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Pembrolizumab (breast cancer 1) –

Addendum to Commission A22-63 (dossier assessment)[1]

Addendum

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[1] Translation of addendum A22-119 *Pembrolizumab (Mammakarzinom) – Addendum zum Auftrag A22-63 (Dossierbewertung)* (Version 1.0; Status: 25 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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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Isabelle Paulußen
- Katharina Hirsch
- Sabine Ostlender
- Regine Potthast
- Volker Vervölgyi

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
cLDA	constrained longitudinal data analysis
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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

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 for Commission A22-63 (Pembrolizumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the following analyses on patient-reported outcomes of the categories of morbidity and health-related quality of life subsequently (using constrained longitudinal data analysis [cLDA]) submitted by the pharmaceutical company (hereinafter referred to as "the company"):

- Morbidity
  - symptoms, recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module (EORTC QLQ-BR23)
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23

The assessment was conducted under consideration of the information provided in the dossier [2].

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

In benefit assessment A22-63 [1], the study KEYNOTE 522 was used to assess the added benefit of pembrolizumab in combination with chemotherapy for neoadjuvant, and thereafter following surgery as monotherapy for adjuvant treatment, in comparison with the appropriate comparator therapy (ACT) in adult patients with locally advanced or early-stage triple-negative breast cancer with a high risk of recurrence. A detailed description of the KEYNOTE 522 study can be found in benefit assessment on commission A22-63 [1].

The company's dossier contained no suitable data for the patient-reported outcomes of the categories "morbidity" and "health-related quality of life" (EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D VAS from the KEYNOTE 522 study. The lack of suitability resulted from the fact that the neoadjuvant and adjuvant treatment phases were each considered separately in the analyses and the results of the change from baseline of the respective treatment phase were presented. The dossier contained no analyses over the entire course of the study.

2.1 Analyses on symptoms (EORTC QLQ-C30, EORTC QLQ-BR23), on health status (EQ-5D VAS) and on health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)

Analyses subsequently submitted by the company are unsuitable

Within the framework of the commenting procedure, the company submitted analyses using cLDA for the scales of the EORTC QLQ-C30 and the EORTC QLQ-BR23 as well as for the EQ-5D VAS over the course of the study during both treatment phases of the KEYNOTE 522 study [3].

It should be noted that the analyses presented include the comparison of the start of the neoadjuvant treatment phase and week 24 of the adjuvant treatment phase. Therefore, the data provided by the company can only cover statements about the treatment duration of approx. 1 year and not about the entire course of the study up to 2 years after randomization.

The data on the patient-reported outcomes in the categories "morbidity" and "health-related quality of life" presented by the company were not interpretable. This is due to the overall strongly decreasing response rates of the questionnaires in the course of observation (at week 24 of the adjuvant treatment phase only approx. 57% in the intervention arm and 64% in the control arm). The decreased response rates between the last visit under neoadjuvant treatment (approx. 79% in the intervention arm and 81% in the control arm) and the first visit under adjuvant treatment (approx. 64% in the intervention arm and 74% in the control arm) is of particular relevance. Overall, due to the high drop-out rates that already existed at the start of the adjuvant phase and increased further in the further course, as well as to the response rates that differed between the treatment arms, it cannot be assumed that these occurred randomly. Thus, in the present data constellation, it is also not assumed that the assumption of a missing at random underlying the analyses presented is fulfilled.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) from dossier assessment A22-63.

The following Table 1 shows the result of the benefit assessment of pembrolizumab in combination with chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) under consideration of dossier assessment A22-63 and the present addendum.

Table 1: Pembrolizumab + chemotherapy (neoadjuvant)/pembrolizumab (adjuvant) – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery	Chemotherapy of physician's choice for the neoadjuvant treatment followed by watchful waiting after surgery	Added benefit not proven[b]
a. Presented is the respective ACT specified by the G¬BA. b. The KEYNOTE 522 study only included patients with an ECOG PS of 0 or 1 and only one male patient. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 and to male patients. ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee		

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. Pembrolizumab (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 11.10.2022]. URL: https://www.iqwig.de/download/a22-63_pembrolizumab_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. MSD Sharp & Dohme. Pembrolizumab (KEYTRUDA); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2022 [Accessed: 11.11.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/847/#dossier.

3. MSD Sharp & Dohme. Stellungnahme zum IQWiG-Bericht Nr. 1430: Pembrolizumab (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/847/#beschluesse in the document "Zusammenfassende Dokumentation"].