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

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 $\leq 2.0$ mg/dL, adequate hepatic function as evidenced by serum total bilirubin $\leq 2.0$ mg/dL, AST/SGOT and ALT/SGPT $\leq 3X$ 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. $\leq 50$ 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 $\geq 38.5^\circ$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/m^2 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/m² 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:**

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Dose Levels:

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<th>Dose of TPI 287 (mg/m²)</th>
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<td>140</td>
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<td>Starting dose/Level 1</td>
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<td>Level 2</td>
<td>180</td>
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<td>Level 3</td>
<td>200</td>
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<td>Additional dose level increases in 20 mg/m² increments</td>
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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 $p_0 = 15\%$. 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 $p_0 = 15\%$) and a false negative (beta) rate of 12\% (under $p_1 = 30\%$). The trial also has a probability of early termination under $p_0$ (i.e., if the true response probability is $p_0 = 15\%$) 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
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? 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