Phase II Study of Temozolomide and Everolimus (RAD001) Therapy for Metastatic Melanoma

Purpose of Study:

Primary
- To estimate the 9-week progression free survival rate for patients diagnosed with stage IV malignant melanoma treated with a regimen of everolimus and temozolomide.

Secondary
- Evaluate overall survival (OS) time.
- Evaluate time to disease progression.
- To assess the toxicity profile of the combination of everolimus and temozolomide when used to treat patients with stage IV malignant melanoma.
- To assess clinical benefit rates (i.e., stable disease, partial remission and complete response rates).

Translational
Describe the impact of therapy on parameters of angiogenesis and immunity (systemic and tumor microenvironment).

Study Status/Accrual:

This study was opened on 01/18/2008 and was closed on 10/03/2008 with a final accrual of 49 patients. There was 1 patient deemed ineligible.

The final complete Status Report was produced Spring, 2010.

References:

Abstract: Background: A recently described escape mechanism of melanoma cells exposed to alkylating agents is the production of the pro-survival cytokine vascular endothelial growth factor (VEGF). We hypothesized that the combination of TMZ and RAD001 could provide an additive therapeutic benefit in metastatic melanoma and impact the antitumor immune response due to the effect of both agents on immune cell function. Methods: We conducted a single arm phase II trial of the combination of RAD001 (10 mg/day for 5 of 7 days) and TMZ (200 mg/m² days 1-5 every 28 days) in patients with stage IV unresectable MM. Patients (pts) began therapy with RAD001 1 week before initiation of TMZ (cycle 1 = 5 weeks, other cycles = 4 weeks). Pts previously treated with systemic therapy (excluding study agents) were eligible. Major exclusion criteria were active brain metastases, abnormal liver/renal function,
and poor performance status (PS > 2). The primary end point was 9 week progression free survival (PFS9) rate. With a sample size of 39, the one-stage study design had a significance level of 0.10 and 90% power to test the hypothesis that the true PFS9 rate is at most 35% vs the alternative of at least 55%. Regimen is considered promising if > 17 patients were PFS9 successes. Secondary end points included therapy associated changes of biomarkers of angiogenesis and immunity. Results: The study accrued 49 pts (1 ineligible) from 01/08-10/08 (median age: 60 years [range 28-84]). The most common metastatic sites were lungs (43%) followed by lymph nodes (28%) and liver (20%), with 27% of patients having prior chemotherapy. Of the first 39 evaluable pts, 17 (44%, 95% CI: 28-60%) were PFS9 successes. Overall 4 of 48 (8%) pts achieved a partial response, the median PFS was 2.4 months (95% CI: 2.1-4.0), and the median OS was 8.6 mos (95% CI: 7.1-12.2). Treatment was well tolerated, only 1 pt discontinued therapy due to toxicity (hyperlipidemia). Results of correlative laboratory studies are forthcoming. Conclusions: The combination of TMZ and RAD001 did not appear to offer a therapeutic advantage over TMZ-alone historic controls. Pending biomarker analysis may offer insights into potential combinations of the current regimen with other treatments in advanced melanoma.