Significance of HER2 Expression in Solid Tumors

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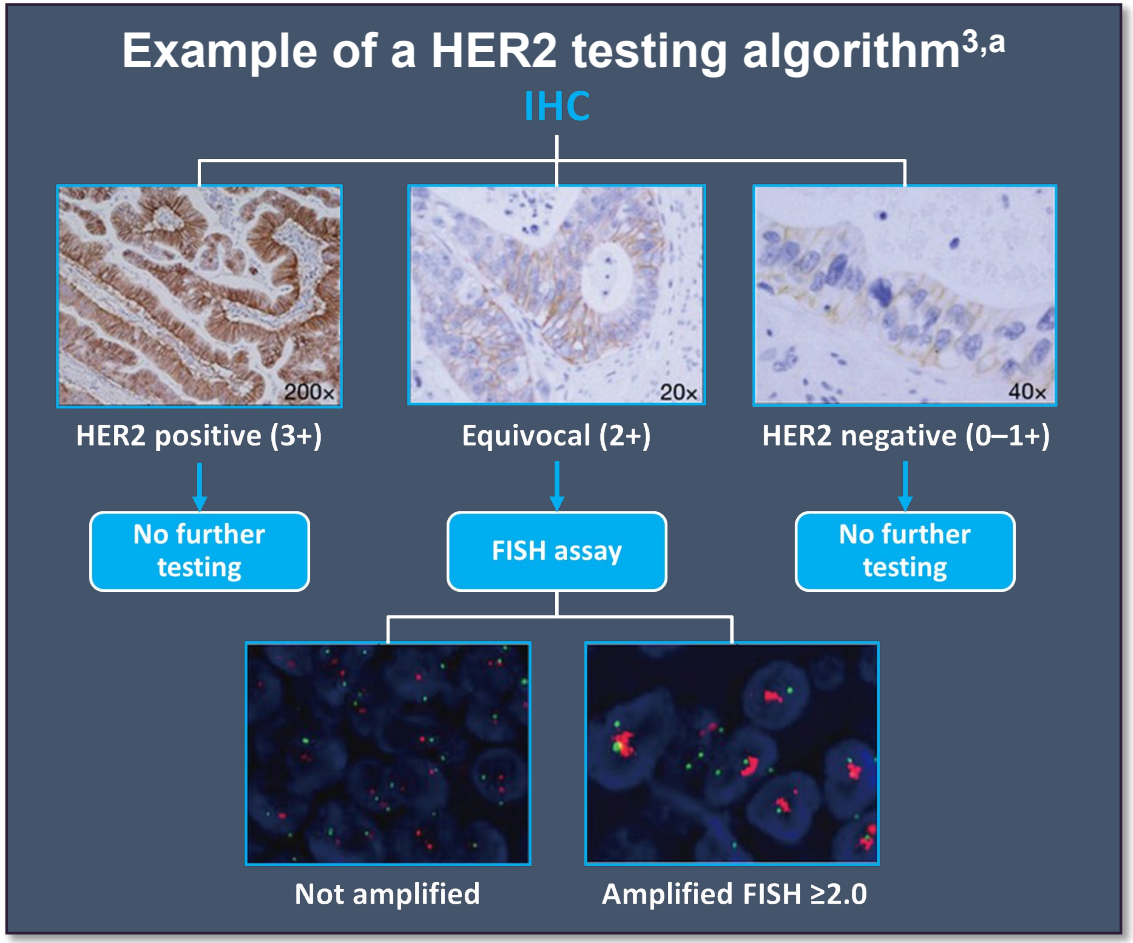
TOTAL CME

From a gynecologic malignancy standpoint, HER2 expression has classically been associated with poor prognosis.

RITU SALANI, MD

HER2 Testing: Protein Expression, HER2 Amplification, and HER2 Gene Mutations

- HER2 testing[1,2]
- HER2 protein expression: IHC
- HER2/neu amplification: FISH
- HER2 mutation
  - Guardant360 CDx (blood)
  - Oncomine Dx Target Test (tissue)



[a] Gastric cancer.
FISH, fluorescence in situ hybridization.
1. Jaber N. Enhertu marks first targeted therapy for HER2-mutant lung cancer. Cancer.gov. September 13, 2022.
2. Imyanitov EN, et al. *Crit Rev Oncol Hematol*. 2021;157:103194. 3. Kelly CM, Janjigian YY. *J Gastrointest Oncol.* 2016;7(5):750-762.

I think that [HER2] expression level really matters when you come to the efficacy of these drugs.

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HER2 Testing Strategies Across Tumor Types Amidst Guidelines Gaps

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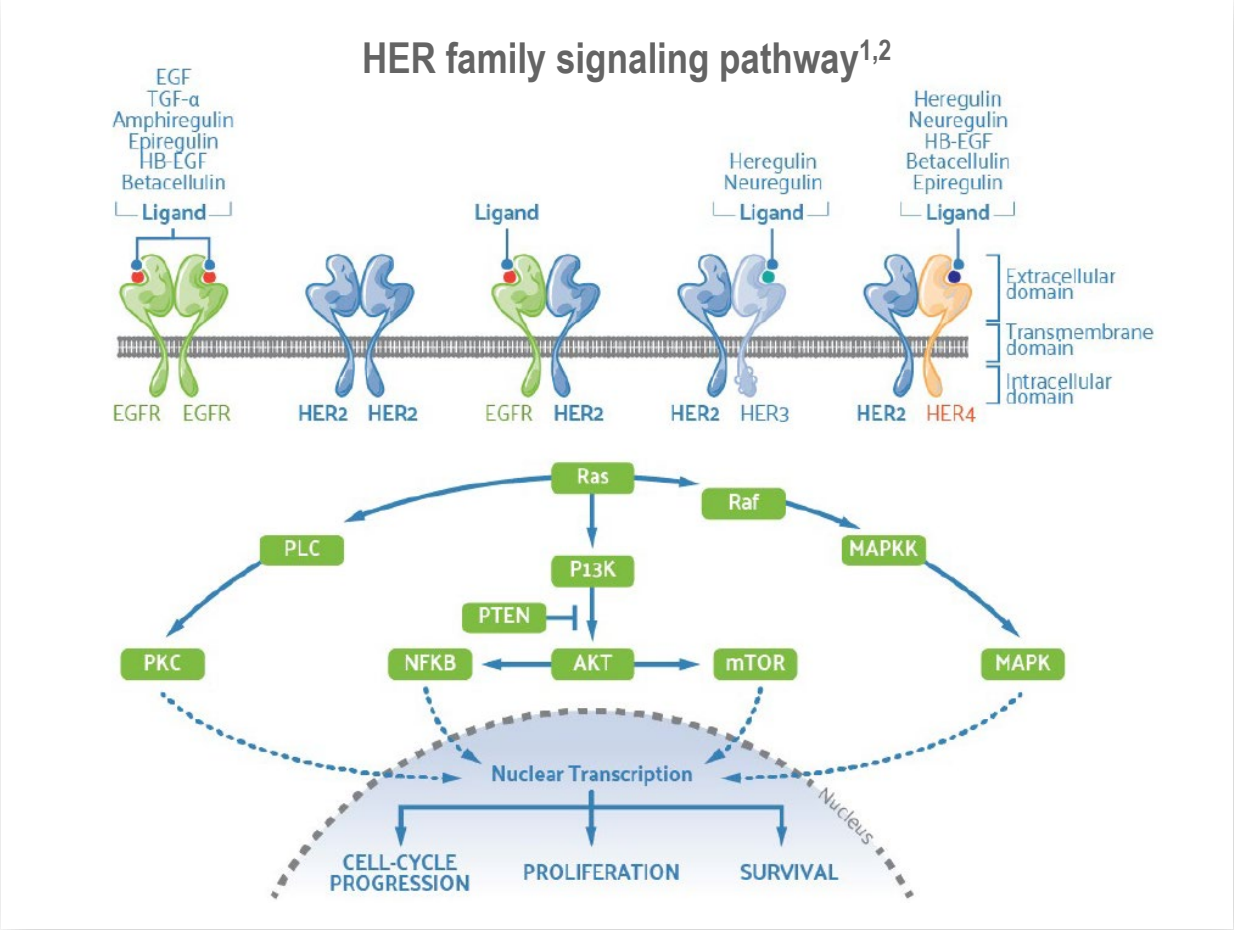
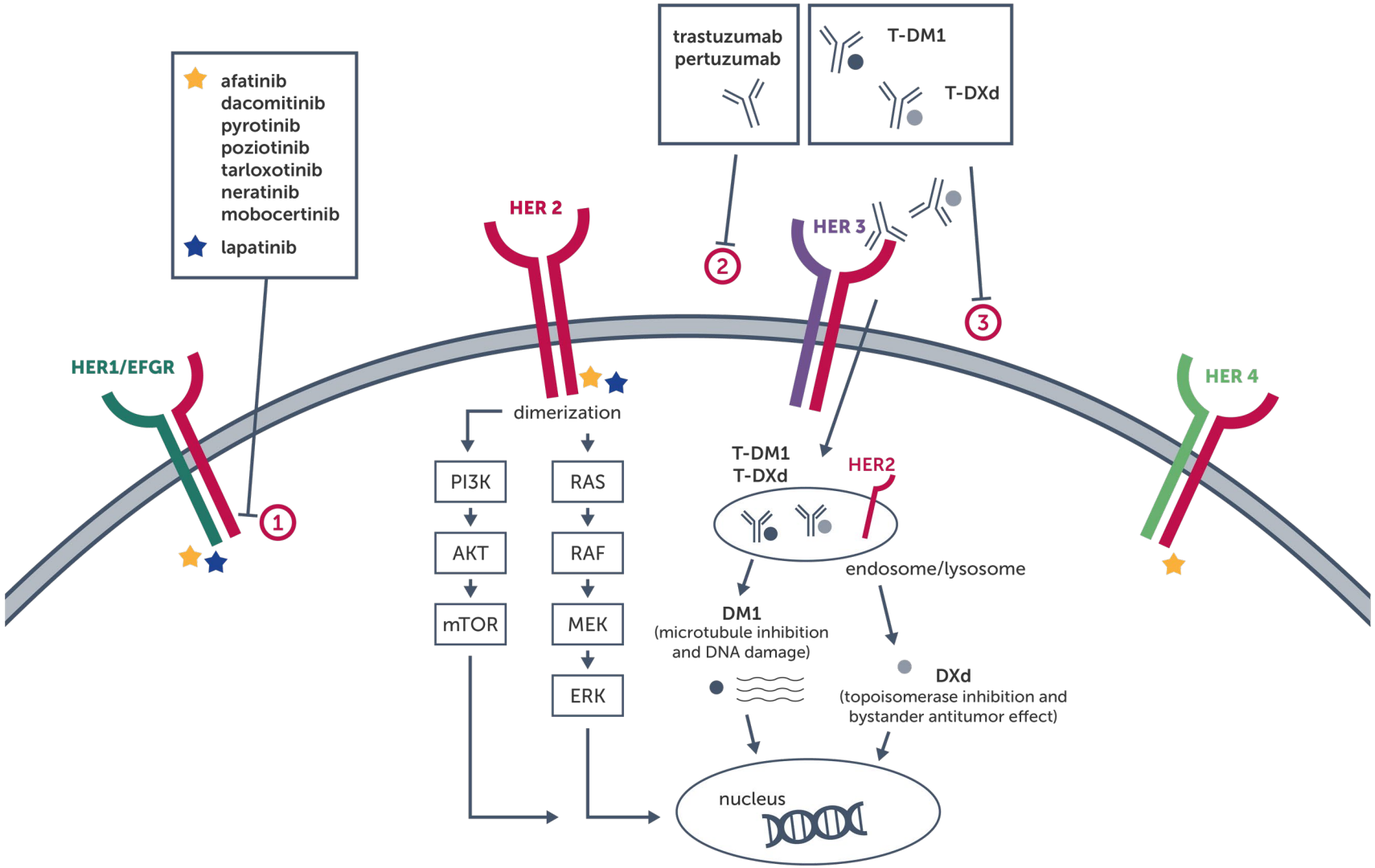
The HER2 Pathway Is Involved in Cell Proliferation, Survival, and Metastasis

- HER2 is part of the ErbB/HER family of transmembrane tyrosine kinase receptors that also includes EGFR/HER1, HER3, and HER4[1]
- HER2 receptors have no known ligand and instead regulate downstream signaling pathways through heterodimerization with their family members or, when HER2 expression level is high, homodimerization with themselves[1,2]
- Downstream transcription factors regulate cell proliferation, survival, differentiation, and invasion and metastasis[1,2]



1. Iqbal N, Iqbal N. *Mol Biol Int*. 2014;2014:852748.
2. Abud HE, et al. *Front Cell Dev Biol.* 2021;9:685665.

HER2 Mutations vs Amplifications



Uy NF, et al. *Cancers (Basel)*. 2022;14(17):4155.

3 Primary Testing Modalities for HER2

- HER2 testing has been traditionally performed by IHC and ISH[1]
- NGS-based techniques are increasingly being used[2]

Immunohistochemistry (IHC)

- Mono/polyclonal antibodies bind to the HER2 protein[1]
- Detects HER2 protein expression in cancer tissue[1,3]
- HER2 testing results using IHC are categorized as positive, equivocal, or negative[1]

In situ hybridization (ISH)

- HER2 DNA probes are labeled, usually with fluorescent dye[1]
- Detects whether HER2 gene amplification is present[2,3]
- Can quantify the level of amplification[3]

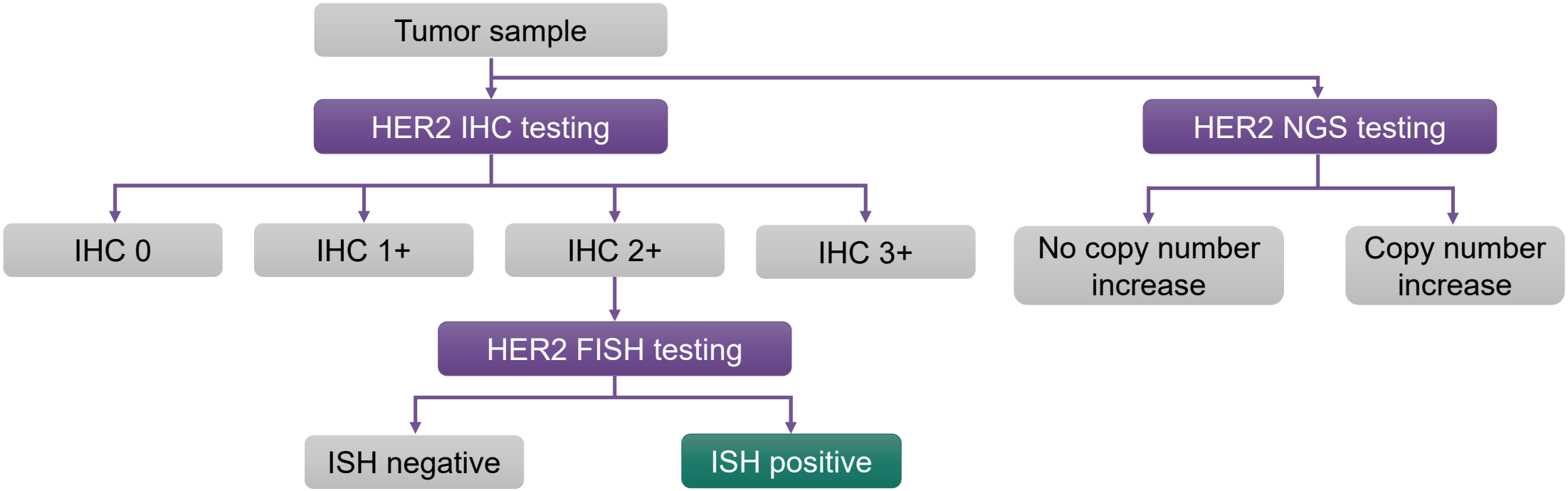
Next-generation sequencing (NGS)

- Measures HER2 copy number differences between normal and tumor tissue[2]
- Allows for concurrent determination of other potential genomic alterations[2]

1. Gutierrez C, Schiff R. *Arch Pathol Lab Med*. 2011;135(1):55-62. 2. Ross DS, et al. *J Mol Diagn*. 2017;19(2):244-254.
3. Wolff AC, et al. *J Clin Oncol*. 2018;36(20):2105-2122.

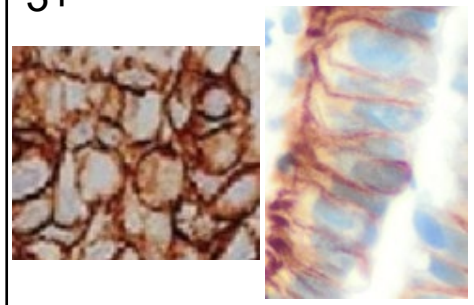
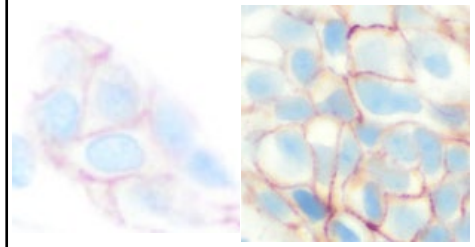
NGS Testing for HER2 Amplification

- NGS may be used as an alternative to sequential IHC/ISH testing, particularly when comprehensive molecular profiling is sought[1]
- Together, the 3 diagnostic modalities are used to determine whether treatment with HER2-targeted therapy is appropriate[1-3]

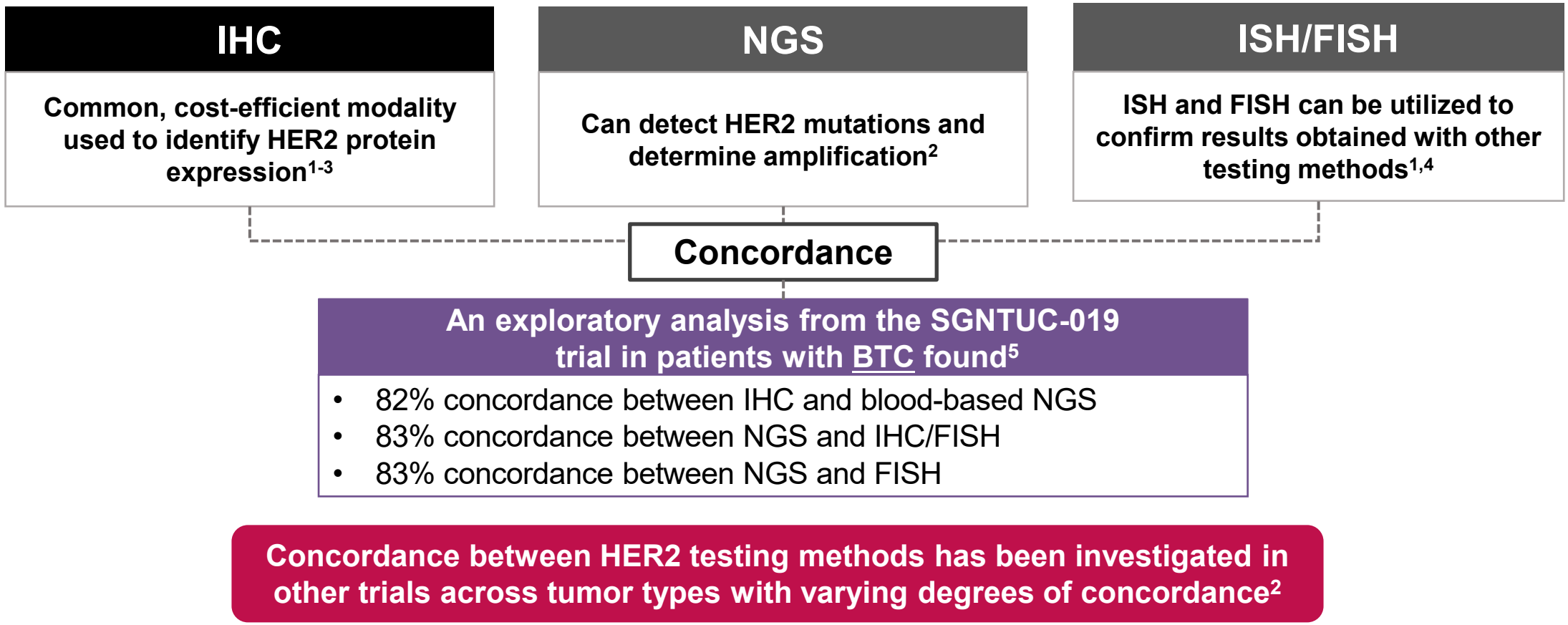


1. Ross DS, et al. *J Mol Diagn*. 2017;19(2):244-254. 2. Gutierrez C, Schiff R. Arch *Pathol Lab Med*. 2011;135(1):55-62. 3. Wolff AC, et al. *J Clin Oncol*. 2018;36(20):2105-2122.

HER2 Scoring Algorithms in Breast, Gastric, and Colorectal Cancers

IHC interpretation	Breast criteria (ASCO/CAP)	Gastric/esophageal resection (ASCO/CAP)	Gastric/esophageal biopsy (ASCO/CAP)	Colorectal (HERACLES)
3+ 	Complete circumferential **intense** membrane staining in >10% of cells **POSITIVE**	Complete or basolateral **intense** membrane staining in ≥10% of cells **POSITIVE**	Complete or basolateral **intense** membrane staining in ≥5 **cohesive** cells **POSITIVE**	**Intense** membrane staining: >50% of cells – **POSITIVE** 10%-50% of cells – **do ISH** <10% of cells – negative
2+ 	Complete **weak-moderate** membrane staining in >10%, or complete **intense** membrane staining in ≤10% of cells **EQUIVOCAL (do ISH)**	Complete or basolateral weak to moderate membrane staining in ≥10% of tumor cells – **EQUIVOCAL (do ISH)**	Complete or basolatereral weak to moderate membrane staining in ≥5 cohesive cells – **EQUIVOCAL (do ISH)**	**Moderate** membrane staining: <50% cells – negative ≥50% – **EQUIVOCAL (do ISH)**
1+	**Incomplete**, faint/barely perceptible membrane staining in >10% of cells	Incomplete or weak membrane staining in ≥10% of cells	Weak or barely perceptible membrane staining, irrespective of percentage	Faint membrane staining in any number of cells
0	No or weak incomplete staining in ≤10% of cells	No staining or <10% of cells	No staining	No staining

Testing Modalities for HER2 Alterations and Associated Concordance Rates



1. Zhao D, et al. *J Hematol Oncol*. 2019;12(1):50. 2. Niu D, et al. *Pathol Oncol Res*. 2020;26(4):2577-2585. 3. Abrahao-Machado LF, et al. *World J Gastroenterol*. 2016;22(19):4619-4625. 4. Oh DY, Bang YJ. *Nat Rev Clin Oncol*. 2020;17(1):33-48. 5. Nakamura Y, et al. *J Clin Oncol*. 2023;41(36):5569-5578.

Remember, if you do not test, you will not find, so you have to do both HER2 amplification and HER2 gene mutation.

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Diversity in HER2 Expression Among Gynecologic Cancers

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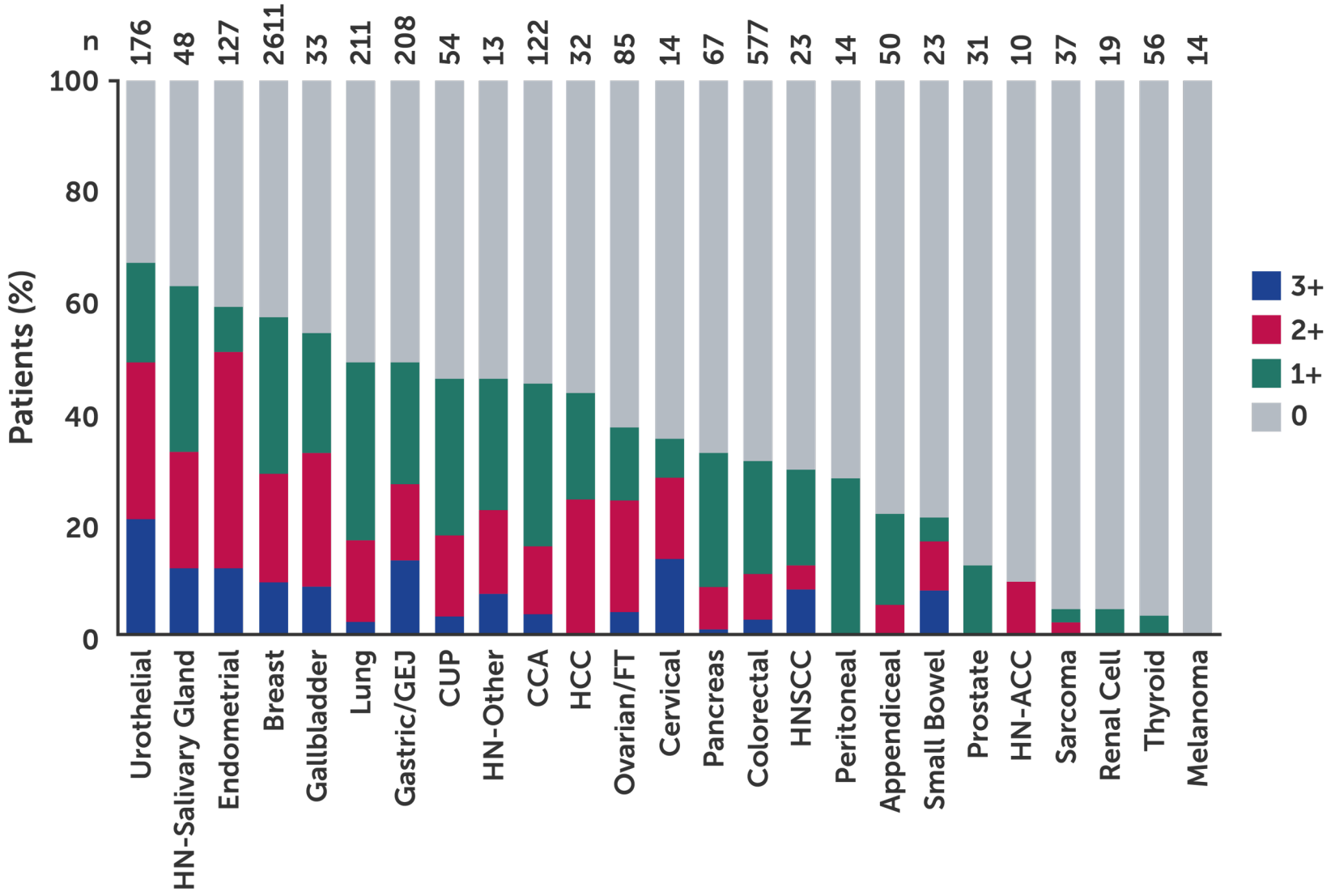
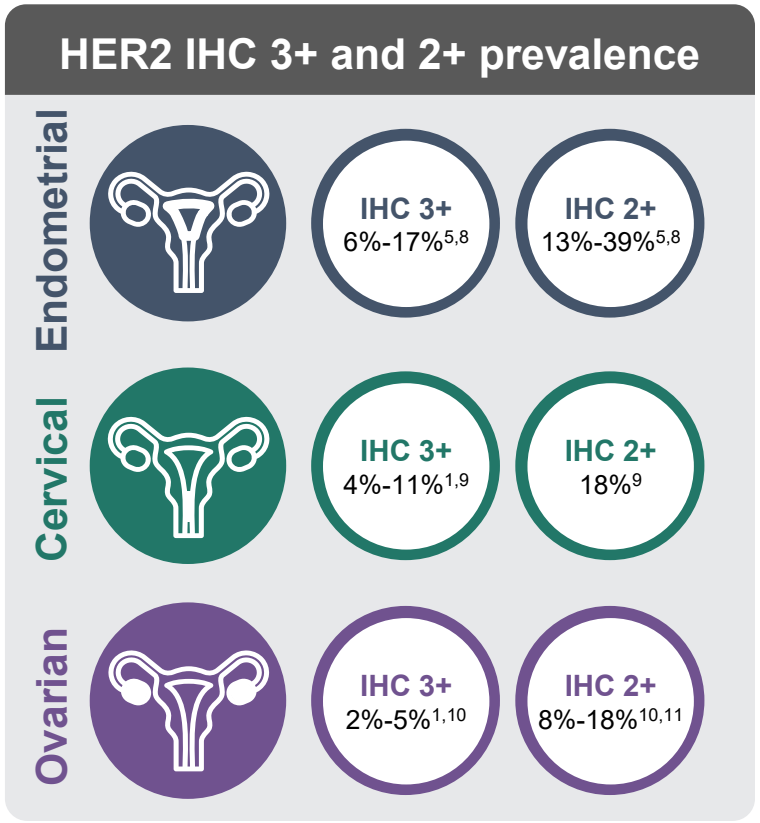
HER2 Expression Across Tumor Types



Uzunparmak B, et al. *Ann Oncol*. 2023;34(11):1035-1046.

Unmet Need in HER2-Expressing Tumors

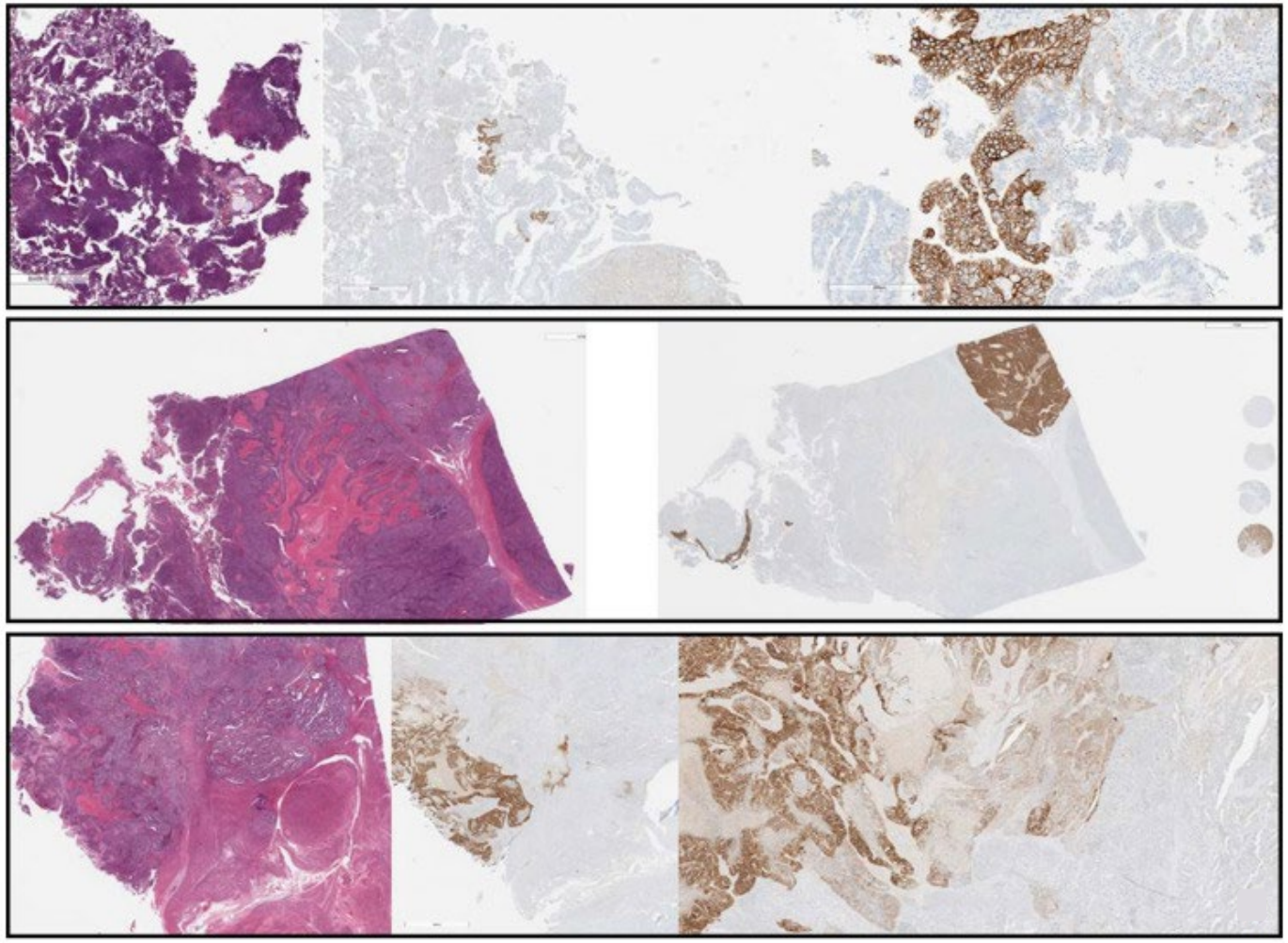
- HER2 expression is seen in a wide range of solid tumors, including gynecological tumors, and is associated with a biologically aggressive phenotype[1-5]
- In DESTINY-PanTumor02, T-DXd demonstrated clinically meaningful response rates, progression-free survival, and overall survival in HER2-expressing tumors, with particular benefit in gynecological tumors[6]
- Antitumor activity was observed with T-DXd in heavily pretreated patients with endometrial, cervical, and ovarian tumors across HER2 IHC expression levels and in ISH+ or plasma *ERBB2*-amplified subgroups[7]



ERBB2, erb-b2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan.

1. Yan M, et al. *Cancer Metastasis Rev*. 2015;34(1):157-164. 2. Li Z, et al. *EBioMedicine*. 2020;62:103074. 3. Uzunparmak B, et al. *Ann Oncol*. 2023;34(11):1035-1046. 4. Xing F, et al. *Mol Cancer*. 2023;22(1):6. 5. Halle MK, et al. *Br J Cancer*. 2018;118(3):378-387. 6. Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58. 7. Lee JY, et al. IGCS 2023. Abstract 1550. 8. Vermij L, et al. *Cancers (Basel)*. 2020;13(1):44. 9. Shi H, et al. *J Pathol Clin Res*. 2021;7(1):86-95. 10. Tuefferd M, et al. *PLoS One*. 2007;2(11):e1138. 11. Ersoy E, et al. *Int J Gynecol Pathol*. 2022;41(4):313-319.

Intratumoral Heterogeneity of HER2 Expression in Endometrial Cancer



Endometrial curettage specimen

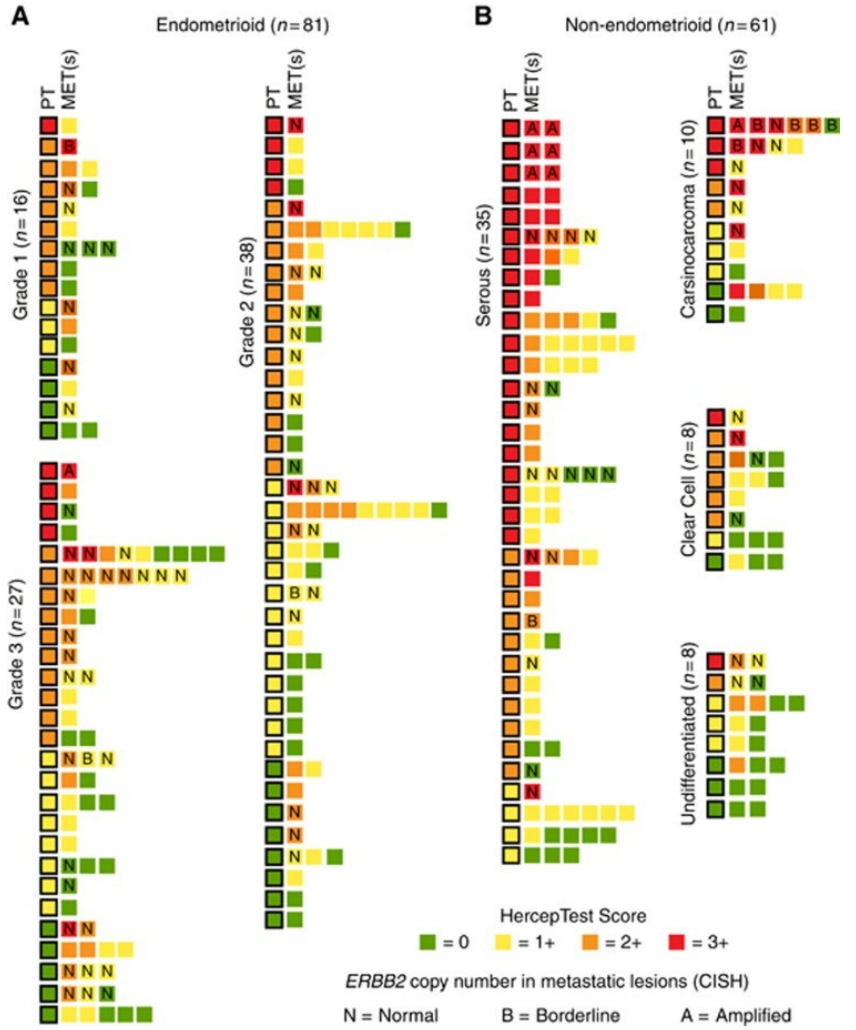
Hysterectomy specimen

Hysterectomy specimen

Plotkin A, et al. *Cancers (Basel)*. 2024;16(11):2100.

HER2 Expression in Metastatic Lesions vs Primary Tumor of Endometrial Cancer

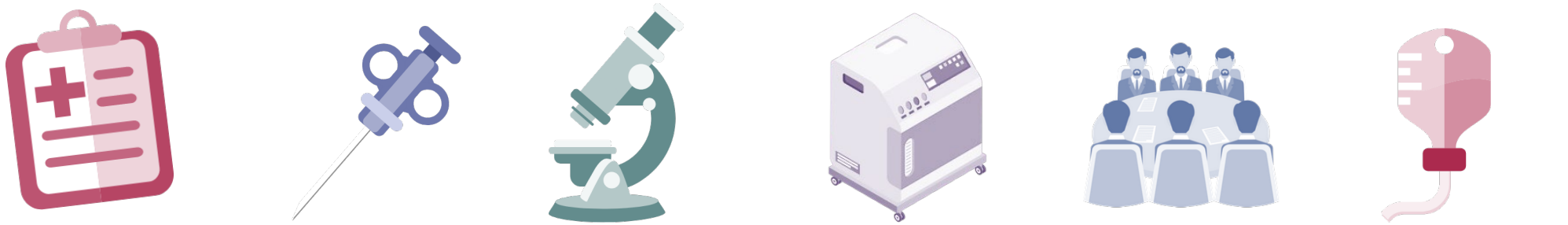
- Discordant HER2 expression between paired primary and metastatic lesions
- Substantial reduction in HER2 expression from primary to metastatic disease
- Loss of HER2 expression is common in metastatic endometrial cancer lesions



Halle MK, et al. *Br J Cancer*. 2018;118(3):378-387.

Tumor Journey for HER2 Testing

Processes[1-5]



Tests for HER2 protein on cell surface[3]

- Immunohistochemistry (IHC)
- Enzyme-linked immunosorbent assay (ELISA)
- Western blot

Tests for copy number of *HER2* gene in cell nucleus[3]

- In situ hybridization (ISH)
- Fluorescence in situ hybridization (FISH)
- Chromogenic in situ hybridization (CISH)
- Silver-enhanced in situ hybridization (SISH)
- Differential polymerase chain reaction (PCR)

1. Malone ER, et al. *Genome Med.* 2020;12(1):8. 2. De Las Casas LE, et al. *Am J Clin Pathol.* 2021;155(6):781-792. 3. HER2. Testing.com. 2020. https://www.testing.com/tests/her2/ 4. Iams WT, Konduri K. *Adv Ther.* 2023;40(12):5567-5578. 5. Rubin E, et al. *Int J Mol Sci*. 2024;25(2):1064.

Different HER2 Testing Used in Gyn Cancers

	Breast (ASCO/CAP 2007)	Breast (ASCO/CAP 2013)	Breast (ASCO/CAP 2018)	Gastric (ASCO/CAP 2016)	Colorectal (HERACLES trial)	UPSC (Fader et al.)
HER2 IHC 3+	>30% strong, uniform, complete	>10% circumferential, strong, complete	>10% circumferential, strong, complete	≥10%, strong complete or basolateral/lateral	≥50% strong, complete or basolateral/lateral	>30% strong complete or basolateral/lateral
HER2 FISH amplification	HER2/CEPT17 ratio >2.2 Patients with HER2/CEPT17 ratio 2-2.2 eligible	HER2/CEPT17 ratio ≥2.0 OR ratio <2.0 and HER2 signal ≥6.0/nucleus	HER2/CEPT17 ratio ≥2.0 OR ratio <2.0 and HER2 signal ≥6.0/nucleus (if IHC 2+ or 3+)	HER2/CEPT17 ratio ≥2.0 OR ratio <2.0 and HER2 signal ≥6.0/nucleus	HER2/CEPT17 ratio ≥2.0 in ≥50% of cells	HER2/CEPT17 ratio ≥2.0

Buza N. *Int J Gynecol Pathol*. 2021;40(1):17-23.

It's important to recognize what type of testing was done as this may actually help inform the most appropriate approach for the patient.

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Pivotal Data on Targeting HER2 in HER2-Expressing Solid Tumors

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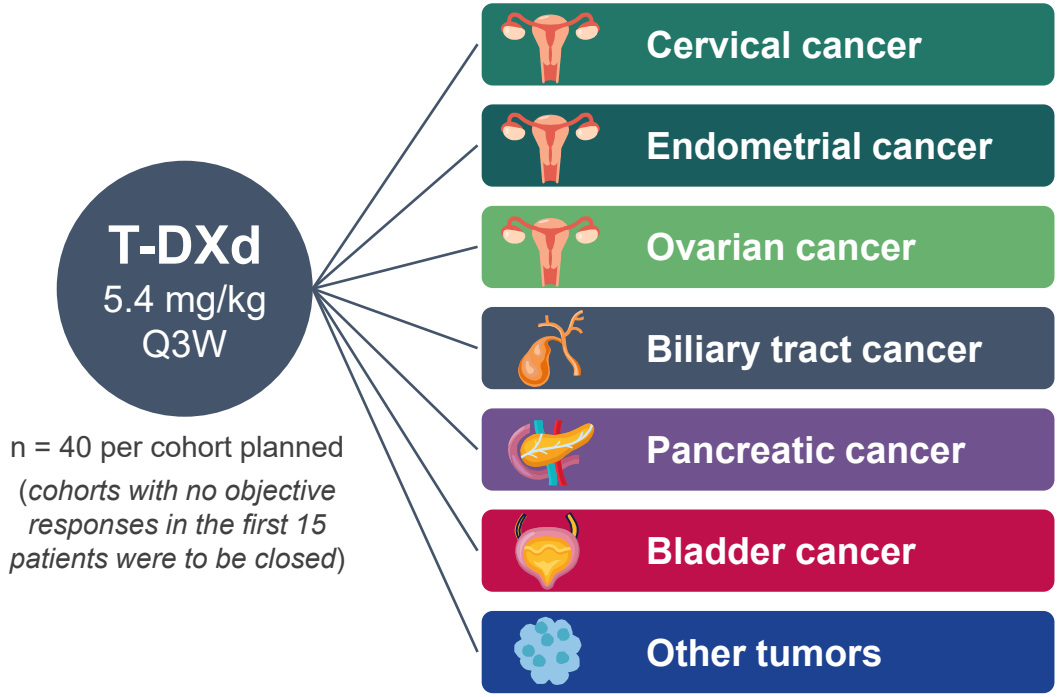
TOTAL CME

DESTINY-PanTumor02: Study Design

- Advanced solid tumors not eligible for curative therapy
- 2L patient population
- HER2 (IHC 3+ or 2+)
- Prior HER2-targeting agents allowed
- ECOG PS 0-1



Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR
- DCR
- PFS
- OS
- Safety

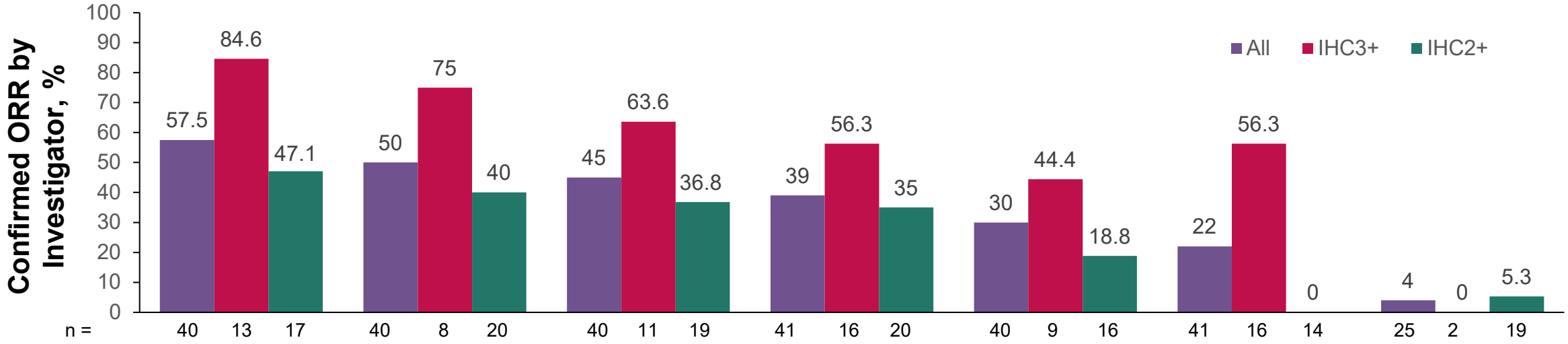
Data cutoff for analysis

- Nov 16, 2022

Meric-Bernstam F, et al. *J Clin Oncol*. 2023;41(17_suppl):LBA3000.

DESTINY-PanTumor02: ORR and DoR

Objective Response and Duration of Response



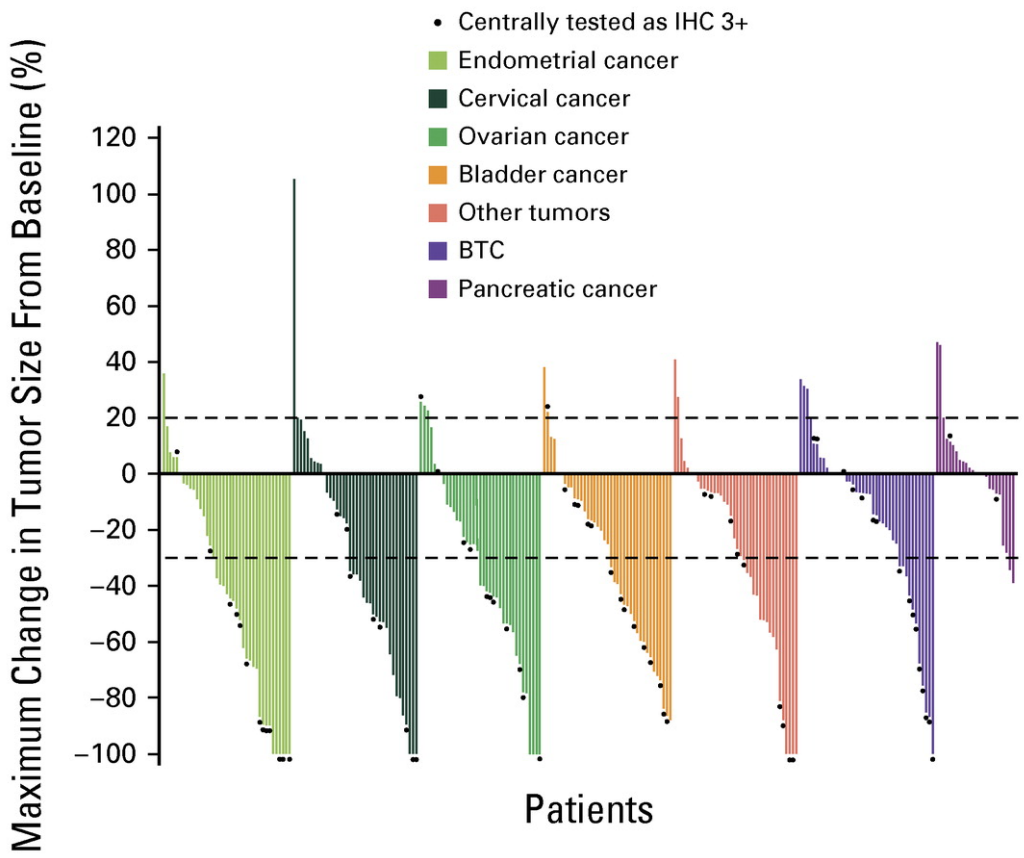
	Endometrial	Cervical	Ovarian	Bladder	Other	BTC	Pancreatic
Median DOR, mo (95% CI)	NR (9.9-NR)	14.2 (4.1-NR)	11.3 (4.1-22.1)	8.7 (4.3-11.8)	22.1 (4.1-NR)	8.6 (2.1-NR)	5.7 (NR-NR)

	All Patients (N = 267)	IHC 3+ (n = 75)	IHC2+ (n = 125)
ORR, % (95% CI)	37.1 (31.3-43.2)	61.3 (49.4-72.4)	27.2 (19.6-35.9)
Median DOR, mo (95% CI)	11.3 (9.6-17.8)	22.1 (9.6-NR)	9.8 (4.3-12.6)

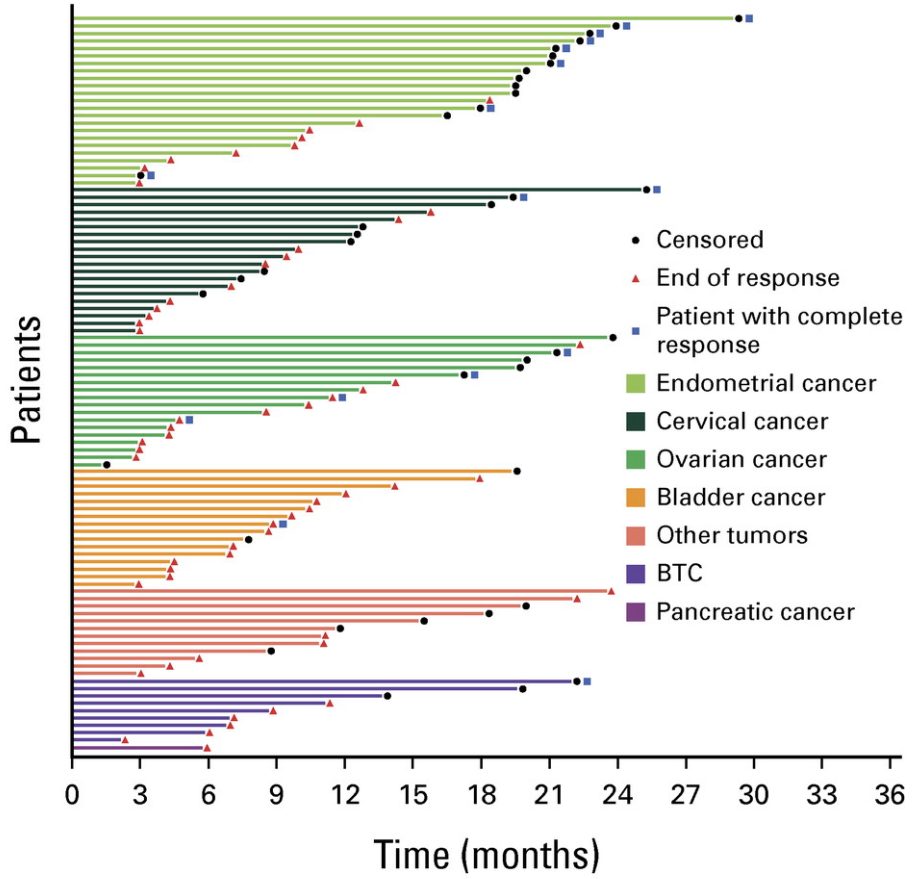
Meric-Bernstam F, et al. ESMO 2023. Abstract LBA34.

Phase 2 DESTINY-PanTumor02 Study: Best Percentage Change in Target Lesion From Baseline

Maximum change from baseline



Duration of response

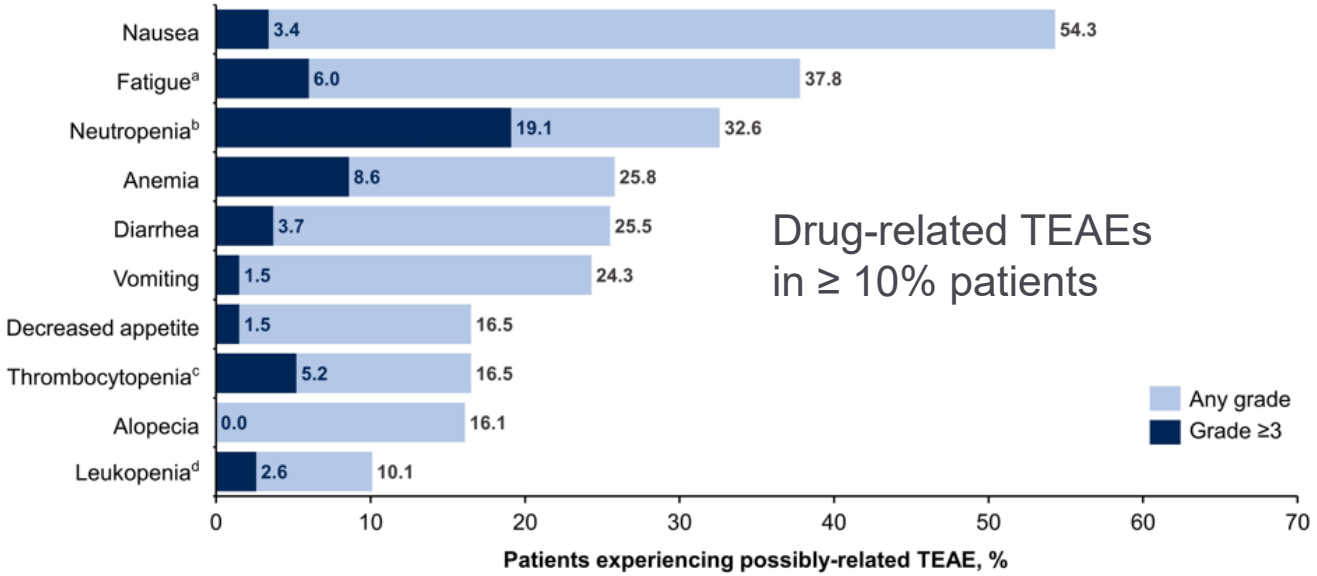


BTC, biliary tract cancer; IHC, immunohistochemistry.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

DESTINY-PanTumor02: Safety

n (%) Overall safety summary	All patients (N=267)
Any drug-related TEAEs	225 (84.3)
Drug-related TEAEs Grade ≥3	103 (38.6)
Serious drug-related TEAEs	32 (12.0)
Drug-related TEAEs associated with dose discontinuations	22 (8.2)
Drug-related TEAEs associated with dose interruptions	49 (18.4)
Drug-related TEAEs associated with dose reductions	50 (18.7)
Drug-related TEAEs associated with deaths	2 (0.7)[a]



*1 patient had grade 3 cardiac failure.

Meric-Bernstam F, et al. *J Clin Oncol*. 2023;41(17_suppl):LBA3000.

ILD/pneumonitis adjudicated as T-DXd related	
Grade	All patients, n (%) n = 267
1	6 (2.2)
2	12 (4.5)
3	1 (0.4)
4	0
5	1 (0.4)
Any	20 (7.5)

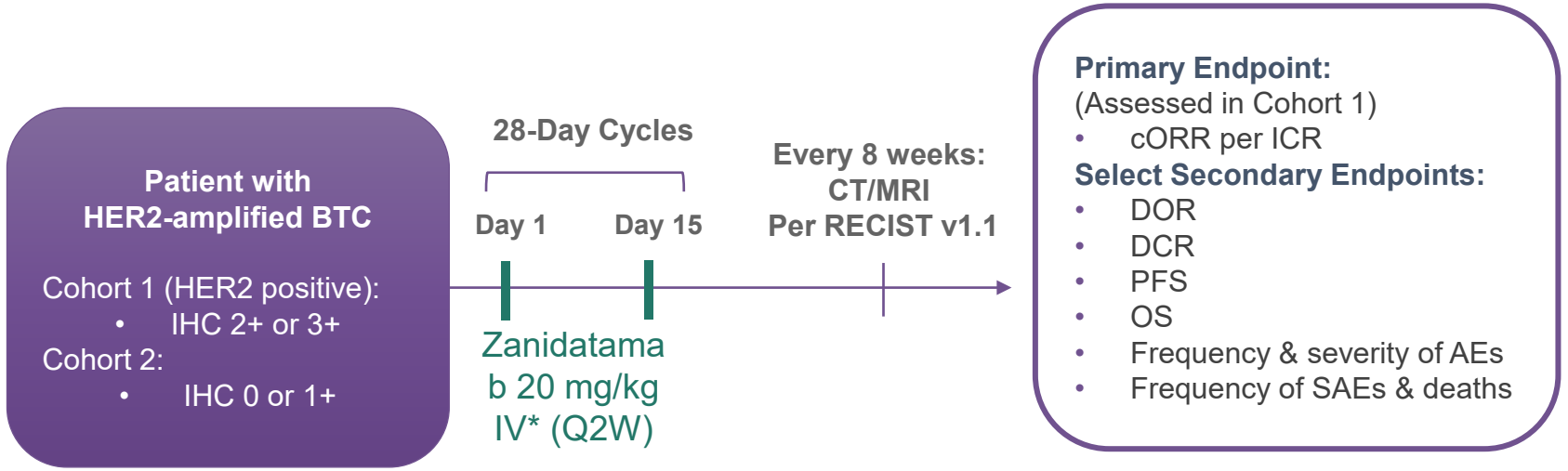
Left ventricular dysfunction*	
Grade	All patients, n (%) n = 267
1	1 (0.4)
2	4 (4.5)
3	1 (0.4)
4	0
5	0
Any	7 (2.6)

HERIZON-BTC-01: Study Design

- Phase 2b study of zanidatamab monotherapy in patients with HER2-amplified BTC

Key Eligibility Criteria

- Locally advanced or metastatic BTC[1]
- Tissue required to confirm HER2 status by central lab
- Progressed after treatment with a gemcitabine-containing regimen
- No prior HER2-targeted therapies
- ECOG PS of 0 or 1



*With mandatory premedication for IRR prophylaxis.

[1] Excludes ampullary.

AE, adverse event; BTC, biliary tract cancer; cORR, confirmed objective response rate; CT, computed tomography scan; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICR, independent central review; IHC, immunohistochemistry; IRR, infusion-related reaction; IV, intravenous; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event.

1. Harding JJ, et al. *Lancet Oncol*. 2023;24(7):772-782. 2. Pant S, et al. *J Clin Oncol*. 2023;41(16_suppl):4008.

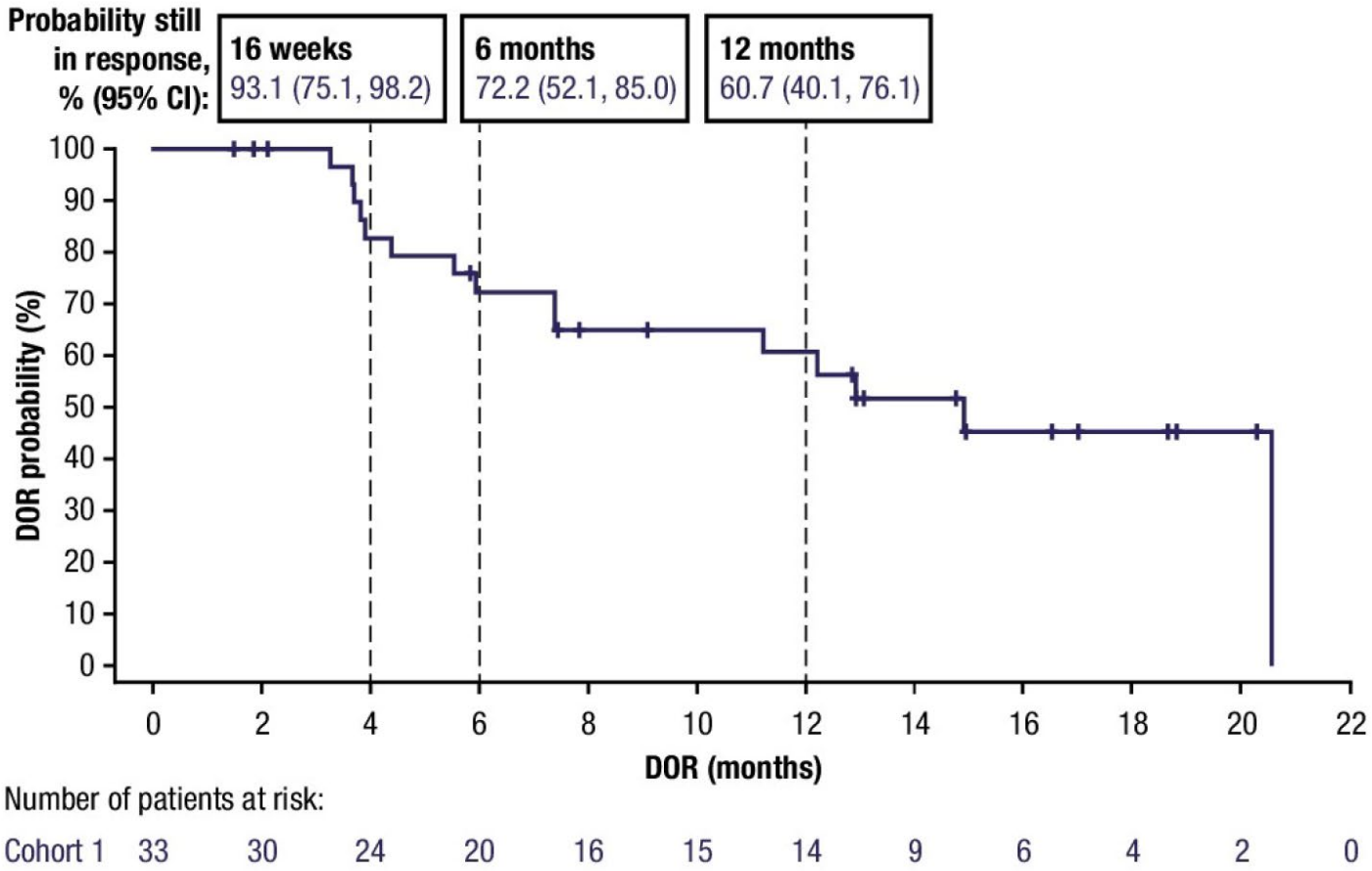
HERIZON-BTC-01: Disease Response in Patients With HER2-Positive BTC (Cohort 1)

Disease Response Endpoints[a]	Cohort 1 (n = 80)
cORR,[b] n (%) [95% CI]	33 (41.3) [30.4, 52.8]
Complete response, n (%)	2 (2.5)
Partial response, n (%)	31 (38.8)
Stable disease, n (%)	22 (27.5)
Progressive disease, n (%)	24 (30.0)
DCR,[c] n (%) [95% CI]	55 (68.8) [57.4, 78.7]
CBR,[d] n (%) [95% CI]	38 (47.5) [36.2, 59.0]
cORR by HER2 expression,[e] % (pre-planned subgroup analysis)	
HER2 IHC3+	51.6%
HER2 IHC2+	5.6%

- The median (range) duration of follow-up was 21.9 (16-34) months
- Zanidatamab treatment was ongoing for 9 (11%) patients, and 11 (14%) patients were in survival follow-up

Data cutoff for this analysis was July 28, 2023.
[a] Efficacy analysis (ie, all patients in cohort 1 who received any dose of zanidatamab) per ICR. [b] One patient was not evaluable. [c] Best overall response of stable disease or confirmed complete response or partial response.
[d] Stable disease ≥24 weeks or confirmed best overall response of complete response or partial response. [e] The trial was not designed to detect treatment effects by HER2 status, in a preplanned subgroup analysis.
BTC, biliary tract cancer; CBR, clinical benefit rate; CI, confidence interval; cORR, confirmed objective response rate; DCR, disease control rate.
Pant S, et al. ASCO 2024. Abstract 4091.

HERIZON-BTC-01: Duration of Response in Patients With HER2-Positive BTC (Cohort 1)



The median DOR, months (95% CI): 14.9 (7.4-NR)

Data cutoff for this analysis was July 28, 2023

Pant S, et al. ASCO 2024. Abstract 4091.

Based on the DESTINY-PanTumor02 data, trastuzumab deruxtecan was approved in the setting after frontline therapy in patients with HER2 3+ positive disease, which was a tumor-agnostic approval.

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Emerging Data Evaluating HER2-Directed Therapies in Gynecologic Cancers

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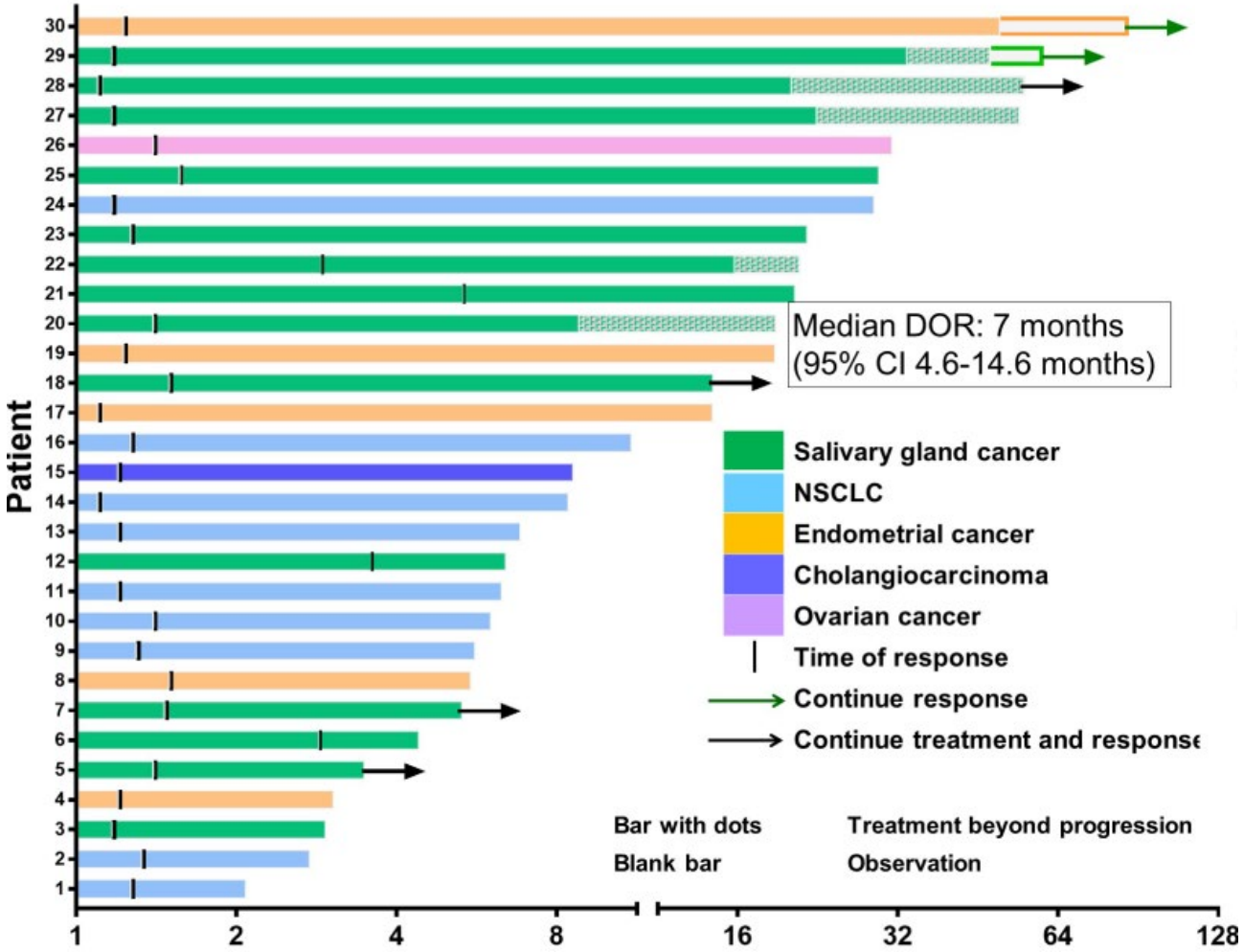
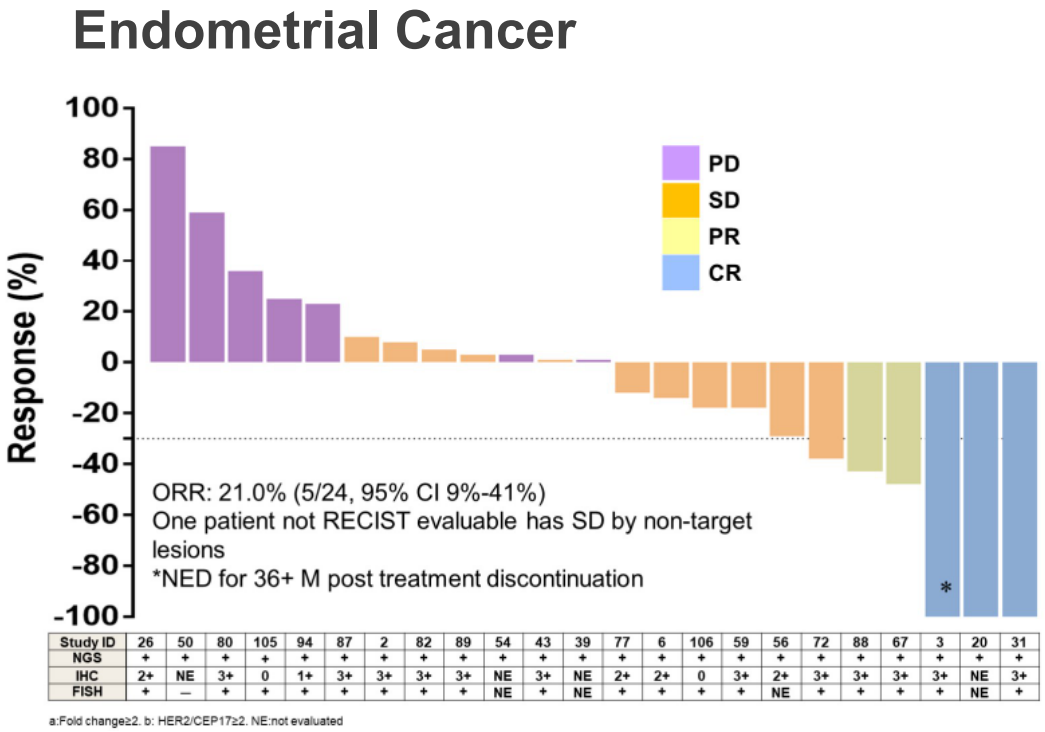
Ado-Trastuzumab Emtansine (T-DM1) in HER2-Amplified Tumors (Basket Trial)



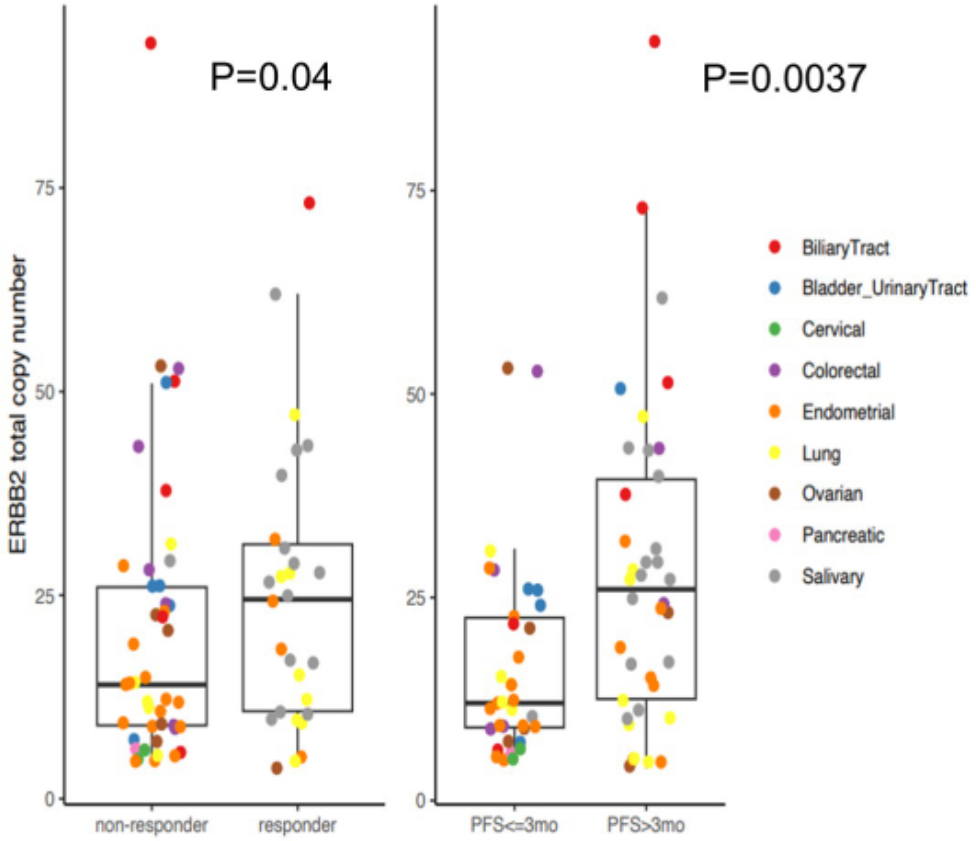


Study ID	26	50	80	105	94	87	2	82	89	54	43	39	77	6	106	59	56	72	88	67	3	20	31
NGS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
IHC	2+	NE	3+	0	1+	3+	3+	3+	3+	NE	3+	NE	2+	2+	0	3+	2+	3+	3+	3+	3+	NE	3+
FISH	+	–	+	+	+	+	+	+	+	NE	+	NE	+	+	+	+	NE	+	+	+	+	NE	+

Liu D, et al. *J Clin Oncol.* 2023;41(16_suppl):3025.

Ado-Trastuzumab Emtansine (T-DM1) in HER2-Amplified Tumors (Basket Trial)

HER2 Amplification Correlates With Response



Liu D, et al. *J Clin Oncol.* 2023;41(16_suppl):3025.

Persistent *HER2* Amplification at Disease Progression

Study ID	Cohort	IHC Pre T-DM1	IHC Post T-DM1	Best response	PFS(M)
85	H&N	3+	3+	PMR-75%	3.0
108	H&N	3+	3+	CMR -100%	30.4
53	Lung	3+	3+	PR-58%	6.0
31	Endometrial	3+	3+	CR -100%	18.8

Study ID	Cohort	FISH Pre T-DM1	FISH Post T-DM1	Best response	PFS(M)
79	H&N	7.6	6.76	CMR -100%	15.8
110	H&N	4.08	4.7	PMR -99%	22.6
69	Lung	2.0	2.6	SD -16%	12.7

Study ID	Cohort	HER2 TCN Pre T-DM1	HER2 TCN Post T-DM1	Best response	PFS(M)
107	H&N	12	29	SD-25%	3.5
85	H&N	11	10	PMR-75.00	3.0
108	H&N	24	43	CMR -100%	20.2
53	Lung	9	12	PR -58%	6.0
69	Lung	4	5	SD -16%	12.7

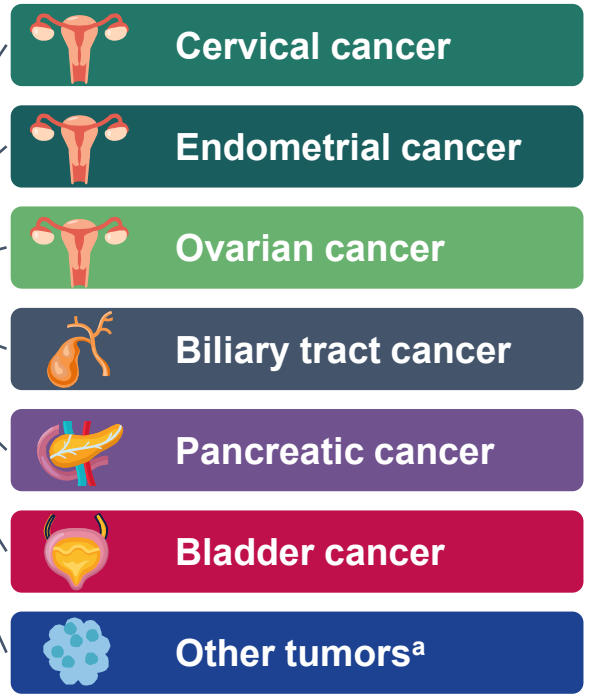
Open-Label, Phase 2 DESTINY-PanTumor02 Study of T-DXd for HER2-Expressing Solid Tumors

Tumor types were selected based on epidemiological frequency, prevalence of HER2 expression, and unmet medical need

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by Hercep Test if local test not feasible (ASCO/CAP gastric cancer guidelines)
- Prior HER2-targeting therapy
- ECOG/WHO PS 0–1 restricted in strenuous activity

T-DXd
5.4 mg/kg
Q3W

n = 40 per cohort planned
(*cohorts with no objective responses in the first 15 patients were to be closed*)



Primary endpoint
- Confirmed ORR (investigator)

Secondary endpoints
- DOR
- DCR
- PFS
- OS
- Safety

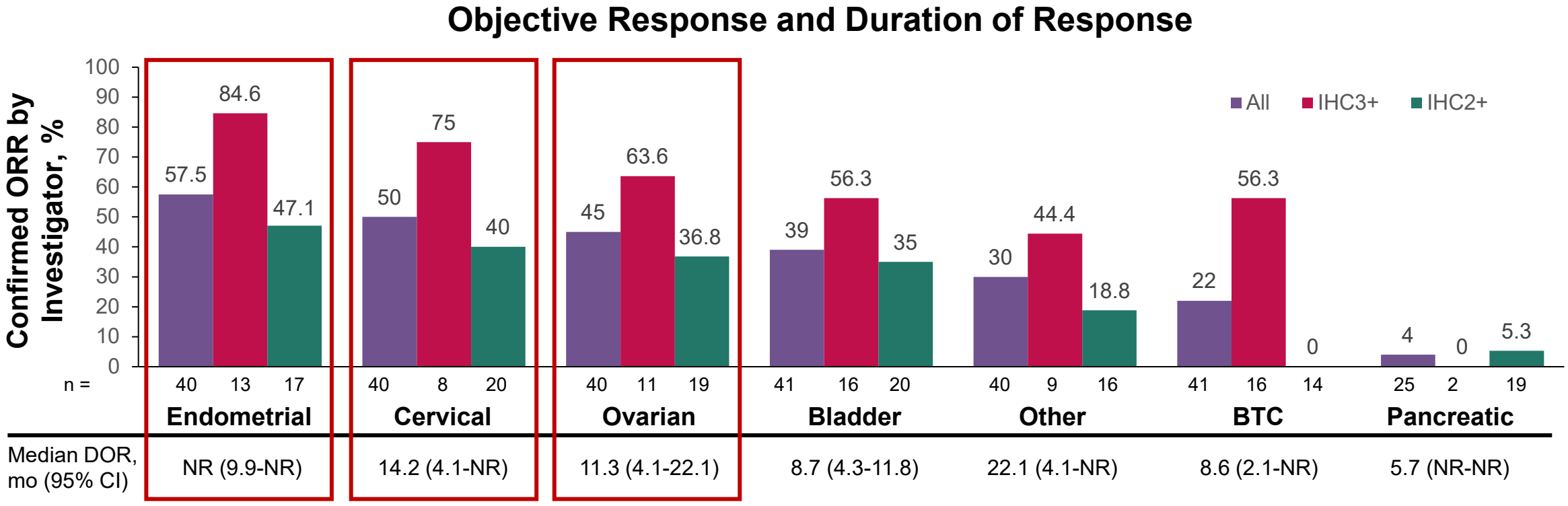
Data cutoff for analysis
- June 8, 2023

[a] Other tumors cohort: Salivary gland cancer (n = 19), malignant neoplasm of unknown primary site (n = 5), extramammary Paget disease (n = 3), cutaneous melanoma (n = 2), oropharyngeal neoplasm (n = 2), adenoid cystic carcinoma, head and neck cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, intestinal adenocarcinoma, appendiceal adenocarcinoma, esophageal squamous cell carcinoma, testicular cancer, and vulvar carcinoma (all n = 1).

2L+, second-line or beyond; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58. ClinicalTrials.gov identifier: NCT04482309.

Phase 2 DESTINY-PanTumor02 Study: Objective Response Rate by HER2 Status—Primary Analysis (N = 267)



	Endometrial	Cervical	Ovarian	Bladder	Other	BTC	Pancreatic
Median DOR, mo (95% CI)	NR (9.9-NR)	14.2 (4.1-NR)	11.3 (4.1-22.1)	8.7 (4.3-11.8)	22.1 (4.1-NR)	8.6 (2.1-NR)	5.7 (NR-NR)

	All Patients (N = 267)	IHC 3+ (n = 75)	IHC2+ (n = 125)
ORR, % (95% CI)	37.1 (31.3-43.2)	61.3 (49.4-72.4)	27.2 (19.6-35.9)
Median DOR, mo (95% CI)	11.3 (9.6-17.8)	22.1 (9.6-NR)	9.8 (4.3-12.6)

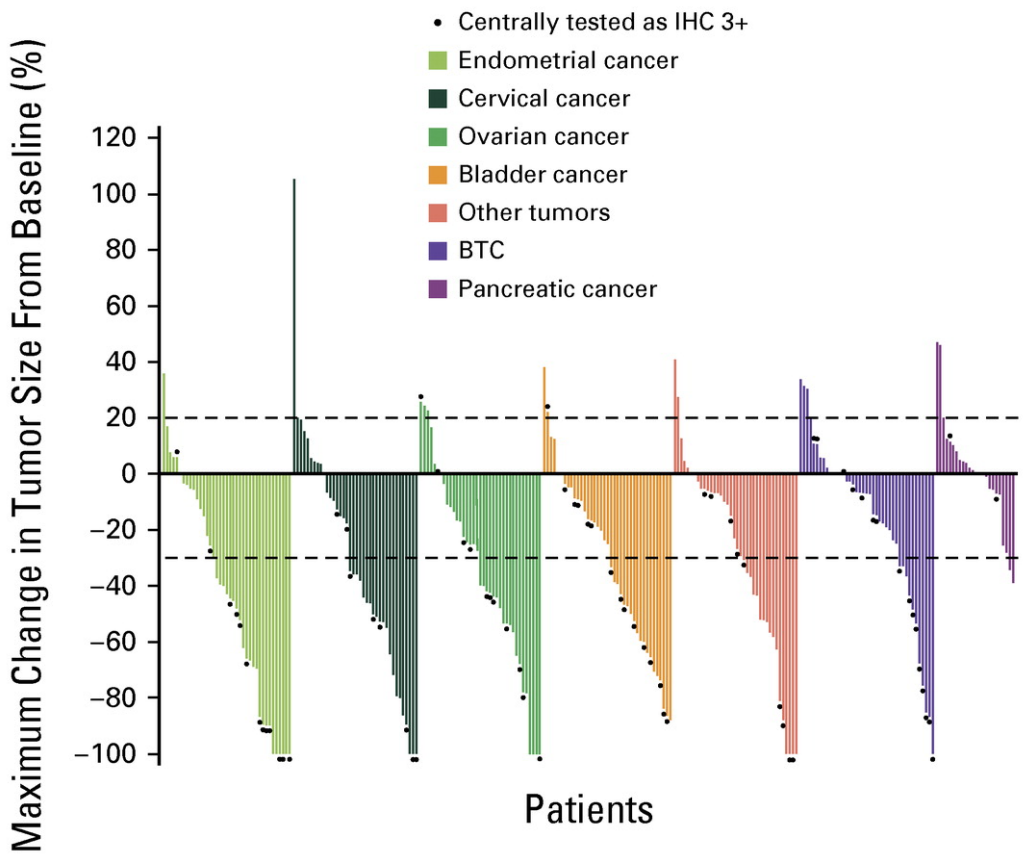
Median follow-up: 12.75 months.

BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NR, not reached; ORR, objective response rate.

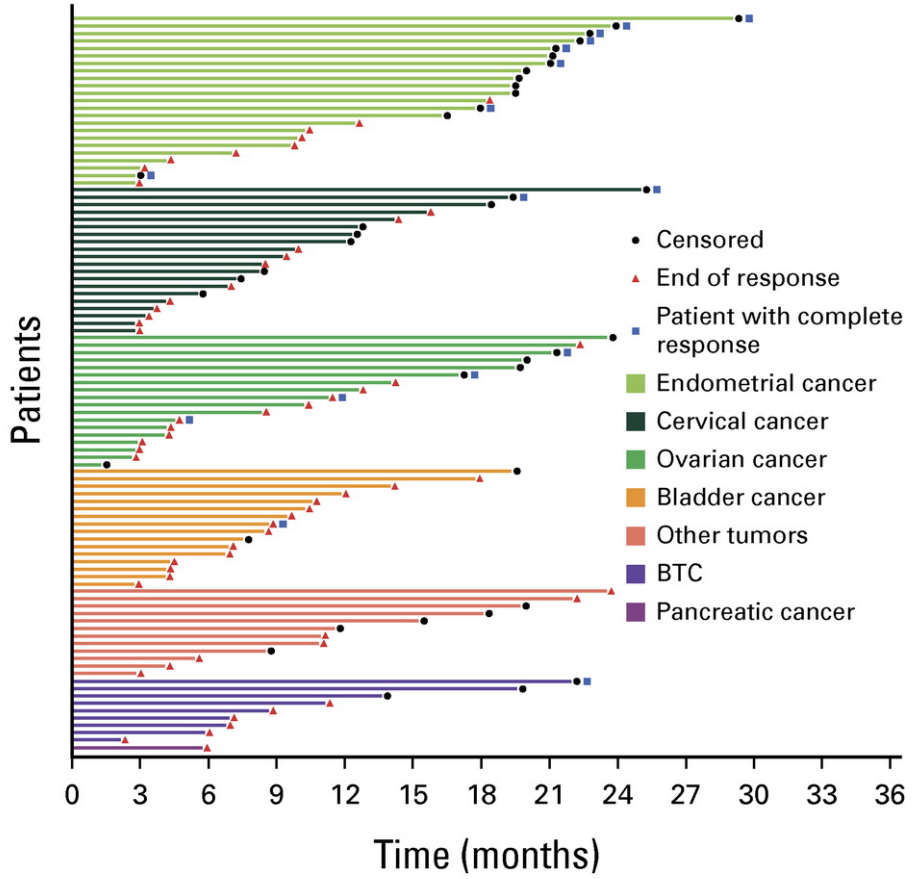
Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

Phase 2 DESTINY-PanTumor02 Study: Best Percentage Change in Target Lesion From Baseline

Maximum change from baseline



Duration of response



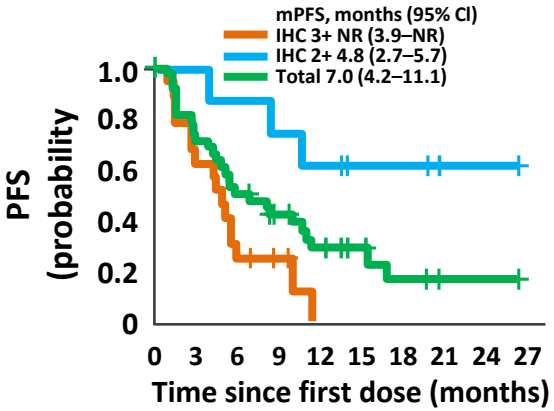
BTC, biliary tract cancer; IHC, immunohistochemistry.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

Phase 2 DESTINY-PanTumor02 Study: PFS (INV) and OS by Tumor Type and HER2 Expression Level

IHC 3+
IHC 2+
All

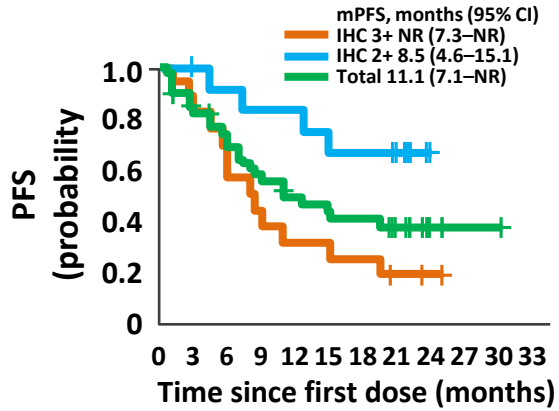
Cervical



Number at risk for cervical cancer

IHC 3+	8	8	7	6	5	3	3	1	1	0
IHC 2+	20	12	5	3	0					
Total	40	28	20	14	9	6	3	1	1	0

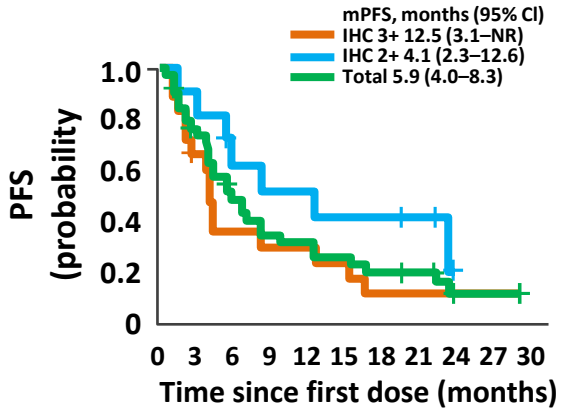
Endometrial



Number at risk for endometrial cancer

IHC 3+	13	12	11	10	10	9	8	5	0		
IHC 2+	17	14	11	7	5	5	4	2	1	0	
Total	40	31	27	21	17	16	14	8	2	1	0

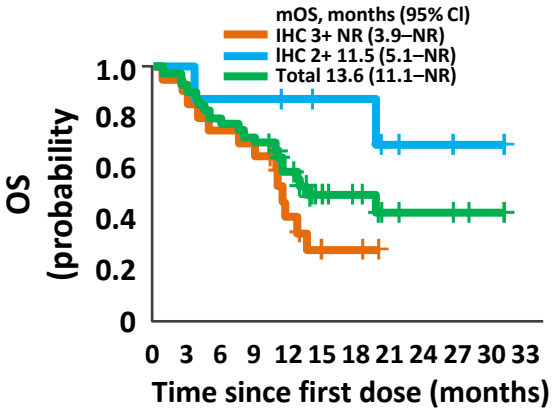
Ovarian



Number at risk for ovarian cancer

IHC 3+	11	10	6	5	5	4	4	3	0		
IHC 2+	19	11	6	5	5	4	2	2	1	1	0
Total	40	28	17	12	11	9	7	6	1	1	0

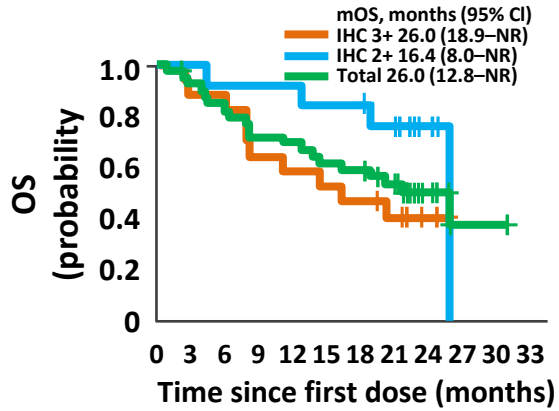
Cervical



Number at risk for cervical cancer

IHC 3+	8	8	7	7	6	6	5	3	2	1	1	0
IHC 2+	20	18	15	14	7	3	3	0				
Total	40	37	32	29	21	11	9	4	3	2	1	0

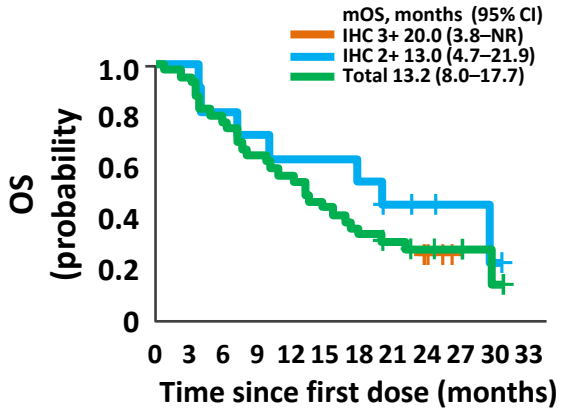
Endometrial



Number at risk for endometrial cancer

IHC 3+	13	13	12	12	12	11	11	9	4	0	
IHC 2+	17	15	15	11	10	9	8	6	3	0	
Total	40	36	33	28	27	24	23	19	9	1	1	0

Ovarian



Number at risk for ovarian cancer

IHC 3+	11	11	9	8	7	7	6	4	3	2	1	0
IHC 2+	19	18	13	12	11	8	6	6	4	1	0	
Total	40	38	30	25	22	17	13	11	8	3	1	0

CI, confidence interval; IHC, immunohistochemistry; INV, investigator assessed; m, median; NR, not reached; OS, overall survival; PFS, progression-free survival.

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

Safety Summary

Adverse Event	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)	Bladder Cancer (n = 41)	Other Tumors (n = 40)	Biliary Tract Cancer (n = 41)	Pancreatic Cancer (n = 25)
Drug-related adverse events, No. (%)	36 (90.0)	36 (90.0)	34 (85.0)	38 (92.7)	34 (85.0)	33 (80.5)	15 (60.0)
Grade ≥3	14 (35.0)	19 (47.5)	21 (52.5)	17 (41.5)	15 (37.5)	16 (39.0)	7 (28.0)
Serious adverse events	4 (10.0)	3 (7.5)	11 (27.5)	4 (9.8)	6 (15.0)	5 (12.2)	3 (12.0)
Leading to discontinuation	3 (7.5)	3 (7.5)	1 (2.5)	4 (9.8)	6 (15.0)	5 (12.2)	1 (4.0)
Leading to dose modification[a]	13 (32.5)	13 (32.5)	18 (45.0)	15 (36.6)	13 (32.5)	13 (31.7)	0
Associated with death	2 (5.0)	0	0	1 (2.4)	1 (2.5)	0	0
Most common drug-related adverse events (>10% of total patients), No. (%)							
Nausea	29 (72.5)	26 (65.0)	22 (55.0)	21 (51.2)	23 (57.5)	19 (46.3)	7 (28.0)
Anemia	7 (17.5)	15 (37.5)	15 (37.5)	12 (29.3)	11 (27.5)	10 (24.4)	4 (16.0)
Diarrhea	16 (40.0)	15 (37.5)	8 (20.0)	13 (31.7)	6 (15.0)	8 (19.5)	3 (12.0)
Fatigue	10 (25.0)	9 (22.5)	11 (27.5)	11 (26.8)	12 (30.0)	9 (22.0)	4 (16.0)
Vomiting	16 (40.0)	10 (25.0)	7 (17.5)	6 (14.6)	15 (37.5)	9 (22.0)	3 (12.0)
Neutropenia	4 (10.0)	8 (20.0)	5 (12.5)	11 (26.8)	9 (22.5)	9 (22.0)	4 (16.0)
Decreased appetite	8 (20.0)	7 (17.5)	8 (20.0)	8 (19.5)	7 (17.5)	7 (17.1)	2 (8.0)
Asthenia	11 (27.5)	9 (22.5)	6 (15.0)	3 (7.3)	8 (20.0)	6 (14.6)	3 (12.0)
Alopecia	9 (22.5)	8 (20.0)	5 (12.5)	5 (12.2)	7 (17.5)	9 (22.0)	2 (8.0)
Thrombocytopenia	2 (5.0)	2 (5.0)	5 (12.5)	6 (14.6)	7 (17.5)	5 (12.2)	3 (12.0)

[a]Dose modification includes adverse events with action taken of dose reduced or drug interrupted. Adverse events associated with death included pneumonia (n = 1), organizing pneumonia (n = 1), pneumonitis (n = 1), and neutropenic sepsis (n = 1).

Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42(1):47-58.

Monitoring and Managing Treatment-Related Adverse Effects Associated With HER2-Directed Agents

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Ritu Salani, MD
Professor, Division Director
University of California, Los Angeles
Los Angeles, CA

TOTAL CME

You can have shortness of breath that can then escalate to severe ILD, so it's important to really keep an eye on this.

RITU SALANI, MD

Interstitial Lung Disease: Recognition and Management

Moderate renal impairment may increase the risk of ILD

- **Advise** patients of risks of ILD prior to start of treatment, as well as signs/symptoms of ILD
- **Monitor** for new or worsening cough, dyspnea, or fever

- Incidental findings on routine scan
- Symptomatic findings

→

If ILD is suspected…

- Exclude other etiologies, including infectious etiologies
- Initiate evaluation without delay, which may include
  - High-resolution CT
  - Consultation with pulmonologist
  - Blood culture and CBC
  - Additional tests, as clinically indicated

→

Grade 1 (asymptomatic)

- Hold T-DXd until resolved
- May resume treatment once fully resolved
- If >28 days to resolve, reduce dose by 1 dose level

Grade 2+ (symptomatic)

- Discontinue T-DXd permanently
- Begin steroid treatment, eg, prednisone ≥1 mg/kg daily with gradual taper

CBC, complete blood (cell) count; CT, computed tomography; ILD, interstitial lung disease; T-DXd, fam-trastuzumab deruxtecan-nxki.

Fam-trastuzumab deruxtecan-nxki (Enhertu®). Prescribing information. Daiichi Sankyo, Inc.; 2022. Swain SM, et al. *Cancer Treat Rev*. 2022;106:102378.

Patient Case: How Do HER2-Directed Therapies Fit Into the Ovarian Cancer Treatment Landscape?

Ritu Salani, MD
Professor, Division Director
University of California, Los Angeles
Los Angeles, CA

Patient Case

- 47-year-old healthy woman diagnosed with stage IIIC high-grade serous ovarian cancer
- She underwent surgery with complete resection
  - Genetic testing: negative
  - Tumor testing: HRD negative, BRCA wild-type, p53 mutated
- 12/2019-4/2020: Carboplatin and paclitaxel x 6 cycles
  - Complete response
- 5/2021: CA125 elevated and CT scan with carcinomatosis
- 6/2021-11/2022: Carboplatin, liposomal doxorubicin, and bevacizumab with stable disease followed by maintenance bevacizumab
- 11/2022: Imaging demonstrated disease progression
- 12/2022: She was still platinum sensitive for carboplatin and gemcitabine; noted to have a rising CA125 and confirmed disease progression after 4 cycles
- 2/2023: She underwent repeat biopsy; tumor testing demonstrated high (80%) alpha folate receptor expression
- 2/2023-9/2023: Mirvetuximab soravtansine x 8 cycles
  - Best response was a partial response and then ultimately disease progression
- 10/2023: Disease recurrence and tumor tested for HER2 status: 3+
- 11/2023-5/2024: Trastuzumab deruxtecan given; she was noted to have a partial response

Key Takeaways

- Patients with ovarian cancer should undergo germline and tumor testing
- Many patients will be platinum sensitive and can be rechallenged with platinum-based therapies
- When patients become platinum resistant, or platinum refractory, additional therapies should be used
- It is important to stay current with the emerging data
- The changing landscape of ovarian cancer can provide exciting treatment opportunities for our patients

Patient Case: How Do HER2-Directed Therapies Fit Into the Biliary Tract Cancer Treatment Landscape?

Shubham Pant, MD
Professor, Dept of GI Medical Oncology
UT MD Anderson Cancer Center
Houston, TX

TOTAL CME

Case

- 56-year-old woman presenting with fatigue, weight loss, and vague abdominal pain
- CT of abdomen and pelvis found a 7-cm hypodense liver lesion with multiple satellite lesions adjacent to dominant liver mass and periportal lymphadenopathy
- PET scan showed the large liver mass was hypermetabolic, in addition to multiple hypermetabolic liver lesions and periportal lymph nodes
- Biopsy revealed adenocarcinoma that was consistent with cholangiocarcinoma
- Molecular testing found the tumor was IDH, FGFR wild-type, and HER2 positive 3+ by IHC
- Patient was started on gemcitabine + cisplatin + durvalumab
- After 6 months, patient's cancer progressed, although her ECOG PS was preserved at 1
- Serum NGS found ERBB2 amplification
- **What treatment would you recommend next?**

NCCN Guidelines Recommendations for Second-Line HER2+ Unresectable/Metastatic BTC

- Trastuzumab + pertuzumab
- Trastuzumab deruxtecan (IHC 3+)
- Tucatinib + trastuzumab

NCCN Guidelines. Biliary Tract Cancers (Version 3.2024). NCCN.org.