmacokinetics of letrozole plus PD 0332991 (oral CDK 4/6 inhibitor) and letrozole single agent for the first-line treatment of ER-positive, HER2-negative advanced breast cancer in postmenopausal women; study A5481003; Zusatzanalysen [unpublished]. 2016.

Pfizer. Study of letrozole with or without palbociclib (PD-0332991) for the first-line treatment of hormone-receptor positive advanced breast cancer: full text view [online]. In: ClinicalTrials.gov. 08.07.2016 [Accessed: 15.12.2016]. URL: https://clinicaltrials.gov/show/NCT00721409.

Pfizer. Study of letrozole with or without palbociclib (PD-0332991) for the first-line treatment of hormone-receptor positive advanced breast cancer: study results [online]. In: ClinicalTrials.gov. 08.07.2016 [Accessed: 15.12.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00721409.

PALOMA-2

Pfizer. A randomized, multicenter, double-blind phase 3 study of PD-0332991 (oral CDK 4/6 inhibitor) plus letrozole versus placebo plus letrozole for the treatment of postmenopausal women with ER (+), HER2 (-) breast cancer who have not received any prior systemic anti-cancer treatment for advanced disease [online]. In: EU Clinical Trials Register. [Accessed: 15.12.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004601-27.

Pfizer. A randomized, multicenter, double-blind phase 3 study of PD-0332991 (oral CDK 4/6 inhibitor) plus letrozole versus placebo plus letrozole for the treatment of postmenopausal women with ER (+), HER2 (-) breast cancer who have not received any prior systemic anti-cancer treatment for advanced disease; study A5481008; clinical study report [unpublished]. 2016.

Pfizer. A randomized, multicenter, double-blind phase 3 study of PD-0332991 (oral CDK 4/6 inhibitor) plus letrozole versus placebo plus letrozole for the treatment of postmenopausal women with ER (+), HER2 (-) breast cancer who have not received any prior systemic anti-cancer treatment for advanced disease; study A5481008; Zusatzanalysen [unpublished]. 2016.

Pfizer. A study of palbociclib (PD-0332991) + letrozole vs. letrozole for 1st line treatment of postmenopausal women with ER+/HER2- advanced breast cancer (PALOMA-2): full text view [online]. In: ClinicalTrials.gov. 06.10.2016 [Accessed: 15.12.2016]. URL: https://clinicaltrials.gov/show/NCT01740427.

2.4 Research question A2: first-line treatment in pre-/perimenopausal women

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on palbociclib (status: 8 September 2016)
- bibliographical literature search on palbociclib (last search on 7 September 2016)
- search in trial registries for studies on palbociclib (last search on 8 September 2016)

To check the completeness of the study pool:

- search in trial registries for studies on palbociclib (last search on 9 December 2016)

The company identified no relevant study. No relevant study was identified from the check either.

Of the 3 studies presented by the company in its dossier, only the PALOMA-3 study [4-7] included pre- or perimenopausal women in first-line treatment. However, the company did not include the study in its assessment of the added benefit for the research question considered here, but only for the assessment of the added benefit for women in second-line treatment (research questions B1 and B2, see Sections 2.5 and 2.6). The company did not investigate the added benefit of palbociclib for pre- or perimenopausal women in first-line treatment.

The ACT for pre- or perimenopausal without prior endocrine therapy was tamoxifen in combination with ovarian suppression (see Section 2.2). The patients in the comparator arm of the PALOMA-3 study were only treated with fulvestrant, however. The study was therefore not relevant for the present research question. In addition, only a subpopulation of the study fulfilled the inclusion criteria for research question A2. Hence no relevant studies were available for the present research question.

2.4.2 Results on added benefit

The company presented no studies for research question A2. This resulted in no hint of an added benefit of palbociclib in comparison with the ACT for this research question. An added benefit for this research question is not proven.

2.4.3 Extent and probability of added benefit

The company presented no data for the assessment of the added benefit of palbociclib as initial endocrine therapy in pre- or perimenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer. An added benefit for these patients is therefore not proven.

This deviates from the approach of the company, which derived major added benefit for the combination of palbociclib with an aromatase inhibitor on the basis of the studies PALOMA-1 and PALOMA-2, irrespective of the patients' menopausal status. The company did not justify this approach.

2.4.4 List of included studies

Not applicable as the company presented no relevant data for this research question.

2.5 Research question B1: second and subsequent line of treatment in postmenopausal women

2.5.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on palbociclib (status: 8 September 2016)
- bibliographical literature search on palbociclib (last search on 7 September 2016)
- search in trial registries for studies on palbociclib (last search on 8 September 2016)

To check the completeness of the study pool:

- search in trial registries for studies on palbociclib (last search on 9 December 2016)

No relevant study was identified from the check.

Study pool of the company

The company included the PALOMA-3 study for the assessment of the added benefit of palbociclib for research question B1. This study was unsuitable to derive conclusions on the added benefit of palbociclib in the present research question. This is justified below.

The PALOMA-3 study was a double-blind RCT comparing palbociclib + fulvestrant with placebo + fulvestrant. The study included pre- and postmenopausal patients with HR-positive, HER2-negative metastatic breast cancer, both in first-line treatment and in second-line treatment.

All postmenopausal patients in the comparator arm of the study received fulvestrant monotherapy. According to the G-BA's specification, fulvestrant is a possible ACT for postmenopausal patients in second-line treatment. However, fulvestrant monotherapy is only ACT for patients with recurrence or progression following anti-oestrogen therapy. For study inclusion, postmenopausal patients in the PALOMA-3 study had to have received an aromatase inhibitor as prior therapy, either adjuvant or as first-line treatment for the advanced breast cancer. Fulvestrant monotherapy is not approved after prior aromatase inhibitor treatment [11], however, as is explicitly stated in a European Medicines Agency (EMA) report. In 2010 the manufacturer of fulvestrant had applied for extension of approval to include treatment with fulvestrant after aromatase inhibitor pretreatment. EMA adopted a negative opinion, however [12]. According to the information provided by EMA, the benefit-risk balance for patients pretreated with an aromatase inhibitor is considered not favourable and the therapeutic efficacy has not been sufficiently demonstrated.

The company stated that, due to the approval of fulvestrant restricted to treatment following anti-oestrogen therapy, it had conducted subgroup analyses for the factor “pretreatment in the adjuvant or metastatic setting with tamoxifen or toremifene” (yes/no). However, the company did not only consider the last previous treatment, which would have been adequate, but any previous treatments. The study documents contained no information on the last previous treatment differentiated by menopausal status. However, only 65 (18.7%) and 30 (17.2%) patients had received anti-oestrogen therapy as last previous treatment already in the total population. As can be expected from the inclusion criteria, these proportions almost exactly concurred with the proportion of premenopausal patients included in the study (72 [20.7%] and 36 [20.7%]). According to the inclusion criteria, only these were to be pretreated with tamoxifen (or endocrine therapy).

Only the subpopulation of postmenopausal patients with prior endocrine therapy for the advanced or metastatic stage of the disease would be relevant for the present research question.

As a consequence, there was no relevant study for research question B1.

2.5.2 Results on added benefit

The company presented no relevant studies for research question B1. This resulted in no hint of an added benefit of palbociclib in comparison with the ACT for this research question. An added benefit for this research question is not proven.

2.5.3 Extent and probability of added benefit

The company presented no relevant data for the assessment of the added benefit of palbociclib in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy. An added benefit for these patients is therefore not proven.

This deviates from the assessment of the company, which did not differentiate between pre-/perimenopausal and postmenopausal patients and derived major added benefit for all women in the present therapeutic indication for the combination of palbociclib and fulvestrant.

2.5.4 List of included studies

Not applicable as the company presented no relevant data for this research question.

2.6 Research question B2: second and subsequent line of treatment in pre-/perimenopausal women

2.6.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on palbociclib (status: 8 September 2016)
- bibliographical literature search on palbociclib (last search on 7 September 2016)
- search in trial registries for studies on palbociclib (last search on 8 September 2016)

To check the completeness of the study pool:

- search in trial registries for studies on palbociclib (last search on 9 December 2016)

No relevant study was identified from the check.

Study pool of the company

The company included the PALOMA-3 study for the assessment of the added benefit of palbociclib for research question B2. More details on this are provided in Section 2.5.1 of the present benefit assessment. This study was unsuitable to derive conclusions on the added benefit of palbociclib in the present research question. This is justified below.

The G-BA specified endocrine therapy specified by the physician as ACT for research question B2. All patients in the comparator arm of the PALOMA-3 study received fulvestrant monotherapy (+ goserelin), however. Endocrine therapy specified by the physician includes the possibility to choose from several treatment options. There was no such choice in the PALOMA-3 study. Current guidelines on breast cancer also provide no consistent recommendation for the use of fulvestrant in the present treatment situation [13-15]. Consequently, suitability of fulvestrant as only ACT cannot be inferred from this. In addition, there were no signs in the study documents as to why fulvestrant might have been the adequate endocrine therapy specified by the physician for all patients included (reasons might have been contraindications to aromatase inhibitors, for example).

Only the subpopulation of pre- or perimenopausal patients with prior endocrine therapy for the advanced or metastatic stage of the disease would be relevant for the present research question.

As a consequence, there was no relevant study for research question B2.

2.6.2 Results on added benefit

The company presented no relevant studies for research question B2. This resulted in no hint of an added benefit of palbociclib in comparison with the ACT for this research question. An added benefit for this research question is not proven.

2.6.3 Extent and probability of added benefit

The company presented no relevant data for the assessment of the added benefit of palbociclib in pre- or perimenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy. An added benefit for these patients is therefore not proven.

This deviates from the assessment of the company, which did not differentiate between pre-/perimenopausal and postmenopausal patients and derived major added benefit for all women in the present therapeutic indication for the combination of palbociclib and fulvestrant.

2.6.4 List of included studies

Not applicable as the company presented no relevant data for this research question.

2.7 Extent and probability of added benefit – summary

Table 21 presents a summary of the extent and probability of the added benefit of palbociclib.

Table 21: Palbociclib – extent and probability of added benefit

Research question	Subindication[a]	ACT[b]	Extent and probability of added benefit
Women with HR-positive, HER2-negative advanced/metastatic breast cancer			
A1	Postmenopausal women, initial endocrine therapy (first-line treatment)	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	*For palbociclib in combination with letrozole:* indication of lesser benefit *For palbociclib in combination with fulvestrant[c]:* added benefit not proven
A2	Pre- and perimenopausal women, initial endocrine therapy (first-line treatment)	Tamoxifen in combination with suppression of the ovarian function	Added benefit not proven
B1	Postmenopausal women who have progressed after endocrine therapy (second and subsequent line of treatment)	Depending on the prior therapy: ▪ tamoxifen or ▪ anastrozole or ▪ **fulvestrant**; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ exemestane; only for patients with progression following anti-oestrogen therapy or everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor	Added benefit not proven
B2	Pre- and perimenopausal women who have progressed after endocrine therapy (second and subsequent line of treatment)	Endocrine therapy specified by the physician under consideration of the respective approval[d]	Added benefit not proven

(continued)

Table 21: Palbociclib – extent and probability of added benefit (continued)

a: It is assumed for the present therapeutic indication that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
b: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
c: In women who have already received adjuvant endocrine therapy.
d: It is assumed that ovarian suppression with a GnRH analogue is continued.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; GnRH: gonadotropin-releasing hormone

Usable data for the benefit assessment were only available for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer who have received palbociclib + letrozole as initial endocrine therapy. For these patients, there is an indication of lesser benefit of palbociclib + letrozole versus letrozole.

The company presented no usable data for any further patients of the target population. The added benefit of palbociclib is therefore not proven for these patients.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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/a16-74-palbociclib-breast-cancer-benefit-assessment-according-to-35a-social-code-book-v.7749.html.