DOSING AND ADMINISTRATION

& ADVERSE EVENT MANAGEMENT OF TRASTUZUMAB DERUXTECAN

INDEX

Trastuzumab Deruxtecan "Enhertu" medicine is not approved across all GCC countries, Please refer to local prescribing information in registered markets for further information.

1- Dosing and Administration & Adverse Event Management of Trastuzumab Deruxtecan

2- Management Strategies for Selected Trastuzumab Deruxtecan Adverse Reactions

2A: Gastrointestinal Adverse Reactions:
Nausea & Vomiting - Diarrhea - Constipation - Decreased Appetite

2B: Hematological Adverse Reactions:
Anemia - Thrombocytopenia

2C: Miscellaneous Adverse Reactions:
Fatigue - Alopecia - Infusion - Related Reactions

3- Warnings & Precautions

DOSING AND ADMINISTRATION OF T-DXd

Metastatic Breast Cancer
Dosing 5.4 mg/kg

T-DXd, trastuzumab deruxtecan.
Trastuzumab deruxtecan (T-DXd) is an investigational product that may not be approved for use in your country.

Overview of the Recommended Dose for T-DXd in Metastatic Breast Cancer

Breast

5.4 mg/kg once every 3 weeks until disease progression or unacceptable toxicity[1,2]

T-DXd is also currently under investigation for the treatment of other HER2-targetable tumors.

Administration of T-DXd in Metastatic Breast Cancer[1]

Once Every 3 Weeks

5.4 mg/kg[1] IV

T-DXd was given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

First Infusion

Administer over **90 minutes.**[1]

Subsequent Infusions

Administer over **30 minutes** if prior infusions were well tolerated.

- Do not substitute T-DXd for or with trastuzumab or ado-trastuzumab emtansine (T-DM1).
- T-DXd is diluted with 5% dextrose injection, USP; do not use sodium chloride.
- T-DXd is administered intravenously; do not administer as a push or bolus.
- Close to completion of administration, or when exact delivery volumes are prepared in the IV bag, flush administration route with 5% dextrose.
- Slow or interrupt the infusion rate if the patient develops infusion-related symptoms.

- **Permanently discontinue T-DXd in case of severe infusion reactions.**[1]
- **Observe patients after administration of T-DXd.**[1]

Metastatic Breast Cancer Dose Modifications for Adverse Reactions[1]

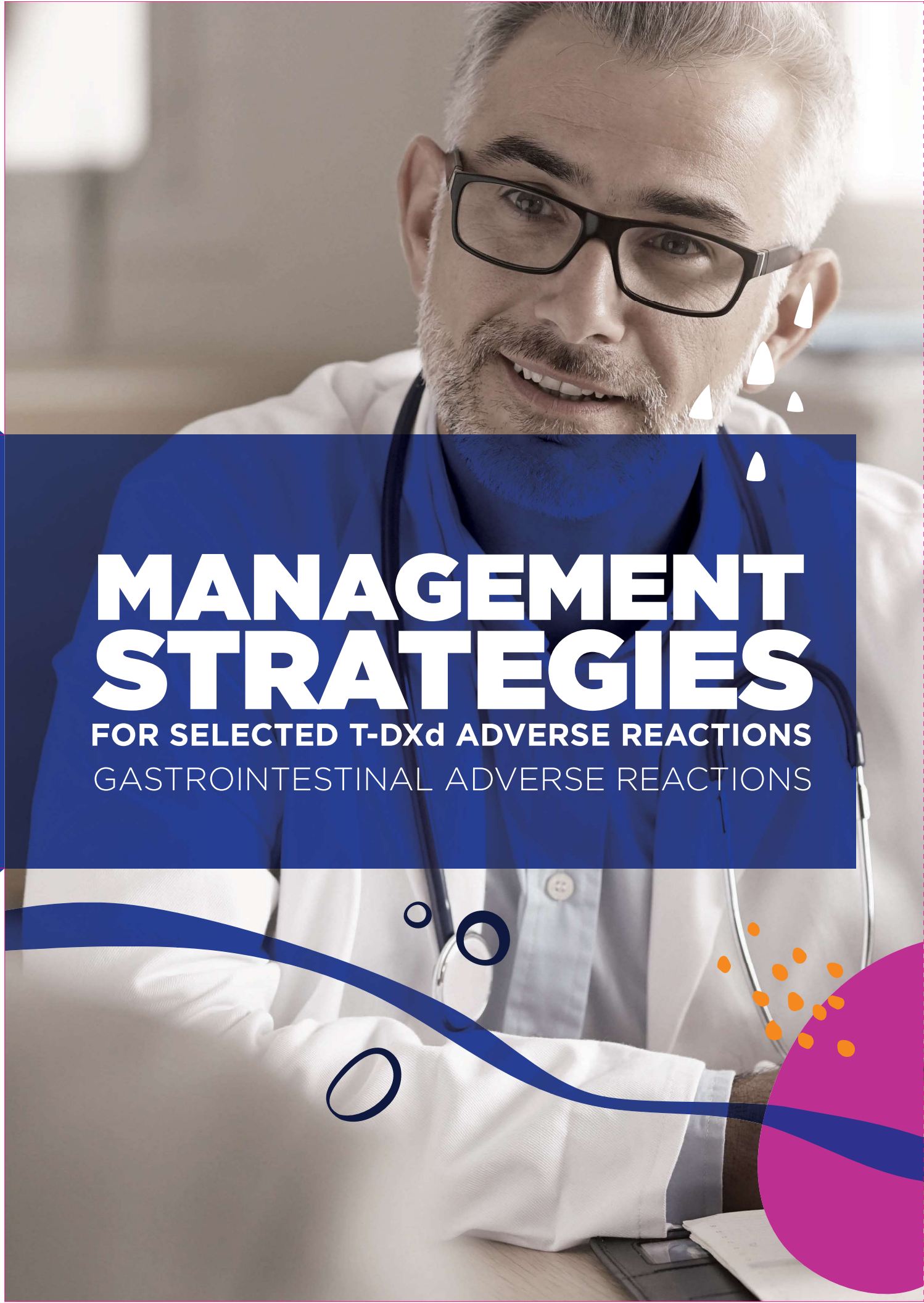
- Management of adverse reactions may require temporary interruption, dose reduction, or treatment discontinuation of T-DXd.
- Do not re-escalate the T-DXd dose after a dose reduction is made.
- If a planned dose is delayed or missed, administer as soon as possible; do not wait until the next planned cycle.
- Adjust the schedule of administration to maintain a 3-week interval between doses.
- Administer the infusion at the dose and rate the patient tolerated in the most recent infusion.

mBC Dosing

Dose Reduction Schedule	Dose to Be Administered
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 treatment

HER2, human epidermal growth factor receptor 2; **T-DXd,** trastuzumab deruxtecan; **USP,** United States Pharmacopeia; **mBC,** metastatic breast cancer.

1. Modi S, et al. *N Engl J Med.* 2020;382(7):610-621. 2. Tamura K et al. *Lancet Oncol.* 2019; 20:816-26.



MANAGEMENT STRATEGIES

FOR SELECTED T-DXd ADVERSE REACTIONS

GASTROINTESTINAL ADVERSE REACTIONS

AND NAUSEA VOMITING

Potential Management Strategies & NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Patient Counseling[1]

- Eat small meals throughout the day
- Avoid food with strong smells Eat food at room temperature
- Sip only small amounts of liquid during meals
- Keep a record of nausea and why
- Wear loose and comfortable clothing
- Sit up or lie with your head raised for one hour after eating

Rx Options[2-4]

Prophylaxis		Breakthrough	
Serotonin (5-HT_3) receptor antagonists	Corticosteroids	Atypical antipsychotics	Phenothiazines
Neurokinin-1 receptor (NK1R) antagonists	Oral antipsychotics	Benzodiazepines	5-HT_3 receptor antagonists
		Cannabinoids	Corticosteroids

PERSISTENT AR

T-DXd Clinical Trial Protocol Guidance

Permitted Therapies in Clinical Trials[5]

Prophylactic Antiemetics:
Administer prior to T-DXd infusion and on subsequent days according to prescribing information or institutional guidelines.

5-HT_3, 5-hydroxytryptamine (serotonin); **T-DXd,** trastuzumab deruxtecan.

1. National Cancer Institute. Nutrition in Cancer Care (PDQ®)–Patient Version. Updated March 16, 2018. www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-pdq. Accessed January 15, 2020. 2. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.1.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed May 17, 2021. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 3. Navari RM, et al. *N Engl J Med* 2016; 374:1356-1367. 4. Navari RM. *Biomed Res* Int 2015;2015:595894. 5. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020.

PERSISTENT AR

T-DXd Clinical Trial Protocol Guidance

Dose Interruption[1]

For Grade ≥ 3 Nausea:
Delay dose until resolved to grade ≤ 1 or baseline values

Resume Therapy[1]

- If resolved in ≤ 7 days, maintain dose
- If resolved in > 7 days, reduce dose 1 level

*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

Dose Modification[1,2]

	mBC
Starting dose	5.4 mg/kg
Initial dose reduction	4.4 mg/kg
Final dose reduction	3.2 mg/kg
Further dose reduction required	Discontinue treatment

Do not re-escalate the T-DXd dose after a dose reduction.[2]

AR, adverse reactions; **mBC,** metastatic breast cancer; **T-DXd,** trastuzumab deruxtecan.

1. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020. 2. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021.

NCCN Guidelines® for Antiemesis:
Acute and Delayed Nausea and Vomiting

National Comprehensive Cancer Network® (NCCN®) Recommended

NCCN guidelines for antiemesis, lists fam-trastuzumab deruxtecan-nxki (Enhertu) as a parenteral anticancer agent with **high emetic risk** and recommends several prophylactic antiemetic regimens to decrease potential vomiting.

High Emetic Risk Parenteral Anticancer Agents
Acute and Delayed Emesis Prevention[f,g,h,i,j]

DAY 1:	Select treatment options A, B, or C	DAYS 2, 3, 4:
	All treatment options are category 1 and should be started before anticancer therapy.[h]	

Treatment option A (preferred), use the following combination:[l]
1. **Olanzapine 5–10 mg PO once**[k]
2. **NK1 receptor antagonist (RA) (choose one)**:
   - ◊ Aprepitant 125 mg PO once
   - ◊ Aprepitant injectable emulsion 130 mg intravenous (IV) once[m]
   - ◊ Fosaprepitant 150 mg IV once
   - ◊ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once
   - ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once
   - ◊ Rolapitant 180 mg PO once[n]
3. **5-HT3 RA (choose one):**[o,p]
   - ◊ Dolasetron 100 mg PO once
   - ◊ Granisetron 10 mg subcutaneous (SQ) once, or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to the first dose of anticancer therapy[q]
   - ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once
   - ◊ Palonosetron 0.25 mg IV once
4. **Dexamethasone 12 mg PO/IV once**[r,s]

Treatment option A:
- Olanzapine 5–10 mg PO daily on days 2, 3, 4[k]
- Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO is used on day 1)
- Dexamethasone 8 mg PO/IV daily on days 2, 3, 4[r,s]

Treatment option B, use the following combination:
1. **Olanzapine 5–10 mg PO once**[k]
2. **Palonosetron 0.25 mg IV once**
3. **Dexamethasone 12 mg PO/IV once**[r,s]

Treatment option B:
- Olanzapine 5–10 mg PO daily on days 2, 3, 4[k]

Treatment option C, use the following combination:
1. **NK1 RA (choose one):**
   - ◊ Aprepitant 125 mg PO once
   - ◊ Aprepitant injectable emulsion 130 mg IV once[m]
   - ◊ Fosaprepitant 150 mg IV once
   - ◊ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once
   - ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once
   - ◊ Rolapitant 180 mg PO once[n]
2. **5-HT_3 RA (choose one):**[o,p]
   - ◊ Dolasetron 100 mg PO once
   - ◊ Granisetron 10 mg SQ once, or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy[q]
   - ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once
   - ◊ Palonosetron 0.25 mg IV once
3. **Dexamethasone 12 mg PO/IV once**[r,s]

Treatment option C:
- Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO is used on day 1)
- Dexamethasone 8 mg PO/IV daily on days 2, 3, 4[r,s]

Moderate Emetic Risk Parenteral Anticancer Agents
Acute and Delayed Emesis Prevention[f,g,h,i,j]

DAY 1:	Select treatment options D, E, or F	DAYS 2, 3:
	All treatment options are category 1 and should be started before anticancer therapy.[h]	

Treatment option D, use the following combination:
1. **5-HT_3 RA (choose one):**
   - ◊ Dolasetron 100 mg PO once
   - ◊ Granisetron 10 mg SQ once (preferred), or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy[q]
   - ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once
   - ◊ Palonosetron 0.25 mg IV once (preferred)
2. **Dexamethasone 12 mg PO/IV once**[r,s]

Treatment option D:
- Dexamethasone 8 mg PO/IV daily on days 2, 3[r,s]

OR
- 5-HT_3 RA monotherapy:[t]
  - ◊ Granisetron 1–2 mg (total dose) PO daily or 0.01 mg/kg (max 1 mg) IV daily on days 2, 3
  - ◊ Ondansetron 8 mg PO twice daily or 16 mg PO daily or 8–16 mg IV daily on days 2, 3
  - ◊ Dolasetron 100 mg PO daily on days 2, 3

Treatment option E, use the following combination:[u]
1. **Olanzapine 5–10 mg PO once**[k]
2. **Palonosetron 0.25 mg IV once**
3. **Dexamethasone 12 mg PO/IV once**[r,s]

Treatment option E:
- Olanzapine 5–10 mg PO daily on days 2, 3[k]

Treatment option F, use the following combination:[u]
1. **NK1 RA (choose one):**
   - ◊ Aprepitant 125 mg PO once
   - ◊ Aprepitant injectable emulsion 130 mg IV once[m]
   - ◊ Fosaprepitant 150 mg IV once
   - ◊ Netupitant 300 mg/palonosetron 0.5 mg (available as fixed combination product only) PO once
   - ◊ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once
   - ◊ Rolapitant 180 mg PO once[n]
2. **5-HT_3 RA (choose one):**[o,p]
   - ◊ Dolasetron 100 mg PO once
   - ◊ Granisetron 10 mg SQ once, or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of anticancer therapy[q]
   - ◊ Ondansetron 16–24 mg PO once, or 8–16 mg IV once
   - ◊ Palonosetron 0.25 mg IV once
3. **Dexamethasone 12 mg PO/IV once**[r,s]

Treatment option F:
- Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1)
- ± Dexamethasone 8 mg PO/IV daily on days 2, 3[r,s]

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial.

Participation in clinical trials is especially encouraged.

5-HT_3, 5-hydroxytryptamine (serotonin); **NCCN,** National Comprehensive Cancer Network; **NK1,** neurokinin 1; **RA,** receptor antagonist.

[f]Emetogenic Potential of Parenteral Anticancer Agents (AE-2). [g]Antiemetic regimens should be chosen based on the drug with the highest emetic risk as well as patient-specific risk factors. [h]Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A). [i]Especially for patients with anticipatory, anxiety-related, or breakthrough nausea, may consider adding lorazepam 0.5–1 mg PO or IV or sublingual (SL) every 6 hours as needed on days 1–4. Use the lowest effective dose and dosage interval possible. May be administered with or without H_2 blocker or PPI if patient exhibits reflux symptoms. Principles of Emesis Control for the Patient with Cancer (AE-1). [j]Pharmacologic Considerations for Antiemetic Prescribing (AE-B). [k]Data suggest that a 5-mg dose of olanzapine is efficacious. Consider this dose especially for patients who are older or who are over sedated. Hashimoto H, et al. *Lancet Oncol* 2020;21:242-249. Mukhopadhyay S, et al. *Future Oncol* 2021;17:2041-2056. Pharmacologic Considerations for Antiemetic Prescribing (AE-B). [l]If not used previously, consider escalating to a 4-drug regimen (option A) if emesis occurred during a previous cycle of anticancer therapy with a 3-drug regimen (olanzapine-containing regimen B or E or NK1 RA-containing regimen C or F). Olanzapine-containing regimens may be useful for patients with severe nausea. Principles for Managing Breakthrough Emesis (AE-C). [m]Aprepitant injectable emulsion is a unique formulation of aprepitant and is NOT interchangeable with the IV formulation of fosaprepitant. [n]Rolapitant has an extended half-life and should not be administered at less than 2-week intervals. [o]If netupitant/palonosetron or fosnetupitant/palonosetron fixed combination product is used, no further 5-HT_3 RA is required. [p]When used in combination with an NK1 RA, there is no preferred 5-HT_3 RA. Principles of Managing Multiday Emetogenic Chemotherapy Regimens (AE-A). [q]Granisetron extended-release injection is a unique formulation of granisetron using a polymer-based drug delivery system. This formulation is specifically intended for subcutaneous administration and is NOT interchangeable with the IV formulation. Granisetron extended-release injection has an extended half-life and should not be administered at less than 1-week intervals. [r]Emerging data and clinical practice suggest dexamethasone doses may be individualized. Higher doses may be considered, especially when an NK1 RA is not given concomitantly. Lower doses, given for shorter durations, or even elimination of dexamethasone on subsequent days (for delayed nausea and emesis prevention) may be acceptable based on patient characteristics. If dexamethasone is eliminated on subsequent days for delayed nausea and emesis prevention, consider other alternative antiemetics (eg, olanzapine). Discussion. [s]Use of corticosteroid premedications should be avoided with cellular therapies. Pharmacologic Considerations for Antiemetic Prescribing (AE-B). [t]No further 5-HT_3 therapy is required if palonosetron or granisetron extended-release injection is administered, or if granisetron transdermal patch is applied, on day 1. [u]A 3-drug prophylactic regimen (E or F) is recommended for select patients with additional patient-related risk factors (AE-1) or previous treatment failure with a corticosteroid + 5-HT_3 RA alone.

NCCN Guidelines® for Antiemesis:
Chemotherapy-Induced Breakthrough Nausea/Vomiting[a]

The General Principle of Breakthrough Treatment Is to Add 1 Agent From a Different Drug Class to the Current Regimen[b]

Atypical Antipsychotic:
- Olanzapine[c,d]

Benzodiazepine:
- Lorazepam[d]

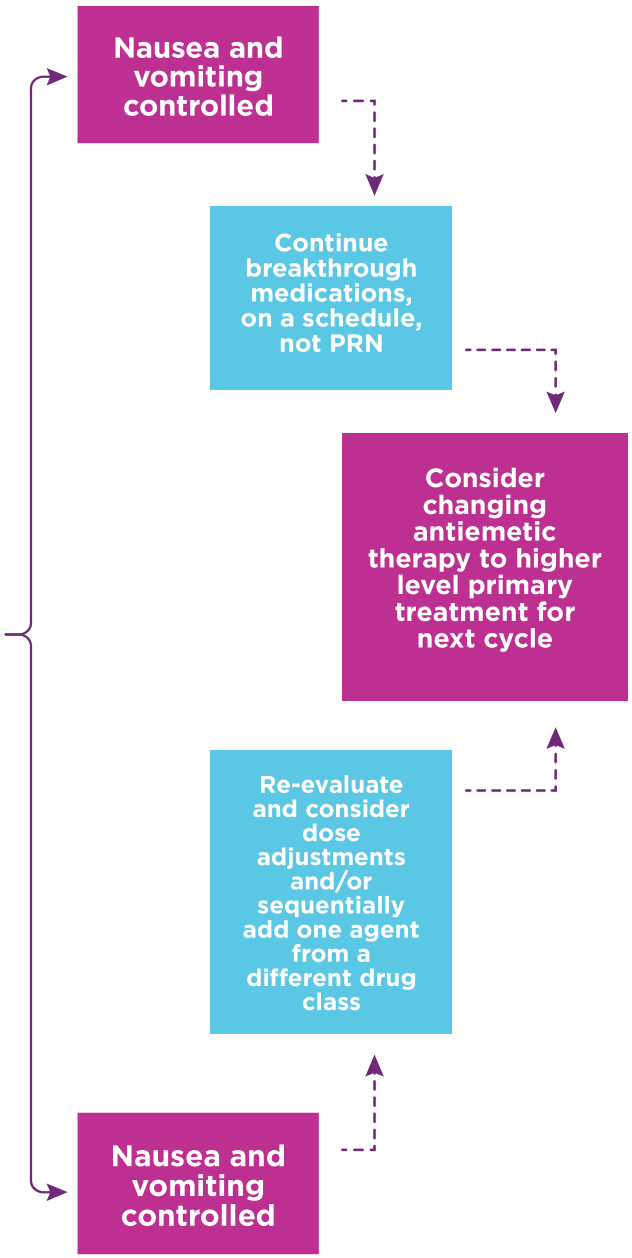
Cannabinoid:
- Dronabinol[e]
- Nabilone

Other:
- Haloperidol
- Metoclopramide
- Scopolamine transdermal patch

Phenothiazine:
- Prochlorperazine suppository
- Promethazine suppository

5-HT$_3$ RA:
- Dolasetron
- Granisetron
- Ondansetron

Corticosteroid:
- Dexamethasone



NCCN, National Comprehensive Cancer Network; **PO,** orally; **PRN,** as needed.

[a]All recommendations are category 2A unless otherwise indicated. Category 2A recommendations indicate uniform NCCN consensus that the intervention is appropriate based on lower level evidence. [b]For details regarding recommendations and specific dosing information, please refer to the NCCN Guidelines for Antiemesis. [c]When not used as part of the acute and delayed emesis prevention regimen. [d]For olanzapine-containing regimens, only use PO lorazepam. [e]Dronabinol oral solution has greater oral bioavailability than dronabinol capsules; 2.1 mg oral solution=2.5 mg capsules.

Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.1.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

DIARRHEA

Potential Management Strategies

Patient Counseling[1]

- Keep track of fluid intake
- Avoid milk or milk products if they make diarrhea worse. Yogurt and firm cheeses are okay
- Reduce fatty food
- Avoid caffeine, alcohol, and tobacco
- Be sure to consume enough potassium
- Patients with diarrhea complicated by cramping, nausea, and vomiting should be evaluated by their HCP

Rx Options[2]

Consider Use of Treatment Such as:

- Loperamide
- Diphenoxylate-atropine sulfate
- Tincture of opium

PERSISTENT AR

T-DXd Clinical Trial Protocol Guidance

Dose Interruption[3]

For Grade ≥ 3 Diarrhea:
Delay dose until resolved to grade ≤ 1 (no longer than 4 weeks)

HCP, healthcare provider; **AR,** adverse reactions; **T-DXd,** trastuzumab deruxtecan.

1. Bossi P, et al. *Ann Oncol*. 2018;29(suppl 4):iv126-iv142. 2. Chemocare.com website. Diarrhea and Chemotherapy. chemocare.com/chemotherapy/side-effects/diarrhea-and-chemo-therapy.aspx. Accessed January 15, 2020. 3. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020.

Resume Therapy[1]

If resolved in ≤ 3 days, maintain dose

If resolved in > 3 days, reduce dose

*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

Dose Modification[1,2]

	mBC
Starting dose	5.4 mg/kg
Initial dose reduction	4.4 mg/kg
Final dose reduction	3.2 mg/kg
Further dose reduction required	Discontinue treatment

Do not re-escalate the T-DXd dose after a dose reduction is made.[2]

mBC, metastatic breast cancer; **T-DXd,** trastuzumab deruxtecan.

1. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020. 2. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021.

CONSTIPATION

Potential Management Strategies

Patient Counseling[1]

Utilize positioning to aid with defecation (eg, assist gravity, small foot stool may help a patient exert pressure more easily)

Eat food that are high in fiber, such as fruits, vegetables, and whole-grain breads and cereals[2]

Keep track of fluid intake

Encourage activity and increased mobility within patient limits

Anticipatory management of constipation when certain medications are prescribed (eg, opioids)

Clinical Evaluation[3]

Evaluate Concomitant Medications That May Contribute to Constipation, Including:

- Opioids
- Anticholinergics (tricyclic antidepressants and phenothiazines)
- Calcium or aluminum - containing antacids
- Iron preparations
- Antiemetics (5-HT_3 antagonists)

Consider use of prophylactic laxatives when such agents are taken on a regular basis.

Non-Rx Options

Patient Management Strategies[4]

- Fluid intake
- Dietary consideration

5-HT_3, 5-hydroxytryptamine (serotonin).

1. Larkin PJ, et al. *Ann Oncol.* 2018;29(suppl 4):iv111-iv125. 2. American Cancer Society website. Constipation. www.cancer.org/treatment/treatments-and-side-effects/-physical-side-effects/stool-or-urine-changes/constipation.html. Accessed January 15, 2020. 3. Avila JG. Cancer Control. 2004;11(3 suppl):10-18. 4. Rumman A, et al. *Expert Rev Qual Life Cancer Care.* 2016;1(1):25-35.

Laxatives[1]

- Evaluate underlying cause(s) of constipation and laxative mechanism of action to inform appropriate intervention.
- Stimulant laxatives play a central role in treatment of constipation in patients with cancer.
- Bulk-forming laxatives are not recommended.

Stool Softeners[1]

- Typically used in combination with stimulant laxatives.

Enemas[1]

- May be necessary in acute cases.
- Not for regular use in standard constipation treatment.

Rx Options[2]

- Consider after failure of OTC options.
- **Consider underlying cause of constipation to inform treatment choice.**
  - Prokinetic agents.
  - Peripherally acting mu-opioid receptor antagonists.
  - Secretagogues.

OTC, over-the-counter.

1. Avila JG. Cancer Control. 2004;11(3 suppl):10-18. 2. Rumman A, et al. *Expert Rev Qual Life Cancer Care.* 2016;1(1):25-35.

DECREASED APPETITE

Potential Management Strategies

Patient Counseling[1]

- Eat several small meals throughout the day
- Avoid drinking liquids with meals; drink liquids in between meals
- Make eating more enjoyable by listening to music, watching TV, or eating with company
- Be as physically active as possible
- Eat food high in protein and/or calories, and keep these types of snacks on hand
- Eat your favorite food any time of day
- Consider consulting a registered dietitian

Rx Options[2]

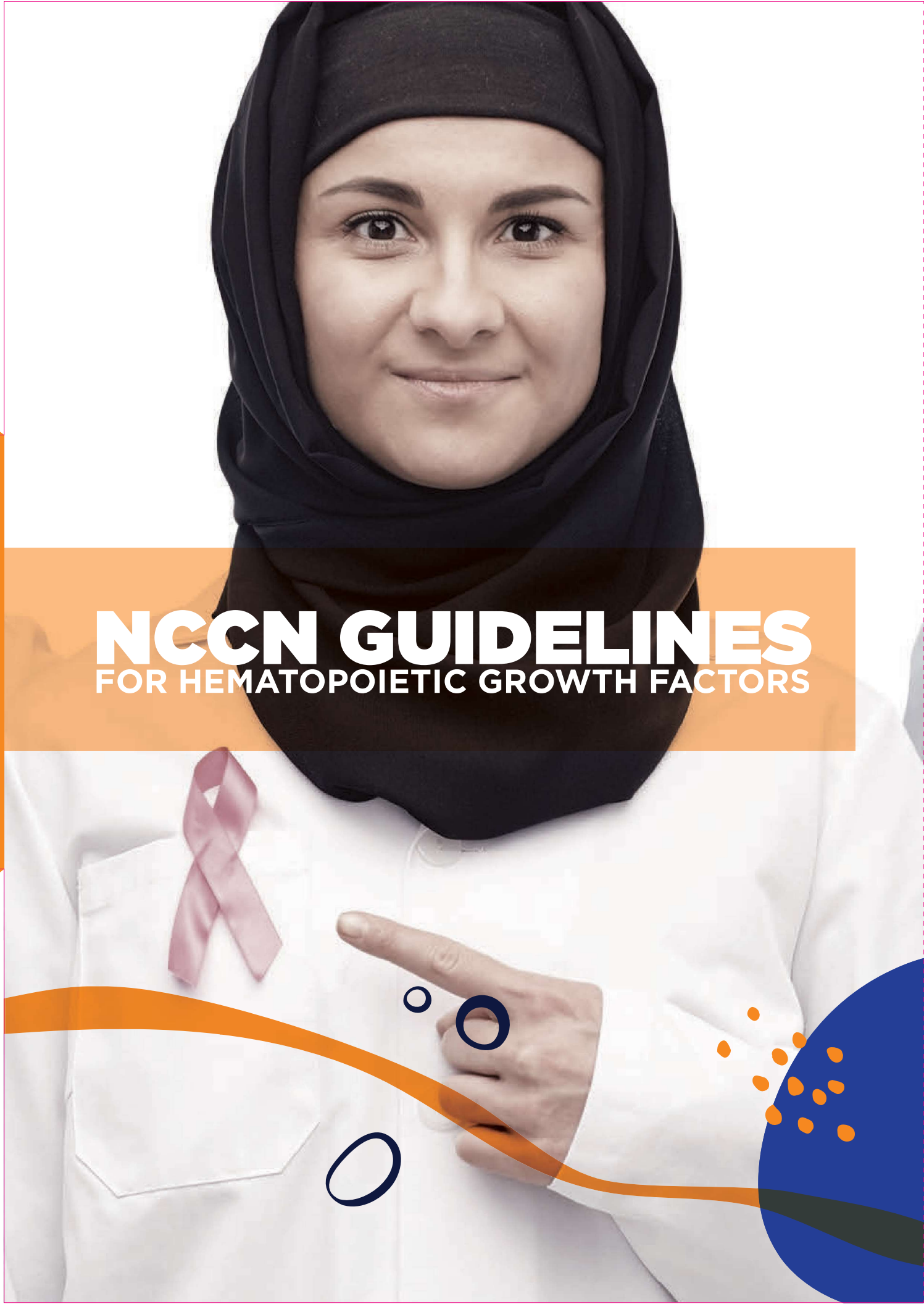
Consider an Appetite Stimulant Such as:

- Megestrol acetate
- Metoclopramide
- Dronabinol
- Steroids

1. American Cancer Society website. Appetite Changes. www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/eating-problems/poor-appetite.html. Accessed January 15, 2020. 2. Chemocare.com website. Cancer and Chemo-Based Lack of Appetite and Early Satiety. chemocare.com/chemotherapy/side-effects/cancer-and-chemobased-lack-of.aspx. Accessed January 15, 2020.

Hematological Adverse Reactions

NCCN GUIDELINES
FOR HEMATOPOIETIC GROWTH FACTORS



ANEMIA

Potential Management Strategies & NCCN Guidelines

Patient Counseling[1]

- Plan ahead and save your energy for the most important activities
- Balance rest and activities
- Eat a balanced diet that includes protein (meat, fish, eggs, cheese, milk, nuts, peas, and beans)
- Drink plenty of nonalcoholic liquids

When to Call Health-Care Provider?

- Severe weakness
- Dizziness or lightheadedness
- Palpitation
- Shortness of breathe or difficulty breathing

Regular blood tests are necessary to monitor for ARs such as treatment-related anemia

PERSISTENT AR

T-DXd Clinical Trial Protocol Guidance

Clinical Evaluation/Rx Options[2,3]

	Consider Use of Treatment Such as:
Clinical Evaluation of Anemia	• Iron Supplement • Multivitamin • Red blood cell transfusion • Consider ESAs as an alternative to RBC transfusions in select patients[4]

AR, adverse reaction; **ESA,** erythropoiesis-stimulating agent; **RBC,** red blood cell.

1. American Cancer Society website. Managing Anemia at Home. www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/managing-anemia-at-home.html. Accessed January 15, 2020.
2. Chemocare.com website. Low Blood Counts. chemocare.com/chemotherapy/side-effects/low-blood-counts.aspx. Accessed January 15, 2020. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed May 17, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

PERSISTENT AR

T-DXd Clinical Trial Protocol Guidance

Dose Interruption[1]

For Grade 3 (Hgb < 8.0 g/dL);

- Transfuse
- Delay dose until resolved to grade ≤ 2

For Grade 4 (Life-Threatening);

- Transfuse
- Delay dose until resolved to grade ≤ 2

Resume Therapy[1]

For Grade 3 (Hgb < 8.0 g/dL);

↻ Maintain dose

For Grade 4 (Life-Threatening);

↓ Reduce dose 1 level

*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

Dose Modification[1,2]

	mBC
Starting dose	5.4 mg/kg
Initial dose reduction	4.4 mg/kg
Final dose reduction	3.2 mg/kg
Further dose reduction required	Discontinue treatment

Do not re-escalate the T-DXd dose after a dose reduction is made.[1]

AR, adverse reaction; **Hgb,** hemoglobin; **mBC,** metastatic breast cancer; **T-DXd,** trastuzumab deruxtecan.

1. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021. 2. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020.

CLINICAL EVALUATION OF ANEMIA[a,b,c]

Hgb ≤ 11 g/dL or ≥ 2 g/dL below baseline[d]

↓

CBC with indices blood smear morphology

↓

Clinical Evaluation[a,b]

Evaluate Anemia for Possible Cause as Indicated[c]

First Check

- Reticulocyte count and mean corpuscular volume (MCV)[e]

Then Consider

- Hemorrhage
- Hemolysis
- Nutritional[f]
- Inherited
- Renal dysfunction
- Radiation-induced myelosuppression
- Hormone dysfunction
- Anemia of chronic-inflammation

Treat as indicated

No cause identified

CBC, complete blood count; **Hgb,** hemoglobin.

[a]All recommendations are category 2A unless otherwise indicated. Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. [b]The NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients. [c]This is a basic evaluation for possible causes of anemia. [d]Consideration of gender in evaluation of anemia is relevant since women have a lower baseline Hgb than men. [e]Correct reticulocyte count for degree of anemia. [f]The ferritin value indicating iron deficiency is laboratory specific. In general, the lower level of ferritin, the higher the probability that the patient has true iron deficiency anemia. However, in the cancer setting, be aware of a chronic inflammatory state, which may falsely elevate the serum ferritin. Additionally, if serum iron studies are not performed while the patient is fasting or if the patient has taken a recent oral iron tablet, serum iron levels may be falsely elevated, and thus also falsely elevate the percent transferrin saturation. Fasting is preferred when testing for serum iron and total-binding capacity.

Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed May 17, 2021. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

EVALUATION OF IRON DEFICIENCY[a]

Evaluation of Iron Deficiency

Iron studies: Iron panel (serum iron, total iron-binding capacity, serum ferritin)[b]

Iron Status

Absolute iron deficiency	Functional iron deficiency in patients receiving ESAs	Possible functional iron deficiency	No iron deficiency
(ferritin < 30 ng/mL ***AND*** transferrin saturation (TSAT) < 20%)[c]	(ferritin 30-500 ng/mL ***AND*** TSAT < 50%)[d,e]	(ferritin > 500-800 ng/mL ***AND*** TSAT < 50%)[d,e,f]	(ferritin > 800 ng/mL ***OR*** TSAT ≥ 50%)

Management

Consider IV ***OR*** oral iron supplementation	Consider IV iron supplementation with erythropoietin therapy[g,h,i]	No iron supplementation needed ***OR*** consider IV iron supplementation for select patients	IV ***OR*** oral iron supplementation is not needed

Hgb increase after 4 weeks	No Hgb increase after 4 weeks
Periodic evaluation (Repeat ferritin and TSAT)	**See pathway for functional iron deficiency**

ESA, erythropoiesis-stimulating agent; **Hgb,** hemoglobin; **NCCN,** National Comprehensive Cancer Network; **TSAT,** transferrin saturation.

[a]All recommendations are category 2A unless otherwise indicated. Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. [b]The ferritin value indicating iron deficiency is laboratory-specific. In general, the lower the level of ferritin, the higher the probability that the patient has true iron-deficiency anemia. However, in the cancer setting, be aware of a chronic inflammatory state, which may falsely elevate the serum ferritin. Additionally, if serum iron studies are not performed while the patient is fasting or if the patient has taken a recent oral iron tablet, serum iron levels may be falsely elevated, and thus also falsely elevate the perfect transferrin saturation. Fasting is preferred when testing for serum iron and total iron-binding capacity. [c]If the ferritin and TSAT are discordant, the low ferritin value should take precedence in determining whether IV iron will be of benefit. [d]In clinical trials using IV iron plus an ESA, a higher response rate is seen when iron is used for patients with a TSAT < 20%, the response rate to IV iron is both diminished and prolonged as the TSAT increased from 20%-50%. Therefore, the decision to offer IV iron to this subset of patients should be reserved for those in whom benefits are likely to outweigh risks. [e]Only one of six studies (Henry DH, et al. *Oncologist* 2007;12:231-242) of IV iron therapy in patients with cancer provided a TSAT guideline for monitoring. [f]Although patients with ferritin levels of > 500-800 ng/mL may have functional iron deficiency, as evidenced by clinical trials in patients with cancer, there are insufficient data to support the routine use of IV iron in this setting. Administration of IV iron to such patients should be individualized with the goal of avoiding allogeneic transfusion. [g]IV iron has superior efficacy and should be considered for supplementation. Oral iron has been more commonly used but is less effective. [h]Although all combinations of serum ferritin and TSAT could be found in at least one of six randomized controlled trials evaluating the use of IV iron with an ESA, eligibility criteria testing for serum ferritin and TSAT generally ranged from > 10 to < 900 ng/mL and > 15% to < 60%, respectively. [i]There are insufficient data to routinely recommend IV iron as monotherapy without an ESA for the treatment of functional iron deficiency anemia.

Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed August 17, 2021. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

RISK ASSESSMENT & INDICATIONS

FOR INITIAL TRANSFUSION IN THE ACUTE SETTING[a,b]

Anemia in Patients With Cancer

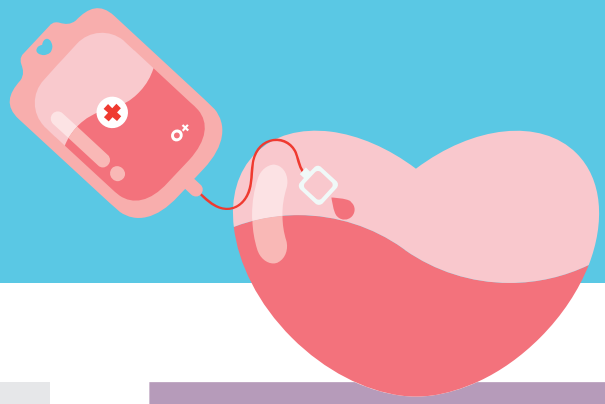
Asymptomatic without significant comorbidities:[c]	**Observe then periodic re-evaluation**
High risk (ie, progressive decline in Hgb with recent intensive chemotherapy or radiation) or asymptomatic with comorbidities:[c] - Cardiac disease - Chronic pulmonary disease - Cerebral vascular disease	**Consider red blood cell (RBC) transfusion per AABB Guidelines[b]**
Symptomatic (physiologic): - Sustained tachycardia - Tachypnea - Chest pain - Dyspnea on exertion - Lightheadedness - Syncope - Severe fatigue preventing work and usual activity[d]	**RBC transfusion per AABB Guidelines[b]**

AABB, American Association of Blood Banks.

[a]All recommendations are category 2A unless otherwise indicated. Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. [b]The AABB has made recommendations regarding appropriate indications for RBC transfusion. [c]Degree of severity of comorbidities in combination with the degree of severity of anemia should be taken into consideration when initiating RBC transfusion. [d]Fatigue (FACT-F) and Anemia (FACT-An) subscales of the Functional Assessment of Cancer Therapy (FACT) and Brief Fatigue Inventory (BFI) are examples of standardized measures for assessing patient-reported fatigue.

Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed August 17, 2021. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

SPECIAL CATEGORIES IN CONSIDERING ESA USE[a]



Cancer and chronic kidney disease (moderate to severe)	**Consider ESAs by FDA dosing/dosing adjustments[b,c]**
Patient undergoing palliative treatment	**Consider based on patient preferences:** • ESAs by FDA dosing/ dosing adjustments[b] • RBC transfusion per AABB Guidelines • Clinical trial
Remainder of patients with anemia on myelosuppressive chemotherapy without other identifiable cause of anemia	
Select patients who refuse blood transfusions	**Consider ESAs by FDA dosing/dosing adjustments[b]**
• Patients with cancer not receiving therapy • Patients receiving non-myelosuppressive therapy • Patients receiving myelosuppressive chemotherapy with curative intent (Examples of cancers for which there is therapy with curative intent: Early-stage breast cancer, Hodgkin lymphoma, Non-Hodgkin's lymphomas, testicular cancer, early-stage non-small cell lung cancer, and small cell lung cancer)[d]	**There is not enough evidence to support ESA use in these patient populations; therefore, ESAs are not recommended at this time**

AABB, American Association of Blood Banks; **ESA,** erythropoiesis-stimulating agents; **FDA,** United States Food and Drug Administration; **RBC,** red blood cell.

[a]All recommendations are category 2A unless otherwise indicated. Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. [b]Patients with previous risk factors for thrombosis are at higher risk for thrombosis with the use of ESAs, evaluate the risk factors for thrombosis: History of thromboembolism, known heritable mutation, hypercoagulopathy, elevated pre-chemotherapy platelet counts, hypertension, steroids, prolonged immobilization, recent surgery, certain therapies for multiple myeloma, hormonal agents, etc. [c]The Hgb threshold for treatment and dosing with ESAs is different for chemotherapy-induced anemia and chronic kidney disease. [d]A few studies suggest that patients with small-cell lung cancer on myelosuppressive chemotherapy may not have an increase in mortality when receiving ESAs. (Nagel S, Kellner O, Engel-Riedel W, et al. Addition of darbepoetin-alfa to dose dense chemotherapy: results from a randomized phase II trial in small-cell lung cancer patients receiving carboplatin plus etoposide. *Clin Lung Cancer.* 2011;12:62-69).

Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed August 17, 2021. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

THROMBOCYTOPENIA

Potential Management Strategies

Patient Counseling[1]

- Only shave with electric razors
- Avoid contact sports or other activities that may lead to injury
- Protect skin from cuts and scrapes
- Use a soft toothbrush, and ask HCP about putting off flossing
- Rinse bleeding gums with ice water
- Avoid blowing nose or coughing with great force
- Keep head level with or above heart by either lying flat or staying upright
- Consider using stool softener to avoid constipation and straining, but check with HCP before taking laxatives
- Avoid putting anything in rectum, such as suppositories, enemas, or thermometers
- Avoid anti-inflammatory pain medicines like aspirin, naproxen, or ibuprofen, unless HCP advises to use them
- Regular blood tests are necessary to monitor for ARs such as treatment-related anemia

Rx Options[2]

Consider Use of Treatment Such as:

- Oprelvekin
- Platelet transfusion

HCP, health care professional.

1. American Cancer Society website. Bleeding or Low Platelet Count. www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/bleeding.html. Accessed January 15, 2020.
2. Chemocare.com website. Low Blood Counts. chemocare.com/chemotherapy/side-effects/low-blood-counts.aspx. Accessed January 15, 2020.

PERSISTENT AR

T-DXd Clinical Trial Protocol Guidance

Dose Interruption[1]

For Grade 3 (platelets < 50 to 25 x 10^9/L):
Delay dose until resolved to x grade ≤ 1

For Grade 4 (platelets < 25 x 10^9/L):
Delay dose until resolved to x grade ≤ 1

*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

Resume Therapy[1]

For Grade 3

If resolved in ≤ 7 days, maintain dose

If resolved in > 7 days, reduce dose

For Grade 4

Reduce dose 1 level

*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

Dose Modification[1,2]

	mBC
Starting dose	5.4 mg/kg
Initial dose reduction	4.4 mg/kg
Final dose reduction	3.2 mg/kg
Further dose reduction required	Discontinue treatment

Do not re-escalate the T-DXd dose after a dose reduction is made.[1]

AR, adverse reaction; **mBC,** metastatic breast cancer; **T-DXd,** trastuzumab deruxtecan.

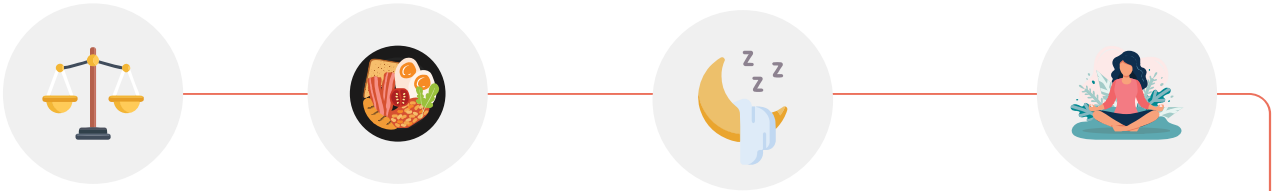
1. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020. 2. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021

MISCELLANEOUS ADVERSE REACTIONS

FATIGUE

Potential Management Strategies & NCCN Guidelines

Patient Counseling[1]



- Balance periods of rest and work
- Eat a healthy diet and drink plenty of fluids
- Sleep therapy (eg, avoid caffeine, keep naps short, and good sleep habits)
- Behavioral techniques (eg, relaxation, social support, and counseling)
- Save your energy and focus on tasks that are most important to you
- Ask family and friends to help with tasks you find tiring
- Stress management

Non-Rx Options[2,a]

Patients Undergoing Active Treatment:

- Physical activity (category 1) (eg, walking, jogging, swimming, weights, and yoga)
- Physically based therapies (category 1) (eg, massage therapy)
- CBT for insomnia (CBT-I)[b]
- Psychosocial interventions (category 1) (eg, CBT/behavioral therapy psycho-educational therapies (category 1)[b,c]
- Nutrition consultation
- Bright white light therapy[d]
- Supportive expressive therapies[e]

Rx Options[2,a]

Patients Undergoing Active Treatment:

- Consider psychostimulants (eg, methylphenidate) after ruling out other causes of fatigue[f]
- Treat for pain, emotional distress, and anemia as indicated per NCCN Guidelines
- Optimize treatment for sleep dysfunction, nutritional deficit or imbalance, and comorbidities

NCCN, National Comprehensive Cancer Network.

[a]All recommendations are category 2A unless otherwise indicated. Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. [b]A type of psychotherapy that focuses on recognizing and changing maladaptive thoughts and behaviors to reduce negative emotions and behaviors and to facilitate psychological adjustment. [c]CBT/behavioral therapy influences thoughts and promotes changes in behavior; it includes a variety of strategies (eg, cognitive restructuring, relaxation, and mindfulness). [d]Bright white light therapy of 10,000 lux is most frequently self-administered in the early morning for 30-90 minutes. Timing needs to be adjusted for those who sleep during the day. [e]Supportive expressive therapies (eg, support groups, counseling, and journal writing) facilitate expression of emotion and foster support from one or more people. [f]Pharmacologic interventions remain investigational, but have been reported to improve symptoms of fatigue in some patients. Methylphenidate should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterized or excluded. Optimal dosing and schedule have not been established for use of psychostimulants in older adults and patients with cancer.

1. National Comprehensive Cancer Network website. Fatigue. www.nccn.org/patients/resources/life_with_cancer/managing_symptomtober s/fatigue.aspx. Accessed August 17, 2021. 2. Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer-Related Fatigue V.1.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

ALOPECIA

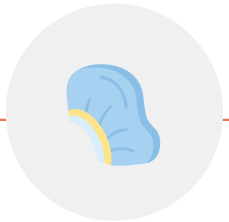
Potential Management Strategies

Patient Counseling[1]

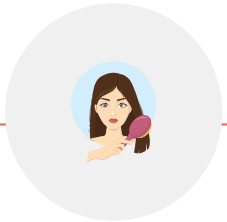
Utilize scalp cooling technologies

You can cut your hair short or shave your head even before hair loss occurs

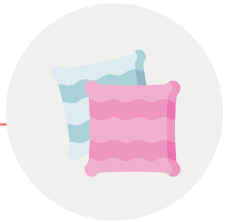
You can use wigs, caps, or other head coverings



If your hair becomes very thin or falls out completely, protect the skin of your scalp from heat, cold, and the sun



Hair loss may be slightly reduced by avoiding too much brushing or washing of hair



Try wearing a hairnet at night, or sleeping on a satin pillowcase

Rx Options

- Minoxidil[2]
- Bimatoprost[3]
- Calcitriol[4]

Non-Rx Options

- Scalp cooling caps (scalp hypothermia)[5]

Warnings & Precautions

1. American Cancer Society website. Coping With Hair Loss. www.cancer.org/treatment/treatments-and-side-effects /physical-side-effects/hair-loss/coping-with-hair-loss.html. Accessed May 17, 2021. 2. Rodriguez R, et al. *Ann Oncol*. 1994;5(8):769. 3. Glaser DA, et al. *Br J Dermatol*. 2015;172(5):1384. 4. Jimenez JJ, et al. *Am J Med Sci*. 1995;310(2):43. 5. Shin H, et al. *Int J Cancer*. 2015;136(5):E442.

Infusion-Related Reactions

CTCAE Grade[1]	T-DXd Clinical Trial Protocol Guidance[2]
Grade 1	• If an IRR (eg, fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and patients should be closely monitored. • If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2	• Administration of T-DXd should be interrupted and symptomatic treatment started (eg, antihistamines, NSAIDs, narcotics, intravenous fluids). • If the event resolves or improves to grade 1, infusion can be restarted at a 50% reduced infusion rate. • Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4	• Administration of T-DXd should be discontinued immediately and permanently. • Urgent intervention indicated. • Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation, etc, should be administered.

- Slow or interrupt the infusion rate if the patient develops infusion-related symptoms.
- Permanently discontinue T-DXd in case of severe infusion reactions.[3]

CTCAE, Common Terminology Criteria for Adverse Events; **IRR,** infusion-related reaction; **NSAID,** nonsteroidal anti-inflammatory drug; **T-DXd,** trastuzumab deruxtecan.

1. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Published May 29, 2009; Revised June 14, 2010. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed August 17, 2021. 2. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020. 3. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021.

WARNINGS & PRECAUTIONS

DIAGNOSING DRUG-INDUCED INTERSTITIAL LUNG DISEASE[1]

Diagnosis of drug-induced ILD is based on **a comprehensive consideration of clinical symptoms, physical findings, detailed medical history, diagnostic imaging, lung function tests, and pathological findings.**[1]

Differential diagnosis is key in treating drug-induced ILD.[1]

Drug-induced ILD should be conclusively distinguished from exacerbation of an underlying pulmonary disease and pulmonary edema.[1]

WHEN INTERSTITIAL LUNG DISEASE IS SUSPECTED[1,2]

Symptoms and Physical Findings:

Skin rash, cough (particularly dry cough), shortness of breath/dyspnea/rales, and fever

Medical History:

- Past/current use of suspected drugs and temporal
- Relationship between drug use and symptom
- Onset, drug's history of ILD, and prior thoracic
- Radiotherapy

Chest X-Rays:

Chest CT (or high-resolution CT) images

Respiratory Function Tests:

Ventilatory or diffusion impairment

Clinical Laboratory Tests:

Blood cell count, differential white blood cell count, CRP, and liver function tests

Differential Diagnosis (Infection, Edema, etc):

- β-D glucan
- Cytomegalovirus antigen
- Expectorated sputum
- Bacterial smear, culture, and DNA analysis
- Acid-fast bacteria smear, culture, and DNA analysis
- Pneumocystis DNA analysis

BALF findings

Histopathological findings in lung biopsy specimens

- Other pulmonary disorder of unknown origin
- Drug-induced ILD
- Progression of an underlying disease
- Concomitant infection

Early diagnosis is key for managing cases of drug-induced ILD.

BALF, bronchoalveolar lavage fluid; **CRP,** c-reactive protein; **CT,** computerized tomography; **DNA,** deoxyribonucleic acid; **ILD,** interstitial lung disease.

1. Kubo K, et al. *Respir Investig*. 2013;51(4):260-277. 2. Raghu G, et al. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68.

AN ILD/PNEUMONITIS MANAGEMENT PROGRAM FOR T-DXd CLINICAL STUDIES HAS BEEN ESTABLISHED

Updated Guidelines (2019)

STEP 1 Monitor

Suspected ILD/Pneumonitis Interrupt Drug

Rule out ILD/pneumonitis if a patient develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea, cough, or fever.

STEP 2 Confirm

Evaluations Should Include:

- High-resolution CT.
- Pulmonologist consultation (infectious disease consultation as clinically indicated).
- Blood culture and CBC. Other blood tests could be considered as needed.
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible.
- PFTs and pulse oximetry.
- Arterial blood gases, if clinically indicated.
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible.

All events of ILD/pneumonitis, regardless of severity or seriousness, should be followed until resolution including after drug discontinuation.

STEP 3 Manage

Drug Must Be Interrupted for Any ILD/Pneumonitis Events Regardless of Grade

Grade 1: Interrupt Until Fully Resolved, Then:

- If resolved in 28 days or less from date of onset, maintain dose.
- If resolved in greater than 28 days from date of onset, reduce dose one level.
- However, if the event Grade 1 ILD/pneumonitis occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued.

Grades 2-4: Permanently Discontinue Treatment

Refer to toxicity management guidelines for trastuzumab deruxtecan.

Data on file. Daiichi Sankyo, Inc; Basking Ridge, NJ.

ILD/PNEUMONITIS MANAGEMENT GUIDELINES FOR T-DXd

Updated Guidelines (2019)

Toxicity Management	Grade 1	Grade 2	Grade 3/4
	• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry. • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • **Consider Starting Systemic Steroids:** (e.g., at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by **gradual taper over at least 4 weeks**. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines. • If patient is asymptomatic, then patient should still be considered as grade 1 even if steroid treatment is given.	• Promptly start and **treat with systemic steroids** (e.g., at least 1 mg/kg/day prednisone or equivalent) for **at least 14 days** or until complete resolution of clinical symptoms and chest CT findings, then followed by a **gradual taper over at least 4 weeks**. • Monitor symptoms closely. • Re-image as clinically indicated. • **If Worsening or No Improvement in Clinical or Diagnostic Observations in 5 Days:** **Consider increasing dose of steroids** (e.g., 2mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g., methylprednisolone). Re-consider additional work-up for alternative etiologies as described above. Escalate care as clinically indicated.	• Hospitalization required. • Promptly **initiate empiric high-dose methylprednisolone IV treatment** (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) **for at least 14 days** followed by a gradual taper over at least 4 weeks. • Re-image as clinically indicated. • **If Still No Improvement within 3 to 5 Days:** Re-consider additional work-up for alternative etiologies as described above. Consider other immuno-suppressants and/or treat per local practice.

Data on file. Daiichi Sankyo, Inc; Basking Ridge, NJ.

MANAGEMENT OF ILD/PNEUMONITIS FOR PATIENTS TREATED WITH T-DXd[1]

- Prescribers should report all adverse events according to their local regulatory requirements and refer to their local prescribing information for management of adverse events, including ILD/pneumonitis.[1]
- The clinical development of T-DXd includes the ongoing characterization of ILD/pneumonitis.[1,2]

ILD, interstitial lung disease; **T-DXd,** trastuzumab deruxtecan; **WHO,** World Health Organization.

1. Data on file. Daiichi Sankyo, Inc; Basking Ridge, NJ.. 2. Powell CA, et al. Poster presented at the AACR Virtual Annual Meeting; April 10-15, 2021. Poster CT167.

COVID-19 IN PATIENTS TREATED WITH T-DXd

There is currently no available data regarding COVID-19 in patients treated with T-DXd.

Due to the overlap between signs and symptoms of COVID-19 and drug-induced ILD/pneumonitis with T-DXd, patients should be carefully monitored and observed for both.

Symptoms of COVID-19 include but are not limited to fever, cough, shortness of breath, and difficulty breathing and sometimes an abnormal chest scan.[1,2,3] Please note that these signs and symptoms can also be those of drug-induced ILD/pneumonitis with T-DXd.

Treatment decisions and management of patients with suspected/confirmed COVID-19 are at the discretion of the treating physician in conjunction with CDC/WHO information for healthcare professionals.

CDC, Centers for Disease Control and Prevention; **COVID-19,** coronavirus disease 2019; **ILD,** Interstitial lung disease; **T-DXd,** trastuzumab deruxtecan; **WHO,** World Health Organization.

1. Symptoms of Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention website. Accessed May 17, 2021. 2. Guan W, et al. *N Engl J Med*. doi: 10.1056/NEJMoa2002032. 3. Q&A on Coronaviruses (COVID-19). World Health Organization website. Accessed May 17, 2021.

NEUTROPENIA

Potential Management Strategies & NCCN Guidelines

Patient Counseling[1]

Reduce Risk of Infection by:[1]

- Washing hands frequently.
- Avoiding contact with people who are sick.
- Not having dental work done while neutrophil count is low.

Regular blood tests are necessary prior to initiation of T-DXd and prior to each dose to monitor for ARs as treatment-related neutropenia.[2]

Potential for developing neutropenia and to immediately contact their healthcare provider should they develop a fever, particularly in association with any signs of infection.[2]

Rx Options[1]

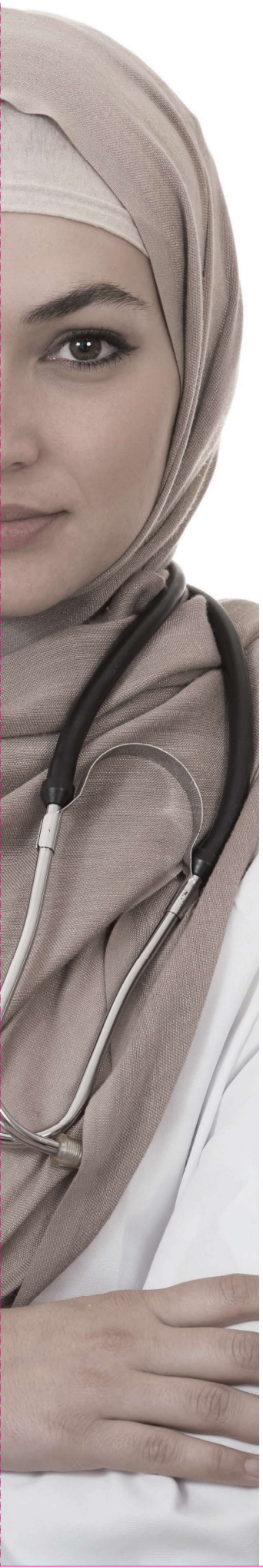
Consider Use of Treatment Such as:

- Filgrastim
- Pegfilgrastim
- Sargramostim

- Antimicrobial medications may be prescribed to prevent specific infections.
- G-CSFs may be given to prevent febrile neutropenia in select patients based on chemotherapy regimen, patient risk factors and treatment intent.[2]

AR, adverse reaction; **G-CSFs,** granulocyte colony-stimulating factors; **T-DXd,** trastuzumab deruxtecan.

1. Chemocare.com website. Low Blood Counts. chemocare.com/chemotherapy/side-effects/low-blood-counts.aspx. Accessed January 15, 2020. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 17, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.



PERSISTENT AR

T-DXd Clinical Trial Protocol Guidance

Permitted Therapies in Clinical Trials[3]

Hematopoietic Growth Factors:
May be used for prophylaxis or treatment based on the clinical judgment of the Investigator.

PERSISTENT AR

T-DXd Clinical Trial Protocol Guidance

Dose Interruption[1]

For Grade 3:
Delay dose until resolved

Resume Therapy[1]

For Grade 3:

↻ Maintain dose

For Grade 4:

↓ Reduce dose 1 level

*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

Dose Modification[2]

	mBC
Starting dose	5.4 mg/kg
Initial dose reduction	4.4 mg/kg
Final dose reduction	3.2 mg/kg
Further dose reduction required	Discontinue treatment

Do not re-escalate the T-DXd dose after a dose reduction is made.[2]

T-DXd, trastuzumab deruxtecan.

1. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020. 2. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021.

FEBRILE NEUTROPENIA

Potential Management Strategies & NCCN Guidelines

If Fever Is Present[1]

- Administer empirical therapy ≤ 1 hour after triage.
- Patients with febrile neutropenia should receive an intravenous dose of therapy while undergoing evaluation.

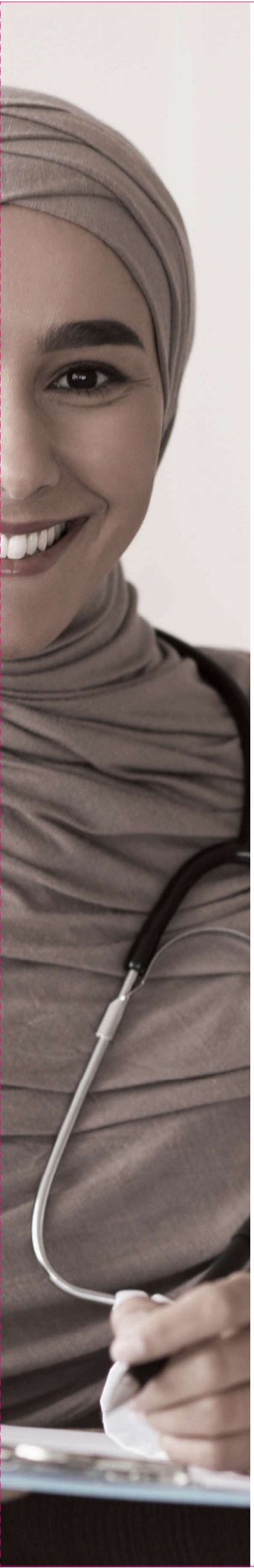
Clinical Evaluation[1]

- Complete history and physical examination; complete blood count with leukocyte differential count, hemoglobin, and platelet count.
- ≥ 2 blood cultures from different sites and cultures from other sites (e.g., urine or wounds).
- Chest imaging for patients with symptoms of lower respiratory tract infection; nasopharyngeal swab for patients with an influenza-like illness.

Empiric Therapy[1]

- An antipseudomonal β-lactam agent is recommended, but other antibacterials may be added for management of complications or if resistance is suspected.
- If patients are appropriate for outpatient management, observe for ≥ 4 hours before discharge.
- G-CSFs may be given to prevent febrile neutropenia in select patients based on chemotherapy regimen, patient risk factors, and treatment intent.[2,a]

1. Taplitz RA, et al. *J Clin Oncol.* 2018;36(14):1443-1453. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 17, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.



T-DXd Clinical Trial Protocol Guidance

Dose Interruption[1]

In the Event of Febrile Neutropenia:
Delay dose until resolved

Resume Therapy[1]

↓ Reduce dose 1 level

*6.4 mg/kg starting dose is an investigational dose for investigational tumors.

Dose Modification[2,3]	mBC
Starting dose	5.4 mg/kg
Initial dose reduction	4.4 mg/kg
Final dose reduction	3.2 mg/kg
Further dose reduction required	Discontinue treatment

Do not re-escalate the T-DXd dose after a dose reduction is made.[2,3]

T-DXd, trastuzumab deruxtecan.

1. Investigator's brochure for trastuzumab deruxtecan. Version 6.0. Basking Ridge, NJ: Daiichi Sankyo, Inc. Effective September 9, 2019. 2. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021. 3. Data on file. Daiichi Sankyo, Inc., Basking Ridge, NJ. 2020.

NCCN Guidelines® for Hematopoietic Growth Factors: Management of Febrile Neutropenia[a]

Evaluation Prior to First Chemotherapy Cycle[e]

Evaluation of risk for febrile neutropenia following chemotherapy in adult patients with solid tumors and non-myeloid malignancies.

Risk Assessment for Febrile Neutropenia[b,c]

- Disease
- Chemotherapy regimen:
  - High-dose therapy
  - Dose-dense therapy[d]
  - Standard-dose therapy
- Patient risk factors
- Treatment intent (curative vs palliative)

Risk and Prophylactic Use of G-CSFs for Febrile Neutropenia in Curative/Adjuvant or Palliative Setting

High (> 20%)	G-CSFs (category 1)
Intermediate (10%-20%)	Consider G-CSFs based on patient risk factors
Low (< 10%)	No G-CSFs

G-CSF, granulocyte colony-stimulating factors; **NCCN,** National Comprehensive Cancer Network.

[a]All recommendations are category 2A unless otherwise indicated. Based upon lower-level evidence, there is uniform NCCN® consensus that the intervention is appropriate. [b]There are many factors that need to be evaluated to determine a patient's risk categorization; these include type of chemotherapy regimen and patient risk factors. [c]Febrile neutropenia is defined as single temperature: ≥ 38.3°C orally or ≥ 38.0°C over 1 h; neutropenia: < 500 neutrophils/mcL or < 1000 neutrophils/mcL and a predicted decline to ≤ 500 neutrophils/mcL over the next 48 h. [d]In general, dose-dense regimens require MGF support to maintain dose intensity and schedule. [e]The NCCN Guidelines for Hematopoietic Growth Factors were formulated in reference to adult patients.

Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors V.3.2021. © 2021 National Comprehensive Cancer Network, Inc. All rights reserved. Accessed August 17, 2021. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Left Ventricular Dysfunction Management[1]
Specific Dose Modifications[1]

LV Dysfunction Severity		Dose or Schedule Modification for T-DXd
LVEF > 45% and absolute decrease from baseline is 10% to 20%		• Continue treatment with T-DXd
LVEF 40% to 45%	and absolute decrease from baseline is < 10%	• Continue treatment with T-DXd • Repeat LVEF assessment within 3 weeks
	and absolute decrease from baseline is 10% to 20%	• Interrupt T-DXd • Repeat LVEF assessment within 3 weeks • If LVEF has not recovered to within 10% from baseline, permanently discontinue T-DXd • If LVEF recovers to within 10% from baseline, resume treatment with T-DXd at the same dose
LVEF < 40% or absolute decrease from baseline is > 20%		• Interrupt T-DXd • Repeat LVEF assessment within 3 weeks • If LVEF of < 40% or absolute decrease from baseline of > 20% is confirmed, permanently discontinue T-DXd
Symptomatic congestive heart failure		• Permanently discontinue T-DXd

EMBRYO-FETAL TOXICITY[1]
SPECIFIC PATIENT COUNSELING INFORMATION[1]

Inform female patients of the potential risk to a fetus.
Advise female patients to contact their healthcare provider of a known or suspected pregnancy.

Advise females of reproductive potential to use effective contraception during treatment with T-DXd and for at least 7 months after the last dose.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with T-DXd and for at least 4 months after the last dose.

LV, left ventricular; **LVEF,** left ventricle ejection fraction; **T-DXd,** trastuzumab deruxtecan.

1. Trastuzumab deruxtecan Summary of Product Characteristics. January 2021.

Not all possible side effects are listed on this card.

Please read the Enhertu® (Trastuzumab deruxtecan) Patient Information Leaflet or talk with your doctor for more information about side effects.
For further information reach out to AstraZeneca Medical Information on:
Email: medinfo-ksa@astrazeneca.com
Phone: +966 11 2249235
Portal: https://contactazmedical.astrazeneca.com
If you experience any side effects, talk to your health care provider. This includes any possible side effects not listed in the Package Leaflet.
You can also report side effects to AstraZeneca patient Safety:
Email: ksa.ae@astrazeneca.com
Phone : +966 11 2249235
Portal: https://contactazmedical.astrazeneca.com
Or SFDA reporting information:
Email: npc.drug@sfda.gov.sa
Toll free phone: 19999
Portal: https: //ade.sfda.gov.sa

AstraZeneca