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Diffuse intrinsic pontine glioma: Unusually long survival of 28 patients (from 3 years to over 29 years) in phase 2 studies with antineoplastons A10 and AS2-1

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SUMMARY

Diffuse Intrinsic Pontine Glioma (DIPG) has one of the worst prognoses in neuro-oncology with median overall survival of approximately 11 months. The Adverse Events (AV) of standard therapy can be very serious. Twenty-eight patients with DIPG were treated with Antineoplastons A10 and AS2-1 (ANP) in Phase II clinical studies at Burzynski Clinic (BC). The unusually long-term survival and lack of chronic toxicity are discussed in this paper. Karnofsky/Lansky (KPS/LPS) performance score of thirty or higher and life expectancy of two months or more were required for admission for the treatment. ANP was administered intravenously via subclavian catheter and infusion pump. The goals of the study were determination of objective response, survival and toxicity. The median of the Kaplan-Meier survival analysis of 165 patients treated was 1.02 years (95% CI 0.93 – 1.15). Twenty-eight patients (16.9%) survived from over three years to over 29 years. Eight patients from this group survived from over 12 years to over 29 years meeting criteria of cure. Age at admission of 28 long-term survivors was between 0.25 and 50 years. Three patients experienced possibly related Serious Adverse Events (SAE) including hypernatremia, vomiting and high fever without a bacterial infection, which were fully reversed. ANP shows promise in the treatment of DIPG.

Keywords: Antineoplastons; Antineoplastons; Diffuse intrinsic pontine glioma; Diffuse midline glioma; H3K27M; Phase II study; Long-term survival

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INTRODUCTION

Patients diagnosed with DIPG face a dismal prognosis. The median overall survival is approximately 11 months, and it is unusual to witness over 3 years overall survival [1,2]. Magnetic Resonance Imaging (MRI) of the brain has permitted the classification of brainstem gliomas into five categories: focal, exophytic, cervicomedullary, midbrain, and DIPG [3]. 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 [3].

When compared to other brainstem tumors, the prognosis for children with DIPG is significantly worse. The pons contains cranial nerve nuclei and other nuclei, which are vitally important for life. Damage to these nuclei from treatment can be life-threatening. Because of this, 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 the ages of 5 and 10. 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 over than 21 years) constitutes only 2% of adult gliomas, with a slight male predominance [4,5]. Median age at diagnosis is in the mid-30s, although brainstem gliomas can occur at any age. We have previously reviewed this clinical entity [6]. The radiographic appearance of adult brainstem glioma varies widely, with only 40% showing enhancement [4,7]. Pediatric DIPG has a prognosis of approximately 10 months and only 10% of patients live more than two years after diagnosis. In contrast, the median survival for adult patients with a brainstem glioma is 30–40 months but only 45% had DIPG [8].

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 and has a much worse prognosis [9].

Due to its anatomical location, obtaining diagnostic biopsies of brainstem gliomas is challenging. Diagnosis is often based solely on brain MRI. However, routine biopsy of patients with suspected DIPG has been performed in Europe since 2003 [10]. 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 [10]. Based on this evidence of relative safety, there is a movement within the pediatric neuro-oncology community toward routine biopsy of patients with suspected DIPG [11].

Genomic studies have identified aberrations in DIPG, such as PDGFRA, MDM4, MYCN, EGFR, MET, KRAS, CDK4, and H3K27M, loss of H3K27 trimethylation, H3.1 (HIST1H3B/C). These aberrations involve genes that regulate cell growth, cell death, and cellular repair pathways [4,12-18].

In 2016, the World Health Organization (WHO) identified histone 3 (H3) K27-altered diffuse midline glioma (DMG) as a distinct category of high-grade glioma [19,20]. DMGs most often develop in the brainstem, thalamus, spinal cord, and cerebellum [21]. DIPG, which was once defined solely by its MRI findings, is now classified based on its molecular signature, like other DMGs [22]. These tumors exhibit H3K27M-related oncogenesis, PRC2 dysregulation, and global hypomethylation [23,24]. DIPGs typically fall under the WHO classification of H3K27M DMGs, but wild-type H3K27 DIPGs, although not explicitly included in this WHO category, have survival rates like H3-K27M DIPGs [20,25,26]. Additionally, about 20% of pediatric glioblastomas harbor H3 K27M mutations [27].

For children three years of age or older with newly diagnosed DIPG, the standard treatment 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 DIPG, which is exacerbated by RT, glucocorticoids are used. About 75% of children with DIPG experience some improvement in their symptoms, in response to RT and steroids. RT prolongs survival for these children by approximately 3 months [28].

Within 3–8 months after completion of RT, most children with DIPG will show clinical or radiographic evidence of Progressive Disease (PD). The pattern of failure is generally local. In one study, 25% of cases with PD involved irradiated tissues while 75% occurred outside the radiation field [28]. 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, an increasing tumor grade is linked to significantly lower survival rates. An analysis of 17 adults with brainstem glioma including 10 DIPG cases, showed a median Overall Survival (OS) of 57 months for low-grade *vs.* 16 months for high-grade gliomas [29]. An M. D. Anderson Cancer Center retrospective analysis of 143 adult brainstem glioma patients, including 27% of DIPG, demonstrated a median OS of 21.1 months for WHO grade 3 anaplastic astrocytoma, and 14.8 months for glioblastoma [7].

Antineoplastons (ANP) A10 and AS2-1 are analogs of naturally occurring derivatives of glutamine, isoglutamine and phenylacetic acid, which were submitted for a number of phase II clinical studies [30-75].

The objectives of this article include 1) reviewing the development and significance of Antineoplaston therapy (ANP), 2) presenting a retrospective analysis of 164 patients with Diffuse Intrinsic Pontine Glioma (DIPG) who received ANP in Phase II clinical trials, 3) highlighting 28 patients in that analysis with unusually long survival after receiving ANP, 3) reviewing the use of magnetic resonance imaging in determining objective response in DIPG, 4) reviewing the results of other therapies for DIPG, 5) discussing new diagnostic criteria for DIPG, including its designation as a diffuse midline glioma, and 6) exploring the future of clinical trials in DIPG.

METHODS

Antineoplaston research began in 1967, when significant deficiencies were noticed in the peptide content of the serum of patients with cancer compared with healthy people. Initially Antineoplastons were isolated from the blood and later from urine [30]. Subsequent studies of the isolated Antineoplastons demonstrated that Antineoplaston A10 (Atengenal) and Antineoplaston AS2-1 (Astugenal) were the most promising formulations. 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 a phenylacetyl residue. The mixture of synthetic phenylacetyl glutaminate (PG) and phenylacetyl isogluatminate (isoPG) in a 4:1 ratio, dissolved in sterile water constitutes an 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 [31].

We discuss here the usefulness of ANP in 1) DIPG patients in Phase II studies seen at the BC between August 1992 and September 2004 and 2) 28 DIPG patients with unusually long-term survival. These DIPG patients were treated according to single arm, two-stage, phase II trials of ANP. In all protocols, IV ANP was used while in some also included oral ANP as maintenance treatment. Patients received gradually increasing doses of IV ANP *via* subclavian catheter and infusion pump, until a maximum tolerated dose of A10 and AS2-1 were achieved. Specifically, before ANP began, a subclavian Broviac catheter was placed. Patients over 18 years of age received ANP starting at 0.1 g of A10 given as 1 ml IV. If the patient did not show side effects 30 minutes after this injection, they received an additional 10.0 g of A10 *via* IV Infusion (100 mg of A10/ml) at 50 ml/hr. In the absence of limiting toxicity, the A10 dosage was subsequently increased by 0.3 g/kg/day until reaching a maximum

tolerated dose. The IV infusion rate was increased to 100 ml/hr. Once a patient reached their maximum dose of A10, AS2-1 was added to the treatment regimen, starting with 0.1 g of AS2-1 administered as 1 ml IV. If the patient showed no side effects for 30 minutes after this injection, they received an additional 10.0 g of AS2-1 *via* IV infusion at 100 ml/hr. In the absence of limiting toxicity, the AS2-1 dose was increased by 0.15 g/kg/day until reaching 0.4 g/kg/day. During this escalation, the IV infusion rate was maintained at 100 ml/hr.

Eligibility criteria included a Karnofsky/Lansky score (KPS/LPS) of 60-100%, and a life expectancy of >2 months. All study patients and/or their legal guardians read, understood, and signed an Informed Consent Document prior to treatment. Outcome criteria were 1) Objective Response (OR) and 2) survival. The safety and tolerance of ANP in patients with brain tumors were also investigated. Disease progression, unacceptable toxicity, physician decision, or patient request resulted in termination of ANP.

Gadolinium-enhanced MRIs of the brain were used in the diagnosis and follow-up of contrast-enhancing lesions. Brain MRIs were usually performed every 8 weeks for the first two years and then less frequently. T2-weighted and T2-FLAIR were used for evaluation of non-enhancing lesions [76]. As determined by MRI of the brain, the product of the two greatest perpendicular diameters of each measurable (>5mm) and enhancing lesion was calculated. Tumor size was defined as the SUM of these products [76,77]. The response criteria were as follows: a Complete Response (CR) indicated complete disappearance of all enhancing tumor(s) while a Partial Response (PR) indicated a 50% or greater reduction in the SUM. 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 the SUM or new measurable and enhancing disease, while Stable Disease (SD) did not meet the criteria for PR or PD [76,77].

Since DIPG shows contrast enhancement in some cases and has a non-enhancing component observed on T2/FLAIR–weighted MRI images, investigators, including ourselves, have proposed the assessment of OR using modified RANO criteria (T2/FLAIR-weighted images).

The Phase II studies were conducted in accordance with the U.S. Code of Federal Regulations, Title 21, Parts 11, 50, 56 and 312; the Declaration of Helsinki (1964) including all amendments and revisions; the Good Clinical Practices: Consolidated Guideline (E6), International Conference on Harmonization (ICH) and the FDA Guidance for Industry. By participating in this study protocol, the investigators agreed to provide access to all appropriate documents for monitoring, auditing, Institutional Review Board (IRB) review and review by any authorized regulatory agency.

RESULTS

A total of 175 patients were treated for DIPG in the Phase II study program. Ten cases were excluded from this report because of the lack of evidence of a high-grade tumor. One patient (#4) had a tumor occupying less than 50% of the pons and another patient (#28) had a diagnosis of infiltrating astrocytoma. Both patients were included as DIPG due to the rapid progression of their disease.

Out of 165 patients included in this report, 52 were treated as study patients, and 113 were treated according to protocol as Special Exception(s), which was permitted by the FDA to address patients in poor general condition (KPS/LPS below 60). Some SE patients had KPS/LPS above 60 but did not meet other eligibility criteria; for example, some of these patients had a KPS/LPS of over 60 and an estimated life expectancy of less than 2 months.

The median age of 165 patients was 7.9 years (range: 0.25 to 57.25 years), with a slight majority of females (49.7% males, 50.3% females). Among long-term survivors, there were 22 solitary tumors, five multicentric tumors, and one multicentric/disseminated tumor. Additional characteristics are provided in **Table. 1.**, "Demographics, Prior Treatment, and Overall Survival from Diagnosis." Radiographic responses were confirmed by external neuro-radiologists. **Table. 2.**describes "Pathology, Prior treatment, and Diagnosis at the start of ANP." The treatment data of the 28 long-term survivors are presented in**Table. 3.**Data is current through August/September 2025.

Kaplan-Meier survival analysis described a median Overall Survival from Diagnosis (OSD) of 1.02 years (95% CI 0.93–1.15) in 165 DIPG patients treated with ANP. See **Figure 1**, Kaplan Maier graph, where the "Time" axis is presented in increments of 5 years. In our observation, survival for these patients extended past 25 years. A group of 28 patients survived more than 3 years up to over 29 years. Eight patients survived more than 12 years up to over 29 years, meeting the definition of cure. Three of 28 patients experienced serious adverse events (10.7%), possibly related to ANP, but all fully recovered.

Two representative cases are described:

Case #1 (please refer to Case #1 on Tables 2 and 3)

At the time of her presentation at BC, the patient was 36 years of age. She had been in good health until just prior to July 21, 1987, when she was diagnosed by MRI and stereotactic biopsy with an anaplastic (High grade) astrocytoma of the pons (DIPG). Genomic studies, such as mutation of H3K27, were not performed at the time of biopsy because such technology was not available.

Recently, genomic analysis of the archival specimen was attempted, but was unsuccessful due to an insufficient amount of preserved tissue.

From August 31, 1987 until October 23, 1987, the patient was treated with 78 cGy of hyperfractionated RT at UCSF. She did not receive further treatment at that time despite evidence of PD documented by MRIs of the brain on February 5, 1988 and April 29, 1988.

Physical examination at BC revealed paralysis of the right side of the face, diplopia, decrease in strength of the left upper extremity and decreased sensation involving the left upper extremity and left thigh. She was experiencing poor balance with difficulty walking, and had dysphagia, right ear hearing loss, memory loss, and headaches. Her KPS was 60. An MRI of the brain performed on April 29, 1988, which confirmed PD after hyperfractionated RT. The patient subsequently received off-protocol treatment at BC with A10, AS2-1, and low dose oral methotrexate. MRI of the brain performed on July 11, 1988 showed a right brainstem lesion measuring 3.4 cm × 2.1 cm (7.14 cm^2) and the patient was enrolled in BT-3 [78].

IV dexamethasone was stopped on September 9, 1988 with the patient receiving no steroids after that date.

On December 1, 1988, after four months of protocol treatment, the patient achieved a PR (58% reduction in two-dimensional size), as shown by a non-contrast MRI of the brain. At that time, gadolinium contrast had not yet been approved by the FDA for MRI studies. After an additional two months of protocol treatment, the patient achieved a CR on January 23, 1989, again demonstrated by a non-contrast brain MRI. In 1989, the CR was also confirmed by gadolinium-enhanced MRIs. ANP infusions were permanently discontinued on August 10, 1989, and were followed by maintenance oral A10 and AS2-1, which were discontinued on January 21, 1990. In October 1991, the MRI findings of a CR were reviewed and confirmed by the NIH Cancer Therapy Evaluation Program (CTEP).

The following Adverse Events (AEs), possibly attributable to ANP, occurred while the patient was treated on BT-3: Mild leukopenia, headaches, dizziness, skin rash, and fever.

Table. 1. Demographics, KPS/LPS, prior treatment, diagnosis, overall survival from diagnosis.

	N=165	N=28
Sex		
Male	82	17
Female	83	11
Ethnicity		
Asian Indian	4	-
Black	4	-
Latin American	16	3
Oriental	3	-
White	138	25
Age (at admission at BC)		
range	0.25-57.25	0.25-50
median	7.9	26.1
Age groups (at admission at BC)		
below 21	136	9
21+	29	19
KPS/LPS (at admission at BC)		
range	30-100	40-90
median	50	50
Prior Treatment (single SOC/multiple SOC)		
NONE	29	10
Bx	2	
Bx, RT	2	1
Bx, RT, Other		1
Bx, CH	1	
Bx, RT, CH	6/4	-/1
Bx, RT, CH, Other	1	-/2
SU	5	
SU, RT		2
SU, RT, CH	2/1	2/1
SU, RT, CH, Other	-/1	
SU, RT, Other		1
RT	32	1
RT, CH	40/3	5
RT, CH, Other	5	1
CH	3	
Pathology		
None	128	17
Anaplastic Astrocytoma	22	6
Anaplastic Astrocytoma/Mixed	1	1
Anaplastic Oligodendroglioma	1	1
Astrocytoma Infiltrating	2	1
GBM	10	1
Gliosarcoma	1	1
Overall Survival from diagnosis		
over 6 months	86.6%	NA
over 3 years	16.9%	100%
over 12 years	4.8%	28.7%

Other treatment: tamoxifen, Accutane, clinical trials of unknown test substance
BC – Burzynski Clinic, Bx – Biopsy, CH – Chemotherapy, GBM – Glioblastoma, KPS/LPS – Karnofsky/Lansky performance status, RT – Radiation Therapy, SOC – Standard-Of-Care, SU – Surgery

Table. 2. Pathology, prior treatment, diagnosis at the baselines at BC.

Case	Dx date	Pathology	By	Prior treatment	Tumor characteristic at admission at BC
1	7/21/1987 **7/29/1987**	MRI Moderately anaplastic astrocytoma	University of California, San Francisco, CA	Bx, RT	DIPG/AA/Solitary-NonE only Contrast was not approved yet by FDA
2	4/22/1988	Anaplastic Astrocytoma	University of Alberta Hospitals, Alberta, Canada	SU, RT, CH	DIPG/AA/Solitary with extension to medulla and tectal plate
3	8/28/1992	Anaplastic Astrocytoma	New York University Medical Center, New York, NY	SU, RT, tamoxifen	DIPG/AA/Solitary
4	3/27/1996	No pathology/dx by MRI	St. John's Regional Health Center, Springfield, MO	None	DIPG due to the rapid progression of disease /Solitary
5	**10/6/1992** 10/13/1992 11/2/1992 11/5/1992 11/11/1992 12/18/1992	Oligodendroglioma Oligodendroglioma, type B Mixed glioma: grade 3 Oligodendroglioma Mixed glioma: grade 3 Glial neoplasm	University of California, Davis Medical Center, Sacramento, CA (in all cases)	SU, Bx, RT, CH	DIPG/AA/Mixed/Multicentric
6	11/12/1997	No pathology/dx by MRI	Children's Hospital Medical Center, Cincinnati, OH	RT, CH	DIPG/Solitary
7	8/12/1998	No pathology/dx by MRI	Long Beach Community Medical Center, Long Beach, CA	None	DIPG/Solitary
8	1/6/1989	Anaplastic astrocytoma	University of California, San Francisco, CA	Bx, RT, 2CH, Accutane, tamoxifen	DIPG/AA/Solitary
9	6/4/1999	GBM	MD Anderson Cancer Center, Houston, TX	SU, RT	DIPG/GBM/Solitary NonE only
10	10/16/1998	No pathology/dx by MRI	The Chester County, West Chester, PA	None	DIPG Solitary NonE only
11	3/10/1995 3/31/1995 8/11/1995 8/15/1997 2/10/1999 **2/26/1999** 3/2/1999 3/10/1999	Astrocytoma, meningioma *vs.* schwannoma Astrocytoma Pilocytic Astrocytoma Astrocytoma Mixed Glioma Gliosarcoma High grade glioma Anaplastic Astrocytoma	St. Joseph Hospital, Orange, CA Children's Hospital Los Angeles, Los Angeles, CA Johns Hopkins Hospital, Baltimore, MD Cedars-Sinai Hospital, Los Angeles, CA St. Joseph Hospital, Orange, CA Ohio State University Medical Center, Columbus, OH St. Joseph Hospital, Orange, CA Children's Hospital Los Angeles, Los Angeles, CA	2SU, Bx, 3RT, 3CH	DIPG/GS/Multicentric
12	5/15/1997	No pathology/dx by MRI	Di Bella Clinic, Florence, Italy	None	DIPG/Solitary NonE only
13	11/15/1996	No pathology/dx by MRI	original report not in file, Canada	RT	DIPG/Solitary NonE only
14	1/11/2002	No pathology/dx by MRI	Good Samaritan Hospital, West Islip, NY	None	DIPG/Solitary
15	8/21/2002	No pathology/dx by MRI	Advanced Imaging Center, Carmichael, CA	None	DIPG/Solitary NonE only
16	**05/19/2000** 10/24/2003	No pathology/dx by MRI High grade Glioma.	Original report not in file University of California, Los Angeles, CA	Bx, RT, 2CH, Accutane	DIPG/Anaplastic Oligodendroglioma/Multicentric
17	9/18/2002	No pathology/dx by MRI	Wojskowy Instytut Medycyny Lotniczej, Warszawa, Poland	None	DIPG/Solitary NonE only
18	3/12/2002	Astrocytoma Anaplastic	University of Colorado Health Sciences Center, Denver, CO	SU, RT	DIPG/AA/Multicentric/ disseminated
19	1/28/2005	No pathology/dx by MRI	Foote Hospital, Jackson, MI	RT, CH	DIPG/Solitary NonE only
20	1/30/1998	No pathology/dx by MRI	University Of Utah Hospitals and Clinics, Salt Lake City, UT	RT, CH	DIPG/Solitary
21	11/1/2005	No pathology/dx by MRI	University of Pittsburg, Presbyterian Medical Center in Pittsburg, PA	None	DIPG/Multicentric NonE only
22	12/2/2005	No pathology/dx by MRI	North Ottawa Community Hospital, Michigan, MI	RT, CH	DIPG/Multicentric
23	7/6/2009	No pathology/dx by MRI	Winthrop University Hospital in New York, New York, NY	RT, CH, Clinical trials	DIPG/Solitary NonE only
24	4/6/2010	Astrocytoma Infiltrating Diffuse	M.D. Anderson Cancer Center, Houston, TX	Bx, RT, anticancer treatment	DIPG/AA/Solitary NonE only
25	9/2/2010	No pathology/dx by MRI	Local Healthcare Center, Sidney, Australia	None	DIPG/Solitary NonE only
26	6/9/2011	No pathology/dx by MRI	Intermountain Healthcare, Logan Regional Hospital, Logan, UT	None	DIPG/Solitary NonE only
27	4/20/2001	No pathology/dx by MRI	University of Southern California University Hospital, Los Angeles, CA	RT, CH	DIPG/Solitary
28	**4/13/2011** 11/8/2011	Glioma Infiltrating Astrocytoma Infiltrating	Fleni Hospital, Buenos Aires, Argentina M.D. Anderson Cancer Center, Houston, TX	Bx, RT, 2CH	DIPG due to the rapid progression of disease /Astrocytoma Infiltrating/Solitary NonE only

Bold date – date used to calculate the OSD

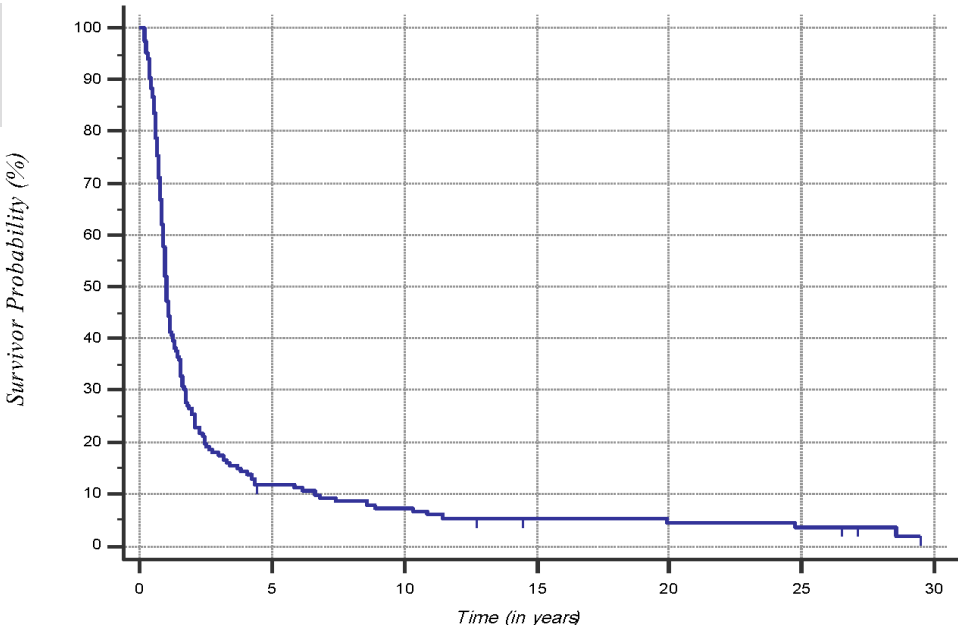
AA – Anaplastic Astrocytoma, BC – Burzynski Clinic, Bx – Biopsy, CH – Chemotherapy, DIPG – Diffuse Intrinsic Pontine Glioma, Dx – Diagnosis, GBM – Glioblastoma Multiforme, GS – Gliosarcoma, MRI – Magnetic Resonance Imaging, NonE – MRI non-enhanced signal, RT – Radiation Therapy, SU - Surgery

Table. 3. Treatment data.

Case	Sex	Age at Admission (Years)	Protocol	Study/SE	Diagnosis at Admission	KPS/LPS at Admission	Start Date	Days on TX	Best Response on Treatment	Post ANP Treatment	Cause of Death or Last Contact Date	OSD Years
1	F	36.41	BT-03	Study	DIPG/AA	60	07/12/1988	394	CR	None	pneumonia	28.60
2	M	26.58	BT-03	Study	DIPG/AA	40	10/30/1989	113	CR	None	chronic toxicity from RT	24.76
3	M	8.25	CAN-01	Study	DIPG/AA	60	10/26/1992	3841	CR	None	unknown	19.92
4	F	11.66	BT-11	Study	DIPG	90	05/08/1996	1014	CR	None	**Alive 9/9/25**	**29.45 (+)**
5	F	29.25	BT-18	Study	DIPG/AA/Mixed	80	07/17/1996	164	SD	None	pneumonia	4.26
6	F	7.16	BT-11	Study	DIPG	80	04/24/1998	1246	PR	None	malignancy	4.37
7	F	0.25	BT-11	SE	DIPG	40	10/14/1998	2094	CR	None	**Alive 8/31//25**	**27.07 (+)**
8	M	42.50	BT-11	SE	DIPG/AA	40	03/19/1999	179	PD	None	malignancy	10.88
9	M	40.41	BT-11	SE	DIPG/GBM	50	09/30/1999	691	CR	None	chronic toxicity from RT	7.40
10	F	22.00	BT-11	SE	DIPG	50	02/10/2000	1129	SD	None	pneumonia	5.87
11	M	9.08	BT-22	SE	DIPG/GS	40	12/03/1999	2505	CR	None	**Alive 8/20/25**	**26.48 (+)**
12	F	23.50	BT-11	SE	DIPG	50	09/05/2000	149	SD	None	Lost for FU 10/19/2021	4.42 (censored)
13	F	24.58	BT-11	SE	DIPG	50	02/06/2001	368	SD	2xCH	possible malignancy	11.44
14	M	2.50	BT-11	SE	DIPG	50	02/15/2002	1335	CR	1xRT	malignancy	4.35
15	M	36.66	BT-09	Study	DIPG	90	09/12/2002	263	SD	1xRT	Lost for FU 5/15/15	12.73 (censored)
16	M	36.41	BT-11	Study	DIPG/Anaplastic Oligodendroglioma	60	11/25/2003	76	PD	1xTT	malignancy	3.84
17	M	20.58	BT-11	SE	DIPG	50	02/18/2004	779	SD	None	possible malignancy	10.29
18	F	45.83	BT-11	SE	DIPG/AA	40	03/23/2005	37	NE	None	malignancy	3.15
19	M	30.58	BT-11	SE	DIPG	50	07/28/2005	1066	SD	None	unknown	6.13
20	M	38.00	BT-11	Study	DIPG	70	08/10/2006	25	NE	None	malignancy	8.60
21	F	21.00	BT-09	Study	DIPG	90	01/12/2007	383	SD	None	unknown	6.63
22	M	36.16	BT-09	Study	DIPG	60	11/06/2008	43	NE	1xCH, 2xTT	malignancy	3.70
23	M	7.91	BT-10	SE	DIPG	50	02/03/2011	555	SD	1xOT	malignancy	3.28
24	M	27.05	BT-09	SE	DIPG/AA	50	01/06/2011	213	SD	None	unknown	8.90
25	M	34.08	BT-11	SE	DIPG	70	08/05/2011	190	SD	1xRT	chronic toxicity from RT	4.04
26	M	16.41	BT-11	SE	DIPG	60	07/15/2011	700	SD	None	unknown	6.81
27	M	50.00	BT-09	SE	DIPG	50	10/27/2011	613	PR	None	unknown	3.40
28	F	25.66	BT-09	SE	DIPG/Astrocytoma Infiltrating	90	02/02/2012	506	SD	None	**Alive 9/9/25**	**14.40 (+)**

AA – Anaplastic Astrocytoma, ANP – Antineoplastons, CH – Chemotherapy, CR – Complete Response, DIPG – Diffuse Intrinsic Pontine Glioma, F – Female, FU – Follow-Up, GBM – Glioblastoma Multiforme, GS – Gliosarcoma, KPS/LPS – Karnofsky/Lansky Performance Score, M – Male, NE – Non-Evaluable, OSD – Overall Survival from Diagnosis, OT – Other Treatment, PD – Progressive Disease, PR – Partial Response, RT – Radiation Therapy, SD – Stable Disease, SE – Special Exception, TT – Targeted Therapy, TX – Treatment

Figure. 1. Shows Kaplan-Meier analysis and survival curve (165 patients)



On March 3, 2016, the patient died from influenza-related pneumonia, not from her previous brain tumor. She had lived a fulfilling life for nearly 30 years following her brain tumor diagnosis.

On October 4, 1991, three members of CTEP, along with an invited neuropathologist and an invited neuroradiologist, visited Dr. Burzynski at the BC to review selected brain tumor cases from Phase II studies. After a thorough review of seven cases chosen by CTEP, five definite or "possible" cases of CR were identified, including the case presented here [78].

Case #2 (please refer to Case #7 on Tables 2 and 3)

This 3½-month-old female was brought to a pediatrician with decreased movement in her left eye and partial weakness on the left side of her face and mouth. On August 12, 1998, an MRI of the brain revealed a mass within the brainstem, involving the pons, medulla, and midbrain. There was a mass effect on the fourth ventricle, but no hydrocephalus. The tumor was suspected to be a brainstem glioma, likely originating in the pons. Surgery, radiation therapy, and chemotherapy were not considered viable treatment options due to the tumor's location 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, but no long tract signs. Babinski was negative bilaterally. Motor reflexes were intact, including grasp and sucking reflexes. The infant's cry was normal, as were the protective reflexes of the throat. Muscle tone was normal, with no posturing or arching.

On October 14, 1998, this 3 ½ month-old female was enrolled as an SE for ANP in accordance with protocol BT-11, a Phase II study of ANP in patients with brainstem gliomas [52,65]. The baseline MRI (October 13, 1988) showed an enhancing lesion measuring 10.73 cm² on coronal images, while axial and sagittal images revealed non-enhancing lesions measuring 12.58 cm² and 14.70 cm². ANP was then delivered according to protocol. The dosages of A10 and AS2-1 were gradually increased to 9.42 g/kg/day and 0.56 g/kg/day, respectively.

On February 22, 1999, enhanced coronal imaging showed that the lesion had disappeared, while the non-enhancing axial and sagittal images now measured 8.12 cm² and 12.04 cm², respectively. By April 23, 1999, the enhancing lesion was no longer visible, confirming that the patient had achieved a CR. On May 19, 2000, the axial and sagittal images revealed an 80% reduction in the size of the non-enhancing lesions, now measuring 2.28 cm² and 3.45 cm², respectively. On June 8, 2000, IV ANP therapy was discontinued, and the patient started oral ANP therapy. An outside neuroradiologist noted, "Measurement of the unenhanced portion of the mass is difficult given the minimal change in signal associated with the T1 sequences..." and he recommended a PET scan to evaluate the response further. On April 8, 2004, a whole-body PET scan revealed no hypermetabolic activity in the brain, particularly in the brainstem, indicating that the residual non-enhancing masses had resolved. On April 2, 2008, an MRI confirmed the persistence of the CR. Previously, on April 7, 2004, at the age of five, the patient weighed 47.5 pounds and was in good health. Her pupils were equal and reactive to light, and her extraocular muscles were intact. Right eye lateral nystagmus was observed, but the initial lateral deviation of the left eye, incomplete closure of the left eyelid, and left-sided facial weakness had resolved. There was minimal weakness in her right-sided extremities and a slightly abnormal gait. Her coordination was good, as demonstrated by finger-nose-finger and heel-to-shin exercises. Motor reflexes were symmetrical and intact, and the Babinski reflex was negative bilaterally.

The patient was seen at BC on March 2, 2024. She was in excellent overall condition, with the only complaint being some minor right-sided weakness. Right-hand grip

strength was 3/5, and overall strength in all extremities was 4/5. As of August 2025 the patient is still alive, living a normal life and has two healthy children.

DISCUSSION

In a recent report using data from the European Society for Pediatric Oncology DIPG/DMG Registry, Baugh and colleagues performed a survival analysis of patients with DIPG [79]. Patients who received no treatment survived for 3.0 months, while those receiving RT alone had a median OS of 10.4 months. The longest OS, 11.7 months, was observed in patients receiving RT combined with Chemotherapy (CH). After multivariate analysis, these treatment differences were found to be statistically significant [79].

Current DIPG research reflects a shift toward molecularly guided interventions. For example, Mackall and colleagues conducted a Phase I clinical trial based on evidence that DMGs express high levels of the disialoganglioside GD2, and that chimeric antigen receptor-modified T cells targeting GD2 (GD2-CART) eradicate DMGs in preclinical models [80]. Following lymphodepletion, patients with DIPG or spinal DMG (sDMG) were administered with one IV dose of autologous GD2-CART at one of two dose levels: 1 × $106kg^{-1}$ and 3 × $106kg^{-1}$. Patients with clinical and/or imaging improvement were eligible for subsequent Intracerebroventricular (ICV) intracranial infusions (10-30 × 106 GD2-CART). Three patients receiving 3 × $106kg^{-1}$ autologous GD2-CART experienced dose-limiting cytokine release syndrome. Three patients achieved a PR, while one patient with sDMG achieved a CR that had persisted for 30 months at the time of publication [80]. Interestingly, on November 13, 2024, the newspaper "USA TODAY", while presenting the sDMG patient with 30+ months OS, reported, "A form of brain cancer called DIPG has killed every child and young adult who has ever been diagnosed" [81].

We report here on 28 long-term DIPG survivors, four of whom are still alive, as of August 2025, with no evidence of disease at 14.04, 22.07, 26.48, and 29.45 years after diagnosis. All these long-term survivors were diagnosed at external academic institutions, and their responses were confirmed by prominent neuro-radiologists, with one case also being verified by a group of experts from NCI [78]. These patients lead normal lives without any chronic toxicity from ANP. They have families and healthy children. The authors are not aware of similar results from other clinical studies.

In our publications, we suggested that the neoplastic process is a disease of information processing [82]. The disease develops due to a network of mutated genes [83-89]. Current technology allows the detection of these genes' DNA in blood at levels as low as one billionth of a gram per milliliter [90]. Several excellent laboratories, including Foundation Medicine, Guardant 360, and Tempus, can deliver results within two weeks, and insurance policies in the US cover these tests. At BC, results are checked against a list of 600 genomic aberrations affected by ANP to determine patient eligibility for ANP. This list was created based on initial laboratory data about the effects of Antineoplastons on the whole genome of Glioblastoma (GBM), along with clinical data from testing blood and tissue from patients treated at BC under the Texas Right to Try Law [84-94]. Several significant aberrations involved in the development of DIPG are listed among the genes affected by ANP. Although blood tests can produce results in only a fraction of DIPG patients [90], we have observed many positive outcomes from testing the blood samples of patients with over 70 different types of cancer.

Our goal is to deliver a radiological and molecular response by removing abnormal DNA from the patient's blood. Based on genomic testing, 110 aberrations were identified and removed from patients' blood, including H3F3A K27, H3F3A K28, PDGFRA, MET, EGFR, CCND2, CCND3, KRAS, PIK3CA, KIT, MYCN, CDKN2A, PTEN, TP53, and ATM, which drive DIPG [13-16]. Some of these changes may be influenced by additional prescription drugs administered to patients with advanced-stage disease. These results will be expanded with new data once the number of tested genes increases (Currently from 600 to 800). It is hoped that the addition of new targeted agents to the treatment will improve the responses.

The 2021 WHO classification reflects a shift from radiographic to molecular genetics in defining DIPG [95]. The classification "DIPG" was updated to "Diffuse Midline Glioma, H3 K27-altered." Biopsy and molecular genetics are essential components of future clinical trials, as this update requires molecular confirmation of the H3K27M mutation or an equivalent epigenetic change for diagnosis. In addition, molecular genetics provides for a better understanding of tumor biology and identification of targetable mutations [23,96].

CONCLUSION

We present here the results of unusually long survival of 28 patients diagnosed with DIPG treated in Phase II clinical studies with ANP. The survival of eight patients for over 12 years indicates that they were cured from their disease [94]. The studies were performed when current genomic testing techniques were not yet available. The new technology will permit better and more accurate results.

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CONFLICT OF INTEREST

All of the authors of this paper have declared that there is no conflict of interest.

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