Exploratory Analysis of Nausea and Vomiting Probability over Multiple Cycles of NEPA (netupitant/palonosetron) Prophylaxis in Metastatic Breast Cancer Patients Treated with Trastuzumab Deruxtecan

San Antonio Breast Cancer Symposium
9-12 December 2025
Poster Number PS1-05-11

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BACKGROUND

- Antibody–drug conjugates (ADCs) have transformed breast cancer (BC) treatment, offering targeted cytotoxic delivery with improved efficacy.
- Trastuzumab deruxtecan (T-DXd) has emerged as a practice-changing ADC across HER2-expressing disease.

T-DXd-induced Nausea and Vomiting

- Nausea and vomiting (NV) are among the most common and burdensome adverse events of T-DXd treatment.[1]
- Across pooled trials in metastatic breast cancer (mBC), all-grade N and V were reported in 75% and 46% of patients, respectively.[2]
- T-DXd–related N often persists beyond day 5, highlighting a long-delayed phase that can markedly impact patients' quality of life (QoL).[3-5]
- Optimizing antiemetic control is critical to preserve QoL, maintain dose intensity[6], and prevent discontinuation, as patients often receive T-DXd for extended duration.
- Preventing NV is also crucial as it may contribute to the development of other adverse events, such as fatigue.[7]

Antiemetic Guidelines

- Evidence-based antiemetic guidelines classify T-DXd as moderate-to-highly emetogenic and recommend an NK_1RA-containing regimen as upfront prophylaxis.[8,9]
- Effective control of NV is imperative from the first cycle of treatment for optimal management throughout subsequent cycles.

NEPA (fixed combination of (fos)netupitant/palonosetron)

- NEPA is a fixed combination of the NK_1 RA, (fos)netupitant, and the 5-HT_3 RA, palonosetron.
- Compared to aprepitant, netupitant exhibits a longer half-life and higher persistent NK_1 receptor occupancy, providing receptor blockade for an extended duration.[10]
- Given the long-delayed NV associated with T-DXd, antiemetics with longer half-lives and extended NK_1 receptor occupancy may offer extended antiemetic prevention.

OBJECTIVE

- The objective of this retrospective analysis was to examine the probability of patients experiencing NV over multiple cycles of T-DXd following antiemetic prophylaxis with NEPA.

METHODS

- This was a single-center, exploratory retrospective analysis of patients with HER2+/HER2-low mBC patients receiving T-DXd.
- Occurrence of NV in patients with HER2-positive or HER2-low mBC over the first 5 cycles of T-DXd for each patient were extracted and analyzed from clinical records at Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy.
- The observational period for assessing NV was the time between 2 consecutive cycles, to better collect prolonged side effects.
- The probability of NV occurring in each of 5 cycles of T-DXd was estimated using a logistic regression with NV as a dependent variable, cycle as an independent variable and with Generalized Estimating Equation to account for repeated measures.

While ADCs like T-DXd represent major advances in breast cancer treatment, they can also lead to long-delayed NV that outlasts the patterns typical of traditional chemotherapy. Optimizing antiemetic control is critical to preserve QoL, maintain dose intensity, and prevent treatment discontinuation. This analysis evaluated NV control over multiple cycles of T-DXd following antiemetic prophylaxis with NEPA, a pharmacologically distinct NK_1/5-HT_3 RA combination characterized by prolonged half-lives of both agents and extended NK_1 receptor occupancy. NEPA demonstrates the potential to prevent NV over repeated T-DXd cycles in mBC patients, reinforcing the need for appropriate antiemetic prophylaxis from the first cycle.

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RESULTS

Patient Demographics

- The analysis included 25 patients, followed for 5 cycles for a total of 118 cycles.
- Patient characteristics are summarized in **Table 1**.
- NEPA with dexamethasone 12 mg was administered as prophylaxis in all but 6 cycles.

Table 1. Patient Characteristics

Characteristic	Total Patients N = 25
Age at start of T-DXd	
Median (range)	**64** (41, 78)
HER2 Status	
HER2-positive	**10** (40%)
HER2-low	**15** (60%)
Line of T-DXd	
1st	**5** (20%)
2nd	**6** (24%)
3rd or later	**14** (56%)

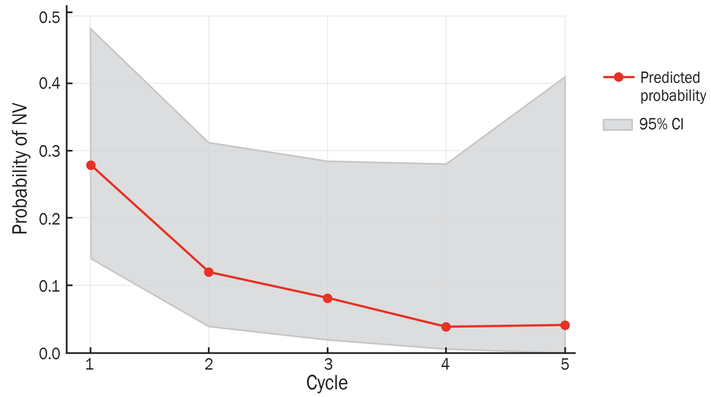
Probability of Nausea & Vomiting Over Cycles

- The estimated probability of developing NV was low and diminished over each cycle (**Table 2 & Figure 1**), suggesting that NV was well-controlled with NEPA from the first cycle onward.

Table 2. Probability of Nausea/Vomiting Occurrence During Each Cycle (Estimates Obtained from a Logistic Regression)

Cycle	Probability of NV occurrence	Lower 95% CI	Upper 95% CI
1	0.2800	0.1397	0.4822
2	0.1200	0.0392	0.3130
3	0.0812	0.0192	0.2856
4	0.0390	0.0042	0.2812
5	0.0408	0.0026	0.4101

Figure 1. Predicted Probability of Nausea/Vomiting Across T-DXd Cycles



CONCLUSIONS

- These exploratory findings indicate that NEPA is likely to be highly effective in preventing NV over multiple T-DXd cycles in mBC patients.
- Because the observation period spanned the entire interval between cycles, these findings suggest that NEPA may help prevent long-delayed NV, likely reflecting its distinct pharmacologic properties.
- It also underscores the value of using an appropriate upfront antiemetic regimen from the first cycle of T-DXd.
- These preliminary findings need to be confirmed in prospective studies.

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