Clinical Background

- EMLALA: a phase III randomized trial of T-DM1 vs capcitabine plus lapatinib (C-L) MBC pts previously treated in first-line with trastuzumab plus taxane
  - DFS: T-DM1 vs C-L was 9.1 mos vs 6.4 mos (p=0.001)
  - OS: T-DM1 vs C-L was 38.3 mos vs 26.9 mos (p=0.001)
- T-DM1 after trastuzumab and pertuzumab (retrospective study)
  - Verma S, et al. NEJM 2012; 367:1783

Secondary Aims

- Objective response rate (ORR)
- Toxicity
- Correlative studies

Primary Aim

- In patients with prior trastuzumab and pertuzumab, activity was seen
- Diarrhea was the dose-limiting toxicity in this dose-escalation trial but manageable with loperamide prophylaxis
- In patients with prior trastuzumab and pertuzumab, activity was seen across all dose-levels of neratinib
  - ORR (CRPR): 12 of 20 (60%)

Future Directions

- A Phase II trial is being conducted at the RP2D and will evaluate PK more fully to determine if any correlation with response and toxicity
- Anti-diarrheal regimens with loperamides and budesonide, which has been shown to decrease occurrence of grade 3 diarrhea*, will be evaluated
- HER2 amplification will be determined on tissue collected at study entry
  - FUNDING SUPPORT – Puma Biotechnology, Inc.

**NCT02236000**

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. 27</th>
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<tbody>
<tr>
<td>Age (Range)</td>
<td>23-69</td>
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<tr>
<td>ER- or PR-positive</td>
<td>14 (52)</td>
</tr>
<tr>
<td>HER2 I/II/III</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Sites of metastatic disease</td>
<td>14 (52)</td>
</tr>
</tbody>
</table>

**Characteristic**

- Confirmed diagnosis of invasive adenocarcinoma of the breast
- Documentation of measurable disease
- Breast cancer determined to be HER2-positive
- Most have had anti-HER2-directed therapy with trastuzumab and pertuzumab as neoadjuvant, adjuvant, or in first-line metastatic disease
- Prior therapy with T-DM1 or any HER2 TKI
- Persistent grade 2 diarrhea
- Symptomatic brain metastases
- Active hepatitis
- Conditions significantly affecting GI function

**Key Ineligibility**

- Chronic obstructive pulmonary disease
- Ongoing use of minocycline
- Oral contraceptive use
- Testicular surgery
- Active hepatitis
- Continuous use of corticosteroids
- Persistent > grade 2 diarrhea
- Previous therapy with T-DM1 or any HER2 TKI
- Persistent > grade 2 diarrhea
- Metastatic HER2-Positive Breast Cancer with Prior Trastuzumab and Pertuzumab Treatment

**Study Entry**

- ER- or PR-positive
- HER2 I/II/III
- Sites of metastatic disease
- Brain: 14 (52)
- Single organ: 6
- Multiple organs: 21

**Neratinib Concentration versus Time Over 24 Hours**

**Neratinib Trough Concentrations Cycle 2 Day 1 at 24 h after Dose of Neratinib**

**Evaluate Patients by Dose-level (RECIST)**

**ORR, CRPR: 12 of 20 (60%)**

**Key Eligibility**

- Confirmed diagnosis of invasive adenocarcinoma of the breast
- Documentation of measurable disease
- Breast cancer determined to be HER2-positive
- Most have had anti-HER2-directed therapy with trastuzumab and pertuzumab as neoadjuvant, adjuvant, or in first-line metastatic disease
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**Neratinib Concentration**

- Day 1 at 24 h after Dose of Neratinib

**Dose-Limiting Toxicities (DLTs) by Dose of Neratinib**

- Oral TX: Ad withdrawn + on treatment

**Future Directions**

- A Phase II trial is being conducted at the RP2D and will evaluate PK more fully to determine if any correlation with response and toxicity
- Anti-diarrheal regimens with loperamides and budesonide, which has been shown to decrease occurrence of grade 3 diarrhea*, will be evaluated
- HER2 amplification will be determined on tissue collected at study entry
- PDX models will be developed to further assess single agent and combination drug activity

**FUNDING SUPPORT – Puma Biotechnology, Inc.**

*Baranec C, et al. AACR 2014 Abstract #6110*