Enhancing CINV Prevention: NEPA vs. Standard of Care in Patients with Multiple Emetic Risk Factors Receiving Moderately Emetogenic Chemotherapy (MEC)

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MASCC/ISOO
Annual Meeting
26-28 June 2025

BACKGROUND

- Antiemetic guideline recommendations are based primarily on the emetogenic potential of the chemotherapy, with agents classified as highly, moderately, low, and minimally emetogenic.[1-3]
- However, several patient-related risk factors can increase the risk of experiencing chemotherapy-induced nausea and vomiting (CINV).[4-6]
- While MASCC antiemetic guidelines recommend a triple NK_1 receptor antagonist (RA)-containing regimen for some MEC agents (eg, oxaliplatin in females <50 years and carboplatin AUC >5), for patients receiving most other MEC, antiemetic guidelines endorse a 5-HT_3RA + dexamethasone (DEX) as standard of care (SOC).[7]
- However, in patients with an elevated emetic risk due to various risk factors, antiemetic prophylaxis consistent with highly emetogenic chemotherapy (HEC) may be warranted.
- To address this unmet need for a more personalized antiemetic strategy, the MyRisk randomized controlled trial (NCT04817189) incorporated a previously validated predictive risk factor algorithm[4] to select patients at increased risk of CINV who may benefit from the addition of an NK_1RA.

OBJECTIVE

- The primary objective of the MyRisk trial was to evaluate whether the use of NEPA (a fixed combination of an NK_1RA, (fos)netupitant, and 5-HT_3RA, palonosetron) was more effective in preventing CINV than guideline-recommended SOC over three consecutive cycles of chemotherapy in patients deemed to be at increased risk of CINV and who were treated with MEC.

METHODS

Study Design

- Phase IV, interventional, open-label, randomized, active-controlled, multicenter and multinational trial.
- Conducted at 19 sites in 7 countries (China, Czech Republic, Germany, Greece, Spain, Switzerland, and the United Kingdom).

Key Eligibility Criteria

- Adult patients ≥18 years, naïve or non-naive to chemotherapy, with a diagnosis of any cancer, an ECOG performance status of 0-2, and scheduled to receive three consecutive cycles of an intravenous (IV) MEC regimen.
- An algorithm incorporating seven predictive risk factors (adapted from Dranitsaris, 2017[4]) was used to select patients at increased risk of CINV (**Table 1**). To be eligible for the trial, patients needed a score of ≥13.

Treatment Groups

- Eligible patients were randomized 1:1 to receive either NEPA + DEX (test arm) or the 5-HT_3 RA + DEX (SOC control arm).

Table 1. Risk Scoring Algorithm Used to Determine Qualifying Emetic Risk*

	Before MEC
Baseline score	**10**
Predictive Risk Factor	**Adjustment to Baseline**
1. Patient < 60 years	+1
2. Expectation (anticipation) of nausea and vomiting	+1
3. History of morning sickness during a previous pregnancy	+1
4. About to receive platinum or anthracycline chemotherapy	+2
5. Use of non-prescribed antiemetic at home in the prior cycle	+3
6. Experienced nausea or vomiting in the prior cycle	+5
7. Number of cycles:	
About to receive 2nd chemotherapy cycle	-5
About to receive ≥3rd chemotherapy cycle	-6

*adapted from Dranitsaris 2017[4]

- At randomization patients were stratified for carboplatin (use and non-use) and by country.
- Patients randomized to the NEPA arm received a single dose of oral NEPA + oral DEX (or equivalent corticosteroid) approximately 1 hour prior to chemotherapy on Day 1.
- Patients randomized to the SOC arm received any guideline-recommended 5-HT_3RA + oral or IV DEX (or equivalent corticosteroid) approximately 1 hour prior to chemotherapy on Day 1.
- In patients receiving MEC with known potential for delayed nausea and vomiting (i.e., oxaliplatin, anthracycline, cyclophosphamide), the use of DEX on days 2 and 3 could be considered. For all other patients receiving the other MEC no additional prophylaxis was allowed.

Efficacy/Safety Endpoints & Statistical Analysis

- The primary efficacy endpoint was complete response (defined as no emesis and no use of rescue medication) during the overall (0-120 h) phase post-chemotherapy over 3 consecutive cycles.
- Complete response rates during the acute (0-24 h), delayed (>24-120 h) and overall phases post-chemotherapy each cycle were also calculated.
- Additional efficacy endpoints (e.g., complete protection (defined as no emesis, no rescue and no significant nausea), no emesis, no nausea, no rescue use) are being analyzed.
- The Multinational Association for Supportive Care in Cancer (MASCC) Antiemesis Tool (MAT) was used to capture nausea and vomiting post-chemotherapy.
- Safety was assessed through collection of treatment-emergent adverse events.
- The efficacy analyses were performed on the full analysis set which follows the intent-to-treat principle and includes all randomized patients who received study drug and had efficacy data collected at least through cycle 1.
- A generalized linear model with generalized estimating equations was used to analyze the primary endpoint of complete response over 3 cycles of MEC with logit link function, binomial distribution, and with study treatment, carboplatin use, and the country as factors.

The novel MyRisk trial was designed to offer a more personalized approach to antiemetic prophylaxis by using a risk factor algorithm to identify patients at increased emetic risk who might benefit from an NK_1RA-containing regimen in the MEC setting. In this trial NEPA (netupitant/palonosetron) + DEX was superior to a guideline-based regimen of a 5-HT_3RA + DEX in preventing CINV over 3 consecutive cycles. Risk factor evaluation should be considered for all patients receiving MEC in order to optimize CINV control.

RESULTS

- A total of 401 patients were randomized and received study drug, while 388 patients (n = 189 NEPA, n = 199 SOC) had data available for the efficacy analysis.

Patient Demographics & Chemotherapy

- Slightly more than half (55%) of patients were male. The mean age was 62.7 years. Most common cancers were colorectal (42%) and lung (19%) and the most common MEC was oxaliplatin (64%) (**Table 2**).
- The mean CINV risk score was 13.6 in both arms (min 13, max 17).
- In the SOC arm, the most used 5-HT_3RA was granisetron (46%) with ondansetron (27%) and palonosetron (26%) administered in about a quarter of patients.

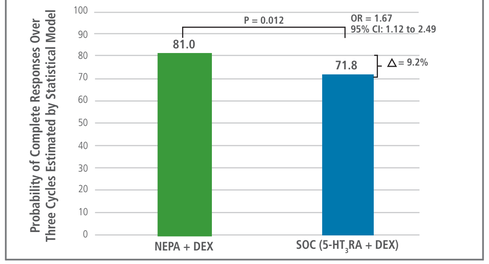
Table 2. Patient Demographics and Chemotherapy (All Patients)

	NEPA (n=196)	SOC (n=205)
Age (mean ± SD, years)	**62.7** (±11.8)	**62.7** (±11.3)
Sex		
Female	**93** (47.4%)	**87** (42.4%)
Male	**103** (52.6%)	**118** (57.6%)
ECOG at Baseline		
0	**110** (56.1%)	**98** (47.8%)
1	**82** (41.8%)	**103** (50.2%)
2	**4** (2.0%)	**4** (2.0%)
Most Common MEC Agents		
Oxaliplatin	**124** (63.3%)	**133** (64.9%)
Carboplatin	**58** (29.6%)	**62** (30.2%)
Other	**14** (7.1%)	**10** (4.9%)
Chemotherapy Naïve	**145** (74.0%)	**159** (77.6%)
Chemotherapy Non-naïve	**51** (26.0%)	**46** (22.4%)
Most Common Cancer Types		
Colon/Colorectal	**83** (42.3%)	**85** (41.5%)
Lung	**35** (17.9%)	**39** (19.0%)
Ovarian	**15** (7.7%)	**15** (7.3%)
Breast	**7** (3.6%)	**1** (0.5%)

Efficacy Outcomes

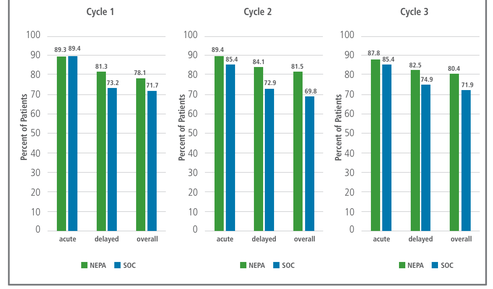
- The model estimated a higher probability of complete response in the NEPA arm (81.0%) compared to the SOC arm (71.8%) (OR=1.67, 95%CI: 1.12 to 2.49; p=0.012) during the overall phase over 3 cycles of chemotherapy (**Figure 1**).

Figure 1. Model-estimated Complete Response Rates (0-120h) Over Three Cycles of Chemotherapy



- Complete response rates were consistently numerically higher in the NEPA group than in the SOC group during both the delayed (>24-120h) and overall phases post-chemotherapy across all three cycles (**Figure 2**).

Figure 2. Percent of Patients with a Complete Response During the Acute, Delayed, and Overall Phases for Each of the Three Cycles of Chemotherapy



Safety Outcomes

- The safety profiles of the NEPA and SOC arms were comparable, with no significant differences observed in the adverse event (AE) profiles. Fatigue, diarrhea and constipation were the most commonly reported treatment-emergent AEs in both treatment groups.

CONCLUSIONS

- This novel trial is, to our knowledge, the first to take a personalized approach to antiemetic prophylaxis by integrating pre-treatment risk factors with planned chemotherapy in assessing antiemetic efficacy of different regimens.
- NEPA plus DEX was superior to guideline-based SOC in preventing CINV in patients with elevated emetic risk, highlighting the benefit of a more personalized approach to antiemetic prophylaxis.
- This is the first study to not only show a benefit of an NK_1RA-containing regimen over a 5-HT_3RA + DEX in at-risk patients receiving MEC, but also the first to evaluate antiemetic efficacy across three chemotherapy cycles.
- These outcomes may be partly explained by NEPA's distinct pharmacologic profile[8,9], and may not be generalizable to other NK_1RA-containing regimens.
- Incorporating risk factor assessment into clinical practice for patients receiving MEC may help optimize CINV control.

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Study sponsored by Helsinn Healthcare, Lugano Switzerland.

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