IQWiG Reports – Commission No. A21-10

Pertuzumab/trastuzumab (breast cancer, neoadjuvant) –

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 (Mammarkarzinom, neoadjuvant) – 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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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

Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Erika Penner
- Charlotte Hecker
- Marco Knelangen
- Stefan Kobza
- Sabine Ostlender
- Cornelia Rüdig
- Anke Schulz
- Beate Wieseler

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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
AE	adverse event
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FEC	5-fluorouracil, epirubicin and cyclophosphamide
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
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)
SPC	Summary of Product Characteristics
tpCR	total pathological complete remission

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 (hereinafter referred to as pertuzumab/trastuzumab [SC]). 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 19 January 2021.

Research question

The aim of the present report was to assess the added benefit of pertuzumab/trastuzumab (SC) in combination with chemotherapy compared with the appropriate comparator therapy (ACT) in neoadjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence.

Table 2 shows the research question of the benefit assessment and the ACT specified by the GBA.

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

Therapeutic indication	**ACT[a]**
Neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence	Therapeutic regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin)[b]
a. Presentation of the ACT specified by the G-BA. b. The implementation of an anthracycline-containing therapy protocol has to be balanced under consideration of the cardiovascular risks. Trastuzumab should not be used in combination with anthracyclines, but sequentially in combination with a taxane. Cardiac functions have to be closely monitored. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company followed the G-BA's specification on the ACT.

Within the framework of the approval, the bio- and efficacy equivalence of the subcutaneous fixed combination and the intravenous free combination of pertuzumab and trastuzumab was proven on the basis of the FeDeriCa study to confirm the non-inferiority with regard to pharmacokinetics. The company therefore derived the added benefit of pertuzumab/trastuzumab independently of the administration form and presented the results of the FeDeriCa study as supplementary information. This approach is principally comprehensible, but the study does not rule out potential advantages of the subcutaneously

administered fixed combination over the intravenous free combination of pertuzumab and trastuzumab for patient-relevant outcomes.

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

Results

Studies included

In its dossier, the company presented results from the studies NeoSphere and PEONY, but only used the NeoSphere study for the benefit assessment. The PEONY study is not suitable for the present benefit assessment, as the adjuvant treatment phase of the study investigates different therapy regimens and the study results can thus not be attributed to the neoadjuvant treatment phase. Moreover, the available data cut-off contains no relevant data for the benefit assessment.

Therefore, only the results of the NeoSphere study, which was already assessed in benefit assessment A15-34 and which investigated the free intravenous combination of pertuzumab and trastuzumab, are available for the benefit assessment of pertuzumab/trastuzumab (SC). Due to the proven bio- and efficacy equivalence of the two administration forms, the results of the NeoSphere study could be transferred to the subcutaneous fixed combination of pertuzumab/trastuzumab. The characteristics and results of the study can be found in benefit assessment A15-34 and are not presented again in this benefit assessment. Individual new aspects (the use of 5-fluorouracil and the transferability of the results on adverse events (AEs) from the free intravenous to the fixed subcutaneous combination) have arisen for the present benefit assessment, which, however, have no effect on the result of the benefit assessment.

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

Based on the results presented in benefit assessment A15-34, the probability and extent of the added benefit of pertuzumab/trastuzumab (SC) in combination with the ACT are assessed as follows:

In summary, there is a hint of lesser benefit of pertuzumab/trastuzumab (SC) in comparison with the ACT for patients with HER2-positive locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence. This lesser benefit was derived due to a negative effect for the outcome “discontinuation due to AEs” (outcome category serious/severe side effects, especially cardiac disorders). This conclusion only refers to the treatment regimens investigated

[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].

in the NeoSphere study, however. The transferability of the study results to the German health care context is questionable.

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

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

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence[b]	Therapeutic regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin)[c]	Hint of lesser benefit

a. Presentation of the ACT specified by the G-BA.
b. Only patients with an ECOG PS of 0 or 1 were included in the NeoSphere study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
c. The implementation of an anthracycline-containing therapy protocol has to be balanced under consideration of the cardiovascular risks. Trastuzumab should not be used in combination with anthracyclines, but sequentially in combination with a taxane. Cardiac functions have to be closely monitored.

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

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

2.2 Research question

The aim of the present report was to assess the added benefit of pertuzumab/trastuzumab (SC) in combination with chemotherapy compared with the ACT in neoadjuvant treatment of adult patients with HER2-positive locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence.

Table 4 shows the research question of the benefit assessment and the ACT specified by the GBA.

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

Therapeutic indication	**ACT[a]**
Neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence	Therapeutic regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin)[b]
a. Presentation of the ACT specified by the G-BA. b. The implementation of an anthracycline-containing therapy protocol has to be balanced under consideration of the cardiovascular risks. Trastuzumab should not be used in combination with anthracyclines, but sequentially in combination with a taxane. Cardiac functions have to be closely monitored. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2	

The company followed the G-BA's specification on the ACT.

Within the framework of the approval [3], the bio- and efficacy equivalence of the subcutaneous fixed combination and the intravenous free combination of pertuzumab and trastuzumab was proven on the basis of the FeDeriCa study [4] to confirm the non-inferiority with regard to pharmacokinetics. The company therefore derived the added benefit of pertuzumab/trastuzumab independently of the administration form and presented the results of the FeDeriCa study as supplementary information. This approach is principally comprehensible, but the study does not rule out potential advantages of the subcutaneously administered fixed combination over the intravenous free combination of pertuzumab and trastuzumab for patient-relevant outcomes.

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

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 additional relevant studies.

2.3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – Randomized controlled trial (RCT), direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] yes/no [citation])
WO20697 (NeoSphere[d])	Yes	Yes	No	No[e]	Yes [5-7]	Yes [8-13]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and other available sources.
d. Hereinafter, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

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

The study pool for the present benefit assessment of pertuzumab/trastuzumab (SC) compared to the ACT consists of the NeoSphere study, which was already assessed within the framework of the benefit assessment of the free intravenous combination of pertuzumab and trastuzumab (benefit assessment A15-34 and the associated addendum [14,15]). The study pool corresponds to that used by the company.

In its information retrieval, the company also identified the ongoing RCT YO28762 (PEONY) [16,17] as a relevant study, but presented the results of the study and a meta-analytical summary of the two studies NeoSphere and PEONY only as supplementary information and derived no added benefit on this basis.

The PEONY study was not relevant for the present benefit assessment

The PEONY study was not included for the present benefit assessment, which is justified below. The characteristics of the PEONY study are presented in Appendix A of the full dossier assessment

Study design

The PEONY study is a double-blind, randomized trial comparing pertuzumab + trastuzumab + docetaxel with placebo + trastuzumab + docetaxel.

The study included treatment-naive adult patients with HER2-positive locally advanced or early-stage breast cancer with primary tumours > 2 cm in diameter and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 1. Patients with inflammatory breast cancer were not included in the study.

The study was conducted in China, Korea, Taiwan and Thailand. A total of 329 patients were assigned either to treatment with pertuzumab + trastuzumab + docetaxel (N = 219) or to placebo + trastuzumab + docetaxel (N = 110) in a 2:1 ratio. The patients were operated after approximately 12-week neoadjuvant treatment with pertuzumab or placebo + trastuzumab + docetaxel. The patients then received adjuvant chemotherapy with 5-fluorouracil, epirubicin and cyclophosphamide (FEC) for 9 weeks, followed by treatment with pertuzumab or placebo + trastuzumab for 39 weeks.

Data for the study were only available on the first data cut-off of 23 October 2017, which, according to the study protocol, took place at the time point of the last patient's surgery. Results for the final data cut-off at the end of the study are not yet available.

Primary outcome of the study was total pathological complete remission (tpCR) as determined by an independent committee. Patient-relevant secondary outcomes were outcomes of the categories "mortality", "morbidity" and "side effects". Outcomes on health-related quality of life were not recorded in the study.

No sufficient patient-relevant data available

For the present benefit assessment, only results from the first data cut-off were available for the ongoing PEONY study, as was described above. This data cut-off took place at the time point of the last patient's surgery. According to the protocol, data on the primary outcome "tpCR" and on AEs were recorded at this time point. However, these data do not permit an assessment of the added benefit of pertuzumab/trastuzumab. On the one hand, this is due to the fact that the outcome "tpCR" is not patient-relevant and was not used for the benefit assessment (see section below on the relevance of the outcome "pathological complete remission (pCR)"). Thus, only data on AEs are available, and these are limited to the period until the first data cut-off. Consequently, not all AEs of the entire therapy regimen have been covered, as part of the therapy regimen was also used after surgery in the adjuvant treatment phase. On the other hand, substantial effects of the neoadjuvant therapy, such as on all-cause mortality or on the occurrence of recurrences, were only recorded in the adjuvant treatment phase. Adequate balancing of the benefits and harms and thus an assessment of the added benefit of pertuzumab/trastuzumab is therefore not possible on the basis of the present first data cut-off.

Different adjuvant therapies in the treatment arms

Depending on their randomization, the patients received pertuzumab and trastuzumab in the intervention arm and placebo and trastuzumab in the comparator arm following surgery and 9-week adjuvant chemotherapy with FEC. Due to the different therapies in the adjuvant phase, an observed effect could no longer be clearly attributed to the neoadjuvant use of pertuzumab/trastuzumab, but would potentially also be influenced by the adjuvant use of pertuzumab/trastuzumab. It is therefore unclear which research question was addressed in the study (neoadjuvant or adjuvant). Therefore, the PEONY study does not allow a conclusion on the added benefit of pertuzumab/trastuzumab in the neoadjuvant use in patients with HER2-postitive locally advanced or early-stage breast cancer at high risk of recurrence, even when the final data cut-off is available.

Further limitations of the PEONY study

As in the NeoSphere study, treatment in the PEONY study was divided into a neoadjuvant and an adjuvant phase. However, according to national and international guidelines, a division of the therapy is advised against [18,19]. Moreover, the use of 5-flurorouracil as part of the FEC therapy regimen is also not recommended, as its additional use does not lead to an improvement of the prognosis on the one hand and increases toxicity on the other [18]. Docetaxel was also used in neoadjuvant therapy at a dose of 75 mg/m^2. However, the Summary of Product Characteristics (SPC) recommends a dose of 100 mg/m^2 when used in combination with trastuzumab or pertuzumab [20-22].

New aspects on the NeoSphere study

Relevance of the outcome "pcR"

For the present benefit assessment, the company submitted the results of the NeoSphere study, which had already been fully assessed in the benefit assessment of the free intravenous combination of pertuzumab and trastuzumab (benefit assessment A15-34). Due to the positive effects in the outcome "pCR", the company derived an indication of considerable added benefit for the present benefit assessment. As already described in the benefit assessment of the free intravenous combination (Section 2.7.2.4.3 of benefit assessment A15-34), the outcome "pCR" was not considered to be patient-relevant. Moreover, the recently published meta-analysis [23] cited by the company is not suitable for proving the surrogate validity of pCR for the outcomes "overall survival" and event-free survival, because the study only describes an association of pCR and patient-relevant outcomes at an individual level and not a correlation of effects. The outcome "pCR" was therefore not included for the present benefit assessment.

Use of 5-fluorouracil

In the NeoSphere study, an FEC treatment regimen was used postoperatively. The use of 5-fluorouracil in the context of anthracycline-based chemotherapy is not listed in guidelines [19] or is even advised against because its additional use does not lead to an improvement of the prognosis on the one hand and increases toxicity on the other [18]. In addition to the limitations described in the benefit assessment of the free intravenous combination (use of anthracyclines

in parallel with trastuzumab, division of therapy into a neoadjuvant and an adjuvant phase), the use of 5-fluorouracil represents a limitation in the transferability of the study results to the German health care context.

AEs of the different administration forms

For the present benefit assessment, the added benefit of the subcutaneous fixed combination of pertuzumab/trastuzumab had to be shown. Basically, the results of the NeoSphere study were transferred to the present research question. The transfer was examined particularly for AE. The results of the NeoSphere study only show AEs of the free intravenous administration form. The side effect profile of subcutaneous administration might differ from this. This applies, for example, to adverse events that are directly attributable to the type of application (e.g. injection site reactions or infusion-related reactions). However, the results of the FeDeriCa study show that the side effect profiles of the two administration forms are largely comparable. This applies in particular to the overall rates of serious AEs (SAEs), severe AEs and discontinuations due to AEs, as well as cardiac AEs and most of the common non-serious/non-severe AEs. The results on AEs of the NeoSphere study can therefore be transferred to the subcutaneous fixed combination pertuzumab/trastuzumab.

Conclusion

Only the results of the NeoSphere study, which was already assessed in benefit assessment A15-34 and which investigated the free intravenous combination of pertuzumab and trastuzumab, were available for the benefit assessment of pertuzumab/trastuzumab (SC). Due to the proven bio- and efficacy equivalence of the two administration forms, the results of the NeoSphere study could be transferred to the subcutaneous fixed combination of pertuzumab/trastuzumab. The previously mentioned new aspects on the NeoSphere study had no effect on the result of the benefit assessment.

2.4 Results on added benefit

Only the data already assessed in the benefit assessment of the free intravenous combination were available for the benefit assessment of pertuzumab/trastuzumab (SC). The results are presented in Section 2.4 of the first benefit assessment (A15-34) and are not listed again in the present benefit assessment.

2.5 Probability and extent of added benefit

Table 6 summarizes the result of the assessment of the added benefit of pertuzumab/trastuzumab (SC) in comparison with the ACT.

Table 6: Pertuzumab/trastuzumab (SC) in combination with chemotherapy - probability and extent of added benefit:

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory or early stage breast cancer at high risk of recurrence[b]	Therapeutic regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin)[c]	Hint of lesser benefit

a. Presentation of the ACT specified by the G-BA.
b. Only patients with an ECOG PS of 0 or 1 were included in the NeoSphere study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
c. The implementation of an anthracycline-containing therapy protocol has to be balanced under consideration of the cardiovascular risks. Trastuzumab should not be used in combination with anthracyclines, but sequentially in combination with a taxane. Cardiac functions have to be closely monitored.

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

In summary, there is a hint of lesser benefit of pertuzumab/trastuzumab (SC) in comparison with the ACT for patients with HER2-positive locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence. This lesser benefit was derived due to a negative effect for the outcome "discontinuation due to AEs" (outcome category "serious/severe side effects, especially cardiac disorders") (see Section 2.5 of A15-34). This conclusion only refers to the treatment regimens investigated in the NeoSphere study, however. The transferability of the study results to the German health care context is questionable.

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit based on the results of the NeoSphere study.

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

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: 13.11.2020]. URL: https://www.iqwig.de/download/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. 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.

4. Tan AR, Im SA, 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.

5. Hoffmann-La Roche. A Study of Pertuzumab in Combination With Herceptin in Patients With HER2 Positive Breast Cancer [online]. 2017 [Accessed: 15.02.2021]. URL: https://ClinicalTrials.gov/show/NCT00545688.

6. F. Hoffmann-La Roche. Estudio de fase II multicéntrico, internacional, randomizado de trastuzumab y docetaxel frente a trastuzumab, docetaxel y pertuzumab, comparado con trastuzumab y pertuzumab en pacientes con cáncer de mama localmente avanzado, inflamatorio o precoz HER2 positivo [online]. [Accessed: 15.02.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-001105-13.

7. Productos Roche. A Study of Pertuzumab in Combination With Herceptin in Patients With HER2 Positive Breast Cancer [online]. [Accessed: 15.02.2021]. URL: https://www.ins.gob.pe/ensayosclinicos/rpec/recuperarECPBNuevoEN.asp?numec=121-08.

8. Gianni L, Pienkowski T, Im YH et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13(1): 25-32. https://dx.doi.org/10.1016/S1470-2045(11)70336-9.

9. Gianni L, Pienkowski T, Im YH et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol 2016; 17(6): 791-800. https://dx.doi.org/10.1016/S1470-2045(16)00163-7.

10. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pertuzumab (neues Anwendungsgebiet) vom 18.02.2016 [online]. 2016. URL: https://www.g-ba.de/downloads/39-261-2498/2016-02-18_AM-TL-XII_Pertuzumab-nAWG_2015-09-01-D-177_BAnz.pdf.

11. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Pertuzumab (neues Anwendungsgebiet) [online]. 2016. URL: https://www.g-ba.de/downloads/40-268-3610/2016-02-18_AM-TL-XII_Pertuzumab-nAWG_2015-09-01-D-177_TrG.pdf.

12. Roche Pharma. Pertuzumab (Perjeta) Dossier zur Nutzenbewertung gemäß § 35a SGB V, Modul 1. Zusammenfassung der Aussagen im Dossier [online]. 2015. URL: https://www.g-ba.de/downloads/92-975-938/2015-08-18_Modul1_Pertuzumab.pdf.

13. Roche Pharma. Pertuzumab (Perjeta) Dossier zur Nutzenbewertung gemäß § 35a SGB V, Modul 4A: Neoadjuvante Therapie des primären Brustkrebses [online]. 2015. URL: https://www.g-ba.de/downloads/92-975-941/2015-08-18_Modul4A_Pertuzumab.pdf.

14. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pertuzumab (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2015 [Accessed: 15.12.2015]. URL: https://www.iqwig.de/download/A15-34_Pertuzumab-neues-AWG_Nutzenbewertung-35a-SGB-V.pdf.

15. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Pertuzumab – Addendum zum Auftrag A15-34 [online]. 2016 [Accessed: 26.02.2016]. URL: https://www.iqwig.de/download/A16-01_%20Pertuzumab_Addendum-zum-Auftrag-A15-34.pdf.

16. Hoffmann-La Roche. Study in Participants With Early-Stage or Locally Advanced Human Epidermal Growth Factor Receptor (HER) 2-Positive Breast Cancer to Evaluate Treatment With Trastuzumab Plus (+) Pertuzumab + Docetaxel Compared With Trastuzumab + Placebo + Docetaxel [online]. 2020 [Accessed: 15.02.2021]. URL: https://ClinicalTrials.gov/show/NCT02586025.

17. Shao Z, Pang D, Yang H et al. Efficacy, Safety, and Tolerability of Pertuzumab, Trastuzumab, and Docetaxel for Patients With Early or Locally Advanced ERBB2-Positive Breast Cancer in Asia: The PEONY Phase 3 Randomized Clinical Trial. JAMA Oncol 2020; 6(3): e193692. https://dx.doi.org/10.1001/jamaoncol.2019.3692.

18. Cardoso F, Kyriakides S, Ohno S et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Ann Oncol 2019; 30(8): 1194-1220. https://dx.doi.org/10.1093/annonc/mdz173.

19. Leitlinienprogramm Onkologie. Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms; Langversion 4.3 [online]. 2020 [Accessed: 08.03.2021]. URL: https://www.awmf.org/uploads/tx_szleitlinien/032-045OLl_S3_Mammakarzinom_2020-02.pdf.

20. Roche. Perjeta [online]. 2020 [Accessed: 08.03.2021]. URL: http://www.fachinfo.de.

21. Roche. Herceptin i. v. [online]. 2020 [Accessed: 08.03.2021]. URL: https://www.fachinfo.de/.

22. Roche. PHESGO [online]. 2020 [Accessed: 08.03.2021]. URL: https://www.fachinfo.de/.

23. Spring LM, Fell G, Arfe A et al. Pathologic Complete Response after Neoadjuvant Chemotherapy and Impact on Breast Cancer Recurrence and Survival: A Comprehensive Meta-analysis. Clin Cancer Res 2020; 26(12): 2838-2848. https://dx.doi.org/10.1158/1078-0432.CCR-19-3492.

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