# Tailoring ADC Therapies Across the HER2 Spectrum in Metastatic Breast Cancer

A PATIENT/CLINICIAN DECISION SUPPORT AID

## Sample Questions for Clinicians to Pose to Patients to Facilitate Shared Decision-Making

- What do you already know and understand about breast cancer?
- Are there any aspects of treatment that you are worried about?
- Are you able to tolerate the treatment we've chosen? If not, why not? How can we provide improved support to enhance your treatment?
- Do you understand the risks and benefits of the different treatment choices we are considering? What else would you like to know about them?
- Are you experiencing any side effects related to your treatment? How has this impacted your lifestyle and quality of life?
- What goals do you have regarding your cancer treatment?

## Sample Questions for Patients to Pose to Clinicians to Facilitate Shared Decision-Making

- Will you tell me about the risks and benefits of the different treatments that we are talking about?
- How do these treatments work?
- What can I expect from the treatments that we are discussing?
- Is there a treatment option that you prefer, and if so, why?
- Are there any ongoing clinical trials that I might benefit from? If there are, where can I learn more about them?
- If I want to consult another physician or other providers before making a treatment decision, do you have any recommendations?
- What financial burden will these treatment options present to me?

Additional questions to pose to your clinician are available from the NCCN Guidelines for Patients (Metastatic Breast Cancer), pages 60-68. This document is available at: https://nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf.

Potential questions to pose to the healthcare team are also available at the Cancer.Net website, https://www.cancer.net/cancer-types/breast-cancer/questions-ask-health-care-team.

## Overview of FDA Approved ADCs in Metastatic Breast Cancer to Help Facilitate Discussion and Collaborative Decision-Making

| Agent | mBC Indications for Adult Patients | NCCN Guideline Statements | Key Trial Results |
|---|---|---|---|
| Trastuzumab deruxtecan (T-DXd) | Unresectable or metastatic HER2+ BC treated with a prior anti-HER2-based regimen in metastatic setting<br><br>Unresectable or metastatic HER2-low BC treated with prior chemotherapy in metastatic setting | Second line: HR+/- and HER2+ unresectable stage IV disease, as well as HER2 IHC 1+ or 2+/ISH- mBC with visceral crisis or endocrine refractory<br><br>Second line: no germline BRCA1/2 mutation and HER2 IHC 1+ or 2+/ISH- mTNBC<br><br>Also possible for first line or later lines in select cases | HER2+: DESTINY-Breast 039 Improved ORR and PFS in patients pretreated with trastuzumab + taxane vs. T-DM1<br><br>HER2-low: DESTINY-Breast 04 Improved ORR, PFS, and OS vs. PC |
| Trastuzumab emtansine (T-DM1) | HER2+ MBC treated previously with trastuzumab and a taxane, separately or in combination. Patients should have received prior therapy for metastatic disease | Third-line and beyond for HR+/-, HER2+ unresectable/ stage IV disease. If not a candidate for T-DXd, T-DM1 could be considered in the second-line | EMILIA Improved PFS and OS relative to lapatinib + capecitabine with less toxicity in patients with HER2+ advanced BC |
| Sacituzumab govitecan (SG) | Unresectable la/ metastatic TNBC treated with ≥2 prior systemic therapies, at least 1 for metastatic disease<br><br>HR+/HER2- IHC 0, IHC 1+ or IHC 2+/ ISH–) la/mBC treated with endocrine based therapy and ≥2 additional systemic therapies in the metastatic setting | Second-line for select patients with HR+ and HER2- unresectable or stage IV (M1) disease with visceral crisis or endocrine refractory<br><br>or metastatic TNBC | TROPiCS-02 Subgroup analysis in HER2-low<br><br>Patients with HER2-low, HR+ BC receiving SG had superior median PFS and ORR relative to PC |

BC, breast cancer; HER2, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; la, locally advanced; mBC, metastatic breast cancer; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PC, physician's choice of treatment; TNBC triple negative breast cancer.

## Select ADC-Associated Adverse Events and Management Strategies

| ADC | Black Box Warnings | Potential Management Approaches |
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| T-DXd | ILD, pneumonitis | • Monitor for any signs or symptoms including cough, dyspnea, fever, or other signs of new/deteriorating respiratory symptoms.<br>• Patients should report these symptoms immediately.<br>• Permanently discontinue T-DXd in patients with grade ≥2 ILD/ pneumonitis. |
| T-DM1 | Hepatotoxicity, cardiac toxicity, embryo-fetal toxicity | • Monitor hepatic function before starting and before each dose.<br>• Modify dosing or discontinue as appropriate.<br>• Assess LVEF prior to initiation, and monitor. Withhold or discontinue treatment as appropriate. |
| SG | Severe/life-threatening neutropenia and severe diarrhea | • Withhold for ANC <1500/$mm^3$ or neutropenic fever.<br>• Monitor blood cell counts periodically during treatment; G-CSF should be considered for secondary prophylaxis.<br>• Immediately start anti-infective treatment for patients with febrile neutropenia immediately.<br>• Monitor patients with diarrhea; give fluids/electrolytes as needed; begin workup for infectious causes; initiate loperamide if not infectious.<br>• For severe diarrhea, withhold SG until resolved to ≤ Grade 1 and lower subsequent doses. |

ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

## Glossary of Key Terms

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|---|---|
| ADC | Antibody-drug conjugate; a cancer treatment consisting of a target-specific monoclonal antibody linked to a cytotoxic molecule payload. |
| IHC | Immunohistochemistry: Method of detecting HER2 expression through protein-binding monoclonal or polyclonal antibodies |
| FISH | Fluorescence in-situ hybridization: Method of evaluating HER2 gene amplification using fluorescence microscopy in which DNA probes are created, labeled, and hybridized to target tissue |
| HER2 | Human epidermal growth factor receptor 2: membrane tyrosine kinase and oncogene that is amplified/overexpressed in approximately 1 in 5 breast cancer cases |
| HER2-low | Human epidermal growth factor receptor 2-low: a potential new nomenclature for breast cancer that has been characterized in the medical literature as IHC 1+ or 2+ with negative ISH |
| HER2-positive | Human epidermal growth factor receptor 2-positive: a subtype of breast cancer marked by HER2 overexpression on IHC evaluation (3+) and/or gene amplification on an in situ hybridization assay on at least one tumor sample. For patients with an IHC2+ score, reflex ISH testing is required to define HER2 status. |

## Importance of Molecular Testing and Patient Counseling

- Histopathologic and molecular features of breast cancer can guide treatment selection.
- HER2 status is a key treatment selection driver, and expression varies widely.
  - Often evaluated with immunohistochemistry (IHC) and molecular analysis with fluorescence in situ hybridization (FISH).
  - Tumors may not be characterized accurately based on conventional testing, particularly with lower degrees of HER2 expression/amplification; new assays and testing approaches may help to optimize tumor characterization and treatment selection.

## Tactics for Weighing the Risks and Benefits of Therapy Selection

- Patient-centered communication is essential to balance risks and benefits of therapy.
- Improving patient knowledge of key treatment aspects, understanding patient cognitive and emotional needs, and implementing shared decision making can be beneficial when selecting treatment options.
  - Agency for Healthcare Research and Quality SHARE Approach:

    **S**eeking out the participation of the patient

    **H**elping the patient to explore and compare therapeutic options

    **A**ssessment of patient preferences and values

    **R**eaching a decision with the patient, and

    **E**valuating the decision of the patient

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