Title: Phase II study of intrathecal ^{131}I-3F8 in patients with GD2-expressing central nervous system and leptomeningeal neoplasms

Therapeutic /Diagnostic Protocol

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1.0 Protocol Summary and/or Schema

This study is designed to test the efficacy and the cumulative toxicity of intrathecal (administered through Ommaya reservoir) ^{131}I-3F8 in children and adult patients with GD2-expressing central nervous system/leptomeningeal neoplasms. Survival is extremely poor in these patients, with median survival of only a few months. In a prior phase I trial, 2 of 13 patients had negative remain alive and in complete remission after 4 years. Patients in this protocol will receive intrathecal ^{131}I-3F8 weekly for a total of four treatment cycles. About 130 patients will be accrued on this study. The primary endpoint is overall survival at six months.

2.1 Objectives and Scientific Aims

- To determine whether, in patients with GD2-expressing central nervous system/leptomeningeal neoplasms, the activity of intrathecal ^{131}I-3F8 is sufficiently promising to warrant further study. Promising activity is defined as a 6 month overall survival rate of 25% or more.

- To determine the response rate to ^{131}I-3F8 in this population.

- To determine the cumulative toxicities of serial injections of intrathecal ^{131}I-3F8.

- To describe the effects of HAMA (human-anti-mouse antibody) on cerebrospinal fluid (CSF) and serum pharmacokinetics following multiple injections of ^{131}I-3F8

3.1 Background and Rationale

3.2 Disease background

With the central nervous system as a sanctuary site, it is increasingly recognized that improved treatment of systemic cancers is associated with a higher incidence of central nervous system relapse and neoplastic meningitis[1-3]. By the time neuraxis metastases are clinically evident, limited palliative options exist; median survival time for most malignancies is 4-14 months[2,4,5]. Stereotactic radiosurgery for small, single metastases (<4cm diameter), surgery for solitary metastases and radiotherapy are used for palliation. New techniques including preoperative functional imaging, image-guided neurosurgery, intraoperative ultrasound and cortical mapping have improved the success of aggressive surgical resection, and lowered the associated surgical morbidity and mortality[6,7]. However, novel therapeutic agents that may prevent or delay the progression of disease are needed to improve overall outcome.

3.3 Rationale for targeted immunotherapy

Tumor-selective radioimmunotherapeutic strategies may have potential in inhibiting leptomeningeal tumor growth[8-10]. The systemic administration of tumor specific monoclonal antibodies has proven useful in the detection and targeted treatment of many human tumors[11,12]. GD2 expression has been demonstrated in neuroblastoma, small cell lung cancer, retinoblastoma, melanoma, high grade astrocytoma, medulloblastoma, osteosarcoma, desmoplastic small round blue cell tumor, and other sarcomas. Expression in normal human tissue is limited to nervous tissue. 3F8 is a murine IgG3 antibody against GD2. The intravenous administration of 3F8 has proven anti-tumor effects and has been incorporated into treatment strategies improving the disease-free survival for patients with metastatic neuroblastoma since 1989[13]. Acute side effects including pain and urticaria are manageable. No long-term side effects have been observed over a 15 year period. 3F8 is easily labeled with 131-I, enabling sensitive and accurate imaging[14].

3.4 Results of Phase I Intraventricular 131-I-3F8

3.4.1 Dosimetry

We studied the radiation dose to the CSF following intraventricular injection of ^{131}I-3F8 in patients diagnosed with GD2-positive LM disease, compared radiation dose estimates by CSF sampling and ROI (regions of interest) analyses, and monitored acute and chronic toxicities following drug administration in a phase I study. Fifteen patients (ages 1-61) received a tracer dose (37-74 MBq, 1-2 mCi) and a second therapeutic injection (370-740 MBq, 10-20 mCi). Dosimetry was evaluated by whole-body gamma camera scanning (4, 24, 48 hours), serial CSF and blood sampling. Pre- and post- treatment clinical, radiographic and cytologic status were evaluated. Total absorbed dose to the CSF was 1.12 – 13.0 Gy, 3.2 – 41.5 Gy to the ventricles and 1.0 – 13.7 Gy to the spinal column. Clearance half-life was 12.5 hr (3.5 - 44 hr). Average ratio of the therapy/tracer administration (Gy/MBq), was 0.88 (±0.58) and 1.08 (±0.66) by CSF counting and ROI analysis, respectively.

Patient	Tumor Type	Activity (mCi) administered	Dose to Blood	Dose to CSF	Dose ratio: CSF:Blood

			(c Gy)	(c Gy)	
#1	melanoma	11.5	26	472	18
#2	ependymoma	9.5	14	141	10
#3	rhabdoid	9.7	15	114	7.6
#4	retinoblastoma	1.1	1	62	44
#5	rhabdoid	10.4	19	771	40
#6	PNET	11.5	12	610	50
#7	medulloblastoma	14.3	28	319	11.4
#8	medulloblastoma	14.3	87	338	4
#9	neuroblastoma	22.6	38	362	9.5
#10	medulloblastoma	10.7	35	441	12.6
#11	neuroblastoma	22.2	30	1301	44
#12	medulloblastoma	21.4	33	315	9.5
#13	PNET	19.7	10	396	38
#14	neuroblastoma	21.8	112	908	8.1
#15	ependymoma	20.1	98	1338	13.6

3.4.2 Pharmacokinetics

Peak CSF radioactivity was generally achieved within the first hour of injection. After an initial antibody redistribution phase within the CSF compartment, the CSF biological half-life was 3-12.9 hours by direct CSF samples, and was in close agreement with the CSF gamma camera estimates derived from region of interest data (7.2-13.1 hours). The average radiation dose to the blood was 0.48 Gy (0.14-1.3). Activity levels in the blood remained low (<0.01% injected dose/cc), peaking 12-48 hours. The activity in the CSF fell much more rapidly than the physical half-life of 8 days; the concentration of the activity (uCi/cc) dropped by two orders of magnitude within 2-3 days after administration. The dose contribution for the time interval 72 hours to infinity was less than 10 %.

3.3.3 Acute toxicities

No toxic deaths were associated with treatment. Acute toxicity including headache, fever, vomiting were self-limited are generally observed in the first 24-48 hours after therapy. At the higher dose levels, transient elevations in intracranial pressure (n=1), asymptomatic bradycardia (n=1) and chemical meningitis (n=1) were seen. All symptoms resolved within the first 2-7 days post therapy. No long term toxicities have been seen 19 months post-injection.

Patient	Tumor Type	Total Dose 131-I-	Acute Toxicity*†

		3F8 Administered	
#1	melanoma	11.5	h/n/v/f after dose 1; exacerbation of pre-existing communicating hydrocephalus after dose 2
#2	ependymoma	9.5	h/n/v/f
#3	rhabdoid	9.7	h/n/v/f
#4	retinoblastoma	1.1	Gr 2 h- exacerbation of pre-existing communicating hydrocephalus
#5	rhabdoid	10.4	v/h
#6	PNET	11.5	h/n/v/f
#7	medulloblastoma	14.3	h/n/v/f, leg pain
#8	medulloblastoma	14.1	h/n/v/f
#9	neuroblastoma	22.6	h/n/v/f
#10	medulloblastoma	10.7	h/v, bone pain
#11	neuroblastoma	22.2	Gr 4 h/n/v/f, back pain, hyponatremia
#12	medulloblastoma	21.4	h
#13	PNET	19.7	Grade 3 h-exacerbation of pre-existing headache and leg pain/n/v/f, bradycardia
#14	neuroblastoma	21.8	h/f
#15	ependymoma	20.1	Gr 3 h/n/v/f, chemical meningitis

*toxicities were grade 1 or 2 unless otherwise indicated.
†h=headache, n=nausea, v=vomiting, f=fever

3.3.4 Response

Although not the primary objective of this study, of 13 evaluable patients, clinical improvement (n=2, patient #1, patient #6), radiographic improvement (n=2, patient #1, patient #13), and cytology clearing of malignant cells (n=2 patient #11, patient # 13) was observed.

Patient #11 cleared CSF of malignant cells after therapy administration, but was observed to have a new spinal metastasis 1 month after treatment. She is alive with disease now 19 months since treatment.

Patient #14 cleared the CSF of malignant cells immediately after injection and has remained off further therapy with negative CSF cytology by Ommaya and lumbar puncture sampling on multiple samplings over a 14 month period; resolution of 3 areas of enhancement on MR imaging was also noted. Patient #14 had an isolated CNS relapse of neuroblastoma. He was treated with surgery, chemotherapy, cranio-spinal radiation therapy, intraventricular 131-I-3F8 and intravenous 3F8. He remains in complete remission now 28 months since relapse and >1.5 years post-^{131}I-3F8.

Although all patients had CSF flow throughout the subarachnoid space, variability in CSF flow dynamics were noted on baseline Indium –DTPA studies. Such variability may be attributed to prior therapies, the presence of bulk and microscopic disease, or the presence of an indwelling shunt all affecting CSF flow and reabsorption. This may in part account for the interpatient variability in CSF dosimetry and clearance is this diverse patient population. Although no patient in this study had measurable serum human-anti-mouse antibody (HAMA) titers at the time of treatment, this would contribute to faster clearance in the systemic circulation and decreased dose to the blood. Previous experiments have shown that, because of the blood-brain barrier, systemic production of HAMA is associated with low titers in the CSF, namely a 14-22 fold difference of HAMA in the CSF versus the blood. In the presence of systemic HAMA, serial injections of intrathecal ^{131}I-3F8are expected to deliver comparable doses of radiation to the CSF space, but with even more rapid systemic clearance. This observation is critical since myelosuppression has been the dose-limiting toxicity of most radioimmunotherapy trials to date.

We concluded from the phase I study that intraventricular administration of ^{131}I-3F8 targeting disialoganglioside GD2 achieves a favorable CSF to blood ratio, is associated with significant but manageable acute toxicities, and may have clinical utility in the treatment of some patients with GD2-positive LM cancers.

There are few other therapeutic options to offer this patient population. This study fills an unmet need at this institution for both pediatric and adult patients and capitalizes on Memorial Sloan-Kettering‟s Cancer Center‟s unique contribution to the field of targeted immunotherapy.

3.4 **Preliminary Results of phase II study: initial cohort of patients**

8 of 10 patients treated with 4 injections of ^{131}I-3F8 as a consolidative therapy following various chemotherapy or external beam radiotherapy doses remain alive and in cytologic and radiographic remission (3 mo+, 8 mo+, 10 mo+, 12 mo+, 12 mo+, 12 mo+, 18 mo+, 22 mo+). 3 of these patients had CNS neuroblastoma, and remain alive and in remission 11 mo, 15 mo and 24 mo since detection of CNS disease. This is significant in that the median time to death from the onset of CNS disease was 5.4 months in our previously published non-intra-Ommaya therapy experience. 3 patients with active disease progression at the time of study enrollment all had radiographic progression of disease after 1 injection. Toxicities included self-limited headache, fever, and vomiting generally resolved within 24-48 hours. No late toxicities have been seen in the 5 patients who remain in remission off therapy for $\geq$1 year since ^{131}I-3F8 injections. Accrual is ongoing. These results support the need to continue this study in a larger cohort of patients, with the goal of decreasing the time between injections and further decreasing the toxicity profile by increasing the specific activity.

4.1 Overview of Study/Design Intervention

4.2 Design

This is a phase II single-arm open-label study that will define responses to therapy with weekly intrathecal ^{131}I-3F8 in patients with central nervous system/leptomeningeal GD2-expressing disease. Dosimetry at plaques of disease and surrounding normal tissues will be determined by a pre-treatment ^{131}I-3F8 (2 mCi) scintigraphy. Pharmacokinetics of the dosimetry

dose of intrathecal ^{131}I-3F8 will be determined by measurements of counts per minute (cpm) of serial CSF and serum samples.

Patients will then receive intrathecal ^{131}I-3F8 treatment cycle (10 mCi/cycle) approximately weekly for a total of 4 cycles. A total dose of 40 mCi ^{131}I-3F8 will be administered. Since the phase I study demonstrated a CSF dose of 15-60 cGy/mCi to the CSF, maximum total anticipated CSF dose of 4 x 10 mCi of ^{131}I-3F8 injections would be 600-2400 cGy; dose to the spinal cord and normal brain is negligible given the short range path length of ^{131}I. At an estimated tumor to CSF dose ratio of 5:1, tumor dose could be as high as 3000-12000 cGy. Myelosuppression is not anticipated at this dose level. The chosen 40 mCi maximum ^{131}I dose is considerably lower than the MTD reported using other intrathecal ^{131}I-monoclonal antibodies for neoplastic meningitis on other phase I studies.[10] To avoid the risk of radiation toxicity in patients who have had previous craniospinal radiation, the CSF radiation dose delivered by ^{131}I-3F8 therapy injections will not exceed 2400 cGy based on the CSF dosimetry estimates from pre-treatment ^{131}I-3F8 / scintigraphy scans. This may require the elimination and/or dose reduction of the 3rd or 4th injection for patients who have had previous craniospinal radiation. There will be no dose modifications for patients who have not had craniospinal radiation. Response to therapy will be assessed by neurologic examination, radiographic imaging and CSF cytology analysis. Other aims will be met by monitoring patients clinically and biochemically for toxicity and by serum assessment of HAMA.

It is quite possible that ^{131}I-3F8 may lead to disease stabilization without complete or partial responses in this population with advanced disease. We therefore propose overall survival at six months as the primary endpoint of this study. Leptomeningeal disease is rapidly fatal. Though some prior studies have reported survival at six months of around 15% these included patients receiving chemotherapy. Patients receiving ^{131}I-3F8 at MSKCC have completed all chemotherapy and are not anticipated to have further oncologic treatment after progressing on this protocol. If ^{131}I-3F8 has zero effect, we would therefore expect no more than 5% of patients to survive for six months. We will therefore use 5% overall survival at six months as the null hypothesis with 25% overall survival at six months as the alternative hypothesis.

Roadmap for the imaging dose of ^{131}I-3F8

Day -5:	Start SSKI and Liothyronine orally
Day -1:	Start Dexamethasone (start ~24 hrs pre-injection and tapered over ~1-2 days) orally
Day 0:	Injection of ^{131}I-3F8 (2 mCi) intrathecally or by Ommaya

Roadmap for each weekly treatment cycle of ^{131}I-3F8

Day -5:	Start SSKI and Liothyronine orally
Day -1:	Start Dexamethasone (start ~24 hrs pre-injection and tapered over ~1-2 days) orally
Day 0:	Injection of ^{131}I-3F8 (10mCi) intrathecally or by Ommaya

* Dose adjustments for age <3 years based on CSF volume:

< 1year: 50% dose reduction/injection

1-3 years: 33% dose reduction/injection

>3 years: Full dose 10 mCi ^{131}I-3F8 per injection

* Dose adjustments for patients with previous craniospinal radiation: The total maximum target CSF dose will be 2400 Gy. This may require a decrease or elimination of the 4th injection to prevent the risk of radiation toxicity for these patients. No dose adjustment will be made for patients who have not received prior craniospinal radiation.

4.3 Intervention

Patients will receive 10mCi intrathecal ^{131}I-3F8 per week. Patients will be pre-medicated with dexamethasone to prevent possible meningeal inflammatory reaction, Liothyronine and SSKI to prevent thyroid accumulation, and acetaminophen and diphenhydramine in anticipation of possible allergic reaction and fever.

4.2.1 Clinical Evaluation

Patients will have pre- and post-treatment clinical assessment including neurologic examination, hematology and serum chemistries, and CSF analysis. Patients without objective disease progression and without unexpected grade 4 toxicity (controllable fever, headache, nausea, vomiting not included) will be eligible for a total of 4 treatment cycles. No patient will receive more than 4 treatment cycles.

4.2.2 Response

MRI studies will be obtained at baseline and after the last injection. Stable disease may be an indicator of response, since most patients with leptomeningeal cancers (especially those with visible disease) historically die within a short time (4 weeks).

4.2.3 Dosimetry

Pharmacokinetics and dosimetry of the dosimetry dose of intrathecal ^{131}I-3F8 will be determined by measurements of counts per minute (cpm) of serial CSF and serum samples and serial scintigraphy images obtained at approximately 4, 24 and 48 hours after injection. Dosimetry estimates will be calculated by Medical Physics physicists in the Dept of Nuclear Medicine.

5.0 Therapeutic/Diagnostic Agents

5.1 131-I-3F8: IND # - BB-IND-2299

5.2 Source and pharmacology: Monoclonal antibody 3F8 is a murine IgG3 antibody. It is raised in BALB/c mice and specifically recognizes the ganglioside GD2.

5.3 Formulation and stability: 3F8 is stored as 2 mg/ml in pH 4.2 citrate phosphate buffer. Vials are stored at -80 C. 3F8 is stable at –80^{o}C, and at –20^{o}C for at least 2 years. For intrathecal administration, ^{131}I-3F8 is diluted into 5% human serum albumin and millipore (0.2 um) filtered before use. Total anticipated amount to be infused per injection is 2-10 mCi, and about 2 mg of total (cold + hot) 3F8. .

5.4 Route of administration: A volume of ~1.0-4.0 ml will be administered intraventricularly via Ommaya catheter at a rate of ~1.0ml over 3-4 minutes using sterile technique. .

5.5 Supplier: 3F8 is commercially prepared by GBI as an investigational agent under cGMP conditions as required by the US FDA, and purified by column chromatography. All lots have to pass sterility, safety, pyrogen, murine viruses, and DNA testing before human use. ^{131}I-3F8 is prepared by the Radiochemistry and Molecular Imaging Probes Core Facility under the direction of Dr. Jason Lewis. It is approved for human use via IND BB-IND-2299. Radiolabeling is performed either on the day of patient infusion or one day prior. Administration to patients occurs within 24 hours of the end-of-synthesis time..

6.0 Criteria for Subject Eligibility

6.1 Patient/subject Inclusion Criteria

6.1.1 Patients must have a histologically confirmed diagnosis of a malignancy known to express G_{D2}. Such tumors include medulloblastoma/primitive neuroectodermal tumor of the CNS, high grade astrocytomas, malignant glioma, neuroblastoma, retinoblastoma, ependymoma, rhabdoid tumors, sarcomas, melanoma or small cell lung carcinoma. For patients with other tumor types, GD2 expression must be confirmed by immunohistochemical staining and assessed by the Department of Pathology using prior frozen tissue, bone marrow or CSF cytology (send to Research Lab).

6.1.2 Patients must have CNS/ leptomeningeal disease including high risk medulloblastoma, or a CNS/leptomeningeal malignancy which is refractory to conventional therapies, or for which no conventional therapy exists, OR a recurrent brain tumors with a predilection for leptomeningeal dissemination (medulloblastoma, PNET, rhabdoid tumor).

6.1.3 Patients must have an absolute neutrophil count (ANC) > 1000/ul and a platelet count > 50,000/ul.

6.1.4 Patients may have active malignancy outside the central nervous system.

6.1.5 Patients who have a programmable shunt will not be excluded.

6.1.6 Both pediatric and adult patients of any age are eligible.

6.1.7 Patients or a legal guardian will sign an informed consent form approved by the IRB and obtained by the Principal or a Co- Investigator before patient entry. Minors will provide assent.

6.2 Patient /Subject Exclusion Criteria

6.2.1 Patients with obstructive or symptomatic communicating hydrocephalus.

6.2.2 Patients with an uncontrolled life-threatening infection.

6.2.3 Patients who are pregnant: Pregnant women are excluded for fear of danger to the fetus. Therefore negative pregnancy test is required for all women of child-bearing age, and appropriate contraception is required during the study period.

6.2.4 Patients who have received cranial or spinal irradiation less than 3 weeks prior to the start of this protocol.

6.2.5 Patients who have received systemic chemotherapy (corticosteroids not included) less than 3 weeks prior to the start of this protocol.

6.2.6 Severe major organ toxicity. Specifically, renal, cardiac, hepatic, pulmonary, and gastrointestinal system toxicity should all be less than or equal to grade 2. Patients with stable neurological deficits (because of their brain tumor) are not excluded. Patients with <= 3 hearing loss are not excluded.

6.2.7 Patients must have no rapidly progressing or deteriorating neurologic examination.

6.2.8 Patients who have already received >45 Gy to the craniospinal radiation or >72 Gy focal brain radiation.

7.0 Recruitment Plan

Patients will be offered the opportunity to participate in this trial if they have the diagnosis of a CNS/leptomeningeal solid tumor (including neuroblastoma, small cell lung cancer, melanoma, retinoblastoma, high grade astrocytoma, medulloblastoma, central nervous system PNET, malignant glioma ependymoma, rhabdoid tumors, osteosarcoma, DSRCT and other tumors that are GD2-positive) and fulfilled the eligibility criteria. The opportunity to participate will be offered to all patients, including women and minority groups. Informed consent will be obtained from the patients or their legal guardians by an investigator authorized to obtain consent. Patient will not receive any payment for their participation in this study.

8.0 Pretreatment Evaluation

8.1 Complete history, physical exam, and detailed neurologic exam.

8.2 CBC with differential and platelet count.

8.3 Serum electrolytes, creatinine, AST, total bilirubin, TSH, HAMA, and in child-bearing females, beta-HCG.

8.4 CSF cytology, total protein, glucose and cell count (these are baseline routine, not for research purposes), HAMA.

8.5 Baseline MRI of the brain and spine (with and without gadolinium) within 3 weeks of the first injection.

8.6 ^{111}Indium Ommaya patency/CSF flow study prior to the first injection.

9.0 Treatment/Intervention Plan

9.1 General outline: Following an initial test dose of 2 mCi ^{131}I-3F8 for dosimetry, four weekly injections 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. Patients can be treated in an outpatient setting or may be hospitalized overnight for supportive care after each injection. All patients will be monitored in accordance with Radiation Safety Guidelines. Patients are not anticipated to need isolation post-treatment.

9.2 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 5 days prior to the test dose with ^{131}I-3F8:

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

Liothyronine (Liothyronine): 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 after the last injection)

To start 1-2 days prior to each 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 week)

To be started about 1 to 2 hours before each injection:

Hydroxyzine (Vistaril): 1 mg/kg IV, then Q 4 hours x 24 hours post-injection (maximum 50 mg).

Acetaminophen (Tylenol): 10 mg/kg po before injection and then Q4 hours x 24 hours post-injection (maximum 325 mg)

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

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

9.2.1 Intraventricular administration of all drugs

The antibody 3F8 is radiolabeled with iodogen method under the supervision of Dr. S Larson and J Lewis according to the FDA requirements specified by the IND. All patients will have an intraventricular reservoir (i.e. Ommaya reservoir). The Ommaya catheter site will be prepped and draped. A volume of CSF equal to the volume of drug to be injected will be removed, the drug will be injected slowly so as not to exceed a rate of 1ml/min. Sterile HSA will be flushed into the reservoir followed by autologous CSF flush. After ^{131}I-3F8 dosimetry injections, patients will have approximately 0.5 cc CSF and 1-2 cc blood obtained for radioactivity levels at approximately, 1 hr, 2 hr, 4-6 hr, 18-24 hr, 44-48 hr, 66-72 hr and ~5-7 days post injection.

9.3 Treatment and dosimetry

9.3.1 * Dose adjustments for age <3 years based on CSF volume:

< 1year: 50% dose reduction

1-3 years: 33% dose reduction

>3 years: Full dose, 10 mCi ^{131}I-3F8 per injection

+averaging approximately 5 mCi of radioiodine/mg 3F8

*** Dose adjustments for patients with prior craniospinal radiation:**

The total maximum target CSF dose by ^{131}I-3F8 injections will be 2400 Gy for patients with prior craniospinal radiation based on ^{131}I-3F8/ scintigraphy dosimetry estimates. This may require a decrease or elimination of the 3rd or 4th injection to prevent the risk of radiation toxicity for these patients.

9.3.2 Dosimetry will be assessed by

*CSF and blood (2 ml/sample) obtained for radioactivity levels at approximately, and 1, 2, 4, 18, and 44 hours after ^{131}I-3F8 dosimetry injection. (CSF samples obtained here are for research purposes). At the time of ^{131}I-3F8 scintigraphy analysis, routine dosimetry estimations will be derived from the serial scintigraphy studies at approximately 4, 24, and 48 hours. Pharmacokinetic data obtained from scintigraphy 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, CSF space, blood and visible tumor nodules.

9.4 Tumor genetic studies

9.4.1 Tumor DNA and matched normal DNA will be used for genomic DNA sequencing, copy number analysis and methylation profiling; tumor RNA will be used for transcriptome and microRNA profiling. The samples will not have any associated patient-specific identifying information, but will be linked to clinical information such as patient age, gender, tumor stage, tumor recurrence status, and tumor site. The identity of individual patients will be kept in a secure database registered with the Office of Clinical Research, under the supervision of Dr. Modak according to HIPAA regulations. This testing will be done in Dr. Cheung"s Lab (Z740). These tests will be done only on the tumor left over after testing for 3F8 binding.

9.4.2 Immunohistochemical profile: Frozen tumors will collected to be tested for tissue antigens and gangliosides [including but not limited to GM2, GD2, GD3]. These tests will only be done on patients whose tumors are not known to bind to 3F8, and therefore are consented to the assessment arm of the protocol.

10.0 Evaluation During Treatment/Intervention

10.1 Evaluation during treatment

10.1.1. Physical exam prior to each injection and after the 4th injection

10.1.2. Neurologic exam prior to each injection and after the 4th injection

10.1.3. MRI of head and spine at baseline and after 4th injection
10.1.4. CSF Flow study prior to the first injection
10.1.5. CBC with differential including platelets prior to each injection and ~1-3 months after 4th injection
10.1.6. Comprehensive profile to each injection and ~1-3 months after 4th injection. *Thyroid protection such as SSKI and Cytomel will be adjusted to ensure adequate thyroid saturation. Serum HAMA (send to Dr. Cheung Laboratory) prior to each injection .
10.1.7. B-HCG for females of child-bearing age prior to injections 1 and 3.
10.1.8. CSF and Blood (2 ml each sample) at ~1-4 hr, 18-24 hours, and 42-48 hours after the ^{131}I-3F8 dosimetry injection

Observation	Prior to test dose with ^{131}I-3F8	Post test dose with ^{131}I-3F8	Prior to 1st injection	Post 1st ^{131}I-3F8 Injection	Prior to 2nd ^{131}I-3F8 injection	Post 2nd injection	Prior to 3rd ^{131}I-3F8 injection	Post 3rd injection	Prior to 4th ^{131}I-3F8 injection	Follow-up, 1-3 months after 4th injection
Physical examination	X		X		X		X		X	X
Neurologic examination	X		X		X		X		X	X
MRI head	X									X
MRI spine	X									X
CSF flow study	X									
CBC w/diff, plts	X		X		X		X		X	X
Comprehensive profile	X		X		X		X		X	X
CSF cytology	X									X
Serum HAMA	X		X		X		X		X	
B-HCG (when applicable)	X						X			
Scintigraphy imaging ^{131}I-3F8		X								
CSF and Blood (2ml/sample) ^{131}I-3F8	X									

10.3 Pharmacokinetic Studies

Study of the intrathecal pharmacokinetics and blood pharmacokinetics of the ^{131}I-3F8 dosimetry dose will be performed. Patients will have approximately 0.5cc of CSF obtained pre-injection, 1 hr, 2 hr, 4-6 hr, 18-24 hr, and 42-48 hr post injection. Blood samples (2 cc of plasma) will be obtained at the time of CSF sampling, and may be obtained via a central venous catheter (if present) or an indwelling heparin lock venous catheter. Additional samples may be collected if needed to adequately characterize pharmacokinetics. Radioactivity will be counted in a gamma counter. The count information will be used for pharmacokinetic data.

10.4 Scintigraphy

Patients will have the CNS (head and upper spinal cord) imaged by ^{131}I-3F8 scintigraphy approximately 4, 24, 48 hours.

10.5 Concomitant Therapy:

Patients may receive systemic chemotherapy starting 3 weeks from the second injection of ^{131}I-3F8. Patients must wait at least 3 weeks before they can resume injection 3 or 4. This will allow assessment of response while avoiding widespread progression of systemic disease.

11.0 Toxicities/Side Effects

11.1 Toxicities will be assessed via the NCI toxicity criteria (CTC 3.0). All toxicities will be recorded in CRDB until 30 days after the last dose of 131-I-3F8.

11.2 Toxicities associated with ^{131}I-3F8 include fever, headache, nausea and vomiting, pain allergic reaction, and/or drug extravasation. Hospitalizations for therapy administration, hyperglycemia or lymphopenia related to dexamethasone and self-limited fever, vomiting, or headache will not be considered serious adverse events (SAE) and will not be reported to the IRB or FDA though they will be captured in the institutional database. However, life-threatening infections or other life-threatening side effects will be considered SAE's and will be promptly reported to the Institutional Review Board of MSKCC and to the FDA.

11.3 Neurologic changes during the study period which meet the criteria for grade 4 neurotoxicity will be assessed by study physicians as being unrelated, possibly or probably caused by the injection. In the absence of clear evidence of tumor progression, it may be assumed that new signs and symptoms are treatment related.

11.4 Any deaths will be reviewed during the study by the Principal Investigators prior to subsequent entry of further patients.

12.0 Criteria for Therapeutic Response/Outcome Assessment

12.1 Adequacy of trial: All patients who fulfill the eligibility requirements, receive two treatment injections of ^{131}I-3F8 and undergo extent of disease evaluation will have an adequate trial.

12.2 The primary endpoint is overall survival at six months from the date of 1st ^{131}I-3F8 injection.

12.3 Response duration is calculated from the 1st day of treatment with ^{131}I-3F8.

12.4 Patients developing progressive disease will be considered a treatment failure under this protocol.

12.5 Response Definitions

12.5.1 Complete Response (CR)

Cytologic and radiographic CR will be evaluated separately, since patients with cytologic clearing and clinical response may continue to have residual abnormalities on MRI scans. Patients with a CR must also have stable or improved neurologic exam.

- Cytologic CR
  Complete clearing of all malignant cells from lumbar and ventricular CSF based on cytospin preparation in leukemia/lymphoma patients and cytology in solid tumor patients. A cytologic CR must be documented by two negative cytologies on two consecutive occasions at least 4 weeks apart (with no interval positive cytologies).

- Radiographic CR
  In patients with evidence of disease on MRI scan, complete clearing of MRI scan evidence of disease on 2 consecutive scans at least 4 weeks apart will be required.

12.5.2 Stable Disease (SD)
Exists when a patient fails to fulfill the criteria for either complete or partial response or progressive disease.

12.5.3 Progressive Disease (PD)
An increase of at least 50% in the absolute number of malignant cells in the CSF OR, in -solid tumor patients, an increase of greater than 25% in the size of measurable lesions on MR scan OR the recurrence of malignant cells in the CSF or new lesions on MR after a patient has attained a complete remission OR evidence of clinical neurologic progression. New sites of or increasing evidence of leptomeningeal enhancement that is not "measurable" will also be considered evidence of disease progression.

13.0 Criteria For Removal From Study

13.1 If at any time the patient develops grade 4 toxicity (other than controllable fever, vomiting, headache) attributed to the study drugs, he/she will be removed from study and receive no further injections.

13.2 If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

13.3 If at time disease progression is observed, the patient will be removed from the study.

13.4 If the patient experiences adverse events, including unacceptable toxicity or exacerbation of underlying disease associated with drug administration and necessitating discontinuation of treatment, he/she will come off the study. Patents who are removed from the study due to adverse events will be treated and followed according to established medical practice. All pertinent information concerning the outcome of such treatment will be entered in the Case Report Form or the Serious Event Report, as applicable.

13.5 Withdrawal of consent: The patient"s desire to withdraw from the study may occur at any time.

13.6 Noncompliance: If at any time the patient is non-compliant with therapy, radiation safety guidelines or requests withdrawal from the study, he/she will be removed.

13.7 Pregnancy: The patient will be removed from study if they are found to be pregnant.

14.0 Biostatistics

This is a phase II study to assess the clinical efficacy of weekly intrathecal ^{131}I-3F8 for a new cohort of 17 patients with GD2-expressing central nervous system and leptomeningeal neoplasms. A "response" is defined as a patient being alive six months after their first treatment. We will test hypothesis that the proportion of responses is 25% or more against a null hypothesis that proportion of responses is 5% or less, with a power of 80% and an alpha of 5%. Using a Simon two-stage optimal design, nine patients will initially be accrued. If at least one responds, then a further 8 patients will be entered on study. If the total number of responses is three or more, the agent will be declared active. Under this design, the probability of declaring the agent inactive at the end of the first stage (0 / 9 responses) is 0.63 if the true response rate is 0.05. This probability decreases to 0.08 if the true response rate is 0.25, The probability of declaring the agent active (3 or more responses / 17) is 0.05 and 0.8 if the true response rate is 0.05 or 0.25, respectively. It is expected that 4-6 patients/yr will be enrolled and that this study can be completed within 2-3 years.

	Reject null hypothesis if:	Reject alternative hypothesis if:
First stage	-	0 / 9 responses
Second stage	≥3 / 17 responses	≤2 / 17 responses

The number of CRs, PRs, SDs and PDs will be reported. Toxicities will be reported by type and grade.

Three additional subgroups will be added for patients with: Medulloblastoma in CR (36 evaluable patients), Medulloblastoma with stable, but minimal disease (36 evaluable patients), and Retinoblastoma or Melanoma (18 evaluable patients). For patients with neuroblastoma or other cancers in the CNS, 18 additional evaluable patients will be added. We have completed the statistics for this agent overall which have shown efficacy on this phase II study; increasing the number of slots will allow for in depth statistical analyses within these subgroups of patients.

15.1 Research Participant Registration and Randomization Procedures

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are

responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Potential risks are outlined above. Procedures to minimize potential risks include prophylactic treatment with acetaminophen, dexamethasone, SSKI drops, liothyronine.. Procedures to minimize radiation exposure to self and others will be in accordance to Radiation Safety Guidelines.

15.3 Enrollment in this protocol is voluntary. In the event of adverse effects, standard medical intervention will be offered where appropriate.

15.4 All hospital records are confidential. The patient's name or any other personal identification will not be used in reports or publications from this study. Laboratory tests, images and X-rays, if any, may be published. The Food and Drug Administration or other authorized agencies (i.e. the National Cancer Institute) may inspect records. Data will be collected and stored in the patient's hospital chart and research file, and be monitored by the principal investigators to ensure the safety of patients.

15.5 There is no extra cost to the patient for being part of this study. If there is an injury as a result of this research study, emergency care, hospitalization and outpatient care will be made available by Memorial Hospital and billed to the patient as part of medical expenses. No money will be provided by the Hospital as compensation for a research-related injury.

15. 6 Randomization

NOT APPLICABLE

16.0 Data Management Issues

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extext and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

17.0 Protection of Human Subjects

The investigators agree to conduct this study in accordance with the International Conference of Harmonization (ICH) principles of Good Clinical Practice and with the Declaration of Helsinki (1989). The investigators will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies. Patients will be both children and adults. Patients of both sexes and all ethnic background are eligible for this study. Alternatives to this study include conventional chemotherapy, radiation therapy, or other phase I agents. Patients are responsible for the costs of physician visits and usual laboratory tests, hospitalizations and outpatient care. If there is an injury as a result of this research study, emergency care, hospitalization, and outpatient care will be made available by Memorial Hospital and billed to the patient as part of the medical expenses. No money will be provided by Memorial Hospital as compensation for research-related injury. Patient will not be billed for the antibody 3F8.

As part of standard care for this medical condition, the patient will be charged for:

*any needed hospitalization

*doctor"s care

*any other drugs besides ^{131}I-3F8 needed for treatment

*standard laboratory tests, but not pharmacokinetic studies

*standard radiographic studies

*clinic visits

17. 1 Privacy

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

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant"s last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject"s initials
- 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
- The grade of the 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
    - 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

- If the SAE is an Unanticipated Problem

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

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1 Reporting Guidelines:

- Patient Consented/registered on the assessment part only: NO SAEs will be reported
- Patient Consented/registered on the treatment part:

All SAEs will be reported to the FDA through the IND office with reference to the IND # BB-IND-2299

SAEs will be defined as grade 4 and 5 toxicities excluding: hospitalizations for therapy administration, hyperglycemia or lymphopenia related to dexamethasone and self-limited fever, vomiting, or headache will not be considered serious adverse events (SAE) and will not be reported to the IRB or FDA

18.1 Informed Consent Procedures

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 References

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