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A trial of radioimmunotherapy, reduced-dose external beam craniospinal radiation therapy with IMRT boost, and chemotherapy for patients with standard-risk medulloblastoma

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

In this pilot study, 20 patients with standard-risk medulloblastoma will be treated post-operatively with intrathecal 131-I-3F8, reduced-dose external beam radiation therapy (1800 cGy craniospinal + primary site boost to 5400 cGy via IMRT), and standard chemotherapy (vincristine, lomustine, cisplatin).

2.0 OBJECTIVES AND SCIENTIFIC AIMS

- To assess the feasibility of combining intrathecal radioimmunotherapy with external beam radiation therapy and chemotherapy.

- To maintain or exceed the current progression-free survival rate for patients with standard-risk medulloblastoma while using the protocol-prescribed regimen that is hypothesized to have less long-term serious morbidity.

- To evaluate the long-term morbidities in patients treated with this regimen, with specific attention to neuropsychological, neuroendocrine, audiometric and growth outcomes.

3.0 BACKGROUND AND RATIONALE

Brain tumors are a significant cause of mortality and severe morbidity in the pediatric age range. They are the most common type of solid tumor in children and recent data have suggested that their incidence has exceeded that of acute lymphoblastic leukemia to represent the most common type of cancer in children. About 3,000 cases are estimated to occur per year in the United States and 30,000 to 40,000 cases are estimated to occur per year worldwide.

Medulloblastoma and other central nervous system primitive neuroectodermal tumors have been estimated to represent 20 to 25% of pediatric brain tumors. SEER data have suggested that approximately 317 cases of medulloblastoma are diagnosed in patients aged 0 to 24 years in the United States per year, with approximately 218 in the group 3 to 24 years old. Approximately 1/2 of these patients are thought to have standard- risk disease, leading to an estimate of 110 patients per year potentially eligible for this study.

Patients with medulloblastoma are divided into 3 groups for clinical trials. Patients older than 3 years of age are divided into standard-risk and high-risk groups. Standard-risk (the group of subjects to be involved in this study) is defined as the absence of metastatic disease (disease beyond the primary site) and the lack of post-operative residual tumor at the primary site greater than 1.5 cm^2. High-risk disease is defined by the presence of either or both of those criteria. Patients less than 3 years of age are usually treated with protocols that attempt to avoid the use of RT due to the high risk of severe

neuropsychological damage associated with its use in these patients with immature brains.

Medulloblastomas are highly malignant tumors that are very unlikely to be cured by surgery alone due to either recurrence at the primary site or dissemination through the cerebrospinal fluid (CSF) to distant leptomeningeal sites. The use of post-operative RT can be curative. The historical approach was to use RT without chemotherapy, with doses of 3600 cGy craniospinal, with a boost to 5400 cGy to the posterior fossa. Several recent studies have indicated that this approach produces an approximate 5-year event-free survival rate of 60% in patients with standard-risk disease. However, these doses of RT are associated with a significant risk of severe chronic neuropsychological and neuroendocrine morbidities, and growth retardation, as will be described below. These problems can be ascribed both to the craniospinal component of the radiation treatment and also to the temporal lobe and auditory apparatus inadvertently receiving a significant proportion of the boost dose when conventional treatment techniques are utilized. An attempt to reduce the craniospinal dose to 2340 cGy without the addition of chemotherapy in patients with standard-risk disease resulted an increased risk of early relapse, early isolated neuraxis relapse and a strong trend towards lower 5-year event-free survival (p=0.080).[1]

However, in single-arm studies, the addition of chemotherapy appears to both improve event-free survival and to allow the use of reduced-dose craniospinal RT. The Children's Cancer Group treated 65 children between 3 and 10 years of age with non-metastatic medulloblastoma with reduced-dose craniospinal RT (2340 cGy) and a boost to the posterior fossa to 5580 cGy. Patients also received weekly vincristine during the RT and beginning 6 weeks after completion of RT began a planned eight cycles of vincristine, cisplatin and lomustine chemotherapy. Progression-free survival was 86% +/- 4% at 3 years and 79% +/- 7% at 5 years. Hearing loss (presumably due to both cisplatin and RT to the auditory apparatus) occurred in 32%. Neuropsychological outcome was not described.[2] This regimen has been explored on a larger scale in CCG-9961. The study completed accrual in December 2000, but results are not yet available.

Only very limited data exist regarding the use of even lower craniospinal radiation doses. Investigators at the Children's Hospital of Philadelphia treated 10 children between 18 and 60 months of age with non-metastatic medulloblastoma with very reduced-dose craniospinal RT (1800 cGy) and a boost to the posterior fossa to 5040 to 5580 cGy. Patients also received weekly vincristine during the RT and beginning 6 weeks after completion of RT began a planned eight cycles of vincristine, cisplatin and lomustine chemotherapy. Actuarial survival at over 6 years was 70% +/- 20%. Of the 3 patients whose tumor recurred, in 1 recurrence was simultaneously appreciated in the primary site and distantly and 2 at distant sites only. IQ testing of the survivors suggested minimal neurocognitive damage.[3]

Neuropsychological outcome of children treated for medulloblastoma was assessed by investigators at St. Jude. They described 22 patients who were treated with RT only and whose craniospinal dose was randomly assigned to 3600 versus 2340 cGy. They noted that the patients that received the lower dose suffered less severe neuropsychological toxicity.[4]

Poor linear growth and adult short stature are extremely common in survivors of medulloblastoma and result from a combination of inadequate production of essential hormones such as growth hormone and thyroxine, and impaired spinal growth. In general, these abnormalities are directly correlated with the dose of radiation. Doses >3500 cGy to the hypothalamus result in growth hormone deficiency in 80-100% of subjects within 5 years.[5-7] Similar doses administered to the whole spine are associated with a 60% incidence of primary hypothyroidism[8] and an estimated loss in height in the range of 5 to 9 cm.[9] Limited data suggest that reducing the dose of craniospinal RT from 2340 cGy to 1800 cGy would result in an improvement in growth and final height,[10] as well as reduce the risks of neurocognitive dysfunction.[11]

Preliminary Data

Radioimmunotherapy

3F8 is an IgG3 murine monoclonal antibody directed against the ganglioside GD2 that is expressed on many human neural tumors, including 20 of 21 medulloblastoma tumors that we have tested (unpublished data). The 3F8 antibody localizes to GD2+ tumors in humans,[12] mediates tumor cell lysis in vitro via interactions with human complement and leukocytes, can be conjugated to 131-I for targeted radioimmunotherapy, and has been effective intravenously in patients with metastatic neuroblastoma.[13] Intrathecal administration of radiolabeled 3F8 to nude rats with GD2+ leptomeningeal neoplastic xenografts demonstrated a tumor dose of 1870 cGy/mCi versus only 40 cGy/mCi using a radiolabeled control antibody. Area under the curve values in tumor tissue were 14-fold greater than in blood.[14] A trial of intrathecal 131-I-3F8 was performed in 8 cynomolgus monkeys at MSKCC. The therapy was tolerable and therapeutically relevant doses of radiation (1900 to 8200 cGy) were delivered to the CSF space.[15] No long-term toxicity was observed with more than 4.5 years of follow-up from treatment.

Intrathecal 131-I-3F8 is currently the subject of a phase I clinical trial at our institution (MSKCC 97-021) in patients with GD2+ leptomeningeal tumors. Ten patients (including 4 with medulloblastoma or PNET), aged 1 to 61 years, have received 22 intrathecal injections of 131-I-3F8. They first received 1 to 2 mCi of intrathecal 131-I-3F8 via Ommaya reservoir, were imaged to obtain dosimetry, and then 7 patients received a second dose of 7.8 to 12 mCi.[16]

Side effects for the 10 patients receiving the dosimetry dose were all transient and $\leq$ grade 2 including fever (n=5), headache (n=5), emesis (n=4), and leg pain (n=2). One

patient had raised intracranial pressure above his baseline for 48 hours, associated with a headache. He was observed without treatment. Three patients had no toxicity.

Seven of the above patients received single therapeutic injections of 7.8 to 12 mCi of intrathecal 131-I-3F8. Pharmacokinetics, dosimetry, imaging and clinical evaluation were carried out in an identical manner and compared to that obtained in the dosimetry doses. Acute toxicities included grade 1 or 2 fever, headache and emesis. One patient with a pre-existing seizure disorder had a generalized seizure 4 days after treatment requiring treatment and hospitalization. This patient was found to have sub-therapeutic anti-convulsant medications and progressive tumor on MRI imaging. One patient with pre-existing communicating hydrocephalus was treated with more than one therapeutic injection; symptoms of raised intracranial pressure occurred after the 4th injection, and required the placement of a ventriculo-peritoneal shunt. No long-term toxicity has been observed in one patient surviving 14 months.

Dosimetry to CSF and marrow appears favorable: the estimated dose received to the CSF was 14.9 to 56.7 cGy/mCi (test doses) and 15 to 78.9 cGy/mCi (therapy doses), with little intra-patient variability. Dose to blood and other organs outside the central nervous system was < 2 cGy/mCi. Radioactivity was detected in the thecal sac by 4 hours and over the convexity by 24 hours. Focal uptake consistent with tumor was seen along the craniospinal axis in most patients; in the 1 patient with a normal MRI, clearance was rapid with no focal uptake. There was close agreement in CSF clearance in patients who received 2 injections, ranging from 6 to 14 hours.

Given the selective tumor uptake, tumor dose is expected to be 5 to 10 fold the CSF dose, and thus we hypothesize that this agent may have clinical utility in the treatment of GD2+ cancers with a high-risk of leptomeningeal dissemination such as medulloblastoma. Only minimal doses of radiation are delivered to the brain and spinal cord parenchyma due to the short path length (~1 mm) of the 131-I isotope. This is potentially advantageous to these patients since parenchymal disease is rare.

The MSKCC neurosurgical staff reviewed the recent institutional experience of placing Ommaya reservoirs in patients for the treatment of prophylaxis of leptomeningeal metastases.[17] Between January 1995 and June 1998, Ommaya reservoirs were placed in 107 patients. Complications occurred in 10 patients (9.3%) and included 2 infections, 5 catheter malpositions, and 3 intracranial hemorrhages. Two deaths occurred secondary to intracranial hemorrhage, but both had risk factors that should not apply to our patients. One was receiving anti-coagulation therapy for a mechanical heart valve and the other had thrombocytopenia secondary to other treatment.

Intensity modulated radiation therapy (IMRT)

IMRT is a new technology for the planning and delivery of RT. It represents a significant improvement over traditional 3-dimensional (3D) planning. IMRT features sophisticated

computer-optimized intensity distributions within a number of radiation beams. This is achieved by using an inverse-planning algorithm with dose and volume constraints for every target and critical tissue in the treatment field. Penalties are set for each constraint in order to set priorities among the various volumes. Treatment is delivered using dynamic multileaf collimators (tiny strips of metal shielding) whose movements throughout each field during the treatment are controlled by a computer. The result is a dramatically higher degree of conformality of dose to the target and significant sparing of adjacent healthy tissues.

IMRT is currently available in only a limited number of centers. There is only 1 publication that we are aware of reporting its use for patients with medulloblastoma. The authors noted that the auditory apparatus received lower doses of radiation when compared to historical patients treated with conventional techniques.[18]

We have treated 10 patients with newly-diagnosed medulloblastoma from July 1999 to the present with IMRT boosts and have shown a significant improvement in dose distributions for every patient compared to 2D and traditional 3D planning. In all cases, the dose conformality to the tumor target volume is improved while doses to the inner ears and other critical tissues are minimized. This decrease is expected to result in improved long-term hearing and a lower risk of endocrine dysfunction and neurocognitive delay, but this has not yet been proven. All 10 patients are currently event-free survivors, suggesting that the smaller boost volume does not adversely effect local control, but follow-up has been short (4 to 34 months, median 20 months, as of 5-31-02) and continued surveillance necessary.

4.0 STUDY DESIGN

This is a single-arm study of post-operative radioimmunotherapy (intrathecal 131-I-3F8), reduced-dose craniospinal radiation therapy (1800 cGy), primary site boost (to 5400 cGy) via IMRT and standard chemotherapy. Statistical stopping rules are defined to minimize the risk of excessive failures. Long-term neuropsychological, neuroendocrine, audiometric and growth parameters will be closely followed to assess long-term morbidities that are hypothesized to be reduced with this regimen.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 131-I-3F8

Source and pharmacology: Monoclonal antibody 3F8 is a murine IgG3 antibody. It is raised in BALB/c mice and specifically recognizes the ganglioside GD2. Formulation and stability: 3F8 is stored as 2 mg/ml in pH 4.2 citrate phosphate buffer. Vials are stored at -80 C.

Route of administration: Intrathecal.

Supplier: 3F8 is produced using FDA guidelines for good laboratory practice within the premises of Memorial Sloan-Kettering Cancer Center. All lots have to pass sterility, safety, pyrogen, murine viruses, and DNA testing before human use. 131-I-3F8 is prepared by the Radiochemistry/Cyclotron Core Facility under the supervision of Dr. R. Finn. It is approved for human use via IND BB-IND-2299.

5.2 Vincristine

Roue of administration: Intravenous

Supplier: Commercially available. NSC-67574.

Formulation: Clear liquid, 1 mg, 2 mg, and 5 mg vials.

Storage: Refrigerate. Protect from light.

Stability: Multiple-dose containers with preservatives are stable 30 days after opening if refrigerated.

5.3 Lomustine

Route of administration: Oral

Supplier: Commercially available.NSC-79037.

Formulation: 10 mg, 40 mg, and 100 mg capsules.

Storage: Room temperature.

5.4 Cisplatin

Route of administration: Intravenous

Supplier: Commercially available. NSC-119875.

Formulation: 50 mg vials.

Storage: Room temperature. Protect from light.

Reconstitution: Reconstitute each vial with sterile water to achieve a final concentration of 1 mg/ml. Cisplatin is compatible with KC1, mannitol, and magnesium but NOT NaHCO3.

Stability: Reconstituted solution is stable for 20 hours at room temperature. May precipitate if refrigerated after reconstitution. Aluminum reacts with cisplatin causing

precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

6.0 CRITERIA FOR PATIENT/SUBJECT ELIGIBILITY

6.1 PATIENT/SUBJECT INCLUSION CRITERIA

- Patients must have histologic proof of medulloblastoma reviewed by the Department of Pathology at the Memorial Sloan-Kettering Cancer Center.
- Patients must begin study prescribed therapy within 42 days of neurosurgical resection of the tumor
- Age ≥ 3-years-old.
- Post-operative head MRI must confirm ≤ 1.5 cm^2 of residual tumor is present.
- Head and spine MRI and lumbar CSF cytology must not show any definitive evidence of leptomeningeal dissemination (Chang stage M-0).
- Examinations evaluating extra-neural sites will not be mandated, but any performed for clinical indications must be free of metastatic disease.
- No prior RT or chemotherapy for the medulloblastoma is permitted.
- Patients must have adequate CSF flow (defined as lack of compartmentalization) on an 111-Indium DTPA flow study.
- Patients must have adequate organ function as defined by:
- Hepatic: total bilirubin < 2.0 mg/dl, AST < 3 x the upper limit of normal.
- Renal: Calculated creatinine clearance or nuclear GFR ≥ 70 ml/min/1.73 m^2.
- The patient, or for minors, a parent or legal guardian, must give informed written consent indicating they are aware of the investigational nature of this study.

6.2 PATIENT/SUBJECT EXCLUSION CRITERIA

- Unable to start study prescribed therapy within 42 days of neurosurgical resection of the tumor
- Age less than 3 years
- > 1.5 cm^2 residual tumor on post-operative head MRI
- Evidence of leptomeningeal dissemination on head or spine MRI or CSF cytology positivity
- Evidence of extra-neural metastases
- Prior radiation therapy or chemotherapy for the medulloblastoma
- Inadequate CSF flow on 111-Indium DTPA flow study
- Patients with signs or symptoms suggestive of increased intracranial pressure (headache, emesis, ocular paresis) will not be eligible until they are cleared by neurology and/or neurosurgery.
- Pregnancy
- Total bilirubin $\geq$ 2.0 mg/dl
- AST $\geq$ 3 x the upper limit of normal
- Creatinine clearance and GFR < 70 ml/min/1.73 m^2

7.0 RECRUITMENT PLAN

Patients will be offered the opportunity to participate in this trial if they meet the eligibility criteria. There will be no discrimination against females or minorities. Informed consent will be obtained from the patient, or if they are non-emancipated minors, their parent or legal guardian. Consent will be obtained by an investigator authorized to obtain consent. Patients will not receive any payment for their participation in this study.

8.0 PRETREATMENT EVALUATION

- Review of the pathology by the Memorial Sloan-Kettering Cancer Center Department of Pathology

- Post-operative head MRI
- Spine MRI
- CSF cytology obtained via lumbar puncture
- 111-Indium DTPA CSF flow study
- Liver function tests: Total bilirubin, AST
- Renal function tests: Creatinine clearance or nuclear GFR study
- For females ≥ 12-years-old, pregnancy test
- All of these pre-treatment evaluations (other than pathology review) should have been performed ≤ 30 days before registration onto study

9.0 TREATMENT/INTERVENTION PLAN

Patients will receive 3 components of therapy, as described below.

9.1 Intrathecal 131-I-3F8

Treatment will be given via an Ommaya reservoir that will be placed by neurosurgery if not already present. If the patient has a ventriculoperitoneal shunt, and CSF flow study using the shunt tubing has confirmed acceptable CSF flow, the shunt may be used for the administration of 131-I-3F8.

9.1.1 Premedications for 131-I-3F8

The following pre-medication guidelines are strongly suggested, but may be altered based on the clinical judgment of the investigators without being considered a protocol violation.

To start about 2 weeks prior to injection:

Levetiracetam (Keppra): Start at 10-20 mg/kg divided BID about 2 weeks prior to injection, after one week increase by 10 mg/kg. The pills come in 250 and 500 mg strength and no liquid preparation is currently available. For patients unable to tolerate oral tablets, phenytoin may be substituted. Taper of the anti-convulsant is recommended (decrease dose by about 50% 2 weeks post-injection, then discontinue medication 3 days later) rather than abrupt discontinuation.

To start about 5 days prior to injection:

SSKI: 7 drops daily (to begin 5 days pre-injection and to continue for 2 weeks post-injection)

Liothyronine (Cytomel): 25 mcg/day if weight less than 25 kg, 50 mcg/day if weight greater or equal to 25 kg (to begin 5 days pre-injection and to continue for 2 weeks post-injection)

To start 1-2 days prior to injection:

Dexamethasone (for those patients not already on a higher dose of dexamethasone): 0.5 mg po bid if weight less than 15 kg, 1 mg po bid if weight greater than or equal to 15 kg (to begin about 24 hours pre-injection and to be tapered over 1 to 2 weeks)

To be started about 1 to 2 hours before injection:

Hydroxyzine (Vistaril): 1 mg/kg IV, then Q 4 hours x 24 hours post-injection

Acetaminophen (Tylenol): 10 mg/kg po before injection and then Q4 hours x 24 hours post-injection

Lorazepam (Ativan): 0.05 mg/kg IV x 1

Hydromorphone (Dilaudid): 0.015 mg/kg/dose x 1, then PRN

9.1.2 Treatment and dosimetry

Patients will receive an intrathecal dose of 2 mCi of 131-I-3F8 via the Ommaya reservoir. Distribution throughout the thecal sac will be confirmed via whole body imaging at approximately 24 hours post-injection. Patients will have CSF and blood (2 ml/sample) obtained for radioactivity levels at approximately 5, 15, and 30 minutes, and 1, 2, 4, 18, and 44 hours post-injection. Pharmacokinetic data obtained from whole body and SPECT imaging will be used in conjunction with direct counting of CSF and blood samples in a well scintillation counter, and combined with MRI anatomical imaging to estimate the absorbed dose to brain, spinal column, blood and visible tumor nodules.

About 1 week after the initial dose, patients will receive a therapeutic dose of 10 mCi. They will have the same CSF and blood monitoring specified in the previous paragraph, but will not have the SPECT imaging.

Patients will be hospitalized overnight for supportive care after each of the 2 131-I-3F8 injections.

9.2 External beam radiation therapy

Dose: A dose of 1800 cGy will be delivered to the craniospinal axis using external beam photons. The posterior fossa tumor bed boost will be treated to a total dose of 5400 cGy (1800 cGy craniospinal + 3600 cGy focal). The whole brain dose is calculated at midplane while the spine dose is calculated at the average anterior cord depth. The IMRT boost will be prescribed to the isodose line that includes at least 95% of the planning target volume (PTV).

Radiation should begin as soon as possible after the patient has recovered from surgery and intrathecal 131-I-3F8. Treatment will be given according to standard fractionation at 180 cGy per day, 5 days per week. All fields shall be treated daily. Days missed due to holidays or for other unavoidable reasons are acceptable but should be kept to a minimum. Holding radiation treatments is allowed at the discretion of the radiation oncologist, but interruptions in radiation therapy should be avoided whenever possible. There are no minimum blood count requirements for radiation therapy and radiation therapy may be given even if chemotherapy is held.

Treatment volume: Radiation will be delivered to the entire craniospinal axis with an inferior border 1 to 2 cm below the thecal sack. Care will be taken to include the cribriform plate while shielding the lenses of the eyes. The clinical target volume (CTV) for the boost to the posterior fossa tumor bed will include the postoperative cavity and any residual disease plus a 1 cm margin in all dimensions. The only exception is that the CTV should not extend into bones (skull base, calvarium, vertebral bodies) and thus the margin may be less than 1 cm in these regions. The PTV is defined as the CTV plus a 0.5 cm margin in all dimensions. The PTV may extend into bones. The entire posterior fossa is NOT intended for treatment in the boost field.

Technique: Patients will receive craniospinal radiation using standard techniques. They will be simulated in the prone position using immobilization casts as well as anesthesia when necessary. A treatment planning CT scan will be performed and images will be fused with a diagnostic MRI scan for better definition of anatomy. The brain will be treated with lateral or lateral oblique fields (depending upon the technique chosen for lens sparing) matched to posterior spine field(s). Appropriate gantry and collimator angles will be calculated to prevent overlapping fields. There will not be a gap between the cranial and spine fields but the match line will be shifted 1 cm half way through treatment, at 900 cGy.

Intensity modulated radiation therapy will be used for focal treatment of the tumor bed boost. The number of fields and orientation of beams will be determined on an individual basis. The general goals of the optimization algorithm are to maximize coverage of the target volume (PTV as defined above) while minimizing heterogeneity within the target and sparing the cochlea to the extent possible. The maximum dose to any point in the brainstem must not exceed 6000 cGy and the maximum dose to any point in the cord must not exceed 5000 cGy in the composite plan (including the craniospinal portion of

treatment). Dose to the hypothalamic-pituitary axis should also be constrained as much as possible. The parotid glands and oral cavity should be contoured and the cumulative mean dose to each of these structures should not exceed 2600 cGy.

All fields will be treated using 6MV photons. Initial and weekly portal films will be taken to ensure correct positioning.

Evaluation on treatment: Patients will be evaluated by a radiation oncologist at least once per week. Complete blood counts will be drawn about weekly.

9.3 Chemotherapy

Starting at about the onset of external beam RT, patients will receive 8 weekly doses of vincristine (1.5 mg/m^2/dose, maximum 2 mg).

Starting about 6 weeks after completion of the RT (about 4 weeks after the 8th dose of vincristine noted above), we will start 8 planned cycles of vincristine, cisplatin, and lomustine chemotherapy. Each cycle consists of:

Vincristine (1.5 mg/m^2/dose, maximum 2 mg) IV push on days 0, 7, & 14.

Cisplatin (75 mg/m^2/dose) IV over about 6 hours on day 0 with mannitol and hydration. A sample order set is included as an appendix.

Lomustine (75 mg/m^2/dose) po on day 0. Because the capsules only are available in 10, 40, and 100 mg doses, the actual dose of lomustine will be rounded off to the closest possible dose.

Cycles are intended to be repeated about every 6 weeks depending on the ANC and platelet count (see below). The post-RT chemotherapy may be given at another center if more convenient for the patient as long as adequate documentation is sent to the MSKCC PI in a timely fashion.

9.4 Chemotherapy dose modification rules:

Hematopoietic toxicity: If the ANC is < 750 or platelet count < 75,000, a cycle should not be started. If the ANC is ≥ 750, but < 1000, or the platelet count is ≥ 75,000 but < 100,000, the cycle may start, but the lomustine dose will be reduced by 50%.

Neurotoxicity: For vincristine neurotoxicity grade 3 or 4 and/or for vincristine neuropathy: motor grade 2 to 4: hold vincristine. When toxicity resolves to less than grade 3 (less than grade 2 for vincristine neuropathy: motor), vincristine may be restarted at 50% dose (0.75 mg/m2). If the neurotoxicity completely resolves, increase to full dosage may be considered.

Hepatotoxicity: If total bilirubin is > 1.9 mg/dl, do not administer vincristine dose. If total bilirubin is 1.5 to 1.9 mg/dl, administer vincristine at 1 mg/m^2 (1.5 mg maximum).

Nephrotoxicity: If the creatinine clearance or GFR are > 60 ml/minute/1.73 m2, administer the full dose. If the creatinine clearance or GFR are 30-60 ml/minute/1.73 m2, administer 50% of the dose (37.5 mg/m2). If the creatinine clearance or GFR are < 30 ml/minute/1.73 m2, do not administer cisplatin.

Ototoxicity: For a decrease in auditory acuity of (1) ≥ 30 decibels at 4000 to 8000 Hz or (2) ≥ 20 decibels at 500 to 3000 Hz or (3) grade 3 ototoxicity (subjective loss correctable with hearing aid), a 50% reduction in cisplatin dosage will be made. For grade 4 ototoxicity (deafness not correctable), cisplatin will be discontinued unless follow-up audiogram shows an improvement in hearing function.

9.5 Supportive care guidelines

Clinical judgment may be used to alter the following guidelines without being a protocol violation.

Patients should receive PCP prophylaxis.

Filgrastim (G-CSF) is allowed to be used according to clinical judgment.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

A tabular summary of the timing of the mandated observations is included as an appendix to the protocol.

Dosimetry studies during phase 1 of the protocol (see section 9.1).

CBC will be obtained about weekly during external beam radiation therapy.

CBC, total bilirubin, AST, creatinine clearance or GFR, and audiograms will be obtained at baseline and prior to each cycle of cisplatin-containing chemotherapy.

Serum for anti-idiotype testing (order as Research test: 1 red top tube to be sent to Dr. Cheung's laboratory, Z-1431) will be obtained about every 6 months.

Neuropsychological battery will be performed at "baseline", and at about 1 year and 4 years post- completion of treatment. The "baseline" testing may be performed up to 4 months post-completion of external beam radiation therapy.

The tests in the assessment battery are presented in Table 1 below for parents and children by age and by functional domain assessed. The attending neuropsychologist may

make necessary modifications to the battery as indicated for an individual patient's special circumstances without it being considered a protocol violation.

Table 1. Neuropsychological and Behavioral Battery					
	Child's Age				
Test	> 3 & ≤ 4 yrs	>4 & ≤ 6 yrs	> 6 & ≤ 12 yrs	> 12 & ≤ 16 yrs	> 16 yrs
Children					
Intelligence					
WPPSI-III (Vocabulary, Block Design) *(15 min)*	X	X			
WISC-IV (Vocabulary, Block Design) *(15 min)*			X	X	
WAIS-III (Vocabulary, Block Design) *(15 min)*					X
Processing Speed/Attention					
WPPSI-III (Symbol Search, Coding) *(10 min)*	X	X			
WISC-IV (Symbol Search, Coding) *(10 min)*			X	X	
WAIS-III (Symbol Search, Coding) *(10 min)*					X
Memory					
NEPSY (Story Memory) *(5 min)*	X (3-5 yrs)				
CMS *(15 min)*		X (≥ 5 yrs)			
CVLT-C *(15 min)*		X (≥ 5 yrs)			
WISC-IV (Digit Span) *(5 min)*			X	X	
WAIS-III (Digit Span) *(5 min)*					X
WMS-III and CVLT-II *(20 min)*					X
Parents					
Attention and Behavior/Social/Emotional Function					
BASC-II *(20 min)*	X				
Executive Function					
BRIEF *(5 min)*	X	X	X	X	X
Quality of Life					
PedsQL 4.0 (Generic Version)	X	X	X	X	X

Index of Test Abbreviations	
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence – 3rd Edition
WISC-IV	Wechsler Intelligence Scales for Children – 4th Edition
WAIS-III	Wechsler Adult Intelligence Scales – 3rd Edition
NEPSY	NEPSY: A Developmental Neuropsychological Assessment
CMS	Children's Memory Scale
CVLT-C	California Verbal Learning Test – Children's Version
WMS-III	Wechsler Memory Scale – 3rd Edition
CVLT-II	California Verbal Learning Test – 2nd Edition
BASC-II	Behavior Assessment System for Children – 2nd Edition
BRIEF	Behavior Rating Inventory of Executive Function Scales
PedsQL 4.0	Pediatric Quality of Life Inventory Version 4

Neuropsychological Battery

As indicated in Table 1 above, the tests that are administered depend on the child's age at the time of the assessment. Procedural information for the tests in the neuropsychological and behavioral battery is provided by age group in Appendix II. General information about each of the measures in the Neuropsychological and Behavioral Battery is provided below.

Wechsler Preschool and Primary Scale of Intelligence – 3rd Edition (WPPSI-III)

The WPPSI-III is a test for assessment of intellectual function in individuals greater than 2 years of age but less than 7 years of age. Four subtests from this measure will be used: 1. Vocabulary will be utilized to assess verbal intellectual function; 2. Block Design will be utilized to assess nonverbal intellectual function; 3. Symbol Search and 4. Coding will be used to assess processing speed. Reliability for this measure has been reported to be between 0.83 and 0.95. Criterion and discriminant validity have been established for this measure.

Wechsler Intelligence Scales for Children – 4th Edition (WISC-IV)

The WISC-IV is a test for assessment of intellectual function in individuals 7-16 years of age. Five subtests from this measure will be used: 1. Vocabulary will be utilized to assess verbal intellectual function; 2. Block Design will be utilized to assess nonverbal intellectual function; 3. Symbol Search and 4. Coding will be used to assess processing speed; and 5. Digit Span will be used to assess short-term memory. Reliability has been reported between 0.79 and 0.97 for this measure. Construct validity has been established for this measure.

Wechsler Adult Intelligence Scales – 3rd Edition (WAIS-III)

The WAIS-III is a test for assessment of intellectual function in individuals greater than 16 years of age. Five subtests from this measure will be used: 1. Vocabulary will be utilized to assess verbal intellectual function; 2. Block Design will be utilized to assess nonverbal intellectual function; 3. Symbol Search and 4. Coding will be used to assess processing speed; and 5. Digit Span will be used to assess short-term memory. Very good reliability as well as concurrent and criterion validity have been established for this measure.

NEPSY: A Developmental Neuropsychological Assessment

The NEPSY is a test for assessment of a wide range of children's neuropsychological function. One subtest, Story Memory, will be utilized for assessing narrative memory in children 3 to 5 years of age. Reliability of this measure has been reported to be between 0.77 and 0.85. Validity has also been established for this measure.

Children's Memory Scale (CMS)

The CMS is a test to assess verbal and visual memory in individuals 5-16 years of age. The following subtests will be utilized: Story Memory, Story Memory Recall, Faces, Faces Recall, Dot Location, and Dot Location Recall. Reliability and validity have been established for this measure.

California Verbal Learning Test – Child (CVLT-C) or Adult 2nd Edition (CVLT-II)

The CVLT-C and CVLT-II involve verbally presenting a list learning task over the course of 5 trials. The test measures multiple aspects of how verbal learning occurs, or fails to occur, as well as the amount of verbal material learned. The CVLT-C is for individuals 5-16 years of age while the CVLT-II is for individuals older than 16 years of age. Test-retest reliability of this measure has been reported to be between 0.80 and 0.84.

Wechsler Memory Scale – 3rd Edition (WMS-III)

The WMS-III is a test to assess verbal and visual memory in individuals greater than 16 years of age. The following subtests will be utilized: Logical Memory I, Logical Memory II, Faces I, Faces II, and Spatial Span. Internal consistency reliability has been reported to be above 0.70 for this measure. Construct, convergent, and discriminant validity have been established for this measure.

Behavior Assessment System for Children – 2nd Edition (BASC-II)

The BASC-II describes the behaviors, thoughts, and emotions of children and adolescents. The parent rating scale will be utilized for individuals older than 2 years of age. The questionnaire yields composite and scale scores in the domains of externalizing, internalizing, school, and other problems as well as adaptive skills and behavioral symptoms. Internal consistency reliability has been reported to be between 0.80 and 0.95, test-retest reliability between 0.72 to 0.92, and interrater reliability between 0.53 and 0.86. Content and construct validity have been established for this measure.

Behavior Rating Inventory of Executive Function Scales (BRIEF)

The 86-item parent-report version of the BRIEF will be used to assess executive function in individuals 6 years of age and older. This pertains to the following functional areas: inhibition and shifting of attention, emotional control, initiation, working memory, planning, organization and self-monitoring. Internal consistency of the BRIEF has been reported from 0.80 to 0.98 and test-retest reliability has been reported between 0.76 and 0.85. The preschool version of the questionnaire will be utilized for individuals younger

than 6 years of age. Construct, content, convergent, and discriminant validity have also been established for this measure.

Pediatric Quality of Life Inventory Version 4 (PedsQL 4.0)

The PedsQL 4.0 is a modular approach to measuring health-related quality of life in healthy children and adolescents as well as in those with acute and chronic health conditions. The Generic Version consists of 23 items, with parent-report for ages 2-4, 5-7, 8-12, and 13-18. The questionnaire yields domain scores for Physical, Emotional, Social, and School Functioning as well as summary scores for Total, Physical Health, and Psychosocial Health. Reliability and validity have been established for this measure.

Neuroendocrine assessment performed at baseline will include standing and sitting height, Tanner staging of puberty, free thyroxine, TSH, and bone age x-ray. For patients > 12-years-old or who have ≥ Tanner 2 puberty, LH/FSH, and testosterone or estradiol will be assessed. Follow-up examinations will be performed until 5 years post-diagnosis and will consist of standing and sitting height, Tanner staging, free thyroxine, and TSH every 6 months. Growth hormone stimulation testing will be performed if yearly growth velocity post-treatment is < 4cm per year or at 2 years post-completion of all therapy, whichever occurs first. Bone age x-ray, and LH/FSH, and testosterone or estradiol for patients > 12 years or who have ≥ Tanner 2 puberty, will be performed annually.

Assessment of tumor status via brain MRI will be performed about 4 weeks after completing RT (pre-cycle 1 chemotherapy), then about every 3 months while on therapy (prior to cycles 3, 5, and 7). After completion of therapy, brain MRI scans will be performed about every 3 months for 1 year, then every 6 months for 2 years, then every 12 months for 1 year. Total spine MRI scans will be performed at about 1 year, 2 years, and 3 years post-completion of therapy. Subsequent scans will be performed at the clinician's discretion and are not mandated by this protocol, but brain MRI scans are recommended to be done about annually.

Mandated evaluations including lab work, audiograms, and MRI scans may be performed at other (non-MSKCC) centers if deemed clinically indicated by an investigator. Outside MRI scans should be submitted to PACS, and reports submitted to medical records, as soon as possible.

11.0 TOXICITIES/SIDE EFFECTS

Toxicities will be assessed via the NCI toxicity criteria. All toxicities will be recorded in CRDB until 30 days after the last dose of 131-I-3F8. Subsequently, only toxicities greater than or equal to grade 3 will be recorded in CRDB.

The most common side effects expected are alopecia (likely), nausea and vomiting due to RT and/or chemotherapy (likely), myelosuppression (blood product transfusions and need for hospitalization for fever and neutropenia both possible), ototoxicity (likely), nephrotoxicity (possible), infertility (possible), and second malignancies due to RT and/or chemotherapy (possible). Hospitalizations for therapy administration, fever and neutropenia, central venous catheter-associated bacteremia, possible septicemia, vomiting, or dehydration will not be considered serious adverse events (SAE) and will not be reported to the IRB or FDA. Non-life threatening grade 3 and 4 toxicities clearly due to the external beam radiation therapy and/or chemotherapy will not be reported as SAE's. However, life-threatening infections or other life-threatening side effects will be considered SAE's and will be promptly reported.

Possible risks include the possibility of unexpected side-effects from the addition of radioimmunotherapy to external beam radiation therapy and chemotherapy, and the possibility of increased failures from the reduced craniospinal radiation dose and reduced boost volume via IMRT.

11.1 131-I-3F8

For patients who received one test dose and one therapeutic dose on MSKCC protocol 97-21, no grade 3 or 4 side effects were seen at dose level 1, the dose to be used in this study. Among the first 7 patients, acute side effects seen included low-grade fever in 2, headache in 2, and emesis in 1. Two patients had no side effects. One patient had elevated opening CSF pressure that remained elevated for 36 to 48 hours post-injection of the test dose.[16] He was observed without any intervention and complications ensued.

11.2 Radiation therapy

Acute toxicities: Nausea with or without emesis is an anticipated side-effect and may be treated with antiemetic medications. Fatigue and a decrease in all blood counts are expected. Patients generally have transient complete alopecia and may have permanent epilation in some regions. Skin erythema is expected but is rarely severe when IMRT is used. Temporary xerostomia and dysphagia as well as diarrhea may occur.

Late effects: The goal of this study is to reduce the incidence and severity of late effects of radiation therapy by reducing the dose of external beam radiation and by treating a focal boost volume using IMRT. Common late effects of radiation for medulloblastoma include neurocognitive dysfunction, growth impairment, hearing loss, and endocrine dysfunction (hypothalamic/pituitary, thyroid, and gonadal). Radiation dose to the gonads may increase the risk of infertility, especially in girls. Rare but severe late effects may include secondary malignancies (approximately 5%) and necrosis of central nervous system tissue, including brainstem and spinal cord (approximately 1-2%).

11.3 Vincristine

Neuromuscular effects, peripheral neuropathy, jaw pain, abdominal pain, mucositis, nausea and vomiting, hypersensitivity, urinary retention, optic atrophy (rare), blindness (rare), constipation, loss of deep tendon reflexes, foot and wrist drop, paresthesia, alopecia, convulsion (rare). Hyponatremia (SIADH). Severe soft tissue damage if extravasated. Vincristine is very irritating and must not be given intramuscularly, subcutaneously or intrathecally. Intrathecal administration of vincristine almost always has resulted in death.

11.4 Lomustine

Myelosuppression. Anorexia, nausea and vomiting, mucosal ulceration. Alopecia. Transient liver function abnormalities. Pulmonary infiltrate and fibrosis. Decreased renal size, progressive azotemia, kidney failure.

11.5 Cisplatin

Myelosuppression. Severe nausea and vomiting. Peripheral neuropathy, seizures, and high frequency hearing loss. Abnormalities in serum creatinine and creatine clearance, renal tubular necrosis, proteinuria, hypocalcemia, hypomagnesemia. Anaphylactic hypersensitivity (tachycardia, wheezing, and hypotension). Optic neuritis, papilledema. Transient liver function abnormalities.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUT COME ASSESSMENT

The study's stopping rule (section 14.0) refers to failures. Failures are defined as unequivocal tumor progression or treatment-associated death. Unequivocal tumor progression may be determined via radiological studies (head or spine MRI) reviewed by the study radiologist or CSF cytology positivity reviewed by the study pathologist. If radiological studies suggest possible, but not unequivocal, progression, biopsy should be strongly considered.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study if grade 4 toxicity due to the test dose of 131-I-3F8 occurs, tumor recurs or progresses post-external beam radiation therapy, if the patient is significantly non-compliant with the treatment plan, if they withdraw consent, or in the event of death.

14.0 BIOSTATISTICS

A total of 20 patients will be enrolled on this pilot study. We have recently seen 3 to 4 patients per year potentially eligible for this study at MSKCC, but it is anticipated that the unique approach proposed in this protocol will allow accrual to be approximately 6 patients per year.

Children with standard-risk medulloblastoma have been reported to achieve 3-year progression-free survival of 86%. Of those who failed, half failed within the first 2 years of diagnosis.[2] CCG-9961 expanded the approach to a larger group of patients, but outcome data are not yet available. If they become available during the conduct of this trial, the statistical considerations described in this section will be revised if necessary.

We will stop the trial if 6 or more patients fail before 3 years. The likelihood of stopping the trial is only 7% if the true 3-yr PFS is comparable to the control data (85%), and increases to 23% if the true PFS is 75% and to 76% if the true 3-yr PFS is only 65%.

Neuropsychological test results will be reported in tabular format for each evaluation time (baseline, and annual post-treatment), using means and standard deviations or medians and ranges, as appropriate. They will be reported both as raw scores and as age/sex-adjusted "z-scores" and tracked for changes over time relative to baseline. Thus, given the relatively small sample size of 20 patients, the analysis of these scores for evidence of neurotoxicity, or lack thereof, will primarily be descriptive.

Should the results of this trial be encouraging, future possibilities would include use of this strategy on a larger scale though the Children's Oncology Group, and/or additional institutional study of further decrease of the craniospinal RT dose, possibly in conjunction with the use of an increased radioimmunotherapy dose.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 RESEARCH PARTICIPANT REGISTRATION

The following person(s) can obtain informed consent:

Oren Becher, MD
Ira Dunkel, MD
Timothy Gershon, MD, PhD
Stephen Gilheeney, MD, MMS
Yasmin Khakoo, MD
Kim Kramer, MD
David Lyden, MD
Mark Souweidane, MD
Suzanne Wolden, MD

Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

All particpants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
MSKCC IRB Protocol#	
Attending of Record (if applicable)	[Last, First Name]
Consenting Professional	[Last, First Name]
Informed Consent Date	
Participant's Full Name	[Last, First Name]
Participant MRN	

15.2 RANDOMIZATION

Not applicable.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. His or her responsibilities will include data collection, abstraction and entry into CRDB, monitoring of compliance, and data reporting.

16.1 QUALITY ASSURANCE

Registration reports will be generated by the RSA on a regular basis to monitor patient accruals and completeness of the registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates

and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period.

17.0 PROTECTION OF HUMAN SUBJECTS

Most patients on this study will be children, adolescents, and young adults, due to the nature of this tumor type. Patients of both sexes and all ethnic backgrounds are eligible for the study. Participation will be voluntary. Potential benefits include comparable event-free survival with hypothesized decreased risk of long-term side effects (neuropsychological, neuroendocrine, audiometric, growth). Alternatives include external beam radiation therapy alone (3600 cGy craniospinal with posterior fossa boost) or reduced-dose radiation therapy (2340 craniospinal with posterior fossa boost) with the same chemotherapy that will be prescribed in this study.

Patients are responsible for all costs of their care including (but not limited to) physician visits, hospitalizations, medications (except for the 3F8 antibody), MRI scans, and laboratory work (except for dosimetry studies).

Patient confidentiality will be protected, but records may be reviewed by appropriate staff of the Memorial Sloan-Kettering Cancer Center or the Food and Drug Administration (FDA).

17.1 Privacy

It is the responsibility of the Research Staff to ensure that Memorial Sloan-Kettering Cancer Center has on file a written acknowledgment of receipt by the subject of the Center's Notice of Privacy Practices. If the subject has not already done so, he/she must sign such an acknowledgment before participating in this study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number

- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. The report will be forwarded to the FDA by the Institutional SAE Manager through the IND Office.

18.0 INFORMED CONSENT PROCEDURES

All patients (or for unemancipated minors, their parents or guardians) will be required to sign an IRB-approved form documenting informed consent. The consent form is included as an appendix to this protocol. It is written in layman's language and includes

The nature and purpose of this study, its objectives and possible benefits

The length of the study and follow-up required

Risks or discomforts involved

Alternatives to the proposed study

The names of the investigators responsible for the study

The patient's rights to refuse participation and to withdraw from the study

A statement that the patient's confidentiality will be maintained

18.1 Research authorization

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate signature from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

19.0 REFERENCES

1. Thomas PRM, Deutsch M, Kepner JL, et al. Low-stage medulloblastoma: final analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. J Clin Oncol 2000; 18:3004-3011.

2. Packer RJ, Goldwein J, Nicholson HS, et al. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group study. J Clin Oncol 1999; 17:2127-2136.

3. Goldwein JW, Radcliffe J, Johnson J, et al. Updated results of a pilot study of low dose craniospinal irradiation plus chemotherapy for children under five with cerebellar primitive neuroectodermal tumors (medulloblastoma). Int J Radiat Oncol Biol Phys 1996; 34:899-904.

4. Mulhern RK, Kepner JL, Thomas PR, et al. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. J Clin Oncol 1998; 16:1723-1728.

5. Clayton PE, Shalet SM. Dose dependency of time of onset of radiation-induced growth hormone deficiency. J Pediatr 1991; 118:226-228.

6. Oberfield SE, Sklar C, Allen J, et al. Thyroid and gonadal function and growth of long-term survivors of medulloblastoma/PNET. In: Green DM, D'Angio GJ, editors. Late Effects of Treatment for Childhood Cancer. New York: Wiley-Liss, 1992:55-62.

7. Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Radiat Oncol Biol Phys 1995; 31:1113-1121.

8. Chin D, Sklar C, Donahue B, et al. Thyroid dysfunction as a late effect in survivors of pediatric medulloblastoma/primitive neuroectodermal tumors. Cancer 1997; 80:798-804.

9. Shalet SM, Gibson B, Swindell R, Pearson D. Effect of spinal irradiation on growth. Arch Dis Child 1987; 62:461-464.

10. Sklar C, Mertens A, Walter A, et al. Final height after treatment for childhood acute lymphoblastic leukemia: comparison of no cranial irradiation with 1800 and 2400 centigrays of cranial irradiation. J Pediatr 1993; 123:59-64.

11. Silber JH, Radcliffe J, Peckham V, et al. Whole-brain irradiation and decline in intelligence: the influence of dose and age on IQ score. J Clin Oncol 1992; 10:1390-1396.

12. Yeh SD, Larson SM, Burch L, et al. Radioimmunodetection of neuroblastoma with iodine-131-3F8: correlation with biopsy, iodine-131-metaiodobenzylguanidine and standard diagnostic modalities. J Nucl Med 1991; 32:769-776.

13. Cheung NKV, Kushner BH, Cheung IY, et al. Anti-G(D2) antibody treatment of minimal residual stage 4 neuroblastoma diagnosed at more than 1 year of age. J Clin Oncol 1998; 16:3053-3060.

14. Bergman I, Pohl CR, Venkataramanan R, et al. Intrathecal administration of an anti-ganglioside antibody results in specific accumulation within meningeal neoplastic xenografts in nude rats. J Immunotherapy 1999; 22:114-123.

15. Kramer K, Cheung NK, Humm J, et al. Pharmacokinetics and acute toxicology of intraventricular 131 I-monoclonal antibody targeting disialoganglioside in non-human primates. J Neurooncol 1997; 35:101-111. Update with unpublished data.

16. Kramer K, Cheung NKV, Humm JL, et al. Targeted radioimmunotherapy for leptomeningeal cancer using 131-I-3F8. Med Pediatr Oncol 2000; 35:716-718, updated with unpublished data

17. Sandberg DI, Bilsky MH, Souweidane MM, Bzdil J, Gutin PH. Ommaya reservoirs for the treatment of leptomeningeal metastases. Neurosurgery 2000; 47:49-54.

18. Huang E, Teh BS, Strother DR, et al. Intensity-modulated radiation therapy for pediatric medulloblastoma: early report on the reduction of ototoxicity. Int J Radiat Oncol Biol Phys 2002; 52:599-605.

20.0 APPENDICES

Appendix A: Model order sheet for Day 0 chemotherapy

Appendix B: Summary of timing of required observations