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A phase I study of TPI 287 in combination with temozolomide for patients with metastatic melanoma

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Abstract

Objectives—TPI 287 is a synthetic taxane derivative with structural modifications allowing for central nervous system (CNS) penetration and potential circumvention of multi-drug resistance efflux pump mechanisms. The objective of this Phase I study was to determine the maximum tolerated dose (MTD) of the combination of TPI 287 and temozolomide in metastatic melanoma.

Methods—Patients with stage IV unresectable or recurrent stage III melanoma were eligible. Stable untreated or treated brain metastases were allowed. Patients with prior taxane exposure were excluded. TPI 287 was given intravenously (i.v.) on Day 1, 8, and 15 and temozolomide was taken oral daily on days 1–5 of a 28-day cycle. Responses were assessed every 2 cycles per WHO criteria.

Results—A total of 21 patients were enrolled. The MTD of the combination at this schedule was determined to be 125 mg/m2 i.v. of TPI 287 and 110 mg/m2 of oral temozolomide. The dose-limiting toxicity was neuropathy and 6 patients experienced Grade III neuropathy. All patients were evaluable for tumor response. There were no complete responses; there were two partial responses and seven patients had stable disease (overall response rate 9.5% and disease control rate 42.9%). Three patients had stable disease in the brain despite progressive extracranial disease.

Conclusions—The combination of TPI 287 and temozolomide is well-tolerated in patients with metastatic melanoma with the exception of neuropathy. The CNS penetration of both agents makes this a rational combination for further testing in primary and metastatic brain lesions.

Keywords

melanoma; TPI 287; temozolomide; brain metastases

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Conflicts of Interest:

RN Amaria has research support from Novartis, Bristol Myers-Squibb and Merck Pharmaceuticals. MA Davies has received research support from GSK, Roche/Genentech, Sanofi-Aventis, Myriad, Oncothyreon, and Astrazeneca, and has served on advisory boards for GSK, Roche/Genentech, Novartis, Vaccinex and Sanofi-Aventis. SP Patel receives research support from Bristol Myers-Squibb, Glaxo SmithKline, Prometheus, Merck, and Novartis, served on the advisory boards for Amgen and Genentech, and holds stock in Provectus.

Introduction

Despite significant progress that has been made in the treatment of metastatic melanoma over the past 5 years following the Food and Drug Administration (FDA) approval of targeted therapy and immunotherapy agents for this disease(1–5), further lines of effective therapy remain limited and most patients with metastatic melanoma will eventually die from their disease. Metastases to the central nervous system (CNS) remain a major cause of morbidity and mortality in melanoma patients. Up to 75% of stage IV melanoma patients will develop brain metastases(6) and the brain is often the first, and sometimes the only, site of disease progression in patients treated with systemic therapies.(7, 8) Thus, therapies with CNS activity are critically needed. Traditionally, CNS metastases in melanoma have been treated with surgery, whole brain radiation, or stereotactic radiosurgery; however, there has been limited success with the use of systemic agents in the treatment of CNS disease.(9–12)

TPI 287 is a novel, synthetic taxane derivative with significant CNS activity *in vivo* and promising results in early phase trials of primary CNS malignancies. Paclitaxel (Taxol) as a single agent in melanoma produces 14% objective response,(13) and the combination of docetaxel, temozolomide, and cisplatin demonstrated a response rate of 32% and stable disease in another 26% of patients.(14)

TPI 287 synthesis involves modifications of the side chain to make the drug more lipophilic. Additionally, modification of the baccatin ring structure prevents the drug from being a substrate for the -glycoprotein (P-gp) pump which drives taxane resistance via drug efflux. (15) *In vitro*, TPI 287 was shown to have comparable cytotoxicity to paclitaxel in several multidrug resistance (MDR)− cell lines, but was 5 – 3900-fold more active than several comparator compounds in MDR+ cells lines.(16) TPI 287 is known to penetrate the blood brain barrier and accumulate in the brains of mice and rats after a single dose.(17) TPI 287 was found to significantly reduce brain metastases in a breast cancer model (18) and demonstrated synergistic activity with temozolomide (Temodar) in a glioblastoma (GBM) model.(17)

Multiple early phase trials of TPI 287 in advanced solid tumors or CNS malignancies have been conducted with various dosing schedules with promising early results.(19–22) The preliminary analysis of a study of TPI 287 combined with bevacizumab in recurrent GBM demonstrated a confirmed RANO(23) response rate of 60% (12/20).(19)

Dacarbazine, an alkylating agent, was the first drug FDA approved for the treatment of melanoma and had long been the standard of care chemotherapy option with response rates of 10–15% in metastatic disease.(24, 25) Temozolomide is a dacarbazine (DTIC) analogue with the advantage of excellent CNS penetration and oral administration.(9) In a multi-institution phase II trial of temozolomide in melanoma patients with previously untreated CNS metastases, the objective response rate was 7% and 29% of patients had stable disease. (9) Temozolomide is FDA approved for primary CNS malignancies including GBM and anaplastic astrocytoma. The combination of TPI 287 and temozolomide has been previously

tested in pediatric patients with refractory neuroblastoma or medulloblastoma with good tolerance and stable disease in 7 of 11 patients.(26)

We conducted this phase I trial of TPI 287 with temozolomide in patients with metastatic melanoma. The primary objective was to determine the maximum tolerated dose (MTD) of the combination.

Patients and methods

Patients

Patients aged 15 years or older with histologically confirmed metastatic melanoma were enrolled in an open-label phase 1 dose-escalation trial. Patients were required to have at least one target lesion which could be used to assess response by the WHO response criteria.(27) Patients with known CNS metastases were allowed on study as long as they were asymptomatic, had stable disease for at least two months as assessed by CT or brain MRI prior to enrollment, individual brain lesions did not exceed 15mm, and if multiple lesions were present, the combined uni-dimensional diameters could not exceed 4.0 cm. Prior whole brain radiation, stereotactic gamma ray therapy or surgery for CNS disease was allowed as were untreated brain metastases. Patients with hemorrhagic CNS metastases were excluded. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG)(28) performance status ≤2 and adequate bone marrow, kidney and liver function. No more than two prior cytotoxic chemotherapy regimens were allowed and use of prior taxane based chemotherapy was prohibited. Prior immunotherapy or targeted therapies were not exclusionary. Patients with documented peripheral neuropathy at baseline were excluded from participation.

This study protocol was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center. All patients provided written informed consent prior to enrollment and initiation of study procedures.

Treatment plan

A classic 3+3 dose escalation scheme was used with the dose levels as shown in Table 1. Given that both of these agents can cause myelosuppression, the starting doses were reduced to <60% of the recommended phase II dose (RPTD) of TPI 287 from prior trials of single agent TPI 287 and <70% of the target dose of temozolomide.

TPI 287, provided by Cortice Biosciences, Inc., was administered intravenously over 60 minutes weekly on days 1, 8 and 15 out of a 28 day cycle. As the TPI 287 formulation contains Cremaphor®, premedication with corticosteroid, antihistamine and H2 blocker was mandated to prevent infusion reactions. Temozolomide was given oral daily for days 1–5 of the 28 day cycle.

Patients continued on study until disease progression, elective withdrawal, or occurrence of dose-limiting toxicity (DLT). Patients were followed every 28 days after the last dose of study drug until all study-related toxicities had resolved or stabilized.

Toxicity evaluation

Patients were evaluated for toxicity using the US National Cancer Institute's Common Terminology Criteria for Adverse Events v4. [15] Patients underwent a physical examination and comprehensive blood tests, including a complete blood count with differential, and a complete metabolic panel, before every treatment cycle to assess toxicity.

DLT was defined as any drug related non hematologic toxicity including ≥ grade 3 (excluding nausea and vomiting), drug related grade 1 or 2 neuropathy lasting over 7 days or failing to stabilize within 3 weeks of holding drug, grade 3 neutropenia lasting over 7 days associated with fever or infection, grade 4 neutropenia of any duration, grade 3 thrombocytopenia lasting over 5 days or grade 4 thrombocytopenia of any duration. Treatment was withheld until toxicity resolved to less than or equal to grade 2 and then resumed at a reduced dose.

Response evaluation

Patients were evaluated with CT scans of the chest, abdomen and pelvis every other cycle. Patients with known CNS metastases had CNS imaging before each cycle. Patients without CNS metastases had brain MRI every other cycle. The WHO response criteria was used to assess response to therapy, with partial response (PR) defined as ≥50% decrease in sum of products of all measureable lesions, and progression as ≥25% increase over baseline or any new lesion. Response duration was measured from the time of response until evidence of disease progression. PFS was measured from the time of treatment initiation to evidence of disease progression or death, and OS was measured from the time of treatment initiation to the time of death or last follow-up. Kaplan–Meier estimates were used to plot survival curves.

Results

Patient characteristics

21 patients were enrolled between February 2010 and April 2013. All patients were evaluable for response. Patient characteristics are shown in Table 2. The median age of patients was 65 and ranged from 25–80. 16 of 21 patients had Stage IVC disease and 10/21 patients had brain metastases (7 previously treated and 3 untreated) at study entry.

Dose escalation and dose-limiting toxicity

No patients experienced a DLT at dose levels 1–3. At dose level 4, one patient experienced Grade II peripheral neuropathy which did not improve after holding treatment for one week, which represented a DLT per protocol. Therefore, the cohort was expanded to six patients. In the expanded cohort, another patient experienced a DLT (Grade II peripheral neuropathy which did not improve after holding treatment for one week). Therefore, three further patients were recruited to dose level 3, none of whom experienced any DLTs. Therefore, the MTD of the combination at this schedule was determined to be 110 mg/m2 of temozolomide and 125 mg/m2 of TPI 287.

Safety

Twenty one patients were evaluable for safety. Anemia was the most common adverse event reported (14 patients, 67%), followed by peripheral neuropathy (12 patients, 57%) and lymphopenia (11 patients, 52%) (Table 3). Grade III/IV toxicities included drug-related peripheral neuropathy (n=5, 24%; one at DL 2, 110 mg/m2 of TPI 287 and 4 at the level of 125 mg/m2), lymphopenia (24%), fatigue (14%), hypokalemia (5%), and pulmonary embolism (5%). All 5 patients with Grade III neuropathy discontinued treatment, after 6 to 15 cycles. Of the patients with Grade III neuropathy, neuropathy did not resolve upon discontinuation of drug, but did improve in the majority. There were no dose reductions and no other patients discontinued therapy due to toxicity.

Efficacy

Twenty one patients were evaluable for tumor response. Patients completed a mean of 5 cycles. There were no complete remissions but there were two partial responses for an ORR of 9.5%, both of which occurred at the MTD of TPI 287. Seven additional patients had stable disease (33.3%) for a disease control rate (DCR) of 42.9%. Of the 7 patients with previously treated brain metastases at study entry, 3 patients had stable disease in the brain despite having either progressive disease in the body. Three patients with previously untreated brain metastases had progression of disease both intra- and extracranially as best response. Of the 11 patients without brain metastases, 2 (18%) developed new brain metastases. Median PFS for the full cohort was 1.8 months (95% CI: 1.0–5.7) and median OS was 9.1 months (95% CI: 5.8–44.5). Of those with brain metastases, the PFS was 1.2 months (95% CI: 0.9, NR) and median OS was 6.1 months (95% CI: 3.7, NR). Of the patients treated at the MTD of both agents or higher (dose levels 3–4), the ORR was 8.3% and DCR was 41.7%, median PFS was 1.8 months (95% CI: 1.3, NR), and median OS was 15.6 months (95% CI: 6.3, NR).

Discussion

Despite the multiple advances made in the last 5 years, there remains a critical need to identify additional active therapies for patients with melanoma, particularly agents with activity in the CNS. The results of this phase I study of two agents with favorable characteristics for the treatment of CNS disease demonstrate that combining TPI 287 and temozolomide is safe, and there is an initial signal of some clinical activity.

As is to be expected with a taxane agent, peripheral neuropathy was a common adverse event and was the DLT in this study. Five patients (24%) experienced Grade III neuropathy leading to treatment discontinuation after 6–15 doses. The rates of peripheral neuropathy are similar to those previously reported with both the weekly and q3 week doses single-agent TPI 287.(20, 21) It is possible, though, that the combination may have increased myelosuppression, as the observed rate of anemia was 67%. However, anemia was entirely Grade I/II only and there were no DLTs for any hematological AEs. The rate of lymphopenia was similar to that seen with single-agent temozolomide. The MTD of TPI 287 in this study based on the weekly dosing schedule in combination with temozolomide was 125 mg/m2 i.v. which is the same MTD found in prior studies at this dosing schedule. The

MTD of temozolomide in this combination was 110 mg/m2 oral daily dose days 1–5 which is lower than the dosage of 150–200 mg/m2 typically given as a single agent for a 5-day dosing schedule.

Treating and preventing brain metastases remains a major challenge in melanoma as 75% of patients with Stage IV melanoma will develop brain metastases at some point and CNS disease is the cause of death in over 50% of patients.(6, 29) The efficacy of traditional cytotoxic chemotherapy is limited by penetration of the blood brain barrier. The CNS penetration of both temozolomide and TPI 287 makes this combination a rational approach to prevent and treat brain metastases, and TPI 287 is currently being evaluated in numerous studies in both primary brain malignancies (glioblastoma (NCT01933815, NCT02047214), and breast and lung cancer metastatic to brain (NCT01332630, NCT02187822), as well as in phase 1 studies of patients with Alzheimer's disease and other neurodegenerative disorders (NCT01966666, NCT02133846).

In this phase I study, two patients achieved partial responses, and a further 7 patients had stable disease. The two partial responses had duration of response over 5 months and both of these responding patients discontinued therapy while they were responding due to peripheral neuropathy and continued on single-agent temozolomide off protocol. In addition, 3 (30%) of the patients with CNS involvement in the study had stable disease in the brain despite having progressive disease extracranially. While FDA-approved immune (ipilimumab, pembrolizumab) and targeted (dabrafenib, vemurafenib) therapies for stage IV melanoma patients have demonstrated activity in patients with active brain metastases,(10–12) the CNS is still a common site of disease progression in patients treated with targeted therapy and remains a challenge with immunotherapy.(7, 8) As progression in the CNS can occur in the setting of controlled or responding non-CNS disease, it is possible that the combination of TPI 287 and temozolomide could have clinical benefit as an adjuvant to control brain metastases However, the lack of activity in patients with previously untreated brain metastases would suggest that this must be combined with local therapy as is currently the practice for single-agent Temozolomide in patients with melanoma brain metastases.

As the treatment landscape for melanoma has dramatically changed over the last 5 years, the role for cytotoxic chemotherapy in metastatic melanoma is unclear at this point. However, despite the marked progress that has been made, many patients continue to die from this disease, and there remain several key unmet clinical needs, particularly treatments for patients without $BRAF^{V600}$ mutations and for patients with CNS metastases. The results of this phase I study support that the combination of TPI 287 and TMZ is safe and well-tolerated. The ability of both of these agents to effectively penetrate the BBB, and the initial signs of clinical activity observed in this phase I trial, support the possibility that this regimen could be of benefit for metastatic melanoma patients.

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Table 1

Dose escalation scheme

Dose level	Temozolomide daily days 1–5 (mg/m^2)	TPI 287 Day 1, 8 and 15 (mg/m^2)	Number of patients treated
0	85	90	3
+1	85	110	3
+2	85	125	3
+3	110	125	6
+4	125	125	6

Table 2

Patient and disease characteristics

Characteristic	Number of patients (%)
Sex	
Male	13 (62)
Female	8 (38)
Age (years)	
Median (range)	65 (25–80)
ECOG performance status	
0	12 (57)
1	9 (43)
Disease stage	
III unresectable	1
IVa	2
IVb	2
IVc	16
LDH	
Elevated	8
Normal	13
Number of prior systemic therapies for metastatic disease	
0	7
1	11
2	2
3	1
Brain metastases prior to study entry	
Yes	10
No	11

Table 3

Drug–related adverse events

Event	Grade I/II	Grade III/IV	Total
Anemia	14 (67%)	0	14 (67%)
Peripheral neuropathy	7 (33%)	5 (24%)	12 (57%)
Lymphopenia	6 (29%)	5 (24%)	11 (52%)
Fatigue	7 (33%)	3 (14%)	10 (48%)
Nausea/vomiting	9 (43%)	0	9 (43%)
Constipation	9 (43%)	0	9 (43%)
Hyperglycemia	8 (38%)	0	8 (38%)
Thrombocytopenia	7 (33%)	0	7 (33%)
Neutropenia	6 (29%)	0	6 (29%)
Anorexia	4 (19%)	0	4 (19%)
Hypokalemia	3 (14%)	1 (5%)	4 (19%)
Pulmonary embolism	0	1 (5%)	1(5%)

* AEs which occurred in ≥15% of patients and all Grade III/IV events are reported.