Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende neratinib til forlænget adjuverende behandling af ER+ og HER2+ brystkræft

Vers. 1.0

Bilagsoversigt

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2. Medicinrådets vurdering vedr. neratinib til behandling af ER+ og HER2+ brystkræft, version 1.1
3. Ansøgers endelige ansøgning
4. Ansøgers tekniske dokument til den sundhedsøkonomiske ansøgning
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Medicinrådets sundhedsøkonomiske afrapportering og Amgros' beslutningsgrundlag er ikke inkluderet, da disse dokumenter ikke har indflydelse på anbefalingen. Det skyldes, at Medicinrådet har vurderet, at neratinib har negativ værdi sammenlignet med ingen behandling.

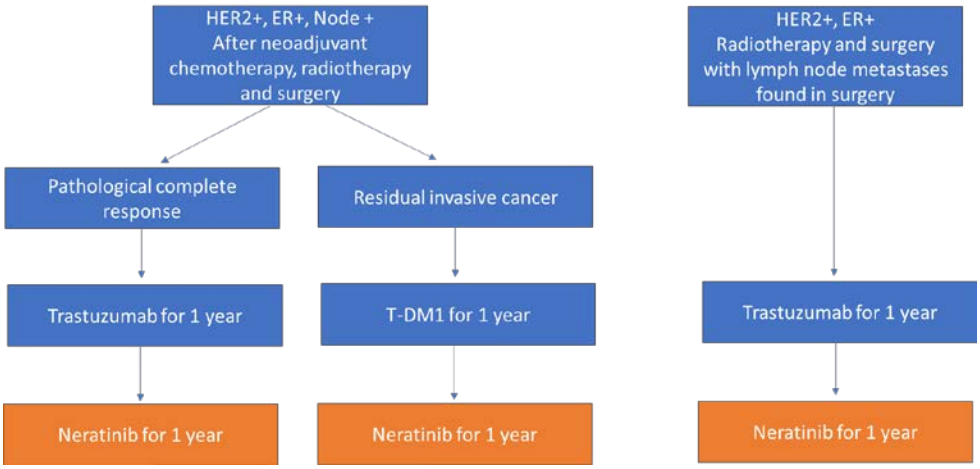
Pierre Fabre

DMC's assessment of neratinib for ER+ and HER2+ breast cancer

Pierre Fabre's comments on Assessment Report Dated 22/10/20

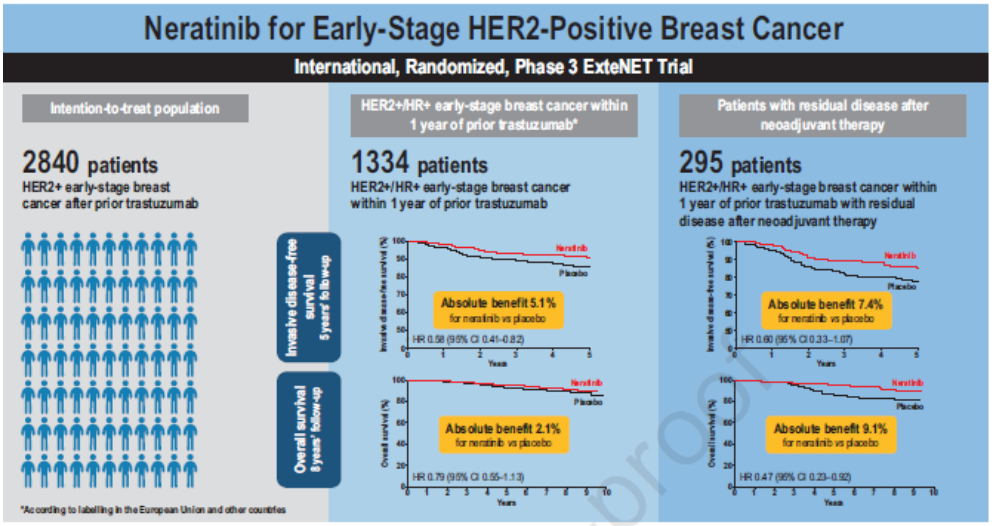
Comment number	Comments
1	**Section 5.1.2: Narrowing of the study population and position of neratinib in the Danish treatment pathway (translated to English):** *In August 2020, trastuzumab-emtansine (T-DM1) was approved by the Danish Medicines Council as standard treatment for patients with HER2+ breast cancer who have not achieved complete pathological response to neoadjuvant treatment, i.e. as an adjuvant treatment. Approx. 74% of patients receiving neoadjuvant treatment do not achieve complete pathological response, and are therefore candidates for T-DM1. These patients are not candidates for neratinib. Thus, it is only approx. 26% of patients (with lymph node metastases who achieve complete response to neoadjuvant therapy), which are candidates for neratinib.* T-DM1 is now used in Danish clinical practice in patients with HER2+ early breast cancer with residual invasive disease after neoadjuvant therapy, based on findings from the KATHERINE trial; however, this study further reinforced the poor prognosis and continued risk of disease recurrence in this patient population. Despite a hazard ratio for iDFS of 0.52 for T-DM1 versus trastuzumab, 17% of lymph node-positive patients with residual disease after neoadjuvant therapy treated with T-DM1 still experienced an invasive disease event after 3 years of follow-up (von Minckwitz 2019). Importantly, the majority of iDFS events after T-DM1 treatment were metastatic distant recurrences in the central nervous system (CNS): in patients with an iDFS event, 47.3% of recurrences with T-DM1 vs. 18.2% with trastuzumab were CNS recurrences (KADCYLA EPAR, Table 21). In addition, 28.5% of patients in KATHERINE discontinued from study treatment, 17.9% due to adverse events (KADCYLA EPAR, Table 7), further highlighting an unmet need for these patients. Finally, not all patients may be eligible for T-DM1 given the precautions of use e.g. left ventricular dysfunction or haematological disorders (see KADCYLA SmPC). Neratinib, as per the EMA label, can be used after any prior adjuvant ***trastuzumab-based*** therapy, which includes patients without a pathological complete response (pCR) after neoadjuvant therapy, who are eligible for treatment with T-DM1 in Denmark. This is supported by the different mechanism of action of neratinib versus trastuzumab-based therapies (please refer to comment 3) and published ExteNET data in patients with and without a pCR after neoadjuvant therapy (see below). This was highlighted in the DMC protocol (No. 74579) which stated that if neratinib is recommended, the current course of treatment will be unchanged as neratinib is placed after preventive treatment with trastuzumab.

Pierre Fabre

	Recently published exploratory subset analyses of the EU label population of ExteNET (Chan 2020) show that patients without pCR (i.e. patients with residual disease) after neoadjuvant therapy showed clinically meaningful improvements with neratinib versus placebo, with an absolute benefit in 8-year OS of 9.1% (hazard ratio 0.47; 95% CI 0.23-0.92). In patients with no pCR (n=295), the absolute benefits in 5-year iDFS and DDFS were 7.4% (hazard ratio 0.60; 95% CI 0.33–1.07) and 7.0% (hazard ratio 0.61; 95% CI 0.32–1.11), respectively. Clinically meaningful improvements were also evident with neratinib in those attaining a pCR (absolute benefits at 5-year iDFS of 9.8% and 8-year OS of 19.6%). This highlights the unmet need in patients with HER2+/HR+ breast cancer who receive neoadjuvant therapy, and that neratinib is a valuable therapeutic option for these patients. It is also important to consider that the prognosis of patients who are HER2+/HR+ and who achieve a pCR has been unclear, with several studies suggesting that clinical outcomes in these patients may not be appreciably better than patients without a pCR. Similarly in ExteNET, 5-year iDFS rates in patients with or without a pCR were similar, i.e. 84% and 85% in the neratinib arm, respectively, and 74% and 78% in the placebo arm, respectively. **For these reasons, Pierre Fabre consider that HER2+/HR+ patients both with and without a pCR after neoadjuvant therapy show a treatment benefit with neratinib, therefore patients previously treated with T-DM1 should be eligible for neratinib in Denmark as per the label, and as illustrated in the proposed treatment pathway in the figure below.** 
2	**Draft conclusion wording (translated to English):** *Neratinib's value on the critical effect measure overall survival cannot be assessed as data for overall survival has not yet been published and the preliminary data available are confidential.* Final overall survival (OS) data for the EU label population in ExteNET have recently been published online on 6th October 2020: Chan et al, Clinical Breast Cancer 2020: epub ahead of print (embedded below).

Chan 2020.pdf

In the EU label population (patients with HER2+, HR+ early breast cancer and ≤1-year from completion of adjuvant trastuzumab-based therapy), neratinib was associated with a numerical improvement in OS at 8 years (absolute benefit, 2.1%; HR=0.79, 95% CI 0.55–1.13). For the 295 HR+/≤1-year patients who received neoadjuvant therapy with residual disease, the results showed an absolute benefit of 7.4% at 5-year iDFS (HR=0.60; 95% CI 0.33–1.07) and 9.1% at 8-year OS (HR=0.47; 95% CI 0.23–0.92) (as reported in the following figure).



These OS analyses comparing neratinib vs. placebo are in line with approved HER2-directed agents in the adjuvant setting, such as trastuzumab emtansine (T-DM1) and trastuzumab. In the KATHERINE trial comparing T-DM1 with trastuzumab, the 3-year OS for the ITT population did not cross the early reporting boundary (HR = 0.70; 95% CI, 0.47-1.05)(von Minckwitz 2019). The HERA trial demonstrated a significant OS benefit for 1 year of trastuzumab vs. observation in the HER2+ ITT population after 12 years of follow-up (HR = 0.74; 95% CI, 0.64-0.86; *P* <0.0001) however, in the HER2+/HR+ cohort, there was not a statistically significant OS benefit (HR = 0.81; 95% CI, 0.65, 1.00; *P* = 0.053)(Cameron 2017).

These OS results reflect the fact that patients with early breast cancer have low mortality rates, so demonstrating OS in the adjuvant setting is challenging, requiring large patient populations, and/or longer follow-up with no adjustments on subsequent treatments to show statistically significant differences between groups. In addition, it is challenging to incorporate the heterogeneity of treatments patients receive in the metastatic setting that may confound any eventual observed OS findings. For these reasons, US FDA guidance for clinical trials recommends iDFS as an acceptable surrogate endpoint in the adjuvant setting (FDA, 2018). In Europe, marketing authorization for HER2-directed adjuvant therapies has also been granted on the basis of iDFS as the primary outcome. Regulatory feedback for neratinib from the EMA regarding the OS data states that these results do not change the benefit/risk balance of neratinib. Even though not statically significant, the numerical OS advantage observed with neratinib in ExteNET confirms the iDFS benefit at 2 years and 5 years.

	In summary, the final published ExteNET results confirm the long-term efficacy of neratinib, reporting a potential survival benefit in the EU label population of 17%, which indeed is a clinically significant advantage for patients with early HER2+/HR+ breast cancer.
3	**Draft conclusion wording (translated to English):** *For the important effect measure IDFS, studies demonstrate an effect which at best corresponds to neratinib having a moderate added value compared to placebo for this endpoint. However, the Danish Medicines Council estimates that the effect will be less in Danish clinical practice, as the patients now receive better treatment than when the study was completed. Therefore, the Danish Medicines Council has assessed that neratinib has a small added value compared to placebo the impact measure IDFS*. In ExteNET, no patients received pertuzumab or T-DM1 according to the original protocol (06/2009), as these two treatments were not approved at time of ExteNET study initiation. However, the EU label specifies that neratinib can be initiated after all trastuzumab-based treatments, including trastuzumab and T-DM1. Pierre Fabre also wishes to highlight that T-DM1 was not approved by the DMC at the start of our application process, a comparison with T-DM1 was not included in the DMC protocol as a clinical question, and was not approved at the time of ExteNET initiation. The addition of neratinib following on from adjuvant therapy with any trastuzumab-based therapy (with or without neoadjuvant therapy) is expected to offer additional efficacy in the extended adjuvant setting on top of the benefit provided by previous trastuzumab-based therapy, as currently there is no further HER2-directed therapy beyond one year of treatment with these trastuzumab-based agents. The use of neratinib in the extended adjuvant setting may be of additional benefit to patients with ER+ disease. Neratinib's intracellular mode of action simultaneously blocks multiple ErbB receptors, and has demonstrated inhibition of bidirectional crosstalk between HER2 and oestrogen receptors (ER) that contributes to drug resistance to both HER2-directed agents and endocrine therapy, something that has not been shown with trastuzumab-based regimens. As pertuzumab and T-DM1 both target the extracellular domain of HER2 via antibody-dependent, cell-mediated cytotoxicity, both are unlikely to influence the bidirectional crosstalk of the ER/HER2 signalling pathway and would have no impact any potential resistance to endocrine therapy. Based on the intracellular mechanism of action of neratinib, it is very unlikely that neratinib should only be effective after trastuzumab, and not after other trastuzumab-based agents, such as T-DM1, which explains its label indication for use in HER2+/HR+ patients who completed adjuvant trastuzumab-based therapy less than one year ago. **In summary, significant added value for neratinib versus placebo was shown through clinically meaningful improvements in the EU label population on the primary outcome iDFS and in patients who do and do not attain a pCR after neoadjuvant therapy (Chan 2020). Clinical benefit was also shown on other important outcomes, such as distant disease-free survival (DDFS) and cumulative incidence of CNS recurrence.**
4	**Draft conclusion wording (translated to English):** *For the critical endpoint of quality of life, neratinib has no documented added value compared to placebo.*

	Neratinib is the first treatment that is currently approved in the extended adjuvant setting with placebo as the comparator. Comparing an active treatment to placebo may lead to a quality of life (QoL) impairment at least during the treatment phase and that was the purpose of the use of EQ-5D and FACT-B (total score and score by subscale). Published QoL analyses in ExteNET show that, even without antidiarrhoeal prophylaxis, there were no clinically meaningful differences in QoL between neratinib and placebo during the trial (with the exception of FACT-B PWB subscale at month 1), despite the increased incidence of neratinib-associated diarrhoea (see comment 5).(Delaloge 2019) These results show that the side effects associated with neratinib have a minimal impact on patient QoL, and the difference does not reach the clinically significant threshold. In real-life clinical practice using the prophylaxis and dose escalation regimens with neratinib as specified in the SmPC, the diarrhoeal side effects associated with neratinib are not expected to impact on a patient's QoL, and will be manageable and transient. When compared with approved HER2-directed adjuvant therapies, transient decreases in QoL were observed with adjuvant T-DM1 in the KATHERINE trial. More patients in the T-DM1 arm reported clinically meaningful deterioration at some point in the study in several symptoms and functioning scales, but by the 6-month follow-up assessment, the proportion reporting clinically meaningful deterioration was generally similar in each arm.(Conte 2020) Peripheral neuropathy is not a life-threatening symptom, but its much higher incidence with T-DM1 can worsen quality of life for prolonged periods (KADCYLA EPAR, Page 94) **In summary, neratinib had no added value on QoL during the treatment phase versus placebo and did not worsen QoL to levels that would have been clinically relevant. In ExteNET, differences in QoL between neratinib and placebo as measured by the FACT-B and EQ-5D-3L, were greatest after 1 month of treatment in favour of placebo. These differences did not cross clinically meaningful thresholds (7 8 points for total FACT-B or previously reported important differences for EQ-5D Index [0.09-0.10 units] or EQ-5D-3L health state [7-10 units]) (Delaloge 2019).**
5	**Draft conclusion wording (translated to English):** *Neratinib is a side effect-heavy treatment compared to placebo. Almost 30% of patients experience grade 3 diarrhoea during the first months of treatment, even when given prophylactic treatment with loperamide. These are not life-threatening side effects, but they are very annoying side effects for patients who have otherwise been declared healthy. The Medical Council therefore also expects that some patients will potentially opt out of neratinib treatment due to the side effects. The negative value regarding side effects weigh heavily in the Danish Medicines Council's overall assessment of the value of neratinib compared with placebo. Based on the above, the Danish Medicines Council therefore assesses overall that neratinib has a negative value* *compared to placebo* No prophylaxis was given to prevent the risk of diarrhoea in ExteNET. The frequency and severity of diarrhoea in ExteNET cannot be equated with the current reality of care using prophylaxis, as specified in the SmPC. Indeed, no systematic antidiarrhoeal prophylaxis was prescribed in the ExteNET study, and diarrhoea was managed if it

	occurred. In ExteNET, adverse events associated with neratinib were generally transient and manageable with dose modifications and/or conventional treatment. Diarrhoea, a known class effect of tyrosine kinase inhibitors, was common with neratinib in the absence of proactive antidiarrhoeal prophylaxis (grade 3, 39%), although most grade 3 events occurred in the first month of treatment (median time to onset, 8 days) and had a short cumulative duration (median, 5 days). This is also an adverse event known by clinicians as being manageable. In the section 4.4 of the SmPC, it is indicated that " *Patients should be instructed to initiate prophylactic treatment with an anti-diarrhoeal medicinal product with the first dose of Nerlynx, and maintain regular dosing of the anti-diarrhoeal medicinal product during the first 1-2 months of Nerlynx treatment, titrating to 1-2 bowel movements per day"*. Moreover, educational materials are in place to guide its management and inform both clinicians and patients. Antidiarrhoeal prophylaxis or neratinib dose escalation (escalating from 160 mg to 240 mg over two weeks) have since been shown to reduce the incidence, severity and duration of neratinib-associated grade ≥3 diarrhoea in the published phase II CONTROL study as compared with ExteNET (Barcenas 2020). The greatest benefits were seen in the dose-escalation cohort of CONTROL, where the rate of grade 3 diarrhoea was 15% (vs 40% in ExteNET), the median cumulative duration of grade 3 diarrhoea was 2 days (vs 5 days in ExteNET), and the rate of discontinuation due to diarrhoea was 3% (vs 17% in ExteNET). Tolerability is also improved with pre-emptive prophylaxis or dose escalations, allowing many patients to complete the full year of neratinib treatment. In support of this, Danish clinical experts consulted in support of our final application (see Appendix) see antidiarrhoeal prophylaxis as standard practice in breast cancer chemotherapy regimens. Further, in recent discussions with Danish breast oncologists; other current treatment options are also linked to gastrointestinal AEs such as diarrhoea, including lapatinib, capecitabine, vinorelbine and abemaciclib. Thus neratinib, as such, would not necessarily introduce an otherwise unknown or uncommon side effect and Danish oncologists are through clinical experience well equipped to handle diarrhoea. Unlike other HER2-directed agents used to treat early breast cancer, neratinib does not have increased incidence of cumulative severe adverse events, such as neutropenia, neuropathy, hepatoxicity and cardiac toxicity. In comparison, the frequency and severity of AEs is increased in patients with early breast cancer treated with T-DM1, including the major safety risks derived from thrombocytopenia, haemorrhage and hepatotoxicity (KADCYLA EPAR, Page 94). **In summary, by applying appropriate standard prophylaxis strategies to manage neratinib-induced diarrhoea, patients are likely to be able to complete their course of therapy and derive greater benefit from the treatment**.
6	**Draft conclusion wording (translated to English**. *Based on the above, the Danish Medicines Council therefore assesses overall that neratinib has a negative value compared to placebo.* In light of the recently published OS data, the new data on the improved treatment effect (particularly in patients with residual disease after neoadjuvant therapy), and the improved tolerability seen with dose escalation in the latest results of CONTROL, Pierre Fabre do not consider the gastrointestinal side effects to outweigh the treatment effect of

	neratinib versus placebo, and would request that the DMC reconsider their conclusions in light of the new published data. As concluded by the EMA's Committee for Medicinal Products for Human Use (CHMP) in its updated assessment report, the balance of benefit/risk is maximised in the EU label population (HR+/≤1 year from trastuzumab), and published data show that this benefit is even greater in patients with residual disease after neoadjuvant therapy (Chan 2020). **In summary, a negative value for neratinib (a first-in-class oral HER2-directed therapy in the extended adjuvant setting) would represent a loss of chance for patients in Denmark with HER2+/HR+ early breast cancer to reduce their risk of disease recurrence**.
7	**Draft wording 5 (translated to English):** *The many changes in the study protocol reduce the subject committee's confidence in the study results.* Three major amendments were applied during the course of the ExteNET study which impacted on eligibility criteria, sample size, and study duration. A single contract research organization ran the study from the start to the end, and all operational aspects remained consistent throughout the study. All major amendments were due to external factors and study blinding was maintained throughout the trial duration. ▪ Amendment #3 (02/2010) was made to incorporate new knowledge about disease prognosis with trastuzumab[1] and to avoid overtreatment of lower risk patients (i.e., limiting the enrolment to stage II-IIIc patients) and ensure that neratinib will be initiated within 1 year of completion of trastuzumab therapy ▪ Amendments #9 (10/2011) and #13 (01/2014) concomitant to the change of sponsors with amendments #13 restoring the long-term follow-up The evaluation of the primary outcome (iDFS at 2 years) was not impacted by these amendments, supported by additional analyses (in the amended ITT population, aITT) (Chan 2016). The validity of iDFS at 5 years is also supported by the comparison of baseline characteristics, the protocol in place for ensuring re-consent and blinding, and the tipping method: the 2-year iDFS hazard ratio was comparable for patients who did or did not re-consent for part B. Tipping point analysis showed that in order to lose statistical significance, there would need to be 35/419 events in the neratinib patients who did not re-consent, compared to 18/335 events in the placebo arm. Simulations based on assuming all non-consenting patients would behave like placebo patients on average gave hazard ratios very similar to those seen in the primary 5-year analysis (0.75 compared to 0.73) (NERLYNX EPAR). **In summary, over the course of ExteNET, 3 different sponsors were involved, resulting in 3 global amendments to the study design. However, these amendments are unlikely to impact on the reliability of the results, as concluded by the EMA's CHMP in its assessment report, which stated: *"Overall, considering the number of significant protocol amendments, there are no major methodological issues."*** [1] Updated results of the NCCTG-N9831 trial and the BCIRG006 study showed that patients with node negative tumours and those receiving concurrent trastuzumab-based chemotherapy had lower rates of recurrence than originally considered in the ExteNET design. A higher risk of recurrence was also reported closer to completion of trastuzumab therapy in these trials.

8	**Draft wording 6 (translated to English):** *EMA requested a subgroup analysis of patients with ER + breast cancer who had received trastuzumab for less than one year ago, which was not pre-specified in the study protocol. Power estimates for the subgroup analysis for all relevant effect measures is not included in the published articles for the study, but is included in the EPAR (but only with a two-year follow-up period). ER status was a stratification factor in the ExteNET study.* Please note that both ER status and time from completion of trastuzumab therapy were pre-specified analyses in ExteNET, and HR+ was a stratification factor. An additional subgroup analysis was requested by the EMA for patients with HR+ disease (stratification factor) who were within 1 year of completion of trastuzumab therapy (systematic post-amendment 3): the EU label population. Although this subgroup was not explicitly defined in the statistical analysis plan, both variables used to define the label population of interest (i.e., HR status and ≤ 1 year from completion of prior trastuzumab-based therapy) were integrated individually in the statistical analysis plan. In addition, the majority of patients in ExteNET in the ITT population had completed trastuzumab within 1 year, with a median time from last trastuzumab dose to randomization of 4.4 months (IQR, 1.6-10.1) with neratinib and 4.6 months (IQR, 1.5-10.8) with placebo (Chan 2016). The EU label population accounts for 47% of the ITT population. Baseline patient characteristics for both the ITT and EMA label population are consistent and there is no imbalance between treatment arms, as highlighted by the DMC. In the ITT population, the primary objective was reached: a statistically significant and clinically relevant reduction of invasive disease recurrence at 2 years by 33% (HR, 0.67; 95% CI: 0.49-0.91), with an absolute iDFS benefit of 2.3% in favour of neratinib. In the EU label population, the results are consistent across all endpoints, and the risk of recurrence at 2 years and at 5 years is significantly reduced. Evaluation of the Kaplan-Meier curves for iDFS in in the EU label population revealed that they separated early (3 months) and continued to separate for the duration of follow-up. The EU label population results from a restriction by EMA (not the sponsor), which considered the following in its decision: ▪ an optimised risk/benefit profile in the EU label population with a 50% reduction of risk of invasive disease recurrence at 2-years and 39% at 5-years ▪ supportive biological rational (i.e. HER2-hormone receptor crosstalk) ▪ appropriate use of neratinib in the treatment setting "... less than one year from the completion of prior adjuvant trastuzumab based therapy". **In summary, in the EU label population, ExteNET results are consistent across all endpoints and the benefit/risk profile for neratinib is maximized, therefore it sets favourable grounds for an efficient budget allocation.**

Medicinrådet

Medicinrådets vurdering af neratinib til forlænget adjuverende behandling af ER+ og HER2+ brystkræft

Versionsnr.: 1.1

Medicinrådet

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om vurderingsrapporten

Vurderingsrapporten indeholder Medicinrådets vurdering af, hvilken værdi lægemidlet har for patienten i forhold til nuværende standardbehandling.

Værdien for patienten og omkostningerne for samfundet danner grundlaget for Medicinrådets beslutning om, hvorvidt lægemidlet anbefales som mulig standardbehandling. Dette sammenfatter vi i Medicinrådets anbefaling vedr. lægemidlet.

Lægemidlet er vurderet efter *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, som du kan finde på Medicinrådets hjemmeside under siden Metoder.

Godkendt af Medicinrådet 4. februar 2021
Dokumentnummer 102873
Versionsnummer 1.1

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www.medicinraadet.dk
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Format: pdf

Indhold

1 Medicinrådets konklusion

Medicinrådet vurderer, at neratinib har **negativ værdi** sammenlignet med placebo til patienter med tidlig ER+/HER2+ brystkræft og lymfeknudemetastaser, som har modtaget adjuverende trastuzumab eller ikke har opnået komplet respons på neoadjuverende behandling.

Neratinibs værdi på det kritiske effektmål *samlet overlevelse* kan ikke kategoriseres. Punktestimatet for den absolutte effektforskel er mindre end den mindste klinisk relevante forskel, og den relative effektforskel kan ikke kategoriseres grundet et bredt konfidensinterval. Medicinrådet vurderer, at effekten vil være mindre i dansk klinisk praksis, nu hvor patienterne får en bedre behandling, end da studiet blev gennemført. Derfor konkluderer Medicinrådet, at det ikke er sandsynliggjort, at neratinib medfører forbedret overlevelse.

Der kan i studiet påvises en effekt for det vigtige effektmål IDFS, som i bedste fald svarer til, at neratinib har en moderat merværdi sammenlignet med placebo for dette effektmål. Medicinrådet vurderer dog, at effekten vil være mindre i dansk klinisk praksis, da patienterne nu får en bedre behandling, end da studiet blev gennemført. Derfor har Medicinrådet vurderet, at neratinib har en lille merværdi sammenlignet med placebo for effektmålet IDFS. For det kritiske effektmål livskvalitet har neratinib ingen dokumenteret merværdi sammenlignet med placebo. Neratinib er en bivirkningstung behandling sammenlignet med placebo. Næsten 30 % af patienter oplever at få grad 3 diarré i løbet af de første måneders behandling, selv når der gives profylaktisk behandling med loperamid. Der er ikke tale om livstruende bivirkninger, men der er dog tale om meget generende bivirkninger for patienter, som ellers er erklæret raske. Medicinrådet forventer derfor også, at en del patienter potentielt vil fravælge behandling med neratinib grundet bivirkningerne. Den negative værdi vedr. bivirkninger vejer tungt i Medicinrådets samlede vurdering af neratinibs værdi sammenlignet med placebo.

På baggrund af ovenstående vurderer Medicinrådet derfor samlet set, at neratinib har **negativ værdi** sammenlignet med placebo.

Medicinrådet kategoriserer lægemidlers værdi i en af følgende kategorier:

• **Stor merværdi:** Der er påvist en stor forbedring i effektforhold i forhold til gældende standardbehandling, eksempelvis markant forbedret overlevelse, markant reduktion i forekomsten af alvorlige symptomer og/eller alvorlige bivirkninger.

• **Moderat merværdi:** Der er påvist en moderat forbedring i forhold til gældende standardbehandling, eksempelvis moderat forbedret overlevelse, moderat reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Lille merværdi:** Der er påvist en lille forbedring i forhold til gældende standardbehandling, eksempelvis en dokumenteret forbedret overlevelse, en reduktion i forekomsten af symptomer og/eller bivirkninger.

• **Merværdi af ukendt størrelse:** Der er påvist en forbedring i forhold til gældende standardbehandling, men størrelsen af forbedring kan ikke bestemmes. Lægemidlets merværdi er som minimum lille, men kunne også være moderat eller stor.

• **Ingen dokumenteret merværdi:** Der er ikke påvist en merværdi i forhold til gældende standardbehandling. Omvendt tyder den tilgængelige evidens heller ikke på, at der er en negativ værdi.

• **Negativ værdi:** Der er påvist en negativ værdi i forhold til gældende standardbehandling.

• **Samlet værdi kan ikke kategoriseres:** På grund af usikkerheder omkring effektforhold er det ikke muligt at kategorisere lægemidlets samlede værdi.

Medicinrådet vurderer kvaliteten af de data, der ligger til grund for vurderingen af lægemidlet (evidensens kvalitet), i en af følgende GRADE-kategorier:

• **Høj:** Nye studier vil med meget lav sandsynlighed ændre konklusionen.

• **Moderat:** Nye studier vil med lav sandsynlighed ændre konklusionen.

• **Lav:** Nye studier vil med moderat sandsynlighed ændre konklusionen.

• **Meget lav:** Nye studier vil med høj sandsynlighed ændre konklusionen.

2 Begreber og forkortelser

CI	Konfidensinterval
DBCG	Danish Breast Cancer Group
EC	Epirubicin og cyklofosfamid
EMA	Det Europæiske Lægemiddelagentur (*European Medicines Agency)*
EORTC-QLQ-BR23	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Breast 23 module*
EORTC-QLQ-C30	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EPAR	*European Public Assessment Report*
ER	Østrogenreceptor (*estrogen receptor*)
GRADE	System til at vurdere evidens (*Grading of Recommendations, Assessment, Development and Evaluation*)
HER2	Human epidermal vækstfaktorreceptor 2 (*human epidermal growth factor receptor 2*)
HR	*Hazard ratio*
ITT	*Intention to treat*
OR	*Odds ratio*
PICO	Population, intervention, komparator og effektmål (*Population, Intervention, Comparator and Outcome)*
PP	*Per-protocol*
RCT	Randomiseret kontrolleret studie *(Randomised Controlled Trial)*
RR	Relativ risiko
SMD	*Standardized Mean Difference*

3 Introduktion

Formålet med Medicinrådets vurdering af neratinib til patienter med tidlige stadier af ER+ og HER2+ brystkræft er at vurdere den værdi, lægemidlet har, sammenlignet med dansk standardbehandling.

Vurderingen er udarbejdet, fordi Medicinrådet har modtaget en endelig ansøgning fra Pierre Fabre Pharma. Vi modtog ansøgningen den 8. september 2020.

Det kliniske spørgsmål er:

Hvilken værdi har neratinib sammenlignet med placebo for patienter med ER+ og HER2+ brystkræft?

3.1 ER+ og HER2+ brystkræft

Brystkræft er den hyppigste kræftform hos kvinder verden over og forekommer oftest hos kvinder over 50 år. I Danmark bliver omkring 4.900 patienter årligt diagnosticeret med brystkræft, og ca. 64.000 patienter lever med diagnosen brystkræft [1,2].
Sygdommen kan opdeles i fire undertyper, afhængigt af om kræftcellerne er hormonfølsomme, dvs. om de udtrykker østrogen receptor (ER) og/eller human epidermal vækstfaktorreceptor 2 (HER2 [3]).
Patienterne testes rutinemæssigt for både ER og HER2 status ved diagnosetidspunktet. ER og HER2 status testes ved immunhistokemi. I tilfælde, hvor resultatet ikke er entydigt, kan in situ hybridisering benyttes i henhold til patologiafsnittet under DBCGs retningslinjer [4]. Hvis over 1 % af tumorcellerne er positive for ER, benævnes tumoren som ER+.

Af de 4.900 patienter, som årligt diagnosticeres med brystkræft i Danmark, vurderer fagudvalget, at ca. 4.600 har tidlig brystkræft (dvs. patienterne har ikke fjernmetastaser). Heraf er der årligt ca. 410 nye danske patienter med tidlig ER+/HER2+ brystkræft, jf. dataudtræk fra DBCG.

Klinikere vurderer stadier af brystkræft ud fra den internationalt anerkendte standardiserede *Tumor, Node, Metastasis* (TNM)-klassifikation. Tumorklassificeringen er baseret på en vurdering af den primære tumors størrelse, om den primære tumor har indvækst i omkringliggende væv (T0-T4), i hvor høj grad tumoren har bredt sig til regionære lymfeknuder (N0-N3), og om der er fjernmetastaser (M1), se tabel 1.

TNM-klassifikation er i høj grad korreleret med prognose. Således har patienter med N0 sygdom og lille primær tumor (< 3 cm) en bedre prognose, dvs. mindre risiko for tilbagefald, end patienter med lymfeknudeinvolvering og/eller større primær tumor [5] [6].

Tabel 1. TNM-klassifikation af kræft

	Stadie	**Definition**
Primær tumor	T0	Ingen primær tumor.
	T1	Vurdering af størrelse samt omfang af primær tumor. Jo højere kategori des større tumor. Ved T4 tumorer er der indvækst i muskel og/eller hud, eller der er tale om inflammatorisk brystkræft.
	T2	
	T3	
	T4a Indvækst i brystmusklen T4b Indvækst i huden T4c Indvækst i både hud og brystmusklen T4d Inflammatorisk brystkræft	
	TX	Primær tumor kan ikke vurderes.
Lymfeknude involvering	N0	Ingen spredning til nærliggende lymfeknuder
	N1	

	N2	Højere kategori reflekterer spredning til flere lymfeknuder i armhulen eller til lymfeknuder langs kravebenet eller brystbenet.
	N3	
	NX	Lymfeknuderne kan ikke vurderes.

Det studie, der bedst belyser langtidsoverlevelsen for patienter med HER2+ brystkræft (HERA-studiet), er et studie af adjuverende trastuzumab-behandling, som viser, at 79 % af patienterne var i live efter 12 år [7]. Fagudvalget forventer dog, at overlevelsen er stigende, da den nuværende brystkræftbehandling, inkl. kirurgi, strålebehandling og systemisk behandling, er bedre, end da HERA-studiet blev udført.

3.2 Neratinib

Neratinib har følgende EMA-indikation:
Neratinib er indiceret til forlænget adjuverende behandling af voksne patienter med tidlige stadier af hormonreceptor-positiv brystkræft med overudtryk af HER-2, som inden for det seneste år har afsluttet en tidligere adjuverende trastuzumab-behandling.

Neratinib er en tyrosinkinasehæmmer rettet mod HER1-, HER-2 og HER-4. Neratinib binder sig til og hæmmer receptorerne, hvilket hæmmer væksten af tumorceller. Neratinib gives oralt, og den anbefalede dosis er 240 mg én gang dagligt, hvilket gives som 6 tabletter a 40 mg. Neratinib gives i op til et år.

Patienter med tidlige stadier af ER+ og HER2+ brystkræft, som har modtaget og afsluttet et års adjuverende trastuzumab-baseret behandling for mindre end et år siden og er recidivfrie, er kandidater til adjuverende behandling med neratinib. Hvis neratinib bliver anbefalet, vil den nuværende behandlingsrækkefølge være uændret, da neratinib indplaceres som en ekstra behandlingslinje efter adjuverende behandling med trastuzumab (se afsnit 3.3).

Fagudvalget vurderer desuden, at en del af de ovenstående patienter ikke vil have gavn af neratinib eller ikke bør tages i betragtning til neratinib, se afsnit 5.1.2 for yderligere information.

Neratinib er ikke godkendt til andre indikationer end brystkræft.

3.3 Nuværende behandling

(Neo)adjuverende behandling af tidlig HER2+ brystkræft

Patienter med tidlig HER2+ brystkræft egnet til (neo)adjuverende behandling vil oftest modtage en kombination af medicinsk behandling, operation og strålebehandling, jf. gældende guidelines fra DBCG [3] og behandlingsvejledningen udarbejdet af RADS [2].

HER2+ patienter tilbydes som regel behandling med kemoterapi (taxan- og antracyklinbaseret) afhængigt af bl.a. brystkræftstadie, alder, komorbiditet og prognose og desuden HER2-rettet behandling. Kemoterapi og HER2-rettet behandling kan gives før operation i bryst og lymfeknuder (neoadjuverende) og/eller efter operation (adjuverende). Neoadjuverende behandling består af epirubicin og cyklofosfamid (EC) samt taxan-baseret kemoterapi i kombination med pertuzumab og trastuzumab, og adjuverende behandling består af EC eller taxan-baseret kemoterapi i kombination med trastuzumab. Trastuzumab er et antistof rettet mod HER-2 receptoren, og pertuzumab er rettet mod HER-2 og HER-3 receptoren. Trastuzumab gives i op til et år (17 behandlinger). Neoadjuverende og adjuverende behandling anses som ligeværdige behandlingsmuligheder for patienter med operabel brystkræft [6] – dog opnår flere patienter brystbevarende operation, når der gives neoadjuverende behandling. For patienter med lokal fremskreden brystkræft er der en bedre prognose ved at

give neoadjuverende behandling. For både patienter med operabel sygdom og inoperabel sygdom, der har modtaget neoadjuverende behandling, tilbydes adjuverende T-DM1 ved restsygdom på operationstidspunktet. Der gives desuden strålebehandling, hvis der er udført brystbevarende operation og/eller ved spredning til lymfeknuder [3].

Efter operation i bryst og lymfeknuder tilbydes patienter med ER+ sygdom desuden antihormonbehandling. Dette tilbud er uafhængigt af, om der er givet adjuverende eller neoadjuverende behandling.

Målet med den (neo)adjuverende behandling er at forebygge tilbagefald. Da tilbagefald oftest er ensbetydende med udvikling af en uhelbredelig brystkræftsygdom (spredning til andre organer eller knogler), vurderer fagudvalget, at det er af stor betydning for patienterne, at tilbagefald forebygges.

Antihormon-efterbehandling, når tumor også er ER+

HER2+ patienter, hvis tumor også er ER+, modtager i tillæg til den HER2+ rettede behandling også antihormonbehandling. Denne består overordnet af tamoxifen i 10 år for de kvinder, der er præmenopausale. Tamoxifen er en selektiv østrogen receptor modulator. For kvinder, der er postmenopausale, består behandlingen af en aromatasehæmmer (AI) i fem år. AI hæmmer dannelsen af binyredannet østrogen, hvorved østrogenniveauet i kroppen falder. Der findes forskellige aromatasehæmmere, der er vurderet at være ligestillede, og i Danmark anvender man letrozol.

4 Metode

Medicinrådets protokol for vurdering af neratinib til behandling af ER+ og HER2+ brystkræft beskriver sammen med *Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser*, hvordan vi vil vurdere lægemidlets værdi for patienterne.

5 Resultater

5.1 Klinisk spørgsmål 1

Hvilken værdi har neratinib sammenlignet med placebo for patienter med ER+ og HER2+ brystkræft?

5.1.1 Litteratur

Nedenfor beskriver og vurderer vi den litteratur, som ansøger har anvendt i sin endelige ansøgning.

Ansøgningen baserer sig på ExteNET-studiet, hvor der er to publicerede artikler, og CONTROL-studiet, som undersøger forebyggende behandling rettet mod neratinib-induceret diarré.

Studiekarakteristika

ExteNET [8,9]: Studiet er et randomiseret, dobbeltblindet, placebokontrolleret fase III-studie, som undersøger effekt og sikkerhed af neratinib til behandling af patienter med tidlig HER2+ brystkræft, som har modtaget adjuverende behandling med trastuzumab. Patienterne (N = 2.840) blev randomiseret 1:1 til et års behandling med neratinib eller placebo. Randomiseringen var stratificeret efter, om patienterne var ER+ eller ER-, om der var lymfeknudeinvolvering (opdelt i status for lymfeknudeinvolvering 0, 1-3 eller 4), og om tidligere adjuverende behandling med trastuzumab blev givet sammen med eller efter kemoterapi.

Det primære effektmål i studiet var IDFS (STEEP-defineret, bortset fra nye kræftformer, der ikke er recidiv, hvilket ikke blev inkluderet). Sekundære effektmål inkluderede overall survival og sikkerhed.

Flere opdateringer af studieprotokollen er blevet foretaget løbende. De mest betydende var, at studiet blev ændret til kun at inkludere patienter med stadie II-IIIC brystkræft og aksil lymfeknudemetastase(r) (se tabel 1 for definitioner af disse). Desuden blev analysen ændret fra at fokusere på patienter, som havde modtaget trastuzumab for under to år siden, til patienter, som havde modtaget trastuzumab for under ét år siden. Recidiv opstår ofte inden for de første 2 år efter primær behandling. Fagudvalget vurderer, at disse ændringer betyder, at studiet inkluderer patienter med den største risiko for tilbagefald. Dette er der klinisk rationale i, men det kan samtidig betyde, at effekten af neratinib bliver overvurderet ift. den oprindelige studiepopulation. Desuden blev der ændret løbende i antallet af patienter, som skulle inkluderes i studiet, i tidspunktet for primæranalysen samt i kriterierne for IDFS (minimumskrav for antal hændelser) og samlet overlevelse (OS) (fra års opfølgningstid til antal hændelser) i analyseplanen. Ændringerne i tidspunktet for primæranalysen for IDFS medførte, at det var nødvendigt at bede om en ny samtykkeerklæring. Dette blev opnået hos ca. 75 % af patienterne. Fagudvalget vurderer, at der ikke er redegjort tydeligt for de resterende 25 % af patienterne, som ikke fornyede samtykke, og at der er forskelle imellem armene, som kan påvirke effektestimaterne.

De mange ændringer i studieprotokollen mindsker fagudvalgets tiltro til studiets resultater.

EMA udbad en subgruppeanalyse af patienter med ER+ brystkræft, som havde modtaget trastuzumab for mindre end ét år siden, hvilket altså ikke var præspecificeret i studieprotokollen. Effektestimater for subgruppeanalysen for alle relevante effektmål indgår ikke i de publicerede artikler for studiet, men indgår i EPAR'en (dog kun med to års opfølgningstid). ER-status var en stratifikationsfaktor i ExteNET studiet.

CONTROL [10]**:** Studiet er et ublindet fase II-studie, som undersøger sikkerhed og tolerabilitet af forebyggende behandling med peristaltik-hæmmende lægemidler (dvs. lægemidler, som modvirker diarré) mod neratinib-induceret diarré til behandling af patienter, som modtager neratinib som forlænget adjuverende behandling. Subgruppe 1 modtog neratinib og profylaktisk loperamid, subgruppe 2 modtog neratinib, loperamid og budesonid, subgruppe 3 modtog neratinib, loperamid og colestipol, og subgruppe 4 modtog neratinib, loperamid og budesonid *pro-re-nata* (PRN). Dertil kom 2 subgrupper, som modtog neratinib efter en dosis-eskalerings-metode, samt en historisk gruppe, der tidligere havde modtaget neratinib uden forbyggende behandling mod diarré (fra ExteNET-studie). Det primære effektmål var hændelsesraten af diarré, hvor længe patienter havde diarré samt sværhedsgraden af diarré ved behandling med neratinib og forebyggende behandlinger mod diarré.

Population

Tabel 2. Baselinekarakteristika ExteNET-studiet

	ITT-population		EMA-population (ER+/HER2+)	
	Neratinib (N = 1.420)	**Placebo (N = 1.420)**	**Neratinib (N = 670)**	**Placebo (N = 664)**
Median alder (range) – år	52 (25-83)	52 (23-82)	51 (25-83)	51 (23-78)
Neoadjuverende behandling, n (%)	342 (24)	397 (27)	162 (24)	192 (29)
Komplet respons	61 (4)	65 (5)	17 (3)	21 (3)
Ikke komplet respons	258 (18)	298 (21)	131 (20)	164 (25)
Ikke oplyst	23 (2)	16 (1)	14 (2)	7 (1)
Menopausal status ved diagnose, n (%)				
Premenopausal	663 (47)	664 (47)	350 (52)	342 (52)
Postmenopausal	757 (53)	756 (53)	320 (48)	322 (49)
Hormon-receptor status, n (%)				
ER-positive, progesteronereceptor-positive, eller begge	816 (58)	815 (57)	670 (100)	664 (100)
ER-negative og progesteronereceptor-negative eller ukendt status	604 (43)	605 (43)		
Tidligere trastuzumab regime, n (%)				
Samtidig med kemoterapi	884 (62)	886 (62)	411 (61,3)	415 (62,5)
Sekventielt med kemoterapi	536 (38)	534 (38)	259 (38,7)	249 (37,5)
Tidligere stråleterapi, n (%)				
Ja	1.130 (80)	1.150 (81)		
Nej	290 (20)	270 (19)		
Type af kirurgi, n (%)				
Mastektomi	951 (67)	908 (64)		
Lumpektomi	468 (33)	511 (36)		
Ikke oplyst	1 (< 1)	1 (< 1)		
Neoadjuverende/adjuverende kemoterapi – antal patienter (%)	136 (10)	135 (10)	67 (10)	58 (9)
Antracyclin alene	962 (68)	965 (68)	435 (65)	445 (67)
Antracyclin + taxan	318 (22)	316 (22)	167 (25)	159 (24)
Taxan alene	4 (< 1)	4 (< 1)	1 (< 1)	2 (< 1)
Hverken taxan eller antracyclin				
Varighed af adjuverende trastuzumab behandling, måneder – median (range)	11,5 (10,9-11,.9)	11,4 (10,8-11,9)	11,4 (1,4-29,1)	11,4 (1,4-24,0)
Tid fra sidste dosis trastuzumab til randomisering, måneder – median (IQR)*	4,4 (1,6-10,4)	4,6 (1,5-10,8)	3,07 (0,2-12,0)	3,30 (0,3-12,0)
Stadie for primær tumor, n (%)				
T1	440 (31)	459 (32)	218 (33)	209 (32)
T2	585 (41)	555 (39)	270 (40)	250 (38)
≥T3	144 (10)	117 (8)	61 (9)	65 (10)
Ukendt status	250 (18)	288 (20)	121 (18)	140 (21)
Lymfeknude status**, n (%)				
Negativ	335 (24)	336 (24)	130 (19)	125 (19)
1-3 positive lymfeknuder	664 (47)	664 (47)	339 (51)	334 (50)
≥ 4 positive lymfeknuder	421 (30)	420 (30)	201 (30)	205 (31)
Type af endokrin behandling				
Antiøstrogen alene	375 (46)	347 (43)	325 (52)	294 (47)
Antiøstrogen og AI	20 (3)	34 (4)	20 (3)	29 (5)
AI alene	362 (44)	379 (47)	275 (44)	302 (48)
Hverken antiøstrogen eller AI	3 (< 1)	4 (< 1)	2 (< 1)	4 (1)
Ingen endokrin behandling	56 (7)	51 (6)	48 (7)	35 (5)

* IQR: Interkvartil range.

Af tabel 2 fremgår både ITT-populationen (patienter med tidlig HER+ brystkræft) og EMA-populationen (patienter med tidlig ER+/HER2+ brystkræft). Fagudvalget vil primært fokusere på, om der er forskelle på de to arme i EMA-populationen, da det er denne population, der indgår i neratinibs EMA-indikation og dermed i fagudvalgets vurdering.

Som tabel 2 viser, er der ingen betydende forskelle mellem baselinekarakteristika i de to behandlingsarmes patientpopulationer. Fagudvalget vurderer, at baselinekarakteristika viser, at behandlingen i studiet er forældet på flere parametre ift. nuværende dansk klinisk praksis:

- Patienterne i studiet er yngre end i dansk klinisk praksis, hvor den gennemsnitlige alder for patientgruppen er ca. 60 år ifølge fagudvalget, hvilket ikke formodes at have prognostisk betydning.
- Trastuzumab bliver ikke længere givet sekventielt med kemoterapi og aldrig med antracyklin alene, da dette vurderes at være en dårligere behandling.
- I dansk klinisk praksis består neoadjuverende behandling af kemoterapi med tillæg af trastuzumab og pertuzumab. Denne dobbeltblokade af trastuzumab og pertuzumab blev ikke givet til patienter i ExteNET, som modtog neoadjuverende behandling. Dette betyder, at patienterne i studiet har modtaget en dårligere neoadjuverende behandling end i dansk klinisk praksis.
- I Danmark er der flere T1-tumorer og færre T2-tumorer end i studiet, da man i Danmark nu screener for brystkræft og derfor opdager tumorerne på et tidligere stadie.
- Ca. 30 % af patienterne i Danmark er lymfeknude-positive, hvor det i studiet er ca. 80 % Det er dermed en højt selekteret højrisikogruppe, der er valgt ud til behandlingen i ExteNET.
- Selvom det er højrisikopatienter, som indgår i studiet, har 20 % ikke fået adjuverende strålebehandling. Det vil ikke være tilfældet i Danmark, hvor alle patienter i højrisikogruppen vil få adjuverende strålebehandling. Det er dog muligt, at det er de patienter uden lymfeknudemetastaser, som er mastektomeret (har fået fjernet brystet), der ikke modtager stråleterapi, hvilket også er den patientgruppe, som i Danmark ikke vil modtage denne behandling. Dette er der dog ikke redegjort for i studiet.
- Antallet af patienter, som har fået mastektomi, er væsentligt højere (ca. 65 %) end i Danmark, hvor ca. 30 % af patienterne får mastektomi. Dette kan dog skyldes, at der er flere patienter i studiet med større tumorer end i klinisk praksis. I Danmark benyttes oftest brystbevarende operation (lumpektomi) i kombination med strålebehandling, medmindre der er kontraindikationer herfor.

I et nyere studie fik 26 % af patienter med tidlig ER+/HER2+ brystkræft og lymfeknudemetastaser komplet respons under neoadjuverende behandling [11]. Da patienter, som ikke opnår komplet patologisk respons, vil blive tilbudt behandling med T-DM1, har det betydning for, hvor mange patienter der kan tilbydes neratinib, se afsnit 5.1.2 for yderligere information.

Desuden vil man i Danmark – hvis neratinib anbefales – påbegynde behandling med neratinib lige efter afsluttet behandling med trastuzumab, da forebyggende behandling generelt er mere effektiv, jo tidligere man sætter ind. Dette kan betyde, at effekten af neratinib bliver undervurderet, da patienter i studiet først får neratinib efter 11 måneders pause. Fagudvalget vurderer dog, at patienterne i studiet har modtaget en dårligere systemisk behandling (inkl. neoadjuverende behandling) og ikke har modtaget strålebehandling, ift. patienter i nutidig dansk klinisk praksis. Fagudvalget vurderer, at dette medfører, at effekten af neratinib overvurderes, i forhold til hvad effekten vil være i dansk klinisk praksis. Fagudvalget vil løbende kommentere på dette under resultatgennemgangen, se afsnit 5.1.5.

5.1.2 Indsnævring af studiepopulation i vurderingen

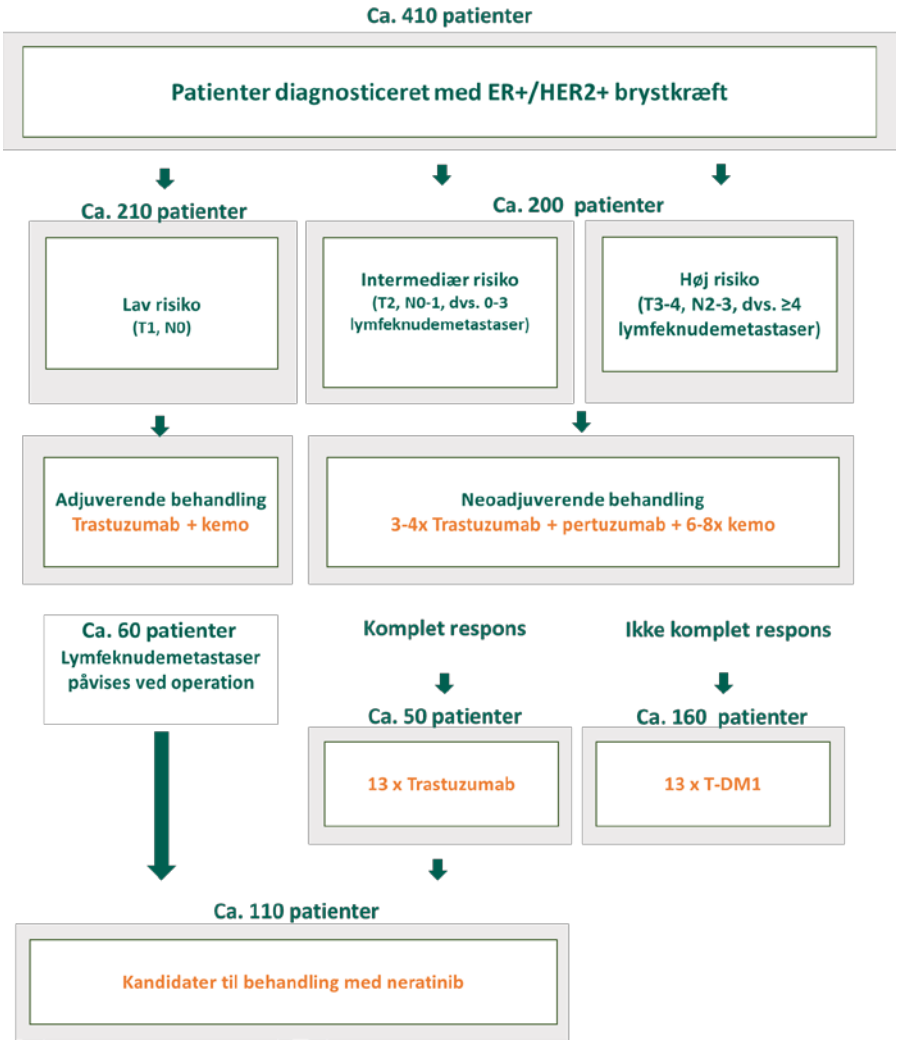
Fagudvalget vurderer, at patientpopulationen, som kan tages i betragtning til behandling med neratinib, bør indskrænkes yderligere i forhold til EMA-indikationen. Fagudvalget vurderer, at det i dansk klinisk praksis vil være patienter med tidlig ER+/HER2+ brystkræft med lymfeknudemetastaser, som har modtaget primær neoadjuverende behandling og opnået komplet respons, og patienter, der opdages at have lymfeknudemetastaser ved primær kirurgi, som kan have gavn af neratinib. Kun 20 % af patienterne i studiet er lymfeknude-negative, og der indgår meget få patienter med små tumorer (T1). Det betyder ifølge fagudvalget, at effekten af neratinib for patienter uden lymfeknudemetastaser er dårligt belyst. Desuden vurderer fagudvalget, at patienter med små tumorer og/eller ingen lymfeknudemetastaser har lav risiko for at få tilbagefald, hvorfor yderligere behandling af denne patientgruppe vil være overbehandling (se også afsnit 3).

Derfor finder fagudvalget, at det kun er relevant at behandle patienterne i høj risiko samt intermediær risiko med lymfeknudemetastaser, se figur 1. Disse patienter vil primært få tilbudt neoadjuverende behandling forud for kirurgi, men nogle patienter vil også have fået foretaget primær kirurgi med fund af lymfeknudemetastaser. Begge disse grupper kan eventuelt tilbydes behandling med neratinib.

I august 2020 blev trastuzumab-emtansin (T-DM1) godkendt af Medicinrådet som standardbehandling til patienter med HER2+ brystkræft, som ikke har opnået komplet patologisk respons på neoadjuverende behandling [12], dvs. som adjuverende behandling. Ca. 74 % af patienter, som modtager neoadjuverende behandling, opnår ikke komplet patologisk respons, og er derfor kandidater til T-DM1 [11]. I studiet, som undersøger effekten af neratinib (ExteNET), har ingen patienter modtaget T-DM1 som adjuverende behandling. Fagudvalget vurderer derfor, at der ikke foreligger evidens for effekten af neratinib efter behandling med T-DM1. Patienter, som modtager adjuverende behandling med T-DM1, er derfor ikke kandidater til neratinib. Dermed er det kun ca. 26 % af patienter (med lymfeknudemetaser, som opnår komplet respons på neoadjuverende behandling), som er kandidater til neratinib.

Fagudvalget vurderer således, at det i alt er ca. 110 patienter, som kan komme i betragtning til behandling med neratinib.

Figur 1. Kandidater til behandling med neratinib



5.1.3 Databehandling og analyse

Nedenfor beskriver vi ansøgers datagrundlag, databehandling og analyse for hvert effektmål.

Der foreligger en direkte sammenligning mellem neratinib og ingen behandling (placebo) for patienter med HER2+ brystkræft i ExteNET-studiet [8,9,13]. De primære publikationer rapporterer dog effektestimaterne for ITT-populationen, dvs. patienter, som er ER+, og patienter, der er ER-. Fagudvalget vurderer, at det for den narrative gennemgang af bivirkninger er bedst at benytte ITT-populationen, da denne giver det bedste datagrundlag. Fagudvalget forventer ikke, at ER-status ændrer typen af bivirkninger eller sandsynligheden for at opleve bivirkninger. For de øvrige effektmål foretrækker fagudvalget dog, at data skal fokusere på EMA-populationen, dvs. patienter med ER+/HER2+ brystkræft. Effektestimater for denne patientgruppe indgår i EPAR'en, dog kun med 2 års opfølgning. Pierre-Fabre har efterfølgende foretaget en sensitivitetsanalyse efter 5 års opfølgning, som er præsenteret ved San Antonio Breast Cancer Symposium i 2018. Da fagudvalget ønsker at benytte data med længst mulig opfølgningstid, har ansøger indsendt *data on file* for effektmålene *IDFS og livskvalitet.* De krav for *data on file*, som Medicinrådet har specificeret i *Kriteriepapiret om anvendelse af upublicerede data*, er opfyldt. Studiets design, metoder og primære resultater er tidligere publiceret i fagfællebedømte fuldtekstartikler, og fagudvalget vurderer, at det er forsvarligt at benytte de upublicerede data, og at dette vil styrke kvaliteten af vurderingen markant.

Derudover drejer det sig om en ustratificeret analyse ift. IDFS, som har været præsenteret på en konference. Firmaet har endelig indleveret en stratificeret analyse (stratificeret for randomiseringsstratifikationsfaktorer), som ikke har været offentliggjort i noget format. Fagudvalget vurderer, at den stratificerede analyse er det bedste datagrundlag for gennemgangen af effektmålet, og vil derfor benytte denne analyse.

Den sensitivitetsanalyse, som foreligger efter 5 års opfølgning, har krævet, at patienterne har indsendt samtykke på ny. Dette lykkedes hos ca. 75 % af patienterne, hvilket betyder, at der er færre patienter i hver arm. Fagudvalget vurderer, at dette medfører nogen usikkerhed om validiteten af data, da det ikke er klart beskrevet, hvilke patienter der ikke kan indhentes nyt samtykke for, men vurderer samtidig, at det er nødvendigt at bruge længst mulig opfølgningstid. Fagudvalget vil derfor benytte analysen ved 5 års opfølgningstid på trods af de usikkerheder, der er forbundet med analysen, men vil tage højde for dette under gennemgangen af data.

I en nylig udgivelse er samlet overlevelse publiceret for både ITT-population og for EMA-populationen [13].

CONTROL-studiet inddrages kun ved gennemgangen af bivirkningsprofilen ifm. håndtering af neratinib-induceret diarré.

5.1.4 Evidensens kvalitet

Fagudvalget har anvendt GRADE til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Nedenfor følger en beskrivelse af vurderingen af de væsentligste domæner for hvert klinisk spørgsmål. Den fuldstændige GRADE-vurdering og begrundelserne er samlet i en GRADE-profil (bilag 1).

Det vurderes overordnet, at studiet har høj risiko for bias, da der er foretaget mange ændringer i studieprotokollen, som kan have indflydelse på effektestimaterne. Dette mindsker tiltroen til studiets resultater. Fagudvalget vurderer dog, at dette primært har indvirkning på resultaterne for OS og IDFS, da opfølgningstiden for hhv. livskvalitet og bivirkninger er 12 og 24 måneder, og størstedelen af bivirkninger forventes inden for de første få måneder af behandlingen.

Der er nedgraderet for ”inkonsistens”, da der kun foreligger et sammenlignende studie. For OS og livskvalitet er der nedgraderet for ”unøjagtighed”, da konfidensintervallerne er brede, hvilket kan betyde forskellige konklusioner for neratinibs effekt. For OS og IDFS er der nedgraderet for ”indirekthed”, da fagudvalget vurderer, at patienternes prognose i dansk klinisk praksis er bedre end i ExteNET. For effektmålet bivirkninger er der ikke nedgraderet for ”indirekthed”, selvom effektmålet er opgjort som *treatment-emergent adverse events* og ikke bivirkninger som specificeret i protokollen. Der er ikke nedgraderet, da fagudvalget ikke forventer, at der er væsentlig forskel på de to indrapporteringer for patientgruppen.

Evidensens kvalitet er meget lav, hvilket betyder, at nye studier med høj sandsynlighed kan ændre konklusionen.

5.1.5 Effektestimater og kategorier

I tabel 3 fremgår de absolutte og relative effektforskelle, de foreløbige og aggregerede kategorier, den samlede kategori og den samlede kvalitet af evidensen for klinisk spørgsmål 1.

Tabel 3. Resultater for det kliniske spørgsmål

Effektmål	Måleenhed (MKRF)	Vigtighed	Forskel i absolutte tal		Forskel i relative tal		Aggregeret værdi for effektmålet
			Forskel (95 % CI)	Foreløbig værdi	Forskel (95 % CI)	Foreløbig værdi	
Samlet overlevelse (OS)*	OS-rate ved 8 år*** (MKRF: 3 %-point)	Kritisk	2,1 %-point	Kan ikke kategoriseres	HR: 0,79 (0,55-1,13)	Kan ikke kategoriseres	Kan ikke kategoriseres
Bivirkninger	Andel patienter, der oplever en eller flere grad 3-4 bivirkninger (MKRF: 5 %-point)	Kritisk	37 %-point (33;40)	Negativ	RR 3,8 (3,3; 4,4)	Negativ værdi	Negativ værdi
	Gennemgang af bivirkningsprofil		Se afsnit 5.1.4 Gennemgang af bivirkningsprofil				
Livskvalitet**	Gennemsnitlig ændring over tid (EQ-5D MKRF: 0,08)	Kritisk	0,02 units (-0,01;0,04)	Ingen dokumenteret merværdi	-	Kan ikke kategoriseres	Ingen dokumenteret merværdi
IDFS**	IDFS-rate ved 5 år (MKRF: 5 %-point)	Vigtig	5,1 %-point	Kan ikke kategoriseres	HR: 0,59 (0,41-0,82)	Moderat merværdi	Lille merværdi
Samlet kategori for lægemidlets værdi		Negativ værdi					
Kvalitet af den samlede evidens		Meget lav					

MKRF = Mindste klinisk relevante forskel, CI = konfidensinterval, RR = relativ risiko, HR = Hazard Ratio, IDFS = Invasive-disease free survival.

* Der er ikke opgjort data for dette effektmål.

** *Data on file.*

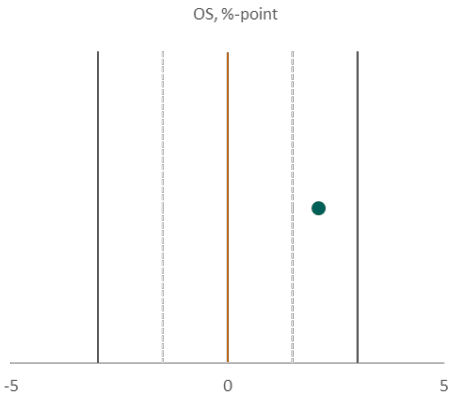
*** I protokollen var MKRF defineret for overlevelsen ved 10 år.

Samlet overlevelse (OS)

Som beskrevet i protokollen er effektmålet *Samlet overlevelse (OS)* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi det er afgørende for patienterne, om behandlingen medfører, at flere bliver helbredt. Fagudvalget havde i protokollen ønsket at få overlevelsesraten ved 10 år opgjort, men accepterer ansøgers indsendte data for 8 års opfølgning.

Data for samlet overlevelse er offentliggjort [13], selvom der endnu er relativt få hændelser grundet patienternes gode prognose. Således er overlevelsesraten opgjort ved 8 år, og her er 89,4 % af patienterne i kontrolarmen i live, mens det er tilfældet for 91,5 % af patienterne i neratinib-armen. Den absolutte effektforskel er dermed 2,1 %-point, hvilket ikke afspejler en klinisk relevant effektforskel (3 %-point). Da der imidlertid ikke kan beregnes et konfidensinterval baseret på Kaplan Meyer-kurver, kan den foreløbige værdi af neratinib på den absolutte effektforskel ikke kategoriseres vedr. OS. Selvom der ikke er vist censureringer i publikationen, noterer fagudvalget, at efter 8 år er kun ca. 50 % af patienterne "at risk", på trods af at det kun er ca. 10 % af patienterne, som er døde. Dermed er der mange patienter, som enten ikke længere bliver fulgt i studiet, eller som er censureret grundet kortere opfølgningstid.

Den absolutte effektforskel er vist i figur 2 nedenfor.



Figur 2: Punktestimat og 95 % konfidensinterval for den absolutte forskel for samlet overlevelse. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Baseret på den relative effektforskel opgjort som en hazard ratio på 0,79 [0,55;1,13] (se tabel 3) har neratinib foreløbig en værdi, som ikke kan kategoriseres vedr. OS grundet det brede konfidensinterval.

Fagudvalget vurderer, at den aggregerede værdi for neratinib **ikke kan kategoriseres** vedr. effektmålet OS. Punktestimatet for den absolutte effektforskel er mindre end den mindste klinisk relevante forskel, og dertil kan den absolutte effektforskel ikke kategoriseres grundet manglende konfidensinterval. Den foreløbige kategori for den relative effektforskel kan ikke kategoriseres grundet et bredt konfidensinterval, men fagudvalget vurderer, at data ikke underbygger, at neratinib har en bedre effekt vedr. OS end placebo.

Dertil lægger fagudvalget vægt på, at der i dansk klinisk praksis nu gives en betydelig mere virkningsfuld behandling ift. (neo)adjuverende medicinsk behandling, type af kirurgisk behandling samt dansk praksis for adjuverende strålebehandling sammenlignet med i studiet. På den baggrund forventer fagudvalget, at den danske patientgruppes prognose er væsentlig forbedret sammenlignet med ExteNET-studiets patientgruppe, og en eventuel effekt af neratinib er dermed overvurderet i studiet. Fagudvalget vurderer derfor, at den aggregerede værdi for neratinib **ikke kan kategoriseres** sammenlignet med placebo for effektmålet OS.

Bivirkninger

Som beskrevet i protokollen er effektmålet *Bivirkninger* kritisk for vurderingen af lægemidlets værdi for patienterne. Fagudvalget finder, at bivirkninger (adverse reactions, AR) er et kritisk effektmål, da det belyser, hvor godt patienterne tolererer neratinib sammenlignet med komparator.

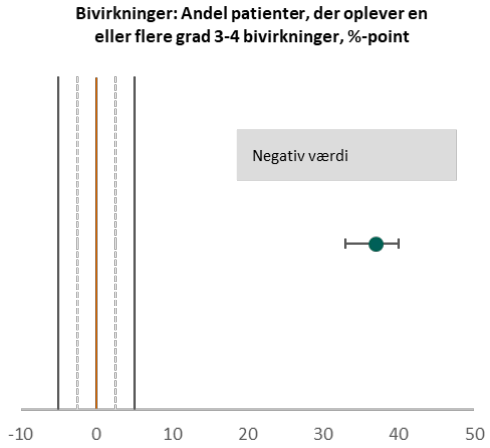
Fagudvalget har valgt at fokusere på ITT-populationen ift. opgørelsen af bivirkninger, da dette giver det største datagrundlag, og da fagudvalget ikke forventer, at hændelsesraten er forskellig imellem patienter baseret på, om de er HR+ eller HR-.

Grad 3-4 bivirkninger

Som beskrevet i protokollen finder fagudvalget, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever en eller flere bivirkninger af grad 3 eller 4, er relevant for vurderingen. Bivirkninger af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE version 4.03 [14]. Data er opgjort som treatment emergent adverse events (TEAE), dvs. uønskede hændelser, som opstår efter start på behandling. Data er således ikke for bivirkninger, hvilket fagudvalget tager højde for i vurderingen af evidensens kvalitet.

Efter 2 år havde 49,7 % i neratinib-gruppen oplevet grad 3-4 uønskede hændelser mod 13,1 % i placebogruppen. Punktestimatet for den absolutte effektforskel er 37 %-point og afspejler en negativ klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på en negativ klinisk relevant forskel end på 0 (ingen effektforskel). Derfor har neratinib foreløbigt en negativ værdi vedr. grad 3-4 bivirkninger.

Den absolutte forskel er vist i figur 3 nedenfor.



Figur 3: Punktestimat og 95 % konfidensinterval for den absolutte forskel for bivirkninger. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Baseret på den relative effektforskel opgjort som en relativ risiko på 3,8 [3,3;4,4] (se tabel 3) har neratinib foreløbigt en negativ værdi vedr. grad 3-4 bivirkninger.

Fagudvalget vurderer, at neratinib aggregeret har en negativ værdi vedr. delmålet grad 3-4 bivirkninger, da den foreløbige værdi for hhv. den absolutte og relative forskel er en negativ værdi. Fagudvalget vurderer dog, at hændelsesraten af grad 3-4 bivirkninger formentlig vil være lavere i dansk klinisk praksis, da man vil give loperamid profylaktisk (se nedenstående gennemgang af bivirkningsprofilen for yderligere informationer). Fagudvalget vurderer dog, at den aggregerede værdi af neratinib ift. delmålet grad 3-4 bivirkninger stadig vil være negativ.

Gennemgang af bivirkningsprofil

Jf. protokollen ønsker fagudvalget en gennemgang af neratinib og komparators bivirkningsprofiler for at vurdere bivirkningernes type, håndterbarhed og reversibilitet.

Gennemgangen er baseret på EMA's produktresume i videst muligt omfang, da denne baserer sig på rapportering fra 1.710 patienter, som har modtaget neratinib monoterapi. Fagudvalget vil supplere med data fra ExteNET-studiet og CONTROL-studiet.

Jf. EMA's produktresume er de hyppigste bivirkninger ved behandling med neratinib diarré (93,6 %), kvalme (42,5 %), træthed (27,3 %), opkast (26,8 %), mavesmerter (22,7 %), udslæt (15,4 %), nedsat appetit (13,7 %), smerter i den øvre maveregion (13,2 %), mundbetændelse (stomatitis, 11,2 %) og muskelkramper (10,0 %). Jf. EMA's produktresume bør patienter, som modtager neratinib, modtage forebyggende behandling mod diarré [15].

Ligeledes er den hyppigste grad 3-4 bivirkning diarré og kvalme, se tabel 4 og tabel 5 for oversigt over grad 3-4 diarré-definitioner. I SpC'et er opgjort median tid, en patient samlet set oplevede diarré (alle grader), hvilket var 59 dage for patienter, som modtog neratinib uden loperamid, mens median længde for grad 3 diarré var 5 dage. I gennemsnit oplevede hver patient 1,4 hændelser af grad 3 diarré.

Tabel 4. Hyppigste bivirkninger ved behandling med neratinib (ExteNET)*

	ITT-population			
	Neratinib (N = 1.408)		**Placebo (N = 1.408)**	
	Grad 1-2	**Grad 3-4**	**Grad 1-2**	**Grad 3-4**
Diarré, n (%)	781 (55)	562 (41)	476 (34)	23 (2)
Kvalme, n (%)	578 (41)	26 (2)	301 (21)	2 (< 1)
Træthed, n (%)	359 (25)	23 (2)	276 (20)	6 (< 1)
Opkast, n (%)	322 (23)	47 (3)	107 (8)	5 (< 1)
Mavesmerter, n (%)	315 (22)	24 (2)	141 (10)	3 (< 1)
Smerter i øvre maveregion, n (%)	201 (14)	11 (1)	93 (7)	3 (< 1)
Udslæt, n (%)	205 (15)	5 (< 1)	100 (7)	0
Nedsat appetit, n (%)	166 (12)	3 (< 1)	40 (3)	0
Muskelkramper, n (%)	157 (11)	1 (< 1)	44 (3)	1 (< 1)
Svimmelhed, n (%)	143 (10)	3 (< 1)	135 (9)	3 (< 1)
Ledsmerter, n (%)	84 (6)	2 (< 1)	158 (11)	4 (< 1)

* Hændelsesrate > 10 %.

Tabel 5. Definitioner af grad 1-4 diarré

	Definition
Grad 1 diarré	Op til 4 afføringer mere pr. dag sammenlignet med normal hyppighed
Grad 2 diarré	4-6 afføringer mere pr. dag sammenlignet med normal hyppighed, forekommende mindre end 5 dage
Grad 3 diarré	≥ 7 afføringer mere pr. dag sammenlignet med normal hyppighed samt inkontinens, hospitalisering kan være nødvendigt, evne til at tage vare på sig selv er begrænset. Forekommende ≤ 2 dage.
Grad 4 diarré	Livstruende diarré, akut behandling på sygehus nødvendigt.

I CONTROL-studiet indgår 137 patienter, som i tillæg til neratinib modtager loperamid profylaktisk mod diarré. Dette reducerer hændelsen af grad 2 diarré fra 33 % til 25 % og grad 3 diarré fra 40 % til 31 % samt median tid, en patient samlet set oplevede diarré (alle grader), til 14 dage. Tilsvarende medfører den profylaktiske behandling, at varigheden af grad 3 diarré reduceres fra fem til to dage. Fagudvalget vurderer, at denne behandling reducerer forekomsten af diarré, men ikke til et niveau, som betyder, at patienterne ikke er generet af diarré. Fagudvalget understreger, at man i dansk klinisk praksis vil give loperamid profylaktisk, og at forekomsten af diarré vil ligne hyppigheden i CONTROL-studiet frem for hyppigheden i ExteNET-studiet.

Overordnet set vurderer fagudvalget, at det er alvorligt, at så mange patienter oplever en grad 3 hændelse ved behandling med neratinib, når det tages i betragtning, at patienterne er erklæret raske og formålet med behandling er at forhindre tilbagefald for en mindre gruppe af patienter. Selvom de primære bivirkninger med neratinib er diarré og kvalme, vurderer fagudvalget, at dette er til stor gene for patienterne og kan betyde, at de vil opleve problemer med at have en normal livsførelse. Fagudvalget vurderer, at det er vigtigt at inddrage, at patienterne er erklæret raske, og at diarré og kvalme kan gøre det vanskeligt at opretholde et almindeligt arbejds- og privatliv. Behandling med neratinib øger dog tilsyneladende ikke risikoen for alvorlige, irreversible bivirkninger.

Dosisreduktion og behandlingsophør:
Neratinib dosis er 240 mg pr. dag. Behandlingspause eller dosisreduktion anbefales, hvis patienten oplever en grad 3 bivirkning. Der er i alt tre dosisreduktioner: 200, 160 eller 120 mg pr. dag. Hvis patienten ikke oplever bedring af bivirkningen ved behandlingspause og dosisreduktion, eller hvis patienten oplever en grad 4 uønsket hændelse, anbefales behandlingsophør.

I CONTROL-studiet indgår 137 patienter, som i tillæg til neratinib modtager loperamid profylaktisk mod diarré. Dette reducerer andelen af patienter, som må tage en behandlingspause, fra 34 % til 15 %, og andelen af patienter, som må dosisreducere, fra 26 % til 7 %. Herimod ændrer behandlingsophør sig ikke (17 % i ExteNET og 20 % i CONTROL). Fagudvalget vurderer, at det er positivt, at der er færre behandlingspauser og færre dosisreduktioner, men at det havde haft større betydning, hvis der sås færre behandlingsophør, hvilket ikke er tilfældet.

Der ses hyppigere behandlingsophør hos ældre patienter (> 65 år), hvilket fagudvalget er særligt opmærksom på, da patienterne er ældre i dansk klinisk praksis end i studiet.

Kontraindikationer:
Det anbefales at reducere dosis af neratinib, hvis patienten samtidig modtager behandling med en CYP3A4-hæmmer. Neratinib-behandling anbefales ikke sammen med stærke induktorer af CYP3A4. Behandling med neratinib anbefales ikke til patienter med eksisterende svær leverpåvirkning (Child-Pugh C).

Samlet kategorisering af effektmålet Bivirkninger

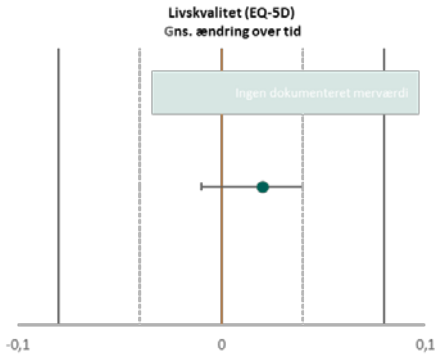
Fagudvalget vurderer, at neratinib aggregeret har en **negativ værdi** vedr. bivirkninger, dels fordi den aggregerede værdi for delmålet grad 3-4 bivirkninger er negativ, dels fordi det ifølge fagudvalget er alvorligt, at så mange patienter oplever en grad 3-4 hændelse ved behandling med neratinib. Det vægter tungt, at patienterne er erklæret raske, og formålet med behandling er at forhindre tilbagefald for en mindre gruppe af patienter.

Livskvalitet

Som beskrevet i protokollen er effektmålet *Livskvalitet* kritisk for vurderingen af lægemidlets værdi for patienterne, fordi livskvalitet er et patientrelevant effektmål, som udover at give indblik i sygdomsbyrden kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet. Data for livskvalitet er opgjort på EQ-5D-3L index efter 12 måneder eller til endt behandling.

Efter 12 måneders behandling var der en ændring i EQ-5D-3L index score på -0,05 i neratinib gruppen mod -0,03 i placebogruppen. Punktestimatet for den absolutte effektforskel er 0,02 og afspejler ikke en klinisk relevant effektforskel. Den nedre grænse for konfidensintervallet er tættere på 0 (ingen effekt) end på en negativ klinisk relevant forskel. Derfor har neratinib foreløbigt ingen dokumenteret merværdi vedr. livskvalitet.

Den absolutte forskel er vist i figur 4 nedenfor.



Figur 4: Punktestimat med 95 % konfidensinterval for den absolutte forskel for livskvalitet. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Den relative effektforskel kan ikke udregnes, og neratinib har derfor foreløbigt en værdi vedr. livskvalitet, der ikke kan kategoriseres.

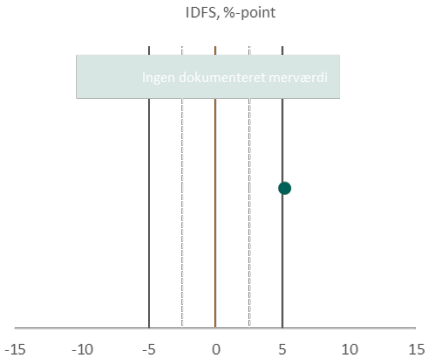
Fagudvalget vurderer, at neratinib aggregeret **har ingen dokumenteret værdi** vedr. livskvalitet, dels fordi det er tilfældet for den foreløbige værdi for den absolutte effektforskel, dels fordi der ikke er data for den relative effektforskel. Fagudvalget forventer, at der vil være et betydeligt fald i livskvalitet, mens behandlingen står på, grundet bivirkningerne relateret til behandlingen. Fagudvalget forventer imidlertid ikke forskelle i livskvalitet imellem placebo- og neratinib-behandling efter endt behandling, hvilket resultaterne ved 12-måneders opfølgningstid afspejler.

IDFS

Som beskrevet i protokollen er effektmålet Invasive-disease free survival (IDFS) vigtigt for vurderingen af lægemidlets værdi for patienterne. IDFS er en brystkræftspecifik udgave af disease-free survival (DFS, sygdomsfri overlevelse). IDFS benyttes primært som et surrogatmål for overlevelse til patientpopulationer med lang overlevelse. Fagudvalget har i protokollen efterspurgt en IDFS-rate ved 5 år. De tilgængelige data herfor på EMA-populationen er en sensitivitetsanalyse designet til at af-/bekræfte en 2-års analyse.

Efter 5 år var IDFS-raten 90,8 % [88,1;93,0] i neratinib-gruppen mod 85,7 % [82,6;88,3] i placebogruppen. Punktestimatet for den absolutte effektforskel er 5,1 %-point og afspejler en klinisk relevant effektforskel. Men da der ikke kan beregnes et konfidensinterval baseret på Kaplan Meyer-kurver, kan den foreløbige værdi af neratinib ikke kategoriseres vedr. IDFS.

Den absolutte forskel er vist i figur 5 nedenfor.



Figur 5: Punktestimatet for den absolutte forskel for IDFS. De optrukne linjer indikerer den mindste klinisk relevante forskel. De stiplede linjer indikerer grænserne for Medicinrådets kategorier svarende til halvdelen af MKRF.

Baseret på den relative effektforskel opgjort som en hazard ratio på 0,59 [0,41;0,82] (se tabel 3) har neratinib foreløbigt en moderat merværdi vedr. IDFS.

Som nævnt i afsnit 5.1.3 har fagudvalget valgt at benytte resultatet fra den stratificerede analyse af IDFS, på trods af at denne er *data on file*, som ikke har været offentliggjort. Den ikke-stratificerede analyse viser tilsvarende resultater (0,58 [0,41-0,82]). Som nævnt i afsnit 5.1.3 har 5-års opgørelsen krævet indhentning af samtykke på ny, hvilket kun lykkedes hos 75 % af patienterne. Fagudvalget har derfor valgt at kvalificere IDFS opgørelsen ved at gennemgå resultaterne fra 2-års opgørelsen, hvor alle patienter indgik. Denne opgørelse viser en absolut effektforskel på 4,5 %-point og en relativ effekt på 0,50 [0,31-0,79]. Fagudvalget vurderer, at disse resultater er sammenlignelige med 5-års opgørelsen, hvilket understøtter fagudvalgets beslutning om at benytte 5-årsopgørelsen på trods af de forbehold, som blev gennemgået i afsnit 5.1.3.

Fagudvalget vurderer, at neratinib aggregeret har en **lille merværdi** vedr. IDFS. Punktestimatet for den absolutte effektforskel er større end den mindste klinisk relevante forskel. Den foreløbige kategori for den relative effektforskel er en moderat merværdi, men fagudvalget vurderer, at dette overestimerer effekten af neratinib. Da der i dansk klinisk praksis nu gives en betydelig mere virkningsfuld behandling ift. (neo)adjuverende medicinsk behandling og type af kirurgisk behandling samt dansk praksis for adjuverende strålebehandling, forventer fagudvalget, at patientgruppens prognose er væsentlig forbedret sammenlignet med ExteNET-studiet. Derfor vurderer fagudvalget, at den aggregerede værdi for neratinib er en lille merværdi sammenlignet med placebo.

5.1.6 Fagudvalgets konklusion

Fagudvalget har vurderet, at patientpopulationen, som kan tages i betragtning til neratinib som forlænget adjuverende behandling, bør indskrænkes til patienter med tidlig ER+/HER2+ brystkræft med lymfeknudemetastaser, som har modtaget neoadjuverende behandling og opnået komplet respons på denne behandling, samt til patienter, der opdages at have lymfeknudemetastaser ved det primære kirurgiske indgreb. Nedenstående konklusion gælder derfor for denne patientgruppe, frem for EMA-indikationen, som fokuserede på patienter med tidlig ER+ og HER2+ brystkræft.

Neratinibs værdi på det kritiske effektmål *samlet overlevelse* kan ikke kategoriseres. Punktestimatet for den absolutte effektforskel er mindre end den mindste klinisk relevante forskel, og den relative effektforskel kan ikke kategoriseres grundet et bredt konfidensinterval. Fagudvalget vurderer, at effekten vil være mindre i

dansk klinisk praksis, nu hvor patienterne får en bedre behandling, end da studiet blev gennemført. Derfor konkluderer fagudvalget, at det ikke er sandsynliggjort, at neratinib medfører forbedret overlevelse.

Der kan i studiet påvises en effekt for det vigtige effektmål IDFS, som i bedste fald svarer til, at neratinib har en moderat merværdi sammenlignet med placebo for dette effektmål. Fagudvalget vurderer dog, at effekten vil være mindre i dansk klinisk praksis, nu hvor patienterne får en bedre behandling, end da studiet blev gennemført. Derfor har fagudvalget vurderet, at neratinib har en lille merværdi sammenlignet med placebo for effektmålet IDFS. For det kritiske effektmål *livskvalitet* har neratinib ingen dokumenteret merværdi sammenlignet med placebo. Neratinib er en bivirkningstung behandling sammenlignet med placebo. 31 % af patienter oplever at få grad 3 diarré i løbet af de første måneders behandling, selv når der gives profylaktisk behandling med loperamid. Fagudvalget finder det derfor sandsynligt, at der særligt i de første måneder efter opstart af behandling vil være reduceret livskvalitet for patienter, som modtager neratinib, grundet bivirkninger. Fagudvalget understreger dog, at der ikke er tale om livstruende bivirkninger, men at der er tale om meget generende bivirkninger for patienter, som ellers er erklæret raske. Fagudvalget forventer derfor også, at en del patienter potentielt vil fravælge behandlingen grundet bivirkningerne. Den negative værdi vedr. bivirkninger vejer tungt i fagudvalgets samlede vurdering af neratinibs værdi sammenlignet med placebo.

Samlet set vurderer fagudvalget derfor, at neratinib har **negativ værdi** sammenlignet med placebo.

6 Andre overvejelser

Indskrænkning af patientpopulationen

TNM-klassifikationen er i høj grad korreleret med prognose, dvs. at en patient med f.eks. T1N0 kan forventes at have væsentlig bedre prognose end en patient med T4N3. Derfor ønskede fagudvalget i protokollen, at effekten af neratinib skulle gennemgås i henhold til patienternes TNM-stadier. Det kliniske studie inkluderede til start med patienter uanset klinisk stadie, men studieprotokollen blev senere ændret til kun at inkludere patienter med tumor stadie II-IIIC. Således indgår kun få patienter (99 patienter fordelt på begge behandlingsarme) med små tumorer, dvs. stadie I, i studiet. Dette er en gruppe patienter med bedre prognose, som potentielt ville være blevet overbehandlet, hvis de havde modtaget en yderligere linje af behandling. Ansøger har desuden leveret IDFS-data for hver enkelt kombination af T- og N-stadier (kliniske stadier). Da der er tale om mange potentielle subgrupper, er antallet af patienter i hvert stadie meget små, og det er derfor ikke muligt at konkludere på, om neratinib-behandling primært har effekt for en bestemt subgruppe. Jf. afsnit 5.1.2 finder fagudvalget det kun relevant at behandle højrisikopatienter med lymfeknudemetastaser med neratinib. Dermed er der taget højde for overvejelser vedr. TNM-stadier, da de patienter, som potentielt kunne blive overbehandlet, ikke er en del af denne population.

Neratinib-behandling ift. respons på neoadjuverende HER2-rettet behandling

T-DM1 blev i juni 2020 godkendt af Medicinrådet som standardbehandling til patienter med HER2+ brystkræft, som ikke opnåede komplet patologisk respons på neoadjuverende behandling. Dette medførte, at behandlingsrækken for HER2-rettet behandling nu skelner imellem patienter, som opnår komplet patologisk respons, og patienter, som ikke opnår komplet patologisk respons. EMA-indikationen for neratinib indikerer, at patienter skal have modtaget et års HER2-rettet behandling for at komme i betragtning til behandling med neratinib. T-DM1 er ikke en af de foregående behandlinger, som indgår i det kliniske studie for neratinib. Derfor finder fagudvalget ikke, at patienter, som har modtaget T-DM1 som adjuverende behandling, kan tages i betragtning til neratinib-behandling.

7 Relation til behandlingsvejledning

Jf. RADS ”Baggrundsnotat for anti-HER2 behandling af brystkræft” er der kun en linje/et års adjuverende behandling for patienter med HER2+ brystkræft. Da neratinib har indikation efter et års HER2-rettet behandling, vil en eventuel anbefaling svare til, at der indføres et nyt behandlingstrin for patientgruppen. Desuden vil fagudvalgets skelnen mellem hhv. patienter med og uden lymfeknudemetastaser ift. potentiel gavn af neratinib medføre, at der indføres nye subgrupper i behandlingsvejledningen.

8 Referencer

1. NORDCAN. Association of the Nordic Cancer. Kræftstatistik: Nøgetal og figurer_brystkræft. 2019.
2. Notkin A, Graversen A. kraeftensbekaempelse.
3. Group DBCC. Medicinsk behandling. 2019;2005:1–49.
4. Retningslinjerne M. Patologi - DBCG. 2017;1–37. Tilgængelig fra: http://www.dbcg.dk/PDF Filer/Kap_3_Patologi_22_juni_2017.pdf
5. Tolaney SM, Guo H, Pernas S, Barry WT, Dillon DA, Ritterhouse L, et al. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2–positive breast cancer. J Clin Oncol. 2019;37(22):1868–75.
6. Asselain B, Barlow W, Bartlett J, Bergh J, Bergsten-Nordström E, Bliss J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19(1):27–39.
7. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet [internet]. 2017;389(10075):1195–205. Tilgængelig fra: http://dx.doi.org/10.1016/S0140-6736(16)32616-2
8. 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 [internet]. 2016;17(3):367–77. Tilgængelig fra: http://dx.doi.org/10.1016/S1470-2045(15)00551-3
9. 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):1688–700.
10. Barcenas CH, Hurvitz SA, Di Palma JA, Bose R, Chien AJ, Iannotti N, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. Ann Oncol. 2020;31(9):1223–30.
11. Gianni L, Pienkowski T, Im Y-H, Roman L, Tseng L-M, Liu M-C, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol [internet]. 2012 [citeret 8. august 2018];13(1):25–32. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/22153890
12. Medicinrådet. Medicinrådets anbefaling vedrørende trastuzumab emtansin til behandling af tidlig HER2+ brystkræft. 2020.
13. Chan A, Moy B, Mansi J, Ejlertsen B, Holmes FA, Chia S, et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. Clin Breast Cancer [internet]. 2020; Tilgængelig fra: https://doi.org/10.1016/j.clbc.2020.09.014
14. Common Terminology Ctriteria for Advers Events v4.0 (CTCAE). National Cancer Institute Cancer Therapy Evaluation Program; 2010 jun.
15. EMA. Produktresume neratinib. EMA. 2012;1–33.

9 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

Medicinrådets fagudvalg vedrørende brystkræft

Formand	**Indstillet af**
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Marianne Johansson Patient/patientrepræsentant	Danske Patienter
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10 Versionslog

Version	**Dato**	***Ændring***
1.1	4. februar 2021	Under høringsprocessen angav Pierre Fabre, at overlevelsesdata, som hidtil ikke var publiceret og dertil var fortrolige, nu var publiceret. Vurderingsrapporten er derfor opdateret med data for samlet overlevelse.
1.0	21. oktober 2020	Godkendt af Medicinrådet.

11 Bilag 1: Evidensens kvalitet

11.1 Cochrane, Risk of Bias

Vurdering af risiko for bias ved Cochranes RoB 2.0 assessment tool.

ExteNET, Martin et al, 2017, Lancet Oncology, NCT00878709

Bias	**Risiko for bias**	**Uddybning**
Risiko for bias i randomiseringsprocessen	**Lav**	Allokering til de to arme var randomiseret, og blindingen var bibeholdt indtil primæranalysen. Der er ingen forskelle i baselinekarakteristika, som angiver, at der var problemer med randomiseringsprocessen.
Risiko for bias grundet afvigelser fra tilsigtet intervention		
Effekt af tildeling til intervention	**Forbehold**	Patienterne var blindet igennem studiet. Ligeledes var klinikere og personale, som udleverede medicinen, blindet igennem studiet. Dog blev blindingen ophævet for analyseholdet ved primæranalysen. Det specificeres, at der opretholdes "en firewall" imellem disse personer og klinikere, som bedømmer progression.
Manglende data for effektmål	**Forbehold**	Grundet ændringer i studieprotokollen, som forlængede tidshorisonten for studiet fra 2 til 5 år, måtte der indhentes samtykke på ny. Dette lykkedes kun for 75 % af patienterne. Der er lige mange, som ikke indgiver samtykke i hver arm, men der er ingen detaljeret gennemgang af, hvem der ikke indgiver samtykke. Det kan derfor ikke vurderes, om det medfører bias i analyserne.
Risiko for bias ved indsamlingen af data	**Lav**	Der er intet, som tyder på bias ved indsamling af data.
Risiko for bias ved udvælgelse af resultater, der rapporteres	**Høj**	Der var mange protokolændringer løbende, inkl. væsentlige ændringer i patientpopulationen, som kan påvirke effektestimater betydeligt. Desuden er EMA-populationen væsentlig anderledes end ITT-populationen, og denne analyse er foretaget efter ophævning af blinding.
Overordnet risiko for bias	**Høj**	Der er foretaget mange ændringer i studieprotokollen, som kan have indflydelse på effektestimaterne. Dette mindsker tiltroen til studiets resultater.

11.2 GRADE-profil

Sikkerhedsvurdering							Antal patienter		Effekt		Sikkerhed	Vigtighed
Antal studier	**Studie-design**	**Risiko for bias**	**Inkonsistens**	**Indirekthed**	**Unøjagtighed**	**Andre overvejelser**	**Neratinib**	**Placebo**	**Relativ (95 % CI)**	**Absolut (95 % CI)**		
Samlet overlevelse (OS)												
1	randomised trials	serious [a]	serious [b]	serious [e]	serious [c]	none	57/670 (8,5 %)	70/664 (10,6 %)	HR 0,79 (0,55 to 1,13)	2,1 %-point	⊕◯◯◯ MEGET LAV	KRITISK
Grad 3-4 bivirkninger, 23 måneder												
1	randomised trials	not serious	serious [b]	not serious	not serious	none	327/662 (49,4 %)	76/657 (11,6 %)	RR 4,27 (3,41 to 5,35)	37,8 %-point (33,3;42,4)	⊕⊕⊕◯ MODERAT	KRITISK
Livskvalitet, 12 måneder												
1	randomised trials	not serious	serious [b]	not serious	serious [c]	none	662	657	-	0,02 units (−0,01;0,04)	⊕⊕◯◯ LAV	KRITISK
IDFS, 5 ÅR												
1	randomised trials	serious [a]	serious [b]	serious [e]	not serious	none	609/670 (90.8 %)	570/664 (85.7 %)	HR 0,59 (0,41 to 0,82)	5,1 %-point	⊕◯◯◯ MEGET LAV	VIGTIGT
Kvalitet af den samlede evidens			MEGET LAV [d]									

[a] Der er nedgraderet ét niveau, da der var nogle forbehold i vurderingen af risiko for bias. Dette vurderes primært at indvirke på OS- og IDFS-effektmålene.
[b] Der er nedgraderet ét niveau, da der kun var ét studie.
[c] Der er nedgraderet ét niveau, da konfidensintervallet er bredt og indeholder både positive og negative konklusioner.
[d] Den samlede evidenskvalitet er vurderet ud fra den laveste kvalitet af de kritiske effektmål.
[e] Fagudvalget vurderer, at patienternes prognose i dansk klinisk praksis er bedre end i ExteNET.

Application for the assessment of neratinib (NERLYNX®) in the extended adjuvant treatment of HER2-positive, hormone receptor–positive early breast cancer after trastuzumab-based therapy

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1 Basic information

Table 1. Contact information

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Name	
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Phone	
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Table 2. Overview of the pharmaceutical

Proprietary name	NERLYNX
Generic name	Neratinib
Marketing authorisation holder in Denmark	Pierre Fabre Pharma Norden AB Karlavägen 108; Plan 9 115 26 Stockholm Sweden
ATC code	L01XE45
Pharmacotherapeutic group	Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors,
Active substance(s)	Neratinib
Pharmaceutical form(s)	Neratinib is administered orally. The recommended dose is 240 mg neratinib, administered as 6 × 40 mg tablets taken once daily and continually for 1 year.
Mechanism of action	Neratinib is an oral, intracellular, irreversible multiple ErbB tyrosine kinase inhibitor (TKI) of HER1, HER2 and HER4 that results in decreased proliferation and increased tumour cell death. Neratinib is the first HER2-directed therapy to be approved in the European Union in the extended adjuvant setting (after the completion of 1 year of adjuvant trastuzumab-based therapy) for the treatment of human epidermal growth factor receptor 2–positive (HER2+)/hormone receptor–positive (HR+) early breast cancer.
Dosage regimen	The recommended dose is 240 mg neratinib, administered as 6 × 40 mg tablets taken once daily and continually for 1 year. Neratinib should be taken with food, preferably in the morning.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Neratinib is indicated for the extended adjuvant treatment of adults with early-stage HR+, HER2+ breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago.

Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Neratinib is prescribed in a hospital or clinic setting under the supervision of an oncology specialist but is an oral drug self-administered by the patient at home. Neratinib will be dispensed by hospital pharmacists.
Combination therapy and/or co-medication	The European Medicines Agency (EMA) label indicates that patients are instructed to start antidiarrhoeal prophylaxis with the first dose of neratinib and maintain regular dosing of the antidiarrhoeal product during the first 1-2 months of treatment, titrating to achieve 1-2 bowel movements per day [1].
Packaging – types, sizes/number of units, and concentrations	40-mg, 180-tablet pack
Orphan drug designation	Not applicable.

2 Abbreviations

AE	adverse event
ASCO	American Society of Clinical Oncology
ATC	Anatomical Therapeutic Chemical Classification System
BCIRG	Breast Cancer International Research Group
BID	twice daily
BL	budesonide + loperamide
cHR	cause-specific hazard ratio
CI	confidence interval
CL	colestipol + loperamide
CL-PRN	colestipol + as-needed loperamide
CNS	central nervous system
CRF	case report form
DCIS	ductal carcinoma in situ
DDFS	distant disease-free survival
DE	dose escalation
DFS	disease-free survival
DFS-DCIS	disease-free survival including ductal carcinoma in situ
DMC	Danish Medicines Council
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
ER	oestrogen receptor
ESMO	European Society for Medical Oncology
EU	European Union
FACT-B	Functional Assessment of Cancer Therapy–Breast
FDA	Food and Drug Administration
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
HRQoL	health-related quality of life
iDFS	invasive disease-free survival
IP	investigational product
IQR	interquartile range

IRT	interactive response technology
I-SPY-2	Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2
ITT	intention to treat
NA	not available
NCCTG	North Central Cancer Treatment Group
NCI-CTC	National Cancer Institute *Common Terminology Criteria*
NCI-CTCAE	National Cancer Institute *Common Terminology Criteria for Adverse Events*
NCT	National Clinical Trial Number
NE	not estimable
OS	overall survival
pCR	pathologic complete response
PR	progesterone receptor
PRN	as needed
QD	once daily
QoL	quality of life
SABCS	San Antonio Breast Cancer Symposium
SAE	serious adverse event
SD	standard deviation
SE	standard error
sHR	subdistribution hazard ratio
SLR	systematic literature review
SmPC	summary of product characteristics
STEEP	standardised definitions for efficacy endpoints
T-DM1	trastuzumab emtansine
TEAE	treatment-emergent adverse event
TID	three times a day
TKI	tyrosine kinase inhibitor
TNM	tumour, node, metastasis
TTDR	time to distant recurrence
VAS	visual analogue scale

3 Summary

In Denmark, breast cancer is the most common cancer in women, with an estimated 4,628 new cases of female breast cancer in 2018 [2]; of these, approximately 4,400 are early breast cancer [3]. Limited Danish epidemiological data are available for the incidence and prevalence of human epidermal growth factor receptor 2–positive (HER2+)/hormone receptor–positive (HR+) breast cancer; however, approximately 10% to 15% of early breast cancers are HER2+ [3]. In the Swedish National Breast Cancer Registry in 2018, of 7,689 women diagnosed with breast cancer with molecular subtyping, 1,040 were HER2+ (13.5%), but HER2+/HR+ was not reported [4]. In the United States, it is estimated that approximately 15% of patients with early breast cancer have tumours that are HER2+, and two-thirds of HER2+ breast cancers are also HR+, meaning approximately 10% of early breast cancers are HER2+/HR+ [5].

The Danish Medicines Council (DMC) has not published treatment guidelines on breast cancer. However, RADS guidelines were published in 2016; for neoadjuvant treatment, patients with HER2+ early breast cancer should receive chemotherapy before surgery and trastuzumab after surgery. For adjuvant treatment, patients should undergo surgery and chemotherapy followed by trastuzumab for 1 year [6, 7]. RADS guidelines do not stipulate if patients need to achieve complete response before starting trastuzumab. Patients with HER2+/HR+ breast cancer also receive adjuvant endocrine therapy, either with tamoxifen or an aromatase inhibitor for 5 years, with the option for extended endocrine therapy for up to 10 years [6-8].

Despite successful treatment with trastuzumab and endocrine therapy, approximately 23% of patients with HER2+/HR+ early breast cancer experience a recurrence within 10 years [9]. As such, there is an unmet need for new interventions to improve on the benefits of trastuzumab-based therapy to reduce the risk of disease recurrence [5, 9, 10]. Alternative HER2-directed adjuvant regimens used in combination with or after 1 year of trastuzumab-based therapy, such as pertuzumab or lapatinib, have shown limited efficacy in further reducing the risk of recurrence in patients with early HER2+/HR+ breast cancer [11-13]. More recently, trastuzumab emtansine (T-DM1) has been approved by the DMC for patients with early HER2+ breast cancer who do not achieve complete response to neoadjuvant therapy and surgery [14]. Patients achieving complete response should be offered trastuzumab as first-line therapy [15].

Neratinib is the only HER2-targeted therapy in the extended adjuvant setting used after trastuzumab. It is administered orally, removing the need for venous access, port maintenance, and risk of clotting or infection [16]. With neratinib, dual blockade of oestrogen receptor (ER) and HER2 signalling pathways may result in enhanced and sustained anti-tumour activity, as extended ErbB blockage has the potential to re-sensitise the ER signalling pathway to endocrine therapy [10, 17].

Clinical data in this application are based on the NERLYNX (neratinib) label defined by the European Medicines Agency (EMA) in the extended adjuvant treatment of adults with early-stage HR+, HER2+ breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago.

The analysis of overall survival (OS) for the EMA label population shows a reduction in mortality (hazard ratio, 0.79; 95% confidence interval [CI], 0.55-1.13) [18]. In this population, it was shown that neratinib significantly improved 2-year and 5-year invasive disease-free survival (iDFS) when given less than 1 year from prior trastuzumab-based adjuvant therapy, versus placebo:

- 2-year iDFS: 95.3% vs. 90.8% (neratinib vs. placebo, respectively; hazard ratio, 0.50; 95% CI, 0.31-0.79; *P* = 0.003). The absolute benefit was 4.5%, resulting in a relative risk reduction of 51% [19].
- 5-year iDFS: 90.8% vs. 85.7% (neratinib vs. placebo, respectively; hazard ratio, 0.59; 95% CI, 0.41-0.82; *P* = 0.002). The absolute benefit was 5.1%, resulting in a relative risk reduction of 42% [19].

Neratinib in the extended adjuvant setting does not have a long-term or clinically significant impact on health-related quality of life (HRQoL) [20, 21].

Safety data are provided from ExteNET and CONTROL trial (a phase 2, open-label safety and tolerability study investigating the effect of antidiarrhoeal strategies). Diarrhoea was the most common side effect in patients treated with neratinib in ExteNET. The CONTROL trial showed that neratinib-associated diarrhoea is manageable [22].

4 Literature search

The DMC conducted a literature search for appropriate full-text articles published in scientific, peer-reviewed journals comparing neratinib with placebo. The literature search identified one full-text paper Martin et al. [23]. For completeness Pierre Fabre conducted a clinical systematic literature review (SLR) to identify studies relevant to neratinib for the treatment of early HER2+/HR+ breast cancer within 1 year of trastuzumab-based therapy. The SLR was last updated in November 2018. Once relevant studies were identified, study characteristics, efficacy, HRQoL, and safety data were extracted, and methodologies were critically appraised according to internationally validated methods. See Appendix B for the full search strategy and details of the process and methods used to identify and select the clinical evidence relevant to the submission.

The clinical SLR identified one study of neratinib that was relevant to the scope of this submission: the ExteNET trial [23, 24]. As the comparator is standard of care with no further HER2-directed therapy, no other relevant studies were identified.

In addition to ExteNET, the CONTROL trial investigated the use of neratinib in people with early HER2+/HR+ breast cancer and is included in the marketing authorisation for neratinib [1, 22, 25-27]. This study was not identified in the clinical SLR because it is not a randomised controlled trial, but it is relevant to the submission and is described in the sections below.

The evidence base to support the clinical efficacy of neratinib reflects the licensed indication and the anticipated use of this treatment in clinical practice in Denmark. No major factors or patient characteristics relating to the evidence have been identified that would likely affect the applicability of the evidence or exert an influence on the clinical response of neratinib in adults with early HER2+/HR+ breast cancer who have completed a course of adjuvant trastuzumab-based therapy less than 1 year ago.

Databases and search strategy

See Appendix B for the full search strategy and details of the process and methods used to identify and select the clinical evidence relevant to the submission.

4.1 Relevant studies

Table 3. Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)
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 Mar;17(3):367-77. Gnant M, Martin M, Holmes F-A, Jackisch C, Chia SK, Iwata H, et al. Efficacy of neratinib in hormone receptor–positive patients who initiated treatment within 1 year of completing trastuzumab-based adjuvant therapy in HER2+ early-stage breast cancer: subgroup analyses from the phase III ExteNET trial. Presented at the San Antonio Breast Cancer Symposium; 4-8 December 2018. San Antonio, TX, USA. 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 Dec;18(12):1688-700. Chan A, Moy B, Mansi J, Ejlertsen B, Holmes FA, Chia S, et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. Clinical Breast Cancer. 2020 Oct 6.	ExteNET	NCT00878709	July 2009 to October 2019
Barcenas CH, Hurvitz SA, Di Palma JA, Bose R, Chien AJ, Iannotti N, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: diarrheal toxicity in the CONTROL trial. Ann Oncol. 2020 May 25.	CONTROL	NCT02400476	February 2015 to May 2021

NCT, National Clinical Trial number.

4.2 Main characteristics of included studies

4.2.1 ExteNET trial: extended adjuvant therapy with neratinib versus placebo

This submission is based primarily on the ExteNET study [23, 24], with supporting safety data from the CONTROL study Barcenas et al. [22]. The main characteristics of the studies are outlined in Section 4.2 and in Appendix A.

ExteNET (NCT00878709, Study 3144A2-3004-WW) is a randomised, double-blind, placebo-controlled, phase 3 pivotal trial that compares extended adjuvant therapy with neratinib versus placebo in women with HER2+ breast cancer who were within 2 years of completing trastuzumab therapy (intention-to-treat [ITT] population). A subpopulation of ExteNET is relevant to this submission: the EMA label population (patients with HER2+/HR+ breast cancer within 1 year of trastuzumab therapy).

Two-year and 5-year efficacy and safety data in the ITT population have been published in two journal articles [23, 24]. The data in the EMA label population relevant to the scope were presented at the 2018 San Antonio Breast Cancer Symposium (SABCS) [19]. Additional analyses of HRQoL data were presented at European Society for Medical Oncology (ESMO) 2017 [28] and SABCS 2018 [27] and in a full publication [20].

Table 4 presents details of the ExteNET methodology; further details on design, endpoints, and statistical analysis are described in Sections 4.2.1.1 to 4.2.1.3. Appendix G presents full details of inclusion and exclusion criteria and permitted and disallowed concomitant medication. ExteNET provides the key efficacy and safety data for neratinib included in the economic model.

Table 4. ExteNET: summary of trial methodology

Location	495 sites in 40 countries in Europe, Asia, Australia, New Zealand, North America, and South America (2 sites in Sweden [n = 7], 12 sites in Denmark [n = 112])
Trial design	International, multicentre, randomised, double-blind, placebo-controlled phase 3 trial
Intervention(s) and comparator(s)	Placebo (ITT: n = 1,420) or neratinib 240 mg (ITT: n = 1,420) taken orally, once daily continuously for 12 months. Treatment was given for 12 months unless disease recurrence or new breast cancer, intolerable adverse events, or consent withdrawal occurred. Neratinib dose reductions (200 mg, 160 mg, and 120 mg per day) were allowed for toxicity, with treatment cessation if the lowest dose was not tolerated or if treatment was interrupted for > 3 weeks. Dose reductions were mandated for grade 3 diarrhoea after resolution to grade 1 or lower within 3 weeks, if a second episode of grade 3 diarrhoea occurred despite optimum medical therapy, and in the event of symptomatic grade 2 pneumonitis or interstitial lung disease and other grade 3 non-haematological events after resolution to grade 1 or lower within 3 weeks. Concurrent adjuvant endocrine therapy for HR+ disease was recommended.
Primary outcomes (including scoring methods and timings of assessments)	Primary endpoint: iDFS at 2 years after randomisation, in which invasive disease was defined as time from randomisation to the first occurrence of the following events: ▪ Invasive ipsilateral breast tumour recurrence ▪ Invasive contralateral breast cancer ▪ Local/regional invasive recurrence ▪ Distant recurrence ▪ Death from any cause Any patient for whom an event had not been observed by the data cut-off was censored at the date of their last physical examination.

Other outcomes used in the economic model/specified in the scope	Secondary endpoints were: ▪ iDFS ▪ DFS-DCIS ▪ Time to distant recurrence ▪ DDFS ▪ Cumulative incidence of CNS recurrences ▪ OS ▪ Safety All time-to-event secondary endpoints were defined as from time of randomisation. Health-related quality of life was an exploratory endpoint, with the EQ-5D-3L and FACT-B version 4, at baseline and months 1, 3, 6, 9, and 12 (end of treatment).
Preplanned subgroups	The primary efficacy analysis was conducted on the ITT population, consisting of all subjects randomised. Prespecified subgroup analyses also included the following: ▪ HR status (HR+ [defined as ER+ or PR+, or both] vs. HR– [defined as ER– and PR–]) ▪ Nodal status (0 vs. 1-3 vs. 4 or more) ▪ Trastuzumab adjuvant regimen (sequentially vs. concurrently with chemotherapy) ▪ All subjects who completed prior trastuzumab ≤ 1 year vs. > 1 year from randomisation ▪ Amended ITT of higher risk patients: (defined as all patients with node-positive disease who were randomly assigned within 1 year of completing previous trastuzumab) ▪ All subjects with node-positive disease ▪ All subjects who were HER2+ based on central testing

CNS, central nervous system; DDFS, distant disease-free survival; DFS-DCIS, disease-free survival including ductal carcinoma in situ; ER, oestrogen receptor; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; iDFS, invasive disease-free survival; ITT, intention to treat; OS, overall survival; PR, progesterone receptor.

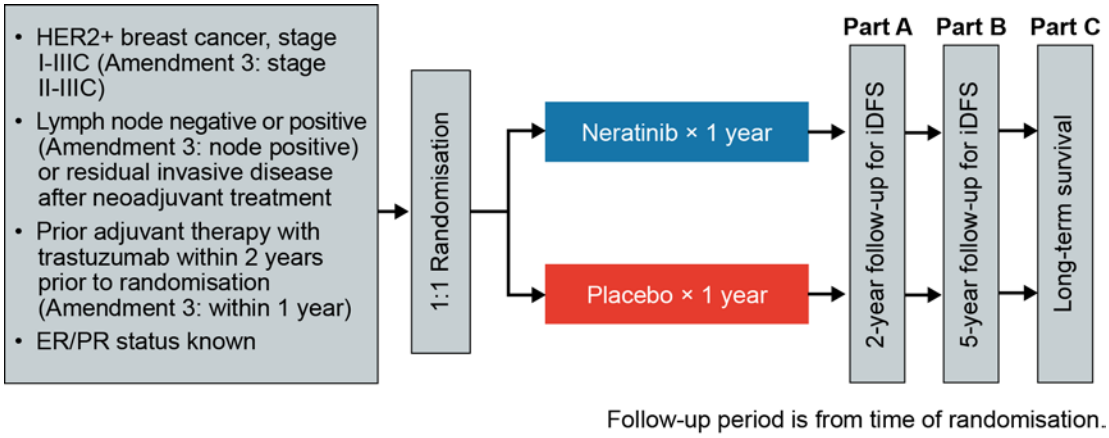
Sources: Chan et al. [24]; Puma data on file [29].

4.2.1.1 ExteNET: study design

The purpose of the ExteNET study was to investigate whether neratinib can further reduce the risk of recurrence from previously diagnosed HER2+ breast cancer after adjuvant treatment with trastuzumab. ExteNET is a three-part, phase 3, multicentre, randomised, double-blind, placebo-controlled trial comparing neratinib versus placebo in women with early-stage HER2-overexpressed/amplified breast cancer who have previously received adjuvant trastuzumab. Patients were randomised in a 1:1 ratio to receive either neratinib or placebo daily for 1 year (Figure 1).

Parts A and B provide key evidence on the efficacy, safety, and tolerability of neratinib. Part A provided the primary efficacy analysis at 2 years, and part B assessed the sensitivity analysis of efficacy endpoints at 5 years; both parts supported the licensing of neratinib. Part C assessed OS (to be done after 248 events), as described in Section 5.1.2.1. Protocol amendments are further described in Table 5.

Figure 1. ExteNET trial design



ER, oestrogen receptor; HER2+, human epidermal growth factor receptor 2–positive; iDFS, invasive disease-free survival; PR, progesterone receptor.

Note: As of Amendment 9, after discontinuing study treatment, patients were followed for disease recurrence and survival for 2 years after randomisation. With Amendment 13, recurrent disease events and deaths were determined for the intention-to-treat population as follows:

Part A: Full physical examinations at baseline and 1 year and physical examinations, including breast and axillary examinations, every 3 months while on treatment and every 4 months during follow-up until the end of year 2. Part B: Expansion of follow-up from 2 to 5 years (+ 90 days) post-randomisation. Recurrent disease events and deaths were determined from patients' medical records upon reconsent of the patients. Statistical evaluations for this part of the study are considered to be sensitivity analyses. Part C: Long-term follow-up of overall survival until 248 deaths have occurred.

Sources: Puma data on file [30]; Chan et al. [24]; Martin et al. [23].

Randomisation was stratified by the following three factors [23, 24, 30]:

- Hormone receptor–positive (HR+, defined as either oestrogen-positive or progesterone receptor–positive, or both [ER+ and/or PR+]) versus hormone receptor–negative (HR−, defined as oestrogen-negative and progesterone receptor–negative [ER– and PR–])
- Nodal status (0, 1-3 vs. 4 or more positive nodes):
  - Patients with residual invasive disease in the breast but node-negative or unknown nodal status in the axilla after neoadjuvant therapy were included under "1-3" positive nodes.
  - In Amendment 3, the inclusion criteria for breast cancer staging and nodal status were revised to include only patients with stage II-IIIC and only patients with axillary node-positive disease.
- Prior trastuzumab given sequentially versus concurrently with chemotherapy:
  - Trastuzumab given sequentially was defined as any regimen in which trastuzumab was started after completion of cytotoxic chemotherapy (e.g., doxorubicin + cyclophosphamide followed by paclitaxel followed by trastuzumab monotherapy for 1 year).
  - Trastuzumab given concurrently with chemotherapy was defined as any regimen in which trastuzumab was started while chemotherapy was being given (e.g., doxorubicin + cyclophosphamide followed by trastuzumab + paclitaxel followed by trastuzumab monotherapy to complete 1 year of trastuzumab).

During the course of the ExteNET trial, the original protocol (29 April 2009) had a total of six global protocol amendments under the supervision of three sponsors, with the last amendment

(Amendment 13) occurring in January 2014 [24]. Three of the global protocol amendments affected the original trial design and are described below and in Table 5. The other three global amendments included the addition of patient-reported outcomes, removal of the requirement to collect unscheduled pharmacokinetic samples, and transfer of sponsorship to Puma. The EMA concluded there were no major methodological issues with ExteNET considering the number of protocol amendments [31].

Table 5. ExteNET protocol amendments affecting trial design

	Original protocol 29 Apr 2009 (Wyeth)	**Amendment 3 25 Feb 2010 (Pfizer)**	**Amendment 9 14 Oct 2011 (Pfizer)**	**Amendment 13 Oct 2013 (Puma)**
Planned sample size	3,850	3,300	2,840 (recruitment was stopped)	2,840
Patient population for the primary analysis	ITT < 2 years from trastuzumab Node positive or negative	Amended ITT < 1 year from trastuzumab Node positive	Amended ITT < 1 year from trastuzumab Node positive	ITT restored to per-protocol primary objective < 2 years from trastuzumab Node positive or negative
Primary endpoint	iDFS	iDFS	iDFS	iDFS
Planned analyses	iDFS events: First interim analysis: 135 Second interim analysis: 236 Final: 337 90% power to detect a difference in iDFS if the hazard ratio was 0.70 in favour of neratinib	No prespecified target iDFS events 90% power to detect a difference in iDFS if the hazard ratio was 0.713 in favour of neratinib	No prespecified target iDFS events 83% power to detect a difference in iDFS if the hazard ratio was 0.667 in favour of neratinib	No prespecified target iDFS events 88% power to detect a difference in iDFS if the hazard ratio was 0.667 in favour of neratinib
Follow-up time (years)	5	5	2	Primary: 2 Descriptive: 5
Secondary endpoint (OS analysis)	Analysis at the 5-year follow-up	Analysis at DFS and 5-year follow-up	Analysis at the 2-year follow-up	Primary analysis at 248 events

DFS, disease-free survival; iDFS, invasive disease-free survival; ITT, intention to treat; OS, overall survival.

Sources: Chan et al. [24]; Martin et al. [23]; Puma data on file [30].

Global Protocol Amendment 3

After study commencement, long-term follow-up data were presented for two adjuvant trastuzumab trials, North Central Cancer Treatment Group (NCCTG) N9831 and Breast Cancer International Research Group (BCIRG) 006 [32, 33]. In both trials, the 5-year disease-free survival (DFS) rate was reported to be approximately 84% for patients treated with adjuvant chemotherapy followed by a taxane plus trastuzumab, which confirmed a risk of tumour recurrence for patients who completed adjuvant trastuzumab therapy. However, the 5-year DFS rate for node-negative cancer treated with adjuvant chemotherapy followed by a taxane plus trastuzumab reported in the BCIRG 006 study was 93%, indicating the recurrence risk was lower than when ExteNET was designed. Additional efficacy data from more mature pivotal adjuvant trastuzumab trials also suggested that patients were at higher risk of recurrence closer to completion of adjuvant trastuzumab and that the risk of recurrence may decrease over time. As a result, ExteNET was amended to include only patients with a higher risk of recurrence (node positive and stage II-IIIC), and patients were to be randomised within 1 year of completion of trastuzumab therapy (i.e., the amended ITT population) [24].

Global Protocol Amendment 9

The trial sponsor chose to stop enrolment of new patients, and follow-up was limited to 2 years after randomisation, which affected the original study objectives of evaluating the long-term efficacy of neratinib in the extended adjuvant setting [24].

Global Protocol Amendment 13

Amendment 13 was made after the publication of results of the I-SPY-2[i] study, which compared neratinib with standard neoadjuvant therapy for high-risk stage II/III breast cancer [34]. I-SPY-2 showed the pathological complete response rate for paclitaxel plus neratinib was higher than for paclitaxel plus trastuzumab. Amendment 13 restored ExteNET to its primary objective—that is, to obtain iDFS and OS data for all randomised patients to evaluate the long-term efficacy of neratinib in the extended adjuvant setting. Collection of recurrent disease events was re-established to 5 years after randomisation, and the primary efficacy analysis was returned to the ITT population [24].

4.2.1.2 ExteNET: Endpoints

The primary endpoint was iDFS—time from randomisation to the first occurrence of the following DFS events[ii]:

- Invasive ipsilateral breast tumour recurrence
- Local or regional invasive recurrence or distant recurrence
- Death from any cause, or invasive contralateral breast cancer

Invasive DFS is a frequently used endpoint in early breast cancer clinical trials in the adjuvant setting. According to US Food and Drug Administration (FDA) guidance on clinical trials, iDFS is an acceptable surrogate endpoint for breast cancer trials in the adjuvant setting [35]. The definition of iDFS used in ExteNET followed the STEEP (standardised definitions for efficacy endpoints) criteria [36], except that

[i] Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2.

[ii] For any patient for whom a DFS event was not observed by the cut-off date of an analysis, DFS was censored at the date of the last physical examination (either scheduled or unscheduled).

secondary primary tumours (occurrence of a non-breast cancer) was not included. This was requested by both the FDA and EMA when the protocol was reviewed.

All time-to-event secondary endpoints were defined as from time of randomisation as follows [29]:

- Disease-free survival including ductal carcinoma in situ (DFS-DCIS): Time from randomisation to the first occurrence of a DFS event (as defined for the primary endpoint) or DCIS. DFS-DCIS events included DCIS and all DFS events. For patients who have a DCIS diagnosis followed by a DFS event, the date of event for DFS-DCIS was the date of DCIS.
- Time to distant recurrence (TTDR): Time between randomisation and the date of the first distant recurrence or death from breast cancer. Time to distant recurrence events included distant recurrence and death from breast cancer.
- Distant disease-free survival (DDFS): Time from randomisation to the first occurrence of distant recurrence or death from any cause. DDFS events included distant recurrence and death from any cause.
- Incidence of central nervous system (CNS) recurrence: Cumulative incidence of CNS recurrence as first distant recurrence (either isolated CNS metastases or diagnosed concurrently with other sites of metastatic disease).
- OS: Time from the date of randomisation until the date of death, censored at the last date known alive.
- Short- and long-term safety (including incidence of grade ≥ 3 diarrhoea).

4.2.1.3 ExteNET: statistical testing

Table 6 provides a summary of the planned statistical analyses in ExteNET.

Table 6. Summary of the statistical analyses of ExteNET

Analysis/parameter	Details
Hypothesis objective	To compare iDFS of women with early-stage HER2-overexpressed/amplified breast cancer following trastuzumab in the adjuvant setting who are receiving neratinib vs. placebo.
Statistical analysis	Time-to-event endpoints were tested with two-sided log-rank tests, either unstratified (EMA label population) or stratified[a] by randomisation factors (intention-to-treat population), and unstratified or stratified[a] Cox proportional hazards models were used to estimate hazard ratios with 95% CIs. Kaplan-Meier methods were used to estimate 2-year survival rates. Cumulative incidence in competing-risk analysis was done for CNS recurrences, and Gray's test was used to compare treatments. Adverse events were graded according to the National Cancer Institute *Common Terminology Criteria*, version 3.0. Changes from baseline in quality of life scores were compared with analysis of covariance, with baseline score as a covariate.
Sample size, power calculation	The study was originally designed to enrol 3,850 patients, with a 90% power to detect a hazard ratio of 0.7 for iDFS at a two-sided 5% significance level. In October 2011, enrolment was stopped after 2,842 patients were randomly assigned, and follow-up was truncated at 2 years. Consequently, the 2-year analysis of iDFS was considered to be the primary analysis; the study was expected to have 241 iDFS events; and the power was projected to be 88% based on a 1-sided log-rank test with a type 1 error of 0.025. No interim analyses were planned owing to cessation of recruitment.
Data management and patient withdrawals	Any patient for whom an event had not been observed by the data cut-off was censored at the date of their last physical examination.
Missing data	The primary analyses did not impute missing values. Patients missing baseline assessments for FACT-B and EQ-5D questionnaires were not included in the analysis of the health outcomes assessments. Partial dates for adverse events: ▪ If the start day was missing, the date was imputed as the first day of the month. ▪ If the end day was missing, the date was imputed as the last day of the month. ▪ If the month, year, both month and year, or the entire date was missing, then no data imputation was implemented; these events were counted with regard to frequency, but the duration was defined as unknown.

CI, confidence interval; CNS, central nervous system; EMA, European Medicines Agency; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2, human epidermal growth factor receptor 2; iDFS, invasive disease-free survival.

[a] Although an unstratified analysis was stated in the protocol, it was revised to a stratified analysis in the statistical analysis plan before unmasking so that the primary analysis was consistent with the stratified design of the trial.

Sources: Puma data on file [30]; Chan et al. [24].

Two efficacy analyses were planned at 2 and 5 years after randomisation [29]:

- Primary analysis: 2-year follow-up analyses to assess the efficacy study data collected during the 2-year follow-up period initiated under Amendment 9
- Sensitivity analysis: 5-year follow-up analyses to assess durability of the treatment effect on iDFS and the impact on OS using the efficacy study data collected during the 5-year follow-up period initiated under Amendment 13

Approximately 75% of patients were reconsented for extended follow-up beyond 24 months. Observations with missing data were censored at the last date of assessment.

The following four prespecified analysis populations were included [29]:

- ITT population (primary): all patients randomised into the study
- Amended ITT population: randomised under Amendment 3 or subsequent amendments; randomised before implementation of Amendment 3 if patients had node-positive disease and randomisation within 1 year from completion of prior trastuzumab therapy
- Centrally confirmed HER2+ population: all patients randomised who were confirmed by central testing
- Safety population: all patients who received at least one dose of study drug

Prespecified subgroup analyses included the following [29]:

- ER/PR status (positive or negative)
- Nodal status (negative vs. 1-3 vs. 4 or more)
- Trastuzumab given sequentially or concurrently with chemotherapy
- Patients who completed prior trastuzumab ≤ 1 year or > 1 year from randomisation

The efficacy endpoints assessed for the subgroups included OS, iDFS, DFS-DCIS, TTDR, and DDFS. The incidence of CNS recurrence was not included in the subgroup analysis because there were insufficient events for meaningful statistical analysis. For any patient for whom a DFS-DCIS or TTDR or DDFS event was not observed by the cut-off date of an analysis, data were censored at the date of the last physical examination. For TTDR, if the patient died of causes other than breast cancer, the TTDR was censored at the date of death.

An additional subgroup analysis was requested by the EMA for patients with HR+ cancer who were within 1 year of completion of trastuzumab therapy. Although this subgroup was not explicitly defined in the statistical analysis plan, both variables used to define the label population of interest (i.e., HR status and ≤ 1 year from completion of prior trastuzumab-based therapy) were prespecified individually in the statistical analysis plan [19]. Moreover, we can observe that time from last dose of trastuzumab to randomisation was a median (interquartile range [IQR]) of 4.4 months (1.6-10.4 months) in the neratinib arm of the ITT population (Table 7).

The ExteNET efficacy results presented in this submission are based on the 2-year and 5-year results for the ITT population [23, 24] and the EMA label subpopulation: adults with HER2+/HR+ breast cancer within 1 year of completion of trastuzumab therapy [19]. Overall survival data have recently been analysed for the ITT and EMA label populations and, although the EMA data are not mature and no OS data have been published, they are presented for completeness.

For the primary HRQoL analysis, evaluable patients were required to have a baseline HRQoL assessment and at least one postbaseline HRQoL assessment. Changes from baseline were compared between treatment groups at each time point using a prespecified analysis of covariance with baseline score as a covariate and no imputation for missing values. Adjusted least squares mean values with 95% CIs were estimated within treatment groups and for differences between treatment groups at each time point. A prespecified secondary analysis was performed using a mixed-effect model that included visit and treatment as covariates. The model incorporated all available data and assumed that any missing postbaseline observations were missing at random [20].

Safety analyses were done in the safety population, defined as all patients who received at least one dose of study treatment. Adverse events (AEs) were graded according to the National Cancer Institute *Common Terminology Criteria* (NCI-CTC), version 3.0 [24].

4.2.1.4 ExteNET: baseline characteristics

Table 7 presents baseline characteristics of the ITT and label populations. Baseline characteristics were similar between both populations, with no notable differences of distribution between treatment arms. Overall, 46.97% (1,334 of 2,840) of the ITT population in ExteNET met the criteria of the EMA label population.

In ExteNET, the median age in the ITT population was 52.3 years (≥ 50 years, 59.9%; ≥ 65 years, 12.3%); 81.0% were white, 2.6% black or African American, 13.6% Asian, and 2.9% other. At baseline, 57.4% had HR+ disease (defined as ER+ and/or PR+), 23.6% were node negative, 46.8% had one to three positive nodes, and 29.6% had four or more positive nodes. Approximately 10% of patients had stage I tumours, approximately 40% had stage II tumours, and approximately 30% had stage III tumours. Median time from the last adjuvant trastuzumab treatment to randomisation was 4.5 months [1]. For patients with HR+ tumours, most patients had been treated previously with endocrine therapy, and concurrent adjuvant endocrine therapy was recommended during the trial period. Concomitant endocrine therapy during ExteNET was similar between treatment arms in both the ITT and EMA label populations [37, 38].

In ExteNET, 25% of the ITT population received neoadjuvant therapy, and 125 patients (4.4%) had pathological complete response, as they were enrolled before Amendment 3. By HR status, fewer patients with HR+ tumours had a pathological complete response, with only 27 patients in the placebo arm and 22 patients in the neratinib arm having achieved pathological complete response after neoadjuvant therapy [39].

For patients with HR+ tumours, most patients had been treated previously with endocrine therapy, and concurrent adjuvant endocrine therapy was recommended during the trial period. Concomitant endocrine therapy during ExteNET was similar between treatment arms in both the ITT and label populations [37, 38].

Patient disposition and flow in the ExteNET trial are described in more detail in Appendix H.

Table 7. ExteNET: baseline patient characteristics, ITT population and EMA label population (HR+ completing prior trastuzumab ≤ 1 year from randomisation)

	ITT		EMA label population	
Characteristic	**Neratinib (n = 1,420)**	**Placebo (n = 1,420)**	**Neratinib (n = 670)**	**Placebo (n = 664)**
Region, n (%)				
North America	519 (37)	477 (34)	237 (35.4)	205 (30.9)
Western Europe, Australia and South Africa	487 (34)	532 (38)	236 (35.2)	264 (39.8)
Asia Pacific, Eastern Europe and South America	414 (29)	411 (29)	197 (29.4)	195 (29.4)
Age, years (median [range])	52 (25-83)	52 (23-82)	51 (25-83)	51 (23-78)
Menopausal status at diagnosis, n (%)				
Premenopausal	663 (47)	664 (47)	350 (52.2)	342 (51.5)
Postmenopausal	757 (53)	756 (53)	320 (47.8)	322 (48.5)
Nodal status,[a] n (%)				
Negative	335 (24)	336 (24)	130 (19.4)	125 (18.8)
1-3 positive nodes	664 (47)	664 (47)	339 (50.6)	334 (50.3)
≥ 4 positive nodes	421 (30)	420 (30)	201 (30.0)	205 (30.9)
HR status, n (%)				
Positive (ER+, PR+, or both)	816 (58)	815 (57)	670 (100.0)	664 (100.0)
Negative (ER– and PR–)	604 (43)	605 (43)	–	–
Previous trastuzumab regimen, n (%)				
Given concurrently with chemotherapy	884 (62)	886 (62)	411 (61.3)	415 (62.5)
Given sequentially with chemotherapy	536 (38)	534 (38)	259 (38.7)	249 (37.5)
T stage, n (%)				
T1	440 (31)	459 (32)	218 (32.5)	209 (31.5)
T2	585 (41)	555 (39)	270 (40.3)	250 (37.7)
≥ T3	144 (10)	117 (8)	61 (9.1)	65 (9.8)
Unknown	250 (18)	288 (20)	121 (18.1)	140 (21.1)
Missing	1 (< 1)	1 (< 1)		
Prior neoadjuvant or adjuvant therapy,[b] n (%)				
Trastuzumab	1,420 (100)	1,420 (100)	670 (100.0)	664 (100.0)
Anthracycline only	136 (10)	135 (10)	67 (10.0)	58 (8.7)

	ITT		EMA label population	
Characteristic	**Neratinib (n = 1,420)**	**Placebo (n = 1,420)**	**Neratinib (n = 670)**	**Placebo (n = 664)**
Anthracycline plus taxane	962 (68)	965 (68)	435 (64.9)	445 (67.0)
Taxane only	318 (22)	316 (22)	167 (24.9)	159 (23.9)
Neither anthracycline nor taxane	4 (< 1)	4 (< 1)	1 (0.1)	2 (0.3)
Duration of prior adjuvant trastuzumab therapy, months (median [range])	11.5 (10.9-11.9)	11.4 (10.8-11.9)	11.4 (1.4-29.1)	11.4 (1.4-24.0)
Time from last dose of trastuzumab to randomisation, months (median [IQR])	4.4 (1.6-10.4)	4.6 (1.5-10.8)	3.07 (0.2-12.0)	3.30 (0.3-12.0)
Concomitant endocrine therapy use for HR+ tumours,[c] n (%)				
No	56 (7)	51 (6)	48 (7.2)	35 (5.3)
Yes	760 (93)	764 (94)	622 (92.8)	629 (94.7)
Anti-oestrogen only	375 (46)	347 (43)	325 (52.3)	294 (46.7)
Anti-oestrogen and aromatase inhibitor (sequential)	20 (3)	34 (4)	20 (3.2)	29 (4.6)
Aromatase inhibitor only	362 (44)	379 (47)	275 (44.2)	302 (48.0)
Non–anti-oestrogen or aromatase inhibitor	3 (< 1)	4 (< 1)	2 (0.3)	4 (0.6)

EMA, European Medicines Agency; ER, oestrogen receptor; HR, hormone receptor; IQR, interquartile range; ITT, intention to treat; PR, progesterone receptor.

[a] The number of positive nodes was at the time of initial diagnosis (for patients who received adjuvant therapy) or surgery (for those who received neoadjuvant therapy). 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] The proportion of patients who received neoadjuvant chemotherapy was 25% (n = 247) in the neratinib group and 27% (n = 282) in the placebo group for ITT, and 24.2% (n = 162) in the neratinib group and 28.9% (n = 192) in the placebo group for the EMA label population.

[c] Percentage is based on the number of patients with HR+ tumours or from stratification factors. Tumours were assessed as being ER+ or PR+ on the basis of local pathology laboratory cut-offs. There was no protocol specification as to whether a 1% or 10% threshold should be used.

Adapted from Martin et al. [23]; Gnant et al. [19].

4.2.2 CONTROL trial: neratinib with antidiarrhoeal prophylaxis

CONTROL (NCT02400476, Study PUMA-NER-6201) [40] is an ongoing, phase 2, open-label safety and tolerability study investigating the effect of antidiarrhoeal strategies (e.g., dose escalation or loperamide prophylaxis) on the incidence and duration of neratinib-associated diarrhoea, the most common side effect observed in the ExteNET trial.

Interim analyses were presented at SABCS 2016 [41], SABCS 2017 [26], the 2017 American Association for Cancer Research Congress [25], SABCS 2018 [27], American Society of Clinical Oncology (ASCO) 2019 [42] and SABCS 2019 [43]. Barcenas et al. [22] recently published the final data analysis for cohorts 1 to 4 and interim data for cohort 5 in the *Annals of Oncology*.

Safety data for neratinib from CONTROL are included in the economic model to reflect the incidence of diarrhoea with neratinib when initiated with an antidiarrhoeal medication, as instructed in the label [16]. Table 8 presents details of the CONTROL methodology; further details on design, endpoints, and statistical analysis are described in Sections 4.2.2.1 to 4.2.2.3. Full details of inclusion and exclusion criteria and permitted and disallowed concomitant medication are described in Table G-2 in Appendix G.

Table 8. CONTROL: summary of trial methodology

Location	59 sites in the United States, Canada, Australia, Austria, France, Germany, and Spain
Trial design	Open-label, phase 2 safety and tolerability study comparing neratinib + antidiarrhoeal prophylaxis (e.g., loperamide with or without budesonide or colestipol) vs. an historical cohort of neratinib without protocol-mandated antidiarrhoeal prophylaxis
Intervention(s) and comparator(s)	▪ Neratinib + loperamide (n = 137, cohort 1) ▪ Neratinib + loperamide + budesonide (n = 64, cohort 2) ▪ Neratinib + loperamide + colestipol (n = 136, cohort 3) ▪ Neratinib + colestipol + loperamide PRN (n = 104, cohort 4) ▪ Neratinib dose escalation starting at 120 mg + loperamide given PRN (n = 60, cohort 5) ▪ Neratinib dose escalation starting at 160 mg + loperamide given PRN (recruitment ongoing, cohort 6) ▪ Neratinib-only historical cohort from ExteNET (n = 1,420, ExteNET cohort, no protocol-mandated loperamide) Loperamide cohort (cohort 1): oral neratinib 240 mg/day for 1 year—thirteen 28-day cycles (with or without hormone therapy as indicated), with oral loperamide prophylaxis (4 mg, 2 tablets/capsules taken 3 times daily) for the first two 28-day cycles and then loperamide (≤ 16 mg/day) PRN after completion of loperamide prophylaxis. Budesonide cohort (cohort 2): oral neratinib 240 mg/day for 1 year—thirteen 28-day cycles (with or without hormone therapy as indicated), with oral budesonide (9 mg daily in the morning) for the first 28-day cycle plus loperamide prophylaxis for the first two 28-day cycles and then PRN, as described above. Colestipol cohort (cohort 3): oral neratinib 240 mg/day for 1 year—thirteen 28-day cycles (with or without hormone therapy as indicated), plus oral colestipol (two 1 g tablets taken twice daily) for one cycle plus loperamide prophylaxis as described above for one cycle and thereafter PRN. Colestipol PRN cohort (cohort 4): 240 mg neratinib orally once daily with food for thirteen 28-day cycles. Colestipol for 1 cycle and loperamide to be administered PRN. Neratinib DE1 cohort (cohort 5): 120 mg neratinib for week 1, followed by 160 mg neratinib starting at week 2, followed by 240 mg neratinib starting at week 3 and thereafter (C1D15 to end of treatment). Loperamide administered PRN. Neratinib DE2 cohort (cohort 6): 160 mg neratinib for the first 2 weeks, followed by 200 mg neratinib for the next 2 weeks, followed by 240 mg neratinib thereafter (C2D1 to end of treatment). Loperamide will be administered on a PRN basis only.

Location	59 sites in the United States, Canada, Australia, Austria, France, Germany, and Spain
Primary outcomes (including scoring methods and timings of assessments)	Primary endpoint: incidence of grade ≥ 3 diarrhoea during treatment with neratinib. All safety analyses were descriptive. Patients were seen on day 1 of cycles 1, 2, 3, 4, 7, and 10 and at the end of cycle 13 and contacted by telephone on days 1-3 after the first neratinib dose to inquire about diarrhoea or other potential AEs, receive guidance on AE management, and confirm the first date of neratinib dosing. Patients used a diary to record study medication intake. Follow-up continued for 28 days after the last neratinib dose.
Other outcomes used in the economic model/specified in the scope	Secondary endpoints included: ▪ Evaluation of the association between antidiarrhoeal treatment exposure and incidence and severity of diarrhoea (e.g., loperamide with or without budesonide or colestipol) ▪ Assessment of the incidence of serious AEs and other AEs of special interest Exploratory endpoint: ▪ HRQoL, including the EQ-5D-5L and FACT-B version 4 questionnaires completed electronically on day 1 of cycles 1, 2, 4, 7 and 10 and at the end of cycle 13 (end of treatment). HRQoL assessments were introduced in November 2015 (protocol Amendment 2).
Preplanned subgroups	None specified

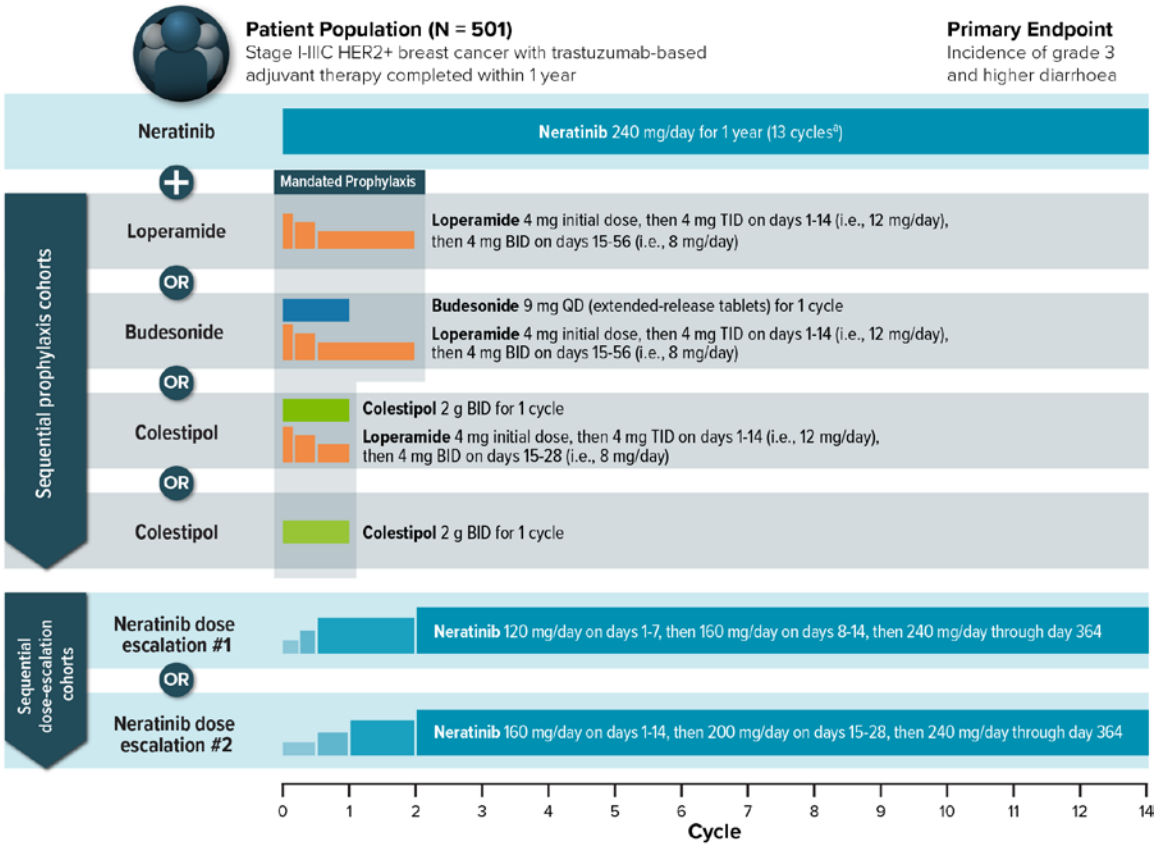
AE, adverse event; DE, dose escalation; FACT-B, Functional Assessment of Cancer Therapy–Breast; HRQoL, health-related quality of life; PRN, as needed.

Sources: ClinicalTrials.gov [40]; Puma data on file [44]; Hurvitz et al. [26].

4.2.2.1 CONTROL: study design

Figure 2 presents five cohorts of CONTROL that have completed recruitment and reported results. Cohorts 1 to 3 received neratinib with structured loperamide prophylaxis after prior treatment with trastuzumab. Separate patient cohorts were treated with budesonide (corticosteroid) or colestipol (bile acid sequestrant) in addition to loperamide to determine if these treatments could further reduce neratinib-associated diarrhoea [26]. Cohort 4 used colestipol without structured loperamide prophylaxis and cohorts 5 and 6 were different neratinib dose escalation regimens, without structured loperamide prophylaxis [40]. As cohort 6 results are not yet mature, this cohort is not discussed further in this dossier. The ExteNET trial, which included an analogous patient population but no protocol-mandated antidiarrhoeal prophylaxis, was used as a reference point [22].

Figure 2. CONTROL trial design



BID, twice daily; HER2, human epidermal growth factor receptor 2; QD, once daily; TID, three times a day.

[a] One cycle = 28 days.

Source: Barcenas et al. [22].

Neratinib treatment consisted of oral neratinib 240 mg once daily with food for 64 days or until disease recurrence (as determined by the investigator), death, unacceptable toxicity, or other specified withdrawal criterion. The neratinib dose could be reduced to 160 mg or 120 mg daily to manage toxicity. Once the neratinib dose was reduced for a patient, all subsequent cycles were to be administered at that dose, unless further dose reduction was required [26].

Loperamide was the primary prophylaxis antidiarrhoeal medication mandated in CONTROL. Loperamide 4 mg (2 tablets/capsules) was taken three times daily during the first two 28-day cycles of neratinib treatment.

In the original protocol, an initial dose of loperamide 4 mg was administered on cycle 1/day 1 concomitantly with the first dose of neratinib. Subsequent 2-mg doses of loperamide were to be taken every 4 hours on days 1, 2 and 3 (for a total daily dose of 12 mg), and then every 6 to 8 hours (for a total daily dose of 6-8 mg) starting on day 4 until the end of the second cycle of therapy (day 56). Prophylaxis was continued in subsequent cycles at the discretion of the investigator [26].

With Amendments 1 and 2, the loperamide dosing schedule was modified to simplify the regimen and to prevent or manage diarrhoea in initially enrolled patients. The amended regimen was as follows:

- For the first 14 days, loperamide 4 mg was self-administered orally by patients three times daily (for a total daily dose of 12 mg).
- Loperamide dose reduction guidelines for constipation were provided.

With Amendment 3, oral budesonide (9 mg daily) was added for cycle 1.

With Amendment 4, colestipol (2 g twice daily) was added for cycle 1.

The final analysis for cohorts 1 to 4 is complete. Enrolment into cohorts 5 and 6 is ongoing; the final analysis of the CONTROL trial will be performed when all patients have completed 12 months of neratinib therapy, anticipated in May 2021 [22, 26].

4.2.2.2 CONTROL: endpoints

The primary objective of CONTROL is to characterise the duration, incidence and severity of diarrhoea in patients with early-stage HER2+ breast cancer treated with neratinib when administered with structured antidiarrhoeal strategies after prior treatment with trastuzumab [26, 44].

The primary endpoint of CONTROL is the incidence of grade ≥ 3 diarrhoea during treatment with neratinib at any time during the study.

Secondary and exploratory endpoints are as follows:

- To evaluate the association between antidiarrhoeal treatment exposure (e.g., loperamide) and incidence and severity of diarrhoea, such as loperamide with and without anti-inflammatory agents, or with and without a bile acid sequestrant
- To assess the incidence of serious AEs and other AEs of special interest
- Patient-reported HRQoL (exploratory endpoint)

As the objective of CONTROL is to provide additional safety data for neratinib, the results presented in this submission are for the entire safety analysis set for CONTROL (i.e., all patients who received neratinib), which includes all patients with early HER2+ breast cancer, regardless of HR status.

4.2.2.3 CONTROL: statistical testing

Table 9 provides a summary of the planned statistical analyses in CONTROL. All safety analyses were descriptive and performed in the safety population (all patients who received ≥ 1 neratinib dose). Adverse events were graded according to NCI *Common Terminology Criteria for Adverse Events* (CTCAE), version 4.0. HRQoL analyses were descriptive and performed in the quality of life (QoL) analysis population (all patients in the safety population with baseline and ≥ 1 postbaseline QoL assessment). Mean (standard error) observed HRQoL scores over time were calculated. The primary analyses did not impute missing values. Changes in HRQoL scores from baseline, if greater than the previously reported lowest estimate for an important difference, were considered clinically meaningful. The ExteNET trial, which included an analogous patient population but no protocol-mandated antidiarrhoeal prophylaxis, was used as an historical control [26].

Table 9. Summary of the statistical analyses of CONTROL

Analysis/parameter	Details
Hypothesis objective	To characterise diarrhoea incidence and severity in patients treated with neratinib plus structured antidiarrhoeal prophylaxis (e.g., loperamide with or without budesonide or colestipol) compared with neratinib plus loperamide as needed.
Statistical analysis	Two-sided 95% Clopper-Pearson CIs will be computed. All safety analyses were descriptive and performed in the safety population (all patients who received ≥ 1 neratinib dose). Adverse events were graded according to National Cancer Institute C*ommon Terminology Criteria for Adverse Events*, version 4.0. HRQoL analyses were descriptive and performed in the QoL analysis population (all patients in the safety population with baseline and ≥ 1 postbaseline QoL assessment). Mean (standard error) observed HRQoL scores over time were calculated.
Sample size, power calculation	The incidence of grade ≥ 3 diarrhoea is assumed to be 15% in this study. A sample size of 120 patients will ensure that the width of the 95% CI of the incidence of grade ≥ 3 diarrhoea is no more than 18.5%. For example, if 18 of 120 patients are observed to have grade ≥ 3 diarrhoea, the incidence and its 95% (two-sided) CIs will be 15.0% (9.1%-22.7%), in which the width of the CI is 13.5%. In addition to the analyses of the overall safety population, antidiarrhoeal prophylaxis regimen–specific subgroup analyses will be performed as needed. Precision of the estimated 95% CIs for the regimen-specific subgroup(s) will be lower than what is provided above for the overall safety population. Starting with Amendment 3, the effect of anti-inflammatory treatments on the incidence, severity, and duration of diarrhoea will be assessed. Starting with Amendment 4, the effect of a bile acid sequestrant will be assessed. A sample size of 40 patients will ensure that the width of the 95% CI of the incidence of grade ≥ 3 diarrhoea is no more than 33%. For example, if 4 of 40 patients are observed to have grade ≥ 3 diarrhoea, the incidence and its 95% (two-sided) CI will be 10.0% (2.8%-23.7%), in which the width of the CI is 21%.
Data management and patient withdrawals	In all cases, the reason(s) for premature discontinuation/withdrawal must be recorded on the case report form, and the primary reason must be indicated. If a patient is prematurely withdrawn from the investigational product or the study for any reason, the investigator must make every effort to perform the evaluations described for the EOT visit (performed within 5 days of the last dose of investigational product as appropriate). If a patient discontinues because of an AE, the patient should be strongly encouraged to undergo the EOT assessments and continue to be under medical supervision until symptoms cease or the condition becomes stable. If a patient is lost to follow-up or voluntarily withdraws from study participation, every effort should be made to determine why a patient is lost to follow-up or withdraws consent. This information, including the date, should also be recorded. All patients will remain on active study treatment until a cause of early treatment discontinuation occurs. These include disease progression, unacceptable toxicity, and withdrawal of consent or until study closure.
Missing data	The primary analyses did not impute missing values.

AE, adverse event; CI, confidence interval; EOT, end of treatment; HRQoL, health-related quality of life; QoL, quality of life.

Sources: Puma data on file [44]; Hurvitz et al. [26].

4.2.2.4 CONTROL: baseline characteristics

At the time of the database cut-off for the interim safety report (21 October 2019), the safety population consisted of the following 501 patients who had received at least one dose of neratinib: loperamide cohort (n = 137), budesonide cohort (n = 64), colestipol cohort (n = 136), colestipol cohort as needed (PRN) (n = 104) and neratinib dose escalation (n = 60; still actively recruiting) [22].

Table 10 presents baseline characteristics of CONTROL compared with the neratinib-treated cohort of the ITT population of ExteNET. Baseline characteristics were similar in CONTROL and ExteNET; however, the following differences were noted: more CONTROL patients had HR+ tumours, more had received taxanes, and fewer had received anthracyclines, but more ExteNET patients had stage III tumours at diagnosis. In addition, 40% to 62% of patients in CONTROL, but none in ExteNET, had received pertuzumab as either neoadjuvant or adjuvant therapy. Finally, ExteNET included patients from South Africa and South America, which were regions not represented in the original five cohorts of CONTROL [22].

The safety population of CONTROL included all patients with early HER2+ breast cancer regardless of HR status, reflecting the ITT population of the ExteNET trial. However, the authorised marketing indication for neratinib (the EMA label population) is narrower: patients with HER2+/HR+ breast cancer who have completed a course of adjuvant trastuzumab-based less than 1 year ago. Baseline demographic data show that most of the safety population of CONTROL had HER2+/HR+ breast cancer (72%-80%), and the median time since last trastuzumab dose in all cohorts was less than 4.2 months. In addition, patients with a median time since last trastuzumab dose of more than 12 months are considered protocol deviations for entry criteria and will be removed from the final analysis [22].

Table 10. Baseline characteristics for the interim analysis population for CONTROL compared with patients treated with neratinib in ExteNET

	CONTROL					ExteNET (ITT population)
Characteristic	**Loperamide cohort**	**Budesonide + loperamide cohort**	**Colestipol + loperamide cohort**	**Colestipol + as-needed loperamide**	**Neratinib dose escalation**	**Neratinib arm (loperamide as needed)**
N (at data cut-off)	137	64	136	104	60	1,420
Median age (range), years	53 (30-86)	49 (29-78)	53 (26-78)	51 (33-77)	51 (29-76)	52 (25-83)
Menopausal status, %						
Premenopausal	30	45	27	37	40	47
Postmenopausal	70	55	71	63	60	53
Not applicable	0	0	2	0	0	0

	CONTROL					ExteNET (ITT population)
Characteristic	**Loperamide cohort**	**Budesonide + loperamide cohort**	**Colestipol + loperamide cohort**	**Colestipol + as-needed loperamide**	**Neratinib dose escalation**	**Neratinib arm (loperamide as needed)**
Tumour stage at diagnosis, %						
I	28	25	16	15	15	10
IIA, IIB	55	47	47	54	47	42
IIIA, IIIB, IIIC	15	23	27	23	28	31
IV	0	0	0	2	0	0
Unknown	2	5	10	6	10	17
Hormone receptor status, %						
Positive (ER+ and/or PR+)	75	72	76	78	80	57
Negative (ER– and PR–)	25	28	24	22	18	43
Prior (neo)adjuvant therapy, %						
Trastuzumab	99	97	99	98	100	100
Taxanes	96	97	99	100	100	90
Anthracycline	26	28	23	28	47	77
Pertuzumab	40	61	62	61	48	0
T-DM1	0	1.6	1.5	0	0	0
Median (range) duration of prior trastuzumab, months	11.5 (2.4-18.2)	10.8 (1.2-16.7)	10.9 (0.6-15.5)	10.9 (2.8-14.9)	10.7 (3.8-13.3)	11.5 (0.7-56.9)
Median (range) time since last trastuzumab dose, months	3.9 (0.1-12.1)	4.1 (0.5-12.1)	2.5 (0.0-12.0)	2.5 (0.5-12.0)	3.2 (0.5-20.2)	4.4 (0.2-30.9)
Median (range) duration of prior pertuzumab, months	3.5 (0-11.1)	3.5 (0-10.5)	3.5 (0-11.8)	3.5 (0-15.5)	3.8 (1.4-12.1)	0
Median (range) time since last pertuzumab dose, months	12.1 (3.3-22.3)	11.5 (2.6-20.0)	11.0 (0.6-20.0)	10.8 (1.4-20.5)	10.4 (0.8-20.2)	0

ER, oestrogen receptor; ITT, intention to treat; PR, progesterone receptor.

Source: Barcenas et al. [22].

5 Clinical question

5.1 What is the value of neratinib compared with placebo in patients with ER+ and HER2+ breast cancer?

5.1.1 Presentation of relevant studies

This submission is based primarily on the ExteNET study, with supporting evidence from the CONTROL study. The subpopulation of ExteNET is relevant to this submission: the EMA label population (patients with HER2+/HR+ breast cancer within 1 year of trastuzumab therapy). In January 2020, an update to the summary of product characteristics (SmPC) was published. The updates were due to a request from the EMA in June 2019 to perform and submit reanalyses of the ExteNET trial, conducted by Puma, with consistent stratification factors—using case report form (CRF) stratification variables instead of interactive response technology (IRT) variables. These reanalyses were submitted through a type 2 variation [16]. In the assessment history documentation, the EMA noted that the reanalyses conducted show that the stratification discrepancies between the IRT and CRF data did not lead to imbalance between the treatment arms that could have caused potential bias nor did they impact the validity of the study conclusions. As a result, in the type 2 variation report, the EMA concluded that "the benefit/risk ratio of neratinib remains unchanged." Results based on the CRF are included in the updated SmPC and are presented here [16].

The DMC requests published clinical evidence for consideration by the committee. For the ExteNET study, data are available from the following three data cut-offs:

- July 2014: Published 2-year analysis (used the IRT stratification factors)
- March 2017: Published 5-year analysis (used the IRT stratification factors)
- July 2019: Published OS and unpublished OS; tumour, node, metastasis (TNM); and HRQoL data (used both CRF and IRT stratification factors)

The DMC requested analysis of OS and iDFS data for each combination of TNM stages based on a July 2019 data cut, neither of which are published. However, for transparency, we have provided the most recent updated OS and TNM data, which are based on the CRF stratifications. Table 11 presents a full description of the location of all results in this submission.

Table 11. ExteNET: summary of results presented in submission

	IRT 2-year data: July 2014	IRT 5-year data: March 2017	IRT: July 2019	CRF: July 2019
Publication status	Published	Published	Published	Unpublished
Baseline characteristics	Section 4.2.1.4	Section 4.2.1.4	Section 4.2.1.4	Not presented
OS	Not presented	Not presented	Section 5.1.2.1	Section 5.1.2.1
iDFS	Section 5.1.2.2	Section 5.1.2.2	Not presented	Not presented
Side effects	Section 5.1.2.3	Section 5.1.2.3	Not presented	Not presented
Quality of life	Section 5.1.2.4 (ITT population)	Not presented	Not presented	Unpublished (EMA population)
TNM classification	Not presented	Not presented	Not presented	Section 5.1.4

CRF, case report form; iDFS, invasive-disease-free survival; IRT, interactive response technology; OS, overall survival; TNM, tumour, node, metastasis.

CONTROL (NCT02400476, Study PUMA-NER-6201) [40] is an ongoing, phase 2, open-label safety and tolerability study investigating the effect of antidiarrhoeal strategies (e.g., loperamide prophylaxis) on the incidence and duration of neratinib-associated diarrhoea, the most common side effect observed in the ExteNET trial.

Table 12 provides a summary of the outcome measures identified in the protocol. The results per outcome are based on the EMA label.

Table 12. Summary of the value of neratinib compared with placebo in patients with ER+ and HER2+ breast cancer

					Absolute difference in effect			Relative difference in effect				
Results per outcome	**Study arm**	**N**	**Result**	**Studies included in the analysis**	**Difference**	**CI**	***P* value**	**Hazard/odds/risk ratio**	**CI**	***P* value**	**Description of methods used for estimation**	**Methods used for quantitative synthesis**
OS (CRF stratification factors)[a]: 8 years All patients (n = 1,339)	Neratinib	671	55 deaths (8.2%) Estimated OS rate, 91.1%	Chan et al. [18]	Difference in estimated OS: 1.7%	NA	NA	HR: 0.83	0.58-1.18	*P* = 0.288	2-sided log-rank test and hazard ratios with 95% CIs were estimated using a Cox proportional hazards model. Kaplan-Meier methods were used to estimate event-free survival rates.	NA
	Placebo	668	68 deaths (10.2%) Estimated OS rate, 89.4%									
OS (IRT stratification factors)[b]: 8 years All patients (n = 1,334)	Neratinib	670	53 deaths (7.9%) Estimated OS rate, 91.5%	Chan et al. [18]	Difference in estimated OS: 2.1%	NR	NA	HR: 0.79	0.55-1.13	*P* = 0.20		NA
	Placebo	664	68 deaths (10.2%) Estimated OS rate, 89.4%									
OS: nodal status[b]				Chan et al. [18]								
Positive (n = 1,079)	NA	NA	NA		NA	NA	NA	HR: 0.79	0.53-1.16	NA		
Negative (n = 255)	NA	NA	NA		NA	NA	NA	HR: 0.82	0.29-2.20	NA		

					Absolute difference in effect			Relative difference in effect				
Results per outcome	**Study arm**	**N**	**Result**	**Studies included in the analysis**	**Difference**	**CI**	***P* value**	**Hazard/odds/risk ratio**	**CI**	***P* value**	**Description of methods used for estimation**	**Methods used for quantitative synthesis**
OS: prior trastuzumab[b]				Chan et al. [18]								
Concurrent (n = 826)	NA	NA	NA		NA	NA	NA	HR: 0.83	0.52-1.31	NA		
Sequential (n = 508)	NA	NA	NA		NA	NA	NA	HR: 0.74	0.41-1.30	NA		
OS: adjuvant or neoadjuvant therapy[b]				Chan et al. [18]								
Adjuvant (n = 980)	NA	NA	NA		NA	NA	NA	HR: 1.10	0.69-1.77	NA		
Neoadjuvant (n = 354) [b]	NA	NA	NA		NA	NA	NA	HR: 0.52	0.28-0.92	NA		
OS: pCR status[b]				Chan et al. [18]								
No (n = 295)	NA	NA	NA		NA	NA	NA	HR: 0.47	0.23-0.92	NA		
Yes (n = 38)	NA	NA	NA		NA	NA	NA	HR: 0.40	0.06-1.88	NA		
iDFS: all patients (n = 1,334) [b]												
2 years	Neratinib	670	95.3% (95% CI, 93.1-96.7)	Puma data on file [45]; Gnant et al. [19]	−4.5%	NA	NA	HR: 0.50	0.31-0.79	*P* = 0.003	Stratified Cox proportional hazards model.	NA

					Absolute difference in effect			Relative difference in effect				
Results per outcome	**Study arm**	**N**	**Result**	**Studies included in the analysis**	**Difference**	**CI**	***P* value**	**Hazard/odds/risk ratio**	**CI**	***P* value**	**Description of methods used for estimation**	**Methods used for quantitative synthesis**
	Placebo	664	90.8% (95% CI, 88.2 92.9)								The log-rank test and Cox model are stratified by randomisation stratification factors: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4).	
5 years	Neratinib	670	90.8 (95% CI, 88.1-93.0)	Gnant et al. [19]; Puma data on file [46]	−5.1%	NA	NA	HR: 0.59	0.41-0.82	*P* = 0.002		NA
	Placebo	664	85.7% (95% CI, 82.6-88.3)									
iDFS (5 years): nodal status[b]				Chan et al. [18]							Time-to-event endpoints were tested with a 2-sided log-rank test, and hazard ratios with 95% CIs were estimated using a Cox proportional hazards model.	
Positive (n = 1,079)	NA	NA	NA		NA	NA	NA	HR: 0.60	0.42-0.85	NA		
Negative (n = 255)	NA	NA	NA		NA	NA	NA	HR: 0.37	0.008-1.24	NA		
iDFS (5 years): Prior trastuzumab[b]				Chan et al. [18]								
Concurrent (n = 826)	NA	NA	NA		NA	NA	NA	HR: 0.62	0.40-0.95	NA		
Sequential (n = 508)	NA	NA	NA		NA	NA	NA	HR: 0.51	0.28-0.91	NA		

					Absolute difference in effect			Relative difference in effect				
Results per outcome	**Study arm**	**N**	**Result**	**Studies included in the analysis**	**Difference**	**CI**	***P* value**	**Hazard/odds/risk ratio**	**CI**	***P* value**	**Description of methods used for estimation**	**Methods used for quantitative synthesis**
iDFS (5 years): adjuvant or neoadjuvant therapy[b]				Chan et al. [18]								
Adjuvant (n = 980)	NA	NA	NA		NA	NA	NA	HR: 0.65	0.41-1.01	NA		
Neoadjuvant (n = 354)	NA	NA	NA		NA	NA	NA	HR: 0.54	0.31-0.90	NA		
iDFS (5 years): pCR status[b]				Chan et al. [18]								
No (n = 295)	NA	NA	NA		NA	NA	NA	HR: 0.60	0.33-1.07	NA		
Yes (n = 38)	NA	NA	NA		NA	NA	NA	HR: 0.44	0.06-1.89	NA		
Side effects												
Any TEAE	Neratinib	662	98.0%	Puma data on file [47]	11.7%	NA	NA	RR: 1.14	1.1-1.17	NA	NA	NA
	Placebo	657	86.3%									
Grade 3 or 4 TEAE	Neratinib	662	49.4%	Puma data on file [47]	37.8%	NA	NA	RR: 4.27	3.41-5.35	NA	NA	NA
	Placebo	657	11.6%									
Quality of life												
FACT-B: 12 months/	Neratinib	574	−3.7 (SD, 12.76)	Delaloge et al. [20]	−0.8		0.24	NA	NA	NA	Mean change from baseline	NA

					Absolute difference in effect			Relative difference in effect				
Results per outcome	**Study arm**	**N**	**Result**	**Studies included in the analysis**	**Difference**	**CI**	***P* value**	**Hazard/odds/risk ratio**	**CI**	***P* value**	**Description of methods used for estimation**	**Methods used for quantitative synthesis**
end of treatment	Placebo	795	−2.8 (SD, 13.31)			−2.2 to 0.6						
	Neratinib	235	−3.8	Pierre Fabre data on file [21]	−0.71	−2.96 to 1.53	0.53	NA	NA	NA	A regression of change from baseline at each month was performed on treatment arm and baseline value	NA
	Placebo	326	−2.9									
EQ-5D index score 12 months/ end of treatment	Neratinib	580	−0.016 (SD, 0.163)	Delaloge et al. [20]	0.00	−0.01 to 0.02	0.60	NA	NA	NA	Mean change from baseline	NA
	Placebo	797	−0.019 (SD, 0.177)									
	Neratinib	239	−0.05	Pierre Fabre data on file [21]	0.02	−0.01 to 0.04	0.140	NA	NA	NA	A regression of change from baseline at each month was performed on treatment arm and baseline value	NA
	Placebo	324	−0.03									
EQ-5D health state 12 months/	Neratinib	580	−2.2 (SD, 14.50)	Delaloge et al. [20]	−0.4	−1.7 to 1.00	0.59	NA	NA	NA	Mean change from baseline	NA
	Placebo	797	−1.6 (SD, 14.11)									

					Absolute difference in effect			Relative difference in effect				
Results per outcome	**Study arm**	**N**	**Result**	**Studies included in the analysis**	**Difference**	**CI**	***P* value**	**Hazard/odds/risk ratio**	**CI**	***P* value**	**Description of methods used for estimation**	**Methods used for quantitative synthesis**
end of treatment	Neratinib	239	−2.4	Pierre Fabre data on file [21]	−0.06	−2.33 to 2.21	0.959	NA	NA	NA	A regression of change from baseline at each month was performed on treatment arm and baseline value	NA
	Placebo	324	−2.2									

CI, confidence interval; CRF, case report form; ER, oestrogen receptor; FACT-B, Functional Assessment of Cancer Therapy–Breast; HER2+, human epidermal growth factor receptor 2–positive; iDFS, invasive disease-free survival; IRT, interactive response technology; NA, not available; NR, not reported; OS, overall survival; pCR, pathologic complete response; RR, risk ratio; SD, standard deviation; TEAE, treatment-related adverse event.

[a] Analysis used CRF stratifications.

[b] Analysis used IRT stratifications.

5.1.2 Results per study

5.1.2.1 Overall survival

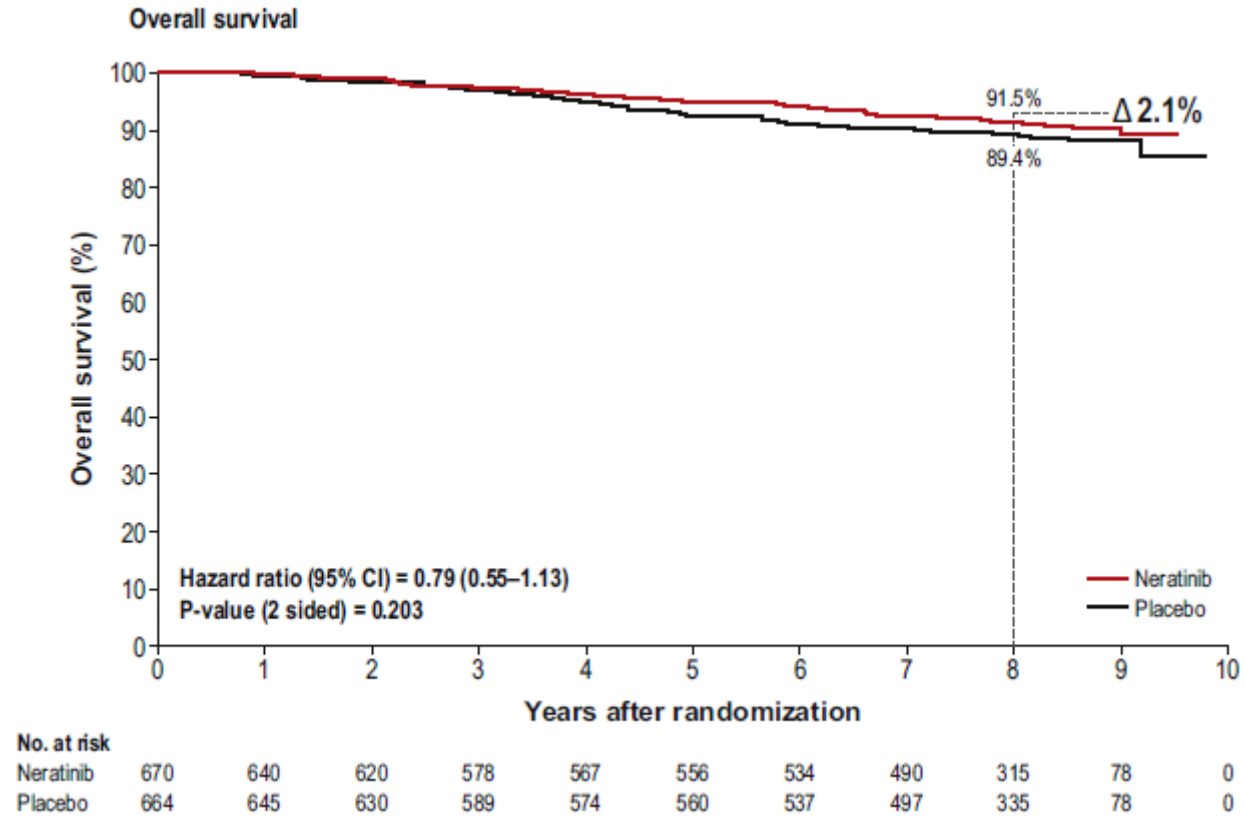
The final OS analysis for the European Union (EU) label population (patients with HER2+, HR+ early breast cancer and ≤ 1-year from completion of adjuvant trastuzumab-based therapy) in the ExteNET trial was recently published in Chan et al. [18]. The primary analysis of OS was to be performed when 248 deaths had occurred in the ITT population. Although the study was not designed to detect a statistical difference in terms of OS in the EMA label population, these analyses [48] have been reported [18]. These data should be interpreted with caution because fewer deaths were observed for meeting the predefined criteria of 248 deaths in the ITT population, and the subgroup analyses were not prespecified. Nevertheless, the data provide some insight into the likely long-term benefit of neratinib in terms of OS. Appendix K presents additional exploratory OS data for the ITT population.

As mentioned in Section 5.1.1, in January 2020, an update to the SmPC was published. Results based on the CRF stratification are included in the updated SmPC and are presented here [16]; however, most of the published OS data are based on IRT stratification unless otherwise stated.

In the OS analysis published by Chan et al. [18] and when using the CRF stratification, median follow-up time was 8.0 years (range, 0-9.8 years), and 671 patients were randomised into the neratinib arm and 668 to the placebo arm. At the OS analysis cut-off date of July 2019, the number of patients with an OS event was 123 (9.2%), with 55 events (8.2%) in the patients treated with neratinib and 68 events (10.2%) in the patients treated with placebo. The hazard ratio for neratinib versus placebo was 0.83 (95% CI, 0.58-1.18). The estimated 8-year OS rates were 91.1% in the patients treated with neratinib and 89.4% in the patients treated with placebo, resulting in an absolute between-group difference of 1.7%.

When using the IRT stratification, the median follow-up was 8.0 years (range, 0-9.8 years), and 670 patients were randomized to the neratinib arm and 664 to the placebo arm. At the OS analysis cut-off date of July 2019, the number of patients with an OS event was 121 (9.1%), with 53 events (7.9%) in the patients treated with neratinib and 68 events (10.2%) in the patients treated with placebo. The hazard ratio for neratinib versus placebo was 0.79 (95% CI, 0.55-1.13); the two-sided *P* value from the log-rank test was *P* = 0.20. The estimated 8-year OS rates were 91.5% (95% CI, 88.9%-93.5%) in the patients treated with neratinib and 89.4% (95% CI, 86.6%-91.6%) in the patients treated with placebo, resulting in an absolute between-group difference of 2.1% (Figure 3) [18].

Figure 3. ExteNET: Kaplan-Meier curve of overall survival in the HR+/≤ 1-year population (n = 1,334)

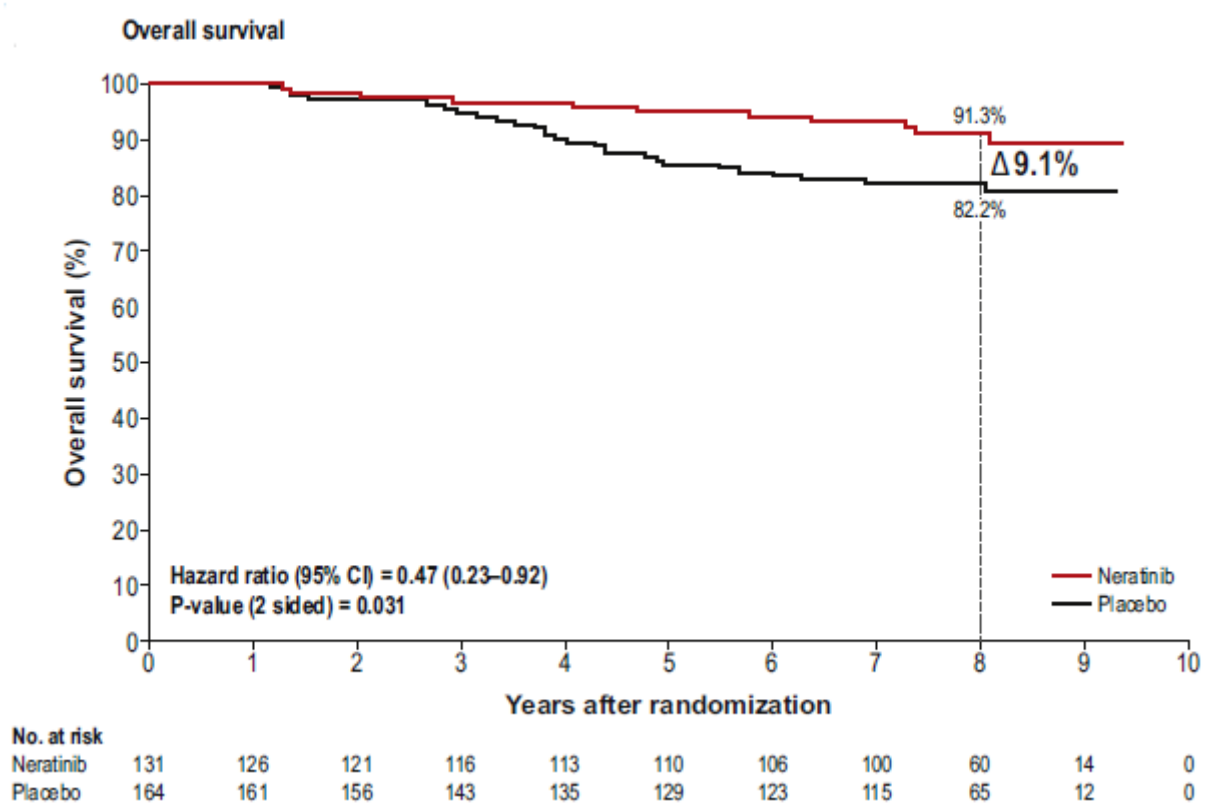


CI, confidence interval; HR+, hormone receptor–positive.

Source: Chan et al. [18].

A total of 295 patients in the EMA population had received neoadjuvant therapy but had residual disease (e.g., no pCR). In these patients, there was an absolute benefit in favour of neratinib of 7.4% in iDFS at 5 years (HR, 0.60; 95% CI, 0.33-1.07; *P* = 0.086) and of 9.1% in OS at 8 years (HR, 0.47; 95% CI, 0.23-0.92; *P* = 0.031) (Figure 4).

Figure 4. ExteNET: Kaplan-Meier curve of overall survival in the HR+/≤ 1-year population with no pathologic complete response after neoadjuvant therapy (n = 295)

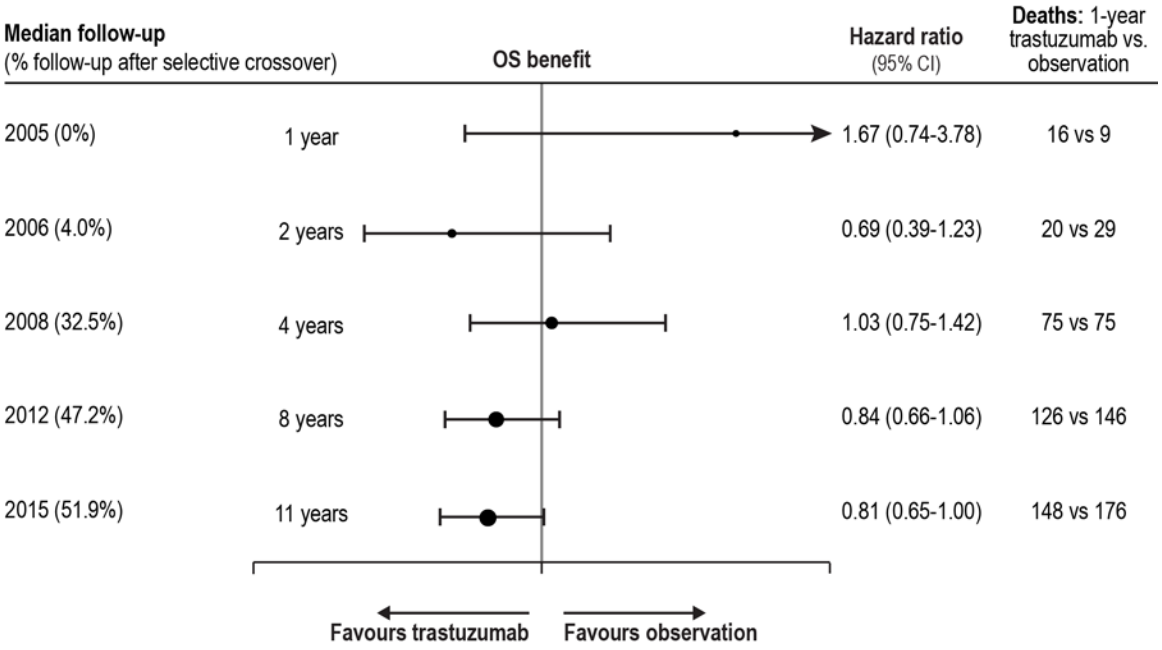


CI, confidence interval; HR+, hormone receptor–positive.

Source: Chan et al. [18].

Despite the OS data analysis having fewer deaths than the predefined criteria of 248, the OS results in the EMA label population (HER2+/HR+ within 1 year of trastuzumab) show a low benefit, which is consistent with other anti-HER2 treatments. The results can be put in perspective with the OS results of trials with trastuzumab in the adjuvant treatment of HER2+ breast cancer (Figure 5) and T-DM1 in the adjuvant treatment of HER2+ breast cancer, which did not obtain a complete pathological response after neoadjuvant treatment with trastuzumab (Figure 6). Of note, the results of these studies did not show any significant difference in OS, regardless of the length of follow-up [9, 49].

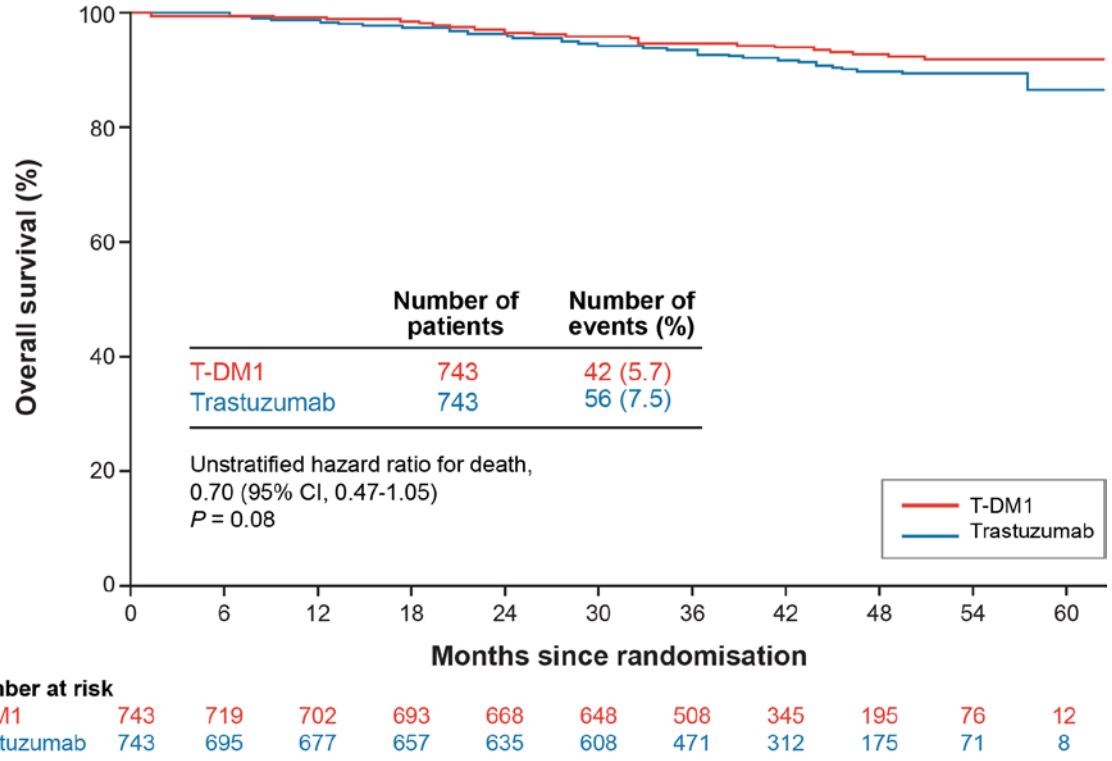
Figure 5. Adjuvant trastuzumab: overall survival for HER2+/HR+ subgroup



CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival.

Source: Cameron et al. [9]

Figure 6. T-DM1: overall survival in residual HER2+ breast cancer



CI, confidence interval; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine.

Source: von Minckwitz et al. [49]

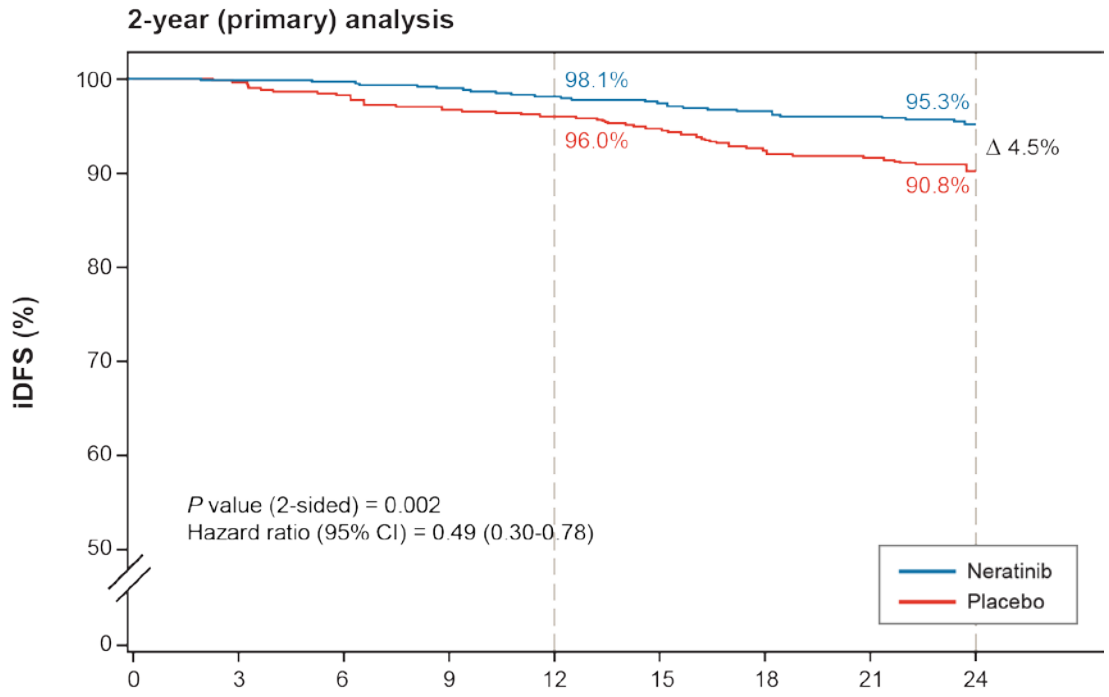
Although, as stated above, the analysis of ExteNET OS data for the EMA label population can only be considered descriptive, this analysis shows a reduction in mortality (hazard ratio, 0.79; 95% CI, 0.55-1.13) despite the number of events for this analysis being insufficient for this population (121 events). Of importance, the trends observed in OS are consistent with the 2- and 5-year analyses of iDFS [23, 24], highlighting greater improvements with neratinib in patients with HR+ disease than in patients with HR− tumours. These OS results confirm those observed for iDFS at 2 years and 5 years and reinforce the validity of the EMA label [18, 48].

5.1.2.2 Invasive disease-free survival

2-Year invasive disease-free survival

Invasive DFS was the primary endpoint for the ExteNET study and showed significant improvements in both the ITT and EMA label populations. In the EMA label population (n = 1,334), the 2-year iDFS rate was 95.3% for neratinib (n = 670) and 90.8% for placebo (n = 664), equating to an absolute benefit of 4.5% and a significant relative risk reduction of invasive disease recurrence or death by 51% versus placebo (26 vs. 55 events; stratified hazard ratio, 0.50; 95% CI, 0.31-0.79; two-sided *P* = 0.003) (Figure 7) [1]. Table 13 summarises iDFS events by site of first occurrence at 2 years [45].

Figure 7. ExteNET: Kaplan-Meier curve of iDFS at 2 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



Number at risk
HR+/≤ 1 year from trastuzumab

Neratinib	670	605	593	577	559	538	516	485	307
Placebo	664	638	619	602	580	563	541	501	326

CI, confidence interval; HR+, hormone receptor–positive; iDFS, invasive disease-free survival.

Sources: NERLYNX® SmPC [1]; Gnant et al. [19].

Table 13. ExteNET: iDFS events at 2 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab

	Neratinib (n = 670)	Placebo (n = 664)
Patients with events, n (%)	26 (3.9)	55 (8.3)
Local/regional invasive recurrence	3 (0.4)	12 (1.8)
Invasive ipsilateral breast tumour recurrence	1 (0.1)	2 (0.3)
Invasive contralateral breast cancer	1 (0.1)	2 (0.3)
Distant recurrence	20 (3.0)	38 (5.7)
Death from any cause	1 (0.1)	1 (0.2)
Patients censored, n (%)	644 (96.1)	609 (91.7)
Kaplan-Meier estimate, % (95% CI)		
12 Months	98.1 (96.7-99.0)	96.0 (94.2-97.3)
24 Months	95.3 (93.1-96.7)	90.8 (88.2-92.9)
Stratified log-rank test *P* value (two-sided)[a]	0.003	
Unstratified log-rank test *P* value (two-sided)	0.002	
Stratified Cox proportional hazards model[a]		
Hazard ratio (95% CI)[b]	0.50 (0.31-0.79)	
Unstratified Cox proportional hazards model		
Hazard ratio (95% CI)[b]	0.49 (0.30-0.78)	

CI, confidence interval; HR+, hormone receptor–positive; iDFS, invasive disease-free survival.

Note: Disease-free survival time is defined as the time from date of randomisation until the first disease recurrence of one of the following events: local/regional invasive recurrence, invasive ipsilateral breast tumour recurrence, invasive contralateral breast cancer, distant recurrence, or death from any cause.

[a] The log-rank test and Cox model are stratified by randomisation stratification factors: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4).

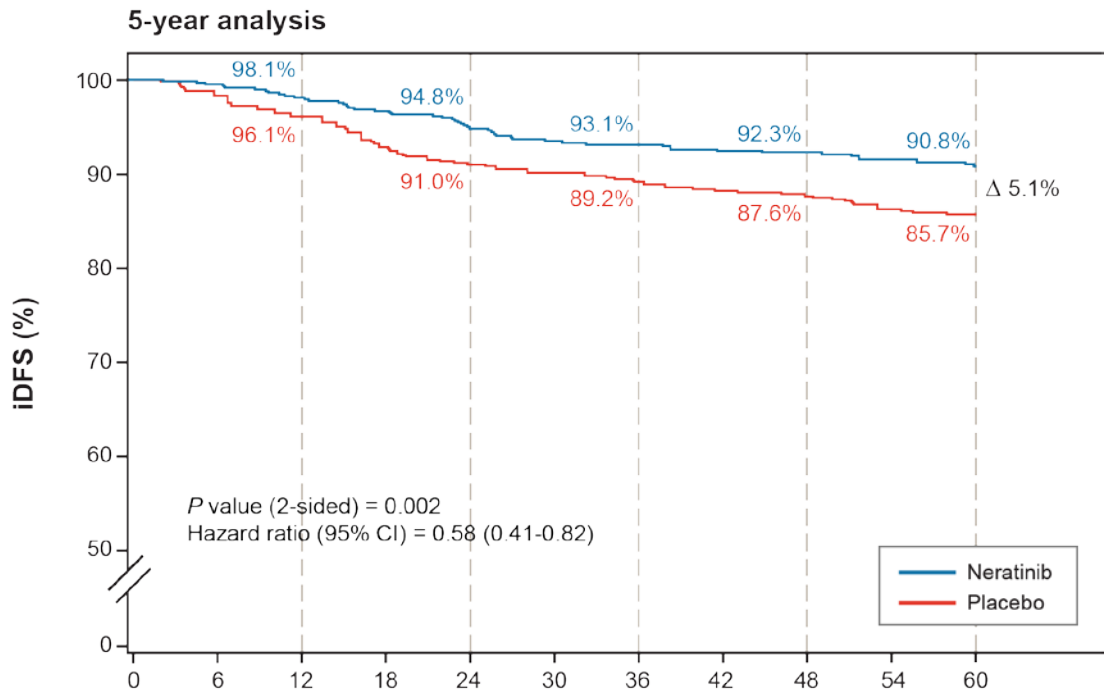
[b] The hazard ratio is presented as neratinib vs. placebo.

Source: Puma data on file [45].

5-Year invasive disease-free survival

The treatment effect of neratinib over placebo was durable at 5 years after randomisation. In the EMA label population, the 5-year iDFS rate was 90.8% for neratinib (n = 670) and 85.7% for placebo (n = 664), equating to an absolute benefit of 5.1% and a significant relative risk reduction of invasive disease recurrence or death by 42% versus placebo (51 vs. 89 events; stratified hazard ratio, 0.59; 95% CI, 0.41-0.82; two-sided *P* = 0.002). Kaplan-Meier curves for iDFS separated after approximately 3 months and remained separate for the rest of the 5-year follow-up (Figure 8) [19]. Table 14 summarises iDFS events by site of first occurrence at 5 years [46].

Figure 8. ExteNET: Kaplan-Meier curve of iDFS at 5 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab



Number at risk
HR+/≤ 1 year from trastuzumab

Neratinib	670	620	599	577	523	469	465	460	457	448	428
Placebo	664	634	609	583	535	481	471	462	458	450	433

CI, confidence interval; HR+, hormone receptor–positive; iDFS, invasive disease-free survival.

Source: Gnant et al. [19].

Table 14. ExteNET: iDFS events at 5 years, HR+ population ≤ 1 year from prior adjuvant trastuzumab

	Neratinib (n = 670)	Placebo (n = 664)
Patients with events, n (%)	51 (7.6)	89 (13.4)
Local/regional invasive recurrence	5 (0.7)	18 (2.7)
Invasive ipsilateral breast tumour recurrence	2 (0.3)	5 (0.8)
Invasive contralateral breast cancer	2 (0.3)	5 (0.8)
Distant recurrence	40 (6.0)	63 (9.5)
Death from any cause	2 (0.3)	3 (0.5)
Patients censored, n (%)	619 (92.4)	575 (86.6)
Kaplan-Meier estimate, % (95% CI)		
12 months	98.1 (96.6-98.9)	96.1 (94.3-97.4)
24 months	94.8 (92.7-96.3)	91.0 (88.5-93.0)
36 months	93.1 (90.7-94.9)	89.2 (86.4-91.4)
48 months	92.3 (89.7-94.2)	87.6 (84.7-90.0)
60 months	90.8 (88.1-93.0)	85.7 (82.6-88.3)
Stratified log-rank test *P* value (two-sided)[a]	0.002	
Unstratified log-rank test *P* value (two-sided)	0.002	
Stratified Cox proportional hazards model[a]		
Hazard ratio (95% CI)[b]	0.59 (0.41-0.82)	
Unstratified Cox proportional hazards model		
Hazard ratio (95% CI)[b]	0.58 (0.41-0.82)	

CI, confidence interval; HR+, hormone receptor–positive; iDFS, invasive disease-free survival.

Note: Disease-free survival time is defined as the time from date of randomisation until the first disease recurrence of one of the following events: local/regional invasive recurrence, invasive ipsilateral breast tumour recurrence, invasive contralateral breast cancer, distant recurrence, or death from any cause.

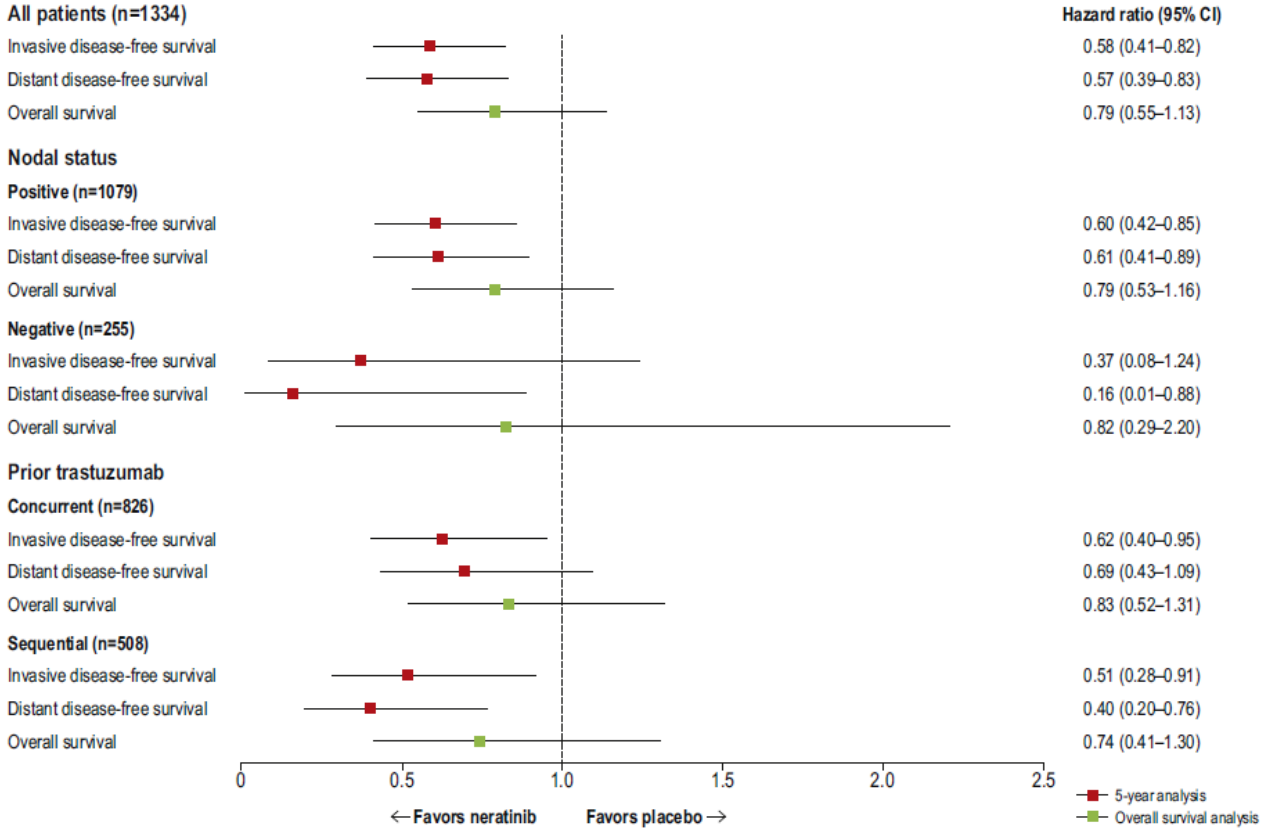
[a] The log-rank test and Cox model are stratified by randomisation stratification factors: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4).

[b] The hazard ratio is presented as neratinib vs. placebo.

Source: Puma data on file [46].

Chan et al. [18] recently published subgroup analyses of iDFS at 5 years. Subgroup analyses based on randomisation stratification factors showed iDFS analysed by nodal status and schedule of administration of prior trastuzumab with chemotherapy were consistently in favour of neratinib compared with placebo (Figure 9) [18].

Figure 9. ExteNET: subgroup analyses of invasive disease-free and distant disease-free survival at 5 years and overall survival according to randomisation stratification factors in the HR+/≤ 1-year population (n = 1,334)

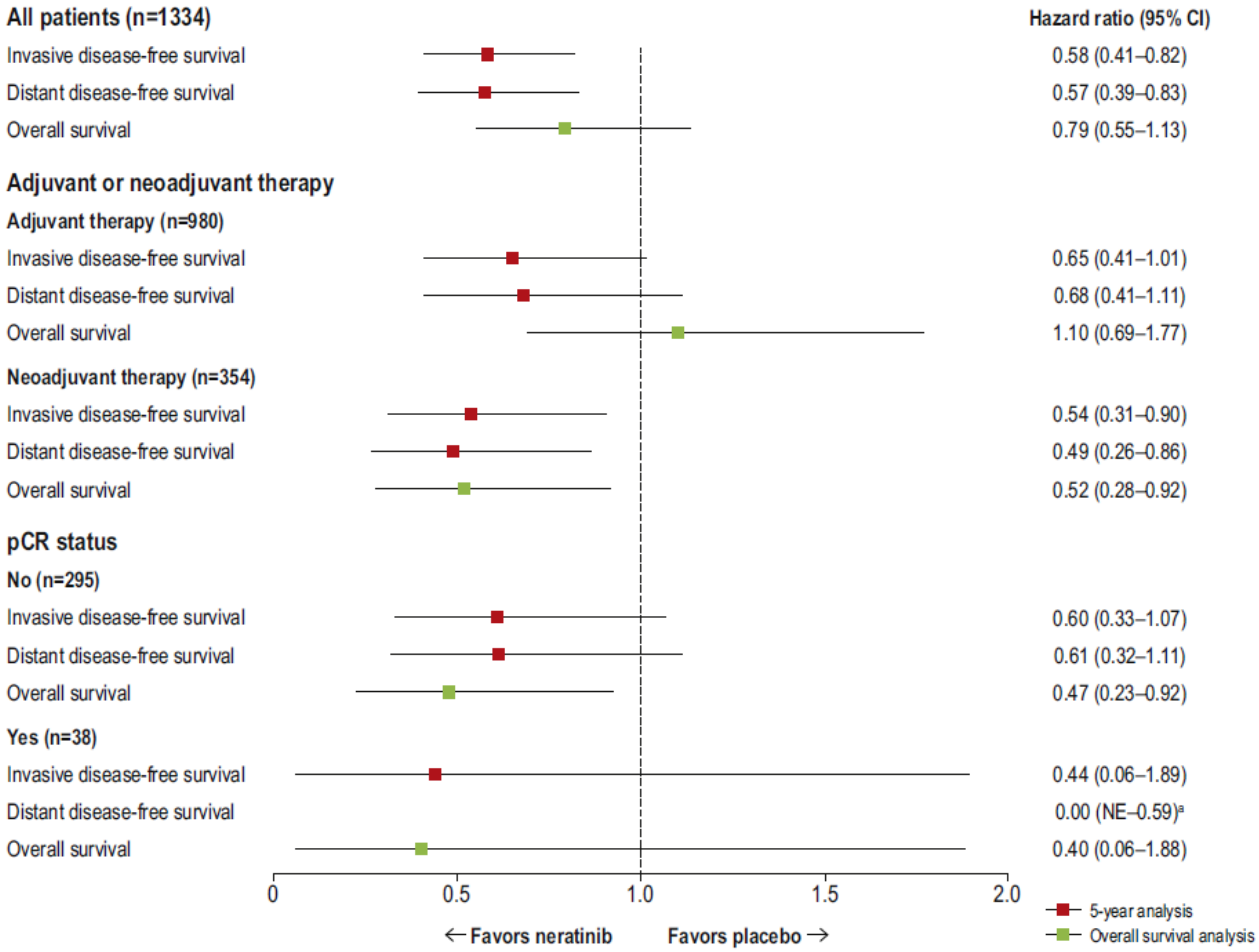


CI, confidence interval; HR+, hormone receptor–positive.

Source: Chan et al. [18].

Similarly, subgroup analyses of adjuvant or neoadjuvant therapy and pathologic complete response status showed iDFS at 5 years for neratinib compared with placebo was consistent with iDFS for the whole EMA population (Figure 10Figure 11) [18].

Figure 10. ExteNET: subgroup analyses of invasive disease-free and distant disease-free survival at 5 years and overall survival in subgroups of clinical interest in the HR+/≤ 1-year population (n = 1,334)



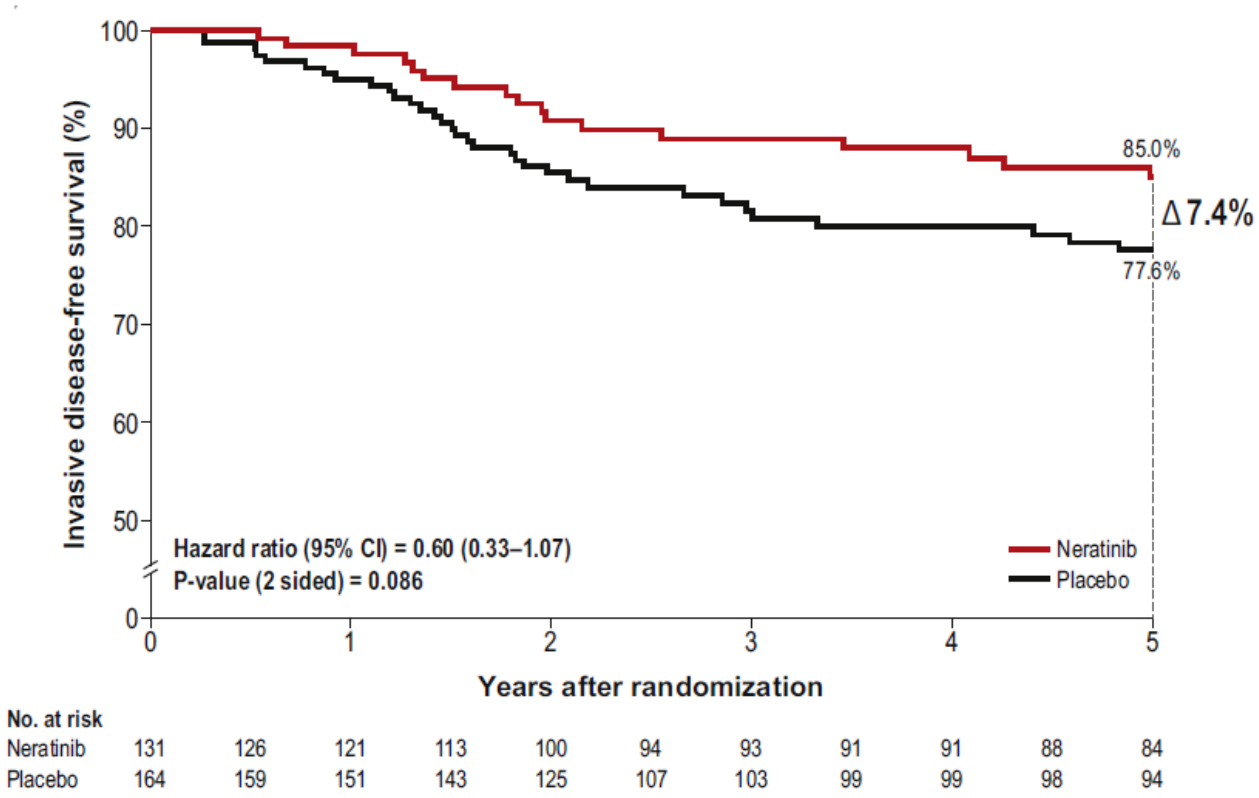
CI, confidence interval; HR+, hormone receptor–positive; NE, not estimable; pCR = pathologic complete response.

[a] Distant disease-free survival results for the pCR (Yes) subgroup are not presented because there were no events in the neratinib group; therefore, it was not possible to estimate the confidence boundary for the hazard ratio.

Source: Chan et al. [18].

Rates of iDFS in patients with no pathologic complete response after neoadjuvant therapy (n = 295) were 85% (95% CI, 77.0%-90.4%) in patients treated with neratinib and 77.6% (95% CI, 69.8%-83.6%) in patients treated with placebo, resulting in an absolute benefit of 7.4% (hazard ratio, 0.60; 95% CI, 0.33–1.07) (Figure 11) [18].

Figure 11. ExteNET: Kaplan-Meier curve of iDFS at 5 years in the HR+/≤ 1-year population with no pathological complete response after neoadjuvant therapy (n = 295)



CI, confidence interval; HR+, hormone receptor–positive; iDFS, invasive disease-free survival.

5.1.2.3 Side effects

Two studies were identified that reported adverse reactions and other safety outcomes with neratinib in early HER2+/HR+ breast cancer: ExteNET and CONTROL. These studies are described here. Feedback from a Danish clinical expert stated that the side effects of neratinib were manageable (see Appendix J). Risk-minimisation materials in the form of physician and patient or carer educational materials have been developed and are available to support the management of diarrhoea.

ExteNET: safety results

In ExteNET, at least one dose of study treatment was received by 2,816 patients (n = 1,408 patients in each group) representing the safety population. Results presented here are the primary 2-year analyses for the entire safety population for ExteNET, regardless of HR status or time from completion of trastuzumab therapy (n = 2,816) [24] and a subgroup analysis for the EMA label population relevant to marketing authorisation in Europe (n = 1,319: neratinib, n = 662; placebo, n = 657) [19, 47]. Median duration of treatment was similar between treatment arms in the EMA label population: 11.5 months in the neratinib group and 11.9 months in the placebo group [19].

Unlike other agents used to treat early breast cancer, neratinib does not have cumulative toxicities or toxicities associated with increased healthcare resources, such as neutropenia, neuropathy, and cardiac

toxicity [50-53]. The profile and frequency of AEs in the safety population and the EMA label population were similar (Table 15 and Table 16) [19, 24]. The most frequently reported treatment-emergent adverse events (TEAEs) with neratinib in both the safety and EMA label population were gastrointestinal disorders, including diarrhoea, nausea, vomiting and abdominal pain (Table 17 and Table 18). Other frequently reported TEAEs included fatigue, headache, rash, decreased appetite, muscle spasms and dizziness (Table 17 and Table 18).

In the safety population, TEAEs causing discontinuation of the study drug occurred in 388 patients (27.6%) with neratinib and 76 (5.4%) with placebo [23]. Serious TEAEs occurred in 103 patients (7.3%) in the neratinib group and 85 (6.0%) in the placebo group (Table 15). The most common serious events in the neratinib group were diarrhoea, vomiting and dehydration. Reported deaths were due to metastatic breast cancer, including metastases that had infiltrated the meninges (n = 1), and acute myeloid leukaemia (n = 1) in the neratinib group and gastric cancer (n = 1) in the placebo group. None of these deaths were attributed to study treatment in either group [23].

For the EMA label population, the profile and frequency of TEAEs leading to dose reductions, dose holds, and hospitalisation were similar to the safety population in 203 (31%), 280 (42%) and 41 (6%) patients in the neratinib group, respectively, and 13 (2%), 75 (11%) and 35 (5%) patients in the placebo group (Table 16) [19].

Table 15. ExteNET: overall summary of TEAEs, safety population

TEAE	Neratinib (n = 1,408), n (%)	Placebo (n = 1,408), n (%)	Total (N = 2,816), n (%)
Any TEAE	1,387 (98.5)	1,240 (88.1)	2,627 (93.3)
Grade 3 or 4 TEAE	700 (49.7)	184 (13.1)	884 (31.4)
Fatal TEAE	2 (0.1)	1 (0.1)	3 (0.1)
SAE	103 (7.3)	85 (6.0)	188 (6.7)
Treatment-related TEAE	1,353 (96.1)	805 (57.2)	2,158 (76.6)
Serious treatment-related TEAE	42 (3.0)	8 (0.6)	50 (1.8)
TEAE leading to treatment discontinuation	388 (27.6)	76 (5.4)	464 (16.5)
TEAE leading to study withdrawal	32 (2.3)	7 (0.5)	39 (1.4)
TEAE leading to dose reduction	440 (31.3)	35 (2.5)	475 (16.9)
TEAE leading to hospitalisation	93 (6.6)	75 (5.3)	168 (6.0)
TEAE leading to dose hold	629 (44.7)	187 (13.3)	816 (29.0)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: Puma data on file [30].

Table 16. ExteNET: overall summary of TEAEs for HR+ patients who completed prior adjuvant trastuzumab within 1 year from randomisation, EMA label safety population

TEAE	Neratinib (n = 662), n (%)	Placebo (n = 657), n (%)	Total (N = 1,319), n (%)
Any TEAE	649 (98.0)	567 (86.3)	1,216 (92.2)
Grade 3 or 4 TEAE	327 (49.4)	76 (11.6)	403 (30.6)
Fatal TEAE	1 (0.2)	0 (0.0)	1 (0.1)
SAE	45 (6.8)	36 (5.5)	81 (6.1)
Treatment-related TEAE	630 (95.2)	360 (54.8)	990 (75.1)
Serious treatment-related TEAE	19 (2.9)	5 (0.8)	24 (1.8)
TEAE leading to treatment discontinuation	178 (26.9)	30 (4.6)	208 (15.8)
TEAE leading to study withdrawal	11 (1.7)	2 (0.3)	13 (1.0)
TEAE leading to dose reduction	203 (30.7)	13 (2.0)	216 (16.4)
TEAE leading to hospitalisation	41 (6.2)	35 (5.3)	76 (5.8)
TEAE leading to dose hold	280 (42.3)	75 (11.4)	355 (26.9)

EMA, European Medicines Agency; HR+, hormone receptor–positive; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Source: Puma data on file [47].

Table 17. ExteNET: grade 1-4 TEAEs occurring in ≥ 10%, safety population

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

TEAE, treatment-emergent adverse event.

Source: Martin et al. [23].

Table 18. ExteNET: grade 1-4 TEAEs occurring in ≥ 10%, EMA label safety population

	Neratinib (n = 662), n (%)			Placebo (n = 657), n (%)		
Adverse event	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Diarrhoea	365 (55.1)	261 (39.4)	0	213 (32.4)	7 (1.1)	0
Nausea	280 (42.3)	9 (1.4)	0	135 (20.5)	2 (0.3)	0
Fatigue	177 (26.7)	13 (2.0)	0	129 (19.6)	2 (0.3)	0
Vomiting	150 (22.7)	24 (3.6)	0	41 (6.2)	2 (0.3)	0
Abdominal pain	145 (21.9)	11 (1.7)	0	58 (8.8)	1 (0.2)	0
Headache	119 (18.0)	6 (0.9)	0	125 (19.0)	1 (0.2)	0
Upper abdominal pain	90 (13.6)	6 (0.9)	0	35 (5.3)	3 (0.5)	0
Rash	90 (13.6)	3 (0.5)	0	40 (6.1)	0	0
Decreased appetite	79 (11.9)	1 (0.2)	0	13 (2.0)	0	0
Muscle spasms	81 (12.2)	0	0	21 (3.2)	1 (0.2)	0

EMA, European Medicines Agency; TEAE, treatment-emergent adverse event.

Source: Puma data on file [54].

ExteNET: incidence of diarrhoea

Diarrhoea was the most common TEAE with neratinib treatment in ExteNET, in both the entire safety population (95.4% with neratinib vs. 35.4% with placebo) [55] and the EMA label safety population (93.7% with neratinib vs. 28.2% with placebo) [56]. Diarrhoea is an expected on-target side effect of an epidermal growth factor receptor (EGFR)–targeted agent and is likely to be attributed to EGFR involvement in calcium-dependent chloride transport and EGFR inhibition (the postulated mechanism of neratinib's effect) potentially resulting in secretory diarrhoea [23]. In ExteNET, no mandatory treatment with antidiarrhoeal prophylaxis was specified in the protocol.

In the safety population, 55% in the neratinib group versus 34% in the placebo group had grade 1-2 diarrhoea; 40% in the neratinib group versus 2% in the placebo group had grade 3 diarrhoea; and one patient (< 1%) in the neratinib group versus none (0%) in the placebo group had grade 4 diarrhoea (Table 19) [24]. Results were similar in the EMA label population, but no patients in either group experienced grade 4 diarrhoea (Table 20) [56].

Severe (grade 3) diarrhoea associated with neratinib occurred early (in the first month of treatment) and was mostly self-limiting (Table 19). In the safety population, grade 3 diarrhoea occurred after a median of 8 days (IQR, 4-33 days) and lasted a median of 5 days (IQR, 2-9 days) per patient. Most grade 3 diarrhoea events occurred in the first month of treatment. Diarrhoea led to neratinib dose reductions in 372 (26%) patients in the neratinib group and 8 (1%) in the placebo group, hospital admission in 20 (1%) versus 1 (< 1%), and drug discontinuation in 237 (17%) (discontinued after a median of 20 days [IQR, 9-56 days]) versus 3 (< 1%) (discontinued after 241 days [IQR, 147-305 days]), respectively [24]. The incidence of grade 3 diarrhoea in the EMA label population was similar (Table 20) [56].

Apart from gastrointestinal events, all other grade 3-4 AEs occurred in fewer than 4% of neratinib-treated patients, with a similar incidence of non-gastrointestinal events in both groups. There was no evidence suggesting a cumulative increase in long-term or irreversible toxicities, specifically symptomatic cardiac toxicity or second primary malignancies in the neratinib group compared with the placebo group [23]. In view of the early occurrence of severe diarrhoea, use of prophylaxis for the first 1 to 2 months of treatment as recommended in the SmPC [16] is expected to effectively reduce the rates of severe diarrhoea.

Table 19. ExteNET: treatment-emergent diarrhoea, safety population

Events	Neratinib (n = 1,408)	Placebo (n = 1,408)
Patients ever experienced treatment-emergent diarrhoea, n (%)	1,343 (95.4)	499 (35.4)
Maximum toxicity, n (%)		
Grade 1	323 (22.9)	382 (27.1)
Grade 2	458 (32.5)	94 (6.7)
Grade 3	561 (39.8)	23 (1.6)
Grade 4	1 (0.1)	0
Drug-related diarrhoea, n (%)	1,330 (94.5)	411 (29.2)
Serious events, n (%)	22 (1.6)	1 (0.1)
Actions taken because of diarrhoea, n (%)		
Withdrawn from study	23 (1.6)	0
Discontinued study drug	237 (16.8)	3 (0.2)
Dose reduction	372 (26.4)	8 (0.6)
Hospitalised	20 (1.4)	1 (0.1)
Dose hold, n (%)		
Once	263 (18.7)	22 (1.6)
Twice	97 (6.9)	2 (0.1)
Three or more times	117 (8.3)	2 (0.1)
Median (IQR) time to onset of diarrhoea, days		
Any grade	2 (2-4)	18 (4-82)
Grade ≥ 2	5 (2-15)	90 (17-189)
Grade ≥ 3	8 (4-33)	124 (21-257)
Duration of grade ≥ 3 diarrhoea per patient, days		
Median (IQR)	5 (2-9)	2 (1-5)
Grade ≥ 3 events per patient, n		
Mean	2.7	1.3

Events	Neratinib (n = 1,408)	Placebo (n = 1,408)
Median (IQR)	2 (1-3)	1 (1-1)
Median (IQR) duration of diarrhoea per event, days		
Any grade	2 (1-3)	2 (1-3)
Grade ≥ 2	1 (1-2)	2 (1-2)
Grade ≥ 3	2 (1-3)	2 (1-4)

IQR, interquartile range.

Source: Chan et al. [24].

Table 20. ExteNET: treatment-emergent diarrhoea by treatment month for patients who completed prior adjuvant trastuzumab within 1 year from randomisation and HR+, EMA label safety population

Events	Neratinib (n = 662)	Placebo (n = 657)
Patients ever experienced diarrhoea, n (%)	626 (94.6)	220 (33.5)
Serious events	8 (1.2)	0 (0.0)
Treatment-related	620 (93.7)	185 (28.2)
Serious treatment-related events	8 (1.2)	0 (0.0)
Action taken because of diarrhoea, n (%)		
IP discontinuation	107 (16.2)	1 (0.2)
Withdrawal from study	10 (1.5)	0 (0.0)
IP reduction	169 (25.5)	4 (0.6)
Temporarily stopping IP	209 (31.6)	9 (1.4)
Hospitalisation	8 (1.2)	0 (0.0)
Concomitant medication	565 (85.3)	94 (14.3)
Other	68 (10.3)	3 (0.5)
Maximum toxicity, n (%)		
Grade 1	153 (23.1)	169 (25.7)
Grade 2	212 (32.0)	44 (6.7)
Grade 3	261 (39.4)	7 (1.1)
Grade 4	0 (0.0)	0 (0.0)
Outcome of the last diarrhoea episode, n (%)		
Persisted	38 (5.7)	7 (1.1)

Events	Neratinib (n = 662)	Placebo (n = 657)
Resolved	588 (88.8)	213 (32.4)
Time to first onset in days (any grade)		
Mean (SD)	5.95 (20.32)	55.30 (85.36)
Median (IQR)	2.00 (2.00-4.00)	12.50 (4.00-68.50)
Time to first onset in days (grade ≥ 3)		
Mean (SD)	38.79 (67.15)	215.86 (124.08)
Median (IQR)	8.00 (3.00-32.00)	240.00 (102.00-325.00)
Cumulative duration per patient in days (any grade)		
Mean (SD)	102.36 (116.69)	39.51 (82.12)
Median (IQR)	52.00 (13.00-160.00)	7.00 (2.00-33.50)
Cumulative duration per patient in days (grade ≥ 3)		
Mean (SD)	8.22 (12.54)	5.14 (8.30)
Median (IQR)	5.00 (2.00-9.00)	1.00 (1.00-8.00)
Duration per episode in days (any grade)		
Mean (SD)	5.94 (26.29)	6.15 (31.17)
Median (IQR)	2.00 (1.00-3.00)	2.00 (1.00-3.00)
Duration per episode in days (grade ≥ 3)		
Mean (SD)	3.02 (6.53)	4.00 (4.50)
Median (IQR)	2.00 (1.00-3.00)	1.00 (1.00-8.00)

EMA, European Medicines Agency; HR+, hormone receptor–positive; IP, investigational product; IQR, interquartile range; SD, standard deviation.

Notes: Worst grade in the specified time period is presented; 1 month = 30 days.

Source: Puma data on file [47].

ExteNET: effects of diarrhoea on HRQoL

The effects of diarrhoea on HRQoL in the ExteNET trial were evaluated using the Functional Assessment of Cancer Therapy–Breast (FACT-B) scale [28]. The highest mean Physical Well-Being score (24.5) was observed for patients with no or grade 1 diarrhoea, followed by patients with grade 2 diarrhoea (22.9), while patients with grade ≥ 3 diarrhoea had the lowest score (21.8). The difference between patients with grade ≥ 3 diarrhoea and those with no or grade 1 diarrhoea was within the previously reported important difference range (2-3 points). For the remaining scales, any differences by diarrhoea grade were less than the important difference range.

CONTROL: safety results

Although the ExteNET trial reported a significantly reduced likelihood of clinically relevant breast cancer relapse, without any significant risk of long-term toxicity, 40% of patients developed grade 3 diarrhoea in the absence of any prophylaxis [23]. ESMO published guidelines in 2018 for the management of diarrhoea in patients with cancer who often experience diarrhoea [57]. The neratinib SmPC states that patients should be instructed to initiate prophylactic treatment with an antidiarrhoeal medicinal product with the first dose of NERLYNX [16]. The CONTROL trial is an ongoing phase 2, open-label safety and tolerability study, initiated to investigate the effect of antidiarrhoeal strategies (e.g., loperamide prophylaxis with and without budesonide or colestipol) on the incidence and duration of neratinib-associated diarrhoea, when compared with a historical cohort from the safety population of the ExteNET trial (no protocol-mandated loperamide prophylaxis) [26]. Further details of the CONTROL methodology and baseline characteristics are described in Section 4.2.2.

Safety results presented here are from a final analysis for cohorts 1 to 4 and an interim analysis of cohort 5 from CONTROL using a cut-off date of October 2019 when all patients in the first four cohorts and 67% of the dose escalation cohort had completed or prematurely discontinued therapy with neratinib. At the October 2019 data cut-off, the median duration of neratinib treatment in the loperamide, budesonide, colestipol, colestipol PRN, and neratinib dose escalation cohorts was 11.63, 11.96, 11.94, 11.96 and 10.96 months, respectively. The median neratinib treatment duration in ExteNET was 11.6 months (range, 2.48-11.93 months) [22].

CONTROL primary outcome: incidence of grade 3 diarrhoea

Analyses of CONTROL show structured loperamide prophylaxis in the first cycle of neratinib treatment reduced the incidence, severity and duration of neratinib-associated diarrhoea compared with that observed in ExteNET [22].

Incidence of grade ≥ 3 diarrhoea at any time during neratinib treatment was 31% in the loperamide cohort, 28% in the budesonide cohort, 21% in the colestipol cohort, 32% in the colestipol PRN cohort and 15% in the neratinib dose escalation cohort compared with 40% without protocol-mandated loperamide prophylaxis in the ExteNET trial [22].

In the CONTROL trial, there were marked reductions in the median cumulative duration of diarrhoea and the median number of diarrhoea episodes per patient with loperamide prophylaxis compared with the ExteNET trial. With loperamide prophylaxis, the median cumulative duration of any grade of diarrhoea was reduced to 14 days (range, 5-54 days) compared with 59 days (range, 14-164 days) without structured prophylaxis in ExteNET [22]. For each of the study cohorts in CONTROL, diarrhoea was characterised by a lower percentage of high-grade diarrhoea (grades 2 and 3) in month 1 and a much lower incidence in months 2 through 12 than was reported in ExteNET. Neratinib dose holds and dose reductions due to diarrhoea were also less common in CONTROL compared with ExteNET. Diarrhoea-related neratinib discontinuation rates decreased in all cohorts except for colestipol PRN (20% for loperamide, 8% for budesonide, 4% for colestipol, 8% for colestipol PRN and 3% for neratinib dose escalation) and were less frequent with budesonide, colestipol and neratinib dose escalation compared with ExteNET (17%) [22]. Table 21 presents a summary of treatment-emergent diarrhoea characteristics.

Table 21. Characteristics of treatment-emergent diarrhoea in CONTROL compared with ExteNET

	CONTROL					
	Loperamide (cohort 1) (n = 137)	**Budesonide + loperamide (cohort 2) (n = 64)**	**Colestipol + loperamide (cohort 3) (n = 136)**	**Colestipol + loperamide as needed (cohort 4) (n = 104)**	**Neratinib dose escalation (cohort 5) (n = 60)**	**ExteNET neratinib arm (loperamide as needed) (n = 1,408)**
Median cumulative duration of diarrhoea, days						
Any grade	14	28	45	73	43	59
Grade ≥ 2	5	6	4	8	6	10
Grade ≥ 3[a]	3	3	4	2	2	5[a]
Median diarrhoea episodes per patient						
Any grade	3	11	5	18	19	8
Grade ≥ 2	2	3	2	4	3	3
Grade ≥ 3[a]	1	1	1	1	2	2[a]
Action taken, %						
Dose hold	15	19	16	14	12	34
Dose reduction	7	5	7	12	3	26
Discontinuation	20	8	4	8	3	17
Hospitalisation	1	0	0	0	0	1

[a] One grade 4 event in ExteNET.

Source: Barcenas et al. [22].

CONTROL: overall adverse events

Aside from diarrhoea, the overall tolerability profile of neratinib with structured antidiarrhoeal prophylaxis (e.g., loperamide given with or without budesonide or colestipol) was similar to that reported in ExteNET, apart from an increase in grade 1 or 2 constipation. Rates of all-grade constipation were 57% for loperamide, 75% for budesonide, 69% for colestipol, 38% for colestipol PRN and 33% for neratinib dose escalation, respectively. No grade 3 or higher constipation has been observed to date. The observed rates of constipation are likely due to the structured loperamide regimens mandated in CONTROL and are not anticipated in clinical practice because the label directs patients to titrate antidiarrhoeal treatment to one or two stools per day [1].

Table 22 presents the most frequently reported grade 3-4 events. Reported grade 4 events (serious AEs) were sepsis and urinary tract infection (both unrelated events in the same patient); there were no fatal AEs reported [22].

Table 22. CONTROL: most common grade 3 or 4 treatment-emergent adverse events (≥ 1% total incidence) versus neratinib-treated patients in ExteNET

Event	CONTROL					ExteNET neratinib arm (loperamide as needed) (n = 1,408)
	Loperamide (n = 137)	Budesonide + loperamide (n = 64)	Colestipol + loperamide (n = 136)	Colestipol + loperamide as needed (n = 104)	Neratinib dose escalation (n = 60)	
Nausea	1	0	1	3	0	2
Constipation	0	0	0	0	0	0
Fatigue	4	8	1	2	2	2
Abdominal pain	1	2	2	1	0	2
Vomiting	1	3	3	2	2	3
Decreased appetite	0	0	1	0	0	< 1
Headache	0	0	0	0	0	1
Abdominal distension	0	0	0	0	0	< 1
Dizziness	0	0	0	0	0	< 1
Muscle spasms	1	0	0	0	0	< 1
Dyspepsia	0	0	0	0	0	< 1

Source: Barcenas et al. [22].

5.1.2.4 Quality of life

ExteNET: exploratory HRQoL endpoints (intention-to-treat population)

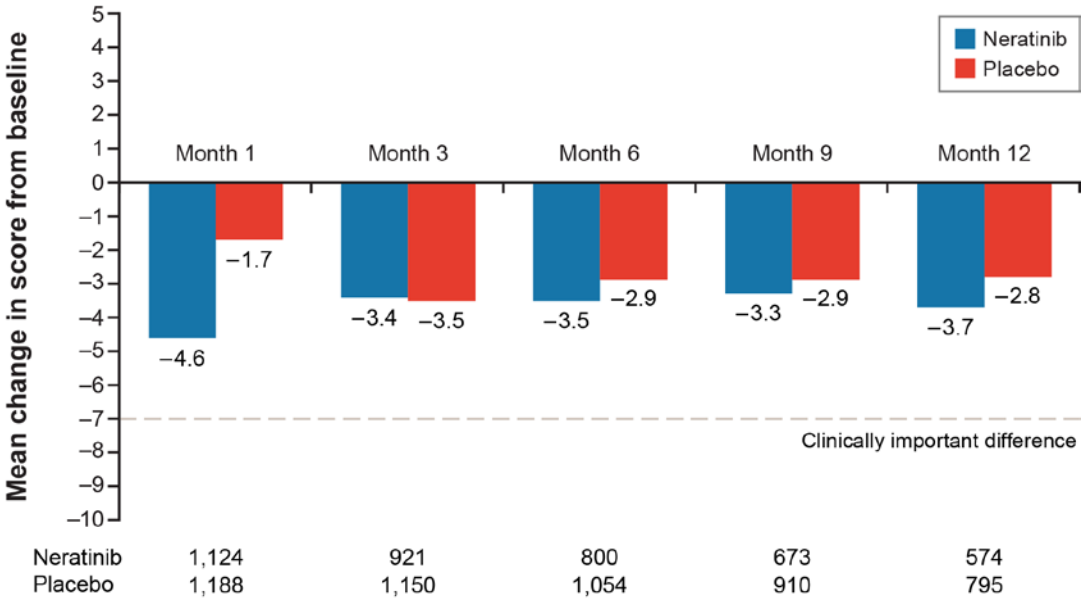
Currently, only the HRQoL data for the ITT population are published; however, unpublished data on the EMA label are also provided for transparency. Patient-reported outcomes were measured as exploratory endpoints in ExteNET using FACT-B, version 4, and EQ-5D-3L at baseline and months 1, 3, 6, 9 and 12 (end of treatment) [20, 27, 28]. In ExteNET, HRQoL data were collected from 2,407 evaluable ITT patients who completed FACT-B questionnaires at baseline and at least one postbaseline visit (neratinib, n = 1,171; placebo, n = 1,236), and from 2,427 evaluable ITT patients who completed EQ-5D-3L questionnaires at baseline and at least one postbaseline visit (neratinib, n = 1,186; placebo, n = 1,241). In ExteNET, questionnaire completion rates were ≥ 85% from baseline to month 6 in both the neratinib and placebo groups; rates at later time points were lower in both groups (range, 69%-79%) because of a protocol amendment (October 2011) that removed the requirement for HRQoL data collection [20].

Health-related QoL differences between neratinib and placebo, as measured by the FACT-B and EQ-5D-3L, were greatest after 1 month of treatment in favour of placebo, but these differences did not cross clinically meaningful thresholds (7-8 points for FACT-B Total score or previously reported important differences for EQ-5D Index [0.09-0.10 units] or EQ-5D-3L health state [7-10 units]) [20]:

- FACT-B Total score: −2.9 points (95% CI, −3.7 to −2.0; *P* < 0.0001)
- EQ-5D-3L Index: −0.02 units (95% CI, −0.03 to −0.01; *P* = 0.004)
- EQ-5D-3L health state: −2.7 units (95% CI, −3.7 to −2.0; *P* < 0.0001)

The decreases in HRQoL observed in the neratinib treatment group after the first month were followed by steady recovery towards baseline over the 12-month study period. Figure 12 and Figure 13 present mean changes from baseline in FACT-B Total scores and EQ-5D-3L health-state summary score in ExteNET. The patterns of changes for the EQ-5D-3L Index and health-state scores were similar to those observed with FACT-B (Figure 14, Figure 15, Figure 16). The decrease in the FACT-B and EQ-5D-3L scores in the neratinib group after month 1 may be attributable to the occurrence of treatment-emergent diarrhoea during month 1. After month 1, the differences between groups in FACT-B scores were minimal (*P* > 0.05). With the exception of the FACT-B Physical Well-Being subscale score at month 1 (mean difference between groups, −2.4 points), which was of borderline clinical significance, all other between-group differences were less than the previously reported important difference (i.e., less than the lowest estimate for an important difference reported in the literature) [20].

Figure 12. ExteNET: mean changes from baseline in FACT-B Total scores by visit, ITT population

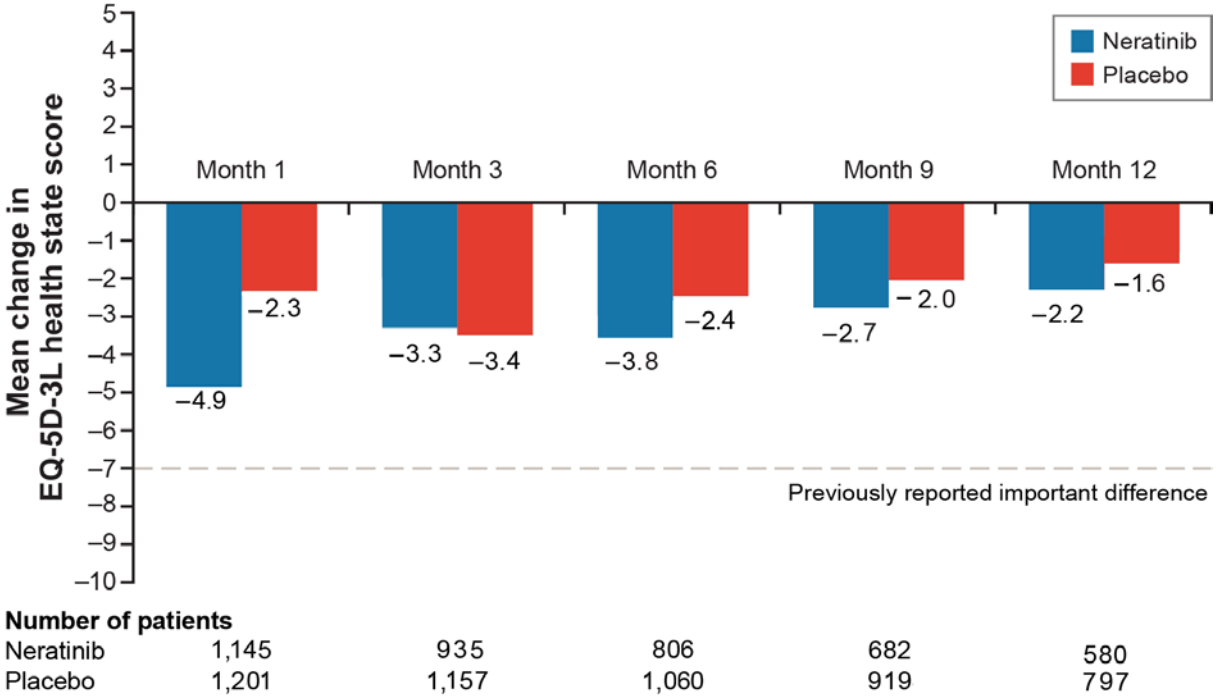


FACT-B, Functional Assessment of Cancer Therapy–Breast; ITT, intention to treat.

Note: A negative change indicates decreased health-related quality of life. The baseline FACT-B score for both neratinib and placebo was 114.4.

Sources: Delaloge et al. [27]; Puma data on file [58].

Figure 13. ExteNET: mean changes from baseline in EQ-5D-3L health-state summary scores by visit, ITT population



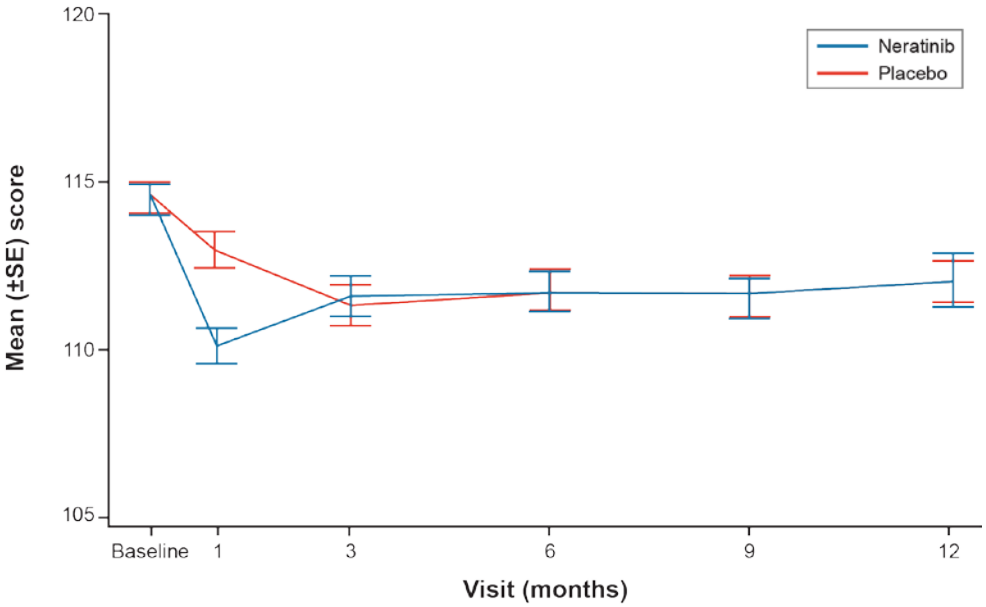
Number of patients					
Neratinib	1,145	935	806	682	580
Placebo	1,201	1,157	1,060	919	797

ITT, intention to treat.

Note: A negative change indicates decreased health-related quality of life. Baseline EQ-5D-3L health-state scores were 81.5 for neratinib and 81.6 for placebo.

Source: Puma data on file [59].

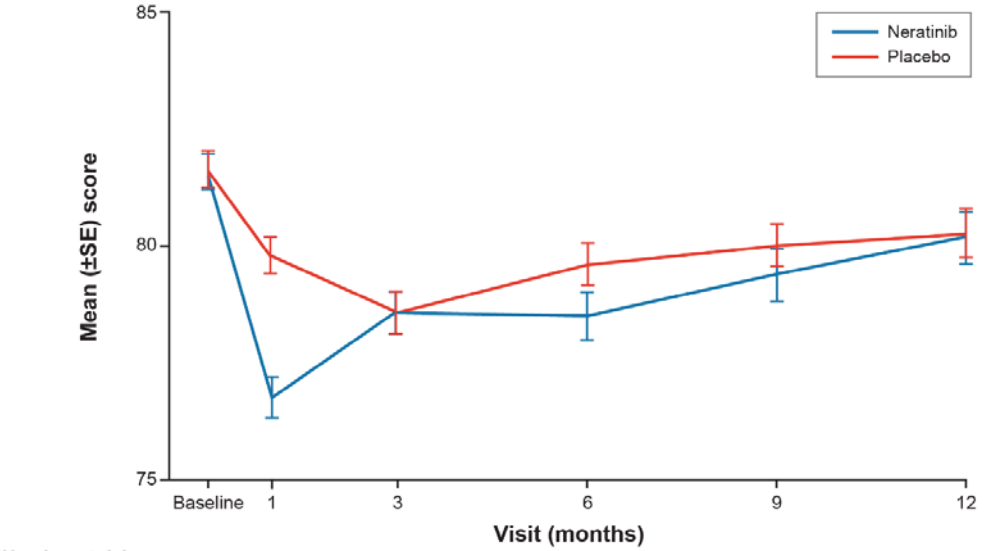
Figure 14. ExteNET: mean FACT-B Total scores from baseline to 12 months by treatment group, ITT population



Neratinib	1,264	1,201	987	853	716	611
Placebo	1,273	1,274	1,236	1,135	978	853

FACT-B, Functional Assessment of Cancer Therapy–Breast; ITT, intention to treat; SE, standard error.
Source: Delaloge et al. [28].

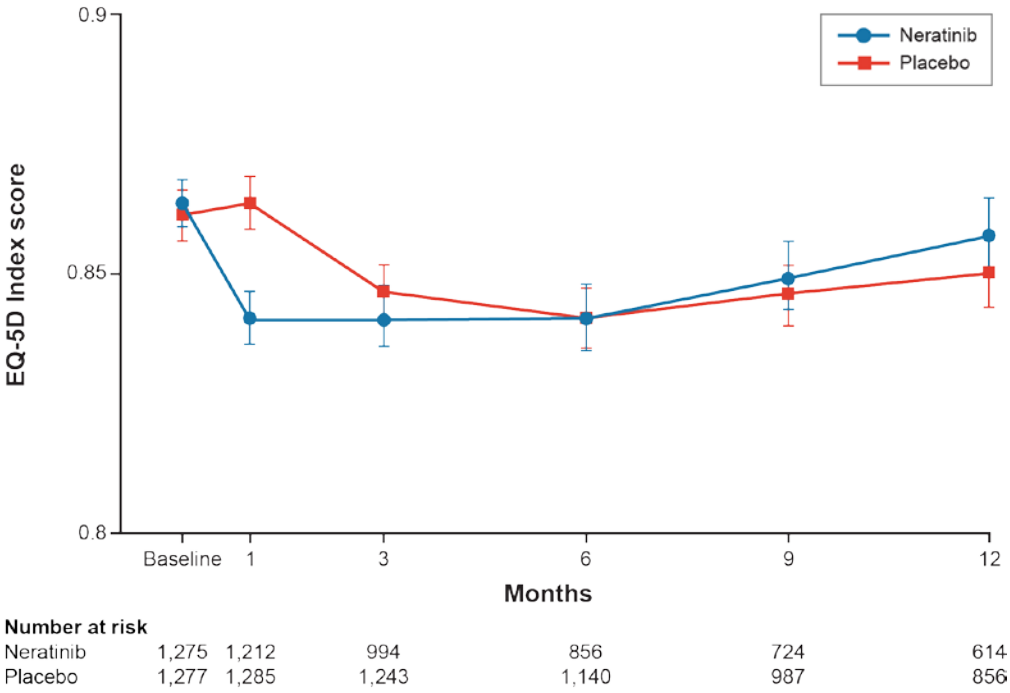
Figure 15. ExteNET: mean EQ-5D-3L health-state scores from baseline to 12 months by treatment group, ITT population



Number at risk						
Neratinib	1,275	1,212	994	856	724	614
Placebo	1,277	1,285	1,243	1,140	987	856

ITT, intention to treat; SE, standard error.
Source: Delaloge et al. [28].

Figure 16. ExteNET: mean EQ-5D-3L Index from baseline to 12 months by treatment group, ITT population



ITT, intention to treat.

Source: Delaloge et al. [28].

ExteNET: exploratory HRQoL endpoints (EMA label population)

HRQoL data for the EU label population were collected from 1,111 evaluable participants who completed FACT-B questionnaires at baseline and at least one postbaseline visit (neratinib, n = 541; placebo, n = 570) and from 1,121 evaluable patients who completed EQ-5D-3L questionnaires at baseline and at least one postbaseline visit (neratinib, n = 549; placebo, n = 572) [21].

HRQoL differences between neratinib and placebo, as measured by the FACT-B and EQ-5D-3L, were greatest after 1 month of treatment in favour of placebo (except for the EQ-5D Index, for which the biggest difference was achieved after 12 months in favour of neratinib). However, the differences observed at month 1 did not cross clinically meaningful thresholds (7-8 points for FACT-B Total score or previously reported important differences for EQ-5D Index [0.09-0.10 units] or EQ-5D-3L health state [7-10 units]) [27, 28]:

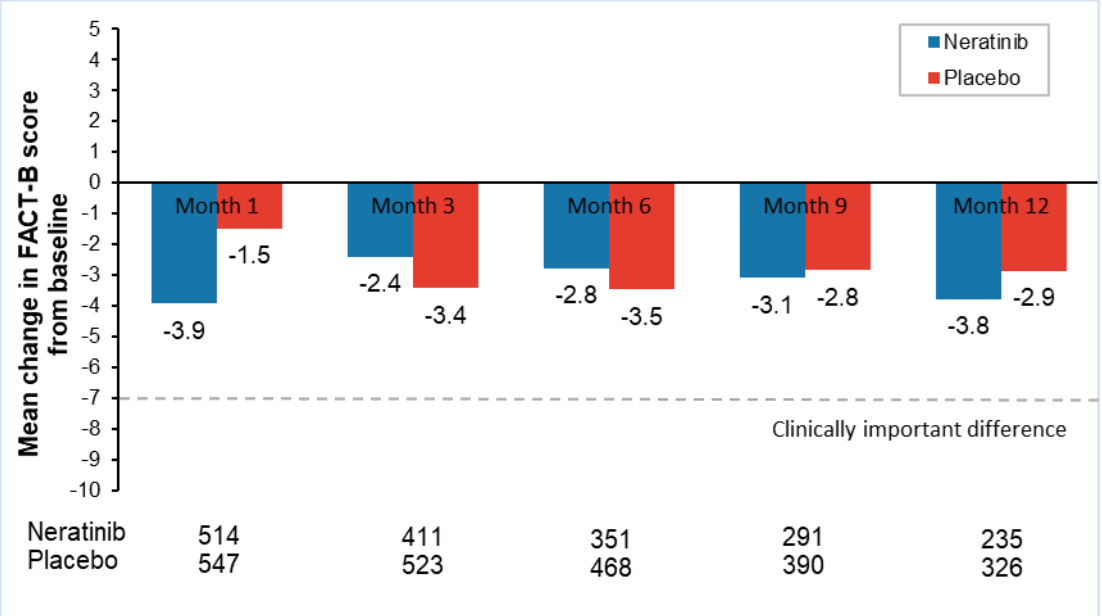
- FACT-B Total score: −2.47 units (95% CI, −3.7 to −1.24*; P* < 0.0001)
- EQ-5D-3L Index: −0.01 units (95% CI, −0.02 to 0.01 ; *P* = 0.4919)
- EQ-5D-3L health state: −1.42 units (95% CI, −2.72 to −0.11; *P* = 0.0340)

The difference in EQ-5D Index after 12 months of treatment also did not cross a clinically meaningful threshold (0.02 units; 95% CI, −0.01 to 0.04; *P* = 0.1401) [21].

The decreases in HRQoL observed in the neratinib treatment group after the first month were followed by steady recovery towards baseline over the 12-month study period. Figure 17 and Figure 18 present mean

changes from baseline in FACT-B Total scores and EQ-5D-3L visual analogue scale (VAS) summary score in ExteNET. The patterns of changes for the EQ-5D-3L Index and VAS scores during the treatment period were similar to those observed with FACT-B (Figure 19, Figure 20, and Figure 21). The decrease in the FACT-B and EQ-5D-3L scores in the neratinib group after month 1 may be attributable to the occurrence of treatment-emergent diarrhoea during month 1. After month 1, the differences between groups in FACT-B scores were minimal ($P > 0.05$). With the exception of the FACT-B Physical Well-Being subscale score at month 1 (mean difference between groups, −2.2 points), which was of borderline clinical significance, all other between-group differences were less than the previously reported important difference (i.e., less than the lowest estimate for an important difference reported in the literature) [21].

Figure 17. ExteNET EU Label population: mean changes from baseline in FACT-B Total scores by visit

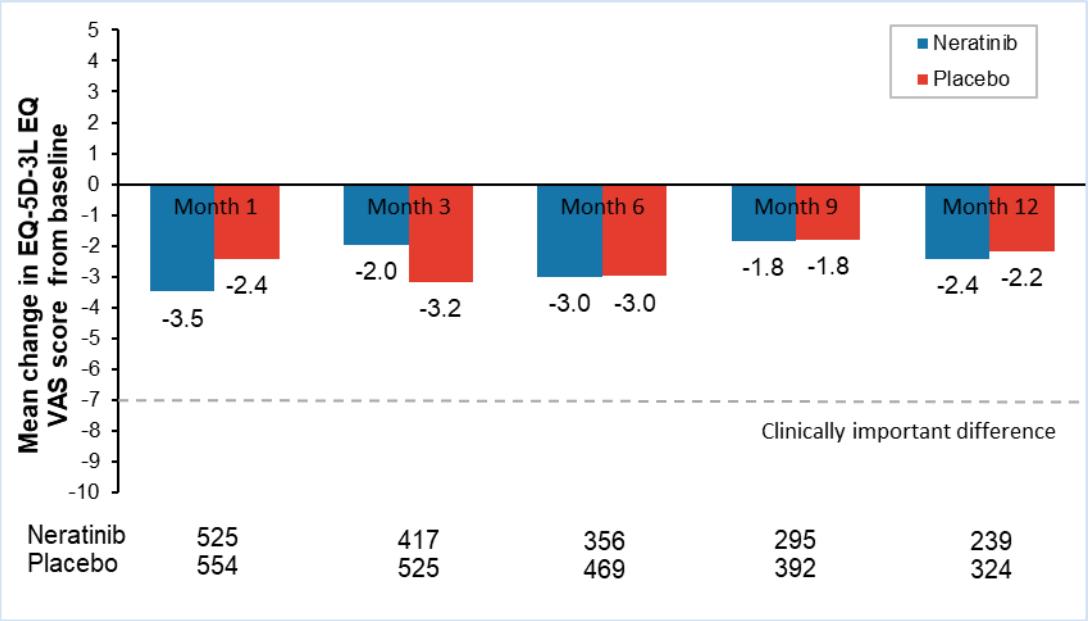


EU, European Union; FACT-B, Functional Assessment of Cancer Therapy–Breast.

Note: A negative change indicates decreased health-related quality of life. Baseline FACT-B scores were 113.0 for neratinib and 112.9 for placebo.

Source: Pierre Fabre data on file [21].

Figure 18. ExteNET EU label population: mean changes from baseline in EQ-5D-3L VAS score summary scores by visit

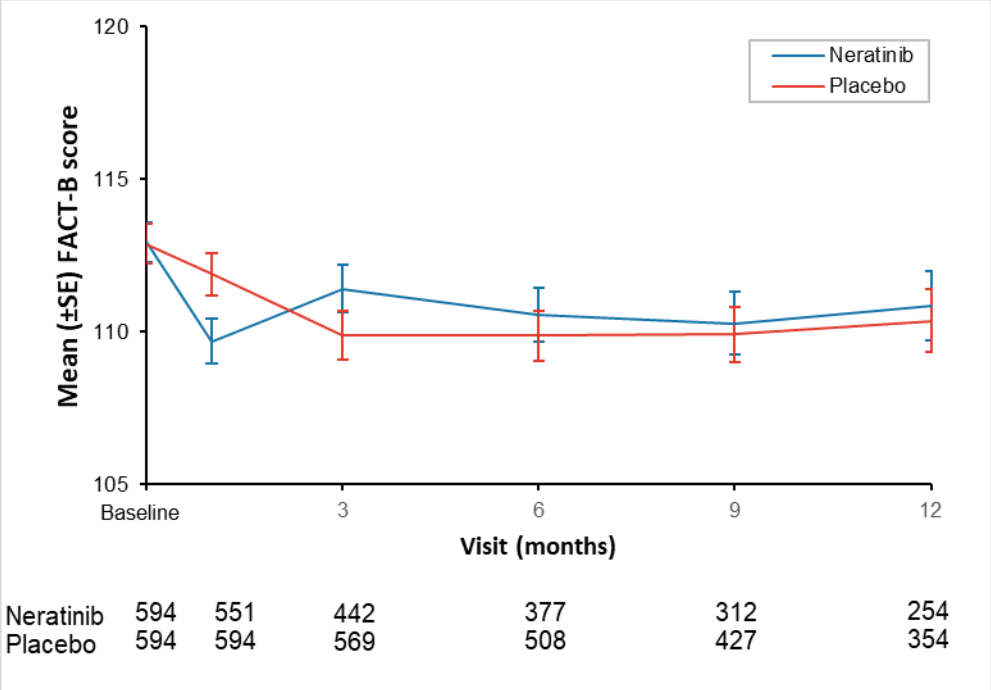


EU, European Union; VAS, visual analogue scale.

Note: A negative change indicates decreased health-related quality of life. Baseline EQ-5D-3L health-state scores were 80.3 for neratinib and 81.1 for placebo.

Source: Pierre Fabre data on file [21].

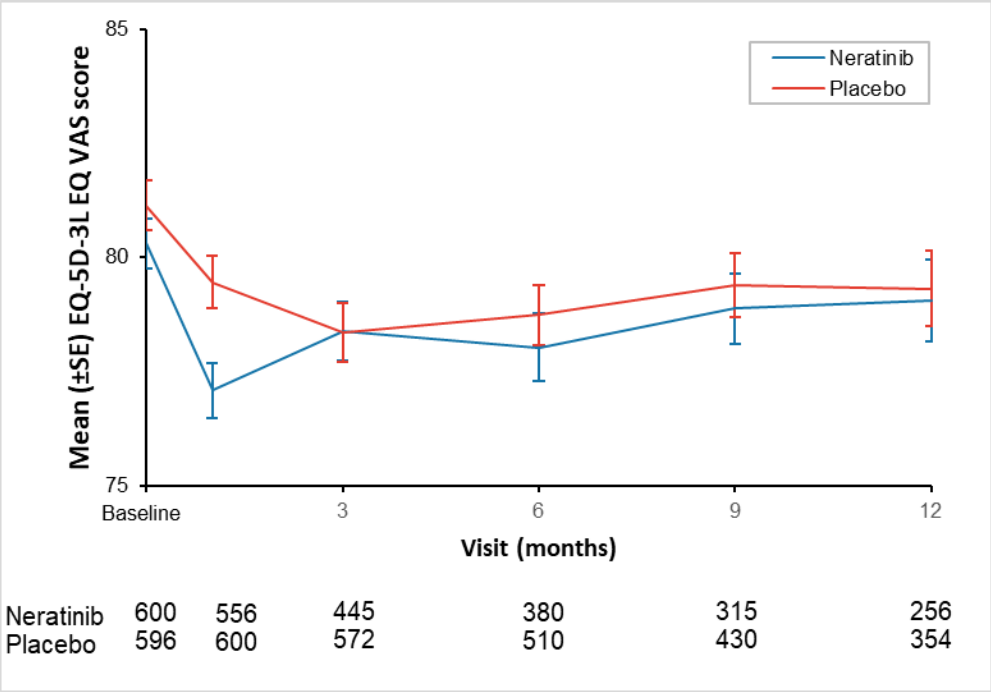
Figure 19. ExteNET EU label population: mean FACT-B Total scores from baseline to 12 months by treatment group



EU, European Union; FACT-B, Functional Assessment of Cancer Therapy–Breast; SE, standard error.

Source: Pierre Fabre data on file [21].

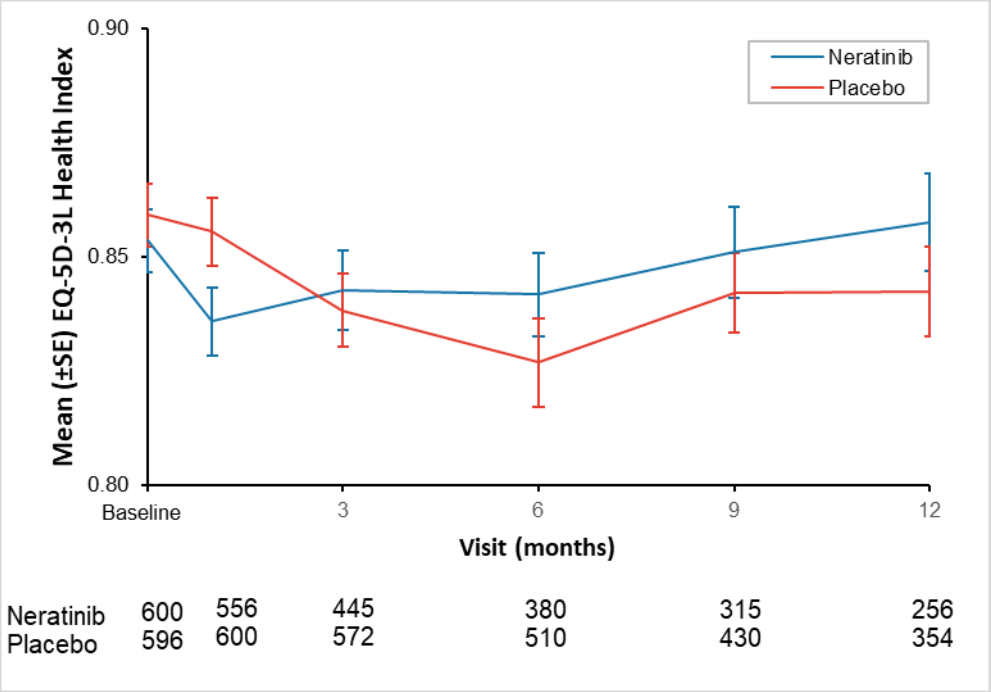
Figure 20. ExteNET EU label population: mean EQ-5D-3L VAS scores from baseline to 12 months by treatment group



EU, European Union; SE, standard error; VAS, visual analogue scale.

Source: Pierre Fabre data on file [21].

Figure 21. ExteNET EU label population: mean EQ-5D-3L Index from baseline to 12 months by treatment group



EU, European Union; SE, standard error.

Source: Pierre Fabre data on file [21].

CONTROL: exploratory health-related quality of life endpoints (intention-to-treat population only)

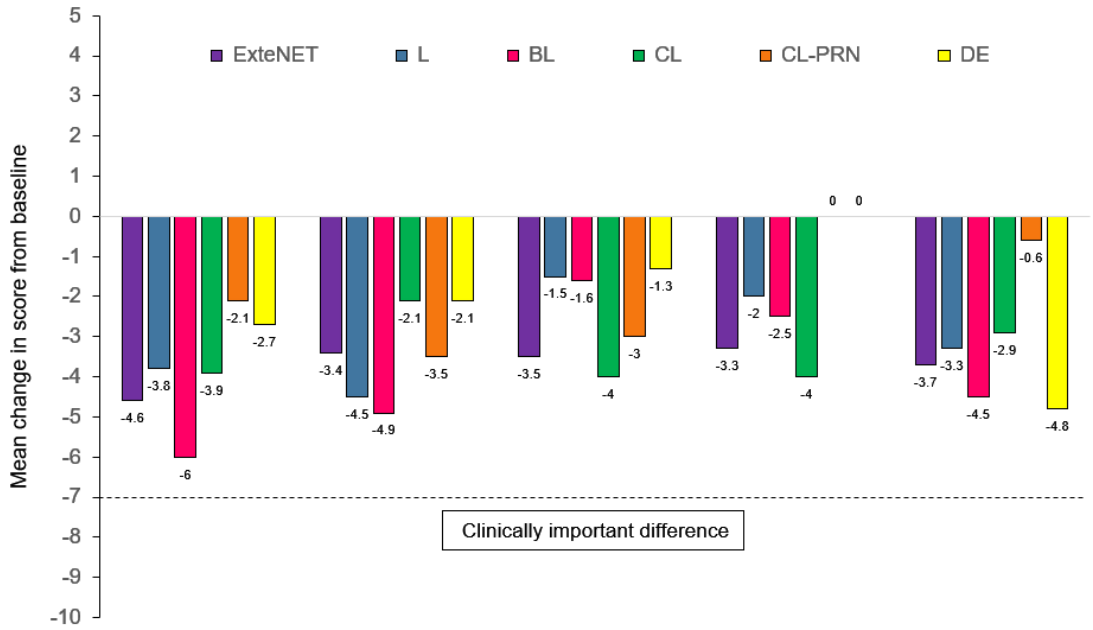
The primary outcome of the CONTROL safety trial was incidence of grade 3 diarrhoea at any time during the study. As CONTROL did not include efficacy assessments and instead focused on safety outcomes, the primary results of the CONTROL trial are presented in Section 5.1.2.3, and only exploratory HRQoL outcomes are presented here [27, 60, 61].

Exploratory HRQoL results presented here are from an interim HRQoL analysis of CONTROL using a cut-off date of October 2018 when all patients in the loperamide and budesonide cohorts had completed therapy with neratinib. Results are for the entire HRQoL population of CONTROL (defined as patients who had received ≥ 1 dose of study treatment, had a baseline HRQoL assessment and ≥ 1 postbaseline HRQoL assessment), regardless of HR status or time to trastuzumab therapy. In CONTROL, 228 patients were included in the HRQoL population (loperamide, n = 40; budesonide + loperamide, n = 62; colestipol + loperamide, n = 126) [27].

FACT-B

Patients in all CONTROL cohorts experienced an early transient decrease from baseline in FACT-B Total scores (Figure 22). Scores subsequently returned towards baseline over the remainder of the 12-month study, as observed in patients treated with neratinib in ExteNET (Figure 23) [27]. The CONTROL study reported mean changes in FACT-B total scores ranged from −6.0 to −1.5 points over the course of study treatment. In the cohorts that had completed follow-up (neratinib + loperamide and budesonide + loperamide), the largest decreases in FACT-B total scores occurred during months 1 and 3, followed by lower decreases. None of these changes reached the clinically meaningful threshold of 7 to 8 points [22].

Figure 22. CONTROL: mean changes from baseline in FACT-B total scores by visit



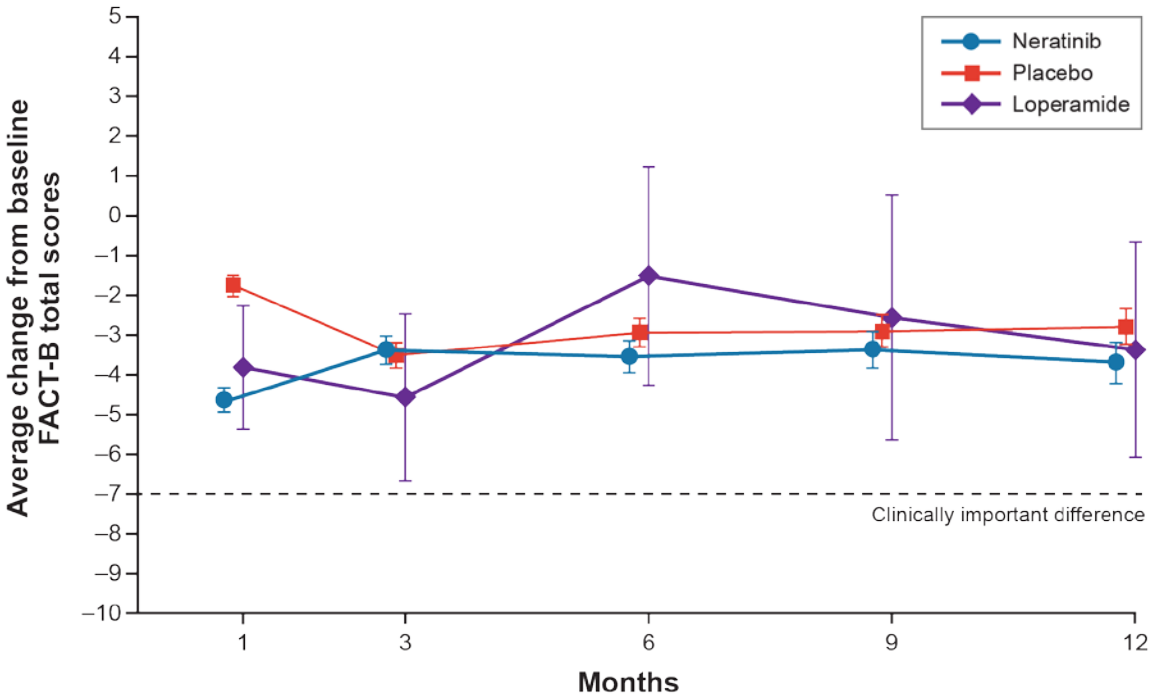
	Month 1	Month 3	Month 6	Month 9	Month 12
No. of patients					
ExteNET	1124	921	800	673	574
L	37	27	22	20	22
BL	59	56	51	50	49
CL	122	109	102	99	98
CL-PRN	93	82	76	72	72
DE	53	48	44	44	22

BL, budesonide + loperamide; CL, colestipol + loperamide; CL-PRN, colestipol + as-needed loperamide; DE, neratinib dose escalation; FACT-B, Functional Assessment of Cancer Therapy–Breast; L, loperamide.

Note: A negative change indicates decreased health-related quality of life.

Source: Barcenas et al. [22].

Figure 23. CONTROL: mean change from baseline in FACT-B total scores in ExteNET and CONTROL loperamide cohort



Number at risk					
Neratinib	1,124	921	800	673	574
Placebo	1,188	1,150	1,054	910	795
Loperamide	37	27	22	20	22

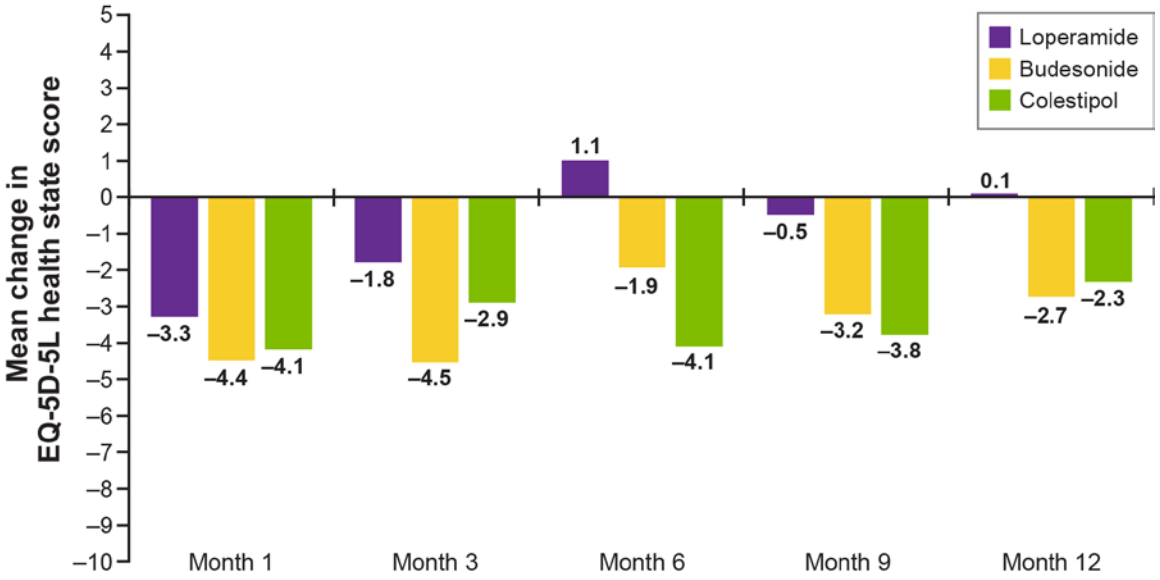
FACT-B, Functional Assessment of Cancer Therapy–Breast.

Source: Hurvitz et al. [26].

EQ-5D

Barcenas et al. [22] did not report on the EQ-5D; therefore, the results reported here are from the earlier cut-off point of November 2017. In CONTROL, the patterns of changes for the EQ-5D-5L health-state scores (Figure 24) and EQ-5D-5L index (Figure 25) were similar to those observed with FACT-B. Between-group differences were less than the previously reported important difference (i.e., less than the lowest estimate for an important difference reported in the literature) [60, 61].

Figure 24. CONTROL: mean changes from baseline in EQ-5D-5L health-state scores by visit

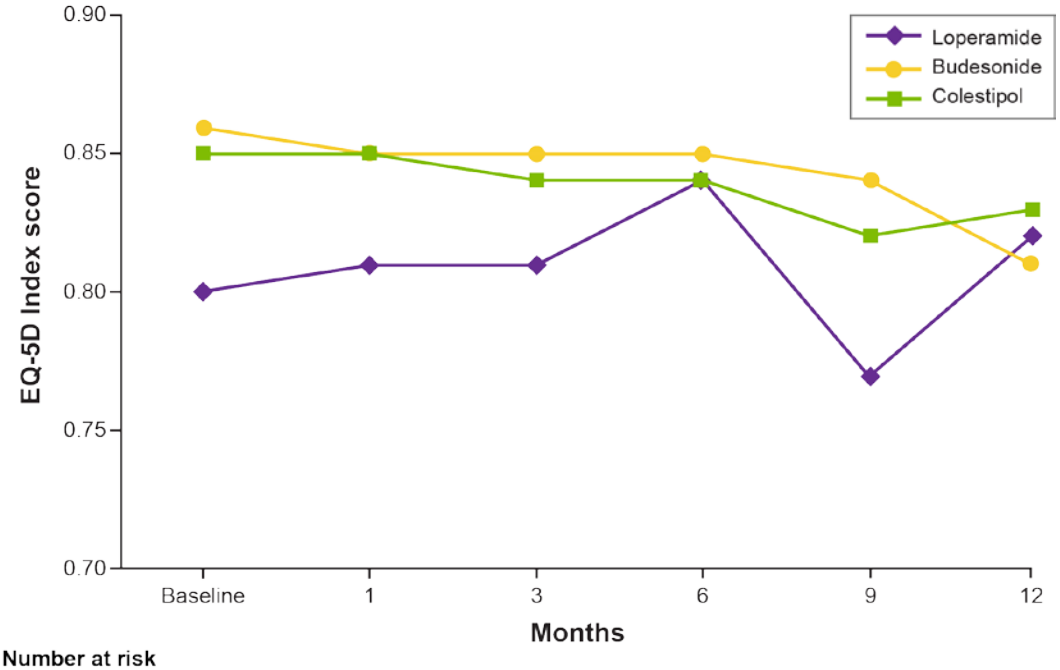


Number of patients					
Loperamide	36	25	20	19	22
Budesonide	59	56	51	50	49
Colestipol	122	108	102	99	90

Note: A negative change indicates decreased health-related quality of life.

Source: Puma data on file [60].

Figure 25. CONTROL: mean EQ-5D-5L Index from baseline to month 12 by treatment group



Number at risk						
Loperamide	40	38	27	22	21	22
Budesonide	62	59	56	51	49	49
Colestipol	124	120	103	100	98	90

Source: Puma data on file [61].

5.1.3 Comparative analyses

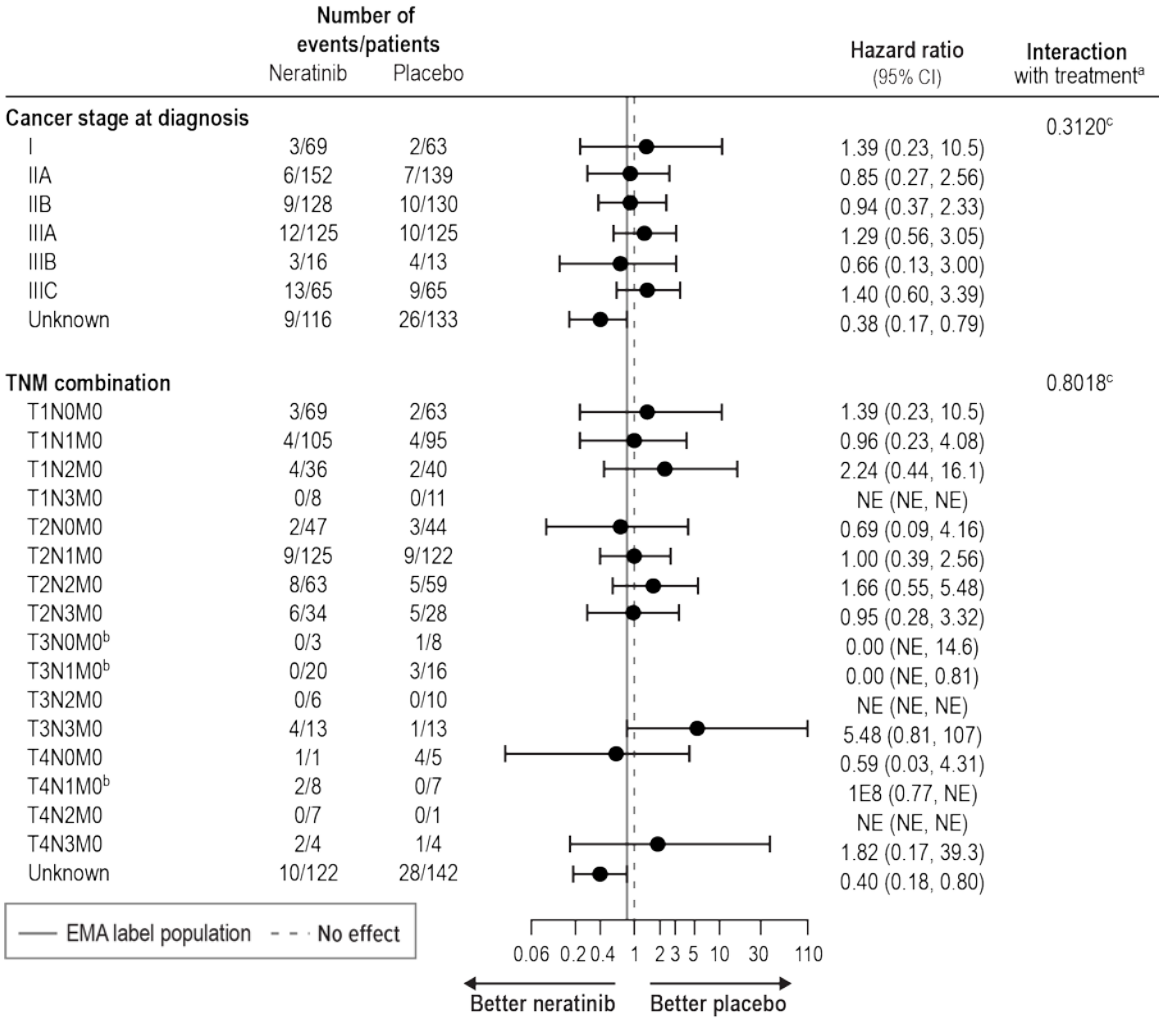
As described in Section 4 and Appendix B, the clinical SLR identified only one head-to-head study of neratinib that was relevant to the scope of this submission: the ExteNET trial [23, 24]. As the only comparator is standard treatment (wait and see approach, equivalent to placebo in the trial), no other relevant head-to-head studies were identified or included in this dossier.

A meta-analysis requires two or more studies that contain the intervention of interest. Therefore, a meta-analysis for the primary efficacy outcome of iDFS was not possible because only one randomised study (ExteNET) has reported iDFS for neratinib.

5.1.4 Other considerations

The protocol requested analysis on OS and iDFS data for each combination of TNM stages. To enable the selection committee to consider whether the effect appears to vary between the combinations of TNM stages included in the clinical study. Figure 26 presents OS by cancer stage and TNM combination for the EMA label population. Figure 27 and Figure 28 present the 2- and 5-year iDFS data by TNM combinations for the EMA label. All of these analyses should be interpreted carefully because the study was not designed to investigate the treatment effect in these subpopulations further due to the number of TNM combinations and the low number of patients in each group. Moreover, the OS data for the EMA label population are immature; therefore, a subgroup analysis on this population cannot be properly interpreted.

Figure 26. Forest plot of overall survival by cancer stage and TNM (EMA label population)



CI, confidence interval; eCRF, electronic case report form; EMA, European Medicines Agency; ER, oestrogen receptor; PR, progesterone receptor; NE, not evaluable; TNM, tumour, node, metastasis.

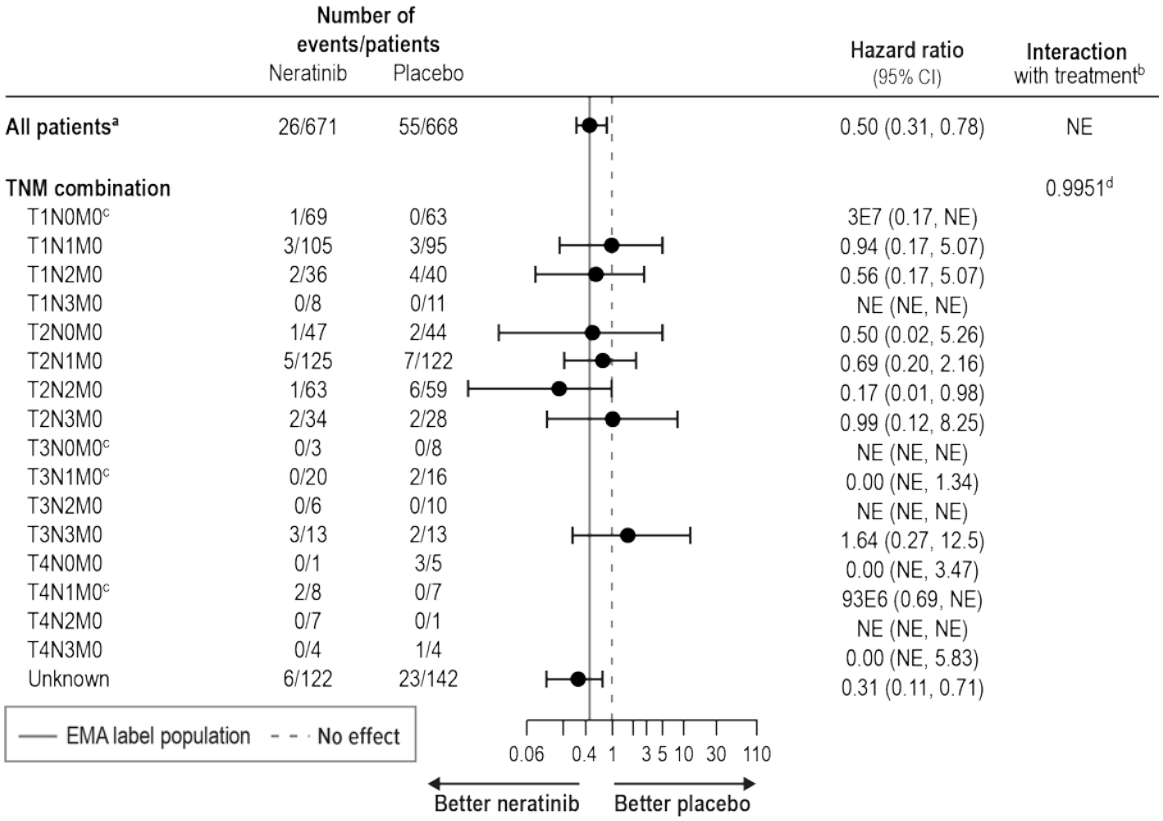
[a] *P* value is from type-3 test result based on Wald test and computed with a Cox model stratified by stratification factors based on eCRF variables: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4) and ER/PR status (positive or negative).

[b] Hazard ratio and 95% CI are extreme values and cannot be displayed.

[c] Stratified by stratification factors based on eCRF variables: prior trastuzumab (concurrent or sequential) and ER/PR status (positive or negative).

Source: Puma data on file [62].

Figure 27. Forest plot of 2-year iDFS by TNM



CI, confidence interval; eCRF, electronic case report form; EMA, European Medicines Agency; ER, oestrogen receptor; iDFS, invasive disease-free survival; NE, not estimable; PR, progesterone receptor; TNM, tumour, node, metastasis.

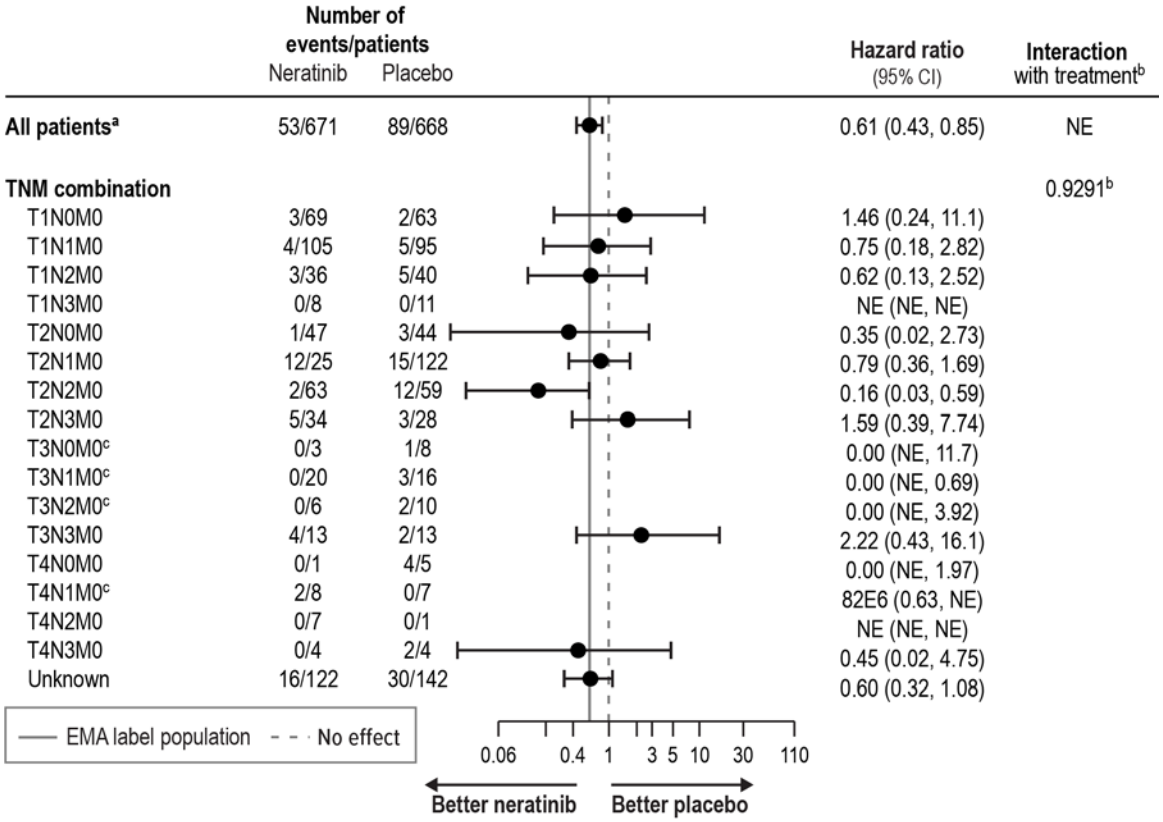
[a] All treatment: Model is stratified by stratification factors based on eCRF variables: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4) and ER/PR status (positive or negative).

[b] *P* value is from type-3 test results based on Wald test and computed with a Cox model stratified by stratification factors based on eCRF variables: prior trastuzumab (concurrent or sequential) and ER/PR status (positive or negative).

[c] Hazard ratio and 95% CI are extreme values and cannot be displayed.

Source: Puma data on file [62].

Figure 28. Forest plot of 5-year iDFS by TNM



CI, confidence interval; eCRF, electronic case report form; EMA, European Medicines Agency; ER, oestrogen receptor; iDFS, invasive disease-free survival; NE, not estimable; PR, progesterone receptor; TNM, tumour, node, metastasis.

[a] All treatment: Model is stratified by stratification factors based on eCRF variables: prior trastuzumab (concurrent or sequential), nodal status (≤ 3 or ≥ 4) and ER/PR status (positive or negative).

[b] *P* value is from type-3 test results based on Wald test and computed with a Cox model stratified by stratification factors based on eCRF variables: prior trastuzumab (concurrent or sequential) and ER/PR status (positive or negative).

[c] Hazard ratio and 95% CI are extreme values and cannot be displayed.

Source: Puma data on file [62].

6 References

[1] NERLYNX® SmPC. NERLYNX® (neratinib) summary of product characteristics. European Medicines Agency; 22 October 2019. Available at: https://www.ema.europa.eu/documents/product-information/nerlynx-epar-product-information_en.pdf. Accessed 28 November 2019.

[2] GLOBOCAN. Estimated number of new cases in 2018, Denmark, females. International Agency for Research on Cancer; 2019. Available at: https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=continents&population=900&populations=208&key=asr&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1. Accessed 9 August 2019.

[3] Danish Medicine Council. Medicinrådets protokol for vurdering af trastuzumab emtansin til behandling af HER2+ brystkræft. 2020. Available at: https://medicinraadet.dk/media/d4gprdqm/medicinr%C3%A5dets-protokol-for-vurdering-af-trastuzumab-emtansin-til-behandling-af-her2-brystkr%C3%A6ft-vers-1-1_adlegacy.pdf. Accessed 22 June 2020.

[4] NKBC. Annual report 2018, population by biological subtype. Swedish National Quality Register for Breast Cancer; 2018. Available at: https://statistik.incanet.se/brostcancer/. Accessed 14 July 2019.

[5] Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014 Apr 28;106(5).

[6] RADS. Treatment instructions including drug recommendation for anti-HER2 treatment of breast cancer. 2 February 2016. Available at: https://rads.dk/media/2120/beh-rek-anti-her-2-feb-2016.pdf. Accessed 9 December 2019.

[7] The Danish Breast Cancer Cooperative Group. 7: Neoadjuvant chemotherapy in breast cancer MHP down-sizing and down-staging. 4 October 2016. Available at: http://dbcg.dk/PDF%20Filer/Kap7_Neoadj_KT_ved_brystkraeft_mhp_down-sizing_og_down-staging_04.10.2016.pdf. Accessed 18 November 2019.

[8] The Danish Breast Cancer Cooperative Group. 6: Medical treatment. 21 February 2019. Available at: http://dbcg.dk/PDF%20Filer/Kap_6_Medicinsk_behandling-21.02.2019.pdf. Accessed 18 November 2019.

[9] Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the Herceptin Adjuvant (HERA) trial. Lancet. 2017 Mar 25;389(10075):1195-205.

[10] Zhao B, Zhao H, Zhao J. Impact of hormone receptor status on the efficacy of HER2-targeted treatment. Endocr Relat Cancer. 2018 Jun;25(6):687-97.

[11] Rampaul RS, Pinder SE, Nicholson RI, Gullick WJ, Robertson JF, Ellis IO. Clinical value of epidermal growth factor receptor expression in primary breast cancer. Adv Anat Pathol. 2005 Sep;12(5):271-3.

[12] Zaczek A, Brandt B, Bielawski KP. The diverse signaling network of EGFR, HER2, HER3 and HER4 tyrosine kinase receptors and the consequences for therapeutic approaches. Histol Histopathol. 2005 Jul;20(3):1005-15.

[13] Berns K, Horlings HM, Hennessy BT, Madiredjo M, Hijmans EM, Beelen K, et al. A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer. Cancer Cell. 2007 Oct;12(4):395-402.

[14] Danish Medicine Council. Medicinrådets anbefaling vedrørende trastuzumab emtansin til behandling af tidlig HER2+ brystkræft. 2020. Available at: https://medicinraadet.dk/media/vyjlbrls/medicinr%C3%A5dets-anbefaling-af-trastuzumab-emtansin-til-tidlig-her2-brystkr%C3%A6ft-vers-1-0_adlegacy.pdf. Accessed 26 June 2020.

[15] Danish Medicine Council. Baggrund for Medicinrådets anbefaling af trastuzumab emtansin til behandling af tidlig HER2+ brystkræft. 2020. Available at: https://medicinraadet.dk/media/rfjkycug/baggrund-for-medicinr%C3%A5dets-anbefaling-af-trastuzumab-emtansin-til-tidlig-her2-brystkr%C3%A6ft-vers-1-0-med-bilag_adlegacy.pdf Accessed 26 June 2020.

[16] NERLYNX® SmPC. Neratinib (NERLYNX) Summary of product characteristics. European Medicines Agency; 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/nerlynx-epar-product-information_en.pdf. Accessed 25 February 2020.

[17] Paplomata E, Nahta R, O'Regan RM. Systemic therapy for early-stage HER2-positive breast cancers: time for a less-is-more approach? Cancer. 2015 Feb 15;121(4):517-26.

[18] Chan A, Moy B, Mansi J, Ejlertsen B, Holmes FA, Chia S, et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. Clin Breast Cancer. 2020 Oct 6.

[19] Gnant M, Martin M, Holmes F-A, Jackisch C, Chia SK, Iwata H, et al. Efficacy of neratinib in hormone receptor-positive patients who initiated treatment within 1 year of completing trastuzumab-based adjuvant therapy in HER2+ early-stage breast cancer: subgroup analyses from the phase III ExteNET trial. Presented at the San Antonio Breast Cancer Symposium; 4-8 December 2018. San Antonio, TX, USA.

[20] 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 Apr 1;30(4):567-74.

[21] Pierre Fabre data on file. ExteNET: FACT-B and EQ-5D-3L data. 2020.

[22] Barcenas CH, Hurvitz SA, Di Palma JA, Bose R, Chien AJ, Iannotti N, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: diarrheal toxicity in the CONTROL trial. Ann Oncol. 2020 May 25.

[23] 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 Dec;18(12):1688-700.

[24] 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 Mar;17(3):367-77.

[25] Ibrahim E, Tripathy D, Wilkinson M, Hurvitz S, Iannotti N, Kellum A. Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients with HER2+ early stage breast cancer: the CONTROL trial. Presented at the 110th Annual Congress of the American Association for Cancer Research; 1-5 April 2017. Washington, DC, USA.

[26] Hurvitz S, Chan A, Iannotti N, Ibrahim E, Chinen J, Chan N, et al. Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients with HER2+ early-stage breast: the CONTROL trial. Presented at the 40th Annual CTRC-AACR San Antonio Breast Cancer Symposium; 5-9 December 2017. San Antonio, TX, USA.

[27] Delaloge S, Hurvitz S, Chan N, Bose R, Jankowirz RC, Thirlwell M. The impact of neratinib with or without anti-diarrheal prophylaxis on health-related quality of life in HER2+ early stage breast cancer: analyses from the ExteNET and CONTROl trials [poster]. Presented at the 41st San Antonio Breast Cancer Symposium; 4-8 December 2018. San Antonio, TX, USA.

[28] Delaloge S, Ye Y, Cella D, Buyse M, Chan A, Barrios CH. Effects of neratinib on health-related quality of life (HRQoL) in early-stage HER2+ breast cancer: longitudinal analyses from the phase III ExteNET trial. Presented at the Annual Meeting of the European Society for Medical Oncology; 8-12 September 2017. Madrid, Spain.

[29] Puma data on file. Neratinib ExteNET protocol (3144A2-3004-WW): 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. 20 April 2014.

[30] Puma data on file. Clinical study report: 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. 3144A2-3004-WW. 20 April 2016.

[31] EMA CHMP. NERLYNX assessment report. European Medicines Agency, Committee for Medicinal Products for Human Use; 13 July 2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/nerlynx-epar-public-assessment-report_en.pdf. Accessed 11 September 2019.

[32] Perez E, Suman V, Davidson N, et al. Results of chemotherapy alone, with sequential or concurrent addition of 52 weeks of trastuzumab in the NCCTG N9831 HER2-positive adjuvant breast cancer trial. Presented at the 32nd Annual CTRC-AACR San Antonio Breast Cancer Symposium; 9-13 December 2009. San Antonio, TX, USA.

[33] Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct 6;365(14):1273-83.

[34] Park JW, Liu MC, Yee D, Yau C, van 't Veer LJ, Symmans WF, et al. Adaptive randomization of neratinib in early breast cancer. N Engl J Med. 2016 Jul 07;375(1):11-22.

[35] FDA. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. US Food and Drug Administration; December 2018. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf. Accessed 18 November 2015.

[36] Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. J Clin Oncol. 2007 May 20;25(15):2127-32.

[37] Puma data on file. ExteNET: Table 14.6.2.3.0. Summary of concomitant endocrine therapy HR+ <1yr. 2019.

[38] Puma data on file. ExteNET: Table 14.6.2.3. Summary of concomitant endocrine therapy, ITT population. 2015.

[39] Puma data on file. ExteNET: patients with pCR. 2019.

[40] ClinicalTrials.gov. A study looking the incidence and severity of diarrhea in patients with early-stage HER2+ breast cancer treated with neratinib and loperamide. 20 December 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT02400476. Accessed 16 January 2019.

[41] Barcenas C, Ibrahim E, Wilkinson M, Hurvitz S, Iannotti N, Kellum A. Incidence and severity of diarrhea with neratinib plus intensive loperamide prophylaxis in patients with early-stage breast cancer: interim analysis from the multicenter, open-label, phase II CONTROL trial. Presented at the 39th Annual CTRC-AACR San Antonio Breast Cancer Symposium; 6-10 December 2016. San Antonio, TX, USA.

[42] Barcenas C. Effect of prophylaxis or neratinib dose escalation on neratinib- associated diarrhea and tolerability in patients with HER2-positive early-stage breast cancer: phase II CONTROL trial [poster P548]. Presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; 31 May to 4 June 2019. Chicago, IL, USA.

[43] Chan A, Hurvitz S, Marx G, Ruiz-Borrego M, Hunt D, McCulloch L, et al. Effect of prophylaxis or neratinib dose escalation on neratinib- associated diarrhea and tolerability in patients with HER2-positive early-stage breast cancer: phase II CONTROL trial. Presented at the San Antonio Breast Cancer Symposium (SABCS); 10-14 December 2019. San Antonio, TX, USA.

[44] Puma data on file. Clinical protocol: an open label study to characterize the incidence and severity of diarrhea in patients with early stage HER2+ breast cancer treated with neratinib and intensive loperamide prophylaxis. Study protocol number PUMA-NER-6201. Amendment 4. 19 August 2016.

[45] Puma data on file. ExteNET: Table 14.2.9.18.2 2-year iDFS events by site, HR+ < 1 yr. 2018.

[46] Puma data on file. ExteNET: Table 14.2.9.18.1. 5-year iDFS events by site, HR+ < 1 yr. 2018.

[47] Puma data on file. ExteNET: Table 14.3.1.1.23. Subgroup analysis of overall summary of treatment-emergent adverse events, HR+< 1year. 2018.

[48] Pierre Fabre data on file. Overall survival analysis with updated EMA stratification. 2020.

[49] von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med. 2019 14 Feb 2019;380(7):617-28.

[50] Xu ZQ, Zhang Y, Li N, Liu PJ, Gao L, Gao X, et al. Efficacy and safety of lapatinib and trastuzumab for HER2-positive breast cancer: a systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2017 Mar 13;7(3):e013053.

[51] Hansen RN, Ramsey SD, Lalla D, Masaquel A, Kamath T, Brammer M, et al. Identification and cost of adverse events in metastatic breast cancer in taxane and capecitabine based regimens. SpringerPlus. 2014;3:259.

[52] Fontanella C, Bolzonello S, Lederer B, Aprile G. Management of breast cancer patients with chemotherapy-induced neutropenia or febrile neutropenia. Breast Care (Basel). 2014 Apr;9(4):239-45.

[53] Issa DE, Gelderblom H, Lugtenburg PJ, van Herk-Sukel MP, Houweling LM, de la Orden M, et al. Healthcare utilisation in patients with breast cancer or non-Hodgkin lymphoma who experienced febrile neutropenia in the Netherlands: a retrospective matched control study using the PHARMO database. Eur J Cancer Care (Engl). 2015 Mar;24(2):232-41.

[54] Puma data on file. ExteNET: Table 14.3.1.3.8.1. Incidence of treatment-emergent adverse events ≥ 10%, HR+<1yr. 2019.

[55] Chan A, Delaloge S, Holmes F, Moy B, Iwata H, Harker G, et al. Neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ breast cancer: 3-year analysis from a phase 3 randomized, placebo-controlled, double-blind trial (ExteNET). Cancer Res. 2016;76(4 suppl):S5-02.

[56] Puma data on file. ExteNET: Table 14.3.1.21. Treatment-emergent diarrhea by treatment month for HR+< 1yr. 2018.

[57] Bossi P, Antonuzzo A, Cherny NI, Rosengarten O, Pernot S, Trippa F, et al. Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018 Oct 1;29(Suppl 4):iv126-iv42.

[58] Puma data on file. ExteNET HRQoL bar charts full set 29Dec2018. 2018.

[59] Puma data on file. ExteNET: Table 14.6.3.10. Summary of Health Outcome - EQ-5D Health State Summary Score, ITT Population. 2015.

[60] Puma data on file. CONTROL: Table 14.6.1.10. Summary of health outcome -EQ-5D-5L health state summary score. 2018.

[61] Puma data on file. CONTROL: Table 14.6.1.11. Summary of health outcome - EQ-5D-5L Index score. 2018.

[62] Puma data on file. ExteNET: TNM subgroup analysis for EMA label. 2020.

Application for the assessment of neratinib (NERLYNX®) in the extended adjuvant treatment of HER2-positive, hormone receptor–positive early breast cancer after trastuzumab-based therapy

DMC Dokumentnummer: 74579

DMC/AMGROS ECONOMIC ANALYSIS: Final

[redacted]

Contents

1 Abbreviations

Abbreviation/term	Definition
AE	adverse event
AIC	Akaike information criterion
AIP	Apoteksindkøbspris
Amgros	Amgros I/S
ATC	Anatomical Therapeutic Chemical Classification System
BIC	Bayesian information criterion
CI	confidence interval
CNS	central nervous system
CT	computed tomography
DDFS	distant disease-free survival
DFS	disease-free survival
DFS-DCIS	disease-free survival including ductal carcinoma in situ
DMC	Danish Medicines Agency
ECHO	echocardiogram
GP	general practitioner
HER	human epidermal growth factor receptor
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
HR	hormone receptor
HR+	hormone receptor–positive
HRQoL	health-related quality of life
HTA	health technology assessment
IBS	Integrated Brier Score
iDFS	invasive disease-free survival
ITT	intention to treat
IV	intravenous
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NE	not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	overall survival

Abbreviation/term	Definition
PDRS	post-distant recurrence survival
PET	positron emission tomography
PICO	population, intervention, comparator and outcomes
SC	subcutaneous
SD	standard deviation
SE	standard error
SmPC	summary of product characteristics
TLV	Swedish Dental and Pharmaceutical Benefits Agency
TTDR	time to distant recurrence
VAT	value-added tax

2 Executive summary

2.1 Disease overview

In Denmark, breast cancer is the most common cancer in women [1] and the most frequent cause of cancer death in women [2]. Breast cancer is a heterogeneous disease composed of distinct histological and molecular subtypes, and treatment depends on the type of breast cancer [3]. Approximately 15% of patients with early breast cancer have tumours that overexpress the human epidermal growth factor receptor 2 (HER2) receptor (i.e., are HER2 positive [HER2+]), and two-thirds of HER2+ breast cancers are also hormone receptor–positive (HR+); thus, approximately 10% of early breast cancers are HER2+/HR+ [4].

2.2 Current management and unmet need

The current standard of care in Denmark, confirmed by two Danish clinical experts (Appendix J), for patients with early HER2+/HR+ breast cancer after surgery, chemotherapy and radiotherapy is routine adjuvant HER2-directed therapy with trastuzumab for 1 year, after which patients do not receive any further HER2-directed therapy in the extended adjuvant setting. Patients with HER2+/HR+ breast cancer can receive adjuvant endocrine therapy, usually with tamoxifen, for up to 10 years [5, 6]. After 10 years of follow-up, approximately 23% of patients with early HER2+/HR+ breast cancer treated with 1 year of trastuzumab will have experienced a recurrence [7]. As such, there is a need for additional interventions to improve on the benefits of trastuzumab-based therapy and reduce the risk of breast cancer recurrence, disease progression and death [4, 7, 8].

2.3 Neratinib

Neratinib is an oral, intracellular, irreversible multiple ErbB tyrosine kinase inhibitor of human epidermal growth factor receptor 1, HER2 and human epidermal growth factor receptor 4, which decreases proliferation and increases tumour cell death. The recommended dose of neratinib is 240 mg (six 40-mg tablets) taken orally once daily for 1 year after the completion of trastuzumab-based therapy [9].

Neratinib is indicated for the extended adjuvant treatment of adults with early-stage HER2+/HR+ breast cancer who have completed adjuvant trastuzumab-based therapy less than 1 year ago [9].

2.4 Clinical evidence

Neratinib significantly reduces the risk of recurrence in patients with early HER2+/HR+ breast cancer in the extended adjuvant setting within 1 year of a trastuzumab-based regimen. Clinical data from ExteNET, a pivotal phase 3 randomised controlled trial, showed that neratinib significantly improved 2-year and 5-year invasive disease-free survival (iDFS) when given after chemotherapy and less than 1 year from prior trastuzumab-based adjuvant therapy.

2.5 Economic evidence

This is the first economic evaluation undertaken for neratinib for the treatment of early HER2+/HR+ breast cancer in the extended adjuvant setting from the Danish perspective. The analysis showed that neratinib is cost-effective, with an incremental cost of DKK 131,902 per patient. The analysis is likely to be directly applicable to clinical practice in Denmark as follows:

- The patient populations from the ExteNET and CONTROL trials, as used in the economic analysis, are likely to be reflective of patients in Denmark.
- The resource use and costs in the analysis have been validated by two Danish clinicians and were sourced from Denmark-based publications and previous Danish Medicines Council (DMC) submissions.

3 Formalities pertaining to this application

Table 1 summarises the Danish submission for neratinib in early breast cancer and the health economic analysis, respectively.

Table 1. Overview of submission to Denmark

Company Name	Pierre Fabre Pharma Norden AB Karlavägen 108; Plan 9 115 26 Stockholm Sweden
Contact person for this assessment	Erik Arver, Market Access Nordics Phone: +46 70 750 87 37 E-mail: erik.arver@pierre-fabre.com
Consulting firm commissioned	RTI Health Solutions
Brand/trade name	NERLYNX®
Active substance	Neratinib
ATC code	L01XE45
Indications	Neratinib is indicated for the extended adjuvant treatment of adults with early-stage HR+, HER2+ breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago.
Pharmaceutical form/method of administration and posology	Neratinib is administered orally. The recommended dose is 240 mg neratinib, administered as 6 × 40 mg tablets taken once daily and continually for 1 year.
Required additional tests/medication	The indicated population is people with HER2+/HR+ breast cancer who have completed a course of trastuzumab-based therapy; however, as receptor and gene testing will already have been completed before initiating a trastuzumab-based therapy, no additional testing of receptor status is anticipated to be required prior to starting neratinib therapy. The label indicates that patients are instructed to start antidiarrhoeal prophylaxis with the first dose of neratinib and maintain regular dosing of the antidiarrhoeal product during the first 1-2 months of treatment, titrating to achieve 1 to 2 bowel movements per day.
Patient population in Denmark the indication applies to (5-year prevalence)	According to Pierre Fabre estimations, based on available Danish population projections, Danish cancer registry statistics and clinical expert opinion, the population over the next 5 years is expected to be approximately as follows:

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Patients	16	33	49	66	82

Clinical experts who have been contacted	Bent Ejlertsen, Rigshospitalet Ann Søegaard Knop, Rigshospitalet

ATC, Anatomical Therapeutic Chemical Classification System; HER2+, human epidermal growth factor receptor 2 positive; HR+, hormone receptor–positive.

4 Scope

This submission follow the Danish Medicines Agency (DMC) protocol (Dokumentnummer 74579) and covers neratinib's full marketing authorisation for the following indication: the extended adjuvant treatment of adults with early-stage HR+, HER2 overexpressed/amplified breast cancer who have completed adjuvant trastuzumab-based therapy less than 1 year ago. Table 2 presents an overview of the scope of the submission in terms of the population, intervention, comparator and outcomes (PICO).

Table 2. Scope for the neratinib submission for Denmark

Population	Patients with early HR+, HER2+ breast cancer who have completed a course of adjuvant trastuzumab-based therapy less than 1 year ago.
Intervention	Neratinib
Comparator(s)	No further HER2-directed treatment, represented by the placebo arm of the ExteNET trial
Outcomes	▪ iDFS (2 years and 5 years) ▪ DFS-DCIS ▪ DDFS ▪ Cumulative incidence of CNS recurrence ▪ TTDR ▪ Overall survival ▪ Adverse effects of treatment ▪ HRQoL
Subgroups considered	None identified
Health economic analysis	Cost analysis and budget-impact analysis over a lifetime horizon, with costs in DKK from a Danish extended healthcare perspective.

CNS, central nervous system; DDFS, distant disease-free survival; DFS-DCIS, disease-free survival including ductal carcinoma in situ; HER2 = human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor–positive; HRQoL, health-related quality of life; iDFS, invasive disease-free survival; TTDR, time to distant recurrence.

5 Health economic analysis and model

5.1 Health economic analysis

5.1.1 Model structure

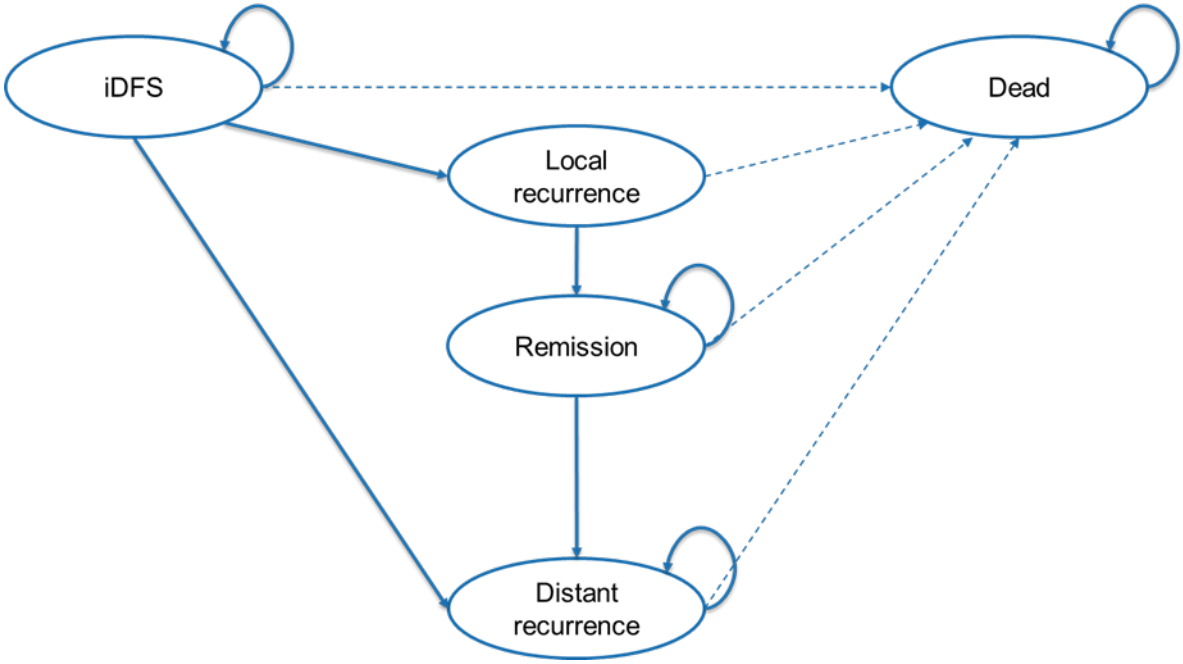
Several different modelling approaches were considered during the development of the model structure. Partitioned survival models are used routinely in economic evaluations in oncology and have been the most commonly used in DMC and Amgros I/S (Amgros) appraisals. [10-12] However, the use of partitioned survival models has been criticised [13]. The challenge of using a partitioned survival model for the neratinib economic evaluation is that no mature overall survival (OS) data are available by treatment arm. Thus, data that would allow for estimation of full health-state occupancy by treatment arm are not available. To overcome this issue, different approaches for modelling were considered, including modelling OS using correlations between iDFS and OS, but all approaches considered were found to have limitations. To assess whether iDFS can be used as a surrogate endpoint for OS, the following three requirements have been proposed [14]: (1) evidence of a strong correlation between iDFS and OS (individual-level association); (2) evidence of a strong correlation between treatment effect on iDFS and treatment effect on OS (trial-level association); and (3) clinical input on the anticipated relationship between iDFS and OS. We performed an analysis to consider whether a strong correlation between the treatment effect on iDFS and the effect of treatment on OS could be identified. This approach was based on scatterplots between *ln(HR DFS)* and *ln(HR OS)* (r = 0.2), when considering all trials of trastuzumab-containing regimens for early breast cancer that were included in a recent Cochrane review [15]. However, a strong relationship could not be identified. Therefore, extreme scenarios—for example, assuming the treatment effect on OS to be equal to the treatment effect on iDFS or assuming no treatment benefit on OS—were considered; but both of these scenarios were considered to be unrealistic. It was clear that iDFS and OS are not fully correlated and that assuming equal treatment effect would likely have overestimated the effect of neratinib. Similarly, recurrence of disease—specifically, distant recurrence—is known to have a significant impact on expected survival; therefore, assuming that a reduced number of recurrences as a function of improved iDFS would not lead to any survival benefits also seems equally unrealistic.

Given the challenges that would be associated with a traditional partitioned survival analysis approach, other potential modelling approaches were reviewed. These included the Markov model structure developed for recent health technology assessment (HTA) appraisals of pertuzumab for adjuvant treatment of early HER2+ breast cancer [16-18]. Specifically, the model structure used for the pertuzumab economic evaluation was investigated; that model included seven health states (iDFS on treatment, iDFS off treatment, non-metastatic recurrence, remission, first-line metastatic breast cancer, second-line metastatic breast cancer and death).

For the current analysis, a five-health-state Markov model was developed to evaluate the incremental cost of neratinib versus standard treatment with no further HER2-directed therapy.

Figure 1 shows the five-health-state model structure. The five health states represent the primary stages of disease in early-stage breast cancer: disease-free, local recurrence, remission, distant recurrence and dead. General mortality data are applied to all health states except distant recurrence. It was assumed that all patients who die from breast cancer move through the distant recurrence health state before transitioning to the dead health state.

Figure 1. Overview of the five-health-state model structure



iDFS, invasive disease-free survival.

The model health states correspond to the primary and secondary endpoints in the ExteNET trial. The model structure allows for variation in risk of recurrence and death over the time horizon, as observed in iDFS data for these patients from ExteNET [19].

Patients enter the iDFS health state and are treated with neratinib or are given no treatment (placebo). Patients remain in the iDFS health state until they experience an iDFS event, local or distant recurrence, or death. After local recurrence, patients enter a tunnel health state in which they receive adjuvant therapy before they transition to either remission or death. For patients with locally recurrent disease who transition to remission, the model assumes that all patients progress to distant recurrence or die from general population mortality.

Patients experiencing distant recurrence while in iDFS transitioned directly to the distant recurrence health sate. No further explicit submodelling of progression-free survival or OS, dependent on the line of therapy, was included in the distant recurrence health state.

Patients can transition to death from any health state. While in the iDFS, local recurrence and remission health states, patients are subject to all-cause mortality. Patients in the distant recurrence health state are subject to post-distant recurrence mortality, based on blinded survival data for both arms of ExteNET because OS data by treatment arm are still immature for the neratinib label population.

Costs are allocated to each health state and multiplied by that health state's occupancy to calculate the weighted costs per cycle. A model cycle length of 1 month was selected to provide precision in tracking the number of patients in each health state over time, and a half-cycle correction was incorporated. The model time horizon was set to 55 years, which was deemed to be equivalent to a lifetime time horizon, given the average age (51 years) of the patient population.

Treatment costs included costs of drug acquisition, administration and monitoring. Costs and disutilities associated with adverse events (AEs) were estimated per episode and were applied once at the beginning of the simulation, based on the proportion of patients in each treatment arm experiencing each AE. Costs were discounted at 4% per annum, in accordance with DMC guidelines.

5.2 Time horizon and analysis perspective

A life-long time horizon (55 years) and societal perspective was used to capture all relevant costs. The model allows the user to change the time horizon in the scenario analyses.

5.3 Clinical data used in the model

5.3.1 Extrapolation of time-to-event data

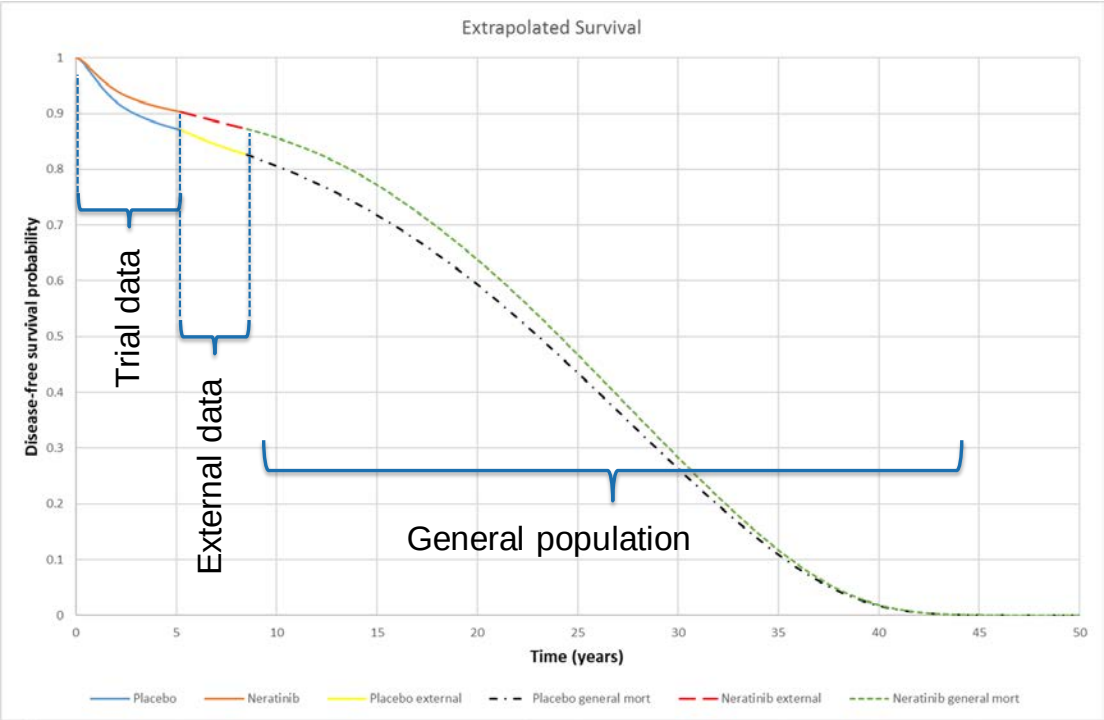
5.3.1.1 Modelling of invasive disease-free survival

In economic evaluations developed to support HTA submissions for cancer treatments, it is common practice to use parametric survival analysis fitted to data derived from pivotal trials for the interventions considered and extrapolate these over the full model time horizon. However, in the pivotal ExteNET trial, a large proportion of patients remained disease-free at the end of the 5-year follow-up. Treatment with neratinib has a curative intent, and analysis of the data suggested that iDFS hazard rates decreased over time (Appendix C). Therefore, functions fitted to the trial iDFS data only would not be expected to adequately predict the natural increase in hazard related to death from other causes at later times in the model. This is because other causes of death make an increasingly large contribution to the risk of an iDFS event over time as breast cancer-related hazards are reduced. (Note that iDFS is defined as time to disease recurrence or death, whichever occurs first.) In addition, more mature DFS data were available from other sources for patient cohorts with characteristics and treatment histories similar to those of the control arm of ExteNET (e.g., from long-term follow-up of patients enrolled in trials investigating trastuzumab). Such data could be valuable in informing or validating iDFS predictions after the ExteNET trial follow-up. As a consequence, both general population mortality data and external data for similar populations were analysed and considered for incorporation into the economic analysis.

A wide range of survival analyses were performed as described in detail in Appendix C. Standard analyses were performed to fit parametric functions to the ExteNET trial data, as recommended in the Danish Medicine Council [20]. In addition, parametric functions were fitted to more mature external disease-free survival (DFS) data, using methods proposed by Guyot et al. [21] and described in Jackson et al. [22].

Full description of these analyses can be found in Appendix C. Briefly, external data were sought to identify one or more studies with long-term DFS estimates for a population similar to that enrolled in ExteNET—specifically, patients with HR+, HER2+ early breast cancer who were eligible for treatment with neratinib—who received standard of care in routine practice. A systematic review of the clinical literature performed for this appraisal (see Appendix B) identified one meta-analysis of randomised controlled trials; the meta-analysis presented long-term follow-up data from studies with patients treated with trastuzumab [23]. This publication also presented a number of external data sources for DFS (see Appendix C). Clinical and health economic external advisers determined that data from the HERA trial [24] to be the most appropriate for inclusion in the survival analysis. Furthermore, HERA data were used for validation of extrapolations in recent appraisals of pertuzumab [16, 17]. External clinical and economic advisers also identified the HERA trial as the most appropriate data source for DFS. DFS data from HERA for patients who had HR+ tumours and a median follow-up of 11 years, as reported by Cameron et al. [7], were used in the current survival analysis (presented in Appendix C). The survival times from Cameron et al. [7] were adjusted so that the mean time since trastuzumab treatment aligned with the ExteNET trial's mean time. As the Cameron et al. [7] data also are not yet mature (approximately 80% of patients are still at risk at the end of follow-up), further extrapolation was required beyond the end of the HERA trial. Thus, OS for the general Danish female population [25, 26] was used for long-term extrapolation of the iDFS curve beyond the follow-up time of ExteNET and HERA. Figure 2 presents the planned use of data for extrapolation of iDFS.

Figure 2. Approach to combining data for iDFS survival extrapolation



iDFS, invasive disease-free survival.

In contrast to the approach taken in the recent appraisals of pertuzumab [16-18], the current survival analysis did not incorporate a cure rate parameter. Although we fully agree that early-stage breast cancer is treated with curative intent, the cure rate reported in the pertuzumab appraisals was included in the pertuzumab model because long-term extrapolation using the clinical trial data had a poor fit to external data. As shown in the following sections, the survival analysis for the current submission does not have these limitations. Estimates from the primary survival analysis in the ExteNET trial combined with general population mortality aligned well with more complex models that directly incorporated external data. Thus, the proportion of patients being cured following treatment is expected to already be captured in the extrapolation of iDFS from ExteNET.

Selection of survival function data included in the model base-case analysis

A wide range of parametric and flexible survival models were fitted to each of the data sets used in the analysis: iDFS data from the ExteNET trial and identified external data for DFS from HERA. The following are the steps we followed to determine the most appropriate survival functions (please see Appendix C for full details):

- Testing for proportional hazards between treatment arms in the ExteNET trial
  - Tests were performed to determine if the data from ExteNET indicated that proportional effects could be assumed. The test for non-proportional hazards (Therneau-Grambsch test) was not significant (chi-squared = 0.314; *P* = 0.575).
  - Clinical expert opinion received during the model development affirmed that a continued treatment effect would be expected (Appendix J).

- Because there was no evidence against the proportional hazard assumption for iDFS and because the proportional hazard assumption was in line with clinical rationale, a pooled survival model with a covariate for treatment effect was deemed the most appropriate approach for the ExteNET data. However, to investigate the impact of the assumption of proportional hazards, a best-fitting model, stratified by treatment arm, also was identified for testing in a scenario.

- Fitting and selection of survival models for all data sets:
  - A range of survival models were fit to the data.
  - Within the various survival models, the Akaike information criterion (AIC), Bayesian information criterion (BIC) and Integrated Brier Score (IBS) goodness-of-fit statistics were assessed to identify differences in statistical fit among the survival models.
  - The choice of survival model used for the base-case economic model was based on the following:
    - Assessing the AIC, BIC and IBS statistics of the survival models, which provides goodness-of-fit to the Kaplan-Meier data from ExteNET and HERA
    - Visual fit compared with the Kaplan-Meier data from ExteNET and HERA

Selection and combination of survival function data included in the model base-case analysis

Table 3 presents the base-case and scenario analysis functions selected to the ExteNET trial data and the HERA trial data.

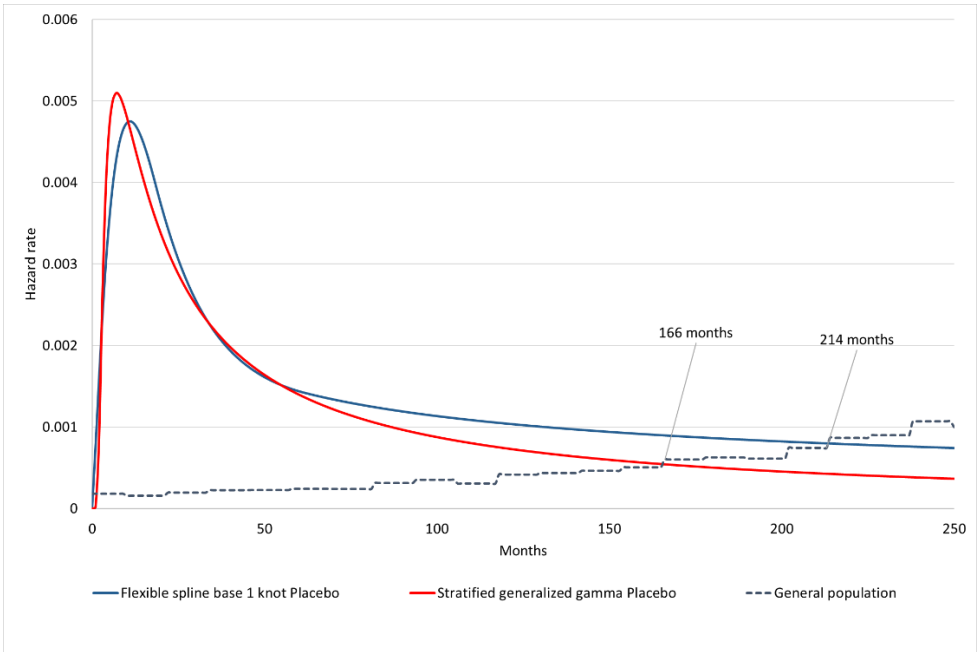
Table 3. Selected distributions for iDFS extrapolation

Data set	Distribution
ExteNET	
Base case	Flexible-spline Weibull 1 knot (proportional hazards)
Scenario	Stratified generalised gamma (non-proportional hazards)
HERA	
Base case	Flexible-spline Weibull 2 knots

iDFS, invasive disease-free survival.

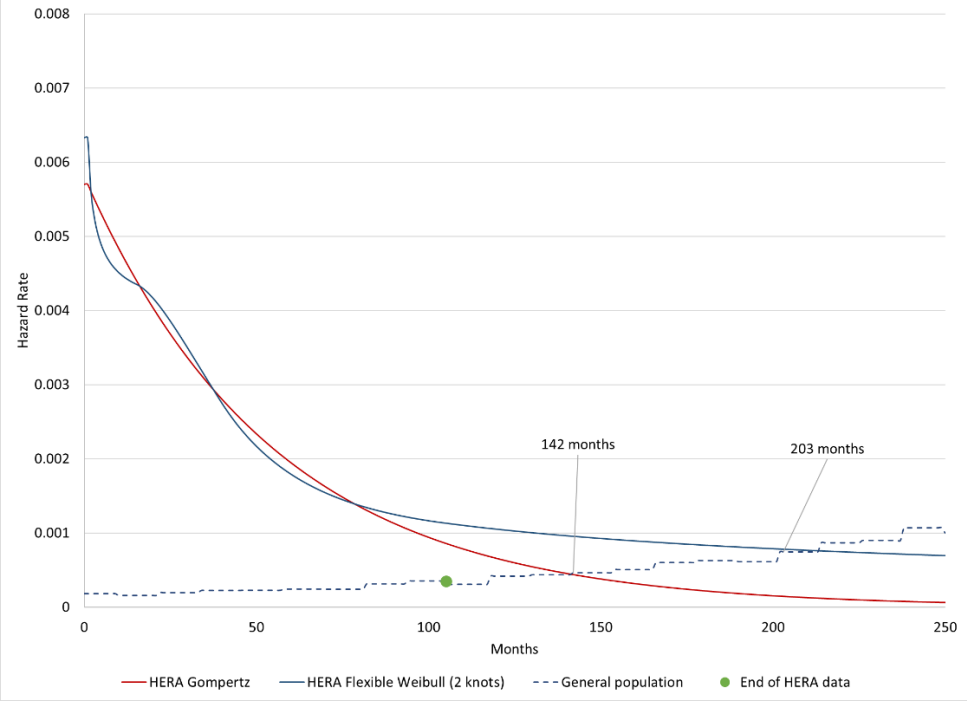
As expected, the extrapolated survival from the ExteNET and HERA trials resulted in the predicted iDFS hazard being lower than the general population mortality from approximately month 140 to month 215, depending on data and distribution (Figure 3 and Figure 4). Thus, it was confirmed that using only the extrapolated iDFS data from the ExteNET trial or with the addition of the data from HERA would not result in plausible long-term predictions of iDFS. This supports the inclusion of general population data in the analysis to avoid implausible extrapolation of long-term survival.

Figure 3. Comparison of hazard rates between the placebo arm iDFS from ExteNET and general population mortality



iDFS, invasive disease-free survival.

Figure 4. Comparison of hazard rates between HERA and general population mortality

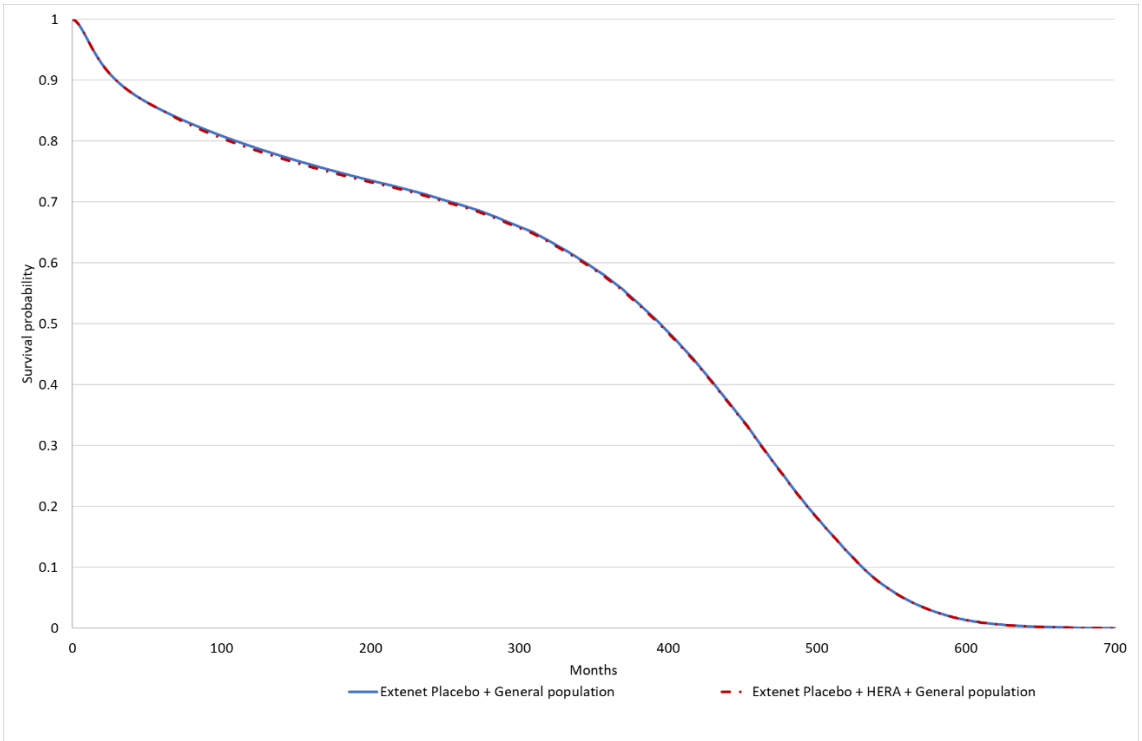


DFS, disease-free survival; HERA, Herceptin Adjuvant trial; iDFS, invasive disease-free survival.

As presented in this section and fully outlined in Appendix C, the intent at the outset of the survival analyses was to use all three data sets (ExteNET, HERA and general population) to predict the long-term iDFS, which is in line with the methods proposed by Jackson et al. [22]. However, after performing all analyses, it was noted that the survival predictions based on ExteNET and general population data were highly consistent with more complex predictions that also incorporated the

HERA data. This is shown in Figure 5, in which survival curves composed of the ExteNET placebo arm, the HERA data and the general population data are overlaid onto survival predictions from the ExteNET placebo arm and from the general population. It is clear that the two approaches lead to only marginally different survival predictions.

Figure 5. Plot of base-case survival curves for predicted iDFS by using HERA data in addition to ExteNET data



HERA, Herceptin Adjuvant trial; iDFS, invasive disease-free survival.

Adding the HERA data explicitly to the survival analysis extrapolation adds additional complexity and uncertainty (because it contributes another set of survival extrapolations to the analysis and is based on DFS rather than iDFS). Furthermore, the HERA data represent the placebo arm well, but their relation to the neratinib arm is less clear and further adjustments would potentially be needed. Thus, the ExteNET data in combination with general population survival data were used for the base-case extrapolation of iDFS in the model. Functions that incorporated the HERA data were used for validation and for supporting scenario analyses in the model. The notable close alignment of the extrapolation based on the ExteNET iDFS data with the more mature HERA DFS data provided important evidence for the validity of the extrapolation of the ExteNET data, on which the model is based.

Transition from ExteNET iDFS to general population mortality

There is limited evidence available regarding the long-term risk of an iDFS event for the HER2+/HR+ patient population and thus from what time point general population mortality could be reasonably assumed. A recent meta-analysis showed that, for patients with HR+ breast cancer, there is a continued risk for recurrence at 20 years after their initial breast cancer diagnosis [27]. To our knowledge, similar data are not available for the HER2+/HR+ population. The HR+ population data are likely not directly transferrable because of a higher incidence of early recurrence in the HER+2/HR+ population than in the HR+ population. Two Danish clinical experts confirmed that, given the curative intent of the treatment and early recurrence in the HER2+/HR+ population, it is plausible to assume that the iDFS risk would approach that of the general population at some point,

although it is difficult to determine at what point. The longest follow-up data available for the relevant population is, to our knowledge, the HERA trial. Thus, we analysed the hazard over time from the HERA trial in relation to the Danish general population mortality. As shown in Figure 4, the iDFS hazard rates at the end of the HERA trial (equal to 8.5 years after initiation of neratinib treatment) are still higher for the HERA population than for the general population. Using the survival curves with best fit to the digitised DFS HERA data (as described in this section and in Appendix C), our analyses showed that the risk of a DFS event was likely to be equal to that of the general population from 142 to 203 months after initiation of neratinib treatment. A similar pattern was seen in the extrapolated hazard rate for the placebo arm of ExteNET (Figure 3), which crosses the general population mortality hazards at approximately 166 to 214 months, depending on the distributions used. Based on this analysis, the model was constructed to allow for switching from the ExteNET iDFS extrapolation to the general population mortality so that extrapolations are based on ExteNET data until hazard rates for the general population exceed hazard rates from the ExteNET trial. This switch is dependent on the treatment arm to account for the differences in hazard rates between treatment arms.

Treatment effect beyond trial follow-up

For proportional hazards survival extrapolations, potential adjustments of treatment effect beyond the end of the trial were assessed to investigate the impact of potential waning of treatment effect over time. During the 5-year follow-up in the ExteNET trial, there was a clear continued treatment effect for the 4-year follow-up time after treatment (Table 4). Therefore, patients continued to benefit from the treatment well beyond 1 year of treatment.

Table 4. ExteNET: annualised hazard ratios for iDFS for HR+ population ≤ 1 year from prior adjuvant trastuzumab

Time period	Hazard ratio (95% CI)
0-12 months	0.49
12-24 months	0.6
24-36 months	0.92
36-48 months	0.5
48-60 months	0.59

CI, confidence interval; iDFS, invasive disease-free survival; HR+, hormone receptor–positive.

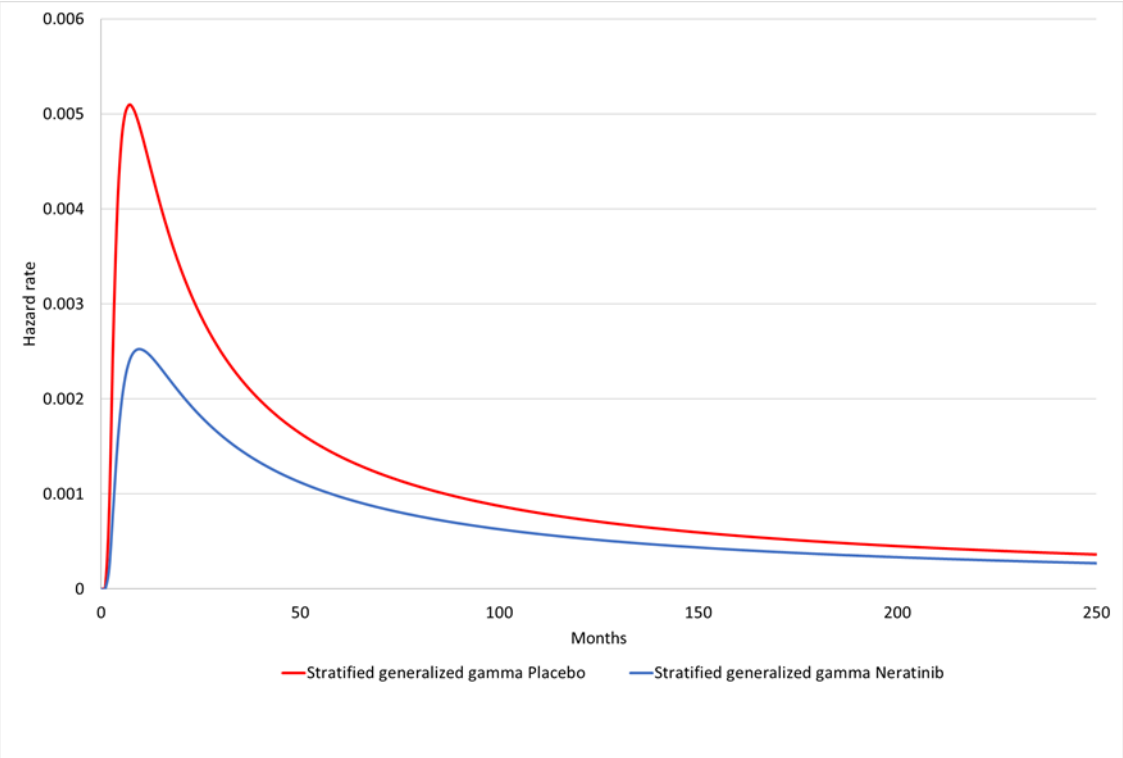
Given the continued treatment effect shown during the trial and the lack of evidence of any considerable waning of treatment effect towards the end of the trial, base-case analyses were based on the extrapolation of data from ExteNET, without further adjustments of treatment effect beyond the trial time horizon. The assumption of continued treatment effect also was partially supported by the Danish expert clinical advisers consulted as part of the model development (Appendix J). Thus, patients in the neratinib arm transition to general population mortality earlier than patients in the placebo arm (e.g., year 14 vs. year 18 with the base-case distributions). As previously described, this transition negates the possibility of neratinib patients having a lower probability of an iDFS event than that of the general population. Such a transition lessens the treatment effect compared with fully relying on the extrapolated survival from the trial.

A more rapid waning of treatment effect was explored in a sensitivity scenario for the base-case extrapolations, assuming proportional hazards. In this scenario, the treatment effect was tapered linearly from the end of the trial until the time point at which placebo arm iDFS hazard was equal to that of the general population (214 months). This scenario follows the clinical input received that

neratinib is likely to provide treatment benefits as long as patients are at risk for an iDFS event but tests the assumption that the treatment effect would decline over time.

For the scenario based on non-proportional hazards extrapolations with stratified generalised gamma, no further waning of treatment effect was incorporated. As can be seen in Figure 6, the stratified extrapolations already predicted decreasing treatment effect over time due to the difference in predicted declining hazard rates over time between the treatment arms. Thus, further waning of treatment effect was already accounted for in the survival predictions itself.

Figure 6. Predicted iDFS hazard rates with stratified generalised gamma for the neratinib and placebo arms from ExteNET



iDFS, invasive disease-free survival.

5.3.1.2 Distant recurrence survival

Mortality from distant recurrence was modelled using the blinded post-distant recurrence survival (PDRS) for both arms of the ExteNET trial, with survival models fitted to extrapolate survival beyond the study time horizon. Figure 7 shows the cumulative survival plot of PDRS for all patients experiencing a distant recurrence in the ExteNET trial.

Figure 7. ExteNET: Kaplan-Meier curve of blinded PDRS, HR+ population ≤ 1 year from prior adjuvant trastuzumab

HR+, hormone receptor–positive; PDRS, post-distant recurrence survival.

Source: Puma data on file [28].

Because time to distant recurrence (TTDR) has previously been shown to have an impact on expected PDRS [29, 30], we investigated the impact of TTDR on PDRS from the ExteNET trial. Figure 8 shows survival, stratified by year of recurrence from randomisation; it is clear that patients with a recurrence within the first year after randomisation appear to have a poorer prognosis than those with a later recurrence. However, there does not appear to be a clear differentiation between time categories of recurrence beyond the first year of the ExteNET trial. This corresponds well to cut-off points previously used in which a 24-month metastatic-free interval from disease onset had been used [30], which would equal 12 months after start of neratinib.

Figure 8. ExteNET: Kaplan-Meier plot of analysis of overall survival post-distant recurrence for HR+ patients who completed trastuzumab ≤ 1 year by time of distant recurrence, ITT population

HR+, hormone receptor–positive; ITT, intention to treat.

Source: Puma data on file [31].

To account for the impact of timing of recurrence in the model, additional analyses of PDRS were performed, using different survival curves for PDRS for patients experiencing distant recurrence ≤ 12 months versus > 12 months from randomisation (Figure 9).

Figure 9. ExteNET: Kaplan-Meier plot of analysis of overall survival post-distant recurrence for HR+ patients who completed trastuzumab ≤ 1 year and had distant recurrence ≤ 12 months versus > 12 months from randomisation, ITT population

CI, confidence interval; HR+, hormone receptor–positive; ITT, intention to treat; NE, not estimable.

Source: Puma data on file [32].

Survival analyses

The process for fitting survival models to patient-level data was based on NICE Decision Support Unit technical support guidance [12]. The choice of survival model was based on the AIC and BIC statistics of the survival models, which provide goodness-of-fit to the Kaplan-Meier data from ExteNET and visual fit compared with the Kaplan-Meier data from ExteNET.

Table 5 summarises the AIC and BIC values for the survival models explored for PDRS. The exponential distribution provided the lowest AIC and BIC, followed by Gompertz distribution. Differences in AIC and BIC were comparatively small between exponential and Gompertz distributions, based on a 3 to 5 difference in AIC/BIC. Consequently, the selection of which of the two curves should be used as the base-case distribution was guided by visual fit. As shown in Figure 10, the Gompertz distribution produced a slightly better visual fit to the data than did the exponential distribution; therefore, Gompertz distribution was selected for the base-case analysis.

Table 5. Summary of goodness-of-fit data for survival models for PDRS

Distribution	AIC	BIC
Exponential	**261.02**	**263.71**
Gompertz	**261.44**	**266.82**
Gamma	262.69	270.77
Weibull	262.83	268.21
Logistic	267.36	272.74
Lognormal	274.06	279.44

AIC, Akaike information criterion; BIC, Bayesian information criterion; PDRS, post-distant recurrence survival.

Figure 10. Plot of survival curves for PDRS, compared with ExteNET Kaplan-Meier curves

PDRS, post-distant recurrence survival.

Source: Puma data on file [32].

Table 6 and Table 7 summarise the AIC and BIC values for the survival models explored for PDRS for time of recurrence ≤ 12 months versus > 12 months from randomisation. Based on the AIC and BIC, the same functions provided the best fit as those models fitted to the data not split by time of recurrence, specifically, exponential distribution followed by Gompertz. Differences in AIC and BIC were smaller between exponential and Gompertz distributions than what would generally be considered a relevant difference. As shown in Figure 11, for patients experiencing a recurrence > 12 months the Gompertz distribution produced a better visual fit to the data than did the exponential distribution; therefore, Gompertz was the preferred distribution for this extrapolation. For the patients experiencing recurrence ≤ 12 months from randomisation, the visual fit of exponential and Gompertz distributions was almost identical and selection of which distribution would be appropriate for this subgroup would have marginal impact on the results. For consistency with the subgroup > 12 months, the Gompertz survival functions also were selected for the subgroup ≤ 12 months.

Table 6. Summary of goodness-of-fit data for survival models for PDRS > 12 months from randomisation

Distribution	AIC	BIC
Exponential	**177.78**	**180.20**
Gompertz	**177.53**	**182.37**
Gamma	179.57	186.83
Weibull	179.24	184.08
Logistic	182.10	186.93
Lognormal	188.10	192.94

AIC, Akaike information criterion; BIC, Bayesian information criterion; PDRS, post-distant recurrence survival.

Source: Puma data on file [33].

Table 7. Summary of goodness-of-fit data for survival models for PDRS ≤ 12 months from randomisation

Distribution	AIC	BIC
Exponential	**81.30**	**82.56**
Gompertz	**83.30**	**85.81**
Gamma	85.07	88.84
Weibull	83.22	85.73
Logistic	84.76	87.28
Lognormal	85.50	88.02

AIC, Akaike information criterion; BIC, Bayesian information criterion; PDRS, post-distant recurrence survival.

Source: Puma data on file [33].

Figure 11. **ExteNET: plot of survival curves for overall survival post-distant recurrence > 12 months and ≤ 12 months from randomisation, compared with ExteNET Kaplan-Meier curves**

Source: Puma data on file [33].

5.3.2 Modelling of proportion of local and distant recurrence

The proportions of patients transitioning from iDFS to local or to distant recurrence were derived from the ExteNET trial. A slight difference in the proportion of distant and other recurrences was observed between arms; consequently, observed proportions for each arm were included in the base-case analysis (Table 8). It is not evident from comparing the 5-year data (Table 8) with the 2-year data (Table 9) that the proportions of sites of recurrence varied over time; hence, proportions from the 5-year data were kept constant through the modelled time horizon.

Table 8. Type of iDFS event observed in ExteNET (5 years)

	Neratinib (n = 670)	Placebo (n = 664)
Patients with events, n (%)	51 (7.6)	89 (13.4)
Local/regional invasive recurrence	5 (0.7)	18 (2.7)
Invasive ipsilateral breast tumour recurrence	2 (0.3)	5 (0.8)
Invasive contralateral breast cancer	2 (0.3)	5 (0.8)
Distant recurrence	40 (6.0)	63 (9.5)
Death from any cause	2 (0.3)	3 (0.5)
Patients censored, n (%)	619 (92.4)	575 (86.6)
Proportion distant recurrence, n (%)	40/49 (81.6)	63/91 (69.2)
Proportion other recurrences, n (%)	9/49 (18.4)	28/91 (30.8)

iDFS, invasive disease-free survival.

Source: Puma data on file [34].

Table 9. Type of iDFS event observed in the ExteNET trial (2 years)

	Neratinib (n = 670)	Placebo (n = 664)
Patients with events, n (%)	26 (3.9)	55 (8.3)
Local/regional invasive recurrence	3 (0.4)	12 (1.8)
Invasive ipsilateral breast tumour recurrence	1 (0.1)	2 (0.3)
Invasive contralateral breast cancer	1 (0.1)	2 (0.3)
Distant recurrence	20 (3.0)	38 (5.7)
Death from any cause	1 (0.1)	1 (0.2)
Patients censored, n (%)	644 (96.1)	609 (91.7)
Proportion distant recurrence, n (%)	20/25 (80.0)	38/54 (70.4)
Proportion other recurrences, n (%)	5/25 (20.0)	16/54 (29.6)

iDFS, invasive disease-free survival.

Source: Puma data on file [35].

5.3.3 Local recurrence pathway

The modelling of local recurrence was aligned with the approach and assumptions used in the several HTA appraisals for treatments in this disease area [16-18, 36-38].

5.3.3.1 Local recurrence

It was assumed that all patients who experience a local recurrence undergo 1 year of additional adjuvant therapy before they transition into the remission health state or die due to all-cause mortality. It was assumed that all patients with local recurrence reside in the local recurrence health state for 12 months before being able to transition to remission after additional adjuvant therapy.

5.3.3.2 Remission

Patients who have completed adjuvant therapy in the local recurrence state and who have not died due to all-cause mortality transition to the remission state after 12 months. When in remission, patients can either die from all-cause mortality or experience another recurrence.

In line with the TLV, Norwegian Medicines Agency and NICE appraisals of pertuzumab [16-18], it was assumed that any recurrence from remission would be distant in nature, as patients in remission will have already experienced a local recurrence. Furthermore, the same monthly transition probability of 0.00757 for transitioning from remission to distant recurrence, as used in the TLV, Norwegian Medicines Agency and NICE appraisals, was used in the current analysis and assumed to be constant with time. That transition probability was obtained from a study by Hamilton et al. [39] that studied a cohort of 12,836 patients with early breast cancer and reported the estimated risk for incurring a second malignancy after adjuvant therapy.

5.3.4 Distant recurrence

Patients entering the distant recurrence health state in the model are assumed to receive an average of two lines of subsequent therapy before eventually transitioning to death. Inclusion of two lines of subsequent therapy was based on clinical input and the TLV, Norwegian Medicines Agency and NICE appraisals of pertuzumab (TA569) [16-18]. However, contrary to the model used for pertuzumab, the current model did not explicitly model the progression-free survival and OS associated with the individual subsequent therapies. As neratinib is not approved in metastatic breast cancer, subsequent treatment will not be influenced by neratinib treatment for early breast cancer. Thus, it was seen as unnecessarily complicated to model PDRS specifically for each treatment. Rather, subsequent treatment was modelled by including the cost of the different subsequent treatments and using PDRS from the ExteNET trial. The model was programmed to allow the risk of death for those patients with distant recurrence to vary with time since recurrence, based on survival functions fitted to the PDRS data from ExteNET.

5.4 Resource use and costs

5.4.1 Intervention and comparators' costs and resource use

The per-treatment drug acquisition costs are presented in Sections 5.4.1.1 and 5.4.1.2, with the unit costs for supportive treatment taken from medicinpriser.dk [40].

5.4.1.1 Neratinib

In line with the licence, the model uses a dose of 240 mg of neratinib, administered orally as 6 × 40 mg tablets taken once daily and continually for 1 year. The retail list price of a 180-tablet pack of neratinib is DKK 38,399.42 (AIP) [40]. Based on the list price, the total cost per patient per 240 mg dose is DKK 1,279.98.

Although neratinib, per the European Medicines Agency label, should be given continually for 1 year, the actual mean treatment duration observed in ExteNET was [redacted] months, after accounting for treatment discontinuation; on this basis, the treatment duration in the model was set to [redacted] months [41].

In line with appraisals of pertuzumab [16, 18, 42] and completed NICE appraisals, such as TA483, TA484, TA569 and TA612 [37, 38, 43-45], the model uses the proportion of planned doses actually received, which more accurately accounts for the real cost of therapy. This proportion was based on the relative actual dose intensity from the ExteNET trial. The relative actual dose intensity is the ratio between actual dose intensity (the actual cumulative dose divided by the treatment duration) and

the prescribed dose (240 mg). The calculation showed that, on average, patients on treatment received [redacted] of the planned doses [46].

The treatment is not expected to have a relevant impact on the patient's number of healthcare visits. Hence, costs in terms of patient time and transportation costs are accounted for in all health states regardless of treatment. This is due to the fact that whether the patient receives neratinib or placebo is not expected to have an impact on the number of visits in each of the various health states per time unit in the health state. However, as neratinib has an impact on the time in the different health states, it has an impact on the total number of visits and total cost.

5.4.1.2 Prophylactic and supportive therapies

The model includes the cost of diarrhoea prophylaxis, specifically loperamide, given to patients receiving neratinib. Unit costs for loperamide were taken from webapoteket.dk [47]. In the CONTROL trial, two treatment protocols were used for loperamide prophylaxis: loperamide received for a period of one or two cycles (28-56 days). The cost-effectiveness analysis assumed the maximum duration as a conservative assumption.

The model also includes the cost of supportive endocrine therapy for patients receiving either neratinib or placebo. Supportive endocrine therapy is modelled with either tamoxifen (anti-oestrogen), with a treatment share of 51.8%, or exemestane (aromatase inhibitor), with a treatment share of 48.2%. Endocrine therapy is given to 93.8% of disease-free patients for 5 years.

Table 10 presents drug unit costs for loperamide and other supportive therapies.

Table 10. Drug unit costs for loperamide and supportive therapies

Treatment	Strength (mg)	Pack size	Cost per pack, including VAT (DKK)	Source
Loperamide	2	10	22.44	Danish Medicines Agency[40]; webapoteket.dk [47]
Tamoxifen	20	100	189.00	
Goserelin	3.6	1	1,015.89	
Anastrozole	1	100	36.99	
Letrozole	2.5	100	194.58	
Exemestane	25	100	3,644.00	

VAT, value-added tax.

5.4.2 Health-state unit costs and resource use

The published literature that explores in detail the resource use associated with adults with early-stage HR+, HER2-overexpressed/amplified breast cancer is limited. The source used for resource utilisation per health state is the resource use previously preferred by HTA authorities in the pertuzumab appraisal for adjuvant treatment of early HER2+ breast cancer [16, 18, 48]. Resource use data were validated and, in some cases, updated by input from the two Danish clinical experts (Appendix J). Costs per resource were sourced from Danish sources where available or converted to DKK where costs from other countries were applied.

5.4.2.1 Health-state resource use

The model contains five health states: disease-free, remission, local recurrence, distant recurrence and dead. Health-state resource use and costs, by health state, are presented in Table 11 through Table 15.

Table 11. Health-state resource use and cost by health state: disease-free

Resource use	Unit cost (DKK)	% of patients	Resource use frequency		Source
			Years 1-4	Years > 4	
Mammogram	665	100	1	1	DRG: 30PR14 Mammografi, ukompliceret [49] and clinical expert input (Appendix J)
Oncologist visit	451.95	100	2	1	Danish Medicines Council [20] and clinical expert input (Appendix J)
Oncologist nurse visit	277.00	100	1	1	Sygeplejersker a 30 min: Danish Medicines Council [20] and clinical expert input (Appendix J)
Resulting cost per 4-week cycle (DKK)			153.83	116.16	

Table 12. Health-state resource use and cost by health state: remission

Resource use	Unit cost (DKK)	% of patients	Resource use frequency			Source
			Year 1	Years 2-5	Years > 5	
Oncologist visit	451.95	100	1	1	1	Danish Medicines Council [20] and clinical expert input (Appendix J)
Mammo-gram	665	40	1	1	1	DRG: 30PR14 Mammografi, ukompliceret [49] and clinical expert input (Appendix J)
ECHO scan	1,526	1	4	0	0	DRG: 30PR11 UL-scanning, ukompliceret [49] and clinical expert input (Appendix J)
MUGA scan	1,862	99	4	0	0	DRG: 30PR07CT-scanning, ukompliceret [49] and clinical expert input (Appendix J)
Resulting cost per 4-week cycle (DKK)			649	30	30	

CT, computed tomography; ECHO, echocardiogram; MUGA, multigated acquisition.

Table 13. Health-state resource use and cost by health state: local recurrence

Resource use	Unit cost (DKK)	% of patients	Resource use frequency	Source
			Per annum	
Oncologist visit	451.95	100%	5	Danish Medicines Council [20] and clinical expert input (Appendix J)
Mammogram	DKK 665.00	100%	1	DRG: 30PR14 Mammografi, ukompliceret [49] and clinical expert input (Appendix J)
ECHO scan	DKK 1,526.00	1%	4	DRG: 30PR11 UL-scanning, ukompliceret [49] and clinical expert input (Appendix J)
MUGA scan	DKK 1,862.00	99%	4	DRG: 30PR07CT-scanning, ukompliceret, [49] and clinical expert input (Appendix J)
CT scan	DKK 1,862.00	80%	1	DRG: 30PR07CT-scanning, ukompliceret, [49] and clinical expert input (Appendix J)
Resulting cost per 4-week cycle (DKK)			987.41	

CT, computed tomography; ECHO, echocardiogram; MUGA, multigated acquisition.

Table 14. Health-state resource use and cost by health state: distant recurrence, first line and second line

Resource use	Unit cost (DKK)	% of patients	Resource use frequency	Source
			Per annum	
Oncologist visit	451.95	100%	4	Danish Medicines Council [20] and clinical expert input (Appendix J)
ECHO scan	DKK 1,526.00	1%	3	DRG: 30PR11 UL-scanning, ukompliceret [49] and clinical expert input (Appendix J)
MUGA scan	DKK 1,862.00	99%	2	DRG: 30PR07CT-scanning, ukompliceret, [49] and clinical expert input (Appendix J)
PET/MRI	DKK 2,348.00	5%	5	DRG: 30PR03 MR-scanning, ukompliceret [49] and clinical expert input (Appendix J)
CT scan	DKK 1,862.00	95%	5	DRG: 30PR07CT-scanning, ukompliceret [49], and clinical expert input (Appendix J)
Resulting cost per 4-week cycle (DKK)			1,247.65	

CT, computed tomography; ECHO, echocardiogram; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PET, positron emission tomography.

Table 15 presents unit costs of resource use items included in the health-state costs.

Table 15. Monitoring unit costs

Resource	Cost per event (DKK)	Source/notes
Blood test/liver function test	49.15	Danish Medicines Council [20]
ECHO scan	550.00	DRG: 30PR11 UL-scanning, ukompliceret [49]
MUGA scan	4,500.00	Assumed to be same as whole body CT
Mammogram	2,550.00	DRG: 30PR14 Mammografi, ukompliceret [49]
CT scan	4,500.00	DRG: 30PR07CT-scanning, ukompliceret [49],
Surgery visit (consultant lead)	451.95	Danish Medicines Council [20]
Clinical Nurse (specialist)	277.00	Sygeplejersker a 30 min: Danish Medicines Council [20]
District Nurse (home visit)	814.36	Danish Medicines Council [20]
GP visit	1,176.00	Kommunallæger a 30 min: Danish Medicines Council [20]
MRI	5,020.00	DRG: 30PR03 MR-scanning, ukompliceret [49]

CT, computed tomography; ECHO, echocardiogram; GP, general practitioner; MRI, magnetic resonance imaging; MUGA, multigated acquisition.

Clinical expert input suggested that additional follow-up would be required for patients on neratinib treatment. The summary of product characteristics states that while on treatment patients should have liver functions monitored at 1 week, then monthly for the first 3 months and every 6 weeks thereafter. The frequency of the liver function tests in the model was calculated on this basis (Table 16).

Table 16. Additional monitoring frequency for neratinib patients

Resource	Frequency	Duration (years)	Source/notes
GP visit	12	1	Puma data on file [50]
Liver function test	10	1	NERLYNX® SmPC [9]

GP, general practitioner; SmPC, summary of product characteristics.

5.4.3 Adverse reaction unit costs and resource use

Differences in the rates of grades ≥ 3 and 4 AEs between treatment arms were observed in the ExteNET trial data; the model considers those AEs occurring in ≥ 1.0% of all neratinib patients. Table 17 presents AE unit costs. Adverse-event costs for each treatment arm were calculated as the product of the cost of each AE and the proportion of AEs observed in the trial, resulting in an average cost per patient that in turn is applied to the modelled population.

Costs detailed in Table 17 are multiplied by AE frequencies detailed in Table 22 and Table 23. All cost in this analysis except adverse event costs were from a Danish setting. Pierre Fabre did not identify relevant adverse event costs for Denmark. One option would be to use DRG costs based on broad DRG categories. In addition to being broad in the categorisation, these are known to be very rough

estimates. The table below list DRG 2020 costs based on DRG codes previously used for these adverse events in Amgros/DMC assessments of drugs.

Table 17. Adverse-event unit costs and DRG cost for reference

Adverse event	Cost per event (DKK)	Source/notes	DRG 2020 per event cost (DKK)	DRG code
Diarrhoea grade 1-2[a]	2,431.30	NHS Improvement [51]; currency selection based on NICE [52] converted to DKK using the exchange rate of 3 December 2019. Prices of 2020.	5297	DRG 06MA11
Diarrhoea grade 3-4[a]	17,708.44		5297	DRG 06MA11
Vomiting[a]	6,264.88	NHS Improvement [51]; currency selection based on NICE [53]; converted to DKK using the exchange rate of 3 December 2019. Prices of 2020.	5297	DRG 06MA11
Nausea[a]	6,264.88	NHS Improvement [51]; currency selection based on NICE [53]; converted to DKK using the exchange rate of 3 December 2019. Prices of 2020.	2343	DRG06MA98
Abdominal pain	12,285.66	NHS Improvement [51]; converted to DKK using the exchange rate of 3 December 2019. Prices of 2020.	2343	DRG06MA98
Alanine aminotransferase increased	3,445.00	NHS Improvement [51]; currency selection based on NICE [53]; converted to DKK using the exchange rate of 3 December 2019. Prices of 2020.	3149	DRG16MA98
Fatigue	25,641.12	NHS Improvement [51]; converted to DKK using the exchange rate of 3 December 2019. Prices of 2020.	4082	DRG23MA03

NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

5.4.4 Subsequent treatment costs following recurrence

Drug costs used in subsequent lines of treatment were taken from the DMC [40] database of pharmaceutical prices (Table 18) [54]. The types of subsequent treatment received by patients in the ExteNET trial were not captured and thus were not available. Therefore, the subsequent treatments used by the model were based on input from the two Danish clinical experts (Appendix J).

Table 18. Subsequent treatment unit costs

Treatment	Strength (mg)	Pack size	Cost per pack (DKK)	Source
Trastuzumab emtansine (Kadcyla)	100 mg	1 vial	12,189.58	Danish Medicines Agency [40]
	160 mg	1 vial	19,453.95	
Trastuzumab IV (Herceptin)	150 mg	1 vial	3,859.21	
Trastuzumab SC (Herceptin)	600 mg	1 vial	11,114.49	
Pertuzumab IV (Perjeta)	420 mg/14 mL	1 vial	19,635.67	
Capecitabine	500 mg	120 tablets	545.00	
Paclitaxel	6 mg/1 mL	1 vial	201.50	
Lapatinib	250 mg	84 tablets	8,680.08	
Vinorelbine	80 mg	1 tablet	1,650.40	
	30 mg	1 tablets	DKK 618.75	
	20 mg	1 tablets	DKK 412.50	

IV, intravenous; SC, subcutaneous; VAT, value-added tax.

Body surface area (1.80 m^2) and weight (72.64 kg), used to estimate the dose needed of each subsequent treatment, were taken from the ExteNET population [46]. Administration costs associated with subsequent therapy were taken from Olsen et al. [55].

Table 19. Subsequent treatment administration costs

Currency description	Cost (DKK)	Source
Administration with infusion	DKK 835.94	Olsen et al. [55]

To align the treatment shares of the subsequent treatments with current clinical practice in Denmark, clinical opinion was sought (see Appendix J). The clinical experts were provided with the type of subsequent treatment used in the TLV, Norwegian Medicines Agency and NICE appraisals of pertuzumab [16-18] and were asked to assess these treatments in relation to their current clinical practice. Table 20 shows the proportion of each type of subsequent treatment used in the model, as provided by the clinical experts.

Table 20. Subsequent treatment after recurrence

Health state	Regimen	No. of cycles	Cost (DKK)	Treatment share	Weighted cost (DKK)	Health-state cost (DKK)
Non-metastatic recurrence	Trastuzumab IV + paclitaxel	17.0	212,642.65	90%	191,378	224,004
	Pertuzumab + trastuzumab + paclitaxel	17.0	326,257.84	10%	32,626	
First-line early metastatic breast cancer						1,603,644
	Pertuzumab + trastuzumab + vinorelbine	37.4	1,603,644	100%	1,603,644	
Second-line early metastatic breast cancer						632,202
	Trastuzumab emtansine	19.3	632,202.32	100%	632,202	

IV, intravenous; SC, subcutaneous.

5.4.5 Transportation and time costs

Pierre Fabre could not identify a reliable source for the patient time related to health care visits and therefore used a conservative estimate of 0.5h per visit. A longer visit duration (such as a 2 hours per visit) would decrease the incremental cost of neratinib as shown by scenario analyses now provided in the document. Cost will likely vary between the different type of visits but overall, this parameter has a minimal impact on the results.

Visits related to adverse events (see Table 17) were also assumed to be assosicated with transportation and time costs. In the model an estimate of 0.5h per visit was used in the base-case.

Table 21. Transportation and time cost

Unit	Unit cost (DKK)	Source
Transport cost per visit	98.56	Danish Medicines Council[20]
Cost for patient time	179.00	

5.5 Summary table of model inputs

Table 22. Summary table of model inputs

Variable	Value	Reference
Age	51.18 years	Puma data on file [56]
Body surface area m^2	1.80	Puma data on file [56]
Body weight	72.64 kg	Puma data on file [56]
Time horizon	55 years	Assumption
Discount rate: outcomes	4%	DMC guidelines [57]
Discount rate: costs	4%	DMC guidelines [57]
Clinical parameters		
Treatment duration	[redacted] months	Puma data on file [56]
% with local recurrence: placebo	31%	Puma data on file [56]
% with local recurrence: neratinib	18%	Puma data on file [56]
Dose intensity	[redacted]	Puma data on file [56]
Survival model: iDFS	ExteNET: flexible-spline Weibull 1 knot General population mortality: flexible-spline Weibull 2 knots	Details in Section 5.3.1
Survival model: PDRS	Gompertz	Details in Section 5.3.1
Adverse event: incidence of diarrhoea and grade ≥ 3 adverse events		
Diarrhoea grade 1/2: neratinib without prophylaxis	55.1%	Puma data on file [56]
Diarrhoea grade 1/2: neratinib with prophylaxis	47.5%	Puma data on file [56]
Diarrhoea grade 1/2: placebo	32.4%	Puma data on file [56]
Diarrhoea grade 3/4: neratinib without prophylaxis	39.4%	Puma data on file [56]
Diarrhoea grade 3/4: neratinib with prophylaxis	30.7%	Puma data on file [56]
Diarrhoea grade 3/4: placebo	1.1%	Puma data on file [56]
Vomiting: neratinib	3.6%	Puma data on file [56]
Nausea: neratinib	1.4%	Puma data on file [56]
Abdominal pain: neratinib	1.7%	Puma data on file [56]
Fatigue: neratinib	2.0%	Puma data on file [56]

Variable	Value	Reference
Alanine aminotransferase increased: neratinib	1.2%	Puma data on file [56]
Vomiting: placebo	0.3%	Puma data on file [56]
Nausea: placebo	0.3%	Puma data on file [56]
Abdominal pain: placebo	0.2%	Puma data on file [56]
Fatigue: placebo	0.3%	Puma data on file [56]
Alanine aminotransferase increased: placebo	0.3%	Puma data on file [56]
Adverse events: mean number of diarrhoea and grade ≥ 3 adverse events per patient with at least 1 event		
Diarrhoea grade 1/2: neratinib without prophylaxis	17.4	Puma data on file [56]
Diarrhoea grade 1/2: neratinib with prophylaxis	5.1	Puma data on file [56]
Diarrhoea grade 1/2: placebo	6.5	Puma data on file [56]
Diarrhoea grade 3/4: neratinib without prophylaxis	2.7	Puma data on file [56]
Diarrhoea grade 3/4: neratinib with prophylaxis	1.6	Puma data on file [56]
Diarrhoea grade 3/4 -placebo	1.3	Puma data on file [56]
Vomiting: neratinib	1.5	Puma data on file [56]
Nausea: neratinib	1.0	Puma data on file [56]
Abdominal pain: neratinib	1.09	Puma data on file [56]
Fatigue: neratinib	1.15	Puma data on file [56]
Alanine aminotransferase increased: neratinib	1.0	Puma data on file [56]
Vomiting: placebo	1.0	Puma data on file [56]
Nausea: placebo	1.0	Puma data on file [56]
Abdominal pain: placebo	1.0	Puma data on file [56]
Fatigue: placebo	1.5	Puma data on file [56]
Alanine aminotransferase increased: placebo	1.0	Puma data on file [56]
Treatment share local recurrence		
Trastuzumab IV + paclitaxel	90%	Clinical expert input (Appendix J)
Trastuzumab SC + paclitaxel	0%	Clinical expert input (Appendix J)
Pertuzumab + trastuzumab + paclitaxel	10%	Clinical expert input (Appendix J)

Variable	Value	Reference
Treatment share, first-line, distant recurrence		
Trastuzumab IV + vinorelbine	0.0%	Clinical expert input (Appendix J)
Pertuzumab + trastuzumab + vinorelbine	100.0%	Clinical expert input (Appendix J)
Vinorelbine	0.0%	Clinical expert input (Appendix J)
Treatment share, second-line, distant recurrence		
Trastuzumab IV + capecitabine	0%	Clinical expert input (Appendix J)
Trastuzumab emtansine	100%	Clinical expert input (Appendix J)
Lapatinib + capecitabine	0%	Clinical expert input (Appendix J)
Trastuzumab SC + capecitabine	0%	Clinical expert input (Appendix J)
Technology acquisition costs (unit costs)		
Neratinib	DKK 38,399	Danish Medicines Agency [40]
Monitoring unit costs		
GP visit	DKK 1,176.00	Kommunallæger a 30 min: Danish Medicines Council [20]
Oncologist visit	DKK 451.95	Danish Medicines Council [20]
Clinical nurse (specialist)	DKK 277.00	Sygeplejersker a 30 min: Danish Medicines Council [20]
District nurse (home visit)	DKK 814.36	Danish Medicines Council [20]
Mammogram	DKK 665.00	DRG: 30PR14 Mammografi, ukompliceret
ECHO scan	DKK 1,526.00	DRG: 30PR11 UL-scanning, ukompliceret
CT scan	DKK 1,862.00	DRG: 30PR07 CT-scanning, ukompliceret, el. osteodensitometri
MUGA scan	DKK 1,862.00	Assumed to be same as CT.
Health-state costs per 4-week cycle		
Disease-free, year 1-4	DKK 153.83	Calculation
Disease-free, year 4+	DKK 116.16	Calculation
Remission, year 1	DKK 649	Calculation
Remission, year 2-5	DKK 30	Calculation
Remission, year 6+	DKK 30	Calculation
Local recurrence, per annum	DKK 987.41	Calculation
Distant recurrence: first line and second line	DKK 1,247.65	Calculation

Variable	Value	Reference
Adverse-event unit costs		
Diarrhoea grade 1-2	2,431.30	NHS Improvement [51]; currency selection based on NICE [52] converted to DKK using the exchange rate of 3 December 2019. 2020 years prices.
Diarrhoea grade 3-4	17,708.44	NHS Improvement [51]; currency selection based on NICE [52] converted to DKK using the exchange rate of 3 December 2019. 2020 years prices.
Vomiting[a]	6,264.88	NHS Improvement [51]; currency selection based on NICE [53]; converted to DKK using the exchange rate of 3 December 2019. 2020 years prices.
Nausea[a]	6,264.88	NHS Improvement [51]; currency selection based on NICE [53]; converted to DKK using the exchange rate of 3 December 2019. 2020 years prices.
Abdominal pain	12,285.66	NHS Improvement [51]; converted to DKK using the exchange rate of 3 December 2019. 2020 years prices.
Alanine aminotransferase increased	3,445.00	NHS Improvement [51]; currency selection based on NICE [53]; converted to DKK using the exchange rate of 3 December 2019. 2020 years prices.
Fatigue	25,641.12	NHS Improvement [51]; converted to DKK using the exchange rate of 3 December 2019. 2020 years prices.
Subsequent therapy cost		
Trastuzumab emtansine (Kadcyla)	DKK 12,189.58	Danish Medicines Agency [40]
Trastuzumab emtansine (Kadcyla)	DKK 19,453.95	Danish Medicines Agency [40]
Trastuzumab IV (Herceptin)	DKK 3,859.21	Danish Medicines Agency [40]
Trastuzumab SC (Herceptin)	DKK 11,114.49	Danish Medicines Agency [40]
Pertuzumab IV (Perjeta)	DKK 19,635.67	Danish Medicines Agency [40]
Capecitabine	DKK 545.00	Danish Medicines Agency [40]
Paclitaxel	DKK 201.50	Danish Medicines Agency [40]

CT, computed tomography; ECHO, echocardiogram; GP, general practitioner; iDFS, invasive disease-free survival; IV, intravenous; MUGA, multigated acquisition; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PDRS, post-distant recurrence survival; SC, subcutaneous; SD, standard deviation; SE, standard error.

6 Economic results

6.1 Cost analysis results

The results of the cost analyses (Table 23) show that treatment with neratinib compared with no extended adjuvant treatment would result in an incremental cost of DKK 131,902. The increased cost of treatment with neratinib is to a large degree offset by reduced costs for subsequent treatments due to the improved long-term clinical outcome for patients treated with neratinib.

Table 23. Cost analysis results

Mean total expected lifetime costs, per patient (DKK, discounted)	Neratinib	Placebo	Incremental
Cost of study treatment			
Study drug	272,622	0	272,622
Diarrhoea prophylaxis	561	0	561
Pharmacy (dispensing cost)	26	0	26
Concomitant endocrine therapy	2,027	1,942	85
Total drug treatment costs	275,237	1,942	273,294
Subsequent treatment			
Local recurrence	3,625	11,794	-8,169
Distant recurrence	183,414	337,911	-154,497
Total subsequent treatment costs	187,039	349,704	-162,665
Health-state costs			
Disease-free	25,312	23,298	2,014
Local recurrence	211	706	-496
Remission	54	171	-117
Distant recurrence	4,503	8,378	-3,875
Total health-state costs	30,080	32,553	-2,473
Other costs			
Additional monitoring	14,555	0	14,555
Adverse events	13,761	4,495	9,266
Total other costs	28,315	4,495	23,820
Patient costs	8,840	8,914	-74
Total	**529,511**	**397,609**	**131,902**

6.1.1.1 Sensitivity and scenario analysis

One-way sensitivity analysis investigating the impact of variation in the model parameters and scenario analyses investigating the impact of assumptions and choices regarding data input in the model were conducted. Table 24 shows the 10 parameters identified to have the largest impact on the incremental cost from the one-way sensitivity analysis. As shown, parameters related to the duration and dose intensity for neratinib treatment resulted in the biggest impact followed by parameters related to distant recurrence mortality and risk of recurrence after remission.

Table 24. Sensitivity analyses

Parameter	Base-case value	Analysis	Values for deterministic sensitivity analysis	Incremental cost per (DKK)
Base-case analysis				**131,902**
Neratinib Treatment Duration	[redacted]	Lower	[redacted]	104,637
		Higher	[redacted]	159,167
Relative Actual Dose Intensity (%)	[redacted]	Lower	[redacted]	104,637
		Higher	[redacted]	159,167
Distant Recurrence >12 Months	2,235,847	Lower	2,012,262	145,305
		Higher	2,459,431	118,500
Distant Recurrence <12 Months	2,235,847	Lower	2,012,262	133,950
		Higher	2,459,431	129,855
Frequency: Neratinib Additional Clinic Visits	12.000	Lower	10.800	129,595
		Higher	13.200	133,033
Duration: Neratinib Additional Clinic Visits	1.0	Lower	0.90	129,595
		Higher	1.10	133,033
Diarrhoea Grade 3/4 - Incidence - Neratinib with prophylaxis	0.31	Lower	0	131,051
		Higher	0	132,754
Diarrhoea Grade 3/4 - Events - Neratinib with prophylaxis	1.55	Lower	1.40	131,051
		Higher	1.71	132,754
AE Costs - Direct - Diarrhea grade 3/4 - Neratinib	17,708	Lower	15,938	131,084
		Higher	19,479	132,721
Local Recurrence Cost Annual	224,004	Lower	201,604	132,719
		Higher	246,405	131,085

The scenario analyses tested the impact of alternative choices regarding iDFS extrapolation and duration of treatment effect. As shown in Table 25, the results were stable across all scenarios tested with the alternative distribution and relaxing the assumption of proportional hazards for iDFS having the largest impact on the incremental cost.

Table 25. Scenario analyses

Scenario	Base-case assumption	Scenario assumption	Incremental cost (DKK)
Base case			131,902
Distribution for iDFS extrapolation	Flexible-spline Weibull 1 knot (proportional hazards)	Stratified generalised gamma (non-proportional hazards)	164,750
HERA data for extrapolation	Only ExteNET data used for extrapolation	HERA data used for extrapolation beyond trial	130,488
Treatment effect waning	Continued treatment effect	Treatment effect waning to HR = 1 at 214 months	148,221
Drug wastage included	No wastage	Half pack wasted per patient	151,102
Patient time per visit	0.5 hours per visit	2 hours per visit	131,513
Administration cost according to DRG code 04MA98	Based on Olsen et al	Based on DRG	127,464
Adverse events according to DRG	Adverse events based on NHS detailed costing	Adverse event costs based on DRG codes from previous DMC assessments	125,517

iDFS, invasive disease-free survival.

6.2 Budget-impact results

The results of the budget-impact analysis (Table 26) show that approximately 330 patients could be eligible for neratinib treatment per year and that 16 patients will be treated with neratinib the first year, increasing to 82 patients by year 5 (Table 27). Based on these patient numbers, the total budget impact of neratinib in year 1 would be DKK 4,512,450, increasing to DKK 19,417,254 by year 5 (Table 28).

Table 26. Patient numbers

Population	No. of patients	Calculation	Source
Number of adult females diagnosed with breast cancer in Denmark in 2018	4,628	–	GLOBOCAN [59]
Number of patients who are stage I-III	4,281	92.50%	Walters et al. [60]

Population	No. of patients	Calculation	Source
Number of patients with HER2+ breast cancer	471	11.00%	Data from Ann Søegaard Knop; In line with 10%-15% from https://www.cancer.dk/
Number of patients with HER2+/HR+ breast cancer	330	70.00%	Data from Ann Søegaard Knop; Howlader et al. [4]

HER2+, human epidermal growth factor receptor 2 positive; HR+, hormone receptor–positive.

Table 27. Market share and expected patient numbers: neratinib

Pharmaceutical	Year 1	Year 2	Year 3	Year 4	Year 5
Neratinib market share	5%	10%	15%	20%	25%
Neratinib patient numbers	16	33	49	66	82

Table 28. Budget impact: neratinib years 1-5

	Year 1	Year 2	Year 3	Year 4	Year 5
If neratinib is not adopted					
Drug treatment costs (DKK)	128,350	250,321	367,704	482,087	594,204
Subsequent treatment costs (DKK)	21,275,231	43,819,507	58,450,471	69,298,448	78,268,972
Health-state costs (DKK)	668,677	1,486,016	2,330,982	3,177,620	4,017,248
Other costs (DKK)	1,481,706	1,481,706	1,481,706	1,481,706	1,481,706
Total cost (DKK)	**23,553,965**	**47,037,550**	**62,630,862**	**74,439,861**	**84,362,130**
If neratinib is adopted					
Drug treatment costs (DKK)	4,631,294	9,256,384	13,877,154	18,495,249	23,111,446
Subsequent treatment costs (DKK)	20,906,372	42,693,728	56,297,897	65,898,113	73,420,606
Health-state costs (DKK)	667,384	1,479,011	2,313,803	3,145,910	3,966,651
Other costs (DKK)	1,875,044	2,268,382	2,661,720	3,055,058	3,448,396
Total cost (DKK)	**28,080,095**	**55,697,505**	**75,150,574**	**90,594,330**	**103,947,099**
Budget impact					
Drug treatment costs (DKK)	4,502,944	9,006,063	13,509,450	18,013,162	22,517,242
Subsequent treatment costs (DKK)	-368,859	-1,125,778	-2,152,574	-3,400,335	-4,848,366
Health-state costs (DKK)	-1,293	-7,005	-17,179	-31,710	-50,597
Other costs (DKK)	393,338	786,676	1,180,014	1,573,352	1,966,690
Total budget impact (DKK)	**4,526,130**	**8,659,955**	**12,519,712**	**16,154,469**	**19,584,969**

7 Discussion on the submitted documentation

7.1 Interpretation and conclusions of economic evidence

This is the first cost analysis undertaken for neratinib for the treatment of early HER2+/HR+ breast cancer in the extended adjuvant setting from a Danish perspective. The analysis showed that neratinib provide clinical value at a reasonable cost. The analysis is likely to be directly applicable to clinical practice in Denmark as follows:

- The patient populations in ExteNET and CONTROL used in the economic analysis are likely to be reflective of patients in Denmark.
- The economic model structure is in line with accepted oncology models from previous breast cancer treatment submissions to HTA authorities and therefore is considered appropriate for decision making. The resource use and costs in the analysis have been validated by Danish clinicians (Appendix J) and were sourced from Danish-based sources and previous HTA submissions [16-18, 54, 61-63].

7.2 Strengths and limitations of the economic evaluation

The economic model used patient-level data from the ExteNET trial, which reported 5 years of follow-up that included initial treatment patterns for both neratinib and placebo. Although 5 years is considered a long follow-up, additional survival extrapolations were essential to estimate iDFS and PDRS within the current model's time horizon. Extensive work was undertaken to investigate possible options of including a combination of trial data and external evidence, to ensure these extrapolations were as robust as possible. The alternative methods and data sets used in the survival extrapolations resulted in highly consistent predictions, strengthening the validity of the modelled data. Limitations in the form of availability of mature OS data per treatment arm were overcome by using the blinded PDRS data from the ExteNET trial, assuming equal PDRS for both arms. In terms of resource utilisation, inputs were validated by clinical experts and identified from Danish sources. As detailed in this report and supported by the scenario analyses performed to investigate alternative cost-assumptions, neratinib is a cost-effective treatment of early HER2+/HR+ breast cancer in the extended adjuvant setting from the Danish perspective.

8 References

[1] Slamon D, Eiermann W, Robert N. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC3T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC3TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. 38th Annual CTRC-AACR San Antonio Breast Cancer Symposium. San Antonio, TX; 2005.

[2] NORDCAN. Standardised rates by cancers (incidence/mortality)—Finland. Association of the Nordic Cancer Registries 2016. Available at: http://www-dep.iarc.fr/NORDCAN/english/Table3.asp?registry=246&sex=2&type=1&age_from=1&age_to=18&sort=2&period=2016&submit=Execute. Accessed: 8 August 2018.

[3] Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019 Jun 4(30):1194-220.

[4] Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014 Apr 28;106(5).

[5] Finnish Breast Cancer Group. National breast cancer recommendation for diagnostics and care. 2019. Available at: https://rintarauhaskirurgia-yhdistysavain-fi-bin.directo.fi/@Bin/e042295d72bd68624695846d9319b8e0/1567676459/application/pdf/177356/Rintasy%c3%b6v%c3%a4n%20valtakunnallinen%20diagnostiikka-%20ja%20hoitosuositus%205.2019.pdf. Accessed: 5 September 2019.

[6] Regional health care and rehabilitation chains in Southwest Finland. Treatment pathway for breast cancer patient. 2019. Available at: http://hoitoreitit.vsshp.fi/toimialueiden_prosessit/t7/rintasyopa2/rintasyopa2_Prosessitaso.htm. Accessed: 2 September 2019.

[7] Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the Herceptin Adjuvant (HERA) trial. Lancet. 2017 Mar 25;389(10075):1195-205.

[8] Zhao B, Zhao H, Zhao J. Impact of hormone receptor status on the efficacy of HER2-targeted treatment. Endocr Relat Cancer. 2018 Jun;25(6):687-97.

[9] NERLYNX® SmPC. NERLYNX® (neratinib) summary of product characteristics. European Medicines Agency; 22 October 2019. Available at: https://www.ema.europa.eu/documents/product-information/nerlynx-epar-product-information_en.pdf. Accessed: 28 November 2019.

[10] Council DM. Medicinrådets anbefaling vedrørende pembrolizumab i kombination med kemoterapi som mulig standardbehandling af planocellulær ikke-småcellet lungekræft. 2019.

[11] Danish Medicine Council. Baggrund for Medicinrådets anbefaling vedrørende atezolizumab i kombination med abpaclitaxel som mulig standardbehandling til lokalt fremskreden eller metastatisk triple-negativ brystkræft. 2020.

[12] Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. March 2013. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf. Accessed: 30 November 2018.

[13] Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU technical support document 19: partitioned survival analysis for decision modelling in health care: a critical review. 2017. Available at: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/06/Partitioned-Survival-Analysis-final-report.pdf. Accessed: 29 November 2018.

[14] EUnetHTA. Guideline: endpoints used in relative effectiveness assessment: surrogate endpoints. 2015. Available at: https://www.eunethta.eu/wp-content/uploads/2018/03/surrogate_endpoints.pdf. Accessed: 4 February 2019.
[15] Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012 Apr 18(4):CD006243.
[16] The Norwegian Medicines Agency (NoMA). Pertuzumab (Perjeta) in combination with trastuzumab and chemotherapy for adjuvant treatment of early HER-2 positive breast cancer. 14 January 2019. Available at: https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/P/Perjeta_adjuvant_brystkreft_2019.pdf. Accessed: 14 October 2019.
[17] NICE. Pertuzumab for adjuvant treatment of early HER2-positive breast cancer (TA569). National Institute for Health and Care Excellence 2019. Available at: https://www.nice.org.uk/guidance/ta569. Accessed: 9 May 2019.
[18] Tandvårds- och läkemedelsförmånsverket (TLV). Underlag för beslut i landstinen Perjeta (pertuzumab) prescribing information. 2018.
[19] Chan A, Delaloge S, Holmes F, Moy B, Iwata H, Harker G, et al. Neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ breast cancer: 3-year analysis from a phase 3 randomized, placebo-controlled, double-blind trial (ExteNET). Cancer Res. 2016;76(4 suppl):S5-02.
[20] Danish Medicines Council. Værdisætning af enhedsomkostninger. 2020.
[21] Guyot P, Ades AE, Beasley M, Lueza B, Pignon JP, Welton NJ. Extrapolation of survival curves from cancer trials using external information. Med Decis Making. 2017 May;37(4):353-66.
[22] Jackson C, Stevens J, Ren S, Latimer N, Bojke L, Manca A, et al. Extrapolating survival from randomized trials using external data: a review of methods. Med Decis Making. 2017 May;37(4):377-90.
[23] O'Sullivan CC, Bradbury I, Campbell C, Spielmann M, Perez EA, Joensuu H, et al. Efficacy of adjuvant trastuzumab for patients with human epidermal growth factor receptor 2-positive early breast cancer and tumors ≤ 2 cm: a meta-analysis of the randomized trastuzumab trials. J Clin Oncol. 2015 Aug 20;33(24):2600-8.
[24] Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, et al. 2 Years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. Lancet. 2013 Sep 21;382(9897):1021-8.
[25] Eurostat Database. Eurostat database. 2019. Available at: http://ec.europa.eu/eurostat/data/database?node_code=demo_mlexpec. Accessed: 6 December 2019.
[26] Statistics Denmark. Life tables. 2020. Available at: https://www.dst.dk/en/Statistik/nyt/relateret?eid=10015. Accessed: 6 December 2019.
[27] Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017 Nov 9;377(19):1836-46.
[28] Puma data on file. ExteNET: Figure 14.2.9.2. Kaplan-Meier plot of analysis of overall survival post distant recurrence for subjects with HR+ and completed trastuzumab ≤ 1 year for the ITT population. 2018.
[29] Llombart-Cussac A, Pivot X, Biganzoli L, Cortes-Funes H, Pritchard KI, Pierga JY, et al. A prognostic factor index for overall survival in patients receiving first-line chemotherapy for HER2-negative advanced breast cancer: an analysis of the ATHENA trial. Breast. 2014 Oct;23(5):656-62.
[30] Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? Br J Cancer. 2015 Apr 28;112(9):1445-51.
[31] Puma data on file. ExteNET: Figure 14.2.8.2 Kaplan-Meier plot of analysis of overall survival post distant recurrence for subjects with HR+ and completed trastuzumab ≤ 1 year by time of distant recurrence for the ITT population. 2018.

[32] Puma data on file. ExteNET: Figure 14.2.7.2. Kaplan-Meier plot of analysis of overall survival post distant recurrence for subjects with HR+ and completed trastuzumab ≤ 1 year who had distant recurrence ≤ 12 months vs >12 months from randomization for the ITT population. 2018.
[33] Puma data on file. Survival analysis: analysis of time to recurrence group considered as two separate subgroups. 2018.
[34] Puma data on file. ExteNET: Table 14.2.9.18.1. 5-year iDFS events by site, HR+ < 1 yr. 2018.
[35] Puma data on file. ExteNET: Table 14.2.9.18.2 2-year iDFS events by site, HR+ < 1 yr. 2018.
[36] NICE. Final scope for ID981: neratinib for treating early hormone receptor-positive HER2-positive breast cancer after adjuvant trastuzumab. National Institute for Health and Care Excellence; 16 November 2018. Available at: https://www.nice.org.uk/guidance/gid-ta10107/documents/final-scope. Accessed: 7 December 2018.
[37] NICE. Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab (TA612). 2019. Available at: https://www.nice.org.uk/guidance/ta612. Accessed: 6 December 2019.
[38] TLV. Underlag för beslut om subvention. Nerlynx. Tand- och läkemedelsförmånsverket 2020.
[39] Hamilton SN, Tyldesley S, Li D, Olson R, McBride M. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radiation to local radiation? Int J Radiat Oncol Biol Phys. 2015 Apr 1;91(5):977-85.
[40] Danish Medicines Agency. Medicinpriser.dk. 2020.
[41] Puma data on file. ExteNET: Table 14.3.0.1.4. Summary of investigational product exposure in HR+ < 1 year. 2018.
[42] Danish Medicines Council. The Council of Medicine's recommendation regarding pertuzumab in combination with trastuzumab as possible standard treatment for adjuvants treatment of early HER2 + breast cancer. 10 October 2018. Available at: https://medicinraadet.dk/media/10024/medicinraadets-anbefaling-vedr-pertuzumab_tidlig-her2plus-brystkraeft_vers10.pdf. Accessed: 9 December 2019.
[43] NICE. Technology appraisal guidance [TA484]: nivolumab for previously treated non-squamous non-small-cell lung cancer. National Institute for Health and Care Excellence 2017. Available at: https://www.nice.org.uk/guidance/ta484/history. Accessed: 9 July 2018.
[44] NICE. Single technology appraisal: nivolumab for treating metastatic, squamous, non-small-cell lung cancer after chemotherapy [ID811]. National Institute for Health and Care Excellence 2017. Available at: https://www.nice.org.uk/guidance/ta483/documents/committee-papers-5. Accessed: 1 February 2019.
[45] NICE. Single technology appraisal: encorafenib with binimetinib for unresectable or metastatic BRAF V600 mutation-positive melanoma [ID923]. National Institute for Health and Care Excellence 2018. Available at: https://www.nice.org.uk/guidance/gid-ta10217/documents/committee-papers. Accessed: 1 February 2019.
[46] Puma data on file. ExteNET: Table 14.3.0.1.4. Summary of investigational product exposure for patients who completed prior adjuvant trastuzumab within 1 year from randomization and hormone receptor positive, safety population. 2018.
[47] webapoteket.dk. webapoteket.dk. 2020. Available at: https://www.webapoteket.dk/. Accessed: 01 July 2020.
[48] NICE. Technology appraisal guidance [TA509]: Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer. National Institute for Health and Care Excellence 2018. Available at: https://www.nice.org.uk/guidance/ta509. Accessed: 18 January 2018.
[49] Sundhetsdatastyrelsen. DRG-takster 2020. https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2020. 2020.
[50] Puma data on file. Meeting minutes: external expert meeting to discuss development of cost-utility model for neratinib in HER2+ breast cancer for puma biotechnologies. 2017.

[51] NHS Improvement. National schedule of reference costs—year 2017-18; NHS Trust and NHS Foundation Trusts. 2018. Available at: https://improvement.nhs.uk/resources/reference-costs/. Accessed: 18 January 2019.
[52] NICE. Technology appraisal guidance [TA347]: nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer. National Institute for Health and Care Excellence 2015. Available at: https://www.nice.org.uk/guidance/ta347. Accessed: 18 January 2019.
[53] NICE. Technology appraisal guidance [TA465]: olaratumab in combination with doxorubicin for treating advanced soft tissue sarcoma. National Institute for Health and Care Excellence 2017. Available at: https://www.nice.org.uk/guidance/ta465. Accessed: 18 January 2019.
[54] Kela (Kansaneläkelaitos). Söktjänst för läkemedel. 2019. Available at: https://asiointi.kela.fi/laakekys_app/LaakekysApplication?kieli=sv. Accessed: 4 December 2019.
[55] Olsen J, Jensen KF, Olesen DS, Knoop A. Costs of subcutaneous and intravenous administration of trastuzumab for patients with HER2-positive breast cancer. J Comp Eff Res. 2018 May;7(5):411-9.
[56] Puma data on file. Clinical study report: 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. 3144A2-3004-WW. 20 April 2016.
[57] Danish Medicines Council. Metodevejledning for omkostningsanalyser af nye lægemidler og indikationer i hospitalssektoren. 2020.
[58] Aleris-hamlet. Priser for røntgen og scanning. 2020. Available at: https://www.aleris-hamlet.dk/hospital/rontgen-og-scanning/priser-rontgen-og-scanning/. Accessed: 6 December 2019.
[59] GLOBOCAN. Estimated number of new cases in 2018, Denmark, females. International Agency for Research on Cancer 2019. Available at: https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=continents&population=900&populations=208&key=asr&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1. Accessed: 9 August 2019.
[60] Walters S, Maringe C, Butler J, Rachet B, Barrett-Lee P, Bergh J, et al. Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. Br J Cancer. 2013 Mar 19;108(5):1195-208.
[61] Synlab. Prislista undersökningar. 2019.
[62] Ålands Hälso- och sjukvård (ÅHS). Ersättningar och övriga avgifter. 2019.
[63] Södra Österbottens sjukvårdsdistrikt (SÖS). Prislista 2018. 2018. Available at: www.epshp.fi/files/7210/Hinnasto_isotoopit_2018.docx. Accessed: 6 December 2019.

Medicinrådet

Medicinrådets protokol for vurdering af neratinib til behandling af ER+ og HER2+ brystkræft

Versionsnr.: 1.0

Om Medicinrådet

Medicinrådet er et uafhængigt råd etableret af Danske Regioner.

Medicinrådet vurderer, om nye lægemidler og indikationsudvidelser skal anbefales som mulig standardbehandling. Medicinrådet udarbejder også behandlingsvejledninger og rekommandationer for anvendelse af medicin på sygehusene. Derudover kan Medicinrådet tage andre typer sager op, der handler om medicinanvendelse.

Om protokollen

Protokollen beskriver, hvordan Medicinrådet vil foretage vurderingen af lægemidlets værdi for patienterne. Den indeholder et eller flere kliniske spørgsmål, som den ansøgende virksomhed skal besvare i deres endelige ansøgning. Til hvert spørgsmål knytter sig en definition af patientgruppen, det lægemiddel vi undersøger, den behandling vi sammenligner med og effektmålene. Udover de(t) kliniske spørgsmål indeholder protokollen også en beskrivelse af, hvordan litteratursøgning, -selektion og databehandling skal foregå.

Protokollen er udarbejdet med udgangspunkt i Håndbog for Medicinrådets proces og metode, som du kan finde på Medicinrådets hjemmeside under siden Metoder, og den ansøgende virksomheds foreløbige ansøgning, der fortæller, hvilke data der findes for lægemidlet.

Fremkommer der nye og væsentlige oplysninger i sagen af betydning for protokollens indhold, kan Medicinrådet tage protokollen op til fornyet behandling. Det samme gælder, hvis der er begået væsentlige fejl i forbindelse med sagsbehandlingen vedrørende protokollen. Hvis Medicinrådet foretager ændringer i protokollen, vil ansøgende virksomhed få besked.

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Indhold

1 Begreber og forkortelser

CI:	Konfidensinterval
DBCG	*Danish Breast Cancer Cooperative Group*
EMA:	*European Medicines Agency*
EORTC-QLQ-BR23:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Breast 23 module*
EORTC-QLQ-C30:	*European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire-Core 30*
EPAR:	*European Public Assessment Report*
ER:	Østrogenreceptor (*estrogen receptor)*
GRADE:	System til vurdering af evidens (*Grading of Recommendations Assessment, Development and Evaluation*)
ER:	Østrogenreceptor (*estrogen receptor*)
HER2:	Human epidermal vækstfaktorreceptor 2 (*human epidermal growth factor receptor 2*)
HR:	*Hazard ratio*
OR:	*Odds ratio*
RR:	Relativ risiko

2 Introduktion

Protokollen er udarbejdet, fordi Medicinrådet har modtaget en foreløbig ansøgning fra Pierre Fabre Pharma, som ønsker, at Medicinrådet vurderer neratinib til patienter med tidlige stadier af HR+ og HER2+ brystkræft, som har modtaget og afsluttet et års adjuverende trastuzumab-baseret behandling for mindre end et år siden. Vi modtog den foreløbige ansøgning den 12. december 2019.

2.1 ER+ og HER2+ brystkræft

Brystkræft er den hyppigste kræftform hos kvinder verden over og forekommer oftest hos kvinder over 50 år. I Danmark bliver omkring 4.700 patienter årligt diagnosticeret med brystkræft, og cirka 64.000 patienter lever med diagnosen brystkræft [1].

Sygdommen kan opdeles i fire undertyper afhængig af, om kræftcellerne er hormonfølsomme, dvs. om de udtrykker østrogenreceptor (ER) og/eller human epidermal vækstfaktorreceptor 2 (HER2). Tumorer der er ER negative (ER-), er mere aggressive end de ER positive tumorer (ER+). HER2 positive (HER2+) tumorer er ligeledes mere aggressive end HER2 negative (HER2-), og blandt de HER2 positive får patienter med ER negativ sygdom tidligere recidiv end patienter med ER positiv sygdom. Patienterne testes rutinemæssigt for både ER og HER2 status ved diagnosetidspunktet. HER2 status testes ved immunhistokemi. I tilfælde hvor resultatet ikke er entydigt, kan in situ hybridisering benyttes i henhold til patologiafsnittet under DBCGs retningslinjer [2]. ER status testes ved immunhistokemi. Hvis over 1 % af tumorcellerne er positive for ER, benævnes tumoren som ER+. Af de 4.700 patienter, som årlig diagnosticeres med brystkræft i Danmark, vil ca. 4.400 have tidlig brystkræft (dvs. patienterne har ikke fjernmetastaser). Af disse patienter vil ca. 15 % være HER2+. Af de HER2+ patienter er ca. 70 % ER+, hvilket vil sige, at der er årligt, er ca. 460 af de danske patienter er ER+/HER2+.

Stadier af brystkræft vurderes ud fra det internationalt anerkendte standardiserede *Tumor, Node, Metastasis* (TNM)-klassifikation. Tumorklassificeringen baseres på en vurdering af den primære tumors størrelse og om den primære tumor har indvækst i omkringliggende væv (T0-T4), samt i hvor høj grad tumoren har bredt sig til regionære lymfeknuder (N0-N3), og om der er fjernmetastaser (M1) se tabel 1.

TNM-klassifikation er i høj grad korreleret med prognose. Således viste et studie, at 98,7 % af patienter med HER2+ brystkræft og med N0 og primær tumor < 3 cm, som havde modtaget adjuverende HER2-rettet behandling sammen med adjuverende paclitaxel, ikke havde oplevet tilbagefald efter 3 års opfølgning [3]. Et andet studie af patienter med HER2+ operabel brystkræft viste, at patienter med N0 sygdom, havde en god prognose, dvs. over 96 % af patienter var sygdomsfrie ved 4 års opfølgning [4].

Tabel 1: TNM-klassifikation af kræft

	Stadie	**Definition**
Primær tumor	T0	Ingen primær tumor
	T1	Vurdering af størrelse samt omfang af primær tumor, jo højere kategori jo større tumor. Ved T4 tumorer er der indvækst i muskel og/eller, hud, eller der er tale om inflammatorisk brystkræft.
	T2	
	T3	
	T4a Indvæks i brystmusklen T4b Indvækst i huden T4c Indvækst i både hud og brystmusklen T4d Inflammatorisk brystkræft	

	TX	Primær tumor kan ikke vurderes.
Lymfeknude involvering	N0	Ingen spredning til nærliggende lymfeknuder
	N1	Højere kategori reflekterer spredning til flere lymfeknuder i armhulen eller til lymfeknuder langs kravebenet eller brystbenet.
	N2	
	N3	
	NX	Lymfeknuderne kan ikke vurderes.

Det studie der bedst belyser overlevelsen for patienter med HER2+ brystkræft (HERA-studiet), er et studie af adjuverende trastuzumab-behandling, som viser, at 79 % af patienterne var i live efter 12 år [5]. Fagudvalget forventer dog, at overlevelsen kan være stigende, da den nuværende generelle brystkræftbehandling inklusiv kirurgi, strålebehandling og systemisk behandling, er bedre end da HERA-studiet blev udført.

2.2 Neratinib

Forventet EMA-indikation:
Neratinib is indicated for the extended adjuvant treatment of adults with early-stage HR+, HER2+ breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago.

Neratinib er en tyrosin kinase hæmmer rettet mod HER1-, HER-2 og HER-4. Neratinib binder til og hæmmer receptorerne hvilket hæmmer væksten af tumor. Neratinib gives oralt, og den anbefalede dosis er 240 mg en gang dagligt, hvilket gives som 6 tabletter a 40 mg. Neratinib gives i op til et år.

Patienter med tidlige stadier af HR+ og HER2+ brystkræft, som har modtaget og afsluttet et års adjuverende trastuzumab-baseret behandling for mindre end et år siden, er kandidater til adjuverende behandling med neratinib, uanset deres TNM-status.

Hvis neratinib bliver anbefalet vil den nuværende behandlingsrækkefølge være uændret, da neratinib indplaceres efter forebyggende behandling med trastuzumab (se afsnit 2.3).

Neratinib er ikke godkendt til andre indikationer end brystkræft.

2.3 Nuværende behandling

Patienter med tidlig HER2+ brystkræft egnet til (neo)adjuverende behandling, vil oftest modtage en kombination af medicinsk behandling, operation og strålebehandling, jf. gældende guidelines fra DBCG og behandlingsvejledningen udarbejdet af RADS.

HER2+ patienter tilbydes som regel behandling med kemoterapi og HER2 antistoffer afhængigt af bl.a. hvilket stadie af brystkræft de har, alder, komorbiditet og prognose. Kemoterapi og HER2-rettet behandling kan gives såvel før operation i bryst og lymfeknuder (neoadjuvernede) eller efter operation (adjuverende). Neoadjuverende og adjuverende behandling med kemoterapi og HER2 antistoffer anses som ligeværdige behandlingsmuligheder for patienter med operabel brystkræft [4], dog med flere patienter der opnår brystbevarende operation, når der gives neoadjuverende behandling. For patienter med lokal fremskreden brystkræft er der en bedre prognose ved at give neoadjuvende behandling. Alle patienter med tidlig HER2+ brystkræft kan være kandidater til neratinib.

Trastuzumab gives til i alt et års behandling. Efter operation i bryst og lymfeknuder tilbydes patienter med ER+ sygdom desuden antihormonbehandling. Dette tilbud er uafhængigt af, om kemoterapi er givet først eller sidst. Når kemoterapi gives sidst, opstartes antihormonbehandling først efter afslutning af kemoterapi.

(Neo)adjuverende kemoterapi til behandling af tidlig brystkræft

Patienter med tidlig HER2+ brystkræft egnet til enten neoadjuverende eller adjuverende behandling, vil oftest modtage en kombination af medicinsk behandling, bestående af kemoterapi i kombination med pertuzumab (hvis det gives neoadjuverende) og trastuzumab ved opstart af taxanbaseret kemoterapi, efterfulgt af operation og evt. strålebehandling, jf. gældende guidelines fra DBCG. Pertuzumab og trastuzumab er begge antistoffer der genkender HER2.

Efter operation gives adjuverende behandling med trastuzumab, så patienter i alt modtager 17 serier. Der gives strålebehandling, hvis der er udført brystbevarende operation og/eller ved spredning til lymfeknuder [6].

HER2+ patienter, hvis tumor også er ER+, modtager i tillæg til den HER2+ rettede behandling, også antihormonbehandling. Antihormon efterbehandling består overordnet af tamoxifen i 10 år for de kvinder, der er præ-menopausale. Tamoxifen er en selektiv østrogen receptor modulator. For kvinder, der er post-menopausale, består behandlingen af en aromatasehæmmer (AI) i fem år. AI hæmmer dannelsen af binyredannet østrogen, hvorved østrogenniveauet i kroppen falder. Der findes forskellige aromatasehæmmere, der er vurderet at være ligestillede, og i Danmark anvender man letrozol.

Målet med den (neo)adjuverende behandling er at forebygge tilbagefald.

3 Kliniske spørgsmål

Medicinrådet bruger kliniske spørgsmål til vores vurderinger af lægemidlers værdi for patienterne. Til hvert spørgsmål knytter sig en definition af patientgruppen (population), af det lægemiddel vi undersøger (interventionen), af den behandling vi sammenligner med (komparator(er)) og af effektmålene.

3.1 Klinisk spørgsmål

Hvilken værdi har neratinib sammenlignet med placebo for patienter med ER+ og HER2+ brystkræft?

Population
Patienter med ER+ og HER2+ brystkræft som har modtaget og afsluttet adjuverende trastuzumab-baseret behandling for mindre end et år siden.

Intervention
Neratinib, 240 mg en gang dagligt

Komparator
Placebo

Effektmål
Effektmålene fremgår af tabel 2 og er beskrevet i afsnit 3.2.

3.2 Effektmål

Medicinrådet mener, at vurderingen af lægemidlets værdi bliver bedst understøttet af de effektmål, vi har nævnt i tabel 2. For hver effektmål har Medicinrådet fastsat en mindste klinisk relevant forskel (MKRF). I det følgende afsnit argumenterer vi for valget af effektmål og de mindste klinisk relevante forskelle.

Tabel 2. Effektmål.

Effektmål	Vigtighed	Effektmålsgruppe	Måleenhed	Mindste klinisk relevante forskel
Samlet overlevelse (OS)	Kritisk	Dødelighed/ overlevelse	OS-rate ved 10 år	3 %-point
IDFS	Vigtig	Livskvalitet, alvorlige symptomer og bivirkninger	IDFS-rate ved 5 år	5 %-point
Bivirkninger	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Andel patienter, der oplever en eller flere grad 3-4 bivirkninger,	5 %-point
			Gennemgang af bivirkningsprofil	Narrativ vurdering
Livskvalitet	Kritisk	Livskvalitet, alvorlige symptomer og bivirkninger	Gennemsnitlig ændring over tid	Forskel i ændring svarende til de validerede mindste klinisk relevante forskelle for de involverede livskvalitetsspørgeskemaer (se nedenfor)

For alle effektmål ønsker vi data med længst mulig opfølgningstid, med mindre andet er angivet.

3.2.1 Kritiske effektmål

Samlet overlevelse (OS)

Samlet overlevelse er defineret som tiden fra randomisering til død uafhængigt af årsag. Det er afgørende for patienterne, om behandlingen forlænger deres liv, og fagudvalget vurderer derfor, at OS er et kritisk effektmål.

Som beskrevet i afsnit 4 er prognosen for denne patientpopulation virkelig god. Fagudvalget vurderer, at en forskel på 3 %-point ved 10 års overlevelse mellem patienter behandlet med neratinib og placebo alene er klinisk relevant.

Bivirkninger

Som nævnt er behandlingsmålet at nedsætte risikoen for tilbagefald, da tilbagefald som oftest vil medføre, at patienterne bliver uhelbredeligt syge. Derfor finder fagudvalget, at bivirkninger (adverse reactions, AR) er et kritisk effektmål, da det belyser, hvor godt patienterne tolererer neratinib sammenlignet med komparator. Fagudvalget ønsker data på nedenstående måleenheder:

Bivirkninger grad 3-4

Fagudvalget finder, at forskellen i andelen af patienter, som i løbet af opfølgningstiden oplever en eller flere bivirkninger af grad 3 eller 4, er relevant for vurderingen. Bivirkninger af grad 3-4 er defineret i henhold til National Cancer Institute CTCAE version 4.03 [7].

Fagudvalget vurderer, at en forskel på 5 %-point i andelen af patienter, der får bivirkninger af grad 3-4, er klinisk relevant.

Gennemgang af bivirkningsprofil

Fagudvalget ønsker en gennemgang af neratinib og komparators bivirkningsprofiler med henblik på at vurdere bivirkningernes type, håndterbarhed og reversibilitet. Ansøger bedes derfor levere bivirkningsdata fra både de kliniske studier og produktresuméet for lægemidlerne, så fagudvalget kan vurdere forskelle mellem de forskellige behandlinger.

Herunder ønsker fagudvalget opgjort, hvor mange patienter, der ophører behandlingen med hhv. neratinib og komparator.

Grad 3-4 er vægtet mest i den samlede vurdering af effektmålet, da man forventer at bivirkningerne generelt er reversible.

Livskvalitet

Livskvalitet er et patientrelevant effektmål, som udover at give indblik i sygdomsbyrden kan indikere, om bivirkningerne ved lægemidlet påvirker patienternes livskvalitet. På baggrund af dette betragter fagudvalget livskvalitet som et kritisk effektmål.

Livskvalitet kan for brystkræftpatienter måles med flere forskellige instrumenter (spørgeskemaer). Fagudvalget vurderer, at nedenstående validerede spørgeskemaer, der er nævnt i prioriteret rækkefølge, er relevante. Fagudvalget lægger i prioriteringen af rækkefølgen vægt på, at man benytter de to førstnævnte i dansk klinisk praksis.

EORTC-QLQ-C30: Dette instrument måler livskvaliteten blandt kræftpatienter [8]. Det består af fem funktionsskalaer, tre symptomskalaer og en "global" livskvalitetsskala. Der anvendes en scoringsskala fra 0-100. En høj score på de fem funktionsskalaer repræsenterer et højt/positivt funktionsniveau. En høj score for global helbredsstatus repræsenterer høj livskvalitet, mens en høj score på de tre symptomskalaer repræsenterer høj forekomst af symptomer/problemer. En lille ændring i livskvalitet er defineret som en ændring på 5-10 point i en publikation, hvor størstedelen af patienterne havde brystkræft [9]. Fagudvalget læner sig op ad denne definition og betragter en forskel på ≥ 10 point mellem neratinib og komparator som klinisk relevant.

EORTC-QLQ-BR23: Dette er et sygdomsspecifikt instrument, der vurderer livskvaliteten blandt patienter med brystkræft [10]. Det er et tillæg til EORTC-QLQ-C30 og består af fire funktionsskalaer og fire symptomskalaer. Scoringen foregår på samme måde som ved EORTC-QLQ-C30. Da der tilsyneladende ikke er defineret en mindste klinisk relevant forskel for instrumentet, benytter fagudvalget sig af definitionen fra EORTC-QLQ-C30. Dette er konsistent med tilgangen i flere studier [11]. Dermed betragter fagudvalget en forskel på ≥ 10 point mellem neratinib og komparator som klinisk relevant.

EQ-5D: Dette er et velvalideret generisk spørgeskema, som anvendes til at vurdere helbredsrelateret livskvalitet [12]. Spørgeskemaet består af fem dimensioner og indeholder desuden en visuel analog skala (VAS), der går fra 0 (værst tænkelige helbred) til 100 (bedst tænkelige helbred). Fagudvalget læner sig op ad definitionerne af mindste klinisk relevante forskelle baseret på britiske kræftpatienter [13]. Dermed finder fagudvalget, at en forskel på ≥ 0,08 i EQ-5D index score og ≥ 7 point i EQ-5D VAS mellem neratinib og komparator er klinisk relevant.

3.2.2 Vigtige effektmål

IDFS

Invasive-disease free survival (IDFS) er en brystkræftspecifik udgave af disease-free survival (DFS, sygdomsfri overlevelse). IDFS benyttes primært som et surrogatmål for overlevelse, til patientpopulationer med lang overlevelse. DFS er hyppigst defineret som tiden fra randomisering til tilbagefald eller død efter en behandling med kurativt formål, men definitionen af DFS kan variere fra studie til studie, f.eks. med henblik på om en sekundær primær tumor tælles med som event eller ej [15]. Denne problemstilling er også set indenfor adjuverende behandling til brystkræft, hvorfor et udvalg har forsøgt at definere brystkræftspecifikke definitioner [16]. Heri blev en definition af IDFS defineret. Fagudvalget bemærker, at der trods dette oplæg til en fælles definition er uenighed om, hvorvidt sekundære tumorer skal indgå som events. Fagudvalget mener, at det er relevant at benytte IDFS. Der foreligger endnu intet bevis for en korrelation mellem IDFS/DFS og OS for adjuverende behandling af HER2+ brystkræft. Dette skyldes at populationen har særdeles lang median overlevelse. IDFS vægtes derfor som vigtigt.

Fagudvalget vurderer, at de fleste tilbagefald sker indenfor de første år, og har derfor valgt at se på IDFS-raten efter 5 år.

4 Litteratursøgning

Medicinrådet har på baggrund af den foreløbige ansøgning undersøgt, om der findes en eller flere fuldtekstartikler publiceret i videnskabelige, fagfællebedømte tidsskrifter, hvor neratinib er sammenlignet direkte med placebo.

Medicinrådet har fundet følgende fuldtekstartikel/fuldtekstartikler, som indeholder en direkte sammenligning mellem neratinib og <komparator>:

- Martin et al, 2017 NEJM [17]

Det er tilstrækkeligt datagrundlag til at besvare de(t) kliniske spørgsmål. Ansøger skal derfor ikke søge efter yderligere fuldtekstartikler, men skal konsultere Det Europæiske Lægemiddelagenturs (EMA) European public assessment reports (EPAR) for både det aktuelle lægemiddel og dets komparator(er).

5 Databehandling og -analyse

Ansøger skal bruge Medicinrådets ansøgningsskema til sin endelige ansøgning. Vær opmærksom på følgende:

Studier og resultater

- Beskriv de inkluderede studier og baselinekarakteristikken af studiepopulationerne.
- Angiv hvilke studier/referencer der er benyttet til at besvare hvilke kliniske spørgsmål.
- Brug som udgangspunkt ansøgningsskemaet til ekstraktion af al relevant data.
- Krydstjek de ekstraherede data med de resultater, der fremgår af de relevante EPARs.
- Angiv årsager, hvis der er uoverensstemmelser mellem resultaterne fra artikler og EPARs.
- Angiv årsager, hvis der er uoverensstemmelser i forhold til PICO mellem protokollen og studierne.
- Vurdér, hvordan uoverensstemmelserne påvirker estimaterne.

Statistiske analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Udfør en komparativ analyse for hvert enkelt effektmål på baggrund af de ekstraherede data.
- Hvis data for et effektmål ikke er baseret på alle deltagere i et studie, skal ansøger ikke gøre forsøg på at erstatte manglende data med en meningsfuld værdi.
- Angiv for hvert effektmål og studie, hvilken analysepopulation (f.eks. intention to treat (ITT), per-protocol) der er anvendt.
- Angiv en sensitivitetsanalyse baseret på ITT-populationen, hvis den komparative analyse ikke er baseret herpå.
- Angiv for hvert effektmål og studie, hvilken statistisk analysemetode, der er anvendt.
- Basér de statistiske analyser for dikotome effektmål på den relative forskel.
- Beregn den absolutte forskel med udgangspunkt i den estimerede relative forskel for et antaget niveau på hændelsesraten i komparatorgruppen (jævnfør Appendiks 5 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Foretag eventuelt en indirekte analyse, hvis der ikke foreligger direkte sammenlignende studier, og hvis intervention og komparator er sammenlignet med samme alternative komparator i separate studier. Anvend eventuelt Buchers metode for indirekte justeret sammenligning.

Metaanalyser

- Foretag en metaanalyse for de effektmål, hvor det er metodemæssigt forsvarligt, hvis der er mere end ét sammenlignende studie.
- Basér metaanalyser vedr. effektmål, hvor forskellige måleinstrumenter er brugt på tværs af de inkluderede studier, på standardized mean difference (SMD). Omregn den estimerede SMD til den foretrukne skala for effektmålet (jævnfør Appendiks 7 i Håndbog for Medicinrådets proces og metode vedr. nye lægemidler og indikationsudvidelser).
- Udfør alene netværksmetaanalyse i de undtagelsesvise situationer, hvor Medicinrådet specifikt beder om det i protokollen. Redegør i disse tilfælde for, i hvilken grad antagelserne om transitivitet og konsistens er opfyldt (gerne ved hjælp af passende statistiske metoder).
- Begrund for alle statistiske analyser valget mellem ’fixed effects’- og ’random effects’-modeller.
- Beskriv den anvendte metode detaljeret.

Narrative analyser

- Begrund valget af syntesemetode (metaanalyse eller narrativ beskrivelse), og lad specifikke analysevalg fremgå tydeligt.
- Syntetisér data narrativt, hvis det ikke er en mulighed at udarbejde komparative analyser baseret på statistiske metoder.
- Beskriv studie- og patientkarakteristika samt resultater fra de inkluderede studier narrativt og i tabelform med angivelse af resultater pr. effektmål for både intervention og komparator(er).
- Beskriv forskelle mellem studier og vurdér, hvorvidt resultaterne er sammenlignelige.

Vær opmærksom på, at Medicinrådets sekretariat forbeholder sig retten til at foretage sensitivitets- og subgruppeanalyser på baggrund af studiernes validitet og relevans, uanset valg af analysemetode.

6 Evidensens kvalitet

Medicinrådet anvender GRADE (Grading of Recommendations, Assessments, Development and Evaluation) til at foretage en systematisk og transparent vurdering af kvaliteten af evidensen. Evidensens kvalitet fortæller, i hvor høj grad vi kan have tiltro til den evidens, vi baserer vurderingen af lægemidlets værdi på.

7 Andre overvejelser

TNM-stadier

TNM-klassifikationen er i høj grad korreleret med prognose, dvs. at en patient med f.eks. T1N0 kan forventes at have væsentlig bedre prognose, end en patient med T4N3. Prognosen er dog også afhængig af patientens respons på neoadjuverende behandling.

Fagudvalget ønsker derfor at ansøger leverer OS- og IDFS-data for hver enkelt kombination af T og N stadier (kliniske stadier). Fagudvalget vil ud fra disse data overveje, om effekten ser ud til at variere mellem de kombinationer af T og N stadier, som er inkluderet i det kliniske studie.

8 Relation til behandlingsvejledning

Der findes ikke en behandlingsvejledning hvor neratinib vil indgå, og fagudvalget vil derfor ikke tage stilling til en foreløbig placering af lægemidlet. FU gør dog opmærksom på, at patienterne der kan komme i betragtning til behandling med neratinib, tidligere i deres behandlingsforløb er behandlet efter RADS' "Baggrundsnotat for anti-HER2 behandling af brystkræft"

9 Referencer

1. NORDCAN. Association of the Nordic Cancer. Kræftstatistik: Nøgetal og figurer_brystkræft. 2019.
2. Retningslinjerne M. Patologi - DBCG. 2017;1–37. Tilgængelig fra: http://www.dbcg.dk/PDF Filer/Kap_3_Patologi_22_juni_2017.pdf
3. Tolaney SM, Guo H, Pernas S, Barry WT, Dillon DA, Ritterhouse L, et al. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2–positive breast cancer. J Clin Oncol. 2019;37(22):1868–75.
4. Asselain B, Barlow W, Bartlett J, Bergh J, Bergsten-Nordström E, Bliss J, et al. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19(1):27–39.
5. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet [internet]. 2017;389(10075):1195–205. Tilgængelig fra: http://dx.doi.org/10.1016/S0140-6736(16)32616-2
6. Group DBCC. Medicinsk behandling. 2011;2005:1–49.
7. National Cancer Institute Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Bd. 2009. 2010.
8. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst [internet]. 1993 [citeret 29. marts 2017];85(5):365–76. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/8433390
9. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139–44.
10. Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol [internet]. 1996 [citeret 4. januar 2018];14(10):2756–68. Tilgængelig fra: http://ascopubs.org/doi/10.1200/JCO.1996.14.10.2756
11. Cortes J, Hudgens S, Twelves C, Perez EA, Awada A, Yelle L, et al. Health-related quality of life in patients with locally advanced or metastatic breast cancer treated with eribulin mesylate or capecitabine in an open-label randomized phase 3 trial. Breast Cancer Res Treat. 2015;154(3):509–20.
12. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy [internet]. 1990;16(3):199–208. Tilgængelig fra: http://www.ncbi.nlm.nih.gov/pubmed/10109801
13. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5(1):70.
14. Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol. 2015;26(8):1547–73.
15. Fiteni F, Westeel V, Pivot X, Borg C, Vernerey D, Bonnetain F. Endpoints in cancer clinical trials. J Visc Surg [internet]. 2014;151(1):17–22. Tilgængelig fra:

http://dx.doi.org/10.1016/j.jviscsurg.2013.10.001

16. Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JAW, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: The STEEP system. J Clin Oncol. 2007;25(15):2127–32.

17. 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):1688–700.

10 Sammensætning af fagudvalg og kontaktinformation til Medicinrådet

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11 Versionslog

Version	Dato	Ændring
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