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Neratinib (breast cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Neratinib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 February 2020). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
FACT-B	Functional Assessment of Cancer Therapy-Breast Cancer
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug neratinib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 29 November 2019.

Research question

The aim of the present report is the assessment of the added benefit of neratinib for the extended adjuvant treatment of patients with early-stage hormone-receptor-positive human epidermal growth factor receptor 2 (HER2)-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago. The G-BA specified watchful waiting as appropriate comparator therapy (ACT).

Table 2: Research questions of the benefit assessment of neratinib

Research question	Therapeutic indication	ACT[a]
1	Extended adjuvant treatment of adult patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago[b]	Watchful waiting[c]

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed that the patients receive additional endocrine therapy because they have a positive hormone receptor status.
c. Adjuvant chemotherapy, radiotherapy or endocrine therapy is not part of the ACT; this does not affect its use as a patient-specific treatment option.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

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

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

Results

Study pool and study characteristics

The study ExteNET was included in the benefit assessment. The ExteNET study was a randomized, double-blind study comparing treatment with neratinib against placebo. The study included adult women with early-stage HER2-overexpressed/amplified breast cancer. The breast cancer had to be histologically confirmed. Men were not included in the study.

Adequate pretreatment was required in order to be eligible for the study. This included surgery, in which the surgical margins had to be free of invasive carcinoma or ductal carcinoma in situ, as well as completed chemotherapy. The patients also had to have been given a previous trastuzumab treatment.

Overall, 2840 patients were randomly allocated in a 1:1 ratio either to treatment with neratinib (N = 1420) or to placebo (N = 1420).

Treatment with neratinib was in compliance with the Summary of Product Characteristics (SPC).

Primary outcome of the study was disease-free survival (DFS); patient-relevant secondary outcomes were recurrence, overall survival, health status, health-related quality of life recorded with the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B), and adverse events (AEs).

Protocol amendments

In the course of the ExteNET study, there were a total of 13 protocol amendments to the original protocol from 29 April 2009. The most significant changes for the present benefit assessment included changes in the inclusion criteria towards patients with a higher risk of recurrence (inclusion of patients with American Joint Committee on Cancer [AJCC] stages II–IIIc), discontinuation of the recording of patient-reported outcomes on morbidity and health-related quality of life, as well as discontinuation of follow-up observation in the study after 2 years and later resumption. Due to the discontinuation and resumption of the follow-up observation in the study, the patients had to provide a new consent to participate in the study. The outcomes "recurrence" and "overall survival" were recorded from patient records and no longer within an examination scheme in the framework of the study.

Data cut-offs

A total of 3 data cut-offs are available for the ExteNET study. The first data cut-off (7 July 2014) was the primary analysis on the 2-year period after randomization and provided results on the following relevant outcomes for the benefit assessment: recurrence, overall survival (no comparative analysis at this time point, as this was planned only for the time point after 248 deaths), health status (visual analogue scale [VAS] of the European Quality of Life-5 Dimensions [EQ-5D] questionnaire), health-related quality of life (FACT-B) and AEs. The later data cut-offs (second data cut-off from 15 April 2016 [at the request of the Food and Drug Administration (FDA) and the European Medicines Agency (EMA)]; third data cut-off from 1 March 2017) were updates of the primary analysis as well as interim and final planned analysis for the 5-year period after randomization for the outcome "recurrence". There is no comparative analysis for overall survival at these time points, as this was planned only for the time point after 248 deaths.

The first data cut-off was used for the present benefit assessment; the later data cut-offs (both after discontinuation and resumption of the follow-up observation in the study) were considered unusable. After discontinuation and resumption of follow-up observation in the study, structural equality between the treatment arms was no longer guaranteed, since a considerable proportion of patients did not consent to continue participation in the study (about 31% at the second data cut-off and about 25% at the third data cut-off). Besides, the ACT was no longer implemented after resumption of the follow-up observation (see also below). Hereinafter, all information and results refer to the first data cut-off. Hence, sufficiently valid data for the outcome "recurrence" were only available for a period of 2 years.

Relevant population for the benefit assessment

The ExteNET study included both hormone-receptor-positive and -negative women whose trastuzumab therapy had been completed less than 2 years ago. The analyses presented by the company comprised the subpopulation of hormone-receptor-positive patients regardless of the duration from completion of trastuzumab therapy to randomization. However, neratinib is only approved for hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago. The subgroup analyses presented by the company included data for the population defined in accordance with the approval, however (N = 670 versus N = 664). Hereinafter – unless stated otherwise – the results of this subpopulation, i.e. hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago, are described below and referred to as "relevant subpopulation".

Implementation of the appropriate comparator therapy watchful waiting

The investigations carried out in the ExteNET study sufficiently reflect the recommendations of the S3 guideline up to the first data cut-off. Due to a lack of data, it remains unclear how much time elapsed between the primary treatment of the patients and randomization. However, given the duration of the previous trastuzumab therapy and the time between trastuzumab therapy and randomization, it can be estimated that the patients were on average in the second year after primary treatment at the time point of randomization. Physical examinations were planned at baseline, after 1, 3, 6, 9 and 12 months, and every 3 months in the second year after randomization. Mammography was to be performed annually, imaging techniques (e.g. magnetic resonance imaging) according to clinical indication.

However, after discontinuation and resumption of follow-up observation in the ExteNET study, the ACT can no longer be considered implemented. Regular examinations within the study were no longer planned, and study documents show that the examination intervals were clearly above the recommendations for a high percentage of the patients at the second data cut-off.

Risk of bias

The risk of bias across outcomes was rated as low for the study. In contrast, the risk of bias for the results for all outcomes relevant for the benefit assessment was rated as high. The reason for this was the unclear proportion of values imputed with the last observation carried forward

(LOCF) method in the results for the outcome "recurrence". The risk of bias of the results on the patient-reported outcomes "health status" (EQ-5D VAS) and "health-related quality of life" (FACT-B) was rated as high because, on the one hand, the proportion of patients not included in the analysis was high (> 10%), and, on the other, blinding was not guaranteed due to the characteristic side effect profile of neratinib (such as gastrointestinal events). The risk of bias of the results on the outcomes "serious adverse events (SAEs)", "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" and "specific AEs" was rated as high, as the observations may be incomplete for potentially informative reasons. A high risk of bias was assumed for the results on the outcomes "discontinuation due to AEs" and "further specific AEs" because blinding may not have been fully guaranteed.

Mortality

Overall survival

No analyses were planned for the relevant data cut-off and therefore no results are available for this outcome. As a result, there was no hint of an added benefit of neratinib in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Recurrence

A statistically significant difference in favour of neratinib in comparison with placebo was shown for the composite outcome "recurrence". This resulted in a hint of an added benefit of neratinib in comparison with watchful waiting.

Health status (EQ-5D VAS)

There was no statistically significant difference between neratinib in comparison with placebo for the outcome "health status" recorded with the EQ-5D VAS. As a result, there was no hint of an added benefit of neratinib in comparison with watchful waiting; an added benefit is therefore not proven.

Health-related quality of life

(FACT-B total score)

There was no statistically significant difference between neratinib in comparison with placebo for the outcome "health-related quality of life" recorded with the FACT-B (total score). As a result, there was no hint of an added benefit of neratinib in comparison with watchful waiting; an added benefit is therefore not proven.

Side effects

Serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

There was a statistically significant difference between the treatment groups to the disadvantage of neratinib in comparison with placebo for SAEs, severe AEs (CTCAE grade ≥ 3) and

discontinuation due to AEs. This resulted in a hint of greater harm of neratinib in comparison with watchful waiting for SAEs and discontinuation due to AEs. Due to the large effect, high certainty of results was assumed for the severe AEs (CTCAE grade ≥ 3) despite the high risk of bias. This resulted in an indication of greater harm of neratinib in comparison with watchful waiting for the outcome "severe AEs (CTCAE grade ≥ 3)".

Specific adverse events

Severe AEs (CTCAE grade ≥ 3): gastrointestinal disorders (including: diarrhoea); AEs: muscle spasms

There was a statistically significant difference between the treatment groups to the disadvantage of neratinib in comparison with placebo for the specific AEs "gastrointestinal disorders (including diarrhoea)" and "muscle spasms". Since the specific AE "diarrhoea" is represented by the SOC "gastrointestinal disorders", it was not considered separately. In view of the magnitude of the observed effect in each case, it is not assumed that the biasing aspects call the observed effect into question. Hence, a high certainty of results in these outcomes is assumed despite the high risk of bias. In each case, this resulted in an indication of greater harm of neratinib in comparison with watchful waiting.

Severe AEs (CTCAE grade ≥ 3): fatigue, metabolism and nutrition disorders, nervous system disorders, investigations; AEs: skin and subcutaneous tissue disorders

There was a statistically significant difference between the treatment groups to the disadvantage of neratinib in comparison with placebo for the following specific AEs: fatigue, metabolism and nutrition disorders, nervous system disorders, investigations, and skin and subcutaneous tissue disorders. In each case, this resulted in a hint of greater harm of neratinib in comparison with watchful waiting.

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

Based on the results presented, probability and extent of the added benefit of the drug neratinib in comparison with the ACT are assessed as follows:

In the overall consideration, there was one positive effect and several negative effects of neratinib. The positive effect consisted of a hint of major added benefit in the outcome "recurrence". The added benefit in the outcome "recurrence" was based on a period of follow-up observation of 2 years from randomization. The advantage in the outcome "recurrence" was

[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].

accompanied by important disadvantages in side effects during the treatment phase. The decisive aspect for the negative effects was the indication of harm of major extent in the outcome category of serious/severe side effects in the outcome "gastrointestinal disorders".

In summary, an added benefit of neratinib versus the ACT watchful waiting is not proven for patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified breast cancer and who completed trastuzumab therapy less than 1 year ago.

No conclusions can be drawn on longer-term effects of neratinib therapy in the present therapeutic indication, since the observation period in the ExteNET study was a maximum of 2 years for recurrences and a maximum of 1 year for the outcomes "health status", "health-related quality of life" and "side effects" at the time point of the usable data cut-off.

Table 3 shows a summary of probability and extent of the added benefit of neratinib.

Table 3: Neratinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Extended adjuvant treatment of adult patients with early-stage hormone-receptor-positive HER2-overexpressed/ amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago	Watchful waiting	Added benefit not proven[b]
a. Presentation of the respective ACT specified by the G-BA. b. Only women were included in the ExteNET study. It remains unclear whether the observed effects can be transferred to men. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2		

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

2.2 Research question

The aim of the present report is the assessment of the added benefit of neratinib for the extended adjuvant treatment of patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago. The G-BA specified watchful waiting as ACT.

Table 4: Research questions of the benefit assessment of neratinib

Research question	Therapeutic indication	ACT[a]
1	Extended adjuvant treatment of adult patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago[b]	Watchful waiting[c]

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed that the patients receive additional endocrine therapy because they have a positive hormone receptor status.
c. Adjuvant chemotherapy, radiotherapy or endocrine therapy is not part of the ACT; this does not affect its use as a patient-specific treatment option.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

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

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on neratinib (status: 19 September 2019)
- bibliographical literature search on neratinib (last search on 19 September 2019)
- search in trial registries for studies on neratinib (last search on 19 September 2019)

To check the completeness of the study pool:

- search in trial registries for studies on neratinib (last search on 9 December 2019)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: neratinib vs. placebo

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
3144A2-3004-WW (ExteNET[b])	Yes	No	Yes

a. Study for which the company was sponsor.
b. In the following tables, the study is referred to with this abbreviated form.

RCT: randomized controlled trial; vs.: versus

Section 2.6 contains a reference list for the studies included.

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: neratinib vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ExteNET	RCT, double-blind, parallel	Adult women with ▪ early-stage histologically-confirmed primary adenocarcinoma of the breast ▪ stage I to stage IIIc[b] ▪ HER2-overexpressed/amplified ▪ prior adjuvant[c] therapy with trastuzumab[d] (up to 2 years before randomization)	Neratinib (N = 1420) placebo (N = 1420) Relevant subpopulation thereof[f]: neratinib (n = 670) placebo (n = 664)	Screening: 28 days Treatment: 1 year[g] Observation[h]: outcome-specific Study phases: Part A: until 2 years after randomization Part B: up to 5 years after randomization Part C: long-term follow-up until death of the last patient	476 centres in 39 countries[i] 7/2009–ongoing; Primary data cut-off: 7 July 2014 Further data cut-offs[j]: 15 April 2016 1 March 2017	Primary: disease-free survival Secondary: recurrence, overall survival, health status, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. According to AJCC classification (6th edition); following Protocol Amendment 3 (25 February 2010): stages II to IIIc and axillary node-positive disease.
c. Following Protocol Amendment 3 (25 February 2010), patients with prior neoadjuvant therapy (chemotherapy with or without neoadjuvant trastuzumab, irrespective of their nodal status at first diagnosis) were only included provided they had residual invasive disease in the breast and/or axilla after completion of neoadjuvant therapy.
d. The patients were unsuitable for further trastuzumab therapy, i.e. either (1) completion of the planned therapy or (2) discontinuation of the therapy due to side effects (the side effects should have subsided in the meantime).
e. Following Protocol Amendment 3 (25 February 2010), the period between completion of trastuzumab therapy and randomization had to be < 1 year.
f. The relevant subpopulation comprises patients with early-stage hormone-receptor-positive, HER2-overexpressed/amplified breast cancer after < 1 year of (post neo)adjuvant trastuzumab therapy.
g. As long as the treatment was tolerated, no recurrence or new illness occurred, or the informed consent was not withdrawn.
h. Outcome-specific information is provided in Table 9.
i. Australia, Bahamas, Belgium, Bulgaria, Canada, China, Colombia, Croatia, Czech Republic, Denmark, France, Germany, Great Britain; Greece, Hong Kong, Hungary, Israel, Italy, Japan, Lithuania, Malaysia, Malta, Mexico, Netherlands, New Zealand, North Macedonia, Peru, Poland, Romania, Serbia, Singapore, Slovakia, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, USA.
j. Final analysis planned after 248 deaths.

AE: adverse event; AJCC: American Joint Committee on Cancer; HER2: human epidermal growth factor receptor 2; n: relevant subpopulation; N: number of randomized (included) patients; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: neratinib vs. placebo

Study	Neratinib	Placebo
ExteNET	Neratinib 240 mg once daily, orally (6 tablets of 40 mg)	Placebo once daily, orally
	Dose adjustments, treatment interruptions and discontinuation due to intolerance permitted[a]; dose reductions in 40 mg steps down to 120 mg; treatment discontinuation in case of intolerance of the 120 mg dose	
	Required pretreatment ▪ mastectomy or breast-conserving surgery ▪ completed treatment with a neoadjuvant or adjuvant chemotherapy regimen (anthracycline and/or a taxane or any CMF regimen) ▪ trastuzumab therapy for at least 8 weekly doses or 3 doses every 3 weeks, completed > 2 weeks and < 1 year[b] before randomization **Non-permitted pretreatment** ▪ HER1 or HER2 inhibitors other than trastuzumab ▪ mediastinal irradiation except internal mammary node irradiation for the present breast cancer **Permitted concomitant treatment** ▪ loperamide and other drugs for the treatment of diarrhoea ▪ standard therapies for pre-existing medical conditions and for medical and/or surgical complications ▪ adjuvant endocrine therapy for hormone-receptor-positive disease ▪ bisphosphonates[c] ▪ selective oestrogen receptor modulators for the prevention of osteoporosis or osteopenia **Non-permitted concomitant treatment** ▪ during the treatment phase: chemotherapy, radiation therapy, immunotherapy, biotherapy, or surgery for the treatment of breast cancer	

a. Toxicity-related dose adjustments up to treatment discontinuation were made without relevant deviation from the requirements of the SPC.
b. Before Amendment 3 (25 February 2010), the period between completion of trastuzumab therapy and randomization had to be < 2 years.
c. Before Amendment 3 (25 February 2010), only allowed for specific therapeutic indications.

AE: adverse event; CMF: cyclophosphamide, methotrexate and 5-fluorouracil; HER: human epidermal growth factor receptor; RCT: randomized controlled trial; SPC: Summary of Product Characteristics; vs.: versus

The ExteNET study was a randomized, double-blind study comparing treatment with neratinib against placebo. The study included adult women with early-stage HER2-overexpressed/ amplified breast cancer. The breast cancer had to be histologically confirmed. Men were not included in the study.

Adequate pretreatment was required in order to be eligible for the study. This included surgery, in which the surgical margins had to be free of invasive carcinoma or ductal carcinoma in situ, as well as completed chemotherapy. The patients also had to have been given a previous trastuzumab treatment. If this lasted less than 12 months, at least 8 weekly doses or 3 doses every 3 weeks were required. The patients were not allowed to be eligible for further trastuzumab therapy.

If the patients had received neoadjuvant therapy, they were eligible for the study, provided they did not show pathological complete response. Patients were excluded from participation in the study if they had a ductal carcinoma in situ and a pathological complete response in the axilla.

Overall, 2840 patients were randomly allocated in a 1:1 ratio either to treatment with neratinib (N = 1420) or to placebo (N = 1420). Randomization was stratified by hormone receptor status (positive/ negative), nodal status (0/1–3/≥ 4), type of administration of prior trastuzumab therapy (concurrent with chemotherapy/sequential to chemotherapy).

Treatment with neratinib was in compliance with the SPC [3]. The patients were treated with neratinib or placebo until occurrence of recurrence or another criterion for discontinuation (patient request, AEs, protocol violation, or death), but at most for 1 year. Following disease progression or for emergency treatment of AEs, the patient and physician could be unblinded individually upon request to the sponsor.

Primary outcome of the study was DFS; patient-relevant secondary outcomes were recurrence, overall survival, health status, health-related quality of life, and AEs.

Protocol amendments

In the course of the ExteNET study, there were a total of 13 protocol amendments to the original protocol from 29 April 2009. Only the most important changes are presented below.

Amendment 3 (25 February 2010)

Originally, the patients in the study had to be node-negative or node-positive and have AJCC stage I–IIIc disease. Following Amendment 3 (25 February 2010), the inclusion criteria were revised to only include patients with a higher risk of recurrence. This means that the patients had to be node-positive and have AJCC stage II–IIIc disease. In clinical practice, neratinib is also administered to patients with a low risk of recurrence, i.e. node-negative or positive and stage I–III [3].

Also with Amendment 3, the time between the end of trastuzumab therapy and randomization in the ExteNET study was limited to a maximum of 1 year. Originally, the patients had to have completed their trastuzumab therapy within 2 years before randomization.

Amendment 9 (14 October 2011)

With Amendment 9 (14 October 2011), enrolment of new patients was stopped. The overall number of 337 recurrence events planned for the final analysis (equivalent to about 5 years of follow-up observation) and 2 planned interim analyses were cancelled. The follow-up period for recurrence and overall survival was limited from 5 to 2 years after randomization. Besides, the recording of patient-reported outcomes on health status and health-related quality of life was discontinued.

Amendment 13 (16 January 2014)

With Amendment 13 (16 January 2014), the previously shortened follow-up period for the outcome "recurrence" was extended again for all patients to 5 years after randomization and for the outcome "overall survival" until death of the last included patient. It was then attempted to obtain new consent for participation in the study from all randomized patients. The outcomes "recurrence" and "overall survival" were to be recorded from medical records.

A detailed description of the effects of the discontinuation and the resumption of the follow-up observation in the ExteNET study can be found in Section 2.7.4.1 of the full dossier assessment.

Data cut-offs

A total of 3 data cut-offs are available for the ExteNET study.

- First data cut-off (7 July 2014): primary analysis on the 2-year period after randomization (Part A), results on the following relevant outcomes for the benefit assessment: recurrence, overall survival (no comparative analysis at this time point, as this was planned only for the time point after 248 deaths), health status, health-related quality of life, AEs
- Second data cut-off (15 April 2016): updates of the primary analysis for the investigation of the influence of the rate of treatment discontinuations in the primary analysis, interim analysis in the 5-year period after randomization (Part B), at the request of the FDA and the EMA, results on the outcomes "recurrence" and "overall survival" (no comparative analysis at this time point, as this was planned only for the time point after 248 deaths)
- Third data cut-off (1 March 2017): new updates of the primary analysis for the investigation of the influence of the rate of treatment discontinuations in the primary analysis, final planned analysis for the 5-year period after randomization (Part B), results on the outcomes "recurrence" and "overall survival" (no comparative analysis at this time point, as this was planned only for the time point after 248 deaths)

The first data cut-off was used for the present benefit assessment. The results of the later data cut-offs were not considered usable. This was due to 2 reasons: Firstly, structural equality between the treatment arms was no longer guaranteed, as a considerable proportion of patients did not consent to re-participation for the recording of recurrences and overall survival (see Amendment 13). Secondly, the ACT was not implemented after resumption of the study. Detailed comments on this are provided in Section 2.7.4.1 of the full dossier assessment. Hence, sufficiently valid data for the outcome "recurrence" were only available for a very short period of 2 years. The S3 guideline specifies a follow-up of at least 10 years in the present therapeutic indication [4]. Hereinafter, all information and results refer to the first data cut-off. The company also used the first data cut-off for the dossier of the present benefit assessment, but presented the other data cut-offs as supplementary information. It did not provide a justification for its approach.

Relevant population for the benefit assessment

The ExteNET study included both hormone-receptor-positive and -negative women whose trastuzumab therapy had been completed less than 2 years ago. The analyses presented by the company comprised the subpopulation of hormone-receptor-positive patients regardless of the duration from completion of trastuzumab therapy to randomization. This subpopulation comprised 816 patients in the neratinib arm and 815 patients in the placebo arm. However, neratinib is only approved for hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago. The company conducted subgroup analyses for the characteristic "time between last trastuzumab therapy and randomization (< 1 year/≥ 1 year)". These analyses included the population defined in accordance with the approval (N = 670 versus N = 664). Hereinafter – unless stated otherwise – the results of this subpopulation, i.e. hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago, are considered below and referred to as "relevant subpopulation".

Appropriate comparator therapy

Operationalization of watchful waiting

For the present benefit assessment, the ACT watchful waiting, as determined by the G-BA, was operationalized as a follow-up strategy, which comprises in particular the diagnosis of recurrences according to the S3 Guideline on Early Detection, Diagnostics, Therapy and Follow-up of Breast Cancer [4]. Follow-up includes medical history, physical examinations, medical consultation, care and support as well as imaging diagnostics. According to the S3 guideline, the time frame for follow-up should be at least 10 years.

Table 8 shows the follow-up regimen of the S3 guideline [4].

Table 8: Follow-up regimen according to S3 guideline

Examination	**Time since primary treatment**					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6–10**
S3 guideline (2019)						
Physical examination	Every 3 months			Every 6 months		Annually
Mammography	Once a year, supplemental sonography					
Imaging diagnostics/laboratory	Non-standard prevention, indicated for clinical abnormalities					

Implementation of watchful waiting in the ExteNET study

For the period of the 2 years after randomization, i.e. for the period up to the first data cut-off, the examination scheme applied in the ExteNET study was considered sufficiently appropriate for the benefit assessment. Due to a lack of data, it remains unclear how much time elapsed between the primary treatment of the patients and randomization. However, given the duration of the previous trastuzumab therapy and the time between trastuzumab therapy and randomization, it can be estimated that the patients were in the second year after primary treatment at the time point of randomization. In the study, physical examinations were planned

at baseline, after 1, 3, 6, 9 and 12 months, and every 3 months in the second year after randomization. Mammography was to be performed annually, imaging techniques (e.g. magnetic resonance imaging) according to clinical indication. This procedure is sufficiently similar to current guidelines, in which quarterly clinical examination is recommended in the first 3 years after primary treatment of breast cancer, and 6-monthly clinical examination in the fourth and fifth year after primary treatment [4,5].

After discontinuation and resumption of follow-up observation in the ExteNET study, the ACT is no longer considered implemented. This is explained in Section 2.7.4.1 of the full dossier assessment.

Treatment/dose reductions

In the ExteNET study, treatment with neratinib was conducted according to the regimen described in Table 7 and was in compliance with the SPC. According to this, the dose of the study medication was to be taken for 1 year and reduced in case of unacceptable toxicity. Results on dose reductions due to AEs were not available for the relevant subpopulation. In the total population, 439 (31.2%) of the patients in the neratinib arm and 36 (2.6%) of the patients in the placebo arm experienced AEs that resulted in dose adjustment.

Subsequent therapies

Subsequent therapies could be conducted without restrictions after discontinuation of the study medication. There were no data on subsequent therapies for the relevant subpopulation. Regarding the subpopulation of hormone-receptor-positive patients, irrespective of the duration from completion of trastuzumab therapy to randomization, considered by the company, a total of 3.3% of the patients in the neratinib arm and 6.5% of the patients in the placebo arm received subsequent antineoplastic therapy. Although one of the study's inclusion criteria was that the patients should no longer be eligible for trastuzumab therapy, 2.0% of the patients in the neratinib arm and 4.2% of the patients in the placebo arm received trastuzumab as subsequent therapy. These small proportions had no influence on the benefit assessment, however.

The version of the original protocol from 29 September 2009 mandated patients to switch from the placebo arm to the neratinib arm after completion of the treatment phase if the study produced positive results for neratinib. This possibility was ended by Amendment 9 of 14 October 2011.

Subsequent therapies in the subpopulation of hormone-receptor-positive patients, regardless of the time from completion of trastuzumab therapy to randomization, are presented in Table 31 in Appendix C of the full dossier assessment.

Planned duration of follow-up observation

Table 9 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 9: Planned duration of follow-up observation – RCT, direct comparison: neratinib vs. placebo

Study **Outcome category** **Outcome**	**Planned follow-up observation**
ExteNET	
Mortality	
Overall survival	Until death or withdrawal of consent[a, b]
Morbidity	
Recurrence	Until 5 years + 90 days[b] after randomization or discontinuation due to occurrence of distant metastases
Health status (EQ-5D VAS)[c]	Until final study visit after discontinuation of the study medication
Health-related quality of life	
FACT-B[c]	Until final study visit after discontinuation of the study medication
Side effects	
All outcomes in the category "side effects"	Until 28 days after discontinuation of the study medication[d] or until initiation of subsequent therapy (in case of non-serious AEs)

a. Final analysis planned after 248 deaths.
b. In the framework of Protocol Amendment 9 (14 October 2011), the observation period was limited to 2 years and extended again with Amendment 13 (16 January 2014).
c. The recording of patient-reported outcomes was stopped with Amendment 9 (14 October 2011).
d. SAEs, if known, were to be reported also after the 28 days after discontinuation of study medication.

AE: adverse event; EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes "health status", "health-related quality of life" and "side effects" were systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 28 days). Furthermore, the observation periods for the outcomes "health status" and "health-related quality of life" were shortened by the discontinuation of the recording with Amendment 9 (14 October 2011). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for recurrence and overall survival.

Information on the characteristics of the study population is not available for the relevant subpopulation, but only for the subpopulation of hormone-receptor-positive patients, regardless of the duration from completion of trastuzumab therapy to randomization. Table 10 shows the characteristics of these patients in the included study.

Table 10: Characteristics of the study population (hormone-receptor-positive patients regardless of the duration from completion of trastuzumab therapy) – RCT, direct comparison: neratinib vs. placebo (multipage table)

Study **Characteristics** **Category**	**Neratinib** **N[a] = 816**	**Placebo** **N[a] = 815**
ExteNET		
Age [years], mean (SD)	51 (10)	51 (10)
Sex [F/M], %	100/0	100/0
Region[b], n (%)		
Europe	389 (47.7)	403 (49.4)
North America	303 (37.1)	275 (33.7)
Rest of the world	124 (15.2)	137 (16.8)
Family origin, n (%)		
Caucasian	690 (84.6)	675 (82.8)
Asian	89 (10.9)	98 (12.0)
African American	15 (1.8)	25 (3.1)
Other	22 (2.7)	17 (2.1)
Nodal status, n (%)		
0 positive lymph nodes	187 (22.9)	188 (23.1)
1–3 positive lymph nodes	393 (48.2)	394 (48.3)
≥ 4 positive lymph nodes	236 (28.9)	233 (28.6)
AJCC stage at diagnosis, n (%)		
Stage I	94 (11.5)	100 (12.3)
Stage II	347 (42.5)	328 (40.2)
Stage III	240 (29.4)	233 (28.6)
Unknown	135 (16.5)	154 (18.9)
Menopausal status, n (%)		
Premenopausal	425 (52.1)	417 (51.2)
Postmenopausal	391 (47.9)	398 (48.8)
ECOG PS, n (%)		
0	764 (93.6)	741 (90.9)
1	50 (6.1)	72 (8.8)
Unknown	2 (0.2)	2 (0.2)
Time between first diagnosis and randomization [months], mean (SD)	23.8 (7.9)	23.6 (7.3)
Prior endocrine therapy, n (%)		
Yes	772 (94.6)	774 (95.0)
No	44 (5.4)	41 (5.0)
Time between last trastuzumab therapy and randomization, n (%)		
< 1 year	670 (82.1)	664 (81.5)
≥ 1 year	146 (17.9)	151 (18.5)

Table 10: Characteristics of the study population (hormone-receptor-positive patients regardless of the duration from completion of trastuzumab therapy) – RCT, direct comparison: neratinib vs. placebo (multipage table)

Study **Characteristics** **Category**	**Neratinib** **N[a] = 816**	**Placebo** **N[a] = 815**
Duration of prior trastuzumab therapy, n (%)		
< 1 year	649 (79.5)	659 (80.9)
≥ 1 year	162 (19.9)	154 (18.9)
Unknown	5 (0.6)	2 (0.2)
Type of administration of prior trastuzumab therapy, n (%)		
Concurrent with chemotherapy	506 (62.0)	508 (62.3)
Sequential to chemotherapy	310 (38.0)	307 (37.7)
Type of prior chemotherapy, n (%)		
Anthracycline plus taxane	534 (65.4)	543 (66.6)
Taxane only	197 (24.1)	192 (23.6)
Anthracycline only	84 (10.3)	78 (9.6)
Anthracycline- and taxane-free	1 (0.1)	2 (0.2)
Prior radiotherapy, n (%)		
Yes	648 (79.4)	671 (82.3)
No	168 (20.6)	144 (17.7)
Prior surgery, n (%)		
Mastectomy	530 (65.0)	510 (62.6)
Breast-conserving surgery	285 (34.9)	305 (37.4)
Unknown	1 (0.1)	0
Treatment discontinuation, n (%)	324 (39.7)[c, d]	136 (16.7)[c, d]
Study discontinuation, n (%)	177 (21.7)[d]	136 (16.7)[d]

a. Number of randomized patients of the hormone-receptor-positive population regardless of the duration from completion of trastuzumab therapy. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. North America: Bahamas, Canada, USA; Europe: Belgium, Bulgaria, Croatia, Czech Republic, Denmark, France, Germany, Great Britain, Greece, Hungary, Italy, Lithuania, Malta, Netherlands, North Macedonia, Poland, Romania, Serbia, Slovakia, Spain, Sweden, Switzerland, Turkey; rest of the world: Australia, China, Columbia, Hong Kong, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, South Korea, Taiwan.
c. The 9 patients in the neratinib arm and 7 patients in the placebo arm who did not receive any study medication are not considered as treatment discontinuations.
d. Institute's calculation.

AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Even though the therapeutic indication according to the approval refers to women and men, all study participants were women. The mean age of the patients in the subpopulation of hormone-receptor-positive patients, regardless of the duration since completion of trastuzumab therapy,

was 51 years. Half of the study participants lived in Europe, 1 third in North America. About 70% of the patients were in AJCC stages II and III. As can be expected in the present therapeutic indication, the majority of patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0. All patients had previously undergone surgery to treat breast cancer. In almost 2 thirds of the patients, this surgery was mastectomy. Overall, the demographic and clinical characteristics in the population of hormone-receptor-positive patients, regardless of the duration from completion of trastuzumab therapy to randomization, were comparable between the treatment arms.

Table 11 shows the mean and median treatment durations of the patients and the mean and median observation periods for the individual outcomes. Information on the treatment duration and the observation period is not available for the relevant subpopulation, but only for the subpopulation of hormone-receptor-positive patients, regardless of the duration from completion of trastuzumab therapy.

Table 11: Information on the course of the study (hormone-receptor-positive patients regardless of the duration from completion of trastuzumab therapy) – RCT, direct comparison: neratinib vs. placebo

Study **Duration of the study phase** **Outcome category**	**Neratinib** **N = 816**	**Placebo** **N = 815**
ExteNET		
Treatment duration [months] (first data cut-off 7 July 2014)		
Median [Q1; Q3]	11.5 [1.9; 11.9]	11.9 [11.5; 12.0]
Mean (SD)	8.1 (4.9)	10.7 (2.9)
Observation period [months] (first data cut-off 7 July 2014)		
Mortality (overall survival)		
Median [Q1; Q3]	24.6 [23.8; 26.9]	24.7 [23.9; 27.2]
Mean (SD)	23.8 (8.7)	24.8 (6.7)
Morbidity (recurrence)		
Median [Q1; Q3]	24.0 [19.8; 25.0]	24.0 [22.0; 24.9]
Mean (SD)	20.0 (7.9)	21.1 (6.5)
Morbidity (health status [EQ-5D VAS])		
Median [Q1; Q3]	8.8 [1.9; 11.8]	11.6 [6.1; 12.0]
Mean (SD)	7.1 (4.7)	9.2 (3.8)
Health-related quality of life (FACT-B)		
Median [Q1; Q3]	8.8 [1.8; 11.8]	11.5 [6.1; 12.0]
Mean (SD)	7.1 (4.8)	9.2 (3.9)
Side effects		
Median [Q1; Q3]	12.5 [2.8; 12.9]	12.8 [12.4; 12.9]
Mean (SD)	9.0 (4.9)	11.6 (2.9)

EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

The median treatment duration was similar in both study arms (neratinib arm 11.5 months versus placebo arm 11.9 months), but the mean treatment duration differed notably (8.1 versus 10.7 months). Neither the median nor the mean observation periods for the outcomes “overall survival” and “recurrence” differed between the arms. Both the mean (7.1 versus 9.2 months) and the median (8.8 versus 11.6 and 11.5 months) observation periods of the patient-reported outcomes “health status” and “health-related quality of life” differed between the arms. Regarding side effects, the median values of the neratinib and placebo arm were quite similar (12.5 versus 12.8 months), but the mean values differed notably (9.0 versus 11.6 months).

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: neratinib vs. placebo

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			
ExteNET	Yes	Yes	Unclear[a]	Unclear[a]	Yes	Yes	Low

a. Due to the known side effect profile of neratinib, blinding of patients and treating staff may not be fully guaranteed.

RCT: randomized controlled trial; vs.: versus

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

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - recurrence
  - health status measured with the EQ-5D VAS
- Health-related quality of life
  - health-related quality of life measured with the FACT-B
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.4.3 of the full dossier assessment).

Table 13 shows for which outcomes data were available in the study included.

Table 13: Matrix of outcomes – RCT, direct comparison: neratinib vs. placebo

Study	Outcomes								
	Overall survival	Recurrence[a]	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Diarrhoea (PT, severe AEs)	Further specific AEs[b]
ExteNET	No[c]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Proportion of the patients with distant metastases, invasive contralateral breast cancer, invasive ipsilateral breast cancer, local/regional recurrence, ductal carcinoma in situ or death from any cause (see Section 2.7.4.3.2 of the full dossier assessment).
b. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, CTCAE grade ≥ 3), fatigue (PT, CTCAE grade ≥ 3), metabolism and nutrition disorders (SOC, CTCAE grade ≥ 3), muscle spasms (PT, AE), nervous system disorders (SOC, CTCAE grade ≥ 3), skin and subcutaneous tissue disorders (SOC, AE), and investigations (SOC, CTCAE grade ≥ 3).
c. No analysis was planned at the time point of the first data cut-off (see Section 2.7.4.3.2 of the full dossier assessment).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: neratinib vs. placebo

Study	Study level	Outcomes								
		Overall survival	Recurrence[a]	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade ≥ 3)	Diarrhoea (PT, severe AEs)	Further specific AEs[b]
ExteNET	L	–[c]	H[d]	H[e, f]	H[e, f]	H[g]	H[f]	H[g]	H[g]	H[g, f]

a. Proportion of the patients with distant metastases, invasive contralateral breast cancer, invasive ipsilateral breast cancer, local/regional recurrence, ductal carcinoma in situ or death from any cause (see Section 2.7.4.3.2 of the full dossier assessment).
b. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, CTCAE grade ≥ 3), fatigue (PT, CTCAE grade ≥ 3), metabolism and nutrition disorders (SOC, CTCAE grade ≥ 3), muscle spasms (PT, AE), nervous system disorders (SOC, CTCAE grade ≥ 3), skin and subcutaneous tissue disorders (SOC, AE), and investigations (SOC, CTCAE grade ≥ 3).
c. No analysis was planned at the time point of the first data cut-off (see Section 2.7.4.3.2 of the full dossier assessment).
d. Unclear proportion of LOCF-imputed values; in the population of hormone-receptor-positive patients, 19.1% discontinued the study.
e. Large proportion of patients not included in the analysis (> 10%); increasing proportion of missing values in the course of the study, which also differs notably between the treatment arms.
f. Possibly not fully guaranteed blinding in subjective recording of outcomes (exception: severe specific AEs) or in subjective request for discontinuation (discontinuation due to AEs).
g. Incomplete observations for potentially informative reasons.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; H: high; L: low; LOCF: last observation carried forward; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The risk of bias for the results for all outcomes relevant for the benefit assessment was rated as high. The reason for this was the unclear proportion of values imputed with the LOCF method in the results for the outcome "recurrence". The risk of bias of the results on the patient-reported outcomes "health status" (EQ-5D VAS) and "health-related quality of life" (FACT-B) was rated as high. The reasons were, on the one hand, that blinding in subjective recording of outcomes was not guaranteed due to the characteristic side effect profile of neratinib (such as gastrointestinal events). On the other, there was a large proportion of patients (> 10%) who were not considered in the respective analyses. The risk of bias of the results on the outcomes "SAEs", "severe AEs (CTCAE grade ≥ 3)" and "specific AEs" was rated as high, as the observations may be incomplete for potentially informative reasons. For the results for the outcome "discontinuation due to AEs" and for further non-serious or severe specific AEs, a

high risk of bias was also assumed due to the possibly not fully guaranteed blinding in subjective recording of outcomes or subjective request for discontinuation (detailed explanations can be found in Section 2.7.4.2 of the full dossier assessment).

This deviates from the assessment of the company, which assumed a low risk of bias except in the patient-reported outcomes. The company considered the risk of bias of the patient-reported outcomes as high due to the discontinued recording based on Amendment 9 (14 October 2011).

2.4.3 Results

Table 15, Table 16 and Table 17 summarize the results on the comparison of neratinib with placebo in patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified breast cancer and who completed trastuzumab therapy less than 1 year ago (relevant subpopulation). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. If available, Kaplan-Meier curves on the outcomes included are presented in Appendix A of the full dossier assessment.

Tables with the common AEs, SAEs, severe AEs and discontinuations due to AEs can be found in Appendix B of the full dossier assessment. The company did not present analyses for all System Organ Classes (SOCs) and Preferred Terms (PTs) for the relevant subpopulation. The available analyses for common AEs according to SOC and PT were from the subgroup analyses conducted by the company on the characteristic "time between last trastuzumab therapy and randomization". Due to the methods used for conducting the subgroup analyses, there were no analyses on isolated common AEs, SAEs and severe AEs for the relevant subpopulation. In the corresponding places, the numbers of AEs from the population of hormone-receptor-positive patients, regardless of the time since completion of trastuzumab therapy, were presented and marked accordingly.

Table 15: Results (mortality, side effects, time to event) for hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago – RCT, direct comparison: neratinib vs. placebo

Study	Neratinib		Placebo		Neratinib vs. placebo
Outcome category **Outcome**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
ExteNET					
Mortality					
Overall survival	No analysis planned at the relevant data cut-off[b]				
Side effects					
AEs (supplementary information)	662	0.1 [ND[c]] 649 (98.0)	657	0.8 [0.6; 0.9] 567 (86.3)	–
SAEs	662	NA 45 (6.8)	657	NA 36 (5.5)	1.56 [1.00; 2.43]; 0.047
Severe AEs (CTCAE grade ≥ 3)	662	8.6 [5.8; NC] 327 (49.4)	657	NA 76 (11.6)	6.28 [4.92; 8.12]; < 0.001
Discontinuation due to AEs	662	NA 178 (26.9)	657	NA 30 (4.6)	7.00 [4.83; 10.51]; < 0.001
Gastrointestinal disorders (SOC, CTCAE grade ≥ 3)[d]	662	NA 280 (42.3)	657	NA 14 (2.1)	27.10 [16.47; 48.66]; < 0.001
Including: diarrhoea (PT, CTCAE grade ≥ 3)	662	NA 261 (39.4)	657	NA 7 (1.1)	49.55 [25.29; 116.28]; < 0.001
Fatigue (PT, CTCAE grade ≥ 3)	662	NA 13 (2.0)	657	NA 2 (0.3)	7.51 [2.07; 48.08]; 0.002
Metabolism and nutrition disorders (SOC, CTCAE grade ≥ 3)	662	NA 20 (3.0)	657	NA 10 (1.5)	2.36 [1.13; 5.26]; 0.023
Muscle spasms (PT, AE)	662	NA 81 (12.2)	657	NA 22 (3.3)	4.71 [2.99; 7.73]; < 0.001
Nervous system disorders (SOC, CTCAE grade ≥ 3)	662	NA 19 (2.9)	657	NA 8 (1.2)	2.73 [1.24; 6.64]; 0.013
Skin and subcutaneous tissue disorders (SOC, AE)	662	NA 221 (33.4)	657	NA 139 (21.2)	2.05 [1.66; 2.54]; < 0.001
Investigations (SOC, CTCAE grade ≥ 3)	662	NA 20 (3.0)	657	NA 8 (1.2)	3.10 [1.41; 7.49]; 0.004

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each unstratified.
b. Analysis of overall survival in the study is to be conducted only with the 248th death (see Section 2.7.4.3.2 of the full dossier assessment). There are no data on deaths for the relevant subpopulation. In the population of hormone-receptor-positive patients, regardless of the time from completion of trastuzumab therapy to randomization, there were 9 deaths in the neratinib arm and 14 deaths in the placebo arm at the first data cut-off.
c. The company indicates the 95% CI for the median time to event as "not achieved". This is not plausible in view of the frequency of events, however.
d. Includes the PTs "abdominal pain", "diarrhoea", "vomiting".

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 16: Results (morbidity, dichotomous) for hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago – RCT, direct comparison: neratinib vs. placebo

Study Outcome category Outcome	Neratinib N	Neratinib Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Neratinib vs. placebo RR [95% CI]; p-value[a]
ExteNET					
Morbidity					
Recurrence[b]	670	26 (3.9)	664	60 (9.0)	0.43 [0.27; 0.67]; < 0.001
Events included in the composite outcome					
Distant metastases	670	20 (3.0)	664	38 (5.7)	–[c]
Invasive contralateral breast cancer	670	1 (0.1)	664	2 (0.3)	–[c]
Invasive ipsilateral breast cancer	670	1 (0.1)	664	2 (0.3)	–[c]
Local/regional invasive recurrence	670	3 (0.4)	664	12 (1.8)	–[c]
Ductal carcinoma in situ	670	0 (0)	664	5 (0.8)[d]	–[c]
Death from any cause	670	1 (0.1)	664	1 (0.2)	–[c]
Recurrence-free survival[b] (supplementary presentation)	670	Median time to event: NA	664	Median time to event: NA	HR: 0.45 [0.28; 0.71]; < 0.001[e]

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [6]).
b. Composite outcome consisting of the following components: distant metastases, invasive contralateral breast cancer, invasive ipsilateral breast cancer, local/regional invasive recurrence, ductal carcinoma in situ, or death from any cause, whichever occurred first (see Section 2.7.4.3.2 of the full dossier assessment); the components are presented in the lines underneath.
c. No calculation of the effect estimations. The presented events do not completely represent the outcome. Only events that were relevant for the formation of the composite outcome are presented.
d. Institute's calculation.
e. HR and CI: Cox proportional hazards model; p-value: log-rank test; each unstratified.

CI: confidence interval; CSZ: convexity, symmetry, z score; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 17: Results (morbidity, health-related quality of life, continuous) for hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago – RCT, direct comparison: neratinib vs. placebo

Study Outcome category	Neratinib			Placebo			Neratinib vs. placebo
Outcome Subscale	N[a]	Values at baseline mean (SD)	Change[b] Mean [95% CI][c]	N[a]	Values at baseline mean (SD)	Change[b] Mean [95% CI][c]	MD [95% CI]; p-value[c]
ExteNET							
Morbidity							
Health status (EQ-5D VAS[d])	549	ND	−2.96 [−3.85; −2.07]	568	ND	−2.50 [−3.32; −1.68]	−0.46 [−1.67; 0.75]; 0.459
Health-related quality of life							
FACT-B (total score)[d]	541	ND	−3.74 [−4.69; −2.79]	566	ND	−3.09 [−3.97; −2.22]	−0.64 [−1.94; 0.65]; 0.329
Presented as supplementary information:							
BCS	541	ND	0.45 [0.15; 0.76]	566	ND	−0.17 [−0.45; 0.11]	0.62 [0.20; 1.04]; 0.004
PWB					ND		
SWB					ND		
EWB					ND		
FWB					ND		

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at baseline (possibly at other time points) may be based on other patient numbers.
b. Averaged over months 1–12.
c. Mean and CI (change per treatment group) and MD, CI and p-value (group comparison): least-square estimation from MMRM adjusted for treatment, visit and baseline value, and interaction terms for treatment and visit.
d. A positive change from baseline to end of study indicates improvement; a positive effect estimation indicates an advantage for the intervention.

BCS: Breast Cancer Subscale; CI: confidence interval; EWB: emotional well-being; EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; FWB: functional well-being; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; PWB: physical well-being; RCT: randomized controlled trial; SD: standard deviation; SWB: social and family well-being; VAS: visual analogue scale; vs.: versus

On the basis of the available data, due to the high risk of bias, at most hints, e.g. of an added benefit, can be determined for the following outcomes: recurrence, health status, health-related quality of life, SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs, and specific AEs. The outcome-specific certainty of the results may not be downgraded, however.

For the present benefit assessment, the added benefit was derived on the basis of the relevant subpopulation (hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago). This deviates from the approach of the company, which used hormone-

receptor-positive patients regardless of the duration from completion of trastuzumab therapy until randomization.

Mortality

Overall survival

No analyses were planned for the relevant data cut-off and therefore no results are available for this outcome. A final analysis was to be conducted after 248 deaths. In the population of hormone-receptor-positive patients, regardless of the time from completion of trastuzumab therapy to randomization, there were 9 deaths in the neratinib arm and 14 deaths in the placebo arm. As a result, there was no hint of an added benefit of neratinib in comparison with watchful waiting; an added benefit is therefore not proven.

This concurs with the company's assessment, but on the basis of the population considered by the company.

Morbidity

Recurrence

A statistically significant difference in favour of neratinib in comparison with placebo between the treatment groups was shown for the composite outcome "recurrence". This resulted in a hint of an added benefit of neratinib in comparison with watchful waiting.

This deviates from the company's assessment. The company interpreted the morbidity outcomes together and derived an indication of an added benefit, but on the basis of the population considered by the company.

Health status (EQ-5D VAS)

There was no statistically significant difference between neratinib in comparison with placebo for the outcome "health status" recorded with the EQ-5D VAS. As a result, there was no hint of an added benefit of neratinib in comparison with watchful waiting; an added benefit is therefore not proven.

This deviates from the company's assessment. The company interpreted the morbidity outcomes together and derived an indication of an added benefit, but on the basis of the population considered by the company.

Health-related quality of life

FACT-B (total score)

There was no statistically significant difference between neratinib in comparison with placebo for the outcome "health-related quality of life" recorded with the FACT-B (total score). As a result, there was no hint of an added benefit of neratinib in comparison with watchful waiting; an added benefit is therefore not proven.

This concurs with the company's assessment, but on the basis of the population considered by the company.

Side effects

Serious adverse events, severe adverse events (CTCAE grade ≥ 3) and discontinuation due to adverse events

There was a statistically significant difference between the treatment groups to the disadvantage of neratinib in comparison with placebo for SAEs, severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs. This resulted in a hint of greater harm of neratinib in comparison with watchful waiting for SAEs and discontinuation due to AEs. Due to the large effect, high certainty of results was assumed for the severe AEs (CTCAE grade ≥ 3) despite the high risk of bias. This resulted in an indication of greater harm of neratinib in comparison with watchful waiting for the outcome "severe AEs (CTCAE grade ≥ 3)".

This deviates from the company's assessment for SAEs and discontinuation due to AEs, but concurred with the company's assessment for severe AEs (CTCAE grade ≥ 3). The company interpreted the side effect outcomes together and derived an indication of greater harm, but on the basis of the population considered by the company.

Specific adverse events

Severe AEs (CTCAE grade ≥ 3): gastrointestinal disorders (including: diarrhoea); AEs: muscle spasms

There was a statistically significant difference between the treatment groups to the disadvantage of neratinib in comparison with placebo for the specific AEs "gastrointestinal disorders (including diarrhoea)" and "muscle spasms". Since the specific AE "diarrhoea" is represented by the SOC "gastrointestinal disorders", it was not considered separately. In view of the magnitude of the observed effect in each case, it is not assumed that the biasing aspects call the observed effect into question. Hence, a high certainty of results in these outcomes is assumed despite the high risk of bias. In each case, this resulted in an indication of greater harm of neratinib in comparison with watchful waiting.

This concurs with the company's assessment. The company interpreted the side effect outcomes together and derived an indication of greater harm, but on the basis of the population considered by the company.

Severe AEs (CTCAE grade ≥ 3): fatigue, metabolism and nutrition disorders, nervous system disorders, investigations; AEs: skin and subcutaneous tissue disorders

There was a statistically significant difference between the treatment groups to the disadvantage of neratinib in comparison with placebo for the following specific AEs: fatigue, metabolism and nutrition disorders, nervous system disorders, investigations, and skin and subcutaneous tissue disorders. In each case, this resulted in a hint of greater harm of neratinib in comparison with watchful waiting.

This deviates from the company's assessment. The company interpreted the side effect outcomes together and derived an indication of greater harm, but on the basis of the population considered by the company.

2.4.4 Subgroups and other effect modifiers

No results on subgroups or other effect modifiers are available for the subpopulation of hormone-receptor-positive patients who completed trastuzumab therapy less than 1 year ago, which is the subpopulation relevant for the benefit assessment.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.5.1 Assessment of the added benefit at outcome level

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

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

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

Recurrence

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

Discontinuation due to adverse events

It remains unclear whether the events included in the outcome "discontinuations due to AEs" were rather serious/severe or non-serious/non-severe. The outcome was therefore allocated to non-serious/non-severe outcomes.

Specific adverse events

Almost exclusively non-serious/non-severe events were included in the specific AEs "muscle spasms" (PT, AE) and "skin and subcutaneous tissue disorders" (SOC, AE), which is why these outcomes were allocated to the same category.

Table 18: Extent of added benefit at outcome level: neratinib vs. placebo (multipage table)

Outcome category **Outcome**	**Neratinib vs. placebo** **Median time to event (months) or proportion of events (%) or mean** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	No analysis planned at the time point of the relevant data cut-off[c]	Lesser benefit/added benefit not proven
Morbidity		
Recurrence	Proportions of events: 3.9% vs. 9.0% RR: 0.43 [0.27; 0.67] p < 0.001 probability: "hint"	Outcome category: serious/severe symptoms/late complications CI_u < 0.75, risk ≥ 5% added benefit, extent: "major"
Health status (EQ-5D VAS)	Mean: −2.96 vs. −2.50 MD: −0.46 [−1.67; 0.75] p = 0.459	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-B (total score)	Mean: −3.74 vs. −3.09 MD: −0.64 [−1.94; 0.65] p = 0.329	Lesser benefit/added benefit not proven
Side effects		
SAEs	NA vs. NA months HR: 1.56 [1.00; 2.43] HR: 0.64 [0.41; 1.00][d] p = 0.047 probability: "hint"	Outcome category: serious/severe side effects CI_u ≥ 0.90 greater harm[e], extent: "minor"[f]
Severe AEs (CTCAE grade ≥ 3)	8.6 vs. NA months HR: 6.28 [4.92; 8.12] HR: 0.16 [0.12; 0.20][d] p < 0.001 probability: "indication"[g]	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs	NA vs. NA months HR: 7.00 [4.83; 10.51] HR: 0.14 [0.10; 0.21][d] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Gastrointestinal disorders (SOC, CTCAE grade ≥ 3)	NA vs. NA months HR: 27.10 [16.47; 48.66] HR: 0.04 [0.02; 0.06][d] p < 0.001 probability: "indication"[g]	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Including: diarrhoea (PT, CTCAE grade ≥ 3)[h]	NA vs. NA months HR: 49.55 [25.29; 116.28] HR: 0.02 [0.01; 0.04][d] p < 0.001	

Table 18: Extent of added benefit at outcome level: neratinib vs. placebo (multipage table)

Outcome category **Outcome**	**Neratinib vs. placebo** **Median time to event (months) or proportion of events (%) or mean** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Fatigue (PT, CTCAE grade ≥ 3)	NA vs. NA months HR: 7.51 [2.07; 48.08] HR: 0.13 [0.02; 0.48][d] p = 0.002 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% greater harm, extent: "considerable"
Metabolism and nutrition disorders (SOC, CTCAE grade ≥ 3)	NA vs. NA months HR: 2.36 [1.13; 5.26] HR: 0.42 [0.19; 0.88][d] p = 0.023 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Muscle spasms (PT, AE)	NA vs. NA months HR: 4.71 [2.99; 7.73] HR: 0.21 [0.13; 0.33][d] p < 0.001 probability: "indication"[g]	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Nervous system disorders (SOC, CTCAE grade ≥ 3)	NA vs. NA months HR: 2.73 [1.24; 6.64] HR: 0.37 [0.15; 0.81][d] p = 0.013 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Skin and subcutaneous tissue disorders (SOC, AE)	NA vs. NA months HR: 2.05 [1.66; 2.54] HR: 0.49 [0.39; 0.60][d] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Investigations (SOC, CTCAE grade ≥ 3)	NA vs. NA months HR: 3.10 [1.41; 7.49] HR: 0.32 [0.13; 0.71][d] p = 0.004 probability: "hint"	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: neratinib vs. placebo (multipage table)

Outcome category **Outcome**	**Neratinib vs. placebo** **Median time to event (months) or proportion of events (%) or mean** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
a. Probability provided if a statistically significant and relevant effect is present. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. Analysis of overall survival in the study is to be conducted only with the 248th death (see Section 2.7.4.3.2 of the full dossier assessment). d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. e. The result of the statistical test is decisive for the derivation of the added benefit. f. Discrepancy between CI and p-value probably due to rounding; the extent is rated as "minor". g. Due to the size of the effect, no downgrading of the certainty of results despite high risk of bias (see Section 2.7.4.2 of the full dossier assessment). h. The PT "diarrhoea" (CTCAE grade ≥ 3) is included in the SOC "gastrointestinal disorders" (CTCAE grade ≥ 3). AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-B: Functional Assessment of Cancer Therapy-Breast Cancer; HR: hazard ratio; MD: mean difference; NA: not achieved; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus		

2.5.2 Overall conclusion on added benefit

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

Table 19: Positive and negative effects from the assessment of neratinib in comparison with watchful waiting

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Recurrence: hint of an added benefit – extent: "major"	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "minor" ▪ Severe AEs (CTCAE grade ≥ 3): indication of greater harm – extent: "major" ▪ Specific AEs (CTCAE grade ≥ 3): ▫ gastrointestinal disorders (SOC)[a]: indication of greater harm – extent: "major" ▫ fatigue (PT), metabolism and nutrition disorders (SOC), nervous system disorders (SOC), investigations (SOC): hint of greater harm – extent: "considerable"
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs; hint of greater harm – extent: "considerable" ▪ Specific AEs: ▫ muscle spasms (PT): indication of greater harm – extent: "considerable" ▫ skin and subcutaneous tissue disorders (SOC): hint of greater harm – extent: "considerable"
a. Including: diarrhoea (PT). AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class	

In the overall consideration, there was one positive effect and several negative effects of neratinib. The positive effect consisted of a hint of major added benefit in the outcome "recurrence". The added benefit in the outcome "recurrence" was based on a period of follow-up observation of 2 years from randomization. The advantage in the outcome "recurrence" was accompanied by important disadvantages in side effects during the treatment phase. The decisive aspect for the negative effects was the indication of harm of major extent in the outcome category of serious/severe side effects in the outcome "gastrointestinal disorders".

In summary, an added benefit of neratinib versus the ACT watchful waiting is not proven for patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified breast cancer and who completed trastuzumab therapy less than 1 year ago.

No conclusions can be drawn on longer-term effects of neratinib therapy in the present therapeutic indication, since the observation period in the ExteNET study was a maximum of 2 years for recurrences and a maximum of 1 year for the outcomes "health status", "health-related quality of life" and "side effects" at the time point of the usable data cut-off.

The result of the assessment of the added benefit of neratinib in comparison with the ACT is summarized in Table 20.

Table 20: Neratinib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Extended adjuvant treatment of adult patients with early-stage hormone-receptor-positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago	Watchful waiting	Added benefit not proven[b]

a. Presentation of the respective ACT specified by the G-BA.
b. Only women were included in the ExteNET study. It remains unclear whether the observed effects can be transferred to men.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The assessment described above deviates from that of the company, which overall derived an indication of considerable added benefit.

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

2.6 List of included studies

Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016; 17(3): 367-377.

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Delaloge S, Cella D, Ye Y, Buyse M, Chan A, Barrios CH et al. Effects of neratinib on health-related quality of life in women with HER2-positive early-stage breast cancer: longitudinal analyses from the randomized phase III ExteNET trial. Ann Oncol 2019; 30(4): 567-574.

Iwata H, Masuda N, Kim SB, Inoue K, Rai Y, Fujita T et al. Neratinib after trastuzumab-based adjuvant therapy in patients from Asia with early stage HER2-positive breast cancer. Future Oncol 2019; 15(21): 2489-2501.

Martin M, Holmes FA, Ejlertsen B, Delaloge S, Moy B, Iwata H et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18(12): 1688-1700.

Mortimer J, Di Palma J, Schmid K, Ye Y, Jahanzeb M. Patterns of occurrence and implications of neratinib-associated diarrhea in patients with HER2-positive breast cancer: analyses from the randomized phase III ExteNET trial. Breast Cancer Res 2019; 21(1): 32.

Pierre Fabre Pharma. A randomized, double-blind, placebo-controlled trial of neratinib (HKI-272) after trastuzumab in women with early-stage HER-2/neu overexpressed/amplified breast cancer; study 3144A2-3004-WW; Zusatzanalysen [unpublished]. 2019.

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Puma Biotechnology. A randomized, double-blind, placebo-controlled trial of neratinib (HKI-272) after trastuzumab in women with early-stage HER-2/neu overexpressed/amplified breast cancer: study 3144A2-3004-WW; clinical study report [unpublished]. 2016.

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Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-98-neratinib-breast-cancer-benefit-assessment-according-to-35a-social-code-book-v.12835.html.