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A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy

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Background: Antiemetic guidelines recommend co-administration of agents that target multiple molecular pathways involved in emesis to maximize prevention and control of chemotherapy-induced nausea and vomiting (CINV). NEPA is a new oral fixed-dose combination of 300 mg netupitant, a highly selective NK_1 receptor antagonist (RA) and 0.50 mg palonosetron (PALO), a pharmacologically and clinically distinct 5-HT_3 RA, which targets dual antiemetic pathways.

Patients and methods: This multinational, randomized, double-blind, parallel group phase III study (NCT01339260) in 1455 chemotherapy-naïve patients receiving moderately emetogenic (anthracycline–cyclophosphamide) chemotherapy evaluated the efficacy and safety of a single oral dose of NEPA versus a single oral dose (0.50 mg) of PALO. All patients also received oral dexamethasone (DEX) on day 1 only (12 mg in the NEPA arm and 20 mg in the PALO arm). The primary efficacy end point was complete response (CR: no emesis, no rescue medication) during the delayed (25–120 h) phase in cycle 1.

Results: The percentage of patients with CR during the delayed phase was significantly higher in the NEPA group compared with the PALO group (76.9% versus 69.5%; $P = 0.001$), as were the percentages in the overall (0–120 h) (74.3% versus 66.6%; $P = 0.001$) and acute (0–24 h) (88.4% versus 85.0%; $P = 0.047$) phases. NEPA was also superior to PALO during the delayed and overall phases for all secondary efficacy end points of no emesis, no significant nausea and complete protection (CR plus no significant nausea). NEPA was well tolerated with a similar safety profile as PALO.

Conclusions: NEPA plus a single dose of DEX was superior to PALO plus DEX in preventing CINV following moderately emetogenic chemotherapy in acute, delayed and overall phases of observation. As a fixed-dose antiemetic drug combination, NEPA along with a single dose of DEX on day 1 offers guideline-based prophylaxis with a convenient, single-day treatment.

Key words: neurokinin-1 receptor antagonist, NEPA, netupitant, palonosetron, CINV, moderately emetogenic

introduction

The pathophysiology of chemotherapy-induced nausea and vomiting (CINV) is multifactorial involving several neurotransmitters and receptors [1]. Combination antiemetic regimens targeting multiple molecular pathways associated with emesis have become the standard of care for prevention of CINV. This is supported by compelling clinical research and antiemetic guidelines [2, 3] which recommend a prophylactic combination of a 5-HT_3 receptor antagonist (RA) [palonosetron (PALO) as 'preferred'] and dexamethasone (DEX) when administering moderately emetogenic chemotherapy (MEC) and a 5-HT_3 RA, DEX and a neurokinin-1 (NK_1) RA when administering highly emetogenic chemotherapy (HEC).

Anthracycline–cyclophosphamide (AC) chemotherapy is still considered to be moderately emetogenic according to regulatory authorities and evidence-based emetogenicity classification schemes [3]. Patients receiving AC tend to have additional patient-

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related risk factors (e.g. young age, female gender) which put them at greater risk for CINV; studies have shown that the addition of a NK_1 RA to the 5-HT_3 RA and DEX regimen is beneficial in this setting [4]. Therefore, guidelines recommend that this group of patients also receive a triple-combination antiemetic therapy on day 1.

While data support the reputed notion that guideline conformity will improve CINV control for patients, unfortunately, adherence to antiemetic guidelines is suboptimal [5]. Consequently, even with effective agents available, many patients still suffer from CINV, particularly nausea during the delayed (25–120 h) phase following chemotherapy [2].

NEPA is an oral fixed-dose combination of netupitant (NETU), a new highly selective NK_1 RA and PALO, a pharmacologically distinct [6] and clinically superior [2] 5-HT_3 RA. The unique pharmacological characteristics of PALO result in long-lasting inhibition of the 5-HT_3 receptor function. PALO has also been shown to inhibit the cross-talk between the 5-HT_3 and NK_1 receptors and, recently, the combination of PALO with NETU has been shown to work synergistically in enhancing inhibition of the substance *P* response compared with either antagonist alone [7]. These findings offer a possible explanation behind its unique efficacy during the delayed phase and also suggest the potential to enhance prevention of delayed CINV when used in combination with NETU.

In a phase II dose-ranging study [8] in patients receiving HEC, the NEPA combination of NETU 300 mg + PALO 0.50 mg was the most effective dose studied, with an incremental clinical benefit over lower NEPA doses for all efficacy end points. This was the basis for the selection of the fixed-dose combination in the current trial. This phase III study was designed to demonstrate the superiority of NEPA over PALO in preventing CINV in patients receiving AC-based MEC and to evaluate NEPA's safety.

patients and methods

study design

This was a phase III, multicenter, randomized, double-blind, double-dummy, parallel group study conducted at 177 enrolling sites in 15 countries (Argentina, Belarus, Brazil, Bulgaria, Croatia, Germany, Hungary, India, Italy, Mexico, Poland, Romania, Russia, Ukraine and the United States) between April 2011 and November 2012. The protocol was approved by ethical review committees, all patients provided written informed consent, and all study sites followed GCP, ICH, Declaration of Helsinki principles, local laws and regulations.

patients

Eligible patients were ≥18 years, naïve to chemotherapy, and scheduled to receive their first course of an AC MEC regimen for treatment of a solid malignant tumor. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. Patients were not eligible if they were scheduled to receive: (i) HEC from day 1–5 or additional MEC from day 2–5 following chemotherapy, (ii) radiation therapy to the abdomen or pelvis within 1 week before day 1 or between day 1 and 5, or 3) a bone marrow or stem-cell transplant. Patients were not allowed to receive any drug with known or potential antiemetic efficacy within 24 h before day 1 and were excluded if they experienced any vomiting, retching or mild nausea within 24 h before day 1. Patients were not to have had any serious cardiovascular disease history or predisposition to cardiac conduction abnormalities, with the exception of incomplete right bundle branch block. Because NETU is a moderate inhibitor of CYP3A4, use of any CYP3A4 inducer within 4 weeks, use of a strong or moderate inhibitor within 1 week or scheduled to receive CYP3A4 inhibitors, inducers or certain substrates as concomitant medication was prohibited (supplementary Table S1, available at *Annals of Oncology* online).

treatment

Patients were randomly assigned to receive either NEPA (NETU 300 mg/PALO 0.50 mg) plus 12 mg DEX or PALO 0.50 mg plus 20 mg DEX on day 1 of chemotherapy. Due to the increased exposure to DEX when given in combination with NETU [9], the DEX dose in the NEPA group was reduced to achieve DEX exposure similar to that in the PALO group. The 0.50 mg oral PALO dose was selected based on a noninferiority efficacy trial evaluating three oral PALO doses, 0.25, 0.50 and 0.75 mg, compared with i.v. PALO 0.25 mg [10]. NEPA and PALO were administered 60 min and DEX 30 min before chemotherapy on day 1.

Patients were stratified by region [United States, Latin America/Mexico, Europe, Commonwealth of Independent States (i.e. former Soviet Republics) and Asia] and age class (<55 and ≥55 years). Blinding was maintained in all groups with the use of matching identical placebos. The chemotherapy consisted of either cyclophosphamide i.v. (500–1500 mg/m^2) and doxorubicin i.v. (≥40 mg/m^2) or cyclophosphamide i.v. (500–1500 mg/m^2) and epirubicin i.v. (≥60 mg/m^2).

The use of rescue medication for treatment of nausea/vomiting was considered treatment failure. Metoclopramide tablets were provided; however, the investigator was authorized to use an alternative rescue (excluding 5-HT_3 or NK_1 RAs as well as PALO) at his/her discretion.

After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1. There was no prespecified limit of the number of repeat consecutive cycles. Findings from this multiple-cycle extension will be the subject of a separate publication.

assessments

From the start of chemotherapy infusion on day 1 through the morning of day 6 (0–120 h), each patient completed a diary, capturing information pertaining to the timing and duration of each emetic episode, severity of nausea and rescue medications taken. An emetic episode was defined as one or more continuous vomits or retches. Severity of nausea was evaluated on a daily basis (for the preceding 24 h) using a 100-mm horizontal visual analog scale (VAS). The left end of the scale (0 mm) was labeled as 'no nausea,' and the right end of the scale (100 mm) was labeled as 'nausea as bad as it could be'.

The Functional Living Index-Emesis (FLIE) questionnaire [consisting of nine nausea-specific (nausea domain) and nine vomiting-specific (vomiting domain) items] was used to assess the impact of CINV on patients' daily lives. Patients completed this questionnaire on day 6, assessing the impact of CINV on their daily functioning during the 120 h after chemotherapy administration. The proportion of patients with scores reflecting 'no impact on daily life' (NIDL) (i.e. nausea/vomiting domain score >54, total FLIE score >108) was evaluated.

The primary efficacy end point was complete response (CR: no emesis, no rescue medication) during the delayed phase after the start of chemotherapy of cycle 1. Key secondary efficacy end points included CR during the acute (0–24 h) and overall (0–120 h) phases; other secondary efficacy end points were complete protection (CR + no significant nausea), no emesis and no significant nausea (VAS score of <25 mm) during the acute, delayed and overall phases while other efficacy end points included FLIE scores during the overall phase. Safety was assessed by adverse events, clinical laboratory evaluations, physical examinations, vital signs and electrocardiograms (ECGs).

statistical analysis

The primary aim of this study was to demonstrate the superiority of NEPA over PALO based on the proportion of patients with a CR during the delayed phase of cycle 1. The primary efficacy analysis was carried out using a two-sided Cochran–Maentel–Haenszel (CMH) test including treatment, age class and region as strata. NEPA was to be declared superior to PALO if the two-sided *P*-value was ≤0.05 and in favor of NEPA. A hierarchical procedure was applied to control type I error inflation (i.e. CR during the delayed, acute and overall phases were tested sequentially only if the previous test succeeded). No emesis, complete protection, no signification nausea and FLIE were also analyzed utilizing the CMH test.

The sample size was estimated to be 1460 patients (730 per group). The assumption was a responder rate of 60% during the delayed phase for NEPA and 51% for PALO. For a two-sided test of difference, using $\alpha = 0.050$, a sample size of 661 assessable patients per group was needed to ensure 90% power to detect the 9% difference. This number was increased to 730 per group to ensure an adequate number of assessable patients.

The number of patients who experienced treatment-emergent adverse events or ECG abnormalities was listed and summarized by treatment group.

The full analysis set population (efficacy analyses) was defined as all patients who were randomized and received protocol-required MEC and study treatment. The safety analysis population consisted of all patients who received study treatment and had at least one safety assessment after the treatment administration.

results

A total of 1455 patients were randomized into the study. Five patients did not receive the protocol-required MEC and study drug and one additional patient received study drug but not MEC; therefore, 1450 and 1449 patients represented the safety and full analysis set populations, respectively (Figure 1).

Baseline characteristics were similar between treatment groups (Table 1).

efficacy

For the primary efficacy comparison, NEPA was superior to PALO during the delayed phase with a CR rate of 76.9% versus 69.5% ($P = 0.001$) (Figure 2). CR rates were also significantly higher for NEPA compared with PALO during the acute and overall phases.

Similarly, NEPA was consistently more effective than PALO during the delayed and overall phases for secondary efficacy end points of no emesis, no significant nausea and complete protection as well as during the acute phase for no emesis (Table 2). For the FLIE assessment, a greater proportion of NEPA-treated patients reported NIDL for the nausea, vomiting and combined domains compared with PALO (Figure 3).

safety

The overall incidence, type, frequency and intensity of treatment-emergent adverse events were comparable between the two treatment groups. Among the patients reporting adverse events, the majority (85%) reported adverse events of mild/moderate intensity. Of the 94 NEPA-treated patients who experienced a severe adverse event, only 5 (0.7%) had a severe treatment-related adverse event. The most common treatment-related adverse events were headache and constipation (Table 3).

There were no treatment-related adverse events leading to discontinuation, and there were very few (0.7%) severe and no serious treatment-related adverse events or deaths for NEPA-treated patients. Changes from baseline in 12-lead ECGs were similar between treatment groups at each time point.

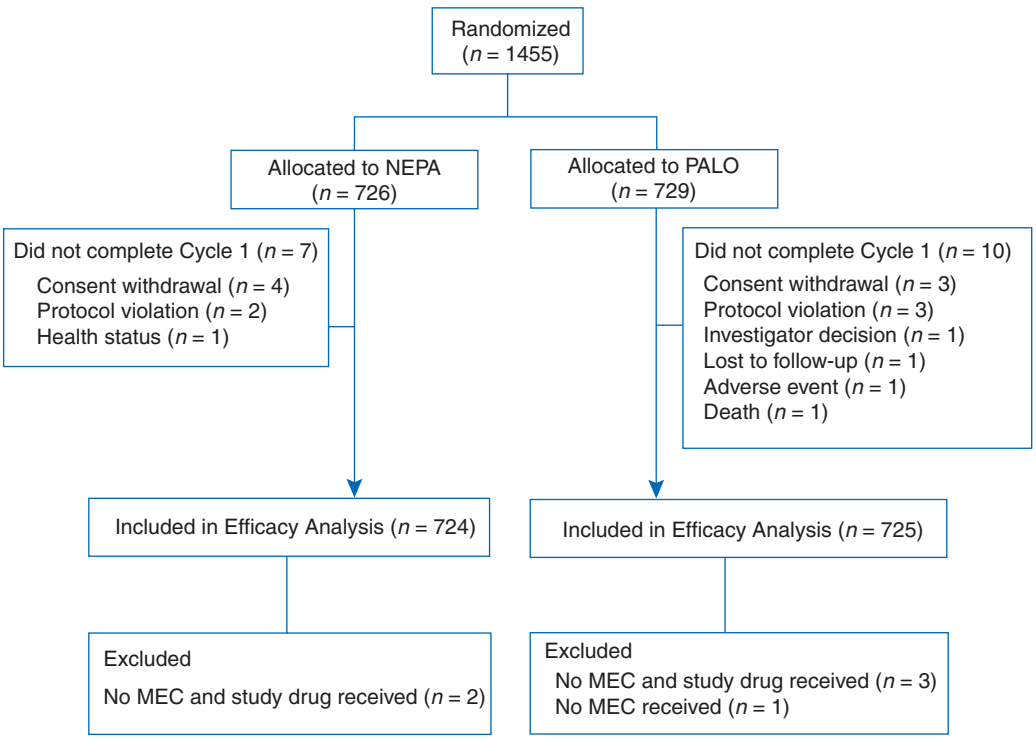

Figure 1. Consort diagram of the disposition of patients.

Table 1. Patient baseline and disease characteristics

Characteristic	NEPA ($N = 724$)	PALO ($N = 725$)
Gender		
Female	98.2%	97.9%
Male	1.8%	2.1%
Age (years)		
Median	54.0	54.0
<55	51.2%	51.3%
≥55	48.8%	48.7%
Ethnic group		
White	79.1%	80.0%
Asian	14.0%	14.2%
Hispanic	6.4%	5.0%
Black	0.1%	0.3%
Other	0.4%	0.6%
Cancer type		
Breast	97.7%	97.2%
Other	2.3%	2.8%
ECOG Performance Status		
0	69.6%	69.1%
1	29.6%	30.8%
2	0.8%	0.1%
Chemotherapy		
Cyclophosphamide	99.9%	100%
Doxorubicin	68.0%	63.7%
Epirubicin	32.0%	36.3%

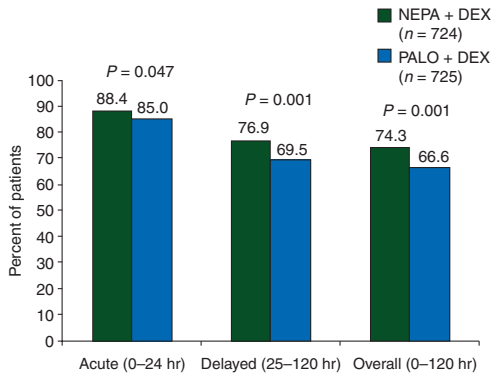

Figure 2. Complete response (no emesis, no rescue medication).

Table 2. Secondary efficacy end points

	NEPA ($N = 724$)	PALO ($N = 725$)	P-value
No emesis			
Acute	90.9%	87.3%	0.025
Delayed	81.8%	75.6%	0.004
Overall	79.8%	72.1%	<0.001
No significant nausea			
Acute	87.3%	87.9%	0.747
Delayed	76.9%	71.3%	0.014
Overall	74.6%	69.1%	0.020
Complete protection			
Acute	82.3%	81.1%	0.528
Delayed	67.3%	60.3%	0.005
Overall	63.8%	57.9%	0.020

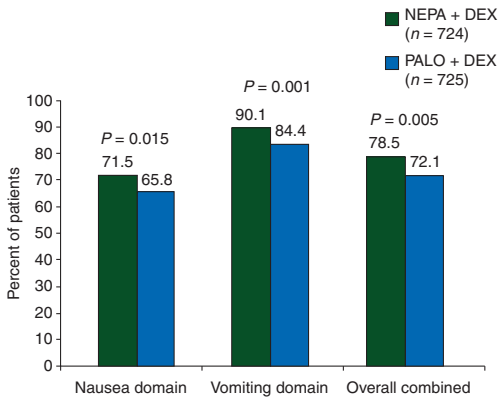

Figure 3. Proportion of patients with no impact on daily living (NIDL) based on Functional Living Index-Emesis (FLIE): Overall 0–120 h.

Table 3. Overall summary of adverse events

N (%) of patients with	NEPA ($N = 725$)	PALO ($N = 725$)	Overall ($N = 1450$)
At least one adverse event (AE)	551 (76%)	507 (69.9%)	1058 (73%)
Serious AE	13 (1.8%)	12 (1.7%)	25 (1.7%)
Serious treatment-related[a] AE	0	0	0
Any treatment-related[a] AE	59 (8.1%)	52 (7.2%)	111 (7.7%)
Most common treatment-related[a] AE			
Headache	24 (3.3%)	22 (3.0%)	46 (3.2%)
Constipation	15 (2.1%)	15 (2.1%)	30 (2.1%)
Any treatment-related[a] AE leading to discontinuation	0	2 (0.3%)	2 (0.1%)

[a]Those considered by the investigator to be possibly, probably or definitely related to study drug.

discussion

NEPA, a novel combination of the new NK_1 RA, NETU and best-in-class 5-HT_3 RA, PALO, has been designed to overcome potential barriers hindering antiemetic guideline adherence by conveniently packaging guideline-recommended agents in a single oral fixed-dose. A single day 1 dose of NEPA along with DEX only on day 1 seems suitable for prevention of CINV through the 5 days after chemotherapy.

This large, phase III, registration study was designed to demonstrate the superiority of NEPA over PALO in chemotherapy-naïve patients receiving AC-based MEC. NEPA significantly improved CR rates compared with PALO during all phases after chemotherapy, with the incremental benefit being greatest during the delayed and overall phases. Regardless of the efficacy endpoint, NEPA was consistently superior to PALO during the 5-day period following chemotherapy. In particular, NEPA resulted in significantly greater no emesis rates during all phases and no

significant nausea and complete protection rates during the delayed and overall phases. The consistent superiority of NEPA over PALO across all end points during the delayed phase is particularly opportune, in that patients are protected during a period which has remained a challenge in most clinical settings.

Control of delayed nausea does not reach the same level of benefit as that of emesis and remains a clinical unmet need [2, 3]. Although it was a secondary end point, it is encouraging that NEPA demonstrated a delayed nausea benefit which was also seen in the phase II trial in patients receiving cisplatin-based HEC [8], providing additional support of its efficacy. The utilization of the FLIE instrument confirmed that by improving control of CINV, NEPA significantly reduced the impact of CINV on patients' functioning. This was seen consistently in all domains of the FLIE assessment.

As DEX may be associated with a range of side-effects, there is particular interest in minimizing its dose/frequency, especially in patients who experience DEX-related side-effects. Consistent with the recommendation by MASCC/ESMO in the AC setting, DEX was given on day 1 only. Therefore, the complete antiemetic regimen in this study was administered just before chemotherapy. In a study in a similar population of chemotherapy-naïve breast cancer patients, a single dose of PALO plus DEX on day 1 showed similar CR rates as PALO (day 1) plus DEX (day 1–3) [11] (the recommended antiemetic regimen in AC at the time of the study). The authors speculated that the unique pharmacology of PALO may have explained the extended protection in the delayed phase, without the need for multiple day DEX. The response rates seen in the current trial were generally higher than those seen in prior NK_1 RA trials [4] where DEX was administered on day 1 only concomitantly with an older generation 5-HT_3 RA. The present result validates the guideline recommendations of a single day of DEX in patients receiving AC and provides encouraging evidence that DEX beyond day 1 is not necessary when using NEPA in patients at higher risk for CINV.

While AC are still classified by some guideline groups as chemotherapy that present a moderate emetic risk, although separately from other MEC [3], other committees developing antiemetic guidelines have included AC in the high-risk category [12]. This is a simplification related to the fact that the same NK_1RA/5-HT_3RA/DEX treatment is recommended for both HEC and AC, while, in other MEC, the use of NK_1RAs is an option which varies according to the perceived risk. There is already limited data on how NEPA performs in a non-AC MEC population [13].

As already demonstrated in the large phase II trial, NEPA was very well tolerated with a comparable adverse event profile to PALO. There was a very low incidence of treatment-related adverse events, none of which led to discontinuation and no serious treatment-related adverse events or deaths for NEPA-treated patients. There were no cardiac safety concerns for either NEPA or PALO based on cardiac AEs/ECGs.

In conclusion, NEPA resulted in superior prevention of CINV than PALO in patients receiving MEC. As a combination agent targeting dual antiemetic pathways, a single dose of NEPA plus DEX offers convenient guideline-based prophylaxis. This provides an opportunity to overcome barriers interfering with guideline adherence and in doing so offers promise for improving control of CINV for patients.

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disclosure

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A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy

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Background: Safe, effective and convenient antiemetic regimens that preserve benefit over repeated cycles are needed for optimal supportive care during cancer treatment. NEPA, an oral fixed-dose combination of netupitant, a highly selective NK_1 receptor antagonist (RA), and palonosetron (PALO), a distinct 5-HT_3 RA, was shown to be superior to PALO in preventing chemotherapy-induced nausea and vomiting after a single cycle of highly (HEC) or moderately (MEC) emetogenic chemotherapy in recent trials. This study was designed primarily to assess the safety but also to evaluate the efficacy of NEPA over multiple cycles of HEC and MEC.

Patients and methods: This multinational, double-blind, randomized phase III study (NCT01376297) in 413 chemotherapy-naïve patients evaluated a single oral dose of NEPA (NETU 300 mg + PALO 0.50 mg) given on day 1 with oral dexamethasone (DEX). An oral 3-day aprepitant (APR) regimen + PALO + DEX was included as a control (3:1 NEPA: APR randomization). In HEC, DEX was administered on days 1–4 and in MEC on day 1. Safety was assessed primarily by adverse events (AEs), including cardiac AEs; efficacy by complete response (CR: no emesis, no rescue).

Results: Patients completed 1961 total chemotherapy cycles (76% MEC, 24% HEC) with 75% completing ≥4 cycles. The incidence/type of AEs was comparable for both groups. Most frequent NEPA-related AEs included constipation (3.6%) and headache (1.0%); there was no indication of increasing AEs over multiple cycles. The majority of AEs were mild/moderate and there were no cardiac safety concerns based on AEs and electrocardiograms. The overall (0–120 h) CR rates in cycle 1 were 81% and 76% for NEPA and APR + PALO, respectively, and antiemetic efficacy was maintained over repeated cycles.

Conclusions: NEPA, a convenient single oral dose antiemetic targeting dual pathways, was safe, well tolerated and highly effective over multiple cycles of HEC/MEC.

Key words: neurokinin-1 receptor antagonist, NEPA, netupitant, palonosetron, CINV, multiple chemotherapy cycles

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