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A phase II study of radioimmunotherapy with intraventricular ^{131}I -3F8 for medulloblastoma

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Abstract

Background: High-risk and recurrent medulloblastoma (MB) is associated with significant mortality. The murine monoclonal antibody 3F8 targets the cell-surface disialoganglioside GD2 on MB. We tested the efficacy, toxicity, and dosimetry of compartmental radioimmunotherapy (cRIT) with intraventricular ^{131}I -labeled 3F8 in patients with MB on a phase II clinical trial.

Methods: Patients with histopathologically confirmed high-risk or recurrent MB were eligible for cRIT. After determining adequate cerebrospinal fluid (CSF) flow, patients received 2 mCi (where Ci is Curie) ^{124}I -3F8 or ^{131}I -3F8 with nuclear imaging for dosimetry, followed by up to four therapeutic (10 mCi/dose) ^{131}I -3F8 injections. Dosimetry estimates were based on serial CSF and blood samplings over 48 hr plus region-of-interest analyses on serial imaging scans. Disease evaluation included pre- and posttherapy brain/spine magnetic resonance imaging approximately every 3 months for the first year after treatment, and every 6–12 months thereafter.

Results: Forty-three patients received a total of 167 injections; 42 patients were evaluable for outcome. No treatment-related deaths occurred. Toxicities related to drug administration included acute bradycardia with somnolence, headache, fatigue, and CSF pleocytosis consistent with chemical meningitis and dystonic reaction. Total CSF absorbed dose was 1,453 cGy (where Gy is Gray; 350.0–2,784). Median overall survival from first dose of cRIT was 24.9 months (95% confidence interval [CI]:16.3–55.8). Patients treated in radiographic and cytologic remission were

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at a lower risk of death compared to patients with radiographically measurable disease (hazard ratio: 0.40, 95% CI: 0.18–0.88, $P = 0.024$).

Conclusions: cRIT with ^{131}I -3F8 is safe, has favorable dosimetry to CSF, and when added to salvage therapy using conventional modalities, may have clinical utility in maintaining remission in high-risk or recurrent MB.

Keywords

CNS tumors; intrathecal therapy; medulloblastoma; radioimmunotherapy; 3F8

1 | INTRODUCTION

Few curative treatment options exist for recurrent medulloblastoma (MB). Some studies support a role for high-dose chemotherapy with autologous hematopoietic cell rescue, although cure for patients with previously irradiated recurrent MB is unlikely.^{1–3} Direct intrathecal delivery of radiolabeled tumor-specific antibodies or peptides may aid in both detection and treatment of recurrent leptomeningeal disease.^{4–11}

We previously described a murine monoclonal IgG3 antibody, 3F8, that recognizes disialoganglioside GD2, a tumor antigen homogeneously distributed on the cell membrane of solid tumors of neuroectodermal origin, including MB.^{12–14} Gangliosides are cell membrane associated lipid-sugar compounds thought to influence a variety of cellular functions including those affecting tumorigenesis. 3F8 is nonreactive with most normal human tissues including bone marrow, colon, stomach, heart, lung, muscle, thyroid, testes, pancreas; expression is found on central neurons and peripheral nerves. Intravenous anti-GD2 therapy is standard of care for patients with metastatic neuroblastoma.^{15,16} 3F8 radiolabeled with I-124 and I-131 retains its immunoreactive properties.^{17,18} Improvement in overall survival (OS) has been noted with the incorporation of compartmental intraventricular radioimmunotherapy (cRIT) including ^{131}I -labeled 3F8 for patients with relapsed central nervous system neuroblastoma.¹⁹

We evaluated the efficacy, dosimetry, and toxicity of cRIT with ^{124}I - and ^{131}I -labeled 3F8 via Ommaya catheters in patients with high-risk (<3 years of age with nondesmoplastic histology and no prior radiation therapy or with refractory M3 disease) or recurrent MB/primitive neuroectodermal tumor (PNET) on a phase II clinical trial at Memorial Sloan Kettering Cancer Center (MSK) between 2006 and 2016.

2 | PATIENTS AND METHODS

Study NCT00445965 is an open study available for adult and pediatric patients with GD2-expressing CNS malignancies including MB. The primary aim of this study was to determine the OS of patients with MB following intra-Ommaya ^{131}I -3F8, to determine the response rate to ^{131}I -3F8 in this population, and secondarily, to determine the cumulative toxicities of serial injections of intra-Ommaya ^{131}I -3F8.

2.1 | 3F8 monoclonal antibody (MoAb)

MoAb 3F8 was purified at MSK. ^{124}I -3F8 and ^{131}I -3F8 radiolabeling and dose preparation were performed at the MSK Radiochemistry and Molecular Imaging Probe Core. For every patient dose, 2 mg of 3F8 were radiolabeled using the iodogen method. Every batch was quality control tested to assure conformance to the acceptance specifications detailed in an US Food and Drug Administration (FDA) acknowledged investigative new drug application. The total mass of 3F8 in both 2 mCi (where Ci is Curie) dosimetry doses and 10 mCi therapy doses was adjusted to approximately 2 mg with cold 3F8.^{12,17,18}

2.2 | Eligibility

The subject of this analysis includes all patients with a histologically confirmed diagnosis of high-risk or recurrent MB or PNET. High-risk patients were those less than 3 years of age at diagnosis with non-desmoplastic histology and no history of radiation therapy or those with refractory M+ disease following radiation and chemotherapy. Patients with high-risk disease who had residual disease after initial surgery, radiation therapy, and chemotherapy were also eligible for cRIT upfront prior to disease progression.

All other patients had recurrent MB following standard therapy. Molecular grouping by WNT, SHH, or CMYC status was generally not performed. Patients demonstrated a normal or less than grade 3 kidney and liver profile, platelets $>50,000/\mu\text{l}$ and absolute neutrophil count $>1,000/\mu\text{l}$. Prior focal or craniospinal radiation therapy was permitted, but not within 3 weeks prior to 3F8 injections. Prior radiation limits were confined to less than 72 Gy (where Gy is Gray) focal brain or 45 Gy craniospinal radiation therapy. Adequate cerebrospinal fluid (CSF) flow was confirmed by a pretreatment intra-Ommaya Indium-111 diethylenetriaminepentaacetic acid biodistribution study. Patients with obstructive or symptomatic communicating hydrocephalus were excluded. The protocol (MSK 05-122, NCT00445965) was approved by the MSK Institutional Review Board (IRB) and performed under an FDA-approved investigational new drug. Informed consent was obtained in accordance with MSK IRB policy.

2.3 | cRIT therapy

Pretreatment evaluation included a detailed history, physical examination, complete blood count, metabolic profile, liver function, and thyroid function tests. CSF from the indwelling Ommaya catheter was examined for total protein, glucose, cell count, and cytology. Patients had a magnetic resonance imaging (MRI) of the brain and spine with and without gadolinium within 3 weeks prior to the dosimetry injection. To minimize the uptake of radioiodine by the thyroid, patients were premedicated with oral saturated solution of potassium iodide drops and liothyronine starting 5–7 days prior to the first injection and continued for 2 weeks after the last injection. To prevent a possible allergic or meningitic reaction, patients received oral acetaminophen and diphenhydramine prior to each injection. Oral or intravenous dexamethasone 0.5–1 mg (twice daily for a total of six doses) was given with each injection. The dexamethasone was a flat dose (older patients or >20 kg received 1 mg). Ceftriaxone was given approximately 1 hr after each injection.

All patients received an initial dosimetry dose (2 mCi and 2 mg total MoAb) ^{124}I -3F8 or ^{131}I -3F8 in week 1, followed by a weekly 10 mCi (2 mg) ^{131}I -3F8 therapy injection up to four injections. All injections were performed with a syringe fitted with a 0.22 μm filter. In the first cohort of patients, dosimetry was assessed by Ommaya CSF and blood sampling and serial ^{124}I -3F8 PET/CT (where PET is positron emission tomography) through 48 hr; the trial was later changed to dosimetry using CSF sampling and serial ^{131}I -3F8 single-photon emission computed tomography (SPECT) through 48 hr (Figs. 1A and 1B). Toxicity was defined by the Common Terminology Criteria for Adverse Events Version 3.0. Patients had follow-up on the second and third day after the dosimetry injection, and then once per week during the therapy injection period. After completing cRIT injections, patients were evaluated via history, physical examination, serology, CSF cytology, MRI brain, and spine approximately 1 month later.

2.3.1 | Evaluation of response—Conventional MRI brain imaging included sagittal and axial T1-weighted, axial T2-weighted, axial fluid-attenuated inversion recovery (FLAIR), axial diffusion weighted images, apparent diffusion coefficient and exponential, and postcontrast T1-weighted sequences in axial, sagittal, and coronal planes. In particular, diffusion restriction, in conjunction with enhancement on postcontrast images, indicated MB as they are hypercellular and therefore diffusion restrict.

At the time of study entry, tumor size was evaluated on contrast-enhanced MRI brain and spine with gadolinium. Any patient with disease seen on contrast-enhanced MRI of the brain or spine, or with extrinsic cells in the CSF cytology obtained by ventricular sampling, was considered to have evaluable disease. Patients were considered to be in remission at the time of cRIT, if CSF cytology by ventricular testing was negative for malignant cells and if radiographically identifiable tumor was absent on comparison scans. A complete response post-therapy was defined as the absence of all identified disease utilizing MRI and/or clearance of CSF cytology. A partial response was defined at least 50% decrease in tumor size demonstrable by MRI or decrease in leptomeningeal enhancement; stable disease (SD) was defined as less than 50% decrease or no reduction in tumor size demonstrable by MRI, or tumor growth that is less than the criteria defined as progressive disease. Progressive disease was defined as the disease in previously uninvolved areas or clinical or radiological evidence of increased volume of greater than 25% in tumor area with maximum perpendicular diameters in any site of residual disease compared to immediate prestudy area, or increased leptomeningeal enhancement on MRI. Brain and spine MRI were performed approximately 1 month after the last cRIT 3F8 injection and approximately every 3 months for the first year, and every 6–12 months annually thereafter. OS and progression-free survival (PFS) were determined using the Kaplan-Meier method whereby OS was calculated from the date of diagnosis or recurrence until death or last follow-up. OS from the time of first cRIT injection until death or last follow-up was also calculated. 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 OS at 6 months as an endpoint of this study. Patients receiving ^{131}I -3F8 on this trial have typically completed standard initial and subsequent salvage chemotherapy. OS at 6 months was the primary endpoint for this study. The study contained all histologies, while the analysis presented herein includes only the

patients with MB. Therefore, no power analysis was planned in advance for this component of the study.

2.3.2 | Dosimetry—Dosimetry to the CSF in the ventricles and within the thecal sac was determined by region-of-interest analysis ^{124}I -3F8/PET imaging or ^{131}I -3F8/SPECT gamma camera imaging obtained at approximately 4, 24, and 48 hr after injection of a 2 mCi administered activity as previously described.⁴ ^{124}I -3F8/PET was the preferred tracer but both availability and expense of ^{124}I -3F8/PET precluded its regular use, where ^{131}I -3F8/SPECT was always available at a significantly reduced cost. CSF and blood dosimetry was also concurrently estimated by corresponding samples obtained at the same time points postinjection and measured aliquots were radioassayed in a scintillation well counter calibrated for ^{124}I or ^{131}I . The pharmacokinetic data obtained from PET or gamma-camera imaging and CSF sampling were combined with anatomical imaging information to estimate the absorbed dose to brain, spinal cord, and blood as previously described.^{20–22} Given the risk of radionecrosis in the setting of prior conventional craniospinal radiation therapy with cRIT was unknown, a conservative estimate for cumulative dosing was used, recognizing the general spinal cord tolerance limit is 45 Gy. To avoid the risk of radiation toxicity in patients who had prior craniospinal radiation, the administered activity (dose) was reduced to ensure that the CSF radiation dose delivered by ^{131}I -3F8 did not exceed 2,400 cGy as determined by CSF sampling and serial nuclear medicine scans. In such patients, the maximum cumulative dose allowed by cRIT therapy injections was 2,400 cGy to the CSF, thereby requiring a dose adjustment to avoid exceeding this maximum.

Patient and treatment characteristics were described using frequencies and percentage for categorical variables, and medians and ranges for continuous variables. OS was calculated from the time of first I-3F8 injection until death. Patients alive at last follow-up were censored. PFS was calculated from the time of first I-3F8 injection until progression or death. Patients alive and disease-free at last follow-up were censored. OS and PFS were graphically displayed using Kaplan-Meier plots, and median, 6-month, 1-year, and 5-year Kaplan-Meier survival estimates were provided. The relationship between OS and patient characteristics was assessed with univariate Cox proportional hazards regression. *P*-values less than 0.05 were considered statistically significant, and all analyses were performed using SAS 9.4 (The SAS Institute, Cary, NC).

3 | RESULTS

Forty-three patients with high-risk ($N = 8$) and recurrent ($N = 35$) MB received 167 injections cRIT ^{131}I -3F8 (124 therapy injections; 43 dosimetry injections). With limitations in patients who received prior craniospinal radiation therapy, 18 patients received 4 full-therapy doses as planned, 13 patients received 3, 6 patients received 2, and 6 patients received 1 full-therapy dose. One patient was removed following the dosimetry dose due to clinical and radiographic progression of disease; he did not receive any subsequent therapy injections.

In total, 42 patients were evaluable. Patient demographics are presented in Table 1. Changing stages prior to cRIT included M0 (n = 2), M2 (n = 5), M3 (n = 33), and M3/M4 (n = 2).

3.1 | Response

One patient was removed from the study because of clinical deterioration prior to ever receiving a therapy injection of ^{131}I -3F8. Of 22 patients starting cRIT with radiographically evaluable disease on MR, 20 had a CSF cytology positive for MB at some point in the course of treatment. Of these 22, MRI brain and spine remained stable in 9 patients; 1 patient had improvement/near resolution of leptomeningeal enhancement, and 12 had progression of disease, including 3 with progressing bulky disease when starting cRIT. Of the remaining 20 patients who started cRIT with no evaluable radiographic or cytologic disease, 15 remained free of disease post-cRIT; 5 had progression of disease.

3.2 | Survival

By the end of follow-up, 27 patients had died with a median OS of 24.9 months (95% confidence interval [CI]: 16.3–55.8 months). Six-month, 1-year, and 5-year OS estimates were 88.1% (95% CI: 73.7–94.9%), 78.6% (95% CI: 62.9–88.2%), and 44.9% (95% CI: 29.0–59.5%), respectively (Fig. 2A). Median PFS was 11 months (95% CI: 2.0–16.8 months); 11 patients were alive and progression-free at the end of follow-up. Six-month, 1-year, and 5-year PFS estimates were 57.1% (95% CI: 40.9–70.4%), 47.6% (95% CI: 32.1–61.6%), and 23.7% (95% CI: 11.7–38.0%), respectively (Fig. 2B).

There was one death in a long-term survivor from second malignancy, an 8-year-old male who died of secondary glioblastoma multiforme 5.5 years after initial MB diagnosis. Another 5-year-old female achieved CNS remission for 1-year postrelapse, but died of extraneural MB 1.5 years later.

Of the 15 patients alive, 12 remain well off all therapy, while 2 have received maintenance therapy including oral etoposide, oral Temodar with irinotecan, intravenous bevacizumab, and intrathecal arabinoside; one patient has been receiving therapy for extraneural metastases. Characteristics of long-term survivors can be found in Table 2.

Age (hazard ratio [HR]: 1.03, 95% CI: 0.98–1.07, $P = 0.22$) or having prior irradiation (HR: 2.00, 95% CI: 0.47–8.49, $P = 0.35$) was not significantly associated with OS. Anaplastic histology was marginally associated with OS where patients with anaplastic histology were at a higher risk of death (HR: 2.29, 95% CI: 0.96–5.46, $P = 0.06$). Status at the time of cRIT was associated with OS where patients in remission were at a lower risk of death compared to patients with radiographically measurable disease (HR: 0.39, 95% CI: 0.18–0.88, $P = 0.024$). No association was found between CSF dose and OS (HR: 1.00, 95% CI: 1.00–1.01, $P = 0.29$).

3.3 | Acute side effects of cRIT ^{131}I -3F8

A secondary aim of this study was assessment of acute and long-term toxicities. cRIT 3F8 was routinely administered in the outpatient setting, with supportive care provided

throughout the day of each injection. Patients were treated awake at the bedside. There were no treatment-related deaths during the injection period or postinjection observation period. Adverse events were self-limited, occurring in the first several hours after injection, and most commonly after the first (dosimetry) injection. This injection was commonly associated with grade 2 or 3 fever, headache, nausea, and vomiting; symptoms were less commonly observed with subsequent injections. In addition to these anticipated toxicities, other unexpected grade 3 but reversible adverse events possibly or definitely related to drug administration included transient acute bradycardia with somnolence requiring inpatient observation (N = 2), headache, fatigue, and CSF pleocytosis consistent with chemical meningitis treated with corticosteroids (N = 1), and acute dystonic reaction treated with both benzodiazepine and antihistamine (N = 1). The administered activities of cRIT ^{131}I -3F8 therapy injections were primarily limited by the maximum allowed by protocol,⁴ or by dosimetry estimates such that 2,400 cGy to the CSF was delivered for patients with prior craniospinal radiation therapy. There were no complications related to raised intracranial pressure, hemorrhage, or infection.

3.4 | Long-term toxicities

There were no long-term toxicities directly attributed to cRIT 3F8. We specifically note the absence of radionecrosis in any patient in this cohort, despite receiving prior conventional radiation therapy, and additional radiation therapy delivered by cRIT. However, among long-term survivors with a history of prior high-dose induction chemotherapy, +/- myeloablative regimens, craniospinal radiation therapy, and cRIT 3F8, toxicity included symptomatic Moyamoya syndrome (N = 1) and symptomatic small-vessel angiopathy (N = 1). One patient with Gorlin syndrome developed a meningioma, ovarian fibrothecoma, and basal cell carcinoma, all developing more than 6 years after cRIT.

3.5 | Dosimetry

All patients had distribution of the cRIT 3F8 demonstrated throughout the thecal sac on serial nuclear scans through 48-hr postdosimetry injection, although some irregularity in distribution around cerebral convexities was seen in some patients. By CSF sampling, the median dose to the CSF was 47.9 cGy/mCi (14.8–207.6) and to the blood 1.6 cGy/mCi (0.1–9.2). The median total dose delivered to the CSF was 1,453 cGy (350.0–2,784). The dosimetry estimations with ^{124}I -3F8 PET scans were generally similar to those of CSF sampling, while that with ^{131}I -3F8 gamma camera imaging were generally higher, more so for ventricular doses than for spinal canal region (Table 3). The protocol mandated CSF and blood sampling only after the first dose, but to see how reproducible dosimetry estimates were, there were nine patients who had additional blood and CSF tested after each therapy injection.

Among nine patients who had blood and CSF samples analyzed for all four ^{131}I -3F8 cRIT therapies, there was large variability for both blood (%SD = 30–169%) and CSF (%SD = 15–98%) dose estimates with sampling (Supplementary Table S1). It was observed that dosimetry did not seem to be dependent on disease status.

4 | DISCUSSION

cRIT with intraventricular ^{131}I -3F8 appears safe with manageable acute adverse events, even in a very heavily pretreated patient population. Injections were routinely given in the outpatient setting, with supportive care treating anticipated acute toxicities. Although the dose-limiting toxicity for most radioimmunotherapy trials is myelosuppression, the dosing employed in this study was not associated with severe myelosuppression. Antitumor effect is attributed to the direct effect of beta plus gamma irradiation from ^{131}I -emission, although it is plausible that antitumor cytotoxicity may be in part due to complement activation within the CSF space. Previous observations in patients treated with rituximab suggested the activation of complement C3 and C5b-9 in the CSF after intraventricular administration for recurrent CNS lymphoma.²³

Although preliminary data have shown that some young children with MB may be cured with chemotherapy alone, the poor survival results for patients with recurrent MB have been noted in many series.^{1-3,24-28} Given experience with targeted immunotherapy efficacy when used as consolidation in the setting of minimal residual disease, this trial allowed for patients to enter cRIT without radiographically evaluable disease. It is acknowledged, however, that because of this, it is not appropriate to compare efficacy directly to other studies that mandated evaluable disease. However, given the extended survival for this cohort of patients, which includes patients with high-risk disease that still had evidence of leptomeningeal tumor after upfront chemotherapy and radiation therapy, cRIT ^{131}I -3F8 is encouraging, particularly when noting the progression-free and OS rates for patients with relapsed MB in other series published to date (Table 4). Status at the time of cRIT was related to OS, where patients in near radiographic and cytologic remission were at a lower risk of death compared to patients with progressive or radiographically measurable disease. It is important to note that we did not find an association between dose and OS. This would suggest that current cRIT ^{131}I -3F8 dosing is adequate to improve survival. Eleven of 15 long-term survivors received cRIT in the setting of radiographic and cytologic remission and remained in radiographic and cytologic remission; the other 4 patients had minimal and unchanged persistent focal nodularity on MRI. However, at the 10 mCi therapy dose, there does not appear to be a benefit of GD2-directed cRIT 3F8 in the setting of bulky progressive MB. Given that the maximum CSF dose allowed on this study for patients with prior craniospinal radiation therapy was 2,400 cGy, it is possible that increasing the number of injections and total dose to the CSF may contribute to disease control for patients with measurable disease. Importantly, given the absence of radionecrosis in this study cohort, a dose escalation should be considered in future studies.²⁹ Although this was not a randomized comparison between second remission consolidation with or without cRIT, the prolonged survival for patients receiving cRIT suggest a survival advantage compared to historical estimates.²⁴

An important aim of this study was to determine the doses delivered to the CSF by cRIT, with an understanding that the dose to tumor cells binding antibody can be many times higher than the average dose estimates to the CSF.^{20,21,30} CSF dosimetry was performed using two independent methods. The first used direct measurement of the activity concentrations derived from serial CSF samples removed from the ventricular reservoir; the

second used quantitative serial gamma camera images acquired at three nominal time points. CSF samples obtained from the Ommaya reservoir may not be representative of CSF in other areas of the thecal space. In contrast, the gamma camera method determines counts from the entire CSF, where calibration of gamma camera counts into units of activity is critical. While dose estimates from the CSF sampling correlated with those from the gamma camera method for some patients, others were discrepant. Of note was the fairly consistent dose to blood, a surrogate for red marrow in all patients, while the CSF cGy/mCi dose was variable. This is likely a reflection of variable rates of CSF flow based on prior surgery, radiation, presence or absence of bulk lesions, all leading to inherent CSF flow differences prior to cRIT. As CSF volumes were corrected for age as is standard for intrathecal drug delivery, it is not anticipated that CSF volume/body size of the child impacted CSF dose estimates. However, a high therapeutic index of tumor to blood was achieved in all patients. In general, the dosimetry obtained by serial ^{124}I -3F8 PET scans provided the most precise estimates of cGy delivered to various sites including the ventricles, cervical, thoracic, and lumbosacral spine; as a less precise imaging modality, dosimetry-based ^{131}I -3F8 PET (Figs. 1A and 1B) consistently yielded higher ventricular dose than either CSF sampling or PET imaging. The choice of dosimetry method could affect treatment planning.

Further studies may incorporate an analysis of GD2 expression with response and survival. In addition, patients with both classic MB and PNET were eligible for this study, so while recent data suggest that the tumors are not as related as once thought, all patients were included in this analysis. Moving forward, the distinction between MB and PNET will be made. Additional efforts are being made to subgroup patients prospectively, but at the time this trial accrued patients, this molecular subgroup analysis was not routinely undertaken. In the present era of molecular profiling of MB into distinct subtypes with prognostic implications, it is now possible to consider dose reduction of therapies with known neurocognitive risks such as CSI. The findings presented suggest that prolonged survival with cRIT treatment is possible in a subset of patients. Finally, we note that although this study used a MoAb targeting GD2, other tumor-associated antigens may similarly be exploited; we have developed another antibody 8H9 targeting B7-H3, also found to be highly overexpressed on MB and may also be considered for cRIT.³¹

5 | CONCLUSIONS

Intraventricular radioimmunotherapy can be successfully incorporated into treatment strategies as consolidation for relapsed and high-risk MB. The role of cRIT in patients with bulky tumors at the current dosing levels is questionable. Future studies are warranted to evaluate feasibility of higher dosing or differentiate treatment strategies in those with bulky disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST

Antibody 3F8 was licensed to Ymabs, Inc., by MSKCC. MSKCC and NKC have financial interest in Ymabs.

Abbreviations:

cRIT	compartmental radioimmunotherapy
Ci	Curie
CI	confidence interval
CSF	cerebrospinal fluid
FDA	US Food and Drug Administration
Gy	Gray
HR	hazard ratio
IRB	Institutional Review Board
MB	medulloblastoma
MoAb	monoclonal antibody
MRI	magnetic resonance imaging
MSK	Memorial Sloan Kettering Cancer Center
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PNET	primitive neuroectodermal tumor
SPECT	single-photon emission computed tomography

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FIGURE 1. Whole body images of a fused MRI and PET scan following intraventricular injection of radiolabeled antibody (3F8) showing activity in the ventricles (A), subdural space, and spinal canal via sagittal images (B)

FIGURE 2.

Kaplan-Meier demonstrating overall survival (A) and progression-free survival (B) from the date of first cRIT injection for 42 patients

TABLE 1

Summary of 42 patients treated for medulloblastoma with cRIT-3F8

Characteristics		N (%)
Age at initial diagnosis (years)	Median (range)	5 (1–33)
Age at first cRIT injection (years)	Median (range)	7 (2–43)
Histology	Classic	29 (69)
	Anaplastic	8 (19)
	PNET	3 (7.1)
	Desmoplastic	1 (2.4)
	Medullomyoblastoma	1 (2.4)
Stage at diagnosis	M0	28 (66.7)
	M3	14 (33.3)
Craniospinal radiation treatment at initial diagnosis	Yes	29 (69)
# Relapses prior to cRIT	0	8 (19)
	1	16 (38.1)
	2	12 (28.6)
	3	3 (7.1)
	4	1 (2.4)
	5	2 (4.8)
Prior treatment with myeloablative chemotherapies prior to cRIT	Yes	40 (95.2)
Stage at relapse	M0	2 (4.8)
	M2	5 (11.9)
	M2/M3	1 (2.4)
	M3	31 (73.8)
	M3/M4	3 (7.1)
Positive CSF cytology at any time	Yes	19 (45.2)
Status when treated with cRIT	Stable evaluable disease	19 (45.2)
	Progressive evaluable disease	3 (7.1)
	Radiographic/cytologic remission	20 (47.6)

Numbers represent frequencies with percentage in parentheses unless otherwise specified.

TABLE 2

Clinical demographics for 15 survivors treated with cRIT

Patient no.	Age at initial diagnosis (years)	Stage at initial diagnosis	Therapy at initial diagnosis	Treatment given prior to cRIT	Treatment given after cRIT	Age at start of cRIT (years)	Follow-up time from 1st cRIT (years)
1	8.5	M0	Multiagent chemotherapy; 2,340 cGy CSI; LM relapse 30 months later	First relapse: HD thiotepa × 3, focal reirradiation;	No treatment Second recurrence 18 months post-cRIT; retreated with oral etoposide, second cRIT, metronomic therapy	11.81	9.8 ^a
2	0.8	M0	Multiagent chemotherapy, primary site relapse 21 months later	First relapse: surgery, HD thiotepa × 3; no radiation ever given	No treatment	3.22	7.4
3	0.9	M0	Multiagent chemotherapy; progressed on therapy with CSF disease	First relapse: focal RT; ICE × 5 pre-cRIT; Refractory LM post-cRIT; second progression: CSI 39 Gy	CSI	2.30	5.6
4	8.6	M0	Multiagent chemotherapy; first focal relapse 27 months later; second relapse 45 months later	First relapse: HD thiotepa, REMATCH, vaccine; second relapse: surgery, CSI 36 Gy	No treatment	12.68	3.6
5	3.9	M0	HS3; LM relapse 19 months later	CSI 36 Gy	Oral etoposide 4 cycles	5.93	8.1
6	2.4	M3	18 Gy CSI; multiagent chemotherapy	cRIT treatment postchemotherapy and CSI	Metronomic chemotherapy 6 cycles	3.27	6.3
7	1.3	M3	Multiagent chemotherapy; LM relapse 18 months later	Gamma knife, oral etoposide	RT, vorinostat, retinoic acid	3.22	4.8
8	5.2	M3	Multiagent chemotherapy; 36GyCSI	cRIT treatment postchemotherapy and CSI	Metronomic chemotherapy 6 cycles	6.02	8.8
9	1.9	M0	Multiagent chemotherapy	HD thiotepa; no radiation ever given	No treatment	2.46	4.4
10	2.6	M0	Multiagent chemotherapy	HD thiotepa; no radiation ever given	No treatment	3.51	6.3
11	2.4	M3	Multiagent chemotherapy; 23GyCSI	cRIT treatment postchemotherapy and CSI	Temodar and cis-retinoic acid 6 cycles	3.66	1.7
12	12.4	M3	Multiagent chemotherapy; 36 Gy CSI; LM relapse 30 mon later	Irinotecan/temozolomide/bevacizumab	Temozolomide, bevacizumab Irinotecan 5 cycles, metronomic chemotherapy	16.01	2.3 ^a
13	16.4	M3	Multiagent chemotherapy; 36 Gy CSI; LM relapse 48 mon later	Bevacizumab/ thalidomide/ etoposide/ cyclophosphamide/ reirradiation 18 Gy	Bevacizumab, intrathecal liposomal cytarabine Third recurrence 32 months later, retreated with second cRIT	24.05	3.7
14	8	M3	HS2; HD thiotepa; 2,340 cGy CSI	cRIT treatment postchemotherapy and CSI	No treatment	8.91	0.9
15	28.7	M3	Multiagent chemotherapy; 36 Gy CSI; extraneural relapse 15 months later and CSF relapse 2 years later	Cyclophosphamide; temozolomide irinotecan; etoposide	3rd recurrence (extraneural) prompted high-dose chemotherapy	31.10	0.9 ^b

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HD, high dose; CSI, craniospinal radiation therapy; LM, leptomeningeal; VCR, vincristine; CCNU, lomustine; HS, head start.

^a Continues intermittently on maintenance chemotherapy.

^b Chemotherapy resumed for extraneural MB progression.

TABLE 3

cRIT results in 42 patients

Characteristics		Median (range) or N (%)
Median CSF dose (cGy/mCi) by sampling		47.9 (14.8–207.6)
Median blood dose (cGy/mCi) by sampling	(N = 41)	1.6 (0.1–9.2)
Median total CSF dose by sampling (cGy)		1,453 (350.0–2,784)
Evaluated with	¹²⁴ I–3F8 PET	19 (45%)
	¹³¹ I–3F8SPECT	23 (55%)
Median ventricular dose ¹²⁴ I–3F8 PET (cGy/mCi)	(N = 15)	31.1 (13.6–177.0)
Median ventricular dose ¹³¹ I–3F8SPECT (cGy/mCi)	(N = 21)	89.2 (21.7–222.0)
Median thoracic spine dose ¹²⁴ I–3F8 PET (cGy/mCi)	(N = 17)	17.2 (7.2–57.0)
Median thoracic spine dose ¹³¹ I–3F8SPECT (cGy/mCi)	(N = 22)	19.6 (8.4–89.6)
Patients receiving 4 cRIT injections	Yes	18 (43%)
Post-cRIT response	Stable	25 (60%)
	Progressive disease	17 (41%)

Numbers represent frequencies with percentage in parentheses unless otherwise specified.

TABLE 4

Progression-free and overall survival rates for recurrent medulloblastoma in large series

Author	Number of patients with standard chemo, or RT, or both up/front	Intervention	Survival
Koschmann et al. ²⁴	14	Chemo (temozolomide, irinotecan, CCNU, topotecan, vorinostat, isotretinoin, HD chemo/stem cells (N = 10), re-RT (N = 6), gamma knife (N = 5), re-CSI (N = 2), surgery (N = 3), phase I trials (N = 4)	Median survival 10.3 months (1.3–80.5)
Gunurungan et al. ³	30	HD chemo/stem cells (N = 19), or standard salvage chemo (cyclophosphamide, etoposide, platinum compounds, methotrexate, irinotecan temozolomide, intrathecal busulfan, or VNP40101M +/- RT (N = 11); with or without re-RT	3-year overall survival for previously nonirradiated patients 14%; previously irradiated patients median follow-up of 35 months (range, 7–49 months), all died of progressive disease; standard salvage patients all died median 26 months (range, 3–112 months)
Shih et al. ²⁵	13	HD chemo/stem cells	
Dunkel et al. ²	25	HD chemo/stem cells +/- focal RT or CSI	6/25 progression-free survivors; progressive disease median 8.5 months (N = 16) ; 3 died of toxicity
Bakst et al. ²⁶	11	Re-RT +/- surgery	Median F/U 30 months; PFS 48% at 5 years
Robison et al. ²⁷	8	5 drug oral regimen (continuous oral celecoxib, thalidomide, fenofibrate, alternating 21-day cycles cyclophosphamide, etoposide)	1CR, 1 PR, 1SD, 5 PD

HD, high dose; chemo, chemotherapy; RT, radiation therapy; CSI, craniospinal radiation therapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.