Horizon Scanning in Oncology

Neratinib for the treatment of patients with HER2-positive breast cancer after trastuzumab-based adjuvant therapy

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The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is neratinib?
A0022	Who manufactures neratinib?
A0007	What is the target population in this assessment?
A0020	For which indications has neratinib received marketing authorisation?
Health problem and current use	
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D0011	What is the effect of neratinib on patients' body functions?
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Safety	
C0008	How safe is neratinib in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying neratinib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of neratinib?
A0021	What is the reimbursement status of neratinib?

2 Drug description

Generic/Brand name/ATC code:

Neratinib/HKI-272

B0001: What is neratinib?

irreversible pan-HER inhibitor

Neratinib is an irreversible pan-human epidermal growth factor receptor (HER) inhibitor. It targets the tyrosine-kinase activity of the epidermal growth factor receptors EGFR/HER1, HER2 and HER4. Neratinib activates downstream signalling pathways and reduces phosphorylation through the inhibition of tyrosine-kinase activity at the intracellular domain of the HER receptors [2-4].

once daily 240 mg orally

In clinical trials, 240 mg of oral neratinib were administered continuously once daily for 12 months until disease recurrence, new breast cancer or intolerable adverse events (AEs).

A0022: Who manufactures neratinib?

Puma Biotechnology, Inc.

3 Indication

A0007: What is the target population in this assessment?

for patients with HER2-positive breast cancer

Neratinib is indicated for patients with early-stage HER2-positive breast cancer, who had received trastuzumab-based adjuvant therapy.

4 Current regulatory status

A0020: For which indications has neratinib received marketing authorisation?

not authorised for marketing in the US and in Europe

Neratinib has not yet received marketing authorisation from the US Food and Drug Administration (FDA) or from the European Medicines Agency (EMA) for any indication. However, Puma Biotechnology, Inc. has submitted a New Drug Application for neratinib to the FDA.

5 Burden of disease

A0002: What is breast cancer?

heterogeneous disease that arise from the tissue of the breast

Owing to the molecular pathogenesis of breast cancer, it is designated as a heterogeneous malignancy. It arises from the tissues of the breast and most commonly originates in the cells that line the ducts due to dysregulation of the cell cycle. Breast cancer can be characterised by the pattern of expression of the hormone receptors (oestrogen receptor [ER] and progesterone receptor [PR]), the HER2 receptor, a clinically relevant third molecular marker, the stage of diagnosis and the rate of growth [5, 6]. Prognostically and therapeutically, a distinction can be made between precancerous conditions like in situ tumours (obligatory precancerous condition: ductal carcinoma in situ [DCIS]; optional precancerous condition: lobular carcinoma in situ [LCIS]) and invasive breast cancer.

A0004: What is the natural course of breast cancer?

stages of breast cancer

Mostly, cancer begins in the cells of the ducts, called ductal carcinoma. Abnormal cells are found in the lining of the ducts; however, they have not spread into the surrounding tissue and thus state a precancerous condition like DCIS (stage 0) [7, 8]. Normally, LCIS accompanies with DCIS, whereas aggressive subtypes often do not show DCIS. In fact, the development of type A, ductal hyperplasia over DCIS, into invasive breast cancer is not veritable. Invasive breast cancer (stage I) is restricted to the area where the first abnormal cells arose. In stage II, abnormal cells have spread beyond the ducts or glands into the breast tissue (invasive ductal carcinoma [IDC] or invasive lobular carcinoma [ILC]). Stage III breast cancer is stratified according to the tumour size and includes tumours >5 cm involving the skin, underlying muscle, lymph nodes or inflammatory breast cancer (IBC) [9]. If the cancer has spread to distant parts of the body (stage IV) via the lymph system or the blood, it can also be referred to as metastatic breast cancer (MBC) [7].

AJCC-TNM staging system

Breast cancer can be staged by using the American Joint Committee on Cancer (AJCC) tumour node metastasis (TNM) staging system. It involves important tumour characteristics as well as survival data to support the estimation of outcomes. The TNM staging system classifies tumours on the basis of primary tumour characteristics (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastases (M) [10]. The TNM staging system is especially relevant for inflammatory and stage IV breast cancer.

A0006: What are the consequences of breast cancer for the society?

increasing incidence of cancer

Due to the aging population and in combination with the fact that higher age is a main risk factor for cancer, the incidence of cancer will increase over time [11]. Globally, around 30.0% of the patients with early breast cancer develop advanced or MBC [9]. In Austria, breast cancer accounts for approximately 28,000 (2.6% of total) life-years lost due to premature deaths [12]. Moreover, the incidence of breast cancer is highest for higher socioeconomic groups, whereas survival is lowest in lower socioeconomic groups [13].

highest incidence rate in higher socioeconomic groups

A0023: How many people belong to the target population?

incidence rate based on the European Standard Population: 64.3 per 100,000 persons/year

About 30% of all malignant neoplasm cases in Austria are due to breast cancer. It is the most common cause of death due to cancer in females. The age standardised incidence rate for the European Standard Population (2013) is 64.3 per 100,000 persons per year. In 2014, 5,454 persons were newly diagnosed with breast cancer in Austria, of whom approximately 98.0% were women. Moreover, around 86.0% of female breast cancer patients and 78.0% of male breast cancer patients (all stages are included) are alive at least five years after diagnosis [14]. The median age at diagnosis of breast cancer is 62 years, ranging from 55 to 64 years [15]. HR-positive disease accounts for approximately 65.0% and 80.0% of breast cancers in pre- and postmenopausal women, respectively, and 15.0% to 23.0% of all breast cancer patients have HER2 disease [16].

median age at diagnosis: 62 years

A0005: What are the symptoms and the burden of breast cancer?

main symptoms: breast mass, skin irritation, pain

A hard, immovable, single dominant lesion (breast mass) with irregular borders is the most common symptom of breast cancer [15, 17, 18]. In addition, symptoms like swelling of the whole or only parts of the breast, skin irritation or dimpling (peau d'orange), breast or nipple pain, nipple retraction, redness, scaliness, or thickening of the nipple or breast skin, nipple discharge or axillary adenopathy can occur [15, 18, 19]. In advanced stages of breast cancer weight loss and reduced performance can be present [19]. Symptoms due to metastases include swelling of the arm by lymphedema in lymph node metastases of the axilla, bone pain in skeletal metastases, cough and dyspnoea in pulmonary and/or pleural metastases, jaundice and hepatic failure in advanced liver metastases, or neurological symptoms in cerebral metastases [15, 19, 20].

A0003: What are the known risk factors for breast cancer?

main risk factors: age, gender, race, obesity, genes, menopausal status

Established high-risk factors for developing breast cancer are an increasing age, female gender and white race. Indeed, obesity as well as certain genes like BRCA2, BRCA1 and TP53 are associated with an increased risk of breast cancer in premenopausal and postmenopausal women [19-23]. In addition, increased exposure to oestrogen like menarche or late menopause can also be a risk factor for the diagnosis of breast cancer [19, 21]. Furthermore, reproductive factors that increase risk are a first pregnancy at late age, absence of breastfeeding and nulliparity [21, 22]. Other risk factors that may lead to breast cancer are alcohol consumption, smoking, family and personal history of breast cancer [22].

A0024: How is breast cancer currently diagnosed according to published guidelines and in practice?

diagnosis of breast cancer via mammography, CBE, biopsy, blood chemistry and x-ray tests

There are several ways to diagnose breast cancer, such as the clinical breast exam (CBE), the x-ray mammography or radiological examinations like the ultrasound exam or magnetic resonance imaging (MRI). However, an abnormal mammogram detected in countries with established screening programs is the most common reason for suspecting breast cancer. Additionally, blood chemistry studies or biopsies can be conducted. If breast cancer is suspected via a mammography, a biopsy (punch biopsy and vacuum-assisted biopsy) and a sonography (in women ≤40 years) are performed. An additional breast MRI can increase the detection rate of additional lesions, but it does not improve the prognosis [19]. In the later stage of the disease, liver function tests, brain MRIs, abdominal diagnostic scans, bone scans, sodium fluoride positron emission tomographies (PETs) or fluorodeoxyglucose (FDG) can be applied [24].

additional use of MRI possible to detect further lesions

HR and HER2 status

As breast cancer is a heterogeneous disease, it is essential to establish the HR and HER2 status [7, 24]. Additionally, the stratification into the different disease stages, described in the section "A0004: What is the natural course of breast cancer?" is crucial to ensure the best therapy.

stratification into disease stage

6 Current treatment

A0025: How is breast cancer currently managed according to published guidelines and in practice?

factors for therapeutic decisions

In general, breast cancer can be treated by radiotherapy, surgery and systematic therapies [19]. To determine which treatment strategy is the most suitable for the patient, several factors are important [19, 25]:

- stage of cancer (AJCC TNM staging system)
- grade of disease
- tumour site
- menopausal status
- patient health
- HER2 and HR status
- proliferation rate estimated by means of a Ki67 test

durative treatment options for stage ≤3 breast cancer

The treatment of stage ≤3 breast cancer, where no distant metastases have been detected, has a curative intention and is dependent on the eligibility of a breast-conserving therapy (BCT) and whether it is a clinically node-negative or node-positive breast cancer. For patients who are eligible for a BCT, the following treatment options (in this sequence) may be applied [19]:

- primary neoadjuvant systematic therapy (node-negative breast cancer)
- surgery (sentinel lymph node biopsy [SLNB])
- axillary node dissection
- adjuvant systematic therapy
- adjuvant radiation therapy

stage IV breast cancer treatment options with a palliative intent

For patients who are not eligible for a BCT and for locally advanced breast cancer (stage IIB, IIIA/B), the previously mentioned treatment options can be applied as well. However, instead of a BCT, a mastectomy may be applied. In the case of metastatic disease (stage IV), treatment with a palliative intent (systematic therapy, best supportive care, etc.) can be used [19].

adjuvant treatment strategies

Adjuvant treatment options for HER2-positive breast cancer (stage II-III) are [19, 26]:

- adjuvant radiation therapy 4–6 weeks after surgery
- adjuvant endocrine therapy for HR-positive patients
  - premenopausal women: tamoxifen or tamoxifen/exemestane and eliminating or suppressing ovarian function
  - postmenopausal women: aromatase inhibitors (e.g., anastrozole, letrozole, exemestane) and tamoxifen
- adjuvant therapy with trastuzumab (>1 year) in combination or sequentially with chemotherapy; weekly treatment with paclitaxel in elderly patients or node-negative breast cancer can be used instead of chemotherapy

7 Evidence

systematic literature search in 5 databases: 376 hits

A literature search was conducted on 27 December 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "Neratinib", "HKI-272", "breast cancer", "breast neoplasms" and "mamma carcinoma". The manufacturer was also contacted and submitted three references (two of which had already been identified by systematic literature search). A manual search identified 21 additional references (web documents and journal articles). Overall, 397 references were identified. Included in this reported are:

included: 1 phase III and 1 phase II study

- One phase III study, assessing neratinib in early-stage HER2-positive breast cancer patients who had received trastuzumab-based adjuvant therapy [27, 28]
- One phase II study, assessing neratinib in patients with advanced HER2-positive breast cancer [29]

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

The methodological quality of the evidence was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for RCTs [26, 30]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

To evaluate the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [31]. Additionally, an adapted version (due to perceived

limitations) of the ESMO-MCBS was applied [32]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

7.1 Clinical efficacy and safety – phase III studies

ExteNET: efficacy and safety of neratinib in 2,840 women

The ExteNET trial (a randomised, multicentre, double-blind, placebo-controlled phase III study) was conducted to assess the efficacy and safety of neratinib after trastuzumab-based adjuvant treatment in patients with early stage HER2-positive breast cancer [27, 28].

permuted block randomisation

A total of 2,840 women were randomly assigned in a 1:1 ratio to receive either neratinib (n = 1,420; 240 mg daily) or matching placebo (n = 1,420). The stratification of randomisation (permuted block randomisation) was based on the hormone receptor status (hormone receptor-positive [OR- or PR-positive or both] vs. hormone receptor-negative [OR- and PR-negative]), nodal status (0, 1–3, or ≥4), and trastuzumab adjuvant regimen (sequentially vs. concurrently with chemotherapy). It was centrally implemented by an interactive voice and web-response system. Patients, investigators, caregivers, outcome assessors as well as trial sponsors were masked to treatment allocation.

amendments of the study protocol

On 25 February 2010 a global amendment of the study was done to restrict the recruitment to higher-risk patients who were defined as patients with node-positive disease and had completed prior trastuzumab therapy for up to one year. 1,580 patients had already been recruited until 25 February 2010. After the changes had been applied, 1,248 further patients were enrolled. Therefore, the efficacy population was changed from the intention-to-treat (ITT) to the amended ITT (aITT). Two additional changes were applied in 2011: to cease enrolment and to shorten follow-up from five years to two years from randomisation. As of January 2014 the study was continued with this design until the current sponsor changed the population of the primary endpoint back to the ITT of the original protocol.

median age of 52 years and ECOG performance status of 0–1

Enrolled patients had a median age of 52 years. The study population had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, normal organ function and a left ventricular ejection fraction within normal institutional range. Patients had to have locally confirmed invasive HER2-positive breast cancer without evidence of recurrence. At 24 months follow-up, central HER2 testing was performed in 1,705 (60%) of primary tumour specimens. The HER2 status was confirmed centrally using the PathVysion HER2 DNA dual probe (Abbott Molecular, Des Plaines, IL, USA). The HER2 amplification was defined as a ratio of HER2 to CEP17 of ≥2.2. Detailed patient characteristics, together with including inclusion and exclusion criteria, can be found in Table 4 of the Appendix.

median follow-up: 24 months

The median follow-up of the study was 24 months (IQR 20–25) in the neratinib group and 24 months (IQR 22–25) in the placebo group. At the time of 24 months follow-up (July 2014), 70 invasive disease-free survival (DFS) events in the neratinib group and 109 DFS events in the placebo group had occurred. The primary endpoint of the study was invasive DFS. Secondary outcomes included DFS, taking account of ductal carcinoma in situ, cumulative incidence of recurrences in the central nervous system (CNS), overall

primary study endpoint: invasive DFS

survival (OS) and safety. Health-related quality of life was an exploratory endpoint.

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of neratinib on mortality?

immature OS data

At the time of primary analysis OS data was immature, since the target number of events had not been reached. Therefore, OS will continue to be monitored by the Independent Data Monitoring Committee.

D0006: How does neratinib affect progression (or recurrence) of breast cancer?

2-year invasive DFS rate: neratinib: 93.9% placebo: 91.6%

After a 24-month follow-up, significantly fewer invasive DFS events had occurred in the neratinib group (70 vs. 109 events). Compared with the placebo group, the hazard ratio (HR) for invasive DFS events was 0.67 (95% CI 0.50–0.91; p = 0.0091). The two-year invasive DFS rate was 93.9% (95% CI 92.4–95.2) and 91.6% (95% CI 90.0–93.0) in the neratinib and placebo groups, respectively. DFS including ductal carcinoma in situ (DCIS) events was significantly improved in the neratinib group (93.9%, 95% CI 92.4–95.2) compared to the placebo group (91.0%, 95% CI 89.3–92.5) (HR 0.63, 95% CI 0.46–0.84; p = 0.0017). No statistically significant difference between the study groups could be shown for distant DFS and for the time to distant recurrence. In the neratinib group the two-year incidence of CNS recurrence was 0.91% (95% CI 0.49–1.59) and 1.25% (95% CI 0.75–1.99) in the placebo group (p = 0.44). The pre-specified subgroup analysis of invasive DFS showed a higher improvement in hormone receptor-positive breast cancer (HR 0. 51, 95% CI 0. 33–0. 77; p = 0. 0013) compared to the population with hormone receptor-negative disease (HR 0.93, 95% CI 0.60–1.43; p = 0.74). In patients with centrally confirmed HER2-positive breast cancer, invasive DFS was significantly improved in the neratinib group (n = 741) compared to the placebo group (n = 722, HR 0.51, 95% CI 0.33–0.77; p = 0.0015).

patients with centrally confirmed HER2-positive disease showed a significant improvement in invasive DFS

D0005: How does neratinib affect symptoms and findings (severity, frequency) of breast cancer?

No evidence was found to answer this research question.

D0011: What is the effect of neratinib on patients'body functions?

No evidence was found to answer this research question.

D0012: What is the effect of neratinib on generic health-related quality of life?

D0013: What is the effect of the neratinib on disease-specific quality of life?

no clinically significant difference in QoL

Two instruments were used to measure quality of life (QoL): the EQ-5D for health-related QoL and the Functional Assessment of Cancer Therapy-Breast, FACT-B for disease-specific QoL. The greatest difference in QoL between the two study groups was at month one for both measures (EQ-5D, -2.7 [95% CI -3.7 to -1.7], FACT-B, -2.9 [95% CI -3.7 to -2.0]). In none of the

two study groups was the difference clinically significant and after the first month of treatment it declined.

Table 1: Efficacy results of the ExteNET trial (estimated disease-free survival rate at two years)

Descriptive statistics and estimate variability	Treatment group	Neratinib	Placebo
	Number of subject	1,420	1,420
	Invasive DFS events, n	70	109
	Invasive DFS, %	93.9 (92.4–95.2)	91.6 (90.0–93.0)
	DFS-DCIS, %	93.9 (92.4–95.2)	91.0 (89.3–92.5)
	Two-year cumulative incidence of CNS recurrence, %	0.91 (0.49–1.59)	1.25 (0.75–1.99)
	Distant DFS	95.1 (93.7–96.2)	93.7 (92.2–94.9)
	Time to distant recurrence	95.4 (94.1–96.5)	93.9 (92.4–95.0)
	OS	NA	NA
Effect estimate per comparison	*Comparison groups*		*Neratinib versus placebo*
	Invasive DFS	HR	0.67
		95% CI	90.0–93.0
		Log-rank test p-value	0.0091
	DFS-DCIS	HR	0.63
		95% CI	0.46–0.84
		Log-rank test p-value	0.0017
	Distant DFS	HR	0.75
		95% CI	0.53–1.04
		Log-rank test p-value	0.089
	Time to distant recurrence	HR	0.71
		95% CI	0.50–1.00
		Log-rank test p-value	0.054
	Two-year cumulative incidence of CNS recurrence	Gray's test p-value	0.44
	EQ-5D	AMD of changes in QoL	-2.7
		95% CI	-3.7 – -1.7
	FACT-B	AMD of changes in QoL	-2.9
		95% CI	-3.7 – -2.0

Abbreviations: AMD = adjusted mean difference, CI = confidence interval, CNS = central nervous system, DCIS = ductal carcinoma in situ, DFS = disease-free survival, FACT-B = Functional Assessment of Cancer Therapy-Breast, HR = hazard ratio, NA = not available, QoL = quality of life

7.1.2 Safety

C0008: How safe is neratinib in relation to the comparator(s)?

The most common treatment-emergent AE in the neratinib group was diarrhoea. In over 90% of patients in the neratinib group diarrhoea of any grade occurred. 458 patients (33%) had grade 2 diarrhoea, 561 (40%) grade 3 diarrhoea and one patient had grade 4 diarrhoea. In the placebo group 94 patients (7%) had grade 2 diarrhoea, 23 (2%) had grade 3 diarrhoea and none had grade 4 diarrhoea. Moreover, the second most common AEs, nausea (grade 1–2: 41%, grade 3: 2%) and fatigue (grade 1–2: 25%, grade 3: 2%) were observed in patients of the neratinib arm. QT prolongation occurred in 49 patients (3%) who received neratinib and in 93 patients (7%) who received placebo.

most common AE: diarrhoea

>90% of patients in the neratinib group had diarrhoea of any grade

SAEs:
neratinib: 103 patients (7%)
placebo: 85 patients (6%)

Serious AEs occurred in 103 patients (7%) of the neratinib group and in 85 patients (6%) of the placebo group. Four patients in the neratinib group and three patients in the placebo group died after study drug discontinuation. Of the four patients in the neratinib group, two patients died due to a primary tumour (brain and acute myeloid leukaemia). For the other two patients the cause of death is unknown. In the placebo group the causes of death for the three patients were brain haemorrhage, myocardial infarction and gastric cancer.

C0002: Are the harms related to dosage or frequency of applying neratinib?

dose reductions due to diarrhoea: neratinib: 26% placebo: 1%

Due to diarrhoea, dose reductions were necessary for 372 patients (26%) in the neratinib group and for eight patients (1%) in the placebo group, hospital admission for 20 patients (1%) versus one patient (<1%), and drug discontinuation for 237 patients (17%) versus three patients (<1%).

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of neratinib?

gastrointestinal & cardiovascular toxicities

HER2-targeted agents are associated with an increased incidence of different cardiovascular AEs and gastrointestinal toxicities [33, 34]. Therefore, patients with a history of gastrointestinal or heart disease could be harmed when treated with neratinib. Since neratinib has not been investigated in pregnant women, special caution has to be applied in this patient population.

Table 2: Most frequent treatment-related adverse events[1]

Adverse Event (according to CTCAE version 3.0)	**Intervention** (n = 1,408)			**Control** (n = 1,408)		
	Grade 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Diarrhoea	781 (55)	561 (40)	1 (<1)	476 (34)	23 (2)	0 (0)
Nausea	579 (41)	26 (2)	0 (0)	301 (21)	2 (<1)	0 (0)
Fatigue	359 (25)	23 (2)	0 (0)	276 (20)	6 (<1)	0 (0)
Vomiting	322 (23)	47 (3)	0 (0)	107 (8)	5 (<1)	0 (0)
Abdominal pain	314 (22)	24 (2)	0 (0)	141 (10)	3 (<1)	0 (0)
Headache	269 (19)	8 (1)	0 (0)	269 (19)	6 (<1)	0 (0)
Upper abdominal pain	201 (14)	11 (1)	0 (0)	93 (7)	3 (<1)	0 (0)
Rash	205 (15)	5 (<1)	0 (0)	100 (7)	0 (0)	0 (0)
Decreased appetite	166 (12)	3 (<1)	0 (0)	40 (3)	0 (0)	0 (0)
Muscle spasms	157 (11)	1 (<1)	0 (0)	44 (3)	1 (<1)	0 (0)
Dizziness	143 (10)	3 (<1)	0 (0)	125 (9)	3 (<1)	0 (0)
Arthralgia	84 (6)	2 (<1)	0 (0)	158 (11)	4 (<1)	0 (0)

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

[1] Treatment-related adverse events occurring in at least 10% of patients in the safety population (patients who have received at least one dose of study treatment).

7.2 Clinical effectiveness and safety – further studies

efficacy and safety of neratinib in advanced HER2-positive breast cancer

Neratinib has not been investigated in any additional phase II or III trial for this specific indication and patient population before. However, a multicentre, open-label, phase II trial [29] evaluated the safety and efficacy of neratinib in two patient cohorts with advanced HER2-positive breast cancer. Patients in cohort A received prior trastuzumab-based treatment and patients of cohort B did not receive prior trastuzumab treatment. A total of 66 patients were included in cohort A and 70 patients were enrolled in cohort B. The daily administered oral dose of neratinib was 240 mg. The primary endpoint was a 16-week PFS rate assessed by independent review; secondary endpoints included objective response rate, safety and duration of response.

16-week PFS rate
cohort A: 59%
cohort B: 78%

The 16-week PFS rate in patients of cohort A was 59% and 78% for patients of cohort B. The median PFS was 22.3 weeks and 39.6 weeks, respectively. The objective response rate for patients of cohort A was 24% and 56% for patients of cohort B. The most frequent AEs were diarrhoea, nausea, vomiting and fatigue. The most common grade 3–4 AE was diarrhoea, occurring in 30% of patients of cohort A and in 13% of patients of cohort B. This consequently led to discontinuation in 29% and 4% of patients, respectively.

8 Estimated costs

A0021: What is the reimbursement status of neratinib?

no price estimates available for Austria

Since neratinib has not yet received marketing authorisation in Europe or in the US for any indication, no price estimates are available at the moment. Additional costs will incur due to the monitoring of blood tests, as well as for monitoring and managing toxicities owing to neratinib (e.g., cardiotoxicities and gastrointestinal toxicities) [33-35].

9 Ongoing research

one ongoing phase III study investigating neratinib in HER-positive breast cancer patients

In January 2017, a search in databases http://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/ was conducted. The following ongoing phase III trial is investigating neratinib in HER2-positive breast cancer patients:

- NCT00878709: A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer who have received two or more prior HER2 directed

regimens in the metastatic setting. Estimated study completion date is May 2018.

Currently, various phase I and II studies are ongoing in different treatment lines in patients with breast cancer, either using neratinib monotherapy or combination treatment (e.g., NCT01494662, NCT01008150, NCT00398567, and NCT00777101).

10 Discussion

not approved in Europe and US

Neratinib is not approved for any indication in the US or in Europe at present. However, Puma Biotechnology, Inc. has submitted a New Drug Application to the FDA concerning neratinib for the extended adjuvant treatment of patients with early stage HER2-overexpressed breast cancer who have received prior adjuvant trastuzumab-based therapy.

ExteNET: significantly fewer DFS events

OS data and DFS in months were not available

no clinical significant difference in QoL

A randomised, multicentre, double-blind, placebo-controlled phase III study, ExteNET [27, 28], compared neratinib with placebo in patients with early-stage HER2-positive breast cancer after prior trastuzumab-based adjuvant therapy. The study enrolled a total of 2,840 women. After 24 months significantly fewer invasive DFS events occurred in the neratinib group (70 vs. 109 events, p = 0.0091). The two-year invasive DFS rate was 2.3% higher in the overall population of the neratinib group and 2.9% higher in patients with DCIS compared to the placebo group. Patients with hormone receptor-positive disease showed a higher improvement in invasive DFS compared to hormone receptor-negative patients (HR 0.51 vs. 0.93). QoL data showed no clinical significant difference between the two study groups. OS data was immature at the time of analysis.

0.5 month gain of the restricted mean survival time compared to the placebo group

Criticism has risen in regard to the use of the HR to demonstrate treatment benefit in clinical trials. It could be possible that the HR has no meaningful clinical benefit, since estimations of hazard functions for each study group are challenging without modelling over time [36-38]. A correspondence from Hasegawa and Uno [39] implied that the stated 24-month invasive DFS rate might not gather the overall patient profile. They suggested to alternatively use the restricted mean survival time to quantify and better illustrate the treatment benefit, whereby survival means invasive DFS. They estimated the restricted mean survival time for neratinib (calculating the area under the Kaplan-Meier curve) to be 23.5 months and 23.0 months for the placebo group. This would imply that patients treated with neratinib for 24 months show a mean invasive DFS of 23.5 months, which is a gain of 0.5 months compared to the placebo group.

further follow-up and mature OS data needed

A study (HERA trial) of one-year trastuzumab treatment compared to observation alone in 3,399 patients showed a decline in efficacy over an eight-year follow-up period [40]. Therefore, to verify the current findings of neratinib, mature OS data as well as further follow-up data are needed. In addition, to better reflect the most affected patient population, neratinib should also be investigated in an older patient population (median age of study population: 52), as the median age of breast cancer diagnosis is 62 years [41].

most common grade ≥3 diarrhoea: 41% vs. 2%

dose reductions due to diarrhoea: 26% vs. 1%

With regard to safety outcomes, grade 3–4 AEs occurred more commonly in patients of the neratinib group. The most frequent grade 3–4 AE in the neratinib group was diarrhoea (neratinib: 41% vs. placebo: 2%). The second most common events of any grade were nausea (43% vs. 23%), fatigue (27% vs. 21%) and vomiting (26% vs. 9%). Owing to diarrhoea, dose reductions in 380 patients of both study groups were necessary, of whom 372 patients belong to the neratinib group. Drug discontinuation was applied in 237 patients (17%) of the neratinib group versus three patients (<1%) of the placebo group.

reducing the incidence of diarrhoea may lead to additional cardiac AEs

Over 90% of the patients in the neratinib group have experienced diarrhoea of any grade. A current study (CONTROL trial [42]) is investigating whether the additional administration of loperamide to neratinib can reduce the incidence and severity of diarrhoea in patients with early stage HER2-positive breast cancer. Although loperamide may reduce the risk of gastrointestinal toxicities, it is associated with other side effects as well, in particular, including special precautions for combinations with other drugs that are known to prolong the QT interval (neratinib: 3% of patients). Moreover, loperamide used concomitantly with CYP3A4 or CYP2C8 inhibitors has also shown to increase the risk of cardiac AEs [43].

targeted therapies are associated with cardiac toxicities

Currently, approved targeted therapies (e.g., trastuzumab, lapatinib and bevacizumab) for the treatment of breast cancer have demonstrated increased incidences of cardiovascular events [33, 35]. Although neratinib does not seem to be associated with the increased risk of cardiac toxicity, scarce clinical experience is currently available. A longer follow-up period and a greater number of treated patients will therefore be needed to exclude any toxic effects on the cardiovascular system.

role of pertuzumab in the adjuvant treatment setting

The ExteNET trial included patients who received neoadjuvant and/or adjuvant trastuzumab-based treatment. In addition, pertuzumab is currently under investigation in combination with trastuzumab and chemotherapy in an adjuvant treatment setting (APHINITY trial [44]) for HER2-positive breast cancer. Pertuzumab is already used in a neoadjuvant setting in combination with trastuzumab and chemotherapy for the treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence [45]. If pertuzumab plays a prospective role in the adjuvant treatment of HER2-positive breast cancer, it will be important to verify whether the effect of neratinib is also applicable for patients who received prior pertuzumab-containing treatment. Moreover, a comparison of adjuvant pertuzumab-containing treatment and sequential neratinib treatment could help to identify the best treatment sequence for this patient population.

biomarkers in order to select the appropriate patient population

The identification of the appropriate patient population will be of high interest in the future. For patients who have HER2-positive and hormone receptor-positive breast cancer, neratinib therapy was more beneficial than in patients with the hormone receptor-negative disease. However, for the proper patient selection biomarkers will be needed to predict the response and resistance to neratinib. Further data will also be required to define patients who are likely to benefit the most [46, 47].

no costs available

additional costs due to biomarker and toxicities

unfavourable benefit-risk ratio

No cost estimations are currently available for neratinib in the US or in Europe, since it has not been approved for any indication yet. In addition, costs for possible prospective biomarkers will be incurred and costs due to the treatment of potential gastrointestinal and cardiac toxicities will increase. Although neratinib offers an improvement in invasive DFS, the gastrointestinal toxicities in combination with possible cardiac toxicities suggest an unfavourable benefit-risk ratio. Further studies are needed to select the appropriate patient population and to verify the long-term benefit, as well as to exclude toxic effects of the cardiovascular system.

Table 3: Benefit assessment based on ESMO-MCBS[3] and adapted benefit assessment based on ESMO-MCBS [31, 32]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	Efficacy				Safety		AJ	FM
						DFS rate	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
adapted ESMO-MCBS	neratinib	early stage breast cancer	adjuvant therapy	DFS	1	intervention: 93.6% control: 91.6%	0.67 0.50–0.91	improvement in DFS alone: HR 0.65–0.80, without mature OS data	B	+46% grade 3–4 AEs (-1)[2]	ND	-1	**C**
ESMO-MCBS	neratinib	early stage breast cancer	adjuvant therapy	DFS	1	intervention: 93.6% control: 91.6%	0.67 0.50–0.91	improvement in DFS alone: HR 0.65–0.80, without mature OS data	B	-	-	-	**B**

Abbreviations: AJ = Adjustments, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, ND = no difference, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[2] One level downgrade because >10% grade ≥3 adverse events.

[3] European Society for Medical Oncology - Magnitude of Clinical Benefit Scale

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12 Appendix

Table 4: Characteristics of the ExteNET trial

Title: Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase III trial [27, 28]			
Study identifier	NCT00878709, EudraCT number 2008-007345-31, ExteNET		
Design	Phase III, randomised, multicentre, double-blind, placebo-controlled trial		
	Duration		Enrolment: 9 July 2009 to 24 October 2011 Median follow-up time: neratinib: 24 months (IQR 20–25), placebo: 24 months (IQR 22–25) For consenting patients long-term survival in a follow-up is ongoing.
Hypothesis	Superiority This study was powered to detect differences in invasive DFS between the two study arms. The planned sample size of the study was 3,850 patients to provide 90% power at a two-sided 5% significance level for the log-rank test and to detect an HR of 0.7. Due to amendments the enrolment was stopped in October 2011 after 2,842 patients were included in the study. The power was then projected to be 88% (HR 0.667) at a two-sided 5% significance level.		
Funding	Puma Biotechnology, Inc.		
Treatments groups	Intervention (n = 1,420)		Neratinib was administered orally at a daily dose of 240 mg.
	Placebo (n = 1,420)		Placebo was administered orally at a daily dose of 240 mg.
Endpoints and definitions	Invasive disease-free survival (primary outcome)	DFS	Invasive DFS two years after randomisation. Invasive disease was defined as: invasive ipsilateral tumour recurrence, invasive recurrence, distant recurrence, or death from any cause.
	Disease-free survival including ductal carcinoma in situ	DFS-DCIS	Time from randomization to the first occurrence of any DFS event or DCIS
	Distant disease-free survival	DDFS	Time from randomization to the first distant recurrence or death from any cause
	Time to distant recurrence	TTDR	Time between randomization and the date of the first distant recurrence, or death from breast cancer
	Incidence of CNS recurrence	-	Time from randomization to central nervous system recurrence as the first distant recurrence
Results and Analysis			
Analysis description	**Primary analysis** Efficacy analyses (primary and secondary endpoints) were performed in the intention-to-treat population, which was defined as all randomly assigned patients. Safety analyses were performed in the safety population, which was defined as all patients who received at least one dose of study treatment. All time-to-event endpoints were tested with two-sided log-rank tests stratified by randomisation. To estimate HRs with 95% CIs, stratified Cox proportional-hazards models were used. Two-year survival rates were estimated by using Kaplan-Meier methods. Gray's test was used to compare treatments and to evaluate CNS recurrences cumulative incidence competing-risk analyses were performed. For the QoL evaluation (changes from baseline in QoL scores) an ANCOVA was used, with baseline score as a covariate.		

Title: Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase III trial [27, 28]

Study identifier	NCT00878709, EudraCT number 2008-007345-31, ExteNET			
Analysis population	Inclusion	❊ Age ≥18 years (or ≥20 years in Japan) ❊ ECOG performance status 0–1 ❊ Original inclusion criteria: stage I-III HER-2/erbB-2 positive breast cancer with node positive and node-negative disease without evidence of recurrence ❊ Global amendment Feb 2010: Stage II through IIIC HER-2/erbB-2 positive breast cancer with node-positive disease without evidence of recurrence ❊ Been treated for early breast cancer with standard of care duration of trastuzumab (up to two years, amendment to one year) ❊ Could have been treated in a neoadjuvant setting but have not reached pCR ❊ Patients with normal organ function and a left ventricular ejection fraction within normal institutional range		
	Exclusion	❊ Positive clinical and radiologic assessments for local or regional recurrence of disease at the time of study entry ❊ History of heart disease ❊ QTc interval >0.45 seconds ❊ History of gastrointestinal disease with diarrhoea as the major symptom ❊ Patients with psychiatric comorbidities ❊ Patients who were unable to swallow oral medications		
	Characteristics		Intervention (n = 1,420)	Control (n = 1,420)
	Median age (range), years		52 (45–59)	52 (45–60)
	Age at randomisation in years, n (%) <35 35–49 50–59 ≥60		 46 (3) 523 (37) 497 (35) 354 (25)	 55 (4) 515 (36) 488 (34) 362 (25)
	Region, n (%) North America Western Europe, Australia, New Zealand, South Africa Asia Pacific, Eastern Europe, South America		 519 (37) 487 (34) 414 (29)	 477 (34) 532 (37) 411 (29)
	Race, n (%) White Black Asian Other		 1,165 (82) 27 (2) 188 (13) 40 (3)	 1,135 (80) 47 (3) 197 (14) 41 (3)
	Menopausal status at diagnosis, n (%) Premenopausal Postmenopausal		 663 (47) 757 (53)	 664 (47) 756 (53)
	Nodal status[A], n (%) Negative 1–3 positive nodes ≥4 positive nodes		 335 (24) 664 (47) 421 (30)	 336 (24) 664 (47) 420 (30)
	Hormone receptor status, n (%) Positive (ER-positive, PR-positive or both) Negative (ER and PR negative)		 816 (57) 604 (43)	 815 (57) 605 (43)
	Previous trastuzumab regimen, n (%) Concurrent Sequential		 884 (62) 536 (38)	 886 (62) 534 (38)
	T stage, n (%) T1 T2 ≥T3 Unknown Missing		 440 (31) 585 (41) 144 (10) 250 (18) 1 (<1)	 459 (32) 555 (39) 117 (8) 288 (20) 1 (<1)

Title: Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase III trial [27, 28]			
Study identifier	NCT00878709, EudraCT number 2008-007345-31, ExteNET		
Analysis population (continuation)	Histological grade of tumour, n (%) Undifferentiated or poorly differentiated Moderately differentiated Well differentiated Unknown	 670 (47) 461 (32) 76 (5) 213 (15)	 689 (49) 416 (29) 65 (5) 241 (17)
	Previous surgery, n (%) Lumpectomy only Mastectomy Missing	 468 (33) 951 (67) 1 (<1)	 511 (36) 908 (64) 1 (<1)
	Previous radiotherapy, n (%) Yes No	 1,130 (80) 290 (20)	 1,150 (81) 270 (19)
	Previous neoadjuvant or adjuvant therapy[B], n (%) Anthracycline only Anthracycline plus taxane Taxane only Non-anthracycline or taxane	 136 (10) 962 (68) 318 (22) 4 (<1)	 135 (10) 965 (68) 316 (22) 4 (<1)
	Duration of previous adjuvant trastuzumab therapy[C] months (range) n	 11.5 (10.9–11.9) 1,413	 11.4 (10.8–11.9) 1,416
	Time from last dose of trastuzumab to randomisation months (range)	 4.4 (1.6–10.4)	 4.6 (1.5–10.8)
	Concomitant endocrine therapy for hormone receptor-positive disease [D], n (%) Yes Anti-oestrogen only Anti-oestrogen and aromatase inhibitor (sequential) Aromatase inhibitor only Non-anti-oestrogen or aromatase inhibitor	 760 (93) 375 (46) 20 (3) 362 (44) 3 (<1)	 764 (94) 347 (43) 34 (4) 379 (47) 4 (<1)

Abbreviations: CNS = central nervous system, ECOG = Eastern Cooperative Oncology Group, ER = oestrogen receptor, IQR = interquartile range, pCR = pathological complete response, PR = progesterone receptor, QoL = quality of life, QTc = Corrected QT Interval, [A] the number of positive nodes at the time of initial diagnosis or surgery, patients with residual invasive disease in the breast, but node-negative disease or unknown nodal status in the axilla, after neoadjuvant therapy were included under 1–3 positive nodes. [B] Number of patients who received neoadjuvant chemotherapy was 342 (24%) in the neratinib group and 379 (27%) in the placebo group. [C] Patients with missing or partial dates of trastuzumab administration were not included in the analysis. [D] Based on the number of hormone receptor-positive patients.

Table 5: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [30]

Criteria for judging risk of bias		**Risk of bias**
Adequate generation of randomisation sequence: permuted block randomisation		yes
Adequate allocation concealment: centrally by an interactive voice and web response system		yes
Blinding: double-blind	**Patient**	yes
	Treating physician	yes
Selective outcome reporting unlikely:		yes
No other aspects which increase the risk of bias: industry funded, changes in the study protocol during the study (patient number, patient population …)		no
Risk of bias – study level		low