2011-116 Prevention of Nausea and Vomiting Secondary to FOLFIRINOX Chemotherapy in Gastrointestinal Cancer Patients

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Table of Contents

1)	Objectives	3
2)	Background and Rationale	3
3)	Drug Information	5
4)	Patient Selection	8
5)	Pre-study Evaluation	9
6)	Treatment	9
7)	Dose Adjustment	10
8)	Criteria for Evaluation and Endpoint Assessment	10
9)	Reason for Removal From Study	10
10)	Statistical Considerations	10
11)	Study Administration and Investigator Obligations	12
Appendix 1: SWOG Performance Scale		14
Appendix 2: Data Safety Monitoring Board		15
Appendix 3: Baseline Nausea Form		16
Appendix 4: FOLFIRINOX chemotherapy		17
Appendix 5: Study Calendar		18
Appendix 6: Daily Diary		19
References		20

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1) **Objectives:**

Primary:

To evaluate efficacy of the addition of fosaprepitant in controlling acute and delayed vomiting with the standard prophylactic anti-emetic combination of 5-HT3 receptor antagonist and dexamethasone for gastrointestinal cancer patients receiving FOLFIRINOX (5-FU, oxaliplatin and irinotecan) chemotherapy. The primary objective is to determine the rate of complete response (no emetic episode and no rescue medication) in the combined acute and delayed phase from 0-120 hours after chemotherapy.

Secondary:

To determine the incidence of nausea and vomiting in both acute (<24 hours) and delayed (24-120 hours) setting in patients receiving FOLFIRINOX chemotherapy.

Tertiary:

Follow overall survival in patients receiving FOLFIRINOX chemotherapy.

2) Background and Rationale:

Nausea and vomiting are symptomatic side effects of chemotherapy that are both physically and psychologically burdensome. Until the advent of the serotonin receptor antagonists, control of nausea and vomiting for patient receiving high-dose chemotherapy was inadequate. According to the American Society of Clinical Oncology guidelines, the current approach for prophylaxis of nausea and vomiting caused by chemotherapy deemed highly emetogenic is 5-HT3 antagonists (ondansetron or granisetron) combined with corticosteroids and aprepitant.[1] At Karmanos Cancer Institute, ondansetron is the preferred 5-HT3 antagonist used for chemotherapy associated nausea and vomiting. Neurokinin 1 receptor antagonists (NK1RA) are a class of anti-emetic compounds that can block NK_1 receptor in the gastrointestinal fibers and the brainstem and is thought to play a key role in emesis induction when these receptors are stimulated by radiation and/or chemotherapy.[2] Mechanism of action for NK1RA appears distinct from the 5-HT3's, which act mainly at peripheral sites. Aprepitant (an antagonist at this receptor) was first tested in animal models including ferrets and displayed potent and long-acting anti-emetic activity.[3] NK1RA's antagonize a much broader range of emetic stimuli than the 5-HT3's in animal models.[4]

The benefit of combining aprepitant with 5-HT3 receptor antagonists and corticosteroids for the prevention of chemotherapy induced nausea and vomiting (CINV) was initially shown in two phase III trials that included 1099 patients receiving cisplatin-containing chemotherapy (≥70 mg/m2 per cycle).[5] [6] In both trials, patients were randomly assigned to ondansetron (day 1) plus dexamethasone (days 1 to 4) with either aprepitant (125 mg by mouth on day 1, followed by 80 mg orally on days 2 and 3) or placebo. The end point of both studies was complete protection from emesis with no need for any rescue antiemetic. Acute emesis was blocked more effectively in patients receiving aprepitant (overall 86 percent versus 73 percent with placebo). The aprepitant-containing regimen maintained its advantage in controlling CINV over multiple treatment cycles. Similar results were seen in a third phase III trial, in which patients were randomly assigned to a three-drug regimen including aprepitant, ondansetron, and dexamethasone or to ondansetron plus dexamethasone only. The overall, acute, and delayed complete response rates were significantly better with the aprepitant regimen (72 versus 61, 88

versus 79, and 74 versus 63 percent, respectively) compared to ondansetron plus dexamethasone alone.[7]

Fosaprepitant is the prodrug of aprepitant that is converted to aprepitant in vivo after intravenous (IV) administration. It is approved in 41 countries as an alternative to the 125 mg oral dose on day 1 of the three-day regimen, with oral aprepitant administered on Days 2 and 3 in combination with a $5HT_3$ antagonist and dexamethasone for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC). A Phase III study was recently conducted utilizing fosaprepitant, at a dose of 150 mg as a single dose alternative to the 3-day regimens in cancer patients for the prevention of chemotherapy induced nausea and vomiting. The study enrolled 2,322 patients, 1,147 in the fosaprepitant regimen and 1,175 in the aprepitant regimen. The treatment regimens were similar with regard to baseline demographics. Patients ranged in age from 19-86 years. The most common primary tumor types were respiratory, gastrointestinal cancer, reproductive cancer, and genitourinary cancer. The primary endpoint was the proportion of patients with Complete Response in the overall phase (0 to 120 hours following initiation of cisplatin chemotherapy). Complete Response is defined as the absence of vomiting episodes, retching or dry heaves (no vomiting) and no use of rescue medication. The fosaprepitant group had a complete response of 72% as compared to 72% in patient receiving aprepitant for 3 days. Acute and delayed phase had similar outcome 89% vs. 88% and 74% vs. 74%. No vomiting was noted in 73% treated with fosaprepitant while 75% had no vomiting in the aprepitant group.[8]

Adverse events were reported for 1,389 (60.1%) patients, 671 (58.7%) in the fosaprepitant regimen group and 718 (61.4%) in the aprepitant regimen group. The adverse events were generally comparable between the fosaprepitant and aprepitant groups. In general, the adverse event profile observed was typical of a patient population with cancer receiving highly emetogenic chemotherapy. The most frequently reported clinical adverse events reported in both the fosaprepitant regimen group and the aprepitant regimen group were asthenia (10%), constipation (10%), anorexia (7.9%), diarrhea (8.3%), and nausea (6.5%).[8] These adverse events occurred at a similar incidence between patients receiving the fosaprepitant regimen and patients receiving the aprepitant regimen with the exception of asthenia and anorexia, which occurred at a slightly higher incidence in the aprepitant regimen group. Overall, the adverse events observed in these studies were comparable to the types of adverse events observed in patients with cancer receiving highly emetogenic chemotherapy.

Pancreatic adenocarcinoma is one of the most lethal cancers with a 1-year and 5-year survival rates of at best 20%, and 5%, respectively.[9] Palliative cytotoxic therapy remains a frequently used treatment modality in patients with pancreas cancer. The pivotal trial by Burris et. al in 1997 made single agent gemcitabine as a standard of care for the past decade.[10] This was a prospectively designed study that compared 5-fluorouracil to gemcitabine therapy in 126 patients. 5-FU was given as a bolus at $600mg/m^2$ weekly and gemcitabine was given at $1000mg/m^2$ for 30 minutes weekly for seven weeks followed by one week of rest, then it was given weekly for 3 weeks followed by one week of rest. The results showed statistically significant improvement in the primary endpoint of clinical benefit response (CBR: defined as composite of measurements of pain, performance status and weight) and 5 weeks improvement in median survival. However the median survival for gemcitabine arm was still a dismal 5.65 months with 1 year survival rate of 18%. More than 10 large randomized clinical trials were conducted to improve the clinical outcome in pancreas cancer but the results were all disappointing.

In 2010 American Society of Clinical Oncology meeting, a randomized phase 3 trial comparing the FOLFIRINOX regimen (oxaliplatin and irinotecan plus fluorouracil and leucovorin) to gemcitabine in advanced pancreatic cancer was presented.[11] Results showed an overall survival increased from 6·8 months to 11·1 months ($p<0·0001$). More interestingly, almost half the patients in the FOLFIRINOX group were alive after 1 year, and response rate was 31·6%—the highest rate seen in phase 3 pancreatic cancer trials. However the side effects of treatment was worse in the FOLFIRINOX group. Patients had 61% vomiting with grade III nausea and vomiting in 15%. In another FOLFIRINOX study in advanced colorectal cancer, up to 79.4% had vomiting and 91% had nausea.[12] Based on the above data, FOLFIRINOX is considered highly emetogenic chemotherapy since most of the above studies have utilized 5HT3 antagonist as anti-emetic drugs and still experienced major nausea and vomiting episodes. Although the toxicity of FOLFIRINOX regimen is higher than single agent, such superior outcome has led many clinicians to use this regimen in advanced pancreatic cancer patients. Since quality of life is important in palliative setting, improving nausea and vomiting in gastrointestinal cancer would be important. Many clinical trials have demonstrated that aprepitant can improve the nausea and vomiting in both highly and moderately emetogenic population.[13] [14]

In this open labeled study, the goal is to improve complete response to nausea and vomiting from about 30% in historical control to about 60% with addition of fosaprepitant in patients receiving FOLFIRINOX chemotherapy. Hopefully this study could elucidate the impact of fosaprepitant in the GI cancer patients receiving FOLFIRINOX chemotherapy.

3. Drug Information:

A. **Description:**

Fosaprepitant Dimeglumine, (EMEND™ for Injection) is a phosphoryl prodrug of aprepitant (EMEND™[2]) that can be administered intravenously (IV). Fosaprepitant is rapidly (within 30 minutes) converted to aprepitant after IV administration. Aprepitant is a selective high affinity antagonist of substance P/neurokinin 1 (NK1) receptors. It has little or no affinity for serotonin, dopamine and corticosteroid receptors.

Fosaprepitant is an off-white, odorless powder that is highly soluble in water or 0.9% solution of sodium chloride (about 55 mg/mL as free acid equivalent). It is prepared by a multistep chemical synthesis as the bis-meglumine salt, which has a molecular formula of $C_{23}H_{22}F_7N_4O_6P•(C_7H_{17}NO_5)_2$ and a molecular weight of 1004.83 (61.1% of which is attributable to the free acid). The neat solid is thermally unstable and degrades at about 155°C to aprepitant by loss of the phosphate group. It is also unstable in aqueous solutions and it must be formulated as a lyophilized powder in order to prevent its degradation during storage.

Fosaprepitant will be supplied for clinical use in 10-mL vials as a sterile, lyophilized preparation; each vial contains an overage of 5% to account for non-withdrawable loss after reconstitution of the lyophilized product in order to deliver appropriate dose. The lyophilized product per 115 mg vial contains 120.8 mg free acid equivalent of active drug substance, 60.4 mg polysorbate 80, 302.0 mg lactose, as well as 15.1 mg of edetate disodium and nitrogen as an inert gas. The lyophilized product per 150 mg vial contains 157.5 mg free acid equivalent (150 mg label claim) of active drug substance, 78.8 mg polysorbate 80, 393.8 mg lactose, as well as 19.7 mg of edetate disodium and nitrogen as an inert gas. Sodium hydroxide or hydrochloric acid may be added to the pre-lyophilization drug solution in the amount sufficient to obtain pH 9.2 during

manufacturing. The lyophilized product must be stored at 2 to 8°C. Prior to use, the preparation will be reconstituted with 0.9% Sodium Chloride Injection, USP to a final concentration of 1 mg/mL. The final drug solution is stable for 24 hours at ambient room temperature. This product allows for reconstitution in normal saline taken from any package including PVC bags and do not require specialized IV infusion equipment. Fosaprepitant is incompatible with Lactated Ringer's Solution (LRS) or any other solutions containing divalent cations. Fosaprepitant should be reconstituted or mixed with solutions for which physical and chemical compatibility has been established.

B. **Pharmacology:**

1. Pharmacokinetics:

Following a single intravenous dose of fosaprepitant administered as a 15-minute infusion to healthy volunteers the mean AUC of aprepitant was 31.7 (± 14.3) mcg•hr/mL and the mean maximal aprepitant concentration (Cmax) was 3.27 (± 1.16) mcg/mL. The mean aprepitant plasma concentration at 24 hours post dose was similar between the 125-mg oral aprepitant dose and the 115-mg intravenous fosaprepitant dose.

2. Distribution:

Fosaprepitant is rapidly converted to aprepitant. Aprepitant is greater than 95% bound to plasma proteins. The mean apparent volume of distribution at steady state (Vdss) is approximately 70 L in humans. Aprepitant crosses the placenta in rats and rabbits and crosses the blood brain barrier in humans.

3. Metabolism:

Fosaprepitant was rapidly converted to aprepitant in vitro incubations with liver preparations from nonclinical species (rat and dog) and humans. Furthermore, fosaprepitant underwent rapid and nearly complete conversion to aprepitant in S9 preparations from multiple other human tissues including kidney, lung and ileum. Thus, it appears that the conversion of fosaprepitant to aprepitant can occur in multiple extra hepatic tissues in addition to the liver. In humans, fosaprepitant administered intravenously was rapidly converted to aprepitant within 30 minutes following the end of infusion.

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. In healthy young adults, aprepitant accounts for approximately 24% of the radioactivity in plasma over 72 hours following a single oral 300-mg dose of [14C]-aprepitant, indicating a substantial presence of metabolites in the plasma. Seven metabolites of aprepitant, which are only weakly active, have been identified in human plasma.

4. Excretion:

Following administration of a single I.V. 100-mg dose of [14C]-fosaprepitant to healthy subjects, 57% of the radioactivity was recovered in urine and 45% in feces. Aprepitant is eliminated primarily by metabolism; aprepitant is not renally excreted. The apparent terminal half-life of aprepitant ranged from approximately 9 to 13 hours.

C. **Drug Interactions**

Drug interaction studies with oral midazolam have shown that IV fosaprepitant has a dose-dependent weak to moderate inhibitory effect on CYP3A4. In addition, in a study of diltiazem, there was a moderate increase in plasma diltiazem concentrations when co administered with a single IV dose of fosaprepitant consistent with an inhibitory effect of aprepitant on CYP3A4-mediated metabolism of diltiazem.

D. **Toxicology**

Clinical studies of various formulations of fosaprepitant including fosaprepitant PS80 have indicated that fosaprepitant is generally safe and well tolerated, with an adverse event profile comparable to both the oral aprepitant (EMEND™) 3-day regimen, as well as the comparator therapies used in the clinical trials. Infusion-related adverse events that have been reported with the use of the market formulation of fosaprepitant include infusion site pain, infusion site redness, infusion site itching, and induration. Isolated reports of immediate hypersensitivity reactions including flushing, erythema, and dyspnea have occurred during infusion of fosaprepitant. These hypersensitivity reactions have generally responded to discontinuation of the infusion and administration of appropriate therapy. It is not recommended to reinitiate the infusion in patients who experience hypersensitivity reactions. The overall safety of aprepitant was evaluated in approximately 6,500 individuals. Since fosaprepitant is converted to aprepitant, those adverse events associated with aprepitant might also be expected to occur with fosaprepitant. The most common drug-related adverse events in patients that were treated with aprepitant in combination with ondansetron and dexamethasone include: hiccups, asthenia/fatigue, ALT increased, constipation, headache and anorexia. The adverse event profile was typical of cancer patients receiving cisplatin based chemotherapy. Other symptoms in patient receiving chemotherapy included fatigue. The incidence of clinical and laboratory adverse events were generally similar to the Standard therapy regimen (ondansetron and dexamethasone) for both groups. Overall, EMEND™ is safe and well-tolerated.

E. Special Population

1. Gender

Following oral administration of a single 125-mg dose of aprepitant, no difference in AUC0-24hr was observed between males and females. The Cmax for aprepitant is 16% higher in females as compared with males. The half-life of aprepitant is 25% lower in females as compared with males and Tmax occurs at approximately the same time. These differences are not considered clinically meaningful. No dosage adjustment is necessary based on gender.

2. Geriatric

Following oral administration of a single 125-mg dose of aprepitant on Day 1 and 80 mg once daily on Days 2 through 5, the AUC0-24hr of aprepitant was 21% higher on Day 1 and 36% higher on Day 5 in elderly (≥65 years) relative to younger adults. The Cmax was 10% higher on

Day 1 and 24% higher on Day 5 in elderly relative to younger adults. These differences are not considered clinically meaningful. No dosage adjustment is necessary in elderly patients.

3. Pediatric

Fosaprepitant has not been evaluated in patients below 18 years of age.

4. Race

Following oral administration of a single 125-mg dose of aprepitant, the AUC0-24hr is approximately 25% and 29% higher in Hispanics as compared with Whites and Blacks, respectively. The Cmax is 22% and 31% higher in Hispanics as compared with Whites and Blacks, respectively. These differences are not considered clinically meaningful. There was no difference in AUC0-24hr or Cmax between Whites and Blacks. No dosage adjustment is necessary based on race.

5. Hepatic Insufficiency

Fosaprepitant is metabolized in various extrahepatic tissues; therefore hepatic insufficiency is not expected to alter the conversion of fosaprepitant to aprepitant. Oral aprepitant was well tolerated in patients with mild to moderate hepatic insufficiency. Following administration of a single 125-mg dose of oral aprepitant on Day 1 and 80 mg once daily on Days 2 and 3 to patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), the AUC0-24hr of aprepitant was 11% lower on Day 1 and 36% lower on Day 3, as compared with healthy subjects given the same regimen. In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the AUC0-24hr of aprepitant was 10% higher on Day 1 and 18% higher on Day 3, as compared with healthy subjects given the same regimen. These differences in AUC0-24hr are not considered clinically meaningful; therefore, no dosage adjustment is necessary in patients with mild to moderate hepatic insufficiency. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9)

6. Renal Insufficiency

A single 240-mg dose of oral aprepitant was administered to patients with severe renal insufficiency (CrCl<30 mL/min) and to patients with end stage renal disease (ESRD) requiring hemodialysis. In patients with severe renal insufficiency, the AUC0-∞ of total aprepitant (unbound and protein bound) decreased by 21% and Cmax decreased by 32%, relative to healthy subjects. In patients with ESRD undergoing hemodialysis, the AUC0-∞ of total aprepitant decreased by 42% and Cmax decreased by 32%. Due to modest decreases in protein binding of aprepitant in patients with renal disease, the AUC of pharmacologically active unbound drug was not significantly affected in patients with renal insufficiency compared with healthy subjects. Hemodialysis conducted 4 or 48 hours after dosing had no significant effect on the pharmacokinetics of aprepitant; less than 0.2% of the dose was recovered in the dialysate. No dosage adjustment is necessary for patients with renal insufficiency or for patients with ESRD undergoing hemodialysis.

4. **Patient Selection**

A. Inclusion Criteria

1. Patient receiving FOLFIRINOX chemotherapy
2. SWOG Performance status 0 or 1 (See appendix 1)

3. Age > 18
4. Ability of patient or guardian to understand and to provide voluntary written informed consent

B. Exclusion Criteria

1. Patient with current illness requiring chronic systemic steroids use or requiring chronic use of anti emetics
2. Patients with GI obstruction who cannot take oral medication
3. Active peptic ulcer disease.
4. Known Hypersensitivity to any component of the study regimen
5. Patients taking any of the following medications: Oral Contraceptives (except for the administration of stopping menses), tolbutamide, phenytoin, midazolam, ketoconazole, rifampin, paroxetine, and Diltiazem
6. Pregnant or nursing women
7. Patients using illegal drugs

Protocol Registration

The attending physician will consider the patient for the study. All patient information will be forwarded to the Data Management office (313-576-9385) for determination of eligibility. Upon informed consent and eligibility confirmation, the patient will be registered to the study.

5. Pre-Study Evaluation

1. Patients will undergo evaluation for chemotherapy treatment for advanced gastrointestinal cancer and planned for FOLFIRINOX chemotherapy.
2. History and physical exam, weight, performance status would be documented
3. Following labs are required
   - **a.** BUN, creatinine
   - **b.** electrolytes
   - **c.** alkaline phosphatase, AST, ALT
   - **d.** albumin
   - **e.** bilirubin
   - **f.** CBC+D
   - **g.** Female patients must have a pregnancy test unless they have had a hysterectomy or menopause

4. Patients will fill out a form on baseline nausea state including number of emetic episodes that day

6. Treatment

Patients will be treated with FOLFIRINOX chemotherapy every 2 weeks as standard of care for gastrointestinal cancer. The acceptable regimen for the clinical trial is shown in appendix 4.The premedication would include ondansetron (zofran) 16mg IVPB, dexamethasone 12 mg orally and the study drug which is fosaprepitant 150mg given intravenously 30 min prior to treatment. Dexamethasone 8mg orally will be given twice daily on days 2-4. Patients are to keep a diary daily from days 1-5 (5 days). They will record following information:

1. Number of emetic episodes per day
2. Date and time of each episode
3. Use of any rescue nausea medication

Patients will return on D3 for 5-FU pump removal and will be asked to bring in their diary for assessment of the nausea and vomiting. On day 5 of the chemotherapy, patients will be contacted by phone for toxicity assessment by the study coordinator for the first cycle. In the subsequent cycles (cycle 2), diary would be used to collect the episode of nausea and vomiting and use of rescue nausea medications. The patient may continue on treatment and to take IV fosaprepitant with chemotherapy after cycle 2 if there is clinical benefit noted by the investigator. After cycle 2 only survival data will be collected.

7. Dose Adjustments

Fosaprepitant will be held at the discretion of the PI with any of the Grade II toxicities that is likely related to use of the study medication. Fosaprepitant will be discontinued if patient develops Grade IV toxicity following administration. Investigator can use NCI common toxicity criteria for any toxicity encountered that is not specifically listed here and use instructions above. Patients will be considered treatment failure if more then two vomiting occurs within an hour and will be treated using other antiemetics.

8. Criteria for evaluation and Endpoint assessment

Nausea and vomiting will be assessed in two different time periods

1. 0-24 hours will be defined as the acute phase
2. 25-120 hours will be defined as the delayed phase

Emesis Response

1. Complete: Defined as no emetic episodes and no rescue medications
2. Partial Response: 0-2 emetic episodes and no use of rescue medications
3. Failed Response: >2 emetic episodes and/or use of rescue medications

Patient will fill a diary from Days 1-5 (5 days), documenting detailed account of vomiting episodes. Patient will be assessed for delayed vomiting on a follow up visit with the study investigators or coordinator on Days 3.

9. Reasons for removal from study

a. Death
b. Participant withdrawal
c. Grade 3-5 toxicity from fosaprepitant (probably or definitely attributed to treatment) as judged by primary investigator
d. Non- compliance to study drug during cycle 1 or cycle 2

10. Statistical Considerations

10.1 Objectives

The primary objective of this study is to determine whether fosaprepitant has sufficient efficacy in controlling nausea and vomiting in patients receiving FOLFIRINOX chemotherapy as defined as complete response (no emetic episode

and no rescue medication) in the combined acute and delayed phase from 0-120 hours after first cycle of chemotherapy.

The secondary objectives are to estimate the rates of control of a) acute and delayed vomiting and b) nausea..

The tertiary objective is to estimate overall survival of enrolled patients. This endpoint will be assessed every 6 months from the start of cycle 1 using medical record data.

10.2 Endpoints

The primary endpoint is control of vomiting in the first cycle of chemotherapy. This endpoint will have been achieved if a patient has no episodes of vomiting and requires no rescue medication during the first 120 hours after fosaprepitant administration.

The secondary endpoints are a) control of acute and delayed vomiting following fosaprepitant administration; b) control of acute and delayed nausea during the first five days following fosaprepitant administration.

The tertiary endpoints is overall survival defined as time of initiation of treatment until death or censor.

10.3 Design

A single stage optimal design was used for testing the null response (defined in the first paragraph in Section 10.1) rate (0.30) versus the alternative response rate (0.60). A sample size of 25 patients and a critical value of 12 responses results in a 0.038 probability of concluding that the new treatment is effective, if the new treatment is actually not effective (Type I error). If the new treatment is actually effective, there is 0.922 power of concluding that it is effective. If the total number of patients who respond is 12 or more, then the response rate hypothesis under the null (0.30) is rejected in favor of the alternative (0.60). If the total number of patients who respond is 11 or less, then we fail to reject that the response rate hypothesis is 0.30.

10.4 Statistical Analysis of the Primary Endpoint

If the total number of patients who respond is 12 or more, then the response rate hypothesis under the null (0.30) is rejected in favor of the alternative (0.60). If the total number of patients who respond is 11 or less, then we fail to reject that the response rate hypothesis is 0.30.

10.5 Statistical Analyses of the Secondary Endpoints

The secondary endpoints (control of acute and delayed vomiting, control of nausea and toxicity) will be described with a point estimate and a Wilson's two-sided 90% confidence interval.

10.6 Statistical Analyses of the Tertiary Endpoint

The response rate will be described with a point estimate and a Wilson's two-sided 90% confidence interval. The Kaplan-Meier method will be used to estimate the survival curve for overall survival.

10.7 Accural and study duration

At this institution we see approximately 20-24 patients annually who would be eligible for this trial. To account for patients who may not be able to complete the treatment due to toxicity of chemotherapy, we propose to accrue an additional 5 patients, resulting in a total of 30 patients. Thus, we expect that the study will require approximately 15 to 18 months to complete accrual. Allowing for 2 months of follow-up to obtain all endpoint information on the last patient enrolled and 2 months to assemble, analyze and interpret the data the total study duration is projected to be at most 22 months for all endpoints excluding overall survival. We will assess the overall survival endpoint every 6 months when the administrative database is updated.

10.8 Toxicity Monitoring

We have chosen a safety threshold of 0.25 to monitor toxic side effects. All enrolled patients will be evaluated for toxicity. We would recommend reconsidering the study for safety reasons if there were X many occurrences of grade 3 or higher toxicity (using the CTCAE guidelines) among the first N (or fewer) patients treated, as it would result in an upper confidence limit greater than 0.25:

N	X	p	UCL
8	1	0.125	0.255
13	2	0.154	0.256
18	3	0.167	0.253
22	4	0.182	0.261
27	5	0.185	0.256

In the above table, N = the number of patients treated; X = the cumulative number of patients with a grade 3 or higher toxicity currently observed; p = the observed toxicity rate; and UCL = the exact 1-sided upper 80% confidence limit for p, using Wilson's method without a continuity correction.

11. Study Administration and Investigator Obligations

a. Review Boards

The study must have the approval of the Protocol Review and Monitoring Committee of the Clinical Trials Office at the Karmanos Cancer Institute and of the Wayne State University Institutional Review Board (IRB).

b. Informed Consent

It is the responsibility of the investigator to design the Informed Consent form. The consent form has been designed using appropriate National or Regional guidelines (equivalent to the American Federal Guidelines (Federal Register July 27, 1981 or 21 CFR Part 50)

c. Adverse Events

Definitions: A serious adverse event is any experience that suggests significant hazard, contraindication, side effect, or precaution. A serious adverse event includes any experience that:

1. Is fatal or immediately life threatening
2. Is severely or permanently disabling
3. Requires or prolongs hospitalization

All adverse effects will be noted in the patient's medical record. The adverse reactions must be reported to the data manager's office, principal investigator and the local IRB using the following procedures:

1.Unexpected and/or severe toxicities: any unexpected Grade 2 or 3 toxicity (not previously reported in the literature or package insert) must be reported in writing on an Adverse Drug Reaction Form to the data manager's office. Any Grade 4 or 5 toxicity must be reported by phone to the data managers' office within 24 hours of the event. An Adverse Drug Reaction Form must be sent to the data manager's office.

2. Deaths: within 30 days of study medication should be reported except if cause is secondary to cancer progression**.**

3. Adverse Event reporting to the FDA:

FDA shall be notified by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA review division that has responsibility for review of the IND. Principal investigator shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected. Each notification shall be made as soon as possible and in no event later than 15 calendar days after initial report of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format and shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted along with a FDA Form 1571 to the FDA division that has responsibility for review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted. In each written IND safety report, the investigator shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.

d. Termination of Study

Specific instances that may precipitate termination are: The incidence and/or severity of adverse drug experiences in this or other studies indicating a potential health hazard caused by the treatment.

e. Study Amendments

If the protocol requires an amendment, the amendment must be submitted to the IRB for approval together with a revised consent form, if applicable.

f. Data Safety and Monitoring: Appendix 2

Appendix 1: SWOG Performance Scale

Grade	Scale
0	Fully active; able to carry on all pre-disease activities without restriction (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60)
3	Capable of only limited self-care; confined to bed or chair (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20)
5	Dead

APPENDIX 2: DATA SAFETY AND MONITORING PLAN

Adverse Event Reporting:
Unexpected Grade 4 or 5 toxicities are to be reported to the Karmanos Clinical Trial Data Management Office by telephone (313-576-9385) within 24 hours of the event. Unexpected Grade 2 and 3 toxicities are to be submitted in writing to 87 E. Canfield MM03CT, Detroit, MI 48201. Proper documentation will be submitted to the Wayne State University Institutional Review Board if it meets reporting requirements.

Patient safety will be monitored by the PI and protocol data manager(s) on a monthly basis. At this time the safety of protocol participants, i.e., adverse event reporting will be reviewed. Merck Sharp & Dohme Corp. (Attn: Worldwide Product Safety; FAX 215 993-1220) will be provided with copies of all serious adverse experiences, regardless of causality, within two working days. Additionally, any pregnancy occurring in association with use of a Merck Product will be reported to Merck Sharp & Dohme Corp. (Attn: Worldwide Product Safety; FAX 215 993-1220). A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators by the investigator. This submission will be cross referenced according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, a copy of these reports will be submitted to Merck Sharp & Dohme Corp. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA. In studies involving human subjects, serious adverse experience means any experience that suggest a significant hazard, contraindication, side effect or precaution. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose. Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

Quarterly reporting of summary data will be provided to the Data and Safety Monitoring Committee for oversight of monitoring. Overall assessment of accrual, toxicities and responses will be done at this time to determine whether significant benefits or risks are occurring that would warrant study closure. Adherence to the protocol, i.e., protocol violations, and data completeness and integrity will also be reviewed at this time.

One month prior to anniversary date of the IRB original approval, a yearly summary report of trial activities will be made to all participating co-investigators and the Data and Safety Monitoring Committee. This report will include the number of patients on the trial, the number of patients treated, a summary of all adverse events reported to date using CTC 3.0 grading (http://ctep.cancer.gov/forms/CTCAEv3.pdf), a specific list of serious adverse events requiring immediate reporting and any significant developments that may affect the safety of the participants or ethics of the study.

Appendix 3: Baseline Nausea and Vomiting Form

Patient Initials ___-___-___ Accrual Number _____.

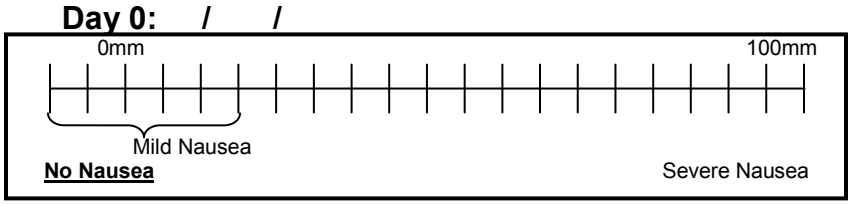
Date of assessment ___/___/____

Number of emetic episodes within the last 24 hours _____.

An emetic episode is defined as:

1. A single vomit or retch
2. Continuous vomiting or retching separated by one minute.

Number of nausea episodes within the last 24 hours _____.



Appendix 4: FOLFIRINOX chemotherapy

The regimen is comprised of oxaliplatin 85 mg/m(2) and irinotecan 180 mg/m(2) plus leucovorin 400 mg/m(2) followed by bolus 5-FU 400 mg/m(2) on day 1, then 5- FU 2,400 mg/m(2) as a 46-hour continuous infusion given every two weeks. The key components are oxaliplatin, irinotecan and infusional 5-FU. Bolus 5-FU and leucovorin doses can be modified or dropped per investigator's discretion at any time. Oxaliplatin and irinotecan dose can be modified or dropped secondary to toxicity issues as per standard of care. Use of biologic agents like bevacizumab and cetuximab that does not affect nausea and vomiting is also allowed per investigator.

Appendix 5; Study Calendar

		Cycle 1					Cycle 2					
Baseline	**PreStudy**	**D1**	**D2**	**D3**	**D4**	**D5**	**D1**	**D2**	**D3**	**D4**	**D5**	**FU**
H& P	X						X					
PS	X						X					
Weight	X						X					
Height	X						X					
Cbc w/diff	X						X					
Multi phasic	X						X					
Pregnancy test	X											
Nausea/vomiting evaluation Form Baseline	X											
Study drug		X					X					
FOLFIRINOX		X					X					
Diary	X	X	X	X	X	X	X	X	X	X	X	
Research Nurse/Study coordinator Evaluation				X								
Phone contact by Research nurse or study coordinator						X						
FU every 6 mos from start of cycle 1 using medical records												X

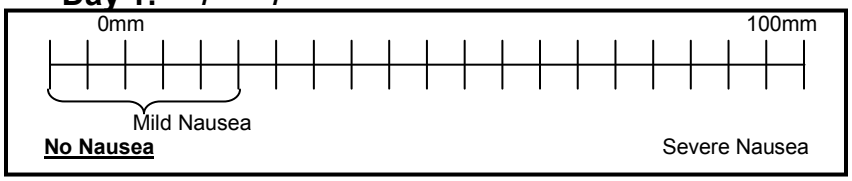
<u>The patient may continue to take IV fosaprepitant with chemotherapy after cycle 2 if there is clinical benefit noted by the investigator.</u>

Appendix 6: Daily Diary
(Day 1- 5)

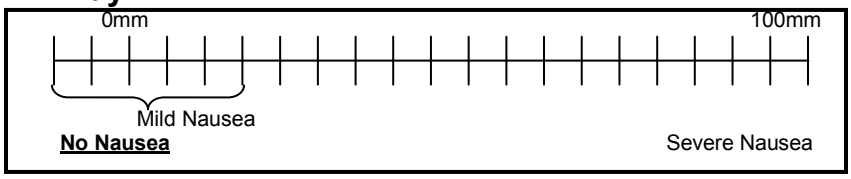
Patient Initials ___ - __ - ___ Accrual Number_____.

Please mark on the rulers below at what level your nausea is each morning.

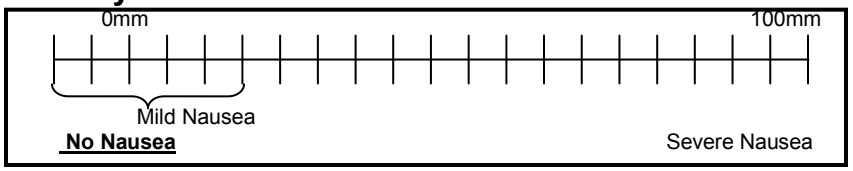
Day 1: / /



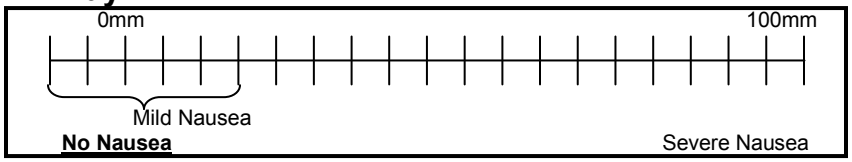
Day 2: / /



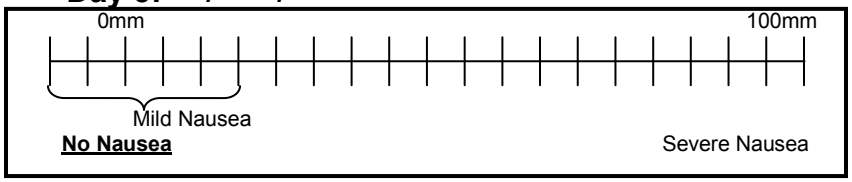
Day 3: / /



Day 4: / /



Day 5: / /



Emesis diary

Episode Number	Date	Time	Rescue Medication Used
1			
2			
3			
4			
5			
6			

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