3F8/GM-CSF Immunotherapy Plus 13-Cis-Retinoic Acid for Consolidation of First Remission After Non-Myeloablative Therapy in Patients with High-Risk Neuroblastoma: A Phase II Study

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This phase II study of the anti-G_{D2} murine IgG3 monoclonal antibody 3F8 combined with granulocyte-macrophage colony stimulating factor (GM-CSF) will assess relapse-free survival in patients who are in first complete/very good partial remission (CR/VGPR) but are at very high risk of relapse of neuroblastoma. The high-dose 3F8 usage is four fold greater than the standard 3F8 dosage used in prior phase II studies. 13-*cis*-Retinoic Acid will be used in this protocol after patients are evaluated for response to 3F8/GM-CSF. We will apply real-time quantitative RT-PCR methodology targeting G_{D2} synthase mRNA for monitoring response in bone marrow; we will test the hypothesis that early bone marrow response has prognostic importance.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives

- Assess the impact of high-dose 3F8/GM-CSF on relapse-free survival in patients in first complete or very good partial remission, but at high risk of relapse.

Secondary Objectives

- Apply real-time quantitative RT-PCR to test the hypothesis that the minimal residual disease content of bone marrow after the first treatments with 3F8/GM-CSF has significant prognostic impact on relapse-free survival.

- Monitor safety of the high-dose antibody treatment, to assure no side-effects or noxious sequelae develop or emerge that were not seen in the prior phase I study.

3.0 BACKGROUND AND RATIONALE

3.1 <u>Disease background:</u> Neuroblastoma (NB) is the most common extracranial solid tumor of childhood; 50-60% of patients present with an unresectable primary tumor and metastases in bone marrow (BM).[1] Intensive induction chemotherapy and aggressive surgery have improved remission rates in young patients[2-4]; results have been less impressive in adolescents and adults in whom NB is especially chemoresistant.[5,6] Realization of an effective strategy for eradicating minimal residual disease (MRD) has remained a formidable challenge. Post-surgical use of local radiotherapy helps control MRD in the primary site.[7] Myeloablative therapy (with stem-cell support) has been the most common approach for eradicating MRD in distant sites. The long-term relapse-free survival rate in a recent national study was only ~20%, although the vitamin A derivative 13-*cis*-retinoic acid helped to improve overall survival.[8] These results, plus the potentially severe toxicities of chemotherapy and radiotherapy, are compelling reasons for pursuing novel therapeutic approaches, including immunotherapy mediated by anti-GD2 monoclonal antibodies (MoAbs)[9-22] which interact with granulocytes.[23]

3.2 Rationale for 3F8: 3F8 is a murine IgG3 MoAb that is well suited for targeted immunotherapy. The reasons are several. First, the intensive chemotherapy required to produce in NB patients the minimal disease state optimal for immunotherapy results in prolonged lymphopenia. This setting is unfavorable for active immunotherapy but allows passive immunotherapy since the patient is unable to reject allogeneic, xenogeneic, or genetically-engineered MoAbs. Second, 3F8 recognizes the ganglioside G_{D2}.[24] This target antigen is highly expressed on NB (but has restricted distribution in normal human tissues), is not modulated from the cell surface when bound by MoAbs, and is genetically stable (unlike tumor-associated antigens such as immunoglobulin idiotypes on lymphoma cells).[25-27] Third, scintigraphy using ^{131}I-3F8 confirms that 3F8 localizes selectively to G_{D2}(+) tumor deposits in patients.[28] The excellent targeting potential of 3F8 was evidenced by its high tumor to non-tumor ratio, the high percent injected dose per gram uptake, and the limited, if any, nonspecific liver and spleen uptake.[28,29] Fourth, 3F8 mediates destruction *in vitro*, in a dose-dependent manner, of G_{D2}(+) human tumor cells by human complement[30] and by human lymphocytes, cultured monocytes, and neutrophils.[31-33] Finally, the capacity of 3F8 to activate complement (C') on NB cells (which lack decay accelerating factor[34]) raises the possibility of C'-mediated lysis in patients and the release of C' fragments that may elicit an inflammatory influx of granulocytes capable of lysing 3F8-labeled tumor cells. Furthermore, the deposition of C' fragments C3b and iC3b on NB cells may enhance ADCC because the receptor for iC3b – variously called Mac-1, CR3, CD11b/CD18, or $\alpha_M\beta_2$-integrin – is a key element in anti-G_{D2} MoAb-mediated tumor-cell kill by neutrophils,[35,36] which are the most abundant circulating class of leukocyte.

3.3 Rationale for GM-CSF: GM-CSF can amplify 3F8 anti-NB activity in patients via effects on granulocytes and macrophages. Reasons for combining GM-CSF with 3F8 include the following. First, granulocyte production is only transiently suppressed by chemotherapy, and GM-CSF increases neutrophil and eosinophil production and is well tolerated compared to other cytokines such as interleukin-2.[37] Second, granulocytes from patients receiving chemotherapy and normal volunteers mount ADCC against NB cells via non-oxidative mechanisms, and GM-CSF enhances the ADCC.[36,38-42] Third, eosinophilic infiltration of some cancers has favorable prognostic significance, and eosinophils exhibit potent antitumor activity in animal models.[43,44] Fourth, activated monocytes-macrophages efficiently phagocytose NB cells, and exposure *in vitro* or *in vivo* to GM-CSF primes monocytes-macrophages for greater antineoplastic cytotoxicity.[33,39,45-50] Fifth, GM-CSF enhances the proliferation, maturation, and function of antigen-presenting cells, including antigen processing and presentation by macrophages and dendritic cells[37,51,52] - effects that might promote induction, or antitumor activity, of an idiotypic network.[53-56] Finally, GM-CSF is not a growth factor for NB cells in vitro.[57]

3.4 Rationale for quantitating BM disease by real-time RT-PCR: Curative strategies for stage 4 NB must encompass control of both the primary mass and distant disease. Dose-intensive chemotherapy has had a favorable impact on resectability of primary tumors and surgical removal of all visible tumor, followed by local radiotherapy, reduces the risk of relapse in the primary site to <10%.[4,7] Dose-intensive chemotherapy eliminates histologically evident BM involvement in 90% of high-risk cases.[3] These encouraging results have shifted the focus of curative strategies to the problem of MRD – which is readily assessed in BM.

Adjuvant treatments, such as immunotherapy with MoAbs, may make gradual and not quantum changes in MRD, which by definition is beyond the sensitivity of conventional histologic[58] or radiologic techniques. The availability of more sensitive methods for quantitating occult tumor cells in sequential BM specimens can allow determination of the efficacy and optimal duration of adjuvant treatment. The absence of detectable tumor cells in BM can serve as a surrogate end point for the adjuvant treatment strategy, while quantitative data on BM disease will help detect relapse earlier and indicate a need for a change in treatment.

We[58-65a] and others[66-70] have reported a series of studies aimed at improving the utility of BM testing, focusing on immunological and molecular methods for identifying MRD. The limit of detection for immunocytology is $1/10^5$ to $1/10^6$ cells; RT-PCR has slightly superior sensitivity with a range of $1/10^5$ to $1/10^7$ cells. *The results suggest that G_{D2} synthase might serve as a sensitive marker of MRD in BM and that its level might reflect clinical disease status as well as correlate with histologic response to immunotherapy.*

Histologic examination of aspirates and biopsies from bilateral posterior iliac crests has been the standard method for detecting NB in BM. We have routinely also obtained specimens from bilateral anterior iliac crests since sampling from multiple sites increases detection rates.[65a] Histologic studies alone, however, yield an underestimate of BM involvement, as shown by immunocytology with MoAbs.[68.69] For >15 years, we have used anti-GD2 immunocytology to enumerate NB cells in BM of patients.[92] Molecular markers have also been tested for detecting NB. Thus, the gene transcript for tyrosine hydroxylase, which is a key enzyme in the catecholamine biosynthesis pathway, is useful for identifying NB in BM but its expression is down-regulated in some cells.[64,67] We found cancer-testis antigen *GAGE* to be comparable in sensitivity to immunocytology in detecting NB in BM,[59] and results with *GAGE* proved to have prognostic significance.[61]

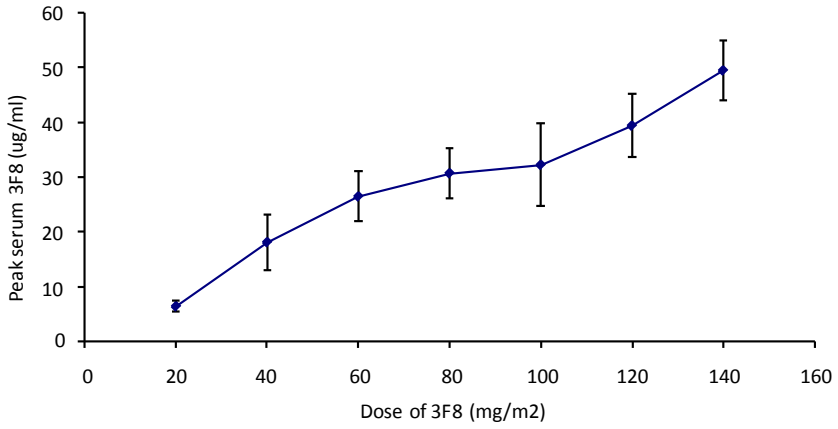
Ease of use, superior sensitivity, and greater specificity prompted us to study the utility of real-time quantitative RT-PCR of GD2 synthase mRNA for the detection of rare NB cells in BM. The marker GD2 synthase is particularly pertinent because NB cells express ganglioside GD2 at high density, with little heterogeneity within tumors or among patients, and this surface antigen has limited expression in normal human tissues.[25-27] The key enzyme required for GD2 synthesis is GD2 synthase (β1,4-N-acetylgalactosamineyltransferase, EC 2.4.1.92).[62]

In a study of 155 BM samples (100 patients), the transcript levels correlated well with the number of NB cells in BM as measured by immunocytology.[63] Further, in a study of BM findings in 86 NB patients treated with 3F8 and GM-CSF, molecular responders had a significantly lower risk of disease progression.[65] The data provide compelling support for the utility of this molecular approach for assessing MRD.

3.5 Clinical experience with 3F8/GM-CSF: Prior clinical studies of 3F8/GM-CSF established 1) this combination's excellent activity against refractory BM disease (IRB protocols 94-018 and 03-077); 2) the safety of markedly augmented 3F8 dosing (IRB protocol 05-015: "3F8 antibody dose escalation plus granulocyte-macrophage colony-stimulating factor in high-risk neuroblastoma: A phase I trial") [71a] compared to dosages derived from pilot studies in the 1980s, an important finding since *in vitro* studies show a 3F8 dose-dependent lysis of NB cells (see section 3.2); and 3) the superiority of subcutaneous over intravenous (iv) use of GM-CSF, for both anti-NB effect and treatment simplification (which helps patients and medical staff - and promotes wide availability of this treatment)[71-73]

The long-standing standard daily dosage of 3F8 has been 20 mg/m^2. In the IRB protocol 05-015 dose escalation phase I study, 3F8 dosages up to 160 mg/m^2 were possible without dose-limiting toxicity, as reported[71a] (That protocol also used a small dose of heat-modified 3F8 – 2 mg/m^2, iv over ~5 minutes – administered just before the treatment dose, as a way to modify the major acute toxicity of pain.) For the current protocol, we chose daily 3F8 dosage 80 mg/m^2 because in the dose escalation phase I study, serum levels were not significantly different at a 3F8 daily dosage of $\geq$80 mg/m^2 (see Figure 1), and excellent anti-NB activity was seen at 80 mg/m^2.

Figure 1:



3.6 HAMA response/idiotypic network: In a study of 34 patients with MRD treated with 3F8 alone, patients with a self-limited (transient) HAMA response had significantly better PFS than patients who had persistently high HAMA titers or no HAMA formation.[15] This association of a transient low level HAMA/anti-idiotype (Ab2) antibody response with better PFS was a seemingly paradoxical finding since HAMA/Ab2 blocks 3F8 binding to tumor cells. The unexpected observation regarding HAMA/Ab2 and survival led to the hypothesis of a host idiotypic network induced by 3F8 (Ab1) and responsible for long-term tumor control. The idiotypic network was first postulated by Jerne[75] for immune regulation and later demonstrated in human disease models, including cancer patients.[76-79] Anti-idiotypic antibodies (Ab2) in the HAMA pool may mimic antigen G_{D2} and stimulate an Ab3 antibody response. We previously reported the association of anti-anti-idiotype (Ab3) with prolonged survival among patients who underwent myeloablative therapy with autologous stem-cell rescue.[53] Other investigators have postulated the development of an idiotypic network in patients treated with 17-1A antibodies, where both Ab3 antibodies as well as anti-idiotypic and anti-anti-idiotypic T cells have been demonstrated.[54,55]

In our study of 34 patients, consistent with the emergence of an idiotypic network, Ab3 (anti-anti-idiotype) and Ab3' (anti-G_{D2}) response at 6-14 months after treatment with 3F8 alone correlated with improved PFS, and higher Ab3 titers showed a stronger correlation with improved outcome, while non-idiotype antibody responses (anti-mouse or anti-tumor nuclear antigen) had no apparent impact on outcome.[56] Since G_{D2} is an auto-antigen, induced Ab3' response represented a breakdown in self-tolerance. We hypothesized that significant rises in Ab3 or Ab3' would not be possible unless suppressor pathways were removed and naive T or B cells were allowed to repopulate. Following intensive chemotherapy that eliminates a large part of the lymphoid system, exposure to tumor-selective Ab1s (3F8) might induce unique Ab2s that could bias the recovering repertoire towards the G_{D2} antigen network. The potential for biasing the immune system towards specific antigens has been well documented in murine models[80] and human disease states.[81,82] If true, one would expect such an idiotypic network to be most successful following intensive immunosuppressive therapy, and not easily induced in immunocompetent patients. In fact, we found that myeloablative therapy suppressed HAMA and Ab2 but was followed by the appearance of Ab3 which in turn correlated with prolonged survival.[53,56] The prerequisite of strongly immunosuppressive therapy may explain why in most clinical studies of MoAbs, such an idiotypic network is not commonly observed. However, when found in patients with colorectal or ovarian carcinoma treated with specific MoAbs, the idiotypic network gave patients superior survival advantage.[54,55,76,77,83-87]

3.7 **Isotretinoin (13-*cis*-retinoic acid)** was shown in a randomized national study to significantly decrease the risk of early relapse in patients treated in complete remission and to significantly improve overall survival.[8] This agent subsequently became standard of care for NB patients in remission. It will be used in this protocol after patients are evaluated for response to 3F8/GM-CSF – same dosage, same timing as in the predecessor 3F8/GM-CSF (IRB 03-077) protocol.

3.8 **Interpretations and implications:** Various strategies have undergone clinical testing to promote immune-mediated attack against cancer. However, few clinical trials have used MoAb-targeted immunotherapy against solid tumors in children or adults, especially with ADCC as the principal underlying immune cytotoxic mechanism. Also, an antineoplastic role for granulocytes has received scant attention.[23] A treatment program combining 3F8 and GM-CSF thus represents a step towards filling a gap in the emerging field of immunotherapy.

This phase II trial exploits recent findings that promise to optimize the anti-NB activity of 3F8/GM-CSF – namely, high dosing of 3F8 and subcutaneous use of GM-CSF. Further, RT-PCR analysis of response in BM, which has proved informative in past studies, will be applied to monitor anti-NB activity of the immunotherapy, with an emphasis on early recognition of treatment efficacy. The studies focus on BM; findings may not reflect total body tumor burden. Metastatic NB is, however, a systemic disease, and, as with leukemia,[88] BM status appears to approximate the overall disease state. If the RT-PCR method proves to be sensitive, it will provide a useful tool for measuring NB-cell content in BM as a patient goes through treatment. The ability to identify patients not likely to benefit from further use of a given adjuvant therapy will allow a more timely switch to a possibly better treatment. We hypothesize that quantifying G_{D2} synthase transcript levels will help stratify patients by tumor load, define tumor thresholds that correlate with favorable clinical outcome, and provide prognostic classification for patients receiving immunotherapy. Risk-related molecular guidelines can be rapidly incorporated into future treatment programs.

Our RT-PCR method provides a quantitative measure, such that the percentage of patients who achieve CR in BM, and the degree of response with 3F8/GM-CSF, can be calculated and compared to other adjuvant treatments. With NB, where randomized trials are difficult to carry out because of the small number of affected patients, such quantitative analyses acquire even greater utility for rapidly identifying both the best agent and its optimal use in a curative treatment program.

The findings regarding RT-PCR utility in the adjuvant setting, granulocyte activation, and idiotypic network will have general implications for MoAb-based therapeutic strategies against solid tumors in humans.

The ease of administration of the treatments (a subcutaneous injection of GM-CSF, which is given at home, and a 30-minute iv infusion of 3F8 in the outpatient clinic), plus their transient acute side-effects, are compatible with usage of this regimen beyond our hospital – a strong positive factor in furthering product development, which in fact is underway in a multi-institutional study of 3F8/GM-CSF using the previous 3F8 dosage.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This phase II, open-label, single arm trial assesses the anti-NB activity of high-dose 3F8 (80 mg/m^2/day), which is used in cycles 1-2, with return to standard 3F8 dosage (20 mg/m^2/day) in subsequent cycles. Clinical results will be compared to those in the predecessor trials which used only the standard 3F8 dosage.

Starting with A(8), patients no longer receive high dose 3F8 but receive only standard dose 3F8 (20mg/m2/day) for all cycles.

The patients are in 1st complete/very good partial remission (CR/VGPR)[89] after conventional therapy, with no evidence of NB by standard studies, but are at high risk for relapse.

Real-time quantitative RT-PCR[63-65] will be used to assess MRD in BM. 13-*cis*-retinoic acid is started after cycle 2.

4.2 Intervention

Road Map/Schema (1st CR/VGPR after conventional therapy): A cycle consists of treatment with 3F8 for 5 days. GM-CSF is started 5 days in advance of each 3F8 cycle. The break between end of a cycle of 3F8/GM-CSF and start of next cycle is approximately 2-to-4-weeks through 4 cycles; subsequent breaks are ~6-8 weeks. 13-*cis*-retinoic acid is started after cycle 2.

Cycle 1	high-dose 3F8* + GM-CSF
2-4 weeks off	
Cycle 2	high-dose 3F8* + GM-CSF
2-4 weeks off– 13-*cis*-retinoic acid x14 days on, x14 days off	
Cycle 3	3F8 + GM-CSF
2-4 weeks off– 13-*cis*-retinoic acid x14 days on, x14 days off	
Cycle 4	3F8 + GM-CSF
6-8 weeks off – 13-*cis*-retinoic acid x14 days on, x14 days off, x14 days on	
Cycle 5	3F8 + GM-CSF
6-8 weeks off – 13-*cis*-retinoic acid x14 days on, x14 days off, x14 days on	
Cycle 6	3F8 + GM-CSF

Continue with ~6-8-week breaks through 24 months from 1st dose of 3F8. The treatment schedule may require minor adjustment as clinically indicated (e.g., due to PDH closure for holidays). Patients can complete the missed day of 3F8 the following week, so they receive

a full 5-day cycle. GM-CSF will be continued through the 3F8 make-up day at the 500 mcg/m^2 dose.

*High-dose 3F8 will be administered only for patients enrolled on protocol from A(0) to A(7). Starting with A(8), patients receive standard dose (20mg/m^2/day) during cycles 1 and 2.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 3F8 monoclonal antibody (IND number of BB-IND-8449)

5.1.1 Source and Pharmacology: Monoclonal antibody 3F8 is purified by column chromatography. The final product is tested to assure that it is free of nucleic acid, murine viruses, bacteria, fungi, mycoplasma and pyrogens. Supplier: 3F8 is manufactured as an investigational agent.

5.1.2 Formulation and Stability: The purified antibody is frozen at –80°C, at 2 mg/mL 0.1 M citrate-phosphate pH 4.2 buffer in glass vials. At –80°C it is stable for at least 3 years. For iv administration, 3F8 should be diluted into 10 ml 5% human serum albumin and millipore (0.2 μm) filtered before use. Route of Administration: iv infusion.

5.2 Yeast-derived human recombinant granulocyte-macrophage colony stimulating f actor GM-CSF; LEUKINE (sargramostim)) is produced by Berlex Laboratories, Seattle, WA.

5.2.1 LEUKINE is a sterile, white, preservative-free, lyophilized powder suitable for iv infusion upon reconstitution of 250 mcg vials; these vials should be reconstituted aseptically with 1.0 ml Sterile Water for Injection, USP (without preservative). The reconstituted LEUKINE solutions are clear, colorless, isotonic with a pH of 7.4 ± 0.3, and contain 250 mcg/ml of Sargramostim. The single-use vial should not be re-entered or reused. Do not save any unused portion for later administration. Vials containing 500 mcg of LEUKINE are already in solution and are multiple dose vials.

5.2.2 During reconstitution the Sterile Water for Injection, USP should be directed at the side of the vial and the contents gently swirled to avoid foaming during dissolution. Avoid excessive or rigorous agitation; do not shake.

5.2.3 Dilution for iv infusion should be performed in 0.9% Sodium Chloride Injection. USP. If the final concentration of LEUKINE is below 10 mcg/ml, Albumin (Human), add 1 mg Albumin (Human) per 1 ml 0.9% Sodium Chloride Injection, USP (e.g. use 1 ml 5% Albumin [Human] in 50 ml 0.9% Sodium Chloride Injection, USP).

5.2.4 An in-line membrane filter is not to be used for iv infusion of LEUKINE.

5.2.5 LEUKINE contains no antibacterial preservative and therefore should be administered as soon as possible, and within 6 hours following reconstitution and/or dilution for iv infusion. Store LEUKINE powder, reconstituted solutions, or diluted solutions under refrigeration at 2-8°C (36-46°F); do not freeze or shake. LEUKINE vials are intended for single use only; discard any unused solution after 6 hours. Do not use beyond the expiration date printed on the vial.

5.2.6 In the absence of compatibility and stability information, no other medication should be added to infusion solutions containing LEUKINE. Use only 0.9% Sodium Chloride Injection, USP to prepare iv infusion solutions.

5.2.7 Aseptic technique should he employed in the preparation of all LEUKINE Solutions. To assure correct concentration following reconstitution, care should be exercised to eliminate any air bubbles from the needle hub of the syringe used to prepare the diluent. Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

5.3 13-*cis*-Retinoic Acid (NDC #0004-0155-01,0004-0169, 0004-0156-01-ISOTRETINOIN, ACCUTANE)

5.3.1 Source and Pharmacology: The exact mechanism of retinoic acid (RA)-induced maturation of tumor cells is not known. In NB cell lines it has been shown to down regulate *MYCN* RNA and protein expression, and such down regulation correlates with the ability of isotretinoin to induce tumor cell growth arrest. Recent studies using gene transfection directly implicate down regulation of *MYCN* expression by isotretinoin as a key event in achieving sustained arrest of NB cell proliferation. RA also appears to enhance normal hematopoietic differentiation by increasing the responsiveness of myeloid and erythroid progenitor cells to the action of myeloid colony stimulating activity and erythropoietin, respectively. Metabolism: RA is 99.9% bound in plasma (almost entirely to albumin) and has a half-life of 10-20 hours. The major metabolite is 4-oxoisotretinoin, and excretion is in the urine and feces. A single oral dose of 100mg/m^2 isotretinoin will produce peak plasma levels of 1-2mM. The mean peaktime as 3.2 hours after 80mg orally, with a terminal $t_{½}$ of 10 to 20 hours. Administering 160 mg/m^2/day to children after autologous bone marrow transplantation has been shown to achieve 13-cis-RA levels of 5 to 7 micromolar.

5.3.2 Formulation and Stability: Isotretinoin, which is the 13-*cis* isomer of retinoic acid, will be used. This is a yellow-orange crystalline powder with a molecular weight of 300.44. Isotretinoin is sensitive to light and oxygen, and so it should not be removed from the capsule for longer than one hour prior to administration to the patient and it should be kept in subdued light as much as possible.

5.3.3 Guidelines for Administration: PO with fat-containing food or milk to enhance absorption. Administration of the entire capsule is to be encouraged and small children can be trained to swallow them using similar sized candy.

5.3.4 Supplier: Isotretinoin is available commercially under the trade name ACCUTANE (Roche Laboratories) in 10mg, 20mg, and 40mg soft gelatin capsules. See package insert for further information.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

6.1.1 Diagnosis of NB as defined by a) histopathology (confirmed by the MSKCC Department of Pathology), or b) BM metastases or MIBG-avid lesion(s) plus high urine catecholamine levels.

6.1.2 High-risk NB as defined by risk-related treatment guidelines[1] and the International NB Staging System,[89] i.e., stage 4 with (any age) or without (≥18 months of age) *MYCN* amplification, *MYCN*-amplified stage 2 or stage 3 (any age), or *MYCN*-amplified stage 4S.

6.1.3 The patients are in first CR/VGPR after conventional therapy. They have no measurable MIBG-avid soft tissue tumor assessable for response.

6.1.4 Signed informed consent indicating awareness of the investigational nature of this program.

6.2 Subject Exclusion Criteria

6.2.1 Creatinine > 3.0 mg/dL

6.2.2 ALT, AST and Alkaline Phosphatase > 5.0 times the upper limit of normal

6.2.3 Bilirubin > 3.0 mg/dL

6.2.4 Patients with grade 3 or higher toxicities (using the CTCAE v4.0) related to cardiac, neurological, pulmonary or gastrointestinal function as determined by physical exam. Patients must have normal blood pressure for age.

6.2.5 Progressive disease

6.2.6 History of allergy to mouse proteins.

6.2.7 Active life-threatening infection.

6.2.8 Human anti-mouse antibody (HAMA) titer >1000 Elisa units/ml.

6.2.9 Inability to comply with protocol requirements.

7.0 RECRUITMENT PLAN

In each of the past 2 years, 46 patients were treated on the predecessor of this protocol. We anticipate at least maintaining this accrual rate, which will allow rapid realization of preliminary conclusions, with completion of the trial in 3-4 years. Given the favorable prior efficacy-toxicity profile with 3F8/GM-CSF, we expect that all patients will complete the trial. Patients will be offered participation in this study by their attending physician in the Department of Pediatrics, Memorial Sloan-Kettering Cancer Center. No patient will be identified by chart review or direct advertising. The attending physician will be responsible for explaining the study, obtaining written informed consent, and registering the patient on study. Patients will mainly be children and adolescents because of the nature of NB (90% of patients are <6 years old at diagnosis). Patients of both sexes and all ethnic backgrounds are eligible for this study.

8.0 PRETREATMENT EVALUATION

Pretreatment evaluations should be completed within 30 days of start of treatment. Refer to Table 1.

8.1 Complete history and physical examination.

8.2 Complete blood count, serum creatinine, blood urea nitrogen, serum aspartate aminotransferase, serum alanine aminotransferase, and serum total bilirubin

8.3 Echocardiogram.

8.4 Complete extent-of-disease evaluation.

8.4.1 Urine catecholamine levels - optional.

8.4.2 BM aspirates from bilateral anterior and bilateral posterior iliac crests, and biopsies from any two separate sites. The specimens are studied by:

- Standard histochemical methods for the presence of tumor cells.
- Immunocytology using a panel of monoclonal antibodies that react with antigens associated with NB (to Dr. Cheung's lab).

- RT-PCR quantitation of tumor cells (to Dr. Cheung's lab)

8.4.3 CT or MRI of primary tumor site, plus other suspected sites of tumor.

8.4.4 Scintigraphic studies (MIBG scan[90] or PET scan[91]).

8.5 Biologic (blood) studies for phenotypes of leukocytes, and for DNA to do HLA and KIR typing, FcR2A and FcR3A polymorphism (to be drawn prior to treatment).

9.0 TREATMENT/INTERVENTION PLAN

9.1 Schedule: For patients consented on A(0) to A(7), 3F8 is dosed at 80 mg/m^2/day (cycles 1-2) or 20 mg/m^2/day (cycles 3 and beyond) and infused iv over 30-90 minutes. Starting with A(8), patients receive 3F8 at 20 mg/m^2/day for all cycles. To modulate pain from 3F8, patients are premedicated with analgesics (e.g., hydromorphone) and antihistamines (e.g., diphenhydramine or hydroxyzine). 3F8 is started ~1 hr after GM-CSF. GM-CSF is dosed at 250 mcg/m^2/day from day –5 to day +1 (i.e. Wednesday to Tuesday is customary), and is 500 mcg/m^2/day on days +2 to +4 (i.e. Wednesday to Friday), as in the predecessor protocols.[18,74] Patients come off study if progressive disease occurs or if there is life-threatening grade 4 toxicity from 3F8.

The break from end of a cycle to start of next cycle is approximately 2-to-4 weeks through 4 cycles; subsequent breaks are ~6-8 weeks. 13-*cis*-retinoic acid is started after cycle 2. Road map/schema is in section 4.2.

Patients who develop HAMA which precludes timely treatments with 3F8/GM-CSF are eligible to receive low-dose maintenance regimens such as irinotecan alone,[92] temozolomide alone,[93] irinotecan-temozolomide,[94] or cyclophosphamide-topotecan.[95] They can also receive anti-HAMA agents such as rituximab and cyclophosphamide. They resume treatment with 3F8/GM-CSF if HAMA becomes negative.

9.2 3F8/GM-CSF Treatment Schedule

9.2.1 Treatment Schedule Cycles 1-2*:

Days -5 to -1: GM-CSF 250 mcg/m^2/day, subcutaneously.

Days 0 and +1: GM-CSF 250 mcg/m^2/day, subcutaneously.

3F8 80 mg/m^2/day by iv infusion over 30-90 minutes.

Days +2 to +4: GM-CSF 500 mcg/m^2/day, subcutaneously.

3F8 80 mg/m^2/day by iv infusion over 30-90 minutes.

*For patients enrolled on protocol from A(0) to A(7)

9.2.2 Treatment Schedule Cycle 3 and onwards for patients enrolled on A(0) to A(7) and Treatment Schedule for all Cycles for patients enrolled on A(8) and onwards:

Days -5 to -1: GM-CSF 250 mcg/m^2/day, subcutaneously.

Days 0 and +1: GM-CSF 250 mcg/m^2/day, subcutaneously.
3F8 20 mg/m^2/day by iv infusion over 30-90 minutes.

Days +2 to +4: GM-CSF 500 mcg/m^2/day, subcutaneously.
3F8 20 mg/m^2/day by iv infusion over 30-90 minutes.

Note: GM-CSF is not administered if the ANC is >20,000/ul. If HAMA develops, cycles are deferred until HAMA titer decreases to <1000 Elisa units/ml.

9.3 13-*cis*-retinoic acid is dosed at 160 mg/m^2/day, divided into two doses, x14 days. If a dose is missed, it can be made up at the end of the cycle. It is not taken on same days as 3F8. The treatment can be repeated after a minimum rest period of 14 days. 13-*cis*-retinoic acid is started after cycle 2 of 3F8/GM-CSF, but it can be started sooner if early HAMA develops. All patients take a total of 6 cycles of 13-*cis*-retinoic acid. Dose reductions due to expected side effects of 13-*cis*-retinoic acid (e.g., headaches, dry skin, etc.) are allowed.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Note: If for any reason tests cannot be completed on day 0, they will be completed on day 1

10.1 CBC on day 0 and +3 of each cycle.

10.2 C3 and CH50, on day 0 and +4 (i.e. Monday and Friday) of cycles 1 and 2.

10.3 Phenotype of leukocytes, on day 0 prior to treatment and day +4 (i.e. Monday and Friday) of cycles 1 and 2.

10.4 Serum (2-5 ml) for 3F8 levels pre 3F8 infusion on Day 0 (i.e. Monday) and post-3F8 infusion on Day 4 (i.e. Friday) for cycle 1 and 2.

10.5 Blood for HAMA is obtained approximately every 1-2 months while on study (to Dr. Cheung's lab).

10.6 Liver and kidney function blood tests on day 0 and +4 of each cycle.

10.7 Assessment of response is the same as in prior studies,[96] including the predecessor 3F8/GM-CSF (IRB 03-077) protocol: BM studies (8.4.2) after cycle 2 and complete extent-of-disease evaluation (section 8.4) after cycle 4 of 3F8/GM-CSF and at least every 3 months through 2 years. BM studies are repeated in conjunction with MIBG or PET scan (section 8.4.4) through 2 years in patients with history of BM or cortical bone involvement, but are repeated ~every 6 months in other patients (e.g., patients who were stage 4 by virtue of metastases in distant lymph nodes, patients with *MYCN*-amplified stage 4S lacking BM involvement, or patients with *MYCN*-amplified stage 2 or stage 3).

10.8 Pregnancy screen (females of child-bearing age) before starting *cis*-retinoic acid.

10.9 Blood to study minimal residual disease (to Dr. Cheung's lab)[98]

10.10 Patients receiving 80 mg/m^2 of 3F8 will be monitored for their blood pressure for at least 2 days after 3F8 until a normal blood pressure has been assured. Not applicable starting with A(8)

Table 1. PRETREATMENT AND DURING THE STUDY EVALUATION

WHAT?	WHEN?
Complete history and physical examination.	Pretreatment evaluation
Complete blood count	1. Pretreatment evaluation 2. On day 0 (i.e. Monday) and +3 (i.e. Thursday).
Liver and kidney function blood tests	1. Pretreatment 2. On day 0 (i.e. Monday) and +4 (i.e. Friday)
Blood for studies of DNA to do HLA and KIR typing, FcR2A and FcR3A polymorphism (to Dr. Cheung's lab)	Pretreatment or on Cycle 1 Day 0 prior to 3F8.
Blood for studies of phenotypes of leukocytes (to Dr. Cheung's lab)	Day 0 (i.e. Monday) prior to treatment and Day 4 (i.e. Friday), cycles 1 and 2
Blood (2-5 ml) for 3F8 levels (to Dr. Cheung's lab)	1. Pre 3F8 infusion day 0 (i.e. Monday), cycles 1 and 2 2. Post 3F8 infusion day 4 (i.e. Friday), cycles 1 and 2
Blood for minimal residual disease studies (to Dr. Cheung's lab)	1. Drawn with post cycle 2 bone marrow studies **2.** Drawn with bone marrows during first work-up (~3 months from start of study)
C3, CH50	On day 0 and +4 (i.e. Monday and Friday), cycles 1 and 2.
HAMA (Red Top Tube) (to Dr. Cheung's lab)	~Every 1-2 months while on study.

Bone marrow studies (including 10 ml heparinized for immunocytology and/or RT-PCR, to Dr. Cheung's lab)	1. Pretreatment 2. At end of cycle 2 3. Subsequently, • BM studies are repeated with MIBG or PET through 2 years for patients with history of BM or cortical bone involvement. • But are repeated ~every 6 months in other patients (e.g., patients who were stage 4 by virtue of metastases in distant lymph nodes) while on study.
CT or MRI	1. Pretreatment: of primary tumor site, plus other specific or suspected sites of tumor. 2. Followup: of primary site ~every 3 months through 1 year.
MIBG scan[90] or PET scan[91]	Pretreatment and ~every 3 months through 2 years
Echocardiogram	Pretreatment
Urine catecholamine levels (optional)	1. Pretreatment 2. ~Every 3 months through 2 years.
Pregnancy screen (females of child-bearing age)	Before starting 13-*cis*-retinoic acid.
Blood pressure monitoring with 80 mg/m^2 of 3F8 – not applicable starting with A(8)	Measured for at least 2 days after 3F8 until normal blood pressure is assured.

Note: If for any reason tests cannot be completed on day 0, they will be completed on day 1
*** Pretreatment evaluation should be completed within 30 days of treatment**

11.0 TOXICITIES/SIDE EFFECTS

11.1 Toxicities are graded by the Common Toxicity Criteria (Version 3.0) developed by the National Cancer Institute (NCI) of the USA. All toxicities during cycle 1 will be recorded. After cycle 1, only toxicities ≥ grade 3 will be recorded.

11.2 3F8: Reversible side-effects include pain, paresthesia, hypertension, hypotension, tachycardia, urticaria, fever, nausea, emesis, and rarely, diarrhea, serum sickness, hyponatremia, somnolence and posterior reversible encephalopathy syndrome (PRES). Other potential side-effects that may occur are bronchospasm, anaphylaxis, peripheral neuropathy, impaired accommodation of the eye and poor reactivity of pupils to light.

11.2.1 The definition of unacceptable pain is the same as in the IRB 05-015 phase I 3F8 dose-escalation study, as reported[71a]: ≥7 doses of opioids administered within two hours. One dose of analgesic is defined as hydromorphone 0.015 mg/kg or equianalgesic dose of morphine sulfate.

11.2.2 The definition of unacceptable hypertension is the same as in the IRB 05-015 phase I 3F8 dose-escalation study, as reported[71a]**:** hypertension necessitating medicinal intervention for >24 hours.

11.3 GM-CSF: Common side-effects include bone pain, flushing, local reaction at site of injection, leukopenia shortly after injection, and decrease in platelet count. Rare side-effects (predominantly in adults) include allergic reactions, weight gain, pleural or pericardial effusion, pericardial embolism, thrombosis, and difficulty breathing after first injection.

11.4 Isotretinoin: Dry skin, dry mouth, cheilitis, dry eyes, hypercalcemia, pseudotumor cerebri, rash, muscle or bone pain, fatigue, headache, cholesterol, nausea and vomiting, changes in skin color, upset stomach, dizziness, low red and white blood cells, retinoic acid syndrome, hepatotoxicity, teratogenic effect on fetus, depression, suicidal ideation.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Response duration is calculated from first day of treatment with 3F8.

12.2 Patients are considered a treatment failure if progressive disease develops.

12.3 Disease status is defined by the International NB Response Criteria.[89]

- Complete response/remission (CR): no evidence of disease by imaging studies and standard BM histology (section 8.4).
- Very good partial response/remission (VGPR): >90% decrease in all disease markers, except bone scan unchanged or improved; BM must be free of disease by histology and by scintigraphic studies.
- Partial response/remission: >50% decrease in all disease markers, except bone scan unchanged or improved; $\leq$1 positive BM site; MIBG scan must be negative or improved in all abnormal sites.
- Minor response: >50% decrease in $\geq$1 but not all disease markers; MIBG scan must be negative or improved in at least one site.
- No response: <50% decrease in all tumor markers, no change in MIBG scan.
- Progressive disease (PD): new lesion, or >25 % increase in any disease marker.

12.4 All patients who fulfill the eligibility requirements and receive a first dose of 3F8 will be included in the analysis.

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1 PD any time after cycle 1. However, if a patient develops recurrent disease that can be completely eliminated surgically or eliminated by other means, that patient may remain on study at the discretion of the Principal Investigator as long as the patient does not receive systemic therapy and the recurrence is promptly eliminated.

13.2 Life-threatening grade 4 toxicity clearly attributable to 3F8.

13.3 The investigators will make every reasonable effort to keep each patient in the study until all planned treatments and assessments have been performed. The investigators may discontinue study drug treatment for the following reasons:

- **Adverse events**, including unacceptable toxicity or exacerbation of underlying disease, associated with study drug administration and necessitating discontinuation of treatment. Patients who are removed from the study due to adverse events will be treated and followed according to established, acceptable medical practice. All pertinent information concerning the outcome of such treatment will be entered in the Case Report Form or on the Serious Event Report, as applicable.

- **Withdrawal of consent.** The patient's desire to withdraw from the study may occur at any time. The investigator should carefully consider whether the patient's withdrawal of consent is due to an adverse event, and if so, record the adverse event as the reason for withdrawal.

- **Withdrawal by the physician** for clinical reasons not related to study drug treatment, for example, clinical need to administer a concomitant medication that is excluded by the protocol, in the absence of an adverse event.

- **Violation of the study protocol**, including failure to return for required treatments or assessments. Patients who fail to return for treatments will be withdrawn from the study if more than 4 scheduled doses are missed

13.4 Patients will not be removed from study in order to receive radiotherapy.

13.5 Patients removed from the study will not be replaced. Every effort will be made to follow these patients, with extent-of-disease evaluations performed at least every 3 months through $\geq$2 years from study enrollment.

14.0 BIOSTATISTICS

The objective of this phase II trial is to assess the anti-NB activity of high-dose 3F8 plus GM-CSF in patients in first CR/VGPR from high-risk NB after conventional therapy. The 3F8 dosing is four fold greater than the standard 3F8 dosage used in prior phase II studies.

In A(8), treatment was changed to use standard dose 3F8 (20 mg/m^2/day) for all cycles instead of high-dose 3F8 for cycles 1 and 2. Patients treated as such are evaluable for toxicity only.

14.1 Primary Endpoint

The primary endpoint is two-year relapse-free survival (RFS).

14.2 Sample Size

We will use a Simon's two-stage design.[97] The type I error rate is set as 0.1 and the type II error rate as 0.1.

In the predecessor trial (IRB 03-077: 3F8 at standard dosage of 100 mg/m^2/cycle, (administered initially as 10 mg/m^2/day x10 days per cycle, and subsequently as 20 mg/m^2/day x5 days per cycle) combined with GM-CSF, plus 13-cis-retinoic acid, the 56 patients treated in CR/VGPR after conventional therapy achieved 70% two-year RFS. By taking into account of the small sample variation, we will consider a two-year RFS rate 0.64 as not promising and 0.80 as promising with the new treatment. Twenty-two patients will be accrued initially, and if there are less than 15 RFSs, further accrual to the protocol will be stopped and the new treatment will be declared ineffective in this protocol. If there are at least 15 RFSs, then an additional 36 patients will be accrued for a total of 58. If at least 42 RFSs out of 58 patients, the protocol would be considered to have a positive result and the new treatment would be considered worthy of further testing in this patient population. The probability of stopping the study earlier is 57% under the null hypothesis.

14.3 Accrual Rate

We expect to accrue 10-15 patients per year. This trial can be completed within 3-4 years. The accrual will continue after the first stage of the study, and the two-stage design is used to guard against many early recurrences.

14.4 Secondary Endpoint

The association between histologic examination and real time RT-PCR regarding BM status will be assessed by the Wilcoxon statistic. The clinical significance (relapse-free survival) of histologic results and real time RT-PCR findings will be assessed by log-rank test and Cox regression model.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

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

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.

All participants 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. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

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 extent 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.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

Institutional monitoring plan for phase I and phase II trials: Memorial Sloan-Kettering Cancer Center (MSKCC) has established standard procedures for data safety monitoring of clinical research (see appendix). For Phase II trials, these procedures include consideration of accrual rates, toxicity, adherence to dose-escalation schedules, adverse event notification and data recording.

Therapeutic responses are logged on a central database and approximately 50% are reviewed by an independent committee. An annual report of the trial's progress is sent to the IRB. All of the procedures for Phase II studies outlined in MSKCC's policy are applicable to the current trial and will be followed by the investigators. The analysis of safety will include all patients who receive at least one dose of study medication. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by body system, according to dosage of study medication (single dose as well as cumulative doses of 3F8 and GM-CSF), and according to severity or toxicity grade. Laboratory data will be tabulated and summarized by descriptive statistics, as well as on the basis of MSKCC specified normal ranges.

17.0 PROTECTION OF HUMAN SUBJECTS

The investigator agrees to conduct this study in accordance with the International Conference on Harmonization (ICH) principles of Good Clinical Practice and with the Declaration of Helsinki (1989). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

Most patients will be children, adolescents, and young adults because of the nature of these tumors. Patients of both sexes and all ethnic backgrounds are eligible for this study. Alternative treatments are available and will be discussed with patient or legal guardian. Patients are responsible for the costs of physician visits and usual (routine) laboratory tests, all scans, usual (standard) bone marrow tests, hospitalizations, and outpatient care, GM-CSF, and isotretinoin. There is no charge for 3F8. 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.

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

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org 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.

17.2.1 All SAEs must be entered into the CRDB SAE form page.

SAEs are defined as grade 4 toxicities other than fatigue, weight loss or weight gain, anorexia, nausea, anxiety, constipation, urinary retention from opioid analgesics, somnolence/hallucinations/ disorientation/confusion/ agitation/anxiety from anti-histamine and opioid premedications, hypomagnesemia, fever, rash, dry skin from Accutane, urticaria from 3F8 or GMCSF, myelosuppression from the combination of 3F8 and GM-CSF, pain and transient hypoxia from opioids, and breath-holding with or without transient oxygen requirement. Preexisting conditions e.g. hearing loss, hyperbilirubinemia or elevated LFTs from TPN, alopecia are not counted as SAEs. Hospitalizations that arise from complications of chemotherapy are considered part of standard care and therefore will not be reported.

18.0 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.

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20.0 APPENDICES

Appendix A: Patient diaries.