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## Phase II study of CCI-779 in patients with recurrent glioblastoma multiforme

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**Key words:** chemotherapy, CCI-779, rapamycin, glioblastoma multiforme, recurrent, efficacy

### Summary

**Purpose:** Loss of PTEN, which is common in glioblastoma multiforme (GBM), results in activation of the mammalian target of rapamycin (mTOR), thereby increasing mRNA translation of a number of key proteins required for cell-cycle progression. CCI-779 is an inhibitor of mTOR. The primary objectives of this study were to determine the efficacy of CCI-779 in patients with recurrent GBM and to further assess the toxicity of the drug. **Experimental Design:** CCI-779 was administered weekly at a dose of 250 mg intravenously for patients on enzyme-inducing anti-epileptic drugs (EIAEDs). Patients not on EIAEDs were initially treated at 250 mg; however, the dose was reduced to 170 mg because of intolerable side effects. Treatment was continued until unacceptable toxicity, tumor progression, or patient withdrawal. The primary endpoint was 6-month progression-free survival. **Results:** Forty-three patients were enrolled; 29 were not on EIAEDs. The expected toxicity profile of increased lipids, lymphopenia, and stomatitis was seen. There were no grade IV hematological toxicities and no toxic deaths. One patient was progression free at 6 months. Of the patients assessable for response, there were 2 partial responses and 20 with stabilization of disease. The median time to progression was 9 weeks. **Conclusions:** CCI-779 was well tolerated at this dose schedule; however, there was no evidence of efficacy in patients with recurrent GBM. Despite initial disease stabilization in approximately 50% of patients, the durability of response was short. Because of the low toxicity profile, CCI-779 may merit exploration in combination with other modalities.

### Introduction

Novel therapeutic strategies are needed for the treatment of patients with recurrent glioblastoma multiforme (GBM), for whom the median survival is currently 4 to 6 months. Recent advances in the understanding of aberrant molecular and cytogenetic pathways involved in GBM pathogenesis and progression have led to the rational targeting of some of these pathways. A significant percentage of GBM have altered PTEN gene suppression activity [1], which results in the increased activity of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. The PI3K/Akt pathway activates the mammalian target of rapamycin (mTOR), increasing translation of a number of key proteins required for cell-cycle progression. The presence of PTEN gene alterations and the subsequent

activation of these downstream pathways have been associated with poor prognosis in anaplastic astrocytoma, anaplastic oligodendroglioma, and GBM [2–4]. Restoration of PTEN function or targeting of the components of the PI3K/Akt/mTOR pathways can result in cell-cycle arrest, apoptosis, or reduced tumorigenicity and are rational targets for clinical evaluation.

CCI-779 is a dihydroxymethyl propionic acid ester of the immunosuppressive agent sirolimus (rapamycin, Rapamune<sup>®</sup>) that targets the mTOR pathway. CCI-779 binds to FKBP-12 to form a complex that interacts with mTOR, which results in cell-cycle arrest by means of inhibition of RNA translation [5–7]. CCI-779 is lipid soluble and inhibits the growth of a number of human tumor lines in nude mouse models, including GBM [8]. Based on these promising pre-clinical studies, there was an interest

in evaluating this novel agent in patients with recurrent GBM.

There is increasing evidence that brain tumor patients receiving P450 enzyme-inducing anti-epileptic drugs (EIAEDs) have markedly altered pharmacokinetics, resulting in accelerated drug metabolism. CCI-779 and rapamycin are substrates for the cytochrome P450 isoenzyme 3A4. A North American Brain Tumor Consortium phase I study established the maximum tolerated dose of CCI-779 in patients with malignant glioma who are taking EIAEDs at 250 mg [9].

We report on the results of a phase II study of CCI-779 in patients with recurrent GBM. The primary objectives of this study were to determine the efficacy (defined by 6-month progression-free survival) of patients with recurrent GBM treated with CCI-779 and to further assess its toxicity.

## Methods

### *Patient eligibility*

Patients at least 18 years of age were eligible for participation if they had histopathologically confirmed GBM with recurrence documented by neuroimaging. Patients were also eligible if they had a prior low-grade glioma and a subsequent histological confirmation of GBM. Patients must have relapsed after prior treatment with radiation therapy, with an interval of at least 4 weeks from treatment with radiation therapy, and could not have undergone treatment for more than 2 prior relapses. Patients were required to have a Karnofsky Performance Scale (KPS) score of at least 60, an estimated survival of >8 weeks, hematologic, renal, and hepatic status within the normal ranges, levels of cholesterol <350 mg/dl, and levels of triglyceride <400 mg/dl. No exclusions were made based on gender, race, minority status, or economic status. Female patients were not pregnant or nursing, and all patients (both men and women) agreed to practice birth control during and for 3 months after completing the study. Patients or their surrogates signed an institutionally approved Committee on Human Research consent form. Patients did not have any serious intercurrent illness or disease that obscured or altered drug metabolism.

### *Study design*

Patients were treated with CCI-779 as a 30-minute intravenous (IV) infusion weekly with no rest period required. For the purpose of evaluation, a cycle was defined as every 4 weeks. Because of the documented side effect of lipid elevation, allowance for the use of lipid-lowering agents was incorporated into the phase II study. After every 2 cycles of treatment, patients underwent re-staging

with neuro-imaging and clinical evaluation including neurological examination and assessment of corticosteroid use. Determination of tumor status was made using standard criteria [10]. Therapy with CCI-779 was continued as long as the tumor was stable or smaller in size and the patient was clinically stable or improved on stable or decreasing corticosteroid doses. Treatment continued indefinitely as long as there were no unacceptable toxicities, patient refusal to continue participation, or tumor progression. For all patients, the initial phase II dose was 250 mg IV weekly. Toxicities were graded according to the NCI Common Toxicity Criteria (CTC Version 2.0) scale.

### *Statistical considerations*

Enrollment of 32 patients would give a 92% probability of successfully detecting a 35% 6-month progression free-survival (PFS) rate and a 90% probability of rejecting the drug if the 6-month progression-free survival (PFS) rate was 15% or less. The study would be considered worth pursuing if at least 8/32 patients had 6-month progression-free survival.

## Results

Forty-three patients were enrolled (65% male). All patients enrolled had primary GBM. The median age was 48 years (range 26–71 years) and the median KPS was 90. Patients' characteristics are shown in Table 1. For patients not on EIAEDS, the initial dose was 250 mg weekly; however, this was reduced to 170 mg weekly in many patients because of intolerable side effects (stomatitis). Thirteen patients were treated at 250 mg and 16 patients at 170 mg. The 14 patients on EIAEDs were treated at 250 mg. The major toxicities observed were elevation in lipid profiles, lymphopenia, and stomatitis (Table 2). Twenty-one patients were started on lipid-lowering agents during the study; none were on lipid-lowering agents at the time of enrollment. There were no grade IV hematological toxicities and no toxic deaths.

Two patients were lost to follow-up and were censored for the endpoint of progression-free survival. Of the 41 evaluable patients, only 1 patient was progression free at 6 months. There were 2 partial responses and 20 patients who had stabilization of disease; however, the median time to progression was short, at 9 weeks. The Kaplan Meier estimate for time to progression is shown in Figure 1.

## Discussion

Mutations of the PTEN gene result in constitutive activation of the PI3K pathway, resulting in increased

Table 1. Patients' characteristics

	Patients taking NEIAEDs (N = 29)	Patients taking EIAEDs (N = 14)
Median Age in years (range)	51 (29–71)	46 (26–71)
Karnofsky Performance Status		
90–100	13 (44.8%)	4 (28.6%)
≤80	16 (55.2%)	10 (71.4%)
Sex		
Female	10 (34.5%)	5 (35.7%)
Male	19 (65.5%)	9 (64.3%)
Race		
Black	2 (6.9%)	0 (0%)
White	27 (93.1%)	14 (100%)
Prior Chemotherapy Regimens		
0	2 (6.9%)	0 (0%)
1	22 (75.9%)	9 (64.3%)
2	2 (6.9%)	5 (35.7%)
3	3 (10.3%)	0 (0%)

Table 2. Grade III and IV toxicities observed (n = 43 patients) using the National Cancer Institute common toxicity grading system

Toxicity	Grade III (%)	Grade IV (%)
Lymphopenia	14	–
Anemia	5	–
Stomatitis	2	2
Elevated cholesterol	9	7
Elevated triglyceride	5	5

proliferation, dysregulation of the cell cycle, and resistance to chemotherapy-induced apoptosis. This is relevant in glioma therapy, as PTEN mutations are present in approximately 40% to 60% of all GBM, and alterations

in PTEN are of prognostic significance [1]. One of the downstream pathways of PTEN involves mTOR, which is inhibited by CCI-779. Based on preclinical data on CCI-779, which showed potential antiglioma activity, we evaluated this agent in patients with recurrent GBM. Because CCI-779 and rapamycin are metabolized by the p450 hepatic enzyme system, and concurrent use of EIAEDs may result in increased clearance of CCI-779, the appropriate phase II dose in patients on enzyme-inducing anti-epileptic agents was established first [9]. The agent was well tolerated, with side effects as described at a similar dosing schedule in solid cancers [11].

This phase II study sought to evaluate the efficacy of CCI-779 as defined by 6-month progression-free survival in patients with recurrent GBM irrespective of the use of EIAEDs. Unfortunately, despite good tolerance of the agent, CCI-779 did not demonstrate sufficient antitumor activity to warrant further study as a single agent. There are possibly several reasons for this lack of efficacy. Although the pharmacokinetic results suggested adequate systemic concentrations of the drug to block mTOR [9], actual drug concentration within the tumors had not been documented. The presence of the blood-brain barrier and inadequate penetration of the agent to the infiltrative tumor cells may be a barrier for drug delivery. This emphasizes the challenges of performing clinical trials of novel agents in patients with malignant glioma [12]. A small pilot study being performed by the North American Brain Tumor Consortium involves 10 patients who will be administered CCI-779 prior to planned surgical resection of a recurrent malignant glioma. In addition to evaluation of inhibition of mTOR, measurements of tumor drug levels are planned and may help in answering this question.

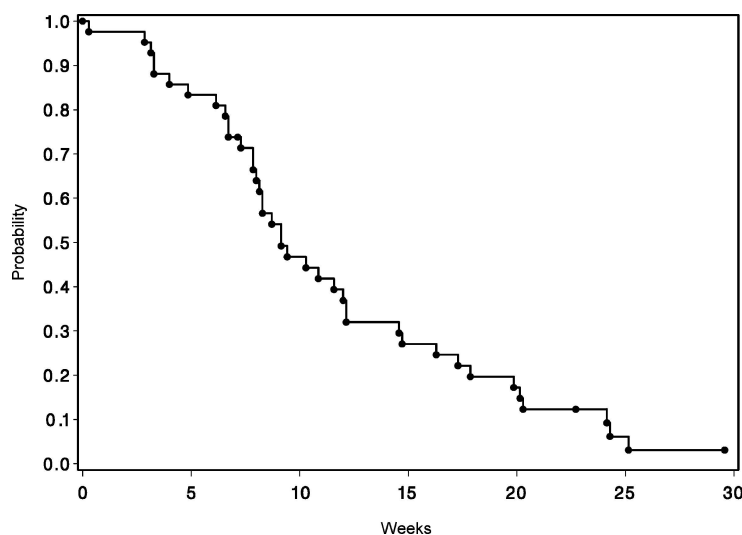


Figure 1. Kaplan Meier estimate for time to progression for 41 patients with recurrent GBM treated with CCI-779.

PTEN status of the tumors at the time of enrollment was not required or mandated. As with any 'targeted' therapy, enrollment of patients lacking the specific genetic abnormality may cause underestimation of the true efficacy of the agent. This poses a significant challenge in the selection of patients, given the invasive nature of tissue acquisition. Retrospective analysis of tissue samples is also fraught with potential for misinterpretation, as the specimens analyzed tend to be representative of the tumor at the time of initial diagnosis and not at the time of recurrence following therapy with radiation and/or chemotherapy. Changes in the molecular targets could theoretically occur with time, and the most informative sample would be at the time of treatment with the targeted agent.

It is well accepted that many cell-signaling pathways overlap, and there may actually be an interdependence of activity within these pathways. Targeting only one aspect of a pathway may be successful in proof-of-principle studies; however, this may unfortunately not translate into a benefit of clinical significance for the patient. An example of this is the recent demonstration of the alterations in cyclin D1/*c-myc* expression as critical determinants of cell sensitivity to mTOR inhibitors, which suggested that excessive transcription of these genes in tumors may inhibit the effectiveness of mTOR inhibitors [13]. Other relationships between signaling molecules have been demonstrated *in vivo* by Choe et al., using human GBM tissue microarrays [14]. In addition to the well-accepted relationship of the PTEN and PI3K pathways, the authors show correlation of PTEN with the family of forkhead transcription factors as well as the mutant epidermal growth factor receptor vIII. Others have also described the relationship of epidermal growth factor receptor (EGFR) with this particular signaling pathway [15]. This is particularly relevant for GBM, as frequent mutation of EGFR is seen and is known to confer an unfavorable prognosis [16]. There may be a scientific rationale for the combination of EGFR inhibitors with mTOR inhibitors given these findings. These studies also suggest that the signaling abnormalities specific to the individual patient may be important information for stratification into clinical trials of these targeted agents.

In addition to these reasons for the limited efficacy of CCI-779 observed in this study, potential mechanisms of resistance to rapamycin and its analogs include mutation of the binding proteins FKBP-12, alteration of the downstream effectors of mTOR, and mutation of mTOR itself [17, 18]. Many of these mechanisms are being elucidated, but their clinical significance needs to be further studied.

It is anticipated that many of these cytostatic agents that target specific signaling pathways are unlikely to have durable control of tumor growth as single agents because of the reasons described above. There is the danger of discarding a potentially useful agent that could be used

in combined modality therapy because of its lack of efficacy as a single agent. Preclinical data support the use of mTOR inhibitors in combination with radiation and chemotherapy [19–21]. The current paradigm of evaluating the efficacy of these drugs as single agents first rather than in combination with radiation therapy, chemotherapy, or other targeted therapies may inherently delay appropriate use of these novel compounds. Given that the agent is well tolerated, proceeding with the study of these combinations may be worthy of further study.

## Conclusions

This phase II study of CCI-779 in patients with recurrent GBM on and off enzyme-inducing anti-epileptic drugs failed to demonstrate any efficacy as a single agent. Because CCI-779 was well tolerated, further combination strategies may merit evaluation.

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