U.S. FOOD & DRUG ADMINISTRATION

NDA 208051
Neratinib

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Proposed Indication

Neratinib as a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab based therapy.

Topics for Discussion

1. Benefit-risk profile of neratinib in early and often curative disease setting.

2. Multiple adaptations to ExteNET study design
   - FDA statistical analyses consistently show an effect of neratinib.
   - Magnitude of benefit remains uncertain.

3. Totality of evidence of neratinib's efficacy
   - Context of FDA adjuvant breast cancer approvals.
   - Overall development program.

Background

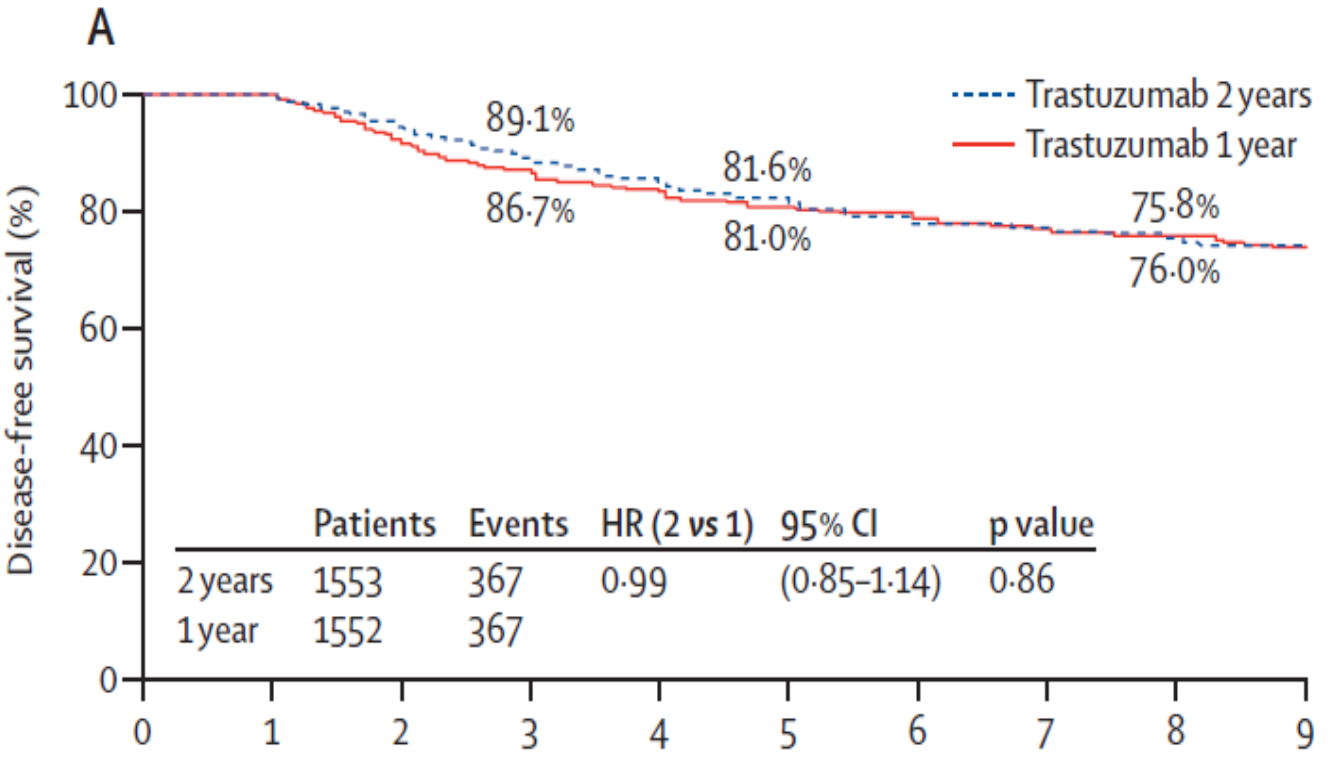
- Standard of care of HER2+ breast cancer

  - adjuvant chemotherapy + 1 year trastuzumab +/- endocrine therapy.[1]

- FDA adjuvant approvals.
- Neratinib in the context of other adjuvant approvals.
- Neratinib clinical development program.

[1]Piccart-Gebhart et al, N Engl J Med. 2005

Natural History Post 1 Year of Trastuzumab



Number at risk										
Trastuzumab 2 years	1553	1553	1442	1361	1292	1223	1153	1051	633	194
Trastuzumab 1 year	1552	1552	1413	1319	1265	1214	1180	1071	649	205

Goldhirsch A et al, Lancet. 2013

FDA Adjuvant Approvals

Trial designs: add-on, placebo-controlled, active comparator

Median follow up: from 24 months – 68 months

Absolute improvements in Disease-free Survival events:
1.8% (with an active comparator)- 9%

Hazard ratio (HR): Active comparator: 0.69-0.87
Placebo-controlled: 0.62
Add-on: 0.48-0.78

In addition: Overall Survival benefit in some drugs at time of approval.

All had prior FDA approvals in metastatic setting.

https://www.accessdata.fda.gov/scripts/cder/daf/

ExteNET in Context

Points to consider:

- Low rate of DFS events; possibly due to extended adjuvant setting.
- Use of placebo control should be considered when assessing magnitude.
- Magnitude of benefit similar to early approvals, but with different toxicity profile.

Inconsistent Benefit in HR* Subgroups

Neoadjuvant Trials

- I-SPY 2 (n= 87)[1]
- NSABP FB-7 (n= 126)[2]

Primary endpoint: pCR**

pCR rate in HR-negative > HR-positive

* HR=Hormone Receptor
**pCR=pathologic complete response

Adjuvant Trial

- ExteNET (n= 2840)

Primary endpoint: invasive Disease-free Survival (iDFS)

iDFS in HR-positive > HR-negative

o possibly due to cross-talk between HR and HER2 pathways

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

Metastatic Trials - Neratinib

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 (0.81, 1.27)	12.9 months
	Trastuzumab + paclitaxel (n=237)		12.9 months

PFS: Progression-free Survival

Studies 3003 and 3005 did not meet their primary endpoint.

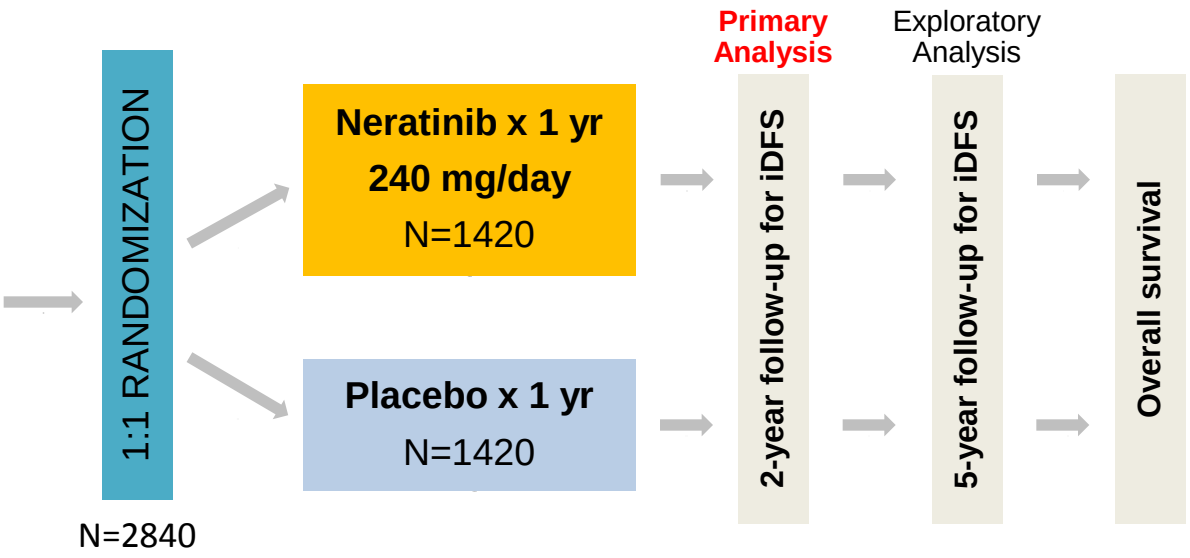
STUDY DESIGN
MAJOR AMENDMENTS

ExteNET – Study Design

Early Stage Breast Cancer
HER2+

Stratification Factors:

- Nodes 0, 1-3, vs 4+
- ER/PR status
- Concurrent vs sequential trastuzumab



- Primary endpoint: invasive Disease-Free Survival (iDFS)

Chan et al. Lancet Oncol 2016 Clinicaltrials.gov identifier: NCT00878709

ExteNET: Major Amendments

2009 Wyeth	Study initiated with planned 5-yr follow up in an event-driven analysis	Planned N: 3850 DFS events: 337
2010 Pfizer	Enriched enrollment and limited primary analysis to higher risk patients, excluding: • Stage 1 and node negative • Decreased time from trastuzumab (1 vs 2 years)	Planned N: 3300 DFS events: 375
2011 Pfizer	Recruitment stopped (business purposes), Shortened follow up from 5 to 2 years	Enrolled N: 2840
2014 Puma	• Analysis population reverted back to ITT • Applicant to reconsent ITT patients for 5-year follow up	Enrolled N: 2840

Impact of Major Amendments

- Multiple unplanned adaptations to Statistical Analysis Plan as a result of multiple amendments
  - changes in sample size and ITT population.
  - shift from event-driven to time-driven analysis.
  - missing data in follow up period.

- Per the Applicant, all changes were due to outside factors, not motivated by premature unblinding.

EFFICACY RESULTS

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)
Patients who did not complete study*	300 (21)	215 (15)

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

FDA STATISTICAL ANALYSIS

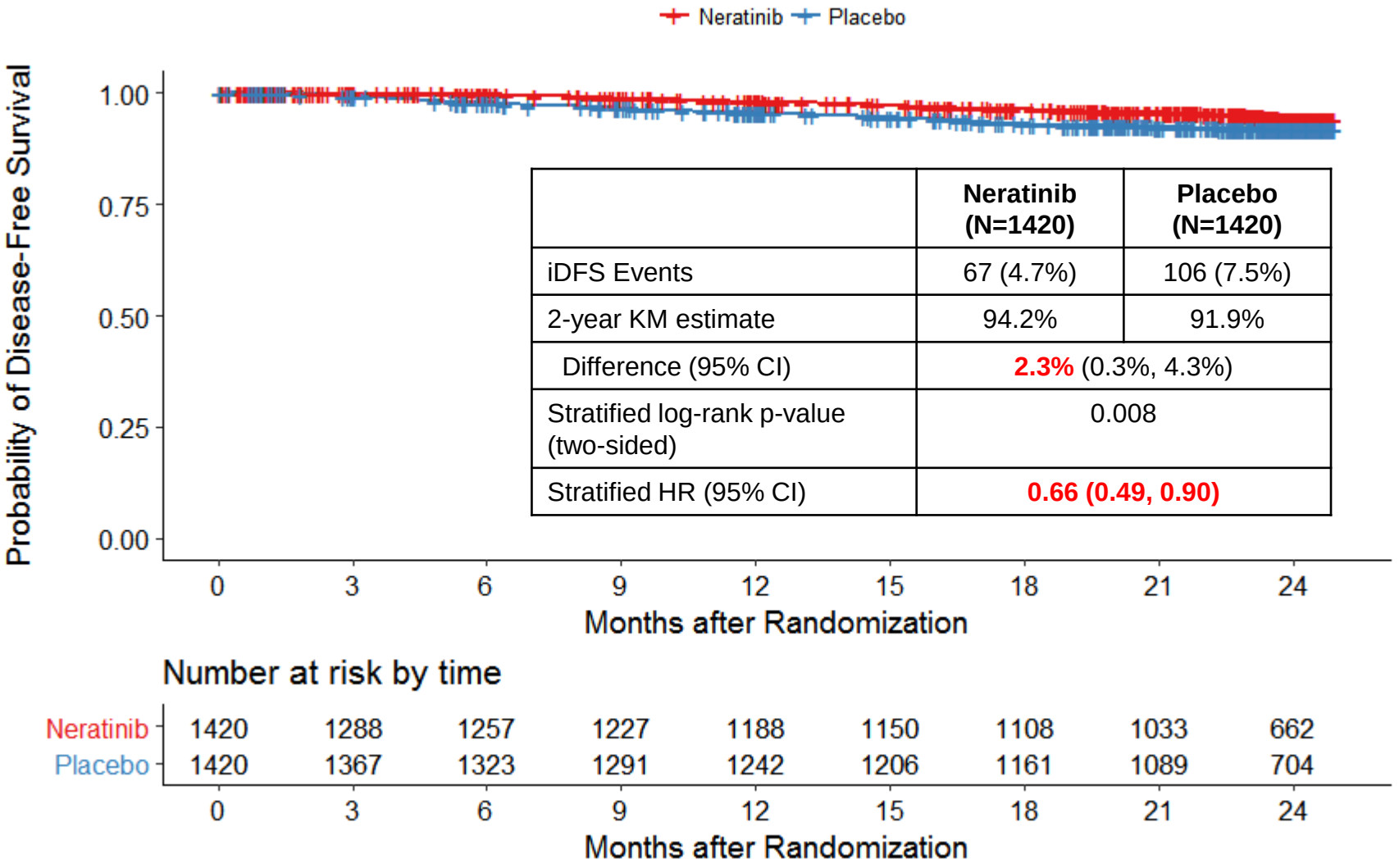
Outline

1. ExteNET Efficacy Results and Impact of Major Amendments.

2. FDA Sensitivity and Subgroup Analyses.
   - Simulation to address impact of early dropouts.
   - Tipping point analysis to address impact of missing data.
   - Exploratory subgroup analyses.

3. FDA Statistical Summary.

ExteNET Primary Efficacy Results (2-year follow-up)



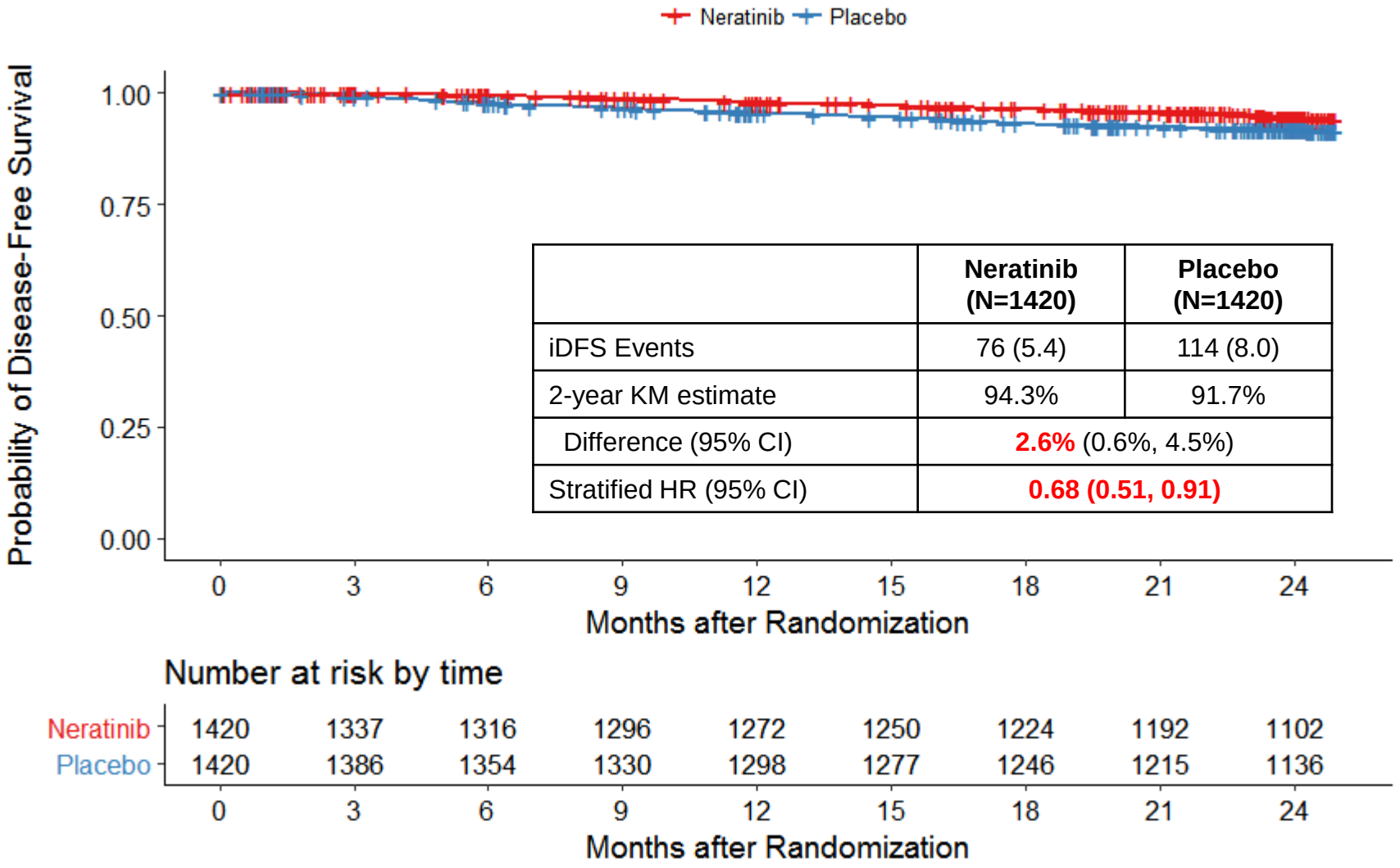
	Neratinib (N=1420)	Placebo (N=1420)
iDFS Events	67 (4.7%)	106 (7.5%)
2-year KM estimate	94.2%	91.9%
Difference (95% CI)	**2.3%** (0.3%, 4.3%)	
Stratified log-rank p-value (two-sided)	0.008	
Stratified HR (95% CI)	**0.66 (0.49, 0.90)**	

Statistical Impact of Major Amendments

- Study follow-up was truncated from 5-years to 2-years due to organizational changes.
- Event-driven analysis changed to time-driven.
- Reconsent process was implemented to collect extended follow-up from 2-years through 5-years.

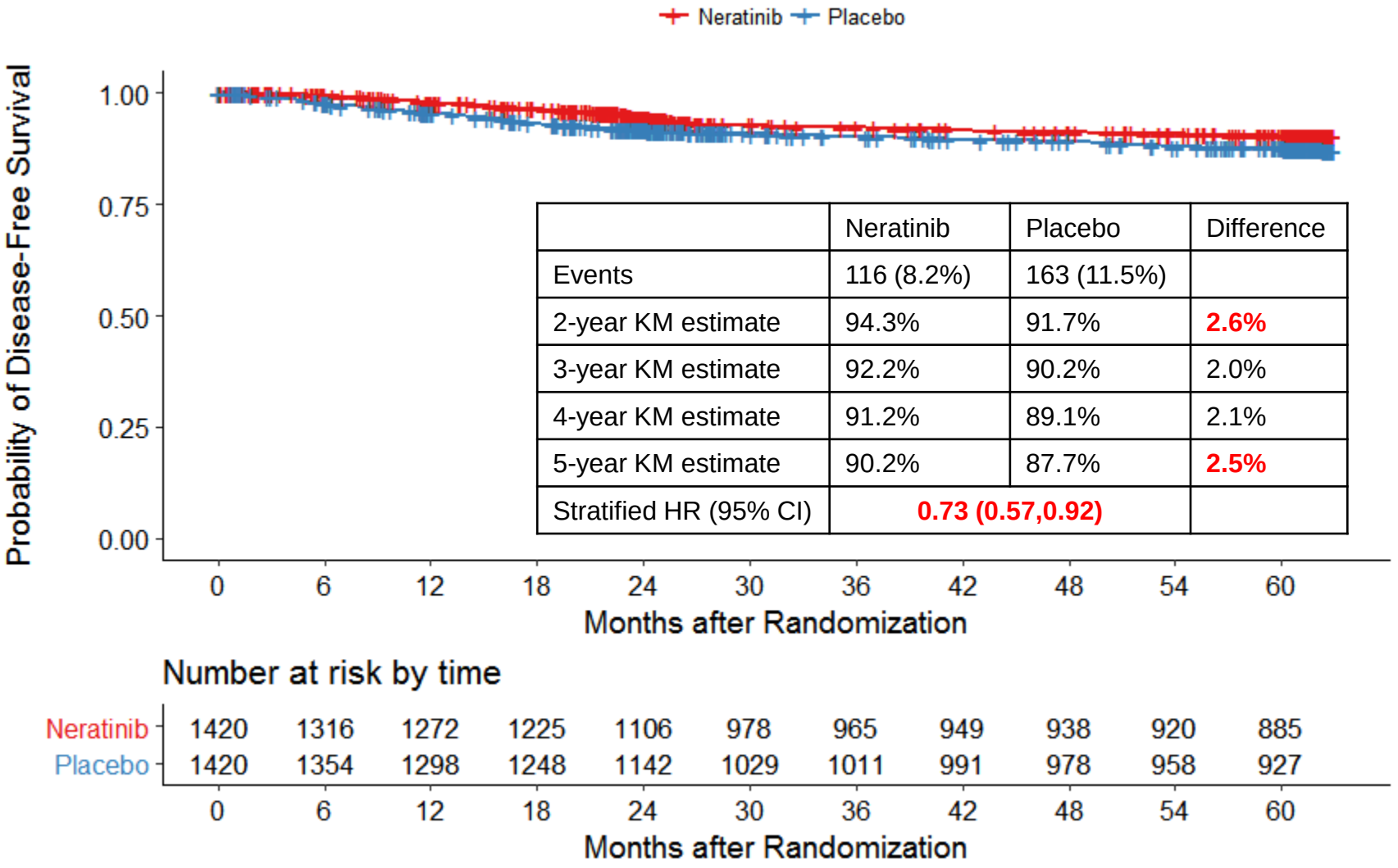
Per Applicant, all changes were due to external information. Unlikely to have impact on the Type I error rate.

Exploratory Updated 2-year Analysis (75% reconsented)



	Neratinib (N=1420)	Placebo (N=1420)
iDFS Events	76 (5.4)	114 (8.0)
2-year KM estimate	94.3%	91.7%
Difference (95% CI)	**2.6%** (0.6%, 4.5%)	
Stratified HR (95% CI)	**0.68 (0.51, 0.91)**	

Exploratory 5-year Analysis (75% reconsented)



	Neratinib	Placebo	Difference
Events	116 (8.2%)	163 (11.5%)	
2-year KM estimate	94.3%	91.7%	**2.6%**
3-year KM estimate	92.2%	90.2%	2.0%
4-year KM estimate	91.2%	89.1%	2.1%
5-year KM estimate	90.2%	87.7%	**2.5%**
Stratified HR (95% CI)	**0.73 (0.57,0.92)**		

ExteNET Efficacy Results

	Absolute Difference (Kaplan-Meier estimate), (95% CI)	Stratified HR (95% CI)
Primary Analysis (2-yr)	2.3% (0.3%, 4.3%)	0.66 (0.49, 0.90)
Updated* 2-yr Analysis	2.6% (0.6%, 4.5%)	0.68 (0.51, 0.91)
5-yr Extended* Analysis	2.5% (0%, 5.0%)	0.73 (0.57, 0.92)

* After reconsent of 75% of ITT patients

FDA Sensitivity & Subgroup Analyses

- Sensitivity analyses addressed the following two areas:
  1. Impact of Imbalance in Early Dropouts.
  2. Impact of Missing Data in Extended Follow-up.

- Exploratory Subgroup analyses for stratification factors were also conducted.

Impact of Early Dropouts

- Imbalance between arms in patients who dropped out early (censored at <3 months):
  - 130 neratinib vs. 44 placebo (primary analysis), 80 vs. 25 (updated 2-year analysis).
  - Most common reasons for neratinib dropouts: Adverse Events and Subject Request.
  - Censoring could be informative since patients dropped out due to treatment related toxicity.

A simulation with imputation was conducted to assess the impact of early dropouts.

Impact of Early Dropouts

FDA simulation with imputation from updated data:

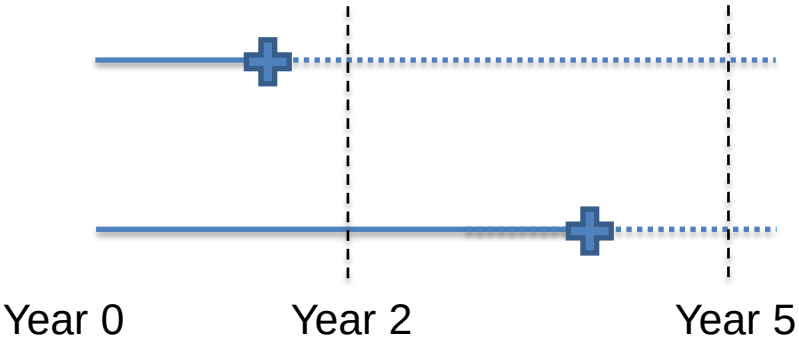
Simulation Results*		Primary Analysis
Average stratified HR (95% CI)	0.69 (0.52, 0.91)	0.66 (0.49, 0.90)
Average difference in 2-year iDFS rates (95% CI)	2.5% (0.6%, 4.5%)	2.3% (0.3%, 4.3%)

*Resampled from 50 updated neratinib patients for 80 remaining neratinib early dropout patients

Results after imputation were similar to results from the primary analysis.

Impact of Missing Data in Extended Follow-up

Last patient was randomized in 2011.
Missing data in **754** patients:



622 Patients not reconsented with censored iDFS times

132 Patients reconsented with iDFS times censored before 5-years

The number of events that occur among these patients could have an impact on results.

A Tipping Point Analysis was conducted to evaluate the impact of missing data.

Impact of Missing Data in Extended Follow-up

- A Tipping Point Analysis is a sensitivity analysis with imputation that searches for a tipping point that will reverse the study conclusion.

- Question: What rate of new events on the neratinib arm is needed to reverse significance (p-value>0.05)?

- Results: 8.4%, high compared to expected (5.1% based on patients reconsented) – potentially unlikely to occur.

- Missing data has minimal impact.

Exploratory Subgroup Analyses

Population	Number of Events		KM Estimate of iDFS at 24 months		Unstratified HR (95% CI)*
	Neratinib	Placebo	Neratinib	Placebo	
ER positive	29/816	63/815	95.6	91.5	0.49 (0.31, 0.75)
ER negative	38/604	43/605	92.2	92.4	0.93 (0.60, 1.43)
Nodal status: ≤ 3	38/999	58/1000	95.3	93.8	0.70 (0.46, 1.04)
Nodal status: > 3	29/421	48/420	91.4	87.3	0.62 (0.39, 0.97)
Concurrent prior trastuzumab	49/884	66/886	93.2	92.0	0.80 (0.55, 1.16)
Sequential prior trastuzumab	18/536	40/534	95.8	91.6	0.46 (0.26, 0.78)

* There was no multiplicity adjustment for these analyses. Results should be considered exploratory only.

FDA Statistical Summary

- Primary efficacy results from ExteNET showed a statistically significant treatment effect with neratinib with hazard ratio of 0.66.

- FDA analyses to address early dropouts and missing data showed an effect in favor of neratinib.

- The true magnitude of benefit remains uncertain:
  - Additional data causes the hazard ratio estimate to increase (0.68 to 0.73).

SAFETY RESULTS

Overview of Safety

- GI toxicities, especially diarrhea, are common and lead to frequent dose modifications and discontinuations.
- Prophylactic antidiarrheal regimens may improve tolerability (under investigation).
- In general, toxicities are non-serious and reversible.
- No known long-term sequelae.

ExteNET - Adverse Events

	Neratinib % (N=1,408)	Placebo % (N=1,408)
Any AE	99	88
≥ Grade 3 AE	50	13
≥ Grade 3 Diarrhea	40	1.6
Any Serious AE	7.3*	6.0
Deaths	0.1	0.1

* All but 2 SAEs were reversible: one patient with chronic herpes zoster opthalmicus and one patient with paresis in setting of glioblastoma.

Dose Modifications and Discontinuations

	Neratinib % (N=1,408)	Placebo % (N=1,408)
Interruptions	60%	44%
Reductions	37%	8%
Discontinuations		
due to AE	28%	5%
due to subject request	8%	5%

NCI-CTCAE: Diarrhea

Grade 1	Grade 2	Grade 3	Grade 4
Increase < 4 stools per day over baseline	Increase of 4-6 stools per day over baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization; limiting self care ADL	Life-threatening consequences; urgent intervention indicated

NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events

Cohorts in Study 6201

Cohort	N	Median duration of therapy (months)
Loperamide	137	10.6
Loperamide + Budesonide	64	5.1
Loperamide + Colestipol	26	1.7

Common AEs with and without Loperamide Prophylaxis

	ExteNET Neratinib Arm % (N=1,408)		Study 6201 Loperamide Cohort % (N=137)	
	All Grades	Grade 3	All Grades	Grade 3
Diarrhea	95	40	77	31
Nausea	43	2	56 ↑	1
Abdominal Pain	36	2	26	1
Fatigue	27	2	53 ↑	4
Constipation	8	0	56 ↑	0

Dose Modifications and Hospitalizations Due to Diarrhea

Diarrhea	ExteNET Neratinib Arm % (N=1,408)	Study 6201 Loperamide Cohort % (N=137)
Interruptions	34%	15%
Reductions	26%	7%
Discontinuations	17%	20%
Hospitalizations	1.4%	1.5%

Discontinuations

	ExteNET Neratinib Arm % (N=1,408)	Study 6201 Loperamide Cohort % (N=137)
Discontinuations		
Any AE	28%	37%
Subject request	8%	4%

Summary of Safety

- GI toxicities, especially diarrhea, are common and lead to frequent dose modifications and discontinuations.
- Prophylactic antidiarrheal regimens may improve tolerability (under investigation).
- In general, toxicities are non-serious and reversible.
- No known long-term sequelae.

Overall Summary

- FDA exploratory analyses to address missing data showed a consistent trend in favor of neratinib.
- The magnitude of benefit remains uncertain.
- Tolerability is a concern; however, toxicities are reversible.

Questions to the ODAC

- **Vote:**
  - Is the risk-benefit profile of neratinib sufficient to support treatment in the proposed indication?

As a single agent for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy.

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Back up Slides

PRO Analysis

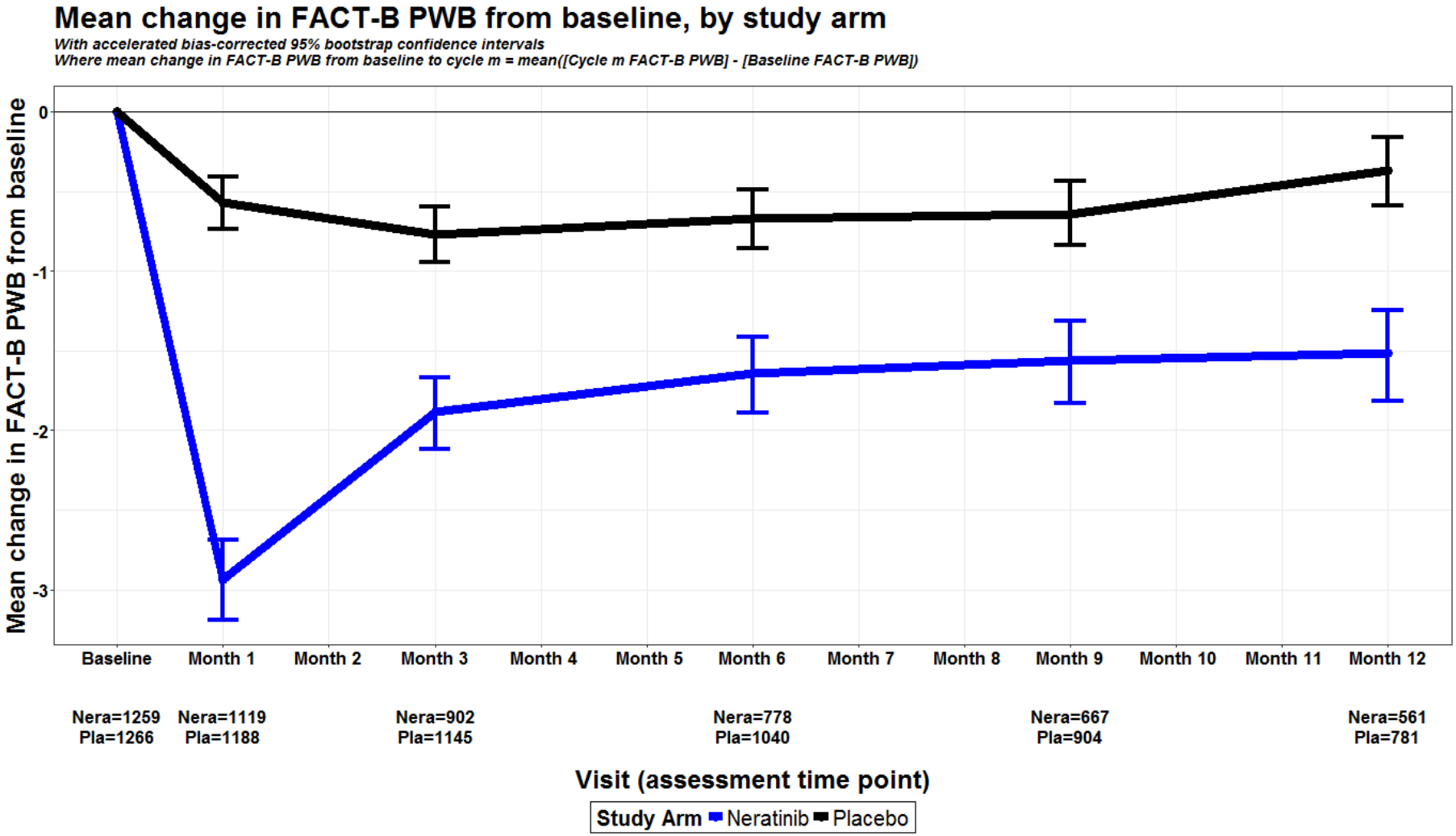
- EQ-5D and FACT-B.
- Baseline and q3 months (until amendment 9).
- Overall scores are difficult to interpret.
- None of the instruments captured diarrhea.

FACT-B Item Level Analysis

FACT-B (Version 4)

Below is a list of statements that other people with your illness have said are important. By **circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4


Mean change in FACT-B PWB from baseline, by study arm
With accelerated bias-corrected 95% bootstrap confidence intervals
Where mean change in FACT-B PWB from baseline to cycle m = mean([Cycle m FACT-B PWB] - [Baseline FACT-B PWB])
Mean change in FACT-B PWB from baseline
0
-1
-2
-3
Baseline
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6
Month 7
Month 8
Month 9
Month 10
Month 11
Month 12
Nera=1259 Pla=1266
Nera=1119 Pla=1188
Nera=902 Pla=1145
Nera=778 Pla=1040
Nera=667 Pla=904
Nera=561 Pla=781
Visit (assessment time point)
Study Arm Neratinib Placebo