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Palbociclib (breast cancer, combination with an aromatase inhibitor 1) –

Addendum to Commission A22-66 (dossier assessment)[1]

Addendum

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Status: 24 November 2022

[1] Translation of addendum A22-120 *Palbociclib (Mammakarzinom, Kombination mit einem Aromatasehemmer) – Addendum zum Auftrag A22-66 (Dossierbewertung)* (Version 1.0; Status: 24 November 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.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Technology 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)
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 08 November 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A22-66 (Palbociclib – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the review of the corrected Kaplan-Meier curves for the outcomes of serious adverse events (SAEs), severe AEs (Common Technology Criteria for Adverse Events [CTCAE] grade ≥ 3) and discontinuation due to AEs from the studies PALOMA-2 and PALOMA-4 subsequently submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2], taking into account the information in the dossier [3].

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

2 Assessment

The randomized controlled trials (RCTs) PALOMA-1, PALOMA-2 and PALOMA-4 were included in the benefit assessment of palbociclib in combination with an aromatase inhibitor.

As already described in the dossier assessment of palbociclib (A22-66) [1], 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. In the commenting procedure [2], the company presented corrected Kaplan-Meier curves for these outcomes. These are plausible and concur with the values in the result tables presented in Module 4 A of the dossier. The Kaplan-Meier curves on the outcomes of SAEs, severe AEs and discontinuation due to AEs from the studies PALOMA-2 and PALOMA-4 are presented below.

Kaplan-Meier curves

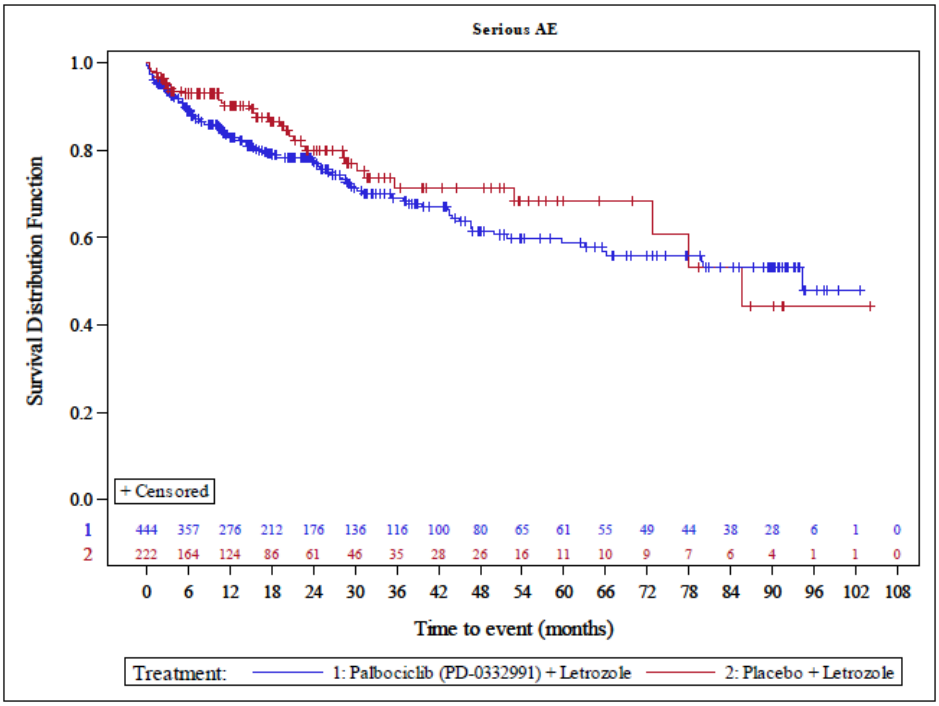

Figure 1: Kaplan-Meier curves for the outcome “SAEs” of the PALOMA-2 study - RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (data cut-off: 15 November 2021)

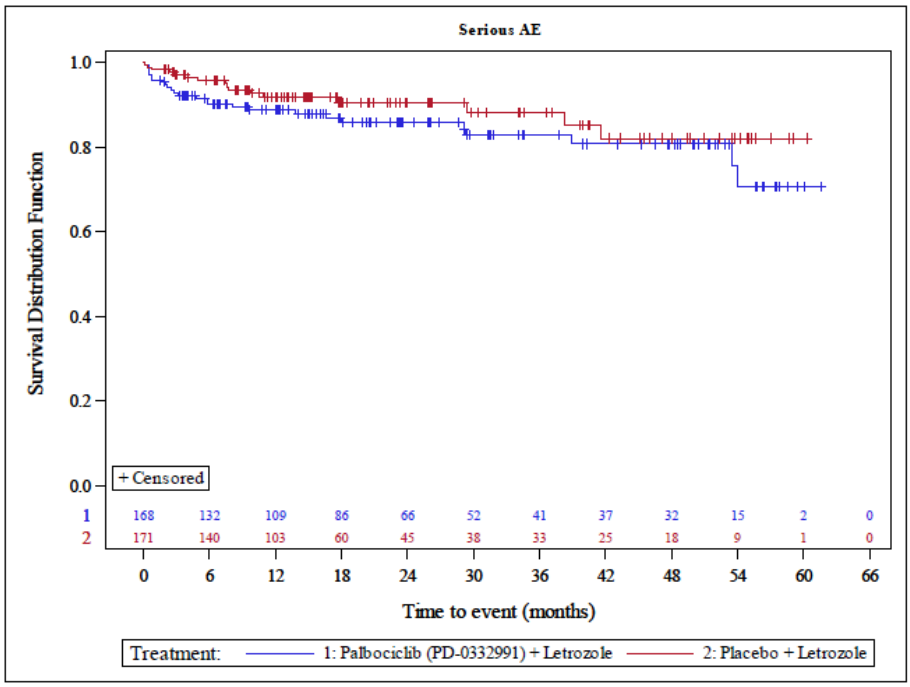

Figure 2: Kaplan-Meier curves for the outcome "SAEs" of the PALOMA-4 study - RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (data cut-off: 31 August 2020)

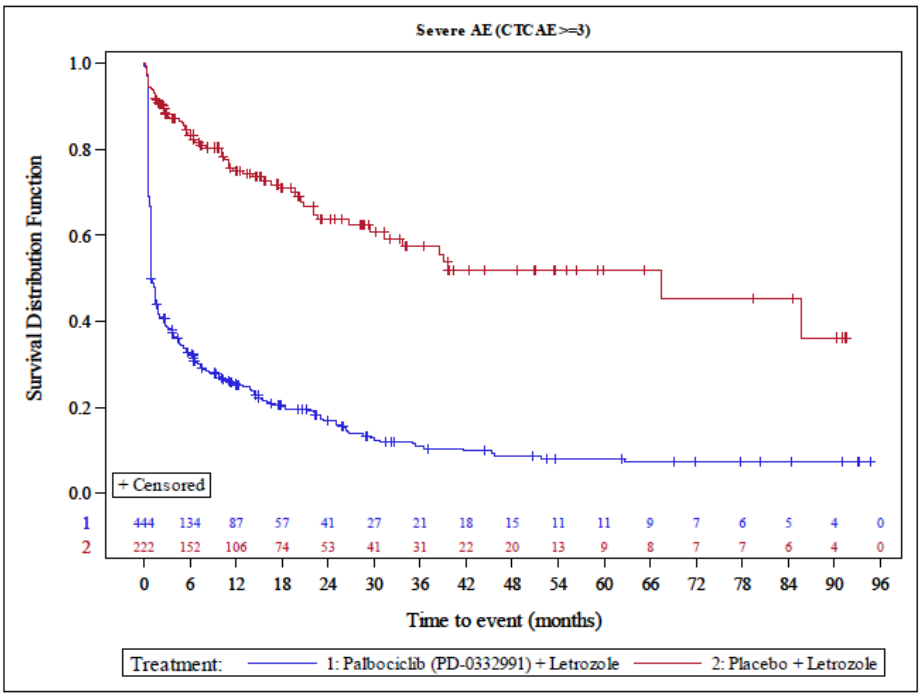

Figure 3: Kaplan-Meier curves for the outcome "severe AEs (CTCAE grade ≥ 3)" of the PALOMA-2 study – RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (data cut-off: 15 November 2021)

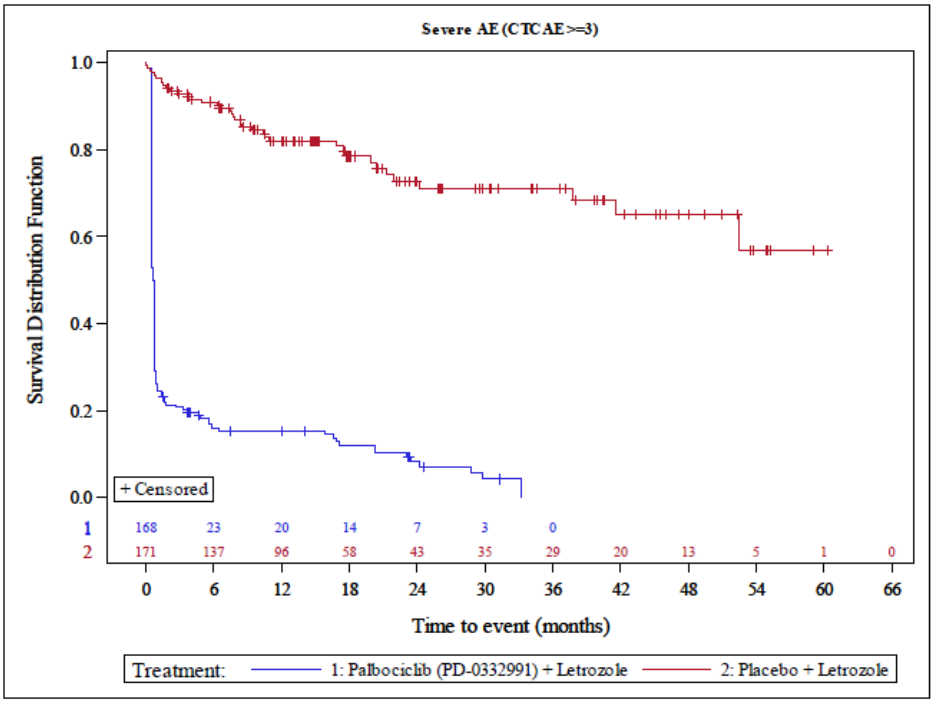

Figure 4: Kaplan-Meier curves for the outcome "severe AEs (CTCAE grade ≥ 3)" of the PALOMA-4 study - RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (data cut-off: 31 August 2020)

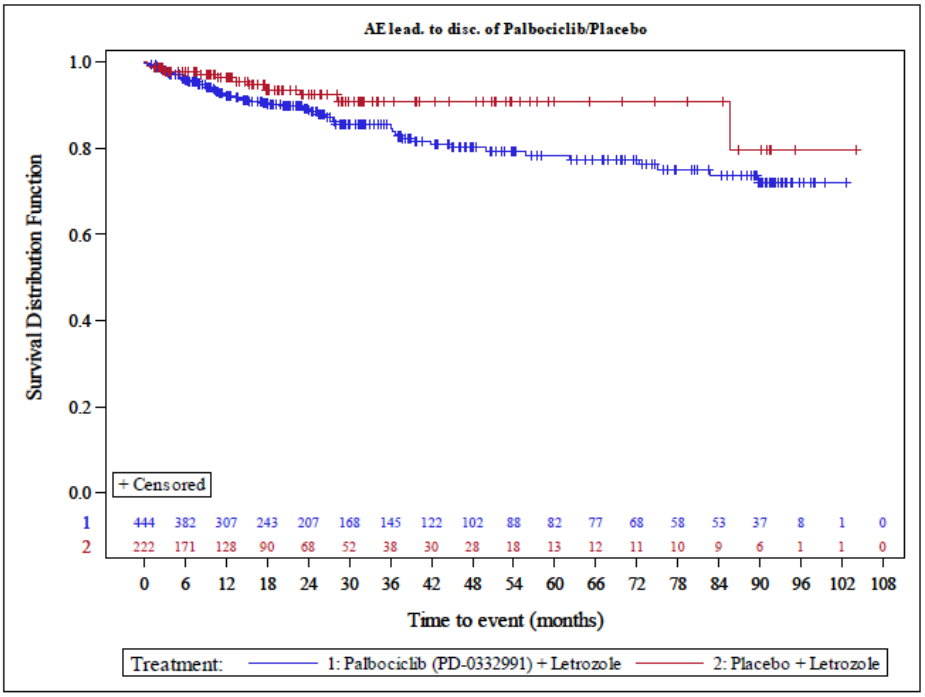

Figure 5: Kaplan-Meier curves for the outcome "discontinuation due to AEs (discontinuation of palbociclib or placebo due to AEs)" of the PALOMA-2 study - RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (data cut-off: 15 November 2021)

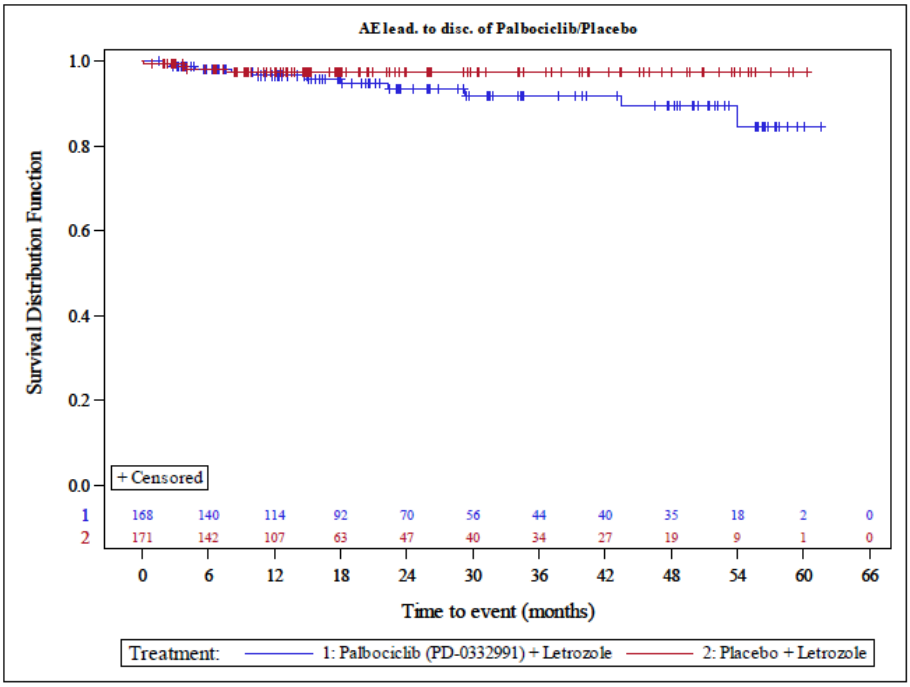

Figure 6: Kaplan-Meier curves for the outcome "discontinuation due to AEs (discontinuation of palbociclib or placebo due to AEs)" of the PALOMA-4 study - RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (data cut-off: 31 August 2020)

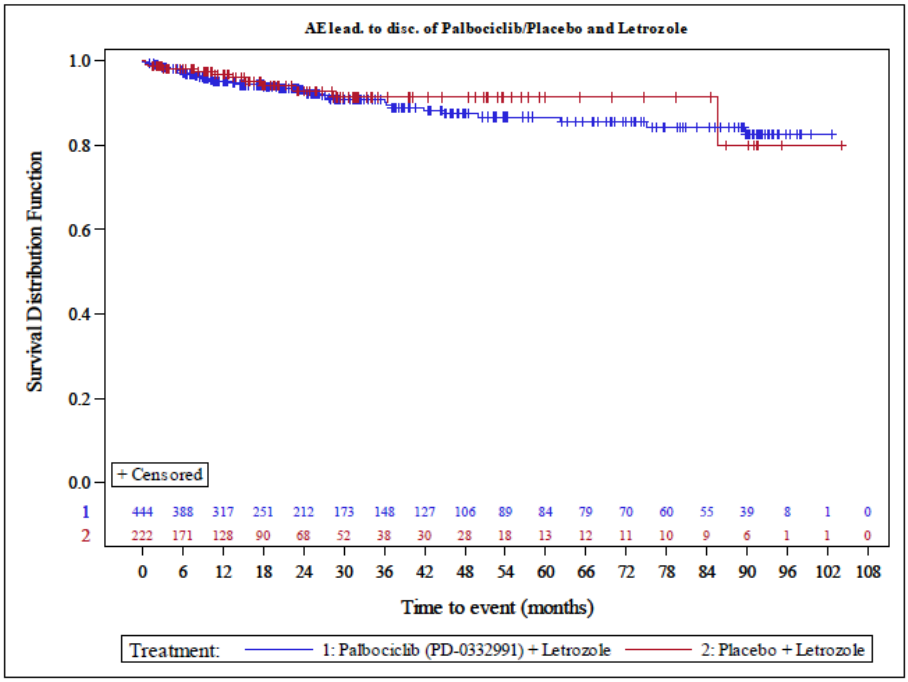

Figure 7: Kaplan-Meier curves for the outcome "discontinuation due to AEs (discontinuation of all drug components due to AEs)" of the PALOMA-2 study, which are presented as supplementary information - RCT, direct comparison: palbociclib + letrozole vs. placebo + letrozole (data cut-off: 15 November 2021)

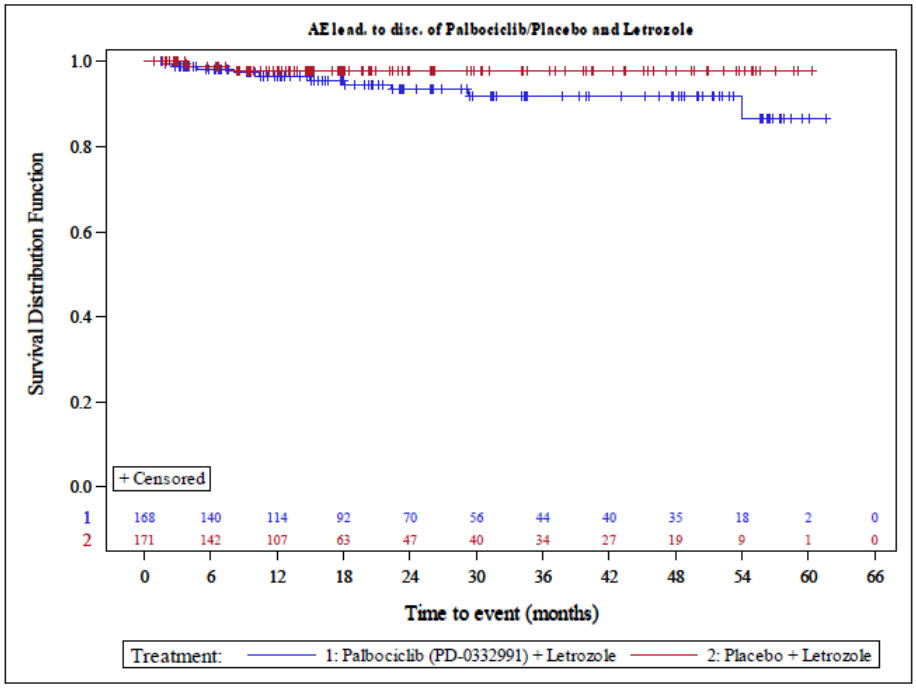

Figure 8: Kaplan-Meier curves for the outcome "discontinuation due to AEs (discontinuation of all drug components due to AEs)" of the PALOMA-4 study, which is presented as supplementary information - RCT, direct comparison: palbociclib + letrozole vs. placebo + + letrozole (data cut-off: 31 August 2020)

2.1 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of palbociclib from dossier assessment A22-66.

The following Table 1 shows the result of the benefit assessment of palbociclib, taking into account dossier assessment A22-66 and the present addendum.

Table 1: 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 G-BA decides on the added benefit.

3 References

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Palbociclib (Mammakarzinom, Kombination mit einem Aromatasehemmer) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung); Dossierbewertung [online]. 2022 [Accessed: 11.10.2022]. URL: https://www.iqwig.de/download/a22-66_palbociclib_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Pfizer. Stellungnahme zum IQWiG-Bericht Nr. 1431: Palbociclib (Mammakarzinom, Kombination mit einem Aromatasehemmer) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung). [Demnächst verfügbar unter: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/845/#beschluesse im Dokument "Zusammenfassende Dokumentation"].

3. Pfizer Pharma. Palbociclib (IBRANCE); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2022 [Accessed: 27.10.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/845/#dossier.