Clinical Cancer Research

U.S. Food and Drug Administration Approval: Neratinib for the Extended Adjuvant Treatment of Early-Stage HER2-Positive Breast Cancer

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Abstract

On July 17, 2017, the FDA approved neratinib (NERLYNX; Puma Biotechnology, Inc.) for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy. Approval was based on data from ExteNET, a randomized, double-blind, placebo-controlled multicenter trial. Women with early-stage HER2-positive breast cancer and within 2 years of completing adjuvant trastuzumab were randomized to neratinib ($n = 1{,}420$) or placebo ($n = 1{,}420$) for 1 year. The primary endpoint was invasive disease-free survival (iDFS), defined as the time between randomization date to first occurrence of invasive recurrence (local/regional, ipsilateral, or contralateral breast cancer), distant recurrence, or death from any cause, with 2 years and 28 days of follow-up. The trial showed a statistically significant treatment effect favoring neratinib with a stratified HR of 0.66 [95% confidence interval (CI), 0.49–0.90, $P = 0.008$]. The estimated iDFS rate at 2 years was 94.2% (95% CI, 92.6%–95.4%) in patients treated with neratinib versus 91.9% (95% CI, 90.2%–93.2%) in those receiving placebo. Diarrhea was the most common adverse event (AE), with a 40% incidence of grade 3 or 4 diarrhea, and represents the most common AE leading to treatment discontinuation. Other frequent AEs (>10% incidence) were nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, and muscle spasms. Other than diarrhea, neratinib is associated with a low incidence of severe AEs; toxicities are generally reversible and manageable with dose interruptions, dose reductions, and/or standard medical care. This article summarizes FDA decision-making and data supporting the neratinib approval. *Clin Cancer Res; 24(15); 3486–91. ©2018 AACR.*

See related commentary by Unni et al., p. 3483

Introduction

Breast cancer is the most frequently diagnosed malignancy in women and is the leading cause of cancer-related mortality in women worldwide. HER2-positive breast cancer comprises approximately 20% to 25% of the entire breast cancer population (1). HER2 protein overexpression or *HER2* gene amplification in breast cancer tumors is associated with more aggressive clinical disease and poorer prognosis (2). The standard adjuvant systemic therapy for patients with HER2-positive early breast cancer is chemotherapy and 1 year of trastuzumab (3). However, approximately 20% of patients with HER2-positive early breast cancer will experience a recurrence within 5 years after adjuvant therapy (4).

Trastuzumab (Herceptin; Genentech), a humanized HER2-directed mAb, is approved for the treatment of HER2-overexpressing breast cancer, both in the metastatic and the adjuvant settings. In addition, in December 2017, the FDA granted approval to pertuzumab for use in combination with trastuzumab and chemotherapy as adjuvant treatment for patients with HER2-positive early breast cancer at high risk of recurrence. Women with HER2-positive early-stage breast cancer treated with adjuvant concurrent chemotherapy and trastuzumab had a 4-year estimated disease-free survival (DFS) rate of 85.9% per the North American combined analysis. In the HERA trial, the 3-year estimated DFS rate was 80.6% for patients treated with trastuzumab after adjuvant chemotherapy (5). In the BCIRG 006 trial, the average 5-year DFS rate of two trastuzumab-containing arms was 82.5% (trastuzumab began concurrently with the chemotherapy; ref. 1). No approved therapies have improved upon the benefits of trastuzumab for HER2-positive patients in the adjuvant setting. For patients with hormone-receptor positive disease, several approved hormonal therapies are available for patients to take after completion of trastuzumab-based therapy in the adjuvant setting. A summary of these prior approvals is included in Table 1.

Chemistry

Neratinib maleate is described chemically as (E)-N-{4-[3-chloro-4-(pyridine-2-yl mehtoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl}-4-(dimethylamino)but-2-enamide maleate. It is a

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member of the 4-anilino quinoldine class of protein kinase inhibitors. The commercial neratinib drug product (NERYLNX; Puma Biotechnology, Inc.) is marketed as an immediate-release, film-coated tablet in one strength—40 mg.

Nonclinical Pharmacology and Toxicology

Neratinib is a kinase inhibitor that irreversibly binds to EGFR, HER2, and HER4. *In vitro*, neratinib inhibited cell proliferation, EGFR and HER2 autophosphorylation, downstream MAPK and AKT signaling pathways, and cell-cycle regulatory pathway activities in HER2- and EGFR-dependent cancer cell lines. Neratinib human metabolites M3, M6, M7, and M11 inhibited the activity of EGFR, HER2, and HER4 *in vitro*. *In vivo*, oral administration of neratinib inhibited tumor growth in mouse xenograft models with tumor cell lines expressing HER2 and EGFR.

The predominant target organs of toxicity for neratinib in rats and dogs following repeat dosing were the liver, lymph nodes, skin, gastrointestinal system, and mammary gland in males. Toxicity findings were consistent with the clinical adverse reactions reported in clinical trials, the majority of which (e.g., gastrointestinal and skin) are likely related to the pharmacologic inhibition of EGFR, HER2, or HER4. In a rat model of neratinib-induced diarrhea, budesonide was the most effective intervention tested against neratinib-induced diarrhea, which may guide future studies aimed at testing mitigation strategies for neratinib-induced diarrhea.

Neratinib and its metabolites were not genotoxic. Administration of neratinib to pregnant rabbits during organogenesis resulted in abortions, embryo-fetal death, and fetal abnormalities at maternal exposures (AUC) approximately 0.2 times exposures in patients at the recommended dose. Oral administration of neratinib to pregnant rats from gestation day 7 until lactation day 20 resulted in effects on long-term memory in male offspring at maternal doses less than the maximum recommended clinical dose on a mg/m^2 basis. Neratinib was not carcinogenic in a 26-week carcinogenicity study in rasH2 transgenic mice.

Clinical Pharmacology

Following oral absorption of neratinib tablet formulation, median time to peak neratinib plasma concentration (T_{max}) ranged from 2 to 8 hours after dosing. The food-effect assessment was conducted in healthy volunteers who received neratinib 240 mg under fasting conditions and with high-fat food or standard breakfast. A 2.2-fold increase in exposure was observed with a high-fat meal and a less than 20% increase in exposure with a standard breakfast. Neratinib is therefore recommended to be administered once daily with food. The oral volume of distribution of neratinib is approximately 6433 L. Neratinib is highly protein bound in human plasma (99%). The mean elimination half-life ranged from 7 to 17 hours, and the clearance (CL/F) at a steady state is estimated to be 281 L/hour. Increased exposure to neratinib has been observed in patients with severe hepatic impairment; thus, the dose of neratinib should be decreased in these patients. Dosage adjustment is not required in patients with renal impairment.

Neratinib is metabolized primarily by CYP3A and to a lesser extent by flavin-dependent monooxygenases. Concomitant use with a strong CYP3A4 inhibitor or strong CYP3A4 inducer dramatically changed neratinib exposures; thus, it is recommended to avoid concomitant use with strong CYP3A inhibitors and strong CYP3A inducers. Postmarketing requirement (PMR) and postmarketing commitment (PMC) studies were requested to evaluate the potential impact of a moderate CYP3A4 inhibitor and a moderate CYP3A4 inducer, respectively, on the pharmacokinetics of neratinib and its active metabolites to assess the magnitude of changed drug exposure and to determine appropriate dosing recommendations. In addition, concomitant use with a proton pump inhibitor (PPI) decreased exposure to neratinib by 65%, and concomitant use with treatments that alter gastrointestinal pH such as PPIs and H2-receptor antagonists should also be avoided.

Clinical Trials

The approval of neratinib was primarily based on a randomized, double-blind, placebo-controlled multicenter trial (Study 3004/ExteNET) of 1 year of neratinib versus placebo in 2,840 women with early-stage HER2-overexpressed/amplified breast cancer after adjuvant treatment with trastuzumab. Enrollment was limited to patients with stage 2 to 3 breast cancer after a major protocol amendment. Concurrent adjuvant endocrine therapy for hormone-receptor–positive disease was recommended. Patients were randomized from July 9, 2009, through October 24, 2011. The primary endpoint was invasive DFS (iDFS), defined as the time from randomization to the first occurrence of invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause. Randomization was stratified by hormone receptor status, nodal status (negative, 1–3 positive nodes or $\geq$4 positive nodes), and whether trastuzumab was given sequentially versus concurrently with chemotherapy. At initial study design, the applicant planned to follow patients for 5 years; however, a series of major amendments truncated the study design, decreasing follow-up time from 5 years to 2 years. In addition, the primary analysis was changed from event driven to time driven. After study completion, the applicant re-consented approximately 75% of the patients to collect extended follow-up data for up to 5 years after randomization. Recurrent disease was ascertained from the patients' medical records upon their re-consent. Expanded follow-up was conducted to evaluate the durability of the treatment effect on iDFS and the impact on OS. Other efficacy endpoints included overall survival (OS), defined as the time from the date of randomization until the date of death, with patients censored at the last date known alive.

Patient-reported outcomes (PRO) were collected for exploratory purposes at baseline, at months 1 and 3, then every 3 months thereafter during treatment until October 2011, when a major amendment ceased collection of PRO data. The instruments used included the Functional Assessment of Cancer Therapy for Patients with Breast Cancer (FACT-B) and the EuroQol five-dimension questionnaire (EQ-5D). The FACT-B questionnaire has 37 items consisting of the four primary domains of the Functional Assessment of Cancer Therapy—General (FACT-G), including physical well-being (PWB), social/family well-being, emotional well-being and functional well-being, and an additional breast cancer-specific subscale. The EQ-5D is a generic instrument for health status consisting of five items, including five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and a health state score measured with a vertical visual analog scale.

Table 1. FDA-approved hormonal adjuvant breast cancer therapies since 1999[a]

FDA approval drug and year	Treatment arms	DFS events (*N*)	Median follow-up (months)	Absolute difference in DFS event rate	HR
Placebo-controlled trial of letrozole 2004[b,c]	Letrozole	$N = 2,582$ 122 (4.7%)			
	Placebo	$N = 2,586$ 193 (7.5%)	28	2.8%	0.62
	CMF	$N = 360$ 169 (47%)			
Tamoxifen 1999	Approval based on overview of adjuvant therapy of 10-year outcome data ($N = 36,689$), 55 randomized trials 10-year OS: 61.4% tamoxifen vs. 50.5% control Recurrence-free rate at 10 years: 79.2% tamoxifen vs. 64.3% control				
Exemestane 2005	Tamoxifen	$N = 2,372$ 307 (13%)	35	4%	0.69
	Exemestane	$N = 2,352$ 213 (9%)			
Anastrozole 2005	Tamoxifen	$N = 3,116$ 651 (21%)	68	3%	0.87
	Anastrozole	$N = 3,125$ 575 (18%)			
Letrozole[c] 2005	Tamoxifen	$N = 4,007$ 369 (9.2%)	26	1.8%	0.79
	Letrozole	$N = 4,003$ 296 (7.4%)			

Abbreviation: CMF, cyclophosphamide, methotrexate, and fluorouracil.
[a]At the time of approval, some drugs also demonstrated an improvement in OS.
[b]Approval in extended adjuvant setting after 5 years of tamoxifen.
[c]Accelerated approval later converted to regular approval with additional follow-up data.

Demographics, Disease Characteristics, and Prior Treatment

All patients had locally confirmed invasive HER2-positive breast cancer stage 1 to 3 without evidence of recurrence. Patients must have received adjuvant trastuzumab within 1 or 2 years before registration. The median age was 52 years (range, 23–83), and 12% of patients were 65 or older. The majority of patients were white (81%), and most patients (99.7%) had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. Fifty-seven percent (57%) of patients had hormone receptor–positive disease [defined as estrogen receptor (ER) positive and/or progesterone receptor (PR) positive], 24% were node negative, 47% had one to three positive nodes, and 30% had four or more positive nodes. Thirty-one percent (31%) of patients had T1 disease, 41% had T2 disease, and 10% had T3 disease. The majority of patients (81%) were enrolled within 1 year of completion of trastuzumab treatment. Median follow-up time was approximately 2 years on both the neratinib and placebo arms.

Efficacy Results

The primary iDFS results at 2 years and 28 days following randomization are presented in Table 2 and Fig. 1. A statistically significant improvement in iDFS was observed in patients receiving neratinib compared with placebo. Notable results in select exploratory subgroups, including the stratification factors, are shown in Table 3. Approximately 75% of patients were re-consented for extended follow-up beyond 24 months. Observations with missing data were censored at the last date of assessment. This exploratory analysis suggests that the iDFS results at 5 years are consistent with the 2-year iDFS results observed in ExteNET. At the time of the primary iDFS analysis, 2% of patients had died, and OS data were immature.

Safety Results

Safety was evaluated in 1,408 patients treated with neratinib. The most common (greater or equal to 5%) adverse reactions included diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increase, nail disorder, dry skin, abdominal distension, decreased weight, and urinary tract infection. The most frequently reported grade 3 or 4 adverse reactions were diarrhea (40%), vomiting (3%), nausea (2%), and abdominal pain (2%). The median cumulative duration of any-grade diarrhea was 59 days (range, 1–523), and the median cumulative duration of grade $\geq$3 diarrhea was 5 days (range, 1–139). Serious adverse events (AE) occurred in 7.3% of patients receiving neratinib, with diarrhea occurring most frequently (1.6%). No deaths were reported within 28 days of the last neratinib dose. Thirty-one percent of patients treated with

Table 2. Efficacy iDFS results for the ITT population

Number of events/total *N* (%)		Estimated iDFS at 24 months[a] (%, 95% CI)		Stratified[b] HR (95% CI)	*P*[c]
Neratinib	Placebo	Neratinib	Placebo		
67/1,420 (4.7)	106/1,420 (7.5)	94.2 (92.6–95.4)	91.9 (90.2–93.2)	0.66 (0.49–0.90)	0.008

Abbreviation: ITT, intent-to-treat.
[a]Kaplan–Meier estimate.
[b]Stratified by prior trastuzumab (concurrent vs. sequential), nodal status (0–3 positive nodes vs. $\geq$4 positive nodes), and ER/PR status (positive vs. negative).
[c]Stratified log-rank test.

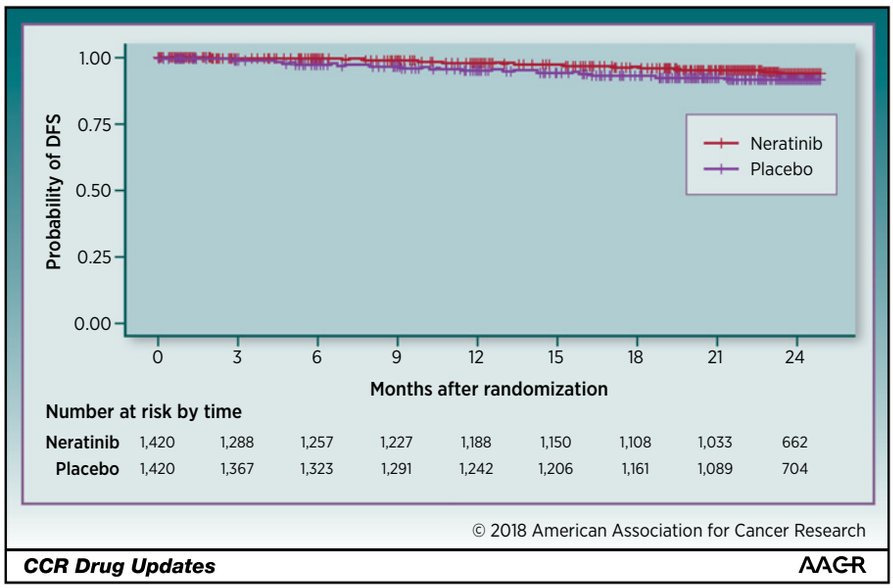

Figure 1.
Kaplan–Meier plot of DFS in the intent-to-treat population.

neratinib had at least one dose reduction due to an adverse reaction while on study, and 27% of patients in the neratinib group required treatment discontinuation. The most frequent AEs leading to dose reduction of neratinib were diarrhea (26.4%), nausea (2.8%), abdominal pain (1.6%), vomiting (1.3%), and fatigue (1.2%).

Diarrhea leading to severe dehydration, renal insufficiency, and electrolyte abnormalities is uncommon and reversible with treatment interruption and/or discontinuation. Results from an ongoing phase II study suggest that antidiarrheal prophylaxis decreases the incidence and severity of diarrhea; however, there may be a trade-off in terms of toxicities, with more constipation and nausea in the setting of loperamide prophylaxis, and approximately one fourth to one third of patients still discontinued treatment due to toxicity.

PRO Results

The FDA's descriptive analysis of available PRO data focused on the PWB subscale of the FACT-B questionnaire, as this subscale captured several aspects of patient-reported toxicities of neratinib, including lack of energy, nausea, and side effect bother. There was an unfavorable effect on the PWB scale when compared with baseline for those taking neratinib, which was largest at month 1 and persisted through month 12. Item-level analysis revealed a consistent worsening on the neratinib arm

Table 3. Exploratory subgroup analyses[a]

	Number of events/total *N* (%)		Kaplan–Meier estimate for iDFS at 24 months (%, 95% CI)		
Population	**Neratinib**	**Placebo**	**Neratinib**	**Placebo**	**Unstratified HR (95% CI)**
Hormone receptor status					
Positive	29/816 (3.6)	63/815 (7.7)	95.6 (93.8–96.9)	91.5 (89.2–93.3)	0.49 (0.31–0.75)
Negative	38/604 (6.3)	43/605 (7.1)	92.2 (89.4–94.3)	92.4 (89.8–94.3)	0.93 (0.60–1.43)
Nodal status					
Negative	7/335 (2.1)	11/336 (3.3)	97.2 (94.1–98.7)	96.5 (93.7–98.0)	0.72 (0.26–1.83)
1–3 positive nodes	31/664 (4.7)	47/664 (7.1)	94.4 (92.2–96.1)	92.4 (90.0–94.2)	0.68 (0.43–1.07)
≥4 positive nodes	29/421 (6.9)	48/420 (11.4)	91.4 (87.9–94.0)	87.3 (83.4–90.2)	0.62 (0.39–0.97)
Prior trastuzumab					
Concurrent	49/884 (5.5)	66/886 (7.4)	93.2 (91.0–94.8)	92.0 (89.9–93.7)	0.80 (0.55–1.16)
Sequential	18/536 (3.4)	40/534 (7.5)	95.8 (93.4–97.3)	91.6 (88.7–93.8)	0.46 (0.26–0.78)
Completion of prior trastuzumab					
≤1 year	58/1,152 (5)	95/1,145 (8.3)	93.8 (92.0–95.2)	90.9 (89.0–92.5)	0.63 (0.45–0.88)
1–2 years	9/262 (3.4)	11/270 (4.1)	95.8 (92.0–97.8)	95.7 (92.3–97.6)	0.92 (0.37–2.22)
Tumor size					
T1	10/440 (2.3)	15/459 (3.3)	97.2 (94.8–98.5)	96.4 (94.1–97.8)	0.75 (0.33–1.66)
T2	24/585 (4.1)	41/555 (7.4)	94.9 (92.5–96.6)	91.9 (89.2–94.0)	0.58 (0.34–0.95)
T3 and above	11/144 (7.6)	12/117 (10.3)	91.2 (84.6–95.0)	89.0 (81.4–93.6)	0.77 (0.33–1.76)
Clinical stage[b]					
I	1/139 (0.7)	3/152 (2.0)	99.1 (93.9–99.9)	97.8 (93.5–99.3)	0.41 (0.02–3.21)
II	15/596 (2.5)	27/564 (4.8)	97.0 (95.0–98.2)	94.8 (92.6–96.4)	0.55 (0.29–1.03)
III	30/444 (6.8)	40/430 (9.3)	91.9 (88.5–94.3)	89.7 (86.2–92.4)	0.75 (0.46–1.19)

[a]Exploratory analyses without adjusting for multiple comparisons.
[b]Stage II includes stage IIA and IIB patients; stage III includes stage IIIA, IIIB, and IIIC patients.

for the question "I am bothered by the side effects of my treatment," and there was a smaller but consistent worsening for "I have nausea."

Regulatory Insights

One important clinical trial objective is the collection of PRO data that can inform tolerability. The FDA is open to assessment of symptomatic AEs and their descriptive analyses for patients on therapy including impact of treatment on patient's functioning (i.e., physical function) and other aspects of health-related quality of life (HRQL). A limitation of the FACT instrument is that the subscales (such as PWB) combine treatment symptoms, disease symptoms, and impacts into a single score, making interpretation and communication of the subscale result challenging. In addition, neither FACT-B nor EQ-5D specifically captured patient-reported diarrhea or other gastrointestinal toxicities that were important clinical results, as previously described.

Disease-specific subscales such as the breast cancer–specific subscale of FACT-B do not have the flexibility to adapt to differing toxicities. For instance, the FACT-B asks patients about hair loss, an unanticipated side effect of neratinib, whereas diarrhea (a labeled adverse drug reaction requiring dose modification) and other important toxicities were not assessed within this disease-specific subscale. This is not unique to the FACT-B, as other static disease subscales can be problematic due to inability to adapt to different trial settings. The FDA encourages complementing HRQL assessments with item libraries where a selection of symptoms can be tailored to the symptomatic toxicities and disease symptoms that are relevant to the treatment and disease context under study.

Discussion

DFS in the adjuvant setting has been used in applications for oncology drugs to support approval. Approval of a drug under the provisions of 21 C.F.R. 314, subpart D (regular approval; ref. 6) is based on endpoints demonstrating clinical benefit, that is, how a patient feels, functions, or survives. DFS is a direct measure of clinical benefit and has been the primary basis of approval for adjuvant breast cancer, in which a large population of patients are expected to have cancer symptoms at the time of recurrence. An improvement in DFS represents a delay of recurrence or metastatic disease, as well as a delay of need for toxic therapy. In December 2003, at an Oncologic Drugs Advisory Committee (ODAC) meeting, the consensus was that DFS prolongation represented clinical benefit if the magnitude of this benefit outweighed the toxicity of the adjuvant treatment (7).

One of the major considerations during review of the neratinib application was assessing the magnitude of clinical benefit of DFS at 2 years for patients with early-stage HER2-overexpressed/amplified breast cancer following adjuvant trastuzumab-based therapy. The time-driven endpoint of 2-year DFS improvement was shorter than most other approvals in the adjuvant breast cancer setting, with an unclear risk–benefit relationship given the toxicity profile. However, the assessment of the relative risks and benefits of the use of neratinib for the treatment of early-stage HER2-positive breast cancer is based on the totality of evidence included in the new drug application (NDA) and consideration of expert opinion. During the review of the neratinib application, there was some uncertainty in the magnitude of treatment effect due to unplanned adaptations from multiple amendments and changes of industry sponsorship, an imbalance of early dropouts between treatment arms, and incomplete extended follow-up data. However, the unplanned adaptations appeared to have resulted from external information and not from any examination of internal data, thereby maintaining the integrity of the data. In addition, the FDA conducted sensitivity analyses via simulation to address the remaining issues of early dropouts in the primary analysis and missing data in the extended follow-up collected. Results showed that neither issue was likely to have a large impact on the study's overall results, providing supportive confidence that there was an effect of neratinib.

Another review issue surrounded exploratory subgroup analyses, which suggested that patients with hormone receptor–positive tumors, and those closer to completion of 1 year of trastuzumab treatment may derive greater benefit from treatment with neratinib. However, the study was not designed to assess treatment effects in any particular subgroup, so all subgroup analyses were considered exploratory or hypothesis generating, and no formal inference could be drawn. Furthermore, there was no detriment from treatment in any subgroup, thus supporting approval in a broad population.

An ODAC was convened on May 24, 2017, to discuss and provide advice on this NDA (8). Overall, the committee supported the benefit–risk profile for neratinib for its intended indication. The ODAC members commented that the proposed indication may be too broad, with different subsets of patients more responsive to neratinib therapy than others. Many committee members commented that a full description of the study population and subgroups should be provided in labeling, so providers and patients could make an informed decision about treatment. Committee members also commented that the data presented by the sponsor and the FDA were consistent and demonstrated efficacy. There was concern about the AE of diarrhea, but committee members noted that this AE was short-lived and manageable with the available antidiarrheal medications and reversible on discontinuation. Given increasing interest in patient experience data, members voiced concern that the PRO strategy for this trial did not allow for longitudinal patient-reported data to enhance understanding of the impact of diarrhea on patients. Ultimately, ODAC voted 12 to 4 that the risk–benefit profile of neratinib was sufficient to support treatment in the proposed indication.

On the basis of the advice of ODAC, the FDA provided a detailed description of exploratory subgroup analyses in labeling. The timing of initiation for this indication was clarified in the wording of the indication, "for extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, *to follow adjuvant trastuzumab therapy*." It is interesting to note that the ExteNET trial was conducted before the approval of pertuzumab in early-stage HER2-positive breast cancer. There is currently no available data describing outcomes of patients who receive pertuzumab and trastuzumab before neratinib. This remains an important clinical question. To address the issue of toxicity management, the FDA created a subsection in the label and added directions for the required antidiarrheal prophylaxis treatment to increase the prominence of this information and promote mitigation of common and potentially serious adverse reactions.

In summary, in the HER2-positive extended adjuvant setting, neratinib demonstrated efficacy superior to placebo, with a statistically significant improvement in iDFS with 2 years of follow-up. This improvement in iDFS is considered clinically meaningful and was supported by additional follow-up data. The safety profile of neratinib at 240 mg daily appears acceptable. Therefore, based on a favorable benefit–risk profile and substantial evidence of safety and efficacy, neratinib was granted regular approval for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

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