BURZYNSKI
RESEARCH INSTITUTE, INC.

October 27, 1995

Richard Klausner, M.D.
Director
National Cancer Institute
National Institutes of Health
Bethesda, MD 20892

Dear Dr. Klausner,

I was shocked to read the Cancernet "fact sheet" the NCI has been distributing about the cancellation of the clinical trials of antineoplastons, the anti-cancer drugs I discovered and developed. I find it scandalous that a government agency is putting out a public document containing such blatantly false information.

Let me remind you that the only reason the clinical trials of antineoplastons were stopped is that NCI would not conduct them as per our written agreement.

NCI's "fact sheet" tries to obscure that simple fact with misinformation such as the following:

> "In 1991, a 'best-case series' review was conducted by the National Cancer Institute (NCI) to evaluate clinical response in a group of patients treated at Dr. Burzynski's Houston facility. For this review, Dr. Burzynski selected from his entire clinical experience seven brain tumor patients whom he felt had a beneficial effect from antineoplastons."

This misstatement is obviously calculated to make the reader think that in my entire clinical experience I have had only seven patients who benefited from antineoplaston treatment, which is wildly untrue. In fact, I prepared not seven but dozens of cases for the NCI reviewers. As you must know, the reviewers were able to spend just one day at the clinic--enough time to review only seven cases.

Cancernet then compounds that misstatement with the following:

> "This series did not constitute a formal clinical trial, since it was a retrospective review of medical records, *did not include all available patient information*, and included only cases selected by Dr. Burzynski" (my italics).

To the contrary, the patient medical records that NCI scientists reviewed were exhaustive and *did* contain "all available patient information." In fact, Michael Hawkins, M.D., leader of the site visit team, specifically complimented me on how complete and well-organized they were.

The next misstatement is the following:

> "The reviewers of this series determined that there was presumptive evidence of antitumor activity . . . "

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Now that the NCI's Cancer Therapy Evaluation Program (CTEP) is under fire for misconduct in these clinical trials, it is rewriting history.

The statement of the NCI scientists who actually reviewed patient records was quite different from the above. Their report (minutes of Decision Network Committee meeting enclosed) stated that 'The site visit team determined that antitumor activity was documented in this best case series and that the conduct of Phase II trials was indicated *to determine the response rate*" (my italics).

In other words, according to the site visit team, there was no question that the treatment worked in the cases reviewed. All that remained to be determined were the numerator and the denominator.

Even the NCI's own previous "fact sheet" on antineoplastons, dated 2/17/94 (enclosed), states that 'The NCI reviewed seven cases of patients with primary brain tumors that were treated by Dr. Burzynski with antineoplastons and *concluded that antitumor responses occurred*" (my italics).

But by far the most outrageous misstatement is the following:

> "On August 18, 1995, the studies were closed because a consensus could not be reached with Dr. Burzynski on the proposed changes in the protocol to increase accrual, and there was no hope of completing the studies in a timely manner."

The NCI never made any effort to "reach a consensus." Instead, it simply violated the written protocol we had agreed upon. Without informing me, NCI changed the rules to allow patients with any size or number of tumors, low performance scores, and spinal cord metastases. In other words, NCI was accepting patients whose brains and spinal cords were literally consumed by large malignant tumors--patients so advanced as to have no chance whatsoever.

When I found out and insisted that NCI either conduct the study as agreed or inform patients that I felt it was conducting the study improperly, NCI cancelled it.

The above is all well documented. While we were still in the negotiating stage, Michael Friedman, M.D. of the NCI wrote me in a letter dated November 2, 1993 (enclosed) ". . . we will accede to all the modifications that you have stipulated."

Dr. Friedman specifically agreed to exclude patients with:

* tumors larger than 5cm (2 inches)
* multiple tumors
* metastases to spinal cord
* Karnofsky performance scores less than 70%.

Based on Dr. Friedman's written assurance that NCI would honor this exclusion criteria, I provided NCI with a large quantity of antineoplastons, and the clinical trial began.

On March 23 1994, Mario Sznol, M.D. of the NCI wrote me proposing that NCI drop the exclusion for multiple tumors and spinal cord metastases, increase the maximum tumor size from 5 to 8cm, and lower the Karnofsky score from 70 to 60 (enclosed).

In a response dated April 19, 1994 (enclosed), I wrote back that I would be glad to help NCI design a *separate* trial for such advanced patients, using a more aggressive dosage schedule. But I made it clear that it would be unethical to use the current dosage schedule on such patients since my experience had shown that such patients do not respond well to it.

As proof, I pointed out that in the NCI's own review of patients treated with antineoplastons, the only ones who had less than 50% tumor shrinkage were exactly those with tumors greater than 5cm.

I did not hear back from NCI and assumed the matter had been dropped.

Nearly one year later--in March, 1995--I learned that NCI had made all the changes to which I had objected. In fact, NCI went even further. Rather than raising the maximum tumor size from 5 to 8cm as the NCI earlier suggested, it began accepting patients with *any* size tumor.

I insisted that NCI either honor our agrement or change the Informed Consent statement (which patients must read and sign) to reflect the fact that I, the drug's discoverer and developer, felt that the treatment was unlikely to be effective in such advanced patients in the doses being used.

Rather than honor its commitment to conduct the study as agreed, NCI cancelled it.

I find it particularly curious that now neither NCI nor Memorial Sloan-Kettering Cancer Center (MSK) will take responsibility for changing the exclusion criteria, and are instead pointing fingers at each other. In his letter of April 3, 1995 (enclosed), Dr. Sznol repeatedly refers to the "revised eligibility criteria *proposed by the [Memorial Sloan-Kettering] investigators*" (my italics).

But, in a letter to John Lewis, M.D. of Memorial Sloan-Kettering's Institutional Review Board dated January 31, 1995 (enclosed), the Chief Investigator, MSK's Mark Malkin, M.D., writes that "Further amendments, as described below, have been made *at the request of NCI*" (my italics).

If the changes to the protocol are as proper as NCI would have the world believe, why is everyone connected to them scurrying to disavow responsibility?

An even more serious matter is what apears to be the investigators' relentless violations of the *treatment* protocol. Looking at the treatment summaries compiled by Theradex Corporation, the medical reporting company hired by NCI to compile and tabulate patient treatment data, it would appear that investigators violated the agreed-upon protocol in every patient treated. Apparent violations include the removal of patients from treatment who had no tumor growth (including one patient who, during subsequent surgery, was found to have no cancer cells remaining), and the removal of a patient for "skin reactions" caused not by antineoplastons, but by another drug the patient was receiving, DPH. This is clear due to the fact that the patient's skin condition worsened when he was taken off antineoplastons. It improved only after DPH was discontinued.

The summaries provided by Theradex are somewhat sketchy, so I asked to review the complete records of patients treated--which Dr. Friedman had specifically promised to provide. NIH lawyer Robert Lanman replied in a letter dated August 23, 1995 (enclosed) that NCI did not have any such records.

In fact, several patients were treated at NCI and of course NCI has their complete medical records. When I demonstrated this by sending Mr. Lanman copies of patient records obtained by a patient's family from NCI, he admitted that in fact NCI *does* have patient records, but refused to release them. And he disregarded his own misstatements of fact by saying that "Given that you apparently have already obtained at least one of the patient's records, we fail to understand why you are pursuing this matter" (letter from Robert Lanman dated October 5 1995 enclosed).

Mr. Lanman also claims that NCI has "no such commitment" to release medical records of patients treated with antineoplastons. And Dr. Friedman, in a letter dated September 19, 1995 (enclosed), writes that Dr. Burzynski's request for "detailed records" has been satisfied by the sketchy Theradex treatment summaries.

Both these statements directly contradict Dr. Friedman's letter of November 2, 1993 (enclosed), in which he promises that "In accordance with your letter, we will arrange a review of data after accrual of the first 5-6 patients, which should occur 6 months after the study has been initiated. This should be sufficient to assure that the conduct of the study is satisfactory. The Theradex database *is also available . . .*" (my italics).

In other words, Dr. Friedman promised to provide me with patient medical records, recognizing that the Theradex summaries are something quite separate.

In that same September 19, 1995 letter, Dr. Friedman writes that "We have no individual patient records in our possession in addition to the Theradex reports." Either he is deliberately misstating the facts, or he is out of touch with the Cancer Therapy Evaluation Program that he runs.

Dr. Klausner, I request that you immediately withdraw the "fact sheet" the NCI is distributing which contains numerous and outrageous misstatements and distortions of fact.

Thank you for your attention to this matter.

Sincerely,

S. R. Burzynski, M.D., Ph.D.

SRB/cf

cc: The Honorable Donna Shalala, Department of Health & Human Services
Harold Varmus, M.D., National Institutes of Health
Dr. Jan Buckner
Dr. Jay Greenblatt
Dr. Wayne Jonas
Dr. Mark Malkin
Dr. Ralph Moss
Dr. David Parkinson
Dr. Edward Sondik
Dr. Mario Sznol
Dr. Dorothy Tisevich
Dr. Alan Trachtenberg
Dr. Robert Wittes
Dr. Daniel Eskinazi
Mr. Richard Jaffe
Ms. Mary McCabe
Mr. Frank Wiewel
Mr. Robert Lanman
Rep. Berkley Bedell
Rep. Joe Barton, Chairman, Investigations & Oversight Subcommittee, House Commerce Committee
Rep. Thomas Bliley, Chairman of House Commerce Committee
Rep. Bill Archer
Rep. Jim Greenwood, Investigations & Oversight Subcommittee, House Commerce Committee
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Les Kretman, NBC News
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Sylvia Castaneda, KCRP-TV
Robyn Howard, KNWS-TV
Lydia Lum, The Houston Chronicle
Ruth Sorrelle, The Houston Chronicle
Michael Tolson, The Houston Chronicle
Terri Langford, Associated Press
Franklin Hoke, The Scientist Magazine
Rhonda Roland, CNN
Tom Elias, Scripps-Howard Newspapers
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Peggy Dace, Whitaker Wellness Institute
Anthony Chiaramonte
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Peter Barton Hutt
Steve and Mary Jo Siegel, Burzynski Patient Action Group
Liad Lazarus, Ivanhoe Broadcasting
Sam Kazman
Rush Limbaugh
Tom Jipping, National Empowerment TV
Fred Blayhutt, The Spotlight
Michael Ellis, Crawford Broadcasting Network
Zoh Hieronymus
Jonathan Wright, M.D.
Governor Bush
Mike Rosen, M.D.
Shelly Kofler, WFAA TV
Steve Dunn, Internet Cancer Pages
Bob Guccione, Penthouse Magazine
Jonathan Collin, M.D., Editor for The Townsend Letter for Doctors
John Crewdson, Tribune Media Center
Dr. Willix
Charlet Blachbourn, National Health Federation
Michael A. Friedman, M.D.

Patrick McGrady, Jr., CANHELP
William Mask, M.D.
Michael Driscoll, Harris County Attorney General
Carlton Hazlewood, Ph.D., Baylor College of Medicine
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CancerNet from the National Cancer Institute

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National Cancer Institute-Sponsored Clinical Trials of Antineoplastons

Antineoplastons are a group of compounds originally isolated from urine by Dr. Stanislaw Burzynski, who claims that they inhibit cancer cell growth. Dr. Burzynski has used these compounds to treat patients with various cancers.

In 1991, a "best-case series" review was conducted by the National Cancer Institute (NCI) to evaluate clinical responses in a group of patients treated at Dr. Burzynski's Houston facility. For this review, Dr. Burzynski selected from his entire clinical experience seven brain tumor patients whom he felt had a beneficial effect from antineoplastons. This series did not constitute a formal clinical trial, since it was a retrospective review of medical records, did not include all available patient information, and included only cases selected by Dr. Burzynski. The reviewers of this series determined that there was presumptive evidence of antitumor activity and NCI then proposed that Phase II clinical trials be conducted to evaluate more definitively the response rate and toxicity of antineoplastons in adult patients with refractory brain tumors. The decision by NCI to sponsor a study of an agent in a clinical trial does not indicate that the agent is or will be useful in the treatment of cancer patients, only that it merits further evaluation in a research setting.

Efforts to study antineoplastons in a scientifically rigorous manner have required complex interactions among NCI, clinical investigators, the National Institutes of Health's (NIH) Office of Alternative Medicine, the Food and Drug Administration, advocates from the alternative medicine community, and Dr. Burzynski. Two protocols were developed by the participating Cancer Center investigators with extensive review and input from NCI and Dr. Burzynski. These studies began in 1993 at Memorial Sloan-Kettering Cancer Center, Mayo Clinic, and the NIH Clinical Center. However, accrual to these studies was very slow and only nine patients were enrolled.

On August 18, 1995, the studies were closed because a consensus could not be reached with Dr. Burzynski on the proposed changes in the protocol to increase accrual, and there was no hope of completing the studies in a timely manner. Because these studies were closed prior to completion, no conclusions can be made about the effectiveness or toxicity of antineoplastons. It is rare that this kind of NCI-sponsored clinical study cannot be successfully completed. The NCI is disappointed by this outcome but is continuing to evaluate related compounds in clinical trials in order to determine if they may be of benefit in the treatment of patients with cancer.

# # #

The Cancer Information Service (CIS), a program of the National Cancer Institute, provides a nationwide telephone service for cancer patients and their families, the public, and health care professionals. CIS information specialists have extensive training in providing up-to-date and understandable information about cancer and cancer research. They can answer questions in English and Spanish and can send free printed material. In addition, CIS offices serve specific geographic areas and have information about cancer-related services and resources in their region. The toll-free number of the

Date Last Modified: 10/95

Minutes of the Meeting of the NCI's Decision Network Regarding Antineoplastons A10 and AS2-1

December 2, 1991

B. Candidates for DN Stage IV

Antineoplastons A10 and AS2-1, NSCs 648539D and 620261/#2

The antineoplastons have been considered an unconventional method of cancer treatment because there have been very few independent interpretable scientific data on their potential clinical efficacy. Based on a recent report of observed responses in brain cancer patients treated with antineoplastons at the Burzynski Research Institute (founded by Dr. S.R. Burzynski) in Houston, Texas, the Cancer Therapy Evaluation Program (CTEP) conducted a site visit to review a "best case" series of clinical responses to antineoplastons in the treatment of brain tumors at that Institute. This case series does not constitute a clinical trial; the cases were selected on the basis of positive response from many different studies of antineoplaston treatment at the Institute. The site visit team determined that antitumor activity was documented in this best case series and that the conduct of Phase II trials was indicated to determine the response rate. The antineoplastons were presented as DN Stage IV candidates for the conduct of Phase II trials in glioblastoma multiforme, anaplastic astrocytoma, pediatric brain tumors, and low-grade gliomas, to confirm the observations in brain tumors at the Burzynski Institute. It was proposed that the same treatment regimen as that used at the Institute would be used in the Phase II trials. A decision regarding subsequent trials (e.g., other tumors, additional Phase I development, Phase III trials in brain tumors) would be deferred until the results of these initial trials were known. If the antineoplastons are approved for Phase II study, Dr. Burzynski will provide supplies of the materials for the clinical trials to the NCI free of charge.

Dr. Burzynski presented background on antineoplaston research. His research is based on the hypothesis that antineoplastons are components of a biochemical defense system against cancer. The antineoplastons are medium and small size peptides and amino acid derivatives that form the defense against cancer by inducing differentiation in neoplastic cells. Initial study on antineoplastons was concentrated on isolation of peptides in blood and urine of healthy people.

Two main groups of antineoplastons have been isolated -- one including compounds with broad spectrum activity in many different cell lines and the other with a narrow spectrum of activity against single cell lines. Of the broad-spectrum antineoplastons, five, including antineoplastons A1, A2, A3, A4, and A5, have been isolated from normal human urine. Antineoplaston A10 was the first active ingredient that has been reproduced synthetically. Antineoplaston AS2-1 and AS2-5 are metabolites of antineoplaston A10 that have also been synthesized. Dr. Burzynski cited experiments that have shown that antineoplaston A10 intercalates in a stereospecific manner between base pairs in double-helical DNA. The main mechanism of action of antineoplaston AS2-1 appears to be inhibition of incorporation of glutamine into proteins in cancer cells. The other antineoplastons all seem to have different mechanisms of action involving inhibition of methylation of RNA and DNA.

The potency of the antineoplastons has been confirmed in tissue cultures, but with relatively low specificity. No significant activity was seen in NCI tissue culture studies when low concentrations were used. Tests in various models for induction of cell differentiation (e.g., human promyelocytic leukemia, fibrosarcoma) showed that antineoplastons can induce cell differentiation. Antineoplastons also showed activity against human breast cancer in athymic mice.

Acute and chronic toxicity studies of antineoplastons showed that antineoplastons A10 and AS2-1 have extremely low toxicity. The LD_{50} of antineoplaston A10 was greater than 10 g/kg in mice and rats; the LD_{50} of AS2-1 was approximately 3 g/kg in mice and rats. There was no apparent toxicity in mice given daily injections of 1 g/kg/day for 1 year. The compounds were not found to be mutagenic.

PK studies of both the oral and injectable forms of antineoplastons A10 and AS2-1 showed that both compounds are absorbed rapidly. The maximum concentration of AS2-1 can be detected in urine approximately 3 hours after oral administration. A10 is absorbed somewhat

slower, reaching the highest concentration in blood approximately 3 hours after oral administration. The compounds are cleared more rapidly after i.v. administration; A10 cannot be detected in the blood approximately 2 hours after i.v. administration. Thus, frequent dosing or continuous infusions is indicated for clinical studies.

From studies in mice, it was also noted that antineoplaston A10 is retained in brain tissue. A concentration of approximately 500 μg/g of brain tissue in mice was reached about 1 hour after oral administration; however, the concentration dropped to a negligible amount within about 6 hours.

A review of the best case series of seven patients with brain tumors was provided by Dr. N. Patronas (neuroradiologist, NIH Clinical Center) who participated in the NCI site visit to the Burzynski Institute. All patients received a combination of antineoplastons A10 and AS2-1. Some patients initially progressed on a study using oral antineoplastons with low-dose methotrexate. All of the responses were seen after i.v. antineoplaston administration, and, therefore, the proposed Phase II studies would be conducted using the i.v. regimen (i.e., 1 g/kg/day of A10 and 0.5 g/kg/day of AS2-1). The results of the review were presented as follows, with case histories distributed to all DNC members:

- Marked decrease in tumor size and possible complete response (CR) of approximately 4-months' duration in a 46-year-old female with glioblastoma multiforme.
- Possible CR, thus far of 2-years' duration, in a 36-year-old female with anaplastic astrocytoma.
- Partial response, or possible CR, in a 47-year-old male with aggressive, infiltrating glioma (astrocytoma or mixed astrocytoma/oligodendroglioma).
- Substantial decrease in tumor size in 7-year-old male with well-differentiated astrocytoma.

- Decrease in tumor size in a 40-year-old female with an unusually large glioblastoma multiforme tumor.
- CR, thus far of approximately 1½-years' duration, in a 10-year-old male with anaplastic astrocytoma.
- Good response, possible CR, in a 30-year-old male with anaplastic astrocytoma.

It was noted that several of the patients received antineoplaston treatment shortly after failing radiation therapy, and the question of the possibility of a confounding effect of residual continued improvement following radiotherapy on evaluating response to antineoplastons was raised. However, complete resolution of both postradiation-edema and tumor enhancement was demonstrated on CT scans in several cases, therefore negating the possible problem of differentiating between progression of tumor and postradiation edema.

In discussion, it was clarified that the proposed Phase II trials would utilize the combination of antineoplastons A10 and AS2-1, without any other therapy. No problems were foreseen with filing the INDA on the pharmaceutical preparation provided by Dr. Burzynski. The primary rationale for using a mixture of the two antineoplastons in the proposed trials is to duplicate exactly the regimen used in the studies at the Burzynski Institute.

Decision: Antineoplastons A10 (NSC 648539D) and AS2-1 (NSC 620261/#2) passed DN Stage IV.

CANCER FACTS
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Antineoplastons/Dr. Stanislaw Burzynski

Dr. Stanislaw Burzynski of the Burzynski Research Institute in Houston, Texas, has identified a group of peptides produced by the body, which he calls "antineoplastons." Dr. Burzynski and his colleagues claim that these peptides are produced in individuals as part of a "biochemical defense system" that inhibits cancer cell growth. According to Dr. Burzynski, "The failure of the system and deficiency of antineoplastons will result in perpetuation of neoplastic growth and development of cancer." His treatment, therefore, consists of restoring this "cancer defense system" by giving antineoplastons to people with cancer.

The National Cancer Institute (NCI) reviewed seven cases of patients with primary brain tumors that were treated by Dr. Burzynski with antineoplastons A10 and AS2-1 and concluded that antitumor responses occurred. To evaluate further the effects of treatment with antineoplastons, NCI is conducting phase II clinical trials (treatment studies) using antineoplastons in adult patients with refractory brain tumors. One trial at Memorial Sloan-Kettering Cancer Center in New York City opened in late 1993. A second trial is to be carried out at Mayo Comprehensive Cancer Center in Rochester, Minnesota.

The NCI's decision to study an agent in clinical trials does not indicate that the agent will be useful in the treatment of cancer, only that it merits evaluation. The NCI currently has more than 160 investigational agents in clinical trials and recommends that antineoplastons, like any other experimental cancer treatment, be administered only in the context of appropriately conducted and independently monitored clinical trials. Cancer patients are encouraged to remain in the care of trained oncologists.

# # #

The Cancer Information Service (CIS), a program of the National Cancer Institute, is a nationwide telephone service for cancer patients and their families, the public, and health care professionals. CIS information specialists have extensive training in providing up-to-date and understandable information about cancer. They can answer questions in English and Spanish and can send free printed material. In addition, CIS offices serve specific geographic areas and have information about cancer-related services and resources in their region. The toll-free number of the CIS is 1-800-4-CANCER (1-800-422-6237).

DEPARTMENT OF HEALTH & HUMAN SERVICES

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November 2, 1993

Dr. Stanislaw Burzynski
Burzynski Research Institute, Inc.
6221 Corporate Drive
Houston, Texas 77036

Dear Dr. Burzynski:

With regard to your letter of October 26, 1993, you specifically state "The medicine will be sent to you immediately once you make the corrections to the protocol that we have requested". We have substantial factual disagreements and scientific reservations with many of the comments made in your October 26th letter, including your preposterous claim that the NCI wasted eight months. Nonetheless, we will accede to all the modifications that you have stipulated. We do so because we are committed to beginning the clinical studies as quickly as possible. We presume that these are your final comments, since all the changes will have been made and we will have addressed all of your concerns regarding these studies. The revised protocol will be sent to you as soon as it is received from the investigators. Based on the promise in your letter, we expect that the drug will be shipped to the NCI repository the next day.

The changes to be made to the protocols are as follows:

1. The dose and schedule will be modified exactly as you require. We believe this to be the dose and schedule found in your protocol BT6, with dose escalation and maximum dose guidelines for adults clarified in your letter of October 13, 1993.

2. The Memorial study, as written, has two separate components, one for patients with glioblastoma multiforme and one for patients with anaplastic astrocytoma. Accrual to each stratum proceeds independently, and analyses of each stratum is separate. However, we will ask the investigators from Mayo Clinic to join the Memorial study, rather than conducting an independent trial. This will effectively evaluate on the one hand patients with glioblastoma multiforme, and on the other those with anaplastic astrocytoma.

Patients with either disease will be enrolled at both Memorial and Mayo sites. This modification has two advantages -- it limits total accrual to 35 patients per histology, as was your request; and it accelerates accrual, since each institution can enter both types of patients on the studies.

3. As you stipulated, Fleming's original statistical design will be used utilized. Fifteen patients will be entered independently to each stratum; for each stratum, if there is 1 response, accrual will proceed to a total of 35 patients. Thus, total accrual will be 70 patients if both strata proceed past the first stage (the initial 15 patients per histology).

4. According to your wishes, all scans for tumor measurements and laboratory tests will be performed within 7 days of initiating protocol therapy, rather than the standard 14 days now specified in the protocol.

5. The eligibility criteria will be modified to accept only patients with a Karnofsky performance status of 70-100%.

6. As you require, the protocol response criteria will be based on objective tumor measurements and will not include assessment of neurologic status. Neurologic status will be assessed separately.

7. In accordance with your letter, we will arrange a review of data after accrual of the first 5-6 patients, which should occur 6 months after the study has been initiated. This should be sufficient to assure that the conduct of the study is satisfactory. The Theradex database is also available to precisely determine if the conduct of the study has followed protocol guidelines; the study centers will also be audited on-site by Theradex (independent contractors) every 3 months.

In your letter you express concern regarding what you perceive to be bias against alternative treatments by Mayo Clinic and Memorial investigators. Please note that the investigators participating in the antineoplaston studies volunteered to do so because of the findings of the NCI review of your best case series. To my knowledge none of the participating investigators have expressed (publicly or privately) a position for or against Antineoplastons. Both institutions have a distinguished record in clinical investigations, and have been leaders in subjecting all treatments (including alternative interventions) to fair and objective clinical research. We are confident that credible clinical studies will be conducted.

Finally, if even after modifying these studies in accordance with your stated wishes, you are unwilling to supply the antineoplaston materials, please inform me as quickly as possible. We will then seek alternative sources of this family of molecules for proper clinical evaluation.

Sincerely yours,

MA Friedman

Michael A. Friedman, M.D.
Associate Director,
Cancer Therapy Evaluation Program
Division of Cancer Treatment, NCI

cc:
Dr. Samuel Broder
Dr. Jan Bruckner
Dr. Bruce Chabner
Dr. Jay Greenblatt
Dr. Joseph Jacobs
Dr. Mark Malkin
Ms. Mary McCabe
Dr. David Parkinson
Dr. Mario Sznol
Ms. Dorothy Tisevich

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Services
National Institutes of Health
National Cancer Institutes
Bethesda, MD 20892

March 23, 1994

S. R. Burzynski, M.D., Ph.D.
President
Burzynski Research Institute
12000 Richmond, Suite 260
Houston, Texas, 77082-2431

Dear Dr. Burzynski,

As you know, the NCI-sponsored trials of antineoplastons have been initiated and some patients have been enrolled. However, a great many more have sought access to the trial but have not been allowed to participate because of their inability to meet all the eligibility criteria. Because of this, there is strong interest on our part and that of the investigators to broaden the eligibility criteria. While we recognize the need for and value of clear eligibility criteria, we believe that the protocol now excludes some patients who would otherwise be good candidates for the trial. Specifically, we would propose the following changes in the eligibility criteria:

1. Change the allowable Karnofsky performance status from 70 to 60, as originally written in the protocol.

2. Change the exclusion for size of tumor from greater than 5 cm to greater than 8 cm.

3. Drop the exclusion for multifocal tumors or leptomenigeal spread.

By keeping the performance status score at 60 as a requirement for entry, we believe that the protocol will still be safe for patients, and the drug will get a fair test for antitumor efficacy. We have noted that your protocols for adults (copies of which you have provided to CTEP) have similar eligibility criteria to those proposed above (ie, KPS of 60 required and no exclusion for size of tumor, multifocal tumors, or leptomeningeal spread).

We have also noted that some patients not eligible for treatment on NCI-sponsored protocols appear to have been told by your staff that they could receive the antineoplastons at your Institute. They have asked us the obvious question, that is, if you have enough evidence of efficacy to offer the antineoplastons as treatment to these patients, why is it that they would not be good candidates for a protocol attempting to determine and confirm the antitumor activity of the agent? We would appreciate any help you might give us in responding to these inquiries.

Sincerely,

Mario Sznol, M.D.
Head, Biologics Evaluation Section
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment
National Cancer Institute

cc: David Parkinson, M.D
Mike Friedman, M.D.
Dale Shoemaker, Ph.D.
Jay Greenblatt, Ph.D.
Dean Mouscher, BRI
Mary McCabe
Samuel Broder, M.D.
Bruce Chabner, M.D.

BURZYNSKI
RESEARCH INSTITUTE, INC.

April 19, 1994

Mario Sznol, M.D.
Head, Biologics Evaluation Section
Investigational Drug Branch
CTEP, DCT, National Cancer Institute
6130 Executive Plaza North, Room 715F
Rockville, MD 20852

Dear Dr. Sznol,

I am glad to learn from your letter of March 23, 1994 that some patients have already been enrolled in the NCI-sponsored trials of Antineoplastons and there is a strong interest of the NCI and the Investigators to broaden the study.

While I think that, ultimately, Antineoplastons will prove useful in the treatment of more advanced cases of malignant brain tumors, I think that to expand the trials now through admission of such difficult cases is premature. The first stage of the studies which are currently in progress should be completed in order to have the most accurate preliminary evaluation of anticancer activity.

I sincerely hope that the Investigators conducting the study will report good results in the treatment of at least some of the initial fifteen patients involved in stage I. However, if the reverse is true, then it won't make any sense to conduct trials in very advanced cases if less advanced cases do not respond.

I would expect that there will be a significant difference in response between the patients admitted under current acceptance criteria and the expanded eligibility criteria proposed in your letter of March 23, 1994. Therefore, I think that such patients should be involved in a separate trial for large and multifocal tumors, and treated and evaluated according to a modified protocol.

12000 RICHMOND AVE., SUITE 260 • HOUSTON, TEXAS 77082-2431 • (713) 597-0111 • FAX (713) 597-1166

Sincerely,

S. R. Burzynski, M.D., Ph.D.

SRB/cf
cc: David Parkinson, M.D.
Mike Friedman, M.D.
Dale Shoemaker, Ph.D.
Jay Greenblatt, Ph.D.
Dean Mouscher, BRI
Mary McCabe, R.N.
Samuel Broder, M.D.
Bruce Chabner, M.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Services
National Institutes of Health
National Cancer Institutes
Bethesda, MD 20892

April 3, 1995

S. R. Burzynski, M.D., Ph.D.
President
Burzynski Research Institute
12000 Richmond, Suite 260
Houston, Texas, 77082-2431

Dear Dr. Burzynski,

Dr. Friedman asked me to respond to your letter of 3/29/95 regarding the change we have been considering in eligibility criteria for the Memorial Sloan-Kettering and Mayo Clinic phase II studies of antineoplastons. At the investigators' request, the amendments to modify the eligibility restrictions for size of tumor, number of tumors, and leptomeningeal spread, and to allow entry of patients with KPS of 60, have been approved. These amendments were initiated by the investigators when it became apparent that many good candidates for the study were being excluded because of what were perceived to be overly stringent and unnecessary eligibility restrictions.

Approximately a year ago, we wrote to you asking for your concurrence to make similar changes to the protocol (see enclosed letter). We have documented that the revised eligibility criteria are consistent with those used in your very own protocols that employ identical or nearly identical treatment regimens. Furthermore, in a review of the 7 patients in the best case series presented to NCI, we have found that perhaps 4 of the 7 patients who apparently had tumor shrinkage would not have been eligible to enter the NCI phase II studies under the original stringent eligibility criteria (see attached). These types of patients will now be eligible for study using the revised eligibility criteria proposed by the investigators and recently approved by CTEP.

Despite the difficulties in accrual, we are committed to completing the phase II evaluation of the antineoplastons. Our goals remain unchanged, that is, we wish to determine whether the drugs used in the similar manner as you recommend, and in the similar population of patients, will yield results consistent with those in the best case series. As noted above, our careful evaluation of the materials you have provided indicate that the amendments to the eligibility criteria do not deviate from the eligibility criteria and methods you have employed in your experience. We would appreciate the opportunity to review your data, alluded to in your letter, that support the contention that inclusion of these patients requires a different treatment regimen or is unsafe. In the meantime, we will allow the amendments to stand, since all evidence you have provided to date indicates that these newly eligible patients may have a chance for benefit without undue risk of harm, and are appropriate candidates for evaluation of the drug.

We will forward the data on the first five patients in a separate mailing as you requested.

However, you have asked that we suspend accrual while you review the data. There is no medical or regulatory reason to suspend accrual at this time. Suspending accrual will likely further damage the efforts the investigators have made to increase accrual to the trial.

Sincerely,

Mario Sznol

Mario Sznol, M.D.

cc: Dottie Tisevich
Michael Friedman, M.D.
Mary McCabe
Office of Alternative Medicine

ANTINEOPLASTON CASES

1.	Histology	parietal lobe glioblastoma multiforme
	Size	2.3 cm largest diameter
	Response	CR possible
	prior Tx	RT, Surgery
2.	Histology	anaplastic astrocytoma stage IV grade 3
	Size	3.0 tumor 3.5 tumor & edema
	Response	CR possible
	prior Tx	RT
3.	Histology	infiltrating glioma (astrocytoma or mixed astrocytoma/oligodendroglioma)
	Size	4.4
	Response	good PR, possible CR
	prior Tx	RT & BUdR; Procarbazine, CCNU, VCR; B-Interferon; DFMO & MGBG
4.	Histology	well differentiated Stage IV astrocytoma, possibly juvenile pilocytic astrocytoma
	Size	5.5 X 3.3
	Response	40-50% decrease of solid component
	prior Tx	vitamins & laetrile
5.	Histology	glioblastoma multiforme
	Size	6.5 x 5.0
	Response	39% decrease
	prior Tx	RT
6.	Histology	glioma consistent with anaplastic astrocytoma, differential: anaplastic astrocytoma or spindle cell variant of oligodendroglioma
	Size	5.1 x 2.2
	Response	CR
	prior Tx	RT
7.	Histology	Infiltrating anaplastic astrocytoma
	Size	4.0 (L) 4.8 (bifrontal)
	Response	good response - possible CR
	prior Tx	RT

January 31, 1995

T93-0078

John L. Lewis, M.D.
Chairman, Institutional Review Board
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10021

RE: Protocol # 93-105

Dear Dr. Lewis:

You will find appended to this covering letter an amended version of the approved IRB protocol # 93-105, entitled "**Phase II Study of Antineoplastons A10 and AS2-1 in Patients with Advanced Recurrent Malignant Gliomas**". Further amendments, as described below, have been made at the request of NCI.

The minor textual changes expand the pool of eligible patients, thus permitting us to recruit patients more rapidly; however, they do not otherwise alter the overall design of the protocol.

1. In Sections 1.1-b) and 6.1-i) the permissible Karnofsky Performance Status Score has been lowered from 70% to 60%.

2. In Sections 1.1-k) and 6.2-a) the exclusion criteria have been changed.

The statement:

> "Patients with tumors > 5 cm in diameter, multifocal tumors, or with leptomeningeal or systemic metastases are excluded"

has been replaced by the statement:

> "There will be no exclusion based on tumor size, multifocality, or leptomeningeal or systemic metastases".

I thank you for your assistance in this matter.

Sincerely,

Mark Malkin, M.D.

xc Jerome Posner, M.D., Charles Young, M.D.
Mario Sznol, M.D. (NCI)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the General Counsel

Public Health Division
Room 2B-50, NIH Bldg. 31
9000 Rockville Pike
Bethesda, Maryland 20892
(301) 496-4108
Fax (301) 402-1034

August 23, 1995

Richard A. Jaffe, Esq.
1710 Summit Tower
11 Greenway Plaza
Houston, TX 77046

Dear Mr. Jaffe:

This is in response to the issues raised in your July 21, 1995 letter.

First, you raised questions as to how clinical trials of antineoplastons could proceed absent Dr. Burzynski's concurrence. Although NCI clearly prefers to conduct or sponsor studies with the ongoing support and cooperation of a drug's inventor, the permission of such an individual is not required. In the present case, even assuming that the clinical trials involved some of Dr. Burzynski's patented products or processes, the use of antineoplaston would be permissible under the research exemption. However, in light of the recent decision to close the studies at the Mayo Clinic and at Memorial Sloan-Kettering, conveyed to Dr. Burzynski in a letter from Dr. Michael A. Friedman dated August 18, 1995, these issues now seem moot.

In addition, you requested in your letter that we provide you or Dr. Burzynski with the medical records of patients treated by the Principal Investigators. To our knowledge, Dr. Burzynski has received, on an ongoing basis, complete copies of the reports prepared by Theradex after the Principal Investigators submit their data. Dr. Burzynski has received precisely the same information that is provided to the National Cancer Institute (NCI). The NCI does not possess any individual patient records to provide to Dr. Burzynski.

Finally, we are not aware of any "committee" investigating Dr. Burzynski's allegations regarding the protocols.

Yours sincerely,

Robert B. Lanman
NIH Legal Advisor

cc: M. Friedman, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the General Counsel

Public Health Division
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(301) 496-4108
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October 5, 1995

Richard A. Jaffe, Esq.
1710 Summit Tower
11 Greenway Plaza
Houston, TX 77046

Dear Mr. Jaffe:

This is in response to your September 8, 1995 letter in which you reiterate your request for copies of individual patient records and argue that the protocol for the study of Antineoplastons specifically provides that medical records of patients treated by the Principal Investigators will be provided to Dr. Bruzynski.

We have reviewed the protocols and have not found any such commitment. Moreover, it is not the practice of the National Cancer Institute (NCI) to obtain individual patient records from Principal Investigators. It is our understanding that NCI offered to allow Dr. Bruzynski to participate in an interim and final meeting in which patient data from the study was to be reviewed. However, these meetings never took place because of the insufficient patient accrual and decision not to complete the study.

With regard to the portion of the medical record that you forwarded, the stamp does indicate that the patient was seen at the National Institutes of Health's Clinical Center. We have learned that two patients were enrolled in the Sloan-Kettering study through the Clinical Center and hence, even though the Clinical Center did not have its own protocol, it has medical records for these two individuals. However, without the consent of the patient or the next of kin in the event that the patient is deceased, we cannot release these records. See 45 CFR § 5b.9. Given that you apparently have already obtained at least one of the patient's records, we fail to understand why you are pursuing this matter.

Yours sincerely,

Robert B. Lanman
NIH Legal Advisor

cc: D. Parkinson, M.D.
M. McCabe, R.N.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
Building : EPN
Room : 742
(301) 496- 6138

September 19, 1995

Dr: Stanislaw Burzynski
President, Burzynski Research Institute
12000 Richmond Avenue
Houston, Texas 77082-2431

Dear Dr. Burzynski:

I am replying to your August 29, 1995, letter in which you requested "detailed records" of the patients treated in the National Cancer Institute sponsored trials of antineoplastons.

Our records indicate that data has been regularly supplied to you by our contractor, Theradex, as listed below:

Date	Report
July 18, 1994	Clinical Studies Summary
August 24, 1994	Clinical Studies Summary
September 19, 1994	Clinical Studies Summary
October 24, 1994	Clinical Studies Summary Monitors Detail Report, Clinical Studies Detail Report
November 14, 1994	Clinical Studies Summary
December 19, 1994	Clinical Studies Summary
January 13, 1995	Clinical Studies Summary, Monitors Detail Report, Clinical Studies Detail Report
February 21, 1995	Clinical Studies Summary
March 15, 1994	Clinical Studies Summary
April 10, 1995	Clinical Studies Summary Monitors Detail Report, Clinical Studies Detail Report

I am enclosing a summary of the categories of data that are included in the reports you have received. These reports are the same ones that have been provided to us by the contractor during the conduct of the Antineoplaston studies. Both the format and frequency of these reports are routine for reporting data of ongoing NCI Phase II trials to the Cancer Therapy Evaluation Program staff. These are also the same types of reports that are provided to pharmaceutical companies when they are cosponsors of a study.

We have no individual patient records in our possession in addition to the Theradex reports. As of the last report provided to you on April 10, 1995, prior to the studies being put on hold and subsequently closed, you were sent the same reports that were provided to CTEP staff and protocols T93-0078 and T93-0134. However, enclosed for your convenience is a recent print-out of the data that was prepared for our staff in a slightly different format. Once the routine quality control review of data entry has been completed, we will send you a final print-out.

Sincerely yours,

Michael A. Friedman, M.D.
Associate Director,
Cancer Therapy Evaluation Program
Division of Cancer Treatment, NCI

cc:
Senator Joseph Biden
Senator Barbara Boxer
Senator Diane Feinstein
Senator Tom Harkin
Senator Barbara Mikulski
Congressman Berkley Bedell
Congresswoman Nacy Pelosi
Dr. Jan Buckner
Mr. Richard Jaffe
Dr. Wayne Jonas
Dr. Robert Justice
Mr. Robert Lanman
Ms. Mary McCabe
Dr. Mark Malkin
Dr. Ralph Moss
Dr. David Parkinson
Dr. Alan Rabson
Dr. Mario Sznol
Ms. Dorothy Tisevich
Mr. Frank Wiewel
Dr. Robert Wittes

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
Building : EPN
Room : 742
(301) 496- 6138

November 2, 1993

Dr. Stanislaw Burzynski
Burzynski Research Institute, Inc.
6221 Corporate Drive
Houston, Texas 77036

Dear Dr. Burzynski:

With regard to your letter of October 26, 1993, you specifically state "The medicine will be sent to you immediately once you make the corrections to the protocol that we have requested". We have substantial factual disagreements and scientific reservations with many of the comments made in your October 26th letter, including your preposterous claim that the NCI wasted eight months. Nonetheless, we will accede to all the modifications that you have stipulated. We do so because we are committed to beginning the clinical studies as quickly as possible. We presume that these are your final comments, since all the changes will have been made and we will have addressed all of your concerns regarding these studies. The revised protocol will be sent to you as soon as it is received from the investigators. Based on the promise in your letter, we expect that the drug will be shipped to the NCI repository the next day.

The changes to be made to the protocols are as follows:

1. The dose and schedule will be modified exactly as you require. We believe this to be the dose and schedule found in your protocol BT6, with dose escalation and maximum dose guidelines for adults clarified in your letter of October 13, 1993.

2. The Memorial study, as written, has two separate components, one for patients with glioblastoma multiforme and one for patients with anaplastic astrocytoma. Accrual to each stratum proceeds independently, and analyses of each stratum is separate. However, we will ask the investigators from Mayo Clinic to join the Memorial study, rather than conducting an independent trial. This will effectively evaluate on the one hand patients with glioblastoma multiforme, and on the other those with anaplastic astrocytoma.

Patients with either disease will be enrolled at both Memorial and Mayo sites. This modification has two advantages -- it limits total accrual to 35 patients per histology, as was your request; and it accelerates accrual, since each institution can enter both types of patients on the studies.

3. As you stipulated, Fleming's original statistical design will be used utilized. Fifteen patients will be entered independently to each stratum; for each stratum, if there is 1 response, accrual will proceed to a total of 35 patients. Thus, total accrual will be 70 patients if both strata proceed past the first stage (the initial 15 patients per histology).

4. According to your wishes, all scans for tumor measurements and laboratory tests will be performed within 7 days of initiating protocol therapy, rather than the standard 14 days now specified in the protocol.

5. The eligibility criteria will be modified to accept only patients with a Karnofsky performance status of 70-100%.

6. As you require, the protocol response criteria will be based on objective tumor measurements and will not include assessment of neurologic status. Neurologic status will be assessed separately.

7. In accordance with your letter, we will arrange a review of data after accrual of the first 5-6 patients, which should occur 6 months after the study has been initiated. This should be sufficient to assure that the conduct of the study is satisfactory. The Theradex database is also available to precisely determine if the conduct of the study has followed protocol guidelines; the study centers will also be audited on-site by Theradex (independent contractors) every 3 months.

In your letter you express concern regarding what you perceive to be bias against alternative treatments by Mayo Clinic and Memorial investigators. Please note that the investigators participating in the antineoplaston studies volunteered to do so because of the findings of the NCI review of your best case series. To my knowledge none of the participating investigators have expressed (publicly or privately) a position for or against Antineoplastons. Both institutions have a distinguished record in clinical investigations, and have been leaders in subjecting all treatments (including alternative interventions) to fair and objective clinical research. We are confident that credible clinical studies will be conducted.

Finally, if even after modifying these studies in accordance with your stated wishes, you are unwilling to supply the antineoplaston materials, please inform me as quickly as possible. We will then seek alternative sources of this family of molecules for proper clinical evaluation.

Sincerely yours,

MA Friedman

Michael A. Friedman, M.D.
Associate Director,
Cancer Therapy Evaluation Program
Division of Cancer Treatment, NCI

cc:
Dr. Samuel Broder
Dr. Jan Bruckner
Dr. Bruce Chabner
Dr. Jay Greenblatt
Dr. Joseph Jacobs
Dr. Mark Malkin
Ms. Mary McCabe
Dr. David Parkinson
Dr. Mario Sznol
Ms. Dorothy Tisevich