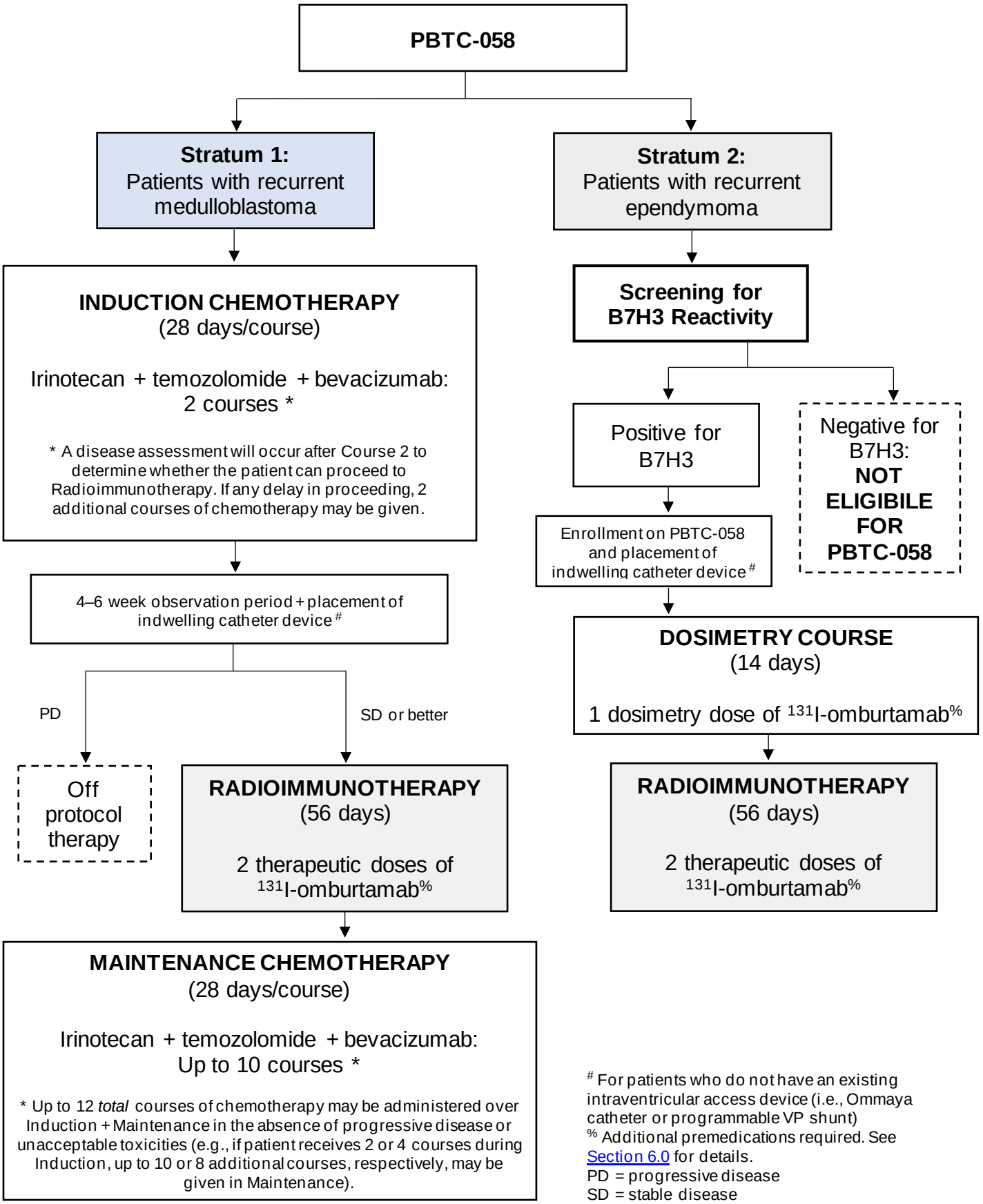
Phase 2 Study of Intraventricular Omburtamab-based Radioimmunotherapy for Pediatric Patients with Recurrent Medulloblastoma and Ependymoma

ABSTRACT & SCHEMA

Stratum 1: This is a phase 2 single-arm open-label study that will define event-free survival (EFS) and overall survival (OS) following therapy with irinotecan, temozolomide, bevacizumab, and compartmental (intraOmmaya) radioimmunotherapy (cRIT) ^{131}I-omburtamab in patients with recurrent medulloblastoma. Patients with recurrent medulloblastoma will undergo surgery if feasible prior to study entry, followed by Induction Chemotherapy with irinotecan, temozolomide, and bevacizumab on study as per the Children's Oncology Group (COG) trial ACNS0821. Following 2 or 4 courses of chemotherapy and if radiographic disease status is stable or improved, patients may continue to Radioimmunotherapy to receive 2 therapeutic doses (50 mCi each) of cRIT ^{131}I-omburtamab. Following Radioimmunotherapy, patients may resume to Maintenance Chemotherapy with irinotecan, temozolomide, and bevacizumab for up to 12 total courses of chemotherapy or until disease progression, whichever occurs sooner. The primary comparison for this study will be the medulloblastoma cohort treated on ACNS0821 on the irinotecan + temozolomide + bevacizumab arm (N=52).

Stratum 2: This is a feasibility cohort. The primary objective is to assess feasibility of incorporating cRIT ^{131}I-omburtamab for patients with recurrent ependymoma and to assess dosimetry. Patients must have progressed after initial surgery, radiation therapy, or other therapies. Patients will undergo surgery (if feasible) prior to study entry with the goal of achieving stable or better disease. Tumors (archived or new) will be tested for B7H3 prior to enrollment. If positive, patients will enroll on Stratum 2 and receive one dosimetry dose (2 mCi) of cRIT ^{131}I-omburtamab with nuclear medicine scintigraphy using SPECT during the Dosimetry Course (14 days in length). Following the Dosimetry Course and within 2 weeks of the dosimetry dose, patients may continue to Radioimmunotherapy to receive 2 therapeutic doses (50 mCi each) of cRIT ^{131}I-omburtamab.



For patients who do not have an existing intraventricular access device (i.e., Ommaya catheter or programmable VP shunt)
% Additional premedications required. See Section 6.0 for details.
PD = progressive disease
SD = stable disease

1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1 **Stratum 1 – Recurrent Medulloblastoma:** To estimate the event-free survival (EFS) of patients with relapsed medulloblastoma treated with irinotecan, temozolomide, bevacizumab, and compartmental radioimmunotherapy (cRIT) ^{131}I-omburtamab.

1.1.2 **Stratum 2 – Recurrent Ependymoma:** To assess feasibility of incorporating cRIT ^{131}I-omburtamab for patients with recurrent ependymoma.

1.2 Secondary Objectives

1.2.1 **Stratum 1 – Recurrent Medulloblastoma:** To estimate the overall survival (OS) of patients with recurrent medulloblastoma treated on this study including intraOmmaya ^{131}I-omburtamab.

1.2.2 **Stratum 2 – Recurrent Ependymoma:** To assess the B7H3 expression profile on ependymoma tumors.

1.2.3 **Stratum 2 – Recurrent Ependymoma:** To estimate the EFS and OS of patients with recurrent ependymoma following incorporation of intraOmmaya ^{131}I-omburtamab.

1.2.4 **Stratum 2 – Recurrent Ependymoma:** To assess dosimetry to whole-body, organs, cerebrospinal fluid (CSF), and/or tumor (if applicable).

1.2.5 **Both strata –** To determine the acute and cumulative toxicities of serial injections of cRIT ^{131}I-omburtamab.

1.3 Exploratory Objectives

1.3.1 **Both strata –** To explore the significance of cfDNA and exosome signature in CSF and blood before and after ^{131}I-omburtamab in assessing minimal residual disease.

3.0 PATIENT SELECTION

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. Imaging studies to establish eligibility must be done within 2 weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

3.1 Stratum 1 – Eligibility Criteria for Enrollment

3.1.1 Diagnosis

Patients with a histologically confirmed diagnosis of medulloblastoma that is recurrent, progressive, or refractory to standard therapy. All tumors must have histologic verification at either the time of initial diagnosis or recurrence.

Note: For this study, refractory disease is specifically defined as the presence of persistent abnormality on conventional MRI that is further distinguished by histology (tissue sample) or CSF cytology.

3.1.2 Disease Status

Patients must have disease, defined as tumor that is measurable in two perpendicular diameters on MRI OR diffuse leptomeningeal disease OR clear MRI evidence of disease that may not be measurable in two perpendicular diameters.

Patients may have tumor cells in the CSF with or without radiographic evidence of disease at the time of enrollment.

3.1.3 Age

Patients must be < 22 years of age at the time of enrollment.

3.1.4 Intraventricular Access Device

Protocol treatment with radioimmunotherapy (^{131}I-omburtumab) will require the presence of an appropriate intraventricular access device (e.g., programmable ventriculoperitoneal [VP] shunt or Ommaya reservoir). Patients are not required to have an existing programmable VP shunt or Ommaya at the time of study enrollment but must be willing and able to undergo a surgical procedure to have one placed prior to Radioimmunotherapy.

Note: Patients with an existing intraventricular VP shunt without a programmable component must be willing and able to undergo modification of the shunt before treatment with ^{131}I-omburtumab.

3.1.5 Prior Therapy

Patients must have recurrent, progressive, or refractory medulloblastoma after prior craniospinal irradiation (CSI) therapy with or without prior chemotherapy, unless CSI is contraindicated or determined to be not in the best interest of the patient due to underlying medical conditions or declined by the patient/family. Patients must have experienced no more than two recurrences of medulloblastoma or have refractory disease.

Note: Patients with contraindications to radiation therapy are still eligible.

3.1.5.1 *Chemotherapy*

Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days (3 weeks) prior to enrollment or at least 42 days (6 weeks) if prior nitrosourea.

3.1.5.2 *Investigational/Biologic Agent*

- Biologic or investigational agent (anti-neoplastic):

Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the investigational or biologic agent ≥ 7 days prior to study enrollment.

  - For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

- Monoclonal antibody treatment and agents with known prolonged half-lives:

Patient must have recovered from any acute toxicity potentially related to the agent and received their last dose of the agent ≥ 21 days prior to study enrollment.

3.1.5.3 *Radiation*

Patients must have had their last fraction of:

- Craniospinal irradiation, whole brain radiation, total body irradiation, or radiation to ≥ 50% of pelvis or spine 24 weeks prior to study enrollment. The tumor designated as "measurable" for protocol purposes must not have received radiation within 12 weeks prior to study enrollment.
- Focal radiation to areas of symptomatic metastatic disease at least 14 days prior to study enrollment.

3.1.5.4 *Stem Cell Transplant (SCT)*

For autologous SCT, ≥ 3 months must have elapsed prior to study enrollment.

3.1.6 Neurologic Status

- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to enrollment. A baseline detailed neurological exam should clearly document the neurological status of the patient at the time of study enrollment.
- Patients with seizure disorders may be enrolled if seizures are controlled and on non-enzyme inducing anticonvulsants. Patients must not be taking enzyme-inducing antiepileptic medicines within 1 week prior to study enrollment.

3.1.7 Performance Status

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within 2 weeks prior to study enrollment must be ≥ 50%. Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

3.1.8 Organ Function

Patients must have:

3.1.8.1 *Adequate bone marrow function (including status post SCT) defined as:*

- Peripheral absolute neutrophil count (ANC) ≥ 1 x 10^9/ L (unsupported)
- Platelet count ≥ 100 x 10^9/ L (unsupported, defined as no platelet transfusion within 7 days prior to study enrollment)
- Hemoglobin ≥ 8.0 g/dL (may receive packed red blood cell [PRBC] transfusions)

3.1.8.2 *Adequate renal function defined as:*

- Serum creatinine based on age/gender as noted in Table 1. Patients that do not meet the criteria in Table 1 but have a 24 hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m^2 are eligible.

Table 1. Serum Creatinine for age/gender

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

3.1.8.3 Urine protein should be screened by dipstick analysis. If protein ≥ 2+ on dipstick, then Urine Protein Creatinine (UPC) ratio should be calculated. If UPC ratio > 0.5, 24-hour urine protein should be obtained, and the level should be < 1000 mg/24 hours for patient enrollment.

Note: UPC ratio of spot urine is an estimation of the 24-urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulae:

- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

3.1.8.4 *Adequate liver function defined as:*

- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)

- ALT (SGPT) and AST (SGOT) < 5 x institutional upper limit of normal (ULN)

3.1.8.5 *Adequate coagulation defined as:*
- INR/PT ≤ 1.5 x institutional upper limit of normal (ULN)

3.1.9 Hypertension

Hypertension must be well controlled (≤ 95th percentile) on stable doses of medication. (See the PBTC Members Webpage for tables of blood pressure based on age and gender at: https://www.pbtc.org/members/Protocols/CRA_Nursing/generic_forms_templates.htm.)

3.1.10 Patients must have recovered from any surgical procedure before enrolling on this study (see table below for examples of major, intermediate, and minor surgical procedures):

a) Patients with a major surgical procedure within 28 days prior to enrollment should be excluded.
b) Patients with an intermediate surgical procedure within 14 days prior to enrollment should be excluded.
c) For minor surgical procedures (including Broviac line or infusaport placement), patients should not receive the first planned dose of bevacizumab until the wound is healed and at least 7 days have elapsed.

Examples of Major, Intermediate, or Minor Surgical Procedures

Major Procedures	Intermediate Procedures	Minor Procedures
Major craniotomy for tumor resection	VP-shunt placement	Incision and drainage of superficial skin abscesses
Organ resection	Ommaya placement	Punch biopsy of skin lesions
Bowel wall anastomosis	Stereotactic brain biopsy	Superficial skin wound suturing
Arteriovenous grafts		Bone marrow aspirate and/or biopsy
Exploratory Laparotomy		Fine needle aspirations
Thoracotomy		Broviac line or infusaport placement
		Paracentesis or thoracocentesis

Note: Lumbar punctures or placement of PICC lines are not considered minor procedures and may occur at any time prior to or during therapy.

3.1.11 Infectious Diseases

3.1.11.1 *Human Immunodeficiency Virus (HIV) Infected Individuals*

Patients who are known to be Human immunodeficiency virus (HIV)-infected must be on effective anti-retroviral therapy with undetectable viral load within 6 months prior to study enrollment.

3.1.11.2 *Hepatitis B Chronically Infected Individuals*

For patients with known evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.11.3 *Hepatitis C (HCV) Infected Individuals*
Patients with a known history of hepatitis C virus (HCV) infection must have been treated and cured. Patients with known HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load.

3.1.12 Corticosteroids
Patients who are receiving dexamethasone at a stable or decreasing dose for at least 7 days prior to study enrollment are eligible.

3.1.13 Growth Factors
Patients must be off all colony-forming growth factor(s) for at least 1 week prior to enrollment (e.g., filgrastim, sargramostim, or erythropoietin) or at least 2 weeks for pegfilgrastim.

3.1.14 Pregnancy
Pregnant women are excluded from this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. Female patients of childbearing potential must have a negative serum or urine pregnancy test prior to enrollment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.1.15 Pregnancy Prevention
Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study and for at least 6 months after the completion of bevacizumab therapy.

3.1.16 Informed Consent
The patient or parent/guardian can understand the consent and is willing to sign a written informed consent document according to institutional guidelines.

3.2 **Stratum 1 – Exclusion Criteria**

3.2.1 Patients must not have previously received the combination of bevacizumab, irinotecan, and temozolomide therapy.

3.2.2 Patients with a serious or non-healing wound, ulcer, or bone fracture are not eligible for this study.

3.2.3 Patients must not have a history of abdominal fistula, gastrointestinal perforation, or intraabdominal abscess within 6 months prior to study enrollment.

3.2.4 Patients must not have a known bleeding diathesis or coagulopathy.

3.2.5 Patients must not have had significant vascular disease (e.g., aortic aneurysm requiring surgical repair, deep venous or arterial thrombosis) within the last 6 months prior to study enrollment.

3.2.6 Patients must not have a known thrombophilic condition (i.e., protein S, protein C

or antithrombin III deficiency, Factor V Leiden, Factor II G20210A mutation, homocysteinemia or antiphospholipid antibody syndrome). Testing is not required in patients without thrombophilic history.

3.2.7 Patients must not have evidence of new CNS hemorrhage on baseline MRI obtained within 14 days prior to study enrollment.

3.2.8 Patients with a history of stroke, myocardial infarction, transient ischemic attack (TIA), severe or unstable angina, peripheral vascular disease, or grade II or greater congestive heart failure within the past 6 months are not eligible.

3.2.9 Patients must not have serious and inadequately controlled cardiac arrhythmia.

3.2.10 Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies are not eligible.

3.2.11 Patients must not be currently taking NSAIDS, clopidrogel, dipyridamole, or aspirin therapy > 81 mg/day.

3.2.12 Breast-feeding

Female patients who are breastfeeding are not eligible for this study unless they agree not to breastfeed.

3.2.13 Concurrent Illness

- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic, or other organ dysfunction) that in the opinion of the investigator would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity, or would interfere with the study procedures or results.
- Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen for this trial.

3.2.14 Concomitant Medications

- Patients who are receiving any other anti-cancer or investigational drug therapy are ineligible.
- Patients currently receiving any of the following medications and cannot be discontinued 7 days prior to enrollment (see Appendix E for details) are ineligible:
    - Known strong and moderate inducers or inhibitors of CYP3A4/5, including enzyme-inducing anti-convulsant drugs (EIACDs), grapefruit, echinacea, grapefruit hybrids, pummelos, starfruit, and Seville oranges
    - Substrates of CYP3A4/5 with a narrow therapeutic index
    - Herbal preparations/medications (except for vitamins) including, but not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to enrollment.

3.2.15 Inability to participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to drug administration plan, other study procedures, and study restrictions.

3.3 Stratum 2 – Eligibility Criteria for Screening

All subjects must meet the following screening criteria without exception.

3.3.1 Screening consent

For patients with a histological diagnosis of ependymoma, a screening consent for B7H3 must be obtained prior to enrollment on PBTC-058.

3.3.2 B7H3 Reactivity

Patients must have evidence of tumor reactivity for B7H3 (CD276) to be eligible for treatment. Results from prior testing of tumor reactivity for B7H3 (CD276) using a CLIA-certified immunohistochemistry (IHC) assay may be used. For patients who do not have prior B7H3 testing results from a CLIA lab, samples **must** be sent to MSKCC **within 3 days of reservation** as outlined in Section 5.3.

3.3.3 Diagnosis

Patients with a histologically confirmed diagnosis of ependymoma that is recurrent, progressive, or refractory to standard therapy. All tumors must have histologic verification at either the time of initial diagnosis or recurrence.

Note: For this study, refractory disease is specifically defined as the presence of persistent abnormality on conventional MRI that is further distinguished by histology (tissue sample) or CSF cytology. Previously irradiated lesions that are stable will not be considered refractory without pathology or cytological evidence of active tumor.

3.3.4 Disease Status

Patients may have tumor cells in the CSF with or without radiographic evidence of disease at the time of screening.

3.3.5 Age

Patients must be < 22 years of age at the time of screening.

3.3.6 Potential Eligibility for Study Enrollment

Patients screened for this trial should be expected to meet the criteria for treatment as outlined in Section 3.4.

3.4 Stratum 2 – Eligibility Criteria for Enrollment

3.4.1 Diagnosis

Patients with a histologically confirmed diagnosis of ependymoma that is recurrent or progressive to standard therapy. All tumors must have histologic verification at either the time of initial

diagnosis or recurrence.

3.4.2 B7H3 Status

Patients must be positive for B7H3 reactivity by IHC performed in a CLIA-certified lab.

3.4.3 Disease Status

Patients may have tumor cells in the CSF with or without radiographic evidence of disease at the time of enrollment. Patients are not required to have measurable or evaluable disease at the time of study enrollment.

3.4.4 Age

Patients must be < 22 years of age at the time of enrollment.

3.4.5 Intraventricular Access Device

Protocol treatment with radioimmunotherapy (^{131}I-omburtumab) will require the presence of an appropriate intraventricular access device (e.g., programmable ventriculoperitoneal [VP] shunt or Ommaya reservoir). Patients are not required to have an existing programmable VP shunt or Ommaya at the time of study enrollment but must be willing and able to undergo a surgical procedure to have one placed prior to Radioimmunotherapy.

Note: Patients with an existing intraventricular VP shunt without a programmable component must be willing and able to undergo modification of the shunt before treatment with ^{131}I-omburtumab.

3.4.6 Prior Therapy

Patients must have recurrent or refractory ependymoma after having received either focal or craniospinal irradiation (CSI) therapy, unless CSI is contraindicated or declined by the patient/family. There are no restrictions on the number of prior recurrences for this stratum.

Note: Patients with contraindications to radiation therapy are still eligible.

3.4.6.1 *Chemotherapy*

Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days (3 weeks) prior to enrollment or at least 42 days (6 weeks) if prior nitrosourea.

3.4.6.2 *Investigational/Biologic Agent*

- Biologic or investigational agent (anti-neoplastic):

Patients must have recovered from any acute toxicity potentially related to the agent and received their last dose of the investigational or biologic agent ≥ 7 days prior to study enrollment.

  - For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

- Monoclonal antibody treatment and agents with known prolonged half-lives:

Patients must have recovered from any acute toxicity potentially related to the agent and received their last dose of the agent ≥ 21 days prior to study enrollment.

3.4.6.3 *Radiation*

Patients must have had their last fraction of:

- Craniospinal irradiation, whole brain radiation, total body irradiation or radiation to ≥ 50% of pelvis or spine 24 weeks prior to study enrollment.
- The tumor designated as "measurable" for protocol purposes must not have received radiation within 12 weeks prior to study enrollment.
- Focal radiation to areas of symptomatic metastatic disease 14 days prior to study enrollment.

3.4.7 Neurologic Status

- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to enrollment. A baseline detailed neurological exam should clearly document the neurological status of the patient at the time of study enrollment.
- Patients with seizure disorders may be enrolled if seizures are controlled and on non-enzyme inducing anticonvulsants. Patients must not be taking enzyme-inducing antiepileptic medicines within 1 week prior to study enrollment.

3.4.8 Performance Status

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within 2 weeks prior to study enrollment must be ≥ 50%. Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

3.4.9 Organ Function

Patients must have:

3.4.9.1 *Adequate bone marrow function (including status post SCT) defined as:*

- Peripheral absolute neutrophil count (ANC) ≥ 1 x 10^9/ L (unsupported)
- Platelet count ≥ 100 x 10^9/ L (unsupported, defined as no platelet transfusion within 7 days prior to study enrollment)
- Hemoglobin ≥ 8.0 g/dL (may receive PRBC transfusions)

3.4.9.2 *Adequate renal function defined as:*

- Serum creatinine based on age/gender as noted in Table 1. Patients that do not meet the criteria in Table 1 but have a 24 hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m^2 are eligible.

Table 1. Serum Creatinine for age/gender

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10 to < 13 years	1.2	1.2

13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

3.4.9.3 *Adequate liver function defined as:*

- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) for age
- ALT (SGPT) and AST (SGOT) < 5 x institutional upper limit of normal (ULN) for age

3.4.10 Infectious Diseases

3.4.10.1 *Human Immunodeficiency Virus (HIV) Infected Individuals*
Patients who are known to be Human immunodeficiency virus (HIV)-infected must be on effective anti-retroviral therapy with undetectable viral load within 6 months prior to study enrollment.

3.4.10.2 *Hepatitis B Chronically Infected Individuals*
Patients with known evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.4.10.3 *Hepatitis C (HCV) Infected Individuals*
Patients with a known history of hepatitis C virus (HCV) infection must have been treated and cured. Patients with known HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load.

3.4.11 Corticosteroids

Patients who are receiving dexamethasone at a stable or decreasing dose for at least 7 days prior to study enrollment are eligible.

3.4.12 Growth Factors

Patients must be off all colony- forming growth factor(s) for at least 1 week prior to enrollment (e.g., filgrastim, sargramostim or erythropoietin) or at least 2 weeks for pegfilgrastim.

3.4.13 Pregnancy

Pregnant women are excluded from this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. Female patients of childbearing potential must have a negative serum or urine pregnancy test prior to enrollment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.4.14 Pregnancy Prevention

Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study and for at least 40 days after the last dose of ^{131}I-omburtamab.

3.4.15 Informed Consent

The patient or parent/guardian can understand the consent and is willing to sign a written informed consent document according to institutional guidelines.

3.5 Stratum 2 – Exclusion Criteria

3.5.1 Breast-feeding

Female patients who are breastfeeding are not eligible for this study unless they agree not to breastfeed.

3.5.2 Concurrent Illness

- Patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction) that in the opinion of the investigator would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.
- Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen for this trial.

3.5.3 Concomitant Medications

Patients who are receiving any other anti-cancer or investigational drug therapy are ineligible.

3.5.4 Inability to participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to drug administration plan, other study procedures, and study restrictions.

3.6 Inclusion of Women and Minorities (Both Strata)

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

3.7 Treatment at the Primary Institution (Both Strata)

All experimental protocol therapy should be dispensed and all on-treatment imaging studies should be obtained at a PBTC institution. Laboratory studies, excluding pharmacokinetic and biologic assays, may be performed at a CLIA certified laboratory of the investigator's choice. Imaging utilized to determine eligibility may be performed at an outside institution if all required imaging sequences are included and the study is deemed of adequate quality by the treating team. All required physical examinations, laboratory parameters need to be performed at the primary PBTC

institution during the dose finding period of the protocol.

3.8 **Criteria to Start Treatment (Both Strata)**

- Subjects must start therapy within 2 weeks (14 days) of enrollment for Stratum 1, and within 3 weeks (21 days) of enrollment for Stratum 2.
- Laboratory values must be no older than 7 days prior to the start of therapy. If a test that is repeated post-enrollment and prior to the start of therapy is outside the limits for eligibility, it must be rechecked within 48 hours prior to the start of therapy. If rechecks are still outside the limits for eligibility, the patient may not receive protocol therapy and will be considered off study.