DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892
715 Executive Plaza North

Memorandum

Date: November 15, 1991

From: Chief, Investigational Drug Branch

Re: Antineoplaston

To: Decision Network

Attached is a summary of a review of a best case series of antineoplastons in the treatment of brain tumors which was conducted by CTEP at the Burzynski Research Institute and some background information on antineoplastons A10 and AS2-1. Seven patient cases were presented at the site visit and the records, pathology slides and scans documenting response were reviewed. It was the opinion of the site visit team 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.

At the DN meeting, Dr. Burzynski will present some brief background data on antineoplastons and Dr. Nicholas Patronas, a neuroradiologist from the Clinical Center who was on the site visit team, will review the radiologic findings for the committee.

Antineoplastons are being proposed for DN IV (Phase II trials). We feel the first step is to confirm the observations of Dr. Burzynski in brain tumors. Initially 3 or 4 Phase II trials would be conducted (one trial in each of the following diseases: glioblastoma multiforme, anaplastic astrocytoma, pediatric brain tumors and possibly low grade astrocytomas) using antineoplastons A10 and AS2-1 in exactly the same manner Dr. Burzynski gave them in the cases we reviewed. A decision regarding subsequent trials (e.g.--other tumors, additional Phase I development, Phase III trials in brain tumors, etc) would be deferred until the results of these initial trials were known.

Dr. Burzynski is willing to provide sufficient antineoplaston A10 and AS2-1 for these studies. The only impact on DCT would be the IND filing and the use of our clinical trials resources.

Michael J. Hawkins, M.D.

cc: Dr. Burzynski

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October 30, 1991

Stanislaw R. Burzynski, M.D., Ph.D.
6221 Corporate Drive
Houston, TX 77036-3494

Dear Dr. Burzynski:

Enclosed is a copy of the report summarizing our review of the responses seen in seven brain tumor cases treated by you with Antineoplastons A10 and AS2-1. Dr. Michael Hawkins will be communicating with you at a later date with regard to the question of possibly conducting a confirmatory trial under Division of Cancer Treatment sponsorship.

We thank you for your help and cooperation in making these cases available for our review, and for your kind hospitality during our visit.

Sincerely,

Dorothy Macfarlane

Dorothy K. Macfarlane, M.D.
Head, Quality Assurance and
Compliance Section
Regulatory Affairs Branch
Cancer Therapy Evaluation Program

cc: Dr. Michael Hawkins

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
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Memorandum

Date October 30, 1991

From Head, Quality Assurance and Compliance Section, RAB, CTEP

Subject Review of Brain Tumor Cases Treated With Antineoplastons

To See Distribution

On October 4, 1991, CTEP staff (Dr. Michael Hawkins, Dr. Michael Hamilton, Dr. Dorothy Macfarlane) and invited consultants (Dr. Nicholas Patronas, neuroradiologist, NIH Clinical Center, and Dr. James Nelson, neuropathologist, AFIP) visited the offices of Dr. Stanislaw Burzynski in Houston, Texas to review seven selected brain tumor cases which Dr. Burzynski felt represented the best responses achieved with Antineoplastons A-10 and AS2-1 treatment. Following is a summary of each case history, as described by Dr. Burzynski, and the assessment of slides and scans by the review team.

Patient #1 (E.L.)

46 year old white female who experience Jacksonian seizures and was diagnosed as having right parietal lobe glioblastoma multiforme in October 1987. Resected 11/10/87 at University of Maryland Hospital, and received radiation therapy following surgery. Tumor recurred in February 1988.

Presented to Dr. Burzynski in March 1988. Treated initially with Antineoplaston A10 capsules, AS2-1 injections and oral low dose methotrexate. Received only 8 days of MTX. Received intermittent steroids from 4/6/88 through 6/1/88. Considered a CR by 11/28/88 CT scan. Continued on full-dose treatment (0.5 to 1.0 gm A10 capsules daily, plus 2 gm AS2-1 IV daily) until 4/3/89. At that time, she was placed on AS2-1 capsules for maintenance therapy. In summer of 1989 patient discontinued treatment and in 8/89 recurrence was documented on MRI scan. Resection for recurrent glioblastoma multiforme at Johns Hopkins 11/28/89. Died 4/90.

Pathology review: Slides from 11/10/87 resection confirm glioblastoma multiforme.

Radiology review: Marked decrease in tumor size, possible complete response from 11/28/88 through 3/28/89 by CT. Recurrence possibly as early as 5/30/89 CT.

Patient #2 (P.W.)

36 year old female who first presented in 1974 with Bell's palsy. It is not clear that this event was related to the

later tumor which was first suspected in summer 1987. A stereotactic biopsy of the brain stem on 7/27/87 revealed anaplastic astrocytoma, stage IV, Grade 3. Received radiation therapy at UCSF (total 73Gy) until October 1987. Progression noted on scans of 2/88 and 4/88.

Presented to Dr. Burzynski in May 1988 with paralysis of right side of face, diplopia, decreased strength in right upper extremity, right ear hearing loss, headaches and problems with balance and memory. Started on Antineoplaston A10 capsules, AS2-1 IV and low dose oral methotrexate from 5/25/88 until 7/12/88, when she was switched to IV A10 (30 gm/day) and IV AS2-1 (15 gm/day) given overnight. This dose and schedule was continued until 8/10/89 when patient was switched to maintenance doses of oral A10 and AS2-1. Received IV Decadron 2mg/day from 5/29/88 through 9/7/88. No steroids given since that date. Called CR at 1/23/89 MRI. All treatment discontinued on 1/21/90 and patient remains in CR (last MRI 1/29/91). Residual facial nerve palsy, no other symptoms.

Pathology review: Slides from 7/21/87 stereotactic biopsy: consistent with anaplastic astrocytoma--small specimen (1 mm fragment) artifact distorts nuclei. Could be lower or higher grade astrocytoma.

Radiology review: From 1/23/89 MRI through latest MRI on 1/29/91 there is only a small cavity (1 cm or less) at the former tumor site which probably represents the site of biopsy. The previously seen tumor parenchyma is no longer present. Possible CR.

Patient #3 (J.K.)

47 year old white male who presented in April 1897 with deafness, progressive weakness and occasional seizures. Subtotal resection at UCSF April 24, 1987. Diagnosed as anaplastic astrocytoma close to the Foramen of Monroe. Patient treated at UCSF with radiation therapy + BUdR, which was stopped because of an exfoliative dermatitis. Patient next treated with combination of Procarbazine, CCNU, and vincristine which led to prolonged leukopenia and peripheral neuropathy. Progressed on treatment and switched to beta interferon (12/87 to spring 88). In June, 1988 started chemotherapy with DFMO and MGBG, but no response.

Presented to Dr. Burzynski 7/13/88 and started daily IV A10 and AS2-1 (overnight infusions). Showed slow progression initially, then stabilization by spring/summer 1989. On 5/22/89, antineoplaston dose was decreased and patient placed on AS2-1 capsules. By spring 1990, CTs showed progression of former tumor and appearance of new lesions. Restarted 4/12/90 on daily IV A10 (1 gm/kg/day) and AS2-1 (0.17 gm/kg/day) by continuous infusion pump. In June dose of AS2-1 was increased to 0.23 gm/kg/day and decadron was added from 6/27/90 to

7/25/90. In September 1991, decreased A10 dose by 60% and AS2-1 dose by 25%. Called PR in 10/91; approaching CR. Telephone follow up on the day of our visit; patient reported some memory deficit, but otherwise fine.

Pathology review: Slides from original subtotal resection showed infiltrating glioma (astrocytoma or mixed astrocytoma/oligodendroglioma), borderline anaplastic glioma.

Radiology review: Very aggressive tumor. Original tumor showed "fleshy" component of 4.5 cm on 8/24/88. Latest CT on 9/6/91 shows cavity of 4.0 cm with "fleshy" component of 1.3 cm, which may be residual tumor or calcium deposit. Numerous new lesions appeared starting with 11/88 CT, but all had disappeared by 12/19/90 CT. Good PR, possible CR.

Patient #4 (P.M.)

7 year old white male who presented with diplopia, nausea and vomiting in 11/85. CT on 11/7/85 showed suprasellar mass and hydrocephalus. Shunt placed 11/8/85. On 11/11/85 underwent craniotomy and biopsy at Mayo Clinic. Diagnosed as Stage IV astrocytoma, histologic Grade 1, inoperable. Treated with vitamins and laetrile originally. At the beginning of 1988, the patient experienced headaches and tumor progression was noted. A second shunt was placed.

Presented to Dr. Burzynski 4/18/88. Started on A10 capsules, AS2-1 IV and low dose methotrexate. In June 1988, a slight increase in tumor size was noted. On 6/23/88 patient was switched to overnight IV A10 (1 gm/kg/day) and IV AS2-1 (0.5 gm/kg/day). Progressive decrease in tumor size was noted; called a PR on basis of 4/17/90 MRI. Changed to continuous infusion A10 and AS2-1 at same doses on 5/29/90. Latest MRI on 8/2/91 shows further decrease in tumor size.

Pathology review: Slides from original biopsy. Well - differentiated astrocytoma, possibly juvenile pilocytic astrocytoma.

Radiology review: Pre-treatment scans show a hypothalamic mass plus trilocular cyst. Main component of cyst + tumor in hypothalamus followed through serial scans. There was a substantial decrease in size of both solid and cystic components, with the decrease in the cystic part more dramatic. Decrease in solid component of approximately 40-50%.

Patient #5 (H.E.)

40 year old white female diagnosed in 12/89. Craniotomy and partial resection on 12/31/89; glioblastoma multiforme of left temporal lobe. Received 6000 rads from January 18 to March 7,

1990. MRI on 4/9/90 showed progression after radiation therapy. Biopsied 5/9/90.

Presented to Dr. Burzynski on 5/24/90 with headaches, right-sided weakness and slurring of speech. Started on continuous infusion A10 (1 gm/kg/day) and AS2-1 (0.33 gm/kg/day). Called PR by 7/25/90 MRI. Progressed and switched to antineoplastons + methotrexate + vincristine. Continued to progress and died 1/1/91.

Pathology review: Slides from 12/31/89 partial resection showed glioblastoma multiforme. Slides from biopsy of 5/9/90 show residual tumor with extensive necrosis, cell density less than original tumor and more giant cells present. These changes are associated with radiotherapy and/or chemotherapy.

Radiology review: Unusually large tumor in 4/90 which decreased in size (39%) after treatment with antineoplastons. Had progressed by next MRI two months later, with former cavity filled in by tumor.

Patient #6 (R.W.)

10 year old male who had a VP shunt on 12/27/87. On 8/18/89 a mass was identified in the region of the hypothalamus. Stereotactic biopsy on 8/28/89 revealed glioblastoma, Stage IV, Grade 3. Received radiation therapy from 10/4/89 to 11/15/89 (total 5500 rads). Progressed 1/2/90, with increased tumor size and enhancement, and new area of tumor in ependyma and lateral ventricle.

Presented to Dr. Burzynski on 4/12/90 with hearing and memory deficits. Started on continuous infusion A10 (1 gm/kg/day) and AS2-1 (0.34 gm/kg/day). Doses decreased 4/17/90 because of high uric acid and given decadron 4/17 and 4/18; returned to full dose antineoplastons 4/24/90. Received decadron for nausea and vomiting 5/2-23/90. Off treatment on 5/9 through 5/11 and again 5/16 through 5/20 because of elevated uric acid. Re-started on 50% original dose 5/21/90. Dose increased on 6/5/90 to A10 (45 gm/day) and AS2-1 (15 gm/day). Single IV dose of decadron on 6/7/90. Decreased antineoplaston doses on 11/1/90 to A10 30gm/day and AS2-1 12.5 gm/day. A10 dose decreased again on 1/2/91 to 24 gm/day. Received single dose IV decadron on 1/16/91; no decadron since. Called CR on 11/1/90 Antineoplaston dose decrease in 4/91; still on treatment and still in CR.

Pathology review: Slides from original stereotactic biopsy in 1989. Glioma consistent with anaplastic astrocytoma. Differential: anaplastic astrocytoma or spindle cell variant of oligodendroglioma.

Radiology review: Original pre-treatment MRI on 1/2/90 showed a hypothalamic mass with subependymal spread; measured main

tumor in hypothalamus only. By 8/22/90, enhancement of ventricle had disappeared. By 10/25/90, there is no enhancement seen. Abnormal, probably scar tissue, in the former tumor bed. CR, which remains unchanged through 7/1/91 MRI.

Patient #7 (H.M.)

30 year old white male who was diagnosed with astrocytoma Stage IIIB following craniotomy and biopsy of left frontal lesion in October 1987. Received radiation therapy during October-November 1987.

Presented to Dr. Burzynski on 7/8/88 with recent increase in right-sided weakness. Started on overnight infusions of A10 (135 gm/kg/day) and AS2-1. Received varying doses of steroids continually from beginning of treatment to present. IV antineoplastons discontinued 3/31/89. Started AS2-1 capsules 4/4/89 and added A10 capsules and low dose methotrexate on 5/17/89. On 11/3/89 progression was noted and intermittent IV bolus AS2-1 begun. Switched to continuous infusion A10 (90 gm/day) and AS2-1 (25 gm/day) on 5/1/90. A10 discontinued on 6/8/90. By August 1990, former tumor appeared calcified.

Pathology review: Infiltrating anaplastic astrocytoma.

Radiology Review: No pre-treatment scans available. A large cavitary mass is present in left frontal lobe on 8/22/88 CT. It demonstrates ring enhancement. A second component of this lesion invades the corpus callosum and crosses the midline invading the opposite frontal lobe. By 8/3/89 CT, no enhancement is seen. Areas of unusual tumor calcification appear. The calcifications increase over time extending into the entire tumor parenchyma and masking any possible enhancement on the CT scans. Remains stable until 9/19/91 when MRI shows definite enhancement. Question of whether difference seen is because 9/19/91 scan is an MRI compared to earlier scans which were all CT. Good response--possible CR?

Dorothy Macfarlane

Dorothy K. Macfarlane, M.D.

Distribution:

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