Abstract ID: 2088

Phase 2 study of verubulin (MPC-6827) for the treatment of subjects with recurrent glioblastoma naïve to treatment with bevacizumab

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Background

Treatment options are limited for recurrent glioblastoma (GBM).[1] GBM are highly vascularized tumors[2,3], and agents that selectively disrupt tumor vasculature (vascular disrupting agents; VDA) may be beneficial in the treatment of GBM.

Verubulin HCl, 4-arylaminoquinazoline hydrochloride (MPC-6827) is a novel small molecule that acts as a microtubule destabilizing agent causing arrest of cell division and apoptosis in a broad range of cancer cell lines *in vitro* and demonstrating anti-tumor activity in multiple xenograft models. Verubulin has also been shown to be a VDA that disrupts tumor neovasculature integrity *in vivo*, resulting in decreased tumor blood supply and cell death.[4,5] Verubulin is not a substrate for multidrug resistance pumps and achieves central nervous system (CNS) concentrations far in excess (14-30 fold) of plasma concentrations in animals.

Due to its anti-tumor activity, lack of cross resistance with alkylator-based therapy and CNS penetration, verubulin may provide therapeutic benefits to patients suffering from recurrent GBM.

The maximum tolerated dose for verubulin monotherapy is 3.3 mg/m^2 with dose limiting toxicities of acute coronary syndrome at higher doses.[6,7] The 3.3 mg/m^2 dose level has been studied in combination with carboplatin in recurrent GBM and in combination with temozolomide in melanoma and has been shown to be safe and well tolerated.[8,9]

Study Design

This clinical trial was done in collaboration with the Brain Tumor Investigators' Collaborative (BTIC) Consortium.

Open-label, multiple-dose study in patients with GBM following first or second recurrence. Patients were stratified into two groups based on treatment history. Group 1, reported here, consisted of GBM patients who were either bevacizumab-naïve or primary refractory (2 or 3 doses of bevacizumab). Group 2 consisted of GBM patients who were bevacizumab responsive (previous response but later progressed) (data presented at 2010 SNO meeting; abstract NO-65).

Patients were treated with 3.3 mg/m^2 of monotherapy verubulin administered intravenously (IV) over 2 hours once weekly for 3 consecutive weeks out of 4 weeks per cycle. Treatment with verubulin was continued until disease progression or unacceptable toxicity.

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Study Endpoints

Study Endpoint – Response based on Macdonald Criteria[10]

- To determine the progression-free survival (PFS) rates in patients with first or second recurrence of GBM.
- The primary endpoint was 6-month progression-free survival (PFS-6), i.e., the patient is alive and free of disease progression at 6 months from initiation of treatment with verubulin.

Patient Eligibility and Assessments

Major Inclusion Criteria

- Histologically proven GBM in first or second relapse
- Failed prior standard therapy
- Karnofsky performance status ≥ 60
- At least 18 years old

Major Exclusion Criteria

- More than two relapses
- Suspected pseudoprogression
- MRI evidence of enlarging or clinically significant intra-tumor hemorrhage
- Cerebrovascular disease (active stroke and/or TIA)
- Increasing steroid requirement indicative of rapidly progressing disease
- Cardiovascular disease (unstable angina or MI, uncontrolled hypertension, etc.) or 45 years old or greater with significant cardiovascular risk factors
- LVEF less than 50% by ECHO or MUGA
- Troponin I or T elevated above the reference range

Safety and Efficacy Assessments

- Standard safety measures were employed with the addition of cardiac monitoring. Adverse Events were coded using MedDRA version 11.0 and graded according to CTCAE version 3.0.
- All patients underwent a CT or MRI scan at screening and at designated follow-up time points; disease was evaluated using the Macdonald criteria.

Patient Demographics and Characteristics

	N = 31
Age (years): median (range)	56 (23 – 74)
Sex Male : Female	20 : 11
Karnofsky performance status: median (range)	90 (70 – 100)
First Relapse n (%) Second Relapse n (%)	24 (77%) 7 (23%)
Number of past chemotherapy regimens: median (range)	2 (0 – 2)
Number of past oncologic surgeries: median (range)	1 (1 – 2)
Number of past radiation therapy courses: median (range)	1 (1 – 3)
Number of verubulin cycles completed: median (range)	2 (0 – 14[a])

a. One patient continues to receive study treatment (cycle 14 ongoing).

Adverse Events Potentially Related to Verubulin[a]

N = 31 Patients	Total n (%)	Grade 1	Grade 2	Grade 3	Grade 4
Preferred Term ↓ / Individual Patients n (%) →	15 (48.4%)	6 (19.4%)	5 (16.1%)	3 (9.7%)	1 (3.2%)
Fatigue	8 (25.8%)	8 (25.8%)	0	0	0
Nausea	3 (9.7%)	2 (6.5%)	1 (3.2%)	0	0
Constipation	3 (9.7%)	3 (9.7%)	0	0	0
Decrease in LVEF	2 (6.5%)	0	2 (6.5%)[d]	0	0
Ventricular arrhythmia[b]	1 (3.2%)	0	1 (3.2%)	0	0
Myocardial infarction[c]	1 (3.2%)	0	0	0	1 (3.2%)[d]
Herpes zoster	1 (3.2%)	0	0	1 (3.2%)	0
Hypophosphataemia	1 (3.2%)	0	0	1 (3.2%)	0
Pulmonary embolism	1 (3.2%)	0	0	1 (3.2%)	0

a. Potentially verubulin-related adverse events includes related, possibly related, or missing relationship to study drug; if a patient reported an adverse event more than once, the highest grade was presented. b. Patient discontinued study due to the grade 2 ventricular arrhythmia. c. Patient had significant cardiovascular risk factors. d. Reported as serious adverse events.

Other potentially related adverse events that occurred in a single patient include grade 1 vomiting, headache, tremor, somnolence, erythema, and orthostatic hypotension, and grade 2 rash at the injection site, gait disturbance, and insomnia. There were no deaths due to a verubulin-related adverse event.

Best Overall Response

Cycles Completed		Best Overall Response			
N	Median (range)	Partial Response[a] (PR)	Stable Disease[b] (SD)	Progressive Disease (PD)	Not Evaluated Post Verubulin[c]
31	2 (0 – 14[d])	2 (6.5%)	6 (19.4%)	20 (64.5%)	3 (9.6%)

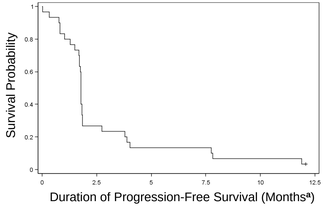
a. The median duration of partial response for both patients was 6 months.
b. The median duration of stable disease was 4 months [90% CI: 3.8, 11.9].
c. Three patients did not complete at least two cycles of treatment and were not evaluated for disease response.
d. One patient continues to receive study treatment (cycle 14 ongoing); patient's best response by Macdonald criteria is stable disease (lesions currently undetectable).

Progression-Free Survival and Overall Survival

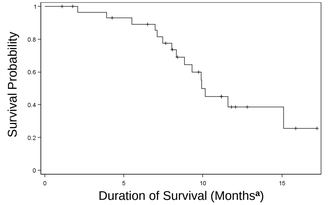
Cycles Completed	PFS-6	Progression-Free Survival		Overall Survival	
N	Median (range)[a]	% (90% CI)	Mean Months (range)[a]	Median Months (90% CI)[a]	Mean Months (range)[a]	Median Months (90% CI)[a]
31	2 (0 – 14[a])	14% (3, 25)	2.9 (0.04 –13.1)	1.8 (1.7, 1.8)	8.8 (1.1 – 17.2)	9.9 (8.8, 15.1)

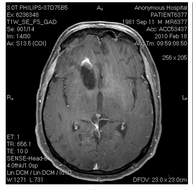
a. One patient continues to receive study treatment (cycle 14 ongoing).

Kaplan-Meier Estimate of PFS Probability

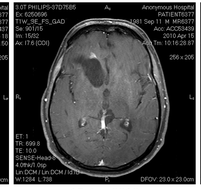


Kaplan-Meier Estimate of Survival Probability

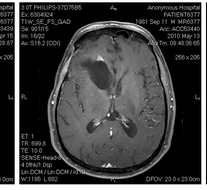




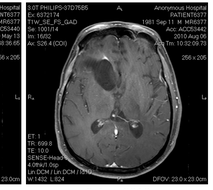
18-Feb-2010
Baseline



15-Apr-2010
End Cycle 2
Partial Response
54% tumor regression
relative to Baseline



13-May-2010
End Cycle 3
Partial Response
Confirmed



6-Aug-2010
End Cycle 6
Partial Response
53% tumor regression
relative to nadir scan Cycle 2

Images from a 29-year old male with an initial diagnosis of primary GBM in June 2009. Prior to enrollment in the verubulin clinical trial, the patient underwent a tumor resection in June 2009 followed by radiation therapy with concurrent and adjuvant temozolomide for six months until disease progression in January 2010.

The patient initiated study treatment in February 2010, was not taking any steroids and had a Karnofsky performance status of 90. The patient had a partial response observed after completion of the second cycle of verubulin with a 54% tumor regression and an additional 53% tumor regression at the end of cycle 6 relative to the nadir scan at the end of cycle 2 (confirmed with end of cycles 2, 3, and 6 MRIs; T1-weighted gadolinium enhanced images presented).

The patient's neurological exam and Karnofsky performance status remained unchanged from baseline throughout the study. The patient was discontinued from the study due to disease progression after completion of 8 cycles. The patient is otherwise healthy and has initiated a new treatment for GBM.

Conclusions

- **Verubulin monotherapy at 3.3 mg/m^2 was well tolerated and associated with acceptable toxicity. The most common, potentially related adverse events were fatigue (26%), nausea and constipation (10% each). One patient discontinued the study due to a grade 2 ventricular arrhythmia. Another patient with significant cardiovascular risk factors had a non-fatal myocardial infarction.**
- **Two patients (6.5%) achieved partial response and 6 patients (19.4%) achieved stable disease, as assessed by Macdonald criteria.**
- **One patient (best response of stable disease by Macdonald criteria) had two lesions at baseline (lesion 1: 7.5 mm x 11.4 mm and lesion 2: 6.8 mm x 17.0 mm) and responded to treatment with both lesions becoming undetectable (lesion 1 end of 2 cycles, lesion 2 end of 13 cycles). This subject is continuing to receive verubulin (cycle 14 ongoing).**
- **In responding patients, the median duration of stable disease was 4 months and the median duration of partial response was 6 months.**
- **The median progression-free duration was 1.8 months (range 0.04-13.1). The median overall survival was 9.9 months (range 1.1-17.2).**
- **These results and previous studies in recurrent GBM[8] have provided support for the initiation of a 2-arm comparative phase 2b study of verubulin in newly diagnosed GBM in combination with radiation therapy and temozolomide.**

References

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