Carcinoma Mammario HER2-low: Ruolo dell'Anatomo-Patologo

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Disclosures

- Receipt of grants/research supports:
 - Roche/Genentech, Ventana Medical Systems, Dako/Agilent Technologies
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Paradigm Shift?

Dichotomous HER2 status (positive/negative)



HER2 positive HER2 negative HER2 low

HER2-low expression does not define a new molecular subtype of breast cancer, rather it is a biomarker common to all molecular subtypes

The changing perspective

Identify HER2-addicted tumors to be treated with drugs that inactivate the HER2 pathway (and stimulate ADCC)

HER2 as a target



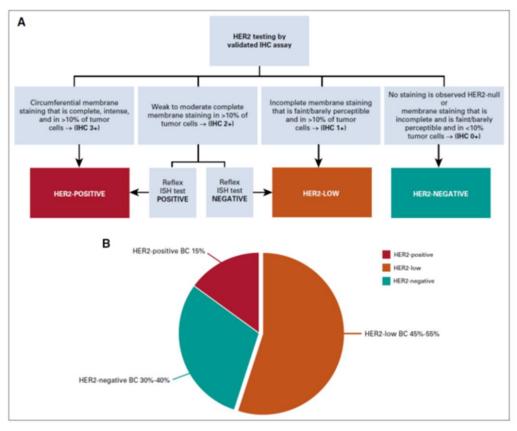
Identify tumors with a gateway to drugs that act like Trojan horses releasing a powerful cytotoxic inside the neoplastic cells

HER2 as a ploy

HER2-low breast cancer

IHC 1+ or IHC 2+ with a negative ISH test

• Approximately 50% of patients with breast cancer

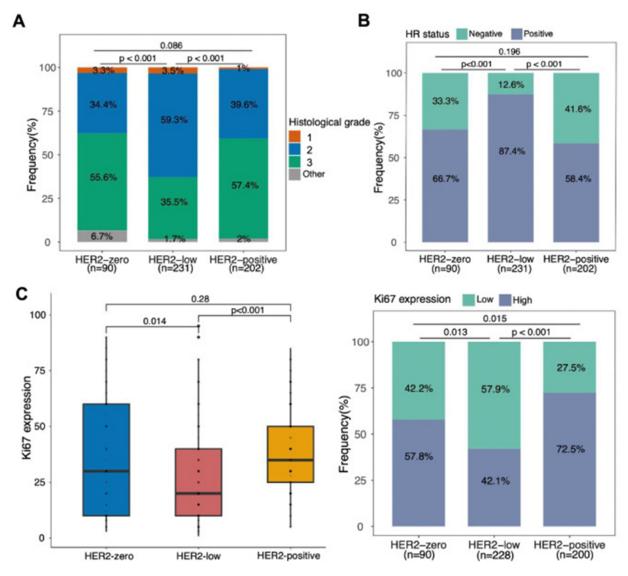


Tarantino P, et al. J Clin Oncol 2020

Subtype	HER2 0	HER2 low	HER2 positive					
	prevalence	prevalence	prevalence					
	(95% CI), %	(95% CI), %	(95% CI), %					
HR positive,	34.1	55.2	10.7					
n=3086	(32.4-35.8)	(53.4-57.0)	(9.6-11.8)					
HR negative,	45.3	28.1	26.6					
n=530	(41.0-49.6)	(24.3-32.1)	(22.9-30.6)					
Triple negative,	61.7	38.3	NA					
n=389	(56.7-66.6)	(33.4-43.3)						
Total breast	35.9	51.1	13.0					
cancer, n=3727	(34.4-37.5)	(49.5-52.8)	(11.9-14.1)					
 Substantial prevalence of HER2 low expression (28.1-55.2% was found across all breast cancer subtypes (Table 3) 								
 55.2% of HR positive breast cancer had HER2 low expression (Figure 1) 								
 38.3% of triple negative breast cancer had HER2 low expression 								

Pathological correlates

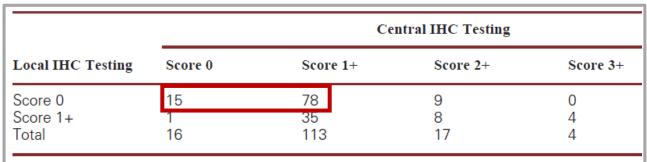
- More ER+
- Less Grade 3
- Lower Ki67

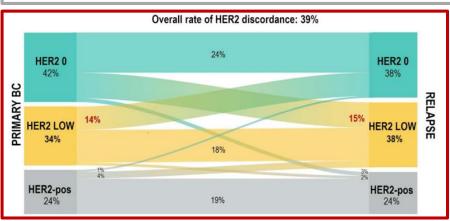


Zhang G, et al. BMC Med 2022

Almost the same challenges as for PD-L1

- Different antibodies and detection systems
- Different platforms
- Different scoring systems (ASCO/CAP vs Ventana)
- Spatial and temporal heterogeneity





and VENTANA 4B5 Assays Under Standard Scoring Conditions **Patient HER2 status Breast Paired** (HercepTest IHC) Classification **HER2 0.** HER2 low, HER2 positive. Total, N=500 n (%) n (%) n (%) n (%) HER2 0. 298 0 (59.6)(1.0)(60.6)n (%) **Patient HER2** status HER2 low, 28 137 (VENTANA (21.6)(5.6)n (%) (0.2)(27.4)4B5 IHC) HER2 positive, (2.6)(12.0)n (%) 46 500 413 Total, n (%) (82.6)(100.0)Patient HER2 status Patient HER2 status HercepTest **VENTANA 4B5** HER2 status HER2 positive HER2 low HER2 0 There was a 73.2% (95% CI: 69.1-77.0%) overall percentage agreement between assays in classification VENTANA 4B5 tends to classify patients into higher HER2 categories than HercepTest, which was the primary driver of the discordance between the assays (Figure 2)

Figure 2. Concordance Cohort: Concordance Between HercepTest

Miglietta F, et al. ESMO Breast 2021; Lambein K, et al. AJCP 2013

Scott M, et al. Poster 1021, ASCO 2021

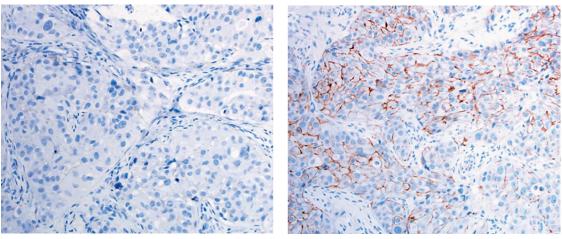
Barriers to the identification of HER2-low breast cancer

- Distinguishing IHC score 0 from score 1+ is not pursued in the daily practice
- Definition of 1+ score is not univocal
 - ASCO/CAP vs 4B5 interpretation guide
- Definition of 2+ score (> reflex ISH) may include or not intense but incomplete membrane staining, and 10% or less positive cells
- Concordance among different antibodies/assays for scores 0 and 1+ has not been fully evaluated
 - Ventana 4B5 vs «old» HercepTest vs «new» HercepTest vs Others

Different results with different antibodies

DAKO Poly-HercepTest

Ventana 4B5 antibody



		PATHWAY 4B5						
		0	1+	2+	3+	Total		
HercepTest (mAb)	0	35	0	0	0	35		
	1+	17	8	0	0	25		
	2+	4	12	13	1	30		
	3+	0	0	2	27	29		
	Total	56	20	15	28	119		

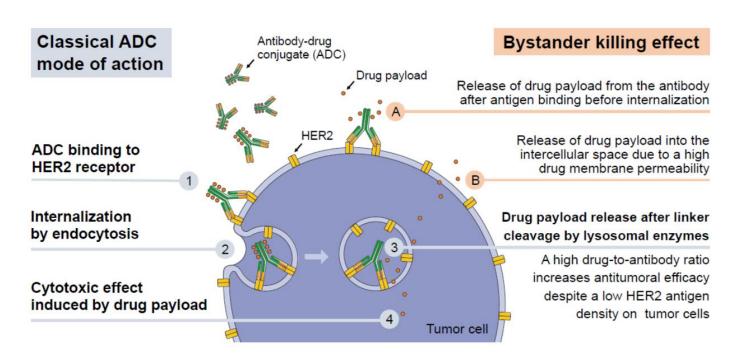
Zhang H, et al. Am J Clin Pathol. 2022;157:328-336

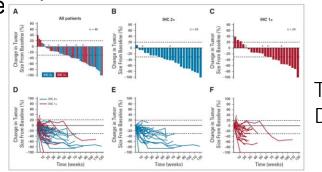
Rueshoff J, et al. Virchows Arch 2022

Why Caring of HER2-Low Breast Cancer?

- The NSABP B47 trial failed to demonstrate any benefit of Trastuzumab for patients with HER2-low breast cancer
- Nowadays several new compounds have been developed and investigated in clinical trials with very promising results

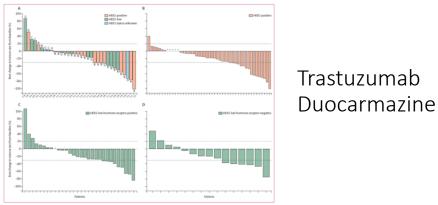
Among these new compounds, ADCs have raised the greatest inte





Trastuzumab Deruxtecan

Modi S, et al. J Clin Oncol 2020



Banerji U, et al. Lancet Oncol 2019

Destiny-Breast04 Study



DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)

Patients^a • HER2-low (IHC 1+ vs IHC 2+/ISH-), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting • HR+ disease considered endocrine refractory T-DXd 5.4 mg/kg Q3W (n = 373) HR+≈ 480 HR-≈ 60 TPC Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel

Primary endpoint

PFS by BICR (HR+)

Key secondary endpoints^b

- PFS by BICR (all patients)
- OS (HR+ and all patients)

Stratification factors

- Centrally assessed HER2 status^d (IHC 1+ vs IHC 2+/ISH-)
- · 1 versus 2 prior lines of chemotherapy
- . HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR-

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review, CDK, cyclin-dependent kinase; DDR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor HIC, immunchistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan;

FPC, Dealment or physician's choice.

If patients had HR+ mBC, prior endocrine therapy was required. Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR- cohort was an exploratory endpoint. TPC was administered accordingly to the label. Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (485) investigational use only IIUO) Assay system.

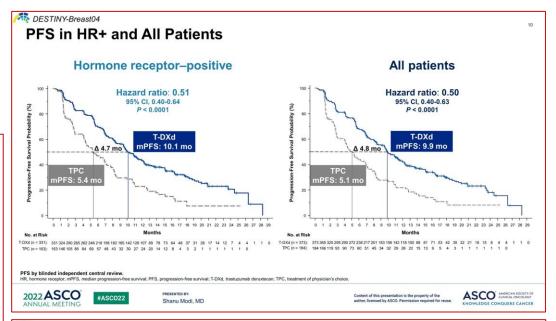
(n = 184)

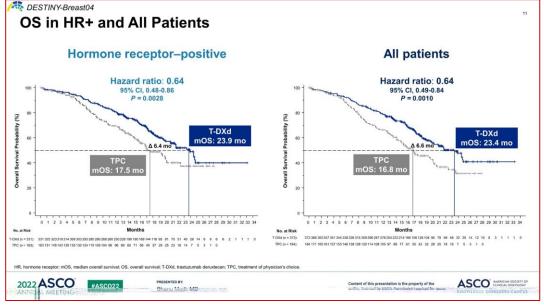




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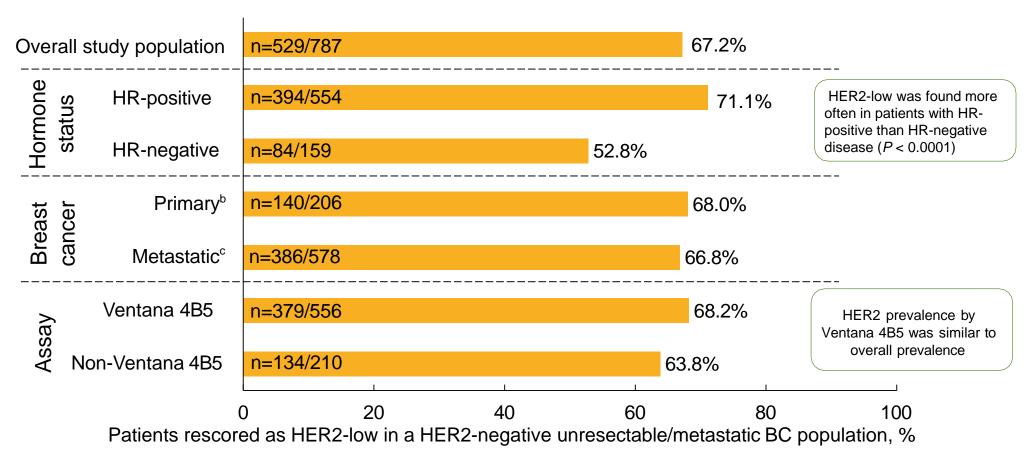




Open questions

- Only 58 pazients with TNBC
 - Exploratory end-point
 - T-DXd vs Sacituzumab Govitecan
- Use of 4B5 (Ventana) and ASCO/CAP scores
 - Will alternative antibodies and platforms be suitable as well?
- For about 1/3 of enrolled patients HER2 testing has been performed on archival samples (including the primary tumour)
 - Can we trust the evaluation made in the past on the primary tumor or do we always have to biopsy the metastasis?
 - If the biopsy of the metastasis is negative (score 0) should we retrieve (and maybe re-score) the primary tumor?

RETRO BC: HER2-Low Prevalence in HER2-Negative Unresectable/Metastatic BC^a

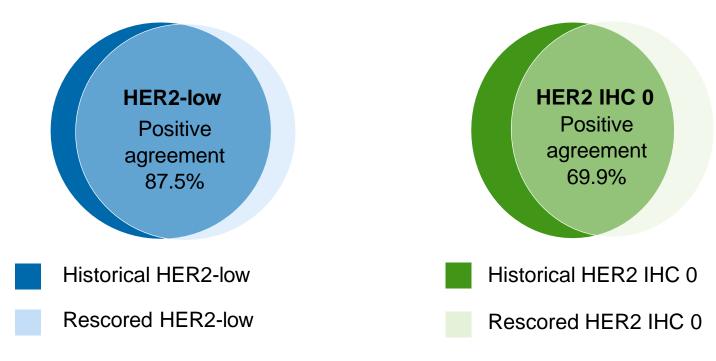


BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

^a Two patients were missing HER2 rescore data. ^b Rescored biopsy sample dated before 30 days prior to unresectable/metastatic BC diagnosis date. ^c Rescored biopsy sample dated on/after 30 days prior to unresectable/metastatic BC diagnosis date.

RETRO BC: Concordance (Rescores vs Historical Scores)¹

Overall concordance 81.3% (n = 639/786)^a Cohen K (95% CI): 0.583 (0.523-0.643)^b



^a Concordance includes only patients with both historical and rescored IHC scores available. ^b Indicates moderate agreement (defined as κ 0.4 to ≤ 0.6).² BC, breast cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

^{1.} Viale G et al. San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-15. 2. Landis JR, Koch GG. Biometrics. 1977;33(1):159-174.

Precision vs prediction

- The exciting results of the clinical studies for HER2-low disease were obtained by selecting patients with an usual IHC test (4B5, Ventana) and with the ASCO/CAP scoring system
- Neither the test nor the scoring system were developed to identify tumors with low HER2 expression
- Many want to change the definition of HER2-low, the test (IHC and/or molecular assays) and the scoring system
- Do we need "precision" or "prediction"?

When I want to read a novel, I write one (Benjamin Disraeli 1804-1881)

HER2 IHC score 0

- · Faint membranous expression in <20% of tumour cells
- · Weak incomplete membranous expression in < 10% of tumour cells

HER2 IHC score 1+

- · Faint membranous expression in ≥20% of tumour cells
- Weak complete membranous expression in ≤10% of tumour cells
- Weak incomplete membranous expression in >10% of tumour cells

 Moderate/Strong incomplete membranous expression ≤10%

HER2 IHC score 2+

- · Weak complete membranous expression in >10%
- Moderate complete or incomplete membranous expression in >10%
- Strong complete membranous expression in ≤10% of tumour cells
- · Strong incomplete membranous expression >10% of tumour cells.

membranous expression ≤10%

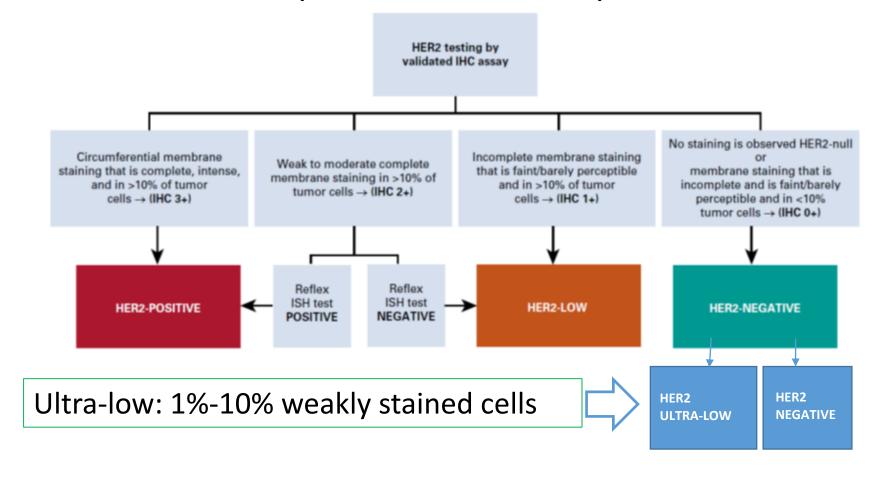
Moderate complete

HER2 IHC score 3+

· Strong complete membranous expression in >10% of tumour cells

Extremely rare or did not exist. If it is seen, repeat on excision specimen should be recommended, if same results, ISH is recommended

HER2 ultra-low (score >0<1+)



DB-06 study

Additional open questions

- Correlation between percentage of cells with (low) expression of HER2 and efficacy of T-DXd (intratumoral heterogeneity)?
 - Heterogeneity is very common in HER2-low tumors
- Correlation between type of intratumoral heterogeneity (cluster, mosaic, scattered) and efficacy of T-DXd?
 - How far can the bystander killing effect go?
- Do outright negative (HER2-null) tumors respond to therapy?
 - Daisy Trial
 - The missed opportunity (DB06)

What to do? (while waiting for the approval of new anti-HER2 low drugs)

- Alert the scientific community on the introduction of the HER2-low concept and of its clinical implications
- Educate and train pathologists for an accurate and reproducible report of HER2 low (& ultra-low) status
- Do not forget that intratumoral heterogeneity of HER2 status might also have an important role in informing the choice of anti-HER2 therapy
 - Should the way we report on HER2 status be amended?
- ESMO Consensus Statement on HER2-low

HER2 reporting: open questions

Today's report

- HER2 negative
- Score 2+ (20% of tumor cells)
- ISH: not amplified

HER2 reporting: open questions

Today's report

- HER2 negative
- Score 2+ (20% of tumor cells)
- ISH: not amplified

- What about the remaining 80% tumor cells?
- Important to know if they (and how many of them) are 1+?
- Should we report on the % of tumor cells without any staining (null)?
- Should we adopt the HER2-low terminology in the report?