

RADIATION THERAPY ONCOLOGY GROUP

RTOG BR-0013

**A PHASE II TRIAL OF CONVENTIONAL RADIATION THERAPY
FOLLOWED BY INTRATUMORAL BLEOMYCIN DELIVERED USING A REFILLABLE,
SUSTAINED RELEASE DEVICE (IND# 46,592) FOR THE TREATMENT OF
SUPRATENTORIAL GLIOBLASTOMA**

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A PHASE II TRIAL OF CONVENTIONAL RADIATION THERAPY FOLLOWED BY INTRATUMORAL BLEOMYCIN DELIVERED USING A REFILLABLE, SUSTAINED DEVICE (IND#46,592) FOR THE TREATMENT OF SUPRATENTORIAL GLIOBLASTOMA

SCHEMA

- R** 60.0 Gy/30 fractions x 2.0 Gy. For the first 46 Gy/23 fractions
- E** the treatment volume should include the volume of contrast-enhancing lesion and surrounding edema on pre-operative
- G** CT/MRI scan plus a 2 centimeter margin. If no edema is present, the margin should be 2.5 cm. After 46.0 Gy, the tumor
- I** volume should include the contrast-enhancing lesion (*without edema*) on the pre-surgery MRI/CT scan plus a 2.5 centimeter
- S** margin.
- T** Within 2-6 weeks after completion of radiation therapy or at
- E** the time a patient experiences disease progression during or immediately after completion of radiation therapy, if clinically
- R** feasible, a modified Ommaya reservoir is implanted with the delivery catheter in the tumor or tumor cyst/cavity. Bleomycin, 15 units per week, is then given via the Ommaya reservoir without interruption for a maximum of two years as long as there is no toxicity above grade 3 (*see details, Section 7.3*) or evidence of disease progression.

Eligibility (See Section 3.0 for details)

- Histopathologically confirmed glioblastoma multiforme (*with areas of necrosis*);
- The tumor must be supratentorial in location, unifocal and limited to one hemisphere without gross invasion of a ventricular surface;
- The tumor must be in a location that can be reached by the drug delivery catheter attached to the Ommaya device as judged by a neurosurgeon;
- Therapy must begin ≤ 4 weeks after surgery;
- Estimated survival of at least 8 weeks;
- Zubrod 0-1;
- Absolute neutrophil count ≥ 1500 , platelets $\geq 100,000$, BUN ≤ 25 , Creatinine ≤ 1.5 , Bilirubin ≤ 2.0 , Hgb ≥ 10 gm, SGPT or SGOT ≤ 2 x normal range;
- No recurrent or multifocal malignant gliomas;
- No major medical illnesses or psychiatric impairments;
- No malignancy (*within the past two years*) except non-melanomatous skin cancer or carcinoma *in-situ* of the cervix;
- No prior radiation therapy to head or neck area that would result in "overlap" of radiation fields;
- No prior chemotherapy or radiosensitizer treatment for this brain tumor;
- Signed study-specific consent form prior to registration.

Required Sample Size: 72

Institution # _____

RTOG BR-0013

ELIGIBILITY CHECK (6/6/01)

Case # _____

(page 1 of 2)

- _____(Y) 1. Does the patient have histologically confirmed supratentorial glioblastoma multiforme?
- _____(Y) 2. Is the tumor and associated edema limited to one hemisphere?
- _____(N) 3. Is the tumor recurrent or multifocal?
- _____(Y) 4. Has the patient recovered from the effects of surgery, post-operative infection or other complications?
- _____(Y) 5. Has a diagnostic contrast-enhanced MRI or CT of the head been performed pre-operatively?
- _____(Y/N) 6. Has a diagnostic contrast-enhanced MRI or CT of the head been performed post-operatively?
_____(Y) If no, did the patient have only a stereotactic biopsy performed?
- _____(Y) 7. Do the patient's laboratory values meet the criteria in Section 3.1.9?
- _____(N) 8. Has the patient received any prior radiotherapy to the head and neck or any chemotherapy or radiosensitizer for this brain tumor?
- _____(Y/N) 9. Has the patient had prior malignancies, except for non-melanomatous skin cancers, or carcinoma *in-situ* of uterus, cervix or bladder?
_____(Y) If yes, has the patient been disease free for ≥ 2 years?
- _____(N) 10. Does the patient have any detected metastases below the tentorium or beyond the cranial vault or tumor and/or associated edema that involves both cerebral hemispheres?
- _____(N) 11. Does the tumor grossly invade a ventricular surface?
- _____(Y) 12. Is the patient's Zubrod Status 0-1?
- _____(Y) 13. Does the patient have an estimated survival of at least 8 weeks?
- _____(N) 14. Does the patient have any major medical or psychiatric illness which in the investigator's opinion will prevent administration or completion of the protocol therapy?
- _____(Y) 15. Is the tumor in a location that can be reached by the drug delivery catheter attached to the Ommaya device as judged by a neurosurgeon?

(cont'd on next page)

Institution # _____

RTOG BR-0013

ELIGIBILITY CHECK (6/06/01)

Case # _____

(page 2 of 2)

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____ (Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ 17. Treatment Assignment
- _____ 18. Medical Oncologist

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Results with all present methods of treatment for glioblastomas have been disappointing. The combination of surgical resection, radiation therapy, and chemotherapy produces a median survival of less than one year.^{1,2} Surgery and radiation have probably reached maximal effectiveness. Chemotherapy has the potential to improve survival, but significant increase has been marginal using either intravenous or intra-arterial administration of conventional agents.^{1,2} Other than tumor insensitivity to particular drugs, the reasons for the failure of chemotherapy include: 1) inability of many chemotherapeutic agents to cross the blood-brain barrier (*BBB*) and reach tumoricidal concentrations in the tumor, 2) lack of sufficient time of exposure of the tumor to the drug to produce an effective kill, and 3) unacceptable systemic toxicity. Many attempts have been made to increase the concentration of drugs in the brain and decrease systemic toxicity, including intra-arterial therapy and intraventricular drugs. These methods have not increased survival.

A drug delivery method that has the potential to overcome many of the problems but has not been thoroughly investigated is the direct intratumoral (*IT*) administration of chemotherapy. Intratumoral chemotherapy has several advantages over intravenous chemotherapy in the treatment of malignant brain tumors. Large amounts of drug can be concentrated in the brain tumor because the blood brain barrier is bypassed. These large concentrations of chemotherapy in the tumor are achieved by giving very small total doses of the chemotherapeutic agent, and so little drug gets into the systemic circulation to cause toxicity. In addition, new classes of drugs that could not be given by vascular routes can now be given directly into tumors. It is also possible to give intratumoral chemotherapy by continuous infusion or by sustained release and maintain high drug concentrations in the tumor for indefinitely long periods of time.

Recently, intratumoral chemotherapy has been given by implanting small wafers (*Gliadel*) into the tumor. Unfortunately, Gliadel is a less than optimum way of giving intratumoral chemotherapy. This method requires a major surgical procedure during which the wafers are placed inside the tumor. The wafers dissolve over several weeks and are not replaceable (*except by doing another open craniotomy*). The only drug used in the wafers is BCNU, a chemotherapeutic agent that has been given for brain tumors for over 30 years but has not been unequivocally shown to be successful at extending survival. Also, the benefit of *intratumoral* BCNU is unclear since the drug is known to penetrate well into brain tumors when given intravenously. In addition, BCNU is not a cell cycle sensitive agent, and so the major benefit of sustained release is lost.

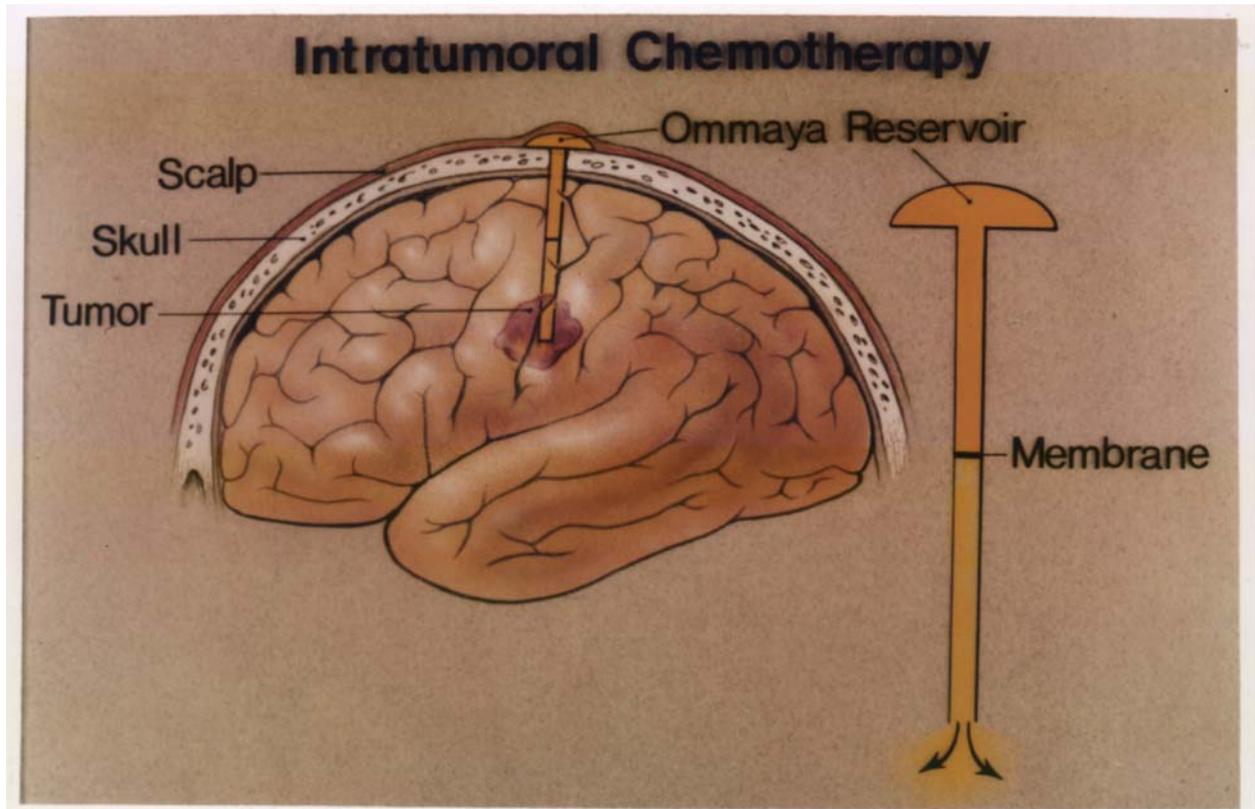
A new way of giving intratumoral chemotherapy involves the delivery of chemotherapy directly into the brain tumor through a catheter. The catheter is connected to a refillable device (*a modified Ommaya reservoir*) that is implanted under the patient's scalp. The Ommaya reservoir has been modified by the addition of a cellophane-like permeable membrane placed between the reservoir and the catheter that regulates the flow of drug into the tumor. The device can be refilled easily, and the patients can receive continuous high-dose intratumoral chemotherapy for indefinitely long periods.

Bleomycin was used in the first clinical study using the new device. The drug has been shown to be effective against animal and human brain tumors in experimental models. Preliminary studies in humans showed bleomycin to be almost free of detectable toxicity when given directly into brain tumors. Bleomycin is a cell cycle sensitive agent whose effect should be substantially enhanced by sustained release. The drug has not been used against human brain tumors in the past because of its poor penetration of the blood brain barrier (*when given intravenously*) and its severe systemic toxicity. Animal studies have shown that, when given intratumorally, bleomycin has relatively good penetration and diffusion into tumor and normal brain.³⁻⁶

The first clinical trial in humans was done to determine the optimum dose of sustained release intratumoral bleomycin. In that phase I study, performed at the University of Kentucky, the modified Ommaya reservoirs and bleomycin were extremely well tolerated. Nine patients with previously irradiated recurrent GBM were enrolled in a dose escalation study and received weekly doses of bleomycin beginning at 4.9 units/wk and escalating up to toxicity. (*One week was the half life of the drug in the device at body temperature.*) Total cumulative doses ranged from 24.5 to 713.3 units of bleomycin. The study determined that the maximum tolerable weekly dose of intratumoral bleomycin was 15 units/wk. Toxicity, when present, was minimal even at much higher weekly doses and, when present, consisted of drowsiness, lethargy, and increased seizure frequency (*in those patients with preexisting seizure disorders*). In addition, two patients who had received cumulative doses in excess of 300 units developed skin ulcers around the injection site. No other nonneurological (*systemic*) toxicity from bleomycin occurred; patients did not experience nausea, hair loss, fatigue, pulmonary fibrosis or myelosuppression. The median survival after start of IT bleomycin therapy was 26 weeks, and this compared very favorably with the 8-12 week expected survival for patients with recurrent GBMs. Two of the nine (22%) patients lived longer than one year. The phase I study showed that the modified Ommaya device worked well without adverse

effects and that IT bleomycin was relatively nontoxic and well tolerated.⁷ A schematic of the modified Ommaya device/delivery system in place is shown below.

Figure 1A



2.0 OBJECTIVES

- 2.1 To determine if bleomycin given intratumorally weekly after conventional RT will improve the median survival time of adults with newly diagnosed supratentorial glioblastoma.
- 2.2 To determine, in a multi-institutional setting, the feasibility of delivering drug intratumorally using a refillable sustained-release device.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

- 3.1.1 Histopathologically confirmed glioblastoma multiforme (*with areas of necrosis*).
- 3.1.2 Diagnosis must be made by surgical biopsy or excision.
- 3.1.3 The tumor must be supratentorial in location.
- 3.1.3.1 The tumor must be unifocal; limited to one hemisphere (*i.e., tumor and/associated edema*) without gross invasion of a ventricular surface and in a location that can be reached by the drug delivery catheter attached to the Ommaya device as judged by a neurosurgeon.
- 3.1.4 The patient must have recovered from the effects of surgery, or post-operative infection and other complications before entry into the study.
- 3.1.5 Therapy must begin \leq four weeks after surgery.
- 3.1.6 Patients must have an estimated survival of at least 8 weeks.
- 3.1.7 Zubrod Performance Status 0-1.
- 3.1.8 A diagnostic contrast-enhanced MRI or CT scan must be performed preoperatively and postoperatively prior to the initiation of radiotherapy. Preoperative and postoperative scans must be the same type.
- 3.1.8.1 Patients diagnosed only by stereotactic biopsy do not require the post-op scan.

- 3.1.9 Hematologic, renal, and hepatic status should be documented. If anemia is present to the extent that the hemoglobin is less than 10 grams and the hematocrit is less than 30%, then correction by transfusion is indicated before entry into the study.

Hematologic: Hemoglobin \geq 10 grams

Absolute neutrophil count \geq 1500 (*ANC*) per mm³

Platelets \geq 100,000 per mm³

Renal: BUN \leq 25 mg/dl

Creatinine \leq 1.5 mg/dl

Hepatic: Bilirubin \leq 2.0 mg/dl

SGPT or SGOT \leq twice normal range

- 3.1.10 The patient must give written study-specific informed consent prior to study entry. If the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the responsible family member.

3.2 Conditions for Patient Ineligibility

3.2.1 Astrocytoma other than GBM.

3.2.2 Recurrent or multifocal malignant gliomas.

3.2.3 Patients in whom tumor is detected below the tentorium or beyond the cranial vault or tumors and/or associated edema that involve both cerebral hemispheres.

3.2.4 Major medical illnesses or psychiatric impairments which in the investigator's opinion will prevent administration or completion of the protocol therapy.

3.2.5 Previous radiotherapy to the head or neck that would result in "overlap" of radiation fields.

3.2.6 Previous malignancies, except for non-melanomatous skin cancers and carcinoma *in situ* of the uterine cervix or bladder, unless disease-free for \geq 2 years.

3.2.7 Prior chemotherapy or radiosensitizer treatment for this brain tumor.

3.2.8 Tumors that grossly invade a ventricular surface.

3.2.9 Patients who have a hypersensitive or idiosyncratic reaction to bleomycin.

3.2.10 Pregnant or lactating women. Bleomycin sulfate can cause fetal harm in a pregnant woman and has been shown to be teratogenic in rats. It is not known whether bleomycin is excreted in human milk; however, there may be a potential for serious adverse reaction in nursing infants.

4.0 PRETREATMENT EVALUATION

4.1 Mandatory Studies

4.1.1 Complete history and general physical examination.

4.1.2 Contrast-enhanced MRI or CT scan performed preoperatively and postoperatively prior to the initiation of radiotherapy (*mandatory for eligibility*). The postoperative scan is not required if the patient was diagnosed by stereotactic biopsy.

4.1.3 CBC with differential, platelet count, BUN, serum creatinine, bilirubin, and SGOT or SGPT.

4.1.4 Chest x-ray.

4.1.5 Steroid doses must be documented.

4.1.6 Detailed neurological examination and Mini-mental status exam immediately prior to beginning protocol treatment course. Request a forms pack from RTOG Headquarters in advance.

4.1.7 Neurosurgical evaluation to judge for eligibility of placement of drug delivery system as specified in Section 3.1.3.1 *Note: Actual procedure for placement of drug delivery system occurs after completion of radiation therapy.*

5.0 REGISTRATION PROCEDURES (8/20/03)

- 5.1 Each institution must submit a Device Shipment Form (Appendix V) to the CTSU Regulatory Office (215-579-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must send Device Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case. Allow adequate processing time (7-10 days) before calling to register the first case. Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY PARAMETERS

6.1 Dose Definition and Schedule

Radiotherapy must begin within 4 weeks of surgery. One treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy over six weeks. All portals shall be treated during each treatment session. Doses are specified as the target dose which shall be to the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

6.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

6.1.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

6.1.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.

6.1.4 Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.

6.1.5 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity. However, if this technique is utilized, the dose shall be specified at the center of the target area.

6.1.6 Other or complex treatment arrangements: at the center of the target volume.

6.2 Physical Factors

Treatment shall be delivered with megavoltage machines of energy ranging from Cobalt 60 up to and including 10 MV photons. Selection of the appropriate photon energy(*ies*) should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies > 10 MV should be utilized only in dual energy beam arrangements using at least one beam with energy \leq 10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Source sizes must be no more than 2 cm in Cobalt 60 machines. For Cobalt 60 machines, secondary collimation is required. Electron, particle or implant boost is not permissible.

6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility. The target volume for both the initial volume and the conedown volume shall be based on the preoperative CT/MRI. The initial target volume shall include the contrast-enhancing lesion and surrounding edema (*if it exists*) demonstrated on CT/MRI plus a 2.0 centimeter margin. If no surrounding edema is present, the initial target volume should include the contrast-enhancing lesion plus a 2.5 centimeter margin.

This initial target volume will be treated to 46.0 Gy in 23 fractions. After 46 Gy the conedown tumor volume should include the contrast-enhancing lesion (*without edema*) on the pre-surgery CT/MRI scan plus a 2.5 centimeter margin.

6.4 Treatment Planning

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. CT/MRI-guided treatment planning is necessary to assure accuracy in the selection of field arrangements.

Isodose distributions for the initial target volume and the conedown target volume are required on all patients, including those treated with parallel opposed fields. A composite plan is required showing the respective target volumes. The inhomogeneity across the target volume shall be kept to a minimum.

The minimum dose to the target volume should be kept within 5% of the dose at the center of the volume. The use of vertex fields requires either a diagram or photograph of treatment position to be submitted to RTOG Headquarters. The maximum dose should be no higher than 5% of the dose at the center of the target volume.

6.5 Dose Limitations to Critical Structures

The lens and cervical spine must be shielded from the direct beam at all times. When possible to do without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 60 Gy, the retina of at least one eye (*but preferably both*) to 50 Gy, and the brain stem to 60 Gy. When the optic chiasm must be included in the full dose, then there may be a finite unknown risk of developing blindness.

6.6 Documentation Requirements

A copy of the pretreatment CT/MRI, the treatment prescription form, treatment calculation form, simulation films and representative portal films of each initial field must be forwarded to RTOG Headquarters according to Section 12.1. At the completion of treatment, the following shall also be forwarded to Headquarters: daily treatment record, all isodose distributions, simulation and portal films of the reduced fields, and the radiotherapy summary.

6.7 Radiation Toxicities

- 6.7.1 Expected toxicities include loss of hair and erythema of the scalp. Reactions in the ear canals and on the ear should be observed and treated symptomatically. If significant increase in reaction of the normal tissue occurs, it should be noted and reported to the Study Chairman.
- 6.7.2 Both acute and delayed or late reactions to radiotherapy are to be recorded and included in the complete toxicity evaluation. Acute (≤ 90 days from RT start) side effects of radiation therapy will be documented using the NCI Common Toxicity Criteria, Version 2.0. Late (> 90 days from RT start) side effects of radiation therapy will be evaluated and graded according to the RTOG Late Radiation Morbidity Scoring Scheme (*Appendix III*).
- 6.7.3 Hematologic toxicities should be rated on a scale of 0-4 as defined in the revised NCI Common Toxicity Criteria, Version 2.0.

7.0 DRUG THERAPY

7.1 Schedule

7.1.1 Bleomycin

Beginning 2-6 weeks after completion of radiotherapy or at the time of disease progression during or immediately after completion of radiation therapy, if clinically feasible, 15 units of bleomycin per week is given intracerebrally via the modified Ommaya delivery system. This should preferably be done on same day of each week. If progression occurs during RT, discontinue the RT and begin treatment with bleomycin.

7.1.2 This schedule will continue without interruption for a maximum of two years as long as there is no toxicity above grade 3 or evidence of disease progression. See Section 7.3 for details.

7.1.3 Use of Modified Ommaya - Drug Delivery Device (IND# 46,592)

The modified Ommaya reservoir is placed surgically by the neurosurgeon (*see Figure 1A*). The modified Ommaya reservoir used in this study differs from the standard Ommaya reservoir in that the semipermeable membrane makes the reservoir a continuous sustained release device. This has been achieved by covering the connector rod with a porous membrane of polyvinyl alcohol. These membranes are non-erodible and biologically inert. The refilling procedure involves the withdrawal of fluid and then the introduction of the same volume of the bleomycin solution into the Ommaya. This is done to insure that the membrane is not ruptured and the correct amount of fluid is maintained inside the reservoir. The technique also minimizes the number of needle sticks required to refill the system. The equipment used for refilling the reservoir consists of a 3-way stopcock, 2 small TB type syringes, and a 22 gauge (*or smaller*) needle.

Before injecting the drug, the skin over the Ommaya should be cleaned with Betadine® (*or other cleansing solution*). The procedure for filling the Ommaya device involves first drawing out fluid from the Ommaya and then putting in the bleomycin. The 3-way stopcock is connected to the needle and the two syringes. One of the syringes has been filled beforehand with a solution of 15 units of bleomycin dissolved in 0.6 cc of sterile water or sterile normal saline. The stopcock is set so that the connection to the bleomycin is closed and the connection to the empty syringe is open. The needle is inserted through the scalp into the Ommaya, and 0.6 cc of fluid from inside the Ommaya is then drawn up into the empty syringe. With the needle still in the Ommaya, the stopcock is turned so that the passage to the empty syringe (*now filled with old Ommaya fluid*) is closed and the path to the bleomycin filled syringe is open. The bleomycin solution is then injected into the Ommaya. The needle is then withdrawn from the Ommaya and scalp.

7.1.4 Distribution of Modified Ommaya Drug Delivery Device (8/20/03)

The Device Shipment Form (*Appendix V*) must be submitted to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must send Device Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case. Allow adequate processing time (*7-10 days*) before calling to register your first case.

After each registration, RTOG will arrange for patient-specific delivery of devices directly to the institution via two-day express mail. There will be no charge to the institutions or to the patient. Unused connectors/devices **may not** be used for non-protocol patients and should be returned to:

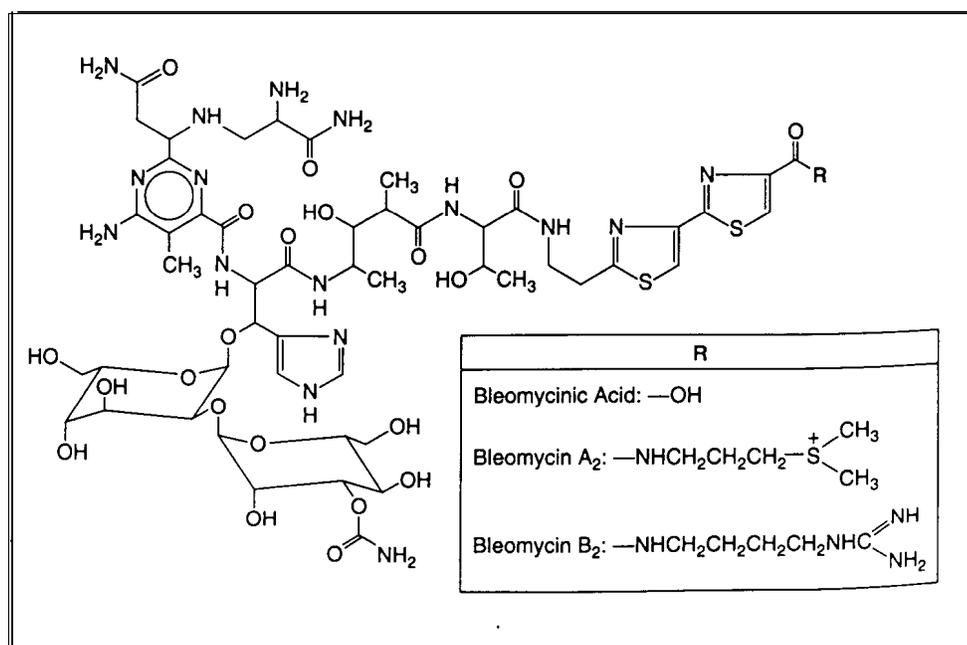
Ms. Jackie Sims, R.T.T. (859) 323-6489
Study Coordinator, RTOG BR-0013 FAX# (859) 257-4931
University of Kentucky
Chandler Medical Center/Radiation Oncology
800 Rose Street
Lexington, KY 40536-0084

7.2 **Bleomycin (Blenoxane™)**

7.2.1 Chemistry

Bleomycin is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*. It is freely soluble in water.

7.2.2 Pharmacodynamics and Pharmacokinetics



Bleomycin has been given directly into brain tumors. It has also been administered parenterally into the bladder for the local therapy of bladder cancer. After i.v. administration high levels are present in the skin and lungs which are major sites of toxicity. Bleomycin crosses the blood brain barrier poorly when given systemically. After i.v. administration of 15 units/m², peak concentrations of 1 to 5 units/ml are achieved in the plasma. The half-life of elimination is approximately 3 hours. The average steady state concentration following continuous i.v. infusion of 30 units daily for 5 days is approximately 0.15 units/ml. Two thirds of the excretion is in the urine by glomerular filtration. Higher serum levels occur in the presence of renal failure. When bleomycin is given by the intrathecal route, these high serum levels have not been encountered.

7.2.3 Toxicology

When given intracerebrally, bleomycin produces little toxicity. In previous studies using intratumoral administration into the brain, headaches, fever, and seizures have occurred. One case of death was reported. At the doses used in a previous phase I trial in humans, headaches, lethargy, and fever were the main complications. When given intravenously, bleomycin causes little myelosuppression. However, it has significant cutaneous toxicities including hyperpigmentation, hyperkeratosis, erythema, and even ulceration.

This applies to bleomycin given systemically. This is unlikely to apply to this study based on the phase I intratumoral bleomycin study. However, possible side effects are listed below.

The most serious adverse reactions involve the lung. Approximately 5-10% of patients receiving systemic bleomycin develop pulmonary problems with a 1% mortality. Bleomycin is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

Pulmonary toxicities occur in 5-10% of i.v. treated patients. In approximately 1%, the nonspecific pneumonitis induced by bleomycin progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent chest x-rays are recommended.

A severe idiosyncratic reaction (*similar to anaphylaxis*) consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with bleomycin. Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses. Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported infrequently. These toxicities may occur, however, at any time after initiation of therapy. Bleomycin sulfate can cause fetal harm when administered to a pregnant woman. It

has been shown to be teratogenic in rats. Administration of intraperitoneal doses of 1.5 mg/kg/day to rats (*about 1.6 times the recommended human dose on a unit/m² basis*) on days 6-15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. Bleomycin is abortifacient but not teratogenic in rabbits, at intravenous doses of 1.2 mg/kg/day (*about 2.4 times the recommended human dose on a unit/m² basis*) given on gestation days 6-18. There have been no studies in pregnant women. If bleomycin is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with bleomycin.

7.2.4 Precautions

- General - Bleomycin clearance may be reduced in patients with impaired renal function. No guidelines have been established for dose adjustments, but bleomycin should be used with extreme caution in patients with significant renal impairment.
- Carcinogenesis, Mutagenesis, and Impairment of Fertility - The carcinogenic potential of bleomycin in humans is unknown. A study in F344-type male rats demonstrated an increased incidence of nodular hyperplasia after induced lung carcinogenesis by nitrosamines followed by treatment with bleomycin. In another study where the drug was administered to rats by subcutaneous injection at 0.35 mg/kg weekly (3.82 units/m² weekly or about 30% of the recommended human dose), necropsy findings included dose related injection site fibrosarcomas as well as various renal tumors. Bleomycin has been shown to be mutagenic both in vitro and in vivo. The effects of bleomycin on fertility have not been studied.
- Nursing Mothers - It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued by women receiving bleomycin therapy.
- Pediatric Use - Safety and effectiveness of bleomycin in pediatric patients have not been established.

7.2.5 How Supplied

Commercially available in 15 unit vials as a white or yellowish lyophilized powder. Manufactured by: Nippon Kayaku Co., Ltd. Tokyo, Japan Distributed by: MeadJohnson.

7.2.6 Storage and Stability

Intact vials are stored in the refrigerator. The sterile powder is stable under refrigeration 2°C (36°F) to 8°C (46°F) and should not be used after the expiration date is reached. After dilution, the resulting solution is stable for at least 1 month if properly preserved and refrigerated, or for 2 weeks at room temperature.

7.2.7 Reconstitution

0.6 ml of sterile distilled water or sterile normal saline is added to the 15 unit vial. Bleomycin should not be reconstituted or diluted with D₅W or other dextrose containing diluents. When reconstituted in D₅W and analyzed by HPLC, bleomycin demonstrates a loss of A2 and B2 potency that does not occur when bleomycin is reconstituted in 0.9% sodium chloride.

7.2.8 Special Considerations

Should not be mixed with solutions containing divalent or trivalent options (*especially copper*) due to chelations. It is inactivated by hydrogen peroxide and compounds containing sulfhydryl groups, and ascorbic acid. Bleomycin should not be reconstituted or diluted with D₅W or other dextrose containing diluents. When reconstituted in D₅W and analyzed by HPLC, bleomycin demonstrates a loss of A2 and B2 potency that does not occur when bleomycin is reconstituted in 0.9% sodium chloride. Prior cisplatin treatment may reduce the renal elimination of bleomycin, resulting in greater toxicity. Use of inhaled oxygen may exacerbate pulmonary toxicity.

7.3 Dose Modifications

7.3.1 Dose Adjustments During Treatment

Skip one week if headache or other symptoms (*e.g., mental status changes or seizure*) develop. If patient experiences grade 4 or greater toxicity, therapy stops. If patient experiences grade 3 toxicity, treatment should be held for one week and then resumed if grade 3 toxicity has resolved. If grade 3 toxicity persists, protocol treatment should be stopped. In the case where a patient has experienced resolution of a grade 3 toxicity and resumption of protocol therapy, protocol therapy should stop if the patient experiences another grade 3 toxic event.

7.3.2 Progression of Disease

- If the patient experiences clinical progression and/or radiographic progression as evidenced on MRI or CT during RT, discontinue the RT and begin treatment with bleomycin if clinically feasible.

Bleomycin will be continued for a maximum of two years as long as there is no toxicity above grade 3 or evidence of continued clinical and/or radiographic progression.

- If clinically feasible, bleomycin will be given after RT if the patient experiences clinical progression and/or radiographic progression as evidenced on the post RT/pre-bleomycin MRI or CT scan. Bleomycin will be continued for a maximum of two years as long as there is no toxicity above grade 3 or evidence of continued clinical and/or radiographic progression.
- If the patient experiences clinical progression and/or radiographic progression as evidenced on MRI or CT scan during bleomycin treatment, the patient will be considered to have progression of disease (PD). Bleomycin will be discontinued, the patient can be treated with any treatment at the discretion of the treating physician.

7.4 Adverse Drug Reaction Reporting Guidelines

7.4.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP Home page (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

7.4.2 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to this protocol and attributed to the commercial agent should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days and telephoned to RTOG Headquarters Data Management and to the Study Chairman within 24 hours of discovery:

7.4.2.1 Any ADR which is both serious (*life threatening, fatal*) and unexpected.

7.4.2.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.4.2.3 Any death on study if clearly related to the commercial agent.

7.4.3 The ADR report should be documented on form FDA 3500 and mailed to:

**Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
Telephone: (24 hours) (301) 230-2330
Fax: (301) 230-0159**

7.4.4 Any death, regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 48 hours of discovery.

8.0 SURGERY

8.1 The extent of surgical resection prior to protocol entry shall be documented as a) biopsy, b) subtotal resection, or c) total resection as described by the operative report and/or post operative imaging.

8.2 Within 2-6 weeks after completion of radiation therapy, a modified Ommaya reservoir is implanted with the delivery catheter placed within the central area of the tumor or tumor cyst/cavity. See Section 7.1.3.

9.0 OTHER THERAPY

9.1 All patients should be maintained on the lowest steroid dose necessary for neurological stability.

10.0 PATHOLOGY

10.1 RTOG Tissue Bank

10.1.1 It is desirable but not required that patients entered in this study submit materials to the RTOG Tissue Bank.

10.1.2 The following must be provided:

10.1.2.1 One H&E stained slide.

10.1.2.2 A paraffin-embedded tissue block of the tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

10.1.2.3 Pathology report documenting that submitted block or slides contain tumor.

10.1.2.4 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.

- 10.1.3 RTOG will reimburse pathologists from submitting institutions \$100 per case if proper materials are submitted (*reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement*).
- 10.1.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).
- 10.1.5 Materials will be sent to:

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 321-5020

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters Table

Assessment	Prior to Therapy	During Radiotherapy	Post RT
Neurological Exam, H&P	X	Weekly	X ^d
Steroid Dose Documentation	X	X	X ^e
CBC and differential, Platelet count	X		X ^c
BUN, Serum Creatinine, Bilirubin, & SGOT or SGPT	X		X ^e
Chest X-ray	X		X ^a
Contrast enhanced Brain CT or MRI	X ^b		X ^f
MMSE	X		X ^d
Toxicity Evaluation		Weekly	X ^g

- a. As clinically indicated.
- b. Both preoperatively and postoperatively prior to RT; postoperative scan not required if patient diagnosis was by stereotactic biopsy only. Post RT then q 3 months.
- c. Every 2 weeks during drug administration.
- d. Every three months; neuro evaluation should be done weekly during the first 2-3 months of drug administration.
- e. Every 4 weeks during drug administration, then at each follow-up.
- f. Within 24 hours after placement of drug delivery system.
- g. Weekly during drug administration.

Important: It is mandatory that patients are followed with the same study (CT vs. MRI) as the baseline study

11.2 Evaluation During Study

- 11.2.1 A neurologic examination shall be performed once a week during radiation therapy, weekly during first 2-3 months of drug administration and every three months thereafter.
- 11.2.2 Skin within the treatment portal shall be examined at least once per week during radiation therapy and weekly with each intra-Ommaya bleomycin treatment.
- 11.2.3 The contrast-enhanced CT/MRI of the brain shall be obtained prior to surgery, post-surgery, prior to initiation of bleomycin therapy, then every 3 months and at the time of neurologic deterioration. Attention is drawn to the occurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post treatment and last up to 6-8 weeks. These transient adverse signs and symptoms spontaneously improve without therapy. They are considered to be due to transient demyelination. Therefore, caution is urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation.
- 11.2.4 While a patient is receiving bleomycin, blood counts are required every two weeks.

11.3 CT/MRI Review

The serial CT/MRI shall be examined at the institution by an independent reviewer, a neuroradiologist. The evaluation of the scans will be compared to and correlated with the patient's clinical course.

11.4 Overall Response

- 11.4.1** Complete Response (CR): shall be defined as the circumstance when the tumor is no longer seen by neuroimaging provided that the patient is completely off of steroids (*or at replacement adrenal levels*) since the last evaluation period.
- 11.4.2** Partial Response (PR): Decrease of $\geq 50\%$ in the product of two diameters provided that the patient has not had his/her dose of steroids increased since the last evaluation period.
- 11.4.3** Minor Response (MR): Decrease in diameter products of $< 50\%$ provided that the patient has not had his/her dose of steroids increased since the last evaluation period.
- 11.4.4** Stable Disease (SD): shall be defined as the circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids.
- 11.4.3** Progression (P): shall be defined as a $> 25\%$ increase in tumor area (*two diameters*) provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. A concomitant decrease in steroid dose will rule out a progression designation at this point.

11.5 Instructions For Administration of Mini-Mental Status Examination (MMSE)

The Mini-Mental Status Exam could be administered by the physician, a nurse or an assistant trained in the administration of such tools. The person administering the Mini-Mental Status Exam needs to be sensitive to when the patient shows embarrassment of their inability to answer these questions. Patients should be assured by telling them that this is another way of telling how the treatment is affecting their brain tumor. It also needs to be made clear to the patient that it is very important to get this type of information directly from them. The person administering the test needs to understand that either the correct answer is given or not. There should be no partial credit for answers short of the mark.

11.6 Criteria for Evaluation of Therapy Effectiveness

- 11.6.1** Tumor response and regrowth can frequently be difficult to measure directly. Serial neurological exams and CT/MRI scans may provide a guide to the actual course. Time interval to progression will be measured from the first day of treatment until deterioration is documented by the individual Investigator using these guides. The patient should consistently be followed with the same diagnostic imaging study (*CT or MRI*).
- 11.6.2** Overall survival will be measured from the time of registration until death.
- 11.6.3** The quality of survival will be measured by neurological functional classification and performance status.
- 11.6.4** Post mortem examination of the cranial contents should be obtained at death whenever possible to evaluate effects of this therapy on malignant and normal brain tissue.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

<u>Data</u>	<u>Due</u>
Demographic Form (A5)	Within two weeks of registration
On-study Form (I1)	
Pretreatment MRI/CT scan (<i>both pre- and post-surgery</i>) (C1) and reports (C3)	
Mini Mental Status Exam (MS)	
<u>Preliminary Dosimetry Information:</u>	Within one week of treatment start
Radiotherapy prescription (T2)	
Simulation & Portal Localization films (T3)	
Central Axis Calculations (T4)	
Radiotherapy Form (T1)	Within one week of completing radiotherapy
<u>Final Dosimetry Information:</u>	
Daily Treatment Record (T5),	
Isodoses (T6),	
Simulation & Port films of all Fields (T8)	
Chemotherapy Report (F1)	Every 3 months for 2 years
Post-RT, pre-drug MRI/CT for documentation of drug delivery system placement (C2) and	Three months post-RT; for grade ≥ 3 RT toxicity and for progression.

Report (C3)

Initial Follow-up Form (FS)	3 months from start of protocol treatment
Follow-up Form (F1) Mini-Mental Status Exam (MS)	Every 3 months for 2 years; q 6 months x 2 years, then annually. Also at progression/relapse and at death (<i>F1 only</i>).
Autopsy Report (D3)	As applicable

12.2 CT/MRI Documentation

The contrast-enhanced MRI/CT taken before surgery and after-surgery-before-radiotherapy begins must be submitted within two weeks of registration. **A post-RT, pre-drug-therapy scan performed within 24 hrs after placement of drug delivery system must also be submitted to Headquarters.** A MRI/CT must be done at the time of neurologic deterioration, suggestive of tumor recurrence and not related to lowered steroid dose, unless the last MRI/CT had been done within one month and was compatible with recurrence. Other causes of neurological deterioration, such as metabolic imbalance, anticonvulsant or interferon toxicities, should be considered and properly investigated. The patient should consistently be followed with the same diagnostic study. Subsequent scans and reports, other than the pre-entry and post-RT scans, should be forwarded to RTOG Headquarters only in the event of a suspected grade ≥ 3 RT toxicity.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Overall survival.

13.1.2 Acute and late toxicities associated with conventional RT followed by intratumoral bleomycin.

13.2 Sample Size

The primary objective of this study is to estimate the median survival time (*MST*) for glioblastoma multiforme (*GBM*) patients treated with conventional RT followed by intratumoral bleomycin. The majority of patients will have a maximum tumor diameter greater than 4.0 cm. Historically, GBM patients with RPA class of III, IV, and V have an estimated MST of 17.9, 11.1, and 8.9 months, respectively.⁸ Excluding patients who died within the first eight weeks results in MST of 18.4, 11.3, and 9.23 months, respectively. A sample size of 54 evaluable RPA class III, IV, and V patients, with an expected distribution of 20%, 49%, and 31%, respectively, followed over 18 months will ensure at least 80% probability of detecting a minimum of 35% improvement in MST compared to the RTOG glioma database at the 0.20 significance level (*one-sided*)⁹. Based on previous RTOG GBM studies, a conservative lower bound of 20% of patients are estimated to expire before week 12. Therefore, adjusting for 95% eligibility/evaluability and 80% of patients starting bleomycin treatment results in 72 patients needed in order to achieve 54 eligible patients receiving bleomycin. In summary, **this study requires a total sample size of 72 patients.**

13.3 Inclusion of Women and Minorities

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into glioma trials failed to show any treatment interaction with gender.⁸ The RTOG found no difference in survival of glioblastoma multiforme patients by race.¹⁰ Since there are no publications found to support a possible interaction between different radiation therapy schedules and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

13.4 Patient Accrual

The patient accrual is projected to be 14 cases per month, based upon the monthly accrual for prior RTOG GBM studies. At this rate, it will take five months to reach the required total accrual of 72 cases. If the average monthly accrual rate is less than three patients, the study will be re-evaluated with respect to feasibility.

13.5 Analyses Plans

13.5.1 Interim Analyses

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- a) the patient accrual rate with a projected completion date for the accrual phase, and compliance rate of treatment delivery with respect to protocol prescription;
- b) the quality of submitted data with respect to timeliness, completeness, and accuracy;
- c) the frequency and severity of the toxicities.

Through examining the above items, the RTOG DMC and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for this study, and, if necessary, the RTOG Executive Committee, so that corrective action can be taken.

13.5.2 Analysis for Reporting the Initial Treatment Results

This analysis will be undertaken when each patient has been potentially followed for a minimum of 18 months. The usual components of this analysis are:

- a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
- b) reporting of institutional accrual;
- c) distribution of important prognostic baseline variables – (*age, ZPS, neurologic function, extent of surgery, time from first symptom, location of primary, and site of tumor*);
- d) observed results with respect to the endpoints described in Section 13.1.
- e) Overall survival of patients who have received bleomycin will be compared to the same proportion of RPA class III, IV, and V patients from the historical control who have survived at least eight weeks, using a one-sided log-rank test with a significance level of 0.20.

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APPENDIX I

RTOG BR-0013

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE II TRIAL OF CONVENTIONAL RADIATION THERAPY FOLLOWED BY INTRATUMORAL BLEOMYCIN DELIVERED USING A REFILLABLE, SUSTAINED RELEASE DEVICE (IND# 46,592) FOR THE TREATMENT OF SUPRATENTORIAL GLIOBLASTOMA

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have a brain tumor called a supratentorial glioblastoma.

Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, *Taking Part in Clinical Trials: What Cancer Patients Need to Know*, is available from your doctor.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) Bleomycin has on patients with your type of brain tumor. Researchers are also studying the device that will be used to deliver the Bleomycin to your brain tumor. They want to find out the effects (good and bad) the use of this method of drug delivery has on your tumor and the rest of your body.

This research is being done because currently there is no effective treatment for your type of cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 72 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

•All patients will receive:

Radiation Therapy: Radiation therapy treatments will be given at your institution once a day, five days a week, for six weeks.

Surgical Procedure: Two to six weeks after the completion of radiation therapy you will undergo a surgical procedure to place a special

type of catheter or tube, called a modified Ommaya reservoir, into the middle of the tumor location in your brain. The only part of the catheter that you will be able to see or feel will be under the skin of your scalp.

Chemotherapy: Bleomycin will be injected into the Ommaya reservoir once a week for two years. The drug injection will be done at your institution.

If you take part in this study, you will have the following tests and procedures:

- Procedures that are part of regular cancer care and may be done even if you do not join the study.

<u>Procedure</u>	<u>Schedule</u>
Physical and Neurological Exam	Prior to study entry, weekly during radiation, then every two months
Chest X-Ray or CT scan	Prior to study entry and as medically indicated
Brain CT or MRI	Prior to study entry
Blood Tests	Prior to study entry
Biopsy	Prior to study entry

- Standard procedures being done because you are in this study.

<u>Procedure</u>	<u>Schedule</u>
Blood Tests	Every 2 weeks while receiving Bleomycin
Brain CT or MRI	After placement of Ommaya reservoir; then every 3 months
Mini Mental Status Exam	At study entry, weekly during first 2-3 months of Bleomycin, then every 3 months while receiving Bleomycin, then at each follow-up.

- Follow-up visits with your physician will be scheduled every three months for two years, every six months for 2 years, then annually thereafter.

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue will be sent to a central office for review and research investigation associated with this protocol.

HOW LONG WILL I BE IN THE STUDY?

You will receive radiation therapy to the brain for six weeks. Your chemotherapy treatments will begin two to six weeks following your radiation therapy and they will continue for two years. Follow-up visits will continue for the rest of your life according to the above schedule.

The researcher may decide to take you off this study if it is in your medical best interest, drug supply is insufficient, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the drug or radiation therapy is stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks Associated with Radiation Therapy

Very Likely

- Scalp redness or soreness
- Permanent hair loss
- Dry mouth or altered taste
- Fatigue, sleepiness
- Headaches, seizure, weakness

Less Likely But Serious

- Hearing loss
- Eye injury resulting in blindness
- Mental slowness, behavioral changes
- Severe damage to normal brain tissue
that may require additional surgery

Risks Associated with Bleomycin

Likely

Headache

Fatigue

Less Likely, But Serious

Seizures

Breathing difficulties

Mental confusion, irritability, nervousness, difficulty concentrating

Severe infection including pneumonia

Risks of damage to brain (similar to a stroke) which could be life-threatening

Less Likely

Sore throat or mouth

Fever, chills, heavy sweating

Nasal congestion

Upset stomach, nausea and/or vomiting

Dark patches on skin and nails

Loss of appetite, taste changes

Skin ulcers at injection site

Reproductive Risks: Because the drug in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask your doctor about counseling and more information about preventing pregnancy.

Risks Associated with Ommaya Reservoir

Infection

Membrane rupture which would result in replacement of the reservoir

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with brain tumors in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the

new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: **1-800-332-8615**

Visit the NCI's Web sites for comprehensive clinical trials information at
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ
<http://cancernet.nci.nih.gov>.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

Patient Signature (*or legal Representative*)

Date

TISSUE AND BLOOD TESTING (RTOG BR-0013)

I agree to the use of my specimens for research and teaching purposes related to my cancer.

Yes No

I agree to be contacted in the future to discuss whether I will give permission for my specimens to be used for genetic research.

Yes No

I agree to allow my specimens to be used for research unrelated to my cancer.

Yes No

Patient Signature *(or legal Representative)*

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction <i>(Karnofsky 90-100).</i>
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work <i>(Karnofsky 70-80).</i>
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours <i>(Karnofsky 50-60).</i>
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours <i>(Karnofsky 30-40).</i>
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair <i>(Karnofsky 10-20).</i>

APPENDIX IV

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent.

Report **by phone** within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days.

- All deaths within 30 days of termination of the agent. As above
- All life threatening (*grade 4*) events which may be due to agent. As above
- First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. ****A written report may be required.**

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours ****A written report must be sent to RTOG within 10 working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)**
- All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. ****A written report to follow within 10 working days.**
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. ****Report in writing** to RTOG Headquarters and IDB within 10 working days.

**** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form**

APPENDIX V (8/20/03)

RTOG BR-0013

A PHASE II TRIAL OF CONVENTIONAL RADIATION THERAPY FOLLOWED BY INTRATUMORAL BLEOMYCIN DELIVERED USING A REFILLABLE, SUSTAINED RELEASE DEVICE (IND# 46,592) FOR THE TREATMENT OF SUPRATENTORIAL GLIOBLASTOMA

DEVICE SHIPMENT FORM

Devices will be mailed only to institutions who have identified a single individual for receipt of shipment. Each institution must submit this form to the CTSU Regulatory Office (Fax 215-579-0206) as soon as the individual responsible for the study device has been identified and prior to registration of the institution's first case. **Canadian Institutions must submit this form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** Allow adequate processing time (7-10 days) before calling to register your first patient.

SHIP TO:

Name: _____

Address: _____

(No P.O. Box Numbers)

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

IRB Approval Date: _____

(attach copies of IRB approval and sample consent form)

Investigator (PI) Signature _____ Date: _____

Investigator Name (Print) _____

Investigator NCI # (Required) _____

Return to:

*CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX 215-569-0206*

RTOG Headquarters Approval _____ Date: _____