BURZYNSKI
RESEARCH INSTITUTE, INC.

August 23, 2001

via Federal Express

Mr. Michael E. Chappell
Food and Drug Adminstration
Dallas District Director
4040 North Central Exp.
Dallas, TX 75204

RE: Response to inspector's observations
IND #(b) (4)
Serial #(b) (4)

Dear Mr. Chappell:

From August 6, 2001 to August 10, 2001, medical officers and investigators of the FDA performed an inspection of our facility at 9432 Old Katy Rd., Ste. 200, Houston, Texas 77055.

Following is our response to inspector's observations (copy attached):

1. **Protocol violations: "subjects were started on antineoplaston treatment prior to the protocol-specified interval following prior chemotherapy and/or radiation therapy".**

   Patient(b) (7)(C)-BT-11-(b) (4)-(b) (4) of the head of April 2, 1998, after completion of chemotherapy revealed increase of tumor size. FDA allows us to admit such patients prior to the protocol-specified interval.

   Patient(b) (7)(C)-BT-22(b) (4) and patient(b) (7)(C) BT-22(b) (4) In the study BT-22 we are evaluating administration of antineoplastons to patients(b) (4) or in whom(b) (4) (b) (4) and(b) (4) In patient (b) (7)(C)-BT-22-(b) (4) of 11/03/99 compared to 08/19/99 revealed "there is a new abnormal peripherally enhancing area", according to radiologist(b) (4) In patient(b) (7)(C) BT-22(b) (4)(b) (4) of the head of 04/27/99 compared to 03/23/99 revealed: "the extent and clarity of contrast enhancement have increased", according to radiologist, (b) (4)

   Patient-PA-02-(b) (4) This patient with pancreatic cancer did not have decrease of tumor size as the result of radiation therapy combined with chemotherapy and developed progressive disease and worsening of his condition. The patient became "wheelchair bound". That is why it was decided to admit him 5 days sooner than(b) (4) (b) (4)

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Generally, in our previous correspondence with the FDA, the agency allowed us to accept patients for administration of antineoplastons when there were signs and symptoms of disease progression, despite shorter than protocol specified interval following prior chemotherapy and/or radiation therapy. In recent correspondence with the FDA of May 16, 2001, we were informed that acceptance of the patient prior to the protocol's specified interval is only a minor violation and we were advised to accept the patient to the study (copy attached).

2. **"Not all serious adverse events and adverse events are reported to the FDA and IRB."**

It was our understanding that it was necessary to report to the FDA only such adverse events which are possibly, probably, and definitely related to study drugs. According to the FDA's request of 12/18/96 we are reporting such adverse events monthly and serious adverse events within 3 days without any indication from the FDA that we should change our reporting to all adverse events, including those not related to study drugs. We are also reporting to IRB within 3 days all serious adverse events and monthly all adverse events related to the study drugs.

We will be glad to report all adverse events on a monthly basis, whether related or not related to the study drugs, if this is your requirement. Please let us know your position on this. If we do not hear from you regarding this, we will report all serious adverse events to the FDA & IRB, but only those (not serious) adverse events which are related to antineoplastons will be reported.

3. **"Special exception treatment request (b) (4) dated 07/31/97 for (b) (7)(C) -PR-04-(b) (4) was approved based on the incorporation of certain statements into the consent form. The consent form signed by (b) (7)(C) did not incorporate these statements".**

The statements which we were required to incorporate into the consent form were probably based on our previous annual report to the FDA and were no longer accurate. We informed Mr. Paul Zimmerman of the FDA about such inaccuracy in our letter of 07/29/97 and added statement which was based on correct and up-to-date information as follows: "Burzynski Research Institute sponsors two Phase II clinical studies with intravenous infusions of Antineoplastons A10 and AS2-1 in cancer similar to yours: (1) Phase II Study of Antineoplastons A10 and AS2-1 in Patients with Adenocarcinoma of the Prostate, according to Protocol PR-4 and (2)(b) (4) Study of Antineoplastons A10 and AS2-1 in Patients with (b) (4) , according to Protocol (b) (4) According to the FDA's classification a complete response is complete disappearance of

all tumors and partial response is more than 50% reduction of the tumors. Out of(b) (4) patients involved in the study according to Protocol PR-4, (b) (4) stable disease and continues the treatment, (b) (4) patients have been classified as progressive disease and (b) (4) patients were not evaluable. Out of(b) (4) patients treated according to Protocol(b) (4), (b) (4) obtained stabilization of the disease, (b) (4) patients have progression of cancer and(b) (4) patients were not evaluable. In addition,(b) (4) of these patients were receiving(b) (4) together with antineoplastons and there are no data on the combination of(b) (4) and antineoplastons; therefore, there is no way to know if receiving antineoplastons in addition to the current regimen of(b) (4) (b) (4) would be of any benefit to you."

4. **"Exception treatment request (b) (4) dated 08/28/97 for(b) (7)(C)-LY-7(b) (4) was approved based on the incorporation of certain statements into the consent form. The consent form that Pt.(b) (7)(C) signed did not incorporate these statements".**

By reviewing the consent form signed by this patient we could not find this statement. We do not have explanation as to why this statement was not included except for human error. We apologize for this error and will do our best to make sure that the statements requested by the FDA will be incorporated in the consent forms of future patients.

5. **"Failure to keep adequate drug accountability records"**

Before the inspection, we informed the FDA that some key employees were away from the country and, because of that, it would be difficult for us to produce all data necessary for FDA review during the inspection. We were assured that the inspection would consist of reviewing only the films of scans and x-rays, radiology reports and case report forms of selected patients on the list provided to us by the FDA. The doctor who is in charge of data processing was away from the country due to his mother having a heart attack. We tried our best to provide FDA inspectors with our accountability records; however, unfortunately, there were some deficiencies.

When the doctor in charge of the data processing came back to work, we were able to learn what we did wrong while trying to produce a drug accountability printout. Please find enclosed complete drug accountability record for Lot 258C (A10 capsules), Lot 058B (AS2-1 capsules), Lot 823-1 (AS2-1, 500 mL bags), Lot 809 (A10 IV bags) and Lot 199 (AS2-1 bags).

We will do our best to train additional employees so that the data may be retrieved from the database in the absence of the supervisor responsible for data processing. We will

also change the way we do drug accountability. Instead of recording all dispensing drugs and then balancing them with drugs received from the production plant, we will start subtracting all drugs being dispensed from the lot received.

6. **"Failure to address and resolve reported patient overdoses in BRI query reports to determine the reason for the possible overdose and to take corrective actions to prevent recurrence".**

(b) (7)(C)-BT-07 (b) (4) – 06/06/96
(b) (7)(C)-BT-11 (b) (4) – 02/15/98
Both patients switched bags of antineoplastons and administered (b) (4) mL of Antineoplaston AS2-1 in single dose. As described in progress notes, both patients were advised to discontinue infusions and were monitored by the research associate physician. No symptoms were reported associated with these events. Both patients restarted administration of antineoplastons on the following day.

(b) (7)(C)-BT-11 (b) (4) – 11/13/98
Patient overdosed Ativan prescribed on 10/26/98 by the local co-investigator, who was responsible for the patient's compliance with this prescription. The patient did not overdose study drugs.

In order to avoid overdose of the study drugs in the future, at the patient's next follow-up visit, we will implement an additional training for patients and the members of the family who may be responsible for overdosing.

7. **"Patient (b) (7)(C)-BT-07 – (b) (4) was observed to be receiving traditional radiation therapy while on the study".**

As recorded in our progress note of 03/11/98, the patient who was away from Houston under the care of her local physician underwent radiation treatment to the brain without our approval and without our knowledge. We were notified about her radiation therapy after she already received such treatment. This patient did not have objective response to antineoplastons.

8. **"Inadequate/Inaccurate record keeping".**

a) Patient (b) (7)(C) BT-17 (b) (4) – After careful checking we found that there is no discrepancy between information on CRF and information on source document. The withdrawal from the study was based on the patient's request. (b) (4) findings revealed further decrease of the tumor size, despite of presence of residual tumor.

Patient(b) (7)(C) BT-13(b) (4) – We found an error in information on CRF, which was already corrected. The patient was withdrawn from the study on 09/11/99 instead of 09/10/99.

We are in the process of auditing our CRF's and entire medical records. During this process we are occasionally finding errors, which are immediately corrected.

Patient(b) (7)(C) BT-20(b) (4) – We found that information in CRF and in source document indicates that the patient decided to discontinue administration of antineoplastons (patient's request).

Patient(b) (7)(C) BT-22(b) (4) – In CRF under "Revisions" the reason for withdrawal was corrected on 2/21/01 to "death".

Patient(b) (7)(C) LY-06(b) (4) - We found no discrepancy between information on CRF and on source document. The patient was advised to consider splenectomy because of the difficulty swallowing a sufficient dose of Antineoplaston A10 and AS2-1 capsules. Since she had other organs involved with lymphoma, it was our advise to restart antineoplastons after splenectomy. Withdrawal from the study was based on the patient's decision (patient's request).

Patient(b) (7)(C) LY-08(b) (4) – By checking the Social Security Death Index, the patient's date of death was confirmed as November 27, 1997.

Patient(b) (7)(C) UP-02(b) (4) – The patient received the last dose of antineoplastons on 07/03/98. Administration of antineoplastons was discontinued because of worsening of her condition. She died approximately 24 hours later on 07/04/98. CRF listed withdrawal date of 07/04/98, which was 24 hours after the last dose of antineoplastons. The reason for withdrawal was changed to "death".

8. **"Cross-outs and additions were made in source documents"**

b) During the inspection we clarified with FDA inspectors that it is allowable to make cross-outs and additions, but with certain statements it may be necessary to add justification for the new statement, which we agreed to do. In this particular patient we did not find discrepancy between statement, "The patient will remain off antineoplastons at this time" and the statement, "The patient will discontinue antineoplastons permanently" and the statement, "The patient will continue to be off antineoplastons at this time". All of these statements indicate that the patient is off antineoplastons. The only new information is that the patient decided to discontinue antineoplastons permanently, which he did. After

we found out that such a decision was made by the patient, we made the proper correction in the progress note.

9. **"The subject case report forms do not always contain complete and concurrent patient information such as:**

   a) **(b) (4) tumor measurements for patients (b) (7)(C) BT-11 (b) (4) or (b) (7)(C) BT-11 (b) (4) do not contain the tumor measurements that were done by the consultants"**

      It was the opinion of our consultants that it is not necessary to add consultant's reports to case report forms. However, based on inspector's suggestions we will add our consultant's reports to case report forms. Until now, the consultant's reports were kept in separate folders attached to the case report forms.

   b) **"The case report forms for patients (b) (7)(C) BT-23 (b) (4) (b) (7)(C) BT-23 (b) (4) and (b) (7)(C) BT-09 (b) (4) do not contain inclusion/exclusion criteria entries".**

      The entries for inclusion/exclusion criteria have been added to case report forms of these patients. We will continue to audit our case report forms and all medical records to make sure that such deficiencies will no longer occur.

Sincerely,

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

cc: Khin Maung U, M.D.
Medical Officer

cc: Mr. Joel Martinez
Investigator

cc: Carlton F. Hazlewood, Ph.D.
Chairman
IRB