Efficacy and Safety of Fosrolapitant and Palonosetron Hydrochloride for Injection for Preventing Nausea and Vomiting in Patients with Esophageal and Lung Cancer Caused by Multiple Cycles of Immunotherapy and Chemotherapy

Version: 2.0

Version date: May 19,2025

Signature Page

Sponsor signature

I will conscientiously fulfill the responsibilities of the sponsor and investigator in accordance with China GCP regulations, personally participate in or directly guide this clinical study. We have read and confirmed this protocol (Version: 2.0, Version Date: May 19,202 5). I agree to perform the relevant duties in accordance with China law, the Helsinki Declaration, China GCP, any applicable laws and regulations, and this study protocol. I confirm that the protocol or revised protocol will only be implemented after approval by the ethics committee, unless measures are necessary to protect the safety, rights, and interests of the subjects.

Affiliated Second Hospital of Zhejiang University School of Medicine_____

Shen Hong _____ _____

Principal Investigator (Printed) Principal Investigator (Signature) Signature Date (Year/Month/Day)

scenario summary

Research Title	Efficacy and Safety of Fosrolapitant and Palonosetron Hydrochloride for Injection for Preventing Nausea and Vomiting in Patients with Esophageal and Lung Cancer Caused by Multiple Cycles of Immunotherapy and Chemotherapy
Version number and date	2 .Version 0, May 19,202 5
Drug name	Fosrolapitant and Palonosetron Hydrochloride for Injection
Principal Investigator	Professor Shen Hong
Research Center	About 5 centers
purpose of research	Evaluating the efficacy and safety of Fosrolapitant and Palonosetron Hydrochloride for Injection for preventing nausea and vomiting in patients with esophageal and lung cancer undergoing multiple cycles of immunotherapy and chemotherapy
study population	Patients with esophageal and lung cancer who are planned to receive a platinum-based, at least 4-cycle immunotherapy and chemotherapy regimen.
research design	This randomized, parallel, cohort study was designed based on Phase III trial data. The first cycle of HR20013 combined with dexamethasone achieved a 90.3% complete response (CR) rate in the extended delayed phase for preventing chemotherapy-induced nausea and vomiting. The combination of fishterapytan, dexamethasone, and palonosetron demonstrated an 86.5% CR rate. With 57 planned participants per group, the study aimed to achieve a 95% confidence interval (CI) width of $\leqslant 0.2$ for the CR rate difference. Accounting for a 5% dropout rate, each group was enrolled with 60 participants. The trial consists of three phases: screening, treatment, and safety monitoring. Eligible participants are administered investigational drugs according to the protocol and undergo scheduled follow-up visits and examinations. During the study period, if clinicians determine that participants require antiemetic rescue medication, they may provide such treatment based on clinical needs. The specific type, dosage, frequency, and administration method of the rescue medication are determined by the investigator.
Administration method	**Queue 1:** • Fosrolapitant and Palonosetron Hydrochloride for Injection: Administered intravenously over 1 hour (plus 10 minutes), once before each chemotherapy cycle. • Dexamethasone acetate: 12mg orally on day 1 of each chemotherapy cycle, followed by 3.75mg twice daily (bid) from days 2 to 4. **Queue 2:** • Fosfotinib and Dipotamide for Injection: 150mg, administered via intravenous infusion over 20-30 minutes, once before each chemotherapy cycle.

	• Pallonosin Hydrochloride: 0.25mg, administered intravenously with a 30-second push, once before each chemotherapy cycle. • Dexamethasone acetate: 6mg orally on the first day of each chemotherapy cycle, 3.75mg on the second day (one dose earlier), and 3.75mg twice daily (bid) on the third and fourth days.
Entry criteria	(1) Age ≥18 years old, gender 不限; (2) Untreated locally advanced/metastatic esophageal cancer and lung cancer confirmed by histopathology or cytology; (3) No prior chemotherapy (antitumor drugs are not used in cancer treatment); (4) The patient is scheduled to undergo a platinum-based regimen combining at least four cycles of chemotherapy with immunotherapy; (5) Expected survival time ≥3 months; (6) Eastern Cooperative Oncology Group (ECOG) physical status score of 0 or 1; (7) The organ function is good and meets the following criteria: a: Neutrophil count ≥1.5×10^9/L; b: Hemoglobin ≥ 90g/L; c: Platelet count ≥ 100×10^9/L; d: Total bilirubin ≤1.5 × ULN; e: For patients without known liver metastases, aspartate aminotransferase (AST) ≤ 2.5 × ULN and/or alanine aminotransferase (ALT) ≤2.5 × ULN (for those with liver metastases, the limit may be relaxed to ≤5 × ULN); f: serum creatinine ≤1.5 × ULN or creatinine clearance ≥50 ml/min; g: ECG: QTc ≤450ms (male) or QTc ≤470ms (female); H: Echocardiography: Left ventricular ejection fraction (LVEF) ≥50%; (8) Female participants of childbearing capacity and male participants whose partners are women of childbearing capacity must use an effective contraceptive method from the date of signing the informed consent form until 6 months after the final drug administration. Female participants must have a negative pregnancy test within 72 hours prior to randomization and must not be breastfeeding. (9) Clearly understand and voluntarily participate in the study, and sign the informed consent form.
Exclusion criteria	(1) Patients who have received or plan to receive abdominal (including the diaphragm and lower regions) or pelvic radiotherapy within the preceding 7 days prior to treatment, or during days 1 to 8 of treatment; (2) Chemotherapy agents with high risk of vomiting are planned to be administered between the 2nd and 8th day after platinum infusion; (3) The patient is scheduled to receive a chemotherapy regimen including standard

	paclitaxel (using castor oil as the solvent); (4) Take antiemetic medications within the first two days of randomization: first-generation 5-HT3 receptor antagonists (e.g., ondansetron), phenothiazines (e.g., prochloraz), butyrophenones (e.g., haloperidol), benzylamides (e.g., metoclopramide), domperidone, cannabinoids, Chinese herbal medicines with antiemetic potential, scopolamine, and cyclosporine. (5) Patients who started benzodiazepine or opioid treatment within the preceding two days (excluding daily monotherapy with triazolam, temazepam, or midazolam); (6) Participants who started morphine use within the preceding 7 days (excluding those on stable doses); (7) Patients must not have received systemic corticosteroids (including but not limited to dexamethasone, hydrocortisone, methylprednisolone, or prednisolone) or sedating antihistamines (e.g., diphenhydramine) within the preceding 7 days (Note: Steroids may be administered once for contrast agent allergy prophylaxis, or via topical application or inhalation, unless a pre-chemotherapy day requires prior steroid treatment). (8) use palonosquin within the first 14 days of randomization; (9) NK-1 receptor antagonists were administered during the first 28 days of randomization; (10) Within 7 days prior to randomization, use of specific CYP3A4 substrates (terfenadine, ciprofloxacin, astemizole) or CYP3A4 inhibitors (ritonavir, clarithromycin, ketoconazole, itraconazole, diltiazem, etc.), or within 28 days prior to randomization, use of CYP3A4 strong inducers (phenobarbital, rifampicin, phenytoin, carbamazepine, etc.) or specific CYP2D6 substrates (thioridazine, pimozide); (11) Vomiting and/or retching, nausea within the preceding 24 hours; (12) subjects with symptomatic brain metastases; (13) Patients with uncontrolled serous cavity effusions, including pleural effusion, ascites, and pericardial effusion (those achieving stable control after treatment for at least 2 weeks may be included); (14) Within the preceding 3 months, patients must have had severe cardiovascular conditions including but not limited to acute myocardial infarction, unstable angina, significant valvular or pericardial diseases, history of ventricular tachycardia, symptomatic chronic heart failure (NYHA classes II to IV), or severe cardiac conduction abnormalities (e.g., torsades de pointes). (15) Randomized, pre-maintenance phase of poorly controlled hypertension (defined as two consecutive resting systolic blood pressure readings ⩾160mmHg and/or diastolic blood pressure ⩾100 mmHg); (16) Individuals with active hepatitis B (HBV DNA ⩾ 2000 IU/mL or 10^4 copies/mL), active hepatitis C (HCV antibody positive with HCV RNA ⩾upper limit

	of normal), acquired immunodeficiency syndrome (AIDS), positive HIV test, or positive syphilis test; (17) Concomitant conditions that contraindicate dexamethasone use, such as active infections (e.g., pneumonia) or any uncontrolled conditions (e.g., diabetic ketoacidosis, gastrointestinal obstruction, etc.); (18) Known contraindications to NK-1 receptor antagonists, 5-HT3 receptor antagonists, or dexamethasone; (19) Having participated in any other clinical trial (including but not limited to the use of the investigational drug) within the preceding 30 days; (20) Subjects who are deemed unsuitable for this study by researchers due to other circumstances.
Termination of study criteria	The subject has the right to discontinue the study treatment at any time for any reason. The reasons for the subject to discontinue the study treatment include, but are not limited to: (1) The subject requests to discontinue the treatment; (2) The occurrence of pregnancy in the subjects during the study; (3) Situations in which the investigator considers that the subject needs to discontinue treatment: a.Any adverse event, abnormal laboratory test or other medical condition that may cause the subject to no longer benefit from continued medication or pose a significant risk to health or safety; b.It is found that the scheme is seriously violated and is no longer suitable to continue to participate in the experiment; c.Other conditions in which continued testing would significantly affect the health or safety of the subject.
Exit study criteria	(1) Participants voluntarily withdrew and declined further follow-up; (2) Lost to follow-up; (3) death; (4) The sponsor terminates the study in advance.
Effectiveness Evaluation	**Primary endpoint** • The proportion of subjects achieving complete response (CR: no vomiting and no rescue treatment) during the extended post-administration phase (120-168 h) of each immunotherapy plus chemotherapy cycle. **Secondary endpoint** • The complete response (CR) rates for each immunotherapy-chemotherapy cycle at the acute phase (0-24 h), delayed phase (24 h-120 h), overall phase (0-120 h), and 0-168 h.

	• Meanwhile, the Kaplan-Meier curve was used to compare the time of first vomiting. • The Functional Life Index-Vomiting (FLIE) was used to assess the impact of chemotherapy-induced nausea and vomiting (CINV) on quality of life.
safety evaluation	Throughout the study, adverse events and serious adverse reactions were monitored, including safety-related issues such as prolonged Q-T interval and constipation.
sample capacity	This randomized, parallel, cohort study was designed based on Phase III trial data. The first cycle of HR20013 combined with dexamethasone achieved a 90.3% complete response (CR) rate in the extended delayed phase for preventing chemotherapy-induced nausea and vomiting. The combination of fishterapytan, dexamethasone, and palonosetron demonstrated an 86.5% CR rate. With 57 planned participants per group, the study aimed to achieve a 95% confidence interval (CI) width of $\leqslant 0.2$ for the CR rate difference. Accounting for a 5% dropout rate, each group was enrolled with 60 participants, totaling 120 participants.
statistical analysis	Analyze people Full Analysis Set (FAS): This includes all enrolled subjects who received the investigational drug, with primary efficacy analysis based on FAS. Safety Analysis Set (SS): Includes all enrolled participants who received at least one dose of the investigational drug. Efficacy Analysis If the subjects assessment of the vomiting attack is missing on any day during the total period, resulting in the inability to determine whether the subject is completely remitted, the subject is filled in as not completely remitted. Sensitivity analysis of the primary estimate: The sensitivity analysis method is the same as the primary estimate method, except for the different rules for filling in missing values. If the subjects assessment of vomiting episodes is missing on any day during the total period, the complete remission of the subject is determined based on the data that are not missing. If the subjects assessment of the vomiting attack is missing on any day during the hyperdelay period, resulting in the inability to determine whether the subject is completely remitted, the subject is filled as not completely remitted. safety analysis The AE will be coded using the MedDRA dictionary. Adverse events (TEAE) occurring

	during treatment will be grouped and summarized according to the System Organ Classification (SOC), preferred terms, and severity. Vital signs, electrocardiograms, and other clinical laboratory test results will be summarized as changes from baseline. Additionally, abnormal clinical laboratory test results will be described separately.
Midterm analysis	This study will conduct a mid-term analysis when 40% of participants have completed the trial, using O Brien & Flemings consumption function to determine the non-binding invalidity threshold. The analysis will include non-blind key efficacy and safety data, to be performed by an independent statistical analysis team. The Independent Data Monitoring Committee (IDMC) will review the mid-term analysis results and provide recommendations to the sponsor.

catalogue

1. Research Background

1.1 Background

Chemotherapy-induced nausea/vomiting (CINV) refers to the adverse effects triggered by anticancer drugs.[1]Approximately 60-80% of patients experience CINV.[2]This is a challenging adverse reaction in anticancer drugs. Chemoradiotherapy-induced nausea and vomiting (CINV) can cause metabolic disorders, impaired self-care capacity, nutritional depletion, loss of appetite, and deterioration of physical and mental health. It may also lead to complications such as wound dehiscence and esophageal tearing, and in severe cases, patients might abandon potentially effective or curative anticancer therapies.[1]CINV occurs in two phases: the acute phase (symptoms appear within 24 hours after chemotherapy) and the delayed phase (which may last up to five days).[3]。

Chemotherapy drugs can activate neurotransmitter receptors in the brains posterior pole or stimulate vagus nerve afferents near intestinal chromaffin cells[4]Within 24 hours of chemotherapy initiation, the oxidative effects of chemotherapeutic drugs free radicals activate peripheral pathways, triggering serotonin release from chromaffin cells in the gastrointestinal tract. Subsequently, serotonin stimulates abdominal afferent vagus nerve fibers, forming part of the peripheral vomiting pathway, which activates the vomiting reflex via the vomiting center (VC).[5]Therefore, the activation of peripheral pathways is primarily associated with acute CINV.[4]Chemotherapy drugs can also induce the release of substance P in both the central and peripheral nervous systems, triggering NK-1-mediated vomiting. [5]Most studies indicate that NK-1 receptors expressed in the central nervous system, particularly in the nucleus accumbens (NTS) and posterior insular cortex, are involved in chemotherapy-induced nausea through the release of substance P.[6-7]The clinical trial results of 5-HT-3 and NK-1 receptor antagonists further support that central NK-1 activation plays a major role in delaying CINV.[8]。

As chemotherapy regimens grow increasingly complex and their efficacy continues to advance, developing effective antiemetic strategies has become crucial, particularly for patients undergoing medium-to-high-emetic chemotherapy (MEC and HEC). To date, combination chemotherapy with cisplatin or other platinum-based agents remains the first-line treatment for various malignancies, including lung, ovarian, cervical, breast, and bladder cancers.[9-14]However, severe platinum-based chemotherapy side effects often significantly impair patients quality of life and may necessitate dose reduction or treatment discontinuation. Chemotherapy-induced nausea and vomiting (CINV), one of the most common adverse effects of cisplatin, occurs in nearly 90% of patients receiving high-dose cisplatin without antiemetic therapy.[15]A phase II study[16]The study demonstrates that the high antiemetic efficacy of the NEPA regimen (Nateopride + Palonosin) achieved in the first cycle of multiple anthracycline and cyclophosphamide (AC) chemotherapy cycles for breast cancer is maintained. Preliminary evidence indicates that patients achieving complete response (CR) throughout the treatment course may also influence the risk of delayed-onset nausea and vomiting (CINV) in each AC cycle. In cisplatin-based multi-cycle

chemotherapy, adding oral NK1 antagonists to standard antiemetic regimens has been shown to prevent nausea and vomiting.[17]In the first cycle, 64% of patients in the NK1 group achieved complete response (CR) compared to 49% in the standard treatment group. By the sixth cycle, the CR rate in the NK1 group remained at 59%, while the standard treatment groups rate had dropped to 34%.

Currently, commonly used antiemetic drugs in clinical practice are roughly divided into 5-HT3 receptor antagonists, NK-1 receptor antagonists, glucocorticoids, atypical antipsychotics, benzodiazepines, phenothiazines, and other types of antiemetic drugs. The "China Expert Consensus on the Prevention and Treatment of Nausea and Vomiting Related to Cancer Drug Therapy" (2019 edition) and the "China Society of Clinical Oncology (CSCO) Guidelines for the Prevention and Treatment of Nausea and Vomiting Related to Antitumor Therapy"[18](2019) For the prevention of chemotherapy-induced nausea and vomiting, a triple-drug regimen is recommended before chemotherapy, with a first-line combination of 5-HT3 receptor antagonists, dexamethasone, and NK-1 receptor antagonists (Class 1 evidence).

Phosphololapitan Palonosin Injection is a combination formulation of an NK-1 receptor antagonist and a 5-HT3 receptor antagonist, used to prevent nausea and vomiting caused by chemotherapy regimens with high emetic potential. The prodrug of lorapitan is rapidly converted into the active form in the body. Lorapitan is a highly selective NK-1 receptor antagonist with minimal affinity for NK-2/NK-3 receptors, other receptors, transporters, enzymes, or ion channels. Palonosin, a second-generation 5-HT3 receptor antagonist, demonstrates superior receptor affinity and a longer half-life (approximately 40 hours, 4 to 10 times longer than those of olanzanemide, granizumab, and dolanemide) compared to first-generation 5-HT3 receptor antagonists. It also exhibits excellent safety profiles. Phase III clinical trials of Phosphololapitan Palonosin Injection... [19]All patients underwent two cycles of HEC treatment, which consisted of a single-dose cisplatin-based regimen (with a cisplatin dose of $\geqslant$60 mg/m²).[2]In the IV, D1, Q3W trial, the injectable formulation of fosolopitan palonosetron plus DEX demonstrated non-inferior efficacy to FAPR+PALO+DEX in preventing nausea and vomiting, with favorable safety profiles. The study further revealed that this combination may enhance clinical outcomes during the extended delay phase. Compared to FAPR+PALO+DEX, the injectable formulation showed potential to improve quality of life in patients undergoing HEC chemotherapy, particularly during the delayed and extended delay phases.

Prolapitan Palonosin, a novel fixed-dose intravenous antiemetic combination of NK-1 receptor antagonist and 5-HT3 receptor antagonist, simultaneously antagonizes neurokinin-1 and serotonin-3 receptors. Given that cancer patients typically undergo multiple chemotherapy cycles, this prospective study evaluated whether the antiemetic efficacy of Prolapitan Palonosin could be maintained in subsequent treatment cycles.

1.2 Preclinical studies of Fosrolapitant and Palonosetron Hydrochloride for Injection

1.2.1 Key pharmacodynamic studies

Given the extensive preclinical and clinical studies confirming the efficacy of rolapitan and palonosin, phosphorolapitan-palonosin primarily conducted in vitro assays to evaluate HRS5580 (a rolapitan prodrug) s antagonistic activity against NK-1/NK-2/NK-3 receptors. Using HEK-293 cell lines stably expressing these receptors, researchers tested HRS5580s antagonistic effects. After incubating HRS5580 or positive controls with the cells for 30 minutes, they added corresponding receptor agonists (substance P, Neurokinin A, or Neurokinin B TFA) and recorded intracellular calcium flow intensity to assess antagonistic activity. Results showed that HRS5580 demonstrated no antagonistic effects against NK-1, NK-2, or NK-3 receptors in vitro.

1.2.2 Secondary pharmacodynamic studies

Using a validated safety evaluation screening model, we investigated the effects of HRS5580 on 42 early-stage drug safety targets. The compounds safety was assessed through functional activity screening to evaluate its agonistic or inhibitory effects on these targets. Results showed that at 10μM concentration, HRS5580 exhibited no significant agonistic or inhibitory effects on all 42 targets, with both agonistic and inhibitory rates below 50%. This indicates a low off-target safety risk.

1.2.3 Pharmacokinetic studies

1.2.3.1 Pharmacokinetic study of a single intravenous Fosrolapitant and Palonosetron Hydrochloride for Injection in rhesus monkeys

When HRS5580 was administered intravenously to rhesus monkeys, the parent drug rapidly metabolized into its active metabolite rolapitan in plasma. With a half-life of merely 0.16 hours, HRS5580 was completely eliminated from plasma within 2 hours of administration, leaving rolapitan as the predominant metabolite. The parent drugs plasma exposure accounted for approximately 1.7% of rolapitans. Following HRS5580 administration, plasma rolapitan exposure matched that of equivalent moles of rolapitan hydrochloride, with an AUC ratio of 98.9%. In contrast, when palonosetron fosilapitan was intravenously injected into rhesus monkeys, HRS5580 underwent rapid conversion to rolapitan, achieving a half-life of 0.13 hours. HRS5580 was undetectable in plasma within 2 hours, with its AUC representing about 2% of rolapitans. The plasma exposure of both HRS5580 and rolapitan was approximately 115% and 100.2% of the respective levels observed in the HRS5580 administration group.

The plasma exposure of rolapitan was 99.1% of that of the equivalent molar dose of rolapitan hydrochloride injection emulsion. After a single intravenous injection of palonosetron, the plasma exposure of palonosetron was 80.7% of that of the equivalent dose of palonosetron monotherapy.

1.2.3.2 Tissue Distribution Study of HRS5580 in SD Rats Following Single Intravenous Administration

After a single intravenous injection of 20 mg/kgHRS5580 in SD rats, only tissues collected 10 minutes post-administration showed detectable concentrations of the parent drug. The majority of tissues exhibited concentrations below 1% of plasma levels, with rolapitan being predominant. Rolapitan was primarily distributed in lung, adrenal, liver, pancreas, ovaries, adipose, kidney,

spleen, and heart tissues, where concentrations consistently exceeded plasma levels. Tissue exposure levels were approximately 10 times higher than plasma exposure. Brain tissue exposure was about 4.7 times higher than plasma exposure, indicating its ability to cross the blood-brain barrier. The concentration ratio of rolapitan in whole blood versus plasma was 0.95, suggesting its entry into red blood cells. Female rats demonstrated approximately three times higher tissue exposure than males. At equivalent molar doses, intravenous administration of HRS5580 in rats resulted in rolapitan exposure levels in most tissues comparable to those following emulsion administration, with exposure ratios ranging from 0.73 to 1.33.

1.2.3.Metabolic profiling of 3HRS5580 in an in vitro hepatocyte system

In hepatocyte systems, HRS5580 undergoes 180-minute incubation, primarily metabolized via amide hydrolysis to form rolapitan. The compound demonstrates high metabolic efficiency across all hepatocyte species, with no significant interspecies differences. Its metabolism is predominantly catalyzed by cytoplasmic free thioglycine-containing enzymes and mitochondrial hydrolytic enzymes, while CES1 and CES2 contribute minimally to hydrolysis.

1.2.3.4HRS5580 Metabolite Studies in Animals

In rats, HRS5580 undergoes extensive metabolism, with 27 metabolites identified. The primary metabolic pathways include hydrolysis to form lorapitan (M1), followed by further metabolization via mono-oxidation (M2), dehydrogenation (M3), mono-oxidation and dehydrogenation (M4), and dual oxidation and dehydrogenation (M5), predominantly excreted through feces. In both rat and rhesus monkey plasma, the predominant metabolite is the hydrolyzed form of lorapitan. Only trace amounts of the parent compound HRS5580 were detected in pooled blood samples collected within 2 hours after intravenous administration, while no HRS5580 was detected in urine or fecal samples.

2. Research Objective

To evaluate the efficacy and safety of Fosrolapitant and Palonosetron Hydrochloride for Injection for preventing nausea and vomiting in patients with esophageal and lung cancer undergoing multiple cycles of immunotherapy and chemotherapy.

3. Research Design and Methods

This study is a randomized, parallel, cohort study, with a plan to enroll 120 subjects, 60 in each cohort, and 40% of the subjects will be analyzed at the midpoint of the study.

The trial consists of three phases: screening, treatment, and safety follow-up. Participants receive medication as prescribed in the protocol, followed by scheduled follow-up visits and examinations according to the trial schedule. If researchers determine that a participant requires antiemetic treatment during the study, they may provide such intervention based on clinical needs. The specific type, dosage, frequency, and administration method of the medication are determined by the investigator.

Research period: June 2025-September 2026

3.1 Selection Criteria

Participants must meet all the following inclusion criteria at the same time during screening and randomization to be included in this study:

(1) Age ≥18 years old, gender 不限;

(2) Untreated, locally advanced/metastatic esophageal cancer and lung cancer confirmed by histology or cytology;

(3) No previous chemotherapy (antitumor drugs are not used for cancer treatment);

(4) The plan is to receive at least 4 cycles of chemotherapy combined with immunotherapy based on cisplatin and carboplatin;

(5) Expected survival time ≥3 months;

(6) Eastern Cooperative Oncology Group (ECOG) physical status score of 0 or 1;

(7) The organ function is good and meets the following criteria:

a: Neutrophil count ≥1.5×10^9/L;

b: Hemoglobin ≥ 90g/L;

c: Platelet count ≥ 100×10^9/L;

d: Total bilirubin ≤1.5 × ULN;

e: For patients without known liver metastases, aspartate aminotransferase (AST) ≤2.5 × ULN and/or alanine aminotransferase (ALT) ≤2.5 × ULN (for those with liver metastases, the limit may be relaxed to ≤5 × ULN);

f: serum creatinine ≤1.5 × ULN or creatinine clearance ≥50 ml/min

g: ECG: QTc ≤450ms (male) or QTc ≤470ms (female);

H: Echocardiography: Left ventricular ejection fraction (LVEF) ≥50%;

(8) Female participants of childbearing capacity and male participants whose partners are women of childbearing capacity must use an effective contraceptive method from the date of signing the informed consent form until 6 months after the final drug administration. Female participants must have a negative pregnancy test within 72 hours prior to randomization and must not be breastfeeding.

(9) Clearly understand and voluntarily participate in the study, and sign the informed consent form.

3.2 Exclusion Criteria

Participants who have any of the following during screening and randomization will not be enrolled in this study:

(1) Patients who have received or plan to receive abdominal (including the diaphragm and lower regions) or pelvic radiotherapy within the preceding 7 days prior to treatment, or during days 1 to 8 of treatment;

(2) Chemotherapy drugs with high risk of vomiting are planned to be given within 2 to 8 days

after platinum infusion;

(3) The patient is scheduled to receive a chemotherapy regimen including standard paclitaxel (using castor oil as a solvent);

(4) Take antiemetic medications within the first two days of randomization: first-generation 5-HT3 receptor antagonists (e.g., ondansetron), phenothiazines (e.g., prochloraz), butyrophenones (e.g., haloperidol), benzylamides (e.g., metoclopramide), domperidone, cannabinoids, Chinese herbal medicines with antiemetic potential, scopolamine, and cyclosporine.

(5) Patients who started benzodiazepine or opioid treatment within the preceding two days (excluding daily monotherapy with triazolam, temazepam, or midazolam);

(6) Participants who started morphine use within the preceding 7 days (excluding those on stable doses);

(7) Patients must not have received systemic corticosteroids (including but not limited to dexamethasone, hydrocortisone, methylprednisolone, or prednisolone) or sedating antihistamines (e.g., diphenhydramine) within the preceding 7 days (Note: Steroids may be administered once for contrast agent allergy prophylaxis, or via topical application or inhalation, unless a pre-chemotherapy day requires prior steroid treatment).

(8) use palonosquin within the first 14 days of randomization;

(9) NK-1 receptor antagonists were administered during the first 28 days of randomization;

(10) Within 7 days prior to randomization, use of specific CYP3A4 substrates (terfenadine, ciprofloxacin, astemizole) or CYP3A4 inhibitors (ritonavir, clarithromycin, ketoconazole, itraconazole, diltiazem, etc.), or within 28 days prior to randomization, use of CYP3A4 strong inducers (phenobarbital, rifampicin, phenytoin, carbamazepine, etc.) or specific CYP2D6 substrates (thioridazine, pimozide);

(11) Vomiting and/or retching, nausea within the preceding 24 hours;

(12) subjects with symptomatic brain metastases;

(13) Patients with uncontrolled serous cavity effusions, including pleural effusion, ascites, and pericardial effusion (those achieving stable control after treatment for at least 2 weeks may be included);

(14) Within the preceding 3 months, patients must have had severe cardiovascular conditions including but not limited to acute myocardial infarction, unstable angina, significant valvular or pericardial diseases, history of ventricular tachycardia, symptomatic chronic heart failure (NYHA classes II to IV), or severe cardiac conduction abnormalities (e.g., torsades de pointes).

(15) Randomized, pre-maintenance phase of poorly controlled hypertension (defined as two consecutive resting systolic blood pressure readings $\geqslant$160mmHg and/or diastolic blood pressure $\geqslant$100 mmHg);

(16) Individuals with active hepatitis B (HBV DNA $\geqslant$2000 IU/mL or 10^4 copies/mL), active hepatitis C (HCV antibody positive with HCV RNA $\geqslant$ upper limit of normal), acquired immunodeficiency syndrome (AIDS), positive HIV test, or positive syphilis test;

(17) Concomitant conditions that contraindicate dexamethasone use, such as active infections (e.g., pneumonia) or any uncontrolled conditions (e.g., diabetic ketoacidosis, gastrointestinal obstruction, etc.);

(18) Known contraindications to NK-1 receptor antagonists, 5-HT3 receptor antagonists, or dexamethasone;

(19) Having participated in any other clinical trial (including but not limited to studies involving the investigational drug) within the preceding 30 days;

(20) Subjects who are deemed unsuitable for this study by researchers due to other circumstances.

3.3 Exit Criteria

Subjects may withdraw from the trial at any time, or may be asked to withdraw by the investigator for safety or behavioral reasons, or for failure to comply with protocol requirements at study visit times or steps at their study center.

Reasons to exit the study may include:

- The subject voluntarily withdrew and refused further follow-up;
- Lost to follow-up;
- die ；
- The sponsor terminates the study prematurely.

If a participant fails to return to the center for follow-up as agreed, every effort should be made to contact them. The investigator must inquire about the reason for withdrawal and request the participant to return for a withdrawal visit. Where applicable, any unresolved adverse events (AEs) should be followed up. If the participant refuses to attend further visits at the research center, the investigator should continue tracking and collecting relevant information until the participant voluntarily withdraws. In such cases, no further research evaluations or data collection should be conducted.

3.4 Medication Plan

Queue 1:

- Fosrolapitant and Palonosetron Hydrochloride for Injection: Administered intravenously over 1 hour (plus 10 minutes), once before each chemotherapy cycle.
- Dexamethasone acetate: 12mg orally on the first day of each chemotherapy cycle, followed by 3.75mg twice daily (bid) from days 2 to 4.

Queue 2:

- Fosfotinib and Dipotamide for Injection: 150mg, administered via intravenous infusion over 20-30 minutes, once before each chemotherapy cycle.
- Pallonosin Hydrochloride: 0.25mg, administered intravenously with a 30-second push, once before each chemotherapy cycle.
- Dexamethasone acetate: 6mg orally on the first day of each chemotherapy cycle, 3.75mg on the second day (one dose earlier), and 3.75mg twice daily (bid) on the third and fourth days.

3.5 Study endpoints

Primary efficacy endpoint

The proportion of subjects achieving complete response (CR: no vomiting and no rescue treatment) during the extended post-administration phase (120-168 h) after initiating chemotherapy in each immunotherapy-chemotherapy cycle.

Secondary efficacy endpoint

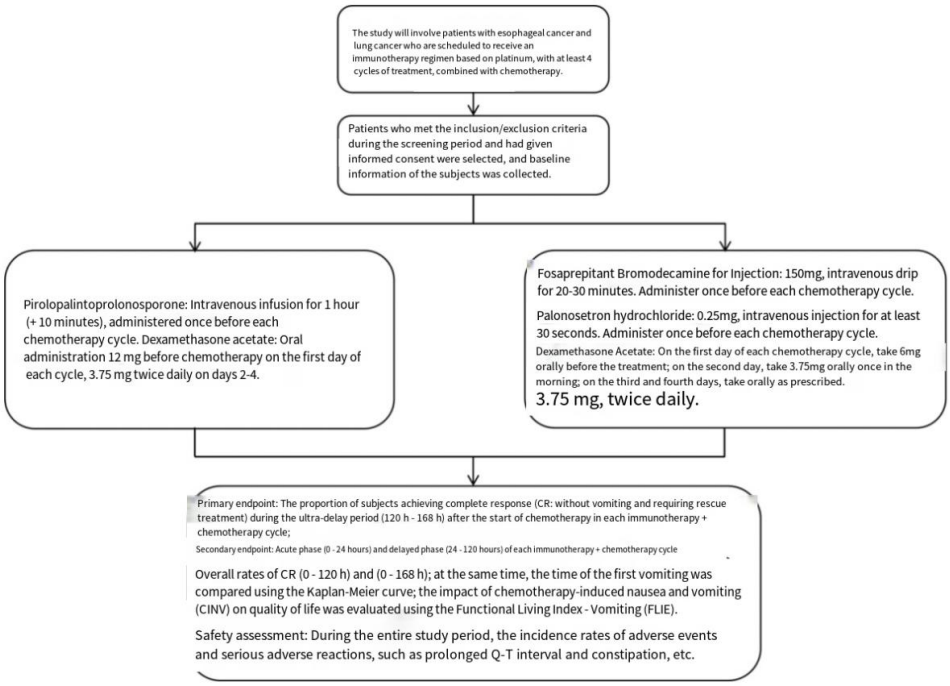
(1) The complete response (CR) rates for each immunotherapy-chemotherapy cycle at the acute phase (0-24 h), delayed phase (24-120 h), overall phase (0-120 h), and 0-168 h;

(2) Compare the time to first vomiting using Kaplan-Meier curves;

(3) Assess the impact of chemotherapy-induced nausea and vomiting on quality of life using the Functional Life Index-Vomiting (FLIE);

(4) Throughout the study period, adverse events and serious adverse reactions occurred, including safety-related issues such as prolonged Q-T interval and constipation.

3.6 Research Flow Chart



3.7 Statistical Analysis

Count data are summarized using frequency and percentage. Measurement data are summarized using mean, standard deviation, median, maximum, and minimum. SAS 9.4 statistical analysis software is used for calculations.

Analyze people

Full Analysis Set (FAS): This includes all enrolled subjects who received the investigational drug, with primary efficacy analysis based on FAS.

Safety Analysis Set (SS): Includes all enrolled subjects who received at least one dose of the investigational drug.

Efficacy Analysis

If the subjects assessment of the vomiting attack is missing on any day during the total period, resulting in the inability to determine whether the subject is completely remitted, the subject is filled in as not completely remitted.

Sensitivity analysis of the primary estimate: The sensitivity analysis method is the same as the primary estimate method, except for the different rules for filling in missing values. If the subjects assessment of vomiting episodes is missing on any day during the total period, the complete remission of the subject is determined based on the data that are not missing.

If the subjects assessment of the vomiting attack is missing on any day during the hyperdelay period, resulting in the inability to determine whether the subject is completely remitted, the subject is filled as not completely remitted.

safety analysis

AEs will be coded using the MedDRA dictionary. Adverse events (TEAEs) during treatment will be grouped and summarized according to System Organ Classification (SOC), preferred terms, and severity. Vital signs, ECGs, and other clinical laboratory test results will be summarized as changes from baseline. Additionally, abnormal clinical laboratory test results will be described separately.

4 Sample size calculation

This randomized, parallel, cohort study was designed based on Phase III trial data. The first cycle of HR20013 combined with dexamethasone achieved a 90.3% complete response (CR) rate in the extended delayed phase for preventing chemotherapy-induced nausea and vomiting. The combination of fishterapytan, dexamethasone, and palonosetron demonstrated an 86.5% CR rate. With 57 participants planned per group, the study aimed to achieve a 95% confidence interval (CI) width of ≤0.2 for the CR rate difference. Accounting for a 5% dropout rate, each group was enrolled with 60 participants, totaling 120 participants.

5 Data Management and Confidentiality

The sponsor is responsible for managing the clinical trial data in this study, utilizing an Electronic Data Capture (EDC) system for data collection and management. All records pertaining to participants identities are kept confidential and not disclosed beyond what is permitted by applicable laws and/or regulations.

5.1 Data Collection

The eCRF is completed by researchers or data entry personnel through the EDC system. It must be filled out promptly, with all data traceable from original files or records. When modifying data in the EDC, researchers must specify the reason for changes as prompted by the system. The modification history and reasons are recorded in the EDC systems audit trail. Researchers or authorized personnel must verify the authenticity, completeness, and timeliness of the eCRF data

and electronically sign it in the EDC system.

Data administrators develop eCRF and validation protocols in the EDC system according to the study protocol, completing user acceptance testing and system deployment prior to the first participant enrollment. All EDC users must complete relevant training and archive training records to obtain access to the studys eCRF. When implementing electronic signatures on the eCRF, users must confirm and agree to the electronic signature usage declaration. Accounts are restricted to the users own use, and passwords must be securely stored and changed regularly. When there are personnel changes in the research team, access permissions must be promptly revoked.

5.2 Data Management

The EDC systems logical verification program conducts integrity and consistency checks on entered data, raising questions about potentially problematic entries. Researchers or data entry personnel may correct the data or provide explanations and confirmations by responding to these queries. Researchers must promptly address questions from the system and data reviewers, with multiple questions potentially being raised until the data issues are resolved.

Forty percent of participants will undergo a mid-term analysis after completing the study. Prior to database locking, the research team must complete data cleaning, compile all protocol deviation events during the trial, and convene a data review meeting to finalize the analysis population. All decisions made during the data review meeting must be documented. Upon approval, the research team will confirm the locking of the study database in the EDC system, after which the data cannot be modified.

Upon completion of the study, all research materials must be preserved and managed in accordance with Good Clinical Practice (GCP) requirements. Investigators must notify the sponsor in advance before destroying any study-related documents or records. The sponsor shall retain clinical trial data for at least five years, whether the investigational drug is approved for marketing or the clinical trial is terminated prematurely.

6. Pre-existing and concomitant therapies

6.1 Prior treatment

The subjects medication and non-medication treatment information during the 30 days prior to randomization must be recorded in the electronic case report form (eCRF). The prohibited treatments and medications before randomization must align with the exclusion criteria.

6.2 Remedial Treatment

Remedy treatment refers to any prescription medication prescribed by the investigator to alleviate nausea or vomiting. This definition must be clearly communicated to participants. Throughout the study, investigators will evaluate both the severity of reported nausea/vomiting and observed clinical manifestations. Remedy treatment should only be administered when clinically necessary based on the investigators assessment, and must not be used if the participant

has not experienced such symptoms. When using remedy treatment, serotoninergic 5-HT3 receptor antagonists (excluding palonosetron) are recommended as the first-line treatment.

6.3 Contraindications in the study

1. The use of remedial drugs for non-remedial purposes is prohibited during chemotherapy;
2. During chemotherapy cycles, the use of medications containing rolapitan, palonosin, or dexamethasone is prohibited except for protocol-prescribed visits.
3. The following drugs are prohibited during the study:

(1) Specific CYP3A4 substrates: terfenadine, ciprofibrate, and astemizole;

(2) Strong CYP3A4 inducers: phenobarbital, rifampicin, phenytoin, and carbamazepine;

(3) CYP3A4 inhibitors: Ritonavir, Clarithromycin, Ketoconazole, Itraconazole, Diltiazem, etc.

(4) Specific CYP2D6 substrates: thiocarbazepine and pimozide.

7. Informed Consent

The rights, safety, and physical/mental well-being of participants are paramount considerations, taking precedence over scientific and societal benefits. After explaining the studys core components and confirming participants understanding of its objectives, researchers must obtain each participants signed and dated Informed Consent Form (ICF). Participants should carefully review and consider their statements before signing, and receive the signed ICF. Before initiating any clinical research procedures, including eligibility screening processes, researchers must obtain the participants signed ICF. Participants may not enter the study without obtaining informed consent.

For subjects unable to sign an informed consent form (ICF) due to any reason, the legal guardian must sign on their behalf. The ICF signed by both the subject and the investigator, including their names and dates, must be properly preserved by the investigator and recorded in the relevant research records.

The confidentiality of participant information is strictly maintained by researchers, participating investigators, and their authorized representatives. This confidentiality extends to biological samples and genetic testing beyond clinical data. Consequently, all study protocols, documentation, data, and related information will be rigorously protected. No unauthorized third parties may access any research or data without written authorization. The research data entry and management systems used by clinical research centers and researchers at Zhejiang University Second Affiliated Hospital are password-protected and confidential. Upon study completion, all identifiable information in research databases will be de-identified and archived at Zhejiang University Second Affiliated Hospital.

8 Adverse Event Report

8.1 Adverse Events

Adverse Events (AE) refer to all adverse medical events occurring in subjects after receiving the investigational drug, which may manifest as symptoms, signs, diseases, or abnormal laboratory

findings, but not necessarily showing a causal relationship with the investigational drug. AE includes but is not limited to:

(1) The worsening of pre-existing medical conditions or diseases (including aggravated symptoms, signs, or abnormal laboratory findings) prior to enrollment in the clinical trial;

(2) Any new AE: Any new medically significant adverse condition (including symptoms, signs, or newly diagnosed diseases);

(3) Abnormal laboratory test values or results with clinical significance (pre-existing prior to screening or newly detected during screening as comorbidities or baseline data, not recorded as adverse events).

8.2 Severity of adverse events and criteria for judgment

Refer to the NCI-CTCAE5.0 criteria for classifying drug-related adverse events (AEs). For AEs not listed in the NCI-CTCAE5.0 table, the following standards apply:

grade	Clinical description of severity
1	Mild: No clinical symptoms or mild clinical symptoms; only clinical or laboratory abnormalities; no treatment required
2	Moderate: Requires minor, localized, or non-invasive treatment; age-appropriate use of tools in ActivitiesofDailyLiving (ADL) is limited, including cooking, shopping, phone calls, and counting money.
3	The condition is severe or presents with serious medical symptoms that do not immediately threaten life, but may lead to hospitalization or prolonged hospital stays, disability, or limitations in self-care ADLs (activities of daily living). These include bathing, dressing, undressing, eating, using the bathroom, and taking medication, rather than being bedridden.
4	Life-threatening; requires urgent treatment
5	AE that caused death

Abbreviations: AE= adverse event; ADL= activities of daily living.

8.3. Determination of causal relationship between adverse events and investigational drug

The determination of causation between an Adverse Event (AE) and a investigational drug involves a comprehensive evaluation to establish whether there is a reasonable likelihood that the AE was caused or contributed to by the investigational drug. Key factors considered include: whether the AE occurred within a reasonable time sequence relative to the investigational drug administration, the drugs characteristics, its toxicological and pharmacological effects, concomitant medication use, the subjects underlying medical conditions, medical history, family history, and the presence of de-irritation and re-irritation responses. Typically, factual evidence or arguments supporting the causation determination must be provided.

For the causal relationship between AE and the investigational drug, the investigator should assess it as definitely related, probably related, probably unrelated, definitely unrelated, or not determined.

8.4. Serious adverse events

A Serious Adverse Event (SAE) is any of the following adverse medical events that occur in a subject after receiving any dose of the investigational drug:

(1) Causing death;

(2) Life-threatening (defined as the subjects risk of death at the time of the event, not implying that the condition would lead to death if aggravated);

(3) Need to be hospitalized or prolong the hospitalization time;

(4) Permanent or apparent disability/loss of function;

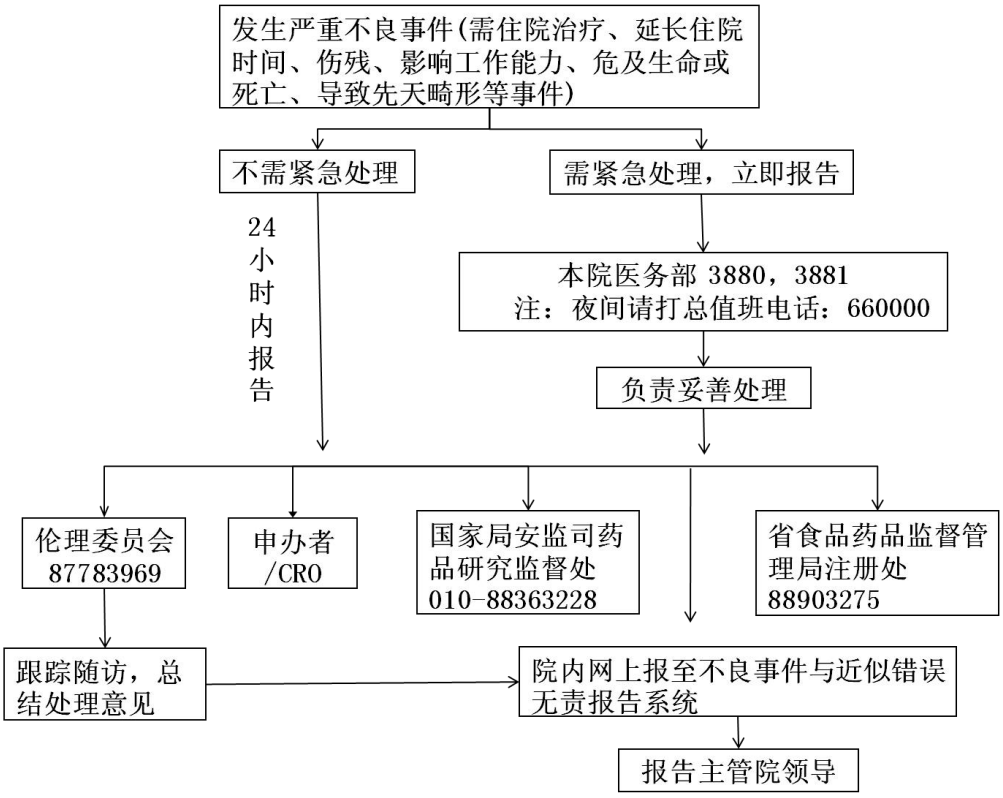
(5) Congenital abnormalities/birth defects;

(6) Other important medical events.

8.5 Reporting System

All adverse events: take timely measures to deal with them and record them in the case report form.

Severe Adverse Events (SAE): Immediate measures should be taken to address the incident, documented in the case report form. The investigator must decide whether to discontinue or reduce the medication, and report to the ethics committee, clinical trial institution, and sponsor immediately. A report must be submitted to the national and provincial food and drug administration within 24 hours. SAEs must be reported through the In-Hospital Network Adverse Event and Similar Error Non-Blame Reporting System. The specific procedure is shown in the figure below.



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Appendix 1: ECOG Physical Status Score

Prior to treatment, patients general health status should be assessed, with physical performance status (PS) being a key indicator. PS reflects a patients overall health and treatment tolerance through their physical condition. The Eastern Cooperative Oncology Group (ECOG) has developed a simplified PS scoring system, as shown in the table below:

ECOG Physical Status Classification

Activity rating	description
0	Asymptomatic, fully active, and able to perform unlimited activities.
1	Symptomatic, able to walk completely, but limited to heavy physical activity, able to do light or sedentary work, such as light housework and office work.
2	Symptoms are present, walking is possible, and life can be self-sufficient, but no physical activity can be performed. More than 50% of the time is awake (bed time during the day is less than 50%).
3	Symptoms, limited ability to take care of oneself, more than 50% of waking time in bed or chair, but not yet bedridden.
4	He lost all his functions and could not take care of himself. He was bedridden.
5	die 。

Appendix II: Functional Life Inventory of Vomiting (FLIE)

The Life Activities with Vomiting (FLIE) is a patient-reported questionnaire assessing the quality of life with nausea and vomiting. It consists of two sections—nausea and vomiting—each containing 9 questions, totaling 18 questions. See the table below for details.

Use an intuitive scale to evaluate each item. Read the questions carefully, as "1" may indicate no impact on your quality of life in some cases, while in others, "1" signifies a significant impact. The numerical value increases progressively as the impact intensifies, with "7" representing the opposite meaning of "1". Calculate the nausea score, vomiting score, and total score by summing responses across categories. Conduct evaluations before each chemotherapy cycle, and at 24h,120h, and 168h post-treatment.

Participants must draw a vertical line on the intuitive simulation scale when answering. The operation example is as follows:

Vomiting Life Activity Scale (FLIE)

1: Have you experienced nausea before chemotherapy, within 1 day after chemotherapy (0-24 hours), within 2-5 days after chemotherapy (24-12 0 hours), or within 6-7 days after chemotherapy (12 0-168 hours)?

1 2 3 4 5 6 7

Not very much

2: Have you experienced nausea that affected your ability to continue your usual recreational or leisure activities before chemotherapy or within 1 day after chemotherapy (0-24 hours), within 2-5 days after chemotherapy (24-120 hours), or within 6-7 days after chemotherapy (120-168 hours)?

1 2 3 4 5 6 7

Not very much

3: Within 1 day (0-24 hours) before/after/2-5 days (24-120 hours) after/6-7 days (120-168 hours) after chemotherapy, has your nausea affected your ability to prepare a meal or do light housework?

1 2 3 4 5 6 7

Not at all

4: How much does your nausea affect your ability to eat during the following time periods: before chemotherapy or within 1 day after chemotherapy (0-24 hours), 2-5 days after chemotherapy (24-120 hours), and 6-7 days after chemotherapy (120-168 hours)?

1 2 3 4 5 6 7

Not very much

5: How much does your nausea affect your ability to enjoy drinks before/1 day after the start of chemotherapy (0-24 hours)/2-5 days after the start of chemotherapy (24-120 hours)/6-7 days after the start of chemotherapy (120-168 hours)?

1 2 3 4 5 6 7

Not very much

6: How much does your nausea affect your desire to visit and spend time with loved ones during the 1 day (0-24 hours) before/after chemotherapy, 2-5 days (24-120 hours) after chemotherapy, and 6-7 days (120-168 hours) after chemotherapy?

1 2 3 4 5 6 7

Not at all

7: Have you experienced nausea that affected your daily activities before chemotherapy, within 1 day after chemotherapy (0-24 hours), within 2-5 days after chemotherapy (24-120 hours), or within 6-7 days after chemotherapy (120-168 hours)?

1 2 3 4 5 6 7

Not very much

8: Please rate the degree of difficulty your nausea is causing you personally within the following time periods: before chemotherapy or 1 day after chemotherapy (0-24 hours), 2-5 days after chemotherapy (24-120 hours), and 6-7 days after chemotherapy (120-168 hours).

1 2 3 4 5 6 7

Not very much

9: Please rate the degree of difficulty your nausea has caused your loved ones life before/1 day after chemotherapy (0-24 hours)/2-5 days after chemotherapy (24-120 hours)/6-7 days after chemotherapy (120-168 hours).

1 2 3 4 5 6 7

Not very much

10: Have you ever vomited before chemotherapy or within 1 day after chemotherapy (0-24 hours), within 2-5 days after chemotherapy (24-120 hours), or within 6-7 days after chemotherapy (120-168 hours)?

1 2 3 4 5 6 7

Not very much

11: Have you experienced vomiting that affected your ability to continue your usual recreational activities before chemotherapy or within 1 day after chemotherapy (0-24 hours), or within 2-5 days after chemotherapy (24-120 hours), or within 6-7 days after chemotherapy (120-168 hours)?

1 2 3 4 5 6 7

Not at all

12: Have you ever vomited and been unable to prepare a meal or do light housework within 1 day (0-24 hours) before/after chemotherapy, 2-5 days (24-120 hours) after chemotherapy, or 6-7 days (120-168 hours) after chemotherapy?

1 2 3 4 5 6 7

Not very much

13: How much does your vomiting affect your ability to eat before/1 day after/2-5 days after/6-7 days after chemotherapy (0-24 hours/24-120 hours/120-168 hours)?

1 2 3 4 5 6 7

Not very much

14: How much does your vomiting affect your ability to enjoy drinks before/1 day after/2-5 days after/6-7 days after chemotherapy (0-24 hours/24-120 hours/120-168 hours)?

1 2 3 4 5 6 7

Not very much

15: How much does your vomiting affect your desire to visit and spend time with loved ones before/1 day after/2-5 days after/6-7 days after chemotherapy (0-24 hours/24-120 hours/120-168 hours)?

1 2 3 4 5 6 7

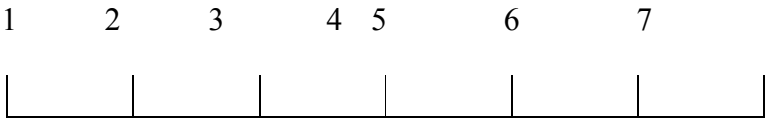
Not at all

16: Have you ever experienced vomiting that affected your daily activities before chemotherapy, within 1 day after chemotherapy (0-24 hours), within 2-5 days after chemotherapy (24-120 hours), or within 6-7 days after chemotherapy (120-168 hours)?

1 2 3 4 5 6 7

Not very much

17: Please rate the degree of difficulty your vomiting has caused you personally before chemotherapy or within 1 day after chemotherapy (0-24 hours), within 2-5 days after chemotherapy (24-120 hours), or within 6-7 days after chemotherapy (120-168 hours).



Not very much

18: Please rate the degree of difficulty your vomiting has caused to the lives of your closest loved ones during the following periods: before chemotherapy, 1 day after chemotherapy (0-24 hours), 2-5 days after chemotherapy (24-120 hours), and 6-7 days after chemotherapy (120-168 hours).

Not at all