



A 25-year-female with Diffuse Intrinsic Pontine Glioma Surviving for More than Nine Years Following Treatment with Antineoplastons

Stanislaw Rajmund Burzynski^{1,*}, Gregory Burzynski¹, Tomasz Janicki¹, Samuel Beenken²

¹Medical Division, Burzynski Clinic, Houston, USA

²Oncology Writings, Calera, USA

Email address:

srb@Burzynskiclinic.com (S. R. Burzynski)

*Corresponding author

To cite this article:

Stanislaw Rajmund Burzynski, Gregory Burzynski, Tomasz Janicki, Samuel Beenken. A 25-year-female with Diffuse Intrinsic Pontine Glioma Surviving for More than Nine Years Following Treatment with Antineoplastons. *International Journal of Clinical Oncology and Cancer Research*. Vol. 7, No. 1, 2022, pp. 1-7. doi: 10.11648/j.ijcocr.20220701.11

Received: December 17, 2021; **Accepted:** January 19, 2022; **Published:** February 5, 2022

Abstract: Rationale: 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. Most DIPGs occur in the pediatric population. Adult brainstem gliomas are rare, constitute less than 2% of adult gliomas, and show a slight male predominance. The case of this 25-year-old female is presented to detail and discuss the use of Antineoplastons A10 (Atengenal) and AS2-1 (Astugenal) in the treatment of DIPG that persisted despite radiation therapy (RT) and temozolomide. Objectives: The patient described was treated at the Burzynski Clinic (BC), as a special exception, according to the phase II protocol, BT-09, which utilized Antineoplastons A10 and AS2-1 (ANP therapy) in the treatment of brain tumors. The delivery of ANP therapy was via a subclavian catheter and infusion pump. Tumor response to therapy was measured by sequential magnetic resonance imaging (MRI) of the brain. Overall Survival (OS) and Adverse Events (AES) were also documented. Findings: At her presentation to the BC, the patient complained of diplopia, left-sided weakness, and difficulty walking. On physical exam, she was alert and orientated. Her cranial nerves were intact. There was weakness of the left-sided extremities. Deep tendon reflexes were equal bilaterally with down-going toes bilaterally. Reports of the original brain MRIs in Argentina suggested a DIPG with extension to the medulla and cerebellum. In addition, tumor biopsy confirmed a grade 3 astrocytoma. Following radiation therapy (RT) and temozolomide in Argentina, the patient was treated at BC for persistent disease with ANP therapy. Sequential MRI imaging of the residual tumor, which was non-enhancing, showed no change in size during therapy. However, the patient did achieve resolution of her neurologic signs and symptoms and has survived more than nine years since first being seen at BC. Correspondence with the patient on September 9, 2021 indicated she was feeling fine, had a healthy child, and was enjoying life. Conclusions: We have presented here the case of an adult female with a DIPG who had resolution of signs and symptoms and survived more than nine years after ANP therapy. For patients with DIPG (or other high-grade astrocytoma), who do not qualify for/refuse RT or show persistent or progressive disease following RT and/or chemotherapy, ANP therapy is an effective therapeutic option. In collaboration with the FDA confirmatory Phase II and Phase III studies have been developed.

Keywords: Brain Tumor, Diffuse Intrinsic Brainstem Glioma, H3-K27M Diffuse Midline Glioma, Antineoplastons, Phase II and III Studies

1. Introduction

Magnetic resonance imaging (MRI) of the brain has permitted the classification of brainstem gliomas into five

categories: focal, exophytic, cervicomedullary, midbrain, and diffuse intrinsic pontine glioma (DIPG) [1]. DIPG is the most common brainstem tumor in children, representing 75–80% of pediatric brainstem tumors, and affecting an estimated 300

children in the United States each year.

When compared to other brainstem tumors, the prognosis for children with DIPG is significantly worse. Because, the pons contains cranial nerve nuclei and other important nuclei, which are vitally important for life, damage to these nuclei by treatment can have life-threatening consequences. Therefore, surgical resection is not an option. Unfortunately, over the past few decades, clinical trials involving a variety of treatments for this tumor have shown no improvement in its outcome.

DIPG is generally a disease of childhood, with the majority of children being diagnosed between 5 and 10 years of age. However, adults can also be affected. Brainstem dysfunction can produce a variety of symptoms including cranial neuropathies (abnormal eye movements, diplopia, facial asymmetry, hearing loss), ataxia (clumsiness, difficulty walking, loss of balance), and long tract signs (hyperreflexia, clonus, increased muscle tone, presence of a Babinski reflex). Obstructive hydrocephalus can produce irritability, nausea and/or vomiting, headache, seizures, and personality/cognitive changes.

Adult brainstem glioma (patient age more than 21 years) constitutes only 2% of adult gliomas, with a slight male predominance [2, 3]. Median age at diagnosis is in the mid-30s, although brainstem gliomas can present in any decade of life. We have previously reviewed this clinical entity [4]. The radiographic appearance of adult brainstem glioma varies widely, with only 40% showing enhancement [2, 5]. Pediatric DIPG has a prognosis of ~10 months and only 10% of patients live more than two years after diagnosis. By comparison, the median survival for adult patients with a brainstem glioma is 30–40 months [6].

In adults, it is clinically important to distinguish between gliomas that involve the midbrain tectum – which often behave indolently – and DIPG, which often does not enhance, as was the case for the patient presented here, and has a much worse prognosis [7].

Due to its anatomical location, diagnostic biopsies of brainstem gliomas are difficult to obtain. Diagnosis is frequently based on brain MRI alone. However, routine biopsy of patients with suspected DIPG has been performed in Europe since 2003 [8]. In a report detailing their experience in 24 children, morbidity was reported in 2 children (cranial nerve palsy, worsening hemiparesis) and was reversible. There was no mortality. The investigators concluded that the procedure was relatively safe in experienced hands using modern neurosurgical techniques [8]. Given this demonstration of relative safety, there is a movement within the pediatric neuro-oncology community toward routine biopsy of patients with suspected DIPG [9].

Genomic studies have identified chromosomal aberrations in DIPG, such as PDGFRA, MDM4, MYCN, EGFR, MET, KRAS, CDK4, and histone H3.3. These chromosomal aberrations involve genes that regulate cell growth, cell death, and cellular repair pathways [10–17].

Histone 3 (H3) K27-mutant (K27M) diffuse midline glioma (DMG) was recognized in 2016 by the World Health

Organization (WHO) as a distinct category of high-grade glioma [18]. DMGs most commonly form in the brainstem, thalamus, spinal cord, and cerebellum. Most DIPGs belong to the WHO classification of H3 K27M DMGs. Wild-type H3 K27 DIPGs, while not being separately designated within this WHO classification, show a similar survival to that of H3-K27M DIPGs [19, 20]. By comparison, ~20% of pediatric glioblastomas are H3 K27M DMGs.

For children three years of age or older with newly diagnosed DIPG, the standard of care is conventional radiation therapy (RT) administered at a dosage of 54–60 Gray, treating the visible tumor and a 1 cm margin around the visible tumor to cover non-visible disease. This total dosage is given in daily 180–200 centi-gray fractions (Monday–Friday), over six weeks. To reduce the edema associated with a DIPG, which is exacerbated by RT, glucocorticoids are administered. In response to RT and steroids, ~75% of children with DIPG will show some improvement in their symptoms. RT prolongs survival for these children by ~3 months [21].

Within 3–8 months after completion of RT, most children with DIPG will have clinical or radiographic evidence of progressive disease (PD). The pattern of failure is generally local. In one study, 25% of cases with PD involved the irradiated tissues while 75% occurred outside the radiation field [22]. Additional therapies for DIPG are not effective and invariably, progressive neurologic deterioration occurs. At some point, many children with DIPG receive adjuvant chemotherapy in an attempt to prevent or treat PD. However, for DIPG, no significant improvement in outcome has ever resulted from the use of chemotherapy.

In adults with DIPG, increasing tumor grade is associated with significantly reduced survival. An analysis of 17 adults with DIPG demonstrated a median OS of 57 months for low-grade vs. 16 months for high-grade gliomas [23]. An M. D. Anderson Cancer Center retrospective analysis of adult brainstem glioma patients demonstrated a median OS of 77.0 months for WHO grade 2 diffuse astrocytoma, 21.1 months for WHO grade 3 anaplastic astrocytoma, and 14.8 months for glioblastoma [5].

The case presented here involves a 25-year-old female who had received RT and chemotherapy prior to being seen at the Burzynski clinic (BC) where she received Antineoplastons A10 and AS2-1 (ANP therapy) and has survived for more than nine years, having no signs or symptoms of disease.

2. Methods

Antineoplon 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 Antineoplastons were isolated from the blood and later from urine [24]. Subsequent studies of the isolated Antineoplastons demonstrated that Antineoplon A10 (Atengenal) and Antineoplon AS2-1 (Astugenal) were the most active Antineoplastons. The chemical name of

Antineoplaston A10 is 3-phenylacetyl-amino-2,6-piperidinedione. It consists of the cyclic form of L-glutamine connected by a peptide bond to a phenylacetyl residue. 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 [25].

Protocol BT-09, a “Phase II Study of Antineoplastons A10 and AS2-1 in Patients with Brain Tumors”, was designed for different types of primary brain tumors in adults that were not curable by standard treatment [26]. It was a single arm, two-stage, phase II trial of ANP therapy as treatment in this high-risk, poor-prognosis population. Recruited patients were over 18 years of age with radiologic evidence of residual, recurrent or progressive tumor by brain MRI.

In protocol BT-09, response to ANP therapy was measured by serial brain MRIs. Tumor size was calculated as the product of the two greatest perpendicular diameters as determined by imaging. The response criteria were as follows: a CR indicated complete disappearance of all enhancing tumor while a partial response (PR) indicated a 50% or greater reduction in enhancing tumor size. CR and PR required a confirmatory brain MRI performed at least four weeks after the initial finding. PD indicated a 25% or greater increase in enhancing tumor size, or new enhancing disease, while stable disease (SD) did not meet the criteria for PR or PD. [27] All brain MRIs were reviewed by a prominent outside radiologist.

The patient presented here was originally seen in February 2011, at an institution in Argentina, because of left leg and arm discoordination and diplopia. MRI of the brain performed in March 2011, showed a pontine tumor with extension to the medulla and cerebellar vermis. On April 4, 2011, stereotactic biopsy of a non-enhancing mass in the vermis was performed. Findings confirmed a diffuse brainstem glioma. This biopsy, which was subsequently interpreted as showing an infiltrating astrocytoma (see below), and the rapid progression of disease confirmed a grade 3 astrocytoma. The tumor was MGMT methylated. H3 K27M status was not obtained as that technology was not yet available.

A glioblastoma treatment protocol was instituted in Argentina with the patient receiving RT for six weeks, to a total dose of 62 Gray, and daily temozolomide at 75 mg/m² daily during the period of RT. This was to be followed by two cycles of adjuvant temozolomide, but the patient could not tolerate the side effects.

With persistence of the patient’s tumor on brain MRI, in November 2011, the patient elected to be seen in consultation at M. D. Anderson Cancer Center where the microscopic slides from the April 4, 2011 biopsy were reviewed. They were reported to show an infiltrating grade 3 astrocytoma. The patient was offered additional temozolomide plus Accutane but refused.

On January 19, 2012, this 25-year-old female was seen at the BC for treatment of persistent left-sided discoordination, diplopia, and a persistent tumor by brain MRI. On physical exam the patient was alert and orientated. Her cranial nerves were intact, but she complained of intermittent diplopia. There was weakness of the left-sided extremities, with left arm weakness being greater than left leg weakness. Deep tendon reflexes were normal bilaterally, with down going toes. There was end point hesitancy on finger-nose-finger testing of the left hand. On January 20, 2012, baseline brain MRI (see Figure 1) showed a persistent low-intensity signal tumor, which was non-enhancing. It extended locally to involve the middle cerebellar peduncle as well as the cerebellar vermis. It measured 1.80 cm X 1.10 cm=1.98cm². The patient was felt to be a good candidate for treatment according to protocol BT-09 even though the study had been closed to accrual. Special exemption status was sought and obtained.

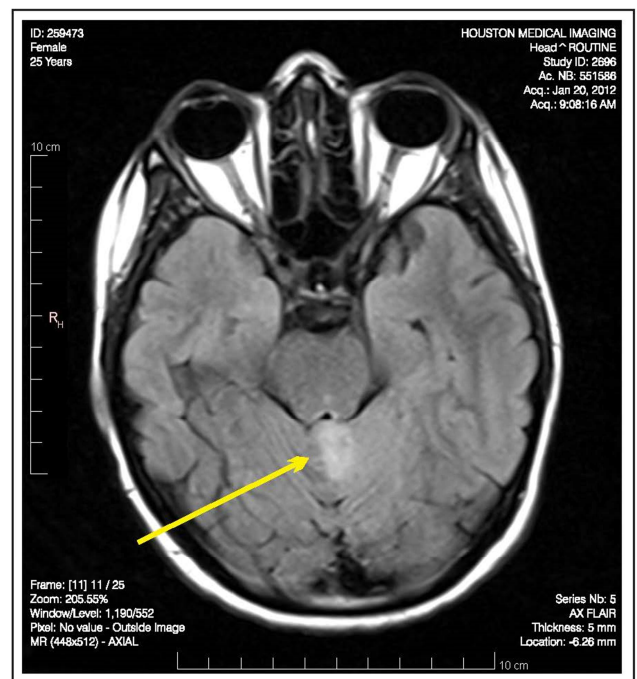


Figure 1. Baseline MRI at the Burzynski Clinic (January 20, 2012): Axial FLAIR MRI image at the level of the cerebellar vermis showing residual low-intensity signal tumor after treatment of DIPG with RT and temozolomide. The corresponding T1-weighted image did not show enhancement. FLAIR=fluid attenuated inversion recovery; MRI=Magnetic Resonance Imaging; DIPG=Diffuse Intrinsic Pontine Glioma; RT=Radiation Therapy.

The patient began ANP therapy on February 3, 2012. As per protocol BT-09, it was delivered via a subclavian catheter and a programmable infusion pump. The dose of ANP therapy was increased until the maximum tolerated dose was achieved. The maximum tolerated dosage of Antineoplaston A10 was 10.07 g/kg/d while the maximum tolerated dosage of Antineoplaston AS2-1 was 0.36 g/kg/d. The patient was maintained on ANP therapy until June 22, 2013. During her time of treatment, the cerebellar lesion did not change on

sequential brain MRIs, but the patient's signs and symptoms cleared. The last follow-up with the patient was on September 9, 2021. She was feeling fine, had no evidence of persistent disease, had a healthy child, and was enjoying life (see Figure 2). The patient gave written permission for use of the figures shown.



Figure 2. Patient with DIPG: Asymptomatic for more than nine years after resolution of clinical sign/symptoms and achievement of a PR following ANP therapy at the BC. DIPG=Diffuse Intrinsic Pontine Glioma; PR=Partial Response; ANP therapy=Antineoplastons A10 and AS2-1; BC=Burzynski Clinic.

The patient tolerated ANP therapy well, experiencing three Adverse Events (AEs), which may have been related to ANP therapy.

3. Discussion

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. ANP therapy's mechanism of action differs from that of RT or cytotoxic chemotherapy. 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. [28, 29] 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.

Dr. S. R. Burzynski developed the Phase II protocol BT-3, "Therapy of Primary Brain Tumors with Antineoplaston A10 and Antineoplaston AS2-1" in 1988 following completion of Phase I studies of A10 and AS2-1. The effectiveness and toxicity of Antineoplastons in the treatment of patients with primary brain tumors were the primary objectives of this protocol. BT-3 led to additional Phase II clinical studies, which involved continuous infusions of higher doses of A10 and AS2-1 utilizing ambulatory infusion pumps, as was the case for protocol BT-09 [26].

Seven brain tumor cases from Phase I and II studies (including BT-3) were reviewed on October 4, 1991 by three

members of the NIH Cancer Therapy Evaluation Program, an invited neuropathologist, and an invited neuroradiologist. Five definite or "possible" complete responses (CRs) were identified [30].

The diagnosis of DIPG is based on characteristic MRI findings combined with a clinical presentation consistent with that which has been described above. On brain MRI, a DIPG appears as an expansible mass intrinsic to the pons as opposed to an extrinsic mass compressing the pons. The epicenter of a DIPG lies within the pons and the lesion typically involves 50% or more of the pons. However, there may also be an exophytic component as the DIPG expands along the path of least resistance. Tumors involving less than 50% of the pons, including exophytic tumors arising in the pons, are classified as DIPG if biopsy of the enhancing lesion reveals anaplastic glioma or glioblastoma histology. In the case presented here, tissue from a stereotaxic biopsy obtained on April 4, 2011 was later interpreted at M. D. Anderson Cancer Center as an infiltrating astrocytoma, consistent with the previous diagnosis of a diffuse brainstem glioma.

DIPGs are usually confined to the brainstem at the time of initial diagnosis and subsequently spread in a contiguous fashion. At the time of local disease relapse, metastasis via the subarachnoid space can occur in up to 30% of cases. In the case presented here, contiguous spread was to the medulla and to the cerebellum.

DIPGs are hypo- or iso-intense on T1- weighted imaging, hyperintense on T2-weighted imaging, and frequently appear relatively homogeneous on fluid attenuated inversion recovery (FLAIR) sequences. Gadolinium enhancement can be seen in T1-weighted images. However, contrast-enhancement is quite variable. Other MRI features of a DIPG include ventral involvement of the pons, and encasement of the basilar artery.

The variable contrast enhancement seen in DIPG becomes problematic when determining an OR in DIPG, since a reduction in enhancement is the diagnostic criteria commonly used for brain tumors [26]. In the case presented here, there was no enhancement. Therefore, in the Phase II and Phase III studies of DIPG developed in collaboration with the FDA (see below), the use of Overall Survival (OS) as an endpoint allows an alternate method for determining optimal therapy.

A review was conducted of 168 DIPG patients treated at BC in six different Phase II protocols under IND # 43,742. Based on the results of this review, we collaborated with the FDA to develop BRI-BT-52, "A Randomized Phase 3 Study of Combination Antineoplaston Therapy [Antineoplastons A10 (Atengenal) and AS2-1 (Astugenal)] Plus Radiation Therapy vs. Radiation Therapy Only in Subjects with Newly Diagnosed Diffuse, Intrinsic Brainstem Glioma" and BRI-BT-55, "A Phase 2 Study of Atengenal (A10) and Astugenal (AS2-1) in Diffuse, Intrinsic, Brainstem Glioma (DIPG)". Both protocols have received IRB approval and will be opened for patient accrual at multiple institutions. The Phase 2 protocol contains sub-group analyses for DIPGs occurring in adults.

4. Conclusion

Under the Burzynski Research Institute's (BRI's) IND # 43,742, multiple Phase II clinical studies of ANP therapy in low- and high-grade brain tumors have been completed and numerous articles have been published [31-64]. We have presented here the case of a 25-year-old female who experienced resolution of signs and symptoms of disease and more than nine years' survival following ANP therapy for persistent tumor after RT plus temozolomide for DIPG. For patients with a DIPG (or other high-grade astrocytoma), who do not qualify for/refuse RT or show persistent or progressive disease following RT and/or chemotherapy, ANP therapy is an effective therapeutic option. In collaboration with the FDA confirmatory Phase II and Phase III studies have been developed.

Acknowledgements

The authors express their appreciation to Carolyn Powers for preparation of the manuscript and to Ramiro Rivera, Mohamed Khan, Jennifer Pineda and Adam Golunski for their involvement.

References

- [1] Epstein F, Farmer JP. (1993) Brain-stem glioma growth patterns. *J. Neurosurg*, 78, 408–412.
- [2] Wu G, Broniscer A, McEachron TA, Lu C, Paugh BS, Becksfort J, et al. (2012) Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet*, 44 (3), 251–3. doi: 10.1038/ng.1102.
- [3] Salmaggi A, Fariselli L, Milanese I, Lamperti E, Silvani A, Bizzi A, et al. (2008) Natural history and management of brainstem gliomas in adults. A retrospective Italian study. *J Neurol*, 255 (2), 171–7. doi: 10.1007/s00415-008-0589-0.
- [4] Burzynski, SR, Janicki, T, Burzynski, GS, Beenken, S. (2021) Long-term survival (27.7 years) following IV Antineoplaston Therapy (ANP) in a 36-year-old-female with a progressive diffuse intrinsic pontine glioma (DIPG). *Int J Radiol Imaging Technol*, 7, 073-078. doi: 10.23937/2572-3235.1510073.
- [5] Theeler BJ, Ellezam B, Melguizo-Gavilanes I, de Groot JF, Mahajan A, Aldape KD, et al. (2015) Adult brainstem gliomas: correlation of clinical and molecular features. *J Neurol Sci*, 353 (1–2): 92–7. doi: 10.1016/j.jns.2015.04.014.
- [6] Kesari S, Kim RS, Markos V, et al. (2008) Prognostic factors in adult brainstem gliomas: A multicenter retrospective analysis of 101 cases. *J Neurooncol*, 88 (2), 175-183. doi: 10.1007/s11060-1.008-9545-1.
- [7] Hu J, Western S, Kesari S. Brainstem glioma in adults. (2016) *Front Oncol*, 6, 180. doi: 10.3389/fonc.2016.00180.
- [8] Roujeau T, Machado G, Garnett M, et al. (2007) Stereotactic biopsy of diffuse pontine lesions in children. *J Neurosurg*, 107, 1–4. doi: 10.3171/PED-07/07/001.
- [9] Cage TA, Samagh SP, Mueller S, Nicolaides T, Haas-Kogan D, Prados M, Banerjee A, Auguste KI, Childs NG. (2013) Feasibility, safety, and indications for surgical biopsy of intrinsic brainstem tumors in children. *Nerv Syst*, 29 (8), 1313-9. doi: 10.1007/s00381-013-2101-0.
- [10] Paugh B, Qu C, Jones C, Liu Z, Adamowicz-Brice M, Zhang J, et al. (2010) Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. *J Clin Oncol*, 28, 3061–3068.
- [11] Paugh B, Broniscer A, Qu C, Miller C, Zhang J, Tatevossian R, et al. (2011) Genome-wide analyses identify recurrent amplifications of receptor tyrosine kinases and cell-cycle regulatory genes in diffuse intrinsic pontine glioma. *J Clin Oncol*, 29, 3999–4006.
- [12] Zarghooni M, Bartels U, Lee E, Buczkowicz P, Morrison A, Huang A, et al. (2010) Whole-genome profiling of pediatric diffuse intrinsic pontine gliomas highlights platelet-derived growth factor receptor α and poly (ADP-ribose) polymerase as potential therapeutic targets. *J Clin Oncol*, 28, 1337–1344.
- [13] Barrow J, Adamowicz-Brice M, Cartmill M, Macarthur D, Lowe J, Robson K, et al. (2011) Homozygous loss of ADAM3A revealed by genome-wide analysis of pediatric high-grade glioma and diffuse intrinsic pontine gliomas. *Neuro Oncol*, 13, 212–222.
- [14] Warren K, Killian K, Suuriniemi M, Wang Y, Quezado M, Meltzer P. (2011) Genomic aberrations in pediatric diffuse intrinsic pontine gliomas. *Neuro Oncol*, 14, 326–332.
- [15] Grill J, Puget S, Andreiulo F, Philippe C, Macconail L, Kieran M. (2012) Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. *Pediatr Blood Cancer*, 58, 489–491.
- [16] Li G, Mitra S, Monje M, Henrich K, Bangs C, Nitta R, et al. (2012) Expression of epidermal growth factor variant III (EGFRvIII) in pediatric diffuse intrinsic pontine gliomas. *J Neurooncol*, 108, 395–402.
- [17] Wu G, Broniscer A, McEachron TA, et al. (2012) Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. *Nat Genet*, 44 (3), 251-3.
- [18] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*, 131, 803–20.
- [19] Castel D, Philippe C, Calmon R, et al. (2015) Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. *Acta Neuropathol*, 130 (6), 815–827. doi: 10.1007/s00401-015-1478-0.
- [20] von Bueren AO, Karremann M, Gielen GH, et al. (2018) A suggestion to introduce the diagnosis of “diffuse midline glioma of the pons, H3 K27 wildtype (WHO grade IV)”. *Acta Neuropathol*, 36 (1), 171–173. doi: 10.1007/s00401-018-1863-6.
- [21] Haas-Kogan D, Banerjee A, Poussaint T, Kocak M, Prados M, Geyer J, et al. (2018) Phase II trial of tipifarnib and radiation in children with newly diagnosed diffuse intrinsic pontine gliomas. *Neuro Oncol*, 13 (3), 298-306.
- [22] Grigsby P, Garcia D, Ghiselli R. (1989) Analysis of autopsy findings in patients treated with irradiation for thalamic and brain stem tumors. *Am J Clin Oncol*, 12, 255–258.

- [23] Reyes-Botero G, Laigle-Donadey F, Mokhtari K, Martin-Duverneuil N, Delattre JY. (2014) Temozolomide after radiotherapy in recurrent “low grade” diffuse brainstem glioma in adults. *J Neurooncol*, 120 (3), 581–6.10.1007/s11060-014-1589-9.
- [24] Burzynski SR. (1976) Antineoplastons: Biochemical defense against cancer. *Physiol Chem Phys*, 8, 275-279.
- [25] Burzynski SR. (1986) Synthetic antineoplastons and analogs: Drugs of the future, 11, 679-688. Reyes-Botero G, Laigle-Donadey F, Mokhtari K, Martin-Duverneuil N, Delattre JY. (2014) Temozolomide after radiotherapy in recurrent “low grade” diffuse brainstem glioma in adults. *J Neurooncol*. 120 (3), 581–6.10.1007/s11060-014-1589-9.
- [26] Burzynski SR, Janicki T, Burzynski G. (2015) A phase II study of Antineoplastons A10 and AS2-1 in adult patients with primary brain tumors: Final report (Protocol BT-09), *J Cancer Ther*, 6, 1063-1074. doi.org/10.4236/jct.2015.612116.
- [27] Wen, PK, Macdonald DR, Reardon DA, et al. (2010) Updated response criteria for high-grade gliomas: Response Assessment in Neuro-Oncology (RANO) working group. *J Clin Oncol*, 28 (11), 1963-1972.
- [28] Burzynski SR, Patil S. (2014) The effect of Antineoplastons A10 and AS2-1 and metabolites of sodium phenylbutyrate on gene expression in glioblastoma multiforme. *J Cancer Ther*, 5, 929-945.
- [29] Hawkins MG, Friedman MA. (1992) National Cancer Institute’s evaluation of unconventional cancer treatments. *J Natl Cancer Inst*, 84, 1699-1702.
- [30] Burzynski SR, Janicki T, Burzynski G. (2015) Comprehensive genomic profiling of recurrent classic glioblastoma in a patient surviving eleven years following antineoplastic therapy. *Cancer Clin Oncol*, 4 (2), 41-52.
- [31] Burzynski SR, Conde AB, Peters A, Saling B, Ellithorpe R, Daugherty JP, Nacht CH. (1999) A Retrospective Study of Antineoplastons A10 and AS2-1 in Primary Brain Tumors. *Clin Drug Invest*, 18, 1-10.
- [32] Burzynski SR, Weaver RA, Bestak M, Lewy RI, Janicki TJ, Jurida G, Paszkowiak JK, Szymkowski BG, Khan MI. (2003) Phase II study of Antineoplastons A10 and AS2-1 (ANP) in children with recurrent and progressive multicentric glioma: A preliminary report. *Neuro Oncol*, 5, 358.
- [33] Burzynski SR, Lewy RI, Weaver R, Janicki T, Jurida G, Khan M, Larisma CB, Paszkowiak J, Szymkowski B. (2004) Long-term survival and complete response of a patient with recurrent diffuse intrinsic brain stem glioblastoma multiforme. *Integ Cancer Ther*, 3, 257-261. doi: 10.1177/1534735404267748.
- [34] Burzynski SR, Weaver R, Lewy R, Janicki T, Jurida G, Szymkowski B, Khan M, Bestak M. (2004) Phase II study of antineoplastic A10 and AS2-1 in children with recurrent and progressive multicentric glioma: A preliminary report. *Drugs R&D*, 5 (6), 315-326.
- [35] Burzynski SR, Weaver R, Bestak M, Janicki T, Jurida G., Szymkowski B, Khan M, Dolgoplov V. (2004) Phase II studies of antineoplastons A10 and AS2-1 (ANP) in children with atypical teratoid/rhabdoid tumors (AT/RT) of the central nervous system: A preliminary report. *Neuro Oncol*, 6, 427.
- [36] Burzynski SR, Weaver R, Bestak M, Janicki T, Szymkowski B, Jurida G, Khan M, Dolgoplov V. (2004) Treatment of primitive neuroectodermal tumors (PNET) with antineoplastons A10 and AS2-1 (ANP): Preliminary results of phase II studies. *Neuro Oncol* 6, 428.
- [37] Burzynski SR, Weaver RA, Janicki T, Szymkowski B, Jurida G, Khan M, Dolgoplov V. (2005) Long-term survival of high-risk pediatric patients with primitive neuroectodermal tumors treated with Antineoplastons A10 and AS2-1. *Integ Cancer Ther*, 4 (2); 168-177. doi: 10.1177/1534735404267748.
- [38] Burzynski SR. (2006) Targeted Therapy for Brain Tumors. In: Yang AV, editor. *Brain Cancer Therapy and Surgical Interventions*. Nova Science Publishers, Inc, New York.
- [39] Burzynski SR, Janicki TJ, Weaver RA, Burzynski B. (2006) Targeted therapy with Antineoplastons A10 and AS2-1 of high grade, recurrent, and progressive brainstem glioma. *Integ Cancer Ther*, 5 (1), 40-47. doi: 10.1177/1534735405285380.
- [40] Burzynski SR. (2006) Treatments for astrocytic tumors in children: Current and emerging strategies. *Ped Drugs*, 8, 167-168. doi.org/10.2165/00148581-200608030-00003.
- [41] Burzynski SR. (2007) Recent clinical trials in diffuse intrinsic brainstem glioma. *Cancer Ther*, 5, 379- 390.
- [42] Burzynski S, Janicki T, Burzynski G, Marszalek A. (2014) Long-term survival (>13 years) in a child with recurrent diffuse pontine glioma: A case report. *J Ped Hematol Oncol*, 36: 433-439. doi: 10.1097/MPH.0000000000000020
- [43] Burzynski SR, Janicki TJ, Burzynski GS, Marszalek A. (2014) A phase II study of antineoplastons A10 and AS2-1 in children with high-grade glioma: Final report (Protocol BT-06) and review of recent trials. *J Cancer Ther*, 5, 565-577. doi.org/10.4236/jct.2014.56065.
- [44] Burzynski SR, Janicki TJ, Burzynski GS. (2014) A phase II study of antineoplastons A10 and AS2-1 in adult patients with recurrent glioblastoma multiforme: Final report (Protocol BT-21). *J Cancer Ther*, 5, 946-956. doi.org/10.4236/jct.2014.510100.
- [45] Burzynski SR, Burzynski GS, Janicki TJ. (2014) Recurrent glioblastoma multiforme: A strategy for long-term survival. *J Cancer Ther*, 5, 957-976. doi.org/10.4236/jct.2014.510101.
- [46] Burzynski SR, Janicki TJ, Burzynski GS, Marszalek A, Brookman S. (2014) A phase II study of antineoplastons A10 and AS2-1 in children with recurrent, refractory or progressive primary brain tumors: Final report (Protocol BT-22). *J Cancer Ther*, 5, 977-988. doi.org/10.4236/jct.2014.510102.
- [47] Burzynski SR, Janicki TJ, Burzynski GS, Brookman S. (2014) Preliminary findings on the use of targeted therapy with pazopanib and other agents in combination with sodium phenylbutyrate in the treatment of glioblastoma multiforme. *J Cancer Ther*, 5, 1423-1437.
- [48] Burzynski GS, Janicki TJ, Marszalek A. (2014) Long-term survival (>20 years) of a child with brainstem glioma treated with antineoplastons A10 and AS2-1: A case report. *Neuro Oncol*, 11, 16.
- [49] Burzynski SR, Janicki TJ, Burzynski GS, Marszalek. (2014) The response and survival of children with recurrent diffuse intrinsic pontine glioma based on phase II study of antineoplastons A10 and AS2-1 in patients with brainstem glioma. *Childs Nerv Syst*, 30; 2051-2061. doi.org/10.1007/s00381- 014-2401-z.

- [50] Burzynski SR, Burzynski G, Janicki J, Marszalek A. (2015) Complete response and Long-term survival (>20 years) of a child with tectal glioma: A case report. *Pediatr Neurosurg*, 50, 99-103. doi: 10.1159/000369907.
- [51] Burzynski SR, Janicki TJ, Burzynski G. (2015) A phase II study of Antineoplastons A10 and AS2-1 injections in adult patients with recurrent anaplastic astrocytoma: Final report (Protocol BT-15). *Cancer Clin Oncol*, 442, 13-23.
- [52] Burzynski SR, Janicki TJ, Burzynski GS, Marszalek A. (2015) A Phase II Study of Antineoplastons A10 and AS2-1 in adult patients with newly-diagnosed anaplastic astrocytoma: Final report (Protocol BT-08). *Cancer Clin Oncol*, 4, 28-38.
- [53] Burzynski SR, Burzynski GS, Marszalek A, Janicki J, Martinez-Canca J. (2015) Long-term survival (over 20 years), complete response and normal childhood development in medulloblastoma treated with Antineoplastons A10 and AS2-1. *J Neurol Stroke*, 2 (3), 00054.
- [54] Burzynski SR, Burzynski GS, Marszalek A, Janicki TJ, Martinez-Canca JF. (2015) Long-term survival over 21 years and pathologically confirmed complete response in pediatric anaplastic astrocytoma: A case report. *J Neurol Stroke*, 2 (6), 00072.
- [55] Burzynski SR, Burzynski GS, Brookman S. (2015) A case of sustained objective response of recurrent/progressive diffuse intrinsic pontine glioma with phenylbutyrate and targeted agents. *J Cancer Ther*, 6, 40-44. doi: 10.4236/jct.2015.61006.
- [56] Burzynski SR, Janicki T, Burzynski G, Marszalek A. (2015) A phase II study of antineoplastons A10 and AS2-1 in patients with brainstem gliomas: The report on non-diffuse intrinsic pontine glioma (Protocol BT-11). *J Cancer Ther*, 6, 334-344. doi: 10.4236/jct.2017.82015.
- [57] Burzynski SR, Janicki TJ, Burzynski GS. (2016) Primary CNS tumors and leptomeningeal, disseminated and/or multicentric disease in children treated in Phase II studies with Antineoplastons A10 and AS2-1. *Cancer Clin Oncol*, 5 (2), 38-48.
- [58] Burzynski SR, Janicki TJ, Burzynski GS. (2016) A phase II study of antineoplastons A10 and AS2-1 in children with low-grade astrocytomas: Final report (Protocol BT-13). *J Cancer Ther*, 7 (12): 837-850.
- [59] Burzynski SR, Janicki TJ, Burzynski GS. (2017) Antineoplastons A10 and AS2-1 in the treatment of children with optic pathway glioma: Final report for protocol BT-23. *Cancer Clin Oncol*, 6 (1), 25-35.
- [60] Burzynski SR, Janicki TJ, Burzynski GS, Marszalek A. (2017) A phase II study of Antineoplastons A10 and AS2-1 in children with brain tumors: Final report (Protocol BT-10). *J Cancer Ther*, 8, 173-187.
- [61] Burzynski SR, Janicki T, Beenken S. (2019) Treatment of recurrent glioblastoma multiforme (rGBM) with Antineoplastron AS2-1 in combination with targeted therapy. *Cancer Clin Oncol*, 8, 1-15.
- [62] Burzynski SR, Burzynski GS, Janicki T, Beenken S. (2021) Long-term survival (23 years) in a 26-year-old male after Antineoplastron therapy for a progressive, diffuse intrinsic pontine glioma: A case report. *Int J Brain Disord Treat*, 6, 038-044. doi.org/10.23937/2469-5866/.
- [63] Burzynski SR, Janicki T, Burzynski GS, Beenken S. (2021) 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. *Biomed Res Clin Prac*, 6: doi: 10.15761/BRCP.1000220.
- [64] Burzynski SR, Janicki T, Burzynski GS, Beenken S. (2021) Diffuse intrinsic pontine glioma in an 11-year-old female treated with antineoplastons: Complete response and > 25-year survival. In Press.