NANT 2017-01: A PHASE I STUDY OF 131I-MIBG WITH DINUTUXIMAB +/- VORINOSTAT FOR RELAPSED/REFRACTORY NEUROBLASTOMA

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NEW APPROACHES TO NEUROBLASTOMA THERAPY (NANT) CONSORTIUM

NANT 2017-01: A PHASE I STUDY OF ^{131}I-MIBG WITH DINUTUXIMAB +/- VORINOSTAT FOR RELAPSED/REFRACTORY NEUROBLASTOMA

IND# 137554

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ABSTRACT

Relapsed neuroblastoma is incurable in the majority of cases. One of the most effective therapies utilized when patients have refractory or relapsed disease is ^{131}I-Metaiodobenzylguanidine (^{131}I-MIBG). Previous studies have proven that it is safe to combine ^{131}I-MIBG with putative radiation sensitizers, and an ongoing clinical trial seeks to determine if MIBG in combination with these agents is more efficacious than giving MIBG alone. Dinutuximab, a chimeric 14.18 monoclonal antibody that targets the tumor cell surface marker glycosphingolipid GD2 ganglioside (GD2), has significantly improved the event-free survival for patients with high-risk neuroblastoma when given as part of upfront therapy. A recent study performed by the Children's Oncology Group (COG) has demonstrated that dinutuximab can be safely given with cytotoxic chemotherapy, and unlike previous studies with dinutuximab as a single agent, can produce responses even in patients with bulky disease. Data from pre-clinical and adult studies suggest that radiation can enhance the efficacy of immunotherapy and targeted therapies such as dinutuximab. We propose a phase I, dose-escalation study of ^{131}I-MIBG given in combination with dinutuximab (Part A). The primary objective of this part of the study is to define the recommended phase 2 dose (RP2D) of ^{131}I-MIBG and dinutuximab when given in combination, and to define and describe the toxicities. In Part B, we will add vorinostat to the ^{131}I-MIBG and dinutuximab combination, at the RP2D determined in Part A. The rationale for this is based on pre-clinical data demonstrating that vorinostat increases GD2 cell surface expression in neuroblastoma cells, leading to increased anti-tumor activity when combined with anti-GD2 antibody in murine models of neuroblastoma, and clinical data from NANT 11-01 demonstrating that the addition of vorinostat to therapeutic ^{131}I-MIBG produces a higher objective response rate compared to ^{131}I-MIBG alone. The primary objective of Part B is to define the RP2D of vorinostat in combination with ^{131}I-MIBG and dinutuximab, and to define and describe the toxicities of this combination.

SIGNATURE PAGE
NANT 2017-01: A Phase I Study of ^{131}I-MIBG with Dinutuximab +/- Vorinostat for Relapsed/Refractory Neuroblastoma
Amendment #5 Protocol Version: 02/21/2022

This protocol has been approved by:

Name: Araz Marachelian, M.D., M.S. Study Role: NANT Medical Director

Signature: _____ Date: 02/21/2022

Name: Thomas Cash, M.D., M.Sc. Study Role: Study Chairperson

Signature: _____ Date: 02/21/2022

This protocol describes the NANT 2017-01 ^{131}I-MIBG with Dinutuximab +/- Vorinostat study and provides information about procedures for patients taking part in this study.

This protocol has been reviewed and acknowledged by:

Name: _____ Study Role: Site Principal Investigator

Signature: _____ Date: _____

TABLE 1: EXPERIMENTAL DESIGN SCHEMA FOR PART A

DAY	1	2-7	8	9	10	11	12	13	14	15	16	17	18-28
^{131}I-MIBG (M) dose level assignment	M												
GM-CSF (G) 250 mcg/m^2			G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D) dose level assignment			D	D	D	D							
Stem Cell Infusion (HSC)										HSC +/- 2d			

DAY	29	30	31	32	33	34	35	36	37	38	43-57
GM-CSF (G) 250 mcg/m^2	G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D) dose level assignment	D	D	D	D							
Disease Evaluation (Eval)											Eval

Patients receive ^{131}I-MIBG on Day 1. The dose of ^{131}I-MIBG and dinutuximab will be based on the dose level assigned at the time of patient registration. Dinutuximab is given intravenously on Days 8-11 and 29-32 of therapy, with GM-CSF 250mcg/m^2 given on Days 8-17 and 29-38. All patients receive autologous hematopoietic stem cell infusion on Day 15 (+/- 2) of therapy. This must occur at a NANT site.

Course duration is defined as 57 days. All patients will undergo disease restaging between Days 43 – 57. Patients may receive up to two courses of therapy as long as all protocol-defined criteria are met prior to the start of the second course.

TABLE 2: Dose Escalation Schema for Part A

	Dose Level	^{131}I-MIBG (mCi/kg/dose)	Dinutuximab (mg/m^2/dose)
	0	12	14
Starting Dose Level:	**1**	12	17.5
	2	15	17.5
	3	18	17.5

Dose escalation will begin at Dose Level 1, with escalation up to Dose Level 3 following the Rolling 6 dose escalation design. If Dose Level 1 is deemed intolerable per the dose escalation rules, then Dose Level 0

will be evaluated. Patients will be treated at the assigned dose of ^{131}I-MIBG and dinutuximab. There will be no intrapatient dose escalation.

TABLE 3: EXPERIMENTAL DESIGN SCHEMA FOR PART B

DAY	0	1	2-7	8	9	10	11	12	13	14	15	16	17	18-28
Vorinostat (V) dose level assignment	V	V	V	V	V	V	V	V	V					
^{131}I-MIBG (M) dose level assignment		M												
GM-CSF (G) 250 mcg/m^2				G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D) 17.5 mg/m^2				D	D	D	D							
Stem Cell Infusion (HSC)											HSC +2d / -1d			

DAY	29	30	31	32	33	34	35	36	37	38	43-57
GM-CSF (G) 250 mcg/m^2	G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D) dose level assignment	D	D	D	D							
Disease Evaluation (Eval)											Eval

Patients receive vorinostat on Days 0 to +13 (14 days) followed by ^{131}I-MIBG on Day 1. The dose of vorinostat and ^{131}I-MIBG will be based on the dose level assigned at the time of patient registration. Dinutuximab 17.5 mg/m^2 will be given intravenously on Days 8-11 and 29-32 of therapy, with GM-CSF 250 mcg/m^2 given on Days 8-17 and 29-38. All patients will receive autologous hematopoietic stem cell infusion on Day 15 (+ 2d/-1d) of therapy. There must be at least 24 hours between the last dose of vorinostat and stem cell infusion. Stem cell infusion must occur at a NANT site.

Course duration is defined as 57 days. All patients will undergo disease restaging between Days 43 – 57. Patients may receive up to two courses of therapy as long as all protocol-defined criteria are met prior to the start of the second course.

TABLE 4: Dose Escalation Schema for Part B

	Dose Level	Vorinostat (mg/m^2/dose)#	^{131}I-MIBG (mCi/kg/dose)	Dinutuximab (mg/m^2/dose)
Starting Dose Level	**4**	180	18	17.5
	4a*	150	18	17.5

#Maximum vorinostat dose: 400 mg
*De-escalation Dose Level 4a to enroll only if Dose Level 4 is not tolerated

The starting dose level for Part B will be Dose Level 4. Patients on this dose level will receive vorinostat at 180 mg/m^2/dose,^{131}I-MIBG at 18 mCi/kg/dose, and dinutuximab at 17.5 mg/m^2/dose. Enrollment will follow the Rolling 6 dose escalation design. If Dose Level 4 is deemed intolerable per the dose escalation rules, then Dose Level 4a will be evaluated. There will be no intrapatient dose escalation. Once the RP2D is established in Part B, we will enroll a 6-patient expansion cohort to obtain additional toxicity and biologic correlate data with the MIBG, dinutuximab, and vorinostat combination.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

a. To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of ^{131}I-MIBG administered with fixed doses of dinutuximab in children with relapsed or refractory neuroblastoma.

b. To define and describe the toxicities of ^{131}I-MIBG in combination with dinutuximab administered on this schedule to this population.

c. To determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of vorinostat in combination with ^{131}I-MIBG and dinutuximab in children with relapsed or refractory neuroblastoma.

d. To define and describe the toxicities of vorinostat in combination with ^{131}I-MIBG and dinutuximab administered on this schedule to this population.

1.2 Secondary Aim

a. To preliminarily define the response rate of ^{131}I-MIBG in combination with dinutuximab in patients with relapsed or refractory neuroblastoma within the confines of a Phase I study.

b. To preliminarily define the response rate of vorinostat in combination with ^{131}I-MIBG and dinutuximab in patients with relapsed or refractory neuroblastoma within the confines of a Phase I study.

1.3 Exploratory Aims

a. To assess the immune and cytokine profile of patients on this regimen and describe the relationship between immune and cytokine profile and response to treatment.

b. To describe the production of human anti-chimeric antibodies (HACA) and neutralizing anti-drug antibodies (ADA) when ^{131}I-MIBG is given in conjunction with dinutuximab +/- vorinostat.

c. To assess peripheral blood and bone marrow minimal residual disease at study entry and following treatment with ^{131}I-MIBG and dinutuximab +/- vorinostat, quantified using a neuroblastoma-specific NB-5 assay by TaqMan low density array (TLDA).

d. To assess the tumor immune-microenvironment (gene expression; immune effector cells, activities and signaling molecules; immune target expression) following treatment with ^{131}I-MIBG and dinutuximab +/- vorinostat.

e. To study the association between changes in the tumor immune-microenvironment (gene expression; immune effector cells, activities and signaling molecules; immune target expression) with response following treatment with ^{131}I-MIBG and dinutuximab +/- vorinostat.

2.0 BACKGROUND

2.1 Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood. While it comprises only 8% of all childhood cancer cases, neuroblastoma is responsible for 12% of cancer deaths in children under 15 years of age (1,2). Approximately 50% of neuroblastoma patients are classified as high-risk, and over half of these children will die from their disease despite intensive multi-modal therapy (3,4). The prognosis is even more grim for patients whose disease is refractory to initial therapy or who experience a recurrence of their tumor during or after completion of therapy, as the vast majority of these patients cannot be cured (5,6).

2.2 Clinical Experience with 131I-MIBG for Neuroblastoma

Metaiodobenzylguanidine (MIBG) is a norepinephrine analog that is selectively taken up by sympathetic nervous system tissue through the cell surface norepinephrine transporter (7). Approximately 90% of neuroblastoma tumors accumulate MIBG, making this a potential therapeutic target (8,9). MIBG labeled with iodine-123 (^{123}I-MIBG) has become a key component of the diagnostic, staging, and response evaluation in neuroblastoma. MIBG labeled with iodine-131 (^{131}I-MIBG) can be used as a systemic, targeted radiotherapy and has demonstrated activity in both relapsed/refractory and newly diagnosed patients (10-15). In a single-agent phase I dose-escalation study, ^{131}I-MIBG showed a response rate of 37% in children with relapsed disease, with 10 mCi/kg being the minimum dose at which responses were seen (16). A phase II study at the recommended phase II dose of 18 mCi/kg, showed a 36% response rate with another 34% of patients with stable disease (17). The primary toxicity of ^{131}I-MIBG is myelosuppression, particularly thrombocytopenia, and about one-third to one-half of patients will require autologous hematopoietic stem-cell transplantation (AHSCT) (16-18). Because of this, it is now standard practice to prophylactically perform an AHSCT in the majority of patients approximately 2 weeks after MIBG infusion. Non-hematologic toxicity is rare, with grade 3 or 4 hepatic toxicity in 5%, pulmonary toxicity in 3.6%, infectious toxicity in 10.9%, and febrile neutropenia in 9.7% (17).

2.3 Clinical Experience with ^{131}I-MIBG in Combination with Other Agents for Neuroblastoma

Several clinical trials have sought to improve upon the success of single agent ^{131}I-MIBG by combining it with other chemotherapeutic agents. The New Approaches to Neuroblastoma Therapy (NANT) consortium conducted a phase I study of ^{131}I-MIBG in combination with vincristine and irinotecan. This combination was well-tolerated at a maximum ^{131}I-MIBG dose of 18 mCi/kg. Dose-limiting toxicities (DLTs) included grade 3 diarrhea (dose level 15 mCi/kg), grade 3 ALT elevation (dose level 18 mCi/kg), and grade 3 hallucination (dose level 18 mCi/kg). There were no unexpected hematologic toxicities and the objective response rate was 25% (19). A subsequent pilot study showed that by giving the irinotecan over one week instead of two that you could reduce the amount of grade 3 or 4 diarrhea without compromising the efficacy (20). A second phase I study conducted by NANT tested ^{131}I-MIBG in combination with vorinostat. The recommended phase II doses were ^{131}I-MIBG 18 mCi/kg and vorinostat 180 mg/m2/day. At this dose level, 0 of 5 patients had a DLT and the objective response rate was 17% (21). These two trials have proven that ^{131}I-MIBG can be safely given with other systemic anti-cancer agents, with toxicities limited to those specific to the known side effects of the concomitant chemotherapy. A phase II trial comparing these two regimens to single-agent ^{131}I-MIBG is ongoing.

2.4 Clinical Experience with Dinutuximab for Neuroblastoma

Dinutuximab is a chimeric (ch) 14.18 monoclonal antibody that targets the disialoganglioside GD2. While GD2 is nearly ubiquitously expressed on neuroblastoma cells, its expression on human tissues is limited to peripheral neurons, melanocytes, and peripheral pain fibers, making it an ideal therapeutic target (22-24). Phase I and II clinical trials of ch 14.18 both alone and in combination with cytokines such as GM-CSF and/or interleukin-2 (IL2) have demonstrated signals of efficacy against neuroblastoma (25-28). This led to a randomized phase III trial performed by the Children's Oncology Group (COG) comparing dinutuximab combined with GM-CSF, IL2, and isotretinoin to isotretinoin alone as post-consolidation therapy. This trial was stopped early because the event-free survival (EFS) for patients treated with dinutuximab was significantly better than for patients treated with isotretinoin alone (66% vs. 46%; P = 0.01) (29). Very few patients with bulk disease achieved an objective response, a finding that has been supported by other studies (29,30). Despite this, dinutuximab is now considered part of the standard upfront therapy for patients

with high-risk neuroblastoma. While this immunotherapy has proven to be effective, it has a significant side effect profile, especially when given with IL2; however, these toxicities are typically manageable. Common grade 3 or 4 toxicities include neuropathic pain (52%), hypotension (18%), fever (39%), acute capillary leak (23%), hypersensitivity reactions (25%), infection (39%), hyponatremia (23%), hypokalemia (35%), and ALT elevation (23%) (29).

2.5 Pre-clinical and Clinical Experience with Dinutuximab in Combination with Chemotherapy for Neuroblastoma

Preclinical studies suggest that anti-GD2 monoclonal antibodies (mAb) can augment the effects of cytotoxic chemotherapy. In a small cell lung cancer (SCLC) cell line, the combination of cisplatin and anti-GD2 mAb resulted in enhanced cytotoxicity, at least in part due to the anti-GD2 mAb inducing direct apoptosis of the SCLC cells (31). In a second study with a neuroblastoma cell line (IMR-32), the addition of the anti-GD2 14G2a antibody resulted in additive effects on cell killing when combined with carboplatin and synergistic effects when combined with doxorubicin and topotecan (32).

A recent phase II trial conducted by the Children's Oncology Group (COG) randomized patients to receive either dinutuximab or temsirolimus with chemotherapy (irinotecan and temozolomide) for the treatment of high-risk neuroblastoma patients with primary refractory disease and those in first relapse. Among the 17 patients randomized to the dinutuximab arm, 9 (53%) had an objective response (partial response = 4, complete response = 5), which included 3 patients with bulky disease and 3 patients with prior anti-GD2 exposure (33). This 53% objective response rate (ORR) was remarkably better than the 15% ORR seen with irinotecan/temodar alone (34). No unanticipated toxicity was experienced in patients treated on the dinutuximab arm, and this stratum was determined to be the optimal combination for further study (33).

A study being conducted by St. Jude Children's Research Hospital is testing the safety and efficacy of giving their anti-GD2 antibody, hu14.18K332A, to all newly diagnosed high-risk neuroblastoma patients (NCT01576692). Preliminary data from an interim analysis show that the response rate on this study after two cycles of anti-GD2 antibody plus topotecan/cyclophosphamide is 80%, and that the regimen-related toxicity was tolerable (35). This response rate is notably better than the 40% response rate seen in a previous study that gave topotecan/cyclophosphamide alone (36).

These two studies combining an anti-GD2 antibody with cytotoxic therapy suggests that this approach is safe and may produce better response rates than either of the agents given alone.

2.6 Rationale for Combining Dinutuximab with Radiation Therapy

Additional data combining dinutuximab with other therapies are limited, however preclinical and clinical studies in adult malignancies have shown that the effects of immunotherapy can be augmented if patients are first exposed to radiation (37-41). This is supported by the clinical phenomenon known as the abscopal effect where tumor regression occurs at sites distant to the irradiated field through radiation-induced, immune-mediated anti-tumor mechanisms. Data have shown that this occurs through the release of pro-inflammatory cytokines and enhanced expression of tumor-associated antigens, death receptors, and co-stimulatory molecules on tumors cells exposed to radiation which increases their recognition and killing by T cells (42-47). Given antibody-based therapies rely on antibody-dependent cellular cytotoxicity (ADCC), radiation, by promoting systemic activation of the immune system, creates the optimal environment to augment immunotherapy anti-tumor response.

In adult clinical trials across a variety of malignancies, clinical responses have been seen when radiation therapy has been combined with several different types of immunotherapy including dendritic cell (DC) vaccines, immune checkpoint blockade, cytokines and other immunoadjuvants (48-55). In a case reported by Hiniker et al., a patient with metastatic melanoma had complete regression of all metastatic lesions when treated with ipilimumab and concurrent radiation (54 Gy in three fractions)(56). Grimaldi et al. reported 21 patients with melanoma who had progressed on immune checkpoint blockade, and 11 (52%) of these subsequently demonstrated an abscopal response when treated with radiation (51). In a phase I trial, intratumoral injections of autologous DCs were given to patients with advanced hepatocellular carcinoma 2 days after a single fraction of radiotherapy (52). A partial response was reported in 2/14 patients. In a

different study where DCs were injected into sarcomas during fractionated radiotherapy given as neoadjuvant treatment, 12 of 17 patients were free from progression of their cancer at 1 year (57). This preliminary data and data from multiple other studies have served as the background for scores of ongoing clinical trials testing the radiation plus immunotherapy approach (58).

These pre-clinical and clinical data provide rationale for combining a systemic radiation therapy such as ^{131}I-MIBG with the immunotherapy dinutuximab. In an effort to take advantage of the systemic, radiation-induced, inflammatory-mediated, anti-tumor effect (abscopal effect) potentially produced by the ^{131}I-MIBG, we will administer the ^{131}I-MIBG prior to the dinutuximab. This sequence will allow us to administer the dinutuximab at a time when the immune system is already activated and primed to augment the anti-tumor effects produced by the immunotherapy dinutuximab.

2.7 Summary and Rationale for Clinical Use of ^{131}I-MIBG with Dinutuximab

Relapsed/refractory neuroblastoma is incurable in the majority of cases, underscoring the critical need for novel therapeutic approaches. ^{131}I-MIBG, a targeted, systemic radiotherapy, is the most effective salvage therapy available for this population of patients, and recent data suggests it can be safely combined with chemotherapy. Dinutuximab, an anti-GD2 monoclonal antibody, has significantly improved the outcomes for patients with newly diagnosed neuroblastoma. Dinutuximab, when given in combination with chemotherapy, can be administered safely and produces promising response rates against even bulky relapsed/refractory neuroblastoma. Lastly, radiation therapy induces systemic, anti-tumor immune responses to augment the effects of immunotherapy. We therefore propose a phase I trial testing ^{131}I-MIBG with dinutuximab for patients with relapsed/refractory neuroblastoma. In order to maximize the systemic, immune-mediated, anti-tumor effects of this combination and determine the optimal dosing to produce this synergy, we will administer the standard dose of dinutuximab (17.5 mg/m^2/dose) to all patients while escalating the ^{131}I-MIBG.

2.8 Correlative and Biology Studies

2.8.1 Characterization of Immune and Cytokine Profile Following ^{131}I-MIBG Therapy

Dinutuximab works by binding to cell surface GD2 and inducing cell lysis. This occurs via antibody-dependent cell-mediated cytotoxicity (ADCC) mediated mainly by natural killer (NK) cells, neutrophils, and monocytes, and to a lesser degree by complement-dependent cytotoxicity (CDC) (29,59-62). Immune-activating cytokines augment the ADCC by increasing the number of granulocytes and macrophages (GM-CSF), as well as NK cells and antigen-specific T cells (IL-2) (59,61).

^{131}I-MIBG is a myelosuppressive therapy that requires autologous stem cell rescue in up to 50% of patients (16-18). The median time to platelet nadir post ^{131}I-MIBG is 24 days (range: 8-47) and median time to absolute neutrophil count (ANC) nadir is 42 days (range: 10-68) (63). While ^{131}I-MIBG causes neutropenia in the majority of cases, it is unclear what impact ^{131}I-MIBG has on the other effector cells of the immune system and the cytokines they produce, or what impact this has on the patient's ability to activate ADCC. We will collect blood at baseline and at serial time points to evaluate the number and function of the effector cells involved with ADCC, as well as the pro-inflammatory cytokines that may augment the effects of immunotherapy and stimulate an immune-mediated anti-tumor response.

2.8.2 Descriptive Profile of Human Anti-Chimeric Antibody (HACA) and Neutralizing Anti-Drug Antibody (ADA)

Due to the chimeric nature of dinutuximab, some patients will develop HACA as part of their immune response. Studies performed in neuroblastoma patients have shown that the development of HACA does not occur in a significant number of patients, and the development of neutralizing ADA occurs rarely. However, a recent pharmacokinetic study of ch14.18 antibody suggested that while non-neutralizing antibodies may not have a biologic effect, they can still form immune complexes that are removed by the reticuloendothelial system leading to increased clearance of the drug (64). Also, the clinical impact of ADA may be dependent on the titer of the antibody (64). There are no data describing the effect of ^{131}I-MIBG on the development of HACA or neutralizing ADA. We will describe the HACA and ADA profile in patients post-^{131}I-MIBG therapy and during treatment with dinutuximab, and correlate this with anti-tumor response.

2.8.3 Five Gene NB-5 Assay by TLDA for Neuroblastoma Tumor Cell Detection

Dr. Robert Seeger's laboratory developed the NB-5 assay, a five gene TLDA array for sensitive detection of neuroblastoma tumor cells in peripheral blood and bone marrow. Five genes [chromogranin A (CHGA), doublecortin (DCX), dopadecarboxylase (DDC), paired-like homeobox 2B (PHOX2B), and tyrosine hydroxylase (TH)] are highly expressed by neuroblastoma cell lines and tumors. These same genes are rarely expressed by normal blood cells, peripheral blood stem cells (PBSC), and bone marrow. Four housekeeping genes are used for quality control and data analysis. Heterogeneity in expression of the detection genes among neuroblastoma cell lines (n=22) and primary untreated stage 4 neuroblastoma tumors (n=23) is minimal. However, the use of five genes assures that heterogeneity will not impact tumor cell detection.

Spiking experiments demonstrate the sensitivity of neuroblastoma cell detection using this 5-gene signature. Detection sensitivity with five genes (including TH) is superior to that of a single gene (TH). The five-gene detector has nearly 100% sensitivity to detect neuroblastoma RNA at a dose of 10-5, whereas the TH-only detector has sensitivity of <60%. In terms of neuroblastoma cell detection, the 5-gene signature can detect a 10-6 neuroblastoma cell frequency in PBMC with 81% probability compared to <30% for a TH-alone detector.

NB-5 Detection Gene Score (DG score) is highly correlated with Immunocytology Score (number of tumor cells/10^6 total cells) when Immunocytology is positive in bone marrow. Forty-four unselected fresh bone marrow specimens were tested by both assays. The rank correlation between the TLDA DG Score and Immunocytology Score was r = -.93 ($p < 0.001$), which demonstrates a clear relationship between the two assays. The NB-5 assay also can detect tumor cells in bone marrow that are not detected by Immunocytology. Thirty-six of the 44 bone marrows were negative by Immunocytology, but 20 of these were positive by NB-5. These data further confirm that the NB-5 assay is more sensitive than Immunocytology for detecting tumor cells. Moreover, detection of occult bone marrow tumor cells by NB-5 appears to have clinical relevance. In patients with newly diagnosed high-risk neuroblastoma, detection of tumor cells by TLDA in a bone marrow sample negative by Immunocytology at the end of therapy was associated with significantly worse event-free survival than bone marrow samples negative for tumor cells by TLDA assay.
In the NANT biology study, mRNA for CHGA, DCX, DDC, PHOX2B, and TH was quantified in BM and blood from 101 patients concurrently with clinical disease evaluations (65). Correlation between NB-mRNA (delta cycle threshold [ΔCt] for the geometric mean of genes from the TaqMan® Low Density Array NB5 assay) and morphologically-defined tumor cell percentage in BM, ^{123}I-meta-iodobenzylguanidine (MIBG) Curie score, and CT/MRI-defined tumor longest diameter was determined. Time-dependent covariate Cox regression was used to analyze the relationship between ∆Ct and progression-free survival (PFS). NB-mRNA was detectable in 83% of BM (185/223) and 63% (89/142) of blood specimens, and their ∆Cts were correlated (Spearman r=0.67, p<0.0001) although BM Ct was 7.9±0.5 Ct stronger than blood Ct. When BM morphology, MIBG, or CT/MRI were positive, NB-mRNA was detected in 99% (99/100), 88% (100/113), and 81% (82/101) of BMs. When all three were negative, NB-mRNA was detected in 55% (11/20) of BMs. BM NB-mRNA correlated with BM morphology or MIBG positivity (p<0.0001 and p=0.007). BM and blood ΔCts correlated with PFS (p<0.001; p=0.001) even when BM was morphologically negative (p=0.001; p=0.014). Multivariate analysis showed that BM and blood ΔCts were associated with PFS independently of clinical disease and *MYCN* gene status (p<0.001; p=0.055). This five-gene NB5 assay for NB-mRNA improves definition of disease status and correlates independently with PFS in relapsed/refractory NB.

The current study includes an exploratory aim to evaluate neuroblastoma cell detection in blood and bone marrow by NB5 assay within the context of this study. These samples will be obtained as part of the companion NANT biology study (N04-05).

2.8.4 Evaluation of the Tumor Microenvironment (TME) and Immune Response Genetic Signatures

Recent studies in neuroblastoma have demonstrated an increasingly important role of the TME in contributing to neuroblastoma cell growth, metastasis, drug resistance, and evasion from immune-mediated destruction (66,67). An analysis of tumor tissue from patients with high-risk neuroblastoma demonstrated higher infiltration of tumor-associated macrophages (TAMs) in metastatic compared to locoregional tumors,

and patients with metastatic tumors at age ≥ 18 months had higher expression of inflammation-related genes than those with metastatic tumors at age < 18 months (66). This so-called inflammatory subtype of neuroblastoma is thought to have a high risk of recurrence and a poor prognosis. In this study we will evaluate the most recently obtained soft tissue tumor samples when present for the presence of TAMs, as well as tumor infiltrating lymphocytes (TILs), and correlate this with response to therapy. We will also evaluate for the presence of the immune checkpoint proteins CD274 (PDL1) and CD276 (B7H3) as these may affect the activity of the effector T and NK cells and impact immune activation and potentially ADCC. Furthermore, expression of immune response related genes may be predictive of anti-tumor effect and ADCC in patients treated with dinutuximab and ^{131}I-MIBG. RNA samples obtained from the blood prior to and following therapy, and samples collected after administration of ^{131}I-MIBG and dinutuximab will be used for analysis of expression of a panel of genes related to immune function (including cell surface receptors, proteases, cytokines and cytokine receptors, cell cycle and protein kinases, etc.) and for more global analysis via RNASeq (68). We will also perform these analyses on tumor tissue when available.

2.9 Preclinical Experience with Vorinostat in Neuroblastoma

Vorinostat, known as a pan-histone deacetylase (HDAC) inhibitor due to its ability to inhibit both class-I and class-II HDACs, is a potent inhibitor of HDAC activity at low nanomolar concentrations (69). A variety of HDAC inhibitors have demonstrated the ability to promote apoptosis and differentiation across multiple neuroblatoma cell lines (70-74). Preclinical testing of vorinostat in xenograft mouse models derived from neuroblastoma cell lines demonstrated statistically significant prolongation of event-free survival in 4/6 cell lines tested (75). Preclinical studies have demonstrated additional potential benefits of vorinostat in neuroblastoma, such as the ability to increase expression of the norepinephrine transporter and increase MIBG uptake *in vitro* and *in vivo* within 24 hours of vorinostat exposure (76). Vorinostat has also been shown to sensitize neuroblastoma cells to the effects of ionizing radiation, and enhance the efficacy of radiation when given in combination (77). These data provided rationale for the NANT 07-03 phase 1 study testing ^{131}I-MIBG plus vorinostat in patients with relapsed/refractory neuroblastoma (21).

2.10 Rationale for Testing Vorinostat in Combination with ^{131}I-MIBG and Dinutuximab

Preclinical data demonstrate that vorinostat upregulates GD2 cell surface expression *in vitro* (murine 9464D, human IMR-32 and SKNAS cell lines) and *in vivo* (C57Bl/6 mice bearing 9464D tumors) neuroblastoma models (69,78). While the exact mechanism of how vorinostat increases GD2 expression remains unclear, preliminary investigations suggest that it either works directly by affecting the acetylation of GD2 synthase or indirectly through transcriptional regulation of the GD2 synthase stabilizing gene (69). By increasing the number of macrophages with activating Fc receptors and decreasing the number of myeloid-derived suppressor cells, vorinostat creates a permissive tumor microenvironment for anti-GD2 immunotherapy (69). Most importantly, Kroesen et al., using their TH-MYCN transgenic mouse model, demonstrated that the anti-GD2 antibody plus vorinostat combination was synergistic, and led to both significantly superior inhibition of neuroblastoma tumor growth and survival compared to vorinostat alone (9/9 mice alive at day 45 in combination compared to 4/9 mice in single agent). This provides rationale for clinically testing vorinostat in combination with anti-GD2 antibody therapy in patients with relapsed/refractory neuroblastoma.

The NANT 2011-01 study was a randomized, pick-the-winner, phase 2 trial that sought to determine whether the addition of one of two different putative radiation sensitizers, vincristine/irinotecan (Arm B) or vorinostat (Arm C), given in combination with ^{131}I-MIBG (18 mCi/kg), produced superior response rates compared to ^{131}I-MIBG monotherapy (Arm A) in patients with relapsed/refractory neuroblastoma. Patients treated on Arm C of N11-01 received vorinostat at 180 mg/m^2/day on days -1 to +12 (14 days) with ^{131}I-MIBG on day 1 (18 mCi/kg) based on the preceeding phase 1 trial (NANT 07-03) that established this as the RP2D and demonstrated that this combination was safe and well-tolerated (21). On NANT 11-01, after one course of therapy in 105 response-evaluable patients, the objective response rate (ORR) on Arms A (N=36), B (N=35), and C (N=34) were 17% (95% CI: 7-33%), 14% (95% CI: 5-31%), and 32% (95% CI: 18-51%), respectively (79). An additional 7 patients on Arm C met criteria for a minor response per NANT criteria. Rates of ≥ grade 3 non-hematologic toxicity were comparable between the ^{131}I-MIBG monotherapy and ^{131}I-MIBG + vorinostat arm, accounting for the known vorinostat toxicities. These data demonstrate that the addition of vorinostat to ^{131}I-MIBG produces almost twice the ORR compared to ^{131}I-MIBG monotherapy.

We will administer vorinostat on the same dose and schedule, unless intolerable, as was utilized in the N11-01 study.

Potential overlapping toxicities between vorinostat and dinutuximab may include GI toxicities such as loss of appetite, abdominal pain, nausea/vomiting, diarrhea, and elevated liver function tests, and nephrotoxicities such as elevated creatinine and electrolyte wasting. We do not expect increased hematologic toxicity from the vorinostat + dinutuximab combination. The NANT phase 1 trial (NANT 08-02) that combined vorinostat with cis-retinoic acid showed that ≥ grade 3 non-hematologic toxicity from vorinostat is infrequent (80). In 28 DLT-evaluable patients, there were no grade 4, cycle 1 treatment-related, non-hematologic events, and grade 3 events were limited to pain (N=3 events), cheilitis (N=1), nausea (N=1), vomiting (N=1), AST/ALT elevation (N=3), and rash (N=1). NANT 11-01 demonstrated that only one-third of the patients treated on Arm C (^{131}I-MIBG + vorinostat) experienced a $\underline{\geq}$ grade 3 non-hematologic toxicity, and no patients experienced ≥ grade 3 diarrhea (74). The first 2 dose levels (N=11) of NANT 17-01 have shown low rates of treatment related non-hematologic toxicity, with no episodes of grade 4 non-hematologic toxicity, and grade 3 events limited to abdominal pain (N=2), GGT increased (N=1), and hypokalemia (N=1). Based on these data, we anticipate that any overlapping toxicities between vorinostat, ^{131}I-MIBG, and dinutuximab will be low grade and easily managed.

2.11 Rationale for Protocol Amendments

Amendment #1

Pre-activation amendment dealt with updates and clarifications in required observations, drug information, and statistical design, in addition to administrative changes.

Amendment #2

The 3+3 design was replaced by Rolling 6 design. Due to the long duration of each course the study committee deemed the Rolling 6 design to be more efficient; especially in the light of recent approval from the FDA to charge patients for the investigational use of ^{131}I-MIBG**.** In addition, language was updated regarding plasma and PBMC separation and storage (Appendix VI). This new language simplifies the process through using CPT tubes, removes the need for sites to make the freeze media as this will be provided by Emory. As a result, Appendix VII is no longer needed and specific instructions were provided for the volume of freeze media to add. Language was also added to allow sites to use local procedures for plasma and PBMC isolation if approved by study committee. After discussion with FDA, NDP was removed supplier for ^{131}I-MIBG. At this time Jubilant Radiopharma will be the only supplier for ^{131}I-MIBG. The GM-CSF toxicity table in the consent was revised to better reflect the package insert and protocol**.** A new subsection was added to outline general instructions for ordering dinutuximab. After discussion with study committee, HACA and ADA collection time points were revised to be consistent with HACA and ADA collection time points in current NANT studies. Two additional sampling times were added to complete HACA/ADA levels analysis.

Amendment #3

Based on review of hepatic toxicity in patients treated on this protocol, DLT language was revised to exclude Grade 3 GGT (attributable to protocol therapy) as a DLT since ALT, AST and bilirubin are the main parameters used for eligibility and required observations, and are the parameters that are most clinically meaningful. Statistical language was updated to reflect Rolling 6 design. Additional administrative edits were implemented throughout the protocol.

Amendment #3A

Language was revised in sample consent regarding risk and results of germline genetic testing. Language was added in section 6.0 (Drug Information) regarding unit dose vials and radiochemical purity testing.

Amendment #4A

Based on results of the NANT 2011-01 study and preclinical data suggesting HDAC inhibitors can synergize with anti-GD2 antibody, this amendment added Part B which will test vorinostat in combination with ^{131}I-MIBG and dinutuximab/GM-CSF. We will test one dose level of vorinostat in combination with the MTD/RP2D of ^{131}I-MIBG /Dinutuximab/GM-CSF from Part A of this study (18 mCi/kg/dose), with 1 dose de-escalation level if needed, and then enroll to an expansion cohort testing the vorinostat, ^{131}I-MIBG, and dinutuximab/GM-CSF combination. Eligibility changes to reflect part B requirements were made. Changes related to GM-CSF were made to exclude patients who previously had to permanently discontinue GM-CSF due to toxicity, clarify GM-CSF administration, and remove any minimum requirement of GM-CSF received to be evaluable for dose-escalation purposes. To align with other NANT trials, the definition of evaluable for response was modified to state that any patient on Part A who receives ^{131}I-MIBG or any patient that receives a dose of vorinostat on Part B will be evaluable for response. Patients previously treated on study prior to amendment #4A will have their response re-classified using this updated definition, and all patients enrolled on study after amendment #4A will have to meet this updated definition to be considered evaluable for response. Additionally, the definition of evaluable for dose escalation consideration (DLT-evaluable) was modified with this amendment. The new definition of evaluability applies only for patients treated on the Part A dose expansion cohort and patients on Part B. Patients treated on the Part A dose escalation cohort both before and after amendment #4A will continue to use the previous definition of DLT-evaluable (i.e., patients treated on study prior to amendment #4A will not be re-classified using the amendment #4A definition of DLT-evaluable). A new Informed consent for Part B was added. In addition, changes to response to clarify version 2.0 for bone marrow response were included. Other administrative changes were made to the protocol.

Amendment #5

The protocol was amended to remove the ^{131}I-MIBG radiochemical purity testing requirement prior to ^{131}I-MIBG infusion that was previously mandated on this protocol. This change was made for consistency with the most up-to-date Jubilant Radiopharma Nuclear Medicine Manual (Version 8). Prior references to “Jubilant Draximage” were updated to “Jubilant Radiopharma” to correspond with the company’s name change. Additionally, editorial changes have been made throughout the protocol document.

3.0 PATIENT ELIGIBILITY CRITERIA AND REGISTRATION

3.1 Patient Preparation for Study Entry and Registration

The NANT Operations Center will accept treatment reservations for this study once the patient has been reviewed at an ^{131}I-MIBG treatment center as a possible candidate for this study.

3.1.1 Patient Registration on Study

NANT trials have two components for data entry workflow: 1. Data collection on paper CRF and data entry at the NANT Operations Center through the CAFÉ database and 2. Remote data entry via Medidata Rave clinical data management system.

This is a dose escalation study and treatment slots are obtained through the standard NANT reservation process by sending an email to NANTrsvp@chla.usc.edu

Sites begin the reservation process by completing a subject screen form in Medidata. This generates a unique subject screen number (S-xxx). The site uses this number to reserve a treatment slot for the patient with the NANT Operations Center (NANTrsvp@chla.usc.edu) . Once assigned a treatment slot by the NANT Operations Center, sites should send signed informed consent/assent and all source documentation confirming eligibility to the NANT Operations Center at Children's Hospital Los Angeles by email to nantcrf@chla.usc.edu or if unable to email by FAX at 323-361-1803, Monday through Friday, 8:30am – 5:00pm Pacific Time except holidays.

Once all necessary source documentation is received in the NANT Operations Center, sites can complete the enrollment process by submitting the eligibility form in Medidata Rave. The NANT Operations Center will verify eligibility and assign a unique NANT registration and study subject number in Medidata Rave. The dose level for treatment will be assigned by the NANT Operations Center at the time of study registration. Once study registration is completed, the NANT Operations Center will send an email to the site confirming registration and dose level for treatment. This registration email **must** be received prior to starting any protocol therapy or the patient will be declared ineligible. The registration email will be sent to the treating facilities, Study Chair, Study Vice-Chair, and relevant committee members. The registration steps are summarized in Table 3 below.

Table 5: Summary of Registration Steps

Step	Process	Comment
1	Site completes a subject screen form in Medidata-Rave and communicates the assigned unique patient screening number to NANT Operations Center. NANT Operations Center assigns a treatment slot for the patient and notifies the site. Treatment slots are assigned based on reservation requests processed through the NANT Operations Center.	Use email address: NANTRSVP@chla.usc.edu for treatment slot reservations.
2	Site completes demographics and eligibility form in Medidata Rave in addition to required paper CRFs.	
3	NANT Operations Center verifies eligibility and assigns unique NANT registration and study subject number in Medidata Rave. NANT Operations Center assigns the dose level for treatment.	
4	NANT Operations Center sends an email confirming registration.	Confirmation sent to the treating facilities, Study Chair, Study Vice-Chair, and relevant committee members.
5	Patient can begin treatment as specified in the protocol	

A registration worksheet is available on the web site (www.NANT.org) in the data forms packet to assist institutions with registration requirements for this protocol. Please contact NANT Operations Center at the contact information below for questions on registration.

Contact Person:

Research Coordinator
NANT Operations Center
Children's Hospital Los Angeles
4650 Sunset Blvd, MS #54
Los Angeles, CA 90027
Phone: (323) 361-5687
FAX: (323) 361-1803
nantcrf@chla.usc.edu

To allow non-English speaking patients to participate in this study, bilingual health services will be provided in the appropriate language when feasible.

Timing of Registration and Treatment Initiation:
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than seven (7) days after the date of study registration. Contact NANT Operations Center for any situations which may delay the start of protocol therapy beyond 7 days after study registration.

3.1.2 Co-Enrollment on NANT 2004-05
Co-enrollment on NANT 2004-05 (NANT Neuroblastoma Biology Study) is required for all patients enrolling on this trial. Patients are strongly encouraged to submit bone marrow as well as blood prior to starting therapy on NANT 2017-01 and continue to submit with each disease evaluation.

IMPORTANT NOTE:
The eligibility criteria listed below are interpreted literally and cannot be waived. These criteria apply to Part A and B of the study unless otherwise specified.

3.2 Inclusion Criteria

3.2.1 Age
Patients must be ≥ 1 year and < 30 years of age at the time of study registration.

3.2.2 Diagnosis
Patients must have a diagnosis of neuroblastoma either by histologic verification of neuroblastoma and/or demonstration of tumor cells in the bone marrow with increased urinary catecholamines.

3.2.3 Disease Risk Group
Patients must have high risk neuroblastoma according to COG risk classification at the time of study registration. Patients who were initially considered low or intermediate risk, but then reclassified as high risk are also eligible.

3.2.4 Response to Prior Therapy (using INRC definitions)
Patients must have at least ONE of the following:

3.2.4.1 **Recurrent/progressive disease** after the diagnosis of high risk neuroblastoma at any time prior to study registration – regardless of response to frontline therapy. Note that this excludes patients initially considered low or intermediate risk that progressed to high risk disease but have **not** progressed after the diagnosis of high risk neuroblastoma.

3.2.4.2 **If no prior history of recurrent/progressive disease since the diagnosis of high risk neuroblastoma**

3.2.4.2.1 **Refractory disease**: A best overall response of no response/stable disease since diagnosis of high risk neuroblastoma AND after at least 4 cycles of induction therapy.

3.2.4.2.2 **Persistent disease:** A best overall response of partial response since diagnosis of high risk neuroblastoma AND after at least 4 cycles of induction therapy:

i. If a patient with persistent disease has 3 or more MIBG avid sites (including all soft tissue and/or bone lesions) OR a Curie Score of ≥ 3, then no biopsy is required for eligibility.

ii. If a patient with persistent disease has only 1 or 2 MIBG avid sites (including all soft tissue and/or bone lesions) then biopsy confirmation of neuroblastoma and/or ganglioneuroblastoma in at least one site (bone marrow, bone, or soft tissue) is required. Bone and/or soft tissue lesions may be biopsied at any time point prior to study registration, bone marrow must be done at the time of study registration.

3.2.5 Sites of Disease: MIBG Uptake

Patients must have evidence of MIBG uptake into tumor at ≥ 1 site (bone or soft tissue) within 28 days prior to study entry and subsequent to any intervening therapy.

3.2.6 Autologous peripheral blood stem cells (PBSC)

- The minimum dose for peripheral blood stem cells is 2.0 x 10^6 viable CD34+ cells/kg. Patients who do not meet this minimum requirement for available PBSCs are not eligible.
- Only un-purged stem cells are allowed unless a center has separate FDA approval for infusion of purged stem cells.
- For patients whose body weight exceeds ideal body weight (IBW) by more than 20%, adjusted body weight may be used for the calculation of PBSC dose (Reference: Bone Marrow Transplant. 40(7):665-9; Appendix III).

3.2.7 Performance Status

Patients must have must have a Lansky (≤ 16 years) or Karnofsky (> 16 years) score of ≥ 50 (Appendix I).

Note: Subjects who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

3.2.8 Prior Therapy

3.2.8.1 Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to study registration. Patients must not have received the therapies indicated below within the specified time period **prior to** study **registration** on this study as follows:

	Therapy Type	Administration Restriction WITHIN the Specified Time Period Prior to Study Registration	Comments
1	**Myelosuppressive chemotherapy** **Biologic antineoplastics**	14 days	Includes cytotoxic agents given on a low dose metronomic schedule as well as retinoids
2	**Investigational medications** • Covered under another IND	14 days	
3	**Monoclonal antibodies (MoAb)** • Includes dinutuximab	7 days or 3 half-lives but not longer than 30 days	With recovery of any associated toxicities. MoAb half-life table at www.nant.org for MoAb specific half lives
4	**Cellular Therapy** • Modified T-cells, NK cells, dendritic cells etc.	21 days	With recovery of any associated toxicities.
5	**External Beam Radiation**		
5a	• Small port radiation	14 days	
5b	• Large field radiation	12 weeks	Craniospinal, whole abdominal, total lung, >50% marrow space
5c	• Other substantial bone marrow radiation	6 weeks	
6	**^{131}I-MIBG Treatment (therapeutic dosing)**		
6a	• Last ^{131}I-MIBG infusion	12 weeks	
6b	• No disease progression on first restaging after any previous ^{131}I-MIBG therapy		
6c	• Cumulative lifetime dose of ^{131}I-MIBG not to exceed 20 mCi/kg		
7	**Hematopoietic Stem Cell Transplant (autologous infusion only)**		
7a	• Following myeloablative therapy	12 weeks	
7b	• Following non-myeloablative therapy	Eligible at any time as long as other eligibility criteria are met.	

3.2.9 Concomitant Medications

3.2.9.1 Patients must not have received the concomitant medications indicated below within the specified time period **prior to** study **registration or planned treatment start date** on this study as follows:

	Therapy Type	Administration Restriction WITHIN the Specified Time Period Prior to Study Registration	Comments
1	**Other anti-cancer agents or radiotherapy**	At time of study registration or while on study	
2	**Systemic corticosteroids at pharmacologic doses**	7 days	• Inhaled steroids are permitted to treat asthma • ≤ 2mg/kg of hydrocortisone or equivalent is permitted as blood product premedication to avoid allergic reactions • Physiologic dosing is permitted for patients with known adrenal insufficiency
3	**Medications that prolong QTc (Part B only)**	7 days	• Patients must not be receiving medications known to prolong the QT interval (see first column of table in Appendix VII) • Note this includes pentamidine, azithromycin and methadone among other medications
4	**Valproic acid (Part B only)**	30 days	
5	**Medications interfering with ^{131}I-MIBG uptake**	7 days before planned ^{131}I-MIBG treatment start date **AND** 7 days after ^{131}I-MIBG infusion	Refer to Appendix IV
6	**IVIG**	14 days before planned treatment start date	

3.2.10 Organ Function Requirements

3.2.10.1 Hematologic Function:
Patients must meet the following hematologic criteria for enrollment regardless of bone marrow disease involvement:

a. ANC ≥ 750/uL (no short-acting hematopoietic growth factors within 7 days of blood draw documenting eligibility and no long-acting hematopoietic growth factors within 14 days of blood draw documenting eligibility); and
b. Platelet count ≥ 50,000/µl, transfusion independent (no platelet transfusions or platelet growth factors within 7 days of blood draw documenting eligibility).
c. There is not an eligibility criterion for hemoglobin; however, patients must have hemoglobin ≥ 10 g/dL on the day of or prior to each ^{131}I-MIBG infusion (PRBC transfusions permitted).

3.2.10.2 Renal Function:
Patients must have adequate renal function defined as age-adjusted serum creatinine ≤ 1.5 x normal for age (see below):

Age	Maximum Allowable Serum Creatinine
≤ 5 years	0.8 mg/dL
>5 and ≤ 10 years	1.0 mg/dL
>10 and ≤ 15 years	1.2 mg/dL
>15 years	1.5 mg/dL

3.2.10.3 Liver Function:

a. Total bilirubin ≤ 1.5 x ULN for age; and,

b. SGPT (ALT) < 3 x ULN for age (Note that for ALT, the upper limit of normal (ULN) for all NANT sites is defined as 45 U/L.).

3.2.10.4 Lung Function:
Normal lung function with no dyspnea at rest, exercise intolerance, or oxygen requirement.

3.2.10.5 Central Nervous System (CNS) Function:

a. Patients with a history of intraparenchymal or leptomeningeal based CNS disease must have no clinical or radiological evidence of active CNS disease at the time of study enrollment.
b. Patients with skull based tumors with direct intracranial extension are eligible as long as there are no neurologic signs or symptoms related to the lesion.

3.2.10.6 Cardiac Function:

a. Normal ejection fraction (≥ 55%) documented by either echocardiogram or radionuclide MUGA evaluation OR normal fractional shortening (≥ 27%) documented by echocardiogram
b. Corrected QT (QTc) interval ≤ 480 msec (Part B only)

3.2.10.7 Reproductive Function

a. All post-menarchal females must have a negative serum or urine beta-HCG within 7 days prior to study registration.
b. Male and female subjects of reproductive age and childbearing potential must agree to use two acceptable methods of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) or to abstain from heterosexual intercourse for the duration of their participation in the study, or for 3 months after last dose of protocol therapy, whichever is longer.

3.2.10.8 Physician deems that there is reasonable ability to obtain vorinostat via commercial supply (Part B only).

3.3 Exclusion Criteria

3.3.1 Pregnancy, breast feeding, or unwillingness to use effective contraception during the study participation

3.3.2 Patients and/or families who, in the opinion of the investigator, may not be able to comply with the safety monitoring/radiation isolation requirements of the study.

3.3.3 Patients with disease of any major organ system that would compromise their ability to withstand therapy.

3.3.4 Patients must not have received prior allogeneic stem cell transplant.

3.3.5 Subjects who have received prior solid organ transplantation.

3.3.6 Patients must not have received prior total body irradiation.

3.3.7 Patients who are on hemodialysis.

3.3.8 Patients with an active or uncontrolled infection.

3.3.9 Known active infection with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C. (testing of patients not known to be infected with these viruses is not required prior to study registration).

3.3.11 Patients with a history of having to permanently discontinue anti-GD2 antibody therapy, GM-CSF, or vorinostat (Part B only) due to toxicity are not eligible.

3.3.12 Prior anti-GD2 therapy given in combination with therapeutic ^{131}I-MIBG, including those treated on Part A of NANT 2017-01.

3.3.13 Prior HDAC inhibitor given in combination with therapeutic ^{131}I-MIBG (Part B only).

3.3.14 The maximum total allowable dose of ^{131}I-MIBG that can be given per institutional guidelines must be at least 90% of the calculated ^{131}I-MIBG dose or the patient is not eligible.

3.3.15 Patient declines participation in NANT 2004-05, the NANT Biology Study.

3.3.16 Patients with a history of deep venous thrombosis that was not associated with the presence of a central venous catheter (Part B only).

3.4 Regulatory

3.4.1 Informed Consent

The patient and/or the patient's legally authorized guardian must acknowledge in writing that consent to become a study subject has been obtained, in accordance with institutional policies approved by the US Department of Health and Human Services.

3.4.2 Protocol Approval

All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

4.1 Treatment Overview

4.1.1 Part A

Patients receive ^{131}I-MIBG on Day 1. The dose of ^{131}I-MIBG and dinutuximab will be based on the dose level assigned at the time of patient registration. Dinutuximab is given intravenously on Days 8-11 and 29-32 of therapy, along with GM-CSF 250 mcg/m^2 on Days 8-17 and 29-38. All patients receive autologous hematopoietic stem cell infusion on Day 15 (+/- 2) of therapy. This must occur at a NANT site.

Course duration is defined as 57 days or longer if hematopoietic recovery to eligibility criteria occurs after Day 57. All patients will undergo disease restaging between Days 43 – 57 or later if recovery to start ourse 2 is delayed. Patients may receive up to two courses of therapy as long as all protocol-defined criteria are met prior to the start of the second course.

DAY	1	2-7	8	9	10	11	12	13	14	15	16	17	18-28
^{131}I-MIBG (M) dose level assignment	M[1]												
GM-CSF (G) 250 mcg/m^2			G[2]	G	G	G	G	G	G	G	G	G[2]	
DINUTUXIMAB (D) dose level assignment			D[3]	D	D	D							
Stem Cell Infusion (HSC)										HSC +/- 2d			

DAY	29	30	31	32	33	34	35	36	37	38	43-57
GM-CSF (G) 250 mcg/m^2	G[2]	G	G	G	G	G	G	G	G	G[2]	
DINUTUXIMAB (D) dose level assignment	D[3]	D	D	D							
Disease Evaluation (Eval)											Eval[4]

[1]It is strongly encouraged to begin ^{131}I-MIBG on Tuesday – Thursday to allow biologic correlates to be received on Wednesday – Friday. Contact NANT Operations Center/Study Chair if treatment is delayed and will not start on a Tuesday-Thursday schedule.

[2]GM-CSF is administered for 10 doses starting on the same day as the Day 8 and Day 29 dinutuximab dose respectively. If the start of dinutuximab is delayed, the GM-CSF dose should be held and started on the first day of the dinutuximab infusion. If the Day 8 or Day 29 GM-CSF dose is given but then the respective dinutuximab dose is not started the same day, additional doses of GM-CSF should not be given beyond the planned 10 doses with each cycle of dinutuximab unless required for Grade 4 neutropenia (ANC < 500/µL). Refer to Section 4.2.4.2 for extending GM-CSF administration beyond Day 17 and 38.

[3]Refer to protocol Section 4.2.3.3 for criteria to receive dinutuximab on Day 8 and Day 29.

[4]Disease evaluation is to occur between Days 43-57. In case of treatment delays with dinutuximab during Course 1, the time interval between performing end of Course 1 disease evaluation and administration of Course 2 ^{131}I-MIBG is not to exceed 4 weeks.

4.1.2 Part B

Patients receive vorinostat on Days 0 to +13 (14 days) and ^{131}I-MIBG on Day 1. The dose of vorinostat and ^{131}I-MIBG will be based on the dose level assigned at the time of patient registration. Patients will receive a total of 14 doses of vorinostat. Missed doses may be made up provided there is at least 24 hours between vorinostat and infusion of stem cells, and stem cell infusion is not delayed beyond Day 17; vorinostat should not be administered after stem cell infusion regardless of the number of doses received. Patients should not exceed 14 total doses of vorinostat for any reason. If a patient vomits within 15 minutes of vorinostat dose administration, the patient should be re-dosed. If the patient vomits after the second dose, the patient should not be re-dosed again. If a patient vomits more than 15 minutes from dose administration, the patient should not be re-dosed. Refer to Section 4.2.5.1 and 6.5.4 for vorinostat drug administration guidelines.

Dinutuximab 17.5 mg/m^2 is given intravenously on Days 8-11 and 29-32 of therapy, along with GM-CSF 250 mcg/m^2 on Days 8-17 and 29-38. All patients receive autologous hematopoietic stem cell infusion on Day 15 (+2/-1) of therapy. This must occur at a NANT site.

Course duration is defined as 57 days or longer if hematopoietic recovery to eligibility criteria occurs after Day 57. All patients will undergo disease restaging between Days 43 – 57 or later if recovery to start Course 2 is delayed. Patients may receive up to two courses of therapy as long as all protocol-defined criteria are met prior to the start of the second course.

DAY	0	1	2-7	8	9	10	11	12	13	14	15	16	17	18-28
Vorinostat (V) dose level assignment	V	V	V	V	V	V	V	V	V[5]					
^{131}I-MIBG (M) dose level assignment		M[1]												
GM-CSF (G) 250 mcg/m^2				G[2]	G	G	G	G	G	G	G	G	G[2]	
DINUTUXIMAB (D) 17.5 mg/m^2				D[3]	D	D	D							
Stem Cell Infusion (HSC)											HSC[5] +2d/-1d			

DAY	29	30	31	32	33	34	35	36	37	38	43-57
GM-CSF (G) 250 mcg/m^2	G[2]	G	G	G	G	G	G	G	G	G[2]	
DINUTUXIMAB (D) dose level assignment	D[3]	D	D	D							
Disease Evaluation (Eval)											Eval[4]

[1]It is strongly encouraged to begin ^{131}I-MIBG on Tuesday – Thursday to allow biologic correlates to be received on Wednesday – Friday. Contact NANT Operations Center/Study Chair if treatment is delayed and will not start on a Tuesday-Thursday schedule.

[2]GM-CSF is administered for 10 doses starting on the same day as the Day 8 and Day 29 dinutuximab dose, respectively. If the start of dinutuximab is delayed, the GM-CSF dose should be held and started on the first day of the dinutuximab infusion. If the Day 8 or Day 29 GM-CSF dose is given but then the respective dinutuximab dose is not started the same day, additional doses of GM-CSF should not be given beyond the planned 10 doses with each cycle of dinutuximab unless required for Grade 4 neutropenia (ANC < 500/μL). Refer to Section 4.2.4.2 for extending GM-CSF administration beyond Day 17 and 38.

[3]Refer to protocol Section 4.2.3.3 for criteria to receive dinutuximab on Day 8 and Day 29.

[4]Disease evaluation is to occur between Days 43-57. In case of treatment delays with dinutuximab during Course 1, the time interval between performing end of Course 1 disease evaluation and administration of course 2 ^{131}I-MIBG is not to exceed 4 weeks.

[5]There must be at least 24 hours between the last dose of vorinostat and stem cell infusion. Infusion of stem cells should not be delayed beyond Day 17.

4.2 Drug Administration

4.2.1 ^{131}I-MIBG Therapy

DOSE: Based on dose level assignment at study registration. Refer to Section 4.3 dose escalation.

DAY: Day 1 of therapy intravenously via either a central or a peripheral IV catheter over 1.5 to 2 hours.

Starting therapy on Tuesday – Thursday is strongly encouraged. Notify NANT Operations Center/Study Chairperson if treatment is delayed for any reason and will not start on a Tuesday – Thursday.

The primary ^{131}I-MIBG supplier for this study is Jubilant Radiopharma, Canada.

4.2.1.1. General Instructions for Drug Ordering and Administration

- To allow time for appropriate planning, the weight that is used to order the ^{131}I-MIBG dose can be obtained at the time of initial consult or consent. However, due to the potential for significant weight changes while waiting to initiate therapy, the ^{131}I-MIBG dose that is administered MUST be calculated based on a weight obtained within 7 days before the date of ^{131}I-MIBG administration.

  Sites will use the "^{131}I-MIBG Order Notification Form for NANT 2017-01", available on the NANT website, and the site specific ^{131}I-MIBG Order form provided by Jubilant Radiopharma to order a ^{131}I-MIBG dose from supplier. NANTCRF@chla.usc.edu is to be copied on all drug orders and correspondence regarding ^{131}I-MIBG dose planning between site and supplier.

- The therapeutic dose of ^{131}I-MIBG will be infused intravenously over 1.5-2 hours on Day 1 of therapy with appropriate hydration, radiation isolation, thyroid blocking with potassium iodide (SSKI), and bladder protection with a Foley catheter.

- The maximum absolute dose of ^{131}I-MIBG that may be infused on this protocol is 1200 mCi. The dose administered should be within 10% of the prescribed dose. There will be no adjustment for obesity except to cap the absolute dose at 1200 mCi.

  - Radiopurity is checked by the supplier prior to shipment. As of 10/20/21, radiochemical purity testing at clinical sites following receipt of ^{131}I-MIBG is no longer required. Should clinical sites still wish to perform radiochemical purity testing, a suggested technique can be found in Appendix V.

- The patient will remain in a radiation protected isolation room until radiation emissions meet institutional/state guidelines. Radiation levels will be measured at least once daily by Radiation Safety using a handheld monitor standing at a distance of one meter from the patient. It usually takes 3-5 days for the patient to be cleared and then they can be discharged.

- **Patients should be transfused as needed to achieve a documented hemoglobin of ≥ 10 g/dL on the day of or one day prior to ^{131}I-MIBG administration.**

4.2.1.2 Hydration

In order to ensure adequate hydration, patients will receive a minimum of 1.5-times maintenance rate IV fluids starting the night prior to ^{131}I-MIBG infusion and continuing until the radiation dose rate is < 7 mRem/hr at 1 meter. Once < 7 mRem/hr, IV hydration is at the discretion of the treating institution.

4.2.1.3 Bladder Protection

A Foley catheter is strongly recommended for all patients prior to ^{131}I-MIBG infusion and required of all patients < 12 years of age. Patients ≥ 12 years of age may decline Foley catheter placement at investigator discretion if they agree to void every 2 hours throughout the first 48 hours after ^{131}I-MIBG infusion. If for physical/anatomic reasons it is not possible to successfully place or retain a catheter, then the treatment may proceed for continent patients who are able to comply with voiding every 2 hours throughout the first 48 hours following the infusion. For continent patients, the catheter may be removed after 72 hours or after the patient's dose rate at 1 meter is < 7 mRem/hr, whichever occurs earlier. For incontinent (diapered) patients, the catheter is recommended to remain in place until the patient is released from radiation isolation.

4.2.1.4 Thyroid Protection

Potassium iodide solution (SSKI) will be given in a loading dose of 6 mg/kg by mouth 8-12 hours prior to the infusion of ^{131}I-MIBG on Day 1, and then 1 mg/kg/dose by mouth starting 4-6 hours after completion of the ^{131}I-MIBG infusion, and continuing every 4 hours on protocol Days 1 to 7, and then 1 mg/kg/dose by mouth once daily on protocol Days 8 to 45.

If ^{131}I-MIBG infusion is delayed due to shipment or other issues and the patient has already received their loading dose, a suggested practice is to hold any further SSKI and to repeat the loading dose as above; this is to spare the patient and family an additional day of q4h SSKI dosing. An acceptable alternative approach is to just start the subsequent SSKI doses on schedule as though the ^{131}I-MIBG infusion had been completed on schedule.

4.2.1.5 Radiation Isolation

Following the ^{131}I-MIBG infusion, patients must remain in radiation isolation until the patient's radiation emissions meet state/institutional guidelines for release.

4.2.1.6 Imaging

An MIBG imaging study similar to the diagnostic scan will be done at the time of release from radiation isolation and will not require an additional injection. This is to confirm tumor MIBG uptake and to survey for occult sites of disease. SPECT is not required for this MIBG scan. Sedation is generally not necessary for this scan.

4.2.1.7 Whole Body Dosimetry

Whole body dosimetry will not be calculated in real time. However, serial measurements of radiation levels will be obtained. While in radiation isolation, whole-body monitoring will be performed using a ceiling-mounted meter at consistent patient geometry. The person obtaining the measurement should be certain the patient is centered under the monitor and that the height of the bed has not been changed.

All times are noted from the beginning of the ^{131}I-MIBG infusion and assume a 2-hour infusion. The minimum whole body measurements will be taken as follows, and saved in the computer log. All times are measured from the beginning of the MIBG infusion.

TIME	**SCHEDULE**
Infusion	0, 1, 2 (including end infusion, with time marked)
Post-Infusion Hours 2-8	Every 30 minutes hours 2-8
Post-Infusion Hours 8-24	Hours 8, 12, 16, 20, 24
Subsequent Days	Every 8 hours until hospital discharge or hour 120, whichever occurs first

If the ceiling mounted monitor is not functional for any reason, then measurements will be taken with a handheld ion chamber at 1 meter from the umbilicus with consistent geometry and distance beginning at the completion of the infusion (hour 2) and at hours 3, 4, 5, 6, 7, 8, then every 8 hours thereafter.

4.2.2 Autologous Peripheral Stem Cell Infusion

DOSE: Minimum dose 2.0 x 10^6 viable CD34+ cells/kg.

DAY: Day 15 +/- 2 days (Part A) or +2/-1 day (Part B) to avoid weekend or holiday infusion, to accommodate logistical/scheduling issues, or to avoid occurring within 24 hours of last dose of vorinostat.

Stem cell infusion is planned for 14 days after ^{131}I-MIBG infusion. If the ^{131}I-MIBG infusion is delayed, the date of stem cell infusion should be re-dated for 14 days after ^{131}I-MIBG infusion.

Stem cells must be infused at the treating NANT institution.

4.2.2.1 General Instructions for Peripheral Stem Cell Administration

- In situations in which the DMSO concentration in the stem cell product would exceed an accepted level for infusion within a 24-hour period, stem cell products may be infused over two days to meet this standard.

- Stem cell infusion may occur sooner than Day 15 if indicated (i.e. due to an infectious or bleeding complication) after consultation with the Study Chairperson or designee.

- For patients whose body weight exceeds ideal body weight (IBW) by more than 20%, adjusted body weight may be used for calculation of PBSC dose (Reference: Bone Marrow Transplant. 40(7):665-9; Appendix III).

4.2.2.2 Pre-medications for Stem Cell infusion

Stem cells will be infused following institutional guidelines for prophylaxis of hypersensitivity reactions and monitoring.

4.2.2.3 Location of Stem Cell Infusion

Stem cell infusion is considered a supportive care measure on this protocol. **Stem cells must be infused at the treating NANT institution.**

4.2.3 Dinutuximab

DOSE: Based on dose level assignment at study registration for Part A. Refer to Section 4.3 dose escalation. All patients on Part B will receive 17.5 mg/m^2/dose.

DAY: Days 8-11 and Days 29-32 intravenously over approximately 10 hours if tolerated.

Refer to Section 4.2.3.1 Instructions for Dinutuximab Administration, Section 4.2.3.2 Criteria to Receive Dinutuximab and Sections 4.2.3.3 – 4.2.3.5 for recommendations on pre-medication, pain management and monitoring during infusion.

4.2.3.1 General Instructions for Drug Ordering

- Sites will use the "Dinutuximab Order Form for NANT 2017-01", available on the NANT website, to place an order for dinutuximab. A copy of the drug order form is to be sent to NANTCRF@chla.usc.edu

- **To conserve dinutuximab vials, recommendation has been made to not use 2 vials per day until patient's BSA exceeds 1.1 m^2. For patients between BSA 1.0-1.1 m^2, this is less than a 10% deviation; which is allowed.**

4.2.3.2 Instructions for Dinutuximab Administration

- Each daily dose of dinutuximab should be infused IV over approximately 10 hours, starting at 0.88 mg/m^2/hr x 0.5 hr, then increasing to 1.75 mg/m^2/hr for the remainder of the dose, if tolerated. The infusion duration may be extended up to 20 hours for anticipated toxicities (pain, fever, tachycardia, tachypnea, hypotension), not responding to other supportive measures, and the duration should be recorded.

- The maximum infusion time is 20 hours; dinutuximab administration must be stopped after 20 hours even if the total dose has not been administered. The total dose given in 20 hours should be recorded.

4.2.3.3 Criteria to Receive Dinutuximab

- Day 8 Dose

The day 8 dinutuximab dose can be given anytime from Day 6 until Day 11 as long as ALL of the following criteria are met:

  - Cleared the ^{131}I-MIBG (radiation level < 7 mRem/hr at 1 meter)
  - No evidence of infection, or if present, infection under control with negative blood culture
  - ALT ≤ 450 U/L (10 x ULN where ULN = 45 U/L).
  - Total bilirubin ≤ 5 x ULN (Grade 2)
  - Creatinine ≤ 3 x ULN (Grade 2)
  - If the Day 8 dose is delayed beyond Day 11 then patient is off protocol therapy. If the delay is the result of toxicity, this event would be considered a DLT
  - QTc ≤ 480 msec (Part B only)

- Day 29 Dose

The start of the Day 29 dinutuximab infusion may be delayed up to 2 weeks if needed to meet the following criteria:

  - At least 3 weeks have passed since the start of the Day 8 dinutuximab infusion
  - Meet the renal function requirements as outlined in Section 3.2.9.2
  - ALT ≤ 225 U/L (5 x ULN (grade 2) where ULN = 45 U/L).
  - Absolute phagocyte count (APC) ≥ 750/µL
  - No evidence of infection, or if present, infection under control with negative blood culture
  - No DLT prior to start of the Day 29 infusion
  - If the Day 29 dose is delayed beyond 2 weeks then patient is off protocol therapy. If the delay is the result of toxicity, this event would be considered a DLT

4.2.3.4 Recommended Premedications:

- Hydroxyzine (0.5-1 mg/kg; max dose 50 mg) PO or diphenhydramine (0.5-1 mg/kg; max dose 50 mg) IV over 10 minutes to start approximately 20 minutes prior to dinutuximab infusion; may be repeated every 6 hours as needed during dinutuximab infusion. **Note**: intravenous hydroxyzine is NOT recommended.

- Acetaminophen (10-15 mg/kg; max dose 650 mg) PO given approximately 20 minutes prior to dinutuximab infusion; may be repeated every 4-6 hours either scheduled or as needed for fever.

4.2.3.5 Recommended Pain Management:

- Morphine sulfate loading dose immediately prior to dinutuximab administration. A dose of 50 mcg/kg is recommended, though this may be adjusted based on a given patient's pain history or institutional guidelines. Other narcotics such as hydromorphone or fentanyl can be used instead of morphine.
- Continue with morphine sulfate drip titrated to effect. The recommended dose range for the continuous infusion is 20-50 mcg/kg/hr to continue for 2 hours after completion of the dinutuximab infusion, although institutional standards may be utilized. Other narcotics such as hydromorphone or fentanyl can be used instead of morphine.

- Gabapentin may be used in conjunction with other pain medications per institutional practice.

- If additional or alternative pain medications (lidocaine, ketamine, etc.) are needed, it is strongly recommended that this be done in consultation with pediatric pain management specialists.

4.2.3.6 Monitoring during Dinutuximab Infusion:

- Vital signs should be assessed every 15 minutes for the first hour of the infusion, then hourly during the remainder of the infusion if stable after the first hour. More frequent assessment may be required based on the patient's clinical condition. Between antibody doses, vitals should be assessed every 4 hours.

- Strict observation of intake and output is required on the days of dinutuximab administration.

- Patients should be weighed daily on the days of dinutuximab administration.

4.2.4 Sargramostim (GM-CSF)

DOSE: 250 mcg/m^2/dose.

DAY: Once daily on Days 8-17 and Days 29-38.

4.2.4.1 Instructions for GM-CSF Administration

- The standard route of administration is subcutaneous (SQ); use of an insuflon catheter is permitted.
- In extenuating circumstances, IV administration over 2 hours is permitted. The reason for IV administration of this agent must be documented.
- See Section 4.2.4.2 for criteria to extend GM-CSF administration.
- If the Day 8 or Day 29 GM-CSF dose is given but then the respective dinutuximab dose is not started the same day, additional doses of GM-CSF should not be given beyond the planned 10 doses with each cycle of dinutuximab.

4.2.4.2 Growth Factor Support Outside Planned GM-CSF Doses on Days 8-17 and Days 29-38

- It is strongly recommended that GM-CSF be the only growth factor used on this study. The use of filgrastim (G-CSF) or pegfilgrastim, even if the patient experiences febrile neutropenia, is strongly discouraged.
- GM-CSF is strongly recommended for any patient who develops Grade 4 neutropenia [absolute neutrophil count (ANC) < 500/μL]. If GM-CSF is started or continued during this time, it is recommended that it be continued until the ANC is > 2000/μL.
- If a patient experiences Grade 4 neutropenia while receiving vorinostat prior to the Day 8 dinutuximab/GM-CSF dose, GM-CSF can be initiated early once they clear radiation isolation. If GM-CSF is started prior to the Day 8 dinutuximab dose, the GM-CSF should still be continued at least until the Day 17 GM-CSF dose, i.e. the patient should still receive the full 10 doses of GM-CSF associated with the Day 8 dinutuximab dose.

4.2.5 Vorinostat

DOSE: Based on dose level assignment at study registration. Refer to Section 4.3.2 dose escalation. The maximum vorinostat dose is 400 mg.

DAY: Days 0 to +13 (14 total doses) of therapy once daily by mouth, NG, or G-tube

4.2.5.1 Instructions for Vorinostat Administration

- Vorinostat will be given for 14 days continuously, even if the ^{131}I-MIBG portion of therapy is delayed due to production or other logistical reasons or if dinutuximab start date is delayed.
- Missed doses may be made up provided there is at least 24 hours between vorinostat and infusion of stem cells, and stem cell infusion is not delayed beyond Day 17; vorinostat should not be administered after stem cell infusion regardless of the number of doses received. Patients should not exceed 14 total doses of vorinostat for any reason.
- If a patient vomits within 15 minutes of vorinostat dose administration, the patient should be re-dosed. If the patient vomits after the second dose, the patient should not be re-dosed again. If a patient vomits more than 15 minutes from dose administration, the patient should not be re-dosed.
- For patients unable to swallow capsules, vorinostat will be given as a 50 mg/mL extemporaneous liquid suspension (see Section 6.6.4 for preparation instructions) with dosing according to the nomogram in Appendix VIII. The maximum vorinostat dose is 400 mg. (Please contact NANT Operations if extemporaneous liquid suspension is not available)
- Patients who are able to swallow capsules may receive vorinostat capsules instead of suspension if their calculated vorinostat dose is within +/- 10% of a 100 mg increment (e.g. 100 mg, 200 mg,

300 mg, or 400 mg). Otherwise, they will need to receive vorinostat as suspension and dosed according to the nomogram in Appendix VIII. The maximum vorinostat dose is 400 mg.
- Vorinostat should be taken with food or within 30 minutes after a meal. The dose should be taken in the morning whenever possible.

4.2.5.2 Instructions for Ordering Vorinostat
- Vorinostat will be obtained via commercial supply.

4.3 Dose Escalation Schedule

4.3.1 Part A

	Dose Level	^{131}I-MIBG (mCi/kg/dose)	Dinutuximab (mg/m^2/dose)
	0	12	14
Starting Dose Level:	**1**	12	17.5
	2	15	17.5
	3	18	17.5

Dose escalation will begin at Dose Level 1, with escalation up to Dose Level 3 following the Rolling 6 dose escalation design. If Dose Level 1 is deemed intolerable per the dose escalation rules, then Dose Level 0 will be evaluated. Patients will be treated at the dose of ^{131}I-MIBG and dinutuximab assigned at study registration. There will be no intrapatient dose escalation.

The starting dose of ^{131}I-MIBG is 12 mCi/kg at Dose Level 1. The dinutuximab dose is 17.5 mg/m^2/dose. If the starting dose level (Dose Level 1) is not tolerated, patients will be enrolled to Dose Level 0, which keeps the ^{131}I-MIBG dose at 12 mCi/kg, but reduces the dinutuximab dose to 14 mg/m^2/dose.

4.3.2 Part B

	Dose Level	Vorinostat (mg/m^2/dose)$^{\#}$	^{131}I-MIBG (mCi/kg/dose)	Dinutuximab (mg/m^2/dose)
Starting Dose Level	**4**	180	18	17.5
	4a*	150	18	17.5

$^{\#}$Maximum vorinostat dose: 400 mg
*De-escalation dose level 4a to enroll only if dose level 4 is not tolerated

The starting dose level for Part B will be Dose Level 4. Patients on this dose level will receive vorinostat at 180 mg/m^2/dose and ^{131}I-MIBG at 18 mCi/kg/dose (the MTD/RP2D determined in Part A). Dinutuximab will be given at 17.5 mg/m^2/dose. Enrollment will follow the Rolling 6 dose escalation design. If Dose Level 4 is deemed intolerable per the dose escalation rules, then Dose Level 4a will be evaluated. Patients will be treated at the assigned dose of vorinostat and ^{131}I-MIBG. There will be no intrapatient dose escalation. Once the MTD/RP2D is established in Part B, we will enroll 6 evaluable patients in an expansion cohort to further test the MIBG, vorinostat, and dinutuximab/GM-CSF combination.

4.4 Definition of Dose-Limiting Toxicity (DLT)

Toxicity will be graded using the CTCAE criteria, version 5. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (**http://ctep.cancer.gov**). Any dose-limiting toxicity should be reported immediately through the NANT Operations Center to the Study Chairperson.

4.4.1 Definition of Evaluable for Dose Escalation

A patient will be considered evaluable for dose escalation purposes if they receive ≥ 90% of the assigned dose of ^{131}I-MIBG, ≥ 80% of the assigned doses of dinutuximab and GM-CSF (GM-CSF criterion only applicable to Part A dose-escalation), and ≥ 78% of the assigned doses of vorinostat (at least 11 days; Part B only) during Course 1. Patients who receive less than 90% of the assigned ^{131}I-MIBG dose, less than 80% of the assigned dinutuximab or GM-CSF doses (Part A dose-escalation only), or less than 78% of the assigned vorinostat doses (less than 11 days; Part B only) for reasons other than toxicity will be replaced for the purposes of evaluating the dose level for dose escalation/de-escalation purposes, unless they experience a DLT in first course. All patients who receive ^{131}I-MIBG in Part A or vorinostat in Part B are evaluable for toxicity reporting.

4.4.2 Definition of Dose-Limiting Toxicity

DLT will be defined as any of the following events that are possibly, probably, or definitely attributable to study regimen. Only dose limiting toxicities as described below that occur during Course 1 that are possibly, probably or definitely related to the regimen (and not excluded in Section 4.4.3 below) will be used for determination of the MTD/RP2D of ^{131}I-MIBG (Part A) or vorinostat (Part B) although all DLTs during any course will be reported. Patients who experience a DLT during the first course of therapy will not be offered further treatment on study.

Certain frequently observed side effects known to be related to dinutuximab are transient, and can be well-controlled clinically. These transient side effects, if well-controlled clinically, will not be used in this study to determine dose limiting toxicity. The list of toxicities that will NOT be considered DLT are outlined in Section 4.4.3.

4.4.3 Non-Hematologic Dose Limiting Toxicity

Non-hematologic dose-limiting toxicity is defined as any Grade 3 or Grade 4 non-hematologic toxicity that is possibly, probably, or definitely attributable to the combination of therapy with the specific exclusion of the following:

1	Grade 3 nausea or vomiting
2	Grade 3 or 4 serum amylase elevation that resolves to grade 2 within 14 days and is not accompanied by grade 2 lipase elevation or grade ≥ 3 salivary gland toxicity (dry mouth; parotid pain).
3	Grade 3 infection
4	Grade 3 fever
5	Grade 3 febrile neutropenia
6	Grade 3 fatigue lasting ≤ 72 hours
7	Pupillary dilation and/or accommodation defects not accompanied by vision loss
8	Grade 3 pain that resolves to ≤ grade 2 within 72 hours
9	Grade 3 diarrhea that resolves to ≤ grade 1 with supportive care within 5 days
10	Grade 4 fever (ie. Temp > 40◦ C) during dinutuximab administration that resolves within 48 hours of dinutuximab completion
11	Grade 3 skin toxicity that improves to ≤ grade 2 with treatment (e.g. IV Benadryl) within 48 hours
12	Grade 3 urine output decreased that resolves within 24 hours of completion of dinutuximab
13	Grade 3 proteinuria that returns to ≤ grade 1 within 5 days of completion of dinutuximab
14	Grade 3 weight gain that resolves to ≤ grade 2 within 3 days of completion of dinutuximab

15	Grade 3 weight loss or anorexia that resolves to ≤ Grade 2 within 3 days
16	Grade 3 dehydration that resolves to ≤ Grade 2 within 3 days
17	Grade 3 electrolyte abnormality (Na, K, Cl, CO2, Ca, Mg, PO_4) that returns to ≤ Grade 2 within 3 days with or without treatment
18	Grade 3 hypoalbuminemia
19	Grade 3 hypotension and grade 3 hypertension that resolves to < Grade 1 within 48 hours
20	Grade 4 hypotension associated with dinutuximab that resolves to ≤ Grade 2 with supportive care not including pressors
21	Grade 3 or Grade 4 AST that returns to ≤ Grade 2 within 7 days
22	Grade 3 or Grade 4 ALT that returns to ≤ Grade 2 within 7 days. Note: The ALT ULN = 45 U/L on this study.
23	Grade 3 GGT; Grade 4 GGT that returns to ≤ grade 2 within 7 days
24	Grade 3 bilirubin elevation that returns to ≤ Grade 2 within 7 days
25	Grade 3 or Grade 4 alkaline phosphatase elevation that returns to ≤ Grade 2 within 7 days
26	Grade 3 neurotoxicity (i.e. interference with function plus objective weakness) will not be a DLT if transient and reversing within 3 days of completion of dinutuximab for any course, or within 2 weeks of completion for grade 3 sensory changes interfering with daily activities. Subjective findings (e.g. tingling, hot or cold hands, taste change, etc.) are expected and will not be a DLT.
27	Grade 3 allergic reactions or anaphylaxis that is readily controlled with supportive anti-allergic (non-steroidal) treatments (ie: Benadryl, epinephrine)
28	Grade 3 capillary leak syndrome
29	Grade 3 cough, dyspnea, hypoxia and bronchospasm that decrease to ≤ Grade 2 within 72 hours
30	Grade 3 or Grade 4 somnolence that resolves to < Grade 2 on stopping supportive care medications (ie; narcotics, diphenhydramine, meperidine, etc.) during dinutuximab

Note: Any non-hematologic toxicity that leads to a patient receiving < 78% of assigned vorinostat doses will also be classified as a DLT in Part B.

4.4.4 Definition of Engraftment and <u>Hematologic Dose Limiting Toxicity</u>

4.4.4.1 Definition of Engraftment

- Neutrophil engraftment will be defined as an ANC ≥ 500/μL for a minimum of 3 days following neutrophil nadir, with or without growth factor support. Date of neutrophil engraftment will be the first day of 3 days with ANC ≥ 500/μL.

- Platelet engraftment will be defined as platelets ≥ 20,000/μL for a minimum of 3 days following platelet nadir without platelet transfusion for one week. Date of platelet engraftment will be the first day of 3 days with platelets ≥ 20,000/μL. If a patient has a platelet transfusion and then does not have another platelet count < 20,000/μL, the date of platelet engraftment will be the first date with platelet count ≥ 20,000 following platelet transfusion.

4.4.4.2 Definition of Hematologic Dose Limiting Toxicity

- Once stem cell infusion is given, hematologic dose limiting toxicity will be defined as any of the following in the absence of progressive bone marrow disease:
    - Neutrophils (ANC) < 500/μL at 28 days after stem cell infusion
    - Platelets < 20,000/μL at 56 days after stem cell infusion
    - Infusion of additional stem cells for any medical reason after the initial stem cell infusion has been given AND prior to engraftment of neutrophils or platelets after that initial stem cell infusion.

4.5 Dose Modification and Recommendations for Management of Dinutuximab/GM-CSF Toxicity

4.5.1 There will be no dose reductions of either ^{131}I-MIBG or dinutuximab on this study. The infusion rate of dinutuximab may be decreased due to toxicity as outlined below. Patients who experience a DLT will come off protocol therapy at that point in time.

4.5.2 Treatment of dinutuximab-induced hypotension (without evidence of allergic reaction)

If hypotension is severe and accompanied by poor perfusion, end organ dysfunction, or acidemia, Pediatric Advanced Life Support (PALS) guidelines should be followed and dinutuximab infusion should be discontinued.

A. If moderate hypotension is observed (without poor perfusion, end organ dysfunction, or academia):
    - Immediately hold dinutuximab
    - Give normal saline bolus (20 mL/kg as rapidly as possible)
    - Stop or adjust doses of narcotics and sedating H1 blockers
    - Consider use of Trendelenberg position

B. If hypotension persists after the above measures have been taken:
    - Reassess perfusion and end organ function; follow PALS algorithm if needed
    - Repeat NS bolus
    - Consider use of albumin if albumin < 3 gm/dL
    - Consider use of PRBCs if Hb < 10 gm/dL
    - Consider transfer to intensive care setting

C. If hypotension persists following 2 volume boluses, give an additional bolus and prepare to administer pressors
    - Epinephrine is preferred over dopamine if possible

D. Resumption of dinutuximab
For patients whose hypotension resolves promptly and completely with limited volume resuscitation and without requirement for pressor support, dinutuximab may be restarted at 50% of the previous infusion rate. The dinutuximab may be restarted on the same day if it is possible to do so within 20 hours of the start of the day's infusion. If blood pressures are stable for 2 hours, the infusion may be given at full rate for that day and subsequent days. If the patient again experiences hypotension requiring multiple volume boluses (e.g., > 60 mL/kg) when dinutuximab is given at full rate but tolerates the 50% infusion rate, the remaining days' doses of dinutuximab should be given at the 50% rate of infusion. If > 20 hours have elapsed since the start of the infusion, restart dinutuximab the following day.

    - If blood pressures are stable for 2 hours after resumption of dinutuximab at the reduced rate, the remainder of the antibody infusion may be given at the full rate.

    - If hypotension recurs at the reduced rate, the measures above should again be taken and no further dinutuximab should be given that day. The antibody infusion may be restarted

the following day after ensuring that the patient is volume replete. The antibody rate upon resumption of treatment should be 50% of the initial rate. If blood pressures are stable for 2 hours, the infusion may be given at full rate for that day and subsequent days. If the patient's blood pressures are only stable at the 50% rate and not at full rate, the remaining days' doses of dinutuximab should be given at the 50% rate of infusion.

For patients who require multiple volume boluses for hemodynamic stabilization, dinutuximab should be resumed the following day at 50% of the initial infusion rate.

- If blood pressures are stable for 2 hours after resumption of dinutuximab at the reduced rate, the remainder of the antibody infusion may be given at the full rate.

- If hypotension recurs at the reduced rate, the measures above should again be taken and no further dinutuximab should be given that day. The antibody infusion may be restarted the following day after ensuring that the patient is volume replete. The antibody rate upon resumption of treatment should be 50% of the initial rate. If blood pressures are stable for 2 hours, the infusion may be given at full rate for that day and subsequent days. If the patient's blood pressures are only stable at the 50% rate and not at full rate, the remaining days' doses of dinutuximab should be given at the 50% rate of infusion.

- For patients who require pressors for treatment of hypotension, if blood pressure is stable off pressors for at least 6 hours, administration of dinutuximab may be resumed at 50% of the initial infusion rate on the day following the hypotensive episode. Care should be taken to ensure that the patient is volume replete. Dinutuximab should not be given to patients who continue to require pressor support. Patients who require pressor support for ≥ 24 hours due to treatment-related hypotension despite appropriate volume resuscitation should discontinue protocol therapy. Patients who again require pressor support when dinutuximab is resumed should discontinue protocol therapy.

4.5.3 Treatment of Allergic Reactions/Infusion Reactions
Note: Coughing may herald the onset of bronchospasm and if occurs, patients should be closely monitored.

4.5.3.1 Mild allergic reactions/infusion reactions to dinutuximab infusion

- Mild allergic reaction is limited to rash, flushing, urticaria, mild dyspnea – Grade 1 or 2

- The following recommendations do NOT apply to Grade 3 or 4 allergic reactions, including anaphylaxis

- Management
    a. Administer H1 blocker (diphenhydramine, cetirizine recommended)
    b. Administer H2 blocker
    c. Meperidine may be used for rigors
    d. Can decrease rate of dinutuximab to 50% of the full rate if clinically indicated
    e. When symptoms resolve, if the rate has been reduced, resume original infusion rate
    f. If symptoms recur when original rate is resumed (after a rate reduction), decrease to 50% rate again
    g. Infusion must be stopped after 20 hours (whether the full dose of dinutuximab has been administered or not); document total amount of drug given in the 20 hour time period

4.5.3.2 Moderate to severe allergic reactions/infusion reactions to dinutuximab infusion

- Moderate to severe reactions include any of the following: symptomatic bronchospasm, allergy-related edema/angioedema, hypotension, or anaphylaxis – Grade 3 or 4

- The following recommendations do NOT apply to Grade 1 or 2 allergic reactions

- Management
  a. Immediately hold dinutuximab
  b. Assess airway, breathing and circulation
  c. Follow institutional guidelines for rapid response team notification if clinically indicated

  d. For airway concerns
     - Administer oxygen and albuterol immediately for bronchospasm
     - Administer IV diphenhydramine
     - Administer epinephrine (1:1000 IM recommended) immediately if upper airway involved or if airway issues are accompanied by cardiovascular collapse
     - Administer IV hydrocortisone (1-2 mg/kg) if the patient has frank anaphylaxis with cardiorespiratory collapse OR if ≥ 2 doses of epinephrine are required OR if moderate to severe symptoms recur upon rechallenge with dinutuximab

  e. For hypotension in the setting of allergic reaction
     - Give normal saline bolus (20 mL/kg as rapidly as possible)
     - Stop or adjust doses of narcotics and sedating H1 blockers
     - Consider use of Trendelenberg position
     - See previous section for management of persistent hypotension

  f. For patients with mild bronchospasm or angioedema that does not impact breathing, completely resolves without the use of epinephrine and hydrocortisone and for patients whose hypotension resolves following volume bolus, dinutuximab may be resumed at 50% of the previous rate of infusion on the same day as the reaction occurred. If symptomatic angioedema or asymptomatic bronchospasm recurs when the dinutuximab is restarted, discontinue immunotherapy for that day and if symptoms/signs resolve completely that day, resume the next day with additional premedication of hydrocortisone 1-2 mg/kg IV. For this re-challenge, the infusion should be given in an ICU setting.

  g. For patients whose bronchospasm or angioedema requires the use of systemic epinephrine, protocol therapy should be discontinued.

  h. For patients with bronchospasm or angioedema that does not require systemic epinephrine but whose hypotension requires more extensive volume resuscitation, guidance in Section 4.5.2 should be followed.

4.5.4 Management of capillary leak syndrome (≥ Grade 3) due to dinutuximab

***** Capillary leak syndrome should be managed aggressively.**
See Section 4.5.2 for management of hypotension, anemia and hypoalbuminemia

- Hold dinutuximab infusion
- Provide oxygen and fluids as needed
- Consider use of albumin if albumin < 3 gm/dL, especially prior to diuretics
- Consider use of PRBCs if Hb < 10 gm/dL
- Do NOT resume dinutuximab therapy if symptoms of severe capillary leak syndrome persist on the same day or subsequent days of a given 4-day dinutuximab cycle. Only resume dinutuximab therapy when the capillary leak syndrome resolves or requires less significant intervention (Grade 2 or less).
- If capillary leak resolves, may resume dinutuximab infusion at 50% rate the same day and for subsequent doses during a given 4-day dinutuximab cycle. The infusion may be given at the full rate at the start of the day 29 dose, or during course 2 when applicable.
- If mechanical ventilation (any duration) or pressor support for ≥ 24 hours is required due to therapy-related capillary leak syndrome, the patient should discontinue protocol therapy.

4.5.5 Management of renal insufficiency (unrelated to hypotension) while receiving dinutuximab

- Consider the possibility of renal hypoperfusion in the context of borderline hypotension; administer volume if appropriate
- If the patient's creatinine is elevated to ≥ 2 x the upper limit of normal for age/gender (see table in Section 3.2.9.2) and elevation persists despite optimized fluid management, hold dinutuximab
- Modify dosing of concomitant medications that may contribute to or be affected by renal insufficiency
- When creatinine returns to < 2 x upper limit of normal for age/gender, resume dinutuximab at 50% rate. If renal function normalizes by the following day, dinutuximab may be administered at full rate. If renal function is not sufficiently improved (creatinine < 2x ULN for age/gender) by the planned end date of the 4-day dinutuximab cycle, no further dinutuximab should be given during that 4 day cycle of dinutuximab therapy. Subsequently, if renal function meets criteria to start the day 29 dinutuximab or a second course of therapy if applicable, retreatment with dinutuximab is permitted.

4.5.6 Management of hyponatremia (≥ Grade 3; Na < 130 mEq/L) while receiving dinutuximab

- Change hypotonic fluids to isotonic fluids as compatibilities permit
- Avoid administration of oral free water
- Correct fluid losses due to diarrhea
- 3% saline as indicated
- If Grade 4 hyponatremia occurs, discontinue dinutuximab. This will be considered a DLT and the patient will be taken off of protocol therapy.

4.5.7 Management of fever in the absence of hypotension while receiving dinutuximab

- Administer antipyretics
- Adjust fluids to account for insensible losses if fever is persistent
- For a temperature ≥ 39◦ C, obtain a blood culture per institutional standards. Additional blood cultures are only needed for a positive blood culture or clinical decompensation (hypotension, concern for sepsis, etc.).
- For temperature ≥ 39◦ C, after drawing a blood culture, the decision whether to administer antibiotics will be determined by institutional guidelines. If the patient is neutropenic (ANC ≤ 500), broad spectrum antibiotics should be administered per institutional guidelines for febrile neutropenia. If the patient has a positive blood culture, treat per institutional guidelines.

4.5.8 Management of treatment-related pain due to dinutuximab

- No further dinutuximab therapy should be given to patients who experience treatment-related pain that cannot be controlled by narcotics. Treatment with gabapentin or similar agent should be initiated if not already being administered. If pain that is not controlled with narcotics recurs during a subsequent 4-day dinutuximab cycle, the patient should discontinue protocol therapy

- For patients with treatment-related pain requiring intravenous narcotics for ≥ 48 hours following completion of dinutuximab therapy, gabapentin or similar agent should be initiated if not already being administered. If pain requiring prolonged intravenous narcotics (≥48 hours following completion of dinutuximab therapy) recurs during a subsequent 4-day dinutuximab cycle despite this intervention, the patient should discontinue protocol therapy.

4.5.9 Management of visual changes due to dinutuximab

Occasionally, dinutuximab may cause impaired accommodation and/or dilated pupils with sluggish light reflex +/- photophobia. If this occurs, no modifications, dose reductions, or changes in infusion rate should be made unless there is vision loss. If the patient experiences vision loss or a grade 4 event then dinutuximab should be stopped and protocol therapy should be discontinued.

4.5.10 Management of serum sickness due to dinutuximab

- Identification of serum sickness – signs and symptoms include arthralgias/arthritis, splenomegaly, lymphadenopathy, glomerulonephritis in the presence of persistent fevers, cutaneous eruptions
- Serum sickness typically develops 1 to 3 weeks after administration of the causative agent, but can develop within 12-36 hours in patients who have previously been sensitized to the causative agent
- Patients with ≥ Grade 3 serum sickness should discontinue protocol therapy and receive appropriate treatment for this condition.
- For Grade 2 serum sickness, antihistamines should be prescribed.

4.5.11 Management of neurotoxicity due to dinutuximab

- Patients who develop Grade 4 neurotoxicity should discontinue protocol therapy.
- Dinutuximab should be discontinued for the remainder of the current treatment course (8-11 or 29-32) of therapy for patients who develop Grade 3 sensory neuropathy or Grade 3 motor neuropathy. If this occurs during Days 8-11, gabapentin or a similar agent should be initiated if not already being administered. If abnormalities resolve by the start of the next course of dinutuximab (either Day 29 or the start of the second course if applicable) the patient may receive dinutuximab at full dose. If symptoms do not completely resolve or recur with dinutuximab then the patient should discontinue protocol therapy.

4.5.12 Management of GM-CSF related toxicities

- Hold GM-CSF if total white blood cell count is > 50,000/μL; resume at 50% dose when the count is < 20,000/μL. Administer full dose subsequently (starting with Day 29 dose or with the second course if applicable) and modify again if the count exceeds 50,000/μL. If GM-CSF is being used for neutropenia following ^{131}I-MIBG then full dose should be used.
- Localized skin reactions to GM-CSF are common, and GM-CSF can be continued when reactions are mild. Rotation of sites of injections is recommended rather than use of insuflon for subcutaneous injection when skin reactions occur. Consider use of antihistamines. If ≥ Grade 3 injection site reactions occur, stop GM-CSF and discontinue all subsequent GM-CSF doses.

- A syndrome characterized by respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia has been reported following the administration of the first dose of GM-CSF

in a particular cycle. This syndrome generally resolves with symptomatic treatment and usually does not recur with subsequent doses of GM-CSF. For safety purposes in this study, if such a "first dose reaction" occurs, the GM-CSF dose will be reduced to 50% for the next dose (i.e., GM-CSF dose 125 mcg/m^2). If a similar reaction occurs at the 50% dose, the GM-CSF will be discontinued for that patient. If the first dose at 50% does not cause any recurrent severe symptoms, subsequent doses can be escalated back to 100%. If recurrent severe symptoms are observed at 100% dose, then the dose will be reduced to 50%. If 50% is tolerated, that dose should be administered for all subsequent protocol treatment for that patient. If recurrent severe symptoms are seen at the 50% dose, the GM-CSF will be discontinued.

4.6 Dose Modifications for Vorinostat

Any dose modification of vorinostat should be reported to the study chair and to the NANT Operations Center. **Vorinostat will NOT be held for hematologic toxicity unless patients become platelet transfusion refractory while receiving vorinostat.**

4.6.1 Patients who develop Grade 4 neutropenia while receiving vorinostat will continue to receive vorinostat at the prescribed dose and schedule. GM-CSF can be initiated early per Section 4.2.4.2 once the patient clears radiation isolation. If GM-CSF is started prior to the Day 8 dinutuximab dose, the GM-CSF should still be continued at least until the Day 17 GM-CSF dose, i.e. the patient should still receive the full 10 doses of GM-CSF associated with the Day 8 dinutuximab dose.

4.6.2 Patients who develop Grade 4 thrombocytopenia while receiving vorinostat will continue to receive vorinostat at the prescribed dose and schedule unless they become platelet transfusion refractory.

4.6.3 Patients who experience non-hematologic DLT (Section 4.4.3) while receiving vorinostat should have vorinostat discontinued.

4.7 Criteria to Receive a Second Course of Therapy

Patients who meet all of the following criteria at the end of the first course of therapy may proceed to a second course of therapy as long as they meet ALL of the following criteria:

- Adequate stem cells to support a second course per Section 3.2.6;
- Organ function criteria in Section 3.2.10;
- No other intervening anti-cancer therapy between first course and planned second course;
- Day 1 of planned second course may start no earlier than Day 57 of first course and no later than 4 weeks from end of Course 1 disease evaluation;
- In the case of treatment delays during Course 1, Day 1 of planned second course may not begin earlier than 3 weeks from the start of the most recent 4 day dinutuximab infusion. No protocol defined dose limiting toxicity in first course of therapy Section 4.4);
- Disease response of stable disease or better at end of first course (Section 11.0);
- Grade 3 vision toxicity due to pupillary dilation and/or accommodation defects must be stable to improved.

4.8 Concomitant Therapy

- Immunosuppressive drugs (other than corticosteroids used to treat side effects of protocol therapy) are not allowed during protocol therapy. Dexamethasone should be avoided as an anti-nausea/antiemetic therapy.
- Corticosteroid therapy should be utilized only for life threatening conditions.
- No other cancer chemotherapy, immunomodulating agents, or biologics can be used during protocol therapy.
- External beam radiation therapy can NOT be used during protocol therapy.
- Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary for good patient care.
- No medications that interfere with MIBG uptake should be given while patient is receiving protocol therapy.

- IVIG should not be given while patient is receiving protocol therapy.
- No other investigational agents may be given while the patient is receiving protocol therapy.
- Patients on Part B may not receive valproic acid until disease re-evaluation following the last planned course of therapy has been completed.
- Patients on Part B may not receive other medications known to prolong the QTc interval within 1 week prior to or 1 week following vorinostat (Appendix VII; note that this list prohibits the use of pentamidine and cautions investigators with the use of ondansetron).
- Vorinostat treatment may result in mild increases in serum creatinine. Caution should be exercised with the use of nephrotoxic medications while patients are receiving vorinostat.

5.0 SUPPORTIVE CARE

5.1 Prophylaxis for *Pneumocystis Jiroveci* Pneumonia (PJP)

All patients must receive prophylaxis against *Pneumocystis jiroveci* pneumonia (PJP) using Bactrim or other appropriate agent according to institutional guidelines.

5.2 Use of Myeloid Growth Factors

See Section 4.2.4. **It is strongly recommended that GM-CSF be the only growth factor used on this study.** The use of filgrastim (G-CSF) or peg-filgrastim, even if the patient experiences febrile neutropenia, is strongly discouraged.

5.3 Antiemetics

Dexamethasone should not be used as anti-nausea / antiemetic therapy. The use of alternative anti-emetics will be at the investigator's discretion. Symptomatic patients should be treated with standard anti-nausea / antiemetic therapy such as ondansetron or an appropriate serotonin antagonist as necessary.

5.4 Fever During MIBG

Patients who develop a fever as defined by institutional guidelines during the first 24 hours after the ^{131}I-MIBG infusion should be given a single dose of ceftriaxone or appropriate substitute without sending a blood culture or other labs, as blood cannot be safely sent to the lab during this time due to radioactivity. If the patient is neutropenic, has an allergy to cephalosporins, or there is clinical concern for a more severe infection, alternative antibiotics can be used per institutional guidelines. The need for subsequent antibiotics will be determined based on blood culture results, clinical status, and presence/absence of neutropenia. For fever that occurs > 24 hours after the ^{131}I-MIBG infusion, institutional guidelines for fever in the non-neutropenic or neutropenic patient may be utilized.

5.5 Supportive Care During Dinutuximab Therapy

Most laboratory findings in patients receiving dinutuximab are transient during therapy and can be corrected with appropriate supportive care. Consider keeping albumin > 3 g/dL by infusing with 1gm/kg of 25% albumin. In addition, consider keeping hemoglobin >10 g/dL to help support intravascular volume.

5.6 Other

Unless specifically excluded by the protocol, additional supportive care measures should be utilized as needed to provide good patient care.

6.0 DRUG INFORMATION

6.1 ^{131}I-Meta-Iodo-Benzyl-Guanidine (Jubilant Radiopharma® Therapeutic ^{131}I-MIBG)

[Jubilant Radiopharma (JRP) IND # 76,227]

Common name:	Iobenguane sulfate (m-Iodobenzylguanidine sulfate, MIBG)
Active ingredient:	3-[^{131}I]-iodobenzylguanidine Sulfate
Pharmacologic class:	Radiopharmaceutical therapeutic agent
Molecular formula:	[C8H10IN3]•1/2 H2SO4
Molecular weight:	324.13 g/mol
Physical form:	Colorless crystals
Solubility:	Soluble in water
Melting point:	Decomposition occurs between 166-167°C.
Purity:	MIBG (cold raw material): not less than 99%
Formulation:	The MIBG sulfate is synthesized by Jubilant Radiopharma (Kirkland, Quebec, Canada), with the following formulation: 3-Iodobenzylguanidine Sulfate < 0.83 mg Niacinamide 16 mg Sodium Chloride 9 mg Benzyl Alcohol 9 µL Sodium Acetate Trihydrate 0.68 mg Cupric Nitrate (II) Trace Hydrochloric Acid Trace Sodium Hydroxide Pellets Trace Water for Injection q.s. to 1.0 mL
Specific activity:	Not less than 30 mCi/mg (1110 MBq/mg) MIBG at the calibration date.
Radiochemical purity	As of 10/20/21, radiochemical purity testing at clinical sites following receipt of ^{131}I-MIBG from Jubilant Radiopharma is no longer required. Sites are still to check for discoloration and particulate matters prior to product administration to the patient. Additionally, if a “Temperature Alarm” is detected on the temperature monitor provided in the ^{131}I-MIBG shipment, sites are NOT to use the product and should store the vial of ^{131}I-MIBG in the lead pot and call JRP Customer Service immediately for further instructions. Should clinical sites still wish to perform radiochemical purity testing, a suggested technique is provided in Appendix V.
Radiolytic decay:	^{131}I decays by beta emission and associated gamma emission with a physical half-life of 8.04 days.

How supplied: ^{131}I-MIBG from Jubilant Radiopharma is supplied in a single-dose 30 mL glass vial or two 30-mL glass vials depending on the dose required for one patient. Unit dose vial may also be available. Please refer to current nuclear medicine manual.

Storage: The product will be shipped frozen and should be stored at 2 °C to 8 °C upon arrival.

Stability: The product is stable at 2 °C to 8 °C for 2 days with excursions permitted at room temperature.

Distribution: Jubilant Radiopharma® Therapeutic ^{131}I-MIBG will be provided by Jubilant Radiopharma®, Canada. Place order 4 weeks prior to infusion. If the procedure will be cancelled, Jubilant Radiopharma should be notified as soon as it becomes evident that the procedure will not proceed.

Calls for drug supply are to be made to Jubilant Radiopharma Customer Service at:

Phone: 1-888-633-5343; 8am – 5pm Eastern Time
(514) 630-7080
Fax: 1-866-431-4288
Fax: 1-514-694-3865
Email: customerservice@jubl.com
Web: www.jubilantradiopharma.com

Toxicity:

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
• Myelosuppression (anemia, thrombocytopenia, leukopenia, neutropenia) • Nausea • Dry mouth • Hyperamylasemia	• Hypothyroidism • Sterility • Hair thinning • Vomiting • Fatigue • Infection • Bleeding/bruising • Anorexia • Changes in blood pressure during and after MIBG infusion (hypotension & hypertension)	• Pain in salivary glands or mouth • Decreased function of adrenal gland • Decreased heart function • Hepatotoxicity • Secondary leukemia • Pneumocystis pneumonia • Bronchiolitis obliterans with organizing pneumonia (BOOP) • Hyperthyroidism

6.2 Dinutuximab (Chimeric Monoclonal Antibody 14.18; Chimeric MOAB 14.18; human/murine anti-GD2 monoclonal antibody; chimeric anti-GD2; chimeric mAb 14.18; ch14.18; Unituxin®) NSC# 764038

6.2.1 Source and Pharmacology

Dinutuximab is an anti-GD2 monoclonal antibody composed of the variable region heavy and light chain genes of the murine mAb 14.G2a and the human constant region genes for heavy chain IgG1 and light chain kappa. Dinutuximab exerts its antitumor effect by binding specifically to the disialoganglioside GD2, an antigen found in human tumors of neuroectodermal origin such as melanoma and neuroblastoma. This chimeric antibody has been shown to lyse melanoma and neuroblastoma cells through the process of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). By targeting the GD2 antigen on the cell surface, dinutuximab may also prevent attachment of circulating malignant cells to the extracellular matrix. Additionally, dinutuximab mediates lysis of several melanoma and neuroblastoma cell lines in a dose dependent manner in the presence of potent mediators of ch14.18-dependent cytotoxicity, such as human peripheral blood mononuclear cells and granulocytes. This is most profound with neutrophils, especially in the presence of recombinant human granulocyte-macrophage colony-stimulating factor.

The PK profile of ch14.18 has been determined in adults with melanoma and children with neuroblastoma. Although the plasma clearance for both groups of patients follow a two-compartment model, circulating antibody is cleared from the plasma at a much faster rate in children than adults (mean $t_{½}\beta$ = 66.6 ± 27.4 hours in children versus 123 ± 29 hours and 181 ± 73 hours in two adult trials, respectively). Maturation of the hepatic and renal systems with age is thought to impact on drug metabolism and elimination and could account for these differences. In general, the mAb half-life following the first course of treatment was longer than the half-lives following subsequent courses in a given patient.

6.2.2 Toxicity

The expected adverse reactions of dinutuximab:

Likely Happens to 21-100 children out of every 100	Occasional Happens to ≤ 20 children out of every 100	Rare Happens to < 3 children out of every 100
Blood and Lymphatic System Disorders		
	Anemia	Hemolytic uremic syndrome[1]
	Disseminated Intravascular Coagulation	
Cardiac Disorders		
	Sinus tachycardia	Cardiac arrest
		Sinus bradycardia
Eye Disorders		
		Eye disorders – Other (eye disorders)[2]
Gastrointestinal Disorders		
	Abdominal pain	
	Diarrhea	
	Nausea	
	Vomiting	
General Disorders and Administration Site Conditions		
Fever	Edema limbs	Infusion related reaction
Pain		Sudden death NOS
Immune System Disorders		
	Allergic reaction	Anaphylaxis

	Serum sickness	
Infections and Infestations		
	Infection[3]	
Investigations		
Investigations – Other (elevated c-reactive proteins)	Increased alanine aminotransferase (ALT)	
	Increased aspartate aminotransferase (AST)	
	Increased blood creatinine	
	Decreased lymphocyte count	
	Decreased neutrophil count	
	Decreased platelet count	
	Decreased white blood cell count	
Metabolism and Nutrition Disorders		
	Decreased appetite	
	Hyperkalemia	
	Hypoalbuminemia	
	Hypocalcemia	
	Hypokalemia	
	Hyponatremia	
	Back pain	
	Pain in extremity	
Nervous System Disorders		
	Neuralgia	Tranverse myelitis/myelitis
	Peripheral sensory neuropathy[4]	Peripheral motor neuropathy
		Reversible Posterior encephalopathy syndrome[b]
Renal and Urinary Disorders		
	Proteinuria	Renal and urinary disorders-other (atonic urinary bladder)[4]
	Urinary retention[4]	
Respiratory, Thoracic and Mediastinal Disorders		
Cough	Bronchial obstruction	
	Dyspnea	
	Hypoxia	
	Stridor	
Skin and Subcutaneous Tissue Disorders		
Maculo-papular rash	Pruritus	
	Urticaria	
Vascular Disorders		
	Capillary Leak Syndrome	
	Hypertension	
	Hypotension	

[1]There have been rare instances of a typical hemolytic uremic syndrome in the absence of documented infection and resulting in renal insufficiency, electrolyte abnormalities, anemia and hypertension

[2]Neurological disorders of the eye including blurred vision, diplopia, cycloplegia, mydriasis, photophobia, optic nerve disorder, eyelid ptosis, and fixed pupils have been observed.

[3]Infection includes all 75 sits of infection under the Infections and Infestations SOC

[4]Acute urinary retention may occur during therapy and is though to be due to fluid shifts and narcotic administration that accompanies dinutuximab administration. Atonic urinary bladder may result in chronic urinary retention (CUR) that requires intermittent urethral catheterization days to weeks following dinutuximab administration

6.2.3 Formulation and Stability

Dinutuximab is provided as a sterile solution in single-dose vials containing 17.5 mg/5 mL (3.5 mg/mL) in 20 mM Histidine, 150 mM NaCl, 0.05% Tween 20 at pH 6.8. Intact vials should be stored in the refrigerator (2ºC to 8ºC) in the outer carton to protect from light. Stability studies of the intact vials are ongoing.

Withdraw the required volume of dinutuximab from the single-use vial and inject the exact volume into a 100 mL bag of 0.9% Sodium Chloride injection, USP. Mix by gentle inversion. DO NOT SHAKE. Discard unused content of the vial. Discard diluted dinutuximab solution > 4 hours after preparation.

The use of a filter during preparation is not required. Do not freeze or shake vials.

The final prepared product of dinutuximab in Normal Saline is stable at room temperature for 24 hours when diluted to a concentration between 0.044 and 0.56 mg/mL; however, the final dosage form should be prepared immediately prior to administration as there is a maximum infusion time of 20 hours. The minimum infusion time for the antibody infusion is 10 hours.

6.2.4 Guidelines for Administration: See Treatment, Dose Modifications and/or Supportive Care sections of the protocol.

6.2.5 Supplier

Manufactured and supplied by United Therapeutics. Dinutuximab will be distributed by Almac, Inc. for this study. All drug orders will be submitted to Almac from the NANT Operations Center. Refer to the NANT website for ordering information. **Do NOT use commercial supply.**

The drug supply must be stored in a locked limited access area. Dinutuximab is for investigational use only, and is to be used only within the context of this study. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, subjects, or clinics, or allow supplies to be used other than directed by this protocol.

6.2.6 Agent Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and disposal or return of the drug, will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Almac. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. All unused, unopened, Dinutuximab should be held until confirmation that the last patient registered into the study has completed the treatment period. The site will maintain detailed records of the drug reconciliation with the study files, and all material containing study drug will be treated as hazardous waste in accordance with governing regulations.

6.3 SARGRAMOSTIM (Granulocyte Macrophage Colony Stimulating Factor, rhu GM-CSF, rGM-CSF, GM-CSF, Leukine®) NSC #613795

6.3.1 Source and Pharmacology

Sargramostim (recombinant human GM-CSF) is a glycoprotein produced in yeast (S. cerevisiae) by recombinant DNA technology. rGM-CSF is a hematopoietic growth factor which supports survival, clonal expansion, and differentiation of hematopoietic progenitor cells. rGM-CSF induces partially committed progenitor cells to divide and differentiate in the granulocyte-macrophage pathways. rGM-CSF stimulates the production of monocytes, granulocytes, erythrocytes, and sometimes, megakaryocytes in the bone marrow. It also induces mature neutrophil and monocytes to increase phagocytosis, superoxide generation, ADCC, tumoricidal killing and cytokine production (IL-1 and tumor necrosis factor). Recombinant human GM-CSF is a glycoprotein of 127 amino acids characterized by three primary molecular masses of 15500, 16800, and 19500 daltons. The amino acid sequence differs from the natural sequence by a substitution of leucine at position 23 and the CHO moiety may be different from the native protein. After subcutaneous administration of sargramostim, peak levels were obtained in 1-4 hours and were detectable at therapeutic levels for 12-16 hours post injection. The elimination t½ ranges from 1.5-2.7 hours after SQ or IV administration.

6.3.2 Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1- 2 days of receiving drug	Headache, malaise, fatigue, rash, pruritus, bone pain, myalgia, arthralgia, fever, chills	Abdominal pain, weakness, anorexia, nausea, local injection reactions	Anaphylaxis, "first dose reaction" (hypoxia, dyspnea, hypotension, fever, tachycardia, diaphoresis, flushing, back pain), vomiting, diarrhea, phlebitis, SVT, pericardial effusion
Prompt: Within 2- 3 weeks, prior to the next course		Weight gain	In high doses: capillary leak syndrome: (pleural effusion, peripheral edema, ascites, weight gain, hypotension), pneumonitis, peripheral edema, elevation of creatinine, bilirubin and hepatic enzymes in patients with preexisting renal or hepatic dysfunction
Delayed: Any time later during therapy		Thrombocytopenia	
Unknown Frequency and Timing:	**Fetal and teratogenic toxicities**: It is not known whether sargramostim can cause fetal harm or affect reproduction capacity when administered to a pregnant woman. It is unknown whether the drug is excreted in breast milk.		

6.3.3 Formulation and Stability

Sargramostim is available as a lyophilized sterile, white, preservative free powder with 250 mcg (1.4 million International Units) per vial and as a sterile, preserved injectable solution in a 500 mcg/mL (2.8 million International Units/mL) 1 mL vial. The sargramostim reconstituted lyophilized vial contains 40 mg/mL mannitol, USP; 10 mg/mL sucrose, NF; and 1.2 mg/mL tromethamine, USP, as excipients. The liquid formulation also contains 1.1% benzyl alcohol (11 mg/mL). Store refrigerated at 2-8°C (36-46°F). Do not freeze or shake.

6.3.4 Guidelines for Administration

See Treatment, Dose Modifications, and Supportive Care sections of the protocol.

Reconstitute lyophilized powder for injection with 1 mL SWFI or 1 mL Bacteriostatic Water for Injection. Use SWFI without benzyl alcohol for neonates, infants, and children < 2 years of age or patients with hypersensitivity to benzyl alcohol. During reconstitution, direct the diluent at the side of the vial and gently swirl the contents to avoid foaming during dissolution. Avoid excessive or vigorous agitation; do not shake. Reconstituted solutions prepared with Bacteriostatic Water for Injection (0.9% benzyl alcohol) or the liquid preserved solution may be stored for up to 20 days following the first entry into the vial at 2°-8°C (36°-46°F). Discard reconstituted solution after 20 days have elapsed. Reconstituted solutions prepared with SWFI (without preservative) should be administered as soon as possible and within 6 hours following reconstitution.

Use sargramostim for subcutaneous injection without further dilution. Perform dilution for IV infusion in NS. If the final concentration is < 10 mcg/mL, add albumin (human) at a final concentration of 0.1% to the saline prior to addition of sargramostim to prevent adsorption to the components of the drug delivery system. For a final concentration of 0.1% albumin (human), add 1 mg albumin (human) per 1 mL NS. For example, for a final volume of 50 mL NS, add 50 mg (or 1 mL) of 5% albumin [human]. Intravenous dilutions are stable for up to 48 hours at room temperature or refrigerated but should be used within 6 hours due to microbiological concerns. Do not use an in-line membrane filter for IV infusion.

6.3.5 Supplier

Sargramostim is commercially available in the U.S and so will be obtained from commercial supply. See package insert for more detailed information. Only sargramostim (yeast-derived recombinant human GM-CSF) will be used in this study. The *Escherichia coli*-derived product (molgramostim) will not be used.

6.4 POTASSIUM IODIDE (KI, SSKI)

Formulation: Oral solution 1 gram / milliliter.

Therapeutic MIBG Treatment: Loading dose of 6 mg/kg by mouth 8-12 hours prior to infusion of MIBG on Day 1, and then 1 mg/kg/dose by mouth starting 4-6 hours after completion of MIBG infusion and continuing every 4 hours on protocol Days 1 to 7 and then 1 mg/kg/dose by mouth once daily on protocol Days 8-45.

Storage: Room temperature

Toxicity:

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
	• Gastrointestinal distress (nausea / vomiting / diarrhea / stomach pain)	• Vasculitis • Flare up of adolescent acne • Irregular heartbeat • Confusion • Tiredness • Fever • Hypersensitivity (hives) • Burning of mouth / throat • Metallic taste • Rash • Hypothyroidism with overuse • Swelling of lymph glands

6.5 VORINOSTAT (ZOLINZA™)

6.5.1 Structure and Molecular Weight
The chemical names for vorinostat are N-hydroxy-N'-phenyl-octane-1,8-diotic acid diamide or N-hydroxylN'-phenyl (9CI) octanediamide. The molecular formula is: C14H20N203. The molecular weight is 264.32.

6.5.2 Description
Vorinostat is a histone deacetylase (HDAC) inhibitor. HDACs are a group of proteins that regulate gene transcription by affecting the acetylation status of histones. Vorinostat binds to the catalytic pocket of HDAC enzymes and inhibits their activity.

6.5.3 Supplier
Vorinostat is commercially available in the U.S. and so will be obtained from commercial supply. See package insert for more detailed information.

6.5.4 Guidelines for Administration and Compounding
Vorinostat is administered orally or via NG tube or G-tube. Vorinostat should be taken with food or within 30 minutes after a meal. The dose should be taken in the morning whenever possible. Altered taste and decreased food and liquid intake are associated with vorinostat administration. These toxicities can be actively managed with fluid management and nutritional consult and support. During the period of vorinostat administration, patients are recommended to consume adequate fluid daily to prevent dehydration. Patient

may require electrolyte replacement. Early use of anti-emetics is encouraged. If a patient vomits within 15 minutes of vorinostat dose administration, the patient should be re-dosed. If the patient vomits after the second dose, the patient should not be re-dosed again. If a patient vomits more than 15 minutes from dose administration, the patient should not be re-dosed. If patients experience dysgeusia, popsicles or Gatorade may be successful in maintaining oral intake. Missed doses may be made up provided there is at least 24 hours between vorinostat and infusion of stem cells, and stem cell infusion is not delayed beyond Day 17. Vorinostat should not be administered after stem cell infusion regardless of the number of doses received. Patients should not exceed 14 total doses of vorinostat for any reason. Patients should not double-up on missed doses during treatment.

Patients will receive vorinostat as a liquid suspension or as capsules. Capsules can be used only for patients with a calculated dose within +/- 10% of a 100 mg dosing increment (e.g. 100 mg, 200 mg, 300 mg, or 400 mg).

The COG phase I study of vorinostat, NANT 2007-03, and NANT 2011-01 all used the following formula for preparing a liquid suspension with a final vorinostat concentration of 50 mg/mL.

Required components
Vorinostat 100 mg capsules (20)
OraPlus or Suspensol S 20 mL
OraSweet 20 mL

Instructions
Add 20 mL of Suspensol S or OraPlus into an amber or clear glass 4 ounce bottle. Place the contents of 20 capsules of vorinostat 100 mg into the same bottle and shake to disperse. Shaking may take up to 3 minutes. Once dispersed, add 20 mL of OraSweet to achieve a total volume of 40 mL. Shake again to disperse. Final concentration is 50 mg/mL. Store at room temperature. The suspension is stable for 4 weeks when stored at room temperature, away from excessive heat and humidity. The suspension should not be mixed with food or beverages.
If there are any issues with ability to compound, please contact NANT Operations at nantcrf@chla.usc.edu.

The maximum daily dose of vorinostat on this protocol is 400 mg.

6.5.5 Potential Drug Interactions
The major pathways of vorinostat metabolism involve glucuronidation and β-oxidation. As vorinostat is not eliminated via CYP450 pathways, no drug-drug interactions are expected with known CYP450 inhibitors or inducers.

Although vorinostat is not a potent reversible CYP450 inhibitor, studies performed to monitor gene expression changes indicated some potential for CYP2C9 and CYP3A4 activity suppression. However, these changes were observed at concentrations higher than the pharmacologically relevant concentration.

6.5.6 Special Handling
Vorinostat is an anticancer drug. Clean powder spills from broken or damaged vorinostat capsules carefully minimizing inhalation. Wash spill area at least 3 times with ethyl alcohol, followed by water.

6.5.7 Patient Care Implications
Because vorinostat's dose limiting toxicities in previous studies included anorexia, dehydration, diarrhea, and fatigue, patients should maintain adequate fluid and food intake.

6.5.8 Toxicity
The most common drug-related adverse reactions can be classified into 4 symptom complexes: gastrointestinal symptoms (diarrhea, nausea, anorexia, weight decrease, vomiting, constipation), constitutional symptoms (fatigue, chills), hematologic abnormalities (thrombocytopenia, anemia), and taste disorders (dysgeusia, dry mouth). The most common serious drug-related adverse reactions were pulmonary embolism and anemia.

Serious Adverse Reactions
The most common serious adverse reactions in the 86 Cutaneous T Cell Lymphoma patients in two clinical trials were pulmonary embolism reported in 4.7% (4/86) of patients, squamous cell carcinoma reported in 3.5% (3/86) of patients and anemia reported in 2.3% (2/86) of patients. There were single events of cholecystitis, death (of unknown cause), deep vein thrombosis, enterococcal infection, exfoliative dermatitis, gastrointestinal hemorrhage, infection, lobar pneumonia, myocardial infarction, ischemic stroke, pelviureteric obstruction, sepsis, spinal cord injury, streptococcal bacteremia, syncope, T-cell lymphoma, thrombocytopenia and ureteric obstruction.

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
• Thrombocytopenia • Fatigue • Diarrhea • Nausea • Dysgeusia • Anorexia	• Weight loss • Muscle spasms • Alopecia • Dry mouth • Blood creatinine increased • Hyperglycemia • Electrolyte abnormalities (hypocalcemia, hypophosphatemia, Hypomagenesemia, hyponatremia) • Elevated Liver enzymes (AST, ALT, Alk phos and bilirubin) • Proteinuria • Lymphopenia • • Chills • Vomiting • Constipation • Dizziness • Anemia • Heartburn • Dehydration • Peripheral edema • Headache • Pruritis • Cough • Infection • Pyrexia with and without neutropenia • Thrombosis	• Squamous Cell Carcinoma • Skin necrosis • PT Prolongation • Gastrointestinal Bleeding • Prolonged QTc (Low-grade prolonged QTc interval has rarely been reported in patients receiving vorinostat, though the relationship to vorinostat remains undetermined)

Based on its mechanism of action and findings from animal studies, ZOLINZA can cause fetal harm when administered to a pregnant woman

Note: Vorinostat in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.0 REQUIRED OBSERVATIONS/MATERIAL AND DATA TO BE ACCESSIONED

7.1 Clinical and Laboratory Assessments

All clinical and laboratory examinations must be obtained within 14 days of study registration except for β-HCG pregnancy test if applicable which must be done within 7 days of study registration. If more than 7 calendar days elapse between the date laboratory studies to determine eligibility were obtained and the start date of treatment, then the following studies must be repeated prior to initiating protocol therapy:

- CBC with differential
- Total bilirubin
- ALT
- Serum Creatinine

Labs not meeting eligibility criteria if repeated after study registration may again be repeated within 48 hours up to 7 days after the initial result not meeting eligibility criteria was obtained. Please note that β-HCG pregnancy test if applicable must be performed within 7 days of study registration and may need to be repeated if there is a week delay. Subjects will be off protocol therapy if repeated laboratory values have not met eligibility criteria by 7 days after the initial result not meeting eligibility criteria was obtained.

Tumor disease evaluation (including appropriate imaging studies and bilateral bone marrow aspirate and biopsy for standard histology) and echo are required within 28 days prior to study enrollment and subsequent to any prior therapy. All patients regardless of marrow disease status at study registration are REQUIRED to have repeat bone marrow evaluations at each subsequent disease evaluation. Initiation of protocol therapy is required within 7 days of study registration.

OBTAIN OTHER STUDIES AS NEEDED FOR GOOD PATIENT CARE.

Studies	Screening for study entry	Day 1-56 Part A Day 0-56 Part B Courses 1 & 2	Day 57/ Prior to Course 2[6]	Day 57/ End of Therapy[6]
History, physical exam, vital signs, height, weight and BSA[1,3]	X	Days 0[11], 1[12], 8, 15[3], 29, 36[3], 43[3] Daily during dinutuximab administration	X	X
Performance Status[1]	X		X	X
CBC[3], differential, platelets[1]	X	Twice weekly until engraftment then weekly[1,4]	X	X
Electrolytes, calcium, albumin, BUN, creatinine[1]	X	Weekly; Daily during dinutuximab administration	X	X
AST, ALT[1], total bilirubin[1]	X	Weekly[9]	X	X
Direct bilirubin, PO_4, and Mg^{2+}	X	Obtain weekly ONLY if abnormal at screening	X	
PT, INR	X	Weekly	X	
Serum or urine β-HCG[1,5]	X		X	
TSH, Free T4	X		X	X
Echocardiogram[1, 6]	X		X	X
Electrocardiogram (Part B only)[1, 6]	X	One time between Days 4 and 8[10]	X	X
Urine HVA and VMA[6]	X[6]		X[6]	X[6]
Bilateral BM aspirate + biopsy for morphology[1,2]	X		X	X
Tumor imaging (CT or MRI scan)[1, 2]	X		X	X
MIBG diagnostic scan WITH SPECT (REQUIRED)[1,2] Use same isotope with each scan	X		X	X
MIBG whole body scan (SPECT NOT required)		Upon release from radiation isolation		
Whole body dosimetry		Days 1-5[8]		
Radiation level monitoring[7]		Beginning ~24 hours after MIBG infusion and continuing at least daily until cleared[7]		
Correlative biology studies (blood/tumor)	Refer to Section 8.0			
Blood and bone marrow for N04-05	X		X	X

1. Required for verification of eligibility. An eligibility checklist is available and may be used as a source document with PI signature or by uploading directly into patient EMR.
2. Tumor imaging = CT and/or MRI (Chest, abdomen, pelvis) plus CT/MRI imaging of any other sites with MIBG uptake for optimum visualization of all areas of bulk tumor (primary & metastasis) excluding extremities. If patient has a history of tumor lesions in the skull, orbits or brain, OR if MIBG scan shows uptake in these same areas, then a CT or MRI of the brain/orbits is strongly suggested. MRI is the recommended imaging technique for patients with epidural or hepatic tumor lesions. FDG-PET is required if used at baseline to document evaluable soft tissue tumor lesion(s) for response. ^{123}I-MIBG scans are preferred for disease status evaluation. SPECT is required on this study. All patients are required to

have a diagnostic bone marrow sent with each disease evaluation. All disease status tests must be performed within 28 days prior to study entry and subsequent to any intervening therapy

3. Vital signs should be done more frequently when indicated per Section 4.2 and for good patient care. Examinations may be performed +/- 2 days for D15, D36 and D43. Height and BSA only needed at screening, Day 29 of Course 1 and 2, and prior to Course 2.
4. Continue twice weekly (required once during week of ^{131}I-MIBG infusion (Day 1 – Day 7) until ANC > =500 cells/μL and platelet count > = 20,000 cells/μL x 3 days without transfusion, and then obtain weekly through the end of the course.
5. Obtain for females 10 years of age and older or post-pubertal. Women of childbearing potential require a negative pregnancy test prior to starting treatment (Course 1 & Course 2). Male and female subjects of reproductive age and childbearing potential must agree to use two acceptable methods of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) or to abstain from heterosexual intercourse for the duration of their participation in the study.
6. The end of course evaluations (clinical labs, echocardiogram, electrocardiogram, correlative studies) are to be performed between Days 46 - 57 except for disease status evaluation (tumor imaging by CT/MRI and bilateral bone marrow aspirate/biopsy) which may be performed between Days 43 and 57 of each course. In case of treatment delays with dinutuximab during Course 1, the time interval between performing end of Course 1 disease evaluation and administration of Course 2 ^{131}I-MIBG is not to exceed 4 weeks. Urine catecholamines are no longer required as part of patient disease status evaluation submitted to NANT Operations Center and may be obtained at investigator discretion.
7. The patient will remain in a radiation protected isolation room until radiation emissions meet institutional/state guidelines, but at least until the radiation level is < 7 mRem/hr at 1 meter. Radiation levels will be measured at least once daily until the patient is cleared by Radiation Safety using a handheld monitor standing at a distant of one meter from the patient.
8. See Section 4.2.1.7 for dosimetry guidelines.
9. If total bilirubin result ≥ Grade 3 then fractionate and obtain a direct bilirubin along with total bilirubin until total bilirubin ≤ Grade 2.
10. One EKG to be obtained prior to Day 8 dinutuximab dose. Patient must have a QTc interval ≤ 480 msec prior to proceeding with Day 8 dinutuximab dose (Part B only; see Section 4.2.3.3).
11. Part B only
12. Part A only

7.2 Recommended Follow-Up Observations

The following are recommendations only, but may be altered at discretion of treating physician. Repeat the following if abnormal on a monthly basis until stable or normalized after the end of therapy. If normal at the end of therapy then repeat only as clinically indicated:

- History, physical exam (Ht, Wt, VS)
- CBC/Differential, Platelets, AST, ALT, Bilirubin, BUN, Creatinine
- T4, TSH and MIBG scan every 3 months until 1 year post treatment, then every 6 months until progression, death or other therapy.

After completion of protocol therapy, the disease status, sites of relapse, and last alive date will be recorded until first relapse/progression or until patient receives another non-protocol therapy, after which only last alive date will be reported, as well as date of death and cause of death (if applicable).

7.3 Documentation of Tumor Response

Patients will undergo complete disease re-staging between Day 43 and Day 57 of each course of therapy. If there are treatment delays during Course 1, disease restaging after Course 1 may be delayed. This delay is not to exceed 4 weeks before the start of Course 2. It is recommended that all scans and tests previously done to document tumor lesions be performed in subsequent evaluations of disease status.

All patients will have diagnostic bone marrows performed with each disease evaluation, regardless of involvement at study registration. To confirm a bone marrow response of CR, an additional bone marrow examination for morphology (for a total of 2 bone marrow exams) must be done a minimum of three weeks apart (Section 11.0).

Once a patient receives therapy other than prescribed on this protocol, no further scans or bone marrow evaluations will be required for this protocol since the patient will no longer be evaluable for response to dinutuximab and ^{131}I-MIBG.

8.0 CORRELATIVE BIOLOGY STUDIES (See Appendix II)

Collection of samples for correlative biology studies is to be performed during the first course of therapy only. If the scheduled start of the first day of dinutuximab infusions on Day 8 and/or Day 29 are delayed, then the corresponding Day 8 and/or Day 29 biologic correlate sampling should also be delayed until the first day of dinutuximab infusion is given. The Day 15 biologic correlates should be obtained BEFORE stem cell infusion.

NOTE: It is strongly encouraged to begin ^{131}I-MIBG on Tuesday – Thursday to allow biologic correlates to be received at the processing laboratory on a Wednesday – Friday. Please contact the NANT Operations Center/Study Chairperson if treatment is delayed and will not start on a Tuesday – Thursday schedule.

8.1 Characterization of Immune and Cytokine Profile Following ^{131}I-MIBG Therapy (Required)

We will obtain preliminary data regarding the number of T, B, and NK cells present in the circulation at baseline and after treatment with ^{131}I-MIBG, and will also perform a more detailed analysis of NK cells. This T-B-NK panel quantifies these cells using flow cytometry. We will also freeze additional peripheral blood mononuclear cells (PBMCs) for future immunophenotyping studies. The additional PBMCs will be obtained from the blood collected for the cytokine profiling studies as detailed below in Section 8.1.2.2.

Below is the panel that we will test by flow cytometry:

Lineage Panel	Live/Dead (L/D), CD45, CD3, CD4, CD8, CD19, CD14, CD45RA, CD197, CD25, CD127, HLA-DR
NK Cell Panel	L/D, CD45, CD3, CD8, CD16, CD56, CD57, CD107a, CD158, CD314, CD335

We will also evaluate the pro-inflammatory cytokines that may augment the effects of immunotherapy, stimulate an immune-mediated anti-tumor response, and help establish the TME. The key cytokines and chemokines that will be analyzed are included below. This testing will be performed using a multiplex cytokine array on a Luminex platform.

39-plex: IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL- 13, IL-15, IL-17, EGF, Eotaxin, FGF-2, Flt-3-ligand, Fractalkine, G-CSF, GM-CSF, GRO, IFN-α2, INF-γ, IP-10, MCP-1, MCP-3/CCL7, MDC/CCL22, MIP-1α, MIP-1β, TNFα, TNFβ, VEGF, sCD40L, TGFas, IL-2R

Single-plex: sIL6-R

8.1.1 Sampling Requirements and Schedule (COURSE 1 ONLY)

Samples are to be collected Tuesday through Thursday only for delivery Wednesday through Friday.

A. Immune Profiling by Flow Cytometry
- Collect 5 mL of peripheral blood into a sodium heparin (green top) tube

B. Cytokine Profiling and Future Immunophenotyping Studies
- Collect 8 mL of peripheral blood into a sodium heparin cell preparation tube (CPT) tube

Part A: Samples (A & B) should be obtained at the following time points:

- After study registration through Day 1 but before ^{131}I-MIBG infusion[%].
- Day 8: prior to starting dinutuximab infusion[#]
- Day 15: prior to stem cell infusion[#]
- Day 29: prior to dinutuximab infusion[#,%]
- End of Course 1[#,%]

[#]If start of dinutuximab infusion is delayed, delay blood draw accordingly. Stem cell infusion may take place +/- 2 days of Day 15, draw blood to correspond with stem cell infusion date. Day 15 samples must be drawn prior to stem cell infusion. End of course sample may be drawn with corresponding end of course blood work.

%A single sample at this time point will be used to analyze both cytokine and HACA/ADA levels.

Part B: Samples (A & B) should be obtained at the following time points:

- After study registration through Day 0 but before vorinostat is given.
- Day 1, before MIBG infusion[%]
- Day 8: prior to starting dinutuximab infusion[#]
- Day 15: prior to stem cell infusion[#]
- Day 29: prior to dinutuximab infusion[#,%]
- End of Course 1[#,%]

[#]If start of dinutuximab infusion is delayed, delay blood draw accordingly. Stem cell infusion may take place +2 days/ - 1 day of Day 15, draw blood to correspond with stem cell infusion date. Day 15 samples must be drawn prior to stem cell infusion. End of course sample may be drawn with corresponding end of course blood work.

%A single sample at this time point will be used to analyze both cytokine and HACA/ADA levels.

8.1.2 Sample Processing

8.1.2.1 Immune Profiling by Flow Cytometry – Fresh whole blood (Sample 8.1.1 A)

- Samples should be kept at room temperature until shipped. Sample should not be refrigerated or frozen. Specimen will be shipped at room temperature for overnight delivery. Refer to Sections 8.1.3 / 8.3 for labeling and shipping instructions.
    - For subjects enrolled at Children's Healthcare of Atlanta (CHOA), this specimen will be taken directly to the Children's Clinical and Translational Discovery Core (CCTDC). A specimen transmittal form must be created for these specimens using the NANT Specimen Transmittal Form application.

8.1.2.2 Cytokine Profiling and Future Immunophenotyping Studies – Frozen plasma and viably frozen PBMCs (Sample 8.1.1 B)

- Samples must be processed within 30 MINUTES OF COLLECTION. The specimen will be spun down and the plasma will be aliquotted and frozen for future cytokine analysis and HACA and ADA analysis (refer to Section 8.2). The PBMCs obtained from processing this blood draw will be viably frozen for future flow cytometry studies. Refer to Appendix VI for the recommended procedure for isolating and storing plasma and PBMCs. Alternative methods may be used if first approved by the study chair and CCTDC.

Frozen specimens (aliquotted plasma and PBMCs) will be batch shipped at the completion of the study. Refer to Sections 8.1.3 / 8.3 for labeling and shipping instructions.

8.1.3 Sample Labeling and Shipment

Label tubes in the following manner:

- Patient's NANT Registration Number (N0xxx)
- Study identifier:
  - Flow: for flow cytometry samples (fresh whole blood)
  - Cytokine: for cytokine profiling samples (frozen plasma)
  - Immune: for future immunephenotyping samples (frozen PBMCs)
- Date and time blood was drawn
- Protocol sampling time point (ie: Day 8 etc.)

Refer to Section 8.3 for shipping instructions.

For the immune profiling studies (refer to Section 8.1.2.1), each sample should be sent on the same day it was obtained. The sample should be shipped at room temperature via Fed Ex Priority Overnight Delivery.

Frozen specimens for cytokine profiling (plasma) and future flow cytometry (PBMCs) [refer to section 8.1.2.2] will be stored at the treating NANT site and batch shipped on dry ice via Fed Ex Priority Overnight Delivery at the end of Course 1.

- For sites that don't have liquid nitrogen storage for PBMCs, refer to Section 8.3 /Appendix VI.

8.2 Human anti-Chimeric Antibody (HACA) and Neutralizing Anti-Drug Antibody (ADA) Levels (Required)

8.2.1 Sampling Requirements and Schedule (COURSE 1 ONLY)

The peripheral blood drawn per Section 8.1.1 B (cytokine profiling) and processed per section 8.1.2.2 will provide the frozen plasma to be used in performing HACA/ADA levels on Day 0 (Part B) or Day 1 (Part A), 29 and at end of course. Two additional samples (8 mL into a sodium heparin CPT tube) will be collected on Day 11 and Day 32 to analyze HACA/ADA levels. Please refer to Appendix II for overview of specimen collection time points.

Part A: Samples should be obtained at the following time points:

- After study registration through Day 1 but before ^{131}I-MIBG infusion[%].
- Day 11: prior to dinutuximab infusion[#]
- Day 29: prior to dinutuximab infusion[#,%]
- Day 32: prior to dinutuximab infusion[#]
- End of Course 1[#,%]

[#]If start of dinutuximab infusion is delayed, delay blood draw accordingly. End of course sample may be drawn with corresponding end of course blood work.
%A single sample at this time point will be used to analyze both cytokine and HACA/ADA levels

Part B: Samples should be obtained at the following time points:

- After study registration through Day 0 but before vorinostat is given[%].
- Day 11: prior to dinutuximab infusion[#]
- Day 29: prior to dinutuximab infusion[#,%]
- Day 32: prior to dinutuximab infusion[#]
- End of Course 1[#,%]

[#]If start of dinutuximab infusion is delayed, delay blood draw accordingly. End of course sample may be drawn with corresponding end of course blood work.
%A single sample at this time point will be used to analyze both cytokine and HACA/ADA levels

8.2.2 Sample Processing

Refer to 8.1.2.2 for specimen processing. The specimen will be spun down and aliquotted into two vials of 200 µL each of plasma for HACA and neutralizing ADA levels. Store together with frozen plasma for cytokine analysis.

8.2.3 Sample Labeling and Shipment

Label tubes in the following manner:

- Patient's NANT Registration Number (N0xxx)
- Study identifier:
  - HACA
- Date and time blood was drawn
- Protocol sampling time point (ie: Day 11 etc.)

These frozen specimens will be batch shipped to the CCTDC at Emory University at the end of Course 1. Refer to section 8.3 for shipping instructions.

8.3 Shipping Instructions

Samples should only be shipped on Mondays-Thursdays to allow for weekday delivery.

Include NANT specimen transmittal form and corresponding correlative study worksheet(s) with each shipment.

NANT Operations Center will email the Emory Lab at cctdc@emory.edu with the tracking number at the time of sample shipment.

All specimens will be shipped by Federal Express Priority Overnight delivery to the following address:

Emory University Children's Clinical and Translational Discovery Core (CCTDC)
Health Sciences Research Building – E264
1760 Haygood Drive
Atlanta, GA 30322
Phone: 404-727-2342
Email: cctdc@emory.edu

8.3.1 Shipping Timing

A. Immune Profiling studies (fresh whole blood - refer to section 8.1.2.1) should be sent on the same day it was obtained. The sample should be shipped at room temperature overnight via Fed Ex Priority Overnight delivery.

B. Frozen specimens for cytokine profiling (plasma) and future immunophenotyping (PBMCs) [refer to section 8.1.2.2] will be stored at the treating NANT site and batch shipped on dry ice via Fed Ex Priority Overnight Delivery at the completion of Course 1.

- For sites that don't have liquid nitrogen storage available for PBMCs, follow these instructions for storing and shipping all the frozen samples. Refer to Appendix VI.
    - Day 0 (Part B only), Day 1, Day 8, Day 15 PBMC samples:
        - Store in a - 80^0C freezer.
        - Ship these 3 samples to the Emory CCTDC (8.3) on dry ice via Fed Ex Priority Overnight Delivery after Day 15 draw is completed.
    - Day 29 and End of Course PBMC samples:
        - Store in a – 80^0C freezer
        - Ship these 2 samples PLUS batched frozen plasma samples (cytokine/HACA-ADA) on dry ice via Fed Ex Priority Overnight Delivery after the End of Course draw is completed.

C. Frozen specimens for HACA and ADA analysis (refer to Section 8.2) will be stored at the treating NANT site and batch shipped on dry ice via Fed Ex Priority Overnight Delivery at the completion of Course 1. These specimens may be sent with the frozen specimens collected in 8.1.2.2. Refer to 8.3.1B above.

D. Frozen PAXgene tubes for the optional RNA gene expression studies (refer to Section 8.5) will be stored at the treating NANT site and batch shipped on dry ice via Fed Ex Priority Overnight Delivery at the completion of Course 1.

8.4 Minimal Residual Disease by TaqMan low density array (NB5/TLDA) (Required)

All patients are required to co-enroll onto the NANT Biology Study, NANT 2004-05. Patients should submit blood and/or bone marrow at study entry and at the time of Day 43-57 restaging studies. Submission of blood and bone marrow for TLDA will be according to the instructions in NANT 2004-05. Patients can submit only bone marrow for NB5 assay if blood volumes for research do not allow for blood submission.

8.5 RNA Gene Expression Studies (Optional)

In consenting patients, 2.5 mL peripheral blood will be drawn at the following time points in a PAXgene RNA tube for analysis of immune response related genes, future RNA profiling and protein expression studies.

8.5.1 Sampling Requirements and Schedule (Course 1 Only)

Collect 2.5 mL of peripheral blood into a PAXgene RNA tube at each time point.

PART A:

- Screening: After study registration through Day 1 but before ^{131}I-MIBG infusion.
- Day 8: prior to starting dinutuximab infusion#
- Day 11: prior to discharge after completion of dinutuximab
- Day 15: prior to stem cell infusion#
- Day 29: prior to dinutuximab infusion#
- Day 32: prior to discharge after completion of dinutuximab
- Day 36#,%
- End of Course

#If start of dinutuximab infusion is delayed, delay blood draw accordingly. Stem cell infusion may take place +/- 2 days of Day 15, draw blood to correspond with stem cell infusion date. Day 15 samples must be obtained prior to stem cell infusion. End of course sample may be drawn with corresponding end of course blood work.
%Day 36 labs should be collected four days post last dose of dinutuximab

PART B:

- After study registration through Day 0 but before vorinostat is given.
- Day 1, before MIBG infusion%
- Day 8: prior to starting dinutuximab infusion#
- Day 11: prior to discharge after completion of dinutuximab
- Day 15: prior to stem cell infusion#
- Day 29: prior to dinutuximab infusion#
- Day 32: prior to discharge after completion of dinutuximab
- Day 36#,%
- End of Course

#If start of dinutuximab infusion is delayed, delay blood draw accordingly. Stem cell infusion may take place + 2 days/ - 1 day of Day 15, draw blood to correspond with stem cell infusion date. Day 15 samples must be obtained prior to stem cell infusion. End of course sample may be drawn with corresponding end of course blood work.
%Day 36 labs should be collected four days post last dose of dinutuximab

8.5.2 Sample Processing and Labeling

- Gently invert PAXgene tube 8-10 times after collection. Keep tube at room temperature for 2 – 72 hours and then freeze upright in a wire rack (NOT STYROFOAM HOLDER) for 24 hrs at -20◦C and then transfer to -70◦C or -80◦C freezer until ready to batch ship at the completion of the study.
    - It is strongly suggested that each PAXgene tube be placed in a ziplock bag to avoid losing the sample if the PAXgene tube bursts during freezing. Contact the Study Chairperson if this event occurs.

- Label PAXgene tubes in the following manner:
    - Patient's NANT Registration Number (N0xxx)
    - Study identifier:
        - RNA
    - Date and time blood was drawn
    - Protocol sampling time point (ie: Screening, Day 8 etc.)

8.5.3 Shipping

All samples will be stored frozen at NANT site and batch shipped at the end of Course 1. Refer to Section 8.3 for shipping instructions and address.

8.6 Isolation of DNA for Future Gene Expression Studies (Optional)

In consenting patients, two 250µL aliquots (approximately 0.25 mL) of whole blood previously collected for immune profiling by flow cytometry (Section 8.1.2.1) will be processed and stored at Emory University. No additional blood needs to be drawn from the patient to perform these studies.

8.7 Storage of Remaining Biologic Samples for Future Analysis (Optional)

The NANT Biology Study (NANT 2004-05) provides a mechanism to allow for banking of biologic specimens collected through other NANT protocols. Consenting patients will be asked to allow storage/banking of samples leftover from correlative testing on this study for future analysis to address scientific questions related to ^{131}I-MIBG, dinutuximab, neuroblastoma or other childhood cancers. A decision to perform such exploratory research studies would be based on outcome data from this study or from new scientific findings related to the drugs or disease.

8.8 Evaluation of the Tumor Microenvironment (Optional)

In consenting patients, archival tumor tissue from the most recent biopsy of a soft tissue lesion obtained prior to study registration will be collected from those patients who have adequate tumor tissue to submit. We will use this tissue to evaluate the tumor microenvironment (TME). Tumor samples will be evaluated for the presence of TILs and TAMs, as well as the immune checkpoint proteins CD274 (PDL1) and CD276 (B7H3) by immunohistochemistry. We will also perform RNAseq and exome sequencing to evaluate for immune response genes. Three mL of peripheral blood will be drawn for germline DNA and the tumor sequencing will be interpreted in the context of these results.

For consenting patients, in the future, if a biopsy is performed for clinical reasons prior to starting therapy subsequent to this protocol treatment, we will request that tumor tissue be submitted. This tumor tissue will be analyzed for changes in the TME that occur as a consequence of the ^{131}I-MIBG + dinutuximab therapy, and will be compared to pre-study samples when available.

8.8.1 Sample Requirements

Coordinate to collect blood so blood and tumor may be shipped together at the same time.

- Collect 3 mL peripheral blood in purple top (EDTA) tube. This sample must arrive in the CHLA lab NO LATER THAN 48 hours after it was drawn.
    - Confirm there is tumor specimen available that can meet the sampling requirements below prior to arranging for blood to be drawn.
- One FFPE block; OR
- 10 tissue scrolls 15 µm thick AND 10-25 unstained slides

  If scrolls AND slides are submitted, they should be cut sequentially from one representative block.

8.8.2 Sample Labeling

Label blood:

- Patient's NANT Registration Number (N0xxx)
- Collection date (MM/DD/YY)

Label tumor samples in the following manner:

- Patient's NANT Registration Number (N0xxx)
- Specimen type: P for primary or M for metastatic site
- Surgical pathology ID number and block number from corresponding pathology report
- Study identifier:
    - Tissue

8.8.3 Sample Shipment

Samples should only be shipped on Mondays-Thursdays to allow for weekday delivery. NANT Operations will email Rebekah Kennedy with the tracking number at the time of sample shipment.

Samples should be shipped at room temperature by Federal Express Priority Overnight Delivery to the address below:

Include NANT specimen transmittal form and correlative study worksheet with each shipment.

NANT Biology Specimen Bank
Attn: Rebekah Kennedy
Children's Hospital Los Angeles
Smith Research Tower, Room 506
4650 Sunset Boulevard, MS 57
Los Angeles, CA 90027
Lab Phone: (323) 361-4503
Lab FAX: (323) 361-4902
Lab Contact: Rebekah Kennedy
E-mail: rekennedy@chla.usc.edu or sasgharzadeh@chla.usc.edu

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy

a. Disease progression before active treatment
b. Disease progression, relapse during active treatment
c. Patient/parent withdrawal/refusal before beginning protocol therapy
d. Patient/parent withdrawal/refusal after beginning protocol therapy
e. Unacceptable adverse events by protocol criteria[#]
f. Other adverse event / side effects / complications
g. Patient off treatment for other complicating disease
h. Initiation onto another therapeutic study and/or another anti-cancer therapy
i. Treatment completed per protocol criteria
j. No treatment (includes patients unable to get vorinostat)
k. Lost to follow-up
l. Death while on protocol therapy

#: When determining criteria for removal from protocol therapy, Day 8 dinutuximab dose delayed beyond Day 11 and Day 29 dinutuximab dose delayed by more than 2 weeks will be classified as unacceptable adverse events by protocol criteria.

Patients who are off protocol therapy are to be followed until they meet the criteria for off study. Patients who are removed from therapy prior to progression will be followed for progressive disease until they progress, die, or start another therapy (in which case the date of the new therapy and the type of therapy will be recorded). All patients will be followed until death for survival analysis, unless consent is withdrawn or patient is lost to follow-up. Protocol follow-up forms will be completed every 6 months after patient comes off protocol therapy for the first year and then once a year thereafter (see data submissions schedule for further detail).

9.2 Off Study Criteria

a. Death
b. Lost to follow-up
c. Patient/Parent withdrawal of consent

10.0 STATISTICAL CONSIDERATIONS

Part A: This is a Phase I trial with a dose escalation portion using a Rolling 6 design, followed by a brief expansion cohort of 6 evaluable patients at the recommended Phase II dose (RP2D).

Part B: **Enrollment to Part B of the study will not begin until enrollment of the Part A expansion cohort is complete.** Part B will test 1 dose level of vorinostat with a de-escalation dose level if needed, using a Rolling 6, Phase 1 trial design. This will be followed by a brief expansion cohort of 6 evaluable patients at the RP2D.

10.1 Sample Size and Study Duration

10.1.1 Part A
A maximum of four dose levels is planned for this part of the study (see Table in Section 4.3.1). Dose Level 1 (12 mCi/kg dose of ^{131}I-MIBG and 17.5 mg/m^2/dose of dinutuximab) will be the starting dose; in Dose Levels 2 and 3, the dose of ^{131}I-MIBG will be escalated to 15 and then 18 mCi/kg, with the dose of dinutuximab fixed at 17.5 mg/m^2/dose. If the starting dose level (Dose Level 1) is not tolerated (i.e. 2+ patients experience DLT), then 3-6 subsequent patients will be enrolled to Dose Level 0, which keeps the ^{131}I-MIBG dose at 12 mCi/kg, but reduces the dinutuximab dose to 14 mg/m^2/dose.

A minimum of 3 (or 2 if the 1st 2 patients at a dose level experience DLT) and maximum of 6 patients evaluable for toxicity (as defined in Section 10.2.1) will be entered at each dose level. Once the final MTD/RP2D has been determined, a maximum of 6 additional DLT-evaluable patients will be enrolled at the MTD/RP2D. The number of evaluable patients needed during the expansion will be determined when a robust cohort, treated at the MTD/RP2D, has been established to describe toxicity, response, and immune correlated data. Thus a minimum of 4 DLT-evaluable patients (if the 1st 2 patients at Dose Level 1 experience DLT and the 1st 2 patients at Dose Level 0 experience DLT) and a maximum of 30 DLT-evaluable patients (if 6 DLT-evaluable patients are enrolled at all 4 dose levels and Dose Level 0 is the MTD: 4x6+6=30) could be enrolled on this study. Based on NANT 17-1 enrollments to date and 20%-30% patients may be DLT-inevaluable, we anticipate that 30 to 32 patients will be enrolled.

Review of accrual to previous NANT studies indicates that up to 15 patients per year should be accrued; however, given that NANT 11-01 will be open concurrently, and there will be study closures for dose level evaluation, we anticipate that it will take 3 years to complete this part of the study, i.e. about 10 patients per year accrual.

10.1.2 Part B
A maximum of two dose levels is planned for this part of the study (see Table in Section 4.3.2). Dose Level 4 (180 mg/m^2/dose of vorinostat, 17.5 mg/m^2/dose of dinutuximab, and 18 mCi/kg/dose ^{131}I-MIBG) will be the starting dose. If the starting dose level (Dose Level 4) is not tolerated (i.e. 2+ patients experience DLT), then 3-6 subsequent patients will be enrolled to Dose Level 4a, which keeps the ^{131}I-MIBG (18 mCi/kg/dose) and dinutuximab (17.5 mg/m^2/dose) dose the same, but reduces the vorinostat dose to 150 mg/m^2/dose.

A minimum of 3 (or 2 if the 1st 2 patients at a dose level experience DLT) and maximum of 6 DLT-evaluable patients evaluable for toxicity (as defined in Section 10.2.1) will be entered at each dose level. Once the final MTD/RP2D has been determined, an additional 6 DLT-evaluable patients will be enrolled at the MTD/RP2D. Thus a minimum of 4 DLT-evaluable patients (if the 1st 2 patients at Dose Level 4 experience DLT and the 1st 2 patients at Dose Level 4a experience DLT) and a maximum of 18 DLT-evaluable patients (if 6 DLT-evaluable patients are enrolled at both dose levels and Dose Level 4a is the MTD: 2x6+6=18) could be enrolled on this study. We anticipate that 15 to 18 patients will be enrolled, based on the NANT 17-1 enrollments to date that 20%-30% patients may be DLT-inevaluable.

NANT 2017-01 was opened to accrual in September of 2018, and 20 patients have been enrolled since that time, i.e. ~10 patients per year accrual. Based on this, we anticipate that it will take 1.5 to 2 years to complete this part of the study.

10.2 Definitions

10.2.1 Evaluable for Inclusion in Dose Escalation Consideration (i.e. "DLT-Evaluable")

Dose escalation considerations will be based on Course 1 data only. Toxicity will be assessed and reported on all patients who begin protocol therapy. The definition of DLT is given in Section 4.4.

Part A Dose Escalation Cohort: A patient will be considered evaluable for inclusion in dose escalation/expansion/de-escalation decisions if he/she has received at least 90% of the assigned dose of ^{131}I-MIBG, and at least 80% of the assigned doses of dinutuximab and GM-CSF during Course one AND are followed until Day 57 or until platelet and neutrophil engraftment (defined in Section 4.5.2.1), whichever occurs last. In addition, patients who experience DLT at any time after the first dose of dinutuximab are evaluable for inclusion in dose escalation consideration. Toxicity will be assessed and reported on all patients who begin protocol therapy.

Part A Dose Expansion and Part B Cohorts: A patient will be considered evaluable for inclusion in dose escalation/expansion/de-escalation decisions if he/she has received at least 90% of the assigned dose of ^{131}I-MIBG, at least 80% of the assigned dose of dinutuximab, and at least 78% of the assigned doses of vorinostat (at least 11 days; Part B only) during Course one AND are followed without receiving any non-protocol therapy at least through 14 days after the last dose of dinutuximab or until platelet and neutrophil engraftment (defined in Section 4.5.2.1) or resolution of all non-hematologic toxicities at least possibly related to protocol therapy to ≤ Grade 2, whichever occurs last. In addition, patients who experience DLT at any time after the first dose of dinutuximab are evaluable for inclusion in dose escalation considerations. Toxicity will be assessed and reported on all patients who begin protocol therapy.

Patients who receive less than 90% of the assigned ^{131}I-MIBG dose, less than 80% of the assigned dinutuximab or GM-CSF doses (Part A dose-escalation phase only), or less than 78% of the assigned vorinostat doses (less than 11 days; Part B only) for reasons other than toxicity AND/OR are not followed through 14 days after the last dose of dinutuximab without receiving any non-protocol therapy, or until platelet and neutrophil engraftment (defined in Section 4.5.2.1), or until resolution of all non-hematologic toxicities at least possibly related to protocol therapy to ≤ Grade 2, whichever occurs last will be replaced for the purposes of evaluating the dose level for dose escalation/de-escalation purposes, unless they have DLT in first course.

Certain adverse events associated with dinutuximab are known to occur and to be patient dependent. These will not be considered DLTs even if they result in treatment delays or skipped doses. If doses are eliminated or treatment is terminated because of these toxicities, so that the patient is no longer DLT-evaluable, this patient will also be replaced. The number of these patients and toxicities will be evaluated by the study management committee and the incidence compared to standard dinutuximab therapy.

Patients who do not meet definition of hematologic engraftment DLT (Section 4.5.2.1) and begin other therapy prior to platelet and/or neutrophil engraftment will not be fully evaluable for hematologic toxicity and will be replaced.

10.2.2 Evaluable for Response

Eligible patients with measurable or evaluable disease (which will include all patients since the trial requires that a patient have MIBG-avid disease at study entry) who (a) have received any dose of protocol therapy and (b) have at least one evaluation of tumor status as mandated in required observations OR have tumor progression demonstrated on at least one parameter (CT/MRI, MIBG, or bone marrow) OR have clinical evidence of progression per treating physician OR who die due to toxicity, will be classified as "evaluable for response". Patients who are not

evaluable for response will NOT be replaced. Response will be described for all patients entered on study.

All patients who are registered onto the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories (see Section 11.6):

a. Complete Response
b. Complete Response MD
c. Partial Response
d. Progressive Disease
e. Stable Disease
f. Stable Disease-Non-Target Lesions
g. Minor Response
h. Minimal Disease
i. Not Evaluable
j. No Progression
k. Not Done

All eligible patients who receive any amount of ^{131}I-MIBG will be included in the initial, primary analysis of response. Patients in groups a through c will be classified as responders; patients in groups d through j will be classified as non-responders. In a second analysis, the proportion of responders (patients in groups a through c) will be calculated from the subset of patients who are evaluable for response (as defined above).

10.2.3 Maximum tolerated dose (MTD)

The MTD is the highest dose level tested at which 0/6 or 1/6 patients experience DLT (that is possibly, probably, or definitely related to the study drug(s) as defined in Section 4.5) with at least 2/3 or 2/6 patients encountering DLT at the next higher dose. If 0/6 or 1/6 patients experience DLT at the 3rd and highest dose level, then Dose Level 3 is the highest tested dose and will be called the MTD.

10.2.4 Recommended Phase II Dose (RP2D)

The RP2D will be the MTD, pending comprehensive review of all toxicities (for example if the patient receives more than one course). If the RP2D is not the MTD, then the protocol will be amended to explain the decision.

10.3 Dose Escalation

Toxicity will be graded using the CTCAE criteria, version 5.0 which can be downloaded from the CTEP home page (http://ctep.cancer.gov). The definition of dose limiting toxicity (DLT) is given in Section 4.5.

10.3.1 Dose Levels 0, 1-3, 4, and 4a:

This study will utilize the Rolling 6 design for dose escalation (81). This design is a modification of the classic 3+3 dose escalation strategy. With this design, three to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with toxicity data pending at the current dose level. Accrual at a dose level is suspended when a cohort of six has enrolled or when the study endpoints have been met. In order to facilitate the safe conduct of the Rolling 6 design, NANT operations and sites will remain in close contact to monitor occurrence of DLT in a timely fashion with increased reporting requirements from sites and study committee oversight.

The rules for the Rolling 6 design are as follows:

- At each dose level, up to 6 patients can be enrolled.

- Unless 2+ patients experience DLT, a minimum of 3 patients will be enrolled at each dose level.
- At most 6 evaluable patients will be treated at each dose level.

- At any time if 2+ patients experience DLT at a dose level, then the MTD has been exceeded.
  - At Dose Levels 1 and 2: dose escalation will be stopped, and the dose level will be de-escalated, if there are fewer than 6 patients at the next lower dose level.
  - At Dose Levels 3 and 4: dose level will be de-escalated, if there are fewer than 6 patients at the next lower dose level.
  - At Dose Level 0 and 4a: the protocol will be terminated or amended.
- If 6 patients have been enrolled and evaluated, and only 0 or 1 patients have experienced at DLT, the following rules apply.
  - At Dose Levels 1 and 2: the next patient will be enrolled at the next higher dose level.
  - At Dose Levels 0, 3, 4 and 4a: the current Dose Level will be labeled the MTD.
- Once 3-5 patients have been treated at a dose level and only 0 or 1 have experienced a DLT, then the following rules will be followed as listed in the Table below.

Rules for Dose Expansion/Escalation when 3-5 Patients have been Enrolled and Only 0 or 1 Patient has Experienced a DLT				
At the Current Dose Level				
Number of Patients Enrolled	**Number of Patients Who Have Experienced a DLT**	**Number of Patients Who NOT Have Experienced a DLT**	**Number of Patients with Data Pending**	**Assignment of the Next Patient**
3	0	0	3	Enroll at Current Dose Level*
3	0	1	2	Enroll at Current Dose Level*
3	0	2	1	Enroll at Current Dose Level*
3	0	3	0	Dose Levels 1 and 2: Enroll at Next Dose Level Dose Levels 0 and 3: Phase I Part A completed with current Dose Level the MTD Dose Levels 4 and 4a: Phase I Part B completed with current Dose Level the MTD
3	1	0	2	Enroll at Current Dose Level
3	1	1	1	Enroll at Current Dose Level
3	1	2	0	Enroll at Current Dose Level
4	0	0	4	Enroll at Current Dose Level*
4	0	1	3	Enroll at Current Dose Level*
4	0	2	2	Enroll at Current Dose Level*
4	0	3	1	Enroll at Current Dose Level*
4	0	4	0	Dose Levels 1 and 2: Enroll at Next Dose Level Dose Levels 0 and 3: Phase I Part A completed with current Dose Level the MTD Dose Levels 4 and 4a: Phase I Part B completed with current Dose Level the MTD
4	1	0	3	Enroll at Current Dose Level
4	1	1	2	Enroll at Current Dose Level
4	1	2	1	Enroll at Current Dose Level
4	1	3	0	Enroll at Current Dose Level
5	0	0	5	Enroll at Current Dose Level*
5	0	1	4	Enroll at Current Dose Level*
5	0	2	3	Enroll at Current Dose Level*
5	0	3	2	Enroll at Current Dose Level*
5	0	4	1	Enroll at Current Dose Level*
5	0	5	0	Dose Levels 1 and 2: Enroll at Next Dose Level Dose Levels 0 and 3: Phase I Part A completed with current Dose Level the MTD Dose Levels 4 and 4a: Phase I Part B completed with current Dose Level the MTD

5	1	0	4	Enroll at Current Dose Level
5	1	1	3	Enroll at Current Dose Level
5	1	2	2	Enroll at Current Dose Level
5	1	3	1	Enroll at Current Dose Level
5	1	4	0	Enroll at Current Dose Level
*Study Committee may opt to hold accrual until all patients have been evaluated				

When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

In this study, the MTD will be defined as the highest dose tested in which 0 or only 1 patient – out of a total of 6 patients – experiences a DLT during the first course of therapy.

Operating Characteristics of the Rolling 6. This trial was designed to select an MIBG dose that, combined with dinutuximab, has a DLT rate that is 25% or less. The operating characteristics of the Rolling 6 rules, in terms of the probability of DLT at the selected MTD, are very similar to those of the 3+3 rules. Both tend to select an MTD with a probability of DLT in the range 0f 0.10 to 0.25. The tables below estimates the characteristics of the proposed design for a variety of scenario, using the 3+3 rules in which the dose can be escalated over 3 doses, with a single dose reduction if too many DLT's are observed at Dose Level 1.

Note: There are different tables for Part A and B.

Operating Characteristics Part A						
Probability of DLT at Dose Level				**Probability that MTD has DLT Rate of 10% to 25%**	**Probability that MTD has DLT Rate of 30% or Greater**	**No Dose Selected as MTD**
0	**1**	**2**	**3**			
0.02	0.05	0.15	0.25	0.78	0.00	0.00
0.02	0.05	0.15	0.30	0.44	0.33	0.00
0.02	0.05	0.15	0.35	0.51	0.25	0.00
0.05	0.10	0.20	0.30	0.63	0.27	0.00
0.05	0.10	0.20	0.35	0.69	0.20	0.00
0.05	0.10	0.20	0.40	0.75	0.15	0.00
0.05	0.15	0.25	0.35	0.64	0.16	0.01
0.05	0.15	0.25	0.40	0.68	0.11	0.01
0.05	0.15	0.25	0.45	0.72	0.08	0.01
0.05	0.15	0.30	0.40	0.44	0.36	0.01
0.05	0.15	0.30	0.45	0.44	0.35	0.01
0.05	0.15	0.30	0.50	0.44	0.35	0.01
0.10	0.20	0.30	0.40	0.65	0.31	0.04
0.10	0.20	0.30	0.45	0.66	0.31	0.04
0.10	0.20	0.30	0.35	0.65	0.31	0.04
0.10	0.20	0.35	0.45	0.73	0.24	0.04
0.10	0.25	0.35	0.40	0.75	0.20	0.05
0.10	0.25	0.35	0.45	0.75	0.20	0.05
0.10	0.25	0.35	0.50	0.75	0.20	0.05
0.15	0.30	0.40	0.45	0.44	0.44	0.13
0.15	0.30	0.40	0.50	0.44	0.44	0.13
0.15	0.30	0.45	0.50	0.44	0.43	0.13

Operating Characteristics Part B				
Probability of DLT at Dose Level		Probability that MTD has DLT Rate of 10% to 25%	Probability that MTD has DLT Rate of 30% or Greater	No Dose Selected as MTD
4a	4			
0.02	0.10	0.89	0.00	0.00
0.05	0.10	0.89	0.00	0.00
0.05	0.15	0.78	0.00	0.01
0.10	0.15	0.97	0.00	0.03
0.10	0.20	0.96	0.00	0.04
0.15	0.20	0.92	0.00	0.08
0.15	0.25	0.90	0.00	0.10
0.20	0.25	0.84	0.00	0.16
0.20	0.30	0.38	0.42	0.20
0.25	0.30	0.31	0.42	0.27
0.25	0.35	0.36	0.32	0.32
0.30	0.35	0.00	0.61	0.39

10.3.2 Expansion Cohort at the RP2D/MTD

Once the MTD of dinutuximab and ^{131}I-MIBG in Part A and vorinostat, dinutuximab, and ^{131}I-MIBG in Part B has been determined, an expansion cohort will be enrolled at the RP2D/MTD of each part of the study. This number of additional patients will provide a maximum of 12 DLT-evaluable patients (3-6 DLT-evaluable patients already treated at the RP2D/MTD plus 6-9 new DLT-evaluable patients in the expansion cohort) treated at the RP2D/MTD. If one or more patients are not DLT evaluable and evaluable for response (see definitions above), then they will be replaced..

The purpose of the expansion cohort is to provide a more precise assessment of the tolerability and toxicities of this regimen when dosed at the RP2D/MTD as well as provide additional biologic correlate data. In addition, this expansion cohort will provide preliminary data regarding the anti-tumor activity at the RP2D/MTD. The number of DLT-evaluable patients needed during expansion will be determined when a robust cohort, treated at the RP2D/MTD, has been established to describe toxicity, response, and immune correlated data.

Detailed toxicity data will be collected on patients in the expansion cohort in a manner identical to the toxicity data collection in the dose-escalation portion of the study. Toxicities observed in the expansion cohort will not alter the defined MTD from the dose-escalation portion of the study, but may impact on the final selection of the RP2D, and on the study committee's recommendation for supportive care with this regimen and for the role of this regimen in the future.

Accrual to the MTD expansion cohort will be continuous and will not depend upon completion of treatment of the previous patients in the expansion cohort. There will not be formal rules for continuing or terminating enrollment to the expansion cohort. However, we will adopt the following guideline:

Toxicity Monitoring Guideline: if a second DLT is observed in the patients in either expansion cohort, then cumulative toxicities will be reviewed prior to enrolling the next patient. The table below summarizes the probability of observing 2 or more patients with DLT (out of 6 in each of the two expansion cohorts) for a range of DLT rates.

Probability of Observing 2+ Patients of the 6 Enrolled in Each Expansion Cohort								
DLT Rate	5%	10%	15%	20%	25%	30%	35%	40%
Probability of 2+ DLTs	0.03	0.11	0.22	0.34	0.47	0.58	0.68	0.77

The group of all DLT-evaluable patients (dose escalation + expansion) treated at the MTD of each part of the study will also provide additional preliminary information regarding the anti-tumor activity of this regimen at the MTD. The overall response rate will be determined. In addition, MIBG response rates, bone marrow response rates, and CT/MRI response rates will be documented.

Including the dose-expansion phase, the total number of patients treated on this study will not exceed 35 patients in Part A and 20 patients in Part B.

10.4 Analysis of Results

The outcome status (in terms of toxicity, engraftment, response, reason off study, progression, and survival) of all registered patients will be reported.

If a patient is found to be ineligible and does not receive any protocol treatment, or if an eligible patient refuses treatment and receives no protocol therapy, then the enrollment of that patient will be documented but that patient will not be included in any analyses.

If a patient is found to be ineligible after he or she has begun treatment on this trial, then data from that patient will continue to be collected and recorded as long as he or she continues treatment and then for a minimum of 30 days afterwards or until resolution of toxicities – whichever comes last. In the reporting of results, the enrollment of that patient will be documented but that patient will not be included in any analyses. For completeness, the toxicities and adverse events experienced by that patient will be listed separately.

Finally, if an eligible patient, who began treatment, subsequently withdrew consent for further treatment, then data from that patient will continue to be collected and recorded as long as he or she continues treatment and then for a minimum of 30 days afterwards or until resolution of toxicities – whichever comes last. However, if the patient consents to continued follow-up, these data will also be collected. The results of this patient will be included in all analyses as with all the other eligible patients, unless he or she requests that his or her data not be used.

10.4.1 Toxicity

All toxicities observed will be summarized in terms of type (organ affected or laboratory determination), severity (by NCI CTCAE v5), and attribution. Tables will be created to summarize theses toxicities and side effects by dose level and by course. All eligible patients who begin treatment will be included in these summaries. Ineligible patients who begin treatment will be listed separately.

10.4.2 Response/Outcome

All eligible patients who begin treatment will be included in the analysis of survival, time-to-failure, and best response. Patients with measurable or evaluable tumor who receive ^{131}I-MIBG or who progress prior to completion of therapy will be included in a planned subset analysis of tumor response.

10.4.3 Evaluation of Patients Receiving Multiple Courses of Therapy

It is anticipated that one-third of patients will receive a second course of therapy. Therefore, toxicity and response from a second course of therapy will be reported descriptively. In addition, if any patient experiences a protocol-defined dose limiting toxicity in the second course of therapy, the study committee will discuss the event and determine whether future patients should continue to be offered a second course of therapy.

10.5 Monitoring Plan for Specific Toxicities

10.5.1 Monitoring plan for opportunistic infection

Opportunistic infections are anticipated to be rare events in these patients, particularly as all patients will be required to receive PCP prophylaxis. Any diagnosis of an opportunistic infection within 90 days of stem cell infusion will be reviewed by the Study Committee and IND sponsor and decision will be made to close the trial, modify the trial, or continue unchanged; in addition, it will be determined if the event requires that new information be added to the informed consent.

10.5.2 Monitoring plan in the event of death prior to engraftment or within 2 months of stem cell infusion (whichever occurs last)

Any time that a patient dies while undergoing treatment prior to a stem cell infusion, or within two months of stem cell infusion, the status of the study will be examined. Information reviewed will include the specific details of the patient who died, the timing of the death, the specifics of all patients who experienced the same type of toxicity that did not lead to death, and all toxicities observed to date.

Each death on study not due to tumor will be reviewed by the NANT Study Management Committee, reported to NANT DSMB and a decision in consultation with NANT DSMB and IND sponsor will be made to close the trial, modify the trial, or continue unchanged; in addition, it will be determined if the event requires that new information be added to the informed consent. Each death occurring within 30 days of completing the last dose of dinutuximab regardless of cause will be reviewed and reported to the NANT DSMB and to the FDA according to standard procedure.

10.6 Analysis of Correlative Studies

Summary statistics and descriptive plots will be generated for the correlative biology studies. The changes will be assessed using a paired t-test or Wilcoxon matched pairs signed rank sum test when appropriate. Linear mixed models (with appropriate transformation if necessary) may also be considered to take advantage of the repeated measurements. All these analyses will be descriptive, exploratory, and hypotheses generating in nature.

10.7 Inclusion of Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past NANT studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. The small number of patients entered into this trial will obviate any analysis of variation in response rate with gender or ethnicity.

11.0 NANT RESPONSE CRITERIA v2.0

For evaluation of response this study will utilize the New Approaches to Neuroblastoma Therapy (NANT) Response Criteria v2.0. **Since patients on this study must have MIBG avid tumors, any reference to MIBG non-avid tumors is not applicable, but the language is retained here to present the NANT response criteria in its entirety.**

Overall response will incorporate all three parameters: Soft Tissue Response, Bone Response, and Bone Marrow Response with Overall Response defined as outlined in Section 11.6. Response for each parameter and overall response will be reported by the treating site using the criteria below. However, the final statistical analysis of response will utilize responses as graded by central review, using the same criteria below.

11.1 Soft Tissue Response Criteria

Soft tissue lesions will be evaluated by CT/MRI, using the definitions of measurable disease from the Response Evaluation Criteria in Solid Tumors (RECIST 1.1; European Journal Cancer 45: 228-247, 2009) modified per the criteria below to define target lesions (lesions which are measurable AND evaluable for response).

Note that the response criteria for lymph nodes measured by short axis will only be applied to discrete lymph nodes (i.e. cervical, axillary) that are not adjacent to the primary site and are not composed of a coalesced mass of multiple lymph nodes. Coalesced masses of lymph nodes should be assessed using non-lymph node criteria and measured using longest dimension.

11.1.1 DEFINITION OF SOFT TISSUE TARGET LESIONS:

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Soft tissue target lesions that will be followed for response must meet criteria 1 and 2, OR criteria 3 below:

1. A target lesion must be measurable, defined as a soft tissue lesion that can be accurately measured in at least one dimension with a longest diameter ≥ 10mm, or for discrete lymph nodes ≥ 15mm on short axis. (The short axis is measured after identifying the longest diameter of a lymph node, and then measuring the longest perpendicular diameter to that as the short axis). For coalesced masses of multiple lymph nodes, the longest diameter will be used.
2. A target lesion must also be MIBG avid OR FDG-PET avid (if tumor known to be MIBG non-avid), and have a biopsy if required in the eligibility criteria. If one avid soft tissue or bone lesion present at enrollment is biopsied showing neuroblastoma or ganglioneuroblastoma at any time point prior to enrollment, then all other avid soft tissue lesions present at enrollment are considered target lesions.
3. A lesion that is measurable but does not have either MIBG or FDG-PET uptake will be considered a target lesion if a biopsy done at any time prior to enrollment demonstrates neuroblastoma and/or ganglioneuroblastoma.

NOTE: Soft tissue components of bone lesions will be considered measurable soft tissue lesions if > 10mm in at least one dimension, and target lesions evaluable for response if MIBG avid (or FDG-PET-avid if tumor known to be MIBG non-avid).

Serial measurements of target lesions are to be done with the same method of assessment (either CT or MRI) used to characterize each lesion reported at baseline. The sum of diameters (longest for non-nodal lesions and coalesced masses of multiple lymph node, short axis for discrete nodal lesions) for all target soft tissue lesions will be calculated and reported as the **sum of diameters**.

11.1.2 DEFINITION OF NON-TARGET SOFT TISSUE LESIONS:

a. Leptomeningeal tumor and tumor in cerebrospinal fluid cytology.
b. Lesions that are considered likely to be active tumor by the treating physician based on clinical correlation (for example, hepatic and pulmonary nodules)

11.1.3 The following lesions will NOT be followed to evaluate response either as target lesions or non-target lesions, if they meet the criteria below **AND** the treating physician feels they are unlikely to represent active tumor (an exception for active tumor will be made for c. below):

a. Measurable non-lymph node and coalesced masses of lymph node soft tissue lesions ≥ 10mm and discrete lymph nodes ≥15 mm that are not MIBG avid or FDG-PET avid (if tumor known to be MIBG non-avid) and if biopsied did not show neuroblastoma or ganglioneuroblastoma.
b. Non-measurable non-lymph node soft tissue lesions < 10mm or non-measurable discrete lymph nodes (defined as lymph nodes >10 to <15mm on short axis).
c. Intramedullary bone lesions will not be followed for CT/MRI response even though they are felt to represent active tumor since they will be evaluated with MIBG scans (or FDG-PET scans if MIBG non-avid), and since bone changes on CT/MRI are known to persist after resolution of active tumor.

11.1.4 SOFT TISSUE RESPONSE CRITERIA:

11.1.4.1 Complete Response (CR)
All target and non-target soft tissue lesions have longest diameter < 10 mm. Discrete lymph nodes identified as target lesions must decrease to a short axis < 15 mm. Resolution of all MIBG uptake (FDG-PET uptake if tumor known to be MIBG non-avid).

11.1.4.2 Partial Response (PR)
At least a 30% decrease in sum of diameters of target soft tissue lesions (using longest diameter for non-nodal and coalesced masses of lymph node lesions and short axis for discrete lymph node lesions), taking as reference the measurement of target lesions performed at study enrollment. Non-target soft tissue lesions must be stable to smaller in size. No new lesions. MIBG (FDG-PET for MIBG non-avid tumors) uptake may still be present in lesions positive at enrollment.

11.1.4.3 Progressive Disease (PD)
At least a 20% increase in sum of diameters of target soft tissue lesions (using longest dimension for non-nodal and coalesced masses of lymph node lesions and short axis for discrete lymph node lesions) taking as reference the smallest sum of diameters while on study (this includes the baseline if that is the smallest while on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm. A new target or non-target soft tissue lesion seen on CT/MRI without MIBG or PET uptake is considered PD, but may be biopsied to rule out PD. An overall substantial worsening of non-target soft tissue lesions is also considered as a criteria for PD (guidance for substantial includes a 73% increase in volume, or sufficient worsening of overall non-target disease such that the treating physician feels a change in therapy is indicated).

New uptake of MIBG (or FDG-PET for MIBG non-avid tumors) at target and/or non-target soft tissue lesions which are stable in size, will also be considered PD. Biopsy of such lesions can be done to rule out PD for the MIBG (or FDG-PET) response.

11.1.4.4 Stable disease (SD)
(Applies only to patients with target soft tissue lesions)
Neither sufficient shrinkage in sum of diameters to qualify for PR nor does the patient meet any criteria for PD. No new soft tissue lesions. Non-target soft tissue lesions must be stable to smaller in size.

11.1.4.5 Stable disease-no target lesions (SD-NTL) (Applies to patients with non-target soft tissue lesions only)
Non-target soft tissue lesions are still present; may be smaller or stable in size, and do not meet criteria for PD. No new soft tissue lesions and no new uptake of MIBG (FDG-PET if tumor known to be MIBG non-avid) at existing non-target soft tissue lesions. New lesions or lesions with new MIBG (FDG-PET) uptake may be biopsied to rule out PD.

11.1.4.6 Not involved (NI): No target or non-target soft tissue lesions

11.1.4.7 Not evaluable (NE)
CT/MRI scans and/or MIBG scans (FDG-PET if tumor known to be MIBG non-avid) are of inadequate quality as assessed by central reviewer, or scans are not repeated of all anatomic sites with tumor documented at entry. (Note that patients not evaluable at a given time point may be evaluable for response at later time points if all scans done with adequate quality at later time point) or if based on Study Management Committee / PI review it is deemed that there is insufficient data to grade response.

11.1.4.8 Not done (ND)
No CT/MRI scans were done at the given time point.

11.2 Bone Marrow Response Criteria

Methodology:

1. Routine morphology with immunohistochemistry will be used for all bone marrow evaluations. Immunohistochemistry (with antibodies that are used per local site's standard procedure) is recommended for evaluating percentage of tumor but it is not required. If immunohistochemistry is not done on the baseline bone marrow, then BM response should be graded based on routine morphology only at all time points.
2. The percentage of tumor in the bone marrow at study entry (baseline) and all subsequent time points reported will use the highest tumor percentage noted among the four samples (bilateral aspirates and biopsies).
3. The percentage of tumor in an aspirate will be calculated as the number of tumor cells divided by the number of total nucleated cells.
4. The percentage of tumor in a biopsy will be calculated as the percent of tumor cells (including neuroblasts, mature and maturing ganglion cells) based on the bone marrow parenchymal surface area examined. Schwannian stroma only is considered negative.

   Bone marrow response will be graded using the bone marrow done at study entry as the reference point. The baseline bone marrow must include an attempt to obtain bilateral aspirates and biopsies, and will be considered as evaluable if at least one biopsy sample is adequate to determine the percentage tumor involvement. At baseline, or any subsequent time point, the percentage tumor from the unilateral evaluable biopsy will be used to grade bone marrow response. Patients with ≤ 5% tumor (including patients with tumor seen by immunohistochemistry only) on all samples of the bilateral bone marrow aspirate and biopsies at the baseline evaluation will be evaluable for bone marrow response, but defined separately from patients with > 5% at study entry as outlined below.

   Central review will be performed on bilateral biopsies only, unless BM tumor is seen only on aspirates. If a patient meets protocol criteria for central review of BM response, morphology slides will be requested.

11.2.1 Complete Response (CR)
Greater than 5% tumor at study entry, with no tumor seen at one subsequent time point

11.2.2 Complete Response Minimal Disease (CR-MD)
≤ 5% tumor at study entry, with no tumor seen at one subsequent time point.

11.2.3 Partial Response (PR)
Greater than 20% tumor at study entry, with >0 to ≤ 5% tumor at a subsequent time point.

11.2.4 Minimal Disease (MD)
One of the following:

A. No tumor at study entry, with >0 to ≤5% tumor at a subsequent time point
B. >0 to <5% tumor at study entry, with >0 to ≤5% tumor at a subsequent time point
C. ≥5-<20% tumor at study entry, with > 0 to <5% at a subsequent time point.

11.2.5 Progressive Disease (PD)
Patients with any amount of tumor in the bone marrow at study entry will be considered to have PD if one subsequent evaluation shows >20% tumor on any one bone marrow sample AND there is a greater than 2 times increase in the amount of tumor compared to study entry.

Patients with ≤ 5% tumor at study entry must increase to > 20% tumor to have PD; a patient with 30% tumor at study entry must increase to ≥60% tumor. If patients have an increase in tumor amount which is less than the amount specified for PD, the response will be classified as SD.

Patients with no tumor at study entry will be considered PD if ONE subsequent evaluation shows >5% tumor.

Patients who are deemed to have bone marrow progression based on review of prior bone marrows by physician assessment and confirmed by the study management committee.

11.2.6 Stable Disease (SD)
Persistence of an amount of tumor in the bone marrow that does not meet criteria for progressive disease or PR or MD, and is > 5%. .

11.2.7 Not Evaluable (NE)
Patients for whom follow-up bone marrow evaluations do not include an attempt to obtain bilateral aspirates and biopsies and do not have at least one adequate biopsy sample, as assessed by local site's pathology report for that time point or if based on Study Management Committee / PI review it is deemed that there is insufficient data to grade response.

11.2.8 Not involved (NI)
Patients with no evidence of neuroblastoma in the bone marrow at study entry, and bone marrow remains negative on subsequent evaluations.

11.2.9 Not done (ND)
Bone marrow evaluation not done at a given time point.

11.2.10 EXAMPLES OF GRADING BONE MARROW RESPONSE:

BASELINE	**TP 1 or any subsequent timepoint***	**BM Response**
0	0	NI
0	>0-<=5	MD
0	>5	PD
>0-<=5	0	CR-MD
>0-<=5	>0-<=5	MD
>0-<=5	>5-20	SD
>0-<=5	>-20	PD

>5-20	0	CR
>5-20	>0-<=5	MD
>5-20	>5-20	SD
>5-20	>-20 and doubled compared to baseline	PD
>20	0	CR
>20	>0-<=5	PR
>20	>5-20	SD
>20	>20 but not doubled compared to baseline	SD
>20	>-20 and doubled compared to baseline	PD

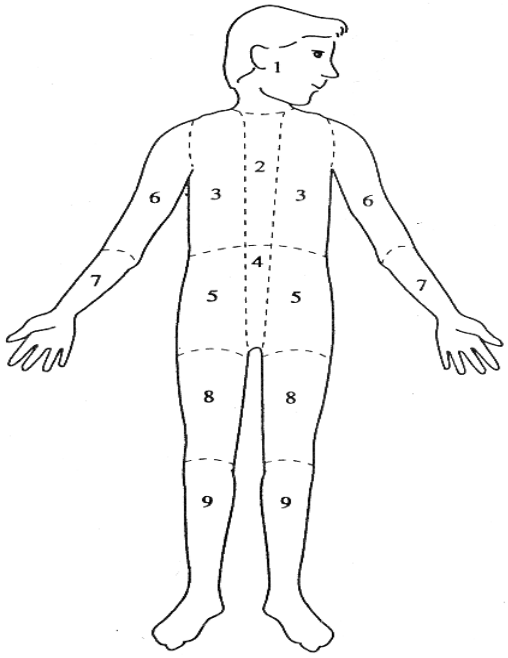
11.3. Bone Response Criteria Using MIBG Scans (for MIBG avid tumors)

Bone response will be evaluated using MIBG scans for MIBG avid tumors. FDG-PET scans (see section 11.4) may be substituted for MIBG scans to assess bone response only if the tumor is known to be MIBG non-avid. Bone response will be graded using a modification of the Curie scoring scale (Eur J Cancer 1995;31A:256-261). The treating site will report the Bone Response using MIBG scoring done at local site, however the statistical endpoint of Bone Response will utilize the MIBG score from the central reviewer.

MIBG scans will be scored for 9 anatomic regions for bone metastases only, MIBG uptake in soft tissue disease will NOT be included, since this uptake is utlized as part of evaluating Soft Tissue Response. SPECT scans are strongly encouraged to be used for MIBG scoring, if SPECT is available at baseline and subsequent time points. If SPECT scans are not available at all time points, then conjugate planar imaging alone should be used to score each region, and SPECT may be used only as an adjunct to help delineate the location of the MIBG avid lesion.

Table 7: Scoring of Bone Disease Regions 1 – 9

Scoring	MIBG uptake
0	No MIBG uptake
1	1 focal lesion
2	> 1 focal lesion
3	> 50% of a region



The **absolute extension score** is obtained by adding the scores of all nine regions. The presence of a MIBG avid lesion, and NOT the "intensity" of MIBG-avidity, determines the scoring within a particular region.

REGIONS 1 – 9 / BONE DISEASE: Cranio-facial disease is scored in Region 1, cervico-thoracic spine in Region 2, ribs / sternum / clavicles / scapula in Region 3, lumbar-sacral spine in Region 4, pelvis in Region 5, humeri in Region 6, distal upper extremities in Region 7, femurs in Region 8, and distal lower extremities in Region 9 (see figure above).

The **relative score** is calculated by dividing the absolute score of bone lesions at each time by the corresponding pre-treatment overall absolute score. The relative score of each patient is calculated at each response assessment and classified as below:

a. Complete response: all areas of bone uptake on MIBG scan completely resolved.
b. Partial response: Relative score $\geq$ 0.1 to $\leq$ 0.5
c. Stable disease: Relative score $>$ 0.5 to $<$ 1.2
d. Progressive disease: New bone lesions on MIBG scan compared to most recent prior MIBG scan OR a relative score $\geq$ 1.2. Biopsy of new lesions may be done to rule out progressive disease. If biopsy is negative for tumor (neuroblastoma and/or ganglioneuroblastoma), patient will not meet definition of PD.
e. Not evaluable (NE): MIBG scan of inadequate quality as assessed by central reviewer.
f. Not involved (NI): No MIBG avid bone lesions at study entry and subsequent response time points.
g. Not done (ND): MIBG scan not done at a given response time point

11.4 Bone Response Criteria Using FDG-PET Scans (only for MIBG non-avid tumors)

Patients known to be non-avid for MIBG should have FDG-PET scans performed for monitoring bone response. FDG-PET avid bone lesions will be scored by the presence or absence of a lesion with uptake that is two times above background. For MIBG non-avid patients, uptake of FDG-PET in soft tissue lesions will be utilized in the Soft Tissue Response (see section 11.1).

11.4.1 Complete response (CR)

Resolution of all FDG-PET uptake in all FDG-PET avid bone lesions identified at baseline and no new FDG-PET avid bone lesions.

11.4.2 Partial response (PR)
Reduction of number of bone lesions by FDG-PET by ≥50%. No new FDG-PET avid bone lesions.

11.4.3 Stable disease (SD)
Changes that do not meet the criteria for PR or PD.

11.4.4 Progressive disease (PD)
New bone lesions on FDG-PET scan. Note: biopsy may be done to exclude causes of FDG-PET uptake other than tumor. If biopsy of the new lesion is negative for tumor (neuroblastoma and/or ganglioneuroblastoma), patient will not meet definition of PD.

11.4.5 Not evaluable (NE)
FDG-PET scan of inadequate quality to evaluate bone response or if based on Study Management Committee / PI review it is deemed that there is insufficient data to grade response.

11.4.6 Not involved (NI)
No FDG-PET uptake in bone sites that is two times above background.

11.4.7 Not done (ND)
FDG-PET scan not done at a given time point.

On central review, FDG-PET avid bone lesions will be evaluated by both the MIBG scoring method outlined in Section 11.3 and also by enumeration of lesions to grade bone response.

11.5 Urine Catecholamines

Due to variance with diet and concomitant medications, frequently missing dopamine levels, and lack of standardized methodology for this assay, urine catecholamines will not be utilized in grading response. Results of urine catecholamines will not be requested.

11.6 Definition of Overall Response

The criteria below will be used to define the overall response for each patient, with consideration of all three individual response parameters: Soft tissue Response, Bone Response, and Bone Marrow Response.

11.6.1 Complete Response (CR)
Response of CR or NI for soft tissue and bone, soft tissue with bone marrow response of CR or CR-MD.

11.6.2 Complete Response MD (CR-MD)
Soft tissue and bone response are both NI, with BM response of CR-MD

11.6.3 Partial Response (PR) includes any one of the following:

a. Response of PR for soft tissue, bone response of PR, and BM response of CR, CR-MD, PR, MD, or NI.
b. Response of CR, SD-NTL or NI for soft tissue, with bone response of PR, and BM response of CR, CR-MD, PR, MD, or NI.
c. Soft tissue response of PR; with bone response of CR or NI; and BM response of CR, CR-MD, PR, MD, or NI.
d. CR for soft tissue and bone response, with MD for bone marrow response

11.6.4 Progressive Disease (PD) includes either one of the following:

a. PD for at least one response parameter, including soft tissue, bone, and bone marrow response. If PD is found by one parameter, the other two parameters are not required to be evaluated to define an overall response of PD.

b. Treating physician grades patient as progressive disease based on clinical assessment without radiographic or bone marrow evaluations.

11.6.5 Stable disease (SD)
Response of stable disease for at least one parameter, with response of SD, NI, MD, or SD-NTL for other parameters.

11.6.6 Stable disease-Non-target lesions (SD-NTL)
Response of SD-NTL for soft tissue, with response of NI for bone and bone marrow.

11.6.7 Minor response (MR)
Complete response, Complete-MD response, and/or partial response for one parameter (i.e. soft tissue, bone, or bone marrow), with response of stable disease for a second parameter and any response other than PD for third parameter.

11.6.8 Minimal disease (MD)
Soft tissue and bone marrow responses are both NI, with bone marrow response of MD.

11.6.9 Not evaluable (NE)
Response of Not evaluable for one or more response parameters including soft tissue, bone, or bone marrow for any parameter that had sites evaluable for response at study enrollment. However, if one parameter is done and demonstrates PD this is defined as an overall response of PD. The SMC will review all patients where one or more parameters were graded as not evaluable, and make the final determination if the overall response is evaluable at that time point. In addition, response may be declared not evaluable if review by the Study Management Committee (SMC) that there is insufficient data to grade response. The SMC may also declare response at a given time point evaluable if only one parameter is missing and was not involved at study enrollment.

11.6.10 No progression
Baseline status at enrollment was NI for soft tissue response, NI for bone marrow response, NI for bone response, and there has NOT been PD for any of the three parameters since on protocol therapy

11.6.11 Not done (ND)
Response not assessed at this time point. If only one parameter is not done at a given response time point, the SMC and PI will review and make the final determination if the overall response is evaluable at that time point.

11.6.12 Summary
The overall response as assessed at any particular time point based on consideration of each of the three parameters as defined above is summarized in the following table:

TABLE 8: RESPONSE CATEGORIZATION

SOFT TISSUE RESPONSE	BONE RESPONSE	BONE MARROW RESPONSE	OVERALL RESPONSE
CR	CR	CR	CR
NI	CR	CR	CR
CR	NI	CR	CR
NI	NI	CR	CR
CR	CR	CR-MD	CR
NI	CR	CR-MD	CR
CR	NI	CR-MD	CR
CR	CR	NI	CR
NI	CR	NI	CR
CR	NI	NI	CR
NI	NI	CR-MD	CR-MD
PR	CR	CR	PR
SD-NTL	CR	CR	PR
CR	PR	CR	PR
SD-NTL	PR	CR	PR

NI	PR	CR	PR
PR	NI	CR	PR
SD-NTL	NI	CR	PR
PR	CR	CR-MD	PR
SD-NTL	CR	CR-MD	PR
CR	PR	CR-MD	PR
PR	PR	CR-MD	PR
SD-NTL	PR	CR-MD	PR
NI	PR	CR-MD	PR
PR	NI	CR-MD	PR
SD-NTL	NI	CR-MD	PR
CR	CR	PR	PR
PR	CR	PR	PR
SD-NTL	CR	PR	PR
PR	PR	CR	PR
NI	CR	PR	PR
CR	PR	PR	PR
PR	PR	PR	PR
SD-NTL	PR	PR	PR
NI	PR	PR	PR
CR	NI	PR	PR
PR	NI	PR	PR
SD-NTL	NI	PR	PR
NI	NI	PR	PR
CR	CR	MD	PR
PR	CR	MD	PR
SD-NTL	CR	MD	PR
NI	CR	MD	PR
CR	PR	MD	PR
PR	PR	MD	PR
SD-NTL	PR	MD	PR
NI	PR	MD	PR
CR	NI	MD	PR
PR	NI	MD	PR
PR	CR	NI	PR
PR	PR	NI	PR
SD-NTL	CR	NI	PR
CR	PR	NI	PR
SD-NTL	PR	NI	PR
NI	PR	NI	PR
PR	NI	NI	PR
SD	CR	CR	MINOR
SD	PR	CR	MINOR
CR	SD	CR	MINOR
PR	SD	CR	MINOR
SD	SD	CR	MINOR
SD-NTL	SD	CR	MINOR
NI	SD	CR	MINOR
SD	NI	CR	MINOR
SD	CR	CR-MD	MINOR
SD	PR	CR-MD	MINOR
CR	SD	CR-MD	MINOR
PR	SD	CR-MD	MINOR
SD	SD	CR-MD	MINOR
SD-NTL	SD	CR-MD	MINOR
NI	SD	CR-MD	MINOR
SD	NI	CR-MD	MINOR
SD	CR	PR	MINOR
SD	PR	PR	MINOR
CR	SD	PR	MINOR
PR	SD	PR	MINOR
SD	SD	PR	MINOR
SD-NTL	SD	PR	MINOR
NI	SD	PR	MINOR
SD	NI	PR	MINOR
SD	CR	MD	MINOR

SD	PR	MD	MINOR
CR	SD	MD	MINOR
PR	SD	MD	MINOR
CR	CR	SD	MINOR
PR	CR	SD	MINOR
SD	CR	SD	MINOR
SD-NTL	CR	SD	MINOR
NI	CR	SD	MINOR
CR	PR	SD	MINOR
PR	PR	SD	MINOR
SD	PR	SD	MINOR
SD-NTL	PR	SD	MINOR
NI	PR	SD	MINOR
CR	SD	SD	MINOR
PR	SD	SD	MINOR
CR	NI	SD	MINOR
PR	NI	SD	MINOR
SD	CR	NI	MINOR
SD	PR	NI	MINOR
CR	SD	NI	MINOR
PR	SD	NI	MINOR
NI	NI	MD	MD
SD	SD	MD	SD
SD-NTL	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
SD-NTL	NI	MD	MD
SD	SD	SD	SD
SD-NTL	SD	SD	SD
NI	SD	SD	SD
SD	NI	SD	SD
SD-NTL	NI	SD	SD
NI	NI	SD	SD
SD	SD	NI	SD
SD-NTL	SD	NI	SD
NI	SD	NI	SD
SD	NI	NI	SD
SD-NTL	NI	NI	SD-NTL
NI	NI	NI	NO PROGRESSION
PD	ANY	ANY	PD
ANY	PD	ANY	PD
ANY	ANY	PD	PD
NOT EVALUABLE	ANY EXCEPT PD	ANY EXCEPT PD	NOT EVALUABLE*
ANY EXCEPT PD	NOT EVALUABLE	ANY EXCEPT PD	NOT EVALUABLE*
ANY EXCEPT PD	ANY EXCEPT PD	NOT EVALUABLE	NOT EVALUABLE*
NOT EVALUABLE	NOT EVALUABLE	NOT EVALUABLE	NOT EVALUABLE*
NOT DONE	NOT DONE	NOT DONE	NOT DONE*
NOT DONE (and required at this time point)	ANY EXCEPT PD	ANY EXCEPT PD	NOT DONE*
ANY EXCEPT PD	NOT DONE (and required at this time point)	ANY EXCEPT PD	NOT DONE*
ANY EXCEPT PD	ANY EXCEPT PD	NOT DONE (and required at this time point)	NOT DONE*

** The Study Management Committee will review patients with overall response of Not Evaluable and/or Not Done to make the final determination of overall response.

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the data collection packet for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting through the use of a written IND safety report (MedWatch) to the Food and Drug Administration (FDA).

Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5. A copy of the CTCAEv5 can be downloaded from the CTEP home page (http://ctep.cancer.gov).

12.2 Definitions

Adverse Event (AE): An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event.

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not available, is not consistent with the risk information described in the general investigational plan.

Serious Adverse Events (SAE) or Serious Suspected Adverse Reactions: An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

Table 9: Severe Adverse Events or Reactions	
Death of Patient	An event that results in the death of a patient.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result in fetal loss.

Persistent or Significant Disability/ Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (*e.g.,* sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

12.3 Expedited Serious Adverse Event Reporting to NANT Operations

For any serious adverse event, both **expected and unexpected**:

- Contact the Study Chairperson and the NANT Operations Center to alert them to the existence of the serious adverse event within 24 hours of learning of the event.
- Within 48 hours of learning of the event, complete the NANT SAE form online through Medidata Rave. If access to Medidata Rave is unavailable for some reason, use the paper SAE form found on the NANT website (see NANT website (www.nant.org) and email to NANTstaff@chla.usc.edu.

- Follow-up information should be submitted online in an updated report through Medidata Rave as soon as relevant information is available.

Copies of all serious adverse event reports will be kept on file in the NANT Operations Center. All NANT institutions are to file SAE reports with their Institutional Review Boards according to local institutional policy**.**

12.4 Expedited Adverse Event Reporting to the FDA

Per CFR 312.32 (c), the sponsor of the IND, Araz Marachelian, MD, must notify the FDA and all participating investigators in a written IND safety report of any adverse experience **associated with use of the drug** that is **both serious and unexpected.** Each written notification shall be made as soon as possible, and in no event later than **15 calendar** days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A (MedWatch) or in a narrative format and must bear prominent identification of its contents, i.e., "IND Safety Report". Follow-up information to a safety report should be submitted as soon as the relevant information is available.

The sponsor must also notify FDA **by telephone** or by **facsimile** transmission of any **unexpected fatal or life-threatening experience associated with use of the drug** in the clinical studies conducted under the IND as soon as possible but in no event later than **7 calendar** days after initial receipt of the information.

Each telephone call or facsimile transmission to the FDA shall be transmitted to the FDA division that has responsibility for review of the IND; a specific contact person is assigned to each IND at the time the application is filed, and this will be included in the FDA's correspondence acknowledging receipt of the IND application.

12.5 NANT Operations Center Role in Expedited Adverse Event Reporting to the FDA and Participating Sites

For purposes of this protocol, the MedWatch Report Form (FDA 3500A) will be submitted to the FDA by NANT on behalf of the IND sponsor, Araz Marachelian, MD. These forms will be submitted to the appropriate FDA division and will serve as the written IND safety report. The NANT Operations Center will file all expedited adverse event reports as well as other adverse events with the FDA and other relevant authorities or investigators. The IND sponsor, Araz Marachelian, MD, has also delegated to the NANT Operations Center the telephone/facsimile FDA notification responsibilities for unexpected fatal or life-threatening experiences. All IND submissions will be maintained in a master file at the NANT Operations Center.

For Adverse Events associated with the use of the drug that are both Serious and Unexpected:

- The MedWatch form will be drafted by the NANT Operations Center based on the SAE form within 10 days of the adverse event and reviewed with PI at treating site and the study chair. Final MedWatch form will be submitted to FDA by NANT Operations Center. Electronic version of MedWatch form is available from NANT Operations Center or MedWatch website www.fda.gov/medwatch. NANT will forward the completed report to the FDA and other relevant authorities or investigators on behalf of the IND Sponsor, Araz Marachelian, MD.
- Follow-up information should be submitted as soon as relevant information is available.

For Adverse Events associated with the use of the drug that are Unexpected or Life Threatening:

- Notify the NANT Operations Center (who will notify the FDA and other relevant authorities and investigators) by telephone or fax as soon as possible but no later than 7 calendar days from the occurrence of the event.

  FDA PHONE: 1-800-332-1088
  FDA FAX: 1-800-332-0178

- The MedWatch form will be drafted by the NANT Operations Center based on the SAE form within 10 days of the adverse event and reviewed with PI at treating site and the study chair. Final Medwatch form will be submitted to FDA and other relevant authorities or investigators by NANT Operations Center on behalf of the IND Sponsor, Araz Marachelian, MD.
- Follow-up information should be submitted as soon as relevant information is available.

A cover letter to accompany the MedWatch report will be prepared by the NANT Operations Center in collaboration with the IND sponsor, Araz Marachelian, MD. The cover letter will be submitted with MedWatch report to the FDA and other NANT institutions and relevant authorities. Contents will include:

1. An assessment of the adverse event and its significance/relevance to the study. And the impact on the risk/benefit ratio of the study.
2. A statement as to whether this adverse event has been reported previously, and if so, whether the frequency is considered unusually high.
3. A statement as to whether the protocol and/or informed consent should reflect changes in the potential risks involved.

Copies of all adverse event reports will be kept on file in the NANT Operations Center. All NANT institutions are to file AE reports with their Institutional Review Boards according to local institutional policy.

12.6 Adverse Event Reporting Requirements for United Therapeutics Corporation

NANT will notify United Therapeutics Corporation (UT) of all serious adverse events, both expected and unexpected, and copy all forms and related correspondence to UT within seven (7) days after initial notification from NANT site.

12.7 Adverse Event Reporting Requirements for Jubilant Radiopharma

NANT will notify Jubilant Radiopharma of all serious adverse events, both expected and unexpected, and copy all forms and related correspondence to Jubilant Radiopharma within twenty four (24) hours after initial notification from NANT site.

12.8 Reporting Secondary AML/MDS

Within two weeks of an AML/MDS diagnosis or other secondary malignancy following treatment for cancer, submit the following to the NANT Operations Center:

- A completed NANT SAE Form
- A copy of the pathology report confirming the AML/MDS or other malignancy
- A copy of the cytogenetics report (if applicable)

The NANT Operations Center will submit the form and accompanying reports to the FDA via MedWatch and to Araz Marachelian, MD (IND Sponsor). All NANT institutions are to file the secondary malignancy reports with their Institutional Review Boards according to local institutional policy.

12.9 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study drug(s). All pregnancies and suspected pregnancies will be reported to by the NANT Operations Office (see Section 3.1.1 for contact information) immediately. If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to by the NANT Operations Office immediately.

13.0 RECORDS AND REPORTING

See separate Data Forms Packet which includes the data submission schedule in the member section on the NANT web site (www.NANT.org).

The following are required to be submitted for all patients entered:

1. Study case report forms, bone marrow reports (including aspirate and biopsy reports), , and radiology reports (CT/MRI/MIBG/PET scans). Study case report form data is collected and accessed remotely through Medidata Rave. Disease response reports detail reports (CT/MRI, MIBG/PET, Bone marrow) are sent by email as electronic files to NANTCRF@chla.usc.edu at the end of each course of therapy or as delineated in the Required Observations section 7.0 of this document.
2. For all patients on study, CT/MRI and MIBG/PET scans done as baseline tumor evaluation at study entry and for determination of over overall response will be submitted for central review.
3. For all patients who report an overall response of CR, PR, minor response, or who have SD for at least 4 courses will submit all CT/MRI scans, MIBG scans, PET scans, and bone marrow aspirate and biopsy slides done, during therapy and at end of protocol therapy for central review upon request by NANT Operations Center. Additional scans may also be requested by the NANT Operations Center to clarify response.
4. Radiology scans are submitted into NANT PACS electronic repository, which is managed by the ICL (Imaging Core Lab) at Children's Hospital Los Angeles. The Imaging CoreGrid DICOM Dropbox software is functional at all NANT sites and is used for all NANT clinical trials for central review of tumor response. (See NANT SOP regarding Central Review of Response Procedures for details).
5. For all patients, slides from bone marrow aspirates done at the time of study entry, during therapy and at end of therapy, are required to be submitted upon request to NANT Operations Center.

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15.0 SAMPLE INFORMED CONSENT
There are separate sample informed consent documents for Part A and B.

15.1 Part A

NANT 2017-01: A PHASE I STUDY OF ^{131}I-MIBG WITH DINUTUXIMAB FOR RELAPSED/REFRACTORY NEUROBLASTOMA

FOR PATIENTS ON PART A

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

The word "you" used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?
This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest safe dose of ^{131}I-MIBG that can be given with dinutuximab to children with refractory or recurrent neuroblastoma without causing severe side effects
- To find out what side effects there are from giving ^{131}I-MIBG and dinutuximab together on this schedule at different dose levels
- To see if your tumor gets smaller after treatment with ^{131}I-MIBG and dinutuximab
- To learn what happens to your immune system and other proteins that cause inflammation when giving different doses of ^{131}I-MIBG with dinutuximab.
- To see what effect giving different doses of ^{131}I-MIBG has on your body in making an antibody to the dinutuximab
- To see what effect treatment with ^{131}I-MIBG in combination with dinutuximab has on the cells of your immune system that surround and invade your tumor
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The research is being done because:
Currently there is no known effective treatment for neuroblastoma that has returned or that has not responded to treatment.

This study will use a chemical agent called metaiodobenzylguanidine (MIBG) together with an intravenous (IV) drug called dinutuximab. MIBG is taken up by neuroblastoma tumor cells. MIBG can be combined with radioactive iodine (^{131}I) in the laboratory to form the radioactive compound ^{131}I-MIBG. ^{131}I-MIBG delivers radiation to the neuroblastoma cancer cells and causes them to die. ^{131}I-MIBG lowers the number of blood forming cells (called stem cells) in the bone marrow when it is given at higher doses as in this study. Because of this, all patients will get back their own stem cells to help the bone marrow recover from this therapy.

Dinutuximab works differently than most standard chemotherapy drugs. Dinutuximab is a monoclonal antibody. Monoclonal antibodies are proteins made in the lab, designed to attach to specific targets on cancer cells. When dinutuximab attaches to neuroblastoma cells, the body's immune system is stimulated to attack and kill the neuroblastoma cells. Dinutuximab represents a new kind of cancer therapy called immunotherapy which, unlike chemotherapy and radiation, targets the cancer cells without destroying nearby healthy cells.

Laboratory studies have shown greater anti-cancer effects when radiation is given before an immunotherapy treatment. Some clinical responses have been seen in adults when radiation has been combined with different types of immunotherapy in treating their cancers.

Giving dinutuximab together with ^{131}I-MIBG may help the ^{131}I-MIBG kill more neuroblastoma cells. This is the first study to test giving dinutuximab together with ^{131}I-MIBG. We want to find out if giving increasing doses of ^{131}I-MIBG along with dinutuximab can be tolerated. We also want to see how effective this drug combination is against relapsed or refractory neuroblastoma.

Dinutuximab is a drug that has been approved by the Food and Drug Administration (FDA) for treating newly diagnosed patients with neuroblastoma. The use of dinutuximab in combination with ^{131}I-MIBG for the treatment of relapsed or refractory neuroblastoma is considered experimental.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be a maximum of 30 patients enrolling to this part of the study. Between 9 and 24 people will take part in the dose escalation part of the study. When you join the study, you will be assigned a certain ^{131}I-MIBG and dinutuximab dose. This study will test up to three ^{131}I-MIBG doses in groups of 3-6 patients. The starting ^{131}I-MIBG dose for the first group of patients is about 2/3 of the standard dose when ^{131}I-MIBG is given alone as treatment. The dose of dinutuximab is the standard dose used for patients with neuroblastoma. The dinutuximab dose will not be increased during the study. If the first dose level is tolerated without serious side effects, then the ^{131}I-MIBG dose will be increased ("dose escalation") in groups of 3-6 patients until the third dose level or until serious side effects are seen. At that point, investigators will have found the highest dose of ^{131}I-MIBG that can be given in combination with dinutuximab without bad side effects (called maximum tolerated dose). This part of the trial is called the dose escalation phase.

Once the maximum tolerated dose is determined, a group of 6 more patients will be enrolled and treated at this dose of ^{131}I-MIBG and dinutuximab, known as the dose expansion part of the study. The purpose of the dose expansion part of the study is to gather more information about side effects seen in patients treated at the maximum tolerated dose of ^{131}I-MIBG in combination with dinutuximab. The dose expansion cohort will not enroll patients until the dose escalation part of the study is completed and the highest dose of ^{131}I-MIBG that can be safely given in combination with dinutuximab without serious side effects is found.

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

<u>Before You Begin the Study</u>

Before you can get treatment on this study, blood stem cells must be available that meet the study requirements. We will check your child's previously stored stem cells to make sure that they can be used for the stem cell infusion.

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor.

A medical history & physical exam	Bone marrow tests[2] to check your tumor
Blood tests	Various scans[3] to check your tumor
Pregnancy test (urine or blood)[1]	Echocardiogram to check the heart function
Urine tests	

[1]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. You will be informed of a positive pregnancy test. Reporting of a positive pregnancy test to your parent or guardian will depend on local and/or state regulations. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[2]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

[3]Various scans are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG scans. We will recommend scans specific for your case and we will answer your questions about these scans.

During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, ^{131}I-MIBG will be given on Day 1 and dinutuximab will be given on Days 8-11 and Days 29-32 of each treatment course. The growth factor GM-CSF is given on the same days as the dinutuximab and continues after the dinutuximab has finished for a total of 10 doses (days 8-17 and days 29-38). All patients will be given an infusion of their stem cells on Day 15 of each course. Each course is 57 days long and you may receive up to two treatment courses of ^{131}I-MIBG and dinutuximab as long as you are benefiting from the treatment and meet the criteria to continue the treatment safely.

DAY	**1**	**2-7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18-28**
^{131}I-MIBG (M)	M												
GM-CSF (G)			G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D)			D	D	D	D							
Stem Cell Infusion (HSC)										HSC +/- 2d			

DAY	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**43-57**

GM-CSF (G)	G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D)	D	D	D	D							
Disease Evaluation (Eval)											Eval

Treatment with ^{131}I-MIBG
Patients will be assigned a certain dose level of ^{131}I-MIBG at time of study registration. If you are enrolled early in this study you may get a lower dose than those who are enrolled later. Whatever ^{131}I-MIBG dose you start at, this dose will not be increased during the study. Dosing is done this way because we do not yet know the best dose to use in children when it is used together with dinutuximab.

Treatment with ^{131}I-MIBG will be done at a hospital that is set up to take care of patients that are treated with radioactive substances. This means that you may need to travel some distance to another hospital to get this treatment. Your health care team will talk with you and help you plan for the trip to get this treatment.

Patients will be admitted to an ^{131}I-MIBG treatment center one day before starting ^{131}I-MIBG therapy. On the following day (Day 1), ^{131}I-MIBG is given into a temporary IV or in your central venous catheter over 90-120 minutes. IV fluids for hydration and other medicines will be given through your central venous catheter.

Patients who get ^{131}I-MIBG are considered to be “hot” or radioactive and you will stay in the special room until your radiation measurement reaches a safe level, usually 3 - 5 days, since you could expose others to radiation. Special care precautions include:

- A single room in a bed surrounded by a lead shield to keep family and the staff who take care of you from being exposed to radiation from the ^{131}I-MIBG treatment. This usually takes about 5 days.

- The length of time family can visit inside the room in front of the protective lead shield that is around your bed will depend on how much radiation is measured in the room each day by the radiation specialist. Usually family can visit for a total of 30-45 minutes on the first day and longer on the days after that because there will be less radiation measured in the room each day.

- Family may visit anytime outside of the room or behind a lead shield. You will be able to see who is visiting over this shield.

- No one will be able to spend the night in this special room with you during this time.

Your urine will be radioactive after treatment with ^{131}I-MIBG. A urinary catheter will be inserted to drain the radioactive urine from your body. A urinary catheter is a soft tube that is inserted into your urethra (the hole where urine comes out of your body) and up into the bladder (the place where urine waits inside your body until you go to the bathroom). The catheter is strongly recommended for all patients but is required for patients < 12 years of age. If the catheter comes out for any reason, it will most likely have to be replaced. The catheter will be removed at the time of discharge (3-5 days).

You will also take a medicine by mouth [potassium iodide (SSKI)] to prevent thyroid damage from the radioactive iodine contained in the ^{131}I-MIBG compound. The medicine will be taken together by mouth beginning before treatment and continuing for a total of 6 weeks. This will be taken every 4 hours for the first 7 days after the MIBG infusion and then daily for the remainder of the 6 weeks.

Treatment with Dinutuximab and GM-CSF
All patients on this study will receive the same dose of dinutuximab. It will be administered IV over 10-20 hours, once daily for four consecutive days in the hospital. Patients will also receive GM-CSF beginning

with dinutuximab and continuing for a total of 10 doses. GM-CSF is a substance that is similar to one made by the body. Under normal circumstances, the body makes small amounts of GM-CSF that help it to produce normal infection fighting white blood cells. It is now possible to make GM-CSF outside of the body and give humans much higher doses than their own bodies make. There is some evidence that, in the lab and in animals, GM-CSF increases the anti-cancer effect of monoclonal antibodies like dinutuximab. GM-CSF is administered under the skin [subcutaneously (SQ)] except in special circumstances when it can be given IV

Stem Cell Infusion
All patients on this study will receive an autologous stem cell infusion on Day 15. You will receive your stored stem cells back by vein two weeks after the ^{131}I-MIBG infusion. This may be done as a day visit to the hospital or may require a brief (one night) stay in the hospital. The stem cells can be given at any NANT hospital.

If you develop a low white blood count, you may receive GM-CSF (Leukine/sargramostim), G-CSF (Neupogen), or pegfilgrastim (Neulasta) in order to help your white blood cells recover faster after treatment, though it is strongly recommended that GM-CSF be the only growth factor used. GM-CSF, G-CSF, or pegfilgrastim will be given under the skin (SQ). You may also get a dose (or doses) of one of these medicines after you have received your stem cells, even if your blood counts are not low yet.

You can receive this therapy two times as part of this study, as long as:
- your tumor is not getting worse;
- you have not had any other anti-cancer treatments since the first course;
- you have enough stem cells to get a second course; and
- you have not had any bad side effects from the first course.

The second course cannot start earlier than 8 weeks from the date of the first ^{131}I-MIBG infusion. The following tests and procedures will be done during the study. They are part of regular cancer care.

A medical history & physical exam	Bone marrow tests to check your tumor
Blood tests	Various scans to check your tumor
Pregnancy test (urine or blood)	Echocardiogram to check the heart function
Urine tests	

NANT Biology Study (NANT 2004-05)
You will also be expected to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover samples is optional and will not affect your ability to participate in this treatment study with ^{131}I-MIBG and dinutuximab. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

When You Have Finished Treatment with ^{131}I-MIBG and Dinutuximab
After you stop treatment on this study, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ function, tests are recommended by the study to be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Bone marrow tests & various scans to check your tumor[1]

Blood tests	

[1]Bone marrow tests and various scans (CT/MRI, MIBG) are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.
A table detailing the tests and procedures required before, during and after the study has been attached to the end of this consent.

Additional Tests in this Study
We would like to do some extra tests called correlative biology studies. These tests will help us learn more about treatment with ^{131}I-MIBG and dinutuximab and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not. All of these tests (required and optional) will be done only during the first course.

Evaluation of Immune Function – Required
During this study blood samples will be collected to look at changes in your immune function before and after treatment with ^{131}I-MIBG and dinutuximab. We will look at changes in the number and function of certain cells of the immune system, as well as measure levels of certain proteins that cause inflammation in the body. We will collect 13 mL (~2.5 teaspoons) of blood with each sample at 5 different time points during course 1 ONLY. The total amount of blood drawn for testing will be 65 mL (13 teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to Children's Healthcare of Atlanta for testing.

Testing for Antibodies Against Dinutuximab – Required
During this study blood samples will be collected to look for antibodies that attach to dinutuximab, and also to look at how many of these antibodies make it so the dinutuximab can't attack your neuroblastoma. The amount of blood required for this test is < 1 mL (less than ¼ teaspoon) and it will be taken from the amount collected as part of the immune functions studies at 3 of the 5 time points, and two additional time points. We will collect 8 mL (~1.5 teaspoon) of blood at each of these two additional time points, both to test for the antibodies against dinutuximab and to save for future testing of changes in your immune function.

Other Biology Research Tests in this Study - Optional
You will be asked if you want to participate in other optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. Your care will be unaffected even if you say "no" to participating in any or all of these optional research studies. There are checkboxes at the end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study.

- **Using extra blood to look for proteins and genetic changes in your cells.**
  Part of the research goal for this study is to look for the presence of and changes in certain proteins and genes in the blood that might affect your response to treatment. We would like to collect this blood before, during, and after treatment on this study.

  - For the tests looking at the genes in your cells (DNA), no additional blood draw is required. The sample would be obtained from the blood that is collected for the testing of the cells of your immune system at the 5 time points described above.

- For the tests looking at proteins or at certain genes that affect your body's immune response, an additional 2.5 mL (1/2 teaspoon) of blood will be collected at 8 different time points during course 1. The total amount of blood drawn for this testing will be 20 mL (4 teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to Children's Healthcare of Atlanta for testing.

- **<u>Evaluate tumor tissue for immune system cells that surround and invade your tumor.</u>**
  Part of the research goal for this study is to learn more about the cells of your immune system that surround and invade your tumor, and learn how these cells change after treatment with ^{131}I-MIBG and dinutuximab. We would also like to perform genetic studies on a small amount of your blood in addition to the tumor tissue to better understand your immune response. These tumor samples and tests would be used to see whether we can predict response to treatment based on the kinds of cells we see around and inside your tumor.

  - If you agree we would ask for three mL (approximately 1/2 teaspoon) of peripheral blood to be drawn and leftover tumor tissue from the most recent time point in the past when tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) to be sent together to a research laboratory for testing. The laboratory uses the blood sent with your tumor for determining the genetic make-up of your normal cells (known as germline testing) that is used to compare to the genetic make-up of your tumor. The researchers will look for any changes in the genetic make-up of the tumor that are different from those changes found in your normal genetic material obtained from your blood sample.
  - To see how treatment with MIBG and dinutuximab affects the immune cells around and in your tumor, if you agree, we would also like to ask for tumor tissue that might be collected in the future if your doctor thinks it is in your best interest to have more of your tumor removed for any reason. This would happen after you have finished treatment on this study, but before you receive any additional therapy for your neuroblastoma.

  We will not remove tissue just for these additional studies. The tissue will be sent to a research laboratory at Children's Hospital of Los Angeles for testing.

HOW LONG WILL I BE ON THIS STUDY?
You can get two treatment courses with ^{131}I-MIBG and dinutuximab as long as you are not having bad side effects and as long as your tumor is not getting worse.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment; or whether you have developed any additional cancer. Your doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?
Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely. There are certain time points in the study where it would be strongly recommended that you complete the medical supportive care required to avoid very bad and/or fatal side effects.

- Once you have gotten ^{131}I-MIBG treatment, you will stay in the special room until you are no longer radioactive (usually 5 days), since you could expose others to radiation.

- Once you have gotten ^{131}I-MIBG treatment, it would be strongly recommended that you complete the

medical supportive care needed to avoid very bad and/or fatal side effects. This includes the stem cell infusion and the potassium iodide for thyroid protection.

Your doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow study rules, or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?
This is a Phase 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of ^{131}I-MIBG in combination with dinutuximab. Though subjects will be assigned to different dose levels of ^{131}I-MIBG, all doses of ^{131}I-MIBG being tested have been shown to be effective against neuroblastoma.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache, itching). Many side effects go away soon after you stop taking the study medications but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped if bad side effects develop. There may also be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study.

While on the study, you are at risk for the side effects listed below:

Possible Risks of ^{131}I-MIBG

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
• Decrease in the number of red and white blood cells and platelets made in the bone marrow. You may need blood and platelet transfusions and sometimes stem cell infusions are necessary. (Stem cells are required on this trial) The dose of ^{131}I-MIBG used in this study will lower your blood counts. • Nausea • Dry mouth • Increase in blood marker of salivary gland irritation (your serum amylase will increase)	• Decreased function of the thyroid gland. This causes tiredness (fatigue), weight gain, constipation, and lower blood pressure. Treatment for life with a medicine to supplement the thyroid gland (i.e. Synthroid or related thyroid supplement) may be needed. • Not being able to get pregnant or father a child • High or low blood pressure during or after the ^{131}I-MIBG infusion • Thinning of the hair • Vomiting • Infection due to low white blood cells • Fatigue due to low red blood cells • Bleeding/bruising due to low platelets • Loss of appetite	• Pain in salivary glands or mouth • Decreased function of adrenal gland. This affects your activity level and growth. It causes tiredness (fatigue), weight changes and blood pressure changes. You may need to take medicine to supplement the adrenal gland. • Decreased heart function • Irritation of the liver. Because some of the radioactive ^{131}I-MIBG is taken up by the liver, there is a possible risk of future liver damage from the ^{131}I-MIBG alone. • Second cancer (such as leukemia) that is different from the kind of cancer you have now • Trouble breathing due to infection or damage to the lung

		• Overactive thyroid gland

Possible risks from having a bladder catheter placed
In order to safely receive MIBG therapy, you will need to a have a tube or catheter called a Foley catheter temporarily placed in your bladder. The catheter may cause you some discomfort and may increase your risk for getting a bladder infection.

Possible Risks of Potassium Iodide

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
	• Gastrointestinal distress (nausea / vomiting / diarrhea / stomach pain)	• Tingling, pain or weakness in arms and legs • Flare up of acne in teenagers • Irregular heartbeat • Confusion • Tiredness • Fever • Allergic reaction (hives) • Burning of mouth / throat • Metallic taste • Rash • Decreased function of the thyroid gland with overuse • Swelling of lymph glands

This medication is given for 45 days after the ^{131}I-MIBG infusion to protect your thyroid gland.

Possible Risks of Dinutuximab

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
• Fever • Pain • Cough • Rash	• Anemia, kidney problems which may cause tiredness, or may require blood transfusion or dialysis • Blood clot • Abnormal heartbeat • Diarrhea, nausea, vomiting • Swelling of arms, legs • Allergic reaction, which may cause rash, low blood pressure, wheezing, shortness of breath, swelling	• Heart stops beating • Vision changes which may include changes in the pupils of the eye • Death • Swelling of the spinal cord • Muscle weakness • Brain damage which may cause headache, seizure, blindness (reversible posterior

	of the face or throat and difficulty speaking • Infection, especially when white blood count is low • Bruising, bleeding • Loss of appetite • Numbness, tingling or pain of the arms and legs • Difficulty emptying the bladder, which may require catheterization during therapy, and in rare cases catheterization may be required after discharge from the hospital • Itching, hives • Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles • High blood pressure which may cause dizziness, blurred vision • Low blood pressure which may cause feeling faint	leukoencephalopathy syndrome)

Possible Risks of Sargramostim (GM-CSF)

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
• Headache • Bone pain • Joint pain • Muscles aches • Rash • Fever • Chills • Itching	• Stomach pain • Weakness • Nausea • Reaction to injection site • Lack of appetite	• Reaction during or following injection of drug which may cause fever, chills, rash, low blood pressure, fast heartbeat, shortness of breath and swelling of the face or throat • Vomiting • Diarrhea • Abnormally fast heartbeat • Fluid around the heart which may cause shortness of breath and/or chest pain • Inflammation of veins which may cause pain and swelling • In high doses: fluid in the organs which may cause low blood pressure, shortness of breath and/or swelling of ankles

Possible Risks Associated with Stem Cells

- ANY TIME BEFORE STEM CELL INFUSION: The freezer where PBSC are stored could malfunction, the container holding them could break and the stem cells could be damaged so they could not be used. This is expected to be an extremely rare event. However, if this occurs, another stem cell collection may be attempted or the back-up stem cells (if available) may be used if they were not damaged.

- If stem cells need to be shipped from one location to another, they could be lost or damaged during shipping such that they could not be used. This is expected to be an extremely rare event. If this occurs, another stem cell collection may be attempted or the back-up stem cells, if available, may be used.

- Some patients may need extra fluids given into the vein after getting their stem cells. This is to protect the kidneys from the red blood cells mixed in with the stem cells.

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
	• Fever and chills	• Allergic reaction. Can cause difficulty breathing and low blood pressure. • High blood pressure • Infection • Infusion of tumor cells. Tumor cells may still be present in the harvested stem cells and they could regrow after stem cells are infused. • Cough • Chest Tightness • Flushing • Nausea and/or vomiting • Rash • Irregular Heart Beat

Herbs and Supplements

Some drugs or supplements may interact with your treatment plan. Talk to your doctor, pharmacist, or study team before starting any new prescription drugs, over-the-counter drugs, herbals, or supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

Possible Risks to Unborn Child

Patients who agree to participate in this study should not become pregnant while on this study. Patients and their sexual partners should avoid sex and/or use two effective methods of contraception that are medically appropriate based on your personal doctor's recommendation at that time and should be used for as long as you participate in this study. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Risks to the Caregiver(s) of the Patient Getting ^{131}I-MIBG Treatment

Caregivers (example: parent, other family member, guardian, friend, partner) will be exposed to radiation while you are being treated with MIBG. Caregivers who could possibly become pregnant during this time need to avoid contact with the patient because the radiation exposure may increase the unborn baby's risk of developing cancer or other health problems.

If your caregiver is pregnant, then special precautions should be used to avoid contact with you during and for 4 weeks after getting MIBG treatment. Should your caregiver or your caregiver's sexual partner be found to have been pregnant while you were getting MIBG treatment and did not know it at the time, please contact your doctor immediately.

Possible Long Term Risk of This Treatment

- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of puberty
- Increased risk of a second cancer (such as leukemia) different from the kind of cancer you have now.
- Patients who have more than one ^{131}I-MIBG treatment will have greater doses of radiation to the normal organs than those patients having one treatment. It is possible that there may be later damage to the normal function of the liver or other organs.

Possible Risks from Having Blood Drawn

The risks from having your blood taken are minimal, but can include an infection or a blood clot. You may also experience some pain or bruising at the site your blood was drawn. Experienced doctors or nurses will perform these blood draws to minimize this risk. You will be asked to sign a separate consent for any procedure that needs sedation.

Possible Risks from Germline Genetic Testing

If you agree to participation in the optional test looking at immune system cells in your tumor and immune response, a small amount of your blood will be collected. Researchers will use the blood sent with your tumor for determining the genetic make-up of your normal cells (known as germline testing) that is used as a baseline to compare to the genetic make-up of your tumor. This helps the laboratory in identifying the genetic changes they may see in your tumor tissue.

The germline genetic testing is for research purposes only and is performed on de-identified samples, and so the information can't be linked back to your child. Hence, the results will not be sent to you or your physician.

Unknown Risks

This treatment combination may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines, or ^{131}I-MIBG without dinutuximab
- Treatment with other experimental agents that may be available
- No neuroblastoma therapy at this time, with care to help you feel more comfortable

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA), Health Canada, or European regulatory agency(ies) involved in keeping research safe for people.
- Jubilant Radiopharma (supplier of ^{131}I-MIBG)
- United Therapeutics Corporation (manufacturer of dinutuximab)

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

The ^{131}I-MIBG will be supplied by Jubilant Radiopharma. The cost of ^{131}I-MIBG and its administration costs will be billed to your/your child's insurance company.

Dinutuximab will be provided free of charge by United Therapeutics, Inc while you are taking part in this study. United Therapeutics does not cover the cost of getting dinutuximab ready and giving it to you so your insurance company may have to pay for this.

GM-CSF is a commercially available agent. You will pay for the amount of drug needed to complete this study. This cost is normally covered by your insurance company.

The correlative biology studies will be done at no cost to you. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, car fare, travel to and from the hospital for treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not be covered by your insurance company. Please ask about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's website at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you tell your study doctor, _____ *[investigator's name(s)]* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?
Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of you legal rights to seek payment by signing this form.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may visit the NCI Web sites at http://cancer.gov/
For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.
You will get a copy of this consent form. If you want more information about this study, ask your doctor.

CONSENT FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional for all patients in the study. You may still participate in the study even if you do not agree to these tests.

1. <u>Using extra blood to look for proteins and genetic changes in your cells.</u>

Initial next to YES if you agree to let researchers use some of the blood (less than ¼ teaspoon) already drawn for one of the required studies to look at certain immune cell genes and how changes in these genes might affect how you respond to the treatment. No extra blood needs to be drawn from you to do this optional test. The results of this test will be confidential and not made available to you or your treating physician.

Initial next to NO if you do not want researchers to use some of the blood already drawn for a required test to look at immune cell genes.

_____Yes _____No

Initial next to YES if you agree to let researchers take an extra half teaspoon (2.5 mL) of blood 8 different times to look for certain proteins and changes in these proteins that might affect your response to treatment with ^{131}I-MIBG and dinutuximab. This blood would be drawn at a time when blood was being drawn for clinical purposes. The results of this test will be confidential and not made available to you or your treating physician.

Initial next to NO if you do not want researchers to take extra blood above what is needed for clinical purposes.

_____Yes _____No

2. <u>Evaluate tumor tissue for immune system cells that surround and invade your tumor and the genes that cause an immune response, and if possible also comparing immune system cells in tumor samples from before and after treatment with MIBG and dinutuximab.</u>

Initial next to YES if you agree to let researchers collect 3 mL (about ½ teaspoon) of blood to be sent together with any leftover tumor (if available from an earlier procedure) to a laboratory so researchers can learn more about the immune system cells that surround and invade your tumor and genes that cause an immune response. Looking at the immune response genes involves comparing your normal genetic information gotten from the blood sample (called germline) to the genetic information of your tumor and determining what is different between the two. The results of these tests will be confidential and not made available to you or your treating doctor.

Initial next to NO if you do not want extra blood drawn and leftover tumor from an earlier procedure, if it is available, to be sent to a research laboratory.

_____Yes _____No

Initial next to YES if you agree to have leftover tumor sent to the research lab if a biopsy is done in the future for clinical care and this happens after finishing this protocol therapy and before starting the next treatment for your tumor. The purpose of this part of the test is to see if the ^{131}I-MIBG had any effect on the immune cells that surround and invade your tumor.

Initial next to NO if you do not want leftover tumor from a future procedure to be sent to a research laboratory.

_____Yes _____No

3. <u>Storage of left over specimens obtained on this study for future use in research</u>

The NANT Biology Study (N2004-05) provides a way to allow for banking of leftover specimens from this study for future research to answer questions about MIBG and dinutuximab treatment, neuroblastoma or other childhood cancers.

Initial next to YES if you agree to storage of any specimens leftover from this study for future research.

Initial next to NO if you do not want leftover specimens from this study stored for future research

_____Yes _____No

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____
Print Patient Name

_____ _____/_____/_____
Print Name of Parent or Guardian Date

_____ _____/_____/_____
Signature of Parent or Guardian Date

_____ _____/_____/_____
Signature of Patient (If > 7 years old) Date

_____ _____/_____/_____
Signature of Physician or Date
Responsible Investigator

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator Date

Consent Addendum I: Tests That Will Be Done On This Study

<table>
<tr><th rowspan="2">Observation</th><th rowspan="2">Before Entry</th><th colspan="2">Days 1 to Day 56 of Course 1 & 2</th><th rowspan="2">End of treatment</th></tr>
<tr><th>All other days during course</th><th>During dinutuximab infusions only
Day 8-11 and Day 29-32</th></tr>
<tr><td>Physical Exam</td><td>X</td><td>Weekly</td><td>Daily</td><td>X</td></tr>
<tr><td>Blood Tests</td><td>X</td><td>Twice weekly for blood counts,
Weekly for other tests</td><td>Daily</td><td>X</td></tr>
<tr><td>Urine tests</td><td>X</td><td></td><td></td><td>X</td></tr>
<tr><td>Pregnancy test</td><td>X</td><td></td><td></td><td>X</td></tr>
<tr><td>Heart test (echocardiogram)</td><td>X</td><td></td><td></td><td>X</td></tr>
<tr><td>MIBG scan after MIBG treatment
(no extra MIBG is given to you to do this scan)</td><td></td><td>After you get out of your radiation isolation room</td><td></td><td></td></tr>
<tr><td>Blood correlative studies (Required)</td><td></td><td>Course 1 only
2 times</td><td>Course 1 only
4 times</td><td rowspan="2">Course 1 only
1 time</td></tr>
<tr><td>Blood for correlative studies
(Optional)</td><td></td><td>Course 1 only
3 times</td><td>Course 1 only
4 times</td></tr>
<tr><td>Blood & Tumor sample sent for research (optional)</td><td colspan="4">Blood & Tumor sample can be sent any time during the study</td></tr>
<tr><th colspan="5">Disease Evaluation Tests[#]</th></tr>
<tr><td>Bone marrow aspirate/biopsy</td><td>X</td><td colspan="2" rowspan="2">Day 43 – 57 of Course 1</td><td>X</td></tr>
<tr><td>CT, MRI and/or MIBG scans</td><td>X</td><td>X</td></tr>
</table>

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study N04-05 consent form for more information.

Consent Addendum II
Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

15.2 Part B

NANT 2017-01: A PHASE I STUDY OF ^{131}I-MIBG WITH DINUTUXIMAB +/- VORINOSTAT FOR RELAPSED/REFRACTORY NEUROBLASTOMA

FOR PATIENTS ON PART B

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

The word "you" used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?
This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest safe dose of vorinostat that can be given with ^{131}I-MIBG and dinutuximab to children with refractory or recurrent neuroblastoma without causing severe side effects
- To find out what side effects there are from giving vorinostat, ^{131}I-MIBG, and dinutuximab together on this schedule
- To see if your tumor gets smaller after treatment with vorinostat, ^{131}I-MIBG, and dinutuximab
- To learn what happens to your immune system and other proteins that cause inflammation when giving vorinostat and ^{131}I-MIBG with dinutuximab.
- To see what effect giving vorinostat and ^{131}I-MIBG has on your body in making an antibody to the dinutuximab
- To see what effect treatment with vorinostat and ^{131}I-MIBG in combination with dinutuximab has on the cells of your immune system that surround and invade your tumor
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The research is being done because:
Currently there is no known effective treatment for neuroblastoma that has returned or that has not responded to treatment.

This study will use an intravenous (IV) chemical agent called metaiodobenzylguanidine (MIBG) together with an oral drug called vorinostat and an IV drug called dinutuximab. MIBG is taken up by neuroblastoma tumor cells. MIBG can be combined with radioactive iodine (^{131}I) in the laboratory to form the radioactive compound ^{131}I-MIBG. ^{131}I-MIBG delivers radiation to the neuroblastoma cancer cells and causes them to die. ^{131}I-MIBG lowers the number of blood forming cells (called stem cells) in the bone marrow when it is given at higher doses as in this study. Because of this, all patients will get back their own stem cells to help the bone marrow recover from this therapy.

Vorinostat is a drug that is FDA-approved to treat a certain type of cancer mainly seen in adults. Vorinostat affects the way the DNA that carries our genes is folded in cells. In the laboratory, vorinostat causes neuroblastoma cells to stop growing. This effect is even greater when vorinostat is combined with radiation.

A recent clinical trial has shown that giving vorinostat together with ^{131}I-MIBG increases the number of patients who respond to ^{131}I-MIBG compared to giving ^{131}I-MIBG by itself. Laboratory studies also show that dinutuximab may work better when it is given with vorinostat; however, combining vorinostat with dinutuximab either with or without ^{131}I-MIBG has never been tested in a clinical trial.

Dinutuximab works differently than most standard chemotherapy drugs. Dinutuximab is a monoclonal antibody. Monoclonal antibodies are proteins made in the lab, designed to attach to specific targets on cancer cells. When dinutuximab attaches to neuroblastoma cells, the body's immune system is stimulated to attack and kill the neuroblastoma cells. Dinutuximab represents a new kind of cancer therapy called immunotherapy which, unlike chemotherapy and radiation, targets the cancer cells without destroying nearby healthy cells.

Laboratory studies have shown greater anti-cancer effects when radiation is given before an immunotherapy treatment. Some clinical responses have been seen in adults when radiation has been combined with different types of immunotherapy in treating their cancers.

Giving dinutuximab together with vorinostat and ^{131}I-MIBG may kill more neuroblastoma cells. This is the first study to test giving dinutuximab together with vorinostat and ^{131}I-MIBG. We want to find out if giving the combination of vorinostat, ^{131}I-MIBG, and dinutuximab can be tolerated. We also want to see how effective this drug combination is against relapsed or refractory neuroblastoma.

Dinutuximab is a drug that has been approved by the Food and Drug Administration (FDA) for treating newly diagnosed patients with neuroblastoma. The use of dinutuximab in combination with vorinostat and ^{131}I-MIBG for the treatment of relapsed or refractory neuroblastoma is considered experimental.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

This study has two parts. In the first part of the study, the dose of ^{131}I-MIBG and dinutuximab will be determined (Part A). 30 patients are expected to take part in the first part of the study. This second part of the study (Part B) will add vorinostat to this combination. There will be approximately 18 patients enrolling on this part of the study (Part B). You are being asked to participate in Part B of this study. When you join the study, you will be assigned a certain dose of vorinostat. The doses for ^{131}I-MIBG and dinutuximab will be the same for all patients on Part B of this study. This study will test one dose of vorinostat in 3-6 patients. The starting dose of vorinostat will be the dose that has been proven safe and effective in previous trials giving vorinostat in combination with ^{131}I-MIBG. The ^{131}I-MIBG and dinutuximab doses will be the doses that were demonstrated to be safe to give together in Part A of the study. This dose of vorinostat will be given in 3 to 6 patients. If too many patients have serious side effects then a lower dose of vorinostat will be tested in 3 to 6 more patients. The dose level tolerated without serious side effects will be the highest dose of vorinostat and ^{131}I-MIBG that can be given in combination with dinutuximab (called the maximum tolerated dose).

Once the maximum tolerated dose is determined, a group of 6 more patients will be enrolled and treated at this dose of vorinostat in combination with ^{131}I-MIBG and dinutuximab, known as the dose expansion part of the study. The purpose of the dose expansion part of the study is to gather more information about side effects seen in patients treated at the maximum tolerated dose of vorinostat in combination with ^{131}I-MIBG and dinutuximab.

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Before You Begin the Study

Before you can get treatment on this study, blood stem cells must be available that meet the study requirements. We will check your child's previously stored stem cells to make sure that they can be used for the stem cell infusion.

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor.

A medical history & physical exam	Bone marrow tests[2] to check your tumor
Blood tests	Various scans[3] to check your tumor
Pregnancy test (urine or blood)[1]	Echocardiogram and electrocardiogram to check the heart function
Urine tests	

[1]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. You will be informed of a positive pregnancy test. Reporting of a positive pregnancy test to your parent or guardian will depend on local and/or state regulations. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[2]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

[3]Various scans are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG scans. We will recommend scans specific for your case and we will answer your questions about these scans.

<u>During the Study</u>
If the exams, tests and procedures show that you can participate in the study, and you choose to take part in the study, the following will be your treatment plan:

- **Vorinostat** will be given on Days 0 to +13 (14 days)
- **^{131}I-MIBG** will be given on Day 1
- **Dinutuximab** will be given on Days 8-11 and Days 29-32 of each treatment course.
- The growth factor **GM-CSF** will be given on the same days as the dinutuximab and continue after the dinutuximab has finished for a total of 10 doses (Days 8-17 and Days 29-38).
- All patients will be given an infusion of their **stem cells** around Day 15 of each course.
- Each course is around 57 days long.
- You may receive up to two treatment courses of vorinostat, ^{131}I-MIBG, and dinutuximab as long as you are benefiting from the treatment and meet the criteria to continue the treatment safely.

The following is the schematic of the days of treatment outlined above.

DAY	0	1	2-7	8	9	10	11	12	13	14	15	16	17	18-28
Vorinostat (V) dose level assignment	V	V	V	V	V	V	V	V	V					
^{131}I-MIBG (M) dose level assignment		M												
GM-CSF (G) 250 mcg/m^2				G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D) 17.5 mg/m^2				D	D	D	D							
Stem Cell Infusion (HSC)											HSC			

DAY	29	30	31	32	33	34	35	36	37	38	43-57
GM-CSF (G)	G	G	G	G	G	G	G	G	G	G	
DINUTUXIMAB (D)	D	D	D	D							
Disease Evaluation (Eval)											Eval

Treatment with Vorinostat
Patients will be assigned a certain dose level of vorinostat at time of study registration. The vorinostat dose you are assigned to will not be increased during the study. Dosing is done this way because we do not yet know the best dose of vorinostat to use in children when it is used together with ^{131}I-MIBG and dinutuximab.

The vorinostat is given by a pill or a liquid depending upon your size. If you cannot take medicines by mouth, the vorinostat can be given into a tube placed in the nose or stomach. You will receive vorinostat orally once daily for 14 days (Days 0 to +13). One day after starting vorinostat, ^{131}I-MIBG will be given (Day 1). If you vomit within 15 minutes of taking the vorinostat you should retake the dose. If you vomit again with the second dose you should not try to take the dose again. If you vomit more than 15 minutes after taking the vorinostat you should not try to retake the dose.

Treatment with ^{131}I-MIBG
Patients will be given the ^{131}I-MIBG dose that has been shown can be safely given with dinutuximab during the first part of this study (Part A). Treatment with ^{131}I-MIBG will be done at a hospital that is set up to take care of patients that are treated with radioactive substances. This means that you may need to travel some distance to another hospital to get this treatment. Your health care team will talk with you and help you plan for the trip to get this treatment.

Patients will be admitted to an ^{131}I-MIBG treatment center one day before starting ^{131}I-MIBG therapy. On the following day (Day 1), ^{131}I-MIBG is given into a temporary IV or in your central venous catheter over 90-120 minutes. IV fluids for hydration and other medicines will be given through your central venous catheter.

Patients who get ^{131}I-MIBG are considered to be radioactive and you will stay in the special room until your radiation measurement reaches a safe level, usually 3 - 5 days, since you could expose others to radiation. Special care precautions include:

- A single room in a bed surrounded by a lead shield to keep family and the staff who take care of you from being exposed to radiation from the ^{131}I-MIBG treatment.

- The length of time family can visit inside the room in front of the protective lead shield that is around your bed will depend on how much radiation is measured in the room each day by the radiation specialist. Usually family can visit for a total of 30-45 minutes on the first day and longer on the days after that because there will be less radiation measured in the room each day.

- Family may visit anytime outside of the room or behind a lead shield. You will be able to see who is visiting over this shield.

- No one will be able to spend the night in this special room with you during this time.

Your urine will be radioactive after treatment with ^{131}I-MIBG. A urinary catheter may be inserted to drain the radioactive urine from your body. The catheter is strongly recommended for all patients but is required for patients < 12 years of age. If the catheter comes out for any reason, it will most likely have to be replaced. The catheter will be removed at the time of discharge (3-5 days).

You will also take a medicine by mouth [potassium iodide (SSKI)] to prevent thyroid damage from the radioactive iodine contained in the ^{131}I-MIBG compound. This medicine will be taken by mouth or by tube before beginning treatment and will continue to be taken for a total of 6 weeks. This will be taken every 4 hours for the first 7 days after the ^{131}I-MIBG infusion and then daily for the remainder of the 6 weeks.

Treatment with Dinutuximab and GM-CSF
All patients on this study will receive the same dose of dinutuximab. It will be administered IV over 10-20 hours, once daily for four consecutive days in the hospital. Patients will also receive GM-CSF beginning with dinutuximab and continuing for a total of 10 doses. GM-CSF is a substance that is similar to one made by the body. Under normal circumstances, the body makes small amounts of GM-CSF that help it to produce normal infection fighting white blood cells. It is now possible to make GM-CSF outside of the body and give humans much higher doses than their own bodies make. There is some evidence that, in the lab and in animals, GM-CSF increases the anti-cancer effect of monoclonal antibodies like dinutuximab. GM-CSF is administered under the skin [subcutaneously (SQ)] except in special circumstances when it can be given IV.

Stem Cell Infusion
All patients on this study will receive an autologous stem cell infusion (an infusion of your previously collected stem cells) at about Day 15 which is around 2 weeks from the ^{131}I-MIBG infusion. You will receive your stored stem cells back by vein. This may be done as a day visit to the hospital or may require a brief (one night) stay in the hospital. The stem cells can be given at any NANT hospital.

If you develop a low white blood count, you may receive GM-CSF (Leukine/sargramostim), G-CSF (Neupogen), or pegfilgrastim (Neulasta) in order to help your white blood cells recover faster after treatment, though it is strongly recommended that GM-CSF be the only growth factor used. GM-CSF, G-CSF, or pegfilgrastim will be given under the skin (SQ). You may also get a dose (or doses) of one of these medicines after you have received your stem cells, even if your blood counts are not low yet.

You can receive this therapy two times as part of this study, as long as:

- your tumor is not getting worse;
- you have not had any other anti-cancer treatments since the first course;
- you have enough stem cells to get a second course; and
- you have not had any bad side effects from the first course.

The second course cannot start earlier than 8 weeks from the date of the first ^{131}I-MIBG infusion. The following tests and procedures will be done during the study. They are part of regular cancer care.

A medical history & physical exam	Bone marrow tests to check your tumor
Blood tests	Various scans to check your tumor
Pregnancy test (urine or blood)	Echocardiogram and electrocardiogram to check the heart function
Urine tests	

NANT Biology Study (NANT2004-05)

You will be required to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be required to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover samples is optional and will not affect your ability to participate in this treatment study with vorinostat, ^{131}I-MIBG, and dinutuximab. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

When You Have Finished Treatment with Vorinostat, ^{131}I-MIBG, and Dinutuximab

After you stop treatment on this study, you will continue to have tests and scans done (listed below) to see how you are doing. If test results show you have abnormal organ function, tests are recommended by the study to be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Bone marrow tests & various scans to check your tumor[1]
Blood tests	

[1]Bone marrow tests and various scans (CT/MRI, MIBG) are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this consent.

Additional Tests in this Study

We would like to do some extra tests called correlative biology studies. These tests will help us learn more about treatment with vorinostat, ^{131}I-MIBG, and dinutuximab and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not. All of these tests (required and optional) will be done only during the first course.

Evaluation of Immune Function – Required
During this study blood samples will be collected to look at changes in your immune function before and after treatment with vorinostat, ^{131}I-MIBG, and dinutuximab. We will look at changes in the number and function of certain cells of the immune system, as well as measure levels of certain proteins that cause inflammation in the body. We will collect 13 mL (~2.5 teaspoons) of blood with each sample at 6 different time points during Course 1 ONLY. The total amount of blood drawn for testing will be 78 mL (~15.5 teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to Children's Healthcare of Atlanta for testing.

Testing for Antibodies Against Dinutuximab – Required
During this study blood samples will be collected to look for antibodies that attach to dinutuximab, and also to look at how many of these antibodies make it so the dinutuximab can't attack your neuroblastoma. The amount of blood required for this test is < 1 mL (less than ¼ teaspoon) and it will be taken from the amount collected as part of the immune functions studies at 3 of the 5 time points, and two additional time points. We will collect 8 mL (~1.5 teaspoons) of blood at each of these two additional time points, both to test for the antibodies against dinutuximab and to save for future testing of changes in your immune function.

Other Biology Research Tests in this Study - Optional
You will be asked if you want to participate in other optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at the end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study.

- **<u>Using extra blood to look for proteins and genetic changes in your cells.</u>**
  Part of the research goal for this study is to look for the presence of and changes in certain proteins and genes in the blood that might affect your response to treatment. We would like to collect this blood before, during, and after treatment on this study.

  - For the tests looking at the genes in your cells (DNA), no additional blood draw is required. The sample would be obtained from the blood that is collected for the testing of the cells of your immune system at the 6 time points described above.

  - For the tests looking at proteins or at certain genes that affect your body's immune response, an additional 2.5 mL (1/2 teaspoon) of blood will be collected at 9 different time points during course 1. The total amount of blood drawn for this testing will be 22.5 mL (4.5 teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to Children's Healthcare of Atlanta for testing.

- **<u>Evaluate tumor tissue for immune system cells that surround and invade your tumor.</u>**
  Part of the research goal for this study is to learn more about the cells of your immune system that surround and invade your tumor, and learn how these cells change after treatment with vorinostat, ^{131}I-MIBG, and dinutuximab. We would also like to perform genetic studies on a small amount of your blood in addition to the tumor tissue to better understand your immune response. These tumor samples and tests would be used to see whether we can predict response to treatment based on the kinds of cells we see around and inside your tumor.

- To see how treatment with vorinostat, ^{131}I-MIBG, and dinutuximab affects the immune cells around and in your tumor, if you agree, we would also like to ask for tumor tissue that might be collected in the future if your doctor thinks it is in your best interest to have more of your tumor removed for any reason. This would happen after you have finished treatment on this study, but before you receive any additional therapy for your neuroblastoma.
- If you agree we would ask for 3 mL (approximately 1/2 teaspoon) of peripheral blood to be drawn and leftover tumor tissue from the most recent time point in the past when tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) to be sent together to a research laboratory for testing. The laboratory uses the blood sent with your tumor for determining the genetic make-up of your normal cells (known as germline testing) that is used to compare to the genetic make-up of your tumor. The researchers will look for any changes in the genetic make-up of the tumor that are different from those changes found in your normal genetic material obtained from your blood sample

We will not remove tissue just for these additional studies. The tissue will be sent to a research laboratory at Children's Hospital of Los Angeles for testing.

HOW LONG WILL I BE ON THIS STUDY?
You can get two treatment courses with vorinostat, ^{131}I-MIBG, and dinutuximab as long as you are not having bad side effects and as long as your tumor is not getting worse and your insurance allows you to get vorinostat and GM-CSF.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment; or whether you have developed any additional cancer. Your doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?
Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely. There are certain time points in the study where it would be strongly recommended that you complete the medical supportive care required to avoid very bad and/or fatal side effects.

- Once you have gotten ^{131}I-MIBG treatment, you will stay in the special room until you are no longer radioactive (usually 5 days), since you could expose others to radiation.

- Once you have gotten ^{131}I-MIBG treatment, it would be strongly recommended that you complete the medical supportive care needed to avoid very bad and/or fatal side effects. This includes the stem cell infusion and the potassium iodide for thyroid protection.

Your doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow study rules, or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?
This is a Phase 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking vorinostat and ^{131}I-MIBG in combination with dinutuximab. The dose of ^{131}I-MIBG you will receive has been shown to be effective against neuroblastoma, and a recent study has shown that giving vorinostat with ^{131}I-MIBG increases the number of patients who will respond to ^{131}I-MIBG.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache, itching). Many side effects go away soon after you stop taking the study medications but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped if bad side effects develop. There may also be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study.

While on the study, you are at risk for the side effects listed below:

Possible Risks of Vorinostat

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
• Low blood counts, including low red blood cells (which can cause fatigue or pale appearance) and platelets (which can cause bruising or bleeding). • Fatigue • Anorexia • Diarrhea • Nausea • Change in taste	• Decrease in specific types of blood cells (white blood cells which can cause increased risk of infection • Weight loss • Decreased kidney function • High blood sugar • Fever, with or without low blood counts • Chills • Hair loss • Vomiting • Constipation • Dehydration • Dry mouth • Heartburn • Infection • Headache • Changes in liver blood tests • Changes in blood salts • Muscle spasm or weakness • Dizziness • Cough • Blood clot • Protein in the urine • Blood creatinine increased • Lymphopenia • Anemia • Swelling in the hands and feet • Pruritis	• Skin breakdown • Changes in a specific part of the heart tracing known as an EKG. (Mild changes in a specific part of the heart tracing known as an EKG has been rarely reported in patients treated with vorinostat, though it is not clear whether vorinostat caused these changes or not.) • A kind of skin cancer called Squamous cell carcinoma • Bleeding from GI tract • An increase in the time it takes for your blood to clot

Possible Risks of ^{131}I-MIBG

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
• Decrease in the number of red and white blood cells and platelets made in the bone marrow. You may need blood and platelet transfusions and sometimes stem cell infusions are necessary. (Stem cells are required on this trial) The dose of ^{131}I-MIBG used in this study will lower your blood counts. • Nausea • Dry mouth • Increase in blood marker of salivary gland irritation (your serum amylase will increase)	• Decreased function of the thyroid gland. This causes tiredness (fatigue), weight gain, constipation, and lower blood pressure. Treatment for life with a medicine to supplement the thyroid gland (i.e. Synthroid or related thyroid supplement) may be needed. • Not being able to get pregnant or father a child • High or low blood pressure during or after the ^{131}I-MIBG infusion • Thinning of the hair • Vomiting • Infection due to low white blood cells • Fatigue due to low red blood cells • Bleeding/bruising due to low platelets • Loss of appetite	• Pain in salivary glands or mouth • Decreased function of adrenal gland. This affects your activity level and growth. It causes tiredness (fatigue), weight changes and blood pressure changes. You may need to take medicine to supplement the adrenal gland. • Decreased heart function • Irritation of the liver. Because some of the radioactive ^{131}I-MIBG is taken up by the liver, there is a possible risk of future liver damage from the ^{131}I-MIBG alone. • Second cancer (such as leukemia) that is different from the kind of cancer you have now • Trouble breathing due to infection or damage to the lung • Overactive thyroid gland

Possible risks from having a bladder catheter placed
In order to safely receive ^{131}I-MIBG therapy, you will need to a have a tube or catheter called a Foley catheter temporarily placed in your bladder. The catheter may cause you some discomfort and may increase your risk for getting a bladder infection.

Possible Risks of Potassium Iodide

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
	• Gastrointestinal distress (nausea / vomiting / diarrhea / stomach pain)	• Tingling, pain or weakness in arms and legs • Flare up of acne in teenagers • Irregular heartbeat • Confusion • Tiredness • Fever • Allergic reaction (hives) • Burning of mouth / throat • Metallic taste • Rash • Decreased function of the thyroid gland with overuse • Swelling of lymph glands

This medication is given for 45 days after the ^{131}I-MIBG infusion to protect your thyroid gland.

Possible Risks of Dinutuximab

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
• Fever • Pain • Cough • Rash	• Anemia, kidney problems which may cause tiredness, or may require blood transfusion or dialysis • Blood clot • Abnormal heartbeat • Diarrhea, nausea, vomiting, abdominal pain • Swelling of arms, legs • Allergic reaction, which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat and difficulty speaking • Infection, especially when white blood count is low • Bruising, bleeding • Loss of appetite • Numbness, tingling or pain of the arms and legs • Difficulty emptying the bladder, which may require catheterization during therapy, and in rare cases catheterization may be	• Heart stops beating • Vision changes which may include changes in the pupils of the eye • Death • Swelling of the spinal cord • Muscle weakness • Brain damage which may cause headache, seizure, blindness (reversible posterior leukoencephalopathy syndrome)

	required after discharge from the hospital • Itching, hives • Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles • High blood pressure which may cause dizziness, blurred vision • Low blood pressure which may cause feeling faint • Back pain	

Possible Risks of Sargramostim (GM-CSF)

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
• Headache • Bone pain • Joint pain • Muscles aches • Rash • Fever • Chills • Itching	• Stomach pain • Weakness • Nausea • Reaction to injection site • Lack of appetite • Weight gain	• Reaction during or following injection of drug which may cause fever, chills, rash, low blood pressure, fast heartbeat, shortness of breath and swelling of the face or throat • Vomiting • Diarrhea • Abnormally fast heartbeat • Fluid around the heart which may cause shortness of breath and/or chest pain • Inflammation of veins which may cause pain and swelling • In high doses: fluid in the organs which may cause low blood pressure, shortness of breath and/or swelling of ankles

Possible Risks Associated with Stem Cells

- ANY TIME BEFORE STEM CELL INFUSION: The freezer where PBSC are stored could malfunction, the container holding them could break and the stem cells could be damaged so they could not be used. This is expected to be an extremely rare event. However, if this occurs, another stem cell collection may be attempted or the back-up stem cells (if available) may be used if they were not damaged.

- If stem cells need to be shipped from one location to another, they could be lost or damaged during shipping such that they could not be used. This is expected to be an extremely rare event. If this occurs, another stem cell collection may be attempted or the back-up stem cells, if available, may be used.

- Some patients may need extra fluids given into the vein after getting their stem cells. This is to protect the kidneys from the red blood cells mixed in with the stem cells.

Likely (happens to 21-100 children out of every 100 children)	**Less Likely** (happens to 5-20 children out of every 100 children)	**Rare** (happens to < 5 children out of every 100 children)
	• Fever and chills	• Allergic reaction. Can cause difficulty breathing and low blood pressure. • High blood pressure • Infection • Infusion of tumor cells. Tumor cells may still be present in the harvested stem cells and they could regrow after stem cells are infused. • Cough • Chest Tightness • Flushing • Nausea and/or vomiting • Rash • Irregular Heart Beat

Herbs and Supplements

Some drugs or supplements may interact with your treatment plan. Talk to your doctor, pharmacist, or study team before starting any new prescription drugs, over-the-counter drugs, herbals, or supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

Possible Risks to Unborn Child

Patients who agree to participate in this study should not become pregnant while on this study. Patients and their sexual partners should avoid sex and / or use two effective methods of contraception that are medically appropriate based on your personal doctor's recommendation at that time and should be used for as long as you participate in this study. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Risks to the Caregiver(s) of the Patient Getting ^{131}I-MIBG Treatment

Caregivers (example: parent, other family member, guardian, friend, partner) will be exposed to radiation while you are being treated with ^{131}I-MIBG. Caregivers who could possibly become pregnant during this time need to avoid contact with the patient because the radiation exposure may increase the unborn baby's risk of developing cancer or other health problems.

If your caregiver is pregnant, then special precautions should be used to avoid contact with you during and for 4 weeks after getting ^{131}I-MIBG treatment. Should your caregiver or your caregiver's sexual partner be found to have been pregnant while you were getting ^{131}I-MIBG treatment and did not know it at the time, please contact your doctor immediately.

Possible Long-Term Risks of This Treatment

- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of puberty
- Increased risk of a second cancer (such as leukemia) different from the kind of cancer you have now.

- Patients who have more than one ^{131}I-MIBG treatment will have greater doses of radiation to the normal organs than those patients having one treatment. It is possible that there may be later damage to the normal function of the liver or other organs.

Possible Risks from Having Blood Drawn
The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk. You will be asked to sign a separate consent for any procedure that needs sedation.

Possible Risks from Germline Genetic Testing
If you agree to participation in the optional test looking at immune system cells in your tumor and immune response, a small amount of your blood will be collected. Researchers will use the blood sent with your tumor for determining the genetic make-up of your normal cells (known as germline testing) that is used as a baseline to compare to the genetic make-up of your tumor. This helps the laboratory in identifying the genetic changes they may see in your tumor tissue.

The germline genetic testing is for research purposes only and is performed on de-identified samples, and so the information can't be linked back to your child. Hence, the results will not be sent to you or your physician.

Unknown Risks
This treatment combination may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines, or ^{131}I-MIBG without dinutuximab
- Treatment with other experimental agents that may be available
- No neuroblastoma therapy at this time, with care to help you feel more comfortable

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA), Health Canada, or European regulatory agency(ies) involved in keeping research safe for people.
- Jubilant Radiopharma (supplier of ^{131}I-MIBG)
- United Therapeutics Corporation (manufacturer of dinutuximab)

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

The costs of vorinostat will be billed to your/your child's insurance company. If your insurance company will not pay for the vorinostat you/your child may not continue on study. Your physician will speak with you about other options that are available for future treatment.

The ^{131}I-MIBG will be supplied by Jubilant Radiopharma. The cost of ^{131}I-MIBG and its administration costs will be billed to your/your child's insurance company.

Dinutuximab will be provided free of charge by United Therapeutics, Inc while you are taking part in this study. United Therapeutics does not cover the cost of getting dinutuximab ready and giving it to you so your insurance company may have to pay for this.

GM-CSF is a commercially available agent. You will pay for the amount of drug needed to complete this study. This cost is normally covered by your insurance company.

The correlative biology studies will be done at no cost to you. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, car fare, travel to and from the hospital for treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not be covered by your insurance company. Please ask about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's website at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you tell your study doctor, _____ *[investigator's name(s)]* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?
Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of you legal rights to seek payment by signing this form.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may visit the NCI Web sites at http://cancer.gov/
For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.
You will get a copy of this consent form. If you want more information about this study, ask your doctor.

CONSENT FOR OPTIONAL RESEARCH STUDIES

The following tests are optional for all patients in the study. You may still participate in the study even if you do not agree to these tests.

1. <u>Using extra blood to look for proteins and genetic changes in your cells.</u>

Initial next to YES if you agree to let researchers use some of the blood (less than ¼ teaspoon) already drawn for one of the required studies to look at certain immune cell genes and how changes in these genes might affect how you respond to the treatment. No extra blood needs to be drawn from you to do this optional test. The results of this test will be confidential and not made available to you or your treating physician.

Initial next to NO if you do not want researchers to use some of the blood already drawn for a required test to look at immune cell genes.

_____Yes _____No

Initial next to YES if you agree to let researchers take an extra half teaspoon (2.5 mL) of blood 9 different times to look for certain proteins and changes in these proteins that might affect your response to treatment with vorinostat, ^{131}I-MIBG, and dinutuximab. This blood would be drawn at a time when blood was being drawn for clinical purposes. The results of this test will be confidential and not made available to you or your treating physician.

Initial next to NO if you do not want researchers to take extra blood above what is needed for clinical purposes.

_____Yes _____No

2. <u>Evaluate tumor tissue for immune system cells that surround and invade your tumor and the genes that cause an immune response, and if possible also comparine immune system cells in tumor samples from before and after treatment with vorinostat, ^{131}I-MIBG and dinutuximab.</u>

Initial next to YES if you agree to let researchers collect 3 mL (about ½ teaspoon) of blood to be sent together with any leftover tumor (if available from an earlier procedure) to a laboratory so researchers can learn more about the immune system cells that surround and invade your tumor and genes that cause an immune response. Looking at the immune response genes involves comparing your normal genetic information gotten from the blood sample (called germline) to the genetic information of your tumor and determining what is different between the two. The results of these tests will be confidential and not made available to you or your treating doctor.

Initial next to NO if you do not want extra blood drawn and leftover tumor from an earlier procedure, if it is available, to be sent to a research laboratory.

_____Yes _____No

Initial next to YES if you agree to have leftover tumor sent to the research lab if a biopsy is done in the future for clinical care and this happens after finishing this protocol therapy and before starting the next treatment for your tumor. The purpose of this part of the test is to see if the ^{131}I-MIBG had any effect on the immune cells that surround and invade your tumor.

Initial next to NO if you do not want leftover tumor from a future procedure to be sent to a research laboratory.

_____Yes _____No

3. <u>Storage of left over specimens obtained on this study for future use in research</u>

The NANT Biology Study (NANT2004-05) provides a way to allow for banking of leftover specimens from this study for future research to answer questions about vorinostat, ^{131}I-MIBG, and dinutuximab treatment, neuroblastoma or other childhood cancers.

Initial next to YES if you agree to storage of any specimens leftover from this study for future research.

Initial next to NO if you do not want leftover specimens from this study stored for future research

_____Yes _____No

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____
Print Patient Name

_____ _____/_____/_____
Print Name of Parent or Guardian Date

_____ _____/_____/_____
Signature of Parent or Guardian Date

_____ _____/_____/_____
Signature of Patient (If > 7 years old) Date

_____ _____/_____/_____
Signature of Physician or Date
Responsible Investigator

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator Date

Consent Addendum I: Tests That Will Be Done On This Study

Observation	Before Entry	Days 0 to Day 56 of Course 1 & 2		End of treatment
		All other days during course	During dinutuximab infusions only Day 8-11 and Day 29-32	
Physical Exam	X	Weekly	Daily	X
Blood Tests	X	Twice weekly for blood counts, Weekly for other tests	Daily	X
Urine tests	X			X
Pregnancy test	X			X
Heart tests [echocardiogram and electrocardiogram (EKG)]	X	EKG once between Days 4-8		X
MIBG scan after MIBG treatment (no extra MIBG is given to you to do this scan)		After you get out of your radiation isolation room		
Blood correlative studies (Required)		Course 1 only 3 times	Course 1 only 4 times	Course 1 only 1 time
Blood for correlative studies (Optional)		Course 1 only 4 times	Course 1 only 4 times	
Blood & Tumor sample sent for research (optional)	Blood & Tumor sample can be sent any time during the study			
Disease Evaluation Tests[#]				
Bone marrow aspirate/biopsy	X	Day 43 – 57 of Course 1		X
CT, MRI and/or MIBG scans	X			X

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study N04-05 consent form for more information.

Consent Addendum II
Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

16.0 SAMPLE INFORMED ASSENT
There are separate sample assent documents for Part A and B.

16.1 Part A

NANT 2017-01: A PHASE I STUDY OF ^{131}I-MIBG WITH DINUTUXIMAB +/- VORINOSTAT FOR RELAPSED/REFRACTORY NEUROBLASTOMA

FOR PATIENTS ON PART A

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. Dr. _____ is doing a research study about the treatment of neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma with two medicines called **MIBG** and **dinutuximab** to see what effects (both good and bad) this medicine has on patients and their cancer. The doctors think that giving MIBG with dinutuximab may kill more neuroblastoma cancer cells. They also want to find out what the side effects are when MIBG is given together with dinutuximab.

3. **If you agree to be in this study this is what will happen:**

   You can get up to two courses of this therapy as long as your tumor doesn't get worse and you don't have too bad of side effects.

   ^{131}I-MIBG

   ^{131}I-MIBG is a radioactive medicine given into an IV over 2 hours on the first day. Because of this radiation treatment you will need to stay in your hospital room until you go home. This is usually about 5 days. Your parents cannot sleep in your room but they will be able to stay just outside your room and you will be able to see and talk to them anytime you want. They can visit inside your room for a short time each day.

   Because not all hospitals can give the ^{131}I-MIBG, you might have to go with your parents to another hospital to get the MIBG part. Your doctor will talk with you and your parents about the different hospitals that can give the MIBG, and which one will be the best for you.

   You may need to have a **urinary catheter** placed to help drain your urine while you are getting the ^{131}I-MIBG treatment. A soft tube will be put inside your urethra (the hole where urine comes out of our bodies), and up into your bladder (the place where urine waits inside our bodies until we go to the bathroom). Because the ^{131}I-MIBG will be in your urine, and can cause damage to your bladder, the catheter is necessary to prevent this from happening by keeping your bladder completely empty all the time.

Stem Cells

^{131}I-MIBG is a medicine that can lower the numbers of your normal blood cells. Stem cells make all the normal blood cells your body needs to be healthy. This includes white blood cells that fight infection, platelets that stop you from bleeding, and red blood cells that carry oxygen to your body. When ^{131}I-MIBG is given at higher doses it can damage stem cells so they don't make enough of the normal blood cells we need to live. Your stem cells which were collected during your initial visit will be given back to you like a blood transfusion after the ^{131}I-MIBG and other treatments are finished. This is called Stem Cell Infusion or Stem Cell Rescue. Two weeks after getting ^{131}I-MIBG, we will give the stem cells back through your central line either in the hospital or in the clinic. It is a lot like getting a platelet transfusion – the stem cells look like watery blood.

Dinutuximab

You will get dinutuximab in your IV once a day for 4 straight days on Days 8-11 and Days 29-32. The dinutuximab is given over 10-20 hours. You will be in the hospital when dinutuximab is given.

Sargramostim/GM-CSF

The GM-CSF helps the dinutuximab work better and also helps the blood cells grow back faster after treatment. GM-CSF is given through your IV or as an injection (shot) from a very small needle into your leg that your parents will learn how to give you. It is given one time a day. You will get GM-CSF during the 4 days you are receiving dinutuximab and then for 6 days afterwards (total of 10 days with each dinutuximab; Days 8-17 and 29-38). You may also get GM-CSF if your blood cells are low after getting ^{131}I-MIBG, or your doctor may choose to give you a different medicine such as G-CSF or pegfilgrastim. If you are given GM-CSF because your blood cells are low it will be continued until your blood cells have started to grow back. We will know when the blood counts are high enough to stop the GM-CSF by doing a blood test.

Coming to See the Doctors:

During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;

- Blood tests (we will do this twice each week to start with, and then less often)
- MRI, CT, and MIBG Scans (special pictures of your tumor)
- Bone marrow test (to look for tumor in your bone marrow)
- Tests for your heart and your kidneys
- Check your urine
- Feel your belly, look into your eyes and ears, and listen to your heart and lungs.
- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.
- You may have to come to the clinic to have blood and platelet transfusions when the blood counts are low or stay in the hospital if you have a fever with low blood counts.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.

4. **When you are in a research study, sometimes good things and bad things can happen.**
Sometimes things happen to kids in research studies that may make them feel bad. These are called "risks". Some of the risks of this study are:
    - You may feel sick to your stomach and you may throw up.
    - You may feel tired.
    - You may have a bad appetite.

- You may have pain or your body may hold onto too much fluid when you are getting the dinutuximab.
- You might have a fever and maybe an infection where you will need to be in the hospital to get medicines to treat the infection.
- You may feel tired and weak and need a blood transfusion or you may get bruises or have bleeding (most often a nosebleed) and need a platelet transfusion.
- During ^{131}I-MIBG**,** the urinary catheter may be uncomfortable, and some people feel embarrassed having it – but you will only need it for a few days. It may also be hard to be in a room for a long time by yourself until the radiation levels are low enough that it is safe for your parents and everyone else to be around you all the time.
- The treatments may not work, and your tumor may grow, or it might come back again after the treatment has finished. If this happens we will try other ways to stop the tumor from growing.
- You could get a different kind of cancer, this doesn't happen often, but can happen years later.
- It is possible that you could die from the treatment or cancer.
- Not all of these things may happen to you. Or things may happen that the doctors don't know about yet.

5. Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:
    - This treatment might make your neuroblastoma tumor stay the same size or get smaller for some time.
    - We hope to learn more about this new treatment which could help other children with neuroblastoma

6. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

7. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" <u>you</u> can still decide not to do this.

8. Being in this study is up to you. You do not have to be in this study if you don't want to. You may stop being in this study at any time but there are two times where you would be at more risk for being sick or having side effects or being dangerous to other people if you stopped being in the study.
    1) If you got ^{131}I-MIBG and left the special room before the doctors said it was ok to leave, then you would still be radioactive and this would be dangerous to everyone who was around you since you would give them radiation from your body.
    2) If you decided to stop treatment after getting ^{131}I-MIBG but before you were given your stem cells back, the high dose of ^{131}I-MIBG could kill your blood cells so they would not grow back on their own without getting back your stem cells. In this case you would not be able to make your own blood cells and could have bad infections or bleeding, and you could die from not having enough normal blood cells.

9. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time you see me.
    - Study doctor's phone number: _____

10. Special Study Tests:

You will have blood tests done to measure changes in the number and function of certain cells of your immune system, as well as to measure levels of certain proteins that cause inflammation in the body. You will also have blood tests done to look for antibodies that attach to the dinutuximab and make it so it can't attack your neuroblastoma. These blood tests will be done 7 times over the first course of treatment. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. These extra tests are done for research only so the results won't be told to your doctor or to you.

#1: Check YES if it is ok for us to take 1/2 teaspoon of extra blood at different 8 times to learn more about how the body responds to this treatment. There will be no extra blood draw. We will draw this blood at the same time blood is being drawn to take care of you.

Check NO if it is not ok for us to take this extra blood.

_____ YES, you can draw the extra blood

_____ NO, I don't want to have the extra blood drawn

#2: Check YES if it is ok to use a little bit of blood (less than half a teaspoon) that was drawn to do another test on this study to look at the genes in charge of how your immune system responds to this treatment. No extra blood draws are needed to do this test.

_____ YES, you can do this test.

_____ NO, I don't want this test done.

#3 Check YES if it is OK to let us look at some leftover tumor collected from a surgery you had before as part of your treatment to learn more about the immune cells that are inside your tumor and outside surrounding it, and the genes that are in charge of your body's immune response. In order to do this test, researchers also need to collect a small about of blood (half teaspoon) that would be sent to the laboratory at the same time as the tumor sample.

_____ YES, you can use my tumor samples and draw the extra blood

_____ NO, I don't want my tumor samples to be used or have extra blood drawn for this test.

#4 Check YES if you agree to let researchers have a tumor sample if you have tumor surgery sometime after you finish treatment with MIBG on this study. Researchers want to see if the MIBG had any effect on the immune cells that are around and invade your tumor.

_____ YES, you can use my tumor samples collected in the future

_____ NO, I don't want my tumor samples to be used

Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Patient: _____

_____ Yes, I want to be in the study.

_____No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or Responsible Investigator **Date**

16.2 Part B

NANT 2017-01: A PHASE I STUDY OF ^{131}I-MIBG WITH DINUTUXIMAB +/- VORINOSTAT FOR RELAPSED/REFRACTORY NEUROBLASTOMA

FOR PATIENTS ON PART B

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. Dr. _____ is doing a research study about the treatment of neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma with three medicines called **vorinostat**, **^{131}I-MIBG**, and **dinutuximab** to see what effects (both good and bad) this medicine has on patients and their cancer. The doctors think that giving MIBG with dinutuximab and vorinostat may kill more neuroblastoma cancer cells. They also want to find out what the side effects are when MIBG is given together with dinutuximab and vorinostat.

3. **If you agree to be in this study this is what will happen:**

   You can get up to two courses of this therapy as long as your tumor doesn't get worse and you don't have too bad of side effects.

   Vorinostat
   You will take vorinostat by mouth or by a tube inserted through the nose or stomach once a day for 14 days. If you vomit within 15 minutes of taking the vorinostat you should retake the dose. If you vomit again with the second dose you should not try to take the dose again. If you vomit more than 15 minutes after taking the vorinostat you should not try to retake the dose.

   ^{131}I-MIBG
   ^{131}I-MIBG is a radioactive medicine given into an IV over 2 hours on the first day. Because of this radiation treatment you will need to stay in your hospital room until you go home. This is usually about 5 days. Your parents cannot sleep in your room but they will be able to stay just outside your room and you will be able to see and talk to them anytime you want. They can visit inside your room for a short time each day.

   Because not all hospitals can give the ^{131}I-MIBG, you might have to go with your parents to another hospital to get the ^{131}I-MIBG part. Your doctor will talk with you and your parents about the different hospitals that can give the ^{131}I-MIBG, and which one will be the best for you.

   You may need to have a **urinary catheter** placed to help drain your urine while you are getting the ^{131}I-MIBG treatment. A soft tube will be put inside your urethra (the hole where urine comes out of our bodies), and up into your bladder (the place where urine waits inside our bodies until we go to the bathroom). Because the ^{131}I-MIBG will be in your urine, and can cause damage to your bladder, the catheter is necessary to prevent this from happening by keeping your bladder completely empty all the time.

Dinutuximab
You will get dinutuximab in your IV once a day for 4 straight days on Days 8-11 and Days 29-32. The dinutuximab is given over 10-20 hours. You will be in the hospital when dinutuximab is given.

Sargramostim/GM-CSF
The GM-CSF helps the dinutuximab work better and also helps the blood cells grow back faster after treatment. GM-CSF is given through your IV or as an injection (shot) from a very small needle into your leg that your parents will learn how to give you. It is given one time a day. You will get GM-CSF during the 4 days you are receiving dinutuximab and then for 6 days afterwards (total of 10 days with each dinutuximab; Days 8-17 and 29-38). You may also get GM-CSF if your blood cells are low after getting ^{131}I-MIBG, or your doctor may choose to give you a different medicine such as G-CSF or pegfilgrastim. If you are given GM-CSF because your blood cells are low it will be continued until your blood cells have started to grow back. We will know when the blood counts are high enough to stop the GM-CSF by doing a blood test.

Stem Cells
^{131}I-MIBG is a medicine that can lower the numbers of your normal blood cells. Stem cells make all the normal blood cells your body needs to be healthy. This includes white blood cells that fight infection, platelets that stop you from bleeding, and red blood cells that carry oxygen to your body. When ^{131}I-MIBG is given at higher doses it can damage stem cells so they don't make enough of the normal blood cells we need to live. Your stem cells which were collected from you from your initial visit will be given back to you like a blood transfusion after the ^{131}I-MIBG and other treatments are finished. This is called Stem Cell Infusion or Stem Cell Rescue. Two weeks after getting ^{131}I-MIBG, we will give the stem cells back through your central line either in the hospital or in the clinic. It is a lot like getting a platelet transfusion – the stem cells look like watery blood.

Coming to See the Doctors:
During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;

- Blood tests (we will do this twice each week to start with, and then less often)
- MRI, CT, and MIBG Scans (special pictures of your tumor)
- Bone marrow test (to look for tumor in your bone marrow)
- Tests for your heart and your kidneys
- Check your urine
- Feel your belly, look into your eyes and ears, and listen to your heart and lungs.
- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.
- You may have to come to the clinic to have blood and platelet transfusions when the blood counts are low or stay in the hospital if you have a fever with low blood counts.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.

4. **When you are in a research study, sometimes good things and bad things can happen.**
Sometimes things happen to kids in research studies that may make them feel bad. These are called "risks". Some of the risks of this study are:
    - You may feel sick to your stomach and you may throw up.
    - You may feel tired.
    - You may have a bad appetite.
    - You may have pain or your body may hold onto too much fluid when you are getting the dinutuximab.

- You might have a fever and maybe an infection where you will need to be in the hospital to get medicines to treat the infection.
- You may feel tired and weak and need a blood transfusion or you may get bruises or have bleeding (most often a nosebleed) and need a platelet transfusion.
- During ^{131}I-MIBG**,** the urinary catheter may be uncomfortable, and some people feel embarrassed having it – but you will only need it for a few days. It may also be hard to be in a room for a long time by yourself until the radiation levels are low enough that it is safe for your parents and everyone else to be around you all the time.
- The treatments may not work, and your tumor may grow, or it might come back again after the treatment has finished. If this happens we will try other ways to stop the tumor from growing.
- You could get a different kind of cancer, this doesn't happen often, but can happen years later.
- It is possible that you could die from the treatment or cancer.
- Not all of these things may happen to you. Or things may happen that the doctors don't know about yet.

5. Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:
    a. This treatment might make your neuroblastoma tumor stay the same size or get smaller for some time.
    b. We hope to learn more about this new treatment which could help other children with neuroblastoma

6. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

7. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" <u>you</u> can still decide not to do this.

8. Being in this study is up to you. You do not have to be in this study if you don't want to. You may stop being in this study at any time but there are two times where you would be at more risk for being sick or having side effects or being dangerous to other people if you stopped being in the study.
    1) If you got ^{131}I-MIBG and left the special room before the doctors said it was ok to leave, then you would still be radioactive and this would be dangerous to everyone who was around you since you would give them radiation from your body.
    2) If you decided to stop treatment after getting ^{131}I-MIBG but before you were given your stem cells back, the high dose of ^{131}I-MIBG could kill your blood cells so they would not grow back on their own without getting back your stem cells. In this case you would not be able to make your own blood cells and could have bad infections or bleeding, and you could die from not having enough normal blood cells.

9. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time you see me.
    - Study doctor's phone number: _____

10. <u>Special Study Tests:</u>

You will have blood tests done to measure changes in the number and function of certain cells of your immune system, as well as to measure levels of certain proteins that cause inflammation in the body. You will also have blood tests done to look for antibodies that attach to the dinutuximab and make it so it can't attack your neuroblastoma. These blood tests will be done 8 times over the first course of treatment. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. These extra tests are done for research only so the results won't be told to your doctor or to you.

#1: Check YES if it is ok for us to take 1/2 teaspoon of extra blood at different 8 times to learn more about how the body responds to this treatment. We will draw this blood at the same time blood is being drawn to take care of you.

Check NO if it is not ok for us to take this extra blood.

_____ YES, you can draw the extra blood

_____ NO, I don't want to have the extra blood drawn

#2: Check YES if it is ok to use a little bit of blood (less than half a teaspoon) that was drawn to do another test on this study to look at the genes in charge of how your immune system responds to this treatment. No extra blood draws are needed to do this test.

_____ YES, you can do this test.

_____ NO, I don't want this test done.

#3 Check YES if it is OK to let us look at some leftover tumor collected from a surgery you had before as part of your treatment to learn more about the immune cells that are inside your tumor and outside surrounding it, and the genes that are in charge of your body's immune response. In order to do this test, researchers also need to collect a small about of blood (half teaspoon) that would be sent to the laboratory at the same time as the tumor sample.

_____ YES, you can use my tumor samples and draw the extra blood

_____ NO, I don't want my tumor samples to be used or have extra blood drawn for this test.

#4 Check YES if you agree to let researchers have a tumor sample if you have tumor surgery sometime after you finish treatment with MIBG on this study. Researchers want to see if the MIBG had any effect on the immune cells that are around and invade your tumor.

_____ YES, you can use my tumor samples collected in the future

_____ NO, I don't want my tumor samples to be used

Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Patient: _____

_____ Yes, I want to be in the study.

_____No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or Responsible Investigator **Date**

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		**Karnofsky**		**Lansky***	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II: SUMMARY FOR CORRELATIVE STUDIES

Summary of Research Blood Samples: Blood volumes below are maximum values. For patients with a weight below the minimum required to tolerate all blood draws requested for correlative studies, please consult with study chair to determine prioritization of samples. The correlative studies are to be drawn only during the first course of therapy with exception of the N04-05 specimens. Please refer to the N04-05 for complete collection requirements.

When immune and cytokine profiling (section 8.2) and NB5 (TLDA assay) (N04-05) samples coincide, the priority is to collect the immune and cytokine profiling first and if maximum blood volume allowable for research purposes has not been surpassed then the NB5 (TLDA) sample may be collected (refer to protocol section 8.3). Patients can submit only bone marrow for NB5 (TLDA) if blood volumes for research do not allow for blood submission.

This table is a summary overview of correlative studies. Refer to specific protocol section for all details regarding specimen collection timing, processing, labeling and shipping.

NOTE: There are separate tables for Part A and Part B.

Part A

Phase of Therapy COURSE 1 ONLY	Required Study Specimens			Optional Study Specimens		
	Immune Profiling Section 8.1.2.1	Cytokine Profiling Section 8.1.2.2 (Refer to Appendix VI) and HACA/ADA levels Section 8.2	NB5 assay by TLDA Refer to NANT 2004-05	DNA for future gene expression (Section 8.6)	RNA Gene Expression Section 8.5	Tumor Microenvironment Section 8.8
	Fresh whole blood	Frozen plasma	Fresh whole blood and BM aspirate	Fresh whole blood	Frozen whole blood	Soft tissue tumor and fresh whole blood
	Green top tube	CPT tube	Refer to NANT 2004-05	Refer to immune profiling	PAXgene tube	3mL peripheral blood in purple top (EDTA) tube and FFPE block or tissue scrolls/slides
Shipping	Overnight (Section 8.3)	Batch ship Course #1 (Section 8.3)			Batch ship Course #1 (Section 8.3)	Overnight any time course #1 (Section 8.8)
Screening			X			Submit tumor tissue if available at following time points: A. Most recent biopsy performed before study registration and 3mL fresh blood B. Any biopsy done post completion of N17-01 therapy and subsequent to start of any other therapy.
After study registration or Day 1#,*	5 mL	8 mL	ALL COURSES	X		
Day 1#,*					2.5 mL	
Day 8^,*	5 mL	8 mL (Cytokine only)		X	2.5 mL	
Day 11$		8 mL (HACA/ADA only)			2.5 mL	
Day 15*,& +/- 2 days	5 mL	8 mL (Cytokine only)		X	2.5 mL	
Day 29^,*	5 mL	8 mL		X	2.5 mL	
Day 32$		8 mL (HACA/ADA only)			2.5 mL	
Day 36					2.5 mL	
End of Course*	5 mL	8 mL	X	X	2.5 mL	

Specimen may be drawn earlier than day 1if study registration has been completed. If performed on Day 1, please draw specimen prior to ^{131}I-MIBG infusion.
^To be drawn prior to dinutuximab infusion on day 8 and day 29; delay accordingly if start of dinutuximab is delayed.
$ To be drawn prior to dinutuximab infusion on day 11 and day 32; delay accordingly if start of dinutuximab is delayed.
* Specimens collected on these days will undergo PBMC freezing.
& Must be drawn prior to stem cell infusion.

Part B

Phase of Therapy COURSE 1 ONLY	Required Study Specimens			Optional Study Specimens		
	Immune Profiling Section 8.1.2.1	Cytokine Profiling Section 8.1.2.2 (Refer to Appendix VI) and HACA/ADA levels Section 8.2	NB5 assay by TLDA Refer to NANT 2004-05	DNA for future gene expression (Section 8.6)	RNA Gene Expression Section 8.5	Tumor Microenvironment Section 8.8
	Fresh whole blood	Frozen plasma	Fresh whole blood and BM aspirate	Fresh whole blood	Frozen whole blood	Soft tissue tumor and fresh whole blood
	Green top tube	CPT tube	Refer to NANT 2004-05	Refer to immune profiling	PAXgene RNA tube	3mL peripheral blood in purple top (EDTA) tube and FFPE block or tissue scrolls/slides
Shipping	Overnight (Section 8.3)	Batch ship Course #1 (Section 8.3)			Batch ship Course #1 (Section 8.3)	Overnight any time course #1 (Section 8.8)
Screening			X			Submit tumor tissue if available at following time points: A. Most recent biopsy performed before study registration and 3mL fresh blood B. Any biopsy done post completion of N17-01 therapy and subsequent to start of any other therapy.
After study registration or Day 0#,*	5 mL	8 mL	ALL COURSES	X	2.5 mL	
Day 1@,*	5 mL	8 mL (Cytokine only)		X	2.5 mL	
Day 8^,*	5 mL	8 mL (Cytokine only)		X	2.5 mL	
Day 11$		8 mL (HACA/ADA only)			2.5 mL	
Day 15*,& +/- 1 day	5 mL	8 mL (Cytokine only)		X	2.5 mL	
Day 29^,*	5 mL	8 mL		X	2.5 mL	
Day 32$		8 mL (HACA/ADA only)			2.5 mL	
Day 36					2.5 mL	
End of Course*	5 mL	8 mL	X	X	2.5 mL	

Specimen may be drawn earlier than day 0 if study registration has been completed. If performed on Day 0, please draw specimen prior to first dose of vorinostat.

^ To be drawn prior to dinutuximab infusion on day 8 and day 29; delay accordingly if start of dinutuximab is delayed.

$ To be drawn prior to dinutuximab infusion on day 11 and day 32; delay accordingly if start of dinutuximab is delayed.

* Specimens collected on these days will undergo PBMC freezing.

& Must be drawn prior to stem cell infusion.

@ Must be drawn prior to MIBG infusion.

APPENDIX III: ADJUSTED BODY WEIGHT CALCULATION FOR STEM CELL DOSING

For patients whose actual body weight exceeds ideal body weight (IBW) by more than 20%, the dose of stem cells may be based on adjusted body weight (ABW) rather than actual body weight.

IBW Formulas:
1-17 years: height is in cm, weight is in kg
IBW = (height^2 x 1.65)/1000

1-17 years and 5 feet or taller:
IBW in kg (male) = 39 + (2.27 x height in inches over 5 feet)
IBW in kg (female) = 45.5 + (2.27 x height in inches over 5 feet)

18 years and older:
IBW in kg (male) = 50 + (2.3 x height in inches over 5 feet)
IBW in kg (female) = 45.5 + (2.3 x height in inches over 5 feet)

ABW is determined:
ABW=IBW + 0.4 x (actual BW-IBW)

(Reference: Bone Marrow Transplant. 2007; 40(7):665-9)

APPENDIX IV: COMPOUNDS THAT INTERFERE WITH ^{131}I-MIBG METABOLISM AND UPTAKE

1. Drugs Known To Reduce Uptake of ^{131}I-MIBG

Drug	Mechanism
Sympathomimetics# Phenylephrine Phenylpropanolamine Pseudoephedrine, ephedrine	Depletion of storage vesicle contents. These drugs occur in numerous non-prescription decongestants and diet aids. Their use should be excluded.
Antihypertensive / cardiovascular Labetalol Reserpine	Inhibition of catecholamine uptake. Depletion of storage vesicle contents. Depletion of storage vesicle contents. Inhibition of vesicle active transport.
Calcium-channel blockers Amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine , nisoldipine, verapamil	Uncertain (also enhances retention of previously stored norepinephrine and MIBG by blocking Ca++ mediated release from vesicles)
Tricyclic antidepressants Amitriptyline, amoxapine, desipramine , doxepin, imipramine, nortriptyline , protriptyline, trimipramine	Inhibition of catecholamine uptake
Cocaine	Inhibition of catecholamine uptake

#: Systemic use

2. Drugs Expected To Reduce Uptake of ^{131}I-MIBG

Drug	Mechanism
Sympathomimetics Amphetamine and related compounds **Beta-sympathomimetics#** Dobutamine, Dopamine, Metaraminol	Depletion of storage vesicle contents.
Atypical antidepressants Maprotiline Trazodone	Inhibition of catecholamine uptake.
Antipsychotics (major tranquilizers) Phenothiazines* Thioxanthines Butyrophenones	Inhibition of catecholamine uptake.
Antihypertensive / cardiovascular Adrenergic neuron blockers Guanethidine, guanadrel, bethanidine, debrisoquine, bretylium, reserpine, metyrosine	Depletion of storage vesicle contents. Competition for transport into vesicles.

#: Systemic use. Effect unlikely with aerosol administration

*Occasionally used as an antiemetic/antipruritic agent

APPENDIX V: QUALITY CONTROL FOR FREE IODINE IN ^{131}I-MIBG (DETECTION OF RADIOLYTIC DECOMPOSITION)

NOTE: As of 10/20/21, radiochemical purity testing at clinical sites following receipt of ^{131}I-MIBG from Jubilant Radiopharma is no longer required. Sites are still to check for discoloration and particulate matters prior to product administration to the patient. Additionally, if a "Temperature Alarm" is detected on the temperature monitor provided in the ^{131}I-MIBG shipment, sites are NOT to use the product and should store the vial in the lead pot and call JRP Customer Service immediately for further instructions.

Should clinical sites still wish to perform radiochemical purity testing, the below is a suggested technique:

Radiopharmaceutical	^{131}I-MIBG from Jubilant Radiopharma
Preparation	Receipt of therapeutic ^{131}I-MIBG from supplier
Materials	Waters Accell Plus CM Sep-Pac Ethanol Sterile water 10 ml test tubes
Instrumentation	Capintec well counter Calculator

Procedure

1. Using a Waters Accell Plus CM Sep-Pac cartridge, wet the Sep-Pac with 5 ml ethanol. the long tip of the Sep-Pac must be connected to the flushes
2. Rinse with 5 ml sterile water
3. Add one drop to 1/20 ml mibg to Sep-Pac. Dilute to around 0.5 uCi
4. Flush Sep-Pac with 5 ml sterile water into a 10 ml test tube (flush tube)
5. Place cartridge into a second 10 ml test tube (A)
6. Place the cartridge tube into a well counter and record (A), set counter on 131-I
7. Count both tubes (A and flush) in the well counter, add counts together and record (B), set counter on 131-I
8. A/A+B x 100 = % tagged. Must be greater than 95% for Jubilant Radiopharma product- compare to TLC

Comments

Procedure must be performed within 24 hours of receipt of dose from supplier. Results of bound iodine should be greater than 95% for Jubilant Radiopharma product. Record results on worksheet. Contact physicians if there is an aberrant or low result.

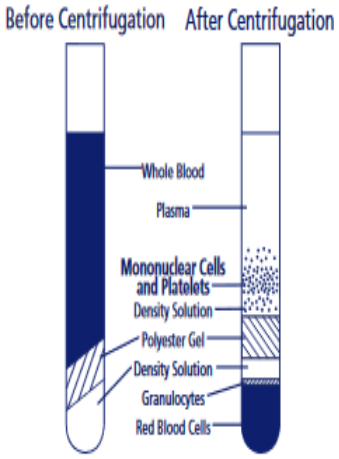
All centers administering ^{131}I-MIBG therapy must perform an assay for radiolytic decomposition; the above is a suggested technique. Other techniques may be used provided they meet institutional radiopharmaceutical guidelines.

APPENDIX VI: Isolation and Storage of Plasma and Peripheral Blood Mononuclear Cells (PBMCs)

Purpose

To isolate Plasma and Peripheral Blood Mononuclear Cells (PBMCs) for long-term storage. This protocol applies to blood samples that have been collected in Sodium Heparin Cell Preparation Tubes (CPT).

Equipment and Material Required



- Blood Samples in 8mL Sodium Heparin CPT tube
- Centrifuge (capable of centrifugation at 3,000 x rcf)
- Pipette and Pipette Tips
- 1.0 mL and 1.8 mL cryovials (capable of being stored at -80˚C or -150˚C)
- Extra collection tubes (to counterbalance during centrifugation)
- PBS with 2% FBS (room temperature)
- Freeze Media 1 and Freeze Media 2 (room temperature)

Note

- After collection, store tube upright at room temperature until centrifugation.
- Blood samples should be centrifuged within 2 hours of blood collection.

Procedure

1. Gently invert tubes 5 times before placing in the centrifuge.
2. Counter balance extra collection tubes for centrifugation.
3. Centrifuge samples in a horizontal (swing bucket) rotor for 15 minutes at 1,600 rcf at room temperature.
4. Remove blood collection tubes from centrifuge and ensure that tubes are kept in the upright position.
5. Using a sterile serological pipette, draw off (transfer) the upper layer (plasma) into a new 15mL conical tube labeled “plasma”. Leave the mononuclear layer undisturbed (see image above).
6. Using a sterile pipette, transfer everything remaining above the polyester gel layer (plasma, mononuclear cells, platelets, and density solution) into a new 15 mL conical tube labeled “PBMCs.”
7. Discard blood collection tubes in the appropriate biohazard waste container.

Additional Plasma Processing (after step 5)

8. Counter balance extra 15 mL conical tubes for centrifugation.
9. Centrifuge plasma for 10 minutes at 3,000 rcf at room temperature.
10. Aliquot platelet-free plasma into the provided cryovials as described in the table below.

11. Place all cryovials in the provided 81-place cryobox and store the box, upright, in a - 80˚C freezer.

Tube Number	Volume	Label
1	0.2 mL	Cytokine
2	0.2 mL	Cytokine
3	0.2 mL	HACA
4	0.2 mL	HACA
5	0.2 mL	Cytokine
6	0.2 mL	Cytokine
7	0.5 mL (if available)	Extra
8	0.5 mL (if available)	Extra
9	0.5 mL (if available)	Extra

Additional Peripheral Blood Mononuclear Cell (PBMC) Processing (after step 6)

12. Using a sterile serological pipette, bring the total volume in the 15mL conical tube (containing plasma, mononuclear cells and platelets, and density solution) to 15 mL using PBS with 2% FBS.
13. Close the cap of the 15 mL centrifuge tube and mix the cells by gently inverting the tube 5 times.
14. Centrifuge the sample at 300 rcf for 15 minutes at room temperature.
15. Aspirate or decant (gradually pour off) as much supernatant as possible without disturbing the cell pellet.
16. Resuspend the cells by gently vortexing or tapping the tube with your index finger.
17. Using a sterile serological pipette, add 10 mL of PBS with 2% FBS to the 15 mL conical tube containing the cell pellet.
18. Close the cap of the 15 mL centrifuge tube and mix the cells by gently inverting the tube 5 times.
19. Centrifuge the sample at 300 rcf for 10 minutes at room temperature.
20. Aspirate or decant (gradually pour off) as much supernatant as possible without disturbing the cell pellet.
21. Resuspend the cells by gently vortexing or tapping the tube with your index finger.
22. Using a pipette and sterile pipette tip, add 1 mL of Freeze Media 1 to the 15 mL conical tube containing the resuspended cell pellet.
23. To ensure adequate resuspension of cells, pipette the freeze media/cell suspension up and down 8 times.

24. Using a pipette and sterile pipette tip, add 1 mL of Freeze Media 2 dropwise to the 15 mL conical tube containing the resuspended cell pellet.

25. To ensure adequate resuspension of cells, pipette the freeze media/cell suspension up and down 8 times.

26. Aliquot 1 mL of cells/freeze media into each of 2 x 1.8 mL cryovials.

27. Transfer cryovials into a controlled cell freezing apparatus (Mr. Frosty) and place in -80˚C freezer for 24 hours.

28. Transfer cells to a liquid nitrogen freezer for storage.

    ***NOTE: For ONLY sites that don't have liquid nitrogen storage available:** Store the day 1, 8, and 15 samples at -80 ˚C and then after the day 15 draw, ship these 3 samples overnight on dry ice to the CCTDC. Then, store the day 29 sample at -80 ˚C until after the end of course sample is drawn, and then ship these 2 samples, **along with the tubes for cytokine analysis (sites without liquid nitrogen storage only)**, overnight on dry ice to the CCTDC.

APPENDIX VII: MEDICATIONS ASSOCIATED WITH PROLONGED QTc

The use of the following medications should be avoided during vorinostat therapy if reasonable alternatives exist. This is not an all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references. For the most current list of medications, please refer to the following reference: www.Crediblemeds.org.

Drugs that are generally accepted as having a known risk of causing Torsades de pointes **Prohibited within one week of vorinostat on Arm C**	Drugs that are generally accepted as having a possible risk of causing Torsades de pointes **Use with caution in patients on Arm C**
Amiodarone (Cordarone®, Pacerone®)	Aripiprazole (Abilify, Aripiprex)
Anagrelide (Agrylin®, Xagrid®)	Atomoxetine (Strattera)
Arsenic trioxide (Trisenox®)	Bedaquiline (Sirutro®)
Azithromycin (Zithromax®, Zmax®)	Bendamustine
Bepridil (Vascor)	Betrixaban (Bevyxxa)
Chloroquine (Aralen®)	Bortezomib (Velcade)
Chlorpromazine (Thorazine®)	Bosutinib (Bosulif)
Cirpofloxacin (Cipro)	Buprenorphine
Citalopram (Celexa®, Cipramil®)	Cabozantinib
Clarithromycin (Biaxin®)	Capecitabine
Disopyramide (Norpace®)	Certinibi
Dofetilide (Tikosyn®)	Clozapine (Clozaril®
Donepezil (Aricept)	Cobimetinib
Dronedarone (Multaq®)	Crizotinib
Droperidol (Inapsine®) (not on US mkt)	Dabrafenib
Erythromycin (E.E.S.®)	Dasatinib
Escitalopram (Cipralex®, Lexapro®)	Desipramine
Flecainide (Tambocor®)	Dexmedetomidine
Fluconazole (Diflucan)	Dolasetron (Anzemet®)
Haloperidol (Haldol®)	Encorafenib
Hydroxychloroquine (Plaquenil)	Entrectinib (Rozlytrk)
Ibutilide (Corvert®)	Eribulin (Havalen®)
Levofloxacin (Levaquin)	Felbamate (Felbatol®)
Methadone (Dolophine®)	Fingolimod (Gilenya®)
Moxifloxacin (Avelox®, Avalox®)	Flurouracil (5FU)
Oxaliplatin (Eloxatin)	Gemifloxacin (Factive®)
Pentamidine (NebuPent®, Pentam®)	Gilteritinib (Xospata)
Pimozide (Orap®)	Glasdegib (Daurismo)
Procainamide (Pronestyl®, Procan®)	**Granisetron (Kytril®)**
Quinidine (Quinaglute®, Duraquin®)	Iloperidone (Fanapt®)
Sevoflurane (Ulane®)	Imipramine (Tofranil)
Sotalol (Betapace®)	Inotuzumab ozogamicin (Besponda)
Thioridazine (Mellaril®)	Isradipine (Dynacirc®)
Vandetanib (Caprelsa®)	Ivosidenib (Tibsovo)
	Lapatinib (Tykerb®)
	Lefamulin (Xenleta)
	Lenvatinib (Lenvima)
	Leuprolide (Lupron)
	Levetiracetam (Keppra)
	Lithium (Eskalith®)

	Midostaurin (Rydapt)
	Mirtazapine (Remeron®)
	Moxepril/HCTZ (Uniretic®)
	Nicardipine (Cardene®)
	Nioltinib (Tasigna®)
	Norfloxacin
	Nortriptyline (Pamelor)
	Ondansteron (Zofran) [A]
	Ofloxacin (Floxin®)
	Oxytocin (Pitocin®)
	Paliperidone (Invega®)
	Palonosetron (Aloxi)
	Panobinostat (Farydak)
	Pazopanib (Votient)
	Promethazine (Phenergan®)
	Proprofol (Diprivan) [B]
	Ribociclib (Kisqali)
	Romidepsin (Istodax)
	Rucaparib (Rubraca)
	Selpercatinib (Retevmo)
	Sorafenib (Nexavar)
	Sunitinib (Sutent®)
	Tacrolimus (Prograf®)
	Tamoxifen
	Tazmetostat (Tazverik)
	Televancin (Vibativ)
	Telithromycin (Ketik)
	Tizanidine (Zanaflex®)
	Tolterodine (Detrol®)
	Tramadol
	Vemurafenib (Zelvoraf)
	Venlafaxine (Effexor®)

A-Risk of QTc prolongation demonstrated in doses of 32mg. Doses ≤ 8 mg demonstrated to NOT induce prolongation of QTc.
www.Fda.gov
Krammes SK, Jacobs T, Clark JM, Lutes RE. Effect of Intravenous Ondansetron on the QT Interval of Patients' Electrocardiograms. *Pediatr Emerg Care*. 2018;34(1):38-41

B-QTc prolongation reported in those with a baseline QTc > 500 msec
Safaeian R, Hassani V, Mohseni M, et al. Comparison of the Effects of Propofol and Sevoflurane on QT Interval in Pediatrics Undergoing Cochlear Implantation: A Randomized Clinical Trial Study. *Anesth Pain Med*. 2019;9(4):e88805. Published 2019 Aug 5.

APPENDIX VIII: VORINOSTAT DOSING NOMOGRAM

For patients unable to swallow capsules, vorinostat will be given as a 50 mg/mL extemporaneous liquid preparation (see section 6.6.4 for compounding instructions) rounded to the nearest 10 mg according to the following dosing nomogram.

Patients who are able to swallow capsules may receive vorinostat capsules instead of suspension if their calculated vorinostat dose is within +/- 10% of a 100 mg increment (e.g. 100 mg, 200 mg, 300 mg, or max dose 400 mg). Otherwise, they will need to receive vorinostat as suspension and dosed according to the following dosing nomogram.

Body Surface Area (m^2)	**Dose Level 4 Vorinostat 180 mg/m^2**	**Dose Level 4a Vorinostat 150 mg/m^2**
0.3-0.35	60	50
0.36-0.39	70	60
0.4-0.45	80	60
0.46-0.49	90	70
0.5-0.55	90	80
0.56-0.59	100	90
0.6-0.65	110	90
0.66-0.69	120	100
0.7-0.75	130	110
0.76-0.79	140	120
0.8-0.85	150	120
0.86-0.89	160	130
0.9-0.95	170	140
0.96-0.99	180	150
1.0-1.05	180	150
1.06-1.09	190	160
1.1-1.15	200	170
1.16-1.19	210	180
1.2-1.25	220	180
1.26-1.29	230	190
1.3-1.35	240	200
1.36-1.39	250	210
1.4-1.45	260	210
1.46-1.49	270	220
1.5-1.55	270	230
1.56-1.59	280	240
1.6-1.65	290	240
1.66-1.69	300	250
1.7-1.75	310	260
1.76-1.79	320	270
1.8-1.85	330	270
1.86-1.89	340	280
1.9-1.95	350	290
1.96-1.99	360	300
2.0-2.05	360	300
2.06-2.09	370	310
2.1-2.15	380	320
2.16-2.19	390	330
> 2.2	400	340