IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A15-34

Pertuzumab (new therapeutic indication) – 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 (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 November 2015). 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 (new therapeutic indication) – Benefit assessment according to §35a SGB V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
20 August 2015

Internal Commission No.:
A15-34

Address of publisher:
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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
FEC	5-fluorouracil, epirubicin, 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)
pCR	pathological complete response
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 referred to as "the company"). The dossier was sent to IQWiG on 20 August 2015.

Research question

The aim of the present report was to assess the added benefit of pertuzumab in combination with trastuzumab and 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.

The G-BA specified a therapeutic regimen containing trastuzumab, a taxane (paclitaxel, docetaxel) and, if applicable, an anthracycline (doxorubicin, epirubicin) as ACT for the present therapeutic indication. The combination of trastuzumab with an anthracycline has to be balanced under consideration of the cardiovascular risks, and cardiac functions have to be closely monitored.

The company followed this specification and chose trastuzumab and docetaxel as comparator therapy.

The company's choice of the comparator therapy was followed. The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

Results

One relevant study (NeoSphere) was available for the benefit assessment. This was an open-label, randomized controlled trial (RCT). Treatment-naive adult women with locally advanced, inflammatory, or early-stage invasive HER2-positive breast cancer with primary tumours > 2 cm in diameter and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤ 1. Overall, the criteria of the approved therapeutic indication were regarded as being fulfilled for the patient population investigated in the study.

A total of 417 patients were randomly assigned to 4 study arms. However, only 2 study arms were used for the assessment of the added benefit: pertuzumab + trastuzumab + docetaxel and trastuzumab + docetaxel.

The study can be divided into 3 phases: the neoadjuvant treatment phase followed by surgery, the adjuvant treatment phase, and the follow-up phase. In the neoadjuvant study phase, the patients in both study arms received a treatment regimen consisting of trastuzumab followed by docetaxel. The patients in the study arm with the investigational intervention additionally received pertuzumab. In the adjuvant treatment phase, the patients in both relevant study arms received the same treatment regimen: trastuzumab, partly parallel with the FEC regimen (FEC: 5-fluorouracil, epirubicin, cyclophosphamide).

The treatment regimens investigated in the study complied with the recommendations provided in the corresponding Summaries of Product Characteristics (SPCs) regarding dosages and number of treatment cycles or were within a possible dosage range stated in the guidelines. Due to the type of use of the therapeutic regimen in the adjuvant treatment phase, the transferability of the study results to the German health care context is limited, however. This limitation resulted, on the one hand, from the fact that trastuzumab was used in parallel with the anthracycline-containing FEC regimen in the study, although this combination is not recommended in the SPC of trastuzumab. On the other hand, the chemotherapy was divided into a neoadjuvant and an adjuvant part, although guidelines advise against this division. Due to the described limitations, the conclusions on the added benefit of pertuzumab based on the NeoSphere study were limited to the treatment regimens investigated.

Pathological complete response (pCR) was the primary outcome of the study. Patient-relevant secondary outcomes were recurrence, breast-conserving surgery and adverse events (AEs). The recording of all-cause mortality was conducted in the framework of the recording of the AEs as number of deaths and, beyond disease progression, disease recurrence or discontinuation, not systematic. Health-related quality of life was not investigated in the study.

Risk of bias

The risk of bias at study level for the NeoSphere study was rated as low. The risk of bias for the outcome “all-cause mortality” was assessed as high. The risk of bias was rated as low for the outcomes “recurrence”, “serious adverse events (SAEs)”, and “severe AEs Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3”. The risk of bias was rated as high for the outcomes “breast-conserving surgery” and “discontinuation due to AEs”.

Mortality

All-cause mortality

No statistically significant difference in the proportion of deaths was shown between the 2 treatment groups for the outcome “all-cause mortality”. There was no hint of an added benefit of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome “all-cause mortality”; an added benefit is therefore not proven.

Morbidity

Recurrence

Both analyses showed no statistically significant difference between the 2 treatment groups for the outcome "recurrence" (shown with the recurrence rate and disease-free survival). Hence there was no hint of an added benefit of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome "recurrence"; an added benefit is therefore not proven.

Breast-conserving surgery

For the outcome "breast-conserving surgery", there was no statistically significant difference between the 2 treatment groups. Hence there was no hint of an added benefit of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome "breast-conserving surgery"; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life was not investigated in the study. Hence there was no hint of an added benefit of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome "health-related quality of life".

Adverse events

Serious adverse events and severe adverse events CTCAE grade ≥ 3

There was no statistically significant difference between the 2 treatment groups for the overall rate of SAEs and severe AEs CTCAE grade ≥ 3. There was no hint of greater or lesser harm of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcomes "SAEs" and "severe AEs CTCAE grade ≥ 3"; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + docetaxel between the treatment groups was shown for the outcome "discontinuation due to AEs". 4 of the 6 recorded AEs that led to treatment discontinuation in the pertuzumab + trastuzumab + docetaxel arm were cardiac events. There was a hint of greater harm of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome "discontinuation due to AEs".

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

On the basis of the results presented, the extent and probability of the added benefit of the drug pertuzumab versus the ACT is assessed as follows:

Overall, a negative effect (hint) for greater harm in the outcome "discontinuation due to AEs" (outcome category "serious/severe AEs)" with the extent "non-quantifiable" remains for pertuzumab.

There were no statistically significant differences between the treatment groups regarding further outcomes in the categories "mortality", "morbidity" and "AEs". In addition, health-related quality of life was not investigated in the study.

In summary, there is a hint of lesser benefit of pertuzumab in comparison with the ACT for patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence. 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.

Table 2 presents a summary of the extent and probability of the added benefit of pertuzumab.

Table 2: Pertuzumab – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Pertuzumab is indicated in combination with trastuzumab and chemotherapy in neoadjuvant treatment of adult patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence.	A therapeutic regimen containing **trastuzumab**, a taxane (paclitaxel or **docetaxel**) and, if applicable, an anthracycline (doxorubicin, epirubicin)[b]	Hint of lesser benefit
a: Presentation of the appropriate comparator therapy specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold. b: The combination of trastuzumab with an anthracycline has to be balanced under consideration of the cardiovascular risks, and cardiac functions have to be closely monitored. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

[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 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, no added benefit, or less benefit). For further details see [1,2].

The approach for deriving an overall conclusion on 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 in combination with trastuzumab and 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.

The G-BA specified a therapeutic regimen containing trastuzumab, a taxane (paclitaxel, docetaxel) and, if applicable, an anthracycline (doxorubicin, epirubicin) as ACT for the present therapeutic indication. The combination of trastuzumab with an anthracycline has to be balanced under consideration of the cardiovascular risks, and cardiac functions have to be closely monitored.

The company followed this specification and chose trastuzumab and docetaxel as comparator therapy. The company's information regarding the choice of the taxane component was inconsistent (see Section 2.7.1 of the full dossier assessment). This remained without consequence for the present benefit assessment because the company searched for studies with both taxanes and identified no relevant study with paclitaxel.

The company's choice of the comparator therapy was followed. The assessment was conducted based on patient-relevant outcomes and on 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 (status: 17 June 2015)
- bibliographical literature search on pertuzumab (last search on 15 June 2015)
- search in trial registries for studies on pertuzumab (last search on 17 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on pertuzumab (last search on 4 September 2015)

No additional relevant study was identified from the check.

2.3.1 Studies included

The WO20697 study (hereinafter referred to as "NeoSphere") 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)
NeoSphere (W020697)	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			

The study pool for the benefit assessment of pertuzumab corresponded to that of the company.

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Table 4 and Table 5 describe the study used for the benefit assessment.

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]
NeoSphere	RCT, open-label, parallel	Adult patients with HER2-positive locally advanced, inflammatory or early-stage breast cancer with primary tumour > 2 cm in diameter and ECOG PS ≤ 1	Pertuzumab + trastuzumab + docetaxel (N = 107) trastuzumab + docetaxel (N = 107) trastuzumab + pertuzumab (N = 107)[b] pertuzumab + docetaxel (N = 96)[b]	Screening[c]: ▪ day -7 to day -1 Treatment phase: ▪ neoadjuvant: cycle 1 to 4 (until week 12) ▪ breast surgery: (between week 13 and 14) ▪ adjuvant: cycle 5 to 17[d] (from week 15 to 54) Observation phase: ▪ outcome-specific, at most 5 years after randomization of the last patient or until disease progression/recurrence in all patients	59 study centres in 16 countries: Australia, Austria, Brazil, Canada, Italy, Mexico, Peru, Poland, Republic of Korea; Russian Federation, Spain, Sweden, Switzerland, Taiwan, Thailand, United Kingdom 12/2007 until 10/2014 Data cut-offs: 1) 22 Dec 2009 2) 9 Mar 2012 3) 12 Jul 2013 4) 20 Oct 2014	Primary: pathological complete response Secondary: recurrence, breast-conserving surgery, AEs (including deaths)[e]

(continued)

Table 4: Characteristics of the study included – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel (continued)

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is not shown in the next tables.
c: An "offset dosing scheme" was conducted in selected study centres to investigate initial biological effects of the antibody therapy in the tumour tissue. The patients received the antibody therapy 7 days before the official dosing scheme. A biopsy was taken on study day 1 (cycle 1), and the remaining part of the first study medication was administered. A total of 31 (14.5%) patients in the relevant study arms received the "offset dosing scheme". For these patients, the screening phase was conducted from day -14 to day -8.
d: Duration of the adjuvant treatment phase only presented for the relevant study arms.
e: No systematic recording of deaths outside the recording of the AEs.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel; study NeoSphere

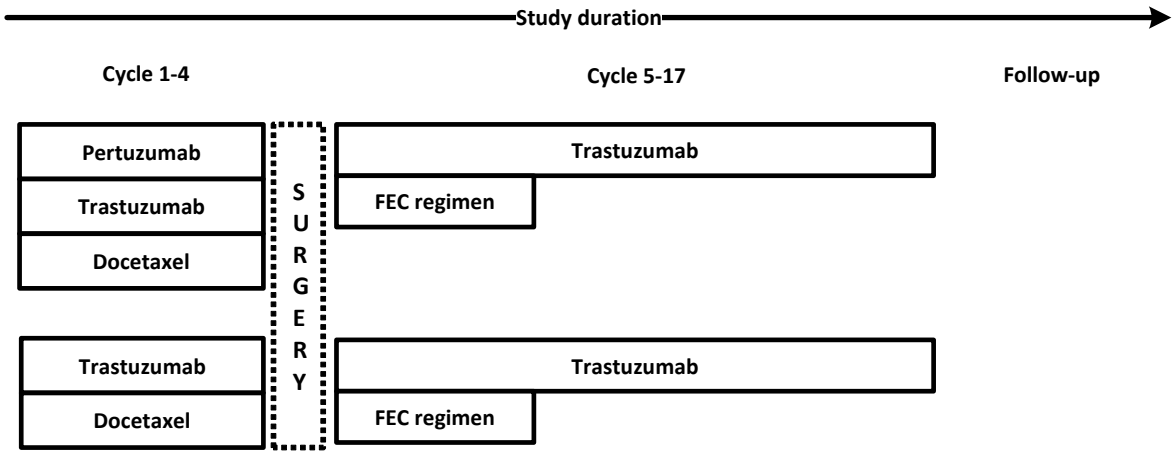
Intervention	Comparison
Neoadjuvant treatment phase (cycle 1 to 4)	
▪ Pertuzumab[a]: ▫ cycle 1: 840 mg IV ▫ cycle 2–4: 420 mg/kg IV every 3 weeks ▪ Trastuzumab[a]: ▫ cycle 1: 8 mg/kg IV ▫ cycle 2–4: 6 mg/kg IV every 3 weeks ▪ Docetaxel[b]: ▫ cycle 1: 75 mg/m^2 IV ▫ cycle 2–4: 100 mg/m^2 IV every 3 weeks if no dose-limiting toxicity occurred	▪ Trastuzumab[a]: ▫ cycle 1: 8 mg/kg IV ▫ cycle 2–4: 6 mg/kg IV every 3 weeks ▪ Docetaxel[b]: ▫ cycle 1: 75 mg/m^2 IV ▫ cycle 2–4: 100 mg/m^2 IV every 3 weeks if no dose-limiting toxicity occurred
Breast surgery	
Adjuvant treatment phase (cycle 5 to 17)	
▪ Trastuzumab[a]: 6 mg/kg IV every 3 weeks from cycle 5 to 17, up to 1 year in total; ▪ thereof parallel use with FEC regimen[c] consisting of: ▫ 5-fluorouracil 600 mg/m^2 IV (1200 mg maximum) ▫ epirubicin 90 mg/m^2 IV ▫ cyclophosphamide 600 mg/m^2 IV (1200 mg maximum) every 3 weeks from cycle 5 to 7	
Concomitant therapies Allowed treatments: ▪ premedication for the therapy of accompanying diseases could be continued during the study treatment ▪ following adjuvant chemotherapy, the patients could receive radiotherapy and/or hormone therapy according to local treatment standards Non-permitted treatments: ▪ treatments for breast cancer: cytotoxic chemotherapy, radiotherapy (except adjuvant radiotherapy on completion of the chemotherapy), immunotherapy and biological anti-cancer treatments ▪ steroid treatment except hormone replacement therapy and short-term use of corticosteroids ▪ high-dose systemic corticosteroids (> 20 mg dexamethasone per day [or equivalent]) for > 7 consecutive days ▪ start of treatment with herbal drugs ▪ hormonal methods (oral, injected or implanted) of contraception	
a: No dose modifications allowed. b: Dose reductions were to be conducted according to the SPC. Stepwise reduction was allowed from 100 mg/m^2 to 75 mg/m^2, and from 75 mg/m^2 to 60 mg/m^2. The reduced dose was to be maintained. c: FEC regimen: Dose delays or reductions were allowed according to the SPC and the local treatment standard. FEC: 5-fluorouracil, epirubicin, cyclophosphamide; IV: intravenous; RCT: randomized controlled trial; SPC: Summary of Product Characteristics vs.: versus	

Study design

The NeoSphere study was an open-label RCT. The study was conducted in a total of 16 countries, distributed in the regions Europe, North and South America and Asia-Pacific. Treatment-naive adult women with locally advanced, inflammatory, or early-stage invasive HER2-positive breast cancer with primary tumours > 2 cm in diameter and an ECOG PS of ≤ 1. Patients with one affected breast were suitable for participation. The diagnosis had to be histologically confirmed. Overall, the criteria of the approved therapeutic indication were regarded as being fulfilled for the patient population investigated in the study (see Section 2.7.2.4.1 of the full dossier assessment). This concurs with the company's assessment.

A total of 417 patients were randomly assigned in a ratio of 1:1:1:1 to 4 study arms: pertuzumab + trastuzumab + docetaxel, trastuzumab + docetaxel, trastuzumab + pertuzumab or pertuzumab + docetaxel. Randomization was stratified by type of breast cancer (operable [T2-3, N0-1, M0], locally advanced [T2-3, N2-3, M0; T4a-c, N0-3, M0] or inflammatory [T4d, N0-3, M0] breast cancer) and by positivity for oestrogen and/or progesterone receptors. However, only 2 study arms were used for the assessment of the added benefit: pertuzumab + trastuzumab + docetaxel and trastuzumab + docetaxel. This concurs with the company's assessment.

Figure 1 shows a schematic representation of the design of the NeoSphere study (relevant study arms).



FEC: 5-fluorouracil, epirubicin, cyclophosphamide

Figure 1: Design of the NeoSphere study (relevant study arms)

The study can be divided into 3 phases: the neoadjuvant treatment phase (4 cycles) followed by surgery, the adjuvant treatment phase (another 13 cycles), and the follow-up phase. Each treatment cycle lasted 3 weeks. On completion of the adjuvant treatment phase, the patients were followed-up for a maximum of 5 years after randomization of the last patient or until

occurrence of disease progression (or recurrence) in all patients (see Table 6 for the planned examinations).

In the neoadjuvant study phase, on day 1 of the respective cycle, patients in both study arms received a treatment regimen consisting of the following drugs: Trastuzumab (cycle 1: 8 mg/kg; from cycle 2: 6 mg/kg) followed by docetaxel (cycle 1: 75 mg/m^2; from cycle 2: 100 mg/m^2). The patients in the study arm with the investigational intervention additionally received pertuzumab on the same day (cycle 1: 840 mg; from cycle 2: 420 mg), administered after the trastuzumab infusion.

In the adjuvant treatment phase, the patients in both relevant study arms received the same treatment regimen. Between the cycles 5 to 7, trastuzumab (6 mg/kg) was administered on day 1 of the respective cycle, followed by the FEC regimen (5-fluorouracil [600 mg/m^2], epirubicin [90 mg/m^2] and cyclophosphamide [600 mg/m^2]). Starting from cycle 8, only trastuzumab (6 mg/kg) was administered until a total of one year of trastuzumab treatment was achieved.

The treatment regimens investigated in the study complied with the recommendations provided in the corresponding SPCs [3,4] regarding dosages and number of treatment cycles or were within a possible dosage range stated in the guidelines [5,6] (see also Section 2.7.2.4.1 of the full dossier assessment).

Due to the type of use of the therapeutic regimen in the adjuvant treatment phase, the transferability of the study results to the German health care context is limited, however. This limitation resulted, on the one hand, from the fact that trastuzumab was used in parallel with the anthracycline-containing FEC regimen in the study, although this combination is not recommended in the SPC of trastuzumab. On the other hand, the chemotherapy was divided into a neoadjuvant and an adjuvant part, although guidelines advise against this division (see also Section 2.7.2.4.1 of the full dossier assessment). Irrespective of this problem, the NeoSphere study met the conditions of the ACT regarding the drugs administered and was used for the assessment of the added benefit. Due to the described limitations, the conclusions on the added benefit of pertuzumab based on the NeoSphere study were limited to the treatment regimens investigated.

Outcomes and data cut-offs

The primary outcome of the study was pCR (referred to as “pathological complete remission in the breast” by the company in Module 4 A of the dossier). Patient-relevant secondary outcomes were recurrence, breast-conserving surgery and AEs. All-cause mortality was recorded in the framework of the recording of AEs as number of deaths. Health-related quality of life was not investigated in the study.

Table 6 shows the planned duration of follow-up of the patients for the individual outcomes.

Table 6: Planned duration of follow-up – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Study **Outcome category** **Outcome**	**Planned follow-up**
NeoSphere	
Mortality	
All-cause mortality	▪ There was no systematic recording of mortality beyond disease progression, recurrence or (presumably study) discontinuation. The available data were recorded and presented in the study report in the framework of the analysis of the AEs.
Morbidity	
Recurrence[a]	▪ Until first documented disease progression (recurrence) or death ▪ Examination for disease recurrence was conducted ▫ in the adjuvant treatment phase in a clinical examination/examination of the breast (according to local practice) in each cycle; mandatory mammography was only planned at the end of the adjuvant treatment phase ▫ on completion of the adjuvant treatment phase in a clinical examination (every 3 months in the first year, then every 6 months for 3 years), and (if needed) with imaging techniques; mandatory mammography was not planned ▫ until at most 5 years after randomization of the last patient or until disease progression (or recurrence) in all patients
Breast-conserving surgery	▪ Evaluated at the time point at which the last patient had surgery; no follow-up
Health-related quality of life	Outcome not recorded
Adverse events	
AEs/SAEs	▪ Until 28 days[b] after the last dose of pertuzumab and/or chemotherapy

a: Presented using the recurrence rate and disease-free survival.
b: Symptomatic LVSD (grade ≥ 3; grading according to NCI CTCAE and NYHA classification) was reported as SAE under the term "congestive heart failure" and was documented up to 24 months after the last administration of the study medication.

AE: adverse event; LVSD: left ventricular systolic dysfunction; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA: New York Heart Association; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Of the outcomes included, all-cause mortality was not systematically recorded beyond disease progression, recurrence or discontinuation in the NeoSphere study. The examinations for disease recurrence were conducted until at most 5 years after randomization of the last patient or until progression/recurrence or death in all patients. No follow-up was required for the outcome "breast-conserving surgery", which was recorded once at the time point of the surgery. AEs were recorded for up to 28 days after the end of treatment, certain cardiac events for up to 24 months after the last administration of the study medication.

A total of 4 data cut-offs were performed during the study. The first data cut-off (on 22 December 2009) was conducted on the date when the last patient was operated on. The

second data cut-off (on 9 March 2012) was conducted after all patients had completed their adjuvant treatment phase. The third data cut-off (on 12 July 2013) was conducted mid-follow-up phase. Both the second and the third data cut-off exclusively included data on AEs. The final fourth data cut-off (on 20 October 2014) conducted after the end of the study included data on disease recurrence and AEs among other things.

Characteristics of the study population

Table 7 shows the characteristics of the patients in the study included.

Table 7: Characteristics of the study populations – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Study Characteristics Category	Pertuzumab + trastuzumab + docetaxel N[a] = 107	Trastuzumab + docetaxel N[a] = 107
NeoSphere		
Age [years]		
Mean (SD)	50 (10)	51 (9)
Median [min; max]	50 [28, 77]	50 [32, 74]
Sex [F/M], %	100/0	100/0
Ethnicity, n (%)		
Black	2 (1.9)	0 (0)
Caucasian	77 (72.0)	80 (74.8)
Oriental[b]	23 (21.5)	25 (23.4)
Other	5 (4.7)	2 (1.9)
Female reproductive status, n (%)		
Postmenopausal	45 (42.1)	48 (44.9)
Surgically sterilized	7 (6.5)	7 (6.5)
Continuous contraception	55 (51.4)	52 (48.6)
ECOG PS, n (%)		
0	96 (89.7)	100 (94.3)
1	11 (10.3)	6 (5.7)
Tumour size [mm]		
Median[c] [min, max]	55 [20, 150]	50 [20, 200]
Histological tumour grade, n (%)		
Well differentiated	2 (1.9)	1 (0.9)
Moderately differentiated	33 (30.8)	37 (34.6)
Poorly differentiated	34 (31.8)	31 (29.0)
Unknown	38 (35.5)	38 (35.5)
Hormone receptor status		
ER– and PR–	57 (53.3)	57 (53.3)
ER+ and/or PR+	50 (46.7)	50 (46.7)
Breast cancer type[d], n (%)		
Inflammatory	10 (9.3)	7 (6.5)
Locally advanced	32 (29.9)	36 (33.6)
Early[e]	65 (60.7)	64 (59.8)
Nodal status, n (%)		
Node-positive (N1/N2/N3)	75 (70.8)	75 (70.1)
Node-negative (N0)	31 (29.3)	32 (30.0)
Treatment discontinuation, n (%)	13 (12.1)[f]	9 (8.4)[f]
Neoadjuvant treatment phase	5 (4.7[f])	4 (3.7[f])
Adjuvant treatment phase	8 (7.5[f])	5 (4.7[f])

(continued)

Table 7: Characteristics of the study populations – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel (continued)

Study Characteristics Category	Pertuzumab + trastuzumab + docetaxel N[a] = 107	Trastuzumab + docetaxel N[a] = 107
Study discontinuation, n (%)	24 (22.4)[f]	30 (28.0)[f]
Neoadjuvant treatment phase	3 (2.8[f])	1 (0.9[f])
Adjuvant treatment phase	2 (1.9[f])	8 (7.5[f])
Follow-up phase	19 (17.8[f])	21 (19.6[f])

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Discrepant designation of this category between the CSR and the publication on the NeoSphere study. This category is referred to as "Asian" in the publication.
c: Discrepancy between Module 4 A and Module 5 of the dossier and the publication on the NeoSphere study. Information taken from Module 5 of the dossier.
d: Staging according to TNM classification (T: diameter of the primary tumour; N: regional lymph node metastasis, M: distant metastasis): inflammatory: T4d, N0-3, M0; locally advanced: T2-3, N2-3, M0; T4a-c, N0-3, M0; early: T2-3, N0-1, M0.
e: Referred to as "operable" in the study documents of the company and in the publication on the study.
f: Institute's calculation.
CSR: clinical study report; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER+/−: oestrogen receptor-positive/negative; F: female; M: male; max: maximum; min: minimum; N: number of randomized (or included) patients; n: number of patients in the category; PR:+/–: progesterone receptor-positive/negative; RCT: randomized controlled trial; SD: standard deviation; TNM: tumour-node-metastasis; vs.: versus

The demographic and disease-specific characteristics of the study population were largely comparable between the 2 relevant treatment arms. The mean age of the patients was 50 years and most of them were of Caucasian origin. Characteristics important to assess the recurrence risk – such as nodal status, hormone receptor status, histological tumour grade – were similarly distributed between the treatment arms. The proportion of patients with treatment discontinuation was somewhat higher in the pertuzumab + trastuzumab + docetaxel arm than in the trastuzumab + docetaxel arm (12.1% versus 8.4%). The overall proportion of patients with study discontinuation, in contrast, was somewhat lower in the pertuzumab + trastuzumab + docetaxel arm than in the trastuzumab + docetaxel arm (22.4% versus 28.0%).

Duration of treatment and follow-up

Table 8 shows the median treatment duration of the patients and the follow-up period for individual outcomes.

Table 8: Information on the course of the study – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Study **Duration of the study phase** **Outcome category**	**Pertuzumab + trastuzumab + docetaxel** **N = 107**	**Trastuzumab + docetaxel** **N = 107**
NeoSphere		
Treatment duration [weeks]		
Neoadjuvant treatment phase		
Median [min; max]	17.0 [5, 23]	17.0 [8, 26]
Adjuvant treatment phase		
Median [min; max]	41.0 [2, 57]	41.0 [12, 48]
Treatment duration [weeks]		
Total study phase		
Median [min; max]	266.0 [6, 329]	263.0 [13, 304]
Morbidity (recurrence[a])		
Median [min; max]	249.0 [ND]	246 [ND]
Adverse events		
Median[b] [min; max]	62.0 [ND]	62.0 [ND]

a: Recorded from the time point of the surgery; estimated from the information on the neoadjuvant phase and the total study phase.
b: Information estimated from the time of treatment under consideration of the follow-up period of 28 days for adverse events.
max: maximum; min: minimum; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; vs.: versus

The median treatment durations were comparable in both treatment arms both for the neoadjuvant and for the adjuvant treatment phase. The observation periods for the relevant outcomes were also comparable between the treatment arms.

Risk of bias at study level

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. 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**			
NeoSphere	Yes	Yes	No	No	Yes	Yes	Low

RCT: randomized controlled trial; vs.: versus

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

Restrictions resulting from the open-label study design and the partly unsystematic recording of the data are described in Section 2.4 and in Section 2.7.2.4.2 of the full dossier assessment under the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - recurrence
  - breast-conserving surgery
- Health-related quality of life
- Adverse events
  - SAEs
  - discontinuation due to AEs
  - severe AEs CTCAE grade ≥ 3
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes or partly different operationalizations in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Study	Outcomes						
	All-cause mortality	Recurrence[b]	Breast-conserving surgery	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs CTCAE grade ≥ 3
NeoSphere	Yes[a]	Yes	Yes	No[c]	Yes	Yes	Yes

a: Not systematically recorded in the study beyond disease progression, recurrence or discontinuation.
b: Presented using the recurrence rate and disease-free survival.
c: Outcome not recorded.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The available documents contained data for all relevant outcomes except for health-related quality of life, which was not recorded in the NeoSphere study. The fourth data cut-off from 20 October 2014 was used in the present assessment for the outcomes "all-cause mortality", "recurrence" and for the outcomes on harm. For the outcome "breast-conserving surgery", the first data cut-off from 22 December 2009 was used (see Section 2.7.2.4.3 of the full dossier assessment for information on this choice). This concurs with the company's approach.

2.4.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Study		Outcomes						
	Study level	All-cause mortality	Recurrence[b]	Breast-conserving surgery	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs CTCAE grade ≥ 3
NeoSphere	L	H[a]	L	H[c]	–[d]	L	H[e]	L

a: Not systematically recorded in the study beyond disease progression, recurrence or discontinuation.
b: Presented using the recurrence rate and disease-free survival.
c: Open-label study design; decision on breast-conserving surgery possibly influenced by the patient's or the investigator's subjective expectations.
d: Outcome not recorded.
e: Open-label study design.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias for the outcome "all-cause mortality" was assessed as high. It was decisive for this assessment that the recording of this outcome was not systematic beyond disease progression, recurrence or discontinuation in the NeoSphere study. This does not concur with the assessment of the company, which included deaths in the outcomes on AEs and assessed the risk of bias for these outcomes jointly as low (see Section 2.7.2.4.2 of the full dossier assessment).

The risk of bias was rated as low for the outcomes "recurrence (presented with the recurrence rate and disease-free survival), "SAEs" and "severe AEs CTCAE grade ≥ 3". For the outcomes "SAEs" and "severe AEs CTCAE grade ≥ 3", this concurs with the assessment of the company. The company considered recurrence exclusively using the outcome "disease-free survival", for which the company assumed a low risk of bias.

The risk of bias was rated as high for the outcomes "breast-conserving surgery" and "discontinuation due to AEs". For both outcomes, this is due to the open-label study design of the NeoSphere study. It cannot be excluded that the decision for or against treatment discontinuation or breast-conserving surgery or mastectomy was influenced by the patient's or the treating physician's subjective expectations. This does not concur with the company's evaluation, which assumed a low risk of bias for both outcomes. Furthermore, the company considered the outcome "breast-conserving surgery" using a different subpopulation of the study and in a different operationalization (see Section 2.7.2.4.3 of the full dossier assessment).

2.4.3 Results

Table 12 and Table 13 summarize the results on the comparison of pertuzumab + trastuzumab + docetaxel with trastuzumab + docetaxel in patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. The Kaplan-Meier curve of the survival time analysis on the outcome "recurrence" presented using disease-free survival is shown in Figure 2, Appendix A of the full dossier assessment.

Table 12: Results (outcomes on mortality, health-related quality of life, AEs) – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Study **Outcome category** **Outcome**	**Pertuzumab + trastuzumab + docetaxel**		**Trastuzumab + docetaxel**		**Pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
NeoSphere **(data cut-off 20 October 2014)**					
Mortality					
All-cause mortality[a]	107	8 (7.5)	107	6 (5.6)	1.33 [0.48; 3.71]; 0.682[b]
Health-related quality of life	Outcome not recorded				
Adverse events					
AEs (supplementary information)	107	105 (98.1)	107	107 (100.0)	Not applicable
SAEs	107	22 (20.6)	107	21 (19.6)	1.05 [0.61; 1.79]; 0.922[b]
Discontinuation due to AEs	107	6 (5.6)[c]	107	0 (0)	–[d] 0.014[b]
Severe AEs CTCAE grade ≥ 3	107	78 (72.9)	107	87 (81.3)	0.90 [0.77; 1.04]; 0.151[b]

a: Data on all-cause mortality were not systematically recorded beyond disease progression, recurrence or discontinuation. Data were recorded if these were available.
b: Institute's calculation, unconditional exact test (CSZ method according to [7]).
c: The company only reported 5 patients with event in Table 4-49 in Module 4 A of the dossier. As described by the company in the subsequent text, there was one additional patient with event, who was not included in the table due to a mistake in the database.
d: No precise estimation of effect estimate (RR) possible with 95% CI.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 13: Results (outcomes on morbidity) – RCT, direct comparison: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Study **Outcome category** **Outcome**	**Pertuzumab + trastuzumab + docetaxel**		**Trastuzumab + docetaxel**		**Pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
NeoSphere **(data cut-off 20 October 2014)**					
Morbidity					
Breast-conserving surgery[a]	107	27 (25.2)	107	25 (23.4)	1.08 [0.67; 1.73][b] 0.819[c]
Recurrence:					
Recurrence rate	101[d]	14 (13.9)[e]	103[d]	18 (17.5)	0.79 [0.42; 1.51][b] 0.532[c]
	N	**Median survival time in months [95% CI]** **Patients with event n (%)**	**N**	**Median survival time in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value**
Disease-free survival	101[d]	67.2 [67.2; 72.2] 15 (14.9)[f]	103[d]	NA 18 (17.5)	0.60 [0.28; 1.27]; 0.185

a: Analysed at the data cut-off on 22 December 2009.
b: Institute's calculation.
c: Institute's calculation, unconditional exact test (CSZ method according to [7]).
d: Number of patients who had surgery.
e: Uncertainty regarding the number of patients with recurrence in the study documents of the company (13 or 14 patients).
f: The analysis of disease-free survival, besides recurrence, also included 2 deaths (in the pertuzumab + trastuzumab + docetaxel arm). One further patient with disease progression was not included in disease-free survival, but presumably in the recurrence rate.
CI: confidence interval; CSZ: convexity, symmetry, z score; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Only one relevant study was available for the assessment of pertuzumab. The NeoSphere study did not meet the particular requirements placed on the derivation of proof of an added benefit from a single study [1]. Hence, at most "indications" could be derived from the data.

Mortality

All-cause mortality

No statistically significant difference in the proportion of deaths was shown between the 2 treatment groups for the outcome "all-cause mortality". There was no hint of an added

benefit of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome "all-cause mortality"; an added benefit is therefore not proven.

In contrast, the company concluded on the basis of a high association between the outcome "pCR", which is not patient-relevant (see Section 2.7.2.9.4 of the full dossier assessment), and all-cause mortality that there was a non-quantifiable added benefit for the outcome "all-cause mortality".

Morbidity

Recurrence

Both analyses showed no statistically significant difference between the 2 treatment groups for the outcome "recurrence" (shown with the recurrence rate and disease-free survival). Hence there was no hint of an added benefit of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome "recurrence"; an added benefit is therefore not proven.

The company exclusively presented the result on survival time analyses for disease-free survival and also derived no added benefit from this analysis.

Breast-conserving surgery

For the outcome "breast-conserving surgery", there was no statistically significant difference between the 2 treatment groups. Hence there was no hint of an added benefit of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome "breast-conserving surgery"; an added benefit is therefore not proven.

This concurs with the assessment of the company, which was based on a different operationalization and subpopulation of the study, which, in addition, was unsuitable from the company's point of view to show the treatment success of pertuzumab.

Health-related quality of life

Health-related quality of life was not investigated in the study. Hence there was no hint of an added benefit of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome "health-related quality of life"; an added benefit is therefore not proven.

The company, in contrast, stated that no conclusions on the added benefit for the outcome "health-related quality of life" are possible.

Adverse events

SAEs

There was no statistically significant difference between the 2 treatment groups for the overall rate of SAEs. There was no hint of greater or lesser harm of pertuzumab + trastuzumab +

docetaxel in comparison with trastuzumab + docetaxel for the outcome "SAEs"; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + docetaxel between the treatment groups was shown for the outcome "discontinuation due to AEs". 4 of the 6 recorded AEs that led to treatment discontinuation in the pertuzumab + trastuzumab + docetaxel arm were cardiac events (see Table 22 in Appendix B of the full dossier assessment). There was a hint of greater harm of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcome "discontinuation due to AEs".

This assessment deviates from that of the company, which derived no greater or lesser harm of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel.

Severe AEs CTCAE grade ≥ 3

There was no statistically significant difference between the 2 treatment groups for severe AEs CTCAE grade ≥ 3. There was no hint of greater or lesser harm of pertuzumab + trastuzumab + docetaxel in comparison with trastuzumab + docetaxel for the outcomes "severe AEs CTCAE grade ≥ 3"; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.4 Subgroups and other effect modifiers

In order to uncover possible effect differences between the patient groups, the following potential effect modifications were investigated:

- age (< 65/≥ 65 years)
- ethnicity (Caucasian/black/oriental/other)
- geographical region (Asia-Pacific/Europe/America)
- breast cancer type (operable/locally advanced/inflammatory)
- hormone receptor status (progesterone receptor-positive [PR+] and/or oestrogen receptor-positive [ER+]/progesterone receptor-negative [PR−] and oestrogen receptor-negative [ER−])

The prerequisite for proof of different effects is a statistically significant interaction test ($p < 0.05$). A p-value between 0.05 and 0.2 provides an indication of differing effects.

Subgroup analyses on the characteristics named above were available for the majority of the outcomes included in the assessment.

However, a different operationalization than the one for which the company presented subgroup analyses was used for the outcome "breast-conserving surgery". Subgroup analyses for this outcome in the relevant operationalization could not be calculated by the Institute on the basis of the available data.

Subgroup analyses on the outcome "recurrence" were not available for the analysis as recurrence rate. The company, however, presented subgroup analyses for the analysis on disease-free survival, which were used for the present assessment.

There was no proof ($p < 0.05$) of an effect modification from any of the subgroup analyses. There was an indication of an effect modification for the outcome "all-cause mortality" for the characteristic "geographical region", the outcome "recurrence" (presented with disease-free survival) for the characteristics "geographical region" and "hormone receptor status" and the outcome "SAEs" for the characteristic "age". Since no statistically significant differences between the treatment groups were shown for these outcomes for the total population or for any of the subgroups, the individual subgroup results are not presented.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit 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 the *General Methods* of IQWiG [1].

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 the added benefit.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in a hint of greater harm from pertuzumab for the outcome "discontinuation due to AEs". Due to the fact that 2 of the total of 6 events that led to treatment discontinuation in the pertuzumab arm were SAEs and that it could not be excluded with certainty for the remaining 4 events that they were also serious, the outcome "discontinuation due to AEs" was allocated to the outcome category "serious/severe AEs".

The extent of the respective added benefit at outcome level was estimated from these results (see Table 14).

Table 14: Extent of added benefit at outcome level: pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel

Outcome category **Outcome**	**Pertuzumab + trastuzumab + docetaxel vs. trastuzumab + docetaxel** **Quantile of time to event** **Effect estimate [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	7.5% vs. 5.6% RR: 1.33 [0.48; 3.71] p = 0.682	Lesser benefit/added benefit not proven
Morbidity		
Recurrence:		
Recurrence rate	13.9% vs. 17.5% RR: 0.79 [0.42; 1.51] p = 0.532	Added benefit not proven
Disease-free survival	14.9% vs. 17.5% HR: 0.60 [0.28; 1.27] Median: 67.2 vs. NA p = 0.185	Added benefit not proven
Breast-conserving surgery	25.2% vs. 23.4% RR: 1.08 [0.67; 1.73] p = 0.819	Added benefit not proven
Health-related quality of life		
	Outcome not investigated	
Adverse events		
SAEs	20.6% vs. 19.6% RR: 1.05 [0.61; 1.79] p = 0.922	Greater/lesser harm not proven
Discontinuation due to AEs	5.6% vs. 0% RR: –[c] p = 0.014[d] probability: "hint"	Outcome category: serious/severe AEs greater harm, extent: "non-quantifiable"[e]
Severe AEs CTCAE grade ≥ 3	72.9% vs. 81.3% RR: 0.90 [0.77; 1.04] p = 0.151	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: No precise estimation of effect estimate (RR) possible with 95% CI.
d: The statistical significance was assessed on the basis of the p-value [1].
e: The extent for this outcome could not be determined because no precise estimation of the RR with 95% CI was possible.
AE: adverse event; CI: confidence interval, CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; NA: not achieved; RR: relative risk; SAE: serious adverse event; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 15: Positive and negative effects from the assessment of pertuzumab + trastuzumab + docetaxel compared with trastuzumab + docetaxel

Positive effects	Negative effects
-	Hint of greater harm – extent "non-quantifiable" (serious/severe AEs: discontinuation due to AEs)
AE: adverse event	

Overall, a negative effect (hint) for greater harm in the outcome "discontinuation due to AEs" (outcome category "serious/severe AEs)" with the extent "non-quantifiable" remains for pertuzumab.

There were no statistically significant differences between the treatment groups regarding further outcomes in the categories "mortality", "morbidity" and "AEs". In addition, health-related quality of life was not investigated in the study.

In summary, there is a hint of lesser benefit of pertuzumab in comparison with the ACT for patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence. 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 doubtful (see Section 2.7.2.4.1 of the full dossier assessment).

The result of the assessment of the added benefit of pertuzumab in comparison with the ACT is summarized in Table 16.

Table 16: Pertuzumab – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Pertuzumab is indicated in combination with trastuzumab and chemotherapy in neoadjuvant treatment of adult patients with HER2-positive locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence.	A therapeutic regimen containing **trastuzumab**, a taxane (paclitaxel or **docetaxel**) and, if applicable, an anthracycline (doxorubicin, epirubicin)[b]	Hint of lesser benefit
a: Presentation of the appropriate comparator therapy specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the choice of the company is printed in bold. b: The combination of trastuzumab with an anthracycline has to be balanced under consideration of the cardiovascular risks, and cardiac functions have to be closely monitored. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

This deviates from the company's approach, which derived an indication of a non-quantifiable added benefit on the basis of the outcome "pCR", which is not patient-relevant.

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

2.6 List of included studies

NeoSphere

F. Hoffmann-La Roche. A randomised, multicenter, multinational phase II study on trastuzumab plus docetaxel versus trastuzumab plus docetaxel plus pertuzumab versus trastuzumab plus pertuzumab versus pertuzumab and docetaxel in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer [online]. In: EU Clinical Trials Register. [Accessed: 7 September 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-001105-13.

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F. Hoffmann-La Roche. A randomized, multicenter, multinational phase II study on trastuzumab plus docetaxel versus trastuzumab plus docetaxel plus pertuzumab versus trastuzumab plus pertuzumab versus pertuzumab and docetaxel in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer: study WO20697; update clinical study report [unpublished]. 2013.

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Roche. A randomized, open label study to compare the complete pathological response rate achieved with 4 combinations of Herceptin, docetaxel and pertuzumab in patients with locally advanced, inflammatory or early stage HER2 positive breast cancer: trial results [online]. In: Roche Clinical Trial Results Database. 1 June 2011 [accessed: 19 June 2015]. URL: http://www.roche-trials.com/trialDetailsGet.action?studyNumber=WO20697.

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Please see full dossier assessment for full reference list.

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