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HER2 Immunohistochemistry Testing in Metastatic Breast Cancer: Guiding Treatment Decisions and the Role of Sacituzumab Govitecan

Description:
The purpose of this document is to discuss the clinical utility and implications of human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) testing in metastatic triple-negative breast cancer (mTNBC) and metastatic hormone receptor-positive HER2-negative (mHR+/HER2-) breast cancer. It also reviews current treatment approaches for these two subsets of metastatic breast cancer, with a focus on the role of sacituzumab govitecan (SG).

Background:

- HER2 is commonly overexpressed on the surface of breast cancer cells and HER2 testing should be performed on all new primary or newly metastatic breast cancers[1]
- HER2 testing occurs in a two-step process: first with IHC, then with in-situ hybridization (ISH) testing if IHC results are uncertain or equivocal (see table below)[1,2]

Table 1. HER2 protein expression by IHC assay[1,2]

Score	Description	Interpretation
0	No membrane staining observed	HER2 negative/null
0+	Faint/barely perceptible incomplete staining in <10% of tumor cells	HER2 ultralow Treat as HER2 negative
1+	Faint/barely perceptible incomplete membrane staining in >10% of tumor cells	HER2 low Treat as HER2 negative
2+	Weak to moderate complete membrane staining in >10% of tumor cells Or Complete membrane staining that is intense but within ≤10% of tumor cells	HER2 equivocal → reflex to FISH testing If ISH negative: HER2 low If ISH positive: HER2 positive
3+	Intense, complete circumferential membrane staining in >10% of tumor cells	HER2 positive

- HER2-negative and HER2-low (IHC 1+ or 2+/FISH negative) tumors may be considered for treatment with antibody drug conjugate (ADC) therapy, including SG, in the second line or beyond setting
- In the phase III ASCENT trial[4] (SG vs physician choice, single-agent chemotherapy in mTNBC patients)
    - SG improved PFS and OS in both HER2 IHC0 and HER2-Low patients
    - ORR was improved for SG vs chemotherapy in HER2 IHC0 and HER2-Low patients

PQI Process:

- Confirm HER2 and HR status
- Evaluate prior lines of therapy and performance status
- Determine appropriate treatment recommendations based on patient's biomarker results and treatment history

Table 2. Guideline-Recommended Treatment for mTNBC[1]

Setting	Biomarker	Regimens
First Line	PD-L1 CPS ≥ 10 regardless of germline BRCA 1/2 mutation status	• Chemotherapy + Pembrolizumab (category 1, preferred) • **Sacituzumab govitecan** + pembrolizumab **(preferred)**
	PD-L1 CPS < 10; no germline BRCA 1/2 mutation	• **Sacituzumab govitecan (category 1, preferred)** • Datopotamab deruxtecan (other recommended) • Systemic chemotherapy
Second Line	Germline BRCA 1/2 mutation	• PARP inhibitor (category 1, preferred)
	Any	• **Sacituzumab govitecan (category 1, preferred)** • Systemic chemotherapy or targeted agents
	No germline BRCA 1/2 mutation HER2 IHC 1+ or 2+/FISH-	• Fam-trastuzumab deruxtecan *(other recommended regimen)*

Table 3. Guideline-Recommended Treatment for endocrine refractory mHR+/HER2-negative disease[1]

Setting	Biomarker	Regimens
Second Line	HER2 IHC 1+ or 2+/ISH negative	• Fam-trastuzumab deruxtecan (category 1, preferred)
	HER2 IHC 0+	• Fam-trastuzumab deruxtecan (other recommended regimen)
	Not a candidate for fam-trastuzumab deruxtecan	• **Sacituzumab govitecan (category 1, preferred)** • Systemic chemotherapy • Targeted therapy • For HER2 IHC 0, 1+, or 2+/FISH negative: Datopotamab deruxtecan *(other recommended regimen)*

If proceeding with SG[3]:

- SG is a trophoblast cell-surface antigen 2 (TROP2) directed ADC linked to a topoisomerase I inhibitor chemotherapy payload
- TROP2 does not require biomarker testing; it is found in high amounts of the surface of breast cancer cells
- Administer SG 10 mg/kg IV on Days 1 and 8 of a 21-day cycle
- Boxed warnings for diarrhea and neutropenia
- Patients with UGT1A1*28 genotype and reduced UGT1A1 activity and are at increased risk for toxicity
- High emetic risk: provide prophylactic antiemetics
- Risk of febrile neutropenia: provide primary G-CSF prophylaxis if patient has additional risk factors (prior chemotherapy, age > 65, renal dysfunction, etc)

Patient-Centered Activities:

- Discuss the importance and implications of HER2 testing, including how results influence treatment selection
- Review the NCODA PQI document, *Sacituzumab govitecan: Prophylaxis and Management of Adverse Events*, prior to providing patient education
- Provide chemotherapy patient education sheet for sacituzumab govitecan
- Reinforce importance of early symptom reporting (e.g., diarrhea, nausea/vomiting, fever, fatigue)

References:

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.4.2025.
2. Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update. J Clin Oncol. 2023 Aug 1;41(22):3867-3872. doi: 10.1200/JCO.22.02864.
3. Trodelvy® (sacituzumab govitecan) [prescribing information]. Foster City, CA: Gilead Sciences Inc; March 2025.
4. 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 May 20;42(15):1738-1744. doi: 10.1200/JCO.23.01409.