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RESEARCH ARTICLE

Unusually Long Survival (More Than Five Years to More Than 31 Years) in Twelve Patients with Relapsed Medulloblastoma Treated with Antineoplastons in Phase II Studies

Stanislaw Rajmund Burzynski[1,*], Gregory Stanislaw Burzynski[1], Tomasz Jan Janicki[1], Radoslaw Jan Siwiec[2], and Samuel Warner Beenken[3]

ABSTRACT

Background: **Medulloblastoma (MB), a grade 4 embryonal neoplasm, is the most common malignant brain tumor in children and adolescents. Relapsed MB (RMB) carries a poor prognosis with less than 10% surviving more than 5 years post-relapse.**

Objective: **Twelve patients with RMB were treated with Antineoplastons A-10 and AS-2-1 (ANP) according to phase II clinical studies. They are presented here, emphasizing unusually long survival and a lack of long-term negative sequelae.**

Methods: **For clinical studies, the eligibility criteria had to include a Karnofsky/Lansky (KPS/LPS) score of at least sixty and at least a 2-month life expectancy. IV ANP was given to all patients, while some also received maintenance treatment with oral ANP. IV ANP infusions utilized a subclavian catheter and an automated pump. The maximum tolerated doses of A10 and AS2-1 were achieved. Outcome criteria were objective response, survival, and toxicity after ANP therapy.**

Results: **The Kaplan-Meier Survival analysis for the 46 RMB patients gave a median survival of 2.42 years. Twelve of 46 RMB patients survived from more than 5 years to more than 31 years (26.1%). Five of these patients survived more than 12 years, a definition of cure. The patients were between the ages of 1.5 to 29.7 years old with a 9.2-year median age. LPS/KPS ranged from 50 to 100 with a median score of 60. One patient experienced a serious adverse event (somnolence), possibly attributed to ANP, from which he quickly recovered fully.**

Conclusions: **ANP therapy shows promise for the long-term survival of RMB patients with no long-term toxicity.**

Keywords: Antineoplastons, medulloblastoma, phase II studies, relapsed medulloblastoma.

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[1] *The Burzynski Clinic, United States.*
[2] *Lubgen Farma, Poland.*
[3] *Oncology Writings, United States.*

* ***Corresponding Author:***
e-mail: srb@burzynskiclinic.com

1. Introduction

Medulloblastoma (MB), a grade 4 embryonal neoplasm primarily affecting the posterior fossa, is the most common malignant brain tumor in children and adolescents (ages 0–19 years). It accounts for 69.1% of cases of malignant brain tumors in this age group, with a reported average yearly incidence of 311 cases in the USA. Average yearly incidence in all age groups was 431 [1]. MB primarily affects children, ages 1–9, ten times more frequently than it affects adults [2]. In the children and adolescent group, males were affected 1.7 times more frequently than females [1].

The diagnosis of MB involves clinical signs and symptoms, and imaging studies, histological examination, and molecular studies of the tumor tissue. The imaging study of choice is magnetic resonance imaging (MRI) of the

brain and spinal column, which can be performed with or without gadolinium. MRI demonstrates the anatomical relationship between the tumor and its surroundings, as well as tumor location, size, and the extent of edema and necrosis.

The definitive diagnosis of MB is most often based on histological examination and molecular studies of post-surgical tissue specimens. In the 2021 World Health Organization (WHO) classification, medulloblastoma is grouped into two categories: histologically defined medulloblastoma and molecularly defined medulloblastoma [3]. It recognizes four histological subtypes: classic MB, desmoplastic/nodular MB, MB with extensive nodularity, and large cell/anaplastic MB, as well as "four major molecular groups: Wingless/INT1 (WNT)-activated, sonic hedgehog (SHH)-activated (includes TP53-wildtype and TP53-mutant groups), non-WNT/non-SHH group 3, and non-WNT/non-SHH group 4" [4].

The clinical signs and symptoms for MB often progress over several weeks to several months. Nonspecific symptoms such as nausea, vomiting, and headaches can appear early on. These symptoms can be caused by increased intracranial pressure due to the obstruction of cerebrospinal fluid (CSF) flow by the tumor. Blurred vision, somnolence, confusion, ataxia, seizures, and unconsciousness may subsequently occur [5]. Diagnosing MB in infants can be difficult because of the lack of specific symptoms/signs. Open fontanelles and suture lines in the skull allow for its expansion, which can compensate for hydrocephalus. However, its clinical presentation can include macrocephaly associated with irritability and decreased oral intake [6]. Dissemination of MB to spinal leptomeninges is demonstrated by MRI in 20-25 % of pediatric patients at the time of the diagnosis [7].

The current standard of care for MB includes maximal safe surgical resection (SU), craniospinal irradiation (CSI), and adjuvant chemotherapy (CH). Because of the considerable toxicity associated with the use of CSI for tumors in the developing brain, treatment of infants and young children with MB typically consists of only surgery and chemotherapy [8]. The aims of surgery are maximal safe resection, relief of the mass effect, tissue diagnosis, and management of symptomatic hydrocephalus [5], [7].

These standard of care therapies provide a survival rate of 70%, while 30% of patients progress or relapse [9]. Moreover, MB survivors experience serious treatment-related adverse events. Younger patients (diagnosed before 8 years of age) develop cognitive impairment with lower IQ, memory, and executive function scores. Health-related quality of life (HRQoL) is significantly lower in most survivors, with only one-third of survivors achieving HRQoL scores equivalent to those of healthy children [10].

Relapsed MB (RMB), defined as tumor regrowth despite treatment, confers a poor prognosis with less than 10% of patients surviving over 5-years post-relapse [11], [12]. Relapses are exceedingly difficult to treat, especially when they present with distant spread [12]. The treatment for RMB centers on further resection, additional CSI, and high dose chemotherapy. The rare long-term survivor of RMB experiences serious neurocognitive sequelae [11].

2. Methods and Materials

"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" [13]–[15]. Subsequent studies of isolated Antineoplastons demonstrated that A10 and AS2-1 were the best candidates for further studies. A mixture of synthetic phenylacetylglutamine (PG) and phenylacetylisoglutaminate "(isoPG) in a 4:1 ratio, dissolved in sterile water, constitutes the Antineoplaston A10 intravenous (IV) injection. Antineoplaston A10 further metabolizes into phenylacetate (PN). Both PG and PN metabolites exhibit anticancer activity. The mixture of PN and PG in a 4:1 ratio, dissolved in sterile water, constitutes Antineoplaston AS2-1 IV injection" [13 (p. 2)], [15].

ANPs have been utilized in many Phase II clinical studies [16]–[65]. Here, we present the efficacy of ANP in the treatment of, 1) 46 RMB patients seen at the Burzynski Clinic (BC) in Phase II clinical studies between April 1994 and April 2012, and 2) a subset of 12 RMB patients with unusually long-term survival (more than 5 years to more than 31 years). The eligibility criteria for protocol therapy included a Karnofsky/Lansky score of at least 60, and a life expectancy of at least 2 months. All patients were treated according to single-arm, two-stage, phase II studies of Antineoplastons A10 and AS2-1 (ANP), which was administered by IV injection to all patients, while some also received oral ANP for maintenance. IV ANP infusions utilized a subclavian catheter and an automated pump. The maximum tolerated doses of A10 and AS2-1 were achieved. "All study patients and/or their legal guardians read, understood, and signed an Informed Consent Document prior to treatment. Outcome criteria were objective response (OR)" [13 (p. 2)] and survival. "The safety and tolerance of ANP in" [13 (p. 2)] RMB patients "were also investigated. Disease progression, unacceptable toxicity, physician decision, or patient request resulted in termination of ANP" [13 (p. 2)].

MRIs of the brain, with gadolinium enhancement, were utilized for the diagnosis and follow-up of all study patients. During the first two years of the ANP protocol, the patient's received an MRI of the brain serially every 8 weeks. Subsequently, they were utilized as needed during follow-up. T2-weighted, T2-FLAIR, and T1 weighted, (non-contrast and with contrast) images were obtained. RMBs exhibit "gadolinium-enhancement and sequential T1-weighted contrast- enhanced images were utilized to determine the effect of therapy [66]. As determined by MRI of the brain and spinal cord, the product of the two greatest perpendicular diameters of each measurable ($\geq$ 5 mm) and enhancing lesion was calculated. Tumor size was defined as the SUM of these products" [21 (p. 2)], [66], [67]. 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 the SUM. CR and "PR required a confirmatory brain MRI performed at least four weeks after the initial finding. Progressive disease (PD) indicated" new disease or a 25% or greater increase in

the SUM [21 (p. 3)]. Stable disease (SD) was present when neither the PR nor PD criteria were met. [66], [67].

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; and the Good Clinical Practices: Consolidated Guideline (E6), International Conference on Harmonization (ICH) and Guidance for Industry (FDA)." By participating in these study protocols, the investigators agreed to provide access to all appropriate documents for monitoring, auditing, Institutional Review Board review and review by any authorized regulatory agency [68 (p. 3)].

3. Results

A total of 46 patients were treated for RMB in Phase II studies at the Burzynski Clinic (BC) between April 13, 1994, and April 9, 2012. Out of 46, 31 were treated as special exceptions, which were permitted by the FDA due to the patient's poor general condition, i.e., KPS/LPS < 60, estimated life expectancy < 2 months, or the absence of other inclusion criteria.

The age range for these 46 patients when seen at BC was 1.5 to 46.0 years with a median age of 9.1 years when seen at BC. Out of 46, 34 (73.9%) of the patients were male and 12 (26.1%) were female. A total of 32 patients had SU+RT+CH, 1 had SU+RT, 8 had SU+CH, and 5 had SU only. See Table I.

Among the 46 RMB patients, there were 12 long-term RMB survivors ranging in age from 1.5 to 29.7 years with a median age of 9.2 years when seen at BC. There were 2 adult patients (16.7%) and 10 children (83.3%). Out of the 12, 8 (66.6%) of the patients were male and 4 (33.3%) were female, a slight increase in proportion of females when compared to the group of 46 RMB patients. Out of the 12 patients, 7 had SU+RT+CH, 2 had SU+CH, and 3 had SU only, which is like the profile of prior treatment compared to the whole group. See Table I.

TABLE I: Demographics, Prior Treatment, and Survival

	N = 46	N = 12
Sex		
Male	34	8
Female	12	4
Age (at admission at BC)		
Range	1.5–46	1.5–29.7
Median	9.1	9.2
Age groups (at admission at BC) per CBTRUS		
0–14	36	10
15–39	9	2
40+	1	0
LPS/KPS (at admission at BC)		
Range	30–100	50–100
Median	50	60
Prior Treatment		
SU, CH, RT	32	7
SU, CH	8	2
SU, RT	1	
SU	5	3
Overall Survival from diagnosis		
Over 6 months	95.7%	–
Over 5 years	26.1%	100%
Over 12 years	10.9%	41.7%

Note: BC-Burzynski Clinic, CBTRUS-The Central Brain Tumor Registry of the United States, CH-chemotherapy, RT-radiation therapy, SU-surgery.

The diagnoses for all 12 long-term survivors were established at academic institutions. Four patients had more than one line of standard of care (SOC). Only one patient had CSF dissemination on admission. Details of the diagnosis, prior treatment, and tumor status at the start of ANP are presented in Table II.

Seven of these RMB patients were granted a special exemption status after review by the FDA, six due to low KPS/LPS at admission to BC, and one due to an administrative decision by the FDA. Two patients received oral ANP for maintenance, one as allowed by the protocol and one under IND 22029.

All ORs were confirmed by prominent neuroradiologists who were not affiliated with BC. Out of 12 RMB patients, 8 received no additional treatment after discontinuation of ANP, and 3 were alive at the time of this publication and survived more than 18 years from diagnosis and from the start of ANP. The details and outcomes of BC treatment are presented in Table III.

Out of 12 long-term RMB patients, 4 experienced 15 serious adverse events (SAEs), and only 1 SAE (somnolence) could possibly be attributed to ANP. With the temporary stoppage of ANP, the SAE was resolved within a few hours.

Kaplan-Meier Survival analysis showed a median overall survival from diagnosis (OSD) of 2.45 years (95% CI 1.56 to 3.21). See Fig. 1, where the "Time" axis is presented in increments of 5 years and survival extended past 30 years in our observation.

Two case studies are presented for illustrative purposes.

Case #1. A two-year-old male was first seen at the Burzynski Clinic (BC) on April 11, 1994, He was diagnosed with MB on March 1, 1994, following suboccipital craniectomy and subtotal resection of the tumor on February 28, 1994. No subsequent RT or CH was performed. At the BC, the patient was observed to have a normal performance status with an LPS of 100. Physical examination results were within normal limits. On March 8, 1994, the postoperative MRI of the brain revealed RMB with hydrocephalus, postoperative changes, and three nodules in the resection area, including one involving the cerebellum. They measured 0.8 cm × 1.5 cm = 1.2 cm^2, 0.8 cm × 1.0 m = 0.8 cm^2 and 1.0 cm × 1.5 cm = 1.5 cm^2 giving a baseline "SUM" of 3.5 cm^2.

This male child was admitted to the CAN-01 protocol and was treated with IV and oral ANP. On June 1, 1994, a scheduled MRI of the brain showed no enhancing lesions, indicating CR. He has survived for more than 31 years since his RMB diagnosis and remains in excellent health. The patient has five healthy children. During ANP administration, the patient experienced two serious adverse events and recovered completely.

Case #2. A one-year-old male was first seen at the BC on March 6, 2001. He was diagnosed with MB on

TABLE II: Diagnosis, Prior Treatments, Results of Prior Treatment, and Details of Recurrence

Case	Date of Histological Diagnoses m/d/y	Diagnoses	Prior treatment	Tumor status at admission to clinical trials
1	03/01/94	Medulloblastoma	SU-subtotal	Cerebellopontine angle lesion
2	02/08/95	Medulloblastoma	SU-total, CH, RT	Relapsed at fourth ventricle and recurrent to frontal fossa
3	05/28/96	Medulloblastoma	SU-resection	Progressed to fourth ventricle, posterior fossa, and brainstem
4	10/16/97	Medulloblastoma	SU-resection	Progressed to fourth ventricle
5	03/16/92 03/11/94	1. Medulloblastoma 2. Medulloblastoma	1. SU-total, RT 2. SU-total, RT, CH 3. CH (Clinical trials)	Progressed to brainstem, midbrain and meningeal
6	12/07/94 09/03/97	1. Medulloblastoma 2. Medulloblastoma	1. SU-total, RT 2. SU (unknown), CH	Recurrences to optic chiasm, meningeal surfaces of posterior fossa, and fourth ventricle. CSF dissemination
7	09/14/99	Medulloblastoma	SU-debulking, CH	Infratentorial progression, new tumor at cervicomedullary junction, and new frontal lesions
8	09/14/94 12/23/99 05/09/00 10/30/00	PNET PNET Medulloblastoma Cerebral neuroblastoma	1. Bx, RT, CH 2. SU debulking, CH 3. SU debulking 4. SU (unknown)	Recurrent as bifrontal lesions, at Sylvian fissure
9	12/23/00	Medulloblastoma	SU-total, CH	Recurrent as multifocal cerebellar lesions
10	09/18/96 04/13/01	1. Medulloblastoma 2. Medulloblastoma	1. SU-total, CH 2. SU-subtotal	Recurrent at suprasellar (temporal) area, Sylvian fissure
11	09/13/00	PNET/WHO Grade 4	SU-subtotal, CH, RT, additional SU after 2 months	Recurrent as multiple intraventricular metastases and to posterior fossa and lateral ventricle
12	08/28/06	Medulloblastoma	SU (unknown), RT, CH	Progressed to fourth ventricle and medulla

Note: Bx–biopsy, CH-chemotherapy, CSF-cerebral spinal fluid, PNET-primitive neuro-ectodermal tumor, RT-radiation therapy, SU-surgery, WHO-World Health Organization.

December 23, 2000, following a posterior fossa craniotomy with gross total resection of the tumor. A right frontal ventriculostomy was also performed at that time. On January 2, 2001, a postoperative MRI of the brain and spine showed no evidence of residual tumor or CSF spread. Subsequent treatment included vincristine and cyclophosphamide chemotherapy (CH). During which RMB developed. This was documented by MRI of the brain on March 2, 2001, showing recurrent and multifocal disease of the cerebrum with a tumor SUM of 9.10 cm^2. The parents gave a history of "headaches" while initial physical examination revealed slight weakness of the left upper and lower extremities. A delay in the development of motor skills was observed when the child was unable to walk or crawl.

This child was treated according to the BT-12 protocol as a special exception (LPS = 50) and received IV and oral ANP. On September 18, 2001, no enhancing tumor was seen, indicating CR. The patient survived more than 24 years after his RMB diagnosis. During ANP administration, the patient experienced four serious adverse events and recovered fully.

4. Discussion

RMB has a poor prognosis regardless of the treatment(s). However, there is a lack of effective standard of care. Most studies describing the survival benefits of different treatments include a small number of patients and heterogenous groups [12], [69]–[71]. Challenges abound as new clinical trials for RMB are developed. The types and subtypes of MB, defined by the molecular features presented in the 2016 and 2021 WHO classifications of CNS tumors, [5], [72] will require subgroup analyses, numerous study subjects, and many study institutions.

In a significantly larger study, Hill et al. reported on the clinical features of RMB and compared them with clinical and molecular features at initial MB diagnosis [73]. The study included 230 patients from 16 United Kingdom Children's Cancer and Leukemia Group institutions and four collaborating centers. Patients with MB who received early cranial-spinal RT survived longer than those who did not ($p < 0.0001$). In those patients receiving early cranial-spinal RT, the MB Group 3 cohort survived longer than the MB Group 4 cohort ($p = 0.0043$). These and several other observations from this study suggest that the initial

TABLE III: Treatment at BC, Best Response, Status at Last Follow-Up and OSD

Case	Sex	Age at admission	Protocol ANP	LPS/KPS at admission	ANP Start date	Days receiving ANP	Best response	Status at last Follow-up	OSD (years)
1	M	2	CAN-01	100	4/13/1994	1067	CR (in remission)	Alive (04/23/25)	31.14 (+)
					3/15/1997	823 (po)			
2	M	7	BT-12^{SE}	80	09/28/95	595	CR	Died—RMB	6.28
3	M	4	BT-12	80	07/08/96	260	SD	Alive (06/21/23)	27.06 (+)
4	M	9	BT-12	100	05/08/98	179	PD	Alive (04/25/25)	27.52 (+)
5	F	12	BT-22 ^{SE}	50	05/25/99	24	NE	Died—RMB	7.26
6	M	23	BT-09	70	05/27/99	117	SD	Died—unknown	5.81
7	M	3	BT-12 ^{SE}	50	05/19/00	640	PR	Died—RMB	5.69
8	F	13	BT-12 ^{SE}	50	11/08/00	33	NE	Died—pneumonia	6.33
9	M	1.5	BT-12 ^{SE}	50	03/13/01	638	CR (in remission)	**Alive** (04/23/25)	**24.33 (+)**
						249 (po)			
10	F	8	BT-12^{SE}	50	05/22/01	203	SD	Died—unknown	6.97
11	M	9	BT-12	80	02/06/04	717	CR	Died—RMB	6.12
			BT-12^{SE}			74 (po)			
12	F	29	BT-09^{SE}	50	04/26/07	195	PR	**Alive** (04/25/25)	**18.65 (+)**

Note: ANP-antineoplastons, CR-complete response, KPS-Karnofsky Performance Score, LPS-Lansky Performance Score, NE-non-evaluable, OSD-overall survival from diagnosis, PD-progressive disease, PO-maintenance treatment "per os" (capsules), PR-partial response, RMB-recurrent medulloblastoma, SD-stable disease, SE-special exemption.

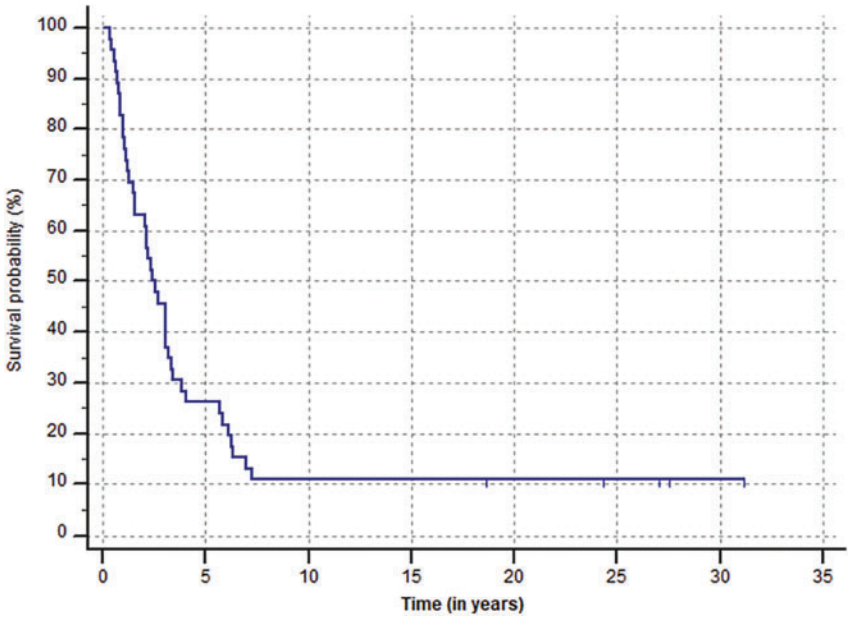

Fig. 1. Kaplan-Meier survival curve for 46 RMB patients.

treatment and the MB molecular subgroup are associated with the nature of RMB and its disease course. These findings may improve the accuracy of subsequent phase II and III clinical studies.

Here we report a survival analysis of 46 patients with MB who were treated at the BC between April 1994 and April 2012. Twelve patients (26.1%) survived more than five to more than 31 years while five of the RMB patients survived more than 12 years, a definition of cure [74].

"Growth of normal cells is controlled by cell cycle progression genes (oncogenes) and by cell cycle arrest genes (tumor suppressor genes). In cancer, the alteration of these

control genes in malignant cells favors aggressive cell proliferation" [75 (p. 6)]. Evidence shows that the mechanism of action of ANP differs from that of RT or CH Affecting more than 448 gene aberrations "in the malignant genome, it functions as a "molecular switch" which "turns on" tumor-suppressor genes and "turns off" oncogenes [76]. "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" [13 (p. 6)].

We found many genomic aberrations to be affected by ANP when assessing the blood samples of patients with over 70 different cancer diagnoses, including brain cancer [17]–[20]. The goal was to correlate radiological and molecular response based on ANP's removal of aberrant DNA from a patient's blood.

Several aberrations that are important in the pathogenesis of MB are on the list of genes affected by ANP. Blood tests can provide results in only a small percentage of MB patients, but we found many positive results from evaluating the samples of patients in over 70 different cancer diagnosis. The goal was to provide radiological and molecular response based on the removal of aberrant DNA from the patient's blood. Based on genomic testing, 83 aberrations were affected and removed from the patient's blood including *PTCH, KDM6A, PIK3CA, MYCN, CDK6, TP53 and APC* which are driving MB [77], [78]. Some of these changes could be influenced by additional prescription drugs taken by patients with poor prognosis. These results will be supplemented by new data once the number of tested genes increases (currently from 600 to 800).

5. Conclusions

RMB, defined as MB regrowth despite treatment, confers a poor prognosis with less than 10% of patients surviving more than five years post-relapse [11], [12]. However, the survival data reported here for 12 patients diagnosed with RMB and treated in Phase II clinical studies with ANP is very unusual (OSD of more than 5 years to more than 31 years). Out of the 12 patients, 5 survived more than 12 years, which is the definition of cure. In addition, these patients had no chronic AEs related to ANP and lived normal lives with healthy children. The authors are unaware of equivalent results from other clinical studies.

"ANP has proved to be an attractive option for a wide spectrum of patients with persistent, recurrent, disseminated, and/or metastatic brain tumors. Multiple Phase II clinical studies of Antineoplaston therapy in a variety of low-and high-grade brain tumors under Burzynski Research Institute's IND # 43,742 have now been completed, and numerous articles have been published" [21 (p. 5)], [15]–[65], [74].

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Conflict of Interest

All authors of this paper declare that there is no conflict of interest.

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