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REVIEW

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Nausea and vomiting in an evolving anticancer treatment landscape: long-delayed and emetogenic antibody-drug conjugates

Yeon Hee Park[a], Giampaolo Bianchini[b,c], Javier Cortés[d,e,f], Luca Licata[b], María Vidal[g,h], Hirotoshi Iihara[i], Eric J. Roeland[j], Karin Jordan[k,l], Florian Scotté[m], Lee Schwartzberg[n], Rudolph M. Navari [o], Matti Aapro[p] and Hope S. Rugo[q]

[a]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [b]Department of Medical Oncology, IRCCS San Raffaele Hospital, Milan, Italy; [c]School of Medicine and Surgery, Vita-Salute San Raffaele University, Milan, Italy; [d]International Breast Cancer Center (IBCC), Pangaea Oncology, Quironsalud Group, Barcelona, Spain; [e]IOB Madrid, Hospital Beata María Ana, Madrid, Spain; [f]Faculty of Biomedical and Health Sciences, Department of Medicine, Universidad Europea de Madrid, Madrid, Spain; [g]Department of Medical Oncology, Hospital Clinic, Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain; [h]Department of Medicine, University of Barcelona, Barcelona, Spain; [i]Department of Pharmacy, Gifu University Hospital, Gifu, Japan; [j]Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA; [k]Department of Hematology, Oncology and Palliative Medicine, Ernst von Bergmann Hospital, Potsdam, Germany; [l]Department of Medicine V, Hematology, Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany; [m]Interdisciplinary Cancer Course Department, Gustave Roussy Cancer Institute, Villejuif, France; [n]Renown Health-Pennington Cancer Institute, University of Nevada, Reno, NV, USA; [o]World Health Organization, Mount Olive, AL, USA; [p]Genolier Cancer Centre, Clinique de Genolier, Genolier, Switzerland; [q]University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

ABSTRACT

Nausea and vomiting are common, distressing side effects associated with chemotherapeutic regimens, resulting in reduced quality of life and treatment adherence. Appropriate antiemetic prophylaxis strategies may reduce/prevent chemotherapy-induced nausea and vomiting (CINV). Historically, investigators assessed antiemetics up to 120 hours after chemotherapy. However, CINV can extend beyond this time. Thus, the effect of antiemetics during the long-delayed period (>120 hours) requires investigation. Emerging treatment options, including certain antibody-drug conjugates (ADCs), are associated with high rates of acute and late-onset nausea and vomiting that can last for extended duration. With the increasing number of ADCs approved and in development, there is urgency to control nausea and vomiting in patients receiving these new therapies. In this narrative review, we present the emetogenic potential of ADCs and CINV in the long-delayed period along with antiemetic prophylaxis strategies used to date. We also discuss the promising role of the fixed-combination antiemetic NEPA ([fos]netupitant plus palonosetron) in controlling long-delayed nausea and vomiting, addressing characteristics that may contribute to its longer efficacy duration compared to other antiemetics. Finally, we highlight encouraging results with NEPA in patients receiving the ADCs trastuzumab deruxtecan or sacituzumab govitecan, which suggest NEPA may be an effective antiemetic prophylaxis in these settings.

PLAIN LANGUAGE SUMMARY

Patients with cancer who are treated with chemotherapy often have nausea and vomiting as side effects. These symptoms can be very uncomfortable, negatively impact the quality of life, and may cause patients to stop treatment. Using the right antinausea and vomiting medications can help to reduce symptoms and enable patients to stay on therapy.

Many studies have looked at how effective different combinations and doses of these medications are in reducing or preventing nausea and vomiting in the 5 days after chemotherapy treatment. However, it is now clear that nausea and vomiting can last longer than this time period. Newer treatments called antibody-drug conjugates (ADCs) are being used to treat patients with cancer but may also cause nausea and vomiting after 5 days (known as long-delayed nausea and vomiting). To make sure patients receive the best possible care to prevent these symptoms, it is important to understand how well antinausea and vomiting medications work over longer periods of time.

This paper discusses how often this long-delayed nausea and vomiting occurs in patients after they have received chemotherapy or ADCs. We also look at different medications that are being used to prevent nausea and vomiting, including a drug called NEPA (netupitant and palonosetron). NEPA is a combination of two antinausea and vomiting medications. It may be a good option for preventing long-delayed nausea and vomiting, as it is effective over longer time periods than other similar medications. NEPA has shown very promising results in studies so far.

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CONTACT Yeon Hee Park yeonh.park@samsung.com Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro Gangnam-gu, Seoul 06351, Republic of Korea

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Article highlights

- Chemotherapy-induced nausea and vomiting (CINV) is a common and distressing side effect associated with many chemotherapeutic drugs and regimens that is highly troublesome for patients and can impede ongoing receipt of chemotherapy.
- CINV has traditionally been classified as "acute" (≤24 hours) or "delayed" (>24–120 hours), depending on its timing with respect to chemotherapy administration.
- Some antibody-drug conjugates (ADCs) were unexpectedly found to induce nausea and vomiting in a high proportion of patients, with nausea being the most frequent treatment-emergent adverse event seen in multiple clinical trials.
- Recognition of the emetogenic potential of ADCs has resulted in trastuzumab deruxtecan and sacituzumab govitecan being incorporated as emetogenic agents in guidelines.

Nausea and vomiting beyond the delayed phase

- It has become clear that CINV can persist beyond 120 hours and this phenomenon ("long-delayed" CINV) has been poorly characterized, highlighting an unmet need to continue assessing CINV beyond day 5 after chemotherapy initiation.
- Some ADCs are associated with long-delayed nausea and vomiting, and with the improved progression-free survival seen with ADC treatment, this risk is particularly relevant for patients due to the long treatment duration.

Preventing nausea and vomiting in the long-delayed phase

- The fixed-combination antiemetic NEPA has a long plasma elimination half-life and duration of receptor occupancy, characteristics that make it suitable for providing long-lasting antiemetic prophylaxis.
- NEPA had high efficacy in both the traditionally defined delayed phase and in multiple studies investigating the effect of NEPA in the long-delayed phase.
- Limited studies on antiemetic prophylaxis for patients treated with ADCs have highlighted the need for early and adequate treatment, and have shown promising results with NEPA.

Summary and discussion

- Effective antiemetic prophylaxis for preventing long-delayed nausea and vomiting is a growing unmet need for patients receiving traditional chemotherapy or ADCs, and NEPA-based regimens may be appropriate in this setting.

1. Introduction

1.1. Chemotherapy-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a side effect associated with many anticancer chemotherapies. CINV is common and distressing and can impact patients' lives significantly; it can result in decreased quality of life, higher cancer-related fatigue [1], and reduced adherence to chemotherapy. As a result, CINV is a highly troublesome toxicity for patients and impedes their ongoing receipt of chemotherapy [2–5]. Different antineoplastic treatments can induce distinct patterns of emesis. For example, cisplatin induces a biphasic course of emesis, and researchers have used it as the gold-standard emetic stimulus in many clinical trials [6,7]. Generally, an initial emesis peak is observed between 6 and 8 hours after cisplatin administration, followed by a temporary reduction in symptoms and a second nausea and emesis phase between 24 and 72 hours. This second peak can persist over 5 days in many patients [6,8,9]. Based on this biphasic pattern, CINV can be classified as "acute" or "delayed," depending on its timing with respect to chemotherapy administration. Acute CINV occurs within the first 24 hours after administration of chemotherapy, while historically, delayed CINV has been defined as occurring >24–120 hours after chemotherapy [2,10–12].

Over time, there have been advances in the understanding of mechanisms by which chemotherapeutic agents can induce nausea and vomiting. CINV's pathophysiology is multifactorial and very complex. The two main mechanisms of CINV, the peripheral and central pathways, are shown in Figure 1. The peripheral pathway is primarily triggered by serotonin release in the GI tract, activating 5-hydroxytryptamine-3 (5-HT_3) receptors in the intestine and resulting in acute emesis (<24 hours). In contrast, the central pathway is mainly triggered by the release of substance P in the brain, activating neurokinin-1 (NK_1) receptors and resulting in delayed emesis (>24–120 hours). A more detailed examination of the diverse mechanisms underlying CINV can be found in Gupta et al. [13] and Farhat et al. [14]. Although nausea and vomiting are frequently clinically associated [15] and often considered a unified symptom, the precise physiology contributing to nausea is less well characterized, and its assessment remains a clinical challenge due to its subjective nature [15–19].

1.2. Antibody-drug conjugate-induced nausea and vomiting

Newly developed treatment options entering clinical practice have also been associated with emetogenic potential. Chief among these are the antibody-drug conjugates (ADCs), which consist of three main components: a monoclonal antibody that is aimed at a specific tumor-associated antigen, a potent cytotoxic small molecule (the payload), and a linker to connect the two [20]. Currently, 15 ADCs have been approved by the US Food and Drug Administration, the European Medicines Agency, and/or other government agencies for treating hematologic malignancies and solid tumors, and over 100 ADCs are in clinical development [21,22]. Originally, ADCs were not expected to cause nausea and vomiting due to the targeted release of the payload to tumor cells. However, off-target release of the payload in the circulation may result in toxicities, including nausea and vomiting [23]. These cytotoxic payloads are suspected to cause nausea and vomiting through a similar mechanism as that of CINV, although the exact mechanism by which ADCs induce nausea and vomiting remains unclear [14]. A meta-analysis that included 169 clinical trials involving 22,492 patients investigated over 20 ADCs and identified nausea (44.1%) as one of the top three most common any-grade adverse events seen, next to lymphopenia (53.0%) and neutropenia (43.7%) [24].

Among ADCs, the anti-HER2–targeted ADC trastuzumab deruxtecan (T-DXd) [25] had a likelihood for any-grade adverse events of 98% [24]. Specifically, phase 2 and 3 trials investigating T-DXd in breast cancer, lung cancer, colorectal cancer, gastric cancer, and different solid tumors all reported a high incidence of nausea and vomiting (Table 1) [26–34]. In these studies, treatment-emergent any-grade nausea rates ranged from 55–78%, and any-grade vomiting rates ranged from 25–52% [26–34]. While nausea and vomiting rates showed some variation between tumor types, nausea was the most frequent treatment-emergent adverse event in each of the trials. As with CINV, ADC-induced nausea and vomiting can lead to dose reduction. In a recent pooled, post-hoc analysis of clinical trials involving

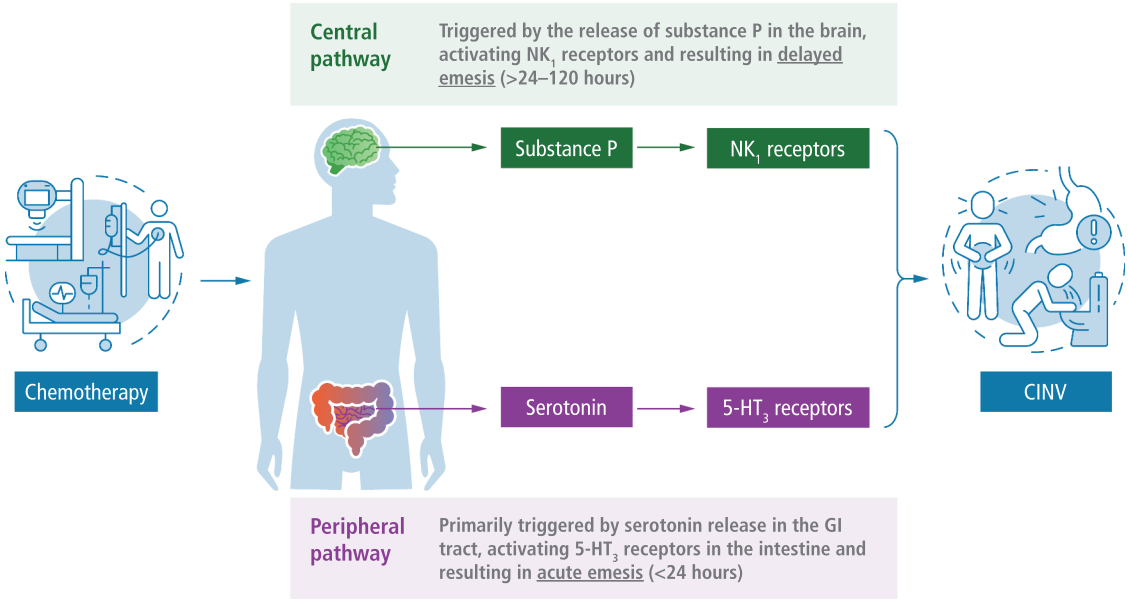

Figure 1. Pathophysiology of CINV. Two mechanisms resulting in emesis are the peripheral and central pathways. The peripheral pathway is primarily triggered by serotonin release in the gastrointestinal tract, activating 5-HT_3 receptors in the intestine and resulting in acute emesis (<24 hours). The central pathway is triggered by the release of substance P in the brain, activating NK_1 receptors and resulting in delayed emesis (>24–120 hours).

5-HT_3: 5-hydroxytryptamine-3; CINV: chemotherapy-induced nausea and vomiting; GI: gastrointestinal; NK_1: neurokinin-1.

Table 1. Nausea and vomiting rates in patients receiving T-DXd in the DESTINY trials.[a]

Trial	Reference	Patient population	Nausea, %		Vomiting, %	
			Any grade	Grade ≥3[b]	Any grade	Grade ≥3[b]
Treatment-emergent adverse events reported						
DESTINY-Breast01	[26]	*N* = 184 HER2-positive metastatic breast cancer	78	8	46	4
DESTINY-Breast02	[27]	*N* = 404 HER2-positive metastatic breast cancer	73	7	38	4
DESTINY-Breast03	[28]	*N* = 261 HER2-positive unresectable or metastatic breast cancer	77	7	52	2
DESTINY-Lung02	[29]	*N* = 152 (*n* = 101 5.4 mg/kg; *n* = 50 6.4 mg/kg) Metastatic *HER2*-mutant non-small cell lung cancer	67 (5.4 mg/kg) 82 (6.4 mg/kg)	4 (5.4 mg/kg) 6 (6.4 mg/kg)	32 (5.4 mg/kg) 44 (6.4 mg/kg)	3 (5.4 mg/kg) 2 (6.4 mg/kg)
DESTINY-CRC01	[30]	*N* = 86 HER2-expressing metastatic colorectal cancer	62	6	31	1
DESTINY-Gastric01	[31]	*N* = 125 HER2-positive advanced gastric cancer	63	5	26	0
DESTINY-PanTumor02	[32]	*N* = 267 Locally advanced or metastatic HER2-expressing solid tumors	55	N/A	25	N/A
Treatment-related adverse events reported						
DESTINY-Breast04	[33]	*N* = 371 HER2-low metastatic breast cancer	73	5	34	1
DESTINY-Lung01	[34]	*N* = 91 Metastatic *HER2*-mutant non-small cell lung cancer	73	9	40	3

[a]The DESTINY trials did not include a consistent recommendation for the use of antiemetics. Many patients were treated with antiemetics after experiencing nausea and/or vomiting.
[b]Adverse events were graded per National Cancer Institute Common Terminology Criteria for Adverse Events.
HER2: human epidermal growth factor receptor 2; N/A: not available; T-DXd: trastuzumab deruxtecan.

1,449 patients receiving T-DXd, the incidence of dose reduction due to any-grade nausea and vomiting was 4.8% and 1.4%, respectively [35].

Another ADC associated with high rates of nausea and vomiting is the anti-Trop-2–targeted ADC sacituzumab govitecan (SG). The phase 1/2 single-group, multicenter IMMU-132-01 trial enrolled 108 patients with previously treated metastatic triple-negative breast cancer to receive SG monotherapy. Overall, 67% experienced nausea, and nearly half reported vomiting [36]. In addition, the phase 2 open-label TROPHY-U-01 trial reported nausea and vomiting rates of 60% and 30%, respectively, in patients with metastatic urothelial carcinoma treated with SG [37]. The randomized, phase 3 TROPiCS-02 trial compared SG and chemotherapy in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer and observed higher rates of nausea and vomiting among patients treated with SG than those receiving standard chemotherapy: nausea rates were 55% and 31%, and vomiting rates were 19% and 12% for SG and chemotherapy, respectively [38]. Similarly, in the international, multicenter, phase 3 ASCENT

study of 235 patients with metastatic triple-negative breast cancer treated with SG, 57% experienced nausea and 29% experienced vomiting [39].

1.3. Antiemetic prophylaxis

Appropriate antiemetic prophylaxis per evidence-based guidelines [10–12] can reduce CINV. Historically, chemotherapeutic agents have been divided into different categories based on the emetic risk posed during the acute phase in the absence of antiemetic prophylaxis: highly emetogenic chemotherapy (HEC) causes CINV in over 90% of patients, moderately emetogenic chemotherapy (MEC) causes CINV in 30–90% of patients, and low emetogenic chemotherapy causes CINV in < 30% of patients [40]. Evidence-based antiemetic guidelines have clear recommendations for CINV. For adult patients, recommendations for patients receiving HEC include prophylaxis with combinations of an NK_1 receptor antagonist (RA), olanzapine, a 5-HT_3 RA, and a corticosteroid (primarily dexamethasone). For patients receiving MEC, guidelines recommend a 5-HT_3 RA with dexamethasone and an NK_1 RA for select patients [10–12]. The greatest impact of 5-HT_3 RAs is primarily during the acute phase, while NK_1 RAs impact the delayed phase [2]. NK_1 RAs used for preventing CINV include (fos)aprepitant, (fos) netupitant, and rolapitant; 5-HT_3 RAs include ondansetron, granisetron, and palonosetron [10–12].

The emetogenic potential of T-DXd and SG is increasingly being recognized, with incorporation in the list of emetogenic agents in guidelines; yet, a lack of agreement remains on their level of emetogenicity due to the paucity of evidence. As the high rates of nausea and vomiting were not anticipated with T-DXd, the DESTINY trials did not explore antiemetic therapy. There were no consistent recommendations for antiemetic use in the trial protocols, but many patients were reactively treated with antiemetics after experiencing nausea and/or vomiting [26–34]. For example, during DESTINY-Breast04, 51% of patients in the T-DXd arm received antiemetic prophylaxis administered per local guidelines, but 73% of patients still suffered from nausea [33,41]. Moreover, patients perceived that nausea and vomiting were worse with T-DXd than with standard chemotherapy [42]. National Comprehensive Cancer Network (NCCN) guidelines classified T-DXd and SG as highly emetogenic [12]. In contrast, the American Society of Clinical Oncology (ASCO) guidelines categorized T-DXd as moderately emetogenic [10]. The Multinational Association of Supportive Care in Cancer and European Society for Medical Oncology (MASCC/ESMO) guidelines designated both T-DXd and SG as moderately emetogenic, while highlighting that the emetic potential falls at the high end of the MEC category [11]. Therefore, effective antiemetic prophylaxis is required for patients receiving T-DXd or SG. Similarly, patients receiving other ADCs may require effective antiemetic prophylaxis.

2. Nausea and vomiting beyond the delayed phase

2.1. Long-delayed CINV

Most studies using antiemetics to prevent CINV have prospectively evaluated the impact up to 120 hours after the administration of chemotherapy (i.e., the end of the conventional delayed phase). However, CINV can persist beyond 120 hours [43–45], a phenomenon that has been poorly characterized over the last three decades. Several factors may have contributed to the under-recognition of this issue. The evaluation, prevention, and treatment of nausea and vomiting often differ between clinicians and patients, leading to potential discrepancies. In addition, in most clinical studies on antiemetic therapies, treatment typically lasted only 5 days, and there is a lack of research investigating the effects beyond this time frame. Consequently, the lack of longer-term data may have hindered the identification and understanding of this problem. The occurrence of CINV >120 hours is described as "long-delayed" CINV (LD-CINV) [46]. This CINV category is separate from the concept of chronic nausea and vomiting, which is persistent nausea and vomiting in patients with advanced cancer that is unrelated to chemotherapy [47]. While LD-CINV may have a chronic nature, its cause is related to antineoplastic therapy.

Several studies have highlighted the existence of LD-CINV as an unmet need. A survey among healthcare professionals in Japan assessed the presence of CINV for an extended period (i.e., >120 hours) following chemotherapy. The 809 survey respondents included physicians ($n = 533$), pharmacists ($n = 174$), and nurses ($n = 102$). Most respondents (91%) indicated they observed patients who experienced CINV on days 5–7 after chemotherapy [48]. In addition, a meta-analysis found that 31% of patients who received HEC ($n = 1333$) and 24% of patients who received MEC ($n = 715$) reported nausea during the long-delayed phase (>120 hours). Vomiting was experienced by 6% of patients receiving HEC and MEC each during this phase. The degree of CINV during the long-delayed phase was as severe as during the historically defined delayed phase, and patients who experienced nausea or vomiting on days 4 or 5 were at increased risk of having LD-CINV [46]. A retrospective, real-world study investigating treatment outcomes, resource utilization, and costs associated with antiemetics for patients who received cisplatin-based chemotherapy found nausea and vomiting occurring on days 8–14 after chemotherapy [49]. The NCCN guidelines also highlight that emesis associated with cisplatin reaches its maximal intensity at 48–72 hours after administration but can persist for 6–7 days [12]. Finally, a prospective real-world study in China included a "beyond the risk period" time frame defined as days 8–21 from start of chemotherapy and found an incidence of CINV of 36% in this period among 1110 patients receiving HEC or MEC. Nausea was seen in 35% of patients and vomiting in 11%. Most patients received antiemetic regimens; however, only 22% of patients received this per NCCN guidelines [50]. Taken together, these data indicate an unmet need to continue assessing CINV beyond day 5 after chemotherapy initiation.

2.2. Long-delayed ADC-induced nausea and vomiting

The existence of long-delayed nausea and vomiting may be more relevant than ever with the changing landscape of cancer treatment, as ADCs have also been associated with this phenomenon. In addition, ADCs are correlated with improved

progression-free survival over older treatment regimens [51], leading to an extended treatment duration and increased risk of long-delayed, ADC-induced nausea and vomiting. Results from DESTINY-Breast04 highlighted that T-DXd–induced nausea and vomiting occurred late with extended duration: the median time to onset for nausea was 3 days, and the median duration was 10 days; the median time to onset for vomiting was 9.5 days, and the median duration was 3 days [41]. This late onset and extended duration indicate that patients could experience nausea for nearly half of the treatment duration while receiving T-DXd. As T-DXd treatment can continue for several months until disease progression or the occurrence of unacceptable toxicities, this continued nausea increases the overall burden for patients. While the reasons for the late onset remain unclear, the pharmacokinetic profile of T-DXd, with its long half-life and slow release of deruxtecan over time, may explain the temporal pattern of nausea and vomiting observed in clinical trials [52,53]. Similar to T-DXd, nausea and vomiting induced by SG could have a late onset and extended duration: the median time to onset for any-grade nausea was 8 days, with a median duration of 5.5 days; the median time to onset for vomiting was 24.5 days, with a median duration of 1.5 days [54].

3. Preventing nausea and vomiting in the long-delayed phase

The need to optimize nausea and vomiting prophylaxis beyond the 5-day overall phase is clear [43,44,54–59]. However, it remains uncertain what the most effective regimen is to provide long-lasting prophylaxis. While antiemetic guidelines provide clear, evidence-based recommendations for CINV prophylaxis for the first 120 hours after chemotherapy administration, guidance for later periods is lacking [10,12,60,61]. In addition, because T-DXd and SG have become available only recently, no evidence-based guidance for antiemetic prophylaxis exists for patients treated with these compounds. MASCC/ESMO guidelines indicate that no definitive antiemetic treatment recommendations can currently be made for T-DXd or SG. However, they note that the emetogenic potential of these ADCs appears comparable to high-dose carboplatin. For carboplatin, MASCC/ESMO guidelines recommend a three-drug regimen including an NK_1 RA, a 5-HT_3 RA, and dexamethasone [11]. NCCN recommends a regimen with an NK_1 RA, a 5-HT_3 RA, olanzapine, and dexamethasone for agents with high emetic risk such as T-DXd or SG [12] (Figure 2). Identifying the most effective antiemetic protocols for patients receiving ADCs, including T-DXd and SG, is an unmet need to optimize treatment completion and efficacy.

3.1. NEPA (oral and IV) and fosnetupitant single-agent plus palonosetron for prevention of LD-CINV

NEPA is currently the only available fixed-combination antiemetic, composed of an NK_1 RA (netupitant [oral] or fosnetupitant [intravenous]) and a 5-HT_3 RA (palonosetron). NEPA is administered as a single dose prior to chemotherapy, offering simplicity and convenience while targeting both main emetic pathways for effective CINV prophylaxis [62]. NEPA may be a particularly effective regimen for preventing LD-CINV, given the much longer plasma elimination half-life of netupitant (88 hours) compared to the NK_1 RA aprepitant (9–13 hours) [63,64]. In addition, netupitant has demonstrated a long

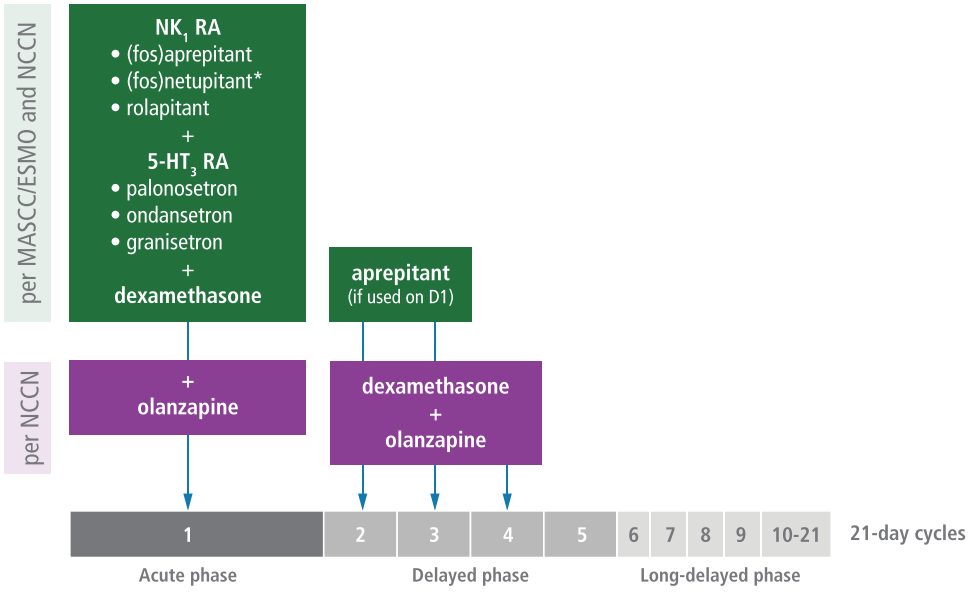

Figure 2. Antiemetic recommendations for patients treated with T-DXd or SG. MASCC/ESMO guidelines recommend a 3-drug regimen including an NK_1-receptor antagonist, a 5-HT_3-receptor antagonist, and dexamethasone for patients receiving T-DXd or SG. No dexamethasone (or other antiemetic) should be routinely administered after day 1. NCCN guidelines recommend a 4-drug regimen including an NK_1-receptor antagonist, a 5-HT_3-receptor antagonist, dexamethasone, and olanzapine as the preferred option for patients receiving T-DXd or SG. Dexamethasone and olanzapine should be routinely administered on days 2–4 as well. *Netupitant or fosnetupitant is administered with palonosetron as part of the fixed-dose combination agent NEPA.

5-HT_3: 5-hydroxytryptamine-3; ESMO: European Society for Medical Oncology; MASCC: Multinational Association of Supportive Care in Cancer; NCCN: National Comprehensive Cancer Network; NK_1: neurokinin-1; SG: sacituzumab govitecan; T-DXd; trastuzumab deruxtecan.

duration of receptor occupancy: in the striatum, receptor occupancy with netupitant reached 90% as early as 2.2 hours after administration and remained >75% after 120 hours; in the occipital cortex, the anterior cingulate, and the frontal cortex, receptor occupancy remained close to 90% up to 120 hours postdosing [65]. Another study applied pharmacodynamic modeling using data from previous pharmacokinetic studies to estimate the rate, duration, and extent of NK_1 receptor occupancy in the striatum up to 240 hours after netupitant administration. NK_1 receptor occupancy was predicted to reach 90% at 2.2 hours after administration, followed by a slow decline after 24 hours to 59% at 240 hours [66,67].

Patients who experience CINV during days 4 and 5 after chemotherapy appear to be at increased risk for LD-CINV [46,68], indicating a need for effective control in the historically defined delayed phase. Superior outcomes with NEPA compared with aprepitant regimens have been observed in the delayed phase and significantly fewer patients receiving NEPA experienced breakthrough CINV and breakthrough significant nausea on individual days 3–5 following chemotherapy [69,70]. Several studies have investigated the efficacy of NEPA beyond 120 hours after chemotherapy. All studies discussed here defined complete response as no emesis and no use of rescue medication. Single-dose NEPA was compared to a 3-day aprepitant regimen in a pragmatic prospective study of patients receiving MEC that included an extended overall phase up to 144 hours. Complete response rates were significantly higher for patients receiving NEPA than those receiving an aprepitant regimen during the extended overall phase (0–144 hours; 77% vs 58%, $p = 0.003$). Moreover, in the extended delayed phase (>24–144 hours), complete response rates were numerically higher for NEPA than the aprepitant regimen (90% vs 83%, $p = 0.159$) [45]. Further, a multicenter, open-label, phase 2 study evaluated whether NEPA's efficacy during cycle 1 would be maintained over subsequent cycles in patients with breast cancer receiving adjuvant anthracycline plus cyclophosphamide. Complete response during the overall study period significantly improved even in the LD-CINV setting (during days 6–21) over all treatment cycles [44]. The efficacy of a single intravenous dose of fosnetupitant in combination with palonosetron and dexamethasone was assessed in a randomized, double-blind, phase 2 study where nausea and vomiting rates were recorded until 168 hours after administration of cisplatin-based chemotherapy. The complete response rate with fosnetupitant was numerically higher than with placebo during the extended delayed phase (24–-168 hours; 75% vs 53%) [58]. The phase 3 CONSOLE study compared the efficacy of fosnetupitant and fosaprepitant in combination with palonosetron and dexamethasone in patients receiving cisplatin-based chemotherapy, assessing nausea and vomiting rates until 168 hours after treatment administration. Complete response rates for fosnetupitant and fosaprepitant were similar during the historically defined acute, delayed, and overall phases. However, a significantly higher complete response rate was observed for fosnetupitant (74%) than fosaprepitant (67%, $p = 0.0450$) during the extended overall phase (0–168 hours) and a nearly significant difference was seen between fosnetupitant (87%) and fosaprepitant (82%, $p = 0.0523$) during the long-delayed phase (120–168 hours) [59,71]. A pooled analysis of the previous two studies compared the efficacy of fosnetupitant and fosaprepitant and found that the complete response rate was significantly higher for fosnetupitant than fosaprepitant in the long-delayed phase (87% vs 81%, $p = 0.03$). This study also noted that treatment failure in the first 120 hours after chemotherapy was related to LD-CINV risk [68]. A retrospective study compared CINV outcomes of two antiemetic regimens, fosnetupitant as part of the fixed combination with palonosetron (IV NEPA) and fosaprepitant in combination with palonosetron, within 14 days after cisplatin-based chemotherapy. NEPA was associated with significantly lower rates of nausea and vomiting, CINV-related healthcare resource utilization, and costs compared to fosaprepitant-based regimens [49]. In a recent single-arm, open-label, phase 2 study conducted in Denmark, investigators evaluated the efficacy and safety of NEPA in patients undergoing radiotherapy and weekly cisplatin (40 mg/m^2) for cervical cancer. NEPA effectively prevented nausea and vomiting over an extended period of 35 days [72]. A real-world study recently conducted in India assessed the effectiveness and safety of intravenous NEPA in preventing LD-CINV in patients receiving HEC and MEC. NEPA showed high efficacy during the long-delayed phase (>120–240 hours), resulting in a complete response rate of 94% for patients receiving HEC and 98% for patients receiving MEC [73,74]. In addition, nausea was effectively managed; no nausea was reported in 87% of patients receiving HEC and in 97% of patients receiving MEC in the long-delayed phase, with no reports of moderate or severe nausea [75].

Collectively, these data and the observed long half-life suggest that NEPA may provide a long-lasting control of CINV and that the benefit of NEPA may extend beyond the historically defined delayed phase.

3.2. Prophylaxis for ADC-induced nausea and vomiting

There are currently no evidence-based recommendations for the prevention of nausea and vomiting in patients treated with T-DXd or SG.

3.2.1. T-DXd-induced nausea and vomiting

Experts have agreed that T-DXd–induced nausea and vomiting should be addressed from the first cycle of therapy, preferably with an NK_1 RA-containing regimen [56,57,76]. Several studies have begun to investigate drug regimens for antiemetic prophylaxis in patients treated with T-DXd. An open-label phase 2 study compared two-drug and three-drug antiemetic regimens for patients treated with T-DXd. Fourteen centers in Japan were included in the study, enrolling patients with breast cancer scheduled to receive T-DXd who were randomly assigned to receive granisetron and dexamethasone or granisetron, aprepitant, and dexamethasone. Complete response rates in the extended overall phase of 0–168 hours were 32% and 70% for the two- and three-drug regimens, respectively. No nausea rates were 11% and 52% and no vomiting rates were 53% and 81% in the extended overall phase for the two- and three-drug regimens, respectively [77]. These results indicate that combining an NK_1 RA, 5-HT_3 RA, and dexamethasone appears more effective than a 5-HT_3 RA and dexamethasone

for preventing T-DXd–induced nausea and vomiting. Other investigators evaluated the efficacy of NEPA with dexamethasone compared to a 5-HT_3 RA and dexamethasone in a retrospective study of 53 patients treated with T-DXd. NEPA was preferentially offered to patients at high risk of nausea and vomiting according to their individual risk factors. During cycle 1 of treatment, 28% of patients received a three-drug regimen (with NEPA) and 72% received a two-drug regimen; the frequency of vomiting was lower in the group receiving NEPA (0% vs 21%). Further, 15 out of 22 patients who received a two-drug regimen in cycle 1 and experienced nausea received NEPA-based prophylaxis in cycle 2, which significantly decreased the incidence of both nausea (from 100% to 53%, $p = 0.022$) and vomiting (from 47% to 13%, $p = 0.046$) [78]. The multicenter, randomized, double-blind, placebo-controlled, phase 2 study ERICA (jRCTs031210410) investigated the efficacy of prophylactic olanzapine combined with a 5-HT_3 RA and dexamethasone in preventing nausea and vomiting in 168 patients with HER2-positive or HER2-low metastatic breast cancer receiving their first cycle of T-DXd treatment. The atypical antipsychotic olanzapine is not approved as an antiemetic, but its broad activity on multiple receptors involved in the pathophysiology of nausea and vomiting has led to its use for managing CINV. It has been suggested that olanzapine may be particularly effective for the prevention of nausea [47,79]. Olanzapine is also recommended for prevention of CINV by the antiemetic guidelines [10–12]. The primary endpoint of the study was the complete response rate during the delayed phase. Secondary endpoints included capturing patients' experience of nausea and vomiting over a 21-day period following the start of T-DXd. Olanzapine 5 mg or placebo was administered once daily for days 1–6, and all patients received a 5-HT_3 RA selected by the investigator and dexamethasone (6.6 mg intravenous or 8 mg oral) on day 1. The addition of olanzapine resulted in increased complete response (70% vs 56%) and no nausea rates (58% vs 38%) in the delayed phase. These differences were maintained during the long-delayed phase for both complete response (64% vs 44%) and no nausea rates (51% vs 32%). A significant proportion of patients taking olanzapine experienced somnolence (25%), dry mouth (8%), hyperglycemia (8%), or dizziness (6%) [80].

Currently, new studies are further investigating the use of antiemetics to prevent T-DXd–induced nausea and vomiting. With the lengthy treatment duration of T-DXd, control of long-delayed nausea and vomiting is a clear concern and clinical challenge. The ongoing multicenter, observational, real-world study EUROPA T-DXd (NCT05458401) will report on patients treated with T-DXd who received prophylaxis for nausea and vomiting. This study enrolled 256 adult patients with advanced/metastatic HER2-positive breast cancer treated with T-DXd through a named patient program [81].

3.2.2. SG-induced nausea and vomiting

To date, few studies have investigated prophylactic antiemetics for patients receiving SG. Antiemetic treatment was allowed in the IMMU-132-01 trial, and 92% of patients received antiemetic premedication; however, no specific regimen was prescribed, making it difficult to assess the impact of these regimens [36]. In the ASCENT trial, it was recommended to manage nausea and vomiting using a two- or three-drug combination of 5-HT_3 RA and dexamethasone with or without an NK_1 RA. In total, 86% of patients received antiemetic prophylaxis during the study. Any-grade nausea was seen in 57% of patients receiving SG and any-grade vomiting in 29% [39]. A real-world, single-center retrospective analysis collected data from patients with metastatic triple-negative breast cancer receiving SG treatment between October 2020 and April 2023, and all patients received NEPA as antiemetic prophylaxis per institutional protocols. In this hypothesis-generating study, investigators evaluated adverse effects from 43 eligible patients, discovering that the incidence of nausea and vomiting was substantially lower than previous reports in the IMMU-132-01 and ASCENT studies [36,39]. Any-grade nausea and vomiting occurred in 21% and 9% of patients compared to 67% and 49% in IMMU-132-01 and 57% and 29% in ASCENT [82], suggesting a benefit of NEPA.

4. Summary and discussion

Optimal prophylaxis for nausea and vomiting continues to evolve with novel insights and the ever-increasing available and effective antineoplastic therapies, including ADCs. New anticancer treatments have novel mechanisms of action and different pharmacokinetics than conventional chemotherapy and may require antiemetic prophylaxis during the long-delayed phase. ADCs, such as T-DXd and SG, have shown nausea and vomiting as common adverse events [24] due to the off-target release of the ADC payload [23,24,83]. Given the half-life of ADCs, using historical definitions of acute and delayed nausea and vomiting may not fully capture patients' experience, as symptoms extend beyond previously studied time frames. Evidence suggests that patients receiving ADCs can suffer from nausea and vomiting much longer or later than 120 hours after treatment [41,54]. Patients require effective antiemetic prophylaxis to mitigate long-lasting ADC-induced nausea and vomiting, enhance adherence, and improve quality of life. Although T-DXd–induced nausea and vomiting was observed to be generally low-grade [35], the late onset and extended duration can severely impact patients' quality of life [41,84]. Similarly, LD-CINV occurs with traditional chemotherapy [46], and this has been under-recognized in the past. The full impact of long-term nausea and vomiting on quality of life likely remains underestimated. Increased awareness of the existence of long-delayed nausea and vomiting is needed, as it requires continued monitoring for toxicities over an extended period to be documented.

As ADCs are highly effective and well tolerated, patients may receive these therapies for months to years, especially as growing evidence shows ADCs are associated with prolonged progression-free survival [51]. This extended use makes adequate control of adverse events such as nausea and vomiting even more vital. During DESTINY-Breast03 and –04, anorexia and decreased appetite (26–29% of patients) were also observed, which can reduce treatment efficacy and exacerbate fatigue [84]. While there is no specific measure to target T-DXd–related anorexia, effective prevention of nausea and vomiting is a critical first step [84]. Due to the protracted

temporal pattern seen with T-DXd–induced nausea and vomiting, experts recommended the use of daily patient-reported outcomes between cycles to characterize the long-term course of nausea and vomiting further [84]. While more robust evidence is needed, existing clinical data indicate that a three-drug regimen for antiemetic prophylaxis may be more beneficial than a two-drug regimen in patients receiving ADC therapy [76–78]. A recent survey among healthcare professionals assessed their experience and perceptions of emetogenicity associated with some ADCs and collected information about their approach to antiemetic prophylaxis [85]. The results highlighted a need for education on the potential emetogenicity of each individual ADC and the specific features of the nausea and vomiting profile associated with these compounds, such as the potential for long-delayed nausea and vomiting.

Aside from T-DXd and SG, many more investigational ADCs and other therapies with novel mechanisms of action may similarly require antiemetic prophylaxis, particularly in the long-delayed phase. In addition, the treatment of LD-CINV needs to be optimized further. NEPA is a promising regimen for preventing long-delayed nausea and vomiting due to the long plasma elimination half-life [63,64] and duration of receptor occupancy observed with netupitant [65,66]. The difference in half-life and NK_1 receptor occupancy between netupitant and aprepitant is underscored by studies showing that prolonging the use of aprepitant to 6 days or adding a second dose of fosaprepitant on day 3 is more effective in preventing CINV than the standard regimen of 3-day aprepitant and 1-day fosaprepitant [86,87]. Building on the improved control of CINV with NEPA over aprepitant in the delayed phase and daily on days 3–5, early evidence suggests enhanced effectiveness in the long-delayed phase [45,68,69,72,73,75,78,82] requiring further prospective characterization in patients receiving ADCs. So far, most data on long-delayed nausea and vomiting with ADCs have come from patients treated with T-DXd. Deruxtecan is metabolized by CYP3A4 and netupitant, like aprepitant, is a moderate inhibitor of CYP3A4 [88]; however, no dose adjustment is recommended for patients receiving T-DXd who are receiving inhibitors of CYP3A [89]. In addition, based on the half-life of netupitant and palonosetron, no or only very modest accumulation of either compound would be expected if NEPA were to be administered every 3 weeks in conjunction with ADC treatment. For patients receiving treatment every 3 weeks, ~99% of netupitant and ~100% of palonosetron from prior NEPA administration should be eliminated by the time the next NEPA dose is received [90].

In conclusion, effective antiemetic prophylaxis for preventing long-delayed nausea and vomiting is a growing unmet need for patients receiving traditional chemotherapy or ADCs, and NEPA-based regimens may be appropriate in this setting.

5. Future perspective

International antiemetic guidelines have established recommendations for preventing ADC-induced nausea and vomiting aimed at assisting physicians in selecting the appropriate antiemetic prophylaxis. However, there currently is an absence of robust prospective studies. Considering the increasing number of patients receiving treatments such as T-DXd and SG, future prospective studies must identify the most effective antiemetic prophylaxis regimens.

The characteristics of netupitant, including the long plasma elimination half-life, duration and extent of NK_1 receptor occupancy, as well as the preliminary data on NEPA's efficacy in preventing long-delayed ADC-induced nausea and vomiting make NEPA a likely valuable option for nausea and vomiting prevention. These preliminary data require further prospective investigation.

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ORCID

Rudolph M. Navari http://orcid.org/0000-0002-8513-896X

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Fukuoka K, Yasutaka Y, Murata Y, et al. Factor analysis of fatigue in the early stages of cancer chemotherapy. Yakugaku Zasshi. 2023;143(11):971–976. doi: 10.1248/yakushi.23-00099
2. Navari RM, Aapro M, Longo DL. Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. N Engl J Med. 2016;374(14):1356–1367. doi: 10.1056/NEJMra1515442
3. Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. Ann Oncol. 2015;26(6):1081–1090. doi: 10.1093/annonc/mdv138
4. Fernández-Ortega P, Caloto MT, Chirveches E, et al. Chemotherapy-induced nausea and vomiting in clinical practice: impact on patients' quality of life. Support Care Cancer. 2012;20 (12):3141–3148. doi: 10.1007/s00520-012-1448-1
5. Van Laar ES, Desai JM, Jatoi A. Professional educational needs for chemotherapy-induced nausea and vomiting (CINV): multinational survey results from 2388 health care providers. Support Care Cancer. 2015;23(1):151–157. doi: 10.1007/s00520-014-2325-x
6. Martin M. The severity and pattern of emesis following different cytotoxic agents. Oncology. 1996;53(suppl 1):26–31. doi: 10.1159/000227637
7. Olver I, Molassiotis A, Aapro M, et al. Antiemetic research: future directions. Support Care Cancer. 2011;19(suppl S1):S49–S55. doi: 10.1007/s00520-010-1036-1
8. Kris MG, Cubeddu LX, Gralla RJ, et al. Are more antiemetic trials with a placebo necessary? Report of patient data from randomized trials of placebo antiemetics with cisplatin. Cancer. 1996;78(10):2193–2198. doi: 10.1002/(SICI)1097-0142(19961115)78:10<2193::AID-CNCR22>3.0.CO;2-T
9. Hesketh PJ, Van Belle S, Aapro M, et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. Eur J Cancer. 2003;39(8):1074–1080. doi: 10.1016/S0959-8049(02)00674-3
10. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO guideline update. J Clin Oncol. 2020;38(24):2782–2797. doi: 10.1200/JCO.20.01296
11. Herrstedt J, Clark-Snow R, Ruhlmann CH, et al. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO Open. 2024;9 (2):102195. doi: 10.1016/j.esmoop.2023.102195
12. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Antiemesis. Version 1.2024. cited 2025 Feb 19]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf
13. Gupta K, Walton R, Kataria SP. Chemotherapy-induced nausea and vomiting: pathogenesis, recommendations, and new trends. Cancer Treat Res Commun. 2021;26:100278. doi: 10.1016/j.ctarc.2020.100278
14. Farhat J, Sakai H, Tsurutani J. Management of nausea and vomiting induced by antibody–drug conjugates. Breast Cancer. 2025 [cited 2025 Feb 18];8(2):278–285. doi: 10.1007/s12282-025-01670-1
15. Bošnjak SM, Gralla RJ, Schwartzberg L. Prevention of chemotherapy-induced nausea: the role of neurokinin-1 (NK_1) receptor antagonists. Support Care Cancer. 2017;25(5):1661–1671. doi: 10.1007/s00520-017-3585-z
16. Aapro M. CINV: still troubling patients after all these years. Support Care Cancer. 2018;26(suppl 1):5–9. doi: 10.1007/s00520-018-4131-3
17. Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology and therapeutics. Therap Adv Gastroenterol. 2016;9(1):98–112. doi: 10.1177/1756283X15618131
18. Napadow V, Sheehan JD, Kim J, et al. The brain circuitry underlying the temporal evolution of nausea in humans. Cereb Cortex. 2013;23(4):806–813. doi: 10.1093/cercor/bhs073
19. Varangot-Reille C, Sanger GJ, Andrews PLR, et al. Neural networks involved in nausea in adult humans: a systematic review. Auton Neurosci. 2023;245:103059. doi: 10.1016/j.autneu.2022.103059
20. Thomas A, Teicher BA, Hassan R. Antibody–drug conjugates for cancer therapy. Lancet Oncol. 2016;17(6):e254–e262. doi: 10.1016/S1470-2045(16)30030-4
21. Riccardi F, Dal Bo M, Macor P, et al. A comprehensive overview on antibody-drug conjugates: from the conceptualization to cancer therapy. Front Pharmacol. 2023;14:1274088. doi: 10.3389/fphar.2023.1274088
22. Filis P, Zerdes I, Soumala T, et al. The ever-expanding landscape of antibody-drug conjugates (ADCs) in solid tumors: a systematic review. Crit Rev Oncol Hematol. 2023;192:104189. doi: 10.1016/j.critrevonc.2023.104189
23. Nguyen TD, Bordeau BM, Balthasar JP. Mechanisms of ADC toxicity and strategies to increase ADC tolerability. Cancers (Basel). 2023;15 (3):713. doi: 10.3390/cancers15030713
24. Zhu Y, Liu K, Wang K, et al. Treatment-related adverse events of antibody–drug conjugates in clinical trials: a systematic review and meta-analysis. Cancer. 2023;129(2):283–295. doi: 10.1002/cncr.34507
25. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin Cancer Res. 2016;22(20):5097–5108. doi: 10.1158/1078-0432.CCR-15-2822
26. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382(7):610–621. doi: 10.1056/NEJMoa1914510
27. André F, Hee Park Y, Kim SB, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023;401(10390):1773–1785. doi: 10.1016/S0140-6736(23)00725-0

28. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet. 2023;401 (10371):105–117. doi: 10.1016/S0140-6736(22)02420-5
29. Goto K, Goto Y, Kubo T, et al. Trastuzumab Deruxtecan in patients with *HER2* -mutant metastatic non–small-Cell lung cancer: primary results from the randomized, phase II DESTINY-Lung02 trial. J Clin Oncol. 2023;41(31):4852–4863. doi: 10.1200/JCO.23.01361
30. Yoshino T, Di Bartolomeo M, Raghav K, et al. Final results of DESTINY-CRC01 investigating trastuzumab deruxtecan in patients with HER2-expressing metastatic colorectal cancer. Nat Commun. 2023;14(1):3332. doi: 10.1038/s41467-023-38032-4
31. Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382(25):2419–2430. doi: 10.1056/NEJMoa2004413
32. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol. 2023;42(1):47–58. doi: 10.1200/JCO.23.02005
33. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med. 2022;387(1):9–20. doi: 10.1056/NEJMoa2203690
34. Li BT, Smit EF, Goto Y, et al. Trastuzumab Deruxtecan in *HER*2 -mutant non–small-Cell lung cancer. N Engl J Med. 2022;386 (3):241–251. doi: 10.1056/NEJMoa2112431
35. Park YH, Cortés J, Modi S, et al. Pooled analysis on characteristics of nausea and vomiting in patients receiving trastuzumab deruxtecan (T-DXd) in clinical studies. J Clin Oncol. 2024;42(suppl 16):12118. doi: 10.1200/JCO.2024.42.16_suppl.12118
• **Post hoc analysis highlighting the high incidence of nausea and vomiting in clinical trials with trastuzumab deruxtecan.**
36. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. N Engl J Med. 2019;380(8):741–751. doi: 10.1056/NEJMoa1814213
37. Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. J Clin Oncol. 2021;39 (22):2474–2485. doi: 10.1200/JCO.20.03489
38. Rugo HS, Bardia A, Marmé F, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. Lancet. 2023;402(10411):1423–1433. doi: 10.1016/S0140-6736(23)01245-X
39. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med. 2021;384 (16):1529–1541. doi: 10.1056/NEJMoa2028485
40. Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—state of the art. Support Care Cancer. 2011;19(suppl 1):S43–S47. doi: 10.1007/s00520-010-1003-x
41. Rugo HS, Jacot W, Tokunaga E, et al. 185O trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in patients (pts) with HER2-low unresectable and/or metastatic breast cancer (mBC): a detailed safety analysis of the randomized, phase III DESTINY-Breast04 trial. ESMO Open. 2023 Aug;8(suppl 4):101374. doi: 10.1016/j.esmoop.2023.101374
•• **Detailed analysis of selected treatment-emergent adverse events in the DESTINY-Breast04 trial, noting a higher incidence of nausea/vomiting with trastuzumab deruxtecan vs treatment of physician's choice.**
42. Ueno NT, Jacot W, Yamashita T, et al. Patient-reported outcomes (PROs) from DESTINY-Breast04 a randomized phase III study of trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice (TPC) in patients (pts) with HER2-low metastatic breast cancer (MBC). Ann Oncol. 2022;33(suppl 7):S632–S633. doi: 10.1016/j.annonc.2022.07.256
43. Bossi P, Cortinovis D, Fatigoni S, et al. A randomized, double-blind, placebo-controlled, multicenter study of a ginger extract in the management of chemotherapy-induced nausea and vomiting (CINV) in patients receiving high-dose cisplatin. Ann Oncol. 2017;28(10):2547–2551. doi: 10.1093/annonc/mdx315
44. Caputo R, Cazzaniga ME, Sbrana A, et al. Netupitant/Palonosetron (NEPA) and dexamethasone for prevention of emesis in breast cancer patients receiving adjuvant anthracycline plus cyclophosphamide: a multi-cycle, phase II study. BMC Cancer. 2020;20 (1):232. doi: 10.1186/s12885-020-6707-9
45. Zelek L, Navari R, Aapro M, et al. Single-dose NEPA versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy. Cancer Med. 2023;12(15):15769–15776. doi: 10.1002/cam4.6121
46. Chow R, Yin LB, Baqri W, et al. Prevalence and predictors of long-delayed (> 120 h) chemotherapy-induced nausea and vomiting (CINV)—a systematic review and individual patient data meta-analysis. Support Care Cancer. 2023;31(8):505. doi: 10.1007/s00520-023-07978-y
•• **Review and meta-analysis that reports on the prevalence of and risk-factors for long-delayed chemotherapy-induced nausea and vomiting.**
47. Navari RM, Pywell CM, Le-Rademacher JG, et al. Olanzapine for the treatment of advanced cancer–related chronic nausea and/or vomiting. JAMA Oncol. 2020;6(6):895–899. doi: 10.1001/jamaoncol.2020.1052
48. Scotté F, Aapro MS, Ruhlmann CH, et al. Evaluation of chemotherapy-induced nausea and vomiting beyond the delayed phase: results of a survey of healthcare providers in Japan. Ann Oncol. 2023;34(suppl 2):S1093–S1094. doi: 10.1016/j.annonc.2023.09.860
49. Navari RM, Nelson WW, Shoaib S, et al. Real-world treatment outcomes, healthcare resource use, and costs associated with antiemetics among cancer patients on cisplatin-based chemotherapy. Adv Ther. 2023;40(7):3217–3226. doi: 10.1007/s12325-023-02537-7
50. Sun Y, Zheng Y, Yang X, et al. Incidence of chemotherapy-induced nausea and vomiting among cancer patients receiving moderately to highly emetogenic chemotherapy in cancer centers in Sichuan, China. J Cancer Res Clin Oncol. 2021;147(9):2701–2708. doi: 10.1007/s00432-021-03554-1
51. Liang Y, Zhang P, Li F, et al. Advances in the study of marketed antibody-drug conjugates (ADCs) for the treatment of breast cancer. Front Pharmacol. 2024;14:1332539. doi: 10.3389/fphar.2023.1332539
52. Tarcsa E, Guffroy MR, Falahatpisheh H, et al. Antibody-drug conjugates as targeted therapies: are we there yet? A critical review of the current clinical landscape. Drug Discov Today Technol. 2020;37:13–22. doi: 10.1016/j.ddtec.2020.07.002
53. Doi T, Shitara K, Naito Y, et al. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody–drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. Lancet Oncol. 2017;18(11):1512–1522. doi: 10.1016/S1470-2045(17)30604-6
54. Rugo HS, Tolaney SM, Loirat D, et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. NPJ Breast Cancer. 2022;8(1):98. doi: 10.1038/s41523-022-00467-1
•• **Analysis that reports on the safety profile of sacituzumab govitecan in the phase III ASCENT trial.**
55. Bardia A, Harnden K, Mauro L, et al. Clinical practices and institutional protocols on prophylaxis, monitoring, and management of selected adverse events associated with trastuzumab deruxtecan. Oncologist. 2022;27(8):637–645. doi: 10.1093/oncolo/oyac107
56. Chiu JWY, Lee SC, Jcm H, et al. Clinical guidance on the monitoring and management of trastuzumab deruxtecan (T-DXd)-related adverse events: insights from an Asia-Pacific multidisciplinary panel. Drug Saf. 2023;46(10):927–949. doi: 10.1007/s40264-023-01328-x

57. Bianchini G, Arpino G, Biganzoli L, et al. Emetogenicity of antibody-drug conjugates (ADCs) in solid tumors with a focus on trastuzumab deruxtecan: insights from an Italian expert panel. Cancers (Basel). 2022;14(4):1022. doi: 10.3390/cancers14041022
   - **Expert panel outcomes on experiences with antibody-drug conjugates in clinical trials and practice, including antiemetic therapy for patients receiving trastuzumab deruxtecan.**
58. Sugawara S, Inui N, Kanehara M, et al. Multicenter, placebo-controlled, double-blind, randomized study of fosnetupitant in combination with palonosetron for the prevention of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Cancer. 2019;125(22):4076–4083. doi: 10.1002/cncr.32429
59. Hata A, Okamoto I, Inui N, et al. Randomized, double-blind, phase III study of fosnetupitant versus fosaprepitant for prevention of highly emetogenic chemotherapy-induced nausea and vomiting: CONSOLE. J Clin Oncol. 2022;40(2):180–188. doi: 10.1200/JCO.21.01315
60. Scotté F, Schwartzberg L, Iihara H, et al. 2023 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following moderately emetic risk antineoplastic agents. Support Care Cancer. 2023;32(1):45. doi: 10.1007/s00520-023-08222-3
61. Herrstedt J, Celio L, Hesketh PJ, et al. 2023 updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following high-emetic-risk antineoplastic agents. Support Care Cancer. 2023;32(1):47. doi: 10.1007/s00520-023-08221-4
62. Aapro M, Jordan K, Scotté F, et al. Netupitant-palonosetron (NEPA) for preventing chemotherapy-induced nausea and vomiting: from clinical trials to daily practice. Curr Cancer Drug Targets. 2022;22(10):806–824. doi: 10.2174/1568009622666220513094352
63. Akynzeo 300 mg/0.5 mg hard capsules. 01/2020. Dublin, Ireland: Helsinn Birex Pharmaceuticals Ltd; 2020.
64. Emend (aprepitant) capsules. 03/2010. NJ (USA): Whitehouse Station, NJ: Merck Sharpe & Dohme Corp.; 2010.
65. Baron-Hay S, Aapro M, Bernareggi A, et al. Timing flexibility of oral NEPA, netupitant-palonosetron combination, administration for the prevention of chemotherapy-induced nausea and vomiting (CINV). Support Care Cancer. 2019;27(4):1309–1317. doi: 10.1007/s00520-019-4640-8
66. Scotté F, Zelek L, Giuliano C, et al. Assessing model-predicted neurokinin-1 (NK1) receptor occupancy (RO) of netupitant to support efficacy over an extended time period. Ann Oncol. 2023;34(suppl 4):S1640. doi: 10.1016/j.annonc.2023.10.541
67. Aapro M, Iihara H, Olivari Tilola S, et al. Model-predicted neurokinin-1 (NK1) receptor occupancy of netupitant versus aprepitant over an extended time period: implications for controlling nausea and vomiting associated with antibody-drug conjugates (ADCs). In: Poster session presented at: San Antonio Breast Cancer Symposium; San Antonio, TX; 2024 Dec 10–13.
68. Inui N, Toi Y, Yoneshima Y, et al. Pooled analysis of studies evaluating fosnetupitant and risk factors for cisplatin-induced nausea and vomiting during the extended overall phase. Adv Ther. 2023;40(11):4928–4944. doi: 10.1007/s12325-023-02648-1
69. Navari RM, Binder G, Bonizzoni E, et al. Single-dose netupitant/palonosetron versus 3-day aprepitant for preventing chemotherapy-induced nausea and vomiting: a pooled analysis. Future Oncol. 2021;17(23):3027–3035. doi: 10.2217/fon-2021-0023
70. Navari RM, Inui N, Tyler T. Individual patient data meta-analysis of NEPA vs. aprepitant antiemetic regimens in the prevention of chemotherapy-induced nausea and vomiting (CINV). Support Care Cancer. 2024;32(suppl 1):434.
71. Hata A, Shiraishi Y, Inui N, et al. Exploratory analysis comparing fosnetupitant versus fosaprepitant for prevention of highly emetogenic chemotherapy-induced nausea and vomiting (CINV): a randomized, double-blind, phase 3 study (CONSOLE). Oncol Ther. 2022;10(1):253–262. doi: 10.1007/s40487-022-00188-2
72. Detlefsen SS, Andersen DS, Knudsen AØ, et al. Safety and antiemetic efficacy of weekly administration of palonosetron/netupitant plus dexamethasone during five weeks of concomitant chemo-radiation. Support Care Cancer. 2024;32(suppl 1):434.
73. Barkate HV, Pednekar A, Shukla P, et al. An Indian real-world experience of intravenous fosnetupitant-palonosetron (IV NEPA) in preventing delayed and extended delayed CINV. J Clin Oncol. 2024;42(16 suppl):12070. doi: 10.1200/JCO.2024.42.16_suppl.12070
74. Verma AK, Pednekar A, Barkate HB, et al. Effectiveness of intravenous fosnetupitant & palonosetron for CINV prophylaxis in patients receiving highly emetogenic chemotherapy regimens: subgroup analysis from a phase IV Indian study. Ann Oncol. 2024;35(suppl 2):S1100–S1101. doi: 10.1016/j.annonc.2024.08.1973
75. Pednekar A, Shukla P, Valame S, et al. Efficacy of intravenous FosNEtupitant-PAlonosetron (IV NEPA) in preventing chemotherapy-induced nausea (CIN): a first real-world experience from India. Support Care Cancer. 2024;32(suppl 1):434.
76. Stankowicz M, Mauro L, Harnden K, et al. Management of chemotherapy-induced nausea and vomiting with trastuzumab deruxtecan: a case series. Breast Care (Basel). 2021;16(4):408–411. doi: 10.1159/000511049
77. Iihara H, Shimokawa M, Bando H, et al. Doublet or triplet antiemetic prophylaxis for nausea and vomiting induced by trastuzumab deruxtecan: an open-label, randomized, and multicenter exploratory phase 2 study. J Cancer. 2023;14(14):2644–2654. doi: 10.7150/jca.87169
   - •• **Exploratory phase II study reporting on efficacy and safety of antiemetic treatment for trastuzumab deruxtecan-induced nausea and vomiting.**
78. Notini G, Naldini MM, Sica L, et al. Management of trastuzumab deruxtecan-related nausea and vomiting in real-world practice. Front Oncol. 2024;14:1374547. doi: 10.3389/fonc.2024.1374547
   - **Retrospective single-center study reporting on the efficacy of antiemetic regimens in patients receiving trastuzumab deruxtecan.**
79. Jordan K. Beyond the usual window: persistent nausea with trastuzumab deruxtecan calls for new management strategies. Ann Oncol. 2025;36(1):3–5. doi: 10.1016/j.annonc.2024.10.017
80. Sakai H, Tsurutani J, Ozaki Y, et al. A randomized, double-blind, placebo-controlled phase II study of olanzapine-based prophylactic antiemetic therapy for delayed and persistent nausea and vomiting in patients with HER2-positive or HER2-low breast cancer treated with trastuzumab deruxtecan: ERICA study (WJOG14320B). Ann Oncol. 2024;36(1):S0923–7534(24)03995–4. doi: 10.1016/j.annonc.2024.09.001
81. De Laurentiis M, García-Sáenz JA, Bianchini G, et al. European real-world experience of patients with HER2+ advanced/metastatic breast cancer accessing trastuzumab deruxtecan through a named patient program: first interim analysis of EUROPA T-DXd. Cancer Res. 2024;84(9 suppl):O3–16–12. doi: 10.1158/1538-7445.SABCS23-PO3-16-12
82. Reinisch M, Bruzas S, Spoenlein J, et al. Safety and effectiveness of sacituzumab govitecan in patients with metastatic triple-negative breast cancer in real-world settings: first observations from an interdisciplinary breast cancer centre in Germany. Ther Adv Med Oncol. 2023;15:17588359231200454. doi: 10.1177/17588359231200454
83. D'Arienzo A, Verrazzo A, Pagliuca M, et al. Toxicity profile of antibody-drug conjugates in breast cancer: practical considerations. EClinicalMedicine. 2023;62:102113. doi: 10.1016/j.eclinm.2023.102113
84. Ciruelos E, García-Sáenz JÁ, Gavilá J, et al. Safety profile of trastuzumab deruxtecan in advanced breast cancer: expert opinion on adverse event management. Clin Transl Oncol. 2024;26(7):1539–1548. doi: 10.1007/s12094-024-03383-x
85. Bianchini G, Park YH, Rugo HS, et al. Perceptions of antibody drug conjugate (adc)-induced nausea and vomiting: results of a survey of healthcare providers at ESMO. Poster session presented at. In: ESMO Breast Cancer Annual Congress; Berlin, Germany; 2024 May 15–17.
   - **Survey results highlighting a gap between scientific data and perceptions of antibody-drug conjugates, including emetogenicity and approach to antiemetic prophylaxis, among healthcare professionals.**

86. Li Y, Sun Y, Liu B, et al. Prolonged administration of aprepitant improves cisplatin-based chemotherapy-induced nausea and vomiting. Future Oncol. 2022;18(20):2533–2543. doi: 10.2217/fon-2021-1523
87. Li Y, Wan Y, Yang X, et al. Two doses of fosaprepitant induced prophylactic treatment for the three-day cisplatin-based chemotherapy induced nausea and vomiting. J Cancer Res Clin Oncol. 2024;150(6):290. doi: 10.1007/s00432-024-05766-7
88. Calcagnile S, Lanzarotti C, Rossi G, et al. Effect of netupitant, a highly selective NK_1 receptor antagonist, on the pharmacokinetics of palonosetron and impact of the fixed dose combination of netupitant and palonosetron when coadministered with ketoconazole, rifampicin, and oral contraceptives. Support Care Cancer. 2013;21(10):2879–2887. doi: 10.1007/s00520-013-1857-9
89. Enhertu [Summary of product characteristics]. Daiichi Sankyo Europe GmbH; 2024.
90. Gilmore J, Bernareggi A. Complementary pharmacokinetic profiles of netupitant and palonosetron support the rationale for their oral fixed combination for the prevention of chemotherapy-induced nausea and vomiting. J Clin Pharmacol. 2019;59(4):472–487. doi: 10.1002/jcph.1338