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Olanzapine for the Prevention of Chemotherapy Induced Nausea and Vomiting in Gynecologic Oncology Patients

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Phase III randomized control trial investigating olanzapine for the prevention of chemotherapy induced nausea and vomiting in patients with gynecologic malignancies receiving every 3-week carboplatin and paclitaxel chemotherapy

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Study Drug: Olanzapine, Zyprexa

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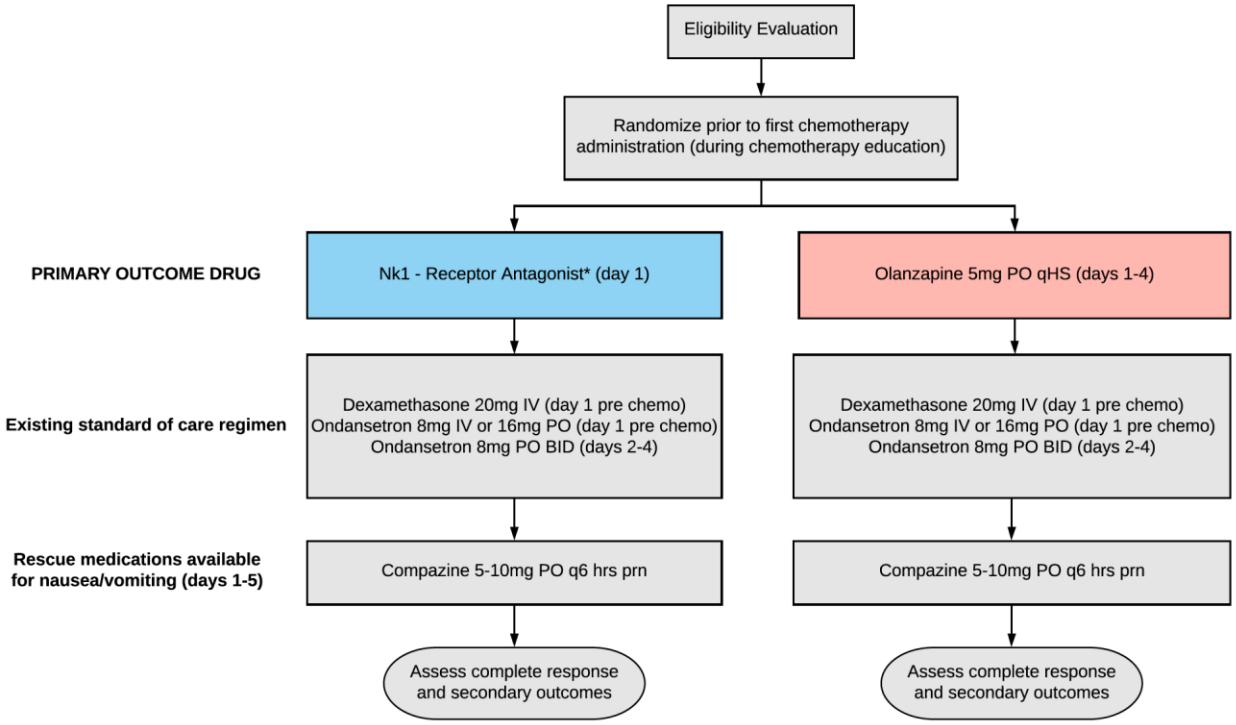
ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
DSMB	Data and Safety Monitoring Board
H&P	History & Physical Exam
IRB	Institutional Review Board
IV (or iv)	Intravenously
NCI	National Cancer Institute
PI	Principal Investigator
p.o.	per os/by mouth/orally
SAE	Serious Adverse Event
UaP	Unanticipated Problem

STUDY SCHEMA



* IV NK1-Receptor Antagonist on formulary

STUDY SYNOPSIS

Title	Phase III randomized control trial investigating olanzapine for the prevention of chemotherapy induced nausea and vomiting in patients with gynecologic malignancies receiving every 3-week carboplatin and paclitaxel chemotherapy
Phase	Phase III
Methodology	Randomized
Study Duration	24 months
Study Center(s)	Single center
Objectives	Primary: To compare complete response (CR - no emetic episodes and no use of rescue medications) between the two arms for the overall (0-120 hours post-chemotherapy) period for patients with gynecologic malignancies receiving every three-week carboplatin / paclitaxel chemotherapy. Secondary: 1) To compare complete response between the two arms for the acute (0-24 hours post-chemotherapy) and delayed (24-120 hours post-chemotherapy) periods. 2) To compare rates of no nausea between the two arms for the acute, delayed, and overall periods. 3) To compare average levels of undesired sedation between the two arms on days 1-5 of chemotherapy. 4) To compare average levels of undesired increased appetite between the two arms on days 1-5 of chemotherapy.
Number of Subjects	170 (85 per arm)

Inclusion Criteria	1. Diagnosis of gynecologic malignancy 2. No chemotherapy in the last 12 months 3. Scheduled to receive Carboplatin (AUC>=4) and Paclitaxel every three weeks 4. Age >= 18 years and <90 5. ECOG performance status 0 or 1 6. English speaking 7. Appropriate laboratory parameters: a. Serum creatinine <= 2.0mg/dL b. AST and ALT <= 3x upper limit of normal c. Absolute neutrophil count (ANC) >= 1000/mm^3 8. No vomiting in the 24hours prior to initiating chemotherapy 9. If childbearing potential exists, negative pregnancy test within 7 days prior to registration
Exclusion Criteria	1. Significant cognitive compromise 2. History of CNS disease (e.g. brain metastases, seizure disorder, dementia) 3. Current or recent (within 30 days) treatment with another antipsychotic agent (antidepressant medications are OK) 4. Concurrent radiotherapy treatment 5. Known hypersensitivity to olanzapine 6. Known cardiac arrhythmia, uncontrolled congestive heart failure or acute myocardial infarction within the last six months 7. History of diabetes mellitus on medication (insulin or oral glycemic agent) 8. Alcohol abuse / chronic alcoholism 9. History of closed angle glaucoma 10. Current enrollment in other clinical trials
Study Product(s), Dose, Route, Regimen	Olanzapine: 5mg per day orally at bedtime for days 1-4 of chemotherapy
Duration of Administration	4 days (with each of six chemotherapy cycles)
Reference Therapy	Nk1 inhibitor (Aprepitant, Fosaprepitant)
Statistical Methodology	Outcomes will be compared between the two arms using chi-square and paired sample t tests. All statistical analyses will be performed using STATA.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Chemotherapy induced nausea and vomiting (CINV) is one of the most feared and distressing side effects of cytotoxic chemotherapy.[1,2] It has significant quality of life (QoL) implications and may interfere with treatment adherence / response.[3–5] CINV is typically classified as either acute (hours 0-24 after chemotherapy administration) or delayed (hours 24-120 after chemotherapy administration). Prophylactic antiemetic regimens are prescribed based on the emetogenic potential of the chemotherapy agent(s). When studying control of CINV, outcomes of interest typically include 1) complete response (CR - no emesis and no use of rescue medications) during the time period(s) of interest and 2) no nausea during the same time period(s).[6]

Improvement in the control of CINV was initially achieved with the use of 5-hydroxytryptamine$_3$ receptor antagonists (5HT$_3$- RA) and dexamethasone. More recently, the addition of neurokinin-1 receptor antagonists (NK1-RA) and/or olanzapine, an antipsychotic which blocks several neurotransmitters, have shown promise in improving control of CINV in highly and/or moderately emetogenic chemotherapy regimens.[6]

In patients with gynecologic malignancies, namely cancer of the ovary (including fallopian tube/primary peritoneal) and uterus, first line chemotherapy typically consists of carboplatin (AUC 5-7) and paclitaxel. Historically, carboplatin fell under the moderately emetogenic classification for which a two-drug antiemetic prophylactic combination was recommended (5HT3-RA and dexamethasone). More recently, it has been recognized that carboplatin doses of AUC >=4 typically result in higher levels of nausea and vomiting than other drugs in the moderate category. As such, the most recent clinical practice update published in 2017 from the American Society of Clinical Oncology (ASCO) made specific recommendations for a three-drug antiemetic prophylactic combination (NK1-RA, 5HT3-RA, and dexamethasone) for chemotherapy regimens including carboplatin AUC >=4. The most recent National Comprehensive Cancer Network (NCCN) guidelines are in agreement with this – despite re-classifying carboplatin AUC >=4 into the highly emetogenic category, they specifically state that the above three-drug regimen is preferred with carboplatin.[7] These recommendations are based on several studies that showed improved complete response with the addition of a NK1-RA to the previously used two drug (5HT3-RA and dexamethasone) regimen for carboplatin AUC >=4.[8-10] This triple-drug antiemetic prophylactic combination is what our institution currently uses as standard of care for the prevention of CINV in gynecologic oncology patients receiving carboplatin and paclitaxel chemotherapy.

NK1-RAs are expensive and despite some improvement in the control of CINV in the gynecologic oncology population, it remains a significant issue (with high

cost) for many patients. Previous studies investigating the prevention of CINV using a triple drug regimen (NK1-RA, 5HT3-RA and dexamethasone) in gynecologic oncology patients receiving carboplatin-based chemotherapy show a wide range of complete response from 62-90% that is, on average, lower than what is reported in other populations. Additionally, investigators note worse control in the delayed versus acute period as well as for nausea specifically, suggesting a need for improvement in this area.[8,9] Unique factors about our patient population that may contribute to these findings include: 1) female patients are at higher risk for CINV, as compared to their male counterparts; and, 2) our population is one of the few intra-peritoneal malignancies that is treated with carboplatin (or another highly emetogenic chemotherapy) in the upfront setting.

The use of olanzapine has been studied primarily in other, non-carboplatin based HEC regimens and has shown improvement in not only CR but also nausea control when compared to non-olanzapine prophylactic regimens.[11–13] A randomized, phase III trial comparing olanzapine to aprepitant (a NK1-RA) for the prevention of CINV in selected HEC regimens (cisplatin or cyclophosphamide and doxorubicin) showed a statistically significant improvement in rates of no nausea (both delayed and overall) in the olanzapine group (69% vs 38%).[14] Given the aforementioned guidelines, olanzapine is not considered standard of care in the gynecologic oncology population and few studies have investigated the use of olanzapine in this context. However, evidence suggests that it could be of substantial benefit and may even be superior to NK1-RAs.

Additionally, few studies have focused on whether the efficacy of antiemetic prophylactic regimens is sustained or varies with subsequent chemotherapy cycles. Limited evidence suggests that both olanzapine and NK1-RAs sustain their effect over subsequent chemotherapy cycles.[14] However, because the sustained response to antiemetic prophylactic regimens is multifactorial -- including, but not limited to, chemotherapy agents used -- it is important to investigate these trends for specific populations of interest. One study evaluating the response to an NK1-RA in the ovarian cancer population found that rates of complete response and no nausea were sustained over six cycles but with a decreasing trend, suggesting the need for more data in this area.

In summary, CINV, and particularly delayed nausea, remains a major issue for many patients with gynecologic malignancies despite the addition of NK1-RAs.[15] Olanzapine has been shown to be effective in controlling CINV in other HEC regimens and may even be superior to NK1-RAs, particularly in nausea control. These data suggest that olanzapine has the potential to provide benefit in our patient population that is 1) more vulnerable to CINV and 2) has a multifactorial etiology of nausea and vomiting, including both burden of intra-abdominal disease as well as chemotherapy. But, few studies have focused on the efficacy of olanzapine within the gynecologic oncology and/or carboplatin based chemotherapy population.[11,16] As such, the purpose of this study is to compare the

efficacy of olanzapine versus an NK1-RA in patients with gynecologic malignancies receiving carboplatin and paclitaxel chemotherapy.

1.2 Study Agent(s) Background and Associated Known Toxicities

Olanzapine is an antipsychotic agent approved by the Food and Drug Administration (FDA) for schizophrenia. It inhibits several neurotransmitter receptors including: dopamine at D_1 - D_4 receptors; serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, and 5-HT_6 receptors; catecholamines at alpha 1-adrenergic receptors; acetylcholine at muscarinic receptors; and histamine at H_1 receptors.[11,12,14] It is thought that olanzapine's activity at multiple receptors, some of which may play a role in nausea and vomiting (namely D_2, 5-HT_{2c}, and 5-HT_3), results in its antiemetic effects.[11,12,14] Several studies have demonstrated it efficacy in improving control of emesis and nausea in CINV involving HEC and MEC regimens.[11]

The most common side effects of olanzapine include short-term mild sedation as well as increased appetite with associated weight gain and increased risk of diabetes mellitus (with prolonged use >6 months).[12] Other known potential toxicities include: dizziness, headache, fatigue, increased prolactin, increased ALT, and weakness. Most of these side effects/toxicities are for chronic, daily use. Given the short term, intermittent nature of olanzapine's use, most of these side effects are not applicable in the context of this study. The major exceptions are its sedation potential and effects on appetite.

The majority of previous studies investigating the use of olanzapine in prophylaxis of CINV used a dose of 10mg with one of the main side effects being increased sedation / somnolence. A recent randomized phase II study compared 5mg and 10mg doses of olanzapine for prophylaxis of CINV in HEC regimens and found that the 5mg dose resulted in higher rates of CR and lower somnolence rates.[17] It was thus recommended that the 5mg dose be used for further phase III studies and is the basis upon which 5mg was chosen for this study. These prior studies also supported the safety of using olanzapine on a short term, intermittent basis in the context of CINV. There were no observed grade 3 or 4 toxicities that were thought to be attributable to olanzapine.[12,14,16]

Pharmacokinetics:

- Absorption: Readily absorbed. Peak concentrations are reached approximately 6 hours after oral dose. Food does not affect absorption.
- Distribution: Half-life is ~21-54 hours. Half-life is 1.5 times longer in elderly patients.
- Metabolism: Significant first pass metabolism (~40% of the dose is metabolized before reaching systemic circulation). Direct glucuronidation and cytochrome P450 mediated oxidation via CYP1A2 (major) and CYP2D6 (minor) are primary metabolic pathways.

- Elimination: Primarily eliminated through the urine. Smoking increases clearance by ~40%. Female sex decreases clearance by 30%.

1.3 Other Agents

Ondansetron

Ondansetron is a 5HT3-RA FDA approved for the prevention of CINV. Recent guidelines from both ASCO and NCCN recommend the use of a 5HT3-RA in prophylactic combination regimens for CINV in both MEC and HEC.[9,10]

Dexamethasone

Dexamethasone is a synthetic glucocorticoid most often used as an anti-inflammatory or immunosuppressive agent. It has also been shown to be effective in preventing both acute and delayed CINV.[18] Similar to ondansetron, recent guidelines from both ASCO and NCCN recommend the use of dexamethasone in prophylactic combination regimens for CINV in both MEC and HEC.[9,10] Given significant side effects associated with dexamethasone, including insomnia, hyperglycemia, indigestion/epigastric discomfort, agitation, increased appetite, weight gain, and acne, effort has been made to try to limit dose and duration of dexamethasone use in CINV by combining it with other effective agents.[10,14] The most recent NCCN and ASCO guidelines suggest that dexamethasone should be limited to day 1 only in patients receiving carboplatin.[9,10]

The dose chosen for this study is also influenced by concomitant use of paclitaxel chemotherapy. In this context, dexamethasone is also used to prevent infusion-related hypersensitivity reactions, for which intravenous and oral regimens exist.[19] Given the oral regimen requires taking multiple doses of dexamethasone prior to chemotherapy, our institution typically gives dexamethasone 20mg IV prior to chemotherapy infusion to avoid compliance issues.

Neurokinin-1 Receptor Antagonists

Fosaprepitant and aprepitant are highly selective substance P neurokinin-1 receptor antagonists which are approved for prevention of acute and delayed CINV. Several studies have supported the efficacy of NK1-RAs in combination with dexamethasone and a 5HT3-RA for prevention of CINV in carboplatin based chemotherapy.[7,8,20] These data are reflected in the most recent ASCO and NCCN guidelines as described above.[9,10]

1.4 Rationale

CINV, and particularly delayed nausea, remains a significant issue for many patients with gynecologic malignancies, despite the costly addition of NK1-RAs as recommended by ASCO and NCCN.[9,15] Olanzapine is recommended for prophylaxis of CINV in other HEC regimens but is not currently standard of care in the gynecologic oncology population. Previous studies comparing olanzapine to an NK1-RA in other HEC regimens show that it may be superior.[10,14] These data suggest that olanzapine has the potential to provide substantial benefit to our

patient population that is 1) more vulnerable to CINV and 2) has a multifactorial etiology of nausea and vomiting including both chemotherapy and burden of intraperitoneal disease. As such, the purpose of this study is to compare the efficacy of olanzapine versus an NK1-RA in patients with gynecologic malignancies receiving every three-week carboplatin and paclitaxel chemotherapy. Additionally, we seek to investigate sustained response of prophylactic regimens over multiple chemotherapy cycles. If an olanzapine triple-drug regimen is superior to a NK-1 RA triple-drug regimen as predicted, there are significant cost-saving implications of this finding. We believe olanzapine has the potential to not only improve the care of our patients but provide a cost-effective alternative to the current standard of care.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1. To compare complete response (CR - no emetic episodes and no use of rescue medications) between the two arms for the overall (0-120 hours post-chemotherapy) period for patients with gynecologic malignancies receiving every three-week carboplatin / paclitaxel chemotherapy.

2.2 Secondary Objectives

1. To compare complete response between the two arms for the acute (0-24 hours post-chemotherapy) and delayed (24-120 hours post-chemotherapy) periods.
2. To compare rates of no nausea between the two arms for the acute, delayed, and overall periods.
3. To compare average levels of undesired sedation between the two arms on days 1-5 of chemotherapy.
4. To compare average levels of undesired increased appetite between the two arms on days 1-5 of chemotherapy.

2.3 Exploratory Objectives

1. To investigate differences in sustained efficacy between the regimens over six cycles of treatment.
2. To investigate the efficacy of adding a fourth agent (whichever drug – olanzapine or NK1-RA – that the patient is not already receiving) to the regimen for those patients that have poor control of CINV with the regimen to which they were randomized.

2.4 Endpoints

Primary Endpoint

Complete response (CR) in the overall time period. CR is defined as no episodes of emesis and no use of rescue medications. Patient reported diaries for days 1-5

of chemotherapy will be used to measure this outcome (patients will complete diaries on days 2-6 about the preceding 24 hours, please see Appendix C - E).

Secondary Endpoints

1. Complete response in the acute and delayed periods. Outcome will be measured using patient reported diaries.
2. No nausea in the acute, delayed and overall time periods. Patients will record daily levels of nausea on days 1-5 of chemotherapy using a Likert scale ranging from 0 to 10 with 0 indicating no nausea and 10 indicating maximum level of nausea.[21] This will be recorded in the patient diaries cited in 2.4.1.
3. Undesired sedation during days 1-5 of chemotherapy. Patients will record levels of undesired sedation each day for days 1-5 of chemotherapy using a Likert scale ranging from 0 to 10 with 0 indicating no undesired sedation and 10 being maximum amount of undesired sedation. This will be recorded in the patient diaries cited in 2.4.1.
4. Undesired increase in appetite during days 1-5 of chemotherapy. Patients will record levels of undesired increase in appetite each day for days 1-5 of chemotherapy using a Likert scale ranging from 0 to 10 with 0 indicating no undesired increase in appetite and 10 being maximum amount of undesired increase in appetite. This will be recorded in the patient diaries cited in 2.4.1.

Exploratory Endpoint

1. Sustained efficacy of each regimen over six cycles of treatment, as defined by maintaining rates of complete response and no nausea
2. Rates of complete response and no nausea in those patients for whom a fourth agent is added in the setting of poorly controlled CINV with the regiment to which they were randomized.

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Inclusion Criteria

1. Diagnosis of gynecologic malignancy
2. No chemotherapy in the last 12 months
3. Scheduled to receive Carboplatin (AUC>=4) and Paclitaxel every three weeks
4. Age >= 18 years and <90
5. ECOG performance status 0 or 1
6. English speaking
7. Willing and able to provide informed consent

8. Appropriate laboratory parameters:

Serum Creatinine	<= 2.0 mg/dL
AST and ALT	<= 3x upper limit of normal
Absolute neutrophil count (ANC)	>= 1000/mm^3

9. No vomiting in the 24 hours prior to initiating chemotherapy
10. If childbearing potential exists (premenopausal with reproductive organs intact), negative pregnancy test within 7 days prior to registration

3.2 Exclusion Criteria

10. Significant cognitive compromise
11. History of CNS disease (e.g. brain metastases, seizure disorder, dementia)
12. Current or recent (within 30 days) treatment with another antipsychotic agent (antidepressant medications are OK)
13. Concurrent radiotherapy treatment
14. Known hypersensitivity to olanzapine
15. Known cardiac arrhythmia, uncontrolled congestive heart failure or acute myocardial infarction within the last six months
16. History of diabetes mellitus on medication (insulin or oral glycemic agent)
17. Alcohol abuse / chronic alcoholism
18. History of closed angle glaucoma
19. Current enrollment in other clinical trials

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

After informed consent is obtained and PRIOR to the initiation of protocol therapy all patients satisfying the inclusion/exclusion criteria must have eligibility confirmed. Once informed consent is obtained and eligibility confirmed, patients will be randomized using a web-based tool, the University of Michigan computerized randomization system (TATUM – "Treatment Assignment Tool – UM"). Subjects will be randomized to either the NK1-RA or Olanzapine arm at a 1:1 allocation ratio. Blocked randomization with random block sizes will be used to ensure group balance. The randomization code will be generated by an independent statistician.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 7 business days of enrollment to the study. Protocol therapy will be administered in relation to single day outpatient chemotherapy for each of six cycles. Patients will be permitted to take rescue antiemetic medication as needed based on clinical circumstances.

REGIMEN DESCRIPTION

Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
Ondansetron	None	8mg IV **OR** 16mg PO	IV **OR** PO	Day 1 pre-chemo	3 weeks (21 days)
		8mg BID	PO	Days 2-4	
Dexamethasone	None	20mg	IV	Day 1 pre-chemo	
NK1-RA on formulary Fosaprepitant	None	150mg	IV	Day 1 pre-chemo	
Olanzapine	Take at night	5mg	PO	Days 1-4	
Compazine	None	5-10mg	PO	Available as prn rescue medication days 1-5	

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.1). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Toxicity Dose Reductions	
CTCAE Grade	**Olanzapine**
0-2	No change from original starting dose
3	Hold until resolved to ≤ Grade 2, then resume 5mg dose
Second episode of grade 3 or 1st episode 4 toxicity	Hold until resolved to ≤ Grade 2, then resume 5mg dose
Third episode of grade 3 or 2nd episode 4 toxicity	Remove subject from treatment

5.3 Concomitant Medications/Treatments

The following concomitant drugs and/or treatments are prohibited:

1. Any antipsychotic agent (anti-depressant medications are OK)

The following concomitant drugs and/or treatments may be used, but only with caution:

1. Fluvoxamine - decreases clearance of olanzapine. Dose reductions should be considered
2. Diazepam - may potentiate orthostatic hypotension that can be observed with olanzapine

3. Antihypertensives, CNS acting medications, alcohol - olanzapine may potentiate the effects of these medications
4. Levodopa and dopamine agonists- olanzapine may antagonize the effects
5. Carbamazepine: increased olanzapine clearance

5.4 Duration of Therapy

Olanzapine will be given for 4 days with each chemotherapy cycle. In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles or until one of the following criteria apply:

- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient voluntarily withdraws from treatment **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.5 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.4 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.6. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.6 Duration of Follow-Up

Patients will not be followed after removal from treatment. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.7 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

1. Patient withdraws consent (termination of treatment and follow-up);

2. Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;

3. Patient is unable to comply with protocol requirements;

4. Treating physician judges continuation on the study would not be in the patients' best interest;

5. Patient becomes pregnant (pregnancy to be reported per institutional guidelines);

6. Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

7. Termination of the study by The University of Michigan, Sponsor, or the FDA;

8. Patient completes protocol treatment and follow-up criteria.

5.8 Patient Replacement

Patients will not be replaced.

6.0 STUDY PROCEDURES

6.1 Time and Events Table

	Pre-study	Pre-Chemo[3]	Day 1[3]	Days 2-4	Days 5-6	Follow-Up
Assessment	X					
Informed Consent	X					
History and PE Height & Weight	X					
Performance Status	X					
Toxicity Evaluations		X[5]		X[6]	X[6]	X[3]
Baseline patient questionnaire	X					
Pre chemo questionnaire			X			
Patient Diaries				X[3]	X[3]	
CBC[1]	X	X				
Randomization	X					
Concomitant Medication Review	X		X			
Contraceptive Counseling[4]	X					
Differential[1]	X	X				
CMP[1]	X	X				
Pregnancy Test[2]	X		X			
Study Drug Administration			X	X[3]		

[1]Routinely ordered prior to chemotherapy. Will not be ordered separately for the study.
[2]For all women of childbearing potential, as defined above
[3]For each of six cycles

[4]For women of childbearing potential (premenopausal with reproductive organs intact), contraceptive counseling will occur at time of informed consent and pregnancy testing.
[5]Cycles 2-6
[6]Cycle 1 only (patient phone calls only scheduled for cycle 1)

7.0 MEASUREMENT OF EFFECT

Protocol therapy will be administered in relation to single day outpatient chemotherapy for each of six cycles. Patient demographic information (age, height, weight, BMI, race/ethnicity), relevant co-morbid diseases, and malignancy related factors (primary site of disease, whether they have had prior chemotherapy and when, whether current chemotherapy is neoadjuvant or adjuvant therapy, current burden of disease, ECOG performance status) will be obtained through a combination of baseline patient questionnaires (see Appendix A) and extraction from the electronic medical record. Data for primary and secondary outcomes will be collected through patient diaries, which contain questionnaires that ask about daily episodes of emesis, use of rescue medications, and daily levels of nausea, undesired sedation, and undesired increase in appetite (see Appendix C - E). Patients will be given a booklet with each chemotherapy cycle to complete and bring with them to their next visit for the subsequent chemotherapy cycle. The baseline questionnaire (Appendix B) will be completed on the day of chemotherapy, prior to treatment for every cycle. They will then receive daily text reminders to complete the questionnaire for each of five days after chemotherapy. Because our analyses of primary and secondary outcomes will focus mainly on data from cycle one, a study team member will also call the patients daily to remind them to complete their questionnaires (in addition to sending text reminders, see Appendix F). Patients will receive text reminders only for cycles 2-6.

Our analyses of primary and secondary outcomes will focus on data from cycle 1. Data will be collected through all 6 cycles to allow for identification of variation over time. Additionally, for patients that have poor control of CINV (>=2 episodes of emesis in 1 day and/or use of >2 rescue medications/day for >=2 days for emesis or nausea and/or any emergency room/urgent care visits for nausea/vomiting), the agent they are not receiving (olanzapine or NK1-RA) will be added so that they receive a four drug regimen for their next cycle (also an NCCN approved prophylactic regimen). We will then assess for improved control of CINV in subsequent cycles.

7.1 Safety/Tolerability

Analyses will be performed for all patients having received at least one cycle of study drug. The study will use the CTCAE version 5.0 for reporting of adverse events.

8.0 ADVERSE EVENTS

8.1 Experimental Therapy

Not applicable.

8.2 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment through 30 days after the last cycle. Any serious adverse event that occurs more than 30 days after the last study treatment and is considered related to the study treatment must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.2, occurring from the initial study treatment administration through 30 days following the last cycle of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event.

8.3 Definitions

1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or

disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

1. Serious Adverse Event

An adverse event is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event
  An adverse even is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be

considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

2. Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

3. Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.4 Adverse Event Characteristics

1. CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site. (http://ctep.cancer.gov)

2. Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

8.5 Serious Adverse Event Reporting Guidelines

1. The Principal Investigator must be notified within 1 business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of attribution, occurring during the study or within 30 days of the last administration of the study related treatment.

2. The investigator must report all events meeting the criteria and definition of a serious adverse event as per the local IRB reporting requirements.

8.6 Routine Reporting

All other adverse events are to be reported annually as part of regular data submission as per institutional guidelines**.**

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB according to the local IRB policies.

8.8 Stopping Rules

Given overall moderate risk of this study as well as non-safety endpoints, we do not anticipate needing to interrupt or stop this study.

9.0 DRUG INFORMATION

9.1 Olanzapine

- Other names for the drug: Zyprexa
- Description: 5mg tablets, 12 tablets per bottle
- Classification - type of agent: Atypical antipsychotic
- Mode of action: Neurotransmitter receptor antagonist with action against several neurotransmitters including: dopamine at D_1 - D_4 receptors; serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, and 5-HT_6 receptors; catecholamines at alpha 1-

adrenergic receptors; acetylcholine at muscarinic receptors; and histamine at H_1 receptors

- Pharmacokinetics:
  - Absorption: Readily absorbed. Peak concentrations are reached approximately 6 hours after oral dose. Food does not affect absorption.
  - Distribution: Half-life is ~21-54 hours. Half-life is 1.5 times longer in elderly patients.
  - Metabolism: Significant first pass metabolism (~40% of the dose is metabolized before reaching systemic circulation). Direct glucuronidation and cytochrome P450 mediated oxidation via CYP1A2 (major) and CYP2D6 (minor) are primary metabolic pathways.
  - Elimination: Primarily eliminated through the urine. Smoking increases clearance by ~40%. Female sex decreases clearance by 30%.

- Contraindications: There are no absolute contraindications. See exclusion criteria and restricted concomitant medications/treatments above.

- Warnings and Precautions:
  - Significant cognitive compromise
  - Elderly patients with dementia: increased risk of death and cerebrovascular disease
  - Metabolic changes: prolonged use associated with increased risk of diabetes mellitus
  - Orthostatic hypotension: use with caution in patients with diseases that could affect hemodynamic compromise
  - History of seizures: use with caution as may lower seizure threshold
  - Hyperprolactinemia: may increase prolactin level

- Side effects: Please see a complete list of potential side effects in FDA package insert for olanzapine. Side effects most likely to occur in the context of short-term, intermittent use in this study include somnolence and increased appetite.

- Drug Interactions:
  - Diazepam: may potentiate orthostatic hypotension
  - Alcohol: may potentiate orthostatic hypotension
  - Carbamazepine: increased olanzapine clearance
  - Fluvoxamine: may increase olanzapine levels
  - CNS acting drugs: caution should be used with other centrally acting drugs
  - Antihypertensives: may potentiate orthostatic hypotension
  - Levodopa and dopamine agonists: olanzapine may antagonize their effects
  - Other antipsychotics: based on specific antipsychotic agent (see package insert for specific drug)

- Storage and Stability: Store at room temperature (20-25^{o} C)

- Preparation and Dispensing: Olanzapine will be prescribed and provided by the patient's pharmacy per their standard preparation and dispensing protocols.

- Availability: commercially available

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

Study Design: Randomized controlled trial
Study Endpoints:

Primary Endpoint: Complete response in the overall time period.
Secondary Endpoints: 1) Complete response in the acute and delayed time periods; 2) No nausea in the acute, delayed, and overall time periods; 3) Undesired sedation during days 1-5 of chemotherapy; and 4) Undesired increase in appetite during days 1-5 of chemotherapy.

10.2 Sample Size and Accrual

A prior study investigating the use of an NK1-RA in carboplatin-based chemotherapy found a complete response rate of 80% in those that received the NK1-RA in combination with a 5HT3-RA and dexamethasone. We considered a 15% change in this proportion to be clinically meaningful. Using nQuery 8.4.1.0, we calculated that we would need a sample size of 152 patients (76 per arm) to obtain 80% power with a Type 1 error level of 0.05. We then increased the total number of patients to account for a 10% dropout rate.

A subject is considered evaluable if they complete cycle 1 of carboplatin and paclitaxel chemotherapy. Dose reductions in chemotherapy agents are allowed per standard clinical protocols.

10.3 Data Analyses Plans

The proportion of patients with complete response and no nausea will be calculated for the acute, delayed and overall periods in both arms. Proportions will be compared using a chi-square test using a significance level of 0.05%.

Baseline rates of somnolence and increased appetite will be assessed prior to each cycle of chemotherapy (Appendix B). Mean somnolence and increased appetite scores for each day of chemotherapy will be compared to baseline means using paired t-tests.

The proportion of patients with complete response and no nausea in each arm will be calculated for six cycles. To investigate the sustained efficacy of each regimen, the proportions will be compared within each arm over six cycles using repeated measures of variance.

For patients with uncontrolled CINV, as defined above, and for whom a fourth prophylactic agent is added in a subsequent cycle, complete response and rates of no nausea will be compared before and after the addition of the fourth agent using McNemar's test.

11.0 DATA AND SAFETY MONITORING

The study team will meet every 3 months or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants, validity and integrity of the data, enrollment rate relative to expectations, characteristics of the participants, retention of participants, adherence to protocol, and data completeness. At these meetings, a report will be drafted with this information and submitted to an independent Data and Safety Monitoring Board (DSMB).

The data, safety and quality of the trial will be monitored through an independent, external DSMB. The DSMB will include experts in oncology, biostatistics, and safety who are not participating in this trial and do not have affiliation with the Sponsor or other significant conflicts of interest.

The DSMB will consist of the following members:

Michael Frumovitz, MD MPH, Gynecologic Oncologist, MD Anderson Cancer Center

Ritu Salani, MD MBA, Gynecologic Oncologist, OSU Cancer Center

Rebecca Stone, MD MS, Gynecologic Oncologist, Johns Hopkins

Colleen Rivard, MD, Gynecologic Oncologist, University of Minnesota

Leslie Clark, MD, Gynecologic Oncologist, University of North Carolina

Sarah Monsell, Biostastician, University of Washington

DSMB meetings will be held approximately every 3 months. Ad hoc meetings will take place if needed. DSMB recommendations will be provided to the PI and submitted to IRBMED per institutional guidelines.

12.0 REFERENCES

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13.0 APPENDICES

Appendix A. Baseline patient questionnaire

Date: _____/_____/_____
Age: _____

Race/Ethnicity:

- ☐ White
- ☐ Black
- ☐ Asian
- ☐ American Indian or Alaska Native
- ☐ Other: _____

Health history (*please indicate whether you have any of the following conditions):*

- ☐ Gastric ulcers
- ☐ Gastroparesis (delayed stomach emptying)
- ☐ Irritable bowel syndrome
- ☐ Cyclical vomiting syndrome
- ☐ History of prolonged nausea/vomiting with pregnancy (e.g. hyperemesis gravidarum)

Social history:

Do you currently smoke tobacco? ☐ Yes ☐ No
If "yes", how many cigarettes per day: _____

Do you currently smoke marijuana? ☐ Yes ☐ No
If "yes", how much per day: _____

Appendix B. Pre-chemotherapy patient questionnaire

Date: _____/_____/_____

For the following 3 questions, please circle the one number (0-10) that best describes the way you felt over the *past 24 hours*.

1. Please rate your worst nausea over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No nausea at all										Nausea as bad as it can be

2. Please rate any undesired sedation that you had over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No undesired sedation at all										Undesired sedation as bad as it can be

3. Please rate any undesired appetite increase that you had over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No undesired appetite increase at all										Undesired appetite increase as bad as it can be

Appendix C. Daily patient questionnaire (day 2)

Date: _____/_____/_____

Please verify that you took the following medications as prescribed in the preceding 24 hours:

If in Olanzapine arm:
Olanzapine 5mg at night: ☐ Yes ☐ No
If "no", please provide reason: _____

Check one option in each box, then continue and answer questions 1-3 below.

	*Vomiting (check one)	#of **EXTRA** nausea/vomiting pills (Compazine) taken because you developed nausea/vomiting
Last 24 hours	__None __Once __Twice __More than twice, please indicate amount: ___	__None __One __Two __More than two, please indicate amount: ___

*A single episode of vomiting is defined as:

- a single vomit of sold or liquid stomach contents
- a single retch, or 'dry heave', that did not produce solid or liquid stomach contents
- any episode of continuous vomiting or retching

Note: episodes separated from each other by the absence of retching or vomiting for at least 1 minute should be considered separate emetic episodes

For the following 3 questions, please circle the one number (0-10) that best describes the way you felt over the *past 24 hours*.

1. Please rate your worst nausea over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No nausea at all										Nausea as bad as it can be

2. Please rate any undesired sedation that you had over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No undesired sedation at all										Undesired sedation as bad as it can be

3. Please rate any undesired appetite increase that you had over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No undesired appetite increase at all										Undesired appetite increase as bad as it can be

Appendix D. Daily patient questionnaire (days 3-5)

Date: _____/_____/_____

Please verify that you took the following medications as prescribed in the preceding 24 hours:

Ondansetron 8mg twice a day: ☐ Yes ☐ No
If "no", please provide reason: _____

If in Olanzapine arm:
Olanzapine 5mg at night: ☐ Yes ☐ No
If "no", please provide reason: _____

Check one option in each box, then continue and answer questions 1-3 below.

	*Vomiting (check one)	#of **EXTRA** nausea/vomiting pills (Compazine) taken because you developed nausea/vomiting
Last 24 hours	__None __Once __Twice __More than twice, please indicate amount: ___	__None __One __Two __More than two, please indicate amount: ___

*A single episode of vomiting is defined as:

- a single vomit of sold or liquid stomach contents
- a single retch, or 'dry heave', that did not produce solid or liquid stomach contents
- any episode of continuous vomiting or retching

Note: episodes separated from each other by the absence of retching or vomiting for at least 1 minute should be considered separate emetic episodes

For the following 3 questions, please circle the one number (0-10) that best describes the way you felt over the *past 24 hours*.

1. Please rate your worst nausea over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No nausea at all										Nausea as bad as it can be

2. Please rate any undesired sedation that you had over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No undesired sedation at all										Undesired sedation as bad as it can be

3. Please rate any undesired appetite increase that you had over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No undesired appetite increase at all										Undesired appetite increase as bad as it can be

Appendix E. Daily patient questionnaire (day 6)

Date: _____/_____/_____

Check one option in each box, then continue and answer questions 1-3 below.

	*Vomiting (check one)	#of **EXTRA** nausea/vomiting pills (Compazine) taken because you developed nausea/vomiting
Last 24 hours	__None __Once __Twice __More than twice, please indicate amount: ___	__None __One __Two __More than two, please indicate amount: ___

*A single episode of vomiting is defined as:

- a single vomit of sold or liquid stomach contents
- a single retch, or 'dry heave', that did not produce solid or liquid stomach contents
- any episode of continuous vomiting or retching

Note: episodes separated from each other by the absence of retching or vomiting for at least 1 minute should be considered separate emetic episodes

For the following 3 questions, please circle the one number (0-10) that best describes the way you felt over the *past 24 hours*.

1. Please rate your worst nausea over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No nausea at all										Nausea as bad as it can be

2. Please rate any undesired sedation that you had over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No undesired sedation at all										Undesired sedation as bad as it can be

1. Please rate any undesired appetite increase that you had over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No undesired appetite increase at all										Undesired appetite increase as bad as it can be

Appendix F. Research Coordinator Contact Form

Day of Telephone Contact (*check one*):
☐ Day 2 ☐ Day 3 ☐ Day 4 ☐ Day 5 ☐ Day 6

Date of telephone contact or date of attempted contact: _____/_____/_____

Were you able to contact the patient? ☐ Yes ☐ No
If yes, list time of day contacted: ___:___

*Please remind the patient to complete their questionnaire. Offer to go through the questionnaire with them over the phone and have them fill it out at the same time. Please explain the rescue nausea medication information specifically "number of **extra (PRN)** nausea and vomiting pills taken."*

Please also ask about adverse events and answer the following:

Did patient have any adverse events? (*check one*) ☐ Yes ☐ No
If yes, fill out AE: Record all adverse events, including event, grade, and attribution.

Comments:
_____
_____