



IQWiG Reports – Commission No. A18-41

Pertuzumab (breast cancer) –

Benefit assessment according to §35a Social Code Book V¹

Extract

¹ Translation of the executive summary of the dossier assessment *Pertuzumab (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 September 2018). Please note: This document was translated by an external translator and 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:

- Michael Köhler
- Ulrich Grouven
- Marco Knelangen
- Stefan Kobza
- Petra Kohlepp
- Christopher Kunigkeit
- Katrin Nink
- Daniela Preukschat
- Christoph Schürmann
- Beate Wieseler

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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug pertuzumab. 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 21 June 2018.

Research question

The aim of this report is to assess the added benefit of pertuzumab for the adjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer at high risk of recurrence (node-positive or hormone receptor-negative disease). Pertuzumab is administered exclusively in combination with trastuzumab and chemotherapy.

To define the appropriate comparator therapy (ACT) for this therapeutic indication, the G-BA selected a treatment regimen including trastuzumab, a taxane (paclitaxel or docetaxel), and, if appropriate, an anthracycline (doxorubicin or epirubicin). The addition of anthracycline to the treatment regimen must be weighed in consideration of cardiovascular risks. If anthracycline is added to the regimen, trastuzumab is to be used sequentially – not simultaneously. Cardiac function must be closely monitored.

Table 2²: Research questions for the benefit assessment of pertuzumab

Research question	Indication	ACT ^a
1	Adjuvant therapy of HER2-positive early breast cancer at a high risk of recurrence (node-positive or hormone receptor-negative)	A treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel), and, if appropriate, an anthracycline (doxorubicin or epirubicin) ^b
a: Presentation of the ACT specified by the G-BA. b: Presumably, patients with positive hormone receptor status receive additional endocrine therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor 2		

The company followed the G-BA’s specification of the ACT.

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

² Table numbers start with “2” as numbering follows that of the full dossier assessment.

Results

Study pool and study characteristics

The study pool for the benefit assessment comprises the APHINITY study. This is a randomized, double-blind, 2-arm study which included adult patients with early, HER2-positive breast cancer. Primary tumours and any involved lymph nodes were surgically excised before the start of the study. Within 56 days after surgery, a total of 4805 patients were randomly allocated in a 1:1 ratio to one of the two treatment arms (pertuzumab + trastuzumab + chemotherapy, or placebo + trastuzumab + chemotherapy).

Pertuzumab is approved for patients at high risk of recurrence, defined as node-positive or hormone receptor-negative disease. About three-fourths of the study population met this definition. Unless noted otherwise, the below information applies to this subpopulation, which is the population relevant for the benefit assessment.

All patients received adjuvant chemotherapy after surgery. Chemotherapy was provided either with or without anthracycline, but it had to include a taxane. All patients additionally received anti-HER2 therapy consisting of pertuzumab and trastuzumab in the intervention arm and placebo and trastuzumab in the comparator arm. Anti-HER2 therapy was administered for 52 weeks. It was started simultaneously with taxane-containing chemotherapy and after completion of anthracycline treatment, if any.

If indicated, patients received adjuvant radiotherapy at the same time as anti-HER2 treatment after completion of chemotherapy. Hormone receptor-positive patients were to additionally receive endocrine therapy consisting of tamoxifen or an aromatase inhibitor.

The primary outcome of the study was invasive disease-free survival. Relevant secondary outcomes included disease-free survival (particularly recurrences), symptoms, health-related quality of life, overall survival, and adverse events.

Risk of bias on the study and outcome levels

For the APHINITY study, the risk of bias on the study level was rated as low. The outcome-specific risk of bias was low for most outcomes. The risk of bias was rated as high only for outcomes surveyed using the symptom and function scales of the EORTC QLQ-C30 and -BR23 questionnaires.

Results

Overall survival

For the outcome overall survival, no statistically significant difference between treatment groups was found. Consequently, there is no hint of added benefit for pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. An added benefit is therefore not proven for this outcome.

In addition, the company used the results of disease-free survival (DFS) as a surrogate for deriving an added benefit for overall survival. The company largely based this approach on a validation study which it sponsored and according to which DFS is a valid surrogate for overall survival in patients with HER2-positive early breast cancer undergoing anti-HER2 antibody treatment.

However, on the basis of the results of the presented validation study, no effect on overall survival can be derived in this case.

Morbidity – Recurrences

For the outcome “recurrences”, a statistically significant effect in favour of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy was found. This results in an indication of added benefit for this outcome.

Morbidity – Symptoms

Symptom-related outcomes were surveyed using the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. The percentage of patients with a deterioration by ≥ 10 points at 2 different time points (end of anti-HER2 therapy, 36-month-follow-up) is considered in each case.

Fatigue, diarrhoea, chest symptoms

For the outcomes fatigue, diarrhoea, and chest symptoms, statistically significant differences between treatment groups were found. For fatigue and chest symptoms, differences were found only at the end of anti-HER2 therapy, while for diarrhoea, they were at both time points. All differences at the end of HER2 therapy are to the disadvantage of pertuzumab + trastuzumab + chemotherapy. While the difference at the 36-month follow-up for diarrhoea is in favour of pertuzumab + trastuzumab + chemotherapy, it is no more than marginal for an outcome of the category non-serious/non-severe symptoms/late complications. Consequently, for each of the outcomes fatigue, diarrhoea, and chest symptoms, there is a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

Appetite loss

For the outcome appetite loss, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was found at the end of anti-HER2 therapy. However, at this time point, a statistically significant interaction was found with the attribute of age. For patients ≥ 65 years of age, this results in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT.

Nausea and vomiting

For the outcome nausea and vomiting, no statistically significant difference between treatment groups was found in the overall population. However, at the end of anti-HER2-therapy, a statistically significant interaction with the attribute of age was found; for patients ≥ 65 years

of age, there was a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy. For these patients, this results in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT.

Additional outcomes regarding symptoms

For each of the other outcomes of pain, dyspnoea, insomnia, constipation, systemic side effects, arm symptoms, and being upset by hair loss, no statistically significant difference between treatment groups was found for either time point. Consequently, there are no hints of added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. An added benefit is not proven for these outcomes.

Health-related quality of life

Health-related quality of life was measured using the function scales and the scale for measuring global health status of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. The percentage of patients with a deterioration by ≥ 10 points at 2 different time points (end of anti-HER2 therapy, 36-month-follow-up) is considered in each case.

Emotional functioning

For the outcome emotional functioning, at the 36-month follow-up, there is a statistically significant difference between treatment groups in favour of pertuzumab + trastuzumab + chemotherapy. This results in a hint of added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for this time point.

Physical functioning

For the outcome physical functioning, a statistically significant interaction with the attribute of age was found at the end of anti-HER2 therapy. However, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was found only for patients ≥ 65 years of age. For these patients, this results in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT.

Role functioning

For the outcome role functioning, a statistically significant interaction with the attribute of age was found at the 36-month follow-up. However, a statistically significant difference in favour of pertuzumab + trastuzumab + chemotherapy was found for patients < 65 years of age only. For these patients, this results in a hint of added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT.

Other function scales, global health status

For the outcomes global health status, cognitive functioning, social functioning, body image, sexual functioning, sexual enjoyment, and future perspective, no statistically significant difference between treatment groups was found. Consequently, there is no hint of an added

benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy; an added benefit is therefore not proven for these outcomes.

Adverse events – SAEs

For the outcome SAEs, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was found. This results in an indication of greater harm of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

Adverse events – severe AEs (CTCAE Grade ≥ 3)

For the outcome severe AEs, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was found. However, a statistically significant interaction was found with the attribute geographic region. The result for Western Europe, the region relevant for the benefit assessment, differed from the result for the overall population. No statistically significant difference between treatment groups was found for Western Europe.

Due to the result for Western Europe, there is therefore no hint of greater or lesser harm of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. Consequently, an added benefit is not proven for severe AEs.

Adverse events – discontinuation due to AEs

For the outcome discontinuation due to AEs, no statistically significant difference between treatment groups was found. Consequently, there is no hint of greater or lesser harm of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. An added benefit of pertuzumab is not proven for this outcome.

Adverse events – specific AEs

Diarrhoea (AE and SAE)

For diarrhoea in general as well as for serious diarrhoea, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was found. This results in an indication of greater harm of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

Heart failure (SAE)

For the outcome serious heart failure, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was found. This results in an indication of greater harm of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

Metabolic and nutritional disorders (SAE)

For the outcome serious metabolic and nutritional disorders, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was found. This results in an

indication of greater harm of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

Since age was a relevant effect modifier consistently found across several outcomes, the overall conclusion on added benefit below is drawn separately for patients < 65 years of age and \geq 65 years of age.

Patients < 65 years of age

Overall, positive and negative effects of pertuzumab were found for patients < 65 years of age.

On the positive side, for the outcome recurrences, there is an indication of minor added benefit, and for individual dimensions of health-related quality of life (role functioning and emotional functioning at the 36-month follow-up), there are hints of minor added benefit.

On the other hand, indications of negative effects of minor and considerable extent were found for SAEs and specific AEs. In the treatment phase, some of these effects are also reflected by patient-reported outcomes on symptoms (diarrhoea).

In this situation, the negative effects during the treatment phase offset the positive effects of pertuzumab. In summary, there is no proof of added benefit of pertuzumab as adjuvant therapy in comparison with the ACT, which was defined as a treatment regimen including trastuzumab, a taxane and possibly an anthracycline, for patients < 65 years of age with HER2-positive early breast cancer and a high risk of recurrence.

Patients \geq 65 years of age

Overall, positive and negative effects of pertuzumab were found for patients \geq 65 years of age as well.

On the positive side, there is an indication of minor added benefit for the outcome regarding recurrences and a hint of minor added benefit for emotional functioning as a dimension of health-related quality of life (at the 36-month follow-up).

On the other hand, there are indications of negative effects of minor and considerable extent for SAEs and specific AEs. For the treatment phase, there are additionally hints of symptom

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].

burdens for several outcomes (nausea and vomiting, appetite loss, and diarrhoea) of minor and considerable extent as well as physical functioning as a dimension of health-related quality of life (extent: minor). Altogether, the burdens from therapy are greater for patients ≥ 65 years of age than for younger patients.

In summary, in this situation, the negative effects outweigh the positive effects of pertuzumab for patients ≥ 65 years of age, and a lesser benefit is derived. Since the certainty of conclusions regarding the added harm is rated as being no more than a hint, there is consequently a hint of lesser benefit of pertuzumab in comparison with the ACT.

Table 3 presents a summary of the probability and extent of the added benefit of pertuzumab.

Table 3: Pertuzumab – probability and extent of added benefit

Indication	ACT ^a	Probability and extent of added benefit
Adjuvant therapy of HER2-positive early breast cancer at a high risk of recurrence (node-positive or hormone receptor-negative)	A treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if appropriate, an anthracycline (doxorubicin or epirubicin)	<ul style="list-style-type: none"> ▪ Age < 65 years: Added benefit not proven ▪ Age ≥ 65 years: Hint of lesser benefit
<p>a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor 2</p>		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

Note:

An addendum (A18-76) to dossier assessment A18-41 has been published.

References for English extract

Please see full dossier assessment for full reference list.

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