cornerstone specialty network™

CHALLENGING CASES

HR+ HER2-low Breast Cancer

Challenging Cases conducted: April 8, April 16, April 22, and May 14, 2025

Challenging Cases in…

Breast Cancer

Program conducted:
April – May 2025

Note: Aggregated results and high-level summary based on 4 practices (21 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of presentation.

Participating Practices

• Fort Wayne Medical Oncology Hematology (n=5)	April 8, 2025
• The Center for Cancer and Blood Disorders (n=5)	April 16, 2025
• Ironwood Cancer & Research Centers (n=6)	April 22, 2025
• Northwest Cancer Centers (n=5)	May 14, 2025

High-level Summary

Challenging Cases in…

Breast Cancer

- Most advisors determine a patient has endocrine-resistant disease 6-12 months after starting initial endocrine therapy treatment, which will lead to consideration of other strategies
- After tumor progression on endocrine therapy, almost all order testing or retesting to determine next treatment option
  - ESR1 mutations are rare (~5%) at diagnosis but can emerge in up to 40% of cases after endocrine exposure
    - Liquid biopsy (blood-based tissue) test is best done on blood rather than tissue. Recommended to do biopsy at every progression because ESR1 mutations are something that can be acquired later on.
  - Frequent detection of PIK3CA mutations after prior endocrine exposure. Phosphoinositide 3-Kinase mutation is often identified in tissue or blood biopsy.
    - PI3K inhibitors are difficult to tolerate for many patients, with GI toxicities often limiting use despite confirmed mutations.
  - Advisors always or most of the time test/ retest for HER2 status on progression
    - Tissue testing is preferred with archived tissue if fresh is not available as liquid biopsies can miss HER2 expression
    - Some advisors noted challenges when requesting a revisit of HER2 staining from pathologists; however, there's increasing national awareness and CAP guidance supporting re-evaluation.
- Once a patient is identified as endocrine refractory (tumor progression on all endocrine therapy), advisors move to ADC therapies or chemotherapy if fast control is needed for a limited time (e.g., liver mets)

High-level Summary

Challenging Cases in…

Breast Cancer

- In general, T-DXd is the preferred ADC in HR+ HER2-low, endocrine-refractory patients after progression on endocrine therapy and CDK4/6 inhibitors.
  - Durability of response noted in multiple cases, with some advisors sharing long-term responders (50+ doses) and responses in patients near hospice.
  - Physicians comfortable using ENHERTU early post-CDK4/6i progression, sometimes even before traditional chemotherpay, due to its efficacy and tolerability.
  - The risk of pneumonitis (~9-10%) with T-DXd presented some concern in selection, although most clinicians have not experienced significant issues; careful selection and monitoring emphasized especially for patients with prior pneumonitis or on oxygen
- ENHERTU is the preferred option for endocrine-refractory HR+ HER2-low patients with brain or bone metastases.
- Most are currently used to sequencing T-DXd followed by sacituzumab govitecan (SG); other options include chemotherapy or Dato-DXd.
  - Sequencing is guided by disease bulk, prior toxicity, and urgency of response.
  - No clear standard ADC sequencing yet, but success with SG in post-ENHERTU setting is emerging.
- Some noted patient preference such as hair loss (younger patients with social life) can impact decision to utilize T-DXd; others noted challenges with sides effects with SG although some patients "cruise through"; others noted challenges with capecitabine that can be alleviated with creative dosing as well as the use of diclofenac gel for associated foot and mouth; olanzapine was noted by at least two advisors as effective at controlling nausea when given nightly at 2.5 mgs

Challenging Cases in…

Breast Cancer

HR+ HER2-Low Breast Cancer

Patient Case: Advanced disease

- Diagnostic and therapeutic considerations after endocrine-based therapy for advanced disease
- What role do ADCs play in the management of patients with HR+/HER2 low advanced breast cancer?
  - How could they be sequenced to optimize patient outcomes?

Initial Case Presentation

Patient Data

- ***69-year-old***
  - ECOG PS: 1
  - Past Hx: Hypertension
  - Non-smoker
- **Metastatic diagnosis**
  - *February 2022*
- **Site of 3 mets**
  - *Liver*

Diagnostics

- HER2: IHC 1+
- ER +: 80%
- PR+: 20%
- PD-L1: CPS 30

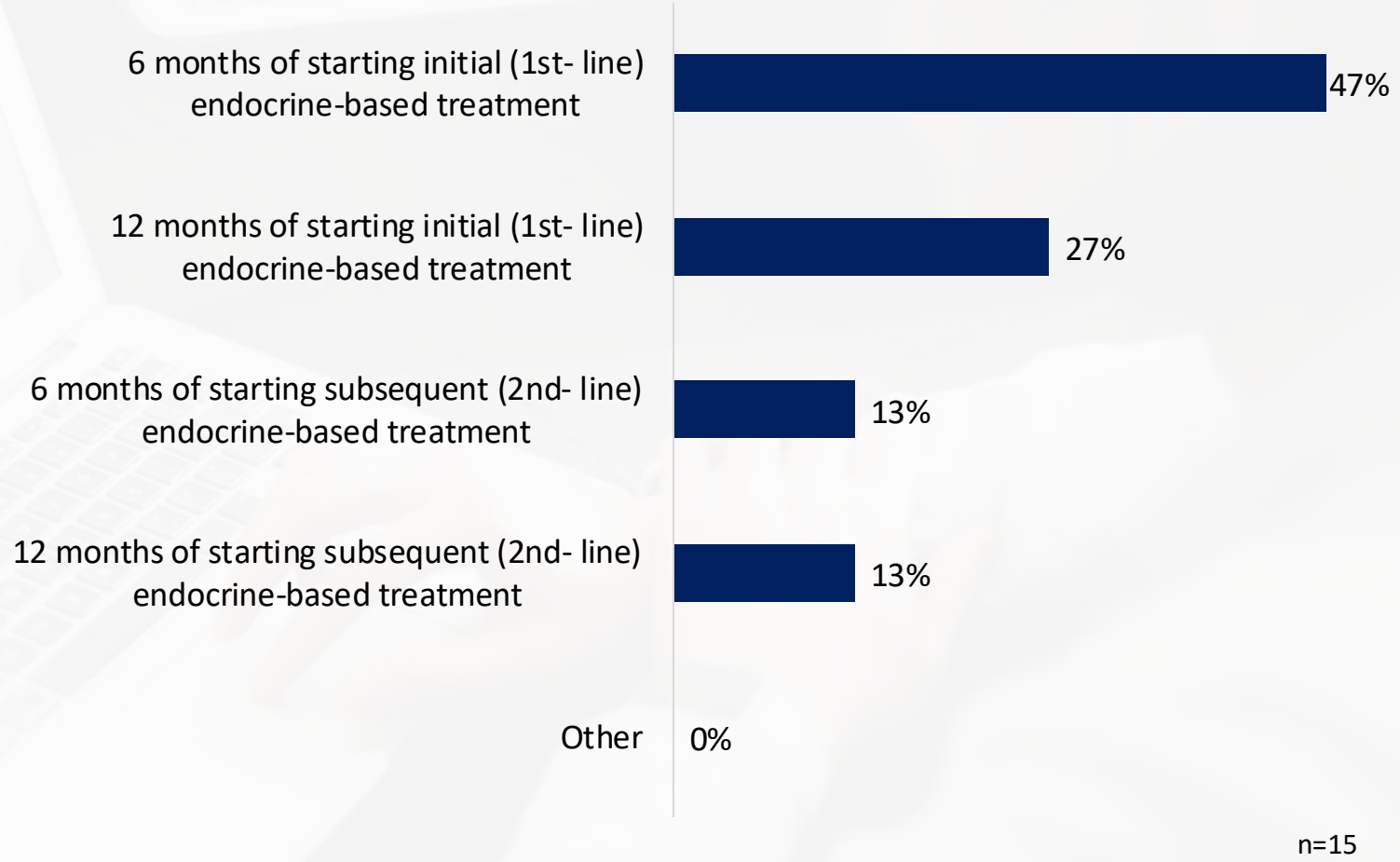
Initial metastatic treatment:

Endocrine therapy + CDK4/6 inhibitor

CPS = combined positive score

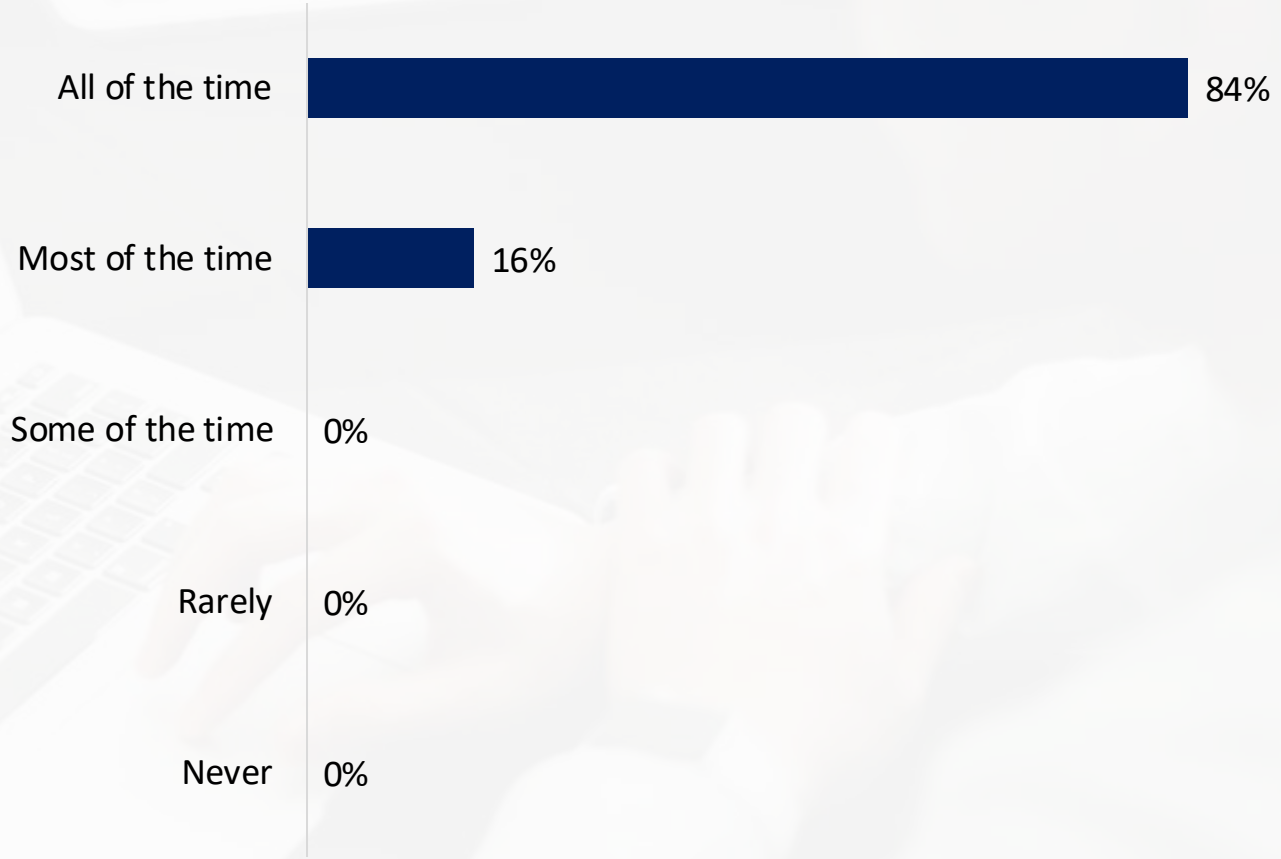
ARS Results from HCP Participants

At what point do you determine a patient has endocrine resistant disease, which will lead to consideration of other strategies?



ARS Results from HCP Participants

Do you order NGS testing, including evaluation for PIK3CA/AKT1/PTEN-alterations and ESR1 mutation before deciding your next treatment option after tumor progression to one endocrine therapy?



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Targeted Treatments: EMERALD, CAPItello-291, INAVO120

HR+/HER2-	***EMERALD*** (elacestrant)		***CAPItello-291*** (capivasertib)		***INAVO120*** (inavolisib)	
Indication	***January 27, 2023:**, the FDA approved **elacestrant** (Orserdu, Stemline Therapeutics, Inc.) for postmenopausal women or adult men with ER+, HER2-neg, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.*		***November 16, 2023**: the FDA approved **capivasertib** (Truqap, AstraZeneca Pharmaceuticals) **with fulvestrant** for adult patients with HR+, HER2-neg locally advanced or MBC with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy*		**October 10, 2024:** the FDA approved **inavolisib** (Itovebi, Genentech, Inc.) with **palbociclib and fulvestrant** for adults with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.	
Study Design	**Elacestrant (n=115)**	**SOC endocrine monotherapy of investigator's choice (n=113)**	**Capivasertib plus fulvestrant (n=355)**	**Placebo plus fulvestrant (n=353)**	**Inavolisib + palbociclib and fulvestrant (n=161)**	**Placebo + palbociclib and fulvestrant (n=164)**
Median PFS, months	**3.8** months	**1.9** months	**7.3** months	**3.1** months	**15.0** months	**7.3** months
	HR **0.55** (95% CI: 0.39 – 0.77; *P*=0.0005)		HR **0.50** (95% CI: 0.38 – 0.65; *P*=0.0001)		HR **0.43** (95% CI: 0.32 – 0. 59; *P*<0.0001)	
Median OS,	*OS at interim analysis: not statistically significant*		*OS immature*		*OS immature*	
With prior CDK4/6i	**8.61** months (n=78)	**1.91** months (n=81)	**5.5** months (n=248)	**2.6** months (n=248)	---	
	HR **0.41** (95% CI: 0.26 – 0.63)		HR **0.59** (0.48-0.72)			
Without Prior CDK4/6i	---	---	**10.9** months (n=107)	**7.2** months (n=105)		
			HR **0.59** (0.48-0.72)			

J Clin Oncol. 2022 Oct 1; 40(28): 3246–3256. N Engl J Med. 2023 Jun 1;388(22):2058-2070 N Engl J Med. 2024 Oct 31;391(17):1584-1596

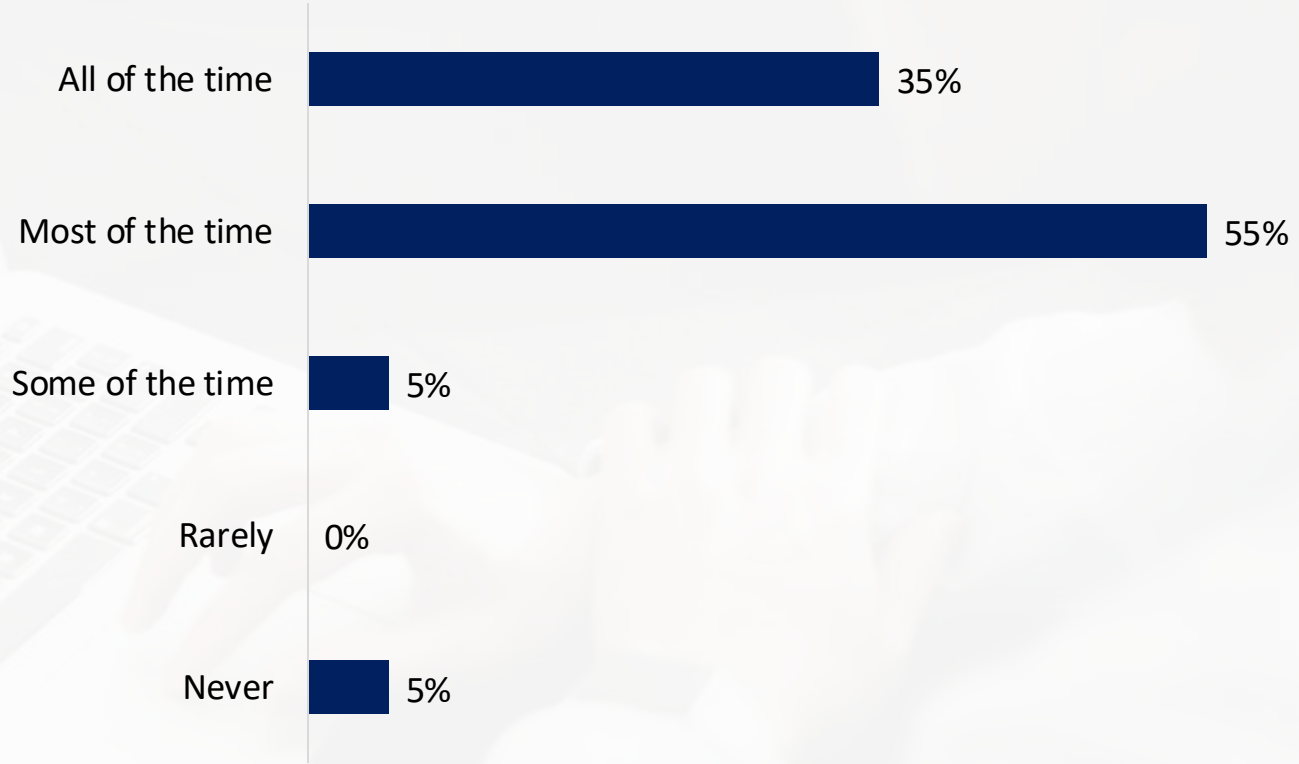
Highlights of Prescribing Information

	ORSERDU™ (elacestrant)	TRUQAP® (capivasertib)	ITOVEBI (inavolisib)
Black box warnings	**None**	**None**	**None**
Contraindications	**None**	Severe hypersensitivity to TRUQAP or any of its components	**None**
Warnings And Precautions	• Dyslipidemia • Embryo-Fetal Toxicity	• Hyperglycemia • Diarrhea • Cutaneous Adverse Reactions • Embryo-Fetal Toxicity	• Hyperglycemia • Stomatitis • Diarrhea • Embryo-Fetal Toxicity
Adverse reactions	**(>10%)** Musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia	**(>20%)** Diarrhea, cutaneous adverse reactions, increased random glucose, decreased lymphocytes, decreased hemoglobin, increased fasting glucose, nausea, fatigue, decreased leukocytes, increased triglycerides, decreased neutrophils, increased creatinine, vomiting and stomatitis.	**(>20%)** Decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache
Drug Interactions	Strong and Moderate CYP3A4 Inducers and Inhibitors	Strong CYP3A Inhibitors Moderate CYP3A Inhibitors Strong and Moderate CYP3A Inducers	---
Specific Populations	Avoid in: Lactation, Hepatic impairment	Avoid in: Lactation	Avoid in: Lactation

How do adverse events influence your treatment decision between available targeted therapies?

ARS Results from HCP Participants

Do you test or retest for HER2 status on progression?



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NCCN Guidelines
Version 3.2025 — March 18, 2025

PRINCIPLES OF BIOMARKER TESTING
HER2 TESTING[a,b]

- HER2 testing should be performed on all new primary or newly metastatic breast cancers using methodology outlined in the ASCO/CAP HER2 testing guideline.[a]
- A re-review of the pathology with consideration for repeat or consultative HER2 testing should be made if a Grade 1 (any histologic type), pure mucinous, pure tubular, or pure cribriform carcinoma tests HER2-positive.[a]
- 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 (eg, 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.[a]

HER2 testing by validated immunohistochemistry (IHC) assay[b,c]

- IHC 0,1+[d] → HER2 (-)
- IHC 2+ → Equivocal result → Must reflex test with ISH (if same specimen), or order new test with IHC or dual probe ISH (if new specimen available).
- IHC 3+ → HER2 (+)

HER2 testing by validated dual-probe[e] ISH assay[b,c]

- **HER2-Negative:**
  - (Group 5) HER2/CEP17 ratio <2.0 AND average HER2 copy number <4.0 signals/cell
- **HER2-Negative[f] (Determined by concurrent IHC and ISH results):**
  - (Group 2) HER2/CEP17 ratio ≥2.0 AND average HER2 copy number <4.0 signals/cell and concurrent IHC 0-1+ or 2+
  - (Group 3) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥6.0 signals/cell and concurrent IHC 0-1+
  - (Group 4) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 0-1+ or 2+
- **HER2-Positive[f] (Determined by concurrent IHC and ISH results):**
  - (Group 2) HER2/CEP17 ratio ≥2.0 AND average HER2 copy number <4.0 signals/cell and concurrent IHC 3+
  - (Group 3) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥6.0 signals/cell and concurrent IHC 2+ or 3+
  - (Group 4) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 3+
- **HER2-Positive:**
  - (Group 1) HER2/CEP17 ratio ≥2.0 AND average HER2 copy number ≥ 4.0 signals/cell

[a] NCCN endorses the ASCO/CAP HER2 testing guideline. "Principles of HER2 Testing" modified with permission from Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36:2105-2122.
[b] Laboratory must participate in a quality assurance accreditation program for HER2 testing. Otherwise, tissue specimen should be sent to an accredited laboratory for testing. Health care systems and providers must cooperate to ensure the highest quality testing.
[c] Evidence from trastuzumab adjuvant trials show that HER2 testing by ISH or IHC have similar utility to predict clinical benefit from HER2-targeted therapy.
[d] The distinction between HER2 IHC 0 with no membrane staining from IHC 0+ with faint, partial membrane staining in ≤10%, 1+, or 2+/ISH negative results (on primary or metastatic samples) is currently clinically relevant since patients with metastatic disease may be eligible for treatment targeting non-amplified levels of HER2 expression.
[e] Single-probe ISH assays are not preferentially recommended but if used, cases with average HER2 copy number ≥4.0 and <6.0 signals/cell should base final results on concurrent IHC and if 2+ reflexed to dual probe ISH testing.
[f] For ISH Groups 2–4 final ISH results are based on review of concurrent IHC, with recounting of the ISH test by a second reviewer if IHC is 2+ (per 2018 CAP/ASCO Update recommendations). Additional report comments are recommended for negative final results in these ISH groups.

Note: All recommendations are category 2A unless otherwise indicated.

BINV-A
1 OF 2

d The distinction between HER2 IHC 0 with no membrane staining from IHC 0+ with faint, partial membrane staining in ≤10%, 1+, or 2+/ISH negative results (on primary or metastatic samples) is currently clinically relevant since patients with metastatic disease may be eligible for treatment targeting non-amplified levels of HER2 expression.

Discuss challenges with identification and reporting of HER2 IHC 0+

Case Presentation (tumor progression after ET)

Progression

- ***71-year-old***
  - *ECOG PS 1*
- ***Subsequent metastatic progression***
- ***Site of Mets:***
  - *Liver, lung, bone*

Diagnostics

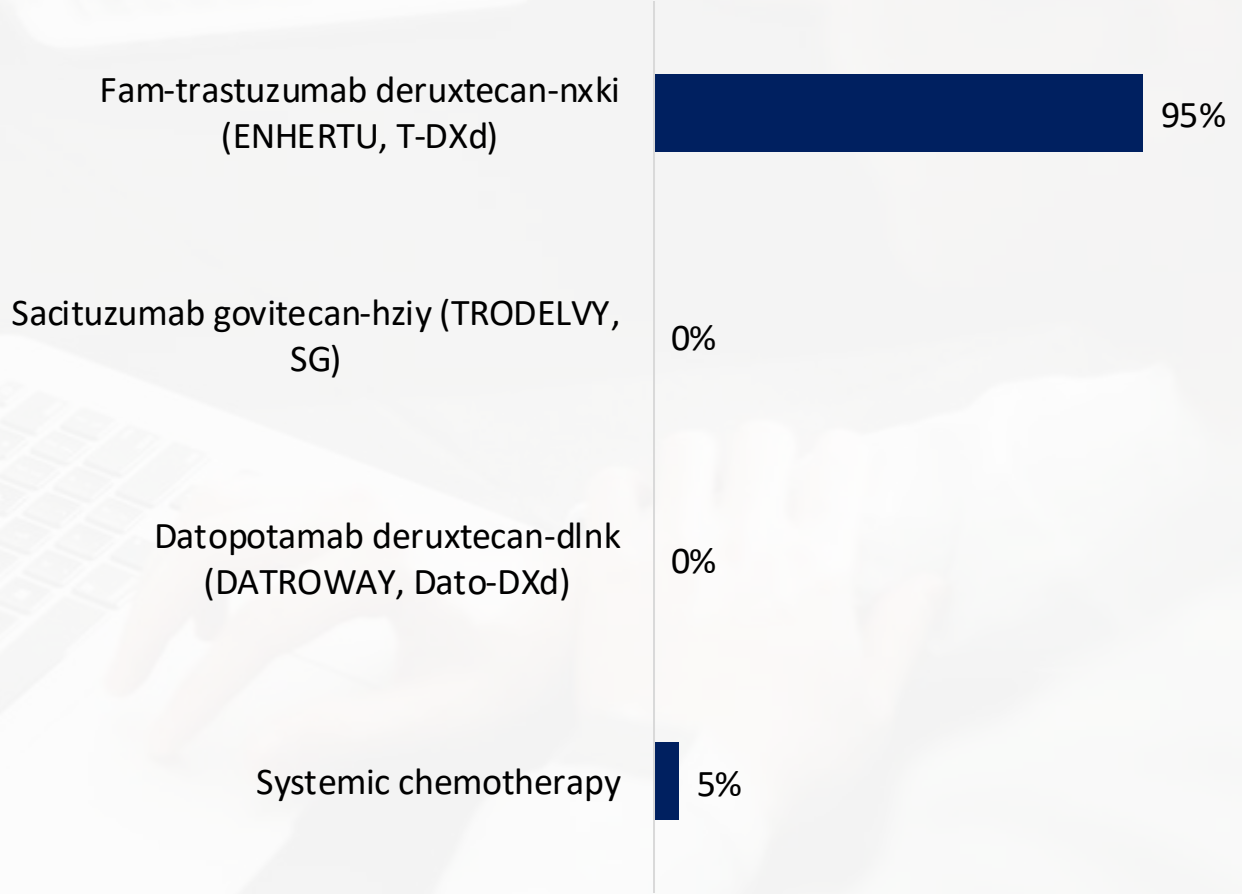
- ***New tissue biopsy:***
  - HER2 IHC 1+
  - ER +: 80%
  - PR+: 20%
  - PD-L1: CPS 15%
- No targetable mutations

What treatment do you recommend on subsequent progression?

ET = endocrine therapy

ARS Results from HCP Participants

What treatment do you recommend on subsequent progression (after exhausting endocrine-based and / or targeted therapy)?



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NCCN Guidelines
Version 3.2025 — March 18, 2025

SYSTEMIC THERAPY FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis[†] or Endocrine Refractory		
See BINV-Q (1) for Considerations for Systemic Therapy.		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b] and/or HER2 IHC 0+, 1+, or 2+/ISH negative[d]	Systemic chemotherapy[e] (category 1, preferred) BINV-Q (5), or fam-trastuzumab deruxtecan-nxki[e,f] (other recommended regimen)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 0+, 1+, or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[f] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan-nxki	Sacituzumab govitecan[g] (Category 1, preferred)
		Systemic chemotherapy BINV-Q (5)
		Targeted therapy BINV-Q (6) and BINV-Q (7)
		For HER2 IHC 0, 1+, or 2+/ISH negative:[d] Datopotamab deruxtecan-dlnk[h] (other recommended regimen)
Third Line and beyond	Any	Systemic chemotherapy BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents and emerging biomarker options BINV-Q (6), BINV-Q (7), and BINV-Q (8)

[†] According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1623-1649) for advanced breast cancer visceral crisis is defined as: "severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy."

[a] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.
[b] Assess for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARPi therapy.
[c] PARPi can be considered for a later line for those with germline BRCA1/2 mutation, however available evidence suggests it is more effective if used earlier.
[d] Principles of HER2 Testing (BINV-A). The distinction between HER2 test results of IHC 0 with no membrane staining, IHC 0+ with faint, partial membrane staining in ≤10%, IHC 1+, or 2+/ISH negative is currently clinically relevant for therapy selection.
[e] Systemic chemotherapy (eg, oral chemotherapy) is generally preferred in the first-line setting. Selection of systemic therapy versus fam-trastuzumab-nxki for first-line therapy should be individualized based on clinical features and patient preference.
[f] Fam-trastuzumab deruxtecan-nxki may be used for HER2 IHC 0+, 1+ or 2+/ISH negative, previously treated with at least one line of endocrine-based therapy in the metastatic setting. Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.
[g] Sacituzumab govitecan-hziy may be used after prior treatment including endocrine therapy, a CDK4/6 inhibitor, and at least two lines of chemotherapy, one of which was a taxane, and at least one of which was in the metastatic setting. It may be considered for later line if not used as second line therapy.
[h] Datopotamab deruxtecan-dlnk is indicated as second- or subsequent-line therapy for those who have received a prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease. Datopotamab deruxtecan-dlnk did not meet the OS endpoint in the TROPION-Breast01 trial. Whereas the previously approved antibody drug conjugates (ADC), fam-trastuzumab deruxtecan-nxki and sacituzumab govitecan have shown a benefit in OS in randomized phase III trials. The benefit of using datopotamab deruxtecan-dlnk in patients with prior ADC treatment are not known as the TROPION-Breast01 trial did not include patients with prior ADC treatment.

Note: All recommendations are category 2A unless otherwise indicated.

e Systemic chemotherapy (eg, oral chemotherapy) is generally preferred in the first-line setting. Selection of systemic therapy versus fam-trastuzumab-nxki for first-line therapy should be individualized based on clinical features and patient preference. f Fam-trastuzumab deruxtecan-nxki may be used for HER2 IHC 0+ 1+ or 2+/ISH neg

Does NCCN Guidelines influence your treatment decision in the first line setting?

Payer challenges?

TROPION-Breast01 vs TROPiCS-02 vs DESTINY-Breast04 vs DESTINYBreast06

HR+/HER2-	DESTINY-Breast06 (T-DXd)		TROPION-Breast01 (Dato-DXd)		TROPiCS-02 (Saci)		DESTINY-Breast04 (T-DXd)	
Indication	**January 27, 2025:** for adult patients with **unresectable or metastatic HR-positive, HER2-low (IHC 1+ or IHC 2+/ISH-) or HER2 ultralow (IHC 0 with membrane staining)** breast cancer, as determined by an FDA-approved test, that has **progressed on one or more endocrine therapies** in the metastatic setting.		**January 17, 2025**: for adult patients with **unresectable or metastatic, HR-positive, HER2-negative (IHC 0, IHC1+ or IHC2+/ISH-) breast cancer** who have received **prior endocrine-based therapy and chemotherapy** for unresectable or metastatic disease.		**February 3, 2023**: for patients with unresectable locally **advanced or metastatic HR-positive, 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.		**August 5, 2022:** for adult patients with **unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer** who have received **a prior chemotherapy** in the metastatic setting or developed **disease recurrence during or within six months** of completing adjuvant chemotherapy.	
Study Design	**T-DXd vs TPC** **HR+, HER2-low or HER2-ultralow** **IHC 0 with membrane staining, IHC 1+ or IHC 2+/ISH-** **Chemotherapy-naïve**		**Dato-DXd vs TPC** **HR+, HER2 negative** **IHC 0, IHC 1+ or IHC 2+/ISH-** **1-2 lines of chemotherapy**		**SG vs TPC** **HR+, HER2 negative** **IHC 0, IHC 1+ or IHC 2+/ISH-** **2-4 previous lines of chemotherapy**		**T-DXd vs TPC** **HR+, HER2-low** **IHC 1+ or IHC 2+/ISH-** **1-2 lines of chemotherapy**	
N with HR+ tumor	**436** **[Low 359: ultralow 77]**	**430** **[Low 354: ultralow 76]**	**365**	**367**	**272**	**271**	**331**	**163**
Median PFS, mo	**13.2**	8.1	**6.9**	4.9	**5.5**	4.0	**10.1**	5.4
	HR **0.64**; 95% CI: 0.54, 0.76; P<0.0001		HR **0.63** (0.52-0.76) *P* < 0.0001		HR **0.66** (0.53-0.83) *P* = 0.0003		HR **0.51** (0.40-0.64) *P* < 0.0001	
Median OS, mo	*OS data not mature*		*OS data not mature*		**14.4**	11.2	**23.9**	17.5
					HR **0.79** (0.65-0.96) *P* = 0.02		HR **0.64** (0.48-0.86) *P* = 0.0028	
ORR, %	**62.6%**	34.3%	**36.4%**	22.9%	**21%**	14%	**52.9%**	16.6%

Bardia et al., N Engl J Med. 2024;391(22):2110-2122 | Bardia et al., Future Oncol. (2023) 20(8), 423–436 | Rugo et al., Lancet. 2023 Oct 21;402(10411):1423-1433. | Modi et al., N Engl J Med. 2022 Jul 7;387(1):9-20.

TPC: physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine (TROPiCS-02 and TP01/ paclitaxel, or nab-paclitaxel (DB04))

Highlights of Prescribing Information

	ENHERTU® (fam-trastuzumab deruxtecan-nxki)	DATROWAY® (datopotamab deruxtecan-dlnk)	TRODELVY® (sacituzumab govitecan-hziy)
Black box warnings	**Interstitial Lung Disease** **Embryo-fetal toxicity**	**None**	**Neutropenia** **Diarrhea**
Contraindications	None	None	Severe hypersensitivity reaction
Warnings And Precautions	• Neutropenia • Left Ventricular Dysfunction	• Interstitial Lung Disease (ILD) and Pneumonitis • Ocular Adverse Reactions • Stomatitis/Oral Mucositis • Embryo-Fetal Toxicity	• Hypersensitivity and Infusion-Related Reactions • Nausea/Vomiting • Patients with Reduced UGT1A1 Activity • Embryo-Fetal Toxicity
Adverse reactions	**(>20%)** Decreased white blood cell count, nausea, decreased hemoglobin, decreased neutrophil count, decreased lymphocyte count, fatigue, decreased platelet count, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood alkaline phosphatase, vomiting, alopecia, constipation, decreased blood potassium, decreased appetite, diarrhea, and musculoskeletal pain.	**(>20%)** Stomatitis, nausea, fatigue, decreased leukocytes, decreased calcium, alopecia, decreased lymphocytes, decreased hemoglobin, constipation, decreased neutrophils, dry eye, vomiting, increased ALT, keratitis, increased AST, and increased alkaline phosphatase	**(>25%)** Decreased leukocyte count, decreased neutrophil count, decreased hemoglobin, diarrhea, nausea, decreased lymphocyte count, fatigue, alopecia, constipation, increased glucose, decreased albumin, vomiting, decreased appetite, decreased creatinine clearance, increased alkaline phosphatase, decreased magnesium, decreased potassium, and decreased sodium.
Drug Interactions	---	---	UGT1A1 inhibitors or inducers
Specific Populations	Avoid in: Lactation, Females and Males of Reproductive Potential	Avoid in: Lactation, Females and Males of Reproductive Potential	Avoid in: Lactation

https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true

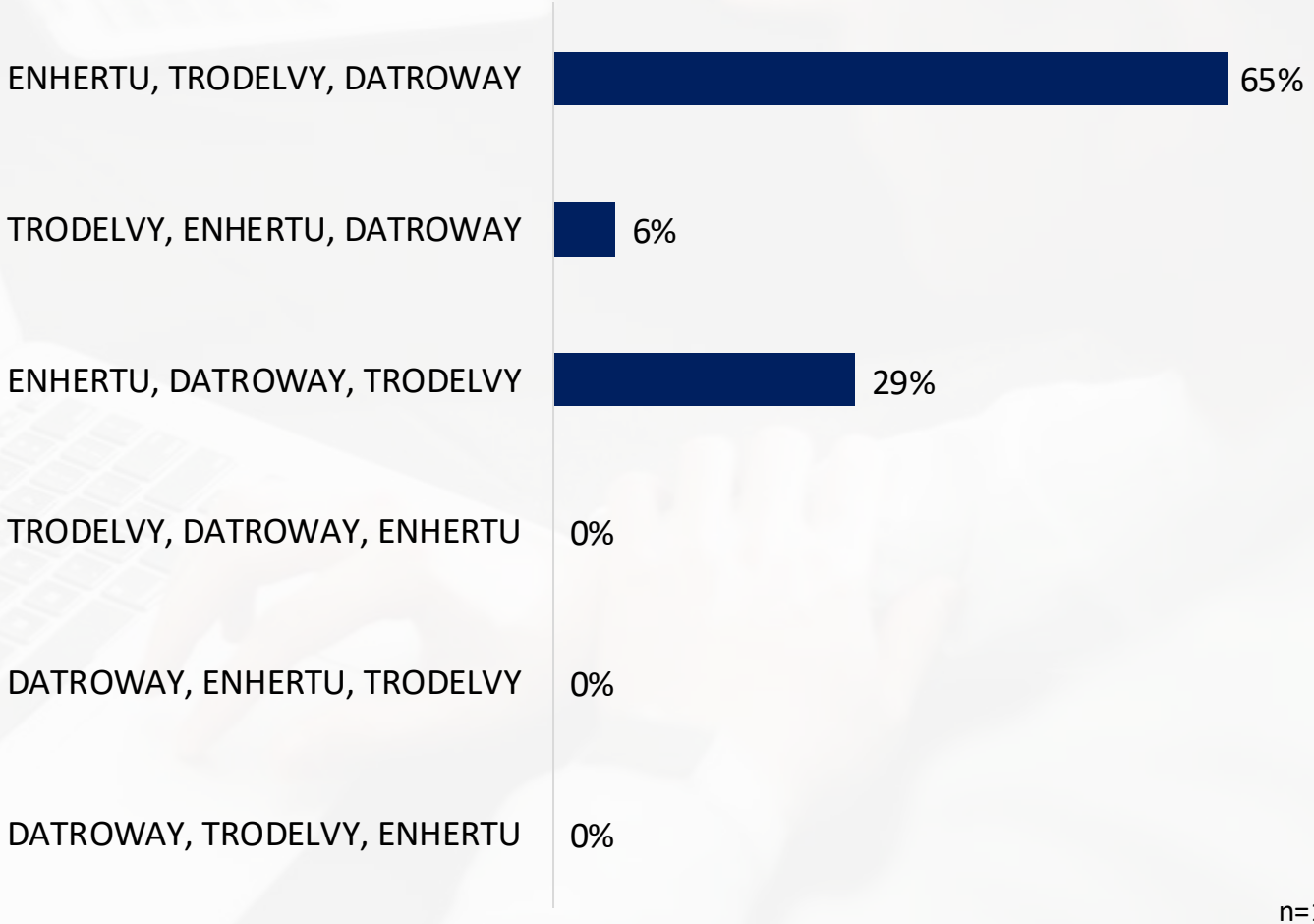
https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Datroway&inline=true

https://www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.pdf

How do adverse events influence your treatment decision between ADCs?

ARS Results from HCP Participants

What is your preferred order for sequencing ADCs in HR+/HER2 low/ultralow when you decide to recommend an ADC --- in the context of single agent chemotherapy?



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Metastatic Breast Cancer: Case Summary and Approach

de novo metastatic HR+/HER2- breast cancer with bone involvement

1st Line:

- AI/OS + CDK4/6i (Ribociclib, Abemaciclib, Palbociclib)
- Fulvestrant + Palbociclib + Inavolisib (PIK3CAm, ET refractory)

NGS
Biopsy/ctDNA @ baseline
ctDNA @ progression

2nd Line:

- Fulvestrant +/- Abemaciclib
- Fulvestrant + Alpelisib
  Or Inavolisib + palbociclib + fulvestrant (PIK3CAm)
- Fulvestrant + Capivasertib (PIK3CAm, AKTm, PTENm)
- Elacestrant (ESR1m)
- Olaparib (BRCAm)
- Trastuzumab deruxtecan (HER2-low/ultralow)
- Chemotherapy (many choices)

NGS
ctDNA at progression

3rd Line (*and beyond*):

- Anti-estrogen + Everolimus
- Trastuzumab deruxtecan (ADC, HER2-low)
- Sacituzumab govitecan (ADC)
- Datopotamab deruxtecan-dlnk (ADC)
- Chemotherapy (many choices)

Ongoing clinical trials exploring:

- New anti-estrogens
- New CDK4/2 inhibitors
- New targeted agents (PI3K, RAS pathway)
- New ADCs

cornerstone specialty network

Key Takeaways

Breast Cancer: Patient Case

HR+ HER2-Low Advanced Breast Cancer

- New options are available
  - ADCs are better than single-agent chemotherapy in terms of PFS, RR, and OS
  - New data on T-DXd before chemotherapy for advanced disease
- NGS testing and HER2 testing critical for decision making
- FDA approvals and NCCN Guidelines play a pivotal role in directing treatment pathways
- Awareness of clinical trial data provides new treatment options for patients