

Redefining Treatment Across the Spectrum of HR+/HER2-Expressing Metastatic Breast Cancer

A SHARED DECISION-MAKING POCKET REFERENCE GUIDE

Importance of Molecular Testing and Patient Counseling^{1,2}

- 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^{3,4}

- 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:
 - Seeking out the participation of the patient
 - Helping the patient to explore and compare therapeutic options
 - Assessment of patient preferences and values
 - Reaching a decision with the patient, and
 - Evaluating the decision of the patient

Glossary of Key Terms

ADC	Antibody-drug conjugate: A cancer treatment consisting of a target-specific monoclonal antibody linked to a cytotoxic molecule payload ¹⁴
IHC	Immunohistochemistry: Method of detecting HER2 expression through protein-binding monoclonal or polyclonal antibodies ¹⁵
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 ¹⁵
HER2	Human epidermal growth factor receptor 2: Membrane tyrosine kinase and oncogene that is amplified/overexpressed in approximately 1 in 5 breast cancer cases ¹⁵
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 ¹⁶
HER2-ultra low	Human epidermal growth factor receptor 2-ultra low: A potential new nomenclature for breast cancer that has been characterized in the medical literature as IHC 0 with faint, partial membrane staining in $\leq 10\%$ of tumor cells ¹¹
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 IHC 2+ score, reflex ISH testing is required to define HER2 status. ¹

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

ADC	mBC Indications for Adult Patients ^{6,7}	NCCN Guideline Statements ⁸	Key Trial Results
Trastuzumab deruxtecan (T-DXd)	<p>Unresectable or metastatic HER2+ BC treated with a prior anti-HER2-based regimen in the metastatic setting or in the neoadjuvant or adjuvant setting with disease recurrence during or within 6 months of completing therapy.</p> <p>Unresectable or metastatic HER2-low BC treated with prior chemotherapy in the metastatic setting or in the adjuvant setting with disease recurrence during or within 6 months of completing therapy.</p>	<p>Second line: HR+/- and HER2+ unresectable or stage IV disease, as well as HR+ and HER2 IHC 1+ or 2+/ ISH- unresectable or stage IV disease (Category 1, preferred)</p> <p>Second line: no germline <i>BRCA1/2</i> mutation and HER2 IHC 1+ or 2+/ ISH- unresectable or stage IV TNBC (Category 1, preferred)</p> <p>May be considered in the first-line or later-line settings for select patients</p>	<p>HER2+ DESTINY-Breast 03⁹ Improved ORR and PFS in patients pretreated with trastuzumab + taxane vs. T-DM1</p> <p>HER2-low DESTINY-Breast 04¹⁰ Improved ORR, PFS, and OS vs. PC</p> <p>HER2-low/HER2-ultra low DESTINY-Breast 06¹¹ Improved ORR and PFS vs. PC</p>
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 or developed disease recurrence during or within 6 months of completing adjuvant therapy.	Third-line and beyond: HR+/- and HER2+ unresectable or stage IV disease; if not a candidate for T-DXd, T-DM1 could be considered in the second-line	EMILIA ¹² Improved PFS and OS relative to lapatinib + capecitabine with less toxicity in patients with HER2+ advanced BC
Sacituzumab govitecan (SG)	<p>Unresectable la/metastatic TNBC treated with ≥2 prior systemic therapies, at least 1 for metastatic disease.</p> <p>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.</p>	<p>Second-line: HR+ and HER2- unresectable or stage IV disease who are not candidates for T-DXd (Category 1, preferred)</p> <p>Second-line: unresectable or stage IV TNBC (Category 1, preferred)</p>	TROPiCS-02 Subgroup analysis in HER2-low ¹³ Patients with HER2-low, HR+ BC receiving SG had superior median PFS and ORR relative to PC

ADC, antibody-drug conjugate; BC, breast cancer; HER2, human epidermal growth factor receptor 2; 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 Strategies⁵⁻⁷

ADC	Black Box Warnings	Potential Management Approaches
T-DXd	ILD, pneumonitis, and embryo-fetal toxicity	<ul style="list-style-type: none"> • Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms • Permanently discontinue T-DXd in all patients with grade ≥ 2 ILD/pneumonitis • Advise patients of the risk and to immediately report symptoms
T-DM1	Hepatotoxicity, cardiac toxicity, and embryo-fetal toxicity	<ul style="list-style-type: none"> • Monitor hepatic function before starting and before each dose • Modify dosing or permanently discontinue as appropriate • Assess LVEF prior to initiation, and monitor; withhold dosing or discontinue treatment as appropriate
SG	Neutropenia and diarrhea	<ul style="list-style-type: none"> • Withhold for ANC $< 1500/\text{mm}^3$ or neutropenic fever • Monitor blood cell counts periodically during treatment; G-CSF should be considered for secondary prophylaxis • Immediately start anti-infective treatment for patients with febrile neutropenia • Monitor patients with diarrhea; give fluids/electrolytes as needed; begin workup for infectious causes; initiate loperamide if not infectious • For severe diarrhea, withhold SG until resolved to \leq grade 1 and lower subsequent doses

ADC, antibody-drug conjugate; 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.

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?

I Sample Questions for Patients to Pose to Clinicians to Facilitate Shared Decision-Making^{17,18}

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 54-62. 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.org website, <https://www.cancer.org/cancer/types/breast-cancer/understanding-a-breast-cancer-diagnosis/questions-to-ask-your-doctor-about-breast-cancer.html>

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