THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Phase II, randomized, placebo-controlled study of minocycline for reducing symptom burden in patients with colorectal cancer
2013-0323

Core Protocol Information

Short Title	Phase II study of Minocycline for reducing symptom burden in colorectal patients
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary Outcome

The primary objective of this protocol is to examine the **clinical efficacy** of minocycline in reducing acute peripheral neuropathy during oxaliplatin-based chemotherapy in patients with colorectal cancer (CRC).

1.2 Secondary Outcomes

1.21 To examine the clinical efficacy of minocycline in reducing fatigue during oxaliplatin-based chemotherapy in patients with CRC.

1.22 To examine the impact of socioeconomic status (SES) on the **clinical efficacy** of minocycline in reducing acute peripheral neuropathy during oxaliplatin-based chemotherapy in patients with CRC, and to determine if the level of neuropathy is the same after patients are taken off study medications.

1.23 To examine the interaction between SES and inflammation (circulating cytokines and activation of immune cells) and the effect of these variables on symptom severity in CRC patients.

1.24 To explore the relationship between objective measures of neuropathy and patient-reported symptom outcome measures and health status.

2.0 Background

Despite increased public awareness and use of proven screening methods, colorectal cancer (CRC) is the third-most-common cancer and the second-leading cause of cancer death for men and women combined in the United States (Siegel et al., 2012). Oxaliplatin, a standard chemotherapy agent for CRC, not only confers significant clinical benefit, but also causes acute and chronic neurotoxicity (Grothey, 2010). As a dose-limiting toxic effect, oxaliplatin chemotherapy-induced peripheral neuropathy (CIPN) interferes with functional ability, causes distress, and persists into survivorship for thousands of patients; it also can compromise adherence to therapy. Nearly 40% of patients with CRC receiving oxaliplatin-based chemotherapy experience neuropathy that is significant enough to cause dose reduction or withdrawal. Although neuropathy might be seen as a small negative consequence of treatment compared with the prolongation of overall survival conferred by such treatment, a well-founded mechanistic strategy could effectively and actively manage CIPN.

Effective management of CIPN is lacking; it is often addressed with “treatment holidays” or dose reductions. A paucity of research on biological attributes is a key hindrance to providing mechanism-driven care for treatment-related toxicity and high symptom burden. However, preclinical animal modeling has provided strong evidence that the common antibiotic **minocycline** has a neuroprotective effect on oxaliplatin-induced (Boyette-Davis & Dougherty, 2011) and taxane-induced (Cata et al., 2008) hyperalgesia. Minocycline has long-lasting effects in preventing neuropathic pain (Padi & Kulkarni, 2008; Raghavendra et al., 2003) and neurodegenerative disorders (Noble et al., 2009); it was safe and effective for patients with

rheumatoid arthritis in a 48-week double-blind placebo-controlled trial (Tilley et al., 1995).

Others have reported that minocycline has a wide range of anti-inflammatory activity in the brain and peripheral nervous system, which it accomplishes by inhibiting microglial activation and proliferation through inhibition of the inflammation pathway (Henry et al., 2008). An increase in inflammation is a prime candidate for the mechanism behind increases in treatment-related symptoms, including CIPN. We have reviewed the evidence of the impact of inflammation on several cancer-related symptoms (Lee et al., 2004). The insult of cancer treatment, including chemotherapy, increases production of inflammatory cytokines, especially interleukin (IL)-6 and tumor necrosis factor (TNF) variants (Linard et al., 2004; Linard et al., 2005). Both paclitaxel and cisplatin are known to cause a rise in the levels of cytokines, especially IL-6, in cancer patients (Endo et al., 2004). High levels of IL-6 have been found in patients with inoperable lung cancer receiving cisplatin along with combination treatment (Mantovani et al., 2000). Cytokines have been suggested to have a role in the increase of IL-6 in response to paclitaxel chemotherapy in breast cancer (Pusztai et al., 2004), and IL-6 has been associated with reported symptoms in allogeneic hematopoietic stem cell transplantation and chemoradiation therapies (Wang et al., 2008; Wang et al., 2012). Although the specific causes of CIPN remain to be fully elucidated, its severity may be reduced by inhibition of proinflammatory cytokines.

This project is a Phase II, two-arm, randomized, placebo-controlled study of patients with CRC receiving oxaliplatin-based chemotherapy. As a primary objective, we will pursue prevention and reduction of CIPN via broad pro-inflammatory cytokine blockade by minocycline. As secondary objectives, we will examine minocycline's efficacy in reducing the severity of fatigue and also compare its efficacy in patients seen at a private/academic cancer center (The University of Texas MD Anderson Cancer Center) versus a public hospital (Lyndon B. Johnson General Hospital [LBJ]) where patients are highly likely to have low socioeconomic status (SES). Patients of low SES, often referred to as the medically underserved, are at greater risk for severe symptoms (Cleeland et al., 2011). Specifically, we have found that CIPN is disproportionally more severe in the medically underserved, and the control of CIPN should therefore be even more important for this group of patients. In several ongoing Phase II, randomized studies of minocycline in patients with pancreatic cancer, non-small cell lung cancer (NSCLC), or head and neck cancer at MD Anderson, we have found no increased toxicity for patients.

Our proposed study is **innovative** because (1) little literature is focused on the biobehavioral mechanisms underlying disease-related symptoms and the toxic effects of treatment in medically underserved cancer patients, and (2) this study provides a direct test of the effects of modulating inflammation as a potential treatment for CIPN in CRC, with potentially greater benefit for low SES patients. As a US Food & Drug Administration (FDA)-approved drug, minocycline is inexpensive and safe, such that positive results from this study could be applied relatively rapidly in clinical practice.

2.1 Colorectal Cancer and Oxaliplatin-based Chemotherapy

Overall survival for advanced CRC has improved in the past decade, most strikingly because of rapid advances in chemotherapeutic regimens combining 5-fluorouracil with the newer cytotoxic agents (eg, irinotecan, ox-aliplatin) and targeted therapies. Oxaliplatin, a third-generation platinum, is a key chemotherapeutic agent used in first and subsequent lines of therapy for metastatic CRC and also in adjuvant therapy for CRC (André et al., 2004; Goldberg et al., 2004). The median survival for patients with metastatic CRC has been extended to 2 years and beyond, such that metastatic CRC is no longer viewed as an acute illness associated with a rapidly progressive course and early demise, but rather as a chronic disease requiring a long-term approach to treatment. Hence, for a patient with surgically unresectable disease, palliative chemotherapy is provided for the lifespan of the patient. Treatment goals no longer involve the use of intensive chemotherapy to salvage a few additional months of life, but now focus on enhancing quality of life with limited symptom burden—the so-called continuum-of-care paradigm (Goldberg et al., 2007).

2.2 CIPN and Inflammation

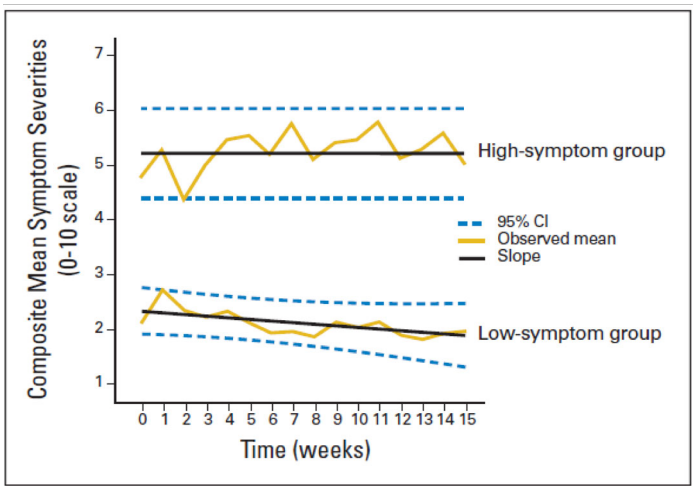
It has been reported that macrophage accumulation and activation in the dorsal root ganglia (DRG) of paclitaxel-treated rats contribute to the development of neuropathy. The DRG of the spinal cord are the primary locations of cisplatin damage in the central nervous system (Meijer et al., 1999; Rabik & Dolan, 2007). Ledeboer et al (2007) demonstrated that paclitaxel-induced neuropathic pain is associated with induction of TNF-a and IL-1b in the lumbar DRG. This suggests that macrophages are the potential sources of these pro-inflammatory cytokines that in turn sensitize primary sensory afferents and modify sensory input to the spinal dorsal horn to facilitate pain. Experimental studies have shown that glial cell inhibitors such as propentofylline, thalidomide, and minocycline (selective for microglia) attenuate paclitaxel/vincristine-induced neuropathic pain (Cata et al., 2006; Sweitzer et al., 2006), further supporting a role for activated microglial cells in CIPN.

2.3 Socioeconomic Status and Activation of Innate Inflammatory Pathways

Disparities in treatment and SES largely explained reduced survival among CRC patients who were African-American and had low SES (Le et al., 2008). Independent of personal income or educational attainment, adults living in less-advantaged neighborhoods exhibit higher levels of circulating proinflammatory markers than do residents of more-affluent areas. This association helps explain the increased risk of atherosclerotic cardiovascular morbidity and mortality conferred by low community-level SES (Petersen et al., 2008). The large population-based MIDUS study (Friedman & Herd, 2010) also suggested a link between social position and inflammatory markers of illness in the United States. After adjustment for demographic factors, health status, and health behaviors, those in the lowest quintile of pretax household-adjusted income or with less-than-high-school education had significantly higher levels of the inflammatory marker IL-6, the acute-phase response protein C-reactive protein (CRP), and fibrinogen.

2.4 Disparity in Symptom Burden

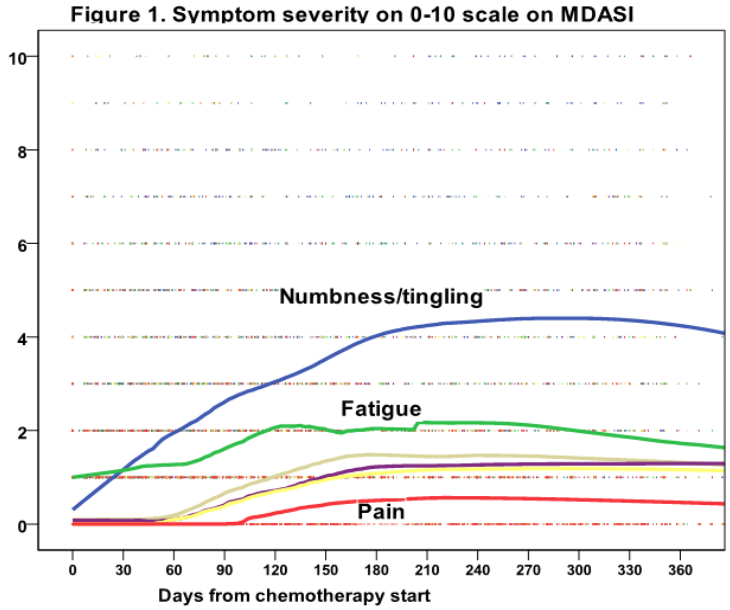
We have previously documented that patients with advanced NSCLC treated at LBJ Hospital reported a significantly more-severe symptom burden than patients treated at MD Anderson with the same standard chemotherapy (**Figure 1**) (Cleeland et al., 2011). The most-severe symptoms were pain, fatigue, disturbed sleep, shortness of breath, drowsiness, and coughing; 30% of patients were in the high-symptom group. Lower education (OR=2.6 (1.3-5.2), *p*=.01) and non-white ethnicity (OR=2.8 (1.4-5.4), *p*=.002) were significant predictors of membership in the high-symptom group. We also found significantly more severe numbness/tingling (CIPN symptoms) in underserved patients (*p*=.018; unpublished data). This NSCLC symptom study provides a rationale for studying CIPN disparities in CRC patients seen at public versus private/academic hospitals (as proposed herein) and demonstrates the established research collaboration between MD Anderson and LBJ. MD Anderson faculty provide standard oncology care at each of these treatment sites.



Patient-reported symptom outcomes raise a further research question regarding inflammatory mechanisms underlying high symptom burden and toxicity in low-SES patients undergoing standard therapy. In this study, we will investigate the quantitative relationship between inflammatory markers and neurotoxicity, as well as the potential differential effect of an anti-inflammatory and neuroprotective agent in patients seen in a private/academic center versus a public hospital.

2.5 Symptom Profiles of Patients with CRC Undergoing Oxaliplatin-Based Chemotherapy In a recently completed prospective study of patients with CRC (MD Anderson protocol 2007-0637; PI: XS Wang), symptoms were documented in 100 patients for 12 months after the start of oxaliplatin-based chemotherapy, using the M. D. Anderson Symptom Inventory (MDASI). This study established collaborations between the Departments of Symptom Research and GI Medical Oncology at MD Anderson, demonstrated the feasibility of enrollment and data gathering for CRC patients, provided pilot-tested statistical methods for analyzing the symptom data, and provided a longitudinal symptom profile of neuropathy (numbness/tingling) during oxaliplatin-based chemotherapy.

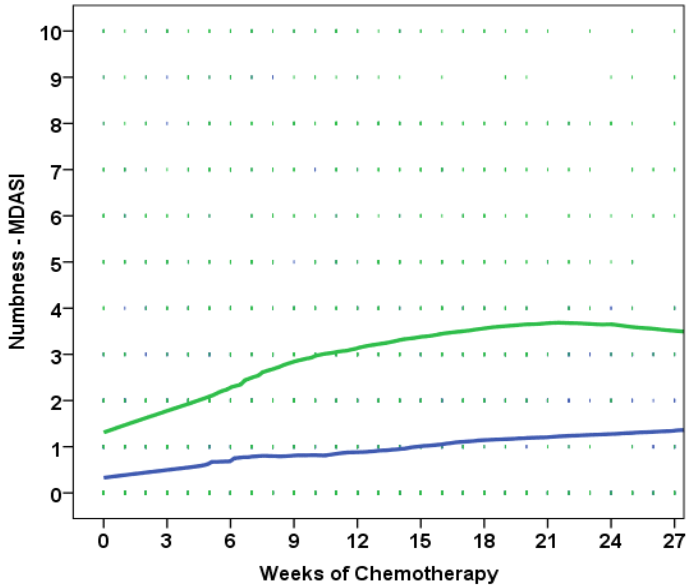
The Loess curves (**Figure 2**) show trends in symptom development in CRC patients over 12 months. Numbness/tingling increased much more rapidly in severity and remained most severe after chemotherapy. In contrast, pain severity remained low during the first 3 months of chemotherapy and increased thereafter. Fatigue was the second-most-severe symptom during the study. Further, case-cluster trajectory analysis of symptom severity confirmed the clinical impression that not all patients suffered from high symptoms. On the basis of repeated symptom data and a 3-group cluster analysis of numbness data, 20% of patients had the highest severity, 50% had rapid increase in severity in response to chemotherapy, and 30% reported low severity over 12 months.



We collected serum samples and MDASI symptom ratings from 31 of the 100 patients with CRC (n=175 observations) and tested a panel of markers (IL-1RA, CRP, MCP-1, IL-6, IL-6R, TNF-á, sTNF-R1, sTNF-R2) (Wang et al., 2011). Mixed modeling, controlled for age, sex, cancer stage, number of chemotherapy cycles received, and body mass index (BMI), showed an association between inflammatory cytokines and the development of symptom burden. sTNF-R1 and IL-6 were significantly and positively associated with the severity of the component score of the five most severe symptoms (fatigue, distress, drowsiness, disturbed sleep, and poor appetite). sTNF-R2 was associated with pain, and increased **IL-6** was associated with the development of numbness/tingling (most relevant for this study).

We observed significantly more severe neuropathy in patients with NSCLC treated at the public

hospital (2.76 vs. 1.29 for mean numbness, effect size=0.515, $p<.001$). **Figure 3** presents the average numbness severity from both groups (upper green line=LBJ). This unpublished CIPN result is consistent with the disparity in symptom burden for many other symptoms, which we reported in 2011 (Cleeland et al., 2011).



2.6 Symptom Intervention Agent: Minocycline

2.61 Anti-inflammatory Effects

Conceptually, modulation of treatment-induced immune dysregulation presents a potential mechanism for reducing treatment-induced symptoms (Hannestad et al., 2011; Miller, 2003; Wang et al., 2010; Wood et al., 2006). Minocycline has broad anti-inflammatory and antioxidant properties, even though it is most often used as a synthetic antibiotic (Mishra & Basu, 2008). The anti-inflammatory effect of minocycline is manifest in both the peripheral and central nervous systems. In the former, minocycline has been proposed to treat rheumatoid arthritis and inflammatory bowel disease, although it is less effective than cytokine antagonists. At the level of the central nervous system, minocycline readily enters the brain because of its lipophilic properties (Aronson, 1980). It potently downregulates activated microglia, the inflammatory products of which lead to symptoms. The anti-inflammatory effects of minocycline and other tetracycline derivatives may be attributable to PARP-1 inhibition (Alano et al., 2006). Among other consequences, minocycline-induced inhibition of PARP-1 probably leads to the inhibition of p38 MAPK activation that has been observed in microglia exposed to minocycline (Sapadin & Fleischmajer, 2006; Tikka et al., 2001). In the context of our current studies on the pivotal role of inflammation in cancer-related symptoms, the downregulation of inflammatory signaling pathways by minocycline is the primary reason for selecting this drug for symptom prevention clinical trials.

As we gain more understanding of cytokine networks, we may move away from single, well-defined pathways of inflammation toward a cytokine-targeting therapeutic strategy that blocks upstream cytokines with fewer side effects (Kopf et al., 2010). Minocycline could potentially provide this modulation.

2.62 Neuroprotective Effects

Animal studies have shown that minocycline abrogates the brain cytokine response to systemic lipopolysaccharide (LPS) and the development of LPS-induced sickness and depression (O'Connor et al., 2009). This effect, along with the inhibition of microglial activation caused by nerve damage, explains the neuroprotective action of minocycline that is observed in animal models of a number of diseases, including stroke, diabetic retinopathy, multiple sclerosis, and Parkinson disease. Minocycline prevents neuropathic pain (Padi & Kulkarni, 2008; Raghavendra et al., 2003). Minocycline prevented LPS-induced microglia/macrophage activation and cytokine responses in spinal cord and dorsal root ganglia, but did not affect the activation of astrocytes or satellite cells (Yoon et al., 2012).

Dr. Patrick Dougherty's group at MD Anderson has published other studies suggesting that minocycline's profound immunomodulatory actions may provide a treatment option for the prevention or reversal of chemotherapy-related pain (Cata et al., 2008) and prevent taxane-induced hyperalgesia (Boyette-Davis et al., 2011). Minocycline effectively prevents the loss of intraepidermal nerve fiber density in oxaliplatin-treated rats (Boyette-Davis & Dougherty, 2011). Minocycline is also active in neurodegenerative disorders (Noble et al., 2009), and HIV (Zink et al., 2005). Our colleagues' results directly support our proposal that *early mechanistic intervention* might reduce numbness symptoms in patients with CRC receiving oxaliplatin-based chemotherapy. The clinical neurotoxicity produced by both chemotherapy agents is consistent; furthermore, observation of the preclinical effects of minocycline on CIPN supports the validity of translating the science from bench to bedside in this proposed study.

2.63 Anticancer Effects

The tetracycline family includes tetracycline, doxycycline, and minocycline. The potent matrix metalloproteinase (MMP)-inhibitory activities of tetracyclines (especially their chemically modified analogs), combined with their relatively well-tolerated pharmacological profile, led several researchers to investigate their anticancer potential in a variety of cancers, including melanoma and lung, breast, and prostate cancers. Tumors from rats treated with chemically modified nonantibiotic tetracyclines (CMT-3) demonstrated reduced angiogenesis and increased apoptosis; both emerged as mechanisms of CMT-3 action (Lokeshwar, 2011). MMPs are important mediators of metastasis formation in the bone, contributing largely to the morbidity of patients with breast or prostate cancer. The natural osteotropism of tetracyclines would allow them to be highly effective in the inhibition of MMPs produced by osteoclasts or tumor cells in the bone. This hypothesis has now been confirmed by experimental evidence showing that doxycycline reduces tumor burden in a mouse model of breast cancer-derived osteolytic bone metastasis. This effect is likely due to a combination of multiple roles of doxycycline, including MMP inhibition and a negative effect on osteoclast differentiation and survival (Saikali & Singh, 2003).

Minocycline inhibits cell proliferation and colony formation and downregulates cyclins A, B, and E, leading to arrest of cells in the G0 phase of the cell cycle and suppression of DNA synthesis. Furthermore, minocycline causes DNA laddering, activation of caspase-3, and cleavage of PARP-1. In nude mice bearing subcutaneous tumors, minocycline suppressed tumor proliferation index, angiogenesis, and tumor growth. This provided the initial basis for further evaluation of minocycline in the treatment of ovarian cancer (Pourgholami et al., 2012) and a potential role for minocycline in suppressing IL-6 expression and activity (Ataie-Kachoie et al.,

2013), and supports the use of this agent in cancer patients.

2.64 Safety

Minocycline has been used safely in thousands of patients over many years to treat a variety of clinical indications. It has a very low toxicity in preclinical studies and a sufficient safety profile as demonstrated in many studies of long-term use in humans. Common side effects of minocycline include light-headedness, vestibular symptoms, and nausea (Gump et al., 1977), without a correlation between serum concentration and toxicity. Minocycline was suspected in less than 2.5% of all common adverse events reported to the FDA (http://www.drugcite.com/?q=minocycline).

Minocycline has been used safely in CRC patients. A randomized double-blind, placebo-controlled trial (Scope et al., 2007) reported the usefulness of prophylactic oral minocycline in reducing acneiform rash in initial cetuximab treatment in CRC patients. Minocycline's *long-lasting effects in preventing neuropathic pain* (Padi & Kulkarni, 2008; Raghavendra et al., 2003) and its potential role as a remedy for human inflammatory bowel disease (Huang et al., 2009), neurodegenerative disorders (Noble et al., 2009), and HIV (Zink et al., 2005) have been reported. Minocycline was safe and effective for patients with rheumatoid arthritis in a 48-week double-blind, placebo-controlled trial (Tilley et al., 1995). In clinical trials of minocycline for Fragile X Syndrome (Paribello et al., 2010), vitiligo (Parsad & Kanwar, 2010), and schizophrenia (where it was used to block nitric oxide-induced neurotoxicity) (Levkovitz et al., 2010), the agent showed significant benefit and was well-tolerated.

3.0 Background Drug Information

Minocycline hydrochloride (Minocin®, manufactured by Triax Pharmaceuticals, LLC, Cranford NJ) is a semisynthetic antibiotic derived from tetracycline. It has the unusual side effect of markedly suppressing proinflammatory cytokine release, the primary reason we will include it as an intervention in this study (Appendix C). Preclinical data suggests that minocycline reduces neural inflammation and prevents apoptosis of neural cells. Animal studies have demonstrated that minocycline reduces the levels of the proinflammatory cytokines IL-6, TNF-a, IL-b and interferon (IFN)-g (Ledeboer et al., 2005; Zanjani et al., 2006). Minocycline's anti-inflammatory effect prevents subacute pathological change in lungs due to inflammation produced by peripheral LPS administration in animals (Yamaki et al., 1998). Minocycline was found to decrease IL-6 and CRP levels in patients with rheumatoid arthritis (Kloppenburg et al., 1996).

3.1 Minocycline Common Adverse Reactions

Published FDA data show a very low incidence (< 2.34%) of minocycline-related side effects, including pyrexia (fever), rash, arthralgia, light-headedness, and nausea (http://www.drugcite.com/?q=minocycline). Commonly associated side effects of minocycline include light-headedness, vestibular symptoms (such as dizziness and vertigo), headache, and nausea (Case, 2001; Gump et al., 1977), with no correlation seen between serum concentration and toxicity (Kloppenburg et al., 1995). Another side effect is photosensitization. Other adverse effects reported include serum sickness-like reactions, ototoxicity, azotemia, pulmonary infiltrate formation with associated eosinophilia, and discoloration of the sclera or teeth. A rare but serious reported side effect is pseudotumor cerebri.

3.2 Absolute Contraindications to Study Symptom Intervention Agent Minocycline

3.21 Hypersensitivity to any tetracycline

3.22 Pregnancy

3.23 Hepatotoxicity (aspartate aminotransferase (AST) or alanine aminotransferase (ALT)

3.3 Minocycline Clinical Pharmacology

3.31 Metabolism

Minocycline is metabolized to a significant degree; however, the nature of the metabolic products or sites of metabolism has not been elucidated with certainty (Allen, 1976).

3.32 Pharmacokinetics

Minocycline has a long serum half-life and can be administered at 12-hour intervals.

3.33 Time to Peak Concentration

Oral: 1 to 4 hours (Prod Info Dynacin®, 2011); (Prod Info Minocin®, 2008) (Macdonald et al., 1973; Simon et al., 1976).

- One to four hours after a single dose of two 100-mg minocycline capsules was given to 18 healthy fasting adults, the Cmax ranged from 2.1 to 5.1 micrograms per milliliter (mcg/mL) (Prod Info Minocin®, 2008) (Simon et al., 1976)
- One hour after a single dose of two 100-mg minocycline capsules was given to 10 normal adult volunteers, the Cmax ranged from 0.74 mcg/mL to 4.45 mcg/mL (Prod Info Minocin®, 2008)

3.4 Minocycline Monitoring Parameters

3.41 Minocycline: LFTs, BUN, Sr Cr

3.42 Signs of acute hepatitis: rash, fever, malaise, abdominal pain, and vomiting Evidence: Hepatotoxicity (e.g., elevated hepatic enzymes, hyperbilirubinemia, hepatic cholestasis, hepatic failure with some fatalities, hepatitis with autoimmune features, and jaundice) has also been reported. Abdominal complaints may suggest hepatotoxicity; the incidence of this effect is roughly 4.7%. Liver toxicity is possible with excessive accumulation of the drug, which can occur in patients with renal impairment receiving even usual oral or parenteral doses.

3.5 Minocycline Drug Interactions

3.51 Antacids containing calcium, magnesium, or aluminum, bile acid sequestrants, bismuth, oral contraceptives, iron, zinc, sodium bicarbonate, penicillins, and quinapril may decrease absorption of minocycline; **avoid taking within 2 hours of using this medication.**

3.52 Methoxyflurane anesthesia: when concurrent with minocycline, may cause fatal nephrotoxicity.

3.53 Retinoic acid derivatives: may increase risk of pseudotumor cerebri.

3.54 Warfarin: anticoagulant response may be increased with tetracyclines; **monitor INR closely during initiation or discontinuation.**

3.6 Storage Information
Store at 20°C to 25°C (68°F to 77°F).

***References for intervention agent:**
1. MD Anderson Cancer Center Formulary: http://www.crlonline.com/crlsql/servlet/crlonline

2. Micromedex – Healthcare Series: http://www.thomsonhc.com/home/dispatch

3. Micromedex: Minocycline Drugdex Drug Evaluation and Armodafinil Drugdex Drug Evaluation and Turmeric Drug Evaluation by Martindale.

4. Lexi-Comp: Minocycline

5. Clinical Pharmacology: Minocycline

3.7 Serious Adverse Events for Minocycline
No serious adverse events (SAEs) have been reported for this trial agent.

Other references include:
1. www.fda.gov, drug information

2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Susceptibility Tests—Eighth Edition; Approved Standard. NCCLS Document M100-S8, Vol.18, No.1, NCCLS, 940 West Valley Road, Suite 1400, Wayne PA, January 1998.

3. http://www.drugs.com/pro/minocycline.html

4.0 Study Design

The primary objective of the proposed clinical trial is to examine whether minocycline**,** an anti-inflammatory agent shown to modulate the inflammatory pathway and biomarkers, will reduce or prevent cumulative oxaliplatin-induced peripheral neuropathy in patients with CRC, compared with placebo. A secondary objective is to examine the impact of mechanism-driven intervention with minocycline on levels of inflammatory markers (especially in low-SES patients with CRC). A translational agenda that includes a T-cell cellular cytokine assay will improve our understanding of inflammatory mechanisms.

Design: Phase II randomized, 2-arm, double-blind, placebo-controlled trial

Sample: Patients with a pathologically proven diagnosis of CRC (N=84 evaluable patients), qualifying for oxaliplatin-based chemotherapy and minocycline treatment.

Stratification by socioeconomic status (SES): Patients will be stratified by recruitment site (MD Anderson or LBJ) as a proxy for SES, which is typically determined via received education (years) and self-reported income (Friedman & Herd, 2010). For this study, we will verify low SES as the lowest quintile of pretax household-adjusted income and less than high school education (Gallo et al., 2005). Our assumption is that patients at LBJ are primarily low SES and

patients at MD Anderson are not low SES.

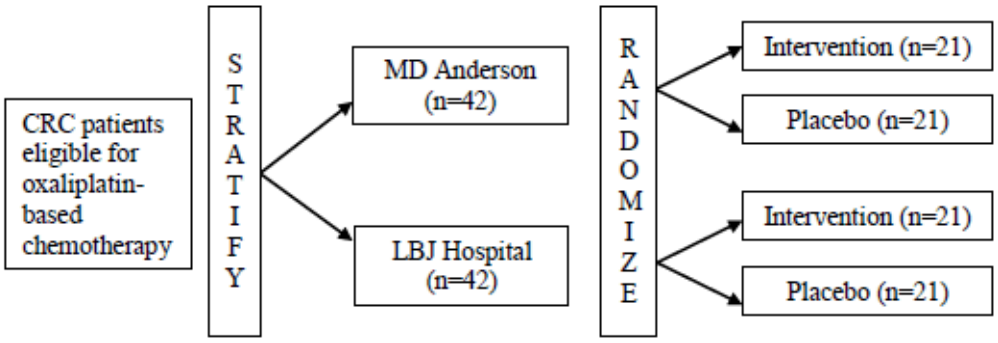
Intervention Agent: Minocycline, 100 mg twice a day

Study Period: Six months. Symptom intervention by minocycline/placebo throughout 4 months of oxaliplatin-based chemotherapy; symptoms will be reassessed at the 2-month follow-up visit, for a **total trial period of 6 months** per patient. Assuming that patients accrue at a rate of 3-4 per month, we anticipate completion of recruitment in 40 months.

The rationale for the 4-month intervention period is: (a) patients receiving a minimum dosage of oxaliplatin chemotherapy would be expected to reach a cumulative oxaliplatin dose (780 mg/m2) sufficient for development of peripheral neuropathy within 4 months; (b) in our previous study, the symptom profile of painful neuropathy over 4 months (8 cycles) of oxaliplatin showed a clear dynamic change; (c) patients are likely to have a tumor evaluation after 8 cycles of an oxaliplatin-based regimen; (d) considering that median progression-free survival (PFS) in stage IV CRC is about 10-12 months, a 4-month assessment timeframe will avoid any worsening of disease-driven symptom burden before progression in these patients. In sum, for this Phase II study that aims to demonstrate the principle, 4 months is a sufficient and appropriate time frame to observe the modulating effect of minocycline on peripheral neuropathy (primary outcome).

Primary Outcome Variable: Area under the curve (AUC) for peripheral neuropathy (the "numbness/tingling" item from the MDASI gastrointestinal module [MDASI-GI]) over 4 months.

Schema:



5.0 Patient Eligibility

5.1 Inclusion Criteria

5.11 Patients with a pathologically proven diagnosis of CRC seen either at MD Anderson or LBJ.

5.12 Patients $\geq$ 18 years old.

5.13 Patients who qualify for oxaliplatin-based chemotherapy (in the adjuvant or metastatic setting) and are likely to receive at least 3 months of oxaliplatin.

5.14 Patients who speak English or Spanish (due to language options for the MDASI

version being used in this study, we are only recruiting English-speaking or Spanish-speaking patients).

5.15 Patients with an NCI-CTCv4 sensory neuropathy score of 0 (Appendix D).

5.16 Patients with adequate renal function (serum creatinine must be < 1.5 times the upper limit of the institutional normal range) and no prior renal disease that in the opinion of the attending physician would make the patient ineligible to receive the study drug. Test results must be no more than 3 months old.

5.17 Patients with adequate hepatic function (total bilirubin must be < 2.0 times the upper limit of the institutional normal range; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be < 3.0 times the upper limit of the institutional normal range). Test results must be no more than 3 months old.

5.18 Patients willing and able to review, understand, and provide written consent.

5.2 Exclusion Criteria

5.21 Patients continuously taking any minocycline within the last 15 days. Patients who have conditions that potentially preclude use of minocycline as determined by the treating physician.

5.22 Patients continuously taking systemic steroids within the last 15 days.

5.23 Patients with autoimmune disorders (for example, systemic lupus erythematosus or rheumatoid arthritis), who have been treated in the last 3 years.

5.24 Patients who are pregnant; the absence of pregnancy will be confirmed by negative urine test.

5.25 Hypersensitivity to any tetracyclines, or a history of other allergies or drug reactions that in the treating physician's judgment make the patient inappropriate for this study.

5.26 Patients receiving vitamin K antagonist (warfarin).

5.27 Patients with a BMI >40 (Obese Class III criteria)

5.28 Patients who will receive cetuximab or other targeted therapy where physicians may use topical doxycycline to reduce the rash associated with therapy.

6.0 Patient Enrollment and Registration

6.1 Patient Enrollment

The proposed clinical trial will be conducted by the Department of Symptom Research in collaboration with the GI Medical Oncology and General Oncology departments at MD Anderson. Dr. Cathy Eng will serve as the protocol PI and Dr. Nishin Bhadkamkar will serve as site PI at LBJ.

Patients will be screened for eligibility and recruited for enrollment in the GI Medical Oncology clinics at MD Anderson and the Medical Oncology clinic at LBJ before their chemotherapy starts. Research staff will maintain a log of all patients screened; the reasons that patients do not enter the study will be documented. Patients who agree to enroll in the study will provide written

informed consent.

At enrollment, patients will be informed that they will receive a stipend in the total amount of $60 for participation in the study. The stipend will be distributed in $20 increments three times during the study. Stipends will be distributed to participants after completion of MDASI-GI at baseline, and at the end of months 4 and 6 of chemotherapy treatment.

All enrolled patients will be registered into the MD Anderson Clinical Oncology Research System (CORe).

6.2 Patient Randomization and Assignment to Treatment Arm

In order to reach our targeted number of evaluable patients, the study will accrue up to166 patients (83 patients each in the placebo and minocycline groups). A randomization list will be generated by our biostatistician collaborator from the Department of Biostatistics for all 166 patients; it will state the group to which each patient will be randomized. This list containing the accrual number and treatment group information will be set up in the Clinical Trial Conduct website. Study staff will be blinded to randomization arm.

After a patient is enrolled, the Investigational Pharmacy will retrieve the randomized treatment arm information from the Clinical Trial Conduct website. Once a patient is randomized to a treatment arm, Investigational Pharmacy will relay the information to the dispensing Pharmacy.

6.3 Pretreatment Evaluation

In order for study staff to determine patient eligibility, patients must have had the following tests prior to initiating chemotherapy and the study trial agent. These tests will be completed by their treating physician, as part of their standard prechemotherapy evaluation.

6.31 Blood chemistries (albumin, creatinine, SGOT**,** total bilirubin, ALT, and AST) and complete blood count (WBC, Hgb, platelets) will be reviewed; we will also document other lab data if available in the patient medical records (Appendix E).

6.32 Pregnancy test, if the patient is a female of childbearing potential.

6.33 History and physical examination (including documentation of current medications and Eastern Cooperative Oncology Group performance status (ECOG PS).

7.0 Administration of Pharmacological Agent

Preparation and dispensing of intervention medication (minocycline or placebo) for each patient will be coordinated by the investigational pharmacies at MD Anderson and LBJ. The study medication will be compounded at the GreenPark pharmacy, which has done this same minocycline/placebo compounding for several of our other studies. Matching capsules for placebo and minocycline will be compounded. The presentation will be a 100-mg capsule containing a powder. Patients will pick up the assigned study medications at one of the outpatient pharmacy stations at MD Anderson or the pharmacy at LBJ, or study medication will be mailed to the patient by the MD Anderson pharmacy. Patients will be given instructions on the study medication, and the study research staff will provide a Minocycline Patient Education Leaflet on how to take the drug and its interactions (Appendices W and X). Administration of minocycline for patients randomized to receive it will be 200 mg/day, an effective dose used safely for up to 18 months in other studies (Case, 2001).

Information on potential contraindications and interactions appears in Section 3.0, Background Drug Information. The interaction screening will be the responsibility of the dispensing Pharmacy. Research staff will review all medications being taken by the patient prior to initiating treatment. During the intervention, the research staff will capture all drug interactions causing an adverse event on the Adverse Event form. We plan to document important symptom control medications that patients will be or have been using during the trial. Minocycline will begin at the start of chemotherapy and continue daily through the 4-month intervention period.

The participants will take study medication twice daily, including weekend days, starting on day one of chemotherapy. The table below displays the symptom intervention agent and the dosing schedule (Lexi-Comp).

Symptom Intervention Agent	Dosage Form	Initial Intervention Dose (first day of chemotherapy)	Initial Placebo Dose (first day of chemotherapy)
Minocycline	100-mg capsules	100 mg two times a day (200 mg)	Matching placebo

Study staff will contact patients every cycle to check for adverse events (either during routinely scheduled clinic visits or via telephone calls).

Patients will be asked to bring their study medication container to the clinic at each chemotherapy cycle start so that study staff can perform a capsule count during a scheduled appointment. Unused drugs will be returned to the investigational pharmacy by the study staff. Study staff will contact patients every cycle to check medication use (either during routinely scheduled clinic visits or via telephone calls).

Patients and family members will be asked to notify the research team if the patient is hospitalized or moves to another location. Patients hospitalized because of complications will be identified and tracked by the research coordinator. Tracking of patient hospital admissions will be conducted either through (1) checking admissions through the institutional database; (2) contacting the closest relative; (3) and/or follow-up with the outpatient clinic nurse in the clinic. The reason for hospital admission will be recorded. When a family member or health care provider notifies the research coordinator of the death of a patient, the date of death will be recorded.

8.0 Data Collection

8.1 Patient-Reported Outcome (PRO) Measures

8.11 Symptom Measurement (Appendix F)

The MDASI is a multiple-symptom measure of the severity of cancer-related symptoms and the functional interference caused by symptoms that is sensitive to disease and treatment changes (Cleeland et al., 2000). This instrument is brief, easily understood, and validated in the cancer population. Patients rate the severity of 13 physical, affective, and cognitive symptoms on 0–10 numeric scales, ranging from "not present" to "as bad as you can imagine." The MDASI also assesses 6 items related to symptom interference with functioning, also on a 0–10 numeric scale ranging from "did not interfere" to "interfered completely."

For this study, symptom data will be collected using the gastrointestinal module of the MDASI (MDASI-GI). The MDASI-GI includes the 13 symptoms and 6 interference items from the core MDASI, along with 5 additional symptoms known to be important in assessing patients with CRC (constipation, diarrhea/watery stools, difficulty swallowing, change in taste, and feeling bloated). The MDASI-GI takes less than five minutes to complete. MDASI-GI items will be used to calculate the symptom AUC.

We will collect MDASI-GI assessments weekly. We will use paper or a secure electronic method when the patient is in the clinic, and use an interactive voice response (IVR) system, phone calls by field coordinators, secure web access, or regular mail when patients are away from the clinic. The method of collecting the MDASI-GI assessments weekly will be based on patient preference and may be varied throughout the study based on patient request. See Section 8.5.

The IVR System. An IVR system can greatly facilitate the longitudinal tracking of symptoms in patients. IVR systems are programmed to call patients at home for symptom assessment. The IVR system asks patients to rate each symptom and interference item on the MDASI-GI's 0–10 numeric scales using the keypad of a touchtone telephone.

Participants electing to use the IVR system may be provided with an informational brochure outlining the steps to complete an IVR call (Appendix G). A telephone number will be provided in the event of questions or problems. Patients will also be given a Patient Identification Number (PIN) for access to the system. IVR calls will be scheduled at a time that is convenient for the patient.

Completion or failure of calls will be monitored by the research staff. In the event of missed calls, a notification screen will appear in the IVR system to alert the research staff. The research staff will then contact the patient, check on their status and, if possible, complete the assessment with the patient during the telephone interview. The system will continue calling the patient at the preset schedule.

The IVR symptom and interference data will be available on an MD Anderson intranet site with access limited to authorized project staff only. Patient data will be identified by subject study number.

8.12 Measure of Quality of Life (Appendix H)

The EuroQol (EQ-5D) is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D was originally designed to complement other instruments but is now increasingly used as a stand-alone measure. The EQ-5D descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels, reflecting "no health problems" (level 1), "moderate health problems" (level 2), and "extreme health problems" (level 3). A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Each unique health state described by the instrument has an associated 5-digit descriptor ranging from 11111 for perfect health to 33333 for the worst possible state. The resulting descriptive system defines 243 health states. In addition, "unconscious" and "immediate death" are included in the EQ-5D valuation process but are not a part of the descriptive system. We will collect this data at baseline, end of symptom intervention and end of the trial.

Reporting Requirement

If in the course of assessing symptoms the patient reports severe levels of sadness (7 or above on the MDASI-GI) or extreme anxiety or depression (" I am extremely anxious or depressed" on the EQ-5D), the clinical data coordinator will notify the patient's treating physician immediately to make him/her aware of the patient's condition.

Patients using the IVR system when away from the clinic will be instructed by the research team to report severe symptoms to their physician or go to the emergency room. The research staff will notify the clinical service should patients report a high symptom-severity level. These patients will receive standard care at MD Anderson or LBJ.

8.13 Measures of Chemotherapy-Induced Peripheral Neuropathy (Appendices I and J)

The Chemotherapy-Induced Neuropathy Assessment Scale (CINAS) is a newly developed tool that asks patients to rate their neuropathy during the last 24 hours on a 0–10 scale (Thomas et al., 2012). The severity of sensory and motor neuropathy will be assessed with the EORTC QLQ-CIPN-20. The sensory neuropathy subscale includes the cumulative score for nine questions that assess sensory toxicities, with total scores ranging from 0 to 36. The motor neuropathy subscale includes the cumulative score for seven questions that assess motor toxicities, with total scores ranging from 0 to 28. The sensory neuropathy subscale includes questions about tingling, numbness, and burning pain in the hands or feet and problems standing or walking because of an inability to feel the ground beneath one’s feet. The motor subscale asks questions about cramps in the hands and feet, difficulty holding a pen, difficulty manipulating small objects, difficulty opening a jar or bottle because of weakness in one’s hands, difficulty walking because one’s feet dropped downwards, and difficulty climbing stairs or getting out of a chair because of weakness in one’s legs. The EORTC QLQ-CIPN 20 was shown in pretesting to have internal reliability with Cronbach alpha scores of 0.82 and 0.73 for the sensory and motor neuropathy subscores, respectively (Postma et al., 2005). The CINAS is available in English only.

8.14 Tobacco History Form (Appendix K)

The Tobacco History Form is a short questionnaire that asks about smoking history.

8.15 Other Data to be Collected

The study coordinator will collect in RedCap demographic, disease, and treatment information from the medical record (if the information is available), such as but not limited to: birth date, gender, race, marital status, diagnosis, date of diagnosis, disease stage, past and current cancer treatment, BMI, symptom management, routine laboratory values, and comorbidities. The research coordinator will assess the patient's ECOG PS and maximum CTC toxicities scores and date for sensory and motor neuropathy and diarrhea in the last 7 days or since the last assessment, document these assessments, and record the data in RedCap. The coordinator will query the patient for education, employment status, yearly income, and number of people living in the patient's home, document the patient's answers, and record the data in RedCap. The research coordinator will query the patient as to number of doses of study medication the patient has taken and missed since the last assessment, note the number of pills dispensed from the patient's pill bottle, and count the number of pills remaining in the bottle. This information will be documented and the data collected in RedCap. If the patient does not return the pill bottle, the information on number of pills dispensed and returned will not be documented or collected. When the patient goes off study, the research coordinator will document the reason and the date and record the data in RedCap. Assessments will be performed and data collected according to the schedule in 8.3.

8.2 Objective Measure: Bumps Detection Test

Impairment in touch sensation was especially pronounced in patients with CRC when measured using the Bumps detection test (Boyette-Davis et al., 2012), which is a relatively new, objective measure of neuropathy (Kennedy et al., 2011). The Bumps test will be administered in the clinic by research staff. Patients use a fingertip to detect small particles (bumps) of varying height (bumps detection) on a smooth surface. The Bumps device consists of 3 etched glass plates (11.5 cm x 15 cm), each of which contains twelve 1.5 x 1.5 inch squares. Within each square, there are 5 flat circles, each of a different color. Located over one of the circles within each square is a bump that is 550 mm in diameter. Bumps on plate 1 vary from 2.5 to 8.0 mm in height, bumps on plate 2 vary from 8.5 to 14.0 mm in height, and bumps on plate 3 range from 14.5 to 26 mm in height. Participants will be instructed to use the index finger of the dominant hand to explore the 5 circles within each square, beginning with the upper left square and moving from left to right and top to bottom. Patients will not able to see the location of the bump and must report to the examiner in which colored circle they perceive the bump.

8.3 Assessment Schedule

Time point by chemotherapy cycle	***Baseline Pre MIN Tx***[1]	***Every 3 to 4 weeks***[8]	***~1m (at clinic visit)***[2]	***~2m (at clinic visit)***[2]	***~3m (at clinic visit)***[2]	***End of MIN Tx (~4m)***	***End of trial (~6m)***[3]
On-study	X						

Charlson Comorbidity Index	X						
Demographic	X						
Clinical Monitoring		X		X		X	X
Laboratory Data	X	X		X		X	X
Study Medication Accountability[4]		X	X	X	X	X	
CTC Toxicity	X	X		X		X	
Final Study Status							X
MDASI-GI [4, 5]	X	X		X		X	X
EQ-5D [4]	X					X	X
CINAS[4, 6], EORTC CIPN-20[4]	X	X		X		X	X
Tobacco History[4]	X						X
Bumps test and research blood draw for markers[7]	X			X		X	X

1. Baseline: within 3 weeks before the first dose of chemotherapy is administered.
2. At the chemotherapy cycle closest to the time point.
3. End of trial: completion of 6-month study or upon patient withdrawal.
4. Patient-dependent forms will be completed if the patient can be contacted and is willing and able to complete.
5. The MDASI-GI will be completed weekly.
6. The CINAS will be administered to English-speaking patients only.
7. Blood for biomarkers will be collected if possible. The Bumps test will be administered when possible at Harris Health LBJ Hospital.
8. Assessments may be completed within +/- three days.

8.4 Blood Sample Collection for Inflammation Marker Testing

We will sample blood for testing of serum cytokines/chemokines and T-cell mitogen-induced cytokine/chemokine production using CD3/CD28 antibodies. Monocyte cytokines/chemokines will be induced by in vitro stimulation with LPS. We will concurrently track biomarkers of inflammation at baseline, 2 months, 4 months (end of intervention), and at the end of the trial at 6 months. For patients undergoing surgery, we will not collect blood for the first 4 weeks after surgery.

Blood (10 mL) for amino acids and amino acid metabolytes will be collected into ethylene diamine tetra acetic acid (EDTA) tubes and kept on ice; 10 mL of blood will be collected in a tube containing Na-heparin and kept at room temperature; and 10 mL of blood for serum

inflammatory markers will be collected and kept on ice. Heparinized blood will be diluted 1/10 with culture medium in the presence of either CD3/CD28 antibodies or LPS. 18 hours after LPS stimulation or 72 h after T cell mitogen stimulation, culture supernatants will be collected and stored at –80C until batch-wise analysis of cytokine/chemokine profiles using multiplex technology. Cytokines and chemokines that will be measured are: IL-1, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-17, IFN-g, TNF-a, IP-10, MIF, MCP-1, sTNFRI and sTNFRII, sIL6R as described by us before (van Zuiden M, Heijnen CJ, 2011). Plasma levels of the downstream markers albumin, neopterin and CRP will be assessed as previously described (Capuron et al., 2011; Wang et al., 2008). Plasma levels of tryptophan, kynurenine, phenylalanine, and tyrosine will also be determined by HPLC to study their possible association with on the one hand cytokine/chemokine profiles and on the other hand with fatigue and mood changes will be assayed (Capuron et al., 2011).

NF-kB analysis: NF-kB is a master transcriptional regulator of cytokine and chemokine production. We will test the activity of NF-kB by determining NF-kB activation after culturing whole blood for 3, 5 and 10 minutes with LPS or antiCD2/CD28 followed by FACS analysis using cellular activation kits consisting of labeled antibodies against NF-kB p50/p65 (Becton and Dickinson, USA). All the parameters have been extensively tested for validity and interindividual variation in our laboratory of Neuroimmunology of Cancer-Related Symptoms (NICRS).

Markers of inflammation are selected from among the effector components of the inflammatory response (cytokines and their soluble receptors). Circulating cytokines/chemokines to be measured include proinflammatory and anti-inflammatory cytokines and receptors (IL-1RA, IL-6, IL-8, sIL-6R, IL-10, MCP-1, sTNF-R1, and sTNF-R2). We will also test the kynurenine/tryptophan ratio that associated with increased plasma levels of neopterin, a marker of macrophage activation, which points to activation of the tryptophan-catabolizing enzyme IDO.

8.5 Data Confidentiality Plan

All patient-reported outcome, laboratory, and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study. Patient folders containing case report forms are kept in locked cabinets in the Department of Symptom Research.

Data is collected either (1) on scannable paper-and-pencil Teleforms that can be administered face-to-face in the clinic, through phone calls by field coordinators, or by regular mail, or (2) via Health Insurance Portability and Accountability Act (HIPAA)-compliant, institutionally approved, secure electronic data-capture methods (eg, tablet PCs in the clinic, the IVR system, or the web-based REDCap application hosted by MD Anderson). Electronic capture eliminates the need for hand data entry. All data resides in a relational database with audit tracking for efficient data retrieval. All data and software related to the patient data is password protected with controlled access.

A custom software application performs protocol tracking, along with data management and

quality assurance for symptom outcome data. The software monitors patients as they progress through the protocol from screening to off-study and informs the data coordinators of protocol events and what case report forms to administer. The protocol tracking software also tracks when patient data is collected, scanned, and monitored. Routine data processing is made expeditious by simplifying the creation of custom algorithms and storing them for future use. These algorithms check the data for potentially erroneous values, and then automatically write them to an error log for later review. Data set review also consists of reviewing labels, value codes of the data, and logic checks. Should the data require correction, the changes are made to the data themselves, and the description of those changes is documented in the error log. The data management application also allows for easy dataset construction using several pre-loaded architectural paradigms.

REDCap (Research Electronic Data Capture) electronic data capture tools (www.project-redcap.org) is a secure, web-based application hosted at MD Anderson with controlled access designed to support data capture for research studies (Harris et al., 2009). REDCap provides: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and MD Anderson's Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. Users are authenticated against MD Anderson's Active Directory system. External collaborators are given access to projects once approved by the project sponsor. The application is accessed through Secure Socket Layer (SSL). All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number. After publication, study data will be archived in REDCap.

In addition, after all analysis has been completed and all study results have been reported, patient data will be permanently and securely stored in an institutional big data warehouse and made available to all research and clinical faculty, with appropriate validation and access controls, so it can facilitate research cross-fertilization and speed insight discovery.

9.0 Reporting Requirements

9.1 Adverse Events (AE)

Patients will be seen in the outpatient clinics for each chemotherapy cycle, allowing for close monitoring of potential adverse events (AEs) by clinic and research staff. Treatment-related toxicities (NCI Common Terminology Criteria for Adverse Events, version 4) will be monitored by both clinic and research staff at the patient's regular clinical appointments or by phone call.

Grade 1 and Grade 2 AEs will not be reported. AEs that are Grade 3 and above are considered to be serious adverse events (SAEs) and will be reported. SAEs that are **unexpected and related** (definitely, probably, or possibly related) to the study medication will be reported promptly according to institutional policies (see Section 9.2 below). SAEs that are either (1) **expected** or (2) **unexpected but unrelated** (unrelated or unlikely to be related) to the study medication will be summarized on the continuing review report. The principal investigator and the treating physician will determine whether or not an AE is related to the study medication.

When clinically indicated, all patients will receive standard supportive care, including but not limited to antiemetics, antibiotics, nutrition, and pain management. Patients will stop taking minocycline if grade 3 toxicity occurs.

A list of adverse events known to be associated with primary treatment is listed in section 4.0 of the protocol.

9.2 Serious Adverse Events (SAE)

9.21 Definition

A serious adverse event is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death.
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above may also be considered SAEs. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the Clinical Research Support Center.

9.22 Reporting Serious Adverse Events

It is the responsibility of the PI and the research team to ensure SAEs are reported according to the Code of Federal Regulations, Good Clinical Practices, protocol guidelines, the

sponsor's guidelines, and MD Anderson Institutional Review Board (IRB) policy.

All events occurring during the conduct of the protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas MD Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events." Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the MD Anderson IRB **within five working days** of knowledge of the event, regardless of attribution.

All **life-threatening or fatal events**, expected or unexpected, and regardless of attribution to the study drug, must be reported to the MD Anderson IRB in writing within 24 hours (next working day) of knowledge of the event.

Additionally, any SAEs that occur more than 30 days after the last dose of study drug that are related to the study treatment must be reported to the MD Anderson IRB Office. This may include the development of a secondary malignancy.

The MD Anderson "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the MD Anderson IRB.

10.0 Unblinding

In the event of an SAE (as defined above) or an emergency situation that is likely due to the symptom trial agents as determined by the treating physician or PI, the investigational pharmacy at either MD Anderson or LBJ, as appropriate, will be asked to unblind the symptom trial agents for the affected study subject. Pharmacy staff will proceed with unblinding and will contact the PI with the symptom trial agent information so that the treating clinicians can appropriately manage the SAE and confirm the specific source of the SAE. All incidents of unblinding will be documented by the study team and will also be maintained on file in the Investigational Pharmacy Services for reference. The Investigator must notify the MD Anderson IRB when unblinding occurs.

11.0 Criteria for Removal from the Study

11.1 Development of an SAE related to the study drug.

11.2 Inability to comply with protocol requirements at baseline or within three months of study start is defined as an inevaluable case.

11.3 If it is determined that patient is unable to comply with protocol requirements (specifically study medication), or if treatment with oxaliplatin is discontinued after three months of study start, patient will remain on study for PRO data collection unless patient requests to be removed from study.

11.4 Pregnancy during the study period.

11.5 Any of these values are met or exceeded:

11.51 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 times the upper limit of normal

11.52 Total bilirubin > 2.0 times the upper limit of normal

11.53 Signs and symptoms of severe rash (CTC ≥ grade 3) and hypersensitivity; if these appear, the study drug must be stopped immediately and the patient must be removed from the study

11.54 INR > 1.5; treating physician notified so that medical management occurs

11.6 Completion of study**.**

12.0 Statistical Analysis Plan

12.1 Sample Size and Randomization

Patients will be randomized equally to the 2 arms (minocycline and placebo) and stratified by SES. We will use the treatment setting (MD Anderson versus LBJ) as the stratification variable, as LBJ is likely to enroll patients with low SES. A balanced randomization scheme using a random permuted block method will be implemented (see schema, Section 5.0). Study staff will be blinded to randomization arm.

The primary outcome variable is the AUC for numbness/tingling over ~4 months. The area under the curve (AUC) will be calculated using trapezoidal approximation. The base of a trapezoid corresponds to the number of days between assessments while the heights correspond to two adjoining symptom responses. The number of trapezoids depends on the number of symptom assessments. The sum of the area for all the trapezoids represents the AUC of a particular patient. Our preliminary data in CRC chemotherapy show that the average 4-month numbness AUC is 205.76 (equivalent to a mean daily AUC of 1.7), with a standard deviation of 168.3. With 42 evaluable patients per arm, we will be able to detect a difference of 103.5 (standardized difference of 0.61) on the symptom AUC between the 2 arms with 80% power and a 2-tailed 5% significance test. We will continue to accrue patients until we have reached the specified evaluable patients per arm. Because we expect that approximately 49% of the patients may become inevaluable, we will accrue up to 166 patients.

Patients who drop out of the study after entering three months of AUC data will be included by carrying their last symptom data forward for the remaining study period. If patients stop the study intervention after 3 months of trial, but continue to provide PRO data, this data will be included in the AUC analysis, instead of using the carryover method for missing timepoints.

12.2 Analysis Plan

12.21 Primary Outcome

Estimates of treatment effect will be obtained using standard linear regression techniques in which AUC values are regressed on indicator variables that represent treatment received. We will include the effect of SES status, prior oxaliplatin treatment, age, gender, BMI, and disease stage in the regression model. If the distribution of the outcome variables cannot reasonably be regarded as Gaussian, we will investigate transformations of both response and explanatory variables to a scale upon which a Gaussian model can be employed. To assess the effect of patients who drop out of the study, we will use a selection model to account for informative dropouts and include the effect of SES status, prior oxaliplatin treatment, age, gender, BMI, and disease stage as well as those baseline characteristics that are unbalanced between the dropouts and completers as covariates in the model.

In addition to the formal evaluation of treatment effects on the primary outcome, we will also examine the prognostic effects of baseline sensory deficit from the Bumps test (if available), tumor response, ECOG PS, comorbidity, and supportive-care agent used, if any, in predicting the outcome variable. Supplementary analysis will be performed by fitting linear mixed models with symptom scores as the dependent variable with time, treatment group, and other covariates as independent variables.

An interim analysis will be performed after 50% of the targeted number of patients (84) are evaluable; that is, after 42 patients are evaluable. An evaluable patient is one who has contributed PRO data for at least three months of the trial period and whose 4-month AUC can be calculated. We propose that the trial be stopped if there is evidence that the numbness AUC between the minocycline and placebo arm is significantly different at $p<.005$. The test of the numbness AUC between the groups at the end of the trial will be tested at $p<.048$. These critical values are based on the O'Brien-Fleming approach (O'Brien and Fleming, 1979) with two looks.

12.22 Secondary Outcomes

12.221 To examine the clinical efficacy of minocycline in reducing fatigue during oxaliplatin-based chemotherapy in patients with CRC. We will examine the effect of minocycline on fatigue using the same approach under the primary outcome but with fatigue AUC instead of numbness/tingling AUC as dependent variable in a regression model consisting of an indicator variables that represent treatment received, SES status, prior oxaliplatin treatment, age, gender, body mass index and disease stage.

12.222 To examine the effect of SES on the clinical efficacy of minocycline in reducing acute peripheral neuropathy during oxaliplatin-based chemotherapy in patients with CRC and to determine if the level of neuropathy remains the same after patients are taken off study medications.

To test the hypothesis that the benefit of minocycline is greater for patients with low SES, we will compute and compare the difference scores between placebo and minocycline within the low-SES and high-SES groups. We expect the difference scores for the low-SES group to be greater than the difference scores for the high-SES group. To determine if neuropathy level is stable after patients are off their study medications, we will calculate change in numbness/tingling from month 4 to month 6 (end of study period). We will test whether the

change scores are significantly different from zero. This finding will be interpreted with caution, as patients who remain on the study are likely to report lower or stable symptoms.

12.223 To examine the interaction between SES and inflammation (circulating cytokines and activation of immune cells) and the effect of this interaction upon symptom development in CRC patients. We will correlate neuropathy, numbness, and fatigue levels with reduction in expression of inflammatory markers (serum proinflammatory cytokines and T-cell cytokine release in response to *ex vivo* activation with a mitogen) within the low-SES and high-SES groups. We hypothesized that the reduction in inflammatory markers will be greater in low-SES patients.

12.224 To explore the relationship between objective measures of neuropathy and fatigue and patient-reported symptom outcome measures and health status. If Bumps test results are available, **w**e will compare differences between the CINAS and Bumps test results at baseline and end of trial and we will report the effect sizes of these change scores. We will use the EQ-5D dimensions as dependent variables to explore whether health status differs between patients treated with minocycline vs. placebo and to estimate these effects.

As with any clinical trial, missing data and early withdrawal is a challenge. To address dropout related to the outcome, we will include a dropout variable in the mixed models and an interaction term with treatment groups to determine whether there is differential dropout between groups. We will also compare results from mixed models using (1) all available data and (2) data from only those patients who complete the entire study.

13.0 References

Alano CC, Kauppinen TM, Valls AV, Swanson RA. Minocycline inhibits poly(ADP-ribose) polymerase-1 at nanomolar concentrations. *Proc Natl Acad Sci U S A* 103(25): 9685-9690, 6/2006.

Allen JC. Minocycline. *Ann Intern Med* 85(4): 482-487, 10/1976.

André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350(23): 2343-2351, 6/2004.

Aronson AL. Pharmacotherapeutics of the newer tetracyclines. *J Am Vet Med Assoc* 176(10 Spec No): 1061-1068, 5/1980.

Ataie-Kachoie P, Morris DL, Pourgholami MH. Minocycline suppresses interleukine-6, its receptor system and signaling pathways and impairs migration, invasion and adhesion capacity of ovarian cancer cells: in vitro and in vivo studies. *PLoS One* 8(4): e60817, 2013.

Boyette-Davis J, Dougherty PM. Protection against oxaliplatin-induced mechanical hyperalgesia and intraepidermal nerve fiber loss by minocycline. *Exp Neurol* 229(2): 353-357, 6/2011.

Boyette-Davis J, Xin W, Zhang H, Dougherty PM. Intraepidermal nerve fiber loss corresponds to the development of Taxol-induced hyperalgesia and can be prevented by treatment with minocycline. *Pain* 152(2): 308-313, 2/2011.

Boyette-Davis JA, Eng C, Wang XS, Cleeland CS, Wendelschafer-Crabb G, Kennedy WR, Simone DA, Zhang H, Dougherty PM. Subclinical peripheral neuropathy is a common finding in colorectal cancer patients prior to chemotherapy. *Clin Cancer Res* 18(11): 3180-3187, 6/2012.

Capuron L, Schroecksnadel S, Feart C, Aubert A, Higueret D, Barberger-Gateau P, Laye S, Fuchs D. Chronic low-grade inflammation in elderly persons is associated with altered tryptophan and tyrosine metabolism: role in neuropsychiatric symptoms. *Biol Psychiatry* 70(2): 175-182, 7/2011.

Case JP. Old and new drugs used in rheumatoid arthritis: a historical perspective. Part 2: the newer drugs and drug strategies. *Am J Ther* 8(3): 163-179, 5/2001.

Cata JP, Weng HR, Dougherty PM. The effects of thalidomide and minocycline on taxol-induced hyperalgesia in rats. *Brain Res* 1229: 100-110, 9/2008.

Cata JP, Weng HR, Lee BN, Reuben JM, Dougherty PM. Clinical and experimental findings in humans and animals with chemotherapy-induced peripheral neuropathy. *Minerva Anestesiol* 72(3): 151-169, 3/2006.

Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 47(11): 1245-1251, 11/1994.

Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, Engstrom MC. Assessing symptom distress in cancer patients: the M. D. Anderson Symptom Inventory. *Cancer* 89(7): 1634-1646, 10/2000.

Cleeland CS, Mendoza TR, Wang XS, Woodruff JF, Palos GR, Richman SP, Nazario A, Lynch GR, Liao KP, Mobley GM, Lu C. Levels of symptom burden during chemotherapy for advanced lung cancer: differences between public hospitals and a tertiary cancer center. *J Clin Oncol* 29(21): 2859-2865, 7/2011.

Endo S, Sato Y, Hasegawa T, Tetsuka K, Otani S, Saito N, Tezuka Y, Sohara Y. Preoperative chemotherapy increases cytokine production after lung cancer surgery. *Eur J Cardiothorac Surg* 26(4): 787-791, 10/2004.

Friedman EM, Herd P. Income, education, and inflammation: differential associations in a national probability sample (The MIDUS study). *Psychosom Med* 72(3): 290-300, 4/2010.

Gallo LC, Bogart LM, Vranceanu AM, Matthews KA. Socioeconomic status, resources, psychological experiences, and emotional responses: a test of the reserve capacity model. *J Pers Soc Psychol* 88(2): 386-399, 2/2005.

Goldberg RM, Rothenberg ML, Van Cutsem E, Benson AB, III, Blanke CD, Diasio RB, Grothey A, Lenz HJ, Meropol NJ, Ramanathan RK, Becerra CH, Wickham R, Armstrong D, Viele C. The continuum of care: a paradigm for the management of metastatic colorectal cancer. *Oncologist* 12(1): 38-50, 1/2007.

Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 22(1): 23-30, 1/2004.

Grothey A. Reintroduction of oxaliplatin: a viable approach to the long-term management of metastatic colorectal cancer. *Oncology* 79(5-6): 389-399, 2010.

Gump DW, Ashikaga T, Fink TJ, Radin AM. Side effects of minocycline: different dosage regimens. *Antimicrob Agents Chemother* 12(5): 642-646, 11/1977.

Hannestad J, DellaGioia N, Ortiz N, Pittman B, Bhagwagar Z. Citalopram reduces endotoxin-induced fatigue. *Brain Behav Immun* 25(2): 256-259, 2/2011.

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 42(2):377-81, 2009.

Henry CJ, Huang Y, Wynne A, Hanke M, Himler J, Bailey MT, Sheridan JF, Godbout JP. Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. *J Neuroinflammation* 5: 15, 2008.

Huang TY, Chu HC, Lin YL, Ho WH, Hou HS, Chao YC, Liao CL. Minocycline attenuates 5-fluorouracil-induced small intestinal mucositis in mouse model. *Biochem Biophys Res Commun* 389(4): 634-639, 11/2009.

Kennedy WR, Selim MM, Brink TS, Hodges JS, Wendelschafer-Crabb G, Foster SX, Nolano M, Provitera V, Simone DA. A new device to quantify tactile sensation in neuropathy. *Neurology* 76(19): 1642-1649, 5/2011.

Kloppenburg M, Brinkman BM, de Rooij-Dijk HH, Miltenburg AM, Daha MR, Breedveld FC, Dijkmans BA, Verweij C. The tetracycline derivative minocycline differentially affects cytokine production by monocytes and T lymphocytes. *Antimicrob Agents Chemother* 40(4): 934-940, 4/1996.

Kloppenburg M, Mattie H, Douwes N, Dijkmans BA, Breedveld FC. Minocycline in the treatment of rheumatoid arthritis: relationship of serum concentrations to efficacy. *J Rheumatol* 22(4): 611-616, 4/1995.

Kopf M, Bachmann MF, Marsland BJ. Averting inflammation by targeting the cytokine environment. *Nat Rev Drug Discov* 9(9): 703-718, 9/2010.

Korenromp IH, Grutters JC, van den Bosch JM, Zanen P, Kavelaars A, Heijnen CJ. Reduced Th2 cytokine production by sarcoidosis patients in clinical remission with chronic fatigue. *Brain Behav Immun* 25(7): 1498-1502, 10/2011.

Le H, Ziogas A, Lipkin SM, Zell JA. Effects of socioeconomic status and treatment disparities in colorectal cancer survival. *Cancer Epidemiol Biomarkers Prev* 17(8): 1950-1962, 8/2008.

Ledeboer A, Jekich BM, Sloane EM, Mahoney JH, Langer SJ, Milligan ED, Martin D, Maier SF, Johnson KW, Leinwand LA, Chavez RA, Watkins LR. Intrathecal interleukin-10 gene therapy attenuates paclitaxel-induced mechanical allodynia and proinflammatory cytokine expression in dorsal root ganglia in rats. *Brain Behav Immun* 21(5): 686-698, 7/2007.

Ledeboer A, Sloane EM, Milligan ED, Frank MG, Mahony JH, Maier SF, Watkins LR. Minocycline attenuates mechanical allodynia and proinflammatory cytokine expression in rat models of pain facilitation. *Pain* 115(1-2): 71-83, 5/2005.

Lee BN, Dantzer R, Langley KE, Bennett GJ, Dougherty PM, Dunn AJ, Meyers CA, Miller AH, Payne R, Reuben JM, Wang XS, Cleeland CS. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation* 11(5): 279-292, 2004.

Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, Fennig S, Treves I, Kron S. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J Clin Psychiatry* 71(2): 138-149, 2/2010.

Linard C, Marquette C, Clarençon D, Galonnier M, Mathieu J, Pennequin A, Benderitter M, Gourmelon P. Acute ileal inflammatory cytokine response induced by irradiation is modulated by subdiaphragmatic vagotomy. *J Neuroimmunol* 168(1-2): 83-95, 11/2005.

Linard C, Marquette C, Mathieu J, Pennequin A, Clarençon D, Mathé D. Acute induction of inflammatory cytokine expression after gamma-irradiation in the rat: effect of an NF-kappaB inhibitor. *Int J Radiat Oncol Biol Phys* 58(2): 427-434, 2/2004.

Lokeshwar BL. Chemically modified non-antimicrobial tetracyclines are multifunctional drugs against advanced cancers. *Pharmacol Res* 63(2): 146-150, 2/2011.

Macdonald H, Kelly RG, Allen ES, Noble JF, Kanegis LA. Pharmacokinetic studies on minocycline in man. *Clin Pharmacol Ther* 14(5): 852-861, 9/1973.

Mantovani G, Macciò A, Lai P, Massa E, Massa D, Mulas C, Succu G, Mudu MC, Manca G, Versace R, Pisano A. Results of a dose-intense phase 1 study of a combination chemotherapy regimen with cisplatin and epidoxorubicin including medroxyprogesterone acetate and recombinant interleukin-2 in patients with inoperable primary lung cancer. *J Immunother* 23(2): 267-274, 3/2000.

Meijer C, de Vries EG, Marmiroli P, Tredici G, Frattola L, Cavaletti G. Cisplatin-induced DNA-platination in experimental dorsal root ganglia neuronopathy. *Neurotoxicology* 20(6): 883-887, 12/1999.

Miller AH. Cytokines and sickness behavior: implications for cancer care and control. *Brain Behav Immun* 17(Suppl 1): S132-S134, 2/2003.

Mishra MK, Basu A. Minocycline neuroprotects, reduces microglial activation, inhibits caspase 3 induction, and viral replication following Japanese encephalitis. *J Neurochem* 105(5): 1582-1595, 6/2008.

Mommersteeg PM, Vermetten E, Kavelaars A, Geuze E, Heijnen CJ. Hostility is related to clusters of T-cell cytokines and chemokines in healthy men. *Psychoneuroendocrinology* 33(8): 1041-1050, 9/2008.

Noble W, Garwood CJ, Hanger DP. Minocycline as a potential therapeutic agent in neurodegenerative disorders characterised by protein misfolding. *Prion* 3(2): 78-83, 4/2009.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials, *Biometrics* 35(3): 549-556, 9/1979.

O'Connor JC, André C, Wang Y, Lawson MA, Szegedi SS, Lestage J, Castanon N, Kelley KW, Dantzer R. Interferon-gamma and tumor necrosis factor-alpha mediate the upregulation of indoleamine 2,3-dioxygenase and the induction of depressive-like behavior in mice in response

to bacillus Calmette-Guerin. *J Neurosci* 29(13): 4200-4209, 4/2009.

Padi SS, Kulkarni SK. Minocycline prevents the development of neuropathic pain, but not acute pain: possible anti-inflammatory and antioxidant mechanisms. *Eur J Pharmacol* 601(1-3): 79-87, 12/2008.

Paribello C, Tao L, Folino A, Berry-Kravis E, Tranfaglia M, Ethell IM, Ethell DW. Open-label add-on treatment trial of minocycline in fragile X syndrome. *BMC Neurol* 10: 91, 2010.

Parsad D, Kanwar A. Oral minocycline in the treatment of vitiligo--a preliminary study. *Dermatol Ther* 23(3): 305-307, 5/2010.

Petersen KL, Marsland AL, Flory J, Votruba-Drzal E, Muldoon MF, Manuck SB. Community socioeconomic status is associated with circulating interleukin-6 and C-reactive protein. *Psychosom Med* 70(6): 646-652, 7/2008.

Postma TJ, Aaronson NK, Heimans JJ, Muller MJ, Hildebrand JG, Delattre JY, Hoang-Xuan K, Lantéri-Minet M, Grant R, Huddart R, Moynihan C, Maher J, Lucey R. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. *Eur J Cancer* 41(8): 1135-1139, 5/2005.

Pourgholami MH, Mekkawy AH, Badar S, Morris DL. Minocycline inhibits growth of epithelial ovarian cancer. *Gynecol Oncol* 125(2): 433-440, 5/2012.

Pusztai L, Mendoza TR, Reuben JM, Martinez MM, Willey JS, Lara J, Syed A, Fritsche HA, Bruera E, Booser D, Valero V, Arun B, Ibrahim N, Rivera E, Royce M, Cleeland CS, Hortobagyi GN. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. *Cytokine* 25(3): 94-102, 2/2004.

Rabik CA, Dolan ME. Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer Treat Rev* 33(1): 9-23, 2/2007.

Raghavendra V, Tanga F, DeLeo JA. Inhibition of microglial activation attenuates the development but not existing hypersensitivity in a rat model of neuropathy. *J Pharmacol Exp Ther* 306(2): 624-630, 8/2003.

Saikali Z, Singh G. Doxycycline and other tetracyclines in the treatment of bone metastasis. *Anticancer Drugs* 14(10): 773-778, 11/2003.

Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol* 54(2): 258-265, 2/2006.

Scope A, Agero AL, Dusza SW, Myskowski PL, Lieb JA, Saltz L, Kemeny NE, Halpern AC. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol* 25(34): 5390-5396, 12/2007.

Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 62(1): 10-29, 1/2012.

Simon C, Malerczyk V, Preuss I, Schmidt K, Grahmann H. [Activity in vitro and pharmacokinetics of minocycline (author's transl)]. *Arzneimittelforschung* 26(4): 556-560, 4/1976.

Sweitzer SM, Pahl JL, DeLeo JA. Propentofylline attenuates vincristine-induced peripheral neuropathy in the rat. *Neurosci Lett* 400(3): 258-261, 6/2006.

Thomas SK, Mendoza TR, Vichaya EG, Wang XS, Sailors MH, Williams LA, Dougherty PM, Cleeland CS. Validation of the Chemotherapy-Induced Neuropathy Assessment Scale [abstract]. American Society of Clinical Oncology 48th Annual Meeting, Chicago IL, Jun 1-5, 2012. *J Clin Oncol* 30(15 Suppl 1), 5/2012; 9140.

Tikka T, Fiebich BL, Goldsteins G, Keinanen R, Koistinaho J. Minocycline, a tetracycline derivative, is neuroprotective against excitotoxicity by inhibiting activation and proliferation of microglia. *J Neurosci* 21(8): 2580-2588, 4/2001.

Tilley BC, Alarcón GS, Heyse SP, Trentham DE, Neuner R, Kaplan DA, Clegg DO, Leisen JC, Buckley L, Cooper SM, Duncan H, Pillemer SR, Tuttleman M, Fowler SE. Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA Trial Group. *Ann Intern Med* 122(2): 81-89, 1/1995.

van Zuiden M, Geuze E, Willemen HL, Vermetten E, Maas M, Amarouchi K, Kavelaars A, Heijnen CJ. Glucocorticoid receptor pathway components predict posttraumatic stress disorder symptom development: a prospective study. *Biol Psychiatry* 71(4): 309-316, 2/2012.

van Zuiden M, Heijnen CJ, van de Schoot R, Amarouchi K, Maas M, Vermetten E, Geuze E, Kavelaars A. Cytokine production by leukocytes of military personnel with depressive symptoms after deployment to a combat-zone: a prospective, longitudinal study. PLoS One. 2011;6(12):e29142. doi: 10.1371/journal.pone.0029142. Epub 2011 Dec 14.

Wang XS, Cleeland CS, Johnson VE, Reuben JM, Fogelman D, Malekifar M, Liao KP, Liu P, Cohen E, Lee BN, Gilmore KR, Eng C. Inflammatory cytokines and toxic effects of oxaliplatin-based chemotherapy in patients with colorectal cancer [abstract]. American Society of Clinical Oncology 47th Annual Meeting, Chicago IL, Jun 3-7, 2011. *J Clin Oncol* 29(15 Suppl), 5/2011; 9094.

Wang XS, Shi Q, Williams LA, Cleeland CS, Mobley GM, Reuben JM, Lee BN, Giralt SA. Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation. *Cancer* 113(8): 2102-2109, 10/2008.

Wang XS, Shi Q, Williams LA, Mao L, Cleeland CS, Komaki RR, Mobley GM, Liao Z. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. *Brain Behav Immun* 24(6): 968-974, 8/2010.

Wang XS, Williams LA, Krishnan S, Liao Z, Liu P, Mao L, Shi Q, Mobley GM, Woodruff JF, Cleeland CS. Serum sTNF-R1, IL-6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. *Brain Behav Immun* 26(5): 699-705, 7/2012.

Wang XS, Shi Q, Dougherty PD, Eng C, Mendoza TR, Williams LA, Fogelman DR, Cleeland CS. Prechemotherapy Touch-Sensation Deficits Predict Oxaliplatin-Induced Neuropathy in Patients with Colorectal Cancer. Oncology. In Press. Published online: 02/17/2016.

Wood LJ, Nail LM, Gilster A, Winters KA, Elsea CR. Cancer chemotherapy-related symptoms:

evidence to suggest a role for proinflammatory cytokines. *Oncol Nurs Forum* 33(3): 535-542, 5/2006.

Yamaki K, Yoshida N, Kimura T, Ohbayashi H, Takagi K. Effects of cytokines and minocycline on subacute lung injuries induced by repeated injection of lipopolysaccharide. *Kansenshogaku Zasshi* 72(1): 75-82, 1/1998.

Yoon SY, Patel D, Dougherty PM. Minocycline blocks lipopolysaccharide induced hyperalgesia by suppression of microglia but not astrocytes. *Neuroscience* 221: 214-224, 9/2012.

Zanjani TM, Sabetkasaei M, Mosaffa N, Manaheji H, Labibi F, Farokhi B. Suppression of interleukin-6 by minocycline in a rat model of neuropathic pain. *Eur J Pharmacol* 538(1-3): 66-72, 5/2006.

Zink MC, Uhrlaub J, DeWitt J, Voelker T, Bullock B, Mankowski J, Tarwater P, Clements J, Barber S. Neuroprotective and anti-human immunodeficiency virus activity of minocycline. *JAMA* 293(16): 2003-2011, 4/2005.