Proposal for Clinical Investigation

PHASE II STUDY OF ANTINEOPLASTONS A10 AND AS2-1 IN PATIENTS WITH ADVANCED RECURRENT MALIGNANT ASTROCYTOMAS*

N.C.I. Protocol # T93-0078

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* Antineoplaston A10 is NSC 648539; Antineoplaston AS2-1 is NSC 620261

1.0 Protocol Summary - Phase II Study of Antineoplastons A10 and AS2-1 in Patients with Advanced Recurrent Malignant Astrocytomas

1.1 Patient Eligibility - a) Histologically or cytologically confirmed diagnosis of malignant astrocytoma, reviewed at MSKCC, progressed during or recurrent following initial therapy, including radiation therapy. b) PS - Karnofsky 100 to 70%, ECOG 0 to 1; life expectancy $\geq$ 4 months. c) Hgb $\geq$ 10 gm/dL, WBC > 2000, granulocytes > 1500, Plt > 100,000, Creatinine $\leq$ 2.0 mg/dl, bilirubin $\leq$ 2.0 mg/dl. d) Informed consent by a patient who is competent to provide it, or by their legal guardian in case of tumor-induced aphasia. e) Geographic location adequate for follow-up. f) No radiation therapy for at least 8 weeks, no chemotherapy for at least 4 weeks prior to starting the protocol (6 weeks for nitrosoureas). Patients must have recovered from the myelosuppressive effects associated with any prior chemotherapy or radiation therapy. g) $\geq$ 18 years of age. h) Patients with a malignancy other than *in situ* carcinoma of the cervix are excluded. i) Patients with known heart disease of New York Heart Association Class III - IV are excluded, as are patients with any history of congestive heart failure, symptomatic coronary vascular disease (as manifest by a myocardial infarction within the previous year or angina requiring medication), or moderate to severe chronic obstructive pulmonary disease. j) Patients who are pregnant or breast feeding are excluded. k) Patients with tumors > 5 cm in diameter, multifocal tumors, or with leptomeningeal or systemic metastases are excluded. l) Patients must be on a fixed dose of corticosteroids or on no corticosteroids for at least one week prior to the baseline scan. m) No prior or concurrent therapy with antineoplastons, phenylacetic acid or phenylbutyric acid.

1.2 Pretreatment Evaluation - a) Complete history and physical examination, including neurologic examination. b) Height, weight and performance status. c) complete blood count and differential, PT, APTT, biochemical screening profile, creatinine, electrolytes, glucose, blood ammonia, baseline levels of anti-epileptic agents, glutamine, and glutamate in the context of the Pharmacology studies. e) Chest x-ray, PA and lateral. f) EKG. g) baseline contrast-CT and/or MRI scan with gadolinium contrast for known areas of tumor involvement. h) Urinalysis.

1.3 Treatment Plan - Treatment will begin within 7 days of the baseline neuroimaging scan. A double lumen Broviac, Groshung or equivalent catheter will be necessary for treatment. The two Antineoplastons are to be administered through separate lumens. Patients will receive gradually escalating doses of the two antineoplastons by multiple intermittent intravenous injections (twice hourly) using a portable programmable pump. The initial day's dosage will be 0.24 g/kg/day for Antineoplaston A10 and 0.12 g/kg/day for Antineoplaston AS2-1; with each succeeding day there will be an escalation of the dose of Antineoplaston A10 by 0.24 g/kg/day and Antineoplaston AS2-1 by 0.12 g/kg/day, as tolerated, until target doses are reached of 1 gram/kg/day of Antineoplaston A10 and 0.4 grams/kg/day of Antineoplaston AS2-1. For a 70 kg patient the daily dosages would be 70 grams of Antineoplaston A10 and 28 grams of Antineoplaston AS2-1. Since the average drug concentration being administered is 80 mg/ml the projected infusate volume/day is 1225 ml in a 70 kg patient. The length of the programmed individual injections will be 15 minutes. Dose adjustments will be made in the event of toxicity; a detailed schedule is provided in Section 5.2.

The initial week of therapy will be undertaken in the hospital in order to assess the patient's tolerance to therapy, to measure the pharmacokinetic parameters for the intermittent injections, and to train the family in the use of the pump and replacement of the infusion bags. Subsequent administration will be on an Outpatient basis, supported by the Center and visits by nurses from a home infusion support company. Duration of