

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION**

OFFICE ADDRESS AND PHONE NUMBER North Central Exp. Dallas, TX 75204 253-5200		DATE(S) OF INSPECTION 8/6-10/01
IND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED Stanislaw R. Burzynski, M.D., Ph.D., sponsor, clinical investigator		FEI NUMBER
NAME Burzynski Research Institute	STREET ADDRESS 9432 Old Katy Rd.	
STATE AND ZIP CODE Dallas, TX 77055	TYPE OF ESTABLISHMENT INSPECTED sponsor / clinical investigator	

IS AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

**Phase II Studies of Antineoplastons A10 and AS2-1 In Children and Adults with Cancer**


**1. Protocol Violations:**

Subjects were started on antineoplaston treatment prior to the protocol-specified interval following prior chemotherapy and/or radiation therapy.

Protocol Patient ID	Prior Therapy	Last Date of Prior Therapy	Date Antineoplastons started	Interval (days)
(b) (7)(C) BT-11 (b) (4)	Etopoxide	(b) (4)	24-Apr-1998	(b) (4)
(b) (7)(C) (b) (4)	Stereotactic radiation		10-Nov-1999	
(b) (7)(C) BT-22 (b) (4)	Etopoxide		30-Apr-1999	
(b) (7)(C) PA-02 (b) (4)	Combined Chemotherapy and Radiation		05-Aug-1999	

2. Not all serious adverse events and adverse events are reported to FDA and IRB. Examples are shown in the following table.

Protocol Patient ID	Date	Serious Adverse Events or Adverse Events
(b) (7)(C) BT-07 (b) (4)	31-Oct-2000	Subject became lethargic, with diarrhea and blood in the urine, and was hospitalized during which significant hematuria persisted.
	04-Dec-2000	Cystoscopy showed severe hemorrhagic cystitis and necrotic bladder mucosa.
(b) (7)(C) BT-08 (b) (4)	17-Jun-2000	Left subclavian vein thrombosis.
	14-Aug-2000	Subject experienced shortness of breath, and his chest X-ray showed suspicious consolidations in right lung base.
	20-Aug-2000	Hospitalized; bronchoscopy and lavage revealed <i>Pneumocystis carinii</i> .
(b) (7)(C) BT-11 (b) (4)	02-Feb-1997	Pancreatitis; antineoplastons were discontinued for one week and restarted on 28-Feb-1997. Patient developed pancreatitis again and required antineoplastons to be discontinued permanently on 10-Mar-1997
(b) (7)(C) BT-11 (b) (4)	18-May-2000	Central line sepsis (blood culture positive for <i>Staphylococcus aureus</i> ) requiring hospitalization.
	20-May-2000	Broviac catheter had to be removed.

SEE REVERSE THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Kevin Mrozinski, M.D., Medical Officer Patrick D. Siroso	DATE ISSUED 08/10/01
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TO: Stanislaw R. Burzynski, M.D., Ph.D., sponsor, clinical investigator

FIRM NAME Burzynski Research Institute	STREET ADDRESS 9432 Old Katy Rd.
CITY, STATE AND ZIP CODE Houston, TX 77055	TYPE OF ESTABLISHMENT INSPECTED sponsor / clinical investigator

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

(b)(7)(C) BT-15 (b)(4)	30-Sep-1999	Hospitalized with fever for pneumonia and sepsis, deteriorated, requiring transfer to ICU. Subject expired on 17-Oct-1999.
(b)(7)(C) BT-21 (b)(4)	08-Mar-1998	Hospitalized for fever, hypotension, central line sepsis; subject also developed an aspiration pneumonia in hospital.
(b)(7)(C) BT-22 (b)(4)	29-Jun-1999	Cushingoid features, steroid myopathy
	13-Sep-1999	Renal acidosis requiring daily treatment with sodium bicarbonate.
	04-Oct-1999	Hypertension, requiring medication, e.g., Vasotec
	07-Oct-1999	Venous thrombosis in left arm confirmed by venogram.
	29-Oct-1999	Central line sepsis, blood culture grew coagulase negative Staphylococcus that required treatment with Vancomycin
	22-Nov-1999	Diarrhea with stool cultures positive for Clostridium difficile for which the subject was treated with Vancomycin
(b)(7)(C) LY-06 (b)(4)	19-Sep-1999	Shortness of breath
	22-Sep-1999	Lung biopsy revealed fibrosis of lung for which the subject was hospitalized and required Oxygen. The subject died on 01-Oct-1999.
(b)(7)(C) (b)(4)	11-Aug-1997	Occlusion of both subclavian veins.
(b)(7)(C) UP-02 (b)(4)	03-Jul-1998	Hospitalized for septic shock (fever, hypotension), was intubated and placed on ventilator the next morning, and died at noon on 04-Jul-1998.

3. Special exception treatment request (b)(4) dated 7-31-97 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 included:
- a) (b)(4) patients with renal cell carcinoma who received antineoplastons had a response.
  - b) (b)(4) patients with prostate cancer receiving antineoplaston infusions had a response.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>Stanislaw R. Burzynski</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Stanislaw R. Burzynski, M.D., Medical Officer F. D. Smith, Ph.D.	DATE ISSUED 08/10/01
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TO: Stanislaw R. Burzynski, M.D., Ph.D., sponsor, clinical investigator

FIRM NAME

Burzynski Research Institute

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CITY, STATE AND ZIP CODE

Houston, TX 77055

TYPE OF ESTABLISHMENT INSPECTED

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

4. Exception treatment request (SN (b)(4) dated 8-28-97 for (b)(4) was approved based on the incorporation of certain statements into the consent form. The consent form that Pt. (b)(4) signed did not incorporate these statements that included:
  - a) An awareness to the patient that protocol (b)(4) is intended to measure response
  - b) To date there have been (b)(4) from patients on this protocol
  - c) (b)(4) in patients on Special Exception
  
5. Failure to keep adequate drug accountability records. For example:
  - a) A random selection of Lot 258C (A10 capsules) revealed that (b)(4) capsules were received at BRI. One accountability record accounts for (b)(4) capsules while a second accountability record accounts for (b)(4) capsules.
  - b) Random selection of Lot 058B (AS2-1) revealed that (b)(4) capsules were received at BRI. Drug accountability records account for (b)(4) on one database and (b)(4) in a second accountability record.
  - c) Random selection of Lot 823-1 (AS2-1 500 ml bags) show that BRI received (b)(4) bags. Accountability records account for only (b)(4)
  - d) Lot 809 (A10 IV bags) show that (b)(4) bags were received. Accountability records can account for (b)(4) bags.
  - e) Receipt records for Lot 199 (AS2-1) show that (b)(4) bags were received. Accountability records can only account for (b)(4)
  
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. For example:
  - a) (b)(4) BT-07 (b)(4) query dated 11-8-00
  - b) (b)(4) BT-11 (b)(4) query dated 4-3-01
  - c) (b)(4) BT-11 (b)(4) query dated 8-7-01

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OF THIS  
PAGE

EMPLOYEE(S) SIGNATURE

*[Handwritten Signature]*

EMPLOYEE(S) NAME AND TITLE (Print or Type)

DEAN MURPHY, MD, Medical Officer  
PATRICIA D. STANCO

DATE ISSUED

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

7. Patient (b)(7)(C) BT-07 (b)(4) was observed to be receiving (b)(4) while on study.

8. Inadequate / Inaccurate Record Keeping:

(a) There are discrepancies between the case report forms and the source documents for the following subjects:

Protocol Patient ID	Information on CRF	Information on Source Document
(b)(7)(C) BT-17 (b)(4)	Withdrawn on 27-Nov-1996; Reason = Patient's request	Patient was withdrawn with MRI findings (18-Jun-1996 vs 30-Sep-1996) suggestive of recurrent tumor
(b)(7)(C) BT-13 (b)(4)	Withdrawn 09-Oct-1999	Patient continued on study until 09-Nov-1999.
(b)(7)(C) BT-20 (b)(4)	Withdrawn on 30-Jul-1996; Reason = Patient's request	Patient was hospitalized on 30-Jul-1996 with grand mal seizures and antineoplaston dose was reduced. Then, the patient decided to stop antineoplastons permanently.
(b)(7)(C) BT-22 (b)(4)	Withdrawn on 27-Nov-1999; Reason = Worsening of clinical condition	Patient died the morning of 27-Nov-1999
(b)(7)(C) LY-06 (b)(4)	Withdrawn on 29-Dec-1999; Reason = Patient's request	On 28-Dec-1999, patient's abdominal CT of 23-Nov-1999 was reported with splenomegaly and patient was recommended on 29-Dec-1999 to undergo splenectomy and stop antineoplaston treatment.
(b)(7)(C) (b)(4)	Patient died on 27-Nov-1997.	Patient died on 27-Dec-1997
(b)(7)(C) UP-02 (b)(4)	Withdrawn on 04-Jul-1998; Reason = Worsening of clinical condition	Patient was hospitalized in ICU on 03-Jul-1998 for bacterial sepsis, and died on 04-Jul-1998.

(b) Cross-outs and additions were made in source documents

For example, in progress notes of Subject (b)(7)(C) BT-07 (b)(4) dated 03-Nov-2000 is the statement "The patient will remain off antineoplastons at this time." This was crossed out and replaced with the sentence "The patient will discontinue antineoplastons permanently." This alteration was made despite many subsequent progress notes that contain the sentence, "The patient will continue to be off antineoplastons at this time."

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>[Signature]</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Stanislaw R. Burzynski, M.D., Medical Officer Pharmaceutical Services	DATE ISSUED 08/10/01
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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

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)(7)(C) or (b)(7)(C) BT-11 (b)(7)(C) do not contain the tumor measurements that were done by the consultants.
  - b) The case report forms for patients (b)(7)(C) BT-23 (b)(7)(C) (b)(7)(C) BT-23 (b)(7)(C) and (b)(7)(C) BT-09 (b)(7)(C) do not contain inclusion/exclusion criteria entries.

10. Failure to address and resolve reported patient overdoses in BRT query reports to determine the reason for the possible overdose and to take corrective actions to prevent recurrence. For example:

JM-

- d) (b)(7)(C) BT-07 (b)(7)(C) query dated 11-8-00
- e) (b)(7)(C) BT-11 (b)(7)(C) query dated 4-3-01
- f) (b)(7)(C) BT-11 (b)(7)(C) query dated 8-7-01

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

JM-

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

- Written response will be submitted

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE <i>Patrick D. Stencso</i>	EMPLOYEE(S) NAME AND TITLE (Print or Type) Patrick D. Stencso, M.D. Medical Officer	DATE ISSUED 08/10/01
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