Surgical Oncology Insight 2 (2025) 100193

Contents lists available at ScienceDirect

Surgical Oncology Insight

journal homepage: www.surgoncinsight.org

Review

Taiwan expert consensus on the clinical integration of antibody-drug conjugates in advanced breast cancer

Li-Chun Kao[a], Chih-Yi Hsu[b,c], Ming-Yang Wang[d,e], Ming-Han Yang[f], Chin-Sheng Hung[g,h], Guo-Shiou Liao[i], Kuo-Ting Lee[j], Wen-Ling Kuo[k,l,m], Meng-Ting Peng[n], Wei-Pang Chung[o,p], Chih-Hao Huang[q], Shou-Tung Chen[r,s,*], Chi-Cheng Huang[t,u,**], Yen-Shen Lu[f,v,w,***], Chun-Yu Liu[b,u,x,****]

[a] Division of Breast Oncology and Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan
[b] Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei 112, Taiwan
[c] Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei 112, Taiwan
[d] Department of Surgery, National Taiwan University Hospital, Taipei 100, Taiwan
[e] Department of Surgical Oncology, National Taiwan University Hospital Cancer Center, Taipei 106, Taiwan
[f] Department of Oncology, National Taiwan University Hospital, Taipei 100, Taiwan
[g] Department of Surgery, School of Medicine, College of Medicine, Taipei Medical University, Taipei 110, Taiwan
[h] Department of Surgery, Division of Breast Surgery, Taipei Medical University Hospital, Taipei 110, Taiwan
[i] Division of General Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei 114, Taiwan
[j] Department of Surgery, National Cheng Kung University Hospital, Tainan 704, Taiwan
[k] College of Medicine, Chang Gung University, Taoyuan 333, Taiwan
[l] Department of General Surgery, Chang Gung Memorial Hospital Linkou Main Branch, Taoyuan 333, Taiwan
[m] Breast Cancer Center, Chang Gung Memorial Hospital Linkou Main Branch, Taoyuan 333, Taiwan
[n] Division of Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital Linkou Main Branch, Taoyuan 333, Taiwan
[o] Center of Applied Nanomedicine, College of Medicine, National Cheng Kung University, Tainan 704, Taiwan
[p] Department of Oncology, College of Medicine, National Cheng Kung University Hospital, National Cheng Kung University, Tainan 704, Taiwan
[q] Division of Breast Surgery, China Medical University Hospital, Taichung 404, Taiwan
[r] Division of General Surgery, Changhua Christian Hospital, Changhua 500, Taiwan
[s] Comprehensive Breast Cancer Center, Changhua Christian Hospital, Changhua 500, Taiwan
[t] Breast Surgery, Department of Surgery, Taipei Veterans General Hospital, Taipei 112, Taiwan
[u] Comprehensive Breast Health Center, Department of Surgery, Taipei Veterans General Hospital, Taipei 112, Taiwan
[v] Department of Medical Oncology, National Taiwan University Cancer Center, Taipei 106, Taiwan
[w] Graduate Institute of Oncology, College of Medicine, National Taiwan University, Taipei 100, Taiwan
[x] Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei 112, Taiwan

ARTICLE INFO

Keywords:
Antibody-drug conjugates
Breast cancer
HER2-low
Trastuzumab deruxtecan
Sacituzumab govitecan
Taiwan expert consensus

ABSTRACT

Background: Antibody–drug conjugates (ADCs) have emerged as potent targeted therapies in advanced breast cancer, offering new options across HER2-positive, HR-positive/HER2-negative, and triple-negative subtypes. To address the rapidly evolving evidence, the Taiwan Breast Cancer Society (TBCS) convened an expert panel to develop consensus guidelines for integrating ADCs into clinical practice.

Methods: A multidisciplinary panel conducted systematic literature review and iterative discussions, identifying nine key topics. They formulated 31 consensus statements, graded by level of evidence and strength of recommendation, all of which reached ≥ 85 % agreement.

Results: Trastuzumab deruxtecan (T-DXd) is recommended as the preferred second-line treatment for HER2-positive metastatic breast cancer, with T-DM1 as an alternative when T-DXd is unavailable. T-DXd retains

* Correspondence to: Division of General Surgery, Changhua Christian Hospital, No. 135, Nanxiao St., Changhua, Changhua 500, Taiwan.
** Correspondence to: Breast Surgery, Department of Surgery, Taipei Veterans General Hospital, No.201, Section 2, Shipai Rd., Beitou Dist, Taipei 112, Taiwan.
*** Correspondence to: Department of Medical Oncology, National Taiwan University Cancer Center, No. 57, Ln. 155, Section 3, Keelung Rd., Da'an Dist, Taipei 106, Taiwan.
**** Correspondence to: Comprehensive Breast Health Center, Department of Surgery, Taipei Veterans General Hospital, No.201, Section 2, Shipai Rd., Beitou Dist., Taipei 112, Taiwan.
E-mail addresses: 1886@cch.org.tw (S.-T. Chen), chishenh74@gmail.com (C.-C. Huang), yslu@ntu.edu.tw (Y.-S. Lu), Cyliu3@gmail.com (C.-Y. Liu).

https://doi.org/10.1016/j.soi.2025.100193
Received 19 May 2025; Received in revised form 30 July 2025; Accepted 22 September 2025

efficacy in HER2-low disease and brain metastases. In HR-positive/HER2-negative MBC, both T-DXd and sacituzumab govitecan (SG) improve outcomes after endocrine therapy and CDK4/6 inhibitors, regardless of HER2-low (IHC 1 +/2 +) or IHC 0 status. In triple-negative breast cancer, SG offers significant survival benefit in refractory cases. There is currently no evidence supporting routine sequential use of multiple ADCs.
Conclusions: The TBCS guideline provides practical recommendations for integrating ADCs into the treatment of advanced breast cancer based on current evidence. It supports biomarker-guided agent selection across subtypes and highlights the need for continued research on sequencing strategies and optimal clinical positioning.

1. Introduction

Breast cancer remains the most common malignancy in Taiwanese women, with advanced breast cancer presenting persistent therapeutic challenges, including the development of drug resistance and managing treatment-related toxicities. While traditional chemotherapy and targeted agents have improved patients' outcomes, the eventual exhaustion of standard treatment options remains a significant hurdle. In recent years, antibody–drug conjugates (ADCs) have emerged as a novel class of therapeutics that combine the specificity of monoclonal antibodies with highly potent cytotoxic payloads.[1,2] This targeted delivery mechanism aims to widen the therapeutic window and minimize systemic exposure and associated toxicities compared to traditional chemotherapy.[1,2] The introduction of ADCs such as trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd), and sacituzumab govitecan (SG) has transformed the treatment landscape of advanced breast cancer, particularly in HER2-positive and triple-negative subtypes.[3–5]

T-DM1 was among the initial antibody–drug conjugates to significantly improve outcomes in HER2-positive metastatic breast cancer (MBC). In the Phase III EMILIA trial, T-DM1 demonstrated superior efficacy compared to conventional therapy, with a median progression-free survival of 9.6 months (versus 6.4 months) and a prolongation of overall survival.[3,6] Subsequently, the second-generation ADC T-DXd showed dramatically improved efficacy in HER2-positive disease. The pivotal DESTINY-Breast03 trial found T-DXd reduced the risk of progression by 72 % compared to T-DM1 in patients previously treated with trastuzumab and taxane (HR = 0.28, $p < 0.001$).[7] Beyond its impact in HER2-positive disease, T-DXd has also shown activity in HER2-low breast cancer—a newly recognized subset defined by low-level HER2 expression (IHC 1 + or IHC 2 +/ ISH-negative). The landmark DESTINY-Breast04 trial established T-DXd as the first effective targeted therapy for HER2-low tumors, significantly improving survival in both HR-positive and HR-negative cohorts.[3] Similarly, SG has represented a significant breakthrough in the treatment of triple-negative breast cancer (TNBC), with the phase III ASCENT trial demonstrating a tripling of median progression-free survival (PFS) versus chemotherapy (5.6 vs 1.7 months) and nearly doubling of median overall survival (OS) (12.1 vs 6.7 months) in heavily pretreated TNBC patients.[4]

With these advances, clinicians now face complex questions regarding the optimal integration of ADCs into the treatment algorithm.[1] Key questions include: identifying the patient populations most likely to benefit from ADCs, determining the optimal timing of administration, and understanding the influence of HER2-low or ultralow status on treatment selection [8,9] and the potential role for sequential use of multiple ADCs.[10] Furthermore, unique toxicities such as interstitial lung disease from T-DXd [11] and severe neutropenia from SG [4] require special consideration in routine practice. In Taiwan, rapid regulatory approvals of T-DXd and SG have expanded access but also necessitate guidance on optimal use. To address these needs, a Taiwanese expert panel was convened to develop consensus recommendations for the clinical integration of ADCs in advanced breast cancer. This article presents the panel's consensus statements along with the supporting evidence and rationale for each, providing a comprehensive framework for oncologists to guide the application of these novel therapies in practice.

2. Methods

2.1. Expert panel composition

The Taiwan Breast Cancer Society (TBCS) assembled a multidisciplinary expert panel of 13 members specializing in breast cancer. Members were selected based on clinical expertise and research experience with breast cancer therapeutics, particularly ADCs. The panel was charged with developing consensus statements on the use of ADCs in advanced breast cancer, focusing on integration into current treatment strategies, biomarker issues, toxicity management, and emerging challenges.

2.2. Literature review

Panel subgroups performed systematic reviews of literature for their assigned topics using sources including Google Scholar, PubMed, and major oncology society websites. Search terms such as "antibody–drug conjugate", "ADC", "mechanism", and "immune effect" were used in various combinations. Given that only three ADCs are currently approved for breast cancer in Taiwan (Table 1), broader inclusion criteria were adopted to reference mechanistic insights from studies beyond breast cancer, particularly where immunologic mechanisms were more clearly described (e.g., Section 1 Statement 2, studies involving multiple myeloma were cited to illustrate immune-related effects of ADCs). Evidence was gathered from clinical trial publications, conference proceedings, existing guidelines (e.g., ASCO, NCCN, ESMO etc.), and relevant meta-analyses or systematic reviews. Key data from pivotal phase II–III trials (EMILIA, DESTINY-Breast series, ASCENT, TROPiCS-02, TROPION-Breast01, etc.) and significant cohort studies were summarized. In total, over 70 publications were considered as the evidentiary basis for the consensus.

2.3. Consensus development

Nine topic areas were predefined by the steering committee (covering ADC mechanism, HER2-ultralow definition, HER2-positive/HR-positive/TNBC treatment pathways, biomarkers, toxicities, brain metastases, and sequential ADC use). For each topic, draft statements were formulated to reflect best practices or recommendations, along with proposed grading of evidence quality and recommendation strength. The panel adopted a modified Delphi process: initial statements were circulated via email for comments and then discussed in a series of virtual meetings between September and November 2024. Statements were revised for clarity and accuracy through iterative feedback until preliminary consensus was achieved.

2.4. Evidence grading

The quality of supporting evidence for each statement was graded as Level I, II, or III, using criteria adapted from the US Preventive Services Task Force and GRADE approach.[12] Level I evidence was defined as evidence from at least one well-conducted randomized controlled trial (or meta-analysis of RCTs). Level II evidence included data from well-designed non-randomized studies, cohort or case-control studies, or large series. Level III evidence was based on expert opinion, case reports, or descriptive studies. Concurrently, the strength of each recommendation was categorized as: A (strong recommendation), B (moderate recommendation), C (weak), or D

Table 1
Taiwan TFDA-approved ADC summary.

ADC Type	Indications	Efficacy data	Toxicity	Monitoring
Trastuzumab deruxtecan	● Unresectable or metastatic HER2-positive breast cancer (IHC 3 + or ISH +) after prior anti-HER2 therapy ● HER2-low metastatic breast cancer (IHC 1 + or 2 + /ISH-) after chemotherapy ● HER2-positive solid tumors after systemic therapy with no alternatives	**DESTINY-Breast03** (HER2-positive, HER2 IHC 3 + or ISH +): ● PFS 28.8 vs 6.8 mo (HR 0.33) ● ORR 78.5 % vs 35.0 **DESTINY-Breast02** (HER2-positive, HER2 IHC 3 + or ISH +): ● PFS 17.8 vs 6.9 mo (HR 0.36) ● OS 39.2 vs 26.5 mo (HR 0.66) ● ORR 69.7 % vs 29.2 % **DESTINY-Breast04** (HER2-low, IHC 1 + or IHC 2 + /ISH-): HR-positive & HR-negative Cohorts ● PFS 9.9 vs 5.1 mo (HR 0.50) ● OS 23.4 vs 16.8 mo (HR 0.64) ● ORR 52.3 % vs 16.3 % HR-positive Cohorts ● PFS 10.1 vs 5.4 mo (HR 0.51) ● OS 23.9 vs 17.5 mo (HR 0.64) ● ORR 52.9 % vs 16.6 %	Nausea, fatigue, vomiting, alopecia, neutropenia, constipation, anemia, decreased appetite, diarrhea, elevated transaminases, musculoskeletal pain, thrombocytopenia, leukopenia, abdominal pain	Monitor for ILD symptoms (cough, dyspnea), CBC before each dose, LVEF before and during treatment
Sacituzumab govitecan	● Unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) after ≥ 2 prior systemic therapies ● HR-positive/HER2-negative metastatic breast cancer after ≥ 2 prior systemic therapies including endocrine therapy	**ASCENT** (TNBC): ● PFS 4.8 vs 1.7 mo (HR 0.43) ● OS 11.8 vs 6.9 mo (HR 0.51) **TROPiCS-02** (HR-positive/HER2-negative mBC): ● PFS 5.5 vs 4.0 mo (HR 0.66) ● OS 14.4 vs 11.2 mo (HR 0.79) ● ORR 21.0 % vs 14.0 %	Decreased WBC count, decreased neutrophil count, decreased hemoglobin, diarrhea, nausea, decreased lymphocyte count, fatigue, alopecia, constipation, increased blood glucose, decreased albumin, vomiting, decreased appetite, decreased creatinine clearance, increased alkaline phosphatase, decreased magnesium, decreased potassium, decreased sodium	Monitor CBC before each dose, manage diarrhea promptly, monitor for hypersensitivity, assess UGT1A1 genotype if needed
Trastuzumab emtansine	● HER2-positive early breast cancer with residual disease after neoadjuvant therapy ● Metastatic HER2-positive breast cancer previously treated with trastuzumab and taxane	**EMILIA** (HER2-positive mBC): ● PFS 9.6 vs 6.4 mo (HR 0.65) ● OS 30.9 vs 25.1 mo (HR 0.68) ● ORR 43.6 % vs 30.8 %	Thrombocytopenia, anemia, nausea, constipation, vomiting, diarrhea, dry mouth, abdominal pain, stomatitis, fatigue, pyrexia, asthenia, chills, urinary tract infection, elevated transaminases, hypokalemia, musculoskeletal pain, arthralgia, myalgia, headache, peripheral neuropathy, insomnia, epistaxis, cough, dyspnea, rash, and bleeding	Monitor LFTs, platelet counts, pulmonary symptoms, and cardiac function (LVEF)

TFDA: Food and Drug Administration, MOHW (Ministry of Health and Welfare); PFS: Progression-free Survival; OS: Overall Survival; ORR: Objective Response Rate; AE: Adverse Event; WBC: White Blood Cell; ILD: Interstitial Lung Disease; CBC: Complete Blood Count; LFT: Liver Function Test; LVEF: Left Ventricular Ejection Fraction

(recommendation against use). By predefined voting rules, a statement required ≥85 % agreement to be assigned a strength of A or B, ≥50 % (but < 85 %) for C, and ≥25 % for D. Statements not achieving consensus were to be revised or discarded.

2.5. Consensus approval

The final consensus meeting was held in person on December 29, 2024, during the "2024 ADC Consensus Symposium" in Taipei. Panel members reviewed the collated evidence and voted anonymously on each statement's acceptance and recommendation grade. All 31 statements across the nine topics met the consensus threshold for acceptance; none required further modification after this meeting. The entire consensus document was then reviewed and officially endorsed by the TBCS Board in February 2025.

2.6. Manuscript preparation

The approved consensus statements and supporting discussions were compiled into this manuscript. For each topic, we present the consensus statements followed by a narrative discussion that elaborates on the clinical evidence, rationale, and relevant contextual considerations. In-text citations and the reference list follow AMA style, numbered by order of appearance. This consensus guideline is intended to aid clinical decision-making in Taiwan and is not intended as a legal standard of care. It will be updated as new data and ADC therapeutics continue to evolve.

3. Results

3.1. ADCs: a novel therapeutic class

ADCs represent a distinct and novel therapeutic class that bridges targeted therapy and chemotherapy.[1,2] Unlike traditional chemotherapy, which circulates systemically and affects both cancerous and healthy proliferating cells, ADCs deliver cytotoxic drugs directly to cancer cells via antigen-specific antibodies. This design markedly improves the therapeutic index by concentrating on the drug effect in tumor tissue while limiting systemic exposure.[1,2] For example, T-DXd couples an anti-HER2 antibody to a topoisomerase I inhibitor, achieving drug concentrations in HER2-expressing tumor cells far higher than could be attained safely with untargeted chemotherapy.[1,2] Based on their unique design and mechanisms of action, the expert panel developed the following consensus statements:

Consensus statements:

1. ADCs are biopharmaceuticals that combine a highly potent cytotoxic payload conjugated to a target-specific monoclonal antibody via a linker, improving the therapeutic window and reducing off-target effects.[1,2,13,14] (QoE: I; SoR: A)
2. The anti-tumor efficacy of ADCs can be attributed to the following mechanisms[15–20]:

(1) Upon binding to the antigen on cancer cells, the ADC is internalized and releases its cytotoxic payload. (QoE: II; SoR: A);
(2) The released payload may induce a bystander effect, killing adjacent tumor cells regardless of target expression. (QoE: II; SoR: A);
(3) The anticancer activity of ADC may also engage in antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) effects. (QoE: III; SoR: C)

3. The innovative mechanisms of ADCs set them apart from conventional targeted chemotherapies. Nevertheless, each ADC exhibits unique properties.[21] (QoE: I; SoR: A)

3.2. Definition, detection, and reproducibility of the HER2-ultralow category

Following the clinical recognition of "HER2-low" breast cancer, interest has extended to defining and accurately identifying HER2-ultralow tumors. These tumors typically appear as IHC 0 by initial assessment but may exhibit trace or incomplete HER2 membrane staining in ≤ 10 % of tumor cells.[8,9] The PATHWAY anti-HER2/neu (4B5) assay is a widely used, analytically validated IHC method with lower inter-assay variability, particularly in detecting low and ultralow HER2 expression.[22] Establishing a clear definition and ensuring reproducible detection of this subgroup are crucial for guiding treatment decisions. The expert panel reached the following consensus:

Consensus statements:

1. HER2-ultralow is defined as HER2 IHC 0 with faint, partial membrane staining in ≤ 10 % of tumor cells).[11] (QoE: I; SoR: A)
2. Due to notable inter-assay variabilities in the HER2 IHC test, one may consider using the 4B5 kit with its validated staining protocol as a companion test.[11,22,23] (QoE: II; SoR: B)
3. Before assigning a score of HER2 IHC 0 (no staining), pathologists should examine the entire tumor area under high-power magnification (40 × objective) to confirm the absence of any faint partial membrane staining.[24] (QoE: II; SoR: B)

3.3. Integrating ADCs into the treatment roadmap of HER2-positive advanced breast cancer

Historically, T-DM1 was the standard second-line ADC for HER2-positive MBC following trastuzumab–pertuzumab plus chemotherapy, based on EMILIA trial.[6] However, DESTINY-Breast03 trial established T-DXd as superior in both PFS and OS, leading it to become the preferred second-line therapy in this setting.[7] T-DXd's enhanced efficacy in HER2-positive disease is likely driven by its potent payload and the bystander effect. Based on evolving evidence and clinical experience, the expert panel provides the following consensus statements for integrating ADCs into the treatment of HER2-positive advanced breast cancer:

Consensus statements:

1. T-DXd is indicated in patients with HER2-positive MBC previously treated with a taxane and trastuzumab with/without pertuzumab in the metastatic setting. Although T-DXd is currently the preferred second-line treatment following trastuzumab-based therapy, it retains clinical activity and may still be considered as a third- or later-line option after prior T-DM1 exposure.[7,25–27] (QoE: I; SoR: A)
2. T-DM1 is indicated in patients with HER2-positive advanced breast cancer, who had been previously treated with a taxane and trastuzumab with/without pertuzumab in the metastatic setting. T-DM1 is a second- or later-line treatment option after progression on a taxane and trastuzumab with/without pertuzumab in cases where/when T-DXd is not available.[28–30] (QoE: I; SoR: A)
3. If T-DXd is discontinued due to toxicity, such as interstitial pneumonitis, T-DM1 may be considered as a subsequent treatment option.[7,25,27] (QoE: II; SoR: A)
4. T-DXd demonstrates central nervous system (CNS) activity in patients with HER2-positive advanced breast cancer. This includes efficacy in those with active brain metastases, both newly diagnosed and previously-treated brain metastases that are progressing.[31,32] (QoE: I; SoR: A)
5. T-DM1 shows potential efficacy as a treatment for HER2-positive breast cancer in patients with brain metastases, particularly when the metastases are stable and in cases where/when T-DXd is not available.[33] (QoE: II; SoR: B)

3.4. Integrating ADCs into the treatment roadmap of HR-positive/HER2-negative advanced breast cancer

In the management of endocrine-resistant HR-positive, HER2-negative MBC, systemic chemotherapy has historically constituted the primary treatment backbone after endocrine therapy failure. However, the therapeutic landscape has evolved significantly with the introduction of novel ADCs. Specifically, T-DXd has emerged as a targeted therapy option for patients with HER2-low disease, demonstrating significant prolongation of both progression-free survival and overall survival in the landmark DESTINY-Breast04 trial.[3] Concurrently, SG, an anti-TROP2 ADC, has also shown improved PFS and OS in heavily pretreated HR-positive MBC patients in the TROPiCS-02 study.[34,35] Both T-DXd and SG have demonstrated efficacy in the HER2-low subgroup within this population, though their optimal positioning within the treatment sequence relative to prior chemotherapy differs, with T-DXd typically utilized after approximately one line of chemotherapy and SG generally after two or more lines. Recently, Datopotamab deruxtecan (Dato-DXd), another TROP2-directed ADC, has demonstrated statistically significant improvements in progression-free survival compared to standard chemotherapy in previously treated HR-positive/HER2-negative MBC. Its favorable safety profile and less frequent hematologic toxicity suggest it may represent an additional therapeutic option in this population.[36] Based on this evolving evidence and clinical experience, the expert panel developed the following consensus recommendations for integrating ADCs into the treatment of HR-positive/HER2-negative advanced breast cancer:

Consensus statements:

1. T-DXd can be used in patients who have progressed upon endocrine therapy and ≥1 line of chemotherapy in HR-positive/HER2 IHC 1 + or 2 + /ISH negative MBC.[3] (QoE: I; SoR: A)
2. T-DXd is an effective treatment for patients with HR-positive/HER2-low or ultralow MBC after ≥ 1 prior line of endocrine therapy (ET).[37] (QoE: I; SoR: A)
3. Anti-TROP2 ADC (e.g., SG) may be used for HR-positive/HER2-negative metastatic or locally advanced unresectable breast cancer after prior treatment including ET, a CDK4/6 inhibitor, and ≥ 2 lines of chemotherapy in the MBC setting.[34,35] (QoE: I; SoR: A)
4. Subgroup analysis demonstrated anti-TROP2 ADC (e.g. SG) used in HR-positive/HER2-negative MBC, including HER2-low and HER2 IHC0, are consistent with that observed in the overall trial population.[34,35] (QoE: II; SoR: A)
5. Both T-DXd and SG have demonstrated activity in patients with metastatic HER2-low, HR-positive MBC after progression on ET. For patients who have received chemotherapy, T-DXd is generally preferred after the first line of chemotherapy; however, no direct comparative data are currently available between T-DXd and SG in the post–second-line chemotherapy setting.[38] (QoE: II; SoR: B)
6. There is currently insufficient evidence to support using ADC after progression on prior ADC in HR-positive/HER2-negative (including HER2-low, -ultralow and IHC0) MBC.[10,39] (QoE: II; SoR: B)
7. Dato-DXd is a potential new option for patients with previously treated, endocrine-resistant HR-positive/HER2-negative MBC. It was associated with improved PFS, regardless of prior duration of CKD4/6 inhibitors and presence/absence of brain metastases at baseline.[36] (QoE: I; SoR: A)

3.5. Integrating ADCs into the treatment roadmap of HR-negative/HER2-negative (Triple-Negative) advanced breast cancer

Historically, HR-negative/HER2-negative, or triple-negative breast cancer (TNBC), has been characterized by aggressive behavior and a lack of durable treatment options following initial chemotherapy for advanced disease. The introduction of SG, an anti-TROP2 ADC, has significantly shifted this paradigm, demonstrating substantial improvements in PFS and OS in heavily pretreated patients based on the pivotal ASCENT trial (PFS: 5.6 vs 1.7 months; OS: 12.1 vs 6.7 months).[4] Furthermore, T-DXd, approved for HER2-low breast cancer, represents a potential treatment option for the subset of TNBC patients whose tumors exhibit HER2-low expression (IHC 1 + or 2 +). Based on the available evidence and clinical experience, the expert panel provides the following consensus recommendations for integrating ADCs into the management of TNBC:

Consensus statements:

1. In TNBC advanced breast cancer, current evidence supports the use of SG for patients who have progressed after at least two prior lines of therapy, including at least one line in the metastatic setting.[40] (QoE: I; SoR: A)
2. In TNBC advanced breast cancer, current evidence supports the use of T-DXd for patients who have progressed after at least one prior line of chemotherapy in the metastatic setting.[41] (QoE: I; SoR: A)
3. No sufficient evidence support using ADC after progression on prior ADC in TNBC MBC.[42,43] (QoE: II; SoR: B)
4. Both T-DXd and SG have shown clinical activity in patients with HER2-low TNBC.[40,41] (QoE: II; SoR: B)
5. SG may be considered before T-DXd in this setting.[40–43] (QoE: II; SoR: B)

3.6. Biomarker issues for ADCs

The efficacy of T-DM1 and T-DXd is dependent on HER2 expression, necessitating a tumor HER2 status of IHC ≥ 1 + (with or without in situ hybridization [ISH] amplification) for patient selection and anticipated clinical benefit.[3,5] In contrast, while TROP2 is the target antigen for SG, the assessment of TROP2 expression level is not mandatory for selecting candidates for SG therapy.[4,44,45] However, there is no specific threshold of TROP2 expression has been established that reliably predicts or precludes patient benefit from SG in routine clinical practice. Accordingly, the expert panel reached the following consensus regarding predictive biomarkers for these ADCs:

Consensus statements:

1. HER2 is the only biomarker to predict the therapeutic efficacy of T-DM1 and T-DXd in breast cancer patients.[3,11,27,28,46] (QoE: I; SoR: A)
2. Based on current evidence, examination of TROP-2 expression level is not necessary when considering SG therapy.[34,35,41] (QoE: I; SoR: A)

3.7. Toxicity profiles and guidance on managing ADC-related toxicity

Understanding the unique toxicity profiles associated with ADCs is crucial for safe clinical practice. Each ADC's toxicity spectrum is intrinsically linked to the interplay of its specific components: the antibody target's expression in normal tissues, the linker's stability (influencing premature payload release), and the payload's intrinsic potency and mechanism of action.[11,47] A critical toxicity requiring vigilance is interstitial lung disease (ILD), observed in approximately 10–15 % of patients treated with trastuzumab deruxtecan (T-DXd), which can be severe and even fatal.[11,47,48] Prompt recognition, immediate drug interruption, and corticosteroid initiation are paramount if ILD is suspected; Grade ≥ 2 ILD necessitates permanent discontinuation.[11,47,48] SG commonly causes hematological toxicities, particularly severe neutropenia, and gastrointestinal adverse events such as diarrhea, reflecting the systemic exposure to its payload (SN-38, an irinotecan metabolite).[4] Ocular toxicities, including dry eye and conjunctivitis, are also recognized adverse events associated with T-DM1, T-DXd, and other next-generation ADCs.[49] While general principles of chemotherapy toxicity management (e.g., use of G-CSF for neutropenia, antiemetics) remain essential, ILD and ocular surveillance represent unique considerations in routine ADC management. Based on the

distinct toxicity profiles and the need for specific management strategies, the expert panel provides the following consensus statements:

Consensus statements:

1. The toxicities associated with ADCs are primarily driven by payload release and target antigen expression in normal tissues. Linker stability and the degree of internalization also influence the toxicity profile. These adverse events may occur as off-tumor toxicities through either on-target or off-target effects.[50,51] (QoE: I; SoR: A)
2. ADC-related toxicities vary depending on both the cytotoxic payload and the target antigen. Some toxicities are unique to specific ADCs, while others may result in severe or potentially life-threatening complications.[49–59] (QoE: I; SoR: A)
3. Management of common ADC-related toxicities generally aligns with principles used for chemotherapy toxicities. Updated guidelines provide practical recommendations for monitoring and intervention. Patient education, clinical vigilance, and timely recognition and management remain essential. This section emphasizes toxicities with potentially serious consequences (e.g., interstitial lung disease [ILD]) and those more frequently observed with ADCs.[49] (QoE: I; SoR: A)
4. Drug-induced pneumonitis or ILD has been reported in approximately 10 % of patients treated with T-DXd and to a lesser extent with other ADCs. Mechanisms may involve direct cytotoxicity or immune-mediated injury. General management principles include[49,52,55]:

   * Careful assessment of clinical symptoms, exposure history, chest imaging, pulmonary function, and laboratory tests for early diagnosis and grading. * Initiation of corticosteroids is recommended for grade ≥ 2 ILD and may be considered for grade 1 * Rechallenge with T-DXd may be cautiously considered only in grade 1 ILD after recovery; permanent discontinuation is warranted for grade ≥ 2 events. Management should follow updated international guidelines.[52] (QoE: II; SoR: A)
5. Ocular toxicities associated with ADCs include corneal epithelial changes, conjunctivitis, and lacrimal duct inflammation. Common symptoms are dry eyes, blurred vision, excessive tearing, and visual disturbances. Routine ophthalmologic evaluation and prophylactic use of lubricating eye drops are advised. The incidence of all-grade ocular toxicity is 3–6 % with T-DM1 and T-DXd, and up to 16–21 % with Dato-DXd, mostly of mild severity.[49,58,60–62] (QoE: I; SoR: A)
6. Oral mucositis or stomatitis occurs in 50–70 % of patients receiving certain ADCs such as Dato-DXd, typically with mild severity. Preventive and supportive care—including dental evaluation, improved oral hygiene, steroid mouthwash, ice chips, antifungal agents, and dietary modifications—may help reduce complications such as bleeding, infection, and malnutrition.[49,63,64] (QoE: II; SoR: A)

3.8. Understanding the activity of ADCs in brain metastasis

Brain metastasis is a significant clinical challenge in HER2-positive MBC, affecting up to 50 % of patients.[32] Historically, management has relied heavily on local interventions such as radiation therapy and surgery. The advent of novel systemic therapies with demonstrable CNS activity has begun to shift this paradigm. T-DXd has shown remarkable intracranial efficacy, achieving high objective response rates (approximately 73.3 %) in patients with active brain metastases in dedicated clinical trials.[32] This potent CNS activity has established T-DXd as a preferred first-line systemic therapy option for patients with HER2-positive MBC and CNS involvement. While less potent and not the preferred option for active disease, T-DM1 has also shown some evidence of CNS benefit and may be considered as an alternative in patients with stable brain metastases when T-DXd is contraindicated or inaccessible.[33] Ongoing prospective trials are further investigating the optimal strategies for integrating these ADCs with local therapy for comprehensive CNS management. Based on the accumulating evidence regarding the CNS activity of ADCs, the expert panel provides the following consensus statements:

Consensus statements:

1. T-DXd has demonstrated efficacy in controlling both systemic disease and brain metastases in patients with HER2-positive MBC. Notably, it offers substantial intracranial activity even in patients with untreated or progressing brain metastases following prior therapies.[32,65] (QoE: I; SoR: A)
2. T-DM1 may provide clinical benefit in patients with HER2-positive MBC and stable brain metastases. It remains a potential alternative in cases where T-DXd is contraindicated or unavailable.[66] (QoE: II; SoR: B)
3. Additional clinical data are needed to identify which subsets of patients with metastatic TNBC and stable brain metastases may derive benefit from SG.[67–69] (QoE: II; SoR: B)

3.9. Sequential use of ADCs with and without interruption

With the increasing availability of multiple ADCs across various breast cancer subtypes, a critical clinical question arises: whether patients who have progressed on one ADC can derive meaningful benefit from treatment with another ADC.[10] The current evidence base addressing sequential ADC use is limited, primarily consisting of retrospective analyses and small series. These data tentatively suggest that switching the antibody target (e.g., from HER2 to TROP2) or utilizing a payload with a different mechanism of action (e.g., from a tubulin inhibitor like DM1 to a topoisomerase I inhibitor like DXd or SN-38) may potentially circumvent mechanisms of acquired resistance developed against the initial ADC.[70] However, robust prospective clinical trials specifically designed to evaluate ADC sequencing strategies are currently lacking. Given this limited evidence, the expert panel emphasizes a cautious approach to routine sequential ADC usage and strongly encourages enrollment in prospective clinical trials whenever possible. More comprehensive real-world data and dedicated "ADC after ADC" prospective studies are essential to clarify the viability, efficacy, and optimal strategies for sequential ADC administration. Reflecting the current evidence limitations and clinical considerations, the expert panel provides the following consensus statements on sequential ADC use:

Consensus statement:

1. Sequential use of one ADC following another may be considered in selected patients. Ideally, the subsequent ADC should differ in either its target antigen or cytotoxic payload. However, sequential use of ADCs with overlapping targets or payload mechanisms is generally associated with reduced efficacy compared to frontline use.[10,39,46,70–75] (QoE: II; SoR: B)
2. Currently, there is no established optimal sequence for ADC therapy. Moreover, the clinical impact of introducing a treatment gap between two ADCs remains unclear.[4,10,35,37,39,70,74,75] (QoE: II; SoR: B)

4. Discussion

These expert consensus statements collectively underscore the transformative impact of ADCs in the management of advanced breast cancer, establishing novel therapeutic pathways across HER2-positive, HER2-low, and triple-negative subtypes. As highlighted in the preceding sections, T-DXd has emerged as the preferred second-line agent in HER2-positive MBC, succeeding T-DM1. Concurrently, SG and T-DXd have significantly expanded treatment options for patients with HR-positive/HER2-negative and triple-negative disease, respectively, based on their demonstrated efficacy in specific patient populations and lines of therapy. The accurate classification of HER2-low status through meticulous pathological assessment is pivotal for determining eligibility

for T-DXd, requiring careful differentiation of ultralow from true HER2 IHC 0 tumors. In contrast, the widespread expression of TROP2 and the lack of an established predictive threshold mean that TROP2 testing is not required for patient selection for SG therapy, simplifying its clinical adoption. Vigilant management of unique ADC-related toxicities is imperative, with particular attention warranted for T-DXd-induced ILD and ocular adverse events associated with certain ADCs. Furthermore, the demonstrated intracranial efficacy of T-DXd represents a significant advancement, enabling systemic treatment approaches for brain metastases in HER2-positive MBC and potentially reducing sole reliance on local interventions.

Despite these significant advances, several key unresolved questions remain regarding the optimal use of ADCs, including defining the optimal sequencing strategies when multiple ADCs are available and exploring the potential for combining ADCs with other therapeutic modalities. Current evidence on sequential ADC use, primarily from retrospective analyses, suggests that altering the target and/or payload of the subsequent ADC may potentially overcome resistance mechanisms from the initial ADC, leading to some level of efficacy. However, routine sequential ADC strategies currently lack robust confirmation from prospective clinical trials. Addressing these gaps necessitates dedicated future research focusing on rigorously evaluating different ADC sequencing regimens, investigating rational ADC combination strategies, identifying predictive and resistance biomarkers beyond current standards, and exploring the expansion of effective ADC use into earlier disease settings. Meanwhile, clinicians in Taiwan and globally can leverage the comprehensive framework provided by this consensus document to guide the integration of ADCs into multidisciplinary cancer care. This guidance supports optimizing patient selection based on evolving biomarker understanding, proactively preventing and managing unique ADC-related toxicities, and coordinating systemic and local therapies effectively. By adhering to these evidence-based recommendations within a multidisciplinary setting, medical oncologists, surgical oncologists, radiation oncologists, pathologists, and other specialists involved in breast cancer care can further individualize therapy, aiming to improve both survival outcomes and quality of life for patients with advanced disease. Continuous updates to this guidance will be essential to reflect new data as the rapidly evolving field of ADCs progresses.

5. Conclusion

ADCs have reshaped the treatment paradigm for advanced breast cancer. This consensus statement by the TBCS offers practical, evidence-based recommendations for integrating ADCs across HER2-positive, HER2-low, and triple-negative subtypes. Key considerations include optimal agent selection based on biomarker status, appropriate treatment line placement, and proactive management of ADC-specific toxicities, such as ILD and ocular adverse events. While the optimal sequencing of ADCs remains under investigation, this document provides a clinical framework to support individualized decision-making in daily practice. Continued updates will be essential as new data emerge to guide sequencing, combination strategies, and biomarker refinement.

6. Contribution

STC, CCH, YSL, CYL contributed to organizing and implementing the process of consensus, serving as academic consultants and verifying the scientific accuracy of consensus statements.

LCK, CYH, MYW, MHY, CSH, GSL, KTL, WLK, MTP, WPC, CHH contributed to confirming the consensus framework, conducting literature review, drafting the consensus statements and manuscript, and grading the QoE and SoR.

All attending experts contributed to reviewing the content of the statements and providing constructive feedback.

Funding

None

Ethical Statement

None

Disclosure

The authors declare no conflicts of interest.

Declaration of Competing Interests

The authors declare no conflicts of interest.

Acknowledgments

The authors would like to express their sincere gratitude to the Taiwan Breast Cancer Society for organizing and supporting the consensus meetings that made the development of this work possible. We also wish to thank the following experts for their participation and for providing valuable feedback and insights throughout the process.

Attending experts: Cheng-Ping Yu, Shih-Che Shen, Shyr-Ming Sheen-Chen, Hsu-Huan Chou, Ching-Hung Lin, Chin-Yao Lin, Ming-Feng Hou, Jyh-Cherng Yu, Chih-Chiang Hung, King-Jen Chang, Chen-Hsiang Chang, Yuan-Ching Chang, Hsien-Kun Chang, Chen Dwan-Ying, Yao-Jen Chang, Chieh-Han Chuang, Wen-Hung Kuo, I-Chun Chen, Fang-Ming Chen, Shin-Cheh Chen, Dar-Ren Chen, Ling-Ming Tseng, An-Chieh Feng, Chiun-Sheng Huang, Po-Hsiang Huang, Hsien-Tang Yeh, Ta-Chung Chao, Tsu-Yi Chao, Liang-Chih Liu, Yi-Fang Tsai, Tsui-Fen Cheng, Jiun-I Lai, Ming-Shen Dai, Kun-Ming Rau

References

1. Lambert JM, Berkenblit A. Antibody-drug conjugates for cancer treatment. *Annu Rev Med.* 2018;69:191–207. https://doi.org/10.1146/annurev-med-061516-121357
2. Leung D, Wurst JM, Liu T, Martinez RM, Datta-Mannan A, Feng Y. Antibody conjugates-recent advances and future innovations. *Antibodies.* 2020;9(1) https://doi.org/10.3390/antib9010002
3. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-Low advanced breast cancer. *New Engl J Med.* 2022;387(1):9–20. https://doi.org/10.1056/NEJMoa2203690
4. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *New Engl J Med.* 2021;384(16):1529–1541. https://doi.org/10.1056/NEJMoa2028485
5. Diamantis N, Banerji U. Antibody-drug conjugates–an emerging class of cancer treatment. *Br J Cancer.* 2016;114(4):362–367. https://doi.org/10.1038/bjc.2015.435
6. Baselga J, Lewis Phillips GD, Verma S, et al. Relationship between tumor biomarkers and efficacy in EMILIA, a phase III study of trastuzumab emtansine in HER2-Positive metastatic breast cancer. *Clin Cancer Res.* 2016;22(15):3755–3763. https://doi.org/10.1158/1078-0432.CCR-15-2499
7. Cortes J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med.* 2022;386(12):1143–1154. https://doi.org/10.1056/NEJMoa2115022
8. Schettini F, Chic N, Braso-Maristany F, et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer.* 2021;7(1):1. https://doi.org/10.1038/s41523-020-00208-2
9. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-Low breast cancer: pathological and clinical landscape. *J Clin Oncol.* 2020;38(17):1951–1962. https://doi.org/10.1200/JCO.19.02488
10. Abelman RO, Spring L, Fell GG, et al. Sequential use of antibody-drug conjugate after antibody-drug conjugate for patients with metastatic breast cancer: ADC after ADC (A3) study. *J Clin Oncol.* 2023;41(16) https://doi.org/10.1200/JCO.2023.41.16_suppl.1022
11. Bardia A, Hu X, Dent R, et al. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *New Engl J Med.* 2024;391(22):2110–2122. https://doi.org/10.1056/NEJMoa2407086
12. Tunkel D, Alade Y, Kerbavaz R, Smith B, Rose-Hardison D, Hoover-Fong J. Hearing loss in skeletal dysplasia patients. *Am J Med Genet A.* 2012;158A(7):1551–1555. https://doi.org/10.1002/ajmg.a.35373
13. Makawita S, Meric-Bernstam F. Antibody-Drug conjugates: patient and treatment selection. *Am Soc Clin Oncol Educ Book.* 2020(40):1–10. https://doi.org/10.1200/EDBK_280775 1548-8756.

14. Adair JR, Howard PW, Hartley JA, Williams DG, Chester KA. Antibody-drug conjugates - a perfect synergy. *Expert Opin Biol Ther.* 2012;12(9):1191–1206. https://doi.org/10.1517/14712598.2012.693473
15. Birrer MJ, Moore KN, Betella I, Bates RC. Antibody-Drug Conjugate-Based therapeutics: state of the science. *J Natl Cancer Inst.* 2019;111(6):538–549. https://doi.org/10.1093/jnci/djz035
16. Staudacher AH, Brown MP. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? *Br J Cancer.* 2017;117(12):1736–1742. https://doi.org/10.1038/bjc.2017.367
17. Tai YT, Mayes PA, Acharya C, et al. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. *Blood.* 2014;123(20):3128–3138. https://doi.org/10.1182/blood-2013-10-535088
18. Radocha J, van de Donk N, Weisel K. Monoclonal antibodies and antibody drug conjugates in multiple myeloma. *Cancers.* 2021;13(7) https://doi.org/10.3390/cancers13071571
19. Barok M, Joensuu H, Isola J. Trastuzumab emtansine: mechanisms of action and drug resistance. *Breast Cancer Res.* Mar 5 2014;16(2):209. https://doi.org/10.1186/bcr3621
20. Iwata TN, Ishii C, Ishida S, Ogitani Y, Wada T, Agatsuma T. A HER2-Targeting Antibody-Drug conjugate, trastuzumab deruxtecan (DS-8201a), enhances antitumor immunity in a mouse model. *Mol Cancer Ther.* 2018;17(7):1494–1503. https://doi.org/10.1158/1535-7163.MCT-17-0749
21. Fu Z, Li S, Han S, Shi C, Zhang Y. Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Signal Transduct Target Ther.* 2022;7(1):93. https://doi.org/10.1038/s41392-022-00947-7
22. Hempenius MA, Eenkhoorn MA, Hoeg H, et al. Quantitative comparison of immunohistochemical HER2-low detection in an interlaboratory study. *Histopathology.* 2024;85(6):920–928. https://doi.org/10.1111/his.15273
23. Salgado RF, Bardia A, Curigliano G, et al. LBA21 human epidermal growth factor receptor 2 (HER2)-low and HER2-ultralow status determination in tumors of patients (pts) with hormone receptor–positive (HR +) metastatic breast cancer (mBC) in DESTINY-Breast06 (DB-06). *Ann Oncol.* 2024;35:S1213–S1214. https://doi.org/10.1016/j.annonc.2024.08.2259
24. Farshid G, Armes J, Dessauvagie B, et al. Development and validation of a HER2-Low focused immunohistochemical scoring system with High-Interobserver concordance: The Australian HER2-Low breast cancer concordance study. *Mod Pathol.* 2024;37(8):100535. https://doi.org/10.1016/j.modpat.2024.100535
25. Cortes J, Hurvitz SA, Im SA, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial. *Nat Med.* 2024;30(8):2208–2215. https://doi.org/10.1038/s41591-024-03021-7
26. Fehm T, Cottone F, Dunton K, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): patient-reported outcomes from a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2024;25(5):614–625. https://doi.org/10.1016/S1470-2045(24)00128-1
27. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-Positive breast cancer. *New Engl J Med.* 2020;382(7):610–621. https://doi.org/10.1056/NEJMoa1914510
28. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *New Engl J Med.* 2012;367(19):1783–1791. https://doi.org/10.1056/NEJMoa1209124
29. Dieras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2017;18(6):732–742. https://doi.org/10.1016/S1470-2045(17)30312-1
30. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol.* 2017;18(6):743–754. https://doi.org/10.1016/S1470-2045(17)30313-3
31. Hurvitz SA, Modi S, Li W, et al. 377O a pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with brain metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03. *Ann Oncol.* 2023;34:S335–S336. https://doi.org/10.1016/j.annonc.2023.09.554
32. Harbeck N, Ciruelos E, Jerusalem G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. *Nat Med.* 2024;30(12):3717–3727. https://doi.org/10.1038/s41591-024-03261-7
33. Montemurro F, Delaloge S, Barrios CH, et al. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial(☆). *Ann Oncol.* 2020;31(10):1350–1358. https://doi.org/10.1016/j.annonc.2020.06.020
34. Rugo HS, Bardia A, Marme F, et al. Sacituzumab govitecan in hormone Receptor-Positive/Human epidermal growth factor receptor 2-Negative metastatic breast cancer. *J Clin Oncol.* 2022;40(29):3365–3376. https://doi.org/10.1200/JCO.22.01002
35. Rugo HS, Bardia A, Marme F, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2023;402(10411):1423–1433. https://doi.org/10.1016/S0140-6736(23)01245-X
36. Bardia A, Jhaveri K, Im SA, et al. Datopotamab deruxtecan versus chemotherapy in previously treated Inoperable/Metastatic hormone Receptor-Positive human epidermal growth factor receptor 2-Negative breast cancer: primary results from TROPION-Breast01. *J Clin Oncol.* 2025;43(3):285–296. https://doi.org/10.1200/JCO.24.00920
37. Curigliano G, Hu X, Dent RA, et al. Trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in patients (pts) with hormone receptor-positive (HR +), human epidermal growth factor receptor 2 (HER2)-low or HER2-ultralow metastatic breast cancer (mBC) with prior endocrine therapy (ET): primary results from DESTINY-Breast06 (DB-06). *J Clin Oncol.* 2024;42(17) https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA1000
38. Gennari A, Andre F, Barrios CH, et al. ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol.* 2021;32(12):1475–1495. https://doi.org/10.1016/j.annonc.2021.09.019
39. Poumeaud F, Morisseau M, Cabel L, et al. Efficacy of administration sequence: sacituzumab govitecan and trastuzumab deruxtecan in HER2-low metastatic breast cancer. *Br J Cancer.* 2024;131(4):702–708. https://doi.org/10.1038/s41416-024-02766-9
40. ESMO Open 2023;8(1).
41. Bardia A, Rugo HS, Tolaney SM, et al. Final results from the randomized phase III ASCENT clinical trial in metastatic Triple-Negative breast cancer and association of outcomes by human epidermal growth factor receptor 2 and trophoblast cell surface antigen 2 expression. *J Clin Oncol.* 2024;42(15):1738–1744. https://doi.org/10.1200/JCO.23.01409
42. Li G, Lei Z, Liao H, Ma X. DTx-based cardio-oncology rehabilitation for lung cancer survivors: a randomized controlled trial. *J Clin Oncol.* 2024;42(16_) https://doi.org/10.1200/JCO.2024.42.16_suppl.12024
43. *NCCN Breast.* 2024;v6.
44. Goldenberg DM, Cardillo TM, Govindan SV, Rossi EA, Sharkey RM. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). *Oncotarget.* 2015;6(26):22496–22512. https://doi.org/10.18632/oncotarget.4318
45. Manna M, Brabant M, Greene R, et al. Canadian expert recommendations on safety overview and toxicity management strategies for sacituzumab govitecan based on use in metastatic Triple-Negative breast cancer. *Curr Oncol.* 2024;31(9):5694–5708. https://doi.org/10.3390/curroncol31090422
46. Hurvitz SA, Hegg R, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. *Lancet.* 2023;401(10371):105–117. https://doi.org/10.1016/S0140-6736(22)02420-5
47. Wekking D, Porcu M, Pellegrino B, et al. Multidisciplinary clinical guidelines in proactive monitoring, early diagnosis, and effective management of trastuzumab deruxtecan (T-DXd)-induced interstitial lung disease (ILD) in breast cancer patients. *ESMO Open.* 2023;8(6):102043. https://doi.org/10.1016/j.esmoop.2023.102043
48. Natsuhara K, Vella M, Behr S, et al. 381P treatment rechallenge after grade 1 trastuzumab-deruxtecan related interstitial lung disease: a real-world experience. *Ann Oncol.* 2024;35:S378. https://doi.org/10.1016/annonc/annonc1579
49. D'Arienzo A, Verrazzo A, Pagliuca M, et al. Toxicity profile of antibody-drug conjugates in breast cancer: practical considerations. 2589-5370 (Electronic). *EClinicalMedicine.* 2023;62:102113. https://doi.org/10.1016/j.eclinm.2023.102113
50. Nguyen TD, Bordeau BM, Balthasar JP. Mechanisms of ADC toxicity and strategies to increase ADC tolerability. *Cancers.* 2023;15(3) https://doi.org/10.3390/cancers15030713
51. de Goeij BE, Lambert JM. New developments for antibody-drug conjugate-based therapeutic approaches. 1879-0372 (Electronic). *Curr Opin Immunol.* 2016;40:14–23. https://doi.org/10.1016/j.coi.2016.02.008
52. Rugo HS, Crossno CL, Gesthalter YB, et al. Real-World perspectives and practices for Pneumonitis/Interstitial lung disease associated with trastuzumab deruxtecan use in human epidermal growth factor receptor 2-Expressing metastatic breast cancer. *JCO Oncol Pr.* 2023;19(8):539–546. https://doi.org/10.1200/OP.22.00480
53. Zhu Y, Liu K, Wang K, Zhu H. Treatment-related adverse events of antibody-drug conjugates in clinical trials: a systematic review and meta-analysis. *Cancer.* 2023;129(2):283–295. https://doi.org/10.1002/cncr.34507
54. Pedersini R, Buffoni M, Petrelli F, et al. Gastrointestinal toxicity of antibody drug conjugates (ADCs) in metastatic breast cancer: a pooled analysis. *Clin Breast Cancer.* 2024;24(5):411–420. https://doi.org/10.1016/j.clbc.2024.04.003
55. Rugo H, Tokunaga E, Iwata H, et al. 267MO pooled analysis of trastuzumab deruxtecan (T-DXd) retreatment (RTx) after recovery from grade (Gr) 1 interstitial lung disease/pneumonitis (ILD). *Ann Oncol.* 2024;9. https://doi.org/10.1016/esmoop/esmoop103324
56. Bianchini G, Arpino G, Biganzoli L, et al. Emetogenicity of Antibody-Drug conjugates (ADCs) in solid tumors with a focus on trastuzumab deruxtecan: insights from an Italian expert panel. *Cancers.* 2022;14(4) https://doi.org/10.3390/cancers14041022
57. Heist RS, Sands J, Bardia A, et al. Clinical management, monitoring, and prophylaxis of adverse events of special interest associated with datopotamab deruxtecan. *Cancer Treat Rev.* 2024;125:102720. https://doi.org/10.1016/j.ctrv.2024.102720
58. Lindgren ES, Yan R, Cil O, et al. Incidence and mitigation of corneal pseudomicrocysts induced by Antibody-Drug conjugates (ADCs). *Curr Ophthalmol Rep.* 2024;12(2):13–22. https://doi.org/10.1007/s40135-024-00322-5
59. Pathak N. P1-02-02: Indirect comparison of sacituzumab govitecan (SG) and datopotamab deruxtecan (Dato-DXd) in advanced breast cancer (aBC): safety and efficacy analysis. presented at: SABCS poster; 2024;
60. Deklerck E, Denys H, Kreps EO. Corneal features in trastuzumab emtansine treatment: not a rare occurrence. *Breast Cancer Res Treat.* 2019;175(2):525–530. https://doi.org/10.1007/s10549-019-05179-y
61. Liu Z, Carvajal M, Carraway CA, Carraway K, Pflugfelder SC. Expression of the receptor tyrosine kinases, epidermal growth factor receptor, ErbB2, and ErbB3, in human ocular surface epithelia. *Cornea.* 2001;20(1):81–85. https://doi.org/10.1097/00003226-200101000-00016

62. Dy GK, Farooq AV, Kang JJ. Ocular adverse events associated with antibody-drug conjugates for cancer: evidence and management strategies. *Oncologist.* 2024;29(11):e1435–e1451. https://doi.org/10.1093/oncolo/oyae177
63. Krop I, Juric D, Shimizu T, et al. Abstract GS1-05: datopotamab deruxtecan in advanced/metastatic HER2- breast cancer: results from the phase 1 TROPION-PanTumor01 study. *Cancer Res.* 2022;82(4) https://doi.org/10.1158/1538-7445.Sabcs21-gs1-05
64. Schmid P, Jung KH, Wysocki PJ, et al. 166MO datopotamab deruxtecan (Dato-DXd) + durvalumab (D) as first-line (1L) treatment for unresectable locally advanced/metastatic triple-negative breast cancer (a/mTNBC): initial results from BEGONIA, a phase Ib/II study. *Ann Oncol.* 2022;33:S199. https://doi.org/10.1016/j.annonc.2022.03.185
65. Andre F, Cortes J, Curigliano G, et al. A pooled analysis of trastuzumab deruxtecan in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer with brain metastases. *Ann Oncol.* 2024;35(12):1169–1180. https://doi.org/10.1016/j.annonc.2024.08.2347
66. Hurvitz SA, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer patients with brain metastases from the randomized DESTINY-Breast03 trial. *ESMO Open.* 2024;9(5):102924. https://doi.org/10.1016/j.esmoop.2024.102924
67. Hurvitz SA, Bardia A, Punie K, et al. Subgroup analyses from the phase 3 ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer. *NPJ Breast Cancer.* 2024;10(1):33. https://doi.org/10.1038/s41523-024-00635-5
68. Dannehl D, Jakob D, Mergel F, et al. The efficacy of sacituzumab govitecan and trastuzumab deruxtecan on stable and active brain metastases in metastatic breast cancer patients-a multicenter real-world analysis. *ESMO Open.* 2024;9(5):102995. https://doi.org/10.1016/j.esmoop.2024.102995
69. Balinda HU, Kelly WJ, Kaklamani VG, et al. Sacituzumab govitecan in patients with breast cancer brain metastases and recurrent glioblastoma: a phase 0 window-of-opportunity trial. *Nat Commun.* 2024;15(1):6707. https://doi.org/10.1038/s41467-024-50558-9
70. Fenton MA, Tarantino P, Graff SL. Sequencing antibody drug conjugates in breast cancer: exploring future roles. *Curr Oncol.* 2023;30(12):10211–10223. https://doi.org/10.3390/curroncol30120743
71. Collins DM, Bossenmaier B, Kollmorgen G, Niederfellner G. Acquired resistance to antibody-drug conjugates. *Cancers.* 2019;11(3) https://doi.org/10.3390/cancers11030394
72. Guidi L, Pellizzari G, Tarantino P, Valenza C, Curigliano G. Resistance to antibody-drug conjugates targeting HER2 in breast cancer: molecular landscape and future challenges. *Cancers.* Feb 10 2023;15(4) https://doi.org/10.3390/cancers15041130
73. Andre F, Hee Park Y, Kim SB, et al. Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2023;401(10390):1773–1785. https://doi.org/10.1016/S0140-6736(23)00725-0
74. Huppert LA, Mahtani RL, Fisch SC, et al. Multicenter retrospective cohort study of the sequential use of the antibody-drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2-low metastatic breast cancer (MBC): updated data and subgroup analyses by age, sites of disease, and use of intervening therapies. 1083-1083 *J Clin Oncol.* 2024;42(16) https://doi.org/10.1200/JCO.2024.42.16_suppl.1083
75. Mai N, Klar M, Ferraro E, et al. Real world outcomes of sequential ADC therapy in metastatic breast cancer: patients treated with sacituzumab govitecan and trastuzumab deruxtecan. 1085-1085 *J Clin Oncol.* 2024;42(16) https://doi.org/10.1200/JCO.2024.42.16_suppl.1085