NSABP PROTOCOL FB-10

A Phase Ib/II 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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CLINICAL QUESTIONS:

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Protocol FB-10 IND #107366 (neratinib), sponsored by the NSABP Foundation, Inc.

Puma Biotechnology, Inc. – Protocol [FB-10]

Version Date: January 3, 2018 (Replaces all other versions)

CONFIDENTIAL

PROTOCOL REVISION RECORD

Original Version: June 6, 2014

Amendment #1: June 26, 2014

NSABP FB-10 Protocol and consent amended prior to activation of the study.

Amendment #2: February 5, 2015

Sections Changed/Added

Cover Page
Glossary of Abbreviations and Acronyms
Section 3.0: 3.3.1, 3.3.4
Section 7.0: 7.4
Section 12.0: 12.3.3

Amendment #3: March 1, 2016

Sections Changed/Added

Cover Page
Section 4.0: 4.2.7
Section 6.0: Table 2 (footnote e added; subsequent footnotes relettered)
Section 9.0: 9.1 (Tables 5, 6, 7, and 8); 9.3.5
Section 10.0: 10.7.3 (Table 11)
Section 11.0: 11.2.3
Appendix C
FB-10 Consents:
Study Consent: Cover page, pages 1, 5, 6, 9, 10; Addendum #1 has been added.
Optional Tumor Collection Consent: Cover page, and page 1.

Amendment #4: October 11, 2016

Sections Changes/Added

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Glossary of Abbreviations and Acronyms
Section 1.0: 1.1
Section 2.0: 2.5
Section 6.0: Table 1
Section 7.0: 7.1 (Table 3), 7.3, 7.4.1, 7.4.2, 7.5, 7.5.1, 7.5.2, 7.6
Section 10.0: 10.5.4
References: References 40-45 were added; subsequent references were renumbered
FB-10 Consents:
Study Consent: Cover page, pages 1, 15-20

Amendment #5: August 8, 2017

Sections Changes/Added

Cover Page

Information Resources

Section 1.0: 1.1, 1.2; figure 1 schema revised

Section 2.0: 2.1, 2.2, 2.4, 2.5

Section 3.0: 3.3, 3.3.2, 3.4

Section 4.0: 4.2.7, 4.2.8

Section 6.0: Table 1, Table 2

Section 7.0: 7.1, Table 3, 7.3.1, 7.4.1, 7.4.2, 7.4.3, 7.4.4, 7.5.1, 7.6.1, 7.7

Section 8.0: 8.0, 8.3

Section 9.0: 9.0, 9.1 Table 5 revised; Tables, 6, 7 deleted; subsequent Tables were renumbered. 9.3.4, 9.4.4

Section 10.0: 10.1, 10.2, 10.2.1, 10.2.2; 10.5 added, subsequent sections renumbered; 10.6, 10.6.1, 10.6.2, 10.6.3, 10.6.4, 10.7, 10.8.1 Table 6, 10.8.2 Table 7, and 10.9 Table 8

Section 11.0: 11.2.4, 11.2.5, 11.2.9

Section 12.0: 12.2 added, subsequent sections renumbered; 12.3.2 deleted, subsequent sections renumbered; 12.7.2

Section 13:0 13.1.1, 13.3

Section 14.0 14.3

Section 16.0: 16.1, 16.2, 16.3, 16.4, and 16.5

Section 18.0: References were added and reformatted

Appendix C

FB-10 Consents have been revised.

Amendment #6: January 3, 2018

Sections Changes/Added

Cover Page

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Section 6.0 Table 1, Table 2

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Section 9.0 9.3.5, 9.3.6 added

Section 11.0 11.2.3

FB-10 Consents have been revised.

TABLE OF CONTENTS

INFORMATION RESOURCES

NSABP Department of Site and Study Management [redacted] Phone: [redacted] E-mail: [redacted]		
For questions regarding: • IRB review & informed consent • Submission of IRB approval • Study entry information • Eligibility • Treatment regimen • Dose modifications/delays • Other clinical aspects of the trial • Adverse event reporting including SAE reporting • eCRF completion • Neratinib shipments	NSABP Department of Site and Study Management (DSSM)	Phone: [redacted] E-mail: [redacted]
For questions regarding data management	DSSM	Phone: [redacted] E-mail: [redacted]
Submission of data forms (including expedited AE reports)	DSSM	E-mail: [redacted]
Requests for study drug (neratinib)	DSSM	E-mail: [redacted]
Questions and submission of tumor and blood samples for correlative science studies *(excluding PDX samples)*	NSABP Division of Pathology 1307 Federal Street, Suite 303 Pittsburgh, PA 15212	E-mail: [redacted] Phone: [redacted] *Refer to FB-10 Pathology and Correlative Science Instructions and to the Champions Oncology Overview-Tumor Collection Logistics PDX Model Development*
Questions and submission of tumor and blood samples for PDX correlative science studies	Champions Oncology	E-mail: [redacted]

GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ADCC	antibody dependent cytotoxicity
AE	adverse event
ALT (SGPT)	alanine aminotransferase
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
ASCO	American Society of Clinical Oncology
AST (SGOT)	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BCIRG	Breast Cancer International Research Group
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CBR	clinical benefit rate
CHF	congestive heart failure
CI	confidence interval
CISH	chromogenic in situ hybridization
CNS	central nervous system
C_{max}	maximum concentration
CR	complete response
CRF	case report form
CT	computed tomography
CTCs	circulating tumor cells
CTCAE v4.0	Common Terminology Criteria for Adverse Events Version 4.0
CTEP	Cancer Therapy Evaluation Program
CYP	cytochrome P450
dbGaP	database of Genotypes and Phenotypes
DLT	dose-limiting toxicity
DSSM	NSABP Department of Site and Study Management
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor 1
EMILIA	An Open-label Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine plus Lapatinib in Patients with HER2-positive Locally Advance or Metastatic Breast Cancer
ER	estrogen receptor
ErbB	epidermal growth factor receptor
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony stimulating factor
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte macrophage-colony stimulating factor
H&P	history and physical
HER2	human epidermal growth factor receptor 2

GLOSSARY OF ABBREVIATIONS AND ACRONYMS (continued)

HERA	A study of Intravenous Herceptin (Trastuzumab) in Women with HER2-positive Primary Breast Cancer
HR	hazard ratio
IB	Investigator's Brochure
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
LD	longest diameter
LLN	lower limit of normal
LV	left ventricular
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MARIANNE	A study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/Pertuzumab Placebo versus Trastuzumab (Herceptin) Plus a Taxane in Patients with Metastatic Breast Cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multi-gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCCTG	North Central Cancer Treatment Group
NeoALTTO	Neo adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Study
NCI	National Cancer Institute
NK	natural killer cells
NOD/SCID	nonobese diabetic/severe combined immunodeficiency
NSABP	NSABP Foundation, Inc.
ORR	overall response rate
p	probability
PBMC	peripheral blood mononuclear cells
pCR	pathologic complete response
PD	progressive disease
PDX	patient derived xenograft
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetics
PO	by mouth
PR	partial response
PTEN	phosphatidylinositol phosphate 3'-phosphatase
q	every
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
RT	radiation therapy
RTK	receptor tyrosine kinase
SAE	serious adverse event
SD	stable disease
TDM	therapeutic drug monitoring
T-DM1	trastuzumab emtansine

GLOSSARY OF ABBREVIATIONS AND ACRONYMS (continued)

TKI	tyrosine kinase inhibitor
tpCR	total pathological complete response
ULN	upper limit of normal
WOCBP	women of childbearing potential

1.0 OVERVIEW OF STUDY DESIGN

1.1 Summary

Note: On May 3, 2017, accrual to the Phase 1b portion of FB-10 was completed. See Addendum below for the rationale for Amendment #5, the Phase II portion of the study.

The FB-10 study is designed as an open label, single arm, Phase Ib/II study with a dose-escalation phase and an expanded cohort (phase II) to evaluate the combination of trastuzumab emtansine (T-DM1) with neratinib in women with metastatic, HER2-positive breast cancer. The primary aim of the phase Ib portion of this study is to determine the safety and tolerability of the two-drug combination. The primary aim of the phase II portion is to demonstrate efficacy.

Patients will receive concurrent therapy with T-DM1 (3.6 mg/kg IV) on Day 1 of a 3-week (21 day) cycle and neratinib as a continuous daily oral dose. The neratinib dose-escalation will include 4 dose levels (120 mg, 160 mg, 200 mg, and 240 mg). At the recommended phase II dose (RP2D) of the T-DM1 and neratinib combination, up to 39 additional patients will be treated.

The neratinib dose-escalation for the study will proceed using a 3+3 design on the basis of dose-limiting toxicity (DLT) during cycle 1. DLT will be defined as the occurrence of 1 or more of the following events during cycle 1: any grade diarrhea that is associated with fever or dehydration requiring IV fluids; grade 3 diarrhea lasting more than 2 days on optimal medical therapy; grade 4 diarrhea of any duration; grade 3 or 4 neutropenia associated with fever; grade 4 neutropenia lasting more than 7 days; grade 4 thrombocytopenia; grade 3 or 4 non-hematological toxicity (excluding grade 3 rash or allergic reaction/hypersensitivity); or any toxicity-related delay of more than 2 weeks to initiate cycle 2. Note: if 2 or more patients assigned to study therapy **Dose level 1, during Cycle 1** experience a DLT due to grade 4 thrombocytopenia, the study will continue with the following actions:

- The T-DM1 dose will be decreased to 3.0 mg/kg (T-DM1 level-1) for all patients subsequently enrolled on study.
- The T-DM1 dose will not re-escalate. T-DM1 dose 3.0 mg/kg will become the starting dose for all other study therapy dose levels. (See Section 10.7.)
- Grade 4 thrombocytopenia will remain a DLT during Cycle 1 for all subsequent dose levels.
- Study therapy dose treatment management, *after* completion of Cycle 1, will continue as described in Section 10. (See Tables 5, 6, and 9.)

Patients will be enrolled at the next dose level when all evaluable patients at the same dose level have completed the first treatment cycle. Enrolled patients will remain on the assigned dose level treatment until toxicity or disease progression.

The sample size of the phase I portion of the study was 27 patients. The sample size of the Phase II portion will be 22 evaluable patients (and 4 replacement patients). The total study enrollment, phase Ib and II, will be a maximum of 50 patients.

1.2 Addendum

On May 3, 2017 the FB-10 DLT evaluation of the four neratinib dose escalation levels was completed determining the maximum tolerated dose (MTD) at dose level 2 (160 mg); [dose level 1 at 120 mg: 6 patients/1 DLT; dose level 2 at 160 mg: 6 patients/0 DLTs; dose level 3 at 200 mg: 8 patients/3 DLTs, and dose level 4 at 240 mg: 3 patients/ 2 DLTs].

Analysis of the secondary aims of progression-free survival (PFS) and clinical benefit rate (CBR) revealed comparable responses within the patient cohorts of Dose level 1 (120mg) and Dose level 2 (160mg).

In the Phase II portion of the FB-10 study women with metastatic, HER2-positive breast cancer will be treated using the RP2D dose level of neratinib 160mg (Phase 1b, dose level 2) in combination with T-DM1.

The sample size of this Phase II study will be 22 evaluable patients. Accrual is expected to occur over 12 to 14 months.

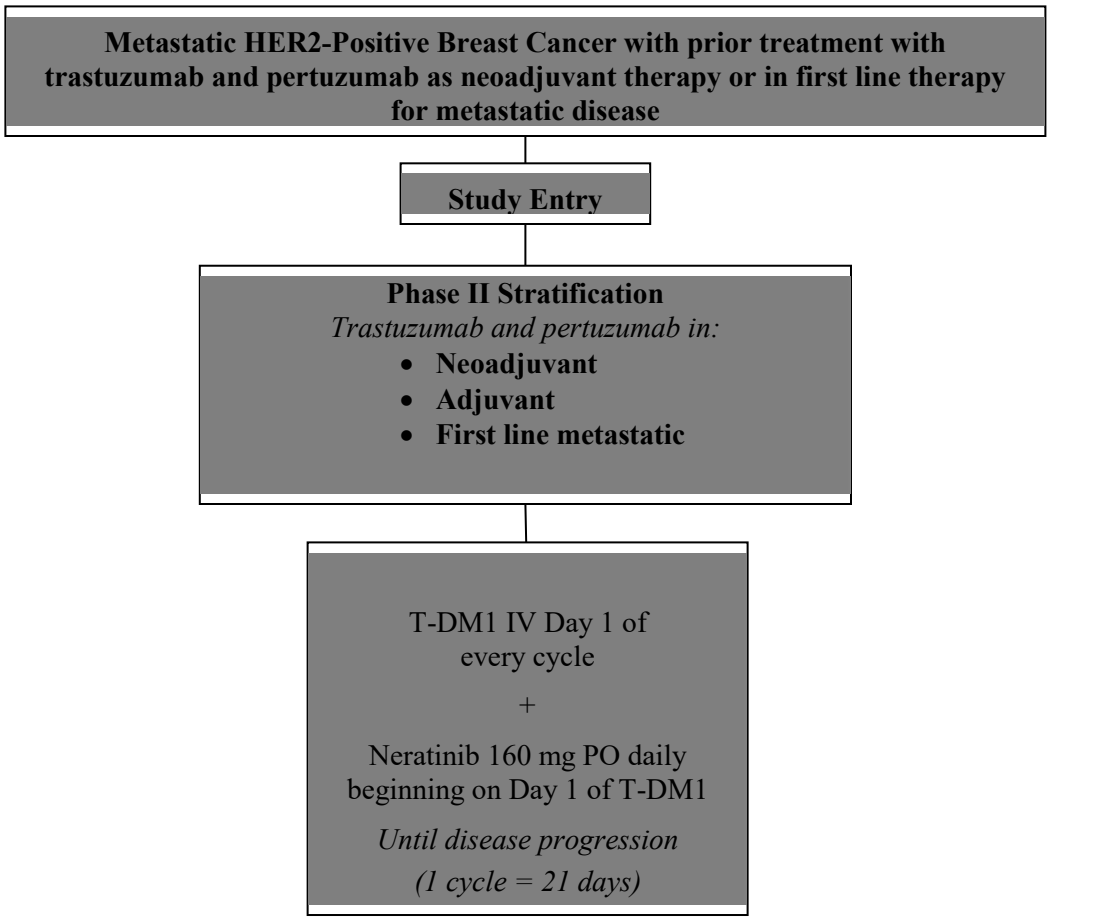
Toxicity will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0.

Submission of diagnostic tumor samples and blood samples for FB-10 correlative science studies will be a study requirement for all patients. Blood samples for pharmacokinetics (PKs) and for future study will be collected prior to administration of study therapy on Cycle 1/Day 1, Cycle 1/Day 8 and Cycle 2/Day 1.

A tumor biopsy will be procured from an accessible site of metastasis before study therapy is initiated (after the patient has signed the consent and has been screened for eligibility). The tissue will be sent to NSABP Division of Pathology for molecular studies including but not limited to confirmation of HER2-positivity and to Champions Oncology Laboratory for engraftment into an NOD/SCID mouse to develop a patient-derived xenograft (PDX) model. The PDX model will undergo drug sensitivity testing and response determination in parallel with the clinical trial (co-clinical trial).

An *optional* blood sample and tumor biopsy will be procured from consenting patients from an accessible site of metastasis at the time of disease progression.

Figure 1
NSABP FB-10 Schema



- T-DM1 3.6 mg/kg IV Day 1 of every cycle
- Neratinib **160 mg** PO daily beginning on Day 1 of T-DM1 and continuing until disease progression or intolerable toxicity

1 cycle = 21 days

2.0 BACKGROUND

2.1 Overview of HER2 targeted therapy

HER2 overexpression occurs in 20 to 25% of breast cancers (Baselga 1996). HER2 activates multiple signaling pathways including the phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) cascades. This results in increased cell proliferation and is associated with a poor clinical outcome. Trastuzumab, a monoclonal antibody, binds to the extracellular domain IV of the HER2 receptor, inhibits downstream signaling which leads to increases in $p27^{kip}$ (Baselga 1996) levels promoting cell cycle arrest and apoptosis (Nahta 2006). Data from in vivo experiments and clinical trials indicate that the efficacy of trastuzumab could be partly related to an immune response via antibody dependent cytotoxicity (ADCC) (Gennari 2004; Cooley 1999; Clynes 2000) The Fcɣ portion of the monoclonal antibody may play a significant role in the in vivo activity as it engages Fcɣ receptors on immune effector cells such as macrophages, NK cells or cytotoxic T cells which release cytotoxic enzymes causing cell lysis. A recent clinical finding is that Fcɣ receptor polymorphisms may be determinants of trastuzumab response in breast cancer patients and supports the potential role of ADCC in trastuzumab-based therapies (Musolino 2008).

The early studies with trastuzumab showed a 12% to 15% response rate as monotherapy in extensively treated patients with metastatic disease (Baselga 1996; Cobleigh 1999). The response rate increased to approximately 50% when combined with chemotherapy in patients with metastatic disease (Slamon 2001). In the adjuvant setting and reported in the joint analysis of NSABP B-31/NCCTG 9831, incorporation of a year of trastuzumab into standard adjuvant chemotherapy regimen in patients with HER2-gene-amplified or protein-overexpressing breast cancer, demonstrated a major improvement in disease recurrence and death. These findings, confirmed by the BCIRG 006 and HERA trials, changed the standard adjuvant therapy for women with the HER2-positive breast cancer subtype (Salamon 2006; Perez 2007; Smith 2007). In the neoadjuvant setting limited to HER2-positive patients, pCR rates of 40% to 60% have been observed, and those that achieve a pCR have a more favorable prognosis than, in particular, those who have residual invasive disease (Buzdar 2005; Gianni 2010). All patients do not benefit from trastuzumab and in patients with metastatic disease (Rimm 2012), the vast majority of responders to trastuzumab eventually develop resistant disease. Mechanisms of resistance to trastuzumab have been intensively studied and in general include: 1) obstacles for trastuzumab binding to HER2 such as truncated HER2, p95HER2 (Scaltriti 2007; Scaltriti 2010); 2) upregulation of HER2 downstream signaling; 3) signaling through alternative pathways; and 4) impaired immune-mediated cytotoxicity, among others (Pohlmann 2009). In an effort to increase the efficacy of ErbB family blockade, two recently conducted neoadjuvant trials have shown that dual blockade of the HER2 receptor with a HER2 antibody and tyrosine kinase inhibitor or two antibodies resulted in higher pathologic complete response (pCR) rates than single agent therapy (Baselga 2012; Gianni 2012). In the NeoALTTO trial (N= 455), patients received lapatinib or trastuzumab or lapatinib plus trastuzumab for 6 weeks followed by the assigned anti-HER therapy plus paclitaxel for 12 weeks, prior to definite surgery (Baselga 2012). Locoregional total pathologic complete response (tpCR) defined as no evidence of invasive disease in breast and lymph nodes was statistically higher with lapatinib/trastuzumab (46.8%) than with trastuzumab (27.6%, p=0.0007) alone with no significant difference between the trastuzumab or lapatinib (20%, p=0.13) alone groups. In the NeoSphere trial (N=417) there were four neoadjuvant arms: trastuzumab plus docetaxel, pertuzumab and trastuzumab plus docetaxel, pertuzumab and trastuzumab or pertuzumab and docetaxel (Gianni 2012). After four cycles, eligible patients went to surgery. Using the same definition for pCR, tpCR rates were 21.5%, 39.3%, 11.2% and 17.7%, respectively. Thus, both studies showed an improved tpCR with dual therapy, and importantly, this was achieved without incurring significant additional toxicity.

Trastuzumab-DM1 (T-DM1) is an antibody-drug conjugate that uses trastuzumab to specifically deliver the maytansinoid anti-microtubule agent DM1 to the antigen-expressing HER2-positive cells improving the therapeutic index of the cytotoxic agent (Lewis Phillips 2008). In vitro studies have shown that T-DM1 and trastuzumab have similar binding affinities for HER2 (Junttila 2011). DM1 and trastuzumab are linked by the chelating agent, succinimidyl 4-[N-maleimidomethyl] cyclohexane-1-carboxylate, through non-reducible thioester bonds. An average of 3.5 DM-1 molecules is conjugated to the Fc region of trastuzumab. The cytotoxic agent DM1, a highly potent antimitotic drug, binds to microtubules similar to vinca alkaloids. While maytansine given systemically demonstrated modest antitumor activity, there was significant toxicity as a free drug. Thus, after binding it is postulated that T-DM1-HER complex is endocytosed and degraded in lysosomes resulting in the intracellular release of an active metabolite, Lys-MCC-DM1 (Austin 2004; Erickson 2006).

Evaluation of other agents such as tyrosine kinase inhibitors that target this pathway have shown promising results in trastuzumab-resistant breast cancer (Geyer 2006; Burstein 2010). There are four receptors in the ErbB family and include: EGFR/ErbB-1, HER-2/ErbB-2, HER-3/ErbB-3, and HER-4/ErbB-4. All four receptors are tyrosine kinases and consist of an extracellular binding domain, a single membrane spanning domain, and regulatory domains. HER1, HER2 and HER4 have an intracellular tyrosine-kinase domain, HER3 does not. HER2 is ligandless but functions as a co-receptor and is actually the preferred partner for the other ErbB family members. Heregulin is the major HER3 ligand which promotes its engagement with HER2 kinase and the subsequent transphosphorylation of HER3 (Wallasch 1995). The heterodimer HER2:HER3 has the most potent downstream signaling. Formation of multiple combinations of ErbB receptor homo- and heterodimers, results in activation of the cytoplasmic kinase domain. This is turn promotes the phosphorylation of specific tyrosine residues, leading to the stimulation of multiple signal transduction pathways (Badache 2004).

Several oral, small molecule, dual tyrosine kinase inhibitors of HER2 and EGFR have demonstrated non-cross resistance with trastuzumab in preclinical studies and activity in women with HER2-positive, metastatic breast cancer progressing on trastuzumab (Geyer 2006; Konecny 2006, Ritter 2007). The FDA approved agent, lapatinib, is a reversible inhibitor that binds to the intracellular domains of HER2 and EGFR at the ATP-binding sites and prevents phosphorylation and activation of downstream signaling pathways.

The investigational agent of interest, neratinib (HKI-272), is an orally administered small molecule and is an irreversible inhibitor of pan ErbB receptor tyrosine kinase, which distinguishes it from the small molecule lapatinib. Because of the high degree of homology between kinase domains of EGFR and HER2, neratinib inhibits the kinase activity both EGFR and HER2 homo- and heterodimers (Rabindaran 2004).

2.2 Background for T-DM1

Data from selected clinical trials of T-DM1 are summarized as follows. In a phase II study (n=110) in which T-DM1 was evaluated in patients having disease progression after at least two HER-directed therapies, trastuzumab and lapatinib, the objective response rate was 32% as assessed by independent review of tumor response (Krop 2012). The only grade 4 adverse event noted was thrombocytopenia in a small percentage of patients.

The EMILIA study (n=991) is a phase III randomized trial involving patients with locally advanced or metastatic HER2-positive breast cancer who previously received trastuzumab and a taxane. In this study T-DM1 was compared with lapatinib plus capecitabine. The progression-free survival in patients receiving T-DM1 was 9.4 months compared to 6.4 months in the lapatinib-capecitabine arm (HR 0.65; 95% CI 0.55 to 0.77; p<0.001). The objective response rate

was higher with T-DM1 compared to lapatinib-capecitabine, 43.6% vs. 30.8% (p, 0.001). Rates of grade 3 or 4 adverse events were higher in the lapatinib-capecitabine arm that in T-DM1 (57% vs. 41%). The frequency of grade 3 or 4 toxicities >2% with T-DM1 include thrombocytopenia (12.9%), elevated AST (4.3%), elevated ALT (2.9%), anemia (2.7%), fatigue (2.4%), hypokalemia (2.2%), and neutropenia (2.0%) (Verma 2012).

A phase III study, MARIANNE (NCT01120184), (n=1095) for HER2-positive patients with recurrent locally advanced or metastatic disease compares T-DM1 plus pertuzumab vs. T-DM1 plus pertuzumab-placebo versus trastuzumab plus taxane in the first-line. This study has completed enrollment and has been reported as an abstract presentation (Ellis 2015). PFS for T-DM1-containing arms were non-inferior to the control arm (trastuzumab + taxane) but was not superior. The ORR for T-DM1 and T-DM1 + pertuzumab was 59.7 % and 64.2% respectively, and PFS was 14.1 months and 15.2 months (p=0.31).

In a retrospective review of the activity of T-DM1 in patients with prior trastuzumab, pertuzumab, the tumor response rate was reported as 17.9% (tumor response was determined by the treating physician in context of routine care taking into account imaging assessment and clinical evaluation). The median duration of therapy was 4.0 months (Dzimitrowicz 2016).

2.3 Background for neratinib

2.3.1 *Data as monotherapy*

In a Phase I clinical trial of neratinib, the dose-limiting toxicities (DLT) were diarrhea, nausea and vomiting, anorexia, and rash. DLT was reached at 320 mg orally per day. The maximum tolerated dose (MTD) for phase II study was determined to be 240 mg/day (Wong 2006). The overall response rate observed in breast cancer patients in the Phase I study was 32% (8/25).

A Phase II study evaluated neratinib as monotherapy at a dose of 240 mg per day in patients with HER2-positive tumors. In 63 evaluable patients (cohort A) with previous treatment with trastuzumab, response was seen in 16 (24%) patients with a progression-free survival of 22.3 weeks; in another cohort of 64 evaluable patients (cohort B) who were trastuzumab-naïve, 36 patients responded (56%) with a progression-free survival of 39.6 weeks. The most common adverse events, all grades, in both cohorts included diarrhea 89% to 97%, nausea 30% to 42%, and rash/dermatitis 13% to 27%. Hand-foot syndrome was not observed. Grade 3 or greater diarrhea occurred in a total of 43% of patients. Diarrhea occurred early in the course of therapy with the median time of onset 2 to 3 days and lasted up to a week. The diarrhea abated with continued treatment. Thus, while 70% to 90% of patients experienced diarrhea during the first week of therapy, this decreased to 10% to 15% with continued therapy and the use of antidiarrheals and dose modification. Rarely did diarrhea necessitate discontinuation of neratinib (Burstein 2010).

2.3.2 *Data for combining neratinib and paclitaxel or trastuzumab*

In a Phase I study, neratinib plus paclitaxel was tested in solid tumor patients with ascending doses of neratinib from 160 mg daily to 240 mg daily with paclitaxel at 80 mg/m^2 on days 1, 8, and 15 of a 28-day schedule. For paclitaxel toxicity the dose could be decreased to 70 mg/m^2. No dose limiting toxicities occurred with the paclitaxel 80 mg/m^2 and neratinib 240 mg dosing (Chow 2013). In the Phase II extension study, 102 patients with measurable, metastatic, HER2-positive breast cancer were treated with neratinib 240 mg daily and paclitaxel 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle. There were two cohorts with Group A including patients with ≤ 1 prior chemotherapy regimen and no prior lapatinib and Group B with ≤ 3 prior chemotherapy regimens and

lapatinib permitted. The most common grade 3/4 toxicities occurring in > 10% of patients included diarrhea (29%), and neutropenia (20%). Dose reductions of neratinib and paclitaxel occurred in 19% and 37% of patients, respectively. The overall response rate was 73%. Response rate observed in patients with prior trastuzumab was 71%, with prior lapatinib 77%, and with prior taxane 81%. The median PFS for all patients was 57.0 weeks (95% CI 47.7-81.6 weeks) (Chow 2013).

A Phase I/II study with the combination of neratinib and trastuzumab in the treatment of patients with advanced breast cancer was reported at ASCO in 2009 (Swaby 2009). In the Phase I portion, standard full doses of trastuzumab were used and neratinib was escalated from 160 mg/day to 240 mg/day. This later dose was taken into the Phase II portion (n=37). At neratinib 240 mg/day and trastuzumab 4 mg/kg loading dose following by a weekly dose of 2 mg/kg weekly, the major grade 3 toxicities included diarrhea (11%), nausea, vomiting, and anorexia < 5%. There was 1 patient with a > 10% fall in LVEF to a value < 50% but without any cardiac symptoms. Dose reductions occurred in 8% of the Phase II patients. The overall response rate was 29%, clinical benefit rate was 35%, and the complete response rate was 7%. The PFS at 16 weeks was 45%.

2.3.3 *Data for combining neratinib, trastuzumab, and paclitaxel*

NSABP FB-8 is a phase I study in heavily pretreated metastatic HER2-positive patients which demonstrated that the three–drug combination of neratinib, trastuzumab and paclitaxel was both safe and efficacious. Diarrhea occurred in 19 patients (grade 1 = 8; grade 2 = 3; grade 3 = 8). No patients experienced grade 4 diarrhea. Most patients experienced diarrhea within one to three days of initiating study therapy, with diminishing symptoms during the first two weeks. Mandatory prophylactic diarrhea management was implemented for all patients at the RP2D of 200 mg/day. With prophylactic management there were no grade 3 or higher diarrhea events at the 200 mg/day dose. Best response was a CR in two patients and PR in six patients resulting in an objective response in eight of 21 patients (38%). One patient experienced complete resolution of skin disease defined as SD (non-CR/non-PD) by RECIST. Two additional patients had SD lasting greater than 24 weeks including a patient with CNS disease who remained stable for 16 months. The overall clinical benefit rate was 11 of 21 patients (52%). Median time to progression (TTP) was 3.7 months. The three patients with prior T-DM1 responded with CR, PR, and SD (Jankowitz 2012).

2.4 Phase Ib results (FB-10) of T-DM1 plus neratinib

T-DM1 binds to HER2 and prevents homodimerization, and to some extent ligand-independent dimerization of HER2: HER3 (Garrett 2011). Its activity likely combines the effects of ADCC and the internalization of the potent maytansinoid anti-tubular agent DM1. It has been demonstrated to overcome resistance to trastuzumab. Neratinib has different mechanism of actions inhibiting kinase activity of the heterodimers of HER1:HER3 and HER2:HER3 and because the kinase inhibition occurs downstream of the antibody binding domain, it is postulated that it would retain activity if HER2 were truncated (p95HER2). Preclinical data combining paclitaxel and neratinib in SKBR-3 breast cancer cells demonstrated a strong additive effect in arresting cell proliferation, suggesting that inhibition of microtubule genes potentiates neratinib drug response (Seyhan 2011). Clinical data seems to support this as demonstrated in a study of previously treated, HER2-positive metastatic breast cancer patients; the combination of neratinib and the anti-tubular agent, paclitaxel, resulted in an ORR of 73% with responses observed in patients with prior trastuzumab (71%), lapatinib (77%), and taxane therapy (81%) (Chow 2013).

The Phase Ib study (NSABP FB-10) enrolled HER2-positive metastatic breast cancer patients who had previously been treated with chemotherapy and the combination of trastuzumab and pertuzumab. Study treatment consisted of the standard dose of ado-trastuzumab emtansine at 3.6 mg/kg administered intravenously every 3 weeks and neratinib administered orally at escalating doses of 120, 160,200 and 240 mg/day. The RP2D was 160 mg/day. For the 16 patients who were evaluable for efficacy, the objective response rate (complete plus partial responses) was 9 of 16 (56%). There were 3 patients with complete responses lasting 17.1 months, 11.9 months and 12+ months. The dose-limiting toxicity was diarrhea. (Abraham 2017).

Taken together, the combination of T-DM1 and neratinib combines agents with different mechanisms of action and different toxicity profiles. The agents as monotherapy have been shown to overcome resistance to trastuzumab.

2.5 Rationale for incorporation of patient-derived xenografts as co-clinical trial

Drug discovery and development in oncology is associated with a high rate of attrition (Di Masi 2013). The highest attrition of new agents occurs in the resource intensive Phase II and III evaluations. Such high attrition rates have renewed interest in developing preclinical models which are more predictive of clinical outcome (Burgenske 2014).

While the opportunity of Next Generation Sequencing (NGS) is the generation of highly detailed tumor genomic data, the information is frequently overly complex and may not directly translate to meaningful treatment decisions. In addition, while NGS generates important genomic hypotheses, this does not guarantee clinical benefit in an individual patient, as not every mutation identified will be the oncogenic driver for a patient's tumor. Ultimately, it is not until the patient has undergone treatment that the clinical benefit can be assessed. Thus, the opportunity to functionally test the NGS-based genomic hypotheses as a corollary to the patient's response to treatment could further optimize future treatment selection. One promising approach that could achieve such benefit is testing of therapeutic options in a preclinical model of the patient's tumor, such as a patient-derived xenograft (PDX) model and taking advantage of adequate tissue samples to investigate mechanisms of response or resistance.

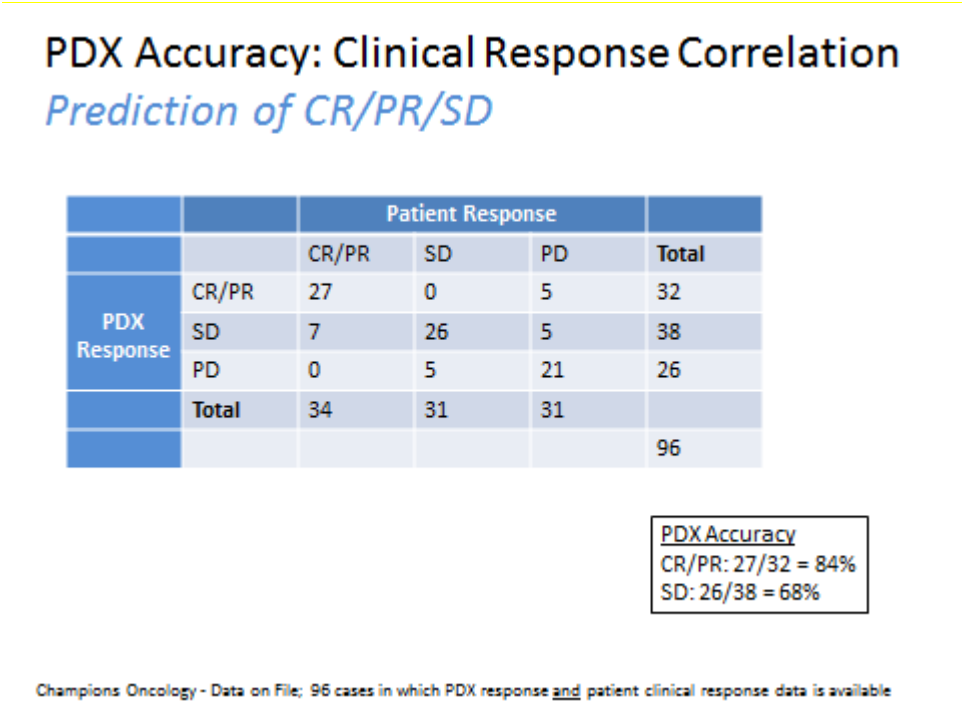
Patient-derived xenografts are generated by direct transfer of human tumor fragments from patients to immune-deficient mice. Serial passage of tumors in mice avoids artificial in vitro cell culture conditions. A number of studies confirm the fidelity between the host tumor and the mouse models derived from them (Stebbing 2014; Garralda 2014; Weroha 2014; Einarsdottir 2014). Histologic concordance has been verified with differentiation between the human and mouse engraftment being virtually identical. Analyses of gene expression profiles, copy-number alterations and exome sequencing data all show no substantive differences between donor tumors and their PDX. Using unsupervised clustering analysis, paired donor tumor and PDX models cluster together in most studies. Genes involved in the stroma compartment and immune function are less represented in the models due to replacement of the human stroma by murine elements.

The rationale for incorporating drug testing in PDX models to correlate with clinical outcome is several-fold. First, there is accumulated evidence that an objective response in the PDX models will predict response in the patient when tested with the same agents (see Figure 2). The rationale being that the best predictor of response is response itself, and in this case response in the patients personalized PDX model. This should avoid future enrollment on the study of a large number of non-responders. Second, target identification and validation are critical in understanding mechanism of response and resistance to a drug combination. It is becoming clear that predicting response to known oncogenes is complex and is altered by different genetic background. Redundancies in signaling pathways may result in lack of response in some patients who express the oncogenic target. While clinical samples from the patient are the most relevant biologic

samples, acquisition of these samples in adequate quantity is difficult, if not impossible. PDX models afford an opportunity to analyze sufficient quantity of tissue to support target identification and functional validation of a target and the opportunity to interrogate the models of responders and non-responders to increase understanding of response and mechanisms of resistance. Thirdly, PDX models provide a viable tumor bank for future hypothesis testing including testing agents of interest to maximize benefit and potentially block resistance pathways.

PDX models have the potential of being informative in the patient population being tested in this study. The results from the clinical trial, Emilia, in which second line T-DM1 was given to patients after first-line metastatic disease treated with trastuzumab and a taxane reported an objective tumor response of 43% (Verma 2012). Since that trial was conducted, the standard treatment for first-line HER2+ MBC includes a taxane plus both trastuzumab and pertuzumab. There is anecdotal evidence that the response to T-DM1 after dual anti-HER2 antibody therapy is substantially reduced. While the current trial is evaluating T-DM1 plus neratinib in patients who have had prior trastuzumab and pertuzumab, testing PDX models with T-DM1 alone, neratinib alone and the combination of T-DM1 plus neratinib may provide evidence as to the value of the combination and an opportunity to determine pharmacodynamic interactions.

Figure 2. PDX accuracy and clinical response correlation



3.0 STUDY AIMS AND ENDPOINTS

3.1 Primary aim and endpoint for the Phase I part of the study

Aim: To determine the safety and tolerability of T-DM1 and neratinib in patients with metastatic HER2-positive breast cancer

Endpoint: Recommended doses of T-DM1 and neratinib that can be administered as a combination in a Phase II trial (RP2D)

3.2 Primary aim and endpoint for the Phase II part of the study

Aim: To determine the overall response rate (ORR) in patients with measurable metastatic breast cancer treated with T-DM1 and neratinib

Endpoint: Objective response rate (CR/PR)

3.3 Secondary aims and endpoints (Phase I and Phase II)

(Note: Secondary aims and endpoints for Phase I and Phase II of the study will be analyzed separately.)

3.3.1 ***Progression-free survival (PFS)***

Aim: To determine the PFS in patients who present with measurable metastatic disease

Aim: To determine the percentage of first progression in the central nervous system (CNS)

Endpoint: Time to progression

3.3.2 ***Clinical benefit rate (CBR)***

Aim: To determine objective tumor decrease and stable disease (SD) by RECIST 1.1 criteria

Endpoint: Measurement of disease status by continuous tumor measurement

3.3.3 ***Toxicity***

Aim: To evaluate the overall toxicity for the combination of T-DM1 and neratinib

Endpoint: Frequency and severity of adverse events categorized using the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0)

3.4 Exploratory translational science

Aim: To explore molecular and genetic correlatives for the degree of benefit from T-DM1 and neratinib.

Aim: To determine pharmacokinetics of neratinib.

Aim: To explore the effect of current and future drugs in PDX models

4.0 PATIENT ELIGIBILITY AND INELIGIBILITY

4.1 Patient selection guidelines

Although the guidelines in Section 4.1 are not inclusion/exclusion criteria, investigators should consider each of these factors when selecting patients for the FB-10 trial. Investigators should also consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for the FB-10 trial.

- Co-morbid conditions should be taken into consideration, but not the diagnosis of metastatic breast cancer.
- ***Submission of breast tumor samples from the diagnostic biopsy is required for all patients*** (see Section 7.1). Therefore, the local pathology department policy regarding release of tumor samples must be considered in the screening process. Patients whose tumor samples are located in a pathology department that by policy will not submit any samples for research purposes should not be approached for participation in the FB-10 trial.

4.2 Conditions for patient eligibility

A patient cannot be considered eligible for this study unless all of the following conditions are met:

4.2.1 The patient must have consented to participate and, prior to study entry, must have signed and dated an appropriate IRB-approved consent form that conforms to federal and institutional guidelines (see treatment consent form).

4.2.2 Patients must be female.

4.2.3 Patients must be ≥ 18 years old.

4.2.4 The ECOG performance status must be ≤ 2 (see Appendix A).

4.2.5 Patients must have the ability to swallow oral medication.

4.2.6 Patients must have histologic or cytologic confirmation of the diagnosis of invasive adenocarcinoma of the breast.

4.2.7 Patients must have had anti-HER2 based therapy with pertuzumab and trastuzumab for neoadjuvant therapy, adjuvant or with first line therapy for metastatic disease (which may include trastuzumab and pertuzumab either sequentially or in combination).

4.2.8 There must be documentation that the patient has evidence of measurable metastatic breast cancer (see Section 13.0) that is accessible to biopsy at study entry.

4.2.9 Patients must have ER analysis performed prior to study entry. If ER analysis is negative, then PgR analysis must also be performed. (Patients are eligible with either hormone receptor-positive or hormone receptor-negative tumors.)

4.2.10 Breast cancer must be determined by local testing to be HER2-positive prior to study entry using ASCO-CAP HER2 test guidelines.

4.2.11 At the time of study entry, blood counts performed within 4 weeks prior to study entry must meet the following criteria:

- ANC must be ≥ 1000/mm^3;
- platelet count must be ≥ 100,000/mm^3; and
- hemoglobin must be ≥ 9 g/dL.

(*Note:* Patient must have discontinued growth factors ≥ two weeks prior to entry labs.)

4.2.12 The following criteria for evidence of adequate hepatic function performed within 4 weeks prior to study entry must be met:
- Total bilirubin must be ≤ 1.5 x ULN, and
- AST and ALT must be ≤ 1.5 x ULN for the lab or ≤ 5 x ULN if liver metastasis.

4.2.13 Serum creatinine performed within 4 weeks prior to study entry must be ≤ 1.5 x ULN for the lab.

4.2.14 The LVEF assessment by 2-D echocardiogram or MUGA scan performed within 90 days prior to study entry must be ≥ 50% regardless of the facility's LLN**.**

4.2.15 Patients with reproductive potential must agree to use an effective non-hormonal method of contraception during therapy, and for at least 7 months after the last dose of study therapy.

4.3 Conditions for patient ineligibility

Any patient with one or more of the following conditions will be ineligible for this study:

4.3.1 Previous therapy with T-DM1 or any HER2 TKI including neratinib for any malignancy.

4.3.2 Symptomatic brain metastases or brain metastases requiring chronic steroids to control symptoms.

4.3.3 Active hepatitis B or hepatitis C with abnormal liver function tests; HIV positive patients receiving antivirals.

4.3.4 Lung disease resulting in dyspnea at rest.

4.3.5 Active infection or chronic infection requiring chronic suppressive antibiotics.

4.3.6 Malabsorption syndrome, ulcerative colitis, inflammatory bowel disease, resection of the stomach or small bowel, or other disease or condition significantly affecting gastrointestinal function.

4.3.7 Persistent ≥ grade 2 diarrhea regardless of etiology.

4.3.8 Conditions that would prohibit intermittent administration of corticosteroids for T-DM1 premedication.

4.3.9 Chronic daily treatment with corticosteroids with a dose of ≥ 10 mg/day methylprednisolone equivalent (excluding inhaled steroids).

4.3.10 Uncontrolled hypertension defined as a systolic BP > 150 mmHg or diastolic BP > 90 mmHg, with or without anti-hypertensive medications. (Patients with hypertension that is well controlled on medication are eligible.)

4.3.11 Cardiac disease (history of and/or active disease) that would preclude the use of any of the drugs included in the treatment regimen. This includes but is not confined to:

Active cardiac disease:
- symptomatic angina pectoris within the past 90 days that required the initiation of or increase in anti-anginal medication or other intervention;
- ventricular arrhythmias except for benign premature ventricular contractions;
- supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication;
- conduction abnormality requiring a pacemaker;
- valvular disease with documented compromise in cardiac function; and
- symptomatic pericarditis

History of cardiac disease:

- myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function;
- history of documented CHF; and
- documented cardiomyopathy.

4.3.12 Other nonmalignant systemic disease that would preclude the patient from receiving study treatment or would prevent required follow up.

4.3.13 Pregnancy or lactation at the time of study entry. ***(Note: Pregnancy testing should be performed within 14 days prior to study entry according to institutional standards for women of childbearing potential.)***

4.3.14 The investigator should assess the patient to determine if she has any psychiatric or addictive disorder or other condition that, in the opinion of the investigator, would preclude her from meeting the study requirements.

4.3.15 Use of any investigational agent within 4 weeks prior to study entry.

5.0 CARDIAC SAFETY MONITORING

5.1 LVEF assessments

5.1.1 *Timing of assessments*

LVEF assessments are required prior to study entry and every 3 months while receiving study therapy. Additional LVEF assessments during study therapy and following discontinuation of study therapy are at the investigator's discretion.

5.1.2 *LVEF assessment guidelines*

- **2-D echocardiogram is the preferred method** for LVEF assessments. However, LVEF assessment by MUGA scan is permitted.
- **All LVEF assessments should be performed by the same method**, either 2-D echocardiogram or MUGA scan that was performed at baseline (before study entry).
- Investigators are strongly urged to schedule the LVEF assessment at the same cardiac imaging facility that performed the patient's baseline LVEF assessment.

5.1.3 *Reporting LVEF assessments*

- The LVEF value must be reported on the LVEF Assessment eCRF as a numerical value that is a whole number.
  - If the facility performing the assessment has not reported the LVEF as a whole number, decimals reported as ≥ 5 should be rounded up and decimals reported as < 5 should be rounded down. For example, an LVEF of 54.5% will be rounded up and reported as 55%; an LVEF of 54.4% will be rounded down and reported as 54%.
  - If the facility performing the assessment will only report the LVEF as a range, the mean (average) of the values used for the range should be calculated so that a single numerical value can be reported.
- **Submission of the eCRF with the echocardiogram or MUGA scan report to DSSM is required within 14 days** after the LVEF assessment. The eCRF must be submitted for every LVEF assessment done for any reason until 3 months following discontinuation of study therapy.

5.2 Protocol-defined cardiac events

The cardiac events listed below, as defined by CTCAE v4.0, are the protocol-defined cardiac events for the FB-10 trial. Follow the instructions in Section 12.0 for SAE and AE reporting requirements.

- Grade 3 or grade 4 left ventricular dysfunction (congestive heart failure).
- Definite cardiac death: Death due to congestive heart failure, myocardial infarction, or documented primary arrhythmia.
- Probable cardiac death: Sudden death without documented etiology.

6.0 REQUIREMENTS FOR STUDY ENTRY DURING TREATMENT, AND FOLLOW-UP

Tests, exams and other studies required prior to study entry are listed on Table 1. Requirements following study entry are outlined on Table 2.

TABLE 1. Tests, exams, and other requirements **prior to study entry**

Required Assessments	Prior to study entry	
Determination of local pathology department's policy regarding submission of tumor samples (Section 4.1)[a]	X	
Consent form signed by the patient	X	
Determination of hormone receptor status (Section 4.2.9)	X	
Determination of HER2 status (Section 4.2.10)	X	
History & physical exam[b]	X	Within 4 weeks
Performance status (Appendix A)	X	
Height & weight	X	
Assessment of concurrent therapies[c]	X	
Assessment of BP and BP meds	X	
Determination of measurable disease	X	
Measurement of target lesion(s) (see Section 13.0)[d]	X	
CBC/differential/platelet count	X	
Serum creatinine	X	
Total bilirubin/alk phos/AST/ALT	X	
Serum chemistries: calcium/potassium/sodium/chloride/bicarbonate or carbon dioxide/albumin/BUN or urea/glucose/total protein	X	
Pregnancy test[e]	X	Within 2 weeks
2-D echocardiogram (or MUGA scan)	X	Within 90 days
Submission of tumor block[f]	X	After consent is signed and eligibility screening is completed
Required core biopsy to procure samples for submission to NSABP Division of Pathology[g]	X	
Core biopsy to procure samples for submission to Champions Oncology[h]	X	
Whole blood to Champions Oncology[h]		

Table 1 continues on the next page.

TABLE 1. Tests, exams, and other requirements prior to study entry *(continued)*

a The archived primary tumor tissue from the diagnostic biopsy must be requested and the pathology department must agree before study entry to archived tumor block (see Section 7.0).
b Complete H&P by physician or other healthcare professional.
c See Sections 9.3.5, 9.3.6, 11.2.3, and Appendix B.
d Imaging technique is at the investigator's discretion.
e *For WOCBP:* Pregnancy testing should be performed according to institutional standards.
f Submission of diagnostic tumor block is required for all patients within 60 days following study entry. See Information resources, Section 7.1, and the *FB-10 Pathology and Correlative Science Instructions*.
g Required submission of tumor tissue (1 core) from an accessible metastatic site in 10% buffered formalin submitted to the NSABP Division of Pathology.
h Required submission of fresh tumor samples (2-3 cores) and whole blood collection submitted to Champions Oncology; see Section 7.0, Section 7.4
See the ***FB-10 Pathology and Correlative Science Instructions***, and the ***Champions Oncology Overview-Tumor Collection Logistics PDX Model Development*** for additional tumor and blood collection and submission instructions.

TABLE 2. Tests, exams, and other requirements **following study entry**

Required studies *(see footnote **a**)*	**Within 72 hours before Day 1 of every cycle unless indicated otherwise** *(Beginning with Cycle 1)*	**Follow-up** *(30 days +/- 7 days f following discontinuation of study therapy)*
History & physical exam[b]	X	X[d]
Weight	X	
Measurement of target lesions[c]	X (every 3 cycles during study therapy)	
Review of concurrent therapies[d]	X	
Adverse event assessment[e]	X	X[d] *(at 30 days)*
CBC/differential/platelets	X	X
Serum creatinine; total bilirubin/AST/ALT/alkaline phosphatase; calcium, potassium, sodium, BUN or urea	X	
2-D echocardiogram (or MUGA scan)[f]	X *(every 3 months during study therapy)*	X *(If not completed in past 4 weeks)*
Submission of tumor block[g]	X	
Required blood samples[h]	X *(Cycle 1/Day 1, Cycle 1/Day 8 and Cycle 2/Day1 only)*	X[i] *(at time of disease progression)*
Optional core biopsy[i]		X *(at time of disease progression)*

a At the discretion of the investigator, additional exams, bloodwork, x-rays, scans, and other testing may be performed as clinically indicated.

b Updated H&P with exams (by physician or other healthcare professional on the FDA 1572)

c Scans will be done every 3 cycles. The same imaging method used at baseline should be used at all other target lesion assessment time points. Assessment of measurable disease is by RECIST 1.1 criteria (see Section 13.0).

d See Sections 9.3.5, 9.3.6, 11.2.3, and Appendix B.

e Should the patient stop study therapy (e.g., due to disease recurrence/progression or second primary) and begin a new treatment *prior* to the 30 day assessment, AE assessment should be collected *only* up to the date the new therapy begins.

f Same method of LVEF assessment that was performed at baseline should be performed.

g Submission of diagnostic tumor block is required for all patients within 60 days following study entry; see Section 7.1, and the FB-10 Pathology and Correlative Science Instructions.

h Blood collection on Cycle 1/Day 1 and Day 8, and Cycle 2/Day 1 ***prior*** to taking neratinib: *Patients should be instructed **not** to take the daily neratinib dose on Cycle 1/Day 1 and Day 8, and Cycle 2/Day 1 until **after** blood collection.* See Section 7.0 .

i When disease progression has been confirmed by imaging per RECIST 1.1 criteria the following *optional* blood and tissue samples are to be collected ***from consenting patients*** within 30 days following discontinuation from study therapy and prior to initiating any new therapy:

- The optional blood sample *will be sent to the NSABP Division of Pathology.*
- The optional core biopsy specimens (2 to 4 cores) from an accessible metastatic site or one that increased in size when compared to the previous imaging scan result. *Samples should be submitted to Champions Oncology on the same day as procurement.* See Section 7.0.

See FB-10 Pathology and Correlative Science Instructions and the ***Champions Oncology Overview-Tumor Collection Logistics PDX Model Development*** for additional instructions.

7.0 PATHOLOGY AND CORRELATIVE SCIENCE STUDIES

7.1 Overview of requirements

Collection and submission of all patient samples are listed below. By signing the FB-10 consent form, the patient has agreed to all required tumor and blood sample collections and submissions. See Table 3. Non-submission of required patient samples will be a protocol violation.

In the phase II portion of FB-10, procurement and submission of core biopsy tumor specimens before study entry (mandatory). At the time of progression an optional biopsy procedure and tissue sample submission will be requested only from consenting patients. (See treatment consent form and optional biopsy consent form.)

TABLE 3. Summary of FB-10 patient sample submission requirements

Study Requirements for ALL Patients *(unless indicated otherwise)*	**Prior to Study Entry**	**Day 1 of Cycle 1**	**Day 8 of Cycle 1**	**Day 1 of Cycle 2**	**At time of disease progression**
Submission of a paraffin block from the diagnostic biopsy sample[a]	Yes[a] *(Samples must be submitted within 60 days after study entry)*				
Core biopsy to procure fresh tumor samples and whole blood for submission to *Champions Oncology*	***Yes[b], after consent signed and eligibility screening is complete*** Samples should be submitted on same day as procurement				Yes[e] *Optional*
Core biopsy to procure a tumor sample for submission to: *NSABP Division of Pathology*[c]	Yes[c], ***after consent signed and eligibility screening is complete*** Samples should be submitted on same day as procurement				
Required collection and submission of blood samples to NSABP Division of Pathology		Yes[d]	Yes[d]	Yes[d]	Yes[f] *Optional*

Table 3 continues on the next page

TABLE 3. Summary of FB-10 patient sample submission requirements (*continued*)

a Submission of an alternative tumor sample is permitted.

b *PDX Samples (whole blood and tumor) to Champions Oncology*:.
Required: Core biopsy specimens (2-3 cores) from an accessible metastatic site, preferably a metastatic hepatic lesion, and a whole blood sample will be collected for PDX prior to study entry from all patients. Fresh tumor and whole blood samples must be submitted overnight on the same day as procurement to Champions Oncology. (see Section 7.5.1) for PDX procurement and submission See Section 7.4.2 and Section 7.4.3.

c **Required:** Core biopsy specimens (1 core) from an accessible metastatic site, preferably a metastatic hepatic lesion, will be collected prior to study entry from all patients. See Section 7.4.2. Submission of tumor samples (1 core) in 10% buffered formalin will be submitted to *NSABP Division of Pathology.*

d Required research and pharmacokinetic (PK) blood sample collection must be drawn prior to neratinib and T-DM1 dosing: Cycle 1/Day 1, Cycle 1/Day 8 and Cycle 2/Day 1. *Patients should be instructed **not** to take the daily neratinib dose on Cycle 1/Day 1, Cycle 1/Day 8, and Cycle 2/Day 1 until **AFTER** blood sample collection. Note: The blood samples will be sent to the NSABP Division of Pathology.* See Section 7.0.

e When disease progression has been confirmed by imaging per RECIST 1.1 criteria, biopsy specimens preferably from a new accessible metastatic lesion or one that increased in size when compared to the previous imaging scan result are to be collected ***from consenting patients***. The *optional* tissue specimen collection must be obtained within 30 days following discontinuation from study therapy and prior to initiating any new therapy. *Tissue samples should be submitted to Champions Oncology on the same day as procurement.* See Sections 7.4.4 and 7.4.5.

f When disease progression has been confirmed by imaging per RECIST 1.1 criteria, blood samples are to be collected ***from consenting patients.*** *The optional samples will be sent to the NSABP Division of Pathology.*

Refer to the ***FB-10 Pathology and Correlative Science Instructions*** for tumor and blood sample submission instructions **and** to the ***Champions Oncology Overview-Tumor Collection Logistics PDX Model Development.***

7.2 Use of specimens

The blood and tumor samples collected in this study will be used for FB-10 studies as described in Section 7.2 and for analyses to be conducted in the future related to the purposes of the FB-10 study but not currently described in the protocol document. Additionally, the specimens procured may be used for future studies involving gene and protein conferring susceptibility to cancer or other diseases. If hereditary genetic studies are conducted, an anonymization process will be used. Results of the correlative science studies, including raw sequencing data, will not be reported directly to the patient or the physician and will not have any bearing on patient treatment.

The results of the study will be communicated through publication, in peer reviewed scientific literature and/or through presentations at scientific meetings. Anonymized or de-identified research data (as deemed appropriate by the NSABP), including genome sequencing data, may be submitted to public research databases for data sharing with controlled access to scientific researchers outside of the NSABP.

7.3 Tumor and blood sample submission procedures

The required FB-10 ***blood samples are submitted to the NSABP Division of Pathology* /or Champions Oncology** (see [redacted]) where the samples will be logged into the database and assigned a unique code number. The samples will be stripped of any remaining patient identifiers (except the NSABP FB-10 Patient ID numbers), processed, and stored. A portion of the samples may be shipped to collaborating laboratories. Refer to the FB-10 Pathology and Correlative Science Instructions for blood specimen collection and submission instructions.

Tumor tissue samples and blood samples, with the ***exception*** of fresh tumor tissue and whole blood for PDX, are to be submitted to the NSABP Division of Pathology ([redacted]) where the samples will be logged into the database and assigned a unique code number. The samples will be identified by the unique code number, processed, and stored. A portion of the samples may be shipped to collaborating laboratories.

7.4 Required tissue and blood samples

7.4.1 *Archived primary tumor tissue block*

Archived paraffin block of primary tumor tissue is required. Submitted diagnostic tumor tissue blocks from the primary tumor will be returned if possible upon requests from the sites. Refer to the FB-10 Pathology and Correlative Science Instructions for tumor tissue specimen collection and submission instructions.

7.4.2 *Required tissue samples*

- *To Champions Oncology*

Core biopsy specimens (2 to 3 cores) from an accessible metastatic site will be collected from all patients prior to starting study therapy for PDX procurement and submission. See Section 7.5.1. Refer to the *Champions Oncology Overview-Tumor Collection Logistics PDX Model Development for tissue and blood collection instructions specific to the processing of PDX samples.*

- *To NSABP Division of Pathology*

  Core biopsy tumor tissue (1 core) will be submitted in 10% buffered formalin.

7.4.3 *Required research blood samples*

To Champions Oncology:

- A blood sample for PDX will be collected with the core biopsy prior to starting study therapy and sent to Champions Oncology. See Section 7.5.1.

To NSABP Division of Pathology:

- Pharmacokinetic (PK) blood samples will be collected on:
  - *Cycle 1/ Day 1*
  - *Cycle 1/Day 8, and*
  - *Cycle 2/Day 1.*

  Note: Patients must be instructed **not to take** the daily neratinib dose on Cycle 1/ Day 1, Cycle 1/Day 8 and Cycle 2/Day1 until **AFTER** blood sample collection.
- Blood samples for future analysis will also be collected at time points coinciding with PKs:
  - *Cycle 1/ Day 1*
  - *Cycle 1/Day 8, and*
  - *Cycle 2/Day 1.*

7.4.4 *Optional blood and tissue sample procurement*

When disease progression has been confirmed by imaging per RECIST criteria the following optional blood and tumor tissue samples should be collected from ***consenting patients*:**

- Core biopsy specimens procured ***from consenting patients,*** preferably from a new accessible metastatic lesion or one that increased in size when compared to the previous imaging scan result. Tissue samples should be submitted to Champions Oncology on the same day as procurement. See Section 7.5.

- Blood samples are to be collected ***from consenting patients.*** The optional samples will be sent to the NSABP Division of Pathology.

  Note: Biopsy specimens and blood samples at the time of progression must be collected within 30 days following discontinuation from study therapy and prior to initiating any new therapy.

7.5 Patient derived xenografts (PDX)

7.5.1 *PDX tissue and blood samples:*

As a requirement of FB-10 phase II, patients will have a baseline fresh tumor tissue biopsy, and a blood sample submitted to Champions Oncology for generation of the PDX model. Upon disease progression an optional biopsy (preferably from a new accessible metastatic lesion or one that increased in size when compared to the previous imaging scan result) will be collected from consenting patients and submitted to Champions Oncology. Specimens will be placed into vials containing transport medium that will be provided by Champions Oncology and labeled with a unique trial number identifier. *Refer to Champions Oncology Overview-Tumor Collection Logistics PDX Model Development for tissue and blood collection instructions specific to the processing of PDX samples.*

- **Tumor Tissue**
  Fresh tumor tissue will be obtained through surgical procedure or biopsy. To maximize the success of tumor engraftment in the immune-deficient mouse, it is requested that 0.5 cm^3 or 3 to 4 x 18 gauge biopsies be obtained.

  Transportation of the specimen to the designated implantation site will be arranged in advance with Champions Clinical Operations team. Ideally, the time from tumor extraction to placement in media should be as soon as possible but less than 30 minutes. Exact times will be recorded. Refer to the Champions Oncology Overview-Tumor Collection Logistics PDX Model Development for tissue collection instructions specific to the processing of PDX samples.

- **Whole Blood Sample**

  A whole blood sample will also be submitted at the time of tumor biopsy or surgical procedure to Champions Oncology. This will enable a comparison of normal DNA profile to tumor DNA. Once collected, whole blood samples will be included with tissue specimen collection in an insulated container for transport to the designated implantation site.

7.6 PDX Model Development

7.6.1 *Tumor graft*

Upon receipt of the tumor specimen at the designated implantation site, tumor tissue will be implanted into immune-deficient mice following the standard operating procedures (SOPs). The expected success rate in generating a viable model in metastatic breast cancer for drug testing is approximately 50%.

7.6.2 *Assessment of response in the tumor graft*

Drugs selected for testing in this model will be determined by the same agents that the patient will receive in the clinical study except in the PDX, the agents will be tested as single agents and in combination.

Agent Efficacy: All test agents will be formulated according to manufacturer's specifications for testing in a mouse model. Cohorts of mice will be randomized into treatment groups. Drug sensitivity testing will last for a total of 28 days. Beginning Day 0, tumor dimensions will measured twice weekly by digital caliper and data, including individual and mean estimated tumor volumes (Mean TV ± SEM), are recorded for each group. Tumor volume was calculated using the formula: $TV= width^2 \times length \times \pi/2$.

Tumor Growth Inhibition: At study completion, percent tumor growth inhibition (%TGI) values will be calculated and reported for each treatment group (T) versus control (C) using initial (i) and final (f) tumor measurements by the formula: $\%TGI=[1-(T_f-T_i)/(C_f-C_i)] \times 100$.

RECIST: Individual mice reporting a tumor volume >120% of the Day 0 measurement are considered to have progressive disease (PD). Individual mice with neither sufficient shrinkage nor sufficient tumor volume increases are considered to have stable disease (SD). Individual mice reporting a tumor volume ≤70% of the Day 0 measurement for two consecutive measurements over a seven day period are considered partial responders (PR). If the PR persisted until study completion, percent tumor regression (%TR) is determined using the formula: $\%TR= (1-T_f/T_i) \times 100$; a mean value is calculated for the entire treatment group. Individual mice lacking palpable tumors for two consecutive measurements over a seven day period are classified as complete responders (CR). All data collected in this study will be managed electronically and stored on a redundant server system.

7.7 Rationale for correlative science studies

Obtaining core biopsy samples pretreatment and at disease progression for molecular profile provides a unique opportunity to discover candidate predictive markers of response or potential resistance to the study drugs and opportunity to understand the mechanism of resistance to study drugs.

Since T-DM1 is an antibody-drug conjugate directed to HER2 overexpressing tumor cells, HER2 expression level is expected to be the main predictor of response, with higher levels associated with better response. On the other hand neratinib is a pan-HER family tyrosine kinase inhibitor and therefore is expected to be effective for tumor cells with dependence on any members of HER family of receptors.

Hence our primary hypothesis is that T-DM1/neratinib in combination would be effective in tumors dependent on any member of the HER family receptors. We hypothesize that intrinsic resistance to T-DM1/neratinib could happen due to activation of other receptor signaling pathway such as IGFR or MET bypassing HER receptors, or through activation of downstream signaling pathway (such as PIK3CA or AKT) due to activating mutation. Since tumor cells with high levels of HER2 expression may be readily killed by T-DM1 regardless of PIK3CA mutation due to its chemotherapy effect, it is hypothesized that HER2 positive tumors with relatively lower levels of HER2 and PIK3CA mutation would be relatively resistant to T-DM1/neratinib combination therapy.

In order to address the hypotheses delineated above, we may perform molecular profiling of procured tumor tissue samples from consenting patients through comprehensive gene expression profiling (using RNAseq or nCounter assay), phosphoprotein profiling with reverse phase protein array, and mutation profiling (with next generation sequencing or hotspot mutation profiling with mass spec). Tissue from PDX models will be obtained to provide greater insight into these molecular analyses.

PDX models have the potential of being informative in the patient population being tested in this study. The results from the clinical trial, Emilia, in which second line T-DM1 was given to patients after first-line metastatic disease treated with trastuzumab and a taxane reported an objective tumor response of 43% (Verma 2012). Since that trial was conducted, the standard treatment for first-line HER2+ MBC includes a taxane plus both trastuzumab and pertuzumab. There is anecdotal evidence that the response to T-DM1 after dual anti-HER2 antibody therapy is substantially reduced, tumor response rate 17% (Dzimitrowicz 2016).

While the current trial is evaluating T-DM1 plus neratinib in patients who have had prior trastuzumab and pertuzumab, testing PDX models with T-DM1 alone, neratinib alone and the combination of T-DM1 plus neratinib may provide evidence as to the value of the combination and provide tissue for understanding potential mechanisms of sensitivity and resistance.

In addition to proposed experiments listed above, blood samples collected on Day 1 of Cycle 1 (prior to receiving the first dose of study therapy), at Cycle 1/Day 8 and also on Day1 of Cycle 2 before study therapy dosing may be used for determinations of pharmacokinetic interactions and therapeutic drug monitoring (TDM). TDM analysis measures the plasma concentrations of a therapeutic agent and metabolites in patients to individualize appropriate drug dosages and schedules (Gao 2012). Individual pharmacokinetic variations in absorption, metabolism and elimination ultimately affect total drug concentration and drug exposure resulting many times in under-dosing of patients or overdosing leading to toxicities. Therefore, TDM can potentially be used to adjust individual drug dosages by correlating with drug exposure and pharmacodynamic response, resulting in maximum drug efficacy while decreasing relative toxicities.

Blood will be collected at various time points before and during treatment and may be used to quantify and characterize circulating tumor DNA (ctDNA), sequencing of circulating free tumor DNA and assay for ADCC as well as other analyses as they pertain to this study.

8.0 DOSE ESCALATION

Note: Accrual to the Phase I dose escalation portion of FB-10 was closed on May 3, 2017.
See Section 9.0 for the study therapy regimen of the Phase II portion.

8.1 Dose escalation design

TABLE 4. Dose escalation design

Dose level	Neratinib	T-DM1	No. of Patients
1	120 mg/day PO	3.6 mg/kg IV Day 1 every 3 weeks	3 to 6
2	160 mg/day PO	3.6 mg/kg IV Day 1 every 3 weeks	3 to 6
3	200 mg/day PO	3.6 mg/kg IV Day 1 every 3 weeks	3 to 6
4	240 mg/day PO	3.6 mg/kg IV Day 1 every 3 weeks	3 to 6

The first cohort will be treated at dose level 1. If 1 of 3 patients in this cohort experiences a DLT, 3 more patients will be added at the same dose level. If 0 of 3 initial patients or 1 of 6 patients in an expanded cohort experiences a DLT, the dose for the next cohort will be escalated to dose level 2; otherwise, the combination will be considered too toxic. However, if 2 or more patients assigned to study therapy **Dose level 1, Cycle 1** experience a DLT due to grade 4 thrombocytopenia, the study will continue with the following actions:

- The T-DM1 dose will be decreased to 3.0 mg/kg (T-DM1 level-1) for all patients subsequently enrolled on study.
- The T-DM1 dose will not re-escalate. T-DM1 dose 3.0 mg/kg will become the starting dose for all other study therapy dose levels.
- Grade 4 thrombocytopenia will remain a DLT during Cycle 1 for all subsequent dose levels.
- Study therapy dose treatment management, *after* completion of Cycle 1, will continue as described in Section 10.

Similarly, at dose level 2 and subsequent dose levels if 1 of 3 patients experiences a DLT, 3 more patients will be added. If ≥ 2 DLTs are experienced at any dose level, the combination will be considered too toxic and the next lower dose level will be considered the MTD. If only 3 patients were treated at the MTD, an additional 3 patients will be entered into the cohort. The MTD at which < 2 of 6 patients experience a DLT will be the RP2D.

In addition to DLT identification that occurs during Cycle 1, the overall emerging toxicity profile will be taken into consideration when determining the MTD. Given that diarrhea is the most frequent DLT, an overall safety profile of < 25% grade 3 diarrhea is expected. Should ≥ 25% grade 3 diarrhea lasting more than 24 hours be observed cumulatively at a given dose level while receiving optimal diarrhea management, the MTD may be decreased by one dose level.

8.2 Definition of dose-limiting toxicity (DLT)

Toxicities should be attributable to the study drugs (possible, probable, or definite) to constitute DLT. Occurrence of one or more of the following during the **first** cycle of treatment will constitute a DLT:

- Diarrhea (any grade) that is associated with fever or dehydration requiring IV fluids

- Grade 3 diarrhea lasting > 2 days on optimal medical therapy
- Grade 4 diarrhea of any duration
- Grade 3 or 4 neutropenia associated with fever
- Grade 4 neutropenia lasting > 7 days
- Grade 4 thrombocytopenia
- Grade 3 or 4 nonhematological toxicity (excluding grade 3 rash or allergic reaction/hypersensitivity)
- Toxicity-related delay of > 2 weeks to initiate cycle 2.

Patients will be enrolled in the next dose level when all evaluable patients at the same dose level have been completed the first treatment cycle.

8.3 **Dose escalation rules**

- Only DLTs observed during Cycle 1 of treatment will affect dose escalation.
- Patients who do not continue on study and are not evaluable for toxicity assessment during the first cycle will be replaced.

9.0 STUDY TREATMENT

Note: On May 3, 2017, the Cycle 1 DLT evaluation of the four neratinib dose escalation levels was completed.

See Section 9.1, Table 5 for the Phase II portion of the study.

9.1 Treatment regimen

Study therapy should begin within 2 weeks following study entry.

TABLE 5. Treatment regimen – **Phase II**

Drug	Dose	Dosing Interval	Planned Duration
T-DM1	*First dose:* 3.6 mg/kg IV over 90 min[a,b] *Subsequent doses:* 3.6 mg/kg IV over 30 min[a,b] *(Premeds at investigator's discretion)*	Day 1 of a 3-week cycle (q 21 days)	Until study therapy is stopped due to toxicity *or* disease progression
Neratinib	**160 mg** PO once daily (40 mg tablets taken with food, preferably in the morning)[c]	Daily beginning on Day 1 of the first T-DM1 cycle	

a The first infusion of T-DM1 will be administered over 90 minutes (+/- 10 minutes).

- Vital signs must be assessed before and after each dose administration. At the physician's discretion, premedication e.g., dexamethasone, diphenhydramine, and an H2-blocker may be used.
- Infusions may be slowed or interrupted for patients experiencing infusion-related symptoms.
- Observe patients for 60 minutes following the initial dose for fever, chills, or other infusion-related symptoms.
- If prior infusions were tolerated well, subsequent doses may be administered over 30 minutes (+/- 10 minutes) with a minimum 30 minute observation period after the infusion.

b See Section 10.5 and Table 8 for instructions regarding T-DM1 infusion-related allergic reactions and anaphylaxis.

c Other neratinib instructions:

See Section 10.6 for mandatory prophylactic antidiarrheal therapy instructions and Appendix C.

- If a neratinib dose is missed at the usual time, it should be taken as soon as possible ***within 12 hours*** following the time the dose should have been taken. If >12 hours, the dose will be missed for that day.
- If a patient vomits after taking neratinib, the patient should be instructed to not take another dose that day (unless the tablets can be seen). The patient should resume taking neratinib at the next scheduled dose. If vomiting persists, the patient should be instructed to notify the investigator. See Section 10.2.1.
- Neratinib absorption is dependent on stomach acidity. See Sections 9.3.5, , and 11.2.3 for neratinib dosing and concomitant medication guidance.
- Mandatory telephone calls are required during Cycle 1 as per Section 10.6.1.

Use of a patient diary, calendar, or other tool for the patient to record neratinib doses should be strongly encouraged.

9.2 Dose determinations

9.2.1 *Calculation of drug doses*

- Starting doses for T-DM1 must be based on the patient's baseline weight.

9.2.2 *Rounding doses*

Rounding of T-DM1 dose is optional. If the treating physician decides to round the dose, follow these guidelines. (These also apply to dose modifications.) T-DM1 should be rounded to the nearest 20 mg. See Table 5, Section 10.8.1 and Table 6.

9.3 Supportive therapy

9.3.1 *G-CSF*

- Prophylactic use of growth factors, e.g., G-CSF, GM-CSF, is not permitted.

9.3.2 *Erythropoietin*

Use of an erythropoiesis-stimulating agent is not permitted. (See Section 10.4 for instructions regarding ≥ grade 3 anemia.)

9.3.3 *Antiemetic therapy*

Antiemetic therapy should be administered according to NCCN or ASCO Clinical Practice Guidelines.

9.3.4 *Management of diarrhea*

Diarrhea is a commonly occurring toxicity with the therapy included in FB-10. Primary antidiarrheal prophylactic medication must begin with the first dose of neratinib. Patients must be instructed to have ready access to antidiarrheal agents (loperamide and budesonide) at home, starting on Day 1 of treatment. Patients must also be instructed regarding the importance of prompt reporting of diarrhea, use of antidiarrheal medications and non-pharmacologic interventions. See Section 10.6 and Appendix C for diarrhea management instructions and Table 8 in Section 10.9 for T-DM1/neratinib treatment management instructions.

Patients taking neratinib who have multiple loose bowel movements in a day or any worsening of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash, or eosinophilia should be promptly evaluated for changes in liver function. (See Appendix C for sample patient instructions for diarrhea management.)

9.3.5 *Proton pump inhibitors*

Avoid concomitant use of proton pump inhibitors (PPI). It has been observed that a single 240-mg dose of neratinib combined with a proton pump inhibitor lowered the absorption of neratinib up to seven-fold. It is not known whether separating the time of taking a proton pump inhibitor and neratinib reduces the interaction.

9.3.6 *H2-receptor antagonists and antacids*

The absorption of neratinib in the stomach is dependent on stomach acidity. Medications that reduce the secretion of gastric acid in the stomach such as H2-receptor antagonists (e.g., ranitidine) may affect how neratinib dissolves in the stomach. It is not known whether separating the time of taking an H2-blocker and neratinib reduces the interaction.

If antacids are necessary, the antacid dose and the neratinib dose should be separated by 3 hours.

9.4 Prohibited therapies

The following types of treatment, in addition to any cancer therapy other than the therapy specified in this protocol, are prohibited while on study therapy.

9.4.1 *Chemotherapy*

Administration of chemotherapy other than the chemotherapy specified in this protocol is prohibited.

9.4.2 *Targeted therapy*

Administration of targeted therapy for malignancy (other than the assigned targeted therapy regimen) is prohibited.

9.4.3 *Radiation therapy*

Radiation therapy (RT) to target lesions is prohibited. Palliative RT to non-target lesions is permitted.

9.4.4 *CYP3A4/5 inhibitors*

Concomitant use of strong CYP3A4/5 inhibitors (such as ketoconazole and itraconazole) with T-DM1 and neratinib should be avoided. An alternate medication with no or minimal potential to inhibit CYP3A4/5 should be considered. If a strong CYP3A4/5 inhibitor is co-administered with study therapy (T-DM1 and neratinib), patients should be closely monitored for reactions. (See Appendix B.)

9.5 Participation in other clinical trials

If an FB-10 patient is considering participation in another clinical trial (including supportive therapy trials), contact the DSSM ([redacted]).

10.0 TREATMENT MANAGEMENT

10.1 General instructions

- The NCI CTCAE v4.0 must be used to grade the severity of AEs.
- All treatment decisions must be based on the AE requiring the greatest modification.
- Drug doses that have been reduced may not be escalated.
- Patient compliance with neratinib must be maintained by pill count prior to beginning each cycle.

10.2 Treatment management for T-DM1 and neratinib

The T-DM1 treatment schedule should be maintained. If necessary, the timing of a treatment may be adjusted to 3 days earlier or 3 days later than the scheduled date of treatment.

10.2.1 *Treatment decisions when therapy must be held*

- See Table 8 for treatment management.
- If T-DM1 and neratinib are held for > 3 days but < 2 weeks, the date when T-DM1 and neratinib are resumed becomes Day 1 of the next cycle.
- If study therapy must be held for > 2 weeks of ***continuous delay***, study therapy must be discontinued (see Section 10.2.2).
- NOTE: If the patient experiences acute vomiting or diarrhea with concomitant T-DM1 and neratinib, on subsequent cycles neratinib may be held for up to 4 days (e.g., Day 1 T-DM1 administered; neratinib held on days 1, 2, 3, 4). Resume neratinib daily. Record doses of neratinib held.

10.2.2 *Treatment decisions when therapy must be discontinued*

- If a patient experiences a T-DM1 adverse event requiring drug discontinuation, neratinib may be continued at the current dose level. If a patient experiences an adverse event attributable to neratinib requiring discontinuation, T-DM1 may be continued at the current dose level. This option is available after a patient has demonstrated an objective response or stable disease per RECIST criteria.
- If alternative (non-protocol) therapy is given at any time, study therapy must be discontinued.
- If study therapy is discontinued, further therapy is at the investigator's discretion.

10.3 Study therapy following tumor progression

If tumor progression occurs during study therapy, study therapy must be discontinued. Further therapy is at the investigator's discretion.

10.4 Management of anemia

Transfusion is acceptable for improving the hemoglobin value to allow therapy to continue without delay. *Use of erythropoiesis-stimulating agents is prohibited.*

10.5 Infusion reactions/allergic reaction - T-DM-1

See Table 8 for treatment management instructions.

- Grade 1 infusion reaction:
  - Slow the infusion and assess the patient; management is at the investigator's discretion.

- Grade 2 infusion reaction:
  - Decrease the infusion rate by 50% (or interrupt) and monitor closely for worsening condition.
  - Administer appropriate therapy per investigator's discretion.
  - Restart at **50%** infusion rate, may increase rate by 50% increments every 30 minutes as tolerated.
  - When symptoms resolve to ≤ grade 1, infusion may be resumed later that day or on the next day with premedications.
  - Premedications should be used for all subsequent treatments.
  - Infusions may be restarted at full rate at the next cycle with appropriate monitoring for all subsequent treatments.
- Grade 3 infusion reaction:
  - If determined by the investigator to be **non-serious**, follow the instructions for grade 2 infusion reaction
  - If determined by the investigator to be **serious**, immediately and permanently discontinue T-DM1.

10.6 Management of diarrhea

Diarrhea is a commonly occurring toxicity with the therapies included in FB-10. Monotherapy with neratinib has a median time of 3 days to onset of diarrhea. With combination therapy, it is anticipated that diarrhea may occur earlier. For the majority of patients, diarrhea subsides after about first cycle. **Therefore it is critical that intensive prophylactic measures begin at the start of therapy.** (See Section 10.6.1 and Appendix C.)

10.6.1 *Intensive primary prophylaxis*

Recent preclinical studies suggest that multiple mechanisms may be involved in the pathogenesis of neratinib-induced diarrhea, including elements of secretory and inflammatory diarrhea (Puma biotechnology, on file). Interim analysis of CONTROL study reported a cohort of patients testing budesonide, a locally acting corticosteroid used for inflammatory gastrointestinal conditions, had reduced grade 3 diarrhea by approximately 50% (to 16%) (Barcenas 2016). Budesonide has a high first-pass metabolism with minimal systemic absorption. It is therefore felt to cause fewer side effects than traditional glucocorticosteroids and to be generally well tolerated (O'Donnell 2010).

Antidiarrheal medications must begin with the first dose of neratinib. Inform patients that they will experience diarrhea while taking neratinib.

- **Loperamide (Imodium®)**
  - Patients must receive an initial dose of **loperamide** 4 mg (2 tablets) with the first dose of neratinib.
  - Following the initial dose of **loperamide** patients should take loperamide 4 mg (2 tablets) every 6 hours for the first 48 hours (total: 8 tablets /day).
  - After the first 48 hours if diarrhea is < grade 2, the patient should be instructed to take loperamide 2 mg (1 tablet) every 4 hours while awake, and 4 mg (2 tablets) at bedtime for the first 2 weeks of therapy. If diarrhea persists, the patient should be instructed to continue loperamide 4 mg (2 tablets) every 6 hours until diarrhea is < grade 2 (see Section 10.6.2 and Appendix C.)

- After the first 2 weeks of Cycle 1, instruct patients to take loperamide 2 mg (1 tablet) every 6 to 8 hours. After Cycle 1 loperamide may be titrated loperamide as needed to keep diarrhea < 4 stools a day. See Appendix C for further patient instructions.

- ***Budesonide*** (Entocort®, Uceris®, or Pulmicort®)
  - Patients must receive an initial dose of **budesonide 9** mg by mouth with the first dose of neratinib and be instructed to take **budesonide** 9 mg once daily during Cycle 1 and Cycle 2.
  - Patients should be instructed to take budesonide 9 mg by mouth (once daily in the morning) with a full glass of water (8 ounces/240 milliliters) with or without food. Patients should be instructed to swallow this medication whole; do not crush or chew. If patients will be using the extended-release tablets, they should not split the tablets unless they have a score line and they are instructed to do so. Patients should swallow the whole or split tablet without crushing or chewing.

(*Note: The participating study site will dispense a packet containing 30 (2 mg) tablets of loperamide to each study patient for the start of diarrheal prophylaxis. Subsequent loperamide doses will be the responsibility of the patient. Loperamide is available OTC. Budesonide will be provided or reimbursed for Cycle 1 and 2.*)

- **Mandatory** telephone calls must be made to patients by a clinical trial team member during Cycle 1, Days 2, 3, and 4 (i.e., approximately 24, 48, and 72 hours after start of study therapy). Documentation should include:
  - Date of call;
  - Response of patient's report of adverse events; and
  - Any action taken.
  - Telephone calls should continue as needed during cycle 1.
- Patients **must** be instructed to:
  - Start prophylactic loperamide on Day 1, with the first dose of neratinib.
  - Start prophylactic budesonide on Day 1, with first dose of neratinib.
  - Continue prophylactic therapy as directed.
  - Promptly report diarrhea symptoms.
    Note: Patients taking T-DM1/neratinib who have multiple loose bowel movements and any worsening of fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash, or eosinophilia should be promptly evaluated for changes in liver function. See Section 10.11.
  - Record the number of stools per day.
  - Record each dose of antidiarrheal medicine taken each day.
  - Report constipation *before* taking any laxatives or stopping antidiarrheal medication.

10.6.2 ***Pharmacologic diarrhea management***

- For patients with persistent grade 1 diarrhea on loperamide, diphenoxylate hydrochloride and atropine sulfate (Lomotil®) 1 tablet every 6 to 8 hours may be added.
- For Grade 3 or Grade 4 diarrhea with complicating features (dehydration, fever, and/or Grade 3-4 neutropenia).
  - Hold study therapy.
  - Administer loperamide: initial dose of 4 mg (2 tablets/capsules) with the first bout of diarrhea followed by 2 mg (1 tablet/capsule) every 4 hours or after every

unformed stool (maximum 16 mg a day) and continue loperamide at this frequency until diarrhea free for 12 hours. Then titrate the amount of loperamide used to keep diarrhea controlled (< 4 stools/day).
  - Use IV therapy as appropriate.
  - Stool cultures should be done to exclude infectious causes of Grade 3 or 4 diarrhea or diarrhea of any grade with complicating features (dehydration, fever, and/or Grade 3 or 4 neutropenia) per the Investigator's discretion. Positive results from occult blood, fecal leukocyte stain, *Clostridium difficile, Campylobacter, Salmonella, and Shigella* testing, if performed, must be reported using the appropriate eCRF.
  - Consider prophylactic antibiotics as needed (e.g., fluoroquinolones) especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia.
  - Recommend dietary measures outlines in Section 10.6.3.
  - See Table 8 for study therapy dose management.
- Patients should be monitored for constipation and prophylaxis adjusted accordingly. Do not discontinue antidiarrheals completely; doses may be adjusted.
- For the second and subsequent cycles, the dose of loperamide should be titrated to keep diarrhea controlled to < 4 stools a day.

10.6.3 *Dietary management*

Instruct patients to:

- Stop all lactose-containing products (milk, yogurt, cheese, etc.).
- Drink 8-10 large glasses (64-80 ounces) of clear liquids per day.
- Eat frequent small meals.
- Maintain a low fat diet enriched with rice, bananas, and applesauce, and/or toast.

10.6.4 *Dose modifications*

For study therapy dose modifications, see Section 10.8, and Table 6, Table 7 and Table 8.

Note: Hematological dose modifications should be made on the basis of values obtained for Day 1 of each cycle and not on interim laboratory values that may be obtained in between cycles. However, should the patient experience clinical symptoms or associated toxicities, dose adjustment may be made at the investigator's discretion in conjunction with the study team.

Refer to the ASCO *Recommended Guidelines for Treatment of Cancer Treatment-Induced Diarrhea* for additional recommendations regarding diarrhea (Benson 2004).

10.7 Management of dermatologic toxicities

10.7.1 *Management of paronychia and fissures in fingertips*

Note: Paronychia and fissures involving the fingertips have not been determined to be an effect of neratinib, but are an effect of similar drugs. Therefore, the following management instructions are provided:

- *Paronychia*
  For treatment of paronychia, antiseptic bathes and topical corticosteroids are recommended. Other topical measures include use of silver nitrate applications. Topical or oral antibiotics should be considered if local infection is present. If no improvement is seen, a dermatology consultation is recommended. See Table 8 for dose modifications and delays for paronychia. (See also Appendix D, Figure 3.)

- *Fissures in fingertips*
  For fissures in the fingertips, an application of zinc oxide 30% (or higher) ointment may be used.

10.8 Dose modifications for T-DM1 and neratinib

Dose modifications for T-DM1 are based on dose level changes outlined in Table 6. Dose level changes for neratinib are outlined in Table 7.

10.8.1 *Dose modifications for T-DM1*

TABLE 6. Dose levels for **T-DM1 (Phase II)**

	Dose Level 0 ***Starting Dose***	**Dose Level −1**	**Dose Level −2**	**Dose Level −3**
T-DM1	3.6 mg/kg	3.0 mg/kg	2.4 mg/kg	Discontinue

10.8.2 *Dose modifications for neratinib*

TABLE 7. Dose levels for **neratinib (Phase II)**

	Dose Level 0 ***Starting Dose***	**Dose Level −1**	**Dose level −2**
Neratinib	160 mg (3 tablets)	120 mg	DC

10.9 Management of toxicities during T-DM1 and neratinib

The instructions for management of toxicities during T-DM1 and neratinib are outlined in Table 8. See Table 9 for T-DM1 and neratinib management based on LVEF assessments.

TABLE 8. Treatment management for **T-DM1 and neratinib (Phase II)**

CTCAE v4.0 Adverse Event	**CTCAE v 4.0 Grade**	**Action to be Taken**	
		T-DM1	**Neratinib**
Blood and lymphatic system disorders			
Febrile neutropenia	3	Hold until ≤ grade 1 *1st appearance:* ↓ one dose level *2nd appearance:*↓ one dose level *3rd appearance:* Discontinue	Hold until ≤ grade 1 *1st appearance:* Maintain dose *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue
	4	Hold until ≤ grade 1 *1st appearance:* ↓ one dose level or Discontinue *2nd appearance:* Discontinue	Hold until clinically stable *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue
Cardiac Disorders			
• **Acute coronary syndrome** • **Myocardial infarction**	2	Hold study therapy and conduct a cardiac evaluation. Based on this evaluation, continuation of study therapy is at the investigator's discretion.	
	3, 4	Discontinue	

Table 8 continued on next 4 pages.

TABLE 8. Treatment management for T-DM1 and neratinib (Phase II) (*continued*)

CTCAE v4.0 Adverse Event	CTCAE v 4.0 Grade	Action to be Taken	
		T-DM1	**Neratinib**
• **Conduction disorder** • **Supraventricular and nodal arrhythmia** • **Ventricular arrhythmia**	2	Hold until rhythm is controlled; then resume (maintain doses)	
	3, 4	Discontinue	
Gastrointestinal disorders			
Diarrhea (Attributed to therapy, *see Sections 10.2.1, 10.6 and Appendix C)*	1	Maintain dose without delay; adjust antidiarrheal medication.	
	2	*Lasting more than 24 hours*:	
		Hold until neratinib can be resumed, then maintain dose	Hold until ≤ grade 1; adjust antidiarrheal medication; *1st appearance:* Maintain dose *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue
	3	*Hold until neratinib can be resumed*, then maintain dose	Hold until ≤ grade 1 *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue
	4	Discontinue	
Mucositis	2	*Hold until neratinib can be resumed*, *1st appearance:*↓ one dose level *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue	Hold until ≤ grade 1 *1st appearance:* Maintain dose *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue
	3, 4	Discontinue	
Vomiting *(Despite anti-emetics)* See Section 10.2.1.	2	Maximize anti-emetics, IV hydration as needed	
		Hold until ≤ grade 1 *1st appearance:* ↓ one dose level *2nd appearance:* ↓ one dose level or Discontinue *3rd appearance:* Discontinue	Hold until ≤ grade 1 *1st appearance:* Maintain dose *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue
	3, 4	Discontinue	
Hepatobiliary Disorders			
For any signs of liver dysfunction ≥ Grade 3 AST/ALT or Grade ≥ 2 bilirubin elevation, discontinue study therapy, and consider patient evaluation by a hepatologist. If there are signs of portal hypertension (e.g., ascites or varices) and a cirrhosis-like pattern on CT scan of the liver, the possibility of Nodular Regenerative Hyperplasia (NRH) should be considered. (See Table 8, "Investigations": AST/SGPT, AST/SGOT, and bilirubin.)			

Table 8 continued on next 3 pages

TABLE 8. Treatment management for T-DM1 and neratinib (Phase II) (*continued*)

CTCAE v4.0 Adverse Event	CTCAE v 4.0 Grade	Action to be Taken	
		T-DM1	**Neratinib**
Immune System Disorders			
Allergic reaction/infusion reaction *See Section 10.5 for instruction on infusion rate adjustments and/or supportive therapy*	1	Maintain dose Adjustments per Section 10.5.	Maintain dose with no delay
	2	Decrease infusion rate by 50% (or interrupt) Adjustments per Section 10.5.	Hold until ≤ grade 1; Maintain dose
	3	Hold until ≤ grade 1; or decrease infusion rate *1st appearance:* ↓ one dose level *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue.	If determined by the investigator to be **non-serious** Hold until ≤ grade 1; Maintain dose If determined by the investigator to be **serious,** or 3rd appearance, permanently discontinue.
	4	Discontinue	
Infections and infestations			
Infection *(By site with normal ANC or grade 1 or 2 decrease in neutrophils)*	3	Hold until ≤ grade 1 *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue	Hold until ≤ grade 1 *1st appearance:* Maintain dose *2nd appearance:* Discontinue
	4	Discontinue	
Paronychia *(Note: See Section 10.7.1 and Appendix D, Figure 3.)*	2	*Hold until neratinib can be resumed*, then maintain dose.	*1st appearance:* Continue without delay ***or*** hold until improvement and maintain dose *2nd appearance:* If recurrent or intolerable, hold until improving and ↓ one dose level *3rd appearance:* Maintain dose or ↓ one dose level or Discontinue *if intolerable*
	3	*Hold until neratinib can be resumed*, *1st appearance:* ↓ one dose level *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue	Hold until ≤ grade 2 *1st appearance:* Maintain dose *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue
	4	Discontinue	

Table 8 continued on next 2 pages.

TABLE 8. Treatment management for T-DM1 and neratinib (*continued*)

CTCAE v4.0 Adverse Event	CTCAE v 4.0 Grade	Action to be Taken	
		T-DM1	**Neratinib**
Investigations			
Alanine aminotransferase (ALT)/Aspartate aminotransferase (AST) increased *(See Sections 10.11 and 12.3.3 for information and reporting requirements related to potential Hy's Law cases.)*	2-3	Hold until stable ≤ grade 1 *1st appearance:*↓ dose level *2nd appearance:* Discontinue	Hold until ≤ grade 1 *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue
	4	Discontinue	
Blood bilirubin increased *(See Sections 10.11 and 12.3.3 for information and reporting requirements related to Hy's Law cases.)*	2	Hold until stable ≤ grade 1 *1st appearance:*↓ dose level *2nd appearance:* Discontinue	Hold until ≤ grade 1 *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue
	3, 4	Discontinue	
Neutrophil count decreased *(See Section 9.3.1)*	3	*Hold until ≥ 1000/mm3.* *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue	*Hold until ≥ 1000/mm3* *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue
	4	Discontinue	
Platelet count decreased *Assessment should be based on the platelet count from the bloodwork for Day 1 of the cycle. (See Section 10.8.1 for T-DM1 dosing.)*	2. 3	*Hold until ≥ 75,000/mm3.* *Hold until neratinib can be resumed*, then maintain dose *1st appearance:* ↓ one dose level *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue	*Hold until ≥ 75,000/mm3* *1st appearance:* Maintain dose *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue
	4	Discontinue	
Nervous system disorders			
Peripheral neuropathy *(associated with T-DM1 infusion)*	3	***Hold until ≤ grade 2***, then: *1st occurrence:* ↓ one dose level *2nd occurrence:* ↓ one dose level *3rd appearance:* Discontinue	**Hold until ≤ grade 2**, then: Continue without delay.
	4	Discontinue	

Table 8 continued on next page.

TABLE 8. Treatment management for T-DM1 and neratinib (*continued*)

CTCAE v4.0 Adverse Event	CTCAE v 4.0 Grade	Action to be Taken	
		T-DM1	**Neratinib**
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	2	Hold study therapy until ≤ grade 1 and CHF and interstitial pneumonitis have been ruled out. • ***If caused by CHF or interstitial pulmonary toxicity***, discontinue study therapy • ***If caused by infection or asthmatic process***, resume therapy when symptoms have resolved to ≤ grade 1	
	3, 4	Discontinue	
Pneumonitis/ pulmonary infiltrates/other pulmonary events **Hypoxia** **Pneumonitis** **Pulmonary fibrosis**	2	***Hold study treatment until pneumonitis is evaluated.*** • If infection is documented, treatment may be resumed when pulmonary AEs have resolved to ≤ grade 1. • If non-infectious interstitial lung disease is confirmed, study must be discontinued	
	3, 4	Discontinue	
Skin and subcutaneous tissue disorders			
Rash acneiform *(See Section 10.7.1)*	2	Hold until neratinib can be resumed, then: *1st appearance:* Maintain dose *2nd appearance:* ↓ one dose level *3rd appearance:* Discontinue	*1st appearance:* hold until improvement then: Maintain dose *2nd appearance:* If recurrent or intolerable, hold until improving and ↓ one dose level *3rd appearance*: Discontinue
	3	*Hold until neratinib can be resumed*, then *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue	Hold until ≤ grade 2 *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue
	4	Discontinue	
Other			
• **Other AEs requiring dose modification per investigator** *(Note: Investigator must determine attribution of AE and only follow dose modifications for the **causal agent**.)*	2	Hold until ≤ grade 1 then: *1st appearance:* ↓ one dose level *2nd appearance:* Discontinue	*1st appearance:* Continue without delay ***or*** hold until improvement; Maintain dose or ↓ one dose level *2nd appearance:* Discontinue
	3, 4	Discontinue	

10.10 Cardiac left ventricular dysfunction

10.10.1 *Symptomatic decrease in LVEF*

- *Congestive heart failure (grade 3):*

  Patients should be monitored for signs and symptoms of CHF (e.g., dyspnea, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema). If the patient develops any of these signs and symptoms, T-DM1 and neratinib must be held.

  The investigator must confirm the diagnosis of CHF with either an echocardiogram or a MUGA scan. Once the diagnosis of CHF is confirmed, study therapy must be discontinued, and all reports must be submitted with FB-10 Form SAER and the appropriate eCRF to DSSM. See Section 12.0 for expedited reporting requirements. Further therapy is at the investigator's discretion.

- *Severe refractory/poorly controlled CHF (grade 4):*

  Discontinue study therapy and submit FB-10 Form SAER and other required forms and materials (if applicable). See Section 12.0 for expedited reporting requirements.

10.10.2 *Asymptomatic decrease in LVEF*

Reminder: Study therapy must be discontinued for patients who have a symptomatic decrease in LVEF (see Section 10.10.1).

- All FB-10 patients will undergo scheduled LVEF assessments by echocardiogram or MUGA scan (see Section 5.1).
- For asymptomatic patients, the decision to continue or stop study therapy is based on the value of the measured ejection fraction.

TABLE 9. **T-DM1 and neratinib management** based on LVEF assessments

Table 9 provides instructions for patients who have an **asymptomatic decrease in LVEF** during study therapy.

LVEF	Asymptomatic decrease in LVEF from baseline
≥ 50%	Continue targeted therapy
45–49%	Continue targeted therapy and repeat echo/MUGA in 3 weeks
≤ 44%	Discontinue study therapy

10.11 Liver dysfunction (Hy's Law)

Hy's Law is based on the observation that pure hepatocellular injury sufficient to cause hyperbilirubinemia is an ominous indicator of the potential for a drug to cause serious liver injury. A diagnosis of potential drug-induced liver injury caused by a study drug can only be determined/inferred by excluding other potential causes of liver injury (e.g., other drugs or viral hepatitis) and by ruling out an obstructive cause for the elevated bilirubin (e.g., alkaline phosphatase should not be substantially elevated)(FDA 2009; Temple 2006).

10.11.1 *Definition of cases potentially meeting Hy's Law criteria*

Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- *Patients with AST or ALT baseline values within the normal range* who subsequently present with AST or ALT ≥ 3 times the ULN concurrent with a total bilirubin

≥ 2 times the ULN with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times the ULN or not available.

- *Patients with pre-existing AST or ALT baseline values above the normal range* who subsequently present with AST or ALT ≥ 2 times the baseline values and ≥ 3 times the ULN, or ≥ 8 times the ULN (whichever is smaller) concurrent with a total bilirubin of ≥ 2 times the ULN and increased by one ULN over baseline or > 3 times the ULN (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times the ULN or not available.

10.11.2 ***Evaluation of potential Hy's Law cases***

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. The possibility of progressive disease should be considered.

Potential Hy's Law cases should be reported as serious adverse events (see Sections 12.4.3 and 12.8.2).

11.0 DRUG INFORMATION

11.1 T-DM1

T-DM1 is available as commercial supply.

For further details regarding the study drug, see the trastuzumab emtansine (T-DM1) U.S. Package Insert as well as local prescribing information.

11.2 Neratinib (HKI-272)

11.2.1 *Description*

Neratinib is an orally administered potent, irreversible pan-epidermal growth factor receptor (erbB) inhibitor that blocks signal transduction through the receptors erbB1, erbB2, and erbB4. The irreversible binding to their respective intracellular tyrosine kinase domains results in sustained inhibition of these growth-promoting pathways.

Neratinib **40 mg** tablets will be provided for the FB-10 study. The open label neratinib will be packaged with 210 tablets per bottle.

11.2.2 *Toxicity*

Refer to the current neratinib IB for toxicity information.

11.2.3 *Concomitant medications and other substances*

- Medications that reduce the secretion of gastric acid in the stomach, proton pump inhibitors (such as lansoprazole), should be avoided. Antacids and H2-receptor antagonists (such as ranitidine) may affect how neratinib dissolves in the stomach. See Section 9.3.5 and 9.3.6.
- Patients should be instructed to avoid agents known to be strong cytochrome P450 (CYP) 3A4 inducers or inhibitors (e.g., ketoconazole) for the duration of the study therapy. Patients should also avoid grapefruit and herbal remedies, including St John's Wort. Refer to Appendix B for a list of selected inhibitors and inducers of the cytochrome P450 CYP3A4, 5, 7 isoenzymes.
- Chronic immunosuppressive therapies should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as premedication for T-DM1, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
- Patients taking concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin) should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes. The dose of anticoagulant should be adjusted as needed.
- Concomitant administration of neratinib and digoxin, a P glycoprotein (P-gp) substrate with a narrow therapeutic window, could result in increased plasma concentrations of digoxin and potential digoxin toxicity. Patients taking concomitant digoxin should have digoxin levels monitored closely and their digoxin dose adjusted as needed. Neratinib monotherapy did not have a significant effect on QTc interval. However, subjects using drugs known to cause QT/QTc prolongation should be monitored closely using ECG.

11.2.4 ***Administration***

- Refer to Section 9.1 (Table 5) for neratinib administration instructions. Patients must be carefully instructed by study staff as to how to take neratinib.
- Patients should be strongly encouraged to use a patient diary, treatment calendar, or other tool to record neratinib doses.
- Instruct patients to bring all unused neratinib and empty bottles to the treating site. Local site personnel must count and record the number of neratinib tablets at the first study visit for each of the treatment cycles. Drug accountability records must be maintained.

11.2.5 ***Procurement of neratinib***

Neratinib will be supplied free of charge by Puma Biotechnologies, Inc., and distributed via an external vendor. Neratinib must be requested by the principal investigator (or his/her authorized designee) at each participating institution. See [redacted] for the e-mail address to be used for ordering study drug. The initial supply of neratinib may be requested at the time the first patient signs the FB-10 consent form. Neratinib will be shipped directly to the investigator whose sites are participating in FB-10.

11.2.6 ***Shipping***

Bottles of neratinib are shipped at room temperature by overnight express delivery ***Monday through Thursday excluding holidays***.

11.2.7 ***Storage/stability***

Neratinib should be stored at room temperature (up to 25°C [77°F]) with desiccant (do not freeze). Unopened bottles of neratinib are stable until the date indicated on the package label when stored at room temperature (up to 25°C [77°F]). Excursions up to 30°C (86°F) are permitted.

11.2.8 ***Transfer of neratinib***

Neratinib may not be used outside the scope of FB-10, nor can neratinib be transferred or licensed to any party not participating in this clinical trial.

11.2.9 ***Destruction of neratinib***

- All unopened, partially used, or empty bottles of neratinib shall be destroyed by study sites in accordance with the local institution standard operating procedures after the monitoring review of neratinib accountability by DSSM.
- Written documentation of destruction must contain the following:
  - identity (batch numbers) of neratinib destroyed;
  - quantity of neratinib destroyed;
  - date of destruction (date discarded in designated hazardous container for destruction); and
  - name and signature of the person who discarded the neratinib in a hazardous container for destruction.

11.2.10 ***Drug accountability***

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drug received through the FB-10 study using an investigational agent accountability record form.

12.0 ADVERSE EVENT REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE), as provided in this protocol. Routine and expedited adverse event report forms and their supporting documentation must be submitted to DSSM according to the instructions in Section 12.0.

12.1 Definition of an AE

An AE is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, laboratory findings, or other physiologic observations occurring in a patient participating in FB-10. The event does not need to be causally related to study therapy or other requirements of the FB-10 trial to be considered an AE.

- Examples of an AE include, but are not limited to, the following:
  - Any toxicity related to study therapy.
  - Any clinically significant worsening of a pre-existing condition.
  - An AE occurring from a symptomatic overdose of any study therapy, whether accidental or intentional. Overdose is a dose greater than that specified in the protocol.
  - A symptomatic AE that has been associated with the discontinuation of the use of any of the agents included in the study therapy.
  - An AE occurring during a clinical study that is not related to the study therapy, but is considered by the investigator or sponsor to be related to the study requirements, for example, an AE may be an untoward event related to a medical procedure required by the protocol.
- Examples of clinical events that should not be considered AEs:
  - Medical or surgical procedure (e.g., endoscopy, appendectomy). Note, the condition that leads to the procedure may be an AE, but the procedure itself is not.
  - Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.2 Definition of adverse events of special interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

The events in this section are considered potential risks with neratinib monotherapy and are not considered ADRs with neratinib at this time. A potential risk is an untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. These AESIs are being closely monitored in clinical studies with neratinib monotherapy and combination therapy.

For instructions on reporting AESIs, see Sections 12.4.2 and 12.8.2.

AESIs observed with neratinib include:

- Interstitial lung disease (ILD)/pneumonitis
- Cardiac toxicity (left ventricular ejection fraction decrease)

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the neratinib Investigator Brochure.

12.3 Definition of an SAE

An SAE is any untoward medical occurrence that, at any dose causes one of the following:

- Results in death.
- Is life-threatening.
  The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  Hospitalization is any inpatient admission to a health care facility even if for less than 24 hours. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered an SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. For example, the following hospitalizations would not require expedited reporting for an SAE:
  - a hospitalization or prolongation of hospitalization needed for a procedure required by the protocol or as part of another routine procedure; or
  - a hospitalization for a pre-existing condition that has not worsened.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

  This is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect

Also, appropriate medical judgment should be exercised in deciding whether SAE reporting is required in other situations, such as important medical events that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of an SAE (Section 12.3). Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

12.4 Events requiring expedited reporting

All events listed in Section 12.4 must be reported in an expedited manner according to the instructions in Section 12.8.

12.4.1 *SAEs*

All events meeting the definition of an SAE (Section 12.3) require expedited reporting.

12.4.2 *Other events requiring expedited reporting*

Other events (such as AESIs ≥ Grade 2; see Section 12.2) that must be recorded, reported, and followed up as indicated for an SAE (see Sections 12.5 and 12.8 for reporting procedures). This includes the following events:

- Pregnancy exposure to study therapy (If a pregnancy is confirmed, use of study therapy must be discontinued immediately. See Sections 12.5.)
- Inadvertent or accidental exposure to study therapy, with or without an AE
- Medication errors involving study therapy with an AE, including overdose, product confusion and potential product confusion. (A medication error is any preventable

event that may cause or lead to inappropriate use or harm while the study therapy is in control of the healthcare professional or patient. Examples of reportable medication error include administration of unassigned treatment and administration of expired neratinib, when associated with an AE/SAE.)

- Death, excluding death due to progression of breast cancer.
- Potential Hy's Law cases (see Sections 12.4.3 and 12.8.2).

12.4.3 ***Clinical laboratory abnormalities***

- Not every laboratory abnormality qualifies as an AE. A laboratory test results should be reported as an AE (and SAE) if it meets any of the following criteria:
  - Accompanied by clinical symptoms
  - Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
  - Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
  - Clinically significant in the investigator's judgment
- Special reporting requirements related to Hy's Law: All cases confirmed on repeat testing as meeting one of the criteria described in Section 10.11.1 with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases regardless of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events (see Section 12.8.2).

12.4.4 ***Disease-related events and/or disease-related outcomes not qualifying as SAEs***

An event which is part of the natural course of breast cancer does not need to be reported as an SAE. Progression and recurrence of breast cancer will be reported on the appropriate page of the CRF.

12.5 Pregnancy

- The investigator will collect pregnancy information on any patient who becomes pregnant while participating in this study. ***The investigator will record pregnancy information on the FB-10 Pregnancy Notification Form and submit it to DSSM within 2 weeks of learning of a patient's pregnancy.***
- Any serious pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring in association with pregnancy brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to study therapy, must be reported to DSSM.

12.6 Protocol-defined AE reporting exceptions

AE reporting is not required for AEs related to estrogen deficiency, e.g., hot flashes, vaginal discharge, vaginal dryness, dyspareunia, sweating, and irregular menses.

12.7 Grading the severity of the AE

The NCI CTCAE v4.0 must be used to determine the grade of the AE. The CTCAE provides descriptive terminology and a grading scale for each AE listed. Information regarding the

CTCAE can be found on the CTEP homepage at http://ctep.info.nih.gov/reporting/ctc.html. If you need further assistance, contact DSSM ([redacted]).

12.8 Expedited reporting instructions

12.8.1 *Time period for reporting SAEs and other events requiring expedited reporting*

- All SAEs and other events as noted in Section 12.2 and 12.4 ***regardless of relationship to study therapy*** will be reported in an expedited manner as described in 12.8.2. Reporting SAEs (and other applicable events) regardless of relationship to study therapy begins with the first dose of study therapy and continues until 30 days after the last dose of study therapy.
- Any ***SAE assessed as related to study participation*** (e.g., protocol-mandated procedures) will be recorded ***from the time a patient consents to participate in the study up to and including the 30 day post study therapy assessment***.
- Following the AE assessment 30 days after the last dose of study therapy, ***only SAEs determined to be related to study therapy*** will be reported in an expedited manner using FB-10 Form SAER.
- The investigator must follow up on all SAEs until the events have subsided, until values have returned to baseline, or until the condition has stabilized.

12.8.2 *Reporting instructions*

All SAEs and other events requiring expedited reporting must be reported using FB-10 Form SAER and submitted to DSSM ***within 1 working day*** of the study site personnel's initial notification of the event ([redacted]).

- When reporting potential Hy's Law cases, Form SAER should include the following:
  - Seriousness Criteria = Important Medical Event
  - Narrative: Include the term "Potential Hy's Law case" in the narrative; the text should also detail what additional study results are available at the time of reporting and what other studies are planned or results pending to further investigate alternative causes of the abnormal ALT/AST or bilirubin that triggered the report. The timing of planned patient follow-up should also be noted.
- NSABP will forward the expedited report forms and their supporting documentation for SAEs that meet reporting requirements to the FDA and also to Puma Biotechnology, Inc.
- Investigators are responsible for reporting AEs that meet specific criteria to their local IRBs.

12.9 Time period and frequency for routine reporting of AEs

- Patients will be monitored for the occurrence of AEs at each scheduled assessment and during any contact with the patient during the study.
- All AEs, including SAEs and other AEs that have been reported on FB-10 Form SAER, regardless of relationship to study therapy, will be recorded on the AE eCRF from the first dose of study therapy until 30 days after the last dose of study therapy (up to the date that a new therapy begins after disease recurrence/progression, or second primary).
- For routine reporting, **all ≥ grade 1 AEs** will be reported on the AE eCRF.
- The investigator must follow up on all AEs until the events have subsided, until values have returned to baseline, or until the condition has stabilized.

- Following the AE assessment 30 days after the last dose of study therapy, routine reporting is no longer required. (See Section 12.9 for expedited reporting requirements.)

12.10 Documentation requested following death

For deaths that occur within 30 days of the last dose of study therapy:

- Autopsy reports should be secured whenever possible and should be submitted to the DSSM.
- A copy of the death certificate should be forwarded to DSSM if it is readily available or if it contains important cause-of-death information that is not documented elsewhere.
- Please submit the last clinic/office note made before the death or the investigator's note summarizing events resulting in death.

13.0 ASSESSMENT OF EFFECT

13.1 Definitions

Tumor response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) (Eisenhauer 2009). Changes in only the longest diameter (unidimensional measurement) of the tumor lesions are used in RECIST. Lesions will be classified as measurable or non-measurable using the criteria below. ***A maximum of five measurable lesions will be used to monitor response.***

13.1.1 *Measurable disease*

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (PET/CT, CT scan, or MRI) or as ≥ 10 mm with spiral CT scan with 5 mm cuts or by clinical exam with caliper measurements. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). The same method (CT or MRI) used at baseline should be used at all other tumor measurement time points.

13.1.2 *Non-measurable disease*

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin, or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

13.1.3 *Bone lesion measurability*

When evaluating bone lesions, the following should be considered:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

13.1.4 *Target lesions*

Up to a maximum of **five measurable lesions** (maximum 2 lesions/organ), should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements by CT scan or MRI. A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

13.1.5 *Non-target lesions*

All sites of disease which are not used as target lesions should be identified as non-target lesions. All sites of non-target lesions must be assessed along with the target lesions.

13.2 Response criteria

13.2.1 *Evaluation of target lesions*

- *Complete response (CR)*
  Disappearance of all target lesions
- *Partial response (PR)*
  At least a 30% decrease in the sum of the of LD of target lesions, taking as reference the baseline sum LD
- *Progressive disease (PD)*
  At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since baseline or the appearance of one or more new lesions
- *Stable disease (SD)*
  Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since baseline.

13.2.2 *Evaluation of non-measurable/non-target lesions*

- *Complete response (CR):* disappearance of all non-target lesions
- *Incomplete response/stable disease (SD):* persistence of one or more non-target lesion(s)
- *Progressive disease (PD):* appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

13.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Refer to Table 10 for a summary of the criteria that contribute to the determination of response.

TABLE 10. Determination of response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

13.4 Symptomatic deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." This is also true for "symptomatic deterioration" after therapy is completed. Every effort should be made to document objective progression even after discontinuation of treatment.

14.0 PATIENT ENTRY PROCEDURES

14.1 Patient consent form

Before study entry, the consent form including any addenda, must be signed and dated by the patient and the person obtaining informed consent. **In addition, before study entry, a copy of the signed and dated consent form must be forwarded to DSSM. All patient signatures (except initials of first, middle, and last names) should be expunged prior to submission.**

14.2 Study entry

DSSM will verify that the institution has current IRB approval for the study. Entry will not take place if the IRB approval is not current for the institution with IRB oversight responsibility.

All patients must be enrolled through DSSM. Once the entry eCRFs have been completed, submit the redacted signed consent form, and supporting documents to [redacted]

The entry material must be received by DSSM no later than **4:00 p.m. Eastern Time, Monday through Friday, excluding holidays**. Once received the review process will begin. When the review is complete and approved, an enrollment confirmation will be sent. **This process could involve some unavoidable delays. Therefore, it is necessary to plan adequate time (at least 24 hours) between study entry and the initiation of the patient's study therapy.**

14.3 Patient study number and treatment assignment

After all the entry materials have been reviewed, the institution will receive the following via e-mail: 1) confirmation of registration and study entry; 2) the patient's study number.

14.4 Investigator-initiated discontinuation of study therapy

In addition to the conditions outlined in the protocol, the investigator may require a patient to discontinue study therapy if one of the following occurs:

- the patient develops a serious side effect that cannot be tolerated or that cannot be controlled with other medications,
- the patient's health gets worse,
- the patient is unable to meet the study requirements, or
- new information about the study drugs or other treatments for breast cancer becomes available.

If study therapy is stopped, study data and other materials should be submitted according to the study schedule unless the patient withdraws from the study.

14.5 Patient-initiated discontinuation of study therapy

Even after a patient agrees to take part in this study, she may stop study therapy at any time. If study therapy is stopped but she still allows the study doctor to submit information, study data and other materials should be submitted according to the study schedule.

14.6 Patient-initiated withdrawal from the study

If a patient chooses to have no further interaction regarding the study, the investigator must provide DSSM with written documentation of the patient's decision to fully withdraw from the study.

15.0 DATA HANDLING AND RECORDKEEPING

Please refer to the "FB-10 eCRF Completion Guidelines" for detailed instructions regarding data collection, AE reporting, and electronic case report form completion.

16.0 STATISTICAL CONSIDERATIONS

16.1 Statistical considerations for the Phase I part of the study

Note: On May 3, 2017, accrual to the Phase 1b portion of FB-10 was completed.

In the phase I portion of this study, the safe dose of neratinib with T-DM1 will be established.

TABLE 11. Dose escalation design

Dose level	Neratinib	T-DM1	No. of Patients
1	120 mg/day PO	3.6 mg/kg IV Day 1 q 3 weeks	3 to 6
2	160 mg/day PO	3.6 mg/kg IV Day 1 q 3 weeks	3 to 6
3	200 mg/day PO	3.6 mg/kg IV Day 1 q 3 weeks	3 to 6
4	240 mg/day PO	3.6 mg/kg IV Day 1 q 3 weeks	3 to 6

The first cohort will be treated at dose level 1. If 1 of 3 patients in this cohort experiences a DLT, 3 more patients will be added at the same dose level. If 0 of 3 initial patients or 1 of 6 patients in an expanded cohort experiences a DLT, the dose for the next cohort will be escalated to dose level 2; otherwise, the combination will be considered too toxic. NOTE: If 2 or more patients assigned to study therapy **Dose level 1, Cycle 1** experience a DLT due to grade 4 thrombocytopenia, the study will continue with the following actions:

- The T-DM1 dose will be decreased to 3.0 mg/kg (T-DM1 level-1) for all patients subsequently enrolled on study.
- The T-DM1 dose will not re-escalate. T-DM1 dose 3.0 mg/kg will become the starting dose for all other study therapy dose levels. (See Section 10.8.)
- Grade 4 thrombocytopenia will remain a DLT during Cycle 1 for all subsequent dose levels.
- Study therapy dose treatment management, *after* completion of Cycle 1, will continue as described in Section 10. (See Tables 5, 6 , 7, and 8.)

Similarly, at dose level 2 and subsequent dose levels if 1 of 3 patients experiences a DLT, 3 more patients will be added. If ≥ 2 DLTs are experienced at any dose level, the combination will be considered too toxic and the next lower dose level will be considered the MTD. If only 3 patient were treated at the MTD, an additional 3 patients will be entered into that cohort. The MTD at which < 2 of 6 patients experience a DLT will be the RP2D.

In addition to DLT identification that occurs during Cycle 1, the overall emerging toxicity profile will be taken into consideration when determining the MTD. Given that diarrhea is the most frequent DLT, an overall safety profile of < 25% grade 3 diarrhea is expected. Should ≥ 25% grade 3 diarrhea be observed cumulatively at a given dose level, the MTD may be decreased by one dose level.

Safety will be assessed by physical examination, interim history, and laboratory assessment. Clinical activity will be assessed by performing tumor measurements/assessments for all subjects at baseline and then after every 2 cycles (6 weeks) of treatment. Patient will continue on therapy until progression or discontinuation of study drugs due to toxicity.

In the phase Ib portion of this study the safety, tolerability, and MTD of neratinib in combination with T-DM1 will be determined. The RP2D will be at the MTD taking into account the toxicity profiles of both study therapy agents. No formal statistical analysis is planned. AE rates will be described by dose level without regard to causality. Analysis of secondary endpoints will be descriptive.

16.2 Statistical considerations for the Phase II part of the study

The purpose of this phase II trial is to reject the experimental treatment (T-DM1 + neratinib) from further study if it were insufficiently active, and to accept it for further study if it were active using the Sargent three-outcome design (Sargent 2001):

- Null hypothesis (H0): 25% Objective Response Rate
- Alternative hypothesis (HA): 45% Objective Response Rate
- Alpha = beta = 10%
- Probabilities of true positive = probability of false negative = 70%

With these assumptions, the sample size required is 22 and the decision rules are to declare success if > 8 responses; to declare failure if < 7 responses; and to consider the trial inconclusive if 7 or 8 responses (7 / 22 = 32%, 8 / 22 = 36%).

So at end of randomized trial, pending toxicity considerations, the following decisions can be made:

Table 12. Response criteria for study continuance

No. responses	Decision
< 7	Drop further development
= 7 or 8	Do further trials
> 8	Do phase III trial

Secondary endpoints will be analyzed with a descriptive intent only, with due allowance for the fact that the sample size is insufficient to yield precise estimates of the secondary parameters.

16.3 Sample size

A sample size of between 2 and 24 evaluable patients is needed in the phase I portion of the trial.

In Phase II, 22 patients will be evaluated. Up to 4 patients can be replaced in order to reach the required sample size of 22 evaluable patients. All patients who receive a dose of neratinib will be considered evaluable. Patients who enter the trial but are not treated for any reason will be replaced.

No formal interim analysis is planned for this study. The FDA does not require or recommend Data Monitoring Committees (DMC) for clinical trials at early stages of product development (FDA 2006).

16.4 Accrual time and study duration

The anticipated accrual rate for the phase II study is approximately 2 patients per month for the first 4 months followed by approximately 3 patients per month for 6 months. Therefore the accrual period is expected to be approximately 12 to 14 months.

16.5 Medical Oversight

- During phase Ib: The Protocol Officer and designated DSSM staff will participate in a weekly call with investigators who have patients enrolled on the FB-10 study. Investigators who have enrolled a patient are required to participate. All FB-10 investigators and study team members are encouraged to attend.
- During phase II: A medical review team comprising the Protocol Chair, NSABP Medical Director, study statistician, designated physician(s), and designated DSSM staff will formally monitor the study on a monthly basis to identify accrual, toxicity, and any endpoint problems that might be developing.
- All grades for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.

17.0 PUBLICATION INFORMATION

The publication or citation of study results will be made in accordance with the publication policy of the NSABP that is in effect at the time the information is to be made publicly available.

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APPENDIX A

ASSESSMENT OF PERFORMANCE STATUS AND ACTIVITIES OF DAILY LIVING

1.0 DETERMINATION OF PERFORMANCE STATUS

ECOG or Zubrod Scale		Karnofsky Score
0	Fully active; able to carry on all pre-disease performance without restriction	90–100%
1	Restricted in physically strenuous activity but ambulatory	70–80%
2	Ambulatory and capable of self-care, but unable to carry out any work activities	50–60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	30–40%
4	Completely disabled	10–20%

2.0 NCI DEFINITION FOR ACTIVITIES OF DAILY LIVING

Activities of daily living (ADL) are the tasks of everyday life. These activities include:

- eating
- dressing
- getting into or out of bed or chair
- taking a bath or shower
- using the toilet

APPENDIX B

CONCOMITANT MEDICATIONS AND OTHER SUBSTANCES PROHIBITED DURING STUDY THERAPY

TABLE B1. List of selected inhibitors and inducers of the Cytochrome P450 CYP3A4, 5, 7 isoenzymes

INHIBITORS*		**INDUCERS***	
3A4	**OTHER**	**34A**	**OTHER**
Clarithromycin	Amiodarone	**Carbamazepine**	Barbiturates
Erythromycin	Cannabinoids	Dexamethasone**	Cotrimoxazole
Fluvoxamine	Fluoxetine	Phenobarbital	Efavirenz
Grapefruit juice	Lopinavir	Phenytoin	Ethosuximide
Grapefruit-containing products	Metronidazole	Primidone	Methadone
Indinavir	**Quinine**	Rifabutin	Metyrapone
Ketoconazole	**Sertraline**	Rifampin	Mexiletine
Mibefradil	**Zafirlukast**	St John's Wort	**Nevirapine**
Miconazole			Oral contraceptives
Nefazodone			Troglitazone
Nelfinavir			
Norfloxacin			
Ritonavir			
Saquinavir			
Troleandomycin			
Voriconazole			

* In **boldface** are identified strong CYP3A4, 5, 7 inducers/inhibitors. This list is not meant to be considered all inclusive. From: Tatro BO. *Drug Interaction Facts 2003: The Authority on Drug Interactions, 2003*.

** Dexamethasone is permitted when given as premedication for T-DM1 (see Section 9.1).

APPENDIX C

NSABP FB-10 SAMPLE PATIENT INSTRUCTIONS FOR THE MANAGEMENT OF DIARRHEA

Please review these instructions with your study doctor/team.
Once all of your questions are answered, make sure you are given a copy of these instructions to take home.

Diarrhea is the most common side effect you may have while taking part in this study. Diarrhea can start within a few hours to a few days of the first dose of study therapy. You will be given antidiarrheal medication on the first day you receive study therapy to take at home to prevent diarrhea from occurring.

If you had diarrhea with previous chemotherapies or trastuzumab/pertuzumab in the past, you may be at high risk for developing diarrhea with neratinib. Make sure you take the antidiarrheal medications as explained by your doctor and described below.

Your study doctor/team will instruct you to take the following medication(s) to prevent the diarrhea:

Loperamide: also known as Imodium®

Loperamide is available without prescription (over-the-counter, [OTC]). You will be given a packet of loperamide to take at home at the start of study therapy to prevent diarrhea. You will need to purchase loperamide OTC for the remainder of your study treatment. Take loperamide as instructed below.

- With the first dose of neratinib, take 4mg (2 tablets) of loperamide.
- Following the first dose of loperamide, take 4mg (2 tablets) by mouth, every 6 hours for the first 48 hours (8 tablets/day):
  - every 6 hours _____, _____, _____, _____, (time) on _____, (Date) and
  - every 6 hours _____, _____, _____, _____, (time) on _____, and _____(Date).

  If you continue to have persistent diarrhea, (4 to 6 stools more per day than is normal for you), continue taking loperamide 4 mg (2 tablets) every 6 hours until your diarrhea decreases to less than 4 stools per day above what is normal for you. If you continue to have diarrhea (more than 4 episodes a day) on the recommended dose of loperamide, you may start taking lomotil as prescribed by your doctor.

You will need to have loperamide at home to continue taking antidiarrheal medication as instructed. You may take up to 8 tablets of loperamide a day for diarrhea.

- After the first 48 hours on _____(Date), or when you are having less than 4 stools per day above what is normal for you, begin taking loperamide 2 mg (1 tablet) every 4 hours during the day (for example: 8am, 12pm, 4pm, 8pm) and take 4mg (2 tablets) at bedtime for the first 2 weeks of therapy, from _____(Date) to _____(Date).
- After two weeks, and if your stools are less than 4 per day, after discussion with your physician, you may begin to take loperamide 2mg (1 tablet) every 6 to 8 hours daily while you are on study therapy.

Budesonide also known as Entocort®, Uceris®, or Pulmicort®

You will be given a packet of budesonide to take at home at the start of study therapy to prevent diarrhea. You will receive an initial dose of budesonide 9 mg to take by mouth with the first dose of neratinib. You will take budesonide 9 mg by mouth once every day during Cycle 1 and Cycle 2.

Take budesonide as instructed below:

- Take budesonide 9 mg by mouth (once daily in the morning) with a full glass of water (8 ounces) with or without food.
- Swallow this medication whole; do not crush or chew the tablets.
- Do not split the tablets unless you are instructed to do so by your study doctor.

Be sure to write in the number of loose stools you have and all antidiarrheal treatment you take during the study on the same record (diary, calendar, etc.) that you use to record your daily dose of neratinib. Bring the completed record at each visit.

If you become constipated, notify your doctor/team. Do not take laxatives or stop loperamide. Your doctor/team will change how often or how much loperamide to take.

Treating diarrhea as soon as it starts is very important to prevent it from getting worse.

Your study doctor/team will advise you about which antidiarrheal medication(s) to have at home.

Call your study doctor/team at phone number _____ to let them know you are having diarrhea, so they can work with you to control the diarrhea.

If you are dizzy or weak because of diarrhea, go to the study doctor's office or go to the hospital immediately.

Provide as much of the information as possible to your study doctor/team, in order to help your study doctor/team to assess the diarrhea and decide on the best treatment for you. Information to provide when talking to your study doctor/team is listed below:

- Number of stools per day compared to your normal bowel habits
- Presence of diarrhea during the night
- Presence of fever, dizziness, abdominal pain/cramping, or weakness
- What the stool looks like, that is, watery stools, blood, or mucus
- When you took your last dose of neratinib
- Any other information that could explain your diarrhea (food, recent travel, contact with other people with diarrhea)
- Name and amount of anti-diarrheal medications that you have been taking.

If you continue to have persistent diarrhea while taking the loperamide, your doctor may add other antidiarrheal medications. Other medications include:

Other medication (study doctor/team to write in name of medication and instructions):

_____

_____

In case of more severe diarrhea and any diarrhea associated with fever, pain, infection, or dehydration, you may receive IV fluids, antibiotics and/or other medications.

Changes to your diet to treat diarrhea

If you have diarrhea, you will:

- Stop all lactose-containing products (milk, yogurt, cheese, etc.)
- Drink 8 to 10 large glasses of clear liquids per day
- Eat frequent small meals
- Eat low-fat foods, including bananas, rice, applesauce, and/or toast.

Your doctor/team may have other suggestions for you (study doctor/team to write in any suggestions).

_____

_____

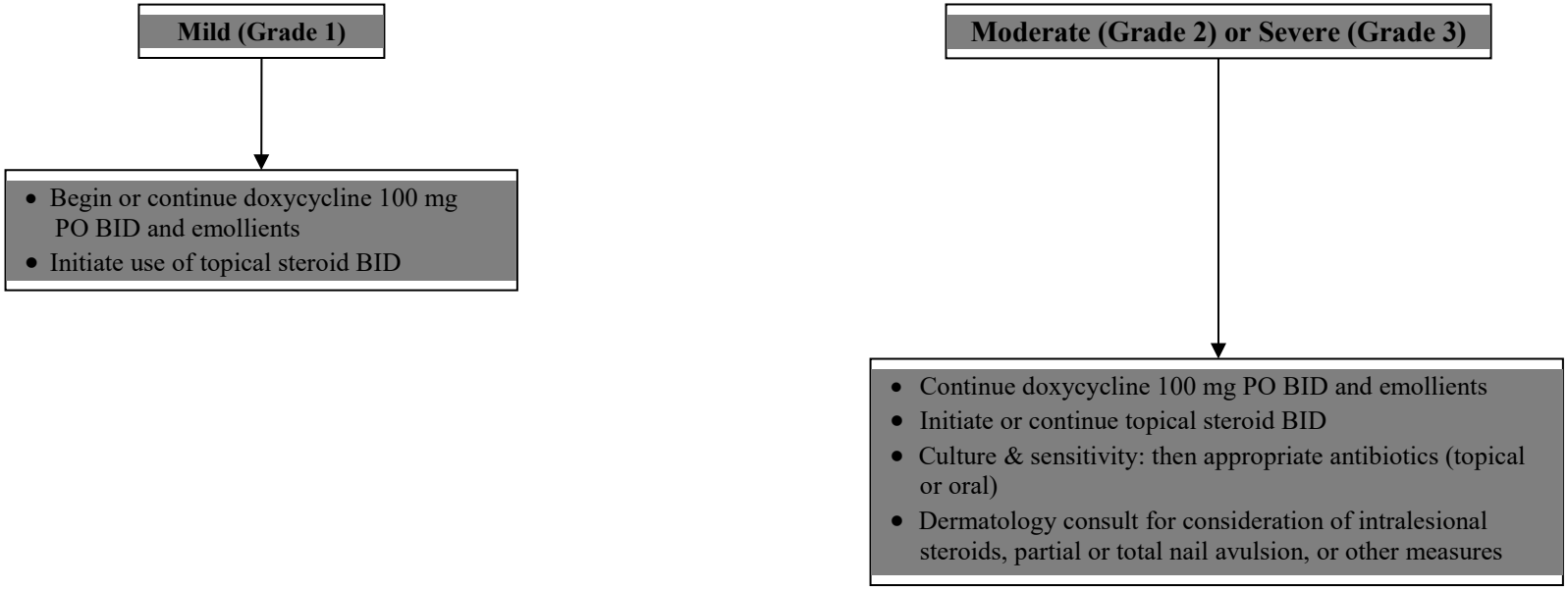
Neratinib adjustments

If you are experiencing a fever, dizziness, abdominal pain, or weakness along with diarrhea while on antidiarrheal medication, stop taking neratinib (if you have not already stopped) and contact your study doctor/team immediately for further instructions.

APPENDIX D

MANAGEMENT OF PARONYCHIA

Figure 3. Management of paronychia
NOTE: See Section 10.7.1 and Table 8 for neratinib dose modification instructions



Notes:
1. Dermatology consultation at the investigator's discretion unless noted otherwise.
2. Emollients (alcohol-free): Eucerin®, Cetaphil®, Aquaphor®, CeraVe®,or other similar product
3. Topical steroid: Hydrocortisone 2.5% cream or alclomethasone 0.05% cream.
4. Treatment with medication(s) referenced should be based on evaluation of the patient and the recommended uses and associated risks with the medication(s) as outlined in the associated prescribing information. (Oiski 2008)