ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A221602

OLANZAPINE WITH OR WITHOUT FOSAPREPITANT FOR THE PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV) IN PATIENTS RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPY (HEC): A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Supplied agent(s): olanzapine (Alliance IND 120137; NSC 754829)

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Activation
[ ] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[X] Informed Consent changes	[ ] Suspension / temporary closure
[ ] Scientific / Statistical Considerations changes	[ ] Reactivation
[ ] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[ ] Other:	

If your site utilizes the CIRB as your IRB of record

No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial.

The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

If your site utilizes a local IRB as your IRB of record

IRB approval (or disapproval) is required within 90 days. Please follow your local IRB guidelines. Expedited IRB Approval is allowed. The proposed changes in this amendment are minor and do not affect the overall risk/benefit ratio.

Re-consent is not required by the Alliance. Please follow the policy of your IRB of record regarding notifying patients of new information contained in this update.

UPDATES TO THE PROTOCOL:

Cover Page (p. 1)

- The email address for [redacted] has been updated.
- [redacted]

Protocol Contacts (p. 2)

- [redacted]
- [redacted]

Section 3.2.20 Required Initial Laboratory Values (p. 18)
"Serum Creatinine" has been updated to "Serum or Plasma Creatinine."

Section 13.9 Inclusion of Women and Minorities (pp. 67-68)
The second sentence in the "Black or African American" definition has been removed.

UPDATES TO THE MODEL CONSENT FORM:

What extra exams, tests, and procedures are involved in this study? (pp. 82-83)
Under "You will be asked to complete the surveys at the following time points," in the last bullet point, "the University of Chicago" has been corrected to "Wayne State University."

Who will see my medical information? (pp. 86-87)
The Certificate of Confidentiality language has been removed, and the first paragraph has been updated with the current NCI informed consent template language.

Where can I get more information? (p. 87)
The second paragraph has been updated with the current NCI informed consent template language.

A replacement protocol document has been issued

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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Supplied agent(s): olanzapine (Alliance IND 120137; NSC 754829)

ClinicalTrials.gov Identifier: NCT03578081

Study Chair

[redacted]

Community Oncology Co-chair

[redacted]

Pharmacogenetics Co-chair

[redacted]

Clinical Economics Co-chair

[redacted]

Health Outcomes Co-chair

[redacted]

Symptom Intervention Committee Chair

[redacted]

Primary Statistician

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Secondary Statistician

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Data Manager

[redacted]

Protocol Coordinator

[redacted]

Participating Organizations

Alliance/Alliance for Clinical Trials in Oncology, ECOG-ACRIN/ ECOG ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/ SWOG

Study Resources:

Expedited Adverse Event Reporting [redacted]	**Medidata Rave® iMedidata portal** [redacted]
OPEN (Oncology Patient Enrollment Network) [redacted]	**Biospecimen Management System** [redacted]

Protocol Contacts:

A221602 Nursing Contacts

[redacted]

A221602 Pharmacy Contact

[redacted]

Alliance Biorepository at Mayo Clinic

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Roxann Neumann [redacted]
Questions regarding drug supply & administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. [redacted] Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website [redacted]). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
Institutions will order the following supplies from the CTSU Operations Office: Questionnaire booklets. Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.		
For clinical questions (i.e. patient eligibility or treatment-related): See Protocol Contacts (page 2)		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		

OLANZAPINE WITH OR WITHOUT FOSAPREPITANT FOR THE PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING (CINV) IN PATIENTS RECEIVING HIGHLY EMETOGENIC CHEMOTHERAPY (HEC): A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

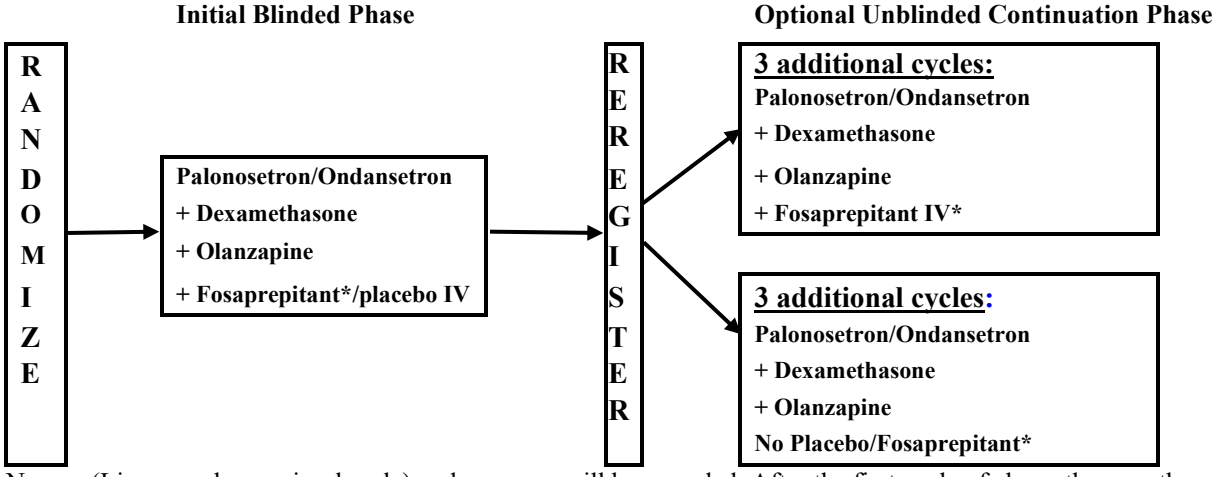
Eligibility Criteria (see Section 3.2)

- Diagnosis of malignant disease.
- No prior history of systemic chemotherapy for any malignancy
- Scheduled to receive IV HEC (either cisplatin-containing regimen or doxorubicin and cyclophosphamide [AC]). (See Section 3.2.3 for additional details)

Required Initial Laboratory Values	
Serum Creatinine	≤2.0 mg/dL
AST or ALT	≤3 x upper limit of normal (ULN)

- No nausea or vomiting ≤24 hours prior to registration.
- Negative pregnancy test (serum or urine) done ≤7 days prior to registration (See Section 3.2.5).
- No known diagnosis of dementia. (See Section 3.2.6)
- No known history of CNS disease (e.g. seizure disorder).
- No treatment with another antipsychotic agent (see Section 3.2.8)
- No chronic phenothiazine administration as an antipsychotic agent (see Section 3.2.9).
- No use of amifostine within 7 days prior to registration.
- No radiotherapy within 7 days prior to registration or planned for one week after the current dose of chemotherapy.
- No use of quinolone antibiotic therapy within 7 days prior to registration.
- No chronic alcoholism (as determined by the investigator).
- No known hypersensitivity to olanzapine.
- No known cardiac arrhythmia, uncontrolled congestive heart failure or acute myocardial infarction within the previous six months.
- No history of uncontrolled diabetes, i.e., no diabetic ketoacidosis; (See Section 3.2.16)
- Age ≥18 years.
- ECOG Performance Status 0, 1 or 2
- Patients must be able to read and comprehend English (See Section 3.2.19)

Schema



Nausea (Linear analogue visual scale) and response will be recorded. After the first cycle of chemotherapy, the patient will be given the option to continue on the same antiemetic regimen for a maximum of three additional cycles. If the patient agrees, he/she will be unblinded (See Section 8.2.2), re-registered (see Section 4.7.1), and allowed to continue for three additional cycles and evaluated for efficacy and any adverse events.

* Aprepitant IV may be used in place of Fosaprepitant IV for sites that have adopted use of Aprepitant.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Table of Contents

1.0 BACKGROUND

1.1. Introduction

Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life and is perceived by patients as a major adverse effect of the treatment [1]. The use of 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists plus dexamethasone has significantly improved the control of acute CINV [1,2]. Studies have demonstrated additional improvement in the control of acute CINV and also delayed CINV with the use of palonosetron, a second generation 5-HT$_3$ receptor antagonist [3], neurokinin-1 (NK-1) receptor antagonists [4,5], and olanzapine, an antipsychotic which blocks multiple neurotransmitters in the central nervous system [6-11].

1.2 Olanzapine Overview

Olanzapine is an FDA-approved antipsychotic that blocks multiple neurotransmitters: dopamine at D1, D2, D3, D4 brain receptors, serotonin at 5-HT$_{2a}$, 5-HT$_{2c}$, 5-HT$_3$, 5-HT$_6$ receptors, catecholamines at alpha1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors [12,13]. Common side effects are sedation and weight gain [14, 15], as well as an association with the onset of diabetes mellitus [16]. Olanzapine's activity at multiple receptors, particularly at the D2, 5-HT$_{2c}$, and 5-HT$_3$ receptors which appear to be involved in nausea and emesis, suggests that this drug may have significant anti-emetic properties.

1.3 Olanzapine and chemotherapy-induced nausea and vomiting

1.3.1 Olanzapine, when added to a 5HT3 receptor antagonist, an NK-1 receptor antagonist (NK1RA), and a corticosteroid, decreases nausea and improves complete response rates

A recently-reported Alliance trial of olanzapine for chemotherapy-induced nausea and vomiting provided a positive result. This was presented at the ASCO Palliative Care Meeting in October 2015 [9]. The manuscript for this trial is now published [11]

This trial demonstrated that olanzapine, when added to a 5-HT3 receptor antagonist, aprepitant/fosaprepitant and dexamethasone, did substantially improve the complete response (CR) rate (no vomiting and no use of rescue medications) and substantially improved the number of patients who had no nausea through the 5-day period of time following the single dose of chemotherapy, when compared to a placebo. The results from this trial, and other recently-reported ones, raise additional interesting questions regarding olanzapine for treating nausea and vomiting related to chemotherapy. These data are summarized in a recently published review manuscript [17].

1.3.2 Pilot data support that olanzapine, when directly compared to an NK-1 receptor antagonist, decreases nausea and provides equivalent complete response rates

A recent single institution phase III trial demonstrated that olanzapine, when combined with a single dose of dexamethasone and a single dose of palonosetron, was very effective in controlling acute and delayed CINV in patients receiving highly emetogenic chemotherapy (HEC) [6] as illustrated in Figures 1a and 1b. Compared to aprepitant, palonosetron, and dexamethasone, the olanzapine, palonosetron, and dexamethasone regimen resulted in equivalent complete responses (no vomiting and no rescue medications) to the aprepitant regime, but was significantly better in controlling nausea. There was excellent control of nausea without the use of multiple days of dexamethasone. These results were confirmed in a recently published randomized, double-blind, phase III, single institution study [10] comparing olanzapine to fosaprepitant in patients with

esophageal or head and neck cancer receiving concurrent chemotherapy and radiation therapy.

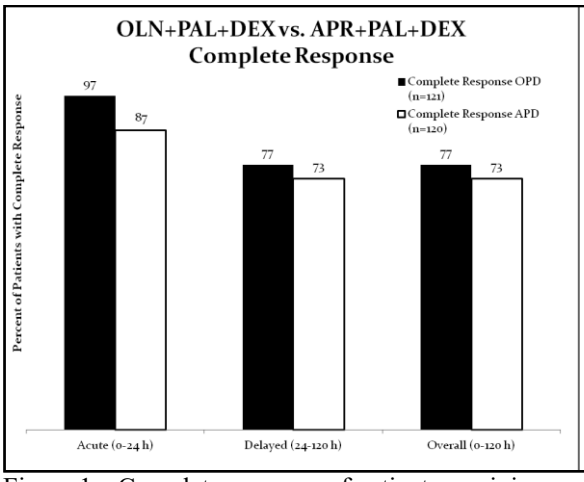


Figure 1a. Complete response of patients receiving olanzapine, palonosetron, and dexamethasone or aprepitant, palonosetron, and dexamethasone prior to HEC.

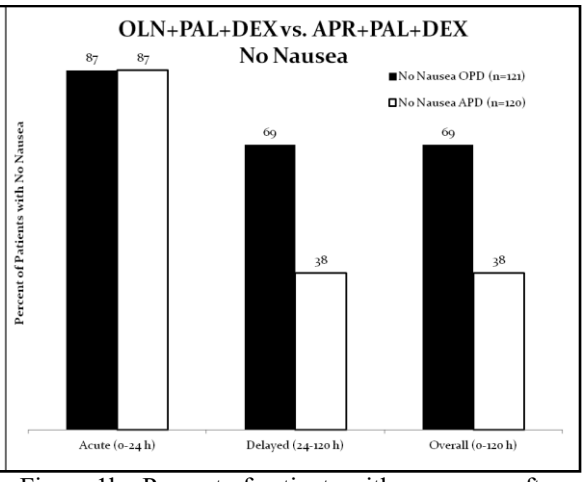


Figure 1b. Percent of patients with no nausea after receiving olanzapine, palonosetron, and dexamethasone or aprepitant, palonosetron, and dexamethasone.

In addition, another phase III study showed that the addition of olanzapine, to the 5-HT3 receptor antagonist azasetron and dexamethasone, improved delayed CINV in patients receiving HEC (Figures 2a and 2b) or moderately emetogenic chemotherapy (MEC) (Figures 3a and 3b) [7].

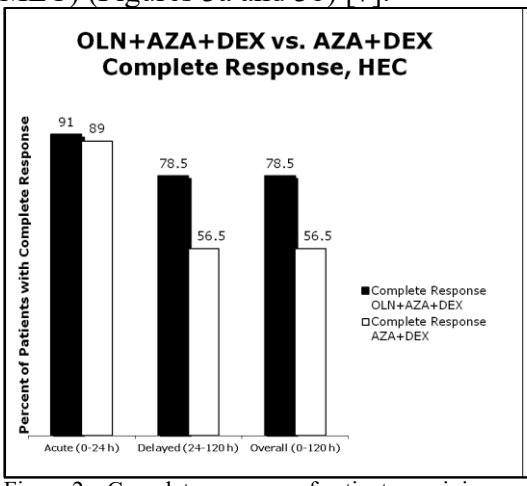


Figure 2a. Complete response of patients receiving olanzapine, azasetron, and dexamethasone or azasetron and dexamethasone prior to HEC.

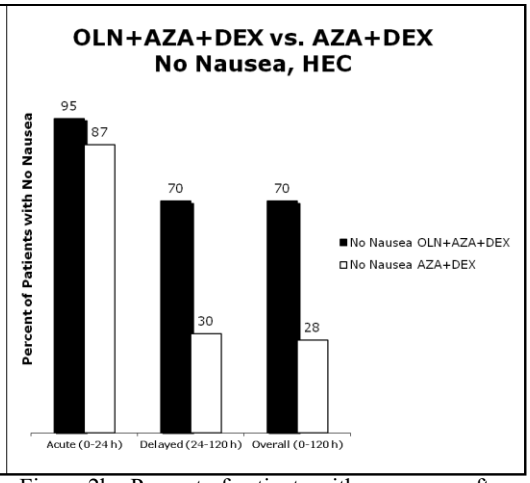


Figure 2b. Percent of patients with no nausea after receiving olanzapine, azasetron, and dexamethasone or azasetron, and dexamethasone.

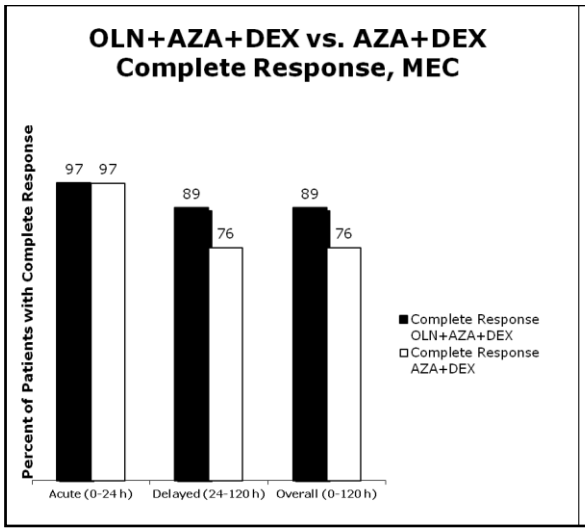


Figure 3a. Complete response of patients receiving olanzapine, azasetron, and dexamethasone or azasetron and dexamethasone prior to MEC

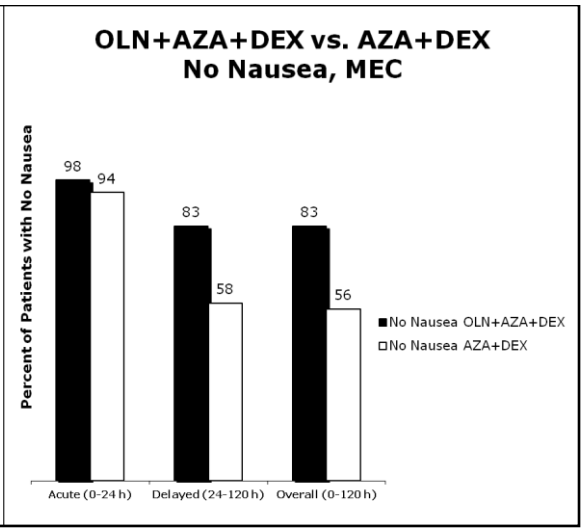


Figure 3b. Percent of patients with no nausea after receiving olanzapine, azasetron, and dexamethasone or azasetron, and dexamethasone.

1.3.3 Randomized data support that olanzapine, when added to palonosetron and dexamethasone (without an NK1RA), markedly improves platinum-caused nausea and vomiting.

A recent randomized controlled (but not patient blinded) trial, involving 100 patients receiving a variety of platinum-based treatments, reported that olanzapine, when added to palonosetron and dexamethasone (without an NK-1 receptor antagonist), led to a complete response rate of 96%, compared to 42% in a control group ($p < 0.0001$), with a corresponding improvement in nausea control ($p < 0.0001$) [32].

1.3.4 Olanzapine appears to be effective for treating breakthrough chemotherapy-induced nausea and vomiting (chemotherapy-induced nausea and vomiting despite previous prophylactic treatment).

A recent study compared olanzapine to metoclopramide for the treatment of breakthrough emesis and nausea in patients receiving HEC and guideline-directed antiemetic prophylaxis [18]. Olanzapine was significantly better than metoclopramide for the treatment of breakthrough emesis and nausea. This was the first phase III study on the treatment of breakthrough emesis and nausea (Figure 4).

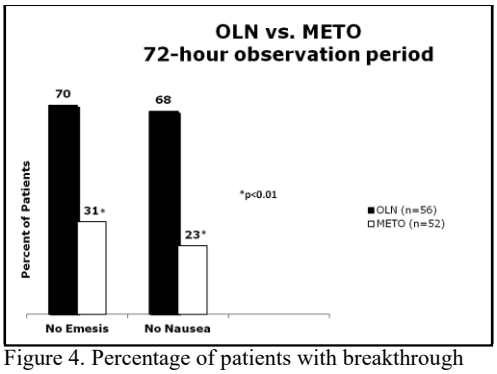


Figure 4. Percentage of patients with breakthrough CINV treated with olanzapine (OLN) or metoclopramide (METO) with no emesis or no nausea over a 72 hour observation period.

1.3.5 Olanzapine may be effective in treating nausea and vomiting in cancer patients with advanced disease

Olanzapine appears to be helpful for treating nausea and vomiting, unrelated to chemotherapy, in patients with advanced disease.

Davis et al.[19] have reported a systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation. There have been case reports on the use of olanzapine as an anti-nausea agent for oncology conditions other than CINV [20-22]. These reports support that olanzapine was effective in treating patients with chronic nausea receiving palliative care, effective for intractable nausea due to opioids, neoplasm, and/or medications, and in controlling refractory nausea and vomiting in patients with advanced cancer [20-22]. An Alliance sponsored pilot placebo-controlled clinical trial is underway to study the use of olanzapine in this situation.

1.4 NK-1 receptor antagonists

Information known about the use of NK-1 receptor antagonists (i.e., aprepitant, fosaprepitant, rolapitant, netupitant) for preventing chemotherapy-induced nausea and vomiting, without concurrent use of olanzapine:

There are substantial data demonstrating the efficacy of NK-1 receptor antagonists (aprepitant, fosaprepitant, rolapitant, and netupitant) for decreasing vomiting in both the acute and delayed phases, with more benefit in the delayed phase. These drugs are virtually always given with the 5-HT3 receptor antagonist and dexamethasone [17]. The literature also demonstrates that the available NK-1 receptor antagonists (aprepitant, netupitant, and rolapitant) are not effective in controlling nausea, suggesting that the NK-1 receptor may not play an important role in nausea control [17].

1.5 Chemotherapy-induced nausea and vomiting guidelines in 2016/early 2017

Information known about chemotherapy-induced nausea and vomiting guidelines in 2016/early 2017:

1.5.1 NK-1 receptor antagonists, without the concurrent use of olanzapine, are still recommended as prophylaxis for patients receiving highly emetogenic chemotherapy

All guidelines standardly recommend NK-1 receptor antagonists, without the concurrent use of olanzapine for patients receiving highly emetogenic chemotherapy [17, 23-25].

1.5.2 Olanzapine, without the concurrent use of NK-1 receptor antagonists, are only recommended by NCCN guidelines [26]

NCCN antiemetic guidelines are the only published antiemetic guidelines to recommend the use of olanzapine, in lieu of aprepitant, as an option for the prevention of chemotherapy-induced nausea and vomiting. This recommendation was based on the randomized data discussed above [6], prior to the availability of the 2016 Alliance publication regarding olanzapine [11].

1.5.3 Olanzapine, with the concurrent use of an NK-1 receptor antagonist, is not recommended as a regimen of choice in MASCC/ESMO antiemetic guidelines that were published in January 2017

Despite the new information from the NCI-supported Alliance trial, that was publically available at the time that MASCC-ESMO guidelines were updated in 2016, the use of olanzapine, for preventing nausea and vomiting in patients receiving highly emetogenic chemotherapy, was not recommended in their most recent antiemetic recommendations published in 2017, noting that this drug could be considered in patients, 'particularly when nausea is an issue' [23].

1.5.4 Olanzapine has been recommended for the treatment of established chemotherapy-induced nausea and vomiting, occurring despite the use of prophylactic treatment

NCCN guidelines do recommend the use of olanzapine for treatment of established chemotherapy-induced nausea and vomiting, occurring despite the use of prophylactic treatment [26].

1.6 Rationale for current study

1.6.1 Introductory comments

While it is clear that olanzapine has definite efficacy for the prevention of chemotherapy-induced nausea and vomiting, it is clear that the full utility of this drug in this situation has not been realized. The study of olanzapine, a generic agent in this clinical trial is very cost effective when compared to a number of other available antiemetic agents that have been the objects of pharmaceutical company-sponsored clinical trials.

1.6.2 Now that it has been established that olanzapine decreases nausea and vomiting in patients receiving highly emetogenic chemotherapy, when given with an expensive NK-1 receptor antagonist, how would it perform without the use of the expensive NK-1 receptor antagonist?

We now have data from two different clinical trial designs that support that olanzapine-containing regimens performed better than regimens that did not include olanzapine. The first of these is from our recent manuscript that demonstrated that olanzapine added to the previous standard NK-1 receptor antagonist-based regimen was more effective than placebo for the prevention of nausea and vomiting [11]. The second of these clinical trial designs consists of the above-noted randomized, controlled (but not definitive) trials that support that olanzapine is better than a standard NK-1 receptor antagonist-based regimen [6,10]. Additionally, as noted above, a recent randomized controlled (but not patient blinded) trial involving 100 patients receiving a variety of platinum-based treatments, reported that olanzapine, when added to palonosetron and dexamethasone (without an NK-1 receptor antagonist), led to a complete response rate of 96%, compared to 42% in a control group ($p< 0.0001$), with a corresponding improvement in nausea control ($p< 0.0001$) [32].

Thus, it appears to be appropriate to compare two olanzapine-containing antiemetic regimens, one with the use of an NK-1 receptor antagonist and one without. This trial should help define how much benefit a relatively expensive NK-1 receptor antagonist (i.e., fosaprepitant) provides when given with an olanzapine-based three regimen arm.

1.7 Other olanzapine study details

We propose 4 days of dexamethasone in this trial because standard practice is to use 4 days of dexamethasone, as per ASCO, NCCN, and MASCC guidelines [23-26]. We extensively discussed using a single day of dexamethasone or allowing this to be physician's choice, but the 4-day choice was chosen to be consistent with the current guidelines.

A potential short-term toxicity of olanzapine is sedation [8,9]. The long-term toxicities include weight gain and hyperglycemia in some patients who take olanzapine for 3-6 months [12-16]. In the published phase II and phase III prophylactic CINV studies [6-11], there has been no evidence that weight gain and hyperglycemia occur when using olanzapine as a preventative agent for CINV during the few days post chemotherapy. In addition, there were no Grade III or IV toxicities reported and accrual did not appear to be impacted by potential toxicities in any of the phase II or phase III trials [6-11]. Sedation will be monitored with the treatment cycle similarly to the recently completed Alliance trial [9, 11]. We will not monitor weight gain or hyperglycemia, since patients will be treated with olanzapine for only 4 days.

With regards to potential drug interactions, olanzapine has been given without any apparent clinical toxicities with other anti-emetics such as dexamethasone and 5-HT3 receptor antagonists [6-11]. While we are unaware of any studies that have monitored interactions between olanzapine and aprepitant, given that the various targeted receptors, mechanisms of action, and metabolism of each of these agents (aprepitant and olanzapine) are markedly different, significant interactions would not be anticipated. Supporting this contention, a Micromedex 2.0 search of interactions among all of these drugs (olanzapine, aprepitant, palonosetron, ondansetron, and dexamethasone) confirms that there are none, aside from the well-known phenomenon that increased systemic exposure to dexamethasone occurs with the concurrent use of aprepitant.

It is particularly important for this to be conducted as a cooperative group study, as opposed to being conducted by a pharmaceutical company, since nausea control is not an on-label indication for olanzapine and the present study is designed to increase our knowledge concerning new mechanisms of nausea control, not to support a label extension for olanzapine. In addition, olanzapine is generic and quite inexpensive.

1.8 Economic analysis of olanzapine and fosaprepitant vs. olanzapine

The objective of the economic analysis is to perform an economic evaluation of olanzapine and fosaprepitant vs. olanzapine in patients receiving HEC (noting that all patients will also receive dexamethasone and a 5HT3 receptor antagonist). We hypothesize that incremental costs of olanzapine and fosaprepitant over olanzapine will be substantial, but health gains will be minimal, and economic evaluation will demonstrate that olanzapine and fosaprepitant is not cost-effective relative to olanzapine at the standard thresholds of $50,000 and $100,000 per quality-adjusted life -year gained[36]. Our approach will be to assess costs between treatment arms and determine cost-effectiveness and cost-utility ratios.

1.8.1 Estimated Drug Costs Per Course of Treatment

Fosaprepitant (One 150mg injection on Day 1): $286.52

Olanzapine (Four 10-mg tablets, 1 on each of Days 1-4): $0.81

Fosaprepitant+ Olanzapine (One 150mg injection on Day 1 + Four 10-mg tablets, Once on each of Days 1-4): $287.33

1.8.2 Study Measures

Preference-based measures of health: To construct cost-utility ratios, an economic measure of the value of a treatment relative to comparator treatments, it is necessary to measure the value of side effects such as nausea, emesis, and sedation and their degrees of severity. Value is measured on the utility scale, where 0 is assigned to health states as bad as death, and health states of 1 are equivalent to full health. The preferred approach in health economics has been to capture these values by asking respondents to make choices or state their preferences between various health states, and to base values on the preferences of community members rather than on those of patients themselves [37]. Generic preference-based measures of health (GPBM) that incorporate multiple attributes (domains or dimensions) of health status can be used in different patient groups and health conditions. These measures have two components in the context of our protocol: (1) a health status classification system, assessed on trial subjects; (2) a preference-based scoring system, assessed among members of the community. GPBMs allow for consistency and comparison between studies and are recommended for use in methodological guidelines [37].

Our economic evaluation uses the EuroQol EQ-5D-3L instrument (Appendix V; at the end of this current document), [38] as our GPBM. We use this instrument for a number of reasons. First, it has been validated for use in cancer patients, including patients receiving chemotherapy [39, 40]. Second, it is the most commonly used GPBM, used in 63% of economic evaluations, [41] thus representing a methodological standard. Third, in a context where different populations have different preferences over health states, it is one of the only GPBMs with a utility scoring system estimated using a representative sample of the US population [40]. Fourth, the questionnaire asks about patient's health today, which matches our daily assessment of it. Finally, it is the simplest GPBM measure, taking approximately one minute to complete, and displays higher completion rates than other instruments among older adults [42]. Further details on the EQ-5D-3L measure are contained in Appendix V.

The EQ-5D-3L will supplement the Nausea and Vomiting Daily Diary/Questionnaire and will be filled out by patients at baseline and on days 2-6. It will capture the health status decrements associated with nausea, emesis, and sedation related to the administered drugs.

1.8.3 Objective measures and Methods:

Patient self-reported resource use will be tracked using the nurse/research coordinator's daily telephone contact (Appendix IV) for the patient's first chemotherapy cycle. This will capture use of protocol and any rescue medications, and any use of other pharmaceuticals and of health care services both at the trial site and at other providers during the 6-day study window of the cycle.

Every two months, the Clinical Economics Co-chair will confer with medical coders and billing staff at Wayne State University to define typical sets of ICD-9, CPT, HCSPS and NDC codes used for billing for each drug and category of service used by patients on protocol during the previous two-month period.

Certain patients treated during each two-month interval will receive more intense or complex services associated with significant health care costs, and self-reported resource use may not be sufficiently precise to confidently assess appropriate billing codes. For any such patient, the Clinical Economics Co-chair or his research assistant will contact the

nurse/research coordinator at the patient's trial site and ask them to obtain all medical insurance claims for that patient during the 6-day study window and deliver them by mail to the co-chair.

If the patient used the services of a provider outside of the enrolling institution, the research nurse will contact the billing department of that facility to obtain medical insurance claims from that provider as well. The provider will need to obtain a HIPAA release from the patient before providing any protected health information regarding the patient's use of health care services to the Alliance study team.

1.8.4 Data Analysis:

The economic data analysis is further described in Section 13.5.

1.9 Study design

All patients eligible for the study receiving HEC in both arms will receive a 5-HT_3 receptor antagonist (palonosetron 0.25 mg IV or ondansetron 8-16 mg IV or 16-24 mg PO, attending clinician choice) on day one and dexamethasone (12 mg PO, day one; 8 mg PO, days 2-4).

Group 1: Patients will also receive the NK-1 receptor antagonist fosaprepitant (150 mg IV), day one; plus olanzapine (10 mg/day PO, days 1 to 4, doses given approximately 24 hours following the prior dose).

Group 2: Patients will also receive a placebo (IV), day one; plus olanzapine (10 mg/day PO, days 1 to 4, doses given approximately 24 hours following the prior dose).

Intravenous fosaprepitant on day 1 is clinically equivalent to oral aprepitant for three days. Fosaprepitant is used in the current study in order to permit the use of an intravenous placebo in the study arms that do not contain an NK-1 receptor antagonist.

The protocol doses of the 5-HT_3 receptor antagonists, dexamethasone, and fosaprepitant listed above are standard doses recommended by various international anti-emetic guidelines [23-25]. One could argue that the effective dexamethasone dose will be a bit different in the arm getting fosaprepitant than the other arm, but there is not a lot of difference between the mildly different doses of dexamethasone [17] and we don't think any small difference is worth the cost and complexity of trying to have different dexamethasone doses. We are requiring fosaprepitant on this trial so that we can use normal saline as a placebo, as opposed to having to obtain costly oral aprepitant placebos.

The protocol dose of olanzapine was determined from the various studies in the literature [6-11, 26]. In a phase I trial of olanzapine as a prophylactic antiemetic, Passik et al [28] determined that 10 mg/day for four days was a dose without much toxicity and minimal sedation. Navari et al [29] used a loading dose of olanzapine (daily for two days prior to chemotherapy), but subsequently determined that a loading dose was not necessary for efficacy and demonstrated that 10mg/day for four days beginning with the day of chemotherapy was highly efficacious in the prevention of nausea and emesis [6-11].

Due to the potential short-term toxicity of sedation with olanzapine, there has been extensive discussion of the use of a 5 mg/day dose for four days instead of the 10 mg daily dose. There have been no published phase III studies using the 5 mg dose to indicate whether this dose would have similar efficacy and/or less sedation than the 10 mg/day dose. A 2016 ASCO abstract [27] reported a phase II trial comparing 5 mg to 10 mg for emesis induced by highly emetogenic chemotherapy with cisplatin and suggested that efficacy and sedation were similar for the two doses. In order to study, additionally, a 5 mg dose in the current proposed trial, additional study arms would need to be added to the proposal and would require significantly more patients. We

have elected to use the 10 mg dose in this proposal given that this was the dose we used in the past trial and that it has been used more frequently.

Patients will be stratified according to gender, their chemotherapy regimen, and the specific 5-HT_3 receptor antagonist used (i.e., palonosetron or ondansetron). Protocol therapy will be instituted for single day chemotherapy for one cycle only.

2.0 OBJECTIVES

2.1 Primary objective

To compare between the two study arms the proportion of patients with no nausea for the overall (0-120 hours post-chemotherapy), acute (0-24 hours post-chemotherapy), and delayed periods (24-120 hours post-chemotherapy) for patients receiving HEC. The overall period is the efficacy period of primary interest and will be used as the primary endpoint to design the study.

2.2 Secondary objective(s)

2.2.1 To compare between the two study arms the complete response (CR) rates (no emetic episodes and no use of rescue medication) in the acute, delayed, and overall periods.

2.2.2 To compare between the two study arms, the incidences of potential toxicities that have been ascribed to olanzapine.

2.2.3 To perform an economic evaluation of olanzapine and fosaprepitant vs. olanzapine in patients receiving HEC (noting that all patients will also receive dexamethasone and a 5HT3 receptor antagonist).

2.2.4 To explore the efficacy of olanzapine in chemotherapy cycles two to four, for patients who elect to continue on the same antiemetic regimen received in cycle one, in chemotherapy cycles two to four (continuation phase), by documenting nausea and complete response.

2.2.5 To explore the safety of olanzapine in chemotherapy cycles two to four, for patients who elect to continue on the same antiemetic regimen received in cycle one, in chemotherapy cycles two to four (continuation phase), by recording any adverse events or drug related toxicities.

2.3 Pharmacogenetics objectives (see also section 14.1.2)

2.3.1 To determine which polymorphisms in olanzapine-related and/or fosaprepitant-related genes are associated with nausea

2.3.2 To determine which polymorphisms in olanzapine-related and/or fosaprepitant-related genes are associated with complete response (see section 2.2.1)

2.3.3 To determine which polymorphisms in olanzapine-related genes are associated with toxicities related to olanzapine including sedation.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks

and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).
- Concomitant treatment with Oral KCL, metoclopramide and anticholinergics is not allowed on this study. Patients taking these drugs should discontinue them prior to registration on the study. Treatment with intravenous KCL is allowed. See Section 8.1 for more information.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ **3.2.1 Diagnosis of malignant disease of any stage. (Stage I through Stage IV)**

___ **3.2.2 No prior history of systemic chemotherapy for any malignancy.**

___ **3.2.3 Scheduled to receive intravenous HEC (Highly Emetogenic Chemotherapy) (either cisplatin-containing regimen or doxorubicin and cyclophosphamide [AC]).**

Cisplatin, given on a single day, at a dose of $\geq$ 70 mg/m^2, with or without other chemotherapy agent(s)

OR

Doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2)

___ **3.2.4 No nausea or vomiting ≤ 24 hours prior to registration.**

___ **3.2.5 Negative pregnancy test (serum or urine) done ≤ 7 days prior to registration**, for women of childbearing potential only.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally

postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.6 No known diagnosis of dementia.** Patients with stable treated brain metastases are eligible to participate.

___ **3.2.7 No known history of CNS disease (e.g. seizure disorder).**

___ **3.2.8 No treatment with another antipsychotic agent** such as olanzapine, risperidone, quetiapine, clozapine, phenothiazine or butyrophenone ≤ 30 days prior to registration.

___ **3.2.9 No chronic phenothiazine administration** as an antipsychotic agent (patients may receive prochloperazine and other phenothiazines as rescue anti-emetic therapy but not within 24 hours prior to registration).

___ **3.2.10 No use of amifostine** within 7 days prior to registration.

___ **3.2.11 No radiotherapy** within 7 days prior to registration or planned for one week after the current dose of chemotherapy.

___ **3.2.12 No use of quinolone antibiotic therapy** within 7 days prior to registration.

___ **3.2.13 No chronic alcoholism** (as determined by the investigator).

___ **3.2.14 No known hypersensitivity to olanzapine.**

___ **3.2.15 No known uncontrolled cardiac arrhythmia, no known uncontrolled congestive heart failure, or no acute myocardial infarction within the previous six months.**

___ **3.2.16 No history of uncontrolled diabetes mellitus,** i.e., no diabetic ketoacidosis; within 6 months prior to registration. Patients are eligible if they have controlled diabetes on diet, oral agents, and/or insulin.

___ **3.2.17 Age ≥18 years.**

___ **3.2.18 ECOG Performance Status 0, 1 or 2**

___ **3.2.19 Patients must be able to read and comprehend English. Local translation, including verbal translation of PROs is not permitted.**

___ **3.2.20 Required Initial Laboratory Values ≤120 days prior to registration**

Serum or Plasma Creatinine	≤ 2.0 mg/dL
AST or ALT	≤ 3 x upper limit of normal (ULN)

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at [redacted]In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

[redacted]

4.2 CTSU Site Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional requirements to obtain an approved site registration status include:

An active Federal Wide Assurance (FWA) number;

An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and

Compliance with all protocol-specific requirements (PSRs).

4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a

Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website [redacted] using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *[Alliance]*, and protocol number *[A221602]*.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Submitting regulatory documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking your site's registration status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sites 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration Requirements

Informed consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patient-Reported Outcomes: This study includes the use of electronic patient-reported outcomes (ePRO). While it is expected that all patients will use ePRO, patients may refuse to use this option for this study if, for example, they do not own an appropriate device or are unwilling to download the patient cloud application. Booklets may be provided to patients who choose to decline ePRO for completion of questionnaires.

Prior to registration, the patient should be asked about the availability of an electronic device and willingness to complete the patient-reported questionnaires on the device. The patient should be informed that the same method of completion must be used by the patient throughout the duration of the study for all time points. See Section 6.1 for further instructions on setting up ePRO.

- **Patient completed booklets:** Patient questionnaire booklets are to be ordered prior to the registration of any patients. A limited number of patient completed booklets can be ordered by downloading and completing the CTSU Supply request form (located under site registration tab of the protocol specific page of the CTSU website) and submitting it through the CTSU regulatory portal. Samples of the booklets are found in Appendices II-V, which are to be used for reference and IRB submission only. They are not to be used for patient completion.

Protected Health Information: Some patients treated on this study may receive additional health care services and incur associated health care costs. For these patients, medical bills, including hospital inpatient and outpatient as well as physician practice bills will be submitted to the clinical economics co-chair per Section 6.2. These patients must complete the institution's own authorization for release of medical records.

4.4 Patient Enrollment (registration/randomization procedures (Step 1))

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

- To receive site reimbursement for bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the Alliance website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

4.5 Registration to Correlative and Companion Studies

4.5.1 Registration to Substudies described in Section 14.0

There is one substudy within Alliance A221602. This correlative science study must be offered to all patients enrolled on Alliance A221602 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A221602 is:

- Olanzapine Pharmacogenomics- chemotherapy induced nausea and vomiting, Alliance A221602-ST1 (Section 14.1)

If a patient answers "yes" to "I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study(ies) described above, "they have consented to participate in the substudy described in Section 14. The patient should be registered to Alliance A221602-ST1 at the same time they are registered to the treatment trial (A221602). Samples should be submitted per Section 6.3.

4.6 Stratification, Grouping Factors and Treatment Assignments

4.6.1 Stratification Factors

4.6.1.1 Gender: Male vs. Female

4.6.1.2 Chemotherapy Regimen: cisplatin-containing regimen vs. anthracycline + cyclophosphamide (AC)

4.6.1.3 5-HT_3 Receptor Antagonist: palonosetron vs. ondansetron

4.6.2 Grouping Factors

4.6.2.1 Previous Protocol Treatment: Fosaprepitant/Aprepitant vs Placebo

4.6.3 Treatment Assignments

The factors defined in 4.6.1 will be used as stratification factors.

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups [36].

- 5-HT_3 receptor antagonist (palonosetron or ondansetron) + dexamethasone + placebo + olanzapine
- 5-HT_3 receptor antagonist (palonosetron or ondansetron) + dexamethasone + fosaprepitant + olanzapine

4.7 Procedures for Double-Blinding the Treatment Assignment

After the treatment assignment has been ascertained by randomization, the Registration Specialist will notify the designated data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be indicated in the OPEN registration system at the time of registration. This contact person may not be involved in assessing adverse events or any other outcome measure and should not be the same person listed on page one of the OPEN registration Form as the person completing the form. The OPEN registration form should provide the source of communication, either fax or e-mail, and the appropriate contact information. The Registration Specialist will then communicate the treatment assignment "active or placebo" to designated contact at the patient's institution.

Once the treatment assignment has been communicated, the designated contact should prepare fosaprepitant, aprepitant or placebo for delivery to the patient.

The dose will be prepared and labeled as "fosaprepitant 150 mg/aprepitant 130 mg or placebo" so that the contents are not discernible to the person administering the treatment.

The pharmacist or designated contact person will maintain records that indicate the identity of the patient and their corresponding treatment assignment. The pharmacist or designated contact person at the treating site will maintain records that indicate the identity of the patient and their corresponding study medication code number.

NOTE: If there is a possibility that patients will receive their medical bill prior to completing the initial phase, institutions should consider holding the bill for the patient for the fosaprepitant/aprepitant until 5 days after IV infusion, in order to preserve blinding.

4.7.1 Continuation Re-registration (step 2) Procedures

Patients who choose to continue protocol treatment after the first cycle of chemotherapy will be unblinded per the unblinding procedures in Section 8.2.2. In order to unblind the patient, site staff must call the Alliance Registration Office (507-284-4130) during regular business hours to find out if the patient was receiving fosaprepitant or placebo (See also, Section 8.2.2). Site staff must ensure that the questionnaires associated with the initial cycle of treatment have been turned in by the patient before proceeding with unblinding, as these are related to the assessment of the primary endpoint of the study.

If a patient is unblinded without following the process specified in Section 8.2.2, it will be treated as a major protocol deviation.

Note: Patient must plan to be on the same chemotherapy cycle, and the same anti-emetic regimen in the continuation phase, to be eligible to participate in the continuation phase. If a patient potentially requires dose modification of the chemotherapy or anti-emetic regimen, he/she is not eligible for the continuation phase. Patient eligibility for continuation phase will not be affected if any AEs are not related to the chemotherapy or study treatment.

If the patient was receiving fosaprepitant/aprepitant he/she will continue receiving the drug for 3 additional cycles. If the patient was receiving placebo, he/she will continue with protocol treatment without placebo (olanzapine, dexamethasone, and 5HT3 receptors only).

Patients who choose to enter the continuation phase will be re-registered as follows:

1. Site staff will log into the OPEN registration system and select the appropriate patient.
2. Then select the next registration step. (Step 2)

3. Complete the OPEN Enrollment Form for the patient to be re-registered for the continuation phase.
4. Verify the patient turned in their questionnaires for the initial cycle of treatment, yes/no.
5. Confirm that patient does not require dose modifications of chemotherapy or the anti-emetic regimen in the continuation phase yes/no.
6. Once the re-registration to the continuation phase is successfully completed, a confirmation email will be sent to the CRP.

If assistance is needed with this process, contact the Alliance Registration Office at [redacted]

Following re-registration, if the patient had been receiving fosaprepitant, the designated contact will be notified by the CRP so that s/he can prepare drug for delivery to the patient.

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals:

To be completed ≤ 28 DAYS before registration: History and physical.

	Prior to Registration	Prior to treatment on Day 1	Days 2-6	Continuation phase for three cycles Days 1-6 of each chemotherapy cycle
Tests & Observations				
History and physical	X			
Height, Weight, ECOG PS	X			
Adverse Event Assessment		X	X (1)	X (4)
Baseline Nausea and Vomiting Questionnaire (Appendix II)*		X		
Nausea and Vomiting Daily Questionnaire*			X (2)	X (2)
Euro QOL(EQ-5D-3L) *		X	X (2)	X (2)
Daily Nurse Telephone Contact			A	
Laboratory Studies				
Serum or Urine HCG	X (3)			
Creatinine, AST or ALT	X (5)			
Correlative Studies				
Blood sample	*To be collected at the time points described in Section 6.3*			

* To be completed using ePRO. See Section 6.1 to register patients to the ePRO Patient Cloud and Appendix VI for other instructions. A copy of Appendix VII to be provided to the patient.

A Nurse/Research Coordinator will contact the patient each day of Cycle 1 (Days 2-6, weekends & holidays included) to remind the patient to complete daily questionnaires, answer questions, and to query adverse events (see Appendices III-V). Daily Nurse Phone contact not required during continuation phase. At sites who don't have research staff available on the weekends, please remind the patients the day before and ensure data collection on the next working day.

1 Adverse events experienced by patients on Day 1 and Day 2 will be collected during the nurse phone call on Day 2. Nurse/research coordinator will also contact the patient in person/ by phone 21 days after the initial phase of study treatment, to collect adverse events associated with the initial phase of treatment. This collection must occur prior to the start of treatment on the continuation phase. For patients who start Cycle 2 prior to Day 21, the form will be completed according to the final contact with patient & AE assessment before continuation treatment begins.

2 Patient is to complete the Nausea and Vomiting Daily questionnaire (Appendix III) and EQ-5D-3L (Appendix V) on days 2-6.

3 For women of childbearing potential (see Section 3.2.5). Must be done ≤7 days prior to registration.

4 Adverse event assessments for continuation phase will be done during chemotherapy cycle visits

5 To be completed ≤120 days prior to registration.

6.0 DATA COLLECTION AND SUBMISSION

Data submission schedule:

A Data Submission Schedule (DSS) is available on the Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

Medidata Rave

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login [redacted] using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > [redacted]

- **Patient-completed questionnaire booklets** for this study are to be ordered prior to the registration of any patients (see Section 4.4). Samples of questionnaire booklets are available in Appendices II-V for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed

to return the booklets to site staff either in person or by mail and site staff will enter patient and caregiver responses into Rave.

- **For electronic patient reported outcomes**, the data from the patients' responses are submitted directly from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

Data Quality Portal:

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

6.1 Medidata patient cloud ePRO registration

This study includes the use of Medidata Patient Cloud electronic patient-reported outcomes (ePRO). After the patient is registered to the trial via OPEN and if the patient is willing to participate in electronic data collection, site staff will then complete a registration for the patient to the Patient Cloud ePRO through iMedidata. Note: Site staff must have already completed required eLearning for the Patient Cloud ePRO application to register a patient and information about the training is in the ePRO Appendix (Appendix VI). The registration to the Patient Cloud ePRO will create a unique patient registration code that site staff will provide to the patient. The patient (with assistance from site staff) should be instructed to download the Patient Cloud ePRO app onto his/her own device (IOS or Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial.

6.1.1 CRP Patient Registration Instructions for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRPs.

i. The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud ePRO Registration link for this study.

ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.

iii. Now the first patient can be registered. Create a subject ID and select a Country/ Language from the drop-down menu, (these are the only required data fields). The

subject initials are optional but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.

iv. The subject is added and will include the date, the subject ID, subject initials, (if included), and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered to the app. When the patient has registered the status will change from "invited" to "registered."

Note that site staff must have already completed the Medidata Patient Cloud training in order to register study participants. Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRPs. [redacted]

For patients who are re-registered to the continuation phase according to Section 4.7.1, and who elected to use patient cloud ePRO for completion of questionnaires, site staff should instruct the patients to log in to the app following re-registration (so that it will automatically re-sync), for the forms related to the continuation phase to become available.

6.2 Medical bills/insurance claims

Submission of medical bills, including hospital inpatient and outpatient as well as physician practice bills will be required for certain patients. These can be obtained from the trial site finance or billing department. Bills will include a list of services and billing codes performed and billed, insurance payments made for those services, as well as dates of visit, admission and/or discharge. Medical bills must be de-identified by institutional staff before mailing them to [redacted] Site personnel MUST remove all protected health information (PHI) from the medical bills (including but not limited to):

- Patient name
- Patient initials
- Date of birth
- Phone numbers
- Social security number
- Medical record number or account number
- Any unique identifying number, characteristic or code

The Alliance patient ID number must be included on each page. De-identified medical bills should be mailed to:

[redacted]

6.3 Specimen collection and submission

- For patients registered to substudy A221602-ST1: All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A221602- ST1, although patient participation is optional. Pharmacogenetic studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, blood will be collected at the following time points for these studies:

	Prior to Treatment	**Storage/ Shipping conditions**	**Submit to:**
	For patients registered to A221602-ST1, submit the following:		
Number and volume of tubes to draw			
Whole Blood[1] (EDTA/lavender top)	1 x 10 mL	Cool pack/ship over night	Mayo BAP Freezer

1 For patients who consent to A221602-ST1 (model consent question, "I agree to have my specimen collected and I agree that my specimen sample and related information may be used for the laboratory study described above").Whole blood is to be used for pharmacogenomic analyses described in Section 14.1.

6.3.1 Specimen Submission Using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A221602 ST1), Alliance patient number, patient's initials, date and type of specimen collected (i.e., whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Ship specimens on Monday through Friday. Shipping by overnight service to assure receipt is encouraged. Do not ship specimens on Saturdays.

All specimens should be sent to the following address:

[redacted]

6.3.2 Blood submission (for pharmacogenomic studies)

For patients who consent to participate, (model consent question, "I agree to have my specimen collected and I agree that my specimen sample and related information may be used for the laboratory study described above"), whole blood samples will be used for the pharmacogenomic studies described in Section 14.1. This sample should be collected prior to the initiation of protocol treatment.

Collect 10 mL of peripheral venous blood in an EDTA (lavender) tube. The tubes should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the Alliance Biorepository. The samples should be shipped the same day that the blood is drawn per Section 6.3.1.

Label samples with the following identification:

1) Procurement date/time of collection
2) Alliance patient number
3) Patient initials
4) Alliance study number (i.e., A221602-ST1)
5) Specimen type (i.e., whole blood)

The 10 mL of blood can be collected in one 10 mL EDTA tube, or two 5 mL EDTA tubes or three 3 mL EDTA tubes, as long as the final volume is ~10 mL.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days following registration. In the initial phase of the study, protocol therapy will be instituted with single day chemotherapy for one cycle only. Patients will be permitted to take rescue therapy of the treating investigator's choice for nausea and/or emesis/retching, based on clinical circumstances.

For questions regarding treatment, please see the study contacts page.

NOTE: Chemotherapy is to be given on Day 1 of protocol treatment.

	Agent	Day 1[a]	Day 2	Day 3	Day 4
1.	**Palonosetron OR**	0.25 mg IV	-	-	-
	Ondansetron	8- 16 mg IV **OR** 16- 24 mg PO	-	-	-
2.	**Dexamethasone**	12 mg PO	8 mg PO	8 mg PO	8 mg PO
3.	**Fosaprepitant/ Aprepitant OR Placebo**	150 mg IV(Fosaprepitant) or 130 mg IV (Aprepitant)	-	-	-
4.	**Olanzapine**	10 mg PO	10 mg PO	10 mg PO	10 mg PO

a) On Day 1, all agents are to be given prior to chemotherapy, with the exception that olanzapine may be taken prior to chemotherapy or at bedtime. If the patient did not take the olanzapine prior to chemotherapy and the patient develops nausea or vomiting prior to bedtime, the patient can take it prior to bedtime.

7.1 Fosaprepitant/Aprepitant /Placebo

Intravenous fosaprepitant/ Intravenous aprepitant on day 1 is clinically equivalent to oral aprepitant for three days. Fosaprepitant is used in the current study in order to permit the use of an intravenous placebo in the study arms that do not contain an NK-1 receptor antagonist.

Fosaprepitant/placebo or aprepitant/placebo should be administered intravenously over 20 to 30 minutes prior to chemotherapy. If 2 minute IV push Cinvanti is used, a matching 2 minute IV push saline placebo should be used.

7.2 Olanzapine

Olanzapine will be given as 10 mg /day for four days beginning on the day of chemotherapy. Olanzapine on the day of chemotherapy (day 1) may be taken prior to chemotherapy or at bedtime (after chemotherapy). Subsequent doses on day 2 to 4 may be taken at bedtime. The patient should record the time of day in the patient diary (Appendix III). Missed doses should not be made up.

7.3 Palonosetron OR Ondansetron

Palonosetron or ondansetron will only be given on Day 1 of chemotherapy.

7.4 Dexamethasone

Dexamethasone will be given on all four days. On Day 1, dexamethasone will be given as 12 mg PO. On Days 2-4, dexamethasone will be given as 8 mg PO. The patient may take it at about the same time of day that he/she received it on Day 1.

The study is designed and measured using dexamethasone PO. If an institution typically gives IV dexamethasone, then the institution's standing protocol must be changed for study participants to receive dexamethasone PO. There is no exception to this study detail.

7.5 Continuation phase after first cycle of chemotherapy

When patients come in for their clinic visit after Cycle 1, they will be encouraged to continue treatment with the study agents for an additional three cycles with chemotherapy. The treating physician and patient may decide to continue study treatment for up to three additional cycles. Patients who elect to continue with study treatment during the Continuation Phase will be unblinded as described in Section 8.2.2.

- If the patient was receiving fosaprepitant/aprepitant, s/he will continue to receive fosaprepitant/aprepitant along with olanzapine, dexamethasone, and palonosetron or ondansetron for a maximum of three more cycles and will be evaluated for efficacy and adverse events.
- If the patient was receiving placebo s/he will continue with olanzapine, dexamethasone, and palonosetron or ondansetron only (with no placebo) for a maximum of three more cycles and will be evaluated for efficacy and adverse events.

7.6 Data Collection and Forms

The patient will complete the Baseline Nausea and Vomiting Questionnaire on day one, prior to the start of treatment. The patient will also complete the Nausea and Vomiting Daily Diary/Questionnaire on days 2-6 at the same time of day as the chemotherapy was given on day 1 (+/- 1 hour). Patients will also complete the EQ-5D-3L health questionnaire to supplement the nausea and vomiting daily diary/questionnaire both at baseline and on Days 2-6.

In addition, the nurse/research coordinator will contact the patient each day of Cycle 1 (Days 2-6, weekends & holidays included) to record adverse events.

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

No dose modifications will be allowed for olanzapine, if doses of olanzapine are modified per physician discretion during the continuation phase, patients must discontinue protocol treatment.

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Concomitant medications

Concomitant treatment with the following are not allowed while taking olanzapine. Patients are prohibited from receiving the following treatments while they are taking olanzapine, as they may interfere with the study drugs:

- Treatment with another antipsychotic agent such as risperidone, quetiapine, clozapine, phenothiazine or butyrophenone.
- Chronic phenothiazine administration as an antipsychotic agent (patients may receive prochloperazine and other phenothiazines as rescue anti-emetic therapy).
- Amifostine.
- Quinolone antibiotic therapy.

In addition, because of drug interactions with Oral KCL, metoclopramide and anticholinergics, use of these drugs while taking olanzapine is not allowed. However, use of inhalers is allowed. Treatment with intravenous KCL is allowed.

Abdominal radiotherapy is also not allowed while taking olanzapine.

8.1.2 Supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

Patients will be permitted to take rescue therapy of the treating investigator's choice for nausea and/or emesis/retching, based on clinical circumstances.

8.2 Unblinding Procedures

Unblinding can be done only in cases of an emergency or if the patient chooses to continue protocol treatment beyond Cycle 1 (see Section 8.2.2). Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded during the initial phase of the study, the patient must discontinue protocol therapy.

8.2.1 Emergency Unblinding Procedures

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling [redacted]

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., "A221602")
- Alliance patient ID number (e.g., "999999")
- Patient initials (e.g., "L,FM")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that an emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation. After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

8.2.2 Protocol-specified Unblinding

Upon completion of one cycle of protocol treatment, trial participants will be asked whether they wish to participate in the continuation phase of the study (See Section 7.5).

Participants who choose to participate in the continuation phase of the study will be unblinded. In order to unblind the patient, site staff must call the Alliance Registration

Office [redacted] during regular business hours to find out if the patient was receiving fosaprepitant or placebo. Site staff must ensure that the questionnaires associated with the initial cycle of treatment have been turned in by the patient before proceeding with unblinding, as these are related to the assessment of the primary endpoint of the study.

Upon confirmation by the data manager that the criteria for one cycle of treatment have been met, the treatment assignment will be unblinded. No Alliance Executive Officer (or designee) approval is required.

All patients who proceed with the continuation phase must be re-registered as described in Section 4.7.1.

Participants who choose <u>not</u> to participate in the continuation phase of the study will not be re-registered to the study.

However, upon completion of the initial cycle of protocol treatment, site staff may request unblinding of the treatment assignment in order to inform subsequent treatment decisions. This elective unblinding is only permitted after at least 120 hours following chemotherapy. Unblinding will be performed by the Registration Office during regular business hours, with confirmation from the data manager that the appropriate criteria have been met.

In order to unblind the patient, site staff must call the Alliance Registration Office [redacted] during regular business hours to find out if the patient was receiving fosaprepitant or placebo. Upon confirmation by the data manager that the criterion that one cycle of protocol treatment has been completed, the treatment assignment may be unblinded. No Alliance Executive Officer (or designee) approval is required.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Events form is used for routine AE reporting in Rave.

There are **no** solicited adverse events for this trial.

9.2 CTCAE Routine Reporting Requirements

The following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

- Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a	a	a
Probable		a	a	a	a
Definite		a	a	a	a

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. 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. The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND ≤ 30 Days of the Last Dose of Treatment[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>• Grade 1 Timeframes</th><th>• Grade 2 Timeframes</th><th>• Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

9.3.2 Expedited AE reporting timelines defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Alliance A221602 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.

Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using study Form, Notice of New Primary.

- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 5.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

- Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 diarrhea and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 mucositis and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 dehydration and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 fatigue and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 1-3 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) with hospitalization resulting from such do not require AERs reporting, but should be reported via routine AE reporting
- Alliance A221602 uses a drug under an Alliance IND. These reporting requirements should be followed for either arm in this trial.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to previous or current treatment. This includes solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 5.0, new malignancies (both second and secondary) should be reported as one of the following: leukemia secondary to oncology chemotherapy; myelodysplastic syndrome; treatment-related secondary malignancy; or neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history of prior tumors, prior treatment/current including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original

tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- All pregnancies and suspected pregnancies occurring in female patient during therapy or within 28 days after completion of treatment on A221602 must be reported via CTEP-AERS using the event term "pregnancy, puerperium and perinatal conditions – other, pregnancy (Grade 3)
- CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g., normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities)
- The CTEP-AERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero to the agent used in this trial should be reported via CTEP-AERS.

CTEP-AERS reports should be submitted electronically.

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at [redacted]The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

Pregnancy loss

• Pregnancy loss is defined in CTCAE as "Death in utero."

• Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.

• A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.

10.0 DRUG INFORMATION

10.1 General Considerations:

All study agents are to be administered at the registering institution.

10.2 Olanzapine (Zyprexa®)

Procurement:

Olanzapine 10 mg tablets will be provided to sites for use in this trial and will be supplied in 30 count bottles.

Sites may choose to repackage and label olanzapine at the time of dispense into a supply sufficient for the cycle or dispense a 30 count bottle to the patient to be used for Cycle 1 and subsequent cycles if patients continue on olanzapine.

If a 30 count bottle is dispensed in the original bottle to patients, **sites are required to relabel the bottle before providing it to the patient in accordance with state pharmacy laws.** A sample label template is provided below:

RX#_____DATE_____

PT NAME_____

INVESTIGATOR: _____

STUDY A221602- Take ONE tablet by mouth ONCE daily for 4 days as directed per study protocol.

Olanzapine 10 mg tablets **Quantity _____**

CAUTION: NEW DRUG LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE ONLY

Any remaining tablets the patient has after completion of the study are to be returned to the site and destroyed per each site's drug destruction policy.

Each participating institution will order a starter supply of olanzapine from McKesson Clinical Research Services. Fax or email the Alliance A221602 Drug Order Request Form (downloaded from the protocol specific page of the Alliance website) to:

[redacted]

Site personnel should reorder additional supplies of olanzapine based on their inventory levels, so that McKesson Clinical Research Services may send further supplies as needed.

Within ninety days after the last patient is treated at the institution, any expired or remaining supplies should be destroyed according to institutional procedure.

Formulation:

Commercial olanzapine tablets used in this trial contain 10 mg of the drug. Inactive ingredients are crospovidone, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The color coating contains hydromellose, polyethylene glycol 400 and titanium dioxide.

Storage and Stability:

Olanzapine tablets are stored at controlled room temperature, 20º to 25ºC (68º to 77ºF). The USP defines controlled room temperature as a temperature maintained thermostatically that

encompasses the usual and customary working environment of 20º to 25ºC (68º to 77ºF) that results in a mean kinetic temperature calculated to be not more than 25ºC and that allows for excursions between 15º and 30ºC (59º and 86ºF) that are experienced in pharmacies, hospitals, and warehouses. Protect olanzapine tablets from light and moisture.

Administration:

Olanzapine will be taken as a single dose once daily Days 1 through 4 without regard to meals (prior to chemotherapy on day of chemotherapy administration or at bedtime and once daily at the same time as the initial dose thereafter).

Drug Interactions:

Olanzapine is a major substrate of CYP1A2 and a minor substrate of CYP2D6. Carbamazepine, a potent inducer of CYP1A2 caused a 50% increase in the clearance of olanzapine. Omeprazole and rifampin may cause an increase in olanzapine clearance. The effects of olanzapine may be decreased by potent inducers of CYP1A2 and should be avoided if possible. Fluvoxamine, an inhibitor of CYP1A2, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant fluvoxamine. Fluoxetine, an inhibitor of CYP2D6, causes a smaller increase (mean 16%) in the maximum concentration of olanzapine and a small decrease in the clearance of olanzapine (mean 16%). The magnitude of impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended. The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine. Olanzapine may potentiate the effects of antihypertensives, CNS acting medications and alcohol. Olanzapine may antagonize the effects of levodopa and dopamine agonists. Olanzapine is an inhibitor of CYP1A2 (weak), CYP2C19 (weak), CYP2C9 (weak), CYP2D6 (weak), CYP3A4 (weak).

Pharmacokinetics:

a) Absorption – Readily absorbed reaches peak concentrations in approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption.

b) Distribution – Linear kinetics with half-life of 21 to 54 hours and apparent plasma clearance from 12 to 47 L/hr. Olanzapine is extensively distributed throughout the body with a Vd of approximately 1000 L. It is 93% bound to plasma proteins (primarily albumin and α_1-acid glycoprotein.

c) Metabolism – Direct glucuronidation and cytochrome P450 mediated oxidation via CYP1A2 (major) and CYP2D6 (minor) are the primary metabolic pathways for olanzapine.

d) Excretion – Urine (57%, 7% as unchanged drug); feces (30%). There is a 40% increase in olanzapine clearance in smokers, 30% decrease in females.

Adverse Events

All of the adverse events discussed below have been associated with olanzapine, but would be considered unexpected in the context of this trial.

[U.S. Boxed Warning]: Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo.

Other warnings and precautions: suicide (particularly when used with fluoxetine), neuroleptic malignant syndrome, hyperglycemia, hyperlipidemia, weight gain, tardive dyskinesia,

orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, seizures, cognitive or motor impairment, hyproprolactinemia.

Common known potential toxicities >10%:

Central nervous system: somnolence, extrapyramidal symptoms, dizziness, headache, fatigue, insomnia

Endocrine/metabolic: prolactin increased

Gastrointestinal: weight gain, appetite increased, xerostomia, constipation

Hepatic: ALT increased

Neuromuscular/skeletal: weakness

Miscellaneous: accidental injury

Less common known potential toxicities 1-10%:

Cardiovascular: chest pain, hypertension, peripheral edema, postural hypotension, tachycardia

Central nervous system: fever, personality changes, restlessness

Dermatologic: bruising

Endocrine/metabolic: breast-related events (discharge, enlargement, galactorrhea, gynecomastia, lactation disorder), menstrual-related events (amenorrhea, hypomenorrhea, menstruation delayed, oligomenorrhea), sexual function-related events (anorgasmia, ejaculation delayed, erectile dysfunction, changes in libido, abnormal orgasm, sexual dysfunction)

Gastrointestinal: abdominal pain, diarrhea, flatulence, nausea, vomiting

Genitourinary: incontinence, UTI

Hepatic: hepatic enzymes increase

Neuromuscular/skeletal: abnormal gait, akathisia, articulation impairment, back pain, falling, hypertonia, joint/extremity pain, muscle stiffness, tremor

Ocular: amblyopia

Respiratory: cough, epistaxis, pharyngitis, respiratory tract infection, rhinitis, sinusitis

Rare, less than 1% (limited to important or life threatening):

Acidosis, agranulocytosis, anaphylactic reaction, angioedema, apnea, atelectasis, atrial fibrillation, cerebrovascular accident, congestive heart failure, deafness, diabetes mellitus, diabetic ketoacidosis, diabetic coma, dystonia, encephalopathy, facial paralysis, glaucoma, heart arrest, heart failure, hemorrhage, hepatitis, hypercholesterolemia, hyper/hypoglycemia, hyper/hypokalemia, hyperlipidemia, hyper/hyponatremia, hypertriglyceridemia, hyperuricemia, hyper/hypoventilation, hypoproteinemia, hypoxia, jaundice, ileus, ketosis, leukocytosis (eosinophilia), leukopenia, liver damage (cholestatic or mixed), liver fatty deposit, lung edema, lymphadenopathy, myasthenia, myopathy, neuralgia, neuroleptic malignant syndrome, neutropenia, pancreatitis, paralysis, pulmonary embolus, rash, rhabdomyolysis, seizure, sudden death, suicide attempt, syncope, tardive dyskinesia, thrombocythemia, thrombocytopenia, transient ischemic attack, venous thrombotic events.

10.2.1 Nursing Guidelines

1. Olanzapine has several drug to drug interactions, many of which can cause an increase in olanzapine clearance and increase the side effects of olanzapine. Assess patient's medication list for any possible drug to drug interactions. Discuss with study doctor.
2. Warn patients of the risk of suicide, especially for patients on fluoxetine.

3. Olanzapine can have significant CNS side effects, including somnolence, extrapyramidal symptoms, dizziness, headache, or insomnia. Rarely patients may experience tardive dyskinesia, seizures, cognitive or motor impairment. Warn patients of these side effects and that they should not drive or do activities that require attentiveness until they know how agent affects them.
4. Warn patient about possible GI side effects including increased appetite, xerostomia, constipation and weight gain. Less commonly nausea, vomiting, abdominal pain, and diarrhea. Treat symptomatically and monitor for effectiveness of intervention.
5. Patients with diabetes should be monitored closely as olanzapine can increase blood sugar levels.
6. Monitor CBC w/differential as agent may cause leukopenia, neutropenia and agranulocytosis. Patients who are on cytotoxic chemotherapy may be at increased risk.
7. Discuss possibility of sexually related side effects.

10.3 Fosaprepitant (Emend IV®) or placebo

Procurement:

Fosaprepitant diemglumine 150 mg, lyophilized powder in single-dose vials for reconstitution will be obtained from commercial supplies at each member institution. Pharmacies are instructed to use commercial supply fosaprepitant diemglumine

Placebo will be not be supplied by this study and is the responsibility of the site. Placebo will be 0.9% Sodium Chloride, USP 150 mL or 250 mL volume (per individual site reconstitution standard for fosaprepitant diemglumine).

Outdated or remaining drug/product should be destroyed on-site per procedures in place at each institution.

Formulation:

Commercial fosaprepitant for injection contains 245.3 mg of fosaprepitant dimeglumine equivalent to 150 mg of fosaprepitant free acid and the following inactive ingredients: edetate disodium (18.8 mg), polysorbate 80 (75 mg), lactose anhydrous (375 mg), sodium hydroxide and/or hydrochloric acid (for pH adjustment).

Storage and Stability:

Fosaprepitant for injection vials must be stored refrigerated at 2° to 8°C (36° to 46°F). The reconstituted final drug solution is stable for 24 hours at ambient room temperature [at or below 25°C (77°F)].

Preparation:

Reconstitute the 150 mg vial with 5 mL 0.9% Sodium Chloride Injection, USP. Add reconstituted fosaprepitant to an infusion bag containing 145 mL 0.9% Sodium Chloride for Injection, USP to yield a total volume of 150 mL and a final concentration of 1 mg/mL. Alternatively, if institutional preference is to administer fosaprepitant in 250 mL 0.9% Sodium Chloride for Injection, USP, sites may follow institutional preparation instructions.

Note, fosaprepitant is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Lactated Ringer's Solution and Hartmann's Solution.

Administration:

Fosaprepitant should be administered intravenously over 20 to 30 minutes prior to chemotherapy.

Drug Interactions:

Fosaprepitant is a prodrug of aprepitant and is a weak inhibitor of CYP3A4. Aprepitant is a substrate, inhibitor and inducer of CYP3A4.

Concurrent CYP3A4 Sensitive Substrates: Use of fosaprepitant with drugs that are CYP3A4 substrates (e.g. alfentanil, everolimus, ibrutinib, lovastatin, midazolam, simvastatin, sirolimus, tacrolimus, triazolam, vardenafil) may result in increased exposure and plasma concentration of the concomitant drug. Concurrent use of pimozide is contraindicated with fosaprepitant due to the risk of significantly increased concentrations of pimozide, potentially resulting in QTc interval prolongation.

Concurrent CYP3A4 strong or moderate inhibitors: Use of fosaprepitant with drugs that are strong or moderate CYP3A4 inhibitors (e.g. ketoconazole, diltiazem) may increase plasma concentrations of aprepitant and result in increased adverse reactions related to aprepitant.

Concurrent CYP3A4 strong inducers: Use of fosaprepitant with strong CYP3A4 inducers (e.g. rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of fosaprepitant.

Pharmacokinetics:

Distribution – Following administration of a single intravenous 150-mg dose of fosaprepitant, a prodrug of aprepitant, the mean AUC of aprepitant was 37.4 (+/- 14.8) mcg*hr/mL and the mean maximal aprepitant concentration (Cmax) was 4.2 (+/- 1.2) mcg/mL. The mean volume of distribution at stead state (Vdss) is approximately 70L in humans. Aprepitant crosses the blood-brain barrier.

Metabolism – Conversion of fosaprepitant to aprepitant occurs in multiple exrahepatic tissues in addition to the liver. Aprepitant undergoes extensive hepatic metabolism. Aprepitant is metabolized primarily by CYP3A4 with minor contributions of CYP1A2 and CYP2C19.

Excretion – Urine (57%), feces (45%). Terminal half-life is 9 to 13 hours.

Adverse Events

Common known potential toxicities > 10%:

Central nervous system: fatigue
Gastrointestinal: diarrhea

Less common known potential toxicities 1-10%:

Central nervous system: peripheral neuropathy, headache
Gastrointestinal: hiccups, anorexia, constipation, dyspepsia, eructation
Genitourinary: urinary tract infection
Hematologic & oncologic: neutropenia, anemia, leukopenia
Hepatic: increased serum ALT, increased serum AST
Local: infusion-site reaction
Neuromuscular/skeletal: weakness, limp pain

Rare, less than 1% (limited to important or life threatening):

Abdominal distention, abdominal pain, abnormal dreams, abnormal gait, acne vulgaris, anaphylaxis, anemia, angioedema, anxiety, bradycardia, candidiasis, cardiovascular signs and symptoms, chest discomfort, chills, cognitive dysfunction, colitis (neutropenic), conjunctivitis, cough, decreased visual acuity, diaphoresis, disorientation, dizziness, drowsiness, dysarthria, dysgeusia, dyspnea, dysuria, edema, epigastric distress, erythema, euphoria, febrile neutropenia, fecal impaction, flatulence, flushing, gastroesophageal reflux, gastroesophageal reflux disease, hallucination, hematuria (microscopic), hot flash, hyperglycemia, hypersensitivity reaction, hypertension, hypoesthesia, hyponatremia, impaired consciousness, increased serum alkaline phosphatase, insomnia, intestinal obstruction, lethargy, loss of consciousness, malaise, miosis, muscle cramps, myalgia, myasthenia, nausea, obstipation, oily skin, palpitations, paresthesia, perforated duodenal ulcer, pharyngitis, pollakiuria, polydipsia, polyuria, post nasal drip, pruritus, seizure, sensory disturbance, SIADH (syndrome of inappropriate antidiuretic hormone secretion), skin lesion, skin photosensitivity, skin rash, sneezing, staphylococcal infection, Stevens-Johnson syndrome, stomatitis, throat irritation, tinnitus, toxic epidermal necrolysis, urticaria, vomiting, weight changes (gain/loss), wheezing, xerostomia.

10.3.1 Nursing Guidelines

1. Use of fosaprepitant with other drugs that are CYP3A4 substrates, may result in increased plasma concentration of the concomitant drug.
2. Use of fosaprepitant with strong or moderate CYP3A4 inhibitors (e.g., ketoconazole, diltiazem) may increase plasma concentrations of fosaprepitant and result in an increased risk of adverse reactions related to fosaprepitant.

3. Use of fosaprepitant with strong CYP3A4 inducers (e.g., rifampin) may result in a reduction in fosaprepitant plasma concentrations and decreased efficacy of fosaprepitant
4. Co administration of Emend with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time.
5. Upon coadministration with fosaprepitant, the efficacy of hormonal contraceptives may be reduced during administration of and for 28 days following the last dose of fosaprepitant
6. Counsel patient for hypersensitivity, and drug interactions
7. Monitor patient for headache and offer appropriate intervention
8. Monitor patient for diarrhea and offer appropriate intervention
9. Monitor patient for bradycardia and hypotension during administration
10. Hiccups can occur with this drug
11. Counsel patient to report systems to health care team

10.4 Aprepitant (Cinvanti®) or Placebo

Procurement:

Aprepitant 130 mg injectable emulsion will be obtained from commercial supplies at each member institution. Pharmacies are instructed to use commercial supply intravenous aprepitant.

Placebo will be not be supplied by this study and is the responsibility of the site. Placebo will be either 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP. The placebo should match the active drug in regard to preparation and administration.

Outdated or remaining drug/product should be destroyed on-site per procedures in place at each institution.

Formulation:

Commercial intravenous aprepitant is a 130 mg/18 mL (7.2 mg/mL) opaque, off-white to amber emulsion in a single dose vial.

Storage and Stability:

Diluted aprepitant solution is stable at ambient room temperature for 6 hours in 0.9% Sodium Chloride Injection, USP or 12 hours in 5% Dextrose Injection, USP.

Preparation:

30-Minute IV Infusion:

Aseptically withdraw 18 mL from the vial and transfer it into an infusion bag filled with 100 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose for Injection, USP to yield a total volume of 118 mL. Gently invert the bag 4 to 5 times. Avoid shaking. Before administration, inspect the bag for particulate matter and discoloration. Discard the bag if particulate and/or discoloration are observed. Use only non-DEHP tubing and non-PVC infusion bags.

2-Minute IV Push:

Aseptically withdraw 18 mL from the vial into a syringe. Do not dilute.

Aprepitant can be prepared according to each site's institutional practice ensuring that the placebo matches the preparation and administration.

Note, intravenous aprepitant is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Lactated Ringer's Solution and Hartmann's Solution.

Administration:

30-Minute IV Infusion

Intravenous aprepitant should be administered intravenously over 30 minutes approximately 30 minutes prior to chemotherapy.

2-Minute IV Push

Administer aprepitant as a 2 minute IV push approximately 30 minutes prior to chemotherapy. Flush infusion line with normal saline before and after administration of aprepitant.

Drug Interactions:

Aprepitant is a substrate, weak-to-moderate (dose-dependent) inhibitor, and an inducer of CYP3A4. Aprepitant is also an inducer of CYP2C9.

Concurrent CYP3A4 Sensitive Substrates: Use of aprepitant with drugs that are CYP3A4 substrates may result in increased exposure and plasma concentration of the concomitant drug. Concurrent use of pimozide is contraindicated with aprepitant due to the risk of significantly increased concentrations of pimozide, potentially resulting in QTc interval prolongation.

Concurrent CYP3A4 strong or moderate inhibitors: Use of aprepitant with drugs that are strong or moderate CYP3A4 inhibitors (e.g. ketoconazole, diltiazem) may increase plasma concentrations of aprepitant and result in increased adverse reactions related to aprepitant.

Concurrent CYP3A4 strong inducers: Use of aprepitant with strong CYP3A4 inducers (e.g. rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of aprepitant.

Concurrent warfarin use: Coadministration of aprepitant with warfarin, a CYP2C9 substrate, may result in a clinically significant decrease in the International Normalized Ratio (INR) of prothrombin time. Monitor the INR in patients on chronic warfarin therapy in the 2-week period, particularly at 7 to 10 days, following initiation of aprepitant with each chemotherapy cycle.

Risk of reduced efficacy of hormonal contraceptives: Upon coadministration with aprepitant, the efficacy of hormonal contraceptives may be reduced during administration and for 28 days following the last dose of aprepitant. Advise patients to use effective alternative or back-up methods of non-hormonal contraception during treatment with aprepitant and for 1 month following administration of intravenous aprepitant.

Pharmacokinetics:
Distribution – Aprepitant is greater than 99% bound to plasma proteins. The mean apparent volume of distribution at steady state (Vdss) was approximately 70 L in humans. Aprepitant crosses the blood brain barrier in humans
Metabolism – Aprepitant undergoes extensive metabolism. *In vitro* studies using human liver microsomes indicate that aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Metabolism is largely via oxidation at the morpholine ring and its side chains. No metabolism by CYP2D6, CYP2C9, or CYP2E1 was detected.

Excretion – Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent terminal half-life ranged from approximately 9 to 13 hours.

Adverse Events
Common known potential toxicities > 10%:
Central nervous system: fatigue
Hematologic & oncologic: neutropenia

Less common known potential toxicities 1-10%:

Cardiovascular: hypotension, bradycardia, flushing, palpitations, peripheral edema, syncope
Central nervous system: headache, dizziness, anxiety, hypoesthesia, hypothermia, malaise, peripheral neuropathy
Dermatologic: pruritus, alopecia, hyperhidrosis, skin rash, urticarial
Endocrine & metabolic: dehydration, decreased serum albumin, decreased serum potassium, decrease serum sodium, hot flash, hypokalemia, hypovolemia, increased serum glucose, weight loss
Gastrointestinal: constipation, diarrhea, dyspepsia, abdominal pain, hiccups, decreased appetite, dysgeusia, eructation, flatulence, gastritis, gastroesophageal reflux disease, nausea, vomiting, xerostomia
Genitourinary: proteinuria
Hematologic & oncologic: neutropenia, anemia, febrile neutropenia, hematoma, thrombocytopenia
Hepatic: increased serum ALT, increased serum AST, increased serum alkaline phosphatase, increased serum bilirubin
Infection: candidiasis, postoperative infection
Local: infusion-site reaction, induration and inflammation at injection site
Neuromuscular/skeletal: weakness, musculoskeletal pain
Renal: Increased blood urea nitrogen
Respiratory: cough, dyspnea, hypoxia, oropharyngeal pain, pharyngitis, respiratory depression

Rare, less than 1% (limited to important or life threatening):
Abdominal distention, abnormal dreams, abnormal gait, acne vulgaris, anaphylaxis, angioedema, anxiety, cardiac disease, chest discomfort, chills, cognitive dysfunction, conjunctivitis, decreased neutrophils, disorientation, drowsiness, dysfunction, dysuria, edema, epigastric distress, euphoria, hematuria, hyperglycemia, hypersensitivity reaction, hyponatremia, increased thirst, lethargy, muscle cramps, myalgia, neutropenic enterocolitis, oily skin, perforated duodenal ulcer, pollakiuria, polyuria, polydipsia, post nasal drip, skin lesion, skin photosensitivity, sneezing, staphylococcal infection, Stevens-Johnson syndrome, stomatitis, throat irritation, tinnitus, toxic epidermal necrolysis, weight gain

10.4.1 Nursing Guidelines

1. Assess patient's concomitant medications, including over the counter agents as there are many drug to drug interactions.
2. Rarely hypersensitivity reactions can occur. Monitor patients during infusions and administer emergency medications as per facility policy.
3. Gastrointestinal side effects may occur including diarrhea, constipation, taste changes, etc. Treat symptomatically and monitor for effectiveness.
4. Monitor patient for bradycardia and hypotension during administration
5. Hiccups can occur with this drug
6. Monitor CBC w/diff as cytopenia, most notably neutropenia can occur. Instruct patients to report any infectious symptoms to the team.
7. Warn patients of fatigue.
8. Monitor LFT's.
9. Injection site reaction can occur with induration.

10.5 Palonosetron for IV Administration (Aloxi®)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Outdated or remaining drug/product should be destroyed on-site per procedures in place at each institution.

Formulation

Solution, (Aloxi Intravenous): 0.25 mg/5 mL (5 mL)

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at 20°C to 25°C (68°F to 77°F; excursions permitted to 15°C to 30°C (59°F to 86°F). Do not freeze. Protect from light. Solutions of 5 mcg/mL and 30 mcg/mL in NS, D5W, D51/2NS and D5LR injection are stable for 48 hours at room temperature and 14 days under refrigeration.

Administration

Refer to the treatment section for specific administration instructions. Flush IV line with 0.9% sodium chloride prior to and following administration. Infuse over 30 seconds beginning approximately 30 minutes prior to the start of chemotherapy.

Drug Interactions

Cytochrome P450 Effect: Substrate of CYP1A2 (minor), CYP2D6 (minor), CYP3A4 (minor);

Increased Effect/Toxicity: apomorphine, serotonin modulators.

Decreased Effect: tapentadol; tramadol

Pharmacokinetics

Distribution Vd: Adults: 8.3 $\pm$ 2.5 L/kg

Protein binding: ~62%

Metabolism: Hepatic (approximately 50% metabolized via CYP enzymes to inactive metabolites)

Half-life elimination: Adults ~40 hours

Excretion: Urine (80%; 40% as unchanged drug)

Adverse Events

Consult the package insert for the most current and complete information.

Less common known potential toxicities 1-10%:

Cardiovascular: Prolonged Q-T interval on ECG, bradycardia, sinus bradycardia, tachycardia, hypotension

Central nervous system: Headache, anxiety, dizziness

Dermatologic: Pruritus

Endocrine & metabolic: Hyperkalemia

Gastrointestinal: Constipation, diarrhea, flatulence

Genitourinary: Urinary retention

Hepatic: Increased serum ALT, increased serum AST

Neuromuscular & skeletal: Weakness

Rare, less than 1% (limited to important or life threatening):

Abdominal pain, allergic dermatitis, amblyopia, anaphylactic shock (very rare), anaphylaxis (very rare), anasarca, anemia, anorexia, arthralgia, cardiac arrhythmia, chills, decreased appetite, decreased blood pressure, decreased gastrointestinal motility, decreased platelet count, dermatological disease (infants, children, and adolescents), distended vein, drowsiness, dyskinesia (infants, children, and adolescents), dyspepsia, electrolyte disturbance, epistaxis, erythema, euphoria, extrasystoles, eye irritation, fatigue, fever, flattened T wave on ECG, flu-like symptoms, glycosuria, hiccups, hot flash, hyperglycemia, hypersensitivity (very rare), hypersomnia, hypertension, hypokalemia, hypoventilation, increased bilirubin (transient), increased liver enzymes, infusion site pain (infants, children, and adolescents), injection site reaction (very rare; includes burning sensation at injection site, discomfort at injection site, induration at injection site, pain at injection site), insomnia, ischemic heart disease, laryngospasm, limb pain, metabolic acidosis, motion sickness, paresthesia, serotonin syndrome, sialorrhea, sinus arrhythmia, sinus tachycardia, skin rash, supraventricular extrasystole, tinnitus, vein discoloration, ventricular premature contractions, xerostomia

10.5.1 Nursing Guidelines

1. Headaches are the most common side effect. Rare episodes of tachycardia and arrhythmias have been observed.
2. Rare hypersensitivity reactions have been observed.
3. May exacerbate symptoms of lactose intolerance.

10.6 Ondansetron for Oral or IV Administration (Zofran®)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Outdated or remaining drug/product should be destroyed on-site per procedures in place at each institution.

Formulation

Tablets: 4 mg, 8 mg

Tablets, orally-disintegrating: 4 mg, 8 mg

Oral Solution, 4 mg/5 mL (50 mL)

Solution (Ondansetron HCl Injection): 4 mg/2 mL (2 mL), 40 mg/20 mL (20 mL)

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store tablets between 2°C and 30°C (36°F to 84°F). Store oral solution between 15°C and 30°C (59°F and 86°F). Protect from light. Store vials between 2°C and 30°C (36°F to 84°F). Protect from light. Stable when mixed in D5W or 0.9% Sodium Chloride for 48 hours at room temperature.

Administration

Refer to the treatment section for specific administration instructions.

Oral: Oral dosage forms should be administered 30 minutes prior to chemotherapy.

Oral disintegrating tablets: Do not remove from the blister until needed. Peel backing off the blister, do not attempt to push tablet through the foil. Using dry hands, place tablet on the tongue and allow to dissolve. Swallow with saliva (no need to administer other liquids).

Intravenous: May be administered IV Push per institutional guidelines undiluted over at least 30 seconds but preferably over 2 to 5 minutes. May administer via IV piggyback diluted over 15 minutes. Give approximately 30 minutes prior to chemotherapy.

Drug Interactions

Cytochrome P450 Effect: Substrate of CYP1A2 (minor), CYP2C9 (minor), CYP2D6 (minor), CYP2E1 (minor), CYP3A4 (major), P-glycoprotein; Inhibits: CYP1A2 (weak), CYP2C9 (weak)

Increased Effect/Toxicity: QTc prolonging agents, metformin, panobinostat, serotonin modulators, tizanidine

Decreased Effect: tapentadol; tramadol

Pharmacokinetics

Onset of action: ~30 minutes

Distribution Vd: Adults: 1.9 L/kg

Protein binding: 70-76%

Metabolism: Hepatic via hydroxylation, followed by glucuronide or sulfate conjugation

Half-life elimination: Adults ~3-6 hours

Excretion: Urine (44-60% as metabolites; ~5% as unchanged drug); feces (~25%)

Adverse Events

Consult the package insert for the most current and complete information.

Common known potential toxicities >10%:

Central nervous system: Headache, fatigue, malaise

Gastrointestinal: Constipation

Less common known potential toxicities 1-10%:

Central nervous system: Drowsiness, sedation, dizziness, agitation, anxiety, paresthesia, sensation of cold

Dermatologic: Pruritus, skin rash

Gastrointestinal: Diarrhea

Genitourinary: Gynecologic disease, urinary retention

Hepatic: Increased serum ALT, increased serum AST

Local: Injection site reaction

Respiratory: Hypoxia

Miscellaneous: Fever

Rare, less than 1% (limited to important or life threatening):

Abdominal pain, accommodation disturbance, anaphylactoid reaction, anaphylaxis, angina pectoris, angioedema, atrial fibrillation, bradycardia, bronchospasm, bullous skin disease, cardiac arrhythmia, cardiorespiratory arrest (IV), chest pain, chills, depression of ST segment on ECG, dyspnea, dystonic reaction, ECG changes, extrapyramidal reaction (IV), flushing, hepatic failure (when used with other hepatotoxic medications), hiccups, hypersensitivity reaction, hypokalemia, hypotension, ischemic heart disease, laryngeal edema, laryngospasm (IV), liver enzyme disorder, mucosal tissue reaction, myocardial infarction, neuroleptic malignant syndrome, oculogyric crisis, palpitations, positive lymphocyte transformation test, prolonged Q-T interval on ECG (dose dependent), second-degree atrioventricular block, serotonin syndrome, shock (IV), Stevens-Johnson syndrome, stridor, supraventricular tachycardia, syncope, tachycardia, tonic-clonic seizures, torsades de pointes, toxic epidermal necrolysis, transient blindness (lasted ≤48 hours), transient blurred vision (following infusion), urticaria, vascular occlusive events, ventricular premature contractions, ventricular tachycardia, weakness, xerostomia

10.6.1 Nursing Guidelines

1. Headaches are the most common side effect. Rare episodes of tachycardia and arrhythmias have been observed.
2. Rare hypersensitivity reactions have been observed.
3. May exacerbate symptoms of lactose intolerance.

10.7 Dexamethasone for Oral Administration (DXM)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Outdated or remaining drug/product should be destroyed on-site per procedures in place at each institution.

Formulation

Commercially available for oral administration as:

Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg

Solution, oral: 0.5 mg/mL (500 mL)

Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL)

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20ºC to 25ºC (68ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF. Store oral liquid at room temperature, do not freeze. Do not use if solution contains a precipitate. Refer to commercial package for drug expiration date.

Administration

Refer to the treatment section for specific administration instructions. May be taken with meals to decrease GI upset.

Drug Interactions

Cytochrome P450 Effect: Substrate of CYP3A4 (major); **Induces** CYP2A6 (weak/moderate), 2C9 (weak/moderate), 3A4, UGT1A1 **Increased Effect/Toxicity:** Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.

Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.

Ethanol/Nutrition/Herb Interactions:

Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).

Food: Dexamethasone interferes with calcium absorption. Limit caffeine.

Herb/Nutraceutical: Avoid cat's claw, Echinacea (have immunostimulant properties)

Pharmacokinetics

Onset of action: Prompt

Duration of metabolic effect: 72 hours

Metabolism: Hepatic

Half-life elimination: adults ~4 hours

Time to peak, serum: Oral: 1-2 hours

Excretion: Urine (~10%)

Adverse Events

Consult the package insert for the most current and complete information.

Common known potential toxicities, frequency not defined:

Cardiovascular: bradycardia, cardiac arrhythmia, cardiac failure, cardiomegaly, circulatory shock, edema, embolism (fat), hypertension, hypertrophic cardiomyopathy (premature infants), myocardial rupture (post-MI), syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis

Central nervous system: Depression, emotional lability, euphoria, headache, increased intracranial pressure, insomnia, malaise, myasthenia, neuritis, neuropathy, paresthesia, personality changes, pseudotumor cerebri (usually following discontinuation), psychic disorder, seizure, vertigo

Dermatologic: Acne vulgaris, allergic dermatitis, alopecia, atrophic striae, diaphoresis, ecchymoses, erythema, facial erythema, fragile skin, hyperpigmentation, hypertrichosis, hypopigmentation, perianal skin irritation (itching, burning, tingling; following IV injection), petechiae, skin atrophy, skin rash, subcutaneous atrophy, suppression of skin test reaction, urticaria, xeroderma

Endocrine & metabolic: Adrenal suppression, carbohydrate intolerance, Cushing syndrome, decreased glucose tolerance, decreased serum potassium, diabetes mellitus, fluid retention, glycosuria, growth suppression (children), hirsutism, HPA-axis suppression, hyperglycemia, hypokalemic alkalosis, menstrual disease, moon face, negative nitrogen balance, protein catabolism, redistribution of body fat, sodium retention, weight gain

Gastrointestinal: Abdominal distention, gastrointestinal hemorrhage, gastrointestinal perforation, hiccups, increased appetite, nausea, pancreatitis, peptic ulcer, pruritus ani (following IV injection), ulcerative esophagitis

Genitourinary: Defective (increased or decreased) spermatogenesis

Hematologic & oncologic: Kaposi sarcoma, petechial, tumor lysis syndrome

Hepatic: Hepatomegaly, increased serum transaminases

Hypersensitivity: Anaphylactoid reaction, anaphylaxis, angioedema, hypersensitivity

Infection: Infection, sterile abscess

Local: Postinjection flare (intra-articular use)

Neuromuscular & skeletal: Amyotrophy, aseptic necrosis of bones (femoral and humoral heads), bone fractures, Charcot-like arthropathy, myasthenia, myopathy (particularly in conjunction with neuromuscular disease or neuromuscular-blocking agents), osteoporosis, rupture of tendon, steroid myopathy, vertebral compression fracture

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, subcapsular posterior cataract

Respiratory: Pulmonary edema

Miscellaneous: Wound healing impairment

10.7.1 Nursing Guidelines

1. Monitor for hypertension, CHF and other evidence of fluid retention.
2. Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.
3. Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.
4. Evaluate signs of infection, particularly local candidal infections and treat appropriately.
5. Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.

11.0 MEASURES

Data from the patient questionnaires (Appendices II-V) will be used to measure treatment effect. The following measures will be used in this study:

11.1 Baseline Nausea and Vomiting Questionnaire (Appendix II)

All patients will be asked to complete the baseline nausea and vomiting questionnaire prior to administering chemotherapy.

11.2 Nausea and Vomiting Daily Diary/Questionnaire (Appendix III)

Patients will complete a daily diary on any experienced nausea and vomiting on days 2 to 6 post-chemotherapy.

11.3 Daily Nurse Telephone Contact (Appendix IV)

Nurse will contact patient daily on days 2-6 following Cycle 1 of chemotherapy (including holidays and weekends), in the initial phase only, to assess any adverse events and to remind them to take the study medication, the dexamethasone, and/or to complete the daily diary. Nurse will also record rescue medications and any additional new medications, as well as self-reported health care utilization for patients with adverse events.

11.4 EQ-5D-3L Health Questionnaire (Appendix V)

Patients will complete the EQ-5D-3L questionnaire prior to administering chemotherapy and on days 2-6.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

The treatment period for this study during the initial phase is a four day anti-emetic regimen, with chemotherapy being administered on Day 1.

Continuation phase: If the patient has minimal or no nausea or emesis after the first cycle of chemotherapy and requests to continue on the same antiemetic regimen, the patient will be permitted to continue on the same antiemetic regimen (with the agreement of the patient's physician) for a maximum of three additional cycles and will be evaluated for efficacy and any adverse events.

12.2 Criteria for discontinuation of protocol treatment/intervention

12.2.1 Stopping study treatment due to toxicity: If the patient experiences a significant adverse event (per patient and physician discretion) felt to potentially be related to any of the study drugs, then the drug to which the adverse event is attributed should be discontinued.

12.2.2 Disease progression or discontinuation of chemotherapy:

If the patient progresses or discontinues chemotherapy, study treatment will be discontinued.

12.3 Follow-up

12.3.1 Duration of follow up for patients who continue study treatment

Starting on the day that chemotherapy is given, patients will be followed from Day 1 through Day 6. For patients who elect to participate in the continuation phase, follow up will also continue through Day 6 of the fourth cycle of protocol therapy.

12.3.2 Follow up for patients who discontinue study treatment early

For patients who discontinue protocol therapy during Cycle 1 due to toxicity, disease progression, or discontinuation of chemotherapy, no follow-up will be required.

Patients who discontinue protocol therapy due to toxicity, disease progression, or discontinuation of chemotherapy during the Continuation Phase, will be followed for toxicities but completion and submission of questionnaires and economic data will not be required.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

Document the reason(s) for discontinuation of therapy on data forms.

Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline and off treatment data submission required. See the Data Submission Schedule accompanying the All Forms Packet

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Overview:

This trial, following extensive discussion with multiple parties, is designed as a multi-center, randomized, double-blind, placebo-controlled study where patients will be randomly assigned at a ratio of 1:1 to receive either olanzapine + fosaprepitant (Group 1) or to olanzapine + placebo (Group 2). Both arms include a 5-HT3 receptor antagonist and dexamethasone.

13.2 Sample Size, Accrual time and Study duration

13.2.1 Sample size

The primary objective of the study is to compare the no nausea rate between the treatment arms. The study is powered using no nausea rate in the overall period (0-120 hours) as the primary endpoint.

Our previous study [11] showed that the rate of no nausea in the overall period after treatment with olanzapine + fosaprepitant was 37%. We hypothesize that olanzapine + placebo is not inferior to olanzapine + fosaprepitant as a treatment for chemotherapy-induced nausea. Based on our experience in clinical practice, we felt if the no nausea rate in the overall period after treatment with olanzapine + placebo is less than 10% lower than the no nausea rate after treatment with olanzapine + fosaprepitant then olanzapine + placebo could be considered non-inferior to olanzapine + fosaprepitant. That is, a non-inferiority margin of 10% is considered to be clinical meaningful. To support that the 10% non-inferiority margin is reasonable, it is noted that in our preceding trial [11], we had noted that a 17.5 % superiority rate was clinically appropriate; in this current trial we are being a bit more stringent by decreasing 17.5% to 10%.

The specific statistical hypotheses being considered are H_o: $p_c - p_t \geq .10$ versus H_a: $p_c - p_t < .10$ where p_c is the no nausea rate during the overall period after treatment with olanzapine + fosaprepitant and p_t is the no nausea rate after olanzapine + placebo. Assuming p_c = 37% and using a one-sided Type I error rate of 0.05 with one planned interim analysis for efficacy and futility (non-binding) occurring after 50% of patients have enrolled and completed the Nausea and Vomiting Daily Diary/Questionnaire, 310 patients per arm will provide 80% likelihood (or power) to conclude that olanzapine + placebo is non-inferior to olanzapine + fosaprepitant if the no nausea rate with olanzapine + placebo is 37%.

We anticipate that as much as 10% of patients will be lost due to cancellation or major violations, and thus the total target sample size will be inflated to 690 (345 per arm).

13.2.2 Accrual Rate and Accrual Duration

The proposed study is a standard antiemetic study for which patient accrual should be very timely and efficient. There are no complex accrual issues and no demands for extensive resources in the protocol. The investigators have extensive experience in conducting phase II and phase III antiemetic studies. The Alliance Symptom Intervention Committee expressed marked interest in participating in this trial. Considering the accrual rate in the previous Alliance olanzapine trial, the patient accrual is estimated to be 40 patients per month, supporting that the accrual will be completed within 18 months.

13.2.3 Primary Endpoint Completion Date for ClinicalTrials.gov Reporting

For purposes of ClinicalTrials.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least 5 days.

13.3 Statistical Design and Analysis of the Primary Endpoint

13.3.1 Primary Endpoint

No nausea is defined as a response of 0 in the nausea item of Nausea and Vomiting Daily Diary/Questionnaire in the overall (0-120 hours), acute (0-24 hours), and delayed (24-120 hours) periods.

13.3.2 Statistical Design

Interim analysis decision rule:

Interim analysis of non-inferiority and of inferiority of olanzapine + placebo as compared to olanzapine + fosaprepitant will be conducted when 50% of patients are enrolled and have completed the Nausea and Vomiting Daily Diary/Questionnaire. The Lan-DeMets family of alpha and beta spending functions corresponding to the O'Brien-Fleming boundary are used for controlling overall type I and type II error rates. Non-inferiority of olanzapine + placebo will be concluded if p-value <= 0.006 (corresponding to $Z > 2.538$) and inferiority of olanzapine + placebo will be concluded if p-value >= 0.370 (corresponding to $Z < 0.331$). The second stage of this clinical trial shall continue if p-value is in the interval of (0.006, 0.370).

Final analysis decision rule:

Final analysis will be conducted when all target patients are enrolled and have completed the Nausea and Vomiting Daily Diary/Questionnaire. Non-inferiority of olanzapine + placebo will be concluded if p-value < 0.048 (corresponding to $Z > 1.662$) and inferiority of olanzapine + placebo will be concluded if p-value >= 0.048 (corresponding to $Z >= 1.662$).

13.3.3 Study Operating Characteristics

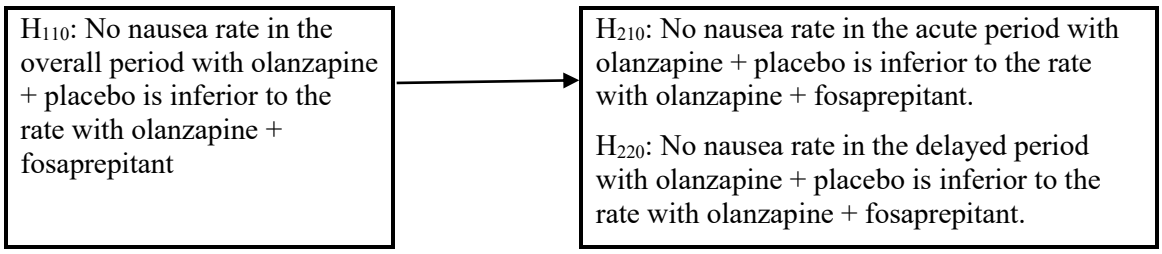
Simulation studies of 10,000 clinical trials are conducted for the proposed group sequential design. The probabilities of early stopping (at the interim analysis) and empirical powers for various scenarios are summarized in the following table. Of particular interest, assuming that the no nausea rate with olanzapine + fosaprepitant in the overall period is 37% and the no nausea rate with olanzapine + placebo is 27% (that is, olanzapine + placebo is inferior to olanzapine + fosaprepitant), there is a 64.72% chance of stopping the trial early to conclude that olanzapine + placebo is inferior and there is a 4.63% chance of the trial concluding that olanzapine + placebo is non-inferior to olanzapine + fosaprepitant (type I error). In another scenario where the no nausea rate with olanzapine + fosaprepitant is 37% and the no nausea rate with olanzapine + placebo is 37% (that is, olanzapine + placebo is truly non-inferior to olanzapine + fosaprepitant), the likelihood of stopping early to conclude inferiority is 7.13% and the likelihood of the trial concluding that olanzapine + placebo is non-inferior to olanzapine + fosaprepitant is 80.38% (power).

Probability of no nausea		Interim analysis conclusion		Early stopping	Final analysis conclusion		Power
olanzapine + fosaprepitant	olanzapine + placebo	Noninferior	Inferior		Noninferior	Inferior	
37%	27%	.54%	64.72%	65.26%	4.09%	30.65%	4.63%
	32%	5.18%	28.51%	33.69%	29.74%	36.57%	34.92%
	37%	23.15%	7.13%	30.28%	57.23%	12.49%	80.38%
	40%	42.52%	2.24%	44.76%	51.69%	3.55%	94.21%

13.3.4 Analysis Plan:

A modified intent-to-treat principle [33] will be applied for statistical analysis of efficacy in evaluable patients. Evaluable patients are defined as all patients meeting the eligibility criteria who did not cancel prior to receiving treatment and had no major violations.

The proportions of patients with no nausea during the overall, the acute, and the delayed period will be summarized by treatment arm. They will be tested in a sequential manner, using a Simes gatekeeping procedure [34] to maintain the overall significance level at the specified by the Lan-DeMets family of alpha spending function [35]. The difference in no nausea proportions between arms will be estimated along with a one-sided 95% confidence interval. The tests and the confidence intervals will be constructed using normal approximation of the binomial distribution adjusted for the non-inferiority margin.[35]



Step 1. The null hypothesis of H_{110} serves as a gatekeeper;

Step 2. The null hypotheses of H_{210} and H_{220} are tested only after H_{110} has been rejected.

As the inference of H_{110} may depend on whether or not some hypotheses (H_{210} or H_{220}) are rejected in the subsequent family, we will adopt the Simes gatekeeping procedure rather than Bonferroni gatekeeping procedure. A SAS macro %GateKeeper will be utilized to implement the decision matrix algorithm for adjusted p-values.

13.4 Analysis of Secondary Endpoints

13.4.1 Secondary Endpoints

a. Complete response (no emetic episodes and no use of rescue medication) during the acute, delayed and the overall periods as measured by the Nausea and Vomiting Daily Diary/Questionnaire.

b. Potential toxicities as ascribed to olanzapine as measured by the Nausea and Vomiting Daily Diary/Questionnaire.

c. Nausea scores (0-10) repeatedly measured by the Nausea and Vomiting Daily Diary/Questionnaire.

d. Frequency of rescue medication as measured by the Nausea and Vomiting Daily Diary/Questionnaire.

13.4.2 Secondary Analysis

The main objective of the secondary endpoints is to help us understand the full picture of patients' experience on these two antiemetic regimens. Our main objective is to estimate difference in these endpoints between the two arms and superiority tests will be used for exploratory comparisons. Analysis of secondary endpoints b. (toxicities) and d. (rescue medication) will only include patients who started their assigned treatment and patients will be analyzed based on the treatment they received (per protocol analysis population). Analysis of secondary endpoints a. (complete response) and c. (nausea score) will use the modified ITT analysis population as described for the primary endpoint. If there is a high rate of drop-out or noncompliance, per protocol analysis of these endpoints will be conducted as a sensitivity analysis. Multiplicity will not be adjusted for secondary analyses, hence, statistically significant findings from secondary analyses are exploratory in nature and therefore shall be interpreted as such.

a) The CR rate for the overall, the acute, and the delayed period will be summarized by treatment arm and will be compared using a Chi-squared test. The difference in CR rates between arms will be estimated along with a 95% confidence interval. Using the CR rates reported in our previous study[59], a sample size of 620 evaluable patients will provide more than 80% power, at a two-sided Type I error rate of 0.05, to detect the following improvement in CR rates:

Period	CR rate		Power (%)
	olanzapine + fosaprepitant	olanzapine + placebo	
Acute (0 – 24 hours)	.86	.93	82
Delayed (25 – 120)	.67	.77	80
Overall (0 – 120)	.64	.76	85

a) b) Incidences of toxicities will be summarized by type and by treatment arm. Incidences of toxicities will be compared between arms using a Chi-squared test or the Fisher's exact test as appropriate. Due to different types of toxicities and varying incidence rates, the power, at a two-sided Type I error rate of 0.05, to detect various differences in toxicity incidences between the arms with this sample size is given below.

Toxicity level	Toxicity incidence		Power (%)
	olanzapine + fosaprepitant	olanzapine + placebo	
Low	.05	.01	84

Medium	.20	.11	88
High (most conservative)	.50	.38	86

In addition, undesired sedation and appetite increase as collected in the Nausea and Vomiting Daily Diary/Questionnaire will be analyzed by repeated measures analyses including descriptive statistics, graphical approaches, and growth curve models to account for the factor of day and time trend.

c) In addition to the primary analysis described in Section 13.3.4, nausea scores (0-10) repeatedly measured by the Nausea and Vomiting Daily Diary/Questionnaire will be analyzed using the repeated measures analyses and growth curve models as described above for undesired sedation and increase in appetite.

d) The proportion of patients taking any rescue medication as reported in the Nausea and Vomiting Daily Diary/Questionnaire will be summarized by treatment arm and will be compared between arms using a Chi-squared test or the Fisher's exact test as appropriate. With this sample size, in the most conservative scenario where the proportion of patient taking rescue medication is 50%, there is an 86% power, at the two-sided Type I error of 0.05, to detect a 12% decrease in the proportion of patients taking rescue medication from 50% in the olanzapine + fosaprepitant arm compared to 38% in the olanzapine + placebo arm.

In addition, the number of pills taken will be analyzed using the repeated measures analyses and growth curve models as described above.

13.5 Economic Data Analysis:

Economic Evaluation Overview: Analyses of costs (in $USD), cost-effectiveness (in $USD per averted nausea), and cost-utility (in $USD per Quality-Adjusted Life Year (QALY) gained) will be performed, will include direct medical costs and will use a 6-day time horizon. Costs will be calculated as quantities X unit costs for each type of health service or pharmaceutical used.

Perspective: We adopt the healthcare sector perspective, which includes all direct medical costs in the cost analysis, including both medical costs borne by the payer and those borne by the patient. The healthcare sector perspective is the predominant perspective used in economic evaluations of drug therapy in oncology [43, 44]. We choose not to also conduct analysis from an exclusively patient perspective because in the trial, unlike in everyday medical practice, patient out-of-pocket costs for the anti-emetic agents are $0. We use Medicare unit prices for the total cost to the payer of these agents, and one might consider predicting what patient out-of-pocket cost would be for Medicare patients off-protocol. However, only 19% of Medicare patients do not have some source of supplemental or alternative coverage to the standard Medicare benefit [45], and it is very difficult to predict out-of-pocket costs for the remaining 81% of patients, which could range from $0 to 100% of the total cost of the drug, depending on the generosity of their insurance benefits. While patients incur other health care costs, past research and our expectations are that drug costs largely determine cost differences between anti-emetic regimens. Therefore, we do not feel we can provide a useful analysis of costs of anti-emetics from the patient perspective; such a study is best conducted outside a clinical trial.

Measurement: Health services and pharmaceuticals used will be assessed by patient self-report, as recorded by the nurse/research coordinator. Medical coders at Wayne State University will define typical sets of ICD-9, CPT, HCSPS and NDC codes used for billing for each drug and category of service. For health care services where the appropriate codes are ambiguous, medical

insurance claims with billing codes will be obtained, as described in the background Section 1.8 of the protocol. Medicare unit costs will be used for consistency to price services and drugs defined by these billing codes for all patients, including for patients covered under other insurance plans.[46-48] EQ-5D-3L health status responses will be converted into utility weights using area-under-the-curve methods applied to the US population value set. [40]

Analysis: Due to the short time window of the intervention, all costs will be valued in 2017 dollars with no adjustment for inflation or time discounting.

Costs: Comparison of costs between treatment arms must account for the right-skewed distribution of costs. We will use nonparametric bootstrap to compare mean costs in a univariate analysis, and generalized linear models with log link and gamma family controlling for stratification factors, baseline fatigue/QOL and other patient characteristics, in a multivariate analysis.

Utilities: We will estimate average health utilities for several patient health status subgroups: nausea vs. no-nausea, emesis vs. no-emesis, sedation vs. no-sedation, and combinations of these conditions.

Cost-effectiveness and cost-utility ratios: The relative value of the olanzapine and fosaprepitant arm over the olanzapine arm is measured by incremental cost-effectiveness and cost-utility ratios: ratios of the difference in average costs over the difference in the proportion of patients with no nausea or in the average QALYs gained between patients in the 2 comparative arms. Stochastic uncertainty around the estimates will be assessed with confidence intervals constructed using the bootstrap percentile method. [49]

13.6 Analysis plan for continuation phase:

The proportion of patients participating in the optional continuation phase will be summarized separately by treatment arm. The no nausea rates at the end of initial cycle will be compared between patients who select to continue vs. those who did not for each arm using a Chi-squared test. The no nausea rates among patients who chose to continue will be compared between treatment arms using a Chi-squared test. Logistic regression will be conducted to compare no nausea rates in the continuation phase between the treatment arms adjusting for patient response to their treatment in the first cycle.

Complete response rates will be analyzed using the same approach.

Adverse events occurring during this treatment phase will be summarized by treatment arm and will be compared between arms using a Chi-squared or a Fisher's exact test as appropriate.

Please note that due to the potential bias resulting from the optional and the unblinded nature of the continuation phase, this comparison is for exploratory purposes only.

13.7 Study Monitoring

13.7.1 Adverse Event Stopping rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as possible, probable, or definite) that satisfy the following criteria:

1. If 7 or more of the first 20 treated patients in either arm (or 35% of all patients after 20 patients have been accrued) experience a grade 3 or higher non-hematologic adverse event.
2. If 3 or more of the first 20 treated patients in either arm (or 15% of all patients after 20 patients have been accrued) experience a grade 4 or higher non-hematologic adverse event.

13.7.2 Accrual monitoring and stopping rule

Slow Accrual: Patient accrual will be closely monitored by the investigators and secondary statistician on a monthly basis. If the accrual rate falls below 50% of expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment.

13.8 Study Reporting

13.8.1 This study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every month as per NCI guidelines.

13.8.2 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrials.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

13.9 Inclusion of Women and Minorities

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	2	1	0	5
Asian	8	6	0	0	14
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	42	37	1	0	80
White	328	238	16	8	590
More Than One Race	0	0	0	0	0
Total	381	283	18	8	690

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	0	0	0	0	0

- Ethnic Categories:
  - Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”
  - Not Hispanic or Latino
- Racial Categories
  - American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

- Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
- Black or African American – a person having origins in any of the black racial groups of Africa.
- Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
- White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be one substudy, Alliance A221602-ST1 and all patients are encouraged to participate.

14.1 Olanzapine Pharmacogenomics and Chemotherapy induced nausea and vomiting

14.1.1 Background

Chemotherapy-induced nausea and vomiting (CINV) is a major severe side effect commonly observed in cancer patients undergoing treatment. This debilitating condition is associated with deterioration in life quality[50-53]CINV occurs in part from stimulation of a reflex pathway controlled by the brain and is triggered by impulses from the chemoreceptor trigger zone, gastrointestinal tract and possibly the cerebral cortex. Neurotransmitters notably dopamine, serotonin, substance P and their receptors have been reported to play critical roles in CINV. [54, 55]

The introduction of 5-hydroxytryptamine$_3$ (5-HT$_3$) receptor antagonists revealed a central role of serotonin in the mechanism of acute emesis [56] with delayed emesis being attributed largely to the activation of neurokinin 1 (NK-1) receptors and substance P. 5-hydroxytryptamine (5-HT$_3$) receptor antagonists plus dexamethasone have significantly improved the control of acute CINV. [50,51] Studies have also demonstrated additional improvement in the control of acute and delayed CINV with the use of palonosetron, a second generation 5-HT$_3$ receptor antagonist [51], aprepitant, a neurokinin-1 (NK-1) receptor antagonist [56]**,** and olanzapine, which blocks multiple neurotransmitter receptors in the central nervous system notably serotonergic receptors.[57]

Presently, many guidelines recommended for highly emetogenic chemotherapy regimens involve a 5-HT$_3$ receptor antagonist, an NK-1 receptor antagonist, and dexamethasone. [58] Despite the use of multiple measures, CINV still persists in some patients, while others have minimal nausea or vomiting. A recent study reported that when olanzapine was added to a 5-HT$_3$ receptor antagonist, aprepitant and dexamethasone there were patients who showed substantial improvements in complete response rate (no vomiting and no use of rescue medications) and patients who had no nausea (through the 5 day period following the single dose of chemotherapy), when compared to patients in a placebo study.[59] The substantial variations shown in improvements in vomiting and nausea could be due in part to individual differences in the function of the genes that metabolize, activate and/or are targets for the antiemetic drugs.

This current proposal focuses on the use of olanzapine, an atypical antipsychotic drug and a multiple neurotransmitter receptor antagonist, in combination with palonosetron or ondansetron (5-HT$_3$ receptor antagonists), dexamethasone and/or fosaprepitant (NK-1 receptor antagonist). One arm of the study proposes to eliminate fosaprepitant, as a step

towards reducing the cost of expensive antiemetic drug treatments during chemotherapy while still maintaining similar levels of control over nausea and vomiting as observed in the olanzapine study. [59]

Olanzapine is metabolized predominantly by oxidation mediated through CYP1A2 with CYP2D6 as a minor metabolizer and it also undergoes glucuronidation by UGT1A4, UGT2B10 and metabolized also by flavin monooxygenases (FMO1 and FMO3).[54,57] Olanzapine also binds strongly to dopaminergic (D1, D2, D3 and D4, Ki=11-31 nM), alpha-1-adrenergic, (α_1, Ki=19nM), histamine H1(Ki=7nM), and muscarinic (M1, M2, M3, and M4, Ki=32-132nM) receptors.[57,61] It also has high affinity for the serotonin receptor subtypes 5-hydroxytryptamine 2 subtypes (5-HT_{2A}, 5-$HT_{2C,}$ Ki=4 and 11nM), 5-hydroxytryptamine 3 (5-$HT_{3,}$ Ki= 57nM), and 5-hydroxytryptamine 6 (HT_6, Ki=5nM) [61,62] Differences in olanzapine plasma concentrations in patients have been reported to contribute to risk of adverse effects and inadequate response to olanzapine.[60] Furthermore pharmacokinetics studies report that olanzapine clearance is lower in women than in men suggesting gender differences in olanzapine metabolism as well.[63]

Aprepitant is the other antiemetic drug that will be eliminated in one arm of the parent study. It is administered intravenously as fosaprepitant, a prodrug of aprepitant and helps to prevent acute and delayed nausea and vomiting associated with chemotherapy. Aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19.[64] CYP3A5 may also metabolize aprepitant as it accounts for about 50% of total hepatic CYP3A.[65] It is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors but has little or no affinity for serotonin (5-HT_3), dopamine, and corticosteroid receptors, the targets of existing therapies for (CINV).[66] All of these enzymes are proteins and the genes encoding them are genetically polymorphic as such conferring variable activities to the proteins. Therefore, performing pharmacogenomic studies may offer some understanding of the genetic factors underlying these variations in CINV response.

Genome wide association studies (GWAS) have been reported for some nausea and vomiting associated conditions such as migraines [67] motion sickness [68] and post-operative nausea and vomiting (PONV). [69] To date, no GWAS studies have been done to determine the gene(s) that are highly linked to the CINV condition and reasons for this may be the cost associated with such studies.

Only the candidate gene (single nucleotide polymorphism, SNP) approach has been reported for evaluating the genetic influence on CINV and a review summarizing those studies was reported recently.[70] Polymorphisms in genes such *as CYP1A2, CYP2D6, CYP3A4, CYP3A5, HTR3A, HTR3B, HTR3C, HTR3D, ABCB1,* and *SLC22A1* have been evaluated in association with antiemetic efficacy of drugs including palonosetron, ondansetron, tropisetron, dexamethasone, aprepitant, and granisetron.[70]

In this proposal, our focus is on the pharmacogenomics of olanzapine. Most studies have reported on olanzapine's use in reducing and preventing CINV and on its metabolism and disposition as well as its target, however, there is little or no information on how variations in the genes that encode all those proteins affect CINV. The pharmacokinetics of olanzapine has been reported to be influenced by polymorphisms in *GSTM3*, and *GRIN2B* while *CYP2C9, TPMT, UGT1A1* and *ABCB1* polymorphisms have been reported to be related to the adverse effects of olanzapine.[71] Interestingly, a *CYP1A2* SNP, rs762551 (CYP1A2*F, C>A), with high basal enzyme activity, was reported to be associated with reduced olanzapine serum concentrations in Caucasian psychiatric patients[72] but other reports have indicated lack of correlation from this same polymorphism.[60,73,74]. In

another report, a SNP upstream of *CYP1A1* and downstream of *CYP1A2,* rs2472297 was shown to influence olanzapine serum levels.[75] As well, there are reports indicating lack of association between *CYP2D6* functional polymorphisms and olanzapine pharmacokinetics except when stratified for smoking[60]suggesting that smoking status may correlate with the variation in olanzapine metabolism and levels. Thus, several of these studies have been inconsistent in associating certain SNPs to the metabolism of and response to olanzapine. These inconsistencies could be due in part to the different populations studied (ethnic variation) and the specific SNPs chosen for genotyping. [76-81]. A list of genes that have been associated with olanzapine and fosaprepitant/aprepitant in literature and in the drug bank is shown below: [redacted]

Genes encoding Protein				
Drug	**Targets**	**Carriers**	**Transporters**	**Metabolizing enzymes**
Olanzapine	*ADRA1A, ADRA1B, ADRA2A, , ADRA2B, ADRA2C, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, DRD1, DRD2, DRD3, DRD4, DRD5, HRH1, HRH2, HRH4, HTR1A, HTR1B, HTR1D, HTR1E, HTR2A, HTR2B, HTR2C, HTR3A, HTR3B, HTR3C, HTR5A, HTR6, HTR7,*	*ALB, ORM1*	*ABCB1*	*CYP1A2, CYP2D6, CY2C19, CYP2C9, FMO3, CYP3A4, CYP1A1, CYP3A5, CYP3A43, FMO1, UGT1A1, UGT1A4, UGT2B10*
Fosaprepitant/ aprepitant	*TACR1*			*CYP3A4, CYP3A5, CYP3A7, CYP1A2, CYP2C9,CYP2C19*

In view of the differences in such reports [70,76-79] and the paucity of any information relating to individual variations in olanzapine associated CINV, we will elucidate, the genetic determinants of CINV focusing primarily on olanzapine's usage in the Alliance protocol A221602. We would systematically identify the polymorphisms in those genes responsible for the pharmacokinetics (metabolism) transport and pharmacodynamics (targets) of olanzapine. As well, as a secondary focus we will also identify the genetic polymorphisms associated with fosaprepitant/aprepitant and evaluate their association with CINV in the patients undergoing treatment. Thus, the two arms of the study could serve as ideal backgrounds for exploring possible associations of specific SNPs with variations in levels of CINV.

14.1.2 Objectives:

1. To determine which polymorphisms in olanzapine and fosaprepitant related genes are associated with nausea in the acute, delayed, and overall periods.
2. To determine which polymorphisms in olanzapine and fosaprepitant related genes are associated with complete response (CR) in the acute, delayed, and overall periods.
3. To determine which polymorphisms in olanzapine-related genes are associated with toxicities ascribed to olanzapine.

Approximately 620 patients will be evaluable for the primary outcome. We anticipate obtaining samples for a total of 496 patients (80% of evaluable patients).

Hypothesis: We hypothesize that SNPs in genes that metabolize (*CYP1A1, CYP1A2, CYP2D6, UGT1A4, UGT2B10, FMO1* and *FMO3)*, that transport (*ABCB1)* and are targets (*HTR2A, HTR2C, HTR3A, HTR6* - serotonergic receptor subtypes; *DRD1-4, dopaminergic* receptors; *ADR1A*, alpha-1-adrenergic receptor; *HRH1,* histaminic receptor; *CHRM1-5*,

muscarinic receptors) for olanzapine will correlate with the severity of CINV in patients undergoing treatment. We further hypothesize that SNPs in *TACR1* and in *CYP1A2*, *CYP2C19*, *CYP3A4, CYP3A5,* will also correlate with the severity of CINV in patients in the fosaprepitant treatment arm.

We propose to achieve this hypothesis by genotyping patient DNA samples for tagSNPs in genes listed above responsible for the metabolism, transport and are targets for olanzapine and correlate these SNPs with the extent of nausea and vomiting. SNPs which have previously been identified and been associated with olanzapine pharmacokinetics and/or pharmacodynamics as well as unique SNPs in genes listed in table under section 14.1.1 will be evaluated or validated for the antiemetic efficacy of olanzapine [60, 61]. A partial list with some tagSNPs to be genotyped is shown below.

Gene	dbSNP rsid	Chromosome	Location/ function	Major allele	Minor allele	Global Minor (variant) Allele Frequency	Variant genotype	% variant genotype frequency
ABCB1	rs868755	7	intron	G	T	0.330	0.109	10.9
ADRA1A	rs1048101	8	500B downstream	G	A	0.352	0.124	12.4
AHR	rs4410790	7	intron	T	C	0.467	0.218	21.8
CYP1A2	rs762551	15	intron	A	C	0.370	0.137	13.7
CYP3A43	rs472660	7	intron	G	A	0.261	0.068	6.8
FMO1	rs7877	1	3-UTR	C	T	0.429	0.184	18.4
HRH1	rs13061242	3	2KB upstream	G	A	0.280	0.078	7.8
HTR2A	rs9567732	13	intergenic	C	T	0.270	0.073	7.3
HTR3A	rs1062613	11	5-UTR	T	C	0.248	0.0615	6.2

14.1.3 Methods

Blood collection: Whole blood sample will be collected in 1 x10 mL EDTA vacutainer tube (lavender top) from patients prior to treatment (See Section 6.3) for germline DNA isolation. Blood samples will be sent to the Mayo Clinic and DNA will be isolated in the Biospecimen Accessioning and Processing (BAP) lab.

SNP selection and Genotyping:

Genotype data from the National Center for Biotechnology Information (NCBI) dbSNP database will be used with programs in National Institute of environmental Health Sciences (https://snpinfo.niehs.nih.gov/), Genome variation server http://gvs.gs.washington.edu/GVS144/) to derive tagged SNPs from an initial list of 27 genes namely *ABCB1, ADRA1A*, *AHR, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5*, *CYP1A1*, *CYP1A2, CYP2D6, CYP3A4, CYP3A43 , CYP3A5, DRD1, DRD2, DRD3, DRD4, FMO1, FMO3, HRH1*, *HTR2A, HTR2C, HTR3A, HTR6, TACR1, UGT1A4* and *UGT2B10.* SNPs with allele frequencies ≥ 20% and r2 ≥ 0.80 will be selected for genotyping. It is important to indicate here that there's ethnic variation in specific SNPs and frequency of SNPs, therefore genotype information from the database should reflect the patient population on the trial. For example, tagSNPs will be derived from genotype data from both Caucasian and African-American databases. The acquired tagSNPs will be genotyped in the Genotyping Core of the Mayo Clinic Medical Genome Facility (MGF) or in any

Alliance associated genotyping core on either the Sequenom or the Illumina GoldenGate custom array. The tagSNPs to be genotyped will include the nine listed in Table 1.

Genotyping: The Agena iPLEX (previously called sequenom) genotyping protocol involves PCR amplification of DNA using SNP specific primers, followed by a base extension reaction using the iPLEX Gold chemistry (Agena Biosciences, San Diego, CA). The protocol has been used for years and will briefly be described here. SNP-specific PCR and extension primers were designed and organized into pools with the Assay Design Suite (Agena). All primers were purchased from Integrated DNA Technologies (Coralville, IA). A QC run was performed with Coriell and CEPH controls, and results were tested for Mendelian inconsistencies. HotStar Taq Polymerase (Qiagen) was used for all PCRs. 15 ng of DNA was added to each 5-ul PCR reaction mixture in a 384-well microtiter plate. The PCR condition was 94°C for 15 min for hot start, followed by 45 cycles of denaturing at 94°C for 20 sec, annealing at 56°C for 30 sec, extension at 72°C for 1 min for 45 cycles, and final incubation at 72°C for 3 min. The PCR products were then treated with SAP (shrimp alkaline phosphatase, Agena) for 40 min at 37°C then ramped to 85°C for 5 min to remove excess dNTPs. The final base extension products were diluted in double distilled water and then treated with 6mg of SpectroCLEAN (Agena) resin per well to remove contaminating salts. 10-18 nl of treated extension product was spotted to the appropriate location on a 384-pad SpectroCHIP II (Agena) using a RS1000 Nanodispenser (Agena, San Diego, CA). A MassARRAY Analyzer Compact MALDI-TOF MS (Agena) was used for data acquisitions from the SpectroCHIP. All resultant genotyping calls were performed in real time by the MassARRAY Typer Analyzer v4.0.26.73 (Agena).

14.1.4 Analyses

SNP analysis: Results from genotyping will be sent to the bioinformatics/statisticians for analyses to correlate the SNPs to CINV and any other clinical outcome the end correlates indicated in protocol A221602 such as: (i) no nausea for the overall (0-120 hours post-chemotherapy), acute (0-24 hours post- chemotherapy), and delayed periods (24-120 hours post-chemotherapy) for patients receiving highly emetogenic chemotherapy; (ii) complete response (CR) rates (no emetic episodes and no use of rescue medication) in the acute, delayed, and overall periods; (iii) incidence of potential toxicities ascribed to olanzapine including sedation.

Statistical Analysis:

The following analyses will be conducted separately for each SNP. Bonferroni correction will be used to account for the number of SNPs considered in the analysis. Due to the exploratory nature and the limited sample size, no multivariable models will be conducted for this aim.

Patients will be classified by the status of their variant genotype (yes vs. no). The no nausea rate and the complete response rate will be summarized separately by variant genotype status and will be compared between variant genotype groups using a Chi-square test for each time period across both treatment arms.

The incidence of toxicities potentially ascribed olanzapine, including sedation, will be summarized by variant genotype status and will be compared between arms using a Chi-squared test.

Similar analyses will be conducted for polymorphism in fosaprepitant-related genes will be conducted among patients in the olanzapine + fosaprepitant arm only.

Additionally, we will explore the association between these polymorphisms with the outcomes described using the same methods treating the polymorphism as three groups (homozygous wild type vs. heterozygous vs. homozygous variant)

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

15.1 Institutional Credentialing

None

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17.0 MODEL CONSENT FORM

Study Title for Study Participants**:**

Testing the effectiveness of olanzapine with or without fosaprepitant in preventing nausea and vomiting in patients receiving chemotherapy

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

Olanzapine with or without fosaprepitant for the prevention of chemotherapy induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC): A Phase III Randomized, Double Blind, Placebo-Controlled Trial.

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services.

What is the usual approach to my diagnosis?

You are being asked to participate in this study because treatments for cancer can cause the side effect of nausea and vomiting. People who do not take part in this study will receive standard medications that have been approved by the Food and Drug Administration for nausea and vomiting.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual approach described above.
- You may choose to take part in a different study, if one is available.

Why is this study being done?

You have cancer and will be receiving chemotherapy that may cause nausea and vomiting. Olanzapine is a medication which has been approved by the Federal Drug Administration (FDA) for the treatment of specific mental illnesses and has been used in many patients over the past 15 years, but it is not FDA approved to treat nausea and vomiting. Olanzapine has been shown to have anti-nausea and anti-vomiting effects in patients receiving chemotherapy. In previous studies, olanzapine was usually given in combination with other drugs, including a drug called fosaprepitant. The purpose of this study is to see if olanzapine given in combination with these

other drugs, is still as effective without using the fosaprepitant. Information from this study will also be used by researchers at Wayne State University to evaluate health care costs when taking treatments used for nausea and vomiting.

There will be about 690 people taking part in this study.

What are the study groups?

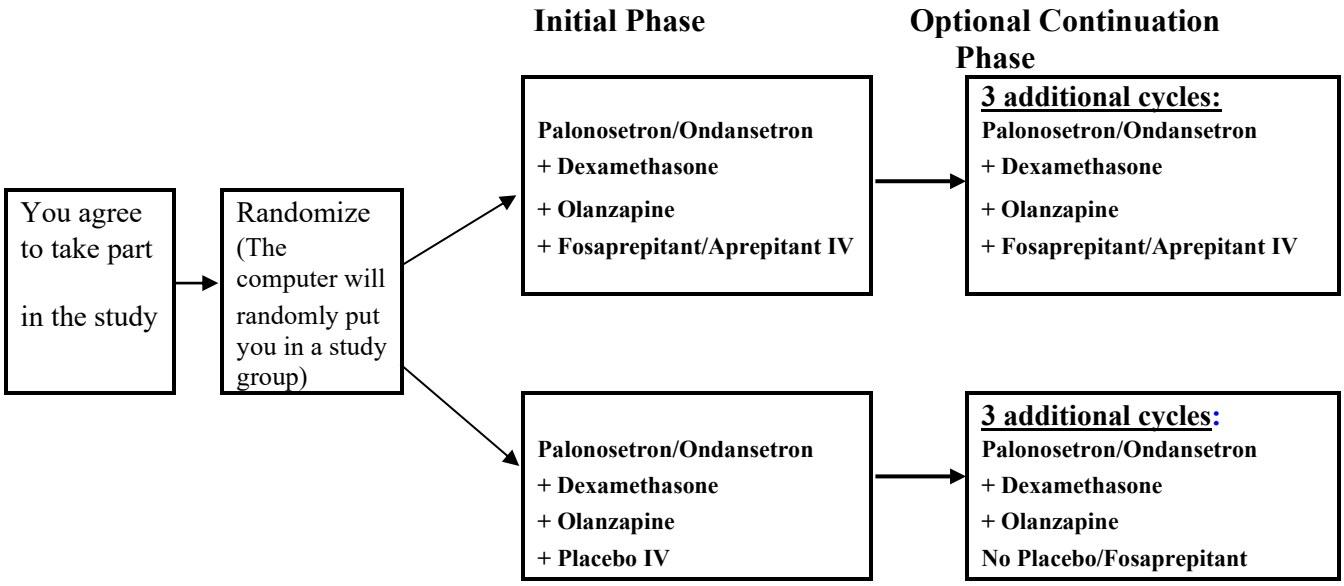
This study has 2 study groups.

- **Group 1** will get the usual chemotherapy drugs used for your type of cancer, either cisplatin or cyclophosphamide and doxorubicin, as well as following anti-nausea/vomiting drugs:
  - **Olanzapine** by mouth on the day of chemotherapy and on days 2, 3, and 4 after chemotherapy
  - **Ondansetron** (by mouth or through a vein in your arm) or **palonosetron** through a vein in your arm on the day of chemotherapy, plus
  - **Dexamethasone** by mouth on the day of chemotherapy and on days 2, 3, and 4 after chemotherapy, plus
  - **Fosaprepitant or Aprepitant** through a vein in your arm on the day of chemotherapy

- **Group 2** will get the usual chemotherapy drugs used for your type of cancer, either cisplatin or cyclophosphamide and doxorubicin, as well as the following anti-nausea/vomiting drugs:
  - **Olanzapine** by mouth on the day of chemotherapy and on days 2, 3, and 4 after chemotherapy
  - **Ondansetron** (by mouth or through a vein in your arm) or **palonosetron** through a vein in your arm on the day of chemotherapy, plus
  - **Dexamethasone** by mouth on the day of chemotherapy and on days 2, 3, and 4 after chemotherapy, plus
  - **Placebo** through a vein in your arm. The placebo looks like one of the IV study drugs but does not contain active medication.

We will use a computer to assign you to one of the study groups (also called "randomization"). This means that you will be put into a group by chance, like flipping a coin. We assign patients in this way because no one knows if one treatment is better or worse than the others.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



Initial Phase: On the first day of protocol treatment (Day 1), before you receive your chemotherapy, you will take all of the study drugs listed above in your group assignment. Olanzapine may be taken before you receive your chemotherapy or at bedtime. On Days 2, 3, and 4 after receiving chemotherapy, you will be asked to take olanzapine and dexamethasone tablets at about the same time of day as the time you received the study drugs on Day 1. This four-day period of treatment is called "one cycle" of study treatment.

	Day 1	**Day 2**	**Day 3**	**Day 4**
Group 1	Olanzapine Ondansetron or Palonosetron Dexamethasone Fosaprepitant/Aprepitant	Olanzapine Dexamethasone	Olanzapine Dexamethasone	Olanzapine Dexamethasone
Group 2	Olanzapine Ondansetron or Palonosetron Dexamethasone Placebo	Olanzapine Dexamethasone	Olanzapine Dexamethasone	Olanzapine Dexamethasone

Continuation Phase: After you complete the first cycle of protocol treatment, you may choose to continue on the same anti- nausea regimen for an additional three cycles. This is called the "Continuation Phase" of the study. When you return to the clinic to receive your next cycle of chemotherapy, clinic staff will ask if you would like to continue on the same regimen. If you decide to participate in this three-cycle Continuation Phase, you will be told whether you were

receiving fosaprepitant or placebo. If you were taking fosaprepitant or aprepitant, you will continue to receive it as part of your anti-nausea treatment, along with olanzapine, ondansetron or palonosetron, and dexamethasone. If you were getting placebo, you will not continue receiving placebo, but you will continue the treatment with the olanzapine, ondansetron or palonosetron, and dexamethasone.

If you decide that you do not want to participate in the Continuation Phase, but would still like to know what treatment you were receiving, research staff at your clinic may contact the Alliance Registration Office during regular business hours to get this information.

	Day 1	**Day 2**	**Day 3**	**Day 4**
Group 1	Olanzapine Ondansetron or Palonosetron Dexamethasone Fosaprepitant/ Aprepitant	Olanzapine Dexamethasone	Olanzapine Dexamethasone	Olanzapine Dexamethasone
Group 2	Olanzapine Ondansetron or Palonosetron Dexamethasone	Olanzapine Dexamethasone	Olanzapine Dexamethasone	Olanzapine Dexamethasone

How long will I be in this study?

You will be in the study for four days of anti-nausea medication plus two additional days to follow how you do with nausea and vomiting. If you choose to participate in the Continuation Phase, you will be in the study for an additional 3 cycles while you are still receiving chemotherapy.

What extra exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests and procedures including a urine pregnancy test if you are a woman of childbearing potential, to make sure it is safe for you to take part. If you join the study, there will be exams, tests, and procedures that will be done to closely monitor your safety and health. Most of these are included in the usual care you would receive even if you were not in a study.

You will be asked to complete questionnaires and telephone surveys as part of this study. The questionnaires will be used to find out more about how you are doing with any nausea or vomiting and how you feel during study treatment. In addition, you will be asked about any costs related to treatment for any nausea and vomiting. You don't have to answer any question that makes you feel uncomfortable.

Electronic surveys: For this study, you will be asked to complete the questionnaires on your personal smartphone or electronic device, which can be used to enter your answers to the questions. If you need help installing and/or using the questionnaire application (or "app") on your phone or tablet, ask for help at your study site. Someone may help you enter your answers in the device if you need.
The use of your own electronic device on a cellular network may result in a small cost to your data plan. Regardless of the device you use, your answers and personal information will not be stored on the device.

Your survey answers will be sent to the research database and will be kept private as described in the section below called, "Who will see my medical information?" Your e-mail address will only be used for this survey and will not be used for mail or marketing purposes. The Alliance will not keep your email address.

If using your phone or a tablet is not possible or if you prefer to complete the questionnaires on paper, a paper survey will be provided.

You will be asked to complete the surveys at the following time points:

During the study:

- You will be asked to complete questionnaires on day 1 prior to study treatment and each day for the next five days following the day of chemotherapy. You will be asked to complete a short questionnaire on the amount of nausea or vomiting you have experienced in the previous 24-hour period. You will also be asked complete a questionnaire about your general well-being and quality of life. These questionnaires should take about five minutes to complete.
- Staff from your clinic will contact you by telephone on days 2-6 of your treatment, to remind you to take your medication and ask about any symptoms you are experiencing. The staff will also ask you whether you made any additional visits to doctors or hospitals or began using other medications.
- If you did make any additional visits to doctors or hospitals, staff from your clinic may collect information from your medical chart and/or from your medical insurance claims regarding the costs of these services or medications. You may be asked to sign a form to allow the release of your personal health information to the study researchers. This information will be used by researchers at Wayne State University to evaluate health care costs when taking treatments used for nausea and vomiting.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- You may spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- The study drug(s)/study approach may not be better, and could possibly be worse, than the usual approach for your diagnosis.

There is also a risk that you could have side effects from the study drugs or study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

You can ask the study doctor questions about side effects at any time. Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different, so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. Keep in mind that there might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible side effects of Olanzapine:

COMMON, SOME MAY BE SERIOUS In 100 people receiving olanzapine, between 20 and 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving olanzapine, 4 to 20 may have:
• Fever • Back Pain • Dry Mouth • Constipation • Vomiting • Discoloration of the skin resulting from bleeding underneath, usually caused by bruising • Indigestion • Difficulty sleeping • Joint Pain • Dizziness • Unsteady walking • Tremor • Stuffy nose • Increased cough • Difficulty swallowing • Weight gain

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving olanzapine, 4 to 20 may have:
• Pain in the hands and feet

RARE, AND SERIOUS In 100 people receiving olanzapine, 3 or fewer may have:
• Chest pain • Severe muscle spasms • Lazy eye • Loss of bladder control • Urinary tract infection • Swelling of arms and legs

Reproductive risks:
You should not get pregnant, breastfeed, or father a baby while in this study. The drugs used in this study could be very harmful to an unborn or newborn baby. Check with the study doctor about what types of birth control to use and for how long.

Tell your study doctor right away if you suspect that you or your partner have become pregnant during the study or within 6 months after your last dose of study drug. Your doctor will ask for health information about the pregnancy until the pregnancy is complete.

What possible benefits can I expect from taking part in this study?

Olanzapine has been shown to have anti-nausea and anti-vomiting effects in patients receiving chemotherapy, and in preventing delayed nausea that occurs following chemotherapy. It is not possible to know at this time if the study drug(s)/study approach is better than the usual approach. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

In turn, the study doctor may remove you from the study, if:

- Your health changes and the study is no longer in your best interest
- New information becomes available
- You do not follow the study rules
- The study is stopped by the sponsor, Institutional Review Board, IRB, or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number).*

What are the costs of taking part in this study?

The olanzapine will be supplied at no charge to you while you take part in this study. It is possible that the olanzapine may not continue to be supplied free while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You or your healthcare plan will be charged for the dexamethasone and palonosetron or ondansetron. If you are randomized to the placebo arm, you will not be charged for the placebo. If you are randomized to the fosaprepitant or aprepitant arm, you or your insurance will be billed for fosaprepitant or aprepitant per usual care. The cost of getting the drugs ready and giving it to you is not paid by the study so you or your insurance company may have to pay for this.

You and/or your health plan/insurance company will need to pay for all of the other costs of care. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You are responsible for all co-pays and deductibles according to your insurance plan.

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

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you have legal rights to receive payment for this injury even though you are in a study.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the database may also be shared with these organizations. They are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Alliance for Clinical Trials in Oncology
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
- Researchers at Wayne State University

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Where can I get more information?

You may visit the NCI web site at [redacted] for more information about studies or general information about cancer. You may also call the [redacted]

A description of this clinical trial will be available on [redacted] as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

Additional Studies Section: *(Indicate clearly to participants that this is a separate section)*

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future.

The results *will not* be added to your medical records and you or your study doctor *will not* know the results.

Neither you nor your insurance will be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the optional studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

1. Optional sample collections for laboratory studies and/or biobanking for possible future studies

Researchers are trying to learn more about cancer and other health problems using samples from people's tissue, blood, urine, or other fluids. By conducting research on these samples, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about how genes affect health and disease and how people respond to treatment. Genes carry information about features that are found in you and your family, from the color of your eyes to health conditions for which you may be at risk. Research that studies your genes is known as genomics or genetics.

If you choose to take part in this optional study, the study doctor for the main study would like to collect blood for research on whether your genes cause differences in how your body responds to treatments.

In addition, the researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The additional research that may be done is unknown at this time. Storing samples for future studies is called "bio banking". The Biobank is being run by the Alliance and supported by the National Cancer Institute

What is involved?

If you agree to take part, here is what will happen next:

1) About 2 teaspoons of blood will be collected from a vein in your arm, before you begin study treatment.

2) Your baseline blood sample and some related health information will be sent to an Alliance researcher at the Mayo Clinic for use in the study described above. Remaining baseline blood samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.
3) Only qualified researchers can receive samples from the Biobank. There will be scientific and ethics reviews to ensure that the research is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted. You will not receive reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that will be available to qualified researchers. Information that could directly identify you will not be included.

What are the possible risks?

1) The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
2) Even without your name or other identifiers, your genetic information is unique to you. There is a risk that someone outside of the research could get access to your personal information in your medical records or trace information in a database back to you. The researchers believe the chance that someone could re-identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent by the biobank to the qualified researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any biobank and Alliance staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom the Alliance sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.

5) If research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the biobank will no longer be used and related health information will no longer be collected. This will not apply to those samples or related information that have already been given to or used by qualified researchers.

What if I have questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

Samples for the laboratory studies:

I agree to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study(ies) described above.

YES NO

Samples for future research studies:

My samples and related information may be kept in a biobank for use in future health research.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the main study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes*'.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____
Date of signature_____

APPENDIX I PATIENT QUESTIONNAIRE

PATIENT INFORMATION SHEET
TREATMENT
Patient Completed Quality of Life Booklet (Baseline)

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

1. This booklet is to be completed day 1 during your clinic visit prior to treatment.

2. The booklet contains 2 set of questions:
    a. Baseline Nausea and Vomiting Questionnaire
    b. EQ-5D-3L Health Questionnaire

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

4. Please return your booklet when you are finished.

Thank you for taking the time to help

PATIENT INFORMATION SHEET
TREATMENT
Patient Completed Quality of Life Booklet (days 2-6)

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

1. This booklet is to be completed days 2-6 (the 5 days following your chemotherapy), ideally, at about the same time your chemotherapy was given (1 hour before to 1 hour after your chemotherapy time).

2. The booklet contains 2 set of questions:
    a. Nausea and Vomiting Daily Diary/Questionnaire
    b. EQ-5D-3L Health Questionnaire

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

4. You may call a member of the study team to answer any questions you might have. You will be given a name and telephone number. You can call anytime with any concerns or questions. A nurse/research coordinator will also call you days 2-6 and they can answer questions you might have.

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

6. When the booklet is complete, return it in the provided envelope.

Thank you for taking the time to help

APPENDIX II BASELINE NAUSEA AND VOMITING 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 trouble 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 III NAUSEA AND VOMITING DAILY QUESTIONNAIRE

Date: ____/____/_____

Please take Olanzapine at the same time that you took it on Day 1 of the study. Record the time that you took the Olanzapine here: _____

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

	Nausea (check one)	*Vomiting (check one)	Number of extra nausea/vomiting pills taken because you developed nausea/vomiting
Last 24 hours	__None __Mild __Moderate __Severe	__None __Once __Twice __More than twice	__None __One __Two __More than two

*A single vomiting episode is defined as:

- a single vomit of solid 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 vomiting 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 trouble 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 IV DAILY NURSE TELEPHONE CONTACT

Nurse/Research Coordinator Contact
Days 2, 3 and 4

Daily Telephone contact *(check one)* ☐Day 2
☐Day 3
☐Day 4

Date of telephone contact or date of attempt to contact was made *(dd MMM yyyy)* _ _-_ _ _-_ _ _ _

Were you able to contact the patient? ☐Yes ☐No (If no, then end form)
If contacted, list the Time of day: HH:MM ___:___

Verify the following with the subject:

Dexamethasone 8 mg PO QD taken today *(check one)* ☐Yes ☐No

If "No", provide reason

_____

Olanzapine 10 mg PO QD taken today? *(check one)* ☐Yes ☐No

If "No", provide reason

_____

Number of vomiting episodes over the past 24 hours _____

Symptom Assessment: (Where 0 is none and 10 is as bad as it can be.)

Worst nausea over the past 24 hours *(circle one)*

0 1 2 3 4 5 6 7 8 9 10

Undesired sedation trouble over the past 24 hours *(circle one)*

0 1 2 3 4 5 6 7 8 9 10

Undesired appetite increase over the past 24 hours *(circle one)*

0 1 2 3 4 5 6 7 8 9 10

Rescue Medication taken? *(check one)* ☐Yes ☐No

(if yes):

Drug Name *(check one or more)*:

☐ Anticholinergics: Scopolamine transdermal patch (Transderm Scop)

☐ Diphenhydramine (Benadryl)

☐ Lorazepam (Ativan)

☐ Haloperidol (Haldol)

☐ Dronabinol (Marinol, Syndros)

☐ Prochlorperazine (Compazine)

☐ Metoclopramide (Reglan)

☐ Ondansetron (Zofran)

☐ Other *(list)*: _____

Dose *(check one or more. If more than one rescue medication, list drug to which that dose refers)*:

☐ 1 pill _____

☐ 2 pills _____

☐ 3 pills _____

☐ 4 pills _____

☐ 1 patch _____

☐ 1 infusion _____

☐ Other *(please specify)*: _____

Number of doses the past 24 hours *(check one or more. If more than one rescue medication, list drug to which that number of doses refers)*:

☐ 1 _____

☐ 2 _____

☐ 3 _____

☐ 4 _____

☐ 5 _____

☐ Other *(please specify)*: _____

Did you start taking any **other** new medications today, **other than** rescue medications, that you were not taking before *Day 1 of the protocol*?

(if yes):

Drug Name *(list one or more)*: _____

Dose *(check one or more. If more than one medication, list drug to which that dose refers*):

☐ 1 pill _____

☐ 2 pills _____

☐ 3 pills _____

☐ 4 pills _____

☐ 1 patch _____

☐ 1 infusion _____

☐ Other *(please specify)*: _____

Number of doses the past 24 hours *(check one or more. If more than one medication, list drug to which that number of doses refers)*:

☐ 1 _____

☐ 2 _____

☐ 3 _____

☐ 4 _____

☐ 5 _____

☐ Other *(please specify)*: _____

Did patient have any adverse events? *(check one)* ☐Yes ☐No

If yes, fill out AE form: Record all adverse events that meet the following criteria: grade 2 with attribution of possible, probable or definite and all grade 3, 4 and 5 regardless of attribution.

Health Care Use:

If the patient experienced an adverse event(s) of grades 2, 3, 4, or 5, **including grade 2 adverse event(s) unlikely related or unrelated to the intervention,** ask the patient if they used any health care for the treatment of the adverse event. Health care use includes any interaction with a health care provider regarding the adverse event(s). Some examples include visiting your oncologist at the hospital or in their office and receiving a prescription for a rescue therapy, calling or emailing the nurse or your primary care physician, visiting the emergency department or being hospitalized. Do not record visits to the pharmacy to fill a prescription for one of the reported medications.

Did you use any health care associated with adverse events in the past 24 hours? *(check one)*
☐Yes ☐No

*(Complete the form on the next page if you checked the **"Yes"** box above.)*

Comments

_____

_____

Please remind the patient to complete the patient diary. If possible, have the patient complete their questionnaire form while on the phone call. Please explain the rescue nausea medication information specifically "Number of extra (PRN) nausea/vomiting pills taken."

Health care use associated with adverse events in past 24 hours

Site of care and Provider types *(check as many Sites of care as apply, and for each one, which Providers were used there)*:

☐ Hospital Outpatient Department

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Emergency Department

☐ Emergency Medicine Physician

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Provider's office

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Phone call to provider

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Email to provider

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Telemedicine

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Hospital Inpatient Department

☐ Hematologist/oncologist ☐ Internal Medicine/Hospital Medicine Physician

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Intensive Care Unit (ICU) Hospital Inpatient Department

☐ Hematologist/oncologist ☐ Internal/Hospital Medicine Physician ☐ Critical/Intensive Care Physician

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Other *(please specify):* _____

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

If hospitalized, date of admission: _____

Name(s) of provider(s) *(record as accurately as patient can recall)*:

_____

Address(es) of provider(s) *(record as accurately as patient can recall)*:

_____

Reasons for use of health care *(check one or more. If more than one Site of Care was used, list Site(s) of Care in which each adverse event was treated)*:

☐ Nausea/Vomiting Reasons for use _____

☐ Sedation _____

☐ Fatigue _____

☐ Anemia _____

☐ Appetite changes _____

☐ Constipation _____

☐ Diarrhea _____

☐ Bleeding _____

☐ Blurred vision _____

☐ Arm or leg swelling _____

☐ Peripheral neuropathy _____

☐ Mental status change _____

☐ Severe headache _____

☐ Fever / Chills / Febrile neutropenia _____

☐ Urine and bladder changes / Proteinuria / Kidney problems _____

☐ Hypertension _____

☐ Blood clot / Venous thromboembolic event _____

☐ Thrombocytopenia _____

☐ Other adverse event *(please specify)*: _____

Laboratory tests *(check one):*

☐Yes ☐No

(if yes, check one or more): ☐Blood ☐Urine ☐Other *(please specify)*:_____

Imaging tests *(check one):*

☐Yes ☐No

(if yes, check one or more and indicate part of body):

☐X-Ray ☐CT ☐MRI ☐Ultrasound ☐Other *(please specify)*:_____

Of which part of body: _____

Nurse/Research Coordinator Contact
Days 5 and 6

Daily Telephone contact (check one)
☐Day 5
☐Day 6

Date of telephone contact or date of attempt to contact was made: *(dd MMM yyyy)* _ _-_ _ _-_ _ _ _

Were you able to contact the patient? ☐Yes ☐No (If no, then end form)
If contacted, list the Time of day HH:MM ___:___

Number of vomiting episodes over the past 24 hours _____

Symptom Assessment: (Where 0 is none and 10 is as bad as it can be.)

Worst nausea over the past 24 hours *(circle one)*

0 1 2 3 4 5 6 7 8 9 10

Undesired sedation trouble over the past 24 hours *(circle one)*

0 1 2 3 4 5 6 7 8 9 10

Undesired appetite increase over the past 24 hours *(circle one)*

0 1 2 3 4 5 6 7 8 9 10

Rescue Medication taken? *(check one)* ☐Yes ☐No

(if yes):

Drug Name *(check one or more)*:

☐ Anticholinergics: Scopolamine transdermal patch (Transderm Scop)

☐ Diphenhydramine (Benadryl)

☐ Lorazepam (Ativan)

☐ Haloperidol (Haldol)

☐ Dronabinol (Marinol, Syndros)

☐ Prochlorperazine (Compazine)

☐ Metoclopramide (Reglan)

☐ Ondansetron (Zofran)

☐ Other *(list)*: _____

Dose *(check one or more. If more than one rescue medication, list drug to which that dose refers)*:

☐ 1 pill _____

☐ 2 pills _____

☐ 3 pills _____

☐ 4 pills _____

☐ 1 patch _____

☐ 1 infusion _____

☐ Other *(please specify)*: _____

Number of doses the past 24 hours *(check one or more. If more than one rescue medication, list drug to which that number of doses refers)*:

☐ 1 _____

☐ 2 _____

☐ 3 _____

☐ 4 _____

☐ 5 _____

☐ Other *(please specify)*: _____

Did you start taking any **other** new medications today, **other than** rescue medications, that you were not taking before *Day 1 of the protocol*?

(if yes):

Drug Name *(list one or more)*: _____

Dose *(check one or more. If more than one medication, list drug to which that dose refers*):

☐ 1 pill _____

☐ 2 pills _____

☐ 3 pills _____

☐ 4 pills _____

☐ 1 patch _____

☐ 1 infusion _____

☐ Other *(please specify)*: _____

Number of doses the past 24 hours *(check one or more. If more than one medication, list drug to which that number of doses refers)*:

☐ 1 _____

☐ 2 _____

☐ 3 _____

☐ 4 _____

☐ 5 _____

☐ Other *(please specify)*: _____

Ask patient the following question (on Day 6 only) : Have you received your medical bill for your recent dose of chemotherapy and nausea medications? ☐Yes ☐No

Did patient have any adverse events? *(check one)* ☐Yes ☐No

If yes, fill out AE form: Record all adverse events that meet the following criteria: grade 2 with attribution of possible, probable or definite and all grade 3, 4 and 5 regardless of attribution.

Health Care Use:

If the patient experienced an adverse event(s) of grades 2, 3, 4, or 5, **including grade 2 adverse event(s) unlikely related or unrelated to the intervention,** ask the patient if they used any health care for the treatment of the adverse event. Health care use includes any interaction with a health care provider regarding the adverse event(s). Some examples include visiting your oncologist at the hospital or in their office and receiving a prescription for a rescue therapy, calling or emailing the nurse or your primary care physician, visiting the emergency department or being hospitalized. Do not record visits to the pharmacy to fill a prescription for one of the reported medications.

Did you use any health care associated with adverse events in the past 24 hours? *(check one)*
☐Yes ☐No

*(Complete the form on the next page if you checked the **"Yes"** box above.)*

Comments

_____

_____

Please remind the patient to complete the patient diary. If possible, have the patient complete their questionnaire form while on the phone call. Please explain the rescue nausea medication information specifically "Number of extra (PRN) nausea/vomiting pills taken."

Health care use associated with adverse events in past 24 hours

Site of care and Provider types *(check as many Sites of care as apply, and for each one, which Providers were used there)*:

☐ Hospital Outpatient Department

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Emergency Department

☐ Emergency Medicine Physician

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Provider's office

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Phone call to provider

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Email to provider

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Telemedicine

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Hospital Inpatient Department

☐ Hematologist/oncologist ☐ Internal Medicine/Hospital Medicine Physician

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Intensive Care Unit (ICU) Hospital Inpatient Department

☐ Hematologist/oncologist ☐ Internal/Hospital Medicine Physician ☐ Critical/Intensive Care Physician

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

☐ Other *(please specify):* _____

☐ Hematologist/oncologist ☐ Internal Medicine/Family Medicine/General Practitioner

☐ Advanced Practice Nurse ☐ Physician Assistant ☐ Other *(please specify):* _____

If hospitalized, date of admission: _____

Name(s) of provider(s) *(record as accurately as patient can recall)*:

_____

Address(es) of provider(s) *(record as accurately as patient can recall)*:

_____

Reasons for use of health care *(check one or more. If more than one Site of Care was used, list Site(s) of Care in which each adverse event was treated)*:

☐ Nausea/Vomiting Reasons for use _____

☐ Sedation _____

☐ Fatigue _____

☐ Anemia _____

☐ Appetite changes _____

☐ Constipation _____

☐ Diarrhea _____

☐ Bleeding _____

☐ Blurred vision _____

☐ Arm or leg swelling _____

☐ Peripheral neuropathy _____

☐ Mental status change _____

☐ Severe headache _____

☐ Fever / Chills / Febrile neutropenia _____

☐ Urine and bladder changes / Proteinuria / Kidney problems _____

☐ Hypertension _____

☐ Blood clot / Venous thromboembolic event _____

☐ Thrombocytopenia _____

☐ Other adverse event *(please specify)*: _____

Laboratory tests *(check one):*

☐Yes ☐No

(if yes, check one or more): ☐Blood ☐Urine ☐Other *(please specify)*:_____

Imaging tests *(check one):*

☐Yes ☐No

(if yes, check one or more and indicate part of body):

☐X-Ray ☐CT ☐MRI ☐Ultrasound ☐Other *(please specify)*:_____

Of which part of body: _____

Nurse/Research Coordinator Contact (Day 21)

Date of telephone contact or date of attempt to contact: *(dd MMM yyyy)* _ _-_ _ _-_ _ _ _

Were you able to contact the patient? ☐Yes ☐No (If no, then end form)
(If contacted), contact time: (HH:MM AM or PM) ___:___

Did patient have any adverse events (*new or continuing grade 2+ adverse events since day 7 of the initial treatment)*? ☐Yes ☐No

If yes, fill out AE form: Record all adverse events that meet the following criteria: grade 2 with attribution of possible, probable or definite and all grade 3, 4 and 5 regardless of attribution. And update the Date of most recent contact on Patient Status: Treatment (Intervention) form accordingly.

Comments

_____

_____

_____

APPENDIX V EQ-5D-3L HEALTH QUESTIONNAIRE

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain / Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

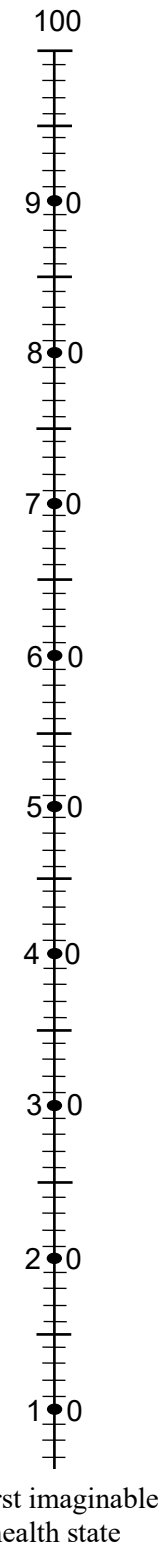
Anxiety / Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX VI ePRO

1.0 Introduction

Electronic collection of patient-reported outcomes is preferred but not mandatory. Patients will need to use their own device (IOS or Android phone or tablet). Short term data will only appear on the patient's device until responses are completed. The patient data will import directly into the database once the patient clicks the submit button and will no longer be on the patient's device.

Site staff access

Site users of ePRO and the Patient Cloud require the same access as those using Rave. Access to the trial in the Patient Cloud is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access the Patient Cloud via iMedidata, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in the Patient Cloud until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance).

Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at [redacted] or [redacted]

2.0 Security

All data are encrypted on the device (128 bit on file +https transfer) and the app requires a user to have a username and password. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks "submit," the data is securely transferred over https between the device and internal relay. No identifying information is stored in iMedidata (only email address is stored).

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and sponsors in the Patient Cloud Relay.

The ePRO application is Part 11 compliant and acts as a gateway between device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud are encrypted and therefore this information cannot be read if intercepted while in transit.

3.0 CRP Training for ePRO

Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs.

4.0 Checklist for activities prior to consenting a patient

- Site staff must have already completed required eLearning for the Patient Cloud ePRO application. See last bullet with hyperlink to training video library. Contact the Study data manager to request appropriate Rave access to register patients in Patient Cloud ePRO
- Accept study invitation at iMedidata.com

  Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO
- Verify the IOS or Android operating system is using the most current version
- Verify Patient Cloud ePRO app is using the most current version
- Refer to [redacted] to review Quick reference guides

5.0 Instructions for ePRO patient registration

Please visit the Medidata Learning Tool for additional screen shots and video tutorials on how to register participants to the study.

i. The patient registration process starts in iMedidata. Begin by clicking on the Patient Cloud Registration link for this study

ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.

iii. Now the first patient can be registered. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The patient initials are optional, but may help in identifying which subject ID maps with which activation code. When finished, click Add.

iv. The patient added will appear at the top of the table and will include the date the patient was added, the subject ID, initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which determines if the patient has registered. When the patient has registered the status will change from invited to registered.

6.0 Patient Users

To use the Patient Cloud ePRO, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Patient compliance: The patient data imports directly from her/his device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

6.1 Patient Instructions for Accessing the Patient Cloud App using their personal device

Downloading the Patient Cloud ePRO App:

If you are using your personal device, and you do not have the Patient Cloud ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud ePRO app is already on the device, or if you are using a provider's device, you can skip this section.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e- mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud ePRO app.
2. Tap the App Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Note: Patient Cloud ePRO is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud ePRO app
2. Tap the Play Store icon.
3. Search for Medidata Patient Cloud and follow the installation instructions.

Registering on the App:

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note: You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud ePRO app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App after registration:

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap Forgot Password, and follow the instructions provided.

Setting a PIN Code:

The first time you log in to the Patient Cloud ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap Forgot PIN and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password:

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms:

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password

APPENDIX VII PATIENT CLOUD EPRO PATIENT INFORMATION SHEET

(Sites: Please print and provide this appendix to the patient who will be using Patient Cloud for completion of questionnaires).

This document will guide you on how to access the research questionnaires and help you know when you need to fill out each questionnaire via the Patient Cloud app.

Questionnaire schedule during each chemotherapy treatment cycle:

BEFORE you receive chemotherapy treatment today:

1. Confirm you are connected to Wi-Fi or data.
2. Open the Patient Cloud app on your personal device (E.g. smartphone or tablet) and login with your email and password or your PIN.
3. Please fill out the following questionnaires on your device BEFORE study treatment.
    - **Electronic Questionnaire 1: Electronic Nausea and Vomiting Questionnaire (Baseline)**
    - **Electronic Questionnaire 2: Electronic EQ-5D-3L (Baseline)**

    Once data is submitted for baseline, the forms will disappear from patient cloud app.

Each day for the next 5 days after receiving chemotherapy treatment, complete below questionnaires for **Initial treatment cycle for Day 2 through Day 6.**

- **Electronic Questionnaire 1: Electronic Nausea and Vomiting Questionnaire (Initial Treatment)**
- **Electronic Questionnaire 2: Electronic EQ-5D-3L (Initial Treatment)**

  Each form is available to you for days 2 through 6 (5 times).

  Initial Treatment (1) = Day 2
  Initial Treatment (2) = Day 3
  Initial Treatment (3) = Day 4
  Initial Treatment (4) = Day 5
  Initial Treatment (5) = Day 6

  Once you submit the above forms, the forms will disappear from the patient cloud app.

Questionnaire schedule for Continuation Phase (Cycles 2-4 if you elect to continue):
Once you are enrolled to continue in the study,
Each day for the next 5 days after receiving chemotherapy treatment for **Cycles 2, 3 and 4,** Please complete below questionnaires for **Continuation treatment cycle for Day 2 through Day 6.**

- **Electronic Questionnaire 1: Nausea and Vomiting (Continuation Treatment Cycle 2)**
- **Electronic Questionnaire 2: EQ-5D-3L (Continuation Treatment Cycle 2)**

- **Electronic Questionnaire 1: Nausea and Vomiting (Continuation Treatment Cycle 3)**
- **Electronic Questionnaire 2: EQ-5D-3L (Continuation Treatment Cycle 3)**
- **Electronic Questionnaire 1: Nausea and Vomiting (Continuation Treatment Cycle 4)**
- **Electronic Questionnaire 2: EQ-5D-3L (Continuation Treatment Cycle 4)**

Once data is submitted, the forms will disappear from the patient cloud app.

APPENDIX VIII EPRO INSTRUCTION FLOW CHART FOR PATIENTS

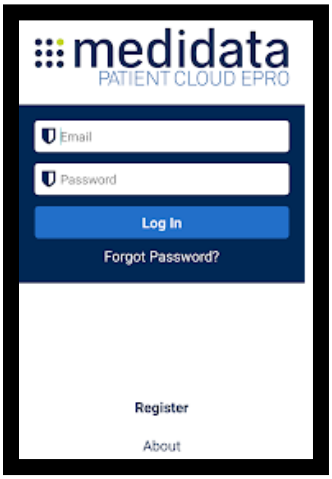
Download the Patient Cloud ePRO app

Create a username and password for the Patient Cloud app by selecting the 'Register' option on the login screen. Use the activation code from your clinic.

Log in to the Patient Cloud app

See your forms on the main screen

Complete, review, and submit your forms



Tip: Your username must be in email format (for example, jodiesmith20@email.com).

Tip: When a form is due, you will see the alarm clock with the date and time the form will close.

For help with the Patient Cloud ePRO app, please ask your study team!