

Electronic supplementary information 2 – Development of recommendations on the monitoring and management of T-DXd-related adverse events

Article title: Clinical guidance on the monitoring and management of trastuzumab deruxtecan (T-DXd)-related adverse events: Insights from an Asia-Pacific multidisciplinary panel

Journal name: Drug Safety

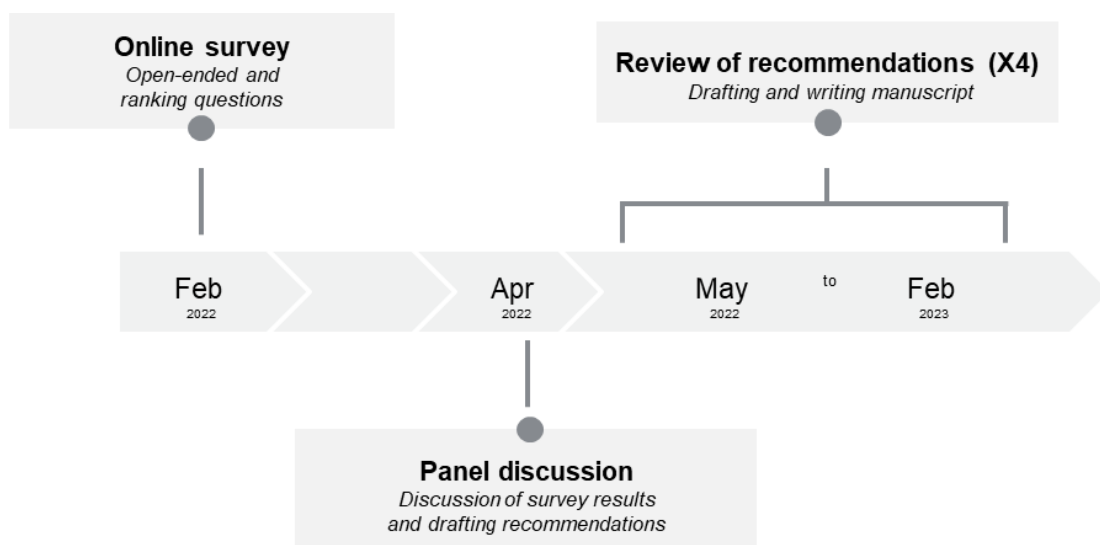
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ESM2 File – Development of recommendations on the monitoring and management of T-DXd-related adverse events

Figure 1. Timeline for developing recommendations on the monitoring and management of T-DXd-related adverse events

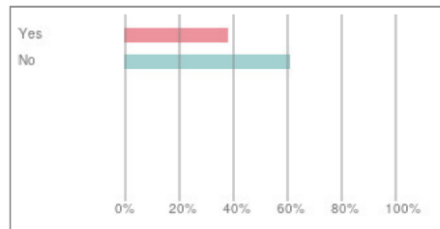


Summary of online survey questions and results

Experience with T-DXd and opinions on its adverse event (AE) profile in Asian patients with human epidermal growth factor receptor 2 (HER2)-positive unresectable or metastatic breast cancer (BC)

1. Outside of clinical trials, have you had experience managing patients with HER2-positive unresectable or metastatic BC treated with T-DXd?

Results of polling from steering committee members



2. Regarding AE management, was there anything particular about the T-DXd clinical trials that were difficult to implement in the real-world?

Summary of steering committee member comments

- a. Detecting mild interstitial lung disease (ILD) / pneumonitis in the real-world setting is a challenge.
- b. Regular chest computed tomography (CT) scans (every 6 weeks) are difficult to implement given its cost and patient reluctance.
- c. Patient education, specialist / out-patient follow-up, and reducing frequency of chest CT scans (every 9 weeks) were proposed real-world solutions.
- d. Provision of antiemetics for moderate-to-severe emetogenic medication might help with T-DXd tolerability, but additional clinical data and guidance might be required.

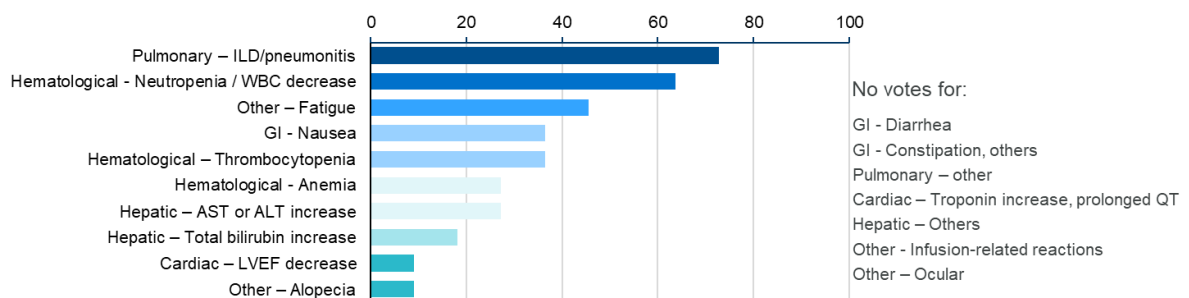
3. Based on your experience, have you observed that Asian patients experience a different AE profile with T-DXd when compared with non-Asian patients?

Summary of steering committee member comments

- a. Opinions on the incidence of gastrointestinal (GI) toxicities in Asians were mixed, with some advisors noting nausea / fatigue were generally lower in frequency.
- b. Fatigue and neutropenia were suggested to be more common in Asian patients.
- c. Alopecia appeared to be more common in Asians versus non-Asians according to clinical experience.
- d. Accurate assessment of the side effect profile in Asians versus non-Asians will require additional data.

4. Certain AEs may have extensive guidance on their management in clinical trials but may be overlooked in the real-world setting. Which of these AEs with T-DXd in Asian patients with HER2-positive unresectable or metastatic BC require additional caution / guidance on their identification, monitoring and management in the real-world setting?

Results of polling from steering committee members



Pulmonary toxicities

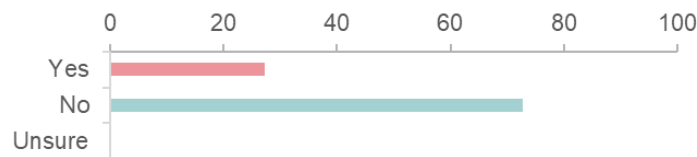
1. In your experience, are pulmonary toxicities, like ILD/pneumonitis, easily identifiable in the real-world setting, outside of clinical trials?

Summary of steering committee member comments

- a. Low grade ILD / pneumonitis appeared to be difficult to detect, and advisors advocated that healthcare providers (HCPs) should be vigilant regarding this side effect and to prevent delayed diagnosis.

2. Do you have an ILD / pneumonitis management protocol in your centers?

Results of polling from steering committee members



3. In your opinion, do you feel that additional education on monitoring and managing pulmonary toxicities, like ILD / pneumonitis, are required at your practice / region?

Summary of steering committee member comments

- a. Advisors overwhelmingly advocated for additional guidance on monitoring and managing pulmonary toxicities, such that HCPs can address these issues quickly and effectively.

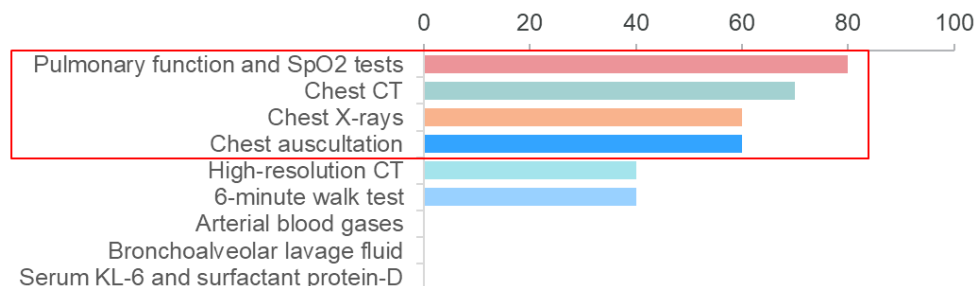
4. In your opinion, are there any risk factors for T-DXd-induced ILD / pneumonitis?

Summary of steering committee member comments

- a. Advanced age
- b. Pre-existing lung disease (or lung surgery)
- c. Smoking history
- d. Certain ethnicities (e.g., Japanese)
- e. Site of tumor (breast or other locations)
- f. Kidney dysfunction
- g. Interactions with other medication

5. In the real-world setting, which of the following evaluations do you feel are essential tests that need to be performed prior to T-DXd initiation and during T-DXd treatment.

Results of polling from steering committee members



Others: SaO2; baseline CT thorax; CBC with differential blood count including eosinophil; bronchoscopy and BAL with or without transbronchial lung biopsy

6. Are there any additional suggestions that can be considered for resource-limited settings (such settings can include places with workforce shortages or limited access to state-of-the-art facilities)?

Summary of steering committee member comments

- a. Regular chest X-rays (both lateral views)
- b. Oxygen saturation of arterial blood (SaO₂) and intermittent oxygen saturation by pulse oximetry (SpO₂; on rest and on exertion)
- c. Checklist for respiratory symptoms and frequent monitoring
- d. Low dose CT scan

7. Are there any other evaluations that can be considered for confirming ILD/pneumonitis?

Summary of steering committee member comments

- a. Exclude possibility of coronavirus disease 2019 (COVID-19) through tests
- b. Empiric antibiotic therapy and microbiological testing
- c. Chest X-rays, SaO₂ and symptoms
- d. Transbronchial lung biopsy

8. Are there any additional suggestions that can be considered for resource-limited settings (such settings can include places with workforce shortages or limited access to state-of-the-art facilities)?

Summary of steering committee member comments

- a. Home pulse oximeter to monitor oxygen saturation and pulse rate
- b. Systemic corticosteroids after antibiotic initiation
- c. Non-contrast CT thorax scans
- d. Chest X-rays and frequent out-patient follow-up

9. If the AE is suspected to be ILD/pneumonitis, treatment with drug should be interrupted pending further evaluations.

Ranked on a scale from 1–5, where 1 = ‘Strongly disagree’ and 5 = ‘Strongly agree’

Results of polling from steering committee members

4.7 out of 5.0

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

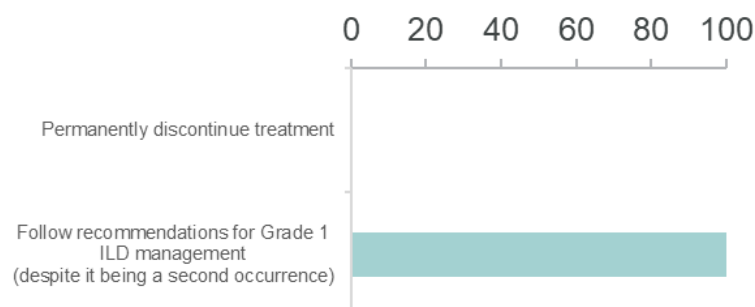
Ranked on a scale from 1–5, where 1 = ‘Strongly disagree’ and 5 = ‘Strongly agree’

Results of polling from steering committee members

4.6 out of 5.0

11. What would be your recommendation if a patient had resolved Grade 1 ILD and treatment was resumed (original or reduced dose), but Grade 1 ILD occurs once again (assuming that the patient has been responding well to treatment)?

Results of polling from steering committee members



Summary of steering committee member comments

- a. If patient is responding well and ILD is very mild, patient can be rechallenged with T-DXd provided that there are monitored very closely (as per tests recommended previously).
- b. If patient has failed other treatments, then T-DXd should be continued but with reduced dose (with the option of including low-dose systemic corticosteroids). Treatment intervals may be extended.
- c. If other treatments are available, then consider discontinuing T-DXd.

Gastrointestinal toxicities

1. American Society of Clinical Oncology (ASCO) 2020 Guideline Update for Antiemesis lists T-DXd as a moderate-emetic-risk (30–90%) intravenous antineoplastic agent in adults in the absence of effective antiemetic prophylaxis. National Comprehensive Cancer Network (NCCN) Guidelines for Antiemesis, lists T-DXd as a parenteral anticancer agent with moderate emetic risk and recommends several prophylactic antiemetic regimens to decrease potential vomiting.

Based on your real-world experience with T-DXd, do you agree with the emetic-risk classification by the NCCN and ASCO especially in Asian patients?

Ranked on a scale from 1–5, where 1 = ‘Strongly disagree’ and 5 = ‘Strongly agree’

Results of polling from steering committee members

4.0 out of 5.0

2. What are the recommendations in your practice regarding nausea and vomiting prophylaxis in patients treated with chemotherapies like T-DXd?

Summary of steering committee member comments

- a. Recommendations in real-world practice in the Asia-Pacific are generally similar to established guidelines.
 - b. Advisors noted that serotonin receptor antagonists (5-HT₃ RA) and dexamethasone were commonly used and adequate for prophylaxis.
 - c. However, dexamethasone for nausea / vomiting prophylaxis appeared to institution / region dependent. Few advisors endorsed the use of dexamethasone; few believed that its use is dependent on response to 5-HT RA.
 - d. Aprepitant and neurokinin-1 receptor antagonists (NK1 RA; netupitant and rolapitant) can be added at the discretion of the oncologist.
3. What are the recommendations in your practice regarding management of breakthrough nausea and vomiting prophylaxis in patients treated with chemotherapies like T-DXd? Do these recommendations differ with the guidelines from NCCN, ASCO, or European Society for Medical Oncology (ESMO)?

Summary of steering committee member comments

- a. As per guidelines, advisors suggested the addition of aprepitant to the current regimen of 5-HT₃ RA and dexamethasone.
 - b. Olanzapine can be included as per guidelines for its potential benefit in improving sleep.
4. The recommended dose modification strategies are appropriate for all patients and no amendments are necessary.

Ranked on a scale from 1–5, where 1 = ‘Strongly disagree’ and 5 = ‘Strongly agree’

Results of polling from steering committee members

3.8 out of 5.0

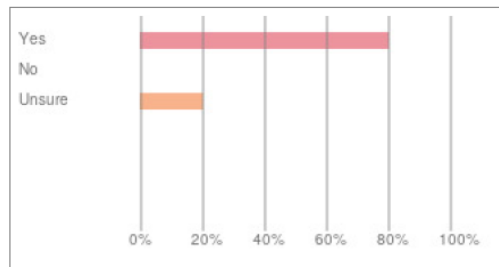
5. The recommended dose modification strategies are appropriate for all patients and no amendments are necessary.

Summary of steering committee member comments

- a. It was suggested that nausea / vomiting should be optimized before considering dose reduction.
- b. After dose modification, antiemetics could be deescalated (e.g., steroid with NK1 RA to 5-HT3 blockade only).
- c. Transdermal patches *pro re nata* can be considered like metoclopramide.

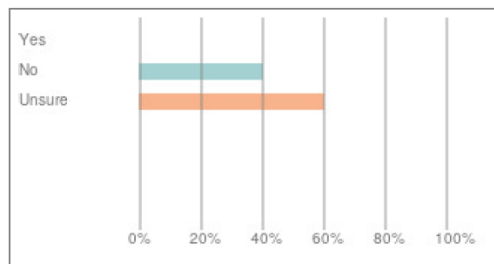
6. Should nausea and vomiting management recommendations be included in the manuscript?

Results of polling from steering committee members



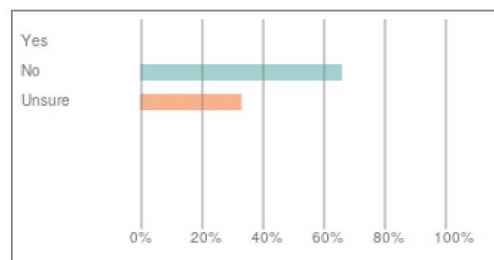
7. Should recommendations on monitoring and managing diarrhea be included in the manuscript?

Results of polling from steering committee members



8. Should recommendations on monitoring and managing constipation be included in the manuscript?

Results of polling from steering committee members



Hematological toxicities

1. What are the recommendations in your practice regarding the use of hematopoietic growth factors as prophylaxis for patients receiving chemotherapies like T-DXd? Are there any differences between guidelines and can you provide any justifications for their differences?

Are there any additional treatments or management recommendations that should be considered to manage neutropenia or decrease white blood cell counts in Asian patients?

Summary of steering committee member comments

- a. ASCO and ESMO guidelines were used to determine the initiation and choice of granulocyte colony-stimulating factor (G-CSF) prophylaxis, but advisors enquired if the risk of febrile neutropenia with T-DXd is 20% or higher.
 - b. Filgrastim or peg-filgrastim were commonly used, but the use of prophylactic antimicrobial differed between institutions / regions.
2. The recommended dose modification strategies are appropriate for all patients and no amendments are necessary (neutropenia).
Ranked on a scale from 1–5, where 1 = ‘Strongly disagree’ and 5 = ‘Strongly agree’

Results of polling from steering committee members

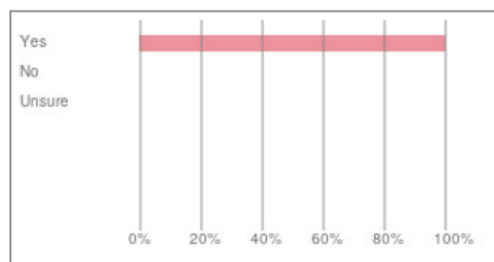
4.2 out of 5.0

3. Are there any additional treatments or management recommendations that should be considered to manage neutropenia in Asian patients?

Summary of steering committee member comments

- a. After grade 3 neutropenia, some may consider prophylactic G-CSF to avoid dose reduction or cycle delays.
 - b. Guidance of recurrent grade 3 neutropenia (without febrile neutropenia) is required.
4. Should neutropenia management recommendations be included in the manuscript?

Results of polling from steering committee members



5. What are the recommendations in your practice regarding the management of decreased platelet count in patients treated with chemotherapies like T-DXd? Do these recommendations differ with the guidelines from NCCN, ASCO, or ESMO?

Are there any additional treatments or management recommendations that should be considered to manage neutropenia or decrease white blood cell counts in Asian patients?

Summary of steering committee member comments

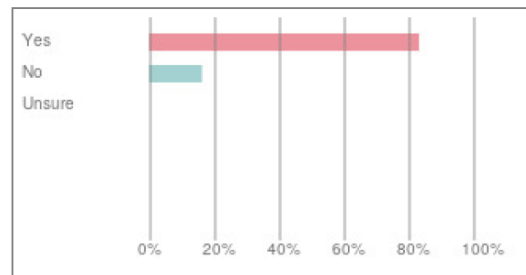
- a. ASCO, NCCN and ESMO guidelines were used to determine the initiation and choice of treatment for thrombocytopenia.
- b. Threshold for transfusion might be higher in certain institutions / regions (20×10^9).
- c. Recommendation on T-DXd dose for patients who have experienced thrombocytopenia with trastuzumab emtansine (T-DM1) was required.

6. The recommended dose modification strategies are appropriate for all patients and no amendments are necessary (thrombocytopenia).
Ranked on a scale from 1–5, where 1 = ‘Strongly disagree’ and 5 = ‘Strongly agree’

Results of polling from steering committee members
4.7 out of 5.0

7. Should thrombocytopenia management recommendations be included in the manuscript?

Results of polling from steering committee members



8. Are management recommendations for anemia well established at your institution and in your practicing country?
Ranked on a scale from 1–5, where 1 = ‘Strongly disagree’ and 5 = ‘Strongly agree’

Results of polling from steering committee members
3.4 out of 5.0

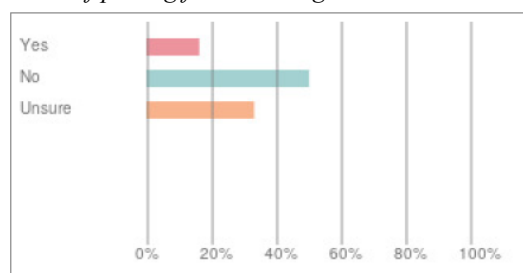
9. If selected 3 or below, what recommendations you would make to improve anemia management in Asian patients receiving T-DXd?

Summary of steering committee member comments

- a. Routine examination of iron, folate and vitamin B12 were recommended as they can be corrected by intravenous supplements.
- b. Outlining dose modification guidelines for anemia with T-DXd might be important as some institutions might not have established guidelines for anemia.

10. Should anemia management recommendations be included in the manuscript?

Results of polling from steering committee members



Fatigue

1. Numerical rating scale (1–10) have been suggested by ASCO and ESMO to help with screening for fatigue. What are the recommendations in your practice regarding the screening of fatigue during treatment with chemotherapies like T-DXd (such as screening tools, frequency of consultation, etc.)?

Summary of steering committee member comments

- a. Assess activity level before and after treatment with questions to the patient.
 - b. Check Karnofsky Performance Scale (KPS) / Eastern Cooperative Oncology Group performance status (ECOG PS) after each visit. Consider the use of Common Terminology Criteria for Adverse Events (CTCAE) to determine if fatigue affects activities of daily living (ADL) and time spent in bed.
 - c. However, in some institutions / regions, tools for monitoring fatigue are not readily employed.
2. Is patient counselling routinely employed at your practice for the management of fatigue, and are there any challenges associated with its implementation in a real-world setting?

Summary of steering committee member comments

- a. Lack of resources and / or time to provide patient counselling, especially in busy cancer centers.
 - b. Priorities may steer oncologists to manage more objective measures of toxicities, like neutropenia, thrombocytopenia, and pneumonitis.
3. Is patient counselling routinely employed at your practice for the management of fatigue, and are there any challenges associated with its implementation in a real-world setting? Are non-treatment options routinely employed at your practice for the management of fatigue, and are there any challenges associated with its implementation in a real-world setting?

Summary of steering committee member comments

- a. Engagement of family, establishing patient support groups, Tai Chi and Xi Gong and medication were additional suggestions to help with fatigue management. Digital apps were cited as another strategy.
 - b. Non-treatment options like physical activity and psychosocial interventions are considered and might be offered to patients but usually in an unstructured / case-by-case manner.
4. What are the recommendations in your practice regarding treatment of fatigue in patients treated with chemotherapies like T-DXd? Do these recommendations differ with the guidelines from NCCN or ESMO?

Summary of steering committee member comments

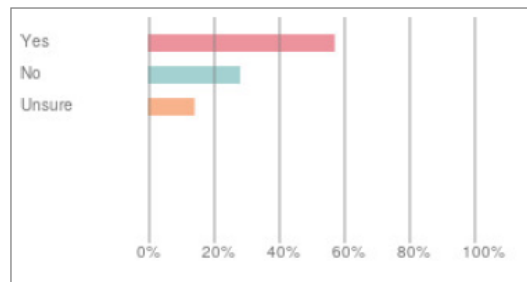
- a. Options for the treatment of pain, emotional distress and anemia were generally well established and considered.
 - b. Psychostimulants and corticosteroids were rarely used.
5. The recommended dose modification strategies are appropriate for all patients and no amendments are necessary.
Ranked on a scale from 1–5, where 1 = ‘Strongly disagree’ and 5 = ‘Strongly agree’

Results of polling from steering committee members

4.3 out of 5.0

11. Should fatigue management recommendations be included in the manuscript?

Results of polling from steering committee members



Alopecia

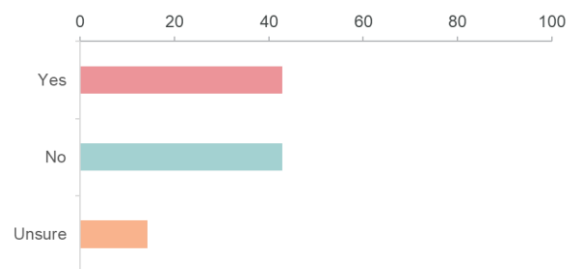
1. Is patient counselling routinely employed at your practice for the management of alopecia, and are there any challenges associated with its implementation in a real-world setting? Are non-treatment / treatment options routinely employed at your practice for the management of alopecia, and are there any challenges associated with its implementation in a real-world setting?

Summary of steering committee member comments

- a. Patients are aware and appear to be routinely counselled on alopecia. Advice on where to get good quality wigs, styling tips and scarves might be welcomed by patients. Some hospitals in South Korea offer beauty shops.
- b. Scalp cooling techniques are available, but there are some resource limitations and might not be as effective and / or could cause discomfort.
- c. Treatment options like minoxidil are not generally used for chemotherapy-induced alopecia.
- d. More active interventional strategies for patients on longer cycles of T-DXd was suggested. A dermatologist referral was also suggested.

2. Should alopecia management recommendations be included in the manuscript?

Results of polling from steering committee members



Cardiac toxicities

1. What are the recommendations in your practice regarding the monitoring of cardiac toxicities (through cardiac imaging or other methods) while on chemotherapies like T-DXd? Do these recommendations differ with the guidelines from NCCN, ASCO, or ESMO?

Summary of steering committee member comments

- a. 3-monthly echocardiography or multigated acquisition (MUGA), similar to anti-HER2 therapies and as per guidelines.
 - b. In resource-limited settings, baseline echocardiogram (ECG), MUGA, or echocardiogram should be conducted and should be repeated if patient is symptomatic.
2. In the context of a real-world setting, are there any additional treatments or management recommendations that should be considered to manage left ventricle ejection fraction (LVEF) decrease in Asian patients treated with T-DXd?

Summary of steering committee member comments

- a. Referral to cardiac specialists if LVEF decrease is observed, and cardiac protective drug treatment such as beta-blocker and angiotensin-converting enzyme inhibitor (ACEi) might be initiated.

Infusion-related toxicities

1. The recommended management strategies for infusion-related reactions are appropriate for all patients and no amendments are necessary.

Ranked on a scale from 1–5, where 1 = ‘Strongly disagree’ and 5 = ‘Strongly agree’

Results of polling from steering committee members

4.7 out of 5.0

2. Should recommendations on monitoring and managing infusion-related adverse events be included in the manuscript? (Note, that recommendations were not included after further discussion among steering committee members)

Results of polling from steering committee members

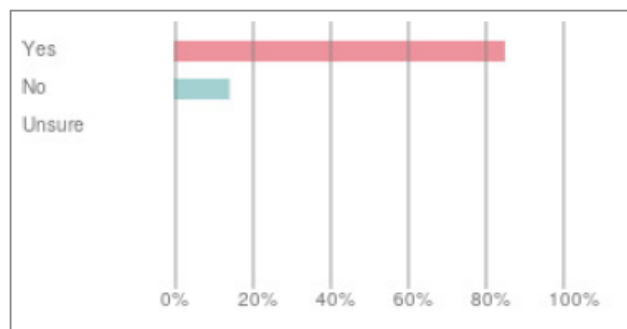


Table 1. Table summarizing the level of agreement to the recommendations on the monitoring and management of T-DXd-related adverse events during the review process

Adverse event	Recommendation	Members of the steering committee who agreed with the recommendation n/N (%) ^a			
		First round	Second round	Third round	Final round
ILD/ pneumonitis	Eligibility for treatment with T-DXd	11/13 (84.6)	12/13 (92.3)	13/13 (100)	13/13 (100)
	Patient education of signs and symptoms of ILD/pneumonitis	13/13 (100)	13/13 (100)	13/13 (100)	13/13 (100)
	CT scanning frequency for ILD/pneumonitis detection	10/13 (76.9)	11/13 (84.6)	13/13 (100)	13/13 (100)
	Chest X-rays for ILD/pneumonitis detection	9/13 (69.2)	13/13 (100)	13/13 (100)	13/13 (100)
	Pulse oximetry and exercise tolerance for ILD/pneumonitis detection	13/13 (100)	12/13 (92.3)	13/13 (100)	13/13 (100)
	Baseline pulmonary function tests for ILD/pneumonitis detection	11/13 (84.6)	13/13 (100)	13/13 (100)	13/13 (100)
	Importance of consultation with supporting specialists (multidisciplinary teams)	12/13 (92.3)	12/13 (92.3)	13/13 (100)	13/13 (100)
	Differential diagnosis from infective causes or other etiologies	10/13 (76.9)	12/13 (92.3)	13/13 (100)	13/13 (100)
	High-resolution CT for ILD/pneumonitis diagnosis	10/13 (76.9)	12/13 (92.3)	13/13 (100)	13/13 (100)
	Bronchoscopy and bronchoalveolar lavage for ILD/pneumonitis diagnosis	13/13 (100)	13/13 (100)	13/13 (100)	13/13 (100)
	Management of Grade 1 ILD/pneumonitis	11/13 (84.6)	13/13 (100)	13/13 (100)	13/13 (100)
	Management of repeated Grade 1 ILD/pneumonitis	11/13 (84.6)	13/13 (100)	13/13 (100)	13/13 (100)
Management of Grade ≥ 2 ILD/pneumonitis	11/13 (84.6)	13/13 (100)	13/13 (100)	13/13 (100)	
Nausea and vomiting ^b	Use of serotonin receptor antagonist and dexamethasone prophylaxis	9/10 (90.0)	10/10 (100)	10/10 (100)	10/10 (100)
	Management of severe or breakthrough cases	9/10 (90.0)	10/10 (100)	10/10 (100)	10/10 (100)
	Use of low-dose olanzapine for delayed nausea	9/10 (90.0)	9/10 (90.0)	10/10 (100)	10/10 (100)
	Limiting dexamethasone use ^c	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)
Neutropenia ^b	Use of primary G-CSF prophylaxis	10/10 (100)	9/10 (90.0)	10/10 (100)	10/10 (100)
	Use of secondary G-CSF prophylaxis for recurring Grade 3 neutropenia	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)
Anemia ^b	Screening for anemia	9/10 (90.0)	9/10 (90.0)	10/10 (100)	10/10 (100)
	Managing Grade ≥ 3 anemia	9/10 (90.0)	9/10 (90.0)	10/10 (100)	10/10 (100)
	Use of erythropoietin stimulating agents	9/10 (90.0)	10/10 (100)	10/10 (100)	10/10 (100)
Thrombocytopenia ^b	Managing Grade ≥ 3 thrombocytopenia	10/10 (100)	9/10 (90.0)	10/10 (100)	10/10 (100)
Fatigue ^b	Patient counselling and support groups and caregiver empowerment	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)
Alopecia ^b	Patient awareness of risk of alopecia	8/10 (80.0)	10/10 (100)	10/10 (100)	10/10 (100)
	Styling techniques and high-quality wigs	9/10 (90.0)	10/10 (100)	10/10 (100)	10/10 (100)
	Use of scalp cooling	9/10 (90.0)	10/10 (100)	10/10 (100)	10/10 (100)
	Cultural considerations on the use of scalp cooling	9/10 (90.0)	10/10 (100)	10/10 (100)	10/10 (100)
Cardiac	Monitoring of cardiac function ^{d,e}	9/11 (81.8)	10/11 (90.9)	11/11 (100)	11/11 (100)
	Recommendation on baseline scans in resource-limited settings ^d	11/11 (100)	11/11 (100)	11/11 (100)	11/11 (100)
	Referral to cardiac specialists ^b	10/10 (100)	10/10 (100)	10/10 (100)	10/10 (100)

^a Disagreement to the recommendations on monitoring or managing T-DXd-related adverse events was determined if members of the steering committee made amends to the recommendations.

^b Level of agreement to recommendations were limited to oncologists in the steering committee (10 out of 13 members) given their expertise in managing such adverse events.

^c Recommendation on the use of dexamethasone was amended after external reviewer suggestion.

^d Level of agreement to recommendations were limited to oncologists and a radiologist in the steering committee (11 out of 13 members) given their expertise in managing such adverse events.

^e Recommendation on monitoring of cardiac function was amended after external reviewer suggestion.

CT computed tomography, G-CSF granulocyte colony-stimulating factor, ILD interstitial lung, T-DXd trastuzumab deruxtecan