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Modified Delphi Study on Oral Mucositis/Stomatitis Prevention and Management in Patients Receiving Datopotamab Deruxtecan

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ABSTRACT

Background: Oral mucositis/stomatitis is a common adverse event during cancer treatment that can disrupt oral functioning and adherence to treatment. Datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody-drug conjugate, has shown promise in treating solid tumors. It has been associated with oral mucositis/stomatitis in clinical trials for breast and lung cancer (TROPION program). Currently, there is a lack of formalized guidelines for managing Dato-DXd-associated oral mucositis/stomatitis. The present study employed a modified Delphi approach to establish expert consensus on preventing, diagnosing, monitoring, and treating oral mucositis/stomatitis secondary to Dato-DXd and to improve patient care and clinical outcomes.

Materials and Methods: A four-stage modified Delphi study engaging 15 oncology experts from Europe and Canada was used to establish consensus on managing Dato-DXd-induced oral mucositis/stomatitis in lung and breast cancer patients. Experts were selected based on their roles as investigators in Dato-DXd clinical trials, including but not limited to TROPION-PanTumor01, TROPION-Lung01, TROPION-Lung05, and TROPION-Breast01, and their experience managing cancer treatment–associated oral

Abbreviations: ADC, antibody-drug conjugate; AESI, adverse event of special interest; CHMP, Committee for Medicinal Products for Human Use; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; LLLT, low-level laser therapy; mBC, metastatic breast cancer; mPFS, median progression-free survival; mTOR, mammalian target of rapamycin kinase; NSCLC, nonsmall cell lung cancer; OS, overall survival; Topo I, topoisomerase I; TROP2, trophoblast cell-surface antigen 2.

mucositis/stomatitis. The Delphi process included an initial meeting, two anonymized surveys, an in-person consensus meeting, and virtual one-to-one sessions for absentees.

Results: Expert consensus was reached on recommendations for managing Dato-DXd-associated oral mucositis/stomatitis, and experts highlighted the importance of establishing guidance to improve patient quality of life and clinical outcomes. Key recommendations included prophylactic dexamethasone mouthwash, patient education, and behavioral changes. Early detection through self-checks and monitoring was emphasized, and recommended treatment strategies were tailored to oral mucositis/stomatitis severity. Treatment recommendations included dose modifications and discontinuation for severe cases.

Conclusions: This study offers expert guidance on managing Dato-DXd-associated oral mucositis/stomatitis, filling a crucial gap in patient care. Ongoing efforts to generate Dato-DXd-specific data will facilitate the creation of standardized, evidence-based protocols to improve patient safety and treatment outcomes.

1 | Introduction

Oral mucositis/stomatitis is a common side effect of a variety of cancer therapies, presenting as inflammation and ulceration of oral mucosa, which can lead to discomfort, impaired oral functioning, and treatment disruption in more severe cases [1, 2]. Oral mucositis/stomatitis manifests differently depending on the specific cancer therapy used. For instance, symptoms secondary to conventional chemotherapy and radiation range from mild discomfort within the oral cavity to large, painful ulcers that severely impact eating and speaking [1, 3]. Oral mucositis/stomatitis induced by epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and immune checkpoint inhibitors display unique characteristics based on the specific treatment and underlying pathogenesis [1, 4–7]. For instance, mammalian target of rapamycin (mTOR) kinase inhibitor–induced oral mucositis/stomatitis produces painful ulcers that are generally small, round, oval, and superficial, with a gray/white pseudomembrane and red border [8–10].

Dato-DXd is an antibody-drug conjugate (ADC) consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a topoisomerase I (Topo I) inhibitor payload via a stable tetrapeptide-based cleavable linker. It is currently under investigation for the treatment of several solid tumor types within the TROPION program [11]. In the TROPION-Lung01 phase III trial (NCT04656652), Dato-DXd significantly prolonged median progression-free survival (mPFS) versus docetaxel in patients with advanced/metastatic nonsmall cell lung cancer (NSCLC), driven by patients with nonsquamous histology (4.4 vs. 3.7 months). Overall survival (OS) showed a numerical benefit but did not reach statistical significance [12]. In the TROPION-Breast01 phase III trial (NCT05104866), Dato-DXd significantly prolonged mPFS versus investigators' choice of chemotherapy in patients with pretreated hormone receptor-positive/human EGFR-2 negative metastatic breast cancer (HR+/HER2-mBC) (6.9 vs. 4.9 months) [13]. Based on this trial, the Committee for Medicinal Products for Human Use (CHMP) recommended Dato-DXd for approval in the European Union for the treatment of patients with pretreated HR+/HER2-metastatic breast cancer [14]. The Food and Drug Administration (FDA) also approved Dato-DXd for the same indication [15].

While Dato-DXd demonstrated a manageable safety profile across all TROPION trials, oral mucositis/stomatitis was identified as an adverse event of special interest (AESI). The occurrence of all-grade oral mucositis/stomatitis was reported in 55.2% of TROPION-Lung01 patients, 66% of TROPION-Lung05 patients, and 55.6% of TROPION-Breast01 patients. Oral mucositis/stomatitis rarely progressed past Common Terminology Criteria for Adverse Events (CTCAE) Grade 2, occurring in 6% of TROPION-Lung01 patients and 7% of TROPION-Breast01 patients [13, 16–18].

Within the Dato-DXd trials, oral mucositis/stomatitis manifests as mucosal blistering, ulceration, inflammation, and pain within the oral cavity [2]. The mechanism linking Dato-DXd and oral mucositis/stomatitis is yet to be confirmed. However, topoisomerase inhibitors are known to induce mucositis, potentially through the activation of caspases, and promotion of MAPK signaling, leading to a reduction in the number of goblet cells [5]. Whether similar molecular pathways are triggered in the oral cavity is not known. TROP2 is expressed in epithelial cells within the oral cavity, and the esophagus, which suggests an on-target but off-tumor effect, may be playing a role [2]. Among TROPION-Breast01 patients, oral mucositis/stomatitis had a median onset time of 22 days, with a median resolution time of 36.5 days [19]. Oral mucositis/stomatitis rarely affected treatment continuation, with 0.7% and 0.3% discontinuation rates associated with this adverse event for TROPION-Lung01 patients and TROPION-Breast01 patients, respectively [12, 19]. Importantly, there were no per-protocol instructions for preventing and managing oral mucositis/stomatitis in Dato-DXd trials, and standalone toxicity management guidelines for oral mucositis/stomatitis management were implemented while TROPION-Lung01 and TROPION-Breast01 trials were ongoing.

Current preventive strategies for oral mucositis/stomatitis secondary to cancer treatment target several key areas, including oral care and hygiene, physical interventions like cryotherapy, and the use of treatments such as analgesics, anesthetics, steroids, antiseptics, antimicrobials, probiotics, and growth factors like palifermin [1, 3, 8, 20–23]. Management strategies for oral mucositis/stomatitis aim to reduce symptoms and enhance patient quality of life and clinical outcomes, with approaches varying based on CTCAE v5.0 grade [4]. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) guidelines for management of oral mucositis secondary to cancer therapy and the evolving guidance for managing oral mucositis/stomatitis secondary to Dato-DXd used in the TROPION program are outlined in Supporting Tables 1 and 2, respectively [2, 21]. Although the guidance for managing oral mucositis/stomatitis secondary to Dato-DXd is regularly updated as new safety data become available, it remains limited by the absence of direct clinical evidence. Efforts to generate these data are ongoing, but expert

guidance is needed in the interim. Furthermore, the underlying mechanisms that link Dato-DXd and oral mucositis/stomatitis remain unconfirmed, further hindering the provision of data-driven approaches for prevention and treatment. The present study uses a modified Delphi method to establish consensus among healthcare professionals for managing Dato-DXd-induced oral mucositis/stomatitis, including prevention strategies, monitoring and diagnosis protocols, and treatment guidance for different CTCAE grades.

2 | Material and Methods

2.1 | Overview of the Modified Delphi Process

The Delphi consensus method aims to achieve consensus among multidisciplinary experts through an iterative process [24]. Experts rate their agreement with statements in sequential surveys and provide anonymized feedback to inform the modification of statements for voting in subsequent rounds. Consensus is determined by a predefined percentage of experts agreeing or disagreeing with a specific statement. Cancer treatment guidelines have been devised using the Delphi process in the past [25, 26].

A modified Delphi method was implemented to fit the specific needs of the research question and comprised a virtual topic prioritization meeting, two anonymized survey rounds, and an in-person consensus meeting with one-to-one virtual meetings for absentees. The virtual prioritization meeting aimed to introduce experts to the Delphi process, allow the exchange of knowledge and experience between experts, and establish the most pertinent topics to address in the first survey. The final consensus meeting allowed for a more nuanced discussion of topics that still lacked consensus. Unanonymized initial and consensus meetings have been implemented in similar Delphi studies [27, 28]. To increase the chances of expert engagement and the likelihood of survey completion, surveys were designed to take no longer than 1 hour to complete. This helped to ensure that the full diversity of opinions was captured from both surveys.

2.2 | Expert Panel Selection

A diverse group of experts were selected to participate in this study to ensure the inclusion of all relevant clinical perspectives, enabling the development of high-quality guidelines (Table 1). In total, 15 experts were recruited from across Europe and Canada, including seven breast cancer specialists, seven lung cancer specialists, and one head and neck cancer and oral mucositis/stomatitis specialist. Specific criteria for inclusion were as follows:

- Experience managing oral mucositis/stomatitis in cancer patients.
- Actively treating and managing adverse events in lung or breast cancer patients.
- Publications on the treatment of patients with nonsmall cell lung cancer, breast cancer, and/or oral mucositis/stomatitis in international peer-reviewed journals within the past 5 years.

TABLE 1 | Expert panelist characteristics.

Characteristic	*n* (%)
Gender	
Male	11 (73)
Female	4 (27)
Primary field	
Medical oncology	14 (93)
Oral medicine	1 (7)
Subspecialty	
Breast cancer	7 (47)
Lung cancer	7 (47)
Head and neck cancer and oral mucositis/stomatitis	1 (7)
Region	
Europe	14 (93)
North America	1 (7)
Country	
Austria	1 (7)
Canada	1 (7)
France	4 (27)
Germany	1 (7)
Italy	4 (27)
Netherlands	1 (7)
Spain	2 (13)
The United Kingdom	1 (7)
Participation in the Dato-DXd TROPION clinical program	
Yes	14 (93)
No	1 (7)

Fourteen of the experts served as investigators in TROPION trials, including TROPION-PanTumor01, TROPION-Lung01, TROPION-Lung05, and TROPION-Breast01, all of whom had experience in managing Dato-DXd-induced oral mucositis/stomatitis.

2.3 | Delphi Rounds

Twelve experts participated in the round 1 virtual prioritization meeting.

The first survey comprised 35 questions across 4 sections with the following goals:

- Establishing the need for specific guidance on managing Dato-DXd-associated oral mucositis/stomatitis.
- Developing an understanding of best practices for the prevention, diagnosis, and treatment of oral mucositis/stomatitis in patients receiving Dato-DXd, including dose modifications.
- Exploring oral mucositis/stomatitis patient management strategies, including patient monitoring, healthcare provider education, and individualization of prevention and treatment plans.

Responses from survey 1 were collected, evaluated, and reported back in survey 2 as consolidated feedback. The results were analyzed qualitatively to identify topics of consensus and areas without consensus for further exploration in survey 2.

Survey 2 comprised 29 questions across 4 sections with the goal of probing three areas for further consensus:

- Prophylactic management approaches.
- Monitoring approaches.
- Recommendations on specific oral mucositis/stomatitis management approaches, including dose modifications.

Responses from survey 2 were collected, evaluated, and reported back in the consensus meeting as consolidated feedback. Results were analyzed qualitatively to identify topics of consensus and areas without consensus for further exploration in the consensus meeting.

Surveys 1 and 2 used a combination of open- and closed-ended questions to gain a broader understanding and probe specific monitoring, prevention, and management options, respectively. Experts rated their agreement or disagreement with closed-ended questions using a nine-point Likert scale (described below).

Round 4 involved an in-person consensus meeting with eight experts, complemented by one-to-one virtual meetings with the seven experts who could not attend in person. Eleven draft statements were discussed based on the results from survey 2, and adjustments were made by the experts to make the statements more clinically relevant. Following a live discussion of these statements, the experts anonymously rated their level of agreement with each one. Statements that did not reach a consensus were discussed further and updated to reflect the majority opinion of experts. During the one-to-one virtual meetings, the results from survey 2 and key discussion points from the consensus meeting were presented, after which experts provided their feedback and voted on the final 11 statements.

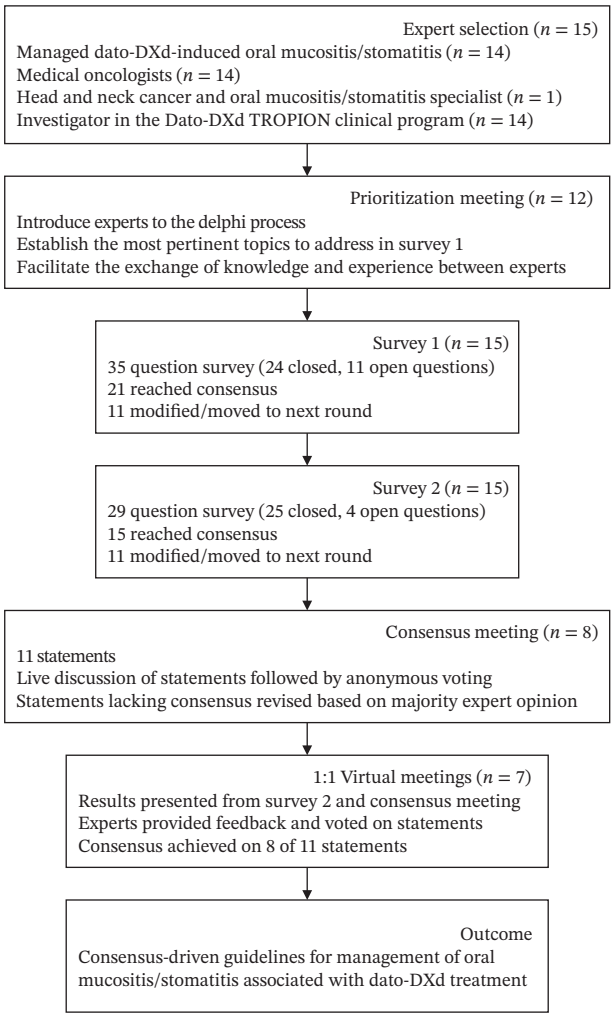

FIGURE 1 | Overview of the Delphi process. Dato-DXd, Datopotamab deruxtecan.

2.4 | Likert Scoring

Closed-ended statements were ranked on a nine-point Likert scale, where 1 represented "*strongly disagree with the statement*" and 9 represented "*strongly agree with the statement*." Consensus agreement was defined as $\geq 80\%$ of experts reporting a score of ≥ 7, and consensus disagreement was defined as $\geq 80\%$ of experts reporting a score of ≤ 3. Statements falling outside these ranges were deemed to have not achieved consensus. Nonresponses were also recorded.

3 | Results

3.1 | Summary of Delphi Rounds

Of the 35 statements scored in survey 1, 21 reached consensus. The remaining statements were revised and included in survey 2, where 29 statements were evaluated, and 15 achieved consensus. Eleven draft statements were presented for discussion during the consensus meeting and the one-to-one virtual meetings, and eight reached consensus (Figure 1 and Table 2). The flow of key topics across Delphi rounds is described in Figure 2. Expert scores for each question in surveys 1 and 2 are reported in Supporting Tables 3 and 4, respectively. The original proposed statements and the final consensus statements from the consensus meeting are reported in Supporting Table 5.

3.2 | Unmet Clinical Need

Oral mucositis/stomatitis is a significant adverse event that impacts patient quality of life and can necessitate modification or cessation of treatment regimens [2]. Most experts had direct experience managing oral mucositis/stomatitis and agreed in survey 1 that this adverse event requires close management. They also agreed that providing specific guidance on managing Dato-DXd-induced oral mucositis/stomatitis would help care teams and healthcare providers improve patient quality of life. They further agreed that specific guidance would help to improve clinical outcomes and mitigate dose reductions, dose delays, or treatment discontinuation.

3.3 | Prophylactic Measures

Prior to Dato-DXd treatment initiation, experts recommended patient education on the risk of oral mucositis/stomatitis, basic oral hygiene, and how to recognize and monitor symptoms. They also recommended additional education on the prescribed prophylactic regimen, emphasizing the importance of adherence

TABLE 2 | Statements that reached consensus across all delphi rounds.

Key topic	Sub-topic		Statement	Consensus reached
Clinical Unmet need	Need for Dato-DXd oral mucositis/stomatitis guidance and treatment goals	1	Oral mucositis/stomatitis associated with Dato-DXd treatment can be persistent and needs close management.	Survey 1
		2	I believe specific guidance on how to manage oral mucositis/stomatitis in patients receiving Dato-DXd treatment would help healthcare professionals and the care team improve patients' quality of life.	Survey 1
		3	I believe specific guidance on how to prevent and manage oral mucositis/stomatitis in patients receiving Dato-DXd treatment would help improve clinical outcomes and mitigate dose reductions, dose delays, or treatment discontinuation.	Survey 1
Prevention measures for oral mucositis/stomatitis	Patient education	4	Prior to Dato-DXd treatment initiation, I would educate my patients on: • The risk of oral mucositis/stomatitis and the importance of oral hygiene and early detection of oral mucositis/stomatitis. • The symptoms of oral mucositis/stomatitis and how to identify them. • The recommended prophylactic regimen (if recommended). • The importance of the prophylactic regimen and adherence to it (if recommended).	Survey 1
		5	I would consider involving a broader care team when educating patients on oral mucositis/stomatitis, including: • Nurses	Survey 2
	Prophylactic approach	6	I would recommend a set of prophylactic measures to reduce the likelihood and severity of oral mucositis/stomatitis.	Survey 1
		7	I would discuss the prophylactic regimen with my patient to determine which approaches they are comfortable with and can access.	Survey 1
	Patient population for prevention measures	8	I believe that Dato-DXd patients with the following attributes should receive a prophylactic regimen to reduce the likelihood and severity of oral mucositis/stomatitis: • All patients starting Dato-DXd	Survey 1
	Timing of prevention measures	9	At Dato-DXd treatment initiation, I would reiterate the importance of the prophylactic regimen and adherence to it (where applicable).	Survey 1
		10	I would initiate the prophylactic regimen (except for behavioral changes) on day 1 of cycle 1 of Dato-DXd treatment initiation.	Survey 2
	Behavioral and general prophylactic measures	11	Before the first cycle of Dato-DXd treatment and continuing throughout the treatment, I would recommend lifestyle changes to reduce the likelihood and severity of oral mucositis/stomatitis, including: • Discontinuing tobacco and alcohol usage (if applicable) • Diet modification—avoiding salty, acidic, spicy, or sharp foods	Survey 1
		12	For patients, I would place on a prophylactic regimen, I would recommend: • Brushing their teeth after meals and at bedtime with a soft toothbrush • Use of a prophylactic steroid-containing mouthwash	Survey 1
	Prophylactic cryotherapy	13	I would consider prophylactic cryotherapy (ice chips held in mouth for the entire duration of the infusion) for patients who have previously experienced [...] while treated with Dato-DXd • Moderate oral mucositis/stomatitis (CTCAE Grade 2) • Dato-DXd dose delays or dose reductions due to oral mucositis/stomatitis	Consensus meeting
		14	I would recommend prophylactic cryotherapy (ice chips held in mouth for the entire duration of the infusion) for patients who have previously experienced severe oral mucositis/stomatitis (CTCAE Grade 3+) while treated with Dato-DXd.	Survey 2
	Mouthwash	15	For patients I would place on a prophylactic regimen, I would recommend the prophylactic 2–4× daily use of a dexamethasone mouthwash (10 mL, 0.1 mg/mL solution).	Survey 2
		16	If a dexamethasone mouthwash is not available, I would recommend another steroid (e.g., prednisone-, prednisolone-, or methylprednisolone-based) mouthwash to my Dato-DXd patients.	Survey 2
		17	I would recommend swishing the steroid-containing mouthwash in the mouth for 1–2 min before discarding.	Survey 2
		18	The use of a steroid-containing mouthwash should be prioritized. However, if no steroid-containing mouthwashes are available, I would consider a bland (i.e., nonalcoholic, saline, and bicarbonate-containing) mouthwash for my Dato-DXd patients.	Consensus meeting
		19	I would instruct my patients to swish the steroid-containing mouthwash around the whole mouth, cheeks, all parts of the gums, between the teeth, and then gargle at the back of the throat before spitting out the mouthwash. It is important not to swallow the mouthwash.	Consensus meeting
	Simplified prophylaxis	20	For patients who have not shown any symptoms of OM/S after 4–6 cycles of Dato-DXd treatment, I would consider reducing the frequency of the steroid-containing mouthwash to once-to-twice daily.	Consensus meeting
		21	For patients who have not shown any symptoms of OM/S after 4–6 additional cycles of Dato-DXd treatment while using the steroid-containing mouthwash at a reduced frequency (1–2x daily), I would consider discontinuing the steroid-containing mouthwash while maintaining other prophylactic measures (e.g., general oral hygiene, behavioral changes, and water or saline mouthwash).	Consensus meeting

(Continues)

TABLE 2 | (Continued)

Key topic	Sub-topic		Statement	Consensus reached
Diagnostic measures and monitoring for oral mucositis/stomatitis	Patient monitoring	22	At Dato-DXd treatment initiation, I would begin to actively monitor for signs of oral mucositis/stomatitis.	Survey 1
		23	I would monitor for and evaluate the following patient outcomes while managing patients treated with Dato-DXd: Pain, difficulty with food intake, mouth sores/ulcers, inflammation, and quality of life.	Survey 2
		24	Upon Dato-DXd treatment initiation, I would encourage patients to perform regular self-checks to identify the onset of oral mucositis/stomatitis and immediately report any signs or symptoms.	Survey 2
	Monitoring frequency	25	For all patients not showing oral mucositis/stomatitis symptoms, I would monitor for oral mucositis/stomatitis symptoms at least once per Dato-DXd treatment cycle (every 3 weeks).	Survey 2
		26	I would monitor my patients with mild oral mucositis/stomatitis (CTCAE Grade 1) for oral mucositis/stomatitis symptoms once per cycle (every 3 weeks).	Survey 2
		27	I would monitor my patients with moderate oral mucositis/stomatitis (CTCAE Grade 2) for oral mucositis/stomatitis symptoms once weekly in person or remotely.	Consensus meeting
		28	I would monitor my patients with severe oral mucositis/stomatitis (CTCAE Grade 3+) for oral mucositis/stomatitis symptoms at least once weekly in person.	Consensus meeting
	Diagnosis methods	29	When determining if a patient has oral mucositis/stomatitis, a physical examination and patient-reported symptoms are sufficient to make a diagnosis.	Survey 1
		30	I would use the CTCAE scale for oral mucositis to determine the grade and severity of oral mucositis/stomatitis	Survey 1

(Continues)

TABLE 2 | (Continued)

Key topic	Sub-topic		Statement	Consensus reached
Treatment measures for oral mucositis/stomatitis in Dato-DXd	Patient population for treatment approaches	31	I would recommend using specific treatments for oral mucositis/stomatitis, regardless of prophylactic regimen, upon seeing the following symptoms: • A patient reports mild oral pain, slight ulceration, and some* change in diet needed without any interference with oral intake (*some solid foods may be limited and some change to diet may be required). • A patient reports moderate oral pain, ulceration, and a moderate change in diet needed without any interference with oral intake. • A patient reports severe oral pain, ulceration, and significant interference with oral intake.	Survey 1
		32	I would use the CTCAE oral mucositis/stomatitis grade to inform my treatment decisions.	Survey 2
		33	For patients reducing dose, I would maintain the reduced dose of Dato-DXd until treatment discontinuation (unless further dose reductions are required).	Survey 1
	General treatment recommendations	34	For patients with any grade of oral mucositis/stomatitis, I would ensure the following prophylactic measures have been tried before considering dose delays and/or dose reductions: • Behavioral changes • General oral hygiene • Use of a steroid-containing mouthwash	Survey 2
		35	For patients using several topical therapeutic measures, I would consider combining them into one mouthwash to increase patient convenience. This mixture must be prepared by a pharmacist.	Consensus meeting
	Mild presentation	36	I would recommend the following treatments for oral mucositis/stomatitis in Dato-DXd patients with mild oral mucositis/stomatitis (CTCAE Grade 1): • Systemic opioids (e.g., oral morphine) to manage pain • Systemic opioids (e.g., transdermal morphine or fentanyl) for long-term pain management • Low-level laser therapy (PBM) • Intralesional steroid injections • Systemic oral corticosteroids (e.g., prednisone or prednisolone) to bring symptoms under control rapidly	Consensus achieved against statement in Survey 1
		37	I would recommend the following Dato-DXd treatment modifications for oral mucositis/stomatitis in Dato-DXd patients with mild oral mucositis/stomatitis (CTCAE Grade 1): • Dato-DXd dose delay • Dato-DXd dose reduction • Dato-DXd discontinuation	Consensus achieved against statement in Survey 1
		38	For patients with mild oral mucositis/stomatitis (CTCAE Grade 1), I would reiterate the importance of adhering to the prophylactic regimen and practice watchful waiting.	Consensus meeting
	Moderate presentation	30	I would recommend the following treatments for oral mucositis/stomatitis in Dato-DXd patients with moderate oral mucositis/stomatitis (CTCAE Grade 2): • Steroid-containing mouthwash (if not used already)	Survey 1
		40	I would recommend the following treatments for oral mucositis/stomatitis in Dato-DXd patients with moderate oral mucositis/stomatitis (CTCAE Grade 2): • Intralesional steroid injections	Consensus achieved against statement in Survey 1
		41	I would recommend the following Dato-DXd treatment modifications for oral mucositis/stomatitis in Dato-DXd patients with moderate oral mucositis/stomatitis (CTCAE Grade 2): • Dato-DXd discontinuation	Consensus achieved against statement in Survey 1
		42	For patients with moderate and severe oral mucositis/stomatitis (CTCAE Grades 2 & 3+), I would consider using a topical steroid gel as spot treatment applied directly on mouth ulcers.	Survey 2
		43	For patients with the first occurrence of moderate oral mucositis/stomatitis (CTCAE Grade 2), I would recommend delaying the next Dato-DXd dose until oral mucositis/stomatitis has reduced to Grade ≤ 1 and reinitiating Dato-DXd at the same dose.	Consensus meeting
		44	For patients with recurrent moderate oral mucositis/stomatitis (CTCAE Grade 2), I would recommend delaying the next Dato-DXd dose until oral mucositis/stomatitis has reduced to Grade ≤ 1 and reinitiating Dato-DXd at a reduced dose.	Consensus meeting
	Severe presentation	45	I would recommend the following treatments for oral mucositis/stomatitis in Dato-DXd patients with severe oral mucositis/stomatitis (CTCAE Grade 3+): • 2% viscous lidocaine • Steroid-containing mouthwash (if not used already)	Survey 1
		46	For patients with severe oral mucositis/stomatitis (CTCAE Grade 3+), I would consider using systemic opioids (oral or transdermal) to manage pain.	Survey 2
		47	For patients with severe oral mucositis/stomatitis (CTCAE Grade 3+), I would recommend both delaying the next Dato-DXd dose until oral mucositis/stomatitis has improved to Grade ≤ 1, at least 1 week, AND reinitiating Dato-DXd treatment at a reduced dose.	Survey 2

Note: Results represent consensus agreement unless stated otherwise.

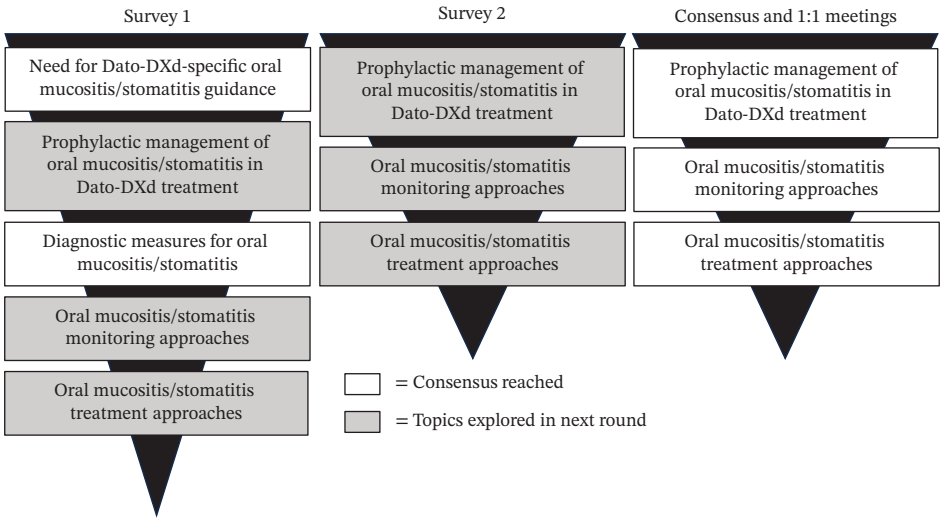

FIGURE 2 | Flow of primary topics across Delphi rounds. Dato-DXd, Datopotamab deruxtecan.

and addressing the patient's comfort with, and access to, these measures. Further recommendations centered on encouraging behavioral changes, including stopping alcohol and tobacco use and avoiding salty, acidic, spicy, or sharp foods.

In survey 1, experts agreed on the importance of implementing a prophylactic regimen for all patients receiving Dato-DXd, starting on day 1 of the first treatment cycle. They agreed on 2–4 times daily use of a dexamethasone-containing mouthwash (10 mL, 0.1 mg/mL solution for 1–2 min) for prophylaxis or another steroid if dexamethasone was unavailable. They also agreed that they would consider reducing usage to 1–2 times daily for patients who had not shown oral mucositis/stomatitis after 4–6 cycles of Dato-DXd treatment. Experts recommended the prophylactic use of cryotherapy for patients who had previously experienced Grade 2 or higher oral mucositis/stomatitis or had required dose delays or reductions. There was no consensus among experts on its use as a standard part of general prophylaxis, with some advocating for its inclusion and others opposing it. The recommended prophylaxis strategy for Dato-DXd-associated oral mucositis/stomatitis is outlined in Figure 3.

3.4 | Diagnosis and Monitoring

Experts considered early detection of oral mucositis/stomatitis key to providing optimal care. To this end, they recommended encouraging patients to routinely self-monitor for early symptoms of oral mucositis/stomatitis upon commencement of Dato-DXd treatment and immediately report any problems to their healthcare team. For patients without symptoms or with Grade 1 oral mucositis/stomatitis, the experts recommended professional monitoring once per Dato-DXd cycle, either through remote assessments or in-person visits. For patients with Grade 2 oral mucositis/stomatitis, the experts recommended weekly monitoring through either in-person or remote assessments. For Grades 3 and above, they advised weekly in-person monitoring only.

3.5 | Treatment

The experts reached a consensus in Survey 2 on using CTCAE grading to help determine the course of treatment for oral mucositis/stomatitis in patients receiving Dato-DXd. They also agreed that treatment approaches should be tailored based on the appearance of specific symptoms regardless of the prophylactic regimen used. For Grade 1 oral mucositis/stomatitis, the experts recommended continued adherence to the prophylactic regimen and vigilant monitoring to assess the worsening of symptoms without making changes to the treatment dosage or schedule. For patients with a first occurrence of Grade 2 oral mucositis/stomatitis, the experts recommended delaying the Dato-DXd dosage and continuing the normal dose once symptoms improved to ≤ Grade 1. For recurrent Grade 2 oral mucositis/stomatitis, they recommended delaying the Dato-DXd dosage and continuing at

Prophylaxis	Priority	Steroid mouth rinse (e.g., dexamethasone): swish and spit 2–4x per day for 1-2 minutes
	Recommended	Oral hygiene: teeth brushing with soft toothbrush
		Patient education: oral mucositis/stomatitis awareness, early signs and symptoms, and oral care routine
		Behavioural changes: discontinuing alcohol & tobacco; avoiding salty, acidic, spicy, or sharp foods
	May be considered	Cryotherapy: ice chips held in the mouth for the entire duration of the infusion (for patients who have previously experienced oral mucositis/stomatitis)

FIGURE 3 | Suggested prophylactic regimen for Dato-DXd-associated oral mucositis/stomatitis. The suggested regimen starts on Day 1 of Cycle 1.

a reduced dose once symptoms improved to ≤ Grade 1. For Grade 3 oral mucositis/stomatitis, experts recommended delaying the next Dato-DXd dose for at least 1 week and continuing the delay until symptoms improved to ≤ Grade 1. They recommended treatment be reinitiated at a reduced dose, which should be maintained permanently. The recommended treatment approaches for each grade of oral mucositis/stomatitis are outlined in Figure 4.

4 | Discussion

Novel therapies are rapidly emerging within the expanding field of personalized cancer care, with the goal of overcoming the toxicity and limited precision associated with traditional treatments. Within this, ADCs are a promising approach that may fill a niche in the current treatment arsenal by coupling antibody-specific targeting with cytotoxic compounds to enable more precise payload delivery and reduced toxicity [29].

In breast cancer, ADCs are primarily used to treat patients with advanced disease who have already received one or more prior therapies [30]. Trastuzumab emtansine, the first FDA-approved ADC for solid tumors, was initially approved for use in HER2+ mBC in patients previously treated with trastuzumab and a taxane, and is now also approved as a post-surgery adjuvant therapy for HER2+ early breast cancer in patients with residual disease after neoadjuvant trastuzumab plus a taxane [31]. Another ADC, sacituzumab govitecan, is approved for the treatment of patients with locally advanced or metastatic triple-negative breast cancer with at least two prior treatments, and for patients with HR+/HER2- unresectable or mBC with prior treatments [32, 33]. Investigations are underway to determine the benefit of expanding the role of ADCs in the management of breast cancer. Current efforts are particularly focused on combinations with HER2-targeting therapies and immunotherapies, while research continues on novel targets, payloads, biomarkers, and linker chemistries to improve efficacy and reduce toxicity [30, 34].

Although the first ADC for NSCLC was not approved until 2022, momentum in this area is now rapidly building [35]. Trastuzumab deruxtecan is approved for the treatment of unresectable or metastatic NSCLC by activating HER2 mutations in patients who have previously received systemic therapy, while telisotuzumab vedotin gained approval in May 2025 for the treatment of

Suggested management	Mild (CTCAE grade 1)	Diet modification: avoiding salty, acidic, spicy, or sharp foods
		Steroid mouthwash: 2–4x per day for 1-2 minutes
		Watchful waiting: no specific treatment measures beyond ensuring adherence to optimal prophylactic measures
		Monitor once per cycle: remote or in-person every 3 weeks
	Moderate (CTCAE grade 2), first occurrence	Dato-DXd treatment delay: until improvement to Grade 1, at least 1 week
		Reinitiate dato-DXd at the same dose
		Steroid mouthwash: 2–4x per day for 1-2 minutes
		Monitor once weekly: either remotely or in-person
	Moderate (CTCAE grade 2), recurrent	Dato-DXd treatment delay: until improvement to Grade 1, at least 1 week
		Reinitiate dato-DXd at a reduced dose
		Steroid mouthwash: 2–4x per day for 1-2 minutes
		Monitor once weekly: either remotely or in-person
	Severe (CTCAE grade 3+)	Dato-DXd treatment delay: until improvement to Grade 1, at least 1 week
		Reinitiate dato-DXd at a reduced dose
		Steroid mouthwash: 2–4x per day for 1-2 minutes
		Consider systemic opioids to manage pain: oral or transdermal
		Monitor at least once weekly in person

FIGURE 4 | Suggested treatment regimen for Dato-DXd-associated oral mucositis/stomatitis. CTCAE, Grade 1: asymptomatic or mild symptoms, intervention not indicated; Grade 2: moderate pain or ulcer that does not interfere with oral intake, modified diet indicated; Grade 3: severe pain, interfering with oral intake; Grade 4: life-threatening consequences, urgent intervention indicated; Grade 5: death. CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, Datopotamab deruxtecan.

locally advanced or metastatic nonsquamous NSCLC with c-Met overexpression [36, 37].

Dato-DXd has shown positive results in TROPION trials for solid tumors, it has and received European Medicines Agency approval in April 2025 for patients with previously treated metastatic HR+/HER2- breast cancer, followed by accelerated FDA approval in June 2025 for patients with locally advanced or metastatic EGFR-mutated NSCLC [13, 38–40]. Thus, the current lack of standardized guidance for managing oral mucositis/stomatitis associated with Dato-DXd treatment necessitated an unbiased approach to collate and harmonize the opinions of relevant healthcare experts. Most (14/15) of the experts who participated in this study have direct experience managing oral mucositis/stomatitis related to Dato-DXd treatment, making them uniquely qualified to offer valuable insights into effective strategies for its prevention and management. The present study employed a modified Delphi method to help establish the best practices for managing oral mucositis/stomatitis, including prevention, diagnosis, monitoring, and treatment.

The absence of clinical data and standardized guidelines was highlighted in the differing approaches among experts for managing oral mucositis/stomatitis, which led to several areas of disagreement. For instance, cryotherapy is a widely used approach for preventing and treating oral mucositis/stomatitis during cancer treatment that involves swirling ice water or ice chips around the mouth (or sucking on water popsicles) before, during, and after chemotherapy infusions [20]. However, there is limited clinical evidence for the benefit of cryotherapy in preventing and treating oral mucositis/stomatitis secondary to chemotherapy. Thus, some experts were hesitant to recommend it. Conversely, other experts have consistently used cryotherapy in Data-DXd treatment cycles and highlighted positive experiences with this method. This divergence resulted in cryotherapy being recommended as a prophylactic measure for patients with recurrent $\geq$ Grade 2 oral mucositis/stomatitis, with the possibility of broader use considered as more clinical data become available.

Many experts reported positive experiences prescribing a daily steroid-containing mouthwash for prophylaxis. During discussions, experts shared experiences of improved patient outcomes when a dexamethasone mouthwash was implemented in prophylactic regimens compared to when it was absent. At the consensus meeting, experts highlighted the need to use dexamethasone or another steroid-containing rinse, as opposed to more bland rinses for which there is limited evidence of effectiveness. However, if a steroid-containing mouthwash is unavailable, experts recommend using a bland mouthwash (i.e., nonalcoholic, saline, and bicarbonate-containing). Many of the breast cancer experts and some lung experts cited the SWISH study, which examined the management of oral mucositis/stomatitis secondary to everolimus in breast cancer patients, as helping to inform their approach when prescribing a steroid-containing mouthwash [22]. Indeed, the method reported in the SWISH protocol (10 mL, 0.5 mg/5 mL solution 4 ×/day, for 2 min) is strongly reflected in the recommendation of the experts in this study, that is, 10 mL, 0.1 mg/mL 2–4×/day, for 1–2 min. Experts agreed on the importance of coating the entire oral cavity and of not swallowing the mouthwash after use. Despite this consensus, the experts noted the lack of Dato-DXd-specific clinical data for the use of steroid-containing mouthwashes, which would help to inform more precise protocols.

Generally, experts agreed on the need for a consistent and thorough approach to prophylaxis given the potentially severe consequences of avoidable occurrences of oral mucositis/stomatitis on patient quality of life and treatment outcomes. Several experts noted the need to provide additional data on the minimum number of Dato-DXd treatment cycles for which prophylaxis should be maintained without modification.

Experts reported differing approaches to treating Grade 1 oral mucositis/stomatitis. Some experts suggested the use of topical NSAIDS, 2% viscous lidocaine, topical steroids, salivary substitutes, or sialagogues for treatment. While experts agreed that continuation of the prophylaxis plan was recommended for the treatment of Grade 1 oral mucositis/stomatitis, they came to a consensus against the use of systemic opioids, low-level laser therapy (LLLT), intralesional steroids, or systemic steroids for mild cases. Other treatment options, such as sugarless chewing gum for severe oral dryness, and increasing the frequency and dosage of steroid-containing mouthwash, were also suggested by some experts but did not reach a consensus. It is worth noting that some experts viewed LLLT and cryotherapy favorably. However, neither reached a consensus, with the expert panel agreeing that more data are needed before these approaches could be recommended more broadly.

Recommended management strategies for Grades 2 and 3 oral mucositis/stomatitis centered around treatment delays, dose reductions, pain management, the use of steroid-containing mouthwash, and monitoring. Experts recommend delaying Dato-DXd treatment for first-time Grade 2 oral mucositis/stomatitis patients until improvement to Grade 1, then resuming the normal dose. For recurrent Grade 2 cases, they advised treatment delay and resumption at a reduced dose upon improvement. In severe Grade 3 cases, experts recommended delaying Dato-DXd treatment until patient recovery to grade $\leq$ 1 with dose reduction thereafter. They also recommended the consideration of systemic opioids for pain management, and weekly in-person monitoring.

The proposed prophylaxis and management measures largely align with preexisting guidance for managing oral mucositis/stomatitis in TROPION trials, with the primary differences being at the level of detail and specificity provided [2]. One notable difference is that the present study suggests that clinicians recommend behavioral changes as part of prophylactic measures, including avoiding alcohol and tobacco use and not consuming foods that are salty, acidic, spicy, or sharp. In addition, this study provides specific guidance on using cryotherapy as a prophylactic measure in patients who have already developed oral mucositis/stomatitis, whereas it was previously mentioned only as a possible consideration for oral mucositis/stomatitis management.

This study offers more detailed recommendations for diagnosing and managing oral mucositis/stomatitis, including specific strategies for monitoring, pain management, dose delays, and treatment reinitiation based on oral mucositis/stomatitis CTCAE grade. The detailed recommendations outlined in this study are expected to offer valuable guidance for clinicians with less experience managing oral mucositis/stomatitis associated with

Dato-DXd treatment. Overall, experts felt that the guidance provided in this study accurately reflects the best current knowledge of how to manage oral mucositis/stomatitis associated with Dato-DXd treatment and expressed confidence in their ability to proactively and reactively manage this adverse event based on the recommendations of this study.

Anonymity is typically maintained throughout Delphi consensus methods [24]; however, in our modified method, it was intentionally removed during the prioritization and consensus meetings. For the prioritization meeting, this helped to ensure that the first survey focused on the most clinically relevant issues while incorporating diverse perspectives. For the consensus meeting, the removal of anonymity facilitated more nuanced and open discussions. While we believe these modifications were essential for the successful completion of the study, they had the potential to introduce some issues.

The lack of anonymity at the early stages may have inadvertently led to a narrowing of the focus for the remainder of the study. Specifically, the initial discussions may have disproportionately shaped the subsequent survey rounds, potentially limiting the diversity of topics explored and excluding ideas that might have emerged under fully anonymous conditions.

Open discussion in both meetings had the potential to introduce bias, such as discussions being dominated by certain participants or responses being influenced by more senior or authoritative experts. The limited number of experts selected for this study may have heightened the risk of deference to more senior participants, especially given that most experts work within the same field. However, this limitation was unavoidable due to the relatively small size of the field and the limited availability of experts who met the selection criteria. The absence of experts from Asia and the United States may limit the applicability of this guidance to those regions where management practices may differ. We direct readers to a recently published United States–based expert Delphi consensus study on the management of stomatitis in patients treated with Dato-DXd for further perspectives [41].

Nonetheless, anonymity was upheld during the survey rounds to maintain the integrity of the process. Furthermore, responses were compiled before proceeding to each subsequent round. Notably, the survey design, the prioritization process, the consensus meeting, and the one-on-one virtual meetings were conducted by an independent third party, not the sponsor. Moreover, the sponsor was not present at any of the meetings. This reduced the likelihood of experts feeling obliged to answer in a way that aligned with the sponsor's interests.

Certain aspects of the survey design may have limited the ability of the study to fully differentiate best practices. For instance, experts were asked to respond based on their approach to managing "severe presentation," which was defined as CTCAE Grade 3+. Separating Grades 3 and 4 could have allowed for greater differentiation in best practices between these distinct severity levels. Regarding the frequency of daily prophylactic mouthwash use (Supporting Table 2: Survey 2, Question 4), experts were provided with an option of "2–4 times per day." More narrowly defined response options, such as 2–3, or 4 times per day, could have enabled a more precise assessment of best practice.

5 | Conclusion

In conclusion, this modified Delphi study fills an important information gap for the safer administration of Dato-DXd to treat cancer. Experts agreed that, in the absence of guidelines, providing guidance on managing oral mucositis/stomatitis associated with Dato-DXd would enhance patient quality of life and treatment outcomes. Consensus was achieved on guidance covering the prevention, diagnosis, monitoring, and treatment of oral mucositis/stomatitis, which was informed by the experts' firsthand experiences and their reference to existing guidelines, such as those outlined in the SWISH study [22].

Experts cited the need for more Dato-DXd-specific clinical data before more defined protocols could be recommended. Ongoing efforts to generate these data will be crucial for developing standardized, evidence-based protocols to improve patient outcomes, reduce treatment-related complications, and ensure the safe and effective use of Dato-DXd as a cancer therapy. Data from real-world populations will also help increase the reproducibility of the preventive and therapeutic strategies provided here.

Author Contributions

Jo Clark and Cecile Matthews conceptualized and designed the Delphi study. Jo Clark, Cecile Matthews, and Lutz Goerke contributed to the development of the study questions, expert selection, Delphi process facilitation, data collection and analysis, interpretation of results, and manuscript writing. Paolo Bossi, Akin Atmaca, Thomas Bachelot, Rupert Bartsch, Giampaolo Bianchini, Quincy Chu, Robin Cornelissen, Enriqueta Felip, Nicolas Girard, Francesco Passiglia, Sonia Pernas, Melissa Phillips, David Planchard, Claudio Zamagni, and Barbara Pistilli provided expertise from their respective fields and shaped the insights and findings of the study.

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Ethics Statement

This study solely involved expert surveys; thus, ethical approval was not required.

Conflicts of Interest

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Data Availability Statement

The data that support the findings of this study are openly available in the supporting information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. *(Supporting Information)*

Supporting Table 1. MASCC/ISOO Guidelines for the Management of Oral Mucositis Secondary to Cancer Therapy. Supporting Table 1 provides the current MASCC/ISOO guidelines for the management of oral mucositis for additional context.

Supporting Table 2. Evolving Oral Mucositis/Stomatitis Management Guidelines Used in TROPION Program. Supporting Table 2 provides the current guidelines for the management of oral mucositis used in the TROPION clinical trials for additional context.

Supporting Table 3. Survey 1 results. Supporting Table 3 contains the aggregated results from the first round of the Delphi survey.

Supporting Table 4. Survey 2 results. Supporting Table 4 contains the aggregated results from the second round of the Delphi survey.

Supporting Table 5. Consensus meeting results. Supporting Table 5 contains the aggregated results from the consensus meeting.