Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium/Magnesium (CaMg) to Prevent Oxaliplatin-Induced Sensory Neurotoxicity, N08CB (Alliance)

Loprinzi, et al

DOI: 10.1200/JCO.2013.52.0536

N08CB

North Central Cancer Treatment Group

A Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium/Magnesium in Two Different Versions to Prevent Oxaliplatin-Induced Sensory Neurotoxicity

For any communications regarding this protocol, please call the protocol resource person on the following page.

Study Chairs: Charles L. Loprinzi, M.D. (Research Base)*
Mayo Clinic
200 First Street, SW
Rochester, MN 55905
507/266-6247
507/284-5280 (FAX)
Loprinzi.charles@mayo.edu

Albert Bernath, M.D. (NCCTG)

Study Cochairs: Axel Grothey, M.D. (Research Base)

Statisticians: Rui Qin, Ph.D. √
507/538-3837
Pamela Atherton, M.S. √
507/284-0660

Drug Availability

Commercial agents: Calcium gluconate and magnesium sulfate

***Investigator having NCI responsibility for this protocol**

√Study contributor(s) not responsible for patient care.

Document History	**(Effective Date)**
Activation	June 22, 2010
Addendum 1	November 26, 2010
Addendum 2	February 11, 2011
Addendum 3	July 22, 2011
Update 1	September 22, 2011

Study Participants	**Date Activated**
Entire NCCTG	June 22, 2010
Note: This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with NCCTG will participate through the CTSU mechanism	June 22, 2010

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	Paula Stellmaker NCCTG *Research Base* Quality Assurance Specialist Phone: 507-266-6247 Fax: 507-284-1902 E-mail: stellmaker.paula@mayo.edu
Drug administration, infusion pumps, nursing guidelines	Lisa Kottschade, RN, MSN, CNP NCCTG *Research Base* Nurse Phone: 507-538-7888 E-mail: kottschade.lisa@mayo.edu Anne Forsman, R.N., BSN, OCN NCCTG Member Nurse Phone: 218-786-3308 E-mail: aforsman@smdc.org
Forms completion and submission	Joan Aresco NCCTG Member Clinical Research Associate Phone: 734-712-3304 Email: arescoj@trinity-health.org
Protocol document, consent form, Regulatory issues	Tracee L. Shevlin NCCTG *Research Base* Research Protocol Specialist Phone: 507- 538-6647 Fax: 507-284-5280 E-mail: shevlin.tracee@mayo.edu
Non-paraffin Biospecimens	Roxann Neumann NCCTG Research Base Biospecimen Resource Manager Phone: 507- 538-0602 Fax: 507-266-0824 E-mail: neumann.roxann@mayo.edu
Adverse Events (AdEERS, MedWatch, Non-AER, AML/MDS)	Patricia G. McNamara NCCTG *Research Base* SAE Coordinator Phone: 507-266-3028 Fax: 507-284-9628 E-mail: mcnamara.patricia@mayo.edu

Add 1

- No waivers of eligibility per NCI

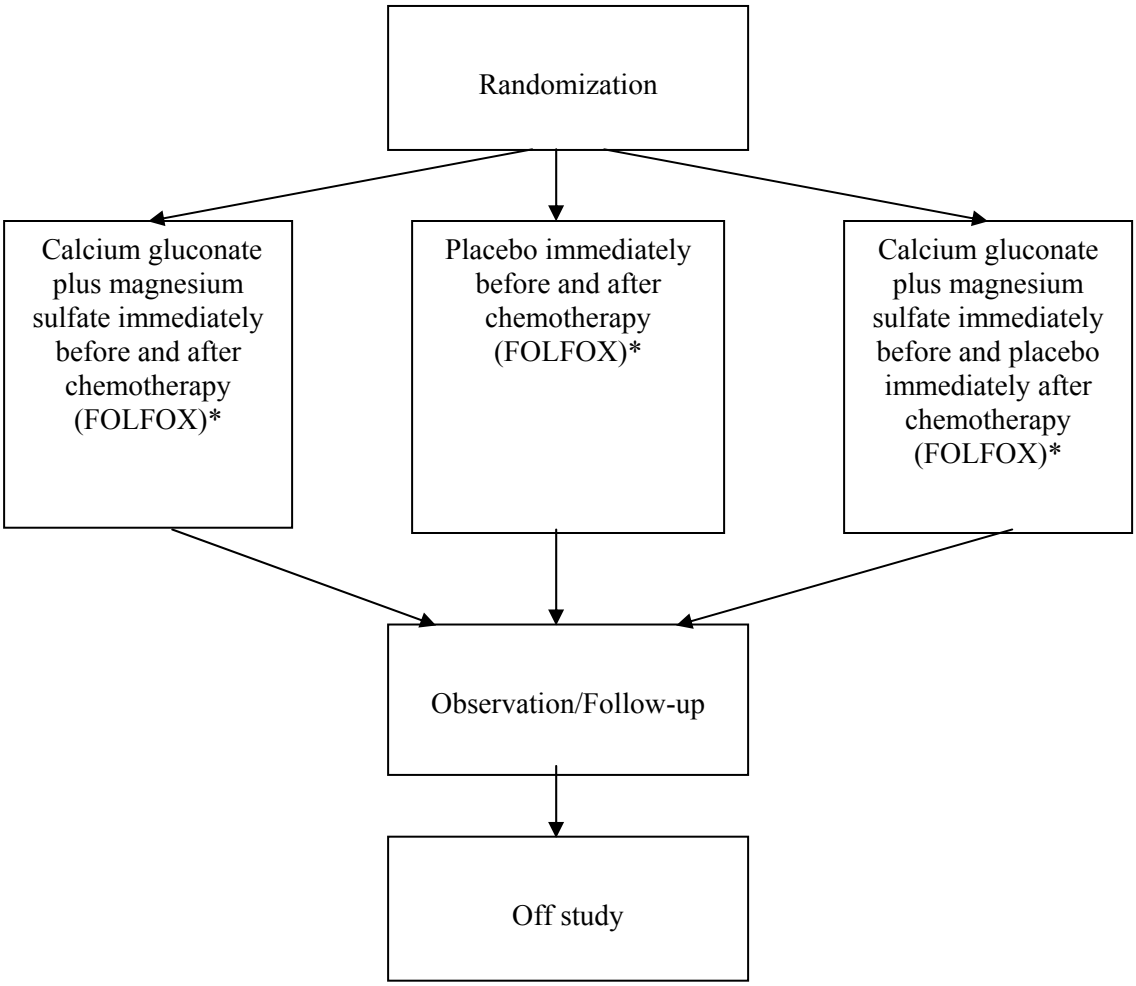
CANCER TRIALS SUPPORT UNIT (CTSU)
CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU (2878) Fax – 215-569-0206 To E-mail regulatory documents – CTSURegulatory@ctsu.coccg.org	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm].	NCCTG Operations Office Mayo Clinic R0 FF 03-24-CC/NW Clinic 200 First Street, SW Rochester, MN 55905 507/266-6247 507/284-1902 (FAX) Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the members' section of the CTSU web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in Appendix IX for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
The CTSU Web site is located at https://www.ctsu.org		

Index

Schema

Calcium/Magnesium for patient receiving FOLFOX as adjuvant chemotherapy for colon cancer



Cycle length = 14 days
Observation cycle length = every 3 months for 6 months after completion of chemotherapy, then Questionnaires only at 12 and 18 months after completion of chemotherapy

Please note: Cycle length is an NCCTG tool to facilitate data entry

*FOLFOX: fluorouracil (infusional/bolus), leucovorin, oxaliplatin

Generic name: Calcium gluconate Brand name(s): NCCTG Abbreviation: CALCIU Availability: commercially available	Generic name: Magnesium sulfate Brand name(s): NCCTG Abbreviation: MGS04 Availability: commercially available	Generic name: Placebo Brand name(s): NCCTG Abbreviation: PLACEB Availability: commercially available

1.0 Background

1.1 Clinical Use of Oxaliplatin in Colorectal Cancer

Oxaliplatin, a third-generation platinum derivative, has become an integral part of various chemotherapy protocols, in particular, in advanced colorectal cancer (CRC). The activity in colorectal cancer is of particular interest since cis- and carboplatin have no notable clinical activity in this tumor type; whereas, oxaliplatin has emerged as an integral part of systemic chemotherapy in this cancer[1]. While oxaliplatin as a single agent has only modest activity against colorectal cancer, combination protocols with fluoropyrimidines such as 5-fluorouracil (5-FU) plus folinic acid (leucovorin; LV) or irinotecan have demonstrated remarkable cytotoxic synergy and efficacy in preclinical models and in clinical trials. In colorectal cancer, combination protocols of 5-FU/LV plus oxaliplatin have emerged as a standard-of-care of first-line therapy in the palliative setting as well as for adjuvant therapy for stage III colon cancer.

1.11 Oxaliplatin-based Combination Protocols as Palliative Therapy of Colorectal Cancer

Oxaliplatin has shown a remarkable synergy with fluoropyrimidines such as 5-FU in preclinical models and clinical practice. Combination protocols using infusional 5-FU/LV plus oxaliplatin confer high activity in advanced colorectal cancer. Three phase III trials comparing 5-FU/LV with 5-FU/LV plus oxaliplatin as first-line treatment of stage IV colorectal cancer unanimously demonstrated that the combination regimen was significantly superior to 5-FU/LV alone in terms of response rate and progression-free survival. In addition, the use of oxaliplatin-based chemotherapy was associated with longer than expected median overall survival of 16.2 to 19.7 months in these trials. Recently, the results of Intergroup trial N9741 verified the superior efficacy of the FOLFOX4 protocol over weekly bolus 5-FU/LV plus irinotecan (IFL) as first-line therapy of advanced CRC. Based on these results, FOLFOX4 has emerged as new standard palliative first-line treatment of CRC and has received FDA approval for this indication in January 2004.

1.12 Oxaliplatin-based Combination Protocols as Adjuvant Therapy of Colorectal Cancer

The superior efficacy of 5-FU/LV/oxaliplatin protocols in advanced CRC formed the rationale for trials assessing oxaliplatin-based combination regimens as adjuvant treatment of colon cancer. Two large trials were conducted in the US and in Europe that used different oxaliplatin/5-FU/LV schedules as adjuvant therapy of stage II and III colon cancer.

1.121 The so-called MOSAIC trial, which was mainly conducted in Europe, randomized 2246 patients with stage II and stage III colon cancer to receive either 6 months of LV5FU2 (bolus plus infusional 5-FU/LV) or FOLFOX4[2]. FOLFOX4 was found to be superior to LV5FU2 in terms of 3-year, disease-free survival (DFS), a parameter that correlates very well with 5-year overall survival[3]. Six year data, presented at a recent ASCO meeting confirm the benefit of this combination[54]. Based on these findings, FOLFOX4 has emerged as the new standard of care in the adjuvant treatment of stage III and high-risk stage II patients. Consequently, 6 months of FOLFOX forms the control arm of the NCCTG/Intergroup trial N0147.

1.122 The NSABP C-07 trial compared standard weekly bolus 5-FU/LV (Roswell Park) with a weekly bolus 5-FU/LV plus oxaliplatin regimen (so-called FLOX protocol). From February 2000 until November 2002, 2492 patients were included in this trial. The results support the value of this regimen[55].

1.2 Sensory Neurotoxicity is the Dose-Limiting Side Effect of Oxaliplatin

Side effects of oxaliplatin, mild hematologic toxicity (rarely Grade 3), gastrointestinal toxicities - mainly nausea/vomiting and diarrhea - drug-induced fever, and hypersensitivity have been reported[4]. However, the most important side effect of oxaliplatin is a neurologic toxicity that has rather unique characteristics and represents the dose-limiting toxicity of oxaliplatin[5].

1.3 Oxaliplatin Induces Two Distinct Forms of Neurotoxicity: Acute Neuropathy and Chronic, Cumulative Neurotoxicity

1.31 Neurotoxicity is inherent to all platinum-containing antineoplastic agents, as with other chemotherapeutics such as taxanes and vinca-alkaloids [6]. Oxaliplatin induces two distinct forms of neuropathy: a very common acute syndrome that is transient and appears during, or shortly after, exposure to oxaliplatin, and a dose-limiting chronic sensory neurotoxicity that is cumulative in nature and resembles characteristics of cisplatin neurotoxicity[7,8].

1.32 Acute Neuropathy

The acute neuropathy observed with oxaliplatin is a common phenomenon and occurs in about 85-95% of all patients exposed to oxaliplatin. It consists of mainly sensory symptoms in form of distal or perioral paresthesias or dysesthesias. One to two percent of patients report characteristic pharyngo-laryngeal dysesthesias with the feeling of difficulties in breathing or swallowing. It is important to note to the patient that this feeling does not mean that there actually is a laryngeal obstruction. Rarely, the acute sensory symptoms are paralleled by tetanic-like muscular contractions of the distal extremities or the jaw resulting, for instance, in the inability to release grip. The resemblance with tetanic cramps suggests hyperexcitability of motor neurons or muscle cells as pathogenetic mechanism of this phenomenon[9].

While these acute symptoms can occur during, or immediately after, the first oxaliplatin infusion, they are generally mild, short-lived, and completely reversible within a few hours or days. A characteristic feature of these acute symptoms is that they can be triggered or aggravated by exposure to cold. Furthermore, the probability and severity of acute neuropathy appears to be schedule-dependent so that prolongation of infusion with lower peak plasma concentrations of oxaliplatin has been successfully used to prevent pharyngo-larnygeal dysesthesias that are often disturbing for patients[10]. As all symptoms associated with acute neuropathy are of transient nature and fully reversible, but very common, educating the patient about these symptoms is of utmost importance before starting treatment with oxaliplatin.

1.33 Chronic, Cumulative Neurotoxicity

Cumulative sensory neurotoxicity is the dose-limiting toxicity (DLT) of oxaliplatin and closely resembles that observed with cisplatin, except that ototoxicity hardly ever occurs. Symptoms consist of sensory impairment of peripheral neural function with distally pronounced dysesthesias and paresthesias of the extremities of gradually prolonged duration that eventually persist between treatment cycles and increase in intensity with the cumulative dose. This chronic neurotoxicity can severely affect

activities of daily living such as buttoning clothes, writing, and handling objects. Sensory ataxia might develop that should not be confused with an involvement of motor neurons since cumulative oxaliplatin neurotoxicity is purely sensory in nature. While chronic sensory neuropathy *per se* – in contrast to acute neuropathy —cannot be triggered by exposure to cold, a recent report suggested exacerbation and aggravation of cumulative neurosensory toxicity following surgery after oxaliplatin treatment[11]. In patients that had already received a median cumulative oxaliplatin dose of 740 mg/m^2, transitory increases in oxaliplatin plasma levels were noted and attributed to intraoperative hemolysis in view of high intra-erythrocytic oxaliplatin concentrations. This phenomenon might deserve attention in neoadjuvant trials using oxaliplatin-based protocols as a radiosensitizer before curative surgery for rectal cancer.

While some form of cumulative neurotoxicity develops in the majority of patients after prolonged treatment with oxaliplatin, in clinical trials sensory symptoms causing functional impairment (i.e., Grade 3 adverse events) have been found in only about 15% of patients after a cumulative dose of 780 to 850 mg/m^2[2,12,13], but in 50% of patients at a cumulative dose of 1170 mg/m^2[2,14]. It is clinically important to note that the onset of tumor response under oxaliplatin-based therapy usually occurs before a cumulative oxaliplatin dose of 700 mg/m^2 has been reached. This fact allows for a clinical decision to continue or stop oxaliplatin in view of the observed efficacy of treatment. Furthermore, oxaliplatin-induced neurotoxicity is generally reversible with a median time to recovery from Grade 3 adverse events of 13 weeks[13].

The incidence and reversibility of oxaliplatin-induced neurotoxicity was investigated in the MOSAIC trial that established FOLFOX as the new standard in the adjuvant therapy for stage III colon cancer and that formed the rational for the NCCTG/Intergroup trial N0147. While in the MOSAIC trial FOLFOX4 demonstrated superior efficacy compared with LV5FU2 in terms of 3-year DFS, it was associated with increased adverse events, in particular, myelosuppression and neurotoxicity[2]. The planned cumulative oxaliplatin dose of 12 applications of FOLFOX4 was 1,020 mg/m^2. The median relative dose intensity of oxaliplatin in 1,123 patients with 11,819 cycles in this trial was 81%. Grade 3 neurotoxicity was observed in 12% of all patients and in 18% of those patients who received the full planned oxaliplatin dose of 1,020 mg/m^2 ((Table 1 below). Only 8% of patients did not report any grade of neurotoxicity. Interestingly, no increased neurotoxicity was observed in elderly patients (65-75 years). One year after discontinuation of therapy, 29% of patients still had some degree of neurotoxicity; however, most of those (24%) only had residual Grade 1 neurotoxicity. Grade 3 residual adverse events further decreased from 1% at 12 months after therapy to 0.5% after 18 months.

Table 1: Incidence and reversibility of sensory neurotoxicity associated with FOLFOX4 in the MOSAIC trial[2]

Paresthesias (% of pts, N=1108) NCI-CTC v.1	At end of treatment	1 year after chemotherapy	18 months after chemotherapy
Grade 0	7.9%	70.5%	76.3%
Grade 1	48.2%	23.6%	19.8%
Grade 2	31.6%	4.8%	3.4%
Grade 3	12.4%	1.1%	0.5%

To account for the reversibility of sensory neurotoxicity, oxaliplatin-specific scales of neurotoxicity have been proposed and used in clinical trials that are distinct from the NCI-CTC classification (Table 2 on the next page)[13]. However, in order to maintain

comparability between the results of different trials, neurotoxicity should always be graded according to the NCI-CTC scale; whereas, oxaliplatin-specific classifications should be regarded as complementary. The experience of NCCTG in study N9741[15] was that these secondary endpoints, assessed by single-item linear analogue assessments, were the most sensitive indicators of the oxaliplatin-specific neurotoxicity. Hence we will include these items as secondary endpoints.

Table 2: Comparison of classification systems for oxaliplatin-induced sensory neurotoxicity

Grade	NCI-CTCAE v4.0	Oxaliplatin-specific scale[16]
I	Asymptomatic, loss of deep tendon reflexes or paresthesia	sensory symptoms of short duration
II	Moderate symptoms, including instrumental	sensory symptoms persisting between cycles
III	Severe symptoms, limiting self care ADL	sensory symptoms causing functional impairment
IV	Life-threatening consequences; urgent intervention indicated	

1.34 "Coasting" Phenomenon

Several reports and personal experience indicate that in about 10-15% of patients symptoms of peripheral sensory neurotoxicity emerge or worsen some time after oxaliplatin was discontinued. This phenomenon was initially described in conjunction with vinca-alkaloid, cisplatin, and taxane-mediated neurotoxicity and was termed "coasting"[17]. While the actual pathomechanism for this interesting observation is unknown, it can be of great clinical importance for affected patients. Exact data on frequency and pattern of occurrence of the coasting phenomenon are unknown, most likely because this adverse event has not consistently been captured in prospective clinical trials. It is of interest in this context that in the recently published adjuvant MOSAIC trial, 12 patients developed Grade 3 sensory neurotoxicity after the end of treatment and that Grade 3 neurotoxicity was persistent in 6 of these patients after one year[2]. This observation demands prospective evaluation and close attention to any delayed occurrence of oxaliplatin-mediated neurotoxicity in clinical trials and clinical practice. In a single electrophysiologic case study, a patient with oxaliplatin-induced cumulative sensory neurotoxicity was followed for 90 weeks after discontinuation of oxaliplatin. Interestingly, the amplitude of the action potential of sensory nerves continued to decline after discontinuation of oxaliplatin with a nadir at week 39 and a subsequent gradual improvement[18].

1.4 Pathomechanisms of Oxaliplatin-Induced Neurotoxicity

The characteristic acute neurotoxicity caused by oxaliplatin has been referred to as "acute channelopathy" based on its clinical similarity with disorders of voltage-gated ion channels like myotonias or intoxication with sodium channel toxins[19]. Channelopathies are characterized by an increased excitability of nerve and muscle cells and some forms of myotonia can be aggravated by exposure to cold[20]. In this context, it has been hypothesized that oxaliplatin affects sodium channels through chelation of free calcium by oxalate, which can be released from oxaliplatin by bicarbonate ions intracellularly[21].

Supportive evidence for the concept of channelopathy comes from the fact that, in patients with acute neuropathy, no morphologic signs of neurotoxicity has been found in sural nerve biopsies. Furthermore, the acute symptoms do not appear to correlate with impaired nerve conduction, but electrophysiological evidence of increased nerve excitability and neuromyotonia are seen[9,22]. In a recent study, needle electromyography and nerve conduction assessment revealed signs of hyperexcitability in the motor nerves in 13 patients with acute neuropathy after oxaliplatin. The pattern of clinical and electrophysiological findings showed characteristics of neuromyotonia[9]. In addition, several reports have suggested a preventive or therapeutic effect of neuromodulatory agents acting on sodium channels, such as carbamazepine, or on sodium currents, such as calcium/magnesium solutions[23,24].

In contrast to acute neuropathy, cumulative oxaliplatin-induced neurotoxicity shows neurophysiologic findings of chronic morphologic damage. Reduced sensory conduction velocity and sensory potential amplitudes of the sural and median nerve become apparent at a cumulative oxaliplatin dose of 410 mg/m^2 and show worsening with higher doses[22]. Sensory-evoked potentials indicate a moderate involvement of ascending sensory axons after a high cumulative dose (>1000 mg/m^2), consistent with the occasional observation of Lhermitte's sign in this dose range. In addition, morphological and functional changes in the dorsal root ganglia (DRG) and the sciatic nerve have been noted in several *in vivo* models[25-27].

Based on these observations, the key question to understand regarding the pathogenesis of cumulative neurotoxicity is whether acute and cumulative effects of oxaliplatin on the neural system are mediated by different, versus common, mechanisms. In other words, could prolonged activation of voltage-gated sodium channels gradually induce cellular stress and ultimately be detrimental to the nerve cell; or, rather, is the neural damage associated with cumulative neurotoxicity caused by a distinct mechanism? The answer to this question is of great importance since therapeutic or prophylactic approaches affecting acute neuropathy might have the potential to translate into an effective way to prevent cumulative neurotoxicity.

The following table (Table 3) summarizes characteristics of neurotoxicities associated with cisplatin and oxaliplatin.

Table 3: Clinical characteristics of neurotoxicity profiles of cisplatin and oxaliplatin

	Cisplatin	Oxaliplatin	
		Acute neuropathy	Chronic neurotoxicity
Incidence	45%	85-95%	Grade 3-4 in 16%
DLT*	yes	no	yes
Symptoms	paresthesia, dysesthesia, sensory ataxia	paresthesia, dysesthesia	paresthesia, dysesthesia, sensory ataxia
Location	extremities	extremities, perioral	extremities
Trigger	none	cold exposure	none (surgery?)
Motor symptoms	none	rare muscle spasms	none
Onset	delayed	acute	delayed
Recovery	slow, incomplete	rapid, complete	less slow, more complete
Schedule dependence	none	yes	probably none
Other	ototoxicity	laryngo-pharyngeal dysesthesias	none

* DLT = dose-limiting toxicity

1.5 Strategies for the Prophylaxis and Treatment of Oxaliplatin-Induced Neurotoxicity

In general, two different strategies to prevent oxaliplatin-mediated neurotoxicity can be distinguished: a Stop-and-Go strategy to decrease the cumulative dose of oxaliplatin administered, and the use of neuromodulatory agents to prevent or mitigate neurotoxicity. It is obvious that Stop-and-Go strategies are more applicable to the palliative treatment of advanced colorectal cancer in which maintaining the dose-intensity of a drug may not be as important as in the adjuvant setting.

1.51 Stop-and-Go Strategy

Based on the observation of reversibility of the neurotoxic symptoms after discontinuation of oxaliplatin, de Gramont and colleagues developed a Stop-and-Go strategy, the so-called OPTIMOX concept which aims to increase the cumulative oxaliplatin dose that can be given to individual patients until the neurotoxic threshold is reached[28]. This concept employs a dose-intensified treatment regimen with purely infusional 5-FU/LV over 46 hours (without bolus) plus oxaliplatin 130 mg/m^2 every 2 weeks (FOLFOX 7) for 6 cycles until a cumulative oxaliplatin dose of 780 mg/m^2 has been administered. Subsequently, oxaliplatin is paused and treatment is continued with 5-FU/LV (sLV5FU2); oxaliplatin is reintroduced after 9 months. This strategy has been evaluated in a

multicenter, international, phase III trial including 621 patients. Results of this trial, presented at ASCO 2003, demonstrated decreased severe neurotoxicity (Grade 3 13% vs. 19%) and neutropenia compared with FOLFOX4[29]. Both arms showed impressive response rates (RR) around 60% and progression-free survivals (PFS) of approximately 9 months. Data on overall survival (OS) have confirmed this benefit[56]. From a clinical point of view, the Stop-and-Go concept appears to be a promising way to decrease the incidence of severe cumulative neurotoxicity in the palliative setting while maintaining overall efficacy.

1.52 Calcium and Magnesium Infusions

The hypothesis that chelation of calcium by oxalate released from oxaliplatin affects sodium channels at the neural plasma membrane and the neuro-muscular synapsis provides the rational for supplementation of calcium ions[42]. In addition, increasing the concentration of extracellular calcium has been demonstrated to facilitate sodium channel closing and thus potentially decreased the observed oxaliplatin-induced hyperexcitability of peripheral neurons[43]. Furthermore, magnesium supplementation has long been established to prevent hypomagnesemia associated with cisplatin[44]. In a non-randomized, open study, 161 patients with advanced colorectal cancer were treated with 3 different oxaliplatin-based protocols[30]. Ninety-six patients of this series received calcium gluconate 1 g and magnesium sulfate 1 g (CaMg) before and after oxaliplatin, the remaining 65 patients served as the control group. The median cumulative oxaliplatin dose that could be administered was 910 mg/m^2 in the CaMg group compared with 650 mg/m^2 in the control group. Only 4% of patients in the CaMg group, compared to 31% of the control group, had to stop chemotherapy due to neurotoxicity (p=0.000003). At the end of treatment, 27% (CaMg group) and 75% (control group) showed signs of neurotoxicity of any grade. Laryngo-pharyngeal dysesthesias affected 9% of patients in the control patients and were never seen in the patients receiving CaMg. Likewise, Grade 3 neurotoxicity was less frequently observed in the CaMg group (8% vs. 20%, p=0.003) and more patients with CaMg remained on chemotherapy after 9 months (15% vs. 9%). It is important to note that overall anti-tumor efficacy of treatment did not appear to be affected. In contrast, patients were able to stay on therapy for a longer period of time, thus potentially enjoying prolonged benefit from oxaliplatin-based therapy.

The NCCTG conducted a randomized trial studying CaMg infusions of 1 gm each, administered prior to and after oxaliplatin. This trial was closed prematurely due to an errant report from another trial whereby it was claimed that CaMg infusions interfered with the anti-tumor activity or FOLFOX.[52] Nonetheless, this was a positive study that was reported at the 2008 ASCO Spring Meeting. In this trial, CaMg infusions decreased grade 2+ neuropathy, compared to a placebo, from 41% to 22%.

MAYO CLINIC

IV Calcium/Magnesium Prevents Oxaliplatin-Induced Sensory Neurotoxicity

Neurotoxicity grade	CaMg (n=50)	Placebo (n=52)	P (Chi-square)
Grade 2+	22%	41%	0.038

Nikcevich D et al: ***ASCO*** Oral presentation, 2008

CP1319390-33

Nonetheless, it has been very apparent that there still is substantial equipoise with regards to whether or not calcium and magnesium clearly decrease oxaliplatin-induced neuropathy. From discussions with colleagues, it is apparent that this has not been widely embraced in clinical practice at this time. There are several reasons for this.

One of the reasons deals with the CONcePT trial story, including the initial report (subsequently showed to be a errant report) that calcium and magnesium infusions were associated with decreased response rates and that the final results of this trial (in the metastatic disease setting) were unable to demonstrate a substantial decrease in neuropathy in the patients who received calcium and magnesium vs. those receiving placebo. This study was hampered by low patient numbers and early study closure, which might explain this phenomenon.

With regards to our own NCCTG trial, results of our data are hampered by a lower than planned number of patients (approximately 100 when we had planned for 300 patients on trial). In addition, when we stopped the study in view of the initial results of CONcePT, the patients who were receiving calcium/magnesium were asked to stop receiving it. Thus, we are lacking intermediate or long term data with regards to the potential benefit of calcium and magnesium.

To our knowledge, there is no good confirmatory study on the horizon. There is a French study, entitled "NEUROXA", which included 144 patients who were randomized, in a double-blind manner, to receive calcium and magnesium vs. a placebo. Early analysis of this trial[57] noted substantially less neurotoxicity in one group vs. the other (5% vs. 24% of grade III, using NCI common toxicity criteria, $p < 0.001$). The blind for this study has not yet been broken so it is not clear which arm is doing better. Although we suspect that this is the calcium and magnesium arm, this study is not as clean a study as is ideal, given that it included patients in both the adjuvant and palliative care settings. In addition, the NEUROXA study did not utilize the more standardized way to assess neurotoxicity which we did in N04C7 with the enhanced NCI-CTC scale including patient-reported outcomes measures.

Given that there is substantial doubt in the clinical and research oncology community with regards to the utility of calcium/magnesium for decreasing oxaliplatin-induced neuropathy, ideally, more definitive data are desirable. Thus, the current trial is design to clarify/replicate the results from the initial NCCTG trial of CaMg. The NCCTG Institution principle investigators were surveyed about their enthusiasm about a study to replicate these results, and there was marked support for such a study.

In discussing this issue with NCI colleagues, it was decided to also address a couple other questions in this trial. One question dealt with whether the post oxaliplatin infusion was necessary. Being able to delete this second infusion would be more cost effective as it would decrease chemotherapy chair time.

1.6 Pharmacogenomic predictors of oxaliplatin-induced neurotoxicity

It is conceivable that genes involved in the detoxification (e.g. glutathione system: GSTP1, GSTM1) or the cytotoxic mechanism (e.g. nucleotide excision repair: ERCC2, XRCC1) of oxaliplatin could serve as genetic predictors of susceptibility to oxaliplatin's neurotoxic effects. This concept was tested in a pharmacogenomic analysis of 288 patients randomized to FOLFOX4 in Intergroup trial N9741[45]. The study showed that patients with the GSTP1 I105V C/C polymorphism were more likely to discontinue FOLFOX due to sensory neurotoxicity (23.7%) than patients with T/T (9.2%) or C/T (10%) variants (p=0.039). Patients with GSTP1 I105V C/C also had a lower cumulative dose of oxaliplatin until onset of grade 3 sensory neurotoxicity compared to T/T or C/T patients (p=0.05). In addition, patients carrying at least one GSTP1 I105V C-allele (C/C or C/T) were more likely to experience rapid onset of grade 3 neurotoxicity than T/T patients, who were more able to tolerate high doses of oxaliplatin (p=0.027 for grade 2, p=0.030 for grade 3 sensory neurotoxicity). No correlation of the development of oxaliplatin-induced sensory neurotoxicity with polymorphisms in GSTM1, ERCC2, and XRCC1 was identified. The study offered early evidence that genetic variations in the GSTP1 gene may serve as predictors of susceptibility to oxaliplatin-induced sensory neurotoxicity. These findings need to be validated in prospective trials until GSTP1 polymorphism can be used to identify patients at risk for early onset of oxaliplatin-mediated sensory neurotoxicity and who are candidates for neuroprotective strategies.

1.7 Background information regarding neurologic testing to be used in consenting Mayo patients for this protocol

To get a feel for whether there are any neurologic sensory abnormalities that develop during the acute and chronic FOLFOX symptoms, neurologic sensory testing, consisting of Quantitative sensory testing [QST] thresholds (see section 11.23), will be conducted in a subset of patients treated at Mayo Rochester. This will be exploratory in nature, and should help determine which neurologic testing will be fruitful in future studies.

2.0 Goals

2.1 Primary

2.11 To determine whether two schedules of CaMg infusions (given before and after oxaliplatin or just before oxaliplatin) can prevent or ameliorate chronic, cumulative neurotoxicity associated with oxaliplatin.

2.2 Secondary

2.21 To determine whether two schedules of CaMg infusions (given before and after oxaliplatin or just before oxaliplatin) can increase the cumulative oxaliplatin doses that can be delivered without dose-limiting chronic neurotoxicity.

2.22 To determine whether two schedules of CaMg infusions (given before and after oxaliplatin or just before oxaliplatin) can ameliorate acute neuropathy associated with oxaliplatin.

2.23 To determine whether two schedules of CaMg infusions (given before and after oxaliplatin or just before oxaliplatin) cause adverse events.

2.24 To investigate whether two schedules of CaMg infusions (given before and after oxaliplatin or just before oxaliplatin) influence patient quality of life.

2.25 To describe baseline and post-treatment neurological quantitative sensory testing abnormalities in the study participants.

2.3 Translational

2.31 To explore if polymorphisms in the GSTP1, GSTM1, ERCC2 and XRCC1 genes are associated with early onset of oxaliplatin-induced neurotoxicity.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 ≥18 years of age.

3.12 Histologically confirmed adenocarcinoma of the colon or rectum.

3.13 Has undergone curative resection and is considered to have stage II or stage III disease or completely resected stage IV disease with no evidence of residual tumor.

3.14 Scheduled to receive 6 months of oxaliplatin-based adjuvant chemotherapy with 85 mg/m2 oxaliplatin every 2 weeks. This includes, for instance, FOLFOX4 or modified FOLFOX6.

Note: Adjuvant FOLFOX can be conducted with or without bolus 5FU.

Definitions
FOLFOX4: 2-hour infusion of LV (200 mg/m2/d) with oxaliplatin
85 mg/m2 as a 2-hour infusion on day 1; followed by a 5FU bolus (400 mg/m2/d) and 22-hour infusion (600 mg/m2/d) for 2 consecutive days every 2 weeks
MODIFIED FOLFOX6: 2-hour infusion of LV (400 mg/m2) with oxaliplatin 85 mg/m2 as a 2-hour infusion on day 1 followed by a 5FU bolus (400 mg/m2) and 46-hour infusion (2400 mg/m2) every 2 weeks

Note: Patients using bevacizumab or cetuximab in combination with FOLFOX as part of a clinical trial or clinical practice are eligible.

3.15 The following laboratory values obtained ≤28 days prior to registration:
- WBC ≥3000
- ANC ≥1500
- PLT ≥100,000
- HgB ≥10.0
- Total bilirubin ≤1.5 x upper normal limit (UNL)
- Serum creatinine ≤1.5 x UNL
- Serum calcium ≤ 1.2 x UNL
- Serum magnesium ≤ 1.2 x UNL

3.16 Negative pregnancy test (serum or urine) done ≤ 7 days prior to registration, for women of childbearing potential only.

3.17 Ability to complete questionnaire(s) by themselves or with assistance.

3.18 ECOG Performance Status (PS) of 0, 1 or 2. This form is now on the NCCTG website https://ncctg.mayo.edu/ncctg/forms/NonProtocolSpecificForms.

3.19a Provide informed written consent.

3.19b Willingness to return to enrolling institution for follow-up.

3.19c Patient willing to provide blood sample for research purposes (see Sections 6.12 and 14.0).

3.19d. Central venous access line present, or scheduled to have a central line placed prior to starting chemotherapy and protocol treatment.

3.2 Exclusion Criteria

3.21 Any of the following:
- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception since this study involves agents that have known genotoxic, mutagenic and teratogenic effects

3.22 Pre-existing peripheral neuropathy of any grade.

3.23 Prior treatment with neurotoxic chemotherapy such as oxaliplatin, cisplatin, taxanes, or vinca alkaloids.

3.24 On digitalis medication.

Add 1

3.25 2nd or 3rd degree AV heart block or a history of 2nd or 3rd degree AV heart block.
Note: Bundle branch blocks are allowed.

Add 1,2

3.26 Treatment with 1) the anticonvulsants carbamazepine (e.g., Tegretol®), phenytoin (e.g., Dilantin®), valproic acid (e.g. Depakene®), gabapentin (Neurontin®); pregabalin (Lyrica®); 2) the following neurotropic agents: venlafaxine (Effexor), desvenlafaxine (Pristiq®), milnacipran (Savella®) or duloxetine (Cymbalta); 3) Tricyclic antidepressants (such as amitryptilline) or 4) any other agent specifically being given to prevent or treat neuropathy.

3.27 Other medical conditions which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

3.28 A family history of a genetic/familial neuropathy.

3.29 Inability to comply with the protocol.

4.0 Test Schedule

	Active-Monitoring Phase				
	Active Treatment			Observation/ follow-up	
Tests and procedures	≤28 days prior to registration	Prior to each cycle of chemotherapy (Day 1)	5 consecutive days after initiation of chemotherapy (Days 2-6)	1 month after last day of chemotherapy[11]	3, 6, 12 and 18 months after last day of chemotherapy
Physical exam	X	X[2]		X	X[10]
History, weight, PS, neurotoxicity evaluation[6] (CTCAE version 4.0 and Oxaliplatin-specific Scale, Appendices VI and VII)	X	X		X	X[10]
AE Assessment	X	X		X	
Height	X				
Hematology group HgB WBC ANC PLT	X	X[7,12]			
Chemistry group Serum Ca, Mg, Na, K Serum creatinine AST, total bilirubin, alkaline phosphatase	X	X[2,12]			
CEA	X[2]			X[2]	X[2]
EKG	X[2]				
Blood draw for translational research[R]		X[5]			
Patient questionnaire "Side Effect Questionnaire"[4] (appendix IIIA)		X[8]			
Patient questionnaire "Side Effect Questionnaire"[4] (appendix IIIB)			X[3]	X	X[10]
Patient questionnaire "Supplemental Quality of Life Questions"[4] (appendix IV)		X[8]		X	X[10]
Patient Questionnaire: EORTC QLQ- CIPN20[4] (appendix V)		X[8]		X	X[10]
Pregnancy test[1] (serum or urine)	X				
Mayo Clinic Rochester only patients: Sensory testing (optional) [R]	X[9]	X[9]			X[9]

Footnotes on following page:

1. For women of childbearing potential only. Must be done ≤7 days prior to registration.
2. If clinically indicated.
3. Completed for 6 consecutive days total.
4. QOL booklets **must** be used.
5. 10 mL whole blood sample will be collected once at any time after registration but prior to the second cycle of treatment with calcium/magnesium/placebo (see Section 14.0).
6. See standardized questions to evaluate neurotoxicity in Appendix VI.
7. Baseline blood tests do not need to be repeated prior to cycle 1 unless clinically indicated.
8. Day 1 of each booklet during active treatment must be completed prior to receiving chemotherapy.
9. Must do baseline testing and plan to do at least 1 other time point. 2nd time point should be 1-2 days after 1st or 2nd cycle. 3rd time point should be 2-10 weeks after last dose of chemotherapy.
10. 12 and 18 month observation is questionnaire booklets only; booklets can be mailed if patient is not seen in the clinic.

Add 3

11. This cycle will be the next consecutive cycle after the last cycle of chemotherapy.
12. +/- 2 days prior to each cycle.

R Research funded (See section 19.0).

5.0 Stratification Factors:

5.1 Age (years): <65 vs. ≥65.

5.2 Gender: Male vs. female.

5.3 Regimen: FOLFOX 4 vs. modified FOLFOX 6 vs. other (see Section 3.14).

5.4 Stage: II vs. III vs. IV.

The stratification factors listed include demographic, prognostic factors and medication that can potentially impact the primary or secondary outcomes, so they need to be distributed evenly among the three arms. The 36 level combinations involved in these four stratification factors are within the maximum recommended of one half of the group sample size for the study [51].

6.0 Registration/Randomization Procedures

Add 3

Note: ALL sites should follow the registration procedures outlined in this section.

6.1 Registration Procedures

6.11 **NCCTG sites only:**
To register a patient fax (507/284-0885) a completed eligibility checklist to the Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

CTSU sites only:
CTSU sites should refer to the CTSU Appendix IX for additional site registration instructions and patient registration/randomization procedures.

The remaining sections pertain to both NCCTG and CTSU sites:

6.12 Registration Office will automatically register patients separately to the translational component of this study (see Section 14.0).

6.13 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: www.ctsu.org/rss2_page.asp. Guidelines can be found under Quick Fact Sheets.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the CTSU Regulatory Office (fax 215-569-0206). If the necessary documentation is not submitted in advance of attempting

patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

6.14 At the time of registration/randomization, Registration Office personnel will verify the following:
- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information. (USA institutions only)

6.15 At the time of registration/randomization, the following will also be recorded:
- Patient has/has not given permission to keep sample(s) for use in future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to keep sample(s) for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- Patient has/has not given NCCTG permission to give sample(s) to outside researchers.

Update 1

6.16 Treatment on this protocol must commence at the accruing membership under the supervision of a NCCTG or CTSU member physician or allied health professional.

6.17 Treatment cannot begin prior to registration and must begin ≤28 days after registration and must commence with the first cycle of chemotherapy.

6.18 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule (see Section 4.0).

6.19a All required baseline symptoms (see Section 10.3) must be documented and graded.

6.19b Study drug availability checked.

6.19c Blood draw kit availability checked.

6.19d Patient questionnaire booklet availability checked; copies are not acceptable for this submission.

6.2 Randomization Procedures:

6.21 The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors.

6.22 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups[58].

- Calcium Gluconate/Magnesium Sulfate IV before and after chemotherapy
- Placebo IV before and after chemotherapy
- Calcium Gluconate/Magnesium Sulfate IV before and placebo IV after chemotherapy

6.23 To ensure that both the patient and the medical professionals who care for the patient are blinded to the identity of the treatment assignment, the randomization specialist will follow the double-blinding procedures outlined below.

6.3 Procedures for Double-Blinding the Treatment Assignment

Add 3

6.31 After the treatment assignment has been ascertained by the registration/randomization application, the randomization specialist will notify the designated data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be entered in the designated space on the eligibility checklist so the Registration Office personnel have it for each patient at the time of registering the patient. Make sure this contact person will be available at the time of the registration so he or she can take the call from the Randomization Specialist. This contact person may not be involved in assessing adverse events or any other outcome measure and should not be the same person listed on page one of the Eligibility Checklist Form as the person completing the form. The last page of the Eligibility Checklist Form should provide the source of communication, either fax or e-mail, and the appropriate contact information. The registration specialist will then communicate the treatment assignment "active or placebo" to designated contact at the patient's institution.

6.32 The treatment assignment will be calcium gluconate and magnesium sulfate, placebo, or calcium gluconate and magnesium sulfate and placebo. The dose will be prepared and labeled as "1 gm calcium gluconate and 1 gm magnesium sulfate OR placebo so that the contents are not discernible to the individual administering the treatment.

6.33 The pharmacist or designated contact person will maintain records that indicate the identity of the patient and their corresponding treatment assignment.

7.0 Protocol Treatment

7.1 Treatment Schedule: Treatment will continue until chemotherapy (oxaliplatin) is discontinued, noting that it is planned to be given for 6 months. The Neurotoxicity Evaluation (appendices IV, V, VI, and VII) must be completed prior to each chemotherapy treatment (see Section 4.0).

Patients are to be followed as long as they continue on FOLFOX (oxaliplatin) chemotherapy (i.e. as long as they are in Active Treatment) even if study treatment (Calcium and Magnesium/Placebo) is discontinued. Patients should continue completing questionnaires and tests. If the patient refuses, they should be removed from the study.

Agent	Dose Level	Route	Day
Calcium gluconate plus magnesium sulfate	1 g of each agent	IV in 100 ml D5W over 30 minutes	Immediately before and after each oxaliplatin administration
Placebo	100 ml bag of D5W	IV over 30 minutes	Immediately before and after each oxaliplatin administration
Calcium gluconate plus magnesium sulfate	1 g of each agent	IV in 100 ml D5W over 30 minutes	Immediately before each oxaliplatin administration
Placebo	100 ml bag of D5W	IV over 30 minutes	Immediately after each oxaliplatin administration

7.2 Physician reported and patient reported tools will be used to characterize and quantify neurotoxicity and quality of life of patients on trial (see Section 11.0). Patient reported items will be contained in a booklet which must be used (Appendix II-V). A new booklet should be given to the patient for each treatment cycle (2 weeks). Booklets should be ordered using the Patient Questionnaire Order form in the Forms Packet.

7.21 Physician Reported: CTCAE version 4.0 and Oxaliplatin-specific Scale.

7.22 Patient Reported: Side Effect Questionnaire, Supplemental Quality of Life Questions and EORTC – QLQ CIPN20 Patient Questionnaire

7.3 The total dose of oxaliplatin and other agents of FOLFOX given will be recorded on the Evaluation Treatment Form.

7.4 In the event of an emergency, call the Registration Office at (507) 284-4130 to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that Registration Office personnel can return the call the next business day.

7.5 **Mayo Clinic Rochester only:**

Neurologic Testing: Patients at the Mayo Rochester location, when feasible, will undergo neurological testing at baseline (before FOLFOX), 1-2 days after the first or second FOLFOX dose and 2-10 weeks following the last planned FOLFOX dose. The following Quantitative sensory testing (QST) tests will be completed:

- Monofilament testing for sensation – toes and plantar foot
- Thermal disks for heat testing (dorsal foot)
- Vibratory detection threshold (VDT) by computer aided sensory evaluator (CASE) hardware, version Ivb – great toe
- Cooling detection threshold (CDT) testing– by CASE hardware, version Ivb – foot
- Heat pain (HP) testing– foot

8.0 Dosage Modification Based on Adverse Events

8.1 Calcium/magnesium (placebo)

If the patient develops any clinically significant adverse event (e.g. arrhythmias, hypotension) attributed to calcium/magnesium (placebo), it should be recorded on the Adverse Event (AE) Log and calcium/magnesium (placebo) should be stopped. The patient should continue to be followed according to protocol criteria.

Laryngo-pharyngeal dysesthesias are not considered adverse events or medical emergencies and should be handled according to the recommendations in the oxaliplatin package insert by increasing the duration of the oxaliplatin infusion.

8.2 Oxaliplatin dose modification (**guidelines only**)

While oxaliplatin dosage is not dictated with this study, these recommendations are included as guidelines for patient treatment. It is recommended that there is dose modification in the event of specific side-effects.

For patients who experience persistent grade 2 sensory neuropathy that does not resolve within 2 weeks, a dose reduction of oxaliplatin to 65 mg/m2 should be considered. For patients with persistent grade 3 sensory neuropathy, discontinuing oxaliplatin should be considered. The 5-FU/LV regimen need not be altered.

A dose reduction of oxaliplatin to 65 mg/m2 and 5-FU by 20% is recommended for patients after recovery from grade 3/4 gastrointestinal toxicity or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$.

9.0 Ancillary Treatment

9.1 **Ancillary Treatment:** Ancillary treatments are allowed per physician judgment except for other drugs that are given as a neuroprotectant.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event monitoring and reporting. The CTCAE version 4.0 can be accessed from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (see Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2). Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.3 and 18.0).

Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

10.12 Expected vs. Unexpected

- The determination of whether an AE is expected is based the agent-specific information provided in Section 15.0 of this protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

10.13 Assessment of Attribution

Note: For this trial, attribution should be assessed with regard to the calcium/magnesium therapy, not the chemotherapy (FOLFOX).

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

10.2 Expedited Adverse Event Reporting Requirements

10.21 Standard Expedited Reporting for Commercial Agents

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE[1]
Submit a full expedited commercial report via AdEERS within 7 working days[2]	X	X

1. Any increased incidence of a known AE (as reported in the package insert or the literature), including adverse events resulting from a drug overdose.

Add 3

2. In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP web site and will NO LONGER be accepted.

10.22 Other Required Expedited Reporting

EVENT TYPE	**REPORTING PROCEDURE**
Secondary AML/MDS	Reporting for this event required during and after completion of study treatment via AdEERS.
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	If an AdEERS report has been submitted, this form does not need to be submitted. Submit the Non-AER form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the CRA is aware of the event(s) necessitating the form.

Add 1

Add 1

10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading unless otherwise stated:

System Organ Class (SOC)	Adverse Event	Baseline	Each evaluation
Gastrointestinal Disorders	#stools per day	X	
	Diarrhea		X
	Nausea	X	X
	Vomiting	X	X

10.31 Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs experienced by a patient and not specified in Section 10.3:

10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure

10.313 Grade 5 AEs (Deaths)

10.3131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.3132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

The assessment of neuropathy and neurotoxicity has seen much attention in recent literature. At present, there is no generally accepted method for measuring neuropathy beyond using the commonly known CTCAE version 4.0 criteria. Further characterization of neuropathic symptoms will be collected using self-administered tools presented to the patient in a professionally-appearing questionnaire booklet.

The following tools will be used to characterize and quantify neurotoxicity and quality of life of patients on trial.

Add 3 11.1 Physician or Health Professional Reported

11.11 CTCAE version 4.0: A widely used scale to quantify the chronic neurotoxicity associated with various cytotoxic drugs such as taxanes and platinum compounds. Therefore, it appears to be a good tool to assess the primary endpoint of our prevention trial: oxaliplatin-induced, cumulative neurotoxicity, which resembles the well-known neurotoxicity induced by cisplatin (see Table 3, Section 1.4). Standardized questions on neurotoxic symptoms and examples of answers that allow classification of patient-reported symptoms as grade 1, 2, 3, or 4 according to NCI-CTCAE version 4.0 are listed in Appendix VI. These clarifying questions are to be used every time the NCI CTCAE criteria are used to judge CIPN in this trial.

11.12 Oxaliplatin-specific scale (Table 2 Section 1.33, reproduced in Appendix VII[16]): Oxaliplatin also mediates unique, acute neuropathic effects that are transitory in nature. To address this issue, an oxaliplatin-specific scale, which has predominantly been used in European phase III trials[16,47], will also be employed to characterize these acute, transitory phenomena.

Grade	CTCAE version 4.0 * (Nervous System Disorders: Peripheral Sensory Neuropathy)	Oxaliplatin-specific scale[16]
0	None	None
1	Mild paresthesia.	sensory symptoms of short duration
2	Moderate symptoms; limiting instrumental activities of daily living	sensory symptoms persisting between cycles
3	Severe symptoms; limiting self care activities of daily living	sensory symptoms causing functional impairment
4	Life threatening consequences; urgent intervention needed.	
5	Death	

*See standardized questions to classify patient-reported symptoms in Appendices VI and VII.

11.2 Patient Reported Questionnaires (Appendix II-V).

Since the relationship between acute and chronic neurotoxic effects have not fully been clarified yet, a questionnaire will be used that will primarily record acute, reversible neurologic symptoms and also try to distinguish between acute neuropathy and chronic neurotoxicity. Patients will be asked to complete the questionnaire immediately before each administration of chemotherapy and for 5 consecutive days thereafter. Acute neurotoxicity will be determined by questions on a Side Effect Questionnaire that patients are to complete during the 5 consecutive days after administration of each dose of oxaliplatin. In addition, to capture delayed-onset sensory neurotoxicity and assess the reversibility of neurotoxic symptoms, the questionnaire will also be filled out by patients 1 month, 3 months, 6 months, 12 months, and 18 months after chemotherapy. Supplemental quality of life questions will be used to evaluate the general health-related well-being during the trial. Patient questionnaires will be provided in booklet form which should be used.

11.21 Side Effect Questionnaire (Appendix III) and Supplemental Quality of Life Questions (Appendix IV): A series of neurotoxicity-related symptoms and gastro-intestinal items are provided. Patients rate each item on a scale ranging from 0 (meaning no symptom, not at all, or does not interfere) to 10 (meaning worst symptoms, as bad as it can be, or completely interferes). This format has been utilized in a variety of NCCTG Cancer Control protocols to obtain patient reported existence, severity and burden of symptoms.

11.22 EORTC QLQ CIPN20 Sensory neuropathy (Appendix V): A 20-item CIPN-specific questionnaire which includes three scales assessing sensory (9 items), motor (8 items), and

autonomic (3 items) symptoms and functioning with each item formatted the same as items of the EORTC QLQ-C30. It was developed to be used in conjunction with the EORTC QLQ-C30 following the EORTC guidelines for module development[60]. The EORTC QLQ-CIPN20 has been tested in cancer patients receiving a variety of chemotherapies and has been shown to have internal consistency reliability based on Cronbach's alpha coefficients of 0.82, 0.73, and 0.76 for the three scales, respectively[61]. The NCCTG used this instrument in study N06CA, where it performed very well. The EORTC QLQ-CIPN20 (sensory subscale) will be used as the primary assessment tool for sensory neuropathy.

11.23 Neurologic Testing: Patients at the Mayo Rochester location, when feasible, will undergo optional neurological testing at baseline (before FOLFOX), 1-2 days after the first or second FOLFOX dose and 2-10 weeks following the last planned FOLFOX dose. The following Quantitative sensory testing (QST) tests will be completed:

- Monofilament testing for sensation – toes and plantar foot
- Thermal disks for heat testing (dorsal foot)
- Vibratory detection threshold (VDT) by computer aided sensory evaluator (CASE) hardware, version Ivb – great toe
- Cooling detection threshold (CDT) testing– by CASE hardware, version Ivb – foot
- Heat pain (HP) testing– foot

11.3 Evaluation tools used toward each specific goal (Section 2.0)

Specific goal (see section 2.0)	Primary tool	Supplemental tools
2.11	EORTC QLQ-CIPN20 (Appendix V)	NCI-CTCAE version 4.0 assessment by health care provider using standardized questions (Appendix VI) and Oxaliplatin-specific neurotoxicity scale (Appendix VII)
2.21	Total cumulative dose of oxaliplatin	
2.22	Side Effect Questionnaire (Appendices III)	
2.23	NCI-CTCAE version 4.0 assessment by health care provider using standardized questions (Appendix VI)	
2.24	Supplemental Quality of Life Questionnaire (Appendices IV)	
2.25	Quantitative sensory testing	
2.31	EORTC QLQ-CIPN20 (Appendix V) and laboratory indicator of GSTP1 and other gene polymorphisms presence	NCI-CTCAE version 4.0 assessment by health care provider using standardized questions (Appendix VI) Oxaliplatin-specific neurotoxicity scale and laboratory indicator of GSTP1 gene and other polymorphisms presence

12.0 Descriptive Factors

12.1 Oral calcium/magnesium supplementation (other than a multivitamin): Yes vs. no.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

Add 2

13.1 Study therapy will be discontinued for any of the following. If chemotherapy is discontinued, the patient will go to Observation. Note: If study therapy (calcium and magnesium) is discontinued, but patient continues on chemotherapy, please see section 7.1.

- Grade 3 sensory or motor neuropathy (as determined using Common Terminology Criteria for Adverse Events [CTCAE version 4.0]), with the exception of acute laryngopharyngeal dysesthesia. Management of the adverse event(s) once the patient is off the study is at the investigator's discretion.
- Any Grade 4 non-hematologic adverse event.
- Grade 3 non-hematologic adverse event that does not diminish to ≤Grade 2 within 2 weeks of the most recent dose of study therapy.
- Grade 4 hematologic adverse event that does not respond to standard therapeutic interventions and/or fails to diminish to ≤Grade 2 within 2 weeks of the most recent chemotherapy dose.
- Clinical necessity to initiate digoxin therapy.
- Discontinuation of oxaliplatin-based therapy.

13.2 Treatment codes should not be broken except for emergencies (see Section 7.4).

13.3 A patient is deemed *ineligible* if at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient never received treatment, on-study material must be submitted

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

13.4 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

13.5 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material (including On-Study Form, Baseline Adverse Events Form, Neurotoxicity Evaluation Form and the Specimen Submission Form) and the End of Active Treatment/Cancel Notification Form must be submitted.

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimen Submission

14.11 Summary Table of Body Fluid Biospecimens for This Protocol

Type of Biospecimen to submit	Mandatory or Optional	When to submit	Reason for submission (background/methodology section)	Where to find specific details for specimen submission
Blood/blood products (EDTA whole blood)	Mandatory	After registration but prior to the second cycle of treatment with CaMg/placebo	Defined translational (section 14.4)	Section 14.2

14.2 Blood/Blood Products Handling

14.21 Kits are required for this study.

14.211 This study will use the "Generic" kit. The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the Fax Supply form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Do not send the unused kits back to Biospecimen Accessioning Processing (BAP).

14.213 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.** Kits will arrive inside the brown colored shipping boxes.

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **NCCTG will <u>not</u> cover the cost for rush delivery of kits.**

14.22 All samples must be collected **Monday-Thursday ONLY**.

14.23 Label specimen tube(s) with protocol number, NCCTG patient ID number, and time and date blood is drawn.

14.24 Collect and process all blood/blood products according to specific kit instructions and table below.

14.241 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	Before 2nd tx with CaMg/ placebo	Additional processing required at site after blood draw?	Storage/ shipping conditions[1]
Mandatory	**EDTA (purple top)**	**10 mL (1)**	**Whole blood**	**X**	**No**	**Refrigerate/ cold pack (DO NOT FREEZE)**

1. After all samples have been processed according to kit instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions).

14.25 Shipping

14.251 Verify ALL sections of the Research Blood Submission Form (see Forms Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. Enter information from the Research Blood Submission Form into the remote data entry system 7 days after specimen collection (see Forms Packet).

14.252 Specimen must be shipped the same day it is drawn.

14.253 Ship the EDTA tube with a properly prepared cold pack. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen.

14.254 Ship the specimen via Priority Overnight service, Monday – Thursday ONLY, to BAP according to kit instructions. Do not send samples on weekends or just prior to federal holidays.

14.255 The BAP kits will include a smart shipper label (3 x 5 white barcoded label) affixed to the shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by NCCTG if this box is used for shipping specimens to BAP.

14.256 The BAP receiving location at 515 1st Ave SE Rochester, MN 55904 will forward the specimen immediately to the NCCTG Research Base BAP Shared Resource processing laboratory, Stabile 13-10A, Attention: BAP Supervisor.

14.257 BAP will process specimens according to Appendix VIII instructions.

14.3 Other Body Fluids Handling: None

14.4 Study Methodology and Storage Information

14.41 Blood/blood product samples will be collected for the following research.

14.411 Storage of white blood cells for future pharmacogenetic assays (e.g., for genetic polymorphisms of enzymes involved in detoxification of oxaliplatin and DNA

repair enzymes as well as polymorphisms in cell membrane ion channels that may correlate with efficacy and tolerability of oxaliplatin. White blood cells will be stored frozen at −70ºC by BAP, according to patient consent information (see Section 6.14) until specific analyses are identified. As protocols are developed, they will be presented for NCCTG and IRB review and approval. (This collection is part of a general strategy of investigation for the majority of NCCTG studies.)

14.412 As part of ongoing NCCTG research, we will collect plasma for future research studies, according to patient consent information (see Section 6.14), on molecular determinants of efficacy and tolerability. Samples will be stored frozen at −70ºC by BAP until specific analyses are identified. As protocols are developed, they will be presented for NCCTG and IRB review and approval.

14.5 Return of Genetic Testing Research Results

For this study, white blood cells specimens are only being banked and no specific genetic testing is being performed. If, at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 Drug Information

15.1 Calcium Gluconate (commercially available)

15.11 Preparation and storage: The 10% Calcium Gluconate solution provides 1000 mg (1 gram) of Calcium Gluconate in 10 mL. Vials of 10% Calcium Gluconate solution are stored at controlled room temperature of 15°-30°C (59°-86°F). This product is intended for intravenous use only. The product should be mixed with magnesium sulfate in 100 ml D5W and infused over 30 minutes.

15.12 Known potential adverse events: Calcium salts are contraindicated in patients with ventricular fibrillation or hypercalcemia. Arrhythmias may occur if the compound is given together with cardiac glycosides (digoxin or digitoxin). Calcium complexes tetracycline antibiotics, rendering them inactive. The two items should not be mixed for parenteral administration. Calcium Gluconate injection has been reported to be incompatible with intravenous solutions containing various drugs. Specialized references should be consulted for specific information. Intravenous calcium gluconate can produce false-negative values for serum and urinary magnesium. Patients may complain of tingling sensations, a sense of oppression or heat waves, and a calcium or chalky taste following intravenous administration.

15.13 Drug procurement: Use Commercial supply. Follow blinding procedures from Section 6. Patients should not be charged. Sites will be reimbursed for the cost of the calcium gluconate.

15.14 Nursing guidelines for Calcium Gluconate:

15.141 Do not administer as IV push. Calcium should be given over 30 minutes.

15.142 Calcium infusions must be administered through a central line (central venous access).

15.142 Warn patient of possible tingling sensation, heat waves, and/or chalky taste that may follow intravenous administration.

15.143 Do not administer in the presence of known hypercalcemia.

15.144 Calcium gluconate is incompatible with many drugs, use dedicated tubing for administration.

15.145 Instruct patient to report any feelings of palpitations, chest pain, or shortness of breath as these may all indicate the presence of arrhythmias.

15.2 Magnesium Sulfate injection, USP 50% (commercially available)

15.21 Preparation and storage: The 50% Magnesium Sulfate solution provides 1000 mg (1 gram) of magnesium sulfate (heptahydrate) in 2 mL. Vials of 50% Magnesium Sulfate solution are stored at controlled room temperature of 15°-30°C (59°-86°F). The solution provides 8.12 mEq each of magnesium (Mg^{++}) and sulfate ($SO_4^{=}$). This product must be diluted prior to intravenous administration. The rate of intravenous injection should not exceed 150 milligrams per minute. The product should be mixed with calcium gluconate in D5W and infused over 30 minutes.

15.22 Known potential toxicities: Rash has been reported with intravenous therapy. Magnesium sulfate should not be administered parenterally to patients with heart block. Magnesium sulfate should be given very cautiously in the presence of serious impairment of renal function since it is excreted almost entirely by the kidneys. The primary hazard of parenteral administration is production of abnormally high levels of magnesium in the plasma. Such high levels may cause flushing, sweating, hypotension, circulatory collapse, and depression of cardiac and central nervous system function. The most immediate danger to life is respiratory depression. Intravenous calcium gluconate has been used to treat magnesium intoxication.

15.23 Drug procurement: Use commercial supply. Follow blinding procedures per section 6.0. Patients should not be charged. Sites will be reimbursed for the cost of the magnesium sulfate.

15.24 Nursing guidelines for Magnesium Sulfate:

15.241 Monitor for signs/symptoms of elevated magnesium. These may include flushing, sweating, hypotension, respiratory depression, shock, and CNS depression. Be prepared to administer emergency treatment under supervision of MD if this occurs.

15.242 Instruct patient to report any rash or itchiness.

15.243 Assess patient for history of heart block. Report to physician as magnesium sulfate should not be given in this patient population.

15.3 Placebo

15.31 Each institution will use 100 ml bags or bottles of 5% Dextrose Injection USP (D5W) as the placebo agent. The placebo will be given by IV over 30 minutes. Each institution will use D5W from their commercial inventory. The NCCTG Research Base Pharmacy will not provide D5W to the NCCTG sites.

15.32 Label as directed in Section 6.32.

16.0 Statistical Considerations and Methodology

This is a study to assess the efficacy of two schedules of CaMg infusions (before and after oxaliplatin or just before oxaliplatin) as a component of adjuvant chemotherapy for prevention and amelioration of chronic, cumulative sensory neurotoxicity.

A three-arm, randomized, placebo-controlled, double-blind, phase III design will be employed. Randomization will be achieved by the NCCTG Registration Office using standard NCCTG- and NCI-approved procedures. The treatment assignment will be implemented using the established NCCTG dynamic allocation procedure that balances the marginal distributions of the stratification factors between the treatment arms.

16.1 Primary Endpoint (Goal 2.11): The oxaliplatin-induced sensory neuropathy as repeatedly measured by EORTC QLQ-CIPN20 sensory subscale during the chemotherapy. This is a multivariate repeated measurement of CIPN with possibly variable cycles for every patient. The CIPN sensory subscale will be calculated by standard scoring algorithm and converted to 0-100 scale. Rather than choosing the CIPN20 sensory subscale at a fixed cycle of chemotherapy, we will adopt a summary measure, area under the curve (AUC) of CIPN20 sensory subscale as the primary endpoint. This AUC will be prorated by the number of chemotherapy cycles patients received.

16.2 Secondary Endpoints: Numerous secondary endpoints will be compared between two schedules of CaMg infusions (before and after oxaliplatin and before oxaliplatin only) versus placebo arms for this study.

16.21 (Goal 2.11): The AUC of EORTC QLQ CIPN20 motor subscale and automatic subscale.

16.22 (Goal 2.11): Percentage of patients experiencing grade 2+ and grade 3+ chronic cumulative neurotoxicity (NCI- CTCAE version 4.0 and oxaliplatin-specific neurotoxicity scale) at any time during or at the end of adjuvant oxaliplatin-based chemotherapy.

16.23 (Goal 2.11): Time to onset of grade 2+ and grade 3+ chronic cumulative neurotoxicity, the duration of the chronic cumulative neurotoxicity during and after the adjuvant oxaliplatin-based chemotherapy.

16.24 (Goal 2.21): Cumulative oxaliplatin doses that can be delivered without dose-limiting chronic neurotoxicity, the percentage of patient discontinuing oxaliplatin-based chemotherapy because of neurotoxicity.

16.25 (Goal 2.22): Percentage of acute neuropathy associated with oxaliplatin as measured by daily Side Effect Questionnaire during and after oxaliplatin-based chemotherapy (1 months, 3 months, 6 months, 12 months, and 18 months).

16.26 (Goal 2.23): Incidence of CaMg-induced adverse events as measured by CTCAE version 4.0.

16.27 (Goal 2.24): The AUC of patient-reported quality of life as measured by the supplemental QoL questionnaire.

16.28 (Goal 2.31): Incidence of expression of GSTP1 or other gene polymorphism with early onset of oxaliplatin-induced neurotoxicity.

16.3 Analysis Plans: The primary objectives of this double-blind study are to compare each of the two schedules of CaMg infusion regimens versus placebo in the treatment of chronic, cumulative neurotoxicity induced by oxaliplatin-based chemotherapy. These two hypothesis testings will be

carried out via a two-sided alternative hypothesis with a 2.5% type I error rate. This will result in an overall approximate type I error rate of a 5% chance of falsely concluding at least one of the two alternative regimens to be significantly different from placebo using the Bonferroni's method. The study is only powered to conduct comparisons of each regimen versus placebo, not direct comparison between the two regimens. However, the 95% confidence intervals of the chronic, cumulative neurotoxicity rate for each regimen will be computed for the purpose of exploring the equivalence between the regimens.

16.31 Primary Analysis (Goal 2.11): Two-sample *t*-tests or Wilcoxon rank-sum tests will be used to compare the AUC of CIPN sensory subscale between each of the two schedules of Ca/Mg infusions vs placebo arms at the 2.5% significance level. If the CIPN sensory subscales are observed to be unbalanced, we will adjust for the baseline CIPN sensory subscale scores from the AUC or incorporate them as a covariate in generalized linear regression model.

16.32 Secondary Analyses: We will not adjust p-values (or significance level) for multiple comparisons among the numerous hypothesis testings of secondary endpoints due to the exploratory nature of these secondary analyses. The significance results from secondary analyses will be interpreted cautiously in a hypothesis-generating fashion.

16.321 (Goal 2.11): Two-sample *t*-tests or Wilcoxon rank-sum tests will be used as in primary analysis.

16.322 (Goal 2.11): Fisher's exact tests or Chi-square tests.

16.323 (Goal 2.11): Kaplan-Meier curves with log-rank tests.

16.324 (Goal 2.21): Two-sample *t*-tests or Wilcoxon rank-sum tests and Fisher's exact tests or Chi-square tests.

16.325 (Goal 2.22): Fisher's exact tests or Chi-square tests with descriptive statistics.

16.326 (Goal 2.23): Fisher's exact tests or Chi-square tests with descriptive statistics.

16.327 (Goal 2.24): Two-sample *t*-tests or Wilcoxon rank-sum tests will be used as in primary analysis.

16.327 (Goal 2.25): These results will be reported in a descriptive manner as not more than 10-15 patients are expected to undergo neurological testing.

16.328 (Goal 2.31): Spearman's correlation and logistic regression (co-dorminant, additive) models for genetic association.

16.329 The following table summarized the statistical plan:

Specific Goals (see Section 2.0)	Endpoint (Tools – see Section 11.3)	Statistical Analysis
2.11 (primary endpoint)	AUC of CIPN sensory subscale	Two-sample *t*-tests or Wilcoxon rank-sum tests, with the Bonferroni's correction of type I error.
2.11	AUC of CIPN motor subscale and automatic subscale	Two-sample *t*-tests or Wilcoxon rank-sum tests
2.11	Percentage of Grade 2+ or Grade 3+ chronic neurotoxicity	Fisher's exact tests or Chi-square tests
2.11	Time to onset of Grade 2+ or Grade 3+ chronic neurotoxicity	Kaplan-Meier curves with log-rank tests
2.21	Cumulative oxaliplatin-dose delivered without dose-limiting toxicity	Two-sample *t*-tests / Wilcoxon rank-sum tests
2.21	Percentage of patients discontinuing therapy due to chronic neurotoxicity	Fisher's exact tests or Chi-square tests
2.22	Percentage of patients with any acute neurotoxicity (determined by side effect questionnaire for 5 days after each oxaliplatin dose)	Fisher's exact tests or Chi-square tests with descriptive statistics
2.23.	Incidence of CaMg-induced adverse event	Fisher's exact tests or Chi-square tests with descriptive statistics
2.24	The AUC of patient-reported quality of life	Two-sample *t*-tests or Wilcoxon rank-sum tests
2.25	Quantitative Sensory Testing	These results will be reported in a descriptive manner as not more than 10-15 patients are expected to undergo neurological testing.
2.31	Incidence of expression of GSTP1 or other gene polymorphism with early onset of oxaliplatin-induced neurotoxicity	Spearman's correlation and logistic regression (co-dorminant, additive) models for genetic association

16.4 Power and Sample Size: Early use of EORTC QLQ-CIPN20 in another NCCTG trial (N06CA) did not provide enough preliminary data on the AUC of sensory subscale due to its one-time CIPN20 measurement at 4 weeks. Instead of guessing the clinically meaningful difference in AUC and its variation, we will use the percentages of grade 2+ chronic sensory neuropathy during the treatment (one of the secondary analysis of primary endpoint) for power analysis and sample size calculation. Results from the N04C7 trial (53) indicated an expected level of grade 2+ and grade 3+ chronic neurotoxicity after oxaliplatin-based chemotherapy will be roughly 40% and 15%, respectively, for the placebo arm.

Add 1

16.41 Primary analysis: Based on a two-sided Fisher's exact test at a significance level of 2.5%, we will need a sample size of 214 patients (107 patients per arm) to provide 80% power to detect a difference in incidence of grade 2+ neuropathic toxicity from 40% in the placebo arm to 20% in either schedules of the CaMg infusion arms. Alternatively, similar sample sizes can be obtained in the range of 112—78 by following a two-sample *t*-test of AUC with an empirical rule of effect size of 0.4—0.5 based on normal approximation.[50] This is considered a moderately small effect size and, more importantly, is clinically meaningful. Sample size will be inflated by 10% to account for missing data (e.g., patient ineligibility, cancellation, or major violations). The total number of patients accrued for three arms hence will be 354 patients (118 patients per arm).

16.42 Accrual and Study Duration: Based on past experience of patient accrual in NCCTG, in particular of the track record of N04C7, we estimate an accrual rate of approximately 13 patients per month and thus expect to complete accrual of 354 patients in approximately two and a half years.

16.5 Missing Data: The extent of missing data will be explored for non-random influences. Sensitivity analysis will be performed using various simple imputation techniques[50], to ensure results are not unduly influenced by the presence of missing data.

16.6 Monitoring: This study will be monitored by the NCCTG External Data Monitoring Committee, an NCI-approved functioning body. Reports containing efficacy, adverse events, and administrative information will be provided to the DMC every six months as per NCI guidelines.

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

Add 3

16.7 Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy the following:

- If 5 or more patients in the first 20 treated patients (or 25% of all patients after 20 are accrued) experience a grade 4 or higher non-hematologic adverse event and the adverse event rate is higher in the active treatment arm.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related," to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

Add 3

16.8 Unblinding: It is recommended by the protocol investigators that it is reasonable for the study team to be unblinded and allowed to see the data for analysis 3 months following the entry of the last patient onto the study.

Add 3

16.9 Gender and minority accrual considerations: This study will be available to all eligible patients regardless of race or ethnic origin. There is no information currently available regarding differential effects of Ca/Mg for prevention of CIPN in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist.

Based on prior NCCTG neuropathy studies, we expect, for the main accrual, about 10% of patients will be classified as minorities by race and about 50% of patients will be women. Subset analysis along ethnic subpopulations will hence have a lack of power to draw substantive conclusions but will provide some data for future meta-analytic procedures and hypotheses generation.

Ethnic Category	**Sex/Gender (%)**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	3	4		7
Not Hispanic or Latino	174	173		347
Ethnic Category: Total of all subjects	177	177		**354**
Racial Category				
American Indian or Alaskan Native	1	1		2
Asian	3	3		6
Black or African American	10	10		20
Native Hawaiian or other Pacific Islander	2	2		4
White	161	161		322
Racial Category: Total of all subjects*	177	177		**354**

These totals must agree. Enter actual estimates (not percentages**)*

Ethnic Categories:
Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories:
American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None

18.0 Records and Data Collection Procedures

Add 3

18.1 Submission Timetable

Forms	Active-Monitoring Phase (Compliance with Test Schedule)		Observation		At each occurrence	
	Initial Material	Follow-up Material				
	≤2 weeks after registration	At each evaluation during chemotherapy	At 1 month after last day of chemotherapy[9]	At 3, 6, 12, and 18 months after last day of chemotherapy	Grade 4 or 5 Non-AER Reportable Events/ Hospitalization	ADR/AER
On-Study Form	X					
Baseline Adverse Events Form	X					
Research Blood Submission Form		X[7]				
Evaluation/Treatment Form		X[4]				
Neurotoxicity Evaluation Form	X	X	X	X[8]		
End of Active Treatment/Cancel Notification Form	X[5]	X[6]				
Evaluation/Observation Form			X[1]	X[1,8]		
Adverse Event Form		X	X			
Patient Questionnaire Booklet[2]		X	X	X[8]		
Patient Questionnaire Booklet Compliance Form		X[3]	X[3]	X[3]		
ADR/AER (see Section 10.0)						X
Grade 4 or 5 Non-AER Reportable Events/ Hospitalization Form					X	

1. Complete at each evaluation during Observation (see Section 4.0).
2. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission. Booklets should be ordered using the order form found in the Forms Packet.
3. This form must be completed **only** if the Patient Questionnaire Booklet contains absolutely **NO** patient provided assessment information.
4. Complete at each evaluation during Active Treatment (see Section 4.0).
5. Submit this form only if withdrawal/refusal prior to beginning protocol therapy occurs.
6. Completed at end of chemotherapy.
7. Submitted once anytime prior to the second cycle of treatment (see Section 14.0).
8. 12 and 18 month follow up is questionnaire booklets only. Can be mailed if patient is not seen in clinic.

Add 3

9. This cycle will be the next consecutive cycle after the last cycle of chemotherapy.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: research blood kits and processing. For Mayo Clinic Rochester only patients: quantitative sensory testing.

19.3 Other budget concerns: Sites will be reimbursed for the cost of the study drugs (calcium gluconate and magnesium sulfate). The reimbursement form can be found in the forms packet.

20.0 References

1. Grothey A, Schmoll HJ: New chemotherapy approaches in colorectal cancer. Curr Opin Oncol 13:275-86, 2001 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11429486

2. Andre T, Boni C, Mounedji-Boudiaf L, et al: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350:2343-51, 2004 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15175436

3. Sargent D, Wieand HS, Benedetti J, et al: Disease-free survival (DFS) vs. overall survival (OS) as a primary endpoint for adjuvant colon cancer studies: Individual patient data from 12,915 patients on 15 randomized trials. Proc Am Soc Clin Oncol 23:246, abstr. 3502, 2004 --

4. Cassidy J, Misset JL: Oxaliplatin-related side effects: characteristics and management. Semin Oncol 29:11-20, 2002 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12422304

5. Raymond E, Chaney SG, Taamma A, et al: Oxaliplatin: a review of preclinical and clinical studies. Ann Oncol 9:1053-71, 1998 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9834817

6. Peltier AC, Russell JW: Recent advances in drug-induced neuropathies. Curr Opin Neurol 15:633-8, 2002 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12352008

7. Screnci D, McKeage MJ: Platinum neurotoxicity: clinical profiles, experimental models and neuroprotective approaches. J Inorg Biochem 77:105-10, 1999 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10626361

8. McKeage MJ: Comparative adverse effect profiles of platinum drugs. Drug Saf 13:228-44, 1995 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8573296

9. Wilson RH, Lehky T, Thomas RR, et al: Acute oxaliplatin-induced peripheral nerve hyperexcitability. J Clin Oncol 20:1767-74, 2002 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11919233

10. Extra JM, Marty M, Brienza S, et al: Pharmacokinetics and safety profile of oxaliplatin. Semin Oncol 25:13-22, 1998 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9609104

11. Gornet JM, Savier E, Lokiec F, et al: Exacerbation of oxaliplatin neurosensory toxicity following surgery. Ann Oncol 13:1315-8, 2002 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12181257

12. Grothey A, Deschler B, Kroening H, et al: Phase III study of bolus 5-fluorouracil (5-FU)/ folinic acid (FA) (Mayo) vs. weekly high-dose 24h 5-FU infusion/ FA + oxaliplatin (OXA) in advanced colorectal cancer (ACRC). Proc Am Soc Clin Oncol 21:129a, abstr. 512, 2002 --

13. de Gramont A, Figer A, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938-47, 2000 -- http://www.ncbi.nlm.nih.gov/htbin-post/Entrez/query?db=m&form=6&dopt=r&uid=0010944126
http://www.jco.org/cgi/content/full/18/16/2938
http://www.jco.org/cgi/content/abstract/18/16/2938

14. Brienza S, Vignoud J, Itzakhi M, et al: Oxaliplatin (L-OHP): global safety in 682 patients (pts). Proc Am Soc Clin Oncol 14, 1995 --

15. Goldberg RM, Sargent D, Morton RF, et al: N9741: FOLFOX (oxaliplatin(Oxal)/ 5-fluorouracil (5-FU)/ leucovorin (LV) or reduced dose R-IFL (CPT-11 + 5-FU/LV) in advanced colorectal cancer (CRC): Final efficacy data from an intergroup study. Proc Am Soc Clin Oncol 23:275, abstr. 3621, 2004 --

16. Levi FA, Zidani R, Vannetzel JM, et al: Chronomodulated versus fixed-infusion-rate delivery of ambulatory chemotherapy with oxaliplatin, fluorouracil, and folinic acid (leucovorin) in patients with colorectal cancer metastases: a randomized multi-institutional trial. J Natl Cancer Inst 86:1608-17, 1994 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7932825

17. Kuncl RW, George EB: Toxic neuropathies and myopathies. Curr Opin Neurol 6:695-704, 1993 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8293140

18. Lehky TJ, Leonard GD, Wilson RH, et al: Oxaliplatin-induced neurotoxicity: acute hyperexcitability and chronic neuropathy. Muscle Nerve 29:387-92, 2004 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14981738

19. Adelsberger H, Quasthoff S, Grosskreutz J, et al: The chemotherapeutic oxaliplatin alters voltage-gated Na(+) channel kinetics on rat sensory neurons. Eur J Pharmacol 406:25-32, 2000 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11011028

20. Moxley IR: Channelopathies. Curr Treat Options Neurol 2:31-47, 2000 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11096735

21. Grolleau F, Gamelin L, Boisdron-Celle M, et al: A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels. J Neurophysiol 85:2293-7, 2001 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11353042

22. Garufi C, Pietrangeli A, Brienza S, et al: Electrophysiological evaluation of oxaliplatin neurotoxicity. Proc Am Soc Clin Oncol 18:244a, abstr. 938, 1999 --

23. Gamelin E, Gamelin L, Bossi L, et al: Clinical aspects and molecular basis of oxaliplatin neurotoxicity: current management and development of preventive measures. Semin Oncol 29:21-33, 2002 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12422305

24. Eckel F, Schmelz R, Adelsberger H, et al: Prevention of oxaliplatin-induced neuropathy by carbamazepine. A pilot study. Dtsch Med Wochenschr 127:78-82, 2002 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11797144

25. Cavaletti G, Tredici G, Petruccioli MG, et al: Effects of different schedules of oxaliplatin treatment on the peripheral nervous system of the rat. Eur J Cancer 37:2457-63, 2001 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11720843

26. Holmes J, Stanko J, Varchenko M, et al: Comparative neurotoxicity of oxaliplatin, cisplatin, and ormaplatin in a Wistar rat model. Toxicol Sci 46:342-51, 1998 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10048138

27. Luo FR, Wyrick SD, Chaney SG: Comparative neurotoxicity of oxaliplatin, ormaplatin, and their biotransformation products utilizing a rat dorsal root ganglia in vitro explant culture model. Cancer Chemother Pharmacol 44:29-38, 1999 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10367746

28. Maindrault-Goebel F, Louvet C, Carola E, et al: Oxaliplatin reintroduction in patients pretreated with leucovorin (LV), 5-FU and oxaliplatin for metastatic colorectal cancer. A Gercor study. Proc Am Soc Clin Oncol 19:255a, abstr. 990, 2000 --

29. Andre T, Figer A, Cervantes A, et al: FOLFOX7 compared to FOLFOX4. Preliminary results of the randomized optimox study. Proc Am Soc Clin Oncol 22:253, abstr. 1016, 2003 -- http://www.asco.org/ac/1,1003,_12-002489-00_18-002003-00_19-00102348-00_28-00RESULTPAGE,00.asp

30. Gamelin L, Boisdron-Celle M, Delva R, et al: Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. Clin Cancer Res 10:4055-61, 2004 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15217938

31. Cascinu S, Graziano F, Ferrau F, et al: Raltitrexed plus oxaliplatin (TOMOX) as first-line chemotherapy for metastatic colorectal cancer. A phase II study of the Italian Group for the Study of Gastrointestinal Tract Carcinomas (GISCAD). Ann Oncol 13:716-20, 2002 - http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12075739

32. Mariani G, Garonne O, Granetto C, et al: Oxaliplatin induced neuropathy: could gabapentin be the answer? Proc Am Soc Clin Oncol 19:609a, abstr. 2397, 2000 --

33. Penz M, Kornek GV, Raderer M, et al: Subcutaneous administration of amifostine: a promising therapeutic option in patients with oxaliplatin-related peripheral sensitive neuropathy. Ann Oncol 12:421-2, 2001 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11332158

34. Gedlicka C, Scheithauer W, Schull B, et al: Effective treatment of oxaliplatin-induced cumulative polyneuropathy with alpha-lipoic acid. J Clin Oncol 20:3359-61, 2002 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12149316

35. Durand JP, Brezault C, Goldwasser F: Protection against oxaliplatin acute neurosensory toxicity by venlafaxine. Anticancer Drugs 14:423-5, 2003 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12853883

36. Willow M, Kuenzel EA, Catterall WA: Inhibition of voltage-sensitive sodium channels in neuroblastoma cells and synaptosomes by the anticonvulsant drugs diphenylhydantoin and carbamazepine. Mol Pharmacol 25:228-34, 1984 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6321945

37. Sechi GP, Traccis S, Durelli L, et al: Carbamazepine versus diphenylhydantoin in the treatment of myotonia. Eur Neurol 22:113-8, 1983 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6341070

38. Cascinu S, Catalano V, Cordella L, et al: Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. J Clin Oncol 20:3478-83, 2002 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12177109

39. Arrick BA, Nathan CF: Glutathione metabolism as a determinant of therapeutic efficacy: a review. Cancer Res 44:4224-32, 1984 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6380705

40. Bates SE, Regis JI, Robey RW, et al: Chemoresistance in the clinic: overview 1994. Bull Cancer 81 Suppl 2:55s-61s, 1994 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7727860

41. Goldberg R, Morton R, Sargent D, et al: N9741: oxaliplatin (oxal) or CPT-11 + 5-fluorouracil (5FU)/leucovorin (LV) or oxal + CPT-11 in advanced colorectal cancer (CRC). Initial toxicity and response data from a GI Intergroup study. Proc Am Soc Clin Oncol 21:128a, abstr. 511, 2002 -- http://www.asco.org/prof/me/html/02abstracts/0020/511.htm

42. Gamelin L, Grolleau F, Boisdron-Celle M, et al: Acute neurotoxicity of oxaliplatin: effects on neuronal voltage-gated soidum channels. Proc Am Assoc Cancer Res 42:935, abstr. 5020, 2001 --

43. Armstrong CM, Cota G: Calcium block of Na+ channels and its effect on closing rate. Proc Natl Acad Sci U S A 96:4154-7, 1999 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10097179

44. Lajer H, Daugaard G: Cisplatin and hypomagnesemia. Cancer Treat Rev 25:47-58, 1999

45. Grothey A, McLeod HL, Green EM, et al: Glutathione S-transferase P1 I105V (GSTP1 I105V) polymorphism is associated with early onset of oxaliplatin-induced neurotoxicity. J Clin Oncol (Meeting Abstracts) 23:3509-, 2005 -- http://meeting.jco.org/cgi/content/abstract/23/16_suppl/3509

46. de Gramont A, Banzi M, Navarro M, et al: Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized mosaic trial. Proc Am Soc Clin Oncol 22:253, abstr. 1015, 2003 --

47. Giacchetti S, Perpoint B, Zidani R, et al: Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 18:136-47, 2000 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10623704

48. Cohen J: Statistical power analysis for the behavioral sciences. Hillsdale, NJ, Lawrence Erlbaum Associates, 1988

49. Fairclough DL, Peterson HF, Chang V: Why are missing quality of life data a problem in clinical trials of cancer therapy? Stat Med 17:667-77, 1998 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9549815

50. Sloan JA, Dueck A: Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. J Biopharm Stat 14:73-96, 2004 -- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15027501

51. Therneau, T. How many stratification factors is too many to use in a randomization plan? Controlled Clinical trials 14: 98-108, 1993.

52. Hochster HS, Grothey A, Childs BH. Use of calcium and magnesium salts to reduce oxaliplatin-related neurotoxicity. Journal of Clinical Oncology 2007;25(25):4028-4029.

53. Nikcevich DA, Grothey A, Sloan JA, Kugler JW, Silberstein PT, Dentchev T, Wender DB, Novotny PJ, Windschitl HE, Loprinzi CL. Effect of intravenous calcium and magnesium (IV CaMg) on oxaliplatin-induced sensory neurotoxicity (sNT) in adjuvant colon cancer: results of the phase III placebo-controlled, double-blind NCCTG trial N04C7. J Clin Oncol 2008; May 20 suppl(abstract 4009).

54. de Gramont A, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Lorenzato C, André T. Oxaliplatin/5FU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial,

including survival, with a median follow-up of six years. *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4007.

55. Wolmark N, Wieand S, Kuebler P J, Colangelo L, O'Connell M. J.et al A phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Survival results of NSABP Protocol C-07. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr LBA4005)

56. Maindrault-Goebel F, Lledo G, Chibaudel B, Mineur L, Andre T, Bennamoun M, Mabro M, Artru P, Louvet C, de Gramont A. Final results of OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC): A GERCOR study. *Journal of Clinical Oncology*, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 4013

57. Gamelin L, Boisdron-Celle M, Morel A, Poirier AL, Berger V, Gamelin E, Tournigand C, de Gramont A. Oxaliplatin-related neurotoxicity: interest of calcium-magnesium infusion and no impact on its efficacy. J Clin Oncol. 2008 Mar 1;26(7):1188-9

58. Pocock SJ, Simon R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics 31(1):103-115, 1975 Mar.:

NCI Informed Consent Template for Cancer Treatment Trials (English Language)

***NOTES FOR LOCAL INVESTIGATORS:** **[NOTE: Retain this section and asterisk item below for NCCTG model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs/* or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

**These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

N08CB, A Phase III Randomized, Placebo-Controlled, Double-Blind Study of Intravenous Calcium/Magnesium in Two Different Versions to Prevent Oxaliplatin-Induced Sensory Neurotoxicity

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have been diagnosed with colon or rectal cancer, which will be treated with a type of chemotherapy, called oxaliplatin (which is standard treatment, not research).

Why is this research study being done?

It is well known that this type of chemotherapy can cause side effects on nerves that result in symptoms such as sensitivity to cold or touch, pain, tingling or numbness of fingers and toes which can interfere with activities of daily living. In some patients, the chemotherapy has to be stopped because of these symptoms.

The purpose of this study is to compare the effects, good and/or bad, of calcium gluconate and magnesium sulfate with a placebo (an inactive agent) on possible nerve damage that could be caused by oxaliplatin chemotherapy treatment. In this study, you will get the calcium gluconate and magnesium sulfate together right before and after each dose of chemotherapy or a placebo right before and after each dose of chemotherapy, or the calcium gluconate and magnesium sulfate before each dose of chemotherapy and a placebo after each dose of chemotherapy. This is to see if 1 dose will be as effective as 2 doses.

How many people will take part in the research study?

About 354 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will be starting chemotherapy treatment with oxaliplatin chemotherapy for your cancer. To start this study, you will need to have a port or catheter so that study medications can be administered into a large vein in your chest.

You will need to have the following exams, tests or procedures to find out if you can be in 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. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical exam, including height and weight and rating of how well you perform activities of daily living.
- Routine blood tests (blood counts, liver tests, a kidney test, and other tests your doctor thinks should be done). About 2 teaspoons of blood will be drawn from a vein in your arm for the blood tests.
- An electrocardiogram of your heart (also known as ECG or EKG) may be obtained if your doctor thinks it should be done.
- Pregnancy test if you are a woman of childbearing potential.

You will need to get the following test to participate in this study:

- Complete pre-chemotherapy questionnaires (about 10 minutes). These questionnaires will contain questions about your feeling of well-being, and about any pain, numbness or tingling you may be feeling.
- **Mayo Clinic Rochester only patients:** Optional Neurologic tests: You will have tests to see how your nerves respond to changes in temperature (hot and cold), touch, and vibration. This testing takes approximately 2 hours. If you agree to have this testing done, you will be scheduled for these tests prior to receiving chemotherapy.

Add 3

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. The following are part of regular cancer care and are not being done more often because of this study.

- Medical history and physical exam, including height and weight and rating of how well you perform activities of daily living, prior to each dose of chemotherapy.

- Routine blood tests. About 2 teaspoons of blood will be drawn form a vein in your arm for the blood tests. These will be obtained one time prior to each planned chemotherapy cycle.

The following is not part of regular cancer care but is being done because of this study.

- Research blood tests. This can be done at the same time as your routine blood tests. An additional 2 teaspoons of blood will be drawn at the same time, for research purposes. This research blood test will only be obtained one time and is required. You will have the option of allowing a portion of this blood sample to be used in future research. Your options are described later in this form. This research test will look at genetic material to see if certain genes are involved in oxaliplatin's effect on nerves. Because the genetic tests in this study are not used for regular medical care, you will not be told the results of the test. The test results will not be put in your medical record either.
- **Mayo Clinic Rochester only patients:** Optional Neurologic tests: You will have tests to see how your nerves respond to changes in temperature (hot and cold), touch, and vibration. This testing takes approximately 2 hours. If you agree to have this testing done, you will be scheduled for these tests 1-2 days after your first or second cycle of chemotherapy, and 2 - 10 weeks after your last cycle of chemotherapy.

Add 3

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance (as in a roll of the dice). A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have a one in three chance of being placed in any group.

If you are in group 1 You will get the study drugs, calcium gluconate and magnesium sulfate, through a vein (IV) over a time period of 30 minutes. You will get the study drugs immediately before you get chemotherapy, and immediately after you get chemotherapy. When your chemotherapy ends, your treatment with the calcium gluconate and magnesium sulfate will end too.

If you are in group 2 You will get the placebo (inactive agent), through a vein (IV) over a time period of 30 minutes. You will get the placebo immediately before and immediately after you get chemotherapy. When your chemotherapy ends, your treatment with the placebo will end too.

If you are in group 3 You will get the study drugs, calcium gluconate and magnesium sulfate, through a vein (IV) over a time period of 30 minutes. You will get the study drugs immediately before you get chemotherapy. You will get the placebo (inactive

agent) immediately after you get chemotherapy. When your chemotherapy ends, your treatment with calcium gluconate and magnesium sulfate/placebo will end too.

We want to find out if the calcium gluconate and magnesium sulfate will help to lessen nerve damage from chemotherapy and make the quality of your life better. Questionnaires will be used to assess changes in your daily life and your feeling of well-being, and about any pain, numbness or tingling you may be feeling. You will be given a booklet that has the questionnaires in them. You will be given a new booklet at each cycle of treatment. It should take you less than 5 minutes each day to complete. You will be asked to continue filling out these booklet questionnaires for as long as you continue receiving chemotherapy. These questionnaires will be for the days of chemotherapy and for 5 days after each dose of chemotherapy. At the end of your chemotherapy treatment, we will ask you to continue filling out a booklet questionnaire at 1 month, 3 months, 6 months, 12 months, and 18 months from your last chemotherapy dose. The booklet questionnaires will be mailed to you, if do not have an appointment with your doctor. If you would like to see these questionnaires before signing the consent form, please ask your study nurse or coordinator for a copy to review.

Add 3 **Optional testing:**

Mayo Clinic Rochester only patients: Optional Neurologic tests: You will have tests to see how your nerves respond to changes in temperature (hot and cold), touch, and vibration. This testing takes approximately 2 hours. If you agree to have this testing done, you will be scheduled for these tests prior to receiving chemotherapy, 1-2 days after your first or second cycle of chemotherapy, and 2 – 10 weeks after your last cycle of chemotherapy.

I want to participate in the optional Neurologic tests.

☐ Yes ☐ No Please initial here:_____ Date:_____

When I am finished taking the calcium gluconate and magnesium sulfate/placebo and chemotherapy

After you are done with chemotherapy, you will have a physical exam, including weight, a rating of how well you perform activities of daily living, and routine blood tests. Further visits will be coordinated by your oncologist as part of the routine follow-up for your cancer.

How long will I be in the research study?

You will be asked to take the study drugs (calcium gluconate and magnesium sulfate, placebo, or calcium and magnesium together and placebo) during your chemotherapy treatment.

After you are finished taking the calcium gluconate and magnesium sulfate or placebo and chemotherapy treatment, the study doctor will ask you to visit the office for follow-up exams at 1 month, 3 months, and 6 months. You will be asked to fill out a monthly questionnaire booklets during these visits. You will also be asked to complete booklets 12 months and 18 months after your last chemotherapy dose. The booklet questionnaires will be mailed to you, if do not have an appointment with your doctor.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the calcium and magnesium can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

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 the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research 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 or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the calcium and magnesium. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the **calcium gluconate** include those which are:
Likely

- Tingling sensations
- A sense of heaviness or heat waves
- A chalky taste right after getting the drug

Less Likely

- Irritation at the IV site
- Fainting
- Low blood pressure
- Abnormal heartbeat
- Slowed heart rate

Rare but serious

- Cardiac arrest (heart stopping)

You should not get this drug if you have an irregular heartbeat or high levels of calcium in your blood. Your study doctor will check these levels before you start oxaliplatin chemotherapy treatment.

Risks and side effects related to the **magnesium sulfate** include those which are:
Likely

- Rash, itchiness
- Flushing or redness
- Sweating

Less Likely

- Trouble breathing or shortness of breath
- Low blood pressure
- Rapid beating of your heart
- Chest pain
- Diarrhea
- Widening or opening (dilation) of blood vessels
- Lowered activity of the nervous system possibly causing sluggishness/sleepiness

Add 1

As with any medication, allergic reactions are a possibility.

The risks of drawing blood include pain, bruising or rarely infection at the needle site.

Reproductive risks: You should not become pregnant or father a baby while on this study because the chemotherapy you are getting to treat you cancer can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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

Add 1 **Mayo Clinic Rochester only patients: (note: other sites can delete this section)**
Risks and side effects related to the neurologic testing:
You should have very little, if any, discomfort during the neurologic testing. If you are uncomfortable, tell the person doing the test. During the neurologic testing you may experience a pin-prick sensation and/or hot and cold sensations. The heat test may cause a brief (1-2 second) burning sensation. At any time you may tell the person doing the test to stop. It is recommended that you not take anything for pain or sleep 12 hours prior to your testing.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope that calcium gluconate and magnesium sulfate will help protect you against the side effects to your nerves from the chemotherapy, there is no proof of this yet. We do know that the information from this study will help doctors learn more about calcium gluconate and magnesium sulfate as a prevention from chemotherapy side effects to the nerves. This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your nerve damage.
Your other choices may include:

- Getting treatment or care for your nerve damage without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

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:

- North Central Cancer Treatment Group (NCCTG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking

part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study is supplying the calcium gluconate and magnesium sulfate at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the study drugs.

Add 1

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 research 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 if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave 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. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

Who can answer my questions about the research 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).* *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study**.**

About Using Biological Samples for Research

This study also has laboratory tests that will be performed to study small samples of blood.

A blood sample will be done by drawing some blood from a vein. The blood will be taken before the first of second cycle of chemotherapy treatment starts.

The blood will be sent to laboratories associated with NCCTG, where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

We would like to keep some of the blood that is/are left over for future research. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your extra blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood. Then any blood that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future.

Benefits

The benefits of research using blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My blood sample(s) may be kept for use in research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. My blood sample(s) may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____ Institutional Review Board _____.

NCCTG has the right to end storage of the sample(s) without telling you.

The sample(s) will be the property of NCCTG. Outside researchers may one day ask for a part of your sample(s) for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, who will contact you.

Please read the following statements and mark your choice:

I permit NCCTG to give my sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

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

You may also visit the NCI Web site 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/**
- **For NCI's general information about cancer in Spanish, go to http://www.cancer.gov/espanol**

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

Signature

I have been given a copy of all _____ *[insert total of number of pages]* **pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

Note: Per CTEP 12-03: The first sentence of the following paragraph ("This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study.") needs to be deleted when a Phase II study is involved and there are ≤100 patients

Note: If the study is going through the CIRB, the signature element needs to appear after the regular consent form language and the optional study language (see N0147 as an example).

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If

the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

PATIENT INFORMATION SHEET

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

These forms sometimes ask repeatedly for similar information. This is done intentionally in order to get a clear understanding of your condition. Please answer all of the questions, even if they sound similar to a question you have already answered.

1. The booklet contains questions to be answered before and after you receive chemotherapy.
    a. Day 1 is the day you receive chemotherapy (FOLFOX).
        On day 1 before chemotherapy you will complete the Supplemental Quality of Life Questions, the EORTC QLQ-CIPN20 Questionnaire and the Side Effect Questionnaire.
    b. Days 2 through 6 are the five days immediately following chemotherapy.
        On these days you will complete the Side Effect Questionnaire each day.

2. Directions on how to complete each set of questions are written on the top of each set.

3. You will be given the nurse's name and telephone number. You can call with any concerns or questions.

4. Please complete the booklet daily.

5. It is very important that you return the booklet to us, whether you finish the study or not.

6. Bring booklet with you to your next clinical visit.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

These forms sometimes ask repeatedly for similar information. This is done intentionally in order to get a clear understanding of your condition. Please answer all of the questions, even if they sound similar to a question you have already answered.

1. This booklet is to be completed when you are finished with all your chemotherapy treatments.

2. This booklet contains the Supplemental Quality of Life Questions, and the EORTC QLQ-CIPN20 Questionnaire, and the Side Effect Questionnaire.

3. Directions on how to complete each set of questions are written on the top of each set.

4. You will be given the nurse's name and telephone number. You can call anytime with any concerns or questions.

5. It is very important that you return the booklet to us, whether you finish the study or not.

6. Bring booklet with you to your next clinical visit, or return the completed booklet in the provided envelope.

Thank you for taking the time to help us.

Side Effect Questionnaire
Baseline, Day 1 prior to chemotherapy, each cycle

1. Did you experience sensitivity to touching cold items within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

2. Did you experience discomfort swallowing cold liquids within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

3. Did you notice any throat discomfort within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

4. Did you suffer from muscle cramps within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

5. Did you have any difficulties buttoning your shirt or tying shoe-laces within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

Side Effect Questionnaire Active Treatment (Days 2-6) and Follow-up

1. Did you experience sensitivity to touching cold items within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

2. Did you experience discomfort swallowing cold liquids within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

3. Did you notice any throat discomfort within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

4. Did you suffer from muscle cramps within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

5. Did you have any difficulties buttoning your shirt or tying shoe-laces within the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

6. Did you experience any other side effects from the chemotherapy treatment that we did not mention?

No ___ Yes___
If Yes, please list_____

Supplemental Quality of Life Questions
Baseline, Active Treatment (Day 1 prior to chemotherapy, each cycle)
and Follow-up

Please circle the one number for each item below that best describes you.

1. How much of a problem has diarrhea been in the past 2 weeks?

0	1	2	3	4	5	6	7	8	9	10
No diarrhea										Worst diarrhea imaginable

2. How much of a problem has constipation been in the past 2 weeks?

0	1	2	3	4	5	6	7	8	9	10
No constipation										Worst constipation imaginable

3. How much of a problem has abdominal (stomach) cramping been in the past 2 weeks?

0	1	2	3	4	5	6	7	8	9	10
No cramping										Worst cramping imaginable

4. How much have bowel problems interfered with your normal activities during the past 2 weeks?

0	1	2	3	4	5	6	7	8	9	10
Does not completely interfere										Interferes

5. How much of a problem has swallowing been in the past 2 weeks?

0	1	2	3	4	5	6	7	8	9	10
No difficulty										Worst difficulty in swallowing imaginable

6. How much of a problem has numbness in your fingers and toes been in the past 2 weeks?

0	1	2	3	4	5	6	7	8	9	10
No Numbness In fingers and Toes										Worst Numbness In fingers and Toes Imaginable

7. How much of a problem has tingling in your fingers and toes been in the past 2 weeks?

0	1	2	3	4	5	6	7	8	9	10
No Tingling In fingers and Toes										Worst tingling In fingers and Toes Imaginable

EORTC QLQ – CIPN20

EGLISH

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
Did you have tingling fingers or hands?	1	2	3	4
Did you have tingling toes or feet?	1	2	3	4
Did you have numbness in your fingers or hands?	1	2	3	4
Did you have numbness in your toes or feet?	1	2	3	4
Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
Did you have shooting or burning pain in your toes or feet?	1	2	3	4
Did you have cramps in your hands?	1	2	3	4
Did you have cramps in your feet?	1	2	3	4
Did you have problems standing or walking because of difficulty feeling the ground underyour feet?	1	2	3	4
Did you have difficulty distinguishing between hot and cold water?	1	2	3	4
Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
Did you have difficulty walking because your feet dropped downwards?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week :	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
Did you have blurred vision?	1	2	3	4
Did you have difficulty hearing?	1	2	3	4
Please answer the following question only if you drive a car				
Did you have difficulty using the pedals?	1	2	3	4
Please answer the following question only if you are a man. This is an optional question.				
Did you have difficulty getting or maintaining an erection?	1	2	3	4

NCI - CTCAE version 4.0
Neurotoxicity Evaluation

Grade	I	II	III	IV
NCI-CTCAE (v4.0)	Mild paresthesia.	Moderate symptoms; limiting instrumental activities of daily living.	Severe symptoms; limiting self care activities of daily living.	Life threatening consequences; urgent intervention needed.
Questions	Sample answers for each toxicity grade			
Do you have problems tying your shoe laces, buttoning your shirts, fastening buckles or pulling up zippers?	"No, I might feel some tingling in my hands, but I have no problems tying laces, buttoning shirts, fastening buckles or pulling up zippers"	"It is a bit harder than before, but I can still tie laces, button shirts, fasten buckles or pull up zippers"	"I have severe difficulties tying shoe laces, buttoning shirts, fastening buckles or pulling up zippers" or "I cannot tie laces, button shirts, fasten buckles or pull up zippers anymore"	"I haven't been able to tie laces, button shirts, fasten buckles or pull up zippers for weeks"
Do you have problems writing?	"No, I might feel some tingling in my hands, but I have no problems writing"	"It is a bit harder than before, but I can still write"	"I have severe difficulties writing" or "I cannot write anymore"	"I haven't been able to write for weeks"
Do you have problems putting on your jewelry or your watch?	"No, I might feel some tingling in my hands, but I have no problems putting on my jewelry or my watch"	"It is a bit harder than before, but I can still put on my jewelry or my watch"	"I have severe difficulties putting on my jewelry or my watch" or "I cannot put on my jewelry or my watch anymore"	"I haven't been able to put on my jewelry or my watch for weeks"
Do your have problems walking?	"No, I might feel some tingling in my feet, but I have no problems walking"	"It is a bit harder than before, but I can still walk"	"I have severe difficulties walking" or "I cannot walk anymore"	"I haven't been able to walk for weeks

Oxaliplatin Specific Neuropathy grading

Grade	**Oxaliplatin-specific scale**[16]
0	None
1	sensory symptoms of short duration
2	sensory symptoms persisting between cycles
3	sensory symptoms causing functional impairment

NCCTG Research Base Instructions for Biospecimen Processing in BAP Shared Resource

Study Number: N08CB

Summary Table of Research Blood/Blood Products Being Received in BAP for This Protocol

Collection tube description and/or additive (color of tube top)	Volume to be collected per tube (number of tubes to be collected)	Blood product to be processed in BAP	After registration but before second treatment	Further processing required by BAP?	Shipping conditions
EDTA (purple)	10 mL (1)	WBC[1], Plasma	X	Yes	Cold pack

[1]White blood cells

1. Record receipt of specimens.

2. Plasma and buffy coat will be isolated from **one** EDTA tube using the protocols entitled "Plasma collection from whole blood samples" and "Buffy Coat Preparation from Whole Blood", respectively. Plasma and buffy coat samples will be stored at −80°C indefinitely for banking.

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. All forms and documents associated with this study can be downloaded from the N08CB Web page on the members' section of the CTSU web site (http://ctsu.org) unless otherwise indicated below. Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

Requirements for N08CB site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet

Pre-study requirements for patient registration on N08CB

- Patient must meet all registration inclusion criteria and no exclusion criteria may apply.
- Patient must have signed and dated all applicable consents.
- Blood draw kit availability checked.
- Patient questionnaire booklet availability checked; copies are not acceptable for this submission.

CTSU Procedures for Patient Registration / Randomization

Contact the CTSU Patient Registration Office by calling 1-888-462-3009 and leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, i.e. within one hour, call the registrar cell phone at 1-301-704-2376. The following forms must be completed:

- CTSU Patient Enrollment Transmittal Form
- N08CB Eligibility Checklist

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check the investigator and site information provided to ensure that all regulatory and special credentialing requirements have been met. The registrar will also check the forms for completeness and will follow-up with the site to resolve any discrepancies.

Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact the NCCTG Registration Office within the confines of their office hours to obtain assignment of a unique NCCTG patient identification number. This number is to be used on all future forms and correspondence. The CTSU registrar will relay the patient identification number to the enrolling site and follow up with a registration confirmation via email or fax. To maintain the blinded treatment assignment, the NCCTG Registration Office will relay the treatment assignment to the designated contact person that was given on the eligibility checklist.

Treatment cannot begin prior to registration and must begin ≤28 days after registration and must commence with the first cycle of chemotherapy

CTSU Procedures for Patient Randomization

To ensure that both the patient and the medical professionals who care for the patient are blinded to the identity of the treatment assignment, the NCCG randomization specialist will follow the double-blinding procedures outlined in protocol section 6.3.

DATA SUBMISSION

All case report forms (CRFs) and other documents associated with this study must be downloaded from the N08CB protocol page located on the members' section of the CTSU web site (http://ctsu.org). CTSU investigators must use the current version of the protocol-specific N08CB forms and adhere to the N08CB schedule for data submission per protocol Section 18.0. CRFs and associated reports must be submitted in the following manner:

- Original and amended CRFs and responses to query and delinquency letters must be mailed directly to the NCCTG Operations Office, RO FF 03 24-CC/NW Clinic, 200 First Street SW, Rochester, MN 55905, ATTN: QAS for N08CB, Fax (507) 284-1902.

- **Copies of clinical reports submitted to the NCCTG Operations Office must include the Patient ID and protocol number on all pages of the report. The patient's name must be redacted.**

SPECIAL MATERIALS

- Per Section 14.0: Blood specimen kits for translational research. Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. **Allow at least two weeks to receive the kits.**
- Per Section 11.0: Patient questionnaire booklet availability must be checked; copies are not acceptable for this submission. Booklets should be ordered using the order form found in the Forms Packet.

ADVERSE EVENT (AE) REPORTING

Assessing and submitting expedited reports

This study will utilize the CTEP Active Version of the CTCAE for toxicity and Adverse Event (AE) reporting. A link to the CTEP Version 4.0 of the CTCAE guidelines is available on the CTSU registered member Web site. CTSU investigators should assess adverse events according to the instructions and tables in Section 10.0 of the protocol. All reporting should be conducted within the time frames specified in Section 10.0 of the protocol.

Events must be reported electronically using the CTEP AdEERS application. A link to the AdEERS application can be found on both the CTSU member homepage and the N08CB Web page on the CTSU member site.

Please do not copy the CTSU on expedited serious adverse event reports.

CTSU institutions must comply with the expectations of their local Institutional Review Board (IRB) regarding submission of documentation of adverse events. Local IRBs must be informed of all reportable serious adverse events.

Secondary AML/MDS/ALL reporting

Add 1,2

All CTSU investigators are required to report secondary malignancies occurring on or following treatment on NCI-sponsored protocols. Events must be reported via AdEERS according to the NCCTG guidelines and conducted within the time frames specified in Section 10 of the protocol.

Pregnancy reporting

If a female patient becomes pregnant during the study, the site should complete the AE Form found in the Forms Packet. Do not submit this form to the CTSU.

DRUG PROCUREMENT - EXCEPT NCIC CTG INSTITUTIONS

Commercial agent: Calcium gluconate and magnesium sulfate (use commercial supply; follow blinding procedures from Section 6. Patients should not be charged. Sites will be reimbursed for the cost of the calcium gluconate.

Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 15.0 of the protocol.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned institutions, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTMB Monitoring Guidelines and are available for download from the CTEP web page http://ctep.cancer.gov/monitoring/guidelines.html.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the informed consent section of this protocol document; however, authorization for the release of Protected Health Information is considered separate and distinct from the Informed Consent process for participation in this clinical trial.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US institutions.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report form