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Study Title: A single arm phase II study to evaluate efficacy of T-DM1 with Palbociclib in the treatment of patients with metastatic HER2 positive breast cancer

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Investigational Product Intervention or Device supplier	Palbociclib Pfizer 235 E 42nd Street New York, NY 10017
Commercial Agent(s) Supplier	T-DM1
Protocol Version(s) and Date(s)	Version 5 – 01/25/2021

Protocol Signature Page

Study Title: A single arm phase II study to evaluate efficacy of T-DM1 with Palbociclib in the treatment of patients with metastatic HER2 positive breast cancer

Protocol Identification : Palbo T-DM1

Sponsor Signature: The signature below constitutes approval of this protocol by the sponsor

Lead Principal Investigator: Pavani Chalasani MD, MPH

Date: Signature:

Investigator Agreement:

I have read, understand and will adhere to the protocol as written, that any changes to the protocol will be approved by the sponsor or sponsor-investigator and the IRB, except changes to eliminate an immediate hazard to study subjects.

I agree to conduct this study in accordance with the current International Conference on Harmonization (ICH) guidance, the Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, FDA regulations, local IRB and legal requirements.

_____ _____

Signature Date (MM/DD/YYYY)

_____

Name of Principal Investigator

Protocol Version History Page

Version	Main Changes
Version 1 – 4/9/18	First version
Version 2 – 6/11/18	• Inclusion criteria – age ≥ 18 years was added • Inclusion criteria - Measurable disease by RECIST 1.1 was added • Exclusion criteria #8 was updated to include: Women of childbearing potential and men should use effective methods of contraception during the entire duration on study and for 6 months after completion • Study schema has been updated (optional research biopsy was removed) • Schedule of events was updated: T-DM1 administration was added to group A, metabolic panel will not be collected at D21, concomitant medication information will not be collected at long term follow-up, tumor measurement in group B will be done every 4th cycles, for women of childbearing potential, pregnancy tests should be done every 2nd cycle. • Clarifications were added to section 13 – data and safety monitoring plan
Version 3- 10/1/18	• Page 7- expanded on T-DM1 abbreviation to Trastuzumab Emtansine (T-DM1) • Clarification of startaification factors- enrolling site was added to that • Inclusion criteria No 7- EF was changed to Left ventricular ejection fraction • Inclusion criteria No 13 was further expanded to define postmenopausal status and about contraception. It was changed to “Female subjects must be surgically sterile or be postmenopausal (defined as surgical removal of ovaries or no menses for 12 consecutive months or monthly gonadotrophin releasing hormone agonist use for ovarian suppresion), or must agree to use effective contraception during the period of therapy. All female subjects with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment and must agree to use effective contraception during the period of therapy. Women of childbearing potential and men should use effective methods of contraception during the entire duration on study and for 7 months after completion” • Exclusion criteria no 9- Calrified about supportive meds. Added “Other supportive care medications can be used if clinically indicated (like growth factor support)”

	• Background section was expanded to add supporting pre-clinical data and the rationale to study the combination therapy • In SOE calendar, Day 21 has been removed • Section 7.1- CTCAE version- has been updated to 4.03 • Section 7.6 for Overdose-has been simplified to "An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses should be reported as a SAE using the SAE forms.
Version 4-6/5/19	• Page 7- expanded number to sites from 10 to 10-20 • Page 7/8- Inclusion crtieria No 6 was changed from measurable disease only to measurable and evaluable disease • Page 8- Inclusion criteria No 8 clarified that serum or plasma creatinine can be use, added IULN for bilirubin • Page 8- Inclusion criteria No 11 , clarified about adjuvant use of pertuzumab, deleted upon discussion with PI • Page 18- exclusion crtieria No 8 and 9 - updated the previously approved exclusion criteria (to make it consistent with synopsis) • Page 19- under palbociclib administration, clarified that it can be given with food , updated side effects based on new IB • Page 20- Drug-related Toxicities for palbociclib was updated. • Page 23 and 24 – updated the SOE to make it easier and deleted a row and column to clarify what procedures are needed, clarified that imaging has to be done every 12wks (or after every 4 cycles), changed need for physical exam from every cycle to every 6wks after cycle 8, clarified about T-DM1 administration days, clarified about long terms survival follow up, deletd tumor measurement for visible or palpable only, clarified about bone imaging (deleted preferred) and clarified that is done per instutional guidelines • Page 33- under tumor evaluation per RECIST 1.1, added about evaluable disease only and discussed about non-measurable disease • Page 37- described about disease progression in non-measurable disease only • Page 38- Table 6 of protocol- clarified about overall response per RECIST 1.1 • Page 41-Defined end points for the objectives
Version 5	• All pages-Header and footer change- protocol version 5 & Date 01/25/2021

	• Page 1, 2, 10- updated **Study Title**: change in study title from randomized to single arm, **Protocol version and date:** change to version 5 and 9/28/20 • Page 8, 9- **Table of Contents**: Page numbers updated • Page 9-**Table of Contents:** Deleted randomization from registration. • Page 10- **Hypotheses**: Changed to "*compared to historical controls*" instead of single agent T-DM1, **Primary objective:** changed to estimate progression free survival of T-DM1+Palbociclib, **Secondary Objectives**: Changed to ▪ Estimate response rates of T-DM1+Palbociclib treatment regimen ▪ Estimate overall survival of T-DM1+Palbociclib treatment regimen ○ **Study design:** changed to single arm study of T-DM1 with Palbociclib. Clarified that all patients going forward will be treated with T-DM1 with Palbociclib, Stratification factors removed to reflect change in study design, **Number of study centers**: Changed from 10-20 to 15, **Number of patients**: Changed from 132 to 46 evaluable patients, **Main criteria for inclusion/exclusion**: **Inclusion Criteria No 6**: Clarified that patients must have measurable or evaluable disease by RECISIT 1.1, • Page 11, 19 **-Exclusion Criteria No 2**: Changed to-Prior treatment with T-DM1 in the metastatic setting, if treated with prior T-DM1 in the neoadjuvant of adjuvant setting, a treatment free interval of at least 12 months, **Exclusion Criteria No 4**: Clarified known active CNS metastases to known active symptomatic CNS metastases.**Exclusion Criteria No 9**: Added-If a patient is already on Gonadotrophin releasing hormone agonist, it can be continued during this study. • Page 12- **Study Schema**: Updated to reflect change in study design, **Sample size calculation**: Updated to reflect change in study design and sample size. • Page 10 -**Primary Objectives**: Updated to reflect Change in study design Kaplan-Meier estimate will be used to estimate progression free survival of combination arm. No longer comparing to single arm using a stratified log rank test, **Secondary Objectives**: Updated to reflect Change in study design overall response of Combination arm will be estimated using exact binomial confidence interval. No longer comparing single arm using chi square test. • **Page 13- Interim monitoring and interim analysis**: Futility analysis clarified based on combination arm only.

	• **Page 13- Feasibility issues**: Randomized changed to single arm. Number of sites changed from 10 to 15, added date of first patient accrued (12/2018), Q3 2018 changed to Q4 2018 Accrual estimates changed from 6 to 2-3/month Added: Q4 2020-enrolled subjects into combination arm are 11, timeline below is for additional 35 subjects and anticipated total of 46 Q3 2020-complete accrual changed to Q42021 • Q4 2020-Q2022 monitor for study completion changed to Q4 2021-Q42022 • Page 13-**Study Duration**: 4 years changed to 5 years. (24 months changed to 36 months' accrual) • Page 10, 18- **Study design**: updated as above. • Page 20-**Formulation:** Pfizer changed the formulation of palbociclib from capsules to tablets. Added: smooth-coated tablet formulation. Monthly supply will contain 3 weekly blister packs of 7 *tablets each along with USPI for the tablet formulation. Tablets should not be removed from the blister pack and placed in a pill caddy. Each strength of tablet has a different shape or color as well as different color carton similar to the way the current bottles have differently colored labels.* **Reconstitution:** Capsules changed to tablets. **Storage and Stability:** Capsules changed to Tablets **Administration:** Clarified patients can take palbociclib with or without food. **Procurement:** Clarified due to change in study design. Removed-*For randomization, Randomization will be done centrally and study site will be notified about that treatment arm* • Page 21-**Drug –related Toxicities**: Added #6: Rare pneumonitis, **Drug interactions**: Clarified drug-drug interactions when taken concomitantly with CYP3A4 substrates and P-glycoprotein substrates. Removed- "*These should be avoided during the course of the study"* • Page 22/23-**Administration:** Added-*If necessary, the administration time can be modified to meet institutional guidelines. The dose of KADCYLA is 3.6mg/kg and can be calculated per cycle or change when weight has changed by 10% (from the weight used to calculate the dose of KADCYLA)* • Page 24-**Schedule of events (Tab**le): Updated to reflect change in study design. Group A removed **Imaging assessments window(column)***:* Clarified and Changed to *after every 4th cycle ±7 days.* **Bottom of table***:* Spelling correction

	• Page 25-**Schedule of events Group B:** Updated to reflect change in study design. Added **(***only applicable for patients currently on single T-DM1)* • Page 29-**Small print bottom of table:** Added-*T-DM1 can be given -3days to +7 days of a 21 day cycle to give flexibility for investigator and patients.* • Page 32- *clarified about imaging schedule "* however if there are any delays in treatment, the imaging should follow 12 week from last imaging schedule" • Page 37-**Registration**-Removed- *randomization* • Page 37-**Analysis population:** Clarified primary analysis sample for efficacy added- *evaluable patients who have completed at least 1 cycle of treatment. If a patient was not able to complete at least 1 cycle of therapy, they will be replaced for the study analysis.* Changed to reflect combination arm study of T-DM1 with Palbociclib. **Safety Analysis:** Changed number of patients for first safety analysis to 16 from 20. Removed *"As this is not an efficacy analysis we will not adjust the overall alpha level."* **Sample Size Calculation:** Updated as above • Page 38-**Statistical analysis:** Updated as above • Page 42-**Data and Safety Monitoring Plan:** Updated change from Criterium suppling all reports to monthly reports. Added designee to PI. Clarified that Study PI and Criterium will provide a monthly DSMB summary report to all study sites on a 6 month basis every January and July. The DSMB summary report will include summary of University of Arizona monthly DSMB reports. Added: if the University of Arizona DSMB identifies any safety concerns, all participating sites and study investigators will be notified by a memo and teleconference.

Table of contents

1. STUDY SYNOPSIS

Title of the study: A single arm phase II study of T-DM1 with palbociclib in the treatment of patients with metastatic HER2-positive breast cancer

Hypotheses: Combination of Trastuzumab Emtansine (T-DM1) with palbociclib improves progression free survival compared to historical controls

Primary objective: Estimate progression free survival of T-DM1 + palbociclib

Secondary objectives

i) Estimate response rates of T-DM1+Palbociclib treatment regimen
ii) Estimate overall survival of T-DM1+Palbociclib treatment regimen

Correlative objectives

i) Investigate predictive biomarkers of response in blood and archived tumor tissue
ii) Investigate mechanisms of resistance for palbociclib in blood and tumor tissue

Study design

This is a multi-center, single arm study of T-DM1 with palbociclib in the treatment of patients with metastatic HER2-positive breast cancer. All patients will be treated with T-DM1 with palbociclib

Number of study center: 15

Number of patients: 46 evaluable patients

Main criteria for inclusion/exclusion

To be eligible all patient must/have

1. Be informed of the investigational nature of the study and all pertinent aspects of the trial
2. Sign and provide written consent in accordance with institutional and federal guidelines.
3. Age ≥18 years
4. ECOG Performance status of 0-2
5. Recurrent or metastatic HER2-positive breast cancer (HER2 positive is defined per ASCO-CAP guidelines)
6. Must have measurable or evaluable disease by RECIST 1.1
7. Adequate cardiac reserve (Left ventricular ejection fraction ≥50%)
8. Serum or plasma creatinine ≤ 1.5 x institutional upper limit of normal (IULN), bilirubin ≤ 2.0 x IULN, and an SGOT/SGPT/alkaline phosphatase ≤ 2.0 x IULN
9. Adequate bone marrow function (ANC ≥1000, Platelets ≥100,000/ml, Hemoglobin ≥10gm/dL)
10. Be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other trial procedures

11. Been treated with pertuzumab previously (neoadjuvant or adjuvant or metastatic setting). Patients who weren't able to tolerate pertuzumab due to side effects can be eligible for study
12. No more than 2 lines of therapy in the metastatic disease setting
13. Female subjects must be surgically sterile or be postmenopausal (defined as surgical removal of ovaries or no menses for 12 consecutive months or monthly gonadotrophin releasing hormone agonist use for ovarian suppresion), or must agree to use effective contraception during the period of therapy. All female subjects with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment and must agree to use effective contraception during the period of therapy. Women of childbearing potential and men should use effective methods of contraception during the entire duration on study and for 7 months after completion.

Patients who fulfill any of the following criteria will be excluded

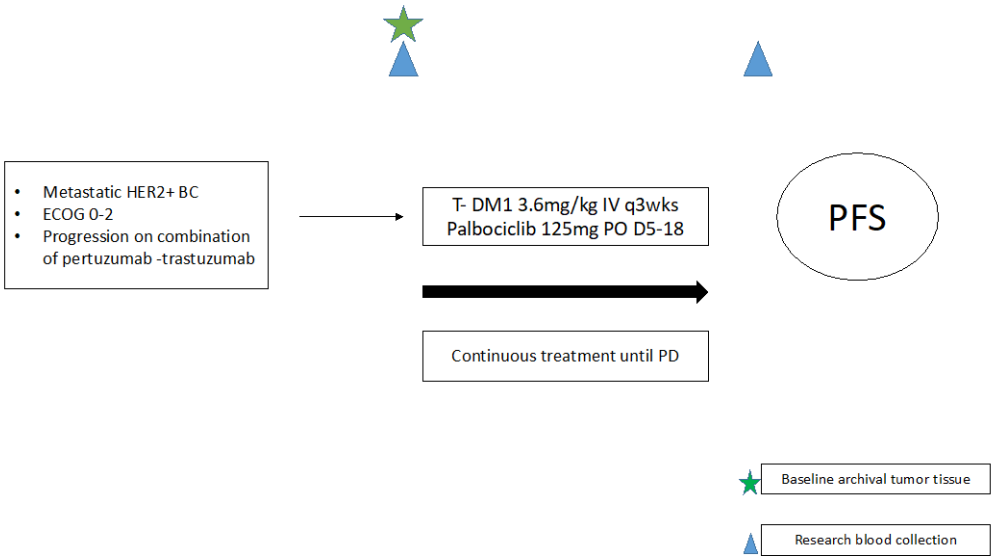
1. HER2 negative tumors
2. Prior treatment with T-DM1 in the metastatic setting. If treated with prior T-DM1 in the neoadjuvant or adjuvant setting, a treatment free interval of at least 12 months
3. Prior treatment with CDK 4/6 inhibitors
4. Known active symptomatic CNS metastases or carcinomatous meningitis. Patients with stable CNS metastases including brain metastases who have completed a course of radiotherapy are eligible for the study provided they are clinically stable. However, oral corticosteroids for control of CNS symptoms are not allowed on study
5. Known documented or suspected hypersensitivity to the components of the study drug(s) or analogs.
6. Uncontrolled systemic illness, including but not limited to ongoing or active infection
7. Symptomatic congestive heart failure, unstable angina pectoris, stroke or myocardial infarction within 3 months
8. Be pregnant or breast feeding.
9. Concurrent hormonal or other anti-neoplastic therapy is not allowed. Patients can receive supportive therapy like bone-directed therapy including bisphosphonates or denosumab. Other supportive care medications can be used if clinically indicated (like growth factor support). If a patient is already on a Gonadotrophin releasing hormone agonists, it can be continued during this study.

Intervention

T-DM1 is administered IV q21days at 3.6mg/Kg. This is available commercially.

Palbociclib is given orally at 125mg on days 5-18 of 21 day cycle (supplied by Pfizer).

Study Schema



Statistical analysis

Sample size calculation

This is a prospective single arm phase II study to estimate progression free survival of combination T-DM1 + palbociclib. Expected PFS for T-DM1 based on the EMILIA trial is 9.6 months. The goal of the study is to detect a PFS of 16.3 months (HR = 0.56) in the combination arm compared to the standard historical control arm, with 80% statistical power and a 0.05 one sided alpha level. We propose enrolling a total of 46 subjects into this trial. Enrollment will continue and will be briefly held after the first 16 subjects complete 12 months of treatment or come off study (whichever comes first) to conduct a futility analysis. If at least 8/16 have PFS beyond 12 months, we will restart accrual for a total of 46 evaluable patients. If at least 24 evaluable subjects have PFS beyond 12 months then we declare the combination as promising for future studies. Our null hypothesis is 40% have PFS at 12mths (median survival of 9.1 months) Alternative hypothesis is 60% survive 12 months.

Primary Objectives

1. Progression free survival of the combination of T-DM1 with palbociclib will be estimated using the Kaplan-Meier

Statistical considerations for secondary aims
Secondary Objectives

1. The overall response (CR + PR + stable disease) will be estimated using an exact binomial confidence interval
2. Overall survival will be analyzed similarly as progression free survival.

Interim monitoring and interim analysis

We propose a futility analysis after the first 16 patients complete either 12 months of treatment or come off study (which ever comes first). If 8 have PFS beyond 12 months, we will continue accrual for a total of 46 evaluable patients (30 additional patients). Enrollment will be held briefly only after the first 16 patients complete either 12 months of treatment or come off study (which ever comes first).

Feasibility issues: This is a multi-site single arm phase II trial (expected number of sites is 15)
01/2018-08/2018-protocol finalizing, contracting with CRO, study sites startups, IND preparation, study protocol to be reviewed by IRB and study site activation
Q4 2018- accrual of first patient (happened 12/2018)
Accrual estimates – approximately 2-3/month (anticipate accrual of total 46 patients)
Q42020- enrolled subjects into combination arm are 11, timeline below is for additional 35 subjects and anticipated total of 46
Q4 2021- complete accrual
Q4 2021- Q4 2022- monitor for study completion
Q1 2023- complete final analysis
Q1 2023- Q2 2023- ASCO presentation, complete manuscript and prepare for submission (JCO/CCR)

Study duration: 5 years (36 months' accrual and 24 months of follow up) from startup and close out would be an additional 10 months.

2. Background and rationale

HER2-positive metastatic breast cancer

Overexpression of the human epidermal growth factor 2 (HER2) oncogene is estimated to occur in 25-30% of all human breast cancers. This subset of breast cancer is classified as HER2-positive cancer, a subtype that is particularly aggressive and associated with greater risk for disease progression and death (Callahan and Hurvitz, 2011). First line therapy for patients with metastatic HER2-positive breast tumors is combination of Taxane with dual HER2 targeted therapy -pertuzumab (perjeta) and trastuzumab (Herceptin), humanized monoclonal antibodies targeting the HER2 extracellular domain (Baselga, 2012). However, despite its dramatic impact on the progression free survival and overall survival treatment of HER2-positive breast cancer, still many patients develop disease progression Subsequent therapy for such patients includes T-DMI. The pivotal EMILIA trial demonstrated superiority of T-DM1 over the lapatinib-capecitabine regimen, and T-DM1 has attained FDA approval for the treatment of HER2-positive breast cancer as a second line treatment (Verma, 2012). However, even with T-DM1, the progression-free survival is only 9.6 mos. It is prudent to know that in EMILIA trial patients had prior exposure to trastuzumab only. The true PFS on T-DM1 after disease progression on combination treatment with pertuzumab and trastuzumab is not well defined. After progression on T-DM1, lapatinib, a small molecule tyrosine kinase inhibitor that targets both HER2 and the epidermal growth factor receptor-EGFR, is typically used in combination with capecitabine (Callahan and Hurvitz, 2011; Moreira and Kaklamani, 2010). This therapy gained FDA approval based on increasing progression-free survival in a phase 3 study of approximately six months. Thus, despite recent advances in the treatment of HER2-positive breast cancer, there is still significant need for novel targeted therapies and combination regimens to address the continuing problem of therapy resistance and recurrence of this aggressive disease.

2.2 Pre-clinical/clinical experience

Mechanism of action, pre-clinical and clinical data for T-DM1

T-DM1 is an antibody conjugate with the therapeutic antibody trastuzumab with derivatized lysine linked via maleimido bonds to the microtubule poison emtansine. Preclinical studies demonstrated that T-DM1 is effective against HER2+ breast cancer models including cell lines and xenografts that are resistant to trastuzumab (Barok, 2011; Junttila, 2011). These studies indicated that T-DM1 kills HER2-positive breast cancer cells both through the cytotoxic effects of emtansine including apoptosis and mitotic catastrophe, while also eliciting antibody mediated cellular toxicity.

T-DM1 has been utilized in the treatment of greater than 500 patients with HER2-positive disease. The phase 1 studies led to the current dosing schedule of 3.6mg/kg by intravenous delivery on a 3-week schedule (Krop, 2010). The main dose limiting toxicity (DLT) was thrombocytopenia. The phase 2 and 3 studies demonstrated efficacy relative to the FDA-approved regimens (Verma, 2012) for recurrent disease previously treated with HER2 antagonists (trastuzumab or lapatinib) with progression-free survival of 4.6-9.6 months reported (Krop, 2012; Verma, 2012; Burris, 2011).

Mechanism of action, pre-clinical and clinical data for Palbociclib

Palbociclib (or PD-0332991) is an orally available, pyridopyridimidine-derived, selective inhibitor of cyclin dependent kinase 4/6-CDK4/6 (Fry, 2004; Toogood, 2005). Functionally, palbociclib is a potent and highly selective inhibitor of CDK4/6-cyclin D1 kinase activity, which ultimately results in the inhibition of retinoblastoma-Rb protein phosphorylation and cell cycle arrest.

In vitro and in xenograft model, palbociclib was observed to inhibit a panel of RB-positive, solid tumor cell lines (Fry, 2004; Finn, 2009; Dean, 2010; Thangavel, 2011). In a genetically engineered syngeneic animal model, palbociclib was effective at inhibiting the proliferation of mammary tumors in MMTV-HER2/Neu transgenic mice (Choi, 2012). Combined, these data suggest that palbociclib will likely be active in advanced breast cancer.

A phase 1 clinical trial with palbociclib in patients with Rb-positive advanced solid tumors demonstrated a therapeutic dose of 125 mg/d for 21d of a 28 d cycle, or 200mg/d for 14d of a 21 d cycle. The principal

dose-limiting toxicity-DLT was myelosuppression (Flaherty, 2011). A phase 2 study (PALOMA-1) of palbociclib with letrozole demonstrated a marked delay in disease progression in patients with advanced ER-positive breast cancer (Finn, 2012). Subsequently a randomized double-blind phase 3 trial (PALOMA-2) conducted in postmenopausal women with ER+/HER2 negative metastatic breast cancer demonstrated significant improvement in PFS (Finn et al, 2016). Based on the data from PALOMA-1, US FDA granted accelerated approval for palbociclib. Results of PALOMA-3 which was a randomized double-blind phase 3 trial for women with HR+/HER2 negative who progressed on or after endocrine therapy in the adjuvant or metastatic setting demonstrated improved PFS for the combination arm (fulvestrant + palbociclib) versus single agent fulvestrant (Turner et al 2015). Based on these results currently palbociclib is indicated for the treatment of HR+/HER2 negative metastatic breast cancer with an aromatase inhibitor as initial endocrine therapy in postmenopausal women or fulvestrant in women with disease progression following endocrine therapy.

Rationale for treatment of HER2 positive metastatic breast cancer with palbociclib

Despite the positive impact of trastuzumab on the treatment of HER2-positive breast cancer, immediate and acquired resistance to this targeted agent remains a significant clinical issue. Furthermore, while drugs such as T-DM1 and lapatinib have demonstrated efficacy in trastuzumab-resistant patients, disease progression remains a challenge (Geyer, 2006; Blackwell, 2009; Blackwell, 2010). Thus, there is still significant need for novel targeted therapies and combination regimens for the treatment of HER2-positive breast cancer. Preclinical studies have demonstrated palbociclib combined with microtubule poison prevented outgrowth of cell clones (McClendon et al., 2012). In addition, other preclinical studies with palbociclib have demonstrated efficacy in HER2-overexpressing cell lines and xenografts as well as mouse tumors in vivo (Witkiewicz et al, 2014). These pre-clinical findings suggest that palbociclib can be particularly effective in delaying progression in HER2 positive breast cancer by suppressing ability of tumors with acquired resistance to expand. These data are further supported by ongoing studies in the field showing cooperation of palbociclib with trastuzumab (NCT02448420).

While such preclinical data are suggestive of cooperation between the various components that constitute T-DM1, none of these studies can accurately model the complexity of human and tumor physiology or predict response.

Rationale for combination of T-DM1 and palbociclib : T-DM1 elicits cytotoxicity via emtansine and can induce ADCC. The CDK4/6 inhibition will be delivered to limit outgrowth of resistant clones and limit progression between the bolus delivery of T-DM1. Pre-clinical studies show that T-DM1 and CDK4/6 inhibition have highly distinct mechanisms of action, and could yield cooperative effects in terms of disease control. CDK 4/6 inhibition provides a potent adjunct to HER2 targeted therapies in preclinical breast cancer models. (Witkiewicz et al, 2014)

It may be a concern that palbociclib could interfere with the immunological effect of T-DM1.This concern is noted however there were several papers published recently that CDK4/6 inhibition (palbociclib) increases anti-tumor immune response eg of one such citation is below. Given this combination would be appropriate and deems further investigation. (Goel et al.2017)

A phase I trial is currently ongoing to evaluate the safety of combination of T-DM1 with palbociclib. In an effort to mitigate any potential toxicity and utilize each drug to its maximal effect, T-DM1 is being given on day 1 (of a 21 day cycle) to target rapidly proliferating tumor tissue. The serum half-life of T-DM1 is about 3.5 days (Krop, 2010). Palbociclib is given on day 5 – day 18 while levels of T-DM1 are diminishing and thereby any cells that have survived T-DM1 will be prevented from proliferation. As palbociclib serum half-life is 24 hours (Schwartz, 2011) the drug is being discontinued four days before the next T-DM1 dose (see section 2.2.4 for detailed study design).

Clinical experience with combination for T-DM1 and palbociclib

There is an ongoing phase I data evaluating the combination of T-DM1 with palbociclib in patients with metastatic HER2-positive breast cancer that have failed prior HER2-targeted therapy (including T-DM1 in

the second line) (NCT01976169) The study is based on the preclinical data with T-DM1 and palbociclib. T-DM1 is delivered at the standard of care dose (IV q21days at 3.6mg/Kg). Palbociclib is administered orally at increasing dose levels (100mg, 150mg and 200 mg) on days 5-18 (of a 21 day cycle) (Figure 1). The rationale of the study was to translate preclinical data investigating if using palbociclib can prevent proliferation of resistant disease when the levels of T-DM1 are diminishing based on the pharmacokinetics of both agents. Standard 3+ 3 phase 1 study design was used to guide dose escalation of palbociclib at 100mg, 150mg and 200mg. The trial accrued 9 patients with three at each dose level. Table 1 lists patient characteristics on the trial. Neutropenia was dose related and grade 3 neutropenia was observed in 1/3 patients at 100mg dose level, 2/3 patients at 150mg and 3/3 patients at 200mg dose. The hematological toxicities were resolved with dose interruption. Table 2 lists all the adverse events observed in the trial. No grade 4 toxicities were observed. 4/9 patients had stable disease and 3/9 patients had partial response with an average of 193 days on study (figure 2).

Figure 1: T-DM1+Palbociclib: Design for Phase I Trial

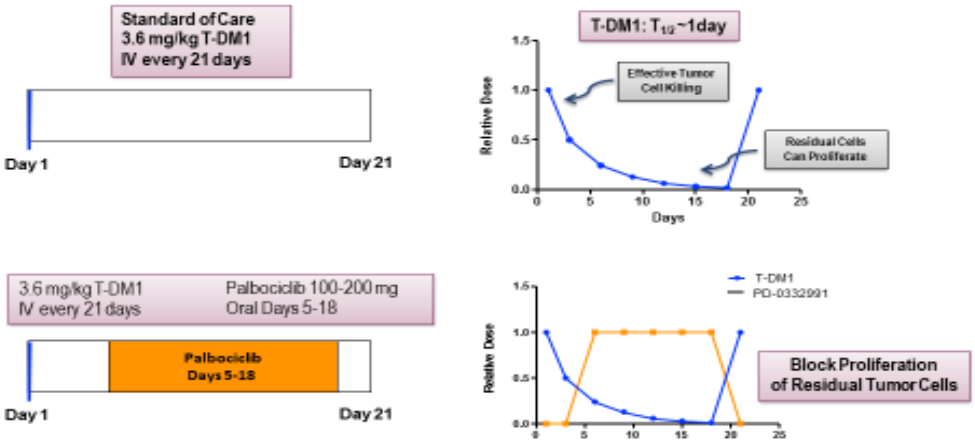


Table 1: T-DM1+Palbociclib: Patient Population

T-DM1 3.6 mg/kg IV every 21 days

+100 mg Palbociclib days 5-18

+150 mg Palbociclib days 5-18

+200 mg Palbociclib days 5-18

Parameter	Value
Median Age (Range)	56 (35-74)
Ethnicity	
Caucasian	8
African American	1
ECOG Performance Status	
0	5 (56%)
1	4 (44%)
2	0 (0)
ER-status	
Postive	6
Negative	3
Prior Therapies	
Median Systemic Therapies (Range)	5 (3-9)
Median Radiation Therapies (Range)	1 (0-3)
Median Surgical Therapy (Range)	2 (0-3)
Prior T-DM1	5

Table 2: T-DM1+Palbociclib: Adverse Events (g3)

TOXICITY (g3)	n (%)	DOSE LEVEL PALBOCICLIB (mg)		
		100	150	200
ANY GRADE 3	6 (66%)	1	2	3
Fatigue (g3)	1 (11%)	1	0	0
Nausea (g3)	1 (11%)	0	0	1
Mucositis Oral (g3)	1 (11%)	0	0	1
Anemia (g3)	1 (11%)	0	1	0
Thrombocytopenia (g3)	3 (33%	1	1	1
Neutropenia (g3)	6 (66%)	1	2	3
Lymphocyte count decreased (g3)	5 (55%)	1	2	2

Hematological toxicity: Recovery with dose interruption

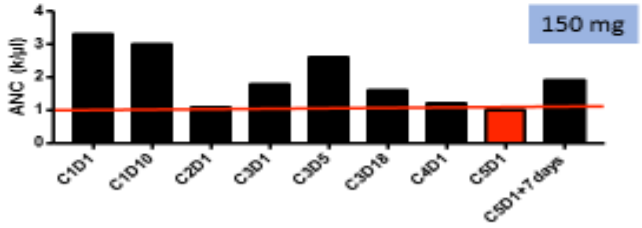
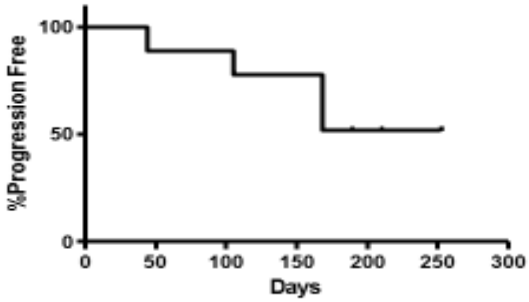


Figure 2: T-DM1+Palbociclib: Clinical Responses

Average time on treatment: 7.3 cycles*
-4 due to progression
-5 due to withdrawal from study

Range of time on treatment: 2-13 cycles



<u>The pre-clinical, clinical and toxicity data support the need for a larger phase II trial with a modifiable dose of 125 mg of palbociclib (which is the approved dose currently, to limit the need for dose delay and allowing for the evaluation of efficacy).</u>

3. <u>Study design</u>

This is a multi-center, single arm, phase II study of T-DM1 with palbociclib in the treatment of patients with metastatic HER2-positive breast cancer. All patients will be treated with combination of T-DM1 and palbociclib.

Selection of study population

3.1 *<u>Inclusion criteria</u>*

1. Be informed of the investigational nature of the study and all pertinent aspects of the trial
2. Sign and provide written consent in accordance with institutional and federal guidelines.
3. Age ≥18 years
4. ECOG Performance status of 0-2
5. Recurrent or metastatic HER2-positive breast cancer (HER2 positivity is defined per ASCO-CAP guidelines)
6. Must have one of the following by RECIST 1.1
    a. Measurable disease or
    b. Evaluable disease
7. Adequate cardiac reserve (Left ventricular ejection fraction ≥50%)

8. Serum creatinine ≤ 1.5 x institutional upper limit of normal (IULN), bilirubin ≤ 2.0 x IULN, and an SGOT/SGPT/alkaline phosphatase ≤ 2.0 x IULN
9. Adequate bone marrow function (ANC ≥1000, Platelets ≥100,000/ml, Hemoglobin ≥10gm/dL)
10. Be willing and able to comply with scheduled visits, treatment plan, laboratory tests and other trial procedures
11. Been treated with pertuzumab previously (neoadjuvant or adjuvant or metastatic setting). Patients who weren't able to tolerate pertuzumab due to side effects can be eligible for study
12. No more than 2 lines of therapy in the metastatic disease setting
13. Female subjects must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of therapy. All female subjects with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment and must agree to use effective contraception during the period of therapy. Women of childbearing potential and men should use effective methods of contraception during the entire duration on study and for 7 months after completion.

3.2 *Exclusion Criteria*

Patients who fulfill any of the following criteria will be excluded

1. HER2 negative tumors
2. Prior treatment with T-DM1 in the metastatic setting. If treated with prior T-DM1 in the neoadjuvant or adjuvant setting, a treatment free interval of at least 12 months
3. Prior treatment with CDK 4/6 inhibitors
4. Known active symptomatic CNS metastases or carcinomatous meningitis. Patients with stable CNS metastases including brain metastases who have completed a course of radiotherapy are eligible for the study provided they are clinically stable. However, oral corticosteroids for control of CNS symptoms are not allowed on study
5. Known documented or suspected hypersensitivity to the components of the study drug(s) or analogs.
6. Uncontrolled systemic illness, including but not limited to ongoing or active infection
7. Symptomatic congestive heart failure, unstable angina pectoris, stroke or myocardial infarction within 3 months
8. Be pregnant or breast feeding.
9. Concurrent endocrine therapy or other anti-neoplastic therapy is not allowed. Patients can receive supportive therapy like bone-directed therapy including bisphosphonates or denosumab. Other supportive care medications can be used if clinically indicated (like growth factor support). If a patient is already on a Gonadotrophin releasing hormone agonists, it can be continued during this study.

4. Study drugs

4.1 **Palbociclib**

4.1.1 Availability

Palbociclib is currently approved in combination with hormonal therapy (aromatase inhibitors or fulvestrant) to treat ER+/HER2 negative metastatic breast cancer. It is experimental for the combination proposed in this trial. Palbociclib is produced by Pfizer with approval of the FDA for investigational purposes (IND BB#69324). Palbociclib will be provided by Pfizer Pharmaceuticals as commercially available preparation, Ibrance and will be shipped directly to participating sites. Individual sites will be responsible for the drug accountability and dispensing.

4.1.2 Pharmaceutical data

a. Formulation

In 02/2020 Pfizer changed the formulation of palbocilcib from capsule to tablet. Palbociclib is supplied as smooth-coated tablet formulation. Monthly supply will contain 3 weekly blister packs of 7 tablets each along with USPI for the tablet formulation. Tablets should not be removed from the blister pack and placed in a pill caddy. Each strength of tablet has a different shape or color as well as a different color carton similar to the way the current bottles have different colored labels.

b. Reconstitution

75, 100 and 125 mg tablets will be used. Patients will use the appropriate number of tablets per day with amount dependent on prescribed dose. Each patient will receive a 14-day supply at the beginning of each cycle (cycle is 21 days).

c. Storage and Stability

Tablets are stored in line at room temperature (15-25 degrees Celsius).

d. Administration

The drug is to be taken orally on days 5-18 (14 days) of each cycle (cycle length 21 days). Starting dose will be 125mg. Patients can take palbociclib with or without food. Patients will be given a drug log to maintain to document compliance with administration.

e. Procurement

Patients are consented at their institution and all required enrollment documents must be emailed to Criterium for confirmation of enrollment prior to treating a patient. Once eligibility is confirmed, study site is notified to register patient. Following patient registration, the study coordinator will notify their IDS Pharmacy for dispensing of drug. Maintenance of a drug accountability record is required for palbociclib. The investigator, or a responsible party designated by the investigator, will maintain a careful record of the receipt, disposition, and return of all drugs supplied for this study.

f. Drug-related Toxicities

Toxicities associated with palbociclib include:

1. 30% or more: decreases in neutrophil blood cells (may increase the risk of infection), decreases in while blood cells (infection fighting cells), infections, fatigue
2. 10 to less than 30%: decreases in hemoglobin (may cause weakness), decreases in platelets (may cause bleeding and/or bruising), inflammation of the mouth, diarrhea, constipation, nausea, vomiting, joint pain, back pain, pain in hands and feet, hair loss, rash, cough, shortness of breath, headache, dizziness, decreased appetite, hot flush, insomnia (inability to sleep), fever, common cold
3. 5 to less than 10%: abdominal pain, indigestion, dry mouth, asthenia (general weakness), swelling of hands and feet, irritation or sores in the lining of hollow organs like mouth, throat, stomach, bowels; pain, influenza (flu) like illness, muscle pain, pain in the muscles and bone including around the chest, muscle cramps, increases in blood liver markers that may indicate liver damage, dry skin, itching, mouth/throat pain, nosebleed, impaired sense of taste,depression, fall, anxiety, high blood pressure, acid reflux (heart burn), increased creatinine level (may indicate abnormal kidney function)
4. The following side effects have been reported in <5% of patients, but still deemed important: Fever associated with dangerously low levels of a type of white blood cells (neutrophils), blurred vision, increased tearing, dry eye. In addition, interstitial lung disease (an inflammation of the lungs which can cause cough and shortness of breath) can occur
5. Serious and life-threatening infections have been observed in some patients treated with palbociclib
6. Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors, including palbociclib when taken in combination with endocrine therapy. Across clinical trials, 1.4% of palbociclib -treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3, and no Grade 4 or fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported

g. Drug interactions

There is the potential for a drug-drug interaction when taken concomitantly with CYP3A4 substrates and P-glycoprotein substrates.

CYP3A Inhibitors: Avoid concurrent use of palbociclib with strong CYP3A inhibitors. If the strong inhibitor cannot be avoided, reduce the starting dose of palbociclib is indicated. Study PI needs to be contacted to review about patient and decide on the starting dose. Trying alternative medications is encouraged to start all patients on the recommended starting dose

CYP3A Inducers: Avoid concurrent use of palbociclib with strong CYP3A inducers

CYP3A Substrates: The dose of sensitive CYP3A4 substrates with narrow therapeutic indices may need to be reduced when given concurrently with

palbociclib. A complete list of concomitant medications should be completed at time of patient screening and should be submitted as a part of their screening package.

4.2 **T-DM1**

4.2.1 Availability

T-DM1 is a licensed drug produced by Genentech with approval of the FDA for treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination and had received prior therapy for metastatic disease or developed disease recurrence during or within six months of completing adjuvant therapy (IND BB#69324 and US approval for sales in 2013). T-DM1 is commercially available, therefore the subject's insurance company will be responsible for the prescription.

4.2.2 Pharmaceutical Data

a. Formulation

Lyophilized powder in single-use vials containing 100 mg per vial or 160 mg per vial.

b. Reconstitution

Using aseptic technique for reconstitution and preparation of dosing solution, appropriate procedures for the preparation of chemotherapeutic drugs should be used. Using a sterile syringe, slowly inject 5 mL of Sterile Water for Injection into the 100 mg KADCYLA vial or 8 mL of Sterile Water for Injection into the 160 mg KADCYLA vial to yield a solution containing 20 mg/mL. Swirl the vial gently until completely dissolved. Do not shake. Inspect the reconstituted solution for particulates and discoloration. The reconstituted solution should be clear to slightly opalescent and free of visible particulates. The color of the reconstituted solution should be colorless to pale brown. Do not use if the reconstituted solution contains visible particles or is cloudy or discolored. The reconstituted lyophilized vials should be used immediately following reconstitution with Sterile Water for Injection. Determine the correct dose (mg) and calculate the volume of 20 mg/mL KADCYLA solution needed. Withdraw this amount from the vial and add to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection. Gently invert the bag to mix the solution in order to avoid foaming. The diluted KADCYLA infusion solution should be used immediately. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C for up to 4 hrs prior to use. Do not freeze or shake.

c. Storage and Stability

Lyophilized powder containing vials may be stored at room temperature. Once reconstituted, the shelf life is 4 hrs at 2°C to 8°C.

d. Administration

The recommended dose of T-DM1 also called KADCYLA is 3.6 mg/kg given as an intravenous infusion Day 1 of every cycle (every 21 days). Administer first infusion over 90 min (C1D1). Subsequent infusions may be administered over 30 min if prior infusions were well tolerated (starting C2 and going forward). If necessary, the administration time and can be

modified to meet institutional guidelines. The dose of KADCYLA is 3.6mg/kg and can be calculated per cycle or change when weight has changed by 10% (from the weight used to calculate the dose of KADCYLA)

e. Procurement

Drug is commercially available and will be procured as standard of care.

f. Drug-related Toxicities

Toxicities associated with T-DM1 include:

Frequent (>10%): fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, constipation.

Less Frequent (>5% and ≤10%): infusion-related reactions, hepatotoxicity, pulmonary toxicity, peripheral neuropathy.

Rare (≤5%): liver failure, heart failure, embryo-fetal toxicity, respiratory failure, hypersensitivity, insomnia, rash, hypertension.

5. Treatment plan

5.1 Schedule of events: T-DM1 + palbociclib

		Day 1 of Each cycle (q21 days)*	End of Treatment (within 30 days of last dose)	Long term Survival Follow up
Visit Schedule of Procedures	**Screening[a]**	**D1**		**Every 6 months[$]**
Informed Consent	X			
Urine or Serum Pregnancy[h]	X	X[h]		
Medical History	X			
Demographics	X			
Physical Exam	X	X[c,j]	X	
Height	X			
Weight	X	X[c]		
Vital Signs	X	X[c]	X	
ECOG performance	X	X[c,j]	X	
Concomitant Medication / Procedure	X	X[c]	X	
Adverse Events	X	X[c]	X[f]	
CBC w Diff and Platelets	X	X[c,k]		
Comprehensive Metabolic Panel[b]	X	X[c,k]		
LVEF assessment (ECHO or MUGA)	X	12 weeks (+/- 7 days)		
Imaging (CT or MRI Chest ,Abd / Pelvis w contrast)	X	12 weeks (+/- 7 days)	X	
Bone Scan or PET scan or PET component of PET/CT scan[g]	X	12 weeks (+/- 7 days)	X	
12-Lead ECG	X		X	
QOL Questionnaires		X[e]	X[e]	
T-DM1 Administration		X*		
Palbociclib compliance Monitoring		X		
Investigational Pharmacy study drug dispensing		X		
Survival information				X
Biomarker plasma		X[e]	X[e]	
Archived tumor tissue collection	X			
Collection of post - study treatment anti Cancer therapy information				X

a-all screening procedures to be done within 28 days of randomization, b- should include creatinine, alkaline phosphatase, ALT, AST and total bilirubin , c- for C1D1 only- does not have to be repeated if done within 14 days prior to start of C1D1, e-C1D1 and end of treatment, f- adverse events should be done 30 days after last treatment, it can be done by phone call if no visit is scheduled, g- for patients with bone metastasis only,if this is done as a part of standard institutional guidelines h- every 6wks for women of childbearing potential only, i-only when applicable, j- can be done q6wks after cycle 8 , k- starting cycle 2 labs can be done on day of treatment (Day 1) or upto 2 days prior * T-DM1 cannot be given before 21 days but can be given up to 7 days later and D1 of every cycle is the day T-DM1 is administered, $-every 6 months upto 5 yrs or until last patient comes off study

5.2 **Schedule of events Group B : T-DM1 (only applicable for patients currently on single T-DM1)**

		Day 1 of Each cycle (q21 days)*	End of Treatment (within 30 days of last dose)	Long term Survival Follow up
Visit Schedule of Procedures	**Screening[a]**	**D1 (**+/- 3/7 days)		**Every 6 months[$]**
Informed Consent	X			
Urine or Serum Pregnancy[h]	X	X[h]		
Medical History	X			
Demographics	X			
Physical Exam	X	X[c,j]	X	
Height	X			
Weight	X	X[c]		
Vital Signs	X	X[c]	X	
ECOG performance	X	X[c,j]	X	
Concomitant Medication / Procedure	X	X[c]	X	
Adverse Events	X	X[c]	X[f]	
CBC w Diff and Platelets	X	X[c,d]		
CMP[b]	X	X[c]		
LVEF assessment (ECHO or MUGA)	X	12 weeks (+/- 7 days)		
Imaging (CT/MRI Chest , Abd / Pelvis w contrast)	X	12 weeks (+/- 7 days)	X	
Bone Scan or PET scan or PET component of PET/CT scan[g]	X	12 weeks (+/- 7 days)	X	
12-Lead ECG	X		X	
QOL Questionnaires		X[e]	X	
T-DM1 Administration		X*		
Survival information				X
Biomarker plasma		X[e]	X[e]	
Archived tumor tissue collection	X			
Collection of post - study treatment anti-Cancer therapy information				X

a-all screening procedures to be done within 28 days of randomization, b- should include creatinine, alkaline phosphatase, ALT, AST and total bilirubin , c- for C1D1 only- does not have to be repeated if done within 14 days prior to start of C1D1e-C1D1 and end of treatment, f- adverse events should be done 30 days after last treatment, it can be done by phone call if no visit is scheduled, g- for patients with bone metastasis only, if this is done as a part of standard institutional guidelines, h- every 6wks for women of childbearing potential only, i-only when applicable, j- can be done q6wks after cycle 8 , * T-DM1 can be given -3 days to + 7 days of a 21 day cycle (to give flexibility for investigator and patients) and D1 of every cycle is the day T-DM1 is administered, $-every 6 months up to 5 yrs or until last patient comes off study

6. Dose modifications

6.1 **Palbociclib**

Management of some adverse events may require temporary dose interruptions/delays and/or dose reductions, or permanent discontinuation as per dose reduction schedules listed in tables 1, 2 and 3 below

Table 1: recommended dose modification for adverse reactions

Dose level	Dose
Recommended starting dose	125mg/day
First dose reduction	100mg/day
Second dose reduction	75mg/day

- If further dose reduction below 75mg/day is required, discontinue the treatment and come off study

6.2 **T-DM1**

If a planned dose is delayed or missed, administer as soon as possible; do not wait until the next planned cycle. Adjust the schedule of administration to maintain a 3-week interval between doses. Administer the infusion at the dose and rate the patient tolerated in the most recent infusion

Table 2 : Recommended Dose Reduction Schedule for Adverse Events

Dose reduction schedule	Dose level
Starting dose	3.6mg/kg
First dose reduction	3mg/kg
Second dose reduction	2.4mg/kg
Requirement for further dose reduction	Discontinue treatment and come off study

Table 3: Recommended dose modifications for T-DM1 and Palbociclib

Adverse Events£	Grade	Palbociclib	T-DM1#
Infusion reaction	2 or 3	Not Applicable	Slow or interrupt
	4	Not Applicable	Permanently discontinue
Transaminases	3	No change	Hold until ≤Grade 2, then one dose level reduced
	4	Permanently discontinue	Permanently discontinue
Bilirubinemia in absence of elevated transaminases	2	No change	Hold until <Grade 1, then same dose
	3	Hold until <Grade 1, then one dose level reduced	Hold until <Grade 1, then one dose level reduced

	4	Permanently discontinue	Permanently discontinue
Transaminases + Bilirubinemia	Transaminases>3xULN + Bilirubin >2xULN	Permanently discontinue	Permanently discontinue
QTc	2 3 4	No change Reversible cause, wait till QTc <480msec, resume same dose; No reversible cause, wait till QTc <480msec, then one dose level reduced. Permanently discontinue	No change No change No change
Nodular generative hyperplasia of liver	Any grade	Permanently discontinue	Permanently discontinue
LVEF	>45% 40-45%, decrease <10% from baseline 40-45%, decrease ≥10% from baseline <40%	No change No change No change No change	Continue Continue, repeat imaging in 3wks Hold, repeat imaging 3wks, if not recovered, discontinue Hold, repeat imaging 3wks, if <40% discontinue
Symptomatic CHF	Any grade	Permanently discontinue	Permanently discontinue
Interstitial lung disease/pneumonitis€	Any grade	Permanently discontinue	Permanently discontinue
Other non-hematologic	2 3-4	No change If related, when Grade ≤1, restart next lower dose level	No change If related, when Grade <1, restart next lower dose level
Neuropathy	Grade 3-4	No change	Hold until ≤Grade 2
ANC	<1000/mcL	Hold until >1000/mcL If Grade 4 neutropenia >1wk or Grade 3 neutropenia >2wks or Grade 3-4 neutropenia complicated by T>38.5°C, then reduce by 1 dose level	Hold until >1000/mcL and resume at the same dose level
Platelets Day 1 of each cycle	<LLN->75,000/mcL, grade 1	No change	No change

	50-75,000/mcL,grade 2	Hold until ≥75,000/mcLand resume at the same dose level	Hold until ≥75,000/mcL and resume at the same dose
	25-50,000/mcLGrade 3	Hold until ≥75,000/mc, then resume at reduced dose by one level	Hold until ≥75,000/mcL and resume at the same dose
	<25,000/mcL, grade 4	Hold until ≥75,000/mc, then resume at reduced dose by one level	Hold until ≥75,000/mcL and resume at reduced dose by one level
£ If adverse events take more than 14 days to resolve, dose for palbociclib and T-DM1 have to be reduced one dose level *Dose levels for T-DM1 are 3.6mg/kg starting dose level and 3.0mg/kg one dose level reduced and 2.4mg/kg two dose levels reduced Palbociclib dose levels are 125mg, 100mg and 75mg #Based on T-DM1 package insert € Based on clinical symptoms and confirmed by CT or imaging findings			

7. Adverse Events (AEs)

7.1 Adverse Events Definition

AEs will be determined using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for Toxicity and Adverse Event reporting. A copy of the CTCAE version 4.03 can be downloaded from CTEP home page (http://ctep.info.nih.gov).

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.2 Serious Adverse Events (SAEs) Definition

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);

- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

7.3 Documentation of AEs

For AEs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Documentation will include, but is not limited to:

- Grade
- Relationship to study drug (not related, unlikely, possible, probable, definitely)
- Causality other than study drug (disease related, concomitant medication related, intercurrent illness, other)
- Date of onset, date of resolution
- Frequency of event (single, intermittent, continuous)
- Event outcome (resolved, ongoing, death)
- Action taken (none, held, dose reduced, discontinued, medication given)

7.4 Documentation of SAEs

AEs that meets the definition of an SAE, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

All SAEs must be recorded as an SAE within the study electronic data capture system and the report must be reported to Protocol PI and Criterium PM via email within 24 hours of learning of its occurrence. Specifics will be noted in the SAE Reporting Guidelines. A paper SAE report form might also be required.

SAEs are to be reported to your IRB in accordance with IRB reporting policies.

All serious adverse events and any deaths will be reported to the DSMB and to the University of Arizona Human Subjects Protection Program per the guidelines set forth in University of Arizona Cancer Center Data and Safety Monitoring Board Charter.

All submitted serious adverse events will be processed by the DSMB Coordinator monthly for initial trend analysis and then reviewed by the DSMB Chair. The assigned QA/QC Monitor will review the SAE reporting process to confirm reporting requirements are met.

7.5 Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 30 days of the subject's last dose of study should be recorded as SAEs. The patient is to be discontinued immediately (within 24 hours) from the study and the female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

Pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Criterium Project Manager & Protocol PI immediately by submitting a completed Pregnancy Report Form via email. Specifics will be outlined in the SAE reporting guidelines.

The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the Criterium Project Manager and Protocol PI on an updated Pregnancy Report Form and submit. If the pregnancy results in the birth of a child, additional follow-up information may be requested. If the pregnancy results in spontaneous abortion or stillbirth, the event should be reported as an SAE. If there are any abnormal outcomes that meet the serious criteria, it must be reported as an SAE.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

7.6 Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses should be reported as a SAE using the SAE forms.

7.7 FDA Expedited Reporting requirements for studies conducted under an IND:

If an investigator deems that an event is a Suspected Unexpected Serious Adverse Reaction (SUSAR), de-identified supporting documentation defining the event and causality within 24 hrs of knowledge of the event should be emailed to the Criterium Project Manager and Protocol PI.

The UACC study manager or designee will report all local and nonlocal events to the UACC IRB and DSMC. It is the responsibility of UACC or designee to ensure that all participating sites are notified of the events and resulting action for events which may modify the risk of the protocol or which otherwise meet FDA requirements for expedited reporting.

If the toxicity is reportable, the study PI at UACC will be responsible for notifying the FDA as per Federal Register §312.32 IND safety reports.

Once the Protocol PI determines an event is a SUSAR, the MedWatch 3500A form will be created by Protocol PI or designee and submitted to the FDA. Protocol PI or designee will also report information to Pfizer per their requirements.

In particular, (1) Written reports. The Protocol PI or designee shall notify FDA in a written IND safety report of any adverse experiences associated with use of the drug that is serious and unexpected. Such notification shall be submitted to the FDA no later than 7 working days after the initial receipt of the information for fatal or life-threatening and 15 calendar days for non-fatal or non-life-threatening . The written notification to the FDA will be transmitted or mailed to the FDA Division of the Center for Drugs and Biologics. (2) Telephone reports. The Protocol PI or designee shall also notify FDA by telephone of any unexpected, fatal or life-threatening experience associated with use of the drug in the clinical study conducted under the IND no later than 3 working days after receipt of the information.
The MedWatch 3500a form can be accessed at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm. (Please be sure and access form 3500a, and not form 3500). UNC, as the Sponsor of the study, will make the final determination regarding FDA submission.

The Criterium PM or designee is responsible for emailing expedited reports to each site on study of all SUSARs reported to the FDA via email as soon as possible.

Questions

Any questions regarding this protocol should be directed to the PI or study team.

Principal Protocol Investigator	Pavani Chalasani MD, MPH University of Arizona Cancer Center Telephone : 520-626-0191 Fax: 520-626-2225
Criterium Project Manager or Designee	Contact information will be provided in the Safety Reporting Guidelines.

8 Study procedures

8.1 Enrollment

Before a subject participates in the trial, the investigator or delegate (as allowed by the IRB of record) is responsible for obtaining written informed consent after adequate explanation of the aims, methods, anticipated benefits, subject responsibilities including the use of adequate methods to prevent pregnancy, and potential hazards of the study and before any protocol-specific screening procedures or any study medications are administered.

Enrollment packets must be approved prior to enrollment. To enroll a patient, all the necessary documents must be submitted to Criterium and will be reviewed and approved by the medical monitor. Materials required to complete the enrollment packet are to be emailed and include, but not limited to the following:

- Consent Form (first page and blinded signature pages)
- HIPAA Authorization (first page and blinded signature pages)
- Eligibility Checklist and all supporting documentation

8.2 Screening

Potential subjects will enter the screening period of the study after a completely executed informed consent has been obtained.

8.3 Registration

After eligibility has been confirmed, a patient identification number will be assigned. The patient will be considered registered, and study treatment may then begin.

For multi-center study registrations, subject identification numbers will begin with the site number and end with a sequential number. Format is to be determined but an example is XX-YYY. XX being the assigned site number (01, 02, 03, etc) and YYY being the sequential patient number for that site (001, 002, 003, etc).

8.4 Follow up

Follow-up visits/procedures will be conducted per schema in section 5. Data regarding further treatments and survival information will be captured for this study every 6 months until the final patient is off treatment or otherwise determined by the sponsor.

8.5 Early treatment termination

Subjects that terminate treatment early (for reasons other than disease progression or side effects) will have an end of treatment (time period i.e. within 30 days of receiving the last treatment). Subjects will then follow up with their treating physician per their standard of care.

8.6 Off study

Subjects will be considered off study when all end of study and follow-up visits have been completed, unless death or withdrawal of consent to continue participation occurs.

9.0 Tumor response evaluation per RECIST 1.1

The revised RECIST 1.1 guidelines (Eisenhauer, 2009) will be used to determine response and progression.

Patients with measurable or non-measurable (evaluable) disease (according to RECIST 1.1) will be evaluated for response or progression. For the purposes of this study, patients will be evaluated by tumor imaging 12 weeks ± 7 days. Whenever possible imaging is done after every 4 cycles prior to their next cycle of treatment (12 weeks ± 7 days) however if there are any delays in treatment, the imaging should follow 12 week from last imaging schedule. At baseline, tumor lesions/lymph nodes/bone lesions will be categorized as measurable or non-measurable based on the definitions provided below.

9.1 Measurable Disease

Measurable disease is defined by the presence of at least one measurable lesion that can be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm); when CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion must be twice the slice thickness.

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm).Only the short axis will be measured and followed at baseline and in follow-up (Schwartz, 2009).

9.2 Non-Measurable Disease

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

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 scan or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurable disease. Blastic bone lesions are considered nonmeasurable disease.

Cystic lesions: Lesions that meet the criteria to be radiographically defined as simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurable disease. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

9.3 Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each lesion at baseline and throughout the study. Imaging-based evaluation must always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but is/are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and are ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). When lesions can be evaluated by both clinical exam and imaging, imaging evaluation must be undertaken, because it is more objective and may also be reviewed at the end of the study.

CT, MRI: CT is the best currently-available and reproducible method for measuring lesions selected for response assessment. If a slice thickness > 5 mm is used for CT scanning, then the minimum longest diameter for a target lesion will be twice the slice thickness.

Tumor markers: Tumor markers may be obtained per institutional guidelines; however, tumor markers cannot be used to assess objective tumor response or PD. Details on tumor markers will be captured in the database.

Cytology and histology: These techniques can be used to differentiate between PR and CR in rare cases when the nature of a residual lesion is in question. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met the criteria for response or stable disease (SD) in order to differentiate between response (or SD) and PD.

9.4 Baseline Documentation of “Target” and Non-Target” lesions

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this estimate as a comparator for subsequent measurements.

Any single lesion that meets the definition of measureable disease (Section 9.1) may be identified as a “Target Lesion” and will be recorded and measured at baseline. When > 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 total (and a maximum of 2 lesions per organ) that are representative of all involved organs will be identified as target lesions and will be recorded and measured at baseline. This means that in instances where patients have only 1 or 2 organ sites involved, a maximum of 2 and 4 lesions, respectively, will be recorded. Target lesions will be selected by size (based on their longest diameter) and whether they lend themselves to reproducible repeated measurements. Occasionally, the largest lesion does not lend itself to reproducible measurement; in this circumstance, the next-largest lesion that can be measured reproducibly will be selected. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measureable unless there has been demonstrated progression in the lesion.

Pathological nodes that are defined as measurable may be identified as target lesions; however, only the short axis of these nodes will contribute to the baseline sum. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions. All other pathological nodes will be considered non-target lesions.

While on study, all lesions (nodal and non-nodal) recorded at baseline will have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, if the lesion is believed to be present and is faintly seen but is too small to measure with any accuracy, a default value of 5 mm will be assigned.

A sum of the diameters (longest diameter for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and will be reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes will be identified as “non-target lesions” and will also be recorded at baseline. Measurements are not required and these lesions will be followed as present, absent, unequivocal progression, or new lesions.

9.5 Evaluation of target lesions

Definitions of the criteria used to determine objective tumor response for target lesions are seen in table 4:

Table 4: Criteria Definitions for Objective Tumor Response for Target Lesions

Tumor response	**Criteria definition**
Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: The appearance of 1 or more new lesions is considered progression.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

9.6 Evaluation of non-target lesions

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are in Table 5. While some non-target lesions may actually be measurable, they need not be measured and instead will be assessed only qualitatively at the time points of radiographic assessments.

Table 5: Criteria Definitions for Objective Tumor Response for Non-Target Lesions (RECIST 1.1)

Tumor response	**Criteria definition**
Complete Response	Disappearance of all non-target lesions and normalization of tumor marker

	level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease	Unequivocal progression of existing non-target lesions. (Note: The appearance of 1 or more new lesions is also considered progression).

Disease progression in subjects with only non-measurable disease

For subjects with only non-measurable disease, disease progression is defined as development of new lesions or "unequivocal progression" of existing lesions. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden, based on the change in non-measurable disease, is comparable in magnitude to the increase that would be required to declare PD for measurable disease, i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

New lesions
The appearance of new malignant lesions denotes disease progression; however, the finding of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.
If a new lesion is equivocal (eg, because of small size), continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

9.7 Evaluation of best overall response per RECIST 1.1

The best overall response is the best response recorded from the start of the randomization until disease progression/recurrence per RECIST, taking as reference for PD the smallest measurements recorded since the treatment started. The patient's best response assignment will depend on the achievement of both measurement and RECIST criteria.

Table 6 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with and without the appearance of new lesions.

Table 6: Overall Responses for Combinations of Tumor Responses per RECIST 1.1

Target lesions	**Nontarget lesions**	**New lesions**	**Overall response**
CR	**CR**	**No**	**CR**
CR	**Non-CR/Non-PD**	**No**	**PR**
CR	**Not evaluated**	**No**	**PR**

PR	**Non-CR/not evaluated**	**No**	**PR**
SD	**Non-PD or not all evaluated**	**No**	**SD**
PD	**Any**	**Yes or no**	**PD**
Any	**PD**	**Yes or no**	**PD**
Any	**Any**	**Yes**	**PD**
Not all evaluated	**Non-PD**	**No**	**Unevaluable**

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease
Subjects with global deterioration of health status requiring discontinuation of treatment without objective
evidence of disease progression at that time should be reported as “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

10. STATISTICAL CONSIDERATIONS

10.1 Analysis population

Patients with recurrent or metastatic HER2 positive breast cancer who are eligible to start treatment with T-DM1 will be enrolled on to this trial. The primary analysis sample for efficacy will be evaluable patients who have completed at least 1 cycle of treatment. If a patient was not able to complete at least 1 cycle of therapy, they will be replaced for the study analysis.

Patients will be treated with T-DM1 and Palbociclib. T-DM1 will be administered 3.6mg/kg IV q21 days. Palbociclib is given orally at 125mg on days 5-18 of every 21 day cycle.

10.2 Safety Analysis

The first safety analysis will be conducted when 16 patients have completed 12 months or come off study (which ever is first) on T-DM1+ Palbociclib arm. Safety data with regards to number of grade 3 or 4 events and unresolved grade 3 or 4 events will be taken into account and if more than 20% of subjects have unresolved grade 3 or 4 events, the study advisory board will meet to discuss dose and schedule modification. After the first 16 patients, additional safety oversight will be provided by the study data monitoring committee (DMC)

10.3 Sample Size Calculation

This is a prospective single arm phase II study to estimate progression free survival of combination T-DM1 + palbociclib. Expected PFS for T-DM1 based on the EMILIA trial is 9.6 months. The goal of the study is to detect an improvement of PFS to 16.3 months (HR = 0.56) in the combination arm compared to the standard historical control arm, with 80% statistical power and a 0.05 one sided alpha level. We propose enrolling a total of 46 subjects into this trial. We will conduct a futility analysis after the first 16 evaluable patients have completed 12 months of treatment or come off study (whichever comes. First). If at least 8 have PFS beyond 12 months, we will continue accrual for additional 30 evaluable patients (for a total of 46 evaluable patients). If at least 24 evaluable subjects have PFS beyond 12 months then we declare the combination

as promising for future studies. Our null hypothesis is 40% have PFS at 12mths (median survival of 9.1 months) Alternative hypothesis is 60% survive 12 months.

Definition of end points

PFS is defined as the time from date of first treatment to the date of investigator-determined objective disease progression as defined by RECIST 1.1 or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment (if available) or date of randomization if no post initiation (that is post baseline) radiographic assessment is available

Response rate
Overall response rate (ORR): the proportion of patients with CR or PR per RECIST 1.1
Disease control rate (DCR): the proportion of patients with CR, PR or SD according to RECIST 1.1
Clinical benefit rate (CBR): the proportion of patients with CR, PR or SD ≥6mths according to RECIST 1:1
Duration of Response(DOR): The time from the date of first evidence of a CR or PR to the date of objective progression or death from any cause,whoever is earlier (this is only defined in responders in both arms)

Overall survival is defined as the time from date of first treatment to date of death due to any cause. Patients last known to be alive are censored at their last contact date

10.4 Statistical analysis

Progression free survival of the combination of T-DM1 with palbociclib will be estimated using the Kaplan-Meier estimate. A Cox proportional hazards model will be used to estimate the hazard rate with 95% confidence interval. Overall survival will be analyzed similarly. The overall response (CR + PR + stable disease) will be estimated using an exact binomial confidence interval.

11. ADMINISTRATIVE PROCEDURES

11.1 Investigator Responsibilities

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, data monitoring will be conducted and the Principal Investigator or designee must provide de-identified source upon request to permit remote verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11.2 Subject Confidentiality

The principal investigator will ensure that the subject's confidentiality is maintained in compliance with Federal regulations, the International Conference on Harmonization (ICH), and Good Clinical Practice (GCP) Guidelines.

Oversight entities and/or regulatory authorities will be permitted direct access to review the subject's original medical records, electronic medical records or certified copies for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

11.3 Study Documentation and Archive

The investigator will maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Delegation of Responsibilities Form.

Source documents, data, and records from which the subject's CRF data are obtained include, but are not limited to, hospital records, clinical/office/research charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source data will include information necessary for the reconstruction and evaluation of the trial.

The principal investigator or sponsor-investigator is responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation as required per ICH Guidelines. This can be accomplished by the PI, through the site's standard operating procedures and/or the institutions infrastructure.

The investigator will follow ICH Good Clinical Practice Guidelines and the Code of Federal Regulations for records and record retention.

11.4 Data

Applicable data as specified as required in the protocol will be reported/submitted in the case report form (CRF). Data reported in the case report forms that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. All the CRF's data will be entered into a central database determined and managed by Criterium, Inc.

Additional procedures and assessments may be performed as the institution's standard of care; however, these data should remain in the medical records and should not be provided as part of the clinical study data unless it pertains to an adverse event or serious adverse event.

The investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational product/intervention/device, or employed as a control in the investigation.

11.5 Protocol Deviations

The investigator will conduct the study in conformance with this protocol, generally accepted standards of Good Clinical Practice and all applicable federal, state and local laws, rules, and regulations.

Approvals or waivers for protocol deviations will be obtained from the sponsor-investigator ***prior to*** occurring, except changes to eliminate an immediate hazard to study subjects. If immediate verbal approval is obtained, it will be documented by the research staff obtaining the approval and followed by a written protocol deviation form per the site standard operating procedures. The sponsor or the sponsor-investigator will sign the Protocol Deviation (Waiver) Approval Form or other similar document. The original will be filed in the regulatory binder and a copy will be placed in the subject's research file.

11.6 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Protocol Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the site IRB for approval prior to implementation.

All sites must submit their informed consent revisions to the Criterium Project Manager or designee for review and approval prior to submission to their IRB.

11.8 Termination Rules

The protocol Principal Investigator and Criterium have the right to terminate this clinical study at any time. The protocol principal investigator and Criterium, as appropriate, will be involved in any decisions regarding terminating the study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment.

Reasons for terminating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is significantly inaccurate or incomplete
- Study site personnel are noncompliant with study procedures
- Pattern of noncompliance is observed

12. Regulatory Obligations

12.1 Informed Consent

Before a subject's participation in the clinical study, the investigator or identified designee is responsible for obtaining written informed consent from the subject or legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specified procedures, investigational product, intervention or device are administered or initiated.

12.2 Institutional Review Board

A copy of the protocol, proposed ICF, and all other applicable subject information will be submitted to the individual site's IRB for written approval. A copy of the written approval of the protocol and ICF must be on file at the individual institution before recruitment of subjects into the study.

The principal investigator at each site is responsible for obtaining IRB approval/renewal at least annually throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be on file at the institution.

The investigator must submit study information to the IRB as required by all applicable guidelines and requirements. The investigator will obtain IRB approval for subsequent protocol amendments; except changes to eliminate an immediate hazard to study subjects, and changes to the informed consent document from the IRB prior to implementation.

The investigator will notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other serious adverse event reports occurring at or received from participating centers as applicable for multi-center trials following the IRB policies and procedures.

All the sites must notify the primary site (UACC) and Criterium of any SAE and notification to their IRB.

13. DATA AND SAFETY MONITORING PLAN

13.1 Identification of the DSMB obligated for oversight responsibilities

University of Arizona will be responsible for the conduct of this study as the DSMB of record, overseeing participant safety, executing the data and safety monitoring (DSM) plan, and ensuring compliance with all reporting requirements to state and federal authorities. Criterium,Inc will provide the site monitoring function for this trial and provide monthly reports to the University of Arizona DSMB. The University of Arizona DSMB is responsible for ensuring data quality and study participant safety. A summary of the DSMC's activities is as follows:

- Conduct internal audits
- Has the authority to close and/or suspend studies for safety or conduct issues
- May submit recommendations for corrective actions to the lead PI

SAEs, SUSARS, and reportable AEs are reported to the DSMC. All SUSARs will be reported to site principal investigators on study. All SAEs and reportable AEs are to be reported to the DSMC monthly for review. All SUSARs will be reported to the DSMC within 5 business days of knowledge.

Criterium is responsible for organizing regularly scheduled teleconferences with all participating sites. Lead PI (or designee) will be responsible for conducting the teleconferences. Criterium will also be responsible for including data from all of the participating sites to include the minutes from these regularly scheduled teleconferences between the sponsor investigator and the sites within the overall trial's six-month DSM report.

Study PI and Criterium will provide a DSMB summary report to all study sites on a six-month basis (every January and July). The DSMB summary report will include summary of University of Arizona monthly DAMB reports, a protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations and protocol amendments. The DSMB report might also include, if applicable, the results of any efficacy or fulity data analysis conducted. Criterium is then responsible for ensuring this letter is submitted to the participating sites for submission to their IRBs of record in accordance with their IRB policy. If University of Arizona DSMB identifies any safety concerns, all participating sites and study investigators will be notified by a memo and teleconferences.

Study audits conducted by the DSMC will consist of a review of the regulatory documents, consent forms, and source data verification. Documentation of the audit conducted by the DSMC will then need to be submitted to the IRB of record at the time of the IRB's continuing review of this trial.

13.2 Identification of the entity obligated for routine monitoring duties

Criterium will perform routine monitoring duties remotely as determined in the Monitoring Plan. Criterium will ensure that the monitoring plan will incorporate monitoring frequencies that are compliant with site requirements.

13.3 Monitoring progress and data review process

The assigned data management personnel at Criteirum will be responsible to review all CRF's for missing data, inconsistencies, data outliers and trends. This is done using internal table listings, programmed study edits and manual study edits. A listing of current study edits is included in the

Data Quality Procedures document. Data management personnel will follow all procedures outlined in the Data Management Plan for the study**.**

13.4 Continuous Monitoring

Continuous monitoring will consist of remotely reviewing portions of the ICF to ensure consenting is properly documented and the use of current version, review of re-consenting when applicable, review of CRF reports that include AEs, SAEs, and dosing, and reconciliation of drug accountability against the CRF entries.

13.5 Routine Safety Monitoring

Plan for assuring data accuracy and protocol compliance:

Routine study activity and safety information will be reported to the DSMB on a monthly basis, or more frequently if requested. These reports will include:

Study activity, cumulative and for the period under review;

- Safety (narrative description on non-serious and serious adverse events, protocol pre-determined early stopping rules for safety or treatment-emergent adverse events);
- Predetermined protocol early stopping rules for efficacy/futility;
- Status of study in relationship to stopping rules;
- Current dose level of study agent;
- Routine monitoring and protocol compliance (describe the monitoring process and identify the status of the monitoring);
- Comments;
- Attachments (AE data reviewed by the PI to compile the report, SAE letters and reports, results of any review(s), applicable correspondence with the IRB or other regulatory agencies.

Data, safety and study progress will be reported to:

- Human Subjects Protection Program (IRB) at least annually;
- Sponsor (if applicable) at least quarterly.

Identification of the sponsor or funding agency, as applicable

The PI will immediately notify, in writing, to Pfizer, if applicable, any action resulting in a temporary or permanent suspension of the study. A copy of this correspondence will also be forwarded to the DSMB and the IRB.

13.6 Removal of Subjects

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. If this occurs, the investigator, or designee, is to discuss with the subject the safe and appropriate processes for discontinuation from the investigational product, intervention or device.

Subjects that wish to discontinue active IP treatment/intervention/device may elect to continue with the other protocol required assessments. The investigator should discuss with the subject

the options for continuation of the study schedule of assessments (i.e. blood work, scans, physical exams, diaries) and collection of data, including endpoints and adverse events.

The investigator or designee must document the change in status of the subject's participation in the study and as applicable, the level of follow up that is agreed to by the subject (i.e. agrees to follow up exams, adverse event review, phone contact, but not to further treatment and/or procedures).

Subject withdrawal of consent for a study indicates that the subject does not wish to receive further protocol required therapies or procedures, and the subject does not wish to, or is unable to continue further study participation. Subject data only up to the time when consent is withdrawn will be included in the analysis of the study.

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Appendix 1: ECOG performance status

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead