NSABP FB-10: Phase IB Dose-Escalation Study Evaluating the Combination of Trastuzumab Emtansine (T-DM1) with Neratinib in Women with Metastatic HER2-Positive Breast Cancer

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The following authors declare the following potential conflicts of interest:

- **Jame Abraham**: Genentech (Speaker); Pfizer (Speaker)
- **Shannon L. Puhalla**: Abbvie, Pfizer, Lilly, Novartis, Incyte, Covance-Bayer, Eisai (Grant/Research support); Abbvie, Medimmune, Alldex (Consultant); Alldex (Data Monitoring Board Member)
- **Marc E. Buyse**: IDDI (Employee and stockholder)

All other authors declare no other potential conflicts of interest.

There will be no discussion of off-label use and/or investigational use in this presentation.
Trastuzumab Emtansine (T-DM1)

- T-DM1 is a conjugated antibody. Trastuzumab is armed to deliver the maytansinoid antimicrotubule agent, DM1, to antigen-expressing HER2-positive cells.
- DM-1, a potent cytotoxic agent, binds to microtubules similar to vinca alkaloids.

Neratinib: Tyrosine Kinase Inhibitor

- Neratinib, an oral TKI, irreversibly inhibits pan-ERBB receptor tyrosine kinases
- Irreversible binding due to covalent interaction between neratinib and cysteine residue within ATP binding site

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Clinical Background

- **EMILIA**, a phase III randomized trial of T-DM1 v capecitabine plus lapatinib (C-L) in MBC pts previously treated in first-line with trastuzumab plus taxane
  - PFS: T-DM1 v C-L was 9.4 mo v 6.4 mo (p<0.001)
  - ORR: T-DM1 v C-L was 43.6% v 30.8 % (p=0.001)

- **T-DM1** after trastuzumab and pertuzumab (retrospective study)
  - 17.9% tumor response rate

- Current preferred regimen in first-line metastatic BC
  - Pertuzumab-naïve pts: trastuzumab/pertuzumab/taxane
  - Pertuzumab-exposed pts: T-DM1

- Neratinib in phase II trial had single-agent activity in trastuzumab-resistant pts
  - PFS: 5.5 mo
  - ORR: 24%

NSABP FB-10 Overview

Metastatic HER2-Positive Breast Cancer with Prior Trastuzumab and Pertuzumab Treatment

Study Entry

Treatment Regimen for All Patients
T-DM1 3.6 mg/kg i.v. Day 1 every 21 days*

Neratinib PO daily beginning on Day 1 of T-DM1 and continuing until disease progression

*T-DM1 Dose level 1
Dose de-escalation will proceed on the basis of dose-limiting toxicity during Cycle 1.

Neratinib Dose Escalation Levels
- Dose level 1: 120 mg/day
- Dose level 2: 160 mg/day
- Dose level 3: 200 mg/day
- Dose level 4: 240 mg/day

Loperamide 4mg q6h initiated with first dose of neratinib
Primary Aim for Phase Ib

Aim: To determine the safety and tolerability of T-DM1 and neratinib

Endpoint: Recommended phase II dose (RP2D) of T-DM1 and neratinib that can be administered in combination
Secondary Aims

- Objective response rate (ORR)
- Progression-free survival (PFS)
- Clinical benefit rate (CR, PR, and SD)
- Toxicity
- Correlative studies
Key Eligibility

• Confirmed diagnosis of invasive adenocarcinoma of the breast
• Documentation of measurable disease
• Breast cancer determined to be HER2-positive
• Must have had anti-HER2-based therapy with trastuzumab and pertuzumab as neoadjuvant, adjuvant, or in first-line metastatic disease
Key Ineligibility

• Previous therapy with T-DM1 or any HER2 TKI
• Persistent $\geq$ grade 2 diarrhea
• Symptomatic brain metastases
• Active hepatitis
• Conditions significantly affecting GI function
### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=22</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>48.3</td>
</tr>
<tr>
<td>Range</td>
<td>34-67</td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>ER- or PR-positive</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
</tr>
<tr>
<td>Trastuzumab + pertuzumab</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>13</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic</td>
<td>6</td>
</tr>
<tr>
<td>Sites of metastatic disease</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>7</td>
</tr>
<tr>
<td>Visceral</td>
<td>14</td>
</tr>
<tr>
<td>Skin/lymph node</td>
<td>13</td>
</tr>
<tr>
<td>Bone</td>
<td>9</td>
</tr>
</tbody>
</table>
Dose-Limiting Toxicities (DLTs) by Dose of Neratinib

<table>
<thead>
<tr>
<th>Cohort, mg/d of neratinib</th>
<th>No. of pts</th>
<th>No. of DLTs</th>
<th>Grade of diarrhea / dehydration (No. of pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>6</td>
<td>1</td>
<td>3 (1)</td>
</tr>
<tr>
<td>160</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>8</td>
<td>3</td>
<td>2 (1) / 3 (1) / 3 (2)</td>
</tr>
<tr>
<td>240</td>
<td>3</td>
<td>2</td>
<td>2 (1) / 3 (1) / 3 (1)</td>
</tr>
</tbody>
</table>
# Treatment-related Adverse Events (All doses)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Grade</th>
<th>Gr 1 #Pts (%)</th>
<th>Gr 2 #Pts (%)</th>
<th>Gr 3 #Pts (%)</th>
<th>Gr 4 #Pts (%)</th>
<th>Gr 5 #Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>85%</td>
<td>3 (14)</td>
<td>11 (52)</td>
<td>4 (19%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>66%</td>
<td>4 (19)</td>
<td>7 (33)</td>
<td>3 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>39%</td>
<td>2 (10)</td>
<td>6 (29)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39%</td>
<td>1 (5)</td>
<td>6 (29)</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47%</td>
<td>7 (33)</td>
<td>3 (14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>49%</td>
<td>6 (30)</td>
<td>1 (5)</td>
<td>3 (14)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>15%</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST elevation</td>
<td>74%</td>
<td>11 (58)</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bilirubin elevation</td>
<td>20%</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29%</td>
<td>1 (5)</td>
<td>3 (14)</td>
<td>2 (10)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
% Change in Size of Target Lesions

5 non-evaluable pts:
Withdrew consent: 1; DLTs: 4
FC-7 and FB-10: Neratinib Trough Concentration at Steady-state, Day 1 of Cycle 2

- Trough levels are overlapping at all study doses
- Need more complete PK data to correlate toxicity and response (peak concentration and AUC)
Progression in skin, contralateral breast mass, lung, and multiple liver lesions

Neratinib 120 mg
Before treatment | Neratinib 120 mg | After 2 cycles of treatment
Conclusions

- Diarrhea was the major dose-limiting toxicity in this dose-escalation trial
- In patients with prior trastuzumab and pertuzumab, activity was seen across all dose-levels of neratinib
  - ORR (CR/PR): 9 of 16 (56%)
- Additional patients are being accrued at 160 mg/d of neratinib to define the RP2D
Future Directions

• A Phase II trial will be conducted at the RP2D and will evaluate PK more fully to determine if any correlation with response and toxicity.

• Phase II study will evaluate anti-diarrheal regimen with loperamide and budesonide, which has been shown to decrease occurrence of grade 3 diarrhea*.
  – Patients experiencing diarrhea on pertuzumab appear to be at high risk for diarrhea on neratinib and may benefit from more intense anti-diarrheal management.

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