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Palbociclib (breast cancer) –

Addendum to Commission A16-74[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PFS	progression-free survival
PRO	patient-reported outcome
QLQ-C30	Quality of Life Questionnaire - Core 30
QLQ-BR23	Quality of Life Questionnaire - Breast Cancer Module
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
STE	surrogate threshold effect
TTP	time to progression

1 Background

On 12 April 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-74 (Palbociclib – Benefit assessment according to §35a Social Code Book V [1]).

In its written comments from 23 March 2017 [2], the pharmaceutical company (hereinafter referred to as "the company") submitted further data on the studies PALOMA-2 and PALOMA-3, which went beyond the information provided in the dossier on palbociclib [3].

The G-BA's commission comprised the following aspects:

Study PALOMA-3

- analysis of the study results under consideration of the additional analyses in the company's comments and under consideration of the information provided in the dossier

Study PALOMA-2

- assessment of the additional analyses of adverse events (AEs) in the company's comments under consideration of the information provided in the dossier

Outcomes "progression-free survival (PFS)" and "time to first (intravenous) chemotherapy" for the studies PALOMA-2 and PALOMA-3

- methodological assessment of the outcomes and presentation of the results based on this assessment

Validation of the surrogate outcome "PFS"

- assessment of the additional analyses for the validation of the surrogate outcome "PFS" for overall survival from the company's comments under consideration of the information provided in the dossier.

The responsibility for the present assessment and the assessment results lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The individual aspects commissioned by the G-BA are assessed in the following sections as follows:

- Section 2.1: Assessment of the results of the PALOMA-3 study
- Section 2.2: Assessment of the additional analyses on AEs of the PALOMA-2 study
- Section 2.3: Assessment of the outcomes "PFS" and "time to first (intravenous) chemotherapy" for the studies PALOMA-2 and PALOMA-3
- Section 2.4: Assessment of the additional analyses for validating the surrogate outcome "PFS"

2.1 Assessment of the results of the PALOMA-3 study

The PALOMA-3 study was a randomized controlled trial (RCT) comparing the combination of palbociclib + fulvestrant with fulvestrant. The company had used this study in its dossier to determine the added benefit of palbociclib in comparison with fulvestrant in women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer who have received prior endocrine therapy (research questions B1 and B2 of dossier assessment A16-74 on palbociclib [1]). The PALOMA-3 study had not been included in the dossier assessment on palbociclib because fulvestrant did not constitute an implementation of the appropriate comparator therapy (ACT) for both research questions. Treatment with fulvestrant is not approved for the population B1. Upon request, this was confirmed by the German regulatory authority Federal Institute for Drugs and Medical Devices (BfArM) [4]. For the population B2, fulvestrant did not constitute an implementation of endocrine therapy specified by the physician under consideration of the approval status (for more details, see dossier assessment A16-74 on palbociclib [1]). This assessment was not changed by the data on the PALOMA-3 study subsequently submitted by the company.

2.1.1 Data cut-offs for the PALOMA-3 study and consequences for the assessment

The company presented results on 4 different data cut-offs for the PALOMA-3 study. The data provided by the company were incomplete, however, because the company did not provide the complete results on patient-relevant outcomes for all data cut-offs.

Data cut-off on 5 December 2014

The clinical study report (CSR) of the PALOMA-3 study presented in Module 5 of the company's dossier was based on the first data cut-off on 5 December 2014. It contained information on all patient-relevant outcomes of the study and on progression-free survival (PFS). The analyses on specific AEs were incomplete, however. In its comments, the company only subsequently submitted data on this data cut-off. These data concerned AEs and patient-reported outcomes (PROs). These subsequently submitted data were again

selective and incomplete for AEs (see Section 2.1.2) and not usable for PROs (see Section 2.1.3).

Data cut-off on 16 March 2015

Following a request by the G-BA, after submission of the dossier, the company subsequently submitted results for the second data cut-off on 16 March 2015. The company presented an update of the PFS analysis and relative frequencies of deaths up to this time point, but no Kaplan-Meier analysis of overall survival. There were also no results on other outcomes including symptoms, quality of life and AEs.

Data cut-off on 31 July 2015

With its dossier, the company also submitted results on the third data cut-off on 31 July 2015. With these results, the company only presented information on AEs that it had also reported for the first data cut-off on 5 December 2014. Data on further AEs and on further outcomes including mortality, PFS, symptoms and quality of life were lacking.

Data cut-off on 23 October 2015

In Module 5 of its dossier, the company had also submitted results on the fourth data cut-off on 23 October 2015. These were another update of the PFS analysis and relative frequencies of deaths up to this time point, but also no Kaplan-Meier analysis of overall survival. Again, there were also no results on other outcomes including symptoms, quality of life and AEs.

Consequences for the assessment of the PALOMA-3 study

The presentation of the data available for the individual data cut-offs shows that the company presented only rudimentary data for the 3 most recent data cut-offs and that the data presented for the first data cut-off were also incomplete. For the first data cut-off on 5 December 2014, results were available for all patient-relevant outcomes (overall survival, morbidity, health-related quality of life and AEs); the analyses on specific AEs were selective, however. For the following 3 data cut-offs, the company only presented analyses on PFS and deaths (second and fourth data cut-off) or selectively for individual AEs.

The described incompleteness of the data provided was relevant for the assessment. Table 1 shows a comparison of the available results on the overall rates of AEs between the first data cut-off on 5 December 2014 and the third data cut-off on 31 July 2015. It also compares results of both data cut-offs as examples for some specific AEs. This comparison shows that an important number of patient-relevant events (in this case AEs) also occurred after the first data cut-off. Consequently, the analyses on health-related quality of life and on symptoms at the data cut-off on 5 December 2014, and thus the data cut-off as a whole, were inadequate for assessing the results of the PALOMA-3 study. An adequate assessment of the PALOMA-3 study requires results on all patient-relevant outcomes of the most recent available data cut-off.

Table 1: Comparison of selected AE outcomes between the first (5 December 2014) und the third data cut-off (31 July 2015), study PALOMA-3

Study **Outcome** **Time point**	**Palbociclib + fulvestrant**		**Placebo + fulvestrant**		**Palbociclib + fulvestrant vs. fulvestrant**
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
SAEs					
Data cut-off 5 December 2014	345	NA [NA; NA] 33 (9.6)	172	NA [10.5; NA] 24 (14.0)	0.66 [0.39; 1.11]; 0.116
Data cut-off 31 July 2015	345	NA [NA; NA] 53 (15.4)	172	NA [NA; NA] 31 (18.0)	0.80 [0.51; 1.24]; 0.318
Severe AEs (CTCAE grade 3 or 4)					
Data cut-off 5 December 2014	345	1.0 [0.9; 1.0] 242 (70.1)	172	NA [NA; NA] 31 (18.0)	6.19 [4.25; 9.02]; < 0.001
Data cut-off 31 July 2015	345	1.0 [0.9; 1.0] 263 (76.2)	172	NA [NA; NA] 39 (22.7)	5.68 [4.05; 7.98]; < 0.001
Discontinuation due to AEs (discontinuation of palbociclib or placebo)					
Data cut-off 5 December 2014	345	NA [NA; NA] 13 (3.8)	172	NA [NA; NA] 7 (4.1)	0.95 [0.38; 2.37]; 0.904
Data cut-off 31 July 2015	345	NA [NA; NA] 19 (5.5)	172	NA [NA; NA] 6 (3.5)	1.55 [0.62; 3.87]; 0.348
Nausea					
Data cut-off 5 December 2014	345	NA [NA; NA] 100 (29.0)	172	10.8 [10.8; NA] 45 (26.2)	1.12 [0.79; 1.60]; 0.514
Data cut-off 31 July 2015	345	NA [NA; NA] 117 (33.9)	172	NA [NA; NA] 48 (27.9)	1.25 [0.90; 1.76]; 0.185
Decreased appetite					
Data cut-off 5 December 2014	345	NA [NA; NA] 44 (12.8)	172	NA [NA; NA] 13 (7.6)	1.68 [0.90; 3.11]; 0.098
Data cut-off 31 July 2015	345	NA [NA; NA] 54 (15.7)	172	NA [NA; NA] 14 (8.1)	1.90 [1.06; 3.43]; 0.029
Infections (SOC)					
Data cut-off 5 December 2014	345	12.1 [NA; NA] 118 (34.2)	172	NA [9.5; NA] 42 (24.4)	1.48 [1.04; 2.10]; 0.030
Data cut-off 31 July 2015	345	14.8 [10.2; NA] 162 (47.0)	172	NA [NA; NA] 53 (30.8)	1.62 [1.18; 2.20]; 0.002
Influenza					
Data cut-off 5 December 2014	345	NA [NA; NA] 3 (0.9)	172	NA [NA; NA] 8 (4.7)	0.18 [0.05; 0.69]; 0.005
Data cut-off 31 July 2015	345	NA [NA; NA] 9 (2.6)	172	NA [NA; NA] 8 (4.7)	0.53 [0.21; 1.38]; 0.189

a: Effect and 95% CI: Cox proportional hazards model; stratified by documented sensitivity to previous hormonal therapy (yes vs. no) and presence of visceral metastases (yes vs. no). p-value: 2-sided log-rank test.

AE: adverse event; CI: confidence interval; number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

For reasons of completeness, Appendix A contains information on the study characteristics, the patient population and the course of the PALOMA-3 study. Appendix A also presents the results of the first data cut-off on 5 December 2014.

2.1.2 Data on AEs subsequently submitted (first data cut-off on 5 December 2014)

With its comments, the company presented survival time analyses on specific AEs, which were not contained in Module 4B of the dossier.

In Module 4B of the dossier, the company stated to present AEs that had occurred in ≥ 10% of the patients in 1 study arm, as well as "AEs of particular interest" (according to the Summaries of Product Characteristics [SPCs] of palbociclib and fulvestrant). The company's choice in its dossier was incomplete, however, because survival time analyses were not presented for all AEs fulfilling this criterion. With its comments, the company therefore subsequently submitted the analyses on AEs it considered to be missing. However, the company only reported analyses on the basis of Preferred Terms (PTs) and only selectively for individual System Organ Classes (SOCs) (eye disorders, cardiac disorders, infections).

In its comments, the company additionally presented results on CTCAE grade 3 or 4 AEs. The choice concurs with the choice for all AEs (see above). This choice of outcomes was also incomplete because, on the one hand, the company again mostly did not present SOCs and, on the other, the company did not include some CTCAE grade 3 or 4 AEs, although they occurred with similar frequency as other AEs that were analysed by the company (e.g. ascites, pathological fracture and hypertension).

Finally, neither Module 4B of the dossier nor the company's comments contained survival time analyses on individual serious AEs (SAEs).

In summary, the data provided by the company on specific AEs were therefore still incomplete.

Table 10 in Appendix A of the present addendum contains an overview of all AEs (SOCs and PTs) that occurred in ≥ 10% of the patients in one study arm.

2.1.3 Data subsequently submitted on symptoms and health-related quality of life (first data cut-off on 5 December 2014)

With its dossier, the company had presented analyses on symptoms and health-related quality of life, recorded with the questionnaires European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30) and EORTC QLQ - Breast Cancer Module (EORTC QLQ-BR23). The analyses (time to deterioration) concurred with the analyses predefined for the PALOMA-3 study. They partly produced results in favour of palbociclib (pain, emotional functioning), partly to the disadvantage of palbociclib (upset by hair loss, sexual enjoyment; see also Table 7 and Table 8 in Appendix A). Overall,

no advantage or disadvantage of palbociclib could be derived in the area of symptoms or health-related quality of life.

With its comments, the company subsequently submitted additional analyses on the symptom scales and the functional scales of the questionnaires EORTC QLQ-C30 and QLQ-BR23. These were responder analyses with a response criterion that was defined post-hoc and changed in comparison with the planning of the study. Whereas the response criterion was "deterioration by 10 points or greater" in the study protocol, the response criterion in the comments was expanded by the criterion "no improvement in comparison with the value at the start of the study". This operationalization was neither described in the protocol of the PALOMA-3 study nor in Module 4B of the dossier. In addition, the company provided no scientific justification that this response criterion was validated or established [2,5]. According to the company's comments, these analyses put additional emphasis on the patient relevance and were shown to "add further weight to [...] the positive effects recorded with patient-reported questionnaires" [2]. Correspondingly, these analyses consistently showed a change of the effects in favour of palbociclib. The corresponding data can be found in Table 8 to Table 10 of the company's comments [2].

The subsequent analyses were presented without referring to the dossier assessment and, according to the date provided in the company's documents, had already been produced before submission of the dossier, i.e. in August 2015 [5].

In summary, the analyses on a scientifically unfounded response criterion, which were produced post-hoc and in knowledge of the data, were not usable.

2.1.4 Menopausal status of the patients in the PALOMA-3 study

As described in the benefit assessment on palbociclib, the PALOMA-3 study included both patients in first-line treatment and in second-line treatment for advanced or metastatic breast cancer. These patients were either pre/perimenopausal or postmenopausal. In accordance with the approval for the treatment options already available, the G-BA specified different ACTs for second-line treatment, depending on the menopausal status. This resulted in the corresponding research questions B1 and B2 [1].

In Module 4B of its dossier, the company presented subgroup analyses on the characteristic "menopausal status", but only for the total population, i. e. combined for first- and second-line treatment. The interaction tests for the items relevant for the assessment showed 2 indications (in each case in 1 subscale of the EORTC QLQ-C30 and of the QLQ-BR23) and 1 proof of an effect modification (for a specific AE). There were no analyses within the population of patients in second-line treatment. Hence it cannot be excluded that there were additional relevant interactions by the characteristic "menopausal status" within second-line treatment. Appendix A shows the results of the total population of the PALOMA-3 study, irrespective of menopausal status and line of treatment.

2.2 Assessment of the additional analyses of adverse events of the PALOMA-2 study

Assessment of the results on side effects subsequently submitted by the company in the comments

Dossier assessment A16-74 on palbociclib did not present the results on survival time analyses of specific AEs because the company had only conducted selective analyses, which were incomplete also for the criterion chosen by the company itself [1].

The company subsequently submitted further survival time analyses on AEs with its comments. Even when the analyses subsequently submitted were supplemented, the analyses were still incomplete. Similar to the situation for the PALOMA-3 study (see Section 2.1), analyses at SOC level were largely missing, as were analyses on individual PTs, although the criterion chosen by the company was fulfilled (e.g. for CTCAE grade 3 or 4 AEs: pneumonia syncope, hypertension). This was both the case for all AEs and for AEs with severity grade 3 or 4. Survival time analyses on specific SAEs were missing completely already in the dossier and were also not subsequently submitted with the comments.

Overall, the analyses on specific AEs of the PALOMA-2 study remain incomplete, also with the analyses subsequently submitted. The AE data from the comments are therefore not presented.

Assessment of the observation periods of AEs in the PALOMA-2 study

In the oral hearing, there was a discussion of possible discrepancies between information on the observation period for AEs provided in the dossier and the observation periods that could be inferred from individual survival time analyses. Specifically, according to the company, AEs were to be recorded up to 28 days after the end of treatment, which, according to the study protocol, generally ended when progression occurred. Hence it could be expected that the median observation period was about 28 days longer than the median treatment duration. However, the information from the survival time analyses presented by the company in addition to the CSR suggests that this was not the case.

An analysis of AEs beyond the time point of progression (or of the end of treatment) resulted in the situation that not only AEs under treatment with the study medication were recorded, but also AEs that occurred under subsequent treatments, including chemotherapy. This has implications for the assessment of the outcome “time to next (intravenous) chemotherapy”, which was included as patient-relevant outcome in the company’s dossier. The company justified the patient relevance of this outcome with the high toxicity of cytostatic chemotherapeutic regimens [3]. Knowledge of the actual recording time of AEs in the PALOMA-2 study is therefore relevant for assessing this outcome.

The median treatment duration was 617.5 days (about 20.5 months) in the palbociclib + letrozole arm and 420 days (about 14 months) in the letrozole arm [6]. Consequently, the median observation period for AEs should be 28 days longer, i. e. about 21.5 months in the

palbociclib + letrozole arm and about 15 months in the letrozole arm. The actual observation period for AEs can be estimated from a survival time analysis for a specific AE that did not occur or that only occurred in few cases. The reason is that, in such an AE, the number provided for the patients at risk correspond to the actual number of observations because only censorings (= end of the observation period) reduce the numbers at risk, but not the events themselves.

An example of such an outcome is shown in Figure 1 (AE pulmonary embolism).

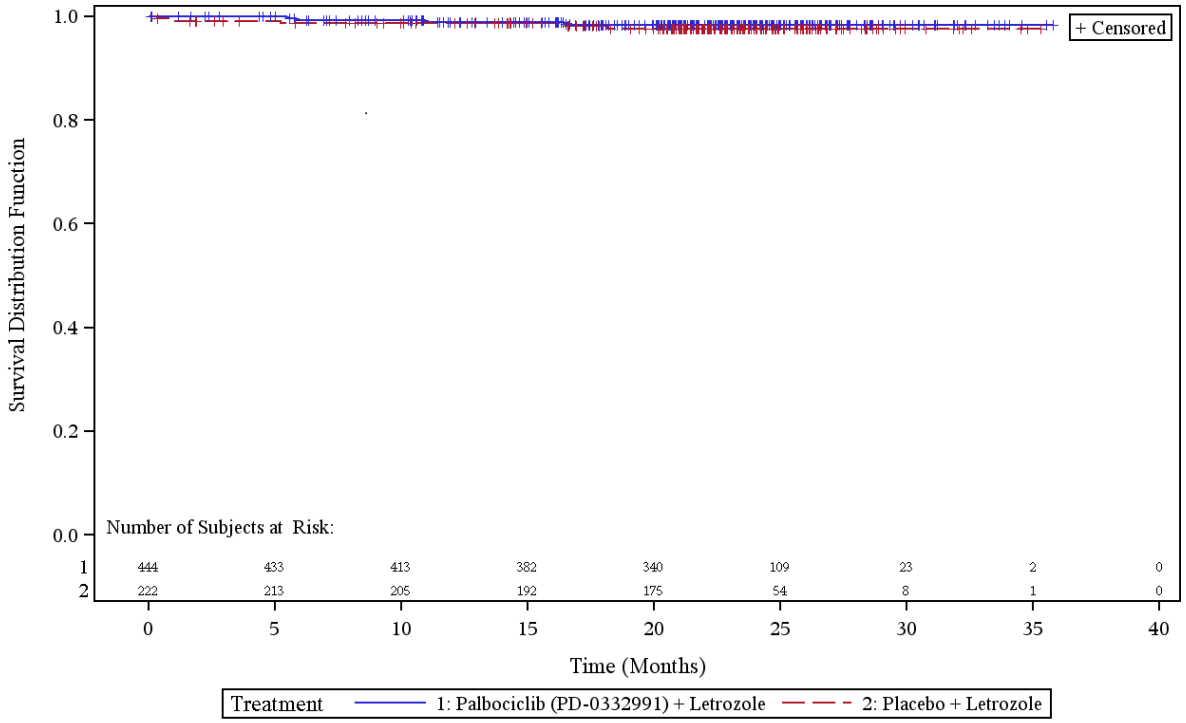


Figure 1: Survival time analysis for the outcome “pulmonary embolism” in the PALOMA-2 study, data cut-off on 26 February 2016

As described above, according to the CSR of the PALOMA-2 study, only about 50% of the patients in the letrozole arm were still under treatment at month 14. Consequently, it could be expected that, 28 days later (at month 15), only about 50% of the patients were under observation for AEs. However, the number of subjects at risk shown in Figure 1 shows that the follow-up period was notably longer: At month 15, 192 of the 222 patients originally included in the letrozole arm were still under observation (about 86%). At month 20, this number was still as high as 175 of 222 patients (about 79%). The fact that, at month 20, a smaller proportion of patients was under observation in the palbociclib + letrozole arm (77%, 340 of 444 patients) than in the letrozole arm, although the median treatment duration was notably longer in the palbociclib + letrozole arm, also indicates that the observation period was independent from the treatment duration. On the basis of the survival time analyses presented by the company it can therefore be assumed that the patients were observed notably longer than 28 days after the end of treatment also for AEs.

It can even be assumed that the observation period for AEs, as for overall survival, did not end prematurely, but that the patients were observed until the end of the study. This assumption is based on the fact that the CSR reports a median observation period of 23 (palbociclib arm) and 22.3 months (letrozole arm) for overall survival. It can be inferred from Figure 1 that the median observation period for AEs in both groups was between 20 months (in each case somewhat less than 80% of the patients still under observation) and 25 months (in each case about 25% of the patients still under observation).

In summary, it can be assumed on the basis of the survival time analyses presented by the company that the analyses on AEs presented by the company comprised the entire study period. Hence they also allow assessing any AEs that occurred after initiation of subsequent therapy (see Section 2.3).

2.3 Assessment of the outcomes "progression-free survival" and "time to first (intravenous) chemotherapy"

The outcomes "PFS" and "time to first (intravenous) chemotherapy" were also recorded in the studies PALOMA-2 and PALOMA-3. In dossier assessment A16-74, these outcomes were assessed to be not directly patient-relevant [1]. This was also in accordance with the company's consultation with the G-BA [7].

Methodological assessment of the outcome "PFS"

Progression, morbidity and health-related quality of life

Regarding PFS, it was stated in the consultation with the G-BA that determination of progression based on radiological findings alone constituted a finding that was not directly patient-relevant [7]. A joint analysis of the PFS with data on health-related quality of life and on morbidity was therefore recommended.

In both studies, PALOMA-2 and PALOMA-3, PFS constituted a composite outcome of death and radiological progression. However, the progression events in both studies were almost exclusively radiological progressions without death (PALOMA-2: 317 of 331 events [96%]; PALOMA-3: 191 of 195 events [98%], first data cut-off on 5 December 2014). Hence the data on morbidity and on health-related quality of life are of great importance for interpreting the PFS results. These results showed no statistically significant result for the PALOMA-2 study (see dossier assessment A16-74 [1]), and no advantage or disadvantage overall for the PALOMA-3 study (see Appendix A). In both cases, prolonged PFS under palbociclib was therefore not associated with an advantage in morbidity or health-related quality of life.

However, it should be pointed out that the PROs on morbidity and health-related quality of life were only analysed until progression occurred and therefore allow conclusions only to be drawn until the time point of progression. The long-term effects of progression on these outcomes cannot be assessed on this basis. Data for the PALOMA-2 study were also recorded beyond progression, but the company's dossier did not contain any analysis under

consideration of the total observation period. Since it was noted in dossier assessment A16-74 that, according to the information provided by the company in Module 4A of its dossier, the PRO analyses did not comprise the total observation period, the company subsequently submitted corresponding analyses with its comments. However, it only presented an isolated analysis of the PRO data after progression in patients with recordings after progression. There was no analysis with a joint consideration of the recordings before and after progression and for all randomized patients. The company stated that the post-progression analysis subsequently submitted and the analysis for the time until progression showed no statistically significant difference between the treatment groups [2].

Progression-free survival as surrogate outcome

In its dossier, the company tried to validate PFS as surrogate outcome for the outcome "overall survival". It was explained in dossier assessment A16-74 that this was not sufficiently proven [1]. The company presented further analyses for this with its comments. These analyses subsequently submitted also did not provide such proof (see Section 2.4).

The company did not present further validation analyses (e.g. for the validation of PFS as surrogate outcome for the outcome "health-related quality of life").

Summary

In summary, both in the PALOMA-2 and in the PALOMA-3 study, the observed differences in the outcome "PFS" were almost exclusively caused by radiological events. It cannot be inferred from the results presented that this radiological progression was associated with worsened morbidity or deterioration of health-related quality of life. It can also not be inferred from them that prolonged progression-free time was associated with prolonged survival.

The PFS results of the PALOMA-2 study are shown in Table 14 in Appendix B; the results of the PALOMA-3 study are shown in Table 9 in Appendix A. The corresponding Kaplan-Meier curves can be found in Appendix C.

Methodological assessment of the outcome "time to first (intravenous) chemotherapy"

Regarding the outcome "time to first subsequent chemotherapy", the G-BA advised the company [7] to take into account that an advantage based on this should be reflected in patient-relevant outcomes, e.g. a reduction in disease-related symptoms, an improvement in health-related quality of life or a reduction in side effects. According to the G-BA, data recording of these outcomes was important beyond the time point of progression. The data presented by the company suggest that there were no such advantages of palbociclib despite a prolonged time to first chemotherapy.

Time to first chemotherapy, symptoms and health-related quality of life

In both studies, PALOMA-2 and PALOMA-3, the time to first subsequent (intravenous) chemotherapy was shorter in the comparator arm than in the palbociclib arm (see Table 9 in Appendix A and Table 14 in Appendix B). This is consistent with the higher rate of

radiological progression in both comparator arms, each in comparison with the palbociclib arm. As described above in connection with the outcome "PFS", it cannot be inferred from the data presented by the company that the higher rate of radiological progression and the shorter time to radiological progression was associated with deterioration of symptoms or quality of life. Correspondingly, this also applies to the shorter time to first chemotherapy.

Time to first chemotherapy and side effects

Regarding side effects, the company's analyses on AEs of the PALOMA-2 study suggest that there was also no advantage of palbociclib from the prolongation of the time to first chemotherapy. For various AEs, there were disadvantages from palbociclib in comparison with the control arm. As described in Section 2.2, it can be assumed that the observation period for AEs in the survival time analyses presented by the company corresponded to the observation period for overall survival. Thus, presumably, any AEs occurring under subsequent chemotherapy would have been recorded as well. Hence it cannot be inferred from these analyses conducted by the company that the harm from palbociclib would be outbalanced by more frequent and earlier chemotherapy in the control arm.

Due to a lack of comparable AE analyses, it is unclear whether this also applies to the PALOMA-3 study.

Mortality not considered

In contrast to the outcome "PFS", where, reasonably, death was also recorded as negative event, the company did not consider death in the outcome "time to first chemotherapy". This is particularly relevant for the PALOMA-2 study. According to the company's analyses, 13.3% of the patients died in the palbociclib + letrozole arm without subsequent intravenous chemotherapy, whereas this number was 9.0% in the letrozole arm, corresponding to an absolute difference of 4.3 percentage points. 16.0% of the patients received subsequent intravenous chemotherapy in the palbociclib + letrozole arm, whereas this number was 23.0% in the letrozole arm, corresponding to an absolute difference of 7.0 percentage points. A joint analysis of death and subsequent chemotherapy would result in an event rate of 29.3% in the palbociclib arm compared with 32.0% in the letrozole arm, corresponding to an absolute difference of 2.7 percentage points. This difference is not statistically significant (relative risk [95% confidence interval], Institute's calculation: 0.92 [0.72; 1.16]; p = 0.486).

The fact that deaths were not considered was of less importance for the PALOMA-3 study because the difference in the rate of chemotherapies was larger and the difference in the deaths that were not considered was smaller. The combination of the events resulted in an event rate of 12.2% in the palbociclib arm and 19.2% in the comparator arm, corresponding to an absolute difference of 7.0%. This difference is still statistically significant (relative risk [95% confidence interval], Institute's calculation: 0.63 [0.42; 0.96]; p = 0.037).

Effect of side effects from palbociclib on the decision regarding subsequent therapy

Both in the PALOMA-2 study and in the PALOMA-3 study, notably more AEs occurred under palbociclib than in the respective comparator group. Particularly the risk of neutropenia classified as severe (CTCAE grade 3 or 4) was notably increased.

Neutropenia is a contraindication to treatment with certain chemotherapeutic agents, including the drugs capecitabine and paclitaxel [8,9]. This even applies to neutropenia with lower severity grade (from CTCAE grade 2 [neutrophil count < 1500/mm^3]). Both in the PALOMA-2 and in the PALOMA-3 study, capecitabine and paclitaxel were by far the most commonly used subsequent chemotherapeutic agents. Hence the side effects caused by palbociclib potentially contributed to the fact that subsequent chemotherapies were used less frequently and later in the palbociclib arm than in the respective comparator arm of each study. The company did not present any analyses to investigate this issue.

Summary

In summary, the results presented did not show that the shorter time to first chemotherapy under the comparator therapy was associated with worsened morbidity, deterioration of health-related quality of life or an outbalancing of the harm caused by palbociclib. Irrespective of this, no advantage of palbociclib was shown in the outcome "time to first intravenous chemotherapy" when the deaths of patients in first-line treatment (study PALOMA-2) were considered. As for patients in first-line treatment, the side effects caused by palbociclib potentially influenced the decision for conducting subsequent chemotherapy for patients in second-line treatment (study PALOMA-3). Due to a lack of analyses, the extent of this influence is unclear.

2.4 Validation of the surrogate outcome "progression-free survival"

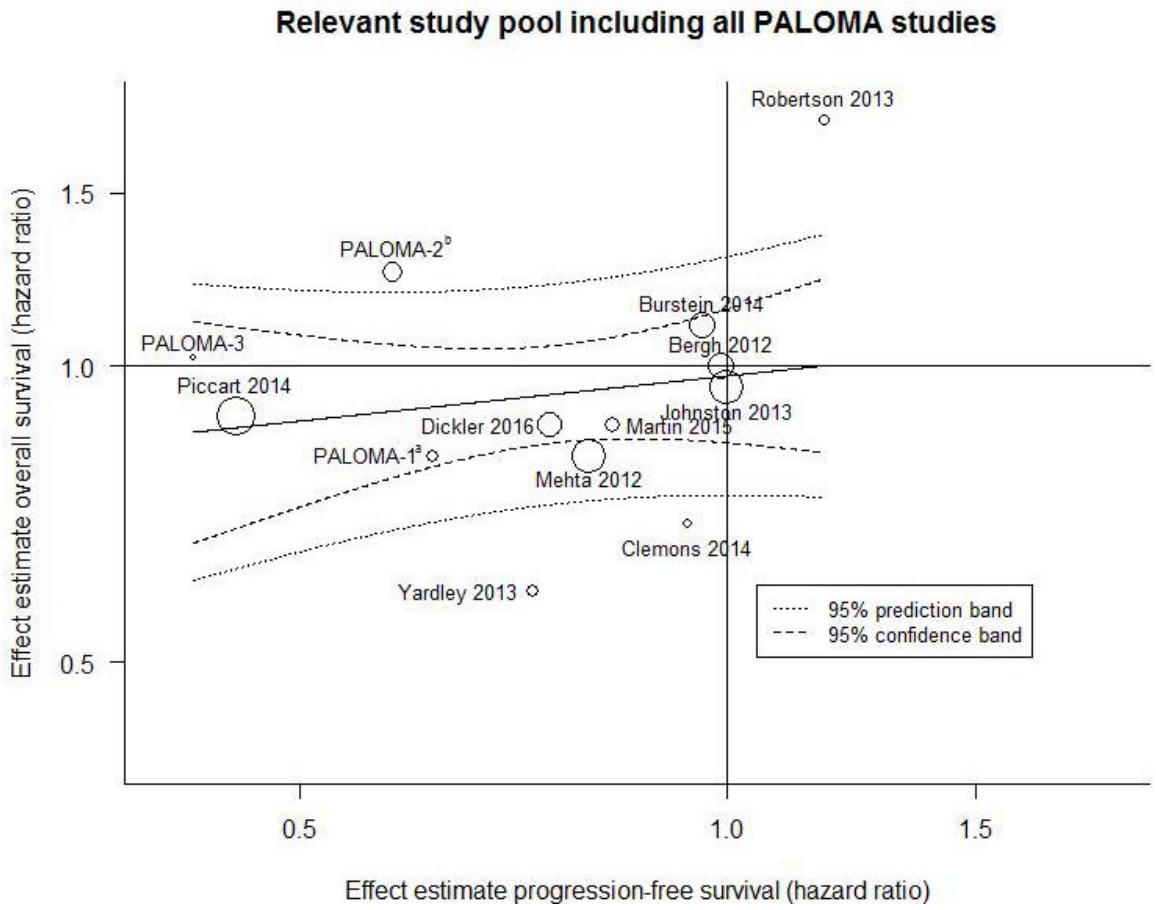
In its comments, the company presented additional analyses for surrogate validation and described why it considered these analyses to be suitable for the derivation of conclusions on the surrogate characteristic of the outcome "PFS" for overall survival.

In its additional analyses, the company tried to show that it followed IQWiG's approach as closely as possible in the surrogate validation. The company particularly considered the use of confidence intervals instead of prediction intervals to be sufficient to determine the surrogate threshold effect (STE). When using this approach, the company referred to IQWiG's rapid report A10-05 *Validity of surrogate endpoints in oncology* [10] and on a dossier assessment on the drug dabrafenib from 2013 [11]. As described in the methods used for the surrogate validation in the dossier assessment on dabrafenib, however, prediction intervals, and not confidence intervals, were used for the derivation of the STE. The company referred to the caption of Figure 1 in the dossier assessment on dabrafenib [11], in which the term "confidence interval" was used. However, it is clear from the detailed description of the methods in the accompanying text that this caption is incorrect. Using these prediction intervals also results from the methods for calculating an STE. This is described in

Burzykowski 2005 [12], for example. As rapid report A10-05, the company itself referred to this publication both in its dossier on palbociclib and in its comments [2]. The analyses subsequently submitted by the company using confidence intervals were therefore not usable.

The approach proposed by the company to only use the point estimate of the surrogate outcome when prediction intervals are used was not followed because this would mean that study-specific variability of the individual study under assessment would not be considered.

In addition, the company pointed out that some of the studies used for the surrogate validation investigated the outcome "time to progression (TTP)" instead of PFS, but that the operationalization of the outcome "TTP" actually concurred with the commonly used operationalization of the outcome "PFS" (radiological progression or death). The company therefore considered the exclusion of these studies to be unjustified. In the 2 studies Bergh 2012 [13] and Llombart-Cussac 2012 [14], the operationalization of the outcome "TTP" actually concurred with the operationalization of PFS. However, one of the studies, Llombart-Cussac 2012, compared 2 monotherapies and was therefore unsuitable for inclusion in the study pool for other reasons (see dossier assessment A16-74 on palbociclib [1]). The analysis presented in A16-74 was supplemented with the Bergh 2012 study, however. This analysis is shown in Figure 2. Concurring with the company's additional analyses, the standard deviation was considered in the presentation. After inclusion of the Bergh 2012 study, the correlation between overall survival and PFS was r = 0.358 (95% CI: [–0.240; 0.759]) and was still not statistically significant (see also confidence interval bands in Figure 1). An STE cannot be derived.



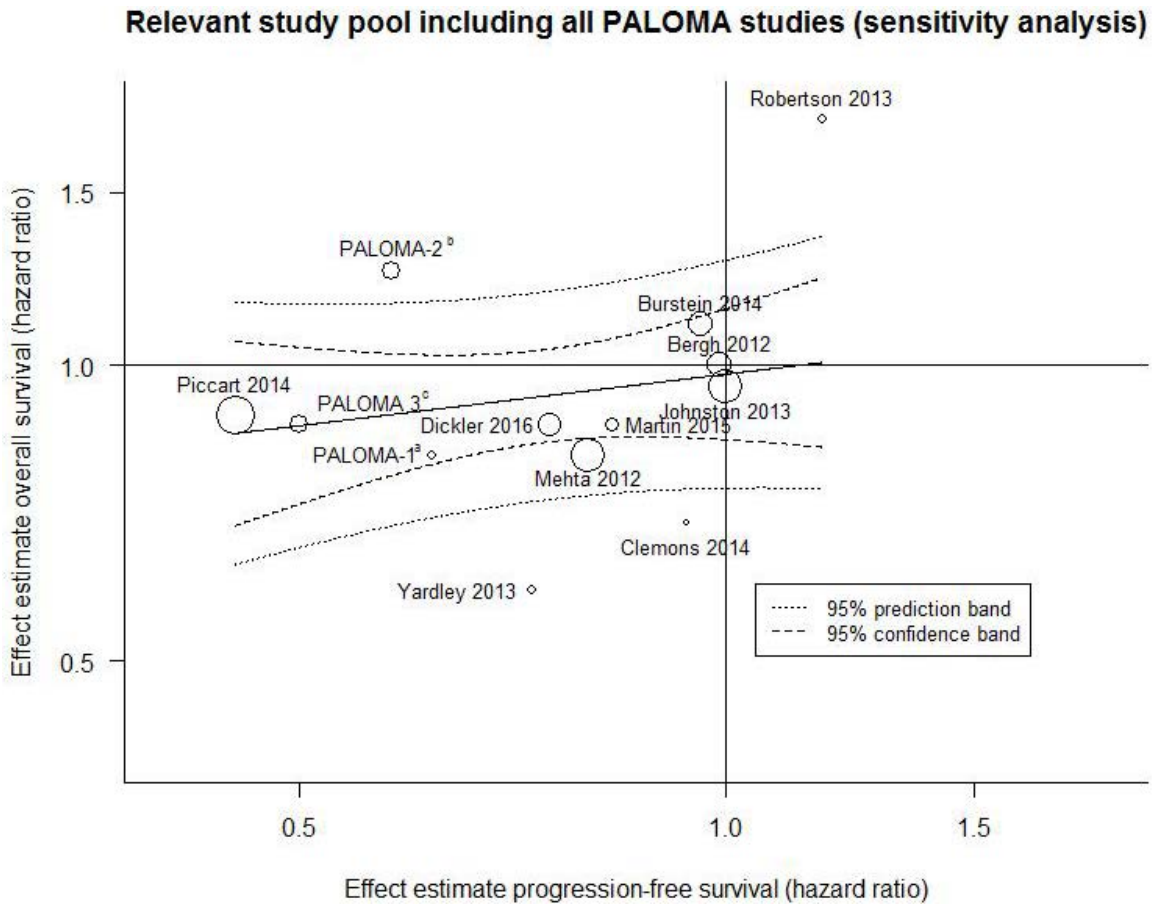
a: In the PALOMA-1 study, the value from the blinded analysis was used for PFS.

b: In the PALOMA-2 study, there was no information on the hazard ratio of overall survival; hence the relative risk was used as an approximation.

Figure 2: Correlation between PFS and overall survival – relevant study pool including all PALOMA studies and the Bergh 2012 study, with confidence and prediction intervals

Using the most recent data cut-off of the PALOMA-3 study

In its update on the PFS from 23 October 2015 for the PALOMA-3 study, the company also presented data on deaths in the study, but no survival time analysis of overall survival. However, since more than 20% of the patients had already died in October 2015, compared with somewhat more than 5% in December 2014, it is investigated below to what extent the use of the effect estimation from the later data cut-off changed the estimated correlation. Since there was no hazard ratio for overall survival for this data cut-off, the relative risk was used as an approximation.



a: In the PALOMA-1 study, the value from the blinded analysis was used for PFS.

b: In the PALOMA-2 study, there was no information on the hazard ratio of overall survival; hence the relative risk was used as an approximation.

c: In the PALOMA-3 study, there was no information on the hazard ratio of overall survival at the data cut-off on 23 October 2015; hence the relative risk was used as an approximation.

Figure 3: Correlation between PFS and overall survival – relevant study pool including all PALOMA studies, under consideration of the most recent data cut-off of the PALOMA-3 study, with confidence and prediction intervals

In this analysis, the correlation between overall survival and PFS was r = 0.44 (95% CI [−0.15; 0.80]) and was not statistically significant. Hence an STE could not be derived, also under consideration of the most recent data cut-off of the PALOMA-3 study from 23 October 2015.

Summary

In summary, the company's analyses subsequently submitted by the company with the comments did not change the assessment of dossier assessment A16-74: There is no sufficient proof that PFS is a valid surrogate outcome for overall survival in the present therapeutic indication.

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Appendix A – Design, characteristics and results of the PALOMA-3 study

Study characteristics

Table 2 and Table 3 describe the PALOMA-3 study.

Table 2: Characteristics of the PALOMA-3 study – RCT, direct comparison: palbociclib + fulvestrant vs. fulvestrant

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PALOMA-3	RCT, double-blind, parallel	Women with hormone-receptor-positive, HER2-negative metastatic[b] or locally advanced breast cancer with progression[c] after prior endocrine therapy	Palbociclib + fulvestrant (N = 347) placebo + fulvestrant (N = 174)	Screening phase: up to 28 days Treatment: until disease progression[d], symptomatic deterioration, necessity of new or additional anticancer therapy, unacceptable toxicity, decision by the patient or the investigator to discontinue, loss to follow-up, death, or withdrawal of consent Follow-up: outcome-specific, at most until death or withdrawal of consent	144 centres in Australia, Belgium, Canada, Germany, Ireland, Italy, Japan, Netherlands, Portugal, Romania, Russia, South Korea, Taiwan, Turkey, Ukraine, United Kingdom, USA 9/2013–1/2017	Primary: PFS Secondary: overall survival, symptoms, health status, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes from the information provided by the company in Module 4B of the dossier.
b: Patients who only had bone metastases or blastic metastases and patients with uncontrolled or symptomatic visceral or uncontrolled or symptomatic CNS metastases were excluded.
c: Progression during or within 12 months after adjuvant therapy with aromatase inhibitors (postmenopausal patients) or tamoxifen (pre/perimenopausal patients) or progression during or within 1 month after treatment with aromatase inhibitors for advanced/metastatic breast cancer (postmenopausal patients) or endocrine therapy for advanced/metastatic breast cancer (pre/perimenopausal patients). Chemotherapy for advanced/metastatic breast cancer was allowed in addition to endocrine therapy.
d: Patients could continue treatment with the study medication beyond progression at the investigator's discretion if this was in the patients' interest and as long as no subsequent therapy was initiated.

AE: adverse event; CNS: central nervous system; HER2: human epidermal growth factor receptor 2; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 3: Characteristics of the interventions – RCT, direct comparison: palbociclib + fulvestrant vs. fulvestrant

Study	Intervention	Comparison	Pretreatment and concomitant treatment
PALOMA-3	Palbociclib 125 mg/day, orally in weeks 1–3 of a 28-day cycle + fulvestrant[a] 500 mg IM, day 1 and 15 in the first cycle, then every 28 days from day 1 Pre/perimenopausal patients: goserelin SC, every 28 days for palbociclib dose reduction (to 100 mg/day or 75 mg/day) or interruption possible in case of toxicity no dose adjustment possible for fulvestrant; delayed administration was allowed	Placebo, orally in weeks 1–3 of a 28-day cycle + fulvestrant[a] 500 mg IM, day 1 and 15 in the first cycle, then every 28 days from day 1 Pre/perimenopausal patients: goserelin SC, every 28 days no dose adjustment possible for fulvestrant; delayed administration was allowed	**Non-permitted pretreatment:** ▪ pretreatment with CDK inhibitors, fulvestrant, everolimus, PI3K-mTOR inhibitors **Non-permitted concomitant treatment:** ▪ other anticancer therapies ▪ strong CYP3A inhibitors and inducers; moderate CYP3A inhibitors and inducers were allowed ▪ drugs that may prolong the QT interval ▪ hormone replacement therapy, topical oestrogens, megestrol acetate and selective oestrogen receptor modulators ▪ anticoagulants, proton pump inhibitors
a: Fulvestrant treatment could be continued as monotherapy after discontinuation of palbociclib or placebo. CDK: cyclin-dependent kinase; CYP3A: cytochrome P450 liver enzymes; IM: intramuscular; PI3K-mTOR: phosphoinositide 3-kinase; RCT: randomized controlled trial; SC: subcutaneous; vs.: versus			

The PALOMA-3 study was a randomized blinded study comparing the drug combination of palbociclib + fulvestrant with fulvestrant. The study included patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer. The definition of HR-positive comprises oestrogen receptor (ER)-positive or progesterone receptor (PR)-positive patients. The participants had to be pretreated with at least 1 endocrine therapy. The inclusion criteria included

- progression of the disease during or up to 12 months after adjuvant endocrine therapy or
- progression during or up to 1 month after endocrine therapy for the treatment of the advanced or metastatic disease.

The company differentiated the patients by their menopausal status: postmenopausal women could only be included after prior therapy with an aromatase inhibitor, whereas pre/perimenopausal women could be included after prior therapy with tamoxifen (in case of adjuvant pretreatment) or with endocrine therapy in general (if pretreated for the advanced or metastatic stage).

A total of 521 patients were randomly allocated in a ratio of 2:1 to treatment with palbociclib + fulvestrant or placebo + fulvestrant. Randomization was stratified by sensitivity to prior hormonal therapy, menopausal status and presence of visceral metastases.

The treatment with palbociclib in the study was in compliance with the SPC [15]. Fulvestrant, in contrast, was not administered in compliance with the approval because the PALOMA-3 study also included patients who had been pretreated with aromatase inhibitors. However, fulvestrant is only approved for the treatment of patients who have been pretreated with an antioestrogen [4,16].

In both study arms, treatment was to be continued until objective disease progression, symptomatic deterioration, necessity of new or additional anticancer therapy, unacceptable toxicity or decision by the investigator or the patient to discontinue treatment. However, treatment with the study medication could be continued beyond the time point of progression if the investigator determined that this was in the patient's best interest and as long as no subsequent anticancer therapy was initiated. Patients who discontinued treatment with palbociclib or placebo during the treatment phase could continue treatment with fulvestrant monotherapy.

Planned duration of follow-up

Table 4 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 4: Planned duration of follow-up – RCT, direct comparison: palbociclib + fulvestrant vs. fulvestrant

Study **Outcome category** **Outcome**	**Planned follow-up**
PALOMA-3	
Mortality	
Overall survival	Every 3 months for the first 9 months after the end of treatment, then every 6 months until death, loss to follow-up or withdrawal of consent
Morbidity	
Health status (EQ-5D VAS)	Until treatment discontinuation
Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23 – symptom scales)	Until treatment discontinuation
Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23 – functional scales)	Until treatment discontinuation
Side effects	
All outcomes in the category "side effects"	28 days after treatment discontinuation
EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus	

Only overall survival was to be observed beyond the end of treatment. The observation periods for all other patient-relevant outcomes may be systematically shortened because, as a rule, they were only to be recorded for the time period of treatment (plus 28 days for side

effects). To be able to draw a reliable conclusion on side effects, morbidity and health-related quality of life over the total study period or the time until death of the patients, it would be necessary to record these outcomes also over the total period of time.

Patient characteristics

Table 5 shows the characteristics of the patients in the PALOMA-3 study.

Table 5: Characteristics of the study population – palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population)

Study **Characteristics** **Category**	**Palbociclib + fulvestrant**	**Fulvestrant**
PALOMA-3	N[a] = 347	N[a] = 174
Age [years], mean (SD)	56.9 (11.7)	56.8 (10.4)
Ethnicity, n (%)		
White	252 (72.6)	133 (76.4)
Black	12 (3.5)	8 (4.6)
Asian	74 (21.3)	31 (17.8)
Other	8 (2.3)	1 (0.6)
No data	1 (0.3)	1 (0.6)
Region, n (%)		
Asia-Pacific	78 (22.5)	36 (20.7)
Europe	111 (32.0)	56 (32.2)
North America	158 (45.5)	82 (47.1)
ECOG PS, n (%)		
0	207 (59.7)	115 (66.1)
1	140 (40.3)	59 (33.9)
Menopausal status (at randomization), n (%)		
Postmenopausal	275 (79.3)	138 (79.3)
Pre/perimenopausal	72 (20.7)	36 (20.7)
Type of last prior therapy in the adjuvant or metastatic setting, n (%)		
Aromatase inhibitors	238 (68.6)	118 (67.8)
Antioestrogen therapy	65 (18.7)	30 (17.2)[b]
Other	44 (12.7)	27 (15.5)[b]
Prior chemotherapy, n (%)		
Yes	251 (72.3)	138 (79.3)
No	96 (27.7)	36 (20.7)
Line of treatment in the metastatic setting, n (%)		
First-line treatment	84 (24.2)	45 (25.9)
Second-line treatment	132 (38.0)	70 (40.2)
Later treatment	131 (37.8)	59 (33.9)

(continued)

Table 5: Characteristics of the study population – palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population) (continued)

Study Characteristics Category	**Palbociclib + fulvestrant**	**Fulvestrant**
PALOMA-3	N[a] = 347	N[a] = 174
Type of recurrence, n (%)		
Locoregional	16 (4.6)	10 (5.7)
Local	18 (5.2)	8 (4.6)
Regional	15 (4.3)	7 (4.0)
Distant metastasis	229 (66.0)	121 (69.5)
Newly diagnosed	67 (19.3)	25 (14.4)
Unknown	2 (0.6)	2 (1.1)
Missing	0 (0)	1 (0.6)
Location of disease, n (%)		
Bone	263 (75.8)	129 (74.1)
Breast	61 (17.6)	19 (10.9)
Liver	127 (36.6)	81 (46.6)
Lungs	103 (29.7)	44 (25.3)
Lymph nodes	138 (39.8)	63 (36.2)
Other	109 (31.4)	46 (26.4)
Treatment discontinuation[c], n (%)	105 (30.3)	97 (55.7)
Study discontinuation, n (%)	25 (7.2)	18 (10.3)

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: 1 patient had received both aromatase inhibitors and antioestrogen therapy as last prior therapy before start of the study.
c: Treatment discontinuation of at least 1 drug. Number of patients who only discontinued palbociclib or placebo: n = 107 (30.8) and n = 97 (56.7).
ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Course of the study

Table 6 shows the median treatment duration of the patients and the observation period for individual outcomes.

Table 6: Information on the course of the study – palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population)

Study **Duration of the study phase** **Outcome category**	**Palbociclib + fulvestrant**	**Fulvestrant**
PALOMA-3 (data cut-off 5 Dec 2014)	N = 345	N = 172
Treatment duration [months][a, b]		
Median [min; max]	4.9 [0.9; 12.8]	4.2 [0.9; 13.2]
Mean (SD)	5.2 (2.3)	4.2 (2.2)
Observation period [months]		
Overall survival		
Median [95% CI]	5.6 [5.3; 6.0]	5.6 [5.1; 6.1]
Mean (SD)	ND	ND
Morbidity, health-related quality of life, side effects	ND	ND

a: Institute's calculation from days.
b: Duration of treatment with at least one drug. Fulvestrant treatment could be continued after discontinuation of palbociclib. Duration of treatment with palbociclib (Institute's calculation from days): median [min; max]: 4.7 [< 0.1; 12.8]; mean (SD): 5.0 (2.5). Duration of treatment with placebo: median [min; max]: 3.9 [0.5; 13.2]; mean (SD): 4.0 (2.4).
max: maximum; min: minimum; N: number of randomized and treated patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

In the PALOMA-3 study, the mean treatment duration with at least 1 drug at the data cut-off on 5 December 2014 was similar in both treatment arms (4.9 versus 4.2 months). The median observation period for overall survival was 5.6 months in both arms. There was no information on the observation period for further outcomes.

Results on patient-relevant outcomes

For the PALOMA-3 study, the risk of bias at study level was low. There were no aspects that would raise doubts about a low risk of bias for individual patient-relevant outcomes, either. Irrespective of this, the overall consideration of specific AEs was potentially biased because the company only presented selective survival time analyses (see Section 2.1.2).

Table 7 and Table 8 show results for patient-relevant outcomes of the PALOMA-3 study for the data cut-off on 5 December 2014. Table 9 shows results on further outcomes (all data cut-offs).

Table 7: Results (mortality, health-related quality of life, side effects – time to first event) – palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population), data cut-off 5 December 2014

Study **Outcome category** **Outcome** **Data cut-off**	**Palbociclib + fulvestrant**		**Fulvestrant**		**Palbociclib + fulvestrant vs. fulvestrant**
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
PALOMA-3					
Mortality					
Overall survival[b]	347	NA [NA; NA] 19 (5.5)	174	NA [NA; NA] 9 (5.2)	1.02 [0.46; 2.25]; 0.970
Morbidity					
EORTC QLQ-C30 symptom scales – time to deterioration[c]					
Fatigue	335[d]	2.1 [1.9; 2.8] 205 (61.2)	166[d]	2.8 [1.9; 4.6] 90 (54.2)	1.15 [0.89; 1.47]; 0.208
Nausea and vomiting	335[d]	6.7 [4.6; NA] 144 (43.0)	166[d]	4.9 [2.8; NA] 72 (43.4)	0.89 [0.67; 1.19]; 0.464
Pain	335[d]	8.0 [5.6; NA] 131 (39.1)	166[d]	2.8 [2.3; 5.4] 83 (50.0)	0.63 [0.48; 0.84]; 0.002
Dyspnoea	335[d]	NA [8.5; NA] 107 (31.9)	166[d]	NA [4.0; NA] 61 (36.7)	0.74 [0.54; 1.01]; 0.060
Insomnia	335[d]	NA [6.6; NA] 125 (37.3)	166[d]	NA [4.7; NA] 56 (33.7)	0.99 [0.72; 1.35]; 0.971
Appetite loss	335[d]	8.3 [6.7; NA] 118 (35.2)	166[d]	8.7 [5.7; 8.7] 54 (32.5)	0.97 [0.70; 1.34]; 0.849
Constipation	335[d]	8.0 [4.9; NA] 133 (39.7)	166[d]	12 [4.9; 12] 60 (36.1)	0.97 [0.72; 1.33]; 0.928
Diarrhoea	335[d]	12.3 [7.7; 12.3] 105 (31.3)	166[d]	10.2 [8.3; 10.2] 47 (28.3)	1.03 [0.73; 1.45]; 0.863
EORTC QLQ-BR23 symptom scales – time to deterioration[c]					
Side effects of systemic treatment	335[d]	6.4 [4.8; 7.2] 151 (45.1)	166[d]	6.6 [4.6; NA] 57 (34.3)	1.10 [0.80; 1.49]; 0.538
Breast symptoms	335[d]	NA [8.4; NA] 72 (21.5)	166[d]	NA [7.9; NA] 34 (20.5)	0.89 [0.59; 1.34]; 0.577
Arm symptoms	335[d]	6.5 [4.9; 8.2] 148 (44.2)	166[d]	4.6 [2.8; 6.5] 77 (46.4)	0.79 [0.59; 1.04]; 0.097
Upset by hair loss[e]	335[d]	NA [6.5; NA] 38 (11.3)	166[d]	NA [NA; NA] 9 (5.4)	2.43 [1.17; 5.07]; 0.014

(continued)

Table 7: Results (mortality, health-related quality of life, side effects – time to first event) – palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population), data cut-off 5 December 2014 (continued)

Study **Outcome category** **Outcome** **Data cut-off**	**Palbociclib + fulvestrant**		**Fulvestrant**		**Palbociclib + fulvestrant vs. fulvestrant**
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
Health-related quality of life					
EORTC QLQ-C30 functional scales – time to deterioration[c]					
Global health status	335[d]	6.2 [4.7; NA] 145 (43.3)	166[d]	3.8 [2.8; NA] 78 (47.0)	0.81 [0.61; 1.06]; 0.136
Role functioning	335[d]	6.5 [4.9; NA] 145 (43.3)	166[d]	4.9 [2.8; NA] 79 (47.6)	0.80 [0.61; 1.06]; 0.127
Physical functioning	335[d]	10.2 [10.2; NA] 103 (30.7)	166[d]	NA [6.5; NA] 48 (28.9)	0.95 [0.67; 1.34]; 0.787
Emotional functioning	335[d]	10.2 [8.0; NA] 101 (30.1)	166[d]	6.5 [3.9; NA] 64 (38.6)	0.66 [0.48; 0.91]; 0.011
Cognitive functioning	335[d]	6.5 [3.7; 8.2] 151 (45.1)	166[d]	4.6 [2.8; 6.8] 76 (45.8)	0.89 [0.67; 1.17]; 0.399
Social functioning	335[d]	10.2 [5.3; NA] 135 (40.3)	166[d]	NA [4.5; NA] 65 (39.2)	0.90 [0.67; 1.22]; 0.538
EORTC QLQ-BR23 functional scales – time to deterioration[c]					
Body image	335[d]	8.3 [6.9; 12.6] 117 (34.9)	166[d]	NA [5.7; NA] 52 (31.3)	0.97 [0.70; 1.35]; 0.840
Sexual functioning	335[d]	10.1 [8.5; NA] 91 (27.2)	166[d]	8.7 [8.7; 10.2] 38 (22.9)	1.12 [0.76; 1.63]; 0.562
Sexual enjoyment[f]	335[d]	8.5 [6.9; NA] 45 (13.4)	166[d]	NA [NA; NA] 15 (9.0)	1.78 [0.99; 3.21]; 0.0496
Perspective on the future	335[d]	10.5 [8.5; 12.1] 96 (28.7)	166[d]	8.6 [5.6; 8.6] 52 (31.3)	0.76 [0.54; 1.07]; 0.107
Side effects					
AEs (supplementary information)	*345*	*ND* *337 (97.7)*	*172*	*ND* *153 (89.0)*	–
SAEs	345	NA [NA; NA] 33 (9.6)	172	NA [10.5; NA] 24 (14.0)	0.66 [0.39; 1.11]; 0.116
Severe AEs (CTCAE grade 3 or 4)	345	1.0 [0.9; 1.0] 242 (70.1)	172	NA [NA; NA] 31 (18.0)	6.19 [4.25; 9.02]; < 0.001
Discontinuation due to AEs					
Discontinuation of palbociclib or placebo	345	NA [NA; NA] 13 (3.8)	172	NA [NA; NA] 7 (4.1)	0.95 [0.38; 2.37]; 0.904
Discontinuation of fulvestrant	345	ND [ND] 11 (3.2)	172	ND [ND] 5 (2.9)	ND [ND]; ND

(continued)

Table 7: Results (mortality, health-related quality of life, side effects – time to first event) – palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population), data cut-off 5 December 2014 (continued)

a: Unless designated otherwise: effect and 95% CI: Cox proportional hazards model; stratified by documented sensitivity to previous hormonal therapy (yes vs. no) and presence of visceral metastases (yes vs. no). p-value: 2-sided log-rank test.
b: At the data cut-off on 16 March 2015, 36 (10.4%) patients had died in the palbociclib + fulvestrant arm and 21 (12.1%) patients had died in the fulvestrant arm, RR: 0.86 [0.52; 1.43], p = 0.617. At the data cut-off on 23 October 2015, 71 (20.5%) patients had died in the palbociclib + fulvestrant arm and 41 (23.6%) patients had died in the fulvestrant arm, RR: 0.87 [0.62; 1.22], p = 0.448 (RR: Institute's calculation).
c: Symptom scales: increase in score by at least 10 points in comparison with baseline; functional scales: decrease in score by at least 10 points in comparison with baseline.
d: Number of patients with value at the start of the study and at least 1 value after the start of the study before end of the study medication (PRO analysis set).
e: The question was only put to patients with alopecia.
f: The question was only put to patients who were sexually active.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; HR: hazard ratio; IV: intravenous; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; ND: no data; PFS: progression-free survival; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 8: Results (morbidity, continuous) – palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population); data cut-off 5 December 2014

Study **Outcome category** **Outcome**	**Palbociclib + fulvestrant**			**Fulvestrant**			**Palbociclib + fulvestrant vs. fulvestrant**
	N[a]	**Values at start of study mean (SD)**	**Change at end of study mean (95% CI)[b]**	**N[a]**	**Values at start of study mean (SD)**	**Change at end of study mean (95% CI)[b]**	**MD [95% CI]; p-value[b]**
PALOMA-3							
Morbidity							
Health status (EQ-5D VAS)	330	72.9 (17.2)	−1.8 [−3.3; −0.3]	164	70.3 (19.8)	−2.6 [−4.8; −0.4]	0.8 [−1.9; 3.5]; 0.552

a: Number of patients considered in the analysis for the calculation of the effect estimate. Number of patients with measurement at the end of treatment: palbociclib + fulvestrant N = 81 and fulvestrant N = 74.
b: Changes, effect, 95% CI and p-value: MMRM with the factors treatment, time and the interaction term treatment*time, and baseline as covariable.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Table 9: Results (PFS and time to first subsequent [intravenous] chemotherapy – time to event), PALOMA-3 – palbociclib + fulvestrant vs. fulvestrant, data cut-off 5 December 2014

Study Outcome Data cut-off	Palbociclib + fulvestrant		Fulvestrant		Palbociclib + fulvestrant vs. fulvestrant
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
PALOMA-3					
PFS	347	9.2 [7.5; NA] 102 (29.4)	174	3.8 [3.5; 5.5] 93 (53.4)	0.42 [0.32; 0.56]; < 0.001
Time to first subsequent chemotherapy (oral or IV)	347	NA [NA; NA] 53 (15.3[c])	174	NA [7.5; NA] 55 (31.6[c])	0.41 [0.28; 0.60]; < 0.001
Time to first IV chemotherapy	347	NA [NA; NA] 26 (7.5)	174	NA [NA; NA] 28 (16.1[c])	0.43 [0.25; 0.74]; 0.002

a: Unless specified otherwise: effect and CI: Cox proportional hazards model, stratified by visceral metastases; p-value: 2-sided log-rank test.
b: The results on PFS are consistent with the second and fourth data cut-off (HR 0.46 [0.36; 0.59]; p < 0.001 and 0.50 [0.40; 0.62]; p < 0.001)
c: Institute's calculation.
CI: confidence interval; HR: hazard ratio; IV: intravenous; N: number of analysed patients; n: number of patients with event; NA: not achieved; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Patient-relevant outcomes with statistically significant difference in the PALOMA-3 study

Morbidity – symptoms

Pain

A statistically significant difference in favour of palbociclib + fulvestrant was shown for the outcome "pain", recorded with the EORTC QLQ-C30 questionnaire.

Upset by hair loss

A statistically significant difference in favour of fulvestrant was shown for the outcome "upset by hair loss", recorded with the EORTC QLQ-BR23 questionnaire.

Health-related quality of life

Emotional functioning

A statistically significant difference in favour of palbociclib + fulvestrant was shown for the outcome "emotional functioning", recorded with the EORTC QLQ-C30 questionnaire.

Sexual enjoyment

A statistically significant difference in favour of fulvestrant was shown for the outcome "sexual enjoyment", recorded with the EORTC QLQ-BR23 questionnaire.

Side effects

Severe AEs (CTCAE grade 3 or 4)

A statistically significant difference in favour of fulvestrant was shown for the outcome "severe AEs".

Patient-relevant outcomes without statistically significant difference in the PALOMA-3 study

There were no statistically significant differences for further patient-relevant outcomes from the categories of mortality, morbidity, health-related quality of life and side effects recorded in the PALOMA-3 study.

Further outcomes of the PALOMA-3 study

A statistically significant difference in favour of palbociclib + fulvestrant was shown for each of the outcomes "PFS" and "time to first subsequent (intravenous) chemotherapy" (see Table 9). An interpretation of the results on these 2 outcomes can be found in Section 2.3 of the present addendum.

Results on side effects of the PALOMA-3 study

Table 10: Common AEs (in the SOC and in the PT ≥ 10% in at least 1 study arm) – RCT, direct comparison: palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population, data cut-off 5 December 2014)

Study	Patients with event n (%)	
SOC[a] PT[a]	Palbociclib + fulvestrant N = 345	Fulvestrant N = 172
PALOMA-3		
Overall rate of adverse events	337 (97.7)	153 (89.0)
Blood and lymphatic system disorders	250 (72.5)	22 (12.8)
Anaemia	88 (25.5)	17 (9.9)
Leukopenia	70 (20.3)	2 (1.2)
Neutropenia	212 (61.4)	3 (1.7)
Thrombocytopenia	40 (11.6)	0 (0)
Eye disorders	59 (17.1)	16 (9.3)
Gastrointestinal disorders	220 (63.8)	97 (56.4)
Constipation	58 (16.8)	24 (14.0)
Diarrhoea	66 (19.1)	30 (17.4)
Nausea	100 (29.0)	45 (26.2)
Stomatitis	40 (11.6)	4 (2.3)
Vomiting	50 (14.5)	21 (12.2)
General disorders and administration site conditions	209 (60.6)	93 (54.1)
Fatigue	131 (38.0)	46 (26.7)
Infections and infestations	118 (34.2)	42 (24.4)
Investigations	150 (43.5)	26 (15.1)
Neutrophil count decreased	73 (21.2)	3 (1.7)
White blood cell count decreased	92 (26.7)	5 (2.9)
Metabolism and nutrition disorders	74 (21.4)	26 (15.1)
Decreased appetite	44 (12.8)	13 (7.6)
Musculoskeletal and connective tissue disorders	150 (43.5)	93 (54.1)
Arthralgia	45 (13.0)	28 (16.3)
Back pain	39 (11.3)	26 (15.1)
Pain in extremity	34 (9.9)	19 (11.0)
Nervous system disorders	131 (38.0)	61 (35.5)
Dizziness	37 (10.7)	16 (9.3)
Headache	73 (21.2)	30 (17.4)
Psychiatric disorders	59 (17.1)	33 (19.2)
Respiratory, thoracic and mediastinal disorders	122 (35.4)	47 (27.3)
Cough	45 (13.0)	18 (10.5)
Dyspnoea	37 (10.7)	11 (6.4)

(continued)

Table 10: Common AEs (in the SOC and in the PT ≥ 10% in at least 1 study arm) – RCT, direct comparison: palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population, data cut-off 5 December 2014) (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Palbociclib + fulvestrant** **N = 345**	**Fulvestrant** **N = 172**
Skin and subcutaneous tissue disorders	145 (42.0)	31 (18.0)
Alopecia	51 (14.8)	10 (5.8)
Vascular disorders	73 (21.2)	34 (19.8)
Hot flush	51 (14.8)	28 (16.3)

a: MedDRA version 17.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 11: Common SAEs (in the SOC and in the PT ≥ 1% in at least 1 study arm) – RCT, direct comparison: palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population, data cut-off 5 December 2014)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Palbociclib + fulvestrant** **N = 345**	**Fulvestrant** **N = 172**
PALOMA-3		
Overall rate of SAEs	33 (9.6)	24 (14.0)
Gastrointestinal disorders	4 (1.2)	2 (1.2)
Ascites	0 (0)	2 (1.2)
General disorders and administration site conditions	8 (2.3)	4 (2.3)
Infections and infestations	7 (2.0)	4 (2.3)
Pneumonia	1 (0.3)	2 (1.2)
Injury, poisoning and procedural complications	0 (0)	4 (2.3)
Investigations	4 (1.2)	0 (0)
Musculoskeletal and connective tissue disorders	2 (0.6)	4 (2.3)
Back pain	1 (0.3)	2 (1.2)
Nervous system disorders	3 (0.9)	3 (1.7)
Respiratory, thoracic and mediastinal disorders	6 (1.7)	7 (4.1)
Pleural effusion	1 (0.3)	3 (1.7)

a: MedDRA version 17.1.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 12: Common treatment discontinuations due to AEs (in the SOC and in the PT ≥ 1% in at least 1 study arm) – RCT, direct comparison: palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population, data cut-off 5 December 2014)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**Palbociclib + fulvestrant N = 345**	**Fulvestrant N = 172**
PALOMA-3		
Overall rate of treatment discontinuations due to AEs[b]	13 (3.8)	8 (4.7)
Blood and lymphatic system disorders	5 (1.4)	0 (0)
Gastrointestinal disorders	1 (0.3)	2 (1.2)
Ascites	0 (0)	2 (1.2)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	4 (2.3)
Pleural effusion	0 (0)	2 (1.2)

a: MedDRA version 17.1.
b: Discontinuation of at least one treatment component.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 13: Common AEs with CTCAE grade ≥ 3 (in the SOC and in the PT ≥ 1% in at least 1 study arm) – RCT, direct comparison: palbociclib + fulvestrant vs. fulvestrant, PALOMA-3 (total population, data cut-off 5 December 2014)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Palbociclib + fulvestrant** **N = 345**	**Fulvestrant** **N = 172**
PALOMA-3		
Overall rate of AEs with CTCAE grade ≥ 3	242 (70.1)	33 (19.2)
Blood and lymphatic system disorders	178 (51.6)	4 (2.3)
Neutropenia	167 (48.4)	0 (0)
Leukopenia	47 (13.6)	0 (0)
Anaemia	8 (2.3)	3 (1.7)
Thrombocytopenia	5 (1.4)	0 (0)
Investigations	84 (24.3)	4 (2.3)
Neutrophil count decreased	53 (15.4)	1 (0.6)
White blood cell count decreased	41 (11.9)	1 (0.6)
Aspartate aminotransferase increased	5 (1.4)	2 (1.2)
Alanine aminotransferase increased	4 (1.2)	0 (0)
General disorders and administration site conditions	16 (4.6)	2 (1.2)
Fatigue	7 (2.0)	2 (1.2)
Gastrointestinal disorders	10 (2.9)	5 (2.9)
Ascites	0 (0)	4 (2.3)
Metabolism and nutrition disorders	10 (2.9)	5 (2.9)
Infections and infestations	6 (1.7)	3 (1.7)
Musculoskeletal and connective tissue disorders	6 (1.7)	8 (4.7)
Back pain	3 (0.9)	4 (2.3)
Pain in extremity	0 (0)	3 (1.7)
Bone pain	2 (0.6)	2 (1.2)
Pathological fracture	0 (0)	2 (1.2)
Respiratory, thoracic and mediastinal disorders	6 (1.7)	6 (3.5)
Injury, poisoning and procedural complications	0 (0)	5 (2.9)
Nervous system disorders	5 (1.4)	4 (2.3)
Vascular disorders	5 (1.4)	1 (0.6)
Hypertension	4 (1.2)	1 (0.6)
Psychiatric disorders	3 (0.9)	2 (1.2)

a: MedDRA version 17.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Appendix B – Results on the outcomes "progression-free survival" and "time to first subsequent chemotherapy" in the PALOMA-2 study

Table 14: Results (PFS and time to first subsequent [intravenous] chemotherapy – time to event), palbociclib + letrozole vs. letrozole

Study Outcome Data cut-off	Palbociclib + letrozole		Letrozole		Palbociclib + letrozole vs. letrozole
	N	Median survival time in months [95% CI] Patients with event n (%)	N	Median survival time in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
PALOMA-2					
PFS	444	24.8 [22.1; NA] 194 (43.7)	222	14.5 [12.9; 17.1] 137 (61.7)	0.58 [0.46; 0.72]; < 0.001
Time to first subsequent chemotherapy (oral or IV)	444	NA [30.8; NA] 107 (24.1)	222	NA [NA; NA] 71 (32.0)	0.70 [0.52; 0.94]; 0.017
Time to first IV chemotherapy	444	NA [30.8; NA] 71 (16.0)	222	NA [30.8; NA] 51 (23.0)	0.66 [0.46; 0.95] 0.024

a: Unless specified otherwise: effect and CI: Cox proportional hazards model, stratified by visceral metastases; p-value: 2-sided log-rank test.

CI: confidence interval; HR: hazard ratio; IV: intravenous; N: number of analysed patients; n: number of patients with event; NA: not achieved; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Appendix C – Kaplan-Meier curves on the results on overall survival and progression-free survival from the studies PALOMA-2 and PALOMA-3

PALOMA-2

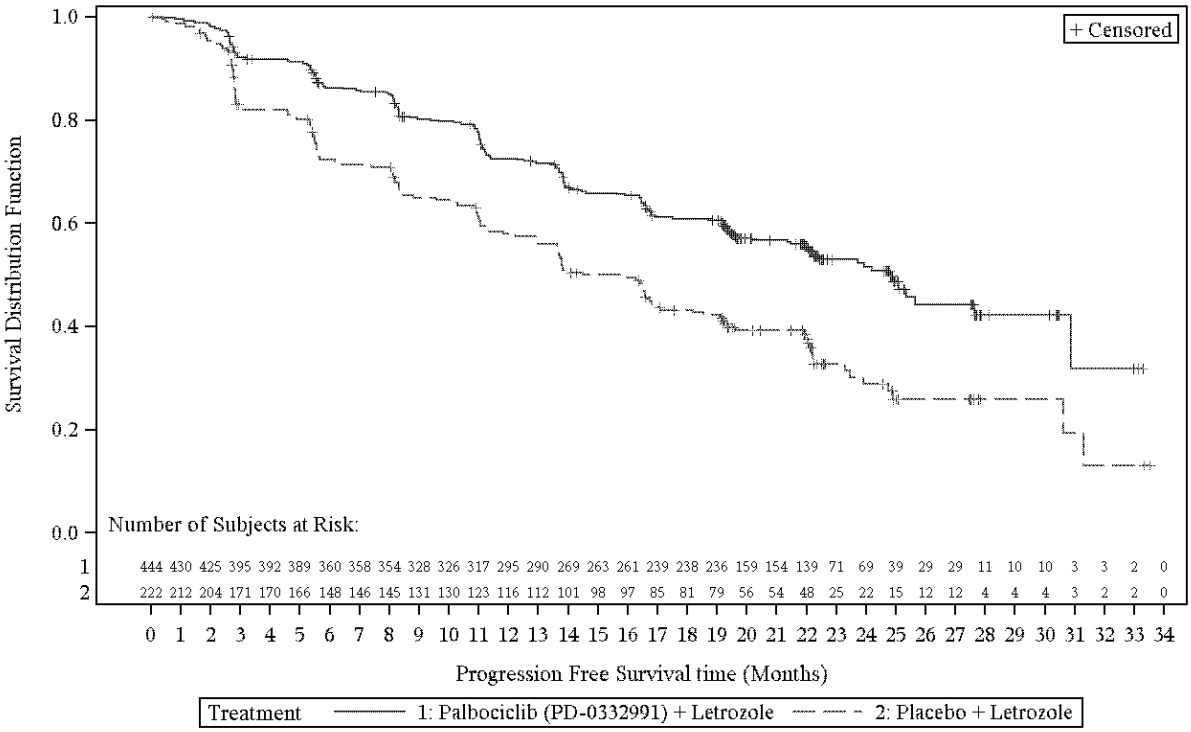

Figure 4: Kaplan-Meier curve for the outcome “progression-free survival” in the PALOMA-2 study, palbociclib + letrozole vs. placebo + letrozole, data cut-off on 26 February 2016

For the PALOMA-2 study, the company presented no survival time analysis for the outcome “overall survival”.

PALOMA-3

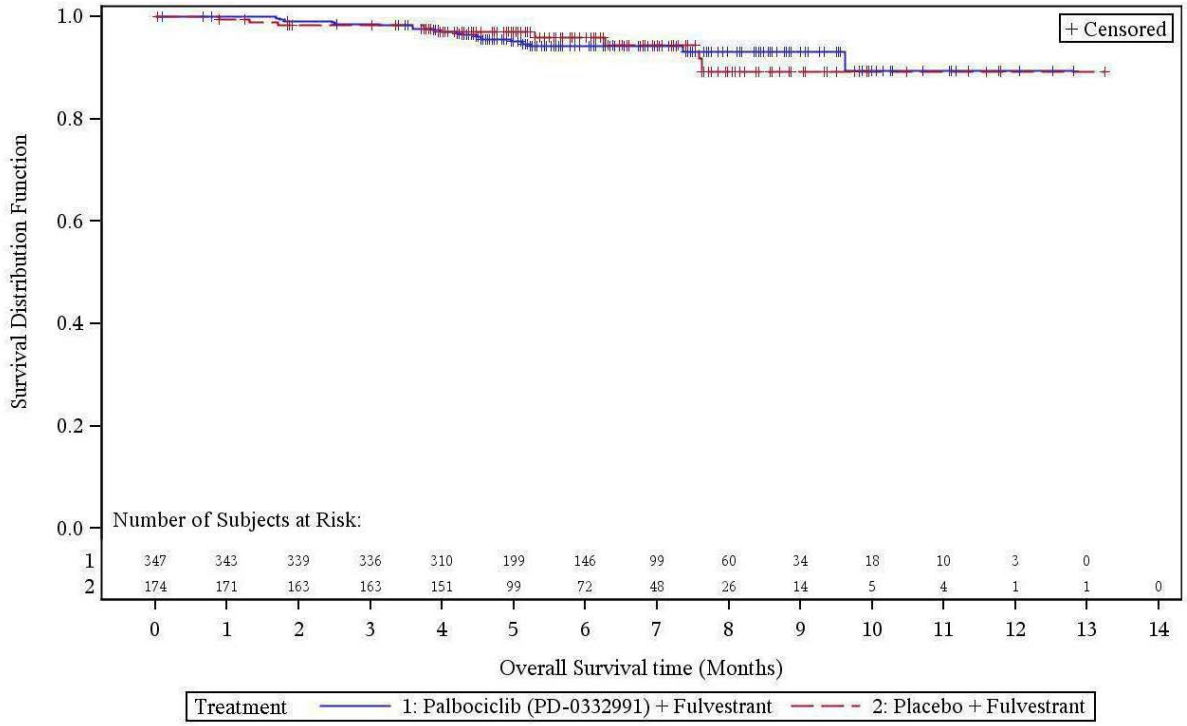

Figure 5: Kaplan-Meier curve for the outcome "overall survival" in the PALOMA-3 study, palbociclib + fulvestrant vs. placebo + fulvestrant, data cut-off on 5 December 2014

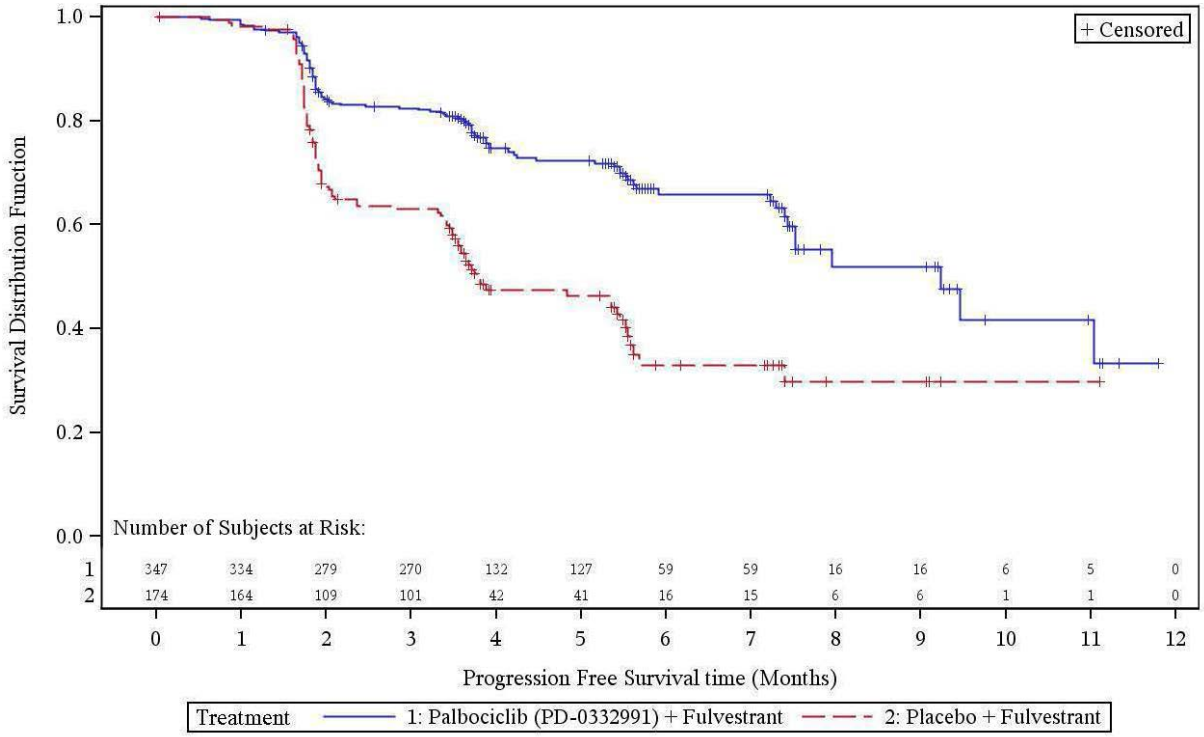

Figure 6: Kaplan-Meier curve for the outcome "progression-free survival" in the PALOMA-3 study, palbociclib + fulvestrant vs. placebo + fulvestrant, data cut-off on 5 December 2014