IQWiG Reports – Commission No. A22-66

Palbociclib (breast cancer, in combination with an aromatase inhibitor) –

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

(expiry of the limitation period)

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Palbociclib (Mammakarzinom, in Kombination mit einem Aromatasehemmer – Nutzenbewertung gemäß § 35a SGB V* (Version1.0; Status: 29 September 2022). 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Palbociclib (breast cancer, in combination with an aromatase inhibitor) – (expiry of the limitation period)

Commissioning agency
Federal Joint Committee

Commission awarded on
1 July 2022

Internal Commission No.
A22-66

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback of persons concerned or patient organizations was received within the framework of the present dossier assessment.

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Keywords: Palbociclib, Breast Neoplasms, Benefit Assessment, NCT00721409, NCT01740427, NCT02297438

Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BICR	blinded independent central review
CI	confidence interval
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ER	oestrogen receptor
FACT-B	Functional Assessment of Cancer Therapy-Breast Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor-2
HR	hormone receptor
IPD	individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summaries of Product Characteristics
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

I 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 (in combination with an aromatase inhibitor). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 July 2022.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. In this procedure, by decision of 15 October 2020, the G-BA limited its decision until 01 July 2022. The time limit was set because the data on overall survival from the included PALOMA-2 study were preliminary at the time of the initial assessment. The final results from the ongoing study were still pending at that time. For the new benefit assessment of palbociclib (in combination with an aromatase inhibitor) after expiry of the decision, all proofs on the extent of the added benefit should be presented in the dossier, including the final study results of the PALOMA-2 study on all outcomes that are relevant for the benefit assessment.

Research question

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

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of palbociclib in combination with an aromatase inhibitor

Therapeutic indication	**ACT**[a]
Postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in first-line therapy[b, c]	▪ Anastrozole or ▪ **letrozole** or ▪ fulvestrant or ▪ possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. According to the G-BA, it is assumed for the present therapeutic indication that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent. c. For this benefit assessment, first-line therapy is defined as the initial endocrine-based therapy of locally advanced or metastatic breast cancer. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor	

The company followed the G-BA's specification and chose letrozole as ACT from the options presented.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Study pool and study design

The RCTs PALOMA-1, PALOMA-2 and PALOMA-4 were included in the benefit assessment of palbociclib in combination with an aromatase inhibitor. In these studies, palbociclib in combination with letrozole (palbociclib + letrozole) is directly compared with letrozole as monotherapy. In the studies PALOMA-2 and PALOMA-4, patients also receive a placebo (placebo + letrozole).

The studies PALOMA-1 and PALOMA-2 are already known from the previous benefit assessment of palbociclib in the present therapeutic indication. At the time of the previous benefit assessment, results were not available for the PALOMA-4 study. In contrast, results from the PALOMA-1 and PALOMA-2 studies were available for the respective 1st planned data cut-off and both studies were still ongoing. In the current dossier, the company presents data on more recent data cut-offs for the studies PALOMA-1 and PALOMA-2. However, in the dossier, the company did not present a complete review of the results relevant to the benefit assessment for the most recent data cut-off for either of the two studies. This leads to incomplete information in terms of content being provided in the dossier, which, however, remains without consequence for the benefit assessment in the present data situation. This is further explained below.

In contrast to the previous benefit assessment in the present therapeutic indication, which was based on the 1st data cut-off of 29 November 2013, a more recent data cut-off of 30 December 2016 is available for the PALOMA-1 study, which apparently represents the final data cut-off on overall survival towards the end of the study. However, the concrete planning of this data cut-off cannot be inferred from the study documents. Although the company stated in Module 4 A of the dossier that it included the PALOMA-1 study in the study pool of its assessment, it did not provide a corresponding preparation of the results in Module 4 A in accordance with the requirements of the dossier template and did not use the study to derive the added benefit. For its benefit assessment, the company only used results from the studies PALOMA-2 and PALOMA-4 as well as, for some outcomes, a meta-analysis of the two studies. It justifies this with the fact that, according to the decision of the G-BA, the final study results for all outcomes in the PALOMA-2 study relevant to the benefit assessment are to be submitted in the dossier for the renewed benefit assessment after the expiry of the decision.

This rationale is not appropriate. In principle, all scientific findings for the assessment of the added benefit that are available at the time of the new benefit assessment must be submitted in the dossier for the new benefit assessment after the expiry of the decision. The fact that according to the decision of the G-BA the results of the PALOMA-2 study are to be presented does not exclude that the results of other studies are also relevant and must be presented.

The PALOMA-1 study is fundamentally relevant for the benefit assessment. As already described in the previous benefit assessment of palbociclib in the present therapeutic indication, there is a high risk of bias for the results of the study. In addition, 2 studies are available with the studies PALOMA-2 and PALOMA-4, each with a larger sample size than in the PALOMA-1 study. Against this background, it is not assumed in the present data situation that the assessment result based on the studies PALOMA-2 and PALOMA-4 is called into question by the results of the PALOMA-1 study. Therefore, the incompleteness of the content regarding the PALOMA-1 study has no consequences for the present benefit assessment, and the benefit assessment is based on the analyses of the PALOMA-2 and PALOMA-4 studies submitted by the company. The analyses of the final data cut-off on overall survival of the PALOMA-1 study also largely confirm the results of the previous benefit assessment. For example, there are still

no statistically significant differences between the treatment groups for the outcome of overall survival and a statistically significant difference to the disadvantage of palbociclib + letrozole for the outcome of severe adverse events (AEs).

For the PALOMA-2 study, the company did not present a complete analysis of the results relevant to the benefit assessment for the most recent data cut-off, but only for the outcomes of the categories "mortality" and "side effects". However, in the present data situation, it is assumed that the assessment result is not called into question by the missing analyses on outcomes of the categories "morbidity" and "health-related quality of life" for the most recent data cut-off. This is explained below.

Study characteristics

PALOMA-2 is a double-blind RCT on the direct comparison of palbociclib + letrozole with placebo + letrozole. This study included postmenopausal patients with oestrogen receptor (ER)-positive and HER2-negative locoregionally recurrent or metastatic breast cancer. On study inclusion, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2 and were not allowed to have received prior systemic therapy for advanced or metastatic disease. A total of 666 patients were randomly allocated in a ratio of 2:1 to treatment with palbociclib + letrozole or placebo + letrozole.

The PALOMA-4 study differs from the PALOMA-2 study only in a few points. Only Asian female patients aged 18 to 70 years could be included. The patients had to have an ECOG PS ≤ 1 on study entry. A total of 340 patients were randomly allocated in a ratio of 1:1 to treatment with palbociclib + letrozole or placebo + letrozole.

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. The primary outcome of both studies was progression-free survival (PFS). Patient-relevant secondary outcomes were "overall survival", "health status", "health-related quality of life", and "AEs".

Data cut-offs and analyses

The two studies PALOMA-2 and PALOMA-4 are still ongoing.

At the time of the present benefit assessment, 3 data cut-offs were available for the PALOMA-2 study. According to the study design, the first data cut-off of 26 February 2016 was intended for the final analysis of PFS and was used within the previous benefit assessment in the present therapeutic indication. In the current dossier, the company presents analyses for this study for 2 different more recent data cut-offs from 31 May 2017 and 15 November 2021, depending on the outcome. The data cut-off from 15 November 2021 was prespecified for the final analysis of overall survival. The data cut-off of 31 May 2017, in contrast, was not planned according to the study design.

At the time of the previous benefit assessment, no data were available for the PALOMA-4 study in the present therapeutic indication. At the time of the present benefit assessment, 1 data cut-off is available for the PALOMA-4 study. According to the study design, this data cut-off of 31 August 2020 was planned for the final analysis of PFS.

Contrary to the conditions of the limitation, the company does not present a complete evaluation of the results for all outcomes relevant to the benefit assessment in the dossier for the planned, current data cut-off of the PALOMA-2 study from 15 November 2021. For the outcomes of the categories of morbidity and health-related quality of life, it only presented analyses on the unplanned 2nd data cut-off of 31 May 2017 instead. It justified this with the fact that at this point in time, treatment had already been completed for 70.5% of the patients in the intervention arm and for 86% of the patients in the comparator arm and assumes that the symptoms and quality of life change significantly under therapy and less in the course of the follow-up and that there are therefore no new findings relevant to the assessment.

The company's argumentation is not appropriate in the present situation, especially since the condition of the limitation was not implemented. Moreover, it should be noted that the outcomes were partly recorded beyond the end of the study treatment and that an assumption that symptoms and quality of life change less in the course of the follow-up is not appropriate per se. According to the conditions of the limitation, the final study results of the PALOMA-2 study on all outcomes that are relevant for the benefit assessment should be submitted in the dossier for the new benefit assessment after the expiry of the decision. The analyses presented for the patient-reported outcomes of the categories of morbidity and health-related quality of life on the unplanned 2nd data cut-off of the PALOMA-2 study are not usable for the benefit assessment. For the present benefit assessment, therefore, only the analyses on the current, planned data cut-off of 15 November 2021 are used, which are available for outcomes in the categories of mortality and side effects. Thus, the results presented by the company for the PALOMA-2 study are incomplete in terms of content, as already described in the previous section.

However, in the present data situation, it is assumed that the assessment result is not called into question by the missing analyses on outcomes of the categories "morbidity" and "health-related quality of life" for the most recent data cut-off. This is due to the fact that for the patient-reported outcomes in the present data situation, no significant gain in information can be assumed from the 3rd data cut-off.

Risk of bias

The risk of bias at study level was rated as low for the PALOMA-2 study. At outcome level, there is a high risk of bias for all outcomes except "overall survival" and "discontinuation due to AEs" because of the high proportion of potentially informative censoring.

For the PALOMA-4 study, the risk of bias at study level was rated as high. This is mainly due to the fact that the assessment of progression conducted by the investigators differed notably

from a blinded independent central review (BICR) conducted retrospectively. 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. There is a high risk of bias for all outcomes. On the one hand, this is due to the high risk of bias at study level. Secondly, there is a high proportion of potentially informative censorings for all outcomes except "overall survival" and "discontinuation due to AEs".

For the outcome of discontinuation due to AEs, the certainty of results is limited in both studies, irrespective of the respective low risk of bias.

Overall, there are no usable data for the patient-reported outcomes of the categories of morbidity and health-related quality of life in the company's dossier due to the incompleteness of the contents of the PALOMA-2 study described above.

Summary assessment of the certainty of conclusions

The assessment is based on the quantitative meta-analytical summary of the results of the studies PALOMA-2 and PALOMA-4. Due to the size of the effect as well as the early occurrence of the events in the course of the study, before censoring sets in to a critical extent, there is a high certainty of results for some outcomes from the PALOMA-2 study despite a high risk of bias (see following section). For the PALOMA-4 study, however, no high certainty of results can be achieved even in such cases due to the bias aspect at study level. Those results of the PALOMA-2 study, which show a high certainty of results, cannot be weakened by adding the results from the PALOMA-4 study, but at best can be enhanced. Therefore, on the basis of the meta-analysis, at most proofs, e.g. of an added benefit, can be derived for those outcomes for which there is a high certainty of results in the PALOMA-2 study, and at most indications for all other outcomes.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Hence, there was no hint of an added benefit of palbociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

Morbidity

Health status (recorded using the EQ-5D VAS)

For the outcome of health status (recorded with the EQ-5D VAS), the dossier provides results on the current data cut-off only for the PALOMA-4 study. However, considered for this outcome alone, these are not meaningful due to the incompleteness of the content with regard to the results of the PALOMA-2 study. Therefore, no usable data are available for this outcome. Hence, there was no hint of an added benefit of palbociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

Health-related quality of life

For the outcome of health-related quality of life (recorded using Functional Assessment of Cancer Therapy-Breast Cancer [FACT-B]), the dossier provides results for the current data cut-off only for the PALOMA-4 study. However, considered for this outcome alone, these are not meaningful due to the incompleteness of the content with regard to the results of the PALOMA-2 study. Therefore, no usable data are available for this outcome. Hence, there was no hint of an added benefit of palbociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". Hence, there was no hint of greater or lesser harm from palbociclib + letrozole in comparison with letrozole; greater or lesser harm is therefore not proven.

Severe AEs

A statistically significant difference to the disadvantage of palbociclib + letrozole was shown for the outcome "severe AEs". Implausible Kaplan-Meier curves are available for this outcome.. However, since in the PALOMA-2 study, the course of the Kaplan-Meier curves for this outcome is assumed to be similar to the one of those specific AEs that significantly determine the outcome “severe AEs” according to the frequencies of events and whose Kaplan-Meier curves are plausible, a high certainty of results is assumed for the large effect of severe AEs in the PALOMA-2 study despite a high risk of bias. Therefore, this resulted in a proof of greater harm from palbociclib + letrozole in comparison with letrozole for this outcome.

Discontinuation due to AEs (discontinuation of palbociclib or placebo)

A statistically significant difference to the disadvantage of palbociclib + letrozole was shown for the outcome "discontinuation due to AEs” (discontinuation of palbociclib or placebo). This resulted in an indication of greater harm of palbociclib + letrozole in comparison with letrozole for this outcome.

Specific AEs

AEs: alopecia and stomatitis

A statistically significant difference to the disadvantage of palbociclib + letrozole was shown for the specific AEs “alopecia” and “stomatitis”. This resulted in an indication of greater harm of palbociclib + letrozole in comparison with letrozole for these outcomes.

Severe AEs: general disorders and administration site conditions

A statistically significant difference to the disadvantage of palbociblib + letrozole was shown for the specific severe AE "general disorders and administration site conditions". This resulted in an indication of greater harm of palbociclib + letrozole in comparison with letrozole for this outcome.

Severe AEs: blood and lymphatic system disorders (including: neutropenia) and examinations (including: neutrophil count decreased)

A statistically significant difference to the disadvantage of palbociclib + letrozole was shown for the specific severe AEs "blood and lymphatic system disorders" (including: "neutropenia") and "examinations" (including: neutrophil count decreased). Due to the size of the respective effect as well as the early occurrence of the events of these outcomes in the course of the study, before censoring sets in to a critical extent, there is a high certainty of results in the PALOMA-2 study despite a high risk of bias. Therefore, there is proof of greater harm from palbociclib + letrozole in comparison with letrozole for each of these outcomes

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

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:

The overall assessment showed only negative effects of palbociclib + letrozole in comparison with letrozole. All these negative effects are related to outcomes in the category of side effects and only refer to the shortened time period until 28 days after discontinuation of treatment.

In the outcome category of serious/severe side effects, proofs a greater harm with the extent "considerable" are shown for severe AEs as well as for various specific AEs included therein. In the present situation, this includes the specific severe AEs blood and lymphatic system disorders (included: neutropenia) and examinations (included: neutrophil count decreased) related in terms of content. For other serious/severe outcomes, including discontinuation due to AEs (discontinuation of palbociclib or placebo), there are indications of greater harm. Moreover, in the outcome category of non-serious/non-severe side effects, indications of greater harm with the extent "considerable" are shown for the specific AEs alopecia and stomatitis.

In summary, there is proof of lesser benefit of palbociclib + letrozole versus the letrozole for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in the first-line setting.

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

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

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in first-line therapy[b, c]	▪ Anastrozole or ▪ **letrozole** or ▪ fulvestrant or ▪ possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant	Proof of lesser benefit[d]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. According to the G-BA, it is assumed for the present therapeutic indication that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. For this benefit assessment, first-line therapy is defined as the initial endocrine-based therapy of locally advanced or metastatic breast cancer.
d. Almost only patients with an ECOG PS of 0 or 1 were included in the studies PALOMA-2 and PALOMA-4. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor

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

I 2 Research question

The aim of the present report was to assess the added benefit of palbociclib in combination with an aromatase inhibitor in comparison with the ACT in the first-line treatment of postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of palbociclib in combination with an aromatase inhibitor

Therapeutic indication	**ACT**[a]
Postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in first-line therapy[b, c]	▪ Anastrozole or ▪ **letrozole** or ▪ fulvestrant or ▪ possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. According to the G-BA, it is assumed for the present therapeutic indication that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent. c. For this benefit assessment, first-line therapy is defined as the initial endocrine-based therapy of locally advanced or metastatic breast cancer. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor	

The company followed the G-BA's specification and chose letrozole as ACT from the options presented.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurs with the company’s inclusion criteria.

I 3 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: 4 April 2022)
- bibliographical literature search on palbociclib (last search on 4 April 2022)
- search in trial registries/trial results databases for studies on palbociclib (last search on 4 April 2022)
- search on the G-BA website for palbociclib (last search on 4 April 2022)

To check the completeness of the study pool:

- search in trial registries for studies on palbociclib (last search on 12 July 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

I 3.1 Studies included

The studies listed in the following Table 5 were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publications and other sources[c] (yes/no [citation])
A5481003 (PALOMA-1[d])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7-11]
A5481008 (PALOMA-2[d])	Yes	Yes	No	Yes [12,13][f], [14,15]	Yes [16,17]	Yes [11,18-33]
A5481027 (PALOMA-4[d])	Yes	Yes	No	Yes [15,34,35]	Yes [36]	No

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
e. For this study, the company did not prepare the study results in Module 4 A in accordance with the dossier template. The company included the study in the study pool of its assessment, but did not use it for the benefit assessment; for reasons, see the following section.
f. The citations refer to the study reports for the 1st data cut-off (26 February 2016) and the 2nd data cut-off (31 May 2017). According to information provided by the company in the dossier, the clinical study report of the 3rd data cut-off relevant for the present benefit assessment (15 November 2021) was not available at the time of submission.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The RCTs PALOMA-1, PALOMA-2 and PALOMA-4 were included in the benefit assessment of palbociclib in combination with an aromatase inhibitor. In these studies, palbociclib in combination with letrozole (palbociclib + letrozole) is directly compared with letrozole as monotherapy. In the studies PALOMA-2 and PALOMA-4, patients also receive a placebo (placebo + letrozole).

The studies PALOMA-1 and PALOMA-2 are known from the previous benefit assessment of palbociclib in the present therapeutic indication [37,38]. At the time of the previous benefit assessment, results were not available for the PALOMA-4 study. In contrast, results from the PALOMA-1 and PALOMA-2 studies were available for the 1st planned data cut-off and both studies were still ongoing. In the current dossier, the company presents data on more recent data cut-offs for each of the two the studies. However, in the dossier, the company did not present a complete review of the results relevant to the benefit assessment for either of the two studies. This leads to incomplete information in terms of content being provided in the dossier, which, however, remains without consequence for the benefit assessment in the present data situation. This is further explained below.

In contrast to the previous benefit assessment in the present therapeutic indication, which was based on the 1st data cut-off of 29 November 2013, a more recent data cut-off of 30 December 2016 is available for the PALOMA-1 study, which apparently represents the final data cut-off on overall survival towards the end of the study. However, the concrete planning of this data cut-off cannot be inferred from the study documents. Although the company stated in Module 4 A of the dossier that it included the PALOMA-1 study in the study pool of its assessment, it did not provide a corresponding preparation of the results in Module 4 A in accordance with the requirements of the dossier template [39] and did not use the study to derive the added benefit. For its benefit assessment, the company only used results from the studies PALOMA-2 and PALOMA-4 as well as, for some outcomes, a meta-analysis of the two studies. It justifies this with the fact that, according to the decision of the G-BA, the final study results for all outcomes in the PALOMA-2 study relevant to the benefit assessment are to be submitted in the dossier for the renewed benefit assessment after the expiry of the decision.

This rationale is not appropriate. In principle, all scientific findings for the assessment of the added benefit that are available at the time of the new benefit assessment must be submitted in the dossier for the new benefit assessment after the expiry of the decision. The fact that according to the decision of the G-BA the results of the PALOMA-2 study are to be presented does not exclude that the results of other studies are also relevant and must be presented. Furthermore, the reasoning of the company could also be applied to the PALOMA-4 study, which it used for its assessment in contrast to the PALOMA-1 study. In this respect, the company proceeded differently for the two studies within the dossier. The company does not provide a justification for this inconsistency in its assessment in the dossier.

The PALOMA-1 study is fundamentally relevant for the benefit assessment. As already described in the previous benefit assessment of palbociclib in the present therapeutic indication, there is a high risk of bias for the results of the study [37]. In addition, 2 studies are available with the studies PALOMA-2 and PALOMA-4, each with a larger sample size than in the PALOMA-1 study (PALOMA-1: N = 165; PALOMA-2: N = 666, PALOMA-4: N = 340). Against this background, it is not assumed in the present data situation that the assessment result based on the studies PALOMA-2 and PALOMA-4 is called into question by the results of the PALOMA-1 study. Therefore, the incompleteness of the content regarding the PALOMA-1 study has no consequences for the present benefit assessment, and the benefit assessment is based on the analyses of the PALOMA-2 and PALOMA-4 studies submitted by the company. The analyses of the final data cut-off on overall survival of the PALOMA-1 study also largely confirm the results of the previous benefit assessment. For example, there are still no statistically significant differences between the treatment groups for the outcome of overall survival and a statistically significant difference to the disadvantage of palbociclib + letrozole for the outcome of severe AEs.

For the PALOMA-2 study, the company did not present a complete analysis of the results relevant to the benefit assessment for the most recent data cut-off, but only for the outcomes of the categories “mortality” and “side effects”. However, in the present data situation, it is

assumed that the assessment result is not called into question by the missing analyses on outcomes of the categories “morbidity” and “health-related quality of life” for the most recent data cut-off. For a detailed explanation of the present data situation for the PALOMA-2 study, see I 3.2.

I 3.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PALOMA-2	RCT, double-blind, parallel	Postmenopausal women (≥ 18 years) with ER-positive, HER2-negative[b], locoregionally recurrent/metastatic[c] breast cancer without prior systemic treatment for the advanced stage[d]	Palbociclib + letrozole (N = 444) placebo + letrozole (N = 222)	Screening: up to 28 days treatment: until disease progression[e], symptomatic deterioration, necessity of additional anticancer therapy, unacceptable toxicity, decision by the patient or the investigator, loss to follow-up or death observation[f]: outcome-specific, at most until death or withdrawal of consent or until 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 and USA 02/2013 – ongoing data cut-offs: ▪ 26 February 2016[g] ▪ 31 May 2017[h] ▪ 15 November 2021[i]	Primary: PFS secondary: overall survival, health status, health-related quality of life, AEs
PALOMA-4	RCT, double-blind, parallel	Postmenopausal, Asian women (18-70 years of age) with ER-positive, HER2-negative[b], locoregionally recurrent/metastatic[c] breast cancer without prior systemic treatment for the advanced stage[d]	Palbociclib + letrozole (N = 169) placebo + letrozole (N = 171)	Screening: up to 28 days treatment: until disease progression[e], symptomatic deterioration, necessity of additional anticancer therapy, unacceptable toxicity, decision by the patient or the investigator, loss to follow-up or death observation[f]: outcome-specific, at most until death or withdrawal of consent or until final survival time analysis[i]	52 centres in China, Hong Kong, Singapore, Taiwan and Thailand 03/2015 – ongoing data cut-off: ▪ 31 August 2020[g]	Primary: PFS secondary: overall survival, health status, health-related quality of life, AEs

Table 6: Characteristics of the studies included – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. The HER2 status was determined with FISH, CISH, dual ISH (in accordance with the information in the study protocol, only in the PALOMA-2 study) or IHC; a positive ER status was confirmed histologically or cytologically based on laboratory results.
c. Patients with advanced symptomatic visceral or uncontrolled or symptomatic CNS metastases were excluded.
d. In the case of previous (neo-)adjuvant treatment with aromatase inhibitors (e.g. anastrozole or letrozole), no recurrence was allowed to have occurred during or within 12 months of this treatment.
e. Patients could continue treatment with the study medication beyond progression at the investigator's discretion if this was in the patients' interest.
f. Outcome-specific information is provided in Table 9.
g. Prespecified final data cut-off on PFS.
h. Unplanned data cut-off on PFS.
i. Prespecified final data cut-off on overall survival.

AE: adverse event; CCND1: cyclin D1; CISH: chromosome in situ hybridization; CNS: central nervous system; ER: oestrogen receptor; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characteristics of the interventions – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole

Study	Intervention	Comparison	Prior and concomitant treatment
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[a] ▪ no dose adjustment possible, interruption was permitted[a]	Placebo in weeks 1–3 of a 28-day cycle + letrozole 2.5 mg/day, orally ▪ for placebo dose reduction (to 100 mg/day or 75 mg/day) or interruption possible in case of toxicity[a] ▪ no dose adjustment possible, interruption was permitted[a]	**Nonpermitted pretreatment** ▪ systemic treatment for locoregionally recurrent or metastatic ER-positive disease ▪ CDK4/6 inhibitors ▪ CYP3A4 inhibitors and inducers and drugs that prolong the QT interval within 7 days before the start of the study **nonpermitted concomitant treatment** ▪ other anticancer therapies ▪ strong/moderate CYP3A inhibitors or inducers ▪ hormone replacement therapy ▪ proton pump inhibitors
PALOMA-4	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[a] ▪ no dose adjustment possible, interruption was permitted[a]	Placebo in weeks 1–3 of a 28-day cycle + letrozole 2.5 mg/day, orally ▪ for placebo dose reduction (to 100 mg/day or 75 mg/day) or interruption possible in case of toxicity[a] ▪ no dose adjustment possible, interruption was permitted[a]	**Nonpermitted pretreatment** ▪ systemic treatment for locoregionally recurrent or metastatic ER-positive disease ▪ CDK4/6 inhibitors ▪ CYP3A4 inhibitors and inducers and drugs that prolong the QT interval within 7 days before the start of the study **nonpermitted concomitant treatment** ▪ other anticancer therapies ▪ strong CYP3A inhibitors or inducers ▪ CYP3A inhibitors and inducers and drugs that prolong the QT interval ▪ hormone replacement therapy ▪ proton pump inhibitors

a. If palbociclib or placebo was discontinued due to toxicity, continuation of letrozole was allowed; if letrozole was discontinued due to toxicity, palbociclib also had to be discontinued.

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

For the present benefit assessment, data from 2 studies relevant to the research question were used: from the studies PALOMA-2 and PALOMA-4. As described in Section I 3.1, the results of the PALOMA-1 study were not used for the benefit assessment due to a lack of adequate preparation. A description of the study can be found in the previous benefit assessment of palbociclib in the present therapeutic indication, [37].

PALOMA-2 is a double-blind RCT on the direct comparison of palbociclib + letrozole with placebo + letrozole. This study included postmenopausal patients with ER-positive and HER2-negative locoregionally recurrent or metastatic breast cancer. On study inclusion, patients had to have an ECOG PS ≤ 2 and were not allowed to have received prior systemic therapy for advanced or metastatic disease. Endocrine therapies in the (neo)adjuvant setting were allowed, whereby in the case of previous (neo-)adjuvant treatment with aromatase inhibitors (e.g. anastrozole or letrozole), no recurrence was allowed to have occurred during or within of 12 months of this treatment. A total of 666 patients were allocated in a ratio of 2:1 to treatment with palbociclib + letrozole (N = 444) or placebo + letrozole (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 the prior (neo)adjuvant anticancer therapy (hormonal therapy versus no hormonal therapy).

The PALOMA-4 study differs from the PALOMA-2 study only in a few of the points listed above. Only Asian female patients aged 18 to 70 years could be included. The patients had to have an ECOG PS ≤ 1 on study entry. A total of 340 patients were randomly allocated in a ratio of 1:1 to treatment with palbociclib + letrozole (N = 169) or placebo + letrozole (N = 171). In addition to the characteristics described above for the PALOMA-2 study, randomization in the PALOMA-4 study was also stratified by region (China vs. other countries), as stated in the study documents.

In both studies, treatment of the patients in the intervention and comparator arm concurred with the SPCs of palbociclib and letrozole [40,41]. 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. A treatment switch from the comparator intervention placebo to the experimental intervention palbociclib was not allowed in either of the two studies.

The primary outcome of both studies was PFS. Patient-relevant secondary outcomes were “overall survival”, “health status”, “health-related quality of life”, and “AEs”.

Data cut-offs and analyses

At the time of the present benefit assessment, the PALOMA-1 study had been completed. As already described in detail in Section I 3.1, in Module 4 A of the dossier, the company did not present any preparation of the results of the PALOMA-1 study in accordance with the requirements of the dossier template (for a summary of the data situation and the available data cut-offs, see also Table 8).

The two studies PALOMA-2 and PALOMA-4 are still ongoing.

At the time of the present benefit assessment, 3 data sections were available for the PALOMA-2 study. According to the study design, the first data cut-off of 26 February 2016 was intended for the final analysis of PFS and was used within the previous benefit assessment in the present therapeutic indication [37]. In the current dossier, the company presents analyses for this study for 2 different more recent data cut-offs from 31 May 2017 and 15 November 2021, depending on the outcome. The data cut-off from 15 November 2021 was prespecified for the final analysis of overall survival. The data cut-off of 31 May 2017, in contrast, was not planned according to the study design. It can be inferred from the study documents that the data cut-off had been performed as a precise estimation of the median PFS including 95% confidence interval (CI) would not have been possible at the time of the first data cut-off.

At the time of the previous benefit assessment, no data were available for the PALOMA-4 study in the present therapeutic indication. At the time of the present benefit assessment, 1 data cut-off is available for the PALOMA-4 study. According to the study design, this data cut-off of 31 August 2020 was planned for the final analysis of PFS. Another data cut-off was prespecified for the final analysis of overall survival. At the time point of the present data cut-off, the number of 247 events required for the outcome had not been achieved yet.

Table 8 shows an overview of the analyses presented by the company for the data cut-offs of the PALOMA-2 study and the results per outcome category reported for this purpose.

Table 8: Analyses for the studies PALOMA-1, PALOMA-2 and PALOMA-4 presented by the company per data cut-off and outcome category

Study data cut-off	Mortality	Morbidity	Health-related quality of life	Side effects
PALOMA-1[a]				
29 November 2013[b]	–[c]	–[c]	–[c]	–[c]
30 December 2016[d]	–[e]	–[e]	–[e]	–[e]
PALOMA-2				
26 February 2016[b]	–[c]	–[c]	–[c]	–[c]
31 May 2017[f]	–	x	x	–
15 November 2021[g]	x	–	–	x
PALOMA-4				
31 August 2020[b]	x	x	x	x

a. For this study, the company did not prepare the study results in Module 4 A in accordance with the dossier template. The company included the study in the study pool of its assessment, but did not use it for the benefit assessment; for reasons, see Section I 3.1.
b. Final analysis of the PFS planned a priori.
c. The data cut-off was the basis of assessment of the previous benefit assessment of palbociclib in the present therapeutic indication; in the current dossier, the company did not present any analyses on this data cut-off.
d. Final data cut-off on overall survival towards the end of the study; the dossier provides no information on the concrete planning of the data cut-off.
e. In its dossier, the company presented results for this data cut-off, but did not prepare the study results in accordance with the dossier template in Module 4 A.
f. Unplanned data cut-off for the analysis of PFS; performed after 405 PFS events according to the assessment of the progression by the investigators, because a precise estimation of the median PFS including 95% CI had not been possible at the time point of the planned final analysis.
g. Final analysis of overall survival planned a priori; the company's dossier includes no clinical study report on this data cut-off.

CI: confidence interval; G-BA: Federal Joint Committee; PFS: progression-free survival

Contrary to the conditions of the limitation, the company does not present a complete evaluation of the results for all outcomes relevant to the benefit assessment in the dossier for the planned, current data cut-off of the PALOMA-2 study from 15 November 2021. For the outcomes of the categories of morbidity and health-related quality of life, it only presented analyses on the unplanned 2nd data cut-off of 31 May 2017 instead. It justified this with the fact that at this point in time, treatment had already been completed for 70.5% of the patients in the intervention arm and for 86% of the patients in the comparator arm and assumes that the symptoms and quality of life change significantly under therapy and less in the course of the follow-up and that there are therefore no new findings relevant to the assessment.

The company's argumentation is not appropriate in the present situation, especially since the condition of the limitation was not implemented. Moreover, it should be noted that the outcomes were partly recorded beyond the end of the study treatment (see Section I 4.1) and that an assumption that symptoms and quality of life change less in the course of the follow-up is not appropriate per se. According to the conditions of the limitation, the final study results of the PALOMA-2 study on all outcomes that are relevant for the benefit assessment should be

submitted in the dossier for the new benefit assessment after the expiry of the decision [42]. The analyses presented for the patient-reported outcomes of the categories of morbidity and health-related quality of life on the unplanned 2nd data cut-off of the PALOMA-2 study are not usable for the benefit assessment. For the present benefit assessment, therefore, only the analyses on the current, planned data cut-off of 15 November 2021 are used, which are available for outcomes in the categories of mortality and side effects. Thus, the results presented by the company for the PALOMA-2 study are incomplete in terms of content, as already described in Section I 3.1.

However, in the present data situation, it is assumed that the assessment result is not called into question by the missing analyses on outcomes of the categories "morbidity" and "health-related quality of life" for the most recent data cut-off. This is due to the fact that for the patient-reported outcomes in the present data situation, no significant gain in information can be assumed from the 3rd data cut-off.

Planned duration of follow-up observation

Table 9 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 9: Planned duration of follow-up observation – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole

Study **outcome category** **outcome**	**Planned follow-up observation**
PALOMA-2	
Mortality	
Overall survival	Until death, study discontinuation or until the final analysis on overall survival
Morbidity	
Health status (EQ-5D VAS)	Until treatment discontinuation
Health-related quality of life (FACT-B)	Until death, study discontinuation or until the final analysis on overall survival
Side effects	
All outcomes in the category of side effects	Until 28 days after treatment discontinuation
PALOMA-4	
Mortality	
Overall survival	Until death, withdrawal of consent, or loss to follow-up
Morbidity	
Health status (EQ-5D VAS)	Until treatment discontinuation or withdrawal of consent
Health-related quality of life (FACT-B)	Until treatment discontinuation or withdrawal of consent
Side effects	
All outcomes in the category of side effects	Until 28 days after treatment discontinuation
FACT-B: Functional Assessment of Cancer Therapy – Breast Cancer; RCT: randomized controlled trial; VAS: visual analogue scale	

According to information provided by the company in Module 4 A, health-related quality of life (recorded with FACT-B) was to be recorded after the end of treatment in both PALOMA-2 and PALOMA-4. The information on the study design in the study documents shows that this was planned in the PALOMA-2 study, but not in the PALOMA-4 study, contrary to the information in Module 4 A. The other information in Module 4 A and the study documents also do not show that a recording of health-related quality of life beyond the end of treatment was carried out in the PALOMA-4 study, contrary to the study protocol.

Therefore, it is assumed that the observation periods for health-related quality of life in the PALOMA-4 study were systematically shortened, because they were only recorded for the period of treatment with the study medication. To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record this outcome over the total period, as was the case for survival.

Although health-related quality of life was to be recorded beyond the end of treatment in the PALOMA-2 study, it cannot be inferred from the information provided by the company in the dossier whether the analyses presented by it included corresponding recordings on the unplanned 2nd data cut-off. A comparable situation already existed in the company's dossier for the previous benefit assessment of palbociclib in the present therapeutic indication for the analyses presented for the first data cut-off [11]. The data situation was already discussed in this procedure and the company subsequently submitted data in the framework of the commenting procedure, which, as described in the justification on the decision of the procedure, were also not usable for the benefit assessment, as it was an isolated analysis of data exclusively after progression [42]. Against this background, the fact that the company again does not address this in the current dossier is not appropriate. Since the analyses submitted by the company for the 2nd data cut-off for health-related quality of life cannot be used for the benefit assessment, as already described above, this remains without consequence for the present dossier assessment.

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

Characteristics of the study populations

Table 10 shows the characteristics of the patients in the studies included.

Table 10: Characteristics of the study populations as well as study/therapy discontinuation – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (multipage table)

Study characteristic category	PALOMA-2		PALOMA-4	
	palbociclib + letrozole	placebo + letrozole	palbociclib + letrozole	placebo + letrozole
	N[a] = 444	N[a] = 222	N[a] = 169	N[a] = 171
Age [years], mean (SD)	62 (11)	61 (11)	54 (9)	54 (9)
Ethnicity, n (%)				
White	344 (77)	172 (77)	0 (0)	0 (0)
Black	8 (2)	3 (1)	0 (0)	0 (0)
Asian	65 (15)	30 (14)	169 (100)	171 (100)
Other	27 (6)	17 (8)	0 (0)	0 (0)
Region, n (%)				
Europe	212 (48)	95 (43)	–	–
China	ND	ND	141 (83)	144 (84)
North America	168 (38)	99 (45)	–	–
Other	64 (14)[b]	28 (13)[b]	28 (17)[c]	27 (16)[c]
ECOG PS, n (%)				
0	257 (58)	102 (46)	84 (50)	81 (47)
1	178 (40)	117 (53)	85 (50)	90 (53)
2	9 (2)	2 (1)	0 (0)	0 (0)
Disease-free interval from the end of the (neo)adjuvant treatment to recurrence of the disease (based on randomization), n (%)				
De novo metastasised	148 (33)	74 (33)	34 (20)	32 (19)
≤ 12 months	89 (20)	44 (20)	55 (33)	54 (32)
> 12 months	207 (47)	104 (47)	80 (47)	85 (50)
Type of prior anticancer therapy in the (neo)adjuvant setting (at randomization), n (%)				
Hormonal therapy	253 (57)	127 (57)	102 (60)	104 (61)
No prior hormonal therapy	191 (43)	95 (43)	67 (40)	67 (39)
Prior chemotherapy in the (neo)adjuvant setting, n (%)				
Yes	213 (48)	109 (49)	126 (75)	129 (75)
No	231 (52)	113 (51)	43 (25)	42 (25)
Current disease stage, n (%)				
IIA	ND	ND	1 (1)	0 (0)
III	ND	ND	3 (2)	0 (0)
IIIB	ND	ND	3 (2)	1 (1)
IIIC	ND	ND	2 (1)	1 (1)
IV	ND	ND	157 (93)	166 (97)
Unknown	ND	ND	3 (2)	3 (2)

Table 10: Characteristics of the study populations as well as study/therapy discontinuation – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (multipage table)

Study characteristic category	PALOMA-2		PALOMA-4	
	palbociclib + letrozole	placebo + letrozole	palbociclib + letrozole	placebo + letrozole
	N[a] = 444	N[a] = 222	N[a] = 169	N[a] = 171
Type of recurrence, n (%)				
No recurrence	0 (0)[d]	0 (0)[d]	3 (2)	1 (1)
Recurrence, not specified in detail	0 (0)[d]	0 (0)[d]	23 (14)	29 (17)
Locoregional	2 (< 1)	2 (1)	0 (0)	1 (1)
Local	6 (1)	3 (1)	1 (1)	0 (0)
Regional	3 (1)	1 (< 1)	1 (1)	1 (1)
Distant metastasis	294 (66)	145 (65)	117 (69)	119 (70)
Newly diagnosed	139 (31)	71 (32)	21 (12)	19 (11)
Unknown	0 (0)[d]	0 (0)[d]	3 (2)	1 (1)
Site of metastases[e], n (%)				
Breast	137 (31)	74 (33)	36 (21)	30 (18)
Bones	325 (73)	162 (73)	97 (57)	108 (63)
Liver	75 (17)	46 (21)	31 (18)	29 (17)
Lungs	150 (34)	71 (32)	72 (43)	83 (49)
Lymph nodes	212 (48)	110 (50)	96 (57)	90 (53)
Treatment discontinuation[f], n (%)				
Discontinuation of palbociclib or placebo	401 (90.3)[g]	217 (97.7)[g]	135 (79.9)[d, h]	155 (90.6)[h]
Discontinuation of letrozole	399 (89.9)[i]	217 (97.7)[i]	135 (79.9)[d, j]	155 (90.6)[j]
Study discontinuation, n (%)	332 (74.8)[k]	178 (80.2)[k]	104 (61.5)[l]	98 (57.3)[l]

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 Australia.
c. Hong Kong, Singapore, Taiwan and Thailand.
d. Institute's calculation.
e. Sites that applied to > 20% of the patients in at least one study arm in at least one study.
f. Information on the number of patients who discontinued at least 1 or both components of the treatment, is not available for the relevant data cut-offs.
g. Data cut-off of 15 November 2021; most common reason for treatment discontinuation in the intervention vs. the control arm was disease progression/recurrence (272 vs. 172 patients).
h. Data cut-off of 31 August 2020; most common reason for treatment discontinuation in the intervention vs. the control arm was disease progression/recurrence (104 vs. 131 patients).
g. Data cut-off of 15 November 2021; most common reason for treatment discontinuation in the intervention vs. the control arm was disease progression/recurrence (281 vs. 171 patients).
j. Data cut-off of 31 August 2020; most common reason for treatment discontinuation in the intervention vs. the control arm was disease progression/recurrence (105 vs. 132 patients).
k. Data cut-off of 15 November 2021; most common reasons for study discontinuation in the intervention vs. the control arm were death (273 vs. 132 patients) and withdrawal of consent (41 vs. 28 patients).
l. Data cut-off of 31 August 2020; most common reasons for study discontinuation in the intervention vs. the control arm were death (79 vs. 86 patients) or lost to follow-up (9 vs. 7 patients).

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

The studies PALOMA-2 and PALOMA-4 are largely comparable regarding the composition of their patient populations. Differences exist mainly with regard to ethnicity, as only Asian patients were included in the PALOMA-4 study. The mean age of the patients in the PALOMA-2 study was about 60 years and they were thus slightly older than the patients in PALOMA-4 whose mean age was 54 years; patients aged > 70 years could not be included in the PALOMA-4 study. Almost all patients in both studies had an ECOG PS of 0 or 1. In the PALOMA-2 study, fewer patients had received previous chemotherapy in the (neo-)adjuvant setting than in the PALOMA-4 study (approx. 50% versus 75%), while in both studies a comparable proportion of patients had received hormonal therapy in the (neo-)adjuvant setting.

Information on the disease stage was only available for the PALOMA-4 study; according to this information, almost all patients had distant metastases (stage IV). Information on the type of recurrence is available for both studies, whereby the proportion of distant metastases is highest for both studies at over 65% each.

The proportions of patients who discontinued treatment differed both between the studies and between the study arms of both studies. Less patients in the intervention arm discontinued treatment with palbociclib or placebo or with letrozole than in the comparator arm of the respective study. The number of study discontinuations is higher in PALOMA-2 than in PaLOMA-4, but roughly comparable between the arms of each study.

Information on the course of the study

Table 11 shows the mean and median treatment durations of the patients and the mean and median observation periods for individual outcomes.

Table 11: Information on the course of the study – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole

Study **duration of the study phase** **outcome category**	**Palbociclib + letrozole**	**placebo + letrozole**
PALOMA-2 (data cut-off 15 November 2021)	N = 444	N = 222
Treatment duration [months]		
Median [Q1; Q3]	22.0 [9.8; 45.7]	13.8 [5.5; 28.1]
Mean (SD)	32.1 (29.1)	20.8 (21.6)
Observation period [months]		
Overall survival[a]		
Median [Q1; Q3]	48.1 [21.5; 87.7]	40.6 [24.8; 78.8]
Mean (SD)	51.8 (30.9)	48.2 (29.5)
Health status, health-related quality of life	N D[b]	N D[b]
Side effects		
Median [Q1; Q3]	23.0 [10.7; 46.6]	14.7 [6.5; 29.0]
Mean (SD)	32.9 (28.9)	21.7 (21.5)
PALOMA-4 (data cut-off 31 August 2020)	N = 168	N = 171
Treatment duration [months]		
Median [Q1; Q3]	19.5 [8.4; 38.7]	14.0 [7.4; 28.2]
Mean (SD)	24.2 (18.6)	19.3 (16.4)
Observation period [months]		
Overall survival[a]		
Median [Q1; Q3]	41.4 [24.6; 52.5]	45.1 [25.9; 52.5]
Mean (SD)	37.4 (17.3)	38.2 (16.9)
Health status (EQ-5D VAS)		
Median [Q1; Q3]	19.4 [8.5; 38.9]	14.0 [6.5; 28.2]
Mean (SD)	24.3 (18.3)	19.1 (16.2)
Health-related quality of life (FACT-B)		
Median [Q1; Q3]	19.4 [8.5; 38.9]	14.0 [6.5; 28.2]
Mean (SD)	24.3 (18.3)	19.1 (16.2)
Side effects		
Median [Q1; Q3]	20.4 [9.4; 39.6]	14.9 [7.9; 29.1]
Mean (SD)	24.9 (18.3)	20.1 (16.2)

a. The observation period was calculated on the basis of the observed time until censoring of all non-deceased patients.
b. No usable data available; for reasons see Section I 3.2 as well as Section I 4.1 of the full dossier assessment.

CI: confidence interval; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; max: maximum; min: minimum; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

In both studies, the treatment durations differed notably between the treatment arms (PALOMA-2: median 22 vs. 14 months, PALOMA-4: median 20 vs. 14 months). Overall, the

median and mean observation periods for the outcome of overall survival are largely comparable across both studies. Individual differences are shown in the median observation period of overall survival in the PALOMA-2 study.

For the outcomes on morbidity (health status) and health-related quality of life in the PALOMA-4 study, the median observation period in the intervention arm is significantly longer than in the comparator arm, while no usable data are available for the corresponding outcomes in the PALOMA-2 study (see Section I 3.2).

With the present benefit assessment, the company presented for the first time information on the median observation periods for the outcomes of side effects in the PALOMA-2 study. As in the PALOMA-4 study, the median observation period for the side effects is significantly longer in the intervention arm than in the comparator arm.

In the hearing on the previous benefit assessment of palbociclib in the present therapeutic indication, discrepancies in the information on the treatment duration in the dossier of the company at that time were discussed for the PALOMA-2 study [11]. Specifically, this concerned information on the duration of treatment compared to information on the number of patients at risk in the survival time analyses submitted by the company. Based on the data available for this procedure, it was assumed in the addendum to the previous benefit assessment that the observation period of patients for AEs was clearly longer than 28 days after the end of treatment and that the analyses on AEs submitted by the company cover the entire study period. Such discrepancies do not exist in the analyses submitted by the company for the present benefit assessment. However, the course of the number of patients at risk in the survival time analyses submitted by the company deviates between the former and the current dossier. In contrast to the assessment for the previous procedure, the information available for the current dossier shows that there is a systematic shortening of the follow-up observation of AEs.

Irrespective of this, the courses of the Kaplan-Meier curves presented by the company in Module 4 A of the dossier for the outcomes of sSAEs, severe AEs and discontinuation due to AEs in the studies PALOMA-2 and PALOMA-4 are implausible (for a detailed explanation, see Section I 4.3). For the present benefit assessment, usable Kaplan-Meier curves are therefore only available for other outcomes (overall survival, specific AEs).

Information on subsequent therapies

Table 12 and Table 13 show which subsequent antineoplastic therapies patients received after discontinuation of the study medication.

Table 12: Information on the first subsequent antineoplastic therapy (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (PALOMA-2 study)

Study **drug class** **drug**	**Patients with subsequent therapy n (%)**	
	palbociclib + letrozole **N = 444**	**placebo + letrozole** **N = 222**
PALOMA-2		
Total	322 (72.5)	190 (85.6)
Chemotherapy		
Capecitabine	36 (8.1)	17 (7.7)
Paclitaxel	28 (6.3)	17 (7.7)
Cyclophosphamide	9 (2.0)	8 (3.6)
Doxorubicin	6 (1.4)	6 (2.7)
Carboplatin	5 (1.1)	2 (0.9)
Docetaxel	4 (0.9)	4 (1.8)
Endocrine therapy		
fulvestrant	91 (20.5)	55 (24.8)
Letrozole	57 (12.8)	26 (11.7)
Exemestane	50 (11.3)	40 (18.0)
Tamoxifen	11 (2.5)	6 (2.7)
Tamoxifen citrate	7 (1.6)	1 (0.5)
Targeted therapy		
Everolimus	33 (7.4)	31 (14.0)
Palbociclib	18 (4.1)	18 (8.1)
Other		
Blinded therapy	9 (2.0)	11 (5.0)
Study medication	7 (1.6)	5 (2.3)

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

Table 13: Information on the first subsequent antineoplastic therapy (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (PALOMA-4 study)

Study **drug class** **drug**	**Patients with subsequent therapy n (%)**	
	palbociclib + letrozole **N = 169**	**placebo + letrozole** **N = 171**
PALOMA-4		
Total	85 (50.3)	116 (67.8)
Chemotherapy		
Capecitabine	24 (14.2)	22 (12.9)
Docetaxel	12 (7.1)	16 (9.4)
Paclitaxel	8 (4.7)	7 (4.1)
Cyclophosphamide	3 (1.8)	4 (2.3)
Vinorelbine	3 (1.8)	4 (2.3)
Epirubicin hydrochloride	3 (1.8)	0 (0)
Liposomal paclitaxel	2 (1.2)	2 (1.2)
Cisplatin	2 (1.2)	1 (0.6)
Xeloda[a]	1 (0.6)	6 (3.5)
Epirubicin	1 (0.6)	3 (1.8)
Gemcitabine	1 (0.6)	3 (1.8)
Doxorubicin	1 (0.6)	2 (1.2)
Pirarubicin	1 (0.6)	2 (1.2)
Vinorelbine tartrate	0 (0)	4 (2.3)
Endocrine therapy		
Exemestane	10 (5.9)	15 (8.8)
Fulvestrant	7 (4.1)	15 (8.8)
Letrozole	5 (3.0)	9 (5.3)
Tamoxifen	3 (1.8)	2 (1.2)
Anastrozole	2 (1.2)	0 (0)
Aromasin[b]	0 (0)	3 (1.8)
Fulvestrant injection	0 (0)	3 (1.8)
Targeted therapy		
Trastuzumab	2 (1.2)	0 (0)
Other		
Toremifene	5 (3.0)	3 (1.8)
Blinded therapy	2 (1.2)	4 (2.3)
Herbal product	1 (0.6)	4 (2.3)
Bicalutamide	0 (0)	2 (1.2)
Study medication	0 (0)	2 (1.2)

a. According to information by the company; Xeloda is a tradename of the drug capecitabine.
b. According to information by the company; Aromasin is a tradename of the drug exemestane.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial

After treatment discontinuation, patients could start subsequent therapy. In the PALOMA-2 study, a large proportion of patients (73% in the intervention arm vs. 86% in the comparator arm) had received at least 1 subsequent antineoplastic therapy at the current 3rd data cut-off. The most common subsequent therapies were endocrine therapies (mostly fulvestrant, letrozole or exemestane), followed by targeted therapies (mostly everolimus and palbociclib). Chemotherapy and endocrine therapies were used in approximately equal proportions in both study arms, while patients in the comparator arm more often received targeted therapy as subsequent therapy.

Compared with PALOMA-2, a smaller proportion of patients (50% in the intervention arm vs. 68% in the comparator arm) had received at least 1 subsequent antineoplastic therapy at the relevant data cut-off in the PALOMA-4 study. The most common subsequent therapy was chemotherapy (mostly with capecitabine, docetaxel or paclitaxel), whereas endocrine or targeted therapies were used less often than in the PALOMA-2 study. Chemotherapy was used in approximately equal proportions in both study arms, whereas endocrine therapy was used slightly more often in the comparator arm.

Chemotherapy was frequently used as second-line treatment in PALOMA-2 and especially in PALOMA-4. However, according to the current German S3 guideline, chemotherapy is not primarily recommended in the treatment situation of the present patient population [43]. After pretreatment with a non-steroidal aromatase inhibitor such as letrozole and a CDK4/6 inhibitor such as palbociclib, subsequent therapy with exemestane and everolimus can be carried out according to the S3 guideline. Depending on the pretreatment, another possible step is the use of anti-oestrogens, ER antagonists or a switch of the aromatase inhibitor from a non-steroidal to a steroidal aromatase inhibitor. These treatment options were used clearly more often in the intervention arm of PALOMA-2 than in the intervention arm of PALOMA-4.

According to the S3 guideline, such drug was to be used in further endocrine-based lines of treatment, if a CDK4/6 inhibitor such as abemaciclib, palbociclib or ribociclib had not been used in the first line yet. In the comparator arm of the PALOMA-2 and PALOMA-4 studies, this treatment recommendation was only implemented in a small proportion of patients.

Comparability of the studies PALOMA-2 and PALOMA-4 for the quantitative interpretation of the results

In Module 4 A, the company presents a meta-analysis with a fixed effect based on individual patient data (IPD) of the studies PALOMA-2 and PALOMA-4 and uses their results to derive the added benefit. The studies are largely comparable with regard to the study design, the inclusion and exclusion criteria and the characteristics of the patients included. Although there are differences with regard to ethnic group, age and prior chemotherapy in the (neo)adjuvant setting, the two studies are overall sufficiently comparable. Therefore, the meta-analysis with IPD presented by the company is used for the assessment.

Risk of bias across outcomes (study level)

Table 14 shows the risk of bias across outcomes (risk of bias at study level).

Table 14: Risk of bias across outcomes (study level) – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
PALOMA-2	Yes	Yes	Yes	Yes	Yes	Yes	Low
PALOMA-4	Yes	Yes	Yes	Yes	Yes	No[a]	High[b]

a. Strongly differing assessment of the progression by the investigators compared to a retrospectively conducted, blinded, independent central review (BICR); see following text section.
b. Due to additional aspects.
BICR: blinded independent central review; RCT: randomized controlled trial

The PALOMA-4 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 central review (BICR) conducted retrospectively. In comparison with the assessment by the investigators, the independent assessment confirmed 8% fewer events (14 of 169 patients) in the intervention arm and 27% fewer events (46 of 171 patients) in the comparator 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.

For the PALOMA-2 study, the company did not provide any information on the assessment of the progression by investigators and BICR for the 3rd data cut-off. However, for the 1st data cut-off, there are much less pronounced differences compared to the PALOMA-4 study (9% vs. 18% fewer events in the intervention vs. the comparator arm). This is confirmed when looking at the information on the unplanned 2nd data cut-off. The risk of bias at study level was rated as low for the PALOMA-2 study.

Transferability of the study results to the German health care context

According to the information provided by the company in Module 4 A, the results of the PALOMA-2 study are fully transferable to the German health care context. He justified this by stating that the use of palbociclib in the intended target group had been carried out in accordance with the SPC, guidelines and recommendations of medical professional societies. The age distribution in the study was consistent with the age distribution of the disease in the German population, where the median age of onset is 64 years. The majority (77.5%) of the patients in the study was white. Thus, the demographic factors of the included study population and the

German target population were largely the same. The company also discusses differences in the localisation of metastases and bone involvement in the patients in the PALOMA-2 study compared to patients registered in the Munich Cancer Registry (MCR) [44]. The company assumed transferability of the study results to the German health care context despite individual differences.

According to the company, the PALOMA-4 study was conducted exclusively in Asia, mainly in China. According to the company, this results in differences in the patient characteristics compared to the PALOMA-2 study, especially in the age of disease onset of the patients. According to the company, this is due to the fact that the PALOMA-4 study mostly included patients from China, in whom breast cancer tends to occur earlier than in Western countries. According to the company, the proportion of prognostically unfavourable visceral metastases is slightly higher in the PALOMA-4 study than in the PALOMA-2 study, while the proportion of prognostically more favourable bone metastases is somewhat lower than in the PALOMA-2 study. Thus, in the PALOMA-4 study - as in the PALOMA-2 study - there was no preferential selection of patients with prognostically more favourable metastases. The treatment of patients in China is based on the guideline of the Chinese Society for Clinical Oncology (CSCO) [45], which - like the German S3 guideline [43] - recommends stratified endocrine-based therapy under consideration of the prior therapy and is thus similar to the recommendations of the German guidelines. The treatment of postmenopausal women with locally advanced or metastatic breast cancer in first-line implemented in the PALOMA-4 study corresponded to the recommended treatment options stated in the guidelines and was reflected in the German treatment standard. With regard to the treatment of the patients in the present therapeutic indication, the results of the study were thus transferable to the German health care context.

In the opinion of the company, the results of the studies are consistent across all subgroups and no effect-modifying influences can be identified that could indicate significant uneven distribution within the studies. From the point of view of the company, the conditions under which the study participants could discontinue treatment in accordance with the protocol correspond to those in the clinical care.

In the opinion of the company, the PALOMA-2 study provides the strongest and most meaningful evidence on palbociclib in the present therapeutic indication for the German health care context; according to the company, the results of the PALOMA-4 study are sufficiently transferable to the German health care context with regard to the treatment of patients.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptoms
  - health status, recorded using the EQ-5D VAS
- health-related quality of life
  - fatigue (recorded using FACT)
- Side effects
  - SAEs
  - severe AEs, operationalized as Common Technology Criteria for Adverse Events [CTCAE] grade ≥ 3
  - discontinuation due to AEs
  - neutropenia, operationalized as Preferred Term (PT) in accordance with the Medical Dictionary for Regulatory Activities (MedDRA), CTCAE grade ≥ 3
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used further outcomes in the dossier (Module 4 A).

Table 15 shows the outcomes for which data were available in the studies included.

Table 15: Matrix of outcomes – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole

Study	Outcomes								
	Overall survival	Symptoms	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Neutropenia (PT, severe AEs[a])[c]	Further specific AEs[d]
PALOMA-2	Yes	No[e]	No[f]	No[f]	Yes	Yes	Yes	Yes	Yes
PALOMA-4	Yes	No[e]	Yes[f]	Yes[f]	Yes	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. Operationalized as discontinuation of palbociclib or placebo due to AEs; results on the discontinuation of all components due to AEs are presented as supplementary information.
c. The events neutropenia (PT, severe AE) and neutrophil count decreased (PT, severe AE) are defined in the studies PALOMA-2 and PALOMA-4 using identical criteria and are considered in the present data situation; for explanation see the running text below.
d. The following events (MedDRA coding) are considered: alopecia (PT, AEs), stomatitis (PT, AEs), general disorders and administration site conditions (SOC, severe AEs[a]), blood and lymphatic system disorders (SOC, severe AEs[a]) and investigations (SOC, severe AEs[a]).
e. Outcome not recorded.
f. No usable data available; in the dossier, the company did not present any analyses for the current 3rd data cut-off of the PALOMA-2 study of 15 November 2021 (see also Section I 3.2 of the present dossier assessment). Due to the incompleteness of the content of the analyses presented by the company for the PALOMA-2 study, the data of the PALOMA-4 study alone are not informative.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-B: Functional Assessment of Cancer Therapy – Breast Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Usability of the analyses presented by the company on the health status and health-related quality of life

As described in Section I 3.2, the analyses presented in the PALOMA-2 study for the patient-reported outcomes of the categories "morbidity" and "health-related quality of life" are incomplete in terms of content. In contrast to the present analyses of the PALOMA-4 study, these outcomes were also partly recorded beyond the end of the study treatment in PALOMA-2. Overall, there are no usable data for the patient-reported outcomes of the categories of morbidity and health-related quality of life in the company's dossier due to the incompleteness of the contents of the PALOMA-2 study. A supplementary presentation of the results of the PALOMA-4 study can be found in I Appendix D of the full dossier assessment.

For the outcomes on health status (assessed using EQ-5D VAS) and health-related quality of life (assessed using FACT-B), the company presented event time analyses for the time to first deterioration for the PALOMA-4 study using the following response criteria:

- EQ-5D VAS: in each case deterioration by ≥ 10 points and ≥ 15% scale range (scale range of EQ-5D VAS: 0 to 100 points)
- FACT-B: in each case deterioration by ≥ 7 points and ≥ 15% scale range (scale range of the FACT-B: 0 to 148 points)

As explained in the *General Methods* of the Institute [46,47], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). Accordingly, the results for deterioration by ≥ 15% of the scale range are presented as supplementary information for the outcomes "EQ-5D VAS" and "FACT-B". As described above, this is only done for the PALOMA-4 study.

Discontinuation due to AEs

In Module 4 A of the dossier, the company shows analyses on AEs for the studies PALOMA-2 and PALOMA-4 that led to the discontinuation of palbociclib or placebo, as well as analyses on AEs that led to the discontinuation of all drug components. Analyses on the discontinuation of ≥ 1 drug component are to be preferred, as any AE leading to the discontinuation of any treatment component is relevant. However, the company did not present analyses on this operationalization in Module 4 A of the dossier. Therefore, in the present situation, the operationalization "discontinuation of palbociclib or placebo due to AEs" is used as an approximation. The operationalization "discontinuation of all drug components due to AEs" is presented as supplementary information.

Neutropenia

According to the study documents of PALOMA-2 and PALOMA-4, the event of neutropenia (PT, severe AE) is defined as absolute neutrophil count < 1000/mm³. This definition corresponds to that of the event "neutrophil count decreased" (PT, severe AE) according to CTCAE criteria. As a large proportion of patients with event was recorded for both PTs, both PTs are used for the benefit assessment in the present data situation.

I 4.2 Risk of bias

Table 16 describes the risk of bias for the results of the relevant outcomes.

Table 16: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole

Study	Study level	Outcomes								
		Overall survival	Symptoms	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	SAEs	Severe AEs[a]	Discontinuation due to AEs[b]	Neutropenia (PT, severe AEs[a])[c]	Further specific AEs[d]
PALOMA-2	L	L	–[e]	–[f]	–[f]	H[g]	H[g]	L[h]	H[g]	H[g]
PALOMA-4	H[i]	H[i]	–[e]	–[f]	–[f]	H[g, i]	H[g, i]	H[i]	H[g, i]	H[g, i]

a. Severe AEs are operationalized as CTCAE ≥ 3.
b. Operationalized as discontinuation of palbociclib or placebo due to AEs; results on the discontinuation of all drug components due to AEs are presented as supplementary information.
c. In the studies PALOMA-2 and PALOMA-4, the events of neutropenia (PT, severe AE) and neutrophil count decreased (PT, severe AE) are defined using identical criteria and are considered in the present data situation; for explanation see Section I 4.1.
d. The following events (MedDRA coding) are considered: alopecia (PT, AEs), stomatitis (PT, AEs), general disorders and administration site conditions (SOC, severe AEs[a]), blood and lymphatic system disorders (SOC, severe AEs[a]) and investigations (SOC, severe AEs[a]).
e. Outcome not recorded.
f. No usable data available; in the dossier, the company did not present any analyses for the current 3rd data cut-off of the PALOMA-2 study of 15 November 2021 (see also Section I 3.2 of the present dossier assessment). Due to the incompleteness of the content of the analyses presented by the company for the PALOMA-2 study, the data of the PALOMA-4 study alone are not informative. Therefore, a comprehensive assessment of the risk of bias is not provided for the corresponding results of the PALOMA-4 study.
g. Large proportion of potentially informative censoring.
h. Despite low risk of bias, the certainty of results for the outcome of discontinuation due to AEs is assumed to be limited (see running text below).
i. High risk of bias at study level.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-B: Functional Assessment of Cancer Therapy – Breast Cancer; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

In the PALOMA-2 study, there was a high risk of bias for all outcomes except "overall survival" and "discontinuation due to AEs" because of the high proportion of potentially informative censoring.

In the PALOMA-4 study, the results on all 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 I 3.2). Secondly, there is a high

proportion of potentially informative censorings for all outcomes except “overall survival” and “discontinuation due to AEs”.

For the outcome of discontinuation due to AEs, the certainty of results is limited in both studies, irrespective of the respective low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome to be recorded, discontinuation due to AEs. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It is impossible to estimate the number of AEs to which this applies.

For the outcomes of the categories of morbidity (health status) and health-related quality of life, no usable data are available for the benefit assessment (for explanation see Sections I 3.2 and Section I 4.1). Hence, the risk of bias of the results is not assessed for these outcomes.

Summary assessment of the certainty of conclusions

As described in Section I 3.2, the assessment is based on the quantitative meta-analytical summary of the results of the studies PALOMA-2 and PALOMA-4. Due to the size of the effect as well as the early occurrence of the events in the course of the study, before censoring sets in to a critical extent, there is a high certainty of results for some outcomes from the PALOMA-2 study despite a high risk of bias (see following section). For the PALOMA-4 study, however, no high certainty of results can be achieved even in such cases due to the bias aspect at study level. Those results of the PALOMA-2 study, which show a high certainty of results, cannot be weakened by adding the results from the PALOMA-4 study, but at best can be enhanced. Therefore, on the basis of the meta-analysis, at most proofs, e.g. of an added benefit, can be derived for those outcomes for which there is a high certainty of results in the PALOMA-2 study, and at most indications for all other outcomes.

I 4.3 Results

Table 17 summarizes the results for the comparison of palbociclib + letrozole with placebo + letrozole in postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in the first-line treatment. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

The Kaplan-Meier curves on the included outcomes are presented in I Appendix B, the results on common AEs, SAEs, and discontinuations due to AEs in I Appendix C, and supplementary results of the studies PALOMA-4 study on the outcomes of health status and health-related quality of life in I Appendix D of the full dossier assessment.

As already described in Section I 3.2, the courses of the Kaplan-Meier curves presented by the company in Module 4 A of the dossier for the outcomes of SAEs, severe AEs and discontinuation due to AEs in the studies PALOMA-2 and PALOMA-4 are implausible, as the courses presented obviously do not match the values presented by the company in the result tables. For example, the median time to event, which, according to information of the company

in Module 4 A, is estimated by the Kaplan-Meier method, is 0.7 months for the outcome of severe AEs in the intervention arm of the PALOMA-4 study. However, the corresponding Kaplan-Meier curve in Module 4 A of the dossier would result in a median time of about 24 months (see Module 4 A p. 1241 [48]). The courses of the Kaplan-Meier curves for further outcomes (overall survival, specific AEs) appear plausible when compared with the results submitted by the company and are presented in I Appendix B.

Table 17: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (multipage table)

Outcome category outcome study	Palbociclib + letrozole N	Palbociclib + letrozole median time to event in months [95% CI] patients with event n (%)	Placebo + letrozole N	Placebo + letrozole median time to event in months [95% CI] patients with event n (%)	Palbociclib + letrozole vs. placebo + letrozole HR [95 % CI]; p-value[a]
Mortality					
Overall survival					
PALOMA-2[b]	444	53.9 [49.8; 60.8] 273 (61.5)	222	51.2 [43.7; 58.9] 132 (59.5)	0.96 [0.78; 1.18]; 0.676
PALOMA-4[b]	169	51.7 [43.0; NC] 79 (46.7)	171	51.5 [41.0; NC] 86 (50.3)	0.95 [0.70; 1.29]; 0.730
Total[c]					0.95 [0.80; 1.13]; 0.589
Morbidity					
Health status (EQ-5D VAS)					
PALOMA-2[b]				No usable data[d]	
PALOMA-4[b]				No usable data[e]	
Health-related quality of life					
FACT-B					
PALOMA-2[b]				No usable data[d]	
PALOMA-4[b]				No usable data[e]	
Side effects					
AEs (supplementary information)					
PALOMA-2[b, f]	444	0.4 [0.3; 0.5] 440 (99.1)	222	0.4 [0.3; 0.5] 213 (95.9)	–
PALOMA-4[b, f]	168	0.5 [NC] 168 (100)	171	1.0 [0.7; 1.4] 155 (90.6)	–
SAEs					
PALOMA-2[b, f]	444	94.2 [65.5; NC] 121 (27.3)	222	85.7 [72.7; NC] 38 (17.1)	1.30 [0.90; 1.87]; 0.166
PALOMA-4[b, f]	168	NA 26 (15.5)	171	NA 16 (9.4)	1.50 [0.80; 2.81]; 0.200
Total[c, f]					1.35 [0.98; 1.85]; 0.066
Severe AEs[g]					
PALOMA-2[b, f]	444	1.0 [1.0; 1.4] 369 (83.1)	222	67.4 [31.4; NC] 69 (31.1)	4.65 [3.59; 6.03]; < 0.001
PALOMA-4[b, f]	168	0.7 [0.5; 0.7] 153 (91.1)	171	NA [52.5; NC] 38 (22.2)	11.29 [7.73; 16.47]; < 0.001
Total[c, f]					6.50 [5.22; 8.09]; < 0.001[h]

Table 17: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (multipage table)

Outcome category outcome study	Palbociclib + letrozole N	Palbociclib + letrozole median time to event in months [95% CI] patients with event n (%)	Placebo + letrozole N	Placebo + letrozole median time to event in months [95% CI] patients with event n (%)	Palbociclib + letrozole vs. placebo + letrozole HR [95 % CI]; p-value[a]
Discontinuation due to AEs					
Discontinuation of palbociclib or placebo due to AEs					
PALOMA-2[b, f]	444	NA 63 (14.2)	222	NA [85.7; NC] 13 (5.9)	1.79 [0.98; 3.27]; 0.054
PALOMA-4[b, f]	168	NA 11 (6.5)	171	NA 4 (2.3)	2.28 [0.72; 7.21]; 0.149
Total[c, f]					1.89 [1.11; 3.23]; 0.018
Discontinuation of all drug components due to AEs (presented as supplementary information)					
PALOMA-2[b, f]	*444*	*NA* *39 (8.8)*	*222*	*NA [85.7; NC]* *12 (5.4)*	*1.19 [0.62; 2.28]; 0.606*
PALOMA-4[b, f]	168	*NA* *10 (6.0)*	*171*	*NA* *3 (1.8)*	*2.79 [0.76; 10.21]; 0.105*
Total[c, f]					*1.45 [0.81; 2.62]; 0.211*
Specific AEs					
Alopecia (PT, AE)					
PALOMA-2[b]	444	NA 150 (33.8)	222	NA 36 (16.2)	2.00 [1.39; 2.88]; < 0.001
PALOMA-4[b]	168	NA 20 (11.9)	171	NA 11 (6.4)	1.84 [0.88; 3.85]; 0.098
Total[c]					1.97 [1.42; 2.73]; < 0.001
Stomatitis (PT, AE)					
PALOMA-2[b]	444	NA 76 (17.1)	222	NA 15 (6.8)	2.39 [1.37; 4.16]; 0.002
PALOMA-4[b]	168	NA 5 (3.0)	171	NA 3 (1.8)	1.56 [0.37; 6.56]; 0.538
Total[c]					2.28 [1.37; 3.81]; 0.001
General disorders and administration site conditions (SOC, severe AE[g])					
PALOMA-2[b]	444	NA 50 (11.3)	222	NA 6 (2.7)	3.30 [1.41; 7.71]; 0.004
PALOMA-4[b]	168	NA 9 (5.4)	171	NA 2 (1.2)	4.45 [< 0.96; 20.59], 0.037[i]
Total[c]					3.56 [1.69; 7.51]; < 0.001

Table 17: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (multipage table)

Outcome category outcome study	Palbociclib + letrozole N	Palbociclib + letrozole median time to event in months [95% CI] patients with event n (%)	Placebo + letrozole N	Placebo + letrozole median time to event in months [95% CI] patients with event n (%)	Palbociclib + letrozole vs. placebo + letrozole HR [95 % CI]; p-value[a]
Blood and lymphatic system disorders (SOC, severe AE[g])					
PALOMA-2[b]	444	6.4 [2.8; 10.2] 280 (63.1)	222	NA 7 (3.2)	28.49 [13.46; 60.34]; < 0.001
PALOMA-4[b]	168	41.6 [23.3; NC] 71 (42.3)	171	NA 3 (1.8)	29.43 [9.27; 93.47]; < 0.001
Total[c]					28.77 [15.33; 53.99]; < 0.001
Including: neutropenia (PT, severe AE[g])[j]					
PALOMA-2[b]	444	9.2 [4.6; 14.3] 261 (58.8)	222	NA 2 (0.9)	90.24 [22.46; 362.59]; < 0.001
PALOMA-4[b]	168	NA [30.8; NC] 63 (37.5)	171	NA 0 (0)	NC[k]
Total[c]					128.31 [31.94; 515.45]; < 0.001
Investigations (SOC, severe AE[g])					
PALOMA-2[b]	444	NA [88.2; NC] 129 (29.1)	222	NA 7 (3.2)	9.33 [4.36; 19.97]; < 0.001
PALOMA-4[b]	168	1.0 [0.7; 17.0] 108 (64.3)	171	NA 13 (7.6)	12.77 [7.17; 22.75]; < 0.001
Total[c]					11.50 [7.24; 18.25]; < 0.001
Including: neutrophil count decreased (PT, severe AE[g])[j]					
PALOMA-2[b]	444	NA 79 (17.8)	222	NA 1 (0.5)	38.47 [5.35; 276.58]; < 0.001
PALOMA-4[b]	168	16.9 [0.8; NA] 89 (53.0)	171	NA 2 (1.2)	61.55 [15.15; 249.98]; < 0.001
Total[c]					53.79 [17.13; 168.90]; < 0.001

Table 17: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (multipage table)

Outcome category outcome study	Palbociclib + letrozole		Placebo + letrozole		Palbociclib + letrozole vs. placebo + letrozole
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95 % CI]; p-value[a]

a. Effect and 95% CI: Cox proportional hazards model, stratified by the presence of visceral metastases (yes vs. no); p-value: 2-sided log-rank test.
b. Data cut-off: PALOMA-2 study: 15 November 2021, PALOMA-4 study: 31 August 2020.
c. Meta-analysis based on individual patient data.
d. In the dossier, the company did not present any analyses for the current 3rd data cut-off of the PALOMA-2 study of 15 November 2021 (see also Section I 3.2 of the present dossier assessment).
e. Due to the incompleteness of the content of the analyses presented by the company for the PALOMA-2 study, the data of the PALOMA-4 study alone are not informative.
f. Without progression events (PT breast cancer, PT breast cancer with metastases, PT neoplasm of the mammary gland).
g. Operationalized as CTCAE grade ≥ 3.
h. In the present data situation (2 studies; clear results in both studies), the joint effect estimate is presented despite statistically significant heterogeneity ($p < 0.001$).
i. Discrepancy between CI and p-value due to different calculation methods.
j. In the studies PALOMA-2 and PALOMA-4, the events of neutropenia (PT, severe AE) and neutrophil count decreased (PT, severe AE) are defined using identical criteria and are considered in the present data situation; for explanation see Section I 4.1.
k. Since no events occurred in one study arm, the HR cannot be estimated.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACT-B: Functional Assessment of Cancer Therapy – Breast Cancer; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

As described in Section I 4.2, due to the size of the effect as well as the early occurrence of the events in the course of the study, before censoring sets in to a critical extent, there is a high certainty of results for some outcomes from the PALOMA-2 study despite a high risk of bias. On the basis of the available information, at most proofs, e.g. of an added benefit, can therefore be derived for these outcomes and for the outcome of overall survival, and at most indications for all other outcomes (for a detailed explanation, see Section I 4.2).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. Hence, there was no hint of an added benefit of palbociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

Morbidity

Health status (recorded with the EQ-5D VAS)

For the outcome of health status (recorded with the EQ-5D VAS), the dossier provides results on the current data cut-off only for the PALOMA-4 study. However, considered for this outcome alone, these are not meaningful due to the incompleteness of the content with regard to the results of the PALOMA-2 study. Therefore, no usable data are available for this outcome. This resulted in no hint of an added benefit of palbociclib + letrozole in comparison with letrozole for the outcome “health status” (recorded with the EQ-5D VAS); an added benefit is therefore not proven.

Health-related quality of life (recorded with the FACT-B)

For the outcome of health-related quality of life (recorded with the FACT-B), the dossier provides results on the current data cut-off only for the PALOMA-4 study. However, considered for this outcome alone, these are not meaningful due to the incompleteness of the content with regard to the results of the PALOMA-2 study. Therefore, no usable data are available for this outcome. This resulted in no hint of an added benefit of palbociclib + letrozole in comparison with letrozole for health-related quality of life (recorded with the FACT-B); an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". Hence, there was no hint of greater or lesser harm from palbociclib + letrozole in comparison with letrozole; greater or lesser harm is therefore not proven.

Severe AEs

A statistically significant difference to the disadvantage of palbociclib + letrozole was shown for the outcome "severe AEs". Implausible Kaplan-Meier curves are available for this outcome. However, since in the PALOMA-2 study, the course of the Kaplan-Meier curves for this outcome is assumed to be similar to the one of those specific AEs that significantly determine the outcome “severe AEs” according to the frequencies of events and whose Kaplan-Meier curves are plausible, a high certainty of results is assumed for the large effect of severe AEs in the PALOMA-2 study despite a high risk of bias. Therefore, this resulted in a proof of greater harm from palbociclib + letrozole in comparison with letrozole for this outcome.

Discontinuation due to AEs (discontinuation of palbociclib or placebo)

A statistically significant difference to the disadvantage of palbociclib + letrozole was shown for the outcome "discontinuation due to AEs” (discontinuation of palbociclib or placebo). This resulted in an indication of greater harm of palbociclib + letrozole in comparison with letrozole for this outcome.

Specific AEs

AEs: alopecia and stomatitis

A statistically significant difference to the disadvantage of palbociclib + letrozole was shown for the specific AEs “alopecia” and “stomatitis”. This resulted in an indication of greater harm of palbociclib + letrozole in comparison with letrozole for these outcomes.

Severe AEs: general disorders and administration site conditions

A statistically significant difference to the disadvantage of palbociclib + letrozole was shown for the specific severe AE "general disorders and administration site conditions". This resulted in an indication of greater harm of palbociclib + letrozole in comparison with letrozole for this outcome.

Severe AEs: blood and lymphatic system disorders (including: neutropenia) and examinations (including: neutrophil count decreased)

A statistically significant difference to the disadvantage of palbociclib + letrozole was shown for the specific severe AEs “blood and lymphatic system disorders” (including: “neutropenia”) and “examinations” (including: neutrophil count decreased). Due to the size of the respective effect as well as the early occurrence of the events of these outcomes in the course of the study, before censoring sets in to a critical extent, there is a high certainty of results in the PALOMA-2 study despite a high risk of bias. Therefore, there is proof of greater harm from palbociclib + letrozole in comparison with letrozole for each of these outcomes.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present benefit assessment:

- age (< 65 years, ≥ 65 years)
- visceral metastases (yes, no)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least 1 subgroup.

Presented are only the results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05). In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results did not show any effect modifications.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, 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 the 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.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Chapter I 4 (see Table 18).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier whether the following side effects outcome is serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Discontinuation due to AEs

For the outcome of discontinuation due to AEs in the PALOMA-2 study, information in the study documents indicates that AEs leading to the discontinuation of ≥ 1 drug component were severe AEs in 60% (26 of 43) of events in the intervention arm and 69% (9 of 13) of events in the comparator arm at the 1st data cut-off. According to the information in the study documents on the first data cut-off, the events leading to discontinuation of palbociclib or placebo were severe AEs in 56% (23 of 41) of events in the intervention arm and 67% (8 of 12) of events in the comparator arm. The dossier provides no information on the severity for events that led to the discontinuation of all drug components. Likewise, no information on the severity of events leading to the outcome of discontinuation due to AEs is available in the dossier for the current 3rd data cut-off. However, it is not plausible that the distribution changes significantly at the 3rd data cut-off or with a different operationalization. For the present benefit assessment, it is assumed that in the PALOMA-2 study, discontinuations due to AEs at the 3rd data cut-off were also predominantly due to severe AEs, irrespective of the operationalization.

For the outcome of discontinuation due to AEs in the PALOMA-4 study, information in the study documents indicates that AEs leading to the discontinuation of ≥ 1 drug component were severe AEs in 77% (10 of 13) of events in the intervention arm and 80% (4 of 5) of events in the comparator arm. The dossier provides no information on the severity for events that led to the discontinuation of palbociclib or placebo or to the discontinuation of all drug components. However, the available data show that in the PALOMA-4 study, the proportions of patients with events did not differ significantly between the different operationalizations of the outcome "discontinuation due to AEs" (see Table 17). It is therefore assumed that in the PALOMA-4 study, discontinuations due to AEs were predominantly due to severe AEs, irrespective of the operationalization.

For the present benefit assessment, the outcome of discontinuation due to AEs (operationalized via the discontinuation of palbociclib or placebo due to AEs or via the discontinuation of all drug components due to AEs) is therefore overall assigned to the outcome category of serious/severe AEs on the basis of the available data on the two studies.

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

Outcome category **outcome**	**Palbociclib + letrozole vs. placebo + letrozole** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Total observation period		
Mortality		
Overall survival	51.7-53.9 vs. 51.2-51.5 HR: 0.95 [0.80; 1.13] p = 0.589	Lesser/added benefit not proven
Shortened observation period		
Morbidity		
Health status (EQ-5D VAS)	No usable data	Lesser/added benefit not proven
Health-related quality of life		
FACT-B	No usable data	Lesser/added benefit not proven
Side effects		
SAEs	94.2–NA vs. 85.7–NA HR: 1.35 [0.98; 1.85] p = 0.066	Greater/lesser harm not proven
Severe AEs	0.7–1.0 vs. 67.4–NA HR: 6.50 [5.22; 8.09] HR: 0.15 [0.12; 0.19][c] p < 0.001 probability: “proof[d]”	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm; extent: “major”
Discontinuation due to AEs (discontinuation of palbociclib or placebo)	NA vs. NA HR: 1.89 [1.11; 3.23] HR: 0.53 [0.31; 0.90][c] p = 0.018 probability: "indication”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm; extent: “minor”
Alopecia (AEs)	NA vs. NA HR: 1.97 [1.42; 2.73] HR: 0.51 [0.37; 0.70][c] p < 0.001 probability: “indication”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
stomatitis (AEs)	NA vs. NA HR: 2.28 [1.37; 3.81] HR: 0.44 [0.26; 0.73][c] p = 0.001 probability: "indication”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”

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

Outcome category **outcome**	**Palbociclib + letrozole vs. placebo + letrozole** **median time to event (months)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
General disorders and administration site conditions (severe AEs)	NA vs. NA HR: 3.56 [1.69; 7.51] HR: 0.28 [0.13; 0.59][c] p < 0.001 probability: indication	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm; extent: "major"
Blood and lymphatic system disorders (severe AEs) Including: neutropenia (severe AEs)	6.4-41.6 vs. NA HR: 28.77 [15.33; 53.99] HR: 0.03 [0.02; 0.07][c] p < 0.001 probability: "proof[d]" 9.2–NA vs. NA HR: 128.31 [31.94; 515.45] HR: 0.01 [< 0.01; 0.03][c] p < 0.001 probability: "proof[d]"	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm; extent: "major"
Examinations (severe AEs) Including: neutrophil count decreased (severe AEs)	1.0–NA vs. NA HR: 11.50 [7.24; 18.25] HR: 0.09 [0.05; 0.14][c] p < 0.001 probability: "proof[d]" 16.9–NA vs. NA HR: 53.79 [17.13; 168.90] HR: 0.02 [0.01; 0.06][c] p < 0.001 probability: "proof"[d]	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5% greater harm; extent: "major"

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. Due to the size of the effect and the early occurrence of the events, the certainty of results is not downgraded despite the high risk of bias (see Section I 4.3).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; HR: hazard ratio; NA: not achieved; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results included 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
Total observation period	
–	–
Shortened observation period	
–	Serious/severe side effects ▪ severe AEs: proof of greater harm – extent: “major” ▫ specific AEs: - general disorders and administration site conditions: indication of greater harm – extent: "major" - blood and lymphatic system disorders (including: neutropenia) and investigations (including: neutrophil count decreased) (severe AEs): in each case proof of greater harm – extent: "major" ▪ discontinuation due to AEs (discontinuation of palbociclib or placebo): indication of greater harm – extent: “minor”
–	Non-serious/non-severe side effects ▪ specific AEs: ▫ alopecia and stomatitis (AEs): indication of greater harm – extent: “considerable”
The data on morbidity and health-related quality of life from the PALOMA-2 study presented by the company are not usable. Due to the incompleteness of the content of the analyses presented by the company for the PALOMA-2 study, the data of the PALOMA-4 study on the respective outcomes alone are not informative. Therefore, no usable data are available for these outcomes overall.	
AE: adverse event; SAE: serious adverse event	

The overall assessment showed only negative effects of palbociclib + letrozole in comparison with letrozole. All these negative effects are related to outcomes in the category of side effects and only refer to the shortened time period until 28 days after discontinuation of treatment.

In the outcome category of serious/severe side effects, proofs a greater harm with the extent “considerable” are shown for severe AEs as well as for various specific AEs included therein. In the present situation, this includes the specific severe AEs blood and lymphatic system disorders (included: neutropenia) and examinations (included: neutrophil count decreased) related in terms of content. For other serious/severe outcomes, including discontinuation due to AEs (discontinuation of palbociclib or placebo), there are indications of greater harm. Moreover, in the outcome category of non-serious/non-severe side effects, indications of greater harm with the extent “considerable” are shown for the specific AEs alopecia and stomatitis.

In summary, there is proof of lesser benefit of palbociclib + letrozole versus the letrozole for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in the first-line setting.

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

Table 20: Palbociclib in combination with an aromatase inhibitor – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in first-line therapy[b, c]	▪ Anastrozole or ▪ **letrozole** or ▪ fulvestrant or ▪ possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ ribociclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ abemaciclib in combination with a nonsteroidal aromatase inhibitor (anastrozole, letrozole) or ▪ ribociclib in combination with fulvestrant or ▪ abemaciclib in combination with fulvestrant or ▪ palbociclib in combination with fulvestrant	Proof of lesser benefit[d]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. According to the G-BA, it is assumed for the present therapeutic indication that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. For this benefit assessment, first-line therapy is defined as the initial endocrine-based therapy of locally advanced or metastatic breast cancer.
d. Almost only patients with an ECOG PS of 0 or 1 were included in the studies PALOMA-2 and PALOMA-4. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor

The assessment described above deviates from that of the company, which derived an indication of minor added benefit.

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

Supplementary information on the implementation of the conditions of the limitation

The G-BA's justification on the first assessment of palbociclib included the following statement:

For the new benefit assessment after expiry of the decision, the final study results from the ongoing PALOMA-2 study for all outcomes used to prove an added benefit were to be presented in the dossier.

The company did not fully meet these requirements in the present dossier.

In its dossier, the company does not present the final study results of the 3rd data cut-off of the PALOMA-2 study for the patient-reported outcomes of morbidity (health status) and health-related quality of life, but instead uses the results of the 2nd data cut-off. As explained in Section I 3.2, this leads to incomplete information in terms of content being provided in the dossier, which, however, remains without consequence for the benefit assessment in the present data situation.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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