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CHALLENGING CASES

Breast Cancer

Challenging Cases in Breast Cancer

Presented by Dr. Edith A. Perez

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The information presented is consistent with FDA Guidelines and includes the latest clinical trial data

This program has been provided as an opportunity for discussion and learning, with insights from key opinion leaders

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Challenging Cases in Breast Cancer

Presented virtually on
December 11th 2023

HR+ HER2-Low Breast Cancer

Patient Case: from initial dx to adjuvant treatment

- *Adjuvant management*
- *Cross comparison of clinical trial data and impact on treatment decisions*
- *Awareness of new clinical trials*
- *Impact of repeat HER2 testing on therapeutic decisions*

Note: Aggregated results and discussion are based on 7 oncologists and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated

Patient History

67-year-old female

Initial diagnosis:

June 2018

Resected Stage 3 disease

Hypertension

Non-smoker

Diagnostics

Tissue biopsy

HER2 IHC 0

ER +: 80%

PR +: 20%

PD-L1: CPS 30

ECOG PS 0

CPS=combined positive score

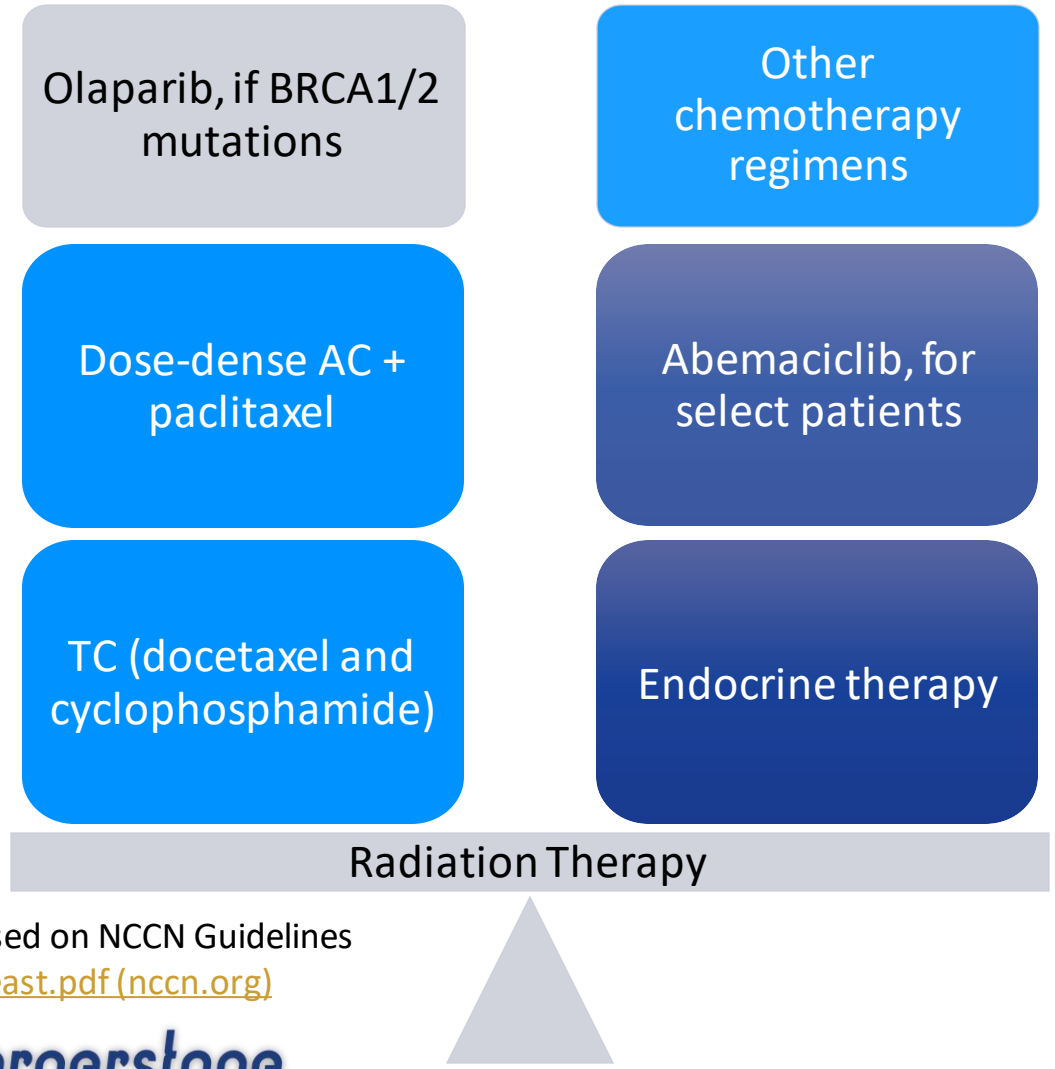
What adjuvant treatment do you initially recommend?

Open-text Response Results from HCP Participants

What adjuvant treatment do you initially recommend?

- *Chemo followed by anti-estrogen plus CDK 4/6 inhibitor*
- *Chemo followed by AI plus CDK 4/6 inhibitor*
- *Chemo followed by antiestrogen plus CDK 4/6 inhibitor*
- *AI*
- *AC then taxol*
- *Onco type*
- *I would ask for oncotype or mammaprint first*

HR+/HER2neg: Adjuvant Treatment Options



Based on NCCN Guidelines
breast.pdf (nccn.org)

Sequence of therapies in the adjuvant setting:

- Chemotherapy and endocrine + CDK 4/6 targeting therapy should be given sequentially, with endocrine/CDK 4/6i Rx after chemoRx
- 1 year of adjuvant olaparib can be given concurrently with endocrine therapy
- In patients with HR+/HER2-, high-risk breast cancer (ie, those with ≥4+ nodes (confirmed preoperatively and/or at surgery), or 1–3+ nodes with one or more of the following: grade 3 disease, tumor size ≥5 cm (on pre-operative imaging and/or at surgery) 2 years of adjuvant abemaciclib can be considered in combination with endocrine therapy (category 1).
- In patients eligible for both adjuvant olaparib and abemaciclib, the optimal sequence is not known
- Sequencing of RT with systemic therapy:
  - It is common for RT to follow chemotherapy when chemotherapy is indicated
  - Sequential or concurrent endocrine therapy with RT is acceptable

COMPARISON

CDK4/6 Inhibitors in the Adjuvant Setting

	Palbociclib (IBRANCE®)		Ribociclib (KISQALI®)	Abemaciclib (VERZENIO®)
FDA approval	*Not in adjuvant*		*Not in adjuvant*	***Approved*** [in combination with ET (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence]
Study	**PENELOPE-B**	**PALLAS**	**NATALEE**	**MONARCH-E**
Study Design	Palbociclib + ET vs ET alone		Ribociclib + NSAI vs NSAI alone	Abemaciclib + ET vs ET alone
Sample Size	1250	5600	5000	4580
Duration of Rx	1 year	2 years	3 years	2 years

Eligibility	• HR+, HER2-negative primary breast cancer without a pathological complete response after taxane-containing NACT
	• At high risk of relapse
	  • clinical pathological staging-estrogen receptor grading score ≥ 3 or 2 and ypN+
		• Stage II – III HR+/HER2-
		• Completion of prior surgery, ± chemotherapy, RT
		• Within 12 months of diagnosis, within 6 months of starting adjuvant ET
			• Pre/postmenopausal women and men with HR+/HER2- EBC
			• Stage IIA
			  • Either N0 with grade 2 and Ki-67 ≥20%, Oncotype DX RS ≥26, or high risk via genomic risk profiling, N0 with grade 3, or N1
			• Stage IIB (N0 or N1)
			• Stage III disease (N0, N1, N2, or N3)
			• Prior ET up to 12 mo permitted, prior (neo)adjuvant CT permitted
				• Women or men with high-risk, node-positive, HR+/HER2- EBC
				• Prior (neo)adjuvant CT permitted
				• Pre- or postmenopausal
				• No distant metastasis
				• ≤16 mo from surgery to randomization
				• ≤12 wk of ET after last non-ET

Median follow-up (months)	42.8	43	17.7	42
iDFS HR (95% CI) (ITT)	**0.93** (0.74 – 1.17)	**0.96** (0.81-1.14)	**0.75** (0.62 – 0.91), *P* 0.0014	**0.65** (0.57 – 0.75), *P* 0.0001
iDFS HR (95% CI) (by Stage)	---	**IIA**: **0.75** (0.48 – 1.19), NS	**II**: **0.76** (0.53 – 1.1)	---
iDFS HR (95% CI) (by node)	---	---	**N0**: **0.63** (0.36-1.65)	---

NS: not significant

Sacituzumab govitecan (SG)

Current Breast Cancer FDA indications

Sacituzumab govitecan (SG), an antibody-drug conjugate (ADC): the topoisomerase 1 inhibitor SN-38 (active metabolite of irinotecan) is linked to a humanized monoclonal antibody targeting the tumor antigen Trop2 and is currently approved for

- Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease
- Unresectable locally advanced or metastatic hormone receptor (HR+), HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting

Sacituzumab govitecan (SG) in HR+/HER2- Breast Cancer			
Neoadjuvant	**NeoSTAR** Phase 2	Status: Recruiting	TNBC data reported. Planned arms include Sacituzumab govitecan +/- pembrolizumab for patients with HR+ breast cancer
Adjuvant	**SASCIA** Phase 3	Status: Recruiting	Sacituzumab govitecan vs treatment of physician´s choice (TPC, defined as capecitabine or platinum-based chemotherapy) for eight cycles or observation
Post-endocrine MBC	**ASCENT-07** Phase 3	Status: Recruiting	Sacituzumab govitecan vs Treatment of Physician's Choice in Patients with HR+)/ HER2- (HER2 IHC0 or HER2-low [IHC 1+, IHC 2+/ISH-]) Inoperable, Locally Advanced, or MBC and Have Received Endocrine Therapy
Post-endocrine MBC	**TROPICS-02** Phase 3	Status: Completed	Sacituzumab govitecan vs Treatment of Physician's Choice (TPC) in Subjects with HR+ HER-MBC who Have Tumor progression at Least 2 Prior Chemotherapy Regimens

Trastuzumab deruxtecan (T-DXd)

Current Breast Cancer FDA indications

Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate (ADC): a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of:

- Adult patients with unresectable or metastatic HER2+ breast cancer who have received a prior anti-HER2-based regimen either:
  - in the metastatic setting, or
  - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
- Adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

Trastuzumab deruxtecan (T-DXd) Trials in HR+/HER2- Breast Cancer			
Neoadjuvant	**TRIO-US B-12 TALENT** Phase 2	Status: Recruiting	Randomized, open-label, two-stage, phase II neoadjuvant trial for early stage, HR+, HER2-low (1+ or 2+ by IHC) BC of neoadjuvant T-DXd either alone or in combination with endocrine therapy
Post-endocrine MBC	**DESTINY-Breast06** Phase 3	Status: Active, not recruiting	Trastuzumab deruxtecan vs investigator's choice chemotherapy in HER2-low, HR+ breast cancer patients whose disease has progressed on endocrine therapy in the metastatic setting.
Post-endocrine MBC	**DESTINY-Breast15** Phase 3	Status: Not yet recruiting	Trastuzumab deruxtecan (T-DXd) in participants with HER2-low or HER2 IHC 0 (who are either HR- or HR+) unresectable and/or MBC

69-year-old

Metastatic diagnosis:

- February 2020

Progression

Site of Metastases:

- Liver

Tissue biopsy of liver lesion

Liquid biopsy

Let's discuss IHC of new metastatic lesions on first progression

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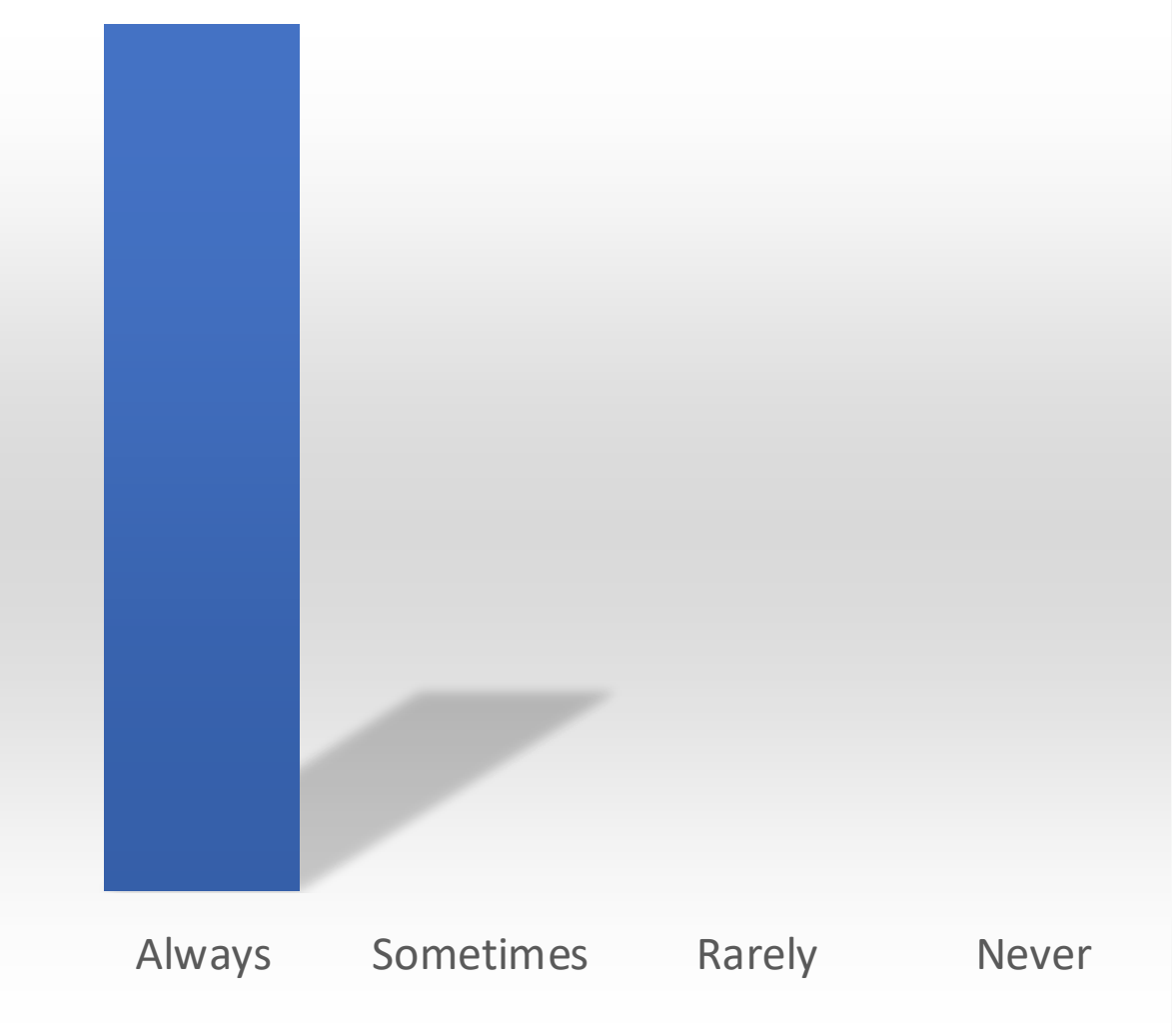
Open-text Response Results from HCP Participants

How often do you test new metastatic lesions on first tumor recurrence (progression)?



Discussion with HCP Participants

How often do you test new metastatic lesions on first tumor recurrence (progression)?

- *5 years ago, I never tested! Now I always test*
- *Tissue if possible, or liquid*
- *ER and PR can change as well as HER2 result*
- *NGS especially when refractory*

Open-text Response Results from HCP Participants

What tests do you typically order?

- *Guardant blood*
- *Guardant*
- *Liquid biopsy, Guardant 360*
- *ER, PR, HER2 by IHC; Next generation: PIK3CA, ESR1, usually used Tempus or Guardant*
- *Tempus*
- *Tempus or Guardant*
- *Caris or Guardant if no tissue*
- *NGS tissue and liquid. Caris or Guardant*

Discussion with HCP Participants

What tests do you typically order?

Reflex to FISH for IHC1+?

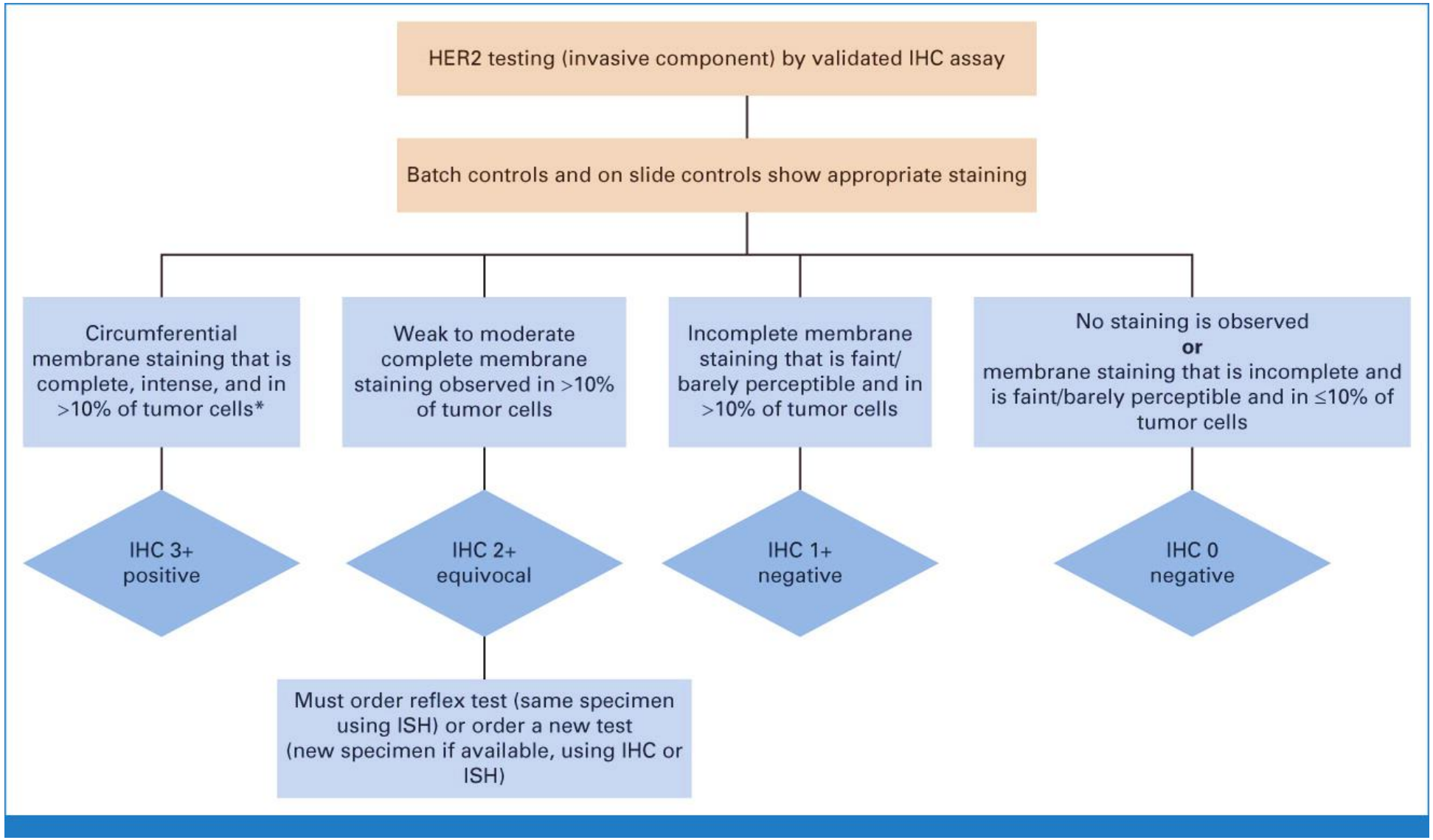
- *Local lab do both IHC and FISH on everyone*
- *Yes, do FISH on everyone*
- *No, do not reflex to FISH on IHC 1+. Should I?*

KOL recommendations:

- *Reflex to FISH for patients that are IHC 1+*

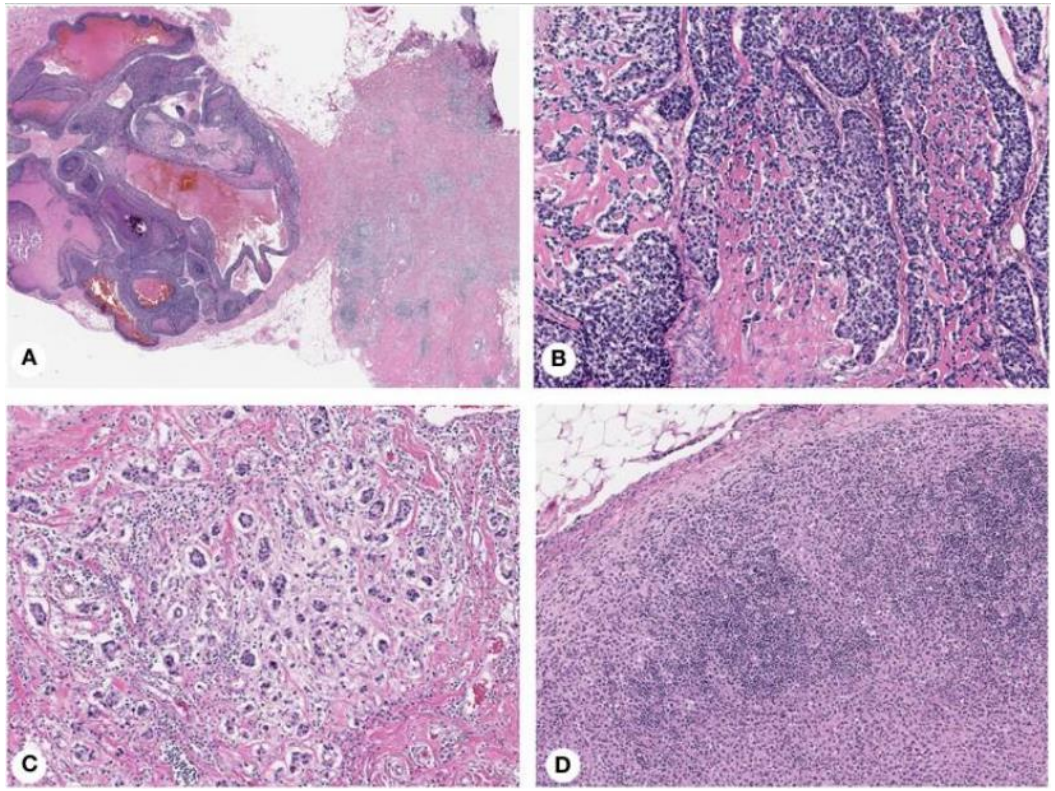
HER2 Immunohistochemistry (IHC) Testing Best Practices Recommendations

Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update | Journal of Clinical Oncology (ascopubs.org)



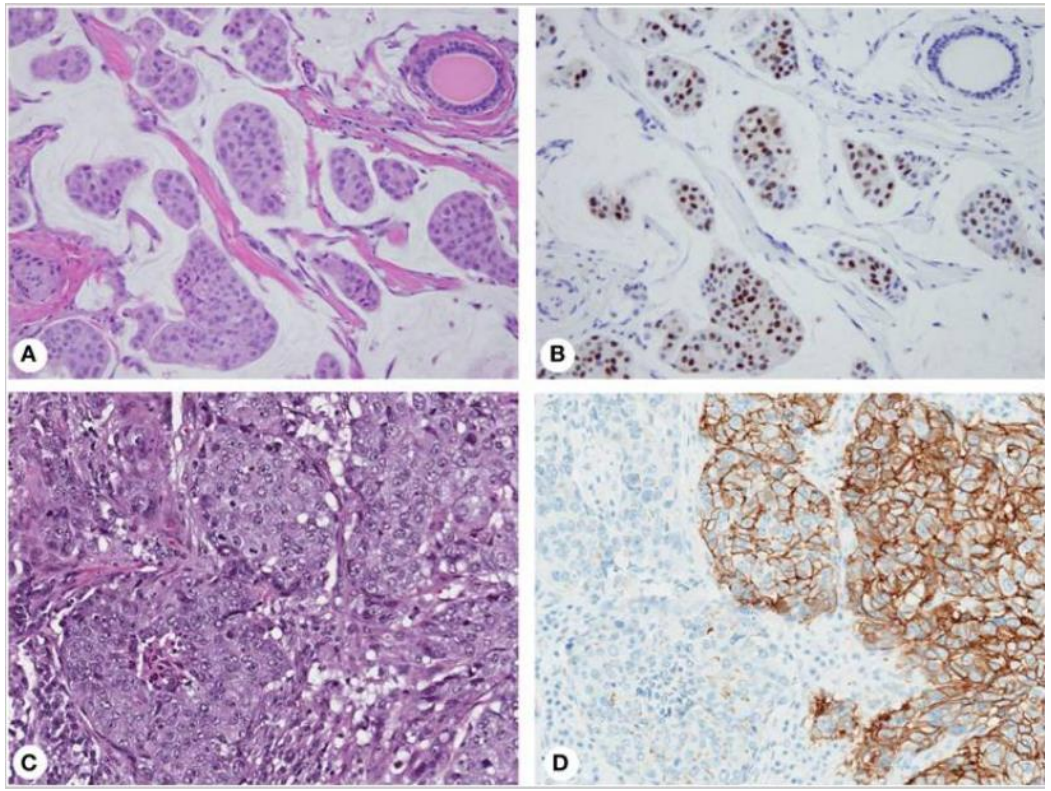
DOI: 10.1200/JCO.22.02864 *Journal of Clinical Oncology* 41, no. 22 (August 01, 2023) 3867-3872.

Tumor heterogeneity in breast cancer



Histopathologic heterogeneity of breast cancer: invasive mammary carcinoma with mixed morphology **(A)**, composed of basaloid areas with osteoid production **(B)** and ductal not otherwise specified **(C)** components. Lymph node metastasis showing a diffuse pattern of tumor growth **(D)**. Magnification: 100× **(A)**, 200× **(B–D)**; Hematoxylin-eosin staining.

Biomarker heterogeneity of breast cancer



Biomarker heterogeneity of breast cancer: mucinous carcinoma (A) with variable expression of estrogen receptor from no immunoreactivity to nuclear staining with weak to strong intensity (B); invasive ductal carcinoma (C) with areas of 3+ (positive) and 1+ (negative) membranous staining for human epidermal growth factor receptor 2 (D). Magnification: 200× (A–D); hematoxylin-eosin staining (A,C) and immunohistochemistry (B,D).

Front Med (Lausanne). 2017; 4: 227.

HER2 Immunohistochemistry (IHC) Testing Best Practices Recommendations

ASCO–College of American Pathologists Guideline Update 2023

HER2 expression (e.g., HER2-Low, HER2-Ultra-Low)

- Best practices to distinguish IHC 0 from 1+ are now clinically relevant
- HER2 testing update affirms prior HER2 reporting recommendations and offers a new HER2 testing reporting comment to highlight the current relevance of IHC 0 versus 1+ results and best practice recommendations to distinguish these often subtle differences (see reporting "Recommended comment" and "Example" in **The Bottom Line** box)

*"Medical oncologists can also consider HER2 IHC results on **prior or concurrent primary samples (or other metastatic sites)** because there may be **heterogeneity** in HER2 expression levels **between samples** and because **metastatic cancer tissue samples may suffer from preanalytic conditions** that are not as well monitored as in primary breast tissue samples."*

ASCO-CAP Update 2023

Pre-analytical Variables:

- Tissue handling
- Type of fixation
- Duration of fixation
- Control samples

Analytical Variables:

- Inter-assay variability
- Inter- and intra-observer variability

*"After a negative HER2 test result on initial biopsy sample, consider **retesting on subsequent surgical or other additional sample** if the initial sample was suboptimal (e.g., minimal invasive cancer was present, cold ischemic time or fixation was suboptimal), testing error is expected, additional samples contain higher grade morphologically distinct cancer from the biopsy, **to rule out heterogeneity in a high-grade cancer, or if it will otherwise aid in clinical decision-making**"*

NCCN Guidelines Versions 4.2023

References:

- Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update | Journal of Clinical Oncology (ascopubs.org)
- breast.pdf (nccn.org)

Note: Current strategy is to continue using anti-HER2 Rx if the initial bx was + and subsequent ones are "negative" - an important area of research for the past 20 years!

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Discussion with HCP Participants

How do you manage a patient with HER2+ status initially that becomes IHC 1+ on progression?

- *Once HER2 positive always HER2 positive*
- *Tumor variability (heterogeneity) can impact test results; treat as HER2 positive*
- *Dependent on patient presentation – treat differently if bone only disease compared to more aggressive disease*
- *Experienced the opposite HER2 status change as well, going form HER2 negative to HER2 positive*

KOL thoughts:

- *If a patient changes HER2 status on progression (from HER2 positive to HER2 negative), can still benefit with HER2 -targeted treatment*
- *T-DXd has been shown to elicit a response across all IHC status but highest response is observed with IHC3+*
- *Heterogeneity of disease should be considered when reviewing test results*

Key Takeaways

HR+ HER2-Low Breast Cancer

Patient Case: from initial dx to adjuvant treatment

- *Chemotherapy followed by aromatase inhibitor plus CDK4/6 inhibitor is the most common adjuvant treatment*
  - *Initial NGS testing can direct treatment decisions and should be considered*
- *Testing and retesting drives treatment strategies*
  - *Testing on first progression is standard*
  - *Reflex to Fish should be considered for IHC 1+ HER2 status*
  - *Heterogeneity of tumor tissue should be considered*
- *Awareness of clinical trial data provides new treatment options for patients*

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