Position Paper on the Value of Extended Adjuvant Therapy with Neratinib for Early HER2+/HR+ Breast Cancer

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Keywords

HER2-positive breast cancer · Co-positive breast cancer · Early breast cancer · Extended adjuvant therapy · Neratinib

Abstract

Background: In August 2018, neratinib – an oral, irreversible pan-HER-tyrosine-kinase inhibitor – was approved by the European Commission for the extended adjuvant treatment of adult patients with early-stage, hormone receptor-positive (HR+), HER2 overexpressed/amplified (HER2+) breast cancer who completed trastuzumab-based adjuvant therapy within the last year. Despite recent improvements in long-term outcome, there is still an unmet need to further reduce the risk of recurrence, especially in patients with poor response to neoadjuvant treatment. **Summary:** National and international guidelines included recommendations for using neratinib. Based on the health technology assessment for neratinib, the Federal Joint Committee (G-BA) in Germany has granted an added benefit for neratinib compared with the standard “watch and wait” strategies. Inclusion in the Reimbursement Code, however, was rejected by the Austrian social insurance companies in July 2020, and neratinib is now in the “No Box” for individual head physician reimbursement. **Key Messages:** We analysed the value of extended adjuvant therapy with neratinib in early HER2+/HR+ breast cancer based on current data and made recommendations for the evidence-based and economical use of neratinib in

Austria. In particular, prognostic factors associated with an increased risk of recurrence following standard therapy are considered. Extended adjuvant therapy should be offered primarily to nodal-positive patients at surgery. For nodal-negative patients, neratinib therapy may be considered in case of large and/or inflammatory primary tumours (T3–4) without pathological complete response after neoadjuvant therapy. For all other patients, neratinib may be considered depending on additional risk factors on an individual basis that should be evaluated by interdisciplinary tumour conferences.

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Published by S. Karger AG, Basel

Introduction

Human epidermal growth factor receptor 2 (HER2) protein overexpression and/or gene amplification of the *HER2/neu* gene occurs in about 15–20% of early breast cancers and is associated with an increased recurrence risk and a poorer prognosis compared to HER2-negative (HER2–) disease without HER2-targeted therapy [1, 2]. HER2+ breast cancer with simultaneous hormone receptor overexpression (HR+) (luminal B/HER2-positive, also called “triple-positive”) affects around 10% of all breast cancer patients [3–7].

In contrast to locally advanced-inoperable and metastatic situations, the potentially curable stages I–III are

Fig. 1. Current therapy algorithm for the treatment of early HER2+ breast cancer. Schematic representation adapted in accordance with the current recommendations of the German working group Gynecological Oncology (AGO) [8] and the European Society of Medical Oncology [15, 18]. The decision on adjuvant systemic therapies should be based on an individual's risk of relapse, the predicted sensitivity to the treatment, the benefit and toxicities [15]. According to the EMA label, neratinib use is approved after

any trastuzumab-based therapy, including (postneo-)adjuvant pertuzumab and/or T-DM1. It should be noted that patients in the ExteNET study did not receive pertuzumab or T-DM1, as these drugs had not been available at study start [31, 32]. HER2, human epidermal growth factor receptor 2; HR, hormone receptor; N, lymph node/nodal status; surgery, operative tumour resection; pCR, pathological complete response; T-DM1, trastuzumab-emtansine.

referred to as early breast cancer and are usually treated with a combination of locoregional surgical therapy (plus radiotherapy if indicated) and chemotherapy combined with HER2-directed targeted neoadjuvant and/or (post-neo)adjuvant systemic therapy plus endocrine therapy in luminal B/HER2-positive disease [8, 9].

The aim of early breast cancer therapy is to prevent locoregional recurrences and development of distant metastases. Although the prognosis of patients with early HER2+ breast cancer has improved significantly in recent decades thanks to the introduction of targeted anti-HER2 therapies [10, 11], up to 31% of patients are at risk of recurrence and/or death after 10 years with adjuvant chemotherapy plus trastuzumab, depending on the individual risk [10]. Patient's prognosis is determined primarily by the stage and biology of the breast cancer and by the presence of individual risk factors. In addition to achieving pathological complete response (pCR), the relevant prognostic factors in early HER2+ breast cancer are hormone receptor status, tumour size, nodal status, and age [12–14].

Treatment Options for Early HER2+ Breast Cancer according to Current Guidelines

In accordance with international guidelines (AGO, ESMO, ASCO, NCCN guidelines), patients receive neoadjuvant and/or (post-neo)adjuvant (perioperative) targeted anti-HER2 therapy (trastuzumab or trastuzumab + pertuzumab and/or T-DM1) embedded in a chemotherapy regimen for the systemic treatment of early HER2+ breast cancer [8, 15–18].

Endocrine therapy is indicated as the standard therapy for all patients with hormone-sensitive breast cancer and is usually administered as an adjuvant therapy for HER2+/HR+ breast cancer [7, 15–19].

Figure 1 shows, in simplified form, the current therapy algorithm according to the European guidelines.

Table 1. Overview of recurrence probabilities and the frequency of peripheral recurrence and brain metastases in early HER2+ breast cancer after various pre-treatments

Study [Ref.] Setting; therapy	Probability of recurrence after 3 years ^a		Probability of recurrence after x years ^a		Frequency of peri- pheral recurrence/BM (total patients with BM)
	all patients	HR+	all patients	HR+	
Pooled analysis ^b [11, 20, 21] ^a Adjuvant; trastuzumab (n = 2,028)	12.0%	7.8%	After 10 years 26.3%	18.6%	11.9%/3.1% (n = 63) after 8.4 years ^c
HERA [10, 22] adjuvant; trastuzumab (1 year) (n = 1,552/1,702)	13.3%	10.4%	After 10 years 31%	28%	17.9%/2.6% (n = 45) after 11 years ^d
APHINITY [12, 23] adjuvant; pertuzumab + trastuzumab (n = 2,400)	5.9% N+: 8.0%	5.2%	After 6 years 9.4% N+: 12.1%	8.8%	5.9%/2.0% (n = 49) after 6.2 years ^e
KATHERINE [13] post-neoadjuvant, non-pCR trastuzumab-emtansine (n = 742)	11.7%	9.3%	n.r.	n.r.	10.5%/5.9% (n = 44) after 3.5 years ^f
Neoadjuvant CT + anti-HER2 therapy Patients with pCR after neoadjuvant CT [14]; (T1–2/N–: n = 212; T3–4/N–; n = 65 T1–2/N+: n = 200; T3–4/N+; n = 60)	n.r.	n.r.	After 5 years n.r.	T1–2/N–: 8.6% T3–4/N–: 13.0% T1–2/N+: 16.4% T3–4/N+: 19.6%	n.r.

^a Calculated with 1 minus Kaplan-Meier estimator at the relevant time; ^b NSABP B-31 and NCCTG N9831 studies; ^{c–f} median follow-up times (^e calculated from 74.1 months; ^f calculated from 41.1 months). BM, brain metastases; HR, hormone receptor; N+/- , nodal-positive/-negative; pCR, pathological complete response; CT, chemotherapy; n.r., not reported.

Recurrence Risk

Despite optimal (neo)adjuvant treatment, distant recurrences are still observed with longer follow-up. The recurrence risk is particularly high for patients who do not achieve a pCR after neoadjuvant therapy. Higher tumour size and nodal involvement additionally increase recurrence risk in these patients. However, for patients with pCR after neoadjuvant therapy, but high initial tumour burden or inflammatory disease (T3–4 and/or involved lymph nodes), there is a considerable risk of recurrence as well (Table 1 [10–14, 20–23]).

Of note, the risk profile and recurrence patterns differ between the non-luminal and luminal B/HER2+ subgroups. In HR/HER2 co-expressing tumours, a lower pCR rate has been described [24], while the correlation between pCR and long-term outcome is less pronounced [25]. For patients with HER2+/HR– disease, the risk of recurrence is especially high within the first 5 years, and decreases constantly thereafter. In contrast, the risk of recurrence is initially lower in the HER2+/HR+ subgroup, but also remains constant beyond the first 5 years (Fig. 2) [26–29], suggesting a potential benefit from the extension of adjuvant therapy.

Neratinib – Overview of the Product Characteristics

- Approved indication(s)
 - July 2017 USA/FDA [30]: “extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.”
 - August 2018 EU/EMA [31, 32]: “extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago.”
 - February 2020 USA/FDA [33]: in addition, “in combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.”
 - March 2020 Switzerland/Swissmedic [34]: “extended adjuvant treatment of adult patients with early-stage hormone-receptor positive HER2-overexpressed/amplified breast cancer who are less than 1 year from the completion of prior adjuvant therapy based on trastuzumab and chemotherapy.”
- Pharmacological classification ATC L01XE45 [32, 35]: Oral, irreversible pan-HER tyrosine kinase inhibitor. Unlike HER2-targeted antibodies (such as trastuzumab,

Fig. 2. Annual hazards and time-dependent hazard ratios for recurrence in HER2+ patients by HR status. **A** Annual hazards for recurrence in HER2+, placebo-treated patients from the TEACH study (lapatinib vs. placebo in patients with adjuvant pre-treatment) by HR status (95% CIs for 2-year intervals). **B** Hazard ratio for recurrence in HER2+, placebo-treated patients from the TEACH study (lapatinib vs. placebo in patients with adjuvant pre-

treatment [chemotherapy, but no trastuzumab]), comparison of HR+ vs. HR- (modified from Strasser-Weippl et al. [28]). Copyright license: © 2015 Strasser-Weippl K, Horick N, Smith IE, et al. Published by Breast Cancer Research under the CC BY license which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. Disclaimer of warranties and limitation of liability apply.

Table 2. Baseline patient characteristics in the intention-to-treat (ITT) population [36] and the EMA label population [38] of the ExteNET study

	Baseline characteristics ITT		Baseline characteristics EMA-label population (HR+, <1 year after trastuzumab)	
	neratinib (n = 1,420)	placebo (n = 1,420)	neratinib (n = 670)	placebo (n = 664)
Median age (range), years	52 (25–83)	52 (23–82)	51 (25–83)	51 (23–78)
Pre-/postmenopausal, %	47/53	47/53	52/48	42/48
Hormone receptor negative/positive, %	43/57	43/57	0/100	0/100
Endocrine therapy simultaneously with neratinib, %	93	94	93	95
0/1–3/≥4 involved lymph nodes, %	24/47/30	24/47/30	19/51/30	19/50/31
Median time after trastuzumab (range), months	4.4 (0.2–30.9)	4.7 (0.3–40.6)	3.1 (0.2–12.0)	3.3 (0.3–12.0)
Patients with previous neoadjuvant therapy, %	24	27	24	29

pertuzumab or T-DM1), which bind extracellularly to the HER2 receptor, neratinib irreversibly binds to the intracellular tyrosine kinase domains of HER1 (EGFR), HER2 and HER4 and therefore impedes intracellular HER2 signal-transduction and the formation of active heterodimers with HER3 (HER3 has no tyrosine kinase domain).

- Dosage [32]:

One orally administered daily dose of 240 mg (equivalent to 6 tablets of 40 mg) for 1 year. Treatment must be initiated within 1 year after completion of trastuzumab-based therapy.

- Prophylaxis [31, 32]:

Concomitant systematic diarrhoea prophylaxis starting with the first dose of neratinib is recommended for the first 1–2 months.

Overview of Study Data on Neratinib with a Focus on the Approved Indication

Approval is based on the international, multicentre, randomised, placebo-controlled phase III study ExteNET, in which 2,840 patients with early HER2+ breast cancer participated [36–38].

Fig. 3. Invasive disease-free survival at 2 years (**A**) and 5 years (**B**), distant disease-free survival at 5 years (**C**), and overall survival (**D**) – EMA label population [38]. Copyright license: © 2020 Chan A, Moy B, Mansi J, et al. Published by Elsevier Inc. under the CC BY-

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Key features of the Phase III ExteNET study (see also Supplementary Fig. 1 [34, 36–38]):

- HER2+ operable breast cancer, stage I–IIIc, HR+/-.
- Extended adjuvant neratinib 240 mg/day versus placebo for 1 year following (neo)adjuvant trastuzumab therapy.
- Primary endpoint: Invasive disease-free survival (iDFS) after 2 years (follow-up analysis after 5 years) in the intention-to-treat (ITT) population.
- Secondary endpoints: overall survival (OS) (analysis planned after 248 events), disease-free survival (including ductal in situ carcinoma), distant disease-free survival (DDFS), time to recurrence of distant metastases, incidence of CNS recurrence, safety, tolerability.
- Inclusion phase: 2009–2011; duration of study: median follow-up at primary analysis: 24 months in both arms; median follow-up at 5-year analysis: 5.2 years

under neratinib versus 5.3 years under placebo; median follow-up for OS at 8.0 years in both arms.

The patient baseline characteristics are summarised in Table 2.

In extended adjuvant therapy following trastuzumab-based (neo)adjuvant treatment, the ExteNET study of neratinib showed a significant improvement in iDFS compared to the placebo (2-year iDFS in the ITT population 93.9 vs. 91.6%; HR 0.67 [95% CI 0.50–0.91]; $p = 0.0091$) [36]. A follow-up analysis 5 years after randomisation confirmed the benefit of neratinib versus placebo [37].

The HR+ subgroup of patients in particular as well as those starting neratinib therapy within 1 year after end of trastuzumab-based therapy benefited from neratinib [36, 38], and the European approval of neratinib was granted for the 1-year extended adjuvant treatment of HER2/HR co-positive breast cancer patients who finished trastu-

Fig. 4. Invasive disease-free survival (A), distant disease-free survival (B), and overall survival (C) – subgroup of non-pCR patients after neoadjuvant therapy from the EMA label population – 5-year analysis [38]. Copyright license: © 2020 Chan A, Moy B, Mansi J, et al. Published by Elsevier Inc. under the CC BY-NC-ND license which permits to share, copy and redistribute the material, provided the original work is properly credited. Disclaimer of warranties and limitation of liability apply.

zumab-based pre-therapy less than 1 year ago (“EMA-label population”) [31, 32]. Table 2 shows baseline characteristics for patients of the ITT population and the EMA-label population [36, 38].

Efficacy in the EMA Label Population of the ExteNET Study

- Significant prolongation of iDFS (endpoint included recurrence of invasive disease in the ipsi- or contralateral breast, locoregional recurrence, distant metastases, death from any cause) with 5.1% absolute and 35.7% relative reduction in the probability of recurrence or death after 5 years (HR 0.58 [95% CI 0.41–0.82], $p = 0.002$, Figure 3B). iDFS after 5 years was 90.8% in the neratinib group and 85.7% in the placebo group [38].
- Significant improvement in DDFS (endpoint included distant metastases, death of any cause) with a 4.7% absolute and 38.2% relative reduction in the probability of occurrence of distant metastases or death after 5 years (HR 0.57 [95% CI 0.39–0.83]; $p = 0.003$; Figure 3C). DDFS after 5 years was 92.4% in the neratinib group and 87.7% in the placebo group [38].
- An exploratory post-hoc analysis showed that those patients who had completed neratinib therapy (≥ 11 months therapy duration, $n = 402$) derived the most pronounced benefit with a 7.4% absolute and 51.4% relative reduction in the probability of recurrence or death after 5 years (HR 0.44 [95% CI 0.28–0.68]). iDFS after 5 years was 93.1% in the neratinib group and 85.7% in the placebo group [39].
- In the cumulative incidence of CNS recurrences, albeit the number of events was low in both arms, there was a numerical difference in favour of the neratinib group after 5 years (neratinib: 0.7% [95% CI 0.2–1.7], 4 CNS events; placebo: 2.1% [95% CI 1.1–3.5], 12 CNS events). CNS-disease-free survival (CNS-DFS) after 5 years was 98.4% in the neratinib group and 95.7% in the placebo group (HR 0.41 [95% CI 0.18–0.85], 9 vs. 23 events) [38].
- After a median follow-up of 8.0 years, 53 out of 670 patients (7.9%) in the neratinib group and 68 out of 664 patients (10.2%) in the placebo group had died (HR 0.79 [95% CI 0.55–1.13]). OS after 8 years was 91.5% in the neratinib group and 89.4% in the placebo group, an absolute difference of 2.1% between the groups [38].
- Of the 354 patients (27% of the EMA label population) who had received neoadjuvant therapy, 295 patients (83%) had invasive residual disease (non-pCR) after completion of neoadjuvant therapy, 38 patients (11%) achieved pCR, and no result was reported for 21 patients (6%) [38].

For patients with residual invasive disease ($n = 295$), the absolute risk reduction for iDFS and DDFS after 5 years was 7.4% (HR 0.60 [95% CI 0.33–1.07]; $p = 0.086$) and 7.0% (HR 0.61 [95% CI 0.32–1.11]; $p = 0.112$, Figure 4A and B), respectively [38]. The OS rates showed an absolute risk reduction of 9.1% (HR 0.47 [95% CI 0.23–0.92]; $p = 0.031$, Figure 4C). In the cumulative incidence of CNS recurrences in these patients, there was a numerical difference in favour of the neratinib group after 5 years (neratinib: 0.8% [95% CI 0.1–4.0], 1 CNS event; placebo: 3.6% [95% CI 1.3–7.8], 5 CNS events). CNS-DFS after 5 years was 98.4% in the neratinib group and 92.0% in the placebo group (HR 0.24 [95% CI 0.04–0.92], 2 vs. 10 events) [38].

For patients without evidence of residual invasive disease (pCR) after neoadjuvant therapy ($n = 38$), the absolute risk reduction for iDFS was 9.8% after 5 years (HR 0.44 [95% CI 0.06–1.89]) and for OS 19.6% after 8 years (HR 0.40 [95% CI 0.06–1.88]) [38]. In the cumulative incidence of CNS recurrences, there was a numerical difference in favour of the neratinib group after 5 years (neratinib: 0 [95% CI NE]; placebo: 5.0% [95% CI 0.3–21.2], 3 CNS events). iDFS after 5 years was 100% in the neratinib group and 81.9% in the placebo group [38]. Due to the low number of patients in this subgroup, no final conclusions regarding the efficacy of extended adjuvant therapy in patients with pCR seem possible.

Patient-Reported Outcomes/Quality of Life in the ITT Population of the ExteNET Study

Therapy with neratinib showed a slight decrease in global health-related quality of life scores as evaluated by FACT-B (Functional Assessment of Cancer Therapy-Breast) and EQ-5D in the first month compared to placebo (adjusted mean differences: FACT-B overall: –2.9 points; EQ-5D index: –0.02); thereafter, the differences between the groups decreased. Except for the FACT-B subscale on physical well-being in month 1, none of the group differences exceeded the “important differences” (IDs) [40]. The FACT-B breast cancer-specific subscale showed small improvements with neratinib in months 3–9, but again below the IDs. Sensitivity analyses taking into account missing data showed no change in outcome.

Safety/Tolerability in the EMA Label Population of the ExteNET Study

In general, the well-described safety profile of neratinib is typical for tyrosine kinase inhibitors of the HER receptor family and therefore predictable [32, 35–38, 41–43]. Unlike other agents used in the therapy of early breast cancer, no cumulative or irreversible toxicities were observed [37, 44–48].

The most common adverse event during neratinib treatment in the EMA-label population of the ExteNET

Table 3. Characteristics of diarrhoea under neratinib therapy in the ExteNET and CONTROL studies (safety population; datacut for dose escalation cohort: Oct 19, 2020, datacut for all other CONTROL study cohorts: Oct 21, 2019) [53, 54]

	CONTROL					ExteNET
	n = 137	n = 64	n = 136	n = 104	n = 60	n = 1,408
Neratinib dose	Neratinib 240 mg/d	Neratinib 240 mg/d	Neratinib 240 mg/d	Neratinib 240 mg/d	Neratinib dose escalation ^c	Neratinib 240 mg/d
Loperamide prophylaxis	Loperamide ^a first 8 weeks	Loperamide ^a first 8 weeks	Loperamide ^b first 4 weeks			No primary prophylaxis
Other diarrhea prophylaxis		Budesonide 9 mg/d for 1 cycle	Colestipol 2g bid for 1 cycle	Colestipol 2g bid for 1 cycle		
Treatment-emergent diarrhoea incidence, n (%)						
No diarrhoea	28 (20)	9 (14)	23 (17)	5 (5)	1 (1.7)	65 (5)
Grade 1	33 (24)	16 (25)	38 (28)	34 (33)	24 (40)	323 (23)
Grade 2	34 (25)	21 (33)	47 (35)	32 (31)	27 (45)	458 (33)
Grade 3	42 (31)	18 (28)	28 (21)	33 (32)	8 (13.3)	561 (40)
Grade 4	0	0	0	0	0	1 (<1)
Characteristics of grade ≥ 3 diarrhoea						
Median episodes/patient (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-3)	2 (n.r.)	2 (1-3)
Median duration of episode, days (IQR)	2 (1-3)	1 (1-2)	1 (1-2)	1 (1-2)	n.r.	2 (1-3)
Median time to first episode, days (IQR)	7 (5-13)	19 (7-45)	41 (7-189)	15 (8-47)	45 (n.r.)	8 (4-33)
Median cumulative duration ^d , days (IQR)	3 (2-6)	3 (1-3)	4 (1-6)	2 (1-6)	2.5 (n.r.)	5 (2-9)
Action taken, n (%)						
Dose hold	20 (15)	12 (19)	22 (16)	15 (14)	7 (11.7)	477 (34)
Dose reduction	10 (7)	3 (5)	10 (7)	12 (12)	2 (3.3)	372 (26)
Discontinuation	28 (20)	5 (8)	5 (4)	8 (8)	2 (3.3)	237 (17)
Hospitalization	2 (1)	0	0	0	0	20 (1)

^a 4 mg initial; days 1–14: 4 mg tid; days 15–56: 4 mg bid; ^b 4 mg initial; days 1–14: 4 mg tid; days 15–28: 4 mg bid; ^c dose escalation regimen #1: days 1–7: 120 mg/d; days 8–14: 160 mg/d, then 240 mg/d; dose escalation regimen #2 (days 1–14: 160 mg/d; days 15–28: 200 mg/d, then 240 mg/d) is not reported here; ^d defined as the sum of the durations of all episodes at that grade. Unless otherwise mandated, all patients received loperamide as needed (16 mg/d maximum) on days 1 – 364. IQR, interquartile range; n.r., not reported.

study was diarrhoea (all grades) at 94.6% [32, 35, 36–38, 44; see also Supplementary Table 1]. Other common adverse events (all grades; ≥20%) were: nausea, 43.7%; fatigue, 28.5%; vomiting, 26.3%; and abdominal pain, 23.6%.

Severe diarrhoea (grade 3) was reported in the EMA-label population of the ExteNET study with a frequency of 39.4% in the neratinib arm and 1.1% in the placebo arm (grade 4 was not observed) [38]. In the neratinib arm, grade 3 diarrhoea was reported to occur relatively early after therapy start (median time to first occurrence: 8 days); the median cumulative duration of grade 3 diarrhoea was 5 days [44].

It should be noted, however, that no systematic anti-diarrhoeal prophylaxis was mandated by the study protocol in the ExteNET study [36–38, 44]. Accordingly, frequency and severity of diarrhoea that occurred in the ExteNET study cannot be equated with the current reality of care.

Diarrhoea Prophylaxis as Part of the Neratinib Risk Management Plan

Based on the summary of product characteristics and the EMA risk management plan established for neratinib, systematic anti-diarrhoeal prophylaxis and detailed therapy management is now required as part of routine treatment – in contrast to the ExteNET study [31, 32, 49–51].

In addition, the multi-cohort phase II CONTROL study has been initiated as a clinical trial for further optimisation of anti-diarrhoeal strategies with neratinib [52–54]. The inclusion criteria are comparable to those of the ExteNET study; the primary endpoint is the frequency of diarrhoea with severity (grade) ≥3.

The interim analysis shows that systematic diarrhoea prophylaxis initiated with the first dose of neratinib, accompanied by an appropriate diarrhoea management, can significantly reduce incidence of diarrhoea, its duration and severity [53, 54] (Table 3):

- In the different cohorts, 13.3–32% of patients had grade 3 diarrhoea; grade 4 diarrhoea was not observed.

Table 4. Guidelines with recommendations for the use of neratinib in the treatment of early HER2+ breast cancer

Guidelines	Recommendation	Evidence level	Grading of recommendation	Sources
ASCO 2020 American Society of Clinical Oncology	Extended adjuvant therapy with neratinib in patients with HER2-positive early breast cancer Neratinib causes relevant diarrhoea and diarrhoea prophylaxis should be applied	High	Moderate	[16]
ESMO 2019 European Society for Medical Oncology	Extended anti-HER2 therapy with neratinib combined with appropriate diarrhoea prophylaxis and treatment may be considered in selected high-risk patients who have not previously been treated with a double blockade (especially HR+ patients)	I	B	[15, 18]
NCCN 2020 National Comprehensive Cancer Network	Neratinib as a therapy option after adjuvant trastuzumab therapy in HER2+/HR+ Mamma CA with a high risk of recurrence (N+); of note: no data is available for patients who have previously received pertuzumab Neratinib as a therapy option after adjuvant trastuzumab therapy in HER2+/HR+ breast cancer and pCR after neoadjuvant therapy with a high risk of recurrence; of note: no data is available for patients who have previously received pertuzumab or T-DM1		2 A	[17]
AGO Gynaecological Oncological Working Group e.V.	Neratinib combined with standard endocrine therapy after 1 year of adjuvant trastuzumab (HR+) Neratinib combined with standard endocrine therapy after 1 year of post-neoadjuvant trastuzumab (HR+, non-pCR) Primary prophylaxis with loperamide	1b/B 3b/B 2b/B	+ +/- ++	[8, 55]

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Mamma CA, breast cancer; N, lymph node/nodal status; pCR, pathological complete response; T-DM1, trastuzumab-emtansine.

Table 5. Latest results for neratinib from European Health Technology Assessment (HTA) procedures [56–60]

Country/Institution	Therapeutic indication	HTA evaluation	Source
Germany Joint Federal Committee (G-BA)	Nerlynx® is indicated for the extended adjuvant treatment of adult patients with hormone receptor-positive, HER2 overexpressed/amplified early-stage breast cancer who completed trastuzumab-based adjuvant therapy less than 1 year ago	Added benefit (category: minor; robustness category: hint) compared to the appropriate comparative therapy, i.e. watch and wait	[56]
UK National Institute for Health and Care Excellence (NICE)	“[...] option for the extended adjuvant treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer in adults who completed adjuvant trastuzumab-based therapy less than 1 year ago only if • trastuzumab is the only HER2-directed adjuvant treatment they have had, and • if they had neoadjuvant chemotherapy-based regimens, they still had residual invasive disease in the breast or axilla following the neoadjuvant treatment, and • the company provides neratinib according to the commercial arrangement”	Recommended	[57]
Scotland Scottish Medicines Consortium (SMC)	“Extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who completed adjuvant trastuzumab-based therapy less than 1 year ago”	Recommended	[58]
Sweden Tandvårds- och läkemedelsförmånsverket, (TLV)	“Indicated for the extended adjuvant treatment of adult patients with hormone receptor positive early-stage HER2 overexpressed/amplified breast cancer who have completed trastuzumab-based adjuvant treatment less than a year ago”	Recommended	[59]
Austria	Nerlynx® is indicated for the extended adjuvant treatment of adult patients with hormone receptor-positive, HER2 overexpressed/amplified early-stage breast cancer who completed trastuzumab-based adjuvant therapy less than 1 year ago	“No Box” Patient-individual request for reimbursement is required, reimbursement can be granted by the insurance-based physician	[60]

Table 6. Simplified overview of the most common situations where the use of extended adjuvant treatment with neratinib may be considered

Prognostic risk factors	Nodal-negative	Nodal-positive
Neoadjuvant pretreatment, non-pCR	T3–4	All T-stages
Neoadjuvant pretreatment, pCR	T3–4	
Adjuvant (no neoadjuvant pretreatment)	<i>Possibly also consider Age, grading, Ki-67</i>	

Ki-67, proliferation marker Ki-67; (non-)pCR, (missing) pathological complete response after neoadjuvant therapy; T, tumour size.

- Grade 3 diarrhoea occurred mainly within the first 1–2 months after starting neratinib therapy.
- Across all cohorts, the median cumulative duration of grade 3 diarrhoea ranged between 2 and 4 days in the CONTROL study, compared to 5 days in the ExteNET study.
- The different anti-diarrhoeal prophylaxis strategies present with different strengths and weaknesses. Thus, the strategy should be chosen on a patient-individual basis, taking into account patient preferences, comorbidities, and lifestyle factors.
- As the dose escalation cohort #2 is still ongoing, results of this cohort are not shown here.

The neratinib dose escalation approach is particularly appealing, with 75% of patients completing the treatment (i.e., treatment duration of 11.06 months or longer) and the lowest incidence of grade 3 diarrhoea across all cohorts [54].

Summary and Conclusions

On the basis of the clinically relevant efficacy data described above, extended adjuvant therapy with neratinib is recommended in the therapeutic indication in accordance with the summary of product characteristics in international guidelines (Table 4 [8, 15–18, 55]).

In the course of various “Health Technology Assessment” procedures in Europe, the competent authorities have attributed an added benefit to neratinib in this setting (Germany) or recommended its use (UK, Scotland, Sweden) (Table 5 [56–59]).

For patients with HER2/HR co-positive breast cancer who are at increased risk of late recurrence, the primary therapeutic goal is to avoid distant metastases. In the pivotal ExteNET trial, the risk of local and distant recurrence was reduced to a statistically significant and clinically relevant extent by extended adjuvant therapy with neratinib compared to placebo, provided that neratinib therapy was started within 1 year after the end of trastuzumab-based adjuvant therapy [38]. Accordingly, this new treatment option was approved by the EMA for these patients.

The medical need for an additional reduction of the risk of recurrence by the use of extended adjuvant neratinib therapy should be assessed on the basis of the patient-specific risk factor constellations. The following factors should be considered:

- pCR or no pCR after neoadjuvant therapy
- Lymph node status
- Tumour size
- Further individual risk factors on a case-to-case basis

In summary, extended adjuvant therapy should be offered primarily to patients with lymph node involvement. For nodal-negative patients, neratinib therapy may be considered in case of large and/or inflammatory primary tumours (T3–4) without pCR after neoadjuvant therapy or – depending on additional risk factors – if pCR was achieved after neoadjuvant therapy or after adjuvant therapy (Table 6).

In addition, individual risk factor constellations may justify the use of neratinib in individual patients based upon the recommendation of an interdisciplinary tumour conference.

In general, regular check-ups while on treatment with neratinib must be carried out by the relevant specialist department or centre or by a medical specialist in oncology.

Acknowledgements

The authors would like to acknowledge editorial support provided by Barbara Möller, Wien, Austria – Input and translation; Berres-Stenzel Grafikdesign, Freiburg, Germany – Graphics Design; Andreas Zähringer, Freiburg, Germany – editorial support.

Statement of Ethics

As this review article/position paper only considered publicly available literature and reports, a separate informed consent process was not implemented and no ethics approval was requested.

Conflict of Interest Statement

Assoc. Prof. Marija Balic has disclosed a consulting role with Amgen, Astra Zeneca, Lilly, MSD, Novartis, Pierre Fabre, Pfizer, and Roche. She is currently receiving research funding from Pfizer and Novartis. She is on the speaker's bureau for Amgen, Astra Zeneca, Daiichi Sankyo, Eli Lilly, MSD, Novartis, Pierre Fabre, and Pfizer and has received travel accommodation and expenses from Astra Zeneca, Lilly, MSD, Novartis, Pfizer, and Roche.

Assoc. Prof. Rupert Bartsch has disclosed Advisory Roles at Astra-Zeneca, Celgene, Daiichi, Eisai, Eli-Lilly, MSD, Novartis, Pfizer, Pierre-Fabre, Puma, Roche, and Samsung; Lecture Honoraria from Accord, Astra-Zeneca, BMS, Celgene, Eli-Lilly, Novartis, Pfizer, Pierre-Fabre, Roche, and Sandoz and Research Support from Daiichi, MSD, Novartis, and Roche.

Dr. Gabriel Rinnerthaler has disclosed a consulting role with Pierre Fabre, Roche, Novartis, Pfizer, and Eli Lilly. He is currently receiving research funding from Roche. He is on the speaker's bureau for Amgen, AstraZeneca, Novartis, Bristol-Myers Squibb, Roche, Pfizer, and Eli Lilly and has received travel and accommodation expenses from Roche, Novartis, Amgen, Pfizer, and Bristol-Myers Squibb.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article apart from those disclosed.

Funding Sources

Pierre Fabre Austria (Wels) provided financial support to fund medical writing activities.

Author Contributions

All named authors participated in the development of the manuscript and in the decision to submit this manuscript for publication. The authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Marija Balic: conceptualization, methodology, writing-original draft preparation, writing-review, and editing; Gabriel Rinnerthaler: conceptualization, methodology, writing-original draft preparation, writing-review, and editing; Rupert Bartsch: conceptualization, methodology, writing-original draft preparation, writing-review, and editing.

Data Availability Statement

Due to the nature of this review article/position paper using solely publicly available literature and reports no new data was generated to be made available by the corresponding author.

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