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WHITE PAPER

Management of trastuzumab deruxtecan-related adverse events in breast cancer: Italian expert panel recommendations

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ABSTRACT

Trastuzumab deruxtecan (T-DXd) – antibody – drug conjugate targeting the human epidermal growth factor receptor 2 (HER2) – has demonstrated high efficacy in clinical studies, with high rates of durable responses and improved outcomes in HER2-positive and HER2-low metastatic breast cancer (mBC) patients. T-DXd has demonstrated a generally manageable safety profile across the DESTINY trials, but there is an emerging unmet need for additional real-world clinical practice information. Italian experts conducted a Delphi panel and several roundtables to develop recommendations for the prevention and practical management of T-DXd-related AEs and toxicities, including nausea and vomiting (N/V), neutropenia, anemia, cardiovascular events, interstitial lung disease/pneumonitis (ILD/P), and treatment safety. ILD/P and N/V are the most challenging AEs associated with T-DXd. Being T-DXd now classified as a Highly Emetogenic Chemotherapy, Italian experts recommend pre-treatment with the triplet (NK1 RA + 5-HT3 RA + dexamethasone) in all patients to prevent acute N/V. Patients must be monitored early on treatment for signs/symptoms of ILD/P and any clinical suspicion should be promptly investigated and managed according to guidelines. These recommendations and proactive surveillance may substantially improve the management of T-DXd-related AEs, maximizing the benefit of this treatment for HER2-positive and HER2-low mBC, and potentially increasing treatment acceptance.

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1. Introduction

Trastuzumab deruxtecan (T-DXd), an antibody – drug conjugate targeting the human epidermal growth factor receptor 2 (HER2) [1], is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer (mBC) who have received one or more prior anti-HER2-based regimens or have developed disease recurrence within 6 months of completing adjuvant chemotherapy, or with HER2-low breast cancer that is unresectable or metastatic who have received prior chemotherapy in the metastatic setting, or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. This drug has proven to be highly efficacious in clinical studies, demonstrating high rates of durable responses and improving the outcomes of these patients [2–7].

Across the DESTINY clinical trials, T-DXd has demonstrated a generally manageable safety profile [8], and the Prescribing Information provides guidance on monitoring/managing T-DXd – related adverse events (AEs) [9] including: nausea and vomiting (N/V) [2,8,10–13], hematological toxicities (neutropenia/anemia), alopecia [2,10], cardiovascular events and especially interstitial lung disease (ILD)/pneumonitis(P), which is the most serious complication of this drug with a fatality rate of approximately 0.5% in recent phase 3 trials [8,14]. However, these recommendations are based on clinical trial evidence, and there is an emerging unmet need for additional information from real-world clinical practice with T-DXd. The recommended or mandatory management strategies for T-DXd within the DESTINY trials have evolved over time, reflecting both the initial uncertainty regarding optimal care and the natural learning curve associated with the clinical introduction of any new compound. The widespread real-world use of T-DXd has further enhanced our understanding of how best to manage this therapy. Building on this extensive experience, the present study aims to bridge the gap between clinical trial – based recommendations and real-world best practices.

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Article highlights

- Trastuzumab deruxtecan (T-DXd) has demonstrated a generally manageable safety profile across the DESTINY trials, but there is an emerging unmet need for additional real-world clinical practice information.
- In light of the 2023 NCCN, MASCC and ESMO guideline updates, which classify T-DXd as a Highly Emetogenic Chemotherapy or place T-DXd on the higher end of the moderate emetic risk category, changing the recommendation to endorse a three-drug antiemetic regimen that includes an NK1 RA for all patients, Italian experts mostly agree on the appropriateness of the recommendation of pre-treatment with the triplet (NK1 RA + 5-HT3 RA + dexamethasone) in all patients.
- The combination of olanzapine with acute and/or delayed phase regimens is not recommended by the Italian Expert Panel.
- Italian oncologists recommend particular attention and close monitoring of nutritional status in elderly patients, who are more severely impacted by chemotherapy-induced nausea and vomiting (N/V),
- Primary prophylaxis with white blood cell growth factors is recommended in patients who are particularly frail or who have major comorbidities
- T-DXd administration does not require primary prophylaxis with erythropoietin or its derivatives in patients without relevant comorbidities.
- Italian experts recommend monitoring the left ventricular fraction before starting therapy and at regular intervals thereafter, and not precluding the use of T-DXd therapy in elderly patients with non-severe cardiologic comorbidities
- Patients must be monitored early on treatment for signs and symptoms of Interstitial Lung Disease/Pneumonitis (ILD/P) and any clinical suspicion should be promptly investigated and managed according to current guidelines
- Future objectives should be to create dedicated pathways for these patients, featuring consultations with other specialists (such as pneumologist) and respiratory function tests, to design a specific surveillance plan, and to define all ILD/P risk factors should be defined, in order to develop more appropriate recommendations.
- The recommendations resulting from the Delphi Scientific Board survey, the clinical appropriateness criteria assessed by the expert panels, and proactive surveillance, may substantially improve the management of T-DXd-related adverse events (AEs), maximizing the benefit of this treatment for HER2-positive and HER2-low mBC, and potentially increasing treatment acceptance.

With T-DXd transitioning from clinical trials to real-world practice, Italian experts conducted a Delphi panel to develop recommendations for preventing AEs and managing T-DXd treatment-related toxicities. They presented their considerations on the necessary assessments regarding the benefit/risk ratio, the clinical appropriateness, and the specific attention to unfit patients.

2. Materials and methods

2.1. Delphi methodology

The Delphi method is used to achieve consensus and identify areas of non-consensus among experts on a particular topic [15]. Experts provide their opinions on statements in a first round and subsequently indicate their agreement/disagreement with cumulative data in subsequent rounds.

This technique requires survey participants to individually and anonymously express their assessments, then collected and compiled by a methodologist. This process helps achieve a stronger collective opinion than what might be developed in meetings, avoiding biases, psychological pressure, or external influences.

A Delphi Survey was used to gather expert opinions and achieve consensus on Italian clinical recommendations for the prevention and practical management of T-DXd-related AEs and toxicities.

2.2. Scientific Board of experts and Delphi survey

The Scientific Board participating in the survey was composed of 10 Italian leading experts in the field.

The Board members received an invitation to participate with a link to round 1 of the survey. Here, they were asked to express, based on their clinical experience and the latest literature, their level of agreement on 37 statements regarding therapeutic management of T-DXd-treated HER2-positive mBC patients. Two Delphi rounds were planned.

The statements were grouped into 7 survey areas: N/V, neutropenia, anemia, alopecia, cardiovascular events, ILD/P, and treatment safety in general. The individual rating of agreement, on each of the proposed statements, by every member of the board, was expressed on a 1–9 (maximum disagreement-agreement) Likert scale. Board members could also raise any relevant issues that were not addressed, suggest additions, or provide considerations they deemed useful for a comprehensive opinion. This laid the foundation for round 2, in which Board members re-voted for statements that had led to disagreement.

The process was conducted using a web platform.

2.3. Consensus process

The criteria for agreement/disagreement between experts were defined as follows: 1) agreement: 85% of panelists' ratings fall within one of the 3-point regions (1–3; 4–6; 7–9); 2) disagreement: 90% of panelists' ratings fall within one of two broader regions (1–6 or 4–9) [15].

Based on the aggregation levels from the Delphi survey, this first phase allowed the identification of expert opinions, unveiling agreement or disagreement within the board. The results were further discussed in a final plenary session.

2.4. Roundtables and appropriateness assessments by the voting panel

The second phase consisted of a series of roundtables in various regions of Italy, each involving different panels of Italian specialists with extensive experience in managing and treating mBC patients, also with T-DXd.

Overall, 39 panelists were identified by the Scientific Board members as suitable to contribute to and benefit from the discussion. These panelists were geographically distributed into 5 roundtables (each including 5–9 participants), which took place between October and December 2023 in various cities across Italy, to ensure a representative sample of the diverse experiences of oncologists and of the different realities in cancer centers. To guarantee efficient and focused discussion on relevant issues during each roundtable: 1) the results of the Delphi survey for each area were presented to the expert panel attending the roundtables by 2 Scientific Board members, providing an overview of all the statements,

including those with dispersed opinions; 2) the presenters actively stimulated and moderated panel discussions, primarily focusing on statements that had reached agreement or disagreement; 3) the panelists were then asked to vote on the clinical appropriateness or non-appropriateness of these statements, based on the clinical practice in their centers.

Items that had led to dispersed opinions, where agreement was unlikely to ever be achieved, were excluded from the voting panel's appropriateness assessment.

Appropriateness, in accordance with the RAND/UCLA method [16], was determined based on the relative risk-benefit ratio of the procedures, which were assessed as *appropriate* when the expected benefits outweighed the risks to the extent that they were considered worth performing.

This phase did not require a consensus to be reached; inevitable differences of opinion reflected the uncertainty concerning AEs prevention and practical management of T-DXd-related toxicities.

Comments, experiences or difficulties raised by the participants during the collegial discussions were noted by a medical writer attending all 5 roundtables.

3. Results

The Scientific Board reached consensus agreement on 24 of 37 statements in the Delphi survey, whereas 3 aroused disagreements among the experts (Table 1): 2 in the N/V area, and 1 regarding secondary prophylaxis with white blood cell (WBC) growth factors in case of febrile neutropenia in patients with comorbidities.

Ten statements led to dispersed opinions, and, as per the Delphi method, were not evaluable in the subsequent appropriateness assessment phase.

Of the 27 statements under consideration in the voting panel's clinical appropriateness assessments, 26 recommendations were mostly considered appropriate (with a 95% mean rate of appropriateness evaluations from the panelists, range 59–100). Specifically, 23 received an appropriateness assessment from > 90% of the voting experts. All the statements which received appropriateness assessments from < 90% of the panel belonged to the N/V area.

Notably, the only recommendation that received a substantial assessment of non-appropriateness, regarding the involvement of olanzapine in combination with acute and/or delayed phase regimens, had also raised disagreement within the Scientific Board.

4. Discussion

4.1. Nausea and vomiting

In light of the 2023 MASCC and ESMO guideline update [17], which places T-DXd on the higher end of the moderate emetic risk category, and the latest version of The NCCN guidelines [18], which classify T-DXd as a Highly Emetogenic Chemotherapy (HEC) and now recommend to endorse a three-drug antiemetic regimen that includes an NK1 RA for all patients [18], the Italian panelists mostly agreed on the appropriateness of the recommendation of pre-treatment with the triplet in all patients. This indicates the importance of optimal prevention of acute N/V, starting from the first cycle of T-DXd, to avoid the onset of a first episode and ensure maximum patient benefit, quality of life, and treatment compliance [19]. Notably, the Delphi survey had shown disagreement of opinions on this statement. However, this result, which seems inconsistent with the appropriateness assessment expressed by almost all the voting oncologists, is likely due to the official endorsement of new classification of T-DXd as HEC occurring while the project was in progress: after the survey, but concurrently with the first roundtables, in which the new recommendation was strongly considered appropriate.

Optimal N/V prophylaxis will improve the control of both acute and delayed N/V. After the antiemetic prophylaxis administered on day 1 before T-DXd administration, the optimal control of delayed N/V (on days 2–3) is achieved by using the combination of dexamethasone ± metoclopramide or continuing 5-HT3 RA or NK1 RA as indicated. Some types of 5-HT3 RA (e.g., palonosetron) and NK1 RA (e.g., netupitant) do not require the administration of these compounds on days 2–3.

Due to limited experience and a perception of limited tolerability to olanzapine [20], the majority of the Italian experts deemed the statement regarding olanzapine as not recommended, similarly to ESMO guidelines. This is in sharp contrast with NCCN guidelines which do recommend olanzapine for N/V management, not only for T-DXd but for most of the highly emetogenic drugs. As recently indicated [21,22], some experts in the panel believe that a lower dose of olanzapine – 5 mg, or only 2.5 mg – might be worthy to be considered for some patients.

Additionally, the oncologists unanimously recommend particular attention and close monitoring of nutritional status in elderly patients. These patients are more severely impacted by chemotherapy-induced N/V, despite its higher incidence in younger patients. Moreover, several experts highlighted the need to focus on potential drug interactions between the nausea control treatment and other concurrent therapies, which are particularly frequent in the elderly.

4.2. Neutropenia

The panelists agreed on the clinical appropriateness of the statements regarding the management of febrile neutropenia [2,10,23]. Firstly, primary prophylaxis with WBC growth factors is not required with the administration of T-DXd in patients without major comorbidities. Instead, it is recommended in patients who are particularly frail or who have major comorbidities. In the case of febrile neutropenia during the previous administration of T-DXd, dose reduction at the following drug administration is recommended for all patients. Moreover, if febrile neutropenia persists despite the previous dose reduction, secondary prophylaxis with WBC growth factors is recommended at the following administration of the drug in all patients, with or without comorbidities.

4.3. Anemia

Considering the < 10% risk of severe anemia during T-DXd, the experts agreed that T-DXd administration does not require primary prophylaxis with erythropoietin or its derivatives in patients without relevant comorbidities. Additionally, in the

Table 1. Areas, statements, respective agreement/disagreement conditions of the Scientific Board's opinions (including dispersed opinions), and overall appropriateness assessments (%) by the voting panelists.

Area	N[1]	Statement	Scientific board's expert opinion	Panelists' appropriateness assessment of (%)[2]
Nausea and Vomiting	1	Trastuzumab Deruxtecan (T-DXd) is considered a Highly Emetogenic Chemotherapy	Agreement	100.0%
	2	For the prevention of acute nausea and vomiting (N/V) at the 1st cycle of T-DXd, pretreatment with a 5-HT3 RA combined with dexamethasone is recommended in non-frail patients without risk factors for emesis and/or not particularly frail	Dispersed Opinions	n.e.[3]
	3	For the prevention of acute N/V at the 1st cycle of T-DXd, pretreatment with a 5-HT3 RA combined with dexamethasone is recommended in all patients	Dispersed Opinions	n.e.
	4	For the prevention of acute N/V at the 1st cycle of T-DXd, pretreatment with a combination of an NK1 RA with a 5-HT3 RA + dexamethasone is recommended in selected patients, at increased risk of emesis or particularly frail	Dispersed Opinions	n.e.
	5	For the prevention of acute N/V at the 1st cycle of T-DXd, pretreatment with a combination of an NK1 RA with a 5-HT3 RA + dexamethasone is recommended in all patients	Disagreement	92.3%
	6	If one decides to start pretreatment with a 5-HT3 RA combined with dexamethasone, in case of suboptimal N/V control, it is essential to instantly proceed with the combination of an NK1 RA with a 5-HT3 RA + dexamethasone from the 2nd cycle of T-DXd	Agreement	79.5%
	7	Once the treatment of the acute phase has been stabilized, in case of persistence of N/V in days 3 and over, the use of metoclopramide ± dexamethasone may be indicated	Agreement	100.0%
	8	For prevention of delayed N/V in days 2–3 after T-DXd administration, pretreatment with the combination of dexamethasone ± metoclopramide or a 5-HT3 RA is recommended	Agreement	59.0%
	9	If the above treatment fails, the combination of an NK1 RA with a 5-HT3 RA ± dexamethasone or dexamethasone ± metoclopramide is recommended for the prevention of delayed N/V in days 2–3 after T-DXd administration	Agreement	79.5%
	10	Olanzapine may be combined with acute and/or delayed phase regimens, if considered appropriate	Disagreement	41.0%
	11	According to literature findings, the incidence of chemotherapy-induced N/V is lower in elderly patients than in young patients, but its impact is greater and requires close monitoring of nutritional status	Agreement	100.0%
Neutropenia	*12*	According to literature findings, the risk of febrile neutropenia with T-DXd is less than 10%. Therefore, in patients without major comorbidities, administration of T-DXd does not require primary prophylaxis with white blood cell growth factors.	Agreement	97.4%
	13	In case of febrile neutropenia during the previous administration of T-DXd, dose reduction at the following drug administration is recommended	Agreement	94.9%
	14	In case of febrile neutropenia during previous administration of T-DXd, dose reduction and secondary prophylaxis with white blood cell growth factors are recommended, in patients with or without comorbidities, at the following administration of the drug	Disagreement	100%
	15	In case of febrile neutropenia, despite previous dose reduction of T-DXd, secondary prophylaxis with white blood cell growth factors is recommended in all patients, at the following drug administration	Agreement	100.0%
Anemia	*16*	According to literature findings, the risk of severe anemia (G3/G4) during T-DXd is less than 10%. Therefore, T-DXd administration does not require primary prophylaxis with erythropoietin or its derivatives in patients without relevant comorbidities	Agreement	100.0%
	17	In case of previous T-DXd-induced severe anemia, T-DXd dose reduction is recommended at the following drug administration	Agreement	100.0%
	18	In case of prior severe anemia during the previous T-DXd administration, dose reduction and, in patients with cardiovascular comorbidities, addition of secondary prophylaxis with erythropoietin or its derivatives to the following cycle are recommended	Dispersed Opinions	n.e.
	19	In case of previous severe anemia, despite previous dose reduction of T-DXd, addition of secondary prophylaxis with erythropoietin or its derivatives to the following cycle is recommended in all patients	Dispersed Opinions	n.e.
Alopecia	*20*	According to literature findings, alopecia can occur in about 1/3 of patients treated with T-DXd. Therefore, after appropriate patient information and consent, the scalp cooling technique may be used in order to reduce the risk of developing alopecia	Dispersed Opinions	n.e.
	21	Considering the long median duration of T-DXd treatment, scalp cooling is not deemed to be an effective tool to prevent the onset of alopecia, but it might be useful to encourage patients to consent to this treatment, given adequate information about it	Dispersed Opinions	n.e.
Cardiovascular Events	*22*	According to literature findings, the risk of left ventricular fraction reduction during T-DXd treatment is less than 3% and, in most but not all cases, is mild and asymptomatic. Therefore, monitoring of the left ventricular fraction is still recommended before starting therapy, and at regular intervals thereafter	Agreement	100.0%
	23	In the absence of cardiologic comorbidities which advise against the use of anti-HER2 drug treatment, the presence of non-severe cardiologic comorbidities should not preclude the use of T-DXd therapy in elderly patients	Agreement	100.0%

(*Continued*)

Table 1. (Continued).

Area	N[1]	Statement	Scientific board's expert opinion	Panelists' appropriateness assessment of (%)[2]
Interstitial Lung Disease/Pneumonitis	*24*	For ILD/P surveillance, it is essential to perform a high-resolution chest computed tomography (CT) scan at baseline and every 6–9 weeks thereafter, according to the risk of developing ILD/P	Dispersed Opinions	n.e.
	25	For ILD/P monitoring, it is appropriate to use the contrast-enhanced chest CT also used for the monitoring of the disease, at the timelines scheduled for follow-up	Dispersed Opinions	n.e.
	26	In case of clinical suspicion of ILD during T-DXd, the treatment should be discontinued, and a high-resolution chest computed tomography (CT) scan without contrast should be performed to confirm or rule out the diagnosis	Agreement	100.0%
	27	In case of confirmation of ILD, this toxicity should be managed in a multidisciplinary setting	Agreement	100.0%
	28	In case of Grade 1 ILD (only radiological evidence, without symptomatology), T-DXd treatment can be reinitiated if the ILD/P resolves to Grade 0	Agreement	100.0%
	29	If Grade 1 ILD/P resolves to Grade 0 within 28 days from its onset, T-DXd may be resumed at the previous dose.	Agreement	92.3%
	30	If Grade 1 ILD/P resolves to Grade 0 after 28 days after its onset, T-DXd dose must be reduced by 1 level	Agreement	92.3%
	31	In case of Grade 2 ILD (radiological evidence and symptomatology), it is generally recommended to discontinue T-DXd treatment permanently and to approach specific treatment immediately	Agreement	100.0%
	32	In case of Grade 3 or 4 ILD, T-DXd treatment must be permanently discontinued, and the patient must be hospitalized	Agreement	94.9%
Treatment Safety	*33*	The activity of anti-HER2 therapy in HER2+ breast cancer is age-independent	Agreement	100.0%
	34	In case of adverse events (AE), except for ILD, the decision on continuation of T-DXd treatment depends on the grade of toxicity/AE that has occurred	Agreement	100.0%
	35	In case of low/moderate grade toxicities (G1-G2), except for ILD, and in the presence of activity, treatment with T-DXd shall be continued	Agreement	100.0%
	36	In case of low/moderate grade toxicity (G1-G2), except for the onset of ILD, and in the presence of activity, the patient's preference must be considered for T-DXd treatment continuation.	Dispersed Opinions	n.e.
	37	Considering the long median duration of T-DXd treatment, to encourage acceptance of this treatment and the potential occurrence of low/moderate grade toxicities (G1-G2), it is useful to provide the patient with adequate information regarding the risk/benefit ratio with this therapy	Agreement	100.0%

[a]Statement number.
[b]Percentage of assessments of appropriateness on a total of 39 votes by each of the panelists who attended the roundtables.
[c]Statements that led to dispersed opinions were not evaluable (n.e.) for the clinical appropriateness assessment.

case of previous T-DXd-induced severe anemia, a one-level dose reduction is recommended at the following administration [24]. Notably, over 60% of the Scientific Board members agreed with the statement that recommended dose reduction in case of prior severe anemia during the previous T-DXd administration and, for patients with cardiovascular comorbidities, the addition of secondary prophylaxis with erythropoietin or its derivatives at the following cycle. However, since the 85% agreement threshold was not reached, the recommendation was excluded from the appropriateness assessment.

4.4. Alopecia

The statements regarding alopecia and scalp cooling were not evaluable for the appropriateness assessment, due the dispersed opinions of the scientific board. However, taking into account factors such as insufficient supporting evidence from literature, the different pharmacokinetics of T-DXd with respect to standard chemotherapy or the scarcity of machines, a general consensus of the non-feasibility of the scalp cooling technique emerged from the discussions amongst the Italian panelists during the roundtables.

4.5. Cardiovascular events

The statements concerning cardiovascular events, which recommend monitoring the left ventricular fraction before starting therapy and at regular intervals thereafter, and not precluding the use of T-DXd therapy in elderly patients with non-severe cardiologic comorbidities, received complete consensus from the Scientific Board and unanimous appropriateness assessment from the voting panel. Moreover, consultation with a cardiologist is advised when necessary.

4.6. Interstitial lung disease/pneumonitis

With an incidence of any-grade(G) Interstitial Lung Disease/Pneumonitis (ILD/P) of 13.6–15%, ILD/P has turned out to be the most relevant AE reported with T-DXd and the most frequent reason of treatment discontinuation not related to progression [9,10,25,26]. Patients must be monitored early on treatment for signs and symptoms of ILD/P and any clinical suspicion should be promptly investigated and managed according to current guidelines [22,27]. Indeed, proactive surveillance and management of ILD/P may help not only to reduce the risk of severe ILD/P associated with T-DXd, but also to reduce the risk of treatment discontinuation (indicated for all G ≥ 2 ILD/P). Nevertheless, the Board members reported dispersed opinions on the two statements regarding ILD/P surveillance (recommendation to perform a high-resolution chest CT scan at baseline and every 6–9 weeks thereafter, according to the risk of developing ILD/P) and monitoring (recommendation to use the contrast-enhanced chest CT also used for disease monitoring at the timelines scheduled for follow-up).

One statement with dispersed opinions asserted that it is essential to perform a high-resolution chest CT scan at baseline and every 6–9 weeks thereafter, according to the risk of developing ILD/P. However, in some hospital settings, which lack resources, it is difficult for such a surveillance to be realistically carried out. When the patient is sent to another center for a CT scan, it is crucial that the radiologist is aware that the patient is in T-DXd treatment to obtain an adequate report.

In addition, some of the expert oncologists believe that if it is not feasible to run more frequent CT scans: a reevaluation every 12 weeks may be sufficient. However, other experts believe that contingency and limitation of the resources could not justify using a suboptimal monitoring of ILD/P, in particular during the first 12-month period. ILD/P is not homogenous over time. The highest incidence and severity of ILD/P are observed during the first 12 months (90–95% of cases), after which they are less frequent and rarely fatal [28]. The interval between evaluations may therefore be increased after the first year of treatment. The following strategies, based on real-world experience, were suggested and endorsed at the ESMO symposium: baseline pulmonary function assessment, chest CT scans (without indication of high resolution), physical examination of respiratory function, routine scans every 8–12-weeks, and identification of risk factors and comorbidities [29–31].

There is a strong agreement among the experts and a very high grade of appropriateness on the current guidelines of management of T-DXd including the criteria of dose interruption and reduction. However, during the informal discussion of the roundtables, some experts highlighted the gap of knowledge on the real risk of continuing T-DXd after recovering from a G ≥ 2 toxicity or in cases with G1 toxicity who does not recover to G0. Indeed, despite the safety of the patients is a critical issue, the impressive efficacy of this drug poses a reasonable concern on the risk of interruption in term of impact on the oncological outcome due to disease progression. Overall, many oncologists believe that this is an area which warrants further investigation. A minority of the oncologist believe that despite the lack of evidence, it is already possible in particular cases that may represent exceptions, to continue T-DXd although not indicated. However, it is very important in this rare and selected cases to share with the patient potential risk which are largely unknown related to this decision, to be balanced with the expected benefit by continuing the treatment.

Another issue pointed out in various roundtables is often the radiologists' lack of adequate experience with ILD/P detection. Few radiologists are familiar with ILD/P and these drugs, and have the proper sensitivity to these scenarios [32]. Therefore, it would be important for radiologists to be properly trained and acquire the ability to recognize G1 toxicities, which are not yet symptomatic. Prompt reports may prevent a worsening to G ≥ 2, preventing the permanent suspension of T-DXd treatment.

It is agreed that it would be ideal to create dedicated pathways for these patients, featuring consultations with a pneumologist and respiratory function tests. Once the picture becomes clearer, a specific surveillance plan should be designed, and all risk factors should be defined, to develop more appropriate recommendations.

Regarding the possible risk factors for developing ILD/P, literature so far reports an increased risk: during the first year of treatment, in patients who have had previous lung diseases (e.g., pulmonary fibrosis or COPD), who are unfit due to comorbidities, in those with renal impairment (even moderate) and increased creatinine, with a baseline oxygen saturation value < 95%, who have mostly received previous chemotherapy, in those receiving higher doses, and in Asian populations [29,30]. Also, central nervous system disease may be an independent risk factor, possibly due to concomitant steroid use, as per the higher rates of ILD/P reported in DESTINY-Breast01 and 02 trials. However, further research, including data from real-world settings, is still necessary to clearly delineate the mechanisms of action that play a role in therapy-related ILD/P [33,34].

Moreover, patient education concerning T-DXd – related side effects' signs and symptoms is important for maximizing treatment benefits, as it is crucial that the patient promptly reports symptoms to the treating physician for optimal management of these AEs. Many experts report that patients, receiving therapy at one center, then access other centers' Emergency Rooms, where the medical staff does not know about the therapy the patient has been receiving or the potential serious side effects, resulting in a waste of valuable time. Therefore, there is a need to educate the patients and possibly provide an informational document to share with healthcare staff at centers other than those where T-DXd is being administered. Medical alert bracelets may be a valuable strategy to alert physicians and community medics of the risk of T-DXd-related ILD/P. Also, educational materials and events for front-line medics and radiologists should be taken into consideration so that they may be aware of the rapidity with which T-DXd-related ILD/P can worsen from G3 to G5 without prompt and aggressive treatment, and of the importance of reporting even subtle interstitial changes as possible G1 ILD/P during T-DXd treatment.

4.7. Treatment safety

Italian experts unanimously agreed on the appropriateness of the treatment safety recommendations, stating that the activity of anti-HER2 therapy in HER2+ breast cancer is age-independent; that the decision to continue T-DXd treatment depends on the grade of AE that has occurred, except for ILD/P, for which several factors must be considered; that T-DXd treatment shall be continued in case of low/moderate grade toxicities – except for ILD/P; and that, considering the long median duration of T-DXd treatment, it would be useful to provide the patient with adequate information regarding the risk/benefit ratio with this therapy to encourage acceptance of this treatment and the potential occurrence of low/moderate grade toxicities (G1-G2). It is important to specifically highlight how, with this treatment, the patient should be approached from a different risk-benefit balance perspective, compared to with other therapies available to date, taking into consideration both the favorable prospects with the use of this drug and the exposure to long-term treatment.

5. Conclusion

ILD/P and N/V remain by far the most challenging and demanding AEs associated with T-DXd. This study reflects a focused effort to thoroughly investigate and address all aspects of their management, including early detection, prevention, and prompt intervention. Given that all leading expert and panelist involved in the Delphi process are practicing physicians with extensive direct experience in T-DXd management across a range of settings including large cancer centers as well as medium- and small-sized general hospitals, we believe that the recommendations resulting from the Delphi Scientific Board survey are broadly applicable and generalizable to diverse clinical contexts, and that, together with the clinical appropriateness criteria assessed by the expert panels, and proactive surveillance, they may substantially improve the management of T-DXd-related AEs, maximizing the benefit of this treatment for HER2-positive and HER2-low mBC, and potentially increasing treatment acceptance.

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