VII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN
Vigo, 20 y 21 de febrero de 2025

Oncología de precisión: problemas y soluciones

Federico Rojo

- Nuevas estrategias diagnósticas moleculares en oncología de precisión
- El uso clínico de NGS y la clasificación ESCAT son suficientes para seleccionar pacientes?
- Podemos ser más precisos en la selección de pacientes con la aplicación de la IA en biomarcadores?

Nuevas estrategias diagnósticas moleculares en oncología de precisión

ESCAT

ESMO Scale for Clinical Actionability of Molecular Targets

Newly added tumour types (2024)

- Advanced non-squamous NSCLC
- **Advanced Breast cancer**
- Prostate cancer
- **Gastrointestinal stromal tumours (GIST)**
- Colorectal cancer
- **Sarcoma**
- Ovarian cancers
- **Thyroid cancer**
- Cholangiocarcinoma
- **Cancer of unknown primary (CUP)**

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Available online 27 May 2024

ANNALS OF ONCOLOGY driving innovation in oncology

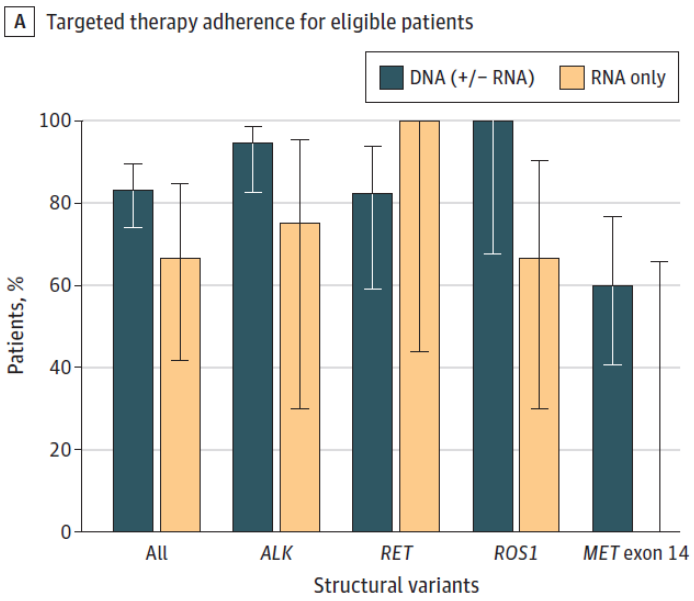
SPECIAL ARTICLE

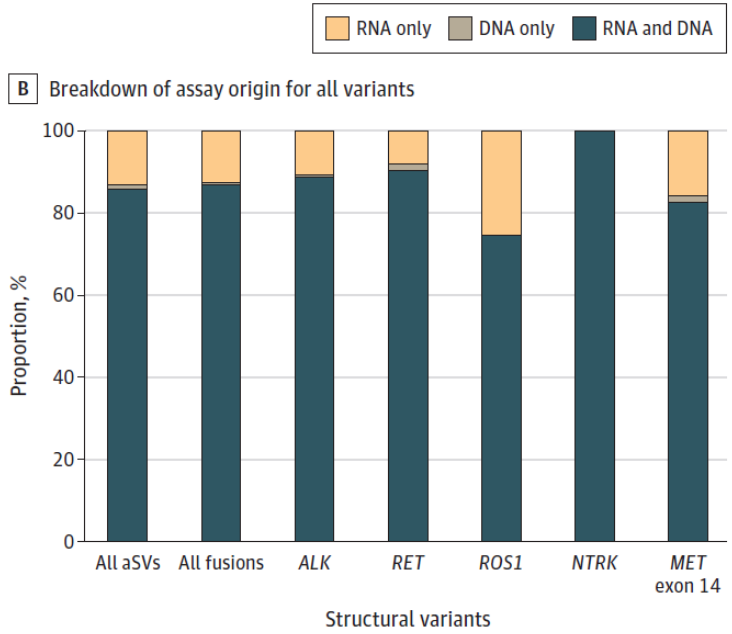
Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group

M. F. Mosele[1,2], C. B. Westphalen[3], A. Stenzinger[4], F. Barlesi[1,2,5], A. Bayle[5,6,7,8], I. Bièche[9], J. Bonastre[7,8], E. Castro[10], R. Dienstmann[11,12,13], A. Krämer[14,15], A. M. Czarnecka[16,17], F. Meric-Bernstam[18], S. Michiels[7,8], R. Miller[19,20], N. Normanno[21], J. Reis-Filho[22†], J. Remon[2], M. Robson[23], E. Rouleau[24], A. Scarpa[25], C. Serrano[11], J. Mateo[11] & F. André[1,2,5*]

Actionable Structural Variant Detection via RNA-NGS and DNA-NGS in NSCLC

- Multisite retrospective cohort with 917 patients with advanced NSCLC for both hybrid capture RNA-NGS and DNA-NGS testing
- Concurrent RNA-NGS and DNA-NGS identified 15.3% more patients harboring a SVs compared with DNA-NGS alone, including 14.3% more patients harboring actionable fusions and 18.6% more harboring MET exon 14 skipping alterations

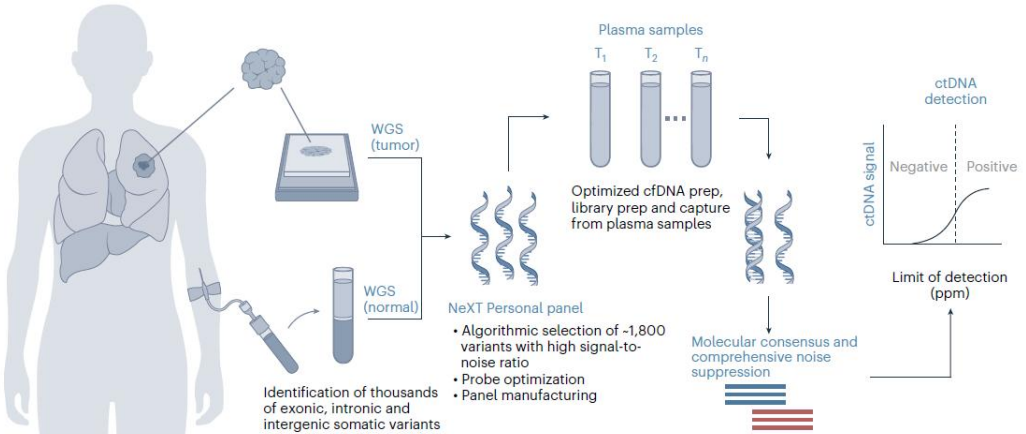


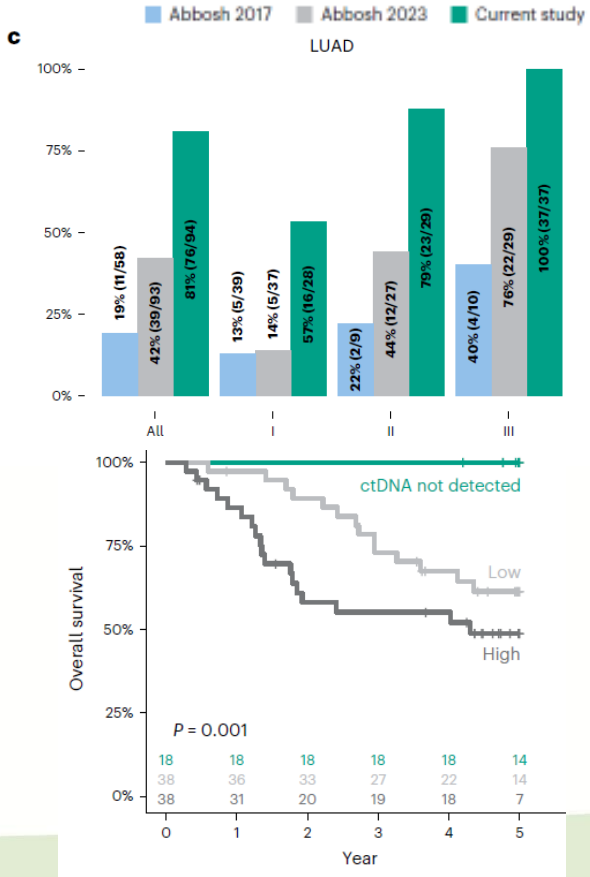


Owen, D et al. JAMA Net Open 2024

Ultrasensitive ctDNA NGS for preoperative disease stratification in early-stage lung adenocarcinoma

- NeXT Personal: whole-genome-based, tumor-informed ultrasensitive ctDNA NGS
- Detection at 1–3 ppm of ctDNA with 99.9% specificity
- From 171 patients with early-stage lung cancer from the TRACERx study, 81% of patients with lung adenocarcinoma (LUAD), including 53% with pTNM stage I had ctDNA pre-operatively
- ctDNA predicted worse clinical outcome





Black, JRM et al. Nat med 2024

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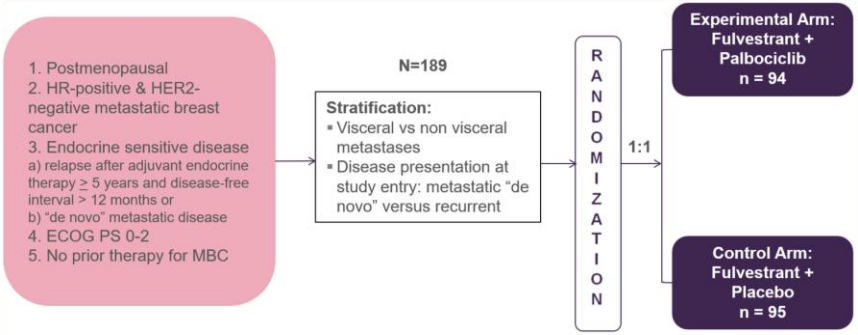
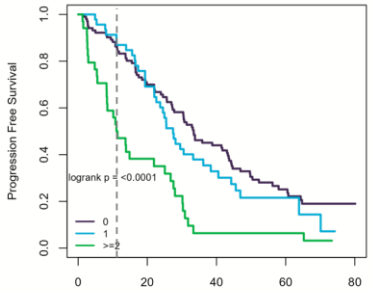
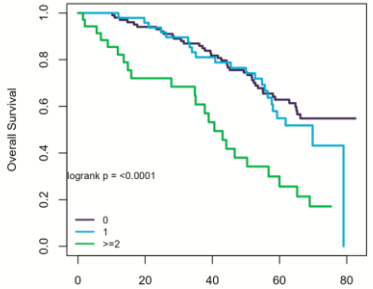
Plasma mutational burden predicts early progression in HR+/ HER2- metastatic breast cancer (GEICAM/2014-12 FLIPPER trial)



PIK3CA/TP53 # of baseline mutations by PFS/OS

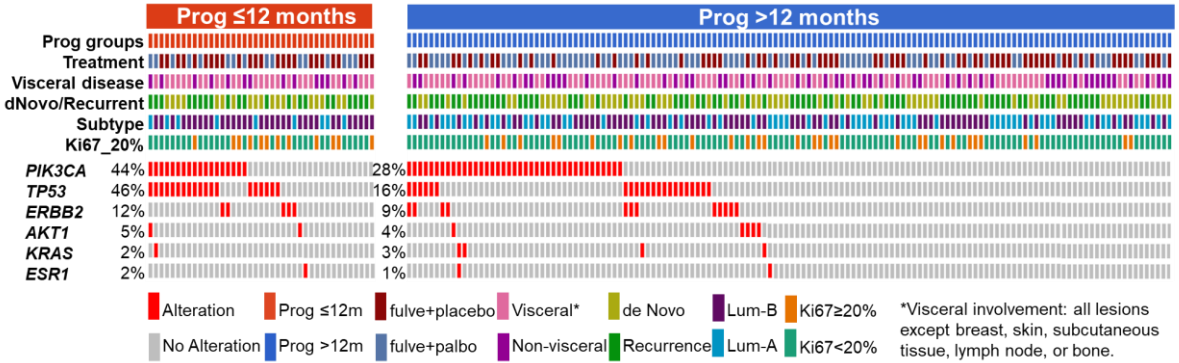




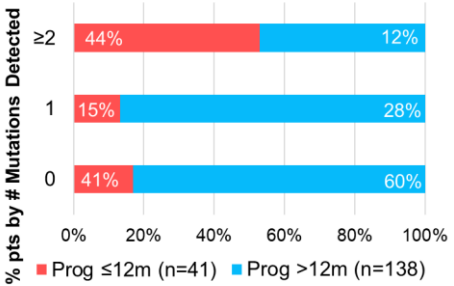
# mut	N	Events	mPFS	HR (CI95%)	p-value
0	103	74(71.8%)	33.38	1	
1	49	36(73.5%)	27.43	1.47 (0.97-2.21)	0.0662
≥2	35	32(91.4%)	11.22	3.6 (2.25-5.76)	<0.0001

# mut	N	Events	mOS	HR (CI95%)	p-value
0	103	40(38.8%)	NR	1	
1	49	22(44.9%)	69.85	1.34 (0.78-2.27)	0.2860
≥2	35	23(65.7%)	40.61	2.92 (1.66-5.12)	0.0002

Baseline mutational profiles by progression groups (PFS-12m)



PIK3CA/TP53 # of baseline mutations by PFS-12m



# mut	N	Prog ≤12m	Prog >12m	OR (CI95%)	p-value
0	100	17 (17%)	83 (83%)	1	
1	45	6 (13.33%)	39 (86.67%)	0.89 (0.31-2.55)	0.8338
≥2	45	18 (52.94%)	16 (47.06%)	5.84 (2.29-14.87)	0.0002

ESR1 mutations emerge in ~40% metastatic breast cancer after endocrine therapy

International guidelines for *ESR1* mutation testing in ER+/HER2- metastatic breast cancer

ASCO (American Society of Clinical Oncology — Knowledge Conquers Cancer)

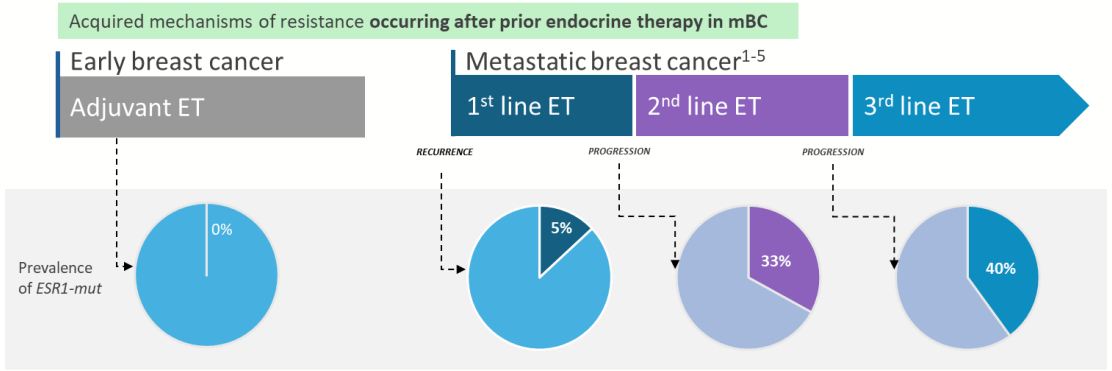
- **Routine testing for *ESR1*-mut at recurrence or PD on ET** (with or without CDK4/6i)
- Use a CLIA-certified assay **on blood or tissue obtained at PD**
- **Blood-based ctDNA testing is preferred**
- Consider **retesting** if *ESR1*-mut is not detected.

ESMO (Good Science, Better Medicine, Best Practice — European Society for Medical Oncology Guidelines)

- Test for *ESR1*-mut at relapse or progression after ET plus CDK4/6i on plasma or tissue

NCCN (National Comprehensive Cancer Network®)

- Assess for ESR1-mut at progression following prior lines of ET with NGS or PCR (tumor tissue or blood)



Testing for *ESR1*-mut should occur at each progession during the metastatic treatment course, if not detected previously

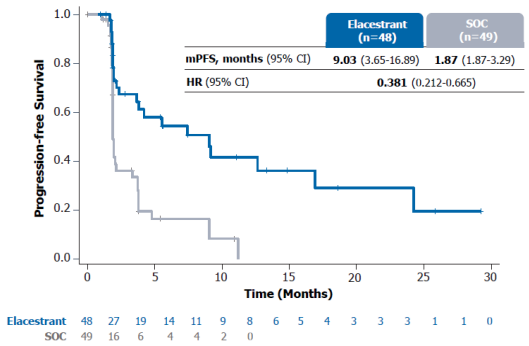
Harold J.Burestein, et al. Journal of Clinical Oncology 2023; 4118, 3423-3425; ESMO Breast CancerLiving Guidelines: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer (accessed Feb 2024); NCCN CLinical Practice Guidelines in Oncology (NCCN Guidelines) Breast Cancer Version 1.2024-Jan 25, 2024

1. Jeselsohn R, et al. Clin Cancer Res. 2014;20:1757-1767; 2. Jeselsohn R, et al. Cancer Cell. 2018;33:173-186.e5; 3. Allouchery V, et al. Breast Cancer Res. 2018;20:40; 4. Schiavon G, et al. Sci Transl Med. 2015;7;313ra182; 5. Brett JO, et al. Breast Cancer Res. 2021;23:85

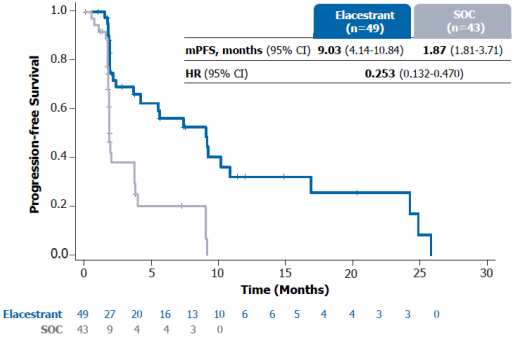
ESR1 mutations emerge in ~40% metastatic breast cancer after endocrine therapy

Elacestrant was associated with a PFS benefit across ESR1 mutation variants (D538G, Y537S, and Y537N)

ESR1*-mut, D538G variant



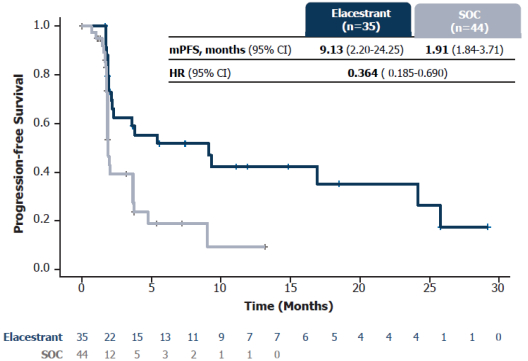
ESR1*-mut, Y537S/N variants



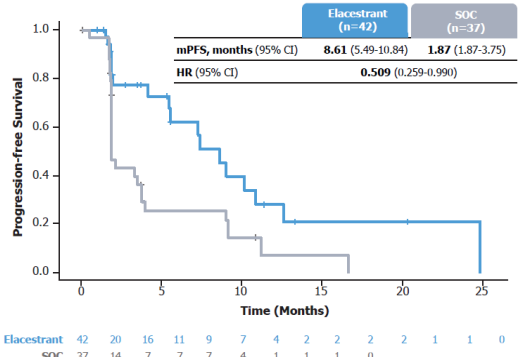
D538G, Y537S and Y537N represent nearly 90% of ESR1 mutations detected

Elacestrant was associated with a clinically meaningful improvement in mPFS independently of ESR1 VAF

High VAF (≥1.2%)



Low VAF (<1.2%)



Bardia, A et al. Clin Cancer Res 2024
Bardia, A et al. SABCS 2024

El uso clínico de NGS y la clasificación ESCAT son suficientes para seleccionar pacientes?

DESTINY-Breast06:
Open-label, randomized, multicenter, phase 3 study

T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low
PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

R 1:1

- **T-DXd** 5.4 mg/kg Q3W (n=436)
- **TPC** (n=430)

HER2-low = 713
HER2-ultralow = 153†

Capecitabine, 59.8%; nab-paclitaxel, 24.4%; paclitaxel, 15.8%

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

ENDPOINTS

Primary

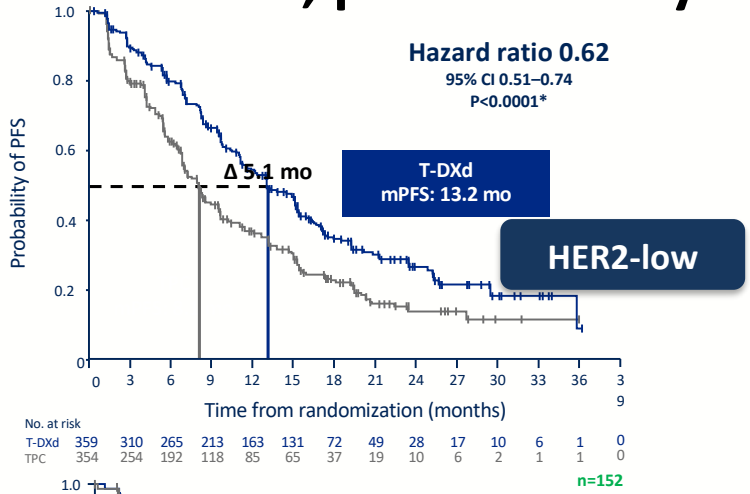
- PFS (BICR) in HER2-low

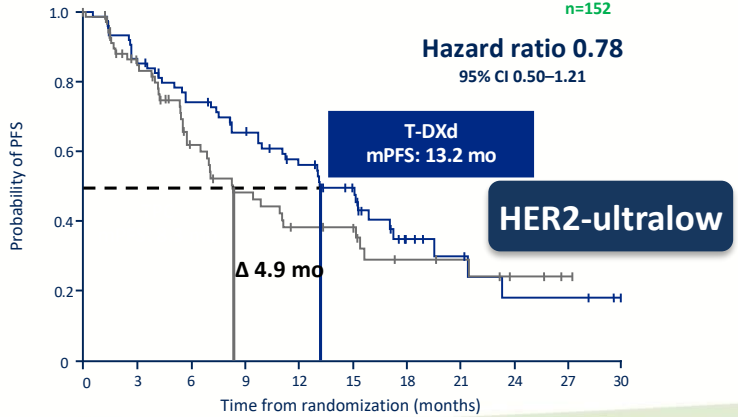
Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes (HER2-low and ITT)

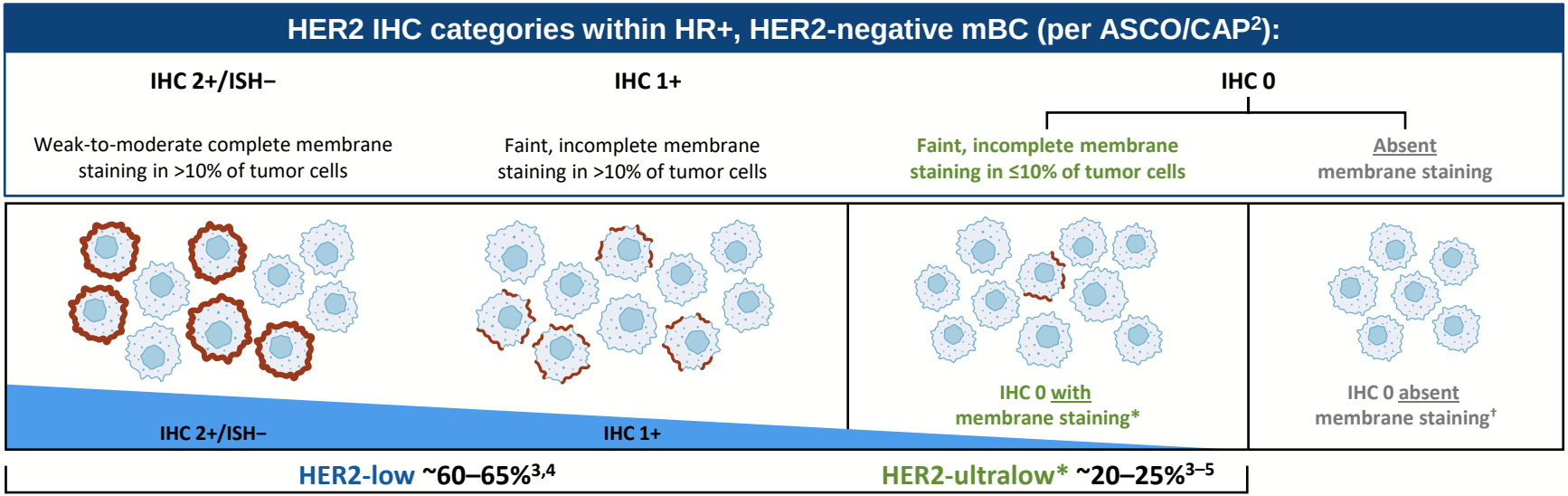




ClinicalTrials.gov. NCT04494425. https://www.clinicaltrials.gov/study/NCT04494425. Accessed May 31, 2024; 2. Curigliano G et al. Presented at: ASCO Annual Meeting; May 31 – June 4, 2024; Chicago, IL. Presentation LBA1000

Targeting ‘low’ and ‘ultralow’ HER2-expressing tumors in mBC[1]

- *In the DESTINY-Breast06 trial, T-DXd’s efficacy is studied in HR+, HER2-low and HER2-ultralow,*
- *Moves T-DXd to an earlier line of treatment in HER2-low mBC (vs DESTINY-Breast04)*
- *Expands the proportion of patients who may benefit from T-DXd to ~85% of HR+, HER2− mBC*



DESTINY-Breast06 patient population: ~85% of HR+, HER2-negative mBC

*HER2-ultralow (HER2 IHC 0 with membrane staining of any intensity in ≤10% of tumor cells) was referred to as HER2 IHC >0 to <1+ in the DESTINY-Breast06 protocol; †no membrane staining is observed

1. Curigliano G et al. Presented at: ASCO Annual Meeting; May 31 – June 4, 2024; Chicago, IL. Presentation LBA1000; 2. Wolff AC, et al. *J Clin Oncol.* 2023;41:3867–3872; 3. Denkert C, et al. *Lancet Oncol.* 2021;22:1151–1161; 4. Chen Z, et al. *Breast Cancer Res Treat.* 2023;202:313–323; 5. Mehta S, et al. *J Clin Oncol.* 2024;42(Suppl. 16):e13156 (Abstract)

DESTINY-PanTumor02: Phase 2 study of T-DXd for HER2-expressing solid tumors

Key eligibility criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd
5.4 mg/kg Q3W

40 per cohort[b]

- Endometrial cancer
- Cervical cancer
- Ovarian cancer
- Bladder cancer
- Other tumors[c]
- Biliary tract cancer
- Pancreatic cancer

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analysis

- Subgroup analyses by HER2 status

Primary analysis
data cutoff: Jun 8, 2023
Median follow up: 12.75 mo

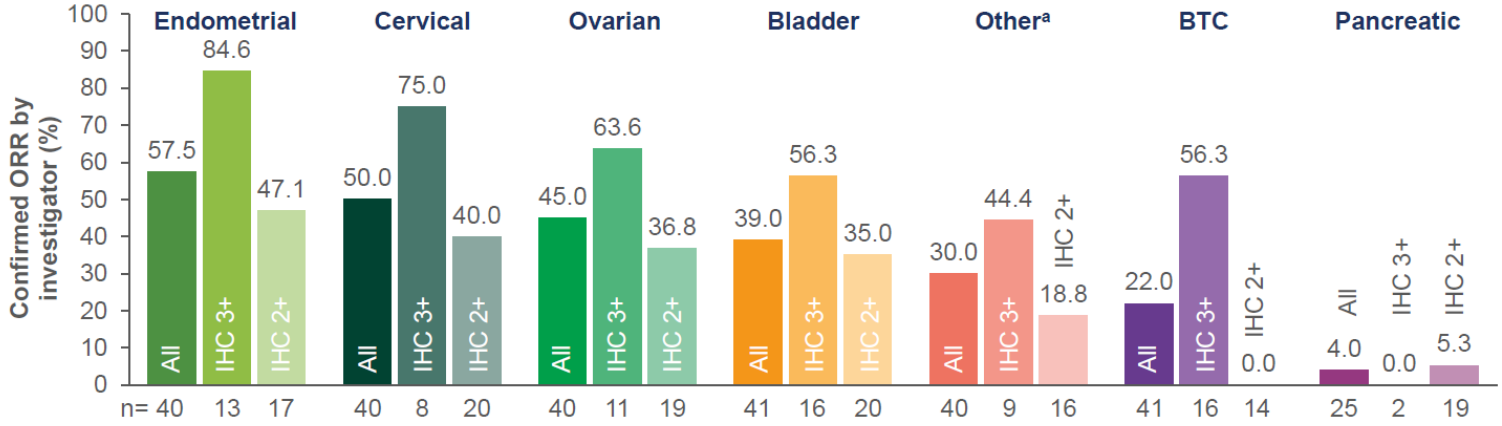
Baseline characteristics

- 267 patients received treatment; 202 (75.7%) based on local HER2 testing
  - 111 (41.6%) patients were IHC 3+ based on HER2 test (local or central) at enrollment, primary efficacy analysis (all patients)
  - **75 (28.1%) patients were IHC 3+ on central testing**, sensitivity analysis on efficacy endpoints (subgroup analyses)
- Median age was 62 years (23–85) and **109 (40.8%) patients had received ≥3 lines of therapy**

Meric-Bernstam, F et al. ESMO 2023

DESTINY-PanTumor02: Phase 2 study of T-DXd for HER2-expressing solid tumors

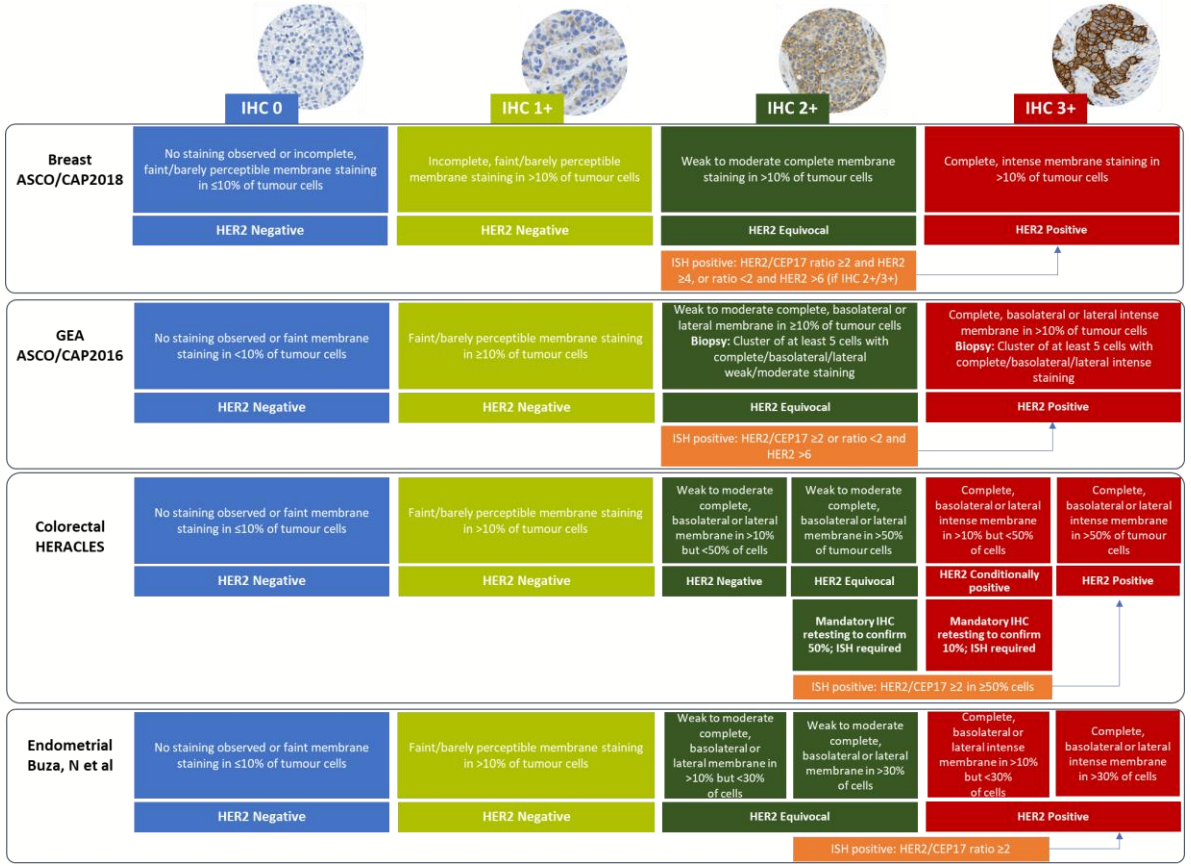
Objective response and duration of response



	All patients (N=267)	IHC 3+ (n=75)	IHC 2+ (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, months (95% CI)[b]	11.3 (9.6, 17.8)	22.1 (9.6, NR)	9.8 (4.3, 12.6)

Meric-Bernstam, F et al. J Clin Oncol 2025

ASCO/CAP have released formal HER2 scoring guidelines for breast and gastroesophageal cancers only



1. Wolff AC et al. Arch Pathol Lab Med 2023. 2. Bartley AN et al. Arch Pathol Lab Med 2016. 3. Hagemann IS et al. Arch Pathol Lab Med 2023. 4. Fader AN et al. J Clin Oncol 2018. 5. Buza N et al. Mod Pathol 2013. 6. Crothers BA et al. CAP (2023). 7. Valtorta E et al. Mod Pathol 2015

Various HER2 scoring used across endometrial serous, colorectal, urothelial or lung carcinomas

The use of different algorithms for HER2 testing may significantly affect the HER2 positivity rate and the proportion of false positive and false negative results

Colorectal Carcinoma

HERACLES trial (Valtorta E. et al.)	ASCO/CAP 2018 Breast	ASCO/CAP 2017 Gastric	Other
30%	16.3%	49.4%	4.3%

Other responses: original US Food and Drug Administration scoring criteria—HercepTest (2), positive versus negative (1), CAP 2013 breast guideline (1), based on ordering physician (1), and MyPathway (1).

Urothelial Carcinoma

	HER2 Score (% of specimens)			
ASCO/CAP Criteria	0	1+	2+	3+
Breast 2018	37%	45%	5%	6%
Gastric 2017	37%	16%	43%	11%

Endometrial Serous Carcinoma

Fader et al.	ASCO/CAP 2018 Breast	ASCO/CAP 2013 Breast	ASCO/CAP 2007 Breast	"overall" positive/negative	HercepTest package insert for Breast	Other
16%	69.4%	1.8%	1.4%	3.6%	5%	2.9%

Other responses: CAP/American Society for Clinical Pathology/ASCO gastroesophageal adenocarcinoma (4) and in-house guideline (1)

Non-Small Cell Lung Cancer

	HER2 Score (% of specimens)			
ASCO/CAP Criteria	0	1+	2+	3+
Gastric 2017	28%	51%	17%	3%

Hagemann IS et al. Arch Pathol Lab Med 2023. Valtorta E. et al. Mod Pathol. 2015;28(11):1481–1491. Fader AN et al. Clin Cancer Res. 2020;26(15):3928–3935. doi:10.1158/1078-0432.CCR-20-0953. Zimpfer A et al. Cancers 2023. Ninomiya K et al. Chest 2019.

Podemos ser más precisos en la selección de pacientes con la aplicación de la IA en biomarcadores?

Datopotamab-DXd vs docetaxel for previously treated advanced or metastatic NSCLC: Randomized Phase III TROPION-Lung01 study

TROPION-Lung01

Study Design (NCT04656652)[1]

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without AGA*
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With AGA
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

Dato-DXd
6 mg/kg q3w
N=299

Docetaxel
75 mg/m² q3w
N=305

Stratified by:
Histology†, AGA‡, anti–PD-(L)1 mAb included in most recent prior therapy, geography§

Dual Primary Endpoints: PFS by BICR; OS
Secondary Endpoints: ORR by BICR; DOR by BICR; Safety

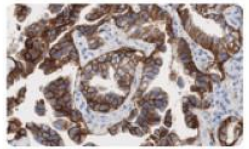
Dr Marina Chiara Garassino | Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung01

Ahn, MJ et al. J Clin Oncol 2024
Garassino, MC et al. WCLC 2024

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

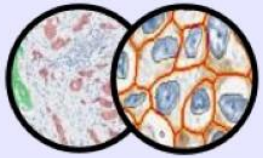
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay



2 Whole Slide Imaging

3 Automated Image Analysis (QCS)

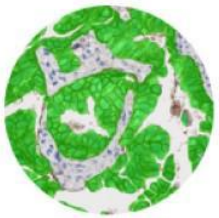


4 Patient Biomarker Status Determination

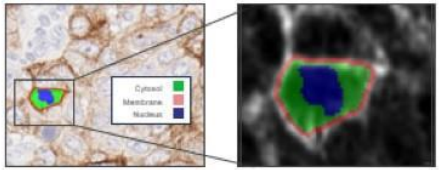
\+ ≥75% of tumor cells with TROP2 NMR ≤0.56

\- <75% of tumor cells with TROP2 NMR ≤0.56*

Differentiates tumor from non-tumor



Measures OD in each tumor cell



Membrane and cytoplasm optical density (OD)

Calculates TROP2 NMR for every tumor cell

$$\frac{\text{Membrane OD}}{\text{Membrane OD + Cytoplasm OD}}$$

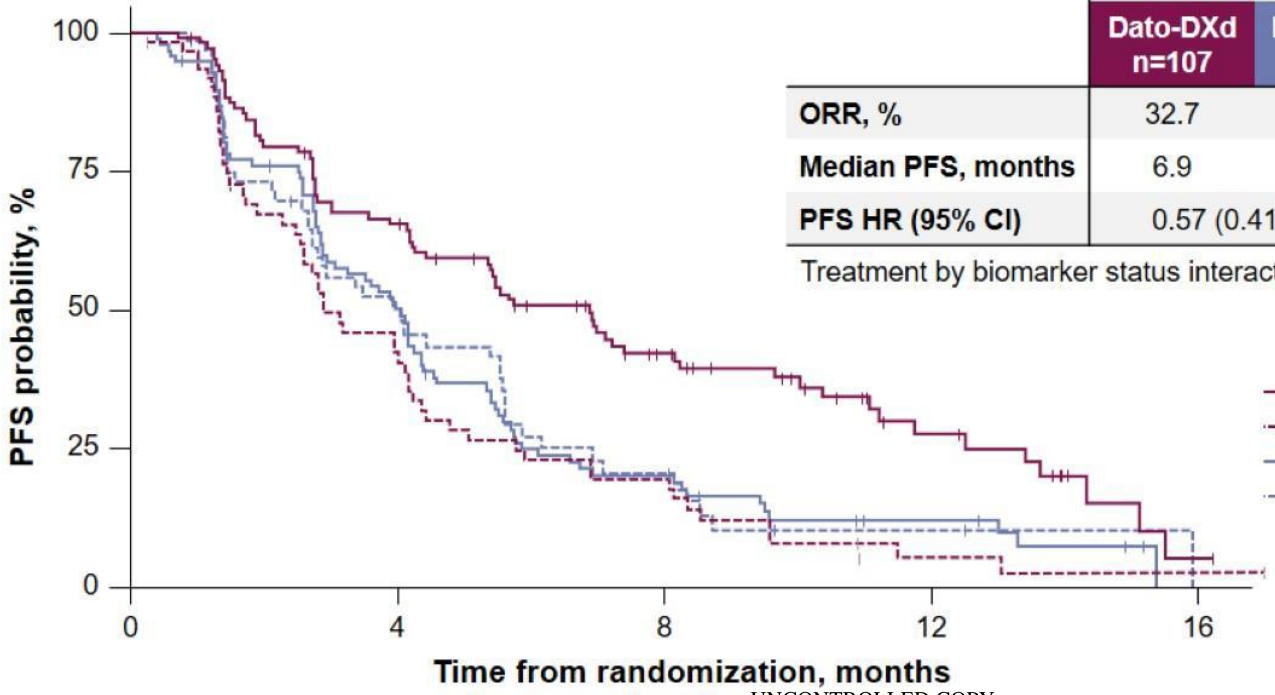
Lower NMR → higher cytoplasm proportion

OD, optical density (a measure of staining intensity).
*Or >25% of cells with an NMR >0.56

Overall BEP: Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the biomarker-evaluable population

Biomarker-evaluable population, n=352



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

Data cutoff: March 29 2023

PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment: Dato-DXd: 0.48 [0.33-0.69]; Docetaxel:0.97 [0.68-1.39]

Mensajes finales

- La NGS de captura híbrida basada en RNA mejora la capacidad de detectar fusiones génicas
- La biopsia líquida crece como herramienta en medicina de precisión (necesidad de alta sensibilidad!!!)
- Algunas dianas ESCAT I requieren aproximaciones basadas en técnicas básicas como la IHC
- HER2 se extiende como biomarcador pantumor, pero abre interrogantes sobre los criterios de interpretación en algunos tumores y sobre el límite más bajo de expresión (HER2-ultralow)
- La IA aparece por primera vez como herramienta imprescindible para la selección de pacientes en medicina de precisión