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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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.

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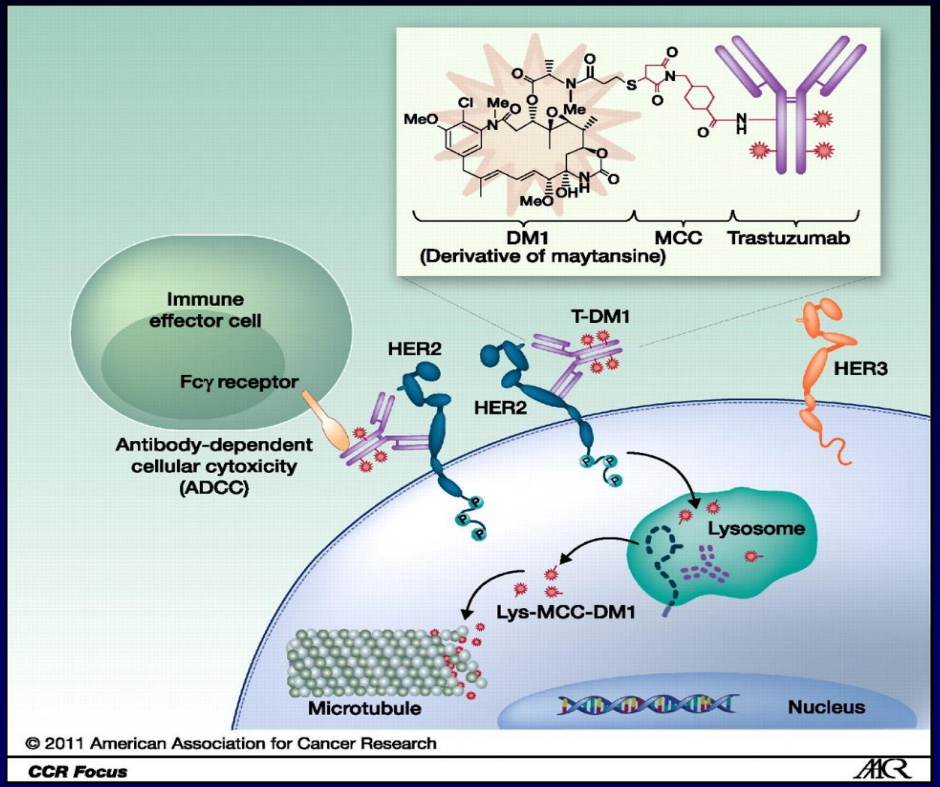
Trastuzumab Emtansine (T-DM1)

- 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



LoRusso PM, et al. *Clin Cancer Res* 2011;17:6437-47

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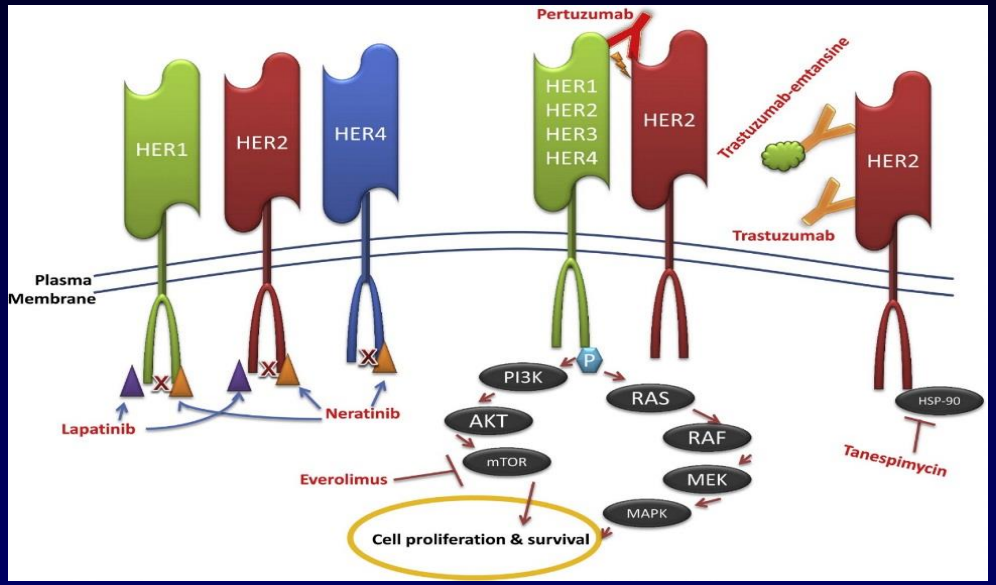
Neratinib: Tyrosine Kinase Inhibitor

- 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



Mohamed A, et al. *Am J Pathol* 2013; 183:1096-12
DOI: 10.1016/j.ajpath.2013.07.005

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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%**

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

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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

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Secondary Aims

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

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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

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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

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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

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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)

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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

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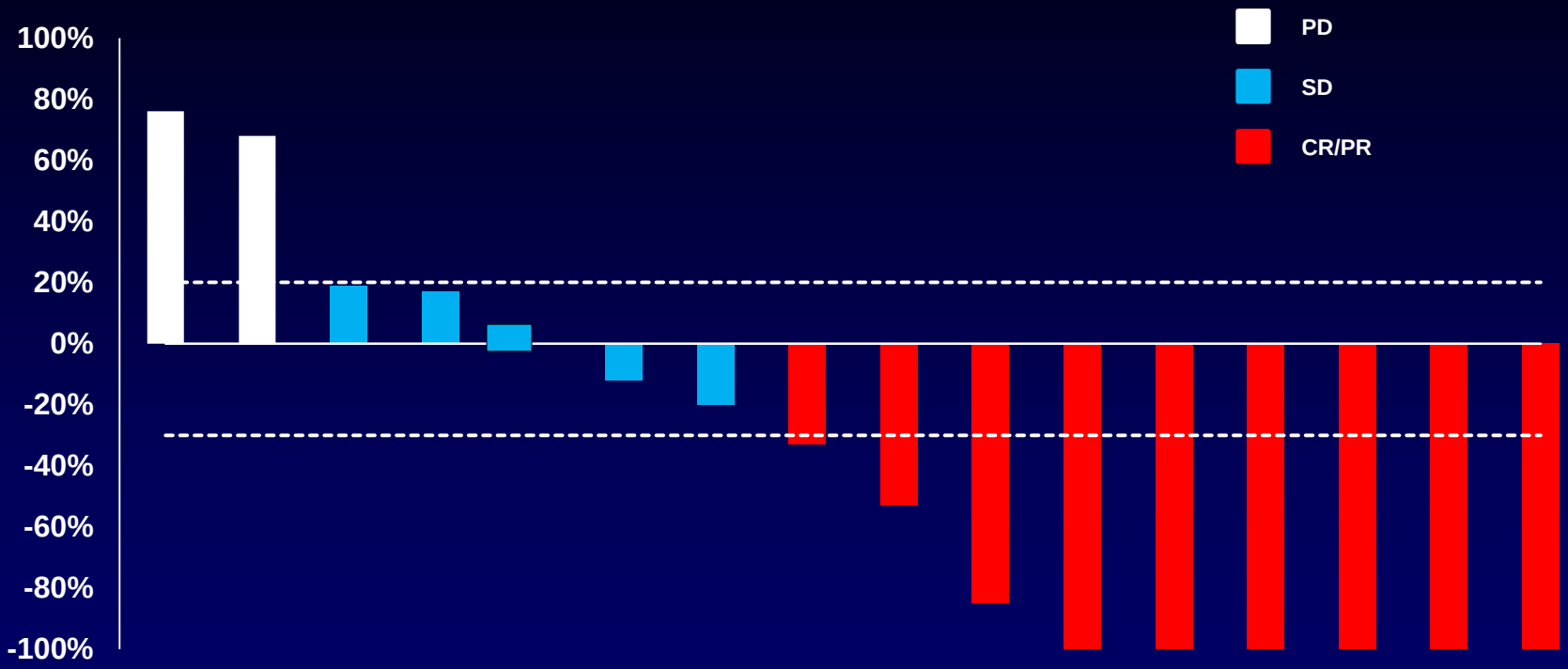
% Change in Size of Target Lesions



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

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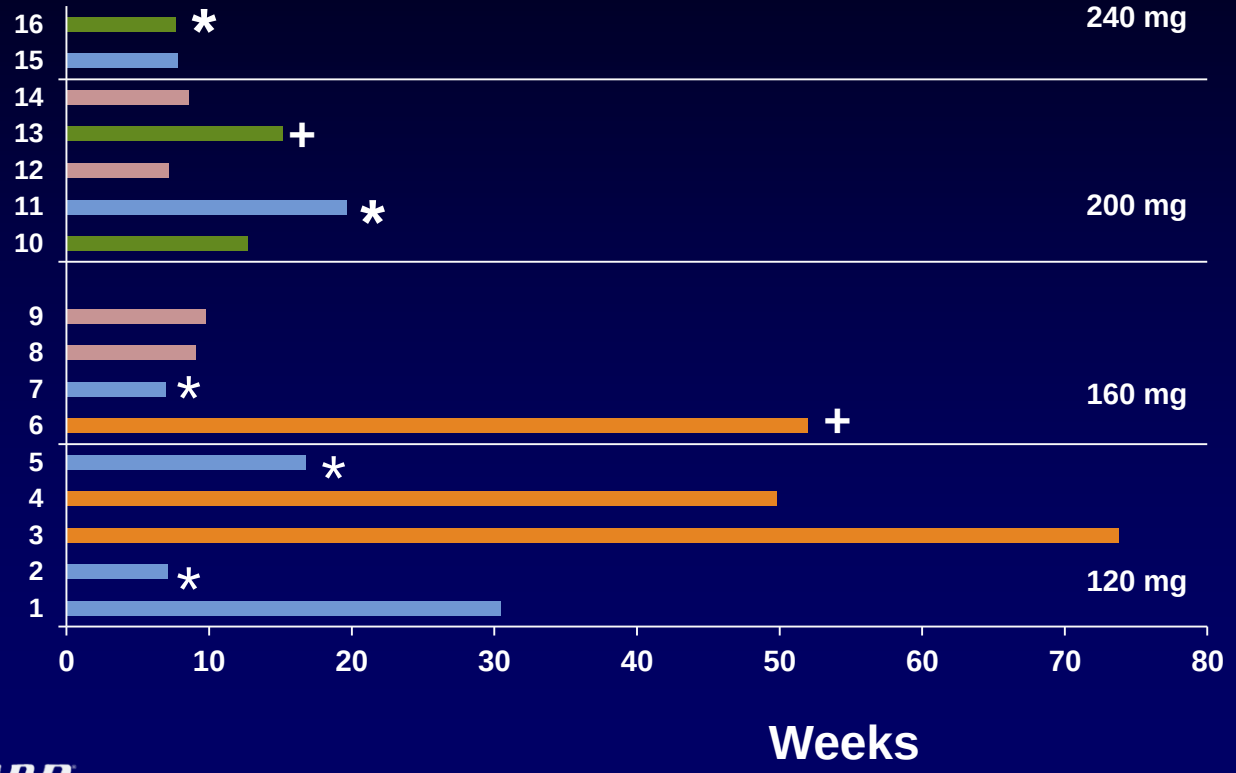
Evaluable Patients by Dose-level (RECIST)



Progressive

Stable

Partial

Complete

+ On treatment

* Off tx AE/withdraw

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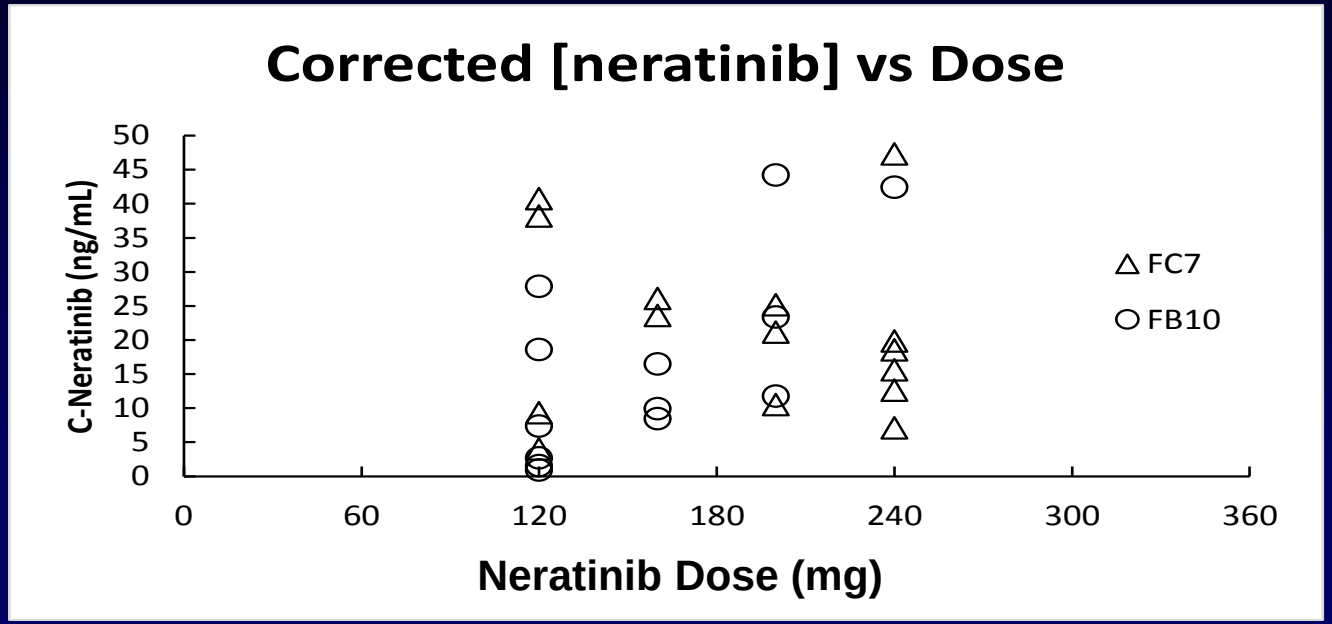
FC-7 and FB-10: Neratinib Trough Concentration at Steady-state, Day 1 of Cycle 2



- Trough levels are overlapping at all study doses
- Need more complete PK data to correlate toxicity and response (peak concentration and AUC)

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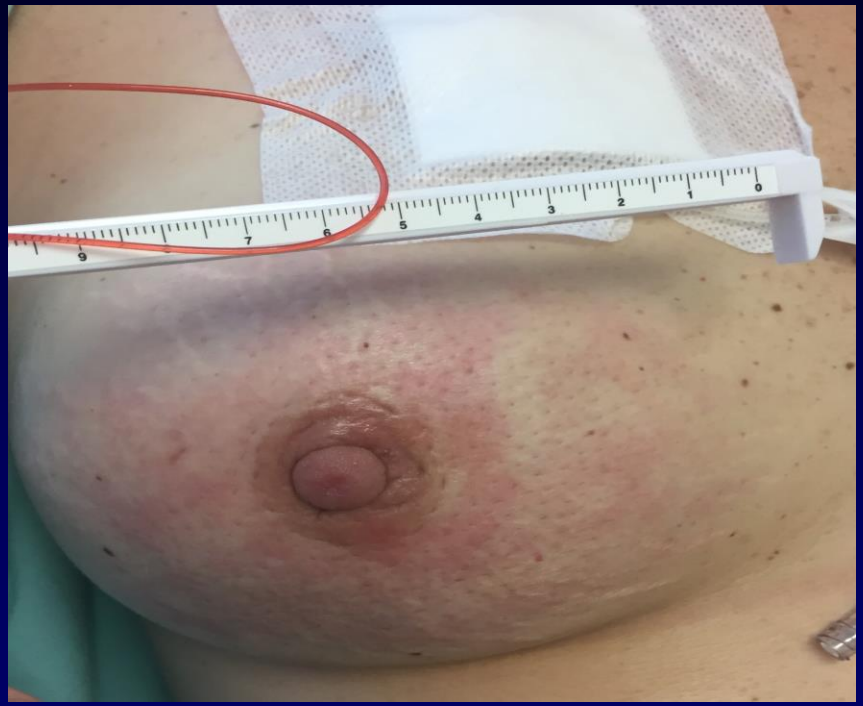
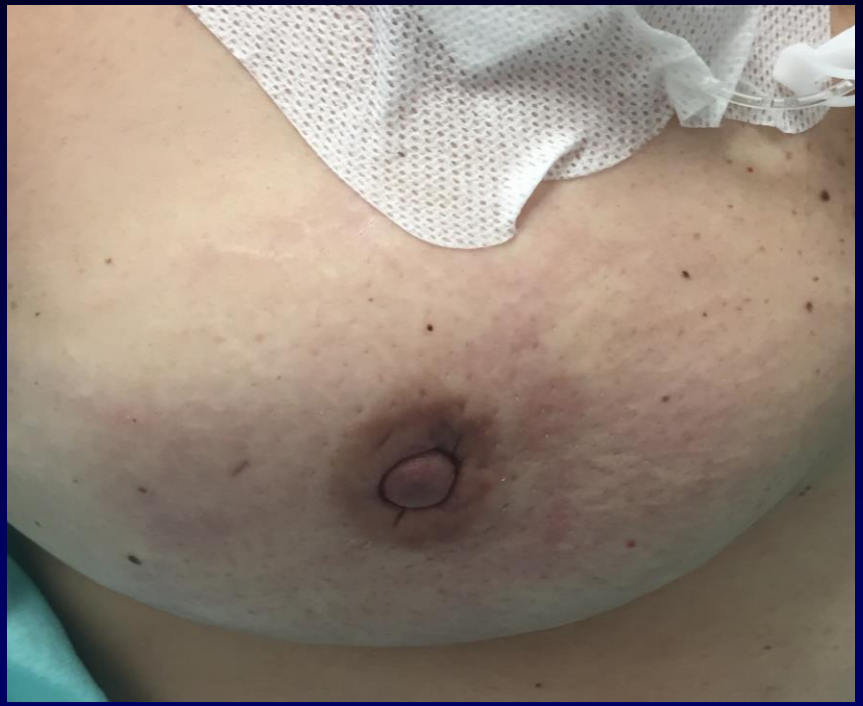
Progression in skin, contralateral breast mass, lung, and multiple liver lesions





Neratinib 120 mg

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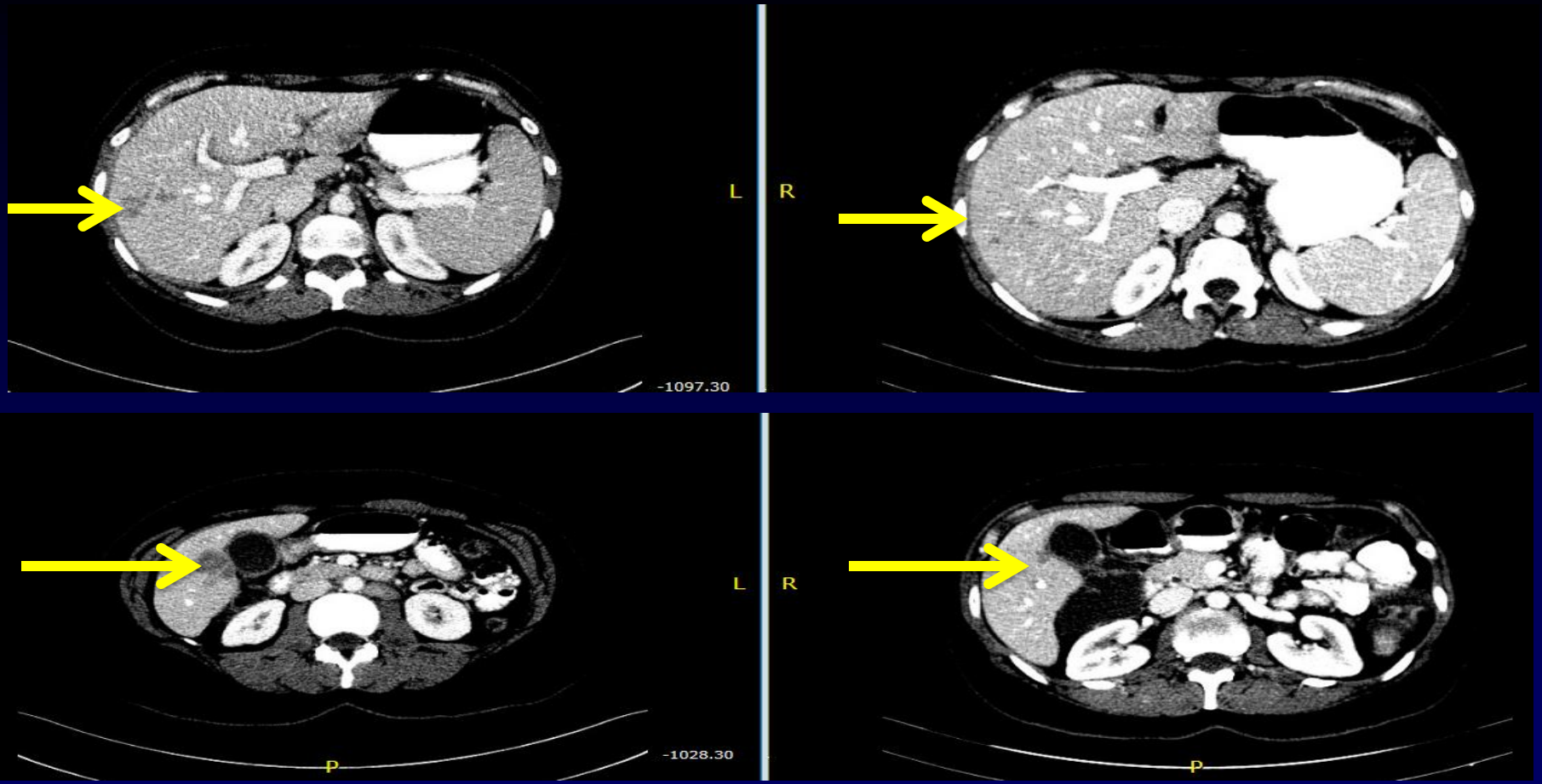

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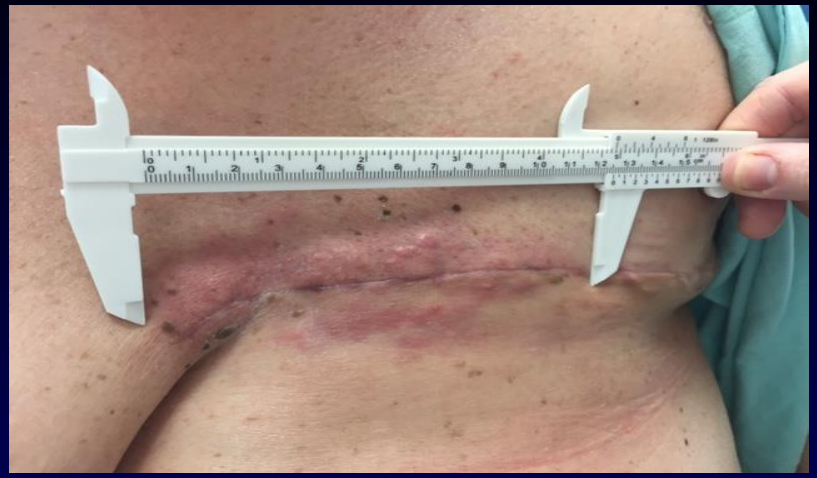
Before treatment

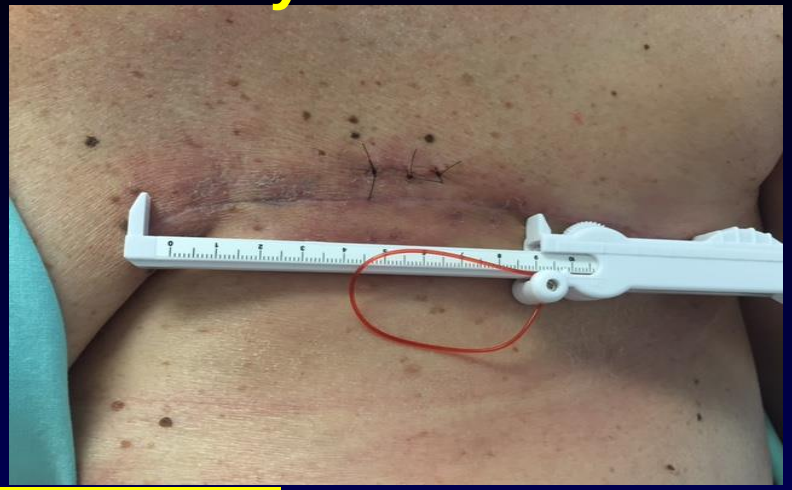
Neratinib 120 mg

After 2 cycles of treatment

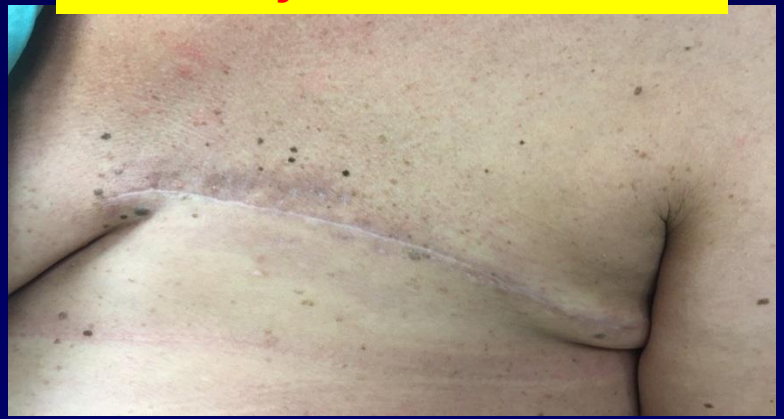
Baseline



After 1 Cycle of Treatment



After 3 Cycles of Treatment



Neratinib 160 mg

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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

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