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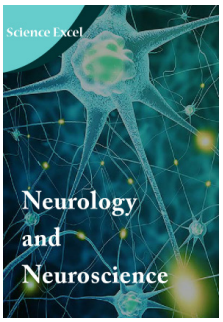

Unusually Long Survival from Diagnosis (More Than Three Years to More Than 29 Years) in 27 Glioblastoma Patients Treated with Antineoplastons in Phase II Studies

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Abstract

Glioblastoma (GBM), the most common malignant primary brain tumor in adults, has a poor prognosis, with a median survival of 12-15 months. The morbidity of standard therapy can be devastating in long-term survivors. Twenty-six patients with GBM and one with gliosarcoma (GS) were treated with Antineoplastons A10 and AS2-1 (ANP) in Phase II clinical studies at the Burzynski Clinic. The unusually long survival and lack of long-term negative sequelae in these patients are emphasized. Eligibility criteria for protocol ANP included a Karnofsky/Lansky (KPS/LPS) score of 60 or higher and a life expectancy of two months or more. IV ANP was given to all patients, while some also received oral ANP. Gradually increasing doses of IV ANP were administered via subclavian catheter and infusion pump until maximum tolerated doses of A10 and AS2-1 were achieved. Outcome criteria were tumor response, survival, and toxicity. The Kaplan-Meier survival analysis for 574 GBM/GC patients receiving protocol ANP yielded a median survival of 0.966 years. Twenty-seven of these patients (4.7%) survived from more than 3 years to more than 29 years. Seven of these 27 patients survived more than 12 years, a definition of cure. Age at admission to BC ranged from 6.5 to 68.0 years, with a median age of 38.4 years. KPS/LPS ranged from 40 to 100 with a median of 50. Patients with a KPS/LPS score of less than 60 received treatment as Special Exceptions. One patient experienced a serious adverse event possibly related to treatment and recovered fully. ANP shows promise in the treatment of GBM/GC.

Introduction

Glioblastoma is the most common malignant primary brain tumor in adults, known for its highly invasive and aggressive nature and its poor prognosis. It is also the deadliest. In the USA, Glioblastoma (GBM) accounts for 13.9% of all brain tumors and 51.5% of all primary malignant brain tumors with an annual incidence rate of approximately 3.27 per 100,000 population [1,2]. It primarily affects older adults (≥ 40 years of age) with a yearly incidence of 7.07/100,000, non-Hispanic whites (3.71/100,000), and males (3.71/100,000) [2]. Incidence rates in European registries range from 3 to 5 cases per 100,000 people annually [3,4]. Lower incidence rates have been reported in Asia and Africa, possibly due to underdiagnosis or underreporting [5]. Genetic and environmental factors contribute to the etiology of GBM. Mutations in TP53, EGFR, and PTEN are often observed [6], while ionizing radiation is the most definitive environmental risk factor [7]. Pesticide exposure is a potential ecological risk factor [8], while a high intake of N-nitroso compounds in the diet may also be a risk factor [9].

Gliosarcoma (GS), consisting of both glial and mesenchymal components and showing infrequent EGFR mutations, is a mesenchymal variant of GBM [10]. The estimated incidence of GS among pediatric GBM is 2% [11]. The GS therapy described in the literature yields an overall survival rate of less than nine months [11]. We have previously reported on the case of a nine-year-old child with recurrent, diffuse pontine GS and survival of more than 13 years after ANP [12]. At last contact, this person's survival is now more than 25 years after ANP and more than 26 years from diagnosis.

The diagnosis of GBM/GS involves clinical signs and symptoms, imaging, and histological examination of tumor tissue. Magnetic resonance imaging (MRI) is a key diagnostic tool for assessing tumor size, location, and the extent of edema and necrosis. A definitive diagnosis, however, depends on histopathological examination, which is usually performed on biopsy specimens following surgery. Histologically, GBM/GS are classified as grade IV tumors by

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the World Health Organization (WHO) due to their cellular polymorphism, necrotic foci surrounded by pseudo-palisading cells, microvascular proliferation, and a high mitotic index, all of which contribute to their poor prognosis [13,14]. Immunohistochemistry can detect antigens such as GFAP (glial fibrillary acidic protein), which confirms the diagnosis of GBM [10].

Bruner and colleagues reported on diagnostic discrepancies and their clinical impact [15]. In 1995, the first five hundred brain/spinal cord biopsies submitted to their neuropathology consultation service were reviewed. Serious disagreements (immediately significant for therapy or intervention) or potentially substantial disagreements (a discrepancy in type or grade of glioma) were found in 140 cases (28.0%). From this, they concluded that an expert neuropathology interpretation was prudent and cost-effective [15].

In the 2021 WHO classification, genomic descriptors of high-grade glioma were emphasized [16,17]. GBM now refers to adult-type IDH wild-type (and mutant) diffuse astrocytic glioma. High-grade pediatric-type diffuse gliomas include methylation of histone 3 (H3) on lysine 27 (H3K27) - altered diffuse midline glioma, glycine 34 of H3 (H3G34) - mutant diffuse hemispheric glioma, H3 wild-type, IDH wild-type pediatric-type diffuse high-grade glioma, and pediatric-type hemispheric glioma [16,17]. Of interest in this regard is the 2003 review by Senger and colleagues in which they summarized the genomic characteristics of GBM while analyzing predictors of survival [18]. They found that abnormalities of TP53 are common in long-term GBM survivors (LTGBMS) and highlighted the potential for molecular profiling, using evolving technologies, with subsequent tailoring of therapy.

MRI protocols for GBM and GS include T1-weighted images, both pre- and post-contrast administration, T2-weighted images, and Fluid-Attenuated Inversion Recovery (FLAIR) sequences. Post-contrast T1-weighted images highlight areas of active tumor, which is shown by contrast enhancement secondary to blood-brain barrier disruption [19]. T2/FLAIR imaging provides information concerning the extent of edema and infiltrative tumor, which appear hyperintense compared to normal brain parenchyma.

Positron Emission Tomography (PET) scans provide information that is not available from conventional MRI scanning. They can detect metabolic activity in GBM and GS, which correlates with tumor viability [20] and can distinguish between tumor recurrence and radiation necrosis [21]. The standard tracer used in oncology PET scans is F-18 fluorodeoxyglucose (18F-FDG), a glucose analog. However, FDG-PET has shown variable effectiveness in the brain with its naturally high glucose uptake, which can mimic tumor activity. As a result, other radiotracers such as 11C-methionine (11C-MET), 18F-fluoroethyl-tyrosine (18-FET), 18F-florbetaben (18-ABETA) and 18F-dopa have been used. These tracers are more effective in differentiating tumor tissue from non-tumor tissue secondary to their lower uptake in healthy brain tissue and higher uptake within tumor tissue [22].

The presenting clinical signs and symptoms for GBM vary depending on the tumor's location in the brain, but include 1) headaches; 2) seizures; 3) neurological defects (weakness, sensory loss, incoordination, imbalance); 4) cognitive/personality changes (memory loss, confusion, misbehavior; altered personality); 5) speech difficulties (problems speaking or understanding); and 6) visual disturbance (blurred-, double-, or loss-of-vision). These signs/symptoms are often progressive.

In a population-based study of GBM [23], Scott and associates determined that 1) GBM carried a minimal chance for long-term survival (≤ 1.8%), 2) near-total or total tumor resection followed by chemotherapy (CH), in high-performance status patients, provided for the possibility of long-term survival, 3) GBM patients with long-term survival (LTGBMS), when compared to control GBM patients, had a younger age, a better performance status, and lower tumor proliferation rates; and 4) LTGBMS patients often developed severe treatment-induced dementia.

Since 2005, the standard treatment for GBM has been maximum surgical resection followed by adjuvant radiation therapy (RT) and adjuvant temozolomide, which improves survival in GBM by enhancing the effectiveness of RT. This combined treatment approach has improved the median survival of patients with GBM [24,25]. The development of new techniques intending to improve resection rates without causing neurological morbidity are being developed: 1) 5-aminolevulinic acid (5-ALA), a natural precursor of hemoglobin, is a fluorescent dye that is preferably picked up by tumor cells after being orally administered 2–3 hours before surgery (fluorescence-guided surgery) [26,27]; 2) Awake surgery allows for real-time monitoring of patient functions; 3) Intraoperative language mapping is performed through a combination of awake surgery and direct cortical stimulation with positive results and relative safety [28]. Since GBMs are highly infiltrative tumors, confocal intraoperative microscopy provides microscopic images of brain tissues in vivo during surgical procedures, thereby improving the resection of tumor margins [29,30].

GBM is associated with poor prognosis. The 5-year mortality rate is > 90% while median survival time is approximately 12-15 months with standard therapy, which, as presented above, includes maximum surgical resection followed by adjuvant RT and temozolomide [31].

In 1998, Salvati and colleagues reported on 11 patients with cerebral GBM who had an overall survival since diagnosis (OSD) of ≥ five years [32]. All patients had surgical resection and adjuvant RT plus CH. After a mean interval of 3.9 years from treatment, five patients (45%) developed local recurrence. After a mean interval from therapy of 8.1 years, seven patients (64%) were alive, while four patients (36%) had died from local recurrence. They concluded that OSD in their patients was influenced by age and treatment. In addition, their review of the literature suggested that the site of a primary GBM (supratentorial vs. infratentorial) may affect survival. For example, Kawauchi and colleagues reported on 134 GBM patients with newly diagnosed IDH-wildtype GBM [33]. Of these, six (4.5%) had infratentorial recurrence and received additional CH. They found that post-recurrence survival was significantly shorter compared to general GBM cases (5.5 vs. 9.1 months, $P = 0.023$), concluding that infratentorial recurrence was associated with a more aggressive disease course.

We present the Burzynski Clinic (BC) experience utilizing Antineoplastons Atengenal (A10) and Astugenal (AS2-1), i.e., Antineoplaston therapy (ANP), in Phase II studies of GBM. Long-term survival and lack of long-term adverse sequelae following ANP are emphasized.

Materials and 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 [34]. Subsequent studies of the isolated Antineoplastons

demonstrated that Antineoplaston A10 and Antineoplaston AS2-1 were the most active Antineoplastons. 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. When given orally, Antineoplaston A10 resists the attack of gastric enzymes. In the small intestine, under alkaline conditions, 30% is digested into phenylacetylglutamine (PG) and phenylacetylisoglutaminate (isoPG) in a ratio of approximately 4:1. The mixture of synthetic PG and isoPG in a 4:1 ratio, dissolved in sterile water, constitutes 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 [35].

We address here the utility of ANP in the context of 1) 27 GBM patients, diagnosed between March 1992 and August 2012, who survived over 3 years - a milestone of LTGBMS, and 2) seven GBM patients surviving more than 12 years from the time of diagnosis (OSD), a definition of cure [18,32]. These patients were seen at the Burzynski Clinic (BC) between August 1992 and December 2012. GBM patients were treated according to single-arm, two-stage, phase II studies of ANP. In all protocols, IV ANP was utilized, while in some, oral ANP was also given. Patients received gradually increasing doses of IV ANP via subclavian catheter and infusion pump, until a maximum tolerated dose of A10 and AS2-1 was achieved. Eligibility criteria included a Karnofsky/Lansky Performance Score (KPS/LPS) of 60-100 and a life expectancy of more than 2 months. Special Exception (SE) status was granted to patients by the Food and Drug Administration (FDA) due to their inability to meet all eligibility criteria. All study patients and/or their legal guardians read, understood, and signed an Informed Consent Document before treatment. Outcome criteria were 1) objective response (OR), 2) OSD, and 3) toxicity. 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 these GBM patients. Brain MRIs were typically performed every 8 weeks for the first two years and then less frequently thereafter. T2-weighted, T2-FLAIR, and T1-weighted images, both non-enhanced and enhanced, were obtained. GBMs exhibit gadolinium enhancement, and sequential T1-weighted contrast-enhanced images were utilized to determine the effect of therapy [36]. As defined 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 [36, 37]. The response criteria were as follows: a complete response (CR) indicated complete disappearance of all enhancing tumors, while a partial response (PR) indicated a 50% or greater reduction in SUM. CR and PR required a confirmatory brain MRI performed at least four weeks after the initial finding. Progressive disease (PD) indicated a 25% or greater increase in SUM or new measurable and enhancing disease, while stable disease (SD) did not meet the criteria for PR or PD [36, 37].

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

Of the 574 GBM/GS patients treated with ANP at BC, twenty-seven patients (4.7%) had an OSD of more than three to more than 29 years. Seven of these patients had an OSD of more than 12 years, a definition of cure [18,32], while two had OSDs of more than 26 years and one of these had an OSD of more than 29 years.

Before being seen at the BC, five of the twenty-seven long-term survivors had surgical resection only, three had surgical resection and RT, and four had surgery, RT, and CH. Based on the decision of the neurosurgeon, two patients did not have initial surgical resection. Twelve patients had more than one surgery, more than one course of RT, and more than one course of CH. Details of demographics, prior treatment, and overall

Table 1. *Demographics, Prior treatment, and Overall survival from diagnosis*

	N=574	N=27
Sex		
Male	337	16
Female	237	11
Age (at admission at BC)		
range	3.3 – 84.1	6.5 – 68.0
median	50.6	38.4
Age groups (at admission at BC) per ABTA		
0-14	38	2
15-39	104	12
40+	432	13
KPS/LPS (at admission at BC)		
range	30 - 100	40 - 100
median	50	50
Prior Treatment - single treatments / multiple treatments		
SU, RT, CH / multiple SU, RT, CH	72 / 150	4 / 12
SU, CH / multiple SU, CH	12 / 5	
SU, RT / multiple SU, RT	80 / 20	3 / 1
RT, CH / multiple RT, CH	24 / 19	1 / 1
SU / multiple SU	109 / 7	5 / 0
CH / multiple CH	5 / 0	
RT / multiple RT	29 / 1	
Biopsy only	39	
MRI only	2	
Overall Survival from diagnosis		
over 6 months	76.10%	NA
over 3 years	4.70%	100%
Over 12 years	1.22%	26.00%

ABTA - American Brain Tumor Association, BC-Burzynski Clinic, CH-chemotherapy, KPS/LPS-Karnofsky Performance Score/Lansky Performance Score; RT-radiation therapy, SU-surgery

***Table 2**: Diagnosis, Prior treatment, and Tumor status at start of ANP*

Case	Date of Histological Diagnosis (m/d/yr)	Histological Diagnosis	Treatment Prior to ANP	Tumor Status at Start of ANP
1	3/31/1992	GBM	SU, RT	Supratentorial; Single; Primary
2	5/3/1993	GBM	Bx, RT, CH, tamoxifen	Supratentorial; Single; Primary
3	5/4/1995 5/22/1995 10/27/1997 1/13/1998	GBM GBM GBM GBM	SU, RT, CH	Supratentorial; Single; Primary
4	10/6/1995 10/20/1995 11/14/1995	GBM GBM GBM	SU	Supratentorial; Single; Primary
5	6/2/1995	GBM	SU, RT, CH	Supratentorial; Single; Primary
6	12/6/1995 12/13/1995 12/27/1995 07/24/1997	GBM GBM Anaplastic oligodendroglioma GBM	SU	Supratentorial; Single; Primary
7	8/2/1994 4/4/1996	GBM /oligodendroglioma Mixed Glioblastoma with Anaplastic Oligodendroglioma	SU, RT, 2CH	Supratentorial; Single; Primary
8	11/17/1993	GBM	SU, RT	Supratentorial; Single; Primary
9	7/3/1996	GBM	SU	Supratentorial; Single; Primary
10	12/10/1992 11/4/1994 6/15/1995	GBM GBM GBM	3xSU, 2xRT, 2xCH, Gene therapy	Supratentorial; Single; Primary
11	8/26/1996	Gliosarcoma	SU, 2xRT, CH	Supratentorial; Single; Primary
12	6/8/1994	GBM	SU, 2xRT, 2xCH, tamoxifen	Supra- and Infratentorial; Multicentric; Primary
13	10/22/1993	GBM	SU, RT, CH	Infratentorial; Single; Primary
14	5/6/1997 6/11/1998	GBM	2xSU, 2xRT	Supratentorial; Single; Primary
		GBM		
15	6/4/1999	GBM of pons	SU, RT	Infratentorial; Single; Primary (DIPG)
16	3/10/1995 3/31/1995 8/11/1995 2/10/1999 2/26/1999 3/2/1999 3/10/1999	Astrocytoma, meningioma vs. schwannoma Astrocytoma Pilocytic astrocytoma Mixed glioma Gliosarcoma High grade glioma Anaplastic astrocytoma	3xSU, 3xRT, 2xCH	Supra- and Infratentorial; Multicentric; Secondary (GS/DIPG)
17	4/15/1999	GBM	Bx, 2xRT, CH	Supratentorial; Single; Primary
18	12/3/2001	GBM, Small Cell type	SU, RT, CH	Supratentorial; Single; Primary
19	12/27/2003	GBM	3xSU, RT, CH	Supratentorial; Single; Primary
20	4/30/2004 6/2/2004	GBM GBM	2xSU, RT, CH	Supratentorial; Single; Primary
21	11/20/2002 3/15/2005	GBM/oligodendroglioma with gemistocytic components GBM	2xSU, RT, 2xCH	Supratentorial; Multicentric; Primary
22	12/23/2002	GBM	SU, RT, CH	Supratentorial; Multicentric; Primary
23	9/15/2006	GBM	SU	Supratentorial; Single; Primary
24	12/14/2004 12/13/2005	GBM GBM	3xSU, 2xRT, 3xCH, TT	Supratentorial; Single; Primary

Case	Date of Histological Diagnosis (m/d/yr)	Histological Diagnosis	Treatment Prior to ANP	Tumor Status at Start of ANP
25	9/10/2007 3/31/2010 7/8/2010	GBM Anaplastic Oligodendroglioma GBM	3xSU, RT, 3xCH, TT	Supratentorial; Single; Primary
26	12/21/2009 9/19/2011	GBM GBM	2xSU, RT, 3xCH, TT	Supratentorial; Single; Primary
27	8/3/2012	GBM /oligodendroglioma	SU	Supratentorial; Multicentric; Primary
ANP-Antineoplaston therapy, Bx-Biopsy, CH-Chemotherapy, DIPG-Diffuse intrinsic pontine glioma, GBM-Glioblastoma, GS-Gliosarcoma, RT-Radiation therapy, TT-Targeted therapy				

Table 3. *Best response to ANP, Overall survival from Diagnosis, and Status at Last Follow-up (August 2025)*

Case	Age at admission	Sex	ANP Protocol	Special Exception?	ANP Start Date (m/d/yr)	Days on ANP	Best Response	Status at Last Follow-up	OSD at Last Follow-up (Years)
1	43	F	CAN-01	No	8/24/1992	1489	CR	Deceased	25.68
2	48	M	CAN-01	No	12/7/1993	932	PR	Deceased	4.32
3	33	F	CAN-01	No	9/26/1995	862	PR	Deceased	3.15
4	37	M	BT-07	No	11/16/1995	243	PR	Alive	29.86+
5	34	F	CAN-01	No	12/27/1995	1184	CR	Deceased	27.44
6	62	M	CAN-01	No	1/5/1996	2303	CR	Deceased	6.52
7	28	F	BT-20	No	4/2/1996	119	CR	Deceased	9.45
8	48	F	BT-20	No	5/8/1996	412	PD	Deceased	3.64
9	34	F	BT-07	No	8/2/1996	199	SD	Deceased	3.53
10	25	M	BT-20	Yes	2/15/1997	139	PD	Deceased	4.64
11	36	M	BT-09	Yes	7/21/1997	219	SD	Deceased	4.06
12	38	M	BT-20	Yes	10/15/1997	290	SD	Deceased	4.32
13	6	F	BT-06	Yes	1/14/1998	107	PD	Deceased	5.08
14	46	F	BT-20	Yes	8/10/1998	948	CR	Deceased	25.47
15	40	M	BT-11	Yes	9/30/1999	691	CR	Deceased	7.40
16	9	M	BT-22	Yes	12/03/1999	2505	CR	Alive	26.48+
17	41	M	BT-20	Yes	12/10/1999	61	NE	Deceased	6.02
18	42	M	BT-21	No	1/16/2002	410	CR	Deceased	15.24
19	61	F	BT-21	Yes	4/27/2004	6	NE	Deceased	3.76
20	59	M	BT-21	Yes	9/24/2004	197	CR	Deceased due to NHL	13.36
21	26	M	BT-21	No	6/16/2005	7	NE	Deceased	3.01
22	45	M	BT-09	Yes	7/28/2005	195	PD	Deceased due to RF	3.13
23	27	M	BT-09	Yes	11/8/2006	80	PD	Deceased	4.44
24	35	F	BT-21	Yes	3/12/2009	29	PD	Deceased	4.46
25	25	M	BT-20	Yes	6/7/20011	62	PD	Deceased	3.91
26	68	F	BT-09	Yes	12/17/2004	29	NE	Deceased	3.13
27	48	M	BT-09	Yes	11/6/2012	99	PD	Deceased	3.41
ANP-Antineoplaston therapy, CR-Complete response, F-Female, M-Male, NE-Non-evaluable, NHL-Non-Hodgkin's lymphoma, OSD-Overall survival from diagnosis, PD-Progressive Disease, PR-Partial response, RF-Respiratory failure, SD-Stable disease									

survival from diagnosis are presented in Table 1.

Among the twenty-seven long-term survivors, twenty-six had GBM and one had GS. One of the GBMs and the GS were secondary tumors. Pathologists with academic affiliations established the histological diagnoses, and thirteen cases were confirmed by educational faculty, including prominent neuropathologists. Details of the diagnosis, prior treatment, and tumor status at the start of ANP are presented in Table 2.

At admission to BC, the age of these patients ranged from six to 68 years. There were eleven females and sixteen males. KPS/LPS scores ranged from 40 to 100 with a median score of 50. Sixteen patients (59.3%) were not eligible for protocol ANP but, after approval by the Food and Drug Administration (FDA), were treated according to protocol as SEs.

All ORs were confirmed by prominent neuroradiologists who were not affiliated with BC. ORs were a CR in nine cases, a PR in three cases, SD in three cases, and PD in eight cases. Four cases were non-evaluable. Seventeen of twenty-seven patients (63.0%) received no additional treatment after discontinuation of ANP. Two of these twenty-seven patients (7.4%) were alive at the time of this publication. They both had OSDs of more than 26 years, while one had an ODS of more than 29 years. Overall Survival from the Start of Treatment (OSS) was more than 25 years and more than 29 years, respectively. Best response to ANP, and overall survival from diagnosis and, status at last follow-up are presented in Table 3.

Kaplan-Meier Survival analysis described a median overall survival from diagnosis (OSD) of 0.966 years (95% CI 0.887 to 1.005) in 574 GBM patients treated with ANP. See Figure 1, where the "Time" axis is presented in increments of 5 years. In our observation, survival for these patients extended past 25 years. Of thirteen serious adverse events (SAEs), only one could possibly be attributed to ANP. The involved patient recovered fully from the SAE.

Three representative cases are briefly described:

Case #1: This 43-year-old female was first seen at the Burzynski Clinic (BC) on August 17, 1992. She had been diagnosed with GBM on March 31, 1992, following resection of a right parietal tumor. Subsequent treatment (April 1992 to June 1992) included RT but no CH. At the BC, the initial physical examination was routine except for a craniotomy scar. KPS was eighty. She was admitted to the CAN-1 protocol and treated with IV and oral ANP. Baseline tumor SUM (August 21, 1992) was 3.20 cm^2. On February 8, 1993, no enhancing tumor was seen, indicating a CR. The patient survived 25.7 years after diagnosis. She had no SAEs related to ANP.

Case #2: This 37-year-old male was first seen at the BC on November 14, 1995. He had been diagnosed with GBM on October 6, 1995, following subtotal resection of a right frontal tumor. There was no subsequent RT or CH. At the BC, initial physical examination revealed forgetfulness and a craniotomy scar. KPS was ninety. He was admitted to the BT-07 protocol and was treated with IV ANP. Baseline tumor SUM (November 14, 1995) was 8.00 cm^2. On February 9, 1996, the tumor SUM was 3.96 cm^2, indicating a PR. The patient was alive at last contact and, at last contact, had survived 29.8 years after diagnosis. During ANP, he had no SAEs related to ANP.

Case #3: This 46-year-old female was first seen at the BC on August 7, 1998. She had been diagnosed with GBM on May 6, 1997, following partial resection of a right temporal tumor. Subsequent treatment included RT (May 1997 to June 1994), partial tumor resection on June 3, 1998, and gamma knife radiosurgery on 10/28/1997. There was no subsequent CH. At the BC, initial physical examination revealed upper extremity ataxia and bilateral fundal blurring, as well as abdominal and craniotomy scars. KPS was fifty. She was treated according to the BT-20 protocol, as a CE, receiving IV and oral ANP Baseline tumor SUM (July 30, 1998) was 1.56 cm^2. On December 8, 1998, no enhancing tumor was seen, indicating a CR. She survived 25.5 years after diagnosis and had no SAEs related to ANP.

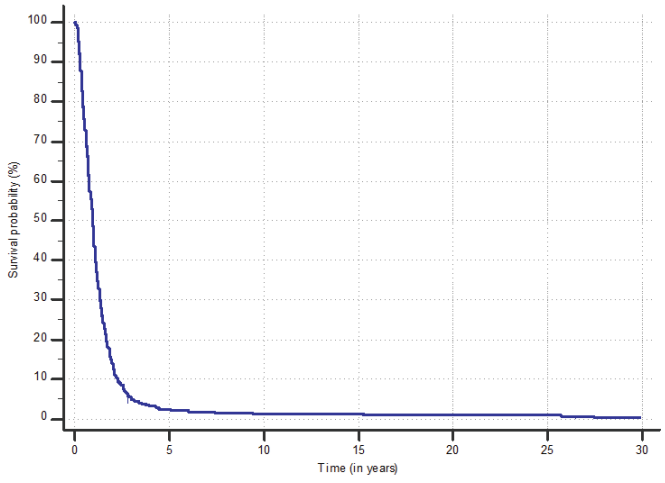

***Figure 1**: Kaplan-Meier Survival Curve for 574 GBM patients*

Discussion

We present here twenty-seven patients with GBM/GS who received ANP in Phase II studies. They had an OSD of more than three years to more than 29 years. Seven patients had an OSD of more than 12 years, a definition of cure [18,32].

In a retrospective, single-center study, O. Aboubakr and colleagues examined the medical records of 976 patients with newly diagnosed IDH-wildtype supratentorial GBMs, who were seen between January 2000 and January 2021 [38]. They analyzed the clinical, imaging, and treatment-related factors associated with 2- and 5-year survival, finding the median overall survival (OS) to be 11.2 months and the median progression-free survival (PFS) to be 9.4 months. Regarding OS, 17.6% of patients survived 2 years (6.6% without progression) while 2.2% survived 5 years (1.1% without progression). Therefore, 11 patients had a PFS of more than 5 years. No OS of more than 5 years was described. Factors consistently associated with 2- and 5-year OS were standard temozolomide CH and O6-methylguanine DNA methyltransferase (MGMT) promoter methylation.

In a retrospective, single-center study, G. Chehade and colleagues examined the medical records of 120 patients with IDH-wildtype GBMs, who were operated on at their institution between 2013 and 2018 [39]. The median follow-up time from the patients' first surgeries was 61.9 months (5.2 years), while the median OS was 12.6 months. Long-term OS was described as more than 3 years; however, OS of more than 6 years and PFS were not reported. The investigators determined that age less than 70 years, at least 95% tumor resection, MGMT promoter

methylation, and adjuvant temozolomide CH were associated with long-term OS.

In patients with GBM, OSD of 12 or more years is rarely reported in the world literature, and this is typically only in reference to solitary case reports. Between August 1992 and September 2004, 574 GBM/GS patients were seen and treated in single-arm, two-stage Phase II studies conducted at BC under the Burzynski Research Institute's IND #43,742. Seventy-six of these patients (13.2%) survived for at least two years, while 27 (4.7%) survived for at least three years, and 7 (1.2%) survived for at least 12 years.

GS is a rare and aggressive variant of GBM characterized by both glial and mesenchymal histopathologic components. It accounts for an exceedingly small percentage of high-grade gliomas and is associated with a poor prognosis. Median survival is less than one year. Compared to GBM, GS exhibits distinct molecular characteristics, including alterations in the PI3K/Akt and RAS/MAPK signaling pathways. PTEN mutations appear to be more frequent in GS than in GBM [40]. A review and meta-analysis of GS found that gross total surgical resection, high-dose RT, and temozolomide CH improve overall survical (OS) in GS patients, but there were no long-term survivors [41].

We present here the first report of long-term OSD in 27 GBM/GS patients being enrolled in Phase II studies. The last follow-up was in August 2025. Those patients who received only surgery and ANP avoided the long-term adverse sequelae of 1) temozolomide CH, including myelodysplastic syndrome, acute myeloid leukemia, aplastic anemia, and opportunistic infections [42] and 2) the long-term adverse sequelae of RT, including cognitive impairment, endocrinopathies, cerebrovascular accidents (CVAs), necrosis, and secondary neoplasms [43].

We have reported previously on the lack of long-term adverse sequelae and the resolution of presenting signs and symptoms in brain-tumor patients treated with ANP [44-61]. In these patients, we have also observed the achievement of ORs with the subsequent development of PD following dosage reduction or cessation of ANP. However, we also observed re-establishment of the ORs in these patients following higher dosages or re-establishment of ANP. This replication of the effectiveness of ANP based on dosage increase and/or re-establishment of ANP adds credence to ANP's efficacy in brain tumors.

The mechanism of action of ANP differs from that of RT or cytotoxic CH. The growth of normal cells is controlled by cell cycle progression genes (oncogenes) and cell cycle arrest genes (tumor suppressor genes). In cancer, alteration of these control genes in malignant cells favors aggressive cell proliferation. Evidence suggests that ANP affects approximately 535 mutated genes in the malignant genome and functions as a "molecular switch" that "turns on" tumor-suppressor genes and "turns off" oncogenes [62,63]. 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.

Genomic analysis was not practiced at the time the twenty-seven patients presented here received ANP at BC. However, in 2015, we reported our genomic analysis of a recurrent glioblastoma (rGBM) patient (case #20 in this report), who survived for more than 13 years [64]. Using a next-generation sequencing (NGS)- based assay of 343 cancer-related genes and introns, comprehensive genomic profiling of tumor tissue obtained from this rGBM patient was performed 11 years after diagnosis, allowing for the assignment of the patient's rGBM to the classical subgroup. The most critical genomic alterations included amplification of the epidermal growth factor receptor (EGFR), loss of cyclin-dependent kinase inhibitors 2A and 2B (CDKN2A/B), loss of phosphatase and tensin homolog (PTEN), and a mutation in telomerase reverse transcriptase (TERT). An analysis of the signaling networks and other targets of ANP was presented [64]. Based on our findings, patients with classical rGBM were deemed to have a reasonable possibility of responding to ANP and obtaining long-term survival.

Of the 650 mutations in the GBM genome, approximately 450 are affected by ANP, leaving approximately two hundred mutations unaffected by ANP. In this setting, ANP will provide an objective response in only some patients. Adding prescribed targeted drugs, such as dasatinib, everolimus, and pazopanib, at one-quarter of their usual dose, and bevacizumab at 10 mg/kg every 2 weeks, resulted in an objective response in six of seven rGBM patients (85.7%) [65]. Tumor response to ANP was assessed by MRIs of the brain and analyzed retrospectively.

In our study, twenty-nine adult rGBM patients were treated between September 11, 2015, and June 23, 2018. Seven of these patients (24.1%) had no prior treatment with bevacizumab, had radiologic evidence of rGBM, and had MRI assessment of tumor response to treatment. These seven rGBM patients formed our study cohort. The median treatment time was 101 days (range, 55-208 days). An OR was seen in six patients (85.7%), with a CR being seen in four patients (57.1%), a PR being seen in two patients (28.6%), and PD being seen in one patient (14.3%). The median time to first response was 29 days (range: 22-96 days) while the median duration of response was 141 days (range: 55 days to more than 739 days). Six-month and 12-month PFS were 57% and 19%, respectively, while 6-month and 12-month OS were 86% and 54%, respectively. Treatment was well-tolerated with no patients experiencing grade 3 or 4 ANP-related toxicity. Regarding response to treatment and toxicity, ANP plus targeted therapy compares very favorably with other reported rGBM therapies, but our findings require confirmation in larger studies.

Conclusion

We present here the unusually long survival (ranging from more than three years to over 29 years) in 26 GBM patients and one GS patient treated with ANP in Phase II studies. Seven of these patients survived more than 12 years, a definition of cure [18]. We also demonstrated a lack of long-term adverse sequelae when using ANP, thereby avoiding the long-term negative sequelae associated with RT and temozolomide CH. In addition to the clinical studies cited above, multiple Phase II clinical studies of ANP, under the Burzynski Research Institute's IND #43,742, have been completed in a variety of low- and high-grade brain tumors, with numerous articles being published [66-94]. Based on our findings, we propose a multi-institutional Phase II clinical study of ANP, in combination with targeted agents, for the treatment of GBM.

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Conflict of Interest

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

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