XVII SIMPOSIUM
BASES BIOLÓGICAS DEL CÁNCER
E INNOVACIÓN TERAPÉUTICA

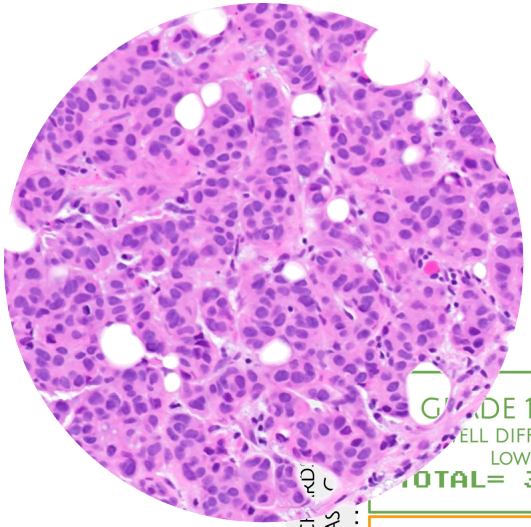
MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

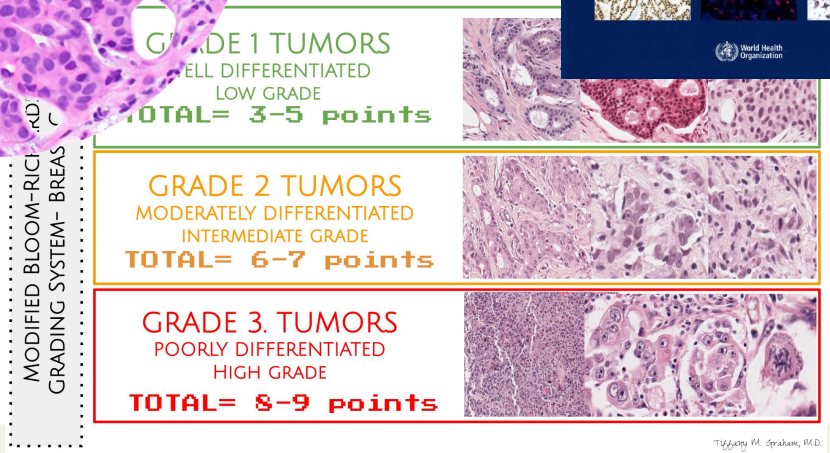
SALAMANCA, 22 Y 23 DE MAYO DE 2025

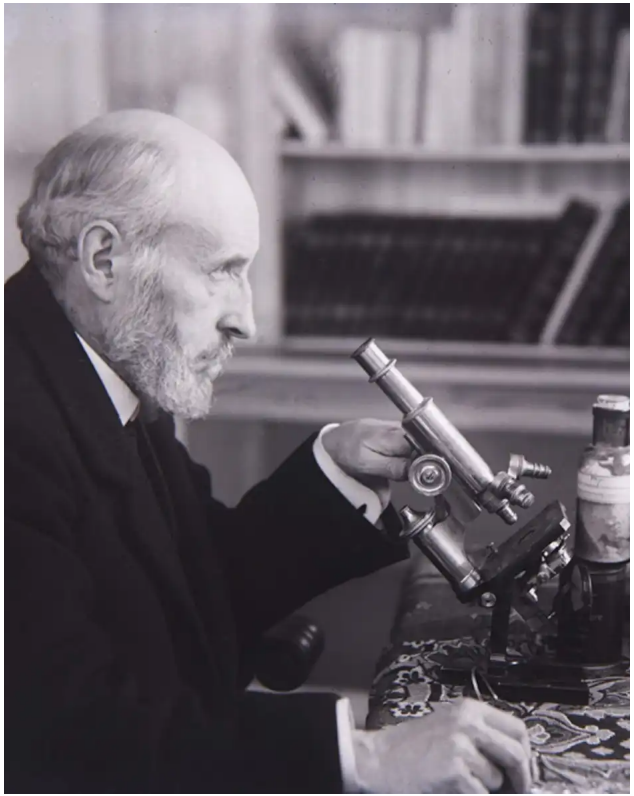
De lo invisible a lo vital: la revolución de la patología en la era molecular

Federico Rojo

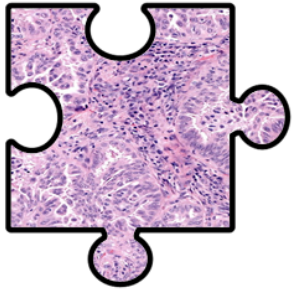
Morphological diagnosis







Morphological diagnosis



Una técnica como la IHC sigue siendo suficiente para seleccionar pacientes para tratamientos dirigidos?

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

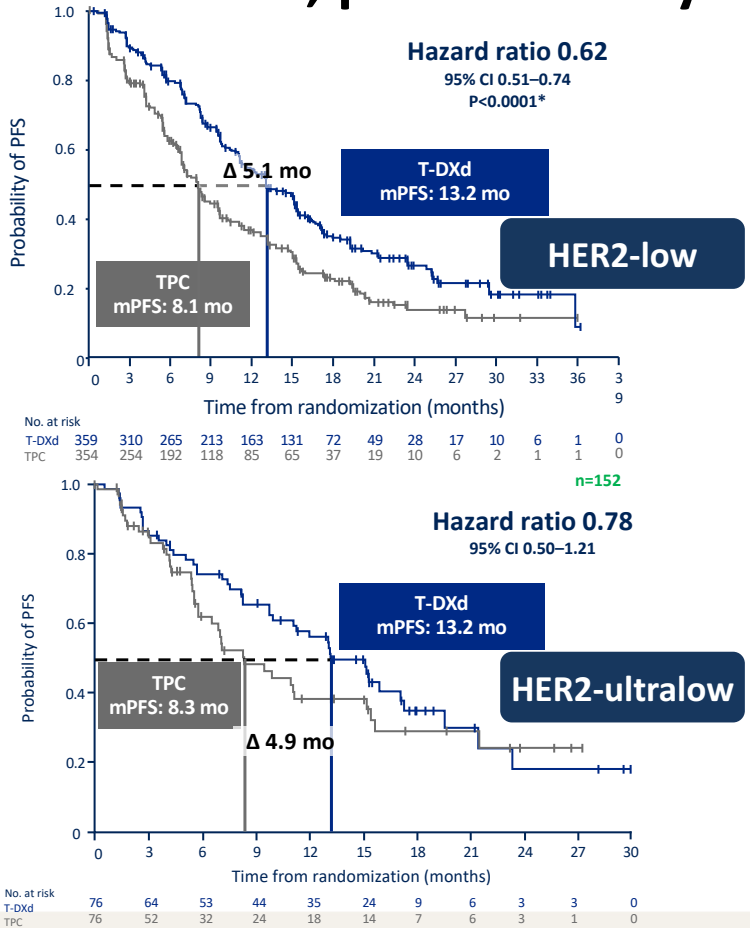
- PFS (BICR) in HER2-low

Key secondary

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

Other secondary

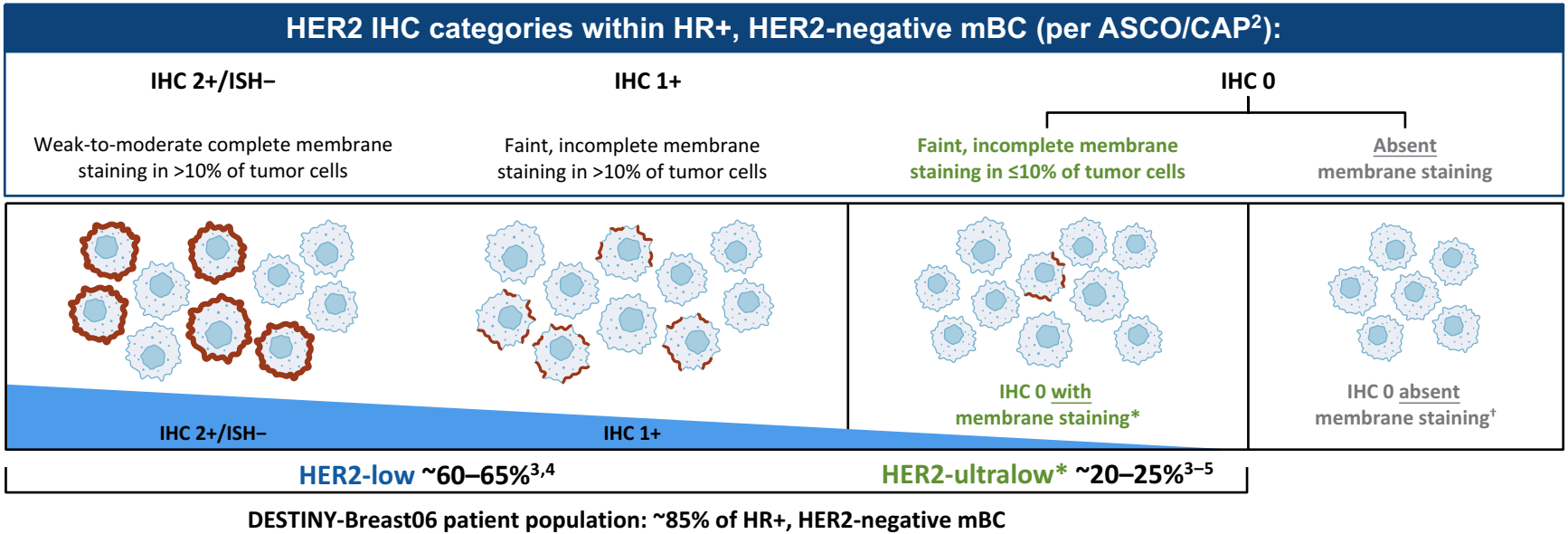
- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes (HER2-low and ITT)



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*



*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

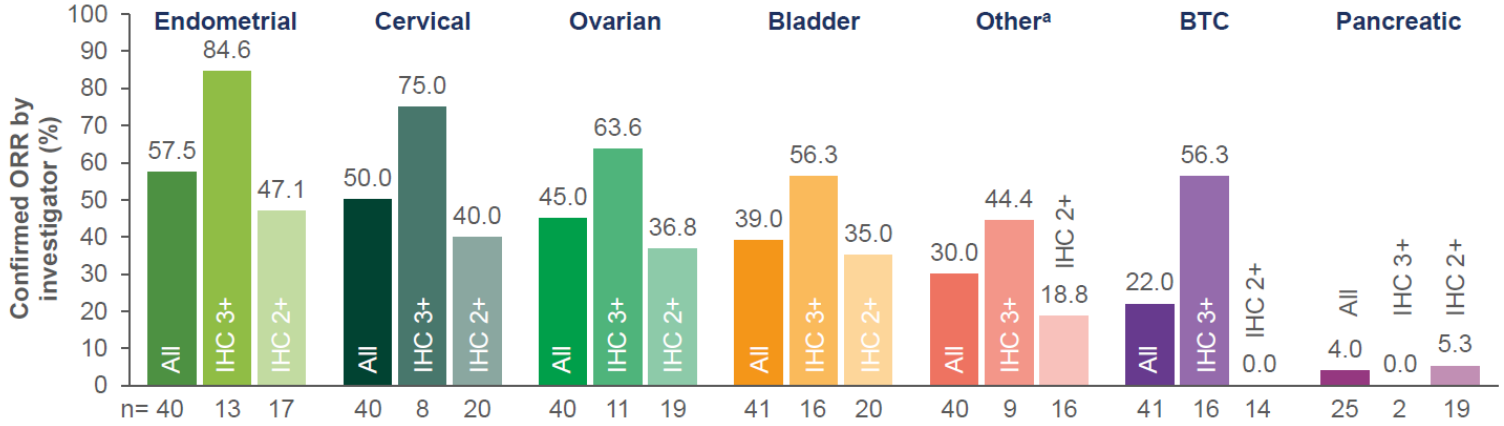
Baseline characteristics

- 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

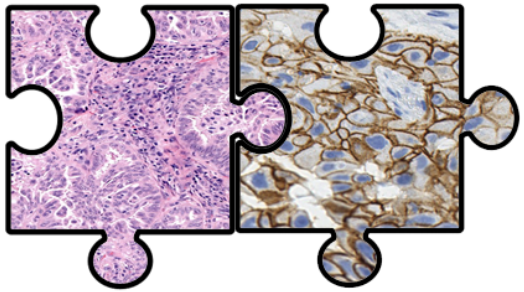
Objective response and duration of response



	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

Morphological and phenotypic diagnosis



Cómo mejorar la precisión (y predicción) en el diagnóstico?

Analysis of genomic alterations drive Precision Oncology

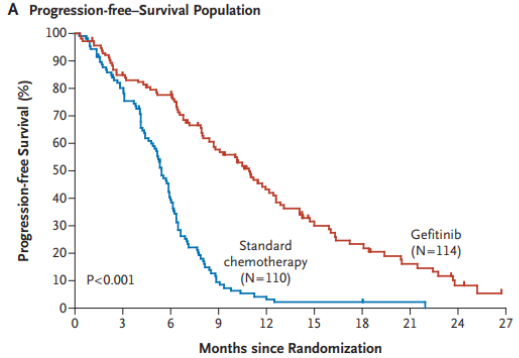
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR

Makoto Maemondo, M.D., Ph.D., Akira Inoue, M.D., Ph.D., Kunihiko Kobayashi, M.D., Ph.D., Shunichi Sugawara, M.D., Ph.D., Satoshi Oizumi, M.D., Ph.D., Hiroshi Isobe, M.D., Ph.D., Akihiko Gemma, M.D., Ph.D., Masao Harada, M.D., Ph.D., Hirohisa Yoshizawa, M.D., Ph.D., Ichiro Kinoshita, M.D., Ph.D., Yuka Fujita, M.D., Ph.D., Shoji Okinaga, M.D., Ph.D., Haruto Hirano, M.D., Ph.D., Kozo Yoshimori, M.D., Ph.D., Toshiyuki Harada, M.D., Ph.D., Takashi Ogura, M.D., Masahiro Ando, M.D., Ph.D., Hitoshi Miyazawa, M.S., Tomoaki Tanaka, Ph.D., Yasuo Saijo, M.D., Ph.D., Koichi Hagiwara, M.D., Ph.D., Satoshi Morita, Ph.D., and Toshihiro Nukiwa, M.D., Ph.D., for the North-East Japan Study Group*

N ENGL J MED 362;25 NEJM.ORG JUNE 24, 2010



Single gene testing for EGFR mutations predicted benefit to TKIs in mNSCLC

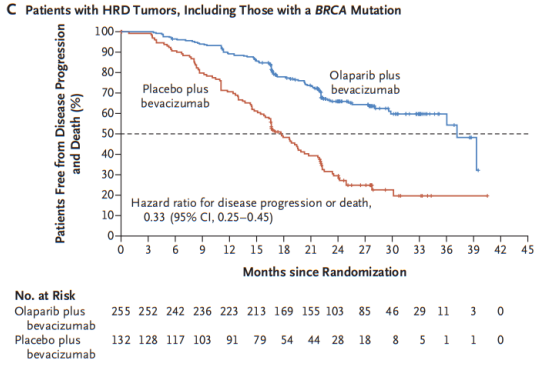
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

I. Ray-Coquard, P. Pautier, S. Pignata, D. Pérol, A. González-Martín, R. Berger, K. Fujiwara, I. Vergote, N. Colombo, J. Mäenpää, F. Selle, J. Sehouli, D. Lorusso, E.M. Guerra Alía, A. Reinthaller, S. Nagao, C. Lefeuvre-Plesse, U. Canzler, G. Scambia, A. Lortholary, F. Marmé, P. Combe, N. de Gregorio, M. Rodrigues, P. Buderath, C. Dubot, A. Burges, B. You, E. Pujade-Lauraine, and P. Harter, for the PAOLA-1 Investigators*

N ENGL J MED 381;25 NEJM.ORG DECEMBER 19, 2019



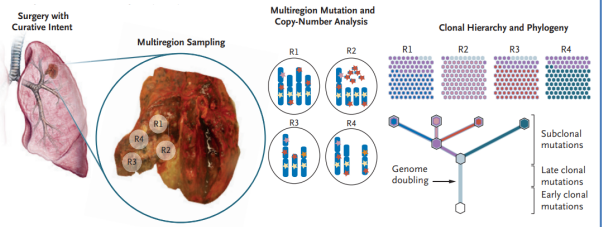
High complexity NGS for detecting genomic instability (HRD) in selecting high grade ovarian cancer patientsto PARPi

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 1, 2017 VOL. 376 NO. 22

Tracking the Evolution of Non–Small-Cell Lung Cancer

M. Jamal-Hanjani, G.A. Wilson, N. McGranahan, N.J. Birkbak, T.B.K. Watkins, S. Veeriah, S. Shafi, D.H. Johnson, R. Mitter, R. Rosenthal, M. Salm, S. Horswell, M. Escudero, N. Matthews, A. Rowan, T. Chambers, D.A. Moore, S. Turajlic, H. Xu, S.-M. Lee, M.D. Forster, T. Ahmad, C.T. Hiley, C. Abbosh, M. Falzon, E. Borg, T. Marafioti, D. Lawrence, M. Hayward, S. Kolvekar, N. Panagiotopoulos, S.M. Janes, R. Thakrar, A. Ahmed, F. Blackhall, Y. Summers, R. Shah, L. Joseph, A.M. Quinn, P.A. Crosbie, B. Naidu, G. Middleton, G. Langman, S. Trotter, M. Nicolson, H. Remmen, K. Kerr, M. Chetty, L. Gomersall, D.A. Fennell, A. Nakas, S. Rathinam, G. Anand, S. Khan, P. Russell, V. Ezhil, B. Ismail, M. Irvin-Sellers, V. Prakash, J.F. Lester, M. Kornaszewska, R. Attanoos, H. Adams, H. Davies, S. Dentro, P. Taniere, B. O'Sullivan, H.L. Lowe, J.A. Hartley, N. Iles, H. Bell, Y. Ngai, J.A. Shaw, J. Herrero, Z. Szallasi, R.F. Schwarz, A. Stewart, S.A. Quezada, J. Le Quesne, P. Van Loo, C. Dive, A. Hackshaw, and C. Swanton, for the TRACERx Consortium*



Whole-exome sequencing reveals dynamic molecular heterogeneity in NSCLC with clinical implications

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Available online 27 May 2024

ANNALS OF ONCOLOGY driving innovation in oncology

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)**

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*]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

ESMO Recommendations on clinical reporting of genomic test results for solid cancers

J. van de Haar[1†], P. Roepman[2†], F. Andre[3,4,5], J. Balmaña[6], E. Castro[7], D. Chakravarty[8], G. Curigliano[9,10], A. M. Czarnecka[11,12], R. Dienstmann[6,13,14], P. Horak[15,16], A. Italiano[17,18,19], C. Marchiò[20,21], K. Monkhorst[22], C. C. Pritchard[23], B. Reardon[24,25], H. E. G. Russnes[26,27], B. Sirohi[28], A. Sosinsky[29], T. Spanic[30], C. Turnbull[31,32], E. Van Allen[24,25,33], C. B. Westphalen[34,35], D. Tamborero[36,†] & J. Mateo[6,†]

Summary

Patient ID: 529893
Tissue ID: T25-17898
Report date: 1-Feb-2024

Patient and sample details

Hospital	University Medical Centre
Patient number	529893 (F)
Date of birth	15-May-1967
Tissue ID	T25-17898
Date of sampling	12-Jan-2024
Sampling anatomical site	Liver
Sample type	Biopsy (FFPE)
Histological cancer type	Adenocarcinoma (NSCLC) (PA-report: T24-12811)
Tumour cell content	Pathology-based: 60% Sequencing-based: 53%
Sample ID(s)	M25-02999, M25-03001
Matched normal DNA	M23-0157
Source of normal	Blood

Assay details

Laboratory	Genomics testing facility
Requested by	Dr. John Doe
Assay description	Comprehensive DNA NGS panel (520 genes), paired tumour-normal analysis, and RNA fusion panel
Assay ID(s)	NGS-DNA-panel01, NGS-RNAfuse-03
Assay run nr(s)	R1565, D9880-1
Report date	1-Feb-2024

Assay quality evaluation

X

PASS, with warnings

Interpretation: The sample is evaluable, but the sensitivity and specificity for gene fusions may be reduced given the relatively low alignment score. Follow-up testing could be considered.

History / Reason for testing

Patient (female) with metastatic NSCLC and a known *ALK* fusion (*EML4-ALK*). Treated with Crizotinib. Sample obtained upon progression after a short initial response. Resistance mechanisms, other targets?

Summary of most relevant findings

Lung adenocarcinoma metastatic biopsy showing:

- *ALK (EML4* ex13 – *ALK* ex20*)* gene fusion. This fusion has also been detected in a previous tumour sample of this patient.

No additional (resistance) mutation are observed. Possible indication for second/third-line ALK inhibitor (e.g. Alectinib, Brigatinib, Lorlatinib, Ceritinib)

- *BRCA1* (p.Ala1708Glu, p.Gln1756fs) inactivation, ESCAT III in lung cancer (possibility for drug repurposing of PARP inhibitors in a clinical trial setting)

- Homologous recombination deficiency (HRD) (score 0.95) confirming the complete (bi-allelic) inactivation of *BRCA1*.

One of the observed *BRCA1* (p.Gln1756fs) mutations is detected in the patient's germline DNA and previously reported as Ashkenazi founder pathogenic variant. Referral to a genetics specialist can be considered.

The combination of two *BRCA1* mutations (bi-allelic) and high a HRD score indicates functional loss of homologous recombination repair function.

To translate these findings into treatment recommendations, further interpretation of the results should be performed by a physician considering the patient's full medical history, if appropriate with support of a molecular tumour board.
An overview of all detected cancer-associated somatic genomic events and germline variants can be found in the report.

The data on which this report is based has been generated using tests that are performed under ISO-17025:2017 TESTING accreditation.
Assay details, sensitivity/specificity specs and clinical validation reports are available via genomics-facility.org/ISO-val-reports/.

Based on a minimal tumour purity of at least 20%, the test has a sensitivity of >95% for detection of genomics variants, >95% for copy number alteration and >95% for detection of gene fusions.

Genes/regions that are covered by the assay(s) design and/or that are included in the clinical reporting can be downloaded here: www.genomics-facility.org/assays/. Further details about the bioinformatics pipeline and analysis parameters can be found on GitHub: (https://github.com/seqfacility/)

This report has been generated on 1-Feb-2025 using the pipeline version 2.1. A user manual to assist in interpretation of this report can be downloaded here: www.genomicsfacility.org/test-manuals/.

For questions, feedback or complaints please contact support@genomics-facility.org

Results

Patient ID: 529893
Tissue ID: T25-17898
Report date: 1-Feb-2024

Mutations

Assay/analysis QC: X

Gene	Type	Transcript	Position	Variant	Effect	Reads	VAF	LoH	Germline	Hotspot	Class
TP53	TSG	NM_000546.6	17:7577124	c.814G>A (p.Val272Met)	missense	372 / 610	61%	yes	no	yes	Likely pathogenic
BRCA1	TSG	NM_007294.4	17:41209079	c.5266dup (p.Gln1756fs)	frameshift	297 / 571	53%	no	yes	yes	Pathogenic
BRCA1	TSG	NM_007294.4	17:41215920	c.5123C>A (p.Ala1708Glu	missense	231 / 662	35%	no	no	yes	Pathogenic
TERT	ONCO TSG	NM_198253.3	5:1295228	c.-124C>T	promoter	238 / 366	65%	no	no	yes	Pathogenic
KEAP1	TSG	NM_203500.2	19:10602583	c.996del (p.Gly332fs)	frameshift	287 / 521	55%	yes	no	no	Likely pathogenic
KDM6A	ONCO TSG	NM_001291415.2	X:44922943	c.1804G>A (p.Gly602Arg)	missense	199 / 398	51%	no	no	no	VUS

Copy number alterations

Assay/analysis QC: X

Gene	Type	Transcript	Region	Event	Gene copy number	Chr arm copies
RB1	TSG	NM_000321.3	13q14.2	loss	0	4
NCOA2	ONCO	NM_006540.4	8q13.3	gain	10	2

Gene fusions

Assay/analysis QC: X
Comment: Warning, low alignment score*

Gene 5'	Transcript 5'	Exon 5'	Gene 3'	Transcript 3'	Exon 3'	Phasing	Reads
EML4	NM_019063.5	13	***ALK***	NM_004304.5	20	in-frame	135/211 (88%)
HEY1	NM_012258.4	3	***NCOA2***	NM_006540.4	10	exon-skipping	6/14 (43%)

**Gene fusions show a relatively low number of aligned reads, indicating a lower sensitivity/specificity, likely due to lower quality of the input tissue. Caution is required for interpretation of the results*

Mutational signatures

Assay/analysis QC: X

Signature	Score	Threshold [range]	Result
Tumour mutation burden (TMB)	2.4	10 [0-100+]	Low
Microsatellite (in)stability	0.1	4 [0-100+]	MSS (stable)
Homologous recombination deficiency	0.95	0.5 [0-1]	Deficient

Genomics aberrations are reported based on the HG37 genome assembly and the MANE select transcript IDs (or the transcript indicated) (last update 01-Jan-2023). For reported (>3variants, a loss-of-heterozygosity status has been determined to indicate complete bi-allelic loss of the wildtype allele. Variants are classified as (likely) pathogenic, variant of unknown significance (VUS). (Likely) benign variants are not included in this report. Variants that are (likely) present in the patient's germline are indicated. Genes are marked as Oncogenes (ONCO) and/or tumour suppressor genes (TSG) and variants in known hotspots codons are indicated. (source: Jackson CKB, as per 1-Jan-2024). More details and an overview of the genes that are considered for variant reporting can be found here: www.genomics-facility.org/assays/variant-reporting/

Copy number alterations are reported for copy gains x chromosomal arm copies). For copy losses, only events are reported that show a complete loss (0 copies). Gene losses are reported for TSG only, gene gains (amplifications) are called for ONCO. More details and an overview of the genes that are considered for fusion reporting can be found here: www.genomics-facility.org/assays/CNV-reporting/

Gene fusion detection has been performed using RNA-based sequencing. Fused gene products are reported in case of in-frame events, including in-frame events that require exon skipping. Gene fusions are preferentially detected on the MANE select transcripts but can also include alternative transcripts. The number and percentage of fusion reads are reported. More details and an overview of the genes that are considered for fusion reporting can be found here: www.genomics-facility.org/assays/fusion-reporting/

Reported genomic signatures include the tumour mutational burden (TMB) as number of missense muts/Mb, microsatellite instability (MSI), and homologues recombination deficiency (HRD). Details of the used procedure and bioinformatics pipeline can be found on GitHub (https://github.com/seqfacility/)

Biomarkers clinical evidence

Patient ID: 529893
Tissue ID: T25-17898
Report date: 1-Feb-2024

Clinical actionability annotation

Gene/Biomarker	Alteration	Match level	Treatment type/ drug	ESCAT	Source
ALK	***ALK-EML4 fusion***	fusion	Alectinib, Lorlatinib, Crizotinib, Ceritinib, Brigatinib	I	CKB-JAX
ALK	***ALK-EML4 fusion***	fusion	Alectinib, Lorlatinib, Crizotinib, Ceritinib, Brigatinib	I	OncoKB
BRCA1	**p.Ala1708Glu, p.Gln1756fs**	inactivation	Olaparib, Talazoparib, Niraparib	III	CKB-JAX
BRCA1	**p.Ala1708Glu, p.Gln1756fs**	inactivation	Rucaparib	III	CKB-JAX
BRCA1	**p.Ala1708Glu, p.Gln1756fs**	oncogenic	Olaparib, Niraparib, Rucaparib	III	OncoKB
HRD	**Positive**	signature	PARP inhibitors	III	CKB-JAX

Clinical trial biomarker matching

Gene/Biomarker	Alteration	Match level	Trial name/number	Phase	Source
BRCA1	p.Gln1756fs	inactivation	NCT04826341 NCT03845296 NCT05700721	I/II II II	CKB-JAX
HRD	Positive	signature	NCT04826341 NCT05700721	I/II II	CKB-JAX

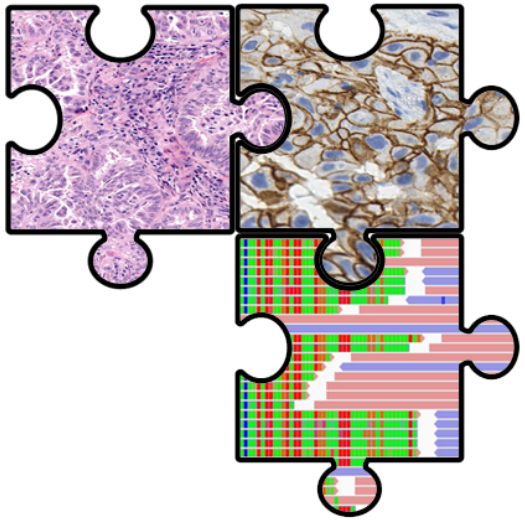
Findings for potential follow-up

Gene/Biomarker	Alteration	Follow-up	Remark
BRCA1	c.5266dup (p.Gln1756fs)	Referral to genetic counselling/cancer genetics specialist	Pathogenic variant also observed in the patient germline DNA. Reported as Ashkenazi founder pathogenic variant.
HEY1::NCOA1	*HEY1* ex3 – *NCOA1* ex10	Confirmatory testing is required if considered for the pathological diagnosis.	Low RNA reads, potential passenger due to *NCOA2* amp.

Reported genomic events are matched against knowledgebases (source: Jackson CKB, OncoKb, as per 1-Jan-2024) for associated clinical evidence regarding potential treatment approaches. ESCAT levels are used for clinical relevance; only evidence items with an ESCAT tier I, II or III are reported. Clinical evidence matching is performed for (likely) pathogenic variants (VUS are not included), copy numbers alterations, fusions and genomics signatures. Only the evidence items with the highest tier match are shown.

Clinical trial matching is performed based on the genomics event and tumour type information only. Other clinical trial eligibility criteria are not considered, and need to be evaluated further if inclusion in a clinical trial is considered.

Morphological and molecular diagnosis



Qué aporta la biopsia líquida al diagnóstico en oncología de precisión?

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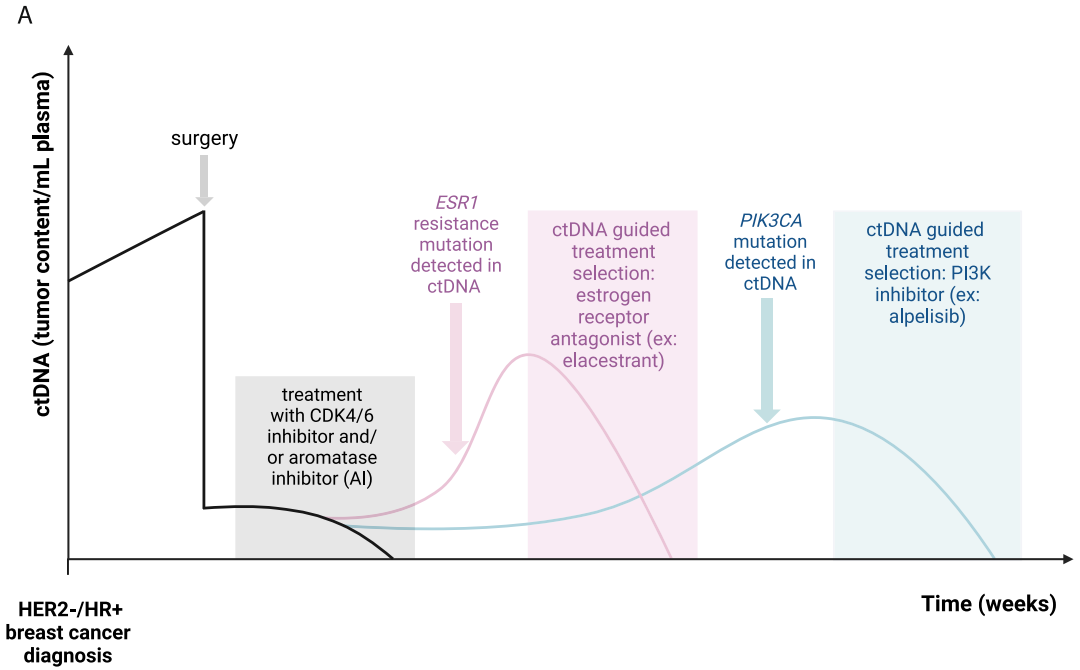


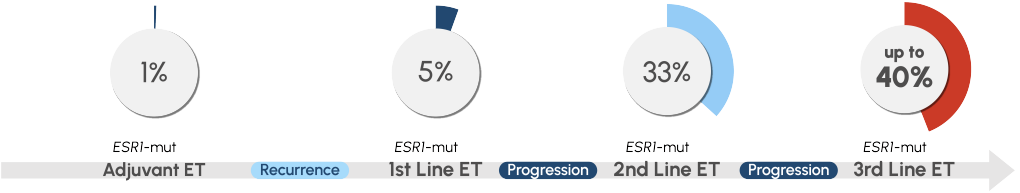
Bartolomucci, A et al. NPJ Precis Oncol 2025

What is the clinical significance of *ESR1* mutations?

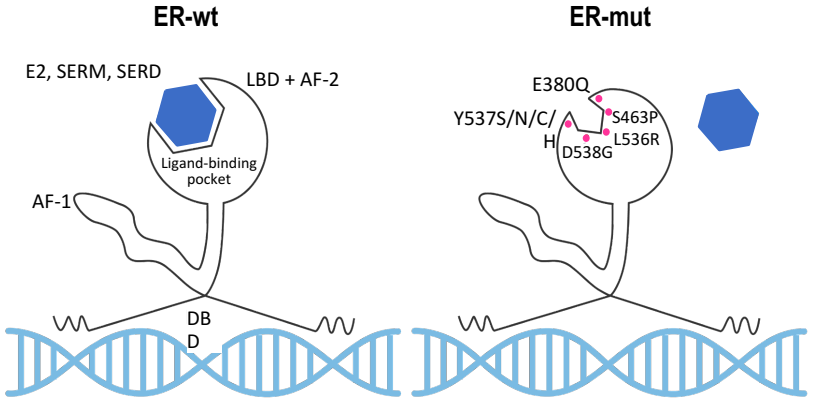
Longer exposure to ET in advanced/metastatic breast cancer Increases the chance of developing *ESR1*-mut during treatment, emerging in up to 40 % of patients

Early BC

Advanced/mBC



***ESR1*-mut stabilizes active ER conformation without the need of a ligand**



Constitutively active conformation

- ↑ basal transactivator function
- ↓ affinity for E2, SERM, SERD
- ↑ proteolytic stability
- ↑ proliferation
- ↑ survival
- ↑ migration
- ↑ AI resistance

AF, activating function; AI, aromatase inhibitor; DBD, DNA binding domain; E2, estrogen; *ESR1,* estrogen receptor 1; ER, estrogen receptor; LBD, ligand binding domain; mut; mutations; NR; nuclear receptor C-terminal domain; SERD, selective estrogen receptor degrador; SERM, selective estrogen receptor modulator; wt, wild type; zf, zinc-finger

1.Piscuoglio S. et al. Ann Oncol. 2018.29(4):787-789. 29522117; 2. Brett J. et al. Breast Cancer Res. 2021.23(1):85. 34392831.

What is the clinical significance of *ESR1* mutations?

PADA1: clinical validity of monitoring emergence ESR1m resistance in HR+ HER2- metastatic breast cancer by ctDNA

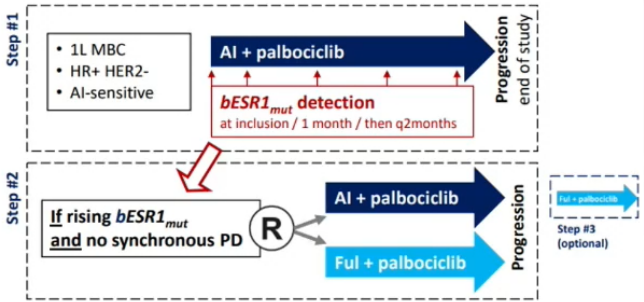
Main inclusion criteria:

- PS 0-2
- HR+ (>10%) HER2- mBC
- No relapse under/<12m from adjuvant AI
- No prior systemic therapy for mBC
- Adequate organ function
- Absence of visceral crisis
- Measurable or evaluable disease

Premenopausal women received LH-RH agonist during therapy.

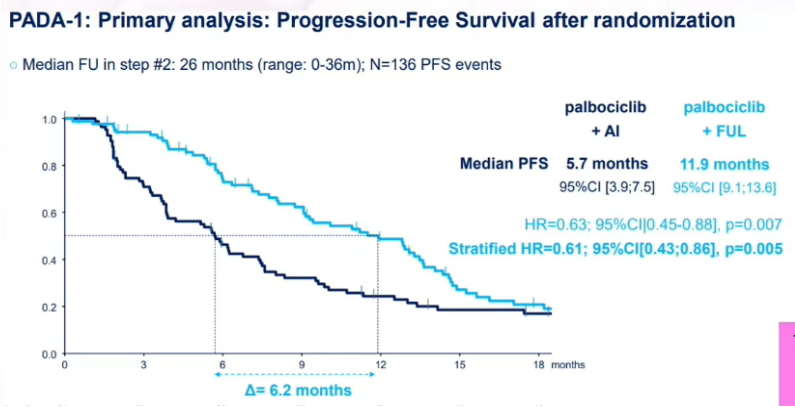
***bESR1$_{mut}$* monitoring with ddPCR:**

- Targets E380, P535, L536, Y537, D538 mutations [1]
- >12,000 samples analyzed in real time
- 2 central platforms (Paris & Toulouse)



Randomization stratified on:

- Time from inclusion to rising ***bESR1$_{mut}$*** detection (</≥ 12 months)
- Presence of visceral metastases



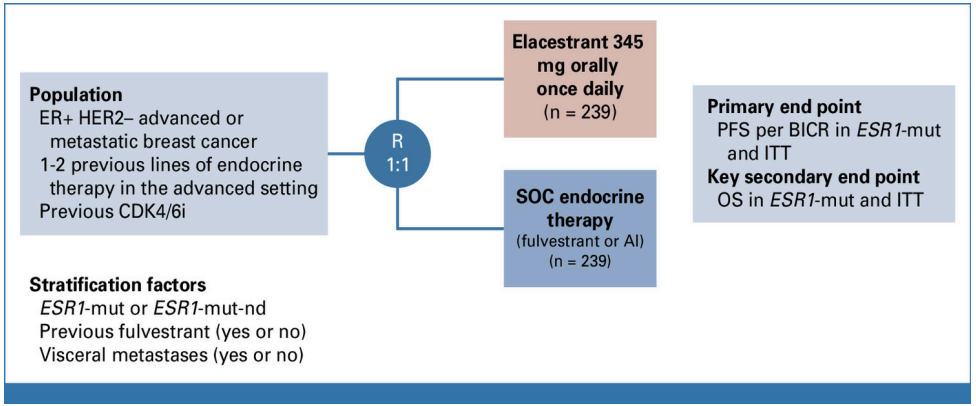
Bidard, F et al. SABCS 2021
Bidard, F et al. Lancet Oncol 2022

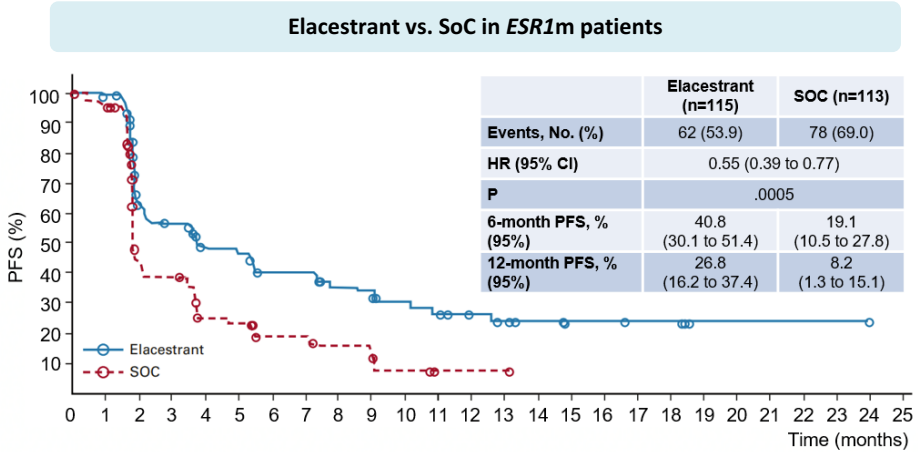
What is the clinical significance of *ESR1* mutations?

	EMERALD[1]	SERENA-6 [10]	SERENA-2[2]	EMBER-3[3]	AMEERA-3[4-6]	acelERA[6-9]
Treatment	**Elacestrant**	**Camizestrant** +/- palbociclib/abemaciclib	**Camizestrant**	**Imlunestrant** +/- abemaciclib	**Amcenestrant**	**Giredestrant**
Control Arm	fulvestrant / AIs	anastrozole/ letrozole	fulvestrant	fulvestrant / exemestane	fulvestrant / AIs / tamoxifen	fulvestrant / AIs
Phase (n)	Phase 3 (478)	Phase 3 (302)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	**Required (100%)**	Permitted	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	**YES**	No	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	**YES**	YES	YES	NO	YES	YES
Data readout	**Positive (Registrational)**	Ongoing (Registrational)	Positive (Non-Registrational)	Ongoing	Endpoint not met	Endpoint not met

What is the clinical significance of *ESR1* mutations?

Rationale for FDA decision to qualify ESR1m as a predictive biomarker for the use of Elacestrant

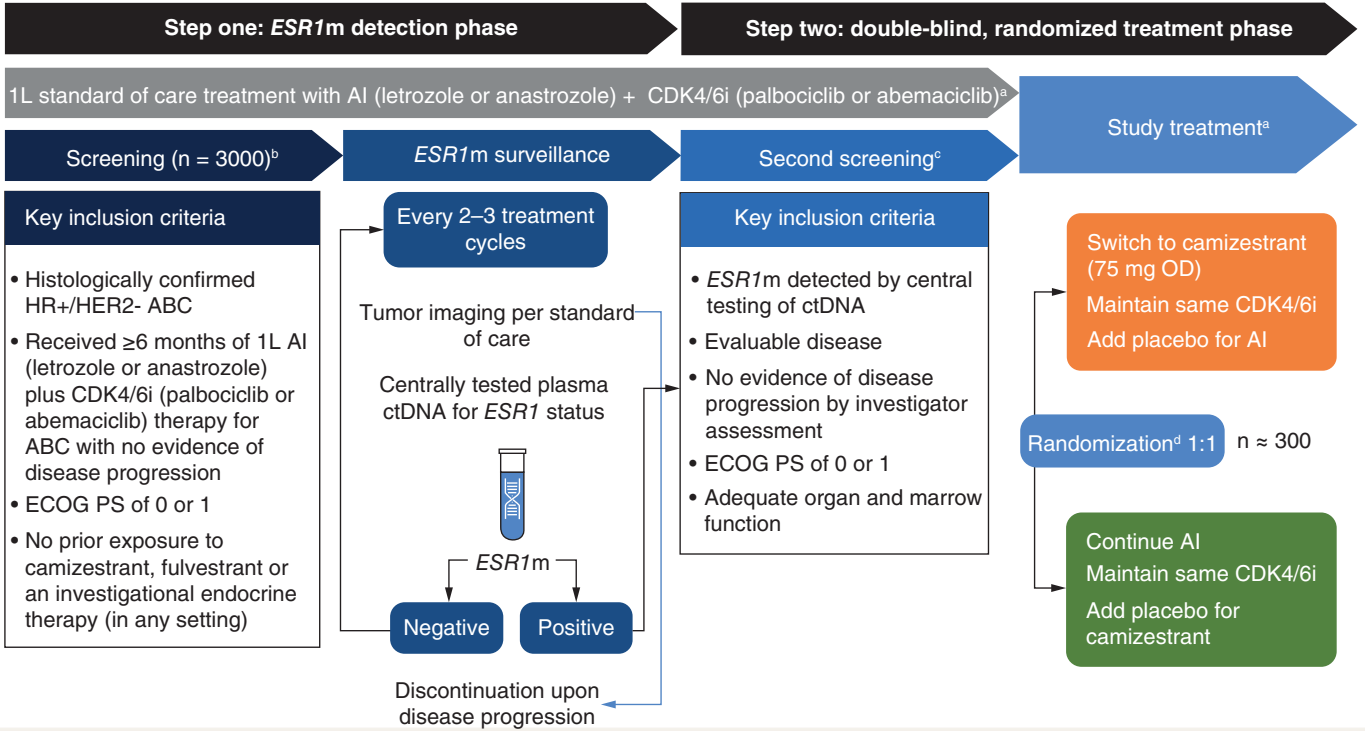




	Elacestrant (n=115)	SOC (n=113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95%)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95%)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

What is the clinical significance of *ESR1* mutations?

SERENA-6 investigates a switch to camizestrant from an AI in patients who develop an ESR1m while on 1L SOC treatment with CDKi + AI



How to test *ESR1* mutations in ctDNA?

Digital droplet PCR and NGS ctDNA analysis for *ESR1* mutation in breast cancer

Real-world Study of *ESR1* Mutation Testing by Liquid Biopsy Using Digital PCR or NGS to Guide Elacestrant Use in Metastatic Breast Cancer Patients

Poster #76P

Federico Rojo,[1] Valentina Guarneri,[2] Andrea Boscolo Bragadin,[2] Stefano Indraccolo,[2,3] Elena Guerini Rocco,[4,5] Nicola Fusco,[4,5] Sandra Zazo,[1] Iván Prieto-Potin,[1] Riccardo Adorisio,[4] Francesco Pepe,[6] Isabelle Vanden Bempt,[7] Daan Hasker,[7] Jeremias Herzog,[8] Marcos Orellana,[8] Umberto Malapelle[6]

[1]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [2]Veneto Institute of Oncology IOV-IRCCS, Padova, Italy; [3]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy; [4]Division of Pathology, European Institute of Oncology, IRCCS, Milan, Italy; [5]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; [6]Department of Public Health, University Federico II of Naples, Naples, Italy; [7]Department of Human Genetics, University Hospitals KU Leuven, Leuven, Belgium; [8]Menarini Group, Florence, Italy

BACKGROUND

- The EMERALD trial (NCT03778931) showed improved progression-free survival (PFS) with elacestrant vs standard of care (SOC) endocrine therapy (ET) in patients with ER+/HER2- metastatic breast cancer (mBC) and tumors harboring *ESR1* mutations after prior ET + CDK4/6i (HR=0.55; 95% CI, 0.39-0.77; *P*=0.0005).[1]
- Findings of the EMERALD trial led to approval of elacestrant by the US FDA, EMA, MHRA, and other regulatory agencies.[2-4]
- An early access program (EAP) was initiated in Europe to enable patient access to elacestrant before reimbursement.
- The availability of elacestrant emphasizes the need for real-time mutation detection upon progression to guide treatments.
- As part of the elacestrant EAP, *ESR1* mutations were analyzed using blood samples in patients with ER+/HER2- mBC resistant to ET.
- Non-invasive liquid biopsy was obtained for analysis of circulating tumor DNA (ctDNA) through droplet digital PCR (ddPCR) and next-generation sequencing (NGS).

OBJECTIVES

- To determine the *ESR1* mutation positivity rate in the samples analyzed.
- To determine the variant allele frequency of the *ESR1* mutations detected.
- To quantify the proportion of patients who present polyclonality (multiple *ESR1* mutations).
- To report the most frequent *ESR1* mutations detected.

This report presents findings from the molecular analysis of mutations in the *ESR1* gene in the ER+/HER2- mBC patient population tested.

METHODS

Study Overview

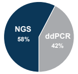
- A prospective study to identify eligible patients for elacestrant, participating in the EAP, was conducted:

288 Institutions | **3** European countries | **4** Analysis performed at academic laboratories

- **Plasma samples were analyzed** using **ddPCR** (Bio-Rad QX200/600 and Thermo QuantStudio Absolute Q) for hotspot *ESR1*-mut, and **NGS** (Sysmex SafeSEQ Breast Cancer Panel and Roche AVENIO ctDNA Expanded Panel) for broader mutational profiling.
- Data cut-off was March 21, 2025.

Study Sample

Database used to evaluate the positivity rate initially contained **1034** records → Excluding those with unevaluable results* **1004** records →



*This data was obtained from the database of the Test Access System Platform (TAS).

METHODS (continued)

Statistical Analysis

Positivity rate	Calculated by determining the number and percentage of positive results out of the total number of samples with available information on mutational status, including the 95% confidence interval (95% CI).
Variant allele frequency (VAF)	The mean, standard deviation (SD), 95% CI of the mean, and the following descriptive values were obtained: minimum, 25th percentile (P25), median, 75th percentile (P75), and maximum. VAF results were calculated for all samples and specifically for each mutation.
Polyclonality	The number of polyclonal samples and the percentage over the total samples were quantified. The number of *ESR1* co-mutations detected in second, third and fourth place and the percentage were obtained.
Most frequent mutations	The times that a given variant and the percentage over all mutations was calculated.

RESULTS

Positivity Rate

- A positive rate of 37% (95% CI: 34.15% - 40.22%) was identify in the 1004 samples evaluated.

Result	N=1004	95% CI
Positive	373 (37.2%)	(34.15% to 40.22%)

Variant Allele Frequency (VAF) of *ESR1* Mutations

- Of the 373 *ESR1* mutation-positive samples, 285 provided individual VAF results for each detection. The remaining 88 samples were analyzed using multiplex assays that simultaneously detected multiple mutations, limiting the precise identification of each mutation.
- The median VAF was 0.5 (Range, 0.01-58.3). Out of the total, 67% of patients had <1% VAF.

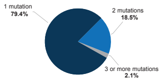
Samples	Median	Range
285	0.5	(0.01 to 58.3)

Note: VAFs obtained through multiplex were excluded.

Analysis of Polyclonality

- Of the total number of positive samples (n=373), 77 (21.6%) showed polyclonality, defined as the coexistence of more than one mutational variant in *ESR1*. The samples that were polyclonal for *ESR1* showed up to four simultaneous mutational variants.

Distribution of the Number of Mutations Per Sample

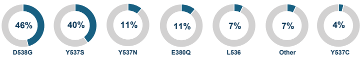


Number of Mutations	N	%
1	296	79.4
2	69	18.5
≥3	8	2.1
Total	373	100

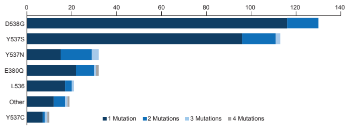
FREQUENCY OF *ESR1* MUTATIONS

- A total of **20 different mutations** in the *ESR1* gene were detected.

Most frequently observed *ESR1* mutations



Prevalence of *ESR1*-Mutation Variants, n=285 Patients



CONCLUSIONS

- This is the first study for *ESR1* mutation prevalence demonstrating clinical utility of ddPCR and NGS-based ctDNA testing in Europe.
- These technologies enable precise identification of *ESR1* mutations, facilitating personalized treatment with elacestrant to improve outcomes.
- In clinical practice, *ESR1* mutation positivity rate can be improved by sample and testing practice optimization.
- Pathologists and physicians caring for patients with ER+/HER2- mBC require education about best practice methodologies for *ESR1* mutation testing.

REFERENCES:

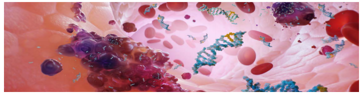
1. Bidard FC, et al. *J Clin Oncol*. 2022;40:3246-3256. 2. Orserdu. Prescribing information. Stemline Therapeutics; 2023. 3. Orserdu. Summary of product characteristics. Stemline Therapeutics B.V.; 2023. 4. Korserdu. Public assessment report. Stemline Therapeutics B.V.; 2024.

ACKNOWLEDGMENTS:

- Study was funded by Menarini Group. Editorial and writing assistance was provided by Claire Gilmore, PharmD, from Phillips Group Oncology Communications, Inc. (Albany, NY, USA) funded by Menarini Group.

Master the sensitivity in ctDNA detection

Plasma-SeqSensei™ Breast Cancer IVD Kit



Target regions for Plasma-SeqSensei™ Breast Cancer IVD Kit

Gene ID#	Transcript ID#	CDS start	CDS end	Most frequent mutation(s) detected (AA change)
AKT1	ENST00000554581	47	69	E17K
ERBB2	ENST00000269571	907	947	S310F
ERBB2	ENST00000269571	2,308	2,360	L755S, D769Y
ERBB2	ENST00000269571	2,258	2,307	V777L
ESR1	ENST00000440973	1,108	1,143	E380Q
ESR1	ENST00000440973	1,378	1,420	S463P
ESR1	ENST00000440973	1,583	1,614	D538G, Y537S/C/N
KRAS	ENST00000256078	8	43	G12D/V/C/R/A/S, G13D
PIK3CA	ENST00000263967	254	278	R88Q
PIK3CA	ENST00000263967	329	352	K111E
PIK3CA	ENST00000263967	353	367	G118D
PIK3CA	ENST00000263967	1,033	1,058	E345K
PIK3CA	ENST00000263967	1,085	1,115	P366R
PIK3CA	ENST00000263967	1,252	1,264	C420R
PIK3CA	ENST00000263967	1,348	1,387	E453K
PIK3CA	ENST00000263967	1,611	1,659	E545K/A, E542K
PIK3CA	ENST00000263967	2,138	2,184	E726K
PIK3CA	ENST00000263967	3,118	3,169	H1047R/L
TP53	ENST00000269305	144	232	W53*
TP53	ENST00000269305	293	375	R110P
TP53	ENST00000269305	376	423	C141Y, C135Y
TP53	ENST00000269305	451	537	R175H, H179R
TP53	ENST00000269305	574	659	R213*, Y220C, R196*
TP53	ENST00000269305	695	782	R248Q/W, G245S
TP53	ENST00000269305	783	856	R273H/C, R282W
TP53	ENST00000269305	888	919	R306*
TP53	ENST00000269305	920	993	Q331*
TP53	ENST00000269305	994	1,080	R342*

Product specifications

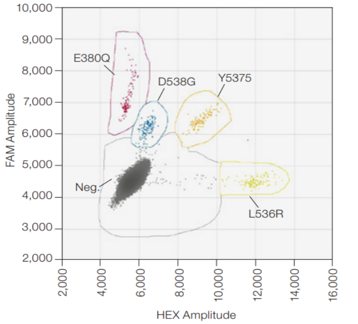
Feature	Description
Starting sample	Whole blood and plasma
Sample capacity	2–16 samples per kit and up to 32 samples with Plasma-SeqSensei™ Extension IVD Kit
QC function	Positive control and no template control (NTC) applied to every run
Input DNA required	4.3–86 ng / 116 µL
Number of amplicons	28
Sensitivity	0.06% allele frequency with 95% certainty in 10,000 wildtype copies
Cut-off	6 mutant molecules
Compatible sequencing instruments	Illumina NextSeq 500/550™

Sample Mutation Status

AKT1	ERBB2	ESR1	KRAS	PIK3CA	TP53
0	0	1	0	0	4

Somatic Mutations Detected

Gene ID	Transcript	Coding DNA Change	Amino Acid Change	COSMIC ID	Mutant Allele Fraction	Mutant Molecules	Validity
ESR1	ENST00000440973.1	c.1609T>A	p.Y537N	COSV52784978	0.355%	21	✓
TP53	ENST00000269305.4	c.215C>G	p.P72R	COSV52666208	67.603%	4012	✓
TP53	ENST00000269305.4	c.488A>G	p.Y163C	COSV52663142	0.253%	15	✓
TP53	ENST00000269305.4	c.586C>T	p.R196*	COSV52663748	0.823%	49	✓
TP53	ENST00000269305.4	c.742C>T	p.R248W	COSV52662035	0.208%	12	✓



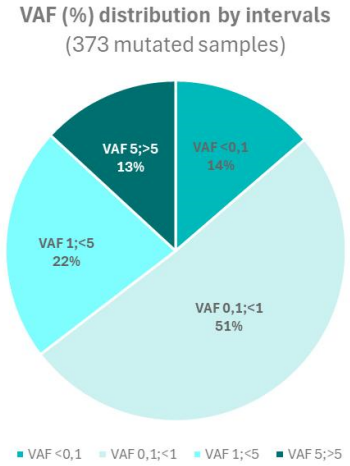
How to test *ESR1* mutations in ctDNA?

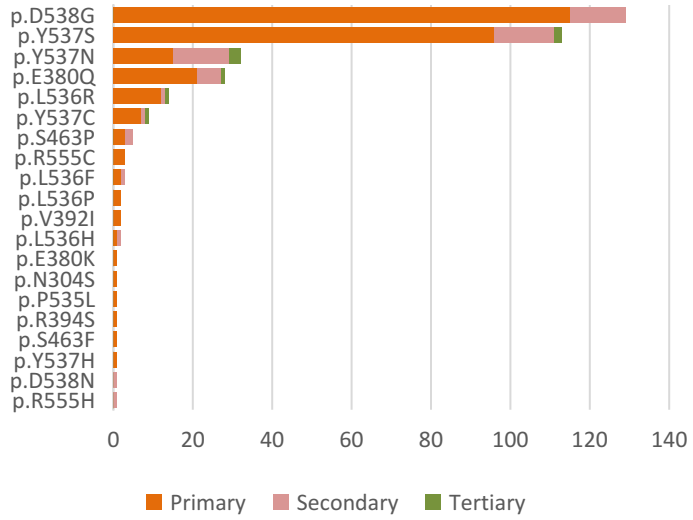
Digital droplet PCR and NGS ctDNA analysis for *ESR1* mutation in breast cancer

In 65% of the patients, *ESR1* MAF is below 1%

A total of different 20 mutations in the *ESR1*
Most frequently mutations: p.D538G (28.8%), and p.Y537S (24.5%) and p.Y537N (6.9%).

ESR1 mutations in 38.6% of metastatic luminal BC after progression to CDK4/6i + ET





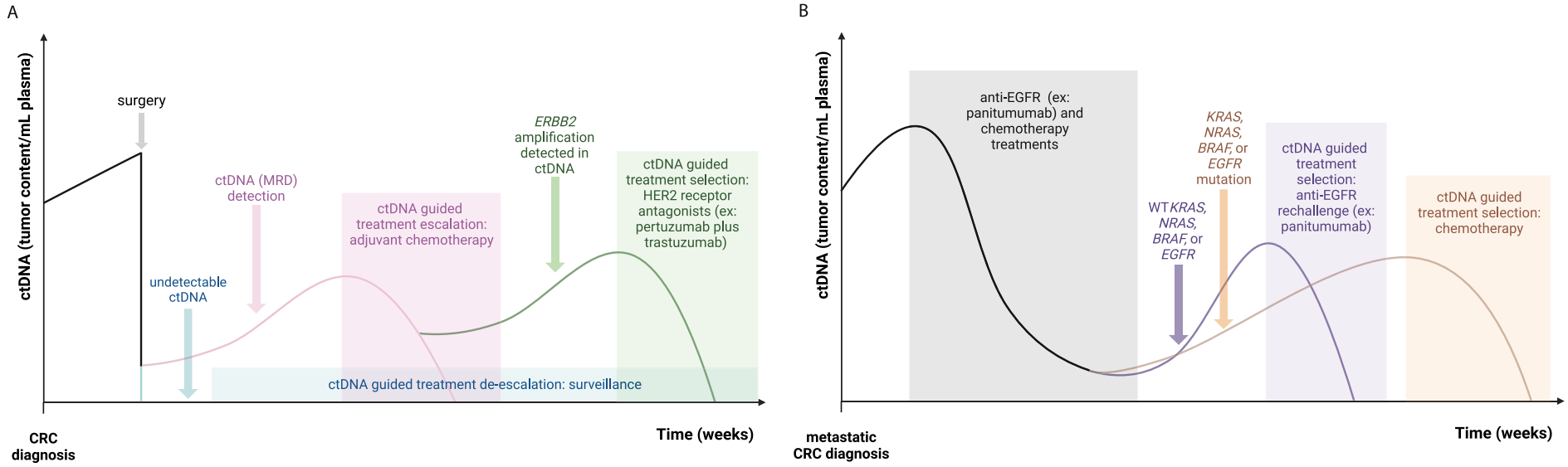
38.6% ESR1 m

NGS 38.8%

ddPCR 38.4%

Samples	IC95%	Median	min	max
285	1.78 - 3.30	0.5	0.01	58.3

Qué aporta la biopsia líquida al diagnóstico en oncología de precisión?



Bartolomucci, A et al. NPJ Precis Oncol 2025

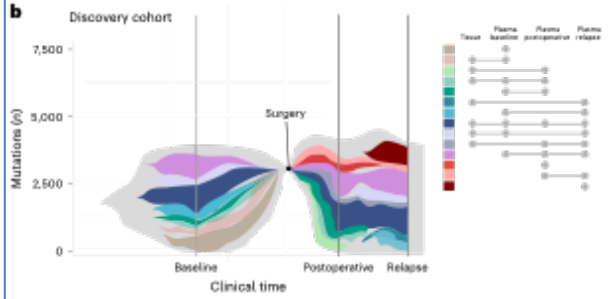
ctDNA analysis in early-stage CRC

nature cancer

Article https://doi.org/10.1038/s43018-025-00960-z

Whole-exome tumor-agnostic ctDNA analysis enhances minimal residual disease detection and reveals relapse mechanisms in localized colon cancer

Jorge Martín-Arana[1,2,11], Francisco Gimeno-Valiente[3,11], Tenna Vesterman Henriksen[4,5,11], Blanca García-Micó[1,2], Belén Martínez-Castedo[1,2], Valentina Gambardella[1], Carolina Martínez-Ciarpaglini[2,6], Brenda Palomar[6], Marisol Huerta[1,2], Daniel G. Camblor[1,2], Miguel García Bartolomé[1], Juan Antonio Carbonell-Asins[7], Amanda Frydendahl[4,5], Kåre Andersson Gotchalck[8], Tania Fleitas[1,2], Roberto Tébar-Martínez[1], David Moro[9,10], Vicente Pla[9,10], Leticia Pérez-Santiago[9,10], José Martín-Arévalo[9,10], David Casado[9,10], Stephanie García-Botello[9,10], Alejandro Espí[9,10], Susana Roselló[1,2], Desamparados Roda[1,2], Claus Lindbjerg Andersen[4,5,11], Andrés Cervantes[1,2,11] & Noelia Tarazona[1,2,11]



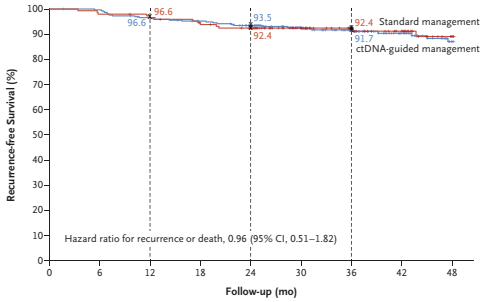
Whole-exome ctDNA in localized colorectal cancer provides deepth molecular characterization and MRD

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 16, 2022 VOL. 386 NO. 24

Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

Jeanne Tie, M.D., Joshua D. Cohen, M.Phil., Kamel Lahouel, Ph.D., Serigne N. Lo, Ph.D., Yuxuan Wang, M.D., Ph.D., Suzanne Kosmider, M.B., B.S., Rachel Wong, M.B., B.S., Jeremy Shapiro, M.B., B.S., Margaret Lee, M.B., B.S., Sam Harris, M.B., B.S., Adnan Khattak, M.B., B.S., Matthew Burge, M.B., B.S., Marion Harris, M.B., B.S., James Lynam, M.B., B.S., Louise Nott, M.B., B.S., Fiona Day, Ph.D., Theresa Hayes, M.B., B.S., Sue-Anne McLachlan, M.B., B.S., Belinda Lee, M.B., B.S., Janine Ptak, M.S., Natalie Silliman, B.S., Lisa Dobbyn, B.A., Maria Popoli, M.S., Ralph Hruban, M.D., Anne Marie Lennon, M.D., Ph.D., Nicholas Papadopoulos, Ph.D., Kenneth W. Kinzler, Ph.D., Bert Vogelstein, M.D., Cristian Tomasetti, Ph.D., and Peter Gibbs, M.D., for the DYNAMIC Investigators*



No. at Risk

Standard management	147	144	142	136	128	97	78	57	33
ctDNA-guided management	294	292	281	273	259	207	155	109	64

A ctDNA-guided approach reduced ACT use without compromising recurrence-free survival.

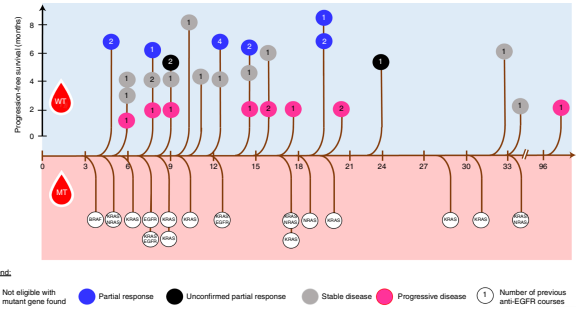
ARTICLES https://doi.org/10.1038/s41591-022-01886-0 nature medicine

Check for updates

OPEN

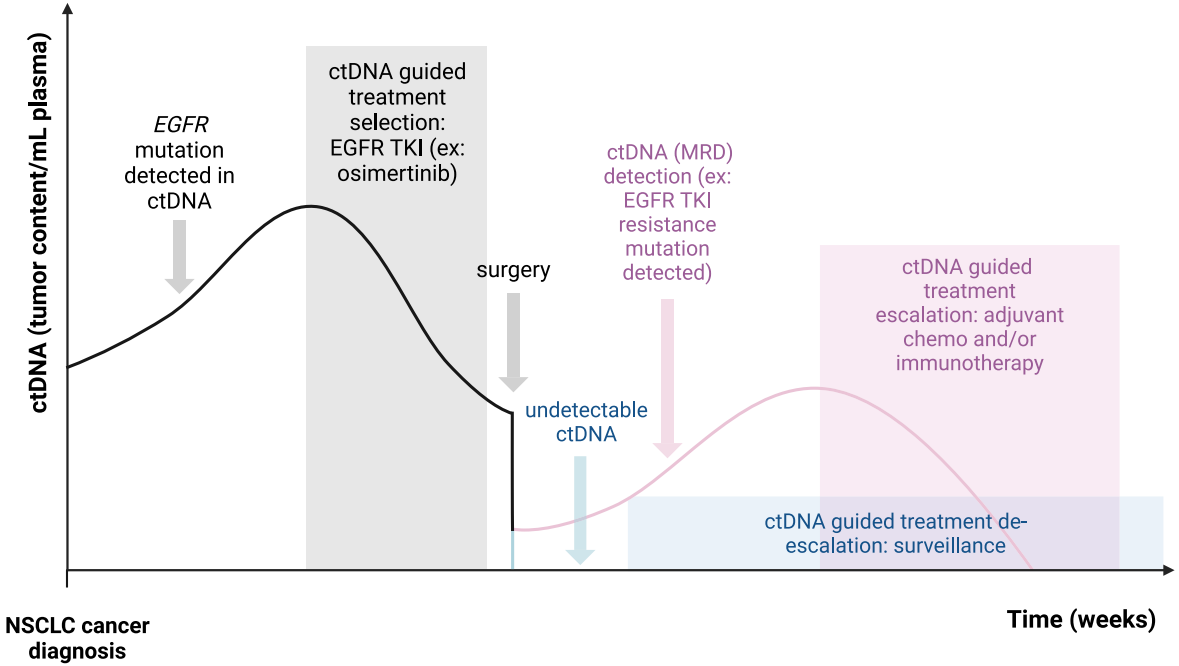
Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial

Andrea Sartore-Bianchi[1,2], Filippo Pietrantonio[3], Sara Lonardi[4], Benedetta Mussolin[5], Francesco Rua[5], Giovanni Crisafulli[5,6], Alice Bartolini[5], Elisabetta Fenocchio[5], Alessio Amatu[2], Paolo Manca[3], Francesca Bergamo[4], Federica Tosi[2], Gianluca Mauri[1,7], Margherita Ambrosini[3], Francesca Daniel[4], Valter Torri[8], Angelo Vanzulli[1,9], Daniele Regge[10,11], Giovanni Cappello[11], Caterina Marchiò[5,12], Enrico Berrino[5,12], Anna Sapino[5,12], Silvia Marsoni[2†3], Salvatore Siena[1,2,13] and Alberto Bardelli[5,6,13]



ctDNA analysis is an effective, safe, and timely method to guide anti-EGFR rechallenge therapy with panitumumab in patients with mCRC.

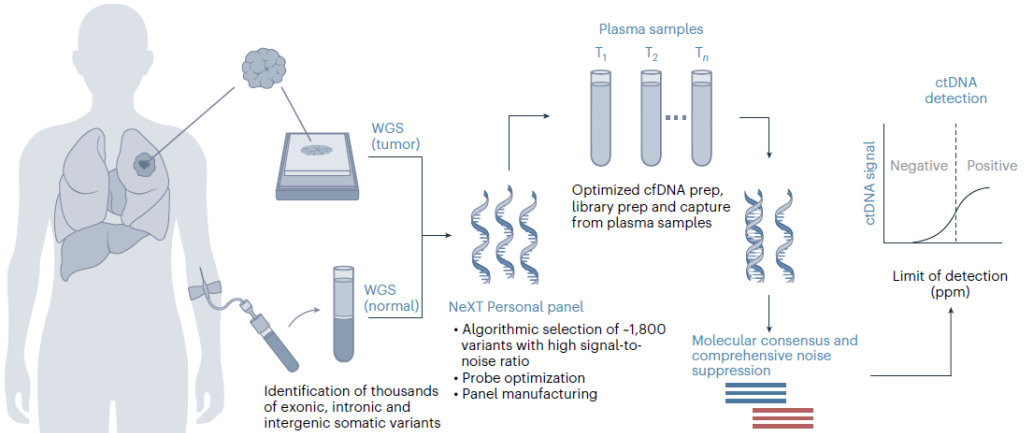
Qué aporta la biopsia líquida al diagnóstico en oncología de precisión?

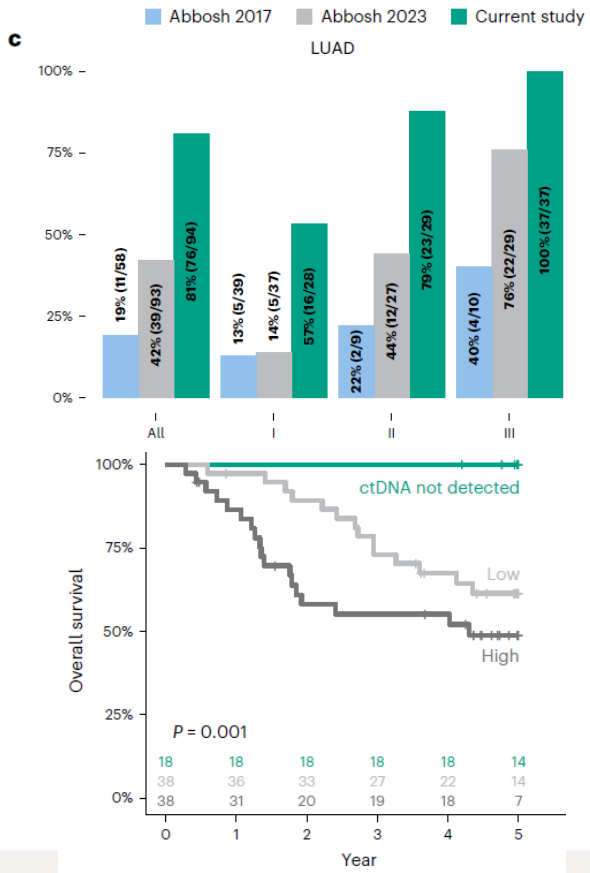


Bartolomucci, A et al. NPJ Precis Oncol 2025

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

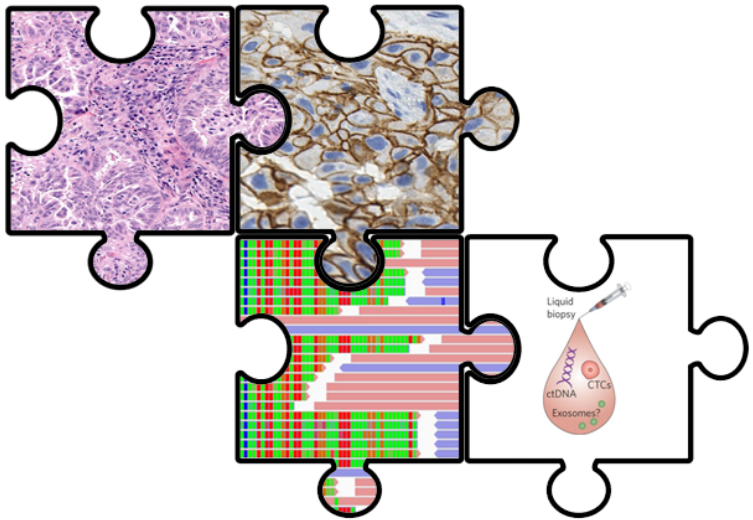
- NeXT Personal: whole-genome-based, tumor-informed ultrasensitive ctDNA NGS
- Detection at 1–3 ppm of ctDNA with 99.9% specificity
- From 171 patients with early-stage lung cancer from the TRACERx study, 81% of patients with lung adenocarcinoma (LUAD), including 53% with pTNM stage I had ctDNA pre-operatively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





Black, JRM et al. Nat med 2024

Morphological and molecular diagnosis, using both tissue and liquid biopsies



Podemos ser más precisos en la selección de pacientes mediante biomarcadores?

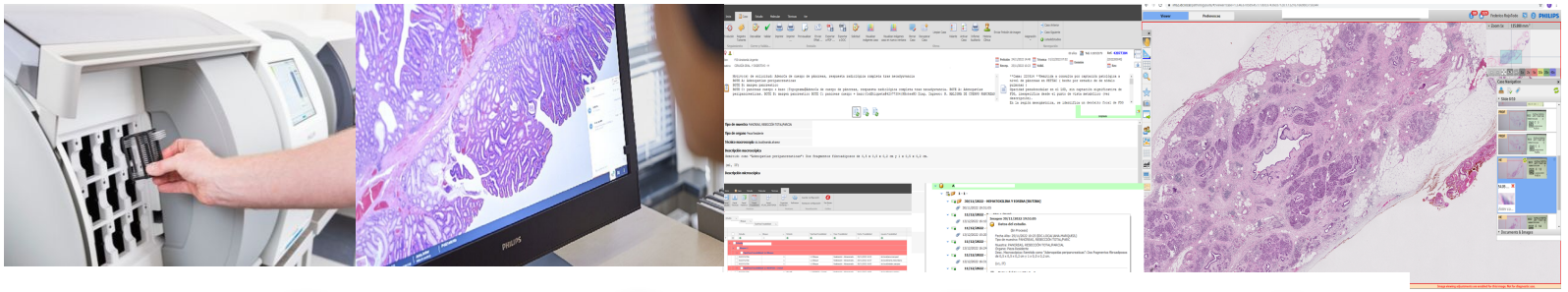
Virchows Archiv
https://doi.org/10.1007/s00428-025-04064-y

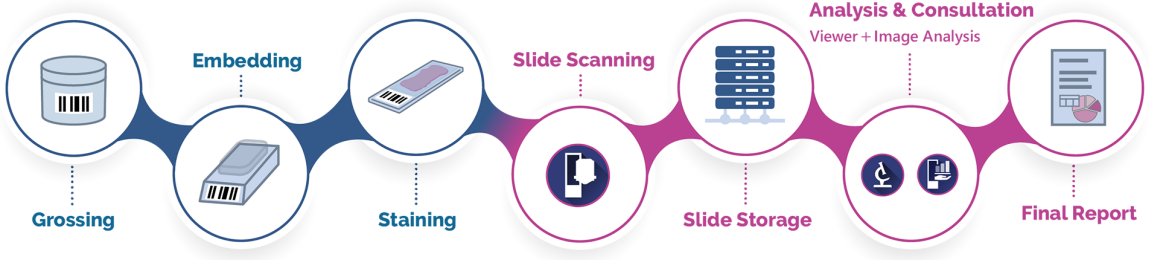
ORIGINAL ARTICLE

Implementing digital pathology: qualitative and financial insights from eight leading European laboratories

Xavier Matias-Guiu[1] · Jordi Temprana-Salvador[2] · Pablo Garcia Lopez[3] · Solene-Florence Kammerer-Jacquet[4] · Nathalie Rioux-Leclercq[4] · David Clark[5] · Christian M. Schürch[6,7] · Falko Fend[6] · Sven Mattern[8] · David Snead[9,10] · Nicola Fusco[11] · Elena Guerini-Rocco[11] · Federico Rojo[12] · Marie Brevet[13] · Manuel Salto Tellez[14,15] · Angelo Dei Tos[16] · Thomas di Maio[17] · Silvia Ramírez-Peinado[18] · Elizabeth Sheppard[19] · Huw Bannister[20] · Anastasios Gkiokas[21] · Mario Arpaia[22] · Ons Ben Dhia[23] · Nazario Martino[24]

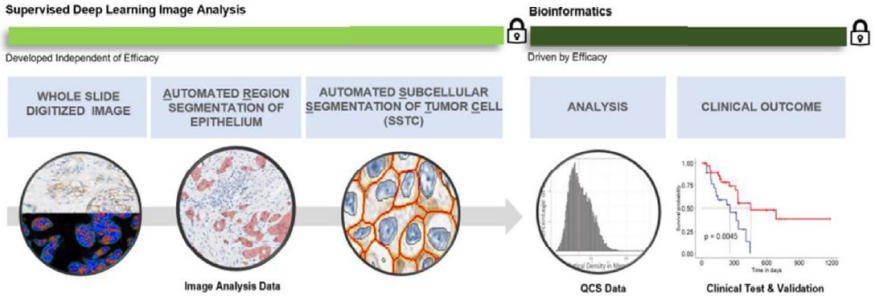
Received: 17 January 2025 / Revised: 13 February 2025 / Accepted: 21 February 2025

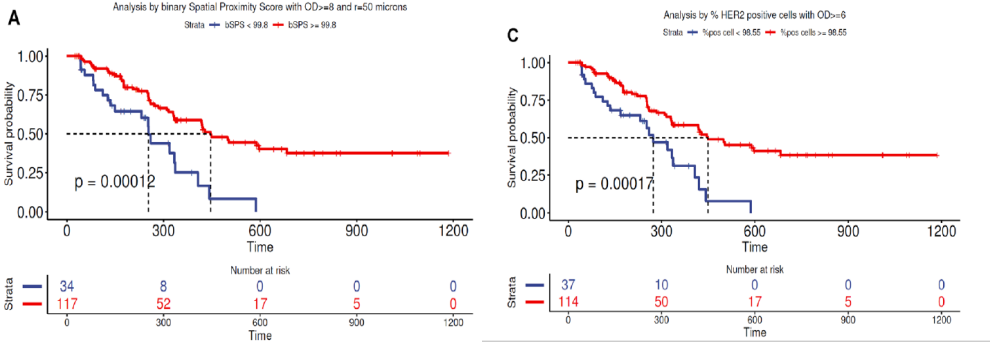


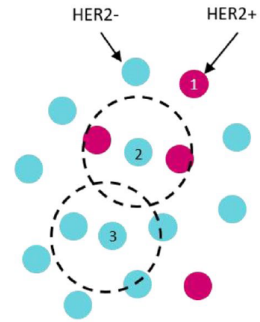


Refine ADC selection by AI interpretation of target expression

HER2 quantitative continuous scoring for patient selection in T-DXd treated HER2-low breast cancer

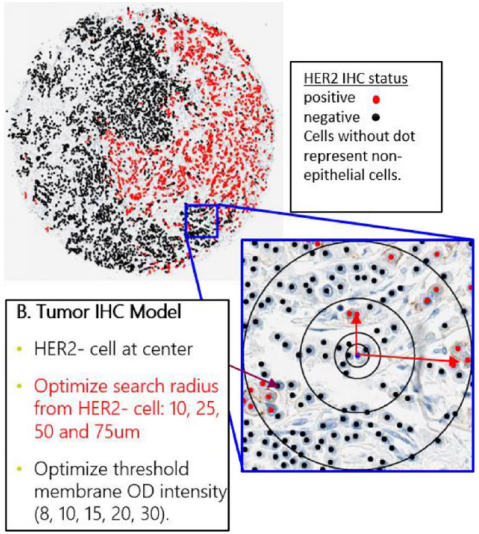






A. HER2 proximity model

1. HER2+ cells
2. HER2- cell **NEAR** HER2+ cell
3. HER2- cell **FAR** HER2+ cell



Kapil, A et al. Sci Rep 2024

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

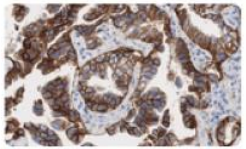
Dr Marina Chiara Garassino | Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung01

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)

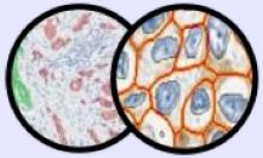
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay



2 Whole Slide Imaging

3 Automated Image Analysis (QCS)

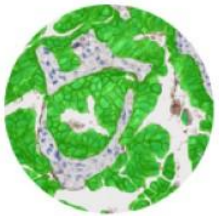


4 Patient Biomarker Status Determination

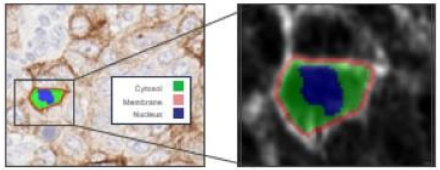
\+ ≥75% of tumor cells with TROP2 NMR ≤0.56

\- <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

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

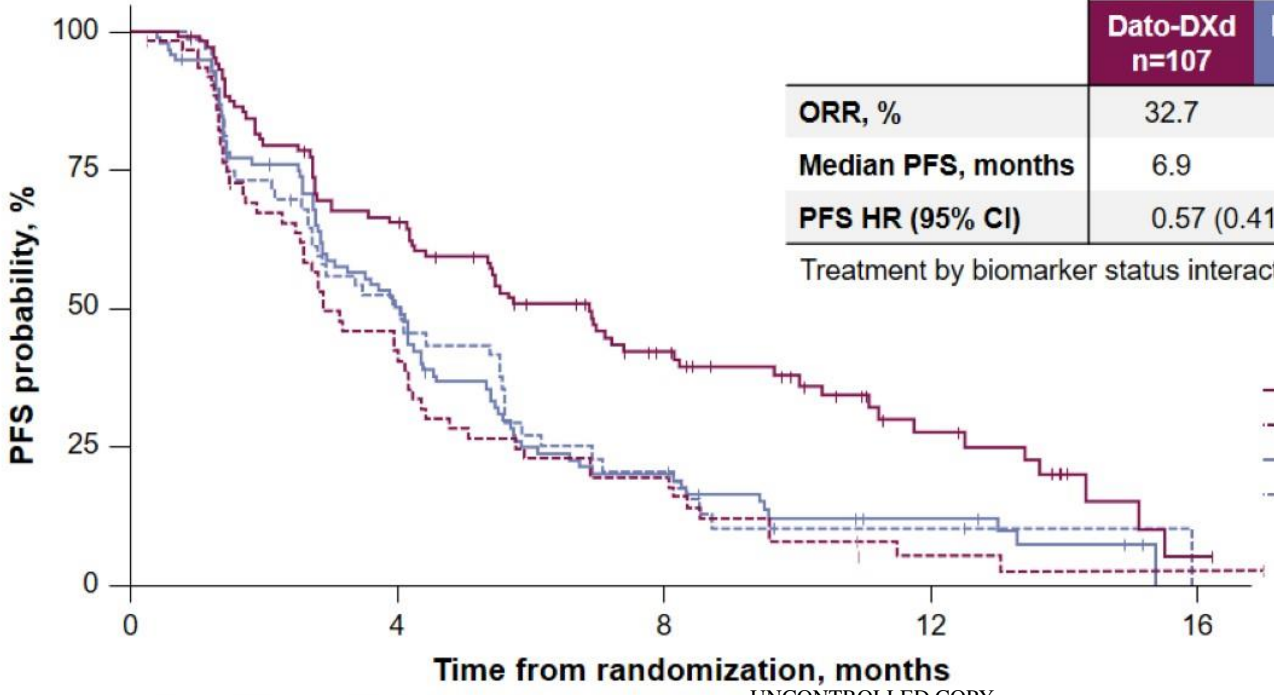
Lower NMR → higher cytoplasm proportion

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



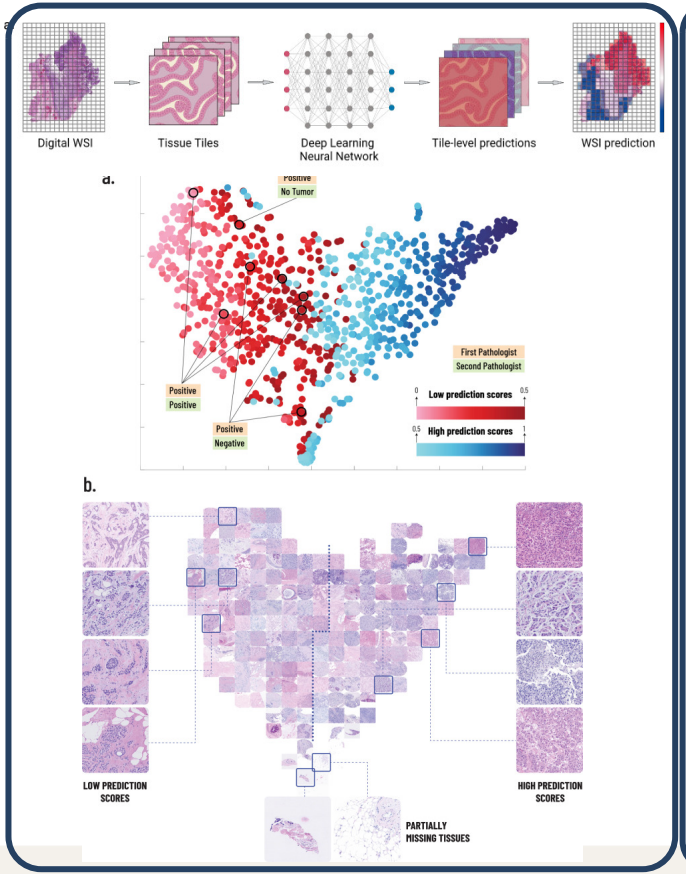
	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

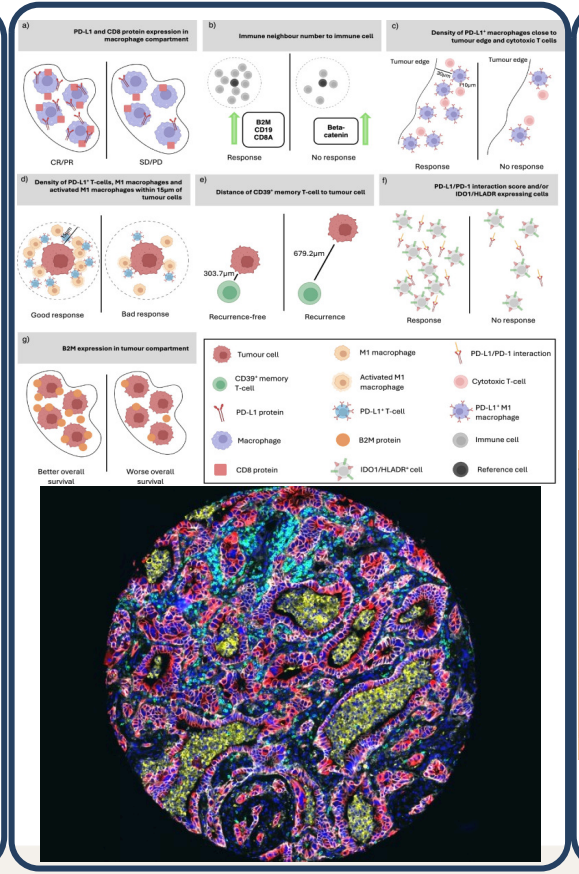
Treatment by biomarker status interaction: p=0.0063

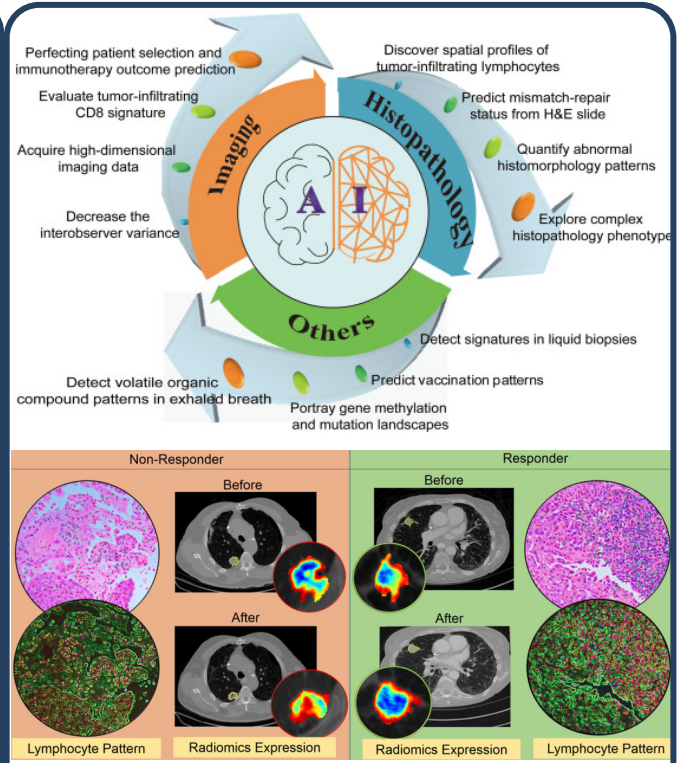
Data cutoff: March 29 2023

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]

AI-driven pathology







Xu, Z et al. Acta Pharm Sin B, 2021
Khorrami, M et al. Can Immun Res 2020
https://www.science.org/content/webinar/using-single-cell-and-spatial-transcriptomics-dissect-cellular-heterogeneity-during
Shamai, G et al. Nat Comm 2022

Morphological and molecular diagnosis, using both tissue and liquid biopsies, implementing new technologies and AI for integrating data