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.

Natural History Post 1 Year of Trastuzumab

![Graph showing disease-free survival with and without Trastuzumab treatment]

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Events</th>
<th>HR (2 vs 1)</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years</td>
<td>1553</td>
<td>367</td>
<td>0.99</td>
<td>(0.85-1.14)</td>
<td>0.86</td>
</tr>
<tr>
<td>1 year</td>
<td>1552</td>
<td>367</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Adjuvant Trial

- ExteNET (n= 2840)

Primary endpoint: invasive Disease-free Survival (iDFS)

iDFS in HR-positive > HR-negative

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

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

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

<table>
<thead>
<tr>
<th>Study 3003</th>
<th>Neratinib (n=117)</th>
<th>Lapatinib + capecitabine (n=116)</th>
<th>PFS HR: 1.19 (0.89, 1.60)</th>
<th>4.53 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 3005</td>
<td>Neratinib + paclitaxel (n=242)</td>
<td>Trastuzumab + paclitaxel (n=237)</td>
<td>PFS HR: 1.015 (0.81, 1.27)</td>
<td>12.9 months</td>
</tr>
</tbody>
</table>

PFS: Progression-free Survival

Studies 3003 and 3005 did not meet their primary endpoint.
STUDY DESIGN
MAJOR AMENDMENTS
Early Stage Breast Cancer HER2+

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

1:1 RANDOMIZATION

Neratinib x 1 yr
240 mg/day
N=1420

Placebo x 1 yr
N=1420

N=2840

2-year follow-up for iDFS

5-year follow-up for iDFS

Overall survival

Primary Analysis

Exploratory Analysis

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

Chan et al. Lancet Oncol 2016    Clinicaltrials.gov identifier: NCT00878709
# ExteNET: Major Amendments

<table>
<thead>
<tr>
<th>Year</th>
<th>Company</th>
<th>Action Description</th>
<th>Planned N</th>
<th>DFS events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Wyeth</td>
<td>Study initiated with planned 5-yr follow up in an event-driven analysis</td>
<td>3850</td>
<td>337</td>
</tr>
</tbody>
</table>
| 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) | 3300 | 375 |
| 2011 | Pfizer | Recruitment stopped (business purposes), Shortened follow up from 5 to 2 years | Enrolled 2840 | |
| 2014 | Puma   | • Analysis population reverted back to ITT  
• Applicant to reconsent ITT patients for 5-year follow up | Enrolled 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

<table>
<thead>
<tr>
<th></th>
<th>Neratinib N= 1420 n (%)</th>
<th>Placebo N=1420 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Randomized</td>
<td>1420 (100)</td>
<td>1420 (100)</td>
</tr>
<tr>
<td>Patients Who Received at least 1 dose of study drug</td>
<td>1408 (99)</td>
<td>1408 (99)</td>
</tr>
<tr>
<td>Discontinued treatment due to AEs</td>
<td>372 (26)</td>
<td>72 (5)</td>
</tr>
<tr>
<td>Patients who did not complete study*</td>
<td>300 (21)</td>
<td>215 (15)</td>
</tr>
</tbody>
</table>

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

### iDFS Events

<table>
<thead>
<tr>
<th></th>
<th>Neratinib (N=1420)</th>
<th>Placebo (N=1420)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iDFS Events</td>
<td>67 (4.7%)</td>
<td>106 (7.5%)</td>
</tr>
<tr>
<td>2-year KM estimate</td>
<td>94.2%</td>
<td>91.9%</td>
</tr>
</tbody>
</table>

**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)

<table>
<thead>
<tr>
<th></th>
<th>Neratinib (N=1420)</th>
<th>Placebo (N=1420)</th>
</tr>
</thead>
<tbody>
<tr>
<td>iDFS Events</td>
<td>76 (5.4)</td>
<td>114 (8.0)</td>
</tr>
<tr>
<td>2-year KM estimate</td>
<td>94.3%</td>
<td>91.7%</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>2.6% (0.6%, 4.5%)</td>
<td></td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td></td>
<td>0.68 (0.51, 0.91)</td>
</tr>
</tbody>
</table>
Exploratory 5-year Analysis (75% reconsented)

<table>
<thead>
<tr>
<th>Events</th>
<th>Neratinib</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>116 (8.2%)</td>
<td>163 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>2-year KM estimate</td>
<td>94.3%</td>
<td>91.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>3-year KM estimate</td>
<td>92.2%</td>
<td>90.2%</td>
<td>2.0%</td>
</tr>
<tr>
<td>4-year KM estimate</td>
<td>91.2%</td>
<td>89.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>5-year KM estimate</td>
<td>90.2%</td>
<td>87.7%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td>0.73 (0.57,0.92)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# ExteNET Efficacy Results

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

*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:

<table>
<thead>
<tr>
<th>Simulation Results*</th>
<th>Primary Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average stratified HR (95% CI)</td>
<td>0.69 (0.52, 0.91)</td>
</tr>
<tr>
<td>Average difference in 2-year iDFS rates (95% CI)</td>
<td>2.5% (0.6%, 4.5%)</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of Events</th>
<th>KM Estimate of iDFS at 24 months</th>
<th>Unstratified HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neratinib</td>
<td>Placebo</td>
<td>Neratinib</td>
</tr>
<tr>
<td>ER positive</td>
<td>29/816</td>
<td>63/815</td>
<td>95.6</td>
</tr>
<tr>
<td>ER negative</td>
<td>38/604</td>
<td>43/605</td>
<td>92.2</td>
</tr>
<tr>
<td>Nodal status: ≤ 3</td>
<td>38/999</td>
<td>58/1000</td>
<td>95.3</td>
</tr>
<tr>
<td>Nodal status: &gt; 3</td>
<td>29/421</td>
<td>48/420</td>
<td>91.4</td>
</tr>
<tr>
<td>Concurrent prior trastuzumab</td>
<td>49/884</td>
<td>66/886</td>
<td>93.2</td>
</tr>
<tr>
<td>Sequential prior trastuzumab</td>
<td>18/536</td>
<td>40/534</td>
<td>95.8</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Neratinib % (N=1,408)</th>
<th>Placebo % (N=1,408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>99</td>
<td>88</td>
</tr>
<tr>
<td>≥ Grade 3 AE</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>≥ Grade 3 Diarrhea</td>
<td>40</td>
<td>1.6</td>
</tr>
<tr>
<td>Any Serious AE</td>
<td>7.3*</td>
<td>6.0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*All but 2 SAEs were reversible: one patient with chronic herpes zoster ophthalmicus and one patient with paresis in setting of glioblastoma.*
# Dose Modifications and Discontinuations

<table>
<thead>
<tr>
<th></th>
<th>Neratinib % (N=1,408)</th>
<th>Placebo % (N=1,408)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interruptions</strong></td>
<td>60%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Reductions</strong></td>
<td>37%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Discontinuations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>due to AE</td>
<td>28%</td>
<td>5%</td>
</tr>
<tr>
<td>due to subject request</td>
<td>8%</td>
<td>5%</td>
</tr>
</tbody>
</table>
## NCI-CTCAE: Diarrhea

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase &lt; 4 stools per day over baseline</td>
<td>Increase of 4-6 stools per day over baseline</td>
<td>Increase of $\geq 7$ stools per day over baseline; incontinence; hospitalization; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>

NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events
## Cohorts in Study 6201

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Median duration of therapy (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide</td>
<td>137</td>
<td>10.6</td>
</tr>
<tr>
<td>Loperamide + Budesonide</td>
<td>64</td>
<td>5.1</td>
</tr>
<tr>
<td>Loperamide + Colestipol</td>
<td>26</td>
<td>1.7</td>
</tr>
</tbody>
</table>
### Common AEs with and without Loperamide Prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>ExteNET Neratinib Arm % (N=1,408)</th>
<th>Study 6201 Loperamide Cohort % (N=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>Nausea</td>
<td>43</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>36</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note: The red arrow indicates an increase in Grade 3 events.*
# Dose Modifications and Hospitalizations Due to Diarrhea

<table>
<thead>
<tr>
<th>Diarrhea</th>
<th>ExteNET Neratinib Arm % (N=1,408)</th>
<th>Study 6201 Loperamide Cohort % (N=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interruptions</td>
<td>34%</td>
<td>15%</td>
</tr>
<tr>
<td>Reductions</td>
<td>26%</td>
<td>7%</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>17%</td>
<td>20%</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>1.4%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>
## Discontinuations

<table>
<thead>
<tr>
<th>Discontinuations</th>
<th>ExteNET Neratinib Arm % (N=1,408)</th>
<th>Study 6201 Loperamide Cohort % (N=137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>28%</td>
<td>37%</td>
</tr>
<tr>
<td>Subject request</td>
<td>8%</td>
<td>4%</td>
</tr>
</tbody>
</table>
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.
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.

<table>
<thead>
<tr>
<th>PHYSICAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Because of my physical condition, I have trouble</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>meeting the needs of my family</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
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Mean change in FACT-B PWB from baseline, by study arm

With accelerated bias-corrected 95% bootstrap confidence intervals

The figure shows the mean change in FACT-B PWB from baseline to cycle $m$ for the study arms. The mean change is calculated as $\text{mean}(\text{Cycle } m \text{ FACT-B PWB}) - \text{Baseline FACT-B PWB}$. The graph plots the mean change for each study arm over the months from Baseline to Month 12, with error bars indicating the 95% confidence intervals.

- **Study Arm**: Neratinib and Placebo
- **Participants**:
  - Baseline: 1259 (Nera), 1266 (Pla)
  - Month 1: 1219 (Nera), 1286 (Pla)
  - Month 2: 1192 (Nera), 1188 (Pla)
  - Month 3: 902 (Nera), 1145 (Pla)
  - Month 4: 778 (Nera), 1140 (Pla)
  - Month 5: 787 (Nera), 1040 (Pla)
  - Month 6: 567 (Nera), 904 (Pla)
  - Month 7: 561 (Nera), 781 (Pla)

**Visit (assessment time point)**

- Study Arm: Neratinib, Placebo