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Pertuzumab/trastuzumab (breast cancer, metastatic/locally recurrent; in combination with docetaxel) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pertuzumab/Trastuzumab (Mammakarzinom, metastasiert/lokal rezidiviert; in Kombination mit Docetaxel) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 2021). 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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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AGO	German Gynaecological Oncology Working Group
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
ESMO	European Society of Medical Oncology
ESO	European School of Oncology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NCCN	National Comprehensive Cancer Network
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code 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 subcutaneously administered fixed combination of pertuzumab and trastuzumab. 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 20 January 2021.

Research question

The aim of the present report is to assess the added benefit of the subcutaneously administered fixed combination of pertuzumab and trastuzumab (hereinafter referred to as pertuzumab/trastuzumab [SC]) in combination with docetaxel versus pertuzumab in free combination with trastuzumab and docetaxel as appropriate comparator therapy (ACT) in adult patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of pertuzumab/trastuzumab (SC) in combination with docetaxel

Therapeutic indication	**ACT[a]**
Adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease	Pertuzumab in combination with trastuzumab and docetaxel
a. Presentation of the ACT specified by the G-BA. The company chose trastuzumab in combination with a taxane (docetaxel or paclitaxel) as comparator therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

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

Deviation of the company from the research question of the present benefit assessment

Deviating from the G-BA's specification, the company chose trastuzumab in combination with a taxane (docetaxel or paclitaxel) as comparator therapy. Moreover, it did not choose pertuzumab/trastuzumab as subcutaneously administered fixed combination as intervention, but the intravenously administered free combination of pertuzumab with trastuzumab, each in

combination with docetaxel. Therefore, the comparison conducted by the company for its benefit assessment does not correspond to the research question of the present benefit assessment.

The deviation of the company from the research question of the present benefit assessment was not appropriate. The company justified its choice of the comparator therapy by stating that the combination of trastuzumab and taxane, in addition to the combination of pertuzumab with trastuzumab and chemotherapy, continued to be a treatment option recommended by guidelines. However, in most cases the guidelines uniformly recommend pertuzumab in combination with trastuzumab and chemotherapy as the preferred therapy option for patients with HER2-positive, metastatic breast cancer in first-line therapy, and thus support the ACT specified by the G-BA. The S3 guideline of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften [AWMF]) describes no alternative therapy option for this patient population besides the ACT specified by the G-BA. Overall, the guidelines provide no sufficient justification for a deviation from the G-BA's specification.

Regarding its choice of intervention, the company argued that the free intravenous combination of pertuzumab and trastuzumab (additionally in combination with docetaxel) was bioequivalent and also had an efficacy equivalent to the subcutaneous fixed combination of pertuzumab/trastuzumab. Moreover, it raised doubts on whether the comparison of two administration forms with identical drugs and comparable drug levels, which results from the G-BA's ACT, is meaningful for the proof of an added benefit. The company's reasoning is not appropriate. The non-inferiority of the fixed combination versus the free combination with regard to pharmacokinetics as well as the total pathological complete remission was proven within the framework of the approval; however, this does not exclude potential advantages of the subcutaneously administered fixed combination of pertuzumab/trastuzumab over the free intravenous combination (each in combination with docetaxel) for patient-relevant outcomes. The company did not provide sufficient justification for its argumentation as to why the comparison of the different administration forms with identical drugs and comparable drug levels should not be meaningful for the proof of an added benefit for the present therapeutic indication.

The argumentation of the company according to which the comparison of the free intravenous combination of pertuzumab with trastuzumab and docetaxel versus trastuzumab in combination with a taxane (docetaxel or paclitaxel) should be suitable for the benefit assessment of pertuzumab/trastuzumab (SC) is not adequate. In the present benefit assessment, pertuzumab/trastuzumab (SC) in combination with docetaxel is therefore compared with the ACT specified by the G-BA.

The evidence presented by the company is unsuitable for the assessment

For its benefit assessment, the company used the CLEOPATRA study to compare the free intravenous combination of pertuzumab + trastuzumab with placebo + trastuzumab, each in

combination with docetaxel, in adult patients with HER2-positive metastatic or locally recurrent, unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. The study deviates from the research question of the present benefit assessment with regard to both the intervention and the ACT and is therefore not suitable for the assessment.

Results

There are no data for the assessment of the added benefit of pertuzumab/trastuzumab (SC) in combination with docetaxel versus the ACT in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Hence, there is no hint of an added benefit of pertuzumab/trastuzumab (SC) in combination with docetaxel in comparison with the ACT; an added benefit is therefore not proven.

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

On the basis of the results presented, the probability and extent of the added benefit of pertuzumab/trastuzumab (SC) in combination with docetaxel versus the ACT are assessed as follows:

Table 3 shows a summary of the probability and extent of the added benefit of pertuzumab/trastuzumab (SC) in combination with docetaxel.

Table 3: Pertuzumab/trastuzumab (SC) in combination with docetaxel - probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease	Pertuzumab in combination with trastuzumab and docetaxel	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. The company chose trastuzumab in combination with a taxane (docetaxel or paclitaxel) as comparator therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

[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].

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of the subcutaneously administered fixed combination of pertuzumab and trastuzumab (hereinafter referred to as pertuzumab/trastuzumab [SC]) in combination with docetaxel versus pertuzumab in free combination with trastuzumab and docetaxel as ACT in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of pertuzumab/trastuzumab (SC) in combination with docetaxel

Therapeutic indication	**ACT[a]**
Adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease	Pertuzumab in combination with trastuzumab and docetaxel
a. Presentation of the ACT specified by the G-BA. The company chose trastuzumab in combination with a taxane (docetaxel or paclitaxel) as comparator therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

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

Deviation of the company from the research question of the present benefit assessment

Deviating from the G-BA's specification, the company chose trastuzumab in combination with a taxane (docetaxel or paclitaxel) as comparator therapy. Moreover, it did not choose pertuzumab/trastuzumab as subcutaneously administered fixed combination as intervention, but the intravenously administered free combination of pertuzumab with trastuzumab, each in combination with docetaxel. Therefore, the comparison conducted by the company for its benefit assessment does not correspond to the research question of the present benefit assessment.

The deviation of the company from the research question of the present benefit assessment is not appropriate. This is explained below.

Deviation of the company from the ACT

The company justified its choice of the comparator therapy by stating that the combination of trastuzumab and taxane, in addition to the combination of pertuzumab with trastuzumab and chemotherapy, continued to be a therapy option recommended by guidelines and in doing so

referred to the guidelines of the German Gynaecological Oncology Working Group (AGO) [3], the European School of Oncology (ESO) and the European Society of Medical Oncology (ESMO) [4] and the National Comprehensive Cancer Network (NCCN) [5]. However, like the S3 guideline of the AWMF [6] and also the guideline of the American Society of Clinical Oncology (ASCO) [7], these guidelines prioritise pertuzumab in combination with trastuzumab and chemotherapy as the preferred treatment option for patients with HER2-positive, metastatic breast cancer in first-line therapy, and thus support the ACT specified by the G-BA. The S3 guideline of the AMWF describes no alternative therapy option for this patient population besides the ACT specified by the G-BA. Overall, the guidelines provide no sufficient justification for a deviation from the G-BA's specification.

Deviation of the company from the intervention

The company used the intravenously administered free combination of pertuzumab and trastuzumab (additionally in combination with docetaxel) as intervention for the benefit assessment. It justified this with the fact that the free intravenous combination was bioequivalent and also had an efficacy equivalent to the subcutaneous fixed combination. Moreover, it raised doubts on whether the comparison of two administration forms with identical drugs and comparable drug levels, which results from the G-BA's ACT, is meaningful for the proof of an added benefit.

The company's reasoning is not appropriate. Differences for all categories of patient-relevant outcomes can potentially result from different administration forms, which could, for example, justify an added benefit of pertuzumab/trastuzumab (SC) versus the free intravenous combination of pertuzumab and trastuzumab, each in combination with docetaxel. Therefore, a study on the comparison of the different administration forms would be suitable for the assessment of the added benefit of pertuzumab/trastuzumab (SC), provided that patient-relevant outcomes were collected. In the dossier itself, the company presented supplementary results from the ongoing FeDeriCa study [8], which, in addition to the non-inferiority with regard to pharmacokinetics and total pathological complete remission, also investigated patient-relevant outcomes (e.g. "overall survival" and "adverse events"). This study investigates the comparison of the subcutaneously administered fixed combination of pertuzumab/trastuzumab with the free intravenous combination (each in combination with chemotherapy), however, in a patient population that deviates from the present therapeutic indication (patients with resectable or locally advanced, inflammatory early-stage HER2-positive breast cancer). The study was therefore irrelevant for the assessment of the added benefit in the present therapeutic indication. Based on the results available from the study so far, the non-inferiority of the fixed combination versus the free combination with regard to pharmacokinetics and total pathological complete remission was proven within the framework of the approval [9]. However, this does not exclude potential advantages of the subcutaneously administered fixed combination of pertuzumab/trastuzumab over the free intravenous combination (each in combination with docetaxel) for patient-relevant outcomes. The company did not provide sufficient justification for its argumentation as to why the comparison of the different administration forms with

identical drugs and comparable drug levels should not be meaningful for the proof of an added benefit for the present therapeutic indication.

Conclusion

The argumentation of the company according to which the comparison of the free intravenous combination of pertuzumab with trastuzumab and docetaxel versus trastuzumab in combination with a taxane (docetaxel or paclitaxel) should be suitable for the benefit assessment of pertuzumab/trastuzumab (SC) is not adequate. In the present benefit assessment, pertuzumab/trastuzumab (SC) in combination with docetaxel is therefore compared with the ACT specified by the G-BA.

2.3 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 pertuzumab / trastuzumab (status: 16 November 2020)
- #bibliographical literature search on pertuzumab / trastuzumab (last search on 16 November 2020)
- search in trial registries/trial results databases for studies on pertuzumab (last search on 17 November 2020)
- search on the G-BA website for pertuzumab (last search on 17 November 2020)

To check the completeness of the study pool:

- search in trial registries for studies on pertuzumab/trastuzumab (last search on 9 February 2021)

The check did not identify any relevant studies for the assessment of the added benefit of pertuzumab/trastuzumab (SC) in combination with docetaxel in comparison with the ACT.

Evidence provided by the company

For its benefit assessment, the company used the CLEOPATRA study [10] to compare the free intravenous combination of pertuzumab + trastuzumab with placebo + trastuzumab, each in combination with docetaxel, in adult patients with HER2-positive metastatic or locally recurrent, unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. The company presented supplementary results from the ongoing PUFFIN study [11], which investigates the same comparison in a Chinese patient population, as well as results from the studies CLEOPATRA and PUFFIN summarized in a meta-analysis. The CLEOPATRA study, in which the free combination of pertuzumab with trastuzumab and docetaxel was assessed, was used for the benefit assessment of pertuzumab (benefit assessment on Commission A13-10 [12]).

The analyses presented by the company for the comparison of the free intravenous combination of pertuzumab + trastuzumab versus placebo + trastuzumab, each in combination with docetaxel, are not suitable for the investigation of the research question of the present benefit assessment (for explanation see Section 2.2).

Moreover, the company presented supplementary results from the FeDeriCa study, which investigates the comparison of the subcutaneously administered fixed combination of pertuzumab/trastuzumab with the free intravenous combination of pertuzumab and trastuzumab, each in combination with chemotherapy, in patients with resectable or locally advanced, inflammatory early-stage HER2-positive breast cancer. This study is irrelevant for the present benefit assessment because the patient population investigated deviates from the present therapeutic indication (see Section 2.2).

2.4 Results on added benefit

There are no data for the assessment of the added benefit of pertuzumab/trastuzumab (SC) in combination with docetaxel versus the ACT in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. Hence, there is no hint of an added benefit of pertuzumab/trastuzumab (SC) in combination with docetaxel in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of pertuzumab/trastuzumab (SC) in combination with docetaxel in comparison with the ACT is summarized in Table 5.

Table 5: Pertuzumab/trastuzumab (SC) in combination with docetaxel - probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease	Pertuzumab in combination with trastuzumab and docetaxel	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. The company chose trastuzumab in combination with a taxane (docetaxel or paclitaxel) as comparator therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

The assessment described above deviates from that of the company, which derived proof of major added benefit.

The G-BA decides on the added benefit.

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.

1. Institute for Quality and Efficiency in Health Care. General methods 6.0 (German version) [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Arbeitsgemeinschaft Gynäkologische Onkologie. Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome [online]. 2020. URL: https://www.ago-online.de/fileadmin/ago-online/downloads/_leitlinien/kommission_mamma/2020/Alle_aktuellen_Empfehlungen_2020.pdf.

4. Cardoso F, Paluch-Shimon S, Senkus E et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020; 31(12): 1623-1649. https://dx.doi.org/10.1016/j.annonc.2020.09.010.

5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology - Breast Cancer, Version 6.2020 [online]. 2020. URL: https://www.nccn.org.

6. Leitlinienprogramm Onkologie. S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms [online]. 2020. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mammakarzinom_4_0/Version_4.3/LL_Mammakarzinom_Langversion_4.3.pdf.

7. Giordano SH, Temin S, Chandarlapaty S et al. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2018; 36(26): 2736-2740. https://dx.doi.org/10.1200/JCO.2018.79.2697.

8. Tan AR, Im S-A, Mattar A et al. Fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection plus chemotherapy in HER2-positive early breast cancer (FeDeriCa): a randomised, open-label, multicentre, non-inferiority, phase 3 study. Lancet Oncol 2021; 22(1): 85-97. https://dx.doi.org/10.1016/S1470-2045(20)30536-2.

9. European Medicines Agency. Phesgo; Assessment report [online]. 2021 [Accessed: 17.03.2021]. URL: https://www.ema.europa.eu/documents/assessment-report/phesgo-epar-public-assessment-report_en.pdf.

10. Swain SM, Miles D, Kim SB et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 2020; 21(4): 519-530. https://dx.doi.org/10.1016/S1470-2045(19)30863-0.

11. Xu B, Li W, Zhang Q et al. Pertuzumab, trastuzumab, and docetaxel for Chinese patients with previously untreated HER2-positive locally recurrent or metastatic breast cancer (PUFFIN): a phase III, randomized, double-blind, placebo-controlled study. Breast Cancer Res Treat 2020; 182(3): 689-697. https://dx.doi.org/10.1007/s10549-020-05728-w.

12. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pertuzumab – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2013 [Accessed: 05.07.2013]. URL: https://www.iqwig.de/download/A13-10_Pertuzumab_Nutzenbewertung-35a-SGB-V.pdf.

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