CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Netupitant/Palonosetron 300 mg/0.5 mg (Akynzeo)

(Purdue Pharma)

Indication: In combination with dexamethasone, once-per-cycle treatment for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy, or with moderately emetogenic cancer chemotherapy that is uncontrolled by a 5-hydroxytryptamine-3 receptor antagonist alone.

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

5-HT$_3$RA	5-HT$_3$ receptor antagonist
AC	anthracycline/cyclophosphamide
AE	adverse event
ASCO	American Society of Clinical Oncology
BCCA	BC Cancer Agency
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
CINV	chemotherapy-induced nausea and vomiting
CCO	Cancer Care Ontario
CR	complete response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
FLIE	Functional Living Index–Emesis
HEC	highly emetogenic chemotherapy
IV	intravenous
MASCC/ESMO	Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology
MEC	moderately emetogenic chemotherapy
NEPA	netupitant/palonosetron
NK$_1$RA	neurokinin-1 receptor antagonist
OR	odds ratio
RCT	randomized controlled trial
SAE	serious adverse event
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

Drug	Netupitant/palonosetron (Akynzeo)
Indication	Netupitant/palonosetron, in combination with dexamethasone, is indicated for once-per-cycle treatment in adult patients for: • Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy • Prevention of acute nausea and vomiting associated with moderately emetogenic cancer therapy that is uncontrolled by a 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist (RA) alone.
Reimbursement Request	As per indication
Dosage Form	300 mg netupitant/ 0.5 mg palonosetron capsules
NOC Date	28-09-2017
Manufacturer	Purdue Pharma

Executive Summary

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common and distressing adverse effect of cancer treatment with chemotherapy drugs, which can occur in the acute phase (0 to 24 hours) or delayed phase (25 to 120 hours). Preventing CINV is important in patients receiving chemotherapy and is achieved using antiemetics. The antiemetic regimen used depends on the emetogenicity of the chemotherapy regimen. In patients receiving highly emetogenic chemotherapy (HEC), a neurokinin-1 receptor antagonist (NK1RA, e.g., aprepitant) and a 5-hydroxytryptamine-3 receptor antagonist (5-HT3RA, e.g., ondansetron, granisetron), in combination with dexamethasone, are recommended. In those receiving moderately emetogenic chemotherapy (MEC), a 5-HT3RA + dexamethasone is recommended.

Netupitant/palonosetron (NEPA; Akynzeo), an NK_1RA and 5-HT_3RA combination, is indicated in combination with dexamethasone as once-per-cycle treatment for prevention of acute and delayed nausea and vomiting associated with HEC or MEC that is uncontrolled by a 5-HT_3RA alone.

The objective of the review was to identify, summarize, and critically assess the beneficial and harmful effects of NEPA in preventing CINV for patients receiving MEC or HEC.

Results and Interpretation

Included Studies

Four eligible studies were identified. Patients were chemotherapy-naive in all studies. NETU 8-18 (N = 1,455) was a phase III, double-blind randomized controlled trial (RCT) that compared the efficacy and safety of NEPA with palonosetron alone in patients receiving HEC with anthracycline/cyclophosphamide. This trial was conducted in the US, Latin America, South America, Europe, and India. In NETU 8-18, 97% of patients had breast cancer. The primary outcome was complete response (CR, defined as no emesis and no rescue medication) in the delayed phase. NETU 7-07 (N = 694) was a phase II, double-

blind, dose-finding RCT which also assessed the efficacy and safety of NEPA to palonosetron alone in patients receiving HEC. This study was conducted in Russia and Ukraine, and the most common cancer diagnoses in this trial were lung (27%), head and neck (21%), and ovarian (16%) cancer. The primary outcome was CR in the overall phase (0 to 120 hours). NETU 10-29 (N = 413) was a phase IV, double-blind RCT designed to assess the safety of NEPA compared with aprepitant/palonosetron (an NK_1RA and 5-HT_3RA combination) in patients receiving MEC or HEC. This trial was conducted in the US, Europe, and India. The most common cancer diagnosis was lung cancer (37.4% of patients). This study also assessed CR in the acute, delayed, and overall phases. Finally, NETU 12-07 (N = 834) was a noninferiority double-blind RCT designed to assess whether NEPA was noninferior to aprepitant/granisetron (an NK_1RA and 5-HT_3RA combination) in patients receiving HEC. The study was conducted in China, Taiwan, Thailand, and South Korea. The most common cancer diagnosis was lung cancer (58% of patients). The primary outcome in NETU 12-07 was CR in the overall phase. In all studies, efficacy outcomes (e.g., CR) were evaluated from patient diaries. The diaries were reviewed by the investigator at each study visit (day 1, 2, and 6) and collected on day 6. The choice of rescue medication was based on the investigator's judgment (the most commonly used drug was metoclopramide).

There were concerns surrounding the relevance of comparators. Both NETU 7-07 and NETU 8-18 compared NEPA with palonosetron alone in patients receiving HEC. However, contemporary treatment guidelines recommend that patients on HEC receive therapy with NK_1RAs and 5-HT_3RAs (e.g., in Canada, aprepitant + ondansetron with dexamethasone). Thus, palonosetron alone was likely not a relevant comparator in these trials in the current context. There were limited data available for patients receiving MEC, as only one trial (NETU 10-29) included patients receiving MEC. The validity of how the noninferiority margin in NETU 12-07 was derived is associated with considerable uncertainty. There were also concerns surrounding use of a diary to capture outcome data, as this method may be prone to recall bias and its reliability is unclear.

Efficacy

Compared with palonosetron alone, NEPA treatment led to a higher proportion of patients achieving CR in the delayed and overall phases. In NETU 7-07, NEPA was statistically superior to palonosetron alone for the proportion of patients achieving CR in the acute phase (absolute difference 8.8%; 95% confidence interval [CI], 3.3% to 14.3%); however, there was no difference in NETU 8-18 (absolute difference 3.4%; 95% CI, –0.1% to 6.9%). Compared with other NK_1RA and 5-HT_3RA combinations, there was no difference in the proportion of patients achieving CR with NEPA in the delayed, acute, or overall phases. In NETU 12-07, NEPA was deemed noninferior to aprepitant/granisetron, as the lower bound of the 95% confidence interval of the between-group difference in the proportion achieving CR in the overall phase was above the –10% noninferiority margin. In the multiple-cycle phase of NETU 10-29, there was no difference in CR for the delayed or acute phases between NEPA and aprepitant/palonosetron in any cycle. In NETU 8-18, NEPA was statistically superior to palonosetron for CR in both the acute and delayed phases in cycles 2, 3, and 4, but not in cycle 5 or 6.

The proportion of patients with CINV having "no impact on daily life" (based on overall Functional Living Index–Emesis [FLIE] scores in the overall phase) was statistically significantly greater in the NEPA arm compared with the palonosetron arm (absolute difference 6.3; 95% CI, 1.9 to 10.7) in NETU 8-18; however, there was no significant

difference in NETU 12-07 for NEPA compared with aprepitant/granisetron. The FLIE questionnaire is not a well-validated measure of patient function, and the clinical significance of these findings is unclear. In NETU 7-07 there was a small, significant difference in global satisfaction between NEPA and palonosetron at 24 hours, as measured by a visual analogue scale out of 100 mm (mean difference 4.26 mm; 95% CI, 0.65 mm to 7.87 mm) and 120 hours (mean difference 4.77 mm; 95% CI, 0.79 mm to 8.75 mm).

The results of the manufacturer-provided indirect treatment comparison (Appendix 6) reported that NEPA provided efficacy similar to that of aprepitant-containing triple regimens (an NK_1RA + 5-HT_3RA with dexamethasone) for MEC and HEC. However, considerable limitations associated with the source data and sparsely populated networks mean the analyses were not robust and were associated with a high degree of uncertainty.

In the multiple-cycle extension phase of NETU 10-29 (Appendix 4), there was no difference in CR for the delayed or acute phases between NEPA and aprepitant/palonosetron in any cycle. In NETU 8-18 (Appendix 4), the proportion of patients achieving CR in the acute or delayed phases appeared to continue to be greater for NEPA compared with palonosetron over multiple cycles of chemotherapy. Neither study was specifically designed to evaluate the comparative efficacy of NEPA over multiple cycles.

Harms

The frequency of harms was generally similar between NEPA and its comparators across trials. While adverse events were very common, patients were also receiving chemotherapy, which commonly causes adverse events. There were no concerns identified regarding the cardiac safety of NEPA; however, the duration of the studies was short. The manufacturer-provided indirect comparison did not assess the comparative safety of NEPA versus its comparator treatments.

Conclusions

A manufacturer-provided noninferiority study and indirect comparison suggest that NEPA has efficacy similar to that of existing NK_1RA/5-HT_3RA combinations in patients receiving MEC and HEC in the acute, delayed, and overall phases. However, there was uncertainty regarding the validity of the noninferiority margin used in the noninferiority trial, and likewise with the results of the indirect comparisons because of limitations associated with the source data and sparsely populated networks. NEPA appears to have a safety profile with adverse event frequencies similar to those of existing NK_1RA/5-5-HT_3RA combination treatments. While it has been suggested that NEPA offers a benefit in terms of convenience and adherence, these were not evaluated in any of the included studies. Thus, based on the evidence reviewed in this report, NEPA does not appear to provide a clear added clinical value over existing NK_1RA/5-HT_3RA in terms of efficacy or safety.

Table 1: Summary of Results in First Cycle

Outcome	NETU 8-18		NETU 7-07		NETU 10-29		NETU 12-07	
	NEPA (N = 724)	PALO (N = 725)	NEPA (N = 135)	PALO (N = 136)	NEPA (N = 309)	APR/PALO (N = 103)	NEPA (N = 412)	APR/GRAN (N = 416)
CR, delayed phase[a]								
n (%)	557 (76.9)	504 (69.5)	122 (90.4)	109 (80.1)	257 (83.2)	80 (77.7)	321 (77.9)	309 (74.3)
Absolute difference (95% CI)	7.4 (2.9 to 11.9)		10.2 (1.9 to 18.6)		5.5 (–2.8 to 15.2)		3.6 (–2.2 to 9.4)	
NNT	14		10		–		–	
CR, acute phase[b]								
n (%)	640 (88.4)	616 (85.0)	133 (98.5)	122 (89.7)	287 (92.9)	97 (94.2)	348 (84.5)	362 (87.0)
Absolute difference (95% CI)	3.4 (–0.1 to 6.9)		8.8 (3.3 to 14.3)		–1.3 (–5.9 to 5.4)		–2.5 (–7.3 to 2.3)	
NNT	–		12		–		–	
Withdrawals								
n (%)	7 (1.0)	10 (1.4)	7 (4.9)	1 (0.7)	6 (1.9)	2 (1.9)	9 (2.2)	5 (1.2)
SAEs								
n (%)	13 (1.8)	12 (1.7)	0	3 (2.2)	18 (5.8)	4 (3.8)	20 (4.8)	19 (4.6)
WDAEs								
n (%)	7 (1.0)	4 (0.6)	0	0	9 (0.6)	0	1 (0.2)	2 (0.5)
Notable harms(s): arrhythmia								
n (%)	1 (0.1)	1 (0.1)	0	0	0	0	0	0

APR = aprepitant; CI = confidence interval; CR = complete response; GRAN = granisetron; NEPA = netupitant/palonosetron; NNT = number needed to treat; PALO = palonosetron; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Delayed phase = occurring more 24 to 120 hours after chemotherapy.

[b] Acute phase = occurring during the first 24 hours after chemotherapy.

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Introduction

Disease Prevalence and Incidence

Chemotherapy-induced nausea and vomiting (CINV) is a common and distressing adverse effect of cancer treatment with chemotherapy drugs. Three types of CINV have been defined: acute emesis (occurring during the first 24 hours after chemotherapy), delayed emesis (occurring more than 24 hours after chemotherapy), and anticipatory emesis (a response in patients previously experiencing CINV).[5] CINV can have a negative impact on patients' quality of life and daily functioning.[6]

Some chemotherapy regimens are more likely to cause emesis than others. Therefore, chemotherapy regimens are grouped into four categories based on their expected risk of causing emesis: highly emetogenic (HEC; risk of emesis > 90%), moderate (MEC; risk 30% to 90%), low (10% to 30%), and minimal (< 10%).[7] While management of CINV has improved over the last 30 years, it continues to be a common adverse effect of chemotherapy.[7] For example, a study of chemotherapy-naive patients receiving MEC in the US found that, despite recommended treatment, vomiting occurred in 21% of patients within five days of receiving chemotherapy, and nausea occurred in 42%.[8]

Standards of Therapy

The primary goal of therapy is to prevent CINV. Thus, prophylactic treatment with antiemetics is the recommended approach. Chemotherapy drugs induce nausea and vomiting by activating various neurotransmitter receptors in the brain. Two of the most important receptors activated are the 5-hydroxytryptamine-3 (5-HT_3) receptor and neurokinin-1 (NK_1) receptor.[5] Thus, contemporary antiemetics — for example 5-HT_3 receptor antagonists (RAs) (e.g., ondansetron, granisetron) and NK_1RAs (e.g., aprepitant) — are targeted at these pathways.[5] The glucocorticoid dexamethasone has been widely used for many years and also forms part of the standard therapy in preventing CINV.[5]

Antiemetics can be used on their own or in combination. The treatment used depends on the emetogenicity of the chemotherapy regimen a patient is receiving (as outlined in the previous section). International guidelines have similar treatment recommendations. For example, in HEC, the 2016 Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO), American Society of Clinical Oncology (ASCO), Cancer Care Ontario (CCO), and BC Cancer Agency (BCCA) guidelines recommend a regimen of a 5-HT_3RA, an NK_1RA, and dexamethasone given before chemotherapy (day 1) for prevention of CINV.[7,9-11] Dexamethasone is also recommended on days 2 to 4, and, if aprepitant is used as an NK_1RA, it is recommended on days 2 and 3 post-chemotherapy. The ASCO and MASCC/ESMO guidelines also recommend considering low-dose olanzapine, although this is not included in the Canadian guidelines.[7,10] For MEC, guidelines recommend a combination of 5-HT_3RA and dexamethasone before chemotherapy (day 1). The ASCO and BCCA guidelines suggest that patients receiving MEC also receive dexamethasone on days 2 to 3, while the CCO guidelines recommend dexamethasone beyond day 1 in HEC only.[9-11]

There are several options available among NK_1RAs and 5-HT_3RAs. Guidelines suggest that efficacy and safety are similar among drugs and do not express a preference for any particular drug over another in HEC.[7,9-11] In MEC, the ASCO guidelines suggest that palonosetron is the preferred 5-HT_3RA, while the MASCC/ESMO, BCCA, and CCO guidelines do not prefer a specific drug.[7,9-11] The clinical expert consulted by CADTH suggested that aprepitant is a commonly used NK_1RA, while granisetron and ondansetron are commonly used 5-HT_3RAs. Aprepitant is given orally, and an intravenous (IV) formulation also exists (fosaprepitant); similarly, 5-HT_3RAs can be administered orally or intravenously. The MASCC/ESMO, ASCO, and CCO guidelines list both oral and IV options for 5-HT_3RAs in treatment recommendations but do not comment on preference for one route over another.[7,10,11] The BCCA guidelines list oral doses only in their treatment recommendations and state that oral and IV administration are considered equally effective.[9] These guidelines suggest that IV administration of antiemetics can be considered if a patient is unable to swallow.[9] The NK_1RAs and 5-HT_3RAs available primarily differ in terms of half-life (Table 2).

Patients who experience CINV despite antiemetic therapy may require additional medication, hydration, and hospitalization.[12]

Drug

The product under review, netupitant/palonosetron (NEPA), is a combination of an NK_1RA (netupitant) and a 5-HT_3RA (palonosetron) in one capsule. It is given orally and is indicated for prevention of acute and delayed CINV. Further details are provided in Table 2. Palonosetron is available in Canada as a separate single product marketed as Aloxi (oral [0.5 mg capsule] and IV [0.25 mg/5 mL] routes of administration). Palonosetron is approved by Health Canada for use in adults for the prevention of acute (oral and IV) and delayed (IV only) nausea and vomiting associated with MEC, and for the prevention of acute nausea and vomiting associated with HEC, including high-dose cisplatin (IV only). Both formulations of palonosetron have been reviewed by CADTH Common Drug Review (CDR), and the CADTH Canadian Drug Expert Committee (CDEC) recommended that they not be reimbursed (at the submitted price for the IV formulation). Netupitant is only available in combination with palonosetron.

Table 2: Key Characteristics of Netupitant/Palonosetron, 5-HT_3RAs, and NK_1RAs

	Netupitant/Palonosetron	NK_1RAs (Aprepitant, Fosaprepitant)	5-HT_3RAs (Palonosetron, Ondansetron, Granisetron)
Mechanism of Action	Netupitant is an antagonist of the NK_1 receptor, and palonosetron is an antagonist of the 5-HT_3 receptor (activation of these receptors causes CINV)	Antagonists of the NK_1 receptor	Antagonists of the 5-HT_3 receptor
Indication[a]	In combination with dexamethasone, once-per-cycle treatment in adults for prevention of acute and delayed nausea and vomiting associated with HEC, or with MEC that is uncontrolled by a 5-HT_3 receptor antagonist alone	Aprepitant: in combination with a 5-HT_3RA and dexamethasone for prevention of acute and delayed nausea and vomiting due to HEC and prevention of nausea and vomiting in women due to MEC Fosaprepitant: in combination with a 5-HT_3RA and dexamethasone for prevention of acute and delayed nausea and vomiting due to HEC and MEC	Ondansetron and granisetron: in adults for the prevention of nausea and vomiting associated with emetogenic chemotherapy (oral and IV; age ≥ 4 years for ondansetron) and radiation (oral only) Ondansetron: in adults for the prevention and treatment of post-operative nausea and vomiting (oral and IV) Palonosetron: in adults for the prevention of acute (oral and IV) and delayed (IV only) nausea and vomiting associated with MEC; the prevention of acute nausea and vomiting associated with HEC (IV only)
Route of Administration	Oral (combination capsule)	Aprepitant: oral Fosaprepitant: IV	Ondansetron: oral or IV Granisetron: oral or IV Palonosetron: oral or IV
Recommended Dose	Netupitant/palonosetron 300 mg/0.5 mg, one capsule per chemotherapy cycle, administered 1 hour before start of cycle	Aprepitant: 125 mg pre-chemotherapy on day 1, then 80 mg daily on days 2 and 3 Fosaprepitant: 150 mg pre-chemotherapy on day 1	Ondansetron: 8 mg oral twice daily on day 1 of chemotherapy or 8 mg IV on day 1 pre-chemotherapy Granisetron: 2 mg oral or 1 mg IV pre-chemotherapy on day 1 Palonosetron: a single 0.5 mg oral dose or a single 0.25 mg IV dose administered pre-chemotherapy on day 1
Serious Side Effects / Safety Issues	ECG changes (QTc prolongation and potential increased risk of related cardiac events), serotonin syndrome, or neuroleptic malignant syndrome–like events Drug interactions with medications metabolized through CYP3A4	Drug interactions with medications metabolized through CYP3A4	ECG changes (QTc prolongation and potential increased risk of related cardiac events); serotonin syndrome or neuroleptic malignant syndrome–like events Contraindicated when used concomitantly with apomorphine (ondansetron, granisetron)
Other	Palonosetron half-life = 40 hours; netupitant half-life = 90 hours	Aprepitant and fosaprepitant half-life = 9 to 13 hours	Ondansetron half-life: 3 to 6 hours (prolonged in hepatic impairment) Granisetron: 5 to 9 hours (IV), 6 hours (oral)

5-HT_3 = 5-hydroxytryptamine-3; CINV = chemotherapy-induced nausea and vomiting; CYP = cytochrome P450; ECG = electrocardiogram; IV = intravenous; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NK_1 = neurokinin-1; RA = receptor antagonist.

[a] Health Canada indication.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of netupitant/palonosetron 300 mg/0.5 mg once per cycle, in combination with dexamethasone, for the prevention of acute and delayed nausea and vomiting associated with HEC, or with MEC that is uncontrolled by a 5-HT_3 receptor antagonist alone.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients receiving HEC, or MEC that is uncontrolled by a 5-HT_3RA alone **Subgroups** HEC (with attention to cisplatin-based therapy) MEC (with attention to anthracycline-based therapy without cyclophosphamide) History of receiving chemotherapy
Intervention	Netupitant/palonosetron 300 mg/0.5 mg in combination with dexamethasone
Comparators	Other NK_1RA and 5-HT_3RA combinations in combination with dexamethasone (NK_1RAs: aprepitant, fosaprepitant and 5-HT_3RAs: ondansetron, granisetron) 5-HT_3RA alone in combination with dexamethasone
Outcomes	**Key efficacy outcomes:** Complete response (no emetic episode and no rescue medication) during the first 24 hours after chemotherapy (acute phase) Complete response 24 hours to 120 hours post-chemotherapy (delayed phase) **Other efficacy outcomes:** Complete response during overall phase (0 to 120 hours) Total control (no emesis, no rescue medication and no nausea [nausea up to a maximum of 5 mm on a VAS out of 100 mm]) during acute, delayed, and overall phases Complete protection (no emesis, no rescue medication, no significant nausea [nausea up to a maximum of 25 mm on a VAS out of 100 mm]) during acute, delayed, and overall phases Patient-reported outcomes (patient satisfaction, function, and QoL) **Harms outcomes:** AEs, SAEs, WDAEs, notable harms: TdP, arrhythmia
Study Design	Published and unpublished phase III or higher RCTs

5-HT_3 = 5-hydroxytryptamine-3; AE = adverse event; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NK_1 = neurokinin-1; QoL = quality of life; RA = receptor antagonist; RCT = randomized controlled trial; SAE = serious adverse events; TdP = torsades de pointes; VAS = visual analogue scale; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were netupitant and palonosetron.

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 15, 2018. Regular alerts were established to update the search until the meeting of CDEC on May 16, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free).

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the eligibility criteria. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Results

Findings from the Literature

A total of 14 reports from four unique studies were identified from the literature for inclusion in the systematic review (Figure 1).

The included studies are summarized in Table 4 and described in the Included Studies section. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

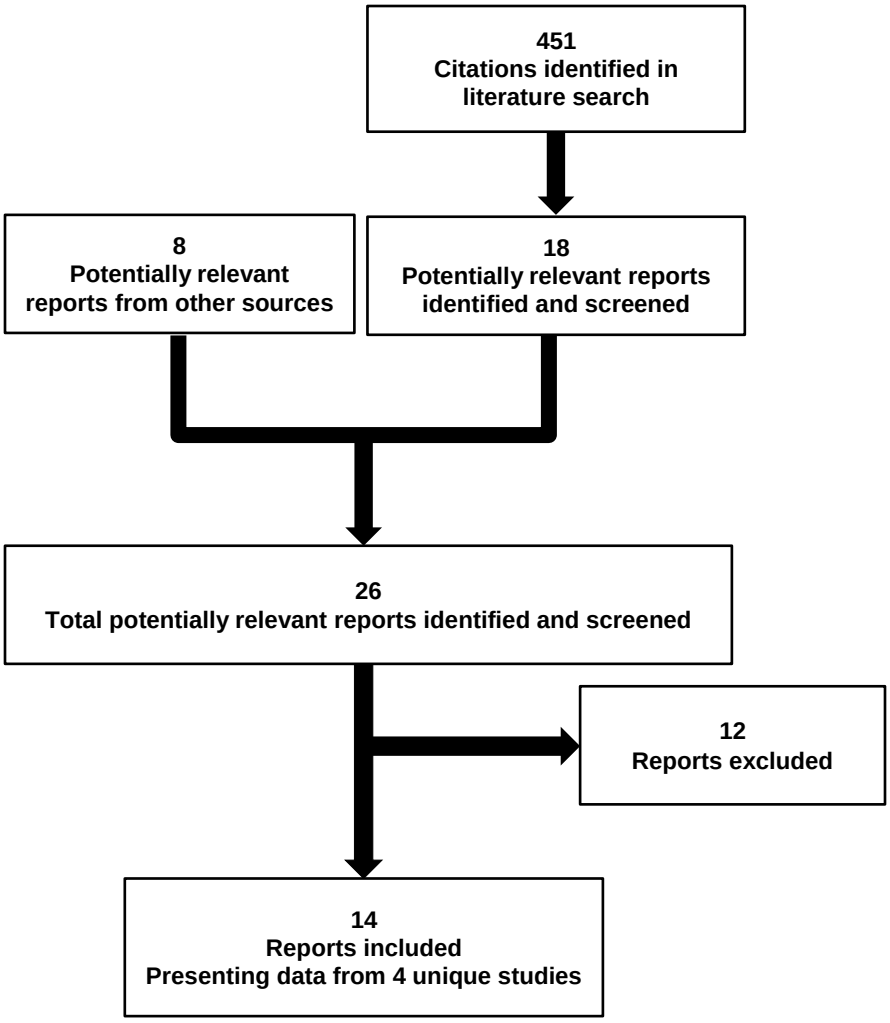


Table 4: Details of Included Studies

		NETU 8-18	NETU 10-29	NETU 12-07	NETU 7-07
Designs and Populations	**Study Design**	DB RCT	DB RCT	Noninferiority DB RCT	DB RCT
	Locations	US, Latin America, South America, Europe, India	US, Europe, India	Asia (China, Taiwan, Thailand, South Korea)	Russia, Ukraine
	Randomized (N)	1,455	413	834	694
	Inclusion Criteria	≥ 18 years, chemotherapy-naive, scheduled to receive AC regimen[a] for treatment of solid malignant tumour, ECOG status 0 to 2 Extension phase: participation considered appropriate by investigator, scheduled to receive same chemotherapy regimen as in cycle 1	≥ 18 years, chemotherapy-naive, malignant tumour, scheduled to receive repeated courses of HEC or MEC, ECOG status 0 to 2	≥ 18 years, chemotherapy-naive, solid tumour malignancy, scheduled to receive cisplatin-based chemotherapy (HEC), ECOG status 0 to 2	≥ 18 years, chemotherapy-naive, solid tumour malignancy, scheduled to receive cisplatin (≥ 50 mg/m^2 HEC), Karnofsky score ≥ 70%
	Exclusion Criteria	Pregnant or lactating; scheduled to receive HEC; radiation to abdomen or pelvis within 1 week before day 1 or between day 1 and 5; bone marrow or stem-cell transplant; vomiting, retching or mild nausea within 24 hours before day 1; previously received NK_1RA; systemic corticosteroid or any medication with potential antiemetic activity within 72 hours of day 1; predisposition to cardiac conduction abnormalities Extension phase: started any restricted medications; any vomiting, retching, or mild nausea within 24 hours before day 1	Pregnant or lactating; scheduled to receive either cyclophosphamide IV and doxorubicin/epirubicin; scheduled to receive MEC or HEC from day 2 to 5; previously received NK_1RA; scheduled to receive bone marrow transplant or stem-cell therapy; systemic corticosteroid use within 72 hours of day 1; predisposition to cardiac conduction abnormalities Extension phase: patient was not scheduled to receive any additional chemotherapy, investigator decision for any medical reason (e.g., disease progression)	Scheduled to receive MEC or HEC from day 2 to 5; scheduled to receive bone marrow or stem-cell transplant, MEC or HEC within 1 week before day 1; any drug with antiemetic potential taken within 24 hours before day 1; any vomiting, retching, or more than mild nausea within 24 hours prior to day 1; systemic corticosteroid therapy within 72 hours before day 1; predisposition to cardiac conduction abnormalities	Scheduled to receive MEC or HEC on day 2 to 5; bone marrow or stem-cell transplant; MEC or HEC within 1 week before day 1; any drug with antiemetic potential within 24 hours before day 1; any vomiting, retching, or more than mild nausea within 24 hours before day 1; predisposition to cardiac conduction abnormalities; pregnant (a negative pregnancy test was required in people of childbearing potential)

		NETU 8-18	NETU 10-29	NETU 12-07	NETU 7-07
Drugs	**Intervention**	NEPA 300 mg/0.5 mg + dexamethasone 12 mg on day 1 of chemotherapy	NEPA 300 mg/0.5 mg + dexamethasone 12 mg on day 1 of chemotherapy (+ 8 mg of dexamethasone on day 2 to 4 if patient receiving HEC)	NEPA 300 mg/0.5 mg + dexamethasone 12 mg on day 1 of chemotherapy (followed by dexamethasone 8 mg daily on day 2 to 4)	Palonosetron 0.5 mg + dexamethasone 12 mg + netupitant 100 mg or 200 mg or 300 mg[b] on day 1, and dexamethasone 8 mg daily day 2 to 4
	Comparator(s)	Palonosetron 0.5 mg + dexamethasone 20 mg on day 1 of chemotherapy	Palonosetron 0.5 mg + aprepitant 125 mg and dexamethasone 12 mg on day 1 of chemotherapy (followed by aprepitant 80 mg on day 2 and 3; if HEC, dexamethasone 8 mg on day 2 to 4)	Granisetron 3 mg IV on day 1 + aprepitant 125 mg on day 1 and 80 mg on day 2 and 3, + dexamethasone 12 mg on day 1 and 8 mg on day 2 to 4	Palonosetron 0.5 mg + 20 mg dexamethasone on day 1, dexamethasone 8 mg b.i.d. from day 2 to 4 Aprepitant 125 mg, ondansetron 32 mg IV + dexamethasone 12 mg on day 1 (followed by aprepitant 80 mg on day 2 and 3 and dexamethasone 8 mg daily day 2 to 4)
Duration	**Phase**				
	Run-in	None	None	None	None
	Double-blind	1 day Extension: for up to 14 repeated cycles	4 days (for up to 6 cycles)	4 days	4 days
	Follow-up	21 days after day 1 for each cycle	Day 21 (after each cycle)	Up to 21 days after day 1	Up to 15 days after day 1
Outcomes	**Primary End Point**	CR (no emesis, no rescue medication) during delayed phase after start of chemotherapy (25 to 120 hours) for cycle 1	Safety and tolerability (assessed by TEAEs, clinical laboratory evaluations, physical examinations, vital signs)	CR in the overall phase	CR in the overall phase
	Other End Points	CR during acute phase (0 to 24 hours) and overall phase (0 to 120 hours) Complete protection (no emesis, no rescue medication, and no significant nausea [nausea up to a maximum of 25 mm on a VAS out of 100 mm]) for acute, delayed, and overall phases	CR during delayed, acute, and overall phases	CR in acute phase and delayed phase Impact on daily life	CR in delayed and acute phase Complete protection in acute, delayed, and overall phases Total control in acute, delayed, and overall phases Global satisfaction

		NETU 8-18	NETU 10-29	NETU 12-07	NETU 7-07
		Total control (no emesis, no rescue medication, and no nausea [nausea up to a maximum of 5 mm on a VAS out of 100 mm]) for acute, delayed, and overall phases Impact on daily life (measured with FLIE)			
NOTES	**Publications**	Aapro et al. 2014[13] Aapro et al. 2017[14]	Gralla et al. 2014[15] Jordan et al. 2016[16]	Zhang et al. 2018[17]	Hesketh et al. 2014[18]

AC = anthracycline/cyclophosphamide; CR = complete response; DB = double-blind; ECOG = Eastern Cooperative Oncology Group; FLIE = Functional Living Index–Emesis; HEC = highly emetogenic chemotherapy; IV = intravenous; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; NK_1 = neurokinin-1; RA = receptor antagonist; RCT = randomized controlled trial; TEAE = treatment-emergent adverse event; VAS = visual analogue scale.

Note: Eight additional reports were included (FDA Medical Report,[19] FDA Statistical Report,[20] European Medicines Agency report,[21] manufacturer's submission,[22] and Clinical Study Reports[1-4]).

[a] This regimen was considered MEC at the time the trial was conducted but has since been reclassified as HEC.[7]

[b] Dose approved by Health Canada (only dose reviewed in this report).

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Included Studies

Description of studies

There were four eligible studies. All studies were double-blind randomized controlled trials. NETU 12-07[3] was a phase III, noninferiority study (conducted February 2014 to August 2015), and NETU 7-07 [4] was a phase II, dose-finding study considered pivotal by the manufacturer (conducted February to November 2008). NETU 8-18[1] was a phase III, superiority efficacy and safety study (conducted April 2011 to November 2012), and NETU 10-29[2] was designed primarily as a phase III, safety study (conducted July 2011 to September 2012). Both NETU 8-18 and NETU 10-29 involved multiple-cycle extensions. In both studies, patients wishing to continue to receive study drug could remain in the trial for future cycles of chemotherapy; studies NETU 12-07 and NETU 7-07 were designed to evaluate NEPA for one cycle (four days) only. In NETU 8-18, patients completed up to eight cycles (only five patients completed all eight), while NETU 10-29 was designed to keep 100 patients in the study for six cycles (the maximum number of cycles was 14, completed by one patient).

Populations

Inclusion and Exclusion Criteria

All studies included only chemotherapy-naive patients. Patients in NETU 8-18, 10-29, and 12-07 were included only if they had an Eastern Cooperative Oncology Group (ECOG) status score of 0 to 2, while in NETU 7-07 patients had to have a Karnofsky score of at least 70% (similar to an ECOG status score of 0 to 2). Patients with nausea or vomiting in the 24 hours before receiving chemotherapy were excluded from all studies except NETU 10-29.

Baseline Characteristics

Baseline characteristics are summarized in Figure 5. The age of the participants was similar across studies. NETU 8-18 involved primarily women with breast cancer, while the other studies involved different types of solid-tumour cancer in both men and women. NETU 12-07 enrolled a higher proportion of patients with lung and respiratory tract cancer compared with other types of cancer, although lung cancer was common in NETU 10-29 and NETU 7-07. Both NETU 12-07 and NETU 7-07 exclusively enrolled patients receiving HEC; while 25% of patients received HEC in NETU 10-29 (the remaining 75% received MEC). In NETU 8-18, patients received an anthracycline and cyclophosphamide combination (AC). At the time of the trial, AC was considered MEC, although AC regimens have since been reclassified as HEC.[7] Hence, the majority of patients in the included trials were receiving what is now considered HEC. In all trials, patients could receive concomitant chemotherapy. The proportion of patients receiving concomitant chemotherapy was lower in NETU 8-18 compared with the other trials (35% versus 85% to 100%).

Table 5: Summary of Baseline Characteristics

	NETU 8-18		NETU 10-29		NETU 12-07		NETU 7-07	
	NEPA (N = 725)	PALO (N = 725)	NEPA (N = 308)	APR / PALO (N = 104)	NEPA (N = 413)	APR / GRAN (N = 416)	NEPA (N = 136)	PALO (N = 136)
Age (years), mean (SD)	53.7 (10.7)	54.1 (10.7)	56.5 (10.4)	56.9 (11.7)	54.5 (9.6)	54.5 (10.2)	54.1 (9.7)	54.2 (9.7)
≥ 55 years of age, n (%)	706 (48.7)		NR		NR		NR	
Male, n (%)	14 (1.9)	14 (1.9)	153 (49.7)	53 (51.0)	291 (70.6)	297 (71.4)	77 (56.6)	78 (57.4)
Race, n (%)								
White	574 (79.2)	579 (79.9)	258 (83.8)	87 (83.7)	0	0	136 (100.0)	136 (100.0)
Black	1 (0.1)	3 (0.4)	3 (1.0)	0	0	0	0	0
Asian	101 (13.9)	103 (14.2)	47 (15.3)	17 (16.3)	412 (100.0)	416 (100.0)	0	0
Hispanic	46 (6.3)	36 (5.0)	0	0	0	0	0	0
Other	3 (0.4)	4 (0.6)	0	0	0	0	0	0
Primary cancer diagnosis, n (%)								
Breast	708 (97.7)	705 (97.2)	NR	NR	NR	NR	9 (6.6)	4 (2.9)
Other	17 (2.3)	20 (2.8)	72 (23.4)	16 (15.4)	NR	NR	3 (2.2)	5 (3.7)
Colorectal	0	0	17 (5.5)	5 (4.8)	NR	NR	NR	NR
Colon	0	0	24 (7.8)	13 (12.5)	NR	NR	NR	NR
Rectal	0	0	9 (2.9)	5 (4.8)	NR	NR	NR	NR
Gastric	0	0	7 (2.3)	1 (1.0)	NR	NR	8 (5.9)	8 (5.9)
Head and neck	0	0	20 (6.5)	11 (10.6)	24 (5.8)	31 (7.5)	33 (24.3)	24 (17.6)
Lung and respiratory	0	0	122 (39.6)	32 (30.8)	254 (61.7)	229 (55.0)	35 (25.7)	41 (30.1)
Ovarian	0	0	33 (10.7)	18 (17.3)	NR	NR	24 (17.6)	23 (16.9)
Bladder	0	0	4 (1.3)	3 (2.9)	NR	NR	NR	NR
Extent at study entry, n (%)								
Primary	593 (81.8)	601 (82.9)	135 (43.8)	54 (51.9)	NR	NR	71 (52.2)	66 (48.5)

	NETU 8-18		NETU 10-29		NETU 12-07		NETU 7-07	
Metastatic	118 (16.3)	113 (15.6)	160 (51.9)	45 (43.3)	NR	NR	61 (44.9)	67 (49.3)
Local recurrence	14 (1.9)	11 (1.5)	13 (4.2)	5 (4.8)	NR	NR	4 (2.9)	3 (2.2)
Chemotherapy, cycle 1, n (%)								
Cyclophosphamide	724 (99.9)	724 (99.9)	8 (3.4)	2 (2.6)	NR	NR	46 (33.8)	40 (29.4)
Doxorubicin	493 (68.0)	461 (63.6)	26 (11.1)	5 (6.4)	NR	NR	22 (16.2)	16 (11.8)
Epirubicin	232 (32.0)	263 (36.3)	4 (1.7)	1 (1.3)	NR	NR	2 (1.5)	1 (0.7)
Cisplatin	NR	NR	72 (23.3)	23 (22.3)	412 (99.8)	416 (100.0)	136 (100.0)	136 (100.0)
Concomitant chemotherapy, n (%)								
No	490 (67.6)	494 (68.1)	15 (4.9)	4 (3.9)	69 (16.7)	91 (21.9)	20 (14.7)	21 (15.4)
Any	235 (32.4)	231 (31.9)	294 (95.1)	99 (96.1)	344 (83.3)	325 (78.1)	116 (85.3)	115 (84.6)
HEC, n (%)	0	0	75 (24.3)	25 (24.3)	412 (99.8)	416 (100.0)	136 (100.0)	136 (100.0)
MEC, n (%)	725 (100)[a]	725 (100)[a]	234 (75.7)	78 (75.7)	0	0	0	0

APR = aprepitant; GRAN = granisetron; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; NEPA = netupitant/palonosetron; NR = not reported; PALO = palonosetron; SD = standard deviation.

[a] At the time of the trial considered MEC, but currently considered HEC.

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Interventions

The intervention in all trials was a combination of netupitant 300 mg and palonosetron 0.5 mg (NEPA) given 30 to 60 minutes before chemotherapy on day 1. One dose was given per chemotherapy cycle. NETU 7-07 was a dose-finding study, which also included different strengths of netupitant (100 mg and 200 mg). This review only considered the 300 mg strength, since this is the dose approved by Health Canada and submitted by the manufacturer.

Different comparators were used. In NETU 8-18 and NETU 7-07, the comparator was palonosetron 0.5 mg given on day 1 of chemotherapy. Study NETU 7-07 also included an aprepitant treatment arm; however, the study was not designed to compare NEPA with aprepitant, and therefore data for the aprepitant arm were not reported in this review. In NETU 10-29, the comparator was a combination of palonosetron 0.5 mg (given orally on day 1) and aprepitant (given orally at a dose of 125 mg on day 1 and 80 mg on day 2 and 3). In NETU 12-07, the comparator was a combination of granisetron (3 mg IV on day 1) and aprepitant (given orally at a dose of 125 mg on day 1 and 80 mg on day 2 and 3).

In all trials, patients received concomitant dexamethasone in both arms (on day 1 only if the patient was receiving MEC and on days 1 to 4 if receiving HEC). The dexamethasone dose was reduced in patients receiving an NK_1RA, according to guideline recommendations (increase in dexamethasone exposure when given with NK_1RAs).[7]

NETU 8-18, 10-29, and 7-07 were double-blind, using study drug and matched placebos. NETU 12-07 had a double-blind/double-dummy approach. Investigators used a placebo matching NEPA, a second placebo matching oral aprepitant, and a third placebo for IV granisetron. Dexamethasone was given open-label in NETU 10-29, as the dosage was identical in both arms. Patients could receive concomitant medications for chronic diseases

and cancer treatment; however, patients were not allowed to take other antiemetics. Rescue therapy for emesis (e.g., metoclopramide) was allowed if needed. The choice of drug was based on the investigator's judgment in NETU 10-29, 8-18, and 7-07 (and was not described in NETU 12-07).

In NETU 8-18 patients were randomized 1:1 using a static, central, blocked randomization scheme, stratified by region and age group (age < 55 years or ≥ 55 years). In NETU 10-29, patients were randomized 3:1 (NEPA: aprepitant/palonosetron) using a static, central, blocked randomization stratified by chemotherapy emetogenicity (MEC, HEC) and gender. For NETU 12-07, randomization was 1:1 using a central, blocked randomization stratified by gender. In NETU 7-07, patients were randomized to treatment 1:1 and were stratified by gender. In NETU 8-18, 10-29, and 7-07, allocation concealment was employed, using an automated system that registered patients to treatment arms before study kits were provided. (In NETU 12-07, allocation concealment was not described.)

Outcomes

The primary efficacy outcome in three of the trials (NETU 8-18, NETU 12-07, and NETU 7-07) was complete response (CR), defined as no emesis and no use of rescue medication. MASCC/ESMO antiemetic guidelines suggest that an improvement of 10% in CR is considered a clinically meaningful difference.[7] The clinical expert consulted by CADTH agreed with this threshold as the minimal clinically important difference (MCID). In NETU 8-18, the primary outcome was CR in the delayed phase (25 to 120 hours after receiving chemotherapy), while, in both NETU 12-07 and NETU 7-07, the primary outcome was CR in the overall phase (i.e., the acute + delayed phases: 0 to 120 hours after receiving chemotherapy). All four trials measured CR in the acute (0 to 24 hours after receiving chemotherapy), delayed, and overall phases.

Both NETU 8-18 and 7-07 measured complete protection and total control in the acute, delayed, and overall phases in addition to CR:

- Complete protection was defined as no emesis, no rescue medication, and no significant nausea (nausea up to a maximum of 25 mm on a visual analogue scale (VAS) of 100 mm, on which 0 mm is no nausea and 100 mm is worst nausea).
- Total control was defined as no emesis, no rescue medication, and no nausea (maximum of 5 mm on VAS out of 100 mm).

The Functional Living Index–Emesis (FLIE) questionnaire assesses the impact of CINV on daily function. The questionnaire contains 18 questions in two domains: nine questions in the nausea domain and nine in the vomiting domain.[23] Questions ask respondents to assess the impact of nausea and vomiting on physical activities, social and emotional functioning, and ability to enjoy meals. Each question is rated on a seven-point scale with anchors "none" or "not at all" and "a great deal"; total scores range from 18 to 126 points.[23] Higher total scores suggest less impact of nausea and vomiting on daily function. A FLIE score of > 108 points was categorized as CINV having "no impact on daily life" in both NETU 8-18 and 12-07. NETU 8-18 collected FLIE data on day 6 (five days after chemotherapy), while NETU 12-07 collected data at 24 hours and four days. In both studies, the investigators compared the proportion of patients with a FLIE score > 108 in each study group (and measured the difference in proportions and/or odds ratios [ORs]). Lindley et al.[23] measured the validity and reliability of the FLIE three days following chemotherapy. The Pearson correlation coefficients between FLIE scores and patient-reported nausea and vomiting were –0.65 and –0.68, respectively. They also reported that

the FLIE score was internally consistent with a Cronbach's alpha > 0.9 (actual value not reported). These authors also noted that they considered a "small change" in FLIE score to be > 2.5 points from baseline to day 3. Any change less than 2.5 points would suggest no effect of CINV on daily function. However, the actual clinical significance of this difference has not been established. Martin et al.[24] evaluated the validity and reliability of the FLIE at day 5. They reported that the FLIE was internally consistent (Cronbach's alpha = 0.79). Martin et al. reported the validity as "acceptable." Construct validity, as assessed by FLIE item-total correlations, was stronger within domains (r = 0.74 to 0.97) than across domains (r = 0.52 to 0.76). They reported moderate to strong negative correlations between FLIE nausea and vomiting domain scores and independent end points of emetic episodes (r = –0.61 to –0.68), nausea ratings (r = –0.68 to –0.86), and use of rescue medications (r = –0.42 to –0.55), interpreted as patients who experienced "less nausea and vomiting were more likely to report favourable outcomes as assessed by the FLIE questionnaire."[24] For example, the proportion of patients for whom CINV had "no impact on daily life" (average item score greater than six out of seven) in a group of patients with total control during antiemetic treatment was statistically significantly greater than those without total control (96.6% versus 52.1%; P < 0.01). Neither of these studies evaluated the MCID for the FLIE questionnaire.

NETU 7-07 measured "global satisfaction" by asking patients to rate their satisfaction on a VAS of 100 mm. No data on validation or MCID could be located.

Efficacy outcomes were measured using information from patient diaries. Patients documented all details of emetic episodes during the 120 hours following the start of each chemotherapy cycle. This included each experience of retching or vomiting, including date and exact time of onset and end of the episode. Emetic episodes were defined as one or more continuous episodes of vomiting (expulsion of stomach contents through the mouth) or retching (an attempt to vomit that is not productive of stomach contents). Rescue medication use was also recorded in the diary, and severity of nausea was evaluated by the patient daily (0 to 120 hours after receiving chemotherapy) using a VAS of 100 mm. The diary was reviewed for completeness on day 1, 2, and 6 by the investigator. The investigator collected the diary on day 6. When reviewing, the investigator checked for errors, ambiguities, or omissions. In NETU 8-18, missing diary data were considered a treatment failure. In NEPA 8-18, there were 0.3% of patients with missing diary data in the NEPA arm versus 0.8% in the palonosetron arm for cycle 1. In NETU 7-07, the extent of missing diary data was not described. However, the investigators reported that the diary was completed by site staff for 1.0% of patients in the NEPA arm versus 4.9% of patients in the aprepitant/palonosetron arm in the first cycle. In NETU 7-07, the investigators did not describe how they handled patients with missing diary information. In this trial, 1.5% of patients in the palonosetron arm were missing diary data versus none in the NEPA arm. In NETU 12-07, patients with missing diary data were considered treatment failures. There were three patients with missing diary data for CR in this trial; however, this was not broken down by treatment arm.

In all trials, safety was evaluated through reporting of adverse events (AEs). Safety assessments were conducted via physical exams, vital signs, electrocardiogram (ECG), left ventricular ejection fraction, cardiac troponin levels, laboratory test, and reporting of AEs. The timing of safety assessments was generally consistent across trials. AEs were assessed at every visit (day 1, 2, 6, and 21 [day 15 was final visit in NETU 7-07]); ECG was assessed at baseline and days 1, 2, and 6; while laboratory assessments and a physical exam were done at baseline and on days 2 and 6.

Statistical Analysis

Statistical analysis approaches in each eligible study are described in Table 6.

Table 6: Statistical Analysis for Eligible Studies

NETU 8-18	The primary analysis was based on the proportion of patients achieving CR in the delayed phase, testing the null hypothesis that there was no difference between the two treatments. Analysis was conducted on the FAS. The OR was calculated using a 2-sided stratum-adjusted CMH test including treatment, age class, and region as strata. Missing data were imputed as treatment failures. The null hypothesis was rejected if the 2-sided *P* value from the CMH test was less than or equal to 0.05. The difference in response rate between the two treatments was summarized along with 95% CIs (calculated using the Newcombe-Wilson score method). The CR in the acute and overall phase was considered a "key" secondary analysis. The approach in the primary analysis was also used for these outcomes. The investigators used a hierarchical procedure for the "key" secondary end points. If the null hypothesis for the primary end point (CR in delayed phase) was rejected, the investigators compared CR in the acute phase. This was done using the same CMH test as for the primary end point (and using 2-sided *P* value from the CMH of 0.05 for significance). If the null hypothesis was rejected for CR in the acute phase, the investigators compared CR in the overall phase using the same procedure. Other secondary outcomes: total control and complete protection (acute, delayed, and overall phases for both) were calculated in each group. For NIDL, the proportion of patients achieving a score on the FLIE of > 108 was calculated in each group. The OR was calculated using the CMH test along with absolute difference and 95% CI for each outcome. There was no adjustment for multiplicity for secondary outcomes. Sample size was based on the primary end point in cycle 1. The calculation was performed assuming an absolute difference in CR rate of 9% between groups. At the 5% significance level, 661 patients per group were needed to achieve 90% power to detect this difference. The investigators increased the target sample size to 1,460 to ensure an adequate number of evaluable patients.
NETU 10-29	Efficacy outcomes were performed on the FAS. The proportion of patients achieving CR (acute, delayed, and overall phases) was calculated, and the difference in proportion between treatment groups was calculated along with the 95% CI (using Newcombe-Wilson score method). The primary aim of the study was to assess safety of NEPA. Sample size was calculated with the aim of "characterizing and quantifying the safety profile of NEPA over a reasonable duration."[2] There was no formal comparison planned between groups with respect to safety outcomes. The study was planned to include more than 100 patients treated for 6 cycles. The investigators stated that "based on current clinical practice, it was expected that 300 patients randomized and treated with [NEPA] at cycle 1 would allow more than 100 patients to be treated…for 6 cycles."[2] With 100 patients over 6 cycles, it was estimated that an AE could be excluded with 95% confidence if it was not observed in at least 3% of patients. Efficacy outcomes were planned, but the study was not powered for efficacy outcomes. Subgroup analyses based on chemotherapy emetogenicity were pre-specified but considered exploratory. For subgroup analysis, the authors calculated a difference in proportions and 95% CI in each subgroup.
NETU 12-07	The primary outcome was the difference in proportion of patients achieving CR in the overall phase. The noninferiority margin was set at –10%. The null hypothesis for the noninferiority comparison was that the difference between treatments was less than or equal to the noninferiority margin of –10%. Noninferiority was demonstrated if the lower limit of the 95% CI for the difference in proportion of patients with CR was greater than –10%. With a type I error of 5%, assuming a dropout rate of 5%, and assuming a CR rate of 75% in both groups, 832 patients were needed to achieve 90% power. The primary analysis was based on the FAS population. The difference in proportions and 95% CI were analyzed using the CMH test with gender as a stratum in the model. The statistical analysis for secondary outcomes was the same as described for the primary outcome with no adjustment for multiplicity.

NETU 7-07	The primary analysis was designed to reject the composite null hypothesis that none of the 3 dosages of NEPA were more effective than palonosetron alone. This was based on CR in the overall phase. Each NEPA dose was compared with palonosetron alone. The difference in proportion of patients achieving CR was calculated. Pairwise comparisons between each NEPA dose and palonosetron were conducted using a chi-square test. The primary test was conducted using a logistic regression model adjusted for gender. A Holm-Bonferroni method was used to control for type I error for the primary outcome. Each dose of NEPA was compared with PALO alone using a logistic regression model, testing the null hypotheses that none of the treatments were superior to PALO alone. The *P* values for each NEPA dose compared with PALO were ordered: $P1 < P2 < P3$. The smallest of the *P* values could not exceed 0.05/3 in order to reject the null hypothesis. If the first hypothesis was rejected, *P*2 could not exceed 0.05/2. If the second hypothesis was rejected, *P*3 could not exceed 0.05 Each dose of NEPA was then compared with each other without adjustment for multiplicity. Analysis was conducted on the FAS excluding patients in the aprepitant arm. The secondary outcomes were analyzed using difference in proportions and 95% CI, with no adjustment for multiplicity. The mean difference and 95% CI was calculated to compare satisfaction between groups. The sample size was calculated assuming a 70% response rate in the NEPA groups and 50% in the PALO group. For a one-sided test of difference in proportions with a type I error of 0.0166, 136 patients per group were needed to achieve 85% power.

AE = adverse event; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; CR = complete response; FAS = full analysis set; FLIE = Functional Living Index–Emesis; NEPA = netupitant/palonosetron; NIDL = no impact on daily life; OR = odds ratio; PALO = palonosetron.

Analysis populations

A description of the analysis populations in each study is in Table 7. The corresponding numbers for each population can be found in Table 8. In the NETU 8-18 multiple-cycle extension, the full analysis set (FAS) was all patients who entered the extension phase and received MEC and study drugs in the first cycle of the extension phase.

Table 7: Definition of Analysis Populations

Population	NETU 8-18	NETU 10-29	NETU 12-07	NETU 7-07
ITT	All patients randomized to treatment Patients were assigned to the study drug group according to the treatment to which they had been randomized.	NR	NR	NR
FAS	All patients randomized who received MEC regimen and study drug Primary analysis population	All patients who were randomized to treatment and received the MEC or HEC regimen according to their schedule and the study treatment Primary analysis population	Patients who had been randomized to treatment and received the HEC regimen and study drugs Primary analysis population	All patients who were randomized to treatment and received a HEC regimen and at least one dose of study treatment The modified FAS excluded patients randomized to aprepitant treatment arm; this population was used as the primary analysis population
PP	All patients included in the FAS who completed the 120-hour study period with no major protocol violations	Not defined for this study	Patients in FAS who complied with the study protocol (i.e., no major protocol violation) up to the end of the treatment period (i.e., through to 120 hours after start of chemotherapy)	All patients included in the FAS who completed the 120-hour study period and were compliant with the study protocol
Safety	All patients who received at least one study drug and had at least one safety assessment after the treatment administration	All patients who received at least one study treatment and had at least one safety assessment after the treatment administration	Patients who received at least one dose of study drug	All patients who received at least one study treatment and had at least one safety assessment after the treatment administration

FAS = full analysis set, HEC = highly emetogenic chemotherapy, ITT = intention-to-treat, MEC = moderately emetogenic chemotherapy, PP = per-protocol.

Patient Disposition

Patient disposition in the first cycle is described in Table 8. NETU 8-18 included a multiple-cycle extension phase that started after the primary outcome assessment at the end of cycle 1. NETU 10-29 was designed as a multiple-cycle study. The disposition for all cycles in these studies is shown in Figure 9. In NETU 8-18, 99.0% of patients in the NEPA arm completed the first cycle compared with 98.6% of patients in the palonosetron arm. In the NEPA arm, 87.5% of patients continued in the extension phase compared with 89.3% in the palonosetron arm. In both NETU 8-18 and NETU 10-29, many patients did not continue in the trial during the extension phase because the study site closed (labelled as “other”). In NETU 12-07, 97.8% of patients completed the first cycle in the NEPA arm compared with

98.8% in the aprepitant/granisetron arm. In NETU 7-07, 5% of patients discontinued in the NEPA arm compared with 0.7% in the palonosetron arm. The patients who discontinued in the NEPA arm were randomized but never treated. In NETU 10-29, there were relatively more deaths in the NEPA arm compared with the aprepitant/palonosetron arm. This was suggested to be due to a higher number of patients with lung cancer in the NEPA arm at baseline. There were no other major differences between groups in any of the trials.

Table 8: Patient Disposition for First Cycle

	NETU 8-18		NETU 10-29		NETU 12-07		NETU 7-07	
	NEPA	**PALO**	**NEPA**	**APR/PALO**	**NEPA**	**APR/GRAN**	**NEPA**	**PALO**
Screened, N	1,634		470		973		NR	
Randomized, N (%)	726 (100.0)	729 (100.0)	309	104	417	417	143	136
Discontinued, n (%)	7 (1.0)	10 (1.4)	6 (1.9)	2 (1.9)	9 (2.2)	5 (1.2)	7 (4.9)	1 (0.7)
Adverse event	0	1 (0.1)	9 (0.6)	0	3 (0.7)	1 (0.2)	1 (0.7)	0
Death	0	1 (0.1)	1 (0.3)	0	0	4 (1.0)	0	0
Protocol violation	2 (0.3)	3 (0.4)	0	0	1 (0.2)	0	0	0
Lost to follow-up	0	1 (0.1)	0	0	1 (0.2)	0	0	0
Withdrawal of consent	4 (0.6)	3 (0.4)	2 (0.6)	1 (1.0)	1 (0.2)	0	2 (1.4)	1 (0.7)
Lack of efficacy	0	0	0	0	0	0	0	0
Sponsor's decision	0	0	0	0	0	0	0	0
Investigator's decision	0	1 (0.1)	1 (0.3)	0	3 (0.7)	0	0	0
Health status	1 (0.1)	0	0	0	0	0	0	0
Other	0	0	0	1 (0.3)	0	0	4 (2.8)	0
ITT, N	724 (99.7)	725 (99.5)	309 (100.0)	103 (99.0)	412 (98.8)	416 (99.9)	135 (94.4)	136 (100)
PP, N	676 (93.1)	684 (93.8)	NR	NR	355 (85.1)	353 (84.6)	131 (91.6)	128 (94.1)
Safety, N	725 (99.9)	725 (99.5)	308 (99.7)	104 (100.0)	NR	NR	136 (95.1)	136 (100)

APR = aprepitant; GRAN = granisetron; ITT = intention-to-treat; NEPA = netupitant/palonosetron; NR = not reported; PALO = palonosetron; PP = per-protocol.

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Table 9: Patient Disposition for All Cycles

	NETU 8-18		NETU 10-29	
	NEPA	**PALO**	**NEPA**	**APR/PALO**
Screened, N	1,634		470	
Randomized, N	726	729	309	104
Completed a cycle but not continuing in next cycle, n (%)	253 (34.8)	245 (33.6)	111 (35.9)	43 (41.3)
Discontinuation during unplanned cycle, n (%)	2 (0.3)	0	0	0
Discontinuation during any cycle, n (%)	18 (2.5)	21 (2.9)	17 (5.5)	6 (5.8)
Adverse event	0	3 (0.4)	3 (1.0)	4 (3.8)
Death	0	1 (0.1)	8 (2.6)	0
Protocol violation	2 (0.3)	6 (0.8)	0	0
Lost to follow-up	0	3 (0.4)	0	0
Multiple-cycle extension screening failure	2 (0.3)	1 (0.1)	NE	NE
Withdrawal of consent	9 (1.2)	6 (0.8)	4 (1.3)	1 (1.0)
Other	5 (0.7)	1 (0.1)	2 (0.6)	1 (1.0)
Reasons for discontinuation or not continuing, n (%)				
Inclusion or exclusion criteria not met	55 (7.6)	66 (9.1)	NR[a]	NR[a]
Adverse event	10 (1.4)	19 (2.6)	19 (6.1)	12 (11.5)
Death	0	2 (0.3)	12 (3.9)	0
Protocol violation	5 (0.7)	6 (0.8)	4 (1.3)	1 (1.0)
Lost to follow-up	0	5 (0.7)	5 (1.6)	1 (1.0)
Withdrawal of consent	65 (9.0)	42 (5.8)	17 (5.5)	7 (6.7)
Lack of efficacy	1 (0.1)	3 (0.4)	0	0
Sponsor's decision	0	0	1 (0.3)	0
Other	136 (18.7)	123 (16.9)	70 (22.7)	28 (26.9)
Treated multiple-cycle extension, n (%)	635 (87.5)	651 (89.3)	279 (90.3)	96 (92.3)
Completed multiple-cycle extension, n (%)	448 (61.8)	458 (62.8)	178 (57.6%)	54 (51.9%)
FAS for multiple-cycle extension, N (%)	635 (87.5)	651 (89.3)	280 (90.6)[b]	96 (92.3)[b]
Safety for multiple-cycle extension, N (%)	635 (87.5)	651(89.3)	279 (90.3)	96 (92.3)

APR = aprepitant; FAS = full analysis set; NE = not evaluated; NEPA = netupitant/palonosetron; NR = not reported; PALO = palonosetron.

[a] Inclusion in subsequent cycles was at Investigator's discretion,

[b] Number treated in cycle 2.

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Exposure to Study Treatments

The extent of exposure was recorded in all trials based on the number of tablets and/or capsules or volume (in milliliters if administered IV), including dexamethasone. In NETU 7-07, the extent of exposure was calculated as the number of days between the first and the last dose of study medication (four days) and summarized by treatment group using descriptive statistics. The extent of exposure was high in all groups (mean and median exposure was four days in all groups). In NETU 8-18, patients were considered adherent with treatment if they took all of the study medication. The total exposure in days (including both cycle 1 and the multiple-cycle extension) was then calculated as the sum of the extents of exposure of each cycle. Adherence was high in all cycles for both groups, ranging from 99.6% to 100%, suggesting high exposure to study drug in all groups. The exposure in NETU 10-29 was also calculated as the number of days on study drug during each cycle. Exposure was high in all groups (mean days on NEPA 1.0, aprepitant 3.0, and palonosetron 1.0) through all cycles. In NETU 12-07, investigators provided data on the proportion of patients receiving study drug on each day. In the NEPA arm, 100% of patients received NEPA, while the aprepitant/granisetron arm, 100% received granisetron and 99.8% received aprepitant. Rescue medications were given at the investigator's discretion — metoclopramide was the most commonly used rescue medication. In NETU 7-07, rescue medication was used by 1.5% in the NEPA arm versus 4.4% in the palonosetron arm. In NETU 8-18, 16.0% in the NEPA arm used rescue medication in cycle 1 compared with 20.4% in the palonosetron arm (the most common rescue medication was metoclopramide in both arms). In NETU 10-29, 12.3% in the NEPA arm used rescue medication during cycle 1 compared with 8.7% in the aprepitant/palonosetron arm (most common was metoclopramide in both arms). Finally, in NETU 12-07, 3.9% of patients in the NEPA arm took metoclopramide as rescue medication compared with 2.7% in the aprepitant/granisetron arm (other rescue medications were used by < 1%).

Critical Appraisal

Internal Validity

The detailed risk of bias assessment can be found in Appendix 5. All studies were at low risk of bias concerning randomization, allocation concealment (except NETU 12-07, which was unclear), and blinding. Dropout was low in the first cycle of all studies and balanced across groups; thus, there were no concerns regarding incomplete outcome data in the first cycle. The studies were generally at low risk of selective reporting. However, NETU 12-07 reported on several subgroup analyses, which were not well-described in the methods. Included studies consisted of different study populations, which made it difficult to judge consistency of findings.

In NETU 8-18, 635 (87.5%) patients in the NEPA arm entered the extension study, compared with 651 (89.3%) in the palonosetron arm. With each subsequent cycle of chemotherapy, the number of patients who did not continue in the trial increased (approximately 60% completed the extension phase), but this was balanced across groups. The number of patients entering the multiple-cycle extension phase was not fixed, and many patients did not continue in the trial because the study site closed. The extension phase in NETU 8-18 was consistent with what was specified in the protocol. The investigators used an intention-to-treat approach (based on the FAS) for the extension data, treating those who did not continue as treatment failures in both arms. While the proportion

of patients who did not continue was balanced between treatment groups in both studies, such a high rate of patients not continuing in the extension phase could bias results if there were a true difference between treatments. For example, if NEPA was superior to palonosetron, this approach would bias toward the null. Neither NETU 8-18 nor NETU 10-29 were powered to detect differences in CR between groups in the extension phase. In NETU 10-29, there were more deaths in the NEPA arm through all cycles. This was suggested to be due to a baseline imbalance in the type of cancer, as the NEPA arm had more patients with lung cancer at baseline than the aprepitant/palonosetron group. The FDA also noted this, but reported no concern that this would introduce bias.[19,25]

Both NETU 8-18 and 7-07 tested and reported on many outcomes (e.g., CR, total control, complete protection, severity of nausea, emesis, use of rescue medication) at three different periods (i.e., acute, delayed, and overall phases). NETU 8-18 used a hierarchical procedure to test for differences between treatment groups for CR in the acute, delayed, and overall phases in the first cycle (Table 7). However, NETU 8-18 applied a hierarchical analysis approach to the pre-defined "key" secondary outcomes but not to other secondary outcomes. NETU 7-07 used a Holm-Bonferroni procedure to correct for multiple outcome testing for CR in the first cycle only (i.e., testing each dose of NEPA against palonosetron alone). However, there was no adjustment for multiplicity when testing each dose against each other. NETU 12-07 was designed to detect a difference in CR in the overall phase, while NETU 8-18 was designed to detect only a difference in CR in the delayed phase. There is a concern regarding inflated type I error from multiple statistical comparisons because the investigators did not adjust for multiple outcome comparisons. NETU 12-07, NETU 8-18, and NETU 7-07 were not powered to analyze any secondary outcomes (with the exception of "key" secondary outcomes in NETU 8-18).

NETU 10-29 evaluated several efficacy outcomes; however, this study was designed as a safety study, not to as a study to assess efficacy through any cycle (efficacy analysis was labelled as exploratory only by the investigators). NETU 10-29 did not adjust for multiplicity in any of the analyses.

NETU 12-07 was a noninferiority study with a pre-specified noninferiority margin of –10% (i.e., noninferiority was demonstrated if the lower limit of the 95% confidence interval for the difference in the proportion of patients with CR in the overall phase [0 to 120 hours] was greater than –10%). There were no empirical data provided to justify this margin. The manufacturer stated that NETU 12-07 was designed and the noninferiority margin agreed upon with input from the China Food and Drug Administration for market access to NEPA in China. The manufacturer noted that the noninferiority margins in other CINV antiemetic trials with CR as the primary outcome have ranged from –7% to –15%.[26-28] The accepted MCID for CR has been reported as a 10% difference between groups, although this appears to be based on clinician consensus rather than to be formally derived from treatment effects on patient-reported outcomes, particularly health-related quality of life.[7] The International Conference on Harmonization guidance indicates that determination of the noninferiority margin, in addition to being specified a priori, should be 1) estimated on the basis of both statistical analysis and clinical judgment and 2) appropriately conservative, reflecting the uncertainty in evidence.[29] Based on the description provided by the manufacturer, it seems that the margin was based primarily on clinical judgment. Therefore, the validity of the noninferiority margin used in NETU 12-07 and the conclusion of noninferiority is uncertain. NETU 12-07 used the FAS for analysis of the primary outcome instead of the per-protocol population, which may bias the effect estimate toward noninferiority.

Outcomes were assessed on the basis of subjective reporting of symptoms and rescue medication use by patients in a diary. The diary was assessed for completeness, errors, missing data, and accuracy on days 1, 2, and 6. However, reporting of these outcomes is still subject to recall bias from patients (particularly if data are being corrected or entered at study visits). The extent of missing or corrected data from diaries was not consistently reported. In NETU 8-18, there were missing diary data for 0.8% of patients in the palonosetron arm versus 0.3% in the NEPA arm. Since missing diary data were treated as a treatment failure in this study, this would bias the effect estimate in favour of NEPA. In NETU 10-29, 4.9% of the diaries needed to be corrected in the aprepitant/palonosetron arm versus 1.0% in the NEPA arm. Thus, results from the aprepitant/palonosetron patients may be more prone to reclassification bias (though the extent to which this may bias the effect estimate is unclear). However, it is unclear how much of the information in the diaries was corrected or entered at study visits in the other studies, as this was not reported. None of the trials reported additional measures to validate diary information (e.g., daily phone calls to patients). The trials did not comment on the reliability and validity of patient diaries to capture outcome data; thus, it is unclear whether this approach alone is a valid and reliable method.

Finally, both NETU 8-18 and NETU 12-07 used the FLIE questionnaire to assess patient function. Two studies were identified that assessed the reliability and validity of the FLIE.[23,24] Based on these studies, the FLIE appears to have internal consistency when administered three and five days after chemotherapy. Its validity in capturing patient function is not well-established because studies did not compare the FLIE questionnaire with patients' actual function and activities. There are no available data on the MCID. While Lindley et al.[23] noted a threshold for a "small change" in FLIE score from baseline to day 3 (> 2.5 points), the clinical relevance of this difference has not been established. Further, neither NETU 8-18 nor 12-07 measured change from baseline in FLIE score. Instead, a responder-type analysis was conducted, in which a FLIE score of > 108 points was categorized as CINV having "no impact on daily life" in both NETU 8-18 and 12-07. This threshold was used because "no impact on daily life" as an outcome is associated with an average item of greater than six on the seven-point scale, indicating that the patients chose the highest category anchored by "none" or "not at all" to describe the level of impact on daily life. A cut-off of > 108 for "no impact on daily life" has not been validated, and thus the validity of the analysis approach used in NETU 8-18 and 12-07 is unclear. And, as mentioned, the clinically meaningful between-group difference in the proportion of patients achieving this threshold is unknown. Lindley et al.[23] suggested that, to understand the impact of nausea and vomiting on daily function, the FLIE should be administered before chemotherapy and afterward (e.g., on day 3). However, NETU 8-18 and 12-07 measured FLIE only after patients received chemotherapy and did not measure FLIE before chemotherapy. The FDA noted that the FLIE questionnaire had not been well-validated and that it is unclear how accurately it captures function in patients with CINV.[19,25] Thus, the FDA considered the reporting of these results exploratory only. Similarly, the global satisfaction measurement in NETU 12-07 has not been validated in patients with CINV, and it is unclear whether this is a valid measurement of patient satisfaction in this context.

External Validity

The median age in the eligible studies was approximately 55 years of age. The clinical expert consulted for this review suggested that this was a relatively young population, since many patients with cancer are older (i.e., > 65 years of age). Thus, there is a question as to whether the efficacy and safety data can be applied in the older population. Further, the

clinical expert noted that patients in the eligible studies were relatively well-functioning (ECOG status 0 to 2) and were chemotherapy-naive. The applicability of the results in patients with poor functional status at baseline and/or those who have previously received chemotherapy (including its effects on anticipatory CINV) is also uncertain. Both NETU 8-18 and 10-29 involved mostly (around 85%) white patients and around 15% Asian patients. The trial NETU 12-07 was conducted in an entirely Asian (Chinese, Taiwanese, South Korean, Thai) population, while NETU 7-07 was conducted exclusively in Russia and Ukraine. Thus, the population studied in NETU 12-07 and 7-07 may not be reflective of the Canadian population. There were limited data on patients receiving MEC. Only one study involved patients receiving MEC (75% of patients in NETU 10-29, n = 312). This trial was not powered for efficacy outcomes; thus, the available evidence in the MEC population is limited. Furthermore, the indication under consideration in this review for patients receiving MEC stipulates that NEPA is indicated only in patients who have failed 5-HT_3RA therapy (in combination with dexamethasone). However, all patients studied were chemotherapy-naive; thus, this indication was not actually studied directly in any of the trials.

In NETU 8-18, patients were receiving AC treatment, which was classified as MEC when the trial was run. However, contemporary guidelines classify AC combinations as HEC, an issue highlighted by the FDA review.[7,19,25] Based on current guidelines, all patients in NETU 8-18 would be recommended to receive triple therapy with a NK_1RA, a 5-HT_3RA, and dexamethasone.[7,9-11] Thus, patients in the palonosetron-alone arm in NETU 8-18 could be considered undertreated according to current guidelines. Similarly, in NETU 7-07, all patients were receiving HEC. In this trial, patients in the palonosetron arm were not receiving guideline-recommended antiemetic treatment. The clinical expert consulted noted that, in HEC patients, palonosetron alone was not a relevant comparator, since NK_1RA, 5-HT_3RA, and dexamethasone triple therapy would be recommended for these patients based on current guidelines and clinical practice.

In NETU 10-29, the comparison was a combination of NK_1RA, 5-HT_3RA, and dexamethasone. All patients were chemotherapy-naive, and 75% were receiving MEC. In chemotherapy-naive patients receiving MEC, current guidelines recommend antiemetic treatment with a 5-HT_3RA and dexamethasone alone (not an NK_1RA).[7,9-11] Thus, patients receiving MEC in NETU 10-29 could be considered overtreated based on current guidelines.

Patients receiving NK_1RAs in all trials received reduced doses of dexamethasone, as NK_1RAs can increase the exposure to dexamethasone. This dose reduction is recommended in treatment guidelines and was considered to be reasonable by the European Medicines Agency review. The dosage of aprepitant and palonosetron in all trials was consistent with recommendations in Canada. However, in NETU 12-07, the dose of granisetron was 3 mg IV on day 1, which is higher than the BCCA- and CCO-recommended dose of 1 mg IV or oral and the Canadian product monograph dose of 2 mg on the day of chemotherapy.[9,11]

The manufacturer suggests that one of the potential benefits of the NEPA formulation is improved convenience and adherence for patients (given the single dose and long half-life); however, this was not evaluated in any of the trials.

Both NETU 12-07 and 7-07 evaluated efficacy and safety of NEPA over only one cycle of chemotherapy treatment. Patients receive multiple cycles of chemotherapy; therefore, the duration of follow-up in these trials is limited (and does not reflect how NEPA may be used in clinical practice). While NETU 8-18 and NETU 10-29 did evaluate safety and efficacy

over multiple cycles of chemotherapy, neither study was powered or designed to detect differences in efficacy outcomes in the extension phases (these analyses were considered exploratory).

Efficacy

Only those efficacy outcomes identified in the review protocol (Objective and Methods section and Table 4) are reported in this section. Key efficacy outcome data in the multiple-cycle extension phase are found in Appendix 4.

Complete Response in the Delayed Phase

In both NETU 8-18 (absolute difference 7.4%; 95% CI, 2.9 to 11.9) and NETU 7-07 (absolute difference 10.2%; 95% CI, 1.9 to 18.6), the proportion of patients achieving CR in the delayed phase was statistically significantly higher for NEPA than for palonosetron alone. In NETU 10-29, there was no statistically significant difference for NEPA compared with aprepitant/palonosetron (absolute difference 5.5%; 95% CI, –2.8 to 15.2) and in NETU 12-07 there was no statistically significant difference compared with aprepitant/granisetron (absolute difference 3.6; 95% CI, –2.2 to 9.4).

Complete Response in the Acute Phase

In NETU 8-18, the odds of achieving CR were significantly higher in the NEPA group than for palonosetron alone (OR 1.37; 95% CI, 1.00 to 1.87). However, the absolute difference in the proportion of patients achieving CR was not statistically significantly different between NEPA and palonosetron alone (absolute difference 3.4%; 95% CI, –0.1 to 6.9). In NETU 10-29 (absolute difference 1.3%; 95% CI, –5.9 to 5.4) and NETU 12-07 (absolute difference 2.5%; 95% CI, –7.3 to 2.3), there were no statistically significant differences in the proportions of patients achieving CR in the acute phase between NEPA and the comparators. In NETU 7-07, NEPA was statistically significantly superior to palonosetron alone (absolute difference 8.8%; 95% CI, 3.3 to 14.3) with respect to the proportion of patients who achieved CR in the acute phase.

Other Efficacy Outcomes

In the overall phase of NETU 7-07, the proportion of patients achieving CR with NEPA was statistically significantly greater than that with palonosetron (absolute difference 13.2; 95% CI, 4.4 to 21.9). In NETU 8-18, NEPA was also superior to palonosetron alone for proportion achieving CR in the overall phase (absolute difference 7.7%; 95% CI, 3.0 to 12.3). In the overall phase of NETU 10-29 and NETU 12-07, there was no statistically significant difference for NEPA compared with aprepitant/5-HT_3RA combination in terms of the proportion of patients achieving CR. In NETU 12-07, the lower limit of the 95% CI of the difference in the proportion achieving CR in the overall phase for NEPA compared with aprepitant/granisetron was greater than –10% (absolute difference 1.5; 95% CI, –4.5 to 7.5). Therefore, NEPA was noninferior to aprepitant/granisetron, based on the pre-specified noninferiority margin of –10% for CR in the overall phase.

NETU 8-18 and 7-07 compared NEPA with palonosetron alone using several other outcomes. In both trials, NEPA was statistically significantly superior to palonosetron alone for complete protection in the overall and delayed phases, but only statistically significantly superior to palonosetron alone for complete protection in the acute phase in NETU 7-07. There was no difference between NEPA and palonosetron for total control (no emesis, no

rescue medication, and no nausea) in any phase, except in NETU 7-07, in which NEPA was statistically significantly superior in the delayed phase only.

The proportion of patients with CINV having "no impact on daily life" (based on overall FLIE scores in the overall phase) was statistically significantly greater in the NEPA arm compared with the palonosetron arm (absolute difference 6.3; 95% CI, 1.9 to 10.7) in NETU 8-18; however, there was no statistically significant difference in NETU 12-07 for NEPA compared with aprepitant/granisetron. In NETU 7-07, there was a small statistically significant difference in global satisfaction, as measured by a VAS out of 100 mm, between NEPA and palonosetron at 24 hours (mean difference 4.26 mm; 95% CI, 0.65 mm to 7.87 mm) and 120 hours (mean difference 4.77 mm; 95% CI, 0.79 mm to 8.75 mm).

In the multiple-cycle extension phase of NETU 10-29 (Appendix 4), there was no statistically significant difference in the proportion achieving CR for the delayed or acute phase between NEPA and aprepitant/palonosetron in any cycle. In NETU 8-18, NEPA appeared to be superior to palonosetron for CR in both the acute and delayed phases in cycles 2, 3, and 4, but not in cycle 5 or 6.

Table 10: Key Efficacy Outcomes for First Cycle

	NETU 8-18		NETU 10-29		NETU 12-07		NETU 7-07	
	NEPA (N = 724)	**PALO (N = 725)**	**NEPA (N = 309)**	**APR/PALO (N = 103)**	**NEPA (N = 412)**	**APR/GRAN (N = 416)**	**NEPA (N = 135)**	**PALO (N = 136)**
Complete Response								
Delayed Phase								
n (%)	557 (76.9)	504 (69.5)	257 (83.2)	80 (77.7)	321 (77.9)	309 (74.3)	122 (90.4)	109 (80.1)
OR (95% CI)	1.48 (1.16 to 1.87)		NR		NR		NR	
Absolute difference (%) (95% CI)	7.4 (2.9 to 11.9)		5.5 (–2.8 to 15.2)		3.6 (–2.2 to 9.4)		10.2 (1.9 to 18.6)	
NNT	14		–		–		10	
P value	0.001		NR		NR		0.018	
Acute Phase								
n (%)	640 (88.4)	616 (85.0)	287 (92.9)	97 (94.2)	348 (84.5)	362 (87.0)	133 (98.5)	122 (89.7)
OR (95% CI)	1.37 (1.00 to 1.87)		NR		NR		NR	
Absolute difference (95% CI)	3.4 (–0.1 to 6.9)		–1.3 (–5.9 to 5.4)		–2.5 (–7.3 to 2.3)		8.8 (3.3 to 14.3)	
NNT	–		–		–		12	
P value	0.047		NR		NR		0.007	

APR = aprepitant; GRAN = granisetron; CI = confidence interval; NEPA = netupitant/palonosetron; NNT = number needed to treat; NR = not reported; OR = odds ratio; PALO = palonosetron.

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Table 11: Other Efficacy Outcomes

	NETU 8-18		NETU 10-29		NETU 12-07		NETU 7-07	
	NEPA (N = 724)	PALO (N = 725)	NEPA (N = 309)	APR/PALO (N = 103)	NEPA (N = 412)	APR/GRAN (N = 416)	NEPA (N = 135)	PALO (N = 136)
Complete Response								
Overall Phase								
n (%)	538 (74.3)	483 (66.6)	249 (80.6)	78 (75.7)	259 (73.0)	257 (72.8)	121 (89.6)	104 (76.5)
OR (95% CI)	1.47 (1.27 to 1.85)		NR		1.08 (0.79 to 1.47)		NR	
Absolute difference (95% CI)	7.7 (3.0 to 12.3)		4.9 (–3.8 to 14.8)		1.5 (–4.5 to 7.5)		13.2 (4.4 to 21.9)	
NNT	13		–		–		8	
P value	0.001		NR		0.22		0.004	
Complete Protection								
Delayed Phase								
n (%)	487 (67.3)	437 (60.3)	NR	NR	NR	NR	114 (84.4)	100 (73.5)
OR (95% CI)	1.36 (1.10 to 1.69)							
Absolute difference (95% CI)	7.0 (2.0 to 11.9)						10.9 (1.3 to 20.5)	
NNT	15						10	
P value	0.005						0.027	
Acute Phase								
n (%)	596 (82.3)	588 (81.1)	NR	NR	NR	NR	131 (97.0)	119 (87.5)
OR (95% CI)	1.09 (0.83 to 1.43)						NR	
Absolute difference (95% CI)	1.2 (–2.8 to 5.2)						9.5 (3.3 to 15.8)	
NNT	–						11	
P value	0.528						0.006	
Overall Phase								
n (%)	462 (63.8)	420 (57.9)	NR	NR	NR	NR	112 (83.0)	95 (69.9)
OR (95% CI)	1.29 (1.04 to 1.60)						NR	
Absolute difference (95% CI)	5.9 (0.9 to 10.9)						13.1 (3.1 to 23.1)	
NNT	17						8	
P value	0.02						0.01	
Total Control								
Delayed Phase								
n (%)	373 (51.5)	340 (46.9)	NR	NR	NR	NR	89 (65.9)	71 (52.2)
OR (95% CI)	1.20 (0.98 to 1.48)						NR	

	NETU 8-18		NETU 10-29		NETU 12-07		NETU 7-07	
Absolute difference (95% CI)	4.6 (–0.5 to 9.7)						13.7 (2.1 to 25.3)	
NNT	–						8	
P value	0.077						0.021	
Total Control								
Acute Phase								
n (%)	497 (68.6)	492 (67.9)	NR	NR	NR	NR	108 (80.0)	97 (71.3)
OR (95% CI)	1.04 (0.83 to 1.30)						NR	
Absolute difference (95% CI)	0.8 (–4.0 to 5.6)						8.7 (–1.5 to 18.7)	
NNT	–						–	
P value	0.730						0.093	
Total Control								
Overall Phase								
n (%)	350 (48.3)	319 (44.0)	NR	NR	NR	NR	82 (60.7)	71 (52.2)
OR (95% CI)	1.19 (0.97 to 1.47)						NR	
Absolute difference (95% CI)	4.3 (–0.8 to 9.4)						9.3 (–2.5 to 21.1)	
NNT	–						–	
P value	0.095						0.118	
No Impact on Daily Life From CINV (Overall Phase)								
n (%)	568 (78.5)	523 (72.1)	NR	NR	313 (76.0)	294 (70.7)	NR	NR
OR (95% CI)	1.43 (1.12 to 1.83)				NR			
Absolute difference (95% CI)	6.3 (1.9 to 10.7)				5.8 (–0.1 to 11.8)			
NNT	16				–			
P value	0.005				NR			
Global Satisfaction at 24 Hours								
n	NR	NR	NR	NR	NR	NR	135	136
Mean (SD)							95.3 (10.8)	91.0 (18.4)
Difference in mean (95% CI)							4.26 (0.65 to 7.87)	
Global Satisfaction 97 to 120 Hours								
n	NR	NR	NR	NR	NR	NR	135	136
Mean (SD)							94.0 (12.2)	89.2 (20.1)
Difference in mean (95% CI)							4.77 (0.79 to 8.75)	

APR = aprepitant; GRAN = granisetron; CI = confidence interval; NEPA = netupitant/palonosetron; NNT = number needed to treat; NR = not reported; OR = odds ratio; PALO = palonosetron.

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Subgroups

The efficacy data from NETU 10-29 for the subgroups by chemotherapy emetogenicity (MEC or HEC) are reported in Table 12. In NETU 10-29, patients were stratified according to chemotherapy emetogenicity during randomization. The investigators reported a difference in proportions and 95% CI for both subgroups. The investigators did not provide *P* values for subgroup analysis and did not report interaction terms.

In patients receiving MEC, the 95% CI included 0 for the difference in proportion achieving CR between NEPA and aprepitant/palonosetron (for both acute and delayed phases). For patients receiving HEC, the proportion of patients with CR in the delayed phase was higher for NEPA than for aprepitant/palonosetron (difference 30.1%; 95% CI, 10.9 to 40.7) in the delayed phase. However, the 95% CI for the difference in proportions included 0 in the acute phase for HEC. No harms data were provided for these subgroups. No other studies provided data on subgroups of interest.

Table 12: Key Efficacy Outcomes for Subgroups

	NETU 10-29 MEC		NETU 10-29 HEC	
Complete Response	**NEPA**	**APR / PALO**	**NEPA**	**APR / PALO**
Delayed Phase				
n/N (%)	192/235 (81.7)	65/77 (84.4)	65/74 (87.8)	15/26 (57.7)
Absolute difference (%) (95% CI)	–2.7 (–11.1 to 8.0)		30.1 (10.9 to 40.7)	
NNT	–		4	
P value	NR		NR	
Acute Phase				
n/N (%)	219/235 (93.2)	72/77 (93.5)	68/74 (91.9)	25/26 (96.2)
Absolute difference (95% CI)	–0.3 (–5.7 to 7.9)		–4.3 (–13.3 to 11.4)	
NNT	–		–	
P value	NR		NR	

APR = aprepitant; CI = confidence interval; NEPA = netupitant/palonosetron; NNT = number needed to treat; NR = not reported; PALO = palonosetron.

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Harms

Only those harms identified in the review protocol are reported in this section (Figure 13 and Table 14).

Adverse Events

The safety profile of NEPA was similar to palonosetron alone and to a combination of aprepitant and a 5-HT_3RA across the trials. In the first cycle of NEPA 8-18, a higher proportion of patients experienced AEs overall in the NEPA group than in the palonosetron-alone group (76.0% versus 69.9%). However, in the extension phase, the proportions were similar (83.9% for NEPA versus 81.0% for palonosetron alone). In the other trials, the proportion of patients experiencing AEs was similar between treatment groups. The most common AEs were gastrointestinal disorders, alopecia, and blood disorders (Table 13). Headache was also common.

Serious Adverse Events

The proportion of patients experiencing serious AEs (SAEs) was similar for NEPA and its comparators, in general. In NETU 10-29, the proportion experiencing SAEs was slightly higher in the NEPA group than in the aprepitant/palonosetron group (5.8% versus 3.8%). However, there was no specific SAE driving this difference, and no individual SAE occurred in more than 1% of the participants. In NETU 10-29, during the extension phase, there were more SAEs in the aprepitant/palonosetron group (18.3%) than in the NEPA group (16.2%).

Withdrawal Due to Adverse Events

Withdrawal due to adverse events (WDAEs) were low and balanced between groups across trials. In the extension phase of NETU 10-29, the proportion experiencing WDAEs was higher in the aprepitant/palonosetron group (12.5%) than in the NEPA group (9.1%). However, there was no specific WDAE that explained this difference.

Mortality

The number of deaths was low and similar between groups in NETU 8-18, NETU 12-07, and NETU 7-07. In NETU 10-29, the proportion of deaths was higher in the NEPA arm (5.2%) compared with the aprepitant/palonosetron arm (1.0%).

Notable Harms

No treatment-emergent arrhythmias were identified in NETU 10-29, NETU 12-07, or NETU 7-07. In NETU 8-18, there was one case in each treatment groups for both the first cycle and extension phases.

Table 13: Harms in First Cycle

	NETU 8-18		NETU 10-29		NETU 12-07		NETU 7-07	
AEs	**NEPA (N = 725)**	**PALO (N = 725)**	**NEPA (N = 308)**	**APR / PALO (N = 104)**	**NEPA (N = 413)**	**APR / GRAN (N = 416)**	**NEPA (N = 136)**	**PALO (N = 136)**
Patients with > 0 AEs, n (%)	551 (76.0)	507 (69.9)	199 (64.6)	64 (61.5)	240 (58.1)	239 (57.5)	68 (50.0)	68 (50.0)
Most common AEs[a]								
Gastrointestinal disorders	99 (13.7)	94 (13.0)	56 (18.2)	21 (20.2)	112 (27.1)	104 (25.0)	18 (13.2)	20 (14.7)
Leukopenia	96 (13.2)	90 (12.4)	38 (12.3)	11 (10.6)	11 (2.7)	11 (2.6)	0	0
Neutropenia	173 (23.9)	182 (25.1)	48 (15.6)	12 (11.5)	NR	NR	0	0
Asthenia	59 (8.1)	50 (6.9)	10 (3.2)	4 (3.8)	NR	NR	13 (9.6)	4 (3.0)
Fatigue	47 (6.5)	38 (5.2)	16 (5.2)	8 (7.7)	28 (6.8)	25 (6.0)		
Headache	64 (8.8)	52 (7.2)	11 (3.6)	1 (1.0)	NR	NR	10 (7.4)	5 (3.7)
Alopecia	253 (34.9)	253 (34.9)	40 (13.0)	10 (9.6)	NR	NR		
Metabolism and nutrition disorders	58 (8.0)	57 (7.9)	28 (9.1)	9 (8.7)	72 (17.4)	81 (19.5)	14 (10.3)	9 (6.6)
Anemia	26 (3.6)	24 (3.3)	22 (7.1)	5 (4.8)	NR	NR	0	1 (0.7)
Infections and infestations	35 (4.8)	30 (4.1)	20 (6.5)	7 (6.7)	14 (3.4)	12 (2.9)	2 (1.5)	0
Investigations	57 (7.9)	51 (7.0)	32 (10.4)	13 (12.5)	73 (17.7)	73 (17.5)	21 (15.4)	19 (14.0)
Musculoskeletal and connective tissue disorders	21 (2.9)	12 (1.7)	8 (2.6)	7 (6.7)	NR	NR	0	3 (2.2)
Respiratory, thoracic, and mediastinal disorders	19 (2.6)	18 (2.5)	21 (6.8)	8 (7.7)	55 (13.3)	50 (12.0)	10 (7.4)	8 (5.9)
Vascular disorders	22 (3.0)	16 (2.2)	13 (4.2)	6 (5.8)	NR	NR		
SAEs								
Patients with > 0 SAEs, n (%)	13 (1.8)	12 (1.7)	18 (5.8)	4 (3.8)	20 (4.8)	19 (4.6)	0	3 (2.2)
WDAEs								
WDAEs, n (%)	7 (1.0)	4 (0.6)	9 (0.6)	0	1 (0.2)	2 (0.5)	0	0
Deaths								
Number of deaths, n (%)	0	1 (0.1)	7	0	0	4 (1.0)	0	0
Most common reasons			NR	NR				
Disease progression	0	1 (0.1)			0	0	0	0
Pulmonary embolism	0	0			0	1 (0.3)	0	0
Respiratory failure	0	0			0	1 (0.3)	0	0
Sudden death	0	0			0	1 (0.3)	0	0
Lung infection	0	0			0	1 (0.3)	0	0

	NETU 8-18		NETU 10-29		NETU 12-07		NETU 7-07	
Notable Harms								
Notable harms, n (%)								
Arrhythmia	1 (0.1)	1 (0.1)	0	0	0	0	0	0

AE = adverse effect; APR = aprepitant; GRAN = granisetron; NEPA = netupitant/palonosetron; NR = not reported; PALO = palonosetron; SAE = serious adverse effect; WDAE = withdrawal due to adverse effect.

[a] Frequency > 5%.

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Table 14: Harms in Extension Phase (NETU 10-29 for Whole Study)

	NETU 8-18		NETU 10-29	
AEs	**NEPA (N = 635)**	**PALO (N = 651)**	**NEPA (N = 308)**	**APR / PALO (N = 104)**
Patients with > 0 AEs, n (%)	533 (83.9)	527 (81.0)	265 (86.0)	95 (91.3)
Most common AEs,[a] n (%)				
Gastrointestinal disorders	129 (20.3)	123 (18.9)	100 (32.5)	38 (36.5)
Leukopenia	138 (21.7)	141 (21.7)	55 (17.9)	18 (17.3)
Neutropenia	226 (35.6)	238 (36.6)	95 (30.8)	29 (27.9)
Asthenia	70 (11.0)	69 (10.6)	30 (9.7)	12 (11.5)
Fatigue	49 (7.7)	49 (7.5)	29 (9.4)	15 (14.4)
Anemia	47 (7.4)	41 (6.3)	58 (18.8)	26 (25.0)
Cardiac disorders	32 (5.0)	30 (4.6)	27 (8.8)	8 (7.7)
Infections and infestations	71 (11.2)	51 (7.8)	53 (17.2)	19 (18.3)
Musculoskeletal and connective tissue disorders	34 (5.4)	31 (4.8)	26 (8.4)	15 (14.4)
Vascular disorders	33 (5.2)	25 (3.8)	24 (7.8)	12 (11.5)
Investigations	99 (15.6)	88 (13.5)	66 (21.4)	25 (24.0)
Metabolism and nutrition disorders	82 (12.9)	92 (14.1)	59 (19.2)	19 (18.3)
Alopecia	152 (23.9)	151 (23.2)	77 (25.0)	32 (30.8)
Headache	53 (8.3)	57 (8.8)	15 (4.9)	7 (6.7)
Cough	17 (2.7)	10 (1.5)	14 (4.5)	8 (7.7)
SAEs				
Patients with > 0 SAEs, n (%)	23 (3.6)	15 (2.3)	50 (16.2)	19 (18.3)
Most common SAEs[b]				
Blood and lymphatic system disorders	12 (1.9)	5 (0.8)	12 (3.9)	5 (4.8)
Gastrointestinal disorders	2 (0.3)	1 (0.2)	14 (4.5)	4 (3.8)
Infections and infestations	5 (0.8)	4 (0.6)	8 (2.6)	4 (3.8)
Renal and urinary disorders	NR	NR	1 (0.3)	3 (2.9)
WDAEs				
WDAEs, n (%)	8 (1.3)	15 (2.3)	28 (9.1)	13 (12.5)
Deaths				
Number of deaths, n (%)	0	1 (0.2)	16 (5.2)	1 (1.0)
Most common reasons				

	NETU 8-18		NETU 10-29	
Cardiac and respiratory failure	0	1 (0.2)	1 (0.3)	0
Renal insufficiency	0	0	0	1 (1.0)
Disease progression	0	0	5 (1.6)	0
Pulmonary embolism	0	0	2 (0.6)	0
Hemoptysis	0	0	1 (0.3)	0
Infection	0	0	2 (0.6)	0
Cancer intoxication	0	0	1 (0.3)	0
Pulmonary insufficiency	0	0	1 (0.3)	0
Stroke	0	0	1 (0.3)	0
Pneumothorax	0	0	1 (0.3)	0
Weakness	0	0	1 (0.3)	0
Notable Harms				
Notable harms, n (%)				
Arrhythmia	1 (0.2)	1 (0.2)	0	0

AE = adverse effect; APR = aprepitant; NEPA = netupitant/palonosetron; NR = not reported; PALO = palonosetron; SAE = serious adverse effect; WDAE = withdrawal due to adverse effect.

[a] Frequency > 5%.

[b] Frequency > 1%.

Source: Clinical Study Reports for NETU 8-18,[1] 10-29,[2] 12-07,[3] and 7-07.[4]

Discussion

Summary of Available Evidence

This clinical review is based on four double-blind randomized controlled trials. Two studies (NETU 8-18, n = 1,455 and NETU 7-07, n = 694) investigated the efficacy and safety of NEPA compared with palonosetron alone in patients receiving HEC, while two studies (NETU 10-29, n = 413 and NETU 12-07, n = 834) evaluated the efficacy and safety of NEPA compared with aprepitant/5-HT_3RAs. Patients in NETU 12-07 received HEC, while, in NETU 10-29, 25% of patients received HEC and 75% received MEC. All patients in the included studies were chemotherapy-naive at randomization.

NETU 10-29 was conducted with the primary objective of assessing safety and was not powered for efficacy outcomes. In NETU
8-18, the primary outcome was CR in the delayed phase, while in NETU 12-07 and 7-07 the primary outcome was CR in the overall phase. NETU 12-07 was a noninferiority study that evaluated whether NEPA was noninferior to aprepitant and granisetron in the overall phase.

Interpretation of Results

Efficacy

Compared with treatment with palonosetron alone, statistically significantly greater proportions of patients receiving HEC achieved CR in the delayed phase and overall phase with NEPA during a single chemotherapy cycle. The absolute difference ranged from approximately 7% to 13%. A slightly higher proportion of patients achieved CR in the acute phase with NEPA compared with palonosetron (absolute difference of about 3% to 8%), although this was not statistically significant in NETU 8-18. The proportion of patients achieving CR may continue to be higher with NEPA versus palonosetron alone over multiple cycles of chemotherapy, based on NETU 8-18; however, this study was not designed specifically to assess the comparative efficacy of NEPA over multiple cycles, and concrete conclusions cannot be drawn in this regard. While these results suggest NEPA may be more efficacious than palonosetron alone, it is important to note that palonosetron alone is not the most relevant comparator to NEPA in patients receiving HEC. In such patients, an NK_1RA and a 5-HT_3RA + dexamethasone would be recommended, not a 5-HT_3RA alone with dexamethasone. Clinical guidance from MASCC/ESMO indicates that CR is a clinically important outcome measure in assessing antiemetics in preventing CINV, and it has been used as the primary outcome in a number of trials of antiemetics for CINV.[7] However, no empirical data were identified evaluating the reliability and validity, as well as a definition of a clinically meaningful response, for CR. The consensus-based MCID for CR is 10%.[7] The clinical expert consulted by CADTH agreed that CR is clinically important. However, the clinical expert noted that, in practice, clinicians do not assess CR in isolation, but assess patient response to antiemetics in combination with impacts on quality of life and daily functioning. The clinical expert stated that patients may report that they still experience CINV to various degrees despite so-called optimal antiemetic therapy, and yet have the capacity to engage in their usual activities.

The patient input summary (Appendix 1) suggests that the efficacy of antiemetics is extremely important to patients; in particular, in helping patients maintain daily functioning despite MEC or HEC. The reviewed evidence suggests that NEPA does not offer improved efficacy over existing NK_1RA and 5-HT_3RA combinations. While NEPA appears to be more

beneficial than palonosetron alone in HEC, patients receiving HEC would not receive palonosetron alone. Thus, these results may not be applicable to contemporary treatment of CINV. Two studies (NETU 8-18 and NETU 12-07) measured the proportion of patients with “no impact on daily life” from CINV, as measured by the FLIE questionnaire. Both studies found the proportion with “no impact on daily life” from CINV was higher in patients taking NEPA (absolute difference 6%, which was statistically significant in NETU 8-18 only). However, an MCID for the FLIE questionnaire was not found in a search of the literature, so the clinical significance of this finding is unclear. The FDA noted that the FLIE questionnaire was not well-validated for assessing its domains (i.e., impact of nausea and vomiting on physical activities, social and emotional function, and ability to enjoy meals) and questioned whether such an outcome measure provides an accurate assessment of patient function. Thus, the effect of NEPA on patient function is unclear. Health-related quality of life was not evaluated in any of the included studies.

Two of the trials compared NEPA with other NK_1RA and 5-HT_3RA combinations. There were no statistically significant differences in the proportions of patients achieving CR in the delayed, acute, or overall phases between NEPA and aprepitant/5-HT_3RA combinations. However, in the subgroup of patients receiving HEC in NETU 10-29, more patients achieved CR in the delayed phase for NEPA compared with aprepitant/palonosetron (absolute difference approximately 30%). In NETU 10-29, there continued to be no difference in the proportion of patients achieving CR across multiple cycles of chemotherapy. However, this study was a safety study and was not designed to assess efficacy of NEPA, and subgroup analyses were exploratory, with no statistical comparisons performed. In NETU 12-07, in which all patients received HEC, NEPA was noninferior to aprepitant/granisetron, based on the pre-specified noninferiority margin of –10%, with respect to the proportion of patients achieving CR in the overall phase. The –10% noninferiority margin used was based on expert consensus and has not been evaluated for validity and reliability in clinical studies.[7] Thus, the validity of the noninferiority findings is uncertain. This study was not ready for submission for review by Health Canada or the FDA for market access, and therefore those agencies did not provide input on the noninferiority margin. Also in NETU 12-07, there were no statistically significant differences between NEPA and aprepitant/granisetron for CR in the acute and delayed phases. The results of these trials suggest that NEPA is at best noninferior to aprepitant/5-HT_3RA combinations for achieving CR. The results of the manufacturer-provided indirect treatment comparison (Appendix 6) suggested that NEPA + dexamethasone provided efficacy (CR in any phase) similar to aprepitant-containing triple regimens (aprepitant, 5-HT_3RA, dexamethasone) in patients receiving HEC/AC. Likewise, the analysis suggested that NEPA + dexamethasone provided efficacy (CR during any time point) similar to aprepitant- or fosaprepitant-containing triple regimens and to 5HT_3RAs + dexamethasone regimens in MEC patients. This reflects treatment guidelines,[7] which do not preferentially suggest one triple regimen over another for HEC, and published indirect comparisons.[30,31] However, a number of limitations with the indirect comparisons mean there is uncertainty with the results, which prevented drawing definitive conclusions regarding the comparative efficacy of NEPA.

There were limited data available in patients receiving MEC in the included studies. In NETU 10-29, in the subgroup of patients receiving MEC, there was no difference in the proportion of patients achieving CR between NEPA and aprepitant/palonosetron. As mentioned, this study was designed as a safety study, and most comparisons related to efficacy outcomes, including subgroup analyses, were descriptive, without formal statistical tests. Another important limitation of this study was that chemotherapy-naive patients receiving MEC would not typically receive triple antiemetic therapy; thus,

aprepitant/palonosetron may not be the most relevant comparator in these patients. NETU 8-18 was initially classified as a study of patients with breast cancer who received a MEC regimen. However, the chemotherapy studied (AC) was subsequently reclassified as HEC.[7,10] The manufacturer likewise reclassified the description of the study population from MEC to HEC but (according to the Health Canada reviewer's report) noted that "it is still well recognized that the AC regimen is not as emetogenic as cisplatin-based chemotherapy."[25] Nevertheless, Health Canada evaluated the results from NETU 8-18 as being based on a HEC population.

The Health Canada reviewer noted uncertainty with respect to the benefit of including a NK_1RA in the prevention of delayed CINV with MEC, but went on to note that "a number of Canadian Practice Guidelines … recommend an NK_1RA (aprepitant) as an optional addition in cases of uncontrolled emesis despite the use of the combination of dexamethasone and a 5-HT3 antagonist."[25] Along with its safety profile (see Harms discussion), the efficacy of NEPA in the predominantly MEC population in NETU 10-29 contributed to the indication for patients treated with MEC.

The manufacturer suggested that NEPA may be preferred over existing therapy because it can be given as a single dose and may be more convenient. However, none of the reviewed studies assessed this. One study, NETU 7-07, measured global satisfaction using a VAS out of 100 mm and found that patients taking NEPA were slightly more satisfied than those taking NEPA (mean difference of 4 mm out of 100 mm); however, no statistical comparisons were reported, and the clinical significance of the results are unknown. Therefore, there was insufficient data to evaluate the manufacturer's claim of increased convenience for patients and adherence to treatments.

Harms

Adverse effects were common in the studies under review. This is not surprising, given that patients were receiving chemotherapy treatment concomitantly, which commonly causes adverse effects similar to those reported. In the eligible studies, the proportion of patients experiencing harms was similar between NEPA and comparators. Health Canada noted that NEPA displayed an acceptable safety profile in clinical trials and that most harms experienced were likely due to underlying conditions and/or concomitant chemotherapy (i.e., the majority of harms were not caused by study drug).[25] NETU 10-29 was specifically designed to test the safety of NEPA compared with aprepitant and palonosetron. In this study, the rate of AEs was similar between groups in both the first cycle and subsequent cycles. Health Canada also reported that the frequency of AEs was consistent across cycles; thus, there was no signal of accumulated toxicity.[25] The European Medicines Agency noted that there was a higher rate of deaths in the NEPA arm compared with the aprepitant/palonosetron arm in NETU 10-29; however, this was explained by the fact that patients in the NEPA arm were sicker at baseline (a higher proportion of patients in the NEPA arm had lung cancer).[21]

One concern with use of 5-HT_3RAs is QTc prolongation and an increased risk of arrhythmias (e.g., torsades de pointes). Thus, patients with underlying cardiac conduction abnormalities were excluded from all trials. The QTc interval was monitored closely in eligible studies. The proportion of patients experiencing QTc changes was similar between groups, and any changes were considered minor and transient. There were no cardiac safety concerns identified in any of the studies.

The manufacturer-provided indirect comparison did not evaluate effects on safety outcomes. Therefore, the comparative safety of NEPA for the prevention of CINV is associated with uncertainty.

Potential Place in Therapy

Major advances in understanding of the etiology and biochemical mediators of CINV have led to significant improvements in managing both the acute and delayed phases, with a focus on specific combinations of drugs for patients receiving HEC or MEC. The use of a 5-HT_3RAs with dexamethasone (on day 1 alone or for multiple days) has been established as standard of care for more than two decades.[32] Recent trials of NK_1RAs have led to further improvements, and their inclusion in HEC and MEC programs (i.e., aprepitant) is now recommended in virtually all jurisdictions.[7,10] With appropriate attention to these guidelines, CR (no vomiting and no rescue medication) of CINV can be achieved in at least 90% of patients in the acute phase and in 80% to 85% in the delayed phase.[7]

While there have been advances in the evidence-based management of CINV, there remain gaps: for example, most of the improvement in management has been in the acute phase, but delayed CINV still afflicts nearly 25% to 30% of patients.[7,33] Additionally, optimum outcomes still depend on initial appropriate doses (including consideration of high intravenous doses) of 5-HT_3RAs, or multiple doses of combination antiemetics over days 1 to 5 of the chemotherapy cycle. As well, beneficial effects on anticipatory nausea and vomiting and on patients' quality of life need to be demonstrated.

The potential advantage of NEPA is primarily an effective and safe single administration per cycle, thereby improving adherence and — from the data reviewed — the control of delayed CINV. With regard to the latter, the observed improvements in various response measures with NEPA, as compared with comparators, was statistically significant but of uncertain clinical significance, given the choice of comparator in certain studies (palonosetron alone in studies NETU 8-18 and NETU 7-07), between-group absolute differences in response of generally < 10%, and the lack of a clear benefit on quality of life or other patient-reported outcomes.

Patients receiving HEC (now including women receiving potentially curative adjuvant AC chemotherapy) or MEC, who would be eligible to receive a three-drug (triple) antiemetic combination (5-HT_3RA, NK_1RA, and dexamethasone) would be eligible for treatment with NEPA. However, the reviewed data do not provide clear evidence that this combination provides added clinical benefit over existing combinations of anti-CINV drugs.

Conclusions

A manufacturer-provided noninferiority study and indirect comparison suggest that NEPA has similar efficacy to existing NK_1RA/5-HT_3RA combinations in patients receiving MEC and HEC in the acute, delayed, and overall phases. However, there was uncertainty regarding the validity of the noninferiority margin used in the noninferiority trial, and likewise regarding the results of the indirect comparisons because of limitations associated with the source data and sparsely populated networks. NEPA appears to have a safety profile with AE frequencies that are similar to those of existing NK_1RA/5-5-HT_3RA combination treatments. While it has been suggested that NEPA offers a benefit in terms of convenience and adherence, these were not evaluated in any of the included studies. Thus, based on the evidence reviewed in this report, NEPA does not appear to provide a clear added clinical value over existing NK_1RA/5-HT_3RA in terms of efficacy or safety.

Appendix 1: Patient Input Summary

No patient input was received for this review. A patient input summary from a previous CDR review for Aloxi (palonosetron) is summarized by CADTH staff in this appendix. It has not been systematically reviewed.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Cancer Survivor Network (CCSN) was the only group that submitted input for Aloxi (palonosetron hydrochloride). The CCSN is a national network of funders, sponsors, patients, families, friends, community partners, and survivors that takes action to promote the very best standards of care in diagnosis, treatment, follow-up care, and support. It works to engage patients, survivors, stakeholder groups, and decision-makers in discussions and actions related to evidence-based best practices that alleviate the emotional, financial, medical, and social costs of cancer. In 2012, CCSN received financial contributions from Amgen, Pfizer, Eisai, Janssen, Merck, and Rx&D.

2. Condition and Current Therapy-Related Information

The information for this section was gathered through one-on-one conversations with patients and patient testimonials.

Highly or moderately emetogenic chemotherapy frequently causes chemotherapy-induced nausea and vomiting (CINV) in patients with cancer. The impact of CINV on patients spans a broad spectrum, from mild nausea to severe disruption in their everyday lives. CINV can also impact patients' ability or desire to continue chemotherapy.

Major impacts on the quality of life and ability to function were noted by patients undergoing chemotherapy. Patients reported that they were unable to live their normal lives. They could not socialize with family or friends, care for their children, work, or study. They felt isolated, cut off, and miserable from constant nausea and vomiting. Some of the following comments illustrate the impact of CINV on patients' lives: the treatment with the various chemotherapeutic drugs was worse than the condition; the CINV was cumulative with each round of chemotherapy and thus the patient felt sick sooner and longer; constant dry-heaving and vomiting brought on migraines in one patient; one patient described vomiting in secret in hospital so that staff believed that she was "keeping food down" and thus would discharge her sooner.

Patients reported that currently available treatments for CINV have not always been made available or were not always effective. Some patients had side effects as well, including nightmares following the treatment for nausea and vomiting. However, patients also reported benefits with the current treatment for CINV: a patient with a cancer relapse noted that the support drugs available now controlled her vomiting more effectively than those available 17 years earlier; another patient-reported nausea during her first treatment but none following the second treatment, as the medication and dose had been changed.

The impact on caregivers is substantial. Caregivers — spouses, parents, or other relatives and friends — often face competing interests including, but not limited to, caring for the patient while juggling job responsibilities, caring for children or elderly parents, and scheduling and keeping a large number of doctor and treatment appointments. Unfortunately, these competing interests can often interfere with their caregiving role, creating additional emotional turmoil for the patient, caregiver, and other family members.

3. Related Information About the Drug Being Reviewed

None of the patients with whom the CCSN had spoken had any experience with Aloxi. However, there is an expectation, based on clinical trial results, that Aloxi may be more effective than some of the current antiemetic drugs and may provide some relief to those who cannot take currently available drugs. CCSN believes that side effects will be similar to currently available treatments (headaches, constipation, tiredness, and fatigue) and that some patients may not benefit from Aloxi or may not be able to tolerate it. Given the negative impact on quality of life that uncontrolled CINV can induce, CCNS advocates the funding of Aloxi as another treatment option.

4. Additional Information

None to report.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE all **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 15, 2018
Alerts:	Bi-weekly search updates until May 16, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; Ovid MEDLINE ALL 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY (MEDLINE, EMBASE)	
#	**Searches**
1	(Akynzeo* or NEPA or "netupitant/palonosetron" or "palonosetron/netupitant").ti,ab,hw,ot,kf,rn,
2	((netupitant or NETU or "Ro 67-3189/000" or r?1124) and (palonosetron or PALO or 2-Qhbiqo or Aloxi* or Onicit* or rs?25259 or rs?25259 197)).ti,ab,hw,ot,kf,rn,nm.
3	(S900006640 or ((290297-26-6 or 7732P08TIR) and (135729-61-2 or 135729-62-3 or 5D06587D6R))).rn,nm.
4	or/1-3
5	netupitant plus palonosetron/
6	(Akynzeo* or NEPA or "netupitant/palonosetron" or "palonosetron/netupitant").ti,ab,kw,tn.
7	*netupitant/ or (netupitant or NETU or "Ro 67-3189/000" or r?1124).ti,ab,kw,tn.
8	*palonosetron/ or (palonosetron or PALO or 2-Qhbiqo or Aloxi* or Onicit* or rs?25259 or rs?25259 197).ti,ab,kw,tn.
9	7 and 8

MULTI-DATABASE STRATEGY (MEDLINE, EMBASE)	
#	**Searches**
10	or/5-6,9
11	4 use medal
12	10 use oemezd
13	conference abstract.pt.
14	12 not 13
15	11 or 14
16	remove duplicates from 15

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	January 2018
Keywords:	Akynzeo (netupitant/palonosetron), acute/delayed chemotherapy-induced nausea and/or vomiting indication
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: a practical tool for searching health-related grey literature (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Hesketh et al. 2017 [34]	Post hoc subgroup analysis
Jordan et al. 2018[35]	Not randomized controlled trial (RCT)
Abdel-Rahman 2016[36]	Not RCT
D'Agostino et al. 2015[37]	Not RCT
Shi et al. 2016[38]	Post hoc subgroup analysis
Jordan et al. 2016[16]	Duplicate
van der Vorst et al. 2015[39]	Not RCT
Aapro et al. 2016[40]	Not RCT
No author 2016a[41]	Not RCT
No author 2016b[42]	Not RCT
Aapro et al. 2017[43]	Post hoc subgroup analysis
Rugo et al. 2017[44]	Not RCT

Appendix 4: Detailed Outcome Data

Table 15: Key Efficacy Outcomes in Multiple-Cycle Extension Phase

	NETU 8-18		NETU 10-29	
	Cycle 2			
Complete Response	**NEPA**	**PALO**	**NEPA**	**APR / PALO**
Delayed Phase				
n/N (%)	519/635 (81.7)	448/651 (68.8)	243/280 (86.8)	79/96 (82.3)
Absolute difference (%) (95% CI)	12.9 (8.2 to 17.5)		4.5 (–3.3 to 14.0)	
NNT	8		–	
Acute Phase				
n/N (%)	571/635 (89.9)	545/651 (83.7)	270/280 (96.4)	88/96 (91.7)
Absolute difference (%) (95% CI)	6.2 (2.5 to 9.9)		4.8 (–0.2 to 12.2)	
NNT	17		–	
	Cycle 3			
Complete Response ()	**NEPA**	**PALO**	**NEPA**	**APR / PALO**
Delayed Phase				
n/N (%)	509/598 (85.1)	451/606 (74.4)	237/259 (90.0)	76/90 (84.4)
Absolute difference (95% CI)	10.7 (6.2 to 15.2)		3.7 (–2.9 to 12.5)	
NNT	10		–	
Acute Phase				
n/N (%)	548/598 (91.6)	508/606 (83.8)	249/259 (96.1)	86/90 (95.6)
Absolute difference (95% CI)	7.8 (4.1 to 11.5)		0.6 (–3.5 to 7.2)	
NNT	13		–	
	Cycle 4			
Complete Response	**NEPA**	**PALO**	**NEPA**	**APR / PALO**
Delayed Phase				
n/N (%)	471/551 (85.5)	433/560 (77.3)	212/233 (91.0)	71/81 (87.7)
Absolute difference (95% CI)	8.2 (3.6 to 12.7)		3.3 (–3.7 to 12.7)	
NNT	13		–	
Acute Phase				
n/N (%)	504/551 (91.5)	486/560 (86.8)	225/233 (96.6)	78/81 (96.3)
Absolute difference (95% CI)	4.7 (1.0 to 8.4)		0.3 (–3.7 to 7.1)	
NNT	22		–	
	Cycle 5			
Complete Response	**NEPA**	**PALO**	**NEPA**	**APR / PALO**
Delayed Phase				
n/N (%)	233/272 (85.7)	199/249 (79.9)	145/156 (92.9)	49/57 (86.0)
Absolute difference	5.7 (–0.7 to 12.3)		7.0 (–1.5 to 18.7)	

	NETU 8-18		NETU 10-29	
(95% CI)				
NNT	–			
Acute Phase				
n/N (%)	242/272 (89.0)	214/249 (85.9)	148/156 (94.9)	56/57 (98.2)
Absolute difference (95% CI)	3.0 (–2.7 to 8.8)		–3.4 (–8.3 to 4.6)	
NNT	–		–	
	Cycle 6			
Complete Response	**NEPA**	**PALO**	**NEPA**	**APR / PALO**
Delayed Phase				
n/N (%)	175/197 (88.8)	159/191 (83.2)	114/124 (91.9)	38/44 (86.4)
Absolute difference (95% CI)	5.6 (–1.3 to 12.6)		5.6 (–3.9 to 19.1)	
NNT	–			
Acute Phase				
n/N (%)	177/197 (89.8)	164/191 (85.9)	118/124 (95.2)	41/44 (93.2)
Absolute difference (95% CI)	4.0 (–2.6 to 10.6)		2.0 (–5.0 to 13.7)	
NNT	–		–	

APR = aprepitant; CI = confidence interval; NEPA = netupitant/palonosetron; NNT = number needed to treat; PALO = palonosetron.

Source: Clinical Study Reports for NETU 8-18[19] and 10-29.[20]

Appendix 5: Detailed Risk of Bias Assessment

Table 16: Risk of Bias Assessment

DOMAIN	NETU 8-18	NETU 10-29	NETU 12-07	NETU 7-07
Randomization	Low Block randomization with computer	Low Block randomization with computer program	Low Block randomization with computer program	Low Automated randomization
Allocation concealment	Low Automated system allocated patient and assigned “study kit”	Low Allocation by automated system, registered assignment as patient allocated / received kit	Unclear Not enough information to judge	Low Appears patient allocated by system and group registered then kit provided
Blinding of participants	Low Drugs identical in colour and appearance	Low Drugs identical in appearance, shape, smell	Low Identical kits and placebo IV used	Low Kits and pills identical
Blinding of outcome assessment	Low Patients blind and outcome assessment based on patient diary	Low Patients blind and outcome assessment based on patient diary	Low Based on patient diary, patients blinded	Low Based on patient diary, patients blinded
Incomplete outcome data	Low 99% completed cycle 1 in both groups; therefore, low dropout rate. Any missing data imputed as treatment failure	Low Low dropout; 98% completed cycle 1. Full analysis set included 100% of patients in NEPA arm and 99% in APR	Low Low dropout rate about 2%; patients not included in full analysis set higher in NEPA group but difference not large; 1.2% versus 0.2% missing data	Low Dropout low overall; slightly higher in NEPA group; more patients did not receive study drug versus other groups but discontinuations after treatment similar; missing data classified as not having CR
Selective reporting	Low Outcomes reported as described	Low Outcomes reported as described	High Many subgroup analyses were poorly described in Methods: “When significant interactions were found, additional analyses were run to understand the reason for the heterogeneity.”	Low Outcomes as reported in Methods section
Other bias	Low	Low	Low	Low

APR = aprepitant; CR = complete response; NEPA = netupitant/palonosetron.

Appendix 6: Summary of Mixed-Treatment Comparisons

Introduction

The following is a summary and critical appraisal of the methods and main findings of a manufacturer-provided indirect comparison to evaluate the comparative efficacy of a fixed-dose combination of netupitant 300 mg/palonosetron 0.5 mg (NEPA; Akynzeo) versus various comparators in the treatment of chemotherapy-induced nausea and vomiting (CINV) in adult patients undergoing highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC).[45]

Methods

Eligibility Criteria

A systematic literature search was performed using the following electronic databases: MEDLINE, Embase, the Cochrane Collaboration, and Health Technology Assessment (HTA) in Cochrane (search strategy was provided). The literature search was limited to English-language articles published between 2000 and August 28, 2013 (expanded to January 9, 2014, for studies on olanzapine). Screening and study selection (conducted in duplicate) was based on pre-specified inclusion and exclusion criteria (Table 17). Data were extracted based on a pre-specified Excel spreadsheet. All included randomized controlled trials (RCTs) were evaluated for quality based on the UK National Institute for Health and Care Excellence (NICE) checklist with the quality assessment criteria adopted from the guidance for evidence submission published by NICE.[46] The indirect comparison did not describe whether the data extraction and quality assessment of included studies were accomplished by two researchers independently.

The main inclusion criteria for the systematic review were blinded RCT (phase II, III, or IV) with ≥ 50 patients; adult (≥ 18 years) cancer patients receiving HEC or MEC for CINV; RCT including at least one of the following antiemetics: 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists (RAs) including palonosetron (PALO), ondansetron (OND), granisetron (GRAN), tropisetron, dolasetron, metoclopramide, or ramosetron; neurokinin-1 receptor (NK_1) RAs including aprepitant (APR), fosaprepitant (FOS), casopitant, ezlopitant, netupitant, or vestipitant; and other drugs including olanzapine, levonantradol, lorazepam, nabilone, dronabinol, and dexamethasone (DEX); studies reporting at least complete response (CR); and studies published in English. The exclusion criteria were duplicate citation, studies not defining CR, and any study that did not meet the inclusion criteria. The interventions of interest were NEPA (+ DEX) compared with any of the aforementioned antiemetics or placebo. The main outcomes of interest for the indirect comparison included CR, complete protection (CP), and total control (TC) reported for acute phase (day 1), delayed phase (days 2 to 5), and overall phase (day 1 to day 5) (Table 17).

Table 17: Pre-specified PICOS Defining the Inclusion and Exclusion Criteria for the Manufacturer-Provided Indirect Comparison

Process	Key questions	Details
P (Patient Population)	For which group do we need information?	Human adults (≥ 18 years) cancer patients receiving highly or moderately emetogenic chemotherapy
I (Intervention or Exposure)	What medical event or treatment do we need to study the effect of?	Studies assessing the efficacy or safety of one of the following antiemetics: • **5 HT-3s**: palonosetron, odansetron, granisetron, tropisetron, dolasetron, metoclopramide, ramosetron • **NK1s**: aprepitant, fosaprepitant, casopitant, ezlopitant, netupitant, vestipitant • **Other**: Olanzapine, levonantradol, lorazepam, nabilone, dronabinol, dexamethasone
C (Comparators)	What interventions are considered as comparators to the intervention of interest?	Placebo or active comparator
O (Outcomes)	What is the effect of the intervention and the comparators on the outcomes of interest for this project?	• At least **complete response**, defined as no emesis/vomiting and no rescue medication • Complete protection, partial response, complete control, total control, time to first emetic episode, time to use of rescue medication, time to treatment failure
S (Study Design)	What study designs are appropriate to consider, given the type of outcomes of interest?	Blinded, randomized controlled trials (≥ Phase 2) with more than 50 patients

5-HT3 = 5-hydroxytryptamine-3; NK1 = neurokinin-1.
Source: NEPA mixed-treatment comparison report.[45]

Indirect Comparison

A feasibility assessment (evaluation of available evidence and a heterogeneity assessment) was performed to assess whether an indirect comparison was feasible. However, no details were provided describing the methods used or findings of the feasibility assessment. Nevertheless, following the feasibility assessment, it was decided that an indirect comparison within a frequentist framework would be conducted for patients receiving MEC (the MEC population) because of the small number of trials identified for inclusion (n = 4). A Bayesian mixed-treatment comparison (MTC) in the HEC and anthracycline/ cyclophosphamide (AC) population was conducted. The outcomes reported in both analyses were CR, CP, and TC (i.e., dichotomous outcomes) because it was reported that there were insufficient data for NEPA and comparators to include continuous outcomes of interest, such as use of rescue medication. A fixed-effects model was used exclusively for the indirect comparison of studies on MEC populations due to the small sample size. Both random-effects and fixed-effects models were evaluated for the MTC in patients receiving HEC; selection of the model was based on goodness-of-fit, as determined based on the deviance information criterion (DIC). Vague prior distributions were used for the Bayesian MTC.

A formal statistical assessment of heterogeneity and consistency could not be performed because of sparsely populated networks with limited closed loops. A qualitative assessment to identify potential effect modifiers with respect to clinical and methodological differences between studies was performed, although no description was provided as to the details of the assessment or the results. In the case that a random-effects model could be used in the MTC, between-study variance (tau-squared) was calculated to assess the degree of heterogeneity.

Several assumptions were made for constructing the analysis networks with respect to variability in interventions (i.e., differences in dose, frequency, and route of administration) in the included studies. For the acute, delayed, and overall phases, the following was assumed:

- Efficacy of treatments in the HEC and AC populations was similar.
- Variation in dexamethasone dose had no impact on efficacy.
- There is no difference in efficacy between OND 32 mg and OND 16 mg, nor any difference in efficacy between different doses of PALO (0.25 mg versus 0.75 mg) or GRAN (1 mg versus 3 mg oral and 10 mcg/kg versus 40 mcg/kg intravenous [IV]).
- The route of administration (IV versus oral) does not affect efficacy.

For delayed and overall phases, the following additional two assumptions were made:

- Efficacy between doses of APR administered during the acute and delayed phases was similar.
- There is no added benefit of combining a 5-HT3RA with a NK1RA during the delayed phase.

The primary analysis in the HEC/AC population incorporated treatments separately and unadjusted for potential effect modifiers. The following secondary analyses were done:

- Univariate meta-regression with age, percentage of females, and chemotherapy type as covariate
- Treatments pooled by class
- Subgroup analysis in the HEC population without the AC population.

The primary analysis in the MEC population compared NEPA + DEX with 5-HT_3RA + DEX for CR. A secondary analysis compared NEPA with individual 5-HT_3RAs for CR. No meta-regression or subgroup analyses were performed for the MEC population because of the small sample size of trials.

For each analysis, the mean odds ratio (OR) was presented with 95% confidence interval (CI) (for MEC indirect comparison) or 95% credible interval (CrI; for HEC and AC analyses). The two end points of the credible interval were approximated by the 2.5% and 97.5% percentiles of the posterior distribution in WinBUGS.

Results

Study and Patient Characteristics

A total of 37 studies were identified in the systematic review. Only minimal information was reported regarding study characteristics, and no details about patient characteristics from the included studies were summarized in the MTC. Sample sizes (N) of the included studies

ranged from 53 to 1,933 patients. Because of insufficient data, not all outcomes and all time periods (acute, delayed, or overall phases) could be assessed for the various treatment comparisons. The most reported outcome was CR.

Efficacy Outcomes

Key results for the indirect comparison in the MEC population and MTC in the HEC/AC population are summarized in Table 18.

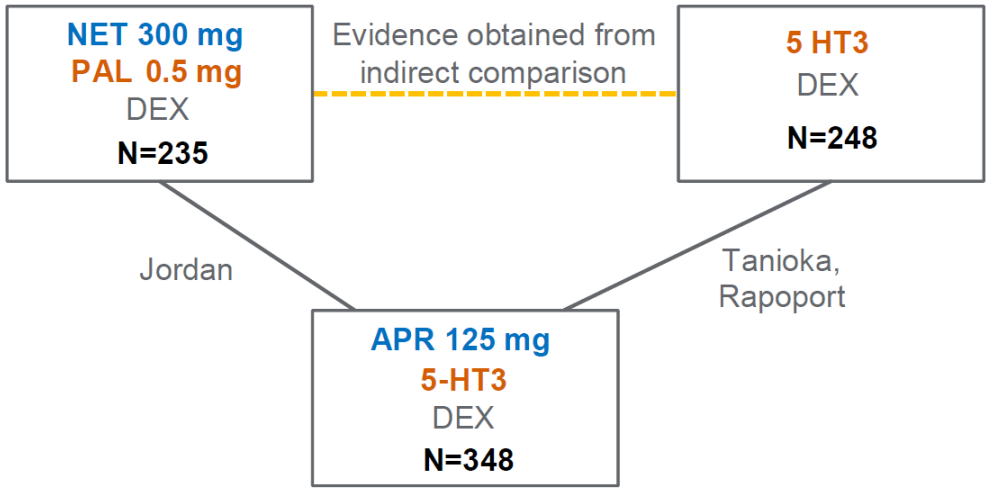
1. Complete response

1.1 Moderately emetogenic chemotherapy population

1.1.1 Moderately emetogenic chemotherapy — acute phase

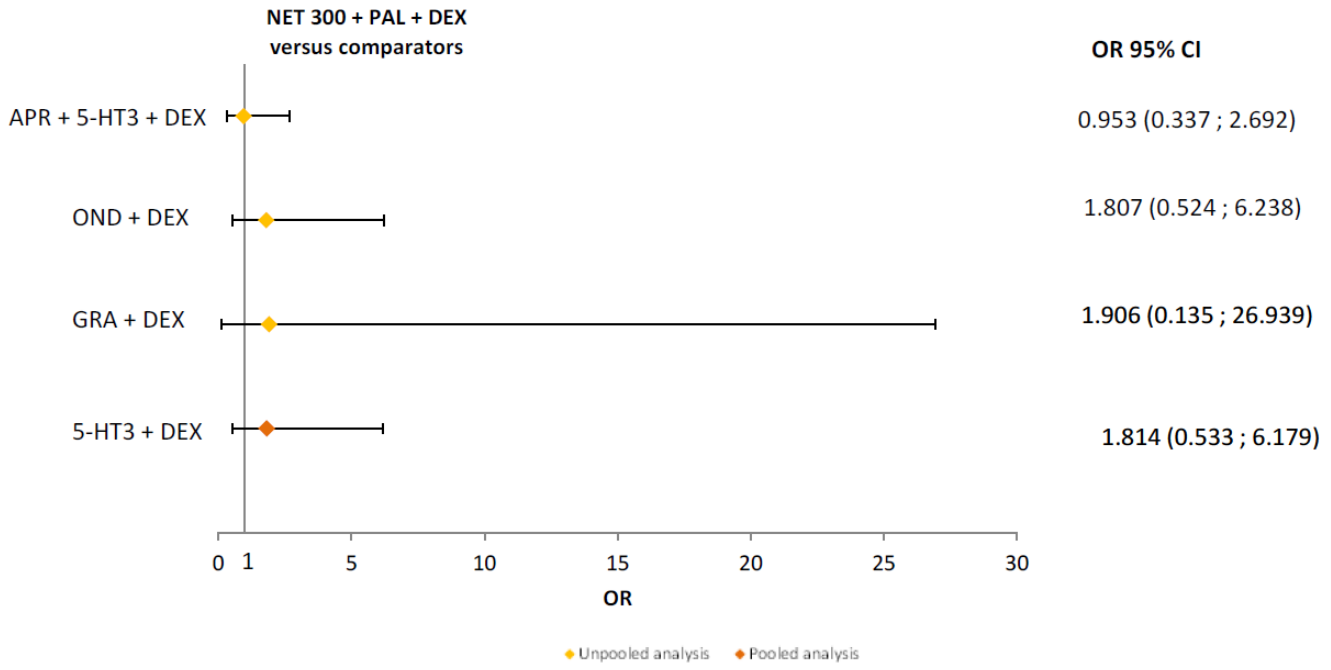
The indirect comparisons for CR in the MEC acute phase population are presented in Figure 2. NEPA + DEX was not statistically significantly different from APR + 5-HT_3RA + DEX for the odds of achieving CR in the acute phase (OR 0.95; 95% CI, 0.34 to 2.69). Compared with 5-HT_3RAs + DEX (individual or pooled), patients treated with NEPA + DEX did not have statistically significantly different odds of CR in the acute phase (Figure 3, Table 18).

Figure 2: Treatment Nodes for Complete Response: Moderately Emetogenic Chemotherapy Acute Phase Indirect Comparison



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; DEX = dexamethasone; NET: netupitant; PAL: palonosetron.
Source: NEPA MTC report.[45]

Figure 3: Netupitant/Palonosetron Versus Comparators for Complete Response: Moderately Emetogenic Chemotherapy Acute Phase



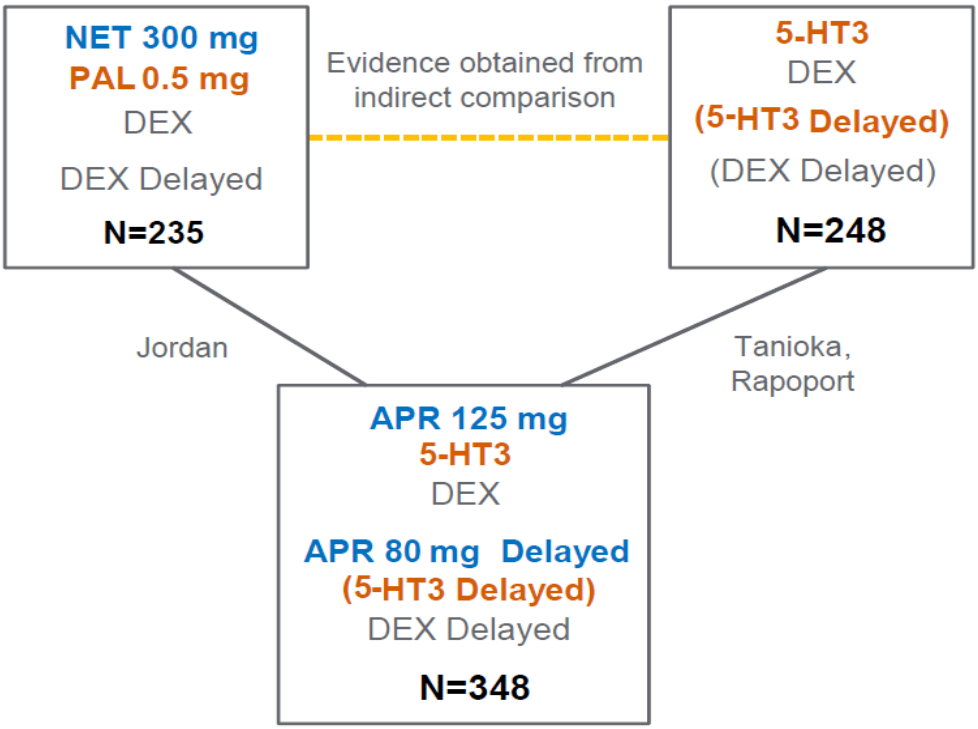
5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CI = confidence interval; DEX = dexamethasone; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

1.1.2 Moderately emetogenic chemotherapy — delayed phase

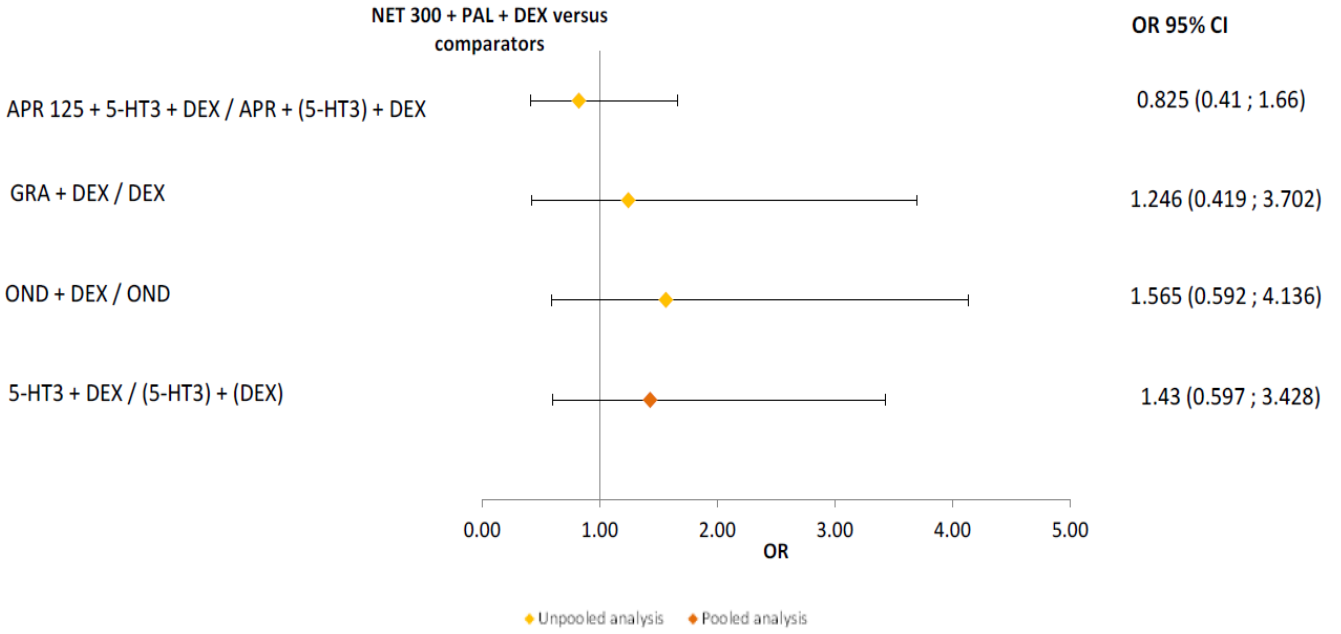
The indirect comparisons for CR in the MTC delayed phase population are presented in Figure 4. The odds of CR in the delayed phase for patients treated with NEPA + DEX versus APR + 5-HT_3RA + DEX were not statistically different (OR 0.83; 95% CI, 0.41 to 1.66; Figure 5). Likewise, no statistically significant differences were found for the odds of CR with NEPA + DEX compared with
5-HT_3RA + DEX (Figure 5 and Table 18).

Figure 4: Treatment Nodes for Complete Response: Moderately Emetogenic Chemotherapy Delayed Phase Indirect Comparison



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; DEX = dexamethasone; NET = netupitant; PAL = palonosetron.
Source: NEPA MTC report.[45]

Figure 5: Netupitant/Palonosetron Versus Comparators for Complete Response: Moderately Emetogenic Chemotherapy Delayed Phase



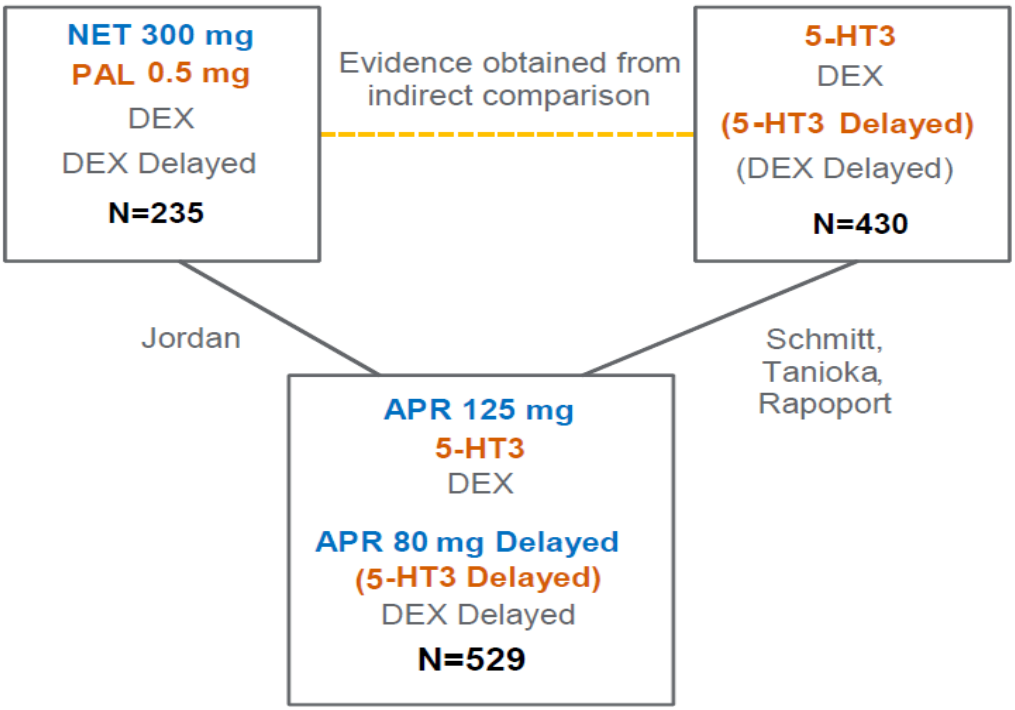
5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CI = confidence interval; DEX = dexamethasone; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

1.1.3 Moderately emetogenic chemotherapy — overall phase

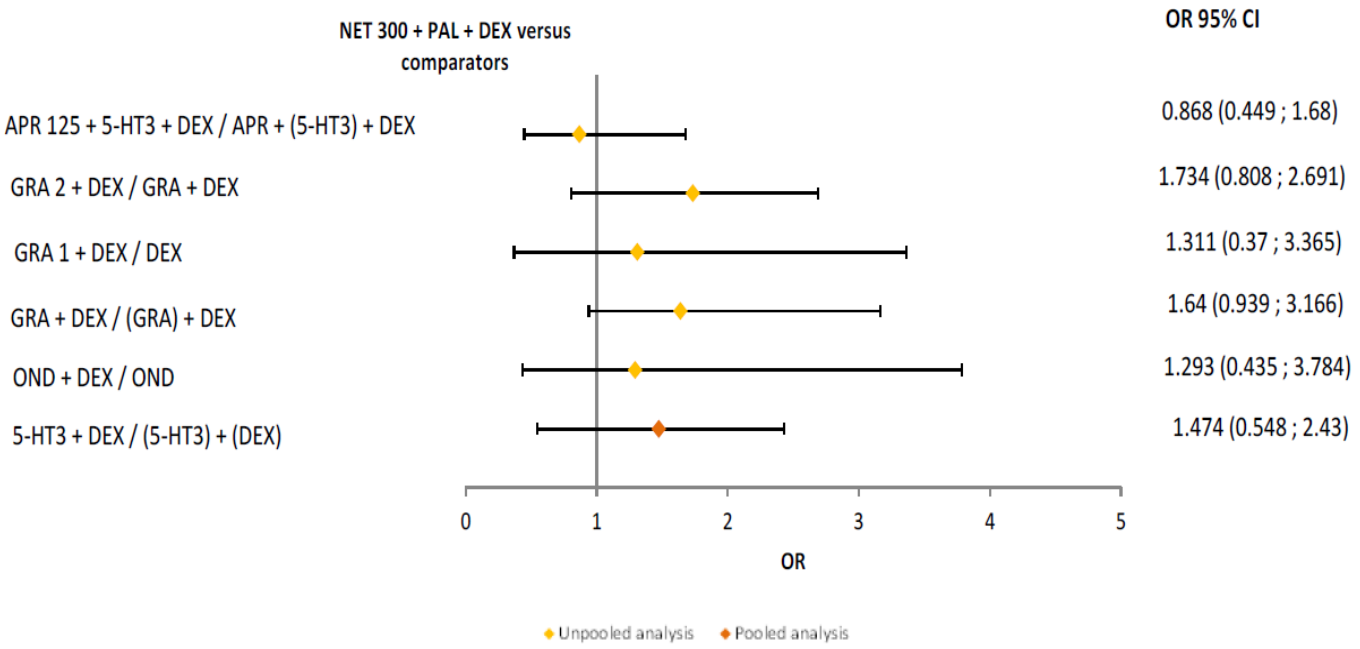
The indirect comparisons for CR in the MTC overall phase population are presented in Figure 6. For the overall phase, there was no statistically significant difference in the odds of CR for patients treated with NEPA + DEX compared with patients treated with APR + 5-HT_3RA + DEX (OR 0.87; 95% CI, 0.45 to 1.68; Figure 7). There was no statistically significant difference in the odds of CR for the comparisons of NEPA + DEX with 5-HT_3RA + DEX (Figure 7 and Table 18).

Figure 6: Treatment Nodes for Complete Response: Moderately Emetogenic Chemotherapy Overall Phase Indirect Comparison



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; DEX = dexamethasone; NET = netupitant; PAL = palonosetron.
Source: NEPA MTC report.[45]

Figure 7: Netupitant/Palonosetron Versus Comparators for Complete Response: Moderately Emetogenic Chemotherapy Overall Phase



5-HT3 = 5-HT$_3$ receptor antagonist; APR = aprepitant; CI = confidence interval; DEX = dexamethasone; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

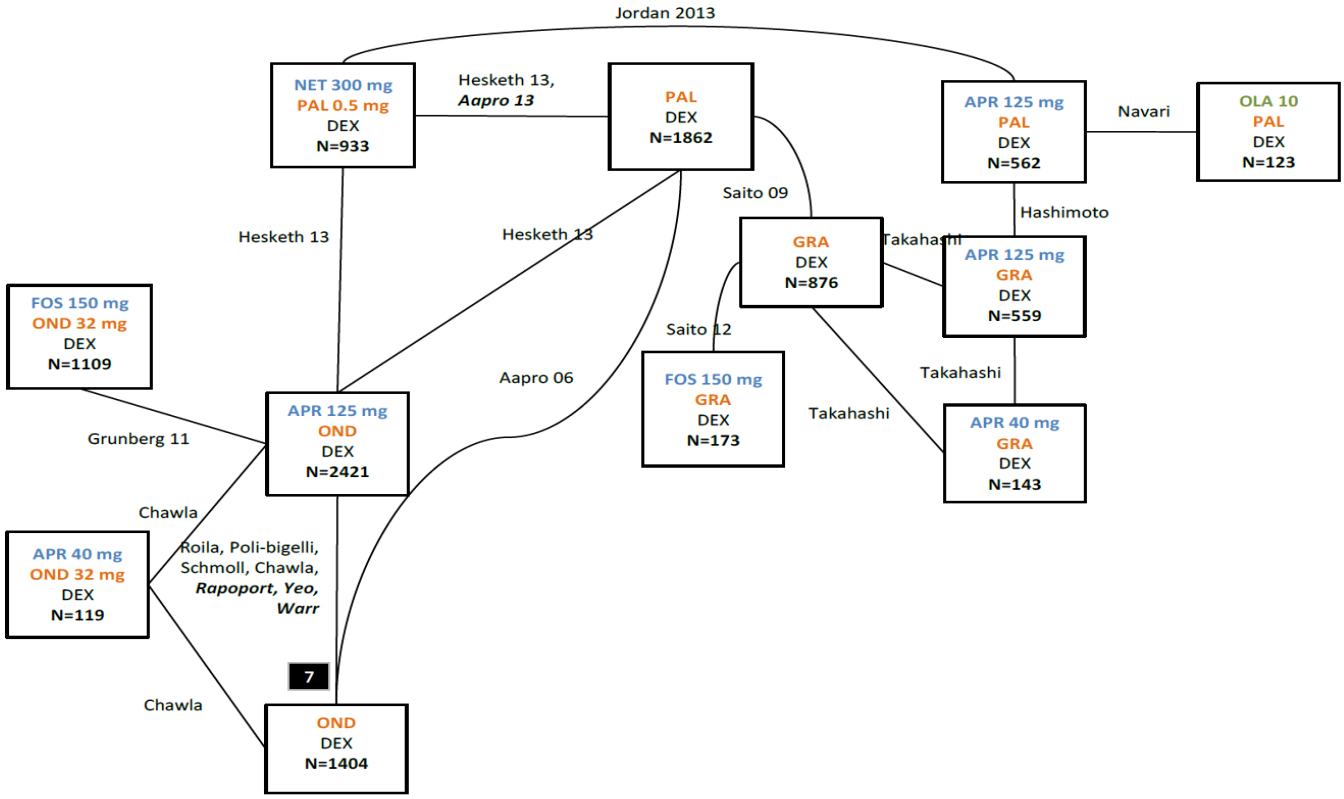
1.2. Highly emetogenic chemotherapy and anthracycline/cyclophosphamide

1.2.1 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide — Acute phase

The network for CR during the acute phase for the HEC and AC population is shown in Figure 8, with AC studies highlighted in bold italics. It was reported that, regardless of whether 5-HT$_3$RA therapies were pooled or unpooled, there were no differences in odds of CR for patients treated with NEPA + DEX compared with any triple-drug therapy (APR or FOS + 5-HT$_3$RA + DEX;

Figure 9, Table 18). However, patients treated with NEPA + DEX were found to have higher odds of CR in the acute phase compared with those treated with PALO + DEX (mean OR 1.68; 95% CrI, 1.05 to 3.74). Patients treated with NEPA + DEX had higher odds of achieving CR compared with those treated with a 5-HT$_3$RA + DEX (mean OR 1.70; 95% CrI, 1.06 to 3.68) (Figure 9 and Table 18).

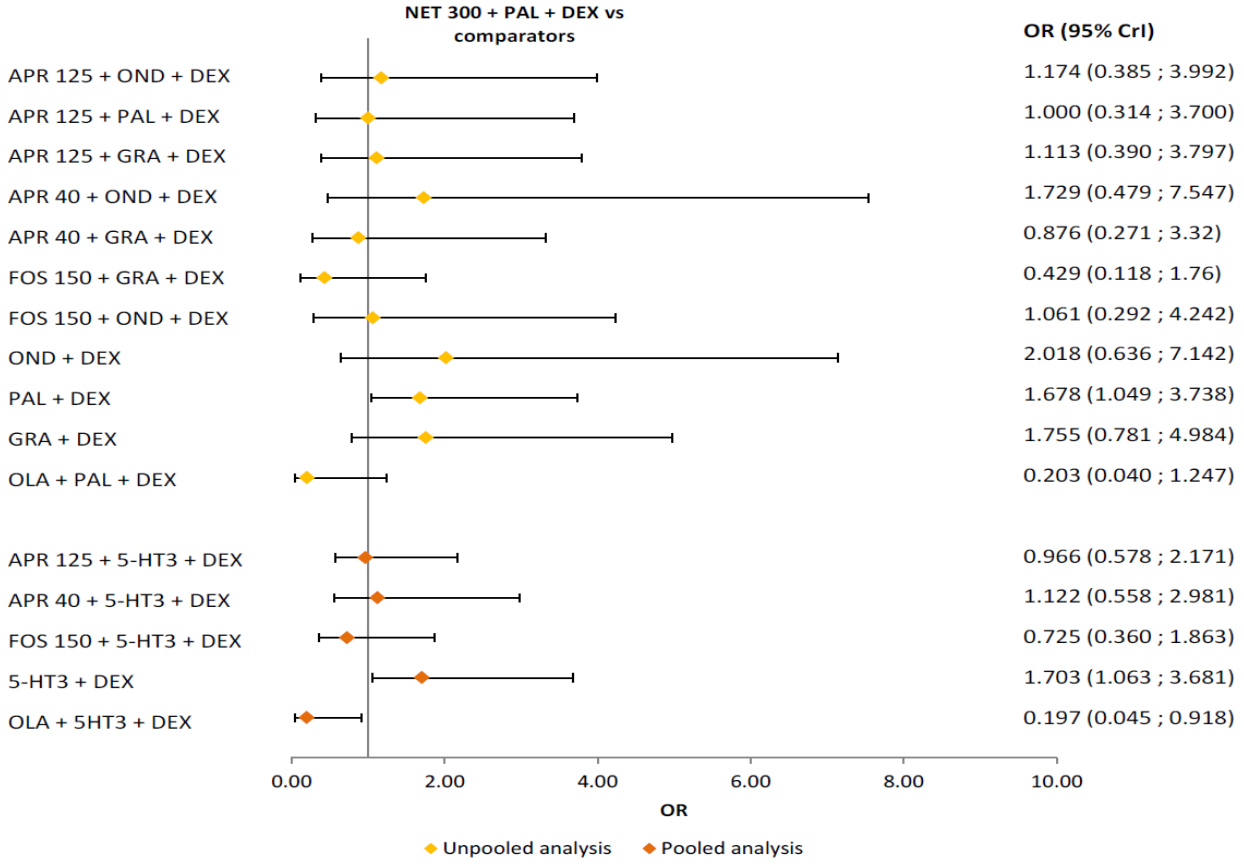
Figure 8: Network for Complete Response: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Acute Phase



5-HT3 = 5-HT_3 receptor antagonist; AC = anthracycline/cyclophosphamide; APR = aprepitant; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OLA = olanzapine; OND = ondansetron; PAL = palonosetron.

Source: NEPA MTC report.[45]

Figure 9: Netupitant/Palonosetron Versus Comparators for Complete Response: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Acute Phase (Random Effects)



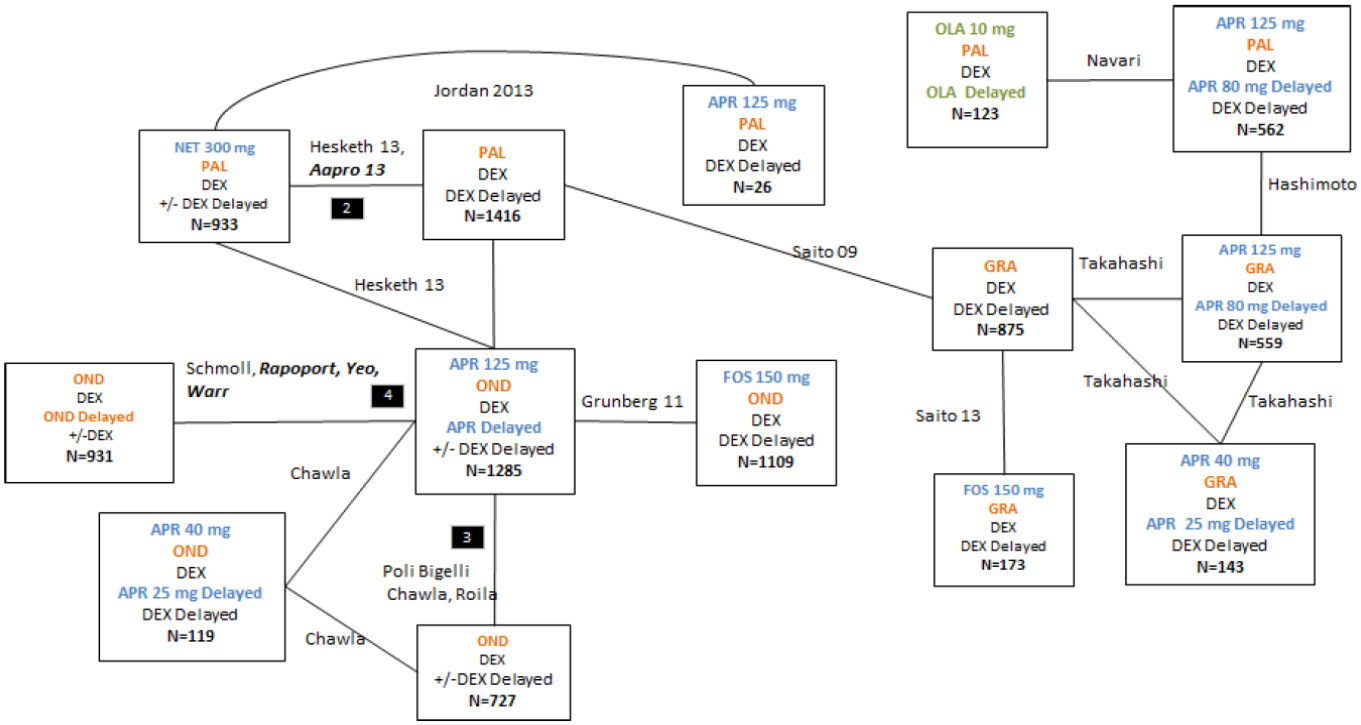
5-HT3 = 5-HT$_3$ receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OLA = olanzapine; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

1.2.2 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide — delayed phase

The network for CR for the delayed phase is shown in Figure 10, with AC studies highlighted in bold italics. In the analysis with unpooled 5-HT$_3$RA therapies, no statistically significant difference was reported in comparisons of NEPA + DEX with any triple combination of APR or FOS, 5-HT$_3$RAs and DEX (Figure 11,Table 18). Patients treated with NEPA + DEX had greater odds of CR during the delayed phase relative to PALO + DEX (OR 1.96; 95% CrI, 1.19 to 3.58) and GRAN + DEX (OR 4.01; 95% CrI, 1.95 to 10.02; Figure 11). Overall, results were consistent between the pooled and unpooled 5-HT$_3$RA analysis. No statistically significant difference was found between NEPA and unpooled doses of APR or FOS + 5-HT$_3$RA + DEX. Consistent with the unpooled 5-HT$_3$RA analysis, NEPA + DEX had a higher odds of CR than pooled 5-HT$_3$RA + DEX (OR 2.11; 95% CrI, 1.40 to 3.68; Figure 11 and Table 18).

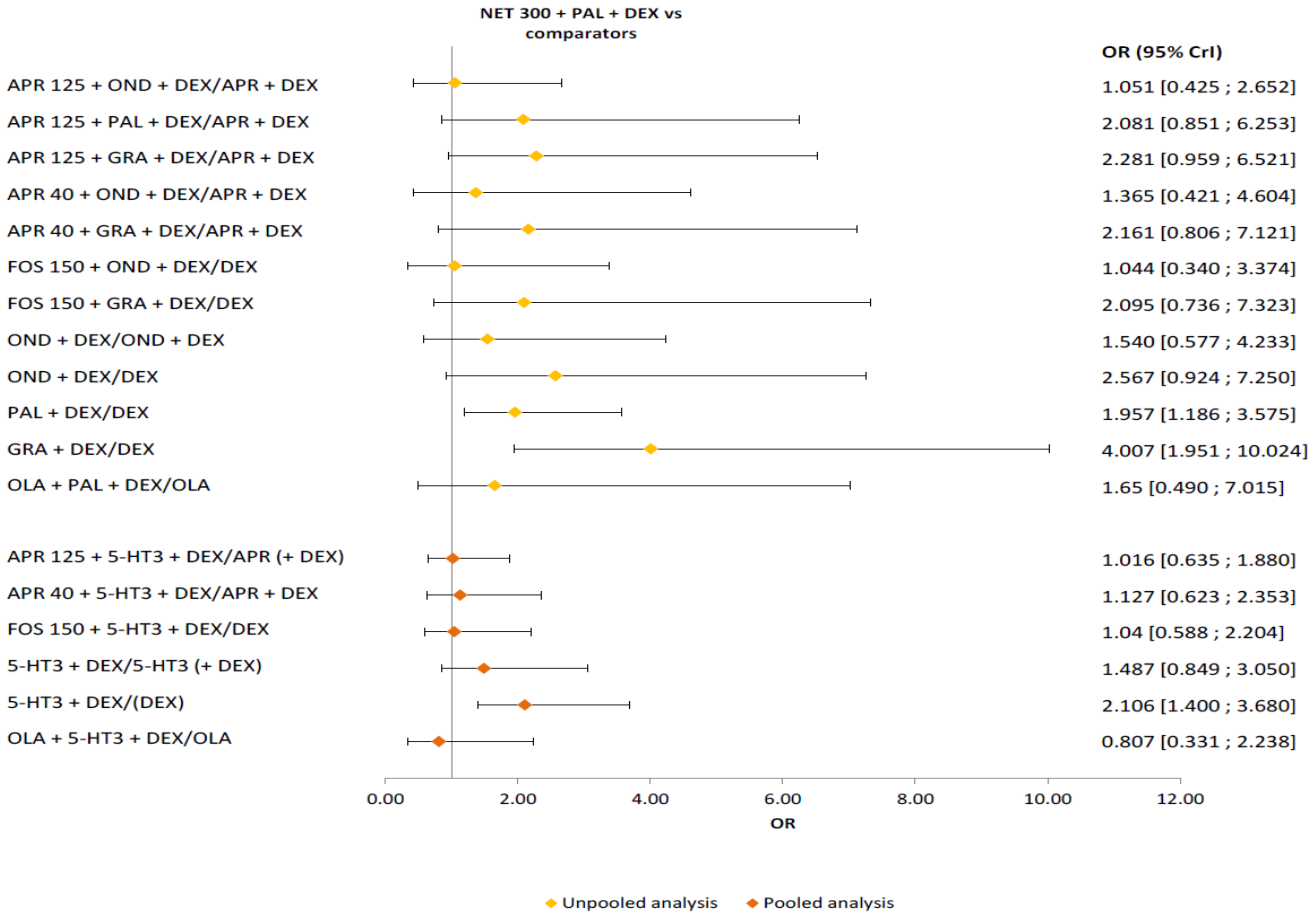
Figure 10: Network for Complete Response: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Delayed Phase



5-HT3 = 5-HT$_3$ receptor antagonist; AC = anthracycline/cyclophosphamide; APR = aprepitant; DEX = dexamethasone; GRA = granisetron; NET = netupitant; OLA = olanzapine; OND = ondansetron; PAL = palonosetron.

Source: NEPA MTC report.[45]

Figure 11: Netupitant/Palonosetron Versus Comparators for Complete Response: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Delayed Phase (Random Effects)



5-HT3 = 5-HT$_3$ receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OLA = olanzapine; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

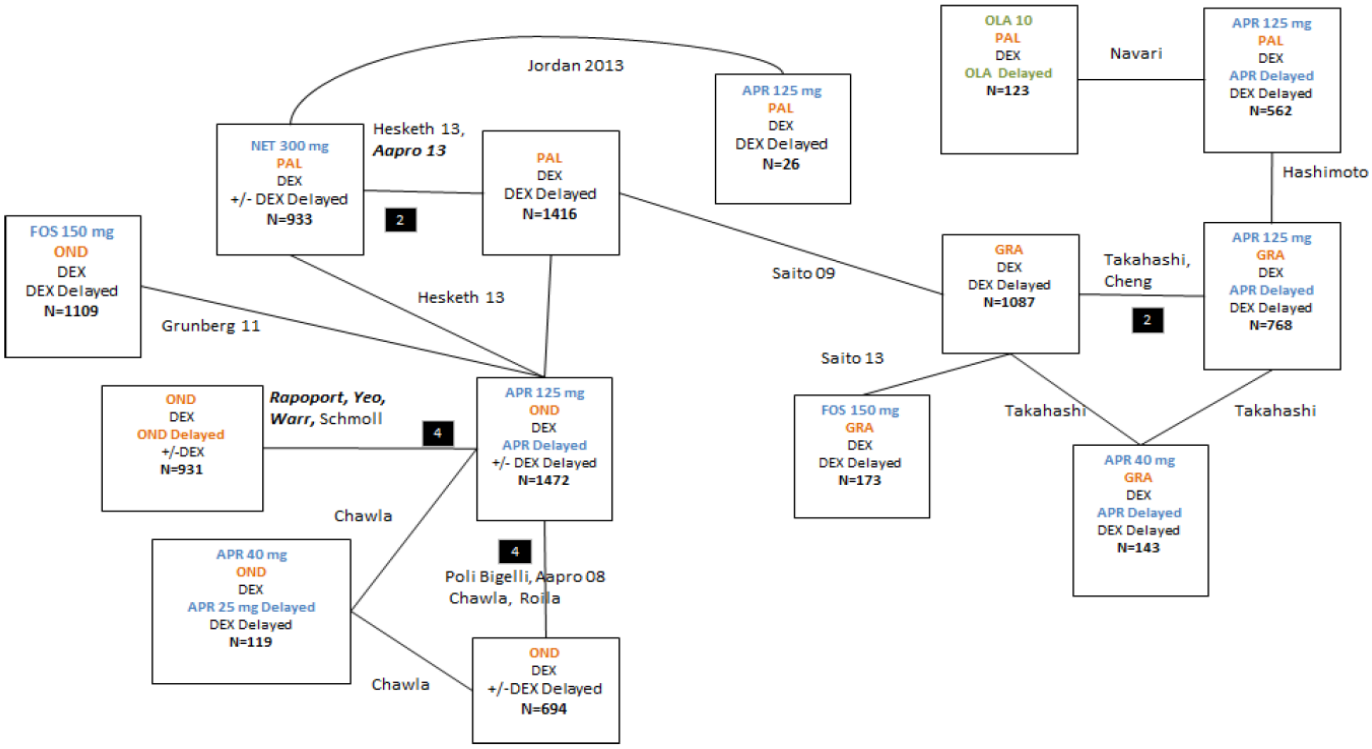
Source: NEPA MTC report.[45]

1.2.3 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide — overall phase

The network for CR in the overall phase is presented in Figure 12, with AC studies highlighted in bold italics.

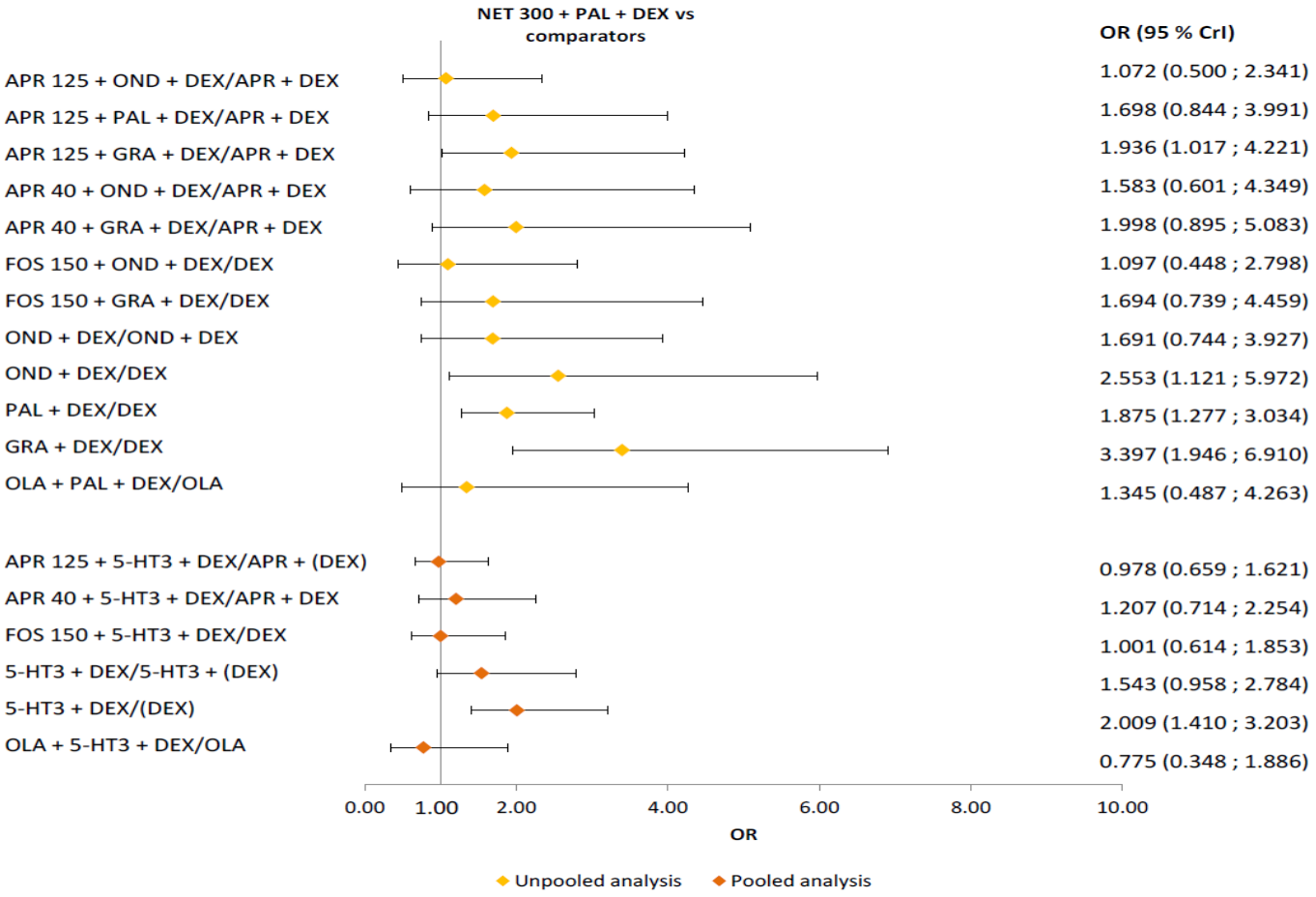
In the analysis of CR for the overall phase with unpooled effect of 5-HT$_3$RA, NEPA + DEX showed higher odds of CR than APR 125 + GRAN + DEX (OR 1.94; 95% CrI, 1.02 to 4.22). No statistically significant difference was demonstrated between NEPA and other NK$_1$RAs + 5-HT$_3$RAs + DEX combination therapies (Figure 13). NEPA + DEX showed higher odds than OND, PALO, or GRAN in combination with DEX. No statistically significant difference was found between NEPA + DEX and unpooled APR or FOS + 5-HT$_3$RAs + DEX. Consistent with the unpooled 5-HT$_3$RA analysis, NEPA + DEX were shown to be more effective than 5-HT$_3$RA + DEX strategies (OR 2.01; 95% CrI, 1.41 to 3.20; Figure 13 and Table 18).

Figure 12: Network for Complete Response: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Overall Phase



APR = aprepitant; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OLA = olanzapine; OND = ondansetron; PAL = palonosetron.
Source: NEPA MTC report.[45]

Figure 13: Netupitant/Palonosetron Versus Comparators for Complete Response: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Overall Phase (Random Effects)



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OLA = olanzapine; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

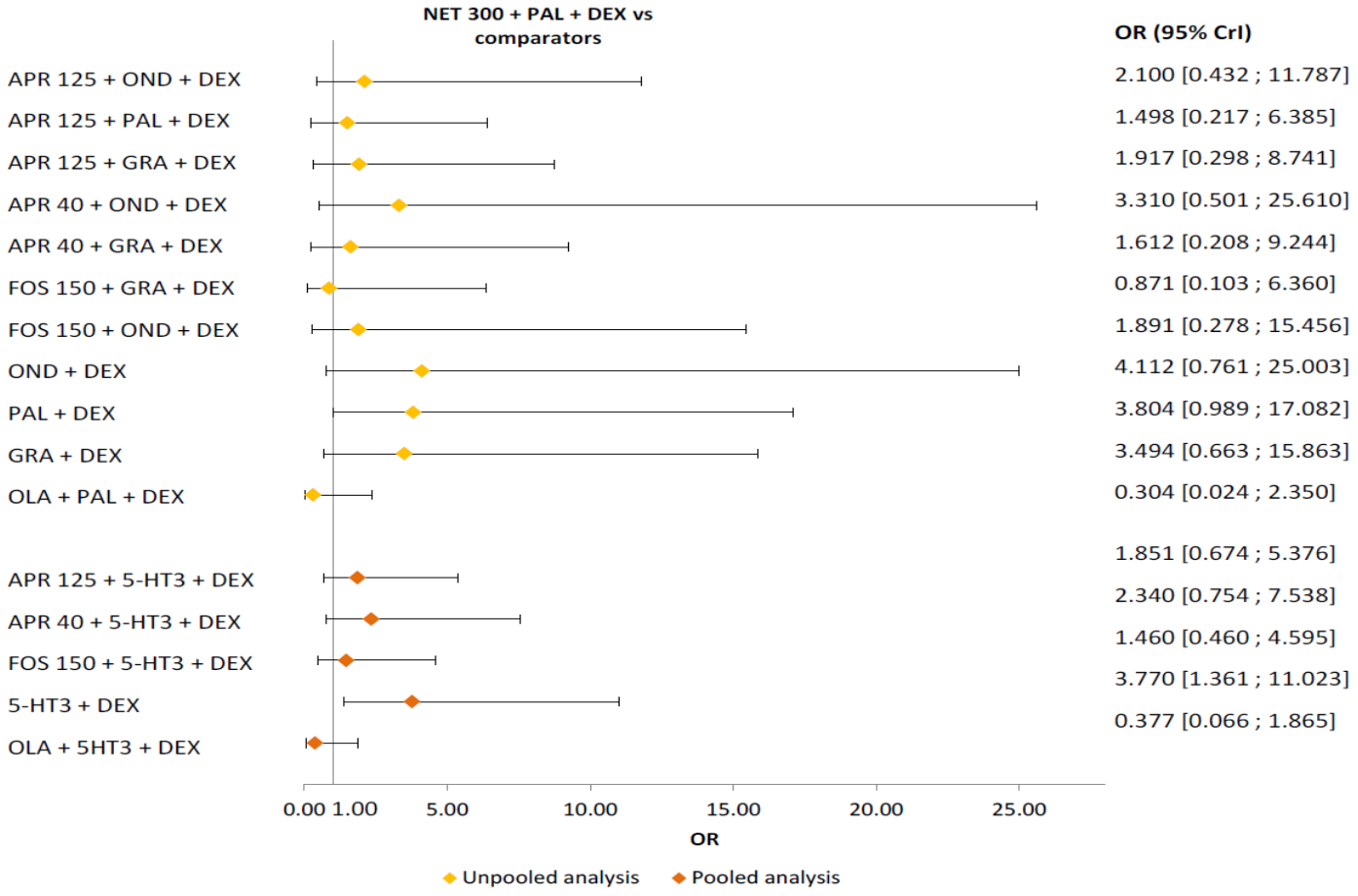
1.3 Highly emetogenic chemotherapy

A subgroup analysis was undertaken for the HEC population only (i.e., excluding AC studies).

1.3.1 Highly emetogenic chemotherapy — Acute phase

In the analysis with unpooled effect of 5-HT_3RA, no statistically significant difference in the odds of CR was found between NEPA and any comparator (Figure 14). The analysis with pooled 5-HT_3RA therapies showed that no statistically significant difference was present between NEPA and triple-drug therapy regimens (APR or FOS + 5-HT_3RA + DEX). Higher odds of CR in the acute phase were found for patients treated with NEPA + DEX compared with 5-HT_3RA + DEX (OR 3.77; 95% CrI, 1.36 to 11.02; Figure 14 and Table 18).

Figure 14: Netupitant/Palonosetron Versus Comparators for Complete Response: Highly Emetogenic Chemotherapy Acute Phase (Random Effects)



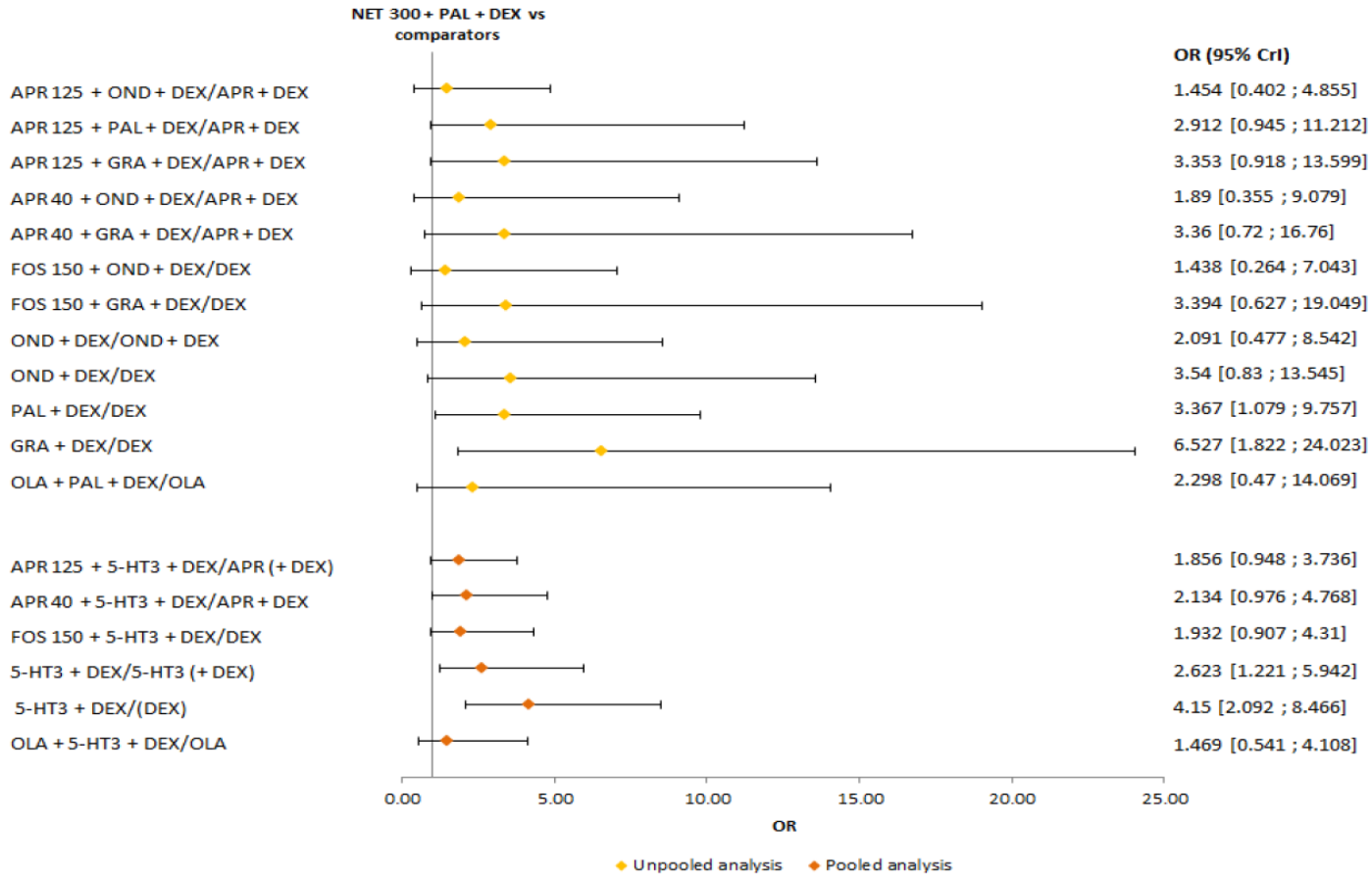
5-HT3 = 5-HT$_3$ receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OLA = olanzapine; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

1.3.2 Highly emetogenic chemotherapy — delayed phase

In the analysis with unpooled effect of 5-HT$_3$RAs, there was no statistically significant difference between NEPA + DEX and NK$_1$RA + 5-HT$_3$RA comparator regimens (Figure 15). Higher odds of CR were found for patients treated with NEPA + DEX compared with PALO + DEX (OR 3.37; 95% CrI, 1.08 to 9.76) or GRAN + DEX (OR 6.53; 95% CrI, 1.82 to 24.02). In the pooled 5-HT$_3$RA analysis, no statistically significant difference was found between the NEPA strategy and other triple-regimen comparators. There were higher odds of CR for patients treated with NEPA + DEX compared with 5-HT$_3$RA + DEX (OR 4.15; 95% CrI, 2.09 to 8.47; Figure 15 and Table 18).

Figure 15: Netupitant/Palonosetron Versus Comparators for Complete Response: Highly Emetogenic Chemotherapy Delayed Phase (Random Effects)



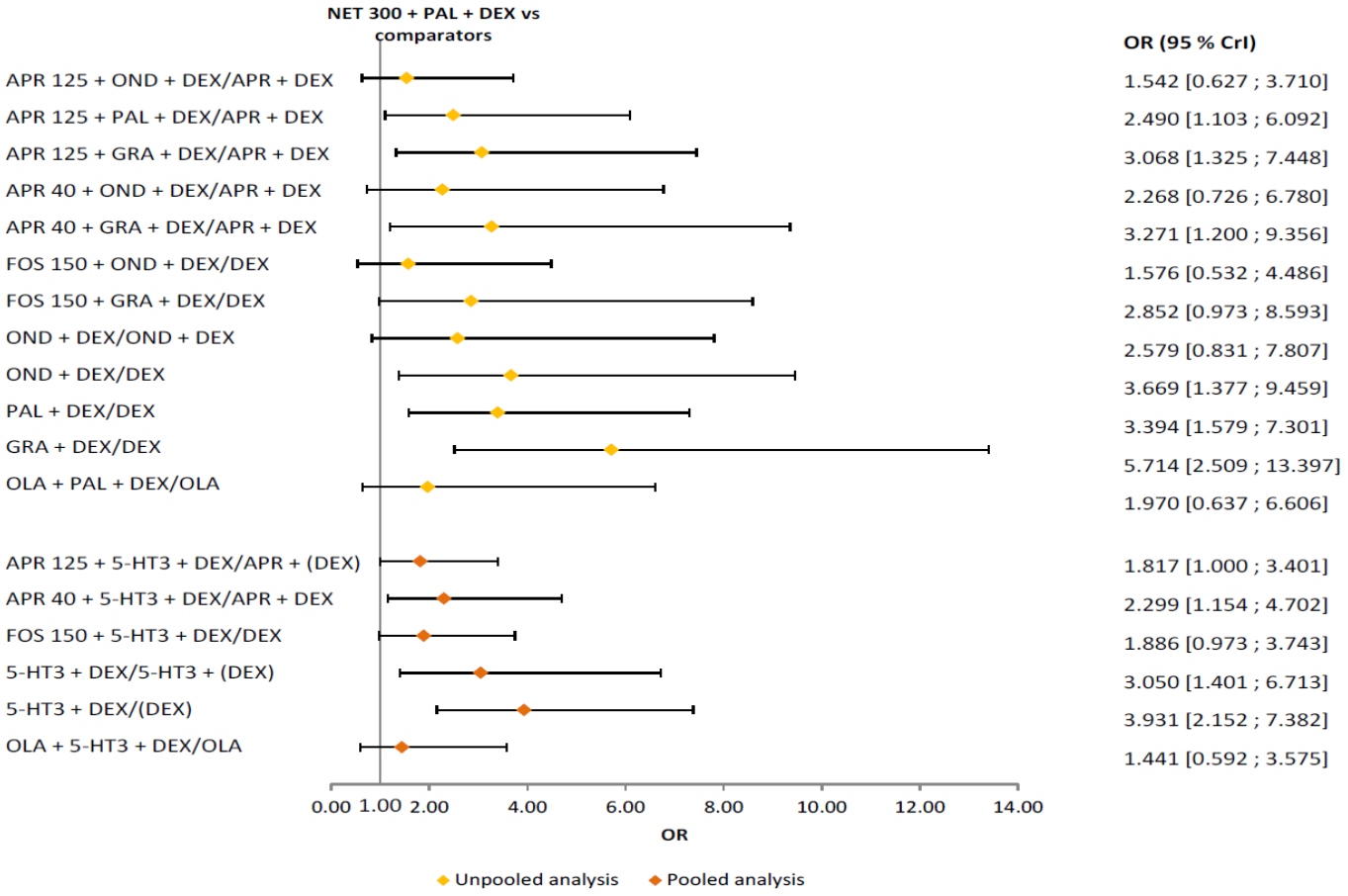
5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OLA = olanzapine; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

1.3.3 Highly emetogenic chemotherapy — overall phase

In the overall phase, the analysis with unpooled effect of 5-HT_3RA therapies indicated that NEPA + DEX achieved higher odds of CR than APR + PALO + DEX or APR + GRAN + DEX (OR 2.49; 95% CrI, 1.10 to 6.09 and OR 3.07; 95% CrI, 1.33 to 7.45; respectively, Figure 16). Patients treated with NEPA + DEX also had higher odds of CR compared with all 5-HT_3RA + DEX except OND + DEX (mean OR 2.58; 95% CrI, 0.83 to 7.81). Based on pooled 5-HT_3RA analysis, NEPA + DEX showed higher odds of CR than APR + 5-HT_3RA + DEX (OR 1.82; 95% CrI, 1.00 to 3.40 and OR 2.30; 95% CrI, 1.15 to 4.70; respectively). NEPA + DEX also had higher odds of CR than the 5-HT_3RA + DEX treatments (Figure 16 and Table 18).

Figure 16: Netupitant/Palonosetron Versus Comparators for Complete Response: Highly Emetogenic Chemotherapy Overall Phase (Random Effects)



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OLA = olanzapine; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

2. Complete protection

2.1 Moderately emetogenic chemotherapy population

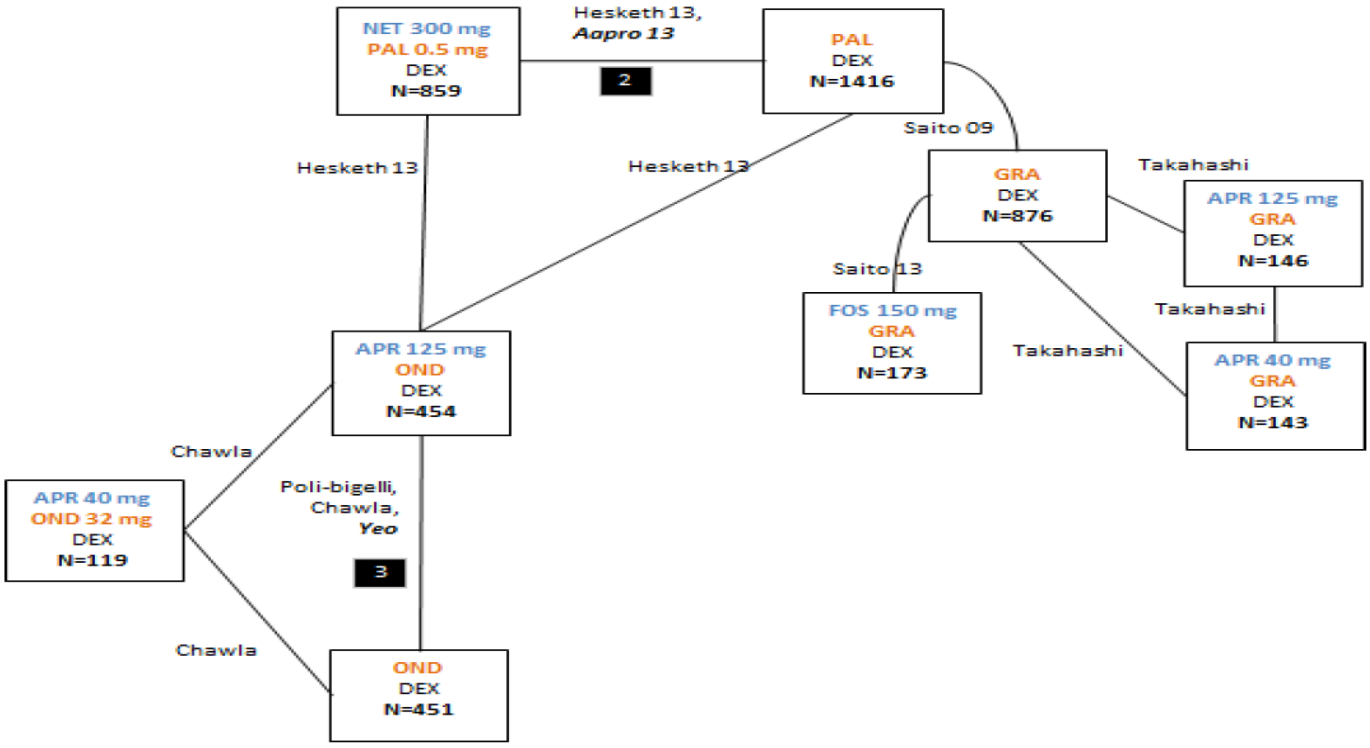
No data for CP were reported for the MEC population.

2.2 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide

2.2.1 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide — acute phase

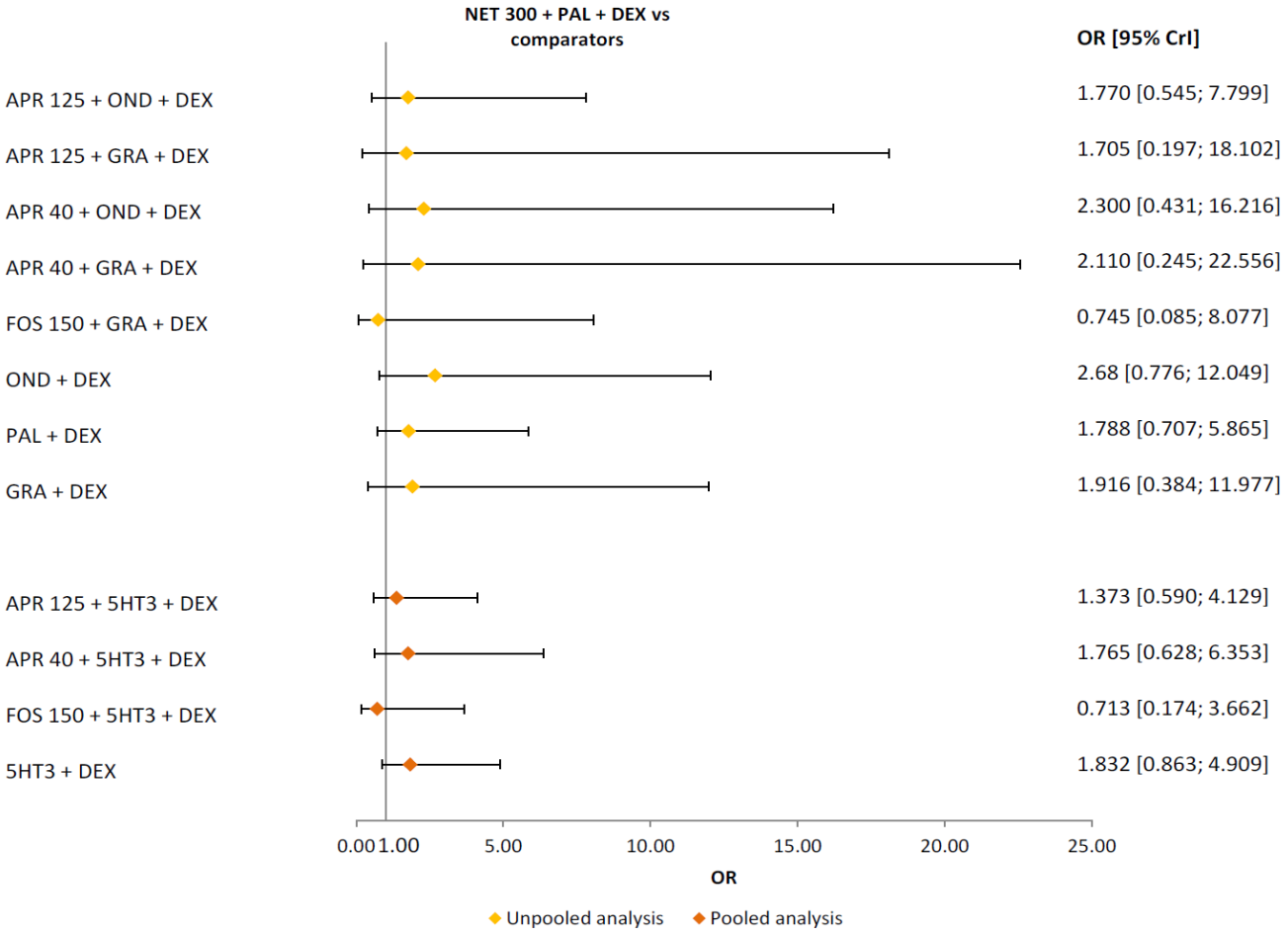
The network for CP in the acute phase for the HEC and AC population is shown in Figure 17. In both the unpooled and pooled 5-HT_3RA analyses, no statistically significant differences were reported between NEPA and other comparator strategies (Figure 18, Table 18).

Figure 17: Network for Complete Protection: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Acute Phase



APR = aprepitant; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; PAL = palonosetron.
Source: NEPA MTC report.[45]

Figure 18: Netupitant/Palonosetron Versus Comparators for Complete Protection: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide – Acute Phase (Random Effects)



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

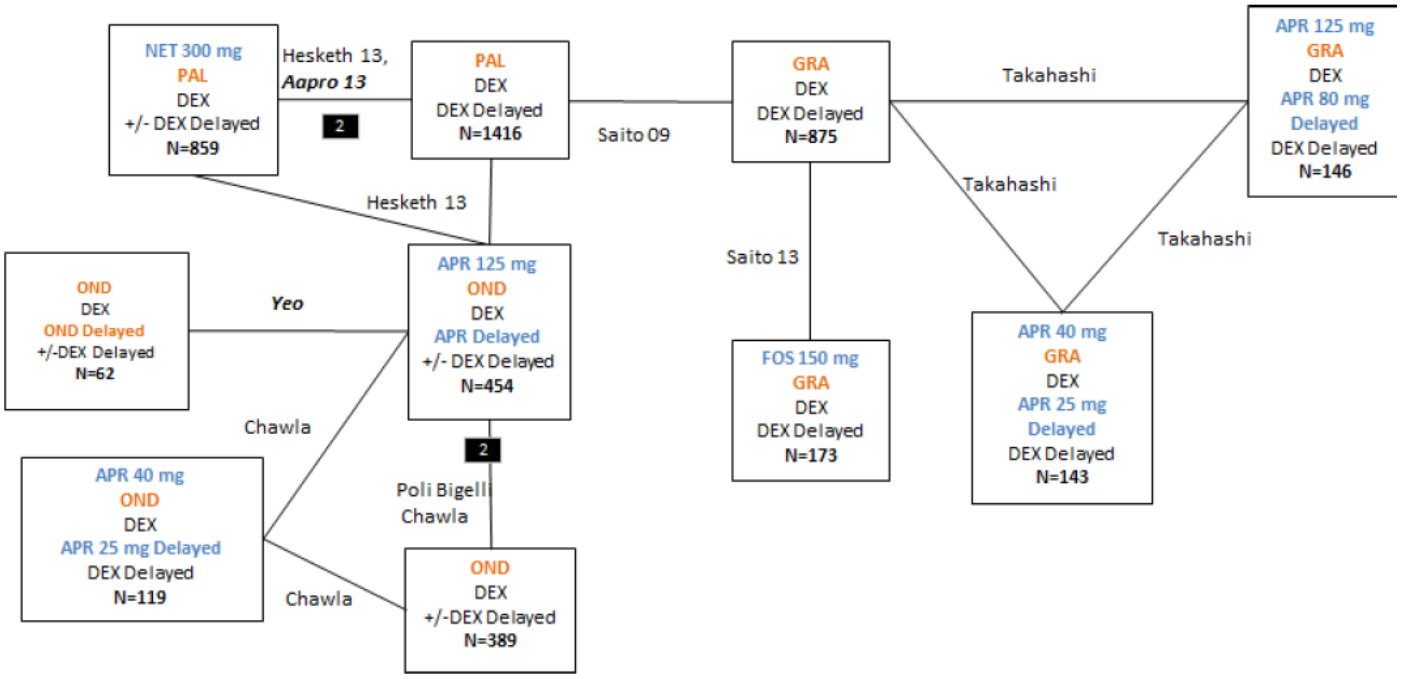
Source: NEPA MTC report.[45]

2.2.2 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide — delayed phase

The network for CP in the delayed phase for the HEC and AC population is presented in Figure 19.

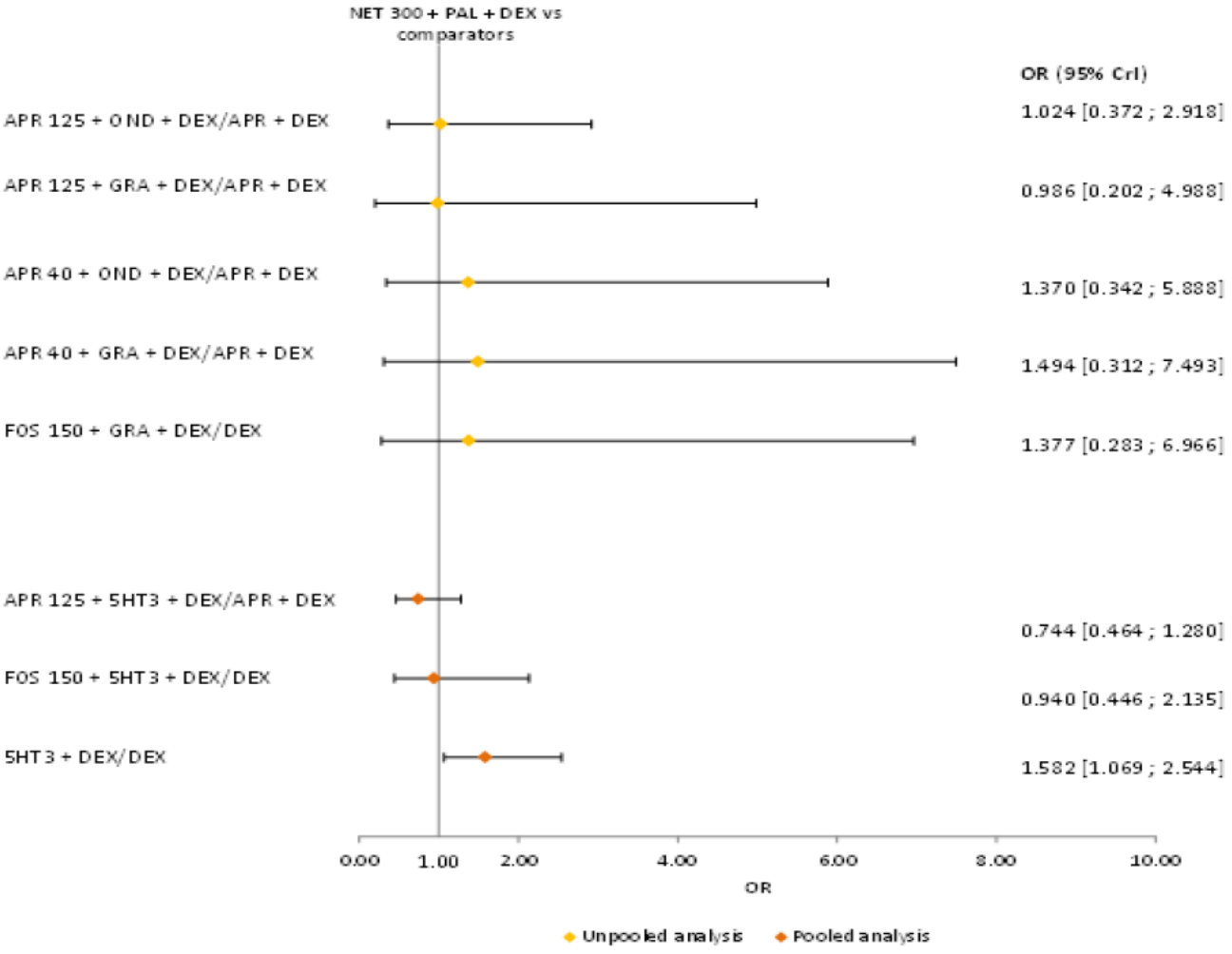
In the analysis using a pooled or unpooled effect of 5-HT_3RA treatments, there was no statistically significant difference in the odds of CP for patients treated with NEPA + DEX and APR- or FOS-based treatments. Patients treated with NEPA + DEX was found to have higher odds of CP compared with patients treated with 5-HT_3RA + DEX (OR 1.58; 95% CrI, 1.07 to 2.54; Figure 20, Table 18).

Figure 19: Network for Complete Protection: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Delayed Phase



APR = aprepitant; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; PAL = palonosetron.
Source: NEPA MTC report.[45]

Figure 20: Netupitant/Palonosetron Versus Comparators for Complete Protection: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide – Delayed Phase (Fixed Effects)



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

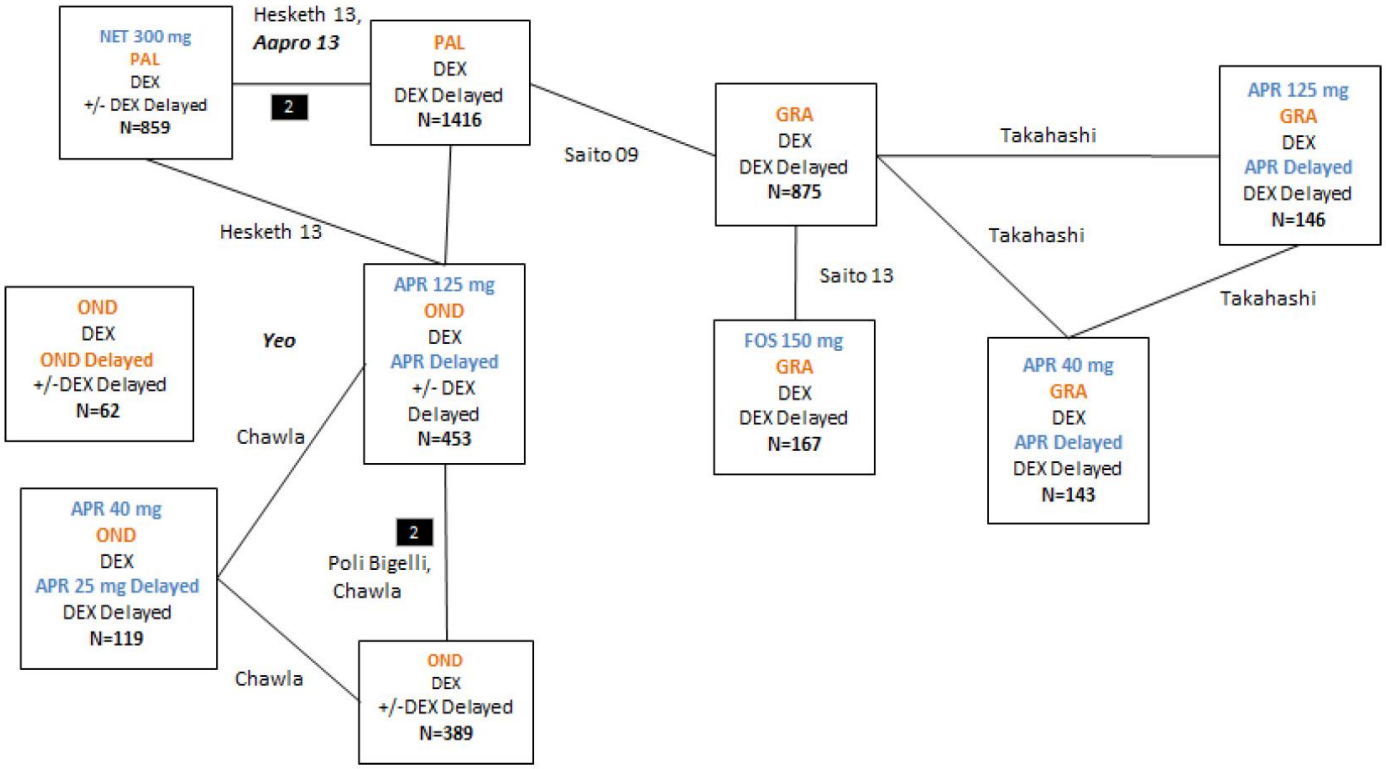
Source: NEPA MTC report.[45]

2.2.3 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide — overall phase

The network for CP in the overall phase for the HEC and AC population is presented in Figure 21.

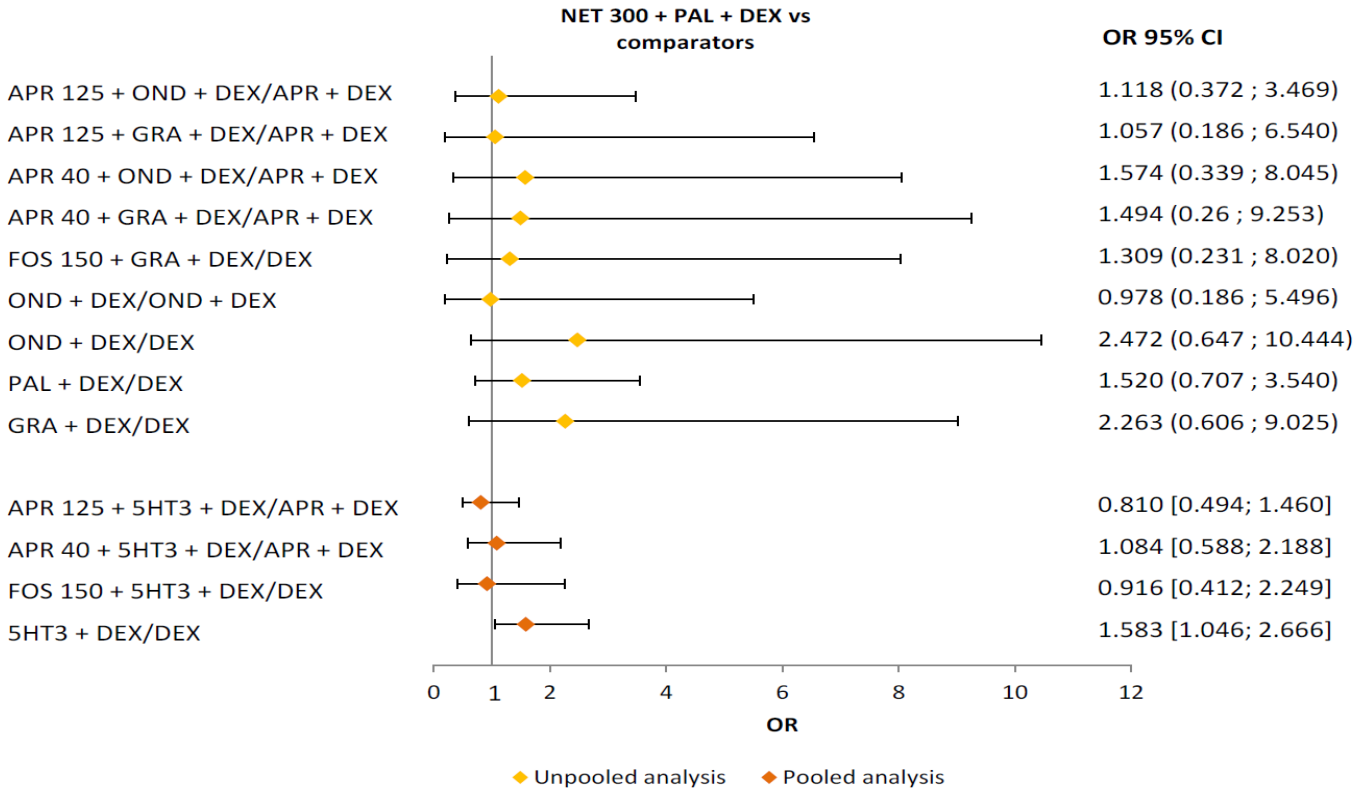
In the analysis with unpooled effect of 5-HT_3RA therapies, there was no statistically significant difference between NEPA and its comparators (Figure 22). In the analysis with a pooled effect of 5-HT_3RA therapies, NEPA + DEX also showed similar odds of CP to APR or FOS + 5-HT_3RA + DEX regimens and had a higher odds of CP than 5-HT_3RA + DEX (mean OR 1.58; 95% CrI, 1.05 to 2.67; Figure 22 and Table 18).

Figure 21: Network for Complete Protection: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Overall Phase



APR = aprepitant; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; PAL = palonosetron.
Source: NEPA MTC report.[45]

Figure 22: Netupitant/Palonosetron Versus Comparators for Complete Protection: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide – Overall Phase (Random Effects)



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

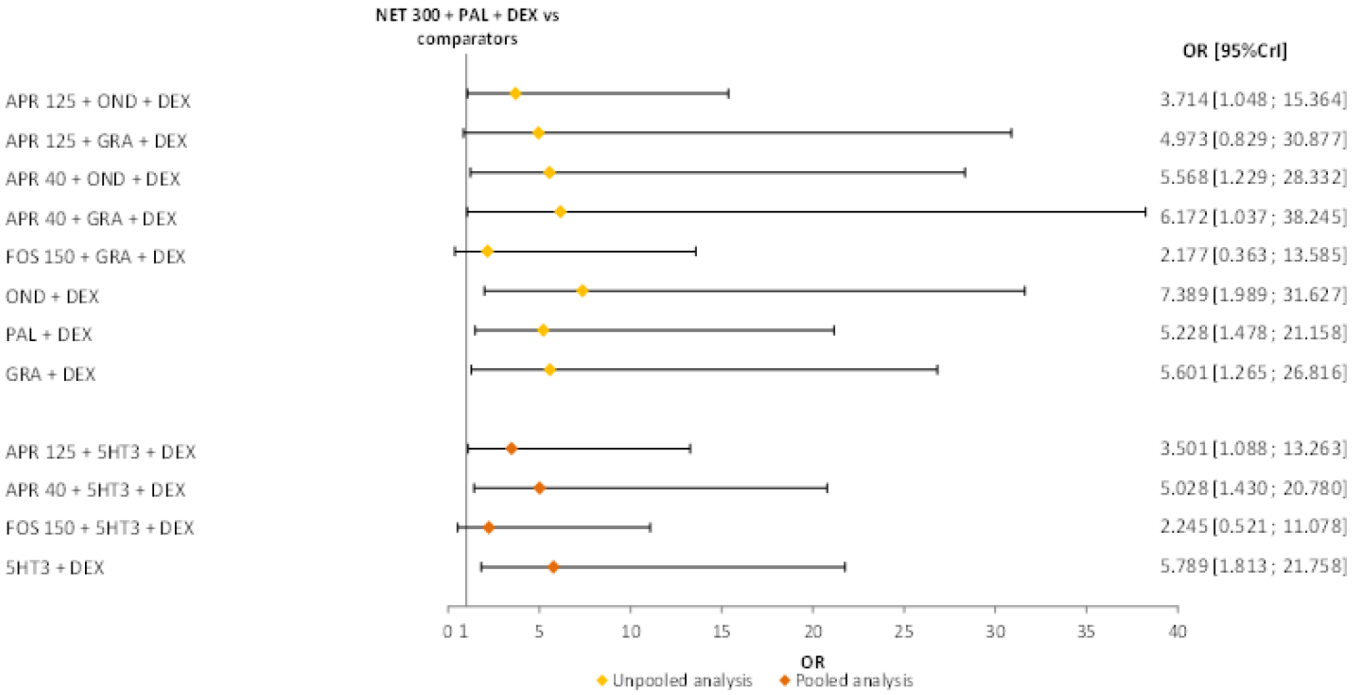
Source: NEPA MTC report.[45]

2.3 Highly emetogenic chemotherapy

2.3.1 Highly emetogenic chemotherapy — acute phase

For the analysis with unpooled 5-HT_3RA treatments, patients treated with NEPA + DEX were found to have higher odds of CP in the acute phase compared with APR + OND + DEX and APR + GRAN + DEX. In addition, patients treated with NEPA + DEX had higher odds of CP compared with all 5-HT_3RA + DEX treatments. With pooled 5-HT_3RA treatments, higher odds of CP were found for patients treated with NEPA + DEX compared with those treated with APR + 5-HT_3RA + DEX and 5-HT_3RA + DEX, but not with those treated with FOS + 5-HT_3RA + DEX (Figure 23 and Table 18).

Figure 23: Netupitant/Palonosetron Versus Comparators Complete Protection: Highly Emetogenic Chemotherapy Acute Phase (Random Effects)



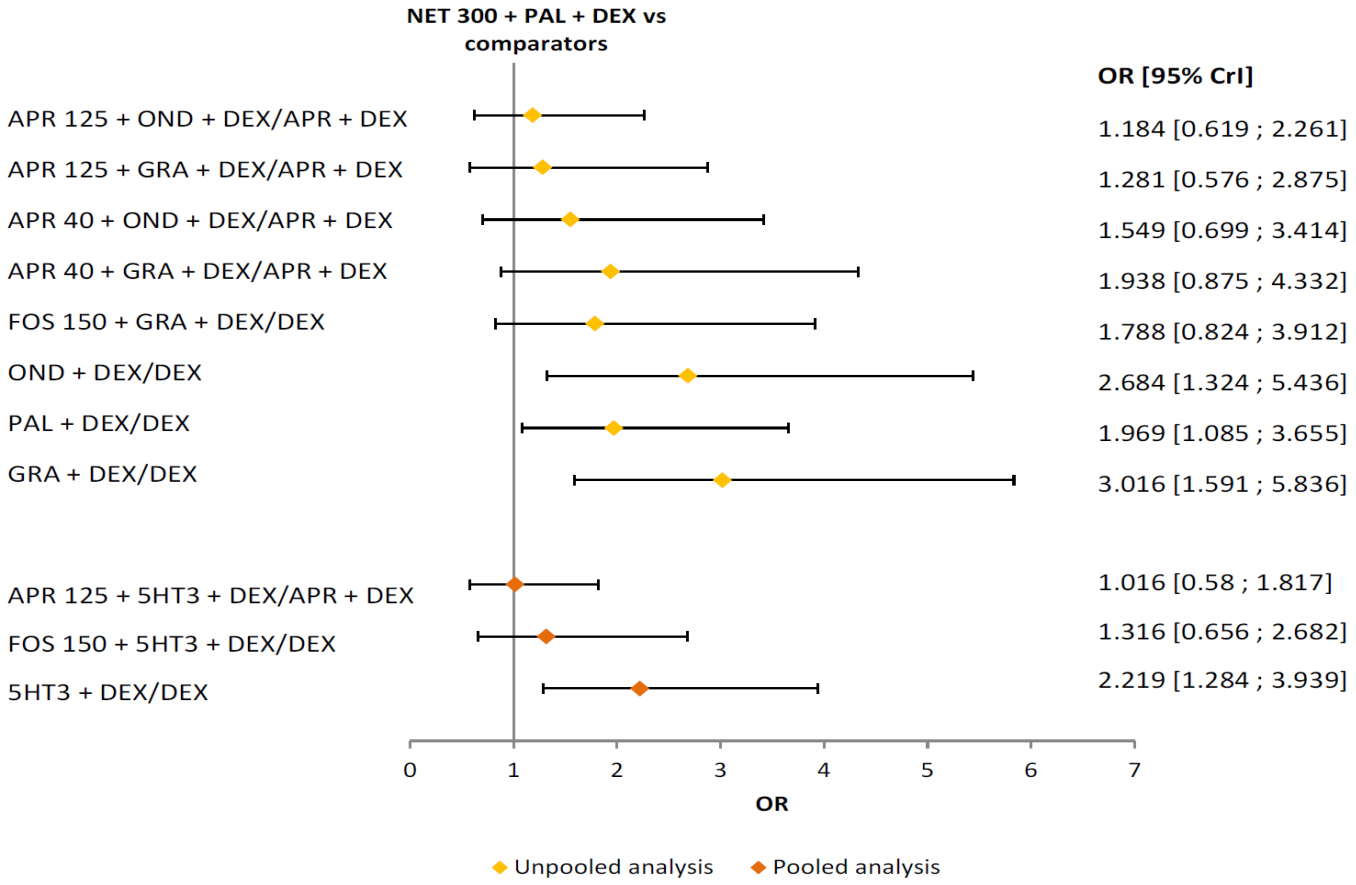
5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

2.3.2 Highly emetogenic chemotherapy — delayed phase

There was no statistically significant difference between NEPA + DEX and APR or FOS + 5-HT_3RA + DEX comparators (Figure 24). Patients treated with NEPA + DEX had higher odds CP in the delayed phase compared with any 5-HT_3RA + DEX. In the pooled 5-HT_3RA analysis, there was no statistically significant difference between NEPA + DEX and APR- or FOS-based treatments (Figure 24 and Table 18). Similar to the unpooled analysis, NEPA + DEX showed a higher chance of CP than a 5-HT_3RA + DEX (OR 2.22; 95% CrI, 1.28 to 3.94; Figure 24 and Table 18).

Figure 24: Netupitant/Palonosetron Versus Comparators for Complete Protection: Highly Emetogenic Chemotherapy Delayed Phase (Random Effects)



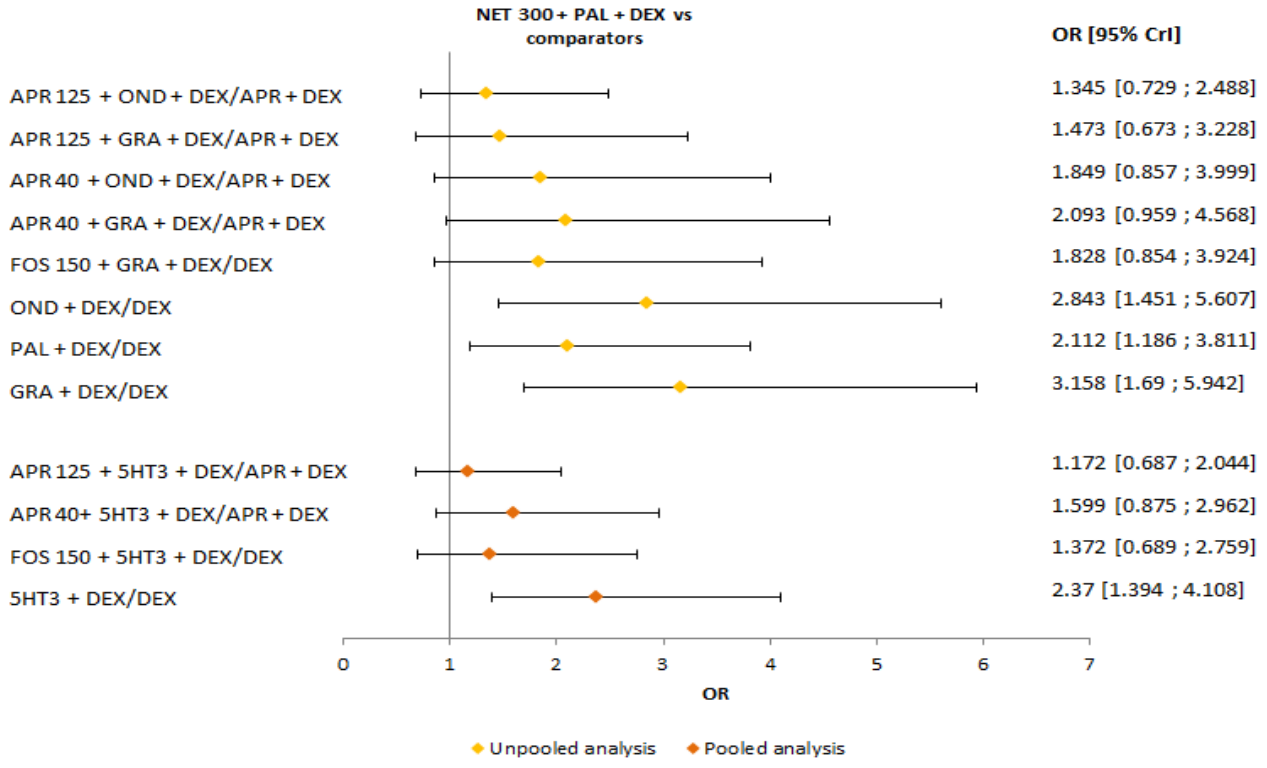
5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

2.3.3 Highly emetogenic chemotherapy — overall phase

In both pooled and unpooled 5-HT_3RA analysis, no statistically significant difference was found between NEPA + DEX and APR or FOS + 5-HT_3 + DEX combination treatments (Figure 25, Table 18). Treatment with NEPA + DEX achieved higher odds of CP than all 5-HT_3RA + DEX treatments.

Figure 25: Netupitant/Palonosetron Versus Comparators for Complete Protection: Highly Emetogenic Chemotherapy Overall Phase (Random Effects)



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

3. Total control

3.1 Moderately emetogenic chemotherapy population

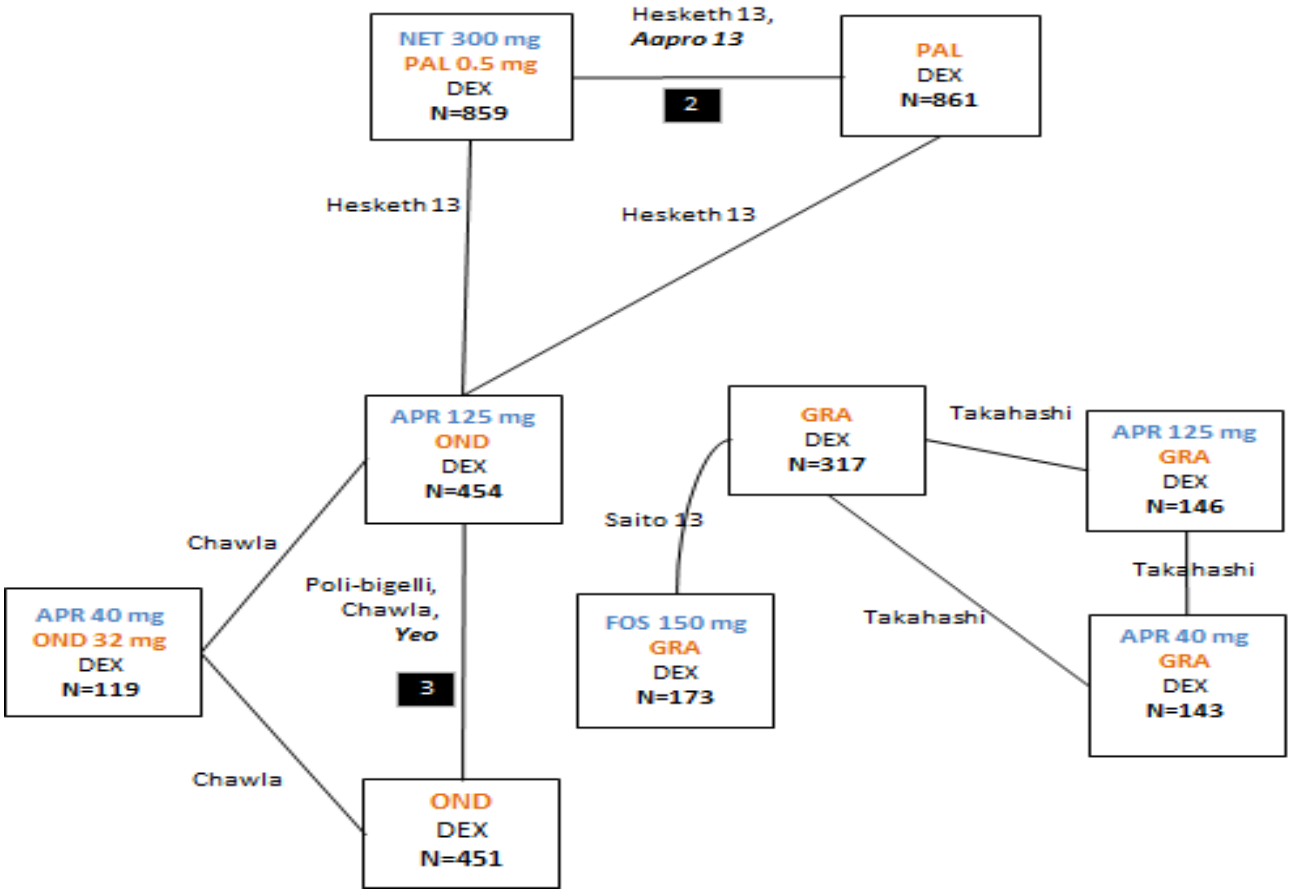
No data for TC were reported for the MEC population.

3.2 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide

3.2.1 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide — acute phase

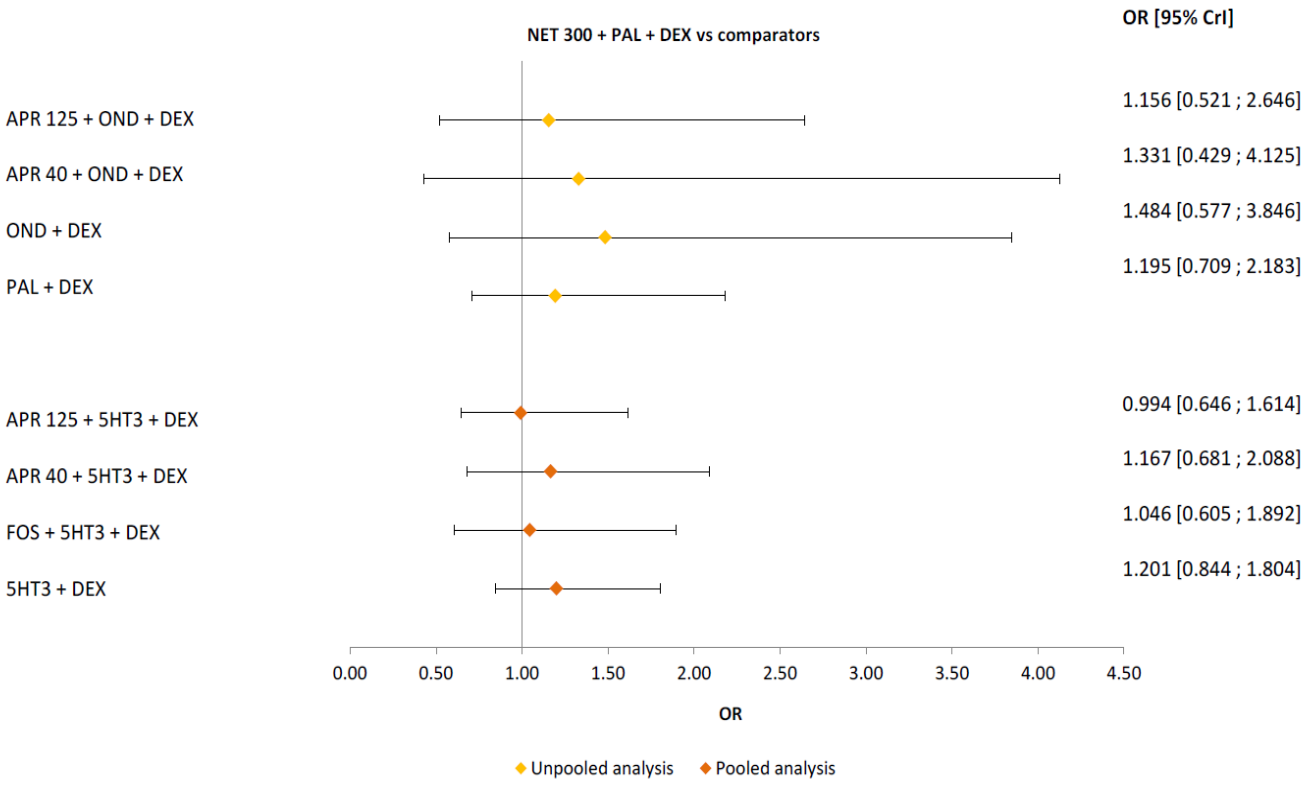
The network for total control in the acute phase for the HEC and AC population is presented in Figure 26. In the analysis with unpooled or pooled 5-HT_3RA treatments, no statistically significant difference between NEPA + DEX compared and other comparators was found in the odds of TC (Figure 27, Table 18).

Figure 26: Network for Total Control: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Acute Phase



APR = aprepitant; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; PAL = palonosetron.
Source: NEPA MTC report.[45]

Figure 27: Netupitant/Palonosetron Versus Comparators for Total Control: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Acute Phase (Fixed Effects)



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

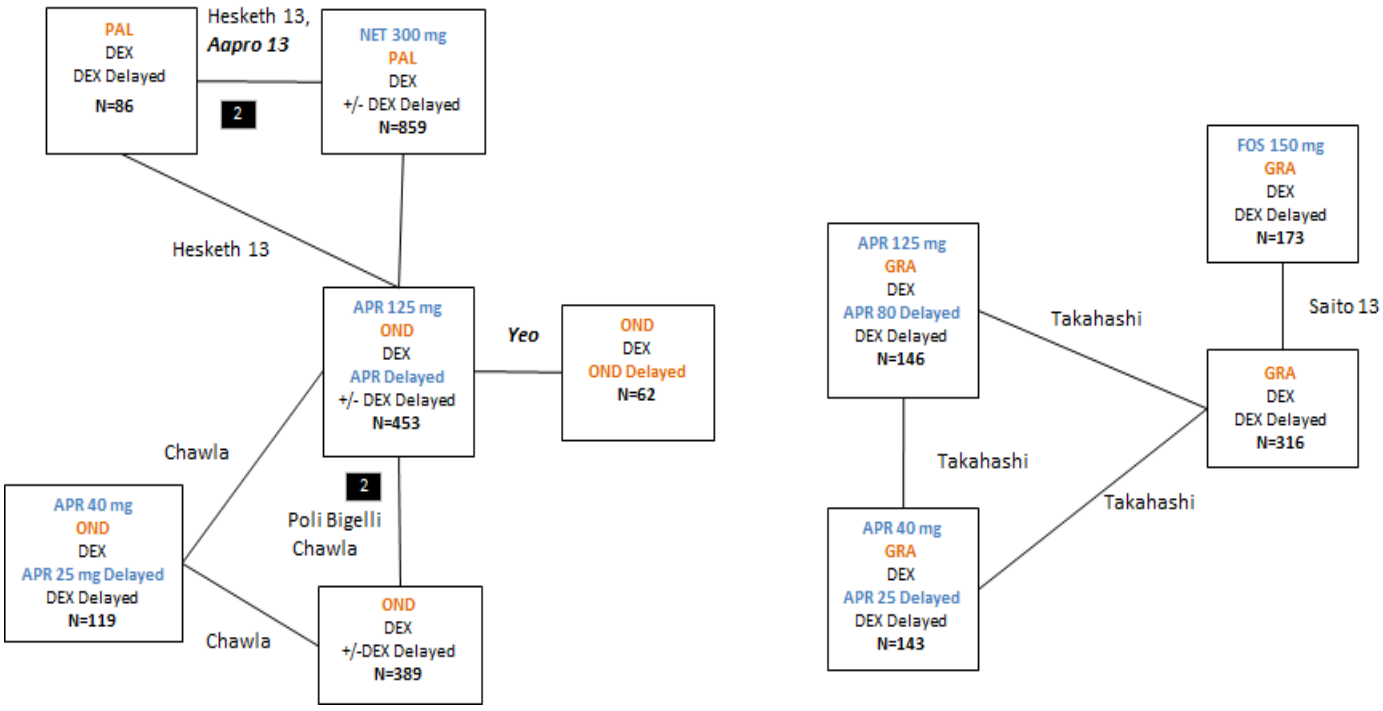
Source: NEPA MTC report.[45]

3.2.2 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide — delayed phase

The network for TC in the delayed phase for the HEC and AC population is presented in Figure 28. For the analysis of unpooled or pooled 5-HT_3RA regimens, there were no statistically significant differences in the odds of TC for patients treated with NEPA + DEX compared with any triple-drug therapy (APR or FOS + 5-HT_3RA, and DEX; Figure 29, Table 18).

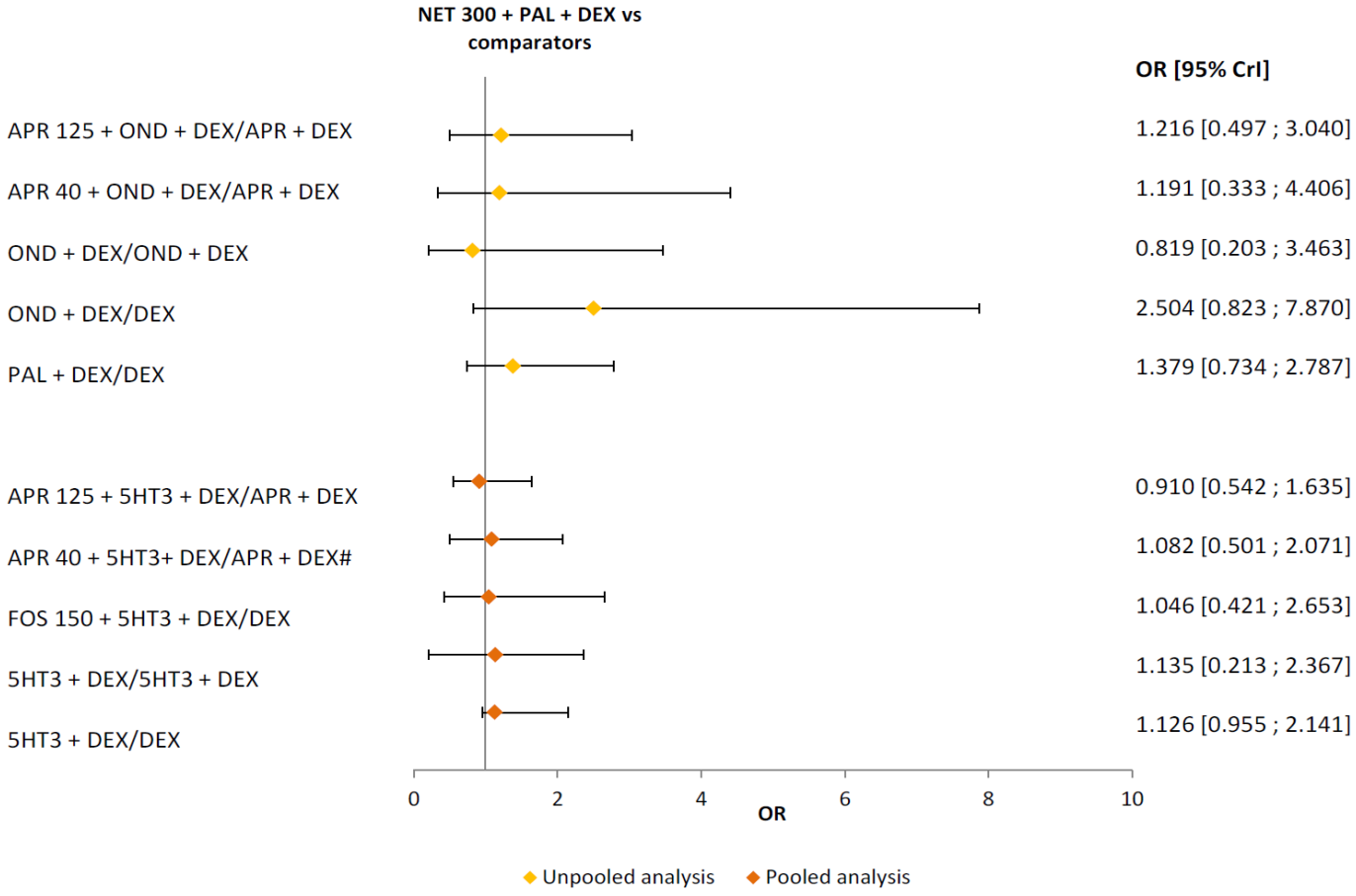
The analysis with a pooled efficacy for 5-HT_3RAs also did not show a statistically significant difference between NEPA + DEX compared with 5HT_3RA +DEX (Figure 29, Table 18).

Figure 28: Network for Total Control: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Delayed Phase



APR = aprepitant; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; PAL = palonosetron.
Source: NEPA MTC report.[45]

Figure 29: Netupitant/Palonosetron Versus Comparators for Total Control: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Delayed Phase (Fixed Effects)



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

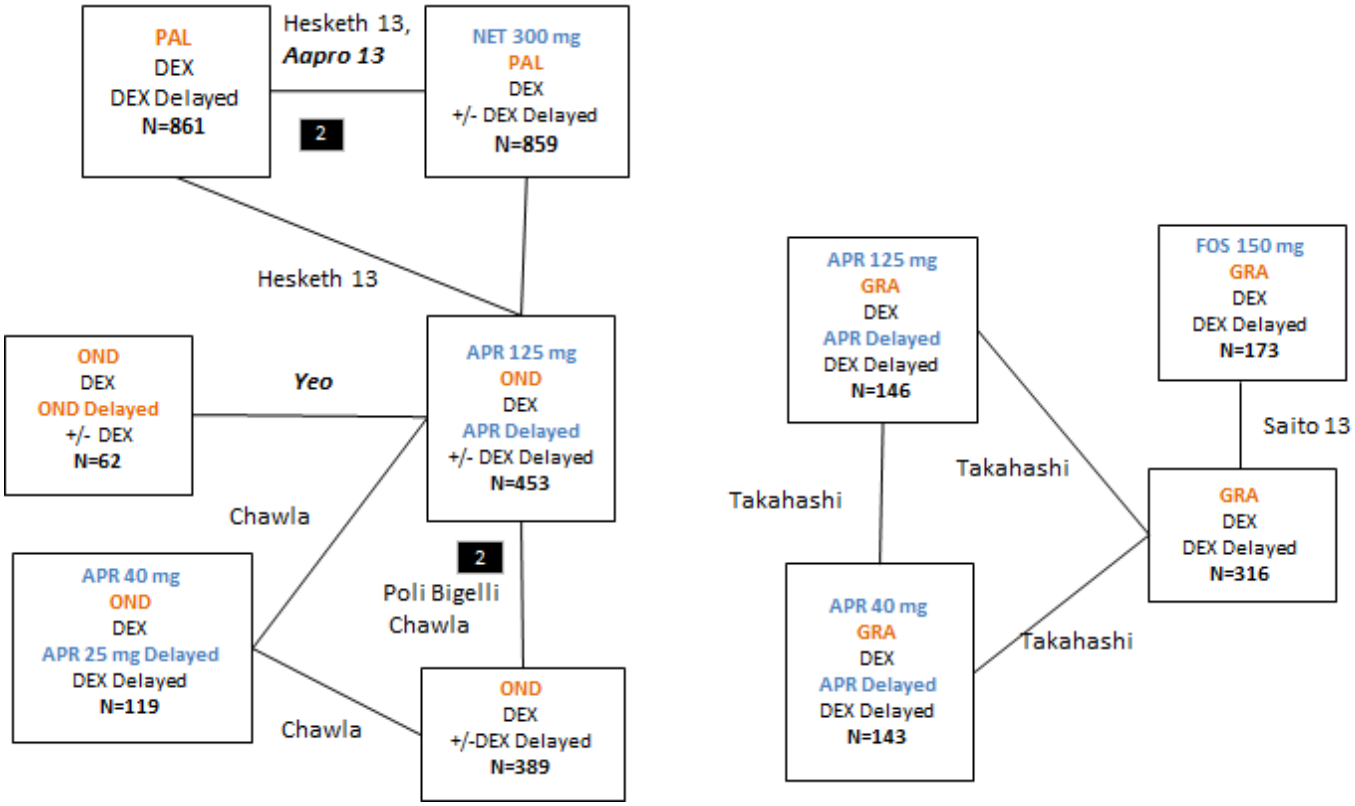
Source: NEPA MTC report.[45]

3.2.3 Highly emetogenic chemotherapy and anthracycline/cyclophosphamide — overall phase

The network for total control in the overall phase for the HEC and AC population is presented in Figure 30.

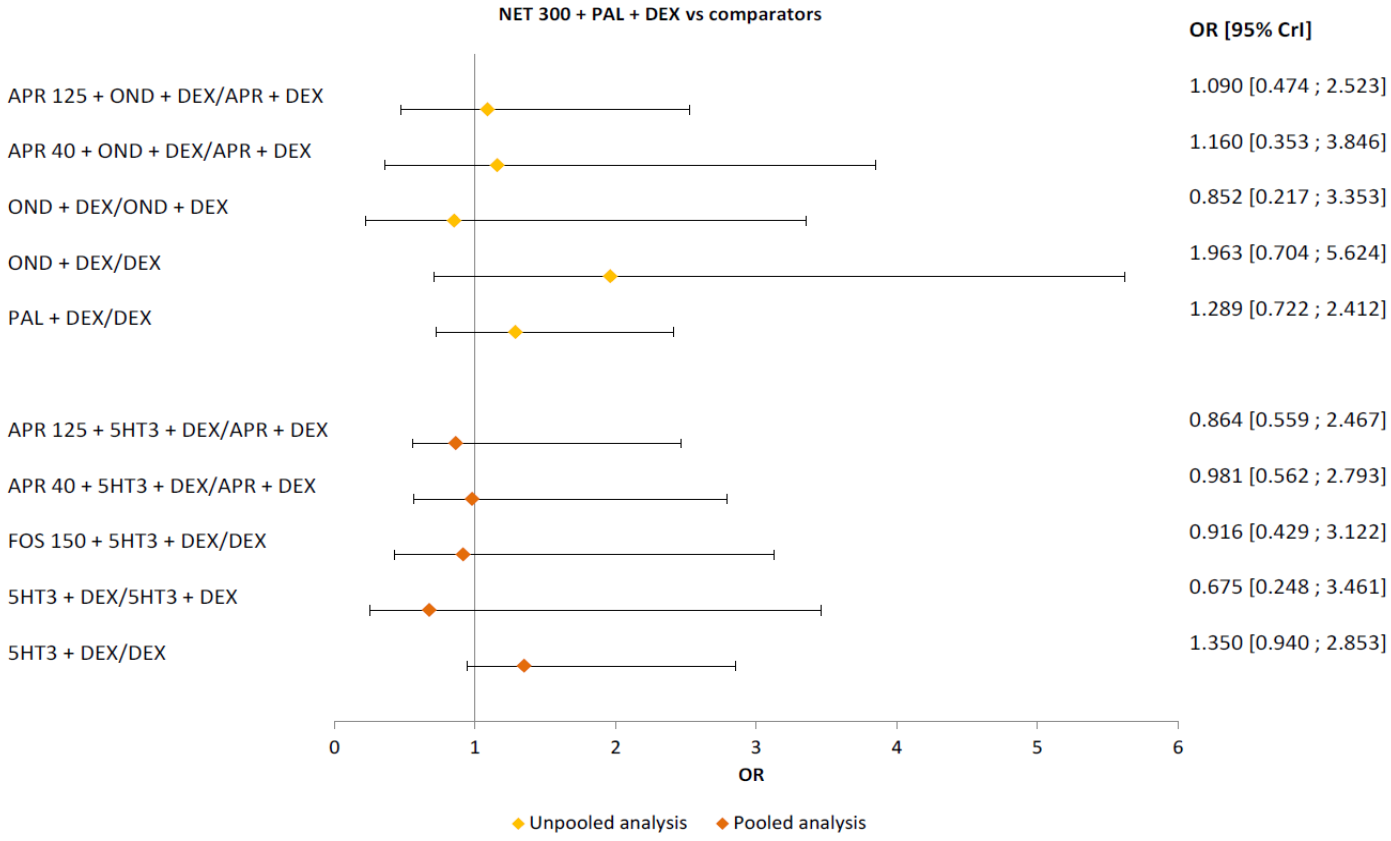
For the analysis of unpooled or pooled 5-HT_3RA treatments, there were no statistically significant differences in odds of TC for patients treated between NEPA + DEX and any NK_1RA containing triple treatments(APR or FOS, 5-HT_3RA, and DEX) or 5-HT_3RA + DEX treatments (Figure 31, Table 18).

Figure 30: Network for Total Control: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Overall Phase



APR = aprepitant; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; PAL = palonosetron.
Source: NEPA MTC report.[45]

Figure 31: Netupitant/Palonosetron Versus Comparators for Total Control: Highly Emetogenic Chemotherapy and Anthracycline/Cyclophosphamide — Overall Phase (Fixed Effects)



5-HT3 = 5-HT_3 receptor antagonist; APR = aprepitant; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; GRA = granisetron; NET = netupitant; OND = ondansetron; OR = odds ratio; PAL = palonosetron.

Source: NEPA MTC report.[45]

3.3 Highly emetogenic chemotherapy

No data for TC were reported for the HEC population.

Critical Appraisal of Indirect Comparison

The quality of the manufacturer-submitted MTC was assessed according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons,[47] and commentary for each of the relevant items identified by ISPOR is provided in Table 19.

Strengths

The MTC was based on a systematic review to identify relevant studies. Validity and quality of all individual studies included in the meta-analysis were assessed using the NICE methodology checklist. The analysis was conducted using an appropriate and well-reported methodology (i.e., frequentist method for MEC population or Bayesian MTC method for

HEC+ AC population). A random- or fixed-effects model was selected, based in part on the DIC. When possible, meta-regressions were conducted to address potential effect modification using appropriate covariates. The outcome measures assessed in the MTC were appropriate and consistent with the key efficacy outcomes assessed in the pivotal studies included in this CADTH Common Drug Review (CDR) review.

Limitations

The search of electronic databases and the strategy were consistent with accepted systematic review methods; however, it was not stated whether other sources were considered (e.g., grey literature). As well, the literature search was restricted to English-language articles only and to a specific time period (limit was set to August 28, 2013, overall and to January 9, 2014, for olanzapine, which was not considered as a comparator for this review). Therefore, at the time of submission of NEPA to CDR (December 2017), the literature search for the meta-analysis was more than four years old. Based on the studies submitted to CDR, at least one manufacturer-conducted trial (NETU 12-07) was excluded from the indirect comparison. It is likely that, over a four-year period, other trials were conducted that could have been included, and the impact of this on the results is unclear.

It was reported that literature search results screening was conducted in duplicate, but there was no mention as to whether data extraction and quality assessment of the individual included studies were performed by two researchers in a duplicate manner.

One of the major limitations of the indirect comparisons was associated with the body of evidence. The population for the indirect comparison and MTC was appropriately defined and aligned with the Health Canada indication and the CDR review. However, only four RCTs in the MEC population were included in analyses, thereby limiting the type of analysis that could be conducted (i.e., fixed-effects frequentist indirect comparison), with insufficient power for conducting subgroup, sensitivity, or meta-regression analyses to truly explore impacts of assumptions, sources of heterogeneity, and consistency with direct data. As well, the assessment in the MEC population was limited to CR as the sole outcome. Therefore, the analysis in the MEC population is not robust and is associated with considerable uncertainty.

It was noted in the indirect comparison report that doses, frequency, and route of administration varied considerably across the included RCTs. As mentioned in the description of the analysis, several assumptions were made to form the analysis networks, such as the assumption that HEC and AC populations were considered similar. The clinical expert consulted in this review indicated that the assumptions were clinically reasonable; however, the validity of the assumption regarding no influence on efficacy from the route of the administration (IV versus oral) may not be universally true. The clinical expert noted that, while in general there is evidence and long clinical experience to indicate that the high bioavailability of oral formulations of the antiemetics make them interchangeable with IV formulations, there are certain subpopulations in which IV may be a better option (e.g., those with difficulty swallowing pills, and those with anticipatory CINV), and there are limited data for equivalence in older patients. The latter point was also made in the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) 2016 guidance on antiemetics for CINV.[7] A subgroup analysis separating the HEC and AC populations was performed, and, in general, the ORs for CR remained similar in magnitude and direction. However, the loss of power did affect certain treatment

comparisons and precision based on wider 95% CrIs. No other formal evaluations of the key assumptions were tested.

The indirect comparison report indicated that there was also variation in the definition of CR in the antiemetic trials; therefore, a pre-specified definition for CR was used to select studies for inclusion and to construct the analysis networks. This is an appropriate approach; however, two different definitions for CR were reported: one in the protocol for the meta-analysis that was the same as that used in the CDR-reviewed trials (i.e., no emesis/vomiting and no rescue medication use), and another definition that added nausea (i.e., defined as no nausea, no vomiting, and no use of rescue medication). It is unclear which of these two definitions for CR were applied to study inclusion and analysis network construction. If the latter definition was used, then the studies for NEPA would not have been eligible for inclusion. It also questions how similar the CR definitions in the other included RCTs were. The exact of impact of the definition discrepancy unclear. Additionally, only the pre-specified dichotomous outcomes (CR, CP, and TC) could be analyzed due to lack of data for the other outcomes pre-specified in the meta-analysis protocol. Of note, other clinically important outcomes such as quality of life, patient functioning, and adverse events were not assessed.

There was very little information provided regarding study and population characteristics of the individual RCTs in the indirect comparison report, making it very difficult to assess how similar the included studies were. It was reported that quality assessment of the individual trials was performed, but the results of the assessment were not presented. Also, it was not reported whether issues such as reporting bias or small-study effects were assessed. The report indicated that a feasibility assessment was conducted to assess whether indirect comparisons were feasible; however, no details or findings from this assessment (other than a MTC that was not feasible for the MEC population) were provided. It was acknowledged in the report that assessing heterogeneity was difficult because of sparsely populated networks. When possible, heterogeneity assessments were conducted using univariate meta-regression with relevant factors (age, sex distribution, and chemotherapy type [HEC as reference]). Although none of the 95% CrIs around the point estimates indicated a meaningful impact of the covariate, the very wide intervals highlight the lack of power in the networks to properly assess impacts of potential effect modifiers and confounders.

Overall, there were few studies included in the analysis, especially for the most relevant comparators (i.e., for NEPA + DEX compared with other triple regimens [NK_1RA + $5HT_3RA$ + DEX]) for patients receiving MEC. Therefore, the sparse nature of the data likely limited power to detect a difference between treatment means, and there is a high degree of uncertainty around the comparisons. However, the clinical expert consulted for this review indicated that the key findings of this MTC is aligned with clinical practice. Two published MTCs were identified in a supplemental search of the literature conducted by CDR reviewers.[30,31] Both analyses suggested that, for patients receiving HEC, there was no difference in achieving CR (during any phase) with NEPA + DEX versus first-generation $5HT_3RA$-based triple therapies. However, neither of these network meta-analyses were reviewed in-depth or critically appraised, so their findings should be interpreted with caution. A protocol for a Cochrane meta-analysis and network meta-analysis was identified, but the review is ongoing and no data are available yet.[48]

Conclusion

Results from the manufacturer-provided indirect comparisons suggested that, in the MEC population, there was no difference in efficacy between NEPA + DEX and APR + 5-HT_3RA + DEX or 5-HT_3RA + DEX for CR at any time point. In the HEC/AC population, NEPA + DEX provides similar efficacy to APR- or FOS-containing triple regimens in terms of CR, CP, and TC in acute, phase, and overall phases. These findings are similar to those of published indirect comparisons[30,31] However, the limitations of the data sources, sparsely populated networks, uncertainty as to outcomes definitions, and inability to test assumptions and/or fully assess sources of heterogeneity in both the MEC and HEC/AC populations (but especially in the MEC population) mean that no concrete conclusions could be drawn for the comparative efficacy of NEPA in these populations. Moreover, the absence of analyses of other clinically relevant outcomes, such as quality of life, patient functioning, and adverse events means the clinical significance of any of the indirect analysis results is unknown.

Table 18: Summary of Mixed-Treatment Comparison Results

MTC Population	Phase	NEPA + DEX vs. NK_1RA + $5\text{-}HT_3RA$ + DEX		NEPA + DEX vs. $5\text{-}HT_3RA$ + DEX
			OR (95% CI or CrI)	OR (95% CI or CrI)
Complete response				
MEC	Acute	NEPA vs. APR 125 mg	0.95 (0.34 to 2.69)	1.81 (0.53 to 6.18)
	Delayed		0.83 (0.41 to 1.66)	1.43 (0.59 to 3.43)
	Overall		0.87 (0.45 to 1.68)	1.47(0.55 to 2.43)
HEC	Acute	NEPA vs. APR 125 mg	1.85(0.67 to 5.38)	3.77 (1.36 to 11.02)
		NEPA vs. APR 40 mg	2.34 (0.75 to 7.54)	
		NEPA vs. FOS 150 mg	1.46 (0.46 to 4.60)	
	Delayed	NEPA vs. APR 125 mg	1.86 (0.95 to 3.74)	4.15 (2.09 to 8.47)
		NEPA vs. APR 40 mg	2.13(0.98 to 4.77)	
		NEPA vs. FOS 150 mg	1.93(0.91 to 4.31)	
	Overall	NEPA vs. APR 125 mg	1.82 (1.00 to 3.40)	3.93 (2.15 to 7.38)
		NEPA vs. APR 40 mg	2.30 (1.15 to 4.70)	
		NEPA vs. FOS 150 mg	1.89 (0.97 to 3.74)	
HEC and AC	Acute	NEPA vs. APR 125 mg	0.97 (0.58 to 2.17)	1.70 (1.06 to 3.68)
		NEPA vs. APR 40 mg	1.12 (0.56 to 2.98)	
		NEPA vs. FOS 150 mg	0.73 (0.36 to 1.86)	
	Delayed	NEPA vs. APR 125 mg	1.02 (0.64 to 1.88)	2.11 (1.40 to 3.68)
		NEPA vs. APR 40 mg	1.13 (0.62 to 2.35)	
		NEPA vs. FOS 150 mg	1.04 (0.59 to 2.20)	
	Overall	NEPA vs. APR 125 mg	0.98 (0.66 to 1.62)	2.01 (1.41 to 3.20)
		NEPA vs. APR 40 mg	1.21 (0.71 to 2.25)	
		NEPA vs. FOS 150 mg	1.00 (0.61 to 1.85)	
Complete protection				
MEC			NR	NR
HEC	Acute	NEPA vs. APR 125 mg	3.50 (1.09 to 13.3)	5.79(1.81 to 21.76)
			5.03 (1.43 to 20.78)	
		NEPA vs. APR 40 mg	2.24 (1.81 to 21.76)	
	Delayed	NEPA vs. APR 125 mg	1.02 (0.58 to 1.82)	2.22 (1.28 to 3.94)
		NEPA vs. APR 40 mg	NR	
		NEPA vs. FOS 150 mg	1.32 (0.66 to 2.68)	
	Overall	NEPA vs. APR 125 mg	1.17 (0.69 to 2.04)	2.37 (1.39 to 4.11)
		NEPA vs. APR 40 mg	1.60 (0.88 to 2.96)	
		NEPA vs. FOS 150 mg	1.37 (0.69 to 2.76)	
HEC and AC	Acute	NEPA vs. APR 125 mg	1.37 (0.59 to 4.13)	1.83 (0.86 to 4.91)
		NEPA vs. APR 40 mg	1.77 (0.63 to 6.35)	
		NEPA vs. FOS 150 mg	0.71 (0.17 to 3.66)	
	Delayed	NEPA vs. APR 125 mg	0.74 (0.46 to 1.20)	1.58 (1.07 to 2.54)
		NEPA vs. APR 40 mg	NR	

MTC Population	Phase	NEPA + DEX vs. NK_1RA + 5-HT_3RA + DEX		NEPA + DEX vs. 5-HT_3RA + DEX
			OR (95% CI or CrI)	OR (95% CI or CrI)
		NEPA vs. FOS 150 mg	0.94 (0.45 to 2.14)	
	Overall	NEPA vs. APR 125 mg	0.81 (0.49 to 1.46)	1.58 (1.05 to 2.67)
		NEPA vs. APR 40 mg	1.08 (0.59 to 2.19)	
		NEPA vs. FOS 150 mg	0.92 (0.41 to 2.25)	
Total control				
MEC			NR	NR
HEC			NR	NR
HEC and AC	Acute	NEPA vs. APR 125 mg	0.99 (0.65 to 1.61)	1.20 (0.84 to 1.80)
		NEPA vs. APR 40 mg	1.17 (0.68 to 2.09)	
		NEPA vs. FOS 150 mg	1.05 (0.61 to 1.89)	
	Delayed	NEPA vs. APR 125 mg	0.91 (0.54 to 1.64)	1.13 (0.96 to 2.14)
		NEPA vs. APR 40 mg	1.08 (0.50 to 2.07)	
		NEPA vs. FOS 150 mg	1.05 (0.42 to 2.65)	
	Overall	NEPA vs. APR 125 mg	0.86 (0.56 to 2.47)	1.35 (0.94 to 2.85)
		NEPA vs. APR 40 mg	0.98 (0.56 to 2.79)	
		NEPA vs. FOS 150 mg	0.92 (0.43 to 3.12)	

5-HT_3 = 5-hydroxytryptamine; AC = anthracycline/cyclophosphamide; APR = aprepitant; CI = confidence interval; CrI = credible interval; DEX = dexamethasone; FOS = fosaprepitant; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; MTC = mixed-treatment comparison; NEPA = netupitant/palonosetron; NK_1 = neurokinin-1; NR = not reported; OR = odds ratio; RA = receptor antagonist; vs. = versus.

Source: NEPA MTC report.[45]

Table 19: Appraisal of Network Meta-Analysis Using ISPOR Criteria

ISPOR Checklist Item[47]		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2.	Does the Methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs were clearly stated. • All treatments were double-blindly administered. • Information sources and search strategy were well reported. • Methods for selection process and data extraction were clearly reported. However, whether the data extraction and quality assessment of the individual included studies were performed by two researchers in a duplicate manner was not reported. • Validity of individual studies was assessed using methodology adopted from the guidance for evidence submission published by NICE.
3.	Are the outcome measures described?	• Outcomes assessed in the network meta-analysis were clearly stated. • Justification of the outcome measures was provided.
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical model was provided. • Analysis framework was provided for all analysis.
5.	Are sensitivity analyses presented?	• Sensitivity analysis was performed and presented. • Meta-regression sensitivity analyses were performed.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A very brief table with study/ patient characteristics was provided. No detail demographic and baseline disease characteristics were presented. • Figures showing the network of studies were provided.
7.	Does the study describe an assessment of model fit?	• Both fixed- and random-effects models were considered.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure, including point estimates and 95% credible intervals as a measure of uncertainty.
9.	Sensitivity/scenario analyses	• Results of the sensitivity analyses were presented in the report.

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial.

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