J Neurol Neurosci©

16 (06) 2025 : 001-015 • CASE REPORT

Unusually long survival (over 33 years) observed in 61 high-grade glioma patients treated in phase II studies of Antineoplastons A10 and AS2-1

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SUMMARY

Background: High-Grade Gliomas (HGGs) are among the most aggressive and deadly primary brain tumors. Standard treatment includes surgery, external beam radiation and temozolomide, which can cause marked toxicity. Despite intensive therapy, the prognosis remains poor.

Objective: To assess long-term outcomes and safety in non-Glioblastoma (non-GBM) HGG patients treated with Antineoplastons A10 and AS2-1 (ANP) at the Burzynski Clinic (BC) under phase II protocols.

Methods: Sixty-one non-GBM HGG patients received intravenous ANP. Eligibility required Karnofsky/Lansky Performance Scores (KPS/LPS) of at least 60 and a life expectancy of at least 2 months. ANP was administered via a subclavian catheter and automated pump. Maximum tolerated doses of A10 and AS2-1 were achieved. Outcomes included objective response, survival and toxicity.

Results: As of October 2025, all 61 patients had survived for at least 5 years, with one patient surpassing 33 years. The criteria of a cure was met when 23 patients survived over 12 years. Ages ranged from 1.08 to 62.66 years (median 35.9). KPS/LPS scores ranged from 40 to 90 (median 60). Four patients experienced six Serious Adverse Events (SAE's) possibly related to ANP (fever without infection, nausea, dizziness and three cases of somnolence); all recovered fully. In a Kaplan-Meier analysis of 310 non-GBM HGG patients treated at BC, median survival was 1.867 years.

Conclusions: ANP therapy shows significant potential for non-GBM HGG, with many long-term survivors and no observed long-term toxicity. This cohort represents the most extensive documented series of HGG survivors with unusually long-term survivals. Findings support ANP as a viable treatment option.

Keywords: Antineoplastons; Glioma; High-grade glioma; Long-term survival; Phase II studies

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Word count: 3998 **Tables:** 03 **Figures:** 01 **References:** 92

Received: 11.11.2025, Manuscript No. ipjnn-25-15774; **Editor assigned:** 13.11.2025, PreQC No. P-15774; **Reviewed:** 27.11.2025, QC No. Q-15774; **Revised:** 04.12.2025, Manuscript No. R-15774; **Published:** 11.12.2025

INTRODUCTION

Arising from glial progenitor cells, gliomas are a diverse group of primary tumors located within the Central Nervous System (CNS) [1]. Mainly affecting older adults, gliomas accounted for 22.9% of all newly diagnosed primary brain and other CNS tumors between 2017 and 2021 in the USA. Among these brain tumors, 14.0% of all tumors and 51.5% of all malignant tumors were Glioblastoma (GBM), a High-Grade Glioma (HGG). In recent years, GBM has caused the deaths of over 7,550 Americans annually [2].

The diagnosis of HGG involves clinical signs and symptoms, imaging studies, histological examination and molecular analysis of tumor tissue. The imaging study of choice is Magnetic Resonance Imaging (MRI) of the brain, which can be performed with or without gadolinium contrast. A brain MRI shows the anatomical relationship between the tumor and surrounding tissue, as well as tumor location, size and the extent of edema and necrosis.

Historically, brain tumor classification has relied on histological features. As a result, classification has been limited by diagnostic discrepancies, variable outcomes and different responses to therapy. However, recent advances in molecular profiling have enabled the integration of both morphological and molecular characteristics of brain tumors [3]. The 2021 World Health Organization (WHO) classification of CNS tumors introduced new types and subtypes often defined by their key molecular features [4]. Additionally, gliomas were categorized by age, with distinctions made between adult and pediatric types [5-7]. Adult-type diffuse HGG was subdivided based on two molecular markers: Isocitrate Dehydrogenase (IDH) and 1p/19q codeletion. Pediatric-type diffuse HGG was subdivided based on tumor location, histone mutations (including H3 K27-altered and H3 G34-mutant) and DNA methylation profiles [5].

Adult-type diffuse gliomas include 1) astrocytoma, IDH-mutant (WHO grades 2-4); 2) oligodendroglioma, IDH-mutant and 1p/19q-codeleted (WHO grades 2-3); and 3) GBM, IDH-wildtype (WHO grade 4). Pediatric-type diffuse high-grade gliomas included 1) diffuse midline glioma, H3 K27-altered (WHO grade 4); 2) diffuse hemispheric glioma, H3 G34-mutant (WHO grade 4); 3) diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype (WHO grade 4) and 4) infant-type hemispheric glioma [5].

HGGs are among the most aggressive and deadly types of brain tumors. They present with a wide range of clinical signs and symptoms that significantly reduce patients' Health-Related Quality of Life (HRQoL). These signs and symptoms can vary depending on tumor location and progression. However, common signs and symptoms include severe or chronic headaches, epileptic seizures, muscle weakness, numbness, nausea, vomiting, drowsiness, visual disturbances, concentration problems, memory loss and personality changes [8,9].

HGG is characterized by rapid growth and resistance to conventional therapies, which makes this tumor type a significant challenge in neuro-oncology. The treatment of HGG conventionally consists of a multimodal approach, which includes maximal safe Surgical Resection (SU), adjuvant Radiation Therapy (RT) and concurrent Chemotherapy (CH) with Temozolomide (TMZ) for six weeks, followed by TMZ for an additional six months [10, 11]. However, this approach is not curative. An available clinical trial is the preferred option [12]. The median Overall Survival (OS) for GBM patients receiving conventional multimodal treatment is approximately 13 months, with survival rates of 82% at six months, 55% at 12 months and 19% at 24 months [13]. Patients experience several side effects related to surgery and chemoradiotherapy, including ataxia, motor or language deficits, fatigue, insomnia and malaise. Long-term adverse effects include atrophy of brain tissue and cognitive deficits [14]. These acute and chronic Adverse Effects (AE) significantly decrease the HRQoL of HGG patients.

Recurrence of HGG, defined as tumor regrowth despite treatment, is a very negative prognostic factor [15]. Nearly all patients with HGG experience recurrence within several months and the prognosis is dismal [16]. In cases of GBM, recurrence in all patients is inevitable [17]. There is no standard therapy for recurrent HGG. Generally, the therapeutic strategy is tailored to each patient's specific requirements and guided by recommendations from a multidisciplinary tumor board that considers prior treatment, time to recurrence, performance status, corticosteroid dependence and molecular markers [12,15]. Again, enrollment in a clinical trial is preferred. Conventional therapy options for recurrent HGG include a second surgery, additional RT, additional TMZ or lomustine and bevacizumab [12]. This extra treatment will lead to additional AEs and further reduce patients' HRQoL.

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 [18]. 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, when dissolved in sterile water, constitutes an Antineoplaston A10 intravenous (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].

Antineoplastons A10 and AS2-1 (ANP) has been used in several phase II clinical studies [20-68]. Here we present 1) unusually long survival (from more than five years to over 33 years) of 61 HGG patients treated at the Burzynski Clinic (BC), between August 1992 and September 2004, according to phase II protocols of ANP and 2) the lack of long-term adverse sequelae. The eligibility criteria for protocol therapy included a Karnofsky/ Lansky Performance Score (KPS/LPS) of 60-100% and a life expectancy of at least 2 months. All patients were treated according to single-arm, phase II studies, which administered ANP by IV injection. Some patients also received oral ANP for maintenance. Gradually increasing doses of IV ANP were administered *via* a subclavian catheter and infusion pump until the maximum tolerated doses of A10 and AS2-1 were achieved. The outcome criteria were 1) objective response (OR), 2) survival and 3) toxicity. All study patients and/or their legal guardians read, understood and signed an Informed Consent Document before treatment. Disease progression, unacceptable toxicity, physician decision, or patient request resulted in the termination of ANP.

MRI scans of the brain with gadolinium enhancement were used for diagnosis, response evaluation and follow-up of these patients. Brain MRIs were performed serially every 8 weeks during the first 2 years of protocol ANP. Afterward, they were conducted as needed during follow-up. T2-weighted, T2-FLAIR, T1-weighted and contrast-enhanced T1-weighted images were obtained. HGG shows gadolinium enhancement so contrast-enhanced T1-weighted images were used to assess treatment effects [69,70]. Based on the brain MRI, the product of the two largest perpendicular diameters of each measurable (>5mm) and enhancing lesion was calculated. Tumor size was defined as the SUM of these products. The response criteria were as follows: a Complete Response (CR) was indicated by the total disappearance of all enhancing tumors. In contrast, a Partial Response (PR) was indicated by 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. Progressive Disease (PD) was indicated by a 25% or greater increase in the SUM, or the presence of new measurable and enhancing disease. Stable Disease (SD) was defined as the absence of CR, PR, or PD [69,70].

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 Guidance for Industry (FDA). 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 310 HGG patients received treatment at the BC between May 1988 and March 2014 as part of Phase II

ANP studies. GBM patients were excluded as they were the subjects of another article [66]. Of these patients, 170 were designated as "Special Exceptions" (54.8%) because they did not meet all eligibility criteria, often due to a KPS/LPS of less than 60. These 170 patients were individually approved by the Food and Drug Administration (FDA). Out of 310 HGG patients, 61 survived over 5 years from HGG diagnosis.

Fifty-nine of 310 non-GBM HGG patients (19.0%) were initially diagnosed with low-grade tumors that subsequently transformed into high-grade tumors. In such cases, only the dates for high-grade diagnoses were used to calculate survival. For these 310 patients, Kaplan-Meier survival analysis showed a median OSD of 1.867 years (95% CI 1.555 to 2.133). See Fig. 1., where the "Time" axis is presented in increments of five years and survival extended to over 30 years in our observation.

Before being seen at the BC, 18 of 61 long-term survivors underwent SU, followed by RT, and CH; 10 patients had SU and RT; 8 patients had SU only, 5 patients had RT only after initial biopsy; 7 patients had biopsy only; 16 patients had some combination of single SU +/- RT +/- CH. Several patients also had other treatments. Demographic details, prior treatment and overall survival are shown in **Tab. 1**.

Fifty-three of the 61 long-term survivors (86.9%) had anaplastic astrocytoma, of which eight were described

Tab. 1. Demographics, prior treatment, pathology and OSD.

	N=310 (All Patients)	**N=61 (OSD >5 years)**
Sex		
Male	200	39
Female	110	22
Age (at admission at BC)		
Range	0.41-76.66	1.08-62.66
Median	37.8	35.9
Age groups (at admission at BC)		
Below 21	64	10
21+	246	51
KPS/LPS (at admission at BC)		
Range	30-100	40-90
Median	50	60
Prior Treatment (single treatments/multiple treatments)		
None	3*	-
Bx only	46/1	7
Bx, RT	21/1	5/-
Bx, RT, CH	23/12	1/2
Bx, RT, CH, Other	2/4	-/1
Bx, RT, Other	1/-	1/-
Bx, CH	3/1	-/1
Bx, CH, Other	1/1	1/-
SU	34/4	7/1
SU, RT	28/11	9/1
SU, CH	5/2	3/-
SU, CH, Other	1/ -	3/-
SU, RT, CH,	18/47	4/6
SU, RT, CH, Other	5/23	-/8
SU, RT, Other	6/1	-/1
SU, Other	3/-	2/-
RT	2**/ -	-
Pathology		
Anaplastic Astrocytoma	189	40
Anaplastic Astrocytoma/BSG	8	-
Anaplastic Astrocytoma/DIPG	22	5
Anaplastic Astrocytoma/Mixed	33	8
Anaplastic Astrocytoma/Mixed/DIPG	1	-
Anaplastic Astrocytoma/Visual Pathway	2	-
Anaplastic Astrocytoma/Spine	2	-
Anaplastic Glioma	1	-
Anaplastic Oligoastrocytoma	2	1
Anaplastic Oligodendroglioma	13	3
Anaplastic Oligodendroglioma/DIPG	1	-
Astrocytoma Fibrillary High Grade	2	-
Astrocytoma Fibrillary High Grade/Spine	1	-
Astrocytoma High Grade/Spine	1	-
Astrocytoma Infiltrating/DIPG	1	1

Glioma High Grade	15	1
Glioma High Grade/Visual Pathway	1	1
Gliomatosis Cerebri	2	-
Oligoastrocytoma High Grade	11	1
Xantoastrocytoma, grade 4	2	-
Overall Survival from diagnosis		
Over 6 months	86.77%	NA
Over 5 years	19.68%	100%
Over 12 years	7.41%	37.70%

Note: BC-Burzynski Clinic, BSG-Brain Stem Glioma, Bx-Biopsy, CH-Chemotherapy, DIPG-Diffuse Intrinsic Pontine Glioma, KPS-Karnofsky Performance Score, LPS-Lansky Performance Score, OSD-Overall Survival from Diagnosis, RT-Radiation Therapy, SU-Surgery

Other treatment: Accutane, artemisinin, Avastin, BCG (Bacillus Calmette-Guérin) immunotherapy, cis-retinoic acid, clinical trial, Dimethyl Sulfoxide (DMSO), electromagnetic therapy, erlotinib, Gleevec, high-dose vitamin C and vitamin E, hyperthermia, Insulin Potentiation Therapy (IPT), interferon, Lymphokine-Activated Killer (LAK) cells, monoclonal therapy, poly ICLC - dsRNA molecule used as an immune stimulant in cancer immunotherapy, shark cartilage, sodium phenylbutyrate, tamoxifen, temozolomide, thalidomide, and unknown alternative therapy

*Three patients had no prior treatment: one patient was diagnosed with a butterfly malignant glioma and the biopsy was not necessary; the second patient had a tumor consistent with malignant glioma and was not a candidate for surgery; the third patient was diagnosed with a high-grade glioma, and the biopsy was not performed because of the possibility of permanent damage to the visual pathway. This patient has also had complications with previous anesthesia.

**Two patients were treated with RT without a biopsy due to the dangerous location of the tumor. One had a brain CT and angiogram, the other had a brain MRI for diagnosis.

as "mixed" and five had histological features of diffuse intrinsic pontine glioma. Eight patients had one of five other HGG diagnoses. Pathologists with academic affiliations, including prominent neuropathologists, made the diagnoses. Details of the diagnosis, prior treatment and tumor status at the start of ANP are presented in **Tab. 2**.

At admission to BC, the age of these patients ranged from 1.08 to 62.66 years, with a median age of 35.9 years. There were 22 females and 39 males. KPS/LPS scores ranged from 40 to 90, with a median score of 60. Twenty-five patients (41.0%) were not eligible for protocol ANP but, after FDA approval, were treated as Special Exceptions (SEs) according to protocol.

All ORs were confirmed by prominent neuroradiologists who were not affiliated with BC. ORs consisted of CR in 13 cases, PR in 4 cases, SD in 20 cases and PD in 14 cases. Ten cases were not evaluable. Overall Survival from Diagnosis (OSD) was more than 12 years in 23 patients, more than 20 years in 8 patients and more than 30 years in 2 patients. As of October 2025, 1 patient had an OSD of more than 33 years. Eight patients (13.1%) were alive and doing well at the last follow-up. The best response to ANP, patient status at last follow-up and OSD following ANP for all 61 long-term survivors are described in **Tab. 3**.

Two representative cases are described:

Case# 1 (Case 8 in Tab. 2. and Tab. 3.)

In November 1993, a 12-year-old Caucasian female, with no prior health issues, was found to have a contrast-enhancing tumor in the left temporal lobe, which crossed the midline and compressed the superior pons. Biopsy revealed pleomorphic tumor cells with mitotic figures. Review of the microscopic sections of tumor tissue by experienced pathologists provided a diagnosis of Anaplastic Astrocytoma (AA). No treatment was started initially, but a brain MRI performed nine weeks later showed tumor progression.

In January 1994, the patient was seen at the BC. Symptoms included headaches, nausea, memory loss, slurred speech and fatigue. She usually experienced four focal seizures per day, some days more, some days less, with occasional grand mal seizures. Physical exam revealed hesitant and slurred speech. LPS was 60. MRI of the brain confirmed a 4.8 cm × 2.1 cm infiltrating, enhancing mass in the left temporal lobe that crossed the midline and compressed the brainstem.

Treatment with IV ANP began on January 7, 1994, per the phase II protocol. Dosages of A10 and AS2-1 were gradually increased until maximum tolerated doses were achieved. Follow-up brain MRIs at 3 and 14 months showed no significant change in tumor size, but by 13 months, all symptoms had been resolved while seizures persisted. Brain MRIs at 23 and 29 months of treatment showed tumor shrinkage by 96% and 98%, respectively, indicating a PR. At 32 months, brain MRI showed no enhancement, indicating achievement of a CR. Persistent seizures were felt to de due to scarring. IV ANP was discontinued at 40 months and oral maintenance ANP was initiated. Brain MRIs at 45, 51 and 55 months revealed a persistent CR. After 56 months of treatment, oral ANP was also discontinued. Three months later, scar tissue in the tumor bed was removed and the seizures ended. Follow-up brain MRIs at 6 and 15 years post-ANP showed no evidence of tumor; the CR was persistent. At the last follow-up in December 2024, the patient was doing well and living a normal life. Her OSD at that time was more than 31 years. There have been no long-term adverse sequelae.

Case #2 (Case 33 in Tab. 2. and Tab. 3.)

In May 2000, a 31-year-old female developed right upper extremity clumsiness and weakness of the right leg. She sought medical attention and was referred to a neurologist. MRI of the brain, performed on May 10, 2000, revealed a 2.0 cm^2 mass in the left parietal lobe. Computerized Tomography (CT) scans of the chest, abdomen and pelvis were performed on May 11, 2000 and found to be normal. On May 15, 2000, the patient underwent a stereotactic biopsy of the parietal tumor. Histological examination of tumor tissue slides revealed an AA.

When the patient presented at the BC, she had not had SU, RT, or CH. A baseline MRI of the brain, with gadolinium contrast, performed on June 1, 2000, showed a 2.0 cm^2

Tab. 2. Diagnosis, prior treatment and tumor status at the start of ANP.

Case	Date	Pathology	Hospital name	Prior treatment	Tumor characteristic
1	02/15/88	Anaplastic Astrocytoma	Cooper Hospital/University Medical Center, Camden, NJ	SU	Supratentorial; Single lesion; Primary
2	07/29/87	Moderately anaplastic astrocytoma	UCSF Medical Center, San Francisco, CA	Bx, RT	DIPG/Solitary/NE only
3	10/19/87	Anaplastic Astrocytoma	National Cancer Institute report	SU, RT	Supratentorial; Single lesion; Primary
4	04/28/87	Moderately anaplastic astrocytoma	UCSF Medical Center, San Francisco, CA	SU, RT, CH	Supratentorial; Single lesion; Primary
5	04/22/88	Anaplastic Astrocytoma	University of Alberta Hospitals, Alberta, Canada	SU, RT, CH	DIPG/Solitary E+NE
6	09/14/90	Giganto-Cellular Anaplastic Astrocytoma	Children's Hospital of Philadelphia, Philadelphia, PA	SU, RT	Supratentorial; Single lesion; Primary
7	08/28/92	Anaplastic Astrocytoma, Osseous Metaplasia.	New York University Medical Center, New York, NY	SU, RT, tamoxifen	DIPG/Solitary E+NE
8	12/03/1993	Anaplastic Astrocytoma	Princess Margaret Hospital for Children, Subiaco, Australia	Bx	Supratentorial; Single lesion; Primary
	01/03/1994	Astrocytoma grade 1-2	Children's Hospital of Philadelphia, Philadelphia, PA		
9	1/y/90	Anaplastic Astrocytoma	Not available	2SU, 4Bx, RT, 2CH, CT – no data, tamoxifen	Supratentorial; Single lesion; Primary
	10/25/93	Oligodendroglioma	National Institute of Health Medical Center, Bethesda, MD		
	12/06/1993	Anaplastic Oligodendroglioma	National Institute of Health Medical Center, Bethesda, MD		
	01/25/94	Anaplastic Oligodendroglioma	National Institute of Health Medical Center, Bethesda, MD		
	11/14/94	Oligodendroglioma	National Institute of Health Medical Center, Bethesda, MD		
	03/21/95	Anaplastic Oligodendroglioma	National Institute of Health Medical Center, Bethesda, MD		
10	12/08/1994	Mixed Glioma grade 3-4	St. Vincent Medical Center, Toledo, OH	SU, RT	Supratentorial; Single lesion; Primary
11	09/29/94	Anaplastic Oligoastrocytoma	The New York Hospital, New York, NY	SU, RT	Supratentorial; Single lesion; Primary
12	08/30/95	Anaplastic Astrocytoma	The Methodist Hospital, Houston, TX	Bx, RT	Supratentorial; Single lesion; Primary
13	02/26/96	High Grade Glioma	The Moses H. Cone Memorial Hospital, Greensboro, NC	SU	Supratentorial; Single lesion; Primary
	03/29/96	Mixed Astrocytoma-Oligodendroglioma	Children's Hospital of Philadelphia, Philadelphia, PA		
14	02/23/96	Anaplastic Astrocytoma	Oregon Health Sciences University, Portland, OR	SU	Supratentorial; Single lesion; Primary
	04/03/1996	Anaplastic Astrocytoma	Children's Hospital of Philadelphia, Philadelphia, PA		
15	9/y/90	Astrocytoma Infiltrating	Medical College of Ohio, Toledo, OH	SU, 2Bx, RT, CH	Supratentorial; Single lesion; Primary
	10/18/95	Astrocytoma Infiltrating	Cleveland Clinic, Cleveland, OH		
	02/06/1996	Astrocytoma infiltrating	Cleveland Clinic, Cleveland, OH		
16	02/16/96	Astrocytoma, possible anaplastic	Air Force USAC Medical Center, Wright Patterson, OH	Bx, RT	Supratentorial; Multifocal; Primary
	03/08/1996	Astrocytoma Infiltrating	Air Force USAC Medical Center, Wright Patterson, OH		
	09/12/1996	Astrocytoma	Children's Hospital of Philadelphia, Philadelphia, PA		
17	10/06/1989	Moderate anaplastic astrocytoma	Huntington Memorial Hospital, Pasadena, CA	Bx, RT	Supratentorial; Single lesion; Primary
18	09/03/1991	Small cell astrocytoma grade 4	Swedish Medical Center, Englewood, Co	2SU, RT, CH	Supratentorial; Multicentric; Primary
	09/05/1991	Glioblastoma Multiforme, small cell variant	University of Colorado Health Science Center, Aurora, CO		
	09/09/1991	Small cell malignant astrocytoma	Mayo Clinic, Rochester, MN		
	02/03/1997	High Grade Glioma	California Pacific Medical Center, San Francisco, CA		
19	12/23/91	Mixed Malignant Glioma.	UCSF Medical Center, San Francisco, CA	2SU, RT, CH	Supratentorial; Multifocal; Primary
	12/15/95	Mixed Malignant Glioma	UCSF Medical Center, San Francisco, CA		
20	02/24/97	Anaplastic astrocytoma	University of Pennsylvania Medical Center, Philadelphia, PA	SU	Supratentorial; Single lesion; Primary
21	07/18/85	Astrocytoma	The Children's Hospital of Philadelphia, Philadelphia, PA	SU, Bx, RT, 2CH	Supratentorial; Single lesion; Primary
	08/10/1992	Anaplastic mixed glioma	Zale Lipshy University Hospital, Dallas, TX		
	03/28/97	Anaplastic astrocytoma	The Children's Hospital of Philadelphia, Philadelphia, PA		

22	04/23/93	Astrocytoma	St. Joseph's Hospital, Houston, TX	2Bx, RT	Supratentorial; Single lesion; Primary
	05/11/1993	Glioma Infiltrating	St. Joseph's Hospital, Houston, TX		
	07/23/96	Anaplastic Astrocytoma	Clinic at the University of Florida, Gainesville, FL		
23	12/10/1996	Anaplastic mixed glioma	North Shore University Hospital, Manhasset, NY	SU, CH	Supratentorial; Single lesion; Secondary
	04/30/97	High grade glioma/Anaplastic Oligodendroglioma	Memorial Hospital for Cancer and Allied Diseases, New York, NY		
	07/25/97	Anaplastic Astrocytoma	North Shore University Hospital, Manhasset, NY		
24	4/y/91	Astrocytoma	University of Pennsylvania Medical Center, Philadelphia, PA	Bx, SU, RT	Supratentorial; Multifocal; Secondary
	06/02/1997	Anaplastic Astrocytoma	University of Pennsylvania Medical Center, Philadelphia, PA		
25	04/24/92	Oligoastrocytoma type III	Centre Hospitalier Sainte Anne, Paris, France	SU, RT	Supratentorial; Single lesion; Primary
26	9/y/91	Mixed glioma grade 2/3	New York Medical Center, New York, NY	2SU, RT, CH	Supratentorial; Single lesion; Primary
	04/27/98	High grade mixed glial-neuronal tumor	University Medical Center, New York, NY		
27	08/21/98	Astrocytoma Fibrillary, grade 3	Foothills Hospital, Department of Histopathology, Calgary, Alberta, Canada	SU	Supratentorial; Single lesion; Primary
28	01/06/1989	Anaplastic Astrocytoma	UCSF Medical Center, San Francisco, CA	Bx, RT, 2CH, Accutane, tamoxifen	DIPG/Solitary E+NE
29	4/y/92	Anaplastic Astrocytoma	Brookhaven Memorial Hospital Medical Center, Patchogue, NY	3SU, RT, 2CH	Supratentorial; Multicentric; Secondary
	08/05/1993	Astrocytoma	Brookhaven Memorial Hospital Medical Center, Patchogue, NY		
	08/20/93	Anaplastic Astrocytoma	Stoney Brook University Hospital, Stoney Brook, NY		
	04/14/94	Anaplastic Astrocytoma	Brookhaven Memorial Hospital Medical Center, Patchogue, NY		
	11/09/1998	Anaplastic Astrocytoma	Memorial Hospital for Cancer and Allied Diseases, New York, NY		
30	12/24/97	Anaplastic Astrocytoma	Not available	2SU, RT, 3CH, tamoxifen	Supra & Infratentorial; Multicentric; Primary
	10/14/98	Anaplastic Astrocytoma	UCSF Medical Center, San Francisco, CA		
31	05/10/1996	Astrocytoma fibrillary, grade 2	Community Hospitals, Indianapolis, IN	Bx	Supratentorial; Single lesion; Primary
	05/15/96	Astrocytoma	Indiana University Medical Center, Indianapolis, IN		
	07/26/96	Astrocytoma Fibrillary, grade 2	The Johns Hopkins Hospital, Baltimore, MD		
32	07/27/98	Anaplastic Astrocytoma	Sutter General Hospital, Sacramento, CA	Bx, RT, CH	Supratentorial; Single lesion; Primary
	08/25/98	Anaplastic Astrocytoma	Roth Medical Group, Sacramento, CA		
33	05/15/00	Anaplastic Astrocytoma	Saint John's Health Center, Santa Monica, CA	Bx	Supratentorial; Multifocal; Primary
34	05/06/1996	Astrocytoma Malignant	Not available	2SU	Supratentorial; Single lesion; Primary
	07/31/00	Anaplastic Astrocytoma	University Jagiellonum Collegium Medicum, Krakow, Poland		
35	11/07/2000	Astrocytoma Fibrillary / Anaplastic Astrocytoma	United Hospital Allina Health System, St. Paul, MN	Bx	Supratentorial; Multifocal; Primary
36	04/26/00	Glial neoplasia, high grade	Beth Israel Medical Center-North Division, New York, NY	2SU, RT	Supratentorial; Single lesion; Primary
	12/20/00	Anaplastic Astrocytoma	Beth Israel Medical Center-North Division, New York, NY		
37	05-12-1995	Anaplastic Astrocytoma	New York University Medical Center, New York, NY	SU, Bx, CH	Supratentorial; Single lesion; Primary
	01/16/98	Oligoastrocytoma, grade 3	UCSF Medical Center, San Francisco, CA		
38	04/30/02	Anaplastic Astrocytoma	UCSF Medical Center, San Francisco, CA	Bx	Supratentorial; Single lesion; Primary
39	11/06/1995	Anaplastic Astrocytoma	Armed Forces Institute Of Pathology, Washington, DC	SU, RT, CH	Supratentorial; Single lesion; Primary
40	07/10/1992	Astrocytoma Infiltrating with pilocytic features grade 2/3	Westchester County Medical Center, Grasslands Reservation Valhalla, NY	SU, CH	Supratentorial; Single lesion; Primary; Visual Pathway
	07/23/92	Juvenile pilocytic astrocytoma	Memorial Sloan-Kettering Cancer Center, New York, NY		
	10/13/92	Anaplastic Astrocytoma	Westchester County Medical Center, Grasslands Reservation Valhalla, NY		
	11/05/1992	Juvenile pilocytic astrocytoma	Memorial Sloan-Kettering Cancer Center, New York, NY		
	07/12/1994	Optic nerve involved by high grade glioma	Westchester County Medical Center, Grasslands Reservation Valhalla, NY		
41	03/09/1998	Anaplastic Astrocytoma	Akron General Medical Center, Akron, OH	Bx	Supratentorial; Single lesion; Primary

42	03/11/1992	Astrocytoma	Hackensack Medical Center, Department of Pathology, Hackensack, NJ	SU, alternative therapy	Supratentorial; Single lesion; Primary /NE only
	02/09/2000	Anaplastic Oligodendroglioma	New York Presbyterian Hospital/Columbia Presbyterian Center, New York, NY		
	03/15/00	Anaplastic Oligodendroglioma	Memorial Hospital for Cancer and Allied Diseases, New York, NY		
43	08/05/2003	Oligoastrocytoma mixed, grade 3	UCLA Medical Center, Department of Pathology in Los Angeles, CA	Bx,2CH	Supratentorial; Single lesion; Primary /NE only
44	02/26/03	Anaplastic Astrocytoma	Hartford Hospital, Harford, CT	Bx, CH, Gleevec	Supratentorial; Single lesion; Primary /NE only
45	06/01/1999	Oligoastrocytoma Mixed	Robert Wood Johnson University Hospital, New Brunswick, NJ	SU, high dose vitamins C and E	Supratentorial; Single lesion; Primary
	07/28/99	Oligoastrocytoma Mixed, grade 3	Department of Defense, Armed Forces Institute Of Pathology, Washington, DC		
	09/01/1999	Oligodendroglioma	Mayo Clinic, Rochester, MN		
	09/07/1999	Oligodendroglioma	University of Kansas Medical Center, Kansas City		
	09/21/99	Astrocytoma	The Johns Hopkins Hospital, Baltimore, MD		
	10/07/1999	Glioneuronal tumor with neuropil-like islands	Robert Wood Johnson University Hospital, New Brunswick, NJ		
46	07/15/83	Astrocytoma Malignant	Medical Center Del Oro Hospital, Houston, TX	5SU, Bx, 2RT, 5CH, interferon, Accutane	Supratentorial; Multicentric; Primary
	03/07/2003	Glioma favor Oligoastrocytoma	St. Luke's Baylor Hospital, Houston, TX		
	11/21/03	Anaplastic mixed glioma	St. Luke's Baylor Hospital, Houston, TX		
	06/28/04	High Grade Glioma	M.D. Anderson Cancer Center, Houston, TX		
	07/05/2004	Anaplastic Astrocytoma	M.D. Anderson Cancer Center, Houston, TX		
47	07/07/2003	Astrocytoma Fibrillary, grade 3	Mayo Clinic, Rochester, MN	4SU, 2RT, 2CH, LAK cells	Supratentorial; Single lesion; Primary
	07/08/2003	Anaplastic Astrocytoma	Hoag Memorial Hospital Presbyterian, Newport Beach, CA		
	07/09/2003	Astrocytoma Fibrillary, grade 3	Hoag Memorial Hospital Presbyterian, Newport Beach, CA		
	03/22/04	Anaplastic Astrocytoma	Hoag Memorial Hospital Presbyterian, Newport Beach, CA		
48	05/28/96	Astrocytoma, grade 2 with focal grade 3	Santa Barbara Cottage Hospital, Santa Barbara, CA	3SU, Bx, 4RT, 5CH, PB, Accutane, thalidomide	Infratentorial; Single lesion; Primary
	06/04/1996	Oligodendroglioma	Massachusetts General Hospital, Boston, MA		
	04/02/1998	Oligoastrocytoma, grade 3	UCSF Medical Center, San Francisco, CA		
	05/02/2001	Glioma infiltrating	UCSF Medical Center, San Francisco, CA		
	02/06/2002	Anaplastic Oligoastrocytoma	UCSF Medical Center, San Francisco, CA		
	03/02/2004	Anaplastic Astrocytoma	UCSF Medical Center, San Francisco, CA		
49	09/28/04	Anaplastic Astrocytoma	Pathology at Massachusetts General Hospital, Boston, MA	3SU, RT, 2CH, Clinical trial CC-8490	Supratentorial; Single lesion; Primary
	10/01/2004	Anaplastic Astrocytoma	Pathology at Massachusetts General Hospital, Boston, MA		
	04/25/05	Astrocytoma	Not readable		
50	7/y/1999	Gemistocytic Astrocytoma	Arhus University Hospital, Arhus, Denmark	2SU, RT, CH	Supratentorial; Single lesion; Secondary
	11/13/01	Anaplastic Astrocytoma			
51	08/24/05	Anaplastic Astrocytoma	UT Southwestern Medical Center, University Hospitals & Clinics, Zale Lipshy Laboratory, Dallas, TX	SU	Supratentorial; Single lesion; L-M, Primary
52	10/07/2003	Anaplastic Astrocytoma	Cedars-Sinai Medical Center, Los Angeles, CA	SU, RT	Supratentorial; Single lesion; Primary
53	06/12/2007	Anaplastic Astrocytoma	St. Anthony Health Services, Denver, CO	SU	Supratentorial; Single lesion; Primary
54	10/20/06	Oligoastrocytoma, astrocytic predominant, grade 2	Mayo Clinic, Rochester, MN	Bx, RT, 2CH	Supratentorial; Single lesion; Primary
	12/09/2006	Anaplastic Astrocytoma	University of Michigan, Ann Arbor, MI		
55	04/06/2010	Astrocytoma Infiltrating Diffuse	M.D. Anderson Cancer Center, Houston, TX	Bx, RT, anticancer treatment unknown	DIPG/Solitary/NE only
56	06/22/07	Anaplastic Astrocytoma	Michael Reese Hospital, Chicago, IL	SU, RT	Supratentorial; Single lesion; Primary
57	02/11/2010	Oligoastrocytoma, grade 2	St. Joseph Hospital and Medical Center, Phoenix, AZ	2SU, Bx, 3RT, CH, bevacizumab	Supratentorial; Multicentric; Primary
	05/12/2010	Astrocytoma with Gemistocytic features, grade 2	St. Joseph Hospital and Medical Center, Phoenix, AZ		
	08/24/10	Anaplastic Astrocytoma, gemistocytic	St. Joseph Hospital and Medical Center, Phoenix, AZ		

58	04/01/2011	Anaplastic Glioma	Royal Free Hampstead NHS Trust, London, U.K.	SU, RT	Supratentorial; Single lesion; Primary
59	04/13/11	Astrocytoma Infiltrating	Fleni Hospital Montañeses 2325, C1428, Buenos Aires, Argentina	Bx, RT, 2CH	DIPG/Single lesion; Primary/NE only
	11/08/2011	Astrocytoma Infiltrating	M.D. Anderson Cancer Center, Houston, TX		
60	01/24/12	Anaplastic Astrocytoma/ thalamic	UPMC- Presbyterian, Pittsburg, PA	Bx	Supratentorial; Single lesion; Primary
61	01/05/2006	Anaplastic Oligodendroglioma	Barnes-Jewish Hospital Washington University Medical Center, St. Louis, MO	2SU, RT, 2CH, PB, Tarceva, pazopanib, bevacizumab	Supratentorial; Single lesion; Primary
	08/05/2011	Anaplastic Oligodendroglioma	Barnes-Jewish Hospital Washington University Medical Center, St. Louis, MO		

Note: ANP-Antineoplastons, Bx-Biopsy, CH-Chemotherapy, DIPG-Diffuse Intrinsic Pontine Glioma, E-Enhanced signal, LAK- Lymphokine-Activated Killer cells, LM – Leptomeningeal involvement, NE-Non Enhanced signal, PB-Phenylbutyrate, RT-Radiation Therapy, SU-Surgery

Tab. 3. Best response to ANP, overall survival from diagnosis and status at last follow-up.

Case	Sex	Age at admission (years)	Protocol	Diagnosis at admission	KPS/LPS at admission	Start Date	Days on protocol	Best response on treatment	Post ANP treatment	Cause of death or last contact date	OSD years
1	F	13.67	BT-03	Anaplastic Astrocytoma	70	01/19/1989	97	PD	None	unknown	11.88
2	F	36.41	BT-03	Anaplastic Astrocytoma/DIPG	60	07/12/1988	394	CR	None	pneumonia	28.60
3	M	30.42	BT-03	Anaplastic Astrocytoma	70	07/08/1988	262	SD	None	unknown	6.18
4	M	48.42	BT-04	Anaplastic Astrocytoma	70	04/12/1990	654	PR	None	HGG	9.25
5	M	26.58	BT-03	Anaplastic Astrocytoma/DIPG	40	10/30/1989	113	CR	None	chronic toxicity from RT	24.76
6	M	9.33	BT-04	Anaplastic Astrocytoma	80	10/08/1990	90	SD	SU 5/91	HGG	5.02
7	M	8.25	CAN-01	Anaplastic Astrocytoma/DIPG	60	10/26/1992	2533 (3641 po)	CR	None	unknown	19.92
8	F	12.50	CAN-01	Anaplastic Astrocytoma	60	01/07/1994	1235 (458 po)	CR	None	Alive 12/5/24	31.03 (+)
9	M	27.25	CAN-01	Anaplastic Oligodendroglioma	90	05/30/1995		NE	None	malignancy	7.55
10	M	32.58	CAN-01	Anaplastic Astrocytoma/Mixed	80	07/26/1995	1639 (876 po)	CR	None	unknown	6.41
11	M	55.25	CAN-01	Anaplastic Astrocytoma/Mixed	70	08/22/1995	433	SD	None	different malignancy - sinus cancer	17.59
12	M	62.67	CAN-01	Anaplastic Astrocytoma	60	01/31/1996	104	SD	None	unknown	5.58
13	M	54.33	BT-18	Anaplastic Astrocytoma/Mixed	80	03/27/1996	519	CR	RT	unknown	14.52
14	F	50.42	BT-08	Anaplastic Astrocytoma	90	04/08/1996	554 (218 po)	SD	None	unknown	7.30
15	M	41.92	BT-15^{SE}	Anaplastic Astrocytoma Infiltrating	70	05/02/1996	130	SD	None	HGG	7.30
16	M	26.58	BT-09	Anaplastic Astrocytoma	80	09/17/1996	1103	PR	SU 10/99	HGG	5.21
17	M	44.50	BT-15	Anaplastic Astrocytoma	60	11/15/1996	377	SD	None	unknown	12.57
18	F	30.67	BT-09	Glioma High Grade	60	02/12/1997	53	PD	None	HGG	5.59
19	M	38.42	BT-18	Anaplastic Astrocytoma/Mixed	60	02/17/1997	35	PD	None	HGG	5.68
20	F	29.75	BT-08^{SE}	Anaplastic Astrocytoma	90	03/27/1997	134	SD	None	unknown	5.62
21	M	44.00	BT-15	Anaplastic Astrocytoma	90	04/12/1997	74	PD	None	HGG	5.10
22	F	45.42	BT-15	Anaplastic Astrocytoma	80	10/14/1998	224 (773 po)	CR	None	unknown	14.96
23	M	26.67	BT-18	Anaplastic Oligodendroglioma	80	06/06/1997	31	PD	RT, SU 07/97	Alive 10/10/25	28.83 (+)

24	F	48.83	BT-15^{SE}	Anaplastic Astrocytoma	50	03/11/1998	133	NE	None	HGG	5.49
25	F	40.83	BT-18	Anaplastic Astrocytoma/Mixed	60	06/17/1998	138	PD	None	unknown	6.66
26	M	35.50	BT-18	Anaplastic Astrocytoma/Mixed	60	06/24/1998	145	PD	None	HGG	7.18
27	F	17.83	BT-10	Anaplastic Astrocytoma	80	10/20/1998	268 (680 po)	SD	SU 01/04, RT	HGG	10.46
28	M	42.50	BT-11^{SE}	Anaplastic Astrocytoma/DIPG	40	03/19/1999	179	PD	None	HGG	10.88
29	M	41.25	BT-15^{SE}	Anaplastic Astrocytoma	40	03/29/1999	85	PD	None (shunt)	septicemia	7.26
30	F	13.75	BT-22^{SE}	Anaplastic Astrocytoma	40	10/01/1999	399	SD	None	unknown	13.16
31	F	36.92	BT-09^{SE}	Anaplastic Astrocytoma	50	10/15/1999	78 (556 po)	SD	SU 03/02, RT	unknown	7.12
32	F	37.25	BT-15	Anaplastic Astrocytoma	60	01/12/2000	184 (763 po)	CR	None	unknown	5.28
33	F	31.92	BT-08	Anaplastic Astrocytoma	60	06/06/2000	56 (454 po)	CR	None	Alive 10/13/25	25.40 (+)
34	M	33.67	BT-09^{SE}	Anaplastic Astrocytoma	50	11/09/2000	197	PD	RT	unknown	5.80
35	M	52.50	BT-08	Anaplastic Astrocytoma	60	02/07/2001	57	NE	SU 8/12, RT, 3xCH, OT	unknown	17.87
36	M	41.50	BT-15	Anaplastic Astrocytoma	60	02/22/2001	162	PR	None	HGG	5.04
37	M	35.92	BT-18^{SE}	Oligoastrocytoma High Grade	50	02/22/2002	90	PD	None	HGG	7.05
38	F	3.58	BT-22^{SE}	Anaplastic Astrocytoma	50	05/23/2002	621	SD	SU 07/04, 2005, RT, CH, OT	unknown	18.55
39	M	40.33	BT-15	Anaplastic Astrocytoma	60	01/23/2003	257 (305 po)	SD	None	HGG	10.05
40	M	12.25	BT-23^{SE}	Glioma High Grade/ Visual Pathway	50	04/09/2003	479 (1983 po)	PR	None	Alive 10/10/25	33.25 (+)
41	F	41.58	BT-09	Anaplastic Astrocytoma	80	05/27/2003	170	PD	SU 11/03	unknown	7.33
42	M	43.08	BT-09	Anaplastic Astrocytoma	90	12/03/2003	664	SD	SU 10/05	unknown	8.47
43	M	49.25	BT-18	Anaplastic Astrocytoma/Mixed	70	02/10/2004	42	NE	2xRT	HGG	8.34
44	F	1.08	BT-06^{SE}	Anaplastic Astrocytoma	50	02/26/2004	841	SD	SU 03/08, 3xCH, TT	unknown	10.98
45	M	33.25	BT-09	Anaplastic Astrocytoma/Mixed	70	04/13/2004	255	SD	SU 02/05, RT,CH	unknown	15.17
46	M	43.25	BT-15^{SE}	Anaplastic Astrocytoma	40	09/22/2004	3	NE	None	HGG	21.25
47	M	37.00	BT-09^{SE}	Anaplastic Astrocytoma	50	02/09/2005	531 (300 po)	CR	None	unknown	14.72
48	M	30.58	BT-15^{SE}	Anaplastic Astrocytoma	50	06/15/2005	37	NE	TT	unknown	10.42
49	M	47.00	BT-15^{SE}	Anaplastic Astrocytoma	50	07/01/2005	298	SD	None	Alive 10/09/25	21.03 (+)
50	M	28.33	BT-15^{SE}	Anaplastic Astrocytoma	50	07/07/2005	9	NE	None	HGG	6.00
51	F	24.42	BT-08^{SE}	Anaplastic Astrocytoma	40	10/17/2005	2193	CR	None	HGG	6.16
52	M	30.58	BT-18	Anaplastic Oligoastrocytoma	70	01/18/2007	84	PD	SU 5/07, CH	unknown	6.37
53	M	36.25	BT-08	Anaplastic Astrocytoma	80	08/17/2007	427	CR	SU 12/08, RT, CH, TT	unknown	13.41
54	F	23.25	BT-15	Anaplastic Astrocytoma	80	09/13/2007	474	SD	None	Alive 10/09/25	18.97 (+)
55	M	27.50	BT-09^{SE}	Anaplastic Astrocytoma/DIPG	50	01/06/2011	213	SD	None	unknown	8.90
56	M	56.00	BT-21^{SE}	Anaplastic Astrocytoma	90	06/30/2011	39	NE	SU 12/11, 2xOT	unknown	5.24

57	M	50.33	BT-15^{SE}	Anaplastic Astrocytoma	50	08/31/2011	95	NE	TT, CH	unknown	6.74
58	F	27.33	BT-09^{SE}	Anaplastic Astrocytoma	50	12/14/2011	535	CR	None	post viral treatment	12.13
59	F	25.67	BT-09^{SE}	Astrocytoma Infiltrating/DIPG	90	02/02/2012	506	SD	None	Alive 09/09/25	14.41 (+)
60	F	20.00	BT-09^{SE}	Anaplastic Astrocytoma	90	03/09/2012	52	PD	RT, CH, TT	Alive 10/23/25	13.75 (+)
61	M	43.50	BT-09^{SE}	Anaplastic Oligodendroglioma	90	07/18/2012	9	NE	None	HGG	6.57

Note: ANP-Antineoplastons, CH-Chemotherapy, CR-Complete Response, DIPG-Diffuse Intrinsic Pontine Glioma, HGG-High Grade Glioma, KPS-Karnofsky Performance Score, LPS-Lansky Performance Score, NE-Non Evaluable, OSD-Overall Survival Since Diagnosis, OT-Other Therapy, PD-Progressive Disease, po-per ora, PR-Partial Response, RT-Radiation Therapy, SD-Stable Disease, SE-Special Exemption, SU-Surgery, TT-Targeted.

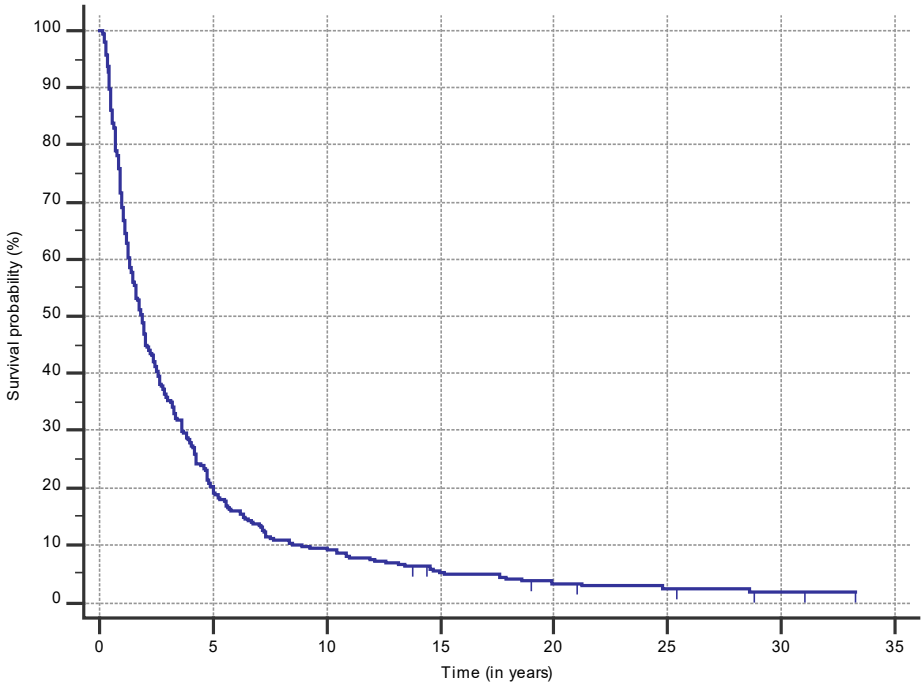

Fig. 1. Kaplan-Meier analysis and survival curve (N=310).

non-enhancing mass and two smaller enhancing masses (0.02 cm^2 and 0.15 cm^2) in the left parietal lobe. On June 6, 2000, the patient began IV ANP therapy and the ANP dosages were gradually increased to the maximum tolerated dosages. Throughout her IV ANP therapy, the patient experienced elevations in transaminases, which, on occasion, interrupted her therapy. MRI of the brain on July 3, 2000, one month after initiation of ANP therapy, demonstrated complete resolution of the enhancing disease in the left parietal lobe, indicating the achievement of a CR. However, the 2.0 cm^2 non-enhancing tumor persisted. The MRI of the brain, performed on July 31, 2000, demonstrated a persistent CR. On August 1, 2000, IV ANP therapy was terminated, while oral maintenance ANP began on August 4, 2000.

The patient continued taking oral ANP until October 31, 2001, when she elected to stop all ANP therapy. Long-term follow-up brain MRI on February 6, 2017, showed a persistent CR and complete disappearance of the 2.0 cm^2 non-enhancing nodule, indicating an enduring CR and complete tumor regression. The patient experienced two serious adverse events possibly related to ANP, both of which were resolved completely.

At the last follow-up in October 2025, she was doing well, had no evidence of tumor recurrence and had an OSD of more than 25 years and five months.

DISCUSSION

An emerging therapeutic approach is Tumor-Treating Fields (TTFields) [71]. These fields are a non-invasive cancer therapy that uses low-intensity, intermediate-frequency, alternating electric fields to disrupt cancer cell division by interfering with mitotic spindle formation and chromosome segregation, resulting in mitotic arrest and apoptosis. Therapy is delivered *via* transducer arrays placed on the scalp and connected to a portable device [71].

The EF-14 phase III trial evaluated TTFields in combination with maintenance temozolomide and following standard chemoradiotherapy in patients with newly diagnosed GBM. Patients receiving TTFields plus TMZ demonstrated significantly improved progression-free survival (6.7 months *vs.* 4.0 months) and overall survival (20.9 months *vs.* 16.0 months) compared to TMZ alone. There was no significant increase in toxicity. Two-year survival rates were also higher in the TTFields arm (43% *vs.* 30%) [71]. Subsequent analyses have confirmed the findings of the EF-14 trial. TTFields therapy has been correlated with survival benefits and with outcomes similar to those observed in EF-14 [72].

The EF-14 results were published in 2014 and the study design did not fully account for the molecular markers that have become increasingly important for cohort

stratification in clinical studies. Because of the diagnostic criteria presented in the 2021 WHO classification of CNS tumors [4,5], challenges to the design of clinical trials for HGG are significant. For example, IDH1/2 mutations define a distinct subset of gliomas with improved survival [73]. Genetic analyses also distinguish primary GBM, characterized by EGFR amplification and PTEN loss, from secondary GBM, arising from lower-grade gliomas with TP53 and IDH mutations [74].

In 2024, Barrera and colleagues reported a retrospective survival analysis of 80 HGG patients who underwent surgical resection and were treated from 2012 to 2015 at the Cancer Institute of the Americas Clinic in Medellin, Colombia [75]. The histological diagnosis was based on the 2007 WHO classification [76], not the diagnostic criteria presented above. Clinical, demographic and lifestyle characteristics were analyzed, along with genetic instability in white blood cells. The Kaplan-Meier analysis indicated an average survival of two years and two months. A Cox proportional hazards model showed that patient age, exposure to polycyclic hydrocarbons at work and the number of sister-chromatid exchanges in lymphocytes at the first sampling were significantly associated with survival in the multivariate analysis.

We report here on a survival analysis of 310 non-GBM HGG patients treated in phase II studies of ANP at BC between May 1988 and March 2014. Survival of more than 5 years up to more than 33 years was observed in 61 patients (19.6%). All these patients were seen after their diagnoses were established at outside academic institutions with prominent neuroradiologists confirming the ORs. The case of one of these patients was reviewed and confirmed by experts from the National Cancer Institute [77].

The mechanism of action of ANP differs from that of RT or CH. The growth of normal cells is controlled by cell cycle progression genes (oncogenes) and by cell cycle arrest genes (tumor suppressor genes). In cancer, alterations in these control genes in malignant cells favor aggressive cell proliferation. Evidence shows that ANP affects more than 535 gene aberrations in the malignant genome and functions as a "molecular switch" that "turns on" tumor-suppressor genes and "turns off" oncogenes [78]. Hence, the antineoplastic action of ANP involves restoration of cell cycle control, induction of programmed cell death and interference with cancer cell metabolism and nuclear transport.

In 1986, we published an article proposing that the neoplastic process is a disease of information processing [79]. The neoplastic process develops according to the "program" encoded in a network of mutated genes [32,79-87]. The technology now utilized can detect the DNA of these mutated genes in blood at concentrations as low as one billionth of a gram/mL [88]. Laboratories, such as Foundation Medicine, Guardant360 and Tempus AI, can provide results within two weeks and many insurance policies in the USA cover the tests.

At the BC, DNA analyses are compared with a list of 535 genomic aberrations compiled from early laboratory data on the effects of ANP on the entire genome of GBM [78] and from clinical data derived from blood and tissue testing of patients treated at the BC [88]. For each patient whose blood was tested, the number of genomic aberrations found to be affected by ANP determined the patient's candidacy for ANP.

We have found the genomic aberrations affected by ANP through our testing of blood samples from patients with over 70 different cancer diagnoses, including brain tumors [89-91]. Our goal is to correlate the ANP-related removal of genomic aberrations from patients' blood with radiological response and survival. Based on our genomic testing, 114 aberrations significant in driving HGG progression [92] were affected and removed from the patients' blood by ANP, including 51 aberrations of TP53, 19 of PIK3CA, 11 of NF1, 9 of PTEN, 5 of EGFR, 3 each of CCND1, IDH, and PDGFRA, and 1 each of CCND2, CDK6, CDKN2A, and CDKN2B. Some of these changes may have been influenced by other prescription drugs given to patients with advanced disease. New data will supplement these results once the number of tested genes increases beyond the 600-800 genes currently being tested. Based on this new information, we will include additional targeting agents along with ANP in treatment regimes, likely improving the rate of ORs and length of survival [87].

The survival of 61 evaluable, non-GBM HGG patients patients from 5 years to 33 years and the survival of 23 evaluable patients in this group from 12 years to 33 years, is very unusual. Surviving patients have no adverse long-term sequelae related to ANP and live normal lives, with healthy children. Thirty patients experienced Serious Adverse Events (SAEs) that were unrelated to ANP and all fully recovered. Four patients experienced six SAEs that were possibly related to ANP (fever without infection, nausea, dizziness and somnolence) and all fully recovered, as well. The authors are not aware of similar findings from other clinical studies of HGG.

Based on the OSD data shown above and the lack of consistently corresponding ORs, it is very likely that another ANP mechanism of action contributes to the unusually long survival observed in the 61 HGG patients. Additional publications describing the unusually long survival of patients receiving ANP in phase II studies of GBM, Recurrent Medulloblastoma (RMB) and Diffuse Intrinsic Pontine Glioma (DIPG) have already been published [66-68].

CONCLUSION

We present here the unusually long OSD seen in 61 non-GBM HGG patients treated in Phase II clinical studies with ANP, a therapy that avoids the long-term sequelae of RT and CH. The survival of 23 HGG patients for more than 12 years implies a cure. Because these studies were performed before current genomic testing techniques were available, these new technologies will permit better clinical trial design, improved cohort stratification and more accurate results.

ANP has proven to be an attractive option for a wide range of patients with persistent, recurrent, disseminated and/or metastatic brain tumors. Multiple Phase II clinical studies of Antineoplaston therapy in various advanced primary brain tumors, conducted under the Burzynski Research Institute's IND # 43,742, have now been completed and numerous articles have been published. The results presented here show that ANP is an effective option for treating HGG without causing long-term toxicity. Our group of HGG patients with exceptionally long-term survival is the largest series of HGG survivors documented in the world literature. Our findings support ANP as a viable treatment choice for these aggressive brain tumors.

ACKNOWLEDGEMENT

The authors would like to express their appreciation to Carolyn Powers and Tanya Miller for their involvement.

CONFLICT OF INTEREST

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

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