ROBERT E. BURDICK, M.D.

The Polyclinic
1145 Broadway
Seattle, Washington 98122
329-1760

Ballard Medical Plaza
1801 NW Market #405
Seattle, Washington 98107

Medical Oncology, Hematology, Internal Medicine

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The Honorable Sim Lake

Your Honor:

Dr. Stanislaw Burzynski asked me to review the case records of 17 patients who were receiving antineoplaston therapy in February of 1996 and were the initial patients included in the FDA approved CAN-1 trial initiated at that time. The purposes of this review, as I understand Dr. Burzynski's request, was to have an independent reviewer critically examine these records to ascertain the veracity of the results, and the toxicity of the treatment and compare those with current standard treatment that is readily available for treatment of brain tumors. For radiologic interpretation of response or failure of these brain tumors I have depended a great deal on the MRI reviews of Dr. Dieter Schellinger, the head of neuroradiology at Georgetown University.

By way of reference, I am in the private practice of medical oncology in Seattle, Washington and have been in the private practice of medical oncology for the last 27 years. I am on the faculty of the University of Washington Medical School and participate in cancer research in Seattle in the State of Washington. As you may know, the clinical practice of oncology generally requires the close coordination between surgical oncologists (those who specialize in cancer surgery), medical oncologists like myself who deal with cancer chemotherapy, and radiation oncologists who deliver x-ray therapy. I am thus intimately familiar with the frustrations that neurosurgeons, radiotherapists and we medical oncologists have regarding our ineffective treatment of malignant brain tumors.

Some information about the natural history of primary brain tumors may be in order at this point. There are some 25 histologically different malignant brain tumors. Some brain tumors are specific to children, some to adults and some tumors span all age groups. In children the most common brain tumor is a low grade astrocytoma with life expectancy, treated or untreated, of one to four years. The next most frequent tumor in the pediatric age group is medulloblastoma involving the brainstem with a similar life expectancy. Medulloblastomas are moderately sensitive to radiation therapy and occasional cures are seen in this age group. Glioblastomas comprise more than 50% of all adult brain tumors with a life expectancy, treated or untreated, of six

months to one year. As you might expect, most of these patients from the onset of their diagnosis to death are incapacitated by neurologic deficits and require tremendous amounts of supportive care.

It is very rare, currently, to ever get a complete remission or cure in a patient who has a malignant brain tumor using our standard modalities of surgery, radiation and chemotherapy. By the time a tumor is large enough to be clinically detected, it has involved such critical structures that to remove it surgically would result in a patient who is left in a vegetative state or was markedly more disabled than he was prior to the surgery. As a rough estimate, neurosurgeons do well to cure 1 in every 1000 brain cancer patients they operate on. Radiation therapy slows the growth of adult tumors gaining perhaps one month of life and again may result in a cure in only 1 in 500-1000 patients, those cures being in the pediatric age group. Similarly, chemotherapy research, despite 30 years of clinical trials, has not resulted in the development of a single drug or drug combination that elicits more than an occasional transient response in primary brain tumors. In fact, to this time, our chances of curing somebody with a brain tumor with chemotherapy are worse than the surgeons or the radiation therapists and are probably on the order of 1 in 5000. Chemotherapy has been shown to be of some benefit in prolonging life in brain cancer patients, but that prolongation averages no more than a few weeks. In fact, chemotherapy in brain tumors is so discouraging that in many parts of the country patients with brain tumors are not even offered the option of chemotherapy. The preceding statistics that I have just cited are echoed in all the standard cancer textbooks including DiVito's Principles and Practice of Oncology, the main medical textbook in the field of oncology.

I have carefully reviewed the patients' clinical records to make sure that the responses seen could not be attributed to prior surgery, radiation or chemotherapy, even though the chances of any of those modalities having a lasting long-term effect on tumor regression would be unlikely. I have compared Dr. Dieter Schellinger's radiologic interpretations of the patients' MRIs (since I am not a radiologist nor have expertise in the interpretation of imaging studies, and since magnetic resonance imaging studies are our main method of evaluation of response or progression of tumors in these patients) with the radiologic interpretation of the MRIs by radiologists around the country who have imaged these patients in the course of their disease.

A word regarding interpretation of partial response, complete response, stable disease and progressive disease may be in order at this point. In order to be classified as a partial response a tumor must, by convention, regress by 50% in volume and that regression must last at least four weeks. A complete response requires the complete resolution of any evidence of tumor and must last at least one month. In order for a response to be classified as stable disease the tumor must cease growing for at least three months. I would further like to indicate that for the purposes of my review I have disqualified any case from being considered for evaluation, except for special circumstances, who had either chemotherapy or radiation therapy within two months of antineoplaston therapy since by consensus any benefit from chemotherapy or radiation occurs within two months of the cessation of these modalities of treatment or not at all. This insures that any delays in response to either of those two modalities cannot be interpreted as a response to antineoplaston therapy.

The following is a summary of the 17 cases that I have reviewed. Of the 17 patients there were 7 complete remissions, one patient having had a second complete remission after he discontinued antineoplaston therapy which resulted in his tumor regrowing. There were nine partial remissions, two cases of stable disease and no disqualifications. The average duration of therapy with antineoplastons necessary to obtain a complete remission was 10 months with a range of 2 to 20 months. The average duration of antineoplaston therapy necessary to obtain a partial response was 8 months with a range of 1 to 14 months. The average duration of complete remissions is 16+ months with all six complete remissions continuing to remain in remission to the best of my knowledge through January 1, 1997. The duration of complete remissions ranged from 3+ months to 40+ months with the duration of partial remissions averaging 18+ months and ranging from 5 to 78+ months.

On a case by case basis, the following capsule summaries may be helpful.

Patient #1 is S.C., a 47-year-old female who developed a glioblastoma of her right lateral brain and presented to her physicians with seizures. She had a surgical subtotal resection of her tumor followed by radiation therapy that was ineffective. Antineoplaston therapy was then instituted by Dr. Burzynski and within five months all evidence of tumor had disappeared on her MRI. That response has continued for 40 months and is still continuing. She had no life-threatening side effects from her therapy, but did have insignificant abnormalities of her liver function tests at various times, protein in her urine at various times, and low serum sodium levels. I feel S.C.'s complete response is due to antineoplaston therapy and not due to her surgery, which was not curative, nor to the radiation therapy to which her tumor was resistant.

Patient #2 is S.H., a 14-year-old female with a glioblastoma involving the left lateral side of her brain and who presented to her private physician with seizures. Following surgery to obtain a histologic diagnosis of her tumor, antineoplaston therapy was begun on 1/7/94 and has continued to the present time. Her seizures disappeared and 20 months after her therapy was begun her MRIs could be categorized as verifying a complete remission. She has had no life-threatening side effects from her therapy, but has had insignificant abnormalities of liver function tests from time to time, intermittent protein in her urine, intermittent anemia and intermittent depression of her white blood cell count. My telephone call to her private physician in Australia two weeks ago confirmed her continuing good health and complete remission. I find no explanation for her tumor response here other than her antineoplaston therapy as she did not have curative surgery nor was she given radiation therapy or standard chemotherapy.

Patient #3 is D.K., a four-year-old male who developed a medulloblastoma and presented to his private physician with intractable vomiting. He had a biopsy of his tumor and a subtotal surgical resection and was then begun on antineoplaston therapy by Dr. Burzynski on 4/11/94. Within just two months he was in complete remission as evidenced by his MRIs. That complete remission has persisted for 30+ months now. His therapy was well tolerated with no life-threatening side effects although he had some insignificant abnormalities of liver function tests, a low blood glucose from time to time,

a low white blood cell count from time to time, some anemia, a few episodes of low platelet counts and some elevated uric acid levels. His remarkable response here can be attributed only to his antineoplaston therapy as he did not receive radiation therapy nor standard chemotherapy nor was his surgery curative.

Patient #4 is T.L., a 47-year-old male with a malignant meningioma in the right front part of his brain who presented to his private physician with headaches. Because this tumor was of low grade histologically, it grew fairly slowly and over a three-year period he had four separate surgical procedures to debulk the tumor. Approximately four years ago he was begun on antineoplaston therapy. Within four months he obtained a complete remission which lasted for six months. The tumor relapsed shortly after he discontinued his antineoplaston therapy, which was then restarted, and within 20 months he was again in complete remission, that remission now lasting more than 7 months. He had no significant or insignificant side effects from the therapy. His complete response cannot be explained on any other basis other than the antineoplaston therapy as his surgery was noncurative and he was not exposed to radiation therapy or standard chemotherapy.

Patient #5 is G.M., a 35 year old male who has an oligodendroglioma and presented to his private physician with seizures. He had a subtotal tumor resection and was started on antineoplaston therapy on 08/12/93 with no prior radiation therapy or standard chemotherapy. For the last 40 months his residual tumor has not changed in size and his response category is best described as stable disease.

Patient #6 is J.T., who has a brainstem glioma and presented to his private physician with difficulty in balance. He was initially treated with chemotherapy but obtained no response. He was then treated with radiation therapy with some response. Eight weeks following the cessation of radiation therapy antineoplaston therapy was initiated and within three months all evidence of his tumor had disappeared on MRI. Unfortunately, that complete response lasted only 12 months and he ultimately died of progressive disease. His response here is due to the antineoplaston therapy as the only other possible therapy that could result in such a response was radiation therapy which was stopped two months prior to initiating the antineoplastons.

Patient #7 is W.T., a 63-year-old male with an anaplastic astrocytoma presenting to his private physician with difficulty speaking. He had a course of radiation therapy with no beneficial effect on MRI and then had eight months of chemotherapy also without a beneficial effect. Antineoplaston therapy was started on 5/7/95 and within 8 months he was in complete remission, that remission currently lasting more than 12 months. His seizures have also diminished. He had no life-threatening side effects from his chemotherapy but did lose 25 lb in weight while receiving antineoplaston therapy. The response here must be attributed to the antineoplaston therapy since his chemotherapy and radiation therapy occurred prior to the initiation of the antineoplaston therapy by a two-month interval and could not be considered as contributing or causing the response seen.

Patient #8 is R.G., a 62-year-old male with oligodendroglioma in the left lateral side of his brain. He presented to his private physician with headaches and had a subtotal resection of his tumor. Shortly following his

surgery on 1/5/96 he began on antineoplaston therapy for the residual tumor with a reduction in tumor volume of 50% within one month of initiating therapy. This partial remission has lasted more than 11 months. He had no life-threatening side effects from his therapy but did have insignificant low blood sugars and protein in his urine from time to time.

Patient #9 is T.H., a 33-year-old patient who presented to her private physician with headaches. She had a subtotal tumor resection for a mixed glioma followed by radiation therapy that was ineffective. Six months following the radiation therapy on 7/26/95, she was begun on antineoplaston therapy and within 11 months her tumor had shrunk by more than 50%, that partial remission persisting now for more than 7 months. She had no life-threatening side effects from her therapy but did have insignificant low white blood cell counts on several occasions.

Patient #10 is P.M., a 16-year-old male with a low grade astrocytoma who presented to his private physician at age 7 with intractable nausea and vomiting. His neurosurgeons determined that because of the location of his tumor any debulking surgery was too risky. Instead, they treated him by placing bypass shunts to allow his brain fluids to circulate normally and to relieve the obstruction caused by the tumor. In early 1988, he began on antineoplaston therapy without prior radiation therapy or standard chemotherapy. Within 13 months his tumor had shrunk by 50% or more, that response having continued for more than 78 months. He had no life-threatening side effects from his therapy, but did have insignificant anemia, abnormalities of his liver function tests, low white blood cell counts from time to time, protein in his urine and an elevated uric acid level. I see no other explanation for his partial remission here other than his antineoplaston therapy, since he was not exposed to radiation therapy, standard chemotherapy, debulking surgery, nor curative surgery.

Patient #11 is K.M., a 42-year-old female who presented with a low grade glioma in the right front of her brain who presented to her private physician with seizures. She had a biopsy but no debulking surgery, no chemotherapy, nor did she have radiation therapy. She was begun on antineoplaston therapy on May 16, 1994 and has continued that to the present time. Within 11 months her tumor had shrunk by at least 50% in volume and her response has continued for 13 months. She had no life-threatening side effects from her antineoplaston therapy, but did have insignificant aching of her joints, fevers, anemia, abnormalities of her liver function tests and some fluid retention. I see no explanation other than the antineoplaston therapy for her response here, inasmuch as she was not exposed to curative surgery, nor to radiation therapy or standard chemotherapy.

Patient #12 is V.P., a 32-year-old female who has glioblastoma and presented to her private physician with headaches. She had a subtotal tumor resection followed by radiation therapy and one of the standard chemotherapies. For three months following her surgery she did well with no evidence of residual tumor on her MRI. However, two weeks following the cessation of her chemotherapy and two months following her radiation therapy, her MRI demonstrated a regrowth of her tumor and on 9/2/95 antineoplaston therapy was started. Within five months her tumor had shrunk by more than 50%. That partial remission then persisted for 5+ months. Her partial remission must be attributed to the antineoplaston therapy since her brain tumor was growing

at the time when she was receiving chemotherapy and was growing shortly after her radiation therapy finished, clearly indicating her tumor was resistant to those two modalities of therapy. She had no life-threatening side effects from the antineoplaston therapy, but did have insignificant elevation of her liver function tests and an occasional low white blood cell count.

Patient #13, is J.S., a 48-year-old male with an oligodendroglioma of the left front part of his brain who presented to his private physician with headaches. He had a subtotal tumor resection followed by radiation therapy. He did well for one year but when his MRI showed a regrowth of his tumor antineoplaston therapy was begun on 5/3/95. Within 2 months of initiating antineoplaston therapy his tumor had shrunk by 50% or more, that response lasting some 12 months until his tumor began to grow again. He had no life-threatening side effects from his therapy but did have insignificant pain in his joints and some swelling in his joints. I believe the response seen here is clearly due to the antineoplaston therapy and cannot be attributed to the prior radiation therapy because of the time intervals involved.

Patient #14 is E.T., a 73-year-old male with glioblastoma who presented to his private physician with headaches. He had a subtotal tumor resection in July of 1995, followed by radiation therapy from 9/12/95 to 10/12/95. On 12/7/95, antineoplaston therapy was initiated. Two months later, his tumor had decreased by 50% in size, that response lasting some five months when MRIs demonstrated that his disease was regrowing. He had no life-threatening side effects from the antineoplaston therapy but did have insignificant low blood sugars, protein in his urine and abnormalities of his liver function tests. I believe that his response here is due to the antineoplastons, and not due to his radiation therapy because of the time intervals involved.

Patient #15 is J.V., a 51-year-old male who presented with seizures and speech difficulties and has a glioblastoma. Following a subtotal resection of his tumor, he had radiation therapy and standard chemotherapy. Antineoplaston therapy was initiated in December of 1993 and within 22 months his tumor had decreased in size by 50% or more. That response has lasted now some 7+ months. He had no life-threatening side effects from his antineoplaston therapy but did have some insignificant abnormalities of his liver function tests. I believe his response here is solely due to his antineoplaston therapy inasmuch as his radiation therapy and chemotherapy occurred two months or more prior to the initiation of his antineoplaston therapy and could have had no appreciable effect on diminishing the size of his tumor.

Patient #16 is J.W., a 12-year-old boy with a low grade astrocytoma who presented to his private physician with premature puberty. His tumor was initially treated with chemotherapy that was ineffective. On 3/6/95, antineoplaston therapy was started and has been continued to the present time. Within 14 months his tumor had shrunk by 50% or more and that partial remission has persisted now for 8+ months. He has had no life-threatening toxicity from his antineoplaston therapy but has had insignificant elevations of his blood uric acid level on several occasions, and his platelet count has diminished from time to time as has his white count. He has had anemia and protein in his urine. It is my opinion that the response here can be attributed only to antineoplaston therapy inasmuch as his tumor increased in

size on the MRI while he was receiving chemotherapy and that chemotherapy was remote in relationship to the initiation of the antineoplaston therapy.

Patient #17 is A.H., a 41-year-old male with oligodendroglioma who had a subtotal surgical resection of his tumor in 1986, followed by a second subtotal resection of the tumor in 1990. That was followed by a course of radiation therapy. His tumor recurred a second time in 1994. At that time he had an eight-month course of standard chemotherapy with some slight response in terms of diminution in the size of his tumor. On 7/17/95, antineoplaston therapy was initiated and has been continued through the present time. No significant diminution or progression of his tumor has been seen on his frequent MRIs and his classification is best described as that of stable disease. He has had no life-threatening side effects from his chemotherapy but has had insignificant abnormal liver function tests.

To summarize my thoughts regarding this review, I would have to stay that I am very impressed with the number of complete and partial responses that I have seen here, compared with the number of such responses that I have seen in my own personal experience. The responses here are also far in excess of any prior series of patients published in the medical literature. This group of 17 patients represents the "responders" from all 40 evaluable primary brain cancer patients who were getting antineoplaston therapy in Dr. Burzynski's clinic in February of 1996 when all of them were admitted to the CAN-1 trial. Dr. Schellinger downgraded 2 of the group of 17 from partial remissions to stable disease. Thus the response rate here is an astounding 33% with a complete remission rate of 15%. Such remission rates are far in excess of anything that I or anyone else has seen since research work on brain tumors began. It is very clear that the responses here are due to antineoplaston therapy and are not due to surgery, radiation or standard chemotherapy. It is also clear that oftentimes responses are slow to develop in these tumors, despite almost daily therapy with antineoplastons and that when antineoplaston therapy is stopped tumors may regrow within a few months. The duration of these responses is long and meaningful. It is also clear that although there is some toxicity associated with antineoplastons, it does not appear life threatening in this small sample of patients.

Research needs to continue on these very promising agents. We need to know such things as the optimal dose of these agents, the optimal route of administration, the optimal duration of treatment and many other details too numerous to mention.

Sincerely yours,

ROBERT E. BURDICK, M.D.
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