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Title: A Phase II Study of Proton Beam Radiotherapy for Medulloblastoma and Pineoblastoma: An Assessment of Acute Toxicity and Long-term Neurocognitive, Neuroendocrine and Ototoxicity Outcomes.

Principal Investigator: Torunn I. Yock, MD MCH - Radiation Oncology
Massachusetts General Hospital

Coordinating Center: Massachusetts General Hospital
CCPO Multi-center Program
ccpo-mcgroup@mgh.harvard.edu

Co-Investigators:
Massachusetts General Hospital (MGH):
Nancy Tarbell, MD, Radiation Oncology
Shannon MacDonald, MD, Radiation Oncology
William Butler, MD - Neurosurgery
David H. Ebb, MD - Pediatrics
Hanne Kooy, PhD - Radiation Physics
Karen Kuhlthau, PhD - Pediatric Research Unit
Beverly LaVally, RN, MS – Pediatric Oncology
Margaret Pulsifer, PhD - Psychology Assessment Center
Helen A Shih, MD, Radiation Oncology

Dana-Farber Cancer Institute (DFCI):
Karen Marcus, MD, Radiation Oncology

MD Anderson Cancer Center (MDACC)
Arnold dela Cruz Paulino, MD, Radiation Oncology (Site Principal Investigator)

Statistician: Beow Yeap, Sc.D., Jackie Szymonifka, MA - Biostatistics Group, MGH

Study Coordinator: at MGH: Miranda Lawell

Responsible Research Nurse: at MDACC: Beth DeGracia, RN, Lerma Ukegbu, RN

Responsible Data Manager: at MGH: Miranda Lawell; at MDACC: Nancy Philip

Agent(s): Proton Beam Radiotherapy (no IND)

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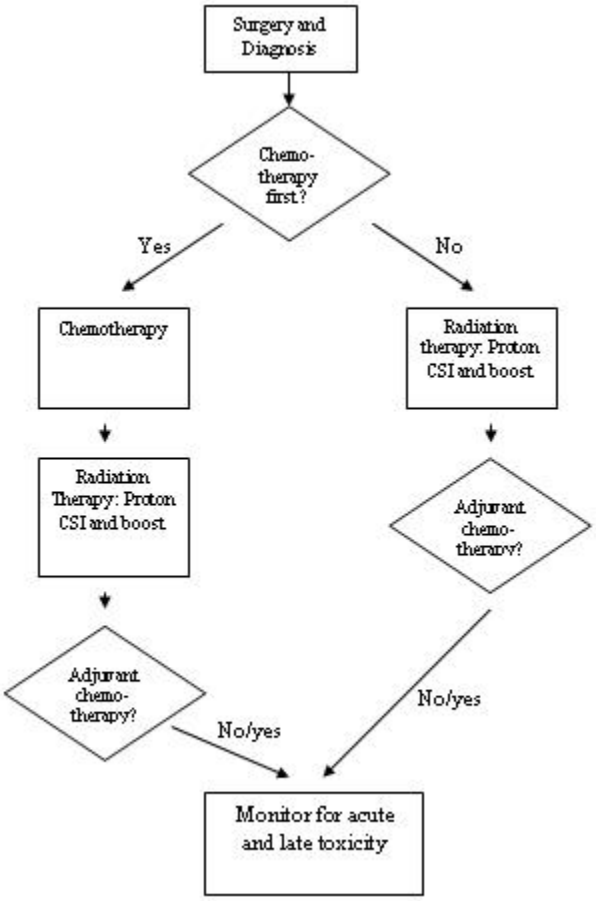
SCHEMA



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1. OBJECTIVES

To describe the acute and late complications from craniospinal and tumor bed irradiation using proton beam therapy in place of conventional photon beam therapy in pediatric patients with medulloblastoma and pineoblastoma.

1.1 Study Design

This trial is a phase II trial that substitutes proton irradiation for photon irradiation and measures toxicity from treatment. Because less normal tissue is irradiated it is presumed that it will be a less toxic treatment.

1.2 Primary Objectives

Analysis of primary objectives outcomes will be done separately for high risk and standard risk groups.

1.2.1 To estimate the incidence and severity of ototoxicity (especially in combination with cisplatin-based chemotherapy) at three (3) and five (5) years following the completion of radiation therapy.

1.2.2 To describe the incidence of endocrine dysfunction (neuroendocrine and end organ defects).

1.2.3 To describe the incidence and severity of neurocognitive sequelae overall and in subgroups based on whether or not methotrexate was used as part of the treatment regimen.

1.3 Secondary Objectives

1.3.1 To determine the 3 and 5-year progression free, event free, and overall survival rate of pediatric medulloblastoma and pineoblastoma patients treated with proton radiotherapy.

1.3.2 To develop a new supine technique to improve the speed of treating patients requiring cranial spinal irradiation and improve the safety of treating patients under anesthesia.

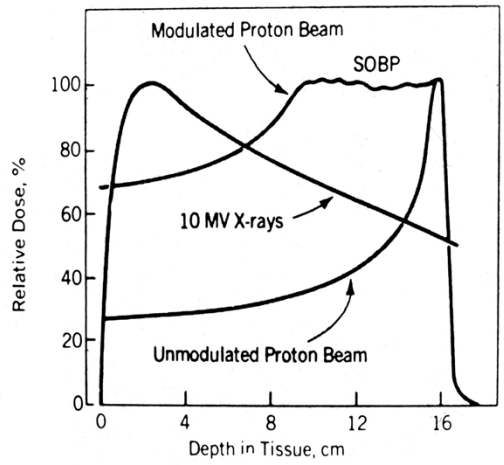
1.3.3 To evaluate the acute side effects from CSI using proton beam therapy**,** including nausea, esophagitis, and weight loss.

2. BACKGROUND

2.1 Study Agent(s): Proton Radiotherapy

The current focus in radiation oncology is to improve dose localization to the tumor. Techniques such as Intensity Modulated Radiotherapy and Tomotherapy are two sophisticated photon techniques that have helped improve outcome in patients, however, there still remains a large amount of normal tissue getting low and intermediate doses of radiation. Proton radiation capitalizes on the different physical characteristics of dose deposition to better localize dose to the target while sparing normal tissues. Unlike photon radiation which entails both an entrance and exit dose to normal tissues in the process of treating a tumor in a given beam line, proton radiation only entails a somewhat lower entrance dose and eliminates exit dose to normal tissues. Proton therapy dose distributions are therefore superior to those of photon therapy by a factor of 2 or greater and this provides the potential to further improve clinical outcomes and specifically decrease toxicity associated with treatment.

2.1.1 The Advantages of Protons for Delivery of Conformal Therapy



Characteristics of Proton Beams

Figure O-1. Proton (Bragg peak and modulated peak) and 10 MV depth dose curves.

The basis for the advantages of proton beams lies in the physical laws that determine the absorption of energy in tissues exposed to photon or proton beams. In a specific tissue, photons are absorbed exponentially whereas protons have a finite range dependent upon the initial proton energy. Therefore, the depth dose characteristics of the two beams are qualitatively different (see Figure O-1). Protons lose their energy in tissue mostly by coulombic interactions with electrons in the constituent atoms; however, a small fraction of energy is transferred through nuclear collisions. The energy loss per unit path length is relatively small and constant as the proton traverses the tissue until near the end of the proton range where the residual energy is lost over a short distance (approximately 0.7 cm in width at 80% of the maximum dose) and the proton comes to rest, resulting in a

distinctive sharp rise in the tissue absorbed dose (energy absorbed per unit mass) - known as the Bragg peak (see the curve labeled "unmodulated proton beam" in Figure O-1). In physical terms, the magnitude of the transfer of energy to tissue per unit path length traversed by the protons is inversely proportional to the square of the proton velocity. The low dose region between the entrance and the Bragg peak is called the plateau of the dose distribution and the dose there is 30-40 percent of the maximum dose.

The Bragg peak is too narrow in extent to irradiate any but the smallest of targets, ablation of the pituitary gland for example. For the irradiation of larger targets/tumors the beam energy is modulated - several beams of closely spaced energies (ranges) are superimposed to create a region of uniform dose over the depth of the target. These extended regions of uniform dose are called "spread-out Bragg peaks" (SOBP). This is shown in Figure O-1 as the “modulated proton beam”.

For comparison, Figure O-1 also shows the depth-dose curve for a 10 MV x-ray beam, an x-ray energy commonly used to treat deep seated tumors. Note that the x-ray beam dose rises to a maximum value at relatively shallow depths, then falls off exponentially to lower doses at the treatment depth.

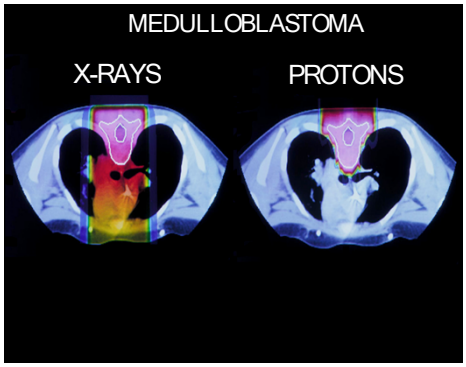


Figure O-2. Posterior, single-beam treatment of the spinal axis.

A clinical comparison of single-beam proton and photon beams is shown in Figure O-2 where a single posterior beam is used for the treatment of the spinal axis in the treatment of medulloblastoma. Note that, for the photon treatment, the heart, mediastinum, esophagus, lung and spinal cord are irradiated by the treatment beam whereas for the proton treatment, the beam stops abruptly distal to the target volume and there is no irradiation of the tissues and organs distal to the target volume.

In the usual clinical situation, more than one radiation beam is used in both x-ray and proton treatments. However, the advantage shown for protons using single beams is present for each and every beam used. Therefore, one cannot overcome the physical disadvantage of x-rays by the use of multiple beams or complex beam arrangements. In modern proton therapy facilities, which have isocentric gantries and sophisticated beam delivery and control systems, proton therapy capabilities are equivalent to those for state-

of-the-art, conformal therapy using x-rays with respect to numbers of beams, beam directions and complex delivery techniques such as intensity modulation.

2.2 Study Disease

Primitive neuroectodermal tumors (PNET) are small hypercellular, round, blue cell tumors of embryonal origin arising from the subependymal zone of the central nervous system (CNS) [1]. Medulloblastoma (MB) and pineoblastoma (PB) are defined as PNET of the posterior fossa or pineal region respectively. These tumors tend to occur predominately in the pediatric population. MB and PB account for ~25% of CNS tumors in children. They have a propensity to spread to other regions of the CNS by subarachnoid seeding. Deutsch reported 46% incidence of CNS spread at presentation for pediatric MB [2]. Likewise, a 30% rate of positive neuraxis involvement was observed by Bloom et al [3]. Thus, approximately one-third of these patients present as high risk medulloblastoma and two-thirds as standard risk.

2.3 Rationale

The treatment of MB and PB of the central nervous system involves a multi-disciplinary approach. Surgery is necessary to obtain histological confirmation and to obtain maximal resection of tumor when feasible as the degree of resection correlates with outcome [4]. Patients are at risk for local and disseminated CNS recurrence even after gross total resection. Adjuvant therapy to the craniospinal axis is therefore essential. Craniospinal irradiation (CSI) is used in this setting for patients greater than 3 years of age. An additional boost of radiation encompassing the residual tumor and surgical bed is routinely given as this region is at highest risk for recurrence.

Photon CSI is associated with many possible acute and long-term sequelae:
Acute toxicity can include the following: bone marrow myelosuppression, fatigue, alopecia, headache, dermatitis, folliculitis, otitis externa, otitis media, anorexia, weight loss, nausea, vomiting, thrush, laryngitis, pharyngitis, esophagitis, gastritis, enteritis, cystitis, acute pericarditis, and temporary worsening of tumor associated neurological symptoms. Prolonged myelosuppression and decreased bone marrow reserve may limit the ability to give chemotherapy after CSI. Somnolence syndrome is a subacute reaction associated with CSI often disabling the patient.

Long-term complications typically occur 3 months or more following completion of photon CSI and tend to be permanent. Complications arising from irradiation of the cranium include induction of second malignancy, permanent hair loss, cataract formation, retinopathy, sensorineural hearing loss due to damage to cochlea apparatus in inner ear, neuroendocrine dysfunction, and neuro-cognitive sequelae, rarely, necrosis and associated persistent vasogenic edema or atrophy. Adverse long term effects from photon irradiation of the spinal axis include: induction of second malignancy, stunting of growth of vertebral bodies and hypoplasia of paraspinal muscles and connective tissue resulting in scoliosis, kyphosis and decreased stature, spinal cord or nerve root damage, primary hypothyroidism, cardiomyopathy, pneumonitis, peptic ulcer disease, small and large bowel enteritis, primary ovarian failure, and decreased marrow reserve. These long-term sequelae can have

devastating effects in children on their future development and quality of life. Some of these complications are described in further detail below.

Ototoxicity:
Conductive hearing loss due to serous otitis media is a well-known acute reaction to RT and stems from mucositis causing blockage of Eustachian tube with transudation of serous fluid. Patients are at increased risk at doses > 40 Gy. Most cases resolve spontaneously.

Sensorineural hearing loss (SNHL) caused by damage to the cochlea and auditory nerve is a late complication from RT and can result in permanent hearing loss. While high doses of radiation are needed in the absence of chemotherapy to invoke SNHL [5-6], it can occur with lower radiation doses when ototoxic platinum chemotherapy agents are used. Evidence exists suggesting a dose response. Schoenthlaer et al reviewed 25 patients treated with high dose proton beam RT for base of skull tumors. Six patients developed decreased hearing acuity as a late complication. All patients with hearing loss received more than 60 cobalt gray equivalent (CGE) to at least 50% of the cochlea and auditory nerve [5]. In contradistinction, no patient receiving less than 60 CGE had hearing loss. Grai et al observed a higher incidence of severe SNHL in nasopharyngeal carcinoma patients receiving > 50 Gy to the inner ear compared to < 50 Gy [6]. Thibadoux et al found no hearing deficits in children receiving prophylactic cranial irradiation for acute lymphocytic leukemia [7]. Patients received 24 Gy in 2 Gy fractions. Hua et al studied the effect of cochlear dose on sensorineural hearing loss in children with brain tumors treated with conformal radiation therapy and no ototoxic chemotherapy. They found that there is significant correlation between radiation dose and the incidence of sensorineural hearing loss in children. Children with a cochlear mean dose of 30 Gy or less had a low incidence of hearing loss, while there was an increased risk at greater than 40-45 Gy [8].

Chemotherapeutic agents such as cisplatin and carboplatin can cause high frequency SNHL. Recent data suggests that the combination of chemotherapy (CTx) and RT can cause more serious ototoxicity. Packer et al from UCSF reviewed their pediatric MB patients treated with concurrent vincristine plus CSI followed by adjuvant cisplatin, CCNU and vincristine. They found 47.6% of patients developed grade 3 to 4 ototoxicity [9]. Twenty six MB pediatric patients treated at the Dana-Farber Cancer Institute (DFCI) with cisplatin and vincristine followed by CSI. Only 19% of patients had normal hearing and 50% of long term survivors required hearing aids [10]. Degree of hearing loss was inversely related to age. Sequencing of CTx and RT may also play a role in ototoxicity [11].

Neurocognitive toxicity:
Although the majority of CNS development occurs during the 1st 3 years of life, myelination continues until puberty. A major radiation insult on the CNS will result in demyelinization with subsequent white matter necrosis and leukoencephalopathy. A large number of studies in the literature have documented decline in intellectual and cognitive functioning in children who have received whole brain radiotherapy (WBRT) for conditions including medulloblastoma, leukemia and other brain tumors [12]. The decline in functioning can be significant often necessitating placement in special education and a variety of therapeutic interventions. The effect of radiation depends upon the age of the child, with younger

children significantly more susceptible to the effects of radiation than older children, gender, with girls possibly more susceptible to decline in verbal function than boys, dose of radiation, with higher doses having more deleterious effects than lower, and time since completion of WBRT. This wide variability in these factors makes it difficult to formulate a clear post-treatment profile for children receiving WBRT.

IQ deficits following cranial irradiation range from 17 to 50%. The Children's Hospital of Philadelphia (CHOP) experience with cerebellar astrocytoma in children compared WBRT in 26 patients versus no RT in 21 patients. IQ declined by a median of 13 points in the irradiated group versus none in the observed group [13]. The volume of brain irradiated influences worsening of intellectual performance. Hoppe-Hirsch et al compared 59 children with MB who received WBRT to 37 children who received posterior fossa RT for ependymoma [14]. 60% of children with posterior fossa only irradiation preserved an IQ > 90 at 10 years of follow up. Conversely, only 10% with WBRT maintained an IQ > 90. Radiation dose also plays a role. Silber et al observed a higher drop in IQ below standard as dose of WBRT increased from 18 to ≥ 36 Gy [15]. A study from Institut Gustave Roussy compared the neurocognitive outcome in 3 groups of pediatric patients who received different doses of radiation to the craniospinal axis. Group 1 consisted of 9 patients with ependymoma who received PF irradiation only, group 2 consisted of 11 patients with standard risk MB who received 25 Gy CSI plus PF boost and group 3 consisted of 11 patients with high risk MB who received 35 Gy CSI plus PF boost [16]. Increasing radiation doses to the brain were found to be correlated with lower full-scale IQ scores with mean IQ scores of 84.5, 76.9 and 63.7 for patients who had received 0 Gy, 25 Gy and 35 Gy to the non-PF brain. The Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) have also compared reduced dose CSI at 23.4 Gy versus the standard 36 Gy dose in low stage pediatric MB patients. Chemotherapy was not used. A reduction in neuropsychologic toxicity was observed in the low dose arm especially in younger children [17], albeit with a higher local failure rate in the reduced CSI arm [18]. Packer et al compared 13 patients treated with WBRT plus cisplatin, CCNU, or vincristine versus 14 patients treated with surgery only for children with cerebellar astrocytoma [19]. WBRT dose was 36 Gy with a boost of 18-20 Gy for children 3 years or older. A decline in full-scale IQ was noted in the irradiated group. 12/18 patients required special education. The effect was most pronounced in younger children.

The cognitive decline in patients from CSI may also be enhanced by the addition of chemotherapy. Chemotherapy without radiation has been implicated as having neurocognitive effects. The best studied population is the ALL (acute lymphoblastic leukemia) population in which many children are never irradiated but still suffer neurocognitive effects. (Moleski, M. (2002) Neuropsychological, neuroanatomical, and neurophsyiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. Archives of Clinical Neuropyschology, 15, 603-630). Methotrexate, both high dose and intrathecal or intraventricular have been shown to cause leukoencephalopathy without radiation, but the addition of radiation appears to worsen outcome (Rutkowski et al, NEJM 352: 2005). However, the use of methotrexate chemotherapy in high doses does appear to improve disease free survival compared with standard regimens in infants and young children (Rutkowski et al, NEJM 352: 978-986, 2005; Chi et al, JCO 22: 2004) with medulloblastoma

and is increasingly gaining favor in the children with the higher risk disease. The other promising strategy is to deliver high dose chemotherapy with thiotepa and carboplatin with stem cell support and both treatment intensification strategies are employed in various institutions and cooperative group settings around the country and world.

Pituitary and hypothalamic toxicity:
Neuroendocrine dysfunction is extremely common following cranial irradiation in children and adults. Published data indicates a radiation dose response [20-22]. Littley et al showed that doses as low as 20 Gy to the hypothalamus and pituitary gland can cause hypopituitarism, primarily anterior lobe dysfunction [21]. Doses exceeding 50 CGE to the pituitary gland and hypothalamus using proton beam RT decreases the incidence of hypopituitarism [22]. Growth hormone deficiency is particularly common following cranial irradiation. Hypogonadism, hypoadrenalism and hypothyroidism can also be observed. Patients often have more than one hormone axis involved. Life long monitoring for hypopituitarism and hormone replacement is often necessary.

Precocious puberty has been described in pre-pubertal patients treated with cranial irradiation [23]. The critical dose for precocious puberty is not well elucidated.

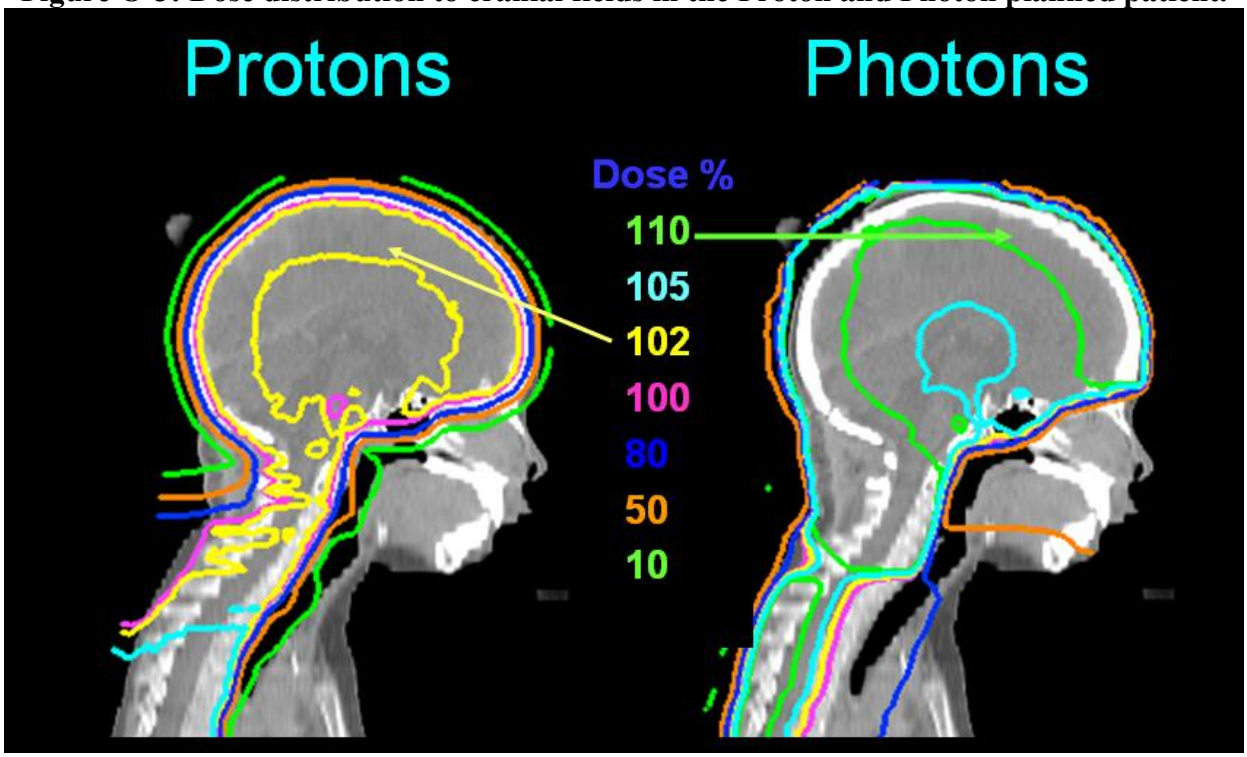
Thyroid gland toxicity:
Primary hypothyroidism after photon beam spinal axis irradiation has been well documented. 59% of patients developed elevated levels of TSH after spinal irradiation in a study by Hirsch et al [24]. A strong correlation between dose and incidence of hypothyroidism has also been demonstrated [24-26]. An incidence of 15% is noted for doses below 30 Gy; this increases to 40-90% for doses between 30 to 44 Gy [27]. For children, a study from Stanford University showed an incidence of 17% for doses < 26 Gy to the thyroid gland and 78% for > 26 Gy [25]. Radiation to the thyroid gland can also cause hyperthyroidism, although this is an uncommon event with a 10 year actuarial risk of < 3.5% [28]. Patients usually present with symptoms of Graves' ophthalmopathy.

Potential Benefits of Protons:

Benefits of spinal dose:
When a proton beam is applied for spinal irradiation, a single posteriorly directed proton beam delivers almost no dose to structures anterior to the treated volume compared to a standard photon treatment plan and even an IMRT plan. As shown in Figure O-2 (above), a direct comparison of a conventional 4 MV posteriorly directed field versus a single posteriorly directed 160 MeV proton beam to treat the spinal axis was made. Note the lack of exit dose to structures anterior to the vertebral bodies using protons compared to standard PA 4 MV photon plan. A comparative treatment plan of protons versus photons has also been published by Miralbell et al recently [29]. A 6 MV photon beam spinal field was compared to a 100 MeV proton beam spinal field. As expected, integral dose by DVH analysis to the heart and liver was zero using protons.

Benefits in cranial technique:
In a separate study, the same investigators were able to demonstrate advantages of a 3 field (2 opposed lateral and a posterior) proton plan for whole brain irradiation in a 3 year old child over parallel opposed 6 MV photon fields, 6 field conformal photon plan, or a 9 field IMRT photon plan [30]. A reduction in dose to the eyes and "low risk" regions of the brain was observed. The estimated risk of an IQ score < 90 in young children ages 4 to 8 was reduced using the proton plan. We have also compared lateral opposed conformal proton plan to standard lateral opposed photon plan and achieved similar benefit in improved dose distribution as noted by Mirabell et al. See figure O-3 below. The dose gradient is improved near the vertex of the head and decrease dose is delivered to the middle and inner ear regions using protons.

Figure O-3: Dose distribution to cranial fields in the Proton and Photon planned patient.



Furthermore, we have refined our technique and use slightly posterior obliqued fields to better spare the lens while still achieving good coverage of the cribiform plate in the younger patients whose sinuses have not pneumatized yet and the brain therefore dips low and in between the orbits. Parallel opposed photon treatment places the child at high risk for cataract formation [31].

We have also demonstrated reduced normal tissue irradiation using protons for the posterior fossa boost field for medulloblastoma patients. A comparison between a conformal proton plan using 15 degree superior anterior oblique field with two 25 degree posterior oblique fields is compared to a comparable field set-up with conformal photons as described by Paulino et al [32], and to a standard lateral opposed 4 MV photon plan. As shown in table 1, a decrease in relative dose to the critical structures such as the cochlea, non-posterior fossa

brain, pituitary gland and hypothalamus is observed with conformal protons and conformal photons compared to that of conventional photons. However, extra dose is delivered to "less critical" normal structures such as the parotid gland and mandible using conformal photons as compared to conformal protons.

Table 1. Posterior fossa irradiation: Comparison of dose to normal structures using 3 different techniques [36]

Organ	% of Prescribed Dose (Dmean/Prescribed Dose)		
	6 MV lateral opposed photons (optimized with wedges)	SAO, RPO, LPO conformal photons	160 MeV SAO, RPO, LPO conformal protons
Cochlea	102.3	55.0	11.7
Non posterior fossa brain	47.1	40.6	26.1
Pituitary gland	80.1	91.1	57.2
Hypothalamus	15.8	47.2	35.0
Parotid Gland	38.8	32.2	0.0
Pharynx	7.3	8.9	0.0
Mandible	6.2	15.0	0.0
TMJ	59.7	33.9	0.0

Protons summary:
Superior dose conformity is therefore achieved with protons compared to other external beam modalities. Advantages in dose distribution are noted for all phases of CSI including spinal, whole brain and posterior fossa portions of treatment. The accuracy of delivering proton therapy is further enhanced by advancements in treatment planning and delivery technology. Improved radiological imaging with CT and MRI, the availability of computer technology for treatment planning and dosimetric calculations (e.g. beam's eye view planning, 3-dimensional image reconstruction, dose volume histogram analysis) have contributed to enhancing the therapeutic ratio using radiation therapy. In other tumors and sites, comparative treatment planning using protons versus photons have shown a clear advantage to protons [33-35].

We have already treated 51 patients on the precedent medulloblastoma protocol with 37 standard risk patients and 14 high risk patients. We have found the following: acute esophagitis/mucositis rates are 12% which is lower than what would be expected which is close to 100% percent. Nausea and vomiting is still present but less severe than it would be for photon techniques in that we have a grade 2 rate of 26% and grade 3 rate of 12%. With regards to ototoxicity, since this is a late endpoint (after 3 years) we don't have full data yet but preliminary data shows that we have 35% grade 2 hearing loss and a 9% grade 3 hearing loss rate. We have had 3 relapses thus far, 2 in the standard risk group and 1 in the high risk cohort. Disease control rates are comparable to those with photons. For the neuropsych

evaluations, there are only 18 patients in the database centrally that have both baseline and follow up data and no conclusions can be made based on the limited follow up to date. Additionally, more follow up data is being entered in the database.

2.4 Correlative Studies Background-- Not applicable

3. PARTICIPANT SELECTION

Laboratory tests required for eligibility must be completed within 14 days prior to study entry. Other non-laboratory tests must be performed within the timeframes described below.

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have undergone biopsy or attempted surgical resection and must have histologically confirmed medulloblastoma or pineoblastoma. Confirmation of pathology at the treating institution is preferred prior to beginning study treatment, but may be received two weeks after radiation start.

3.1.2 Participants may have had a gross total resection, sub-total resection or biopsy only.

3.1.3 For patients with no prior chemotherapy, treatment must start within 35 days of definitive surgery or as indicated if enrolled on therapeutic study.

3.1.4 Age $\geq$3 and $\leq$ 25 at the time of enrollment.

3.1.5 Life expectancy of greater than 3 months.

3.1.7 Radiation is known to be teratogenic, women of child-bearing potential must not be pregnant at the time of study entry. Women and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.8 Signed informed consent document and assent when appropriate.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Patients with more than one previous chemotherapy regimen.

3.2.2 Patients with recurrent or progressive disease after one or more regimens of pre-radiation chemotherapy.

3.2.3 Patients with prior radiation therapy will be excluded.

3.2.4 Any major uncontrolled or poorly controlled intercurrent illness that would limit compliance with study requirements.

3.2.5 Pregnant women are excluded from this study because radiation is a teratogen and it is not safe to the fetus to treat a patient while pregnant.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

We do not expect the inclusion and exclusion criteria to either over or under represent women, minorities, or underrepresented populations.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.
A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 Registration Process for Other Participating Institutions

Eligible participants will be entered on study centrally by the MGH Coordinating Center. Please refer to Section 5.7 of the Data and Safety Monitoring Plan (attached as Appendix A) for details. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Coordinating Center should be notified of cancellations as soon as possible

5. TREATMENT PLAN: RADIATION THERAPY

All charged particle treatment will be given at the Francis H. Burr Proton Therapy Center or MD Anderson Proton Therapy Center. Film or digital images will be taken prior to each treatment in accordance with the proton center's standard practice for all patients. These

images are used to verify the position of the patient and the aperture. These images are permanently stored electronically for each patient. Treatment may start any day of the week but preferably Monday through Thursday. Expected toxicities and potential risks as well as dose modifications are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). Patients with MB will be stratified into standard and high risk for treatment purposes. Physicians are strongly encouraged to enroll patients onto other active protocols. Children's Oncology Group (COG) has specifically designed their protocols to allow for proton radiation which will therefore not preclude co-enrollment.

Documentation of chemotherapy given should be submitted. In order to assess the causes of any possible acute or long term side effects, the total platinum dose given to the patient should be tracked. The cumulative platinum dose, number of cycles, and any dose reductions should be recorded.

5.1 Pre-Treatment Criteria

5.1.1 Baseline Staging Requirements:

- MRI scan with contrast enhancement (with gadolinium) of the entire spinal axis (preferably pre-op)
- Pre-operative MRI scan or CT scan of the brain.
- Post-operative MRI of the brain (within 21 days of surgery, preferably within 72 hours of surgery; intra-operative MRI is allowed).
- CSF sampling for cytology if the patient appears to have M0 disease. CSF sampling is not required for patients with gross M2 or M3 disease by imaging (leptomeningeal spread of disease in the brain or the spine). CSF sampling can be completed any time prior to the start of protocol therapy. If sampling for M0 disease performed less than 10 days after surgery is positive, it should be repeated. CSF sampling must be completed no later than ten days after the start of radiation.

5.1.2 Additional Baseline Assessments:

- Endocrine evaluation to be completed no later than 2 months after the start of radiation. To include TSH, Free T4, Cortisol, IGF-1 and IGF-BP3, LH, FSH, estradiol (females), testosterone (males) (am levels preferred), Tanner Stage assessed by physical exam, bone age (plain film of the wrist), and body proportion measurements. Bone age, Tanner Stage assessment, and body proportion measurements collected will be at the discretion of the study endocrinologist. Recommended measurements include sitting height (sitting height preferred, but pubic symphysis to floor acceptable), standing height, leg span, and arm span.
- Audiogram, to be completed no later than 2 months after the start of radiation.

- Neurocognitive evaluation, as detailed in Section 9.2.3, to be completed no later than 9 months after the start of radiation

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5.2 Radiation Planning Guidelines

5.2.1 Patient Set-up and Immobilization

Patient set-up and immobilization must be determined prior to planning CT scan and may be either prone or supine. For CSI, patient will be positioned in accordance with the treating institution's accepted method of doing so. Head will be positioned such that the spinal cord is as straight as possible. Children unable to cooperate and remain properly immobilized should be sedated or anesthetized for set-up reliability on a day-to-day basis. A nurse anesthetist or anesthesiologist will be supervising and administrating sedation. Sedated patients should be under constant surveillance during treatments with cameras, telemetry, and other devices.

5.2.2 CT Simulation

The patient will have a planning CT scan while in the treatment position and properly immobilized. Physicians are encouraged to use available MRI scans to aid in target and normal tissue delineation. Electronic copies of MRI scans are usually available and can often be registered with planning CT scans to help delineate structures.

5.2.3 Target and Normal Structure Delineation

The following structures will be outlined on planning CT scans. It is recommended that the radiation oncologist outline the GTV. Cumulative dose volume histogram analysis will be completed for structures listed below:

- GTVp and surgical bed (see below for guidelines definitions)
- CTV1 and CTV2 (+/- CTV x…)
- Right and left cochlea
- Lenses
- Optic chiasm
- Pituitary gland
- Hypothalamus
- Esophagus
- Temporal lobes
- Whole brain

ICRU 50 and ICRU 78 [37] recommended terminology will be used to define radiation treatment parameters.

<u>CTV1: Cranial-Spinal Treatment:</u>
CTV1 shall be defined as the cranial spinal portion of the treatment and will include the entire cranial contents including cribiform plate and the thecal sac surrounding the spinal cord and nerve roots. Care should be taken to look at the sagittal spine MRI to define

where the thecal sac ends and an additional margin of 1-2 cm should be added to ensure coverage. When imaging is degraded or incomplete, coverage should extend to S4. The treating physician should use their judgment about whether the target will also include the vertebral body or only the thecal sac. However, in patients that have a significant amount of growth to do it is recommended that the whole vertebral body (or nearly so) be covered so as to avoid uneven growth of the vertebral body resulting in spinal scoliosis.

CTV2: Posterior Fossa or Involved Field Boost:
The GTVp is defined as any post-operative residual tumor seen on MRI or CT scan in addition to the collapsed resection cavity of the primary lesion.

The CTV2 is defined as 1-1.5 cm anatomically constrained margin around the GTVp and any other sites the treating physician judges to be at high risk for microscopically residual disease. Or, if the tumor is arising in the posterior fossa, the entire posterior fossa may be boosted. This is up to the COG protocol or physician discretion after consultation with the patient (if appropriate) or/and their guardians.

Metastases boosts:
Guidelines for boosting metastatic disease (ie M1, M2 or M3) will be in accordance with the COG guidelines and institutional practice, but are briefly outlined below.

CTV 3, 4, 5, etc:
The boosts for the gross metastatic deposits will be targeted with a 5-10 mm margin of CTV and include any other area the treating physician feels is at high risk for local recurrence.

Planning Target Volumes (PTV):
An additional margin for set up uncertainty and motion will be applied according to each institution's regular practices.

The *irradiated volume* includes normal tissue, which receives a clinically significant dose with respect to normal tissue effects.

5.2.4 Dosimetry Planning

Cranial spinal planning will be according to each institution's standard protocol for this technique and will include moving junctions of matched fields for safety.

5.2.5 Dose Specification and Schedule

Physicians are encouraged to enroll patients onto other active protocols (e.g. testing chemotherapy regimens). The radiation dose and fractionation schedule in these cases is in accordance with the co-existing protocol. Patients will usually be treated once per day. Doses will be prescribed such that 95% of the CTV is covered by 100% of the prescription dose. Dose will be reported in GyRBE (where 1 GyRBE = proton dose Gy x

RBE, RBE = 1.1). A RBE of 1.1 has been selected for protons and is based on RBE determinations in animal and cell culture systems [43,44].

Cumulative dose volume histograms using nominal dose distribution will be generated for all structures listed in 5.2.3.

5.2.6 Proton Beam Physical Factors

Proton treatments will be delivered at the Francis H. Burr Proton Therapy Center at the Massachusetts General Hospital using a 240 MeV cyclotron. At MDACC, proton treatments will be delivered at the MDACC Proton Therapy Center using a 250 MeV synchrotron. Treatments will usually be administered as one daily fraction, 5 days per week.

5.2.6 Proton Beam Modification/Blocking

Beam shaping will be accomplished using primary collimation by the gantry jaws. The penumbra is large and field shaping by secondary collimation will be necessary using a downstream custom cut brass aperture. Apertures will be constructed on brass alloy of sufficient thickness to attenuate 99.9% of protons. Apertures will be cut to be parallel to beam divergence. 3-D lucite compensators may be fabricated to conform dose to the target at the distal aspect.

5.2.8 Quality Assurance and Rapid Review of Treatment Plans

To ensure protocol compliance, the treatment plans for the first three patients treated at each site will be reviewed by the Principal Investigator and Participating Site's PI. As described in Section 12.1.3, below, plans will be submitted to the Advance Technology QA Center at Washington University, St Louis (ATC) for this protocol. The plans will be sent to the ATC upon approval by the treating physician, and the PI and/or Participating Site PI will review and confirm protocol compliance within three working days of the start of treatment.

5.2.9 Beam Verification:

Digitally reconstructed radiography (DRR) will be done for treatment planning and verification and will be performed daily during treatment.

5.2.10 Dose Uniformity

Dose gradient in CTV should remain within +7% to –5% of prescribed dose.

5.2.11 Dose Derification

A physicist co-investigator at each participating institution will be responsible for dose verification.

5.2.12 Concurrent Protocol

For patients who are enrolled on co-existing protocols such as COG, physicians will adhere to the radiation therapy guidelines of the companion protocol which specify their own guidelines for the following parameters: total dose, dose per fraction, fractionation schedule and sequencing with other therapy (e.g. chemotherapy). If any questions or discrepancies arise, then contact Dr. Torunn Yock, MD at (617) 726-9441 (tyock@partners.org) before beginning radiation treatments.

5.2.13 Treatment Delay

To avoid treatment delays resulting from the machine being down, photon or electron (if appropriate) beam radiation can be administered. The maximum dose for both the posterior fossa and spine will be 20% of the prescribed dose (e.g. 20% of the spine at 36 Gy would be a maximum of 4 spine treatments or 7.2 Gy). Delay in the start of CSI proton therapy shall not exceed 2 weeks in M0 patients and 1 week in M+ patients.

5.2.14 Emergent Radiation Therapy

For patients who require emergent RT when a proton slot is not available, photon (or electron beam) therapy may be delivered at the maximum dose for the posterior fossa and at 20% of the maximum dose for the spine (e.g. 20% of the spine at 36 Gy would be a maximum of 7.2 Gy).

5.3 General Concomitant Medication and Supportive Care Guidelines

There are no required concomitant medications in this study. No other radiotherapy besides that which was outlined above may be used during study treatment. Patients may receive all concomitant therapy deemed necessary to provide optimal support.

5.4 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment will continue until the prescribed dose of radiation therapy is delivered or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5 Criteria for Removal from Study

Participants will be removed from treatment or active follow up when any of the criteria listed in Section 5.4 applies. Participants removed from treatment or active follow up for disease progression will continue to be followed for survival status only. The reason for removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

5.6 Duration of Follow Up

Participants will be followed for at least 8 years after completion of radiation therapy or until death, whichever occurs first. Participants will be invited to return to the treating institution for annual follow up visits. Participants who do not live in the local area of their treating institution will be allowed to obtain follow up care at home and forward records to the study team at the treating institution. Once participants have reached 5 years post treatment, they may be compensated for a one time return visit to MGH if grant funding is available.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Torunn Yock, MD via the Coordinating Center at ccpo-mcgroup@partners.org.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Toxicity assessments will be done using the CTEP Active Version NCI Common Terminology Criteria for Adverse Events (CTCAE) which is available at: http://ctep.cancer.gov/protocolDevelopment/electronic applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

Acute side effect assessment should include the following:

- Anorexia
- Nausea + vomiting (esp. with vincristine)
- Weight loss
- Fatigue
- Headache
- Skin reactions
- Alopecia (total alopecia expected)
- Thrush (fungal infection of the mouth)
- Sore throat or esophagitis
- Decrease in bone marrow cells
- Constipation (esp. with vincristine)

Any of the above may lead to a need for treatment break or delay in finishing treatments.

Non-physical Risks:

- Inability to perform at school or job

Patient monitoring should be done per usual clinical practice.

Late Effects:

- Permanent hair loss or thinning in region of boost
- Decreased growth overall (GH effects)
- Decreased growth of spine
- Hormonal imbalance
- Hearing impairment
- Neurocognitive effects
- Cataracts
- Hypothyroidism
- Neuroendocrine effects, may lead to an inability to have children
- Abnormal curvature of the spine
- Scarring or damage to the esophagus
- Damage to the spinal cord or brain tissue
- Tumors caused by radiation
- Vascular effects, either asymptomatic or causing stroke

6.2 Toxicity Management

Toxicity that causes a delay or dose modification in radiation therapy is not expected. Once radiation has started it is important to continue with radiation unless it is deemed unsafe for the patient (i.e. they require anesthesia and have pneumonia). If the patient experiences toxicity from chemotherapy, delays and dose modifications should be made according to the concurrent chemotherapy treatment protocol.

6.3 Dose Modifications/Delays

To avoid treatment delays resulting from the proton machine being down, photon beam radiation can be administered. The maximum dose for both the posterior fossa and spine will be 20% of the dose (e.g. 20% of the spine at 36 Gy would be a max. of 4 spine treatments). Delay in the start of CSI proton therapy treatment should not exceed 2 weeks in M0 patients and 1 week in M+ patients.

Radiation treatment delays must be avoided where possible. If a patient is unable to receive a CSI treatment on a given day then consideration should be made to delivering the boost treatment where possible.

7. DRUG FORMULATION AND ADMINISTRATION: N/A

8. CORRELATIVE/SPECIAL STUDIES: N/A

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 35 days prior to start of protocol therapy. Scans must be performed within 6 weeks prior to the start of therapy. CSF sampling can be completed any time prior to start of protocol therapy.

Table 2: Required Data

Tests and Observations	**Pre-Study/ Baseline**	**During Radiation**	**Follow Up** (1)
Informed Consent and registration	X		
Biopsy or attempted resection	X		
Pathology Review	X		
Medical History	X		X (2)
Physical Exam	X	X (2)	X (2)
Endocrine Evaluation	X (3)		X (3)
CSF sampling if M0 disease	X (4)		
CBC	X (5)		X (5)
Serum Chemistries	X (6)		X (6)
MRI or CT of the brain	X (7)		X (7)
MRI of the entire spine	X (8)		X (8)
Audiogram	X (9)	X (9)	X (9)
Neurocognitive Testing	X (10)		X (10)

Notes:

(1) Follow up, except for neurocognitive testing, is to be completed annually (+ or – 6 months) from the completion of study treatment. Follow up is highly recommended, but not required.

(2) Medical history and physical exams during radiation treatment is to be completed weekly and may include only the acute toxicity assessment and other pertinent objective findings. Medical history and physical exams at follow up are recommended, but not required.

(3) Baseline endocrine evaluation to be completed no later than 2 months after the start of radiation. Evaluation includes Tanner stage assessment by physical exam, bone age (plain film of the wrist), and body proportion measurements. Bone age, Tanner Stage assessment, and body proportion measurements collected will be at the discretion of the study endocrinologist. Recommended measurements include sitting height (sitting height preferred, but pubic symphysis to floor acceptable), standing height, leg span, and arm span. Recommended labs for endocrine evaluation are TSH, Free T4, Cortisol, IGF-1, IGF-BP3, LH, FSH, estradiol (females) and testosterone (males) – am levels preferred,
(4) CSF sampling can be done any time prior to the start of protocol therapy. CSF sampling must be completed no later than ten days after the start of radiation. If sampling performed less than 10 days after surgery is positive, it should be repeated.

(5) CBC required labs are ANC, Platelets, Hematocrit. CBC with diff. is required at baseline. Annual follow up CBC's are suggested, but not required

(6) Chemistries required at baseline and that are suggested, but not required, for follow up are: albumin, alk phos, T bili, BUN, calcium, chloride, glucose, potassium, total protein, sodium, AST, ALT, Pregnancy test (if applicable and at pre-study only).

(7) Pre-Study brain MRI or CT includes pre-op and post-op imaging, post-op to be done within 21 days of surgery (preferably within 72 hours of surgery; intra-operative MRI as allowed). Brain MRI or CT at follow up is recommended, but not required.

(8) Pre-study spine MRI should be from the time of diagnosis (preferably pre-op). Spine MRI at follow up is recommended, but not required.

(9) Baseline audiogram must be completed within 2 months after the start of radiation. Audiograms are recommended, but not required, for patients receiving platinum based chemotherapy prior to the beginning of each cycle. Follow up audiograms are recommended annually. Additional audiograms, if done, will be collected and included in the data set.

(10) Baseline neurocognitive testing must be completed no later than 9 months after the start of radiation. Follow up testing is recommended starting one year after the previous exam, at one, three, and five years post-radiation (+ or – 12 months).

Patient Assessments:
The required tests and evaluations prior to, during and following CSI are shown in table 2. Patients will require acute side effect assessment during radiation therapy as detailed in section 9.1 below. Acute side effects from RT are defined as those effects that are attributable to the effects of radiation and occur from commencement of RT to 90 days following completion of RT.

Patients will be assessed for late side effects or complications which are defined as those effects that are attributable to the effects of radiation and occur > 90 days following completion of RT.

9.1 Acute Side Effect Assessment

All patients shall be assessed for acute toxicity on a weekly basis during CSI. Grading of acute toxicity will be done per the CTEP Active Version of CTCAE. Duration of treatment breaks must be recorded along with reason for break.

9.2 Description of special studies

Timing of special tests and assessments are outlined in table 2.

9.2.1 Endocrine

Whenever feasible, a referral to a Pediatric Endocrine specialist should be made for endocrine evaluation. Otherwise, referral to a local endocrinologist should be made. Labs required at baseline for study are TSH, Free T4, Cortisol, IGF-1, IGF-BP3, LH, FSH, estradiol (females), testosterone (males) – am levels preferred. These labs are recommended, but not required, at annual follow up time points. Endocrine evaluation also includes Tanner Stage assessed by physical exam, bone age (plain film of the wrist), and body proportion measurements. Bone age, Tanner Stage assessment, and body proportion measurements collected will be at the discretion of the study endocrinologist. Recommended measurements include sitting height (sitting height preferred, but pubic symphysis to floor acceptable), standing height, leg span, and arm span.

9.2.2 Audiology evaluation

Audiograms are required and should be done prior to start of radiation. Audiograms should be obtained on a yearly basis as well (see table 2). Additionally regular audiograms are recommended but not required to be performed at the patient's home institution prior to each cycle of platinum based chemotherapy in accordance with the standard of care because platinum chemotherapy can cause acute hearing loss. If the baseline audiogram cannot be completed prior to the start of radiation, it must be completed within 2 months of the beginning of radiation therapy. Each ear (left and right) should be tested and recorded separately.

Grading of sensorineural hearing loss will be according to the CTEP Active Version of CTCAE.

9.2.3 Neurocognitive evaluation

Analysis of Neurocognitive Function (NCF) will be limited to English speaking population, as norms for most tests are only available for this population. At baseline, neurocognitive testing will be required for all patients without posterior fossa syndrome. Patients with posterior fossa syndrome will be evaluated and referred if deemed appropriate. Patients will be required to undergo formal NCF evaluation at the Psychology Assessment Center at MGH or at the home institution.

Patients whose premorbid IQ is less than 60 (with no indication that the tumor led to an acute and dramatic decline in IQ) will be excluded from neuro-psychological assessment. Evidence for a dramatic decline will include parental report, school records, variability in IQ profile, gross inattention or lack of motivation/cooperation, and/or concurrent functional illness (e.g., depression).

Subjects will receive a comprehensive neuropsychological evaluation at baseline. Whenever possible, subjects will be evaluated within 9 months of the start of radiation. Following the baseline evaluation, it is recommended that subjects be evaluated at 1, 3, and 5 years post-RT (+ or – 12 months).

The battery of tests administered will be the same at every administration, as much as possible, and should include the following measures:

Function	Measure	Age Range	Administration Time
Intelligence	Wechsler Intelligence Scale for Children –5th Ed. (WISC-V) [a]	6- 16 years	65 minutes
	Wechsler Intelligence Scale for Children –4th Ed. (WISC-IV) [a]	6- 15 years	60 minutes
	Wechsler Preschool & Primary Scales of Intelligence-3rd Ed. (WPPSI-III) [a]	2½ - 5 years	45 minutes
	Wechsler Adult Intelligence Scale-3rd or 4th Edition (WAIS III or IV) [a]	16+ years	60 minutes
Language	Expressive Vocabulary Test-2nd Ed. [a] **OR** Expressive One-Word Vocabulary Test [a]	2½+ years 2½ -25 years	10 minutes 10 minutes
	Peabody Picture Vocabulary Test-4th Ed. (PPVT-4) [b]	2½+ years	10 minutes
Visual-Spatial/Motor	Beery-Buktenica Developmental Test of Visual-Motor Integration Version 5 or 6[a]	3+ years	10 minutes
	Grooved Pegboard Test [a] **OR** Purdue Pegboard Test [a]	5+ years 4-15 years	5 minutes 5 minutes
	Hooper Visual Organization Test [b]	5+ years	10 minutes
	Rey-Osterrieth Complex Figure Test (Copy) [b]	8+ years	5 minutes
Attention / Executive Functioning	Control Oral Word Association (F,A, S; Animals) [a]	6+ years	5 minutes
	Wisconsin Card Sorting Test (64 or 128) [a]	7+ years	15 minutes
	Trail Making Test (A and B) [a]	8+ years	5 minutes
	Continuous Performance Test-2nd Ed [b]	8+ years	20 minutes
	Children's Memory Scale - Subtests: Numbers; Sequences [b]	5 - 15 years	10 minutes
	Wechsler Intelligence Scale for Children-4th Ed. Subtests: Digit Span, Letter-Number Sequencing [b]	6 - 15 years	10 minutes
	Wechsler Adult Intelligence Scale-3rd or 4th Ed. Subtests: Digit Span, Arithmetic [b]	≥16 years	10 minutes

Learning/Memory	Children's Memory Scale - Stories I & II [a] **OR** Children's Memory Scale - Word Lists I & II [a]	6 - 15 years 6 - 15 years	20 minutes 20 minutes
	Wechsler Memory Scale-3: Family Pictures; Logical Memory [a] **OR** Wechsler Memory Scale-3: Word Lists and Spatial Span [a]	16+ years 16+ years	20 minutes 20 minutes
	California Verbal Learning Test-Child version [b] California Verbal Learning Test-II [b] Rey-Osterrieth Complex Figure Test (Delay) [b] Children's Memory Scale - Dots I & II [b]	6 – 15 years 16+ years 8+ years 6 - 15 years	20 minutes 20 minutes 5 minutes 10 minutes
Processing Speed	Wechsler Intelligence Scale for Children- 4th Ed. Subtests: Coding; Symbol Search [a] Wechsler Adult Intelligence Scale-(WAIS-III or WAIS-IV) Subtests: Digit Symbol-Coding; Symbol Search [a]	6 – 15 years ≥16 years	5 minutes 5 minutes
Academic Achievement	Wechsler Individual Achievement Test-II or III Subtests: Word Reading, Numerical Operations, Spelling [a] **OR** Bracken Basic Concept Scale-Revised[b]	5+ years 2½- 5 years	20 minutes 10 minutes
Emotional/ Behavioral	Behavior Assessment System for Children – 2 Parent form [a, d] Behavior Rating Inventory of Executive Function – Parent form [a] Behavior Assessment System for Children – 2 Self-Report form[b, d]	2½ -21 years (if in college to 25 years) 2+ years 8-21 years (if in college to 25 years)	15 minutes 5 minutes 15 minutes
Adaptive/Daily Living	Scales of Independent Behavior- Revised (Short Form)-Parent form[b, d]	1 month +	10 minutes

Notes: The same test version administered at Baseline should always be re-administered at follow up unless the patient has aged out of the norms for that given test.

Test battery was designed to assess patients from infancy to adulthood.

Approximate total administration time: Approximately 3-4 hours for patient measures; however, actual tests administered and the time required depends on the patient's chronological and functional ages. Parent measures require approximately 40 minutes and are completed while the patient is being evaluated.

a. Required test – part of core neurocognitive assessment
b. Recommended tests
c. Weschler Individual Achievement Test – III should be used with all patients enrolled after January 2013

d. If scoring program not available, results may be sent to MGH for scoring.

10. MEASUREMENT OF EFFECT

Tumor response is not an endpoint of this study. Patients will be evaluated for progressive disease based on imaging studies obtained in follow up.

10.1 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression.

10.2 Response Review

There is no central review of radiology assessments as response rate is not a primary endpoint or even a secondary endpoint of the trial. This trial measures toxicity and late effects and therefore central radiology review is not indicated.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) that is available on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

All adverse events experienced by participants from initiation of study treatment, throughout the study treatment, and within 30 days of the last dose of study treatment will be collected and reported as per DFCI guidelines. Participants who experience an ongoing adverse event related to a study procedures and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the the PI and Coordinating Center, IRB, and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11.2 Definitions

11.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.2.2 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.2.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.2.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study radiation.

11.2.3.2. Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.3 Recording Adverse Events

Adverse event information will be obtained at each contact with the participant. All adverse events will be recorded on the appropriate study-specific case report forms (CRFs). After 30 days beyond completion of study treatment, only adverse events that are possibly, probably or definitely related to study treatment will be collected for recording on the CRFs.

11.4 Reporting Adverse Events

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set below. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

The following severe toxicities should be reported to the principal investigator within one business day:

- Transverse myelitis
- Any other grade 4 acute toxicity except myelosuppression
- Death

Each adverse event will be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local policies, and federal guidelines and regulations as appropriate.

It is the responsibility of the participating investigator to notify the Principal Investigator (or Protocol Chair), IRB, and others of all serious adverse events as required in the protocol.

The Principal Investigator (or Protocol Chair) will provide information with respect to adverse events and safe use of the study treatment (e.g., safety reports, Action Letters) to all participating investigators as soon as the information becomes available.

11.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.2, 11.4, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected, except myelosuppression.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within one business day of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within one business day after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Torunn Yock, MD
c/o Coordinating Center
Telephone: 643-6086
Email: ccpo-mcgroup@partners.org
Fax: 617-724-2787

Within the following one to two business days, the participating investigator must provide follow up information on the serious adverse event. Follow up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Non-Serious Adverse Event Reporting:
Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

11.5 Institutional Review Board (IRB) Notification by Investigator

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Torunn Yock, MD
Telephone: 617-643-6086
Email: ccpo-mcgroup@partners.org
Fax: 617-724-2787

The DF/HCC Principal Investigator will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

11.6 Hospital Risk Management Notification by Investigator

The participating investigator will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

Data for this study will be collected and managed by the MGH Biostatistics Center. Electronic case report forms will be posted for use by all participating sites in TrialDB, and study staff at each site will be given access to enter CRF data electronically. Data will be monitored as described in the attached Data and Safety Monitoring Plan (Appendix A).

12.1.2 Data Submission

The schedule for completion and submission of electronic case report forms to the MGH Biostatistics Center can be found in section 5.10 in the attached Data and Safety Monitoring Plan (Appendix A).

The Coordinating Center is responsible for compiling and submitting data for all participants to the Principal Investigator for review.

12.1.3 DICOM Data

De-identified DICOM data for each study subject will be transmitted to the Advance Technology QA Center at Washington University, St. Louis (ATC). ATC will maintain the de-identified image data for analysis by investigators at all participating sites

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet periodically as required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator or Coordinating Center. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Federal Guidelines, and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.
Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

Children over the age of nine will be offered the opportunity to assent to study participation, as appropriate. This will also be documented in the medical record.

13.3 Ethics and Federal Guidelines

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws

- Institutional research policies and procedures
  www.dfhcc.harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the Principal Investigator (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (see Appendix A).

- The Principal Investigator/Coordinating Center is responsible for distributing all Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

14. STATISTICAL CONSIDERATIONS

The primary outcomes are late complications following proton beam irradiation to the craniospinal axis and posterior fossa. Late complications are defined as the delayed effects attributable to radiation which occur > 90 days following completion of CSI, while acute effects are those occurring during radiotherapy or up to 90 days after the last dose. Due to a difference

in the CSI dose used for standard-risk and high-risk patients, the two groups will be analyzed separately and thus have separate accrual goals.

14.1 Study Design/Endpoints

Accrual goals are 60 standard-risk and 30 high-risk patients. In the pediatric MB population treated with conventional photon CSI, 3-year progression-free survival of standard-risk patients is in the 75-80% range depending on the concurrent use of chemotherapy, while 65-70% is reported among high-risk patients. Thus, 48 standard-risk and 20 high-risk patients are projected to be evaluable for late complications at 3 years following the CSI completion; patients who progress or die sooner will not contribute in the analysis of late complications.

The primary endpoint of ototoxicity at 3 years following completion of radiation therapy will be based on failure events defined by grade 3 or 4 sensorineural hearing loss (SNHL) according to COG criteria. They include progressive hearing decrease to grade 3 or 4 following mild or moderate loss (grade 1 or 2) typically experienced during platinum-based chemotherapy. All patients who have audiology assessments prior to censorship will contribute to the actuarial analysis. Patients will be censored in the event of death, drop out or progression of disease. The historical rates of late SNHL is in the 50% range among pediatric MB patients [9, 10] treated with conventional CSI and cisplatin-based chemotherapy. We shall conclude proton therapy leads to an improvement in the high-risk group if 7 or fewer of 20 patients were to experience grade 3 or 4 SNHL at 3 years following completion of radiation therapy. The decision rule is associated with 77% power if the SNHL rate were truly reduced to 30% among the high-risk patients. In contrast, the probability is only 13% for concluding incorrectly an improvement if the underlying SNHL rate were 50%. In the null hypothesis for the standard-risk group, we assume conventional CSI and cisplatin-based chemotherapy is associated with an SNHL rate less than 50% due to their lower CSI dose, in particular, 40%. We shall conclude proton therapy leads to an improvement in the standard-risk group if 14 or fewer of 48 patients were to experience grade 3 or 4 SNHL at 3 years following completion of radiation therapy. The decision rule is associated with 80% power if the SNHL rate were truly reduced to 25% among the standard-risk patients. In contrast, the probability is only 8% for concluding incorrectly an improvement if the underlying SNHL rate were 40%.

Published data on neuroendocrine dysfunction and neurocognitive functioning have been based on small sample sizes, varying CSI doses and heterogeneous populations not directly comparable to the pediatric MB and PB patients in this protocol. Therefore, analysis of these endpoints will be focused mainly on estimation and precision. A standard-risk group of 48 patients will provide exact 95% confidence intervals of less than 30% for estimating the rates of neuroendocrine dysfunction and neurocognitive functioning, while the maximum interval width will be 46% based on 20 patients. Confidence intervals will be narrower in the analysis of acute effects, as more patients will be evaluable because very few losses will occur due to progression or death within 90 days following completion of CSI.

14.2 Sample Size/Accrual Rate

Based on recent clinical experience, the protocol is projected to accrue about 18 patients per year combined between the two participating institutions. Enrollment is planned for 5 years in order to meet the overall accrual goal of 90 patients. The observed risk distribution of MB and PB patients has been approximately a 2:1 ratio so that 60 standard-risk and 30 high-risk patients will be accrued for the sample size requirements. A minimum follow up of 3 years is required for observing the late complications of proton beam irradiation.

14.3 Stratification Factors

Enrollment will be stratified by risk group.

14.4 Analysis of Endpoints

Progression-free survival is measured from the start of radiation therapy to the date of documented disease progression or death in the absence of progression. Patients who have not progressed or died will be censored at the time of last follow up. Progression-free survival will be estimated by the Kaplan-Meier method. Acute effects will be summarized according to specific events with exact 95% confidence intervals for binary data. The incidence of late complications will be based on actuarial estimates, primarily at 3 years. Patients who die, progress, or are lost to follow up prior to 3 years will be censored. Other factors which may influence late complications will be explored in multivariate models, including gender, age, radiation dose to the posterior fossa, dose volume histogram of the normal tissue as well as drugs, dosages and sequencing of the chemotherapy regimen. In addition, we shall control for pre-existing hearing deficits in the analysis of ototoxicity, while methotrexate usage will be of interest in the analysis of neurocognitive functioning among high-risk patients. Multivariate analyses will be primarily exploratory due to the modest patient numbers in each risk group.

14.5 Reporting and Exclusions

14.5.1 Evaluation of toxicity.

All participants will be evaluable for toxicity from the time of their first treatment.

14.5.2 Evaluation of response

Tumor response is not applicable in this protocol.

15. PUBLICATION PLAN

The results will be made public within 24 months of the end of data collection for the primary objective. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of data collection.

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17. APPENDICES

Appendix A: Data and Safety Monitoring Plan
Appendix B: Patient Letter
Appendix C: Funded Visit Letter