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**Scientific Abstract**

Malignant brain tumors are invariably fatal with a very rapid course. Median survival of optimally treated patients (surgical resection, chemoradiation with continuing temozolomide chemotherapy) is 12-15 months and 5-year survival is less than 5%. Most patients will have tumor recurrence within 6 months and there are few options for effective therapy. The objective of the proposed clinical trial is to use a replication conditional HSV expressing the human Interleukin-12 gene to obtain safety information in small numbers of individuals (three to six patients per cohort), with successive cohorts to receive escalating doses of M032. Safety will be assessed at each dose level before proceeding to the next dose. Biologic secondary objectives include characterization of the (i) *in situ* activity of M032 after intratumoral inoculation and (ii) local and systemic immune responses to M032. As a clinical secondary objective, patients will be followed serially by MRI for potential clinical response to M032. The clinical strategy takes advantage of the virus' ability to infect and lyse tumor cells and the potential for enhancement of this effect by the induction of an anti-tumor immune response by IL-12 as well as an antiangiogenic response by this cytokine. Patients with progressive growth of glioblastoma multiforme, anaplastic astrocytoma or gliosarcoma after radiation therapy will be the target population. In this Phase I open-label trial two groups will be enrolled sequentially: Group A: Single dose of M032 infused through catheters into region(s) of tumor defined by MRI; 3-6 patients/dosage level; dosage escalation proceeds only after 14 days of observation, if incidence of Grade III/IV toxicities is acceptable. Dose escalations from  $1 \times 10^5$  to  $3 \times 10^9$  plaque-forming units of M032, a genetically engineered herpes simplex virus type 1 expressing IL-12 will be studied. Group B: Once MTD or maximally planned dose is defined in Group A, we will enroll an additional cohort of patients with 15% of MTD of M032 infused into the tumor, followed 5 to 7 days later by resection with infusion of 85% of MTD into the tumor bed. If DLT is seen *via* this method of administration, further cohorts will be enrolled at dosages that are successively de-escalated by  $\frac{1}{2}$  log until an MTD for this method of administration is reached. Up to 54 patients will be accrued, depending on the follow-up evaluations using routine laboratory analyses and clinical measurements of neurological function and evidence of M032-related toxicity. Studies to evaluate the possibility of M032 shedding will also be conducted. Patients will be observed closely during the planned post-treatment hospitalization period, followed by outpatient evaluations done at one week, then months 1, 3, 6 and 12, subject to disease progression. Study endpoints are as follows: Primary: Highest safe dose/MTD or maximally planned dose if no dose-limiting toxicity observed. Secondary: Time to progression, survival, and assessment of biologic activity.