THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

A Phase 1/2 Open-Label Study of TPI 287 in Patients with Breast Cancer Metastatic to the Brain
2010-0198

Core Protocol Information

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Abstract

Objectives:

Primary objective (Phase 1)

To evaluate the maximum tolerated dose (MTD) and safety of TPI 287 administered once every three weeks in patients with refractory or recurrent breast cancer metastatic to the brain

Primary objective (Phase 2):

To estimate the efficacy of TPI 287 by assessing the overall response rate [ORR (CR + PR)] of recurrent brain metastases using the McDonald Criteria.

Secondary objectives (Phase 1 and 2):

a. To evaluate response duration of breast brain metastases on TPI 287
b. To evaluate rate and duration of the clinical benefit (CR+PR+SD)
c. To assess activity of TPI 287 on extracranial metastatic disease
d. To measure median progression free and overall survival of patients with metastatic breast cancer treated with TPI 287

Rationale: (Be as concise as possible)

The current study proposes to examine a novel microtubule inhibitor TPI 287 that has shown potency and efficacy in a number of taxane sensitive and resistant tumors in

both preclinical and clinical studies. TPI 287 has also been shown to be very well tolerated and exhibits limited myelosuppression at the currently employed doses. It has also been shown that IV TPI 287 can penetrate the brain parenchyma to reach pharmacologically and clinically relevant levels, which suggests that breast cancers metastatic to the brain would be an appropriate target for therapy. There is a significant amount of human safety data for TPI 287 with over 100 adult patients and now 5 pediatric patients who have received drug in prior clinical trials to adequately assess the safety of the clinical trial and the dosing regimen for TPI 287 planned.

A brain-tropic derivative of the MDA-MB-231 “triple negative” breast cancer cell line, 231-BR, has been used to test the efficacy of drugs administered systemically to mice with nascent and established brain tumors. In this assay, paclitaxel, ixabepilone and abraxane (all microtubule inhibitors) did not have significant inhibitory activity. TPI-287 at 18 mg/kg delivered on days 3, 7 and 11 significantly reduced the outgrowth of brain metastases (55% reduction, p=0.028), and reduced proliferation in brain metastases (16% reduction, p=0.008). Based on the results of this preclinical model, the utility of TPI 287 for the treatment of breast cancer metastatic to the brain is being explored in the clinical setting in this current protocol.

In a recent clinical pilot study in glioma patients at MD Anderson Cancer Center dosing at 185 mg/m2 once every three weeks in combination with Avastin showed no dose limiting toxicity. In the initial version of this study, TPI 287 administered at a dose of 125 mg/m2 showed no evidence of any toxicity when administered weekly for three out of every four weeks. However, since it was also suggested by other Phase 2 studies that higher concentrations administered once every three weeks may provide greater efficacy, this amendment provides for a higher starting dose to explore the MTD on this schedule and then to evaluate efficacy.

Eligibility: (List All Criteria)

Inclusion:

1) Patients must have histologically proven breast cancer with metastatic disease to the brain.

2) Patients must have measurable disease on MRI that has progressed after prior therapy. PD will be defined as a>/= 25% increase in the sum of the products of greatest perpendicular diameters of all measurable disease over the smallest sum observed (since treatment started) on Gd-MRI, the appearance of new lesions on scan, or clinical or neurologic worsening despite stable disease on the last 2 scans.

3) Patients may have had any number of prior surgeries, radiation and/or chemotherapy regimens as adjuvant, neoadjuvant or palliative therapy for the treatment of their disease

4) Patients must be >/=18 years of age.

5) Patients must have an ECOG performance status of 0,1 or 2.

6) Patients must have adequate bone marrow function as evidenced by an absolute neutrophil count >/=1,500/microliters and a platelet count >/=100,000/microliter, adequate renal function as evidenced by

serum creatinine </=2.0 mg/dL, adequate hepatic function as evidenced by serum total bilirubin </=2.0 mg/dL, AST/SGOT and ALT/SGPT </= 3X the ULN.

7) Patients must have recovered and healed from the effects of any prior surgery, must have received prior chemotherapy at least 2 weeks prior to dosing with adequate recovery of WBC and platelet counts, and at least 12 weeks must have elapsed from the completion of radiotherapy, unless there are new lesions appearing on imaging within this 12 weeks frame.

8) Women of child-bearing potential (i.e. </= 50 years of age or has had menstrual cycle within the past 12 months, if > 50 years of age. If in doubt, check FSH, LH and estradiol level) must have a negative urine or serum pregnancy test at screening.

9) Sexually active patients must agree to use adequate contraception (abstinence or barrier contraceptives must be used throughout the trial and one month after end of treatment) for the duration of the study .

10) Patients or their legal representative must be able to read, understand and sign an informed consent form (ICF).

11) TPI 287 may interfere with coumadin dosing and patients who are taking this combination will require monitoring of their PT, PTT and INR.

Exclusion:

1) Patients who are receiving concurrent enzyme-inducing anti-epileptic drugs (EIAEDs) (e.g., carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital and primidone) or who received EIAEDs within 2 weeks prior to the first dose of study drug.

2) Patients with uncontrolled intracranial hypertension syndrome (defined as: persistence of headache, transient visual obscurations, and/or diplopia despite optimal clinical management) or uncontrolled seizure activity (i.e. recorded despite optimal medical management).

3) Patients who are not on a stable or decreasing steroid dose for the previous week prior to the first dose of study enrollment

4) Patients who are taking bevacizumab or have taken bevacizumab within the past 2 weeks for treatment of their brain metastases

5) Patients with an active infection (i.e., clinical signs or symptoms, including, but not limited to: bleeding/pustulent skin infections; productive cough associated with fever) on antibiotics or with a fever >/=38.5°C within 3 days prior to registration (i.e. date when the patient signs the consent and/or the patient is registered in CORE).

6) Patients with NYHA Class 3 or 4 congestive heart failure.

7) Patients with known HIV or Hepatitis B or C

8) Patients who are pregnant or lactating or not practicing adequate contraception

9) Patients with any other medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with the patient's ability to sign the ICF or his/her ability to cooperate and participate in the study, or to interfere with the interpretation of the results.

10) Patients who are receiving concomitant systemic therapy for breast cancer.

11) Patients with leptomeningeal disease (LMD) or with a history of LMD will be excluded.

Are patients <18 years of age eligible to participate in this study? ○ **Yes** ● **No**

Studies that include children must meet the criteria for inclusion.
http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc
http://www.hhs.gov/ohrp/policy/populations/children.html

Studies that exclude children must have appropriate justification. Please select all that apply:

Phase I or Phase II study targeting cancer that is very unusual in pediatrics (e.g., prostate, lung, breast, chronic lymphocytic leukemia, etc.)

Are participants >65 years of age eligible to participate in this study? ● **Yes** ○ **No**

Are pregnant women eligible to participate in this study? ○ **Yes** ● **No**

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?
○ **Yes** ● **No**

Disease Group:

Breast

Treatment Agents/Devices/Interventions:

TPI 287

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ **Yes** ● **No**

Is this a blinded or double-blinded study? ○ **Yes** ● **No**

This is an open label, Phase 1/2, exploratory trial evaluating the efficacy and safety of TPI 287 in patients with refractory or recurrent brain metastases from breast cancer.

During Phase 1, the dose of TPI 287 will be escalated in sequential dose cohorts (inter-cohort dose escalation). TPI 287 will be administered at an initial dose of 160 mg/m^2 as a 60-minute (± 10 minutes) intravenous (IV) infusion once every three weeks (i.e., 1 cycle = 21 days). If patients enrolled at this dose have no dose limiting toxicities (DLTs) within 21 days of receiving the first dose of study drug, additional patients will be enrolled in subsequent cohorts of 3 patients at 20 mg/m2 increments (180 mg/m^2, 200 mg/m^2, 220 mg/m^2, etc.) to explore a maximum tolerated dose (MTD) on this schedule for this patient population. If patients experience DLT at the starting dose, one dose level below (Level -1) is also proposed.
If 1 out of 3 patients experiences a DLT within 21 days of receiving the first dose of study drug, an additional 3 patients will be enrolled in that cohort. If >/= 2 patients at

any dose level experience DLT within 21 days of receiving the first dose of study drug, the MTD will be the previous dose level tested.

The MTD determination will be based on the number of patients that experience DLTs within 21 days of receiving the first dose of study drug. DLTs will be considered to be any hematologic toxicity >/= Grade 3 within 21 days of receiving the first dose of study drug that does not recover within 3 weeks or any non-hematological toxicity >/= Grade 3 within 21 days of receiving the first dose of study drug that does not improve to Grade 1 or baseline within 3 weeks

Patients on the Phase 2 portion of the study will be enrolled at the MTD determined during Phase 1. Initially, 25 patients will be enrolled in the Phase 2 portion of the trial; if at least 5 patients are shown to have an objective response, an additional 26 patients will be enrolled.

Patients may continue treatment in the study at any dose until intracranial disease progression or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. Patients will be followed for survival for up to 1 year after enrollment on the study.

Intra-patient dose escalation will be allowed for patients with extracranial progressive disease as long as the response of intracranial disease is stable or better and there is no unacceptable toxicity. Only one dose escalation will be allowed per patient. The dose will be escalated to the next higher dose level (20 mg/m^2 increase); under the condition that this higher dose level was previously shown to be safe per the inter-cohort dose escalation criteria.

Table of Procedures and Assessments:

Event	Screen	Cycle 1			Cycle 2	Subsequent Cycles	Follow-Up Visit
		Day 1	Day 8	Day 15	Day 1		28 ±2 days after last dose
Informed consent	X[2]						
Medical & surgical history[a]	X[4]						
Prior history and therapy for breast cancer[b]	X[4]						
Demographics	X[4]						
Physical examination[c]	X[4]					X[5]	X
Vital signs[d]	X[4]	X				X[1, 6]	X
ECOG performance status	X[4]	X[1]				X[1]	X
Laboratory Studies [e]	X[3]	X[1]	X	X	X	X[1]	X
Urinalysis[e]	X[3]						
Pregnancy test [f]	X[3]						
Brain Gd-MRI [g]	X[2]					X[7]	X[8]
Extracranial disease assessment [g]	X[2]					X[7]	X[8]
Concomitant medications[h]	X[4]	X[4]				X	X
BSA calculation[i]		X[4]				X[1]	
Administration of TPI 287[j]		X[9]			X[9]	X[9]	
AE monitoring[k]	X	X				X[1]	X
Survival [l]						X	X

Description/Definitions of Procedures and Assessments	*Timing*
a Complete medical and surgical history to include pertinent medical conditions and a careful history of all prior medical treatments	1 Prior to dosing with study drug within 7 days of each cycle unless otherwise specified
b Complete history of breast cancer to include date of diagnosis, histologic evidence of disease, dates of prior therapies (including surgery, radiation, chemotherapy) as well as date of documented recurrence/progression	2 Within 28 days of first dose of study drug
c Physical examination (including height and weight), noting all baseline abnormalities including neurologic exam	3 Within 14 (± 3 days) of first dose of study drug
d Temperature, pulse rate, blood pressure (sitting)	4 Within 7 days (± 3 days) days of dose of study drug
e Complete blood count, including RBC, MCV, MCH, MCHC, hemoglobin, hematocrit, WBC with differential, and platelet count (WBC with differential and platelets will be collected weekly for 1st cycle and within 7 days of each subsequent cycles); additional labs to be obtained at these time include sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, creatinine, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST; Dipstick determinations of urinary protein, glucose, ketones, hemoglobin, and bilirubin, but only for the first three cycles and/or if clinical indicated. . Patients who are taking coumadin (warfarin) will have PT, PTT, and INR prior to each cycle of treatment. Patients who have 2+ or greater hemoglobin or protein on a spot urine must have a microscopic examination performed. Urine exam is done only at screening.	5 Prior to dosing as interim update (only note changes from prior record). To be obtained within +/- 3 days.
f For females of childbearing potential only, may be based on serum or urine testing	6 Prior to dosing with study drug and immediately following 60 minute infusion
g Brain Gd-MRI must be obtained as per protocol. Extracranial disease assessments may include CT/MRI scans of chest, abdomen, pelvis as well as bone scans, and as per standard of care otherwise indicated by treating physician. All disease assessments will be performed when clinically indicated.	7 Within 7days prior to odd numbered cycles
h All medications/therapies used within 30 days prior to first dose of study drug	8 If scan has not been obtained within previous 2 cycles
i If weight fluctuates ± 10% from prior measurement, new BSA will be used to calculate next dose	9 Within (+/- 1 day)
j One hour IV infusion of TPI 287 Injection on day 1every 21 days. See Section 5 for Study Drug Administration.	
k All drug-related toxicities must be followed for resolution. Patients are to be followed for up to 30 days (+/- 5 days) after last drug administration for adverse events, regardless of causal relationship.	
l Data will be collected every 3 months from the time the patient is off-treatment up to a period of 1 year from the patient's date of enrollment	

** Note that the timing of assessments may be varied by reasonable adjustments to the times indicated for scheduling or logistical issues Patients whose on study laboratory tests were done >7 days prior to starting treatment and whose clinical condition has changed between the time of these tests and the initiation of treatment will have a repeat chemistry panel prior to the start of treatment.*

Dose Levels:

Level	Dose of TPI 287 (mg/m²)
Level - 1	140
Starting dose/Level 1	160
Level 2	180
Level 3	200
Additional dose level increases in 20 mg/m² increments	

CTCAE version 4 will be utilized in this protocol.

Study Enrollment:
The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC: 69
Estimated monthly accrual at MDACC: 0-1

Accrual Comments:
All patients will be accrued MD Anderson Cancer Center

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Statistical Considerations:

This is an open label, Phase 1/2, exploratory trial evaluating the efficacy and safety of TPI 287 in patients with refractory or recurrent brain metastases from breast cancer.

The primary objective of the Phase 1 portion of the study is to determine the MTD of TPI 287 and in the Phase 2 portion of the study whether TPI 287 can provide clinical benefit for patients with metastatic breast cancer to the brain following failure of prior therapy, as measured by overall response rate.

TPI 287 will be administered intravenously at an initial dose of 160 mg/m2 once every three weeks. Dose escalation will continue in cohorts of 3 patients who will receive increasing doses until 1 out of 3 experience a dose limiting toxicity (DLT) at which time an additional 3 patients will be added at that dose. If >/=2 patients experience a DLT, the MTD will be considered the prior dose level. Dose levels will be 160 mg/m2, 180 mg/m2, 200 mg/m2 and then increased in 20 mg/m2 increments until the MTD is reached.

Once the MTD has been reached an initial cohort of 25 patients will be enrolled; if at least 5 patients are shown to have an objective response, an additional 26 patients will be enrolled.

The following data sets will be used in this study:

- All enrolled and eligible subjects (ITT) population: All eligible subjects who signed the informed consent form.
- All treated and eligible patients (Safety and Efficacy evaluable) population: All patients who received at least one dose of study drug

Efficacy analyses will be performed on the Safety and Efficacy evaluable population in the patients on Phase 2. Safety analysis will be performed on the Safety and Efficacy evaluable population in both portions of the study.

The primary outcome measure will be response rate in the Phase 2 portion of the study. A two-stage patient accrual plan is used for this portion. Based on historical data, responses to chemotherapy in this disease ranged from approximately 30 to 55%; however in most cases these were combined with whole brain radiation therapy. Therefore, a 15% response rate to single agent

chemotherapy will be targeted as a reasonable outcome for this patient population. We target this response rate of 15% because our experience in this heavily pre-treated patient population indicates that almost none of the patients of the patients will respond under the current best-supportive care/hospice care regimen. We used trial and error to get a two-stage design with reasonable operating characteristics for p0 = 15%. One such design would have 25 patients in the first stage and 26 patients in the second stage. It would continue onto the second stage if more than 4 patients had response in the first stage. The trial would be considered a success if 11 or more out of the total 51 patients had response. This trial has a false positive (alpha) rate of 11% (under p0 = 15%) and a false negative (beta) rate of 12% (under p1 = 30%). The trial also has a probability of early termination under p0 (i.e., if the true response probability is p0 = 15%) of 68%.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
This study open label and not randomized.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? No

Provide a rationale for no interim analysis.

This is not a randomized study.

Protocol Monitoring Plan:

The protocol will be monitored by MDACC IND office

Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer? No

Investigational New Drugs (IND):

Does this protocol require an IND? Yes

Who is the IND Holder/Regulatory Sponsor?
MDACC
IND Number: 106,771

Please "Compose" an Investigator's Brochure Cover Letter. For technical assistance, contact the PDOL

Help Desk, 713-745-7365.

Investigational Device (IDE):

Does this study utilize an Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Cortice Biosciences Inc.
Support Type: Industry Funding
Agent Name(s): TPI 287

This Sponsor/Supporter/Granting Agency will receive data.

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? Click here for help	N/A

Biosafety:

Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve human/animal tissue other than blood derived hematopoietic stem cells? No

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?

○ Yes
● No
○ Not Applicable For This Protocol

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study? No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree? No