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Resolution of clinical signs, a complete response, and long-term survival (> 23 Years) in a 3 and ½ month female with a newly diagnosed diffuse intrinsic pontine glioma treated with antineoplastons

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Abstract

Introduction: Diffuse intrinsic pontine glioma (DIPG) is a lethal brain tumor and leading cause of brain tumor–related death in children. Over the past few decades, clinical trials have shown no improvement in outcome. The purpose of this correspondence is to discuss the use of IV and oral Antineoplaston therapy (ANP {A10 + AS2-1}) in the treatment of a 3 and ½ month female with newly-diagnosed DIPG.

Materials and methods: The patient was enrolled as a special exception according to BT-11, a Phase II protocol utilizing IV and oral Antineoplastons A10 and AS2-1 (ANP). Her tumor response to ANP was measured by MRIs of the brain.

Results: At presentation to the Burzynski Clinic (BC), the patient demonstrated prominent Cushingoid features, limited lateral deviation of the left eye and incomplete closure of the left eyelid. There was partial paresis of the left side of the face. There were no long tract signs. The infant's cry was normal as were the protective reflexes of the throat. Motor reflexes were intact, including the grasp and sucking reflexes. Muscle tone was normal and there was no posturing or arching. Babinski was negative bilaterally. Following ANP, the patient achieved resolution of her clinical signs, a complete response (CR) and > 23 years survival.

Conclusions: ANP is an effective treatment for DIPG and for a variety of low- and high-grade brain tumors. Multiple Phase II protocols utilizing ANP have now been completed and its impact on the treatment of brain tumors has been widely published.

Abbreviations: A-10: Antineoplaston; A10 (Atengenal); AE: Adverse event; ANP: Antineoplaston; ANP therapy: A10 (Atengenal) + AS2-1 (Astugenal); AS2-1: Antineoplaston AS2-1 (Astugenal); Astugenal: Antineoplaston AS2-1 (AS2-1); Atengenal: Antineoplaston A10 (A10); BC: Burzynski Clinic; BRI: Burzynski Research Institute; CSF: Cerebral Spinal Fluid; CR: Complete Response; DIPG: Diffuse intrinsic pontine glioma; DMG H3-K27M: Diffuse midline glioma, H3-K27 mutant; FLAIR: Fluid attenuated inversion recovery; FDA: Food and Drug Administration; IV: Intravenous; MRI: Magnetic Resonance Imaging (of the brain); OR: Objective Response; PD: Progressive Disease; PR: Partial Response; RT: Radiation Therapy; SD: Stable Disease; WHO: World Health Organization.

Introduction

Diffuse intrinsic pontine glioma (DIPG) is a malignant pediatric tumor with a median age at diagnosis of 6–7 years. Current treatment options are limited and prognosis is dismal—with less than 10% of patients surviving beyond 2 years from the time of diagnosis [1]. Surgery is not an option, the effects of radiation therapy (RT) are temporary, and no chemotherapeutic agent has demonstrated significant efficacy. Numerous clinical trials of new agents and novel therapeutic approaches have been performed over the course of several decades in efforts to improve the outcome of children with DIPG, but without success. The median survival for children with DIPG is less than one year from diagnosis and no improvement in survival has been realized in more than three decades [2,3].

The diagnosis of DIPG is based on characteristic magnetic resonance imaging (MRI) findings in the face of typical clinical findings such as abnormal or limited eye movements, diplopia, an asymmetric smile, clumsiness, difficulty walking, loss of balance, and weakness. Classic findings on clinical examination include the triad of multiple cranial neuropathies, long tract signs (hyperreflexia, clonus, increased tone, presence of a Babinski reflex), and ataxia.

On MRI, the tumor appears as an expansile brainstem mass. While there may be an exophytic component due to expansion of the tumor via the path of least resistance, the epicenter of a DIPG lies within the pons. DIPGs are hypo- or iso-intense on T1- weighted imaging, hyperintense on T2-weighted imaging, and frequently appear relatively homogeneous

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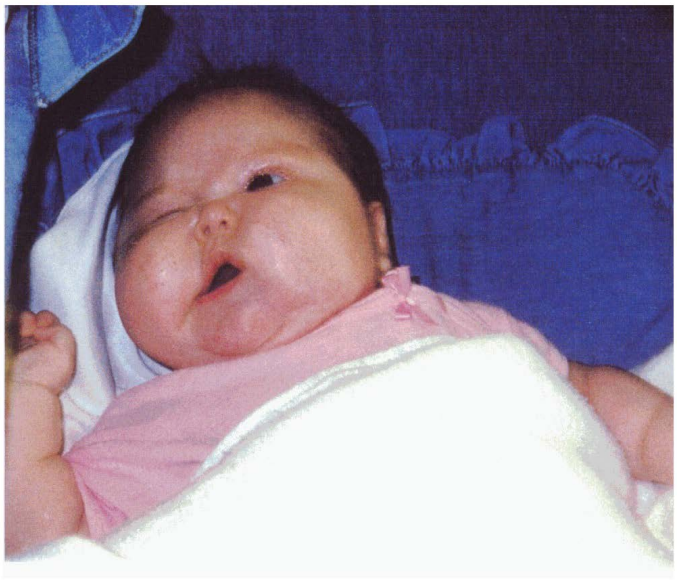

Figure 1. Pre-treatment female patient at ~ 3 and ½ months of age.

on fluid attenuated inversion recovery (FLAIR) sequences. Other MRI features of a typical DIPG include ventral involvement of the pons, and encasement of the basilar artery. Gadolinium contrast-enhancement is variable, but these lesions frequently do not enhance significantly at the time of diagnosis.

The standard of care for children with newly-diagnosed DIPG is focal RT, using a 1 cm margin to cover microscopic disease, to a total dose of 54–60 Gy administered over 6 weeks, usually in daily (Monday– Friday) 180–200 cGy fractions. About 75% of patients will have some improvement in neurological symptoms in response to RT, which appears to control tumor growth for a short period of time, prolonging survival by a mean of ~3 months [4]. Within 3–8 months after completion of RT, most children with DIPG will have clinical or radiographic evidence of disease progression. The pattern of failure is generally local. In one study, 25% of cases with disease progression involved the irradiated volume, while 75% involved the margin of the radiation field [5]. We present the case of a 3½ month old female, with DIPG, who had not received RT or chemotherapy prior to being seen at the Burzynski Clinic (BC).

ANP's mechanism of action differs from that of RT or cytotoxic chemotherapy. Growth of normal cells is controlled by cell cycle progression genes (oncogenes) and by cell cycle arrest genes (tumor suppressor genes). In cancer, alteration of these control genes in malignant cells favors aggressive cell proliferation. Evidence suggests that ANP affects 112 genes in the tumor genome and functions as "molecular switches" which "turn on" tumor-suppressor genes and "turn off" oncogenes [6,7]. Hence, the antineoplastic action of ANP therapy in DIPG involves restoration of cell cycle control, induction of programmed cell death, and interference with cancer cell metabolism and nuclear transport

Materials and methods

This 3½ month old female presented to a pediatrician because of decreased movement of the left eye and partial paresis of the left side of the face and mouth (Figure 1). On August 12, 1998, an MRI of the brain revealed a 3.2 x 2.5 x 4.5 cm mass within the brainstem, involving the pons, medulla, and the midbrain. There was a moderate mass effect on the 4th ventricle, but no hydrocephalus. The tumor was thought to be a brainstem glioma, likely originating in the pons. Surgery, RT, and chemotherapy were not considered viable treatment options because of the location of the tumor and the patient's age. The infant was provided dexamethasone and Mylanta beginning August 15, 1998.

On October 13, 1998, this patient presented to the BC for evaluation. She had a Cushingoid appearance, was in no distress, and was well hydrated, alert, and active, weighing 19 pounds. The pupils were equal and reactive to light. Lateral deviation of the left eye was limited and closure of the left eyelid was incomplete. There was partial paresis of the left side of the face. There were no long tract signs. Babinski was negative bilaterally. Motor reflexes were intact, including the grasp and sucking reflexes. The infant's cry was normal as were the protective reflexes of the throat. Muscle tone was normal and there was no posturing or arching.

On October 14, 1998, this 3 ½ month female was enrolled as a special exception, according to protocol BT-11, for administration of IV ANP. BT-11 was a Phase II study of Antineoplaston 10 (Atengenal) and Antineoplaston AS2-1 (Astugenal) for patients with brainstem gliomas [8]. The protocol was designed to determine an objective response (OR) to ANP therapy. Patients initially received ANP therapy via a subclavian catheter and an infusion pump. Oral ANP therapy was subsequently utilized.

Results and observations

Response to therapy was measured by MRIs with and without gadolinium enhancement. Tumor size was calculated as the product of the two greatest perpendicular diameters as determined by imaging. The response criteria were as follows: a complete response (CR) indicated complete disappearance of all enhancing tumor while a partial response (PR) indicated a > 50% reduction in tumor size. CR and PR required a confirmatory MRI performed at least four weeks after the initial finding. Progressive disease (PD) indicated a > 25 % increase in tumor size while stable disease (SD) did not meet the criteria for PR or PD. All MRIs were reviewed by an outside radiologist. Baseline MRI (October 13, 1988), on coronal images, showed an enhancing lesion measuring 10.73 cm^2 while axial and sagittal images showed a non- enhancing lesion measuring 12.58 cm^2 and a 14.70 cm^2, respectively. The patient was treated with IV ANP therapy per BT-11 [8]. The dosages of A10 and AS2-1 were gradually increased to 9.42 g/kg/d and 0.56 g/kg/d, respectively. While on IV ANP therapy, the patient experienced the following adverse events (AEs), none of which were felt to be due to therapy: diarrhea, hematuria (x2), hyperchloremia, hyperglycemia, hypoglycemia, hypokalemia, urinary tract infection, and vomiting.

On February 22, 1999, the enhancing lesion seen on coronal imaging had disappeared while the non- enhanced axial and sagittal lesion now measured 8.12 cm^2 and 12.04 cm^2, respectively. On April 23, 1999, the enhancing lesion was again not visible, confirming that the patient had achieved a CR. On May 19, 2000, the axial and sagittal projections showed an 80% reduction in the size of the non-enhancing lesion, 2.28 cm^2 and 3.45 cm^2, respectively. Complete disappearance of tumor on the enhanced coronal imaging persisted (Figures 2 and 3). On June 8, 2000, IV ANP therapy was discontinued and the patient began receiving oral ANP therapy. The outside radiologist commented, "Measurement of the unenhanced portion of the mass is difficult given the minimal change in signal associated on the T1 sequences…" He suggested that a PET scan be performed in the future to further quantitate the response. Subsequently, on April 8, 2004, whole body PET scan showed no hypermetabolic uptake in the brain parenchyma, especially the brainstem. The patient's residual non-enhancing mass

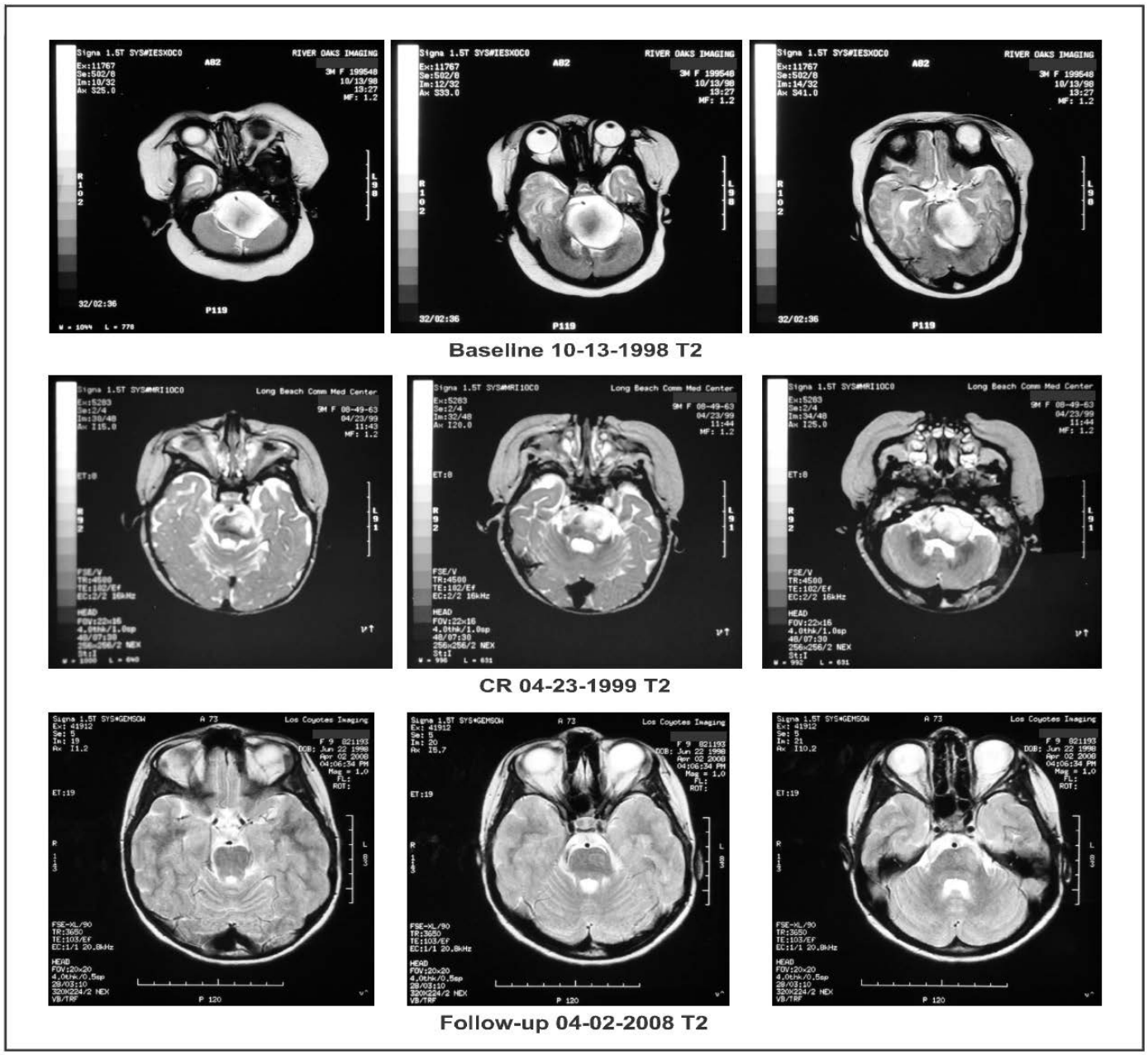

Figure 2. Axial brain magnetic resonance imaging (MRI) weighed in T2: "Baseline" demonstrates a high intensity contrast enhancing mass. "CR" shows a complete response (CR) of the high signal intensity mass following treatment. "Follow-up" shows persistence of the CR.

had resolved. Subsequent MRI performed on April 2, 2008 showed persistence of the CR. The patient was ~5 years of age at the time of her last presentation to the BC on April 7, 2004. She weighed 47.5 lbs. The patient's pupils were equal and reactive to light. The extraocular muscles were intact. There was lateral nystagmus of the right eye. The initial lateral deviation of the left eye, incomplete closure of the left eyelid, and the left-sided facial weakness had cleared. There was minimal weakness of the right-sided extremities and a slightly abnormal gait. As examined by finger-nose-finger and heel-to-shin exercises, the patient's coordination was good. Motor reflexes were intact and equal bilaterally. Babinski was negative bilaterally.

On August 5, 2021, we received an email from the patient who is now 23 years old. She is doing very well, living a fully normal life, and has a four-year old son. Included in the email were photographs of the patient and her son. The patient also provided a signed consent allowing us to utilize her medical information, MRI images, and photographs in a manuscript for publication (Figure 4).

Discussion and conclusions

DIPGs represent 80% of all pediatric brain tumors that occur in the brainstem [9-11] while affecting 200-300 children in the USA every year. MRI has allowed classification of these tumors into distinct subsets of focal, dorsally exophytic, cervicomedullary, or DIPG based

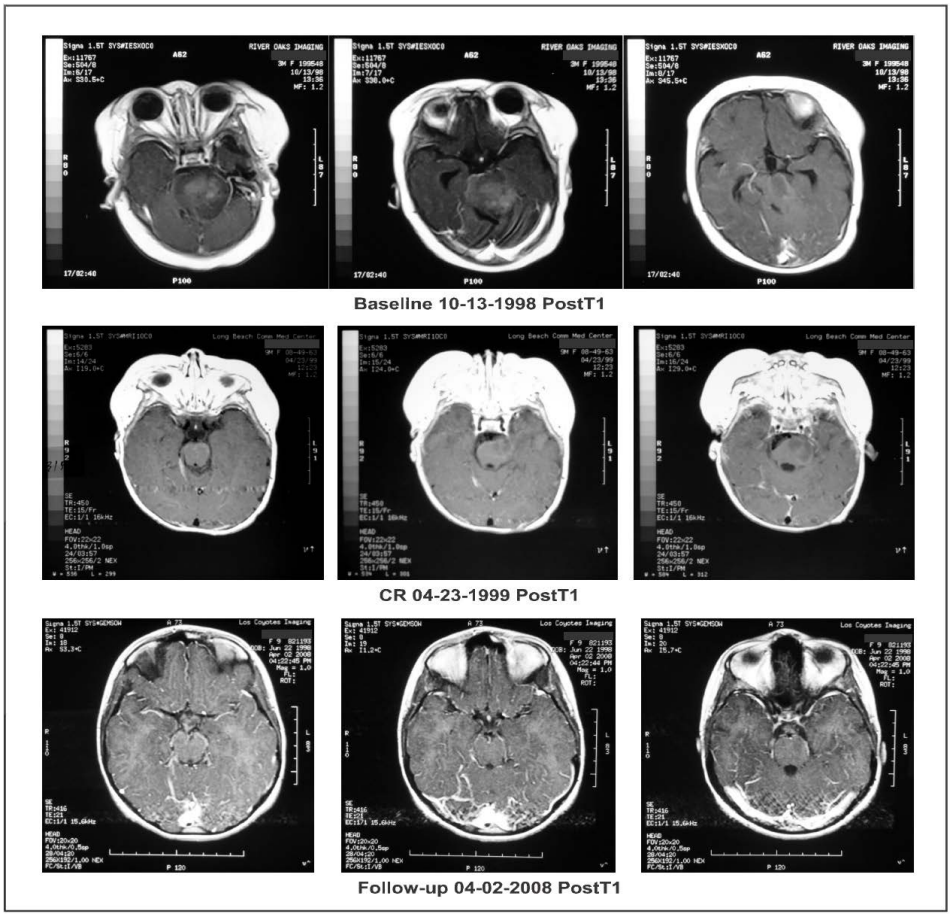

Figure 3. Axial brain magnetic resonance imaging (MRI) post contrast T1: "Baseline" demonstrates a contrast enhancing mass. "CR" shows a resolution of the contrast enhancing mass at a time corresponding with the beginning of complete response (CR). "Follow-up" shows complete resolution of the enhancing and low intensity signal mass.

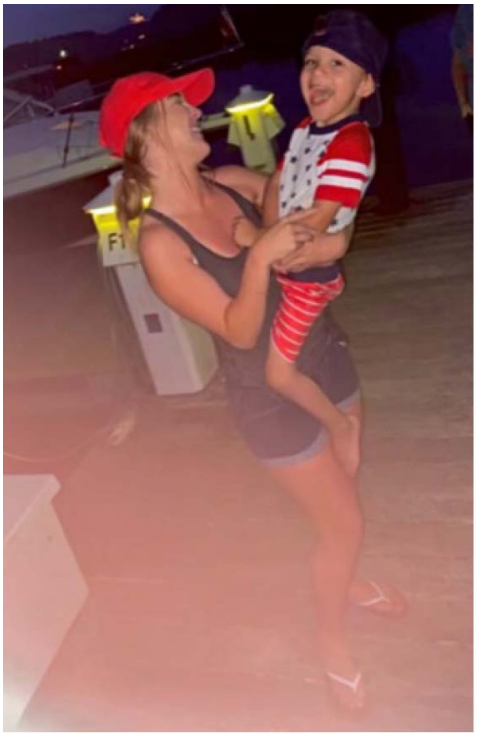

Figure 4. Twenty-three-year-old patient, after ANP therapy, holding her four-year-old son.

on imaging characteristics [9]. The prognosis for children with diffusely infiltrating DIPGs is significantly worse than that of other brainstem tumors.

Histologically, these tumors share features with anaplastic astrocytomas (grade III) or glioblastomas (GBM) (grade IV) [12]. New molecular understanding of pediatric high-grade gliomas has led to the reclassification of DIPG as one member of a family of diffuse gliomas occurring in the midline of the central nervous system that exhibit pathognomonic mutations in genes encoding histone 3 (H3 K27M). Histone H3F3A and HIST1H3B K27M mutations define two subgroups of DIPGs with different prognosis and phenotypes [13,14]. However, DIPG remains a clinically relevant term. Wild-type H3-K27M DIPGs have not yet been separately classified within the revised WHO classification, but show similar survival as mutant H3-K27M DIPGs [15].

Routine biopsy of children with suspected DIPG has been performed in Europe since 2003. [16] In their initial report detailing experience in 24 children, reversible morbidity was described by the investigators in two children (cranial nerve palsy, worsening hemiparesis) with no mortality. It was concluded that the procedure was safe in experienced hands using modern neurosurgical technique. Subsequently, within the pediatric neuro-oncology community, there has been movement toward routine biopsy of patients with suspected DIPG [16,17].

Antineoplaston (ANP) research began in 1967, when significant deficiencies were noticed in the peptide content of the serum of patients with cancer compared with healthy persons. Initially ANPs were isolated from the blood and later from urine [18]. Subsequent studies of the ANPs that were isolated demonstrated that Antineoplaston A10 and Antineoplaston AS2-1 were the most active ANPs. The chemical name of Antineoplaston A10 is 3-phenylacetylamino-2,6-piperidinedione. It consists of the cyclic form of L-glutamine connected by a peptide bond to phenylacetyl residue. When given orally, Antineoplaston A10 resists the attack of gastric enzymes. In the small intestine, under alkaline conditions, 30% is digested into phenylacetylglutamine (PG) and phenylacetylisoglutaminate (isoPG) in a ratio of approximately 4:1. The mixture of synthetic PG and isoPG in a 4:1 ratio, dissolved in sterile water constitutes Antineoplaston A10 IV injection. Further metabolism of Antineoplaston A10 results in phenylacetate (PN). Both metabolites PG and PN have anticancer activity. The mixture of PN and PG in a 4:1 ratio, dissolved in sterile water constitutes Antineoplaston AS2-1 IV injection [19]. The 3½ month female presented here responded to both IV and oral ANP therapy.

In this report, we have presented a 3 1/2 month old female with a newly-diagnosed DIPG, who received ANP therapy, had resolution of her tumor-induced signs and symptoms, has survived for >23 years and maintains a CR. ANP therapy has been utilized in in a variety of low- and high-grade brain tumors under the Burzynski Research Institute's (BRI's) IND # 43,742. Multiple Phase II protocols have been completed and the impact of ANP on the treatment of brain tumors has been widely published [19-51]. In conjunction with the FDA, two additional protocols of ANP therapy in DIPG patients, have been developed, a Phase II protocol and a Phase III protocol (ANP + RT versus RT alone). Both protocols will soon be accruing patients.

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