A Phase 1 Study of TPI 287 Concurrent with Fractionated Stereotactic Radiotherapy (FSRT) in Treatment of Brain Metastases from Advanced Breast and Non-Small Cell Lung (NSCL) Cancer

NCT02187822

Version 1.6

July 7, 2014

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Protocol Number: MCC 17816

IND Number: 123010

Sponsor: H. Lee Moffitt Cancer Center & Research Institute, Inc. (Moffitt Cancer Center), Investigator Initiated Trial

Investigational Product: TPI 287

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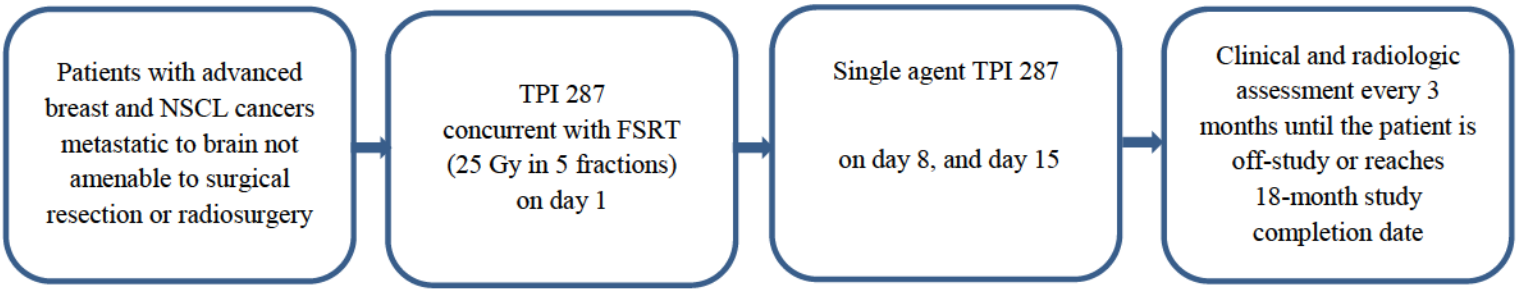
Original Protocol: July 7th, 2014

PROTOCOL SYNOPSIS

TITLE	A Phase 1 Study of TPI 287 Concurrent with Fractionated Stereotactic Radiotherapy (FSRT) in Treatment of Brain Metastases from Advanced Breast and Non-Small Cell Lung (NSCL) Cancer
STUDY PHASE	I
PRIMARY OBJECTIVES	To evaluate the safety, tolerability, and to determine the maximum tolerated dose (MTD) of TPI 287 given concurrently with fractionated stereotactic radiotherapy (FSRT) to treat brain metastases from advanced breast and non-small cell lung cancer.
SECONDARY OBJECTIVES	To characterize the pharmacokinetics and anti-tumor effect of TPI 287 administered concurrently with FSRT in the treatment of patients with breast and NSCL cancers metastatic to the brain; and to evaluate the effect of treatment on measures of quality of life.
HYPOTHESES	TPI 287, given concurrently with FSRT, will improve local control and decrease distant brain failure in patients with brain metastases from advanced breast and NSCL cancers.
STUDY DESIGN	Dose escalation phase: The MTD for TPI 287 given concurrently with FSRT will be determined using the standard 3+3 study design. Dose expansion phase: Patients will be treated with TPI 287 at MTD given concurrently with FSRT to further assess toxicity and tumor response.
PRIMARY ENDPOINTS AND SECONDARY ENDPOINTS	Primary endpoints: ▪ To determine the maximum tolerated dose (MTD) of TPI 287 given concurrently with FSRT to treat brain metastases from advanced breast and NSCL cancers and to determine the recommended phase 2 dose (RP2D) ▪ To determine the safety and toxicity of TPI 287 given concurrently with FSRT to treat brain metastases from advanced breast and NSCL cancers Secondary endpoints: ▪ To determine the local control rate ▪ To determine the distant intra-cranial control rate ▪ To determine the short-term (≤ 30 days post-treatment) and long-term (> 30 days post treatment) adverse effects ▪ To determine the PFS ▪ To evaluate the effect of concurrent therapy with TPI 287 and

	FSRT on measures of quality of life
SAMPLE SIZE	The maximum number for the dose escalation phase will be 36 patients. In the dose expansion phase, a total of 10 patients (including patients treated at the MTD from dose escalation phase) will be enrolled to confirm the safety and to assess radiologic response.
SUMMARY OF SUBJECT ELIGIBILITY	Major inclusion criteria: ▪ Patients age 18 years and older with brain metastasis (up to 3 metastatic brain lesions) from histologically proven advanced breast and NSCL cancers which have not been treated with previous brain radiation. ▪ Maximum diameter of each brain lesion ≤ 5 cm and maximum tumor volume ≤ 120 cc ▪ Adequate organ function ▪ Systemic chemotherapy washout period ≥ 7 days. For investigational drugs and monoclonal antibodies washout period ≥ 5x drug half-life. ▪ ECOG ≤ 2 Major exclusion criteria: ▪ Previous treatment of the target lesions with radiation therapy ▪ Previous whole brain radiotherapy ▪ Pregnant and nursing women ▪ Patients who are unable to give informed consent
INVESTIGATIONAL TREATMENT	TPI 287 will be administered intravenously prior to treatment of brain metastasis with FSRT on day 1 and will be given for 2 more weekly doses.

SCHEMA



Dose Escalation Phase

Dose Escalation Schedule		
Dose Level	**Dose**	
	TPI 287 IV	**Radiotherapy**
Level -1	7 mg/m^2/dose	5 Gy daily fraction
Level 1	14 mg/m^2/dose	5 Gy daily fraction
Level 2	28 mg/m^2/dose	5 Gy daily fraction
Level 3	56 mg/m^2/dose	5 Gy daily fraction
Level 4	85 mg/m^2/dose	5 Gy daily fraction
Level 5	113 mg/m^2/dose	5 Gy daily fraction
Level 6	127.5 mg/m^2/dose	5 Gy daily fraction

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Dose Expansion Phase

Patients will be treated with TPI 287 at MTD
(from dose escalation phase) and FSRT to metastatic brain disease

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1. OBJECTIVES

1.1 Phase 1 Primary Objectives

The primary objectives of this study are to evaluate the safety, tolerability, and to determine the maximum tolerated dose (MTD) of TPI 287 given concurrently with fractionated stereotactic radiotherapy (FSRT) to treat brain metastases from advanced breast and NSCL cancers.

1.2 Secondary Objectives

The secondary objectives are to characterize the pharmacokinetics and anti-tumor effect of TPI 287 administered concurrently with FSRT in the treatment of patients with breast and NSCL cancers metastatic to the brain; and to evaluate the effect of treatment on measures of quality of life.

2. BACKGROUND

2.1 Brain Metastases

Brain metastases are a grave complication of cancer. They exceed the number of primary brain tumours by at least four times and occur in about 25% of all cancer patients totalling approximately 170,000 new cases each year in the United States.[1,2] Brain metastases may originate from lung (40–50%), breast (15–25%), melanoma (5–20%), and kidney (5–10%) primary sites.[2] Moreover, there is evidence that the overall incidence of brain metastases is increasing as a result of improvements in systemic treatments. While these treatments increase the longevity of patients with advanced disease, they do not effectively cross the blood-brain barrier (BBB).[1]

Surgery or radiosurgery (SRS) are important modalities for patients with a single brain metastasis, particularly when favorable prognostic factors and systemic disease control are present. However, more than 70% of patients with brain metastases have multiple lesions at the time of presentation which are not considered to be surgically resectable.[3] Radiation therapy, either as SRS, fractionated stereotactic radiotherapy (FSRT) or whole brain radiotherapy (WBRT) remains the standard of care for treatment of these patients with unresectable brain metastases (NCCN Clinical Practice Guidelines in Oncology, version 2.2013).

FSRT remains an attractive therapeutic strategy for large brain metastases (>2cm diameter) and/or for those located in eloquent critical locations in the brain. SRS for the treatment of these lesions may lead to an unacceptable rate of late toxicity including brain necrosis.[4] Fractionating the radiotherapy allows one to deliver a total dose close to that used in SRS while allowing for a decrease in normal tissue injury. However, this treatment modality is not optimal and response rate ranges from 60-80% for FSRT are seen.[5,6] Radiosensitization may help improve the control of brain metastases treated with FSRT. This strategy may be particularly helpful for those patients who are less likely to have optimal control with FSRT alone.[7]

2.2 TPI 287

Taxanes have well established anti-cancer properties in wide spectrum of malignancies including breast and lung cancer. First generation taxanes (paclitaxel and docetaxel) are one of the main chemotherapeutic agents for the treatment of breast and non-small cell lung cancers. Although these agents are very effective in treatment of extra-cranial disease, minimum efficacy has been shown with their use for intracranial involvement. The efficacy of first generation taxanes on brain metastases is impacted by their inability to permeate the brain. A major limiting factor for their penetration across the BBB is the active efflux back into the circulation by the overexpression of the multidrug-resistant gene product 1 (MDR1) or P-glycoprotein (P-gp).[8]

TPI 287, a new member of taxanes diterpenoid (taxoid) family, is a microtubule-inhibitor with significant cytotoxic activity and brain permeability.[9] TPI 287 has shown comparable (within 2-fold) or increased cytotoxicity/growth inhibition compared to standard chemotherapeutic agents in human cell lines derived from the following tumors: breast (including a brain metastatic breast cancer cell line), lung, squamous cell carcinoma, pancreas, hepatocellular, colon, uterine, ovarian, prostate, Burkitt's lymphoma, head/neck, neuroblastoma, glioblastoma, and medulloblastoma (Investigator's brochure). TPI 287 was shown to be active (TGI > 58%) in mouse xenograft models of the following human tumors: breast adenocarcinoma, colon adenocarcinoma, prostate adenocarcinoma, pancreatic adenocarcinoma, head/neck tumor, glioblastoma, neuroblastoma, and ovarian tumor (Investigator's brochure). Moreover, activity exceeding that of the comparator chemotherapeutic agent has been observed in multiple MDR+ tumor models, including breast, colon, head/neck, and neuroblastoma (Investigator's brochure).

TPI 287 has been investigated in 2 phase 1 clinical trials. The initial phase 1 clinical trial used the once weekly for 3 weeks with the fourth week off treatment schedule in subjects with recurrent or refractory cancers. In this study, 48 patients were enrolled and the MTD of weekly TPI 287 was determined to be 127.5 mg/m^2. Another phase I trial of single agent TPI 287, investigated once every 3 week treatment schedule in 21 patients. In this schedule MTD was 160 mg/m^2. Overall, the most frequent adverse events (≥10%) considered possibly, probably, or definitely related to TPI 287 were peripheral neuropathy (48%), anemia (38%), diarrhea (29%), neutropenia and nausea (24%), fatigue and myalgia (19%), vomiting, asthenia, pyrexia, neuropathy, and alopecia (14%), and leukopenia, thrombocytopenia, abdominal pain, constipation, anorexia, back pain, bone pain, pain in extremity, hypoesthesia, and flushing (10%) (Investigator's brochure).

TPI 287 is a poor substrate for P-gp efflux pump resulting in high brain-to-plasma ratios in the animal models. Brain-to-plasma ratio of this agent after a single injection were as high as 63.8 in the rat and 14.1 in the mouse. Moreover, when used in preclinical model of brain metastasis from breast cancer, TPI 287 resulted in 55% reduction in the formation of large brain metastasis from breast cancer.[9] Hence, this agent rises as a promising compound for treatment of patients with brain metastasis from primary tumors such as breast and non-small cell lung cancer which are deemed taxane-sensitive.

2.3 Concurrent Radiotherapy with TPI 287

First generation taxanes are potent radiosensitizers and have been widely used as radiosensitizers in various tumors.[10,11] Preclinical data have shown that taxanes can enhance radiation sensitivity through two major mechanisms: reoxygenation of radioresistant hypoxic cells and cell arrest in in the radiosensitive G2/M phase of the cell cycle.[12] *In vivo* studies have shown that taxanes can strongly enhance tumor radioresponse, producing enhancement factors of 1.2 to more than 2.0. [12]. Concurrent use of docetaxel and paclitaxel with radiation therapy has shown to be feasible and clinically beneficial in treatment of wide range of malignancies including non-small cell lung cancer, nasopharyngeal cancer, esophageal squamous cell cancer, bladder cancer, and gynecologic cancers.[13-20] RTOG-9705 trial has studied the use of postoperative adjuvant paclitaxel/carboplatin concurrent with thoracic radiotherapy in resected stage II and IIIA non-small cell lung cancer. [21] This phase II trial showed that concurrent use of paclitaxel/carboplatin with radiation therapy to lung is safe and increases progression free survival and overall survival in this group of patients. [21] Similar results have been demonstrated in another phase II trial by Feigenberg et al.[22] Based on these trials concurrent thoracic radiotherapy with paclitaxel/carboplatin has been recommended by NCCN guidelines (version 4.2014) for treatment of resected stage II and IIIA non-small cell lung cancer.
Concurrent chemoradiotherapy to brain has been shown to be feasible and safe and has been established as standard of care for treatment of primary brain tumors such as glioblastoma.[23] However, this potential treatment strategy has not been well developed for metastatic brain disease.
Given the failure rate of FSRT in treating brain metastasis, concurrent chemoradiotherapy could be a potential treatment strategy to overcome resistance to radiotherapy alone. However, brain tissue penetrance has been the limiting factor for the use of taxanes in this setting. With current evidence showing promising data on brain concentration of TPI 287, it would be of great interest to investigate radiosensitizing effect of this agent when used concurrently with radiation therapy for metastatic brain lesions.

2.4 Rationale

In summary brain metastases are grave and challenging complication in patients with metastatic breast and NSCL cancer and result in limited survival. TPI 287 possesses a favorable efficacy and pharmacokinetic profile in pre-clinical models. TPI 287 has been observed preclinically to cross the blood-brain barrier and reach a notable concentration in brain tissue and cerebrospinal fluid.[9] Furthermore, the use of TPI 287 has resulted in reduction of brain metastasis formation in animal models of breast cancer.[9]

Based on available safety pharmacology, toxicology and pharmacokinetic data from phase 1 study of TPI 287, it can be concluded that TPI 287 has been adequately characterized to support the initiation of this phase 1 trial in combination with radiation in patients with metastatic brain lesions from breast and NSCL cancers.

If the combination is tolerable, further studies of efficacy will be warranted to assess whether the

addition of TPI 287 can potentially increase tumor response, maintain neurologic function, improve quality of life, and extend survival.

2.5 Correlative Studies Background

Pharmacokinetic data in animal models indicate that TPI 287 crosses the blood brain barrier and reaches the brain tissue and cerebrospinal fluid (CSF).[9] However, the permeability of this compound through blood-brain barrier has not been investigated in human studies.

3. PATIENT SELECTION

3.1 Eligibility Criteria

- Patients must have histologically or cytologically confirmed non-central nervous system primary breast or non-small cell lung cancer.
- Patients must have pathologically or radiologically confirmed metastatic disease in the brain.
- Patients with up to 3 brain metastases (symptomatic and non-symptomatic) can be treated on this study. Maximum diameter of each brain lesion should be ≤ 5 cm. Maximum tumor volume ≤ 120 cc
- Age ≥18 years.
- ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
- Life expectancy of greater than 12 weeks.
- Patients requiring treatment with corticosteroids are eligible.
- Treatment with non-enzyme inducing anti-seizure medications is allowed.
- Patients must have normal organ and marrow function as defined below:
  - leukocytes ≥3,000/mcL
  - absolute neutrophil count ≥1,500/mcL
  - platelets ≥100,000/mcL
  - total bilirubin within normal institutional limits
  - AS T(SGOT)/ALT (SGPT) ≤2.5 × institutional upper limit of normal
  - creatinine within normal institutional limits OR
  - calculated creatinine clearance ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- Systemic chemotherapy washout period ≥ 7 days. For investigational dugs and monoclonal antibodies washout period ≥ 5x drug half-life. There are no limitations on

number of prior treatment regimens.

- The effects of TPI 287on the developing human fetus is unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of TPI 287 administration.

- Prior brain surgery or radiation is allowed as long as the metastatic lesion(s) to be targeted in this study has not previously been treated with radiation.

- Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

- Patients who have had chemotherapy within 1 week (6 weeks for nitrosoureas or mitomycin C) or investigational therapies/monoclonal antibodies within 5 half-life of investigational compound or those who have not recovered from adverse events due to agents administered more than 1 week earlier. Bisphosphonates, endocrine therapy, and trastuzumab are permitted without restriction.

- Patients who are receiving any other investigational agents.

- Previous treatment of the target lesions with radiation therapy.

- Patients who have previously been treated with whole brain radiation.

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to TPI 287.

- Pregnant women are excluded from this study because TPI 287 is an agent with an unknown but potential risk for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with TPI 287, breastfeeding should be discontinued if the mother is treated with TPI 287.

- Known contraindication to enhanced MRI and CT scan.

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, uncontrolled seizure activity or psychiatric illness/social situations that would limit compliance with study requirements.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. INFORMED CONSENT PROCESS

Eligible patients will be evaluated by a multi-disciplinary team composed of radiation oncologists, neurosurgeons, and a medical oncologist. During their visit, either a physician or a research coordinator will explain the study to the patient. Informed consent form will be provided and if the patient agrees to participate, signed consent form will be obtained prior to participation.

Following registration, patients should begin protocol treatment within 7 days. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled.

5. TREATMENT PLAN

5.1 Pre-Treatment Evaluation

Patients will be evaluated by a multi-disciplinary team composed of medical/neuro oncologists, radiation oncologists, and neurosurgeons to assess for their eligibility. Patient's oncologic history, presenting symptoms, physical examination, pathology, extent of systemic disease, and imaging studies will be reviewed.

5.2 Fractionated stereotactic radiotherapy (FSRT)

Brain metastases will be delineated by gadolinium enhanced magnetic resonance imaging (MRI) (Siemens Sonata, Siemens Medical Systems, Erlangen, Germany) with 1 mm slices for treatment planning purposes performed within 2 weeks prior to the delivery of radiation (MRI Novalis protocol). If MRI Novalis is not possible, CT scan of the brain with contrast or other suitable MRI scan brain may be used for delineation of the brain metastases. Patient immobilization will be achieved by using a commercially available frameless head mask fixation system (BrainlabAG, Feldkirchen, Germany). The image planning data set will be co-registered and fused with 1-2mm slice thickness computed tomography (CT) imaging (General Electric Medical System, Milwaukee, WI) obtained at simulation. The gross tumor volume (GTV) will be designated by the edge of the tumor. The planning target volume (PTV) will include a 1 mm

expansion on the GTV. The prescription dose will be 25 Gy in 5 daily fractions delivered to the PTV. Planning will take place with the BrainLab treatment planning system and FSRT will be delivered via the Novalis linear accelerator with robotic table. Doses will be prescribed to ensure coverage of at least 95% of the PTV with the prescription dose. The maximum dose will not exceed 115% of the prescription dose. Treatments will be delivered using dynamic conformal arcs or intensity modulated radiotherapy (IMRT).

5.3 Drug therapy

TPI 287 will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.

TPI 287 Administrations

TPI 287 will be administered as an intravenous infusion over 60 minutes. A window of ± 15 minutes will be permitted.

Patients will receive the TPI 287 once per week, for total of 3 doses. Treatment with TPI 287 will start the same day of starting FSRT treatment.
On the day of FSRT, TPI 287 will be given 4 (+/-2) hours prior to FSRT.

In order to prevent any potential hypersensitivity reactions, all subjects must be premedicated prior to TPI 287 administration. The following drugs and dosing regimens are provided as guidelines for premedication, which must include a corticosteroid, an antihistamine, and an H2 blocker. The concomitant use of steroids in some subjects should be considered in determining the dose of an additional corticosteroid. Oral (PO) dosing as an alternative to IV dosing for premedication is acceptable where appropriate.

Premedication Regimen	
Dexamethasone*	20 mg PO at 12 hours prior and 20 mg PO at 6 hours prior
Diphenhydramine	50 mg IV push prior
H2 blocker	IV prior (e.g., Cimetidine 300 mg)
**In the event that dexamethasone is not available, methylprednisolone may be substituted at an equivalent dose (4 mg methylprednisolone = 0.75 mg dexamethasone).*	

Subjects will be closely monitored for signs and symptoms of a hypersensitivity reaction during the entire infusion of TPI 287, and 1 hour after completion of TPI 287 infusion. Vital signs will be measured every 30 minutes. If a mild-to-moderate (Grade 1 to 2) hypersensitivity reaction is observed, the TPI 287 infusion will be interrupted. Patient will receive intravenous diphenhydramine 50 mg, hydrocortisone IV 100 mg, and appropriate supportive care until the symptoms resolve. If the signs and symptoms resolve within 1 hour, the TPI 287 infusion will be restarted at a slower infusion rate (half that of the initial attempt), and this slower infusion rate will be used for the remainder of the trial. If the symptoms take longer to resolve, the infusion will not be restarted, and the next dose of TPI 287 will be administered 1 week after the

interrupted dose at a slower infusion rate (half of the rate at which hypersensitivity reaction occurred) pending all signs and symptoms of hypersensitivity have resolved.
If a ≥ Grade 3 hypersensitivity reaction is observed, the TPI 287 infusion will be stopped and appropriate supportive care administered until the symptoms resolve. The subject will be discontinued from the trial.

Dose Definition

Dose Escalation Phase:

The starting dose (i.e., dose level 1) will be 14 mg/m^2 /dose. Provided that MTD has not been reached, the TPI 287 dose will be increased as follows:

Table 1. Dose Escalation Schedule

Dose Escalation Schedule		
Dose Level	**Dose**	
	TPI 287 IV	**Radiotherapy**
Level -2	5 mg/m^2/dose	5 Gy daily fraction
Level -1	7 mg/m^2/dose	5 Gy daily fraction
Level 1	14 mg/m^2/dose	5 Gy daily fraction
Level 2	28 mg/m^2/dose	5 Gy daily fraction
Level 3	56 mg/m^2/dose	5 Gy daily fraction
Level 4	85 mg/m^2/dose	5 Gy daily fraction
Level 5	113 mg/m^2/dose	5 Gy daily fraction
Level 6	127.5 mg/m^2/dose	5 Gy daily fraction

If dose level 1 is found to cause unacceptable toxicity, the dose will be de-escalated to levels -1 or -2.

Dose Expansion Phase:

The TPI 287 dose used in the dose expansion cohort will be MTD determined from the dose escalation phase. TPI 287 will be administered intravenously prior to treatment of brain metastasis with FSRT on day 1 and will be given for 2 more weekly doses. The prescription dose of FSRT will be 25 Gy in 5 daily fractions as described in section 5.2.

Definition of Maximum Tolerated Dose:

The maximum tolerated dose (MTD) is the highest dose of TPI 287 that does not cause unacceptable toxicity in more than one of six patients at that dose level. The MTD is defined as one dose level below the highest toxic dose (i.e., the DLT dose).

5.4 Definition of Dose-Limiting Toxicity

Toxicities will be graded in severity according to the guidelines outlined in the NCI-CTCAE version 4.0. Dose limiting CNS and non-CNS (hematologic and non-hematologic) toxicities will be defined differently and will be based on events that occur during the study period. In order to be declared as dose-limiting toxicity, an adverse event must be related (definite, probable, or possible) to study treatment.

A dose-limiting toxicity (DLT) will be defined as any one of the following adverse events occurring within 8 weeks from last dose of radiation therapy:

CNS toxicities:

Acute CNS toxicities (occurring ≤ 30 days after completing FSRT treatment):

- Any grade 3 or higher central nervous adverse events including but not limited to headache, dizziness, vertigo, new onset seizures, cerebral edema, cerebral hemorrhage, and new onset neurologic deficit.

Delayed onset CNS toxicities (occurring >30 days after completing FSRT treatment):

- Any grade 3 or 4 adverse event arising within the irradiated volume including but not limited to radiation necrosis or focal neurological deficits.

Non-CNS toxicities:

Non-hematologic toxicities:

- Any grade 3 or higher non-hematologic adverse event with the exception of alopecia, fatigue, and anorexia.
- Grade 3 or higher nausea and/or vomiting that persists ≥ 48 hours despite optimal medical management.

Hematologic toxicities:

- Grade 4 neutropenia lasting for ≥ 7 days in duration
- Grade ≥ 3 febrile neutropenia with/without infection

- Grade 4 thrombocytopenia

Dose escalation will be determined based on the occurrence of DLTs. For the purposes of determining whether to advance the dose levels, DLTs will be counted by patient. In the event of the development of any grade 3 or 4 toxicity felt to be at least possibly related to study drug, TPI 287 will be held until resolution to grade 1 or baseline assuming that occurs within 15 day window.

Dose escalation will follow the standard 3+3 design. The enrollment to next higher dose level will be delayed for 8 weeks after the completion of FSRT by the last patient enrolled at the dose level. This period of 8 weeks will allow monitoring potential delayed toxicities. Management and dose modifications associated with the above adverse events are outlined in Section 6. Dose escalation will proceed according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Table 2. Dose Escalation Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
$\geq$2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3 or $\geq$ 2 grade 2 CNS toxicities	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is the dose to be used in the expanded cohort and will be considered recommended phase 2 dose. At least 6 patients must be entered at this dose.

If dose level 1 is found to cause unacceptable toxicity, the dose will be de-escalated to level -1 (7 mg/m^2). Three patients will be enrolled at dose level -1. If no DLT is observed, three additional patients will be enrolled at dose level -1 such that safety is established in at least 6 patients prior to entering dose expansion phase.

Any delayed CNS-toxicity arising within the radiation field but seen beyond the window for DLT registration (> 8weeks following completion of FSRT) will be recorded. Furthermore, occurrence of any delayed-onset treatment related grade 3 or higher central nervous toxicity at any time (during and after DLT period of 8 weeks) will lead to holding dose-escalation and adding 3 patients to the dose level at which toxicity has occurred. Occurrence of additional delayed-onset treatment related grade 3 or higher CNS- toxicity will be reviewed with Protocol Monitoring Committee and IRB to determine whether discontinuation or modification of trial is subsequently warranted.

5.5 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of TPI 287 with other concomitantly administered drugs through the cytochrome P450 system, the use of drugs or herbal supplements that are known to be strong inhibitors/inducers of CYP3A4 and CYP2C8 are not permitted (Appendix B).
Prophylactic use of corticosteroids is allowed during the study to limit symptoms from metastases or radiation.
Non-enzyme inducing anti-epileptic drugs may be utilized to control or prevent seizures.
Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

5.6 Duration of Therapy

Patients will receive TPI 287 on days 1, 8, and 15 (total of 3 doses). On day 1, the TPI 287 will be administered 4 (+/- 2) hours prior to FSRT.

5.7 Duration of Follow Up

Patients will be seen in follow-up on the 3rd, 6th, 9th, 12th, 15th, and 18th month following the first day of treatment with TPI 287. Patients will be followed for 18 months after first treatment on study or until death, whichever occurs first.
The following will be obtained at pre-treatment evaluation and at each follow up visit: Symptoms history, vital signs/ height and weight, physical examination, KPS/ECOG score, Mini-Mental State Examination, steroid use, quality of life questionnaire, and toxicity evaluation.
Radiologic assessment, MRI brain with and without gadolinium, will be performed at pre-treatment and every three months following the end of treatment until the patient is off-study or reaches the 18 month study completion date.
Furthermore, the principal investigator will have close collaboration with oncologists treating the systemic malignancy. Information regarding the status of systemic malignancy such as results of standard imaging evaluations, serum biomarkers measurements, and systemic treatments will be collected and recorded at each visit.

5.8 Criteria for Removal from Study

Patients will be removed from study when any of the below criteria applies:

- Disease progression requiring therapy not allowed in the protocol, including whole brain radiation.
- Intercurrent illness that prevents further administration of treatment: a condition, injury, or disease unrelated to cancer, that renders TPI 287 or radiation treatment unsafe or regular study visits impossible, including, but not limited to, active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, pregnancy, or psychiatric illness that would limit compliance with study requirements.
- Unacceptable adverse event(s) (see adverse events)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition that render the patient ineligible for the study
- Non-compliance with study treatment or protocol-required evaluations and study visits
- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the patient to continue therapy
- Patient who inadvertently becomes pregnant (see reporting of pregnancy)

Patients may withdraw at any time or be dropped from the study at the discretion of investigator should any untoward effects occur. In addition, a patient may be withdrawn by the investigator if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify Cortice Biosciences immediately when a patient has been discontinued/withdrawn due to a serious adverse experience. All trial treatment-related toxicities and SAEs at the time of discontinuation/withdrawal should be followed until resolution or stabilization. Patients who are discontinued from the study will still be followed for disease progression.

All deaths that occur within the trial period or within 30 days after administration of the last dose of trial drug must be reported to Cortice Biosciences for the purposes of serious adverse event (SAE) reporting; however, deaths due to progression are not SAEs.

Patients who discontinue from the study for reasons unrelated to the study (e.g., personal

reasons, or adverse events after registration but prior to receiving study therapy) may be replaced as required for the study to meet its objective. The replacement will generally receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced.

5.9 Stopping Rules

The expected rate of neurologic death with FSRT alone is 13-14%. [24,25] The reported rate for symptomatic radiation necrosis is 7.7%. [24] A higher rate of neurologic death (> 14%) or symptomatic brain necrosis (> 10%) in this study would imply that the combination of FSRT and TPI 287 is excessively toxic and not suitable for further clinical development. In addition grade ≥ 3 delayed-onset toxicity in this study would imply that the combination of FSRT and TPI 287 is excessively toxic and not suitable for further clinical development. In such condition, the results will be discussed with Cortice Bioscience, Protocol Monitoring Committee and IRB and study will be closed. In addition, occurrence of other delayed-onset treatment related grade 3 or higher CNS- toxicity will be monitored closely and reviewed with Protocol Monitoring Committee and IRB to determine whether discontinuation of trial is subsequently warranted.

6. DOSING DELAYS/DOSE MODIFICATIONS/TREATMENT DISCONTINUATION

Table 3. Dose Levels for Dose Modification of TPI 287

Dose Level	TPI 287 Dose
-2	5 mg/m^2/dose
-1	7 mg/m^2/dose
1	14 mg/m^2/dose
2	28 mg/m^2/dose
3	56 mg/m^2/dose
4	85 mg/m^2/dose
5	113 mg/m^2/dose
6	127.5 mg/m^2/dose

Below are dose modification tables for the following adverse events: nausea, vomiting, diarrhea, neutropenia, and thrombocytopenia:

Table 4. Management of Nausea

Nausea	Management/Next Dose for TPI 287
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.*
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: antiemetics.	

Table 5. Management of Vomiting

Vomiting	Management/Next Dose for TPI 287
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: antiemetics.	

Table 6. Management of Diarrhea

Diarrhea	Management/Next Dose for TPI 287
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.*
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Table 7. Management of Neutropenia

Neutropenia	Management/Next Dose for TPI 287
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

Table 8. Management of Thrombocytopenia

Thrombocytopenia	Management/Next Dose for TPI 287
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.*
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

Infusion interruption is required if a subject experiences a hypersensitivity reaction. A ≥ Grade 3 hypersensitivity reaction requires discontinuation. A mild-to-moderate hypersensitivity reaction requires that the infusion rate be slowed (half that of the initial attempt) for the remainder of the trial. The infusion is restarted within 1 hour if the mild-to-moderate signs and symptoms resolve or, if the symptoms take longer to resolve, the infusion is not restarted and the next dose is 1 week at the slower rate.

For each patient, a maximum of one (1) dose reduction of TPI 287 will be allowed after which the patient will be discontinued from the study treatment. If, after interruption of treatment and resolution, treatment is resumed at the same dose and the same toxicity reoccurs with the same severity, next treatment re-initiation must resume at the next dose level irrespective of duration.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease experienced by a study participant while in a clinical study, whether or not considered related to the investigational product. Examples include: reactions or side effects, a pre-existing condition that worsens in severity or frequency, a concurrent illness, an injury, or a clinically significant laboratory abnormality.

7.1 Potential Adverse Events

7.1.1 Radiation

- Early (≤ 30 days from treatment): Expected adverse events include fatigue, headache, neck pain, nausea and vomiting, and lethargy.

- Late (> 30 days from treatment): Possible adverse events include focal neurologic deficits, memory difficulties, dementia, radiation necrosis, and radiation induced neoplasms.

7.1.2 TPI 287

Adverse events (AEs) listed as possibly, probably, or definitely related to TPI 287 for the **single agent** trials **irrespective of dose level and schedule** are summarized below by system organ class:

- **Blood and Lymphatic System Disorders:** anaemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia

- **Cardiac Disorders:** tachycardia

- **Gastrointestinal Disorders:** abdominal pain, abdominal pain lower, abdominal pain upper, ascites, constipation, diarrhoea, dyspepsia, dysphagia, flatulence, gastroenteritis, gastrointestinal bleed, mucositis, nausea, oral pain, stomach discomfort, stomatitis, vomiting

- **General Disorders and Administration Site Conditions:** asthenia, chest discomfort, chest pain, chills, clinical progression, difficulty in walking, disease progression with higher than expected speed of progression, face edema, fatigue, gait disturbance, mucosal inflammation, edema peripheral, pain, pyrexia

- **Hepatobiliary Disorders:** hepatic pain, hyperbilirubinaemia
- **Immune System Disorders:** anaphylactic reaction, hypersensitivity
- **Infections and Infestations:** bacterial sepsis, Candidiasis, enterococcal infection, eye infection, Herpes zoster, infection
- **Injury, Poisoning and Procedural Complications:** Head injury
- **Investigations:** ALT increased, AST increased, blood ALP increased, blood bilirubin increased, gamma-glutamyltransferase increased, granulocyte count decreased, haemoglobin decreased, neutrophil count decreased, protein urine, protein urine present, white blood cell count decreased
- **Metabolism and Nutrition Disorders:** anorexia, decreased appetite, dehydration, failure to thrive, hypokalaemia, hyponatraemia
- **Musculoskeletal and Connective Tissue Disorders:** arthralgia, back pain, bone pain, facial muscle weakness, muscle spasms, muscular weakness, musculoskeletal pain, myalgia, pain in extremity
- **Nervous System Disorders:** amnesia, balance disorder, disturbance in attention, dizziness, dysarthria, headache, hypoaesthesia, motor neuropathy, neuropathic pain, neuropathy, neuropathy peripheral, paraesthesia, peripheral sensory neuropathy, peroneal nerve palsy
- **Psychiatric Disorders:** anxiety, confusion, insomnia, sleep disorder
- **Renal and Urinary Disorders:** dysuria, haematuria, nephrolithiasis, renal failure, urinary incontinence
- **Reproductive System and Breast Disorders:** vaginal haemorrhage
- **Respiratory, Thoracic and Mediastinal Disorders:** cough, dysphonia, dyspnoea, pharyngolaryngeal pain, pneumonia, pulmonary embolism, rhinorrhoea
- **Skin and Subcutaneous Tissue Disorders:** acne, alopecia, dry skin, hyperhidrosis, hypotrichosis, night sweats, pigmentation disorder, rash, skin chapped, skin exfoliation
- **Vascular Disorders:** deep vein thrombosis, flushing, hypotension, orthostatic hypotension

In a phase I trial of TPI 287 administered weekly for 3 weeks, the most frequent AEs (≥10%) considered possibly, probably, or definitely related to TPI 287 were fatigue (40%), nausea

(29%), diarrhoea (21%), anaemia and neuropathy (19%), neuropathy peripheral (17%), vomiting and anorexia (15%), dyspnoea (13%), and dehydration, myalgia, and constipation (10%).

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

For this study, adverse events that are considered by the Investigator to have a Possible, Probable, or Definite relationship to the investigational product are considered to be related to the investigational product.

7.3 Recording & Reporting Adverse Events

AEs will be listed by patient ID number. Deaths and other SAEs will be listed and summarized by patient ID number and treatment duration. Additionally, AEs leading to discontinuations will be listed separately. Incidence of AEs will be summarized by preferred term, maximum grade reported, and relationship to study treatment.

Adverse events should only be recorded by an investigator or by a health-care provider qualified by training and experience. Patients should be asked in an open-ended manner about the occurrence of AEs.

Adverse events will be captured starting from day 1 of receiving TPI 287.

Grade 1 and 2 toxicities unrelated to study treatment will not be captured.

7.4 Adverse Event Reporting Period

Adverse events reporting period will start from day 1 of receiving TPI 287 until the last day of patient's participation in study.

7.5 Immediate Reporting of Serious Adverse Event

Any serious adverse event including, death due to any cause, pregnancy, which occurs to any patient treated on study or within 30 days following cessation of treatment, whether or not related to the investigational product, must be reported to Cortice Biosciences within 24 hours.

It is the Investigator's responsibility to report serious adverse events to the regulatory agencies and Institutional Review Board (IRB) according to the requirements of the IRB/IEC.

Additionally, any serious adverse event considered by an investigator to be possibly, probably, or definitely related to the study treatment that is brought up to the attention of the investigator at any time outside of the time period specified in Table.9 must be reported immediately to Cortice Biosciences.

All patients with serious adverse events must be followed up for outcome.

Serious Adverse Events (SAE) are:

Any untoward medical occurrences that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or,
- Is a congenital anomaly/birth defect

The onset date of an SAE is defined as the date on which it met the criteria for an SAE; e.g., the date of admission to a hospital. The end date is the date on which it no longer met the criteria for an SAE, e.g., the date that the patient was discharged from a hospital.

Expedited Reporting Guidelines

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Table 9. Expedited Reporting Requirements for Adverse Events that Occur within 30

Days of the Last Administration of TPI 287

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the Cortice bioscience within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

7.6 Second Malignancy

Second malignancies require routine reporting to Cortice Bioscience.

7.7 Pregnancy

If a patient inadvertently becomes pregnant while on treatment with TPI 287, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Cortice Biosciences without delay and within 24 hours if the outcome is a serious adverse event (e.g., death, abortion, congenital anomaly, or other disabling or life threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study, the pregnancy must be reported to Cortice Biosciences. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or new born to Cortice Biosciences.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with TPI 287 administered in this study can be found in Section 7.1.2.

Metabolism

In vitro studies have shown that TPI 287 is rapidly metabolized by pooled human S-9 liver fractions with an elimination half-life (t1/2) of 58.5 minutes. Seven putative phase 1 (modification) metabolites were detected. Structures of the two main metabolites (TPI 511 and TPI 513) were confirmed to be dihydroxyl and epoxy derivatives. Based on this and the well-established metabolism of other taxanes by cytochrome P450 3A4 (CYP3A4) and cytochrome P450 2C8 (CYP2C8), the use of drugs or herbal supplements that are known to be strong inhibitors/inducers of CYP3A4 and CYP2C8 are not permitted (Investigator's Brochure).

Supply/Storage

TPI 287 Injection should be stored in the provided packaging (vial) in the upright position, at room temperature (between 68-77°F; 20-25°C) away from direct sunlight. TPI 287 Injection must be diluted prior to administration. TPI 287 injection, 10 mg/mL that has been diluted in the IV bag of 0.9% Sodium Chloride, should be stored at room temperature. The diluted TPI 287 must be prepared within 12 hours of use.

9. CORRELATIVE STUDIES

9.1 Laboratory Correlative Studies

PK studies are optional. However, efforts will be made to obtain PK analysis from at least one patient per dose level.

Cerebrospinal Fluid (CSF) PK
CSF samples will be collected 2-3 hours after completion of TP 287 infusion on day 8 of treatment given there is no contraindication for lumbar puncture.
Patient will undergo lumbar puncture in department of interventional radiology. Procedure will be performed under fluoroscopy.
PK analysis will be performed at Moffitt Cancer Center.
Serum PK
Blood will be collected at the same time as lumbar puncture (2-3 hours post-infusion of TPI 287) on day 8 of treatment.
The blood samples will be processed to plasma and the concentration of TPI 287 will be determined using a validated liquid chromatography/tandem mass spectrometry (LC/MS-MS) method at Moffitt Cancer Center.

CSF/Plasma TPI concentration ratio will be calculated.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. MRI scans must be done ≤2 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Baseline	Concurrent phase	Single agent phase		Final [f]	Follow up [g]
		D1	D8	D15		
TPI-287 infusion		X	X	X		
XRT [a]		X				
Informed Consent	X					
History and Con-meds	X	X	X	X	X	X
Baseline Symptoms [b]	X					
Performance status (Karnofsky performance status/ECOG)	X	X	X	X	X	X
Physical Examination (including neurological assessment)	X	X	X	X	X	X
Vital signs and Height/Weight	X	X	X	X	X	X
Documenting status of systemic disease	X	X	X	X	X	X
Adverse event evaluation		X	X	X	X	X
Quality of life assessment (*QLQ-BN20* and *QLQ-C15-PAL*)	X	X	X	X	X	X
Steroid use assessment	X	X	X	X	X	X
Blood [c]	X	X	X	X	X	
B-HCG	X					
Radiological assessment [d]	X					X
PK samples [e]			X			
Mini-Mental State Examination	X	X	X	X	X	X
Lumbar puncture			X			

[a] Radiotherapy will be delivered once daily Monday through Friday, D1-5 for a total of 5 treatments.

[b] Baseline symptoms include symptoms occurring on D1 prior to receiving TPI 287 and within 1 week prior.

[c] Blood will include CBC and differential, sodium, potassium, chloride, creatinine, AST, ALT, bilirubin, ALP, albumin, calcium, magnesium, phosphate.

[d] Radiologic assessment, MRI brain with and without gadolinium, will be performed at pre-treatment and every three months following the end of treatment until the patient is off-study or reaches the 18 month study completion date.

[e] PK samples (blood and CSF) will be collected on D8.

[f] A final visit will be performed approximately 30 days following completion of treatment with FSRT and/or TPI-287 (whichever treatment occurs last).

[g] Information pertaining to survival and long term assessment of the subject's disease status and adverse events will be collected approximately every 12 weeks beginning after the final visit for period of up to 18 months.

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 3 months. The serial MRI scans shall be examined at the institution by an independent reviewer, a neuroradiologist. The evaluation of scans will be compared to and corrected with the patient's clinical course. In addition to a baseline brain MRI, confirmatory MRIs will also be obtained 4 weeks following initial documentation of an objective response.

11.1 Antitumor Effect

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with TPI 287.

Evaluable for objective response. Only those patients who have received at least one dose of TPI 287 concurrent with FSRT, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Methods for Evaluation

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Evaluation of Target Lesions

Complete Response (CR): The tumor is no longer seen on two sequential MRI scans, and the patient is on no steroids or only adrenal-maintenance dose of steroids.

Partial Response (PR): $\geq$ 50% decrease in the product of two diameters of target lesions on two sequential MRIs, taking as reference the baseline product of two diameters, provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

Minor Response (MR): Decrease in diameter products of $<$ 50% on two sequential MRI scans provided that the patient has not had his/her dose of steroids increased since the last evaluation.

Stable Disease (SD): The scan shows no change, taking as reference the smallest product of diameters while on study. Patient should be receiving stable or decreasing doses of steroids.

Progressive Disease (PD): > 25% increase in the product of two diameters of target lesions; taking as reference the smallest product on study (this includes the baseline product if that is the smallest on study), provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. A concomitant decrease in steroid dose will rule out a progression designation at this point. The appearance of one or more new lesions is also considered progressions.

Furthermore, the response will be also measured with RANO working group criteria for metastatic brain tumors when this guideline is published.

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.2 Criteria for Evaluation of Therapy Effectiveness

Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Quality of life

Quality of life will be measured using the EORTC QLQ-BN20+2 and QLQ-C15-PAL questionnaires. These questionnaires will be given to the patient at the same time points as MMSE during the follow up visits.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Protocol and Regulatory Compliance

The Investigator must conduct the study according to this protocol.

The study must be conducted by all Investigators in compliance with Good Clinical Practices (GCP) as defined as described in the U.S. FDA Code of Federal Regulations 21 CFR 312 (Investigational New Drug Application), 21 CFR 50 (Protection of Human Subjects), 21 CFR 54 (Financial Disclosure by Clinical Investigators), 21 CFR 56 (Institutional Review Boards) and ICH guidelines (Guideline to Good Clinical Practice).

The PI of this study is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol.
All protocols include a Data Safety Monitoring Plan (DSMP) and procedures for its implementation commensurate with the risk and complexity of the study. The DSMP must include a structured adverse event determination, monitoring and reporting system, including standardized forms and procedures for referring and/or treating subjects experiencing adverse events. The plan must include data and safety-monitoring procedures for subjects enrolled who may be receiving a part of their protocol-required treatment at community sites.
The PI of this study will have primary responsibility for ensuring that the protocol is conducted as approved by the SRC and IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to a DSMP and/or to the Protocol Monitoring Committee (PMC) and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

12.2 Document Audits and Monitoring

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

The PMC monitors its assigned ongoing research protocols monthly for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC upon review of any agenda item may approve the study for continuation, require revisions, suspend or close a protocol.

Investigators of studies which are designed to be reviewed by the PMC for data and safety monitoring, shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The external DSMP (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

12.3 Protocol Amendments

Any changes to this protocol will be initiated by the investigators or by the Regulatory Sponsor (Moffitt cancer Center) as a protocol amendment. The Investigator must submit the amendment to the IRB, with a revised Informed Consent Document if applicable. The Investigator must receive written approval from the IRB before the amendment may take effect.

12.4 Regulatory Binder

To be in compliance with GCPs, the Investigator must maintain accurate, complete, and organized documentation supporting the conduct of the study. This documentation includes, but is not limited to, the following: study personnel's qualifications and training, IRB approvals and communications, communications with the Regulatory Sponsor, Site Signature & Responsibility Log, laboratory accreditations and reference ranges, Form FDA 1572s, and Informed Consent Documents (copies of IRB approved versions, signed/dated originals, or copies for all enrolled patients).

12.5 Informed Consent

Prior to the performance of any protocol-specific procedures, informed consent must be obtained and documented by the use of a written Informed Consent Document approved by the Regulatory Sponsor and the IRB. The Informed Consent Document must be signed and dated by the patient or by the patient's legally authorized representative and by the person conducting the informed consent discussion. The Informed Consent Document must fulfill the requirements as contained in the U.S. Code of Federal Regulations (21 CFR 50.25), the ICH guidelines, and the Declaration of Helsinki. The Informed Consent Document must be written in a language understandable to the patient or to the representative.

A signed and dated copy of the Informed Consent Document must be given to the person signing the document. The original must be retained by the Investigator with the study documentation and be available for inspection by persons conducting an audit of the study.

Modifications to this template may be made by study site personnel to be in compliance with national, regional (e.g., state) or local laws and/or institutional requirements.

12.6 Institutional Review Boards

The protocol, Informed Consent Document, patient recruitment procedures (e.g., advertisements), information about payments and compensation available to patients, and any amendments must be approved by a properly constituted IRB in compliance with current regulations of the U.S. FDA, ICH guidelines, and any country-specific regulations.

12.7 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates. The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

12.8 Curriculum Vitae and Medical Licenses

The Principal Investigator is responsible for ensuring that the study is being conducted by qualified personnel. Documentation of these qualifications must be maintained within the Regulatory Binder, and includes the following:

Curriculum Vitae (CV): CVs for the Principal Investigator and all Sub-investigators listed on the Form FDA 1572 must be signed and dated. These CVs must show affiliation with the institution conducting the study and be current within two years of the personnel initiating their participation in the study.

Medical Licenses: Medical licenses (physicians, physician assistants, nurses) listed on the Form FDA 1572 must be kept current, and copies must be maintained in the Regulatory binder during the entire period of the person's participation in the study.

12.9 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. Patient medical information obtained for the purposes of this study is confidential, and disclosure to third parties, other than those noted below, is prohibited. Patients should be identified only by their initials and protocol-assigned patient ID number. For those patients whose surgical specimen is processed and read by the central pathology laboratory, the patient's billing information will be requested by this laboratory and will not be shared with the sponsor or any of its affiliates or representatives.

Study personnel should follow the requirements of the Health Insurance Portability and Accountability Act (HIPAA).

All clinical information is confidential, but data generated for this study must be available for inspection on request to representatives of the U.S. FDA, other national or local regulatory or health authorities, Endo Pharmaceuticals representatives, and the associated IRB.

All records must be kept in a secured area.

12.10 Financial Disclosure

Documentation of each Investigator's proprietary or financial interest is required by the U.S. Code of Federal Regulations (21 CFR 54). A financial disclosure form provided by the Sponsor must be completed, signed, and dated by the Principal Investigator and each Sub-investigator listed on the Form FDA 1572. This form must be executed prior to the personnel's participation in the study. The original form will be retained by the Sponsor. Each Investigator must inform the Sponsor of any change in his/her financial interest in the Sponsor for up to one year after the end of the study.

13. DATA MANAGEMENT AND RECORD KEEPING

Data will be maintained by the Moffitt Cancer Center.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

This is a standard 3+3 design and will include 2 cohorts: 1) dose escalation cohort, and 2) dose expansion cohort.

Endpoints

- **Primary endpoints**
  - To determine the maximum tolerated dose (MTD) of TPI 287 given concurrently with FSRT to treat brain metastases from advanced breast and non-small cell lung cancer
  - To determine the safety and toxicity of TPI 287 given concurrently with FSRT to treat brain metastases from advanced breast and non-small cell lung cancer
- **Secondary endpoints**
  - To determine the local control rate
  - To determine the distant intra-cranial control rate
  - To determine the short-term ($\leq$ 30 days post-treatment) and long-term ($>$ 30 days post treatment) adverse effects
  - To determine the PFS
  - To evaluate the effect of concurrent therapy with TPI 287 and FSRT on measures of quality of life

14.2 Sample Size/Accrual Rate

The number of patients needed for doe escalation phase will depend on the number of dose levels reached. The maximum size for the dose escalation phase will be 36 patients. In the dose expansion phase, a total of 10 patients (including patients treated at the MTD from dose escalation phase) will be enrolled to confirm the safety and to assess radiologic response.

14.3 Data Analysis

Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B LIST OF PROHIBITED DRUGS

1) **Strong CYP3A inhibitors:** Boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole

2) **Strong CYP3A inducers:** Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)

3) **CYP3A substrates with narrow therapeutic index:** Alfentanil, astemizole, cisapride, cyclosporine, diergotamine (dihydroergotamine), ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

4) **Sensitive CYP3A substrates:** Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, indinavir, levomethadyl, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simvastatin, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc

5) **Other investigational and antineoplastic therapies**

6) **Herbal medications:** Herbal medications should be stopped at least 7 days prior to first dose of study drug.

7) **Warfarin and coumarin derivatives:** Therapeutic anticoagulation may be accomplished using low-molecular weight heparin.