COR2ED

THE HEART OF MEDICAL EDUCATION

CLINICAL TOPIC NEWSLETTER

MANAGING ADC TOXICITIES IN HER2+ mBC: SPOTLIGHT ON NAUSEA AND VOMITING

AUGUST 2025

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer

DEVELOPED BY BREAST CANCER CONNECT

This programme is developed by BREAST CANCER CONNECT, an international group of experts in the field of breast cancer.

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EDUCATIONAL OBJECTIVES

1. **Understand the role of ADCs in breast cancer treatment**
   - In HER2-positive mBC
   - In international treatment guidelines
2. **Be able to identify and manage adverse events linked to next-generation HER2-targeted ADC**
   - Recognise the most common AEs associated with T-DXd, with a focus on nausea and vomiting, and acknowledgment of fatigue and ILD
   - Implement evidence-based strategies for monitoring, dose modifications, and supportive care to optimise patient safety

ADC, antibody-drug conjugate; AE, adverse event; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

CLINICAL TAKEAWAYS

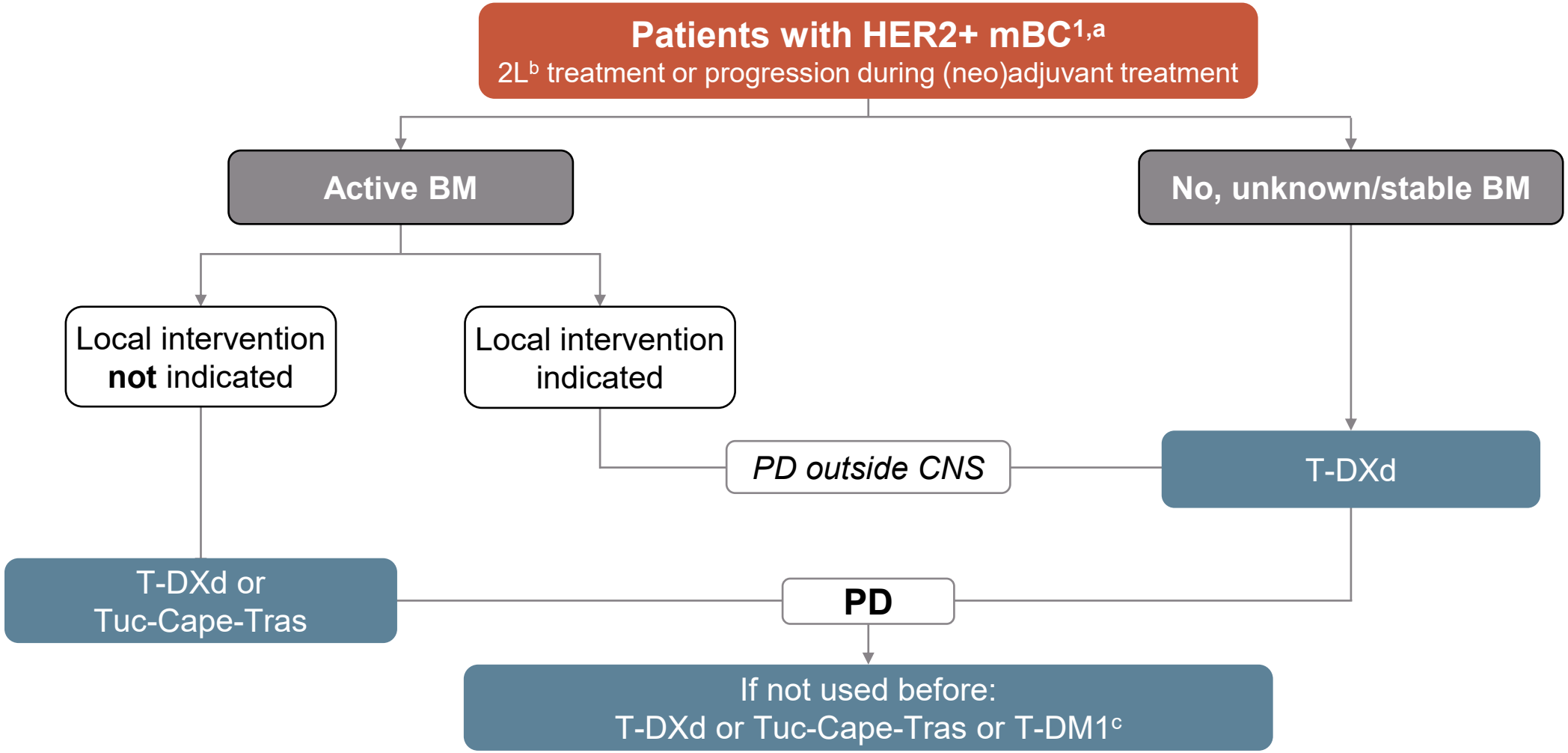
- **T-DXd is a highly emetogenic agent**, warranting prophylaxis with a 3-drug regimen: a 5-HT3 RA, NK1 RA, and dexamethasone. A 4-drug regimen including olanzapine is recommended if prior 3-drug prophylaxis was inadequate or for patients at high-risk (e.g. younger age, history of CINV, anxiety, hyperemesis)
- As **breakthrough nausea and vomiting may occur despite prophylaxis**—within 5 days (acute) or between days 6–21 (delayed) post–T-DXd—upfront prescribing of olanzapine 2.5 mg nocte is recommended for potential acute or delayed symptoms, and ondansetron 8 mg every 8–12 h (16–24 mg total daily dose) as an alternative for delayed nausea, to enable as-needed use
- **Fatigue associated with T-DXd should be proactively managed** through routine screening, assessment of reversible causes, patient education, supportive care, and dose adjustments when needed
- **ILD is a potentially serious adverse event with T-DXd** and should be addressed using the 5S approach: **S**creen regularly, **s**can early, **s**ynergise with the patient and MDT, **s**uspend treatment if ILD is suspected, and initiate **s**teroids promptly if ILD is suspected

5-HT3 RA, serotonin type 3 receptor antagonist; CINV, chemotherapy induced nausea and vomiting; ILD, interstitial lung disease; MDT, multidisciplinary care team; NK1 RA, neurokinin-1 receptor antagonist; T-DXd, trastuzumab deruxtecan

HER2+ METASTATIC BREAST CANCER TREATMENT GUIDELINES

HER2, human epidermal growth factor receptor 2

ADC ROLE IN CURRENT HER2+ mBC TREATMENT GUIDELINES



[a] Algorithm only depicting 2/3L recommendations, 4L is not shown; [b] 2L+ treatment algorithms are expected to evolve, with T-DXd + pertuzumab potentially becoming a new 1L option based on the positive results of the DESTINY-Breast09 trial[2]; [c] T-DM1 is not recommended for patients with active BM for which local intervention is not indicated.

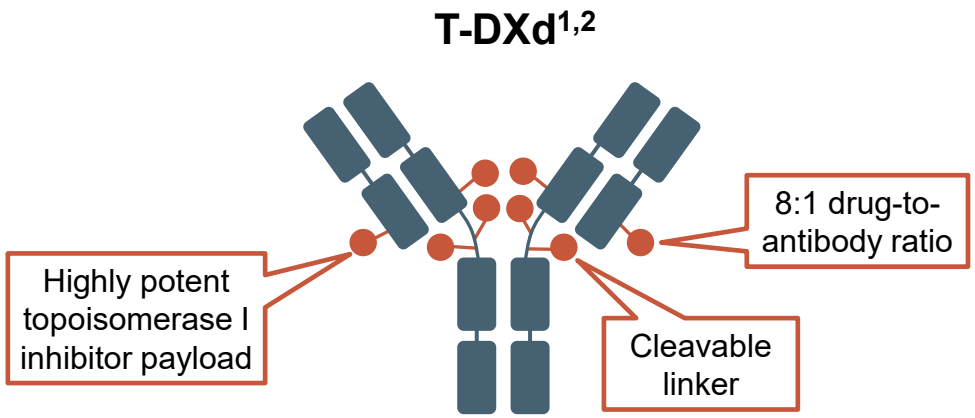
1/2/3/4L, first/second/third/fourth line; BM, brain metastases; CNS, central nervous system; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; PD, disease progression; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; Tuc-Cape-Tras, tucatinib-trastuzumab-capecitabine.

1. Adapted from: Gennari A, et al. Ann Oncol. 2021;32(12):1475-95. ESMO Metastatic Breast Cancer Living Guidelines. V1.2 April 2025. Available here (accessed June 2025);
2. Tolaney S, et al. J Clin Oncol 43, 2025 (suppl 17; abstr LBA1008).

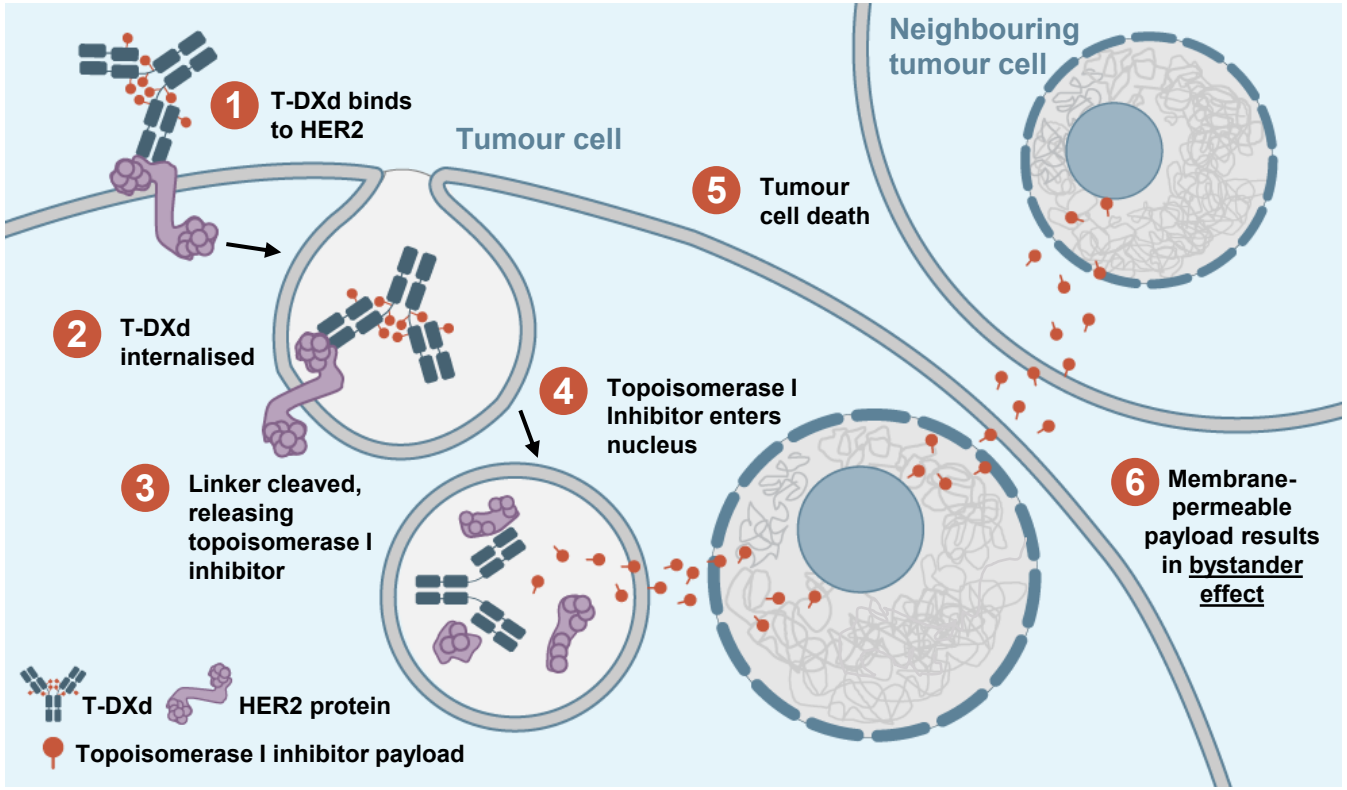
ADC IN HER2+ mBC: MECHANISM OF ACTION

ADC, antibody-drug conjugates; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer

T-DXd MECHANISM OF ACTION



Internalisation of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumour cell and neighbouring tumour cells through the bystander effect[1,2]



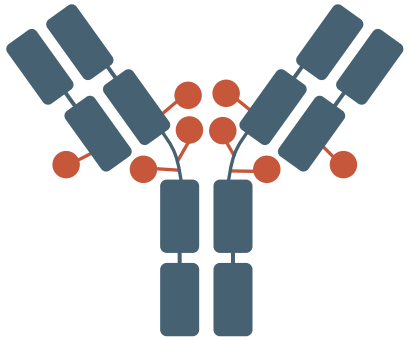
Adapted from Modi S, et al. 2020[3]

HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. Chem Pharm Bull. 2019;67:173-85; 2. Ogitani Y, et al. Clin Cancer Res. 2016;22:5097-108; 3. Modi S, et al. J Clin Oncol. 2020;38:1887-96.

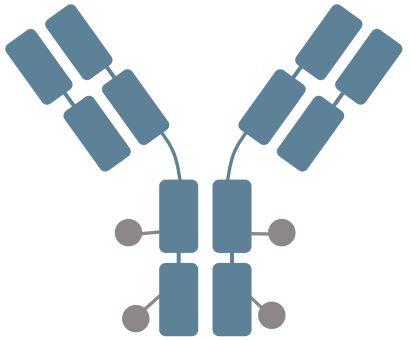
ADC CHARACTERISTIC DIFFERENCES OF T-DXd VS T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumour-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumour effect?**	No

Trastuzumab emtansine (T-DM1)[5]



[a] The clinical relevance of these features is under investigation.

ADC, antibody-drug conjugate; MoA, mechanism of action.

1. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67:173-85; 2. Ogitani Y, et al. Clin Cancer Res. 2016;22:5097-108; 3. Trail PA et al. Pharmacol Ther. 2018;181:126-42; 4. Ogitani Y et al. Cancer Sci. 2016;107:1039-46; 5. LoRusso PM et al. Clin Cancer Res. 2011;17:6437-47.

ADC IN HER2+ mBC: DESTINY-BREAST03 EFFICACY AND SAFETY OUTCOMES

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer

DESTINY-BREAST03: STUDY DESIGN AND EFFICACY RESULTS

Study design

Patients
- Unresectable/metastatic HER2+ breast cancer[a]
- Previously treated with trastuzumab and taxane in a/mBC setting[b]
- Could have stable/treated BM

Stratification factors
- HR status
- Prior treatment with pertuzumab
- History of visceral disease

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=261)

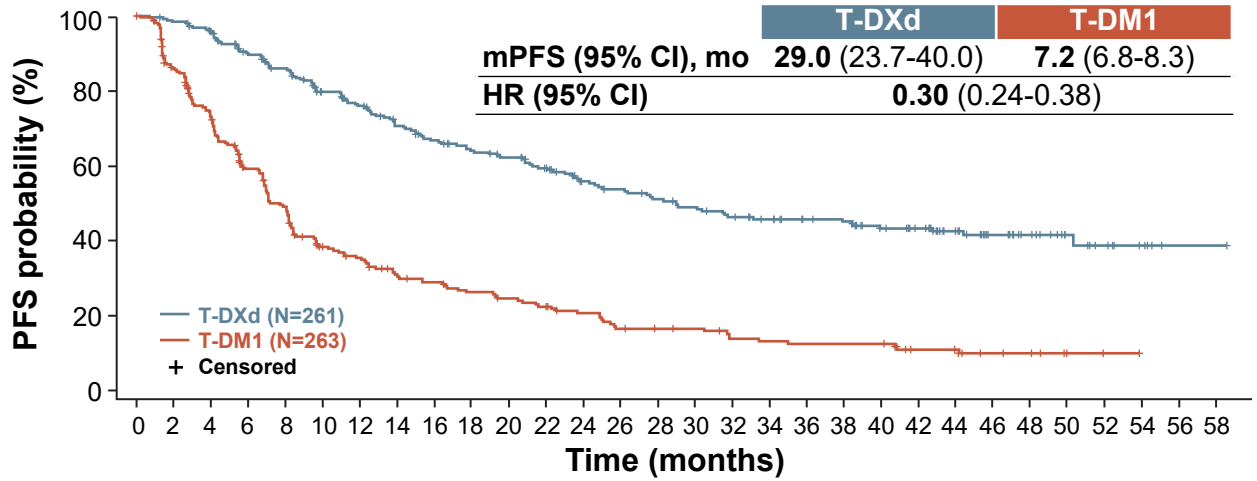
T-DM1
3.6 mg/kg Q3W
(n=263)

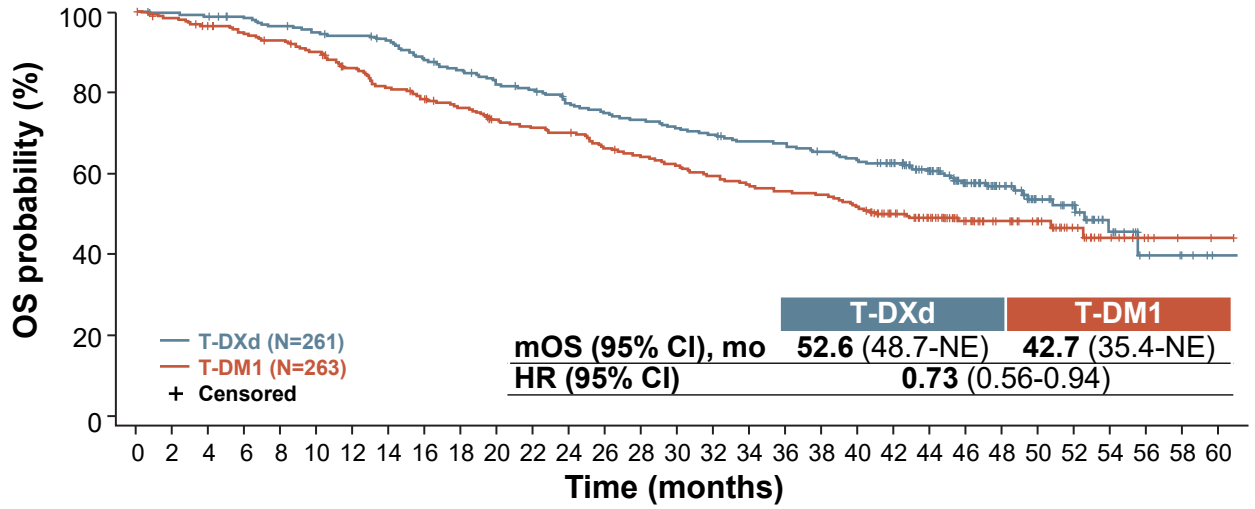
Primary endpoint
- PFS (BICR)

Key Secondary endpoint
- OS

Secondary endpoints
- OR (BICR/investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Efficacy results: PFS and OS





[a] HER2 IHC3+ or IHC2+/ISH+ based on central confirmation; [b] Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane.
a/mBC, advanced/metastatic breast cancer; BM, brain metastasis; BICR, blinded independent central review; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mo, months; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Cortes J, et al. Nat Med. 2024;30(8):2208-15.

DESTINY-BREAST03: DRUG-RELATED TEAEs IN ≥20% OF PTS[1]

System organ class Preferred term, n (%)	T-DXd (N=257)		T-DM1 (N=261)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	29 9 (11.1)	8 (3.1)
Anaemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia[c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia[d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 9 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhoea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue[e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

Adjudicated as drug-related ILD/pneumonitis[g], n (%)						
N (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any grade**
T-DXd (N=257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (N=261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

[a] This category includes the preferred terms neutrophil count decreased and neutropenia; [b] This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased; [c] This category includes the preferred terms white blood cell count decreased and leukopenia. [d]This category includes platelet count decreased and thrombocytopenia; [e] This category includes the preferred terms fatigue, asthenia, and malaise; [f] Grade 1 alopecia: T-DXd = 26.5%, T-DM1 = 2.3%; grade 2, T-DXd = 9.3%; [g] Patients with prior history of ILD/pneumonitis requiring steroids were excluded.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
1. Cortes J, et al. Nat Med. 2024;30(8):2208-15.

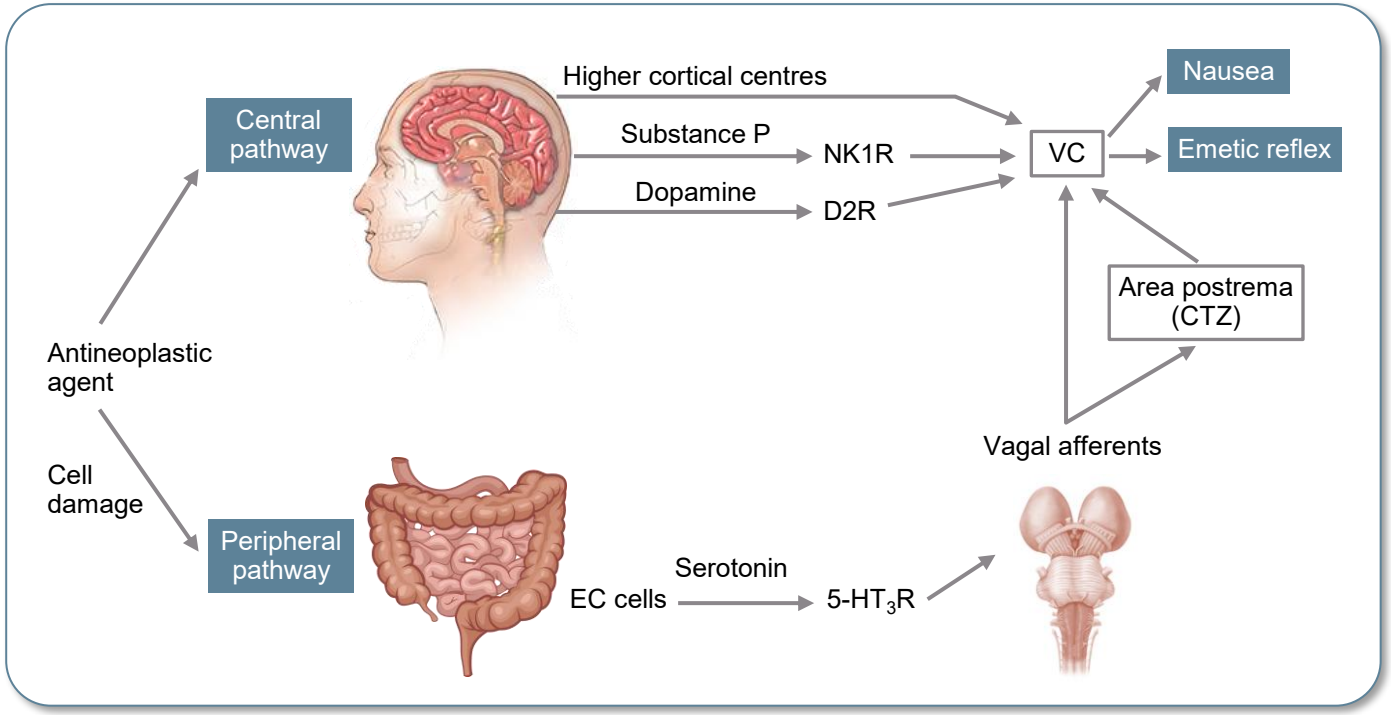
T-DXd INDUCED NAUSEA AND VOMITING MANAGEMENT

T-DXd, trastuzumab deruxtecan

PATHWAYS BY WHICH ANTINEOPLASTIC AGENTS, INCLUDING ADCs, MAY PRODUCE AN EMETIC RESPONSE[1]

Two main emetic pathways: Central and Peripheral

- **Peripheral (acute phase):** Chemotherapy damages gut lining → serotonin release → activates 5-HT3 receptors on vagal nerves → signals to brainstem (NTS, DMNV) → trigger emetic response
- **Central (delayed phase):** CTZ detects circulating toxins → releases serotonin, dopamine, substance P → stimulates emetic centre via 5-HT3, dopamine, and NK1 receptors



Nausea involves cortical processing and is often more difficult to manage than vomiting, even with antiemetics treatment

5-HT3(R), serotonin type 3 (receptor); CTZ, chemoreceptor trigger zone; D2R, dopamine D2 receptor; DMNV, dorsal motor nucleus of the vagus; EC cells, enterochromaffin cells; NK1(R), neurokinin 1 (receptor); NTS, nucleus tractus solitarius; VC, vomiting centre.

1. Farhat J, et al. Breast Cancer. 2025;32(2):278-85.

A 5-STEP FRAMEWORK FOR MANAGING T-DXd INDUCED NAUSEA AND VOMITING[1]

1 Classify Risk

Start by **identifying the emetogenic potential** of the ADC

- Use evidence-based tools (NCCN, ASCO, MASCC/ESMO) to guide **risk stratification and determine prophylaxis needs**

2 Listen & Educate

Engage in anticipatory guidance for patients:

- Set expectations for **when and how** nausea may occur
- Discuss potential impact on **daily life and quality of life**

Use shared decision-making:

- Consider patient preferences and past experiences with CINV
- Provide written instructions and clear follow-up plans

3 Establish Prophylaxis

Select antiemetic regimen:

- **3-drug regimen (standard):** e.g. 5-HT3 RA + dexamethasone + NK1 RA
- **4-drug regimen:** Consider if prior 3-drug prophylaxis was inadequate, or for patients at high-risk (e.g. younger age, history of CINV, anxiety, or hyperemesis)
- **2-drug regimen:** → May be suitable for select low-risk patients, but generally suboptimal with T-DXd → Use with close monitoring and access to rescue therapy
- Advise on **behavioural strategies**

4 Administer & Monitor

Begin prophylaxis **before the first ADC infusion**[2-4]

- Monitor closely during the first cycle to assess effectiveness
- Document patient-reported outcomes and adjust in subsequent cycles as needed

5 Rescue

- Address **breakthrough nausea/vomiting** with **PRN[a] therapy**
- Encourage **early intervention** at the first sign of nausea
- If frequent rescue is needed, consider **adjusting prophylaxis** for the next cycle

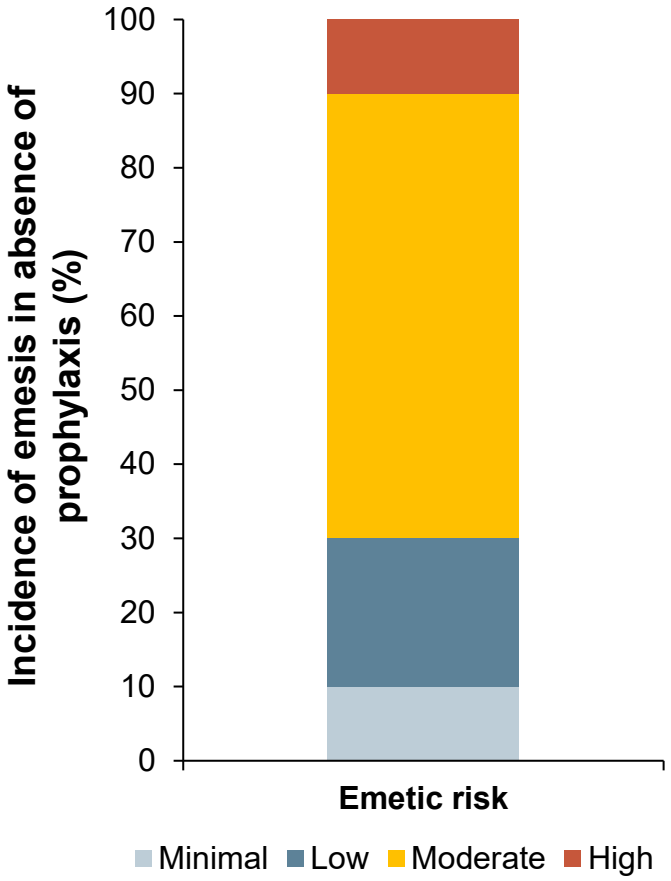
[a]PRN, or *pro re nata*, therapy refers to medications that are not administered on a fixed schedule but are taken only when necessary, based on the patient's symptoms.

5-HT3 RA, serotonin type 3 receptor antagonist; ADC, antibody drug conjugate; ASCO, American society of Clinical Oncology; CINV, chemotherapy-induced nausea and vomiting; ESMO, European Society for Medica; Oncology; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network; NK1 RA, neurokinin-1 receptor antagonist.

1. Framework based on the expert opinion and clinical experience of Dr. Sara Tolaney.

T-DXd: CLASSIFICATION OF EMETOGENICITY

Emetogenicity classification framework[1]



Emetogenic potential of T-DXd per guidelines

		T-DXd
Guidelines	**Last updated**	**Emetogenic potential**
MASCC/ ESMO[2]	2023	High end of moderate emetic risk*
NCCN[3]	2025	High emetic risk
ASCO[4]	2020	Moderate emetic risk

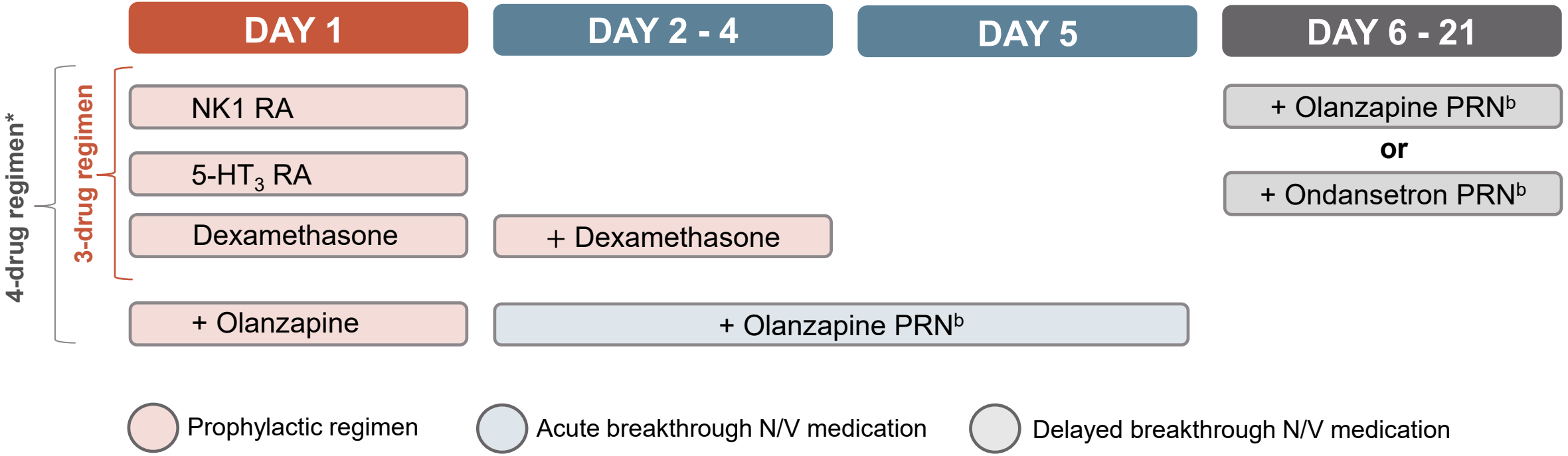
* The emetic potential of trastuzumab-deruxtecan appears to be at the high end of the moderate category, most closely resembling that of carboplatin. While prospective studies are needed, it is suggested to prevent emesis as for carboplatin AUC >5

ASCO, American Society of Clinical Oncology; AUC, area under the curve; ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network; T-DXd, trastuzumab deruxtecan.

1. Sing EPC, et al. Pediatr Blood Cancer. 2019;57(2):191-8; 2. Scotté F, et al. Support Care Cancer. 2023;32(1):45; 3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.1.2025. Available here (accessed June 2025); 4. Hesketh PJ, et al. J Clin Oncol. 2020;38(24):2782-97.

T-DXd: PROTOCOL FOR NAUSEA/VOMITING MANAGEMENT[1,a]

- **Administration of 3/4-drug regimen* occurs ~30–60 minutes before T-DXd infusion** on day 1 of a 21-day cycle



***A 4-drug prophylactic regimen including olanzapine is recommended if prior 3-drug prophylaxis was inadequate, or for patients at high-risk (e.g. younger age, history of CINV, anxiety, or hyperemesis)**

[a] **Detailed protocol on next slide**; [b]**PRN (pro re nata)** refers to medication taken as needed, rather than on a fixed schedule. In this context, it is used when acute (Day 2–5 of the cycle) or delayed (Day 6–21) N/V occur despite appropriate prophylaxis, requiring additional treatment to manage symptoms

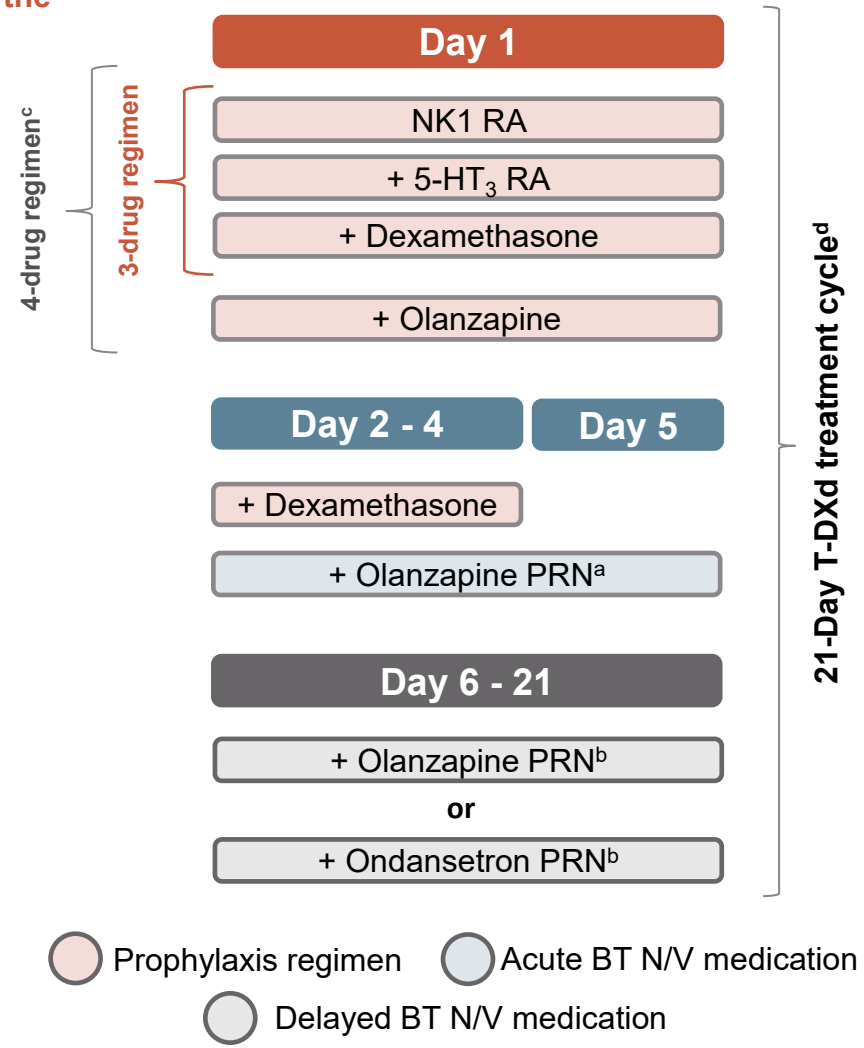
5-HT3 RA, serotonin type 3 receptor antagonist; NK1 RA, neurokinin-1 receptor antagonist; N/V, nausea/vomiting; T-DXd, trastuzumab deruxtecan

1.Protocol based on the expert opinion and clinical experience of Dr. Sara Tolaney

T-DXd: DETAILED PROTOCOL FOR N/V MANAGEMENT[1]

As T-DXd is highly emetogenic, the following protocol is recommended for N/V prevention and for the management of potential breakthrough[a] N/V- whether acute (within 5 days) or delayed (days 6–21)

- **STEP 1 – 3-drug prophylaxis treatment (Day 1):**
  - Administer 3-drug prophylaxis treatment **30–60 min before T-DXd infusion**:
    - NK1 RA (Aprepitant 130 mg IV x1)
    - 5-HT3 RA (Palonosetron 0.25 mg IV x1)
    - Dexamethasone 12 mg IV x1
- **STEP 2 – Continue prophylaxis at home (Days 2–4):**
  - Prescribe Dexamethasone 4–8 mg PO x1 for 3 days
  - **Ensure patient understands the importance of continuing this at home**
  - **If no nausea is reported** during the current cycle, a **reduction in the at-home dexamethasone** dose should be considered
- **STEP 3 – If breakthrough (BT) N/V occurs:**
  - **Acute BT N/V (Days 2–5):** Use Olanzapine 2.5 mg PO at night PRN[a]
  - **Delayed BT N/V (Days 6–21):**
    - Use Olanzapine 2.5 mg PO at night PRN[b], **or**
    - Ondansetron 8 mg PO q8h PRN[b], max 3 doses/day
  - **Ensure rescue medication for potential BT N/V is dispensed before discharge, with clear guidance on use and side effects**
- **STEP 4 – If BT N/V occurred, adjust prophylaxis for next cycle:**
  - Escalate to a **4-drug regimen** on Day 1:
    - Add Olanzapine 2.5 mg PO at night to existing 3-drug prophylaxis



[a] **Breakthrough (BT) N/V** refers to N/V that occurs despite appropriate prophylactic treatment. [b]**PRN (pro re nata)** refers to medication taken as needed, rather than on a fixed schedule. In this context, it is used when acute (Day 2–5 of the cycle) or delayed (Day 6–21) N/V occur despite appropriate prophylaxis, requiring additional treatment to manage symptoms; [c] A **4-drug prophylactic regimen** including olanzapine is recommended if prior 3-drug prophylaxis was inadequate, or for patients at high-risk (e.g. younger age, history of CINV, anxiety, or hyperemesis); [d] T-DXd is given on day 1 of a 21-day cycle.

5-HT3 RA, serotonin type 3 receptor antagonist; IV, intravenous; NK1 RA, neurokinin-1 receptor antagonist; N/V, nausea/vomiting; PO, per os (orally); q8h, every 8 hours; T-DXd, trastuzumab deruxtecan.

1.Protocol based on the expert opinion and clinical experience of Dr. Sara Tolaney.

PATIENT COUNSELING FOR NAUSEA AND VOMITING[1,2]

Behavioral strategies for nausea/vomiting management[1,2,a]

To help manage nausea

- Eat 5-6 **small meals** throughout the day
- **Avoid foods** that can cause nausea (eg, greasy, spicy, with strong smells)
- **Sit upright** or lie with **head raised** for 1 hour after a meal
- Eat food at **room temperature**
- Eat dry toast or crackers **before getting out of bed** if you have nausea in the morning
- **Drink** plenty of **water** and other cold, clear fluid in **slow sips** throughout the day

To help manage vomiting

- **Lie on side** to prevent inhalation of vomit
- Do not eat or drink **until vomiting stops** and drink small amounts of **clear liquids** after vomiting stops
- Once you can drink clear liquids without vomiting, try **full-liquid foods and drinks** or those that are easy on your stomach
- **Sit upright** and **bend forward** after vomiting
- Try **frozen liquids** such as ice chips

Alternative treatments[1] including relaxation techniques, guided imagery, acupuncture, aromatherapy with peppermint oil, acupressure hypnosis, or music therapy

[a]**The listed management strategies are not exhaustive.**

1. Cancer. Treatments and side affects. Updated June 2024. (Accessed June 2025). Available at: https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/nausea-and-vomiting/managing.html. 2. National Cancer Institute. Nutrition in Cancer Care (PDQ®)–Healthcare Professional Version. Updated September 2024. (Accessed June, 2025). https://www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-hp-pdq.

MANAGING T-DXd RELATED FATIGUE

T-DXd, trastuzumab deruxtecan

MANAGING T-DXd RELATED FATIGUE

Screen and assess regularly[1]

- Fatigue is subjective—use validated tools (e.g. Numeric Rating Scale)
- Assess for reversible causes: pain, depression, insomnia, nutrition, comorbidities
- Conduct full clinical and symptom assessment

Treat identified causes[1]

- Follow specific guidelines for reversible contributors (e.g NCCN guidelines)
- Encourage physical activity if feasible
- Consider psychosocial support (e.g. counselling, mind–body techniques)
- Short-term pharmacological options for metastatic patients

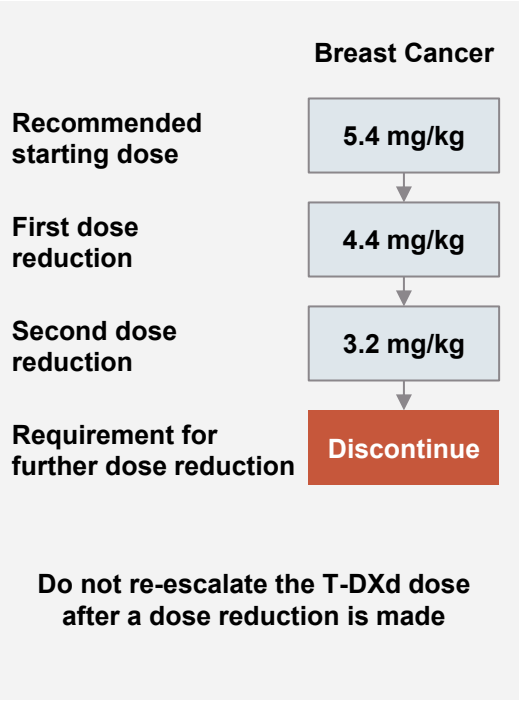
Educate and support[1]

- Ongoing education for patients and caregivers is essential
- Reinforce realistic expectations and coping strategies

Adjust T-DXd if needed[1]

- Dose reductions may alleviate fatigue
- No cumulative fatigue observed in clinical experience (anecdotal)

Dose reduction schedule[2]



T-DXd, trastuzumab deruxtecan.

1. Rugo HS, et al. ESMO Open. 2022 Aug 11;7(4):100553; 2. ENHERTU [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc. and Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2025.

T-DXd AE OF SPECIAL INTEREST: ILD MANAGEMENT

AE, adverse event; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan

FOLLOW THE 5 "S" STRATEGIES TO HELP DETECT AND MANAGE ILD/PNEUMONITIS IN PATIENTS RECEIVING T-DXd

(Part 1/2)

1 SCREEN

Careful patient selection based on baseline risk and screening that continues during treatment is warranted[1]

1.1 Before initiating T-DXd[2,3]

- Complete history and physical exam[a]
- Consider baseline SpO_2, PFT, and high-resolution CT (see **Scan**), if clinically indicated
- Educate patient and engage multidisciplinary team (see **Synergy**)

1.2 Throughout treatment[2,3,4]

- Advise patients to immediately report signs and symptoms that may indicate ILD/pneumonitis:
  - Cough, fever, dyspnoea, new or worsening respiratory symptoms
- Continue to monitor vitals (SpO_2 and PFT, if clinically indicated)
- Investigate potential evidence:
  - Infectious disease evaluation
  - Bronchoscopy, BAL, and/or ABGs, if clinically indicated and feasible

2 SCAN

Radiological scans remain the fundamental diagnostic tool for ILD[1]

2.1 Immediate action[4]

- Promptly investigate evidence of ILD. Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist

2.2 CT scans[1]

- Consider CT scans of the chest for baseline prior to treatment, including high-resolution CT scans, if feasible
- Repeat at least every 12 weeks (or every 6-9 weeks if baseline respiratory symptoms are present), if feasible
- Consult your institution's guidelines for best practices

3 SYNERGY

Work together with the patient, multidisciplinary care team, and staff[1]

3.1 Patient[4]

- Inform patients of the risks of severe/ fatal ILD
- Advise patients to contact their HCP immediately for any of the following: cough, shortness of breath, fever, or other new or worsening respiratory symptoms

3.2 Multidisciplinary team[2]

- Consider consulting a pulmonologist/ radiologist, including for patients with significant lung comorbidities
- Comprehensive education of staff, nurses, patient navigators, and advanced HCP is an important part of ILD monitoring/management

3.2 HCP staff[2]

- Help facilitate open communication with the patient
- Help assess signs/symptoms[3]

[a] Monitor patients with moderate renal impairment more frequently: A higher incidence of grade 1 and 2 ILD/pneumonitis has been observed in these patients[4].

ABG, arterial blood gases; BAL, bronchoalveolar lavage; CT, computed tomography; HCP, healthcare provider; ILD, interstitial lung disease; PFT, pulmonary function test; SpO2, peripheral oxygen saturation; T-DXd, trastuzumab deruxtecan.

1. Tarantino P, et al. JCO Oncol Pract. 2023;19(8):526-7; 2. Rugo H, et al. JCO Oncol Pract. 2023;19(8):539-46; 3. Swain SM, et al. Cancer Treat Rev. 2022;106:102378; 4. ENHERTU [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc. and Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2025.

FOLLOW THE 5 "S" STRATEGIES TO HELP DETECT AND MANAGE ILD/PNEUMONITIS IN PATIENTS RECEIVING T-DXd

(Part 2/2)

4 SUSPEND TREATMENT

Promptly investigate evidence and **interrupt T-DXd treatment as soon as ILD is suspected[a], regardless of grade**[1,2]

4.1 Asymptomatic (G1) ILD/pneumonitis[1]

Interrupt T-DXd until resolved to grade 0, then:

- If resolved in ≤28 days from date of onset, maintain dose
- If resolved in >28 days from date of onset, reduce one dose level (see dose reductions at right)
- Among patients who were **rechallenged with T-DXd** after experiencing G1 ILD (n=44), the **rate of recurrent ILD was low** (n=12), with **most events being grade 1** (9-G1, 2-G2, 1-G3) and no grade 5 events reported.[4]

4.2 Symptomatic (G≥2) ILD/pneumonitis[1]

- **Permanently discontinue T-DXd**

5 STEROIDS

Corticosteroids can be initiated as soon as ILD is suspected, before a pulmonologist consultation[2,3]

5.1 Asymptomatic (G1) ILD/pneumonitis[1]

- Consider corticosteroid treatment (e.g., ≥0.5 mg/kg/day prednisolone or equivalent) as soon as ILD pneumonitis is suspected

5.2 Symptomatic (G≥2) ILD/pneumonitis[1]

- Promptly initiate systemic corticosteroid treatment (e.g., ≥1 mg/kg/day prednisone or equivalent) as soon as ILD/pneumonitis is suspected
- Continue for ≥14 days followed by a gradual taper for ≥4 weeks

Dose reduction schedule[1]

	Breast Cancer
Recommended starting dose	5.4 mg/kg
First dose reduction	4.4 mg/kg
Second dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue

Do not re-escalate the T-DXd dose after a dose reduction is made

[a] Evaluate patients with suspected ILD by radiographic imaging. Consider consultation with a pulmonologist[1].

G, grade; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

1. ENHERTU [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc. and Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2025; 2. Tarantino P, et al. JCO Oncol Pract. 2023;19(8):526-7; 3. Rugo H, et al. JCO Oncol Pract. 2023;19(8):539-46; 4. Hope R, et al. J Clin Oncol. 2025;43(16_suppl):Abstract 1015.

CLINICAL TAKEAWAYS

CLINICAL TAKEAWAYS

- **T-DXd is a highly emetogenic agent**, warranting prophylaxis with a 3-drug regimen: a 5-HT3 RA, NK1 RA, and dexamethasone. A 4-drug regimen including olanzapine is recommended if prior 3-drug prophylaxis was inadequate or for patients at high-risk (e.g. younger age, history of CINV, anxiety, hyperemesis)
- As **breakthrough nausea and vomiting may occur despite prophylaxis**—within 5 days (acute) or between days 6–21 (delayed) post–T-DXd—upfront prescribing of olanzapine 2.5 mg nocte is recommended for potential acute or delayed symptoms, and ondansetron 8 mg every 8–12 h (16–24 mg total daily dose) as an alternative for delayed nausea, to enable as-needed use
- **Fatigue associated with T-DXd should be proactively managed** through routine screening, assessment of reversible causes, patient education, supportive care, and dose adjustments when needed
- **ILD is a potentially serious adverse event with T-DXd** and should be addressed using the 5S approach: **S**creen regularly, **s**can early, **s**ynergise with the patient and MDT, **s**uspend treatment if ILD is suspected, and initiate **s**teroids promptly if ILD is suspected

5-HT3 RA, serotonin type 3 receptor antagonist; CINV, chemotherapy induced nausea and vomiting; ILD, interstitial lung disease; MDT, multidisciplinary care team; NK1 RA, neurokinin-1 receptor antagonist; T-DXd, trastuzumab deruxtecan.

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