

# 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

Jame Abraham,<sup>1</sup> Shannon L. Puhalla,<sup>2</sup> William M. Sikov,<sup>3</sup> Alberto J. Montero,<sup>1</sup> Jan H. Beumer,<sup>2</sup> Marc E. Buyse,<sup>4</sup> Laura M. Adamson,<sup>5</sup> Ashok Srinivasan,<sup>5</sup> Katherine L. Pogue-Geile,<sup>5</sup> Samuel A. Jacobs<sup>5</sup>

<sup>1</sup>NSABP, and The Cleveland Clinic, Cleveland, OH; <sup>2</sup>NSABP, and The University of Pittsburgh Cancer Institute, Pittsburgh, PA; <sup>3</sup>NSABP, and The Women and Infants Hospital of Rhode Island, Providence, RI; <sup>4</sup>International Drug Development Institute (IDDI), Louvain-la-Neuve, Belgium; <sup>5</sup>NSABP, Pittsburgh, PA



Supported by Puma Biotechnology, Inc.

Abstr CT013

**AACR 2017**

## **Disclosure Information**

**The following authors declare the following potential conflicts of interest:**

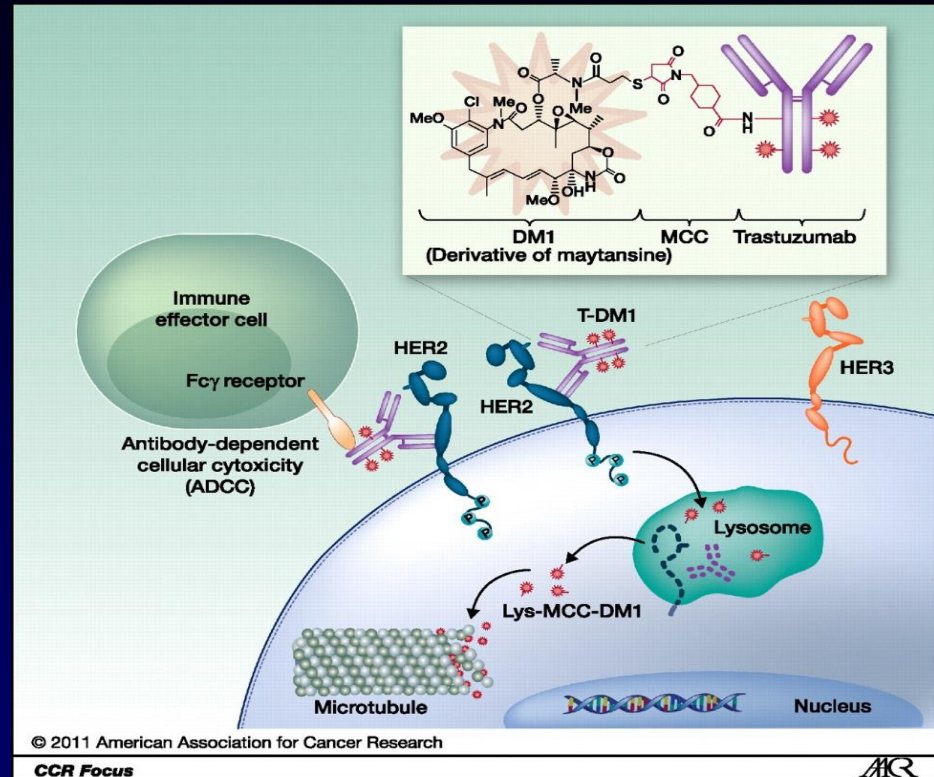
- **Jame Abraham:** Genentech (Speaker); Pfizer (Speaker)
- **Shannon L. Puhalla:** Abbvie, Pfizer, Lilly, Novartis, Incyte, Covance-Bayer, Eisai (Grant/Research support); Abbvie, Medimmune, Alldex (Consultant); Alldex (Data Monitoring Board Member)
- **Marc E. Buyse:** IDDI (Employee and stockholder)

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.

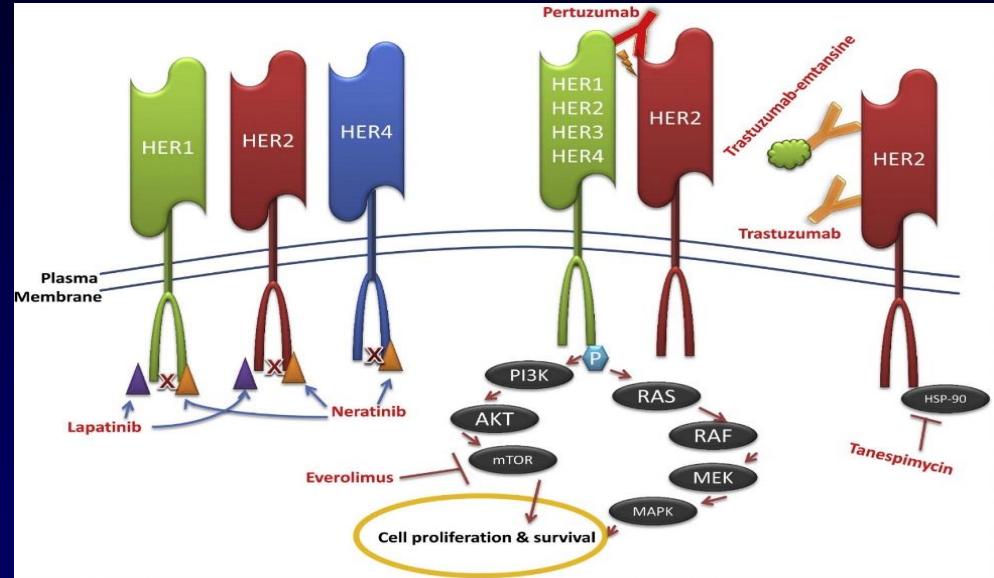
# Trastuzumab Emtansine (T-DM1)

- 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



# 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%**

Verma S, et al. *NEJM* 2012; 367:1783

Krop I, et al. *Lancet Oncol* 2014; 15:689

Burstein H, et al. *J Clin Oncol* 2010; 28:1301

Dzimitrowicz H, et al. *J Clin Oncol* 2016; 34:3511

# 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

Characteristic	N=22
Age	
Mean	48.3
Range	34-67
Performance status	
0	16
1	6
ER- or PR-positive	
Yes	12
No	10
Trastuzumab + pertuzumab	
Neoadjuvant	13
Adjuvant	3
Metastatic	6
Sites of metastatic disease	
Brain	7
Visceral	14
Skin/lymph node	13
Bone	9

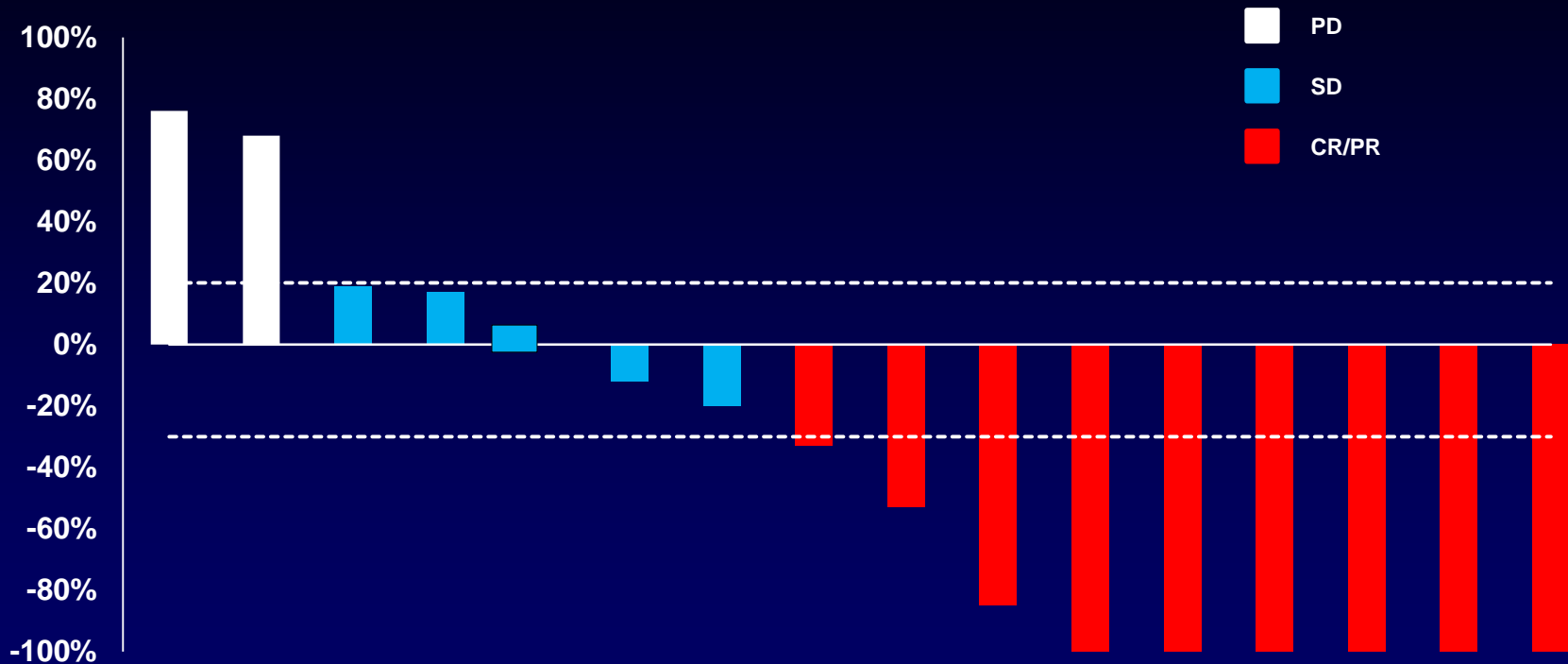
# Dose-Limiting Toxicities (DLTs) by Dose of Neratinib

Cohort, mg/d of neratinib	No. of pts	No. of DLTs	Grade of diarrhea / dehydration (No. of pts)
120	6	1	3 (1)
160	4	0	—
200	8	3	2 (1) / 3 (1) 3 (2)
240	3	2	2 (1) / 3 (1) 3 (1)

# Treatment-related Adverse Events ( All doses)

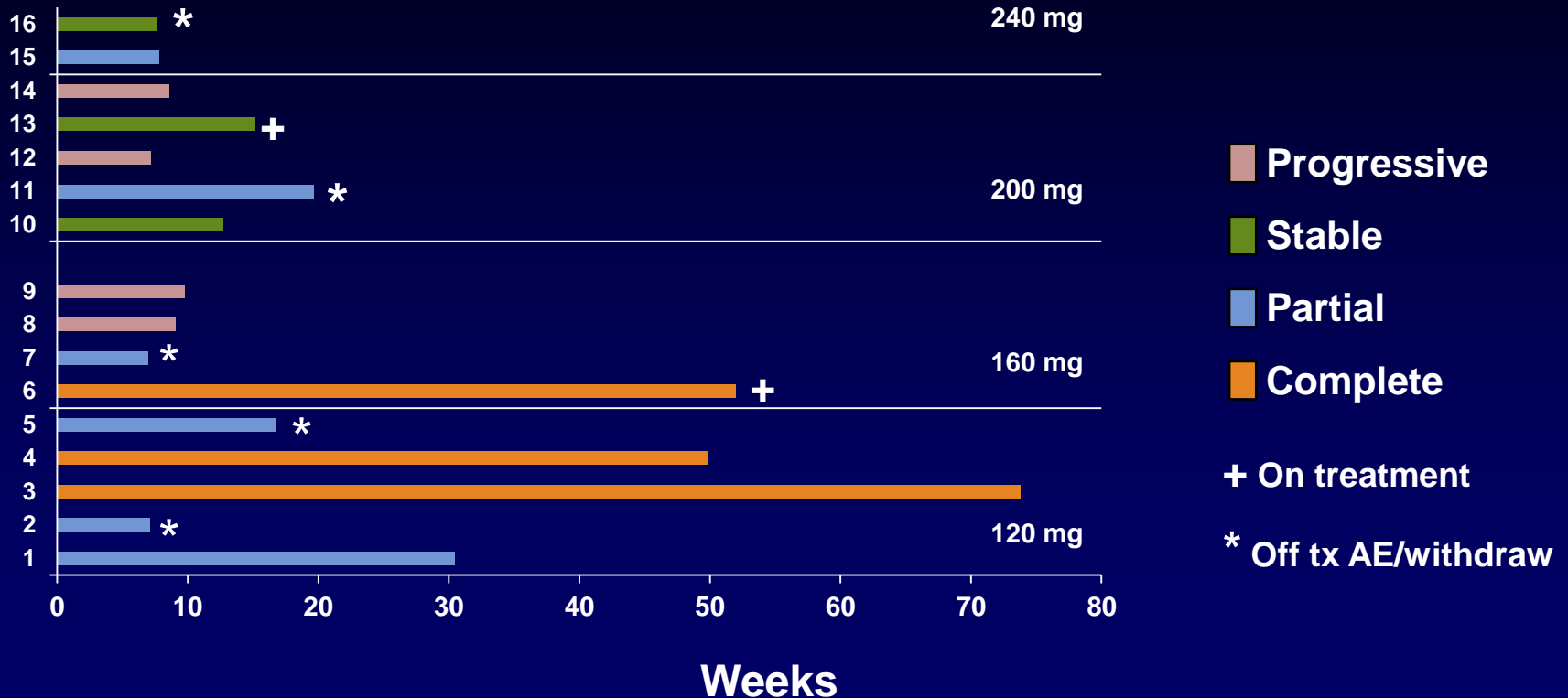
N=21						
Adverse Event	Any Grade	Gr 1 #Pts (%)	Gr 2 #Pts (%)	Gr 3 #Pts (%)	Gr 4 #Pts (%)	Gr 5 #Pts (%)
Diarrhea	85%	3 (14)	11 (52)	4(19%)	0	0
Nausea	66%	4 (19)	7 (33)	3 (14)	0	0
Anorexia	39%	2 (10)	6 (29)	0	0	0
Fatigue	39%	1 (5)	6 (29)	1 (5)	0	0
Vomiting	47%	7 (33)	3 (14)	0	0	0
Thrombocytopenia	49%	6 (30)	1 (5)	3 (14)	0	0
Neutropenia	15%	1 (5)	1 (5)	1 (5)	0	0
AST elevation	74%	11 (58)	2 (11)	1 (5)	0	0
Bilirubin elevation	20%	2 (10)	1 (5)	0	0	0
Hypertension	29%	1 (5)	3 (14)	2 (10)	0	0

# % Change in Size of Target Lesions



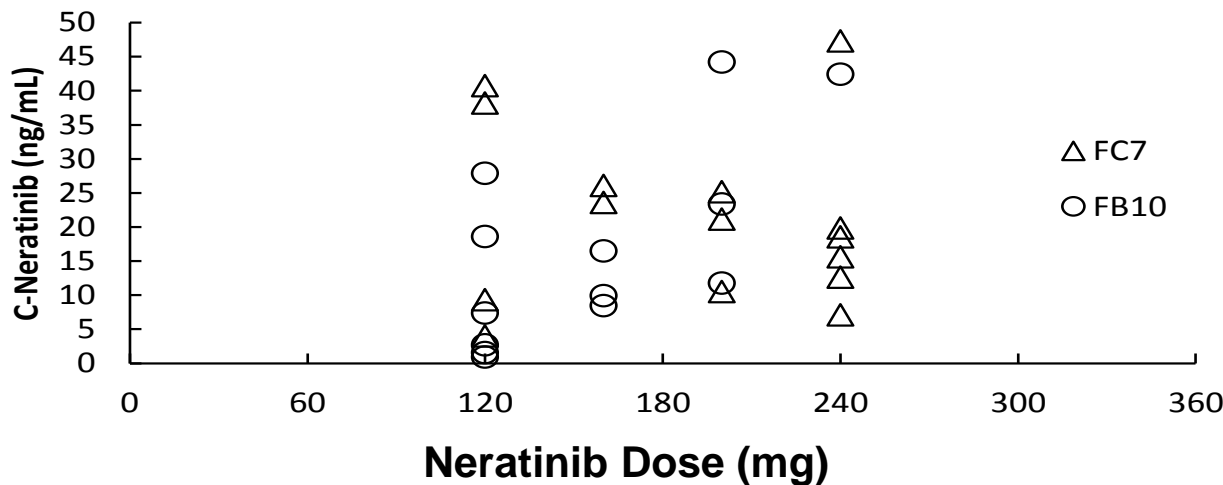
5 non-evaluable pts:  
Withdrew consent: 1; DLTs: 4

# Evaluable Patients by Dose-level ( RECIST)



# FC-7 and FB-10: Neratinib Trough Concentration at Steady-state, Day 1 of Cycle 2

Corrected [neratinib] vs Dose



- 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





L R

-1097.30



L R

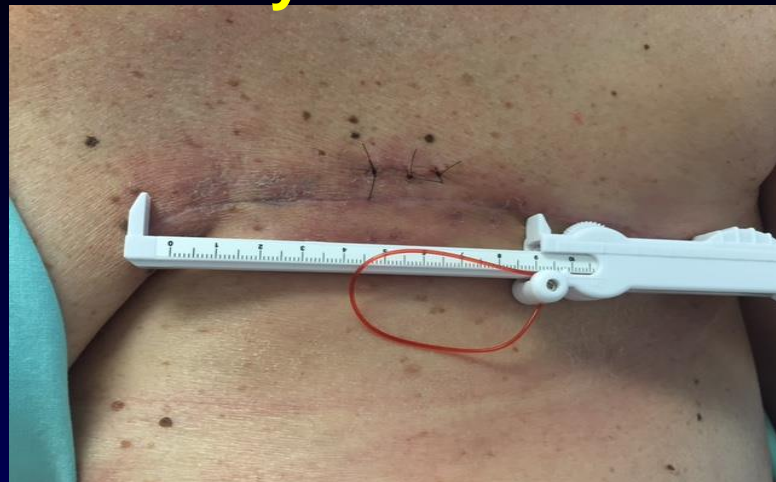
-1028.30



**Baseline**



**After 1 Cycle of Treatment**



**After 3 Cycles of Treatment**



**Neratinib 160 mg**

# 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**

\*Barcenas C et al. SABCS #P2-11-03, 2016

# Acknowledgements

- We thank our patients and their family members
- Our outstanding clinical trial team
- NSABP study team
- Puma Biotechnology, Inc.