IQWiG Reports – Commission No. A22-102

Pertuzumab/trastuzumab (breast cancer, adjuvant) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Pertuzumab/Trastuzumab (Mammakarzinom, adjuvant) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 23 December 2022). 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BICR	blinded independent central review
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	ductal carcinoma in situ
eCRF	electronic case report form
EMA	European Medicines Agency
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
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
OS	overall survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

I 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 pertuzumab/trastuzumab fixed-dose combination for subcutaneous use (in combination with chemotherapy). 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 29 September 2022.

The validity of the G-BA's resolution was limited because further clinical data for the APHINITY study (especially on overall survival and recurrences), which may be relevant for assessing the benefit of the drug, were expected from the planned data cut-off approximately 5 years after the primary analysis.

Research question

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

The G-BA specified a treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if appropriate, an anthracycline (doxorubicin or epirubicin) as ACT for the present therapeutic indication. The implementation of an anthracycline-containing treatment protocol must be weighed against the cardiovascular risks. Trastuzumab should not be used in combination with an anthracycline but sequentially in combination with a taxane. Cardiac functions should be monitored closely.

The research question presented in Table 2 results from the ACT specified by the G-BA.

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 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 appropriate, an anthracycline (doxorubicin or epirubicin)[b]
a. Presented is the respective ACT specified by the GBA. 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.

In the context of the approval, the bioequivalence and efficacy equivalence of the pertuzumab/trastuzumab fixed-dose combination (SC) and the intravenous free combination of pertuzumab + trastuzumab was proven on the basis of the FeDeriCa study conducted to confirm pharmacokinetic non-inferiority. 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 comprehensible in principle, but potential advantages and disadvantages of the SC fixed-dose combination versus the intravenous free combination of pertuzumab and trastuzumab cannot be taken into account for patient-relevant outcomes based on this approach. Benefit assessment A21-11 already found that the results of the APHINITY study can be transferred to the pertuzumab/trastuzumab fixed-dose combination (SC) and that the APHINITY study is therefore suitable for the benefit assessment.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

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 any 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 (one patient was excluded after randomization due to deliberate false declarations) were randomly assigned to one of the 2 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. Hormone receptor-positive patients were additionally to be treated with endocrine therapy for at least 5 years.

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

Risk of bias

The risk of bias across outcomes for the APHINITY study is rated as low. The outcome-specific risk of bias is rated as low for the results of the outcomes of recurrence, serious adverse events (SAEs), severe adverse events (AEs), discontinuation due to AEs, and other specific AEs. For the results on the outcome of overall survival, the risk of bias is rated as high, since due to the lack of information on the subsequent therapies used, it cannot be assessed whether the patients in both treatment arms received adequate subsequent antineoplastic therapies. The risk of bias is rated as high for the results on symptom and health-related quality of life outcomes recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23 (EORTC QLQ-BR23). This is due to the fact that more than 10% of the patients in the relevant subpopulation were not included in the analysis.

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

For the outcome of overall survival, a statistically significant difference between the treatment groups in favour of pertuzumab + trastuzumab + chemotherapy compared with placebo + trastuzumab + chemotherapy was shown at the third data cut-off (10 January 2022). There is a hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for this outcome.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and disease-free survival), there was a statistically significant effect in favour of pertuzumab + trastuzumab + chemotherapy compared with placebo + trastuzumab + chemotherapy for both

operationalizations at the third data cut-off (10 January 2022). There is an indication of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for this outcome.

Symptoms

Symptom outcomes were recorded with the disease-specific instruments EORTC QLQ-C30 and 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 of 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 chest region

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

Appetite loss

For the outcome of appetite loss, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was also shown at the end of anti-HER2 therapy. However, a statistically significant interaction with the characteristic of age was shown at this point in time. There is 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 of nausea and vomiting. However, at the time point of end of anti-HER2 therapy, there was a statistically significant interaction with the characteristic of age; however, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was only shown for patients ≥ 65 years. There is 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 other outcomes of pain, dyspnoea, insomnia, constipation, side effects of

systemic treatment, symptoms in arm region, and upset by hair loss. There are 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 2 time points of 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 of emotional functioning at the time point of 36-month follow-up. There is a hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for this time point.

Physical functioning

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

Role functioning

For the outcome of role functioning, a statistically significant interaction with the characteristic of age was shown at the time point of 36-month follow-up. However, a statistically significant difference in favour of pertuzumab + trastuzumab + chemotherapy was only shown for patients < 65 years. There is 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 treatment groups for the outcomes of global health status, cognitive functioning, social functioning, body image, sexual activity, enjoyment of sex, and future perspective. There is no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy; an added benefit is therefore not proven for these outcomes.

Side effects

SAEs

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the outcome of SAEs at the third data cut-off (10 January 2022). There is 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 third data cut-off (10 January 2022), a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the outcome of severe AEs. However, there was a statistically significant interaction with the characteristic of geographical region. The result in the region of Western Europe, which, in the present data situation is the relevant region for the approximation to the German health care context, differs from the result for the overall population. There was no statistically significant difference between treatment groups for the region of Western Europe.

Based on the result for the region of Western Europe, there is therefore no hint of greater or lesser harm from pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

At the third data cut-off (10 January 2022), no statistically significant difference between the treatment groups was shown for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy; greater or lesser harm is therefore not proven.

Specific AEs

At the third data cut-off (10 January 2022), a statistically significant difference between the treatment arms to the disadvantage of pertuzumab + trastuzumab + chemotherapy compared with placebo + trastuzumab + chemotherapy was shown for each of the following AEs:

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

  cardiac 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, AEs), pruritus (PT, AEs)

In each case, there is an indication of greater harm from pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

A statistically significant interaction with the characteristic of age was shown for the outcome of 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. There is 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 of musculoskeletal and connective tissue disorders (SOC, severe AEs). There is 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]

On the basis of the results presented, the probability and extent of added benefit of the pertuzumab/trastuzumab fixed-dose combination for subcutaneous use (in combination with chemotherapy) in comparison with the ACT are assessed as follows:

Overall, several positive and several negative effects of different extents, with probabilities of hint or indication, were found.

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 a hint of a minor added benefit for the outcome of overall survival, and an indication of a considerable added benefit for recurrence. There is an indication of lesser harm for one specific AE; in addition, there are 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 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 cardiac failures) persisting beyond treatment.
- In addition to the positive and negative effects described for the younger age group (< 65 years), there are further negative effects in patients ≥ 65 years that show greater

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

burdens from the therapies. For the treatment phase, there are 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 one of 9 recorded dimensions of health-related quality of life (extent: "minor").

Overall, the positive effects outweigh the negative effects for both age groups at the third data cut-off, in particular due to the results in the outcome of overall survival and recurrence. There is therefore an indication of minor added benefit of pertuzumab/trastuzumab (SC) in comparison with the ACT for patients with HER2-positive early 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).

Table 3 shows a summary of the probability and extent of 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 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 appropriate, an anthracycline (doxorubicin or epirubicin)	Indication of minor added benefit[b] ▪
a. Presented is the respective ACT specified by the GBA. b. The APHINITY study only included patients with an ECOG PS of 0 or 1 and only 8 male patients. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2 and to male patients. ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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.

I 2 Research question

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

The G-BA specified a treatment regimen containing trastuzumab, a taxane (paclitaxel or docetaxel) and, if appropriate, an anthracycline (doxorubicin or epirubicin) as ACT for the present therapeutic indication. The implementation of an anthracycline-containing treatment protocol must be weighed against the cardiovascular risks. Trastuzumab should not be used in combination with an anthracycline but sequentially in combination with a taxane. Cardiac functions should be monitored closely.

The research question presented in Table 4 results from the ACT specified by the G-BA.

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 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 appropriate, an anthracycline (doxorubicin or epirubicin)[b]
a. Presented is the respective ACT specified by the GBA. 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.

In the context of the approval [3], the bioequivalence and efficacy equivalence of the pertuzumab/trastuzumab fixed-dose combination (SC) and the intravenous free combination of pertuzumab + trastuzumab was proven on the basis of the FeDeriCa study [4] conducted to confirm pharmacokinetic non-inferiority. 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 comprehensible in principle, but potential advantages or disadvantages of the SC fixed-dose combination versus the intravenous free combination of pertuzumab and trastuzumab cannot be taken into account for patient-relevant outcomes based on this approach. Benefit assessment A21-11 [5] already found that the results of the APHINITY study can be transferred to the pertuzumab/trastuzumab

fixed-dose combination (SC) and that the APHINITY study is therefore suitable for the benefit assessment.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

I 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: 18 July 2022)
- bibliographical literature search on pertuzumab/trastuzumab (last search on 18 July 2022)
- search in trial registries/trial results databases for studies on pertuzumab/trastuzumab (last search on 18 July 2022)
- search on the G-BA website for pertuzumab/trastuzumab (last search on 18 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on pertuzumab (last search on 24 October 2022); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The study presented in the following table 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)	CSR (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 [6,7]	Yes [8-12]	Yes [3,13,14]

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

CSR: clinical study report; G-BA: Federal Joint Committee; IV: intravenous; RCT: randomized controlled trial

Results for the free intravenous combination of pertuzumab + trastuzumab can be used for the benefit assessment of the pertuzumab/trastuzumab fixed-dose combination (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 in the benefit assessment of the free intravenous combination of pertuzumab and trastuzumab (Benefit assessment A18-41 [15] and the corresponding addendum A18-76 [16]) as well as in the benefit assessment of the pertuzumab/trastuzumab fixed-dose combination (SC) (Benefit assessment A21-11 [5]). 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.

I 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 with ECOG PS 0 or 1 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)	Interval between surgery until start of treatment: at most 8 weeks Treatment until recurrence, AEs, withdrawal of consent, physician's decision, up to 64 weeks maximum[d] Observation[e]: outcome-specific, at most until death, discontinuation of participation in the study or end of study[f]	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[g]: ▪ 19 December 2016 (primary data cut-off) ▪ 19 June 2019 (second OS interim analysis) ▪ 10 January 2022 (third OS interim analysis)	Primary: invasive disease-free survival (IDFS) Secondary: overall survival, 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 include only 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. When treated with anthracycline-free chemotherapy, the maximum treatment duration is 52 weeks.
e. Outcome-specific information is described in Table 8.
f. The study ends about 15 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.
g. In addition, 2 data cut-offs for safety outcomes were conducted on 30 November 2012 and 22 February 2013, and one data cut-off for the 3-month safety report was conducted on 15 May 2017.

AE: adverse event; DFS: disease-free survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IDFS: invasive disease-free survival; n: relevant subpopulation; N: number of randomized patients; OS: overall survival; RCT: randomized controlled trial

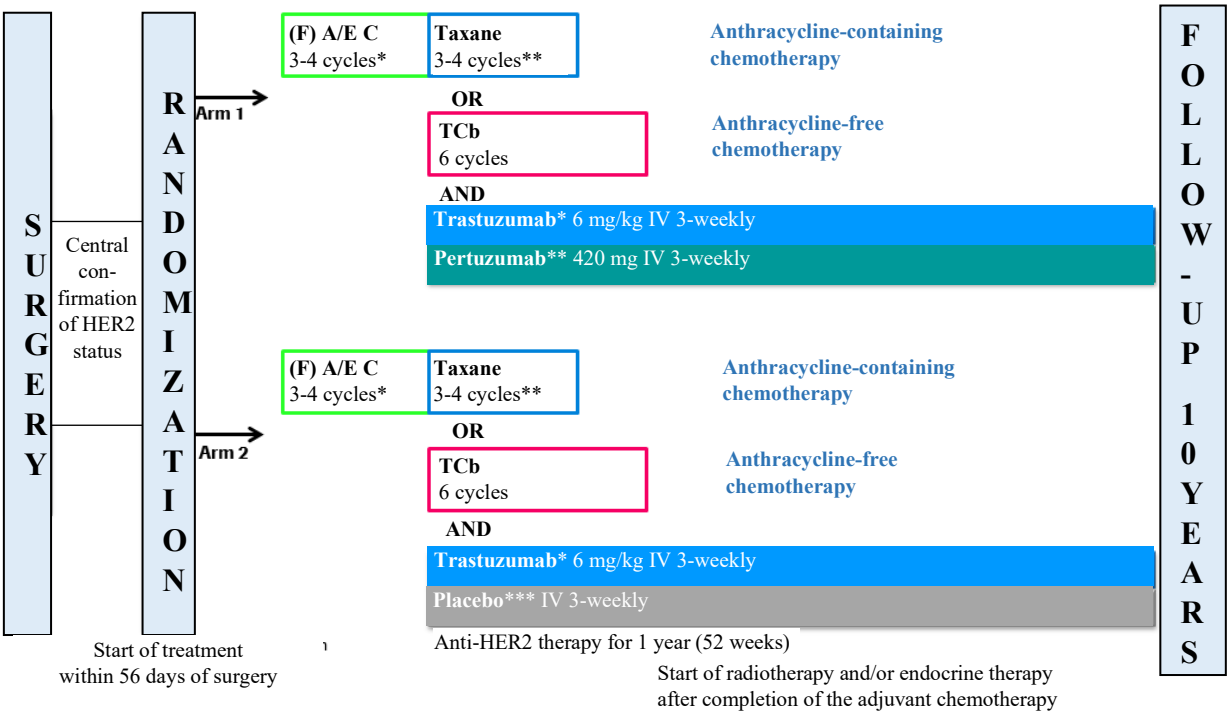
Table 7: Characteristics of the intervention – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (multipage table)

Study	Intervention	Comparison
APHINITY	▪ Pertuzumab[a] ▫ Cycle 1: 840 mg IV ▫ Cycle 2 to 18 maximum: 420 mg IV, q3w ▪ Trastuzumab[a] ▫ Cycle 1: 8 mg/kg, IV ▫ Cycle 2 to 18 maximum: 6 mg/kg, IV, q3w starting with the taxane-containing chemotherapy	▪ Placebo: ▫ Cycle 1 to 18 maximum: IV, q3w ▪ Trastuzumab[a] ▫ Cycle 1: 8 mg/kg, IV ▫ Cycle 2 to 18 maximum: 6 mg/kg, IV, q3w 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 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.

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: intravenous; 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 any 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 (one patient was excluded after randomization due to deliberate false declarations) were randomly assigned to one of the 2 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; C: cyclophosphamide; 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 [17]. This applied to about 3 quarters of the study population. The company presented study results for the relevant subpopulation in Module 4 A 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. Hormone receptor-positive patients were additionally 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. The dossier 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. According to this, 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 A provides no information on which subsequent therapies patients received after recurrence or treatment discontinuation (see text below for more information). In principle, however, subsequent therapies after recurrence could be administered without restriction. The company's dossier contains no separate information on the procedure to be followed in case of recurrence during the 52-week anti-HER2 therapy.

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

Data cut-offs and available analyses

To date, 6 data cut-offs are available for the APHINITY study (30 November 2012, 22 February 2013, 19 December 2016, 15 May 2017, 19 June 2019, 10 January 2022). 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.

For the present benefit assessment, analyses are available for the following 3 data cut-offs:

- First data cut-off (19 December 2016, primary analysis): preplanned efficacy analysis that took place after 381 IDFS events, further analyses on overall survival (OS), efficacy and side effects were conducted at the same time
- Second data cut-off (19 June 2019, second OS interim analysis): preplanned analysis, 2.5 years after the primary analysis, on the outcomes of mortality, morbidity, and side effects
- Third data cut-off (10 January 2022, third OS interim analysis): preplanned analysis, about 5 years after the primary analysis, on the outcomes of 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 patient-reported outcomes of the categories of morbidity and health-related quality of life. The other outcomes in the morbidity category, as well as the outcomes in the mortality and side effects categories, are based on the third data cut-off (10 January 2022).

In each case, the most recent data cut-off is used for the present benefit assessment. The outcomes of the categories of mortality, morbidity (recurrence) and side effects are thus based on the third data cut-off (10 January 2022). The primary data cut-off is 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).

Treatment duration and follow-up observation

Table 8 shows the planned duration of patient follow-up observation 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 15 years after randomization of the last patient
Morbidity	
Recurrence	Up to 15 years after randomization of the last patient
Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23)	After the last dose of the study medication in the follow-up phase until month 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 until month 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; these were recorded beyond 28 days. All AEs were followed up until resolution 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 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event

After benefit assessment A21-11, the observation of overall survival and of recurrences was increased from 10 years to 15 years after randomization of the last patient, according to protocol version E.

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. With a planned study duration of approximately 15 years, these observation periods are nevertheless notably shorter compared with overall survival.

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). Drawing a reliable conclusion on the total study period or the time to patient death, however, would require surveying these outcomes for the total period, as was done for survival and recurrence.

Characteristics of the study population

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

Table 9: Characteristics of the study population and study/treatment discontinuation – 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/< 1	> 99/< 1
Family origin, n (%)		
Caucasian	1252 (69)	1255 (69)
Black	25 (1)	31 (2)
Asian	477 (26)	484 (27)
Other	52 (3)	51 (3)
Geographical region, n (%)		
USA/Canada	265 (15)	260 (14)
Western Europe	827 (46)	822 (45)
Asia-Pacific	490 (27)	512 (28)
Latin America	43 (2)	47 (3)
Other	186 (10)	182 (10)
Female reproductive status, n (%)		
Premenopausal	873 (48)	885 (49)
Postmenopausal	933 (52)	929 (51)
Unknown	3 (< 1)	2 (< 1)
Hormone receptor status, n (%)		
Negative (ER- and PR-negative)	864 (48)	858 (47)
Positive (ER- and/or PR-positive)	947 (52)	965 (53)
Nodal status, n (%)		
N0 and tumour ≤ 1 cm	51 (3)	43 (2)
N0 and tumour > 1 cm	257 (14)	278 (15)
N1-3 positive lymph nodes	907 (50)	900 (49)
N ≥ 4 positive lymph nodes	596 (33)	602 (33)
Type of adjuvant chemotherapy, n (%)		
Anthracycline-containing	1439 (79)	1448 (79)
Anthracycline-free	372 (21)	375 (21)

Table 9: Characteristics of the study population and study/treatment discontinuation – 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
Locoregional radiotherapy (after adjuvant chemotherapy), n (%)	1347 (74)	1350 (74)
Treatment discontinuation, n (%)[b]	278 (15)	241 (13)
Treatment phase completed, n (%)	1533 (85)	1582 (87)
Study discontinuation, n (%)[c]	470 (26)[d]	532 (29)[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. Common reasons for treatment discontinuation in the intervention arm versus the control arm were: AE (47% vs. 49%), patient request (14% vs. 15%), non-compliance (12% vs. 10%).
c. During the follow-up phase until the third data cut-off; data without deaths. Common reasons for study discontinuation in the intervention arm vs. the control arm were: recurrence (34% vs. 44%), patient request (38% vs. 31%), lost to follow-up (12% vs. 11%). Module 4 A 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; max: maximum; min: minimum; 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 therapeutic indication, the study population of the APHINITY study consists almost exclusively of women. On average, the patients of the relevant subpopulation are about 51 years old. Almost 70% are white, another 26% are 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 are 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. The dossier 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 [18].

In about 14% of the patients, treatment with pertuzumab or placebo was not completed. About 28% of the patients discontinued the study during the follow-up phase.

Information on the course of the study

Table 10 shows patients' median treatment duration 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[b] and recurrences		
Median [min; max]	99.7 [0; 120.1]	99.8 [0; 117.3]
Symptoms and health-related quality of life		
Median [min; max]	36 [0; 36][c]	36 [0; 36][c]
Number of patients in the last analysis at month 36 (%)[d]	1327 (73)	1298 (71)
Side effects[e]		
Median [min; max]	14.9 [0.1; 18.5][f]	15.0 [0; 112.8][f]
Number of patients who completed anti-HER2 treatment (%)	1533 (85)	1582 (87)

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 [15]).
b. The observation period is defined as the time from randomization until death or until the third data cut-off if the patient was still alive at this time point.
c. Institute's calculation based on the number of patients for whom data were available when the documentation was carried out.
d. Institute's calculation, data refer to the EORTC questionnaire with the lowest response rate at month 36.
e. 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 third data cut-off is 99.9 (0.1; 120.1) vs. 99.7 (0; 117.3) months for the safety population.
f. Data refer to the safety population of the study (1783 vs. 1822 patients).

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; 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.

The median observation duration for overall survival was almost 3 times longer than the observation duration for patient-reported outcomes, and almost 7 times longer than for side effects outcomes. Hence, the observation durations for these outcomes were notably shortened in comparison with median overall survival. Data for the entire observation period are missing for these outcomes.

Information on subsequent therapies

According to the study documents, subsequent therapies could be administered without restrictions after recurrence and had to be recorded in the electronic case report form (eCRF). However, the company did not present any corresponding analyses of subsequent therapies in its dossier.

This approach is not appropriate. The results of the outcome of overall survival are influenced not only by the initial study medication, but also by subsequent antineoplastic therapies used after disease progression or recurrence. The use of adequate subsequent therapies is thus of great importance for the interpretation of the results of the outcome of overall survival. For the APHINITY study, it is not possible to assess whether the patients in both treatment arms received adequate subsequent therapy due to the lack of information on the subsequent therapies used. This is taken into account when assessing the risk of bias for the results of the outcome of overall survival (see Section I 4.2).

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 is rated as low.

Transferability of the study results to the German health care context

In Module 4 A, the company described the transferability of the study results to the German health care context based on the following characteristics of the patients included in the

APHINITY study: sex, age, family origin, general condition, histology of the carcinoma, and type of chemotherapy regimen.

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

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - Overall survival
- 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
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Further specific AEs, if any

The choice of patient-relevant outcomes deviates from the selection by the company, which used further outcomes in the dossier (Module 4 A).

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

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]	Further 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 following 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 23; 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 of recurrence is a composite outcome and includes the following 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), ductal carcinoma in situ (DCIS) (ipsilateral or contralateral), and death from any cause. The assessment uses the proportion of patients with recurrence and, additionally, the time to recurrence.

The diagnosis of a recurrence or second primary tumour was based on the investigator's assessment – the protocol did not provide for blinded independent central review (BICR). An assessment by means of BICR is explicitly recommended by the European Medicines Agency

(EMA) [19]. However, the missing analysis by BICR remains of no consequence for the present benefit assessment.

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

In its dossier, the company presented responder analyses for the proportion of patients with a deterioration by ≥ 10 points and by ≥ 15% of the scale range (respective scale range 0 to 100) for the EORTC QLQ-C30 and the EORTC QLQ-BR23. As explained in the *General Methods* of the Institute [1,20], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, 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 its additional modules, 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 [21]).

In the APHINITY study, the respective proportions of responders at different selected time points were analysed, without considering responders at earlier time points (including end of taxane therapy, end of anti-HER2 therapy, 18-month follow-up and 36-month follow-up; see also Module 4 A [22] of the benefit assessment of pertuzumab [A18-41]). Based on benefit assessment A18-41 [15], the company presented 2 selected time points (end of anti-HER2 therapy and 36-month follow-up [36 months after randomization]) in Module 4 A. In accordance with the procedure in A18-41 and A21-11, the present assessment uses these time points for the benefit assessment. The results presented here are identical to those in the previous benefit assessments, A18-41 and A21-11, as the analyses for the first data cut-off (19 December 2016) are still used (for the justification for using the first data cut-off, see Section I 3.2).

Notes on side effects

According to the study protocol, the observation periods for the outcomes on side effects comprised the period of treatment with the study medication plus 28 days. In the subsequent follow-up phase, only SAEs that were considered treatment-related, as well as cardiac events and secondary cancer diseases (excluding breast cancer) were recorded. According to the information in Module 4 A, the analysis period for the side effects outcomes includes only the double-blind treatment phase with the associated 28-day follow-up period.

At the first data cut-off (19 December 2016), all patients had completed the treatment phase with the additional 28-day follow-up, providing a complete data set for the side effects outcomes already at that time point (see Section I 3.2). Nevertheless, dossier assessment A21-11 found minor quantitative deviations in event numbers between the first and the second data cut-off for the superordinate side effects outcomes and for some AEs/SAEs at SOC and PT level. The updated analysis at the third data cut-off (10 January 2022) again showed minor quantitative deviations in event numbers compared with the second data cut-off. It is still unclear how these deviations came about. In the comments on benefit assessment A21-11, the company described that, according to the protocol, AEs of any severity grade as well as SAEs

for which a causal relationship to the therapy was assumed continued to be recorded after the end of treatment plus 28 days, and that this could explain the described deviations between the analyses of the first and second data cut-off [23]. The statement of the company on extended follow-up for AEs of any severity grade in the comments does not correspond to the information in the study documents, however (see above and Table 8). However, analyses of AEs of any severity grade after the end of treatment are available in Appendix G to Module 4 A. It remains unclear why these AEs of any severity grade were recorded after the end of the 28-day follow-up, which was in deviation from the specifications in the study protocol. Besides, the fact that events with a potential causal relationship to the therapy were included selectively in the analysis (as described by the company in its comments) would not be appropriate for the benefit assessment and contradicts the information on the analysis period in Module 4 A. Since the analyses between the 3 data cut-offs each involve only minor quantitative deviations, the results for the outcomes in the side effects category for the third data cut-off are used for the benefit assessment despite the described uncertainties. This corresponds to the approach in dossier assessments A18-41 and A21-11 [5,15].

I 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]	Further specific AEs[b, d]
APHINITY	L	H[e]	L[f]	H[g]	H[g]	L	L	L	L

a. Presented via the recurrence rate and disease-free survival; includes the following 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. Missing information on the subsequent antineoplastic therapies used in the patients (see further explanation in Section I 3.2).
f. For the recurrence 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 of recurrence is rated as low.
g. 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; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; 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; SOC: System Organ Class

The outcome-specific risk of bias is rated as low for the results of the outcomes of recurrence, SAEs, severe AEs, discontinuation due to AEs, and other specific AEs.

For the results on the outcome of overall survival, the risk of bias is rated as high, since due to the lack of information on the subsequent therapies used, it cannot be assessed whether the patients in both treatment arms received adequate subsequent antineoplastic therapies. The risk bias is rated as high 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. This is due to the fact that more than 10% of the patients in the relevant subpopulation were not included in the analysis.

I 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 breast cancer at high risk of recurrence. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

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

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

Study **Outcome category** **Outcome**	**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 (third data cut-off: 10 January 2022)					
Overall survival	1811	140 (7.7) median time to event: NA [NC; NC]	1823	175 (9.6) median time to event: NA [NC; NC]	HR[a] 0.798 [0.638; 0.996]; 0.046
Morbidity (third data cut-off: 10 January 2022)					
Recurrence					
Recurrence rate[b]	1811	256 (14.1)	1823	347 (19.0)	0.74 [0.64; 0.86]; < 0.001[c]
Ipsilateral invasive local breast cancer recurrence	1811	16 (6.3)[d]	1823	38 (11.0)[d]	–
Ipsilateral invasive regional breast cancer recurrence	1811	11 (4.3)[d]	1823	14 (4.0)[d]	–
Distant recurrence	1811	132 (51.6)[d]	1823	174 (50.1)[d]	–
Contralateral invasive breast cancer	1811	22 (8.6)[d]	1823	25 (7.2)[d]	–
Secondary primary carcinoma (no breast cancer)	1811	43 (16.8)[d]	1823	52 (15.0)[d]	–
DCIS (ipsilateral or contralateral)	1811	7 (2.7)[d]	1823	16 (4.6)[d]	–
Death from any cause	1811	25 (9.8)[d]	1823	28 (8.1)[d]	–
Disease-free survival[e]	1811	256 (14.1) median time to event: NA [NC; NC]	1823	347 (19.0) median time to event: NA [NC; NC]	HR[a] 0.72 [0.62; 0.85]; < 0.001

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

Study Outcome category Outcome	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 (third data cut-off: 10 January 2022)[f]					
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	1142 (64.0)	1822	1056 (58.0)	1.11 [1.05; 1.16]; < 0.001[h]
Discontinuation due to AEs[i]	1783	220 (12.3)	1822	219 (12.0)	1.03 [0.86; 1.22]; 0.770[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	261 (14.6)	1822	163 (8.9)	1.64 [1.36; 1.97]; < 0.001[c]
Cardiac 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 [1.00; 2.06]; 0.047[c]
White blood cell count decreased (PT, severe AEs)[g]	1783	92 (5.2)	1822	65 (3.6)	1.45 [1.06; 1.97]; 0.019[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, dichotomous) – RCT, direct comparison: pertuzumab + trastuzumab + chemotherapy vs. placebo + trastuzumab + chemotherapy (node-positive or hormone receptor-negative patients) (multipage table)

Study **Outcome category** **Outcome**	**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 [24]).
d. Qualifying 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 or second data cut-off, reasons unclear (see Section I 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; CSZ: convexity, symmetry, z-score; 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; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

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
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

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]**
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

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 [24]).

CI: confidence interval; CSZ: convexity, symmetry, z-score; 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 23; 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
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

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]
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 23; 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 overall survival and the patient-reported outcomes that were recorded using the scales of the EORTC questionnaire, and at most indications can be determined for all other outcomes (see Section I 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 I 5).

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference between the treatment groups in favour of pertuzumab + trastuzumab + chemotherapy compared with placebo + trastuzumab + chemotherapy was shown at the third data cut-off (10 January 2022). There is a hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for this outcome.

Morbidity

Recurrence

For the outcome of recurrence (operationalized as recurrence rate and disease-free survival), there was a statistically significant effect in favour of pertuzumab + trastuzumab +

chemotherapy compared with placebo + trastuzumab + chemotherapy for both operationalizations at the third data cut-off (10 January 2022). There is an indication of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for this outcome.

Symptoms

Symptom outcomes were recorded with the disease-specific instruments EORTC QLQ-C30 and 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 of end of anti-HER2 therapy and 36-month follow-up (see also Section I 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 chest region

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

Appetite loss

For the outcome of appetite loss, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was also shown at the end of anti-HER2 therapy. However, a statistically significant interaction with the characteristic of age was shown at this point in time. There is 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 of nausea and vomiting. However, at the time point of end of anti-HER2 therapy, there was a statistically significant interaction with the characteristic of age; however, a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was only shown for patients ≥ 65 years. There is 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 other outcomes of pain, dyspnoea, insomnia, constipation, side effects of systemic treatment, symptoms in arm region, and upset by hair loss. There are 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 2 time points of 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 of emotional functioning at the time point of 36-month follow-up. There is a hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy for this time point.

Physical functioning

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

Role functioning

For the outcome of role functioning, a statistically significant interaction with the characteristic of age was shown at the time point of 36-month follow-up. However, a statistically significant difference in favour of pertuzumab + trastuzumab + chemotherapy was only shown for patients < 65 years. There is 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 treatment groups for the outcomes of global health status, cognitive functioning, social functioning, body image, sexual activity, enjoyment of sex, and future perspective. There is no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy; an added benefit is therefore not proven for these outcomes.

Side effects

Adverse events of the different administration forms

Benefit assessment A21-11 found that the results on AEs of the APHINITY study can be transferred to the pertuzumab/trastuzumab fixed-dose combination (SC) [5].

SAEs

A statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the outcome of SAEs at the third data cut-off (10 January 2022). There is an indication of greater harm from pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

Severe AEs (CTCAE grade ≥ 3)

At the third data cut-off (10 January 2022), a statistically significant difference to the disadvantage of pertuzumab + trastuzumab + chemotherapy was shown for the outcome of severe AEs. However, there was a statistically significant interaction with the characteristic of 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 treatment groups for the region of Western Europe.

Based on the result for the region of Western Europe, there is therefore no hint of greater or lesser harm from pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

At the third data cut-off (10 January 2022), no statistically significant difference between the treatment groups was shown for the outcome of discontinuation due to AEs. There is no hint of greater or lesser harm from pertuzumab + trastuzumab + chemotherapy compared with trastuzumab + chemotherapy; greater or lesser harm is therefore not proven.

Specific AEs

At the third data cut-off (10 January 2022), a statistically significant difference between the treatment arms to the disadvantage of pertuzumab + trastuzumab + chemotherapy compared with placebo + trastuzumab + chemotherapy was shown for each of the following AEs:

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

  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)

- Non-severe/non-serious AEs:

  diarrhoea (PT, AEs), pruritus (PT, AEs)

In each case, there is an indication of greater harm from pertuzumab + trastuzumab + chemotherapy in comparison with trastuzumab + chemotherapy.

A statistically significant interaction with the characteristic of age was shown for the outcome of 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. There is 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 of musculoskeletal and connective tissue disorders (SOC, severe AEs). There is an indication of lesser harm from pertuzumab + trastuzumab + chemotherapy in comparison with the ACT.

I 4.4 Subgroups and other effect modifiers

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

- age (< 65 years versus ≥ 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 to 3 positive lymph nodes, N ≥ 4 positive lymph nodes)

In Module 4 A, the company presented complete subgroup analyses on these characteristics for all outcomes. The characteristic of sex is 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 IQWiG methods [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 had to be 10 events in at least one subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only 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 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 (first data cut-off: 19 December 2016)						
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 (first data cut-off: 19 December 2016)						
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

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**
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
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

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**
Side effects (third data cut-off: 10 January 2022)						
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	518 (63.6)	824	520 (63.1)	1.01 [0.94; 1.09]	0.824
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)						
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; PT: Preferred Term; 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 of nausea and vomiting, a statistically significant interaction with the characteristic of age was shown at the time point of end of anti-HER2 therapy.

There was no statistically significant difference between the treatment groups in the age group < 65 years. There is 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, there is a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for patients ≥ 65 years of age.

Appetite loss

For the outcome of appetite loss, a statistically significant interaction with the characteristic of age was shown at the time point of end of anti-HER2 therapy.

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 of non-serious/non-severe symptoms/late complications is no more than marginal. For this outcome, there is 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 of physical functioning, a statistically significant interaction with the characteristic of age was shown at the time point of end of anti-HER2 therapy.

There was no statistically significant difference between the treatment groups in the age group < 65 years. There is 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, there is a hint of lesser benefit of pertuzumab + trastuzumab + chemotherapy versus the ACT for patients ≥ 65 years of age.

Role functioning

For the outcome of role functioning, statistically significant interactions with the characteristics of geographical region and age were shown at the time point of 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. In approximation to the German health care context, the region of Western Europe is primarily considered in the present data situation. There is therefore 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, there is 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 treatment groups for the age group ≥ 65 years. There is 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 of cognitive functioning, a statistically significant interaction with the characteristic of geographical region was shown at the time point of 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. In approximation to the German health care context, the region of Western Europe is primarily considered in the present data situation. There is therefore no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for the outcome of cognitive functioning is therefore not proven.

Social functioning

For the outcome of social functioning, a statistically significant interaction with the characteristic of geographical region was shown at the time point of end of 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. In approximation to the German health care context, the region of Western Europe is primarily considered in the present data situation. There is therefore no hint of an added benefit of pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for the outcome of social functioning is therefore not proven.

Side effects

Severe AEs (CTCAE grade ≥ 3)

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

Statistically significant differences, each to the disadvantage of pertuzumab + trastuzumab + chemotherapy, were shown for the regions of USA/Canada and Asia-Pacific. In approximation to the German health care context, the region of Western Europe is primarily considered in the present data situation. However, there is no statistically significant difference between the treatment groups for this region. There is therefore no hint of greater or lesser harm from pertuzumab + trastuzumab + chemotherapy in comparison with the ACT. An added benefit for the outcome of severe AEs is therefore not proven.

Specific AEs

Diarrhoea (AEs)

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

Statistically significant differences, each to the disadvantage of pertuzumab + trastuzumab + chemotherapy, were shown for all regions. In approximation to the German health care context, the region of Western Europe is primarily considered in the present data situation. There is a statistically significant difference between the treatment groups also for this region. For this outcome, there is 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 of age was shown for the outcome of 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, there is 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 treatment groups for the age group ≥ 65 years. There is 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.

I 5 Probability and extent of added benefit

The probability and extent of 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.

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 18).

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

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

The outcome of 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 of death from any cause is a component of the composite outcome of recurrence.

There is no information that allows assignment to a severity category for symptoms recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23. Therefore, these scales were each assigned to the outcome category of non-serious/non-severe symptoms/late complications.

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 **Outcome** **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: 0.798 [0.638; 0.996] p = 0.046 Probability: "hint"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Morbidity		
Recurrence	14.1% vs. 19.0% RR: 0.74 [0.64; 0.86] p < 0.001 Probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ Added benefit, extent: "considerable"
Disease-free survival	14.1% vs. 19.0% HR: 0.72 [0.62; 0.85] p < 0.001 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/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/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 **Outcome** **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]
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/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”
36-month follow-up	9.2% vs. 9.9% RR: 0.92 [0.73; 1.15] p = 0.453	Lesser/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/added benefit not proven
36-month follow-up	23.2% vs. 23.9% RR: 0.97 [0.84; 1.11] p = 0.643	Lesser/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/added benefit not proven
36-month follow-up	20.4% vs. 22.9% RR: 0.90 [0.78; 1.03] p = 0.133	Lesser/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/added benefit not proven
36-month follow-up	23.3% vs. 25.2% RR: 0.93 [0.81; 1.06] p = 0.279	Lesser/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 **Outcome** **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]
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/added benefit not proven[d]
≥ 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/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/added benefit not proven
36-month follow-up	16.1% vs. 15.2% RR: 1.06 [0.89; 1.26] p = 0.537	Lesser/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/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 **Outcome** **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]
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/added benefit not proven
36-month follow-up	23.0% vs. 24.1% RR: 0.96 [0.83; 1.10] p = 0.522	Lesser/added benefit not proven
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/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/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/added benefit not proven
36-month follow-up	23.6% vs. 25.5% RR: 0.92 [0.81; 1.05] p = 0.227	Lesser/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/added benefit not proven
36-month follow-up	24.7% vs. 26.0% RR: 0.89 [0.50; 1.58] p = 0.696	Lesser/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 **Outcome** **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]
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/added benefit not proven
36-month follow-up	21.7% vs. 24.2% RR: 0.89 [0.78; 1.02] p = 0.106	Lesser/added benefit not proven
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/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/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 **Outcome** **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]**
Role functioning		
End of anti-HER2 therapy	24.9% vs. 23.1% RR: 1.08 [0.95; 1.22] p = 0.221	Lesser/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/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/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"
Cognitive functioning		
End of anti-HER2 therapy	39.5% vs. 39.7% RR: 1.00 [0.91; 1.09] p = 0.923	Lesser/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/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 **Outcome** **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]
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/added benefit not proven
36-month follow-up	15.4% vs. 17.9% RR: 0.86 [0.73; 1.02] p = 0.085	Lesser/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/added benefit not proven
36-month follow-up	20.3% vs. 23.0% RR: 0.88 [0.76; 1.02] p = 0.086	Lesser/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/added benefit not proven
36-month follow-up	20.2% vs. 21.5% RR: 0.93 [0.80; 1.09] p = 0.377	Lesser/added benefit not proven
Enjoyment of sex		
End of anti-HER2 therapy	33.6% vs. 33.1% RR: 1.02 [0.85; 1.23] p = 0.829	Lesser/added benefit not proven
36-month follow-up	29.5% vs. 29.4% RR: 1.03 [0.83; 1.27] p = 0.822	Lesser/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 **Outcome** **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]
Future perspective		
End of anti-HER2 therapy	17.9% vs. 18.5% RR: 0.97 [0.84; 1.13] p = 0.697	Lesser/added benefit not proven
36-month follow-up	14.3% vs. 14.4% RR: 0.99 [0.82; 1.19] p = 0.918	Lesser/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	63.6% vs. 63.1% RR: 1.01 [0.94; 1.09] p = 0.824	Greater/lesser harm not proven
Discontinuation due to AEs	12.3% vs. 12.0% RR: 1.03 [0.86; 1.22] p = 0.770	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"
Pruritus (AEs)	14.6% vs. 8.9% RR: 1.64 [1.36; 1.97] 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"

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 **Outcome** **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]**
Cardiac 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 ≥ 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)	5.2% vs. 3.6% RR: 1.45 [1.06; 1.97] RR: 0.69 [0.51; 0.94][c] p = 0.019 Probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Metabolism and nutrition disorders (severe AEs)	4.99% 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: "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 **Outcome** **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]
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, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse 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; NA: not achieved; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer Module 23; QLQ-C30: Quality of Life Questionnaire Core 30; RR: relative risk; SAE: serious adverse event

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account 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 (multipage table)

Positive effects	**Negative effects**
Total observation period	
Mortality ▪ Overall survival: hint of an added benefit – extent "minor"	
Morbidity Serious/severe symptoms/late complications ▪ Recurrence: indication of an added benefit – extent: "considerable"	–
Shortened observation period	
–	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, 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 diarrhoea symptom scale 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"
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; HER2: human epidermal growth factor receptor 2, QLQ-C30: Quality of Life Questionnaire-Core 30; SAE: serious adverse event	

Overall, several positive and several negative effects of different extents, with probabilities of hint or indication, were found.

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 a hint of a minor added benefit for the outcome of overall survival, and an indication of a considerable added benefit for recurrence. There is an indication of lesser harm for one specific AE; in addition, there are 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 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 cardiac failures) persisting beyond treatment.
- In addition to the positive and negative effects described for the younger age group (< 65 years), there are further negative effects in patients ≥ 65 years that show greater burdens from the therapies. For the treatment phase, there are 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 one of 9 recorded dimensions of health-related quality of life (extent: "minor").

Overall, the positive effects outweigh the negative effects for both age groups at the third data cut-off, in particular due to the results in the outcome of overall survival and recurrence. There is therefore an indication of minor added benefit of pertuzumab/trastuzumab (SC) in comparison with the ACT for patients with HER2-positive early 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).

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

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 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 appropriate, an anthracycline (doxorubicin or epirubicin)	Indication of minor added benefit[b]

a. Presented is the respective ACT specified by the GBA.
b. The APHINITY study only included patients with an ECOG PS of 0 or 1 and only 8 male patients. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2 and to male patients.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; 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.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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