COR2ED

THE HEART OF MEDICAL EDUCATION

VIRTUAL EXPERTS KNOWLEDGE SHARE

HER2 TESTING: THE EVOLVING ROLE OF IHC - BEST PRACTICES AND INTERPRETATION OF RESULTS IN LUNG AND OVARIAN CANCER

Tuesday 11th March 2025

DEVELOPED BY PRECISION ONCOLOGY CONNECT

This programme is developed by PRECISION ONCOLOGY CONNECT, an international group of experts in the field of oncology.

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POWERED BY COR2ED

Acknowledgement and disclosures

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Expert disclosures:

- **Prof. Fernando López-Ríos** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: AbbVie, AstraZeneca, Bayer, BMS, Daiichi Sankyo, Janssen, Lilly Merck, MSD, Novartis, Pfizer, Roche, Takeda and Thermo Fisher.
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MEETING OBJECTIVES

- Provide Expert Opinion on HER2 immunohistochemistry in lung and ovarian cancer focusing on best practices, which guidelines exist and scoring criteria to follow
- Understand best practices in HER2 immunohistochemistry
- Be able to implement optimal immunohistochemistry testing and scoring of staining for HER2 expression
- Recognise the appropriate placement of therapies targeting HER2 alterations (including antibody-drug conjugates) across the patient journey in lung and ovarian cancers

AGENDA: TUESDAY 11TH MARCH 2025

HER2 TESTING: THE EVOLVING ROLE OF IHC - BEST PRACTICES AND INTERPRETATION OF RESULTS IN LUNG AND OVARIAN CANCER

Topic	Facilitator	Timings
Welcome and introductions	COR2ED	5 mins
1. Scene setting: an overview of challenges related to HER2 immunohistochemistry, guidance and interpretation of the results	Fernando López-Ríos	10 mins
Q&A		5 mins
2. Targeting HER2 in lung cancer: where does IHC fit in?	Christian Rolfo	20 mins
Q&A	Fernando López-Ríos	5 mins
3. Ovarian cancer: Challenges and considerations for HER2 IHC testing Including a patient case and polling questions	Charlie Gourley	20 mins
Q&A	Fernando López-Ríos	5 mins
Panel discussion and audience questions	All	15 mins
Future perspectives and summary	Fernando López-Ríos	5 mins

INTRODUCING THE SCIENTIFIC COMMITTEE

Prof. Fernando López-Ríos

Pathologist
12 de Octubre University Hospital, Madrid, Spain

Prof. Christian Rolfo

Medical Oncologist
The James, The Ohio State University, USA

Prof. Charlie Gourley

Medical Oncologist
CRUK Edinburgh Centre, Nicola Murray Centre for Ovarian Cancer Research, UK

AN OVERVIEW OF CHALLENGES RELATED TO HER2 IMMUNOHISTOCHEMISTRY

A CALL TO PROVE SOMETHING

Fernando López-Ríos MD, PhD

Pathologist
12 de Octubre University Hospital
Madrid, Spain

POLLING QUESTION

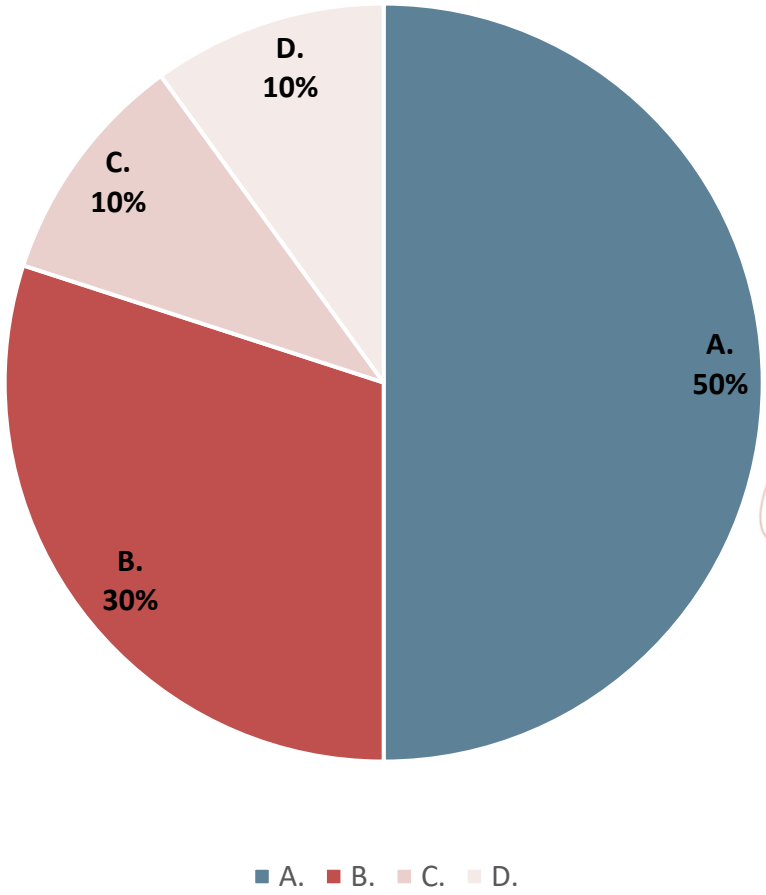
WHEN WOULD YOU ORDER HER2 IMMUNOHISTOCHEMISTRY AS A PREDICTIVE BIOMARKER IN A NEW PAN-TUMOUR PERSPECTIVE?

A. At diagnosis, simultaneously to diagnostic immunohistochemistry

B. After discussion at the clinical/molecular tumour board

C. After I receive the NGS report

D. I leave this decision to the pathologists



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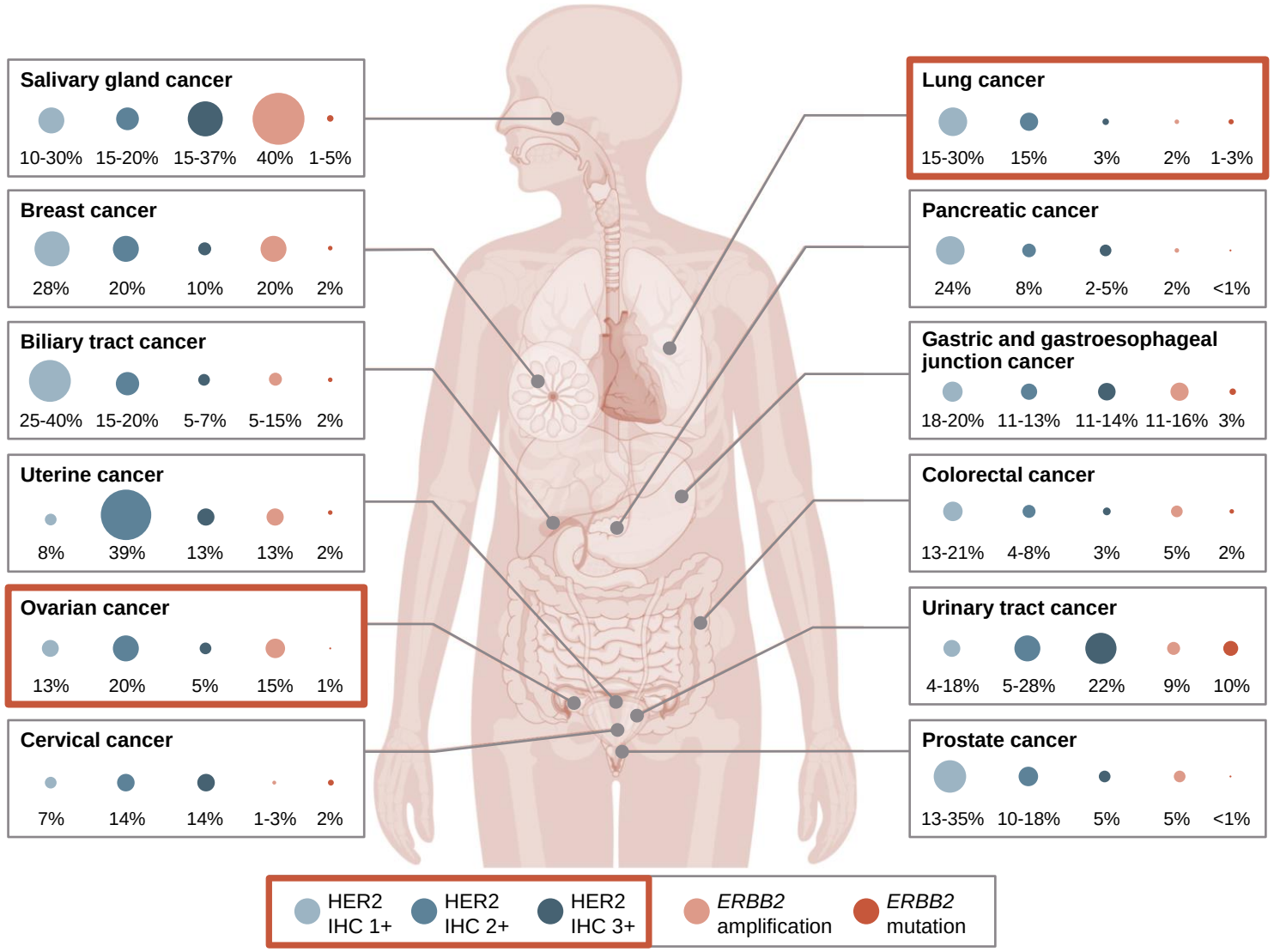
THE CHALLENGE: A HER2 (R)EVOLUTION

A PAN-TUMOUR PERSPECTIVE OF HER2 PROTEIN OVEREXPRESSION



IHC, immunohistochemistry

Yoon J, Oh DY. Nat Rev Clin Oncol. 2024;21:675-700

CONTENTS

THE TOOL

HER2 OVEREXPRESSION CAN BE IDENTIFIED WITH IMMUNOHISTOCHEMISTRY

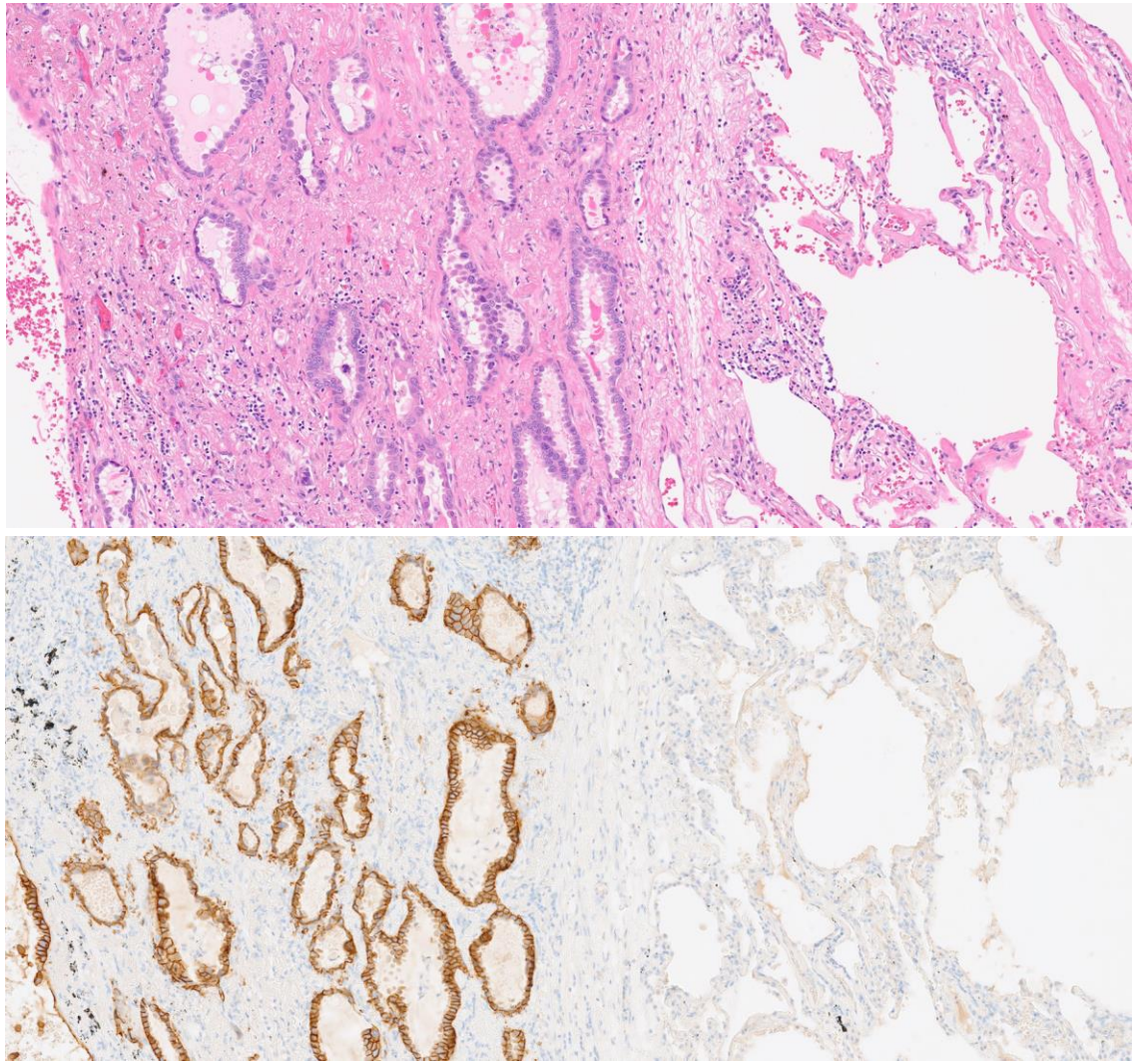
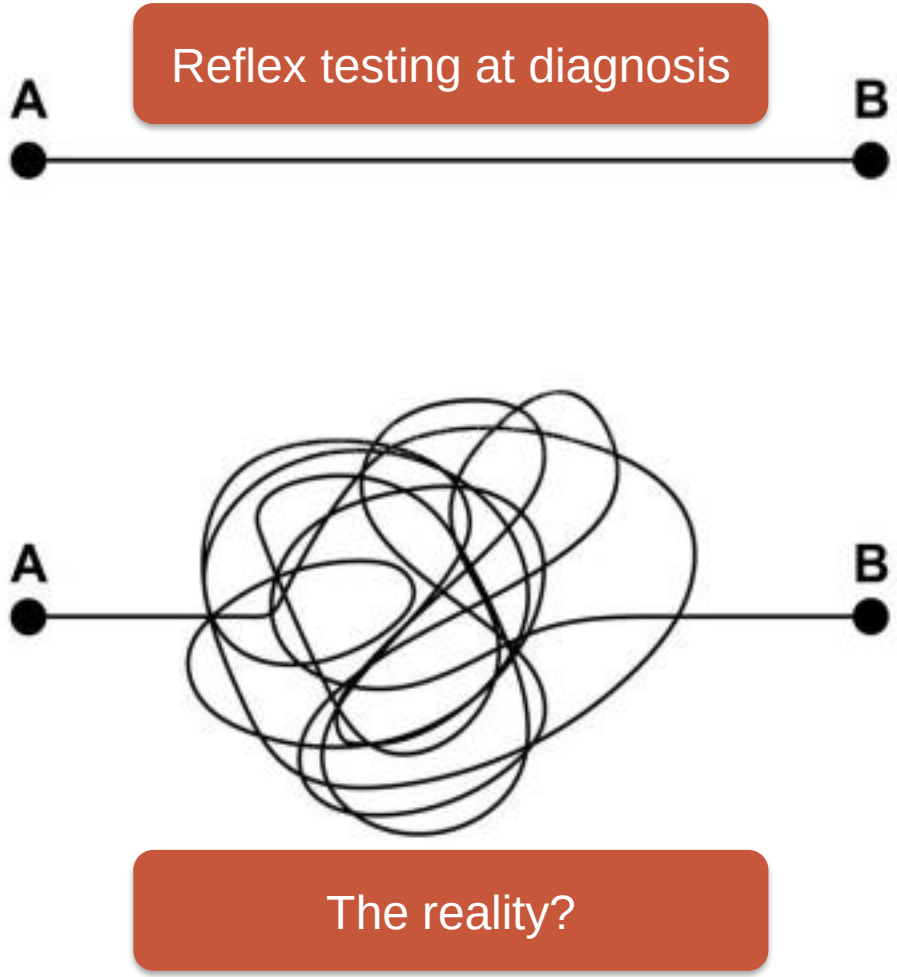


Image: Lung adenocarcinoma stained with the 4B5 clone (VENTANA), ×10 magnification. HERMES 196
Image provided by the presenter. Refer to the QR code for the full image

CONTENTS

THE WORKFLOW

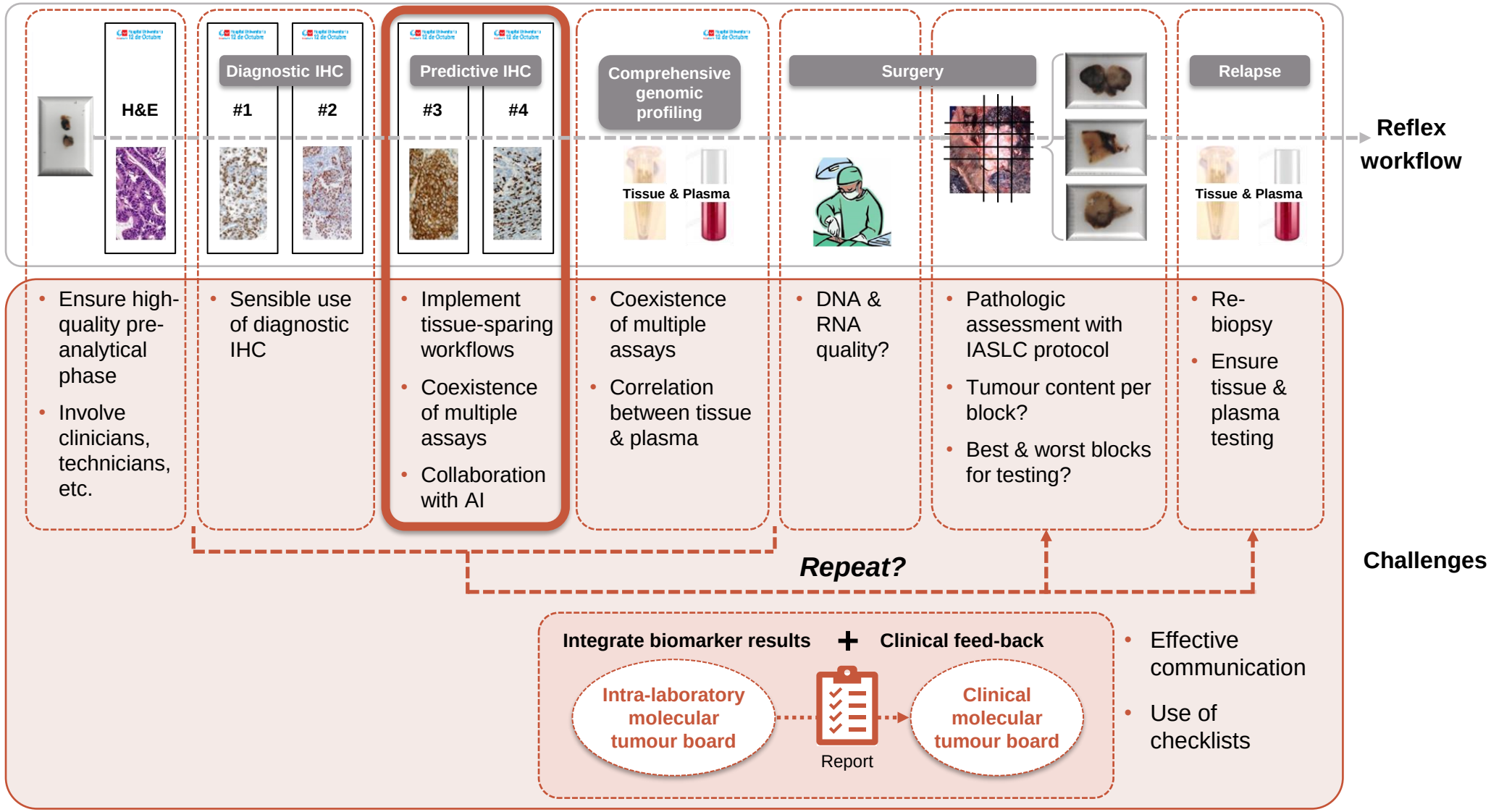
HOW CAN I IMPLEMENT A HIGH-QUALITY HER2 IMMUNOHISTOCHEMISTRY ASSAY? HOW LONG CAN MY PATIENTS WAIT FOR THE RESULTS?



Remember Gall's Law

If you want to build
a complex system that works,
build a simpler system first,
and then improve it over time

A PATIENT-CENTRED UNIVERSAL WORKFLOW FOR PREDICTIVE BIOMARKER TESTING



AI, artificial intelligence; H&E, hematoxylin and eosin; IASLC, International Association for the Study of Lung Cancer; IHC, immunohistochemistry

Figure adapted from Conde E, et al. Mod Pathol. 2022;35:1754-1756

TOP SIX PRE-ANALYTICAL FACTORS FOR TISSUE QUALITY

INVOLVE CLINICIANS AND TECHNICIANS

Time to stabilisation (cold ischemia time)

- 1 hour or less

Method of stabilisation

- Fixative: 10% phosphate-buffered formalin, pH 7.0
- Total time in formalin: at least 6 h, not more than 24-36 h (tissue with high fat content may require 48 h)
- Acid decalcification, before or during stabilisation, is contraindicated for nucleic acid analyses

Method of processing

- Specimen thickness not to exceed 4-5 mm
- Volume to mass ratio 4:1 at a minimum, preferably 10:1, with tissue completely submerged

Tissue processor variables

- Processor maintenance daily per manufacturer's recommendations
- Quality of processing fluids rigorously maintained
  - Maintenance of formalin purity and pH
  - Attention to water (i.e. formalin) contamination of alcohol baths
- Type of paraffin
  - Low-melt paraffin (melts at <60ºC)

Storage conditions

- Dry, pest-free conditions at room temperature (defined as 18-25 ºC)

Documentation data for the aforementioned factors and/or deviations from the recommendations

Note: Tissue specimens considered unacceptable for molecular testing include desiccated tissues or those known to have been improperly collected or stored

h, hours

Compton CC, et al. Arch Pathol Lab Med. 2019;143:1346-1363

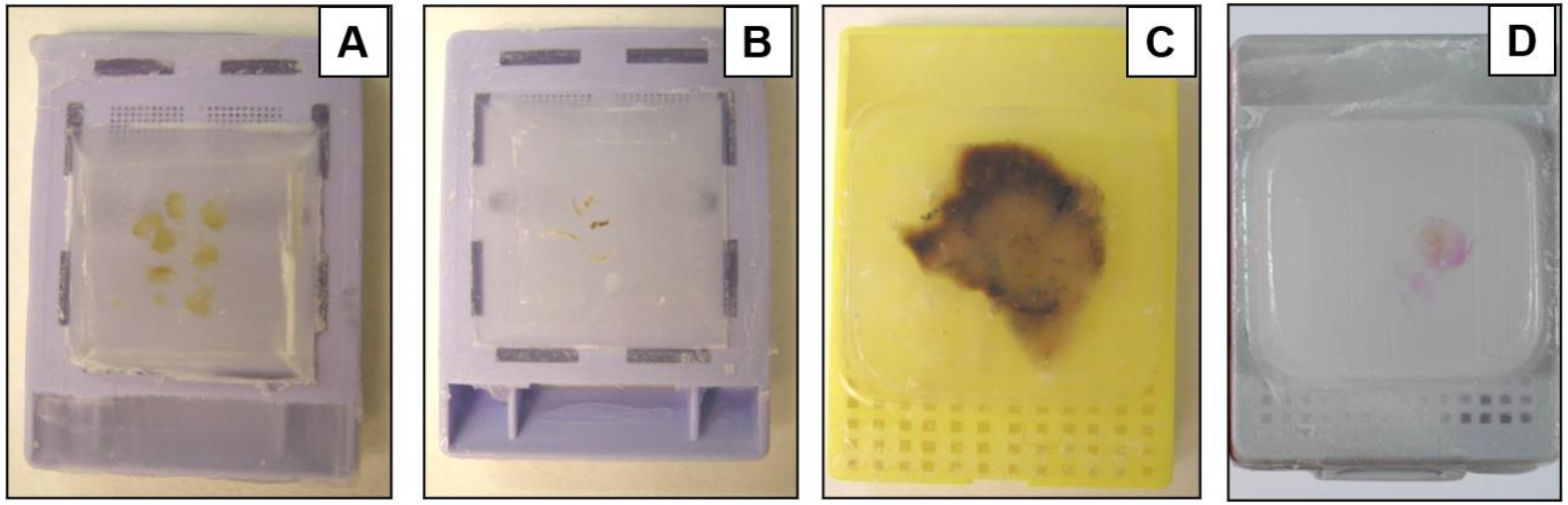
PRE-ANALYTICAL PHASE

CHOOSE WISELY: ADEQUATE TUMOUR CELLULARITY

Tissue
- A. Biopsy
- B. Core needle biopsy
- C. Surgical specimen

Cytology
- D. Cell block

Formalin fixed paraffin embedded (FFPE)



Personal communication, López-Ríos, F

PRE-ANALYTICAL PHASE

LESS IS MORE: SENSIBLE USE OF DIAGNOSTIC IHC

Key questions and recommendations for diagnostic immunohistochemistry in lung cancer

Key questions	Short answers
1. What is the best combination of markers to use in daily practice?	When IHC is needed for the subtyping of NSCC, TTF1 and p40 are the criterion standard, and these two markers are usually sufficient in clinical practice if there are no morphologic features of NE differentiation. p40 is preferable to p63 to identify squamous cell carcinoma
2. What extent of TTF1- and p40-positive reactions should we consider to be positive?	Focal positivity for TTF1 is considered a positive reaction indicating pulmonary adenocarcinoma in the proper clinical context, whereas for p40 the cut-off rate should be positivity in more than 50% of tumour nuclei. Focal or weak positivity for p40 is not diagnostic or squamous cell carcinoma
3. Are there any staining differences in lung adenocarcinoma among TTF1 clones (SPT24, SP141 and 8G7G3/1)?	The staining performance of TTF1 varies among the clones. Among the most commonly used antibodies, 8G7G3/1 is the most specific antibody to identify lung adenocarcinoma
4. Should an NSCC that is diffusely positive for CK7 but negative for TTF1 and p40 be regarded as probably adenocarcinoma?	CK7 is not specific for adenocarcinoma; the marker can be seen in squamous cell carcinoma. The use of CK7 is discouraged for subtyping of NSCC
5. When should NE markers be applied to an NSCC?	NE markers should be applied only in support of NE morphology
6. What is the best antibody panel to differentiate NE tumours from other types of NSCC and which one is the most reliable?	A panel of chromogranin A, synaptophysin and CD56 is the best combination to identify NE tumours. The staining significance of each antibody varies among the sample types, histologic subtypes and extent and/or intensity of positive reactions
7. When should a proliferation marker be used in diagnosis?	The main established role of Ki-67 in lung carcinomas is to help distinguish carcinoids from high-grade NE carcinomas (large cell NE carcinoma and small cell carcinomas), especially in small or crushed biopsy or cytologic samples. The role of Ki-67 in separating typical from atypical carcinoids is not established and needs more investigation

IHC, immunohistochemistry; NE, neuroendocrine; NSCC, non-small cell carcinoma

Yatabe Y, et al. J Thorac Oncol. 2019;14:377-407

ANALYTICAL PHASE

COEXISTENCE OF MULTIPLE ASSAYS: FOLLOW THE MANUFACTURER'S PROTOCOLS

Clinical trial	Assay	Scoring algorithm	Cut-off
DESTINY-Lung01[1]	VENTANA PATHWAY anti-HER-2/neu (4B5)	Gastric	IHC 2+ and 3+
			≥10% cut-off
DESTINY-Lung03[2]	Dako HercepTest mAb pharmDx (Dako Omnis)	Novel lung algorithm	IHC 2+ and 3+
			≥25% cut-off
DESTINY-PanTumor02[3]	Dako HercepTest mAb pharmDx (Dako Omnis)	Gastric	IHC 2+ and 3+
			≥10% cut-off

IHC, immunohistochemistry; mAb, monoclonal antibody

1. Smit EF, et al. Lancet Oncol 2024;25:439-454; 2. Planchard D, et al. Abstract OA16.05, WCLC 2024 (oral presentation); 3. Meric-Bernstam F, et al. J Clin Oncol 2024;42:47-58

ANALYTICAL PHASE

COEXISTENCE OF MULTIPLE ASSAYS: AVOID DECISION PARALYSIS

Principles of analytic validation of immunohistochemical assays – Guideline update[1]

If the laboratory director intends to perform HER2 IHC on CRC cases using a previously validated assay–scoring system combination, the laboratory director has the discretion to extend the initial validation to CRC by assessing a representative sample of CRC. If a laboratory is initially validating a new HER2 assay and intends to use the same scoring criteria in breast and colon cancers, then both cancer types should be included in the set of 20 positive and 20 negative tissues constituting the validation. It is *not* the intent of this recommendation that every assay–scoring system–*tumor type* combination be subject to the requirement of 20 positive and 20 cases for each validation. A similar approach can be applied to the myriad assay–scoring system combinations currently employed for PD-L1 predictive marker testing, so long as the validation design complies with the concept of fit for purpose.

The reader will note that amongst the various indications for PD-L1 testing, different cut-offs may be employed (for example, the use of tumor proportion score ≥1% versus ≥50%; or combined positive score ≥1 versus ≥10). It is at the laboratory director's discretion whether these different thresholds within a scoring system require separate validations.

CRC, colorectal carcinoma; IHC, immunohistochemistry

1. Goldsmith JD, et al. Arch Pathol Lab Med. 2024;148:e111-e153

INTERPRETATION

ONLY DEFINITIVE LINEAR MEMBRANE STAINING SHOULD BE SCORED

Reporting results of HER2 testing by immunohistochemistry (IHC) for trastuzumab-deruxtecan use based on the enrolment criteria for the DESTINY-PanTumor02 trial (NCT04482309)[1]

Result	Criteria for surgical specimens	Criteria for biopsy specimens
Negative (Score 0)	No staining or membrane staining in less than 10% of tumour cells	No staining in any tumour cells
Negative (Score 1+)	Faint/barely perceptible incomplete membrane staining in greater than or equal to 10% tumour cells	Tumour cell cluster[a] with a faint/barely perceptible membrane staining irrespective of percentage of positive tumour cells
Equivocal (Score 2+)	Weak to moderate, complete, basolateral or lateral membrane staining in greater than or equal to 10% of tumour cells	Tumour cell cluster[a] with a weak to moderate, complete, basolateral or lateral membrane staining irrespective of percentage of positive tumour cells
Positive (Score 3+)	Strong, complete, basolateral or lateral membrane staining in greater than or equal to 10% of tumour cells	Tumour cell cluster[a] with a strong, complete basolateral or lateral membrane staining irrespective of percentage of positive tumour cells

[a] Tumour cell cluster denotes five or more tumour cells

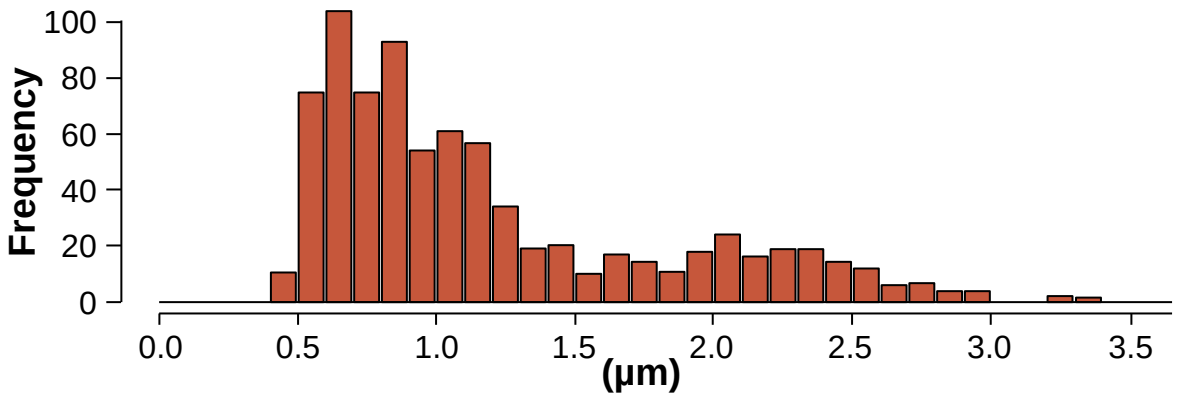
1. College of American Pathologists, Template for reporting results, December 2024. Available at: https://documents.cap.org/protocols/Gynecologic.Bmk_1.2.0.0.-REL.CAPCP.pdf (accessed February 2025)

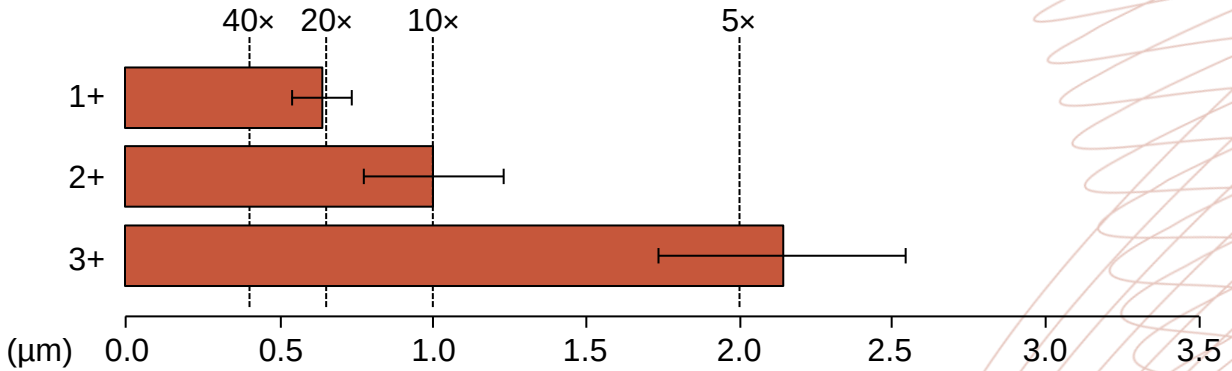
INTERPRETATION

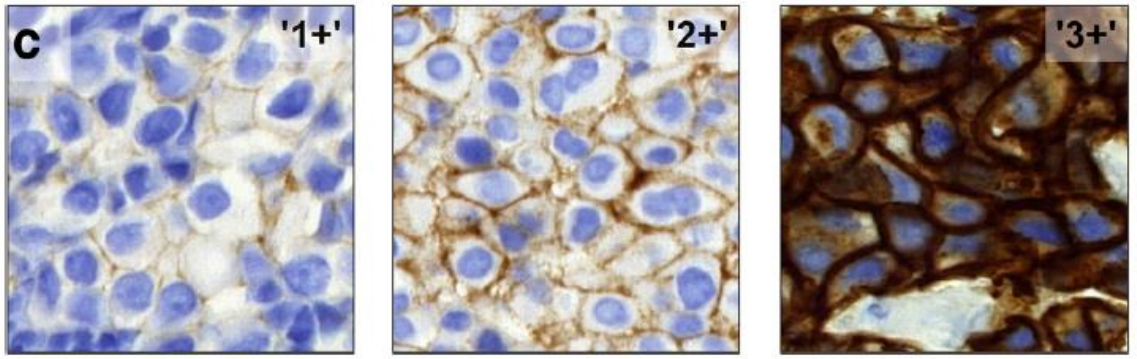
THE MAGNIFICATION RULE MIGHT BE HELPFUL

- HER2 scores correlated with the size of the precipitates

Magnification	40×	20×	10×	5×
Consensus intensity-score	**‘1+’**	**‘2+’**		**‘3+’**
Num. aperture	0.65-0.75	0.40-0.50	0.25-0.30	0.12-0.15
Resolution (µm)	0.40-0.46	0.60-0.75	1.0-1.20	2.0-2.50
DAB-precipitate width ± SD (µm)	0.64 ± 0.1	1.0 ± 0.23		2.14 ± 0.4







DAB, diaminobenzidine; SD, standard deviation

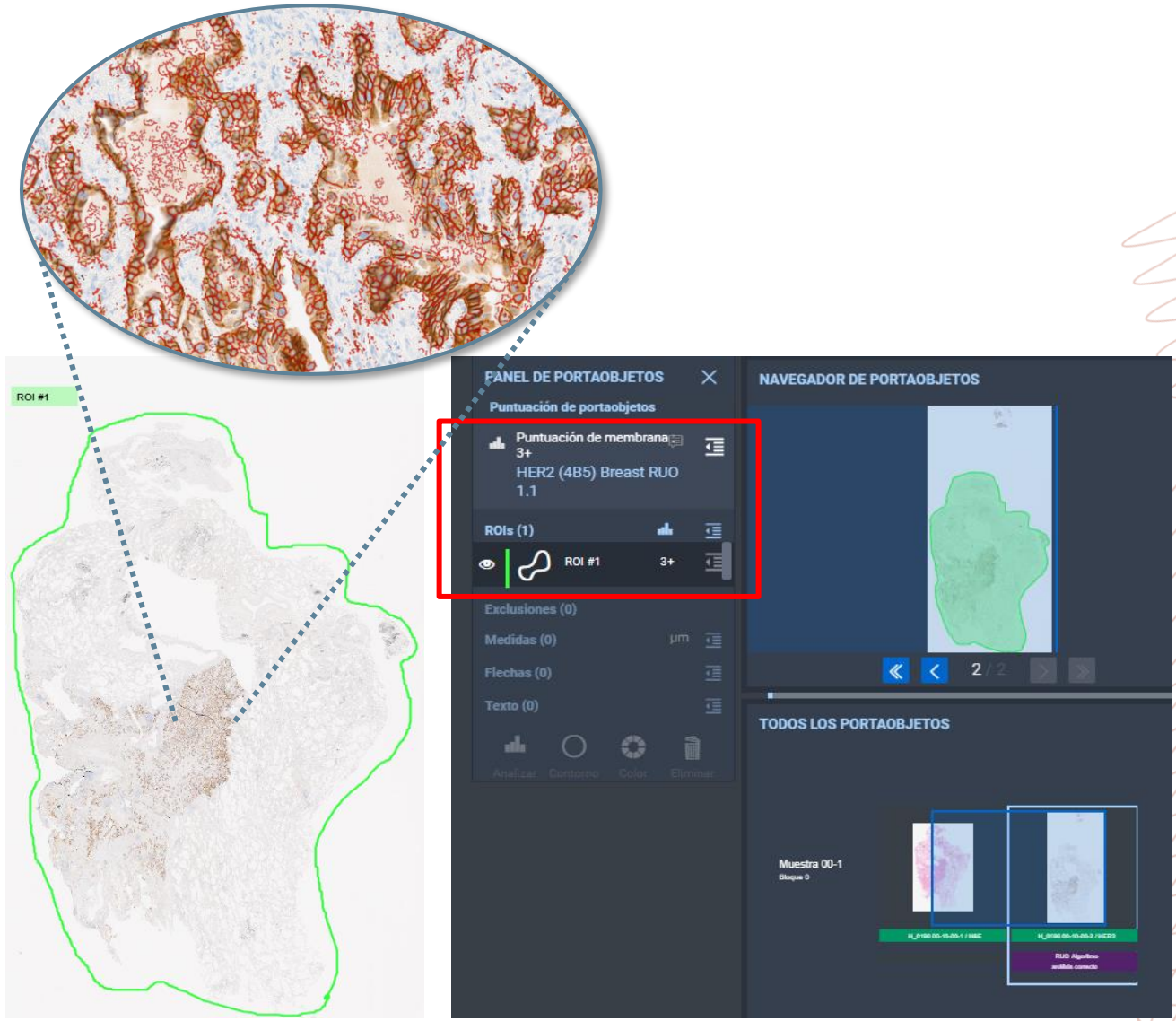
Scheel AH, et al. Diagn Pathol. 2018;13:19

INTERPRETATION

COLLABORATION WITH AI

AI-powered HER2 analyzers may have the potential to:

- Improve turnaround times
- Enhance interobserver reproducibility by reducing variability in interpretation



AI, artificial intelligence;
Navify Digital Pathology (NDP)

INTERPRETATION

CHECKLIST FOR OVARIAN CARCINOMAS: AVOID BEING LOST IN TRANSLATION

___ Based on the enrollment criteria for Trastuzumab-deruxtecan in the DESTINY-PanTumor02 phase II clinical trial (NCT04482309) for endometrial, cervical or ovarian carcinoma

HER2 Status for Trastuzumab-deruxtecan Use

 # Biopsy: No staining in any tumor cells; Surgical specimen: No staining or membrane staining in less than 10% of tumor cells

___ Negative (score 0) for protein overexpression#

Biopsy: Tumor cell cluster (5 or more tumor cells) with a faint / barely perceptible membrane staining irrespective of percentage of positive tumor cells; Surgical specimen: Faint / barely perceptible incomplete membrane staining in greater than or equal to 10% tumor cells

___ Negative (score 1+) for protein overexpression##

Biopsy: Tumor cell cluster (5 or more tumor cells) with a weak to moderate, complete, basolateral or lateral membrane staining irrespective of percentage of positive tumor cells; Surgical specimen: Weak to moderate, complete, basolateral or lateral membrane staining in greater than or equal to 10% of tumor cells

___ Equivocal (score 2+) for protein overexpression###

Biopsy: Tumor cell cluster (5 or more tumor cells) with a strong, complete, basolateral or lateral membrane staining irrespective of percentage of positive tumor cells; Surgical specimen: Strong, complete, basolateral or lateral membrane staining in greater than or equal to 10% of tumor cells

___ Positive (3+) for protein overexpression####

___ Cannot be determined (explain): _____

+HER2 Comment: _____

Test Type

___ Food and Drug Administration (FDA) cleared (specify test / vendor): _____

___ Laboratory-developed test

+___ Non-U.S.-based health systems

+___ Health Canada Approved (specify test / vendor): _____

+___ Other (specify): _____

Primary Antibody

___ 4B5

___ HercepTest

___ A0485

___ SP3

___ EP3

___ CB11

___ Other (specify): _____

College of American Pathologists, Template for reporting results, December 2024. Available at: https://documents.cap.org/protocols/Gynecologic.Bmk_1.2.0.0.-REL.CAPCP.pdf (accessed February 2025)

INTERPRETATION

CHECKLIST FOR CARCINOMAS: AVOID BEING LOST IN TRANSLATION

___ HER2 IHC

HER2 IHC Results

+Interpretation

___ Positive
___ Negative
___ Equivocal
___ Cannot be determined (indeterminate)

+Scoring System

___ Breast
___ Gastric
___ Other (specify): _____

+Score

___ 0
___ 1+
___ 2+
___ 3+
___ Other (specify): _____

+Specify Percentage of Cells with Uniform Intense Complete Membrane Staining:

_____ %

+Comments: _____

Given the potential need for rescoring the HER2 expression depending on the clinical indication, the percentage of tumour cells with strong complete or basolateral/lateral membrane staining may be reported, in addition to the overall HER2 IHC result.

IHC, immunohistochemistry

College of American Pathologists, Template for reporting results, September 2023. Available at: https://documents.cap.org/protocols/IHC.Bmk_1.1.0.1.REL_CAPCP.pdf (accessed February 2025); College of American Pathologists, Template for reporting results, December 2024. Available at: https://documents.cap.org/protocols/Gynecologic.Bmk_1.2.0.0.-REL.CAPCP.pdf (accessed February 2025)

INTERPRETATION

CHECKLIST FOR CARCINOMAS: AVOID BEING LOST IN TRANSLATION

HER2 IHC Methods

+Antibody

___ HercepTest
___ 4B5
___ SP3
___ Other (specify): _____

+Controls

___ External controls available, expected immunoreactivity
___ External controls available; no immunoreactivity in expected cells

+Assay Information

___ Food and Drug Administration (FDA) cleared test / vendor (specify): _____
___ Laboratory-developed test

+Specify Quantitative Imaging Analytics Performed: _____

IHC, immunohistochemistry

College of American Pathologists, Template for reporting results, September 2023. Available at: https://documents.cap.org/protocols/IHC.Bmk_1.1.0.1.REL_CAPCP.pdf (accessed February 2025);

CONTENTS

FURTHER READING

- Compton CC, et al., **Preanalytics and Precision Pathology: Pathology Practices to Ensure Molecular Integrity of Cancer Patient Biospecimens for Precision Medicine.** Arch Pathol Lab Med. 2019 Nov;143(11):1346-1363

- Goldsmith JD, et al., **Principles of Analytic Validation of Immunohistochemical Assays: Guideline Update.** Arch Pathol Lab Med. 2024 Jun 1;148(6):e111-e153

- Yoon J, Oh DY. **HER2-targeted therapies beyond breast cancer - an update.** Nat Rev Clin Oncol. 2024 Sep;21(9):675-700

AN OVERVIEW OF CHALLENGES RELATED TO HER2 IMMUNOHISTOCHEMISTRY

Q&A SESSION

TARGETING HER2 IN LUNG CANCER: WHERE DOES THE IHC TESTING FIT IN?

Prof. Christian Rolfo

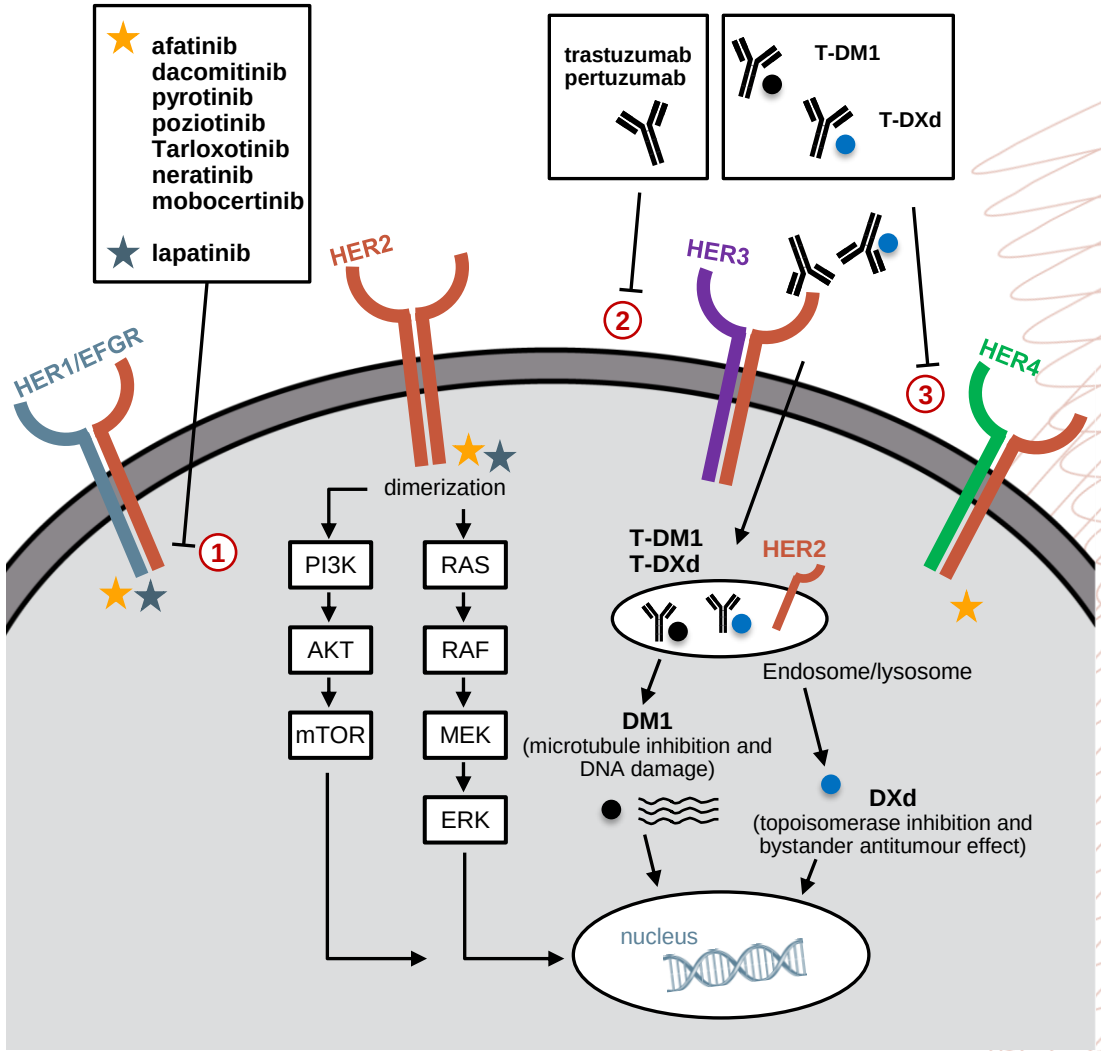
Medical Oncologist

The James, The Ohio State University, USA

HER2 FAMILY AND TARGETS

- TKIs block phosphorylation of the tyrosine kinase residues, inhibiting cell proliferation
- Monoclonal antibodies bind to the extracellular domain of HER2 to block homo and heterodimerisation
- ADCs incorporate the HER2-targeted actions of trastuzumab with a cytotoxic component (microtubule inhibitor or topoisomerase I inhibitor) connected by a cleavable tetrapeptide-based linker

Non-small cell lung cancer HER2 tumorigenesis pathways and targeted therapy mechanisms

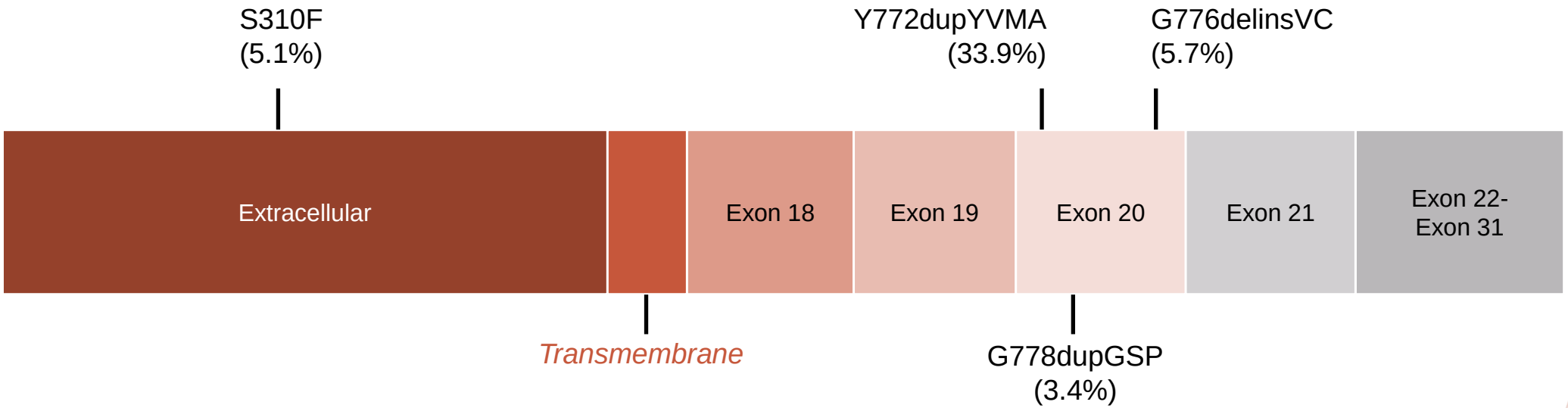


ADC, antibody-drug conjugate; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

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

ACTIONABLE *HER2* MUTATIONS IN NSCLC

Frequency and location of *HER2* mutations found in NSCLC[1]



NCCN and ESMO guidelines recommend broad molecular profiling of patients with NSCLC, including *HER2* mutation testing[2,3]

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NSCLC, non small cell lung cancer;

1. Robichaux JP, et al. Cancer Cell. 2019:14;36:444-457; 2. Ettinger DS, et al. J Natl Compr Canc Netw. 2022;20:497-530;
3. Hendriks LE, et al. Ann Oncol. 2023;34:339-357

TYPES OF HER2 ALTERATIONS IN NSCLC[1-5]

Type	*ERBB2* mutations	*ERBB2* amplification	HER2 overexpression
Frequency (%)	1-4[1]	2-22[5]	7.7-23%[5]
Detection method	NGS, PCR[1]	FISH[1,2]	IHC[5]

Different types of alterations seem to originate from different mechanisms and induce different biological and clinical consequences[1-4]

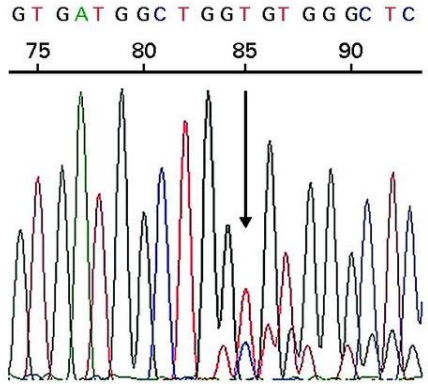
IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; FISH, fluorescence in-situ hybridisation

1. Yu Y, et al. Cancer Treat Rev. 2023;114:102520; 2. Ricciardi GRR, et al. J Thorac Oncol. 2014;9:1750-1762; 3. Lai WV, et al. Eur J Cancer. 2019;109:28-35; 4. Peters S and Zimmermann S. Transl Lung Cancer Res. 2014;3:84-88; Mar N, et al. Lung Cancer. 2015;87:220-225; 5. Ren S, et al. ESMO Open. 2022;7:100395; Sholl LM., et al. J Thorac Oncol. 2015;10:768-777

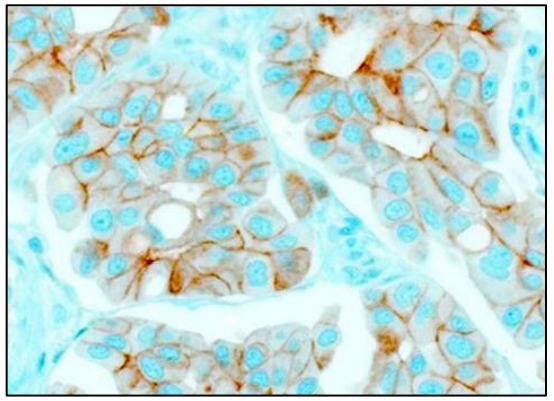
HER2 MUTATIONS IN NSCLC

METHODOLOGY FOR DETECTION

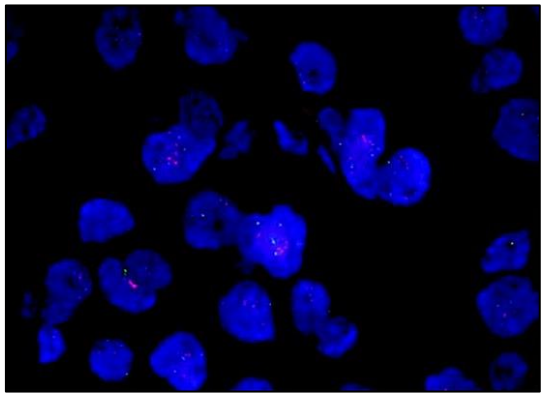
Sanger sequencing read with heterozygous *HER2* exon 20 insertion



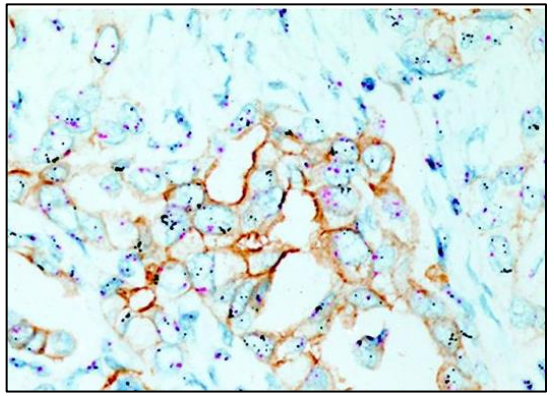
HER2 IHC with score 2+



FISH with *HER2* amplification (*HER2* in red; centromere 17 in green)



Tricolour visualisation of HER2 protein (in brown), *HER2* gene (in black), and centromere 17 (in red)



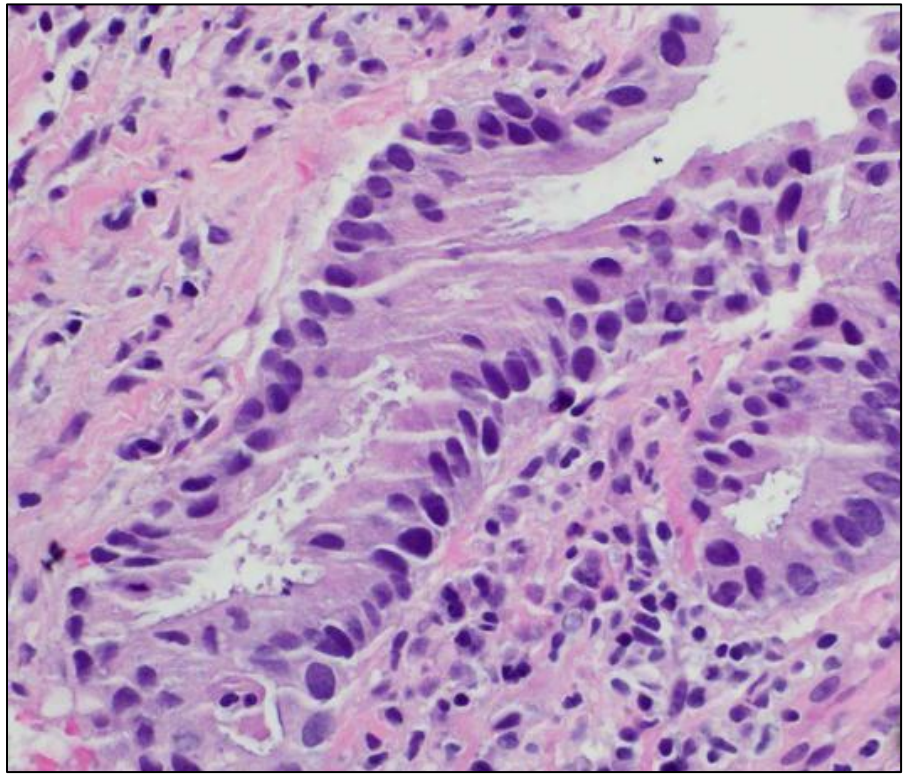
FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer

Mazières J, et al. J Clin Oncol. 2013;31:1997-2003

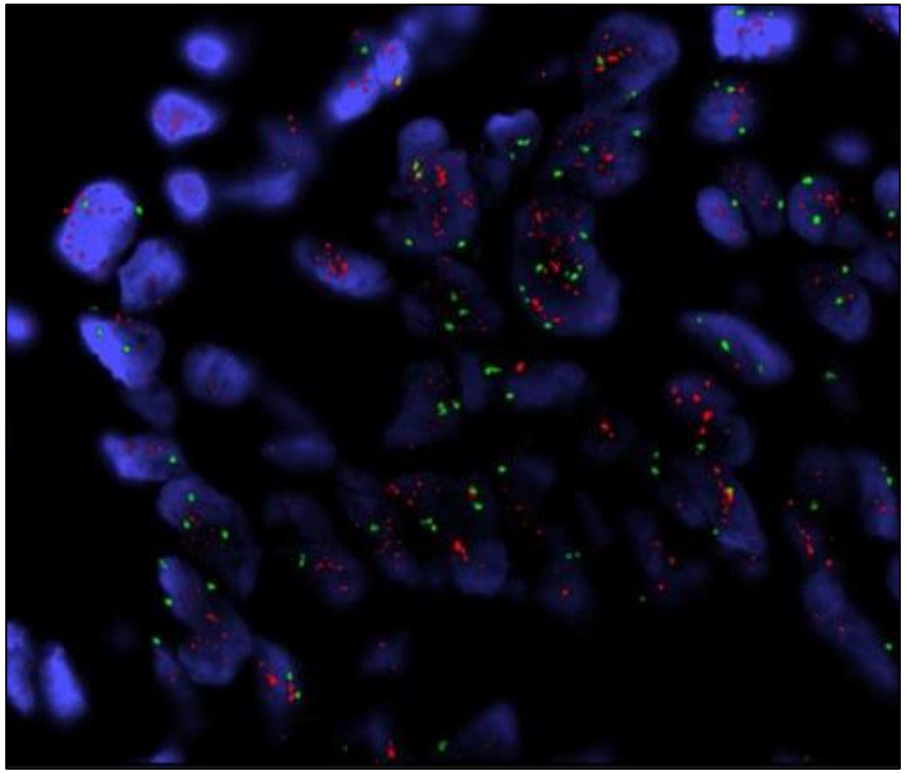
HER2 AMPLIFICATION IN NSCLC

DIAGNOSTIC

Hematoxylin and eosin



FISH



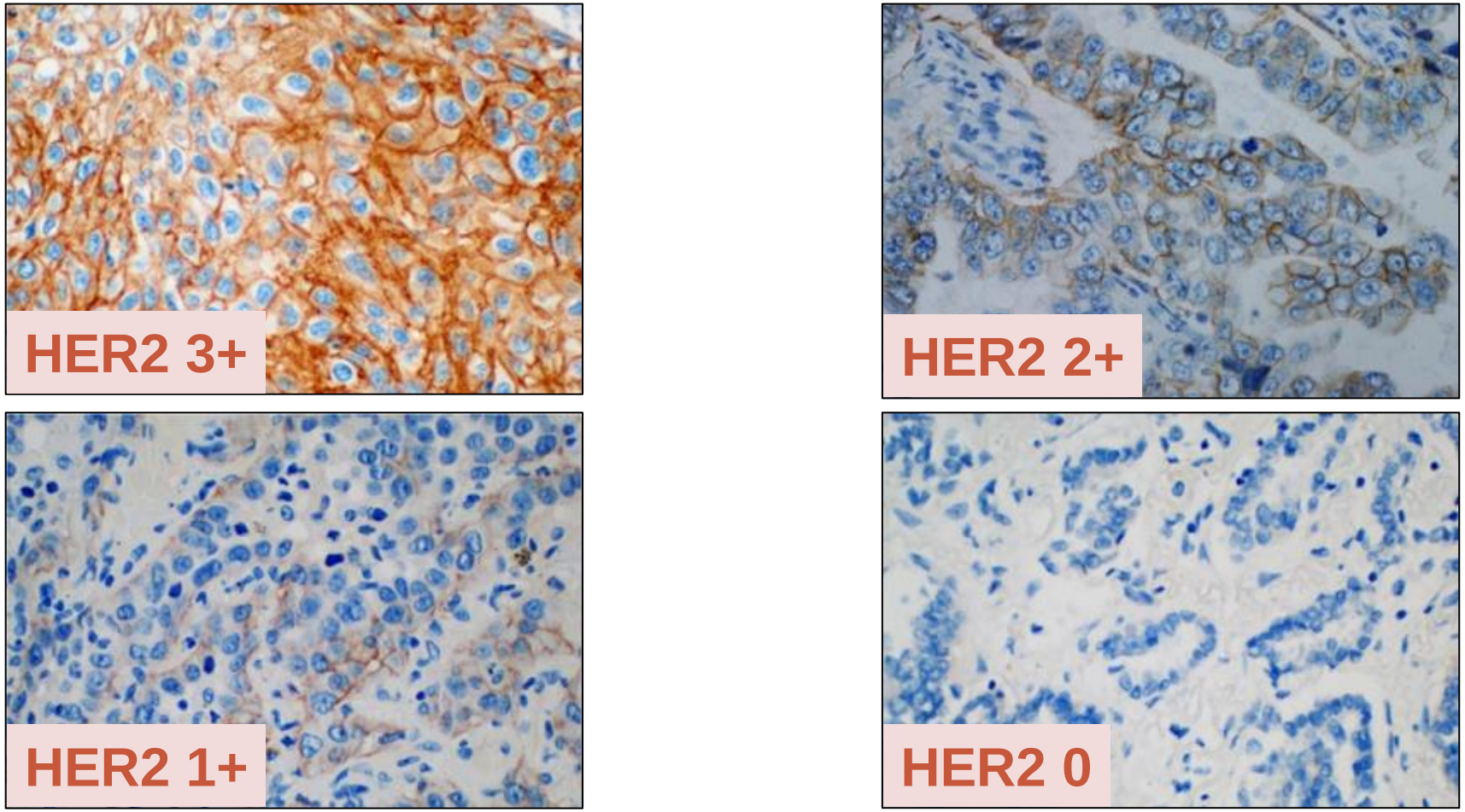
Representative images of lung adenocarcinoma with HER2 *gene amplification*

FISH, fluorescence in-situ hybridisation; NSCLC, non-small cell lung cancer

Li BT, et al. J Thorac Oncol. 2016;11:414-419

HER2 OVEREXPRESSION IN NSCLC USING IHC

DIAGNOSTIC



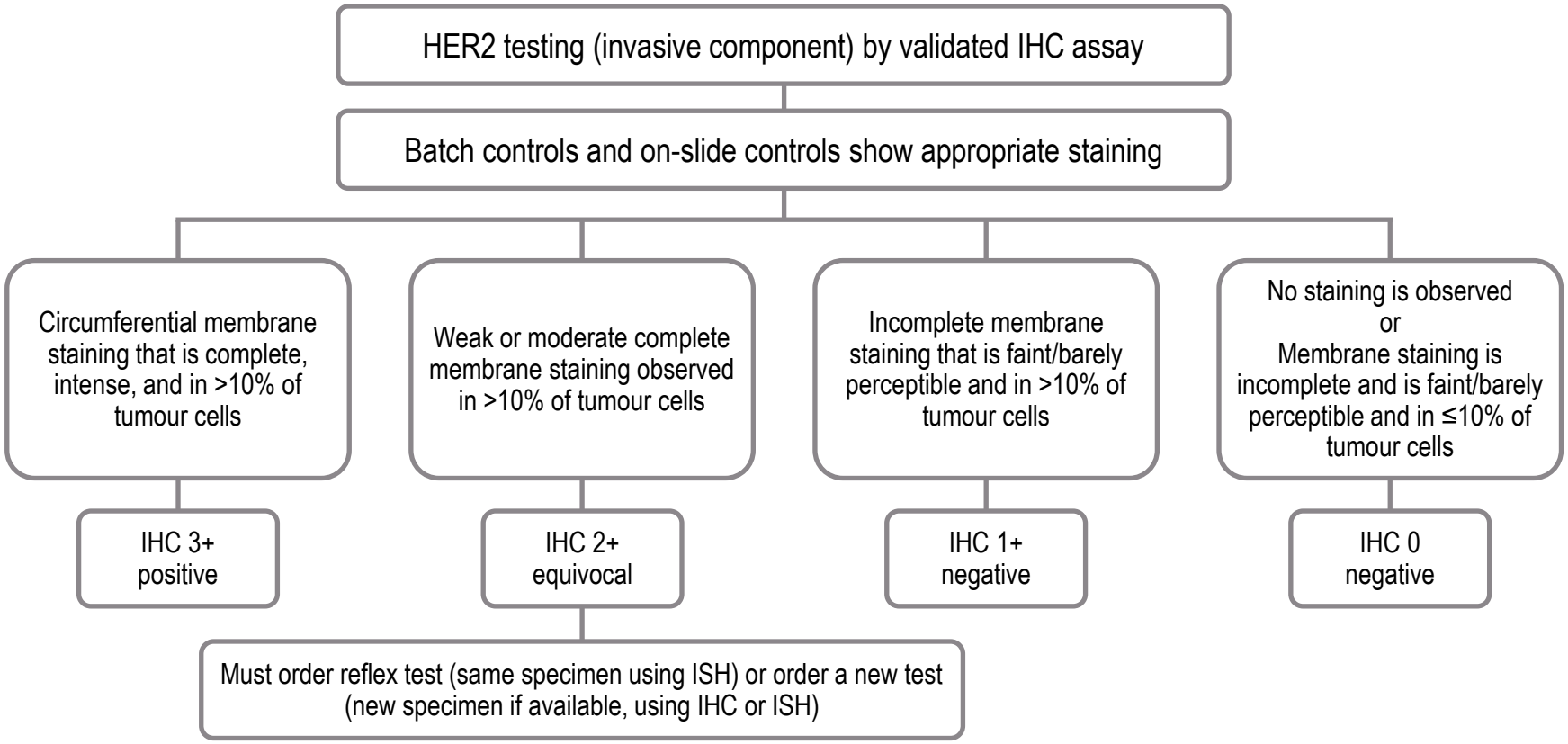
Representative images of HER2 IHC

IHC, immunohistochemistry; NSCLC, non small cell lung cancer

Abu Al Karsaneh O, et al. Diagn Pathol. 2023;18:75

EVALUATION OF HER2 PROTEIN EXPRESSION BY IHC ASSAY

AN ALGORITHM[1]



There is **no consensus** on the definition of HER2 protein overexpression in lung cancer
ASCO/CAP breast cancer guidelines are used to guide diagnosis[2]

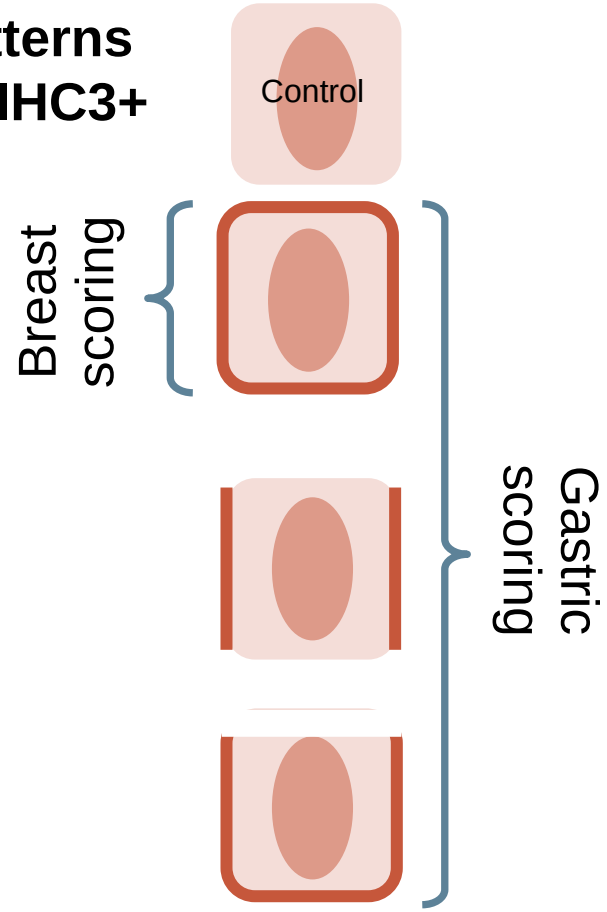
ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; IHC, immunohistochemistry; ISH, in-situ hybridisation

1. Wolff AC, et al. Arch Pathol Lab Med. 2023;147:993-1000; 2. Uy NF, et al. Cancers (Basel). 2022;14:4155

ASCO/CAP HER2 SCORING AND INTERPRETATION GUIDELINES

GASTRIC CANCER HAS SPECIFIC CUT-OFFS TO DETERMINE EACH IHC SCORE

Staining patterns required for IHC3+



IHC scoring for breast cancer[1]	IHC scoring for gastric cancer
Extent: >10%	**Surgical specimen:** ≥10% of tumour cells
	Biopsy specimen: Tumour cell cluster (≥5 tumour cells)
Circularity: a must in IHC 2+/3+	**Circularity:** mostly missing (often only lateral in IHC 2+/3+)

Slide Courtesy of Dr. Bruna Pellini

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; IHC, immunohistochemistry

Rüschoff J, et al. Mod Pathol. 2012;25:637-650

BREAST AND GASTRIC CANCER INTERPRETATION GUIDELINES

HER2 IHC SCORES WERE CONCORDANT FOR 87% SAMPLES

Comparison of HER2 IHC assessment in breast cancer (BC) vs gastroesophageal adenocarcinoma (GEA) across all samples

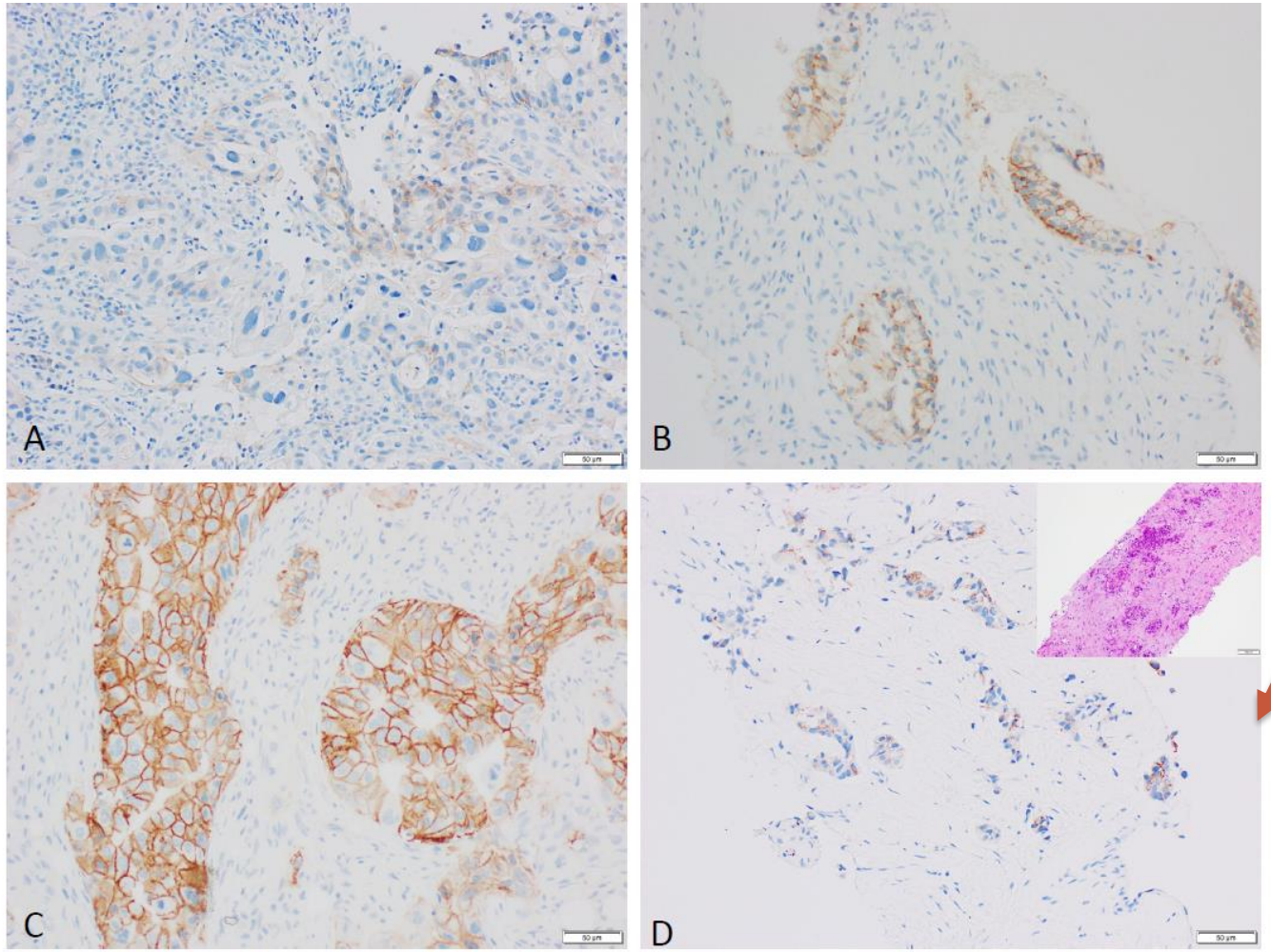
HER2 IHC score				
Breast cancer	Gastroesophageal adenocarcinoma			
	3+	2+	0 or 1+	Total
3+	15 (7.9%)	0 (0%)	0 (0%)	15 (7.9%)
2+	5 (2.6%)	18 (9.4%)	0 (0%)	23 (12%)
0 or 1+	0 (0%)	20 (10%)	133 (70%)	153 (80%)
Total	20 (10%)	38 (20%)	133 (70%)	191 (100%)

IHC, immunohistochemistry

Courtesy of Pellini B. Submitted for publication

ASCO/CAP BC VS GASTRIC/GASTROESOPHAGEAL ADK GUIDELINES

HER2 IHC SCORING DISCREPANCIES



IHC-stained section revealing a **2+ IHC score** based on the ASCO/CAP guideline for **gastric/gastroesophageal** adenocarcinoma, but score is **0** when using the guideline for **breast cancer** (clone: 4B5,x20).

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; IHC, immunohistochemistry

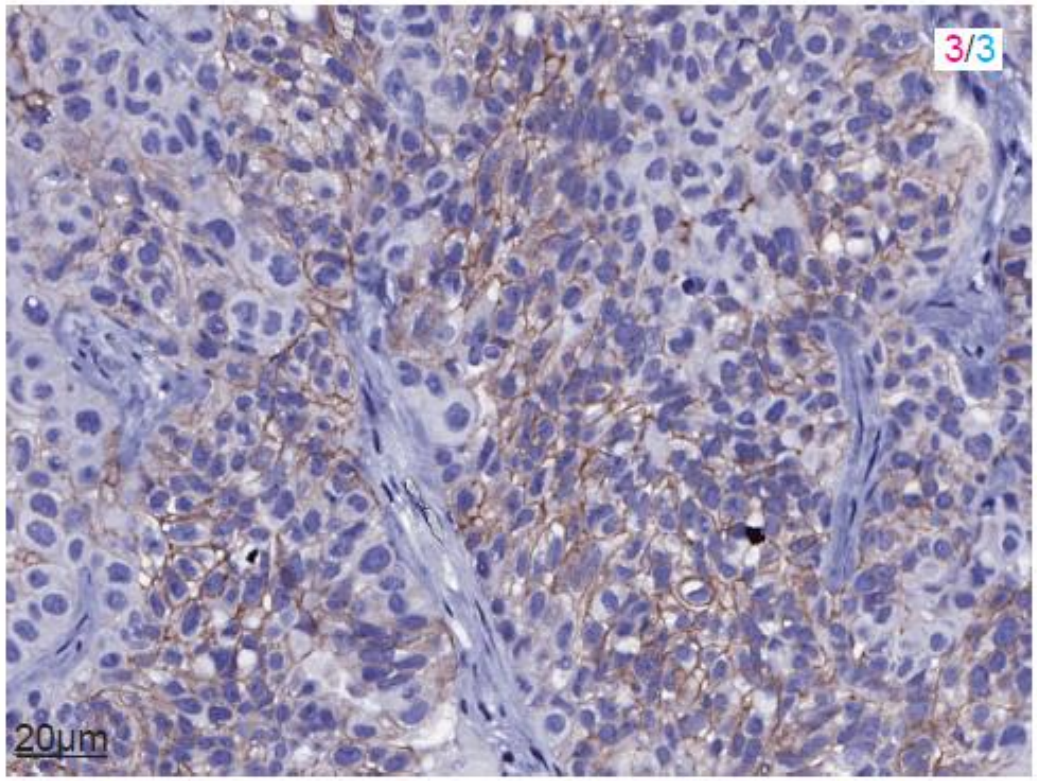
Courtesy of Pellini B. Submitted for publication

ASCO/CAP HER2 IHC GUIDELINES FOR GASTRIC/GEJ CANCER

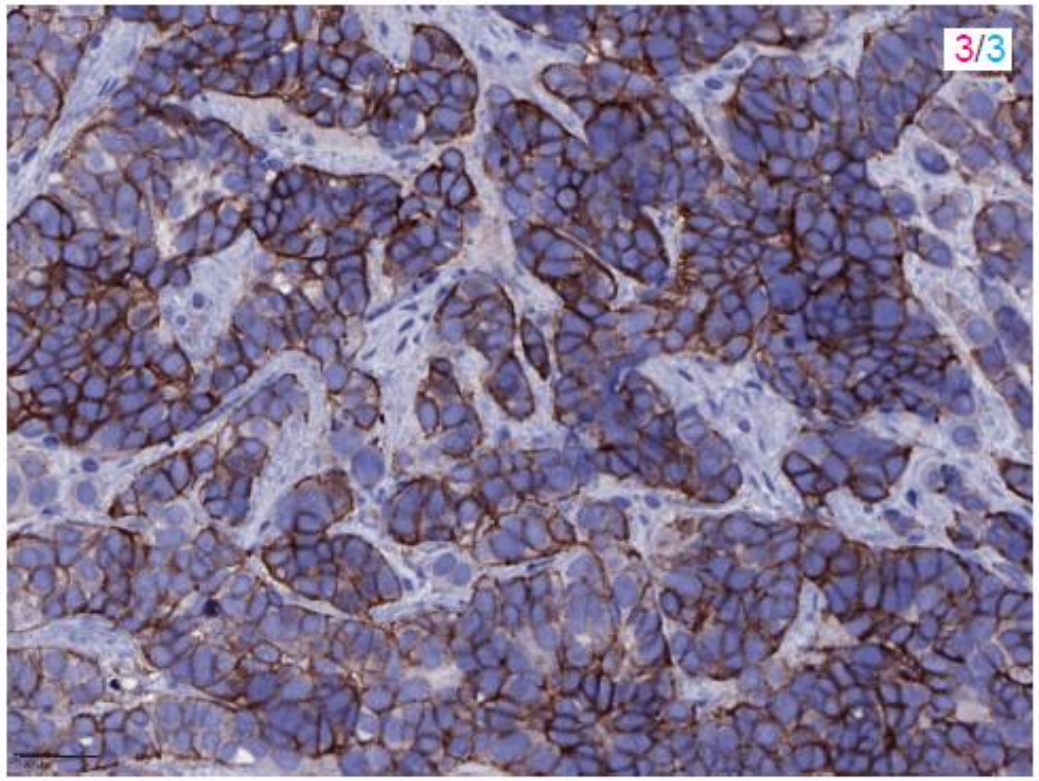
HER2 IHC DIFFERENCES IN STAINING IN NSCLC XENOGRAFT MODELS

Even when the score is 3+

Therapy naïve H358



Sotorasib-treated



HER2 IHC

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; IHC, immunohistochemistry

Courtesy of Pellini B. Submitted for publication

HER2-POSITIVE NCSLC

TREATMENT APPROACHES

NSCLC, non-small cell lung cancer

POLLING QUESTION

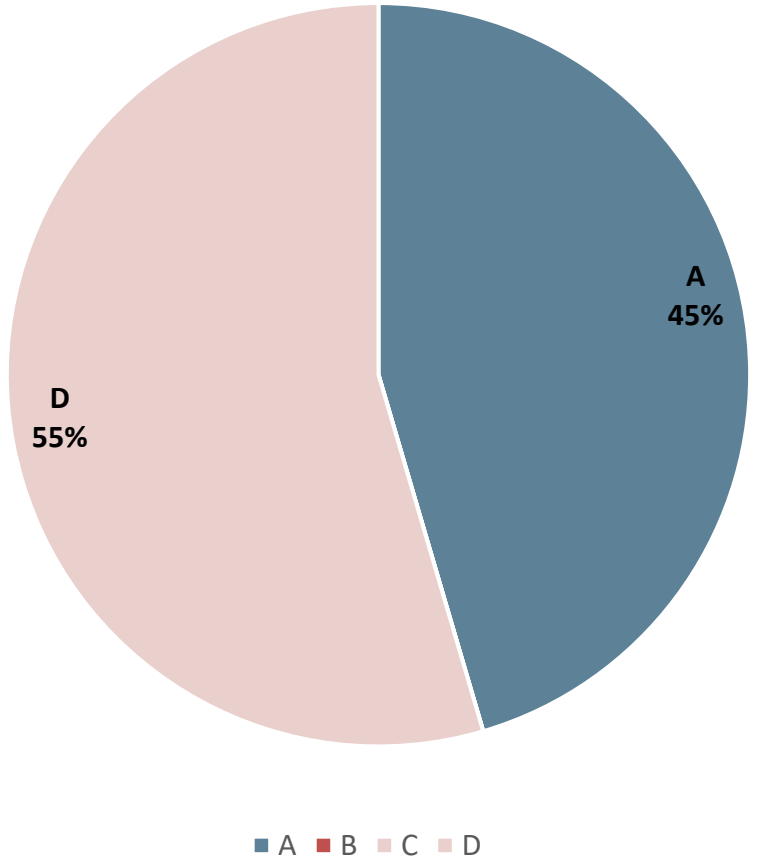
WHICH STATEMENT ABOUT HER2 ALTERATIONS IN LUNG CANCER IS CORRECT?

A. Only HER2 mutations are relevant in lung cancer

B. Only HER2 overexpression is relevant in lung cancer

C. HER2 mutations in lung cancer are most commonly found in squamous cell carcinoma

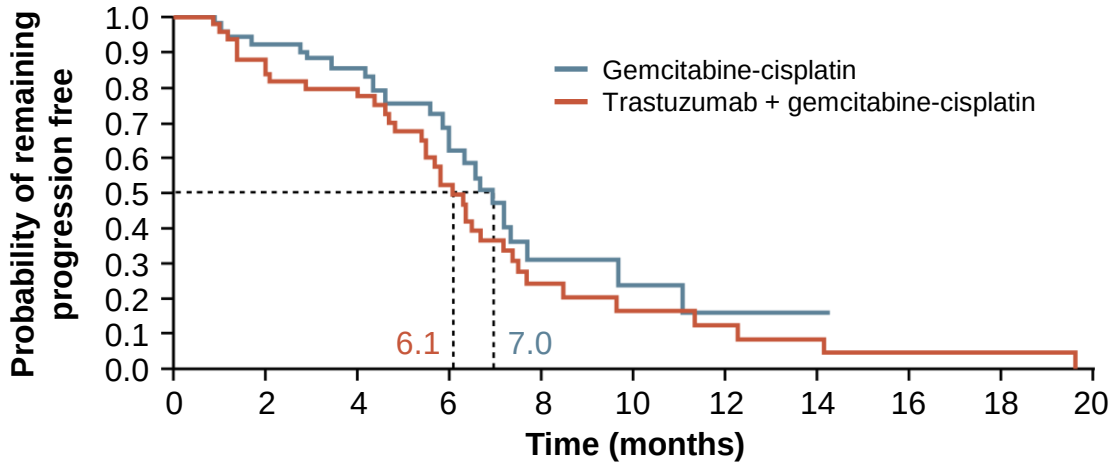
D. HER2-targeted therapies have shown clinical activity in patients with HER2-mutant and HER2 IHC3+ non-small cell lung cancer (NSCLC)



NSCLC; non-small cell lung cancer;

HER2-POSITIVE LUNG CANCER TREATED WITH ANTI-HER2 DRUGS

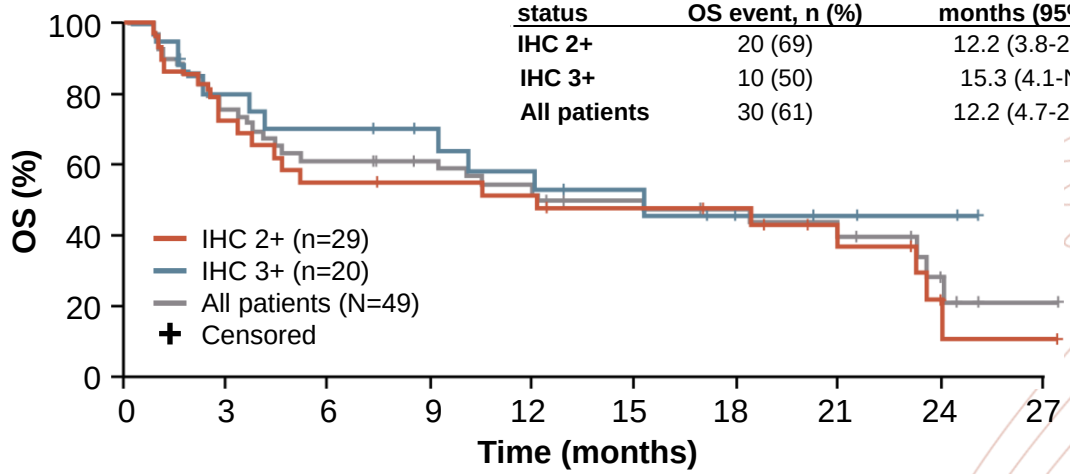
PFS of gemcitabine–cisplatin with or without trastuzumab in HER2-positive NSCLC[1]



NO BENEFIT

T-DM1 in metastatic NSCLC[2]

IHC status	Patients with OS event, n (%)	Median time to OS event, months (95% CI)
IHC 2+	20 (69)	12.2 (3.8-23.3)
IHC 3+	10 (50)	15.3 (4.1-NE)
All patients	30 (61)	12.2 (4.7-23.6)



MINIMUM BENEFIT

- Contrary to **breast cancer**, where HER2 overexpression often occurs concurrently with *HER2* amplification, this co-occurrence has been less consistently observed in **lung cancer**
- Mutations in the *HER2* gene are also not clearly associated with increased levels of *HER2* amplification

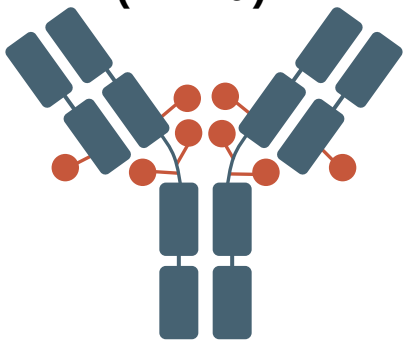
CI, confidence interval; IHC, immunohistochemistry; NE, not evaluable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine

1. Gatzemeier U, et al. Ann Oncol. 2004;15:19-27; 2. Peters S, et al. Clin Cancer Res. 2019;25:64-72

CAN ADCs BE THE TURNING POINT FOR HER2 TREATMENT IN NSCLC?

ADC CHARACTERISTIC DIFFERENCES BETWEEN T-DXd AND T-DM1

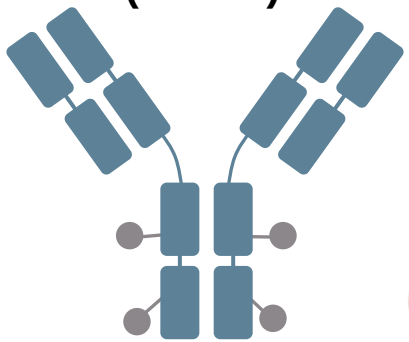
Next generation ADCs
Trastuzumab deruxtecan (T-DXd)[1]



HER2-targeting ADCs with similar mAb backbone

T-DXd[1-4,a]	ADC attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumour-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumour effect?**	No

First-generation ADCs
Trastuzumab emtansine (T-DM1)[5]



ADC, antibody-drug conjugate; mAb, monoclonal antibody; MoA, mechanism of action; NSCLC, non-small cell lung cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

1. Azar I, et al. Lung Cancer (Auck). 2021;12:103-113; 2. Ogitani Y, et al. Clin Cancer Res. 2016;22:5097-108;
3. Trail PA, et al. Pharmacol Ther. 2018;181:126-142; 4. Ogitani Y, et al. Cancer Sci. 2016;107:1039-1046; 5. LoRusso PM, et al. Clin Cancer Res. 2011;17:6437-6447

DESTINY-LUNG01 - PHASE 2 – HER2 MUTANT

TRIAL DESIGN

Key eligibility criteria[1,2]

- Unresectable/metastatic non-squamous NSCLC
- Relapsed following or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases allowed
- ECOG PS 0 or 1
- Locally reported *HER2* mutant (for Cohort 2)

***HER2* mutant**

Cohort 1:[3]
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg q3w
N=49

Cohort 1a:[3]
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg q3w
N=41

Cohort 2:[2]
***HER2* mutant**
T-DXd 6.4 mg/kg q3w
N=42

Cohort 2 expansion:[2]
***HER2* mutant**
T-DXd 6.4 mg/kg q3w
N=49

Primary endpoint[1]

- Confirmed ORR by ICR

Secondary endpoints[1]

- Confirmed ORR by INV
- DoR by ICR and INV
- DCR by ICR and INV
- PFS by ICR and INV
- OS
- Safety

Exploratory endpoint[1]

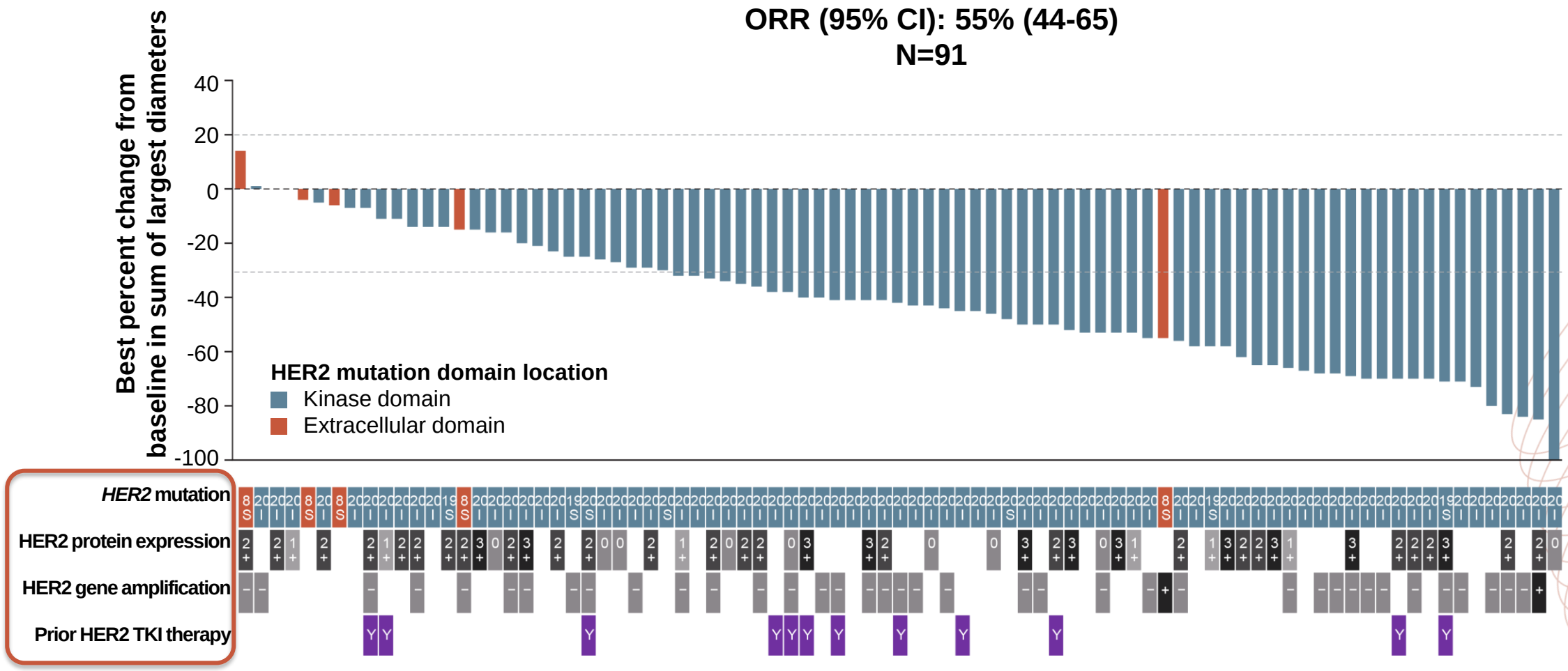
- Biomarkers of response

CNS, central nervous system; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; ICR, independent central review; IHC, immunohistochemistry; INV, investigator assessment; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

1. Li BT, et al. N Engl J Med. 2022;386:241-251 (including protocol); 2. Li B, et al. Ann Oncol. 2023;34 (suppl_2):S755-S851 (presented at ESMO 2023); 3. Smit EF, et al. Lancet Oncol. 2024;25:439-454

DESTINY-LUNG01 – PHASE 2 – HER2 MUTANT

TRASTUZUMAB DERUXTECAN SHOWED DURABLE ANTICANCER ACTIVITY IN PATIENTS WITH PREVIOUSLY TREATED *HER2*-MUTATED NSCLC



CI, confidence interval; NSCLC, non-small cell lung cancer; ORR, objective response rate

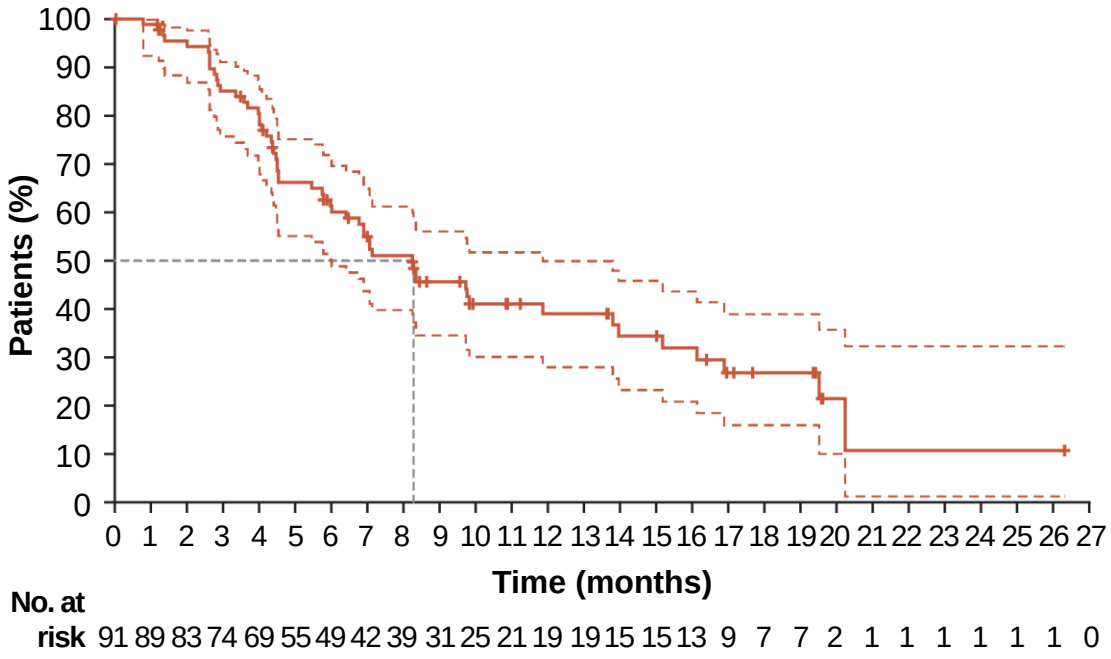
Li BT, et al. N Engl J Med. 2022;386:241-251

DESTINY-LUNG01 – PHASE 2 – HER2 MUTANT

PFS AND OS

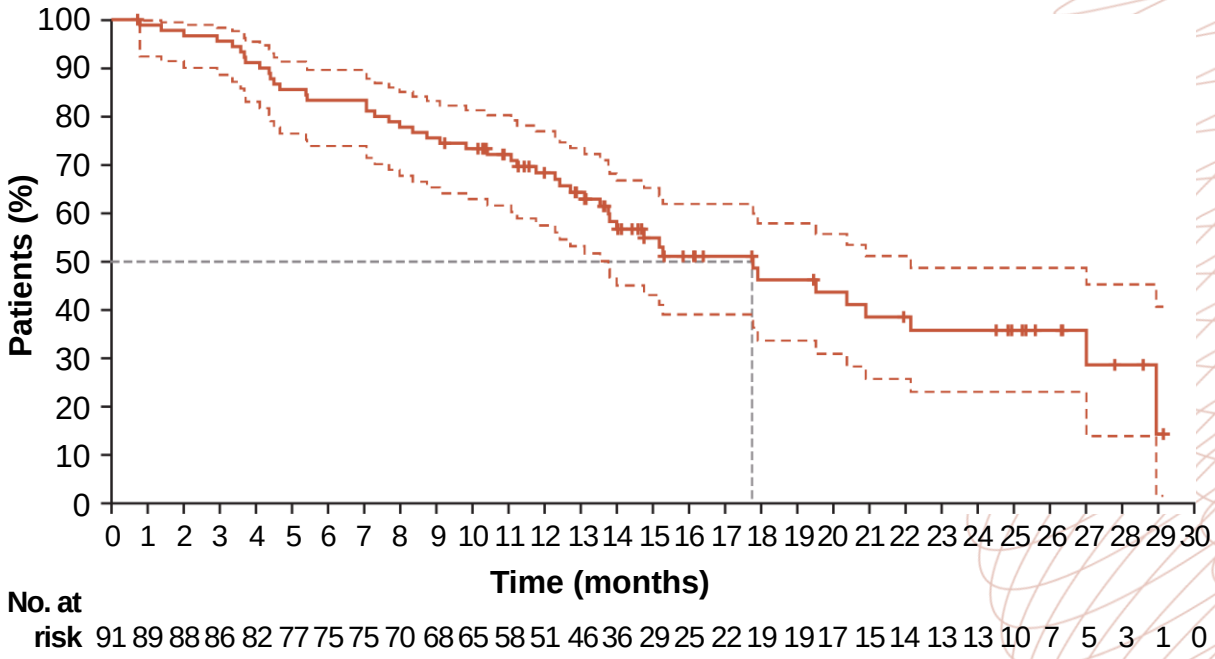
PFS[a]

Median (95% CI), months: 8.2 (6.0-11.9)



OS[a]

Median (95% CI), months: 17.8 (13.8-22.1)



- Safety profile included interstitial lung disease that was fatal in 2 cases
- Observed toxic effects were generally consistent with those in previously reported studies

[a] Dashed lines indicate 95% confidence intervals

OS, overall survival; PFS, progression-free survival;

Li BT, et al. N Engl J Med. 2022;386:241-251

HER2-MUTANT AND HER2-OVEREXPRESSION:

SAME DISEASE BUT DIFFERENT RESULTS

DESTINY-LUNG01 – PHASE 2 – HER2-OVEREXPRESSING

STUDY DESIGN

(IHC 3+ or IHC 2+)

Key eligibility criteria

- Unresectable metastatic non-squamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- ECOG PS of 0 or 1

Cohort 1: HER2-overexpressing
(IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg q3w
n=49

Cohort 1a: HER2-overexpressing
(IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg q3w
n=41

Cohort 2: HER2-mutated
T-DXd 6.4 mg/kg q3w
n=78
(Encore to be presented at WCLC: abstract 1419)

Cohort 2 expansion: HER2-mutated
T-DXd 6.4 mg/kg q3w
n=50

Primary endpoint

- ORR

Secondary endpoints

- PFS
- OS
- DoR
- DCR
- Safety and tolerability

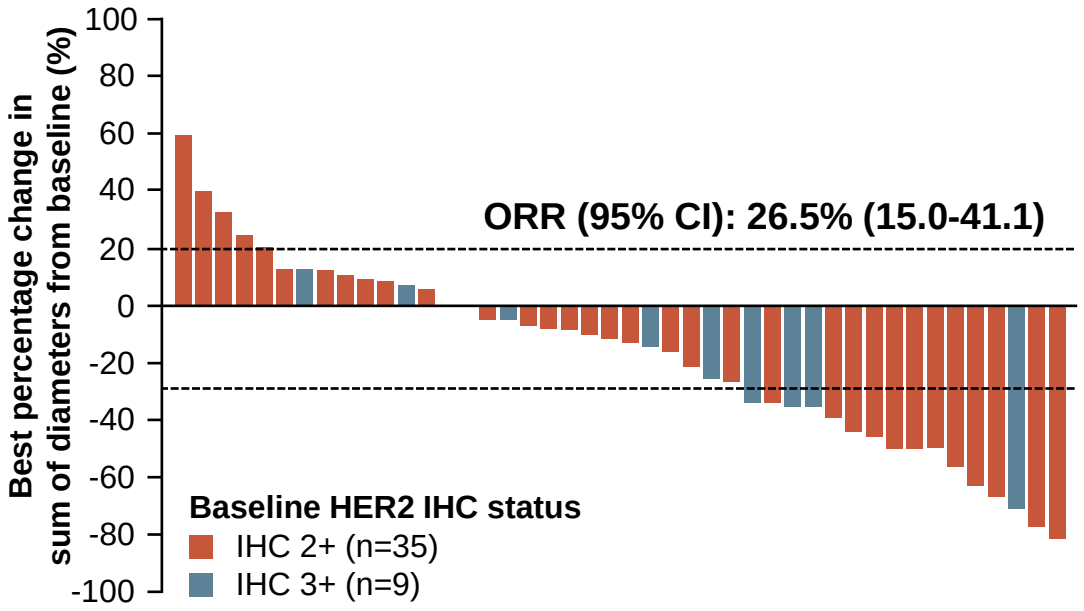
DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Smit EF, et al. Lancet Oncol. 2024;25:439-454

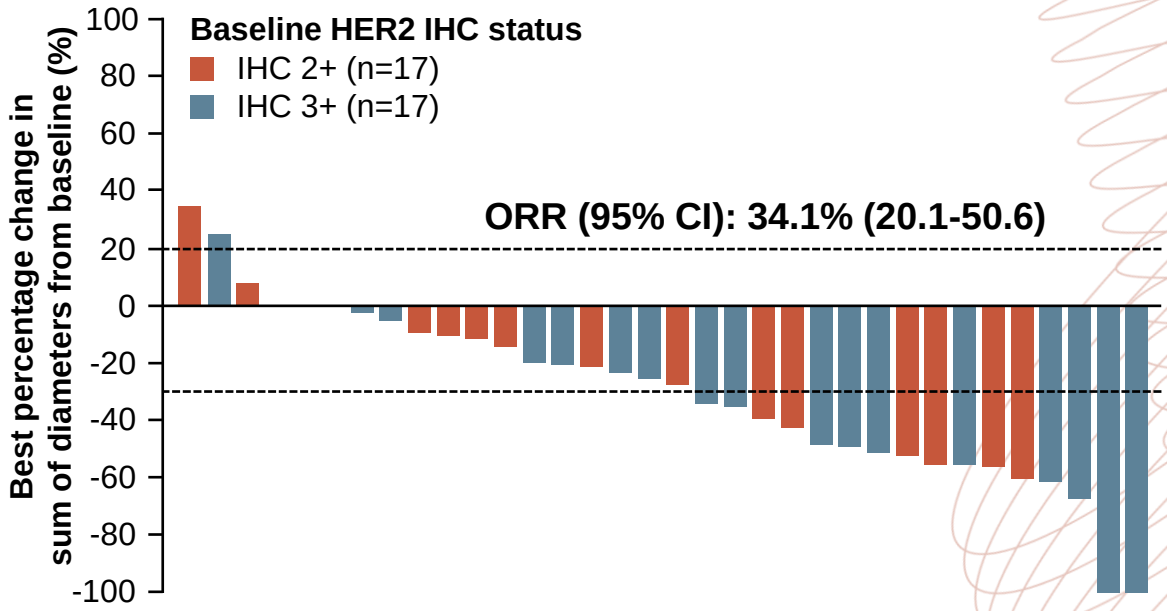
DESTINY-LUNG01 – PHASE 2 – HER2-OVEREXPRESSING

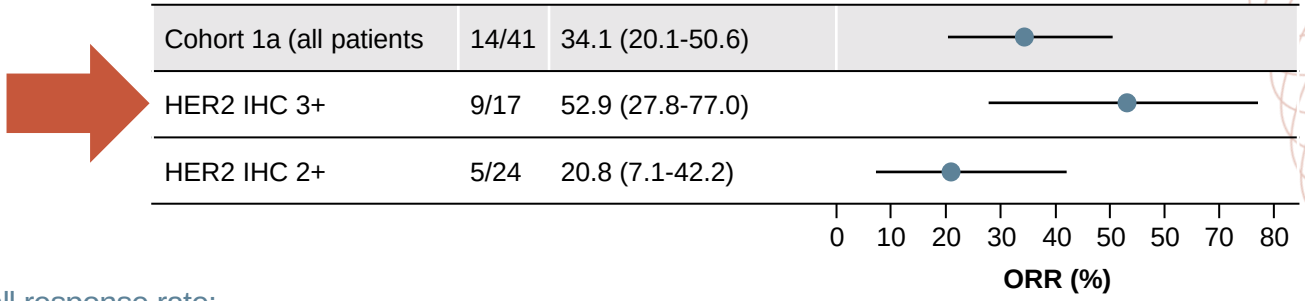
RESULTS

Cohort 1
Trastuzumab deruxtecan 6.4 mg/kg, N=49



Cohort 1a
Trastuzumab deruxtecan 5.4 mg/kg, N=41





52.9%

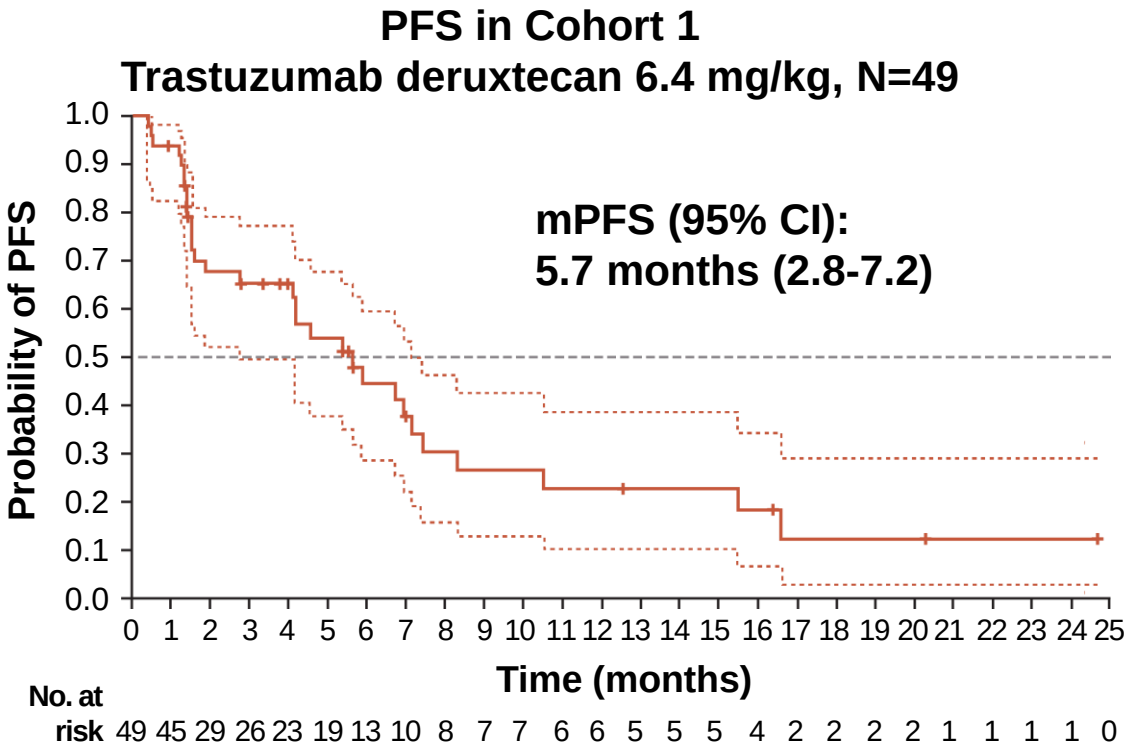
20.8%

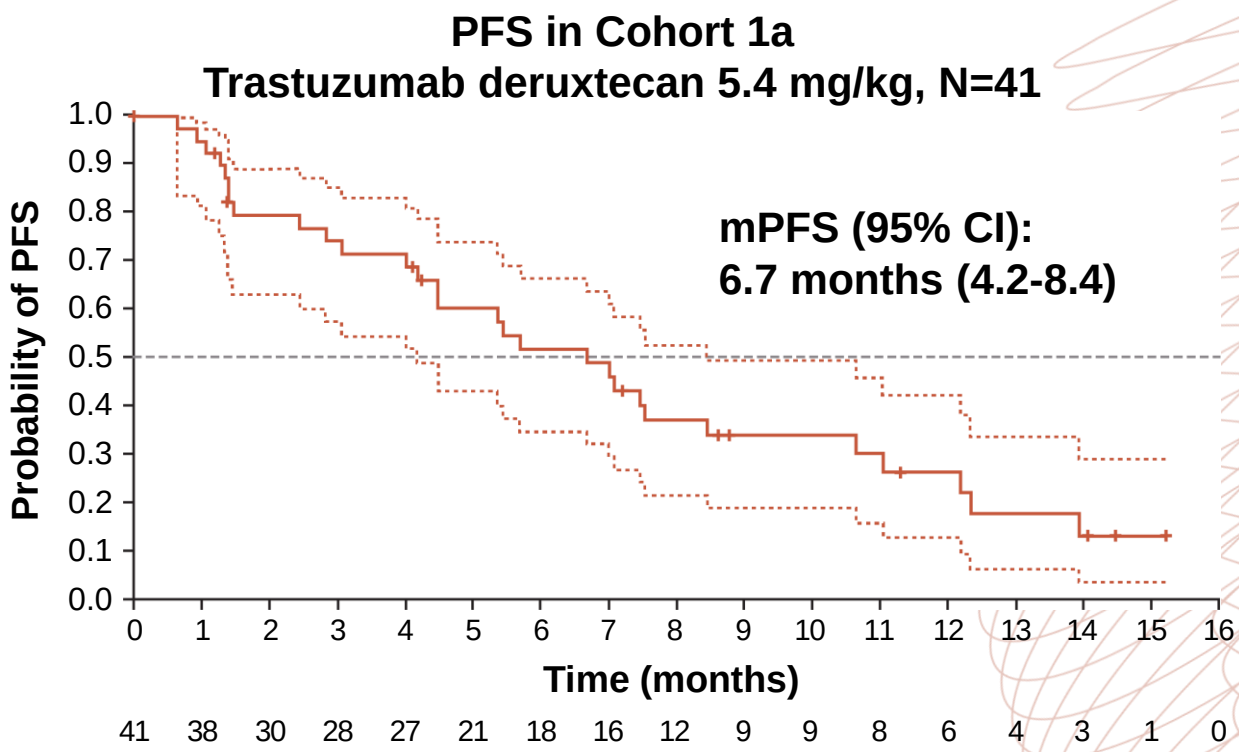
CI, confidence interval; IHC, immunohistochemistry; ORR, overall response rate;

Smit EF, et al. Lancet Oncol. 2024;25:439-454

DESTINY-LUNG01 - PHASE 2 - HER2-OVEREXPRESSING

RESULTS – PROGRESSION FREE SURVIVAL

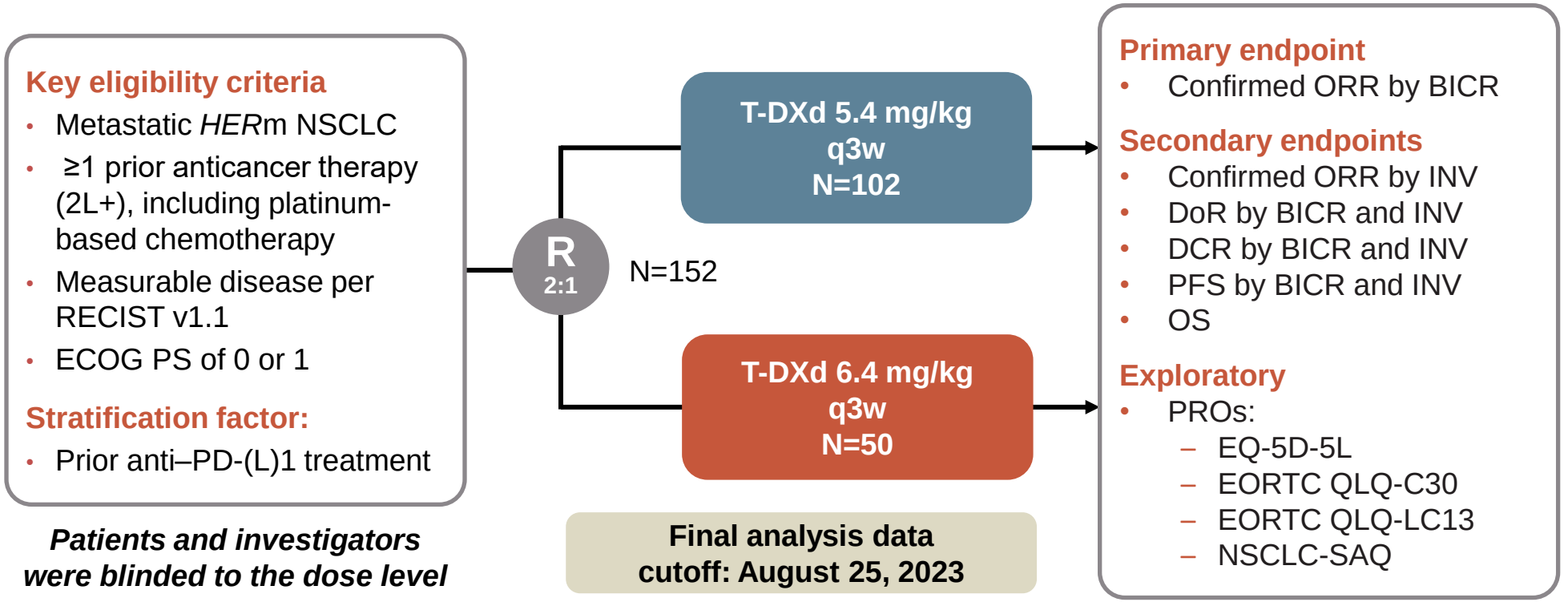




CI, confidence interval; (m)PFS, (median) progression free survival

Smit EF, et al. Lancet Oncol. 2024;25:439-454

DESTINY-LUNG02 – PHASE 2
STUDY DESIGN



2L+, second line of treatment or later; BICR, blinded independent central review; ORR, objective response rate; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13, EORTC Lung Cancer Specific Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5-Dimension, 5-Level Cancer Specific Core Quality of Life Questionnaire; INV, investigator assessment; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1; PFS, progression-free survival; PR, partial response; PRO, patient-reported outcome; q3w, every 3 weeks; R, randomisation; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SAQ, Symptom Assessment Questionnaire; T-DXd, trastuzumab deruxtecan

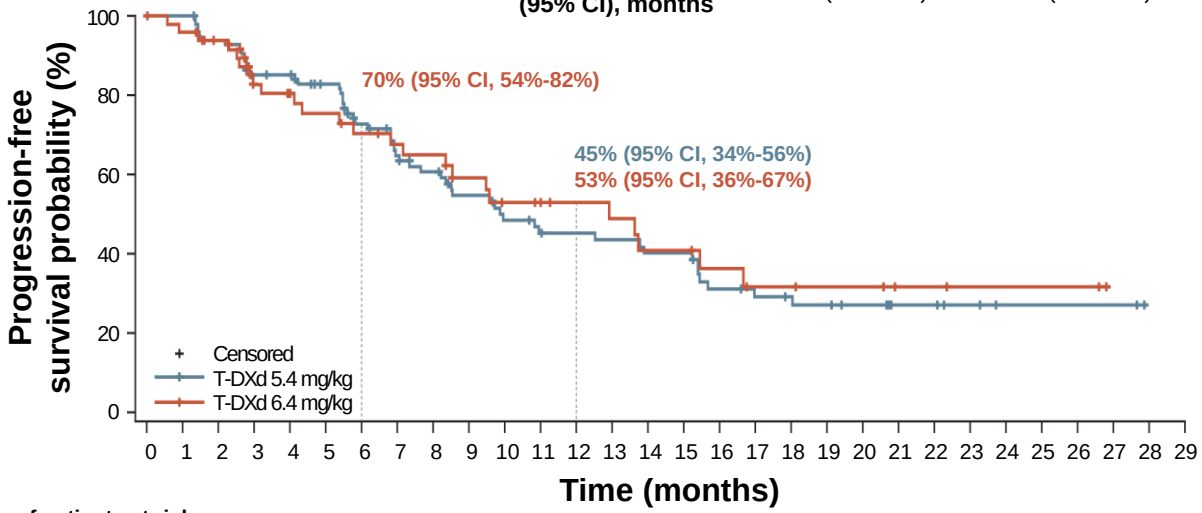
Janne P, et al. J Clin Oncol. 2024;42(no. 16_suppl):8543 (presented at ASCO Annual Meeting I, 2024)

DESTINY-LUNG02 – PHASE 2

T-DXd ALSO DEMONSTRATED AN ORR OF 50% (5.4 mg/kg) AND 56% (6.4 mg/kg) IN 2L+ *HER2*-MUTATED NSCLC

PFS by BICR

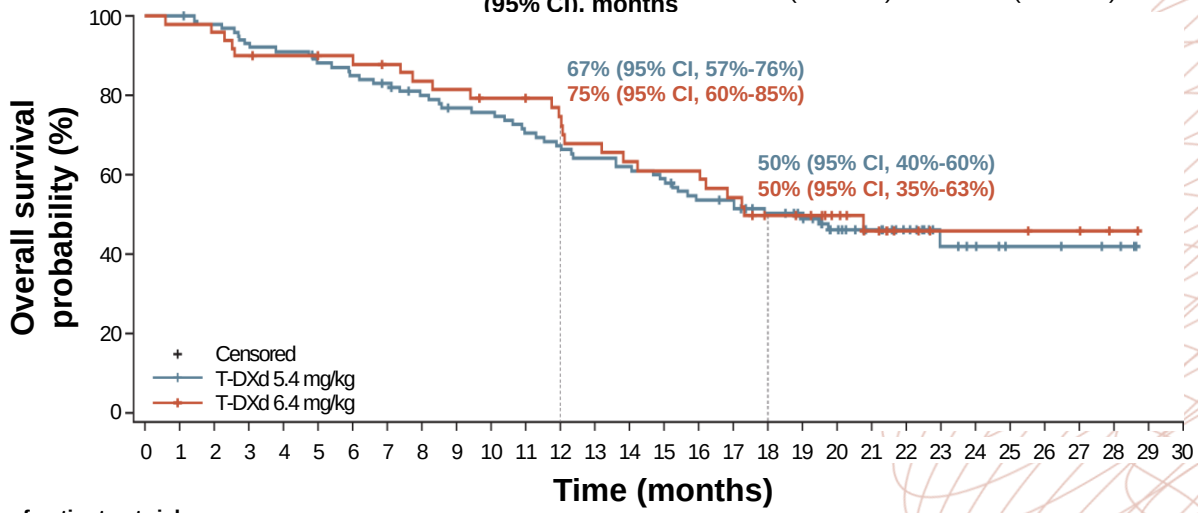
	T-DXd 5.4 mg/kg n=102	T-DXd 6.4 mg/kg n=50
Median PFS (95% CI), months	10.0 (7.7-15.2)	12.9 (7.2-16.7)



No. of patients at risk																													
T-DXd 5.4 mg/kg:	102	100	89	76	75	68	56	48	43	36	31	28	27	26	24	24	17	15	14	13	10	6	6	4	2	2	2	2	0	0
T-DXd 6.4 mg/kg:	50	47	44	36	33	30	27	25	24	19	16	15	13	12	10	10	8	6	6	5	5	3	3	2	2	2	2	0	0	0
No. of events																														
T-DXd 5.4 mg/kg:	0	0	6	14	14	16	24	30	33	37	41	43	43	44	46	46	51	52	52	53	53	53	53	53	53	53	53	53	53	0
T-DXd 6.4 mg/kg:	0	2	3	8	9	11	13	14	15	17	19	19	19	20	22	22	23	24	24	24	24	24	24	24	24	24	24	24	0	0

OS by BICR

	T-DXd 5.4 mg/kg n=102	T-DXd 6.4 mg/kg n=50
Median OS (95% CI), months	19.0 (14.7-NE)	17.3 (13.8-NE)



No. of patients at risk																														
T-DXd 5.4 mg/kg:	102	102	99	94	92	88	85	82	77	73	72	67	64	61	59	56	50	49	43	40	30	23	17	10	8	5	5	4	3	0	0
T-DXd 6.4 mg/kg:	50	49	48	45	44	43	43	41	39	38	36	36	33	30	28	27	27	24	20	19	15	11	6	4	4	4	3	3	1	0	0
No. of events																															
T-DXd 5.4 mg/kg:	0	0	2	7	9	12	15	17	20	23	24	29	32	35	37	40	45	45	48	48	51	51	51	52	52	52	52	52	52	52	0
T-DXd 6.4 mg/kg:	0	1	2	5	5	5	5	6	8	9	10	10	12	15	17	18	18	21	23	23	23	24	24	24	24	24	24	24	24	24	0

2L+, second line of treatment or later; BICR, blinded independent central review; CI, confidence interval; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan;

Janne P, et al. J Clin Oncol. 2024;42(no. 16_suppl):8543 (presented at ASCO Annual Meeting I, 2024)

SAFETY PROFILE OF T-DXd

RESULTS FROM DESTINY-LUNG01 AND DESTINY-LUNG02

DESTINY-Lung01[1] (N=91)[1]	TRAEs, n (%)	
	Any grade	Grade ≥3
Nausea	66 (73)	8 (9)
Fatigue	48 (53)	6 (7)
Alopecia	42 (46)	0
Vomiting	36 (40)	3 (3)
Neutropenia	32 (35)	17 (19)
Anaemia	30 (33)	9 (10)
Diarrhoea	29 (32)	3 (3)
Decreased appetite	27 (30)	0
Interstitial lung disease	24 (26)	6 (7)
Leukopenia	21 (23)	4 (4)
Constipation	20 (22)	0

DESTINY-Lung02[2]	TEAEs, n (%)	
	Any grade	Grade ≥3
5.4 mg/kg (N=101)		
Nausea	66 (65)	NR
Neutropenia	43 (43)	19 (19)
Fatigue	38 (38)	NR
Interstitial lung disease	15 (15)	2 (2)
6.4 mg/kg (N=50)		
Nausea	39 (78)	NR
Neutropenia	28 (56)	19 (38)
Fatigue	23 (46)	NR
Decreased appetite	23 (46)	NR
Interstitial lung disease	16 (32)	2 (4)

T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

1. Li BT, et al. N Engl J Med. 2022;386:241-251; 2. Janne P, et al. J Clin Oncol. 2024;42(no. 16_suppl):8543 (presented at ASCO Annual Meeting I, 2024)

DESTINY-LUNG03 – PHASE 1B – MULTICENTRE, OPEN LABEL, DOSE ESCALATION

IHC HER2 3+/2+

Patient population

- Aged ≥18 years
- **Centrally assessed HER2-OE (IHC 3+/2+)[a] unresectable, locally advanced or metastatic non-squamous NSCLC**
- Measurable disease per RECIST v1.1
- WHO/ECOG performance status 0-1
- Patients in Part 1 had 1 or 2 prior lines of therapy; patients with therapy-targetable alterations must have had prior appropriate targeted therapy

Part 1: dose escalation[b] (enrolment complete)
Arm 1A: T-DXd + durvalumab + cisplatin q3w
Arm 1B: T-DXd + durvalumab + carboplatin q3w

Part 1: T-DXd monotherapy (enrolment complete)
Arm 1D: T-DXd 5.4 mg/kg IV q3w (N=36)

Part 3: dose confirmation and expansion (currently recruiting)
T-DXd + volrustomig ± carboplatin

Part 4: safety run-in and expansion (currently recruiting)
T-DXd + rilvegostomig ± carboplatin

Data cutoff for the Part 1 T-DXd monotherapy arm results: April 1, 2024

Key endpoints for the T-DXd monotherapy arm

- ORR
- DoR
- DCR
- PFS
- OS

Investigator assessed

- Safety and tolerability

Data cutoff for the Part 1 T-DXd monotherapy arm results was April 1, 2024. Part 2 of the study was not initiated owing to a strategic decision by the study sponsor.

[a] HER2 overexpression was defined as ≥25% of tumour cells with IHC 3+ or 2+ by central testing using the Dako HER2-low IHC assay

[b] Arm 1C: T-DXd + durvalumab + pemetrexed treatment was planned but not initiated

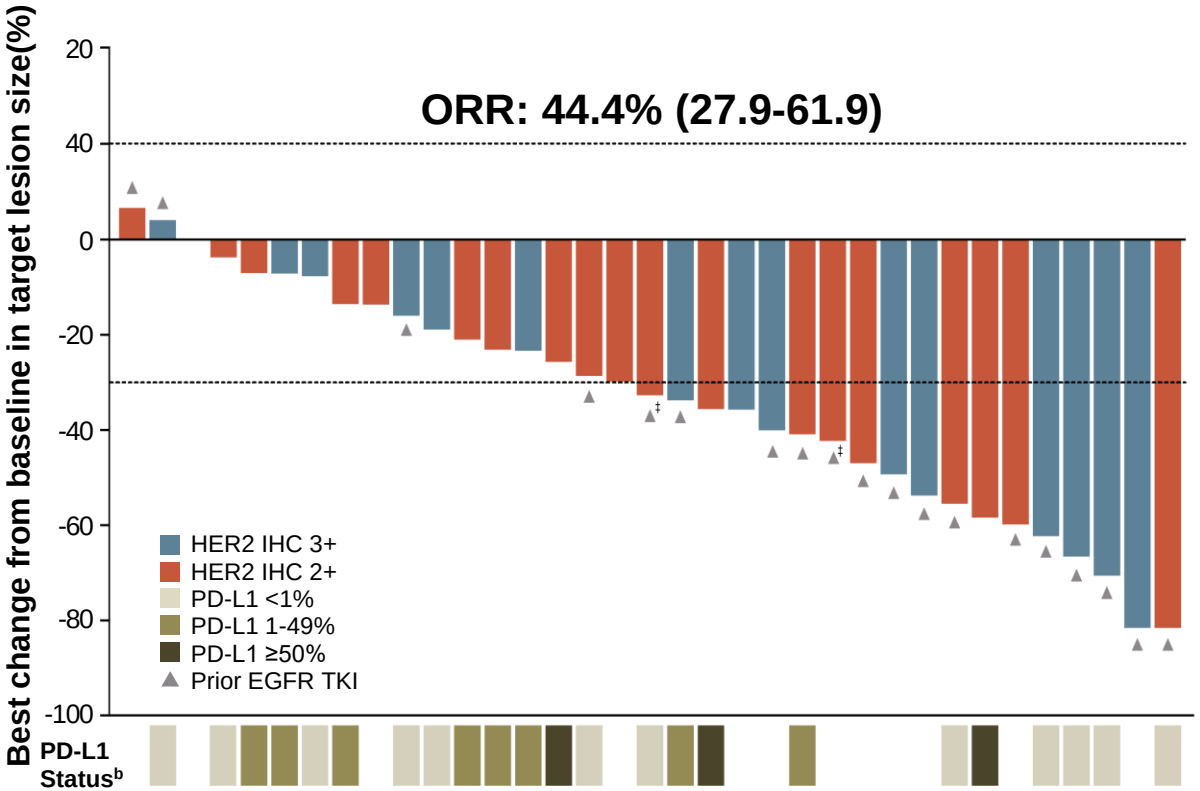
DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization

Planchard D, et al. J Thorac Oncol. 19 (Issue 10, supplement):S46-S47 (presented at WCLC 2024)

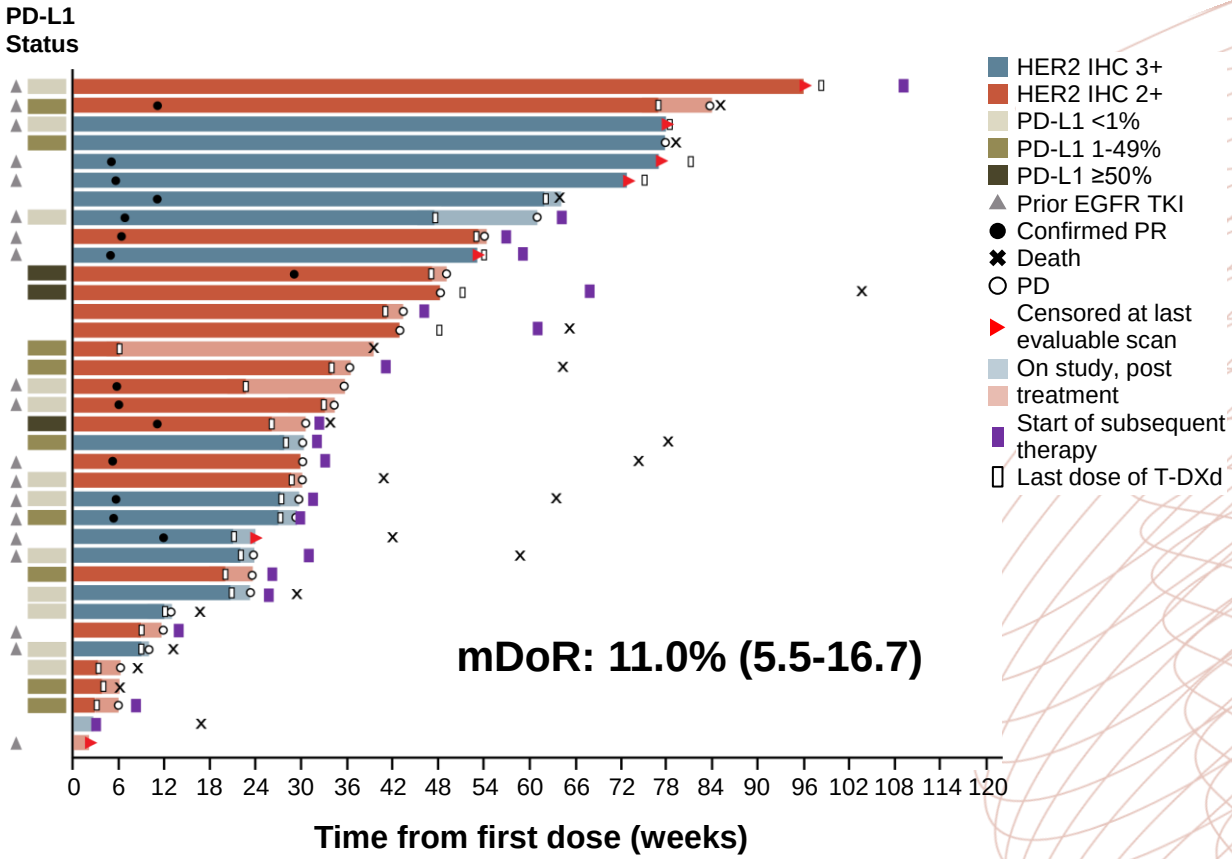
DESTINY-LUNG03 - PHASE 1B

BEST PERCENTAGE CHANGE FROM BASELINE IN TARGET LESION SIZE AND TTP

Part 1: T-DXd monotherapy arm, N=36[a]



Part 1: T-DXd monotherapy arm, N=36



[a] One patient not evaluable

[b] Patients with unknown PD-L1 status represented by white spaces

‡ Unconfirmed response

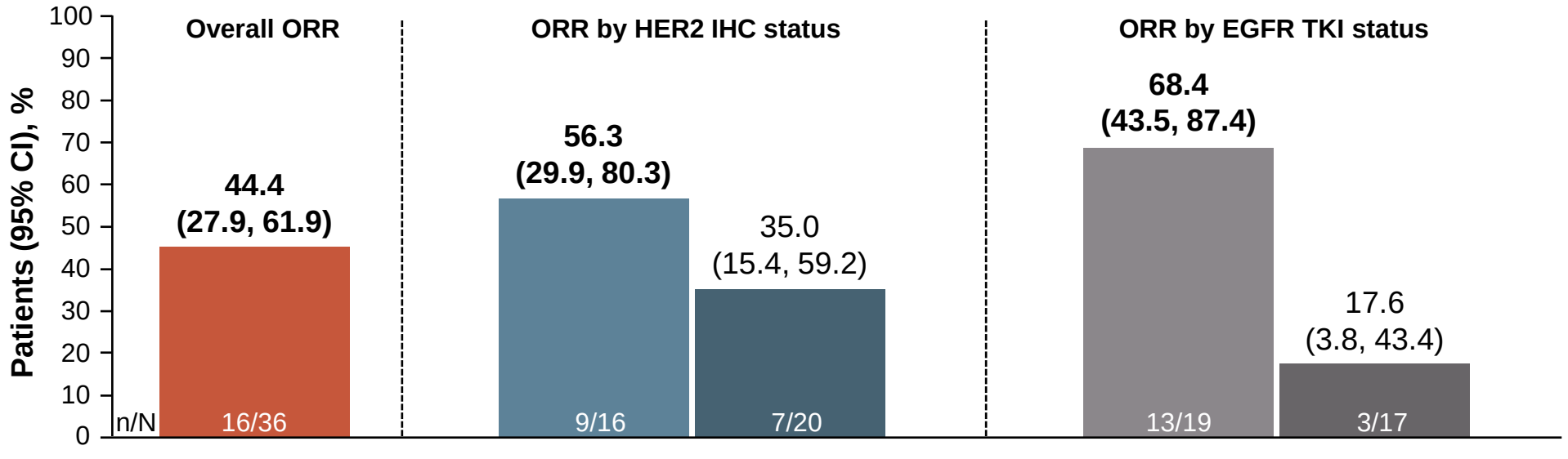
IHC, immunohistochemistry; mDoR, median duration of response; PD-L1, programmed death ligand-1; PR, partial response; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; TTP, time to progression;

Planchard D, et al. J Thorac Oncol. 19 (Issue 10, supplement):S46-S47 (presented at WCLC 2024)

DESTINY-LUNG03 – PHASE 1B

ORR: OVERALL AND BY HER2 IHC STATUS AND PRIOR EFGR TKI EXPOSURE

T-DXd monotherapy, N=36 pts



	Overall	HER2 IHC 3+	HER2 IHC 2+	Prior EGFR TKI	EGFR TKI naïve
Median DoR (95% CI), months	**11.0 (5.5, 16.7)**	**12.5 (5.5, NE)**	6.6 (4.5, 11.0)	**11.7 (5.5, NE)**	4.6 (4.5, NE)
DCR at 12 weeks (95% CI), %	77.8 (60.9, 89.9)	81.3 (54.4, 96.0)	75.0 (50.9, 91.3)	84.2 (60.4, 96.6)	70.6 (44.0, 89.7)

There were no new safety signals identified, and the safety profile was consistent with the known profile of T-DXd

CI, confidence interval; DCR, disease control rate; DoR, duration of response; IHC, immunohistochemistry; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

Planchard D, et al. J Thorac Oncol. 19 (Issue 10, supplement):S46-S47 (presented at WCLC 2024)

EXPLORATORY POOLED BRAIN METASTASES ANALYSES

STUDY DESIGNS DESTINY-LUNG01 AND DESTINY-LUNG02

- Post hoc analysis
- Small number of patients
- Lack of a comparator arm

DESTINY-Lung01[a]

- Unresectable/metastatic non-squamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- ECOG PS of 0 or 1
- Locally reported *HER*m (Cohort 2)
- Asymptomatic BM allowed

Cohort 1: HER2-OE (IHC 3+ or IHC 2+) T-DXd 6.4 mg/kg q3w N=49

Cohort 1a: HER2-OE (IHC 3+ or IHC 2+) T-DXd 5.4 mg/kg q3w N=41

Cohort 2: *HER2*m T-DXd 6.4 mg/kg q3w N=42

Cohort 2: expansion: *HER2*m T-DXd 6.4 mg/kg q3w N=49

DESTINY-Lung02[b]

- Metastatic *HER2*-mutated NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation
- Asymptomatic BM allowed

Stratified by

- Prior anti-PD-(L)1 treatment

R 2:1

T-DXd 5.4 mg/kg q3w N=102

T-DXd 6.4 mg/kg q3w N=50

T-DXd 5.4 mg/kg DL-02 BM (N=32) Non-BM (N=70)

Pooled T-DXd 6.4 mg/kg DL-01 *HER2*m/DL-02 BM (N=54) Non-BM (N=87)

Endpoints

In patients with and without baseline BM:

- Systemic cORR per BICR
- Systemic DoR per BICR
- Sites of progression per BICR
- TEAEs

In patients with measurable baseline BM:

- IC-cORR per BICR
- IC-DCR per BICR
- IC-DoR per BICR

[a] Data cutoff: December 3, 2021. [b] Data cutoff: December 23, 2022.

2L+, second line of treatment or later; BICR, blinded independent central review; BM, brain metastases, cORR , confirmed objective response rate; DCR, disease control rate; DoR , duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; OE, overexpressing; q3w, every 3 weeks; R, randomisation; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; T DXd , trastuzumab deruxtecan; TEAE, treatment emergent adverse event

Li B, et al. Ann Oncol. 2023;34 (suppl_2):S755-S851 (presented at ESMO 2023).

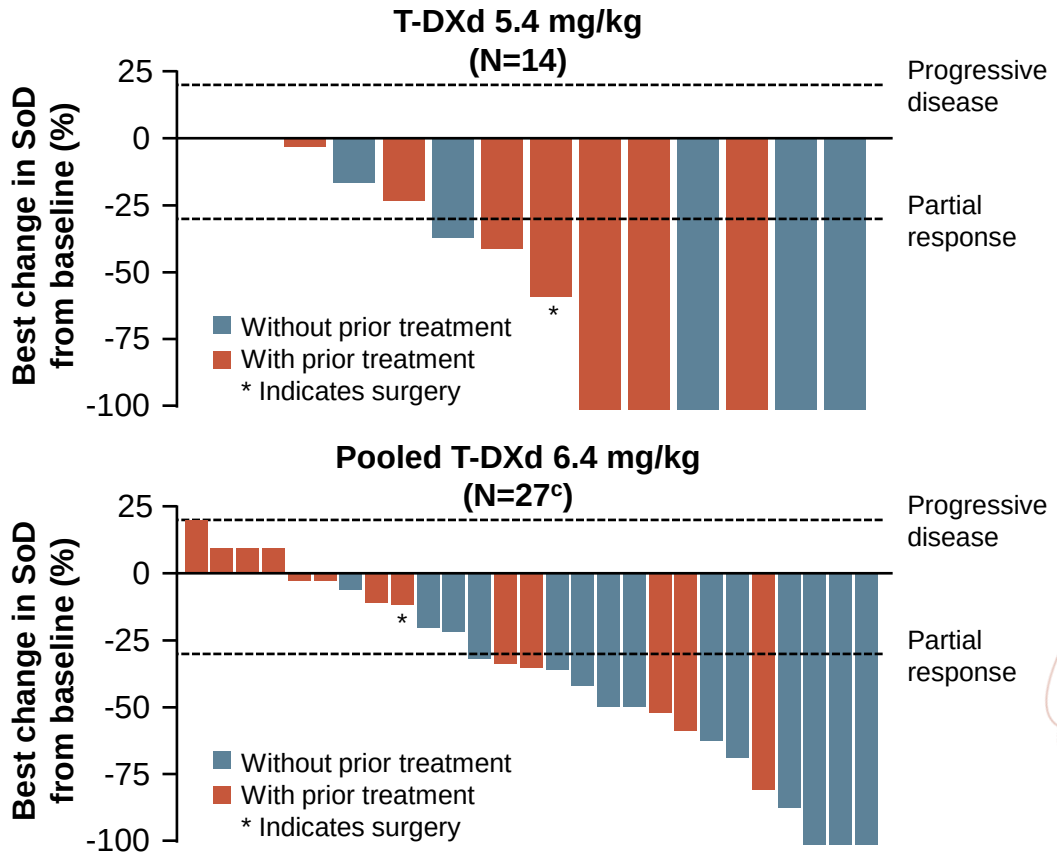
EXPLORATORY POOLED BRAIN METASTASES ANALYSES

DESTINY-LUNG01 AND DESTINY-LUNG02: ORR AND BEST OVERALL RESPONSE

Responses in patients with measurable BM at baseline

	T-DXd 5.4 mg/kg DL-02 BM (N=14)	Pooled T-DXd 6.4 mg/kg DL-01 *HER2*m/DL-02 BM (N=30)
IC-cORR, n (%)[a]	**7 (50)**	**9 (30)**
95% CI[b]	23-77	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30)
SD	6 (42.9)	13 (43.3)
PD	1 (7.1)	4 (13.3)
NE[c]	0	2 (6.7)
Missing	0	2 (6.7)
IC-DCR, n (%)[a]	**13 (92.9)**	**22 (73.3)**
95% CI[b]	66.1-99.8	54.1-87.7
IC-DoR, mo[d]		
Median (95% CI)[e]	9.5 (3.6-NE)	4.4 (2.9-10.2)

12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4-mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response



- Systemic responses to T-DXd were similar in patients with and without BM at baseline
- Patients with and without BM showed similar safety outcomes overall

[a] Denominator for percentage is the number of patients in the full analysis set who have at least one target lesion at baseline, per BICR. [b] Based on Clopper Pearson method for single proportion. [c] For one patient deemed NE in the 6.4 mg/kg group, it was not possible to derive objective response due to missing data of one target lesion; the patient's best over all response however was calculated from available target lesion assessments and included the waterfall plot. [d] Calculated as time from first response in brain until progression in brain. [e] Based on Kaplan-Meier analysis and computed with the Brookmeyer-Crowley method.

BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DL, DESTINY Lung (trial); DoR , duration of response; HER2m, HER2 mutant; IC, intracranial; mo, months; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; T DXd , trastuzumab deruxtecan

1. Li B, et al. Ann Oncol. 2023;34 (suppl_2):S755-S851 (presented at ESMO 2023)

HER2 TARGETED THERAPY IN LUNG CANCER

APPROVALS AND UPCOMING TRIAL

FDA[1,2]

On August 11, 2022, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients **with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumours have activating *HER2* (*ERBB2*) mutations**, as detected by an FDA-approved test, and who have received a prior systemic therapy. This is the first drug approved for *HER2*-mutant NSCLC.

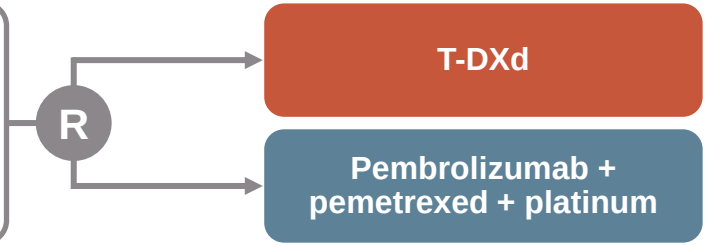
On April 5, 2024, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki for adult patients with **unresectable or metastatic HER2-positive (IHC3+) solid tumours** who have received prior systemic treatment and have no satisfactory alternative treatment options.

EMA[3]

In September 2023, the EMA recommended trastuzumab deruxtecan for approval as monotherapy for the treatment of adult patients **with advanced NSCLC whose tumours have an activating *HER2* (*ERBB2*) mutation** and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy

DESTINY-Lung04[4]

- First-line advanced NSCLC
- *HER2* ex19 or ex20 mutations
  (Estimated enrolment = 450)



- **Endpoint: PFS**

EMA, European Medicines Agency; FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

1. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-mutant non-small cell lung cancer. Available here (accessed Feb 2025);
2. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors. Available here (accessed March 2025); 3. EMA Recommends Extending Indications for Trastuzumab Deruxtecan to Include Treatment of Advanced HER2-mutated NSCLC. Available here (accessed Feb 2025); 4. ClinicalTrials.gov, NCT05048797

CONCLUSIONS

- ***HER2* alterations are different in NSCLC** compared to **other cancer** types such as breast cancer
- There is **variability in HER2 IHC scoring** (guidelines, antibody clones, clinical vs. autopsy samples)
  - There is a need to **standardize** HER2 IHC testing for NSCLC
- **HER2-driven NSCLC** is a **challenging target** with limited therapeutic options for patients
- **Different alteration types** require **different diagnostic techniques** and may have **different predictive effect**
- The **safety profiles** of novel **anti-HER2 treatments** are **acceptable** and **manageable**
  - No significant toxicities were reported in longer follow-up

IHC, immunohistochemistry; NSCLC, non small cell lung cancer

TARGETING HER2 IN LUNG CANCER: WHERE DOES THE IHC TESTING FIT IN?

Q&A SESSION

PANEL DISCUSSION
AND
AUDIENCE QUESTIONS

OVARIAN CANCER: CHALLENGES AND CONSIDERATIONS FOR HER2 IHC TESTING

Prof. Charlie Gourley

Medical Oncologist

CRUK Edinburgh Centre, Nicola Murray Centre for Ovarian Cancer Research, UK

HER2 TESTING IN OVARIAN CANCER

KEY CHALLENGES

Lack of consistency around HER2 scoring systems

Staining issues

Inadequate consideration of histological subtype to date

Lack of reimbursement for downstream therapies

Doubt in routine pathology laboratory about merits of testing

Intra-tumoral heterogeneity of HER2 expression **underexplored**

Inadequate understanding of stability of HER2 expression through the patient journey

HER2 TESTING IN OVARIAN CANCER

KEY CHALLENGES

Lack of consistency around HER2 scoring systems

Staining issues

Inadequate consideration of histological subtype to date

Lack of reimbursement for downstream therapies

Doubt in routine pathology laboratory about merits of testing

Intra-tumoural heterogeneity of HER2 expression **under explored**

Inadequate understanding of stability of HER2 expression through the patient journey

HER2 TARGETED THERAPY IN OVARIAN CANCER

APPROVALS[1,2]

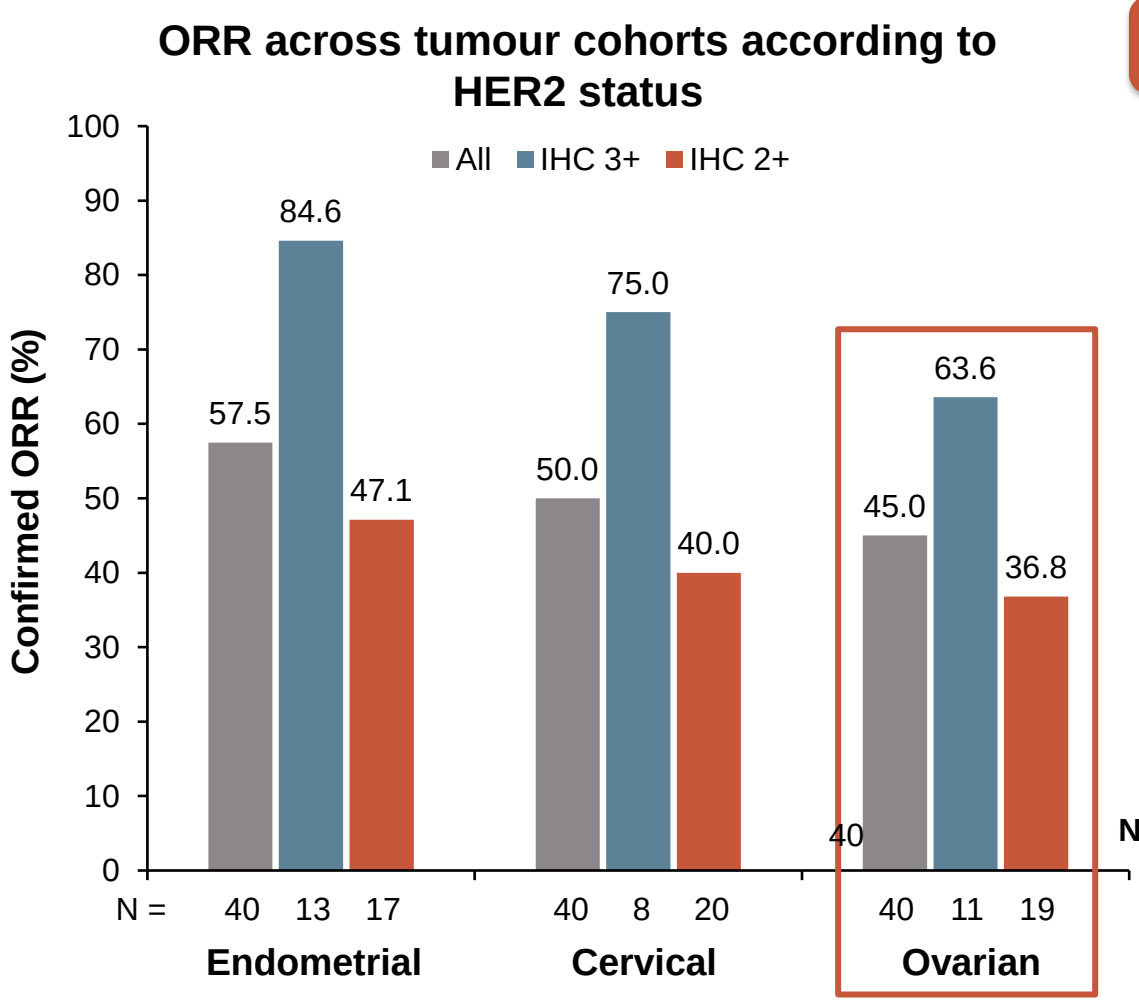
No approval[3]

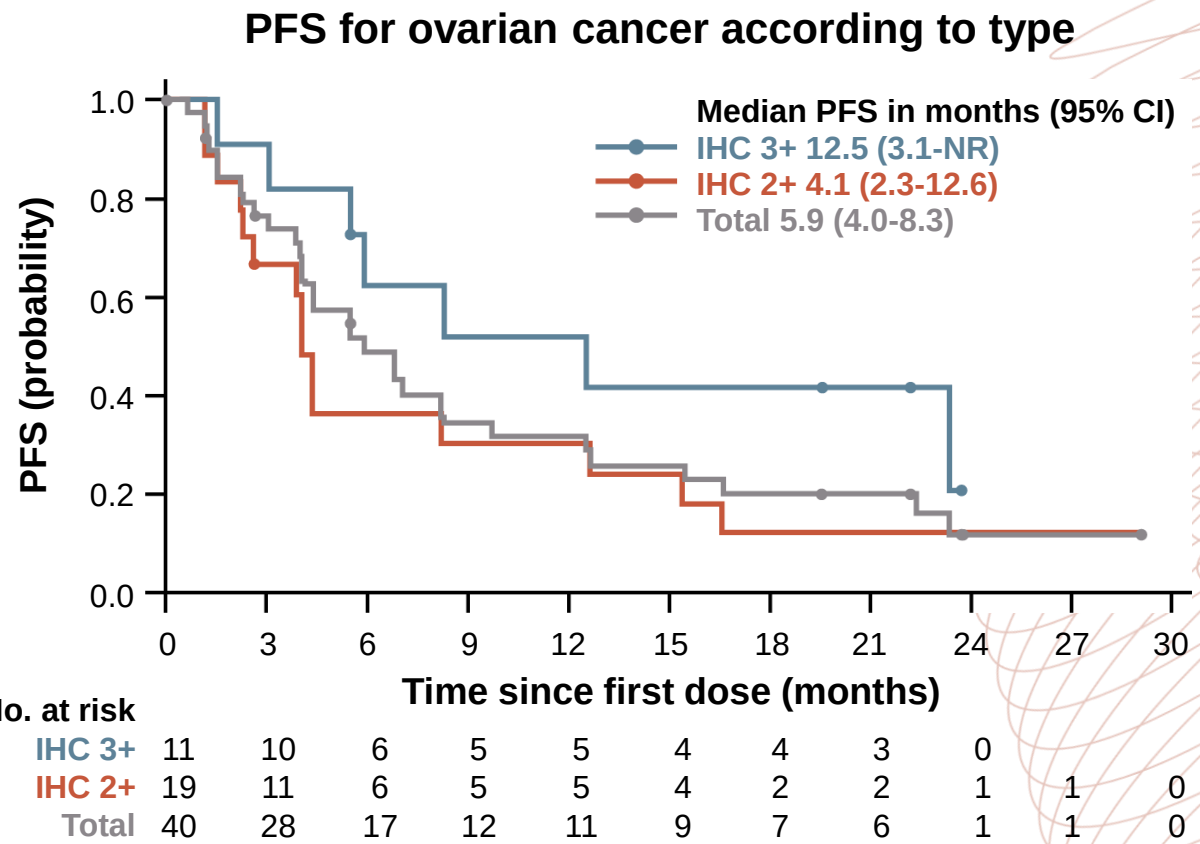
1. Mehta GU, et al. Oncologist. 2024;29:667-671
2. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors. Available here (accessed Feb 2025)
3. The promises of antibody-drug conjugates for ovarian cancer. Available here (accessed Feb 2025)

HER2-TARGETED THERAPY ON THE HORIZON FOR OVARIAN CANCER

DESTINY-PANTUMOR02 PHASE 2 TRIAL OF TRASTUZUMAB DERUXTECAN

HER2 expression (2+ or 3+ by IHC) required





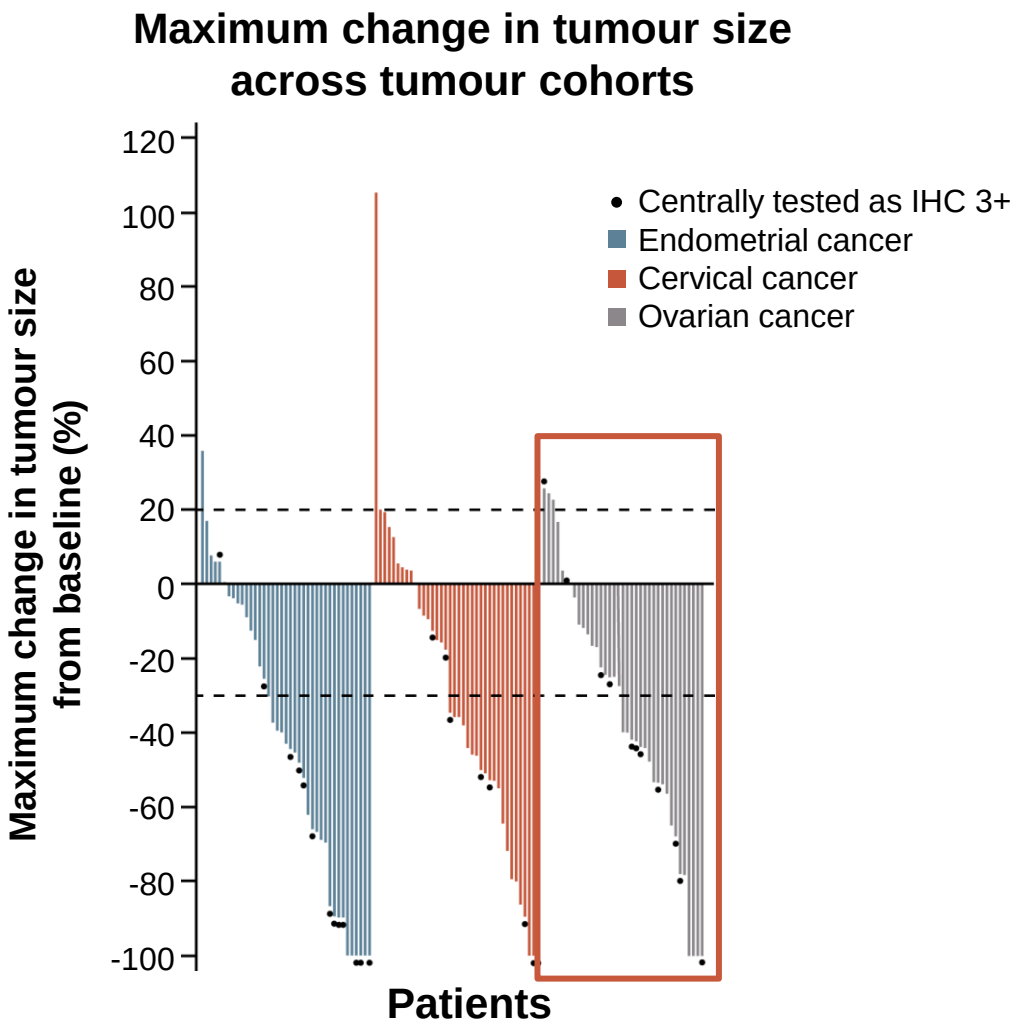
IHC, immunohistochemistry; NR, not reached; ORR, objective response rate; PFS, progression free survival

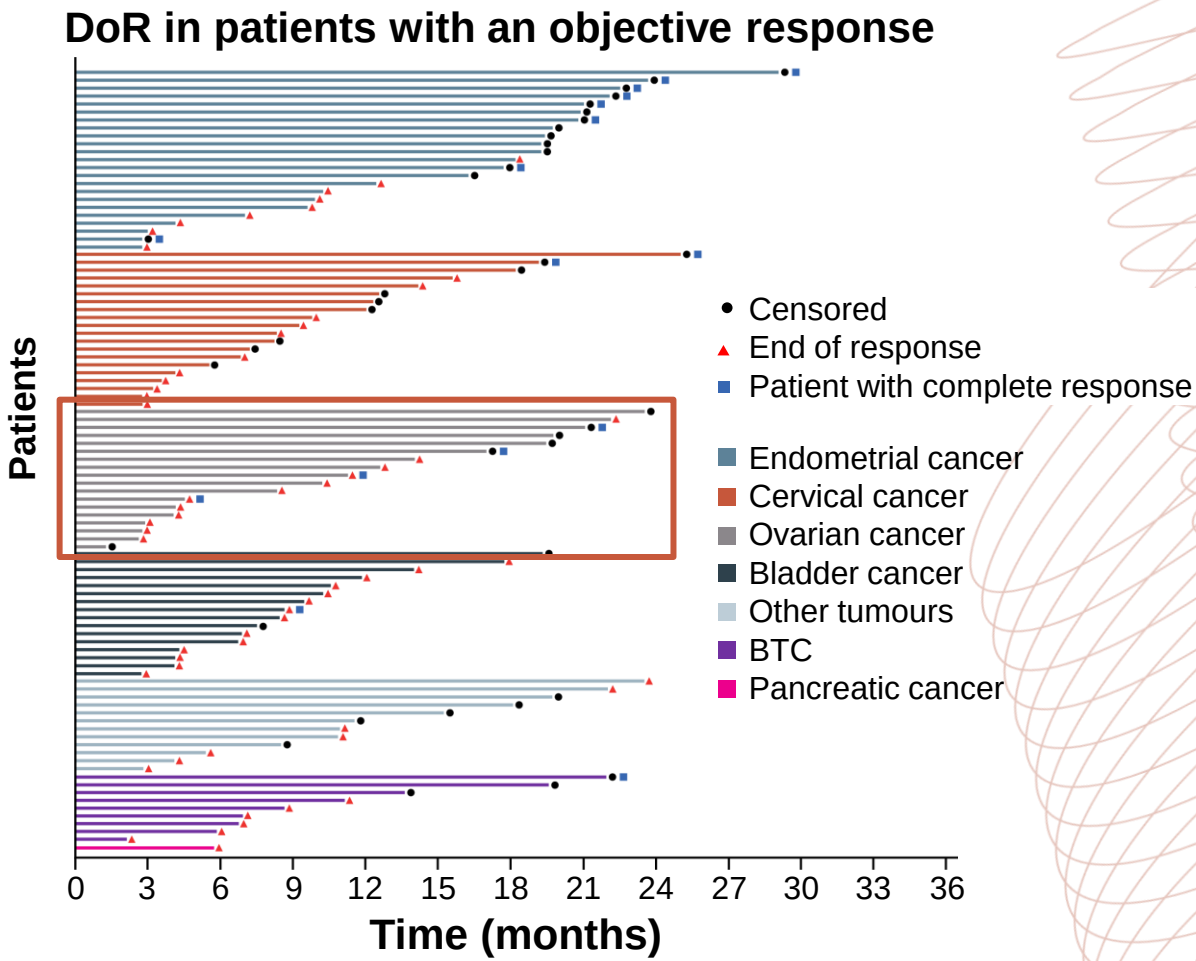
Meric-Bernstam F, et al, J Clin Oncol. 2024;42:47-58

HER2-TARGETED THERAPY ON THE HORIZON FOR OVARIAN CANCER

DESTINY-PANTUMOR02 PHASE 2 TRIAL OF TRASTUZUMAB DERUXTECAN

HER2 expression (2+ or 3+ by IHC) required





BTC, biliary tract cancer; DoR, duration of response; IHC, immunohistochemistry;

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

HER2-TARGETED THERAPY ON THE HORIZON FOR OVARIAN CANCER

IBI354 PHASE 1 STUDY – STUDY DESIGN[1]

TRASTUZUMAB CONJUGATED TO NT3, A TOPOISOMERASE1 INHIBITOR

- Locally advanced/ unresectable or metastatic solid tumour that is refractory to or intolerable with standard treatment
- HER2 alteration (IHC[a] 1+, IHC 2+, IHC 3+ and/or ISH+ and/or NGS mutation or amplification
- At least one measurable lesion
- ECOG PS 0 or 1

Dose escalation (DLT window: 21 days)

Dose levels 0.8 ~ 18 mg/kg Q3W

Dose expansion

- Breast cancer
- **Ovarian cancer**
- **Endometrial cancer**
- **Cervical cancer**
- Colorectal cancer
- Biliary tract cancer
- Other solid tumours

- 12 mg/kg Q3W
- 9 mg/kg Q3W
- 6 mg/kg Q3W

Primary endpoints: Safety, dose-limiting toxicities
Secondary endpoints: Pharmacokinetics, anti-drug antibody, efficacy

Over 65% of patients had tumours with HER2 intensity 1+ by IHC

[a] HER2 expression by immunohistochemistry (IHC) was tested via local lab or central lab according to PATHWAY HER2 (4B5) if local test not feasible (ASCO/CAP gastric cancer guideline[2]). All enrolled patients were required to provide the most recent pre-enrolment tumour samples for central test

DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ISH, in-situ hybridisation; NGS, next-generation sequencing; Q3W, every 3 weeks

1. Shu J, et al. Ann Oncol. 2024;35 (suppl 2):S551 (presented at ESMO 2024); 2. Bartley AN, et al. J Clin Oncol. 2017;35:446-464

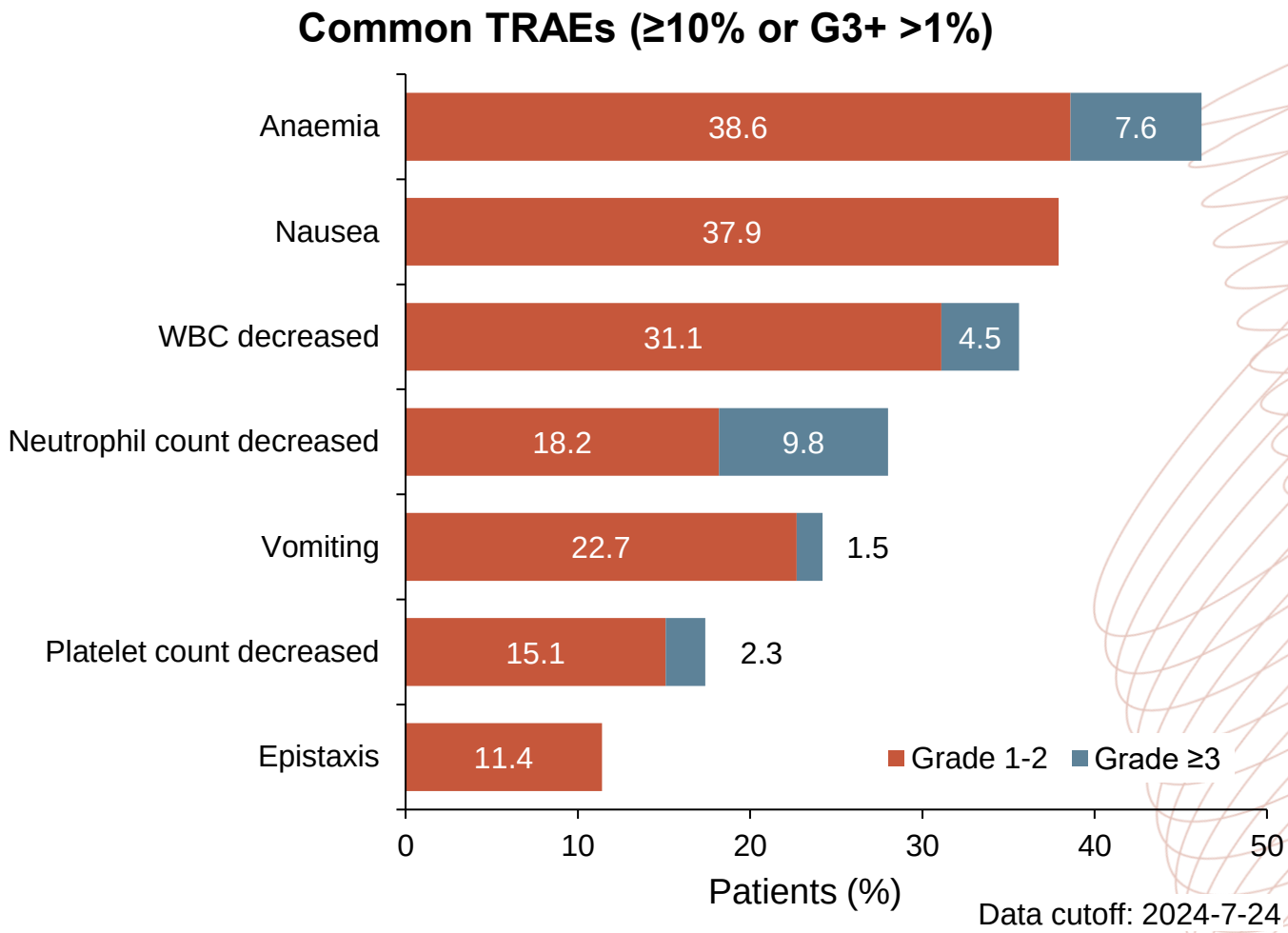
HER2-TARGETED THERAPY ON THE HORIZON FOR OVARIAN CANCER

IBI354 PHASE 1 STUDY – SAFETY

TRASTUZUMAB CONJUGATED TO NT3, A TOPOISOMERASE1 INHIBITOR

AE, n (%)	Overall (N=132)	
	Any grade	Grade ≥3
Any TEAE	127 (96.2)	52 (39.4)
Any TRAE	114 (86.4)	31 (23.5)
ILD[a]	2 (1.5)	0 (0.0)

- Grade ≥3 TRAEs occurred in **23.5%** of patients. Low incidences of Grade ≥3 myelosuppression (including WBC decreased, anaemia, neutrophil count decreased, and platelet count decreased), vomiting (1.5%) and diarrhoea (0.8%). No Grade ≥3 nausea, fatigue and alopecia
- No Grade 5 TRAE
- Low incidence of ILD (Grade 1 in both patients)



[a] ILD, pneumonitis or interstitial lung disease related to IBI354 considered by the investigator

AE, adverse event; G, grade; ILD, interstitial lung disease; TEAE, treatment-emergent AE; TRAE, treatment-related AE; WBC, white blood cell (count)

Shu J, et al. Ann Oncol. 2024;35 (suppl 2):S551 (presented at ESMO 2024)

HER2-TARGETED THERAPY ON THE HORIZON FOR OVARIAN CANCER

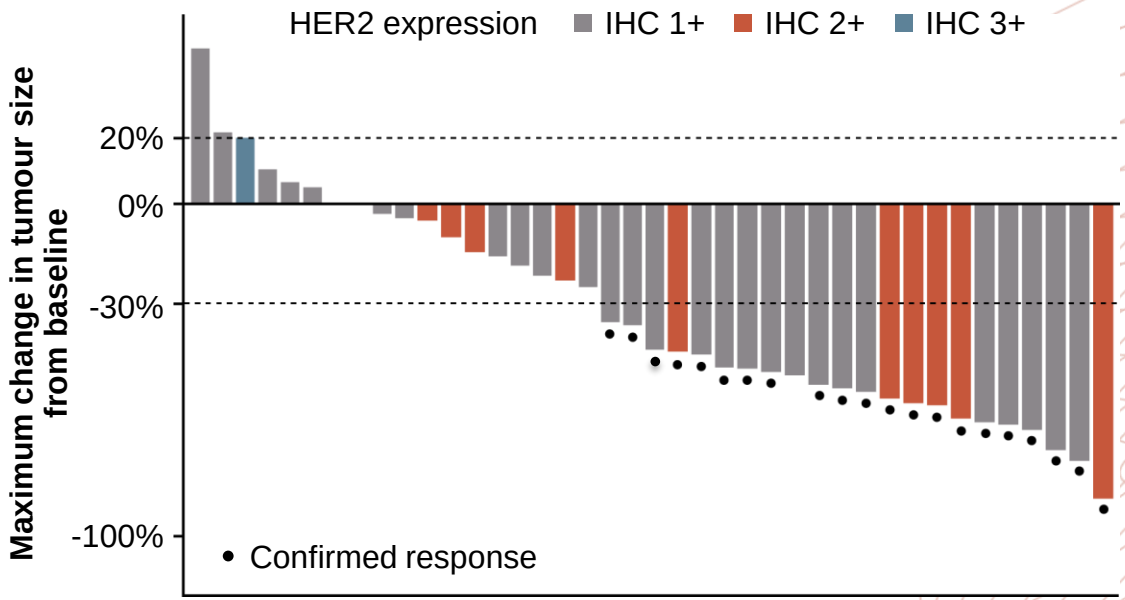
IBI354 PHASE 1 STUDY - EFFICACY

TRASTUZUMAB CONJUGATED TO NT3, A TOPOISOMERASE1 INHIBITOR

Ovarian cancer, n (%)	12 mg/kg Q3W (N=40)	Total (N=87)[a]
Prior treatment regimens ≥3	40 (100.0)	87 (100.0)
Prior platinum	40 (100.0)	87 (100.0)
Platinum-free interval <6 months	35 (87.5)	78 (89.7)
Prior taxanes	39 (97.5)	84 (96.6)
Prior bevacizumab	33 (80.5)	70 (77.8)
Best response		
cPR	21 (52.5)	35 (40.2)
SD	15 (37.5)	36 (41.4)
PD	4 (10.0)	16 (18.4)
cORR	21 (52.5)	35 (40.2)
95% CI	36.1-68.5	29.9-51.3
DCR	36 (90.0)	71 (81.6)
95% CI	76.3-97.2	71.9-89.1

n (%)	Ovarian cancer in 12 mg/kg Q3W dose group (N=40)		
	HER2 IHC 1+ (N=27)	HER2 IHC 2+ (N=12)	HER2 IHC 3+ (N=1)
cORR	15 (55.6)	6 (50.0)	0 (0.0)
95% CI	35.3-74.5	21.1-78.9	0-97.5
DCR	24 (88.9)	12 (100.0)	0 (0.0)
95% CI	70.8-97.6	73.5-100	0-97.5

Patients with ovarian cancer at 12 mg/kg Q3W dose



- In 12 mg/kg Q3W dose group, the confirmed ORR reached 52.5% with a DCR of 90.0% in ovarian cancer
- In 27 (67.5%) patients with HER2 IHC 1+: ORR of 55.6% and DCR of 88.9%

Data cutoff: 2024-7-24

[a] For patients with HER2 IHC 1+, 2+ or 3+ via local lab, who received 6 mg/kg or above, with at least one post-baseline tumour assessment

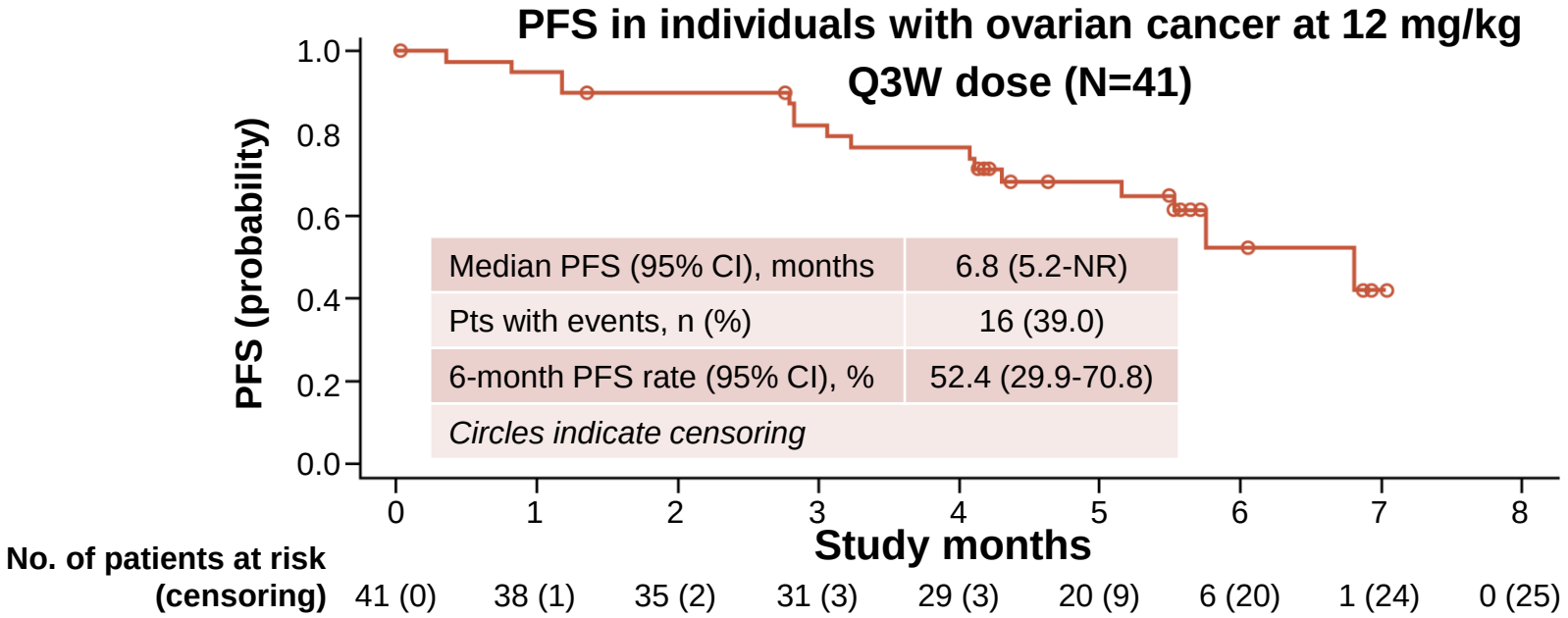
CI, confidence interval; (c)ORR, (confirmed) objective response rate; cPR, confirmed partial response; DCR, disease control rate; IHC, immunohistochemistry; Q3W, every 3 weeks; PD, progressive disease; SD, stable disease

Shu J, et al. Ann Oncol. 2024;35 (suppl 2):S551 (presented at ESMO 2024)

HER2-TARGETED THERAPY ON THE HORIZON FOR OVARIAN CANCER

IBI354 PHASE 1 STUDY - DURABILITY OF CLINICAL BENEFIT

TRASTUZUMAB CONJUGATED TO NT3, A TOPOISOMERASE1 INHIBITOR



- As of July 24, 2024, with a median follow-up of 6.5 (range: 4.4-10.2) months in 12 mg/kg Q3W dose group
- The median DoR was not reached, with events in 3 (14.3%) patients
- The median PFS was 6.8 (95% CI: 5.2-NR) months, with events in 16 (39.0%) patients

HER2-targeting therapies appear safe and effective and will be with us soon in HER2 expressing ovarian cancer

CI, confidence interval; DoR, duration of response; NR, not reached; PFS, progression-free survival; Q3W, every 3 weeks

Shu J, et al. Ann Oncol. 2024;35 (suppl 2):S551 (presented at ESMO 2024)

HER2 TESTING IN OVARIAN CANCER

KEY CHALLENGES

Lack of consistency around HER2 scoring systems

Staining issues

Inadequate consideration of histological subtype to date

Lack of reimbursement for downstream therapies

Doubt in routine pathology laboratory about merits of testing

Intra-tumoral heterogeneity of HER2 expression **under explored**

Inadequate understanding of stability of HER2 expression through the patient journey

INTRA-TUMORAL HETEROGENEITY OF HER2 EXPRESSION

UNDEREXPLORED

- Serous endometrial cancer study[1]
- Paired endometrial curetting/biopsy and hysterectomy
- 40 pairs
- HER2 IHC (Abcam EP3 clone) and/or FISH
- HER2 IHC in curettage and hysterectomy identical in 26/40 (65%) cases
- When FISH included, concordance for HER2 status increased to 31/37 (84%)
- Of the six discordant cases, four were HER2 positive in the biopsy/curettage and negative in the hysterectomy; the other two went in the opposite direction

Proposed HER2 scoring system for endometrial serous carcinoma based on the recent clinical trial patient enrolment criteria[2]

HER2 score	Staining pattern
0	No staining
1+	Faint/barely perceptible, incomplete membrane staining in any proportion, or weak complete staining in <10% of tumour cells
2+	Intense complete or basolateral/lateral membrane staining in ≤30%, or weak to moderate in ≥10% of tumour cells
3+	Intense complete or basolateral/lateral membrane staining in >30% of tumour cells

FISH, fluorescence; ISH, in-situ hybridisation

1. Rottman D, et al. Int J Gynecol Pathol. 2021;40:263-271; 2. Fader AN, et al. J Clin Oncol 2018;36:2044–51

HER2 TESTING IN OVARIAN CANCER

KEY CHALLENGES

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Inadequate understanding of stability of HER2 expression through the patient journey

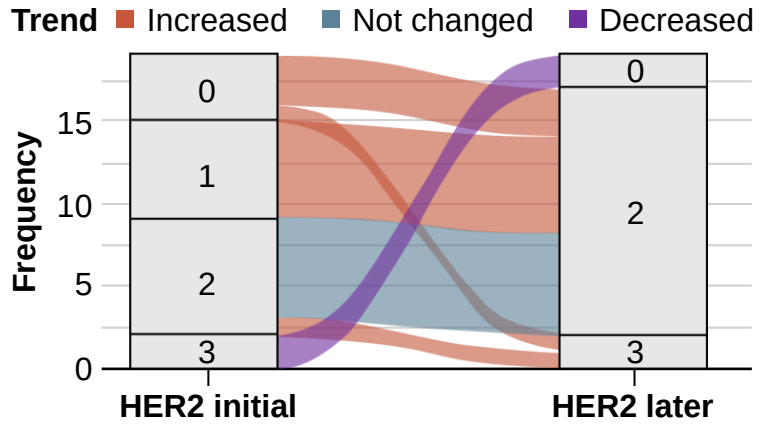
STABILITY OF HER2 EXPRESSION THROUGH THE PATIENT JOURNEY
POORLY CHARACTERISED[1]

- HER2 immunohistochemistry performed on specimens from 200 individuals with ovarian cancer[1]
- Ventana Discovery platform; DAKO antibody[1]
- 28% 2+ and 6% 3+[1]
- By histology:[1]
  - Mucinous 23% 3+
  - Endometrioid 11% 3+
  - Clear cell 9% 3+
  - High grade serous 5% 3+

- 19 patients underwent multiple biopsies: of these, 11 showed increased HER2 expression in later biopsies[1]

HER2 score[2]	Expression pattern	Assessment
0	No reactivity or membranous reactivity in <10% of cancer cells	Negative
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are reactive only in part of their membrane	Negative
2+	Weak or moderate complete, basolateral, or lateral membranous reactivity in ≥10% of cancer cells	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥10% of cancer cells	Positive

Changes in HER2 expression among patients with time-lagged biopsies[1]



Main caveat: this study included all histologies

1. Kim YN, et al. Sci Rep. 2024;14:7992; 2. Kim KM, et al. Asia Pac J Clin Oncol. 2014;10:297-307

STABILITY OF HER2 EXPRESSION THROUGH THE PATIENT JOURNEY

IMPACT OF NEOADJUVANT CHEMOTHERAPY UNKNOWN IN OVARIAN

- Using breast cancer as a better explored comparator[1]
- Changes do occur following neoadjuvant chemotherapy[2-4]
- More common with IHC than with FISH[2,3]
- Of 12 studies investigating IHC before and after neoadjuvant chemo, six showed a change in HER2 IHC in 1-30% of cases; 1-16% were positive to negative and 4-20% were negative to positive[2,3]
- Of seven studies investigating FISH before and after neoadjuvant chemotherapy, only one identified a change (6% positive to negative; 3.5% negative to positive)[2,3]

Possible causes for change in HER2 expression include:

- ↑ protein internalisation
- ↑protein degradation
- Loss of gene amplification

Studies need to be repeated in ovarian cancer

FISH, fluorescence in-situ hybridisation; IHC, immunohistochemistry

1. Kim YN, et al. Sci Rep. 2024;14:7992; 2. Shaaban Am and Provenzano E. Pathobiology. 2022;89:297-308; 3. van de Ven S, et al. Cancer Treat Rev. 2011;37:422-430; 4. Jabbour MN, et al, Breast Cancer Res Treat. 2012;135:29-37;

OVARIAN CANCER: CHALLENGES AND CONSIDERATIONS FOR HER2 IHC TESTING

PATIENT CASE

IHC, immunohistochemistry

PATIENT CASE
OVARIAN CANCER

Clinical history

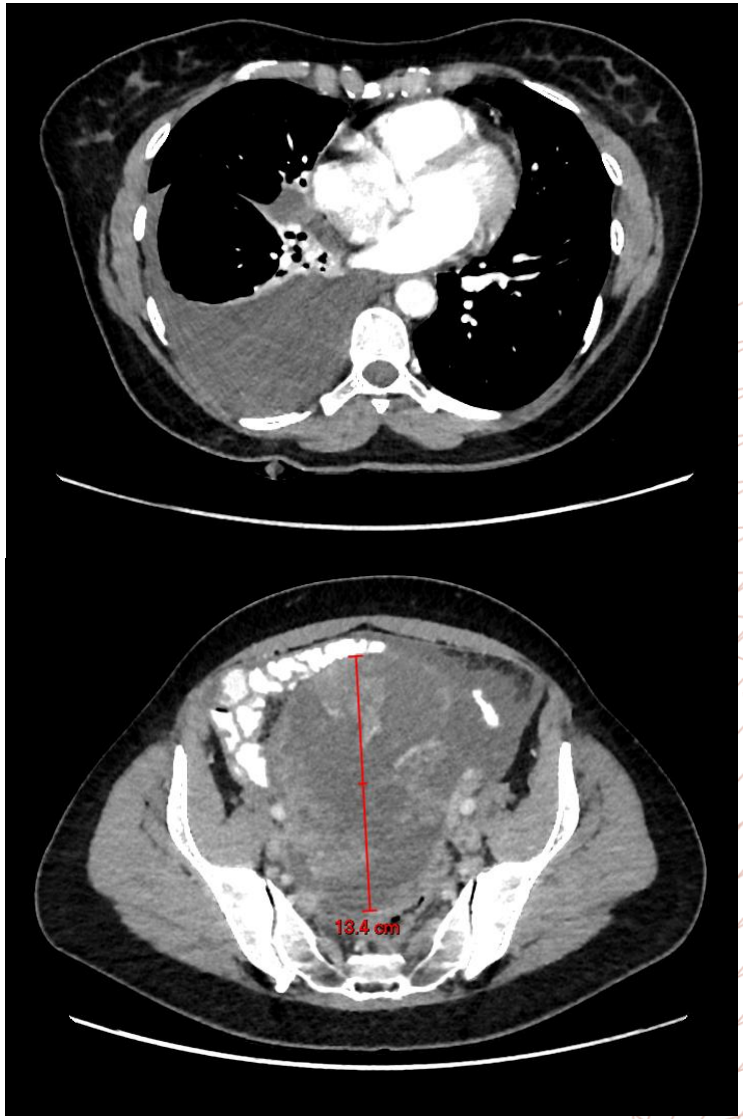
- 47-year-old patient
- Presented to her GP in UK country (not Scotland)
- 1 year history of tightness around her bra and change in her breathing
- Found to have a right pleural effusion
- CA125 496[a]

Initial intervention

- Pleural drainage (1350 mL)
- Cytology: no malignant cells

Surgical intervention

- Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and appendicectomy
- Pathology: Grade 1 stage 1C2 mucinous carcinoma of the left ovary, expansile pattern of invasion



CT: right pleural effusion and left complex ovarian mass with ascites, peritoneal enhancement and omental stranding.

[a] CA125 496 U/mL

CA125, cancer antigen 125; CT, computed tomography; GP, general practitioner

Patient case and images provided by Prof. C Gourley

POLLING QUESTION

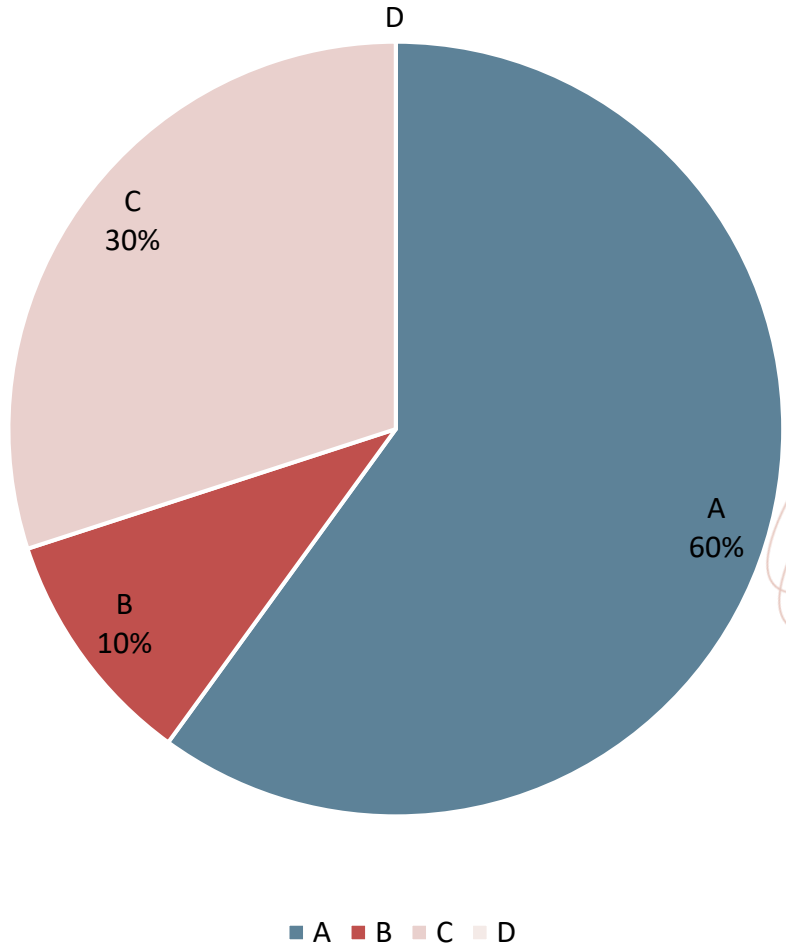
WHAT OTHER MOLECULAR TESTS WOULD YOU ROUTINELY REQUEST IN THIS SITUATION?

A. Nine gene germ-line panel (*BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2, MLH1, MSH2, MSH6*)

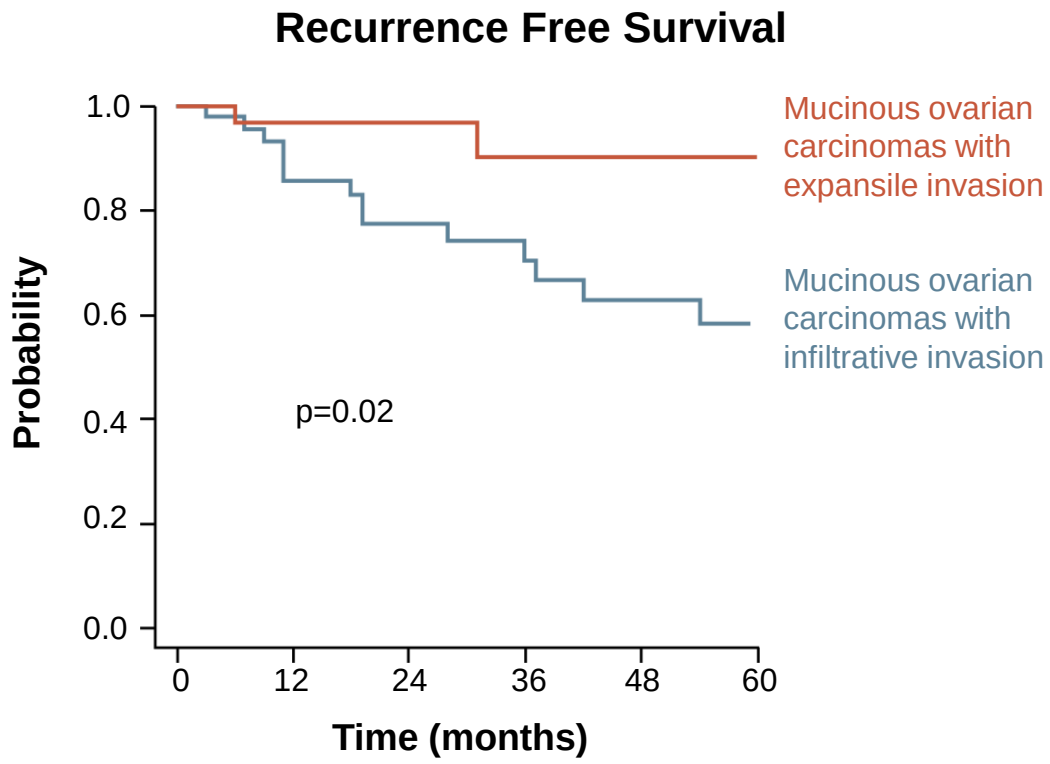
B. Homologous Recombination Deficiency (HRD) testing of tumour

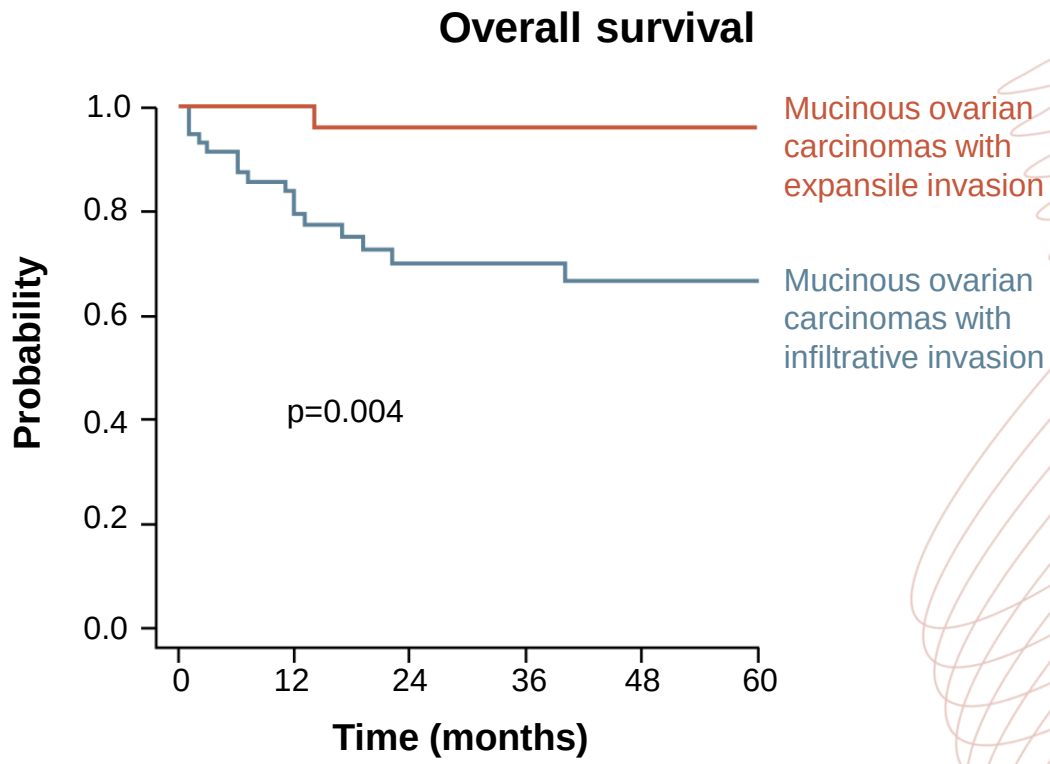
C. *KRAS* sequencing and HER2 immunohistochemistry

D. No additional routine testing indicated at this time



RISK OF RELAPSE OF EXPANSILE MUCINOUS OVARIAN CANCER IS LOW





- 94 cases of mucinous ovarian cancer diagnosed in 13 French centres between Jan 01 2001 and Dec 31 2019
- 35 (37%) expansile and 59 (63%) infiltrative

Huin M, et al, J Clin Med. 2022;11:6120

POLLING QUESTION

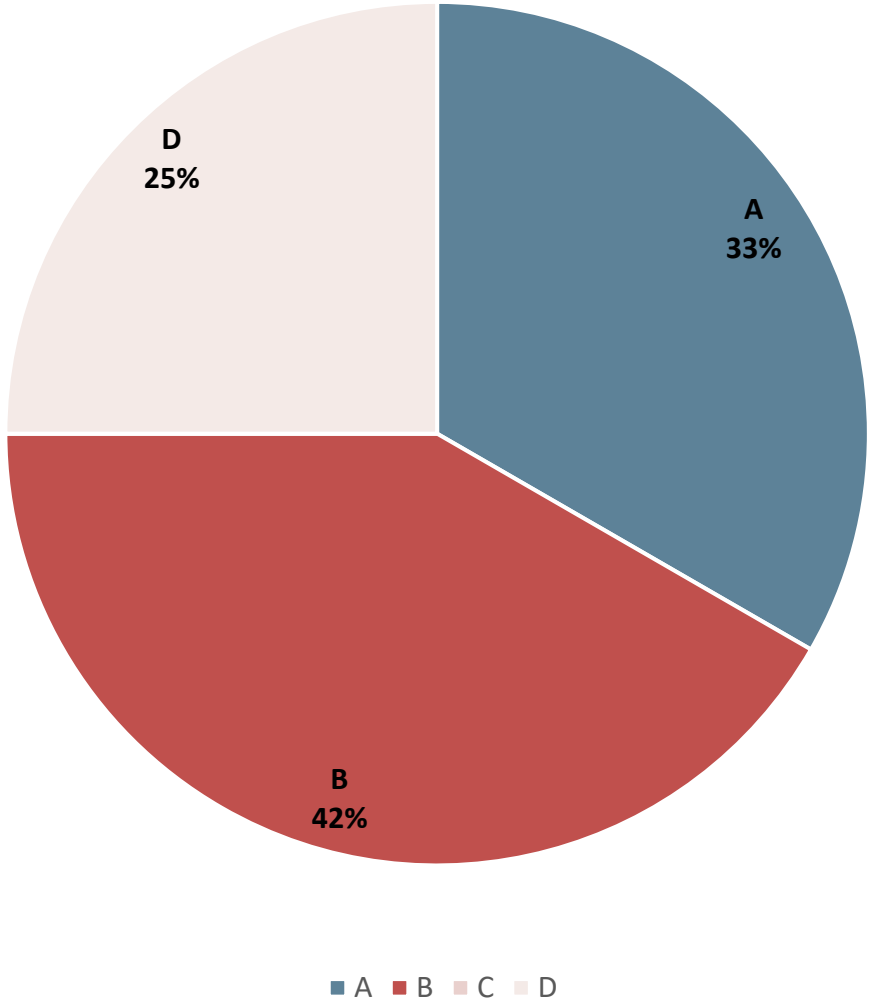
WHAT WOULD BE RECOMMENDED IN THIS SITUATION?

A. Carboplatin and paclitaxel

B. Capecitabine and oxaliplatin

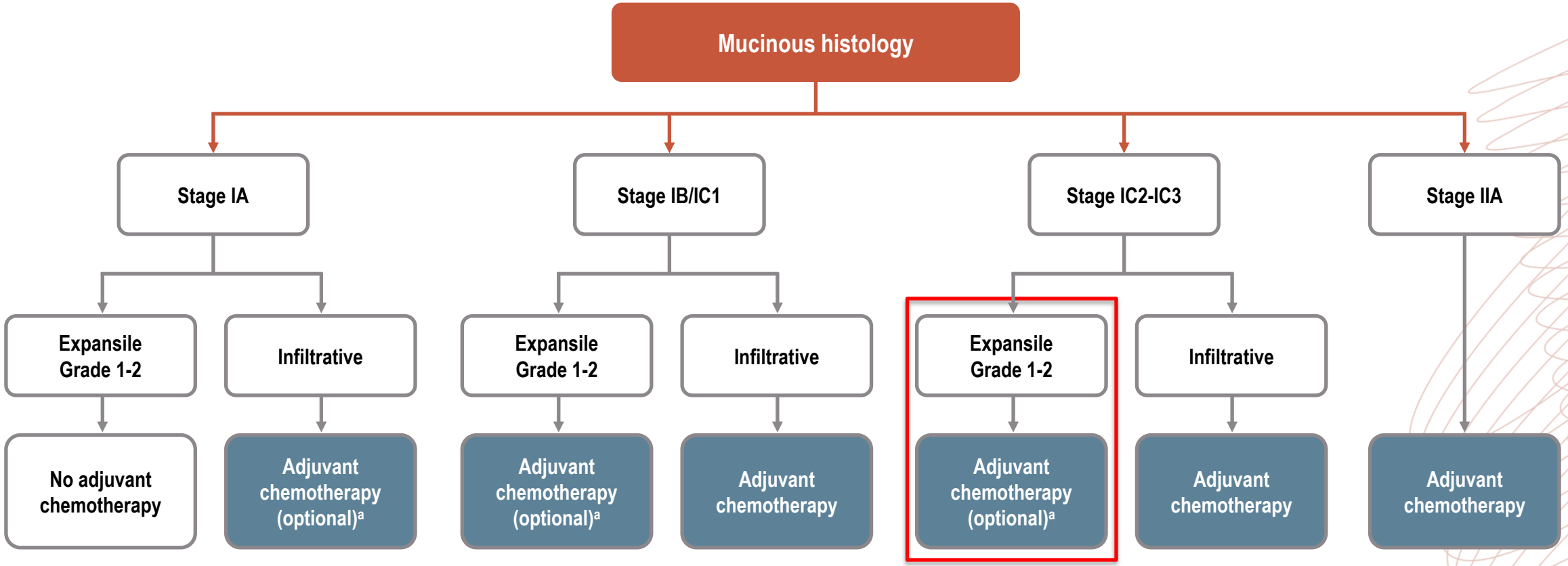
C. Follow-up only

D. Any of the above



ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH EARLY-STAGE MUCINOUS OVARIAN CANCER (STAGE I-IIA)

ESMO–ESGO CONSENSUS CONFERENCE RECOMMENDATIONS



[a] Considered no adjuvant chemotherapy only for patients with complete surgical staging

ESGO, European Society of Gynaecological Oncology; ESMO, European Society for Medical Oncology

Colombo N, et al, Ann Oncol. 2019;30:672-705

PATIENT CASE
OVARIAN CANCER

Immediate post-operative management plan

- No adjuvant therapy recommended
- Regular follow-up by the gynaecological oncology team

During subsequent follow-up

- CA125 started to rise 2 years post-diagnosis (55 U/mL)
- CT scan at this time showed no recurrent disease

Moved to Edinburgh and care transferred here

- CA125 level: 91 U/mL
- CT scan showed relapsed disease

CT: progressive right-sided pleural disease, thickened right hemidiaphragm and enlarged nodules close to the caecum

CA125, cancer antigen 125; CT, computed tomography

Patient case and images provided by Gourley C

PATIENT CASE
OVARIAN CANCER

Right video-assisted thoracoscopic biopsy performed:

- Suspicious nodules seen throughout the parietal pleura
- Talc pleurodesis performed
- Pathology showed metastatic mucinous ovarian adenocarcinoma

Patient case and images provided by Gourley C

POLLING QUESTION

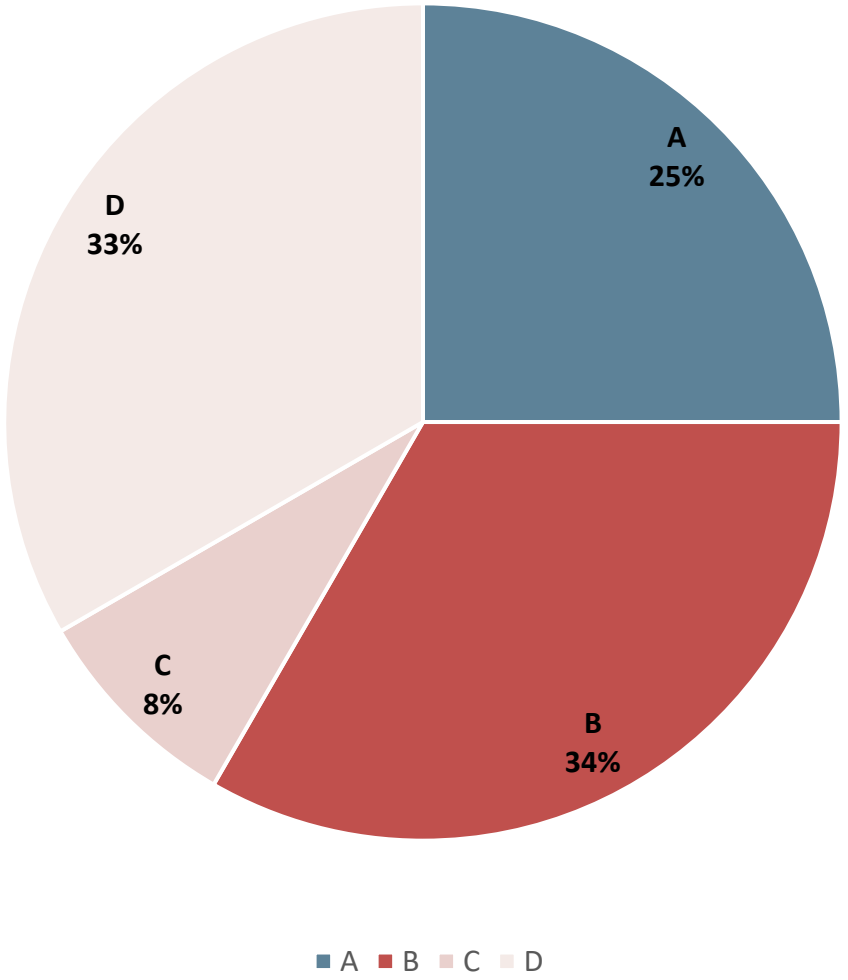
WHICH MOLECULAR ABNORMALITY IS NOT ASSOCIATED WITH MUCINOUS OVARIAN CANCER?

A. ***BRCA1* mutation**

B. *TP53* mutation

C. *KRAS* mutation

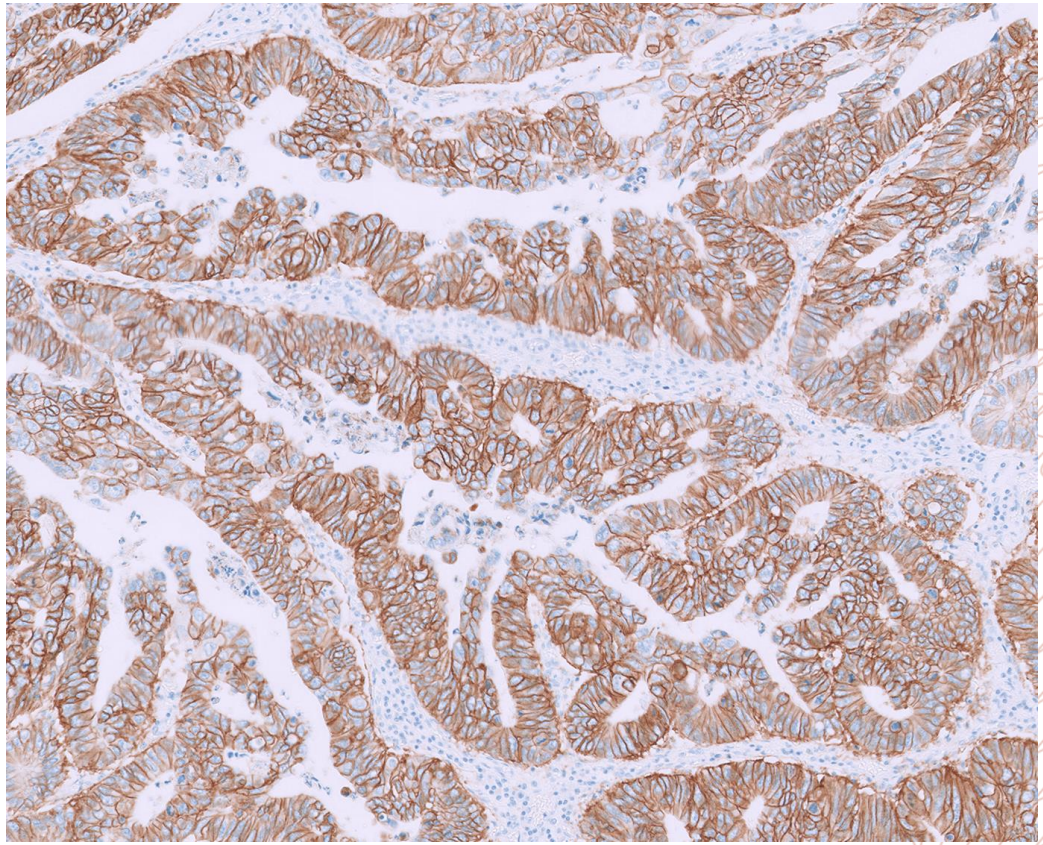
D. *HER2* amplification



PATIENT CASE
OVARIAN CANCER

Right video-assisted thoracoscopic biopsy performed:

- Suspicious nodules seen throughout the parietal pleura
- Talc pleurodesis performed
- Pathology showed metastatic mucinous ovarian adenocarcinoma
- KRAS testing on primary tumour revealed no activating mutations
- HER2 staining on primary tumour suggested over-expression

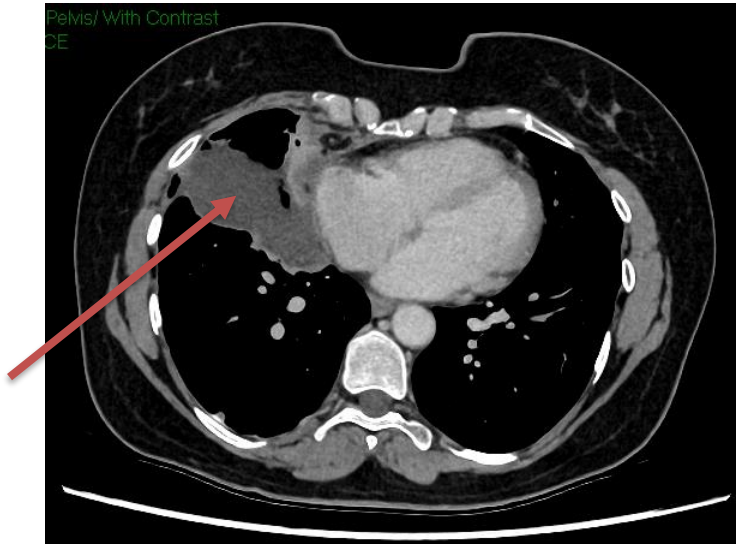


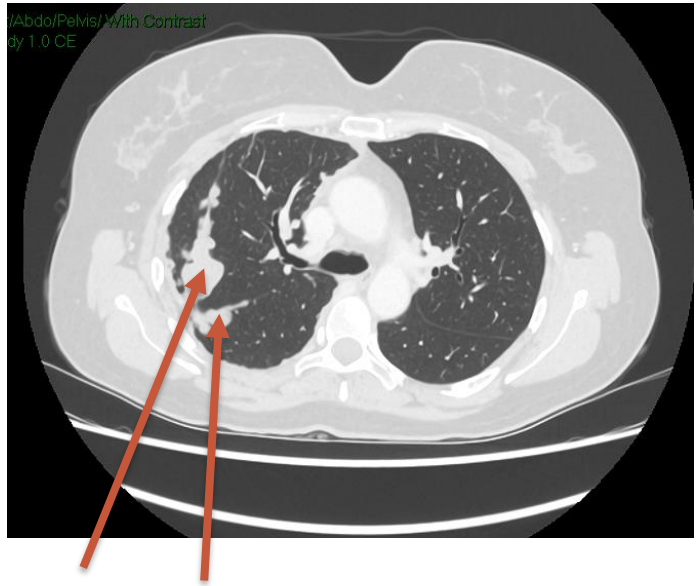
Patient case and images provided by Gourley C

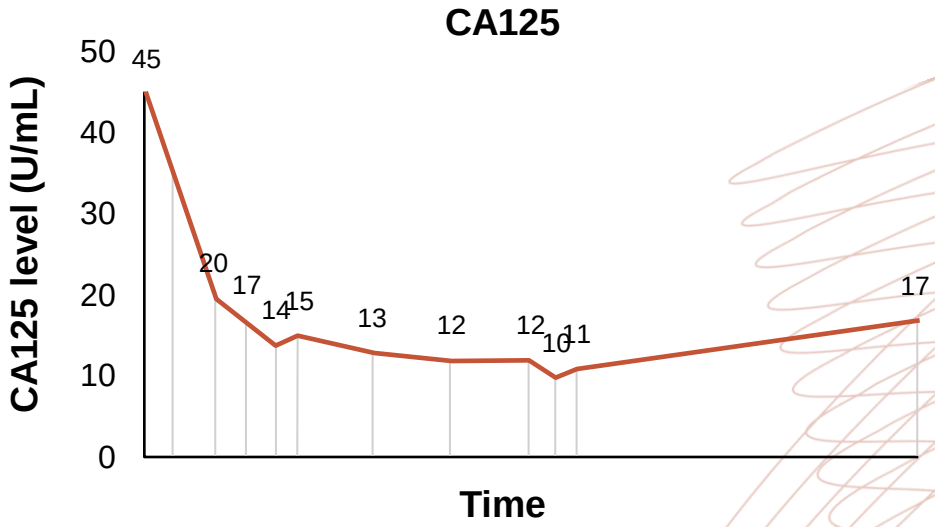
PATIENT CASE
OVARIAN CANCER

Commenced palliative capecitabine and oxaliplatin (CAPOX) chemotherapy

- CT scan after three cycles showed stable disease
- Some response on the basis of CA125
- Chemotherapy discontinued after 4 cycles because of angina (treatment-induced coronary artery spasm)
- CT scan performed two months later showed progression of right pleural disease







CT: Progression in right pleural disease with enlarging solid component extending along fissures and anterior mediastinal pleura with new loculated anterior right pleural effusion. Invasion of right epiphrenic/epicardial fat and suspicion of pericardial involvement

CA125, cancer antigen 125; CT, computed tomography

Patient case and images provided by Gourley C

PATIENT CASE – OVARIAN CANCER

BOUQUET STUDY DISCUSSED WITH PATIENT

- Platform study for multiple rare ovarian cancers; endometrioid, clear cell, low grade serous etc
- Arm decided by Foundation Medicine testing and ER staining

- Measurable persistent or recurrent platinum-resistant rare eOC (LGSOC, clear-cell, mucinous, undifferentiated or grade 1/2 endometrioid carcinoma, carcinosarcoma, malignant Brenner tumour or mesonephric-like adenocarcinoma)
- One to four prior lines of non-hormonal systemic therapy
- ECOG PS 0 or 1
- Tumour sample if available

n=20 per arm, with potential to expand to n=50

Prescreening: Biomarker testing (F1CDx and ER IHC) and pathology

General and arm-specific screening

*PTEN*LOF alteration and/or *PIK3CA*- or *AKT1*-activating mutation	Ipatasertib + paclitaxel
BRAF/KRAS/NRAS-activating mutation and/or *NF1*LOF alteration	Cobimetinib
ERBB2-amplified and/or mutated	Trastuzumab emtansine
Non-matched	Atezolizumab + bevacizumab
ER+	Giredestrant + ademaciclib
PIK3CA-activating mutation	Inavolisib + palbociclib
ER+ and *PIK3CA*-activating mutation	Inavolisib + palbociclib + letrozole
Non-matched	Inavolisib + olaparib
ER+ and *PIK3CA*-activating mutation	Inavolisib + giredestrant
PIK3CA-activating mutation	Inavolisib + bevacizumab
Non-matched	Atezolizumab + bevacizumab cyclophosphamide

Primary efficacy endpoint: investigator-assessed cORR per RECIST v1.1

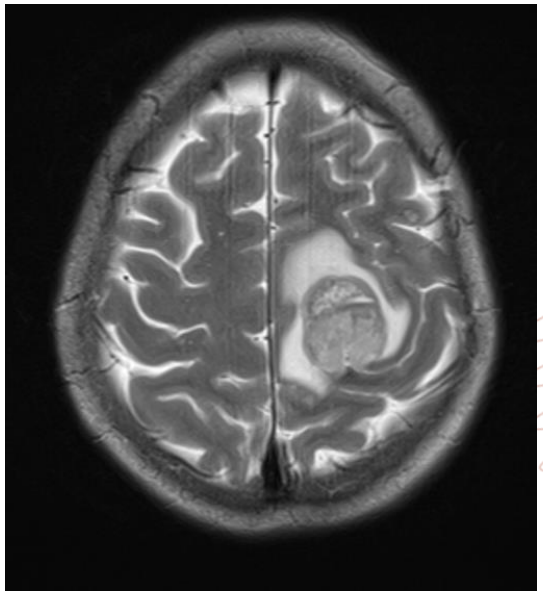
ECOG PS, Eastern Cooperative Oncology Group performance status; eOC, epithelial ovarian cancer; ER, estrogen receptor; IHC, immunohistochemistry; LGSOC, low-grade serous ovarian cancer; LOF, loss of function; RECIST, response Evaluation Criteria in Solid Tumours

https://clinicaltrials.gov/study/NCT04931342

PATIENT CASE
OVARIAN CANCER

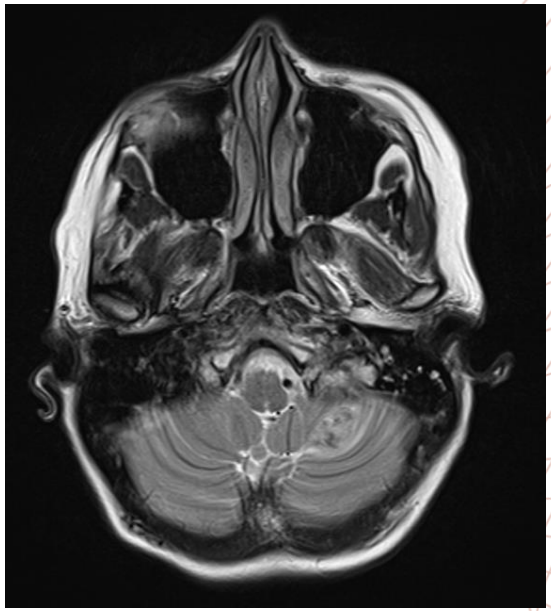
Patient received 17 cycles of 3-weekly trastuzumab emtansine

- Only toxicity was Grade 1 nausea
- Ejection fraction was satisfactory throughout
- Best response on trial was a partial response after 16 cycles
- Tumour markers normalised



Unfortunately, shortly after the scan suggesting partial response suffered an acute right-sided weakness

- Imaging and MRI showed multiple bilateral cerebral and cerebellar metastases
- Treated with palliative whole brain radiotherapy (3000 cGy in five fractions)
- Returned to her home country for end-of-life care



cGy, centigray; MRI, magnetic resonance imaging

Patient case and images provided by Gourley C

OVARIAN CANCER: CHALLENGES AND CONSIDERATIONS FOR HER2 IHC TESTING

CONCLUSIONS

IHC, immunohistochemistry

CONCLUSIONS

HER2-TARGETING THERAPIES FOR OVARIAN CANCER ARE ON THE HORIZON

- **Initially,** HER2-targeting therapies will be used in **relapsed disease** in the **palliative setting**
  - There is a high chance they will be **moved earlier in the patient journey,** in particular for certain ovarian cancer histological subtypes and specific molecular subgroups
- **Uncertainty remains** regarding whether **sensitivity** to these agents will differ between **ovarian cancer histological subtypes** for a given level of HER2 expression
- For ovarian cancer, uncertainties remain regarding:
  - Intra-tumoral heterogeneity of HER2 expression
  - How expression changes during the patient journey
  - The extent to which this is impacted by previous therapy

OVARIAN CANCER: CHALLENGES AND CONSIDERATIONS FOR HER2 IHC TESTING

Q&A SESSION

IHC, immunohistochemistry

PANEL DISCUSSION
AND
AUDIENCE QUESTIONS

FUTURE PERSPECTIVES AND KEY CLINICAL TAKEAWAYS

Fernando López-Ríos MD, PhD

Pathologist
12 de Octubre University Hospital
Madrid, Spain

FUTURE PERSPECTIVES

HER2 TESTING: THE EVOLVING ROLE OF IHC IN LUNG AND OVARIAN CANCER

- **Comprehensive genomic profiling and HER2 IHC for all patients with lung and ovarian carcinomas** to better understand HER2 alterations and guide personalized treatment strategies
  - Integration of ultrafast NGS and AI-powered HER2 scoring
  - AI algorithms: a new member of the clinical/ molecular tumor board

KEY CLINICAL TAKEAWAYS

HER2 TESTING: THE EVOLVING ROLE OF IHC IN LUNG AND OVARIAN CANCER

- Standardise HER2 IHC for lung and ovarian carcinoma patients to ensure consistent and reliable results
- Implement high-quality HER2 IHC testing by:
  - Engaging in pre-analytical processes
  - Using validated IHC assays
  - Adopting scoring and reporting guidelines (e.g., 3+ with a 10% cut-off)
- HER2 alterations in lung carcinoma encompass both amplifications and mutations, highlighting the importance of comprehensive testing for accurate diagnosis and treatment planning
- Incorporate HER2 testing earlier in the patient journey for ovarian carcinoma, to guide timely and informed treatment decisions
- Emerging HER2-targeted therapies with antibody-drug conjugates are showing promise in the treatment of HER2-altered ovarian and lung cancers

IHC, immunohistochemistry

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