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[1,2], Shannon Puhalla[1,3], William M Sikov[1,4], Alberto J Montero[1,2], Mohamad Adham Salkeni[1,5], Wajeeha Razaq[1,6], Jan H Beumer[1,7], Brian Kiesel[1,7], Marc E Buyse[8], Laura M Adamson[1], Ashok Srinivasan[1], Katherine L Pogue-Geile[1,9], Carmen J Allegra[10], Samuel A Jacobs[1,3]

[1]NSABP Foundation, Pittsburgh, PA; [2]Cleveland Clinic, Cleveland, OH; [3]University of Pittsburgh Medical Center, Pittsburgh, PA; [4]Women and Infants Hospital of Rhode Island, Providence, RI; [5]West Virginia University, Morgantown, WV; [6]Peggy and Charles Stephenson Oklahoma Cancer Center, Oklahoma City, OK; [7]University of Pittsburgh Cancer Institute, Pittsburgh, PA; [8]IDDI, Inc., San Francisco, CA; [9]NRG Oncology, Pittsburgh, PA; [10]University of Florida, Gainesville, FL

Clinical Background

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

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Study Entry

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Treatment Regimen for All Patients

T-DM1 3.6 mg/kg i.v. Day 1 every 21 days
– Dose Level 1: Dose de-escalation allowed for toxicity

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

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

NCT02236000

Aims

Primary Aim

- Aim: To determine the safety and tolerability of T-DM1 + neratinib
- Endpoint: Recommended phase II dose (RP2D) of T-DM1 + 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 ≥ grade 2 diarrhea
- Symptomatic brain metastases
- Active hepatitis
- Conditions significantly affecting GI function

Patient Characteristics

Characteristic	N=27
Age	
Mean	48.3
Range	23-69
Performance status	
0	20
1	7
ER- or PR-positive	
Yes	14
No	13
Trastuzumab + pertuzumab	
Neoadjuvant/Adjuvant	14
Metastatic	13
Sites of metastatic disease	
Brain yes/no	7/20
Single organ	6
Multiple organs	21

Dose-Limiting Toxicities (DLTs) by Dose of Neratinib

Cohort, mg/g of neratinib	No. of pts	No. of DLTs*
120	6	1
160	10	0
200	8	3
240	3	2

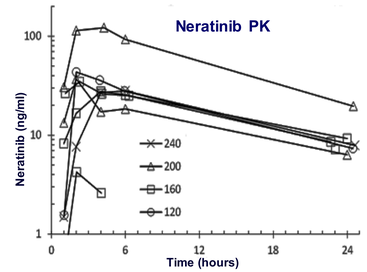
* Grade 3 diarrhea +/- dehydration

Treatment-related Adverse Events (All Doses)

N=27				
Adverse Event	Any Grade* #Pts (%)	Gr 1 #Pts (%)	Gr 2 #Pts (%)	Gr 3 #Pts (%)
Diarrhea	25 (93)	5 (19)	14 (52)	6 (22)
Nausea	18 (67)	5 (19)	10 (37)	3 (11)
Anorexia	13 (48)	3 (11)	10 (37)	0
Fatigue	14 (52)	3 (11)	9 (33)	2 (7)
Vomiting	13 (48)	9 (33)	4 (15)	0
Thrombocytopenia	14 (52)	9 (33)	1 (4)	4 (15)
Neutropenia	4 (15)	0	3 (11)	1 (4)
ALT elevation	13 (48)	10 (37)	2 (7)	1 (4)
Bilirubin elevation	1 (4)	0	1 (4)	0
Hypertension	6 (22)	1 (4)	2 (7)	3 (11)

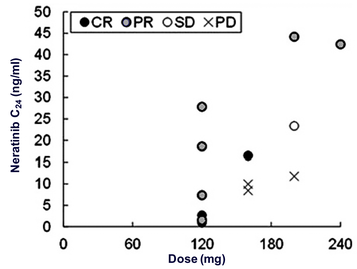
*No grades 4 or 5

Neratinib Concentration *versus* Time Over 24 Hours

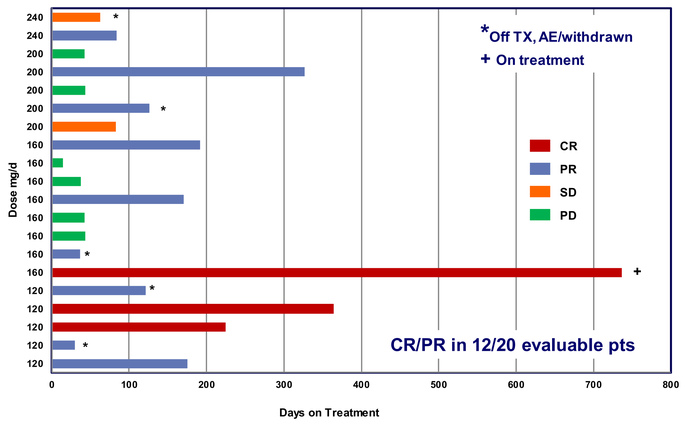


Outlier at 200 mg/day developed a DLT
Outlier at 160mg/day was taking pantoprazole

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



Evaluable Patients by Dose-level (RECIST)



CONCLUSIONS

- The combination of neratinib with T-DM1 was well tolerated at the RP2D of neratinib at 160 mg/day
- 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 (CR/PR): 12 of 20 (60%)
- Peak and trough concentrations of neratinib did not show correlation with dose

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 regimen with loperamide 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 access single agent and combination drug activity

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

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