ONCOLOGIC DRUGS ADVISORY COMMITTEE
SPONSOR BRIEFING DOCUMENT

NERLYNX™ (NERATINIB)

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS

ADL	activities of daily living
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
aITT	amended ITT
Akt	protein kinase B
ALP	alkaline phosphatase
AST	aspartate aminotransferase
AT	aminotransferase (AST or ALT)
AUC	area under the concentration-versus-time curve
AUC_{inf}	area under the concentration-versus-time curve from time zero to infinity
AUC_{ss}	area under the concentration-versus-time curve at steady state
CBR	clinical benefit rate
CI	confidence interval
CL/F	mean apparent oral dose clearance
C_{max}	peak plasma concentration
CNS	central nervous system
CT	computed tomography
DCIS	ductal carcinoma *in situ*
DDFS	distant disease free survival
DFS	disease free survival
DFS-DCIS	disease free survival including DCIS
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EQ-5D	EuroQol-5D
ER	estrogen receptor
ERBB	pan-erythroblastic leukemia viral oncogene homolog
EU	European Union
FACT-B	Functional Assessment of Cancer Therapy for Breast Cancer

LIST OF ABBREVIATIONS (CONTINUED)

FDA	Food and Drug Administration
GI	gastrointestinal
H	Herceptin® (trastuzumab)
HER	human epidermal growth factor receptor
HR	hazard ratio
HRc	hormone receptor
HRQoL	health-related quality of life
IC_{50}	half-maximal inhibitory concentration
iDFS	invasive disease free survival
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
IND	Investigational New Drug
IP	investigational product
ISH	*in situ* hybridization
ITT	intent to treat
LFT	liver function test
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
N, n	number of subjects; number of samples
NA	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New Drug Application
NR	not reported
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSCLC	non-small cell lung cancer
ORR	overall response rate

LIST OF ABBREVIATIONS (CONTINUED)

OS	overall survival
pCR	pathologic complete response
PD	pharmacodynamics
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetics
po	*per os* (by mouth)
PPI	proton pump inhibitor
PR	partial response
qd	*quaque die* (once a day)
QTc	corrected QT interval
SAE	serious adverse event
SD	standard deviation
T	taxane
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time to peak concentration
TTDR	time to distant recurrence
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VAS	visual analogue scale
V_z/F	apparent volume of distribution

1. EXECUTIVE OVERVIEW

1.1. Indication

Puma Biotechnology, Inc. (Puma) is seeking United States (US) Food and Drug Administration (FDA) approval for neratinib (NERLYNX) monotherapy for the extended adjuvant treatment of adult patients with early stage human epidermal growth factor receptor 2 (HER2) over-expressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy. Neratinib is administered at a dose of 240 mg/day by mouth with food for 1 year.

1.2. Unmet Medical Need

The current standard of care adjuvant therapy for patients with HER2 positive early breast cancer includes treatment with chemotherapy (usually taxane based) plus 1 year of trastuzumab. An unmet medical need exists for additional interventions to improve upon the benefits of trastuzumab which targets HER2 and to reduce the risk of recurrence and death from HER2 positive breast cancer. Despite advances in early breast cancer adjuvant therapy for patients whose tumors are HER2 positive (see Section 2), disease recurrence remains a risk. Different strategies to improve disease free survival (DFS) in the adjuvant setting and extended adjuvant setting have been investigated, but have not been successful; these unsuccessful approaches include studies of trastuzumab and lapatinib. Data are pending for a study of pertuzumab which affects HER2 and HER3 dimerization.

Extended trastuzumab treatment was studied in the HERA trial (N=5102), which was designed to determine if 2 years of trastuzumab might be better than 1 year of therapy. The results showed that 2 years of adjuvant trastuzumab therapy did not add any improvement in DFS compared with 1 year of trastuzumab (hazard ratio [HR] 0.99; 95% confidence interval [CI] [0.85-1.14]; p=0.86); further, no improvement in overall survival (OS) was observed (HR 1.05; 95% CI [0.86-1.28]; p=0.63) (Goldhirsch, 2013). In addition, an increase in cardiotoxicity was observed after 2 years versus 1 year of therapy.

Incorporation of lapatinib, an oral tyrosine kinase inhibitor (TKI) targeting HER2 and epidermal growth factor receptor 1 (EGFR1) (HER1), into the adjuvant period was studied in the ALTTO trial (N=8381), where a strategy of dual HER blockade was used by adding lapatinib to trastuzumab. Lapatinib was studied as 1 year of adjuvant therapy following or concurrent with chemotherapy in a randomized 4 arm design: lapatinib + trastuzumab concurrently (N=2093); trastuzumab followed by lapatinib sequentially (N=2091); lapatinib alone (N=2100); and trastuzumab alone (N=2097). Lapatinib monotherapy performed worse than trastuzumab monotherapy in a head-to-head comparison of DFS (HR=1.34; 95% CI [1.13-1.60]; p<0.0005). Further, it did not add meaningful clinical benefit when administered either concurrently (HR=0.84; 97.5% CI [0.7-1.02]; p=0.048 [prespecified level for statistical significance was set at 0.025]) or sequentially (HR=0.96, 97.5% CI [0.8-1.15]; p=0.61) with trastuzumab (Piccart-Gebhart, 2016).

Incorporation of pertuzumab, a monoclonal antibody that binds to HER2 and impacts HER2 and HER3 heterodimerization, is currently being studied in the APHINITY trial (N=4805) where a different dual HER blockade approach is being evaluated by studying 1 year of

adjuvant therapy with the combination of trastuzumab + pertuzumab + chemotherapy vs. trastuzumab + chemotherapy in patients with HER2 positive breast cancer. The prespecified study design targeted a 2.6% difference in invasive disease free survival (iDFS) at 3 years (based on the assumptions of 80% power to achieve HR=0.75 and 3 year iDFS 89.2% vs 91.8% in a prespecified statistical plan) (Zhang, 2013). Pertuzumab received accelerated approval in the neoadjuvant setting based on a surrogate endpoint of improved pathologic complete response (pCR) rate. The APHINITY trial serves as the confirmatory trial in the adjuvant setting, with the intent of demonstrating that the neoadjuvant findings accurately predict adjuvant outcomes (von Minckwitz, 2011). It does not address the treatment of patients in the extended adjuvant setting. While the results of this trial have not been publicly disclosed, the sponsor, Roche/Genentech, issued a press release in March 2017 stating that the study achieved statistical significance for the primary endpoint of iDFS. No data were released, and none have been publicly communicated as of the writing of this briefing document. Therefore, the clinical meaningfulness and risk/benefit of these data are not publicly known.

In summary, there currently exists no HER2 targeted therapy approved in the extended adjuvant setting.

1.3. Clinical Development Program

The New Drug Application (NDA) for neratinib is supported by data from 31 clinical studies, including the pivotal ExteNET Trial, also referred to as Study 3004. An overview of neratinib clinical studies is presented in Table 1; details are provided in Appendix A.

Table 1: Neratinib Clinical Studies

Number of Studies	Phase	Study Population/Indication	Type	Number of Subjects Treated (number treated with neratinib)
1	3	Extended adjuvant HER2 positive breast cancer (ExteNET [3004] study)	Pivotal safety and efficacy monotherapy	Treated: 2816 (1408)[c]
1	2	Extended adjuvant HER2 positive breast cancer (CONTROL [6201[a]] study)	Diarrhea prophylaxis, safety study	211 (211)
9	2	Metastatic breast cancer	Safety, efficacy, and PK monotherapy or combination	1291 (942)
3	2	Advanced or metastatic lung cancer and other tumor types[a]	Safety, efficacy, and PK - monotherapy or combination	405 (405)
5	1	Phase 1 solid tumors	Dose-finding and PK (monotherapy or combination), Japanese studies	176 (176)
12	1	Clinical pharmacology studies in healthy volunteer studies	PK, DDI, TQTc, hepatic impairment, ADME	377 (357)
2	2	Neoadjuvant HER2 positive breast cancer[b]	pCR	319 (199)

Abbreviations: ADME=absorption, distribution, metabolism, and excretion; DDI=drug-drug interaction; NSABP=National Surgical Adjuvant Breast and Bowel Project; pCR= pathologic complete response; PK=pharmacokinetics; TQTc=Thorough QTc study.
[a] Enrollment ongoing for 2 studies (6201 and 5201). Enrollment for Study 5201 is reported as of 120-day Safety Update; for Study 6201, enrollment is from the more recent Feb 2017 update.
[b] Neoadjuvant trials included I-SPY2 and NSABP-FB-7 conducted by cooperative groups with support from Puma. [c]Study 3004 enrolled 2840 patients randomized 1:1 (1420 patients per arm).

1.3.1. Efficacy Findings

The ExteNET Trial (Study 3004) was a Phase 3, randomized, double blind, placebo controlled trial of extended adjuvant therapy in patients with HER2 positive breast cancer who had been previously treated with trastuzumab based adjuvant therapy (N=2840). Patients were randomized in a 1:1 ratio to receive either neratinib monotherapy (N=1420) or placebo (N=1420). The prespecified primary endpoint was iDFS, defined as the time from randomization to first occurrence of invasive ipsilateral tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause. The intent to treat (ITT) population included all randomized patients.

Study 3004 met its prespecified primary efficacy endpoint, demonstrating statistically significant improvement of iDFS in patients treated with neratinib (240 mg/day for 12 months) compared with placebo, based on the primary prespecified ITT population where all patient data were cut at 2 years (stratified HR=0.66; 95% CI [0.49, 0.90]; 2-sided p=0.008) (Table 2). This represents a 34% relative reduction in risk of recurrence. iDFS events within 2 years of randomization occurred in 67 patients (4.7%) in the neratinib group and 106 patients (7.5%) in the placebo group. In addition, the iDFS rate at the landmark of 2 years was higher in the neratinib group than in the placebo group (94.2% vs 91.9%, respectively). These results were supported by favorable outcomes in the sensitivity analyses and secondary endpoints.

Table 2: Results of Primary and Secondary Endpoints with 2 Year and 5 Year Data Cut (Study 3004)

Endpoints	Primary Analysis 2 Year Data Cut (N=2840) Hazard Ratio (p-value) (95% CI)	Sensitivity Analysis 5 Year Data Cut (N=2840) Hazard Ratio (p-value) (95% CI)
iDFS (primary)	**0.66 (p=0.008)** (0.49, 0.90)	**0.73 (p=0.008)** (0.57, 0.92)
DFS-DCIS	**0.61** (0.45, 0.83)	**0.71** (0.56, 0.89)
DDFS	**0.74** (0.52, 1.05)	**0.78** (0.60, 1.01)
TTDR	**0.73** (0.51, 1.04)	**0.79** (0.60, 1.03)

Abbreviations: CI=confidence interval; DDFS=distant disease free survival; DFS-DCIS=disease free survival including ductal carcinoma *in situ*; iDFS=invasive disease free survival; TTDR=time to distant recurrence

Subgroup analyses were also generally supportive, with nearly all HRs favorable for neratinib. Details regarding these analyses are presented in Section 8.4.1.3. There were 2 subgroups of interest, the results of which are presented in Table 3. The first subgroup, hormone receptor (HRc) positive patients, achieved notable benefit, and HRc status had a significant test of interaction ($p<0.05$). In clinical practice it is likely that neratinib will be sequenced shortly after the completion of adjuvant trastuzumab. The results of the adjuvant trastuzumab studies suggest that patients are at a higher risk of recurrence closer to completion of adjuvant trastuzumab, and the risk of recurrence may decrease over time. Therefore the subgroup of patients who were treated with neratinib less than one year after the completion of adjuvant trastuzumab are at a higher risk of recurrence than the subgroup of patients who were treated with neratinib more than one year after the completion of adjuvant trastuzumab (Table 3).

Table 3: Subgroup Analyses of iDFS by HRc Status (Positive/Negative) and Time from Completion of Adjuvant Trastuzumab (≤ 1 year / > 1 year) (Study 3004)

Endpoint (Subgroup)	Primary Analysis 2 Year Data Cut (N=2840) Hazard Ratio (95%CI)	Sensitivity Analysis 5 Year Data Cut (N=2840) Hazard Ratio (95%CI)
HRc Status		
iDFS (N=1631) (HRc positive)	0.49 (0.31, 0.75)	0.60 (0.43, 0.83)
iDFS (N=1209) (HRc negative)	0.93 (0.60, 1.43)	0.95 (0.66, 1.35)
Test for interaction	p=0.045	p=0.063
Time from Completion Adjuvant Trastuzumab		
iDFS (N=2297) ≤1 year from completion trastuzumab	0.63 (0.45, 0.88)	0.70 (0.54, 0.90)
iDFS (N=543) > 1 year from completion trastuzumab	0.92 (0.37, 2.23)	1.00 (0.51, 1.94)
Test for interaction	p=0.529	p=0.406

Abbreviations: CI=confidence interval; HRc=hormone receptor; iDFS=invasive disease free survival

Supportive data from other neratinib clinical trials provide confidence in the efficacy findings of Study 3004. The key findings from trials in metastatic and neoadjuvant HER2 positive breast cancer are as follows:

- Neratinib+chemotherapy demonstrated a consistent magnitude of efficacy as measured by pCR in the neoadjuvant setting in two different cooperative group trials, I-SPY2 (39%) and NSABP FB-7 (33%). Neratinib performed better than trastuzumab in the I-SPY2 trial (particularly in the subgroup of patients that were HRc negative (pCR=56%) and, when added to trastuzumab as part of a dual anti-HER2 strategy, was able to increase the pCR rate to 73.7% in HRc negative patients.
- Neratinib monotherapy in patients with metastatic breast cancer previously treated with trastuzumab achieved independently confirmed objective tumor response rates in more than one clinical trial in the range of 25.4% (Study 201) - 29.1% (Study 3003). This is in the context of historical lapatinib monotherapy response rate of 4.3% (1.4% if independently confirmed) (Burstein, 2008) and 7.7% (5.1% if independently confirmed) (Blackwell, 2009) and afatinib monotherapy response rate of 10% (Lin, 2009).

- Neratinib monotherapy in patients who were naïve to trastuzumab, but previously treated for their metastatic breast cancer, provided an independently confirmed objective tumor response rate of 53.8% (Study 201). This is in context of a historical trastuzumab monotherapy response rate of 22% (Cobleigh, 1999).
- As frontline metastatic breast cancer therapy, neratinib + paclitaxel provided similar efficacy results as the standard of care trastuzumab + paclitaxel, with a median progression-free survival (PFS) of 12.9 months with each combination, and overall response rates (ORRs) of 74.8% and 77.6% respectively (Study 3005).
- Neratinib + paclitaxel treatment may favorably impact central nervous system (CNS) recurrence/progression in the metastatic setting (Study 3005). Cumulative incidence of CNS events was 10.1% in patients treated with neratinib + paclitaxel and 20.2% in patients treated with trastuzumab + paclitaxel.

1.3.2. Safety Findings

The neratinib safety database consists of 31 clinical studies conducted by the sponsor, in which 3252 subjects received neratinib as monotherapy or in combination with other anticancer agents.

The safety profile for neratinib monotherapy in the extended adjuvant setting was evaluated in the context of the Phase 3 randomized, double blind, placebo controlled pivotal trial, Study 3004, and in the ongoing Phase 2 Study 6201 designed to assess different anti-diarrhea prophylaxis regimens. Section 9 of this briefing book focuses on the safety data from these 2 studies; the NDA submission included integrated safety analyses across all 3252 subjects in the safety database. Additional patients were subsequently enrolled in Study 6201 since the original NDA submission.

In Study 3004, the most common adverse event (AE) was diarrhea, which occurred in 95% of patients (all grades) and was Grade 3 in severity in 40% of patients. This is an expected on-target, class effect for EGFR targeting agents. Most diarrheal events occurred in the first month of therapy and lasted a median of 2 days in duration. Complications related to neratinib related diarrhea were infrequent; the rate of hospitalization due to neratinib-associated diarrhea was 1.4%.

Diarrhea was dose limiting in some patients in Study 3004. This prompted further studies to investigate anti-diarrheal prophylaxis regimens to prevent or reduce the incidence of Grade 3 diarrhea and improve the tolerability of neratinib. Study 6201 is an ongoing study investigating 3 prophylaxis regimens: loperamide, loperamide plus budesonide, and loperamide plus colestipol. Data from the first 2 study groups are available and have demonstrated a reduction in the incidence of Grade 3 diarrhea to 31% (loperamide) and 20% (loperamide+budesonide); median duration per episode of diarrhea ranges from 1 day (loperamide+budesonide) to 2 days (loperamide). The addition of prophylaxis in Study 6201 reduced the occurrence and severity of neratinib-associated diarrhea compared to Study 3004. Data from Study 6201 are presented to support patient management strategies for addressing the diarrhea. Other common AEs in Study 3004 occurring more often with neratinib than placebo include nausea, fatigue, vomiting, abdominal pain, rash, decreased appetite, and muscle spasms.

In Study 3004, dose reductions were higher in the neratinib group compared with the placebo group, and these dose reductions were primarily due to diarrhea. An exploratory efficacy analysis of patients who had dose reductions vs. those without dose reductions vs. placebo was conducted. In neratinib treated patients with dose reductions, iDFS remained superior to placebo (HR, 0.67; 95% CI [0.43, 1.01]). The neratinib patients without dose reduction continued to be superior to placebo for iDFS (HR, 0.66; 95% CI [0.46, 0.94]).

Overall, except for diarrhea, neratinib is associated with a low incidence of severe AEs. In 3004, severe dehydration, renal insufficiency, and electrolyte abnormalities were uncommon and reversible with dose hold, dose reduction, and/or dose discontinuation. Neratinib was associated with transient transaminase elevations, which were mainly mild or moderate in severity, and reversible. Higher grade elevations in transaminases were infrequent, asymptomatic, and resolved without sequelae, either without intervention or with dose modification or discontinuation. Elevation in hepatic enzymes in neratinib-treated patients can be managed with monitoring of liver function tests (LFTs) and dose reduction or discontinuation. There is no evidence of cardiac toxicity with neratinib therapy.

1.4. Important Study Design Changes in Study 3004

Since the initiation of Study 3004, several changes have been made in the study sponsorship and study design that are worth noting here. It is critical to note that the study blind was maintained throughout the conduct of the trial, database lock, and analysis of the primary endpoint in July 2014. None of the changes were the result of unblinding.

There were two changes in industry sponsor: Wyeth was acquired by Pfizer in 2009 and study sponsorship was transferred to Puma in 2012.

In 2010, Protocol Amendment 3 stopped enrollment of node negative patients and patients who were greater than 1 year past completing their adjuvant therapy. These groups were to be excluded from the primary analysis, and an amended ITT (aITT) population became the primary analysis population.

In 2011, Protocol Amendment 9 curtailed enrollment resulting in decreased sample size from 3850 to 2840, and the per-patient follow-up period for the primary endpoint (iDFS) was reduced from 5 years to 2 years (business decision).

In 2014, Protocol Amendment 13 restored the primary analysis population to the ITT population; the amendment also reinstituted a 5 year follow up period. This required participating subjects to be re-consented for 3 additional years of follow-up, during which follow-up disease assessment was based on retrospective medical record review (not protocol specified).

A detailed and comprehensive process was implemented to minimize bias for the re-consenting process. Clinical operations infrastructure was maintained to preserve operational consistency, and the Independent Data Monitoring Committee (IDMC) was retained to preserve safety and integrity of blinding. The statistical analysis plan was locked prior to unblinding and specified the ITT analysis of the iDFS endpoint cut at 2 years as the primary analysis with the full 5% alpha allocated. OS is a key secondary endpoint and will be tested at 5% once 248 events are reached.

1.5. Favorable Benefit Risk Profile

Neratinib is an orally administered irreversible TKI that targets EGFR, HER2 and HER4 via the intracellular domain and improves iDFS as extended adjuvant therapy in patients with early stage HER2 positive breast cancer, thereby making it an important new therapeutic tool in the treatment of early breast cancer. For patients with breast cancer whose tumors are positive for HER2 and who have completed the standard of care anti-HER2 adjuvant therapy, 1 year of neratinib provides an important new option for extended adjuvant HER targeted therapy where no other option exists. The ExteNET Study (Study 3004) was designed as a Phase 3, randomized, double blind, placebo controlled trial to determine the benefit of extended adjuvant neratinib therapy in breast cancer patients whose tumors were HER2 positive and who had completed adjuvant therapy containing trastuzumab. The prespecified primary endpoint was invasive DFS (iDFS), assessed as a time to event endpoint and using the ITT population. Data were cut at 2 years, supplemented with a sensitivity analysis using a data cut at 5 years. The overall benefit provided is best represented by the iDFS HR = 0.66 (95% CI 0.49, 0.90; p=0.008, 2 sided) at the 2 year data cut. The 5 year analysis provided further evidence of durability of the benefit with an HR=0.73 (95% CI 0.57, 0.92; p=0.008). As noted above, a reconsenting process was instituted to maximize the number of patients and follow-up data included in the 5 year analysis. The baseline characteristics between the ITT population (N=2840) and the reconsented population (N=2117; neratinib, 1028; placebo, 1089) provides added confidence in the 5 year data cut. The favorable HRs observed across all secondary endpoints that were upheld at the 5 year data cut provide further confidence in the observed outcomes and are supportive of the primary iDFS endpoint. Additional sensitivity and exploratory analysis provide further support and are described in detail in Section 8.

These efficacy benefits need to be weighed against the neratinib safety profile. The large number of patients treated in the neratinib program, including randomized data from Study 3004, provides robust monotherapy experience from which considerable understanding of the risks can be ascertained. Diarrhea is the primary AE observed and the most common AE leading to discontinuation of neratinib. Diarrhea is an expected on-target effect since neratinib targets EGFR and the gastrointestinal (GI) tract has high numbers of EGFRs. Diarrhea with neratinib most commonly occurs during the first month of treatment and then tapers off after that point, even with continued dosing. Dose reductions are permitted and prophylaxis with loperamide reduces the incidence of ≥ Grade 3 diarrhea. During the first month of neratinib therapy, prophylaxis with loperamide and budesonide further reduces the incidence of ≥ Grade 3 diarrhea and reduces the number of patients who discontinue neratinib. With careful management, including prophylaxis with loperamide and budesonide at the initiation of neratinib therapy, most patients would be able to stay on neratinib therapy long term. Notably, neratinib does not increase the risk of cardiotoxicity in the patient population studied and does not increase the toxicities of anti-hormonal therapy such as reduction in bone density, bone fractures, changes in lipid profile, secondary malignancies (e.g., endometrial cancer), arthralgias, and hot flashes.

In addition to assessing the benefits and risks of neratinib in isolation, it is important to consider neratinib within the context of therapies approved in the adjuvant and extended adjuvant setting. Table 4 lists results for a number of approved agents across multiple drug

classes. Over the years, the benefit from each advance has improved the outcomes incrementally for early breast cancer patients when considered cumulatively. The magnitude of benefit provided by neratinib is similar to what has led to prior approvals.

The data in Table 4 are the result of a sponsor analysis of publically available data. The sponsor conducted an analysis of adjuvant and extended adjuvant therapies approved for early breast cancer patients and compiled it along with the top line neratinib results in order to better understand the neratinib clinical benefit as it relates to available therapies. Specifically, the focus of this exploratory assessment was to understand efficacy at Year 2 and Year 5.

The methods for this assessment were as follows. US product labels (USPI or full prescribing information) were used as the primary source of data; this was supplemented, in some cases, with data from publications. HRs, CIs, and p-values were taken directly from the product label for each therapeutic agent. Because the labels do not include the absolute difference at landmark time points, the sponsor used a computer software program to digitize the Kaplan-Meier (KM) DFS curve images that were in the label. With these digitized images of the KM curves, the iDFS rate at specific time points was "read" based on the digital coordinates; in this way, estimates of iDFS rates at Year 2 and Year 5 were made. In cases where the KM curves did not extend out to 5 years, this was noted in the table as not reported (NR). In cases where the KM curves were not included in the label (i.e., letrozole MA-17 and BIG 1-98 studies; trastuzumab HERA study), the primary manuscripts containing the definitive DFS analyses were obtained, and the relevant 2 year or 5 year absolute differences in DFS were applied as reported in the manuscripts (Goss 2003, Piccart-Gebhart 2005, The Breast International Group (BIG) 1-98 Collaborative Group 2005).

Standard precautions with regard to cross study comparisons apply. Complexities of this analysis are that definitions of DFS may have varied between trials and may have varied between the product label and the published manuscript for a given study. Additional aspects of the analyses may differ between product labels and published manuscripts, because the FDA may have required different methodology, for example in terms of censoring. It should be noted that in the Section 2 of this briefing book (Unmet Medical Need), the background information on these adjuvant and extended adjuvant therapies is more extensive and more detailed and relies primarily on published manuscript data; therefore, some of the values reported in Table 4 may differ slightly from data described in Section 2.

The outcome of this analysis is that the absolute percentage point improvement in 2 year DFS estimates fall in the range of 1.6 to 8.4 percentage points. The neratinib results are within this range.

Table 4: Neratinib Extended Adjuvant Breast Cancer Results in the Context of FDA Approved Adjuvant Breast Cancer Therapies: Results and Estimates of Absolute Improvement in 2 Year and 5 Year DFS Rates from Kaplan-Meier Curves

Drug	Trial	Indication (Endpoint)	Population	Hazard Ratio (95% CI)	P-value	Median Follow-up (months)	Absolute DFS Improvement 2-year	Absolute DFS Improvement 5-year
Paclitaxel	CALGB/ECOG/ NCCTG/SWOG	Adjuvant (DFS)	ITT	0.78 (0.67, 0.91)	0.0022	30.1	4.4%	NR
Docetaxel	BCIRG 001/TAX316	Adjuvant (DFS)	ITT	0.74 (0.60, 0.92)	0.0047	55	5.4%	5.8%
Anastrazole	ATAC	Adjuvant (DFS)	ITT	0.87 (0.78, 0.97)	0.0127	68	1.6%	2.7%
Letrozole	BIG 1-98	Adjuvant (DFS)	ITT	0.79 (0.68, 0.92)	0.002	26	1.7%	2.6%
	MA17	Ext Adjuvant (DFS)	ITT	0.62 (0.49, 0.78)	0.00003	28	1.9%	NR
Exemestane	IES 031	Adjuvant (DFS)	ITT	0.69 (0.58, 0.82)	0.00003	34.5	3.1%	NR
Trastuzumab	NCCTG N9831/NSABP B-31	Adjuvant (DFS)	ITT	0.48 (0.39, 0.59)	<0.0001	24	7.2%	NR
	HERA[a]	Adjuvant (DFS)[b]	ITT	0.54 (0.44, 0.67)	<0.0001	12.6	8.4%	NR
	BCIRG 006 ACTH	Adjuvant (DFS)	ITT	0.60 (0.48, 0.76)	<0.0001	NR	5.8%	NR
	BCIRG 006 TCH	Adjuvant (DSF)		0.67 (0.54, 0.84)	0.0006	NR	4.5%	NR

Table 4: Neratinib Extended Adjuvant Breast Cancer Results in the Context of FDA Approved Adjuvant Breast Cancer Therapies: Results and Estimates of Absolute Improvement in 2 Year and 5 Year DFS Rates from Kaplan-Meier Curves (Continued)

Drug	Trial	Indication (Endpoint)	Population	Hazard Ratio (95% CI)	P-value	Median Follow-up (months)	Absolute DFS Improvement 2-year	Absolute DFS Improvement 5-year
Neratinib	ExteNET (Study 3004)	**Ext Adjuvant[f] (2 year iDFS)**	**ITT**	**0.66[c] (0.49, 0.90)**	**0.008**	**24**	**2.3%**	**NR**
		Ext Adjuvant (2 year iDFS)	HRc+	0.49[d] (0.31, 0.75)	0.001	24	4.1%	NR
		Ext Adjuvant (2 year iDFS)	(≤1 year after trastuzumab)	0.63 (0.45, 0.88)	0.006	24	2.9%	NR
		Ext Adjuvant (5 year iDFS sensitivity analysis)	ITT	0.73[e] (0.57, 0.92)	0.008	60	2.6%	2.5%
		Ext Adjuvant (5 year iDFS sensitivity analysis)	HRc+	0.60[e] (0.43, 0.83)	0.002	60	3.7%	4.4%
		Ext Adjuvant (5 year iDFS sensitivity analysis)	(≤1 year after trastuzumab)	0.70 (0.54, 0.90)	0.006	60	3.0%	3.2%

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Abbreviations: CI=confidence interval; DFS=disease free survival; Ext=extended; HRc=hormone receptor; iDFS=invasive disease free survival; ITT=intent to treat; NR=not reported; US=United States

[a] For the HERA trial, only the data for 1 year of adjuvant trastuzumab are provided in this table. Two years of trastuzumab was no better than 1 year of trastuzumab; therefore, approval was based on 1 year.

[b] The DFS endpoint in the HERA trial included ductal carcinoma *in situ* (DCIS), but the trastuzumab package insert definition did not include DCIS.

[c] Primary analysis of Study 3004 (ExteNET)

[d] Subgroup analysis of Study 3004

[e] Sensitivity analysis of Study 3004

[f] Neratinib extended adjuvant therapy was initiated ≤1 year from completion of adjuvant trastuzumab in most patients (2297/2840, 80.9%).

Source: US package insert for each approved product listed; neratinib clinical development program.

1.6. Conclusions

The totality of evidence demonstrating the magnitude of activity of neratinib to treat HER2 positive breast cancer across multiple clinical settings, including the strong neoadjuvant data, provides robust scientific and clinical rationale for proceeding into the adjuvant setting with neratinib. An unmet medical need exists during the "extended adjuvant period" or the time after completion of standard of care adjuvant therapy with other anti-HER2 therapy. Patients who have completed their 1 year of trastuzumab adjuvant therapy have no options for further anti-HER2 treatment and enter into a "watch and wait" period. In the interest of being able to turn this time into a period of active anti-HER2 therapy with the intent to provide further improvement in DFS, neratinib was studied as extended adjuvant therapy in a multicenter randomized, double blind placebo controlled Phase 3 Study 3004 (N=2840) which demonstrated clinically meaningful and statistically significant improvement in iDFS with a manageable safety profile consistent with other approved agents within the class of TKIs targeting EGFR and HER2. The sponsor believes the totality of the data support approval of neratinib 240 mg po qd for 1 year in the extended adjuvant setting in order to provide physicians and patients with a new strategic therapeutic option to reduce the rate of recurrence of HER2 positive breast cancer.

Critical conclusions in regard to clinical data for extended adjuvant therapy with neratinib for 1 year following trastuzumab based adjuvant therapy in the context of standard adjuvant therapies are as follows:

- Neratinib, as an irreversible TKI inhibitor of HER2, EGFR and HER4, provides an extended adjuvant breast cancer treatment option with a non-overlapping mechanism of action (MOA) for patients previously treated with trastuzumab and chemotherapy and reduces the risk of generally fatal breast cancer recurrences.
- The relative (HRs) and absolute (percentage points) improvements in DFS in the adjuvant breast cancer setting have been incremental and cumulative.
- Neratinib Study 3004 results for iDFS are consistent with what has been determined to be clinically meaningful in past studies.
- The side effect profile of other adjuvant therapies that are considered part of standard of care exist on a spectrum. Nonetheless, incremental DFS benefits have been determined to outweigh the risks.
- Neratinib, even with the need to manage diarrhea which is reversible but can be treatment limiting in some patients, has an overall side effect profile that falls within the spectrum of standard breast cancer therapies and has the advantage of not causing serious organ damage or other life threatening toxicities.
- Neratinib would be the only HER2 targeted therapy administered orally in the extended adjuvant setting.
- Neratinib's demonstrated efficacy in the extended adjuvant setting is supported by a large body of evidence of activity in the neoadjuvant setting and metastatic settings.

2. UNMET MEDICAL NEED

Breast cancer is a heterogeneous, phenotypically diverse disease comprised of numerous biologic subtypes with distinct behavior. HER2 positive breast cancer represents approximately 15% to 25% of all breast cancers, affecting approximately 50,000 newly diagnosed women annually in the US (SEER, 2015). Of these, approximately 30,000 will be diagnosed with early stage disease (SEER, 2015). HER2 positive breast cancer is more aggressive with an increased rate of recurrence than other subtypes, and advanced metastatic disease is associated with a poor prognosis (Slamon 1987, Slamon 1989). Surgery, followed by adjuvant therapy, offers the best possibility for cure of early-stage disease. The goal of adjuvant therapy is to administer systemic therapy to eliminate microscopic undetectable disease, thereby preventing recurrence with the ultimate intent of cure. The history of adjuvant therapy can be considered in terms of three strategies: cytotoxic chemotherapy; endocrine therapy; and anti-HER2 targeted therapy. It is helpful to review critical studies that have provided stepwise incremental improvements in the recurrence rates leading to the current standard of care. It is also important to review extended adjuvant therapy strategies that did not improve on the current adjuvant standard of care or demonstrate efficacy in the extended adjuvant setting.

Cytotoxic chemotherapy was the first strategy employed in the postsurgical adjuvant setting; many regimens have been studied over a 30-year period. First generation regimens achieved 30-35% relative improvements in outcomes. In the 1970s, after successes seen with single agent therapies (thiotepa, nitrogen mustard), the first combination regimen (cyclophosphamide/ methotrexate/fluorouracil [CMF]) was proven superior to observation, with a DFS HR of 0.71 (p=0.005) in node-positive patients (Bonnadonna 1976, Bonnadonna 2005). CMF+tamoxifen was superior to tamoxifen alone for DFS (HR 0.65, p=0.001) in node-negative patients (Fisher, 1997). The anthracycline-based regimen doxorubicin/cyclophosphamide (AC) was compared with CMF in NSABP B-15 (in node-positive) and B-23 (node-negative patients); no statistical differences were observed between the two regimens (Fisher 1989, Fisher 1990, Fisher 2001).

With the introduction of taxane therapies, the second generation of combination regimens demonstrated further incremental improvements, albeit smaller in magnitude, in the range of 10-20% relative improvements compared to regimens described in the previous paragraph. Further, such regimens were met with the challenge of anthracyclines and taxanes having increased cardiac toxicity and needing to be administered sequentially. NSABP B-28 compared AC followed by paclitaxel (T) with AC and showed that adding the taxane improved DFS in node-positive patients (HR 0.83, p=0.006) (Mamounas, 2005); a similar trial (CALGB 9344) showed comparable magnitude of benefit HR 0.83, p=0.002 (Henderson, 2003).

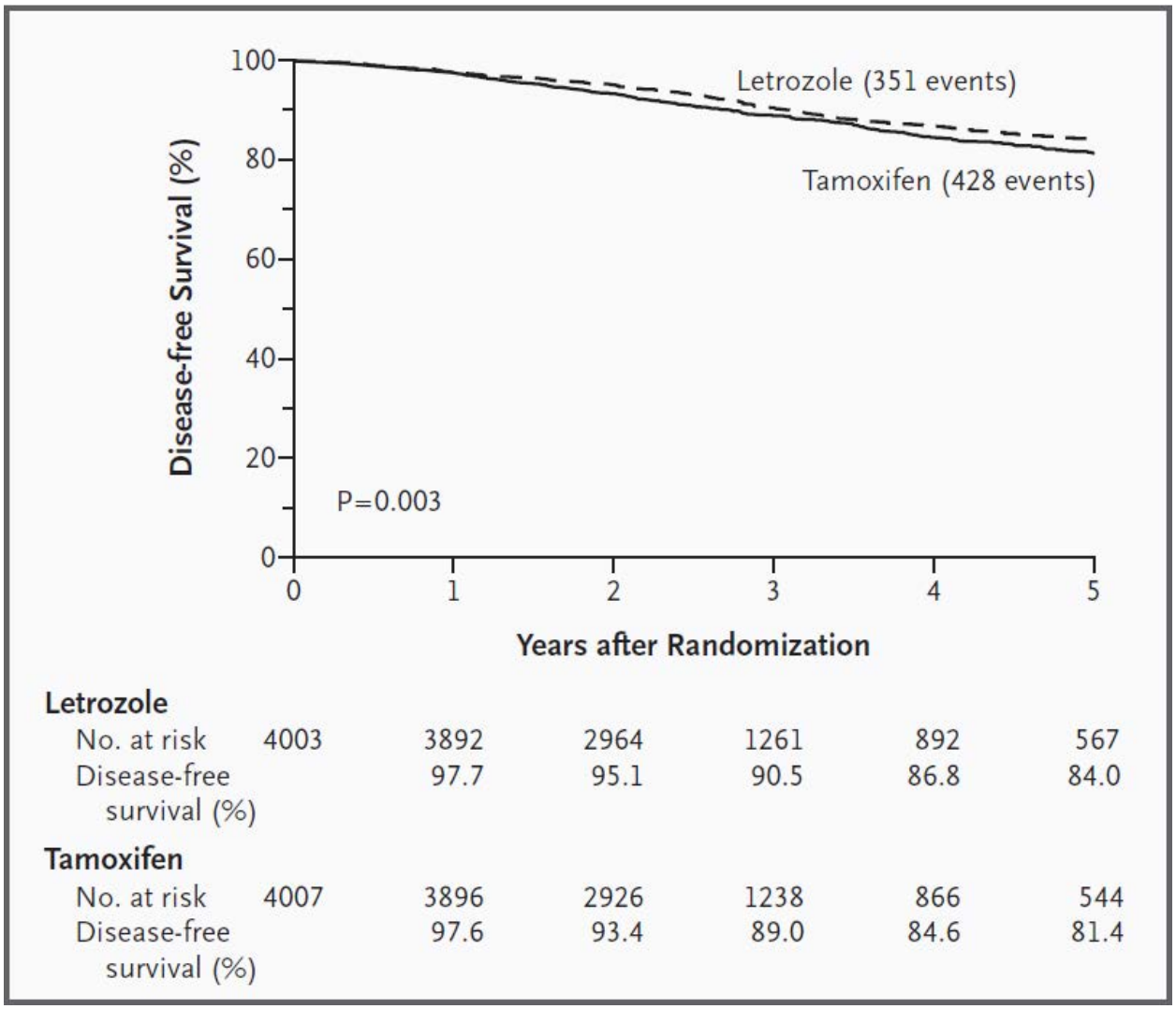
Third generation regimens incorporated docetaxel, which could be administered with anthracyclines; with these regimens, 20% relative improvements were observed over second generation regimens. Study BCIRG 001/TAX316 compared DAC (docetaxel+AC) vs. FAC (fluorouracil+AC) and showed that DAC was superior (HR 0.80 p=0.0043) in node-positive patients (Martin, 2005). These results were confirmed in node-negative patients in a second trial (Martin, 2010). However, toxicity was higher with the DAC regimen.

Dose density was further explored in multiple trials. A meta-analysis of 10 trials demonstrated an advantage for dose-dense regimens (DFS HR=0.83; p=0.005), with benefit primarily observed in patients with HRc negative disease (Bonilla, 2010). Side effects of chemotherapy were significant, especially with dose intensified regimens, and in some cases, were dose limiting. Such side effects included myelosuppression and associated complications (febrile neutropenia, infections, anemia, bleeding); cardiotoxicity, including congestive heart failure; hepatotoxicity; neuropathy; alopecia; and GI side effects including nausea, vomiting, and diarrhea. GI side effects were the most common and debilitating.

Hormonal therapy as a treatment strategy was developed in parallel with combination chemotherapy. In Study NSABP-14, patients with HRc positive breast cancer were initially assigned to receive either tamoxifen or placebo. Patients who received tamoxifen and remained disease free at 5 years were then reassigned to receive either tamoxifen or placebo for another 5 years. Through 10 years of follow-up, 5 years of tamoxifen therapy provided significant benefit in terms of DFS (relative risk 0.66, p=0.0001), and 10 years was no better than 5 years (Fisher, 1996).

With the advent of aromatase inhibitors, further incremental improvements were achieved. Study BIG 1-98, a randomized, phase 3, double-blind trial, compared various hormonal agent regimens in 8010 postmenopausal women with HRc positive breast cancer. Patients were randomly assigned to receive monotherapy with letrozole or tamoxifen for 5 years, letrozole for 2 years followed by tamoxifen for 3 years, or tamoxifen for 2 years followed by letrozole for 3 years. In comparing subjects who received letrozole initially (N=4003) versus those who received tamoxifen initially (N=4007), subjects in the letrozole group had improved DFS (HR, 0.81; p=0.003). The 5-year DFS estimate was 84.0% in the letrozole group and 81.4% in the tamoxifen group, a difference of 2.6%, which was deemed clinically meaningful (Breast International Group 1-98 Collaborative Group 2005). Kaplan Meier estimates of DFS are depicted in Figure 1.

Figure 1: Kaplan Meier Estimates of Disease Free Survival (BIG-1-98 Study)



Letrozole						
No. at risk	4003	3892	2964	1261	892	567
Disease-free survival (%)		97.7	95.1	90.5	86.8	84.0
Tamoxifen						
No. at risk	4007	3896	2926	1238	866	544
Disease-free survival (%)		97.6	93.4	89.0	84.6	81.4

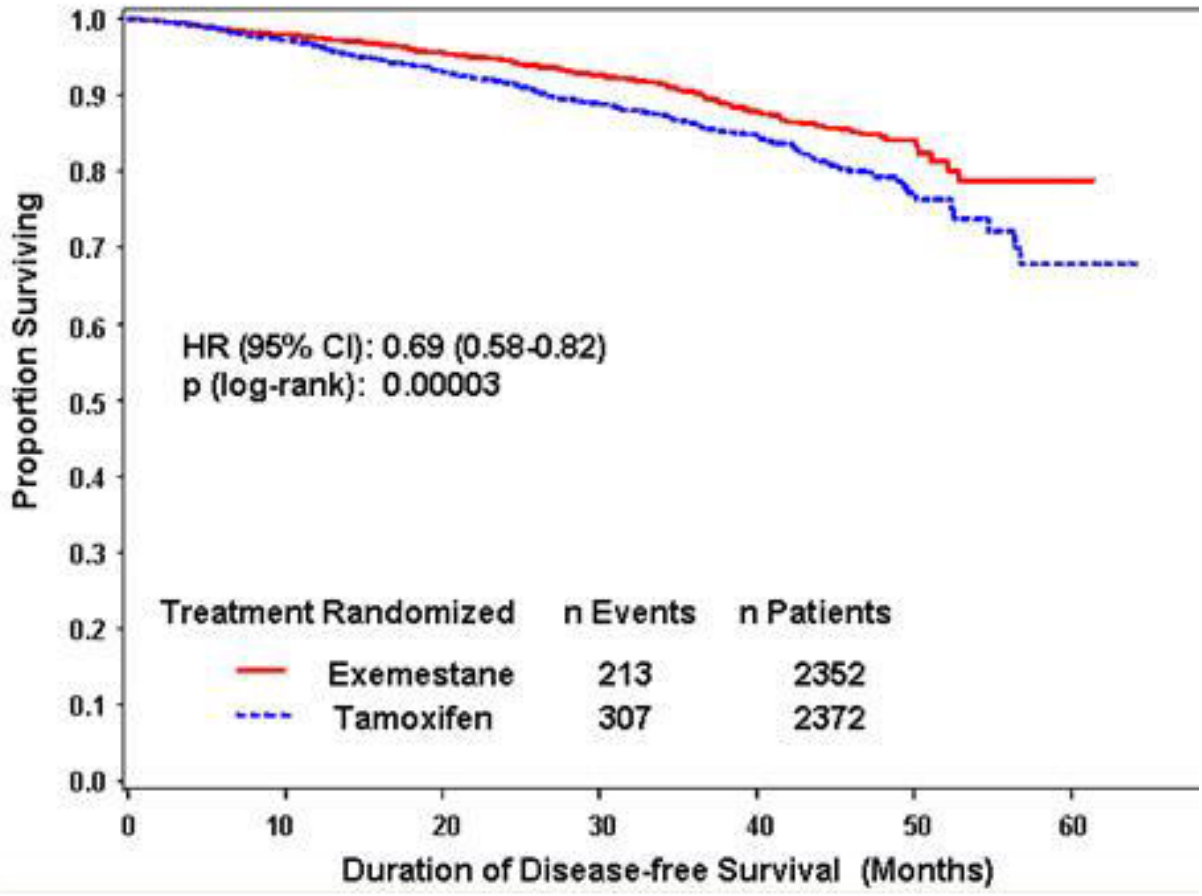
Source: Breast International Group 1-98 Collaborative Group 2005

In the ATAC Study, a randomized double-blind study that compared anastrazole with tamoxifen as adjuvant treatment in postmenopausal women with early-stage breast cancer, DFS was significantly better in HRc positive patients who received anastrazole versus tamoxifen (HR 0.86, 95% p=0.003), with an absolute difference of 2.7% in time to recurrence at 5 years which was deemed to be clinically meaningful (Cuzik, 2010).

Exemestane, another aromatase inhibitor, was studied in an adjuvant setting in the Intergroup Exemestane Study (IES) 031 (N=4724) (US package insert for AROMASIN® [exemestane] tablets). This was a Phase 3, randomized, double blind trial in postmenopausal women with early breast cancer who had completed 2-3 years of adjuvant tamoxifen therapy. Patients were randomized to either exemestane 25 mg qd or tamoxifen at their original dose prior to enrolling into the study and continued treatment for another 2-3 years to complete a full 5 years of adjuvant therapy. The primary endpoint was DFS, defined as time from randomization to local or distant recurrence, contralateral invasive breast cancer, or death

from any cause. With a median follow up of 34.5 months, the exemestane group was superior to tamoxifen in terms of DFS, with a HR of 0.69 (95% CI 0.58, 0.82, p=0.00003) (Figure 2). No statistical difference was observed between treatments for OS (HR=0.86; 95% CI 0.67, 1.10; p=0.23).

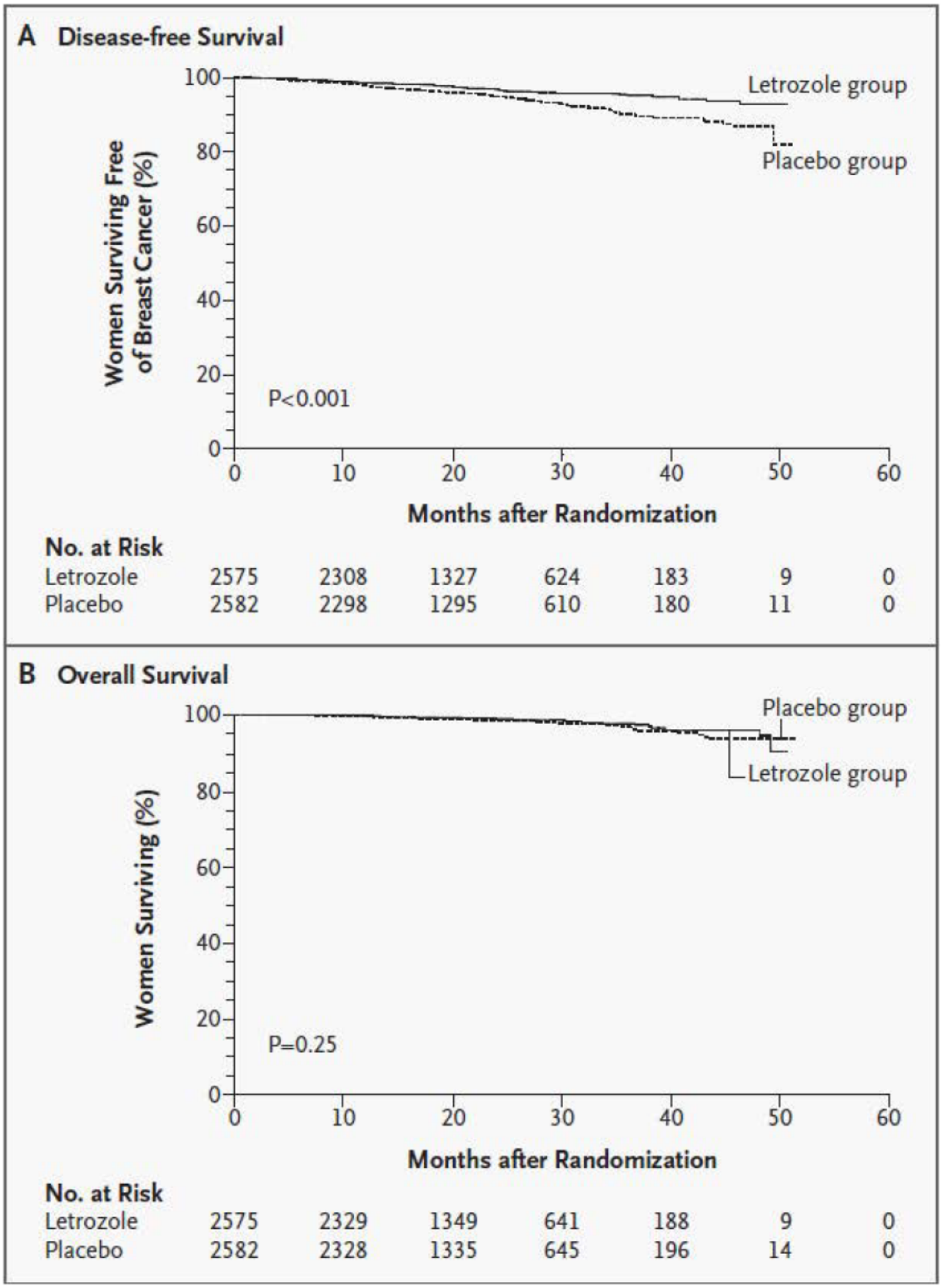
Figure 2: DFS in the IES Study of Postmenopausal Women with Early Breast Cancer (ITT Population)



Abbreviations: DFS= disease free survival
Source: US package insert for AROMASIN® (exemestane) tablets.

In the MA.17 study (N=5157), a double-blind, placebo-controlled trial in postmenopausal women with primary breast cancer, the concept of extended adjuvant therapy was explored. Patients who had received standard adjuvant hormonal therapy with tamoxifen for 5 years were randomized to an additional 5 years of letrozole adjuvant treatment (total 10 years) vs. placebo. The primary endpoint was DFS, defined as time from randomization to recurrence or new primary breast cancer; second type of cancer and death not due to breast cancer were not included in the definition. The primary analysis was conducted with a median follow up of 2.4 years. The estimated DFS rate at 2 years was 96.7% for the letrozole group and 94.8% for the placebo group (HR=1.9; 95% CI [0.6, 3.3]) (Goss, 2003). No difference was observed between treatment groups for OS (Figure 3).

Figure 3: Kaplan Meier Estimates of Disease Free Survival (Panel A) and Overall Survival (Panel B)



Source: Goss, 2003

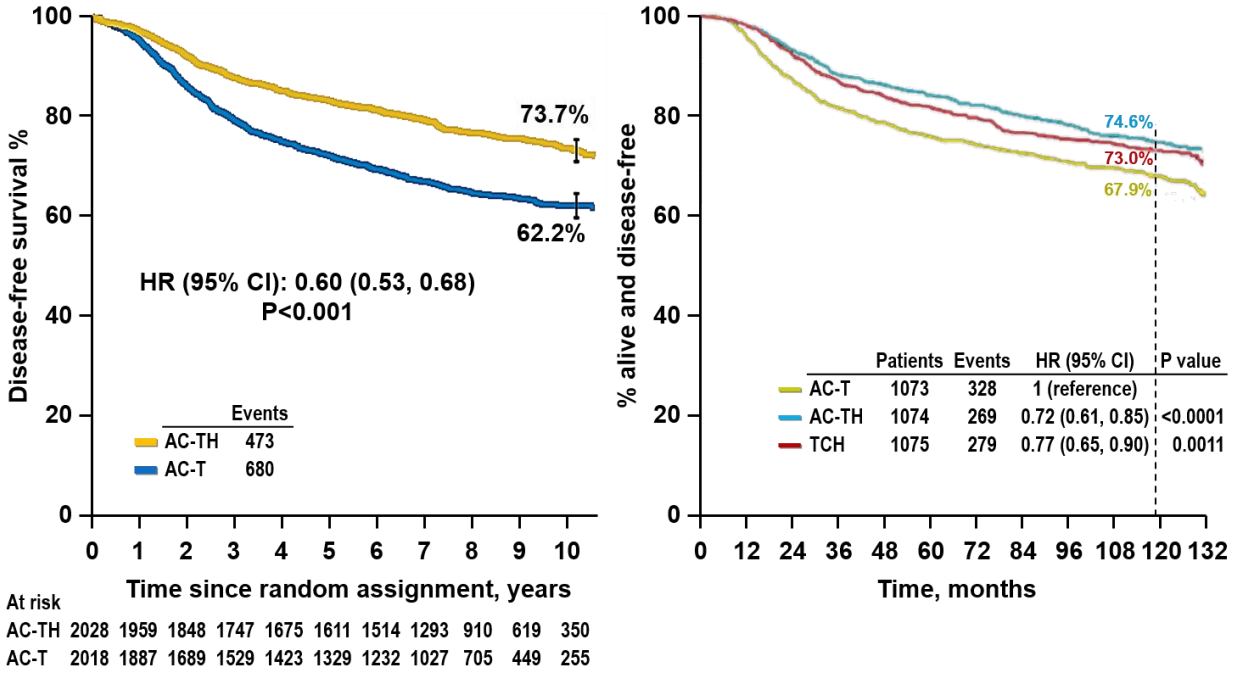
Side effects of hormonal therapies include decreases in bone density and bone fractures, increased lipids, thromboembolism, second malignancies and need for cancer surveillance, cardiac effects, and constitutional symptoms (hot flashes, fatigue, edema, hypertension, arthritis, myalgias, insomnia), that in some cases, may lead to drug discontinuation.

The third strategy, targeting HER2, has provided further benefit for patients whose tumors are positive for HER2 (either overexpression of the receptor or gene amplification). HER2 targeted therapies, starting with trastuzumab (Herceptin), have enabled improvement in the rate of recurrence. However, there is still room for further improvement. Once patients complete adjuvant therapy, including chemotherapy and 1 year of trastuzumab, there are no other non-hormonal therapies proven to be effective after that point. The only option available during the extended adjuvant period is hormonal agents for HRc positive patients and a watch-and-wait strategy for HRc negative patients.

Trastuzumab, a humanized monoclonal antibody against the extracellular domain of HER2, has provided significant incremental improvement over standard chemotherapy for patients whose tumors are HER2 positive (Cobleigh 1999, Dawood 2010, Marty 2005, Perez 2009, Slamon 2001, Vogel 2002, von Minckwitz 2009). Addition of trastuzumab to standard chemotherapy significantly improves both DFS and OS, regardless of tumor size, nodal status, HRc status, and age (Perez 2007, Perez 2014, Piccart-Gebhart 2005, Romond 2005, Slamon 2011, Slamon 2015, Smith 2007). The North Central Cancer Treatment Group (NCCTG) N9831 and National Surgical Adjuvant Breast and Bowel Project (NSABP) B 31 trials assessed the addition of 1 year of trastuzumab (H) to standard anthracycline/cyclophosphamide (AC)/taxane (T)-based chemotherapy: AC→TH vs. AC→T. These 2 trials were designed similarly, enabling a joint integrated analysis that pooled comparable study arms (N=4046). Analysis showed that adding trastuzumab to chemotherapy improved DFS (HR=0.60, 95% CI [0.53-0.68]; p<0.001), with DFS rates of 85.8% at 3.9 years and 73.7% at 10 years for AC→TH, vs. 75.8% and 62.2%, respectively, for AC→T (Figure 4) (Perez 2011, Perez 2014). This resulted in an improvement in OS at 10 years (HR=0.63, 95% CI [0.54-0.73]; p<0.001). However, challenges remained because of issues related to cardiac toxicity, including congestive heart failure, when administering anthracyclines and trastuzumab.

Study BCIRG-006 (N=3222) compared chemotherapy with and without trastuzumab in patients with HER2 positive breast cancer. It also assessed a less cardiotoxic regimen that did not include an anthracycline; it compared two different trastuzumab containing regimens to chemotherapy alone: AC→T vs. AC→TH vs. TCH (docetaxel/carboplatin/trastuzumab). This study not only confirmed the benefit of adding 1 year of trastuzumab to adjuvant chemotherapy for patients with HER2 positive breast cancer (Slamon, 2015), it also demonstrated that a less cardiotoxic regimen, TCH, could achieve similar efficacy as AC→TH (Figure 4).

Figure 4: Standard Trastuzumab-Based Adjuvant Therapy in HER2 Positive Breast Cancer: (A) NCCTG N9831/NSABP B-31 Joint Analysis and (B) BCIRG-006



Abbreviations: AC=anthracycline; CI=confidence interval; H=Herceptin (trastuzumab); HER=human epidermal growth factor receptor; HR=hazard ratio; NCCTG=North Central Cancer Treatment Group; NSABP=National Surgical Adjuvant Breast and Bowel Project; T=taxane
Source: Perez 2014, Slamon 2015

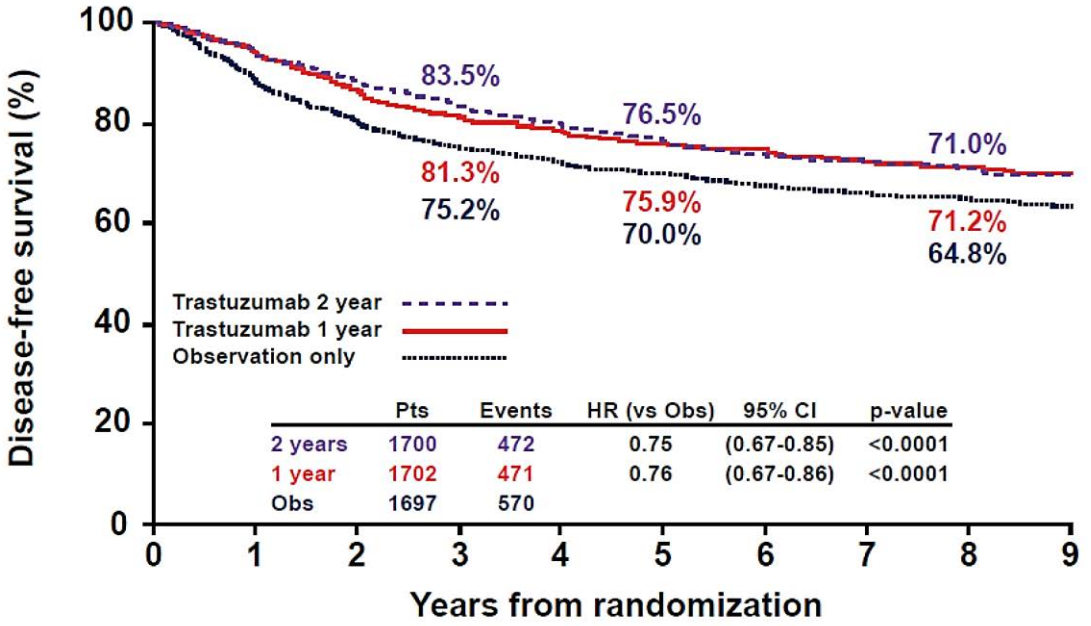
Given the findings from NCCTG N9831, NSABP-31, and BCIRG-006, adjuvant therapy consisting of chemotherapy combined with trastuzumab for 1 year became the standard of care for treatment of early stage HER2 positive breast cancer. Steady step-wise improvements with each successive approach add up to substantive improvements over time.

However, recurrence rates are still substantial, with approximately 25% of patients having a recurrence or death during the 10 years from initiation of adjuvant therapy (Perez 2014, Slamon 2015). Given the large number of women diagnosed with early stage HER2 positive breast cancer, and the dire prognosis associated with recurrence, even the stepwise incremental increases in the DFS rate could save additional lives.

Several strategies have been investigated in an effort to further reduce the rate of disease recurrence. These include longer duration of adjuvant trastuzumab (extended adjuvant), novel combinations of two HER targeting agents, and novel combinations of different targeting agents.

- **Longer duration of trastuzumab therapy**: The HERA trial (N=5102), an international, multicenter, randomized, open-label, phase 3 study, was designed to assess whether extended adjuvant trastuzumab of 2 years could improve DFS over a 1-year duration, which was the standard of care. It also included an observation arm with no trastuzumab. Again, the benefit of 1 year of trastuzumab was confirmed when compared with observation (HR 0.76; 95% CI [0.67-0.86]; p<0.0001). However, the results showed that 2 years of adjuvant trastuzumab therapy did not add any improvement in DFS compared with 1 year of trastuzumab (HR 0.99; 95% CI [0.85-1.14]; p=0.86) (Figure 5) (Goldhirsch, 2013); there was also no improvement in OS (HR 1.05; 95% CI [0.86-1.28]; p=0.63). In addition, an increase in cardiotoxicity was observed after 2 years versus 1 year.

Figure 5: Extended Duration of Adjuvant Trastuzumab Therapy: HERA Trial



Abbreviations: CI=confidence interval; HR=hazard ratio; Obs=observation; Pts=patients
Source: Goldhirsch, 2013.

- Dual anti-HER Therapy
  - **Lapatinib**: In the ALTTO trial (N=8381), an oral TKI, lapatinib, which targets HER2 and HER1 (EGFR), was studied as 1 year of adjuvant therapy following or concurrent with chemotherapy in a randomized 4 arm design: lapatinib + trastuzumab concurrently (N=2093) vs. trastuzumab followed by lapatinib sequentially (N=2091) vs. lapatinib alone (N=2100) vs. trastuzumab alone (N=2097). Lapatinib monotherapy performed worse than trastuzumab monotherapy in a head to head comparison of DFS (HR=1.34; 97.5% CI [1.13-1.60]; p<0.0005). It also did not add meaningful clinical benefit when administered either concurrently with trastuzumab (HR=0.84; CI [0.7-1.02]; p=0.048 but prespecified level for statistical significance was set at 0.025 or sequentially (HR=0.96, CI [0.8-1.15]; p=0.61) (Piccart-Gebhart, 2016).
  - **Pertuzumab**: The APHINITY trial undertook a different dual HER blockade approach by studying 1 year of adjuvant therapy with the combination of trastuzumab + pertuzumab + chemotherapy vs. trastuzumab + chemotherapy in patients with HER2 positive breast cancer. Pertuzumab binds to HER2 and impacts HER2 and HER3 heterodimerization. Pertuzumab received accelerated approval in the neoadjuvant setting based on a surrogate endpoint of improved pCR rate. The APHINITY (N=4805) trial serves as the confirmatory trial in the adjuvant setting, with the intent of demonstrating that the neoadjuvant findings accurately predict adjuvant outcomes (von Minckwitz, 2011). The prespecified study design targeted a 2.6% difference in iDFS at 3 years (based on the assumptions of 80% power to achieve HR=0.75 and 3 year iDFS 89.2% vs 91.8% in prespecified statistical plan) (Zhang, 2013). While the results of this trial have not been publicly disclosed, the sponsor, Roche/Genentech, issued a press release in March 2017 stating that the study achieved statistical significance for the primary endpoint of iDFS. No data were released, and none have been publicly communicated as of the writing of this briefing document. Therefore, the clinical meaningfulness and the risk/benefit of this data is currently not known. Moreover, this study does not address the unmet need in the extended adjuvant setting for patients with HER2 positive tumors.
- Additional Targeted Therapy
  - **Bevacizumab**: Combination of trastuzumab plus other targeted therapy has been evaluated in an effort to further reduce the risk of breast cancer recurrence. In the BETH trial, the addition of bevacizumab to trastuzumab was tested against trastuzumab alone in early stage HER2 positive breast cancer patients. The results of the trial showed that the addition of bevacizumab to trastuzumab did not improve DFS (Slamon, 2013).

Thus far, findings indicate that none of the following are successful treatment strategies: extending trastuzumab anti-HER2 therapy to 2 years; treatment with lapatinib (a reversible HER1 and HER2 inhibitor); adding lapatinib to trastuzumab; or adding bevacizumab to trastuzumab. There are no studies of HER2 targeting agents in the extended adjuvant setting that have been able to add benefit beyond the 1 year of trastuzumab. Additional challenges include anti-HER2 agents that do not cause cardiotoxicity.

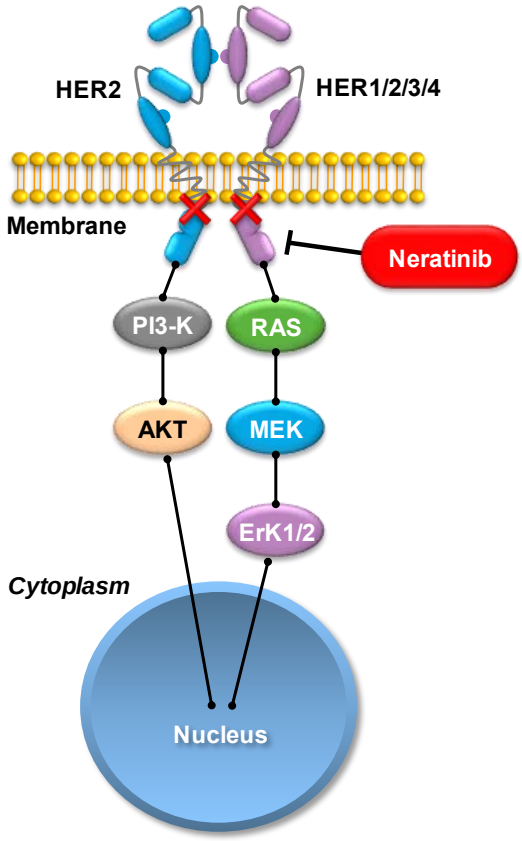
Incorporation of an anti-HER targeting agent that goes beyond targeting HER2 would be beneficial. Providing patients and physicians with another tool in the adjuvant therapy armamentarium would give patients an option after completing 1 year of standard of care with adjuvant trastuzumab based therapy, with the goal of incrementally reducing recurrence rates. Currently, the only choice for patients whose tumors are HER2 positive after 1 year of adjuvant trastuzumab therapy is to watch and wait.

To date, 1 year of trastuzumab remains the standard of care, leaving thousands of patients at persistent risk of developing incurable metastatic disease. Therefore, an important unmet need remains in terms of both efficacy and safety.

3. MECHANISM OF ACTION

Neratinib is a potent, oral, small-molecule pan-erythroblastic leukemia viral oncogene homolog (ERBB) TKI that irreversibly binds at the intracellular tyrosine kinase domains of three growth factor receptors, EGFR or HER1 (ERBB1), HER2 (ERBB2) and HER4 (ERBB4), resulting in sustained inhibition of downstream growth promoting signal transduction pathways (Figure 6). The K_d's for neratinib at EGFR, ERBB2 and ERBB4 receptors are 1.1 nM, 6 nM and 2.4 nM respectively (Davis, 2011). Neratinib has demonstrated antitumor activity in HER1 and/or HER2 expressing carcinoma cell lines with a cellular half-maximal inhibitory concentration (IC_{50}) < 100 nM (Rabindran, 2004). *In vivo*, neratinib has demonstrated antitumor activity in HER1 and HER2 dependent tumor xenograft models when administered orally once daily.

Figure 6: Mechanism of Action of Neratinib



Abbreviations: ERK=extracellular signal-regulated kinase; HER=human epidermal growth factor receptor; MEK=mitogen-activated protein kinase; PI3-K=phosphatidylinositol 3-kinase

The MOA of neratinib differs from that of trastuzumab, which binds to the extracellular domain of the HER2 receptor to prevent activation of its intracellular tyrosine kinase. In HER2 positive BT474 cells, neratinib effectively represses phosphorylation of mitogen-activated protein kinase (MAPK) and protein kinase B (also referred to as Akt) at concentrations consistent with those that inhibit cell proliferation. Furthermore, although the primary effect of neratinib is cell cycle arrest, a dose-dependent increase in the number of cells with sub-G1 deoxyribonucleic acid (DNA) content (indicative of apoptosis) is also observed.

Neratinib's MOA is similar to that of lapatinib, which also inhibits HER1 and HER2. A major difference between neratinib and lapatinib is that lapatinib reversibly inhibits the tyrosine kinase domain whereas neratinib is an irreversible inhibitor. In addition, neratinib also inhibits HER4.

4. NONCLINICAL OVERVIEW

A comprehensive series of nonclinical pharmacology, PK, and toxicology studies of neratinib has been conducted.

The pharmacological effects of neratinib were investigated *in vitro* and *in vivo*. *In vitro* studies in HER2 and EGFR dependent cancer cell lines examined effects on cell proliferation, downstream signal transduction events, and cell cycle pathways. *In vivo* studies were conducted in HER2 positive and EGFR positive expressing tumor xenograft models to evaluate tumor growth with daily oral administration.

In vitro, neratinib inhibits the proliferation of HER1 (EGFR) and HER2 dependent cancer cell lines by inhibiting the mitogenic growth factor signal transduction pathways. *In vivo*, neratinib is active in HER2 and EGFR dependent tumor xenograft models. Neratinib was also found to be a substrate of P-glycoprotein and breast cancer resistance protein. Neratinib metabolites M3, M6, M7, and a human specific metabolite M11 are active in enzyme (binding assays) and cell based assays against cells expressing EGFR, HER2 and HER4.

In animal studies, adverse effects of neratinib were primarily GI related. Neratinib did not produce any effects on the central nervous or respiratory systems of rats. Neratinib did not produce any toxicologically significant effects on the cardiovascular system of dogs. Based on data from an *in vitro* human ether-a-go-go-related gene (hERG) potassium ion channel assay, the calculated IC_{50} for the effect of neratinib on hERG current was determined to be 1.9 µM or 1058 ng/mL, indicating that neratinib is unlikely to prolong the corrected QT (QTc) interval at exposures seen at the most widely used clinical dose of 240 mg/day. No changes were seen in the electrocardiograms (ECGs) of the 1 and 9 month repeat-dose toxicity studies with neratinib in dogs.

In vitro studies, including autophosphorylation assays, have confirmed that neratinib is a highly-selective and potent inhibitor of EGFR, HER2 and HER4 receptor tyrosine kinases (Rabindran, 2004). Neratinib blocks the kinase function of the ERBB receptor in HER2 positive and EGFR positive expressing cells through decreased ligand-independent receptor phosphorylation. Receptor binding by neratinib inhibits key downstream signaling pathways, including MAP and PI3-kinase pathways, resulting in cell cycle arrest at the G1/S phase of cell division (Rabindran, 2004). Inhibition of tumor cell proliferation following neratinib treatment has been demonstrated across a broad spectrum of cell lines that have elevated levels of HER2 and EGFR.

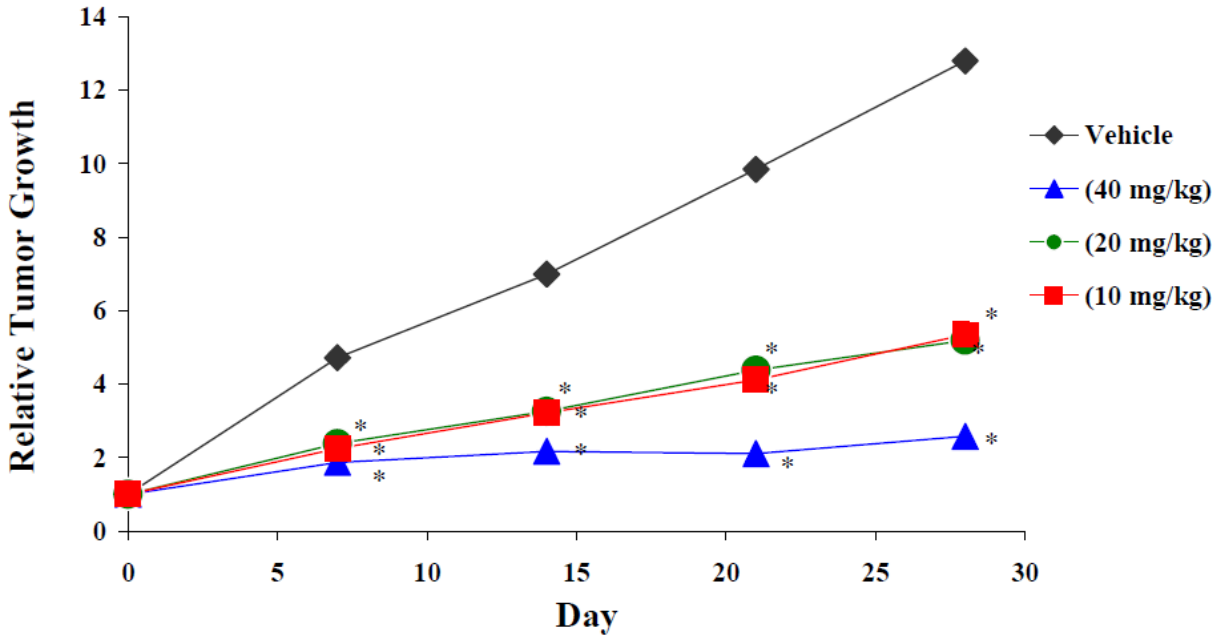
In vivo, neratinib caused significant growth delay in tumor xenografts with high or moderate HER2 and EGFR expression, but not in xenograft models that lack the expression of these receptors (Rabindran, 2004).

In HER2 overexpressing (HER2 positive) 3T3/neu (fibroblast), HER2 positive/estrogen receptor (ER) positive BT-474 (breast) and HER2 positive/HRc negative BCM3613 (breast) xenograft models, daily oral administration of neratinib significantly inhibited tumor growth in a dose-dependent manner. In BT-474 (HER2 positive/ER positive) xenograft models, a dose of 40 mg/kg of neratinib achieved greater than 85% inhibition of tumor growth and the

minimum efficacious dose of neratinib was determined to be 10 mg/kg (Figure 7). In BCM3613 (HER2 positive/ER-/PR-) a dose of 40 mg/kg of neratinib achieved 50% tumor reduction (Figure 8). In all cases, neratinib inhibited tumor growth for as long as the drug was administered. Based on standard scaling from mouse to human, the 40 mg/kg dose in the mouse correlates to an approximate human equivalent dose of 240 mg/day based on body surface area (FDA Guidance 2005).

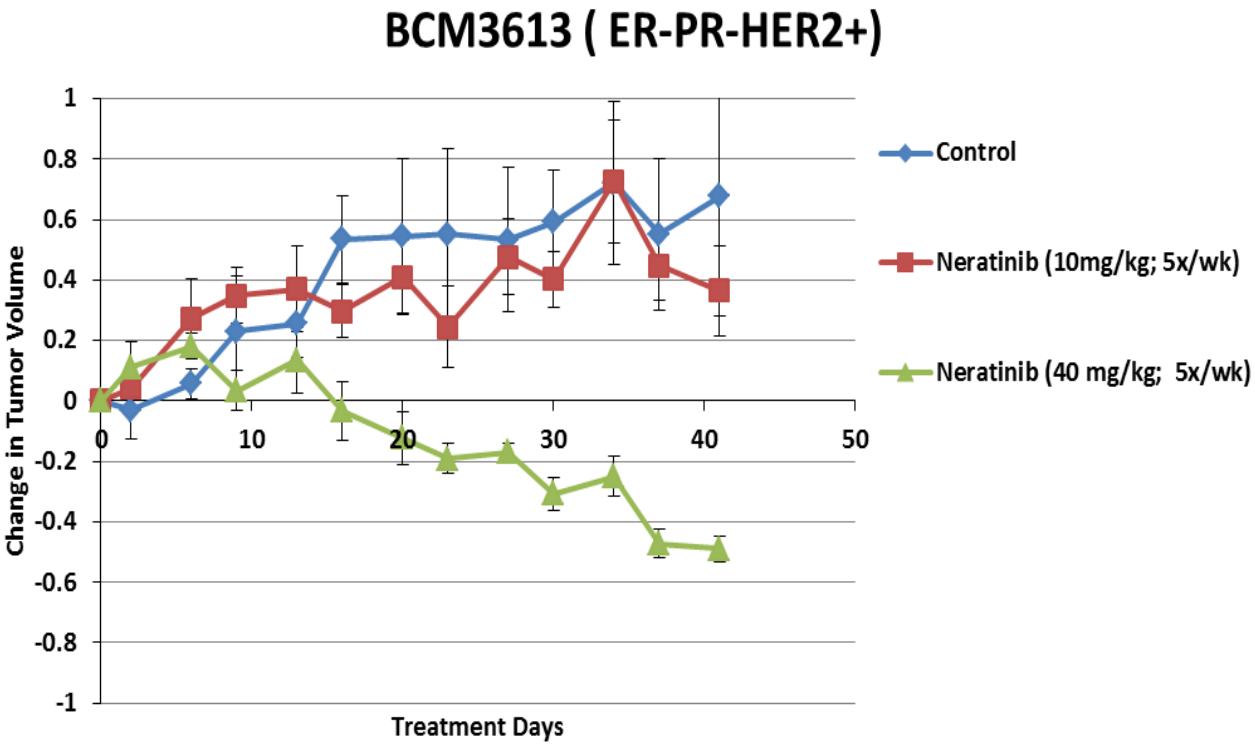
When drug was removed, all tumors showed evidence of re-growth but at a slower rate than was seen in vehicle control animals (RPT-49430) (Rabindran, 2004).

Figure 7: Effect of Neratinib Oral Doses of 10, 20, and 40 mg/kg/day for 20 Consecutive Days on the Growth of BT-474 (HER2 positive/ER positive) Breast Cancer Xenografts in Female Nude Mice



Abbreviations: BT-474=human mammary gland ductal carcinoma cells
Source: Rabindran, 2004

Figure 8: Effect of Neratinib on the Growth of BCM3616 (HER2 positive/ER-/PR-) Breast Cancer Xenografts in Female Nude Mice



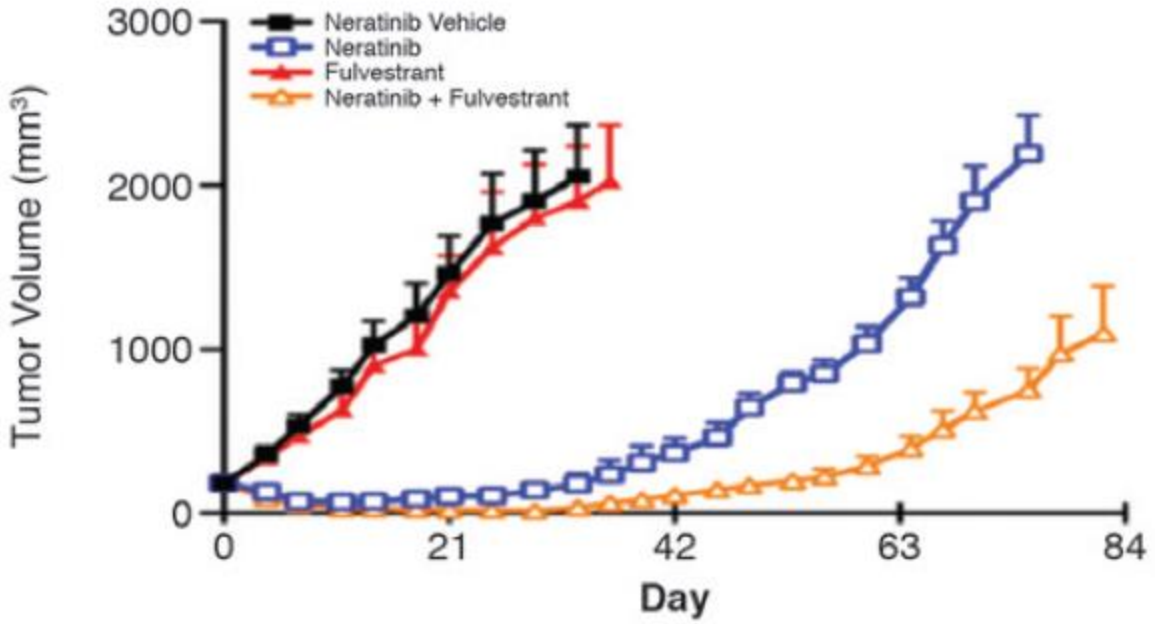
Abbreviations: BCM3613=human mammary carcinoma cells ER-, HER2amp PDX
Source: Zhao, 2017

Because patients with HER2 positive tumors that are also HRc positive [i.e. either ER positive or PR positive] will also be treated with endocrine therapies, it is of interest to understand what the effect of administration of anti-hormonal and anti-HER2 therapy may have on the tumors. In addition, endocrine therapies are not as effective in HER2 positive/HRc positive tumors compared with HER2 negative /HRc positive tumors (Mehta 2014, Prat 2008, Montemurro 2013). This may be explained by preclinical and clinical studies that suggest that bi-directional signaling (crosstalk) between the ER and HER2 or EGFR receptor tyrosine kinases may lead to tumor escape mechanisms and resistance to endocrine or HER2 directed therapies in HER2 positive/HRc positive breast cancers (Mehta 2014, Prat 2008, Montemurro 2013). In addition, blockade of amplified or overexpressed HER2 induces ER gene expression and functions as an adaptive mechanism for tumor survival. Hence co-targeting both HER2 and ER pathways using potent HER2 inhibitors, such as neratinib, together with endocrine therapies may be required for effective blockade of both pathways resulting in optimal treatment of HER2 positive/HRc positive breast cancers.

In HER2 positive/ER positive BT-474 breast tumor xenografts, which are typically unresponsive to anti-estrogen therapy, a significantly enhanced tumor growth inhibition was

observed when neratinib was combined with fulvestrant (a hormonal therapy that is a selective ER degrader, SERD) compared to single-agent or control treatments (Figure 9) (Scaltriti, 2016). These preclinical results suggest that the dual blockade of ER and HER2 signaling pathways in HRc positive tumors results in enhanced and sustained anti-tumor activity and that blockade with neratinib may re-sensitize ER positive pathways to endocrine therapy thereby making combined blockade more effective than monotherapy.

Figure 9: Effect of Neratinib with or without Fulvestrant on the Growth of BT-474 (HER2 positive/ER positive) Breast Cancer Xenografts in Female Nude Mice

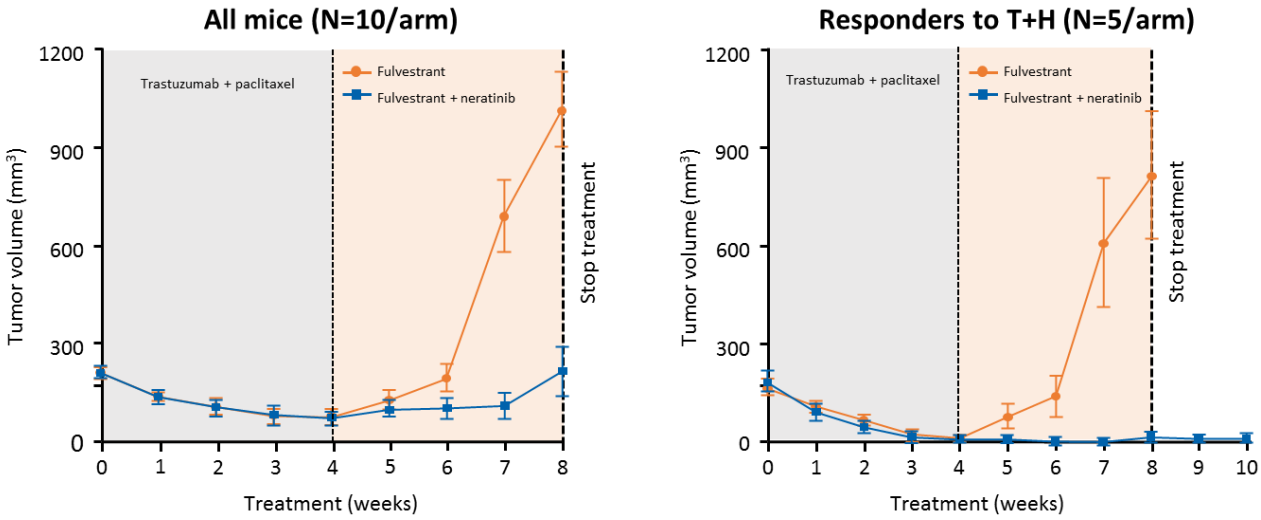


Source: Scaltriti, 2016

Preclinical studies were also conducted that attempted to recapitulate Study 3004. Using an ER+/HER2+ MDA-361 breast xenograft model, established tumors were treated with trastuzumab plus paclitaxel for 4 weeks as an adjuvant therapy which resulted in complete responses in 5/10 animals. Following 4 weeks of treatment with trastuzumab/paclitaxel, mice were then treated with neratinib plus endocrine therapy (fulvestrant) or with endocrine therapy (fulvestrant) alone as an extended adjuvant treatment for an additional 4 weeks. As shown in Figure 10, the results of the study demonstrated that neratinib plus fulvestrant, but not fulvestrant therapy alone in the extended adjuvant treatment setting, suppressed tumor growth completely following adjuvant treatment with trastuzumab + paclitaxel therapy (Schwarz, 2017).

Taken together, these preclinical studies provide support for the interaction between neratinib and endocrine therapy in HER2 positive, ER+ tumors.

Figure 10: MDA-361 ER+/HER2+ Tumor Xenograft Model (Extended Adjuvant Treatment with Fulvestrant + Neratinib Following Trastuzumab + Paclitaxel Therapy)



Source: Schwarz, 2017

5. DOSING

5.1. Recommended dose

The selection of the recommended dose of neratinib, 240 mg po qd, was primarily based on the results of 6 clinical studies: 2 Phase 1 dose escalation studies in solid tumors (Studies 102 and 104) and 1 Phase 2 study in non-small cell lung cancer (NSCLC) (Study 200) that established the safe and tolerable dose used in Phase 2 and Phase 3 studies as well as population PK analyses of exposure and response from 2 monotherapy trials in patients with metastatic breast cancer, with data from Studies 102, 201, 2206 and 3003 contributing to the population PK analyses:

- **Study 3144A1-102-US (Study 102)** was a Phase 1, first-in-human, open label, sequential-group study of ascending oral doses of neratinib (40 mg – 400 mg) in patients with advanced or metastatic solid tumors expressing HER1 or HER2.
- **Study 3144A1-200-WW (Study 200)** was a Phase 2, open-label, nonrandomized study of neratinib in patients with advanced NSCLC.
- **Study 3144A1-104-JA (Study 104)** was a Phase 1, open-label, sequential-group study of ascending doses of neratinib (80 mg – 320 mg) in 21 Japanese patients with metastatic or advanced solid tumors.
- **Study 3144A1-201-WW (Study 201)** was a Phase 2 open label study of neratinib monotherapy 240 mg po qd in women with HER2 positive, locally advanced or metastatic breast cancer that was not curable with available therapy. Two cohorts were enrolled: 1) prior trastuzumab with progression during or after trastuzumab treatment (N=66) and 2) no prior trastuzumab or trastuzumab naïve (N=70).
- **Study 3144A1-2206-WW (Study 2206)** was a Phase 1/2 open label study of neratinib in combination with capecitabine in subjects with solid tumors and ErbB-2 positive metastatic or locally advanced breast cancer. The Phase 1 portion assessed the safety and tolerability of the combination and defined the maximum tolerated dose (MTD) (N=33). The Phase 2 portion enrolled HER2 positive metastatic or locally advanced breast cancer patients (N=72).
- **Study 3144A2-3003-WW (Study 3003)** was a randomized open label Phase 2 study comparing neratinib monotherapy 240 mg po qd (N=117) to the combination of lapatinib + capecitabine (N=116) in women with HER2 positive, locally advanced or metastatic breast cancer who had progressed during or after a trastuzumab containing regimen.

The first Phase 1 dose escalation Study 102 identified the initial recommended Phase 2 dose for neratinib as 320 mg po qd. This was based on 4 of 6 patients experiencing dose limiting toxicity (DLT) of Grade 3 diarrhea at the 400 mg po qd dose level. However, the 320 mg po qd dose was not well tolerated in two subsequent trials. Study 200 and Study 104-JA independently identified 240 mg po qd as the MTD and as the recommended dose for further study. During the conduct of Study 200 in which neratinib monotherapy was administered to

patients with NSCLC, the rate of Grade 3 or higher diarrhea at the 320 mg po qd dose level was determined to be too high (46.2%) resulting in a protocol amendment to reduce the dose to 240 mg po qd. This resulted in a decrease in the rate of Grade 3 or greater diarrhea to 22.7%. In parallel, the Japanese dose escalation Study 104-JA identified the MTD as 240 mg po qd based on the finding of DLTs in 2 of 5 patients at the 320 mg po qd dose level: one patient with Grade 3 diarrhea and Grade 3 anorexia and a second patient with Grade 3 anorexia and Grade 2 diarrhea.

An integrated safety analysis across all dose levels demonstrated an apparent lack of diarrhea-dose response relationship between 120 and 240 mg po qd followed by a threshold effect resulting in a marked increase in the rate of Grade 3 or greater diarrhea between 320 and 400 mg po qd (Table 5).

Table 5: Incidence of Diarrhea by Neratinib Dose (Monotherapy Studies Excluding Single-Dose Studies)

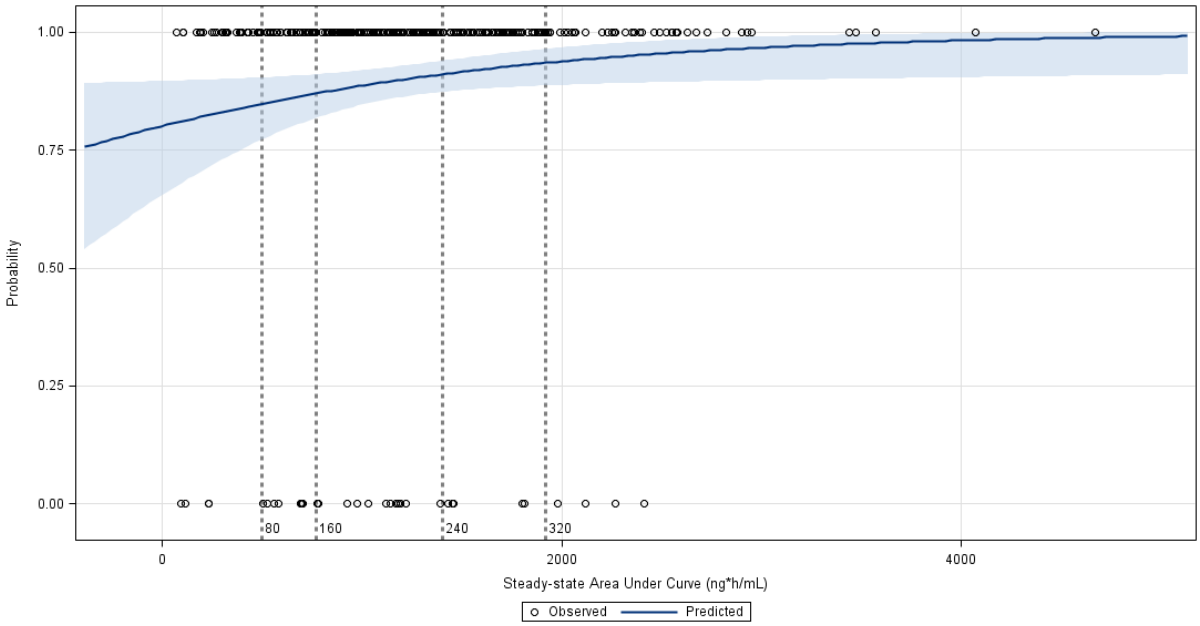
	Patients (%)							
Dose (mg)	**40 N=3**	**80 N=7**	**120 N=4**	**160 N=3**	**180 N=6**	**240 N=141**	**320 N=90**	**400 N=6**
Any grade diarrhea	33.3	57.1	75	100	100	91.5	93.3	83.3
Grade ≥3 diarrhea	0	0	25	33.3	16.7	20.6	38.9	83.3

Note: Data were from Studies 102, 204, and 200.

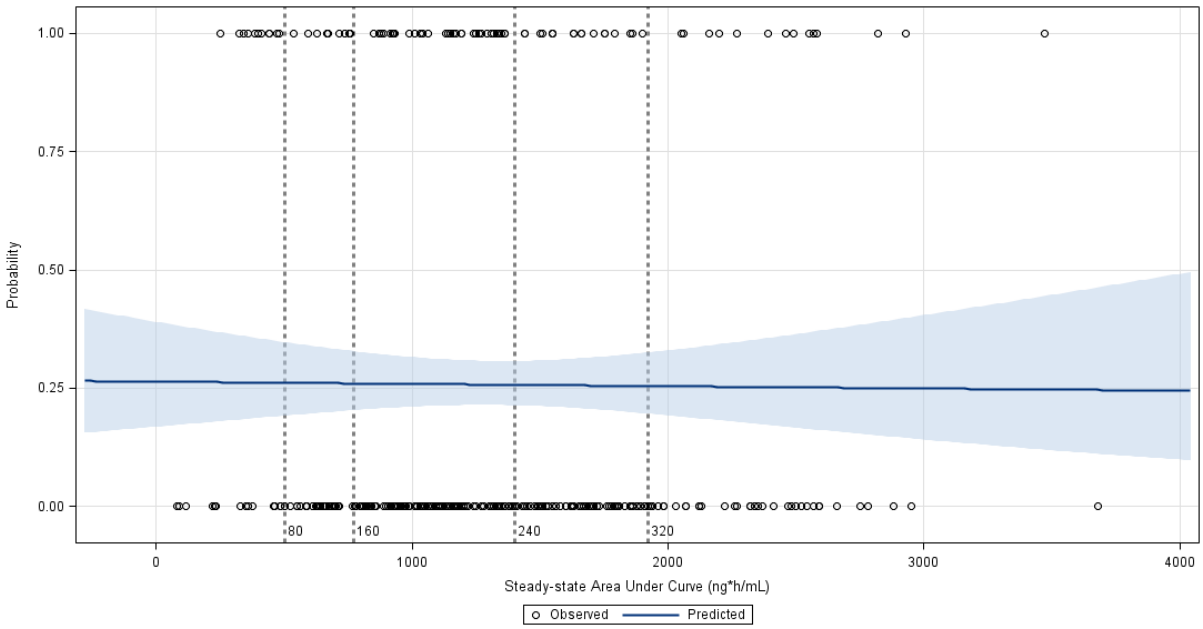
Further, a population based pharmacokinetic analysis of the exposure response relationship of area under the concentration-versus-time curve (AUC) and diarrhea (all grade and Grade 3 or greater), confirms the lack of exposure - response relationship at the mid-range dose levels in regard to events of Grade 3 or greater severity from the 3004 study (Figure 11).

Figure 11: Analysis of Diarrhea (Any Grade and ≥ Grade 3) and Steady State Exposures AUC_{ss} Adjusted by Average Daily Dose of Neratinib (Safety Analysis Set)

Any Grade Diarrhea



≥ Grade 3 Diarrhea

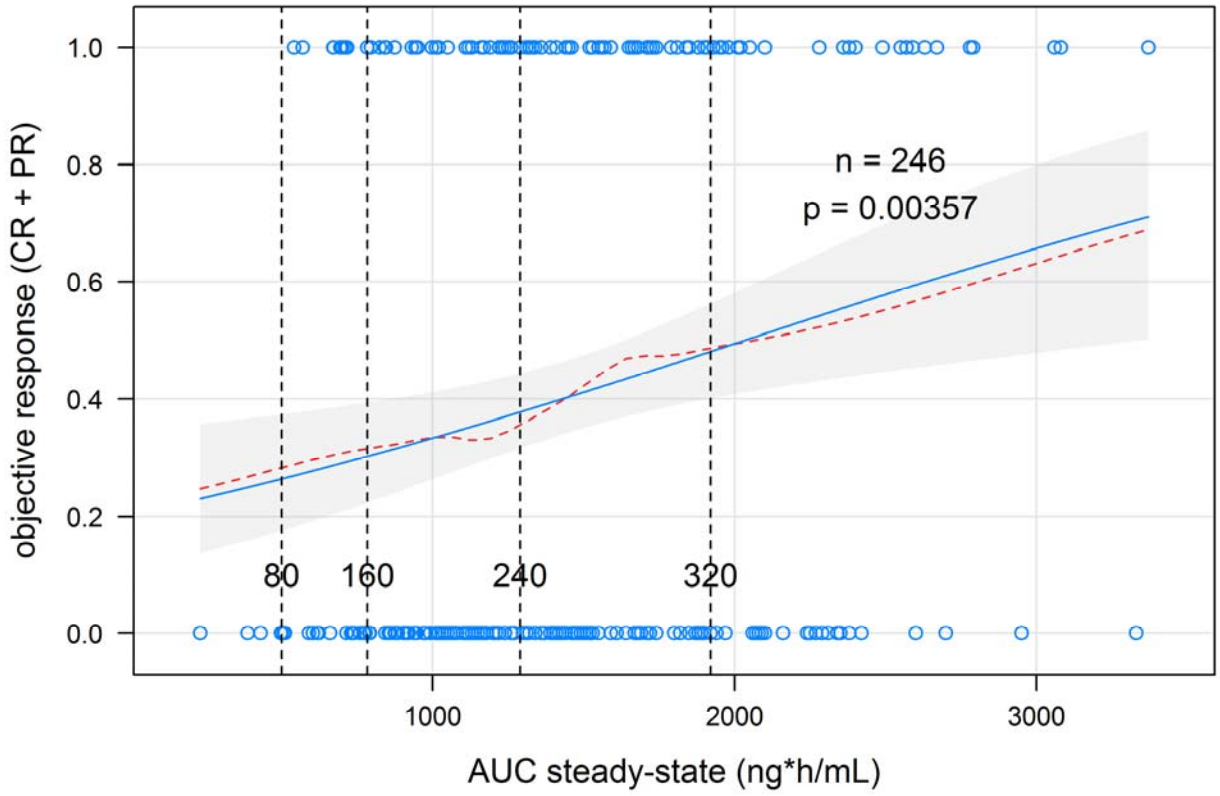


Abbreviations: AUC= area under the concentration-versus-time curve; AUC_{ss}= area under the concentration-versus-time curve at steady state; PK=pharmacokinetics
Note: Steady state AUC was based on the Population PK model. Diarrhea episodes were derived from Study 3004 (neratinib group)

The population PK analyses are helpful in defining the optimal recommended dose. While the population based analysis shows no relationship between exposure and Grade 3 diarrhea, management of individual patients indicates that dose reduction results in better tolerability and can enable patients to continue on therapy.

In order to address the question of whether reducing the dose would impact efficacy outcomes, further refinement of dose selection based on the exposure (AUC) to tumor response relationship in a logistic regression analysis confirmed that 240 mg po qd is the optimal recommended dose. It has been established that there is a linear relationship between the dose of neratinib and plasma exposure of neratinib at the dose levels studied. Applying this to an exposure response analysis using data from trials with neratinib from which pharmacokinetics and pharmacodynamics are available shows a positive correlation between systemic neratinib exposure and efficacy as measured by ORR (Figure 12).

Figure 12: Exposure-Response Analysis with Monotherapy Neratinib AUC vs Objective Response in Metastatic Breast Cancer and Solid Tumors



Abbreviations: CR=complete response; PR=partial response
Note: Steady state AUC was based on the Population PK model. Response from monotherapy neratinib treated patients derived from Studies A1-102, A1-104, A1-201, 2206, and A2-3003.

In summary, logistic regression modeling of safety and efficacy endpoints vs. model-simulated neratinib exposures [E-R modeling] showed a clear increase in objective response

In summary, logistic regression modeling of safety and efficacy endpoints vs. model-simulated neratinib exposures [E-R modeling] showed a clear increase in objective response (OR) for neratinib monotherapy with increasing exposure, but no significant corresponding increase in the probability of diarrhea.

The therapeutic window for neratinib is broad, as demonstrated by the objective tumor response rate of approximately 25% observed with steady state AUC levels corresponding to doses as low as 80 mg po qd. The linear dose response relationship indicates greater exposure is associated with higher response rates. Hence, it is beneficial to initiate patients at the MTD of 240 mg po qd to achieve maximal efficacy. If 240 mg is not tolerated, dose reductions can enable patients to continue on therapy with doses that are well within the therapeutic window.

These population based analyses provide increased confidence in the recommended dose of 240 mg po qd for 1 year. However, in an individual patient, dose reduction within the range of observed efficacy, may be necessary. Guidelines for dose modification were developed within the context of the observed exposure response analysis. Step-wise dose reductions in 40 mg increments to no lower than 120 mg po qd is recommended for patients with intolerable diarrhea in the proposed product labelling (Table 6), as meaningful efficacy levels of tumor response continues to be present at the 120 mg po qd dose level.

Table 6: Modifications of Neratinib Dosage when Diarrhea Occurs

Severity of Diarrhea	Dose Modification
Any grade with complicated features[a]	Interruptneratinib treatment
Grade 2 lasting five days or longer[b]	Interrupt neratinib treatment
Grade 3 lasting longer than 2 days[b]	Interrupt neratinib treatment
Grade 4	Interrupt neratinib treatment
Diarrhea resolves to Grade 1 or Grade 0 in one week or less	Resume neratinib treatment at the same dose
Diarrhea resolves to Grade 1 or Grade 0 in longer than one week	Resume neratinib treatment at reduced dose (reduced from 240 mg/day to 160 mg/day or from 160 mg/day to 120 mg/day)
Diarrhea recurs to Grade 2 or higher at 120 mg per day	Permanently discontinue neratinib treatment

[a] Complicated features include dehydration, fever, hypotension, renal failure, or Grade 3 or 4 neutropenia.
[b] Despite being treated with optimal medical therapy.

5.2. Clinical Pharmacology

The clinical pharmacology program consists of 5 Phase 1 single or multiple oral dose PK studies in healthy volunteers; 4 Phase 1 drug-drug interaction studies in healthy volunteers given a single oral dose of neratinib; 12 Phase 1 or 2 studies evaluating the PK and pharmacodynamics of neratinib (including biomarkers); and 3 special PK or safety studies, including a single oral dose [^{14}C]-labeled excretion study and a study in patients with different degrees of hepatic impairment (Table 7). In addition, *in vitro* permeability, protein

binding, and metabolism studies using human biomaterials and a population PK analysis using sparse and rich sampling data from the PK studies were also performed.

Absorption of neratinib is relatively slow, with t_{max} ranging from 4 to 7 hours; exposure increases in a dose-dependent manner after oral administration. The mean terminal phase elimination half-life (t½) ranges from 10 to 15 hours, supporting once-daily dosing. The apparent distribution (V_z/F or Vz_{ss}/F) of neratinib was large, ranging from 68 to 104 L/kg. Variability was also large, with the coefficient of variation (%CV) values ranging from 32% to 68%. The mean apparent oral dose clearance (CL/F) of neratinib was high and variable (ranging from 159 to 456 L/kg [2.0 to 6.3 L/h/kg]), relatively similar at all doses, and similar in healthy volunteers and cancer patients. Steady state plasma levels of neratinib and its metabolites were achieved by day 4 and remained constant following once-daily administration of neratinib 240 mg in healthy subjects. No major accumulation of neratinib or its metabolites was observed following multiple once-daily doses. Fecal excretion of radiolabeled neratinib accounted for approximately 97% of the total dose administered and is the major route of elimination. There are no sex- or age-related effects observed on the PK profile of neratinib.

The food-effect assessment was conducted in a crossover cohort that received neratinib 240 mg (6 × 40 mg tablets) orally under fasting conditions and with standard breakfast in 52 healthy subjects. Mean peak plasma concentration (C_{max}) values were 38.8 ng/mL and 45.54 ng/mL, respectively, under fasting and fed conditions, and mean values for AUC were 594.3 ng•hr/mL and 658.1 ng•hr/mL, respectively. The time to median t_{max} was 5 hours under both fasting conditions and when neratinib was given with food. C_{max} and AUC from time zero to infinity (AUC_{inf}) were roughly 17% and 13% higher, respectively, under fed conditions compared to fasted conditions. For the 6 × 40 mg tablets, the upper limits of the 90% CIs for the fed versus fasted conditions were close to or marginally greater than the upper criteria limit of 125%, indicating a slight increase in neratinib exposures when administered with food. Neratinib was administered with food in all Phase 2 and Phase 3 studies.

Neratinib undergoes oxidative metabolism in the liver by CYP3A4, and to a lesser extent by flavin-containing monooxygenase (FMO), to form pharmacologically active metabolites M3 (pyridine N-oxide), M6 (N-desmethyl 272), and M7 (dimethylamine N-oxide), and the bis-N-oxide M11. Neratinib exposure (i.e., C_{max} and AUC) in subjects with mild or moderate (i.e., Child-Pugh class A or class B) hepatic impairment is like that in healthy subjects. In subjects with severe chronic liver disease (Child-Pugh class C), however, C_{max} was approximately 2.73 fold and AUC approximately 2.81 fold higher compared with healthy subjects, and CL/F decreased by about 36%. Formal studies of patients with severe renal impairment have not been performed, as < 2% of neratinib is excreted through the kidneys.

Neratinib was not associated with prolongation of the QTc in healthy subjects at doses of 240 mg daily with food, or under conditions of supratherapeutic plasma concentrations obtained by concomitant administration of neratinib 240 mg and ketoconazole 400 mg.

5.3. Drug-Drug Interactions

The solubility of neratinib is pH dependent. Treatments that alter GI pH such as proton pump inhibitors (PPIs), H2-receptor antagonists, and antacids may lower the solubility of neratinib, thus decreasing exposure.

Concomitant administration of strong inhibitors (ketoconazole) or inducers (rifampin) of CYP3A4 alter neratinib concentrations significantly.

Neratinib may inhibit the transport of P-glycoprotein substrates. Thus, neratinib is associated with a significant increase in digoxin concentrations when administered concomitantly.

There were no apparent drug-drug interactions observed for neratinib when administered concomitantly with capecitabine, paclitaxel, trastuzumab, or vinorelbine.

6. OVERVIEW OF NERATINIB CLINICAL DEVELOPMENT

6.1. Neratinib Clinical Trials

The neratinib clinical development program consists of 31 clinical studies conducted by the commercial sponsors in which 3252 neratinib treated patients were included in the safety database of the original NDA submission, plus 2 neoadjuvant studies conducted by oncology cooperative groups. Studies that provided data to support the recommended dose, efficacy in breast cancer, including supportive data for metastatic and neoadjuvant and pivotal data for extended adjuvant setting, and safety of monotherapy are highlighted below in Table 7.

Table 7: Neratinib Clinical Studies

Number of Studies	Phase	Study Population/Indication	Type	Number of Subjects Treated (number treated with neratinib)
1	3	Extended adjuvant HER2 positive breast cancer (ExteNET [3004] study)	Pivotal safety and efficacy monotherapy	Treated: 2816 (1408)[c]
1	2	Extended adjuvant HER2 positive breast cancer (CONTROL [6201[a]] study)	Diarrhea prophylaxis, safety study	211 (211)
9	2	Metastatic breast cancer	Safety, efficacy, and PK monotherapy or combination	1291 (942)
3	2	Advanced or metastatic lung cancer and other tumor types[a]	Safety, efficacy, and PK - monotherapy or combination	405 (405)
5	1	Phase 1 solid tumors	Dose-finding and PK (monotherapy or combination), Japanese studies	176 (176)
12	1	Clinical pharmacology studies in healthy volunteer studies	PK, DDI, TQTc, hepatic impairment, ADME	377 (357)
2	2	Neoadjuvant HER2 positive breast cancer[b]	pCR	319 (199)

Abbreviations: ADME=absorption, distribution, metabolism, and excretion; DDI=drug-drug interaction; pCR=pathologic complete response; PK=pharmacokinetics; TQTc=Thorough QTc study.
[a] Enrollment ongoing for 2 studies (6201 and 5201). Enrollment for Study 5201 is reported as of 120-day Safety Update; for Study 6201, enrollment is from the more recent Feb 2017 update.
[b] Neoadjuvant trials included I-SPY2 and NSABP-FB-7 conducted by cooperative groups with support from Puma. [c]Study 3004 enrolled 2840 patients randomized 1:1 (1420 patients per arm).

6.2. Clinical Trials Supporting Dose Selection

The recommended dose of neratinib was based on data from 3 clinical trials assessing safety, dose, PK, and preliminary efficacy in solid tumors (primarily breast cancer) and 2 trials assessing PK, safety, and efficacy in the setting of metastatic breast cancer (Table 8). See Section 5 for detailed justification of dose selection.

Table 8: Neratinib Monotherapy Clinical Studies Supporting Dose Selection

Study Number	Phase	Study Population/Indication	Type	Number of Subjects Treated
3144A1-102-US	1	Solid Tumors: Advanced; EGFR1 and/or HER2 positive	MTD, PK, PD, safety and preliminary efficacy Doses tested: 40-400 mg po qd	72
3144A1-200-WW	2	NSCLC: Advanced	ORR, CBR, safety Doses tested: 240-320 mg po qdtable	167
3144A1-104-JA	1	Solid Tumors: Advanced	MTD, PK, PD, safety and preliminary efficacy Doses tested: 80-320 mg po qd	21
3144A1-201-WW	2	Breast Cancer: Metastatic; HER2 positive; trastuzumab naïve and previously treated with trastuzumab	Safety, efficacy, PK Dose tested: 240 mg po qd	136
3144A2-3003-WW	2	Breast Cancer: Metastatic: HER2 positive; previously treated with trastuzumab	Comparative safety and efficacy study of neratinib vs. lapatinib+capecitabine	231

Abbreviations: CBR=clinical benefit rate; MTD=maximum tolerated dose; NSCLC=non-small cell lung cancer; ORR=overall response rate; PD=pharmacodynamic; PK=pharmacokinetics

6.3. Clinical Trials Supporting Efficacy in Breast Cancer

The clinical trials supporting efficacy in breast cancer are listed in Table 9.

Table 9: Neratinib Clinical Studies Supporting Efficacy in Breast Cancer

Study Number	Phase	Study Population/Indication	Type	Number of Subjects Enrolled	Number of Subjects Treated
3144A2-3004-WW	Pivotal 3	Breast Cancer: Extended adjuvant; HER2 positive (ExteNET [3004] study) **Monotherapy**	Randomized 1:1 neratinib (N=1420) vs. placebo (N=1420); iDFS Dose tested: 240 mg po qd with food for 1 year	2840	2816
3144A1-201-WW	2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive **Monotherapy**	Group A: previously treated with trastuzumab (N=66) Group B: trastuzumab naïve PFS at 16 weeks; ORR (N=70) Doses tested: 240 mg po qd	136	136
3144A2-3003-WW	2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive **Monotherapy**	Randomized 1:1 neratinib (N=117) vs. lapatinib+ capecitabine (N=116) PFS; OS, ORR Dose tested: 240 mg po qd	233	231
I-SPY 2	2	Breast Cancer: **Neoadjuvant**; HER2 positive[a] Combo with chemotherapy (paclitaxel followed by anthracycline/cyclophosphamide)	Adaptive randomization neratinib+ chemo (N=65) vs. trastuzumab+chemo (N=22)[a] pCR Dose tested: 240 mg po qd	87	87
NSABP-FB-7	2	Breast Cancer: **Neoadjuvant**; HER2 positive Combo with (paclitaxel with or without trastuzumab followed by anthracycline/cyclophosphamide)	Randomized, 3 groups Paclitaxel+trastuzumab (N=42) Paclitaxel+ neratinib (N=42) Paclitaxel+trastuzumab+neratinib(N=42) pCR Dose tested: 240 mg po qd	126	126

Table 9: Neratinib Clinical Studies Supporting Efficacy in Breast Cancer (Continued)

Study Number	Phase	Study Population/Indication	Type	Number of Subjects Enrolled	Number of Subjects Treated
3144A2-3005-WW	2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive **Combo** with paclitaxel	Randomized 1:1 neratinib+paclitaxel (N=242) vs. trastuzumab + paclitaxel (N=237) PFS; OS, ORR Dose tested: 240 mg po qd	479	474
3144A1-202-WW	1/2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive **Combo** with trastuzumab	MTD of combo, PD, safety PFS at 16 weeks; ORR Doses tested: 160-240 mg po qd	45	45
3144A1-203-WW	1/2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive **Combo** with paclitaxel	MTD of combo, PD, safety PFS at 16 weeks; ORR Doses tested: 160-240 mg po qd	110	110
3144A1-2204-WW	1/2	Breast Cancer and Solid Tumors: Metastatic or Locally Advanced; HER2 positive **Combo** with vinorelbine	MTD of combo, PD, safety PFS; ORR Doses tested: 160-240 mg po qd	91	91
3144A1-2206-WW	1/2	Breast Cancer and Solid Tumors: Metastatic or Locally Advanced; HER2 positive **Combo** with capecitabine	MTD of combo, PD, safety PFS; ORR Doses tested: 160 and 240 mg po qd	105	105
10-005	1/2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive or triple negative **Combo** with temsirolimus	ORR Doses tested: 240 mg po qd	99	99

Abbreviations: iDFS=invasive disease free survival; MTD=maximum tolerated dose; ORR=overall response rate; OS=overall survival; pCR=pathologic complete response; PD=pharmacodynamic; PFS=progression-free survival

[a] I-SPY2 enrolled subjects with HER2 positive and HER2 negative breast cancer; only HER2 positive data are represented in this table.

6.4. Clinical Trials Supporting Safety of Neratinib Monotherapy in the Neoadjuvant Setting

The neratinib safety database submitted in the NDA consists of 31 clinical studies conducted by the sponsor in which 3252 subjects received neratinib as monotherapy or in combination with other anticancer agents. A table of all 31 commercial sponsored neratinib clinical studies included in the safety database is provided in Appendix A (Table 51).

The safety profile for neratinib monotherapy in the extended adjuvant setting was evaluated in the context of the Phase 3 randomized, placebo controlled pivotal trial, Study 3004, and in an ongoing Phase 2 Study 6201 designed to assess different anti-diarrhea prophylaxis regimens (Table 10). Section 9 of this briefing book focuses on the safety data from these two studies and the NDA submission also included integrated safety analyses across all 3252 subjects (program wide analysis). Cases of LFT elevations were assessed for possible Hy's laws cases as part of the program wide analysis and that assessment included analysis from an external expert hepatologist; none of the cases were determined to be consistent with Hy's law.

Table 10: Neratinib Extended Adjuvant Studies Supporting Safety

Study Number	Phase	Study Population/Indication	Type	Number of Subjects Treated
3144A2-3004-WW	Pivotal 3	Breast Cancer: Extended adjuvant; HER2 positive (ExteNET [3004] study)	Randomized 1:1 neratinib vs. placebo; iDFS Dose tested: 240 mg po qd with food for 1 year	Treated: 2816 (1408 per group)
PUMA-NER-6201	2	Breast Cancer: Extended adjuvant; HER2 positive (CONTROL [6201] study)	Diarrhea prophylaxis, safety study	211

Abbreviations: iDFS=invasive disease free survival
Note: Enrollment ongoing for 6201; Enrollment reported as of February 2017.

7. EVIDENCE OF ACTIVITY IN BREAST CANCER

Typically, breast cancer drug clinical development and approvals begin with treatment in the metastatic setting then move to earlier lines of therapy. However, the neratinib NDA submission is seeking first approval in the extended adjuvant setting. This proposal is based on the totality of evidence of efficacy of neratinib in breast cancer including studies in the neoadjuvant, extended adjuvant and metastatic patient populations.

Because trastuzumab is such an effective standard of care therapy for patients whose tumors are positive for HER2, introducing new HER2 targeting agents, including those with different mechanisms of action or advantages in terms of MOA, safety profile or convenience of administration, is challenging because head to head comparative studies demonstrating superiority may require very large numbers of patients to achieve statistical significance, and non-inferiority study sample sizes would be even larger. Novel combinations are also options to explore, but again may require large sample sizes. Therefore, identifying areas of unmet medical need and demonstrating efficacy and safety in those settings is necessary to achieve technical and regulatory success.

The neratinib extended adjuvant breast cancer therapy program evolved from these challenges. Clear activity of neratinib monotherapy was demonstrated in the metastatic setting without the cardiotoxicity seen with trastuzumab, but with a similar degree of efficacy and convenience of oral administration. Clear activity of neratinib in combination with other agents, and at a level similar to trastuzumab, was also demonstrated in the metastatic setting. Consistent with that, in the neoadjuvant setting of the I-SPY2 and NSABP-FB-7 trials, neratinib demonstrated sufficient activity to advance forward for further evaluation in I-SPY2 and increased the pCR rate when added to trastuzumab in FB-7. Below are the supportive efficacy results from these metastatic and neoadjuvant breast cancer studies, which set the stage for the neratinib pivotal trial in the extended adjuvant setting.

7.1. Metastatic Breast Cancer Monotherapy

7.1.1. Study 201

Study 3144A1-201-WW (Study 201) is an open-label Phase 2 study of neratinib monotherapy (240 mg/d) in 136 women with HER2 positive locally advanced or metastatic breast cancer incurable with available therapy (Burstein, 2010). This study established the antitumor activity of neratinib in advanced HER2 positive breast cancer, including both patients previously treated with trastuzumab (N=66) and those who were trastuzumab naïve (N=70).

The efficacy endpoints were assessed by an independent review panel. The primary endpoint was the 16-week PFS rate in the evaluable population (prior trastuzumab, N=63; trastuzumab-naïve, N=65) and secondary endpoints included ORR. Results are presented in Table 11.

Table 11: Neratinib Monotherapy Efficacy Results in Metastatic Breast Cancer (Study 201, Independent Tumor Assessments)

Parameter	Metastatic Breast, HER2 positive Prior trastuzumab N=63	Metastatic Breast, HER2 positive Naïve to trastuzumab N=65
PFS at 16 - Weeks % (95% CI)	59 (45.8, 71.9)	77 (66.5, 87.7)
ORR% (95% CI)	25.4 (15.3, 37.9)	53.8 (41, 66.3)
Median Duration of Response - Weeks (95% CI)	40.3 (32.3, 80.1)	60.0 (40, 104.7)

Abbreviations: CI=confidence interval; ORR=overall response rate; PFS=progression-free survival

7.1.2. Study 3003

Study 3144A1-3003-WW (Study 3003) is a Phase 2 randomized study in patients with HER2 positive metastatic breast cancer who progressed during or after a trastuzumab based regimen. This study was originally a Phase 3 superiority study with poor enrollment and was amended to become a Phase 2 non-inferiority study with a prespecified 95% CI of the HR set at 1.15 with 85% power at 2-sided 20% significance level. While neratinib monotherapy was not determined to be non-inferior to combination therapy of lapatinib+ capecitabine, clear monotherapy activity in patients previously treated with anti-HER2 therapy was demonstrated with an ORR of 29.1% confirming the findings of Study 201 (neratinib monotherapy) noted above. Results of Study 3003 appear in Table 12.

Table 12: Summary of Efficacy Results (Study 3003, ITT Population)

Parameter	Neratinib (N=117)	Lapatinib plus Capecitabine (N=116)	Hazard Ratio (95% CI)	P-value
Median PFS (95% CI)	4.53 months (3.12 – 5.65)	6.83 months (5.85 – 8.21)	1.19 (0.89 – 1.60)	0.231
Median OS (95% CI)	19.74 months (18.20 – NE)	23.62 months (18.00 – NE)	1.25 (0.83 – 1.86)	0.280
ORR (95% CI)	29.1% (21.0 – 38.2)	40.5% (31.5 – 50.0)	NA	0.067
Median DOR (95% CI)	12.48 months (8.31, 14.75)	7.98 months (5.49, 11.76)	0.71 (0.42, 1.20)	0.196
CBR (95% CI)	44.4% (35.3 – 53.9)	63.8% (54.4 – 72.5)	NA	0.003

Abbreviations: CI=confidence interval; CBR=clinical benefit rate; NA=not applicable; NE=not estimable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

7.1.3. Discussion of Monotherapy Efficacy in Metastatic Breast Cancer

To put the neratinib monotherapy efficacy data into context with other HER2 targeting agents administered as monotherapy in the metastatic setting, historical data can be considered with the caveat that cross study comparisons should only be undertaken with caution due to a variety of differences such as baseline characteristics and study conduct across clinical trials.

Trastuzumab monotherapy in the metastatic setting for patients whose tumors were HER2 positive achieved an ORR of 22% in the treated population with a median duration of response of 9.1 months (approximately 39 weeks); these patients were trastuzumab naïve and had received prior chemotherapy (Cobleigh, 1999). In a similar though not identical patient population, neratinib achieved an ORR approximately 2-fold higher, 53.8%, with a longer median duration of response of 60 weeks. Trastuzumab has been approved to treat breast cancer since 1998.

A more relevant consideration for interpretation of the activity of neratinib is lapatinib because it is within the same broad class of anti-HER2 TKIs, albeit, lapatinib targets EGFR and HER2 and neratinib targets EGFR, HER2 and HER4. In the metastatic setting for patients whose tumors are HER2 positive and who had previously received trastuzumab therapy, lapatinib monotherapy achieved an ORR of 4.3% by investigator assessment and 1.4% by independent review panel assessment (Burstein 2008). The patient population of this study received a larger number of prior therapies for their metastatic disease compared with the neratinib Study 201 or 3003 patients. With that caveat, the ORR for neratinib treatment of HER2 positive patients previously treated with trastuzumab was in the range of 25-29% with the lowest bound of the 95% CI being 15.3%. In another trial of lapatinib of less heavily pretreated patients (1-2 prior regimens), the ORR was 7.7% by investigator assessment and 5.1% by independent review panel assessment (Burstein, 2008). Lapatinib monotherapy for metastatic breast cancer is not approved by the FDA (only lapatinib combination therapies, with capecitabine or with letrozole, are approved for metastatic breast cancer).

Afatinib is another TKI targeting multiple members of the HER family (HER1, HER2, HER3 and HER4). It was studied in patients with metastatic HER2 positive breast cancer who had progressed following trastuzumab based therapy. The median number of prior therapies was three and the ORR = 10% (4/41) (Lin, 2012). Afatinib is approved for NSCLC and is not approved for breast cancer.

7.2. Metastatic Breast Cancer Combination Therapy

Neratinib has been studied in a number of Phase 1/2 combination regimens including combination with trastuzumab, lapatinib, capecitabine, paclitaxel, vinorelbine, and temsirolimus (Table 9). For purposes of understanding the activity of neratinib in metastatic breast cancer this briefing document will focus upon randomized trials of neratinib combination regimens designed to demonstrate the contribution of neratinib to the efficacy outcomes.

7.2.1. Neratinib/Paclitaxel vs. Trastuzumab/Paclitaxel

Study 3144A-3005-WW (Study 3005) compared neratinib+paclitaxel vs. trastuzumab+paclitaxel as first line therapy for patients with HER2 positive metastatic breast cancer; it was amended as a phase 2 superiority study to detect a 30% improvement in the median PFS from an assumed median of 12 months in the control arm with 80% power at 2-sided 15% significance level. Approximately 90% of patients were trastuzumab naïve. The primary endpoint was median PFS and results between the two regimens was comparable HR=1.015 (95%CI 0.813-1.27; p=0.89) and superiority was not demonstrated. Results for the primary and key secondary endpoints appear in Table 13.

While Study 3005 failed to demonstrate superiority based on the prespecified statistical analysis plan, the results of this randomized trial are nonetheless supportive of the evidence that neratinib is active in treating metastatic breast cancer. Neratinib performed similarly to trastuzumab in the metastatic setting across multiple efficacy endpoints, thereby providing clear evidence of efficacy of neratinib in HER2 positive breast cancer. There is also a suggestion that neratinib may do better in controlling CNS metastases demonstrating a lower incidence of CNS recurrence events (p=0.0023) and a reduction in the risk of CNS progression (HR 0.45, 95% CI 0.26, 0.78, p=0.0036)

Table 13: Summary of Efficacy Results (Study 3005, ITT Population)

Parameter	Neratinib plus Paclitaxel (N=242)	Trastuzumab plus Paclitaxel (N=237)	Hazard Ratio (95% CI)	P-value
Median PFS (95% CI)	12.9 months (11.1 – 14.9)	12.9 months (11.1 – 14.8)	1.015 (0.813 – 1.269)	0.8934[a]
ORR (95% CI)	74.8% (68.8 – 80.1)	77.6% (71.8 – 82.8)	NA	0.5219[b]
Median DOR (95% CI)	13.1 months (11.1 – 15.4)	12.9 months (11.0 – 15.1)	0.974 (0.752 – 1.262)	0.8431
CBR (95% CI)	88.4% (83.7 – 92.2)	85.2% (80.1 – 89.5)	NA	0.2360[b]
Cumulative incidence of CNS events (95% CI)	10.1% (6.4, 14.7)	20.2% (14.8, 26.1)	NA	0.0023[c]
Median time to symptomatic or progressive CNS lesions (95% CI)	NE (NE – NE)	NE (NE – NE)	0.449 (0.259 – 0.780)	0.0036[a]

Abbreviations: CI=confidence interval; CBR=clinical benefit rate; CNS=central nervous system; DOR=duration of response; NA=not applicable; NE=not estimable; ORR=overall response rate; PFS=progression-free survival
a Stratified log-rank test
b Stratified Cochran-Mantel-Haenszel test
c Gray's test (Gray, 1988).

7.2.2. Neratinib/Capecitabine vs. Lapatinib/Capecitabine

Phase 1/2 Study 2206 tested the combination of neratinib + capecitabine in patients with HER2 positive, metastatic breast cancer and demonstrated ORR = 57.1% in patient with prior lapatinib and 63.5% in patients who were lapatinib naïve. Lapatinib + capecitabine was approved for the treatment of patients with advanced or metastatic HER2 positive breast cancer and who were previously treated with an anthracycline, taxane and trastuzumab. In a randomized trial comparing lapatinib + capecitabine vs capecitabine the ORR was 23.7% vs. 13.9% respectively (ref US Package Insert for lapatinib). Therefore, the ORR of 57.1% seen with neratinib + capecitabine in Study 2206 appears promising. Based on results of Study 2206, a Phase 3 randomized study, Study 1301, was initiated in patients with HER2 positive metastatic breast cancer who have received 2 or more prior HER2 targeted therapies for their metastatic disease. The coprimary endpoints are PFS and OS. This study remains ongoing.

7.3. Neoadjuvant Breast Cancer Therapy

Testing novel agents in the neoadjuvant setting has been identified as a strategy to assess predictability of efficacy in the adjuvant setting. In this way, novel agents can be screened and those most likely to achieve success in the adjuvant setting can then be taken forward into the large costly adjuvant trials, while those less likely to achieve success are removed from consideration thereby increasing the efficiency adjuvant breast cancer therapy drug development.

The I-SPY2 trial and the NSABP FB-7 trials tested various experimental therapies being considered for use in the neoadjuvant setting. By incorporating them in the neoadjuvant setting and assessing pCR rates that can be compared with a common control arm, the most promising agents and combinations can be identified for further study. One important note, however, is that endocrine therapies were not included in the neoadjuvant regimens for either study.

7.3.1. I-SPY 2

Neratinib in combination with chemotherapy (paclitaxel followed by AC) compared with trastuzumab plus the same chemotherapy was studied in the I-SPY2 trial (Park, 2016). The neratinib+chemotherapy arm achieved higher pCR rates than the trastuzumab+chemotherapy control arm for all HER2 positive patients and both subgroups of HRc positive and negative patients. Based on the prespecified adaptive design of the study, neratinib passed the prespecified efficacy threshold for the subset of patients that were HER2 positive and HRc negative. Results are presented in Table 14.

Table 14: Neratinib Results in Neoadjuvant Breast Cancer (Study I-SPY2)

Parameter	Neratinib (neratinib+paclitaxel followed by doxorubicin+cytoxan) pCR rate % (95% CI)	Control (trastuzumab+paclitaxel followed by doxorubicin+cytoxan) pCR rate % (95% CI)	Probability of Neratinib Being Superior to Control	Predictive Probability of Success in Phase 3
HER2 positive; any HRc status	39 (28-51) n=65	23 (8-38) n=22	95	73
HER2 positive and HRc positive	30 (18-44) n=NR	17 (3-32) n=NR	91	65
HER2 positive and HRc negative	56 (37-73) n=NR	33 (11-54) n=NR	95	79

Abbreviations: CI=confidence interval; HRc=hormone receptor; NR=not reported; pCR=pathologic complete response
Source: I-SPY2 (Park, 2016)

Based on these results, neratinib combination therapy appears to outperform trastuzumab combination therapy in regard to pCR.

7.3.2. NSABP FB-7 Study

This is a randomized Phase 2 study of 3 different anti-HER2 therapies added to a standard neoadjuvant chemotherapy backbone therapy consisting of paclitaxel followed by AC. Patients with HER2 positive early breast cancer were randomized to one of 3 arms: trastuzumab+chemotherapy (N=42) vs. neratinib+ chemotherapy (N=42) vs. trastuzumab+neratinib+chemotherapy (N=42). The pCR results for the entire group and for subgroups based on HRc status appear in Table 15.

Table 15: Preliminary Results for pCR Rates (NSABP FB-7 Study)

Population	Trastuzumab+chemo pCR rate % (95%CI) [n]	Neratinib+chemo pCR rate % (95%CI) [n]	Trastuzumab + Neratinib +chemo pCR rate % (95%CI) [n]
HER2 positive patients (all)	38.1 (23.6, 54.4) [42]	33.3 (19.6, 49.5) [42]	50.0 (34.2, 65.8) [42]
HER2 positive and HRc positive	29.6 (13.2, 48.7) [28]	27.6 (12.7, 47.2) [29]	30.4 (13.2, 52.9) [23]
HER2 positive and HRc negative	57.1 (28.9, 82.3) [14]	46.2 (19.2, 74.9) [13]	73.7 (48.8, 90.9) [19]

Abbreviations: HRc=hormone receptor; pCR=pathologic complete response
Source: NSABP FB-7 (Jacobs, 2015)

7.3.3. Discussion of Neoadjuvant Data

The results of I-SPY2 and NSABP FB-7 are consistent and demonstrate that both neratinib and trastuzumab are active within a similar response range and that patients with HRc negative tumors appear to benefit more than patients with HRc positive tumors. In addition, NSABP FB-7 demonstrated that adding the two anti-HER2 agents together increases the pCR rate by approximately 50%.

The concept of dual anti-HER2 neoadjuvant therapy was also tested previously in the NeoALTTO study. NeoALTTO studied sequential HER2 targeted therapies without chemotherapy followed by weekly paclitaxel and compared 3 HER2 targeting approaches. The results for each arm are as follows [study arm, n (pCR%)]: trastuzumab N=154 (29.5%) vs. lapatinib N=149 (24.7%) vs. trastuzumab+lapatinib N=152 (51.3%) (Baselga, 2012). The combination arm trastuzumab+lapatinib was statistically superior to each of the single anti-HER arms p=0.0001. There was no significant difference between the single anti-HER2 therapy arms p=0.34.

The concept of targeting both HER2 and HER3 through pertuzumab combination therapy was explored in the NeoSphere neoadjuvant study (Gianni, 2012). Patients were randomized to 4 different combination regimens. The results for each arm are as follows [study arm, n (pCR%)]: trastuzumab+docetaxel, N=107 (31%) vs. trastuzumab+pertuzumab+docetaxel, N=107 (49%) vs. trastuzumab+pertuzumab, N=107 (18%) vs. pertuzumab+docetaxel, N=96 (23%). The trastuzumab + chemotherapy arm was in a range similar to the other neoadjuvant studies and adding pertuzumab improved the outcome. The pertuzumab + chemotherapy

combination was no better than the trastuzumab combination and might be worse. Eliminating chemotherapy had the worst outcome.

The TRYPHAENA Study also explored trastuzumab and pertuzumab combinations in the neoadjuvant setting (Schneeweiss, 2013). Patients were randomized to 3 different combination regimens including different chemotherapy combinations: FEC chemotherapy (5-fluorouracil, epirubicin, cyclophosphamide) or TC (docetaxel, carboplatin). The results for each arm as follows [study arm, n (pCR%)]: FEC→trastuzumab+pertuzumab, N=72 (50.7%) vs. FEC→taxotere+trastuzumab+pertuzumab, N=75 (45.3%) vs. TC+trastuzuamb→pertuzumab, N=76 (51.9%). The multiple HER target combinations with chemotherapy resulted in pCR rates in ranges similar to the multi-agent combination arms in the NSABP FB-7, NeoALTTO, and NeoSphere studies.

The trastuzumab arm performed similarly across the studies I-SPY 2 (23%), NSABP FB-7 (38.1%), NeoALTTO (29.5%) and NeoSphere (31%) and were within the 95% CI reported for the point estimate of the pCR rate for I-SPY2 (8-38%). The neratinib arms performed similarly across the 2 studies I-SPY 2 (39%), NSABP FB-7 (33%). For other HER targeting agents, results were somewhat lower though in a similar range: (24.7%) for lapatinib from NeoALTTO and (23%) for pertuzumab in NeoSphere. Caution in regard to cross study comparisons is warranted due to differences in patient population and backbone chemotherapy. However, it is reasonable to conclude that neratinib is active in the neoadjuvant setting, confirmed in two different trials, demonstrates pCR activity in a range similar to approved anti-HER2 agents (trastuzumab, lapatinib, and pertuzumab) and achieves the expected added benefit when added to trastuzumab therapy as part of a dual anti-HER2 treatment strategy.

7.4. Conclusions Regarding Neratinib Efficacy in Metastatic and Neoadjuvant Settings

Neratinib, an oral irreversible TKI targeting HER1, HER2, and HER4 administered as a monotherapy or as part of a combination regimen demonstrated clear evidence of efficacy in the metastatic and neoadjuvant settings. The key findings as applied to breast cancer patients whose tumors are HER2 positive are as follows:

- Neratinib monotherapy in patients with metastatic breast cancer previously treated with trastuzumab achieves independently confirmed objective tumor response rates in more than one clinical trial in the range of 25.4% (Study 201) - 29.1% (Study 3003). This is in the context of historical lapatinib monotherapy response rate of 4.3% (1.4% if independently confirmed) (Burstein, 2008) and 7.7% (5.1% if independently confirmed) (Blackwell, 2009) and afatinib monotherapy response rate of 10% (Lin, 2009).
- Neratinib monotherapy in patients that are naïve to trastuzumab but previously treated for their metastatic breast cancer achieved independently confirmed objective tumor response rate of 53.8% (Study 201). This is in the context of historical trastuzumab monotherapy response rate of 22% (Cobleight, 1999).

- Neratinib + paclitaxel as frontline metastatic breast cancer therapy achieved similar efficacy results as the standard of care trastuzumab + paclitaxel: median PFS 12.9 months vs. 12.9 months (Study 3005).
- Neratinib + paclitaxel treatment may favorably impact CNS recurrence/progression in the metastatic setting (Study 3005). Cumulative incidence of CNS events was 10.1% in patients treated with neratinib + paclitaxel and 20.2% in patients treated with trastuzumab + paclitaxel.
- Neratinib+chemotherapy demonstrated a consistent magnitude of efficacy as measured by pCR in the neoadjuvant setting in two different cooperative group trials, I-SPY2 (39%) and NSABP FB-7 (33%). Neratinib performed better than trastuzumab in the I-SPY2 trial (particularly in the subgroup of patients that were HRc negative (pCR=56%) and, when added to trastuzumab as part of a dual anti-HER2 strategy, was able to increase the pCR rate to 73.7% in HRc negative patients.

The totality of evidence demonstrating the magnitude of activity of neratinib to treat HER2 positive breast cancer across multiple clinical settings plus the strong neoadjuvant data, provides robust scientific and clinical rationale for studying neratinib in the extended adjuvant setting. An unmet medical need was identified during the "extended adjuvant period" or the time after standard of care adjuvant therapy with other anti-HER2 therapy has completed. Patients who have completed their 1 year of trastuzumab adjuvant therapy have no options for further anti-HER2 treatment and enter into a "watch and wait" period. In the interest of being able to turn this time into a period of active anti-HER2 therapy with the intent to provide further improvement in DFS, neratinib was studied as extended adjuvant therapy in the pivotal 3004 prospectively randomized, double blind, controlled trial, the results of which constitute the bulk of this briefing document.

The ExteNET study (Study 3004) is the pivotal trial upon which the proposed indication in the extended adjuvant setting is being sought for neratinib. The details of this study design and results are provided in Section 8 and Section 9.

8. PIVOTAL STUDY 3004 (EXTENET): EXTENDED ADJUVANT THERAPY

8.1. Study Design and Conduct

8.1.1. Final Study Design

Study 3004 is a multicenter, international, randomized, double-blind, placebo-controlled, extended adjuvant therapy Phase 3 trial of neratinib monotherapy versus placebo in women with early-stage HER2 positive breast cancer following standard locoregional treatment, chemotherapy, and adjuvant treatment with trastuzumab for 12 months (Figure 13). The study was opened at 572 sites in 40 countries.

Eligible patients were randomized in a 1:1 ratio to treatment with neratinib or placebo for a period of 1 year. Randomization was stratified by the following 3 factors:

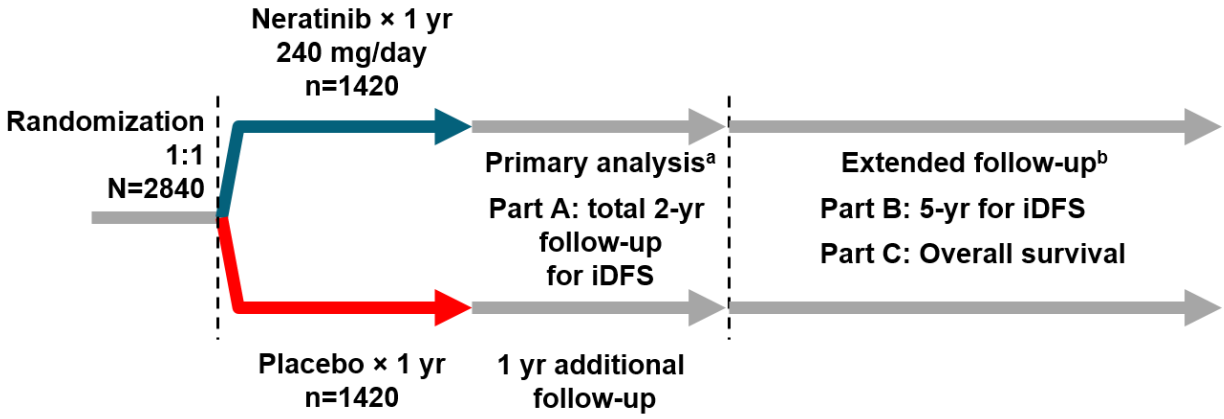
- Locally-determined HRc status (ER and/or progesterone receptor [PgR] positive vs ER and PgR negative)
- Nodal status (0, 1-3, or ≥ 4 positive nodes)
- Trastuzumab adjuvant regimen (sequentially vs concurrently with chemotherapy).

The study consisted of 3 parts:

- Part A (Primary Study): Follow-up period of 2 years (± 28 days) post-randomization. Data collected during this period form the primary analysis for recurrent disease and death.
- Part B (Long-term Follow-up): Expansion of the follow-up period through 5 years (+ 90 days) post-randomization to evaluate the durability of the treatment effect.
- Part C (Long term Follow-up for OS): Primary OS analysis is planned when the requisite 248 events have occurred. An interim OS analysis based on at least 124 events will be performed by the IDMC. The sponsor remains blinded until after the interim analysis.

The ITT population included all randomized patients. The safety population included all patients exposed to investigational product (IP) (either neratinib or placebo).

Figure 13: Final Study Design for 3004



- HER2+ breast cancer (locally determined)
  - IHC 3+ or ISH amplification
- Prior adjuvant trastuzumab and chemotherapy
- Lymph node pos/neg or residual invasive disease after neoadjuvant therapy
- Known hormone receptor status

Abbreviations: HER2 positive=human epidermal growth factor receptor 2 positive; iDFS=invasive disease free survival; IHC=immunohistochemistry; ISH=*in situ* hybridization
[a] Patients were followed for disease recurrence every 3 months during treatment and every 4 months thereafter.
[b] Disease assessments were performed according to standard of care

Study 3004 evaluated neratinib as extended adjuvant therapy for HER2 positive breast cancer patients following 1 year of adjuvant trastuzumab, with a goal of improving outcome and decreasing the recurrence rate. Because there is no standard-of-care comparator in the extended adjuvant setting, the study was placebo-controlled. In regard to the concept of adding extended therapy to existing standard of care, Study 3004 was similar to that of other extended adjuvant trials in breast cancer, including the HERA trial in HER2 positive patients comparing 1 vs. 2 years of adjuvant trastuzumab therapy and the MA-17 trial of extended adjuvant therapy with the aromatase inhibitor letrozole administered after tamoxifen (Goldhirsch 2013, Goss 2005).

8.1.2. Study Design History and Amendments

It is important to note critical aspects in the administrative and operational history of the 3004 trial extending from 2009 to 2014. Details regarding this history are provided in Section 12. None of the changes to the trial were the result of unblinding; procedures to preserve the study blind were maintained and respected throughout the conduct of the study and until the database lock and analysis of the primary endpoint in July 2014. The key changes affecting the trial include the following:

- Changes in corporate ownership and sponsorship during the life of the trial: 1) Wyeth, the original sponsor, became a subsidiary of Pfizer (2009) and 2) Puma

obtained global rights (2011) and assumed Investigational New Drug (IND) sponsorship (2012) from Wyeth/Pfizer.

- 2010 (Amendment 3): Change in the eligibility criteria and primary analysis population following release of BCIRG-006 and N9831/B-31 analyses that identified subgroups at lower risk for recurrence; node negative patients and patients who were greater than 1 year past completing their adjuvant therapy were no longer permitted to enroll or be included in the primary analysis. This new population was defined as the aITT population and was designated to serve as the primary analysis population.
- 2011 (Amendment 9): Enrollment curtailed at 2840 patients (original planned enrollment was 3850 patients) and change in per patient follow-up period for the primary endpoint (iDFS) from 5 years to 2 years; the statistical analysis plan was modified to two-sided alpha = 0.10 (original alpha = 0.05) (corporate business decision).
- 2014 (Amendment 13): The results of the I-SPY2 neoadjuvant trial suggested evidence of neratinib activity that may be superior to trastuzumab; in addition, the HERA trial showed 2 years of trastuzumab was not superior to 1 year, leaving an unmet medical need for extended adjuvant treatment beyond 1 year. Therefore, Study 3004 was changed back to the original primary analysis population, i.e. ITT population, such that patients at lower risk for recurrence were no longer excluded from the primary analysis. In addition, in order to provide data on duration of iDFS, a 5 year follow up period was reinstituted for those patients able to be reconsented. However, follow-up disease assessment during the period from the end of year 2 through the end of year 5 was based on retrospective medical record review of patients' standard of care visits. The statistical analysis plan restored alpha to the original value of 0.05.
- Detailed and comprehensive monitoring and trial integrity plan implemented to reconsent patients for the 5 year follow-up so that as many patients as possible would be included to minimize potential bias.
- Retention of clinical study operation plans remained in place to preserve operational consistency.
- Retention of the IDMC throughout the trial to preserve safety and integrity of blinding.
- Statistical analysis plan was locked prior to the primary analysis unblinding. The primary analysis of iDFS (2 years of follow-up data on each patient) was prespecified to be tested at the 5% 2-sided significance level. OS is to be tested when 248 events are reached. The iDFS analysis with 5 years of follow-up is a sensitivity analysis.

8.1.3. Eligibility Criteria

Women with locally-confirmed invasive HER2 positive breast cancer stage 1 to 3c without evidence of recurrence were eligible; note that after Amendment 3 this was limited to stage 2 or 3. HER2 positivity was determined locally by immunohistochemistry (IHC) 3+ or *in situ*

hybridization (ISH) (fluorescence, silver, or chromogenic) and archived tumor tissue was required to be submitted for central review (the archived tumor tissue requirement was removed in Protocol Amendment 9). Prior adjuvant chemotherapy with anthracycline and/or taxane or CMF type regimen plus trastuzumab and where the trastuzumab was completed no less than 2 weeks and not more than 2 years (changed to 1 year in Protocol Amendment 3) of randomization; patients with less than 1 year of adjuvant trastuzumab were eligible provided they had received at least 8 weekly or 3 q3weekly doses and were either ineligible to receive further trastuzumab or unable to receive trastuzumab due to toxicity. No evidence of recurrence based on imaging studies (mammogram, chest X-ray, bone scan if elevated alkaline phosphatase (ALP), computed tomography (CT)/magnetic resonance imaging (MRI)/ultrasound of chest and abdomen if transaminases or ALP elevated). Known ER/PgR status and normal organ and left ventricular ejection fraction (LVEF) function were required. Eastern Cooperative Oncology Group (ECOG) performance score was 0-1. Concurrent adjuvant endocrine therapy for HRc positive disease was recommended. Antidiarrheal prophylaxis was not mandated per protocol, but treatment for diarrhea was advised at its earliest occurrence. Patients were excluded if they received prior neoadjuvant therapy that resulted in pCR or DCIS and axillary pCR, received prior ERBB1 or ERBB2 directed therapy other than trastuzumab, NYHA Class II-IV heart failure, underlying GI disorders with diarrhea, or other medical conditions that would preclude them from participation.

8.1.4. Dose and Dosing Regimen

Neratinib was dosed at 240 mg orally once daily with food (see Section 5.2). The protocol provided dose adjustment guidelines for Grade 3 or higher toxicities, with dose reductions in increments of 40 mg/d. Study drug was to be withdrawn if neratinib 120 mg/d was not tolerated.

8.1.5. Efficacy and Safety Assessments

8.1.5.1. Efficacy Assessments

Recurrences were defined clinically, and confirmed radiologically or, where possible, pathologically.

Mammograms were performed annually.

Radiological studies (bone scan, chest/abdomen/pelvis CT/MRI/ultrasound) were only performed based on symptoms, physical exam findings or laboratory results and were not performed on a schedule.

Full physical examinations were performed at baseline and at 1 year, targeted physical examinations including breast and axillary exams were performed every 3 months while on treatment and every 4 months during the follow up period until the end of Year 2. From Years 2 through 5 post randomization, recurrent disease events and deaths were ascertained from the patient's medical records upon re-consent of the patient. Physical examination and mammogram schedules were based on the standard of care defined by the patient's treating physician. After local recurrence, patients were followed until distant recurrence.

Complete blood count, chemistries and LFTs were performed both on a regular basis and when indicated based on clinical findings.

Quality of life assessments used the EuroQol 5 Dimensions 3L (EQ 5D) Questionnaire and the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B), version 4. Assessments were performed at screening and at Months 1, 3, 6, 9, and 12. Quality of life assessments were no longer required after Protocol Amendment 9.

8.1.5.2. Safety Assessments

Safety was assessed by AE reporting; standard laboratory tests, including chemistry, hematology, urinalysis panels and LFTs; vital signs; ECGs; and LVEF by multigated acquisition (MUGA) or echocardiogram (ECHO). AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. 12-lead ECGs and assessments of LVEF by MUGA or ECHO were performed locally at screening and at Months 3, 6, 9, and 12.

8.1.6. Efficacy Endpoints

8.1.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint of iDFS was defined as the time from randomization to first occurrence of invasive ipsilateral tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause.

The iDFS endpoint definition was based upon criteria published by a panel of breast cancer experts convened for the purpose of developing a standardized definition of disease free survival (i.e., the STEEP system, 2007) (Hudis, 2007). The only difference between the STEEP iDFS definition and the 3004 definition is that the STEEP definition also included second primary non-breast invasive cancer. Second primary non-breast cancer in 3004 was excluded from the primary endpoint based on regulatory authority feedback in the US and European Union (EU).

Historical clinical studies in the adjuvant setting defined DFS in an inconsistent manner and in some cases also included DCIS. DCIS was excluded from both the 3004 and STEEP Panel definitions. Some historical adjuvant trials with HER2 targeting agents, however, did include DCIS (e.g. HERA Trial). The ALTTO Study includes secondary cancers as part of the definition of DFS. All these factors should be taken into account.

8.1.6.2. Secondary Efficacy Endpoints

Secondary endpoints were:

- Disease-free survival including ductal carcinoma *in situ* (DFS-DCIS): defined as the time from randomization to the first occurrence of DCIS or an iDFS event. (Note: DFS-DCIS is consistent with the DFS definition in some historical adjuvant trials such as the HERA trial.)
- Time to distant recurrence (TTDR): defined as the time between randomization and the date of the first distant tumor recurrence, or death from breast cancer.
- Distant disease free survival (DDFS): defined as the time from randomization to the first occurrence of distant recurrence or death from any cause.

- Cumulative incidence of CNS recurrences: time from randomization to CNS recurrence as first distant recurrence.
- OS: defined as the time from the date of randomization until the date of death, censored at the last date known alive.

8.1.6.3. Exploratory Efficacy Endpoints

- Health-related quality of life (HRQoL) was an exploratory endpoint. Two validated questionnaires were utilized to collect patient reported breast cancer-specific and generic quality of life data.
- Breast cancer specific quality of life (FACT-B): a 37-item questionnaire with 5 subscales assessing physical, social, emotional, functional well-being, and additional concerns more specific to women with breast cancer (9 items) (Brady, 1997).
- Generic quality of life (EuroQol-5D [EQ-5D]): a standardized instrument for use as a measure of general health states preferences, measuring 5 dimensions of health including mobility, self-care, usual activities, pain/discomfort, and anxiety. General health is measured via a vertical visual analog scale.

Note: Quality of life measurements were not required to be collected after implementation of Amendment 9.

8.1.7. Statistical Methods

8.1.7.1. Sample Size

The final protocol and statistical analysis plan specified the ITT population of the entire 2840 randomized patients as the primary analysis population. The power was estimated to be 88% to detect a HR of 0.667 with a 2-sided 5% significance level assuming 241 iDFS events are obtained in the primary analysis cut at 2 years. The study was originally designed to enroll 3850 patients (337 iDFS events) to detect a HR of 0.7 with 90% power. The projected 241 iDFS events in the final protocol followed assumptions in the previous protocol but were not reached at the time of the primary analysis.

8.1.7.2. Blinding

This was a double-blind, placebo-controlled study. Patients, investigators, and all other personnel involved in the conduct of the study were blinded to individual treatment assignments for the duration of the study. All study drugs were identical in size, color, and shape.

The study remained blinded through the protocol amendments and the key for treatment assignments was kept at the statistical Contract Research Organization (Rho, Inc.) who supported the IDMC. The sponsor's standard operating procedure for unblinding was followed which permitted Rho to pass the treatment assignment key to the sponsor at the time of the primary analysis.

8.1.7.3. Statistical Analyses

All analyses of the primary and secondary efficacy endpoints were performed in the ITT population and are presented with two-sided alpha at 0.05 level of significance. With the exception of the primary analysis of the iDFS endpoint, all p-values are provided for descriptive purposes.

The primary analysis of the iDFS was a time to event analysis based on the stratified log-rank test by the 3 randomization factors (i.e., ER and/or PgR positive vs ER and PgR negative, nodal status [≤ 3 nodes vs ≥ 4 nodes], and sequential vs concurrent trastuzumab with chemotherapy), using a 0.05 level of significance. Although an unstratified analysis was stated in the protocol, it was revised to a stratified analysis in the Statistical Analysis Plan prior to unblinding, so that the primary analysis was consistent with the stratified design of the trial. A Cox proportional hazards model with the same stratification factors was used to estimate the HR and its associated CI. Kaplan-Meier estimates were shown in graphs.

For the primary iDFS analysis, all iDFS events up to the cutoff date of 2 years + 28 days for each patient were included in the primary analysis. Events occurring beyond this point were not included in the ITT analysis of this primary endpoint, because only 2 year follow up was mandated for all patients; follow up beyond 2 years was not mandated for all patients per the protocol amendment in 2011 (see discussion of 5 year iDFS analysis for considerations given to sensitivity analyses inclusive of timepoints beyond 2 years). In addition, if an iDFS event occurred after 2 or more missing physical exams, the patient was censored at the last available physical exam prior to the event. Physical exams were scheduled to occur every 3 months during the first year, and every 4 months during the second year of the study. A gap of ≥ 8 months was used to define two or more missing physical exams. Similarly, a gap of ≥ 12 months was used to define two or more missing physical exams during years 2-5 for the supportive 5 year analyses. The censoring of an iDFS event after 2 or more missing assessments is consistent with FDA's guidance on oncology endpoints (FDA Guidance 2007) and was agreed to with the FDA review team as the primary analysis approach. The result was no different from the result if these events were not censored. For patients who didn't experience an iDFS event, they were censored at the last assessment performed within 2 years + 4 months + 28 days.

OS will be tested at the 5% significance level after the test of iDFS is significant. The final OS analysis will be conducted when 248 OS events are reached to ensure 80% power to detect an HR of 0.7. Other secondary efficacy endpoints related to disease recurrence (DFS-DCIS, DDFS, TTDR) were analyzed similarly to the iDFS endpoint and were meant to provide supportive evidence to the primary iDFS endpoint using nominal significance levels of the hypothesis tests.

For CNS recurrences, stratified Gray's test was used to compare the cumulative incidence of CNS recurrence between the two arms (Gray, 1988). For quality of life parameters, changes from baseline were compared between treatments using analysis of covariance, with baseline score as a covariate.

Sensitivity Analyses

Results are presented for sensitivity analyses in 2 prespecified analysis populations for the endpoint of iDFS:

- The aITT population, considered to be patients at higher risk for recurrence and defined as all patients who met the following criteria:

    - Randomized under Protocol Amendment 3 or subsequent amendments, OR
    - Randomized prior to Protocol Amendment 3 if meeting the following key criteria:
        - Node-positive disease AND
        - Randomization within 1 year of completion of trastuzumab therapy.

- The centrally confirmed HER2 positive population, defined as all randomized patients confirmed to be HER2 positive by central testing using PathVysion HER2/CEP17 DNA dual probe. HER2 positive was defined by a fluorescence ISH score ≥ 2.2. Tumor samples for pharmacogenetic testing were no longer collected after implementation of Protocol Amendment 9.
- The 5 year iDFS analysis of all efficacy endpoints in the ITT population will be performed to demonstrate durability of the treatment effect. This analysis includes all randomized patients (N=2840) in the ITT population. Those patients who were reconsented will provide data through the cut off at 5 years from the date of individual patient randomization for each patient. Those patients who were not reconsented will provide data through the cut off at 2 years from the date of individual patient randomization for each patient. The process undertaken for reconsenting included written and email correspondence, phone calls, and face to face visits; all sites were given the same attention, regardless of the number of patients randomized at a site. Extensive effort was undertaken to collect as much data as possible in order to minimize bias.

Subgroup Analyses

Prespecified analyses of subgroups were performed for all stratification factors used in randomization for the ITT population:

- ER and/or PgR positive vs ER and PgR negative (also referred to as HRc positive vs HRc negative)
- Nodal status
- Trastuzumab given sequentially vs concurrently with chemotherapy

An additional prespecified subgroup analysis was based upon completion of prior trastuzumab ≤ 1 vs > 1 year.

Other exploratory subgroup analyses included:

- Age at randomization
- Geographic Region
- Race
- Menopausal status
- Type of surgical treatment

- Prior radiotherapy
- Prior neoadjuvant therapy
- Histology grade of tumor

For subgroup analyses, unstratified log-rank test results and unstratified HRs are presented, since differences between stratified and unstratified results were minor in the ITT population results. Also, the stratified randomization was performed in the ITT population, but not necessarily within a particular subgroup.

The primary analysis cut at 2 years was conducted in July 2014. The planned sensitivity analysis cut at 5 years was conducted in March 2017.

8.2. Disposition

Table 16 presents the disposition of the 2840 patients in the ITT population. The safety population included all patients who were exposed to IP. In all, 2816 (99.2%) patients received IP, 1408 (99.2%) in each group. Among the randomized patients, 24 (12 in each group) did not receive any IP.

All patients who received IP ended treatment. Among patients who received IP and ended treatment, 2027 (72.0%) completed the treatment: 860 (61.1%) in the neratinib group and 1167 (82.9%) in the placebo group. The most frequent reason for discontinuation of treatment other than completion of treatment phase was AEs. A total of 444 (15.8%) of the treated patients discontinued due to AEs: 372 (26.4%) in the neratinib group and 72 (5.1%) in the placebo group. More patients discontinued treatment due to patient request in the neratinib group (121 [8.6%]) than in the placebo group (69 [4.9%]); more patients discontinued treatment due to recurrence in the placebo group (59 [4.2%]) than in the neratinib group (15 [1.1%]).

Table 16: Disposition (Study 3004, ITT Population)

	Neratinib (N=1420) n (%)	Placebo (N=1420) n (%)	Total (N=2840) n (%)
Patients Randomized	1420 (100)	1420 (100)	2840 (100)
Did Not Receive Study Drug	12 (0.8)	12 (0.8)	24 (0.8)
Received Study Drug	1408 (99.2)	1408 (99.2)	2816 (99.2)
Patients Ended Treatment[a]	1408 (100)	1408 (100)	2816 (100)
Treatment Completed[b]	860 (61.1)	1167 (82.9)	2027 (72.0)
Disease Recurrence	15 (1.1)	59 (4.2)	74 (2.6)
Adverse Event	372 (26.4)	72 (5.1)	444 (15.8)
Patient Request	121 (8.6)	69 (4.9)	190 (6.7)
Protocol Violation	12 (0.9)	20 (1.4)	32 (1.1)
Lost To Follow-Up	4 (0.3)	4 (0.3)	8 (0.3)
Other	23 (1.6)	17 (1.2)	40 (1.4)
Missing	1 (0.1)	0	1 (0.0)
Patients Ended Study (Part A)	1420 (100)	1420 (100)	2840 (100)
Study Completed[c]	1095 (77.1)	1183 (83.3)	2278 (80.2)
Patient Request	197 (13.9)	120 (8.5)	317 (11.2)
Investigator Decision	11 (0.8)	6 (0.4)	17 (0.6)
Discontinuation of Study by Sponsor	3 (0.2)	4 (0.3)	7 (0.2)
Lost To Follow-Up	35 (2.5)	33 (2.3)	68 (2.4)
Other	53 (3.7)	51 (3.6)	104 (3.7)
Screen Failure	0	1 (0.1)	1 (0.0)
Missing	1 (0.1)	0	1 (0.0)

Abbreviations: EOT=end of treatment; ITT=intent to treat
[a] Denominator for EOT reason is based on patients who received at least 1 dose of study drug.
[b] Treatment completed refers to the completion of the treatment phase. Some patients did not exactly complete the 12 months of treatment but were entered as treatment completion on the case report form.
[c] Study completed refers to the completion of Part A of the study (2 year follow-up) at the time of the primary analysis.

8.3. Demographics and Baseline Characteristics

All demographic characteristics were well-balanced between the two treatment groups (Table 17). In each treatment group, patients were predominantly white and slightly over half were post-menopausal. Median age was 52.0 years; approximately 12% of patients in each group were ≥ 65 years. Each of three geographical regions contributed approximately one-third of patients.

Table 17: Demographics (Study 3004, ITT Population)

Characteristic	Neratinib (N=1420)	Placebo (N=1420)
Region, n (%)		
North America	519 (36.5)	477 (33.6)
Western Europe, Australia, South Africa	487 (34.3)	532 (37.5)
Asia Pacific, Eastern Europe, South America	414 (29.2)	411 (28.9)
Race, n (%)		
Asian	188 (13.2)	197 (13.9)
Black or African-American	27 (1.9)	47 (3.3)
White	1165 (82.0)	1135 (79.9)
Other	40 (2.8)	41 (2.9)
Age, years		
Mean (SD)	52.31 (10.08)	52.27 (10.28)
Median	52.00	52.00
Range	25.0 – 83.0	23.0 – 82.0
Age group, n (%)		
<35	46 (3.2)	55 (3.9)
35 to <50	523 (36.8)	515 (36.3)
50 to <60	497 (35.0)	488 (34.4)
≥ 60	354 (24.9)	362 (25.5)
< 65	1247 (87.8)	1245 (87.7)
≥ 65	173 (12.2)	175 (12.3)
Menopausal Status at Diagnosis, n (%)		
Premenopausal	663 (46.7)	664 (46.8)
Postmenopausal	757 (53.3)	756 (53.2)
BMI (kg/m^2)		
n	1376	1361
Mean (SD)	27.43 (5.83)	27.45 (5.80)
Median	26.29	26.57
Range	16.8, 56.2	16.2, 65.2

Abbreviations: ITT=intent to treat; SD=standard deviation

Baseline disease characteristics were well-balanced between the two treatment groups (Table 18). Overall, most patients had an ECOG performance score of 0 (92%). The median time from diagnosis to randomization was approximately 22 months. In regard to stratification factors: Approximately 57% were HRc positive and 43% were HRc negative; 24% had negative nodes, 47% had 1-3 positive nodes, and 30% had ≥ 4 positive nodes; and approximately 62% received prior trastuzumab concurrent with chemotherapy while 38% received it sequentially.

Table 18: Baseline Disease Characteristics (Study 3004, ITT Population)

Characteristic	Neratinib (N=1420)	Placebo (N=1420)
ECOG Performance Status, n (%)		
0	1317 (92.7)	1303 (91.8)
1	98 (6.9)	114 (8.0)
Unknown	5 (0.4)	3 (0.2)
Nodal status[a], n (%)		
Negative	335 (23.6)	336 (23.7)
1-3 positive nodes	664 (46.8)	664 (46.8)
≥ 4 positive nodes	421 (29.6)	420 (29.6)
HRc status[a], n (%)		
Positive	816 (57.5)	815 (57.4)
Negative	604 (42.5)	605 (42.6)
Prior trastuzumab regimen[a], n (%)		
Concurrent	884 (62.3)	886 (62.4)
Sequential	536 (37.7)	534 (37.6)
Stage, n (%)		
I	139 (9.8)	152 (10.7)
IIA	328 (23.1)	306 (21.5)
IIB	268 (18.9)	258 (18.2)
IIIA	273 (19.2)	260 (18.3)
IIIB	27 (1.9)	24 (1.7)
IIIC	144 (10.1)	146 (10.3)
Unknown	241 (17.0)	274 (19.3)
T-stage, n (%)		
T1	440 (31.0)	459 (32.3)
T2	585 (41.2)	555 (39.1)
T3 and above	144 (10.1)	117 (8.2)
Unknown	251 (17.7)	289 (20.4)
N-stage, n (%)		
0	383 (27.0)	389 (27.4)
1	598 (42.1)	580 (40.8)
2	270 (19.0)	274 (19.3)

Table 18: Baseline Disease Characteristics (Study 3004, ITT Population) (Continued)

Characteristic	Neratinib (N=1420)	Placebo (N=1420)
3	144 (10.1)	146 (10.3)
Unknown	25 (1.8)	31 (2.2)
Histology Grade, n (%)		
Undifferentiated	7 (0.5)	18 (1.3)
Poorly differentiated	663 (46.7)	680 (47.9)
Moderately differentiated	461 (32.5)	416 (29.3)
Well differentiated	76 (5.4)	65 (4.6)
Unknown	213 (15.0)	241 (17.0)
Primary Cell Type, n (%)		
Ductal carcinoma	1328 (93.5)	1343 (94.6)
Lobular carcinoma	58 (4.1)	41 (2.9)
Tubular/cribriform	8 (0.6)	15 (1.1)
Mucinous	6 (0.4)	7 (0.5)
Medullary	6 (0.4)	6 (0.4)
Metaplastic	3 (0.2)	1 (0.1)
Adenoid Cystic	1 (0.1)	0
Missing	10 (0.7)	7 (0.5)
Time from diagnosis to randomization (months)		
n	1419	1420
Mean (SD)	23.90 (7.90)	23.97 (8.00)
Median	21.82	22.29
Range	7.7, 73.7	7.8, 103.0

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Abbreviations: ECOG= Eastern Cooperative Oncology Group; HRc=hormone receptor; ITT=intent to treat; SD=standard deviation

[a] From stratification factors

Prior anti-cancer therapy is summarized in Table 19. Overall, no notable differences were observed between the 2 treatment groups in terms of prior anti-cancer therapy.

From the 2840 patients, 2280 (80.3%) had received prior radiotherapy; 979 (34.5%) had a lumpectomy and 1859 (65.5%) had a mastectomy. All patients had received prior trastuzumab. Median time from last treatment with trastuzumab to randomization was 4.50 months. The median duration of prior adjuvant trastuzumab was 11.43 months. Most (80.9%) patients had completed adjuvant trastuzumab ≤1 year prior to randomization and 543 (19.1%) had completed adjuvant trastuzumab >1 year prior to randomization. Almost all

patients had received prior chemotherapy and the types of chemotherapy received at any prior time were well balanced across the 2 groups.

Overall, 721 (25.4%) patients had received prior neoadjuvant therapy; of these, 126 (4.4%) had achieved pCR, 556 (19.6%) had not achieved pCR, and 39 (1.4%) patients had a pCR status of unknown. A total of 1546 (54.4%) patients had prior endocrine therapy. The most frequent endocrine therapy used was an anti-estrogen in 763 patients and an aromatase inhibitor in 685 patients. Among 1209 HRc negative patients, 39 had received prior endocrine therapy.

Table 19: Prior Anti-cancer Therapy (Study 3004, ITT Population)

Characteristic	Neratinib (N=1420)	Placebo (N=1420)
Prior Radiotherapy - n (%)		
No	290 (20.4)	270 (19.0)
Yes	1130 (79.6)	1150 (81.0)
Prior Surgery - n (%)		
Lumpectomy only	468 (33.0)	511 (36.0)
Mastectomy	951 (67.0)	908 (63.9)
Prior Anti-cancer Medication - n (%)		
Yes	1420 (100.0)	1420 (100.0)
Trastuzumab	1420 (100.0)	1420 (100.0)
Anthracycline only	136 (9.6)	135 (9.5)
Anthracycline + Taxane	962 (67.7)	965 (68.0)
Taxane only	318 (22.4)	316 (22.3)
Neither Anthracycline or Taxane	4 (0.3)	4 (0.3)
Prior Neo-adjuvant Therapy - n (%)		
No	1078 (75.9)	1041 (73.3)
Yes	342 (24.1)	379 (26.7)
Trastuzumab	232 (16.3)	257 (18.1)
Anthracycline only	40 (2.8)	35 (2.5)
Anthracycline + Taxane	214 (15.1)	258 (18.2)
Taxane only	84 (5.9)	84 (5.9)
Neither Anthracycline or Taxane	4 (0.3)	2 (0.1)
pCR Status After Neoajuvant treatment- n (%)		
pCR	61 (4.3)	65 (4.6)
No pCR	258 (18.2)	298 (21.0)
Unknown	23 (1.6)	16 (1.1)

Table 19: Prior Anti-cancer Therapy (Study 3004, ITT Population) (Continued)

Characteristic	Neratinib (N=1420)	Placebo (N=1420)
Prior Adjuvant treatment, n (%)		
No	5 (0.4)	1 (0.1)
Yes	1415 (99.6)	1419 (99.9)
Trastuzumab	1414 (99.6)	1417 (99.8)
Anthracycline only	146 (10.3)	147 (10.4)
Anthracycline + taxane	723 (50.9)	677 (47.7)
Taxane only	282 (19.9)	289 (20.4)
Non-anthracycline/taxane	264 (18.6)	306 (21.5)
Time from last trastuzumab to randomization (months)		
n	1420	1420
Mean (SD)	6.86 (6.49)	6.93 (6.45)
Median	4.40	4.65
Range	0.2, 30.9	0.3, 40.6
Duration of prior adjuvant trastuzumab treatment (months)		
n	1413	1416
Mean (SD)	11.01 (3.08)	10.91 (2.61)
Median	11.50	11.40
Range	0.7, 56.9	1.4, 38.0
Time from Last Trastuzumab to Randomization, n (%)		
≤ 1 year	1152 (81.1)	1145 (80.6)
>1 year	268 (18.9)	275 (19.4)
Prior Endocrine Therapy Use for HRc Positive Tumors[a], n (%)		
No	44 (5.4)	41 (5.0)
Yes	772 (94.6)	774 (95.0)
Anti-estrogen only	392 (48.0)	371 (45.5)
Anti-estrogen & aromatase inhibitor	47 (5.8)	40 (4.9)
Aromatase inhibitor only	328 (40.2)	357 (43.8)
Non anti-estrogen & aromatase inhibitor	5 (0.6)	6 (0.7)
Prior Endocrine Therapy Use for HRc Negative Tumors[b], n (%)		
No	590 (97.7)	580 (95.9)
Yes	14 (2.3)	25 (4.1)

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Abbreviations: HRc=hormone receptor; ITT=intent to treat; pCR=pathological complete response; SD=standard deviation

[a]Denominator for the percentages is based on the number of HRc positive patients

[b]Denominator for the percentages is based on the number of HRc negative patients

8.4. Efficacy Results (Study 3004)

8.4.1. Primary Efficacy Endpoint (iDFS)

8.4.1.1. Primary Analysis with 2 Year Cut Off

Study 3004 met its primary endpoint, demonstrating a statistically significant improvement in iDFS in patients treated with neratinib (240 mg/day for 12 months) compared with placebo based on the primary prespecified ITT analysis where all patient data was cut off at 2 years (Table 20): stratified HR=0.66; 95% CI, 0.49, 0.90; 2-sided p=0.008. This represents a 34% relative reduction in risk of recurrence. Disease recurrence or death within 2 years of randomization occurred in 67 patients (4.7%) in the neratinib group and 106 patients (7.5%) in the placebo group. In addition, the iDFS rate at the landmark of 2 years was higher in the neratinib than in the placebo group (94.2% vs 91.9%, respectively). As shown in Figure 14, the 2 curves separate at approximately 3 months and remain separate throughout the rest of the neratinib treatment period plus the 1 year follow up after completion of neratinib treatment (total of 2 years from randomization).

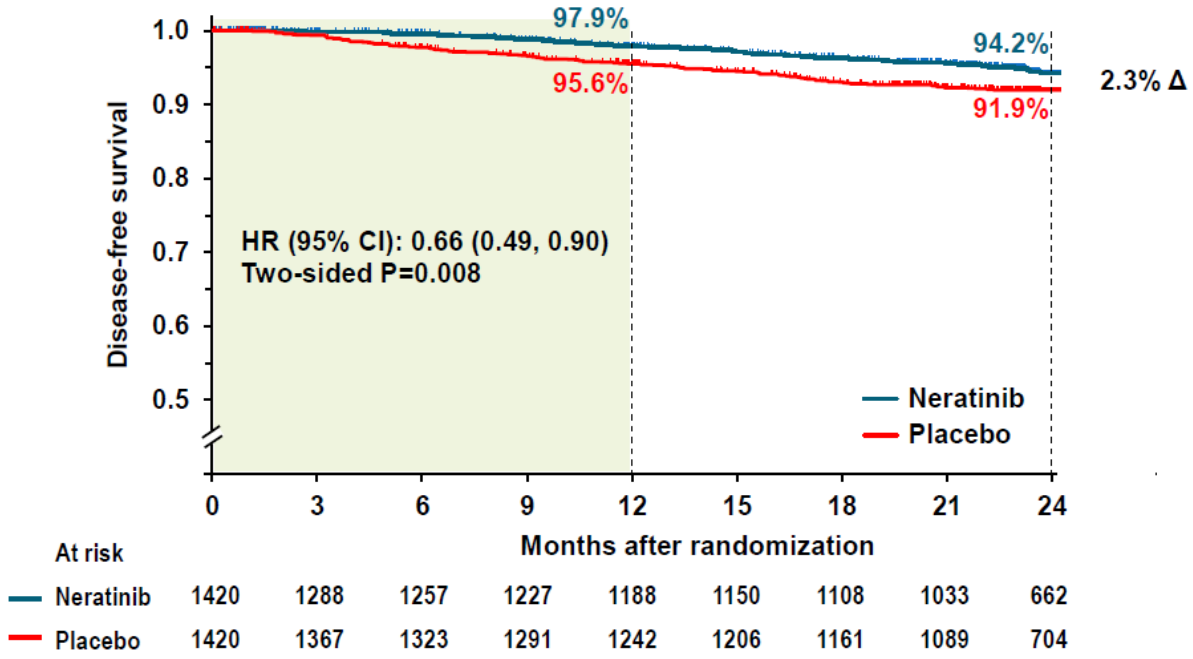
Approximately 70% of the recurrences in each group were distant recurrences. The most frequent site for distant recurrence was bone (1.4% neratinib vs 1.5% placebo), followed by liver (0.9% vs 1.5%) and brain (0.8% vs 1.1%).

Table 20: Primary Analysis of iDFS (Study 3004, ITT Population)

	Neratinib (N=1420)	Placebo (N=1420)
Patients With Events - n (%)	67 (4.7)	106 (7.5)
Local/Regional Invasive Recurrence	8 (0.6)	25 (1.8)
Invasive Ipsilateral Breast Tumor Recurrence	4 (0.3)	4 (0.3)
Invasive Contralateral Breast Cancer	2 (0.1)	5 (0.4)
Distant Recurrence	51 (3.6)	71 (5.0)
Death From Any Cause	2 (0.1)	1 (0.1)
Patients Censored - n (%)	1353 (95.3)	1314 (92.5)
Kaplan-Meier Estimate (%)		
12 Month (95% CI)	97.9 (97.0, 98.6)	95.6 (94.3, 96.5)
24 Month (95% CI)	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)
Stratified Log-rank Test P-value (2-sided)[a]	0.008	
Unstratified Log-rank Test P-value (2-sided)	0.009	
Stratified Cox Proportional Hazards Model Hazard Ratio (95% CI)[b]	0.66 (0.49, 0.90)	
Unstratified Cox Proportional Hazards Model Hazard Ratio (95% CI)[b]	0.67 (0.49, 0.90)	

Abbreviations: CI=confidence interval; ER=estrogen receptor; iDFS=invasive disease free survival; PgR=progesterone receptor
Note: iDFS time is defined as the time from date of randomization until the first disease recurrence of the following events: invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence and death from any cause.
[a] The Log-rank test and Cox model are stratified by randomization stratification factors: prior trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).
[b] The Hazard ratio is presented as neratinib vs. placebo.

Figure 14: iDFS (Study 3004, ITT Population, 2 Year Data Cutoff)



Abbreviations: CI=confidence interval; HR=hazard ratio; iDFS=invasive disease free survival; ITT=intent to treat

8.4.1.2. Sensitivity Analyses

Sensitivity analyses were conducted as specified in the statistical analysis plan or based on post hoc discussions with regulatory authorities. Alpha, or p-value denoting statistical significance was not allocated to these sensitivity analyses and there was no correction for multiplicity. Therefore, p-values, where listed for sensitivity analyses, are provided for descriptive purposes.

aITT Population and Centrally Confirmed HER2 Positive Population (2 year data cut)

Results of two pre-specified sensitivity analyses conducted to support the primary efficacy analysis, the high-risk aITT population (N=1873) and the centrally confirmed HER2 positive population (n =1796), are presented in Table 21.

In the high-risk aITT population, neratinib significantly reduced the iDFS risk by 35% relative to placebo (HR 0.65; 95% CI, 0.46, 0.92) with data cut off at 2 years.

For the centrally confirmed HER2 positive population, Amendment 9 removed the requirement for submission of archived tumor tissue. Therefore, 76.1% (2160/2840) of patients enrolled had tumor tissue ascertained by central testing for HER2 gene amplification at the time of this analysis; of the 2160 patients, 1796 (83.1%) had samples centrally confirmed as positive for HER2. Based on the population with central confirmation, neratinib reduced the iDFS risk by 43% relative to placebo (HR 0.57; 95% CI, 0.39, 0.84) at the 2 year data cut off.

Table 21: Sensitivity Analyses of iDFS (Study 3004)

Population	Number of Events/ Number of Patients		24-Month iDFS Rate (%) (95% CI)		Stratified Hazard Ratio (95% CI)	Stratified Log-Rank Test P value (two-sided)
	Neratinib	Placebo	Neratinib	Placebo		
ITT	67/1420	106/1420	94.2 (92.6 – 95.4)	91.9 (90.2 – 93.2)	0.66 (0.49 – 0.90)	0.008
aITT	53/938	84/935	93.1 (91.1 – 94.7)	90.1 (87.9 – 92.0)	0.65 (0.46 – 0.92)	0.015
Centrally confirmed HER2 positive	42/917	70/879	94.6 (92.7 – 96.0)	91.4 (89.3 – 93.2)	0.57 (0.39 – 0.84)	0.004

Abbreviations: aITT=amended ITT; CI=confidence interval; iDFS=invasive disease free survival; ITT-intent to treat

Sensitivity Analysis of iDFS with Data Cut-off at 5 Years Follow-up in the ITT population (5 Year Analysis)

As prespecified in the statistical analysis plan, iDFS analysis of the ITT population (N=2840) including data cut off at 5 years of follow-up in the reconsented patient population was to be conducted as a sensitivity analysis. Activities to ensure participation from all Study 3004 sites in Amendment 13 and to obtain reconsent were initiated in January 2014 and continued until data cutoff for the 5 year iDFS results. These activities included written and email correspondence, phone calls, and face to face visits; all sites were given the same attention, regardless of the number of patients randomized at a site. Puma personnel participated in 1119 face to face visits at 472 of the 493 sites in 40 countries with at least one randomized patient. Company personnel communicating with the sites and scheduling visits remained blinded to treatment allocation. This substantial effort involved 100% of enrolling sites and achieved reconsent in 2117 (74.5%) patients (1028 in the neratinib group and 1089 in the placebo group). The analysis is inclusive of the protocol scheduled assessments in the ITT population (N=2840) from randomization to the end of year 2 plus retrospectively collected follow up data in the reconsented patients (N=2117) through the end of year 5; this was conducted to support the long-term analysis of iDFS with data cut off at 5 years post-randomization.

Demographics and Baseline Characteristics of the 5 Year Analysis

Demographics, baseline characteristics, and prior anti-cancer therapy for the re-consented patients (N=2117) are presented in Table 22, Table 23, and Table 24. These characteristics were comparable to those observed for the ITT population (N=2840) (Table 17, Table 18, and Table 19).

The median follow-up time was comparable between the 2 treatment groups: 5.22 years (range, 0.00 to 5.25 years) in the neratinib group and 5.25 years (range, 0.00 to 5.25 years) in the placebo group. A total of 885 (62.3 %) and 927 (65.3%) patients in the 2 groups, respectively, have been followed for 5 years for disease recurrence.

When all the visits during Years 2-5 (Part B portion of Study 3004) were analyzed, the median intervals between visits were 6 months in the neratinib group (n=4614 visits) and 6 months in the placebo group (n=4847 visits). This frequency of follow-up is consistent with the American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Guidelines as it applies to patients who have completed their primary adjuvant therapy (Runowicz, 2016).

Table 22: Patient Demographics, Re-consented Patients in Long-term Follow-up (Study 3004)

	Neratinib (N=1028)	Placebo (N=1089)
Region - n (%)		
North America	326 (31.7)	320 (29.4)
Western Europe, Australia and South Africa	369 (35.9)	432 (39.7)
Asia Pacific, East Europe and South America	333 (32.4)	337 (30.9)
Race - n (%)		
Asian	149 (14.5)	157 (14.4)
Black or African American	9 (0.9)	27 (2.5)
White	847 (82.4)	879 (80.7)
Other	23 (2.2)	26 (2.4)
Age (years)		
n	1028	1089
Mean (SD)	52.02 (9.68)	52.47 (10.08)
Median	52.00	53.00
Min, Max	25.0, 83.0	24.0, 81.0
Age Group - n (%)		
< 35 yr	30 (2.9)	34 (3.1)
35 to <50 yr	382 (37.2)	394 (36.2)
50 to <60 yr	375 (36.5)	374 (34.3)
≥ 60 yr	241 (23.4)	287 (26.4)
< 65 yr	917 (89.2)	954 (87.6)
≥ 65 yr	111 (10.8)	135 (12.4)
Menopausal Status at Diagnosis - n (%)		
Premenopausal	486 (47.3)	506 (46.5)
Postmenopausal	542 (52.7)	583 (53.5)
BMI (kg/m^2)		
n	998	1043
Mean (SD)	27.27 (5.70)	27.26 (5.76)
Median	26.22	26.24

Abbreviations: BMI=body mass index; SD=standard deviation

Table 23: Baseline Disease Characteristics, Re-consented Patients in Long-term Follow-up (Study 3004)

	Neratinib (N=1028)	Placebo (N=1089)
ECOG Performance Status - n (%)		
0	961 (93.5)	1013 (93.0)
1	64 (6.2)	75 (6.9)
Unknown	3 (0.3)	1 (0.1)
Nodal Status[a] - n (%)		
Negative	216 (21.0)	261 (24.0)
1-3 Positive Nodes	506 (49.2)	510 (46.8)
≥ 4 Positive Nodes	306 (29.8)	318 (29.2)
HRc Status[a] - n (%)		
Positive	603 (58.7)	615 (56.5)
Negative	425 (41.3)	474 (43.5)
Prior Trastuzumab regimen[a] - n (%)		
Concurrent	621 (60.4)	671 (61.6)
Sequential	407 (39.6)	418 (38.4)
Stage - n (%)		
I	85 (8.3)	114 (10.5)
IIA	234 (22.8)	236 (21.7)
IIB	213 (20.7)	197 (18.1)
IIIA	202 (19.6)	206 (18.9)
IIIB	20 (1.9)	19 (1.7)
IIIC	105 (10.2)	107 (9.8)
Unknown	169 (16.4)	210 (19.3)
T-stage - n (%)		
T1	315 (30.6)	359 (33.0)
T2	431 (41.9)	421 (38.7)
T3 And Above	104 (10.1)	89 (8.2)
Unknown	178 (17.3)	220 (20.2)
N-stage - n (%)		
0	251 (24.4)	303 (27.8)
1	459 (44.6)	446 (41.0)
2	195 (19.0)	211 (19.4)
3	105 (10.2)	107 (9.8)
Unknown	18 (1.8)	22 (2.0)
Histology Grade - n (%)		
Undifferentiated	4 (0.4)	14 (1.3)
Poorly Differentiated	491 (47.8)	524 (48.1)
Moderately Differentiated	331 (32.2)	311 (28.6)
Well Differentiated	57 (5.5)	50 (4.6)
Unknown	145 (14.1)	190 (17.4)

Table 23: Baseline Disease Characteristics, Re-consented Patients in Long-term Follow-up (Study 3004) (Continued)

	Neratinib (N=1028)	Placebo (N=1089)
Primary Cell Type - n (%)		
Ductal Carcinoma	963 (93.7)	1026 (94.2)
Lobular Carcinoma	39 (3.8)	33 (3.0)
Tubular/Cribriform	6 (0.6)	13 (1.2)
Mucinous	4 (0.4)	4 (0.4)
Medullary	4 (0.4)	6 (0.6)
Metaplastic	2 (0.2)	1 (0.1)
Adenoid Cystic	1 (0.1)	0
Missing	9 (0.9)	6 (0.6)
Time from Diagnosis to Randomization (months)		
n	1027	1089
Mean (SD)	24.13 (7.91)	23.91 (7.98)
Median	21.95	22.24
Min, Max	9.5, 71.3	9.8, 103.0

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Abbreviations: ECOG= Eastern Cooperative Oncology Group; HRc=hormone receptor; SD=standard deviation
[a] From stratification factors

Table 24: Prior Anti-Cancer Therapy, Re-consented Patients in Long-term Follow-up (Study 3004)

Characteristic	Neratinib (N=1028)	Placebo (N=1089)
Prior Radiotherapy - n (%)		
No	198 (19.3)	214 (19.7)
Yes	830 (80.7)	875 (80.3)
Prior Surgery - n (%)		
Lumpectomy only	343 (33.4)	392 (36.0)
Mastectomy	684 (66.5)	696 (63.9)
Prior Anti-cancer Medication - n (%)		
Yes	1028 (100.00)	1089 (100.00)
Trastuzumab	1028 (100.00)	1089 (100.00)
Anthracycline only	102 (9.9)	109 (10.0)
Anthracycline + Taxane	725 (70.5)	762 (70.0)
Taxane only	198 (19.3)	216 (19.8)
Neither Anthracycline or Taxane	3 (0.3)	2 (0.2)
Prior Ne-adjuvant Therapy - n (%)		
No	781 (76.0)	807 (74.1)
Yes	247 (24.0)	282 (25.9)
Trastuzumab	162 (15.8)	187 (17.2)
Anthracycline only	32 (3.1)	25 (2.3)
Anthracycline + Taxane	157 (15.3)	204 (18.7)
Taxane only	56 (5.4)	51 (4.7)
Neither Anthracycline or Taxane	2 (0.2)	2 (0.2)
pCR Status- n (%)		
pCR	41 (4.0)	49 (4.5)
No pCR	191 (18.6)	221 (20.3)
Unknown	15 (1.5)	12 (1.1)
Prior Adjuvant treatment, n (%)		
No	4 (0.4)	1 (0.1)
Yes	1024 (99.6)	1088 (99.9)
Trastuzumab	1024 (99.6)	1087 (99.8)
Anthracycline only	111 (10.8)	121 (11.1)
Anthracycline + taxane	546 (53.1)	531 (48.8)
Taxane only	180 (17.5)	211 (19.4)
Non-anthracycline/taxane	187 (18.2)	225 (20.7)

Table 24: Prior Anti-Cancer Therapy, Re-consented Patients in Long-term Follow-up (Study 3004) (Continued)

Characteristic	Neratinib (N=1028)	Placebo (N=1089)
Time from last trastuzumab to randomization (months)		
n	1028	1089
Mean (SD)	6.90 (6.48)	6.78 (6.43)
Median	4.45	4.34
Range	0.2, 30.9	0.3, 40.6
Duration of prior adjuvant treatment (months)		
n	1023	1086
Mean (SD)	11.05 (2.92)	10.93 (2.41)
Median	11.50	11.40
Range	1.4, 46.9	1.4, 29.9
Time from Last Trastuzumab to Randomization, n (%)		
≤ 1 year	833 (81.0)	885 (81.3)
>1 year	195 (19.0)	204 (18.7)
Prior Endocrine Therapy Use for HRc Positive Patients[a], n (%)		
No	33 (5.5)	28 (4.6)
Yes	570 (94.5)	587 (95.4)
Anti-estrogen only	294 (48.8)	281 (45.7)
Anti-estrogen & aromatase inhibitor	31 (5.1)	31 (5.0)
Aromatase inhibitor only	242 (40.1)	272 (44.2)
Non anti-estrogen & aromatase inhibitor	3 (0.5)	3 (0.5)
Prior Endocrine Therapy Use for HRc Negative Patients[b], n (%)		
No	414 (97.4)	454 (95.8)
Yes	11 (2.6)	20 (4.2)

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Abbreviations: HRc=hormone receptor; pCR=pathologic complete response; SD=standard deviation
[a] From stratification factors. Denominator for the percentages is based on the number of HRc positive patients.
[b]Denominator for the percentages is based on the number of HRc negative patients.

Efficacy Results for the iDFS 5 Year Analysis

The ITT population included in the iDFS 5 year analysis included all 2840 patients of whom 74.5% (2117/2840) were reconsented to gather additional data through the 5 year data cut off. The iDFS 5 year analysis results demonstrate durable improvement in iDFS in patients treated with neratinib (240 mg/day for 12 months) compared with placebo based on the prespecified ITT sensitivity analysis with additional data collected through 5 years: stratified HR=0.73; 95% CI, 0.57, 0.92; 2-sided p=0.008 (Table 25). This represents a 27% relative

reduction in risk of recurrence. Disease recurrence or death within 5 years of randomization occurred in 116 (8.2%) patients in the neratinib group and 163 (11.5%) patients in the placebo group. In addition, the iDFS rate at the landmark of 5 years was higher in the neratinib than in the placebo group (90.2% and 87.7%, respectively), an absolute difference of 2.5%.

As shown in Figure 15, the two curves separate at approximately 3 months and remain separate throughout the rest of the neratinib treatment period plus the four year follow up after completion of neratinib treatment (total of 5 years from randomization).

This 5 year analysis of iDFS demonstrates durability of effect seen with the earlier data cut at 2 years.

Table 25: Analysis of 5-Year iDFS (Study 3004, ITT Population)

	Neratinib (N=1420)		**Placebo (N=1420)**
Patients With Events - n (%)	116 (8.2)		163 (11.5)
Local/Regional Invasive Recurrence	12 (0.8)		35 (2.5)
Invasive Ipsilateral Breast Tumor Recurrence	5 (0.4)		7 (0.5)
Invasive Contralateral Breast Cancer	4 (0.3)		11 (0.8)
Distant Recurrence	91 (6.4)		111 (7.8)
Death From Any Cause	4 (0.3)		5 (0.4)
Patients Censored - n (%)	1304 (91.8)		1257 (88.5)
Kaplan-Meier Estimate (%)			
12 Month (95% CI)	97.9 (96.9, 98.5)		95.5 (94.3, 96.5)
24 Month (95% CI)	94.3 (92.9, 95.4)		91.7 (90.1, 93.1)
36 Month (95% CI)	92.2 (90.6, 93.6)		90.2 (88.5, 91.7)
48 Month (95% CI)	91.2 (89.4, 92.7)		89.1 (87.3, 90.7)
60 Month (95% CI)	90.2 (88.3, 91.8)		87.7 (85.7, 89.4)
Stratified Log-rank Test P-value (2-sided)[a]		0.008	
Unstratified Log-rank Test P-value (2-sided)		0.011	
Stratified Cox Proportional Hazards Model[a] Hazard Ratio (95% CI)[b]		0.73 (0.57, 0.92)	
Unstratified Cox Proportional Hazards Model Hazard Ratio (95% CI)[b]		0.73 (0.58, 0.93)	

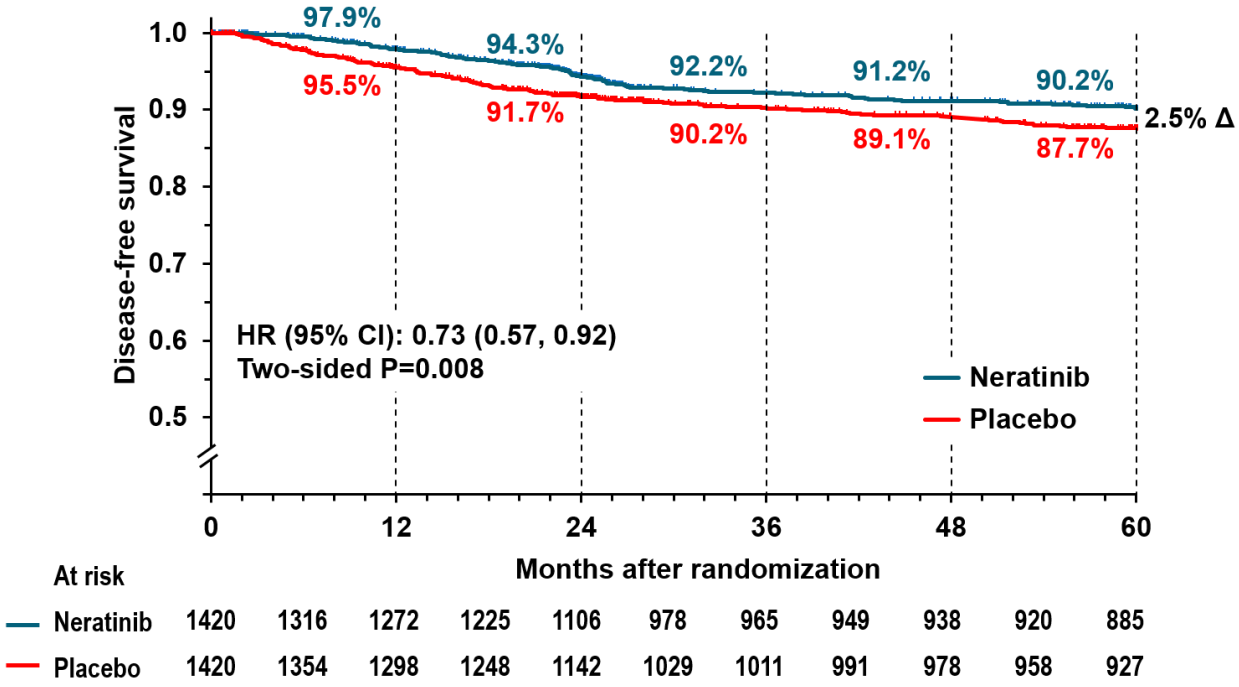
Abbreviations: CI=confidence interval; ER=estrogen receptor; iDFS=invasive disease free survival; PgR=progesterone receptor

Note: iDFS time is defined as the time from date of randomization until the first disease recurrence of the following events: invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence and death from any cause.

[a] The Log-rank test and Cox model are stratified by randomization stratification factors: prior trastuzumab (concurrent or sequential), nodal status (<= 3 or >= 4) and ER/PgR status (positive or negative).

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

Figure 15: Kaplan-Meier Plot of 5-Year iDFS (ITT Population, Study 3004)



8.4.1.3. Subgroup Analyses of the Primary Efficacy Endpoint

Analyses were conducted to assess consistency of treatment effect across important subgroups. Subgroup analyses were conducted and are presented in forest plots. Tests-of-interaction were conducted.

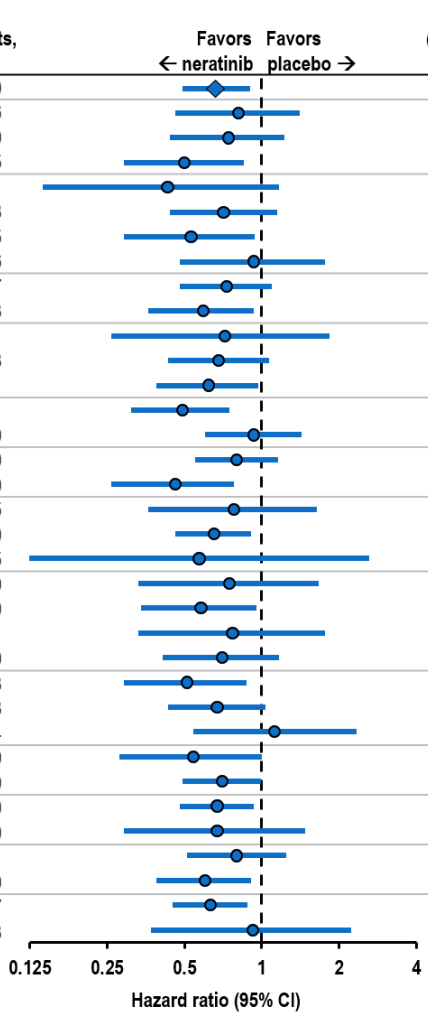
Analysis with 2 Year Cut Off

Results of the subgroup analyses of the primary efficacy endpoint iDFS with a 2 year cut off are depicted in Figure 16. Statistical tests for interaction were conducted.

In the subgroup analyses, the iDFS analyses with the 2 year data cut off were consistent with the primary efficacy analysis; HRs favored neratinib and were < 1.0, with a range of 0.43 to 0.92 (excluding the subgroup of "histology grade unknown"). There are 2 subgroups of interest. The first subgroup, HRc positive patients, achieved notable benefit, and HRc status had a significant test of interaction (p=0.045). In clinical practice it is likely that neratinib will be sequenced shortly after the completion of adjuvant trastuzumab. The results of the adjuvant trastuzumab studies suggest that patients are at a higher risk of recurrence closer to completion of adjuvant trastuzumab, and the risk of recurrence may decrease over time. Therefore the subgroup of patients who were treated with neratinib less than one year after the completion of adjuvant trastuzumab are at a higher risk of recurrence than the subgroup of patients who were treated with neratinib more than one year after the completion of adjuvant trastuzumab.

Figure 16: Forest Plot of iDFS (with 2 Year Cut Off) by Subgroup (Study 3004, ITT Population)

Subgroup		Patients, n	Events, n (neratinib vs placebo)	HR (95% CI)
All patients		**2840**	**67 vs 106**	**0.66 (0.49, 0.90)**
Region of the world	North America	996	23 vs 28	0.81 (0.46, 1.40)
	W Europe and AUS and S Africa	1019	24 vs 38	0.74 (0.44, 1.22)
	Asia and E Europe and S America	825	20 vs 40	0.50 (0.29, 0.85)
Age at randomization, yr	<35	101	5 vs 12	0.43 (0.14, 1.17)
	35-49	1038	28 vs 40	0.71 (0.44, 1.15)
	50-59	985	17 vs 33	0.53 (0.29, 0.94)
	≥60	716	17 vs 21	0.93 (0.48, 1.76)
Menopausal status	Premenopausal	1327	40 vs 56	0.73 (0.48, 1.09)
	Postmenopausal	1513	27 vs 50	0.59 (0.36, 0.93)
Nodal status[a]	Negative	671	7 vs 11	0.72 (0.26, 1.83)
	1-3 positive nodes	1328	31 vs 47	0.68 (0.43, 1.07)
	≥4 positive nodes	841	29 vs 48	0.62 (0.39, 0.97)
Hormone receptor status[a]	Hormone positive	1631	29 vs 63	0.49 (0.31, 0.75)
	Hormone negative	1209	38 vs 43	0.93 (0.60, 1.43)
Prior trastuzumab[a]	Concurrent	1770	49 vs 66	0.80 (0.55, 1.16)
	Sequential	1070	18 vs 40	0.46 (0.26, 0.78)
Race	Asian	385	12 vs 16	0.78 (0.36, 1.64)
	White	2300	53 vs 85	0.65 (0.46, 0.91)
	Black and Other	155	2 vs 5	0.57 (0.08, 2.62)
T-stage at diagnosis	T1	899	10 vs 15	0.75 (0.33, 1.66)
	T2	1140	24 vs 41	0.58 (0.34, 0.95)
	T3 and above	261	11 vs 12	0.77 (0.33, 1.76)
	Unknown	540	22 vs 38	0.70 (0.41, 1.17)
Histology grade	Well/Moderately differentiated	1018	20 vs 36	0.51 (0.29, 0.87)
	Poor/Undifferentiated	1368	33 vs 55	0.67 (0.43, 1.03)
	Unknown	454	14 vs 15	1.12 (0.54, 2.34)
Surgery type	Lumpectomy only	979	14 vs 30	0.54 (0.28, 1.00)
	Mastectomy	1859	53 vs 76	0.70 (0.49, 0.99)
Prior radiotherapy	Yes	2280	57 vs 91	0.67 (0.48, 0.93)
	No	560	10 vs 15	0.67 (0.29, 1.48)
Prior neo-adjuvant therapy	Yes	721	33 vs 48	0.80 (0.51, 1.24)
	No	2119	34 vs 58	0.60 (0.39, 0.91)
Completion of prior trastuzumab	≤1 year	2297	58 vs 95	0.63 (0.45, 0.88)
	>1 year	543	9 vs 11	0.92 (0.37, 2.23)



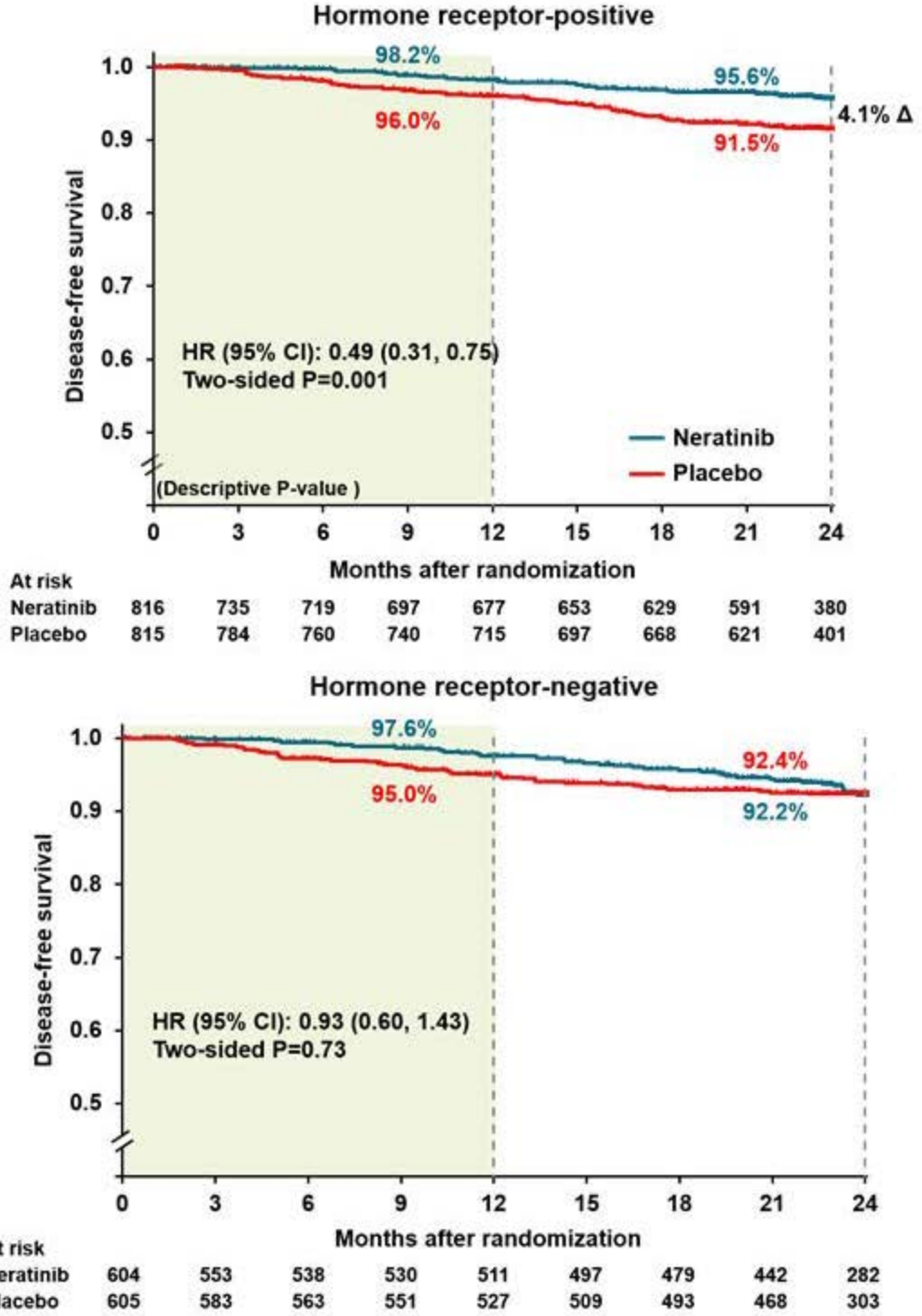
Abbreviations: CI=confidence interval; HR=hazard ratio; iDFS=invasive disease free survival; ITT=intent to treat

[a] From stratification factor.

In the HRc positive subgroup (N=1631), neratinib reduced the 2-year risk of recurrence or death by 51% relative to placebo (HR 0.49; 95% CI, 0.31, 0.75), whereas in HRc negative women (N=1209) the effect was less (HR 0.93; 95% CI, 0.60, 1.43) taking into account the entire 2 year period.

Figure 17 presents KM estimates of iDFS by HRc status using a 2 year cut off.

Figure 17: Kaplan-Meier Estimate of iDFS by HRc Status with 2 Year Cut off (Study 3004, ITT Population)



Abbreviations: CI=confidence interval; HR=hazard ratio; iDFS=invasive disease free survival; ITT=intent to treat

As shown in Figure 17, the K-M curves for the 2 treatment groups separate by 3 months and remain separate throughout the 2-year study period in the subgroup of HRc positive patients. In HRc negative patients, the curves separate by 3 months and remain separate throughout receipt of study drug (i.e., 12 months), but converge at Month 24. The absolute difference at 12 months was similar for both subgroups and numerically better for HRc negative patients: 2.2% for HRc positive and 2.6% for HRc negative.

An exploratory analysis using a cut off at 12 months demonstrates similar magnitude of benefit in both HRc positive and HRc negative patients (Table 26). It is not known if the mandated cessation of neratinib therapy at 12 months impacted the HRc negative patients negatively. HRc positive patients would have continued taking their hormonal therapy the entire 2 year period.

Table 26: iDFS Exploratory Analysis by HRc Subgroup with Data Cut Off at 12 Months (Nominal End of Treatment Period) (Study 3004, ITT Population)

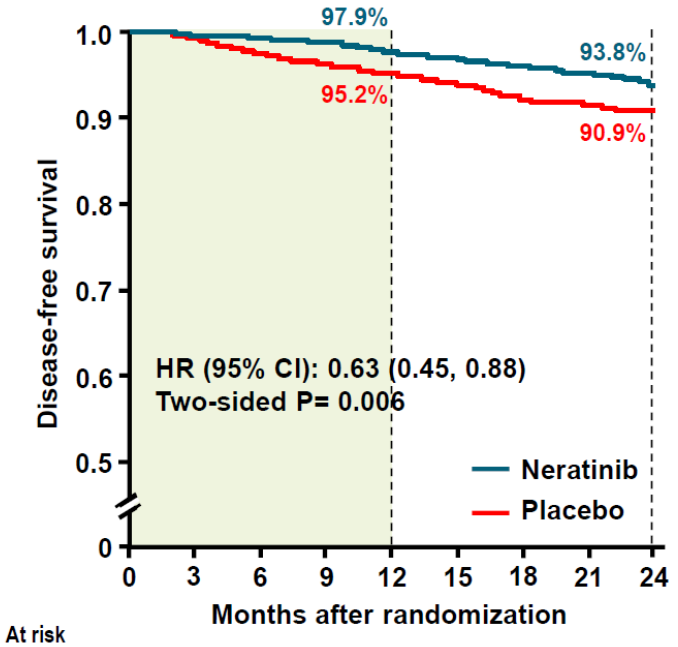
	Number of Events/ Number of Patients		12-Month iDFS Rate (%) (95% CI)		Hazard Ratio	Log-Rank Test P value
Population	Neratinib	Placebo	Neratinib	Placebo	(95% CI)[a]	(two-sided)[a]
All (N=2840)	26/1420	60/1420	97.9 (97.0, 98.6)	95.6 (94.3, 96.5)	0.46 (0.28 – 0.71)	<0.001
HRc positive (N=1631)	13/816	31/815	98.2 (96.9, 98.9)	96.0 (94.4, 97.2)	0.44 (0.22 – 0.83)	0.011
HRc negative (N=1209)	13/604	29/605	97.6 (95.9, 98.6)	95.0 (92.9, 96.5)	0.47 (0.24 – 0.88)	0.020

Abbreviations: CI=confidence interval; HRc=hormone receptor; iDFS=invasive disease free survival; ITT-intent to treat
[a] For the ITT, the analysis was stratified and for subgroups, the analysis was unstratified.

In patients who completed trastuzumab treatment within 1 year prior to randomization (N=2297), neratinib reduced the risk of recurrence or death by 37% relative to placebo (HR 0.63; 95% CI, 0.45, 0.88), but less so in women who completed trastuzumab therapy more than 1 year prior to randomization (N=543) (HR 0.92; 95% CI, 0.37, 2.23) (Figure 18). In the latter group, however, the number of events was low (9 and 11 in the 2 study groups, respectively). A test for interaction was not statistically significant (p=0.529) (Table 3).

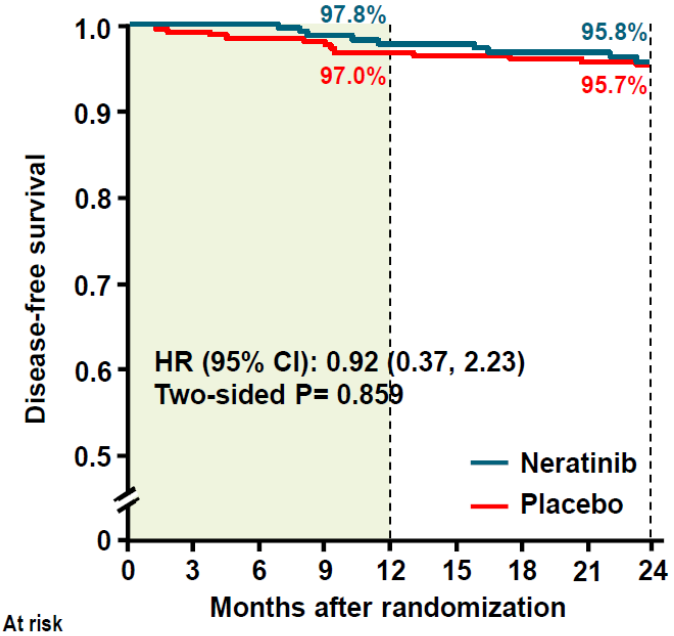
Figure 18: Kaplan-Meier Estimate of iDFS According to Time of Completion of Prior Adjuvant Trastuzumab with 2 Year Cut off (Study 3004, ITT Population)

≤1 year from Randomization



At risk									
Neratinib	1152	1047	1023	1002	971	936	899	833	526
Placebo	1145	1100	1063	1035	997	964	929	865	554

>1 year from Randomization



At risk									
Neratinib	268	241	234	225	217	214	209	200	136
Placebo	275	267	260	256	245	242	232	224	150

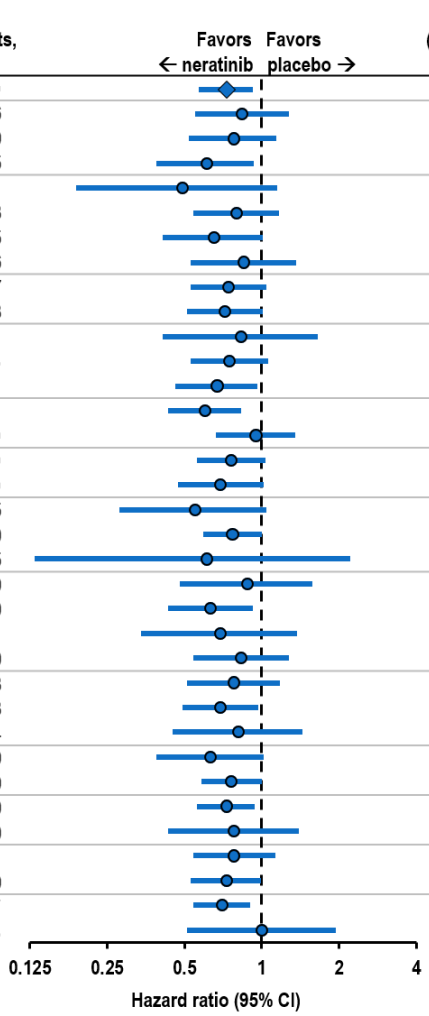
Abbreviations: CI=confidence interval; HR=hazard ratio; iDFS=invasive disease free survival; ITT=intent to treat

Subgroup Analyses with 5 Year Cut Off

Results of the subgroup analyses of the primary efficacy endpoint (with a 5 year cut off) are depicted in Figure 19.

Figure 19: Forest Plot of iDFS (with 5 Year Cut Off) by Subgroup (Study 3004, ITT Population)

Subgroup		Patients, n	Events, n (neratinib vs placebo)	HR (95% CI)
All patients		**2840**	**116 vs 163**	**0.73 (0.57, 0.92)**
Region of the world	North America	996	40 vs 46	0.84 (0.55, 1.28)
	W Europe and AUS and S Africa	1019	43 vs 63	0.78 (0.52, 1.14)
	Asia and E Europe and S America	825	33 vs 54	0.61 (0.39, 0.93)
Age at randomization, yr	<35	101	7 vs 15	0.49 (0.19, 1.15)
	35-49	1038	47 vs 59	0.80 (0.54, 1.17)
	50-59	985	31 vs 48	0.65 (0.41, 1.01)
	≥60	716	31 vs 41	0.85 (0.53, 1.36)
Menopausal status	Premenopausal	1327	60 vs 81	0.74 (0.53, 1.04)
	Postmenopausal	1513	56 vs 82	0.72 (0.51, 1.01)
Nodal status[a]	Negative	671	14 vs 19	0.83 (0.41, 1.65)
	1-3 positive nodes	1328	55 vs 74	0.75 (0.53, 1.06)
	≥4 positive nodes	841	47 vs 70	0.67 (0.46, 0.96)
Hormone receptor status[a]	Hormone positive	1631	59 vs 100	0.60 (0.43, 0.83)
	Hormone negative	1209	57 vs 63	0.95 (0.66, 1.35)
Prior trastuzumab[a]	Concurrent	1770	73 vs 101	0.76 (0.56, 1.03)
	Sequential	1070	43 vs 62	0.69 (0.47, 1.02)
Race	Asian	385	14 vs 26	0.55 (0.28, 1.04)
	White	2300	99 vs 130	0.77 (0.59, 1.00)
	Black and Other	155	3 vs 7	0.61 (0.13, 2.21)
T-stage at diagnosis	T1	899	20 vs 25	0.88 (0.48, 1.57)
	T2	1140	45 vs 69	0.63 (0.43, 0.92)
	T3 and above	261	15 vs 18	0.69 (0.34, 1.37)
	Unknown	540	36 vs 51	0.83 (0.54, 1.27)
Histology grade	Well/Moderately differentiated	1018	41 vs 48	0.78 (0.51, 1.18)
	Poor/Undifferentiated	1368	56 vs 86	0.69 (0.49, 0.97)
	Unknown	454	19 vs 29	0.81 (0.45, 1.44)
Surgery type	Lumpectomy only	979	26 vs 46	0.63 (0.39, 1.02)
	Mastectomy	1859	90 vs 117	0.76 (0.58, 1.00)
Prior radiotherapy	Yes	2280	96 vs 137	0.73 (0.56, 0.94)
	No	560	20 vs 26	0.78 (0.43, 1.39)
Prior neo-adjuvant therapy	Yes	721	48 vs 69	0.78 (0.54, 1.13)
	No	2119	68 vs 94	0.73 (0.53, 0.99)
Completion of prior trastuzumab	≤1 year	2297	99 vs 45	0.70 (0.54, 0.90)
	>1 year	543	17 vs 18	1.00 (0.51, 1.94)

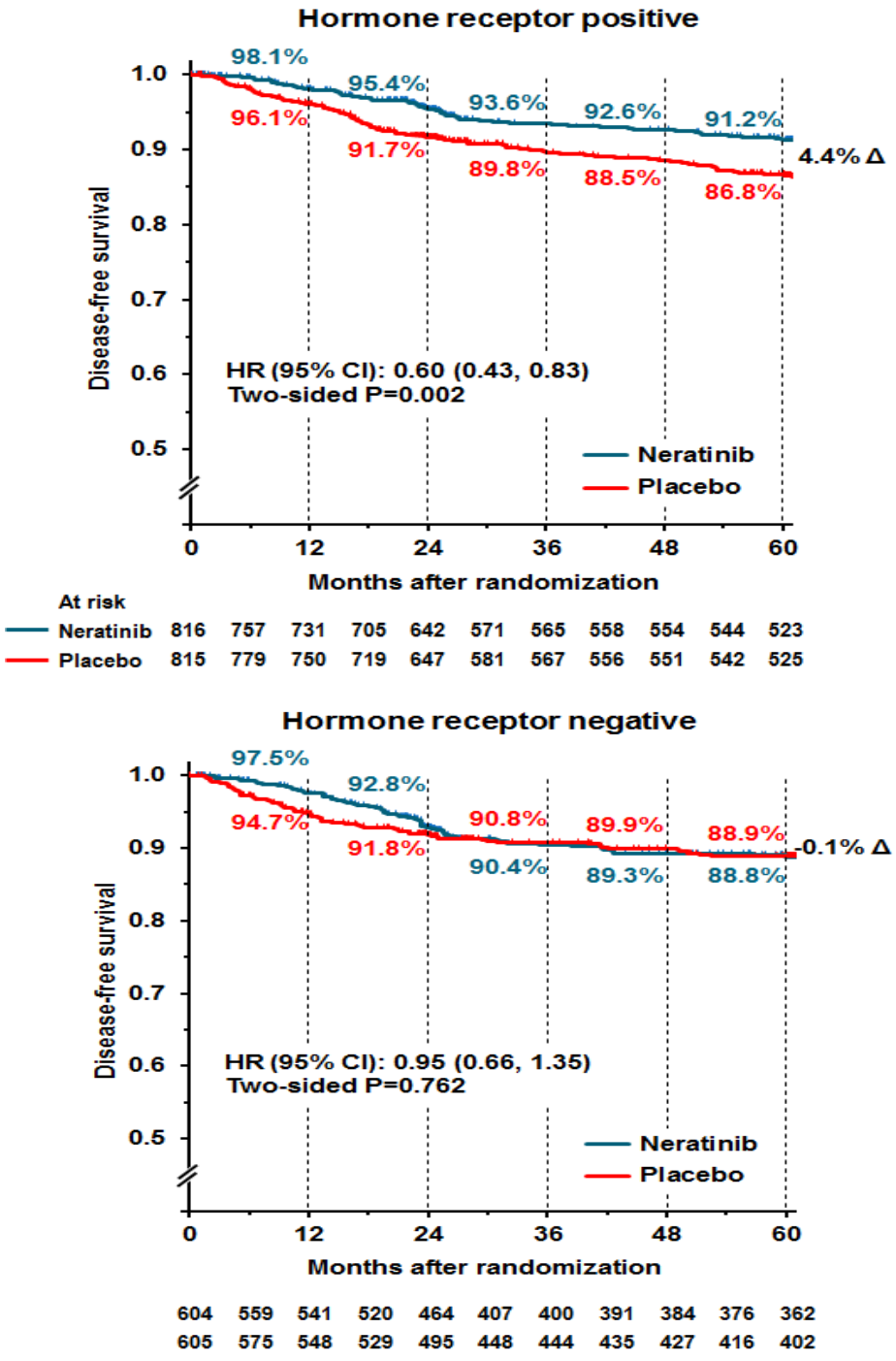


Abbreviations: CI=confidence interval; HR=hazard ratio; iDFS=invasive disease free survival; ITT=intent to treat

[a] From stratification factor.

The results of the subgroup analyses for iDFS with the 5 year cut off appear similar to that observed at the 2 year cut off and demonstrate durability of benefit. As expected, the HRc subgroups analyses showed more benefit over the entire 5 year period for HRc positive patients with HR=0.60 (0.43, 0.83) and considerably less so for HRc negative patients with HR=0.95 (0.66, 1.35) (Figure 20). For patients who completed trastuzumab treatment within 1 year prior to randomization the HR=0.70 (95% CI, 0.54, 0.90) and for patients who completed trastuzumab therapy more than 1 year prior to randomization HR=1.00 (95% CI, 0.51, 1.94) (Figure 21).

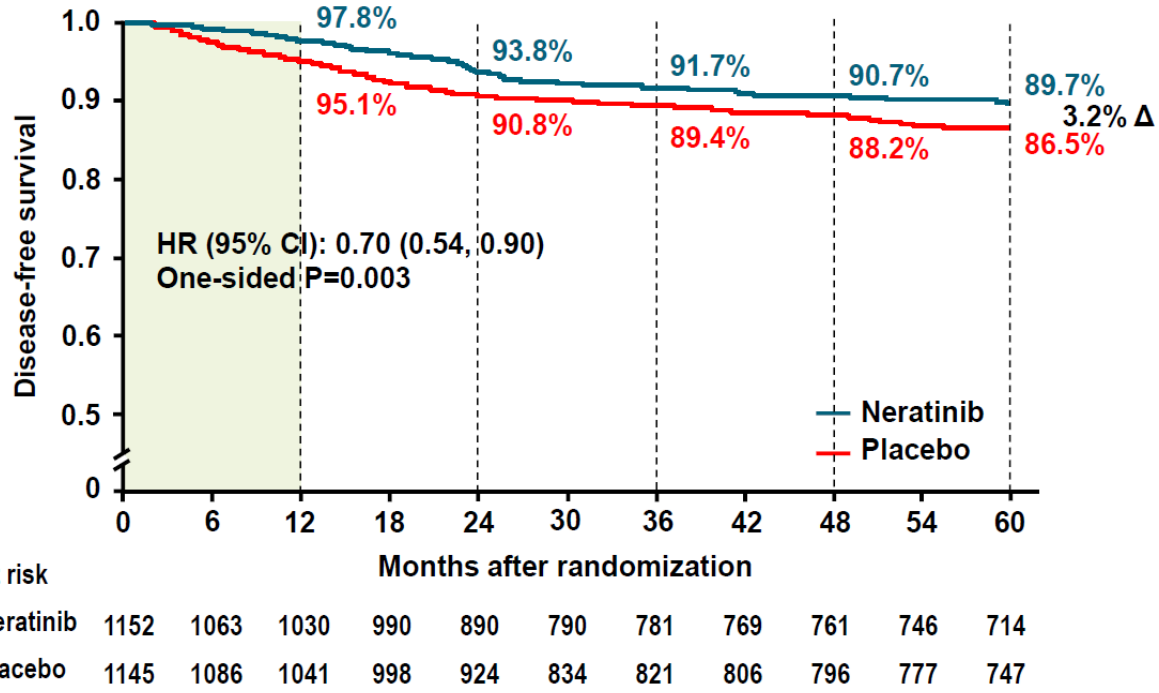
Figure 20: Kaplan-Meier Estimate of iDFS by HRc Status with 5 Year Cut off (Study 3004, ITT Population)



Abbreviations: CI=confidence interval; HR=hazard ratio; iDFS=invasive disease free survival; ITT=intent to treat

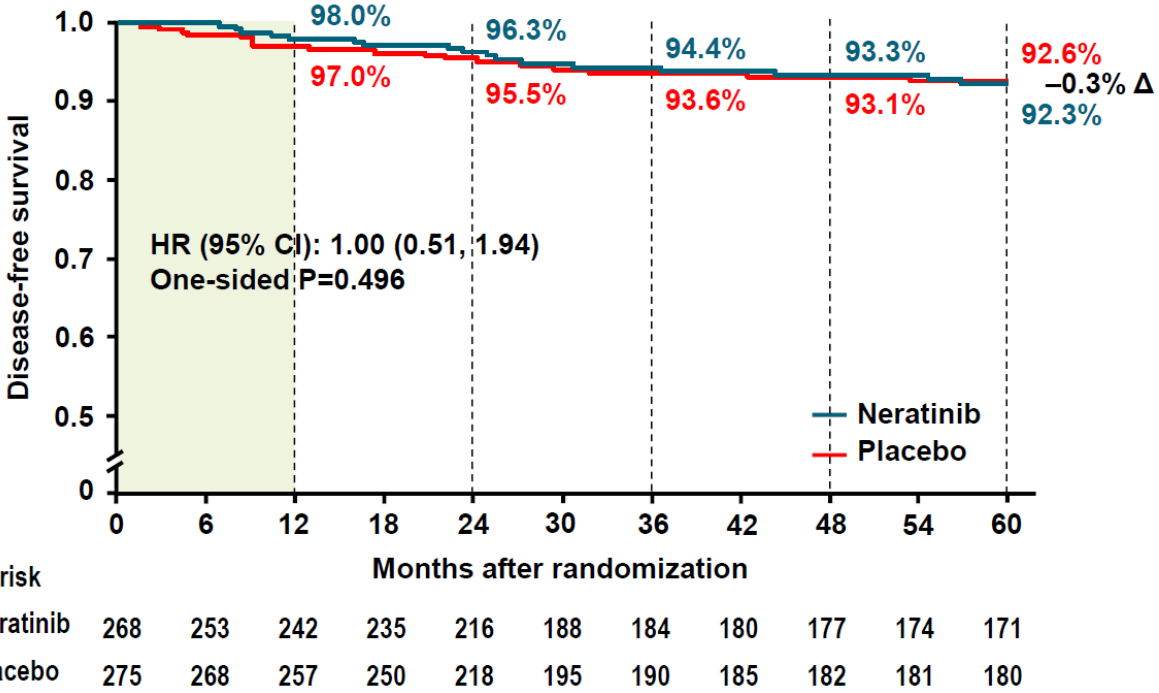
Figure 21: Kaplan-Meier Estimate of iDFS According to Time of Completion of Prior Adjuvant Trastuzumab with 5 Year Cut off (Study 3004, ITT Population)

≤1 year from Randomization



At risk											
Neratinib	1152	1063	1030	990	890	790	781	769	761	746	714
Placebo	1145	1086	1041	998	924	834	821	806	796	777	747

>1 year from Randomization



At risk											
Neratinib	268	253	242	235	216	188	184	180	177	174	171
Placebo	275	268	257	250	218	195	190	185	182	181	180

Abbreviations: CI=confidence interval; HR=hazard ratio; iDFS=invasive disease free survival; ITT=intent to treat

8.4.2. Secondary Efficacy Endpoints

8.4.2.1. Secondary Endpoint Analysis with 2 Year Cut Off

Secondary efficacy endpoint results are provided in Table 27.

Neratinib reduced the risk of DFS-DCIS (HR 0.61; 95% CI, 0.45–0.83; 2-sided p = 0.001), distant DFS (DDFS) (HR 0.74; 95% CI, 0.52–1.05; 2-sided p=0.094), and TTDR (HR 0.73; 95% CI, 0.51, 1.04; 2-sided p=0.087) in the ITT population relative to placebo. Although the study is not powered to show a difference in the secondary endpoints, these data are supportive of the primary outcome of the study.

The cumulative incidence of CNS recurrence was nominally lower in the neratinib group compared to the placebo group: 0.92% (95% CI, 0.49–1.59) vs 1.16% (95% CI, 0.68–1.87), respectively (2-sided p=0.548).

Table 27: Summary of Results of Secondary Efficacy Endpoint Analyses (2 Year Cut Off) (Study 3004, ITT Population)

Parameter	K-M Estimate 2 year Cut Off (%) (95% CI)		Stratified HR (95% CI)[a]	Stratified Log Rank Test P value (2-sided)[a]
	Neratinib (N=1420)	Placebo (N=1420)		
DFS-DCIS	94.2% (92.6%, 95.4%)	91.3% (89.6%, 92.7%)	0.61 (0.45, 0.83)	0.001
DDFS	95.3% (93.9%, 96.4%)	94.0% (92.6%, 95.2%)	0.74 (0.52, 1.05)	0.094
TTDR	95.5% (94.1%, 96.6%)	94.2% (92.8%, 95.3%)	0.73 (0.51, 1.04)	0.087
CNS recurrence cumulative incidence estimate[b]	0.92% (0.49%, 1.59%)	1.16% (0.68%, 1.87%)	NA	0.548

Abbreviations: CI=confidence interval; CNS=central nervous system; DDFS=distant disease free survival; DFS-DCIS=disease-free survival including ductal carcinoma *in situ*; HR=hazard ratio; ITT=intent to treat; TTDR=time to distant recurrence.
Note: DDFS and TTDR include both distant recurrences as first recurrent event and those events that occur after local recurrences
[a] Compared with placebo based on a Cox proportional hazards model stratified by factors used in randomization.
[b] Gray's method (Gray 1988) stratified for prior trastuzumab (concurrent or sequential), nodal status (≤3 and ≥4) and ER/PR status (positive or negative).

8.4.2.2. Secondary Endpoint Analysis with 5 Year Cut Off

Secondary efficacy endpoint results are provided in Table 28.

Neratinib reduced the risk of DFS-DCIS (HR 0.71; 95% CI, 0.56, 0.89; 2-sided p = 0.004), distant DFS (DDFS) (HR 0.78; 95% CI, 0.60–1.01; 2-sided p=0.065), and TTDR (HR 0.79; 95% CI, 0.60, 1.03; 2 sided p=0.078) in the ITT population relative to placebo. Although the study is not powered to show a difference in the secondary endpoints, these data are supportive of the primary outcome of the study.

The cumulative incidence of CNS recurrence was 1.30% (95% CI, 0.77, 2.06) in the neratinib group compared with the placebo group 1.82% (95% CI, 1.19, 2.68): vs (2-sided p=0.333).

Table 28: Summary of Results of Secondary Efficacy Endpoint Analyses (5 Year Cut Off) (Study 3004, ITT Population)

Parameter	K-M Estimate 5 year Cut Off (%) (95% CI)		Stratified HR (95% CI)[a]	Stratified Log Rank Test P value (2-sided)[a]
	Neratinib (N=1420)	Placebo (N=1420)		
DFS-DCIS	89.7 (87.8, 91.3)	86.8 (84.8, 88.6)	0.71 (0.56, 0.89)	0.004
DDFS	91.6 (89.8, 93.1)	89.9 (88.1, 91.5)	0.78 (0.60, 1.01)	0.065
TTDR	91.8 (90.1, 93.3)	90.3 (88.5, 91.8)	0.79 (0.60, 1.03)	0.078
CNS recurrence cumulative incidence estimate[b]	1.30 (0.77, 2.06)	1.82 (1.19, 2.68)	NA	0.333

Abbreviations: CI=confidence interval; CNS=central nervous system; DDFS=distant disease free survival; DFS-DCIS=disease-free survival including ductal carcinoma *in situ*; HR=hazard ratio; ITT=intent to treat; NA=not applicable; TTDR=time to distant recurrence.
Note: DDFS and TTDR include both distant recurrences as first recurrent event and those events that occur after local recurrences
[a] Compared with placebo based on a Cox proportional hazards model stratified by factors used in randomization.
[b] Gray's method (Gray, 1988) stratified for prior trastuzumab (concurrent or sequential), nodal status (≤3 and ≥4) and ER/PR status (positive or negative).

8.4.2.3. Subgroup Analyses of the Secondary Efficacy Endpoints

Further examination of the HRc positive and negative subgroup outcomes for the secondary endpoints at the 2 year analysis demonstrates findings consistent with earlier analyses with benefit primarily in the HRc positive patients (Table 29 and Table 30).

Table 29: Summary of Results of Secondary Efficacy Endpoint Analyses in HRc Positive Patients (2 Year Cut Off) (Study 3004)

Parameter	K-M Estimate 2 year Cut Off (%) (95% CI) Neratinib (N=816)	Placebo (N=815)	Unstratified HR (95% CI)[a]	Unstratified Log Rank Test P value (2-sided)[a]
DFS-DCIS	95.6% (93.8%, 96.9%)	90.8% (88.5%, 92.7%)	0.45 (0.29, 0.69)	<0.001
DDFS	96.4% (94.6%, 97.5%)	93.3% (91.3%, 94.9%)	0.52(0.32,0.84)	0.008
TTDR	96.5% (94.8%, 97.7%)	93.6% (91.6%, 95.2%)	0.52(0.31,0.85)	0.01
CNS recurrence cumulative incidence estimate[b]	0.59% (0.20%, 1.45%)	0.96% (0.43%, 1.91%)	NA	0.445

Abbreviations: CI=confidence interval; CNS=central nervous system; DDFS=distant disease free survival; DFS-DCIS=disease-free survival including ductal carcinoma *in situ*; HR=hazard ratio; HRc= hormone receptor; ITT=intent to treat; NA=not applicable; TTDR=time to distant recurrence.
Note: DDFS and TTDR include both distant recurrences as first recurrent event and those events that occur after local recurrences
[a] Compared with placebo based on a Cox proportional hazards model.
[b] Gray's method (Gray, 1988) stratified for prior trastuzumab (concurrent or sequential), nodal status (≤3 and ≥4) and ER/PR status (positive or negative).

Table 30: Summary of Results of Secondary Efficacy Endpoint Analyses in HRc Negative Patients (2 Year Cut Off) (Study 3004)

Parameter	K-M Estimate 2 year Cut Off (%) (95% CI) Neratinib (N=604)	Placebo (N=605)	Unstratified HR (95% CI)[a]	Unstratified Log Rank Test P value (2-sided)[a]
DFS-DCIS	92.2% (89.4%, 94.3%)	91.8% (89.2%, 93.8%)	0.86 (0.56,1.32)	0.499
DDFS	94.0% (91.5%, 95.8%)	95.0% (92.8%, 96.5%)	1.13 (0.68,1.91)	0.633
TTDR	94.2% (91.8%, 96.0%)	95.0% (92.8%, 96.5%)	1.09 (0.64,1.84)	0.736
CNS recurrence cumulative incidence estimate[b]	1.34 (0.60, 2.63)	1.42 (0.67, 2.68)	NA	0.880

Abbreviations: CI=confidence interval; CNS=central nervous system; DDFS=distant disease free survival; DFS-DCIS=disease-free survival including ductal carcinoma *in situ*; HR=hazard ratio; HRc= hormone receptor; ITT=intent to treat; NA=not applicable; TTDR=time to distant recurrence.
Note: DDFS and TTDR include both distant recurrences as first recurrent event and those events that occur after local recurrences
[a] Compared with placebo based on a Cox proportional hazards model.
[b] Gray's method (Gray, 1988) stratified for prior trastuzumab (concurrent or sequential), nodal status (≤3 and ≥4) and ER/PR status (positive or negative).

Examination of the HRc positive and negative subgroup outcomes for the secondary endpoints at the 5 year analysis demonstrates durability of effect on the secondary endpoints with continued benefit primarily in the HRc positive patients (Table 31 and Table 32).

Table 31: Summary of Results of Secondary Efficacy Endpoint Analyses in HRc Positive Patients (5 Year Cut Off) (Study 3004)

Parameter	K-M Estimate 5 year Cut Off (%) (95% CI)		Unstratified HR (95% CI)[a]	Unstratified Log Rank Test P value (2-sided)[a]
	Neratinib (N=816)	Placebo (N=815)		
DFS-DCIS	91.1 (88.6, 93.0)	86.0 (83.2, 88.3)	0.57 (0.42, 0.79)	<0.001
DDFS	92.7 (90.5, 94.5)	88.7 (86.1, 90.8)	0.60 (0.42, 0.85)	0.004
TTDR	92.9 (90.6, 94.6)	89.1 (86.5, 91.2)	0.61 (0.42, 0.86)	0.006
CNS recurrence cumulative incidence estimate[b]	0.84 (0.35, 1.76)	1.86 (1.04, 3.09)	NA	0.130

Abbreviations: CI=confidence interval; CNS=central nervous system; DDFS=distant disease free survival; DFS-DCIS=disease-free survival including ductal carcinoma *in situ*; HR=hazard ratio; HRc= hormone receptor; ITT=intent to treat; NA=not applicable; TTDR=time to distant recurrence.
Note: DDFS and TTDR include both distant recurrences as first recurrent event and those events that occur after local recurrences
[a] Compared with placebo based on a Cox proportional hazards model.
[b] Gray's method (Gray, 1988) stratified for prior trastuzumab (concurrent or sequential), nodal status (≤3 and ≥4) and ER/PR status (positive or negative).

Table 32: Summary of Results of Secondary Efficacy Endpoint Analyses in HRc Negative Patients (5 Year Cut Off) (Study 3004)

Parameter	K-M Estimate 5 year Cut Off (%) (95% CI)		Unstratified HR (95% CI)[a]	Unstratified Log Rank Test P value (2-sided)[a]
	Neratinib (N=604)	Placebo (N=605)		
DFS-DCIS	87.9 (84.7, 90.5)	87.9 (84.9, 90.4)	0.94 (0.66, 1.32)	0.714
DDFS	90.1 (87.1, 92.4)	91.6 (88.9, 93.6)	1.13 (0.76, 1.69)	0.543
TTDR	90.5 (87.5, 92.7)	92.0 (89.4, 94.0)	1.13 (0.75, 1.71)	0.548
CNS recurrence cumulative incidence estimate[b]	1.92 (0.98, 3.40)	1.78 (0.92, 3.16)	NA	0.908

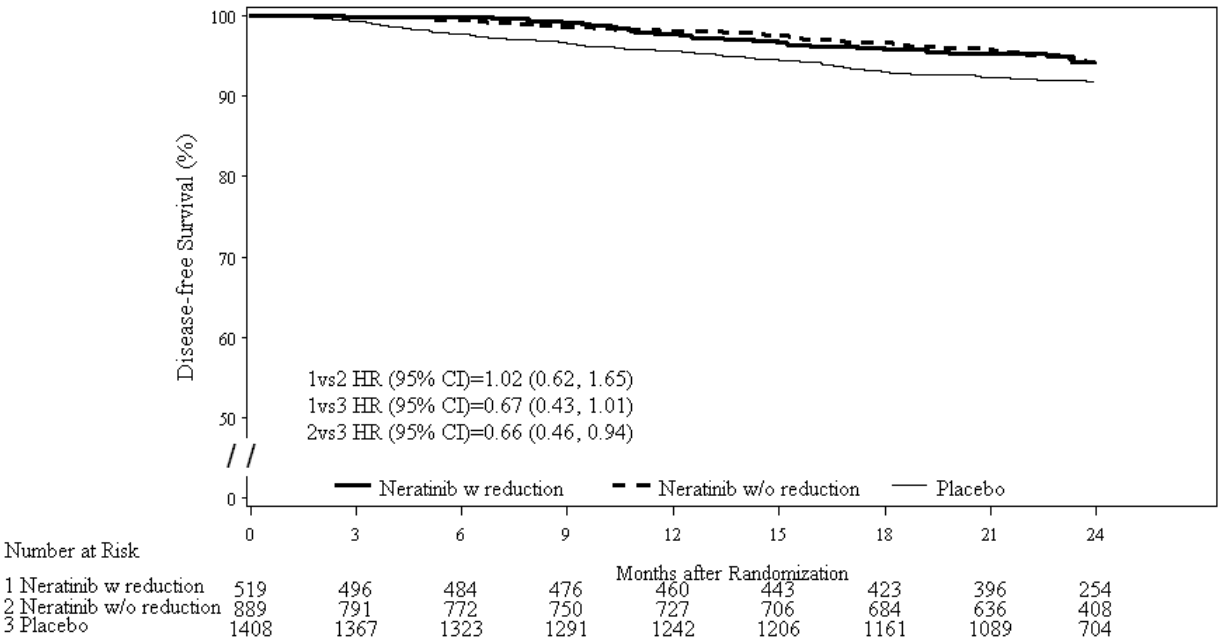
Abbreviations: CI=confidence interval; CNS=central nervous system; DDFS=distant disease free survival; DFS-DCIS=disease-free survival including ductal carcinoma *in situ*; HR=hazard ratio; HRc= hormone receptor; ITT=intent to treat; NA=not applicable; TTDR=time to distant recurrence.
Note: DDFS and TTDR include both distant recurrences as first recurrent event and those events that occur after local recurrences
[a] Compared with placebo based on a Cox proportional hazards model.
[b] Gray's method (Gray, 1988) stratified for prior trastuzumab (concurrent or sequential), nodal status (≤3 and ≥4) and ER/PR status (positive or negative).

8.4.3. Exploratory Analysis of iDFS for Patients in the Neratinib Group with and without Neratinib Dose Reductions

Dose reductions were more commonly observed in the neratinib group (36.9%) than in the placebo group (8.0%). The primary reason for dose reductions was the AE of diarrhea. Because a dose response relationship was observed based on population PK modeling (see Section 5), an exploratory analysis of the primary endpoint, iDFS, was conducted to compare patients who had neratinib dose reductions, patients who did not have neratinib dose reductions, and all placebo patients. In neratinib treated patients with dose reductions, iDFS remained superior to placebo (HR, 0.67; 95% CI [0.43, 1.01]). The neratinib patients without dose reduction continued to be superior to placebo for iDFS (HR, 0.66; 95% CI [0.46, 0.94]). Based on this analysis, dose reductions did not compromise efficacy outcomes. Patients with dose reductions achieved iDFS outcomes comparable in magnitude to the patients without dose reductions

The results are graphically presented as Kaplan Meier plots in Figure 22 below.

Figure 22: Kaplan-Meier Plot of iDFS by Neratinib Dose Reduction Status, Safety Population (Study 3004)



8.4.4. Effect of Early Censoring

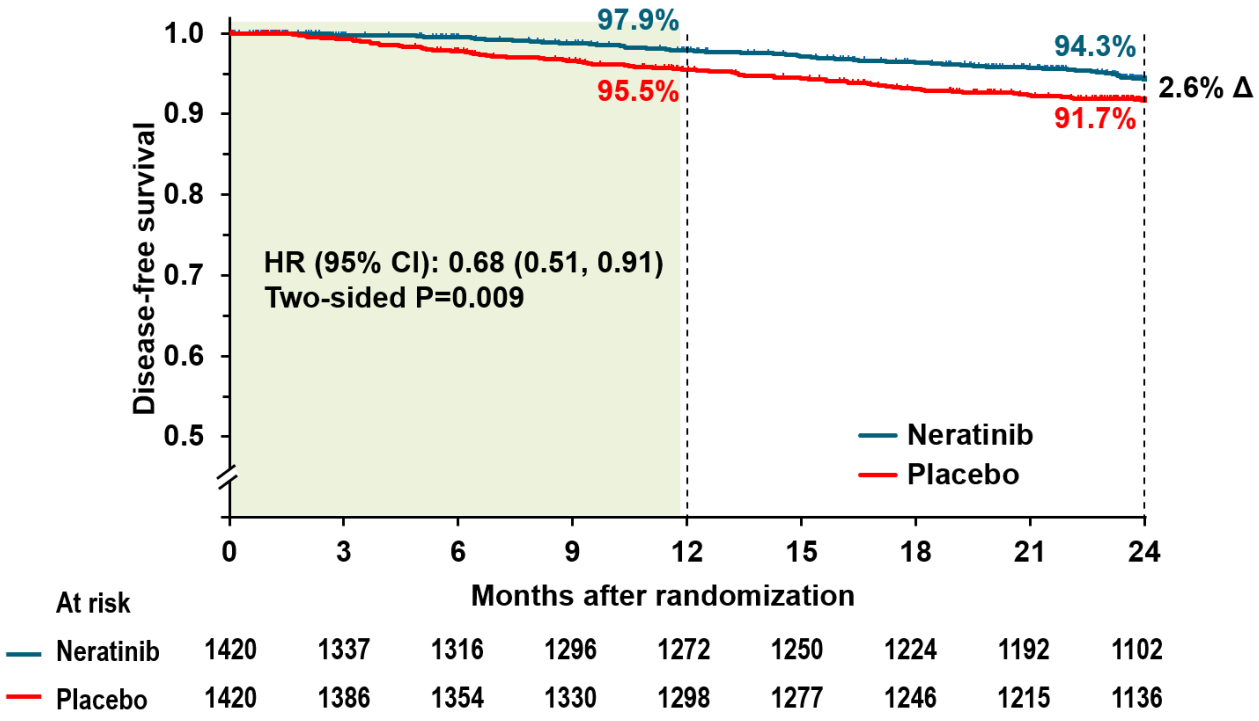
In the primary analysis data cut at 2 years, most patients (65%) had 8 or more physical exams during follow-up and 77.1% had a follow-up duration of >20 months. There were, however, 130 patients in the neratinib group who stopped being followed-up within 3 months of randomization compared with 44 patients in the placebo group. Demographics, baseline disease characteristics, and prior anticancer therapy were similar for patients who dropped out with ≤3 months of follow-up and patients who were followed up for >3 months in the 2 treatment groups.

In addition, a large amount of censoring occurred between Months 21 and 24. This was an artifact of the protocol-defined visit window. Per protocol, patient visits for Months 12 through 24 were to occur every 4 months with a ± 28-day window. Therefore, patients with visits between 21 – 23 months might not have returned for the 24 month visit. For these patients, the most recent visit status prior to Month 24 was used in the iDFS analysis. Of note, the patients who were dropped at 24 months were balanced between the neratinib and placebo groups.

Therefore, the extent of censoring in the iDFS analysis with the data cut at 2 years is a reflection of the low number of patients (48%) at risk at Month 24. This is attributable to both the early drop outs in the trial (between Month 0 and Month 3) and the high amount of censoring at the end of the Part A of the trial (between Month 21 and 24).

The NDA submission contained an updated iDFS analysis with a data cut at 2 years, including additional data collected in Part B of the protocol, and now includes 24-month follow-up data for 1102 (77.6%) patients in the neratinib group and 1136 (80%) patients in the placebo group (Figure 23). This is a substantial increase compared to 662 (47%) patients in the neratinib group and 704 (50%) patients in the placebo group who were followed up for 24 months at the time of the primary analysis cut at 2 years (Figure 14). In addition, the amount of early drop-out at Month 3 was reduced in the updated data. The HR was 0.68 (95% CI 0.51, 0.91; p=0.009), which is consistent with the primary analysis cut at 2 years.

Figure 23: Kaplan-Meier Estimate of Updated iDFS Analysis with 2 Year Data Cut and with Additional Data from Part B (Study 3004, ITT Population)



Abbreviations: CI=confidence interval; FDA=Food and Drug Administration; HR=hazard ratio; iDFS=invasive disease free survival; ITT=intent to treat
Note: Events were within 24 months and patients were censored using FDA's censoring rule and taking into account all available data collected in Part B of the study protocol

The potential impact of early (≤ 3 months follow up) censoring on the primary conclusion of the study was examined. The analysis showed that demographic and baseline characteristics of patients who came off study early were similar to patients who were followed longer (Table 33).

Table 33: Demographic and Baseline Characteristics by Duration of Follow-Up (Study 3004, ITT Population)[*]

	Neratinib		Placebo	
Characteristic	**≤3 months (N=130)**	**>3 months (N=1288)**	**≤3 months (N=44)**	**>3 months (N=1367)**
Region, n (%)				
North America	49 (37.69)	469 (36.41)	16 (36.36)	458 (33.50)
Western Europe, Australia and South Africa	50 (38.46)	436 (33.85)	21 (47.73)	510 (37.31)
Asia Pacific, East Europe and South America	31 (23.85)	383 (29.74)	7 (15.91)	399 (29.19)
Race, n (%)				
White	107 (82.31)	1056 (81.99)	31 (70.45)	1098 (80.32)
Black	6 (4.62)	21 (1.63)	4 (9.09)	43 (3.15)
Asian	14 (10.77)	174 (13.51)	7 (15.91)	187 (13.68)
Other	3 (2.31)	37 (2.87)	2 (4.55)	39 (2.85)
Age at randomization, n (%)				
<35 years	2 (1.54)	44 (3.42)	6 (13.64)	49 (3.58)
35 to <50 years	48 (36.92)	474 (36.80)	15 (34.09)	495 (36.21)
50 to <60 years	41 (31.54)	455 (35.33)	8 (18.18)	479 (35.04)
≥60 years	39 (30.00)	315 (24.46)	15 (34.09)	344 (25.16)
Age, years				
Median	53.50	52.00	50.50	53.00
Menopausal status at diagnosis, n (%)				
Premenopausal	54 (41.54)	608 (47.20)	20 (45.45)	640 (46.82)
Postmenopausal	76 (58.46)	680 (52.80)	24 (54.55)	727 (53.18)
Nodal status, n (%)[a]				
Negative	42 (32.31)	293 (22.75)	8 (18.18)	328 (23.99)
1–3 positive nodes	54 (41.54)	609 (47.28)	22 (50.00)	635 (46.45)
≥4 positive nodes	34 (26.15)	386 (29.97)	14 (31.82)	404 (29.55)

Table 33: Demographic and Baseline Characteristics by Duration of Follow-Up (Study 3004, ITT Population)* (Continued)

	Neratinib		Placebo	
Characteristic	**≤3 months (N=130)**	**>3 months (N=1288)**	**≤3 months (N=44)**	**>3 months (N=1367)**
HRc status, n (%)				
Positive (ER and/or PgR positive)	80 (61.54)	735 (57.07)	27 (61.36)	784 (57.35)
Negative (ER and/or PgR negative)	50 (38.46)	553 (42.93)	17 (38.64)	583 (42.65)
Prior trastuzumab regimen, n (%)				
Concurrent	76 (58.46)	806 (62.58)	21 (47.73)	861 (62.98)
Sequential	54 (41.54)	482 (37.42)	23 (52.27)	506 (37.02)
T-stage, n (%)				
T1	51 (39.23)	389 (30.20)	15 (34.09)	443 (32.41)
T2	51 (39.23)	533 (41.38)	16 (36.36)	534 (39.06)
T3 and above	9 (6.92)	134 (10.40)	4 (9.09)	112 (8.19)
Unknown	19 (14.62)	232 (18.01)	9 (20.45)	278 (20.34)
Histologic grade of tumor, n (%)				
Undifferentiated	1 (0.77)	6 (0.47)	1 (2.27)	17 (1.24)
Poorly differentiated	64 (49.23)	598 (46.43)	16 (36.36)	660 (48.28)
Moderately differentiated	40 (30.77)	421 (32.69)	16 (36.36)	399 (29.19)
Well differentiated	7 (5.38)	69 (5.36)	4 (9.09)	61 (4.46)
Unknown	18 (13.85)	194 (15.06)	7 (15.91)	230 (16.83)
Prior surgery, n (%)				
Lumpectomy only	51 (39.23)	417 (32.38)	12 (27.27)	498 (36.43)
Mastectomy	79 (60.77)	870 (67.55)	32 (72.73)	868 (63.50)
Missing	0	1 (0.08)	0	1 (0.07)
Prior radiotherapy, n (%)				
No	31 (23.85)	258 (20.03)	7 (15.91)	260 (19.02)
Yes	99 (76.15)	1030 (79.97)	37 (84.09)	1107 (80.98)
Prior neoadjuvant therapy, n (%)				
No	104 (80.00)	973 (75.54)	32 (72.73)	1003 (73.37)
Yes	26 (20.00)	315 (24.46)	12 (27.27)	364 (26.63)
Trastuzumab	16 (61.54)	215 (68.25)	7 (58.33)	250 (68.68)
Anthracycline only	2 (7.69)	38 (12.06)	0	34 (9.34)
Anthracycline plus taxane	13 (50.00)	201 (63.81)	10 (83.33)	246 (67.58)

Table 33: Demographic and Baseline Characteristics by Duration of Follow-Up (Study 3004, ITT Population)* (Continued)

	Neratinib		Placebo	
Characteristic	**≤3 months (N=130)**	**>3 months (N=1288)**	**≤3 months (N=44)**	**>3 months (N=1367)**
Prior neoadjuvant therapy, n (%) (Continued)				
Taxane only	11 (42.31)	72 (22.86)	2 (16.67)	82 (22.53)
Neither anthracycline nor taxane	0	4 (1.27)	0	2 (0.55)
Prior adjuvant therapy, n (%)				
No	1 (0.77)	4 (0.31)	0	1 (0.07)
Yes	129 (99.23)	1284 (99.69)	44 (100.00)	1366 (99.93)
Trastuzumab	128 (99.22)	1284 (100.00)	44 (100.00)	1364 (99.85)
Anthracycline only	19 (14.73)	127 (9.89)	6 (13.64)	140 (10.25)
Anthracycline plus taxane	62 (48.06)	660 (51.40)	21 (47.73)	652 (47.73)
Taxane only	28 (21.71)	253 (19.70)	6 (13.64)	281 (20.57)
Neither anthracycline nor taxane	20 (15.50)	244 (19.00)	11 (25.00)	293 (21.45)
Duration of prior adjuvant trastuzumab therapy, months				
n	128	1283	44	1363
Median (Q1, Q3)	11.52 (10.97, 11.99)	11.47 (10.87, 11.93)	11.53 (11.06, 12.06)	11.37 (10.78, 11.89)
Time since last dose of trastuzumab to randomization, months				
n	130	1288	44	1367
Median (Q1, Q3)	6.01 (1.81, 10.81)	4.34 (1.64, 10.33)	5.88 (1.58, 10.74)	4.60 (1.54, 10.84)

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Abbreviations: ER=estrogen receptor; HRc=hormone receptor; PgR=progesterone receptor
*Patients who had iDFS events within the first 3 months were not included in this table.
[a] From IVRS stratification factor.

To assess the potential impact of differential early dropout between treatment groups (patients censored at ≤3 months) on the primary analysis, the following sensitivity analysis (i.e., imputation model) was performed. Patients who dropped out early in the neratinib group were assumed to have iDFS events following the distribution observed in the placebo group. Specifically, imputation of iDFS events for the neratinib early dropout patients was achieved via resampling from the placebo patients by matching HRc status, nodal status, prior trastuzumab regimen (i.e., concurrent vs sequential), and the iDFS time at drop-out. The resampling was done 10,000 times. On average, 9 additional iDFS events were imputed to the neratinib group in the resampled populations, ranging from 1 to 22 events. The average HR was 0.69 (SD=0.03). Among the 10,000 resampled populations, 98.08% of the time the stratified log-rank test yielded 1-sided $p \leq 0.025$ favoring the neratinib arm. Similarly, the early drop-out scenarios were considered in 3-month increments from Month 6 to Month 12.

For each scenario, 10,000 simulations were performed. The results are summarized in Table 34 and support the robustness of the primary analysis.

Table 34: Simulation Results (Study 3004)

Definition of Early Drop-out by Month	Mean (SD) Hazard Ratio	Mean (range) Number of Additional Events	Percent with 1-sided P ≤ 0.025
≤3	0.69 (0.03)	9 (1-22)	98.08
≤6	0.69 (0.03)	11 (1-25)	97.23
≤9	0.70 (0.03)	12 (2, 27)	96.46
≤12	0.70 (0.03)	13 (1-29)	95.65

Abbreviation: SD=standard deviation

8.4.5. Health-Related Quality of Life (Exploratory Endpoint)

In Study 3004, HRQoL was assessed at baseline and at Month 1, 3, 6, 9, and end of treatment; after Protocol Amendment 9, assessment of HRQoL was no longer required. The dropout rate in the first 3 months was higher in the neratinib group than in the placebo group and may have also contributed to the marked decrease in the number of patients with assessments after Month 6. Therefore, caution should be exercised in regard to conclusions that can be derived from these results.

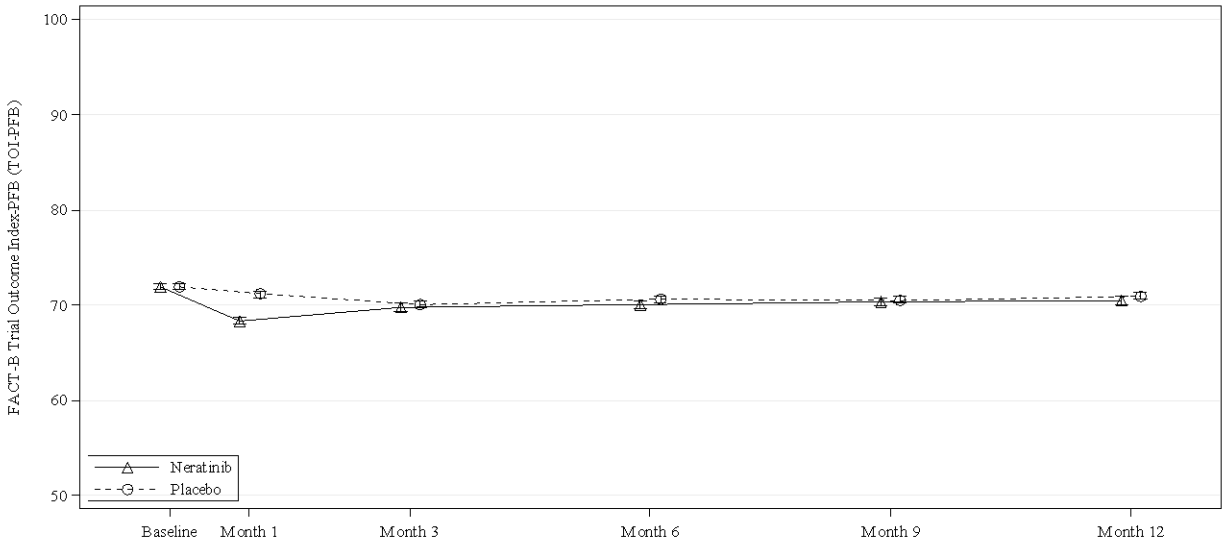
The HRQOL instruments used were the FACT-B and EQ-5D questionnaires. The minimally important difference (MID) is the smallest difference in score in the domain of interest that patients perceive as important, either beneficial or harmful, and which would lead the clinician to consider a change in the patient's management. The MIDs have been reported as 7-8 points for FACT-B, 5-6 points for trial outcome index (TOI), 2-3 points for the Breast Cancer Specific Subscale (BCS) (Eton, 2004); the EQ-5D MIDs have been reported as 0.09 for UK-index scores, 0.06 for US-index scores, and 7-12 for visual analogue scale (VAS) scores (Pickard, 2007).

Within the FACT-B, the Trial Outcome Index (TOI) Physical/Functional/Breast (PFB) and Breast Cancer Specific Subscale (BCS) scores were determined. Results are graphically presented in Figure 24 and Figure 25, respectively.

During the first month of treatment, the mean TOI/PFB score in the neratinib group decreased approximately 3.7 points from baseline, which is less than the MID for TOI (Figure 24). This was likely due to TEAEs associated with neratinib, principally diarrhea. During the same period, the decrease in the placebo group was 1.1 points. By Month 3, TOI/PFB scores were similar between the 2 groups as the scores improved in the neratinib group. Within the limitations of the data as noted above, there appeared to be no long-term adverse effect on quality of life over the 1-year treatment period.

For the FACT-B BCS, neratinib provided a sustained benefit over placebo, but the differences were not clinically meaningful (Figure 25).

Figure 24: Average FACT-B Trial Outcome Index-PFB over Time (Study 3004, All Patients with Assessments)

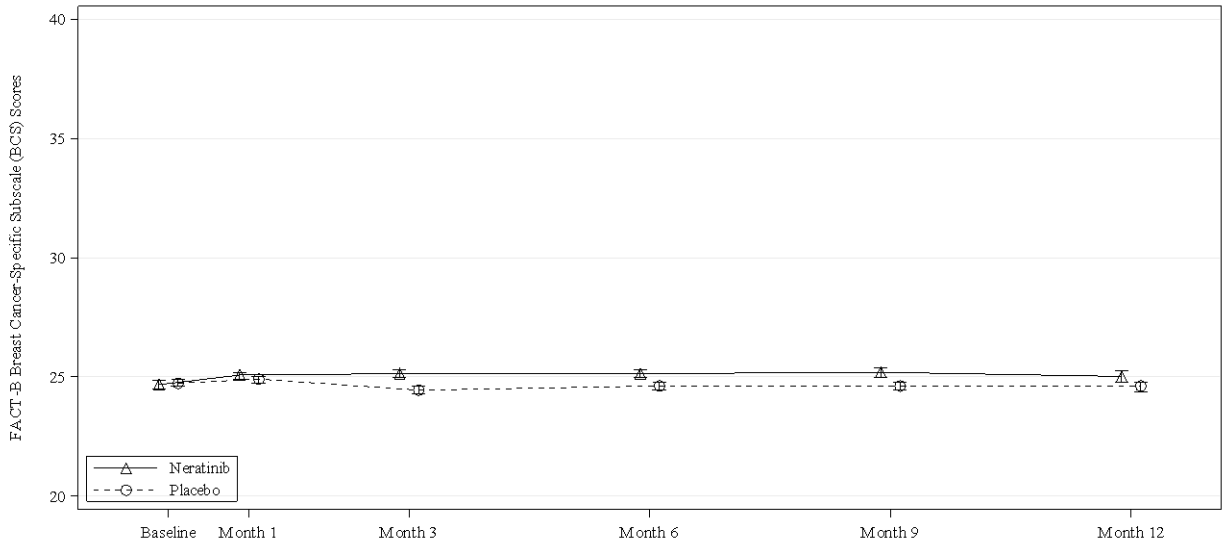


Number of Patients:

Neratinib	1264	1201	987	853	716	611
Placebo	1273	1274	1236	1135	978	853

Abbreviations: PFB: physical well-being, functional well-being, and breast cancer-specific subscales

Figure 25: Average FACT-B Breast Cancer-specific Subscale Scores over Time (Study 3004, All Patients with Assessments)

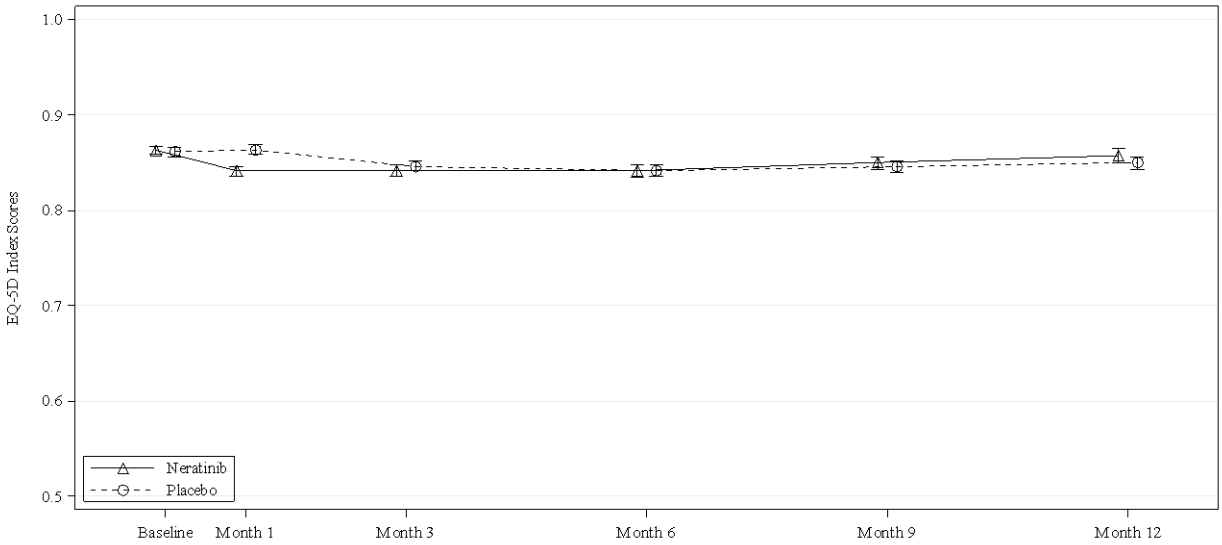


Number of Patients:

Neratinib	1264	1201	987	853	716	611
Placebo	1273	1274	1236	1135	978	853

Within the EQ-5D, the index scores followed a similar pattern (Figure 26), with the largest drop observed during the first month and converging by Month 3. During the first month of treatment, the mean EQ-5D Index Scores in the neratinib group decreased approximately 0.02 points from baseline, which is less than the MID for EQ-5D. These differences were not considered clinically meaningful.

Figure 26: Average EQ-5D Index Scores Over Time (Study 3004, All Patients with Assessments)

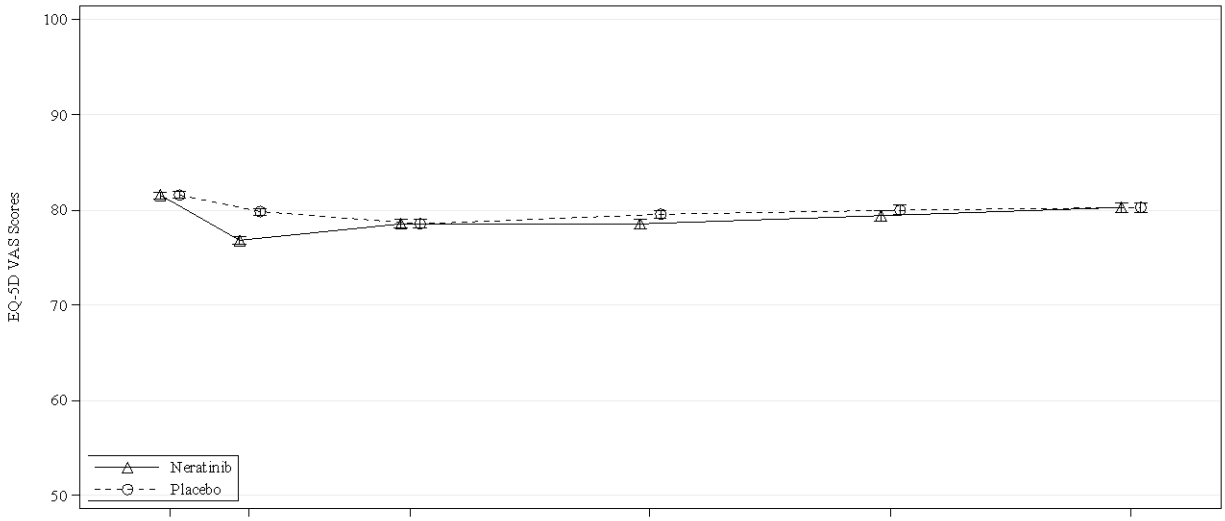


Number of Patients:						
Neratinib	1275	1212	994	856	724	614
Placebo	1277	1285	1243	1140	987	856

Abbreviations: EQ-5D= EuroQol-5D

Mean EQ-5D VAS scores also showed the largest drop at Month 1 and started converging by Month 3 (Figure 27). During the first month of treatment, the mean EQ-5D VAS scores in the neratinib group decreased approximately 5 points from baseline. During the same period, the mean decrease in the placebo group was 2.3 points. The difference between the two groups at Month 1 was 2.7 points. Differences observed between the 2 groups were less than the MID for EQ-5D VAS and were not considered clinically meaningful.

Figure 27: Average EQ-5D VAS Scores over Time (Study 3004, All Patients with Assessments)



Number of Patients:						
Neratinib	1275	1212	994	856	724	614
Placebo	1277	1285	1243	1140	987	856

Abbreviations: EQ-5D= EuroQol-5D; VAS= visual analogue scale

8.4.6. Efficacy Discussion and Conclusions

8.4.6.1. Neratinib Activity in Breast Cancer

There are extensive data demonstrating that neratinib is active in breast cancer across multiple indications: metastatic breast cancer trastuzumab naïve, metastatic breast cancer previously treated with trastuzumab, metastatic breast cancer in combination with chemotherapy (paclitaxel, vinorelbine, capecitabine), and neoadjuvant breast cancer in combination with standard chemotherapy with or without trastuzumab. In addition, when considering these data in the context of available HER2 targeted therapies such as trastuzumab or lapatinib, neratinib monotherapy activity appears to be similar to or in some cases better than existing treatment. Finally, because neratinib is a next generation TKI that targets not only EGFR and HER2 as lapatinib, it also targets HER4, and unlike lapatinib, is an irreversible inhibitor. These data strongly support the observed positive outcome of the 3004 study of neratinib in the extended adjuvant therapy population.

8.4.6.2. Selection of Primary Endpoint iDFS with Data Cut Off at 2 Years

iDFS is an endpoint identified as appropriate for adjuvant breast cancer studies as outlined in report by a breast cancer expert working group (Hudis, 2007). Regulatory authorities in the US and EU provided further feedback resulting in the final definition of iDFS. Older definitions included DCIS and occurrence of another type of cancer in the definition of DFS; these have been removed in the protocol definition of iDFS, though the secondary endpoint of iDFS-DCIS does include DCIS. The data cut off at 2 years was determined as a result of needing to address the historical protocol amendments for the 3004 study and included deliberations with expert statisticians. In Protocol Amendment 13, the primary endpoint of

the trial was changed to an iDFS analysis with a 2 year cut off. The most consistent follow-up data per protocol exist during the first 2 years that a patient was on the study. Between Years 2 and 5 there was not the ability to have regular follow up and required reliance on obtaining medical records for those patients who were reconsented. It was therefore, decided that the iDFS analysis as a time to event analysis with a data truncation at 2 years for each patient was the most valid analysis to conduct as the primary analysis. In addition, since most DFS events are believed to occur within 2 years after completion of adjuvant trastuzumab, this 2 year data cut would capture this information. To provide further assurance in the analysis, an aggressive re-consenting procedure was followed to be able to conduct an analysis with a longer period of follow-up out to 5 years data cut. Ascertainment of nearly 75% was achieved and the analysis was recently updated (01 March 2017). This predefined sensitivity analysis of iDFS with data cut at 5 years demonstrates that the treatment effect of neratinib is durable and provides further support for the robustness of the 2 year iDFS primary endpoint.

8.4.6.3. Magnitude of Clinical Benefit

In considering the magnitude of improvement of iDFS, the context of prior adjuvant and extended adjuvant trials is helpful. The incremental improvement in iDFS observed in the 3004 study is consistent with historical adjuvant trials which demonstrated a meaningful clinical benefit. This is similar to what was observed with a number of adjuvant or extended adjuvant trials that were successful (Table 4).

It is important to look at the absolute iDFS benefit relative to the maximum difference that would be achieved if the goal is to cure 100% of the patients. In the 3004 trial, the placebo group demonstrated a 91.6% iDFS indicating that 8.4% points are available for improvement; in that context, a 2.3% increase in the context of improvement in benefit toward 100% represents a 27% relative iDFS improvement. In addition, neratinib demonstrated benefit in the secondary endpoints with HRs all below 0.75: DFS-DCIS, HR=0.61 (95% CI=0.45, 0.83); DDFS, HR=0.74 (95% CI=0.52, 1.05); and TTDR, HR=0.73 (95% CI=0.51, 1.04).

8.4.6.4. Benefit in Subgroups

Neratinib demonstrated benefit across multiple subgroups, further demonstrating the robustness of the iDFS outcome. Of all the subgroups analyzed only one, HRc status (HRc positive vs negative), had a positive statistical interaction with the iDFS outcome.

Looking specifically at the HRc positive subgroup in 3004, the 4.1% absolute iDFS benefit at 2 years and the 4.4% benefit at 5 years compare very favorably to the other approved drugs for early stage breast cancer. It is important to point out that HRc positive patients continue to take their hormonal therapy concurrently with neratinib and after stopping neratinib. The HRc negative patients stop neratinib at 12 months after which they are on no treatment; their iDFS curves start to move back together between 12 months and 24 months.

One hypothesis is that the dual blockade of the ER and HER2 signaling (i.e., crosstalk) that occurs in patients who are HRc positive and HER2 positive achieve better efficacy. In 3004, dual blockade was created by neratinib irreversibly blocking EGFR and HER2 and by concomitant endocrine therapy (tamoxifen or aromatase inhibitor) blocking the ER.

Support for the dual ER-HER2 crosstalk blockade seen in 3004 can be seen in ER positive, HER2 non-amplified cells that had a HER2 mutation, since treatment with neratinib led to a 5× amplification of the ER, consistent with crosstalk between the ER and the HER2 mutations (Croessmann 2016; Ribas 2017).

Therefore, the benefit of neratinib in the HRc positive subgroup may have resulted from dual ER and HER2 blockade in trastuzumab-treated patients that resulted in enhanced endocrine-responsiveness. Several studies have demonstrated the existence of bidirectional crosstalk between HER2 and the ER pathways (Loi, 2016). Study 3004 results may reflect the existence of crosstalk between HER2 and ER (Osborne 2005, Prat 2008, Shou 2004), and support the clinical hypothesis that in HER2 positive, HRc positive breast cancer, suppression of one pathway may lead to the emergence of the other, and suppression of both pathways may be necessary for optimal clinical outcomes. Combined treatment with neratinib and endocrine therapy may provide additive and durable inhibition, by blocking the HER2 pathway in conjunction with ER signaling.

As part of Amendment 3, a change to the inclusion criteria was that patients must have completed trastuzumab therapy greater than 2 weeks but less than or equal to 1 year prior to randomization. This resulted in 80.1% of patients in the study receiving neratinib within 1 year of completion of trastuzumab making the population more homogeneous. In patients who completed trastuzumab treatment within 1 year prior to randomization (N=2297), neratinib reduced the risk of recurrence or death by 37% relative to placebo (HR 0.63; 95% CI, 0.45, 0.88). It is likely that the use of neratinib will be discussed with patients shortly after diagnosis as part of the treatment options for HER2 positive breast cancer as part of the continuum of care. It would be relevant to begin the administration of neratinib shortly after the completion of trastuzumab based therapy in order to prevent early recurrence.

8.4.6.5. Efficacy Conclusions

Neratinib is the first HER2 targeting agent in the extended adjuvant therapy population to improve clinical outcomes in patients with HER2 positive early breast cancer following 1 year of standard adjuvant trastuzumab treatment. Study 3004 demonstrated that extended adjuvant therapy with neratinib provides a clinically meaningful and statistically significant 34% relative reduction in the risk of invasive disease recurrence over 2 years compared to placebo in the ITT population (HR 0.66; 2-sided p=0.008), and that benefit was durable through 5 years. The benefit of neratinib over placebo was consistently observed in numerous sensitivity and subgroup analyses. Secondary endpoint analyses, which are consistent with and supportive of the primary analysis, confirm the benefit provided by extended adjuvant neratinib therapy in HER2 positive breast cancer.

9. SAFETY OF NERATINIB IN THE EXTENDED ADJUVANT SETTING

The safety and tolerability of neratinib is well characterized based on the safety database of the original NDA submission, which included 31 clinical studies conducted by the sponsor with 3252 individuals exposed to neratinib. Of these, more than 2000 cancer patients were treated with neratinib monotherapy (most received 240 mg/day) and more than 800 cancer patients were treated with neratinib in combination with other agents. Additional patients were subsequently enrolled in Study 6201 since the original NDA submission.

Across studies, it has been consistently demonstrated that diarrhea is the most common and predictable toxicity associated with neratinib treatment. This finding is not unexpected since GI toxicity is a class effect of TKIs that inhibit EGFR (Keefe, 2008). The pivotal 3004 study provided guidance for treatment of diarrhea but did not require primary anti-diarrheal prophylaxis. In an effort to improve the tolerability of neratinib, the Sponsor is studying the effectiveness of loperamide-based anti-diarrheal prophylactic regimens in Study 6201. Other than diarrhea, 1 year of neratinib is not associated with other severe or serious toxicity and there is no evidence for irreversible or cumulative toxicity.

The safety and tolerability of neratinib in the extended adjuvant setting is based on data from the pivotal Study 3004 and the ongoing Phase 2 Study 6201 (using a data cut-off of January 2017). This section focuses on the safety profile of neratinib in these 2 studies. Together, these 2 studies provide neratinib monotherapy (240 mg/qd) safety data in the extended adjuvant setting in approximately 1619 patients.

In the pivotal Study 3004, 2840 patients with HER2 positive early stage breast cancer and who had completed trastuzumab based adjuvant therapy were randomized 1:1 to receive neratinib 240 mg po qd or placebo for 1 year in the extended adjuvant setting. This study provides a comparative assessment of the safety of neratinib monotherapy in the extended adjuvant setting. The patients were permitted to use concomitant supportive care to manage their diarrhea, but they were not administered primary anti-diarrheal prophylaxis. To optimize diarrhea management, a dedicated diarrhea prophylaxis study in the same patient population was undertaken and is referred to as Study 6201.

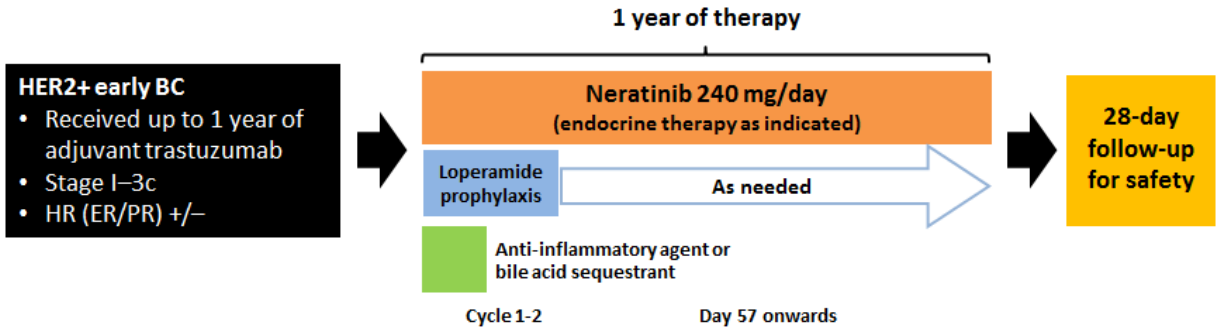
Study 6201, also referred to as the CONTROL Study, is an ongoing phase 2, open-label, single-arm study designed to evaluate the incidence and severity of diarrhea in HER2 positive, early-stage breast cancer patients who had completed trastuzumab based adjuvant therapy and who are receiving neratinib 240 mg po qd with intensive anti-diarrheal prophylaxis in the extended adjuvant setting. Three different prophylaxis regimens are being assessed sequentially. The first cohort was treated with loperamide, the second cohort with loperamide + budesonide, and the third cohort with loperamide + colestipol. Patients self-administer oral neratinib 240 mg once daily for 1 year; neratinib can be dose-reduced to 160 mg or 120 mg, if necessary, to manage neratinib toxicity. Primary prophylactic use of loperamide to minimize the occurrence and severity of diarrhea is mandatory for all patients during the first 2 cycles of neratinib treatment (one cycle is 4 weeks long). Patients self-administer oral loperamide according to a dose reduction schedule during the first 2 neratinib treatment cycles and may continue to receive loperamide as needed during subsequent

treatment cycles. The primary endpoint in Study 6201 is the incidence and severity of diarrhea (Figure 28).

Preclinical models suggest that the MOA of neratinib-associated diarrhea is multi-factorial, including elements of secretory and inflammatory diarrhea. Notably, a reduction in neratinib-associated diarrhea was noted when rats were given budesonide or a bile acid sequestrant. Consequently, other anti-diarrheal agents are being evaluated in combination with loperamide in Study 6201, namely budesonide and colestipol.

As of January 2017, 211 patients have been treated with neratinib in Study 6201. Of these, 137 have received neratinib + loperamide, 64 have received neratinib + budesonide + loperamide, and 10 have received neratinib + colestipol + loperamide. Given the small amount of data available for the neratinib + colestipol + loperamide cohort, this document does not present results for patients who have received this regimen (except for drug-induced liver injury [Table 47]).

Figure 28: CONTROL Study 6201: Study Design



9.1. Extent of Exposure

In Study 3004, neratinib was administered for 1 year; the median duration of treatment was comparable between the neratinib group (11.60 months) and the placebo group (11.83 months; Table 35); however, 26% of patients in the neratinib group received study drug for less than 3 months, primarily due to early discontinuations due to diarrhea. Similarly, the median actual dose intensity was 235.4 mg/day in the neratinib group and 240.0 mg/day in the placebo group; however, 37% of neratinib patients required dose reductions, mostly down 1 dose level to 200 mg/day.

In Study 6201, the median actual dose intensity for neratinib in the neratinib + loperamide group was 237.41 mg/day; in the neratinib + loperamide + budesonide group, the median actual dose intensity for neratinib was 238.82 mg/day. This study is still ongoing so these data may change with additional follow-up (Table 35). The median time on treatment as of January 2017 was 9.07 months in the neratinib + loperamide group and 2.83 months in the neratinib + loperamide + budesonide group.

Table 35: Extent of Exposure (Studies 3004 and 6201)

	Study 3004		Study 6201	
Parameter	**Placebo N=1408**	**Neratinib N=1408**	**Neratinib + Loperamide N=137**	**Neratinib + Loperamide + Budesonide N=64**
Duration of treatment (months)				
Mean (SD)	10.71 (2.85)	8.23 (4.88)	6.87 (5.24)	3.36 (2.08)
Median	11.83	11.60	9.07	2.83
Q1, Q3	11.50, 11.99	2.48, 11.93	0.76, 11.96	1.87, 4.76
Actual dose intensity[a] (mg/day)				
Mean (SD)	235.33 (11.70)	210.35 (43.04)	212.74 (48.38)	222.89 (32.72)
Median	240.0	235.4	237.41	238.82
Q1, Q3	236.65, 240.00	193.82, 240.00	200.00, 240.00	222.14, 240.00
Relative actual dose intensity[b] (%)				
Mean (SD)	98.05 (4.87)	87.64 (17.93)	88.64 (20.16)	92.87 (13.63)
Median	100.0	98.08	98.92	99.51
Q1, Q3	98.60, 100.00	80.76, 100.00	83.33, 100.00	92.56, 100.00

Abbreviation: SD=standard deviation
[a] Actual cumulative dose divided by treatment duration.
[b] Actual dose intensity divided by 240.

9.2. Demographic and Other Baseline Characteristics

Demographic and baseline disease characteristics are summarized for the 3004 safety population and compared with the 6201 population.

Baseline demographic characteristics were well balanced in the two treatment groups in the 3004 study (Table 36). The demographics of patients enrolled in Study 6201 were similar to those enrolled in Study 3004, although most of the patients in Study 6201 were enrolled in North America.

Table 36: Demographics (Studies 3004 and 6201, Safety Population)

	Study 3004		Study 6201	
Parameter	**Placebo N=1408**	**Neratinib N=1408**	**Neratinib + Loperamide N=137**	**Neratinib + Loperamide + Budesonide N=64**
Age (years)				
Mean (SD)	52.27 (10.25)	52.31 (10.08)	53.39 (11.06)	48.77 (11.19)
Median	52.00	52.00	53.00	48.50
Min, max	23.0, 82.0	25.0, 83.0	30.0, 86.0	18.0, 78.0
Age group, n (%)				
<65	1235 (87.7)	1236 (87.8)	116 (84.7)	58 (90.6)
≥65	173 (12.3)	172 (12.2)	21 (15.3)	6 (9.4)
Race, n (%)				
Asian	197 (14.0)	188 (13.4)	8 (5.8)	4 (6.3)
Black or African American	45 (3.2)	25 (1.8)	11 (8.0)	5 (7.8)
White	1125 (79.9)	1156 (82.1)	113 (82.5)	50 (78.1)
American Indian or Alaska Native	---	---	1 (0.7)	0
Other	41 (2.9)	39 (2.8)	3 (2.2)	2 (3.1)
Unknown/Missing	0	0	1 (0.7)	3 (4.7)
Region, n (%)				
North America	474 (33.7)	516 (36.6)	132 (96.4)	52(81.3)
Western Europe, Australia, South Africa	524 (37.2)	479 (34.0)	5 (3.6)	12 (18.8)
Asia Pacific, East Europe, South America	410 (29.1)	413 (29.3)	0 (0)	0 (0)

Abbreviations: SD=standard deviation

In Study 3004, all baseline disease characteristics were well balanced between the 2 groups, and there were no notable differences observed in terms of prior breast cancer therapy (Table 37). Baseline disease characteristics and previous therapies were generally similar in Study 6201. In Study 6201 compared with Study 3004, there were more patients in 6201 whose tumors were HRc positive (75.2% [neratinib + loperamide] and 71.9% [neratinib + loperamide + budesonide] vs 57.5% [Study 3004, neratinib patients]). In addition, in Study 6201 some patients received prior pertuzumab (40.1% [neratinib + loperamide] and 60.9% [neratinib + loperamide + budesonide] vs <1% of neratinib patients in Study 3004).

Table 37: Baseline Disease Characteristics and Prior Therapies (Studies 3004 and 6201, Safety Population)

	Study 3004		Study 6201	
Parameter	Placebo N=1408	Neratinib N=1408	Neratinib + Loperamide N=137	Neratinib + Loperamide + Budesonide N=64
ECOG Performance Status - n (%)				
0	1293 (91.8)	1306 (92.8)	123 (89.8)	57 (89.1)
1	113 (8.0)	98 (7.0)	14 (10.2)	7 (10.9)
2	0	0	0	0
Unknown/Missing	2 (0.1)	4 (0.3)	0	0
Breast tumor stage at diagnosis - n (%)				
I	151 (10.7)	138 (9.8)	39 (28.5)	16 (25.0)
IIA	302 (21.4)	323 (22.9)	48 (35.0)	14 (21.9)
IIB	254 (18.0)	267 (19.0)	27 (19.7)	17 (26.6)
IIIA	259 (18.4)	273 (19.4)	12 (8.8)	9 (14.1)
IIIB	24 (1.7)	27 (1.9)	2 (1.5)	2 (3.1)
IIIC	146 (10.4)	141 (10.0)	6 (4.4)	3 (4.7)
IV	0	0	1 (0.7)	0
Unknown	272 (19.3)	239 (17.0)	2 (1.5)	3 (4.7)
Cell Type at Diagnosis - n (%)				
Ductal	1331 (94.5)	1316 (93.5)	129 (94.2)	62 (96.9)
Lobular	41 (2.9)	58 (4.1)	3 (2.2)	2 (3.1)
Tubular/Cribriform	15 (1.1)	8 (0.6)	1 (0.7)	0
Mucinous	7 (0.5)	6 (0.4)	2 (1.5)	0
Medullary	6 (0.4)	6 (0.4)	0	0
Metaplastic	1 (0.1)	3 (0.2)	1 (0.7)	0
Adenoid cystic	0	1 (0.1)	0	0
Unknown/Missing	7 (0.5)	10 (0.7)	1 (0.7)	0
Time from Diagnosis to Enrollment/Randomization (years)				
n	1408	1407	137	64
Mean (SD)	2.00 (0.668)	1.99 (0.659)	1.60 (0.48)	1.48 (0.43)
Median	1.86	1.82	1.53	1.48
Min, Max	0.65, 8.59	0.64, 6.14	0.2, 4.45	0.3, 2.3

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Table 37: Baseline Disease Characteristics and Prior Therapies (Studies 3004 and 6201, Safety Population) (Continued)

	Study 3004		Study 6201	
Parameter	Placebo N=1408	Neratinib N=1408	Neratinib + Loperamide N=137	Neratinib + Loperamide + Budesonide N=64
Estrogen receptor status - n (%)				
Positive	764 (54.3)	755 (53.6)	100 (73.0)	46 (71.9)
Negative	643 (45.7)	653 (46.4)	37 (27.0)	17 (26.6)
Missing	1 (0.1)	0	0	1 (1.6)
Progesterone receptor status – n (%)				
Positive	603 (42.8)	625 (44.4)	69 (50.4)	36 (56.3)
Negative	789 (56.0)	767 (54.5)	68 (49.6)	27 (42.2)
Missing	16 (1.1)	16 (1.1)	0	1 (1.6)
HRc status - n (%)				
Positive	814 (57.8)	809 (57.5)	103 (75.2)	46 (71.9)
Negative	594 (42.2)	599 (42.5)	34 (24.8)	17 (26.6)
Missing/Unknown	0	0	0	1 (1.6)
Prior radiotherapy - n (%)				
Yes	1142 (81.1)	1120 (79.5)	94 (68.6)	45 (70.3)
No/Missing	266 (18.9)	288 (20.5)	43 (31.4)	19 (29.7)
Prior cancer-related surgery (excluding diagnostic biopsies) - n (%)				
Yes	1407 (99.9)	1407 (99.9)	136 (99.3)	62 (96.9)
No/Missing	1 (0.1)	1 (0.1)	1 (0.7)	2 (3.1)
Prior anti-cancer medication - n (%)				
Yes	1408 (100.0)	1408 (100.0)	137 (100.0)	64 (100.0)
Prior neo-adjuvant or adjuvant therapy - n (%)				
Yes	1408 (100.00)	1408 (100.00)	137 (100.0)	64 (100.0)
Therapy type [a]				
Trastuzumab	1408 (100.00)	1408 (100.00)	136 (99.3)	62 (96.9)
Taxanes	1271 (90.27)	1270 (90.20)	131 (95.6)	62 (96.9)
Anthracycline	1090 (77.41)	1089 (77.34)	36 (26.3)	18 (28.1)
Pertuzumab	1 (0.07)	0	55 (40.1)	39 (60.9)
Trastuzumab emtansine	0	0	0	1 (1.6)

Table 37: Baseline Disease Characteristics and Prior Therapies (Studies 3004 and 6201, Safety Population) (Continued)

Parameter	Study 3004		Study 6201	
	Placebo N=1408	Neratinib N=1408	Neratinib + Loperamide N=137	Neratinib + Loperamide + Budesonide N=64
Duration of prior trastuzumab use (months)				
n	1404	1402	136	62
Mean (SD)	10.91 (2.610)	11.01 (3.092)	11.32 (1.74)	10.32 (2.78)
Median	11.40	11.50	11.53	11.06
Min, Max	1.41, 37.98	0.72, 56.90	2.4, 18.2	1.2, 15.0

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Abbreviations: HRc=hormone receptor; SD=standard deviation

9.3. Treatment-Emergent Adverse Events

In Study 3004, incidences of treatment-related, treatment-emergent adverse events (TEAEs) (96.1% vs 57.2%), TEAEs leading to treatment discontinuation (27.6% vs 5.4%), TEAEs leading to dose reduction (31.3% vs 2.5%), or dose hold (44.7% vs 13.3%), and Grade 3 or 4 TEAEs (49.7% vs 13.1%) were higher in the neratinib group compared with the placebo group (Table 38). The incidence of serious adverse events (SAEs) was 7.3% and 6.0% in the neratinib and placebo groups, respectively; the incidence of TEAEs leading to hospitalization was 6.6% and 5.3%, respectively.

In both cohorts of Study 6201, the incidence of TEAEs was generally comparable to that observed in the neratinib group of 3004 (Table 38). Of note, the incidence of TEAEs leading to treatment discontinuation was higher in the neratinib + loperamide group of Study 6201 (40.1%) compared with the neratinib group of 3004 (27.6%), whereas the incidence was lower in the neratinib + loperamide + budesonide group (14.1%) compared to 3004. Incidences of TEAEs leading to dose reduction or dose hold were lower in both groups of Study 6201 compared with the neratinib group of 3004. In 6201, incidences of TEAEs leading to dose reduction or dose hold were higher in the neratinib + loperamide group than in the neratinib + loperamide + budesonide group.

Table 38: Overview of Treatment-emergent Adverse Events (Studies 3004 and 6201, Safety Population)

	Study 3004		Study 6201	
Category	Placebo N=1408 n (%)	Neratinib N=1408 n (%)	Neratinib + Loperamide N=137 n (%)	Neratinib + Loperamide + Budesonide N=64 n (%)
Any TEAE	1240 (88.1)	1387 (98.5)	137 (100.0)	62 (96.9)
Grade 1	555 (39.4)	193 (13.7)	18 (13.1)	11 (17.2)
Grade 2	501 (35.6)	493 (35.0)	60 (43.8)	28 (43.8)
Grade 3	169 (12.0)	684 (48.6)	58 (42.3)	23 (35.9)
Grade 4	14 (1.0)	15 (1.1)	1 (0.7)	0
Fatal	1 (0.1)	2 (0.1)	0	0
Treatment-related TEAE	805 (57.2)	1353 (96.1)	133 (97.1)	59 (92.2)
SAE	85 (6.0)	103 (7.3)	9 (6.6)	3 (4.7)
TEAE leading to treatment discontinuation	76 (5.4)	388 (27.6)	55 (40.1)	9 (14.1)
TEAE leading to dose reduction	35 (2.5)	440 (31.3)	22 (16.1)	4 (6.3)
TEAE leading to dose hold	187 (13.3)	629 (44.7)	45 (32.8)	14 (21.9)
TEAE leading to hospitalization	75 (5.3)	93 (6.6)	5 (3.6)	2 (3.1)

Abbreviations: SAE=serious adverse event; TEAE=treatment-emergent adverse event

9.3.1. Common Treatment-Emergent Adverse Events

In Study 3004, the most common TEAEs in patients treated with neratinib were diarrhea (95.4% vs 35.4% placebo), nausea (43% vs. 21.5% placebo), fatigue (27.1% vs 20.1% placebo), vomiting (26.2% vs. 8.0% placebo), and abdominal pain (24.1% vs. 10.2% placebo) (Table 39).

In Study 6201, the incidence of GI TEAEs was lower compared with the neratinib group of Study 3004, but the incidence of TEAEs expected to be observed with loperamide use was higher. The incidence of diarrhea was 77.4% with neratinib + loperamide and 75.0% with neratinib + loperamide + budesonide (vs 95.4% in neratinib-treated patients on 3004). The incidence of fatigue was 53.3% with neratinib + loperamide and 40.6% with neratinib + loperamide + budesonide (vs 27.1% in neratinib-treated patients on 3004). Similarly, the incidence of constipation was 55.5% (neratinib + loperamide) and 68.8% (neratinib + loperamide + budesonide) compared with 8.2% for neratinib in Study 3004.

Table 39: Most Common (≥ 10% in any Group) Treatment-Emergent Adverse Events (Studies 3004 and 6201, Safety Population)

	Study 3004		Study 6201	
Preferred Term	**Placebo N=1408 n (%)**	**Neratinib N=1408 n (%)**	**Neratinib + Loperamide N=137 n (%)**	**Neratinib + Loperamide + Budesonide N=64 n (%)**
Diarrhoea	499 (35.4)	1343 (95.4)	106 (77.4)	48 (75.0)
Nausea	303 (21.5)	605 (43.0)	77 (56.2)	30 (46.9)
Fatigue	283 (20.1)	382 (27.1)	73 (53.3)	26 (40.6)
Vomiting	113 (8.0)	369 (26.2)	35 (25.5)	13 (20.3)
Abdominal pain	144 (10.2)	340 (24.1)	36 (26.3)	9 (14.1)
Headache	275 (19.5)	278 (19.7)	26 (19.0)	9 (14.1)
Abdominal pain upper	96 (6.8)	212 (15.1)	5 (3.6)	4 (6.3)
Rash	100 (7.1)	211 (15.0)	5 (3.6)	10 (15.6)
Decreased appetite	40 (2.8)	170 (12.1)	26 (19.0)	9 (14.1)
Muscle spasms	45 (3.2)	159 (11.3)	11 (8.0)	1 (1.6)
Dizziness	128 (9.1)	146 (10.4)	19 (13.9)	5 (7.8)
Abdominal distension	49 (3.5)	73(5.2)	21 (15.3)	3 (4.7)
Constipation	135 (9.6)	115 (8.2)	76 (55.5)	44 (68.8)
Dry mouth	22 (1.6)	47 (3.3)	17 (12.4)	6 (9.4)
Dyspepsia	59 (4.2)	139 (9.9)	11 (8.0)	9 (14.1)

Note: Table includes events that occurred in ≥ 10% of neratinib-treated patients in 3004 or 6201 (either group).

9.3.2. Severity of Treatment-Emergent Adverse Events

With the exception of diarrhea, incidences of Grade 3 and Grade 4 TEAEs were generally low in both 3004 and 6201 (Table 40).

In Study 3004, the incidence of Grade 3 diarrhea was notably higher in the neratinib group (39.8%) than in the placebo group (1.6%).

In Study 6201, the incidence of Grade 3 diarrhea was lower (30.7%, neratinib + loperamide; 20.3%, neratinib + loperamide + budesonide) compared with the neratinib group of Study 3004. The incidence of Grade 3 fatigue was higher in 6201 compared with the neratinib group of 3004.

There was only 1 patient in Study 3004 assessed by the investigator as having Grade 4 diarrhea. The event was 1 day in duration and did not require IV fluid or hospitalization, dose hold, dose reduction, or discontinuation of study treatment.

Table 40: Grade 3 or Grade 4 Treatment-emergent Adverse Events Occurring in ≥ 1.0% of Neratinib-Treated Patients (Studies 3004 and 6201, Safety Population)

	Study 3004		Study 6201	
Preferred Term	Placebo N=1408 n (%)	Neratinib N=1408 n (%)	Neratinib + Loperamide N=137 n (%)	Neratinib + Loperamide + Budesonide N=64 n (%)
Diarrhea				
Grade 3	23 (1.6)	561 (39.8)	42 (30.7)	13 (20.3)
Grade 4	0	1 (0.1)	0	0
Vomiting				
Grade 3	5 (0.4)	47 (3.3)	2 (1.5)	2 (3.1)
Nausea				
Grade 3	2 (0.1)	26 (1.8)	1 (0.7)	0
Fatigue				
Grade 3	6 (0.4)	23 (1.6)	5 (3.6)	4 (6.3)
Abdominal pain				
Grade 3	3 (0.2)	24 (1.7)	2 (1.5)	0
Alanine aminotransferase increased				
Grade 3	3 (0.2)	15 (1.1)	1 (0.7)	2 (3.1)
Grade 4	0	3 (0.2)	0	0
Dehydration				
Grade 3	1 (0.1)	12 (0.9)	2 (1.5)	1 (1.6)
Grade 4	0	1 (0.1)	0	0

Note: Table includes Grade 3 or Grade 4 events that occurred in ≥ 1% of neratinib-treated patients in 3004 or 6201 (either group).

9.3.3. Deaths

In Study 3004, 3 patients (1, placebo; 2, neratinib) had at least one fatal TEAE (Table 38). These events were gastric cancer (placebo), acute myeloid leukaemia (neratinib), and breast cancer metastatic and metastases to meninges (neratinib).

There were no fatal TEAEs in Study 6201 (Table 38).

9.3.4. Serious Adverse Events

In Study 3004, the overall incidence of SAEs was 7.3% in the neratinib group and 6.0% in the placebo group (Table 38). The most common SAEs were diarrhea (1.6% neratinib vs 0.1% placebo), vomiting (0.9% vs 0.1%), and dehydration (0.6% vs 0.1%) (Table 41).

In Study 6201, 6.6% of patients in the neratinib + loperamide group and 4.7% of patients in the neratinib + loperamide + budesonide group developed SAEs (Table 38). In both groups, diarrhea was the most common SAE (1.5%, neratinib + loperamide; 1.6%, neratinib + loperamide + budesonide) (Table 41).

Table 41: Serious Treatment-emergent Adverse Events Occurring in ≥ 3 Neratinib-Treated Patients (Studies 3004 and 6201, Safety Population)

	Study 3004		Study 6201	
Preferred Term	Placebo N=1408 n (%)	Neratinib N=1408 n (%)	Neratinib + Loperamide N=137 n (%)	Neratinib + Loperamide + Budesonide N=64 n (%)
Diarrhea	1 (0.1)	22 (1.6)	2 (1.5)	1 (1.6)
Vomiting	1 (0.1)	12 (0.9)	0	0
Dehydration	1 (0.1)	9 (0.6)	1 (0.7)	0
Cellulitis	4 (0.3)	6 (0.4)	1 (0.7)	0
Erysipelas	0	5 (0.4)	0	0
Alanine aminotransferase increased	0	4 (0.3)	1 (0.7)	0
Aspartate aminotransferase increased	0	4 (0.3)	1 (0.7)	0
Nausea	1 (0.1)	4 (0.3)	1 (0.7)	0
Fatigue	0	3 (0.2)	0	0
Non-cardiac chest pain	0	3 (0.2)	0	0
Pulmonary embolism	3 (0.2)	3 (0.2)	0	0
Renal failure acute	0	3 (0.2)	0	0
Syncope	2 (0.1)	3 (0.2)	0	0

Note: Table includes serious events that occurred in ≥ 3 neratinib-treated patients in 3004 or 6201.

9.3.5. Other Significant Adverse Events

9.3.5.1. Adverse Events Resulting in Treatment Discontinuation

In Study 3004, the proportion of patients who discontinued study treatment due to a TEAE was higher in the neratinib group (27.6%) than in the placebo group (5.4%) (Table 42). The most common event leading to discontinuation was diarrhea (16.8% neratinib vs. 0.2% placebo).

In Study 6201, the proportion of patients who discontinued study treatment due to a TEAE was 40.1% with neratinib + loperamide and 14.1% with neratinib + loperamide + budesonide (Table 42). The most common event leading to discontinuation was diarrhea (20.4%, neratinib + loperamide; 9.4%, neratinib + loperamide + budesonide). Fatigue was more commonly associated with discontinuation in Study 6201 (10.2%, neratinib + loperamide; 4.7%, neratinib + loperamide + budesonide) compared with Study 3004 (1.8%, neratinib-treated patients).

Table 42: Treatment-emergent Adverse Events Leading to Treatment Discontinuation in ≥ 3 Neratinib-Treated Patients (Studies 3004 and 6201, Safety Population)

	Study 3004		Study 6201	
Preferred Term	Placebo N=1408 n (%)	Neratinib N=1408 n (%)	Neratinib + Loperamide N=137 n (%)	Neratinib + Loperamide + Budesonide N=64 n (%)
Any TEAE – n (%)	76 (5.4)	388 (27.6)	55 (40.1)	9 (14.1)
Diarrhea	3 (0.2)	237 (16.8)	28 (20.4)	6 (9.4)
Vomiting	2 (0.1)	54 (3.8)	9 (6.6)	2 (3.1)
Nausea	4 (0.3)	39 (2.8)	12 (8.8)	2 (3.1)
Fatigue	9 (0.6)	25 (1.8)	14 (10.2)	3 (4.7)
Abdominal pain	2 (0.1)	21 (1.5)	2 (1.5)	0
Alanine aminotransferase increased	1 (0.1)	17 (1.2)	1 (0.7)	1 (1.6)
Aspartate aminotransferase increased	1 (0.1)	12 (0.9)	1 (0.7)	0
Ejection fraction decreased	5 (0.4)	13 (0.9)	1 (0.7)	0
Decreased appetite	0	9 (0.6)	5 (3.6)	0
Rash	2 (0.1)	8 (0.6)	2 (1.5)	0
Abdominal pain upper	0	8 (0.6)	0	0
Asthenia	1 (0.1)	5 (0.4)	2 (1.5)	0
Dizziness	2 (0.1)	5 (0.4)	2 (1.5)	0
Weight decreased	0	4 (0.3)	1 (0.7)	0
Dyspepsia	0	4 (0.3)	0	0
Pulmonary embolism	1 (0.1)	3 (0.2)	0	0
Dehydration	0	3 (0.2)	2 (1.5)	0
Headache	2 (0.1)	3 (0.2)	0	0
Renal failure	0	3 (0.2)	1 (0.7)	0
Constipation	0	1 (0.1)	3 (2.2)	0

Note: Table includes events that led to treatment discontinuation in ≥ 3 patients in 3004 or 6201 (either group).

9.3.5.2. Adverse Events Resulting in Dose Reduction or Dose Hold

In Study 3004, the proportion of patients who had a dose reduction due to a TEAE was higher in the neratinib group (31.3% vs. 2.5% placebo), as was the proportion of patients who had a dose hold due to a TEAE (44.7% vs. 13.3% placebo) (Table 43).

In Study 6201, the proportion of patients who had a dose reduction due to a TEAE was 16.1% with neratinib + loperamide and 6.3% with neratinib + loperamide + budesonide; the proportion of patients who had a dose hold due to a TEAE due was 32.8% and 21.9%, respectively. Most events leading to dose reduction or dose hold were GI in nature, with the most common being diarrhea.

Table 43: Overview of Treatment-emergent Adverse Events Leading to Dose Reduction or Dose Hold (Studies 3004 and 6201, Safety Population)

	Study 3004		Study 6201	
Category	Placebo N=1408 n (%)	Neratinib N=1408 n (%)	Neratinib + Loperamide N=137 n (%)	Neratinib + Loperamide + Budesonide N=64 n (%)
TEAE leading to dose reduction	35 (2.5)	440 (31.3)	22 (16.1)	4 (6.3)
TEAE leading to dose hold	187 (13.3)	629 (44.7)	45 (32.8)	14 (21.9)

Abbreviations: TEAE=treatment-emergent adverse event

9.3.5.3. Events of Special Interest

9.3.5.3.1. Diarrhea

Study 3004 did not mandate antidiarrheal prophylaxis, but it was recommended after the development of diarrhea, and most cases of neratinib-associated diarrhea were managed with standard antidiarrheal medications, most commonly loperamide. The clustering of Grade 3 diarrhea at the start of neratinib treatment led to the introduction of a structured loperamide prophylactic regimen administered for the first 1-2 months of therapy in all ongoing Puma initiated clinical trials of neratinib.

The addition of prophylaxis in Study 6201 reduced the occurrence and severity of neratinib-associated diarrhea compared to Study 3004 (Table 45).

In both 3004 and 6201, diarrhea severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Table 44).

Table 44: Diarrhea Grading (NCI CTCAE)

	Definition	
Grade	**Version 3.0 (Study 3004)**	**Version 4.0 (Study 6201)**
Grade 1 (mild)	Increase of <4 stools/day from baseline or mild increase in ostomy output compared to baseline	Increase of <4 stools/day from baseline or mild increase in ostomy output compared to baseline
Grade 2 (moderate)	Increase of 4-6 stools/day over baseline; IV fluids indicated <24 hrs; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living (ADL)	Increase of 4-6 stools/day over baseline or moderate increase in ostomy output compared to baseline
Grade 3 (severe or medically significant)	Increase of ≥7 stools/day over baseline; incontinence; IV fluids ≥ 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
Grade 4 (life-threatening)	Life-threatening consequences (e.g., hemodynamic collapse)	Life-threatening consequences; urgent requiring urgent intervention
Grade 5 (death)	Death	Death

Abbreviations: ADL, activities of daily living; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Diarrhea in 3004

In Study 3004, diarrhea was the most common TEAE associated with neratinib (all grades, 95%). Approximately half of neratinib-treated patients experienced diarrhea of Grade 1 or 2 severity and nearly 40% developed Grade 3 diarrhea. The rate of hospitalization due to neratinib-associated diarrhea was low (1.4%) and there were no diarrhea-related fatalities. Although the observed rate of Grade 3 diarrhea with neratinib was high, neratinib-associated diarrhea has a distinct clinical course after treatment initiation. Diarrhea tended to occur early (median time to onset of 2 days for all-grade events), and most Grade ≥ 3 events occurred within the first month of treatment with a marked drop-off in frequency thereafter. The median cumulative duration of Grade ≥ 2 diarrhea was 10 days; importantly, the median cumulative duration of Grade ≥ 3 diarrhea was 5 days.

Even without the support of primary antidiarrheal prophylaxis in the 3004 study, there are several indicators to suggest that neratinib-associated diarrhea does not follow a complicated course. The overall incidence of weight loss, dehydration, nephrotoxicity, and electrolyte abnormalities with neratinib was low. Dehydration followed a similar time course to Grade 3 diarrhea, with most events observed during the first month of therapy. Nonetheless, some patients found the diarrhea intolerable and approximately 17% of neratinib patients discontinued treatment due to diarrhea, with most discontinuing in the first 2 months.

Overview of Diarrhea in 3004 Versus 6201

As shown in Table 45, the incidence of all grade and Grade 2 and Grade 3 diarrhea was lower in Study 6201 than in 3004. Loperamide prophylaxis in 6201 also limited dose reductions and dose holds/interruptions due to diarrhea compared to 3004. Adding

budesonide to loperamide prophylaxis further decreased the incidence of Grade 3 diarrhea and the number of neratinib dose reductions.

Compared to 3004 (16.8%), the proportion of patients who discontinued study treatment due to diarrhea was lower in the neratinib + loperamide + budesonide group of 6201 (9.4%) but not in the neratinib + loperamide group of 6201 (20.4%).

Table 45: Overall Summary of Diarrhea in Neratinib-Treated Patients (Studies 3004 and 6201, Safety Population)

Category	Study 3004 Neratinib N=1408 %	Study 6201 Neratinib + Loperamide N=137 %	Study 6201 Neratinib + Loperamide + Budesonide N=64 %
Any diarrhea	95.4	77.4	75.0
Grade 1	22.9	24.1	28.1
Grade 2	32.5	22.6	26.6
Grade 3	39.8	30.7	20.3
Grade 4	0.1[a]	0	0
SAE of diarrhea	1.6	1.5	1.6
Diarrhea leading to treatment discontinuation	16.8	20.4	9.4
Diarrhea leading to dose reduction	26.4	7.3	1.6
Diarrhea leading to dose hold/interruption	33.9	13.9	14.1
Diarrhea leading to hospitalization	1.4	1.5	0

Abbreviations: SAE=serious adverse event.
[a] One Grade 4 diarrhea was reported, but the Grade 4 designation was not substantiated by the time course or actions taken as the duration of diarrhea was 1 day, the patient did not require hospitalization or IV fluids and continued on study drug completing the planned course of therapy.

Data from the ongoing Study 6201 show that loperamide prophylaxis reduces the duration of diarrhea per patient compared to no prophylaxis in Study 3004. The median cumulative duration of all-grade diarrhea was reduced from 59 days in Study 3004 to 12 days in Study 6201 for patients who received neratinib + loperamide and to 6 days for patients who received neratinib + loperamide + budesonide (Table 46). Likewise, the median cumulative duration of Grade 2 diarrhea was reduced from 10 days to ≤ 4 days (4 days, neratinib + loperamide; 3 days, neratinib + loperamide + budesonide), and the median cumulative duration of Grade 3 diarrhea was reduced from 5 days to 3 days (regardless of prophylaxis regimen). Adding budesonide to loperamide prophylaxis appears to further diminish the duration of diarrhea. However, Study 6201 is still ongoing and the duration of follow-up is shorter for patients in the budesonide group. Therefore, it is premature to draw firm conclusions regarding duration of diarrhea.

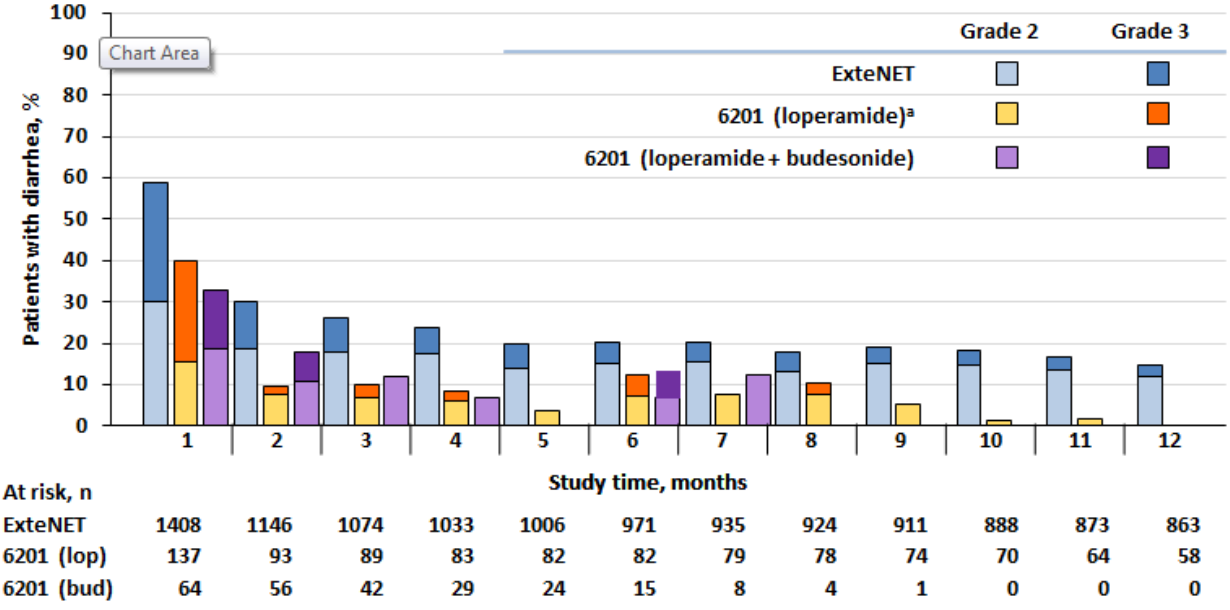
Table 46: Median Duration of Diarrhea per Patient (Studies 3004 and 6201, Safety Population)

	Median (IQR) Cumulative Duration per Patient, Days		
	3004	6201	
Category	Neratinib N=1408	Neratinib + Loperamide N=137	Neratinib + Loperamide + Budesonide N=64
Any grade	59 (14, 164)	12.0 (4.0, 54.0)	6.0 (3.0, 24.5)
Grade ≥2	10 (5, 27)	4.0 (2.0, 11.0)	3.0 (2.0, 6.0)
Grade ≥3[a]	5 (2, 9)	3.0 (2.0, 6.0)	3.0 (2.0, 5.0)

Abbreviation: IQR=interquartile range
[a] No Grade 4 events in the 6201 study; one Grade 4 diarrhea was reported in 3004, but the Grade 4 designation was not substantiated by the time course or actions taken

The available data from Study 6201 suggest that most Grade 2 or 3 diarrhea events were more common during the first few months of treatment (Figure 29). This is in contrast to Study 3004, where a significant proportion of patients continued to have Grade 2 or 3 diarrhea at later time points. In the loperamide cohort, a high proportion of patients with Grade 2 or 3 diarrhea in Month 1 discontinued neratinib prematurely. However, adding budesonide to loperamide prophylaxis appeared to decrease discontinuations in the first months. For patients who were able to tolerate neratinib beyond the first month, the incidence of Grade 2 or 3 diarrhea diminishes substantially for the remainder of the 1-year treatment period, suggesting some adaptation to the effects of neratinib.

Figure 29: Time Course of the Incidence and Severity of Diarrhea: Grades 2 and 3 (Studies 3004 and 6201; Safety Population)



In summary, diarrhea associated with neratinib has a distinct and predictable clinical course. Grade 3 events are generally short-lived and occur within the first month of treatment, permitting targeted preventive management with antidiarrheal prophylaxis early in the course of treatment. Loperamide prophylaxis starting at the first dose of neratinib with or without budesonide reduced the incidence and duration of severe diarrhea and reduced dose holds and dose reductions compared with administration of neratinib without anti-diarrhea prophylaxis (Study 3004); the addition of budesonide to loperamide appears to further improve tolerability by decreasing the incidence of severe diarrhea and, importantly, decreasing premature discontinuation of neratinib. The colestipol cohort only recently began enrollment and further follow-up will determine whether it leads to a reduction in severe diarrhea and additional improvement in tolerability. Based on these findings, Puma is recommending anti-diarrheal prophylaxis in the first month of neratinib treatment.

9.3.5.3.2. Hepatotoxicity

Transient serum transaminase elevations may occur after neratinib initiation, but are usually mild-to-moderate in severity and asymptomatic. These increases tend to either resolve spontaneously or after dose modification or discontinuation.

In Study 3004, a TEAE of hepatotoxicity was reported in 12.4% vs 6.6% of patients in the neratinib and placebo groups, respectively, using a broad search term strategy. Grade 3 hepatotoxicity TEAEs occurred in 1.6% of neratinib-treated patients and in 0.5% of placebo-treated patients; Grade 4 hepatotoxicity events occurred in 0.2% and 0.1% of patients, respectively. Hepatotoxicity SAEs occurred in 0.3% and 0.1% of patients, respectively.

In Study 6201, a TEAE of hepatotoxicity was reported in 9.0% (19/211) of patients using a broad search term strategy. Four (1.9%) patients had a Grade 3 event, and none had a Grade 4 event. SAEs included alanine aminotransferase increased and aspartate aminotransferase increased (1 patient each).

In Study 3004, examination of laboratory data showed that serum transaminase elevations of >3 × upper limit of normal (ULN) and >5 × ULN occurred more frequently in neratinib-treated patients than in placebo-treated patients (Table 47). Elevations >10 × ULN and >20 × ULN were < 1%. In Study 6201, 3 (1.4%) patients had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5× ULN and none had elevations >10× ULN.

Table 47: Incidence of Potential Drug-induced Liver Injury (Studies 3004 and 6201, Safety Population)

Category	Study 3004		Study 6201
	Placebo N=1408 n (%)	Neratinib N=1408 n (%)	Neratinib + Anti-Diarrhea Prophylaxis N=211[a] n (%)
AST or ALT			
>3 × ULN	20 (1.4)	74 (5.3)	11 (5.2)
>5 × ULN	9 (0.6)	24 (1.7)	3 (1.4)
>10 × ULN	2 (0.1)	10 (0.7)	0
>20 × ULN	1 (0.1)	3 (0.2)	0
Total Bilirubin			
>2 × ULN	10 (0.7)	7 (0.5)	0
ALP			
>1.5 × ULN	162 (11.5)	145 (10.3)	5 (2.4)
Elevation of AT and Total Bilirubin			
AT >3 × ULN and bilirubin ≥2 × ULN flag (same day)	1 (0.1)	1 (0.1)	0
AT >3 × ULN and bilirubin >1.5 × ULN flag (same day)	2 (0.1)	4 (0.3)	1 (0.5)
AT >3 × ULN and bilirubin ≥2 × ULN flag (on treatment)	1 (0.1)	3 (0.2)	0
AT >3 × ULN and bilirubin >1.5 × ULN flag (on treatment)	2 (0.1)	5 (0.4)	1 (0.5)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AT= aminotransferase; ULN=upper limit of normal
[a] Includes 10 patients who received neratinib + colestipol + loperamide.

Potential instances of drug-induced liver injury (DILI) were sought in the Program-Wide data set of 2895 patients (healthy volunteers excluded) using FDA guidelines. Six patients had concurrent elevations of ALT and/or AST > 3× ULN and bilirubin ≥ 2 × ULN and ALP < 2 × ULN on the same day of measurement (i.e., met Hy's law laboratory criteria).

An external consultant on Drug Induced Liver Injury/Hepatotoxicity independently reviewed the hepatic AEs and laboratory data, including the profiles for the 6 identified patients, and assessed that alternative etiologies were likely and none of the cases should be viewed as Hy's Law cases in terms of liver safety implications.

Protocol requirements for regular laboratory assessment of hepatic enzymes and dose modification guidelines were effective in early identification and management of hepatic events. To the time of the NDA submission, in the 2895 patients treated with neratinib, there have been no events of drug-induced hepatic failure. Based on this experience, periodic monitoring of LFTs and dose modification is included in the proposed USPI.

9.3.5.3.3. Cardiac Toxicity

There is no evidence to suggest that neratinib is associated with cardiac toxicity. The frequency and severity of cardiac toxicity was low despite previous exposure to other cardiotoxic chemotherapy regimens. However, the eligibility criteria required normal (or ≥ 50%) LVEF and excluded patients with a history of QTc prolongation or torsade de pointes, prolonged QTc at screening, or evidence of active ischemic, cardiac conduction, or cardiomyopathic disease.

In Study 3004, a TEAE of cardiac toxicity was reported in 10.5% and 12.9% of patients in the neratinib and placebo groups, respectively, using a broad search term strategy. Grade 3 TEAEs occurred in 1.4% of neratinib-treated patients and in 0.5% of placebo-treated patients; Grade 4 events occurred in 0.1% and 0% of patients, respectively. Serious cardiac toxicity occurred in 0.4% of patients in each group. In Study 6201, 4.3% of patients had a TEAE of cardiac toxicity. Three (1.4%) patients had a Grade 3 event, and none had a Grade 4 event. None of the patients had a serious event of cardiac.

In Study 3004, cardiac arrhythmia occurred in 3.8% and 4.1% of patients in the neratinib and placebo groups, respectively. Cardiac failure occurred in 6.7% and 8.5% of patients, respectively, and ischemic heart disease occurred in 0.6% and 1.0% of patients. The incidence of TEAEs identified using a broad search for Torsade de pointes/QT prolongation was 4.7% in the neratinib group and 7.3% in the placebo group. No patient had Torsades de pointes reported as the preferred term. In 6201, 4 (1.9%) patients had TEAEs potentially associated with Torsade de pointes/QT prolongation; none had Torsades de pointes reported as the preferred term.

Changes from baseline in LVEF were generally small and not clinically relevant. Three patients (Study 3004) who had baseline LVEF ≥ 50% shifted to postbaseline LVEF < 40%; each had received prior potentially cardiotoxic agents (doxorubicin, cyclophosphamide, paclitaxel, epirubicin) and 1 had comorbid medical conditions (asthma, hypertension, diabetes mellitus) that may have contributed to the decreases in LVEF. All continued on neratinib; 2 patients had repeat assessments that showed normalization of LVEF.

9.3.5.3.4. Other Adverse Events of Special Interest

There is no evidence that neratinib treatment is associated with interstitial lung disease, lung infiltration, pneumonitis, or pulmonary fibrosis. In addition, there is no evidence of an increased frequency of TEAEs indicating hematologic toxicity (i.e., anemia, leukopenia, neutropenia, thrombocytopenia), nephrotoxicity, dermatologic toxicity, or a second primary cancer.

9.4. Overall Safety Conclusions

Neratinib has a well-characterized and manageable AE profile that is consistent across studies involving 3252 patients with cancer who have received neratinib (monotherapy or in combination). Diarrhea, the most common TEAE observed with neratinib, is a class effect of EGFR TKIs and some HER2-directed therapies (Keefe, 2008).

Diarrhea (all grade) associated with neratinib is generally characterized as early in onset, and brief in duration. Compared to Study 3004 (neratinib group), results from Study 6201 show that loperamide antidiarrheal prophylaxis decreased the overall incidence of all-grade diarrhea and reduced the incidence of Grade 2 and Grade 3 diarrhea. Furthermore, loperamide prophylaxis decreased the rate of dose reduction and temporary dose holds due to all grade diarrhea. Adding budesonide to loperamide prophylaxis may further diminish the duration and number of episodes of diarrhea, as well as decrease the number of neratinib dose holds, dose reductions and discontinuations. The proposed label for neratinib will recommend that anti-diarrheal prophylaxis, such as loperamide, be used during the first 1-2 months of neratinib treatment.

Severe diarrhea usually occurs at the end of the first week of treatment and is of limited duration, reversible, and uncomplicated in nature. Hospitalization due to diarrhea is infrequent, and no diarrhea-associated deaths have been reported. Severe diarrhea is generally manageable with anti-diarrheal medication, dose hold, and/or dose reduction. Adding budesonide to loperamide prophylaxis appears to reduce the incidence of discontinuation due to severe diarrhea.

Overall, except for diarrhea, neratinib is associated with a low incidence of severe AEs. Severe dehydration, renal insufficiency, and electrolyte abnormalities are uncommon and reversible with dose hold, dose reduction, and/or dose discontinuation. Neratinib is associated with transient transaminase elevations, which are mainly mild or moderate in severity, and reversible. Higher grade elevations in transaminases are infrequent, asymptomatic, and resolve without sequelae, either without intervention or with dose modification or discontinuation. Elevation in hepatic enzymes in neratinib-treated patients can be managed with LFT monitoring. In contrast to other EGFR- and HER2-targeted agents, there is no evidence of cardiac toxicity with neratinib therapy.

Overall, the safety profile of neratinib as extended adjuvant treatment of early stage breast cancer is acceptable. By controlling early diarrheal events, effective diarrhea prophylaxis may help to improve long-term adherence and ensure that the efficacy benefits of neratinib are realized.

10. BENEFIT-RISK SUMMARY

Neratinib is an orally administered irreversible TKI that targets EGFR, HER2 and HER4 via the intracellular domain and improves iDFS as extended adjuvant therapy in patients with early stage HER2 positive breast cancer, thereby making it an important new therapeutic tool in the treatment of early breast cancer. For patients with breast cancer whose tumors are positive for HER2 and who have completed the standard of care anti-HER2 adjuvant therapy, 1 year of neratinib provides an important new option for extended adjuvant HER targeted therapy where no other option exists. The ExteNET Study or Study 3004 was designed as a Phase 3 randomized, double blind, placebo controlled trial to determine the benefit of extended adjuvant neratinib therapy in breast cancer patients whose tumors were HER2 positive and who had completed adjuvant therapy containing trastuzumab. The prespecified primary endpoint was invasive DFS (iDFS), assessed as a time to event endpoint and using the ITT population. Data were cut at 2 years, supplemented with a sensitivity analysis using a data cut at 5 years. The overall benefit provided is best represented by the iDFS HR = 0.66 (95% CI 0.49, 0.90; p=0.008, 2 sided) at the 2 year data cut. The 5 year analysis provided further evidence of durability of the benefit with an HR=0.73 (95% CI 0.57, 0.92; p=0.008) (Table 48). As noted previously, a reconsenting process was instituted to maximize the number of patients and follow-up data included in the 5 year analysis. The baseline characteristics between the ITT population (N=2840) and the reconsented population (N=2117; neratinib, 1028; placebo, 1089) provides added confidence in the 5 year data cut. The favorable HRs observed across all secondary endpoints that were upheld at the 5 year data cut provide further confidence in the observed outcomes and are supportive of the primary iDFS endpoint. Additional sensitivity and exploratory analysis provide further support for the efficacy of neratinib.

Table 48: Results of Primary and Secondary Endpoints with 2 Year and 5 Year Data Cut (Study 3004)

Endpoints	Primary Analysis 2 Year Data Cut (N=2840) Hazard Ratio (p value) (95%CI)	Sensitivity Analysis 5 Year Data Cut (N=2840) Hazard Ratio (p value) (95%CI)
iDFS (primary)	**0.66 (p=0.008)** (0.49, 0.90)	**0.73 (p=0.008)** (0.57, 0.92)
DFS-DCIS	**0.61** (0.45, 0.83)	**0.71** (0.56, 0.89)
DDFS	**0.74** (0.52, 1.05)	**0.78** (0.60, 1.01)
TTDR	**0.73** (0.51, 1.04)	**0.79** (0.60, 1.03)

Abbreviations: CI=confidence interval; DDFS=distant disease free survival; DFS-DCIS=disease-free survival including ductal carcinoma *in situ*; iDFS=invasive disease free survival; TTDR=time to distant recurrence

There was one subgroup where the statistical test for interaction was positive: HRc status. Patients whose cancers are HER2 positive and HRc positive would have the option to add neratinib to their existing anti-hormonal therapy with the expectation that they would derive clinically meaningful iDFS benefit from 1 year of extended adjuvant neratinib therapy: iDFS 2 year data cut (HR=0.49, 95% CI 0.31, 0.75) and iDFS 5 year data cut (HR=0.60, 95% CI 0.43, 0.83) (Table 49). Patients who are HER2 positive and HRc negative have no other option after completing standard adjuvant therapy; neratinib would offer a new option rather than entering into a period of no therapy or 'watch and wait'. The Kaplan Meier curves suggest that the benefit in this subgroup appears primarily during the time that neratinib is administered (Figure 17) and some patients and physicians would find this of value. The value beyond the first year of neratinib is unclear: iDFS 2 year data cut (HR=0.93, 95% CI 0.60, 1.43) and iDFS 5 year data cut (HR=0.95, 95% CI 0.66, 1.35). HRc positive breast cancer has a longer term risk of recurrence so extended adjuvant treatment is well justified.

The subgroup of patients who had completed trastuzumab adjuvant therapy ≤ 1 year prior to enrolling into Study 3004 also seemed to gain more benefit than patients who had completed trastuzumab >1 year prior to enrollment, though the statistical test for interaction was not significant (Table 49).

The ITT population remains the primary analysis, with the intent to provide physicians and patients the data on the subgroups for the purpose of making fully informed individual patient therapy decisions.

Table 49: Subgroup Analyses of iDFS by HRc Status (Positive/Negative) and Time from Completion of Adjuvant Trastuzumab (≤ 1 year / > 1 year), Study 3004

Endpoint (Subgroup)	Primary Analysis 2 Year Data Cut (N=2840) Hazard Ratio (95%CI)	Sensitivity Analysis 5 Year Data Cut (N=2840) Hazard Ratio (95%CI)
HRc Status		
iDFS (N=1631) (HRc positive)	0.49 (0.31, 0.75)	0.60 (0.43, 0.83)
iDFS (N=1209) (HRc negative)	0.93 (0.60, 1.43)	0.95 (0.66, 1.35)
Test for interaction	p=0.045	p=0.063
Time from Completion Adjuvant Trastuzumab		
iDFS (N=2297) ≤1 year from completion trastuzumab	0.63 (0.45, 0.88)	0.70 (0.54, 0.90)
iDFS (N=543) > 1 year from completion trastuzumab	0.92 (0.37, 2.23)	1.00 (0.51, 1.94)
Test for interaction	p=0.529	p=0.406

Abbreviations: CI=confidence interval; HRc=hormone receptor; iDFS=invasive disease free survival

These efficacy benefits need to be weighed against the neratinib safety profile. The large number of patients treated in the neratinib program, including randomized data from Study 3004, provides robust monotherapy experience from which considerable understanding of the risks can be ascertained. Diarrhea is the primary AE observed and the most common AE leading to discontinuation of neratinib. Diarrhea is an expected on-target effect since neratinib targets EGFR and the GI tract has high numbers of EGFRs. Diarrhea with neratinib most commonly occurs during the first month of treatment and then tapers off after that point, even with continued dosing. Dose reductions are permitted and prophylaxis with loperamide reduces the incidence of ≥ Grade 3 diarrhea. Dose reduction did not impact efficacy outcome for iDFS. During the first month of neratinib therapy, prophylaxis with loperamide and budesonide further reduces the incidence of ≥ Grade 3 diarrhea and reduces the number of patients who discontinue neratinib. With careful management, including prophylaxis with loperamide and budesonide at the initiation of neratinib therapy, most patients would be able to stay on neratinib therapy long term. Notably, neratinib does not increase the risk of cardiotoxicity in the patient population studied and does not increase the toxicities of anti-hormonal therapy such as reduction in bone density, bone fractures, changes in lipid profile, secondary malignancies (e.g., endometrial cancer), arthralgias and hot flashes.

An analysis of efficacy outcome for patients who had dose reductions demonstrated that efficacy among those with dose reductions is the same as those without dose reductions and both were significantly improved compared with placebo. This gives confidence that a diarrhea management strategy that includes dose reductions does not compromise efficacy outcomes. This approach is used with other anti-EGFR TKI such as afatinib.

When considering the overall safety profile of neratinib within the context of other breast cancer adjuvant therapies, the adverse reactions observed with neratinib are manageable and reversible. In contrast, cytotoxic chemotherapy is associated with myelosuppression placing patients at risk for infections including sepsis, febrile neutropenia, anemia and bleeding, alopecia, and GI events (nausea, vomiting, diarrhea), cardiotoxicity and leukemia with anthracyclines, and neuropathy and hepatotoxicity with the taxanes. Trastuzumab can cause significant cardiotoxicity with sometimes permanent reduction in cardiac ejection fraction, while hormonal agents have side effects that can be dose limiting, such as hot flashes, arthralgias and insomnia and result in serious sequelae of bone fractures or endometrial cancer. The toxicities associated with neratinib do not cause major organ damage or long-lasting morbidities. Diarrhea due to neratinib will be challenging for some patients and may lead to discontinuation in some patients, however, it is reversible and with supportive care including prophylaxis, patients who can manage the diarrhea in the initial 1-2 months will experience much less diarrhea during the remaining months of therapy.

The context in which to consider both the efficacy and safety of neratinib is represented below in considering key adjuvant breast cancer trials and one extended adjuvant trial spanning the last 20 years (Table 50). Critical points from this experience are as follows:

- Neratinib, as an irreversible TKI inhibitor of, HER2, EGFR and HER4, provides an extended adjuvant breast cancer treatment option with a non-overlapping MOA for patients previously treated with trastuzumab and chemotherapy and reduces the risk of generally fatal breast cancer recurrences.

- The relative (HRs) and absolute (percentage points) improvements in DFS in the adjuvant breast cancer setting have been incremental and cumulative.
- Neratinib Study 3004 results for iDFS are consistent with what has been determined to be clinically meaningful in past studies.
- The side effect profile of other adjuvant therapies that are considered part of standard of care exist on a spectrum. Nonetheless, incremental DFS benefits have been determined to outweigh the risks.
- Neratinib, even with the need to manage diarrhea which is reversible but can be treatment limiting in some patients, has an overall side effect profile that falls within the spectrum of standard breast cancer therapies and has the advantage of not causing serious organ damage or other life threatening toxicities.
- Neratinib would be the only HER2 targeted therapy administered orally in the adjuvant setting.
- Neratinib's demonstrated efficacy in the extended adjuvant setting is supported by a large body of evidence of activity in the neoadjuvant setting and metastatic settings.

The data in Table 50 are the result of a sponsor analysis of publically available data. The sponsor conducted an analysis of adjuvant and extended adjuvant therapies approved for early breast cancer patients and compiled it along with the top line neratinib results in order to better understand the neratinib results in the context of available therapies. Specifically, the focus of this exploratory assessment was to understand efficacy at Year 2 and Year 5.

The methods for this assessment were as follows. US product labels (USPI or full prescribing information) were used as the primary source of data; this was supplemented, in some cases, with data from publications. HRs, CIs, and p-values were taken directly from the product label for each therapeutic agent. Because the labels do not include the absolute difference at landmark time points, the sponsor used a computer software program to digitize the Kaplan-Meier (KM) DFS curve images that were in the label. With these digitized images of the KM curves, the iDFS rate at specific time points was "read" based on the digital coordinates; in this way, estimates of iDFS rates at Year 2 and Year 5 were made. In cases where the KM curves did not extend out to 5 years, this was noted in the table as not reported (NR). In cases where the KM curves were not included in the label (i.e., letrozole MA-17 and BIG 1-98 studies; trastuzumab HERA study), the primary manuscripts containing the definitive DFS analyses were obtained, and the relevant 2 year or 5 year absolute differences in DFS were applied as reported in the manuscripts (Goss 2003, Piccart-Gebhart 2005, The Breast International Group (BIG) 1-98 Collaborative Group 2005).

Standard precautions in regard to cross study comparisons apply. Complexities of this analysis are that definitions of DFS may have varied between trials and may have varied between the product label and the published manuscript for a given study. Additional aspects of the analyses may differ between product labels and published manuscripts, because the FDA may have required different methodology, for example in terms of censoring. It should be noted that in the Section 2 of this briefing book (Unmet Medical Need), the background information on these adjuvant and extended adjuvant therapies is more extensive and more

detailed and relies primarily on published manuscript data; therefore, some of the values reported in Table 50 may differ slightly from data described in Section 2.

The outcome of this analysis is that the absolute percentage point improvement in 2 year DFS estimates fall in the range of 1.7 to 8.4 percentage points. The neratinib results are within this range.

In conclusion, the totality of evidence demonstrating the magnitude of activity of neratinib to treat HER2 positive breast cancer across multiple clinical settings, plus the strong neoadjuvant data, provides robust scientific and clinical rationale for proceeding into the adjuvant setting with neratinib. An unmet medical need exists during the "extended adjuvant period" or the time after standard of care adjuvant therapy with other anti-HER2 therapy has been completed. Patients who have completed their 1 year of trastuzumab adjuvant therapy have no options for further anti-HER2 treatment and enter into a "watch and wait" period. In the interest of being able to turn this time into a period of active anti-HER2 therapy with the intent to provide further improvement in iDFS, neratinib was studied as extended adjuvant therapy in a multicenter randomized, double blind placebo controlled Phase 3 Study 3004 (N=2840) which demonstrated clinically meaningful and statistically significant improvement in iDFS with a manageable safety profile consistent with other approved agents within the class of TKIs targeting EGFR and HER2. The sponsor believes the totality of the data support approval of neratinib 240 mg po qd for 1 year in the extended adjuvant setting in order to provide physicians and patients with a new strategic therapeutic option to reduce the rate of recurrence of HER2 positive breast cancer

Table 50: Neratinib Extended Adjuvant Breast Cancer Results in the Context of FDA Approved Adjuvant Breast Cancer Therapies: Results and Estimates of Absolute Improvement in 2 Year and 5 Year DFS Rates from Kaplan-Meier Curves

Drug	Trial	Indication (Endpoint)	Population	Hazard Ratio (95% CI)	P-value	Median Follow-up (months)	Absolute DFS Improvement 2-year	Absolute DFS Improvement 5-year
Paclitaxel	CALGB/ECOG/ NCCTG/SWOG	Adjuvant (DFS)	ITT	0.78 (0.67, 0.91)	0.0022	30.1	4.4%	NR
Docetaxel	BCIRG 001/TAX316	Adjuvant (DFS)	ITT	0.74 (0.60, 0.92)	0.0047	55	5.4%	5.8%
Anastrazole	ATAC	Adjuvant (DFS)	ITT	0.87 (0.78, 0.97)	0.0127	68	1.6%	2.7%
Letrozole	BIG 1-98	Adjuvant (DFS)	ITT	0.79 (0.68, 0.92)	0.002	26	1.7%	2.6%
	MA17	Ext Adjuvant (DFS)	ITT	0.62 (0.49, 0.78)	0.00003	28	1.9%	NR
Exemestane	IES 031	Adjuvant (DFS)	ITT	0.69 (0.58, 0.82)	0.00003	34.5	3.1%	NR
Trastuzumab	NCCTG N9831/NSABP B-31	Adjuvant (DFS)	ITT	0.48 (0.39, 0.59)	<0.0001	24	7.2%	NR
	HERA[a]	Adjuvant (DFS)[b]	ITT	0.54 (0.44, 0.67)	<0.0001	12.6	8.4%	NR
	BCIRG 006 ACTH	Adjuvant (DFS)	ITT	0.60 (0.48, 0.76)	<0.0001	NR	5.8%	NR
	BCIRG 006 TCH	Adjuvant (DSF)		0.67 (0.54, 0.84)	0.0006	NR	4.5%	NR

Table 50: Neratinib Extended Adjuvant Breast Cancer Results in the Context of FDA Approved Adjuvant Breast Cancer Therapies: Results and Estimates of Absolute Improvement in 2 Year and 5 Year DFS Rates from Kaplan-Meier Curves (Continued)

Drug	Trial	Indication (Endpoint)	Population	Hazard Ratio (95% CI)	P-value	Median Follow-up (months)	Absolute DFS Improvement 2-year	Absolute DFS Improvement 5-year
Neratinib	ExteNET (Study 3004)	**Ext Adjuvant[f] (2 year iDFS)**	**ITT**	**0.66[c] (0.49, 0.90)**	**0.008**	**24**	**2.3%**	**NR**
		Ext Adjuvant (2 year iDFS)	HRc+	0.49[d] (0.31, 0.75)	0.001	24	4.1%	NR
		Ext Adjuvant (2 year iDFS)	(≤1 year after trastuzumab)	0.63 (0.45, 0.88)	0.006	24	2.9%	NR
		Ext Adjuvant (5 year iDFS sensitivity analysis)	ITT	0.73[e] (0.57, 0.92)	0.008	60	2.6%	2.5%
		Ext Adjuvant (5 year iDFS sensitivity analysis)	HRc+	0.60[e] (0.43, 0.83)	0.002	60	3.7%	4.4%
		Ext Adjuvant (5 year iDFS sensitivity analysis)	(≤1 year after trastuzumab)	0.70 (0.54, 0.90)	0.006	60	3.0%	3.2%

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Abbreviations: CI=confidence interval; DFS=disease-free survival; Ext=extended; HRc=hormone receptor; iDFS=invasive disease free survival; ITT=intent to treat; NR=not reported; US=United States

[a] For the HERA trial, only the data for 1 year of adjuvant trastuzumab are provided in this table. Two years of trastuzumab was no better than 1 year of trastuzumab; therefore, approval was based on 1 year.

[b] The DFS endpoint in the HERA trial included ductal carcinoma *in situ* (DCIS), but the trastuzumab package insert definition did not include DCIS.

[c] Primary analysis of Study 3004 (ExteNET)

[d] Subgroup analysis of Study 3004

[e] Sensitivity analysis of Study 3004

[f] Neratinib extended adjuvant therapy was initiated ≤1 year from completion of adjuvant trastuzumab in most patients (2297/2840, 80.9%).

Source: US package insert for each approved product listed; neratinib clinical development program.

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12. APPENDICES

APPENDIX A. TABLE OF NERATINIB CLINICAL TRIALS

Table 51 provides high level information for all corporately sponsored neratinib clinical studies for which the primary data were included in the NDA submission to the FDA. Not included in this list are the neoadjuvant trials sponsored by cooperative groups (I-SPY2 and NSABP FB-7).

Table 51: Neratinib Clinical Trials Included in NDA Submission

Study Number	Phase	Study Population/Indication	Type	Number of Subjects Enrolled (in neratinib arm)	Number of Subjects Treated (with neratinib)
			Healthy Subjects		
3144A1-105-US/ B1891031	1	Healthy Subjects	QTc, PK, safety Doses tested: Part A: 240 mg po x 1 plus moxifloxacin or placebo Part B: 240 mg p x 1 or placebo plus ketoconazole	60(60)	60(56)
3144A1 106 US/ B1891025	1	Healthy Subjects	DDI ketoconazole, PK, safety Doses tested: 240 mg po x 1 with and without ketoconazole	24(24)	24(23)
3144A1 107 US/ B1891032	1	Healthy Subjects	PK,PD, safety Doses tested: 120-800mg po x 1following fast; 400 and 640 mg cohorts following meal	56(56)	56(42)
3144A1 1108 US/ B1891033	1	Healthy Subjects	PK Doses tested: 200 mg po x 1	6(6)	6(6)
3144A1 1109 US/ B1891034	1	Healthy Subjects	BA, PK Doses tested: 240 mg po x 1	36(36)	36(36)
3144A1 1110 US/ B1891008	1	Healthy Subjects	DDI rifampin, PK, safety Doses tested: 240 mg po x 1 with and without rifampin	24(24)	24(24)
3144A1 1111 EU/ B1891009	1	Healthy Subjects/Subjects with hepatic impairment	PK, safety Doses tested: 120 mg po x 1	27(27)	27(27)
3144A1 1116 US/ B1891010	1	Healthy Subjects	PK, safety Doses tested: 240 mg po qd x 2 weeks vs 120 mg BID x 2 weeks	50(50)	50(50)

Table 51: Neratinib Clinical Trials Included in NDA Submission (Continued)

Study Number	Phase	Study Population/Indication	Type	Number of Subjects Enrolled (in neratinib arm)	Number of Subjects Treated (with neratinib)
Healthy Subjects (Continued)					
3144A1 1117 US/ B1891036	1	Healthy Subjects	BA, PK, safety Doses tested: 240 mg po x 1	24(24)	24(24)
3144A1 1119 US/ B1891011	1	Healthy Subjects	DDI digoxin, PK, safety Doses tested: 240 mg po qd x 6 days with digoxin	27(27)	27(26)
3144A1-1127-US/ B1891021	1	Healthy Subjects	BE, PK, safety Doses tested: 240 mg po x 1	28(28)	28(28)
PUMA-NER-0101	1	Healthy Subjects	DDI PPI, PK, safety Doses tested: 240 mg po x 1 with and without PPI	15(15)	15(15)
Neratinib Monotherapy in Breast Cancer					
3144A2-3004-WW	Pivotal 3	Breast Cancer: Extended adjuvant; HER2 positive (ExteNET [3004] study)	Randomized 1:1 neratinib vs. placebo; iDFS Dose tested: 240 mg po qd with food for 1 year	2840 (1420)	2816 (1408)
PUMA-NER-6201	2	Breast Cancer: Extended adjuvant; HER2 positive (CONTROL [6201] study)	Diarrhea prophylaxis, safety study	211(211)	211(211)
3144A1-201-WW	2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive	Group A: previously treated with trastuzumab (N=66) Group B: trastuzumab naïve PFS at 16 weeks; ORR (N=70) Doses tested: 240 mg po qd	136(136)	136(136)
3144A2-3003-WW	2	Breast Cancer: Metastatic: HER2 positive; previously treated with trastuzumab	Comparative safety and efficacy study of neratinib vs. lapatinib+capecitabine Doses tested: 240 mg	233(117)	231 (116)

Table 51: Neratinib Clinical Trials Included in NDA Submission (Continued)

Study Number	Phase	Study Population/Indication	Type	Number of Subjects Enrolled (in neratinib arm)	Number of Subjects Treated (with neratinib)
Neratinib Monotherapy in Solid Tumors (Including Breast Cancer)					
3144A1 200 WW/ B1891037	2	NSCLC: Advanced	ORR, CBR, safety Doses tested: 240-320 mg po qd	172 (167)	167(167)
3144A1-102-US/ B1891028	1	Solid Tumors: Advanced; EGFR1 and/or HER2 positive	MTD, PK, PD, safety and preliminary efficacy Doses tested: 40-400 mg po qd	73(72)	72(72)
3144A1-104-JA/ B1891030	1	Solid Tumors: Advanced	MTD, PK, PD, safety and preliminary efficacy Doses tested: 80-320 mg po qd	21(21)	21(21)
PUMA-NER-5201	2	Solid tumors:EGFR, HER2, or HER3 mutation or EGFR gene amplification	Safety, efficacy Diarrhea prophylaxis Doses tested: 240 mg po qd	178(178)	178(178)
Neratinib Combination Therapy in Breast Cancer					
10-005	1/2	Breast Cancer: Metastatic; HER2 positive or triple-negative Combination with temsirolimus	Safety, efficacy, PK Diarrhea prophylaxis Doses tested: 240 mg po qd	99(99)	99(99)
3144A1-202-WW	1/2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive Combination with trastuzumab	MTD of combo, PD, safety PFS at 16 weeks; ORR Doses tested: 160-240 mg po qd	45(45)	45(45)
3144A-3005-WW	2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive Combination with paclitaxel	Randomized 1:1 neratinib+paclitaxel vs. trastuzumab + paclitaxel PFS; OS, ORR Dose tested: 240 mg po qd	479 (242)	474 (240)

Table 51: Neratinib Clinical Trials Included in NDA Submission (Continued)

Study Number	Phase	Study Population/Indication	Type	Number of Subjects Enrolled (in neratinib arm)	Number of Subjects Treated (with neratinib)
Neratinib Combination Therapy in Solid Tumors (Including Breast Cancer)					
3144A1 1122 JA/ B1891018	1	Solid tumors: Incurable Combination with capecitabine	Safety, efficacy, PK Doses tested: 240 mg po qd	7(7)	7(7)
3144A1-203-WW	1/2	Breast Cancer: Metastatic or Locally Advanced; HER2 positive Combination with paclitaxel	MTD of combo, PD, safety PFS at 16 weeks; ORR Doses tested: 160-240 mg po qd	110(110)	110(110)
3144A1-2204-WW	1/2	Breast Cancer and Solid Tumors: Metastatic or Locally Advanced; HER2 positive Combination with vinorelbine	MTD of combo, PD, safety PFS at 16 weeks; ORR Doses tested: 160-240 mg po qd	92(91)	91(91)
3144A1-2205-WW/ B1891016	1	Solid tumors: Advanced or metastatic Combination with temsirolimus	Safety, efficacy, PK Doses tested: 120-240 mg po qd	63(60)	60(60)
3144A1-2206-WW	1/2	Breast Cancer and Solid Tumors: Metastatic or Locally Advanced; HER2 positive Combination with capecitabine	MTD of combo, PD, safety PFS at 16 weeks; ORR Doses tested: 160-240 mg po qd	105(105)	105(105)
3144A2 1115 JA/ B1891001	1	Solid tumors: Incurable Combination with paclitaxel	Safety, efficacy, PK Doses tested: 160 mg or 240 mg po qd	10(10)	10(10)

Table 51: Neratinib Clinical Trials Included in NDA Submission (Continued)

Study Number	Phase	Study Population/Indication	Type	Number of Subjects Enrolled (in neratinib arm)	Number of Subjects Treated (with neratinib)
Neratinib Combination Therapy in Solid Tumors (Including Breast Cancer) (Continued)					
3144A2-1118-JA/ B1891002	1	Solid tumors: Advanced or metastatic Combination with vinorelbine	Safety, efficacy, PK Doses tested: 240 mg po qd	6(6)	6(6)
PUMA-NER-4201	2	NSCLC: Advanced Monotherapy and Combination with temsirolimus	Safety, efficacy Diarrhea prophylaxis Doses tested: 240 mg po qd	60 (17 neratinib, 43 neratinib + temsirolimus)	60 (17 neratinib, 43 neratinib + temsirolimus)

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Abbreviations: CI=confidence interval; DFS=disease free survival; Ext=extended; HRc=hormone receptor; iDFS=invasive disease free survival; ITT=intent to treat; NR=not reported; US=United States;

APPENDIX B. REGULATORY HISTORY

The original IND for neratinib was filed in 2003 by Wyeth Pharmaceuticals, which was later acquired by Pfizer in 2009. Puma acquired neratinib in 2011 and has been responsible for product development since that time. Key regulatory milestones are presented in Table 52.

Table 52: Neratinib Regulatory History

Milestone	Date	Sponsor	Description/Information
IND filing	2003	Wyeth	Initial IND submission
ExteNET protocol submitted to IND	2009	Wyeth	--
Transfer IND sponsorship to Pfizer	2009	Wyeth (subsidiary of Pfizer)	Wyeth was maintained as a wholly owned subsidiary of Pfizer
Transfer IND sponsorship to Puma	April 2012	Pfizer	Following licensing from Pfizer
Pre-NDA meeting	March 2016	Puma	--
NDA submission	July 2016	Puma	--

Abbreviations: IND=Investigational New Drug; NDA=New Drug Application.

APPENDIX C. PIVOTAL TRIAL AMENDMENTS, STUDY CONDUCT, AND DATA QUALITY

The ExteNET study (Study 3004) was initiated by Wyeth in 2009. Based on the original design, 3850 patients with node positive or node negative HER2 positive disease up to 2 years after completing a course of adjuvant trastuzumab therapy were to be enrolled. The primary endpoint was an event-driven analysis of iDFS at 337 events using the ITT population. Patients were to be followed for a period of 5 years after randomization. Three major protocol amendments (Amendments 3, 9, and 13) were implemented, which had a major impact on the study design (Table 53).

Table 53: Evolution of ExteNET Study Design

	Original Protocol (Apr 2009) Wyeth	Key Protocol Amendments		
		Amendment 3 (Feb 2010) Pfizer	Amendment 9 (Oct 2011) Pfizer	Amendment 13 (Jan 2014) Puma
N	3850	3300	2840	2840
Primary endpoint	iDFS (event driven: 337)	iDFS (event driven: 375)	2-year iDFS (time-driven)	2-year iDFS (time-driven)
Follow-up	5 yr	5 yr	2 yr	Primary: 2 yr Descriptive: 5 yr
Primary analysis population	ITT Stage 1-3c <2 yr from trast Node pos or neg	aITT Stage 2-3c ≤1 yr from trast Node pos	aITT Stage 2-3c <1 yr from trast Node pos	ITT
Secondary endpoint (OS)	Analysis at 5-yr f/u	Analysis at 5-yr f/u	Analysis at 2-yr f/u	Primary at 248 events
Rationale	NA	Data from trast trials: node-neg pts at low risk of recurrence; pts more likely to recur within 1 year of completing adjuvant trast	Business decision; not driven by any interim analysis	Experts recommended bringing the study back to the original design

Abbreviations: aITT=amended intent to treat; f/u=follow-up; iDFS=invasive disease free survival; ITT=intent to treat; NA=not applicable; neg=negative; OS=overall survival; pos=positive; yr=year.

Details of the 3 major amendments are provided below:

- **Amendment 3 (February 2010):** In light of data from 2 adjuvant trastuzumab trials (NCCTG N9831 and BCIRG 006) suggesting a lower than expected risk of recurrence for node-negative patients, as well as data from the HERA trial suggesting that patients are at higher risk of recurrence closer to completion of adjuvant trastuzumab and that the risk of recurrence may decrease over time (Perez 2009, Slamon 2009, Goldhirsch 2013), the study design and eligibility criteria were revised with Amendment 3 to increase the likelihood of trial success by restricting the eligibility criteria to only include patients with a higher risk of recurrence: node positive patients only, within 1 year from completion of prior trastuzumab therapy. This higher risk group was referred to as the aITT population and allowed for reduction of the sample size from 3850 to 3300 patients. Consequently, the event-driven iDFS analysis increased from 337 events to 375 events for the final analysis. This amendment was not based on any interim analysis of the data or any communication from the IDMC.
- **Amendment 9 (October 2011):** Due to business decisions, enrollment of new patients was stopped immediately at 2840 patients with Amendment 9, and the follow up period was shortened from 5 years after randomization to 2 years after randomization. The scope of the exploratory objectives was also limited. This amendment resulted in a change in the primary endpoint from an event-driven to a time-driven, 2-year iDFS analysis. It was not based on any interim analysis of the data or any recommendation from the IDMC.
- **Amendment 13 (January 2014):** Findings of the 2 year HERA study showed that 2 years of adjuvant trastuzumab was not betterthan 1 year of adjuvant trastuzumab, and results of the I-SPY2 neoadjuvant trial demonstrated that the pCR rate in the paclitaxel plus neratinib arm was significantly higher than the pCR rate in the paclitaxel plus trastuzumab arm. This prompted Puma to re-evaluate the importance of Study 3004 and take the necessary steps to preserve the integrity of the trial. Puma brought in statistical consultants with prior FDA ODAC experience who advised Puma to restore the trialto the original protocol as much as possible. This included changing the primary analysis population back to the ITT population (from the aITT) and restoring the duration of follow up to 5 years. However, Puma had to maintain the primary 2-year iDFS analysis because all patients had completed 2 years and were off study at that time. An OS analysis based on a predetermined number of events was also planned. Thus, Amendment 13 was implemented to obtain additional iDFS and OS data in order to evaluate the long term efficacy of neratinib in the adjuvant setting. Puma remained blinded to study results at the time of Amendment 13 implementation.Which was not driven by analysis or knowledge of the 2 year primary analysis. Reconsent was attempted for all randomized patients who had discontinued follow up at 2 years to obtain disease recurrence and survival data from their medical records.

Despite the changes in study sponsorship and protocol amendments, the study is credible for the following reasons. First, the infrastructure for study conduct remained consistent throughout the study, which maintained the integrity of the study. Second, the amendments were not made based on an early look at the data (the study was unblinded for the primary 2-year analysis in July 2014 but death events remain blinded). Third, the IDMC and monitoring plan remained consistent throughout.

When the trial was amended in 2014, many patients had completed the trial, and some sites had been closed. Therefore, Puma had to reopen all 572 sites in 40 countries, obtain IRB approval, and reconsent all patients for continued follow-up for iDFS and OS. This was a monumental task. Puma reached out to 100% of the study sites and requested that they contact all of their patients who were enrolled in the study, most of whom were still being seen by study doctors for routine follow-up visits. Throughout this entire process, Puma made every effort to avoid introducing any bias.