DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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October 20, 1993

Dr. Stanislaw Burzynski
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Dear Dr. Burzynski:

This letter is in response to your correspondence of October 11, 1993 (addressed to Dr. Sznol) and of October 13, 1993 (to Dr. Greenblatt). Your most recent comments regarding the approved study of antineoplastons in adult brain tumor patients, faxed to Dr. Greenblatt on October 13, 1993, come as quite a surprise. Particularly confusing are your comments regarding dose and schedule of antineoplastons proposed in that study (your comment #1). Originally the dosage and schedule for this study was based on your protocol BT4. This version of BT4 was entitled, "Therapy of high-grade glioma with continuous infusions of antineoplastons A10 and AS2-1", and was accompanied by 12 case histories (patients with either anaplastic astrocytoma or glioblastoma multiforme treated apparently according to BT4). In your letter of April 26, 1993, however you stated that protocol BT4 was only for low-grade gliomas. Furthermore, you noted that protocols BT5 or BT6 should be used for patients with anaplastic astrocytoma and glioblastoma multiforme. In that same letter (April 20, 1993), you noted that AS2-1 was tolerated well at doses of .5 gm/kg/24h by adult patients when administered in intermittent injections (this is method of administration in BT6 and in the IND study). You stated that if given by continuous infusion, adults would experience increased sleepiness and tiredness, and specifically stated that the dosage of AS2-1 by continuous infusion for low-grade gliomas should be reduced to 0.4 g/kg/24h. You did not provide data to support these assertions, nevertheless, based on these comments and our review of the protocols BT4, BT5, BT6, we instructed the investigators to revise their protocol in accordance with your instructions. In the Consensus Review sent May 5, 1993, we instructed the Memorial Sloan Kettering investigators to pattern their protocol according to BT5, which was written for both children and adults. We specifically pointed out that BT6 was written for children. In your letter of June 9, 1993, regarding our Consensus Review, you specifically asked that the investigators use the treatment program according to BT6, knowing that the Memorial protocol was for adults with AA and/or GM. You did not at any time mention that dose escalation should be modified for adults, or mention any dose limitation for adults given the intermittent injections as specified in the BT6 protocol.

Your concerns regarding dose limitation in the previous letter appeared to be related to continuous infusion administration. The letter of June 9, 1993, contained only 4 comments and at that time you had both the protocol and Consensus Review in your possession. We transmitted your letter of 6/9 directly to the investigators, and all your requested changes were made.

Our sincere efforts to attempt to duplicate your findings and follow your recommendations are frustrated by receiving contradictory, incomplete, and inconsistent information from you. We have, at multiple points in the protocol development, solicited your input and followed your guidance in getting recommended dose escalation and modification guidelines for adults.

Please note that, one last time, we will ask the investigator to revise the protocol with regard to dose and schedule in compliance with your latest letter. However, we plan that the study will begin immediately and this will be the last such modification. Although you have not provided data to support each of your specific recommendation, we have incorporated them.

With regard to comment #2 of your Fax of October 13, 1993, you have misinterpreted the protocol. The total number of potential patients is 35/stratum, (ie a total of 70 patients) allowing for an adequate Phase II evaluation of each group of patients.

With regard to the statistical section, your #3 comment, there is little reason to assume that the modified Fleming design currently used in the protocol for the first stage of accrual is less appropriate than a design using 15 patients in the first stage. If the true response rate of the antineoplastons is 20% (standard criteria for activity in all of our phase II trials considered worthy of further study), the chance of proceeding to the second stage of accrual with the current design is 93.1%. The chance of proceeding to the second stage using 15 patients in the first stage of accrual is 96.5%. These differences are not considered meaningful.

With regard to your comment #4, we wish to maintain the standard clinical trials methodology used to evaluate new agents. We know of no evidence that obtaining a brain scan within 7 days of treatment versus within 14 days of treatment will in any way affect the evaluation of activity of a drug in this disease. The protocol clearly states that scans must be obtained within 2 weeks of study entry. Please also note the practical difficulties in scheduling scans and completing the pretreatment work-up in just one week; the cost of repeating tests simply to meet this artificial deadline could not be justified and probably would not be covered by insurance companies.

With regard to your point #5, (performance status) your own protocols allow patients with Karnofsky performance status of 60. We see no reason to demand a more stringent entry criteria for performance status than you have employed for your own patients.

With regard to your point #6, the use of neurologic status as well as CT scan/MRI findings to determine response, this was suggested to the investigators in our Consensus Review of May 5, 1993. You made no comment regarding this in your letter of June 9, 1993. The use of neurologic function as an additional criteria to determine response is an objective measurement and is standard among protocols we sponsor for glioma patients.. It is scientifically acceptable to include the criteria for response as currently written in the protocol. At analysis, both scan data and objective neurologic assessment can be described.

With regard to your letter of October 11, 1993, concerning data reviews, we are satisfied that reviewing the data after accrual of the first 14 patients/stratum is sufficient. We share your concerns about patient safety but believe that these investigators have extensive experience treating glioma patients, are superb and careful physicians, and have extensive experience administering a range of investigational agents to these patients. Furthermore, the patients will be followed carefully, and dose reductions for expected toxicities will be carried out as specified in the protocol.

Nevertheless, your experience with the agents is valuable and the availability of your guidance is much appreciated. If necessary, we will arrange a conference call at the end of treatment of the first 5 patients, or sooner if problems occur. Your participation in such a conference call, if necessary, would be welcome.

We will provide the Theradex (CTMS) printout to you on a monthly basis as we receive it. We do not believe it is practical or necessary to supply data on an every 2 week basis.

The most important unresolved issue at this time is that we are still waiting to receive the promised supply of antineoplastons to conduct these studies. Your letter of November 5, 1992, guaranteed a supply of the antineoplastons by March 31, 1993 (see attached). As of today we still have not received it. Believing that you would be shipping drug to the NCI, and since the protocol is approved at Memorial Sloan Kettering, recruitment of patients has begun. As you point out, these patients have aggressive disease, and cannot afford to wait to begin treatment. We are prepared to try to assist you in meeting this commitment, but we know of no obstacle here at NCI. We urgently request, again, that you ship the drug immediately.

Please be aware that our mission is to find and develop better therapies for cancer patients, and our only obligation is to those patients. Our agreement to pursue these studies with antineoplastons was based on suggestive evidence

of activity noted in your best case series. If you are unable or unwilling to provide the antineoplastons in the near future, we will pursue alternative sources to procure the drug or its active components, and will proceed with a clinical development plan to determine whether these chemicals have activity and are beneficial for patients.

Sincerely yours,

MA Friedman

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cc:
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