

s 22

From: s 47F
Sent: Sunday, 17 November 2019 9:34 PM
To: s 22
Cc: s 22
Subject: Re: Exploratory statistical adjustments for differential drop-outs and other missing data [SEC=OFFICIAL]

Absolutely agree s 22

s 47F

Apologies for typos ipad message

From: s 22
Sent: Friday, November 15, 2019 12:52:32 PM
To: s 47F
Cc: s 22
Subject: Exploratory statistical adjustments for differential drop-outs and other missing data [SEC=OFFICIAL]

s 47F

s 47E

I have attached the entire briefing document for neratinib prepared by the FDA for its ODAC meeting on 24 May 2017. I also have the full multi-disciplinary report, the slide deck for the ODAC meeting and the ODAC meeting transcript, which largely say the same thing about the two exploratory statistical adjustments for differential drop-outs and other missing data.

Pages 20-23 of the attached document present the two issues and the two FDA explorations.

The “tipping point” analysis appears to overlap the “fragility index”. The s 47C, s 47E

s 47C

However, importantly, all three approaches are in the context of confidence in a superiority conclusion. s 47C

s 47C, s 47E

s 47E

s 22

Office of HTA/Technology Assessment and Access Division
Department of Health

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FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

May 24, 2017

NDA 208051

Applicant: Puma Biotechnology, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought neratinib to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 Executive Summary

In July 2016, Puma Biotech submitted a new drug application (NDA) for neratinib (NERLYNX) in support of the following indication:

- NERLYNX as a single agent is indicated for the extended adjuvant treatment of adult patients with early stage ERBB2-positive breast cancer who have received prior adjuvant trastuzumab-based therapy.

Neratinib is a kinase inhibitor that irreversibly binds to epidermal growth factor receptors (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), and HER4.

The efficacy of neratinib in support of this indication is based on the results of Study 3004, a multicenter, randomized, double-blind, placebo-controlled trial of one year of neratinib versus placebo in women with early stage HER2-positive breast cancer after adjuvant treatment with trastuzumab. A total of 2840 patients were randomized 1:1 to receive either neratinib (n=1420) or placebo (n=1420). The primary endpoint of the study was invasive disease-free survival (iDFS) within 2 years and 28 days.

The primary analysis demonstrated a statistically significant stratified hazard ratio of 0.66 (0.49, 0.90) observed with an estimated 2.3% absolute difference in iDFS at two years (94.2% on the neratinib arm vs. 91.9% on the placebo arm). There may be a difference in the magnitude of benefit based on hormone receptor status [HR-positive HR=0.49 (0.31, 0.75), HR-negative HR=0.93 (0.60, 1.43)], however this is an exploratory subgroup analysis.

Throughout the conduct of the trial, there were multiple amendments to the protocol, and multiple changes of sponsor control. Effects of major amendments included:

- Study population enriched with high-risk patients
- Study follow-up time shortened from 5 years to 2 years; analysis changed from event-driven to time-driven
- Reconsent process introduced to extend follow-up to 5 years post randomization

Safety data were evaluated in 1408 patients who received neratinib in Study 3004. Diarrhea was the most frequently reported adverse reaction in the neratinib arm with an overall incidence of 95% and 40% of patients experiencing at least one episode of Grade 3 diarrhea. Twenty eight percent of patients discontinued neratinib due to an adverse event (AE), and the most common AE leading to discontinuation was diarrhea. Other common adverse reactions observed in 10% or more of patients taking neratinib were nausea, abdominal pain, fatigue, vomiting, rash,

stomatitis, decreased appetite, and muscle spasms. Results from an ongoing Phase 2 study (PUMA-NER-6201, also referred to as Study 6201) suggest that antidiarrheal prophylaxis decreases the incidence and severity of diarrhea in patients treated with neratinib in the extended adjuvant setting.

Topics for discussion at the Oncologic Drugs Advisory Committee meeting include:

- Risk-benefit profile of neratinib for extended adjuvant therapy in an early and often curative disease setting
- Is there uncertainty in the magnitude of treatment effect due to unplanned adaptations from multiple amendments, imbalance of early dropouts, and incomplete extended follow-up data?
- The totality of evidence of neratinib's efficacy data in the context of other approvals in the adjuvant setting

2 Background

Breast Cancer

Breast cancer is the most frequently diagnosed malignancy in women and is the leading cause of cancer mortality in women worldwide. HER2 (ERBB2)-positive breast cancer comprises approximately 20 to 25% of the entire breast cancer population (Slamon et al, N Engl J Med. 2011). ERBB2 protein overexpression or ERBB2 gene amplification in breast cancer tumors is associated with more aggressive clinical disease and poorer prognosis (Slamon et al, Science. 1987). Current standard of care for patients with HER2-positive early breast cancer is chemotherapy and one year of adjuvant trastuzumab (Piccart-Gebhart et al, N Engl J Med. 2005). Pertuzumab is also used in combination with trastuzumab and docetaxel as neoadjuvant treatment for selected patients. Approximately 20% of patients with HER2-positive early breast cancer will recur within 5 years after adjuvant therapy (Goldhirsch A et al, Lancet. 2013).

Approved Therapies

There are currently no approved therapies which improve upon the benefits of trastuzumab for HER2-positive patients in the adjuvant setting.

Extended adjuvant treatment was studied in the HERA trial, which randomized 5102 women with HER2-positive early stage breast cancer to one year of trastuzumab vs two years vs observation with DFS and OS as endpoints. The study was event-driven and showed no difference in either DFS or OS for one year of trastuzumab vs. two. However when evaluating

the Kaplan-Meier curves (Figure 1) at the two-year time point, it appears that two years of trastuzumab may improve DFS. With extended follow up, this perceived benefit disappears. These results call into question whether 2 years of follow up is adequate to capture the natural history of HER2-positive breast cancer.

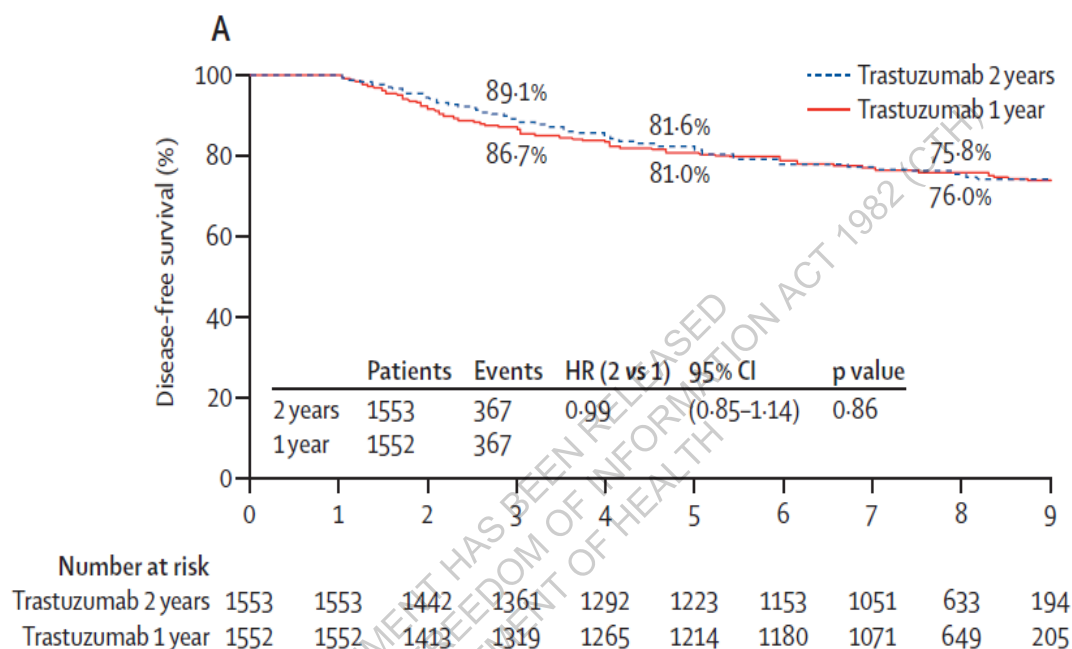


Figure 1: Kaplan-Meier Plot of Disease-free Survival; 2-year vs. 1-year of trastuzumab (HERA)

[Source: Goldhirsch A et al, Lancet. 2013]

The data in Table 1 provides a summary of FDA approvals of adjuvant breast cancer therapies, including the number of DFS events, duration of follow up, and improvement in DFS.

Table 1: FDA Approved Adjuvant Breast Cancer Therapies Since 1999¹

FDA Approval Drug and Year	Treatment Arms	N DFS Events	Median Follow up (months)	Absolute Difference in DFS Event Rate	Hazard Ratio
Add-on design					
Paclitaxel 1999	AC	N=1551 341 (22%)	30	4%	0.78
	AC + T	N=1570 283 (18%)			
Trastuzumab ² 2006	AC →T	N=1880 261 (13.8%)	24	6.7%	0.48
	AC →T + trastuzumab	N=1872 133 (7.1%)			
Placebo controlled					
Letrozole 2004 ^{3,4}	Letrozole	N=2582 122 (4.7%)	28	2.8%	0.62
	Placebo	N = 2586 193 (7.5%)			
Active comparator					
Epirubicin ⁵ 1999	CEF-120	N=356 136 (38%)	60	9%	0.76
	CMF	N=360 169 (47%)			
Tamoxifen 1999	Approval based on overview of adjuvant therapy of 10-year outcome data (N=36, 689), 55 randomized trials 10 year OS: 61.4% Tamoxifen vs. 50.5% control Recurrence-free rate at 10 years: 79.2% Tamoxifen vs. 64.3% control				
Doxorubicin 2002	Approval based on meta-analysis of six trials of ABC trials comparing doxorubicin containing regimens to CMF OS benefit demonstrated with HR 0.91				
Docetaxel 2004	FAC	N=742 206 (28%)	55	7%	0.74
	TAC	N=744 156 (21%)			
Exemestane 2005	Tamoxifen	N=2372 307 (13%)	35	4%	0.69
	Exemestane	N=2352 213 (9%)			

FDA Approval Drug and Year	Treatment Arms	N DFS Events	Median Follow up (months)	Absolute Difference in DFS Event Rate	Hazard Ratio
Anastrozole 2005	Tamoxifen	N=3116 651 (21%)	68	3%	0.87
	Anastrozole	N=3125 575 (18%)			
Letrozole ⁴ 2005	Tamoxifen	N=4007 369 (9.2%)	26	1.8%	0.79
	Letrozole	N= 4003 296 (7.4%)			

AC: doxorubicin, cyclophosphamide T: paclitaxel; CEF-120 regimen: cyclophosphamide + fluorouracil
 CMF: cyclophosphamide, methotrexate, fluorouracil; FAC: fluorouracil, doxorubicin, cyclophosphamide
 TAC: docetaxel, doxorubicin, cyclophosphamide

¹- At the time of approval, some drugs also demonstrated an improvement in OS

²- Four clinical trials showed an improvement with trastuzumab use

³- Approval in extended adjuvant setting after 5 years of tamoxifen

⁴- Accelerated approval later converted to regular approval with additional follow-up data

⁵- Epirubicin approval was based on results from 2 trials.

Neratinib Clinical Trials

The Applicant has conducted several clinical trials using neratinib as monotherapy and in combination with other agents in the neoadjuvant and metastatic breast cancer settings. Studies with mature data are presented in Table 2.

Table 2: Neratinib clinical Studies in HER2-positive Breast Cancer

Study		Treatment Arms	Primary Endpoint	Study Results
Neoadjuvant				
I-SPY 2	HER2+	Neratinib + paclitaxel → AC (n=65)	pCR rate*	39%
		Trastuzumab + paclitaxel → AC (n=22)		23%
	HER2+/ER-	Neratinib + paclitaxel → AC (n=NR)	pCR rate*	56%
		Trastuzumab + paclitaxel → AC (n=NR)		33%
	HER2+/ER+	Neratinib + paclitaxel → AC (n=NR)	pCR rate*	30%
		Trastuzumab + paclitaxel → AC (n=NR)		17%
NSABP FB-7		Neratinib + chemo (n=42)	pCR rate	All : 33.3% ER- : 46.2% ER+ : 27.6%
		Trastuzumab + chemo (n=42)		All : 38.1% ER- : 57.1% ER+ : 29.6%
		trastuzumab + neratinib + chemo (n=42)		All : 50.0% ER- : 73.7% ER+ : 30.4%
Metastatic or Locally Advanced				
Study 3003		Neratinib (n=117)	PFS HR: 1.19 (0.89, 1.60)	4.53 months
		Lapatinib + capecitabine (n=116)		6.83 months
Study 3005		Neratinib + paclitaxel (n=242)	PFS HR 1.015 (0.813, 1.269)	12.9 months
		Trastuzumab + paclitaxel (n=237)		12.9 months

Source: I-SPY 2: Park JW et al, N Engl J Med 375;1; NSABP FB-7: Jacobs S et al. SABCS 2015.

* Estimated pCR rate and not the actual rate; ER: Estrogen Receptor, HR: Hazard Ratio, NR: Not Reported; pCR: pathological Complete Response, PFS: Progression Free Survival

The results of the two neoadjuvant clinical studies are not consistent with those of this adjuvant study, in which the DFS benefit appears to be greater in the HR-positive patients, versus the neoadjuvant studies which demonstrate a greater benefit in patients with HR-negative tumors. In I-SPY 2, neratinib met the prespecified efficacy threshold for the subset of patients that were HR-negative. Of note, the primary endpoint of the neoadjuvant studies was pCR versus the adjuvant study which was invasive DFS. Endocrine therapies were not included in the neoadjuvant regimens for either I-SPY2 or NSABP FB-7 but were recommended for Study 3004.

The metastatic studies did not meet their primary endpoint.

Neratinib in the context of other adjuvant approvals

The neratinib extended adjuvant therapy for breast cancer study results in the context of other FDA approved adjuvant breast cancer therapies:

- Demonstrate a similar rate of benefit in disease-free survival when compared to approvals of adjuvant hormonal therapies, but with a different toxicity profile.
- Uses a placebo control in comparison to an active comparator used in most of other adjuvant approvals in breast cancer. This lack of comparator should be considered when assessing the magnitude of benefit
- Show a lower number of DFS events in the extended adjuvant setting compared to prior approvals. It is not clear whether this is due to the extended nature of the study (i.e., in a population where patients were randomized into the study after receiving at least one year of adjuvant therapy who were disease free at the time of randomization) in that a higher number of events would be anticipated prior to initiation of neratinib.
- Does not have prior FDA approval in the metastatic setting, compared with all prior adjuvant approvals.

2.1 Regulatory Milestones

The major regulatory milestones for this application are as follows:

- | | |
|------|--|
| 2003 | Wyeth submitted the initial investigational new drug (IND) for the treatment of HER2+ metastatic breast cancer and tumors overexpressing HER2 |
| 2009 | FDA denied a request by Wyatt for a Special Protocol Assessment, as efficacy and safety had not been established in patients with metastatic breast cancer |

- 2009 Wyeth submitted Study 3004 (ExteNET) to the IND
- 2009 Wyeth transferred IND sponsorship to Pfizer (Wyeth was maintained as wholly owned subsidiary of Pfizer)
- 2012 Pfizer transferred IND sponsorship to Puma, following licensing from Pfizer
- 3/2016 Pre-NDA meeting with Puma – FDA advised they did not encourage an NDA submission based on the efficacy and safety results of Study 3004. This was due to several study conduct issues which would make interpretation of the results problematic. The Applicant was advised that if an NDA was submitted, an Oncologic Drugs Advisory Committee discussion would be required.
- 7/2016 NDA was submitted

3 Study Design

3.1 Study 3004 (ExteNET)

[Extended Adjuvant Treatment of Breast Cancer with Neratinib; 3144A2-3004-WW]

This application is primarily supported by a single study, 3004, which was a multicenter, randomized, double-blind, placebo-controlled trial of one year of neratinib versus placebo in women with early stage HER2 overexpressed/amplified breast cancer after adjuvant treatment with trastuzumab.

After discontinuing study treatment, patients were followed for disease recurrence for another year. Randomization was stratified by the following:

1. ER and/or PgR positive ER and PgR negative
2. Nodal status (negative, 1-3 positive nodes or ≥ 4 positive nodes)
3. Trastuzumab given sequentially vs. concurrently with chemotherapy

Key Eligibility criteria:

1. Women with locally confirmed invasive HER2-positive breast cancer stage 1 to 3c without evidence of recurrence (note that after Amendment 3 this was limited to stage 2 or 3).
2. HER2 positivity determined locally by immunohistochemistry (IHC) 3+ or in situ hybridization and archived tumor tissue was required to be submitted for central review (the archived tumor tissue requirement was removed in Amendment 9).

3. Prior adjuvant therapy with anthracycline and/or taxane or CMF type regimen plus trastuzumab and where 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 at less than 1 year of adjuvant trastuzumab were eligible provided they had received at least 8 weekly or 3 q3 weekly doses and were either ineligible to receive further trastuzumab or unable to receive trastuzumab due to toxicity.
4. No evidence of recurrence based on imaging studies (mammogram, chest X-ray, bone scan if elevated alkaline phosphatase, CT/MRI of chest and abdomen if transaminases or alkaline phosphatase is elevated).
5. Known ER/PR status and normal organ and left ventricular ejection fraction.
6. ECOG performance score 0-1

Concurrent adjuvant endocrine therapy for HR positive disease was recommended.

Patients were excluded if they received prior neoadjuvant therapy that resulted in pCR or DCIS and axillary pCR, received prior HER2 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.

3.2 Major Amendments and Changes to Statistical Analysis Plan

Study 3004 was held by three different sponsors, leading to several major protocol amendments. Under Wyeth's original protocol (April 2009), the study was designed to enroll 3850 patients in order to observe the 337 DFS events necessary to detect a hazard ratio of 0.70 with 90% power and a one-sided significance level of 0.025. There were two planned interim analyses at approximately 135 (for futility only) and 236 (for futility and efficacy; efficacy boundary: p-value<0.0005) DFS events.

Subsequent major amendments are detailed in Table 3.

Table 3: Major Protocol Amendments and Changes to Statistical Analysis Plan

Amendment	Major Changes to Protocol	Sample Size Requirements
February 25, 2010 Amendment 3 Sponsor: Pfizer (who acquired Wyeth)	Study population was enriched to be more high-risk, excluding those with Stage 1 and/or node negative disease, and restricting to treatment within 1 year of Herceptin treatment instead of 2 years. This was to increase the likelihood of success of the trial based on data from adjuvant Herceptin trials, which showed a higher risk of recurrence closer to completion of Herceptin. Primary analysis was to be conducted on this enriched population, referred to as the amended intent-to-treat (aITT) population.	Sample size was reduced to 3300 to observe 375 events to detect a hazard ratio of 0.713 at 90% power and a one-sided 0.025 significance level. Interim analyses were to be conducted on the aITT population at 150 (for futility only) and 262 (for futility and efficacy; efficacy boundary: $p\text{-value} < 0.0005$) DFS events.
October 9, 2011 Amendment 9 Sponsor: Pfizer	Due to changes in organizational strategy, recruitment stopped and follow up was shortened from 5-years to 2-years after randomization. ¹ Interim analyses were also removed.	Enrollment stopped at 2840 patients. The time-driven analysis precluded a pre-specified number of events but total sample size of the aITT population was expected to be 1700 with a total of 165 events. Assuming a hazard ratio of 0.67 and a one-sided significance level of 0.05, the power of the analysis was expected to be approximately 83%.
January 1, 2012 Amendment 11	Pfizer transferred sponsorship of the IND to Puma	
January 16, 2014 Amendment 13 Sponsor: Puma	Primary analysis population was reverted back to ITT (including lower risk patients). ² Reconsent process was implemented for all randomized patients in an attempt to collect extended follow-up data for 5-	ITT population consisted of 2840 patients. Again no pre-specified number of events in a time-driven analysis but it was expected that 241 DFS events would be observed to

Biotechnology	years post-randomization.	provide approximately 88% power to detect a hazard ratio of 0.667 at a one-sided significance level of 0.025.
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¹The MBC Study 3003 (neratinib vs lapatinib + capecitabine) was presented at SABCS 2011.

²The I-SPY 2 Study (neratinib HER2-negative arm graduation) was presented at ASCO 2014.

Database lock occurred on July 7, 2014. The major changes to the protocol appeared to be the result of outside factors (i.e. external information and changes in organizational strategy). The applicant's decision to attempt reconsent of all patients for extended follow-up data for 5-years post-randomization was driven by advice they received from outside statistical consultants.

3.3 Efficacy Endpoints

Primary Endpoint

- In the final amendment, the primary efficacy endpoint was iDFS defined as the time from randomization to the first occurrence of invasive ipsilateral breast tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause.
- The primary analysis included iDFS events up to a cutoff date of 2 years + 28 days from randomization unless the events occurred after 2 or more missing physical exams.
 - Patients who did not have an iDFS event by cutoff had their iDFS time censored at the date of the last physical exam (including targeted PE), either scheduled or unscheduled, occurring within 2 years, 4 months, and 28 days from randomization.
 - Patients who had an iDFS event after 2 or more missing physical exams (8 month gap) had their iDFS times censored at the last available physical exam prior to the event.
- The primary analysis of iDFS was performed on the ITT population using a stratified log-rank test with type-1 error controlled at a one-sided significance level of 0.025. The stratified Cox proportional hazards model was used to estimate the treatment hazard ratio and corresponding 95% confidence and a Kaplan-Meier plot was created.

Secondary Endpoints

- DFS including Ductal carcinoma in situ (DFS-DCIS), distant disease-free survival (DDFS), time to distant recurrence (TTDR), and incidence of CNS recurrence.
- Analyses of time-to-event related secondary endpoints were similar to that of the primary endpoint but with no planned adjustment of type I error for multiplicity.

4 Efficacy

4.1 Patient Disposition

Table 4 presents the disposition of the patients in the ITT population.

Table 4: Patient Disposition

	Neratinib N= 1420 n (%)	Placebo N=1420 n (%)
Patients Randomized	1420 (100)	1420 (100)
Patients Who Received at least 1 dose of study drug	1408 (99)	1408 (99)
Discontinued treatment due to AEs	372 (26)	72 (5)
Discontinued treatment due to Patient Request	121 (9)	69 (5)
Patients who completed study	1095 (77)	1183 (83)
Patients who did not complete study*	300 (21)	237(17)

*Reasons for not completing the study include patient request, investigator decision, discontinuation of study by sponsor, lost to follow-up, other, and screen failure.

4.2 Demographics and Baseline Characteristics

Demographic characteristics were well balanced between groups. See Table 5.

Table 5: Demographics and Baseline Characteristics

Characteristic	Neratinib N=1420 n (%)	Placebo N=1420 n (%)
aITT population	938 (66)	935 (66)
Non-aITT population	482 (34)	485 (34)
Median age	52	52
Nodal Status		
Negative	335 (24)	336 (24)
1-3 positive nodes	664 (47)	664 (47)
≥4 positive nodes	421 (30)	420 (30)
HR status		
Positive	816 (58)	818 (57)
Negative	604 (43)	605 (43)
Time from last trastuzumab to randomization ≤ 1 year	1152 (81)	1145 (81)

Other demographic factors, such as stage, time from diagnosis, and prior adjuvant therapies were well balanced between arms.

4.3 Primary Analysis of iDFS

Results from the applicant's primary analysis of truncated iDFS with 2 years and 28 days of follow-up are shown in Table 6. A total of 173 iDFS events were observed, consisting of 67 (4.7%) events on the neratinib arm and 106 (7.5%) events on the placebo arm. A statistically significant difference favoring neratinib was observed with a stratified hazard ratio of 0.66 (95% CI: 0.49, 0.90) and two-sided stratified log-rank test (p-value = 0.008). The estimated absolute difference in iDFS rates at 2-years was 2.3% (94.2% on the neratinib arm compared to 91.9% on the placebo arm).

The Kaplan-Meier curves are shown in Figure 1. From the start of the study to 3 months in this analysis, a larger decrease in number at risk on the neratinib arm compared to the placebo arm was observed. This was due to a large amount of censoring on the neratinib arm prior to 3

months and an imbalance between the two arms in the number of patients who stopped treatment early. The effect of these early dropouts will be further discussed in Section 4.5.

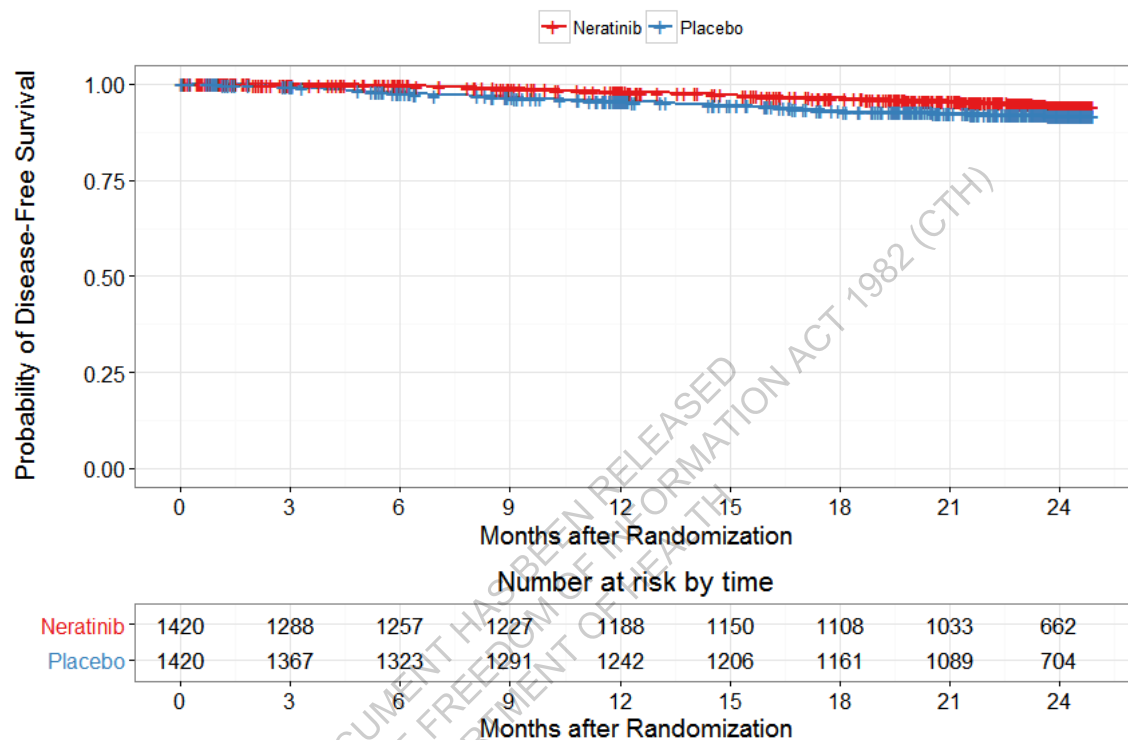


Figure 1: Kaplan-Meier Plot of Disease-free Survival, ITT Population

[Source: FDA Analysis]

Table 6: Primary Analysis of Disease-free Survival, ITT Population

	Neratinib (N=1420)	Placebo (N=1420)
iDFS Events	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	1353 (95.3)	1314 (92.5)
On date of 2 years + 28 days	353 (26.1)	338 (25.7)
On date of last physical exam	963 (71.2)	947 (72.1)
On date of last physical exam 8 months prior to determination of DFS event (2 missed assessments)	3 (0.2)	3 (0.2)
On date of last physical exam prior to death	1 (0.1)	1 (0.1)
On date of latest physical exam which is more than 2 weeks before DFS event	2 (0.1)	4 (0.3)
On randomization date*	31 (2.3)	21 (1.6)
Kaplan-Meier Estimate		
At 12 months	97.9 (97.0, 98.6)	95.6 (94.3, 96.5)
At 24 months	94.2 (92.6, 95.4)	91.9 (90.2, 93.2)
Stratified log-rank p-value (two-sided)	0.008	
Unstratified log-rank p-value (two-sided)	0.009	
Stratified Hazard Ratio	0.66 (0.49, 0.90)	
Unstratified Hazard Ratio	0.67 (0.49, 0.90)	

* Reasons for study withdrawal at randomization were: 1 screen failure, 2 lost to follow-up, 29 by subject request, and 20 for other reasons
[Source: FDA Analysis]

4.4 Applicant's Exploratory Analyses of iDFS with Extended Follow-up

The applicant implemented a reconsent process to acquire extended follow-up data from 2-years through 5-years post-randomization. Per the applicant, recurrent disease and deaths were ascertained from subjects' medical records upon reconsent. The final update submitted April 2017 showed that 2117 (74.5%) of the 2840 primary analysis patients had been reconsented, consisting of 1028 patients on the neratinib arm and 1089 patients on the placebo arm. There appear to be no differences in baseline characteristics between the reconsented population and the full ITT population or between arms among the reconsented patients. Please see Table 5.

Results from the applicant's 5-year analysis with 74.5% of patients reconsented are shown in Table 7 and Kaplan-Meier curves are shown in Figure 2. A total of 279 events were observed with 116 (8.2%) events on the neratinib arm and 163 (11.5%) events on the placebo arm. The stratified hazard ratio was 0.73 (95% CI: 0.57, 0.92) and the estimated iDFS rate at 5-years was 90.2% on the neratinib arm and 87.7% on the placebo arm for an absolute difference of 2.5%.

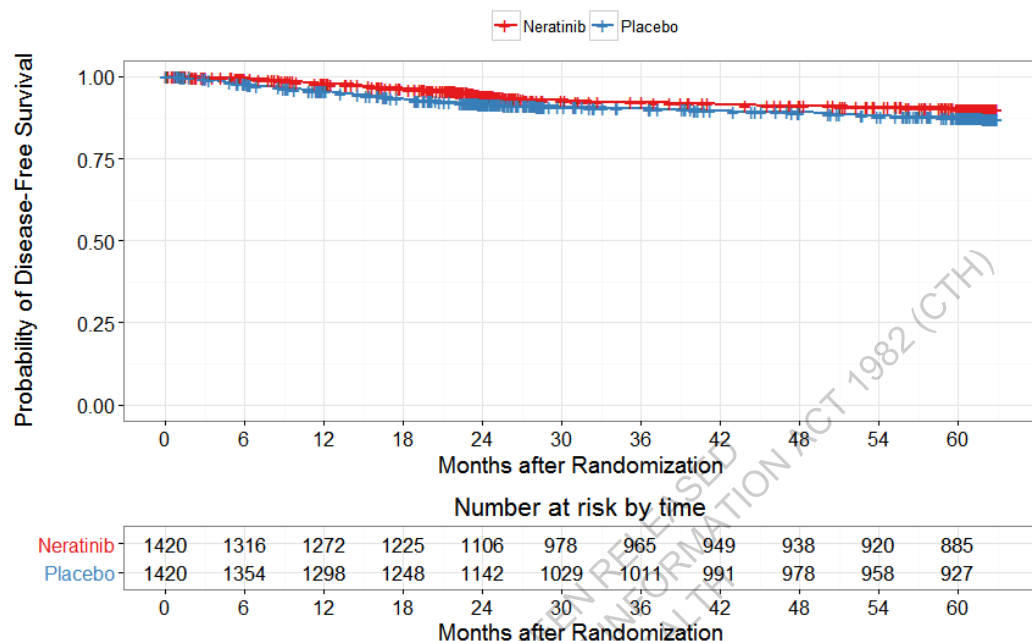
Table 7: Exploratory Analyses of iDFS with Extended Follow-up (74.5% reconsented)

	5-year iDFS	
	Neratinib (N=1420)	Placebo (N=1420)
iDFS Events	116 (8.2)	163 (11.5)
Patients Censored	1304 (91.8)	1257 (88.5)
Kaplan-Meier Estimate		
At 24 months	94.3 (92.9, 95.4)	91.7 (90.1, 93.1)
At 60 months	90.2 (88.3, 91.8)	87.7 (85.7, 89.4)
Stratified log-rank p-value (two-sided)	0.008*	
Stratified Hazard Ratio	0.73 (0.57, 0.92)	

[Source: the sponsor's Analysis]

*nominal p-value without adjusting multiple comparisons

Figure 2: Kaplan-Meier Plot of Disease-free Survival; 5-years of follow-up with 74.5% of patients reconsented



[Source: the sponsor's Analysis]

4.5 FDA Statistical Discussion

Data Truncation and Change from Event-driven to Time-driven Analysis (Amendment 9)

The applicant's decision to truncate follow-up at 2-years and 28 days post-randomization in Amendment 9 modified the primary analysis from being event-driven to time-driven. Time-driven analyses are generally not preferred because they do not allow for a pre-specified number of events and analyses run the risk of being under or over powered depending on the number of events that happen to be observed at the cutoff time.

The truncation was a business decision, and thus this particular truncation cutoff does not appear to have been based on information from the blinded trial.

Early Dropouts in the Primary Analysis

In Study 3004, 23% of patients on the neratinib arm and 17% of patients on the placebo arm did not complete the study. This was relatively higher than prior adjuvant trials whose withdrawals per arm ranged from 4-16% even when patients were followed for longer than 2 years.

The Kaplan-Meier plot for the primary analysis (Figure 1) indicated an imbalance between arms in the number of patients who dropped out at less than 3 months. There were 130 such patients on the neratinib arm compared to only 44 on the placebo arm. The most common reasons for neratinib dropouts were adverse events (58%) and subject request (31%). There is concern that the censoring of these observations in the time-to-event analysis could be informative as patients dropped out due to treatment related toxicity.

The applicant conducted an updated 2-year analysis with data from the exploratory extended follow-up which helped address the early dropouts. Results are shown in Table 8 and are consistent with the primary analysis. After the update, there was a decrease in overall early dropouts as shown in Table 9. Observe that 50 patients on the neratinib arm and 19 patients on the placebo arm had updated iDFS times from the reconsent process.

Table 8: Updated 2-year Analysis

	Neratinib (N=1420)	Placebo (N=1420)
iDFS Events	76 (5.4)	114 (8.0)
Patients Censored	1344 (94.6)	1306 (92.0)
Kaplan-Meier Estimate		
At 24 months	94.3 (92.9, 95.4)	91.7 (90.1, 93.1)
Stratified log-rank p-value (two-sided)	0.009*	
Stratified Hazard Ratio	0.69 (0.51, 0.91)	

[Source: the sponsor's Analysis]

*Nominal p-value without adjusting for multiple comparisons

Table 9: Early dropouts before and after updated data from reconsent

	Neratinib	Placebo	Total
Primary Analysis	130	44	174
After Update	80	25	105

Before the updated data from reconsent was available, the applicant initially addressed the early dropouts with a simulation study assuming the neratinib early dropouts behaved as if they were on placebo. Neratinib early dropout patients were assigned “updated” iDFS times via resampling from the placebo arm. Balance in the stratification factors was maintained by matching patients in each group by these factors prior to resampling. After the updated data from reconsent became available, FDA conducted a similar simulation as a sensitivity analysis. In the FDA’s simulation, the remaining 80 neratinib early dropout patients were assigned “updated” iDFS times via resampling from the 50 neratinib patients with real updated iDFS times. Results from both simulations are summarized in Table 10.

Table 10: Results Across Simulated Trials

	Number of Additional Events, mean (range)	Hazard Ratio, mean (range)	Absolute difference in 2-year iDFS rates, mean (range)
Applicant Simulation (Primary Analysis)	9 (1-23)	0.69 (0.61-0.82)	2.1% (1.1%-2.8%)
FDA Simulation (After Update)	5 (0-13)	0.69 (0.64-0.76)	2.5% (2.0%-2.9%)

[Source: Sponsor Analysis and FDA Analysis]

Missing Data in 5-year Follow up

The applicant’s exploratory analyses of iDFS with extended follow-up appeared to show that the benefit seen in the primary analysis was upheld to 5-years post-randomization but incomplete follow-up lends these results to uncertainty. The follow-up data collected was incomplete in two ways:

1. Of the 723 (25.5%) patients not reconsented, 101 patients had already had an iDFS event, leaving 622 patients (351 neratinib, 271 placebo) with censored iDFS times.
2. Of the 2117 (74.5%) patients reconsented, 132 patients (68 neratinib, 64 placebo) had their iDFS times censored prior to 5-years.

Thus, a total of $622+132=754$ patients (419 neratinib, 335 placebo) had their iDFS times censored prior to 5-years.

To address concerns regarding the missing data, the FDA conducted a tipping point analysis to determine how many of these 754 patients would need to have an event (recurrence) at their next assessment to “tip” the results against the neratinib arm. Assumptions made in the analysis were as follows:

1. A select number of patients on both arms were randomly chosen to have events at their next assessment. This assessment was assumed to occur in 4 months
2. All patients whose iDFS times remained censored were assumed to have been followed for the full 5-years.

Based on what was seen in patients reconsented and followed from 2-years through 5-years, we determined that the rate of new events in these patients was approximately 5.1% on the neratinib arm and 5.8% on the placebo arm.

Given that the placebo patients whose iDFS times were censored before 5-years had events at the same rate, we assumed that 19 additional placebo patients would have events (approximately 5.8% of the 335 with missing data). With this many additional events on the placebo arm, we increased the number of events on the neratinib arm among the 419 missing observations until two tipping points were reached:

1. Tipping Point #1: The p-value exceeds 0.05 (two-sided)
2. Tipping Point #2: The hazard ratio equals or exceeds 0.9

Results for the tipping points are shown in Table 11. In both cases, the results did not tip unless the rate of new neratinib events was higher than the expected 5.1%. These simulations results are limited to the assumptions made.

Table 11: Results of Tipping Point Analyses

	New Neratinib Events	New Placebo Events	Stratified HR	Stratified log-rank p-value (two-sided)
Tipping Point #1	35/419 (8.4%)	19/335 (5.7%)	0.81 (0.65, 1.01)	0.056
Tipping Point #2	51/419 (12.2%)	19/335 (5.7%)	0.90 (0.73, 1.11)	0.339

[Source: FDA Analysis]

4.6 Exploratory Subgroup Analyses

Notable results in select exploratory subgroups based on the stratification factors are shown in Table 12.

Table 12: Study 3004 Exploratory Subgroup Analyses

Population	Number of Events/ Total N		KM Estimate for iDFS at 24 months %			Unstratified HR
	Neratinib	Placebo	Neratinib	Placebo	Absolute Difference	
aITT	53/938	84/935	93.1	90.1	3	0.65 (0.46, 0.91)
Non-aITT	14/482	22/485	96.2	95.1	1.1	0.71 (0.35, 1.36)
HR-positive	29/816	63/815	95.6	91.5	4.1	0.49 (0.31, 0.75)
HR-negative	38/604	43/605	92.2	92.4	-0.2	0.93 (0.60, 1.43)
Concurrent prior trastuzumab	49/884	66/886	93.2	92.0	1.2	0.80 (0.55, 1.16)
Sequential prior trastuzumab	18/536	40/534	95.8	91.6	4.2	0.46 (0.26, 0.78)

Nodal Status: ≤ 3 positive nodes	38/999	58/1000	95.3	93.8	1.5	0.70 (0.46, 1.04)
Nodal Status: ≥ 4 positive nodes	29/421	48/420	91.4	87.3	4.1	0.62 (0.39, 0.97)
Randomized ≤ 1 year from completion of prior trastuzumab	58/1152	95/1145	93.8	90.9	2.9	0.63 (0.45, 0.88)
Randomized > 1 year from completion of prior trastuzumab	9/268	11/275	95.8	95.7	0.1	0.92 (0.37, 2.23)

[Source: FDA Analysis]

4.7 Summary of Secondary Endpoint Analyses

Results from secondary endpoint analyses of DFS-DCIS, DDFS, and TTDR appeared to be generally in favor of the neratinib arm but no multiplicity adjustment was pre-specified and should be considered exploratory.

Overall survival data is not yet mature.

4.8 FDA Efficacy Summary

The major statistical review issues identified in study 3004 were unplanned adaptations due to multiple amendments, imbalance in early dropouts, and incomplete extended follow-up resulting in missing data.

The study underwent major protocol amendments throughout its development program due in part to sponsor changes-the population was enriched to high risk then changed back to all-comers, follow-up was truncated at 2-years changing the primary analysis from event-driven to time-driven, and patients were reconsented for extended follow-up for 5-years post-randomization. However, these changes appear to be due to outside factors (i.e. external information and organizational changes) rather than premature trial unblinding.

The remaining two issues were addressed by sensitivity and tipping point analyses as summarized in Table 13.

Table 13: Summary Table of FDA Sensitivity and Tipping Point Analyses

Statistical Issue	FDA Analysis	Conclusion
Imbalance in early dropouts	<p>In the updated 2-year analysis after reconsent, neratinib early dropouts decreased to 80, with 50 having updated iDFS times.</p> <p>Sensitivity analysis: Resampled from the 50 patients to get “updated” iDFS times for the remaining 80 neratinib early dropouts</p>	Results similar to primary analysis
Incomplete extended follow-up/Missing data	Tipping point analysis to see what it would take for the missing data to “tip” the results against neratinib	Assuming placebo arm has events as expected, results only “tip” when neratinib arm has events at rates higher than expected.

In summary, the sensitivity and tipping point analyses appeared to show that the statistical issues identified were unlikely to have a large impact on the study’s overall results. There remains some uncertainty regarding the true magnitude of the treatment effect since the primary analysis (truncated at 2-years follow-up) observed a hazard ratio of 0.66 (95% CI: 0.49, 0.90) which changed to 0.68 (95% CI: 0.51, 0.91) with the exploratory updated 2-year analysis and the exploratory 5-year analysis observed a hazard ratio of 0.73 (95% CI: 0.57, 0.92).

5 Safety

5.1 Safety Population

The safety analysis of neratinib primarily focuses on 2,816 patients treated on Study 3004 (1,408 patients treated with neratinib and 1,408 patients treated with placebo). Results from Study 6201

(PUMA-NER-6201), an ongoing Phase 2 study investigating the incidence and severity of diarrhea in patients treated with antidiarrheal prophylaxis given during the first two 28-day treatment cycles of neratinib, were also analyzed.

5.2 Safety Overview

In Study 3004, the median duration of exposure to neratinib was 11.6 months (range 0.03 -13.3 months) and the median duration of exposure to placebo was 11.8 months (range 0.1 - 13.2 months). Table 14 summarizes the overall safety profile of neratinib.

Table 14: Overall Summary of Safety Analysis

	Neratinib N=1,408 n (%)	Placebo N=1,408 n (%)
Death ≤ 28 days of last dose	0	0
Discontinuation		
Due to AE; at any time point	388 (28)	76 (5)
Due to AE; during first 3 months of treatment	284 (20)	20 (1)
Interruptions and Reductions		
At least 1 interruption	849 (60)	623 (44)
At least 1 reduction	519 (37)	112 (8)
Treatment Emergent Adverse Events		
Grade 3-4	700 (50)	184 (13)
Fatal ¹	2 (<1)	1 (<1)
Serious AE	103 (7)	85 (6)
Leading to discontinuation	388 (28)	76 (5)
Leading to dose interruption	629 (45)	187 (13)
Leading to dose reduction	440 (31)	35 (3)

Source: Reviewer generated table – summarizing DS, AE (July 7th, 2014 data cutoff date, submitted by applicant)

¹ All 3 patients died > 28 days after last dose of study drug. (Neratinib arm – one patient with metastatic breast cancer, one patient with AML; Placebo arm – one patient with gastric cancer.)



5.3 Adverse Reactions

The most common ($\geq 20\%$) adverse reactions with neratinib are diarrhea, nausea, abdominal pain, fatigue, and vomiting.

Of the 1,408 patients receiving neratinib in Study 3004, 388 (27.6%) experienced an adverse reaction that resulted in permanent discontinuation; the most common adverse reactions leading to discontinuation were diarrhea (16.8%), vomiting (3.8%), and nausea (2.8%). Adverse events leading to dose interruptions occurred in 629 (44.7%) of patients receiving neratinib; the most common were again diarrhea (33.9%), vomiting (5.4%), and nausea (5.4%). Adverse events leading to dose reduction occurred in 440 (31.3%) of patients; the most common were diarrhea (26.4%), nausea (2.8%), and abdominal pain (1.6%).

Tabular listings of adverse reactions by treatment arm for Study 3004 are shown below Table 15.

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Table 15: Common Adverse Reactions Reported in $\geq 10\%$ of Neratinib-Treated Patients on Study 3004

System Organ Class (Preferred Term)	Neratinib N=1,408			Placebo N=1,408		
	Gr 1-4 (%)	Gr 3 (%)	Gr 4 (%)	Gr 1-4 (%)	Gr 3 (%)	Gr 4 (%)
Gastrointestinal Disorders						
Diarrhea	95	40	<1	35	2	0
Nausea	43	2	0	22	<1	0
Abdominal pain ¹	36	2	0	15	<1	0
Vomiting	26	3	0	8	<1	0
Stomatitis ²	14	1	0	6	<1	0
General Disorders and Administration Site Conditions						
Fatigue	27	2	0	20	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	12	<1	0	3	0	0
Musculoskeletal and Connective Tissue Disorders						
Muscle spasms	11	<1	0	3	<1	0
Skin and Subcutaneous Tissue Disorders						
Rash ³	18	1	0	9	0	0

Source: Reviewer generated table – summarizing AE dataset (July 7th, 2014 data cutoff date, submitted by applicant)

¹ Includes abdominal pain, abdominal pain upper, and abdominal pain lower.

² Includes stomatitis, aphthous stomatitis, mouth ulceration, oral mucosal blistering, mucosal inflammation, oropharyngeal pain, mucosal inflammation, oral pain, glossodynia, glossitis, and cheilitis.

³ Includes rash, rash erythematous, rash follicular, rash generalized, rash pruritic, and rash pustular, rash maculo-papular, rash popular, dermatitis, dermatitis acneiform, and toxic skin eruption.

5.4 Serious Adverse Events (SAEs)

Nonfatal serious adverse events occurred in 7.3% of patients on the neratinib arm and 6.0% of patients on the placebo arm in Study 3004. The most frequent treatment-related SAE was diarrhea with 22 patients on the neratinib arm and 1 patient on the placebo arm. SAEs are summarized in Table 16. All SAEs in the neratinib arm were reversible after discontinuation of study drug except one patient with herpes zoster ophthalmicus and one patient with left sided paresis in the setting of glioblastoma.

Table 16: Nonfatal Serious Adverse Reactions Reported in ≥ 5 Neratinib-Treated Patients on Study 3004

Serious Adverse Events	Neratinib N=1,408 n (%)	Placebo N=1,408 n (%)
Any SAE	103 (7.3)	85 (6.0)
Diarrhea	22 (1.6)	1 (0.1)
Vomiting	12 (0.9)	1 (0.1)
Dehydration	9 (0.6)	1 (0.1)
Renal failure ¹	6 (0.4)	0
Cellulitis	6 (0.4)	1 (0.1)
Erysipelas	5 (0.4)	0

Source: Reviewer generated table – summarizing AE dataset (July 7th, 2014 data cutoff date, submitted by applicant)

¹ Includes renal failure, acute renal failure, and blood creatinine increased.

5.5 Antidiarrheal Prophylaxis

Patients on Study 3004 were not required to receive antidiarrheal prophylaxis. Study 6201 (PUMA-NER-6201) is an ongoing open-label, Phase 2 study investigating the incidence and severity of diarrhea in patients with early stage HER2-positive breast cancer treated with neratinib for 1 year with antidiarrheal prophylaxis given during the first two 28-day treatment cycles. The protocol has undergone a number of amendments which has led to changes in the

intensity of antidiarrheal prophylaxis as well as changes in the treatment regimens being studied. As of the January 13th, 2017 safety cutoff date, 137 patients received prophylaxis with Loperamide alone (the Loperamide Cohort), 64 patients with Loperamide plus Budesonide (the Loperamide plus Budesonide Cohort), and 10 patients with Loperamide plus Colestipol (the Loperamide plus Colestipol Cohort). The median duration of treatment with neratinib was 9.07 months for the Loperamide Cohort, 2.83 months for the Loperamide plus Budesonide Cohort, and 0.56 months for the Loperamide plus Colestipol Cohort.

A comparison of common adverse reactions in the Neratinib Arm of Study 3004 and the Loperamide Cohort of Study 6201 is shown in Table 17. The Loperamide Cohort is used as a comparator since this cohort has the longest follow-up with a median duration of treatment with neratinib of 9 months.

Table 17: Common Adverse Reactions in Study 3004 and Study 6201

System Organ Class (Preferred Term)	Study 3004 Neratinib Arm N=1,408			Study 6201 Loperamide Cohort N=137		
	Gr 1-4 (%)	Gr 3 (%)	Gr 4 (%)	Gr 1-4 (%)	Gr 3 (%)	Gr 4 (%)
Gastrointestinal Disorders						
Diarrhea	95	40	<1	77	31	0
Constipation	8	0	0	55	0	0
Nausea	43	2	0	56	1	0
Abdominal pain	36	2	0	26	2	0
Vomiting	26	3	0	26	2	0
General Disorders and Administration Site Conditions						
Fatigue	27	2	0	53	4	0
Metabolism and Nutrition Disorders						
Decreased appetite	12	<1	0	19	0	0

Source: Reviewer generated table – summarizing AE dataset submitted by Applicant (Study 3004: July 7th, 2014 data cutoff) and Interim Safety Update Report (Study 6201: Jan 13th, 2017 data cutoff).

A comparison of dose modifications and discontinuations in the neratinib arm of Study 3004 and the Loperamide Cohort of Study 6201 is shown in Table 18 . Again, the Loperamide Cohort is used as a comparator since this cohort has the longest follow-up.

Table 18: Incidence of Treatment-emergent Diarrhea Leading to Treatment Discontinuation, Dose Reduction, or Dose Hold

	Study 3004 Neratinib Arm N=1,408 n (%)	Study 6201 Loperamide Cohort N=137 n (%)
Discontinuation due to diarrhea	237 (16.8)	28 (20.4)
Dose reduction due to diarrhea	372 (26.4)	10 (7.3)
Dose hold due to diarrhea	477 (33.9)	19 (13.9)

Source: Reviewer generated table – summarizing AE dataset submitted by Applicant (Study 3004: July 7th, 2014 data cutoff) and Interim Safety Update Report (Study 6201: Jan 13th, 2017 data cutoff).

While there were fewer dose reductions and dose holds in the Loperamide Cohort of Study 6201 compared to patients in Study 3004, there remained a substantial rate of discontinuation due to diarrhea despite antidiarrheal prophylaxis with Loperamide (16.8% in Study 3004 and 20.4% in Study 6201). In addition, a higher incidence of constipation and nausea was reported in the Loperamide cohort.

Summary:

The applicant conducted a multicenter, randomized, double-blind, placebo-controlled study of neratinib versus placebo in women with early-stage HER2-overexpressed/amplified breast cancer after adjuvant treatment with trastuzumab. There were several major unplanned amendments made to the trial impacting enrollment, the number of iDFS events observed, and the period of patient follow up. The primary analysis showed an improvement with neratinib with an absolute difference in iDFS of 2.8% after a 2-year follow-up [stratified HR: 0.66 (0.49, 0.90); p value: 0.008]. Despite the unplanned amendments and potential uncertainty introduced with respect to the magnitude of neratinib effect, based on the sensitivity analyses conducted, the results appear to be generally similar to the primary analysis results, supporting an effect of neratinib. The tolerability of neratinib in this patient population is a concern given the frequent



dose interruptions, reductions, and discontinuations observed, mostly due to diarrhea. In Study 3004, nearly all patients experienced any Grade diarrhea and 40% of patients experienced Grade 3 diarrhea. Results from the ongoing Phase 2 Study 6201 suggest that antidiarrheal prophylaxis decreases the incidence and severity of diarrhea.

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