NEW APPROACHES TO NEUROBLASTOMA THERAPY (NANT) CONSORTIUM: NANT 2009-03

NANT 2009-03: PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

IND# 113644

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ABSTRACT

The Aurora A kinase has been shown to play an important role in neuroblastoma growth. Inhibition of Aurora A kinase activity attenuates the growth of neuroblastoma cells. MLN8237 is a selective small molecule inhibitor of Aurora A kinase that has completed pediatric single-agent phase I testing, as well as stage 1 phase 2 testing in patients with Neuroblastoma. MLN8237 showed activity against the NCI-sponsored Pediatric Preclinical Testing Program neuroblastoma *in vivo* panel that exceeded the activity level observed with chemotherapy agents routinely used in the treatment of neuroblastoma. Additional *in vitro* and *in vivo* studies have shown that Aurora A kinase inhibitors result in enhanced cytotoxicity when used in combination with chemotherapy. Irinotecan and temozolomide is a commonly used salvage regimen for patients with relapsed or refractory neuroblastoma. This combination has a modest objective response rate (16%) and is well-tolerated, suggesting that it will provide a useful platform for the study of novel compounds in combination with chemotherapy. Preclinical studies demonstrate marked enhancement of anti-neuroblastoma activity with the addition of MLN8237 to irinotecan and temozolomide. This study therefore evaluates the tolerability and activity of MLN8237 in combination with irinotecan and temozolomide in children with refractory or relapsed neuroblastoma. Patients receive irinotecan (50 mg/m^2/dose IV) and temozolomide (100 mg/m^2/dose orally) once daily for 5 days along with MLN8237 orally once daily for 7 days. The doses of irinotecan and temozolomide will be fixed and the dose of MLN8237 will be dose-escalated. In the phase I portion of the study, the primary aims are to determine the recommended phase II doses of this combination, describe the toxicity of this combination, and characterize the pharmacokinetic profile of MLN8237 and irinotecan when used in combination. In the phase II portion of the study, the primary aim is to determine the objective response rate of this combination in patients with relapsed or refractory neuroblastoma. With Amendment 5, the tolerability and pharmacokinetics of an MLN8237 oral solution will be evaluated. Optional correlative studies will evaluate *UGT1A1* polymorphisms as predictors of toxicity and archival tumor tissue Aurora A expression as a predictor of response with this combination.

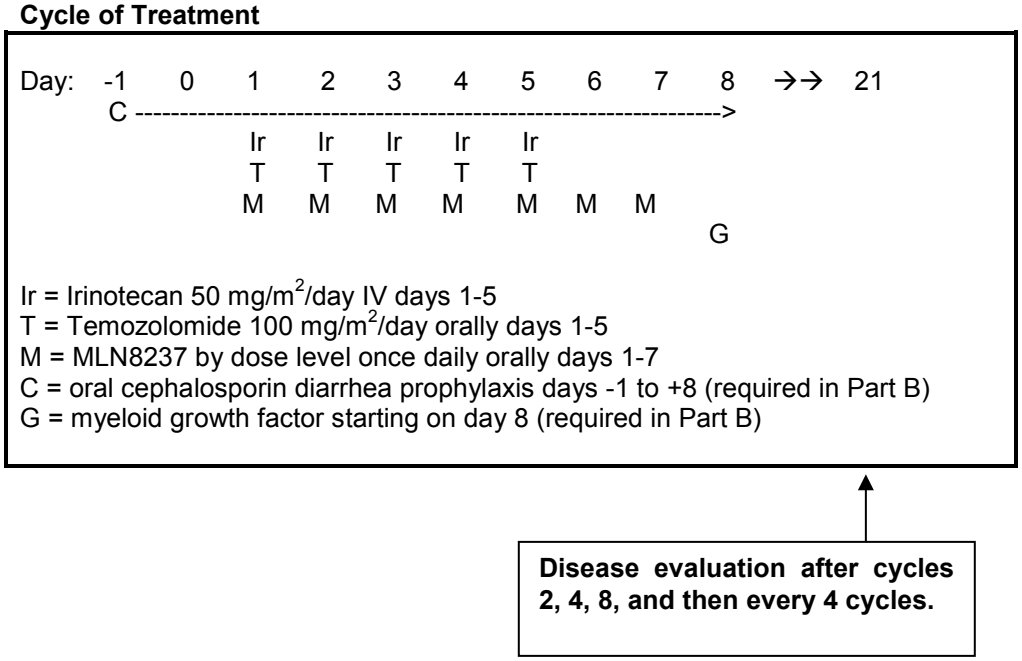
Hypothesis:

We hypothesize that:

1. MLN8237 combined with irinotecan and temozolomide will be tolerable in children with recurrent or refractory neuroblastoma.
2. The primary toxicity of the combination of MLN8237, irinotecan, and temozolomide will be myelosuppression.
3. The combination of MLN8237 with irinotecan and temozolomide will result in enhanced antitumor activity compared with irinotecan and temozolomide.

TREATMENT SCHEMA

Cycle of Treatment



In the completed phase 1 portion, the starting dose of MLN8237 was 45 mg/m^2/day given orally once daily. This dose represented approximately 60% of the pediatric recommended phase 2 dose of 80 mg/m^2/day from COG protocol ADVL0812.

Dose Level	MLN8237 Oral (Days 1-7)	Irinotecan Intravenous (Days 1-5)	Temozolomide Oral** (Days 1-5)	Myeloid Growth Factor Support	Cephalosporin Diarrhea Prophylaxis
-1B	30 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required
1	45 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Optional	Optional
1B	45 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required
2B	60 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required
3B	80 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required

**See section 4.2.2 for doses in patients < 0.5 m^2.

Dose level 1 was completed in Part A of the study. With Amendment 3, evaluation resumed with evaluation of dose level 1B in which all patients receive mandatory myeloid growth factor support and mandatory diarrhea prophylaxis with cefixime or cefpodoxime. Dose levels 1B, 2B, and 3B were evaluated and the maximum tolerated dose with MLN8237 enteric coated tablets was dose level 2B.

With Amendment 5, the phase 2 portion of the study is open to patients who are able to swallow intact pills. All patients on the phase 2 portion will begin therapy at dose level 2B and will utilize the enteric coated tablet formulation.

In addition, with Amendment 5, a cohort evaluating an MLN8237 oral solution is open to patients who are not able to swallow intact pills. Based upon adult bioavailability data, evaluation of this oral solution cohort will begin at dose level 1B, with possible escalation to 2B or de-escalation to -1B. The dose will be assigned at study entry. These patients will be required to participate in pharmacokinetic testing.

Disease evaluation will take place during the third week of cycles 2, 4, 8, and then every 4 cycles. Patients may receive up to 34 cycles of therapy (~2 years) on study in the absence of dose-limiting toxicity (DLT) or progressive disease. Decisions regarding additional therapy on this study will be made by the study chair and treating physician in collaboration with the vice chair and sponsor.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

Primary Aims:

1.1 To estimate the maximum tolerated dose (MTD) of MLN8237 when given together with fixed doses of irinotecan and temozolomide in children and young adults with relapsed or refractory neuroblastoma.

1.2 To describe the toxicities of the combination of MLN8237, irinotecan, and temozolomide in children and young adults with relapsed or refractory neuroblastoma

1.3 To characterize the pharmacokinetics of irinotecan as well as MLN8237 enteric coated tablet and oral solution formulations in patients treated with this regimen

1.4 To determine the response rate for patients with relapsed or refractory neuroblastoma treated with MLN8237, irinotecan, and temozolomide at the identified MTD

Secondary Aim:

1.5 To determine the progression free survival rates for patients with relapsed or refractory neuroblastoma treated with MLN8237, irinotecan, and temozolomide at the identified MTD

Additional/Correlative Aims

1.6 To explore whether *MYCN* status and markers of expression of Aurora A in archival tumor tissue are associated with the antitumor activity of the combination of MLN8237, irinotecan, and temozolomide

1.7 To explore whether *UGT1A1* genotype is associated with toxicity in children with refractory neuroblastoma treated with the combination of MLN8237, irinotecan, and temozolomide

1.8 To explore whether *AURKA* genotype is associated with antitumor activity in children with refractory neuroblastoma treated with the combination of MLN8237, irinotecan, and temozolomide.

2.0 BACKGROUND

2.1 Neuroblastoma

Neuroblastoma is the most common extracranial solid cancer of childhood.[1] Most patients are initially diagnosed prior to 10 years of age. Approximately 50% of patients present with initially metastatic disease. Many of these patients are either refractory to initial therapy or develop recurrent disease after receiving multimodal therapy. The outcome for patients with recurrent or refractory disease remains poor. Novel approaches to treating these patients are required to improve their outcome.

2.2 Irinotecan and Temozolomide for Relapsed and Refractory Neuroblastoma

The combination of irinotecan and temozolomide has demonstrated activity in several pediatric solid tumors. In a pediatric phase I study utilizing a protracted irinotecan schedule (once daily for 5 days each week for two weeks), one patient with Ewing sarcoma achieved a complete response to therapy.[2] Another patient with Ewing sarcoma and a patient with neuroblastoma had partial responses.

With this initial experience, several studies have evaluated this combination specifically in patients with neuroblastoma. A Children's Oncology Group phase II study was conducted in 59 patients with recurrent or refractory disease using temozolomide 100 mg/m^2/day orally x 5 days and irinotecan 10 mg/m^2/day IV once daily for 5 days each week for two weeks.[3] The objective response rate was 16%. Stable disease was documented as best response to therapy in an additional 47% of patients. A second study in patients with neuroblastoma evaluated oral irinotecan together with temozolomide.[4] This combination resulted in 1 patient out of 14 total patients with a complete response as well as stabilization of disease in an additional 6 patients. A report of a single institution study describes 49 patients with neuroblastoma treated with temozolomide 150 mg/m^2/day orally x 5 days and irinotecan 50 mg/m^2/day IV once daily for 5 days every three weeks .[5] One third of patients (12/36) treated in this series showed tumor regression, although only 3 of the 36 patients evaluable for response had a complete or partial response.

The incidence of thrombocytopenia or neutropenia $\geq$ grade 3 associated with this combination appears to be relatively low. In the COG phase II study in neuroblastoma, 9% and 25% of patients experienced $\geq$ grade 3 thrombocytopenia or neutropenia, respectively.[3] In one case series in patients with Ewing sarcoma, 11% and 12% of cycles were associated with $\geq$ grade 3 thrombocytopenia or neutropenia, respectively.[6] These results suggest that an additional myelosuppressive agent could be added to this combination. Moreover, the incidence of grade 3 or 4 diarrhea was < 5% in these studies, suggesting that non-hematologic toxicity is also manageable with this combination.[3,6] Irinotecan-associated diarrhea can be abrogated with the use of oral antibiotics, including cefixime.[7]

This protocol utilizes irinotecan administered once daily for 5 days for one week rather than two weeks. This schedule has been selected for several reasons. First, irinotecan administered with temozolomide on this schedule has activity in patients with neuroblastoma.[5] Second, experience in patients with rhabdomyosarcoma on COG protocol ARST0121 has shown that the antitumor activity of this combination is not compromised by the use of a one week schedule.[8] Third, the one week schedule is advantageous in terms of cost and patient convenience.

2.3 Role of Aurora A Kinase in Neuroblastoma

The Aurora family of serine/threonine protein kinases plays a critical role in the regulation of chromosomal segregation and cytokinesis during mitotic progression.[9]The Aurora A kinase gene is amplified or overexpressed in many tumors, including colon, breast, pancreatic, bladder cancers, and in neuroblastoma cell lines.[10,11]Aurora A overexpression is associated with aneuploidy and centrosome amplification, and overexpression of Aurora A kinase results in the transformation of normal cells, supporting the hypothesis that Aurora A is an oncogene. Given this role, investigators have begun to study this kinase in the context of human cancer.

While its importance in many pediatric solid tumors remains poorly understood, a role for Aurora A kinase in the growth of neuroblastoma has been reported. Otto and colleagues reported that Aurora A interacts with MYCN, and sequesters it from proteolytic degradation.[10]This group further demonstrated that Aurora A stabilizes the MYCN protein through a direct physical

interaction and interferes with ubiquitin-mediated degradation in a kinase independent manner. Aurora A protein expression is enhanced by *MYCN* expression and MYCN protein levels decline if aurora A gene expression is inhibited.[10] Suppression of Aurora A expression using shRNA inhibited the growth of *MYCN*-dependent neuroblastoma cell lines.[10] Additional work has shown that 8 of 9 neuroblastoma cell lines over-expressed Aurora A mRNA and all 9 cell lines showed high levels of Aurora A protein.[12] Aurora A mRNA and protein expression in human neuroblastoma tumors appears to be correlated with established adverse prognostic factors in this disease, including advanced stage and MYCN amplification.[12] Increased Aurora A mRNA level was associated with inferior progression-free survival, even after controlling for COG risk category.

MLN8237 is a small molecule, ATP-competitive, reversible inhibitor of Aurora A kinase that is being developed for the treatment of advanced malignancies. The National Cancer Institute's Pediatric Preclinical Testing Program (PPTP) tested MLN8237 against their *in vitro* panel at concentrations ranging from 1.0 nM to 10 mM and against their *in vivo* panel at a dose of 20 mg/kg administered orally twice daily x 5 days repeated weekly. Treatment duration was 6 weeks for solid tumor xenografts, with a total treatment/observation period of 6 weeks for all xenografts. MLN8237 significantly increased event-free survival EFS in 31 of 38 (82%) evaluable solid tumor xenografts.[13] Maintained complete responses were observed in 4 of 5 neuroblastoma xenografts.[13]The very high level of *in vivo* activity observed against the neuroblastoma panel far exceeds that observed for standard agents evaluated by the PPTP that are used in the treatment of neuroblastoma (e.g., vincristine, cisplatin, and cyclophosphamide).

2.4 Preclinical Activity of Aurora A Kinase Inhibition with Other Cytotoxic Agents

MLN8237 added to docetaxel has been shown to result in synergistic reductions in tumor volume in xenograft models of breast and prostate cancer.[14] In these studies, MLN8237 was given orally daily for 21 days and docetaxel was administered IV once weekly for 3 doses. Synergistic cytotoxicity was observed at both low and high MLN8237 doses.

Additional studies have combined MLN8237 with rituximab in preclinical models of B-cell non-Hodgkin's lymphoma.[15] In these studies, at least additive cytotoxicity was observed with the combination compared with mice treated with single agent therapy. Moreover, mice treated with the combination of MLN8237 and rituximab showed prolonged survival compared to mice treated with single agent therapy. These results suggest that additive effects of MLN8237 are not restricted to combinations with M-phase specific agents.

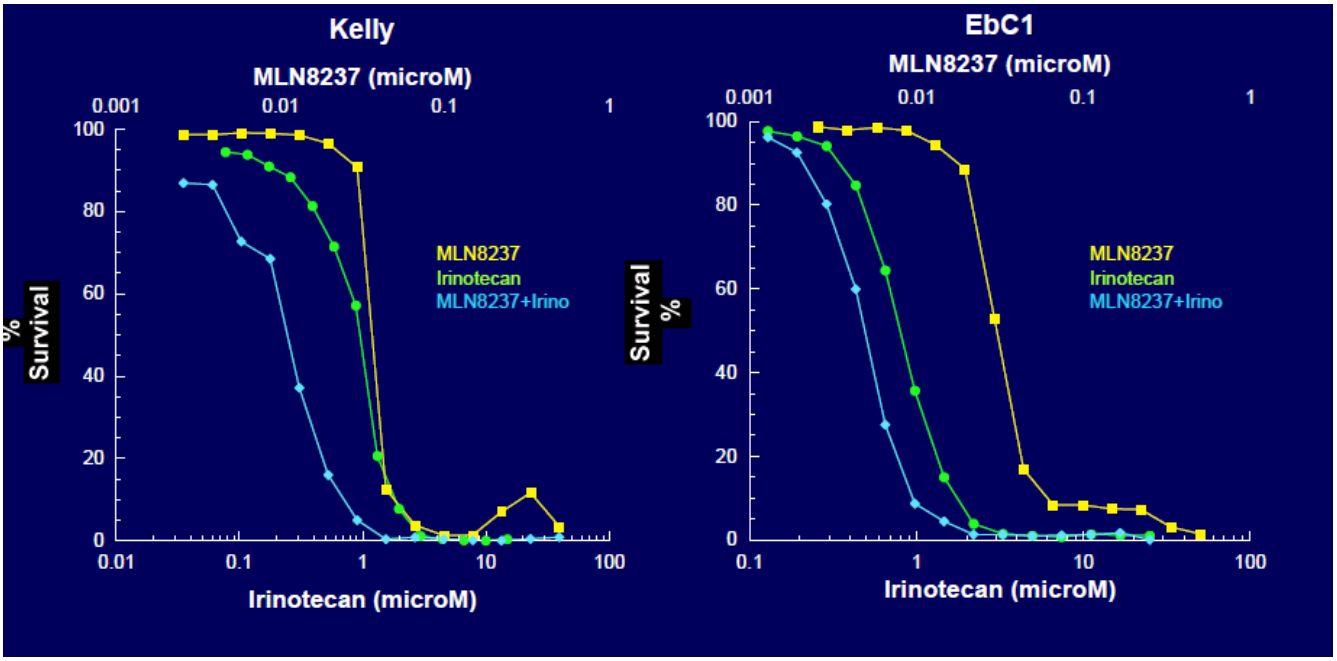


Figure 1. Preclinical in vitro data combining MLN8237 and irinotecan in Kelly and EbC1 neuroblastoma cell lines. Dose-Response Curves demonstrating reduction in cell survival with the combination of irinotecan and MLN8237 (blue curves) compared to either agent alone.

Treatment of neuroblastoma cell lines with siRNA directed against Aurora A significantly attenuates cell growth.[12] Combined treatment of these cells with this siRNA and doxorubicin resulted in enhanced cytotoxicity.[12]Preliminary *in vitro* studies indicate that MLN8237 added to irinotecan or temozolomide results in at least additive cytotoxicity against neuroblastoma cell lines (Y. Mosse,ASCO 2010 Annual Meeting, Abstract #50614; see **Figure 1**for results with irinotecan). Formal evaluation for synergy demonstrated moderate synergy for MLN8237 in combination with irinotecan (combination indices < 1), table 1.

Table 1.

Cell Lines	IC_{50} µM (SD)			Combination Index [CI (SD)] MLN8237+IRN
	MLN8237	IRN	TMZ	
EbC1	0.02 (0.007)	0.83 (0.19)	>100	0.8 (0.3)
SKNBe(2)	0.03 (0.01)	1.2 (0.4)	>100	0.7 (0.4)
Kelly	0.03 (0.01)	0.95 (0.25)	>100	1.0 (0.2)
NB-1691	5.3 (3.4)	10.2 (5.8)	>100	0.4
CHLA-79	0.03 (0.003)	1.7 (0.2)	—	—

Follow-up studies have evaluated MLN8237 in combination with irinotecan and temozolomide in an *in vivo* preclinical model of neuroblastoma.[24] Simultaneous treatment with this combination prevented tumor growth and also resulted in prolonged survival compared to mice treated with either single-agent MLN8237 or irinotecan/temozolomide (Y.Mosse,ASCO 2010 Annual Meeting, Abstract #50614**Figure 2**).These results suggest that MLN8237 provides at least additive cytotoxicity when combined with chemotherapy.

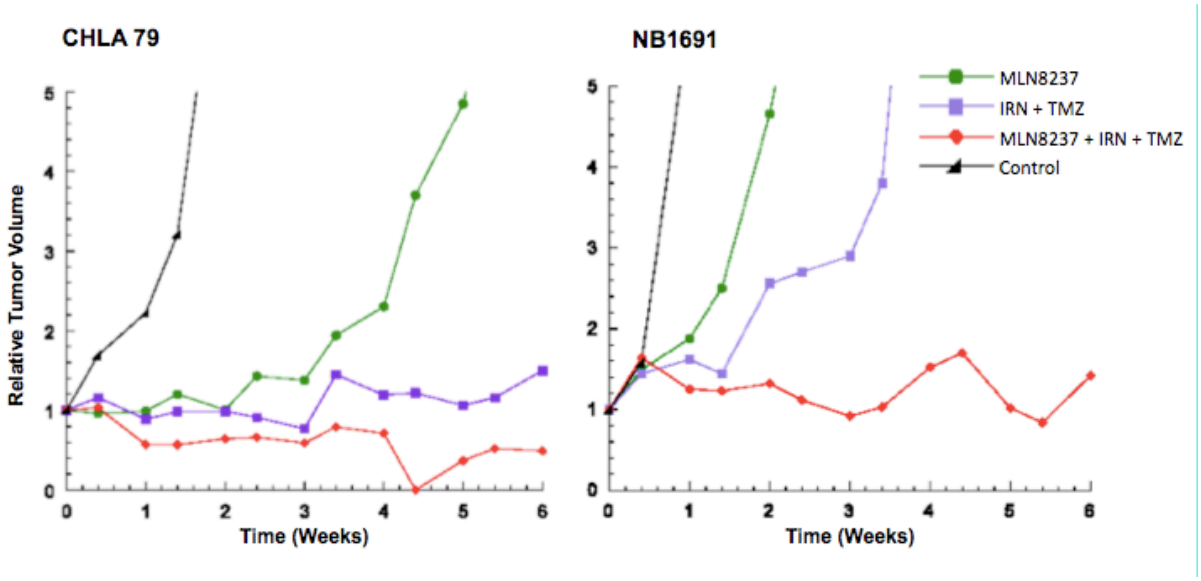


Figure 2. Tumor volume over time from *in vivo* studies in a mouse xenograft model derived from CHLA 79 andNB1691 neuroblastoma cells.

2.5 Preclinical Pharmacokinetic and Toxicity Data of MLN8237

MLN8237 is a selective ATP-competitive inhibitor of Aurora A kinase. The drug shows good oral bioavailability. The major route of metabolism involves glucuronidation. The target plasma concentration for maximal efficacy based on preclinical studies is approximately 1 micromolar. The dose-limiting toxicities observed in animal studies included mucosal toxicity and reversible myelosuppression.

At clinically relevant concentrations, MLN8237 is not anticipated to interact with drugs metabolized by the cytochrome P450 system. Potential drug-drug interactions may occur when MLN8237 is co-administered with a P-glycoprotein substrate. Cross-reactivity with the $GABA_A$ receptor has been observed at plasma concentrations above clinical concentrations, raising the possibility of interactions with benzodiazepines and alcohol.

Specific preclinical modeling of drug-drug interactions between MLN8237 and irinotecan has been performed by Millennium (Sudha Parasuraman, personal communication). Human liver microsome studies evaluated the effect of irinotecan and its metabolites on MLN8237 metabolism as well as the effect of MLN8237 on irinotecan and SN-38 metabolism. MLN8237 glucuronidation and hydroxylation were not inhibited by irinotecan or its metabolites when tested at concentrations up to 10 times their clinically relevant concentrations. In contrast, MLN8237 resulted in concentration-dependent inhibition of the conversion of irinotecan to SN-38 and also glucuronidation of SN-38. The IC_{50} values for inhibition of each of these steps were 18 μM and 4 μM, respectively. Based on the observed C_{max} values of 2-10 μM in COG protocol ADVL0812 with single-agent MLN8237, these IC_{50} values suggest the possibility of an impact on irinotecan metabolism at clinically relevant concentrations of MLN8237. These findings support the inclusion of mandatory pharmacokinetic sampling at Day 4 of cycle 1 during the phase I portion of the study.

2.6 Human Pharmacokinetics and Toxicity with MLN8237

MLN8237 is absorbed orally with a median T_{max} of 2 hours. The half-life is approximately 18 hours and steady state concentrations are achieved after 7 days of once daily dosing. Exposure appears to be dose-proportional over clinically relevant concentrations.

Toxicities observed in adult phase I studies of MLN8237 have been consistent with preclinical studies. The most common toxicities have included mucositis and myelosuppression. Somnolence and confusion have also been observed at higher doses and have been attributed to effects on the $GABA_A$ receptor. While diarrhea has been reported in approximately 40% of patients, no cases of dose limiting diarrhea have been noted. The recommended dose in adults is 50 mg by mouth twice daily for 7 days followed by 14 days of rest.

COG protocol ADVL0812 evaluated MLN8237 (capsule formulation) in children with refractory solid tumors and leukemia (**Table**). Thirty seven subjects were enrolled on the pediatric phase 1 study of MLN8237. Twenty-four subjects were enrolled and 21 were fully evaluable for toxicity on stratum A1 (once daily dosing) and 13 enrolled and 11 fully evaluable on stratum A2 (BID dosing). On stratum A1, hematologic DLTs were not observed until dose level 4 (100 mg/m^2/dose), with 3 subjects experiencing 5 total DLTs (ranging from Grade 4 neutrophils, Grade 4 platelets, and thrombocytopenia that caused a delay of >14 days between treatment cycles). One subject on stratum A1 experienced a Grade 4 mood alteration/depression DLT at dose level 3 (80 mg/m^2/dose) and one patient experience dose-limiting mucositis at dose level 1 (45 mg/m^2/dose). On stratum A2, two of six evaluable subjects experienced a hematologic DLT (Grade 4 neutrophils) at dose level 1 (40 mg/m^2/dose; equivalent to dose level 3 on stratum A1, 80 mg/m^2/day divided BID), and 1 of those subjects also experienced a non-hematologic DLT (Grade 3 mucositis). Therefore, there was a de-escalation to dose level -1 (30 mg/m^2/dose; equivalent to dose level 2 on stratum A1, 60 mg/m^2/day divided BID). In addition, 5/11 patients have had rash/desquamation (grade $\geq$ 2) or hand foot syndrome on the bid schedule versus 1/21 on the once daily dosing schedule. Grade 1 diarrhea was reported in 4 of 21 patients. Higher grade diarrhea was not observed. Of the 5 patients enrolled at dose level -1 of stratum A2, one patient had dose-limiting elevations in alkaline phosphatase. However, despite the fact that the BID dosing regimen appears to be well-tolerated in adult studies, there is a different toxicity profile in pediatric patients with more frequent myelosuppression causing delays as well as hand-foot syndrome. This dosing strategy thus appears to be less tolerable overall in children. Therefore, the recommended phase 2 dose is 80 mg/m^2 dose once daily (dose level 3 on stratum A1).[16]

Following an initial dose at 45-80 mg/m^2, all subjects tested on ADVL0812 showed peak plasma concentrations of MLN8237 well in excess of 1 μM, with peak concentrations in the range of 2-10 μM. MLN8237 was rapidly absorbed after an oral dose, with a median (range) T_{max} of 2.3 (1.1-3.1) hours. At the recommended single-agent phase 2 dose (80 mg/m^2 PO once daily) the mean $AUC_{0-24}$was 75.2 μM•h. Wide interpatient variability in drug disposition was observed. The median (range) half-life was 7.34 (6.13-8.64) hours. The median (range) apparent clearance (CL/F) was 34 (16-59) ml/min/m^2, and CL/F was similar in males (36 ml/min/m^2) and females (32 ml/min/m^2). These preliminary pediatric pharmacokinetic results suggest that drug concentrations used in preclinical studies are clinically attainable at the dosing range proposed in this study.

Table 2. Details of dose escalation on phase I portion of COG protocol ADVL0812.

Dose Level	Number of Evaluable Patients	Number of Courses	Number of Patients with Cycle 1 DLT
45 mg/m^2/dose once daily	6	6	1
60 mg/m^2/dose once daily	5	28	0
80 mg/m^2/dose once daily	6	21	1
100 mg/m^2/dose once daily	4	9	3
80 mg/m^2/day BID	6	9	2
60 mg/m^2/day BID	5	17	1

MLN8237 was initially formulated as a capsule. Considerable inter-patient variability in the pharmacokinetic profile of this agent was observed, and was thought to be at least partially attributable to its formulation. For this reason an enteric-coated tablet has been developed. This formulation results in more consistent pharmacokinetic results. In adults (n=22) the relative bioavailability of the enteric coated tablet formulation in reference to the original powder in capsule formulation was 90% (90% CI, 74.4, 108.8).{Dees, 2012 #34} In addition, the enteric coated tablet formulation has already been shown to be well-tolerated in adults using doses of up to 40 mg by mouth twice daily, which is 80% of the adult MTD with the previous capsule formulation. This study will utilize the enteric-coated tablet formulation for patients who are able to swallow intact pills.

2.7 Clinical Activity of MLN8237

In adult phase I studies of MLN8237, activity was observed in a patient with liposarcoma and ovarian carcinoma. Further single-agent evaluation is ongoing in adults with hematologic malignancies and ovarian cancer. Evaluation of MLN8237 with taxane-based chemotherapy is ongoing in adults with ovarian or prostate cancer.

Initial data regarding the antitumor activity of MLN8237 in pediatric patients have recently been published.[16] Of 33 children with relapsed or refractory solid tumors treated on ADVL0812, one patient with hepatoblastoma had a partial response. In addition, four patients with neuroblastoma had prolonged stable disease for 6, 9, 10, and 35 cycles of single-agent MLN8237.

2.8 *UGT1A1* Polymorphisms and Irinotecan-Associated Toxicity

The active form of irinotecan is SN38. The UGT1A1 enzyme is thought to be the predominant enzyme involved in inactivating SN38 via glucuronidation. A growing body of literature has implicated polymorphisms in the promoter region of *UGT1A1* gene in inter-patient variability in irinotecan exposure and toxicity.[17] The *UGT1A1*28* allele leads to reduced expression of the gene and therefore diminished inactivation of SN38.[17] Several groups have demonstrated that adults who are homozygous for the *UGT1A1*28* allele have an increased risk of irinotecan-associated toxicity, particularly neutropenia.[17-20]Other groups have found that this effect is not seen with lower doses of irinotecan administered on a protracted schedule. [18-20]

MLN8237 also undergoes glucuronidation during its metabolism, which is partially mediated by *UGT1A1*. Therefore, genotyping of *UGT1A1* is of particular interest in this first study evaluating irinotecan used in combination with MLN8237. An optional correlative study will involve genotyping patients for *UGT1A1* promoter polymorphisms and correlating genotype with toxicity in patients receiving irinotecan and MLN8237.

Evaluation of Tissue Aurora A Expression

Increased tumor expression of Aurora A mRNA and protein has recently been shown to correlate with adverse prognostic factors and adverse outcome in patients with neuroblastoma.[12] It remains unclear whether Aurora A mRNA and/or protein expression will correlate with response to Aurora kinase inhibitors, such as MLN8237. An optional correlative study will involve evaluation of Aurora A expression in archival neuroblastoma tumor tissue for correlation with clinical response.

2.9 Evaluation of *AURKA* Polymorphisms and Response to Aurora A Kinase Inhibition

The gene encoding Aurora A kinase, *AURKA*, contains two missense polymorphisms with minor allele frequencies greater than 10%: rs1047972 (18% minor allele frequency) and rs2273535 (30% minor allele frequency). Several studies have evaluated a potential role for these and other *AURKA* polymorphisms in the risk of developing a range of cancers, with mixed results[25-,28]. In addition, there is some evidence that the presence of *AURKA* polymorphism may impact the clinical behavior of breast or gastric cancer [29,30]. To date, only one small study has described the impact of *AURKA* polymorphisms on toxicity and pharmacokinetics of a pan-Aurora kinase inhibitor, with negative findings [31]. It remains unclear whether *AURKA* polymorphisms might be associated with response to a specific Aurora A kinase inhibitor. An optional correlative study will involve evaluation of two common *AURKA* missense polymorphisms and response to protocol therapy.

2.10 Summary and Rationale for Clinical Use of MLN8237 with Irinotecan and Temozolomide

The combination of irinotecan and temozolomide is well-tolerated and provides a modest degree of anti-tumor activity in heavily pre-treated patients. The toxicity profile and activity level suggest that this combination may serve as a useful platform onto which novel compounds may be added. MLN8237 demonstrates compelling single-agent activity in preclinical models of neuroblastoma. Aurora A kinase inhibition results in at least additive cytotoxicity when used in combination with other chemotherapy agents. This trial therefore will evaluate MLN8237 added to irinotecan and temozolomide. While both irinotecan and MLN8237 are metabolized via UGT1A1, neither drug has been shown to induce or inhibit UGT1A1. Patients in the phase I portion of this trial will have detailed pharmacokinetic assessment of irinotecan and MLN8237 levels. Optional studies include assessment of *UGT1A1*and *AURKA* polymorphisms and tumor Aurora A expression levels.

2.11 Rationale for Amendment #3

The protocol initially opened to enrollment using protocol version Amendment #2. Six patients enrolled to dose level 1. Two patients experienced protocol-defined dose-limiting toxicities during the first cycle of therapy. One patient developed grade 3 mucositis, prolonged grade 4 neutropenia, and treatment delay due to ongoing thrombocytopenia, in addition to grade 3 dehydration, anorexia and febrile neutropenia. The other patient had treatment delay due to ongoing neutropenia. In addition, three of six patients experienced grade 3 diarrhea in dose level 1. In dose level 1, the use of myeloid growth factor support and cephalosporin diarrhea prophylaxis were not mandated. After review of the toxicity profile seen in dose level 1, the study committee determined that further development of this combination should include mandatory myeloid growth factor support and cephalosporin diarrhea prophylaxis. Amendment #3 makes this change and resumes evaluation of this combination with dose level 1B that uses the same doses of MLN8237, irinotecan, and temozolomide as evaluated in dose level 1, but with mandatory supportive care measures.

2.12 Rationale for Amendment #5

Amendment #4 was an administrative amendment.

Amendment #5 designates the recommended phase 2 dose for this regimen when used with enteric coated tablets. After Amendment #3, dose levels 1B, 2B, and 3B were evaluated in the phase 1 portion of the study. At dose level 1B, 0 / 6 patients had first-course DLT. At dose level 2B, 1 / 6 patients had first-course DLT (prolonged grade 4 neutropenia). At dose level 3B, 2 / 4 evaluable patients had first-course DLT (prolonged grade 4 neutropenia; failure to meet platelet criteria by Day 35 of course 1). This experience established the recommended phase 2 dose as dose level 2B when used with MLN8237 enteric coated tablets. With Amendment 5, the phase 2 portion of the study is open to patients who are able to swallow intact pills. Patients on the phase 2 portion will begin therapy at dose level 2B and will utilize the enteric coated tablet formulation.

Amendment #5 also adds a cohort of patients treated with an MLN8237 oral solution. This new solution will provide access to patients who are unable to swallow intact pills. The pharmacokinetics of an oral solution formulation of MLN8237 was evaluated in 17 adult patients who participated in a cross-over relative bioavailability study evaluating both the powder-in-capsule formulation (with similar bioavailability to the current enteric coated tablet formulation) and the oral solution. The geometric mean ratios (oral solution in reference to the powder-in-capsule) for exposure (AUC_{inf}) and peak plasma concentration (C_{max}) were determined as 1.26 (90% CI 1.09-1.47) and 1.90 (1.52-2.37), respectively (Investigator Brochure). Based upon these results, pediatric patients receiving single-agent MLN8237 as the oral solution are recommended to receive 60 mg/m^2/dose instead of the standard pediatric dose of 80 mg/m^2 obtained with intact pills. In the context of the current combination regimen in which the recommended phase 2 MLN8237 dose with enteric coated tablets is 60 mg/m^2/dose, patients in the oral solution cohort will begin therapy at dose level 1B with 45 mg/m^2 MLN8237. Patients in this cohort will exclusively receive the oral solution and will be required to participate in pharmacokinetic testing.

Amendment #5 also changes the dose modification procedures to utilize the existing dose levels rather than using 25% dose reductions. This change will facilitate dose rounding in a more uniform manner based upon the existing protocol dosing nomograms.

Amendment #5 also updates NANT response criteria, including criteria for evaluable disease.

2.13 Rationale for Amendment #6

Experience with this regimen prior to Amendment #6 has demonstrated that hematologic toxicity is the primary dose-limiting toxicity (DLT). However, some DLTs have been uncomplicated grade 4 neutropenia for > 1 week (to date, one episode in course 1 in the phase II portion in the absence of other DLT) or uncomplicated thrombocytopenia requiring platelet transfusions more than twice in a 1 week period (to date, one episode in course 1 in the phase II portion in the absence of other DLT). Having grade 4 neutropenia for > 1 week or need for multiple platelet transfusions during a nadir is consistent with the degree of hematologic toxicity seen in other common regimens used for patients with newly diagnosed high-risk neuroblastoma and in some regimens used in patients with relapsed disease. Therefore, with Amendment #6, these elements of the definition of hematologic DLT are removed. Hematologic DLT will be defined solely on the basis of delays in starting subsequent courses beyond day 36 due to failure to recover counts. Day 36 has been updated from Day 35, as that would be a true two week delay, and allowing for patients to stay on a Monday start schedule.

Prior to Amendment #6, the statistical design allowed up to 6 patients from the phase I portion of the trial to contribute to the phase II portion of the trial. Given early evidence of activity of this regimen, there is a desire to complete a full independent phase II evaluation of this regimen. Amendment #6 formally separates the phase I and phase II portions of the study and will require an additional 6 patients evaluable for response. Patient accrual to the phase II portion has been rapid, such that enrolling an additional 6 patients is feasible.

Amendment #6 also updates eligibility and response criteria for uniformity with other current active NANT clinical trials. The consent form and drug information section have been updated to include updated risk tables based upon the most recent MLN8237 Investigators Brochure. Additional minor edits are also included.

2.14 Rationale for Amendment #7

This amendment reflects the change of institution for Steven DuBois, MD, Study Chairperson and IND holder, from University of California, San Francisco to Dana-Farber Cancer Institute. An additional update to NANT participating sites includes a change in Principal Investigator for Hospital for Sick Children, Toronto from Sylvain Baruchel, MD to Meredith Irwin, MD.

2.15 Rationale for Amendment #8

This amendment reflects the change in NANT Site Principal Investigator for Seattle Children's Hospital from Julie Park, MD to Navin Pinto, MD; the change in NANT Site Principal Investigator for Lucile Packard Children's Hospital from Clare Twist, MD to Sheri Spunt, MD; and the change in NANT Site Principal Investigator for C.S. Mott Children's Hospital from Gregory Yanik, MD to Rajen Mody, MD. This also includes the removal of Memorial Sloan Kettering Cancer Center as a participating site.

3.0 PATIENT ELIGIBILITY CRITERIA AND REGISTRATION

3.1 Patient Preparation for Study Entry and Registration

Patient Registration On Study:
Eligible patients will be registered by contacting the NANT Operations Center at Children's Hospital Los Angeles Monday through Friday, 8:30am – 5:00 pm Pacific Time at (323) 361-5687 except holidays. The information requested on the N2009-03 Demographic, Eligibility, and On Study Forms must be completed, and the signed informed consent along with the documentation confirming eligibility must be FAX'd to (323) 361-1803 for registration to occur. Each patient will be assigned a unique NANT registration and study subject number. The dose level will be assigned by the NANT Operations Center at the time of study registration. Once eligibility is verified, the NANT Operations center will send an email confirming registration which must be received prior to starting any protocol therapy or the patient will be declared ineligible. This email will also assign the dose level, and will be sent to the treating facility, Study Chair, and Study Vice-Chair. 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.

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

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

Patients are required to start protocol therapy within 1 week of study enrollment. The start of protocol therapy is defined as the start of oral cephalosporin in Day -1. Protocol therapy must not start until the patient has been enrolled.

Co-enrollment on NANT 2004-05 (Neuroblastoma Biology Study) is strongly encouraged.

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived.

3.2 Inclusion Criteria

3.2.1 Age
Patients must be ≥ 12 months and ≤ 30 years of age when registered on study.

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 Stage/risk group
Patients must have high-risk neuroblastoma according to COG risk classification at the time of study enrollment. Patients who were initially considered low or intermediate risk, but were then reclassified as high risk are also eligible.

3.2.4 Response to Prior Therapy (using INRC definitions):

3.2.4.1 Recurrent/progressive disease at any time prior to enrollment – regardless of response to frontline therapy.

3.2.4.2 Refractory disease: persistent sites of disease after achieving a best overall response of no response to frontline therapy after a minimum of 4 cycles of induction therapy AND patient has never had recurrent/progressive disease.

3.2.4.3 Persistent disease: persistent sites of disease after achieving a best overall response of partial response to frontline therapy after a minimum of 4 cycles of induction therapy AND patient has never had recurrent/progressive disease.

3.2.5 Sites of Disease

Patients must have at least ONE of the following (lesions may have received prior radiation therapy as long as they meet the other criteria listed below):

3.2.5.1 Bone disease

At least one MIBG avid bone site or diffuse MIBG uptake.

a. For recurrent/progressive or refractory disease, a biopsy is not required regardless of number of MIBG avid lesions.

b. For persistent disease, if patient has only 1 or 2 MIBG avid lesions OR a Curie Score of 1-2, then biopsy confirmation of neuroblastoma and/or ganglioneuroblastoma in at least one site present at the time of enrollment (bone marrow, bone, or soft tissue) is required to be obtained at any time point prior to enrollment and two weeks subsequent to most recent prior therapy. If a patient has 3 or more MIBG avid lesions OR a Curie Score of ≥ 3 then no biopsy is required for eligibility.

c. If tumor is known to be MIBG non-avid, then a patient must have at least one FDG-PET avid bone site present at the time of enrollment with biopsy confirmation of neuroblastoma and/or ganglioneuroblastoma obtained at any time prior to enrollment and two weeks subsequent to most recent prior therapy.

3.2.5.2 Any amount of neuroblastoma tumor cells in the bone marrow based on routine morphology (with or without immunocytochemistry) in at least one sample from bilateral aspirates and biopsies.

3.2.5.3 At least one soft tissue lesion that meets criteria for a TARGET lesion as defined by:

a. SIZE: Lesion can be accurately measured in at least one dimension with a longest diameter ≥ 10mm, or for lymph nodes ≥ 15mm on short axis. Lesions meeting size criteria will be considered measurable.

b. **In addition to size, a lesion needs to meet ONE of the following criteria:**

i. MIBG avid. For patients with persistent disease only: If a patient has only 1 or 2 MIBG avid lesions OR a Curie Score of 1 – 2, then biopsy confirmation of neuroblastoma and/or ganglioneuroblastoma in at least one site present at time of enrollment (either bone marrow, bone and/or soft tissue) is required to be obtained at any time point prior to enrollment and at least two weeks subsequent to most recent prior therapy. If a patient has 3 or more MIBG avid lesions OR a Curie Score of ≥ 3 then no biopsy is required for eligibility.

ii. FDG-PET avid (only if tumor known to be MIBG non-avid). These patients must have had a biopsy confirming neuroblastoma and/or ganglioneuroblastoma in at least one FDG-PET avid site present at the time of enrollment done prior to enrollment and at least two weeks subsequent to the most recent prior therapy.

iii. Non-avid lesion (both MIBG and FDG-PET non-avid). These patients must have had a biopsy confirming neuroblastoma and/or ganglioneuroblastoma in at least one non-avid lesion present at the time of enrollment done prior to enrollment and at least two weeks subsequent to the most recent prior therapy.

3.2.6 Ability to Swallow Pills

MLN8237 enteric coated tablets must be swallowed as whole tablets. Therefore, patients must be able to swallow pills to be eligible for the phase 2 portion of the study. Patients who are unable to swallow pills are eligible for the oral solution cohort.

3.2.7 Performance level

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

3.2.8 Prior Therapy

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

Myelosuppressive chemotherapy and/or biologics: Last dose of any myelosuppressive therapy and/or biologics was given at least 3 weeks before the start date for therapy on this protocol.

Radiation: Last dose of radiation was given ≥ 2 wks for local palliative XRT (small port); ≥ 6 weeks for prior MIBG therapy; ≥ 6 months must have elapsed if prior TBI or if ≥ 50% radiation of pelvis; ≥ 6 wks must have elapsed if other substantial BM radiation.

Patients will be excluded if they have received craniospinal radiation.

For patients with only one site of measurable or evaluable disease, radiation must not have been given to that site unless that site still has MIBG uptake or demonstrated clear progression after radiation, or a biopsy of the site demonstrated neuroblastoma at least 2 weeks after the last day of radiation.

Stem Cell Transplant (SCT): Patients are eligible 12 weeks after myeloablative therapy with autologous stem cell transplant (timed from start of protocol therapy). Patients must meet adequate bone marrow function definition (see organ function requirements, below) post-myeloablative therapy. Patients who received stem cell reinfusion following non-myeloablative therapy are eligible once they meet peripheral blood count criteria in 3.2.10.1.

Patients status post-allogeneic stem cell transplant are excluded.

Prior MLN8237, Irinotecan, and Temozolomide

Patients who have received prior MLN8237 are excluded from all phases of the study.

Patients previously treated with irinotecan and/or temozolomide will be eligible if they have not had documented progressive disease during treatment with a regimen containing these agents.

Growth factor(s): All cytokines or myeloid growth factors must be discontinued a minimum of 7 days prior to the start of protocol therapy.

3.2.9 Concomitant Therapy Restrictions

a. Patients must not be receiving any other anti-cancer agents or radiotherapy at the time of study entry or while on study.
b. Patients must not be receiving other investigational medications (covered under another IND) within 30 days of study entry or while on study.
c. Patients must not be receiving cyclosporine, digoxin, tacrolimus, or sirolimus (p-glycoprotein substrates)
d. Patients must not be receiving scheduled benzodiazepine (such as lorazepam or diazepam) therapy. Use of as-needed benzodiazepines is allowed, though discouraged.

3.2.10 Organ Function Requirements

3.2.10.1 Hematologic Function:
Patients must meet the following hematologic criteria for enrollment onto the oral solution cohort of the study regardless of bone marrow disease status:

a. ANC: ≥ 1000/uL (no hematopoietic growth factors within 7 days of the start date of protocol therapy); and
b. Platelet count: ≥ 100,000/µl, transfusion independent (no platelet transfusions within 1 week of the start date of protocol therapy).

Patients with bone marrow disease who meet the above count criteria will be eligible to enroll in the oral solution cohort of the study and will be evaluable for hematologic toxicity.

Patients must meet the following hematologic criteria for enrollment onto the phase 2 portion of the study unless they have bone marrow disease:

a. ANC: ≥ 1000/uL (no hematopoietic growth factors within 7 days of the start date of protocol therapy); and
b. Platelet count: ≥ 100,000/µl, transfusion independent (no platelet transfusions within 1 week of the start date of protocol therapy).

Patients with bone marrow involvement on the phase 2 portion of the study must meet the following hematologic criteria. These patients will not be evaluable for hematologic toxicity or hematologic DLT:

a. ANC ≥ 750/µL (no hematopoietic growth factors within 7 days of the start date of protocol therapy); and
b. Platelet count ≥ 50,000/µL (platelet transfusions allowed).

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 normal for age;
b. SGPT (ALT) ≤135 U/L (≤3x ULN) for the oral solution cohort and ≤ 225 (≤5x ULN) for the phase 2 portion of the study. Note that for ALT, the upper limit of normal for all sites is defined as 45 U/L.

3.2.10.4 Reproductive Function:
All post-menarchal females must have a negative serum or urine beta-HCG. Female subject must either be post-menopausal or surgically sterilized or willing to use an acceptable method of birth control (ie, a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) for the duration of the study. Male subject must agree to use an acceptable method for contraception during the entire study treatment period through 4 months after the last dose of MLN8237.

3.2.11 Body Surface Area
Due to the size of MLN8237 tablets, patients must be at least 0.38 m^2 to be eligible for the phase 2 portion of the study. There is no BSA limit for patients participating in the oral solution cohort.

3.2.12 Coexisting Medical Conditions
Patients with other ongoing serious medical issues must be approved by the study chair prior to registration.

3.3 Exclusion Criteria

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

3.3.2 Patients status post-allogeneic stem cell transplant are not eligible.

3.3.3 Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

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

3.3.5 Patients who are on hemodialysis.

3.3.6 Patients with an active or uncontrolled infection. Patients on prolonged antifungal therapy are still eligible if they are culture and biopsy negative in suspected radiographic lesions and meet other organ function criteria.

3.3.7 Known contraindication (eg allergy) to treatment with cefixime and cefpodoxime.

3.3.8 Patients with known intraparenchymal brain metastasis at study entry are excluded. Patients with metastasis to skull with intracranial extension are not excluded. Patients with a history of previous CNS metastasis only are required to have brain CT and/or MRI to exclude brain metastasis at study entry. Otherwise, in the absence of symptoms to suggest brain metastasis, dedicated CT or MRI of brain is not required prior to study entry.

3.3.9 Treatment with clinically significant enzyme inducers, such as the enzyme-inducing antiepileptic drugs phenytoin, carbamazepine or phenobarbital, or rifampin, rifabutin, rifapentine or St. John's wort within 14 days prior to the first dose of MLN8237 and during the study must not be used as these may interfere with irinotecan metabolism. Non-enzyme inducing anticonvulsants (Keppra, etc.) can be used after discussion with study chair.

3.3.10 Requirement for constant administration of proton pump inhibitor, H2 antagonist, or pancreatic enzymes. Intermittent uses of antacids or H2 antagonists are allowed as described in Section 4.7.6.

3.3.11 Known history of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C. Testing is not required in the absence of clinical findings or suspicion.

3.4 Regulatory

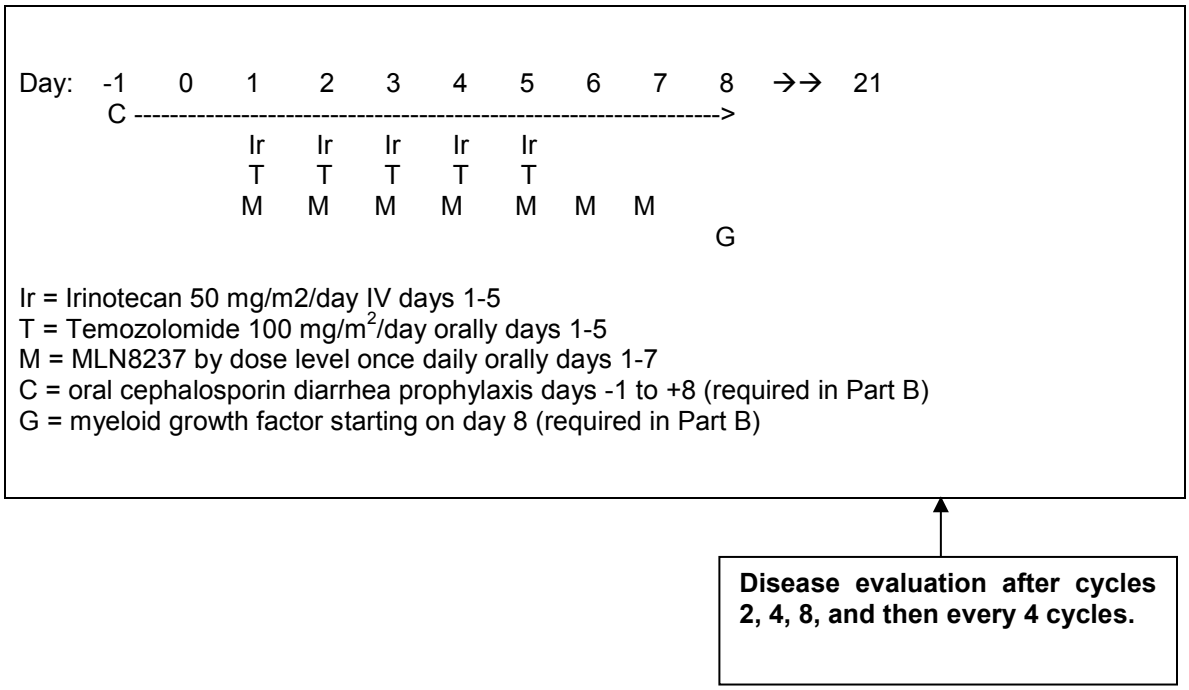
3.4.1 Informed Consent
The patient and/or the patient's legally authorized guardian must acknowledge in writing that consent to become a study subject has been obtained, in accordance with institutional policies approved by the US Department of Health and Human Services.

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

Cycle of Treatment



Prior to the start of each cycle of therapy, patients must meet organ function requirements listed in section 3.2.10, with the exception of platelet and ANC criteria which differ from entry criteria:

- Patients in any portion of the study entering the study with platelets $\geq$ 100,000/uL (transfusion independent) and ANC $\geq$ 1000/uL must recover to platelets $\geq$ 75,000/uL (transfusion independent) and ANC $\geq$ 750/uL (off any myeloid growth factors for more than 24 hours) prior to the start of the next cycle of therapy.Patients in the phase 2 portion entering the study with bone marrow disease and platelets < 100,000/uL or ANC < 1000/uL must recover to platelets $\geq$ 50,000/uL (with transfusions) and ANC $\geq$ 750/uL (off any myeloid growth factors for more than 24 hours) prior to the start of the next cycle.

Disease evaluation will take place during the third week of cycles 2, 4, 8, and then every 4 cycles. Patients may receive up to 34 cycles of therapy (~2 years) on study in the absence of dose-limiting toxicity (DLT) or progressive disease. Decisions regarding additional therapy on this study will be made by the study chair and treating physician in collaboration with the vice chair and sponsor.

4.2 Drug Administration

Please note the need for pharmacokinetic blood draws on Days 4 and 5 when choosing start date for Cycle 1.

Doses should be adjusted based upon height and weight obtained within 1 week prior to the start of each cycle.

Patients who enrolled during the Phase 1 portion and who remain on therapy should continue to follow guidelines for the oral solution cohort with the following exception: patients taking the enteric coated tablet no longer need to fast before or after MLN8237 except as indicated below.

4.2.1 MLN8237

MLN8237 will be given once daily by mouth on days 1-7 of each 21-day cycle. On days 1-5, the dose should be given one hour prior to the start of the irinotecan infusion and at the same time as the dose of temozolomide on those days.

For patients in the phase 2 portion, the dose of MLN8237 will be 60 mg/m^2 (dose level 2B) using exclusively the enteric coated tablet The dose should be rounded to the nearest 10 mg using the dosing table in Appendix II, with doses capped at 2 m^2. Tablets should not be crushed, split, or chewed. The dose can be taken either on an empty stomach or with food on Days 6 and 7, though on Days 1-5 should be taken without food as the dose is taken at the same time as temozolomide (see below). If a patient vomits after taking a dose, it should not be re-dosed.

For patients in the oral solution cohort, the dose of MLN8237 will be based upon the dose level assigned at study entry. The oral solution may be administered by mouth, via nasogastric tube, or via gastrostomy tube. The calculated dose should be rounded down to the nearest 0.5 mg (0.1 mL of the 5 mg/mL oral solution). The dose must be taken on an empty stomach (NPO two hours before and one hour after each dose). If a patient vomits after taking a dose, it should not be re-dosed.

EXAMPLES

- Assigned dose 45 mg/m^2 and BSA 0.83 m^2 → Calculated dose = 37.35 mg → Round down to 37.0 mg → Administer 7.4 mL of 5 mg/mL solution
- Assigned dose 45 mg/m^2 and BSA 0.84 m^2 → Calculated dose = 37.8 mg → Round down to 37.5 mg → Administer 7.5 mL of 5 mg/mL solution

For both formulations of the drug, systemic antacids (both H2 receptor antagonists and proton pump inhibitors) may alter MLN8237 exposure and should be avoided during MLN8237 treatment. Locally-acting antacids should not be taken simultaneously with MLN8237 but antacids can be given up to 2 hours prior or 2 hours following MLN8237 administration.

4.2.2 Temozolomide

Temozolomide will be given at a dose of 100 mg/m^2/dose orally on days 1-5 of each 21-day cycle. The dose for patients < 0.5 m^2 is 3.3 mg/kg/dose, respectively. The dose should be rounded based on the dosing table in Appendix III, with doses capped at 2 m^2. The dose should be given one hour prior to irinotecan infusion and should be given at the same time as the dose of MLN8237. The dose should be taken on an empty stomach (NPO one hour before and one hour after each dose). If a patient vomits within 20 minutes of taking a dose, the dose should be re-dosed. If a patient vomits more than 20 minutes from taking a dose, the dose should not be re-dosed.

For patients unable to swallow pills, temozolomide capsules can be opened and drug administered using the instructions given in Appendix IV. Alternatively, an extemporaneous suspension can be prepared according to the instructions given in section 6.3.

4.2.3 Irinotecan

Irinotecan will be given at a dose of 50 mg/m^2/dose IV over 1 hour on days 1-5 of each 21-day cycle.

For patients with double-lumen central venous catheters who will have pharmacokinetic sampling performed in cycle 1 (i.e. all patients in the oral solution portion of the study and consenting patients in the phase 2 portion of the study), the following administration routine will keep one lumen available for pharmacokinetic sampling and avoid the need for peripheral IV placement for pharmacokinetic sampling:

--Use the same lumen for each of the irinotecan infusions on days 1-4 (leaving one lumen unexposed to irinotecan);

--Run normal saline in the irinotecan unexposed lumen at a rate of 20 mL/hour starting 5 minutes before the start of the irinotecan infusion and continuing until 5 minutes after the completion of the irinotecan infusion;

--Flush and heparinize the irinotecan lumen following institutional standard practice while normal saline is still running in the irinotecan unexposed lumen;

--Flush with normal saline and heparinize the irinotecan unexposed lumen following institutional standard practice after the irinotecan lumen has already been flushed.

Since pharmacokinetic sampling is only performed in cycle 1, this routine need only be used in cycle 1.

4.2.4 Myeloid Growth Factor Support (required in all patients in Part B)
All patients in Part B (dose levels ending in "B"; therefore all patients in the phase 2 portion and the oral solution cohort) receive myeloid growth factor starting on day 8 of the first cycle of therapy. The recommended regimen is filgrastim 5 micrograms/kg subcutaneously starting at least 24 hours after the last dose of MLN8237 and continuing until the ANC exceeds 2,000/μL post-nadir. Filgrastim must be discontinued at least 24 hours prior to the start of the next cycle of therapy. A single dose of pegfilgrastim (100 micrograms/kg; maximum dose 6 mg) given subcutaneously on day 8 may be substituted for filgrastim according to institutional standard practice.

4.2.5 Cephalosporin Diarrhea Prophylaxis (required in all patients in Part B)
All patients in Part B (dose levels ending in "B"; therefore all patients in the phase 2 portion and the oral solution cohort) receive cephalosporin diarrhea prophylaxis with starting with the first cycle of therapy. The recommended regimen is cefixime 8 mg/kg/dose (maximum daily dose 400 mg) given orally once daily starting on day -1 (2 days before the start of irinotecan) and continuing until day +8 of each cycle. An alternative regimen is cefpodoxime 10 mg/kg/day (maximum daily dose 800 mg) divided twice daily starting on day -1 (2 days before the start of irinotecan) and continuing until day 8 of each cycle. If neither cefixime nor cefpodoxime are available, then another oral third generation cephalosporin may be substituted using standard dosing for that agent.

Patients who appear to be on schedule to begin a subsequent cycle of therapy on time should resume cephalosporin diarrhea prophylaxis on Day 20 of the current cycle (two days prior to planned Day 1 of the subsequent cycle).

4.3 Dose Escalation Schedule

In the completed phase 1 portion, the starting dose of MLN8237 was 45 mg/m^2/day given orally once daily. This dose represented approximately 60% of the pediatric recommended phase 2 dose of 80 mg/m^2/day from COG protocol ADVL0812. The dose escalation for the completed phase I portion is given below

Dose Escalation for the Completed Phase I Portion					
Dose Level	**MLN8237 Oral (Days 1-7)**	**Irinotecan Intravenous (Days 1-5)**	**Temozolomide Oral** (Days 1-5)**	**Myeloid Growth Factor Support**	**Cephalosporin Diarrhea Prophylaxis**
-1B	30 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required
1	45 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Optional	Optional
1B	45 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required
2B	60 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required
3B	80 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required

**See section 4.2.2 for doses in patients < 0.5 m^2.

With Amendment 5, the phase 2 portion of the study is open to patients who are able to swallow intact pills. All patients on the phase 2 portion will begin therapy at dose level 2B (60 mg/m^2/day MLN8237) and will utilize the enteric coated tablet formulation.

With Amendment 5, a cohort evaluating an MLN8237 oral solution is open to patients who are not able to swallow intact pills. Based upon adult bioavailability data, evaluation of this oral solution cohort will begin at dose level 1B, with possible escalation to 2B or de-escalation to -1B based on pharmacokinetic data on dose level 1B. The dose will be assigned at study entry. These patients will be required to participate in pharmacokinetic testing.

Dose Escalation for Patients who are Unable to Swallow Intact Pills and Who will Receive the Oral Solution of MLN8237					
Dose Level	**MLN8237 Oral (Days 1-7)**	**Irinotecan Intravenous (Days 1-5)**	**Temozolomide Oral** (Days 1-5)**	**Myeloid Growth Factor Support**	**Cephalosporin Diarrhea Prophylaxis**
-1B	30 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required
1B	45 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required
2B	60 mg/m^2/day	50 mg/m^2/day	100 mg/m^2/day	Required	Required

**See section 4.2.2 for doses in patients < 0.5 m^2.

The dose level will be assigned at the time of patient registration. No intra-patient dose escalations are allowed.

4.4 Definition of Dose-Limiting Toxicity (DLT)

Toxicity will be graded using the CTCAE criteria, version 4.0. 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 Chair.

Definition of Inevaluable for Dose Escalation Evaluation
Patients who (1) receive < 5 of the 7 planned doses of MLN8237, < 4 of the 5 planned doses of irinotecan, or < 4 of the 5 planned doses of temozolomide in cycle 1 and (2) do not experience a DLT, will be replaced for the purposes of evaluating the dose level for dose escalation/de-escalation purposes (see Section 10.2.1).

Definition of Dose-Limiting Toxicity: Note that the definition of DLT changed with Amendment 6. Once a site has IRB approval of Amendment 6, the DLT definition and therefore dose modification decisions in Amendment 6 will be used for assessment and management of any new toxicities for patients enrolling prior to Amendment 6 and who remain on protocol therapy.

DLT is defined as any of the following events that are possibly, probably or definitely attributable to the combination of MLN8237, irinotecan, and temozolomide:

- Any grade 4 or 5 non-hematologic toxicity
- Any grade 3 non-hematologic toxicity, with the exception of:
  --Grade 3 nausea, vomiting, anorexia or dehydration resolving to < = grade 2 within 72 hours
  --Grade 3 transaminase elevation resolving to ≤ grade 1 or baseline within 7 days of drug interruption/completion (if occurring on days 1-7 acceptable to continue drug through day 7 of course) or within 7 days of first occurrence if toxicity first occurs after drug completion. In either case, treating sites are to obtain repeat labs by the seventh day to determine whether the event meets DLT criteria.
  --Grade 3 diarrhea persisting for less than 72 hours
  --Grade 3 fever, infection or febrile neutropenia

--Grade 3 electrolyte disturbance resolving to < grade 1 or baseline within 7 days of drug interruption/completion (if occurring on days 1-7 acceptable to continue drug through day 7 of course) or within 7 days of first occurrence if toxicity first occurs after drug completion. In either case, supplementation is allowed and treating sites are to obtain repeat labs by the seventh day to determine whether the event meets DLT criteria.

- Start of next cycle of therapy later than day 36 due to non-hematologic toxicity and/or not meeting criteria to start subsequent cycle
- Dose-limiting neutropenia is defined as not meeting neutrophil criteria to start a subsequent course by day 36.
- Dose-limiting thrombocytopenia is defined as not meeting platelet criteria to start a subsequent course by day 36.

4.5 Treatment Duration

Patients may receive up to 34 cycles of therapy (~2 years) on study in the absence of progressive disease. Decisions regarding additional therapy on this study will be made by the study chair and treating physician in collaboration with the vice chair and sponsor. Patients experiencing dose-limiting toxicity (DLT) may continue to receive therapy modified as described in section 4.6.

4.6 Dose Modification

4.6.1 Thrombocytopenia

Patients evaluable for hematologic toxicity who develop dose-limiting thrombocytopenia (per section 4.4) should have their dose of temozolomide reduced to 75 mg/m^2 (see Appendix IIIB).

Patients who continue to have dose-limiting thrombocytopenia despite temozolomide dose reduction should have a bone marrow evaluation to exclude progressive bone marrow metastatic disease. In the absence of progressive bone marrow disease, these patients should have their dose of MLN8237 reduced by one dose level. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

Patients with recurrent dose-limiting thrombocytopenia despite dose reductions in both MLN8237 and temozolomide will undergo up to one additional dose reduction of MLN8237 and temozolomide. Temozolomide will be reduced first followed by MLN8237 in the next cycle if the combination continues to result in dose limiting thrombocytopenia. The dose of temozolomide should be reduced to 50 mg/m^2/dose, with dose rounded down to the nearest 5 mg. The dose of MLN8237 should be reduced by an additional dose level. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

Patients with recurrent dose-limiting thrombocytopenia despite two dose reductions in both MLN8237 and temozolomide will be removed from protocol therapy.

Patients who are not evaluable for hematologic toxicity due to low counts and bone marrow involvement at study entry who develop dose limiting thrombocytopenia should undergo bone marrow re-evaluation. If the bone marrow does not show progressive disease, then the dose modification strategy above should be followed.

4.6.2 Neutropenia

Patients who have dose-limiting neutropenia despite myeloid growth factor support should have their dose of temozolomide reduced to 75 mg/m^2 (see Appendix IIIB). These patients should continue to receive myeloid growth factor support.

Patients who continue to have dose-limiting neutropenia despite myeloid growth factor support and temozolomide dose reduction are encouraged to undergo bone marrow evaluation to exclude progressive bone marrow metastatic disease. In the absence of progressive bone marrow metastatic disease, these patients should have their dose of MLN8237 reduced by one dose level. These patients should continue to receive myeloid growth factor support. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

Patients with recurrent dose-limiting neutropenia despite myeloid growth factor support and dose reductions in both MLN8237 and temozolomide will undergo up to one additional dose reduction of MLN8237 and temozolomide in increments of 25% of the starting dose of each agent. Temozolomide will be reduced first followed by MLN8237in the next cycle if the combination continues to result in dose limiting neutropenia. The dose of temozolomide should be reduced to 50 mg/m^2/dose, with dose rounded down to the nearest 5 mg. The dose of MLN8237 should be reduced by an additional dose level. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

Patients with recurrent dose-limiting neutropenia despite myeloid growth factor support and two dose reductions in both MLN8237 and temozolomide will be removed from protocol therapy.

Patients who are not evaluable for hematologic toxicity due to low counts and bone marrow involvement at study entry should undergo bone marrow re-evaluation if they develop dose-limiting neutropenia. If the bone marrow does not show progressive disease, then the dose modification strategy above should be followed.

4.6.3 Mucositis

Patients who develop dose-limiting mucositis (per section 4.4) should have their dose of MLN8237 reduced by one dose level with their next cycle of therapy. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

Patients who continue to have dose-limiting mucositis despite initial MLN8237 dose reduction should have their dose of MLN8237 reduced by another dose level. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

If mucositis remains dose-limiting despite two MLN8237 dose reductions, temozolomide should be reduced to 75 mg/m^2 (see Appendix IIIB). Patients with recurrent dose-limiting mucositis despite these dose reductions should be removed from protocol therapy.

4.6.4 Diarrhea

In addition to oral cephalosporin prophylaxis, other guidelines for patients with dose-limiting diarrhea include consideration of the possibility of cholinergic syndrome if diarrhea occurs within hours of the irinotecan infusion. Patients with early diarrhea may benefit from pretreatment with atropine (0.01 mg/kg IV; max dose 0.4 mg), as well as prolonging the irinotecan infusion to 90 minutes. Additional strategies for treating patients with therapy-associated diarrhea are given in section 5.5.

Patients who continue to have dose-limiting diarrhea despite cephalosporin prophylaxis and other measures above should have the dose of irinotecan reduced by 25% to 37.5 mg/m^2/dose. These patients should continue to receive the above supportive therapies with subsequent cycles.

Patients with recurrent dose-limiting diarrhea despite supportive measures and irinotecan doe reduction should have the dose of irinotecan reduced by another 25% of the initial starting dose to 25 mg/m^2/dose.

If diarrhea remains dose-limiting despite two irinotecan dose reductions, MLN8237 should be reduced by one dose level. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy. Patients with recurrent dose-limiting diarrhea despite these dose reductions should be removed from protocol therapy.

4.6.5 Mood alterations

Patients who develop dose-limiting mood alteration while receiving MLN8237 should have the remainder of the MLN8237 for that cycle held. These patients should have their dose of MLN8237 reduced one dose level with their next cycle of therapy. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

Patients with recurrent dose-limiting mood alteration despite initial MLN8237 dose reduction should have their dose of MLN8237 reduced by another dose level. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

Patients with recurrent dose-limiting mood alteration despite these dose reductions will be removed from protocol therapy.

4.6.6 Other toxicities
Patients who develop other dose-limiting non-hematologic toxicities (per section 4.4) should have their dose of MLN8237 reduced by one dose level. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

Patients with recurrent dose-limiting toxicity despite initial MLN8237 dose reduction should have their dose of MLN8237 reduced by another dose level. Patients already receiving dose level -1B or an absolute dose of MLN8237 of 10 mg and who require dose reduction will be removed from protocol therapy.

Patients with recurrent dose-limiting toxicity despite these dose reductions will be removed from protocol therapy.

4.7 Concomitant Therapy

4.7.1 No other cancer chemotherapy or immunomodulating agents will be used.

4.7.2 Palliative radiotherapy is not allowed on study.

4.7.3 Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary (see Section 5.0).

4.7.4 Patients may not receive cyclosporine, digoxin, tacrolimus, or sirolimus while on study.

4.7.5 Use of as-needed benzodiazepines is allowed, though discouraged. Caution should be taken with concomitant use of as-needed benzodiazepines with MLN8237. Such patients may be at increased risk for mood alteration and sedation due to combined GABA-ergic effects of both drugs.

Use of scheduled benzodiazepines (defined as at least once daily on a chronic scheduled basis) is not allowed.

4.7.6 Systemic antacids (both H2 receptor antagonists and proton pump inhibitors) may decrease MLN8237 exposure and should be avoided during MLN8237 treatment. Locally-acting antacids should not be taken simultaneously with MLN8237 but antacids can be given up to 2 hours prior or 2 hours following MLN8237 administration.

4.7.7 Enzyme-inducing anticonvulsants (phenobarbital, phenytoin, carbamazepine) must not be used as these may interfere with irinotecan metabolism. Non-enzyme inducing anticonvulsants (Keppra, etc.) can be used after discussion with study chair. The use of high dose dexamethasone and the use of aprepitant as antiemetics is not recommended due to effects on irinotecan metabolism

5.0 SUPPORTIVE CARE

5.1 Prophylaxis for Pneumocystis Pneumonia

All patients should receive PCP prophylaxis according to institutional guidelines.

5.2 Use of Myeloid Growth Factors

Myeloid growth factor support is now required for all patients, as above.

5.3 Antiemetics

This combination may be emetogenic. Patients should receive antiemetic(s) starting a minimum of 30 minutes prior to the first dose of oral chemotherapy on days 1-7. Use of benzodiazepines as a scheduled antiemetic is prohibited. Use of benzodiazepines as an as needed antiemetic is discouraged. The use of high dose dexamethasone and the use of aprepitant as antiemetics is not recommended due to effects on irinotecan metabolism.

5.4 Treatment of Irinotecan-Associated Diarrhea

Irinotecan-associated diarrhea can be profuse and can occur either early (minutes to hours) or late (days) in the treatment schedule. Early diarrhea results from cholinergic stimulation, while late diarrhea relates to bacterial processing of irinotecan metabolites.

Early diarrhea: Patients who have the onset of diarrhea during the irinotecan infusion or in the hours following the completion of an irinotecan infusion should receive atropine (suggested dose 0.01 mg/kg IV, maximum dose 0.4 mg). Early onset diarrhea is usually accompanied by cholinergic manifestations (diaphoresis and abdominal cramping). Since irinotecan is being administered on a prolonged schedule (daily x 5), it may be difficult to distinguish early versus late diarrhea. If a patient with presumed early diarrhea does not improve with administration of atropine, they should be instructed to begin treatment for late diarrhea. Patients with suspected early diarrhea should also have the duration of subsequent Irinotecan infusions prolonged to 90 minutes.

Late diarrhea (more than 24 hours after irinotecan administration): Patients will be given loperamide for late diarrhea based on body weight according to the following chart. Each family will be instructed to have loperamide available and begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Families should be given the handout in Appendix V. Patients will also be instructed to contact their physician if any diarrhea occurs.

Maximum dose of loperamide per day: < 6 years: 4mg/day; 6-11 years: 6mg/day; >11 years: 16 mg/day, using the non silicone-containing product.	
Weight: > 43 kg:	4 teaspoons or 2 caplets (4 mg) after the first loose bowel movement, followed by 2 teaspoons or 1 caplet (2mg) every2 hours. During the night the patient may take, 2 caplets (4mg) every 4 hours rather than1 caplet (2mg) every 2 hours.
Weight: 30kg – 43kg:	2 teaspoons or 1 caplet (2mg) after the first loose bowel movement followed by 1 teaspoon or one-half caplet (1 mg) every 2hours. During the night the patient may take, 1 caplet (2 mg) every 4 hours rather than one-half caplet every 2 hours.
Weight: 20kg – < 30kg:	2 teaspoons or 1 caplet (2mg)after the first loose bowel movement followed by 1 teaspoon or one-half caplet (1mg) every 3 hours. During the night, the patient may take 1 caplet (2mg) every 4 hours rather than one-half caplet every3 hours.
Weight: 13kg - < 20kg:	1 teaspoon (1mg) after the first loose bowel movement followed by 1 teaspoon (1mg) every 3 hours. During the night, the patient may take 1 teaspoon (1 mg) every 4 hours rather than every 3 hours.
Weight: < 13kg:	Half teaspoon (0.5mg) after the first loose bowel movement followed by half teaspoon every 3 hours. During the night, the patient may take half teaspoon (0.5mg) every 4 hours rather than every 3 hours.

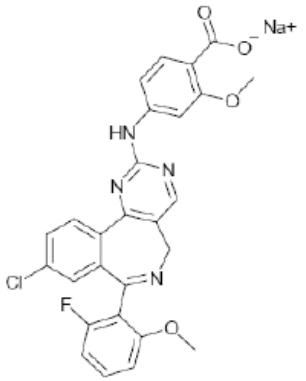
If there is failure of loperamide to control severe diarrhea after 24 hours of use, patients should be considered for treatment with **octreotide** (Sandostatin™) at the dose of **10 micrograms/kg/dose** subcutaneously every 12 hours x 3 days.

Patients receiving prolonged exposure to antibiotics (i.e., cefixime) who develop diarrhea should have stool samples evaluated for *C difficile* toxin, as this is a potentially treatable cause of diarrhea. If patients have fever with diarrhea, or bloody diarrhea, evaluation of stools for bacterial culture should also be performed.

6.0 DRUG INFORMATION

6.1 MLN8237(MLN8237-004) NSC # 747888

Structure and molecular weight: MLN8237 chemical name is sodium 4-{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5*H*-pyrimido[5,4-d][2]benzazepin-2-yl]amino}-2-methoxybenzoate. It is a reversible and selective small molecule inhibitor of the enzyme Aurora A kinase. The structure of MLN 8237-004 is shown in the diagram below:



Pharmacology: Aurora A kinase plays a role in the regulation of chromosomal segregation during mitosis. Evidence to support that Aurora A kinase is a target for the treatment of malignancies comes from several observations. Aurora A kinase gene is amplified and/or overexpressed in many tumors. Over-expression of Aurora A kinase results in the transformation of normal cells, supporting the hypothesis that Aurora A is an oncogene. Published reports have demonstrated that in cultured tumor cells reduction of Aurora A protein content results in mitotic spindle defects, mitotic delay, and apoptosis. Inhibition of Aurora A kinase has the potential to have a role in the progression of malignancies and MLN8237 has demonstrated activity against a broad range of *in vitro* and *in vivo* preclinical tumor models.

The pharmacokinetic properties of MLN8237 were characterized in animal models and *in vitro* studies. Based on these preclinical evaluations, MLN8237 is expected to have low systemic clearance, a moderate volume of distribution at steady state, high plasma protein binding, and good oral bioavailability in humans. Due to potential for alteration of absorption by agents that modify gastric pH, proton pump inhibitors and antacids may influence the drug absorption. . MLN8237 is metabolized by both glucuronidation and oxidation pathways. It is not a mechanism-based inhibitor of cytochrome P450 (CYP) 3A4/5M and is unlikely to inhibit the five major CYP enzymes, 1A2, 2C9, 2C19, 2D6, and 3A4/5, when administered at the projected human efficacious dose. Therefore, it is unlikely that MLN8237 will cause drug-drug interactions (DDIs) via inhibition of CYP-mediated metabolism. MLN8237 is a P-glycoprotein (P-gp) inhibitor. Potential DDIs may occur when MLN8237 is co-administered with a P-gp substrate. Urinary excretion of MLN8237 was negligible in the rat and chimpanzee (<1% of the dose).

Preliminary pharmacokinetic analysis of human studies showed that in the 5-150 mg once daily dose range, there is a dose-dependent increase in the area under the plasma concentration versus time curve from zero to 24 hours (AUC0-24hr) and the maximum plasma concentration (Cmax). Peak drug concentrations were generally achieved by 1 to 4 hours. The terminal half-life (t1/2) was between 30 and 40 hours for doses of 5 to 80 mg and was somewhat shorter (between 10 and 30 hours) at the higher doses of 110 and 150 mg. Comparison between 7-day and 14-day administration suggested that steady-state was achieved following 7 days of dosing with lack of additional accumulation beyond Day 7. Preliminary results from pharmacokinetics studies of once and twice daily drug administration showed moderate rate of absorption with a median Tmax of 2 hours (range 1 to 6 hours) and an overall mean half-life of about 18 hours. Twice daily dosing reduces the peak-to-trough ratio compared to once daily administration and is associated with decreased incidence of somnolence.

Toxicities: Information on MLN8237 toxicity is based on the Investigator's Brochure (Edition 9).

Inhibition of Aurora A kinase is expected to be toxic to proliferating tissues because of the role that this enzyme plays in mitosis. In preclinical experiments in rats and dogs, MLN8237 caused reversible myelosuppression and reversible injury to the gastrointestinal epithelium.

Some of the adverse events that have been observed with MLN8237 include the following**:** Reversible myelosuppression including leukopenia, neutropenia, febrile neutropenia, lymphopenia; thrombocytopenia; anemia; gastrointestinal toxicity including stomatitis/mucositis, oral pain, nausea, vomiting, anorexia, abdominal pain, heartburn, diarrhea, and dehydration; somnolence, confusion and disorientation and associated memory loss and gait disturbances; dependency; withdrawal symptoms; mood alteration; palmer-planter erythrodysesthesia; abnormal liver function tests (including AST, ALT, bilirubin, ALP, and GGT); alopecia; fatigue; infection; sepsis; and fever.

MLN8237 is structurally related to benzodiazepines and has activity against the GABAAα1 receptor. Therefore there is a theoretical risk that MLN8237 could cause dependency and withdrawal symptoms. Mood changes, such as euphoria or depression, are possible. When stopping the drug, withdrawal symptoms could include: anxiety, restlessness, difficulty sleeping, tremors, rapid heart-beat, nausea and vomiting.

The use of benzodiazepines or alcohol should be limited or avoided and subjects should be instructed to avoid potentially hazardous activities that require full alertness and coordination. Concomitant use of opiates should be done with caution. Flumazenil, the selective benzodiazepine receptor antagonist, may be used as an adjunct to, but not as a substitute, for the management of life threatening sedation associated with MLN8237. In studies in adult patients, the central nervous system adverse effect of somnolence appeared to be related to peak concentrations of MLN8237 and was alleviated when dosing was changed from once to twice daily dosing.

This list of potential adverse events is most likely not comprehensive; it is possible that the drug will have other toxicities that have not been observed or predicted from its evaluation in animals or humans to date.

The frequency provided in the following table is approximate:

Adverse Events with Possible Relationship to MLN8237

Likely (>20%)	**Less Likely (<= 20%)**	**Rare but Serious (<3%)**
• **Anemia** • **Diarrhea** • **Mucositis Oral** • **Nausea** • **Vomiting** • **Fatigue** • **Lymphocyte count decreased** • **Neutrophil count decreased** • **Platelet count decreased** • **White blood cell decreased** • **Anorexia** • **Alopecia**	• **Febrile Neutropenia** • **Abdominal Pain/Dyspepsia** • **Constipation** • **Oral pain** • **Edema Limbs** • **Fever** • **Infection (including sepsis)** • **Alanine aminotransferase increased** • **Alkaline phosphatase increased** • **Aspartate aminotransferase increased** • **Blood bilirubin**	• **Palmar-plantar erythrodysesthesia syndrome** • **Dermatitis, bullous**

	increased • **Blood GGT increased** • **Creatinine increased** • **Dehydration** • **Dizziness** • **Headache** • **Cough** • **Dyspnea** • **Weakness** • **Rash** • **Sedation** • **Gait disturbance** • **Mood change and confusion** • **Somnolence**	

Also reported on MLN8237 trials but with the relationship to MLN8237 still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Bone marrow hypocellular
CARDIAC DISORDERS - Left ventricular systolic dysfunction; Restrictive cardiomyopathy; Arrhythmia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
EYE DISORDERS – Keratitis; Blurred Vision
GASTROINTESTINAL DISORDERS - Anal mucositis; Ascites; Colitis; Dry mouth; Dysphagia; Enterocolitis; Flatulence; Hemorrhoids; Gastrointestinal disorders, other (hepatic veno-occlusive disease)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS – Chills; General disorders and administration site conditions – Other (systemic inflammatory response syndrome); General disorders and administration site conditions – Other (increased sweating); Multiorgan failure
INJURY, POISONING OR PROCEDURAL COMPLICATION - Bruising
INVESTIGATIONS - Ejection fraction decreased; Investigations - Other (pancytopenia); Weight loss
METABOLISM AND NUTRITION DISORDERS - Hypokalemia; Hyponatremia Hyperglycemia, Hyperkalemia, Hypocalcemia, Hypomagnesemia, Hypoalbuminemia, Hypercalcemia, Hypoglycemia, Hypophosphatemia,Hypoglycemia, Blood lactate dehydrogenase increased , Metabolism and nutrition disorders – Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorders – Other (rhabdomyolysis); Musculoskeletal and connective tissue disorders – Other (muscle spasm); Pain in extremity, chest or back.
NERVOUS SYSTEM DISORDERS - Ataxia; Depressed level of consciousness; Dysgeusia; Memory impairment; Paresthesia; Nervous system disorders - Other (bradyphrenia); Syncope
PSYCHIATRIC DISORDERS - Confusion; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Urinary incontinence
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Pharyngolaryngeal pain; Pleural effusion; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS – Pruritis; Dry skin
VASCULAR DISORDERS – Hypertension; Hypotension; Thromboembolic event

Note: The MLN8237 oral solution contains propylene glycol. Ingestion of large amounts of propylene glycol can increase the risk of lactic acidosis.

Note: MLN8237 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.

Formulation and Stability: MLN8237 is available as two different formulations.

The phase 1 and 2 portions of the study utilize a 10 mg enteric coated tablet. In addition to the active drug, the tablets also contain sodium bicarbonate, sodium lauryl sulfate, povidone, microcrystalline cellulose, croscarmellose sodium, and sodium stearyl fumarate. The tablets are packaged in high-density polyethylene (HDPE) bottles with a child resistant cap. Each bottle contains 10tablets. Tablets should remain in the provided bottle until dispensing. The exact number of tablets per cycle can be counted and dispensed in prescription HDPE bottles. The tablets are stored at controlled room temperature of 20°-25°C (68°-77°F) with excursions permitted from 15°-30°C (59°-86°F).

The oral solution cohort utilizes a 5 mg/mL oral solution. In addition to the active drug, the solution also contains sodium bicarbonate, polyethylene glycol 400, propylene glycol, glycerol, acesulfame potassium, bubble gum flavor, and purified water. The solution is provided in 60 mL amber polyethylene terephthalate bottles with a child resistant cap. The solution should remain in the provided bottle until ready for dispensing in the clinic or at home. The investigational pharmacist may draw up a patient's dose on the day a patient receives therapy at the study center, but should not draw-up the full 7-day course of therapy into prefilled syringes and dispense that supply to the patient. Instead, parents/guardians will be instructed to draw up each dose at home prior to administration. The bottles are to be stored at controlled room temperature of 20°-25°C (68°-77°F) with excursions permitted from 15°-30°C (59°-86°F). Patients are to start each cycle of therapy with a new supply of bottles, rather than using any remaining solution from previous cycles.

Guidelines for Administration: See also Treatment and Dose Modification in Section 4.0.

MLN8237 is a cytotoxic anticancer drug and should be handled according to published guidelines for handling cytotoxic drugs. Tablets should not be crushed or manipulated in any way.

The oral solution formulation of the drug must be given on an empty stomach, at least one hour before and two hours after food or drink except water.

The tablet must be swallowed whole, but may be given with or without food.

Systemic antacids (both H2 receptor antagonists and proton pump inhibitors) may decrease MLN8237 exposure and should be avoided during MLN8237 treatment. Locally-acting antacids should not be taken simultaneously with MLN8237 but antacids can be given up to 2 hours prior or 2 hours following MLN8237 administration.

Antiemetics may be administered as needed; however, the use of benzodiazepines for the prophylaxis or treatment of nausea or vomiting is discouraged because of the potential benzodiazepine-like effects of MLN8237.

In case of contact with the powder or solution (e.g., from a broken tablet), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes and patients should be instructed to notify medical personnel.

Drug Supply and Accountability: MLN8237 will be supplied by Millennium. MLN8237 will be shipped to treating directly from Millennium to treating NANT institutions. Instructions and forms for ordering MLN8237 from Millennium are posted to the NANT website.

Accountability for MLN8237 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 some of the 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 amount returned to Millennium (or disposal of the drug, if approved by Millennium) 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 Millennium. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. All unused, unopened, or expired MLN8237 can be returned to Millennium or destroyed per local institutional policy upon confirmation that the last patient

enrolled into the study has completed the treatment period. If a site is unable to destroy their remaining supply of study drug, they may using the "Return Drug for Destruction Form" found in the N2009-03 study specific page of the NANT Website. If a site possesses drug destruction capabilities then all study drug is to be destroyed by the site according to the site's drug destruction policy. The site will maintain detailed records of the drug reconciliation and destruction with the study files. Documentation of the site's drug destruction policy may be requested by Millennium Pharmaceuticals (or designee) at any time during the course of this study. All material containing study drug will be treated as hazardous waste in accordance with governing regulations.

6.2 IRINOTECAN(CPT-11, Camptosar™), NSC #616348

Mechanism of Action: Irinotecan is a semisynthetic water-soluble analog of camptothecin that exerts its cytotoxic effect through inhibition of the nuclear enzyme topoisomerase I. Irinotecan is a prodrug that undergoes deesterification to a much more potent topoisomerase-I inhibitor, SN-38. The lactone forms of both irinotecan and SN-38, undergo pH dependent hydrolysis to a hydroxy acid (carboxylate) species. SN-38 is glucuronidated to SN-38G.

Formulation & Stability: Each ml of irinotecan contains 20 mg irinotecan (on basis of the trihydrate salt) ; 45 mg sorbitol ; and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan is supplied in amber, glass, single-dose vials containing 40 mg (2ml) and 100 mg (5ml) of irinotecan hydrochloride (on the basis of trihydrate salt) as a 20 mg/mL solution. The intact vials should be stored at room temperature and protected from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

Guidelines for Administration: Irinotecan must be diluted before infusion. Irinotecan should be diluted in 5% Dextrose Injection USP (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 2.8 mg/mL. The solution is physically and chemically stable for up to 24 hours at room temperature (approx 25^{O}C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2^{O} to 8^{O}C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Care should be taken to avoid extravasation; the use of a central line is suggested.

Irinotecan should be administered as an intravenous infusion over 60 minutes.

Irinotecan Toxicity:

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 -20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
• Diarrhea (can be immediate) • Cholinergic symptoms : rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing. • Mucositis • Nausea and vomiting • Stomach pain • Loss of appetite • Fever • Loss of body water • Loss of strength and energy • Decrease in the number of red and white blood cells and platelets made in the bone marrow • Eosinophilia • Hair loss • Elevations in transaminases, alkaline phosphatase, bilirubin,	• Mildly high liver and kidney function tests • Constipation • Delayed diarrhea • Headaches • Pain at injection site • Blood-clots** • Anemia • Thrombocytopenia • Rash • stomatitis • dyspepsia	• Skin inflammation • Trembling • Blood in the urine • Mildly increased level of protein and glucose in the urine • Low amount of protein in the blood • Mouth sores • Headache • Dizziness & hypotension • Sensation of warmth on face • Inflammation of the large intestine • Ileus • Anaphylaxis, • Dehydration • Bradycardia • Disorientation/confusion, • pain at infusion site • Pneumonitis • Inflammation of the lungs with cough and congestion

**This toxicity is seen more commonly when irinotecan is given in combination with fluorouracil and leucovorin. It may rarely be a life threatening event.

Unknown Frequency and Timing: Fetal toxicities and teratogenic effects of irinotecan have been noted in animals at doses similar or less than those used in humans. Toxicities include: decreased skeletal ossification, multiple anomalies, low birth weight and increased fetal mortality. It is not known if irinotecan is excreted into breast milk but it is excreted into rat milk.

Supplier: Irinotecan is commercially available. See also package insert for further information.

6.3 **TEMOZOLOMIDE**(TEMODAR^{TM}) NSC**#362856**

Pharmacology: An orally administered alkylating agent, a second generation imadazotetrazine. A prodrug of MTIC, temozolomide spontaneously decomposes to MTIC at physiologic pH. The drug exerts its effect by cross-linking DNA. This is likely a site specific alkylation at the O6-position of guanine with some effect at the N7 position. Temozolomide reaches its peak concentration in 1 hour. Food reduces the rate and extent of absorption. It has an elimination half-life of 1.13hr (intraperitoneally) and 1.29hr (orally) with an oral bioavailability of 0.98. Total apparent body clearance is 100ml/min/m2 and plasma elimination half-life is ~100 minutes.

Temozolomide Toxicity:

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 -20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
• Anorexia • Constipation, • Nausea, • Vomiting, • Myelosuppression	• Abdominal pain, • Diarrhea, • Headache, • Rash, itching, • Urinary frequency and/or infection • Mucositis, • Lethargy, • Peripheral edema • Alopecia • Hepatotoxicity	• Convulsions, • Anaphylaxis, • Hemiparesis, • Dizziness, • Ataxia, • Confusion, • Dysphagia, • Anxiety, • Thrombo-embolism (L) • Prolonged lymphopenia with increased risk of infection or death • Amnesia, • Insomnia, • Depression, • Myalgia, • Diplopia, • Visual changes • Secondary tumors or cancer • Hepatic failure

Formulation and Stability: 5mg, 20mg, 100mg, 140mg, 180mg, and 250mg capsules, stored at room temperature.

Guidelines for Administration: See also Treatment and Dose Modifications in Section 4.0.

There is a potential for medication errors involving temozolomide capsules resulting in drug overdosages, which may have been caused by dispensing/taking the wrong number of capsules per day and/or product usage exceeding the prescribed dosing schedule.

Temozolomide capsules are available in six different strengths, each color-coded according to strength. Capsules are available in 5-count and 14-count packages, except the 250 mg capsule strength, which is only available in a 5-count package.

Capsule Strength	**COLOR**
5 mg	Green Cap
20 mg	Yellow Cap
100 mg	Pink Cap
140 mg	Blue Cap
180 mg	Orange Cap
250 mg	White Cap

When dispensing, it is extremely important that prescribing and dispensing include clear instructions on which capsules, and how many of each capsule(s) are to be taken per day. Only dispense what is needed for the course, and clearly indicate how many days of dosing the patient will have and how many days are without temozolomide dosing. When counseling patients, it is important for each patient / parent to understand the number of capsules per day and the number of days that they take temozolomide. It is also important for the patient/parent to understand the number of days that they will be off the medication

Each type of temozolomide capsule must be dispensed in a separate vial or in its original glass bottle. Based on the dose prescribed, determine the number of each strength of temozolomide capsules needed for the full course. For example, 275 mg/day for 5 days would be dispensed as five 250-mg capsules, five 20-mg capsules, and five 5-mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient/parent, making

sure each container lists the strength (mg) per capsule and that he or she understands to take the appropriate number of capsules of temozolomide from each bottle or vial to equal the total daily dose prescribed by the physician.

For children unable to swallow the capsules whole, the oral capsules may be formulated into a suspension. To prepare a 10 mg/mL suspension titrate the contents of ten 100 mg capsules (1000 mg) , 500 mg povidone K-30 and 25 mg anhydrous citric acid dissolved in 1.5 mL purified water in a glass mortar to form a uniform paste. To the paste add 50 mL of Ora-Plus ® by adding a small amount, mixing and then adding the balance. Transfer to a glass graduated cylinder Add Ora-Sweet® or Ora-Sweet® SF to a total volume of 100mL by rinsing the mortar with small amounts of the syrup (Ora-Sweet® or Ora-Sweet® SF). Rinse at least four times. Package in an amber plastic prescription bottle. The packaged suspension is stable for 7 days at room temperature or 60 days in the refrigerator. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension. (Trissel LA, Yanping Z, Koontz SE. Temozolomide stability in extemporaneously compounded oral suspensions. *Int J Pharm Compounding* 10:396-9, 2006).

Alternatively, the capsules can be opened and mixed with apple sauce or juice.

Supplier: Commercially available. See also package insert for further information.

6.4 GRANULOCYTE COLONY STIMULATING FACTOR(G-CSF)

(Neulasta,Pegylated filgrastim Or Neupogen, Filgrastim).

6.4.1 NEULASTA (PEGFILGRASTIM):

Source and Pharmacology:
Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).After subcutaneous injection the elimination half-life of pegfilgrastim ranges from 15 to 80 hours and the time to peak concentration ranges from 24 to 72 hours. Serum levels are sustained in most patients during the neutropenic period postchemotherapy, and begin to decline after the start of neutrophil recovery, consistent with neutrophil-dependent elimination. After subcutaneous administration at 100 mcg/kg in 37 pediatric patients with sarcoma, the terminal elimination half-life was 30.1 (+/- 38.2) hours in patients 0 to 5 years-old, 20.2 (+/- 11.3) hours in patients 6 to 11 years-old, and 21.2 (+/- 16) hours in children 12 to 21 years-old.

Neulasta Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Mild to moderate medullary bone pain	• Local pain or irritation at injection site • Headache • Increased alkaline phosphaste, lactate dehydrogenase and uric acid . • Thrombocytopenia	• Low grade fever, Allergic reactions (anaphylaxis, angioedema, or urticaria), Generalized erythema and flushing, • Splenomegaly, splenic rupture, sickle cell crises in patients with sickle cell disease (SCD), • Excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis) • Adult respiratory distress syndrome

Unknown frequency and timing: Fetal toxicities and teratogenic effects of pegfilgrastim in humans are unknown. Conflicting data exist in animal studies. It is unknown whether the drug is excreted in breast milk.

Supplier: Commercially available. See package insert for further information.

Formulation and Stability:
Supplied as a preservative-free solution containing 6 mg (0.6 mL) of pegfilgrastim (10 mg/mL) in a single-dosesyringe with 27 g, ½ inch needle with an UltraSafe® Needle Guard. The needle cover of the prefilled syringe contains drug natural rubber (a derivative of latex). Store refrigerated at 2º-8ºC(36º-46ºF) and in the carton to protect from light. Prior to injection, pegfilgrastim may be allowed to reach room temperature protected from light for a maximum of 48 hours. Avoid freezing.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol

6.4.2 NEUPOGEN (FILGRASTIM):

Source and Pharmacology: Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E.coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2 to 8 hours.
Formulation and Stability:
Supplied as a clear solution in 300 ug/ml (1 ± 0.6 x 108 U/mg) (1 ml or 1.6 ml) vials. Vials are preservative free and are intended to be single-use vials; do not reuse opened vials. Filgrastim must be stored between 2° and 8°C. Stability has been demonstrated for at least 24 months

when stored under these conditions. Do not use if discolored or if there is particulate matter. For IV use, dilute in D5W to concentrations > 15 ug/ml; G-CSF is incompatible with normal saline. At dilutions from *5* ug/ml to 14 ug/ml, add human serum albumin to a final albumin concentration of 2 mg/ml to protect against absorption of the GCSF to container walls (glass or plastic). Filgrastim, when diluted as described above, is compatible with a number of plastics commonly used in the manufacture of syringes, IV bags, infusion sets, and IV pump cassettes. These include polyvinyl chloride, polyolefin, and polypropylene. Diluted filgrastim should be stored at 2° to 8° C and used within 24 hours. **Do not shake or freeze.**

Guidelines for Administration:
Administer once daily, subcutaneously without dilution or if necessary dilute with 5% dextrose in water, preferably to concentrations of 15 ug/ml or greater for IV administration. Dilutions should be prepared as close to the time of administration as possible (up to 24 hours), since the product is preservative-free. When diluting Filgrastim to *5*-14 ug/ml in D5W, it is necessary at all times to add human serum albumin, to reach a final albumin concentration of 2 mg/ml.

Neupogen Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Mild to moderate medullary bone pain	• Local pain or irritation at injection site • Increased alkaline phosphatase, LDH and uric acid • Thrombocytopenia • Fever	• Allergic reactions (more common with IV than subcutaneous administration) • Skin rash, urticaria and/or facial edema • Respiratory wheezing and/or dyspnea • Hypotension and/or tachycardia • Low grade fever • Splenomegaly • Splenic rupture • Worsening of existing skin rashes • Sickle cell crises in patients with Sickle cell disease • Excessive leukocytosis • Cutaneous vasculitis • Adult respiratory distress syndrome • MDS or AML (in patients with severe chronic neutropenia and long term administration

Supplier: Commercially available. See package insert for further information.

6.5 CEFIXIME (Suprax)

Source and Pharmacology: Cefixime is a third generation cephalosporin antibiotic for oral administration that inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins and interfering with the final transpeptidation step of peptidoglycan synthesis. Its spectrum of activity is similar to other third-generation agents, including Enterobacteriaceae, and β-lactamase producing *H. influenzae* and *N. gonorrhea*, and *Staph. aureus*. It is excreted primarily by the kidney. It has a serum half-life of approximately 3-4 hours.

Formulation: Cefixime is available in a powder for oral suspension, which when reconstituted, provides 100mg/5ml. The powder for oral suspension is strawberry flavored and contains sodium benzoate, sucrose, and xanthan gum. Cefixime is available as 50ml, 75ml & 100ml bottle with powder for reconstitution.

Toxicity:

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 -20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
	• Diarrhea • Abdominal pain • Nausea and vomiting, • Dyspepsia	• Headache • Dizziness • Seizures • Anaphylaxis • Hypersensitivity reactions • Thrombocytopenia, • Leucopenia, • Neutropenia, • Eosinophilia, • Pseudomembranous colitis, • Increase in BUN/SCr and ALKP, • Hepatitis, jaundice • Stevens Johnson, **TOXIC EPIDERMAL NECROLYSIS**

Supplier: Commercially available. See package insert for further information.

6.6 CEFPODOXIMEPROXETIL (Vantin-R)

Source and Pharmacology: Cefpodoxime proxetil is a third generation cephalosporin antibiotic for oral administration that inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins and interfering with the final transpeptidation step of peptidoglycan synthesis. Its spectrum of activity is similar to other third-generation agents, including Enterobacteriaceae, and β-lactamase producing *H. influenzae* and *N. gonorrhea*, and *Staph. aureus*. It is excreted primarily by the kidney. It has a serum half-life of approximately 2-4 hours.

Formulation: Cefpodoxime proxetil is available as 100mg & 200mg oblong tablets & powder for oral suspension, which when reconstituted, provides either 50mg/5ml OR 100mg/5ml. The powder for oral suspension is lemon cream flavored. Cefpodoxime is available as 50ml, 75ml & 100ml bottle with powder for reconstitution.

Cefpodoxime Proxetil Toxicity:

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 -20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
	• Diarrhea • Diaper Rash	• Abdominal pain • Nausea and vomiting, • Headache • Seizures • Anaphylaxis • Chest pain • Hypersensitivity reactions • Thrombocytopenia, • Leucopenia, • Neutropenia, • Eosinophilia, • Pseudomembranous colitis, • Increase in BUN/SCr and ALK Phos • Prolonged PT / PTT • Vaginal candidiasis • Aplastic Anemia • Stevens Johnson / Toxic Epidermal Necrolysis

Supplier: Commercially available. See package insert for further information.

6.7 Drug Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all investigational drugs.

7.0 REQUIRED OBSERVATIONS/MATERIAL AND DATA TO BE ACCESSIONED

7.1 Clinical and Laboratory Studies

All blood and urine studies must be performed within 2 weeks prior to study enrollment. Tumor disease evaluation (including appropriate imaging studies, bilateral bone marrow aspirate and biopsy for standard histology and urine catecholamines) are required within 4 weeks prior to study entry and subsequent to any prior therapy. Patients with marrow disease documented at study entry by morphology are REQUIRED to have repeat bone marrow evaluations at each subsequent disease evaluation. Initiation of protocol therapy is required within 1 week of study enrollment.

OBTAIN OTHER STUDIES AS NEEDED FOR GOOD PATIENT CARE.

Observation	Before Entry	Cycle 1	Cycles 2-34	End of Therapy
Physical Exam[4] (Ht, Wt, BSA, VS) Performance status[4] required only at entry	X	Weekly	Start of each cycle[8]	X
CBC, Diff, Platelets[4]	X	Twice weekly[1]	Weekly[1, 8]	X
AST[4], ALT[4], Total[4] + Direct Bilirubin, Albumin, Electrolytes, Calcium, Magnesium, Phosphorus, BUN, Serum Creatinine[4]	X	Weekly	Start of each cycle[8]	X
Plasma lactate and calculated anion gap (only for patients in the oral solution cohort)	X	Day Four[9]		
Serum β-HCG[2,4]	X			
Urine catecholamines VMA/HVA	X		X[7]	X[7]
Bilateral BM Aspirate + Biopsy for morphology[4, 5, 10]	• X[10]		X[5, 7, 10]	X[7, 10]
Tumor anatomic imaging (CT or MRI scan)[3, 4]	X		X[7]	X[7]
MIBG diagnostic scan[4, 6] Use same isotope with each scan	X		X[7]	X[7]
Patient diary		X	X	
Plasma pharmacokinetic samples (required for patients in oral solution cohort; optional for patients in the phase 2 portion)		See Section 8		
Blood for *UGT1A1*and *AURKA* genotyping (optional)		See Section 8		
Archival tumor tissue submission (if consent)		See Section 8		

1. More frequent CBCs may be needed as part of good patient care.
2. Obtain for females 10 years of age and older or post-pubertal.
3. Tumor imaging = CT and/or MRI for optimum visualization of all areas of bulk tumor (primary & metastasis). All disease status tests must be performed ≤ 4 weeks prior to study entry and subsequent to any intervening therapy.
4. Required for verification of eligibility. All results should be faxed to NANT Operations Center with study registration eligibility. An eligibility worksheet is available in the data forms packet on NANT website (www.nant.org).
5. Patients with bone marrow disease present at study entry should have a diagnostic bone marrow sent with each disease evaluation. All disease status tests must be performed ≤ 4 weeks prior to study entry and subsequent to any intervening therapy. 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 11.2.1).
6. ^{123}I-MIBG scans are preferred. Omit for patients known to be MIBG non-avid and replace with ^{18}FDG-PET (preferred) or bone scan. All disease status tests must be performed ≤ 4 weeks prior to study entry and subsequent to any intervening therapy.
7. Perform disease re-staging after day 14 of cycles 2, 4, 8, and then every 4 cycles thereafter.
8. All observations timed for the start of a cycle are to be obtained prior to the start of Day 1 therapy (and do not necessarily need to be obtained prior to resuming oral cephalosporin on Day -1; if studies obtained between Day -2 and Day 0 and meet criteria to proceed with subsequent cycle, do not need to be repeated on Day 1).
9. If plasma lactate elevated above baseline draw on Day Four draw, obtain a venous blood gas to determine if pH < 7.3 (= grade 3 acidosis in CTCAE version 4 and therefore a potential dose-limiting toxicity).
10. If patient is co-enrolled on NANT 2004-05, please also submit specimens for biology study for these timepoints.

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

Patients will be followed for life for any delayed toxicities related to protocol therapy and for the development of second malignancies.

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

Disease evaluation will take place after day 14 of cycles 2, 4, 8, and then every 4cycles.
It is recommended that all scans and tests previously done to document disease status be performed in subsequent evaluations of disease status.

Patients with bone marrow disease present at study entry should have a diagnostic bone marrow done with each disease evaluation. 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 separated by a minimum of three weeks (section 11.2.1).

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 MLN8237, irinotecan, and temozolomide.

8.0 PHARMACOKINETIC AND BIOLOGY STUDIES

Collection of plasma samples for MLN8237 and irinotecan, pharmacokinetic studies is required during cycle 1 for all patients in the phase 1 portion (completed) and in the oral solution portion of the study. Pharmacokinetic sampling is optional during cycle 1 for patients in the phase 2 portion of the study.

Collection of other samples for correlative biology studies is optional and not required for study entry. Although these studies cannot be mandated, all institutions are strongly urged to submit specimens for all consenting patients.

Please see Appendix VI for a summary of blood draws for correlative studies. 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.

8.1 MLN8237 Pharmacokinetics

Please note that these instructions apply to MLN8237 pharmacokinetics. Samples for irinotecan pharmacokinetics require additional volume and different sample processing (see section 8.2).

8.1.1 Sample requirements

3 mL of blood should be drawn into a 4 mL EDTA purple top tube at each time point. Since MLN8237 is given orally, samples may be drawn via central venous catheter, if applicable.

8.1.2 Sampling schedule

Sampling will take place only during cycle 1 of therapy. Sample timing is based on the timing of MLN8237 dosing, with the time of MLN8237 oral administration on Day 4 considered hour 0. Samples should be obtained at the following time points:

--Day 1, prior to first dose of MLN8237
--Day 4, prior to MLN8237
--Day 4, hour 0.5 (i.e., 30 minutes after Day 4 dose of MLN8237)
--Day 4, hour 1 (i.e., 1 hour after Day 4 dose of MLN8237)
--Day 4, hour 2 (i.e., 2 hours after Day 4 dose of MLN8237 and at the end of Day 4 irinotecan infusion)
--Day 4, hour 3 (i.e., 3 hours after Day 4 dose of MLN8237)
--Day 4, hour 4 (i.e., 4 hours after Day 4 dose of MLN8237)
--Day 4, hour 7 (i.e., 7 hours after Day 4 dose of MLN8237)
--Day 5, prior to Day 5 dose of MLN8237 (approximately 24 hours after Day 4 dose of MLN8237 and 22 hours after completion of Day 4 irinotecan infusion)

In order to accommodate this sampling schedule, patients will need to be reminded to not take Day 4 and Day 5 doses of MLN8237 until instructed to do so once they have arrived at the treating site.

For patients with double lumen catheters following the procedure for keeping one lumen unexposed from irinotecan (section 4.2.3), the Day 4, hour 2 samples should be drawn from the irinotecan-unexposed lumen after completion of the normal saline flush that is to run for an additional 5 minutes after completion of the irinotecan infusion.

8.1.3 Sample processing

At the time of collection, EDTA tubes should be gently inverted 6-8 times. Next, centrifuge the samples in a refrigerated centrifuge (4°C) for 10 minutes at 1500 g or greater. Next, remove the plasma using a transfer pipette and transfer the plasma into two separate 3.5 mL polypropylene tubes. Next, immediately freeze the tubes at -80˚ C.

If samples cannot be centrifuged immediately after sample collection, the tubes may be placed in an ice bath for up to 48 hours before further processing.

8.1.4 Sample labeling
Polypropylene tubes should be labeled with the patient's NANT ID number, the word "MLN", the protocol number NANT0903, the date of blood draw, and exact time of the blood draw.

No other identifiers should be included on the label.

8.1.5 Sample shipment
Samples will be held until all samples have been obtained and then sent as a single batch. Batched samples should be sent frozen on dry ice by FedEx priority overnight to:

Ganesh S. Moorthy
Division of Clinical Pharmacology & Therapeutics
Colket Translational Research Building (CTRB), Room 4200
The Children's Hospital of Philadelphia
3501 Civic Center Blvd
Philadelphia, PA 19104

A copy of the MLN8237 pharmacokinetics specimen transmittal form should accompany the shipment and another copy faxed to the NANT Operations Center at (323) 361-1803.

Samples should only be shipped on a Monday-Thursday to allow for weekday delivery. Email Moorthyg@email.chop.edu with the tracking number at the time of sample shipment.

8.1.6 Methodology
MLN8237 plasma levels will be measured using a validated HPLC MS/MS assay. [23]

8.2 Irinotecan Pharmacokinetics

Please note that these instructions apply to irinotecan pharmacokinetics. Samples for MLN8237 pharmacokinetics require additional volume and different sample processing (see section 8.1).

8.2.1 Sample requirements
2 mL of blood should be drawn into a sodium heparin green top tube at each time point.

The baseline pre-treatment sample drawn on Day 1 can be obtained through a central venous catheter. Since irinotecan is given intravenously, the Day 4 and 5 samples should not be drawn through a central venous catheter lumen through which irinotecan has been infused on days 1-4.

Patients with double-lumen central venous catheters may have irinotecan pharmacokinetic samples drawn on days 4 and 5 through a lumen that has not been used for irinotecan infusion on days 1-4 as long as the routine detailed in section 4.2.3 has been used during each of those irinotecan infusions. For patients with double-lumen central venous catheters using the irinotecan unexposed lumen for pharmacokinetic blood draws, the institutional standard volume of "waste" blood before collecting clinical laboratory specimens should be "wasted" before drawing each pharmacokinetic sample.

8.2.2 Sampling schedule
Sampling will take place only during cycle 1 of therapy. Sample timing is based on the timing of MLN8237 dosing, with the time of MLN8237 oral administration on Day 4 considered hour 0. Samples should be obtained at the following time points:

--Day 1, prior to first dose of MLN8237
--Day 4, prior to MLN8237
--Day 4, hour 2 (i.e., 2 hours after Day 4 dose of MLN8237 and at the end of Day 4 irinotecan infusion)
--Day 4, hour 3 (i.e., 1 hour after completing Day 4 irinotecan infusion)
--Day 4, hour 4 (i.e., 2 hours after completing Day 4 irinotecan infusion)

--Day 4, hour 7 (i.e., 5 hours after completing Day 4 irinotecan infusion)
--Day 5, prior to Day 5 dose of MLN8237 (approximately 24 hours after Day 4 dose of MLN8237 and 22 hours after completion of Day 4 irinotecan infusion)

For patients with double lumen catheters following the procedure for keeping one lumen unexposed from irinotecan (section 4.2.3), the Day 4, hour 2 samples should be drawn from the irinotecan-unexposed lumen after completion of the normal saline flush that is to run for an additional 5 minutes after completion of the irinotecan infusion.

8.2.3 Sample processing
Blood collected into sodium heparin tubes should be gently mixed by immediately inverting the tubes. Blood samples will then be centrifuged immediately for 15 minutes in a refrigerated (4° C) centrifuge set at 3000 rpm. Next, remove the plasma using a transfer pipette and transfer the plasma into two separate 3.5 mL polypropylene tubes. Next, immediately freeze the tubes at -80° C and store until delivery to the Mayo Clinic (See section 8.2.5 for shipping instructions).

8.2.4 Sample labeling
Samples should be labeled with the patient's NANT ID number, the word "Irino", the protocol number NANT0903, the date of blood draw, and exact time of the blood draw.

No other identifiers should be included on the label.

8.2.5 Sample shipment
Samples will be held until all samples have been obtained and then sent as a single batch. Batched samples should be sent frozen on dry ice by FedEx priority overnight to:

Renee McGovern
Oncology Research
Gonda 19-151
Mayo Clinic
200 First Street, SW
Rochester, MN 55905
Telephone: 507-284-4303

A copy of the irinotecan pharmacokinetics specimen transmittal form should accompany the shipment and another copy faxed to the NANT Operations Center at (323) 361-1803.

Samples should only be shipped on a Monday-Thursday to allow for weekday delivery. Avoid holiday shipments. Email Renee McGovern (McGovern.Renee@mayo.edu) with the tracking number at the time of sample shipment.

8.2.6 Methodology
Plasma irinotecan, SN-38, SN-38G, and APC concentrations will be measured by a sensitive and specific HPLC assay with fluorescence detection or by LC/MS/MS, if available. Irinotecan, SN-38, SN-38G and APC plasma concentration-time data will be analyzed by standard non-compartmental methods using the program WINNONLIN. If a sufficient number of patients are enrolled, the data will be analyzed by population pharmacokinetics using the program NONMEM.

8.3 Evaluation of *UGT1A1* and *AURKA* polymorphisms

8.3.1 Sample requirements
A single 5-10 mL sample of whole blood in a purple top EDTA tube is required.

8.3.2 Sampling scheduling
A single sample is required for each patient consenting to this optional study. This sample is best obtained prior to the start of therapy, but may be obtained anytime up until Day 7 of cycle 1.

8.3.3 Sample processing

The sample should be placed on ice, but not frozen.

8.3.4 Sample labeling
Sample should be labeled with the patient's NANT ID number, the protocol number NANT0903, the date and time of blood draw, and the word "Polymorphisms".

No other identifiers should be included on the label.

8.3.5 Sample shipment
Each sample should be sent on the day the sample was obtained. Sample should be shipped cold but not frozen by shipping along with an ice pack, taking care to keep the tube out of direct contact with the ice pack. Samples should be shipped by Federal Express overnight to:

Renee McGovern
Oncology Research
Gonda 19-151
Mayo Clinic
200 First Street, SW
Rochester, MN 55905
Telephone: 507-284-4303

A copy of the Genotyping specimen transmittal form should accompany the shipment and another copy faxed to the NANT Operations Center at (323) 361-1803.

Samples should only be shipped on a Monday-Thursday to allow for weekday delivery. Avoid holiday shipments. Email Renee McGovern (McGovern.Renee@mayo.edu) with the tracking number at the time of sample shipment.

8.3.6 Methodology
Peripheral mononuclear cells from 5 ml of whole blood will be used for DNA extraction by standard technique. Genotyping for *UGT1A1*and for *AURKA* SNPs rs1047972 and rs2273535 will be performed by standard molecular techniques in the Ames Laboratory at Mayo Clinic. No patient identifiers will be available to laboratory personnel conducting the analyses.

8.4 Evaluation of markers of Aurora A expression in archival tumor tissue

For patients who consent to this portion of the study, a paraffin-embedded tissue block should be submitted. If paraffin-embedded tissues blocks are not available, 10 unstained slides may be submitted. Tissue material may be derived from initial diagnosis, primary tumor resection, or biopsy/surgery at the time of relapse, with a priority given to samples from initial diagnosis.

The timing of the sample (diagnosis, primary resection, or relapse) and anatomic location should be indicated on the Aurora A specimen transmittal form. A copy of the specimen transmittal form should be faxed to the NANT Operations Center at (323) 361-1803.

Samples and specimen transmittal form should be sent at room temperature via FedEx to:

NANT Operations Center
4650 Sunset Blvd, MS#54
Los Angeles, CA 90027
323-361-5687

Samples should only be shipped on Mondays-Thursdays to allow for weekday delivery. Email NANT Operations Center at nantcrf@chla.usc.edu with the tracking number at the time of sample shipment.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy

a. Progressive disease
b. Completion of planned therapy
c. Patient/parent withdrawal from therapy
d. Unacceptable adverse events by protocol criteria or physician judgment
e. . Entry onto another therapeutic study and/or another anti-cancer therapy.

Patients who are off protocol therapy are to be followed until they meet the criteria for off study.

9.2 Off Study Criteria

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

10.0 STATISTICAL CONSIDERATIONS

10.1 Sample Size and Study Duration

Design of the Completed Phase I Portion: Two to six evaluable patients will be entered at each dose level for determination of the maximum tolerated dose. The minimum sample size required to identify the MTD is 15 patients. The maximum sample size for the phase 1 portion, assuming all 4-dose levels plus the initial dose level 1 require 6 patients before the MTD is determined, is 30 patients. This estimate assumes that all patients are fully evaluable. Review of the enrollment rate onto recent non-MIBG NANT studies indicates that 1-2 patients per month are available for the phase I portion of the study. For example, NANT protocols N01-03 (CEP-701), N03-01 (oral irinotecan and temozolomide), and N04-04 (oral fenretinide) have each enrolled approximately 8 patients per year, not accounting for closure time due to protocol amendments and drug supply issues. These patient numbers predicted identification of the MTD within approximately 12-18 months. (*The phase 1 portion required 22 patients and 18 months to complete.)*

Phase 2 Portion: The phase 2 portion of the study will enroll 14-20 new patients based on the two-stage design. Review of enrollment to date to the phase 2 portion indicates that 2 patients with neuroblastoma per month are available for this portion of the study. We anticipate that the phase 2 portion of the study will be completed within 12 months.

The oral solution cohort will enroll 6-18 patients, though only patients unable to swallow pills will enroll to this cohort. We expect 1 patient per month will be available, allowing completion of this cohort in 6-18 months.

10.2 Definitions

10.2.1 Evaluable for Inclusion in Dose Escalation Consideration

Patients will be evaluable for inclusion in dose escalation consideration if they have received $\geq$ 5 of the 7 planned doses of MLN8237, $\geq$ 4 of the 5 planned doses of irinotecan, and $\geq$ 4 of the 5 planned doses of temozolomide in cycle 1 AND are followed until Day 21 of the first cycle of therapy. In addition, patients who experience DLT at any time after the first dose of MLN8237 are evaluable for inclusion in dose escalation consideration. Toxicity will be assessed and reported on all patients who begin MLN8237 therapy.

Patients who do not receive at least 5 doses of MLN8237, at least 4 doses of irinotecan, or at least 4 doses of temozolomide (for any reason other than toxicity or tolerability of the regimen) and who do not experience dose limiting toxicity, will not be counted as successfully completing one course of treatment without toxicity and will be replaced.

10.2.2 Evaluable for Response

Eligible patients with measurable or evaluable disease who receive $\geq$ 5 of the 7 planned doses of MLN8237, $\geq$ 4 of the 5 planned doses of irinotecan, and $\geq$ 4 of the 5 planned doses of temozolomide in cycle 1 are evaluable for response. Eligible patients with measurable or evaluable disease who fail to complete one course of therapy because of disease progression are also evaluable for response. 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 or not evaluable. Each patient will be assigned one of the following categories (see Section 11.4):

a. Complete response
b. Very good partial response
c. Partial response
d. Stable disease
e. Mixed response
f. Progressive disease
g. Early death from malignant disease
h Early death from toxicity
i. Early death because of other cause
j. In-evaluable (not assessable, insufficient data, patients off therapy early due to toxicity)

k. Never received any of the study drugs, MLN8237, irinotecan, or temozolomide

All eligible patients who receive study therapy will be included in the initial 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 4.4) 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 highest dose level (dose level 3), then that dose level will be called the MTD.

10.3 Dose Escalation Rules for the Phase 1 and Oral Solution Cohort Portions of Study

The primary endpoint for the phase 1 and oral solution cohort portions of this study will be toxicity that is attributable to the combination of MLN8237, irinotecan, and temozolomide during the first cycle of therapy. Toxicity as graded by CTCAE v4.0 will continue to be recorded and monitored throughout all courses of therapy.

These portions of the study will utilize the rolling-six design for dose escalation.[21] This design is a modification of the classic 3+3 dose escalation strategy. With this design, two to six patients will 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 tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

For example, when three participants are enrolled onto a dose cohort, if toxicity data are available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data are not yet available for one or more of the first three participants and no DLT has been observed, or if ≤1 patients have experienced DLTs, the new participant is entered at the same dose level. Lastly, if two or more patients have experienced DLTs, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. 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.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped.

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.

The initial version of the protocol (Amendment #2) did not include mandatory myeloid growth factor support or mandatory cephalosporin diarrhea prophylaxis. That version included a provision to replace the first patient with dose-limiting neutropenia or dose-limiting diarrhea. Based on the experience from the first 6 patients treated at dose level 1, this provision would have been implemented and a patient replaced. Given the toxicities observed in patients treated at dose level 1, Amendment #3 resumed the phase I portion of the study with evaluation of 6 more patients at dose level 1B with the same doses of irinotecan, temozolomide, and MLN8237 as used in dose level 1, but with mandatory myeloid growth factor support and mandatory cephalosporin diarrhea prophylaxis.

In order to finalize the dose that will be used in the Phase 2 portion, in addition to determination of the MTD, a descriptive summary of all toxicities will be reported. Particular emphasis will be placed on descriptions of diarrhea, mucositis, and myelosuppression.

Preliminary results of pharmacokinetic testing will be examined, including clearance, C_{max}, T_{max}, C_{ss}, and terminal half-life for both MLN8237 and irinotecan. These parameters will be qualitatively compared with estimates from prior studies of MLN8237 and irinotecan as single agents. These results will be reviewed by the study management committee for possible drug-drug interactions. This review will take place prior to activation of the phase 2 portion of the study and prior to escalation from dose level 1B to 2B in the oral solution cohort (if escalation supported by toxicity and PK data in that cohort).

10.4 Statistical Rules for the Phase 2 Portion

The phase II portion at the MTD will enroll patients in two stages. A maximum of 20 patients will contribute response data reflecting patients treated at the recommended dose of the combination of MLN8237, irinotecan, and temozolomide.

	Cumulative Number of Responses	Decision / Action
Stage 1: Enter 14 patients	≤ 0	Terminate the trial because the combination is not sufficiently effective (i.e. ORR < 15%)
	≥ 1	Continue trial (proceed to Stage 2), providing toxicity is acceptable
Stage 2: Enter 6 additional patients (total of 20 patients)		Construct a 95% confidence interval for the objective response rate

Under the hypothesis of a true response rate that is 15% or greater (derived from response rate in COG protocol ANBL0421 with irinotecan and temozolomide), there is a 90% chance that at least 1 of the 14 patients in Stage 1 of the expansion will experience an objective response (hence no responders in 14 patients will lead us to conclude that the true response rate is less than 15%). With 20 patients, the half-width of a two-sided 95% confidence interval will be no more than +/- 0.24 (using the method of Jennison and Tumbull to adjust for the two-stage design). Completion of enrollment to stage 2 is therefore designed to provide a more precise estimate of the response rate of this regimen.

Toxicity Monitoring Plans for the Phase II Portion

For the patients enrolled during the Phase II portion at the MTD, the following rules will be used to monitor toxicity and trigger a formal review of the all the toxicities, with the possibility of reducing the dose (applies to the new patients):

- If 2 patients experience a first course DLT (at least possibly attributed to the study drugs) in the 1st 6 patients
- If 3 patients experience a first course DLT (at least possibly attributed to the study drugs) in the 1st 9 patients
- If 4 patients experience a first course DLT (at least possibly attributed to the study drugs) in the 1st 12 patients
- If 5 patients experience a first course DLT (at least possibly attributed to the study drugs) in the 1st 15 patients
- If 6 patients experience a first course DLT (at least possibly attributed to the study drugs) in the 1st 18 patients
- If 7 patients experience a first course DLT (at least possibly attributed to the study drugs)

Patients who enrolled as inevaluable for hematologic DLT due to marrow involvement and low baseline blood counts will remain inevaluable for hematologic DLT even if their bone marrow disease appears to improve on therapy. The number of these patients who require dose modifications in subsequent courses will be reported descriptively. These patients will follow dose modification guidelines according to sections 4.6.1 and 4.6.2. These patients will be evaluable for response.

The table below summarizes the probability that the boundary indicating excessive DLT's has been crossed according to the rules above. The values in the table below are based on 10,000 simulations and are accurate to ±0.01 (based on a 95% confidence interval).

Table: Probability that the boundary indicating excessive DLT's has been crossed							
True Chance of DLT	5%	10%	15%	20%	25%	30%	35%
Probability of Excessive DLT's	0.04	0.13	0.28	0.44	0.61	0.75	0.85

10.5 Statistical Rules for Oral Solution Cohort

Up to 6 patients evaluable for dose escalation consideration (section 10.2.1) will be enrolled at the starting dose level for this cohort (dose level 1B = one dose level below the phase 2 dose obtained with enteric coated tablets), following the rolling-six rules in section 10.3. After enrollment to this dose level is complete, the toxicity and pharmacokinetic parameters will be assessed by the study committee.

If dose de-escalation is indicated based upon toxicity at dose level 1B, this will occur following the rolling-six rules in section 10.3 and will occur independent of pharmacokinetic results.

If dose escalation appears feasible based upon toxicity at dose level 1B, this will occur following the rolling-six rules in section 10.3 only if the study committee determines that MLN8237 exposures are below predicted levels at dose level 1B. This provision is in place since dose level 2B with the oral solution is predicted to be comparable to dose level 3B with the tablet formulation and that dose level was not tolerable in the phase 1 portion of the study.

Once the MTD with the oral solution has been determined, the study committee will assess the pharmacokinetic parameters to determine if enrollment of up to additional 6 patients at the MTD will be needed to better characterize the pharmacokinetic profile of the oral solution. Interpatient variability and comparison with exposures obtained with oral solution and enteric coated tablets will be used to drive this determination.

10.6 Analysis of Results

The outcome status (in terms of number of courses received, toxicity, response, reason off treatment, progression, and survival) of all registered patients will be reported.

10.6.1 Toxicity

All toxicities observed will be summarized in terms of type (organ affected or laboratory determination), severity (by NCI CTCAE), and attribution. Tables will be created to summarize theses toxicities and side effects by tablet vs. oral solution, by dose level and by course. Particular emphasis will be placed on descriptions of diarrhea, mucositis, and myelosuppression.

10.6.2 Response/Outcome

All eligible patients who begin treatment will be included in the analysis of overall survival, event-free survival (EFS), and best response (defined in Section 11.0 below). Patients with measurable

or evaluable tumor who receive study therapy or who progress prior to completion of therapy will be included in a planned subset analysis of tumor response (per Section 5.2.2).

Overall survival is defined as the time from start of treatment until death due to any cause or time of last follow-up if the patient is alive at the last known follow-up. Event-free survival is defined as time from start of treatment to disease progression, development of a second malignancy, or death – whichever comes first; patients who are alive, have not progressed or developed a new malignancy will be censored at their last follow-up.

10.7 Monitoring Plan for Death within 30 Days of Last Treatment

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 MLN8237 regardless of cause will be reviewed and reported to the NANT DSMB and to the FDA according to standard procedure.

10.8 Pharmacokinetic and Correlative Biology Studies

Routine pharmacokinetic parameters for both MLN8237 and irinotecan will be determined using standard methods and reported descriptively. After completion of the phase II portion of the study, a final pharmacokinetic analysis will be performed that incorporates results from the phase I, phase II, and oral solution cohort portions of the study. Parameters to be determined include exposure, clearance, C_{max}, T_{max}, C_{ss}, and terminal half-life for both MLN8237 and irinotecan. These parameters will be assessed for both the enteric coated tablet formulation and for the oral solution formulation. These parameters will be qualitatively compared with estimates from prior studies of MLN8237 and irinotecan as single agents. In addition, these parameters for MLN8237 will be qualitatively compared between the enteric coated tablet and oral solution formulations.

The correlative biology studies are considered descriptive. For the study of *UGT1A1* genotype and toxicity, patients will first be categorized according to the number of *UGT1A1*28* alleles (0, 1, or 2 copies of the allele). Association between *UGT1A1* genotype and occurrence of (any) DLT and diarrhea will then be examined qualitatively. For the study of Aurora A expression, patients will first be categorized as having “high” or “low” Aurora A tumor expression for both mRNA and protein (using a median split). Association between Aurora A expression, response and EFS will then be examined. Similarly, associations between *MYCN* amplification status and Aurora A expression (mRNA and protein), response and EFS, and will be examined. These descriptive analyses will use contingency tables, scatterplots, and Kaplan-Meier plots, as well as corresponding quantitative measures of association. Association between *AURKA* genotype and objective response will be examined qualitatively. Patients will be categorized according to genotype at the two *AURKA* SNPs of interest (homozygous wild type; heterozygous; homozygous minor allele), with the percent of patients with at least a partial response or better given in each category.

10.9 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 RESPONSE CRITERIA VERSION 1.2

With Amendment #6, response criteria have changed to the following NANT Response Criteria version 1.2. The previous NANT Response Criteria versions 1.0 and 1.1 have been moved to Appendix VII and Appendix VIII, respectively, for reference. For all patients enrolling prior to Amendment #5, sites should continue to utilize version 1.0 to assess and report response. For all patients enrolling with Amendment #5 and after, sites will use version 1.2 to assess and report response. NANT central review of response will utilize version 1.2 for all patients.

Overall response will incorporate all three parameters: CT/MRI; MIBG (FDG-PET is substituted for MIBG non-avid tumors); and bone marrow response with 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 be defined by central review, using the same criteria below.

11.1 Response Criteria for CT/MRI Lesions

For lesions evaluated by CT/MRI, this study will use 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).

11.1.1 Definition of soft tissue TARGET LESIONS on CT/MRI:

Soft tissue target lesions that will be followed for response must meet criteria in a. and b. below:

a. 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 lymph nodes ≥ 15mm on short axis. (The short axis is measured after identifying the longest diameter of a lymph node or nodal mass, and then measuring the longest perpendicular diameter to that as the short axis).
b. A target lesion must also be evaluable for response: To be evaluable, the lesion must also be MIBG or FDG-PET avid (if tumor known to be MIBG non-avid), or have a biopsy as required in the eligibility criteria. If one soft tissue lesion present at enrollment is biopsied showing neuroblastoma or ganglioneuroblastoma at any time point, then all other soft tissue lesions present at enrollment are considered evaluable. Bone marrow positivity does not affect soft tissue evaluability.

NOTE: Soft tissue components of bone lesions will be considered measurable lesions if > 10mm in at least one dimension, and 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, short axis for nodal lesions) for all target lesions will be calculated and reported as the **sum of diameters**.

11.1.2 NON-TARGET SOFT TISSUE LESIONS will include:

a. Leptomeningeal tumor and tumor in cerebrospinal fluid cytology will be considered non-target lesions.
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 soft tissue lesions (≥ 10mm) that are not MIBG avid or PET avid (if tumor known to be MIBG non-avid) and if biopsied did not show neuroblastoma or ganglioneuroblastoma.

b. Non-measurable soft tissue lesions < 10mm or non-measurable 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 The response of the CT/MRI lesions will be defined as outlined below:

11.1.4.1 Complete Response (CR)
Disappearance of all target and non-target CT/MRI lesions.

11.1.4.2 Partial Response (PR)
At least a 30% decrease in sum of diameters of CT/MRI lesions (using longest diameter for non-nodal lesions and short axis for nodal lesions), taking as reference the measurement of target lesions performed at study enrollment. Non-target CT/MRI 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 lesions (using longest dimension for non-nodal lesions and short axis for nodal lesions) taking as reference the smallest sum of diameters while on study (this includes the baseline if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5mm. A new target or non-target tumor 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 CT/MRI 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 lesions which are stable in size, will be captured in MIBG response(or FDG PET response if tumor is MIBG non-avid) and will NOT be graded as CT/MRI progression (CT/MRI would be graded as SD). 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 lesions)
Neither sufficient shrinkage in sum of diameters to qualify for PR and patient does not meet any criteria for PD. No new lesions. Non-target 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 lesions only)
Non-target lesions are still present; may be smaller or stable in size, and do not meet criteria for PD. No new non-target tumor lesions (new lesions may be biopsied to rule out PD).

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

11.1.4.7 Non-target lesions only: Patient has no target lesions, but does have non-target lesions.

11.1.4.8 Not evaluable (NE)
CT/MRI scans are of inadequate quality as assessed by central reviewer, or scans are not repeated of all lesions 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.

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

11.2 Response Criteria for Morphologic Bone Marrow Disease

Routine morphology (with or without routine immunocytochemistry) will be used for baseline evaluation and all subsequent response evaluations performed while on protocol therapy, and at end of protocol therapy. Central review will be performed on bilateral biopsies only, unless tumor is seen only on aspirates.

Patients with ≤ 5% tumor on all samples of the bilateral bone marrow aspirate and biopsies at study entry will be evaluable for bone marrow response, but defined separately from patients with > 5% at study entry.

The percentage of tumor in an aspirate will be calculated as the number of tumor cells divided by the number of total nucleated cells. 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 (excluding Schwannian stroma).

11.2.1 Complete Response (CR)
Greater than 5% tumor cells seen on any one sample of bilateral aspirates/biopsies performed at study entry, with no tumor cells seen on bilateral aspirates and biopsies at one subsequent time point.

11.2.2 Complete Response Minimal Residual Disease (CR-MRD) Percentage of tumor ≤ 5% on all samples of bilateral aspirates/biopsies at study entry, with no tumor cells seen on bilateral aspirates and biopsies at one subsequent time point after starting protocol therapy. If subsequent time points remain negative, then patient is classified as CR-MRD. If subsequent time points are intermittently positive but with ≤ 10% tumor, then response should be reclassified as SD at the negative time points initially reported as CR-MRD.

11.2.3 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 >10% tumor on any one bone marrow sample AND there is a doubling in the amount of tumor compared to study entry (baseline).

For example a patient entering with ≤ 5% tumor in marrow must increase to > 10% tumor to have PD; a patient entering with 30% tumor 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 who enter on study with no tumor seen will be considered PD if ONE subsequent evaluation shows >10% tumor. If ≤ 10% tumor is seen on one subsequent evaluation or intermittently, the response will be classified as SD.

11.2.4 Stable Disease (SD)
Stable disease will be defined as persistence of an amount of tumor in the bone marrow that does not meet criteria for progressive disease or CR or CR- Minimal Residual Disease. (Note that patients who enter with ≤ 5% tumor and have one negative bone marrow which is initially graded as a CR-MRD and then on subsequent time points have 1-10% tumor noted would be then considered as SD at all time points, including the time point initially graded as CR).

11.2.5 Not Evaluable (NE)
Patients for whom follow-up bone marrows 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.

11.2.6 Not involved (NI)
Patients with no evidence of neuroblastoma in the bone marrow at study entry, and remain negative on subsequent evaluations. (Note that such patients may be reclassified as SD if they meet the SD criteria above with intermittent tumor in the bone marrow).

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

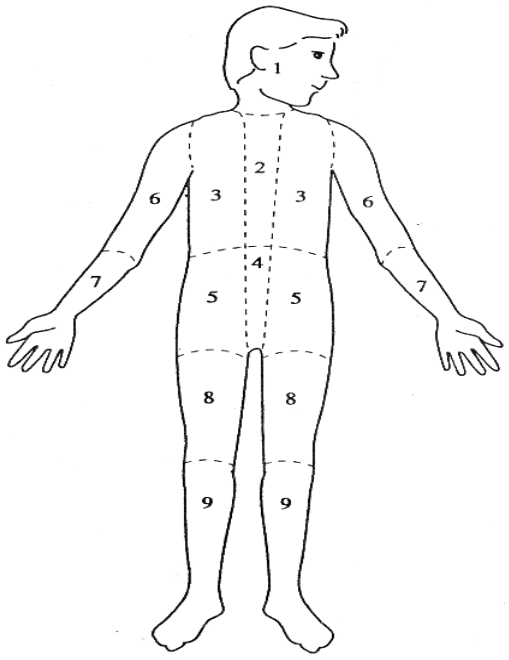
11.3. **Response Criteria for MIBG Avid Lesions**

MIBG 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 MIBG response using Curie, however the statistical endpoint of MIBG response will utilize the Curie score from the central reviewer.

MIBG scans will be scored for 10 regions; 9 anatomic regions for skeletal metastases, and a 10th region for any MIBG avid soft tissue disease.

Each of the 10 regions will be given a score of 0-3, as defined below.

Scoring of Skeletal 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 ten 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 / SKELETAL 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 below).

REGION 10 / SOFT TISSUE DISEASE: Soft tissue disease within the neck, chest or abdomen/pelvis is scored within Region 10. Examples of soft tissue lesions may include MIBG avid cervical, paraspinous, adrenal, renal, retroperitoneal, or hepatic masses.

SCORING SOFT TISSUE DISEASE: Score = 1 indicates an isolated soft tissue mass that encompasses < 50% of that region (chest or abdomen/pelvis). Score = 2 indicates > 1 soft tissue lesion in the neck, chest or abdomen/pelvis. A soft tissue score = 3 indicates MIBG avid soft tissue disease that emcompasses > 50% of either the chest or abdomen/pelvis. (For example, a large adrenal mass in which the MIBG avidity encompasses > 50% of the abdomen/pelvis is scored a 3 for Region 10). Cervical soft tissue disease is included in the chest region.

If no MIBG-avid soft tissue lesions are present, then score 0 for Region 10.

If a solitary soft tissue lesion extends into both the chest and abdomen/pelvic regions, score 3 for that lesion. For example, a large paraspinous mass that extends along the thoracic and lumbar spine would be scored a 3 for Region 10. Any corresponding metastatic bone disease within the thoracic or lumbar spine would be scored separately for the cervico-thoracic spine (Region 2) and lumbar spine (Region 4).

Conjugate planar imaging will be used to score a given region. SPECT scans may be used as an adjunct, but only to help delineate the location of the MIBG avid lesion.

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

a. Complete response: all areas of uptake on MIBG scan completely resolved.
b. Partial response: Relative score ≥ 0.1 to ≤ 0.5
c. Stable disease: Relative score > 0.5 to < 1.2
d. Progressive disease: New lesions on MIBG scan OR a relative score ≥ 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 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 Response Criteria using FDG-PET scans (for MIBG non-avid patients)

Patients known to be non-avid for MIBG should have FDG-PET scans performed for monitoring response. FDG-PET avid lesions will be scored by the presence or absence of a lesion with uptake that is two times above background.

11.4.1 Complete response (CR)
Resolution of all FDG-PET uptake in all FDG-PET avid lesions identified at baseline and no new FDG-PET avid lesions.

11.4.2 Partial response (PR)
Reduction of number of lesions by FDG-PET by > = 50%. No new FDG-PET avid 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 lesions on FDG-PET scan. Note: biopsy may be done to exclude causes of FDG-PET uptake other than tumor. If biopsy 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 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 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 lesions will be evaluated by both the Curie scoring method and by enumeration of lesions to grade 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 still be requested at all response evaluation time points and recorded in database as both actual value and as "elevated" or "not elevated". Catecholamines must be at least 3 standard deviations above the mean for age to be classified as "elevated".

11.6 Definition of Overall Response for Each Patient

The criteria below will be used to define the overall response for each patient, with consideration of all three individual response parameters: CT/MRI, MIBG (FDG-PET if MIBG non-avid), and Bone Marrow.

11.6.1 Complete Response (CR)
Response of CR or NI for MIBG, (FDG-PET if tumor is not MIBG avid), CT/MRI, and bone marrow.

11.6.2 Complete Response MRD (CR-MRD)
Response of CR or NI for MIBG (FDG-PET if tumor is not MIBG avid), CT/MRI response of CR or NI, with BM response of CR-MRD

11.6.3 Partial Response (PR)
Response of PR in both CT/MRI and MIBG (FDG-PET if tumor is not MIBG avid); or response of PR in either CT/MRI or MIBG (FDG-PET if tumor is not MIBG avid) with response of CR, NI, or SD-NTL for other parameter. Bone marrow response of either CR, CR-MRD, NI, or SD for patients with maximum amount of tumor ≤ 5% at baseline.

11.6.4 Progressive Disease (PD)
Either one of the following will define an overall response of PD:

a. At least one response parameter including CT/MRI, MIBG, bone marrow and/or FDG-PET response is PD. 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, or SD-NTL forother parameters.

11.6.6 Minor response (MR)
Complete response, Complete-MRD response, and/or partial response for one parameter (i.e. CT/MRI, MIBG (FDG-PET if MIBG non-avid), bone marrow), with response of stable disease for second parameter and any response other than PD or not evaluable for third parameter.

11.6.7 Not evaluable (NE)

Response of Not evaluable for one or more response parameters including CT/MRI, MIBG (FDG-PET if MIBG non-avid), or bone marrow for any parameter that had measurable/evaluable tumor at study enrollment. However, if one parameter is done and demonstrates PD this is defined as an overall response of PD. In addition, response may be declared not evaluable if review by the Study Management Committee / PI deems that there is insufficient data to grade response.

11.6.8 No progression

Baseline status at enrollment was NI or non-target lesions only for CT, NI for bone marrow, NI for MIBG (FDG-PET if MIBG non-avid) and there has NOT been PD at any site since on protocol therapy

11.6.9 Not done (ND)

Response not assessed at this time point.

11.6.10 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:

Overall Response Assignment

<table>
<tr><th>CT/MRI Response</th><th>MIBG Response*</th><th>Bone Marrow Response</th><th>Overall Response</th></tr>
<tr><td colspan="3">PD for any one parameter with any response (including Not Evaluable or Not Done) for the other 2 parameters. PD may also be defined by clinical assessment of the treating physician only.</td><td>PD</td></tr>
<tr><td>CR</td><td>CR</td><td>CR</td><td>CR</td></tr>
<tr><td colspan="3">CR for one parameter with either CR or NI for other parameters</td><td>CR</td></tr>
<tr><td colspan="2">MIBG response = CR or NI
CT/MRI response = CR or SD-NTL or NI</td><td>CR-MRD</td><td>CR-MRD</td></tr>
<tr><td>CR or PR or SD-NTL or NI</td><td>PR</td><td>CR or CR-MRD or NI
-OR-
SD if ≤ 5% tumor in bone marrow at study entry</td><td>PR</td></tr>
<tr><td>PR</td><td>CR or PR or NI</td><td>CR or CR-MRD or NI
-OR-
SD if ≤ 5% tumor in bone marrow at study entry</td><td>PR</td></tr>
<tr><td colspan="3">SD for one parameter, with SD or NI or SD-NTL for other two parameters</td><td>SD</td></tr>
<tr><td colspan="3">CR or CR-MRD or PR for at least one parameter, SD for a second parameter, and any response other than PD or Not Evaluable for other parameter</td><td>Minor response</td></tr>
<tr><td colspan="3">Response of Not Evaluable for any one of the 3 parameters that had measurable/evaluable tumor at study enrollment and no PD for any parameter.</td><td>Not Evaluable</td></tr>
<tr><td colspan="3">No response evaluations performed for any of the 3 parameters</td><td>Not Done</td></tr>
<tr><td>NI or non-target lesions only at enrollment and no PD on subsequent timepoint</td><td>NI at enrollment and no PD at subsequent time point</td><td>NI at enrollment and no PD at subsequent time point</td><td>No progression</td></tr>
</table>

*For patients who utilize FDG-PET in place of MIBG response, then substitute FDG-PET response for MIBG response in this table to define overall response.

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

Rapid mandatory toxicity case report and hemogram forms will be submitted to the NANT Operations Office weekly for all patients on Course 1.

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 4. A copy of the CTCAEv4 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:

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 (see NANT website www.nant.org under protocol data forms/generic forms packet) and email to NANTstaff@chla.usc.edu.
- Follow-up information should be submitted 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, Steven DuBois, 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, Steven DuBois. 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, Steven DuBois, 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 Med Watch website www.fda.gov/medwatch. NANT will forward the completed report the FDA and other relevant authorities or investigators on behalf of the IND Sponsor, Steven DuBois.
- 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, Steven DuBois.
- Follow-up information should be submitted as soon as relevant information is available.

A cover letter to accompany the Med Watch report will be prepared by the NANT Operations Center in collaboration with the IND sponsor, Dr. DuBois. 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. Does the occurrence of this AE alter 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 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. The NANT Operations Center will also distribute copies of AE reports to Millennium Pharmaceuticals Inc within two working days.

12.6 Adverse event reporting requirements for Millennium Pharmaceuticals Inc

NANT will notify Millennium Pharmaceuticals of all serious adverse events, both expected and unexpected, and copy all Medwatch forms and related correspondence to Millennium. Notification will be via Cognizant at the following contacts:

Fax Number: 1-800-963-6290

Email: TakedaOncoCases@cognizant.com

12.7 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
- A copy of the cytogenetic report (if applicable)

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

12.8 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 Millennium Pharmacovigilance by the NANT Operations Office (see Section 12.4 for contact information) immediately. The pregnancy must be followed for the final pregnancy outcome (ie, delivery, still birth, miscarriage) and Millennium Pharmacovigilance will request this information from the investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium Pharmacovigilance by the NANT Operations Office immediately (see Section 12.4 for contact information). Every effort should be made to follow the pregnancy for the final pregnancy outcome."

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:

- Study case report forms including patient diaries to document administration of temozolomide and MLN8237, bone marrow reports (including aspirate and biopsy reports), urine catecholamine reports, and radiology reports (CT/MRI/MIBG/PET scans). These forms and reports are faxed to the NANT Operations Center at 323-361-1803 or sent by email as electronic files to nantdata@chla.usc.edu at the end of each cycle of therapy.

- For **all** patients on study, CT/MRI and MIBG scans done as baseline tumor evaluation at study entry are required to be submitted into NANT PACS for central review (Bone marrow slides from study entry may also be requested at the discretion of the Operations Center).

- For all patients who report an overall response of CR, CRT-MRD, PR, Minor Response or who have SD for at least 4 cycles will submit all CT/MRI scans, MIBG 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. Radiology scans are requested to be submitted via GRID, however CD/optical disk may also be sent to NANT Operations Center with patient identifiers removed (scans will be identified by NANT patient number/study number).

- 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 AND ASSENT DOCUMENTS

15.1 SAMPLE INFORMED CONSENT: PHASE I, PART B

PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

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

CONSENT FORM FOR PHASE I PORTION OF STUDY, PART B

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 study doctor.

You are invited to participate in this study because you have been diagnosed with neuroblastoma. Your cancer has either grown back (relapsed) or has never gone away (persistent tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy and/or high-dose chemotherapy with a stem cell transplant.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

To find the highest doses of MLN8237, that can be given with irinotecan, and temozolomide without causing severe side effects.

To find out the side effects seen by giving MLN8237 at different dose levels with irinotecan, and temozolomide.

To measure the levels of MLN8237 and irinotecan in the blood at different dose levels

To determine if your tumor gets smaller after treatment with MLN8237, irinotecan, and temozolomide

To determine if specific gene changes makes you more prone to side effects from and/or response to the combination of MLN8237, irinotecan, and temozolomide

To determine if the combination of MLN8237, irinotecan, and temozolomide delays disease progression in patients with relapsed or progressive neuroblastoma

To determine if the amount of something in your tumor called MYCN or Aurora A makes you more likely to have a good response to the combination of MLN8237, irinotecan, and temozolomide

The research is being done because:

Currently there is no known effective treatment for your type of cancer.

This study will combine an oral drug called MLN8237 with two chemotherapy medicines called irinotecan and temozolomide.

MLN8237 is an investigational drug that is not approved by the FDA. MLN8237 blocks the function of a protein that is important in the growth of cancer cells. This drug has been tested as a single-agent in children with relapsed solid tumors, including patients with neuroblastoma. In the laboratory, MLN8237 appears to make neuroblastoma tumors smaller. This effect is even greater when MLN8237 is combined with the chemotherapy drugs, irinotecan and temozolomide.

Irinotecan and temozolomide are both FDA-approved chemotherapy drugs. These drugs are approved for the treatment of certain adult cancers, but have also been used to treat children with cancer. These drugs have been used in combination in many people with neuroblastoma. In some patients with neuroblastoma, this combination reduces the amount of neuroblastoma.

Giving MLN8237 together with irinotecan and temozolomide may increase the effectiveness of this combination. We first need to find out the highest dose of MLN8237 that can be given safely together with irinotecan and temozolomide. This study will be the first study to test giving MLN8237 together with irinotecan and temozolomide. Once we have found out the highest dose of MLN8237 that can be given with irinotecan and temozolomide, we will treat more patients with this combination to determine how effective it is.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

22 people joined this first "phase 1" part of the study. Up to 20 people will take part in a separate "phase 2" part of the study. Another 6-18 people will take part in a different ongoing part of the study if they cannot swallow MLN8237 pills.

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

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

You will need to have the following exams, tests or procedures to find out if you can received the treatment part of the study. 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 study doctor.

- Physical exam
- Blood tests
- Pregnancy test
- Urine tests
- Bone marrow tests[#]
- Various scans*

[#]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.
* Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans, Bone scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans

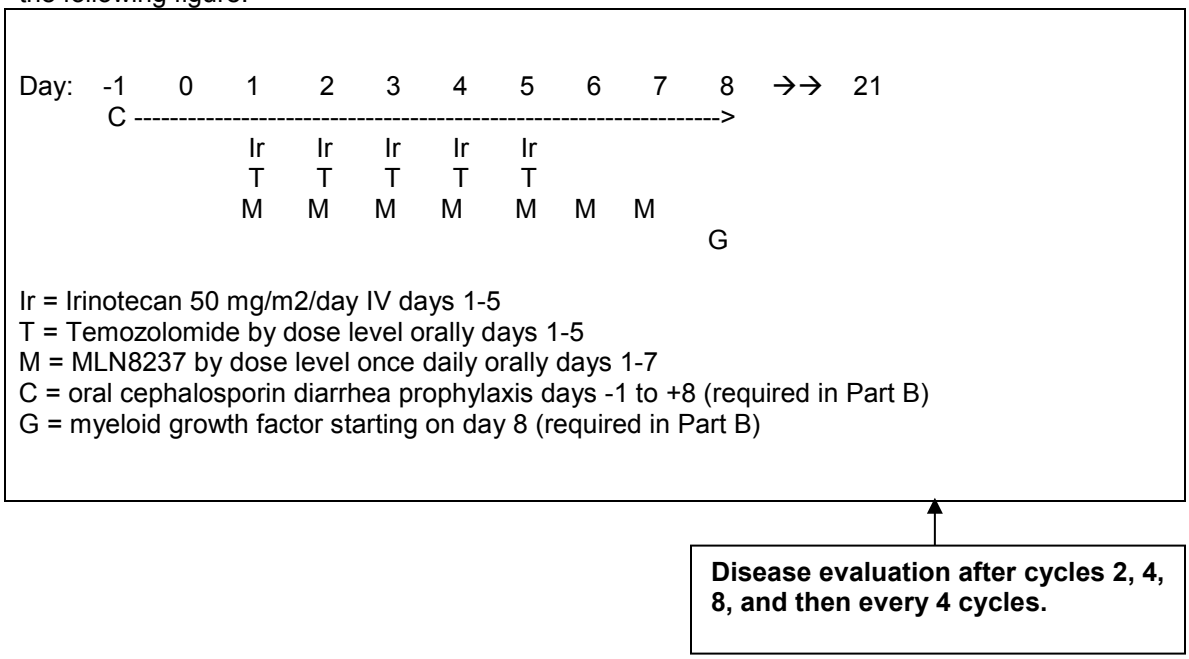
<u>During the Study</u>

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during the study. They are part of regular cancer care.

Physical exam	Bone marrow tests
Blood tests and scans	Various scans
Pregnancy test	
Urine tests	

Treatment Plan

The treatment will be given in cycles that each last 21 days. A diagram of one cycle is shown in the following figure.



You will receive irinotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) over 1 hour on days 1-5. This medicine is typically given in the clinic.

You will receive temozolomide by mouth once a day on days 1-5. The medicine is most commonly given as a capsule. If you have a hard time swallowing capsules, the medicine can also taken out of the capsule and swallowed with applesauce or apple juice. This medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

You will receive MLN8237 by mouth once a day on days 1-7. The medicine can only be given as a tablet. On days 1-5, this medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

You will receive an oral antibiotic (cefixime or cefpodoxime) by mouth once a day or twice a day on days -1 through day +8. This antibiotic is given to reduce the chances of getting diarrhea that can be seen in patients treated with irinotecan.

You will also receive a drug to boost the white blood cells count (filgrastim or pegfilgrastim). This drug will be started on day 8 of each cycle of treatment. Filgrastim is a shot given into the skin each day until the white blood cell count increases. Pegfilgrastim is a long-acting version of filgrastim that is given as a shot into the skin just once per cycle. Your study doctor will talk with you about which of these drugs you will receive.

When you join the study, you will be assigned a certain MLN8237 dose. This study will test up to four MLN8237 doses in groups of 3-6 patients. The starting MLN8237 dose for the first group of patients is about 40% lower than what is currently being given to patients receiving MLN8237 alone without bad side effects. If this is tolerated without serious side effects, then the MLN8237 dose will be increased (“dose escalation”) in groups of 3-6 patients until serious side effects are seen. At that point, investigators will have found the highest dose of MLN8237 that can be given along with irinotecan and temozolomide without bad side effects. This part of the study is called the Phase I part of the study.

The doses of irinotecan and temozolomide are not increased during this study, though the dose of temozolomide may be decreased depending upon the side effects seen in other patients. The doses used are typical doses used to treat patients with neuroblastoma.

After the highest dose of MLN8237 that can be given with irinotecan and temozolomide has been found, another group of 8-20 patients will be treated with that highest dose to help determine how effective this combination is in treating neuroblastoma. This part of the study is called the Phase II part of the study.

You will only participate in the Phase I part of the study.

You can receive up to 34 cycles of treatment (approximately 2 years) as long as you are not having bad side effects and as long as your tumor is not getting worse. Although other participating patients may receive a different dose of MLN8237, your assigned dose of MLN8237 will not change during your participation in this study unless you develop certain side effects that necessitate lowering your dose of MLN8237.

When you have finished treatment with MLN8237, irinotecan, and temozolomide

After you stop treatment with MLN8237, irinotecan and temozolomide, 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 functions, tests will 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
Blood tests	Various scans
Urine tests	

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

Determining blood levels of MLN8237 and irinotecan

One of the main research goals of this study is to find out the amount of MLN8237 and irinotecan in the blood during this treatment. Since this is one of the main goals of the study you are required to submit extra blood samples in order to participate in the overall study.

On the first day of the first cycle of treatment, a small amount of blood (5 mL, or about a teaspoon) will be drawn. If you have a central line (such as a port or a Broviac), this sample can be drawn through that line. Otherwise, you will need to have blood drawn through a vein.

On the fourth day of the first cycle of treatment, a total of 36 mL (or a little more than 7 teaspoons) will be drawn over 24 hours. This schedule of blood draws is typically done as an outpatient. If you have a central line with only one lumen or tube and that lumen or tube is being used to give you the irinotecan, then you will need to have at least 6 of these blood samples drawn through a vein. Your study doctor may recommend placing an IV catheter or tube in one of your veins through which the blood can be drawn. This may reduce the number of pokes needed for this part of the study. If you have a central line with more than one lumen or tube, you may be able to have these blood samples drawn through one of the lumens or tubes that is not being used to give you the irinotecan. Your study doctor can tell you whether you will need some pokes or an IV catheter placed or whether your type of central line can be used to draw these samples.

This amount of blood is considered safe to donate over this amount of time. Samples will be sent to the Children's Hospital of Philadelphia in Philadelphia, PA and to the Mayo Clinic in Rochester, MN for testing.

Other Research Tests in this Study

You will be asked if you want to participate in optional research tests. **This part of the study is optional.** The results of these tests would not be told to you or your doctor 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. You can decide not to let the doctors do these tests and still be able to be treated as part of this clinical study. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in these optional studies.

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

One part of the research goal is to look for genetic changes in normal blood cells of patients to see if these are related to how the liver handles MLN8237 and irinotecan, or whether you will have bad side effects after taking these drugs. We may also look to see if other genetic changes impact how likely a person is to respond to this drug combination. These tests are done on one sample of blood (one-two teaspoons, 5-10 mL) taken from your central line (or port) at the start of the first cycle of therapy. This amount of blood is considered safe to donate. The blood will be sent to the Mayo Clinic in Rochester, MN for testing.

Looking at Aurora A in neuroblastoma tumors

MLN8237 blocks the action of a protein called Aurora A. Another research goal is to look at the amount of Aurora A in neuroblastoma tumors to find out if the amount of Aurora A impacts whether tumors respond to the combination of MLN8237, irinotecan, and temozolomide. These tests are done on stored neuroblastoma tissue from your previous tumor biopsies or surgeries. If you agree to participate in this optional part of the study, we will request that your hospital send us some of your stored neuroblastoma tissue. You will not need to have an extra biopsy or surgery to participate in this part of the study. The tissue will be sent to the University of California in San Francisco, CA.

HOW LONG WILL I BE ON THIS STUDY?

You can receive up to 34 cycles of treatment (approximately 2 years) 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. Researchers will be in contact with your primary care doctor to see how you are doing; 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 oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?

Yes. If you are thinking about stopping the study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

The study doctor may 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?

You will participate in the Phase 1 part of the study. A Phase I study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase I study, some patients may have very serious side effects and could die as a result of these side effects.

In this study, researchers will be looking at side effects seen in patients taking different doses of MLN8237 together with irinotecan and temozolomide. Since subjects will be assigned to different doses of MLN8237, some subjects may receive doses that are too small to be effective while others may receive higher doses that may cause increased side effects.

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 or itching). Many side effects go away soon after you stop taking MLN8237, irinotecan, and temozolomide, 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. Because this combination has never been given to children before, there may 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 on the following pages.

Possible side effects of MLN8237

There is limited experience using MLN8237 in humans. The risks and side effects listed here and their frequencies are anticipated or predicted based on tests in animals and some experience in people. It is expected that MLN8237 toxicities will be reversible, however it is possible that MLN8237 will have their toxicities that have not been observed in or predicted from its evaluation in animal studies and the few studies in adults that have been conducted to date.

The frequency provided in the following table is approximate:

Risks and side effects related to MLN8237 include those which are:

Likely (Anticipated in 21-100 children out of every 100)	**Less Likely** (Anticipated in 5 -20 children out of every 100)	**Rare but Serious** (Anticipated in <5 children out of every 100)
• Fewer red blood cells in the blood* • Diarrhea • Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores) • Nausea • Vomiting • A feeling of extreme tiredness not relieved by sleep • Low numbers of white blood cells* called lymphocytes and neutrophils/granulocytes that may make it easier to get infections which may be life threatening • Fewer platelets in the blood* • Loss of appetite • Hair loss	• Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics* • Pain in the abdomen (belly), heartburn • Constipation • Mouth pain • Swelling caused by fluid build-up in the tissues of the arms and legs • Fever • Infections including those caused by bacteria, virus, and fungus, which may cause you to become very ill. • Increase in the blood level of certain enzymes or bilirubin (a waste product that passes through the liver) which could indicate liver irritation or damage • Increased levels of a chemical (creatinine) in the blood which could mean kidney damage • Excessive loss of water from the body • Back pain • Dizziness • Headache • Cough • Shortness of breath • Low blood pressure	• Severe rash with redness and pain of the skin on the palms of the hands and soles of the feet. • Blistering of the skin.

	• Weakness • Rash • Trouble walking • Changes in mood or confusion • Sleepiness, over-tiredness	

* If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the bloodstream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell count is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a drop in the red blood cell count, the cells that carry oxygen around the body you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Transfusions may be accompanied or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S. (acquired immune deficiency syndrome) and other infections.

MLN8237 has a chemical structure that is similar to a group of drugs called benzodiazepines. These drugs may cause dependence and withdrawal symptoms. Therefore, there is a theoretical risk that MLN8237 could cause dependence and withdrawal symptoms, as well. It is possible that while taking this drug, you will feel changes in your mood such as a sense of euphoria (joy) or a feeling of unhappiness that could lead to depression and thoughts of hurting yourself. When stopping the drug, withdrawal symptoms could include: anxiety, restlessness, difficulty sleeping, tremors, rapid heart-beat, nausea and vomiting.

Since there is a possibility that this drug may cause sedation (or sleepiness), you should not drink alcoholic beverages, since alcohol can also cause sleepiness. If you feel sleepy while you are on this study, you should avoid driving or doing anything that may need your full alertness, such as operating dangerous tools or machinery. This drug may also cause sleepiness if you are currently taking an opiate such as morphine, dilaudid, or fentanyl.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

For more information about risks and side effects, ask your study doctor.

Possible side effects of Temozolomide

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 - 20 children out of 100)	**Rare but serious** (happens to < 5 children out of 100)
•Fewer red and white blood cells and platelets in the blood. •Nausea • Vomiting • Constipation • Loss of appetite	• Diarrhea • Headache • Tiredness • Rash • Itching • Increased need to urinate • Urinary Tract Infections • Mouth sores • Fluid buildup in legs and arms • Hair loss • Elevation in the blood of certain enzymes found in the liver • Pain in the abdomen	• Convulsions Difficulty swallowing • Dizziness • Anxiety or depression • Difficulty sleeping • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever • Low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life-threatening • Partial paralysis or weakness of one side of the body • Loss of memory • Blood clots which may be life-threatening • Visual disturbances that may cause double vision • Forgetfulness or confusion • Aches and pains in muscles • A new cancer or leukemia resulting from this treatment •Lack of muscle coordination which may affect speech, eye movement, swallowing, walking, picking up things. • Liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure.

Possible side effects of Irinotecan

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 - 20 children out of 100)	**Rare but serious** (happens to < 5 children out of 100)
•Diarrhea that can occur during the infusion of irinotecan or immediately after and may be associated with abdominal cramping, a runny nose, tearing, salivation, sweating, flushing (feeling of warmth and red cheeks), and difficulty adjusting your eyes to light. Loss of body water • Nausea and Vomiting • Inflammation and/or sores in the mouth, • Loss of appetite • Stomach pain • Fever • A feeling of weakness and tiredness • Temporary hair loss • Elevation of liver and bone enzymes in the blood and of bilirubin (yellow pigment formed in the liver) • An increase in the blood of a type of white blood cell called an eosinophil. These are sometimes associated with allergic reactions. • Decrease in the number of red and white blood cells and platelets made in the bone marrow	• Fewer red blood cells and platelets in the blood blood. • Diarrhea that may occur later from 1 day to 2 weeks after irinotecan which could cause excessive loss of water and salts from the body • Constipation • Pain at the injection site • Blood clots which may be in rare cases life threatening* • Rash • Inflammation and/or sores in the mouth, throat and/or esophagus • Headache • An upset stomach • Increase in liver and kidney levels	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such and sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening • Inflammation of the lungs with cough and congestion • Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools and abdominal pain • Headache • Skin inflammation • Trembling • Blood in the urine • Mildly increased level of protein and glucose in the urine • Low amount of protein in the blood • Mouth sores • Sensation of warmth on face. • Risk to the unborn child in pregnant patients.** • Pain at infusion site • Disorientation/confusion • Dizziness and low blood pressure • A blockage of the bowel that prevents passage through the bowel • Slow heart beat .

* This toxicity is seen more commonly when irinotecan is given in combination with fluorouracil and leucovorin. It may rarely be a life threatening event.

** Birth defects and other serious abnormalities in the unborn baby have been noted with irinotecan in animal studies at doses similar to or less than those used in humans. The timing and frequency of these effects is as yet unknown. These may include multiple birth defects and abnormalities of bone formation, small size of baby at birth and increased risk of death of the unborn baby. Irinotecan is excreted in rat milk but this is unknown for humans.

Possible side effects of G-CSF (such as Neupogen, filgrastim Or Neulasta, Pegfilgrastim)

G-CSF is not an anti-cancer medicine. It helps the growth of white blood cells that fight infection.

Neupogen (Filgrastim) Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation/pain at the site of the injection. • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • Fever • Lower than normal platelet count in the blood	• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. Or rupture of the spleen. • Difficulty breathing and lung damage that may be due to the white blood cells, , travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome • Bone marrow dysfunction (MDS) or secondary leukemia in patients with very bad ongoing low white cell counts that require prolonged administration of this drug. • Worsening of skin rashes • Low Fever • Inflammation of blood vessels leading to a raised purple rash and bruising

Neulasta (Pegfilgrastim) Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
Aching or pain in bones.	• Local irritation at the site of the injection. • Headache • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • A low number of platelets in the blood.	• Low grade fever • Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • Redness and flushing of the face and body. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. • Markedly higher than normal white blood cell count which may be associated with fever and red, often painful patches on the skin (Sweet's syndrome). • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim , travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome)

Unknown frequency and timing: It is unknown whether pegfilgrastim produces birth defects or other serious abnormalities in the unborn child in humans as there is conflicting data from animal studies. It is also unknown whether this drug is excreted in breast milk.

Possible side effects of Cefixime:

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5-20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
	• Diarrhea • Belly pain • Nausea • vomiting • Indigestion	• Headache • Dizziness • Seizures • Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate • Low number of white blood cells in the blood • Increase in the blood of a type of white blood cells called eosinophils , which are sometimes associated with allergic reactions • Decrease in platelets which may make you bruise or bleed easily. • Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain,. • High blood tests of kidney and liver function • Hepatitis, yellowing of skin and whites of eyes • Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin

Possible side effects of Cefpodoxime (Vantin-R)

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 -20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
	• Diarrhea • Diaper rash	• Belly pain • Nausea and vomiting, • Headache • Seizures • Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate • Chest pain • Decrease in white blood cells, platelets and red blood cells: • Increase in the blood of a type of white blood cells called eosinophils , which are sometimes associated with allergic reactions • Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain. • High blood tests for liver and kidney function • Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin • Change in blood tests showing decreased ability of the blood to form a clot. • Vaginal infection • The inability to produce enough new cells to replenish the amount of red blood cells, white blood cells and platelets in the body.

Possible risks to unborn child and nursing child

Patients who agree to participate in this study should not become pregnant or breast feed while on this study. This study and the medicines used in this study may be hazardous to an unborn child. Patients and their sexual partners should use abstinence and /or an effective method of contraception that is medically appropriate based on your personal doctor's recommendation at that time. Male subjects must agree to use an acceptable method for contraception during the entire study treatment period through 4 months after the last dose of MLN8237.

If you or your partner becomes pregnant while you are participating in this study, please notify your study doctor immediately. For more information about risks and side effects, ask your study doctor.

Possible long term side effects of this treatment

- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of sexual maturity
- Increased risk of a second cancer (such as leukemia) different from the kind of cancer you have now.

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. These have risks that will be discussed with you. You will be asked to sign a separate consent for any procedure that needs sedation.

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?

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

- Treatment with chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No 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), involved in keeping research safe for people.
- Millennium Pharmaceuticals (supplier of MLN8237)

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/clinic charges, and doctors' fees related to your participation in this study.

Irinotecan and temozolomide are commercially available agents. You will pay for the amount of drugs needed to complete this study. This cost is normally covered by your insurance company.

MLN8237 will be provided by Millennium Pharmaceuticals, the company that makes this drug. They will provide the drug at no cost to you. A continuing supply of the drug cannot be guaranteed. If there is a problem getting MLN8237, your study doctor will talk with you about

possible options. If, during the study, MLN8237 becomes approved for use in your cancer, you and/or your health plan may have to pay for MLN8237 needed to complete this study.

The pharmacokinetic studies will be done at no cost to you. The optional tests looking at tumor Aurora A and at gene changes involved in breaking down MLN8237 and irinotecan will be done at no cost to you if you agree to participate in these optional tests. However, you or your health plan may need to pay for the costs of the supplies and personnel who withdraw 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/clinic, car fare, travel to and from the hospital/clinic, parking, and baby sitter fees.

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 Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

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/**

You will get a copy of this consent form. If you want more information about this study, ask your study doctor.

CONSENTS FOR EXTRA STUDIES FOR RESEARCH

The following test is required during the phase I portion of this study. You may not participate in this portion of the study if you do not agree to these tests.

Determining blood levels of MLN8237 and irinotecan

Initial next to YES if you agree to let researchers take blood to study blood levels of MLN8237 and irinotecan. These are extra blood draws that may require blood draws (pokes) or intravenous (IV) catheter placement. The results of these tests 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 samples to study blood levels of MLN8237 and irinotecan. **You will not be able to participate in this portion of the study.**

Patient _____YES _____NO

Parent/Legal Guardian _____YES _____NO

The following test is optional. You may still participate in the study even if you do not agree to these tests.

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

Initial next to YES, if you agree to let researchers take blood to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan. This is one extra blood sample and it can be taken from a central line (such as port or Broviac). The results of these tests 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 an extra blood sample to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan.

Patient _____YES _____NO

Parent/Legal Guardian _____YES _____NO

The following test is optional. You may still participate in the study even if you do not agree to these tests.

Looking at Aurora A in neuroblastoma tumors

Initial next to YES, if you agree to let researchers request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor.

Patient _____YES _____NO

Parent/Legal Guardian _____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.

_____
Patient Name

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

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

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

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

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator (If applicable) Date

Consent Addendum 1: Tests that will be done on this study.

Observation	Before Entry	Cycle 1	Cycles 2-34	End of Therapy
Physical Examination	X	Weekly	Start of each cycle	X
Blood tests	X	Twice weekly**	Weekly	X
Urine tests	X			X
Bone marrow tests	X		X	X
Tumor scans (CT scan, MRI scan, and/or MIBG scan)	X		X	X
Blood for drug level tests		X		
Submission of stored tumor tissue*		X		
Blood to check for gene change involved in breaking down MLN8237 and irinotecan*		X		

***Optional**
****Some blood tests are required twice weekly and others are weekly during cycle 1.**

Consent Addendum #2

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 SAMPLE INFORMED CONSENT: PHASE II

PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

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

CONSENT FORM FOR PHASE II PORTION OF STUDY

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 study doctor.

You are invited to participate in this study because you have been diagnosed with neuroblastoma. Your cancer has either grown back (relapsed) or has never gone away (persistent tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy and/or high-dose chemotherapy with a stem cell transplant.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

To continue to look at the side effects seen by giving MLN8237 with irinotecan, and temozolomide.

To determine if your tumor gets smaller after treatment with MLN8237, irinotecan, and temozolomide.

To measure the levels of MLN8237 and irinotecan in the blood during this treatment

To determine if specific gene changes makes you more prone to side effects from and/or response to the combination of MLN8237, irinotecan, and temozolomide.

To determine if the amount of something in your tumor called MYCN or Aurora A makes you more likely to have a good response to the combination of MLN8237, irinotecan, and temozolomide.

To determine if the combination of MLN8237, irinotecan, and temozolomide delays disease progression in patients with relapsed or progressive neuroblastoma.

The research is being done because:

Currently there is no known effective treatment for your type of cancer.

This study will combine an oral drug called MLN8237 with two chemotherapy medicines called irinotecan and temozolomide.

MLN8237 is an investigational drug that is not approved by the FDA. MLN8237 blocks the function of a protein that is important in the growth of cancer cells. This drug has been tested as a single-agent in children with relapsed solid tumors, including patients with neuroblastoma. In the laboratory, MLN8237 appears to make neuroblastoma tumors smaller. This effect is even greater when MLN8237 is combined with the chemotherapy drugs, irinotecan and temozolomide.

Irinotecan and temozolomide are both FDA-approved chemotherapy drugs. These drugs are approved for the treatment of certain adult cancers, but have also been used to treat children with cancer. These drugs have been used in combination in many people with neuroblastoma. In some patients with neuroblastoma, this combination reduces the amount of neuroblastoma.

Giving MLN8237 together with irinotecan and temozolomide may increase the effectiveness of this combination. In the first part of this study (the "phase 1" part), the side effects and maximum dose of MLN8237 pills given in combination with irinotecan and temozolomide were found. In this "phase 2" part of the study, all patients will start out with the same doses of all three drugs and the number of patients who respond to these drugs will be determined.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

22 people joined the first "phase 1" part of the study. Up to 20 people will take part in this "phase 2" part of the study. Another 6-18 people will take part in a different ongoing part of the study if they cannot swallow MLN8237 pills.

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

Medical Tests Before You Begin the Study

You will need to have the following exams, tests or procedures to find out if you can receive the treatment part of the study. 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 study doctor.

- Physical exam
- Blood tests
- Pregnancy test
- Urine tests
- Bone marrow tests[#]
- Various scans*

[#]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.
* Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans or Bone scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans

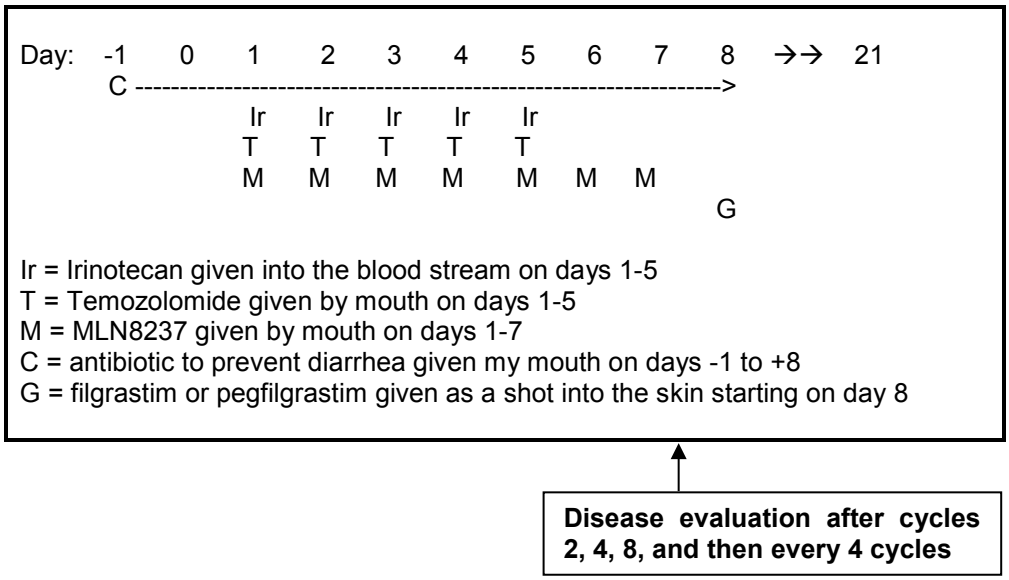
During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during the study. They are part of regular cancer care.

- Physical exam
- Blood tests and scans
- Pregnancy test
- Urine tests
- Bone marrow tests
- Various scans

Treatment Plan

The treatment will be given in cycles that each last 21 days. A diagram of one cycle is shown in the following figure.



You will receive irinotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) over 1 hour on days 1-5. This medicine is typically given in the clinic.

You will receive temozolomide by mouth once a day on days 1-5. The medicine is most commonly given as a capsule. If you have a hard time swallowing capsules, the medicine can also taken out of the capsule and swallowed with applesauce or apple juice. This medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

You will receive MLN8237 by mouth once a day on days 1-7. The medicine can only be given as a tablet. On days 1-5, this medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

You will receive an oral antibiotic (cefixime or cefpodoxime) by mouth once a day or twice a day on days -1 through day +8. This antibiotic is given to reduce the chances of getting diarrhea that can be seen in patients treated with irinotecan.

You will also receive a drug to boost the white blood cells count (filgrastim or pegfilgrastim). This drug will be started on day 8 of each cycle of treatment. Filgrastim is a shot given into the skin each day until the white blood cell count increases. Pegfilgrastim is a long-acting version of filgrastim that is given as a shot into the skin just once per cycle. Your study doctor will talk with you about which of these drugs you will receive.

When you join the study, you will be assigned a certain MLN8237 dose. This dose will be given to all patients entering this part of the study, as it was determined in the first part of the study (phase I portion) to be the highest dose of MLN8237 that can be given along with irinotecan and temozolomide without bad side effects. This part of the study is called the Phase II part of the study.

The doses of irinotecan and temozolomide are typical doses used to treat patients with neuroblastoma.

You can receive up to 34 cycles of treatment (approximately 2 years) as long as you are not having bad side effects and as long as your tumor is not getting worse. Although other participating patients may have received a different dose of MLN8237, your assigned dose of

MLN8237 will not change during your participation in this study unless you develop certain side effects that necessitate lowering your dose of MLN8237.

When you have finished treatment with MLN8237, irinotecan, and temozolomide
After you stop treatment with MLN8237, irinotecan and temozolomide, 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 functions, tests will 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
Blood tests	Various scans
Urine tests	

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

Optional Research Studies
You will be asked if you want to participate in optional research tests. **This part of the study is optional.** The results of these tests would not be told to you or your doctor 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. You can decide not to let the doctors do these tests and still be able to be treated as part of this clinical study. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in these optional studies.

Determining blood levels of MLN8237 and irinotecan

One of the research goals of this study is to find out the amount of MLN8237 and irinotecan in the blood during this treatment. Participating in this portion of the study is optional for patients in this phase II part of the study.

On the first day of the first cycle of treatment, a small amount of blood (5 mL, or about a teaspoon) will be drawn. If you have a central line (such as a port or a Broviac), this sample can be drawn through that line. Otherwise, you will need to have blood drawn through a vein.

On the fourth day of the first cycle of treatment, a total of 36 mL (or a little more than 7 teaspoons) will be drawn over 24 hours. This schedule of blood draws is typically done as an outpatient. If you have a central line with only one lumen or tube and that lumen or tube is being used to give you the irinotecan, then you will need to have at least 6 of these blood samples drawn through a vein. Your study doctor may recommend placing an IV catheter or tube in one of your veins through which the blood can be drawn. This may reduce the number of pokes needed for this part of the study. If you have a central line with more than one lumen or tube, you may be able to have these blood samples drawn through one of the lumens or tubes that is not being used to give you the irinotecan. Your study doctor can tell you whether you will need some pokes or an IV catheter placed or whether your type of central line can be used to draw these samples.

This amount of blood is considered safe to donate over this amount of time. Samples will be sent to the Children's Hospital of Philadelphia in Philadelphia, PA and to the Mayo Clinic in Rochester, MN for testing.

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

Another research goal is to look for genetic changes in normal blood cells of patients to see if these are related to how the liver handles MLN8237 and irinotecan, or whether you will have bad side effects after taking these drugs. We may also look to see if other genetic changes impact how likely a person is to respond to this drug combination. These tests are done on one sample of blood (one-two teaspoons, 5-10 mL) taken from your central line (or port) at the start of the first cycle of therapy. This amount of blood is considered safe to donate. The blood will be sent to the Mayo Clinic in Rochester, MN for testing.

Looking at Aurora A in neuroblastoma tumors

MLN8237 blocks the action of a protein called Aurora A. Another research goal is to look at the amount of Aurora A in neuroblastoma tumors to find out if the amount of Aurora A impacts whether tumors respond to the combination of MLN8237, irinotecan, and temozolomide. These tests are done on stored neuroblastoma tissue from your previous tumor biopsies or surgeries. If you agree to participate in this optional part of the study, we will request that your hospital send us some of your stored neuroblastoma tissue. You will not need to have an extra biopsy or surgery to participate in this part of the study. The tissue will be sent to the University of California in San Francisco, CA.

HOW LONG WILL I BE ON THIS STUDY?

You can receive up to 34 cycles of treatment (approximately 2 years) 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. Researchers will be in contact with your primary care doctor to see how you are doing; 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 oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?

Yes. If you are thinking about stopping the study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

The study doctor may 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?

You may have side effects while on the study. 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 and some patients may have very serious side effects and could die as a result of these side effects.

In the first part of this study, researchers looked at side effects seen in patients taking different doses of MLN8237 together with irinotecan and temozolomide. The dose of MLN you will receive was based on the experience of the first portion of the study that has already been shown to be tolerated without bad side effects in several children with neuroblastoma. Your dose will not change with later courses of treatment, unless it needs to be decreased due to side effects.

Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or itching). Many side effects go away soon after you stop taking MLN8237, irinotecan, and temozolomide, 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. Although this combination has been given to children in the first part of this study, there may 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 on the following pages.

Possible side effects of MLN8237

There is limited experience using MLN8237 in humans. The risks and side effects listed here and their frequencies are anticipated or predicted based on tests in animals and some experience in people. It is expected that MLN8237 toxicities will be reversible, however it is possible that MLN8237 will have their toxicities that have not been observed in or predicted from its evaluation in animal studies and the few studies in adults that have been conducted to date.

The frequency provided in the following table is approximate:

Risks and side effects related to MLN8237 include those which are:

Likely (Anticipated in 21-100 children out of every 100)	**Less Likely** (Anticipated in 5 -20 children out of every 100)	**Rare but Serious** (Anticipated in <5 children out of every 100)
• Fewer red blood cells in the blood* • Diarrhea • Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores) • Nausea • Vomiting • A feeling of extreme tiredness not relieved by sleep • Low numbers of white blood cells* called lymphocytes and neutrophils/granulocytes that may make it easier to get infections which may be life threatening • Fewer platelets in the blood* • Loss of appetite • Hair loss	• Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics* • Pain in the abdomen (belly), heartburn • Constipation • Mouth pain • Swelling caused by fluid build-up in the tissues of the arms and legs • Fever • Infections including those caused by bacteria, virus, and fungus, which may cause you to become very ill. • Increase in the blood level of certain enzymes or bilirubin (a waste product that passes through the liver) which could indicate liver irritation or damage • Increased levels of a chemical (creatinine) in the blood which could mean kidney damage • Excessive loss of water from the body • Back pain • Dizziness • Headache • Cough • Shortness of breath • Low blood pressure • Weakness • Rash • Trouble walking • Changes in mood or confusion • Sleepiness, overtiredness.	• Severe rash with redness and pain of the skin on the palms of the hands and soles of the feet. • Blistering of the skin.

* If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the bloodstream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell count is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a drop in the red blood cell count, the cells that carry oxygen around the body you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.
If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Transfusions may be accompanied or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S. (acquired immune deficiency syndrome) and other infections.

MLN8237 has a chemical structure that is similar to a group of drugs called benzodiazepines. These drugs may cause dependence and withdrawal symptoms. Therefore, there is a theoretical risk that MLN8237 could cause dependence and withdrawal symptoms, as well. It is possible that while taking this drug, you will feel changes in your mood such as a sense of euphoria (joy) or a feeling of unhappiness that could lead to depression and thoughts of hurting yourself. When stopping the drug, withdrawal symptoms could include: anxiety, restlessness, difficulty sleeping, tremors, rapid heart-beat, nausea and vomiting.

Since there is a possibility that this drug may cause sedation (or sleepiness), you should not drink alcoholic beverages, since alcohol can also cause sleepiness. If you feel sleepy while you are on this study, you should avoid driving or doing anything that may need your full alertness, such as operating dangerous tools or machinery. This drug may also cause sleepiness if you are currently taking an opiate such as morphine, dilaudid, or fentanyl.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

For more information about risks and side effects, ask your study doctor.

Possible side effects of Temozolomide

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 - 20 children out of 100)	**Rare but serious** (happens to < 5 children out of 100)
•Fewer red and white blood cells and platelets in the blood. •Nausea • Vomiting • Constipation • Loss of appetite	• Diarrhea • Headache • Tiredness • Rash • Itching • Increased need to urinate • Urinary Tract Infections • Mouth sores • Fluid buildup in legs and arms • Hair loss • Elevation in the blood of certain enzymes found in the liver • Pain in the abdomen	• Convulsions Difficulty swallowing • Dizziness • Anxiety or depression • Difficulty sleeping • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever • Low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life-threatening • Partial paralysis or weakness of one side of the body Loss of memory • Blood clots which may be life-threatening • Visual disturbances that may cause double vision • Forgetfulness or confusion • Aches and pains in muscles • A new cancer or leukemia resulting from this treatment • Lack of muscle coordination which may affect speech, eye movement, swallowing, walking, picking up things. • Liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure.

Possible side effects of Irinotecan

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 - 20 children out of 100)	**Rare but serious** (happens to < 5 children out of 100)
•Diarrhea that can occur during the infusion of irinotecan or immediately after and may be associated with abdominal cramping, a runny nose, tearing, salivation, sweating, flushing (feeling of warmth and red cheeks), and difficulty adjusting your eyes to light. • Inflammation and/or sores in the mouth Loss of body water • Nausea and Vomiting Stomach pain • Loss of appetite • • Fever • A feeling of weakness and tiredness • Temporary hair loss • Elevation of liver and bone enzymes in the blood and of bilirubin (yellow pigment formed in the liver) • An increase in the blood of a type of white blood cell called an eosinophil. These are sometimes associated with allergic reactions. • Decrease in the number of red and white blood cells and platelets made in the bone marrow.	• Fewer red blood cells and platelets in the blood blood. • Diarrhea that may occur later from 1 day to 2 weeks after irinotecan which could cause excessive loss of water and salts from the body • Constipation • Pain at the injection site • Rash • Inflammation and/or sores in the mouth, throat and/or Esophagus • Headache • An upset stomach • Blood clots which may be in rare cases life threatening • Increase in liver and kidney enzymes	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such and sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening • Inflammation of the lungs with cough and congestion• Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools and abdominal pain • Headache • Pain at infusion site • Disorientation/confusion • Dizziness and low blood pressure • A blockage of the bowel that prevents passage through the bowel • Slow heart beat • Skin inflammation • Trembling • Blood in the urine • Mildly increased level of protein and glucose in the urine • Low amount of protein in the blood • Mouth sores • Sensation of warmth on face. • Risk to the unborn child in pregnant patients.** .

* This toxicity is seen more commonly when irinotecan is given in combination with fluorouracil and leucovorin. It may rarely be a life threatening event.

** Birth defects and other serious abnormalities in the unborn baby have been noted with irinotecan in animal studies at doses similar to or less than those used in humans. The timing and frequency of these effects is as yet unknown. These may include multiple birth defects and

abnormalities of bone formation, small size of baby at birth and increased risk of death of the unborn baby. Irinotecan is excreted in rat milk but this is unknown for humans.

Possible side effects of G-CSF (such as Neupogen, filgrastim Or Neulasta, Pegfilgrastim)

G-CSF is not an anti-cancer medicine. It helps the growth of white blood cells that fight infection.

Neupogen (Filgrastim) Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation/pain at the site of the injection. • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • Fever • Lower than normal platelet count.	• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. Or rupture of the spleen. • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim , travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome • Bone marrow dysfunction (MDS) or secondary leukemia in patients with very bad ongoing low white cell counts that require prolonged administration of this drug. • Worsening of skin rashes • Low fever • Inflammation of blood vessels leading to a raised purple rash and bruising

Neulasta (Pegfilgrastim) Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
Aching or pain in bones.	• Local irritation at the site of the injection. • Headache • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • A low number of platelets in the blood.	• Low grade fever • Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • Redness and flushing of the face and body. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. • Markedly higher than normal white blood cell count which may be associated with fever and red, often painful patches on the skin (Sweet's syndrome). • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim , travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome)

Unknown frequency and timing: It is unknown whether pegfilgrastim produces birth defects or other serious abnormalities in the unborn child in humans as there is conflicting data from animal studies. It is also unknown whether this drug is excreted in breast milk.

Possible side effects of Cefixime:

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5-20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
	• Diarrhea • Belly pain • Nausea • vomiting • Indigestion	• Headache • Dizziness • Seizures • Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate • Low number of white blood cells in the blood • Increase in the blood of a type of white blood cells called eosinophils , which are sometimes associated with allergic reactions • Decrease in platelets which may make you bruise or bleed easily. • Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain,. • High blood tests of kidney and liver function • Hepatitis, yellowing of skin and whites of eyes • Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin

Possible side effects of Cefpodoxime (Vantin-R)

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 -20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
	• Diarrhea • Diaper rash	• Belly pain • Nausea and vomiting, • Headache • Seizures • Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate • Chest pain • Decrease in white blood cells, platelets and red blood cells: • Increase in the blood of a type of white blood cells called eosinophils , which are sometimes associated with allergic reactions • Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain,. • High blood tests for liver and kidney function • Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin • Change in blood tests showing decreased ability of the blood to form a clot. • Vaginal infection • The inability to produce enough new cells to replenish the amount of red blood cells, white blood cells and platelets in the body.

Possible risks to unborn child and nursing child

Patients who agree to participate in this study should not become pregnant or breast feed while on this study. This study and the medicines used in this study may be hazardous to an unborn child. Patients and their sexual partners should use abstinence and /or an effective method of contraception that is medically appropriate based on your personal doctor's recommendation at that time. Male subjects must agree to use an acceptable method for contraception during the entire study treatment period through 4 months after the last dose of MLN8237.

If you or your partner becomes pregnant while you are participating in this study, please notify your study doctor immediately. For more information about risks and side effects, ask your study doctor.

Possible long term side effects of this treatment

- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of sexual maturity
- Increased risk of a second cancer (such as leukemia) different from the kind of cancer you have now.

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. These have risks that will be discussed with you. You will be asked to sign a separate consent for any procedure that needs sedation.

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?

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

- Treatment with chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No 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), involved in keeping research safe for people.
- Millennium Pharmaceuticals (supplier of MLN8237)

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/clinic charges, and doctors' fees related to your participation in this study.

Irinotecan and temozolomide are commercially available agents. You will pay for the amount of drugs needed to complete this study. This cost is normally covered by your insurance company.

MLN8237 will be provided by Millennium Pharmaceuticals, the company that makes this drug. They will provide the drug at no cost to you. A continuing supply of the drug cannot be guaranteed. If there is a problem getting MLN8237, your study doctor will talk with you about possible options. If, during the study, MLN8237 becomes approved for use in your cancer, you and/or your health plan may have to pay for MLN8237 needed to complete this study.

The pharmacokinetic studies will be done at no cost to you. The optional tests looking at tumor Aurora A and at gene changes involved in breaking down MLN8237 and irinotecan will be done at no cost to you if you agree to participate in these optional tests. However, you or your health plan may need to pay for the costs of the supplies and personnel who withdraw 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/clinic, car fare, travel to and from the hospital/clinic, parking, and baby sitter fees.

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 Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

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/**

You will get a copy of this consent form. If you want more information about this study, ask your study doctor.

CONSENTS FOR EXTRA STUDIES FOR RESEARCH

The following test is optional. You may still participate in the study even if you do not agree to these tests.

Determining blood levels of MLN8237 and irinotecan

Initial next to YES, if you agree to let researchers take blood to study blood levels of MLN8237 and irinotecan. These are extra blood draws that may require blood draws (pokes) or intravenous (IV) catheter placement. The results of these tests 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 samples to study blood levels of MLN8237 and irinotecan.

Patient _____YES _____NO

Parent/Legal Guardian _____YES _____NO

The following test is optional. You may still participate in the study even if you do not agree to these tests.

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

Initial next to YES, if you agree to let researchers take blood to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan. This is one extra blood sample and it can be taken from a central line (such as port or Broviac). The results of these tests 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 an extra blood sample to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan.

Patient _____YES _____NO

Parent/Legal Guardian _____YES _____NO

The following test is optional. You may still participate in the study even if you do not agree to these tests.

Looking at Aurora A in neuroblastoma tumors

Initial next to YES, if you agree to let researchers request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor.

Patient _____YES _____NO

Parent/Legal Guardian _____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.

_____
Patient Name

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

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

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

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

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator (If applicable) Date

Consent Addendum 1: Tests that will be done on this study.

Observation	Before Entry	Cycle 1	Cycles 2-34	End of Therapy
Physical Examination	X	Weekly	Start of each cycle	X
Blood tests	X	Twice weekly**	Weekly	X
Urine tests	X			X
Bone marrow tests	X		X	X
Tumor scans (CT scan, MRI scan, and/or MIBG scan)	X		X	X
Blood for drug level tests*		X		
Submission of stored tumor tissue*		X		
Blood to check for gene change involved in breaking down MLN8237 and irinotecan*		X		

***Optional**
****Some blood tests are required twice weekly and others are weekly during cycle 1.**

Consent Addendum #2

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.

15.3 SAMPLE ASSENT FORM-Phase II

PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

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. My name is _____.

2. You have a kind of cancer called **Neuroblastoma** that has either grown back or has never gone away after treatment. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using three medicines called **MLN8237, irinotecan,** and **temozolomide** to see what effects (both good and bad) these medicines have on patients and their cancer. MLN8237 is a medicine that is given by mouth as a pill (tablet). Irinotecan is a medicine that is given into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm). Temozolomide is a medicine that is given by mouth, usually as a pill (capsule) though it can be given a different way if you cannot swallow capsules. The doctors think that giving these three drugs together may help get rid of neuroblastoma cancer cells.

3. If you agree to be in this study this is what will happen:

   The medicines will be given in cycles that each lasts 21 days. You will only get the medicine during the first 7 days of each cycle. You will continue to receive cycles of this treatment for up to 2 years unless you have bad side effects or your tumor gets worse.

   MLN8237:
   You will take MLN8237 pills by mouth once a day for the first 7 days every 21-day cycle.
   Irinotecan:
   You will take Irinotecan by I.V. once a day for the first 5 days every 21 day cycle.
   Temozolomide:
   You will take Temozolomide by mouth once a day for the first 5 days every 21-day cycle.

   Other medicines (not chemotherapy):
   You will need to take other medicines to help you with side effects of the three chemotherapy medicines above. These medicines will include Neupogen (given once a day as an injection) or Neulasta (give each cycle as an injection) to help your normal blood cells get better after chemotherapy. To help with diarrhea, you will also take either Cefixime (once per day) or Cefpodoxime (twice each day) by mouth for ten days during each cycle of chemotherapy.

   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, Bone and MIBG Scans (special pictures of your tumor)
   - Bone marrow test (to look for tumor in your bone marrow)
   - 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.

When you are in a research study, sometimes good things and bad things can happen

4. 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 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.
- You may get sores in your mouth that make it difficult to eat and drink. If this happens, you may need some pain medicines and you may need to stay in the hospital.
- You may get diarrhea.
- 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. None of these things may happen. Or things may happen that the doctors don't know about yet.

We will do everything possible to keep your information private.

- 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.

- 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" you can still decide not to do this.

- 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.

- 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. Study doctor's phone number: _____.

- <u>Special study blood tests</u> :

There are extra special tests in this study. These are done solely for research purposes only. Neither you nor your doctor will know the results.

#1 Nineblood samples (about 8 teaspoons total) on day 1 and day 4 during the first cycle of your treatment.

- _____ Yes, it is okay to take an extra blood samples
- _____ No, it is not okay to take an extra blood samples

#2 One blood sample (1-2 teaspoons) is needed on day 1 of the first cycle of your treatment.

- _____ Yes, it is okay to take an extra blood sample
- _____ No, it is not okay to take an extra blood sample

#3 Your stored neuroblastoma tissue sample will be used for research purposes in this study.

- _____ Yes, it is okay to use my stored neuroblastoma tissue sample
- _____ No, it is not okay to use my stored neuroblastoma tissue sample

- 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 Subject: _____

_____ _____
Signature of Subject: **Date**

_____ _____
Signature of Investigator **Date**

_____ _____
Signature of Person Conducting Discussion **Date**

15.4 SAMPLE INFORMED CONSENT: ORAL SOLUTION COHORT

PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

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

CONSENT FORM FOR ORAL SOLUTION COHORT

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 study doctor.

You are invited to participate in this study because you have been diagnosed with neuroblastoma. Your cancer has either grown back (relapsed) or has never gone away (persistent tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy and/or high-dose chemotherapy with a stem cell transplant.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

To find the highest doses of MLN8237, that can be given with irinotecan, and temozolomide without causing severe side effects.

To find out the side effects seen by giving MLN8237 at different dose levels with irinotecan, and temozolomide.

To measure the levels of MLN8237 and irinotecan in the blood at different dose levels, based upon either a pill form or a liquid form of MLN8237

To determine if your tumor gets smaller after treatment with MLN8237, irinotecan, and temozolomide

To determine if specific gene changes makes you more prone to side effects from and/or response to the combination of MLN8237, irinotecan, and temozolomide

To determine if the combination of MLN8237, irinotecan, and temozolomide delays disease progression in patients with relapsed or progressive neuroblastoma

To determine if the amount of something in your tumor called MYCN or Aurora A makes you more likely to have a good response to the combination of MLN8237, irinotecan, and temozolomide

The research is being done because:

Currently there is no known effective treatment for your type of cancer.

This study will combine an oral drug called MLN8237 with two chemotherapy medicines called irinotecan and temozolomide.

MLN8237 is an investigational drug that is not approved by the FDA. MLN8237 blocks the function of a protein that is important in the growth of cancer cells. This drug has been tested as a single-agent in children with relapsed solid tumors, including patients with neuroblastoma. In the laboratory, MLN8237 appears to make neuroblastoma tumors smaller. This effect is even greater when MLN8237 is combined with the chemotherapy drugs, irinotecan and temozolomide.

Irinotecan and temozolomide are both FDA-approved chemotherapy drugs. These drugs are approved for the treatment of certain adult cancers, but have also been used to treat children with cancer. These drugs have been used in combination in many people with neuroblastoma. In some patients with neuroblastoma, this combination reduces the amount of neuroblastoma.

Giving MLN8237 together with irinotecan and temozolomide may increase the effectiveness of this combination. In an earlier part of the study, we found out the highest dose of MLN8237 pills that can be given safely together with irinotecan and temozolomide. In this part of the study, we will look at side effects and blood levels of these drugs when children take MLN8237 in a new liquid form.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

22 people joined the first "phase 1" part of the study. Up to 20 people will join the "phase 2" part of the study using MLN8237 pills. Between 6 and 18 people will be in this part of the study looking at the liquid form of MLN8237.

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

Medical Tests Before You Begin the Study

You will need to have the following exams, tests or procedures to find out if you can receive the treatment part of the study. 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 study doctor.

- Physical exam
- Blood tests
- Pregnancy test
- Urine tests
- Bone marrow tests[#]
- Various scans*

[#]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.
* Various scans that are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans, Bone scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans

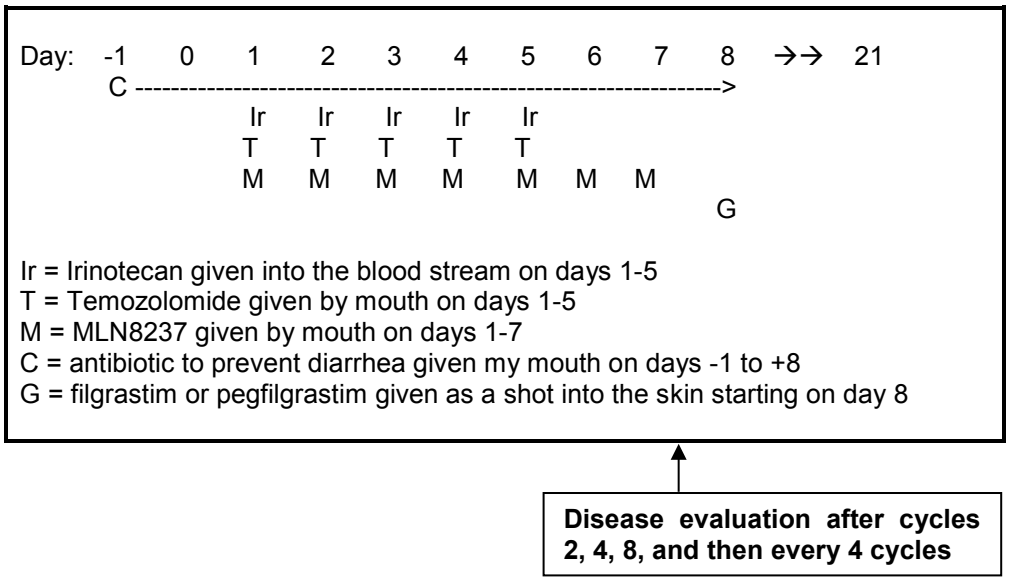
During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during the study. They are part of regular cancer care.

- Physical exam
- Blood tests and scans
- Pregnancy test
- Urine tests
- Bone marrow tests
- Various scans

Treatment Plan

The treatment will be given in cycles that each last 21 days. A diagram of one cycle is shown in the following figure.



You will receive irinotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) over 1 hour on days 1-5. This medicine is typically given in the clinic.

You will receive temozolomide by mouth once a day on days 1-5. The medicine is most commonly given as a capsule. If you have a hard time swallowing capsules, the medicine can also taken out of the capsule and swallowed with applesauce or apple juice. This medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

You will receive MLN8237 by mouth once a day on days 1-7. The medicine will be given as a liquid that can be taken by mouth or put into a feeding tube that goes into the stomach. On days 1-5, this medicine is given 1 hour before the irinotecan is given. This medicine is given on an empty stomach.

You will receive an oral antibiotic (cefixime or cefpodoxime) by mouth once a day or twice a day on days -1 through day +8. This antibiotic is given to reduce the chances of getting diarrhea that can be seen in patients treated with irinotecan.

You will also receive a drug to boost the white blood cells count (filgrastim or pegfilgrastim). This drug will be started on day 8 of each cycle of treatment. Filgrastim is a shot given into the skin each day until the white blood cell count increases. Pegfilgrastim is a long-acting version of filgrastim that is given as a shot into the skin just once per cycle. Your study doctor will talk with you about which of these drugs you will receive.

When you join the study, you will be assigned a certain MLN8237 dose. This study will test up to two MLN8237 doses in groups of 3-6 patients. The starting MLN8237 dose for the first group of patients is about 25% lower than the highest dose of MLN8237 pills that can be given safely together with irinotecan and temozolomide. This is because studies in adults show that about 25% more MLN8237 liquid is absorbed compared with MLN8237 pills. Based on how the first 3-6 patients do with the MLN8237 liquid, it is possible that more patients are treated with the same dose, a higher dose, or a lower dose of MLN8237 liquid.

The doses of irinotecan and temozolomide are not increased during this study. The doses used are typical doses used to treat patients with neuroblastoma.

You can receive up to 34 cycles of treatment (approximately 2 years) as long as you are not having bad side effects and as long as your tumor is not getting worse. Although other participating patients may receive a different dose of MLN8237, your assigned dose of MLN8237 will not change during your participation in this study unless you develop certain side effects that necessitate lowering your dose of MLN8237.

When you have finished treatment with MLN8237, irinotecan, and temozolomide

After you stop treatment with MLN8237, irinotecan and temozolomide, 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 functions, tests will 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
Blood tests	Various scans
Urine tests	

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

Determining blood levels of MLN8237 and irinotecan

One of the main research goals of this study is to find out the amount of MLN8237 and irinotecan in the blood during this treatment. Since this is one of the main goals of the study you are required to submit extra blood samples in order to participate in the overall study.

On the first day of the first cycle of treatment, a small amount of blood (5 mL, or about a teaspoon) will be drawn. If you have a central line (such as a port or a Broviac), this sample can be drawn through that line. Otherwise, you will need to have blood drawn through a vein.

On the fourth day of the first cycle of treatment, a total of 36 mL (or a little more than 7 teaspoons) will be drawn over 24 hours. This schedule of blood draws is typically done as an outpatient. If you have a central line with only one lumen or tube and that lumen or tube is being used to give you the irinotecan, then you will need to have at least 6 of these blood samples drawn through a vein. Your study doctor may recommend placing an IV catheter or tube in one of your veins through which the blood can be drawn. This may reduce the number of pokes needed for this part of the study. If you have a central line with more than one lumen or tube, you may be able to have these blood samples drawn through one of the lumens or tubes that is not being used to give you the irinotecan. Your study doctor can tell you whether you will need some pokes or an IV catheter placed or whether your type of central line can be used to draw these samples.

This amount of blood is considered safe to donate over this amount of time. Samples will be sent to the Children's Hospital of Philadelphia in Philadelphia, PA and to the Mayo Clinic in Rochester, MN for testing.

Other Research Tests in this Study

You will be asked if you want to participate in optional research tests. **This part of the study is optional.** The results of these tests would not be told to you or your doctor 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. You can decide not to let the doctors do these tests and still be able to be treated as part of this clinical study. There are checkboxes on the next to last page of this consent form to mark whether you are willing to participate in these optional studies.

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

One part of the research goal is to look for genetic changes in normal blood cells of patients to see if these are related to how the liver handles MLN8237 and irinotecan, or whether you will have bad side effects after taking these drugs. We may also look to see if other genetic changes impact how likely a person is to respond to this drug combination. These tests are done on one sample of blood (one-two teaspoons, 5-10 mL) taken from your central line (or port) at the start of the first cycle of therapy. This amount of blood is considered safe to donate. The blood will be sent to the Mayo Clinic in Rochester, MN for testing.

Looking at Aurora A in neuroblastoma tumors

MLN8237 blocks the action of a protein called Aurora A. Another research goal is to look at the amount of Aurora A in neuroblastoma tumors to find out if the amount of Aurora A impacts whether tumors respond to the combination of MLN8237, irinotecan, and temozolomide. These tests are done on stored neuroblastoma tissue from your previous tumor biopsies or surgeries. If you agree to participate in this optional part of the study, we will request that your hospital send us some of your stored neuroblastoma tissue. You will not need to have an extra biopsy or surgery to participate in this part of the study. The tissue will be sent to the University of California in San Francisco, CA.

HOW LONG WILL I BE ON THIS STUDY?

You can receive up to 34 cycles of treatment (approximately 2 years) 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. Researchers will be in contact with your primary care doctor to see how you are doing; 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 oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?

Yes. If you are thinking about stopping the study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

The study doctor may 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?

You will participate in the oral solution cohort part of the study. This part of the study looks at how common and serious side effects can be for each patient at a specific dose of a drug. Since we are still learning about the best dose of MLN8237 liquid to use with the other chemotherapy drugs, some patients may have very serious side effects and could die as a result of these side effects.

In this study, researchers will be looking at side effects seen in patients taking different doses of MLN8237 together with irinotecan and temozolomide. Since subjects will be assigned to different doses of MLN8237, some subjects may receive doses that are too small to be effective while others may receive higher doses that may cause increased side effects.

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 or itching). Many side effects go away soon after you stop taking MLN8237, irinotecan, and temozolomide, 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. Because MLN8237 liquid has never been given together with irinotecan and temozolomide before, there may 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 on the following pages.

Possible side effects of MLN8237

There is limited experience using MLN8237 in humans. The risks and side effects listed here and their frequencies are anticipated or predicted based on tests in animals and some experience in people. It is expected that MLN8237 toxicities will be reversible, however it is possible that MLN8237 will have their toxicities that have not been observed in or predicted from its evaluation in animal studies and the few studies in adults that have been conducted to date.

The frequency provided in the following table is approximate:

Risks and side effects related to MLN8237 include those which are:

Likely (Anticipated in 21-100 children out of every 100)	**Less Likely** (Anticipated in 5 -20 children out of every 100)	**Rare but Serious** (Anticipated in <5 children out of every 100)
• Fewer red blood cells in the blood* • Diarrhea • Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores) • Nausea • Vomiting • A feeling of extreme tiredness not relieved by sleep • Low numbers of white blood cells* called lymphocytes and neutrophils/granulocytes that may make it easier to get infections which may be life threatening • Fewer platelets in the blood* • Loss of appetite • Hair loss	• Fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics* • Pain in the abdomen (belly), heartburn • Constipation • Mouth pain • Swelling caused by fluid build-up in the tissues of the arms and legs • Fever • Infections including those caused by bacteria, virus, and fungus, which may cause you to become very ill. • Increase in the blood level of certain enzymes or bilirubin (a waste product that passes through the liver) which could indicate liver irritation or damage • Increased levels of a chemical (creatinine) in the blood which could mean kidney damage • Excessive loss of water from the body • Back pain • Dizziness • Headache • Cough • Shortness of breath • Low blood pressure • Weakness • Rash • Trouble walking • Changes in mood or confusion • Sleepiness, overtiredness.	• Severe rash with redness and pain of the skin on the palms of the hands and soles of the feet. • Blistering of the skin.

* If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the bloodstream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell count is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a drop in the red blood cell count, the cells that carry oxygen around the body you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Transfusions may be accompanied or followed by fever and/or reactions that can cause kidney failure, heart failure, anemia, hepatitis, A.I.D.S. (acquired immune deficiency syndrome) and other infections.

MLN8237 has a chemical structure that is similar to a group of drugs called benzodiazepines. These drugs may cause dependence and withdrawal symptoms. Therefore, there is a theoretical risk that MLN8237 could cause dependence and withdrawal symptoms, as well. It is possible that while taking this drug, you will feel changes in your mood such as a sense of euphoria (joy) or a feeling of unhappiness that could lead to depression and thoughts of hurting yourself. When stopping the drug, withdrawal symptoms could include: anxiety, restlessness, difficulty sleeping, tremors, rapid heart-beat, nausea and vomiting.

There is a chance that a chemical in the MLN8237 liquid could lead to a build up of acid in the blood. Since other liquid drugs contain this same chemical and appear safe, we think the risk of this happening is low. We will test to see if this is happening.

Since there is a possibility that this drug may cause sedation (or sleepiness), you should not drink alcoholic beverages, since alcohol can also cause sleepiness. If you feel sleepy while you are on this study, you should avoid driving or doing anything that may need your full alertness, such as operating dangerous tools or machinery. This drug may also cause sleepiness if you are currently taking an opiate such as morphine, dilaudid, or fentanyl.

We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

For more information about risks and side effects, ask your study doctor.

Possible side effects of Temozolomide

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 - 20 children out of 100)	**Rare but serious** (happens to < 5 children out of 100)
• Fewer red and white blood cells and platelets in the blood. • Nausea • Vomiting • Constipation • Loss of appetite	• Diarrhea • Headache • Tiredness • Rash • Itching • Increased need to urinate • Urinary Tract Infections • Mouth sores • Fluid buildup in legs and arms • Hair loss • Elevation in the blood of certain enzymes found in the liver • Pain in the abdomen	• Convulsions • Difficulty swallowing • Dizziness • Anxiety or depression • Difficulty sleeping • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever • Low numbers of white blood cells called lymphocytes that may last a long time and make it easier to get infections which may be life-threatening • Partial paralysis or weakness of one side of the body • Loss of memory • Blood clots which may be life-threatening • Visual disturbances that may cause double vision • Forgetfulness or confusion • Aches and pains in muscles • A new cancer or leukemia resulting from this treatment • Lack of muscle coordination which may affect speech, eye movement, swallowing, walking, picking up things. • Liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure.

Possible side effects of Irinotecan

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 - 20 children out of 100)	**Rare but serious** (happens to < 5 children out of 100)
• Diarrhea that can occur during the infusion of irinotecan or immediately after and may be associated with abdominal cramping, a runny nose, tearing, salivation, sweating, flushing (feeling of warmth and red cheeks), and difficulty adjusting your eyes to light. • Loss of body water • Nausea and Vomiting • Inflammation and/or sores in the mouth, • Loss of appetite • Stomach pain • Fever • A feeling of weakness and tiredness • Temporary hair loss • Elevation of liver and bone enzymes in the blood and of bilirubin (yellow pigment formed in the liver) • An increase in the blood of a type of white blood cell called an eosinophil. These are sometimes associated with allergic reactions. • Decrease in the number of red and white blood cells and platelets made in the bone marrow	• Fewer red blood cells and platelets in the blood • Diarrhea that may occur later from 1 day to 2 weeks after irinotecan which could cause excessive loss of water and salts from the body • Constipation • Pain at the injection site • Blood clots which may be in rare cases life threatening • Rash • Inflammation and/or sores in the mouth, throat and/or esophagus • Headache • An upset stomach • Increase in liver and kidney levels	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such and sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening • Inflammation of the lungs with cough and congestion • Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools and abdominal pain • Headache • Skin inflammation • Trembling • Blood in the urine • Mildly increased level of protein and glucose in the urine • Low amount of protein in the blood • Mouth sores • Sensation of warmth on face. • Risk to the unborn child in pregnant patients.** • Pain at infusion site • Disorientation/confusion • Dizziness and low blood pressure • A blockage of the bowel that prevents passage through the bowel • Slow heart beat .

* This toxicity is seen more commonly when irinotecan is given in combination with fluorouracil and leucovorin. It may rarely be a life threatening event.

** Birth defects and other serious abnormalities in the unborn baby have been noted with irinotecan in animal studies at doses similar to or less than those used in humans. The timing and frequency of these effects is as yet unknown. These may include multiple birth defects and abnormalities of bone formation, small size of baby at birth and increased risk of death of the unborn baby. Irinotecan is excreted in rat milk but this is unknown for humans.

Possible side effects of G-CSF (such as Neupogen, filgrastim Or Neulasta, Pegfilgrastim)

G-CSF is not an anti-cancer medicine. It helps the growth of white blood cells that fight infection.

Neupogen (Filgrastim) Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation/pain at the site of the injection. • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • Fever • Lower than normal platelet count	• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. Or rupture of the spleen. • Difficulty breathing and lung damage that may be due to the white blood cells, travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome • Bone marrow dysfunction (MDS) or secondary leukemia in patients with very bad ongoing low white cell counts that require prolonged administration of this drug. • Worsening of skin rashes • Low Fever • Inflammation of blood vessels leading to a raised purple rash and bruising

Neulasta (Pegfilgrastim) Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
Aching or pain in bones.	• Local irritation at the site of the injection. • Headache • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • A low number of platelets in the blood.	• Low grade fever • Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • Redness and flushing of the face and body. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. • Markedly higher than normal white blood cell count which may be associated with fever and red, often painful patches on the skin (Sweet's syndrome). • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim , travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome)

Unknown frequency and timing: It is unknown whether pegfilgrastim produces birth defects or other serious abnormalities in the unborn child in humans as there is conflicting data from animal studies. It is also unknown whether this drug is excreted in breast milk.

Possible side effects of Cefixime:

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5-20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
	• Diarrhea • Belly pain • Nausea • vomiting • Indigestion	• Headache • Dizziness • Seizures • Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate • Low number of white blood cells in the blood • Increase in the blood of a type of white blood cells called eosinophils , which are sometimes associated with allergic reactions • Decrease in platelets which may make you bruise or bleed easily. • Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain,. • High blood tests of kidney and liver function • Hepatitis, yellowing of skin and whites of eyes • Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin

Possible side effects of Cefpodoxime (Vantin-R)

Likely (happens to 21-100 children out of 100)	**Less Likely** (happens to 5 -20 children out of 100)	**Rare** (happens to less than 5 children out of 100)
	• Diarrhea • Diaper rash	• Belly pain • Nausea and vomiting, • Headache • Seizures • Allergic reactions which can be life threatening with shortness of breath , low blood pressure, rapid heart rate • Chest pain • Decrease in white blood cells, platelets and red blood cells: • Increase in the blood of a type of white blood cells called eosinophils , which are sometimes associated with allergic reactions • Inflammation of the large intestine which can cause watery diarrhea with blood in stools and cramping abdominal pain. • High blood tests for liver and kidney function • Rash with blistering of the skin and sometimes also lesions in the eyes, lips and mouth. There can also be breakdown of the skin • Change in blood tests showing decreased ability of the blood to form a clot. • Vaginal infection • The inability to produce enough new cells to replenish the amount of red blood cells, white blood cells and platelets in the body.

Possible risks to unborn child and nursing child

Patients who agree to participate in this study should not become pregnant or breast feed while on this study. This study and the medicines used in this study may be hazardous to an unborn child. Patients and their sexual partners should use abstinence and /or an effective method of contraception that is medically appropriate based on your personal doctor's recommendation at that time. Male subjects must agree to use an acceptable method for contraception during the entire study treatment period through 4 months after the last dose of MLN8237.

If you or your partner becomes pregnant while you are participating in this study, please notify your study doctor immediately. For more information about risks and side effects, ask your study doctor.

Possible long term side effects of this treatment

- Recurrence of tumor
- Infection
- Sterility and/or delayed onset of sexual maturity
- Increased risk of a second cancer (such as leukemia) different from the kind of cancer you have now.

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. These have risks that will be discussed with you. You will be asked to sign a separate consent for any procedure that needs sedation.

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?

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

- Treatment with chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No 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), involved in keeping research safe for people.
- Millennium Pharmaceuticals (supplier of MLN8237)

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/clinic charges, and doctors' fees related to your participation in this study.

Irinotecan and temozolomide are commercially available agents. You will pay for the amount of drugs needed to complete this study. This cost is normally covered by your insurance company.

MLN8237 will be provided by Millennium Pharmaceuticals, the company that makes this drug. They will provide the drug at no cost to you. A continuing supply of the drug cannot be guaranteed. If there is a problem getting MLN8237, your study doctor will talk with you about possible options. If, during the study, MLN8237 becomes approved for use in your cancer, you and/or your health plan may have to pay for MLN8237 needed to complete this study.

The pharmacokinetic studies will be done at no cost to you. The optional tests looking at tumor Aurora A and at gene changes involved in breaking down MLN8237 and irinotecan will be done at no cost to you if you agree to participate in these optional tests. However, you or your health plan may need to pay for the costs of the supplies and personnel who withdraw 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/clinic, car fare, travel to and from the hospital/clinic, parking, and baby sitter fees.

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 Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

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/**

You will get a copy of this consent form. If you want more information about this study, ask your study doctor.

CONSENTS FOR EXTRA STUDIES FOR RESEARCH

The following test is required during the oral solution cohort portion of this study. You may not participate in this portion of the study if you do not agree to these tests.

Determining blood levels of MLN8237 and irinotecan

Initial next to YES if you agree to let researchers take blood to study blood levels of MLN8237 and irinotecan. These are extra blood draws that may require blood draws (pokes) or intravenous (IV) catheter placement. The results of these tests 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 samples to study blood levels of MLN8237 and irinotecan. **You will not be able to participate in this portion of the study.**

Patient _____YES _____NO

Parent/Legal Guardian _____YES _____NO

The following test is optional. You may still participate in the study even if you do not agree to these tests.

Evaluating gene changes involved in breakdown and action of MLN8237 and irinotecan

Initial next to YES, if you agree to let researchers take blood to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan. This is one extra blood sample and it can be taken from a central line (such as port or Broviac). The results of these tests 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 an extra blood sample to study gene changes involved in breakdown and action of the drugs MLN8237 and irinotecan.

Patient _____YES _____NO

Parent/Legal Guardian _____YES _____NO

The following test is optional. You may still participate in the study even if you do not agree to these tests.

Looking at Aurora A in neuroblastoma tumors

Initial next to YES, if you agree to let researchers request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to request some of your stored neuroblastoma tumor tissue to study Aurora A levels in the tumor.

Patient _____YES _____NO

Parent/Legal Guardian _____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.

_____
Patient Name

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

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

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

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

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator (If applicable) Date

Consent Addendum 1: Tests that will be done on this study.

Observation	Before Entry	Cycle 1	Cycles 2-34	End of Therapy
Physical Examination	X	Weekly	Start of each cycle	X
Blood tests	X	Twice weekly**	Weekly	X
Urine tests	X			X
Bone marrow tests	X		X	X
Tumor scans (CT scan, MRI scan, and/or MIBG scan)	X		X	X
Blood for drug level tests		X		
Submission of stored tumor tissue*		X		
Blood to check for gene change involved in breaking down MLN8237 and irinotecan*		X		

***Optional**
****Some blood tests are required twice weekly and others are weekly during cycle 1.**

Consent Addendum #2

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.

15.5 SAMPLE ASSENT FORM-ORAL SOLUTION COHORT

PHASE I/II STUDY OF MLN8237 IN COMBINATION WITH IRINOTECAN AND TEMOZOLOMIDE FOR PATIENTS WITH RELAPSED OR REFRACTORY NEUROBLASTOMA

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. My name is _____.

2. You have a kind of cancer called **Neuroblastoma** that has either grown back or has never gone away after treatment. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using three medicines called **MLN8237, irinotecan,** and **temozolomide** to see what effects (both good and bad) these medicines have on patients and their cancer. MLN8237 is a medicine that is given by mouth as a liquid in this part of the study. Irinotecan is a medicine that is given into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm). Temozolomide is a medicine that is given by mouth, usually as a pill (capsule) though it can be given a different way if you cannot swallow the pills. The doctors think that giving these three drugs together may help get rid of neuroblastoma cancer cells.

3. If you agree to be in this study this is what will happen:

   The medicines will be given in cycles that each lasts 21 days. You will only get the medicine during the first 7 days of each cycle. You will continue to receive cycles of this treatment for up to 2 years unless you have bad side effects or your tumor gets worse.

   MLN8237:
   You will take MLN8237 liquid by mouth once a day for the first 7 days every 21-day cycle.
   Irinotecan:
   You will take Irinotecan by I.V. once a day for the first 5 days every 21 day cycle.
   Temozolomide:
   You will take Temozolomide by mouth once a day for the first 5 days every 21-day cycle.

   Other medicines (not chemotherapy):
   You will need to take other medicines to help you with side effects of the three chemotherapy medicines above. These medicines include Neupogen (given once a day as an injection) or Neulasta (give each cycle as an injection) to help your normal blood cells get better after chemotherapy. To help with diarrhea, you will also take either Cefixime (once per day) or Cefpodoxime (twice each day) by mouth for ten days during each cycle of chemotherapy.

   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, Bone, and MIBG Scans (special pictures of your tumor)
   - Bone marrow test (to look for tumor in your bone marrow)
   - 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.
- To measure the amount of medicine in your blood, we will draw 9 blood samples (about 8 teaspoons total) on day 1 and day 4 during the first cycle of your treatment. 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. If you have a central line, your doctor will be able to tell you if that can be used to draw these bloods.

When you are in a research study, sometimes good things and bad things can happen

4. 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 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.
   - You may get sores in your mouth that makes it difficult to eat and drink. If this happens, you may need some pain medicines and you may need to stay in the hospital.
   - You may get diarrhea.
   - 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. None of these things may happen. Or things may happen that the doctors don't know about yet.

5. We will do everything possible to keep your information private.

6. 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.

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" you 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.

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. Study doctor's phone number: _____.

10. <u>Special study blood tests</u> :

    There are extra special tests in this study. These are done solely for research purposes only. Neither you nor your doctor will know the results.

    #1. One blood sample (1-2 teaspoons) is needed on day 1 of the first cycle of your treatment.

    - _____ Yes, it is okay to take an extra blood sample

- _____ No, it is not okay to take an extra blood sample

#2. Your stored neuroblastoma tissue sample will be used for research purposes in this study.

- _____ Yes, it is okay to use my stored neuroblastoma tissue sample
- _____ No, it is not okay to use my stored neuroblastoma tissue sample

11. 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 Subject: _____

_____ _____
Signature of Subject: **Date**

_____ _____
Signature of Investigator **Date**

_____ _____
Signature of Person Conducting Discussion **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. MLN8237 DOSING TABLES FOR PATIENTS RECEIVING ENTERIC COATED TABLETS

Patients receiving the oral solution should have their dose rounded according to section 4.2.1.

(Note that the surface area divisions change at each dose level for rounding purposes)

DOSE LEVEL -1B: 30 MG/M^2/DOSE

Body Surface Area (m^2)	Dose Level -1 (30 mg/m^2)
0.38-0.49	10 mg
0.5-0.83	20 mg
0.84-1.16	30 mg
1.17-1.49	40 mg
1.5-1.83	50 mg
≥ 1.84	60 mg

DOSE LEVELS 1 AND 1B: 45 MG/M^2/DOSE

Body Surface Area (m^2)	Dose Level 1 (45 mg/m^2)
0.38-0.55	20 mg
0.56-0.77	30 mg
0.78-0.99	40 mg
1.0-1.22	50 mg
1.23-1.44	60 mg
1.45-1.66	70 mg
1.67-1.88	80 mg
≥ 1.89	90 mg

DOSE LEVEL 2B: 60 MG/M^2/DOSE

Body Surface Area (m^2)	Dose Level 2 (60 mg/m^2)
0.38-0.41	20 mg
0.42-0.58	30 mg
0.59-0.74	40 mg
0.75-0.91	50 mg
0.92-1.08	60 mg
1.09-1.24	70 mg
1.25-1.41	80 mg
1.42-1.58	90 mg
1.59-1.74	100 mg
1.75-1.91	110 mg
$\geq$ 1.92	120 mg

DOSE LEVEL 3B: 80 MG/M^2/DOSE

Body Surface Area (m^2)	Dose Level 3 (80 mg/m^2)
0.38-0.43	30 mg
0.44-0.56	40 mg
0.57-0.68	50 mg
0.69-0.81	60 mg
0.82-0.93	70 mg
0.94-1.06	80 mg
1.07-1.18	90 mg
1.19-1.31	100 mg
1.32-1.43	110 mg
1.44-1.56	120 mg
1.57-1.68	130 mg
1.69-1.81	140 mg
1.82-1.93	150 mg
$\geq$ 1.94	160 mg

APPENDIX IIIA.TEMOZOLOMIDE DOSING TABLE FOR INITIAL DOSING WITH 100 MG/M^2

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.1-0.49*	3.3 mg/kg*	3.3 mg/kg*
0.50-0.52	50-52	50
0.53-0.57	53-57	55
0.58-0.62	58-62	60
0.63-0.67	63-67	65
0.68-0.72	68-72	70
0.73-0.77	73-77	75
0.78-0.82	78-82	80
0.83-0.87	83-87	85
0.88-0.92	88-92	90
0.93-0.97	93-97	95
0.98-1.0	98-100	100
1.0-1.05	100-105	105
1.06-1.14	106-114	110
1.15-1.24	115-124	120
1.25-1.34	125-134	130
1.35-1.44	135-144	140
1.45-1.54	145-154	150
1.55-1.64	155-164	160
1.65-1.74	165-174	170
1.75-1.84	175-184	180
1.85-1.94	185-194	190
$\geq$ 1.95	195-2.0	200

*Dosing for patients under BSA 0.5 m^2 is by mg/kg, rounded to the nearest 5 mg

APPENDIX IIIB.TEMOZOLOMIDE DOSING TABLE FOR 75 MG/M^2 IF DOSE REDUCTION NEEDED

BSA (m^2)	Calculated daily dose (mg)	Administered daily dose (mg)
0.1-0.49*	2.5 mg/kg*	2.5 mg/kg*
0.50-0.56	37.5-42	40
0.57-0.63	42.75-47.25	45
0.64-0.69	48-51.75	50
0.70-0.76	52.5-57	55
0.77-0.83	57.75-62.25	60
0.84-0.89	63-66.75	65
0.90-0.96	67.5-72	70
0.97-1.03	72.75-77.25	75
1.04-1.09	78-81.75	80
1.10-1.16	82.5-87	85
1.17-1.23	87.75-92.25	90
1.24-1.29	93-96.75	95
1.30-1.36	97.5-102	100
1.37-1.43	102.75-107.25	105
1.44-1.49	108-111.75	110
1.50-1.56	112.5-117	115
1.57-1.63	117.75-122.25	120
1.64-1.69	123-126.75	125
1.70-1.76	127.5-132	130
1.77-1.83	132.75-137.25	135
1.84-1.89	138-141.75	140
1.90-1.96	142.5-147	145
$\geq$ 1.97	$\geq$ 147.75	150

*Dosing for patients under BSA 0.5 m^2 is by mg/kg, rounded to the nearest 5 mg

APPENDIX IV: FAMILY INSTRUCTIONS FOR ADMINISTRATION OF TEMOZOLOMIDE
FOR PATIENTS WHO ARE UNABLE TO SWALLOW CAPSULES

Temozolomide is an oral cancer medicine that your child will be taking for treatment of his/her neuroblastoma. If your child is unable to swallow these capsules, you should use the following instructions to administer this medication safely.

- Temozolomide must be kept in a dark container
- Temozolomide should be taken at the same time everyday
- If your child requires nausea medicine it should be taken prior to the temozolomide
- If the dose of temozolomide is vomited later than 10 minutes after administration (which is unusual), do not repeat the dose
- If the person dispensing this medicine is pregnant or suspects she is pregnant, she should not dispense this medicine

Temozolomide is an anti-cancer agent, and so special precautions must be taken when handling this medicine. There is potential hazard to anyone who handles this medicine once the protective capsule is opened. Since your child is unable to swallow the capsule, you will be required to open the capsules and mix the contents of the capsule in apple sauce or apple juice. This process must be done according to the following guidelines to ensure safe administration of this medicine.

- Find a place that is as free of air flow as possible and is not an area where food is stored or prepared. The work surface should be covered with aluminum foil to reduce exposure to other members of the family.
- Temozolomide can be mixed in apple sauce or apple juice.
- Place the apple sauce or apple juice in a disposable container.
- Put on disposable gloves.
- Open each capsule and place the powder in a medicine cup.
- Add the whole contents of the medicine cup to either apple sauce or apple juice. The medicine will not dissolve completely if mixing in apple juice so have extra apple juice on hand so you can add it to any remaining powder in the bottom of the cup.
- If you need to use additional juice or apple sauce, remove your gloves before touching the main container then place new gloves on before adding the additional juice or apple sauce to the medicine. (You do not want to contaminate the main container with any powder that may be on your gloves.)
- Anything that comes into contact with the medicine must be disposable, such as the spoon used for mixing or eating the apple sauce.
- Once all of the medicine is taken throw away the following in the provided red bag: medicine cup, the container the medicine was mixed in, the cover for the work surface, gloves and anything else that has been in contact with the medicine.

Once a Five-day cycle of temozolomide is completed bring the red bag with you to the clinic so it can be disposed of properly.

APPENDIX V: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Be aware of your/your child's bowel movements. At the first sign they become softer than usual or if your child has any increase in the number of bowel movements over what is normal for him/her, then you/your child should begin taking loperamide (Imodium). **If he/she does not start taking the loperamide right away, the diarrhea may become severe and last several days or require hospitalization.**

Please follow these directions carefully, using dosing guidelines below:

Take _____ loperamide at the first sign of diarrhea.

Continue taking_____ loperamide every ____ hours until your normal pattern of bowel movements returns. Repeat the same doses and frequency if the diarrhea returns.

Do not give more than _____ of loperamide in a 24 hour period.

Please call your doctor if you have any questions about taking loperamide, if your child's diarrhea is not under control after two days, or if he/she is feeling extremely weak, lightheaded, or dizzy.

Make an extra effort to give your child lots of fluids (several glasses of pedialyte, fruit juices, soda, soup, etc.) while your child is participating in this study.

Side effects may include tiredness, drowsiness, or dizziness. If your child experiences these side effects, or if your child is urinating less frequently than usual, please contact your child's physician.

Do not give your child any laxatives without consulting with his/her physician.

Loperamide dosing guidelines:

Loperamide is usually supplied in the following forms: 1 teaspoon = 1mg; 1 caplet = 2mg

Maximum dose of loperamide per day: < 6 years: 4 mg/day; 6-11 years: 6 mg/day; >11 years: 16 mg/day, using the non silicone-containing product.

Weight: > 43 kg:	4 teaspoons or 2 caplets (4 mg) after the first loose bowel movement, followed by 2 teaspoons or 1 caplet (2mg) every2 hours. During the night the patient may take, 2 caplets (4mg) every 4 hours rather than 1 caplet (2mg) every 2 hours.
Weight: 30kg – 43kg:	2 teaspoons or 1 caplet (2mg) after the first loose bowel movement followed by 1 teaspoon or one-half caplet (1 mg) every 2hours. During the night the patient may take, 1 caplet (2 mg) every 4 hours rather than one-half caplet every 2 hours.
Weight: 20kg – < 30kg:	2 teaspoons or 1 caplet (2mg) after the first loose bowel movement followed by 1 teaspoon or one-half caplet (1mg) every 3 hours. During the night, the patient may take 1 caplet (2mg) every 4 hours rather than one-half caplet every3 hours.
Weight: 13kg - < 20kg:	1 teaspoon (1mg) after the first loose bowel movement followed by 1 teaspoon (1mg) every 3 hours. During the night, the patient may take 1 teaspoon (1 mg) every 4 hours rather than every 3 hours.
Weight: < 13kg:	Half teaspoon (0.5mg) after the first loose bowel movement followed by half teaspoon every 3 hours. During the night, the patient may take half teaspoon (0.5mg) every 4 hours rather than every 3 hours.

APPENDIX VI: BLOOD VOLUME SUMMARY FOR INVESTIGATIONAL 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.

Course	Day	Sample Time Points (based on timing of MLN8237 dosing) *	MLN8237 Pharmacokinetics	Irinotecan Pharmacokinetics **	UGT 1A1 Polymorphisms	Total
1	1	(Pre-dose)0 hr	3mL	2mL	10mL	15mL
	4	(Pre-dose) 0 hr	3mL	2mL	----	5mL
		0.5hr	3mL	----	----	3mL
		1 hr	3mL	----	----	3mL
		2 hr	3mL	2mL	----	5mL
		3 hr	3mL	2mL	----	5ml
		4 hr	3mL	2mL	----	5mL
		7hr	3mL	2mL	----	5mL
	5	Pre-day 5 dose of MLN8237	3mL	2mL	----	5mL
					TOTAL :	51 mL

*Refer to sections 8.1.2 and 8.2.2 for further clarification of sample time points.
**See section 8.2.1 for restrictions if patient has a central line.

APPENDIX VII RESPONSE CRITERIA VERSION 1

These criteria are to be used for patients enrolled prior to Amendment #5.

Response Criteria for CT/MRI Lesions

For CT/MRI lesions, this study will use the definitions of measurable disease from the Response Evaluation Criteria In Solid Tumors (RECIST) from the National Cancer Institute. Overall response for each patient will be defined as outlined in Section 11.4.

Definition of Measurable (Evaluable) Disease on CT/MRI scan
The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 20 mm. With spiral CT scan, lesions must be at least 10 mm. The investigator will identify up to 10 measurable target lesions to be followed for response. Note that bone lesions will be considered as non-target lesions for evaluation of CT/MRI response since they will be evaluated with MIBG scans.

Serial measurements of lesions are to be done with CT or MRI. The same method of assessment used to characterize each identified and reported lesion at baseline should be used during follow-up.

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the **disease measurement**. The response of the CT/MRI lesions will be defined as outlined below:

Complete Response (CR)
Disappearance of all target and non-target CT/MRI lesions.

Very Good Partial Response (VGPR)
Greater than 90% decrease of the disease measurement for CT/MRI lesions, taking as reference the disease measurement done to confirm measurable disease at study entry. Non-target CT/MRI lesions stable to smaller in size.

Partial Response (PR)
At least a 30% decrease in the disease measurement for CT/MRI lesions, taking as reference the disease measurement done to confirm measurable disease at study entry. Non-target CT/MRI lesions stable to smaller in size.

Progressive Disease (PD)
At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement since the treatment started, OR a new site of tumor. Non-target CT/MRI lesions stable, smaller, or increased in size.

Stable disease (SD)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started. No new sites of disease.

Response Criteria for Morphologic Bone Marrow Disease

Only those patients with morphologic evidence of neuroblastoma by routine H and E staining (NSE staining only is not evaluable) will be evaluable to assess bone marrow response.

Complete Response
Will be defined as no tumor cells detectable by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least three weeks apart after study entry.

Progressive Disease will be defined as:

Tumor seen on morphology on two consecutive bone marrows done at least three weeks apart in patients who had NO tumor in bone marrow at study entry. (Note: Patient may be declared as progressive disease in bone marrow after only one diagnostic bone marrow at the discretion of the treating physician after discussion with the study chair.)

Patients who enter study with bone marrow tumor by morphology will be considered to have progressive disease if there is a minimum of 25% tumor in the marrow by morphology **AND** a doubling in the amount of tumor in the marrow compared to the level present at study entry. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have PD; a patient entering with 30% tumor must increase to ≥60% tumor).

Stable Disease
Will be defined as persistence of an amount of tumor in the bone marrow by morphology that does not meet criteria for either complete response or progressive disease. Patients who clear morphologic tumor but have immunocytologic tumor will be called SD.

Response Criteria for MIBG Positive Lesions

All patients will be evaluable for MIBG response following the first course of therapy. Patients with persistent MIBG-positive disease after the first course will also be evaluable for MIBG response following the second course of therapy.

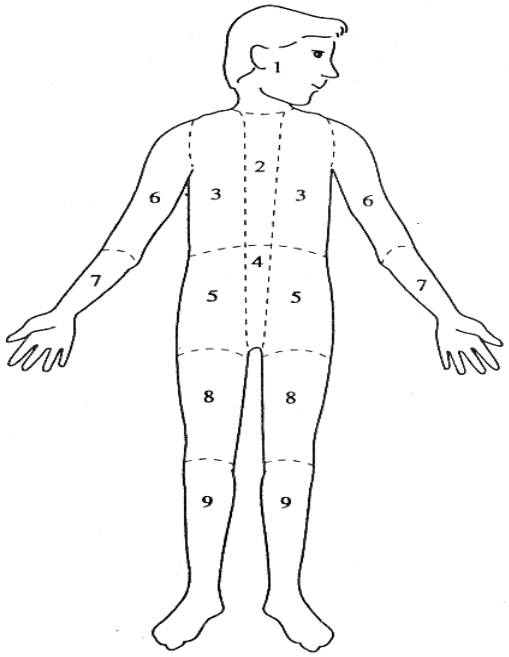
Definition of MIBG Response
The following criteria will be used to report MIBG response by the treating institution on the end of course report forms:

a. Complete response = complete resolution of all MIBG positive lesions
a. Partial response = resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions.
b. Stable disease = no change in MIBG scan in number of positive lesions (includes patients who have same number of positive lesions but decreased intensity)
c. Progressive disease = Development of new MIBG positive lesions

Assessment of MIBG Response
The response of MIBG lesions will be assessed on central review using the Curie scale as outlined below.[22] Central review responses will be used to assess efficacy for study endpoint.

NOTE: This scoring is NOT required to be done by the treating institution for their end of course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10^{th} general sector allocated for any extra-osseous lesions**.** In each region, the lesions are scored as follows. The **absolute extension score** is graded as: 0 = no site per segment, 1 = 1 site per segment, 2 = more than one site per segment, 3 = massive involvement (>50% of the segment). The absolute score is obtained by adding the score of all the segments. See diagram of sectors below:



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

a. Complete response: all areas of uptake on MIBG scan completely resolved.
b. Partial response: Relative score > or = 0.1 (lesions almost disappeared) to < or = 0.5 (lesions strongly reduced),
c. Stable disease: Relative score > 0.5 (lesions weakly but significantly reduced) to < or = 1 (lesions not reduced).
d. Progressive disease: New lesions on MIBG scan.

Definition of Overall Response for Each Patient

The **International Neuroblastoma Response Criteria** were developed to define responses in patients being treated with frontline therapy from diagnosis.[23] These criteria were utilized as a basis for the following response criteria, which integrate response at all sites defined as measurable in this study, including CT/MRI lesions which meet RECIST criteria, MIBG positive lesions, and bone marrow disease. These criteria will be used to define the overall response for each patient.

Complete Response (CR)
Disappearance of all target lesions. No evidence of tumor at any site (chest, abdomen, liver, bone, bone marrow, nodes, etc.), and HVA/VMA normal.

Very Good Partial Response (VGPR)
Greater than 90% decrease of the disease measurement for CT/MRI target lesions, taking as reference the disease measurement done to confirm measurable disease in target lesions at study entry; all pre-existing bone lesions with CR by MIBG; MIBG scan can be SD or CR in soft tissue lesions corresponding to lesions on CT/MRI. CR in bone marrow. No new sites of tumor. HVA/VMA normal.

Partial Response (PR)
At least a 30% decrease in the disease measurement for CT/MRI target lesions, taking as reference the disease measurement done to confirm measurable disease in target lesions at study entry. Bone marrow with CR. MIBG with either PR/CR in bone lesions; MIBG may be SD or CR in soft tissue lesions corresponding to lesions on CT/MRI. HVA/VMA may still be elevated.

Progressive Disease (PD)
Any one of the following:

a. At least a 20% increase in the disease measurement for CT/MRI target lesions, taking as reference the smallest disease measurement recorded since the start of treatment.

b. Appearance of one or more new lesions or new sites of tumor.

c. PD as defined above for either bone marrow or MIBG lesions.

Stable disease (SD)
The patient will be classified as stable disease for overall response if there is stable disease by either CT/MRI lesion, bone marrow, or MIBG criteria. No new lesions; no new sites of disease.

Mixed response (MR)
The patient will be classified as mixed response for overall response if there is complete response, partial response, and/or very good partial response at a minimum of one site (i.e. CT, MIBG, and/or bone marrow), with stable disease at all other sites and any value of catecholamines.

The overall response as assessed at any particular time point based on the various disease sites is summarized in the table below.

Overall Response Assignment

Response by individual site				**Overall response**
CT/MRI lesions	**MIBG lesions**	**Bone marrow**	**Catechols**	
PD	Any	Any	Any	PD
Any	PD	Any	Any	PD
Any	Any	PD	Any	PD
CR	CR	CR	Normal	CR
			Normal	CR
VGPR	CR in bone lesions ; May have SD/CR in soft tissue sites corresponding to lesions on CT/MRI	CR	Normal	VGPR
PR	PR/CR in bone lesions; May have SD/CR in soft tissue sites corresponding to lesions on CT/MRI	CR	Any	PR
SD	SD	SD	Any	SD
SD/PR/VGPR/CR	SD	SD/CR	Any	SD
SD/PR/VGPR/CR	SD/PR/CR	SD	Any	SD
Mixed response: CR, PR and/or VGPR at minimum of one site, with SD at all other sites; any catecholamines				

APPENDIX VIII RESPONSE CRITERIA VERSION 1.1

With Amendment #5, response criteria changed temporarily to the following NANT Response Criteria version 1.1. With Amendment #6, all patients enrolled after Amendment #5 are to use the new NANT Response Criteria version 1.2 in Section 11. The following response criteria 1.1 are included in this appendix solely for reference.

Overall response will incorporate all three parameters: CT/MRI; MIBG (PET is substituted for MIBG non-avid tumors); and bone marrow response. 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 be defined by central review, using the same criteria below.

Response Criteria for CT/MRI Lesions

For CT/MRI lesions, this study will use the definitions of measurable disease from the Response Evaluation Criteria in Solid Tumors (RECIST 1.1; European Journal Cancer 45: 228-247, 2009).

Definition of Measurable (Evaluable) Disease on CT/MRI scan
The presence of at least one lesion that can be accurately measured in at least one dimension with a longest diameter ≥10 mm. In addition, lesions must be MIBG or PET avid (if patient known to be MIBG non-avid), or have a biopsy as required in the eligibility criteria. Up to 5 measurable target lesions will be identified to be followed for response (maximum of 2 in one organ site). Bone lesions will be considered non-target lesions for evaluation of CT/MRI response since they will be evaluated with MIBG scans. Soft tissue components of bone lesions will be considered measurable disease if they meet the size definition of measurable disease noted above.

Serial measurements of 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 (sLD) of the longest diameters for all target lesions will be calculated and reported as the **disease measurement**. The response of the CT/MRI lesions will be defined as outlined below:

Complete Response (CR)
Disappearance of all target CT/MRI lesions. Non-target lesions must be stable to smaller in size.

Partial Response (PR)
At least a 30% decrease in sLD of CT/MRI lesions, taking as reference the measurement of target lesions performed at study enrollment. Non-target CT/MRI lesions must be stable to smaller in size.

Progressive Disease (PD)
At least a 20% increase in sLD AND a minimum absolute increase of 5 mm in sLD, the disease measurement, taking as reference the smallest sLD disease measurement since the treatment started, OR a new site of tumor. Non-target CT/MRI lesions can be stable, smaller, or increased in size.

Stable disease (SD)
Neither sufficient shrinkage in sLD to qualify for PR nor sufficient increase to qualify for PD. No new sites of disease.

Not evaluable (NE)
CT/MRI scans are of inadequate quality as assessed by central reviewer, or scans are not repeated of all 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.)

Not involved (NI)
No measurable CT/MRI lesions present at study entry and scan remains with no measurable CT/MRI lesions.

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

Response Criteria for Morphologic Bone Marrow Disease

Routine morphology (with or without routine immunocytochemistry) will be used for baseline evaluation and all subsequent response evaluations performed while on protocol therapy, and at end of protocol therapy. Patients with < 10% tumor on all samples of the bilateral bone marrow aspirate and biopsies at study entry will be evaluable for bone marrow response, but have separate definitions for response criteria. Tumor percentage will be assessed by the surface area percentage of tumor.

Complete Response (CR)
At least 10% tumor cells seen on any one sample of bilateral aspirates/biopsies performed at study enrollment, with no tumor cells seen on bilateral aspirates and biopsies at one subsequent time point.

Complete Response Minimal Residual Disease (CR-MRD) Less than 10% tumor on all samples of bilateral aspirates/biopsies at study enrollment, with no tumor cells seen on bilateral aspirates and biopsies at one subsequent (post protocol therapy) timepoint.

Progressive Disease (PD)
Patients who enroll on study with any amount of tumor in the bone marrow on the baseline evaluation will be considered to have PD if one subsequent evaluation shows a minimum of 10% tumor in the marrow on any one sample AND there is a doubling in the amount of tumor compared to study entry (baseline). For example, a patient entering with 5% tumor in marrow must increase to ≥ 10% tumor to have PD; a patient entering with 30% tumor must increase to ≥60% tumor. If patients have in increase in tumor amount which is less than the amount specified for PD, the response will be classified as SD.

Patients who enter on study with no tumor seen will be considered PD if ONE subsequent evaluation shows ≥10% tumor. If < 10% tumor is seen on one subsequent evaluation or intermittently, the response will be classified as SD.

Stable Disease (SD)
Will be defined as persistence of an amount of tumor in the bone marrow that does not meet criteria for progressive disease or CR or CR Minimal Residual Disease. .

Not Evaluable (NE)
Patients for whom follow-up bone marrows (including bilateral bone marrow aspirates and biopsies) are of inadequate quality as assessed by central reviewer, will be classified as not evaluable.

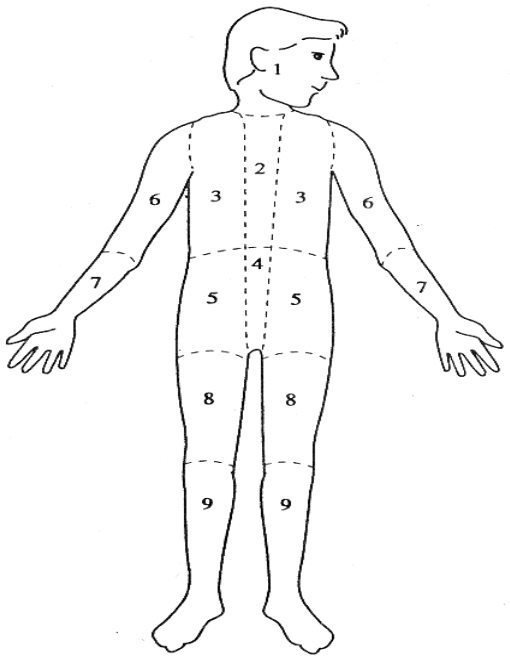
Not involved (NI)
Patients with no evidence of neuroblastoma in the bone marrow at baseline and on subsequent evaluations.

Not done (ND)
Bone marrow evaluation not done at a given timepoint.

Response Criteria for MIBG Avid Lesions

MIBG 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 MIBG response using the scoring outlined belo, however the statistical endpoint of MIBG response will utilize the MIBG score from the central reviewer.

The body is divided into 9 anatomic sectors for metastatic lesions (including bone and soft tissue lesions), with a 10th general sector allocated for residual primary tumor uptake. The **absolute extension score** is graded as: 0 = no involvement, 1=1 site per segment, 2 = more than one site per segment, 3 = massive involvement (>50% of the segment). The absolute score is obtained by adding the score of all the segments. See diagram of sectors below:



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

a. Complete response: all areas of uptake on MIBG scan completely resolved.
b. Partial response: Relative score ≥ 0.1 (lesions almost disappeared) to ≤ 0.5
c. Stable disease: Relative score > 0.5 to < 1.2
d. Progressive disease: New lesions on MIBG scan OR a relative score ≥ 1.2.
e. Not evaluable: MIBG scan of inadequate quality as assessed by central reviewer.
f. Not involved: No MIBG avid lesions at study entry and subsequent response time points.
g. Not done: MIBG scan not done at a given response time point.

Response Criteria using FDG-PET scans (for MIBG non-avid patients)

Patients known to be non-avid for MIBG should have FDG-PET scans performed for monitoring response. The number of FDG-PET avid lesions will be scored at each time point as the total number of avid lesions (ie four lesions = PET score of 4)

Complete response (CR)
Resolution of all FDG-PET uptake.

Partial response (PR)
≥ 50% decrease in the number of FDG-PET avid lesions

Stable disease (SD)
No change or less than 50% decrease in the number of FDG-PET avid lesions

Progressive disease (PD)

Appearance of new FDG-PET avid lesions. Note: biopsy may be done to exclude causes of FDG-PET uptake other than tumor. If biopsy is negative for tumor, patient will not meet definition of PD

Not evaluable (NE)
FDG-PET scan of inadequate quality to evaluate response

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

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,except to confirm an overall response of CR, which will require that urine catecholamines (HVA and VMA) are within 3 standard deviations of normal for patient's age. Urine catecholamineswill still be requested at all response evaluation time points and recorded in database.

Definition of Overall Response for Each Patient

The criteria below will be used to define the overall response for each patient, with consideration of all three individual response parameters: CT/MRI, MIBG (FDG-PET if MIBG non-avid), and Bone Marrow.

Complete Response (CR)
CR for all CT/MRI target lesions with resolution of uptake at all sites on MIBG scan FDG-PET scan if tumor is not MIBG avid). Bone marrow must be CR or Not Involved. Urine catechols must be no more than 3 standard deviations above normal for age.

Complete Response MRD (CR-MRD)
CR or NI for CT/MRI response and MIBG response (FDG-PEG if MIBG non-avid) with BM response of CR-MRD.

Partial Response (PR)
CT/MRI response of PR. MIBG response must be either PR or CR. CT/MRI target lesions may still have MIBG (FDG-PET if MIBG non-avid) uptake. Bone marrow response must not be Progressive Disease. Bone marrow response may be SD if the maximum amount of tumor was < 10% at study enrollment. No new lesions by CT/MRI, MIBG (FDG-PET if MIBG non-avid).

Progressive Disease (PD)
Either one of the following will define an overall response of PD:

a. At least one response parameter including CT/MRI, MIBG, bone marrow and/or FDG-PET response is PD as defined above. 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 alone.

Stable disease (SD)
Response of stable disease for at least one parameter, with response of SD or not involved for all other parameters. No PD by any parameter.

Minor response (MR)
Complete response, Complete-Unconfirmed response, and/or partial response for one parameter (i.e. CT/MRI, MIBG (FDG-PET if MIBG non-avid), bone marrow), with response of stable disease for second parameter and any response other than PD or inevaluable for third parameter.

Not evaluable (NE)
Response of Not evaluable or Not Done for one or more response parameters including CT/MRI, MIBG (FDG-PET if MIBG non-avid), or bone marrow, unless one parameter is done and demonstrates PD which defines an overall response of PD.

Not done (ND)
Response was not assessed for any of the 3 parameters at a given time point.

Unconfirmed
Response of Inevaluable or Not Done for any of the 3 parameters that did not have measurable/evaluable tumor at study entry.

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:

Overall Response Assignment

CT/MRI Response	MIBG Response*	Bone Marrow Response	Overall Response
PD for any one parameter with any response (including Not Done or Inevaluable) for the other 2 parameters. PD may also be defined by clinical assessment of the treating physician only.			PD
CR	CR	CR	CR
CR for one parameter with either CR or NI in other sites			CR
MIBG response= CR, with CT/MRI response either CR or NI -OR- CT/MRI response=CR with MIBG response either CR or NI		CR-MRD	CR-MRD
NI	NI	CR-MRD	CR-MRD
CR or NI	PR	CR or CR-MRD or NI	PR
PR	CR or PR or NI	CR -OR- CR-MRD -OR- SD if < 10% tumor in bone marrow at study entry -OR- NI	PR
SD for one parameter, with SD or NI for other two parameters			SD
CR or CR-MRD or PR for at least one parameter, SD for a second parameter, and any response other than PD or Inevaluable for other parameter			Minor response

Response of Inevaluable or Not Done any one of the 3 parameters that had measurable/evaluable tumor at study entry	Inevaluable
No response evaluations performed for any of the 3 parameters	Not Done
Response of Inevaluable or Not Done for any of the 3 parameters that did not have measurable/evaluable tumor at study entry	Unconfirmed

*For patients who utilize FDG-PET in place of MIBG response, then substitute FDG-PET response for MIBG response in this table to define overall response.