IQWiG Reports – Commission No. A21-11

Pertuzumab/trastuzumab (breast cancer, adjuvant) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Pertuzumab/Trastuzumab (Mammakarzinom, adjuvant) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

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

IQWiG employees involved in the dossier assessment

- Jana Göbel
- Ulrich Grouven
- Charlotte Hecker
- Marco Knelangen
- Stefan Kobza
- Daniela Preukschat
- Annette Pusch-Klein
- Beate Wieseler

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IDFS	invasive disease-free survival
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LVEF	left-ventricular ejection fraction
PT	Preferred Term
QLQ-BR23	Quality of Life Questionnaire-Breast Cancer Module 23
QLQ-C30	Quality of Life Questionnaire-Core 30
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code SGB V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the subcutaneously administered fixed combination of pertuzumab and trastuzumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 19 January 2021.

Research question

The aim of the present report was to assess the added benefit of the subcutaneously administered fixed combination of pertuzumab and trastuzumab (hereinafter referred to as pertuzumab/trastuzumab [SC]) for the adjuvant treatment of adult patients with human epidermal growth factor receptor 2 (HER2)-positive early-stage breast cancer at high risk of recurrence (node-positive or hormone receptor-negative disease). Pertuzumab/trastuzumab (SC) was exclusively administered in combination with chemotherapy.

The G-BA specified a treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin) as appropriate comparator therapy (ACT) for the present therapeutic indication. The implementation of an anthracycline-containing therapy protocol has to be balanced under consideration of the cardiovascular risks. Trastuzumab should not be used in combination with anthracyclines, but sequentially in combination with a taxane. Cardiac functions have to be closely monitored.

The G-BA's specification of the ACT resulted in one research question which is presented in the following Table 2.

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

Therapeutic indication	ACT[a]
Adjuvant treatment of adult patients with HER2-positive early-stage breast cancer at high risk of recurrence (node-positive or hormone receptor-negative)	A treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin)[b]
a. Presentation of the respective ACT specified by the G-BA. b. Trastuzumab was to be administered over a period of 1 year. It is assumed that patients with positive hormone receptor status received additional endocrine therapy. Adjuvant radiotherapy can be used as a patient-specific intervention. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; SC: subcutaneous	

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

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in Module 4 C of the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit.

Study pool and study characteristics

The study pool for the benefit assessment includes the APHINITY study. This study is a randomized, double-blind, 2-arm study that enrolled adult patients with early-stage HER2-positive breast cancer. The primary tumours and, if applicable, the affected lymph nodes were surgically removed before the start of the study. Previous (neo)adjuvant chemotherapies/anti-HER2 therapies or radiotherapies were not allowed. Within 56 days after surgery, the total of 4805 patients were randomly assigned to one of the two treatment arms (pertuzumab + trastuzumab + chemotherapy or placebo + trastuzumab + chemotherapy) in a 1:1 ratio.

The approval of pertuzumab covers patients at high risk of recurrence, defined as node-positive or hormone receptor-negative disease. This applied to about 3 quarters of the study population. Unless otherwise stated, all of the following data refer to the subpopulation relevant for the benefit assessment.

All patients received adjuvant chemotherapy after surgery. This could be an anthracycline-containing or anthracycline-free chemotherapy and in any case contained a taxane. All patients received anti-HER2 therapy consisting of pertuzumab and trastuzumab in the intervention arm and placebo and trastuzumab in the comparator arm. The anti-HER2 treatment was administered for 52 weeks. It started at the same time as the taxane-containing chemotherapy, i.e. after a possible anthracycline treatment had been completed.

If indicated, patients received adjuvant radiotherapy in parallel with anti-HER2 treatment after completion of the chemotherapy. Moreover, hormone-receptor-positive patients were also to be treated with endocrine therapy for at least 5 years.

Primary outcome of the study was invasive disease-free survival (IDFS). Relevant secondary outcomes included “disease-free survival (DFS)” (particularly recurrences), “symptoms”, “health-related quality of life”, “overall survival” and “side effects”.

Risk of bias and certainty of conclusions

The risk of bias across outcomes for the APHINITY study was rated as low. The outcome-specific risk of bias for the results of most outcomes was rated as low. The risk bias was considered to be high only for the results of outcomes on symptoms and health-related quality of life, which were recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. This is due to the fact that more than 10% of the patients in the relevant subpopulation were not included in the analysis. On the basis of the available data and because of the high risk of bias, at most hints, e.g. of an added benefit, can be determined for the patient-reported outcomes that were recorded using the EORTC questionnaire, and at most indications can be determined for all other outcomes.

Results

Based on the APHINITY study, the results for the treatment arms of the APHINITY study and the added benefit at outcome level are described (pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy). Hereinafter, the effects described for the intravenous free combination on the basis of the APHINITY study are used for the benefit assessment of pertuzumab/trastuzumab (SC).

Mortality

Overall survival

At the second data cut-off (19 June 2019), there was no statistically significant difference between the treatment groups for the outcome "overall survival". This resulted in no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. An added benefit is therefore not proven for this outcome.

Morbidity

Recurrence

For the outcome “recurrence” (operationalized as recurrence rate and DFS), there was a statistically significant effect in favour of pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy for both operationalizations at the second data cut-off (19 June 2019). This resulted in an indication of an added benefit for this outcome.

Symptoms

The outcome “symptoms” was recorded with the disease-specific instruments European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire-Breast Cancer Module 23 (QLQ-BR23). Symptoms were considered at 2 time points. The proportion of patients with a deterioration by ≥ 10 points was considered at each of the time points “end of anti-HER2 therapy” and “36-month follow-up”. These analyses were already available at the first data cut-off (19 December 2016).

Fatigue, diarrhoea, symptoms in the chest region

Statistically significant differences between the treatment arms were shown for the outcomes "fatigue", "diarrhoea" and "symptoms in chest region". For "fatigue" and "symptoms in chest region", differences were only shown at the time point "end of anti-HER2 therapy", for "diarrhoea" these differences occurred at both time points. All differences at the time point "end of anti-HER2 therapy" are to the disadvantage of pertuzumab + trastuzumab + chemotherapy. The difference at the 36-month follow-up for diarrhoea is in favour of pertuzumab + trastuzumab + chemotherapy. However, the differences for the outcomes "fatigue", "symptoms in chest region" and "diarrhoea" (36-month follow-up) were no more than marginal for an outcome in the category "non-serious/non-severe symptoms/late complications". Thus, at the end of the anti-HER2 therapy, there was a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy for the outcome "diarrhoea".

Appetite loss

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was also shown for the outcome "appetite loss" at the end of anti-HER2 therapy. However, a statistically significant interaction with the characteristic "age" was shown at this point in time. This resulted in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for patients ≥ 65 years of age.

Nausea and vomiting

In the total population, there was no statistically significant difference between the treatment groups for the outcome "nausea and vomiting". However, at the time point "end of anti-HER2 therapy", there was a statistically significant interaction with the characteristic "age"; however, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was only shown for patients ≥ 65 years. This resulted in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for these patients.

Further symptom outcomes

At both time points, no statistically significant difference between the treatment groups was shown for each of the following outcomes: "pain", "dyspnoea", "insomnia", "constipation", "side effects of systemic treatment", "symptoms in the arm region" and "upset by hair loss". This resulted in no hints of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. An added benefit is therefore not proven for these outcomes.

Health-related quality of life

"Health-related quality of life" was recorded with the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. The proportion of patients with a deterioration by ≥ 10 points was considered at each of the two time points "end of anti-HER2 therapy" and "36-month follow-up". These analyses were already available at the first data cut-off (19 December 2016).

Emotional functioning

A statistically significant difference between the treatment groups in favour of pembrolizumab + trastuzumab + chemotherapy was shown for the outcome “emotional functioning” at the time point “36-month follow-up”. This resulted in a hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for this time point.

Physical functioning

For the outcome “physical functioning”, a statistically significant interaction with the characteristic “age” was shown at the end of the anti-HER2 therapy. However, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was only shown for patients ≥ 65 years. This resulted in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for these patients.

Role functioning

For the outcome “role functioning”, a statistically significant interaction with the characteristic “age” was shown at the time point “36-month follow-up”. However, a statistically significant difference in favour of pertuzumab + trastuzumab + chemotherapy was only shown for patients < 65 years. This resulted in a hint of an added benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for these patients.

Further scales on health-related quality of life

There was no statistically significant difference between the treatment groups for the outcomes “global health status”, “cognitive functioning”, “social functioning”, “body image”, “sexual activity”, “enjoyment of sex” and “future perspective”. This resulted in no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy; an added benefit is therefore not proven for these outcomes.

Side effects

Serious adverse events (SAEs)

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the outcome "SAEs” at the second data cut-off (19 June 2019). This resulted in an indication of greater harm from pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)

At the second data cut-off (19 June 2019), a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the outcome "severe AEs”. However, there was a statistically significant interaction with the characteristic “geographical region”. The result in the region of Western Europe, which is important for the benefit assessment, differs from the result for the overall population. There was no statistically significant difference between the treatment groups for the region “Western Europe”. Based on

the result for the region “Western Europe”, there is therefore no hint of a greater or lesser harm from pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy. An added benefit is therefore not proven for severe AEs.

Discontinuation due to AEs

At the second data cut-off (19 June 2019), no statistically significant difference between the treatment groups was shown for the outcome "discontinuation due to AEs”. This resulted in no hint of greater harm or lesser harm from pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. An added benefit of pertuzumab is therefore not proven for this outcome.

Specific AEs

At the second data cut-off (19 June 2019), a statistically significant difference between the treatment arms to the disadvantage of pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy was shown for each of the following AEs:

- SAEs or severe AEs (CTCAE grade ≥ 3):

  heart failure (Preferred Term [PT], SAEs), anaemia (PT, severe AEs), diarrhoea (PT, severe AEs), stomatitis (PT, severe AEs), fatigue (PT, severe AEs), white blood cell count decreased (PT, severe AEs), metabolism and nutrition disorders (System Organ Class [SOC], severe AEs)

- non-severe/non-serious AEs:

  diarrhoea (PT), pruritus (PT)

This resulted in an indication of greater harm from pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

A statistically significant interaction with the characteristic “age” was shown for the outcome "skin and subcutaneous tissue disorders (SOC, AEs)”. However, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was only shown for patients < 65 years. This resulted in an indication of greater harm from pertuzumab + trastuzumab + chemotherapy versus the ACT for these patients.

There was a statistically significant difference in favour of pertuzumab + trastuzumab + chemotherapy for the outcome "musculoskeletal and connective tissue disorders (SOC, severe AEs)". This resulted in an indication of lesser harm from pertuzumab + trastuzumab + chemotherapy in comparison with the ACT.

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

As "age" is a consistent effect modifier across several outcomes, the results on the added benefit for patients < 65 years and those ≥ 65 years are first described separately below:

- The overall consideration shows positive and negative effects for patients < 65 years. On the positive side, there is an indication of a minor added benefit or of lesser harm for the outcome "recurrence" and for a specific AE, and there are also hints of a minor added benefit for individual dimensions of health-related quality of life. In contrast, there are indications of negative effects with the extents "minor", "considerable" and "major" for the outcomes "SAEs" and "specific AEs". In the treatment phase, these were also partly reflected by the patient-reported symptoms (diarrhoea). There are thus disadvantages during the treatment phase (recording of AEs until end of treatment), with at least some of the reported SAEs (in particular a relevant proportion of serious heart failures) persisting beyond treatment. Overall, the negative effects outweigh the positive effects of pertuzumab/trastuzumab (SC) in this situation.
- In addition to the positive and negative effects described for the younger age group (< 65 years), there were further negative effects in patients ≥ 65 years that show greater burdens from the therapies. For the treatment phase, this results in additional hints of burdens from the symptoms for 2 outcomes ("nausea and vomiting", "appetite loss") with the extents "minor" and "considerable" as well as for "physical functioning" as 1 of 9 recorded dimensions of health-related quality of life (extent: "minor"). However, compared to the previous benefit assessment A18-41, the positive effects for the outcome "recurrence" are based on a longer follow-up period of 6 years, and there are slightly larger absolute differences between the recurrence rates in the treatment groups (3.6% vs. 2.4%). In the present data cut-off, the negative effects of pertuzumab/trastuzumab (SC) therefore no longer predominate over the positive effects. However, the negative effects outweigh the positive ones.

In summary, an added benefit of pertuzumab/trastuzumab (SC) as adjuvant treatment versus the ACT, a therapeutic regimen containing trastuzumab, a taxane and, if applicable, an anthracycline has not been proven for either of both patient groups (< 65 years, ≥ 65 years) with HER2-positive early-stage breast cancer at high risk of recurrence.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

The effects described for the intravenous free combination on the basis of the APHINITY study are used for the benefit assessment of pertuzumab/trastuzumab (SC).

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

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

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of adult patients with HER2-positive early-stage breast cancer at high risk of recurrence (node-positive or hormone receptor-negative)	A treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin)	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; SC: subcutaneous		

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

2.2 Research question

The aim of the present report was to assess the added benefit of the subcutaneously administered fixed combination of pertuzumab and trastuzumab (hereinafter referred to as pertuzumab/trastuzumab [SC]) for the adjuvant treatment of adult patients with HER2-positive early-stage breast cancer at high risk of recurrence (node-positive or hormone receptor-negative disease). Pertuzumab/trastuzumab (SC) was exclusively administered in combination with chemotherapy.

The G-BA specified a treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin) as ACT for the present therapeutic indication. The implementation of an anthracycline-containing therapy protocol has to be balanced under consideration of the cardiovascular risks. Trastuzumab should not be used in combination with anthracyclines, but sequentially in combination with a taxane. Cardiac functions have to be closely monitored.

The G-BA's specification of the ACT resulted in one research question which is presented in the following Table 4.

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

Therapeutic indication	**ACT[a]**
Adjuvant treatment of adult patients with HER2-positive early-stage breast cancer at high risk of recurrence (node-positive or hormone receptor-negative)	A treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin)[b]
a. Presentation of the respective ACT specified by the G-BA. b. Trastuzumab was to be administered over a period of 1 year. It is assumed that patients with positive hormone receptor status received additional endocrine therapy. Adjuvant radiotherapy can be used as a patient-specific intervention. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; SC: subcutaneous	

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

Within the framework of the approval [3], the bio- and efficacy equivalence of the fixed combination of pertuzumab and trastuzumab (SC) and the intravenous free combination of pertuzumab and trastuzumab was proven on the basis of the FeDeriCa study [4] to confirm the non-inferiority with regard to pharmacokinetics. The company therefore derived the added benefit of pertuzumab/trastuzumab (SC) independently of the administration form and presented the results of the FeDeriCa study as supplementary information. This approach is principally comprehensible, but the study does not rule out potential advantages of the subcutaneously administered fixed combination over the intravenous free combination of pertuzumab and trastuzumab for patient-relevant outcomes. Moreover, the transfer of the results for the free intravenous combination was examined, particularly for AEs (see Section 2.4.3).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in Module 4 C of the dossier. RCTs were used for the derivation of the added benefit.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

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

To check the completeness of the study pool:

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

The check did not identify any additional relevant studies.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + docetaxel

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Study report (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
BIG-4-11/BO25126/TOC4939G (APHINITY[d])	Yes[e]	Yes	No	Yes [5,6]	Yes [7-11]	Yes [12-20]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the website of the G-BA and EPAR.
d. In the following tables, the study is referred to with this abbreviated form.
e. Study for the approval of the free intravenous combination of pertuzumab and trastuzumab.

EPAR: European Public Assessment Report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

Results for the free intravenous combination of pertuzumab + trastuzumab can be used for the benefit assessment of the fixed combination pertuzumab/trastuzumab (SC). This means that the study pool of the benefit assessment of pertuzumab/trastuzumab (SC) in combination with chemotherapy versus the ACT consists of the RCT APHINITY, which was presented for the approval of the free intravenous combination and is consistent with the study pool of the company. Below, the treatment arms of the RCT APHINITY are referred to as pertuzumab + trastuzumab + chemotherapy and placebo + trastuzumab + chemotherapy.

The RCT APHINITY was already used for the added benefit of the free intravenous combination of pertuzumab and trastuzumab (Benefit assessment A18-41 [21] and the corresponding addendum A18-76 [22]). Only a subpopulation (population at high risk of recurrence: node-positive or hormone receptor-negative disease) of the study is relevant for the benefit assessment.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
APHINITY	RCT, double-blind, parallel	Adult patients with early-stage, completely resected, HER2-positive[b] breast cancer who receive adjuvant therapy	▪ Pertuzumab + trastuzumab + chemotherapy (N = 2400) ▪ placebo + trastuzumab + chemotherapy (N = 2404) relevant subpopulation thereof (patients at high risk of recurrence due to node-positive or HR-negative[c] disease): ▪ pertuzumab + trastuzumab + chemotherapy (N = 1811) ▪ placebo + trastuzumab + chemotherapy (N = 1823)	▪ Surgery until start of treatment: at most 8 weeks treatment: ▪ anthracycline-containing chemotherapy: 3-4 cycles before the start of anti-HER2 treatment ▪ 52-week anti-HER2 treatment (pertuzumab + trastuzumab) observation[d]: outcome-specific, at most until death, discontinuation of participation in the study or end of study[e]	548 centres in 42 countries: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, China, Colombia, Croatia, Czech Republic, Denmark, El Salvador, France, Germany, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Mexico, Netherlands, New Zealand, Panama, Peru, Philippines, Poland, Romania, Russia, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, Ukraine, United Kingdom, United States 11/2011–ongoing data cut-offs: ▪ 30 November 2012 (only safety outcomes) ▪ 22 February 2013 (only safety outcomes) ▪ 19 December 2016 (primary data cut-off) ▪ 15 May 2017 (3-month safety report) ▪ 19 June 2019 (second OS interim analysis)	Primary: invasive disease-free survival (IDFS) secondary: disease-free survival (DFS), symptoms, health-related quality of life, overall survival, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. HER2 status determined by a central laboratory by means of immunohistochemistry and/or in situ hybridization.
c. HR status determined by a central laboratory via detection of oestrogen receptor (ER) and/or progesterone receptor (PR).
d. Outcome-specific information is provided in Table 8.
e. The study ends about 10 years after the randomization of the last patient, provided that the study objectives have been achieved by then. This may (but need not) coincide with the event-driven OS analysis that takes place when 640 patients have died.

AE: adverse event; HER2: human epidermal growth factor receptor 2, HR: hormone receptor; n: relevant subpopulation; N: number of randomized patients; OS: overall survival; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (multipage table)

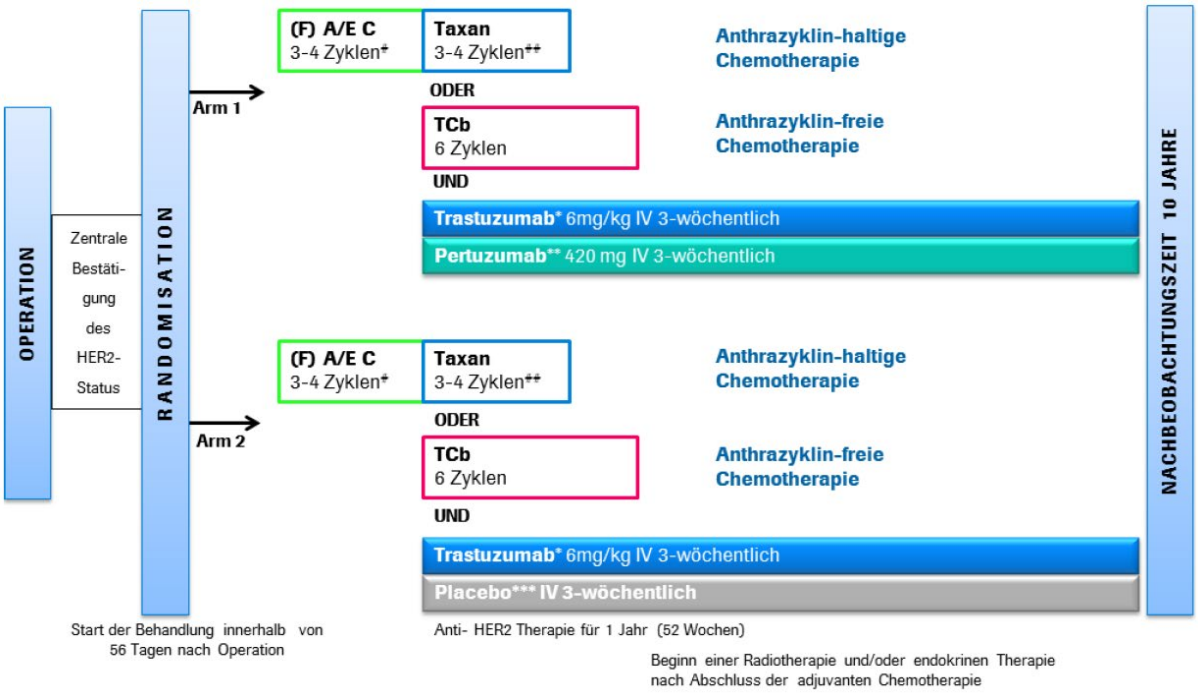
Study	Intervention	Comparison
APHINITY	▪ Pertuzumab[a] ▫ cycle 1: 840 mg IV ▫ cycle 2 up to at most 18: 420 mg IV, every 3 weeks (q3w)	▪ Placebo: ▫ cycle 1 to a most 18: IV, q3w
	▪ trastuzumab[a] ▫ cycle 1: 8 mg/kg IV ▫ cycle 2 up to at most 18: 6 mg/kg, IV, q3w	▪ trastuzumab[a]: ▫ cycle 1: 8 mg/kg IV ▫ cycle 2 up to at most 18: 6 mg/kg, IV, q3w
	Starting with the taxane-containing chemotherapy	Starting with the taxane-containing chemotherapy
	Possible chemotherapies (both treatment arms)	
	Anthracycline-containing chemotherapy[b]: ▪ 3 to 4 cycles of FEC or FAC (both IV q3w) or ▪ 4 cycles AC or EC (both IV q3w or dose-dense every 2 weeks [q2w]) each followed by: ▪ 3 to 4 cycles of docetaxel IV, q3w[c] or ▪ 12 cycles of paclitaxel IV, weekly ▪ **anthracycline-free chemotherapy[d]:** ▪ 6 cycles docetaxel + carboplatin IV, q3w	
	Prior and concomitant treatment	
	Prohibited prior therapies: ▪ anti-HER2 therapies ▪ systemic chemotherapies ▪ radiotherapies **prohibited concomitant treatments (until recurrence):** ▪ other cytotoxic chemotherapies, radiotherapy (except adjuvant radiotherapy), immunotherapies, biological anticancer therapies and anticancer therapies that are also used for the treatment of rheumatoid arthritis (e. g. methotrexate) ▪ targeted anticancer therapies (e. g. lapatinib, neratinib) ▪ chronic treatment with steroids or short-term treatment with more than 20 mg of dexamethasone per day for 7 days (or equivalent) ▪ initiation of phytotherapy after the start of the study ▪ hormonal contraception other than already existing progesterone-containing intrauterine devices ▪ oestrogen replacement therapy	

a. No dose reduction allowed.
b. Dosage: 5-fluorouracil: 500 to 600 mg/m², epirubicin: 90 to 120 mg/m², doxorubicin: 50 mg/m² (if administered with fluorouracil) or 60 mg/m² (if administered without fluorouracil), cyclophosphamide: 500 to 600 mg/m², docetaxel: 75 to 100 mg/m², paclitaxel: 80 mg/m²; maximum cumulative dose 360 mg/m² doxorubicin and 720 mg/m² epirubicin.
c. Several regimens possible: 75 mg/m² over 4 cycles, or 75 mg/m² in the first cycle, then escalation to 100 mg/m² in the subsequent cycles, or 100 mg/m² in 3 to 4 cycles.
d. Dosage: docetaxel: 75 mg/m², carboplatin: AUC 6 mg/ml/min, max. 900 mg.

Table 7: Characteristics of the intervention – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (multipage table)

Study	Intervention	Comparison
AC: doxorubicin + cyclophosphamide; AUC: area under the curve; EC: epirubicin + cyclophosphamide; FAC: 5-fluorouracil + doxorubicin + cyclophosphamide; FEC: 5-fluorouracil + epirubicin + cyclophosphamide; HER2: human epidermal growth factor receptor 2; IV: intravenously; Q2W: every 2 weeks; Q3W: every 3 weeks; RCT: randomized controlled trial		

The APHINITY study is a randomized, double-blind, 2-arm study that included adult patients with early-stage HER2-positive breast cancer. The primary tumours and, if applicable, the affected lymph nodes were surgically removed before the start of the study. Previous (neo)adjuvant chemotherapies/anti-HER2 therapies or radiotherapies were not allowed. Within 56 days after surgery, the total of 4805 patients were randomly assigned to one of the two treatment arms (pertuzumab + trastuzumab + chemotherapy or placebo + trastuzumab + chemotherapy) in a 1:1 ratio. Stratification was based on node status, type of adjuvant chemotherapy regimen, hormone receptor status, geographical region and protocol version (node-negative patients were no longer included from protocol version B and higher).



A: doxorubicin; Cb: carboplatin; E: epirubicin; F: 5-fluorouracil; HER2: human epidermal growth factor receptor 2; IV: intravenous; T: taxane

Figure 1: Design of the APHINITY study

The study started in November 2011 and was still ongoing when this benefit assessment was being performed.

The approval of pertuzumab covers patients at high risk of recurrence, defined as node-positive or hormone receptor-negative disease [23]. This applied to about 3 quarters of the study population. The company presented study results for the relevant subpopulation in Module 4 C of the dossier. Unless otherwise stated, all of the following data refer to the subpopulation relevant for the benefit assessment.

All patients received adjuvant chemotherapy after surgery. This could be an anthracycline-containing or anthracycline-free chemotherapy. In the case of anthracycline treatment, the study participants at first received 3 to 4 cycles (8 to 12 weeks) of a combined therapy with doxorubicin or epirubicin and cyclophosphamide, with or without 5-fluorouracil (in the latter case over 4 cycles). This was followed by taxane-based chemotherapy. This could be administered over 3 to 4 cycles with docetaxel or 12 weekly cycles of paclitaxel. In the case of anthracycline-free chemotherapy, patients received 6 cycles (18 weeks) of a combined therapy with docetaxel and carboplatin. These chemotherapy regimens were administered equally in both treatment arms.

All patients received anti-HER2 therapy consisting of pertuzumab and trastuzumab in the intervention arm and placebo and trastuzumab in the comparator arm. The anti-HER2 treatment was administered for 52 weeks. It started at the same time as the taxane-containing chemotherapy, i.e. after a possible anthracycline treatment had been completed.

If indicated, patients received adjuvant radiotherapy in parallel with anti-HER2 treatment after completion of the chemotherapy. Moreover, hormone-receptor-positive patients were also to be treated with endocrine therapy for at least 5 years.

For both anthracyclines and anti-HER2 antibodies, there is a risk of cardiotoxic side effects. Module 4 C of the company provides no information on which patients were suitable for anthracycline-containing chemotherapy. The chemotherapy was chosen by the investigator prior to randomization. However, the study did not include patients with serious cardiovascular diseases or a left-ventricular ejection fraction (LVEF) below 55%. The LVEF was monitored during the course of the study. An algorithm was defined in the study protocol according to which treatment with pertuzumab and trastuzumab should be interrupted or discontinued. Thereafter, a persistent decline in LVEF by at least 10 percentage points and below 50% in total resulted in treatment discontinuation.

After occurrence of a resectable recurrence, treatment with trastuzumab could be re-initiated at the investigator's discretion. The results of this treatment were no longer recorded as part of the study. Module 4 C provides no information on which subsequent therapies patients received after recurrence or treatment discontinuation. In principle, however, subsequent therapies after recurrence could be administered without restriction. Separate information on the procedure to be followed in case of recurrence during the 52-week anti-HER2 therapy are not found in Module 4 C of the company.

Primary outcome of the study was IDFS. Relevant secondary outcomes included "DFS" (particularly recurrences), "symptoms", "health-related quality of life", "overall survival" and "side effects".

Data cut-offs and available analyses

To date, 5 data cut-offs have been performed for the APHINITY study (30 November 2012, 22 February 2013, 19 December 2016, 15 May 2017, 19 June 2019). Outcomes on side effects were analysed for the data cut-offs of 30 November 2012 and 22 February 2013. Furthermore, the data cut-off of May 2017 was a 3-month safety update requested by the Food and Drug Administration (FDA).

For the present benefit assessment, analyses are available for the following 2 data cut-offs:

- First data cut-off (19 December 2016, primary analysis): preplanned efficacy analysis took place after 381 IDFS-related events, further analyses on overall survival, efficacy and side effects took place at the same time.
- Second data cut-off (19 June 2019, second overall survival (OS) interim analysis): preplanned analysis, 2.5 years after the primary analysis, on the outcomes "mortality", "morbidity" and "side effects"

For the benefit assessment, the company used the analyses on the first data cut-off (19 December 2016) for all outcomes on morbidity and health-related quality of life. The outcomes "mortality" and "side effects" are based on the second data cut-off (19 June 2019).

Deviating from the company's approach, the respective most recent data cut-off was used for the benefit assessment. The outcomes of the categories "mortality", "morbidity (recurrence)" and "side effects" are thus based on the second data cut-off (19 June 2019). The primary data cut-off was used for the analysis of morbidity (symptoms) and health-related quality of life, because at that time all patients had already completed both the treatment phase and the last planned recording of the questionnaires at month 36 after randomization. Thus, all available data of the patients had already been considered at the first data cut-off (19 December 2016).

Following the benefit assessment of pertuzumab (intravenous application, A18-41) based on the APHINITY study, the G-BA originally limited the decision until 2 January 2022 [17] to then analyse data on the 3rd interim analysis of APHINITY. However, the company informed the G-BA that the interim analysis planned to take place 5 years after the primary analysis of 19 December 2016 (third interim analysis for OS) was not going not take place until 10 January 2022. To enable an inclusion of these data in the benefit assessment of pertuzumab after expiry of the deadline, the limitation was extended until 1 October 2022 [19]. Irrespective of this planned assessment of the intravenous application of pertuzumab, the APHINITY study was considered in the present assessment of the subcutaneous application of the fixed combination of pertuzumab and trastuzumab (see above).

Treatment duration and follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 8: Planned duration of the follow-up observation – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy

Study outcome category outcome	Planned follow-up observation
APHINITY	
Mortality	
Overall survival	Up to 10 years after randomization
Morbidity	
Recurrence	Up to 10 years after randomization
Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23)	After the last dose of the study medication in the follow-up phase at months 18, 24 and 36 (± 28 days each) after start of the study
Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23)	After the last dose of the study medication in the follow-up phase at months 18, 24 and 36 (± 28 days each) after start of the study
Side effects	
AEs	Until 28 days after the last dose of the study medication[a]

a. Except for SAEs that were considered treatment-related and cardiac events and secondary cancer diseases (excluding breast cancer) regardless of a suspected causal relationship with the study medication were excluded here; these were recorded beyond the 28-day deadline. All side effects were followed up until regression or until the end of the study.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event

Observation of symptoms and health-related quality of life was not performed over the entire study period, but still up to 36 months after randomization. These outcomes were thus observed over a relevant period, i.e. until 2 years after completion of the treatment.

The observation periods for the outcomes on side effects were systematically shortened because, with a few exceptions such as cardiac events, they were only recorded for the time period of treatment with the study medication (plus 28 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for survival and the recurrences.

Characteristics of the study population

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study population - RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study characteristic category	**Pertuzumab + trastuzumab + chemotherapy N[a] = 1811**	**Placebo + trastuzumab + chemotherapy N[a] = 1823**
APHINITY		
Age [years]		
Mean (SD)	52 (11)	51 (11)
Median [min; max]	51 [24; 86]	51 [19; 85]
Sex [F/M], %	99.9/0.1	99.7/0.3
Family origin, n (%)		
Caucasian	1252 (69.3)	1255 (68.9)
Black	25 (1.4)	31 (1.7)
Asian	477 (26.4)	484 (26.6)
Other	52 (2.9)	51 (2.8)
Geographical region		
USA/Canada	265 (14.6)	260 (14.3)
Western Europe	827 (45.7)	822 (45.1)
Asia-Pacific	490 (27.1)	512 (28.1)
Latin America	43 (2.4)	47 (2.6)
Other	186 (10.3)	182 (10.0)
Female reproductive status, n (%)		
Premenopausal	873 (48.3)	885 (48.7)
Postmenopausal	933 (51.6)	929 (51.2)
Unknown	3 (0.2)	2 (0.1)
Hormone receptor status		
Negative (ER- and PR-negative)	864 (47.7)	858 (47.1)
Positive (ER- and/or PR-positive)	947 (52.3)	965 (52.9)
Node status		
N0 and tumour ≤ 1 cm	51 (2.8)	43 (2.4)
N0 and tumour > 1cm	257 (14.2)	278 (15.2)
N1-3 positive lymph nodes	907 (50.1)	900 (49.4)
N ≥ 4 positive lymph nodes	596 (32.9)	602 (33.0)
Type of adjuvant chemotherapy		
Anthracycline-containing	1439 (79.5)	1448 (79.4)
Anthracycline-free	372 (20.5)	375 (20.6)
Locoregional radiotherapy (after adjuvant chemotherapy)		
Yes	1347 (74.4)	1350 (74.1)
No	464 (25.6)	473 (25.9)
Treatment discontinuation[b], n (%)	278 (15.4)	241 (13.2)

Table 9: Characteristics of the study population - RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study characteristic category	Pertuzumab + trastuzumab + chemotherapy N[a] = 1811	Placebo + trastuzumab + chemotherapy N[a] = 1823
Treatment phase completed, n (%)	1533 (84.6)	1582 (86.8)
Study discontinuation[c], n (%)	362 (20.0)[d]	434 (23.8)[d]

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. Discontinuation of pertuzumab or placebo; most common reasons for discontinuation: AE, patient request and non-compliance.
c. During the follow-up phase until the second data cut-off, the most common reasons being recurrence and patient request; data exclude deaths. In 147 (8.1%) vs. 210 (11.5%) of the patients, treatment was discontinued due to recurrence, and in 215 (11.9%) vs. 224 (12.3%) of the patients the reason for the discontinuation was not a recurrence; data without deaths. Module 4 C does not provide the total number of patients who discontinued the study.
d. Institute's calculation of the percentages.

ER: oestrogen receptor; F: female; M: male; n: number of patients in the category; N: number of randomized (or included) patients; PR: progesterone receptor; RCT: randomized controlled trial; SD: standard deviation

Due to the indication, the study population of the APHINITY study consists almost exclusively of women. On average, the patients of the relevant subpopulation were about 51 years old. Almost 70% were white, another 26% were of Asian origin. Almost half of the study population come from Western Europe, about one quarter from the Asia-Pacific region and just under 15% from North America. Other countries and regions are represented with small shares.

Patients with hormone-receptor-positive and hormone-receptor-negative disease were almost equally represented in the subpopulation. More than 80% of the patients had lymph node involvement, mostly with 1 to 3 positive nodes. With lymph node status N0, the tumour size was over 1 cm in diameter in over 80% of cases.

About 80% of the patients received anthracycline-containing chemotherapy. 3 quarters of the patients received locoregional radiotherapy. Module 4 C of the company provides no information on endocrine therapies for the relevant subpopulation. In the total population, 87.3% of the patients in the treatment arm and 85.8% of the patients in the comparator arm received adjuvant endocrine therapy [15].

In about 14% of the patients, treatment with pertuzumab or placebo was not completed. Slightly more than 20% discontinued the study during the follow-up phase.

Information on the course of the study

Table 10 shows the median treatment duration of the patients and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients)

Study **duration of the study phase** **outcome category**	**Pertuzumab + trastuzumab + chemotherapy** **N = 1811**	**Placebo + trastuzumab + chemotherapy** **N = 1823**
APHINITY		
Treatment duration [weeks], median [min; max]	ND[a]	ND[a]
Observation period [months]		
Overall survival and recurrences		
Median [min; max]	73.6 [0; 89.0]	73.2 [0; 88.5]
Symptoms and health-related quality of life		
Median [min; max]	36 [0; 36][b]	36 [0; 36][b]
Number of patients in the last analysis at month 36 (%)[c]	1327 (73.3)	1298 (71.2)
Side effects[d]		
Median [min; max]	14.9 [0.1; 18.5][e]	15.0 [0; 85.8][e]
Number of patients who completed anti-HER2 treatment (%)	1533 (84.6)	1582 (86.8)

a. Information is only available for the total population (in total: 64 [4; 80] vs. 64 [4; 74] weeks, anthracycline-containing chemotherapy thereof: 11 [4; 26] vs. 13 [4; 18] weeks and pertuzumab/placebo + trastuzumab (+ taxane): 55 [4; 59] vs. 55 [4; 70] weeks [21])
b. Institute's calculation based on the number of patients for whom data were available when the documentation was carried out.
c. Institute's calculation, data refer to the EORTC questionnaire with the lowest response rate at month 36.
d. Data for AEs recorded until 28 days after the last dose of the study medication. In the follow-up phase, the follow-up observation period at the second data cut-off is 73.6 (0.1; 89.0) vs. 73.1 (0; 87.9) months for the safety population
e. These figures refer to the safety population of the study (1783 vs. 1822 patients).

HER2: human epidermal growth factor receptor 2, max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial

The median observation period in the APHINITY study was the same for all outcomes in both treatment arms. In the total population, the duration of treatment was comparable (median 64 months). Therefore, when interpreting the results, the different observation durations did not result in any limitations.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
APHINITY	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the APHINITY study was rated as low. This concurs with the company's assessment.

Transferability of the study results to the German health care context

In Module 4 C, the company described the transferability to the German health care context based on the characteristics "sex", "age", "family origin", "general condition", "histology of the carcinoma" and "type of chemotherapy regimen" of the patients included in the APHINITY study.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - OS
- Morbidity
  - recurrence
  - symptoms, recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23
- Health-related quality of life
  - EORTC QLQ-C30 and EORTC QLQ-BR23
- Side effects
  - serious AEs (SAEs)

- severe AEs (CTCAE grade ≥ 3)
- discontinuation due to AEs
- further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in Module 4 C.

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients)

Study	Outcomes							
	Overall survival	Recurrence[a]	Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Specific AEs[b, d]
APHINITY	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented via the recurrence rate and disease-free survival; includes the events: ipsilateral invasive local breast cancer recurrence, ipsilateral invasive regional breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, secondary primary carcinoma (no breast cancer), DCIS (ipsilateral or contralateral) and death from any cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of treatment with a drug component (chemotherapy, trastuzumab, pertuzumab or placebo)
d. The following events are considered (MedDRA coding): diarrhoea (PT, AEs), pruritus (PT, AEs), cardiac failure (PT, SAEs), anaemia (PT, severe AEs), diarrhoea (PT, severe AEs), stomatitis (PT, severe AEs), fatigue (PT, severe AEs), white blood cell count decreased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs) and skin and subcutaneous tissue disorders (SOC, severe AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DCIS: ductal carcinoma in situ; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Recurrences: consideration of event rate and event time analysis

The outcome “recurrence” is a combined outcome and includes the components “ipsilateral invasive local breast cancer recurrence”, “ipsilateral invasive regional breast cancer

recurrence", "distant recurrence", "contralateral invasive breast cancer", "secondary primary carcinoma (no breast cancer)", "DCIS (ipsilateral or contralateral)" and "death from any cause". Information on the occurred events included in the combined outcome for the individual components was not available for the second data cut-off that is relevant here; information on the first data cut-off can be found in dossier assessment A18-41. The proportion of patients with recurrence and also the time to the occurrence of a recurrence were used for the assessment.

Use of surrogate outcomes: DFS as surrogate for the outcome "overall survival"

The company moreover used the outcome "DFS" as surrogate for the outcome "overall survival" in its benefit assessment, and derived an advantage of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for "overall survival". The surrogate validation SV2 (surrogate validation based on Saad 2019 [24]) presented by the company in Module 4 C (Section 4.5.4 of the full dossier assessment) was already submitted by the company in identical form for dossier assessment A20-07 [25]. The company has now supplemented this surrogate validation with an updated information retrieval [26], in which it did not find any further studies with available results.

The inclusion criteria of the validation study (see also A20-07) are not suitable for a surrogate validation in the present research question. The present research question investigates a comparison of anti-HER2 therapies (in combination with chemotherapy) with sufficient treatment duration and dose. However, the definition of the comparator therapy in the inclusion criteria of the validation study systematically excludes studies in which anti-HER2 therapies are compared with each other in approved dosages and therapy durations (such as the PUMCH-BREAST-AH study). Moreover, with the correlation-based approach chosen by the company, it was also adequate to include the APHINITY study itself in the surrogate validation; an analysis with or without a study to be assessed is useful for assessing the robustness of the results. The extent to which further relevant studies were available beyond the named studies cannot be assessed on the basis of the documents available in the dossier. The updated information retrieval presented by the company is also based on the unsuitable inclusion criteria from Saad 2019 and is therefore not suitable for this reason alone to identify relevant studies in the research question available for the benefit assessment.

Moreover, the study pool of the surrogate validation SV2 included several studies which only offered treatment with chemotherapy in the respective comparator arms, or no active treatment but only observation. The company provided no information on this and also presented no sensitivity analyses that would allow an estimation of the influence these therapies have on the surrogate validation.

In addition, in contrast to Saad 2019, the company presented no analyses in the surrogate validation SV2 that consider the subpopulation of high-risk patients (node-positive or hormone receptor-negative) relevant for the present research question. Moreover, in the present Module 4 C, the company did not calculate a surrogate threshold effect for a comparison with the DFS effect of the APHINITY study.

In the present situation, the surrogate validation SV2 presented by the company is therefore not suitable to derive conclusions on the validity of DFS as a surrogate outcome for the outcome "overall survival" and is consequently not used for the present benefit assessment.

Responder analyses for the outcomes on symptoms and health-related quality of life

In Module 4 C, the company presented responder analyses for the proportion of patients with a deterioration by 10 points for both the EORTC QLQ-C30 and the EORTC QLQ-BR23. As explained in the *General Methods* of the Institute [1,27], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). For the EORTC QLQ-C30 and the EORTC QLQ-BR23, the analysis with a response threshold of 10 points is considered a sufficient approximation to an analysis with a 15% threshold (15 points) and is used for the benefit assessment (for explanation see [28]).

In the APHINITY study, the respective proportions of responders were recorded at 4 selected time points (end of taxane therapy, end of anti-HER2 therapy, 18-month follow-up and 36-month follow-up; see also Module 4 A [16] of the benefit assessment of pertuzumab [A18-41]). Based on benefit assessment A18-41 [21], the company presented 2 selected time points (end of anti-HER2 therapy and 36-month follow-up [36 months after randomization]) in Module 4 C. In the present assessment, these time points were used in accordance with the procedure in A18-41.

Notes on side effects

For the assessment of the side effects, the company for the first time presented a complete breakdown of the side effects at SOC/PT level in addition to the overall rates for the superordinate outcomes (AEs, SAEs, severe AEs [operationalized as CTCAE grade ≥ 3], discontinuation due to AEs). A comprehensive assessment of severe side effects was impossible due to an incomplete list of all severe AEs according to SOC and PT in the previous benefit assessment of pertuzumab A18-41 (see [21]). The observation periods for the outcomes on side effects comprised the period of treatment with the study medication (plus 28 days). Beyond this 28-day deadline (in the so-called follow-up phase), the company only recorded serious AEs that were considered treatment-related, as well as cardiac events and secondary cancer diseases (excluding breast cancer). At the first data cut-off (19 December 2016), all patients had completed the treatment phase with the additional 28-day period and thus a complete data set for AEs and SAEs was already available at that time for the analysis of the treatment phase (treatment with the study medication plus 28 days) (see Section 2.3.2). The updated presentation at the second data cut-off (19 June 2019) shows minor quantitative deviations in the number of events for the superordinate outcomes on side effects (most clearly for severe AEs) and for some AEs/SAEs at SOC or PT level (e.g. in the PT "heart failure", in the SOC "investigations" [SAE each] or in the SOC "gastrointestinal discomfort" [AE]). It is unclear how these deviations can be justified. In Module 4 C, the company described that the accumulated safety data were assessed by an independent data monitoring committee every 6

months and that the most recent data cut-off was taken into account for the present data analysis in order to be able to depict the tolerability using the most recent data.

The SAE-related events during the follow-up phase that are suspected having been associated with the study medication were presented separately by the company in Module 4 C (Appendix 4 G). Module 4 C provides no separate analyses on cardiac AEs and secondary cancer diseases during the follow-up phase. Moreover, a publication on the second data cut-off that is relevant here reports that since the primary analysis, one further primary cardiological event had occurred in the total population in the pertuzumab arm and one patient each in the pertuzumab and placebo arm had one secondary cardiological event [14]. However, the above-mentioned operationalizations “primary cardiological event” and “secondary cardiological event” are not used for the present benefit assessment (for justification, see dossier assessment A18-41 [21]). For the specific SAE “heart failure (PT)” considered in A18-41 and in the present benefit assessment, no separate analyses for the follow-up phase are available, and it is unclear whether the results in Table 14 only cover events that occurred during treatment + 28 days.

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients)

Study		Outcomes							
	Study level	Overall survival	Recurrence[a]	Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23)	Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Specific AEs[b]
APHINITY	L	L	L[e]	H[f]	H[f]	L	L	L	L

a. Presented via the recurrence rate and disease-free survival; includes the events: ipsilateral invasive local breast cancer recurrence, ipsilateral invasive regional breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, secondary primary carcinoma (no breast cancer), DCIS (ipsilateral or contralateral) and death from any cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of treatment with a drug component (chemotherapy, trastuzumab, pertuzumab or placebo)
d. The following events are considered (MedDRA coding): diarrhoea (PT, AEs), pruritus (PT, AEs), cardiac failure (PT, SAEs), anaemia (PT, severe AEs), diarrhoea (PT, severe AEs), stomatitis (PT, severe AEs), fatigue (PT, severe AEs), white blood cell count decreased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs) and skin and subcutaneous tissue disorders (SOC, severe AEs).
e. For the relapse rate, there is a high risk of bias due to the high proportion of patients who discontinued the study and the resulting incomplete observation times. However, as the proportions of patients who discontinued the study are comparable between the treatment groups and the results of the event time analyses for disease-free survival are very similar, the results are considered to be sufficiently robust. Therefore, the risk of bias for the outcome "recurrence" was rated as low.
f. Proportion of patients (> 10%) not considered in the analysis.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DCIS: ductal carcinoma in situ; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-BR23: Quality of Life Questionnaire-Core 23; QLQ-C30: Quality of Life Questionnaire-Lung Cancer 30; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

The outcome-specific risk of bias for the results of most outcomes was rated as low. The risk bias was considered to be high only for the results of outcomes on symptoms and health-related quality of life, which were recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires. This is due to the fact that more than 10% of the patients in the relevant subpopulation were not included in the analysis. This deviates from the assessment of the company, which assumed a low risk of bias also for these results.

Overall assessment on the certainty of conclusions

From the company's point of view, a proof of added benefit could be derived from the APHINITY study included in the benefit assessment. For this purpose, the company cited requirements from IQWiG's General Methods [1], according to which, in order to derive a proof, the present study had to be a multicentre study, with ≥ 10 study centres and at least 1000 patients in each study arm. This requirement was not fulfilled in the APHINITY study. *Moreover, from the point of view of the company, further criteria had to be fulfilled that are listed in the* European Medicines Agency (*EMA*) *guideline "Points to Consider on Application with: 1. Meta-Analyses; 2. One Pivotal Study" [29], the company considers all these points to be fulfilled.*

The company's rationale was not followed, especially with regard to the statistical significance and effects of the study centres. The company considered the p-value of 0.0188, as calculated for the effect in the outcome "DFS" at the first data cut-off to be clearly below the 5% level. In IQWiG's General Methods, however, a threshold of < 0.001 is used as a prerequisite for a proof. Of the outcomes included in the present assessment, the outcome category "side effects" (severe AEs, diarrhoea [AE and severe AE], pruritus [AE], metabolism and nutrition disorders [severe AE]) shows low p-values in the order of < 0.001 in isolated cases. Moreover, the results must be consistent within a study, i.e. for the (sub-)population of interest there are analyses of various other sub-populations (especially subsets of study centres), each of which yields assessable and sufficiently homogeneous effect estimates. A subgroup analyses by region, as can be found in Module 4 C of the company, might be suitable to fulfil this requirement. However, for the superordinate outcome "severe AEs", there is a significant interaction as well as different effects for individual regions. Due to this significant heterogeneity in a superordinate outcome, a consistency across all centres cannot be assumed and thus, also in the outcome category "side effects", at most an indication can be derived at outcome level.

In summary, at most an indication of an added benefit can be derived from the APHINITY study at study level.

2.4.3 Results

Table 14, Table 15 and Table 16 summarize the results of the comparison of pertuzumab + trastuzumab + chemotherapy with placebo + trastuzumab + chemotherapy in patients with HER2-positive early-stage breast cancer at high risk of recurrence. Where necessary, the data from the company's Module 4 C were supplemented by the Institute's calculations.

The Kaplan-Meier curves on the included outcomes are presented in Appendix A, and the results on common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study **outcome category** **outcome** **time point**	**Pertuzumab + trastuzumab + chemotherapy**		**Placebo + trastuzumab + chemotherapy**		**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
APHINITY					
Mortality (second data cut-off: 19 June 2019)					
Overall survival	1811	108 (6.0) median time to event: NA [NC; NC]	1823	130 (7.1) median time to event: NA [NC; NC]	HR[a] 0.82 [0.64; 1.06] 0.136
Morbidity (second data cut-off: 19 June 2019)					
Recurrence					
Recurrence rate[b]	1811	219 (12.1)	1823	287 (15.7)	0.77 [0.65; 0.905] 0.002[c]
Ipsilateral invasive local breast cancer recurrence	1811	ND[d]	1823	ND[d]	—
Ipsilateral invasive regional breast cancer recurrence	1811	ND[d]	1823	ND[d]	—
Distant recurrence	1811	ND[d]	1823	ND[d]	—
Contralateral invasive breast cancer	1811	ND[d]	1823	ND[d]	—
Secondary primary carcinoma (no breast cancer)	1811	ND[d]	1823	ND[d]	—
DCIS (ipsilateral or contralateral)	1811	ND[d]	1823	ND[d]	—
Death from any cause	1811	ND[d]	1823	ND[d]	—
Disease-free survival[e]	1811	219 (12.1) median time to event: NA [NC; NC]	1823	287 (15.7) median time to event: NA [NC; NC]	HR[a] 0.75 [0.63; 0.90] 0.002

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study outcome category outcome time point	Pertuzumab + trastuzumab + chemotherapy		Placebo + trastuzumab + chemotherapy		Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Side effects (second data cut-off: 19 June 2019)					
AEs (supplementary information)	1783	1782 (> 99.9)	1822	1813 (99.5)	-
SAEs	1783	509 (28.5)	1822	446 (24.5)	1.17 [1.05; 1.30]; 0.006[h]
Severe AEs[g]	1783	1141 (64.0)	1822	1055 (57.9)	1.11 [1.05; 1.16]; < 0.001[h]
Discontinuation due to AEs[i]	1783	219 (12.3)	1822	219 (12.0)	1.02 [0.86; 1.22]; 0.809[h]
Diarrhoea (PT, AEs)	1783	1255 (70.4)	1822	824 (45.2)	1.56 [1.47; 1.65] < 0.001[c]
Pruritus (PT, AEs)	1783	258 (14.5)	1822	162 (8.9)	1.63 [1.35; 1.96] < 0.001[c]
Heart failure (PT, SAEs)	1783	25 (1.4)	1822	13 (0.7)	1.97 [1.01; 3.83] 0.043[c]
Anaemia (PT, severe AEs)[g]	1783	120 (6.7)	1822	86 (4.7)	1.43 [1.09; 1.87] 0.010[c]
Diarrhoea (PT, severe AEs)[g]	1783	168 (9.4)	1822	71 (3.9)	2.42 [1.85; 3.17] < 0.001[c]
Stomatitis (PT, severe AEs)[g]	1783	38 (2.1)	1822	18 (1.0)	2.16 [1.24; 3.77] 0.006[c]
Fatigue (PT, severe AEs)[g]	1783	69 (3.9)	1822	49 (2.7)	1.44 [1.004; 2.06] 0.047[c]
White blood cell count decreased (PT, severe AEs)[g]	1783	91 (5.1)	1822	65 (3.6)	1.43 [1.05; 1.95] 0.024[c]
Metabolism and nutrition disorders (SOC, severe AEs)[g]	1783	89 (5.0)	1822	47 (2.6)	1.94 [1.37; 2.74] < 0.001[c]
Musculoskeletal and connective tissue disorders (SOC, severe AEs)[g]	1783	33 (1.9)	1822	55 (3.0)	0.61 [0.40; 0.94] 0.023[c]
Skin and subcutaneous tissue disorders (SOC, severe AEs)[g]	1783	63 (3.5)	1822	36 (2.0)	1.79 [1.19; 2.68] 0.004[c]

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study **outcome category** **outcome** **time point**	**Pertuzumab + trastuzumab + chemotherapy**		**Placebo + trastuzumab + chemotherapy**		**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**

a. Cox model, stratified by nodal status, type of adjuvant chemotherapy, hormone receptor status and protocol version; p-value from stratified log-rank test.
b. Proportion of patients, individual components are presented in the lines below
c. Institute's calculation, 95% CI asymptotic; unconditional exact test, (CSZ method according to [30]).
d. Qualified events that are relevant for the formation of the composite outcome.
e. Operationalized as time from the day of randomization to the first occurrence of an event, for individual components see recurrence rate.
f. Marginal deviations from the first data cut-off, reasons unclear (see Section 2.4.1).
g. Operationalized as CTCAE grade ≥ 3.
h. Unstratified analysis, model-based, p-value from Wald test.
i. Discontinuation of treatment with a drug component (chemotherapy, trastuzumab, pertuzumab or placebo).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; DCIS: ductal carcinoma in situ; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 15: Results (morbidity) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study outcome category outcome time point	Pertuzumab + trastuzumab + chemotherapy		Placebo + trastuzumab + chemotherapy		Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
APHINITY					
Morbidity (first data cut-off: 19 December 2016)					
Symptoms (EORTC QLQ-C30) – patients with deterioration by ≥ 10 points					
Fatigue					
End of anti-HER2 therapy	1538	703 (45.7)	1597	642 (40.2)	1.14 [1.05; 1.24] 0.001
36-month follow-up	1361	437 (32.1)	1327	474 (35.7)	0.90 [0.81; 1.00] 0.054
Nausea and vomiting					
End of anti-HER2 therapy	1542	184 (11.9)	1598	176 (11.0)	1.08 [0.89; 1.32] 0.411
36-month follow-up	1363	125 (9.2)	1328	132 (9.9)	0.92 [0.73; 1.15] 0.453
Pain					
End of anti-HER2 therapy	1541	420 (27.3)	1597	461 (28.9)	0.94 [0.84; 1.05] 0.297
36-month follow-up	1362	316 (23.2)	1328	318 (23.9)	0.97 [0.84; 1.11] 0.643
Dyspnoea					
End of anti-HER2 therapy	1539	392 (25.5)	1592	375 (23.6)	1.08 [0.96; 1.22] 0.214
36-month follow-up	1361	278 (20.4)	1321	303 (22.9)	0.90 [0.78; 1.03] 0.133
Insomnia					
End of anti-HER2 therapy	1538	430 (28.0)	1591	405 (25.5)	1.10 [0.98; 1.24] 0.104
36-month follow-up	1362	318 (23.3)	1322	333 (25.2)	0.93 [0.81; 1.06] 0.279
Appetite loss					
End of anti-HER2 therapy	1538	235 (15.3)	1594	180 (11.3)	1.35 [1.13; 1.62] 0.001
36-month follow-up	1361	121 (8.9)	1326	125 (9.4)	0.95 [0.75; 1.20] 0.647

Table 15: Results (morbidity) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study **outcome category** **outcome** **time point**	**Pertuzumab + trastuzumab + chemotherapy**		**Placebo + trastuzumab + chemotherapy**		**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
Constipation					
End of anti-HER2 therapy	1538	202 (13.1)	1593	248 (15.6)	0.84 [0.71; 1.00] 0.055
36-month follow-up	1363	219 (16.1)	1321	201 (15.2)	1.06 [0.89; 1.26] 0.537
Diarrhoea					
End of anti-HER2 therapy	1532	458 (29.9)	1590	213 (13.4)	2.23 [1.92; 2.58] < 0.001
36-month follow-up	1358	100 (7.4)	1322	128 (9.7)	0.76 [0.59; 0.97] 0.031
Symptoms (EORTC QLQ-BR23) – patients with deterioration by ≥ 10 points					
Side effects of systemic therapy					
End of anti-HER2 therapy	1535	416 (27.1)	1591	426 (26.8)	1.02 [0.91; 1.14] 0.742
36-month follow-up	1358	313 (23.0)	1321	318 (24.1)	0.96 [0.83; 1.10] 0.522
Symptoms in chest region					
End of anti-HER2 therapy	1532	292 (19.1)	1580	246 (15.6)	1.23 [1.05; 1.43] 0.009
36-month follow-up	1355	154 (11.4)	1318	141 (10.7)	1.06 [0.85; 1.31] 0.610
Symptoms in arm region					
End of anti-HER2 therapy	1532	417 (27.2)	1581	454 (28.7)	0.94 [0.84; 1.05] 0.296
36-month follow-up	1355	320 (23.6)	1320	336 (25.5)	0.92 [0.81; 1.05] 0.227
Upset by hair loss					
End of anti-HER2 therapy	57	10 (17.5)	54	16 (29.6)	0.59 [0.29; 1.19] 0.137[b]
36-month follow-up	73	18 (24.7)	77	20 (26.0)	0.89 [0.50; 1.58] 0.696

Table 15: Results (morbidity) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study **outcome category** **outcome** **time point**	**Pertuzumab + trastuzumab + chemotherapy**		**Placebo + trastuzumab + chemotherapy**		**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**

a. RR and p-value from log-binomial regression adjusted for nodal status, type of adjuvant chemotherapy, hormone receptor status and protocol version.
b. Institute's calculation, RR, 95% CI asymptotic; unconditional exact test, (CSZ method according to [30]).

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2, n: number of patients with (at least one) event; N: number of analysed patients; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core 30; RCT: randomized controlled trial; RR: relative risk

Table 16: Results (health-related quality of life) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study outcome category outcome time point	Pertuzumab + trastuzumab + chemotherapy		Placebo + trastuzumab + chemotherapy		Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
APHINITY					
Health-related quality of life (first data cut-off: 19 December 2016)					
EORTC QLQ-C30 – patients with deterioration by ≥ 10 points					
Global health status					
End of anti-HER2 therapy	1532	428 (27.9)	1589	421 (26.5)	1.05 [0.94; 1.18] 0.416
36-month follow-up	1357	295 (21.7)	1320	320 (24.2)	0.89 [0.78; 1.02] 0.106
Physical functioning					
End of anti-HER2 therapy	1543	358 (23.2)	1597	361 (22.6)	1.03 [0.90; 1.17] 0.664
36-month follow-up	1363	236 (17.3)	1329	234 (17.6)	0.98 [0.83; 1.15] 0.800
Role functioning					
End of anti-HER2 therapy	1540	383 (24.9)	1594	368 (23.1)	1.08 [0.95; 1.22] 0.221
36-month follow-up	1362	216 (15.9)	1327	243 (18.3)	0.87 [0.73; 1.03] 0.098
Emotional functioning					
End of anti-HER2 therapy	1535	388 (25.3)	1593	393 (24.7)	1.02 [0.91; 1.16] 0.715
36-month follow-up	1359	302 (22.2)	1324	337 (25.5)	0.87 [0.76; 1.00] 0.047
Cognitive functioning					
End of anti-HER2 therapy	1536	607 (39.5)	1592	632 (39.7)	1.00 [0.91; 1.09] 0.923
36-month follow-up	1360	490 (36.0)	1324	494 (37.3)	0.96 [0.87; 1.06] 0.436
Social functioning					
End of anti-HER2 therapy	1535	349 (22.7)	1590	376 (23.6)	0.96 [0.85; 1.09] 0.540
36-month follow-up	1360	209 (15.4)	1323	237 (17.9)	0.86 [0.73; 1.02] 0.085

Table 16: Results (health-related quality of life) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study outcome category outcome time point	Pertuzumab + trastuzumab + chemotherapy		Placebo + trastuzumab + chemotherapy		Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
EORTC QLQ-BR23 – patients with deterioration by ≥ 10 points					
Body image					
End of anti-HER2 therapy	1521	407 (26.8)	1573	472 (30.0)	0.90 [0.80; 1.00] 0.056
36-month follow-up	1342	272 (20.3)	1304	300 (23.0)	0.88 [0.76; 1.02] 0.086
Sexual activity					
End of anti-HER2 therapy	1456	336 (23.1)	1509	358 (23.7)	0.97 [0.85; 1.11] 0.680
36-month follow-up	1279	258 (20.2)	1251	269 (21.5)	0.93 [0.80; 1.09] 0.377
Enjoyment of sex					
End of anti-HER2 therapy	437	147 (33.6)	481	159 (33.1)	1.02 [0.85; 1.23] 0.829
36-month follow-up	383	113 (29.5)	402	118 (29.4)	1.03 [0.83; 1.27] 0.822
Future perspective					
End of anti-HER2 therapy	1518	272 (17.9)	1576	292 (18.5)	0.97 [0.84; 1.13] 0.697
36-month follow-up	1340	191 (14.3)	1304	188 (14.4)	0.99 [0.82; 1.19] 0.918

a. RR and p-value from log-binomial regression adjusted for nodal status, type of adjuvant chemotherapy, hormone receptor status and protocol version.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2, n: number of patients with (at least one) event; N: number of analysed patients; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core 30; RCT: randomized controlled trial; RR: relative risk

On the basis of the available data and because of the high risk of bias, at most hints, e.g. of an added benefit, can be determined for the patient-reported outcomes that were recorded using the EORTC questionnaire, and at most indications can be determined for all other outcomes (see Section 2.4.2). Hereinafter, the effects described for the intravenous free combination on the basis of the APHINITY study are used for the benefit assessment of pertuzumab/trastuzumab (SC) (see Section 2.5).

Mortality

Overall survival

At the second data cut-off (19 June 2019), there was no statistically significant difference between the treatment groups for the outcome "overall survival". This resulted in no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. An added benefit is therefore not proven for this outcome. This deviates from the assessment of the company, which derived proof of an added benefit for overall survival.

The company's assessment was not accepted. Apart from the fact that the necessary criteria for deriving a proof from a single study were not met in this case (see Section 2.4.2), the assessment of the company was not based on the results for overall survival itself, but on DFS, which the company presented as a valid surrogate for overall survival. For this purpose, the company presented a validation study financed by the company [24,26,31]. The use of surrogate outcomes, in particular DFS as surrogate for overall survival, is described in Section 2.4.1.

Morbidity

Recurrence

For the outcome “recurrence” (operationalized as recurrence rate and DFS), there was a statistically significant effect in favour of pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy for both operationalizations at the second data cut-off (19 June 2019). This resulted in an indication of an added benefit for this outcome.

This deviates from the assessment of the company in that it derived proof of an added benefit on the basis of event time analyses for recurrences in general and distant recurrences (distant recurrence-free interval [DRFI]) and only presented the recurrence rate as supplementary information and only for the first data cut-off.

Symptoms

The outcome “symptoms” was recorded with the disease-specific instruments EORTC QLQ-C30 and the EORTC QLQ-BR23. Symptoms were considered at 2 time points. The proportion of patients with a deterioration by ≥ 10 points was considered at each of the time points “end of anti-HER2 therapy” and “36-month follow-up” (see also Section 2.4.1 [responder analyses]). These analyses were already available at the first data cut-off (19 December 2016). Hereinafter, first the outcomes on symptoms are described for which statistically significant group differences were shown for at least one time point.

Fatigue, diarrhoea, symptoms in the chest region

Statistically significant differences between the treatment arms were shown for the outcomes “fatigue”, “diarrhoea” and “symptoms in chest region”. For “fatigue” and “symptoms in chest region”, differences were only shown at the time point “end of anti-HER2 therapy”, for “diarrhoea” these differences occurred at both time points. All differences at the time point “end of anti-HER2 therapy” are to the disadvantage of pertuzumab + trastuzumab + chemotherapy.

The difference at the 36-month follow-up for diarrhoea is in favour of pertuzumab + trastuzumab + chemotherapy. However, the differences for the outcomes “fatigue”, “symptoms in chest region” and “diarrhoea” (36-month follow-up) were no more than marginal for an outcome in the category “non-serious/non-severe symptoms/late complications”. Thus, at the end of the anti-HER2 therapy, there was a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy for the outcome “diarrhoea”.

Appetite loss

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was also shown for the outcome "appetite loss” at the end of anti-HER2 therapy. However, a statistically significant interaction with the characteristic “age” was shown at this point in time. This resulted in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for patients ≥ 65 years of age.

Nausea and vomiting

In the total population, there was no statistically significant difference between the treatment groups for the outcome "nausea and vomiting". However, at the time point “end of anti-HER2 therapy”, there was a statistically significant interaction with the characteristic “age”; however, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was only shown for patients ≥ 65 years. This resulted in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for these patients.

Further symptom outcomes

At both time points, no statistically significant difference between the treatment groups was shown for each of the following outcomes: “pain”, “dyspnoea”, “insomnia”, “constipation”, “side effects of systemic treatment”, “symptoms in the arm region” and “upset by hair loss”. This resulted in no hints of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. An added benefit is therefore not proven for these outcomes.

This differs from the assessment of the company with regard to the inclusion of subgroup results. Furthermore, the company presented the results, but did not derive an added benefit or lesser benefit of pertuzumab from them, as it did not consider there to be persistent deterioration.

Health-related quality of life

“Health-related quality of life” was recorded with the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. The proportion of patients with a deterioration by ≥ 10 points was considered at each of the two time points “end of anti-HER2 therapy” and “36-month follow-up”. These analyses were already available at the first data cut-off (19 December 2016). Hereinafter, first the outcomes are described for which statistically significant group differences were shown for at least one time point.

Emotional functioning

A statistically significant difference between the treatment groups in favour of pembrolizumab + trastuzumab + chemotherapy was shown for the outcome "emotional functioning" at the time point "36-month follow-up". This resulted in a hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for this time point.

Physical functioning

For the outcome "physical functioning", a statistically significant interaction with the characteristic "age" was shown at the end of the anti-HER2 therapy. However, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was only shown for patients ≥ 65 years. This resulted in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for these patients.

Role functioning

For the outcome "role functioning", a statistically significant interaction with the characteristic "age" was shown at the time point "36-month follow-up". However, a statistically significant difference in favour of pertuzumab + trastuzumab + chemotherapy was only shown for patients < 65 years. This resulted in a hint of an added benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for these patients.

Further scales on health-related quality of life

There was no statistically significant difference between the treatment groups for the outcomes "global health status", "cognitive functioning", "social functioning", "body image", "sexual activity", "enjoyment of sex" and "future perspective". This resulted in no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy; an added benefit is therefore not proven for these outcomes.

Overall, the company derived no added benefit or lesser benefit for the health-related quality of life.

Side effects

AEs of the different administration forms

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

AEs, as well as cardiovascular AEs and most of the common non-serious/non-severe AEs. The results on AEs of the APHINITY study can therefore be transferred to the fixed combination pertuzumab/trastuzumab (SC).

SAEs

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the outcome "SAEs" at the second data cut-off (19 June 2019). This resulted in an indication of greater harm from pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

This deviates from the assessment of the company, which overall derived no added benefit or lesser benefit.

Severe AEs (CTCAE grade ≥ 3)

At the second data cut-off (19 June 2019), a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the outcome "severe AEs". However, there was a statistically significant interaction with the characteristic "geographical region". The result in the region of Western Europe, which is important for the benefit assessment, differs from the result for the overall population. There was no statistically significant difference between the treatment groups for the region "Western Europe".

Based on the result for the region "Western Europe", there is therefore no hint of a greater or lesser harm from pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy. An added benefit is therefore not proven for severe AEs.

This concurs with the company's assessment.

Discontinuation due to AEs

At the second data cut-off (19 June 2019), no statistically significant difference between the treatment groups was shown for the outcome "discontinuation due to AEs". This resulted in no hint of greater harm or lesser harm from pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy. An added benefit of pertuzumab is therefore not proven for this outcome.

This concurs with the company's assessment.

Specific AEs

At the second data cut-off (19 June 2019), a statistically significant difference between the treatment arms to the disadvantage of pertuzumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy was shown for each of the following AEs:

- SAEs or severe AEs (CTCAE grade ≥ 3):

heart failure (PT, SAEs), anaemia (PT, severe AEs), diarrhoea (PT, severe AEs), stomatitis (PT, severe AEs), fatigue (PT, severe AEs), white blood cell count decreased (PT, severe AEs), metabolism and nutrition disorders (SOC, severe AEs)

- Non-severe/non-serious AEs:

  diarrhoea (PT), pruritus (PT)

This resulted in an indication of greater harm from pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

A statistically significant interaction with the characteristic “age” was shown for the outcome "skin and subcutaneous tissue disorders (SOC, AEs)”. However, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was only shown for patients < 65 years. This resulted in an indication of greater harm from pertuzumab + trastuzumab + chemotherapy versus the ACT for these patients.

There was a statistically significant difference in favour of pertuzumab + trastuzumab + chemotherapy for the outcome "musculoskeletal and connective tissue disorders (SOC, severe AEs)". This resulted in an indication of lesser harm from pertuzumab + trastuzumab + chemotherapy in comparison with the ACT.

This deviates from the assessment of the company, which overall derived no added benefit or lesser benefit.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were relevant for the present benefit assessment:

- age (< 65 years vs. ≥ 65 years)
- geographical region (USA/Canada, Western Europe, Asia-Pacific, Latin America, other)
- Nodal status and tumour size (N0 and tumour ≤ 1 cm, N0 and tumour > 1 cm, N 1-3 positive lymph nodes, N ≥ 4 positive lymph nodes)

In its module 4 C, the company presents complete subgroup analyses on these characteristics for all outcomes. The characteristic “sex” was not considered, as the relevant subpopulation only included 8 male patients in total. According to its methods, the company assessed some interactions as not interpretable, including when fewer than 10 patients in total had been observed in a subgroup category and/or fewer than 10 events had been observed in the responder analyses. This does not correspond to the *General Methods* of IQWiG [1]. Interaction tests were used for the present benefit assessment when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must be 10 events in at least one subgroup.

Therefore, using IQWiG's methods, the subgroup analyses with significant interaction test already considered in the previous benefit assessment A18-41 [21] are presented.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 17 summarizes the subgroup results of the comparison of pertuzumab + trastuzumab + chemotherapy with placebo + trastuzumab + chemotherapy in adult patients with HER2-positive early-stage breast cancer at high risk of recurrence (node-positive or hormone receptor-negative disease).

Table 17: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study outcome characteristic subgroup	Pertuzumab + trastuzumab + chemotherapy		placebo + trastuzumab + chemotherapy		Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy	
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]	p-value
APHINITY						
Morbidity						
Symptoms (EORTC QLQ-C30) – patients with deterioration by ≥ 10 points						
Nausea and vomiting (End of anti-HER2 therapy)						
Age						
< 65 years	1361	151 (11.1)	1423	161 (11.3)	0.98 [0.80; 1.21]	0.855
≥ 65 years	181	33 (18.2)	175	15 (8.6)	2.13 [1.20; 3.78]	0.010
Total					Interaction:	0.010
Appetite loss (End of anti-HER2 therapy)						
Age						
< 65 years	1358	192 (14.1)	1419	165 (11.6)	1.22 [1.00; 1.48]	0.049
≥ 65 years	180	43 (23.9)	175	15 (8.6)	2.79 [1.61; 4.83]	< 0.001
Total					Interaction:	0.003
Health-related quality of life						
EORTC QLQ-C30 – patients with deterioration by ≥ 10 points						
Physical functioning (End of anti-HER2 therapy)						
Age						
< 65 years	1362	290 (21.3)	1422	316 (22.2)	0.96 [0.83; 1.10]	0.552
≥ 65 years	181	68 (37.6)	175	45 (25.7)	1.46 [1.07; 2.00]	0.018
Total					Interaction:	0.015
Role functioning (36-month follow-up)						
Geographical region						
USA/Canada	178	29 (16.3)	155	18 (11.6)	1.40 [0.81; 2.43]	0.225
Western Europe	588	104 (17.7)	577	125 (21.7)	0.82 [0.65; 1.03]	0.089
Asia-Pacific	415	66 (15.9)	428	67 (15.7)	1.02 [0.74; 1.39]	0.921
Latin America	34	1 (2.9)	36	7 (19.4)	0.15 [0.02; 1.17]	0.070
Other	147	16 (10.9)	131	26 (19.8)	0.55 [0.31; 0.98]	0.041
Total					Interaction:	0.024

Table 17: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study **outcome** **characteristic** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy**		**placebo + trastuzumab + chemotherapy**		**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy**	
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]**	**p-value**
Age						
< 65 years	1209	173 (14.3)	1185	212 (17.9)	0.80 [0.67; 0.96]	0.017
≥ 65 years	153	43 (28.1)	142	31 (21.8)	1.29 [0.86; 1.92]	0.217
Total					Interaction:	0.033
Cognitive functioning (36-month follow-up)						
Geographical region						
USA/Canada	178	68 (38.2)	155	49 (31.6)	1.21 [0.90; 1.63]	0.212
Western Europe	587	220 (37.5)	574	203 (35.4)	1.06 [0.91; 1.23]	0.455
Asia-Pacific	414	152 (36.7)	428	175 (40.9)	0.90 [0.76; 1.06]	0.215
Latin America	34	13 (38.2)	36	14 (38.9)	0.98 [0.54; 1.78]	0.955
Other	147	37 (25.2)	131	53 (40.5)	0.62 [0.44; 0.88]	0.008
Total					Interaction:	0.030
Social functioning (End of anti-HER2 therapy)						
Geographical region						
USA/Canada	213	45 (21.1)	224	45 (20.1)	1.05 [0.73; 1.52]	0.789
Western Europe	661	178 (26.9)	674	181 (26.9)	1.00 [0.84; 1.20]	0.976
Asia-Pacific	461	95 (20.6)	487	90 (18.5)	1.12 [0.86; 1.44]	0.409
Latin America	38	6 (15.8)	42	15 (35.7)	0.44 [0.19; 1.02]	0.057
Other	162	25 (15.4)	163	45 (27.6)	0.56 [0.36; 0.87]	0.009
Total					Interaction:	0.019
Side effects						
Severe AEs[a]						
Geographical region						
USA/Canada	262	182 (69.5)	252	141 (56.0)	1.24 [1.08; 1.42]	0.002
Western Europe	814	517 (63.5)	824	519 (63.0)	1.01 [0.94; 1.09]	0.825
Asia-Pacific	482	340 (70.5)	517	305 (59.0)	1.20 [1.09; 1.31]	< 0.001
Latin America	42	20 (47.6)	45	24 (53.3)	0.89 [0.59; 1.36]	0.596
Other	183	82 (44.8)	184	66 (35.9)	1.25 [0.97; 1.61]	0.083
Total					Interaction:	0.009
Diarrhoea (PT, AEs)						

Table 17: Subgroups (morbidity, health-related quality of life, side effects) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study outcome characteristic subgroup	Pertuzumab + trastuzumab + chemotherapy		placebo + trastuzumab + chemotherapy		Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy	
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]	p-value
Geographical region						
USA/Canada	262	220 (84.0)	252	168 (66.7)	1.26 [1.14; 1.39]	< 0.001
Western Europe	814	614 (75.4)	824	379 (46.0)	1.64 [1.51; 1.78]	< 0.001
Asia-Pacific	482	307 (63.7)	517	213 (41.2)	1.55 [1.37; 1.75]	< 0.001
Latin America	42	25 (59.5)	45	16 (35.6)	1.67 [1.05; 2.67]	0.030
Other	183	89 (48.6)	184	48 (26.1)	1.86 [1.40; 2.48]	< 0.001
Total					Interaction:	0.002
Skin and subcutaneous tissue disorders (SOC, severe AEs)[a]						
Age						
< 65 years	1564	59 (3.8)	1601	29 (1.8)	2.08 [1.34; 3.23]	0.001
≥ 65 years	219	4 (1.8)	221	7 (3.2)	0.58 [0.17; 1.94]	0.374
Total					Interaction:	0.046

a. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2, n: number of patients with (at least one) event; N: number of analysed patients; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core 30; RCT: randomized controlled trial; RR: relative risk; SOC: System Organ Class

Morbidity

Symptoms, recorded using EORTC QLQ-C30 and EORTC QLQ-BR23

Nausea and vomiting

For the outcome "nausea and vomiting", a statistically significant interaction with the characteristic "age" was shown at the end of the anti-HER2 therapy.

There was no statistically significant difference between the treatment groups in the age group < 65 years. This resulted in no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for patients < 65 years of age is therefore not proven for this outcome.

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the age group ≥ 65 years of age. For this outcome, this resulted in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for patients ≥ 65 years of age.

Appetite loss

At the end of the anti-HER2 therapy, a statistically significant interaction with the characteristic "age" was shown for the outcome "appetite loss".

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for both age groups. However, for the groups of patients < 65 years, the extent of this added benefit for this outcome of the category "non-serious/non-severe symptoms/late complications" was no more than marginal. For this outcome, this resulted in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for patients ≥ 65 years of age.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-BR23

Physical functioning

For the outcome "physical functioning", a statistically significant interaction with the characteristic "age" was shown at the end of the anti-HER2 therapy.

There was no statistically significant difference between the treatment groups in the age group < 65 years. This resulted in no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for patients < 65 years of age is therefore not proven for this outcome.

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the age group ≥ 65 years of age. For this outcome, this resulted in a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for patients ≥ 65 years of age.

Role functioning

For the outcome "role functioning", statistically significant interactions with the characteristics "geographical region" and "age" were shown at the time point "36-month follow-up".

A statistically significant difference between the treatment groups was only shown for the region "other", which includes Eastern Europe, Australia, New Zealand and South Africa. This was in favour of pertuzumab + trastuzumab + chemotherapy. In other regions, including Western Europe, there was no statistically significant difference between the treatment groups, as was the case for the total population. The region of Western Europe is of particular importance for the present benefit assessment. This resulted in no hint of an added benefit of

pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for the patients is therefore not proven for this outcome.

A statistically significant difference in favour of pertuzumab + trastuzumab + chemotherapy was shown for the age group < 65 years of age. For this outcome, this resulted in a hint of an added benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for patients < 65 years of age.

There was no statistically significant difference between the treatment groups in the age group ≥ 65 years. This resulted in no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for patients ≥ 65 years of age is therefore not proven for this outcome.

Cognitive functioning

For the outcome "cognitive functioning", a statistically significant interaction with the characteristic "geographical region" was shown at the time point "36-month follow-up".

A statistically significant difference between the treatment groups was only shown for the region "other", which includes Eastern Europe, Australia, New Zealand and South Africa. This was in favour of pertuzumab + trastuzumab + chemotherapy. In other regions, including Western Europe, there was no statistically significant difference between the treatment groups, as was the case for the total population. The region of Western Europe is of particular importance for the present benefit assessment. This resulted in no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for the outcome "cognitive functioning" is therefore not proven.

Social functioning

For the outcome "social functioning", a statistically significant interaction with the characteristic "geographical region" was shown at the end of the anti-HER2 therapy.

A statistically significant difference between the treatment groups was only shown for the region "other", which includes Eastern Europe, Australia, New Zealand and South Africa. This was in favour of pertuzumab + trastuzumab + chemotherapy. In other regions, including Western Europe, there was no statistically significant difference between the treatment groups, as was the case for the total population. The region of Western Europe is of particular importance for the present benefit assessment. This resulted in no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for the outcome "social functioning" is therefore not proven.

Side effects

Severe AEs (CTCAE grade ≥ 3)

For the outcome "severe AEs", there was a statistically significant interaction with the characteristic "geographical region".

Statistically significant differences, each to the disadvantage of pertuzumab + trastuzumab + chemotherapy, were shown for the regions USA/Canada and Asia-Pacific. For the present benefit assessment, the region of Western Europe is of particular importance, for which, however, there is no statistically significant difference between the treatment groups. This resulted in no hint of greater harm or lesser harm from pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for the outcome "severe AEs" is therefore not proven.

Specific AEs

Diarrhoea (AEs)

For the outcome "diarrhoea", there was a statistically significant interaction with the characteristic "geographical region".

Statistically significant differences, each to the disadvantage of pertuzumab + trastuzumab + chemotherapy, were shown for all regions. For the present benefit assessment, the region of Western Europe is of particular importance, for which there was also a statistically significant difference between the treatment groups. For this outcome, this resulted in an indication of greater harm from pertuzumab + trastuzumab + chemotherapy versus the ACT for patients from Western Europe.

Skin and subcutaneous tissue disorders (severe AEs)

A statistically significant interaction with the characteristic "age" was shown for the outcome "skin and subcutaneous tissue disorders.

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the age group < 65 years of age. For this outcome, this resulted in an indication of greater harm from pertuzumab + trastuzumab + chemotherapy versus the ACT for patients < 65 years of age.

There was no statistically significant difference between the treatment groups in the age group ≥ 65 years. This resulted in no hint of greater harm or lesser harm from pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for patients ≥ 65 years of age is therefore not proven for this outcome.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, 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 the 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 the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 18).

Determination of the outcome category for outcomes on symptoms and side effects

It cannot be inferred from Module 4 C for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

The outcome "recurrence" is considered to be serious/severe. Recurrence of cancer can be potentially fatal, or shows that the curative therapy approach in a potentially fatal disease has not been successful. Besides, the event "death of any cause" was a component of the composite outcome "recurrence".

This concurs with the company's assessment.

In Module 4 C of the company, there is no information that allows assignment to a severity category for "symptoms" or "health-related quality of life" recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23. Therefore, these scales were each assigned to the outcome category "non-serious/non-severe symptoms/late complications".

The company did not assign the mentioned outcomes to a severity category.

For outcomes on specific AEs, preference was given to the consideration of events with severe or serious manifestations (CTCAE grade ≥ 3 or SAEs). All other outcomes on specific side effects with statistically significant effects were assigned to the category of non-serious/non-severe side effects.

The company divided the AEs into serious AEs and severe AEs, the latter being based on the CTCAE grade.

Table 18: Extent of added benefit at outcome level: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Outcome category **Ooutcome** **effect modifier** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median time to event (months): NA vs. NA HR: 0.82 [0.64; 1.06] p = 0.136	Lesser benefit/added benefit not proven
Morbidity		
Recurrence rate	12.1% vs. 15.7% RR: 0.77 [0.65; 0.905] p = 0.002 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Disease-free survival	12.1% vs. 15.7% HR: 0.75 [0.63; 0.90] p = 0.002 probability: "indication"	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23)		
Fatigue End of anti-HER2 therapy	45.7% vs. 40.2% RR: 1.14 [1.05; 1.24] RR: 0.88 [0.81; 0.95][c] p = 0.001	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
36-month follow-up	32.1% vs. 35.7% RR: 0.90 [0.81; 1.00] p = 0.054	Lesser benefit/added benefit not proven
Nausea and vomiting End of anti-HER2 therapy Age < 65 years	11.1 % vs. 11.3 % RR: 0.98 [0.80; 1.21] p = 0.855	Lesser benefit/added benefit not proven
≥ 65 years	18.2% vs. 8.6% RR: 2.13 [1.20; 3.78] RR: 0.47 [0.26; 0.83][c] p = 0.010 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ lesser benefit, extent: "minor"

Table 18: Extent of added benefit at outcome level: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Outcome category **Ooutcome** **effect modifier** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
36-month follow-up	9.2% vs. 9.9% RR: 0.92 [0.73; 1.15] p = 0.453	Lesser benefit/added benefit not proven
Pain		
End of anti-HER2 therapy	27.3% vs. 28.9% RR: 0.94 [0.84; 1.05] p = 0.297	Lesser benefit/added benefit not proven
36-month follow-up	3.2 % vs. 23.9% RR: 0.97 [0.84; 1.11] p = 0.643	Lesser benefit/added benefit not proven
Dyspnoea		
End of anti-HER2 therapy	25.5 % vs. 23.6 % RR: 1.08 [0.96; 1.22] p = 0.214	Lesser benefit/added benefit not proven
36-month follow-up	20.4% vs. 22.9% RR: 0.90 [0.78; 1.03] p = 0.133	Lesser benefit/added benefit not proven
Insomnia		
End of anti-HER2 therapy	28.0 % vs. 25.5% RR: 1.10 [0.98; 1.24] p = 0.104	Lesser benefit/added benefit not proven
36-month follow-up	23.3% vs. 25.2% RR: 0.93 [0.81; 1.06] p = 0.279	Lesser benefit/added benefit not proven
Appetite loss		
End of anti-HER2 therapy		
Age		
< 65 years	14.1% vs. 11.6% RR: 1.22 [1.00; 1.48] RR: 0.82 [0.68; 1.00][c] p = 0.049	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]

Table 18: Extent of added benefit at outcome level: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Outcome category **Ooutcome** **effect modifier** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
≥ 65 years	23.9% vs. 8.6% RR: 2.79 [1.61; 4.83] RR: 0.36 [0.21; 0.62][c] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ lesser benefit, extent: "considerable"
36-month follow-up	8.9% vs. 9.4% RR: 0.95 [0.75; 1.20] p = 0.647	Lesser benefit/added benefit not proven
Constipation		
End of anti-HER2 therapy	13.1% vs. 15.6% RR: 0.84 [0.71; 1.00] p = 0.055	Lesser benefit/added benefit not proven
36-month follow-up	16.1% vs. 15.2% RR: 1.06 [0.89; 1.26] p = 0.537	Lesser benefit/added benefit not proven
Diarrhoea		
End of anti-HER2 therapy	29.9% vs. 13.4% RR: 2.23 [1.92; 2.58] RR: 0.45 [0.39; 0.52][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ lesser benefit, extent: "considerable"
36-month follow-up	7.4% vs. 9.7% RR: 0.76 [0.59; 0.97] p = 0.031	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Side effects of systemic therapy		
End of anti-HER2 therapy	27.1% vs. 26.8% RR: 1.02 [0.91; 1.14] p = 0.742	Lesser benefit/added benefit not proven
36-month follow-up	23.0% vs. 24.1% RR: 0.96 [0.83; 1.10] p = 0.522	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Outcome category **Ooutcome** **effect modifier** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Symptoms in chest region		
End of anti-HER2 therapy	19.1% vs. 15.6% RR: 1.23 [1.05; 1.43] RR: 0.81 [0.70; 0.95][c] p = 0.009	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
36-month follow-up	11.4% vs. 10.7% RR: 1.06 [0.85; 1.31] p = 0.610	Lesser benefit/added benefit not proven
Symptoms in arm region		
End of anti-HER2 therapy	27.2% vs. 28.7% RR: 0.94 [0.84; 1.05] p = 0.296	Lesser benefit/added benefit not proven
36-month follow-up	23.6% vs. 25.5% RR: 0.92 [0.81; 1.05] p = 0.227	Lesser benefit/added benefit not proven
Upset by hair loss		
End of anti-HER2 therapy	17.5% vs. 29.6% RR: 0.59 [0.29; 1.19] p = 0.137	Lesser benefit/added benefit not proven
36-month follow-up	24.7% vs. 26.0% 0.89 [0.50; 1.58] p = 0.696	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 and EORTC QLQ-BR23		
Global health status		
End of anti-HER2 therapy	27.9% vs. 26.5% RR: 1.05 [0.94; 1.18] p = 0.416	Lesser benefit/added benefit not proven
36-month follow-up	21.7% vs. 24.2% RR: 0.89 [0.78; 1.02] p = 0.106	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Outcome category **Ooutcome** **effect modifier** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Physical functioning		
End of anti-HER2 therapy		
Age		
< 65 years	21.3% vs. 22.2% RR: 0.96 [0.83; 1.10] p = 0.552	Lesser benefit/added benefit not proven
≥ 65 years	37.6% vs. 25.7% RR: 1.46 [1.07; 2.00] RR: 0.68 [0.50; 0.93][c] p = 0.018 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ lesser benefit, extent: "minor"
36-month follow-up	17.3% vs. 17.6% RR: 0.98 [0.83; 1.15] p = 0.800	Lesser benefit/added benefit not proven
Role functioning		
End of anti-HER2 therapy	24.9% vs. 23.1% RR: 1.08 [0.95; 1.22] p = 0.221	Lesser benefit/added benefit not proven
36-month follow-up		
Age		
< 65 years	14.3% vs. 17.9% RR: 0.80 [0.67; 0.96] p = 0.017 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
≥ 65 years	28.1% vs. 21.8% RR: 1.29 [0.86; 1.92] p = 0.217	Lesser benefit/added benefit not proven
Emotional functioning		
End of anti-HER2 therapy	25.3% vs. 24.7% RR: 1.02 [0.91; 1.16] p = 0.715	Lesser benefit/added benefit not proven
36-month follow-up	22.2% vs. 25.5% RR: 0.87 [0.76; 1.00] p = 0.047 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”

Table 18: Extent of added benefit at outcome level: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Outcome category **Ooutcome** **effect modifier** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Cognitive functioning		
End of anti-HER2 therapy	39.5% vs. 39.7% RR: 1.00 [0.91; 1.09] p = 0.923	Lesser benefit/added benefit not proven
36-month follow-up		
Geographical region		
Western Europe	37.5% vs. 35.4% RR: 1.06 [0.91; 1.23] p = 0.455	Lesser benefit/added benefit not proven
Social functioning		
End of anti-HER2 therapy		
Geographical region		
Western Europe	26.9% vs. 26.9% RR: 1.00 [0.84; 1.20] p = 0.976	Lesser benefit/added benefit not proven
36-month follow-up	15.4% vs. 17.9% RR: 0.86 [0.73; 1.02] p = 0.085	Lesser benefit/added benefit not proven
Body image		
End of anti-HER2 therapy	26.8% vs. 30.0% RR: 0.90 [0.80; 1.00] p = 0.056	Lesser benefit/added benefit not proven
36-month follow-up	20.3% vs. 23.0% RR: 0.88 [0.76; 1.02] p = 0.086	Lesser benefit/added benefit not proven
Sexual activity		
End of anti-HER2 therapy	23.1% vs. 23.7% RR: 0.97 [0.85; 1.11] p = 0.680	Lesser benefit/added benefit not proven
36-month follow-up	20.2% vs. 21.5% RR: 0.93 [0.80; 1.09] p = 0.377	Lesser benefit/added benefit not proven

Table 18: Extent of added benefit at outcome level: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Outcome category **Ooutcome** **effect modifier** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Enjoyment of sex		
End of anti-HER2 therapy	33.6% vs. 33.1% RR: 1.02 [0.85; 1.23] p = 0.829	Lesser benefit/added benefit not proven
36-month follow-up	29.5% vs. 29.4% RR: 1.03 [0.83; 1.27] p = 0.822	Lesser benefit/added benefit not proven
Future perspective		
End of anti-HER2 therapy	17.9% vs. 18.5% RR: 0.97 [0.84; 1.13] p = 0.697	Lesser benefit/added benefit not proven
36-month follow-up	14.3% vs. 14.4% RR: 0.99 [0.82; 1.19] p = 0.918	Lesser benefit/added benefit not proven
Side effects		
SAEs	28.5% vs. 24.5% RR: 1.17 [1.05; 1.30] RR: 0.85 [0.77; 0.95][c] p = 0.006 probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Severe AEs (CTCAE grade ≥ 3)		
Geographical region		
Western Europe	63.5% vs. 63.0% RR: 1.01 [0.94; 1.09] p = 0.825	Greater/lesser harm not proven
Discontinuation due to AEs	12.3% vs. 12.0% RR: 1.02 [0.86; 1.22] p = 0.809	Greater/lesser harm not proven
Diarrhoea (AEs)		
Geographical region		
Western Europe	75.4% vs. 46.0% RR: 1.64 [1.51; 1.78] RR: 0.61 [0.56; 0.66][c] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

Table 18: Extent of added benefit at outcome level: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Outcome category **Ooutcome** **effect modifier** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Pruritus (AEs)	14.5% vs. 8.9% RR: 1.63 [1.35; 1.96] RR: 0.61 [0.51; 0.74][c] $p < 0.001$ probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Heart failure (SAEs)	1.4% vs. 0.7% RR: 1.97 [1.01; 3.83] RR: 0.51 [0.26; 0.99][c] $p = 0.043$ probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Anaemia (severe AEs)	6.7% vs. 4.7% RR: 1.43 [1.09; 1.87] RR: 0.70 [0.53; 0.92][c] $p = 0.010$ probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Diarrhoea (severe AEs)	9.4% vs. 3.9% RR: 2.42 [1.85; 3.17] RR: 0.41 [0.32; 0.54][c] $p < 0.001$ probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk $\geq 5\%$ greater harm, extent: "major"
Stomatitis (severe AEs)	2.1% vs. 1.0% RR: 2.16 [1.24; 3.77] RR: 0.46 [0.27; 0.81][c] $p = 0.006$ probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Fatigue (severe AEs)	3.9% vs. 2.7% RR: 1.44 [1.004; 2.06] RR: 0.69 [0.49; 0.996][c] $p = 0.047$ probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
White blood cell count decreased (severe AEs)	5.1% vs. 3.6% RR: 1.43 [1.05; 1.95] RR: 0.70 [0.51; 0.95][c] $p = 0.024$ probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"

Table 18: Extent of added benefit at outcome level: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Outcome category **Ooutcome** **effect modifier** **subgroup**	**Pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy** **proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Metabolism and nutrition disorders (severe AEs)	5.0% vs. 2.6% RR: 1.94 [1.37; 2.74] RR: 0.52 [0.36; 0.73][c] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Musculoskeletal and connective tissue disorders (severe AEs)	1.9% vs. 3.0% RR: 0.61 [0.40; 0.94] p = 0.023 probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ lesser harm, extent: "minor"
Skin and subcutaneous tissue disorders (severe AEs) Age < 65 years	3.8 % vs. 1.8 % RR: 2.08 [1.34; 3.23] RR: 0.48 [0.31; 0.746][c] p = 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% greater harm, extent: "considerable"
≥ 65 years	1.8 % vs. 3.2 % RR: 0.58 [0.17; 1.94] p = 0.374	greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2, HR: hazard ratio; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module; QLQ-C30: Quality of Life Questionnaire Core 30; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy

Positive effects	**Negative effects**
Morbidity serious/severe symptoms/late complications ▪ recurrence: indication of an added benefit – extent: "minor"	- -
-	Morbidity non-serious/non-severe symptoms/late complications ▪ nausea and vomiting (end of the anti-HER2 therapy): ▫ age ≥ 65 years: hint of lesser benefit – extent: "minor" ▪ loss of appetite (end of anti-HER2 therapy): ▫ age ≥ 65 years: hint of lesser benefit – extent: "considerable"
Health-related quality of life ▪ role functioning (36-month follow-up): ▫ age < 65 years: hint of an added benefit – extent: "minor" ▪ emotional functioning (36-month follow-up): hint of an added benefit - extent “minor”	Health-related quality of life ▪ physical functioning (end of anti-HER2 therapy): ▫ age ≥ 65 years: hint of lesser benefit – extent: "minor"
Serious/severe side effects ▪ specific AEs (severe AEs): ▫ musculoskeletal and connective tissue disorders; indication of lesser harm, extent: "minor"	Serious/severe side effects ▪ SAEs: indication of greater harm – extent: "minor" ▫ specific AEs (SAEs): - cardiac failure: indication of greater harm – extent: "minor" ▪ specific AEs (severe AEs): ▫ metabolism and nutrition disorders: indication of greater harm – extent: "major" ▫ stomatitis: indication of greater harm – extent "considerable" ▫ skin and subcutaneous tissue disorders: - age < 65: indication of greater harm – extent: "considerable" ▫ anaemia, fatigue, white blood cell count decreased: indication of greater harm - extent: minor ▪ diarrhoea (represented in AEs, severe AEs and symptom scale “diarrhoea” of the EORTC QLQ-C30 [end of anti-HER2 therapy]): indication of greater harm - extent “major”
-	Non-serious/non-severe side effects ▪ specific AEs: ▫ pruritus: indication of greater harm – extent "considerable"
AEs: adverse events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire Core 30; SAE: serious adverse event	

As “age” is a consistent effect modifier across several outcomes, the results on the added benefit for patients < 65 years and those ≥ 65 years are first described separately below:

- The overall consideration shows positive and negative effects for patients < 65 years. On the positive side, there is an indication of a minor added benefit or of lesser harm for the outcome "recurrence" and for a specific AE, and there are also hints of a minor added benefit for individual dimensions of health-related quality of life. In contrast, there are indications of negative effects with the extents “minor”, “considerable” and “major” for the outcomes “SAEs” and “specific AEs”. In the treatment phase, these were also partly reflected by the patient-reported symptoms (diarrhoea). There are thus disadvantages during the treatment phase (recording of AEs until end of treatment), with at least some of the reported SAEs (in particular a relevant proportion of serious heart failures) persisting beyond treatment. Overall, the negative effects outweigh the positive effects of pertuzumab/trastuzumab (SC) in this situation.
- In addition to the positive and negative effects described for the younger age group (< 65 years), there were further negative effects in patients ≥ 65 years that show greater burdens from the therapies. For the treatment phase, this results in additional hints of burdens from the symptoms for 2 outcomes (“nausea and vomiting”, “appetite loss”) with the extents “minor” and “considerable” as well as for “physical functioning” as 1 of 9 recorded dimensions of health-related quality of life (extent: “minor”). However, compared to the previous benefit assessment A18-41, the positive effects for the outcome “recurrence” are based on a longer follow-up period of 6 years, and there are slightly larger absolute differences between the recurrence rates in the treatment groups (3.6% vs. 2.4%). In the present data cut-off, the negative effects of pertuzumab/trastuzumab (SC) therefore no longer predominate over the positive effects. However, the negative effects outweigh the positive ones.

In summary, an added benefit of pertuzumab/trastuzumab (SC) as adjuvant treatment versus the ACT, a therapeutic regimen containing trastuzumab, a taxane and, if applicable, an anthracycline has not been proven for either of both patient groups (< 65 years, ≥ 65 years) with HER2-positive early-stage breast cancer at high risk of recurrence.

The effects described for the intravenous free combination on the basis of the APHINITY study are used for the benefit assessment of pertuzumab/trastuzumab (SC).

The result of the assessment of the added benefit of pertuzumab/trastuzumab (SC) in combination with chemotherapy in comparison with the ACT is summarized in Table 20.

Table 20: Pertuzumab/trastuzumab (SC) in combination with chemotherapy - probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjuvant treatment of adult patients with HER2-positive early-stage breast cancer at high risk of recurrence (node-positive or hormone receptor-negative)	A treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if applicable, an anthracycline (doxorubicin or epirubicin)	Added benefit not proven ▪
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; SC: subcutaneous		

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for all patients.

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

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Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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