IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A13-10

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment "Pertuzumab – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 27 June 2013). 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Pertuzumab – Benefit assessment according to § 35a Social Code Book V

Contracting agency:

Federal Joint Committee

Commission awarded on:

11 March 2013

Internal Commission No.:

A13-10

Address of publisher:

Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Monika Nothacker, Association of Scientific Medical Societies (AWMF), Berlin, Germany

IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect her opinion.

IQWiG employees involved in the dossier assessment:[2]

- Cornelia Rüdig
- Andreas Gerber-Grote
- Wolfram Groß
- Ulrich Grouven
- Kirsten H. Herrmann
- Ulrike Lampert
- Regine Potthast
- Beate Wieseler

Keywords: pertuzumab, breast neoplasms, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

[3] 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
CI	confidence interval
CLEOPATRA	Clinical Evaluation of Pertuzumab and Trastuzumab
CTCAE	Common Terminology Criteria for Adverse Events
FACT-B	Functional Assessment of Cancer Therapy – Breast Cancer
HER2	Human Epidermal Growth Factor Receptor 2
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
i.v.	intravenous
OR	oestrogen receptor
OS	overall survival
PFS	progression-free survival
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	*Sozialgesetzbuch* (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (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 drug pertuzumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 11 March 2013.

Research question

The aim of this report is to assess the added benefit of pertuzumab in combination with trastuzumab and docetaxel compared with trastuzumab/taxane (docetaxel, paclitaxel) as appropriate comparator therapy (ACT) in patients with Human Epidermal Growth Factor Receptor 2 (HER2)-positive metastatic breast cancer and compared with radiotherapy in patients with HER2-positive locally recurrent unresectable breast cancer.

The assessment was based on patient-relevant outcomes. One direct comparative randomized controlled trial (RCT) was included in the assessment.

Results

One relevant study (the CLEOPATRA study), the approval study of pertuzumab, was available for the assessment. The CLEOPATRA study is a double-blind RCT. Adult patients with HER2-positive, metastatic or locally recurrent unresectable breast cancer who had not received previous anti-HER2 therapy or chemotherapy for their metastatic disease were included in the study. The vast majority (98%) of the study population were patients with metastatic breast cancer. The patients were randomly assigned either to a treatment with pertuzumab/trastuzumab/docetaxel or to a treatment with placebo/trastuzumab/docetaxel. A total of 808 patients were randomized.

Patients with HER2-positive locally recurrent unresectable breast cancer without previous anti-HER2 therapy or chemotherapy for the metastatic disease were also included in the CLEOPATRA study (19 out of 808 patients, 2%). But the comparator therapy (trastuzumab/ docetaxel) used in the study did not concur with the ACT specified by the G-BA for this subpopulation (radiotherapy). Hence it was not possible to draw conclusions on the added benefit of pertuzumab/trastuzumab/docetaxel versus the ACT specified by the G-BA. In addition, this subpopulation of the study was too small to lead to informative results. Therefore, the results described below relate solely to the subpopulation of patients with HER2-positive metastatic breast cancer.

The risk of bias at study level was rated as low for the CLEOPATRA study so that, in principle, indications of added benefit or harm could be derived from it.

The risk of bias for the outcome "overall survival (OS)" was rated as low. There were no evaluable data for the outcomes on health-related quality of life because the outcomes were based on a non-validated version of the Functional Assessment of Cancer Therapy – Breast Cancer (FACT-B) and because some of them were defined post-hoc. There were also no evaluable data for the outcomes on adverse events (AEs). The main reason for this was the difference in treatment and observation duration in the two treatment arms of the study. On average, the patients in the pertuzumab group were observed for about 6 months longer than in the comparator group. Moreover, there was no analysis of the AEs in the patient groups that differed with regards to benefit (visceral versus non-visceral metastases).

Mortality (outcome: overall survival)

Treatment with pertuzumab in combination with trastuzumab and docetaxel produced a statistically significant prolongation of OS compared with treatment with placebo/ trastuzumab/docetaxel.

In addition, there was a proof of an effect modification for the outcome OS regarding the type of disease, i.e. the location of the metastases (interaction test: $p = 0.014$). It was therefore necessary to consider the results for patients with visceral and non-visceral metastases separately.

The direction of effect in the two subgroups was opposite. In patients with visceral metastases (metastases in internal organs such as the lungs or the liver), there was a statistically significant advantage of pertuzumab/trastuzumab/docetaxel versus the comparator therapy. In patients with non-visceral metastases (e.g. metastases in bones, lymph nodes, skin or soft tissue), there was no difference between the treatment groups.

Hence there was an indication of an added benefit of pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel solely for patients with visceral metastases. An added benefit is not proven for patients with non-visceral metastases.

Morbidity

The company’s dossier contained no data on morbidity. An added benefit of pertuzumab/ trastuzumab/docetaxel is not proven for this outcome.

Health-related quality of life

The company’s dossier contained no evaluable data on health-related quality of life. An added benefit of pertuzumab/trastuzumab/docetaxel is not proven for this outcome.

Adverse events

The company's dossier contained no evaluable data for the assessment of AEs.

As an effect modification by the type of disease (visceral or non-visceral metastases) was proven for the outcome OS, it is necessary to investigate if there is also such an effect

modification for the outcomes regarding harm. In case of an effect modification, the balancing of benefit and harm has to be conducted separately according to the status of metastases in the subgroups.

For the outcomes regarding harm, the company did not present any subgroup analyses according to the type of disease (visceral or non-visceral metastases) in the dossier. Hence it remained unclear whether the results of the total population of the CLEOPATRA study could be used for the assessment of AEs or whether the subgroup results had to be considered with respect to the type of disease. It was therefore not possible to assess the harm of pertuzumab/ trastuzumab/docetaxel in comparison with trastuzumab/docetaxel.

Moreover, the data based on naive proportions (proportion of patients with at least one event) presented by the company did not constitute an adequate analysis due to the considerably different treatment durations with the study medication (and hence also observation durations) in both treatment arms (median treatment duration with the study medication: 18.5 months in the pertuzumab arm, and 12.4 months in the comparator arm).

A qualitative consideration of the naive proportions of the AEs showed that greater harm from pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel is possible. In the case of a statistically significant disadvantage of pertuzumab/trastuzumab/docetaxel, greater harm versus the ACT is not excluded despite the bias to the disadvantage of pertuzumab. Such a disadvantage was observed for the overall rate of serious adverse events (SAEs), for example.

Hence a possible greater harm from pertuzumab/trastuzumab/docetaxel remains, which cannot be finally assessed because of the different observation durations. Overall, it is therefore not possible to draw a conclusion on the harm of pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

The overall conclusion on the extent of the added benefit will be presented separately for the two subpopulations versus the respective ACT.

[4] 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 1-3 cannot be drawn from the available data), see [1]. 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, no added benefit, or less benefit), see [2].

HER2-positive metastatic breast cancer

On the basis of the results presented, the extent and probability of the added benefit of the drug pertuzumab in combination with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer compared with the ACT trastuzumab/docetaxel is assessed as follows:

Patients with visceral metastases

Overall, a positive effect remains at outcome level for patients with visceral metastases. This consists of an indication of a major added benefit regarding OS.

There were no adequate analyses available for patients with visceral metastases for the outcomes regarding harm. Hence no final conclusion can be drawn on harm. Greater harm from pertuzumab can also not be excluded.

Based on the data available, it is not assumed that a possible harm from pertuzumab/ trastuzumab/docetaxel challenges the added benefit because the effect size of the added benefit for the outcome "mortality" was clearly below the limit for a major extent. At the same time, there is an increased uncertainty because of the inadequate analyses on outcomes regarding harm. Therefore the added benefit regarding the probability was downgraded from an “indication” to a “hint”.

Hence there is a hint of a major added benefit of pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel for patients with HER2-positive metastatic breast cancer with visceral metastases.

Patients with non-visceral metastases

There is no proof of added benefit at outcome level for patients with HER2-positive metastatic breast cancer with non-visceral metastases.

There were also no adequate analyses for the outcomes regarding harm. Hence no final conclusion can be drawn on harm. Greater harm from pertuzumab can also not be excluded.

Overall, an added benefit of pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel is not proven for patients with HER2-positive metastatic breast cancer with non-visceral metastases.

HER2-positive locally recurrent unresectable breast cancer

The dossier contained no data for patients with HER2-positive locally recurrent unresectable breast cancer for a comparison of pertuzumab in combination with trastuzumab and docetaxel with radiotherapy. Hence the added benefit of pertuzumab/trastuzumab/docetaxel compared with radiotherapy is not proven in HER2-positive locally recurrent unresectable breast cancer.

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

2.2 Research question

The benefit assessment of pertuzumab was conducted in accordance with its approval [3] for the following therapeutic indications: treatment of 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 is exclusively approved for use in combination with trastuzumab and docetaxel.

Two subpopulations were derived from the therapeutic indication, for which the G-BA specified one ACT each. Table 2 shows the subpopulations and their respective ACTs.

The company deviated from the G-BA's specification because it did not consider the subpopulations mentioned separately, but derived the added benefit versus trastuzumab/ docetaxel for the total target population.

The dossier assessment was conducted with the ACT specified by the G-BA because the company did not provide sufficient reasons for deviating from the ACT. The assessment was conducted based on patient-relevant outcomes and on RCTs without limitation of the study duration.

Table 2: Overview of the ACT for pertuzumab

Subindication	**ACT specified by the G-BA**	**ACT specified by the company**
Subpopulation 1: **HER2-positive metastatic breast cancer**[a]	Trastuzumab + taxane (docetaxel, paclitaxel)	Trastuzumab + docetaxel
Subpopulation 2: **HER2-positive locally recurrent unresectable breast cancer**[a]	Radiotherapy	
a: Patients who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: Human Epidermal Growth Factor Receptor 2		

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

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 (studies completed up to 10 December 2012)
- Search in trial registries for studies on pertuzumab (last search on 9 January 2013)

The Institute's own search:

- Search in trial registries for studies on pertuzumab to check the search results of the company (last search on 15 April 2013)

For the subpopulation of patients with HER2-positive metastatic breast cancer, this check produced no deviations from the study pool presented in the dossier. For the subpopulation of patients with HER2-positive locally recurrent unresectable breast cancer, there was no study on the comparison of pertuzumab/trastuzumab/docetaxel with the ACT (radiotherapy).

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The approval study CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) listed in the following table was included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. trastuzumab/docetaxel

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CLEOPATRA	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

HER2-positive metastatic breast cancer

Almost exclusively patients with HER2-positive metastatic breast cancer without previous anti-HER2 therapy or chemotherapy for the metastatic disease were included in the CLEOPATRA study (789 out of 808 patients, 98%). Hence in this assessment, the added benefit of pertuzumab/trastuzumab/docetaxel versus the ACT specified by the G-BA (trastuzumab + taxane [docetaxel, paclitaxel]) was assessed on the basis of the total population.

The company also included the study CLEOPATRA in its assessment. However, the company did not derive the added benefit of pertuzumab separately for the subpopulation of patients with HER2-positive metastatic breast cancer mentioned, but for the total study population.

HER2-positive locally recurrent unresectable breast cancer

There was no relevant study for the treatment of patients with HER2-positive locally recurrent unresectable breast cancer.

A small proportion of patients with HER2-positive locally recurrent unresectable breast cancer without previous anti-HER2 therapy or chemotherapy for the metastatic disease were also included in the CLEOPATRA study (19 out of 808 patients, 2%). But the comparator therapy (trastuzumab/docetaxel) used in the study did not concur with the ACT specified by the G-BA for this subpopulation (radiotherapy). In addition, this subpopulation of the study was too small to lead to informative results. Hence it was not possible to draw conclusions on the added benefit of pertuzumab/trastuzumab/docetaxel versus the ACT specified by the G-BA.

This assessment deviated from the approach of the company. The company included the study CLEOPATRA and also described the added benefit of pertuzumab in the subpopulation of patients with HER2-positive locally recurrent unresectable breast cancer versus the ACT of the study (trastuzumab/docetaxel).

Section 2.6 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 4 and Table 5 describe the study used for the benefit assessment in patients with HER2-positive metastatic breast cancer.

Table 4: Characteristics of the study included – RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. trastuzumab/docetaxel

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CLEOPATRA	RCT, double-blind, placebo-controlled, international, multicentre	Adult patients with HER2-positive, metastatic or locally recurrent unresectable breast cancer who had not received previous chemotherapy or biologic therapy for their metastatic disease	Pertuzumab/trastuzumab/ docetaxel (N = 402) Placebo/trastuzumab/ docetaxel (N = 406) Subpopulations: metastatic breast cancer (n = 787) locally recurrent unresectable breast cancer (n = 19) no data (n = 2)	Treatment phase: until disease progression, unmanageable toxicity or study ended by sponsor Observation phase: after the end of study treatment until death, loss of contact, withdrawal of informed consent or study ended by sponsor	Asia, Europe (including Germany), North America, South America Study phase 1 Feb 2008 – May 2011 first data cut-off, confirmatory analysis of PFS, interim analysis of OS Study phase 2 May 2011 – May 2012 second data cut-off, final confirmatory analysis of OS Study phase 3 since May 2012 analysis of OS after 385 deaths	Primary: PFS rated by IRF (PFS) Secondary: OS, AEs

a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes for the present benefit assessment.

AE: adverse event; HER2: Human Epidermal Growth Factor Receptor 2; IRF: independent review facility; N: number of randomized patients; n: relevant subpopulation; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. placebo/trastuzumab/docetaxel

Study	Intervention	Comparison	Concomitant medication
CLEOPATRA	Pertuzumab: starting dose 840 mg/kg, subsequent dosage 420 mg/kg, i.v. infusion every 3 weeks Trastuzumab: starting dose 8 mg/kg, subsequent dosage 6 mg/kg, i.v. infusion every 3 weeks Docetaxel: 75 mg/m^2, i.v. infusion every 3 weeks for at least 6 cycles Docetaxel could be increased to 100 mg/m^2 at the investigator's discretion if toxicity was manageable	Placebo: i.v. infusion every 3 weeks Trastuzumab: starting dose 8 mg/kg, subsequent dosage 6 mg/kg, i.v. infusion every 3 weeks Docetaxel: 75 mg/m^2, i.v. infusion every 3 weeks for at least 6 cycles Docetaxel could be increased to 100 mg/m^2 at the investigator's discretion if toxicity was manageable	Supportive care The patients received comprehensive supportive care including blood transfusions, antibiotics, etc., according to the treatment standard
i.v.: intravenous; RCT: randomized controlled trial; vs.: versus			

The CLEOPATRA study is a randomized, controlled, double-blind approval study sponsored by the company, which is currently in the third study period (after the second interim analysis). It is a multicentre study and is being conducted in Western industrialized nations as well as countries in Asia and Latin America. Adult patients with HER2-positive, metastatic or locally recurrent unresectable breast cancer who had not received previous anti-HER2 therapy or chemotherapy for their metastatic disease were included in the study. Patients with metastatic breast cancer constituted the vast majority of the study population (390 out of 402 patients [97%] in the pertuzumab arm versus 397 out of 406 [98%] in the comparator arm). The patients were stratified according to the previous treatment status and to region and randomly assigned in a ratio of 1:1, either to a treatment with pertuzumab/trastuzumab/ docetaxel or to a treatment with placebo/trastuzumab/docetaxel. A total of 808 patients were randomized (402 patients in the pertuzumab arm; 406 patients in the comparator arm).

Several data cut-offs were performed during the study: The first data cut-off (May 2011, end of first study period), was performed after 381 cases of disease progression. The final confirmatory analysis of the primary outcome "progression-free survival (PFS)" and an interim analysis for OS were performed at this date. One year later (May 2012, end of second study period), another interim analysis of OS was performed after a second data cut-off. At this time, the difference in OS between the treatment arms was statistically significant with sufficient effect size, so that the study was unblinded and the patients in the comparator arm were allowed to crossover to the pertuzumab arm (study period 3). So the second interim analysis of OS was also the final confirmatory analysis for the outcome OS. Study period 3 is currently conducted until 385 deaths have occurred. It will probably end in 2013.

The drugs used in the study – pertuzumab, trastuzumab and docetaxel – were administered according to the current approval status. For pertuzumab, this means a starting dose of 840 mg/kg i.v., followed by 420 mg/kg i.v. every 3 weeks. Trastuzumab was given at a starting dose of 8 mg/kg intravenously (i.v.), followed by 6 mg/kg i.v. every 3 weeks. Docetaxel was given in a dosage of 75 mg/m^2 i.v. every 3 weeks for at least 6 cycles. The dose could be increased to 100 mg/m^2 if toxicity was manageable. Subsequently, the dosage of pertuzumab and trastuzumab was to remain stable. If administration of docetaxel had to be discontinued due to toxicity, treatment with pertuzumab and trastuzumab could be continued.

Table 6 and Table 7 show the characteristics of the patients in the studies included.

Table 6: Characteristics of the study population – RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. placebo/trastuzumab/docetaxel

Characteristics Category	Pertuzumab/trastuzumab/ docetaxel N = 402	Placebo/trastuzumab/ docetaxel N = 406
CLEOPATRA		
Age [years]		
Mean (SD)	53.4 (10.9)	53.5 (11.4)
Median (min, max)	54.0 (22.8)	54.0 (27.9)
Sex f / m [%]	100 / 0	99.5 / 0.5
Type of disease, n (%)		
Non-visceral	88 (21.9)	90 (22.2)
Visceral	314 (78.1)	316 (77.8)
Metastases/recurrence, n (%)[a]		
Locally recurrent disease	11 (2.7)	8 (2.0)
Metastatic disease	390 (97.0)	397 (98.0)
Unknown	1 (0.2)	1 (0.2)
Ethnic group, n (%)		
White	245 (60.9)	235 (57.9)
Asian	128 (31.8)	133 (32.8)
Black	10 (2.5)	20 (4.9)
Other	19 (4.7)	18 (4.4)
Region, n (%)		
Europe	154 (38.3)	152 (37.4)
Asia	125 (31.1)	128 (31.5)
North America	67 (16.7)	68 (16.7)
South America	56 (13.9)	58 (14.3)
ECOG performance status, n (%)		
0	274 (68.2)	248 (61.1)
1	125 (31.1)	157 (38.7)
2	3 (0.7)	0 (0)
3	0 (0)	1 (0.2)

a: Institute's calculation on the basis of the total study population.

ECOG: Eastern Cooperative Oncology Group; f: female; m: male; max: maximum; min: minimum; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Both women and men were enrolled in the study. The proportion of men in the comparator group was very small, however (only 2 patients [0.5%]). There were no important differences between the treatment groups with regards to age, origin or type of disease (visceral or non-visceral metastases). The mean age of the patients was 53 years. About 40% of the patients were from Europe, one third from Asia, and the others from North and South America. The vast majority (about 60%) of the patients was of white ethnicity, and one third was of Asian

origin. 78% of the patients had visceral cancer, i.e. visceral organs like the lungs or the liver were affected. In the other patients, non-visceral organs such as skin, bones or brain were affected.

Overall, the general condition of the patients, which was rated with the Eastern Cooperative Oncology Group (ECOG) status, was good. More than 90% of the patients in both treatment groups had an ECOG status of 0 or 1. The proportion of patients with a status 0 was slightly higher in the pertuzumab group (68%) than in the comparator group (61%).

Table 7: Characteristics of the study population according to the type of previous treatment – RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. placebo/trastuzumab/docetaxel

Characteristics **Category**	**Pertuzumab/trastuzumab/ docetaxel** **N = 402**	**Placebo/trastuzumab/ docetaxel** **N = 406**
CLEOPATRA		
Previous treatment status, n (%)		
(Neo)adjuvant treatment	184 (45.8)	192 (47.3)
De novo	218 (54.2)	214 (52.7)
Previous treatment with trastuzumab, n (%)		
Yes	47 (11.7)	41 (10.1)
Previous neo-adjuvant chemotherapy or biologic therapy, n (%)		
Yes	50 (12.4)	57 (14.0)
Previous adjuvant chemotherapy or biologic therapy, n (%)		
Yes	165 (41.0)	172 (42.4)
Previous treatment with taxanes, n (%)		
Docetaxel	34 (8.5)	38 (9.4)
Paclitaxel	54 (13.4)	57 (14.0)
Taxanes (not specified)	1 (0.2)	0 (0)

N: number of randomized patients, n: number of patients in the category, RCT: randomized controlled trial; vs.: versus

There were no noticeable differences between the treatment groups regarding previous treatment.

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. placebo/trastuzumab/docetaxel

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
CLEOPATRA	yes	yes	yes	yes	yes	yes	low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at the study level was rated as low for the CLEOPATRA study. This concurs with the company's assessment.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-G of the dossier, and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

The following patient-relevant outcomes were considered in this assessment on the subpopulation of patients with HER2-positive metastatic breast cancer (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - OS
- Health-related quality of life
- Adverse events
  - Overall rate of AEs
  - SAEs
  - Treatment discontinuations due to AEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≥ 3)
    - Most common AEs of CTCAE Grade ≥ 3 (> 3%; leukopenia, neutropenia, febrile neutropenia, anaemia, diarrhoea, fatigue, left ventricular systolic dysfunction)

There were no data on morbidity.

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.7.2.4.3 of the full dossier assessment). The outcomes "PFS" and "overall response rate (ORR)" were not used for this

assessment since neither the patient relevance postulated in the dossier (in this study, both outcomes were exclusively recorded using imaging methods) nor the validity of a surrogate characteristic was presented. The outcomes on health-related quality of life could not be used because they were based on a non-validated version of the FACT-B and because some of them were defined post-hoc. More explanations on this can be found in Section 2.7.2.4.3 of the full dossier assessment. The analyses on AEs could not be used because the observation duration differed between the treatment arms and because there were no analyses for the subgroup of patients with added benefit (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment).

Table 9 shows for which outcomes data were available in the study included.

Table 10 shows the risk of bias for these outcomes.

Table 9: Matrix of outcomes – RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. placebo/trastuzumab/docetaxel

Study	Outcomes						
	Overall survival	**Health-related quality of life**	**AEs**	**SAEs**	**Discontinuation due to AEs**	**AEs CTCAE Grade ≥ 3**	**Frequent AEs with CTCAE Grade ≥3[a]**
CLEOPATRA	yes	no[b]	no[c]	no[c]	no[c]	no[c]	no[c]

a: Frequency > 3% in at least one treatment arm.
b: Data on health-related quality of life were recorded, but were not evaluable; see Section 2.7.2.4.3 of the full dossier assessment for reasons.
c: Data on AEs were recorded, but were not evaluable; see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment for reasons.
AE: adverse event, CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 10: Risk of bias at study and outcome level – RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. placebo/trastuzumab/docetaxel

Study	Study level	Outcomes						
		OS	Health-related quality of life	AEs	SAEs	Discontinuation due to AEs	AEs CTCAE Grade ≥ 3	Frequent AEs with CTCAE Grade ≥3[a]
CLEOPATRA	low	low	–[b]	–[b]	–[b]	–[b]	–[b]	–[b]

a: Frequency > 3% in at least one treatment arm.
b: No evaluable data available (see Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment).
AE: adverse event, CTCAE: Common Terminology Criteria for Adverse Events; OS: overall survival; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias for the outcome OS was rated as low. This concurs with the company's assessment.

There were no evaluable data for the outcomes on AEs. The main reason for this was the difference in treatment and observation duration in the two treatment arms of the study. AEs were recorded until the patients discontinued the study or until treatment was discontinued due to disease progression or toxicity. On average, the patients in the pertuzumab group were observed for about 6 months longer than in the comparator group. Due to the differences in treatment time and observation duration, more AEs and treatment discontinuations due to an AE could occur in the pertuzumab group than in the comparator group. This constituted a bias to the disadvantage of pertuzumab.

The interpretation of the results depends on the direction of effect observed. In the case of an advantage of pertuzumab/trastuzumab/docetaxel regarding AEs, it has to be assumed that the true effect is possibly higher. In the case of not statistically significant results between the pertuzumab group and the comparator arm, the bias caused by the longer observation duration in the pertuzumab group could not more than cover up a disadvantage of the comparator therapy – it is not possible that the true effect shows a disadvantage of pertuzumab. If the biased analysis shows a statistically significant disadvantage of pertuzumab/trastuzumab/ docetaxel, however, the effect would rather be overestimated, but it cannot be excluded that the true effect is in fact to the disadvantage of pertuzumab. Overall, the relative risks estimated on the basis of naive proportions were no adequate analysis. More details on this can be found in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

Table 11 summarizes the results on the comparison of pertuzumab/trastuzumab/docetaxel with placebo/trastuzumab/docetaxel in patients with HER2-positive metastatic breast cancer. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations. In addition, data from Module 5 of the dossier were added.

For the subpopulation of patients with HER2-positive locally recurrent unresectable breast cancer, there were no data on the comparison with the ACT specified by the G-BA (radiotherapy).

Table 11: Results – RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. placebo/trastuzumab/docetaxel

Study **Outcome category** **Outcome**	**Pertuzumab/ trastuzumab/ docetaxel**		**Placebo/ trastuzumab/ docetaxel**		**Pert/trast/doce vs. pla/trast/doce**
CLEOPATRA					
	N	**Median survival time [95% CI] (months)**	**N**	**Median survival time [95% CI] (months)**	**HR [95% CI]; p-value**
Mortality					
Overall survival					
Total population	*402*	*n. a. [42; n. a.]*[a]	*406*	*37.6 [34; n. a]*	*0.66 [0.52; 0.84]*[b] *< 0.001*
Subgroups according to type of disease					
Visceral metastases	314	no data[c]	316	no data[c]	0.57 [0.44; 0.74] no data
Non-visceral metastases	88	no data[d]	90	no data[d]	1.42 [0.71; 2.84] no data
					Interaction: p = 0.014
Morbidity	No evaluable data				
Health-related quality of life	No evaluable data				
AEs	No evaluable data				

a: Median survival not yet achieved at the data cut-off date.
b: Stratified according to previous treatment and region.
c: Proportion of patients died at the time of analysis in the subgroup with visceral metastases: pertuzumab arm 29.9%, comparator arm 44.3%.
d: Proportion of patients died at the time of analysis in the subgroup with non-visceral metastases: pertuzumab arm 21.6%, comparator arm 15.6%.

AE: adverse event; CI: confidence interval; doce: docetaxel; HR: hazard ratio; N: number of analysed patients; n. a.: not achieved; pert: pertuzumab; pla: placebo; RCT: randomized controlled trial; trast: trastuzumab; vs.: versus

The CLEOPATRA study did not meet the particular requirements placed on the derivation of proof from a single study (see Section 2.7.2.8.1 of the full dossier assessment). Hence, at most indications – e.g. of an added benefit – could be derived from the data.

This assessment deviates from that of the company, which derived proof of added benefit from the CLEOPATRA study.

The results described below relate solely to the subpopulation of patients with HER2-positive metastatic breast cancer. The company did not present any data on the treatment of patients with locally recurrent unresectable breast cancer versus the ACT (radiotherapy).

Mortality

Overall survival

Treatment with pertuzumab in combination with trastuzumab and docetaxel produced a statistically significant prolongation of OS in the total population compared with treatment with placebo/trastuzumab/docetaxel.

In addition, for the outcome OS, there was a proof of an effect modification regarding the type of disease, i.e. the location of the metastases (interaction test: $p = 0.014$). It was therefore necessary to consider the results in patients with visceral and non-visceral metastases separately.

The direction of effect in the two subgroups was opposite. In patients with visceral metastases (metastases in internal organs such as the lungs or the liver), there was a statistically significant advantage of pertuzumab/trastuzumab/docetaxel versus the comparator therapy. In patients with non-visceral metastases (metastases in bones, lymph nodes, skin or soft tissue), there was no difference between the treatment groups.

Hence there was an indication of an added benefit of pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel solely for patients with visceral metastases. An added benefit is not proven for patients with non-visceral metastases.

Morbidity

The company’s dossier contained no evaluable data on morbidity. An added benefit of pertuzumab/trastuzumab/docetaxel is not proven for this outcome.

Health-related quality of life

The company’s dossier contained no evaluable data on health-related quality of life (see Section 2.7.2.4.3 of the full dossier assessment). An added benefit of pertuzumab/ trastuzumab/docetaxel is not proven for this outcome.

Adverse events

The company's dossier contained no evaluable data for the assessment of AEs.

As an effect modification by the type of disease (visceral or non-visceral metastases) was proven for the outcome OS, it is necessary to investigate if there is also such an effect modification for the outcomes regarding harm. In case of an effect modification, the balancing of benefit and harm has to be conducted separately according to the status of metastases in the subgroups.

The company did not present any subgroup analyses according to the type of disease (visceral or non-visceral metastases) in the dossier. Hence it remained unclear whether the results of the total population of the CLEOPATRA study could be used for the assessment of AEs or whether the subgroup results had to be considered with respect to the type of disease. It was therefore not possible to assess the harm of pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel.

Moreover, the data based on naive proportions (proportion of patients with at least one event) presented by the company did not constitute an adequate analysis due to the considerably different treatment durations with the study medication (and hence also observation durations) in both treatment arms (median treatment duration with the study medication: 18.5 months in the pertuzumab arm, and 12.4 months in the comparator arm) (see Section 2.7.2.4.2 of the full dossier assessment).

A qualitative consideration of the naive proportions of the AEs showed that greater harm from pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel is possible. In the case of a statistically significant disadvantage of pertuzumab/trastuzumab/docetaxel, greater harm versus the ACT is not excluded despite the bias to the disadvantage of pertuzumab. Such a disadvantage was observed for the overall rate of SAEs, for example (see the naive proportions on AEs in Appendix A, Table 20, of the full dossier assessment, and the subgroup analyses on SAEs below).

Hence a possible greater harm from pertuzumab/trastuzumab/docetaxel remains, which cannot be finally assessed because of the different observation durations. Overall, it is therefore not possible to draw a conclusion on the harm of pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel.

Subgroups

To reveal any effect differences between patient groups, the results of the CLEOPATRA study concerning the outcome OS were investigated for a possible effect modification – in addition to the subgroup analysis for the characteristic "type of disease (visceral or non-visceral metastases)", as described above – by the following characteristics:

- previous treatment status (de novo/adjuvant or neo-adjuvant treatment)
- region (Europe, North America, South America, Asia)
- age (<65/≥65) and (<75/≥75)

- ethnic group (white/black/Asian/other)
- oestrogen receptor (OR)/progesterone receptor (PgR) status (ER and/or PgR positive/ER and PgR negative/unknown)
- previous (neo-)adjuvant taxane treatment (yes/no)
- previous (neo-)adjuvant treatment with trastuzumab (yes/no)

The outcomes regarding harm were investigated using the following subgroup characteristics:

- region (Europe, North America, South America, Asia)
- age (<65/≥65) and (<75/≥75)
- ethnic group (white/black/Asian/other)

On a critical note on the subgroup analyses for the outcomes regarding harm, there are no investigations of the effect modification by the type of disease (visceral or non-visceral metastases), although there is proof of an effect modification for OS for this characteristic.

The prerequisite for proof of different effects was a statistically significant homogeneity and/or interaction test ($p < 0.05$). A p-value between 0.05 and 0.2 provided an indication of different effects. The interaction tests were presented in the dossier.

Overall survival

Besides for the characteristic "type of disease (visceral or non-visceral metastases)" described above, there was no effect modification for the outcome OS.

Adverse events

The analysis of the subgroup characteristics presented for AEs showed one single interaction. There was proof of an effect modification by the characteristic "ethnic group" for SAEs (interaction test: $p = 0.026$). The effect estimates in the subgroups indicated an advantage of pertuzumab/trastuzumab/docetaxel for patients of black ethnicity, whereas a disadvantage of pertuzumab/trastuzumab/docetaxel became visible in the other subgroups (whites, Asians, others).

When the subgroups with an effect of the same direction – Asians, whites and others – were grouped together and compared with blacks, there was also proof of an effect modification by these subgroups (interaction test: $p = 0.035$). The combined subgroup of patients of Asian, white and other ethnic groups was homogeneous (p-value of the interaction test 0.452). The overall estimate of the homogeneous subgroup was used for the analysis. There was a statistically significant effect in this subgroup to the disadvantage of pertuzumab/trastuzumab/docetaxel (relative risk [RR] [95% confidence interval (CI)]: 1.36 [1.10; 1.67]). Hence a possible greater harm from pertuzumab/trastuzumab/docetaxel remains for the outcome

SAEs, which cannot be finally assessed, however, because of the high risk of bias due to the different observation durations.

Table 12: Subgroups: outcome SAEs according to the characteristic "ethnic group" (naive proportions), RCT, direct comparison: pertuzumab/trastuzumab/docetaxel vs. placebo/trastuzumab/docetaxel

Study Characteristic Subgroup	Pertuzumab/ trastuzumab/ docetaxel		Placebo/trastuzumab/ docetaxel		Pert/trast/doce vs. pla/trast/doce	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
CLEOPATRA						
Total	408	148 (36.3)	396	115 (29.0)	1.25 [1.02; 1.53]	0.029
Ethnic group						
White	250	75 (30.0)	226	56 (24.8)	1.21 [0.90; 1.63]	0.203
Asian	128	61 (47.7)	133	40 (30.1)	1.58 [1.15; 2.17]	0.004
Black	10	2 (20.0)	20	12 (60.0)	0.33 [0.09; 1.21]	0.058
Other	20	10 (50.0)	17	7 (41.2)	1.21 [0.59; 2.49]	0.600
					Interaction:	0.026
Homogeneous subgroup of the patients of Asian, white and other ethnic groups						
Total	398	146 (36.7)	376	103 (27.4)	1.36 [1.10; 1.67]	0.004
Ethnic group						
White	250	75 (30.0)	226	56 (24.8)	1.21 [0.90; 1.63]	0.203
Asian	128	61 (47.7)	133	40 (30.1)	1.58 [1.15; 2.17]	0.004
Other	20	10 (50.0)	17	7 (41.2)	1.21 [0.59; 2.49]	0.600
					Interaction:	0.452

CI: confidence interval; doce: docetaxel; N: number of analysed patients; n: number of patients with event; pert: pertuzumab; pla: placebo; RCT: randomized controlled trial; RR: relative risk; trast: trastuzumab; vs.: versus

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit for each subquestion is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on added benefit.

2.5.1 Assessment of added benefit at outcome level

HER2-positive metastatic breast cancer

Based on the data presented in Section 2.4, there is an indication of an added benefit regarding OS for patients with HER2-positive metastatic breast cancer with visceral metastases. There is no indication of an added benefit for patients with non-visceral metastases. No evaluable data are available for other outcomes (particularly including the outcomes regarding harm). The extent of the respective added benefit at outcome level was estimated from these results (see Table 13).

Table 13: Extent of added benefit at outcome level: pertuzumab/trastuzumab/docetaxel vs. trastuzumab/docetaxel

Outcome category **Outcome**	**Pertuzumab/trastuzumab/docetaxel vs. trastuzumab/docetaxel** **Effect estimates [95% CI]** **p-value** **probabilitya**	**Derivation of extentb**
Mortality		
OS		
Type of disease -		
visceral metastases	HR: 0.57 [0.44; 0.74] Median: no data p-value = no data Probability: "indication"	Outcome category: survival time $CI_o < 0.85$ Added benefit, extent: “major”
non-visceral metastases	HR: 1.42 [0.71; 2.84] Median: no data p-value = no data	Lesser benefit/added benefit not proven
Morbidity	No evaluable data available	
Health-related quality of life	No evaluable data available	
AEs	No evaluable data available	

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_o.
AE: adveres event; CI: confidence interval; CI_o: upper limit of the confidence interval; HR: hazard ratio; OS: overall survival; vs.: versus

HER2-positive locally recurrent unresectable breast cancer

The company did not present any data on the comparison with the ACT (radiotherapy) for patients with HER2-positive locally recurrent unresectable breast cancer.

2.5.2 Overall conclusion on added benefit

The overall conclusion on the extent of the added benefit will be presented separately for patients with HER2-positive metastatic breast cancer and for patients with HER2-positive locally recurrent unresectable breast cancer.

HER2-positive metastatic breast cancer

Patients with visceral metastases

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit for patients with visceral metastases.

Table 14: Positive and negative effects from the assessment of pertuzumab/trastuzumab/docetaxel compared with trastuzumab/docetaxel for patients with visceral metastases

Positive effects	Negative effects
Indication of an added benefit – extent “major” (survival time: all-cause mortality)	No conclusion possible

Overall, on the basis of the available and evaluable results, a positive effect remains at outcome level for patients with visceral metastases. This consists of an indication of a major added benefit regarding OS.

There were no adequate analyses available for patients with visceral metastases for the outcomes regarding harm. Hence no final conclusion can be drawn on harm. Greater harm from pertuzumab can also not be excluded.

Based on the data available, it is not assumed that a possible harm from pertuzumab/ trastuzumab/docetaxel challenges the added benefit because the effect size of the added benefit for the outcome "mortality" was clearly below the limit for a major extent. At the same time, there is an increased uncertainty because of the inadequate analyses on outcomes regarding harm. Therefore the added benefit regarding the probability was downgraded from an “indication” to a “hint”.

Hence there is a hint of a major added benefit of pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel for patients with HER2-positive metastatic breast cancer with visceral metastases.

Patients with non-visceral metastases

There is no proof of added benefit at outcome level for patients with HER2-positive metastatic breast cancer with non-visceral metastases.

There were also no adequate analyses for the outcomes regarding harm. Hence no final conclusion can be drawn on harm. Greater harm from pertuzumab can also not be excluded.

Overall, an added benefit of pertuzumab/trastuzumab/docetaxel in comparison with trastuzumab/docetaxel is not proven for patients with HER2-positive metastatic breast cancer with non-visceral metastases.

HER2-positive locally recurrent unresectable breast cancer

The dossier contained no data for patients with HER2-positive locally recurrent unresectable breast cancer for a comparison of pertuzumab in combination with trastuzumab and docetaxel with radiotherapy (see Section 2.3.1). Hence the added benefit of pertuzumab/ trastuzumab/docetaxel compared with radiotherapy is not proven in HER2-positive locally recurrent unresectable breast cancer.

2.5.3 Extent and probability of added benefit – summary

An overview of the assessment of pertuzumab/trastuzumab/docetaxel in comparison with the ACT for the 2 subpopulations is given below (see Table 15).

Table 15: Pertuzumab: extent and probability of added benefit – summary

Therapeutic indication	ACT	Extent and probability of added benefit
Subpopulation 1: Treatment of HER2-positive metastatic breast cancer		
with visceral metastases	Trastuzumab + taxane (docetaxel)	Hint of a major added benefit
with non-visceral metastases	Trastuzumab + taxane (docetaxel)	Added benefit not proven
Subpopulation 2: Treatment of HER2-positive locally recurrent unresectable breast cancer	Radiotherapy	Added benefit not proven

The overall assessment deviates considerably from that of the company. The company claimed a proof of a major added benefit for both subpopulations.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

CLEOPATRA

Baselga J, Cortes J, Kim SB, Im SA, Hegg R, Im YH et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012; 366(2): 109-119.

Baselga J, Swain SM. CLEOPATRA: a phase III evaluation of pertuzumab and trastuzumab for HER2-positive metastatic breast cancer. Clin Breast Cancer 2010; 10(6): 489-491.

Roche. A phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer: research report no. 1046288; study WO20698-TOC4129g; clinical study report [unpublished]. 2011.

Roche. A phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer: research report no. 1053649; study WO20698-TOC4129g; update clinical study report [unpublished]. 2012.

Roche. Zusätzliche Analysen zur CLEOPATRA-Studie (WO20698) [unpublished]. 2013.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23 September 2011 [accessed: 05 May 2012]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to § 35a Social Code Book V; extract; commission no. A11-02 [online]. 29 May 2011 [accessed: 05 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Roche. Perjeta 420 mg Konzentrat zur Herstellung einer Infusionslösung: Fachinformation [online]. March 2013 [accessed: 18 March 2013]. URL: http://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/de/projekte_ergebnisse/projekte/arzneimittelbewertung/a13_10_pertuzumab_nutzenbewertung_gemaess_35a_sgb_v_dossierbewertung.3636.html.