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

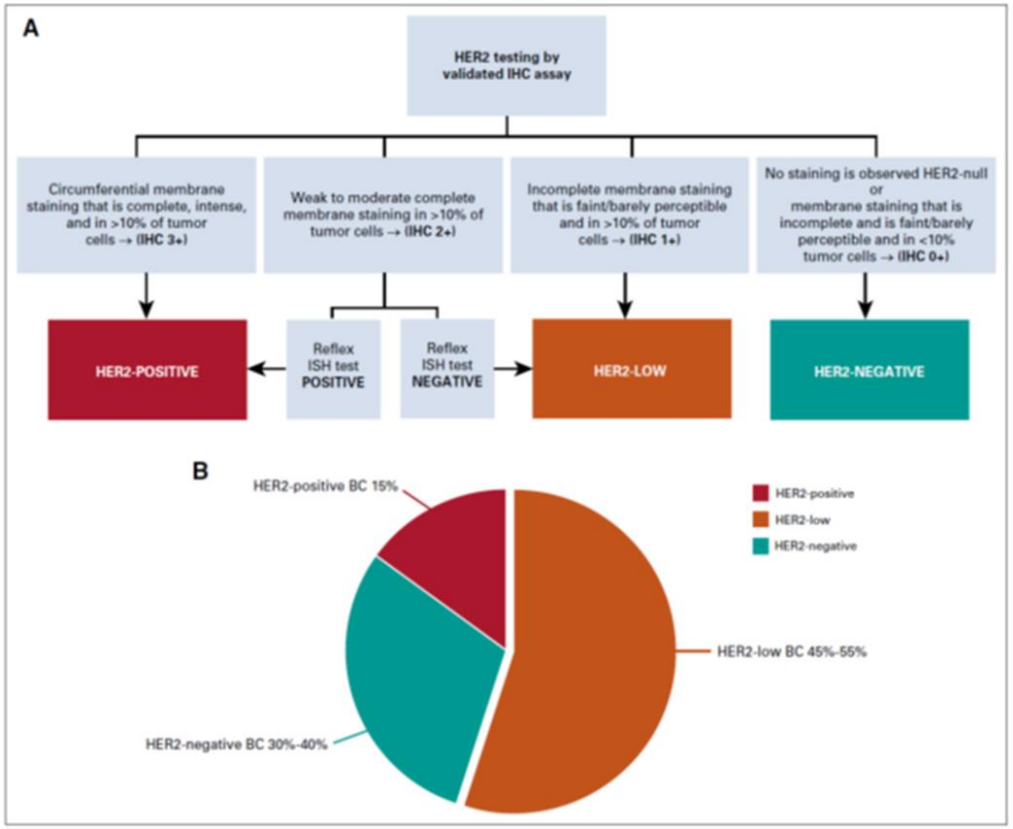
Identify tumors with a gateway to drugs that act like Trojan horses releasing a powerful cytotoxic inside the neoplastic cells

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

Table 3. RWD Sample Set: HER2 Low Prevalence by Breast Cancer Subtype

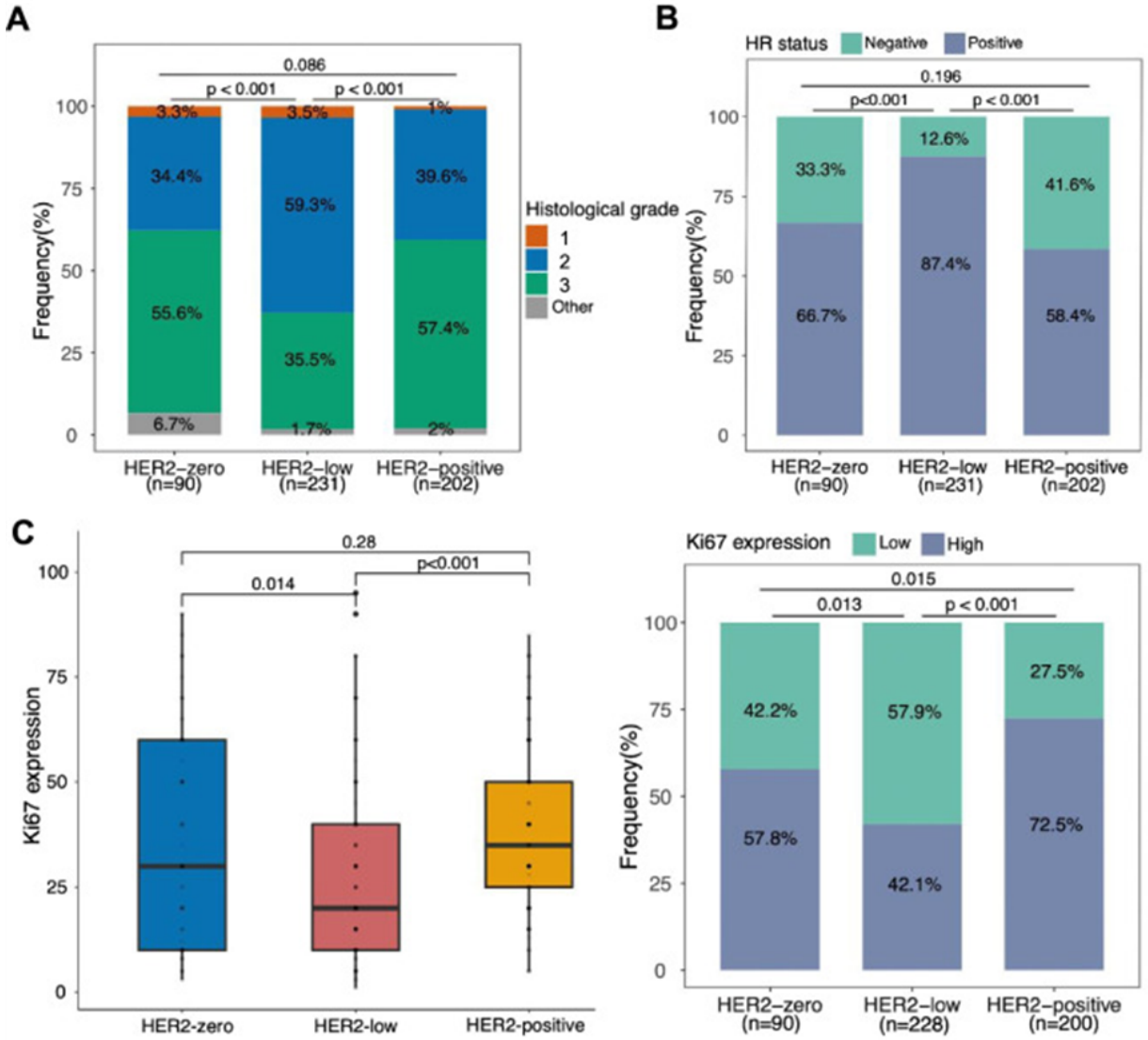
Subtype	HER2 0 prevalence (95% CI), %	HER2 low prevalence (95% CI), %	HER2 positive prevalence (95% CI), %
HR positive, n=3086	34.1 (32.4-35.8)	55.2 (53.4-57.0)	10.7 (9.6-11.8)
HR negative, n=530	45.3 (41.0-49.6)	28.1 (24.3-32.1)	26.6 (22.9-30.6)
Triple negative, n=389	61.7 (56.7-66.6)	38.3 (33.4-43.3)	NA
Total breast cancer, n=3727	35.9 (34.4-37.5)	51.1 (49.5-52.8)	13.0 (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

Scott M, et al. Poster 1021, ASCO 2021

Pathological correlates

- More ER+
- Less Grade 3
- Lower Ki67

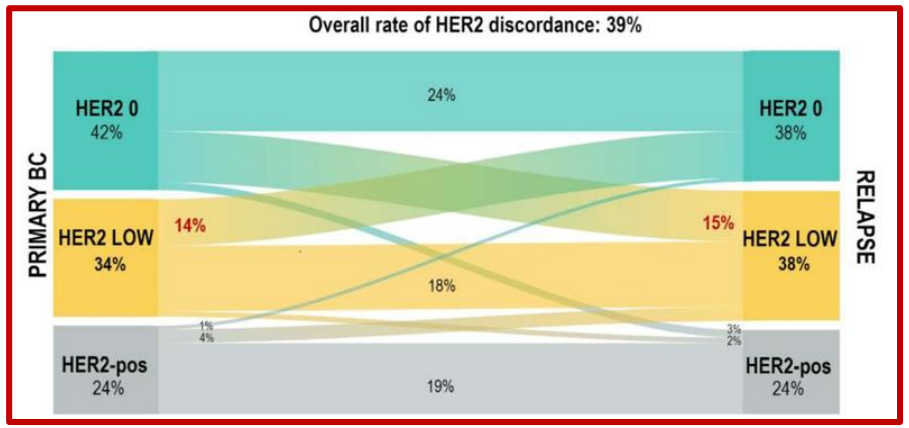


Zhang G, et al. BMC Med 2022

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

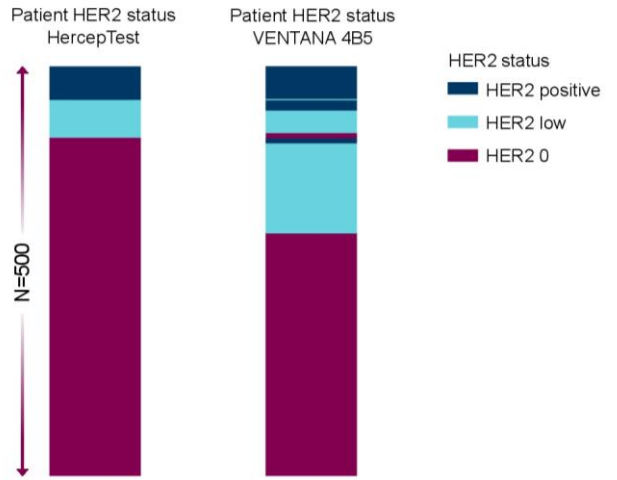
	Central IHC Testing			
Local IHC Testing	**Score 0**	**Score 1+**	**Score 2+**	**Score 3+**
Score 0	15	78	9	0
Score 1+	1	35	8	4
Total	16	113	17	4



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

Figure 2. Concordance Cohort: Concordance Between HercepTest and VENTANA 4B5 Assays Under Standard Scoring Conditions

Breast Paired Classification N=500		Patient HER2 status (HercepTest IHC) HER2 0, n (%)	HER2 low, n (%)	HER2 positive, n (%)	Total, n (%)
Patient HER2 status (VENTANA 4B5 IHC)	HER2 0, n (%)	298 (59.6)	5 (1.0)	0	303 (60.6)
	HER2 low, n (%)	108 (21.6)	28 (5.6)	1 (0.2)	137 (27.4)
	HER2 positive, n (%)	7 (1.4)	13 (2.6)	40 (8.0)	60 (12.0)
Total, n (%)		413 (82.6)	46 (9.2)	41 (8.2)	500 (100.0)



- 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**)

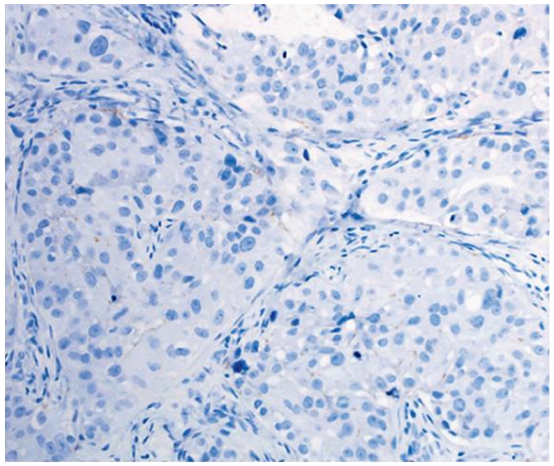
Scott M, et al. Poster 1021, ASCO 2021

Barriers to the identification of HER2-low breast cancer

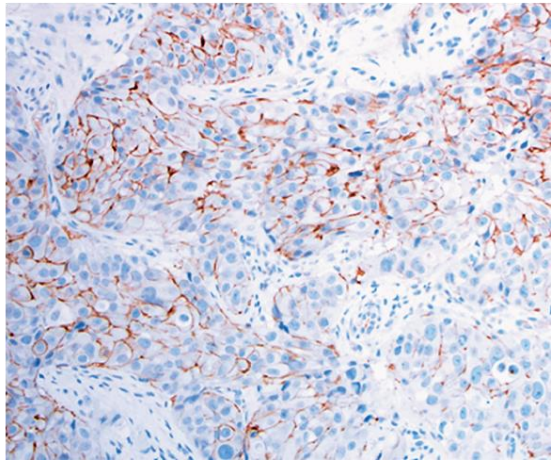
- Distinguishing IHC score 0 from score 1+ is not pursued in the daily practice
- Definition of 1+ score is not univocal
  - ASCO/CAP *vs* 4B5 interpretation guide
- Definition of 2+ score (> reflex ISH) may include or not intense but incomplete membrane staining, and 10% or less positive cells
- Concordance 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



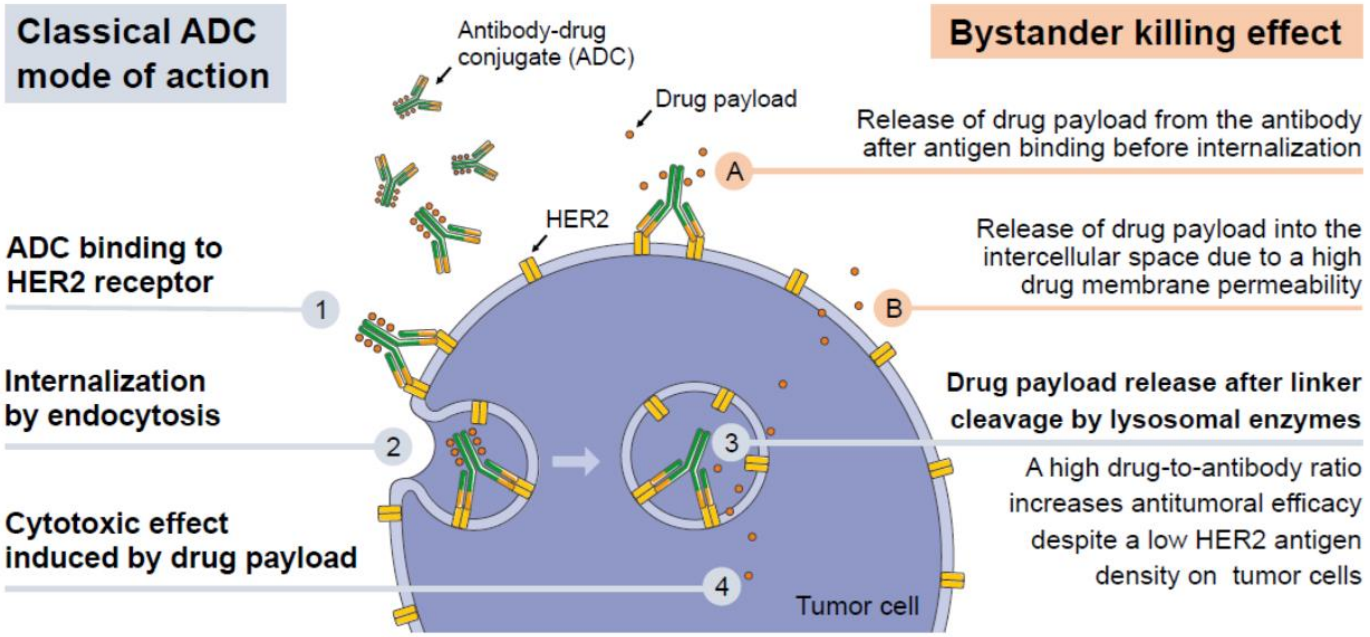
Zhang H, et al. Am J Clin Pathol. 2022;157:328-336

		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**

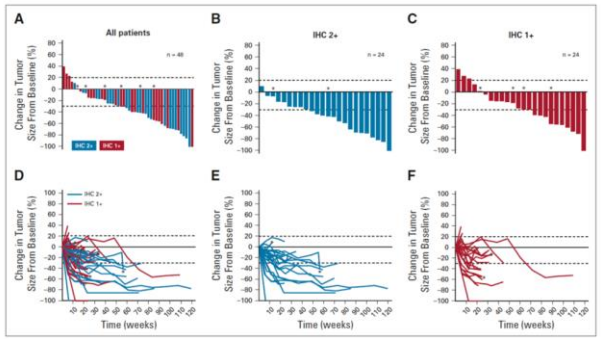
Rueshoff J, et al. Virchows Arch 2022

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

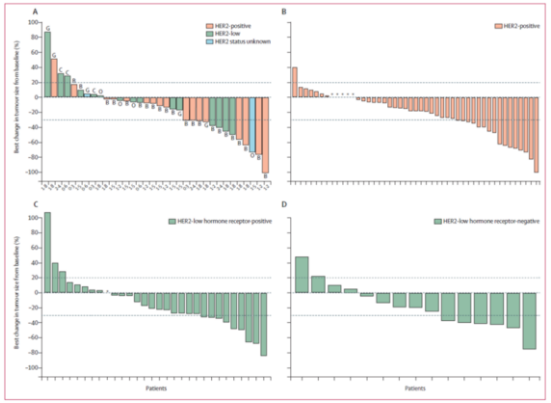


Rinnerthaler G, Int J Mol Sci 2019



Trastuzumab Deruxtecan

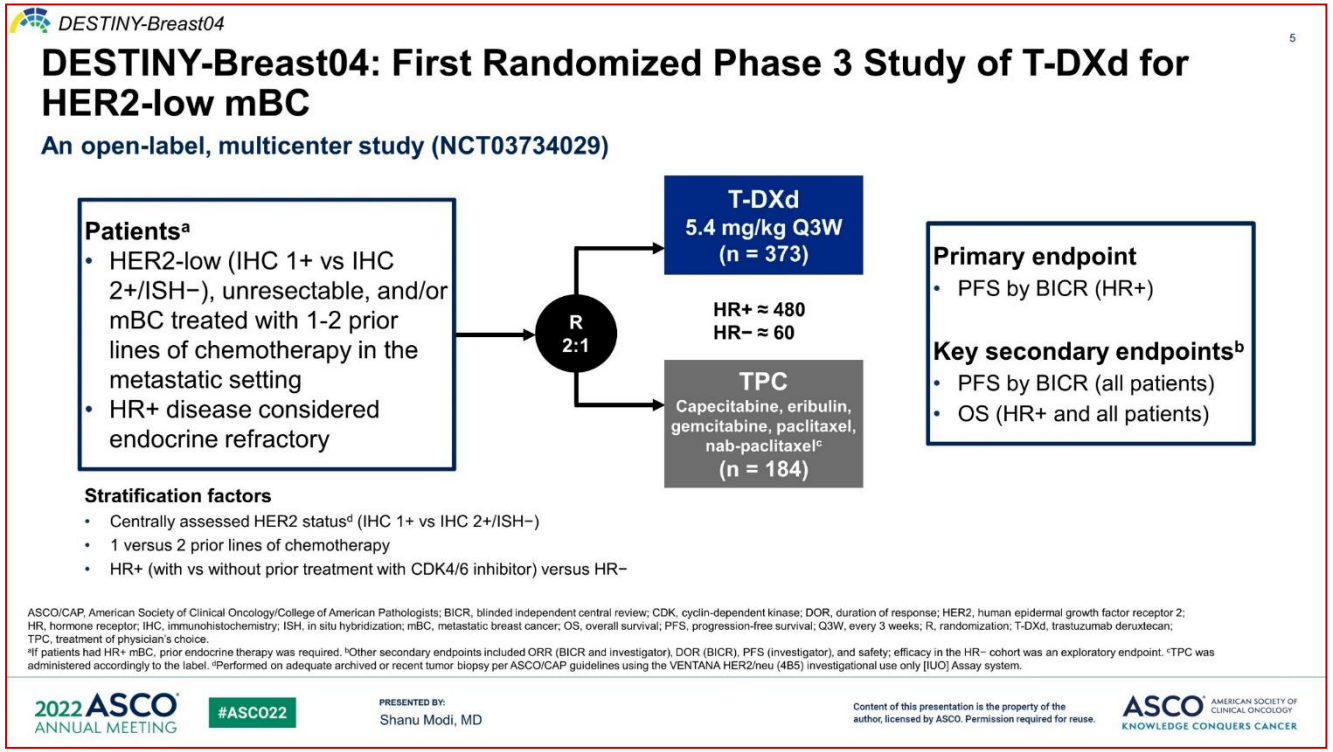
Modi S, et al. J Clin Oncol 2020

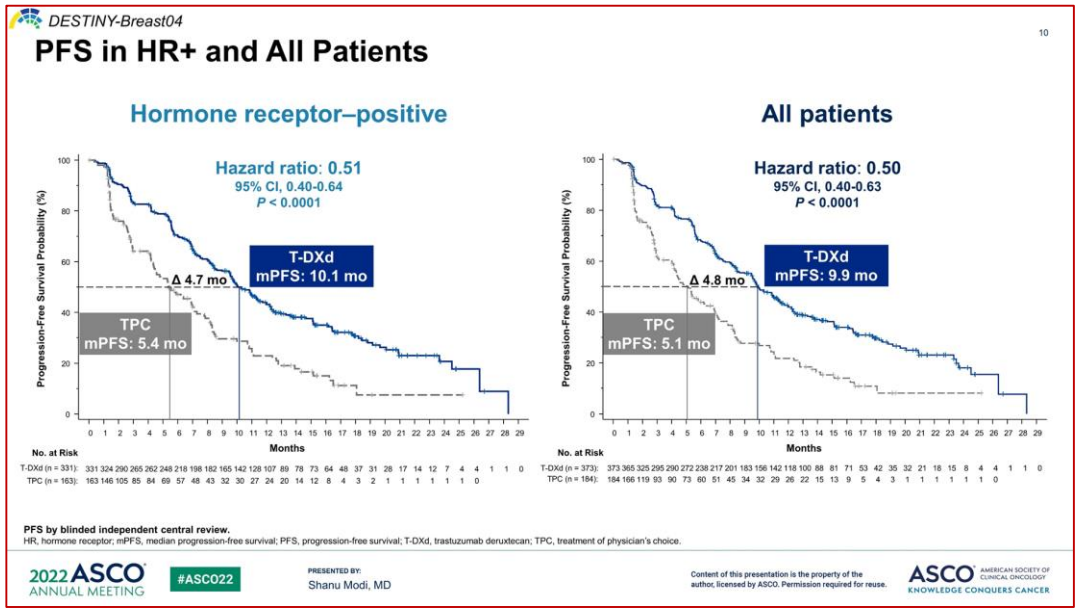


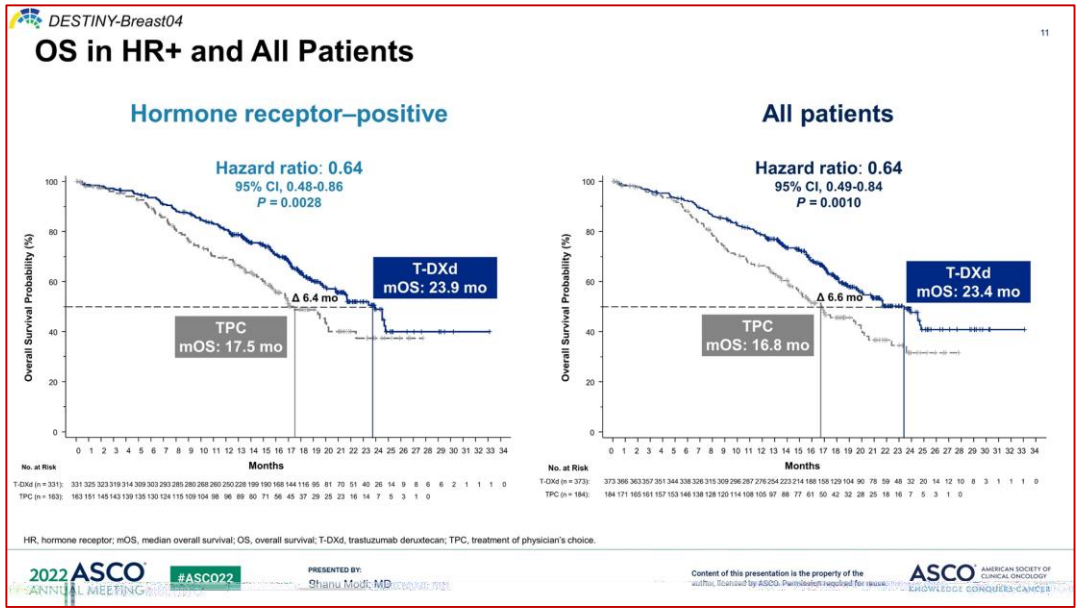
Trastuzumab Duocarmazine

Banerji U, et al. Lancet Oncol 2019

Destiny-Breast04 Study



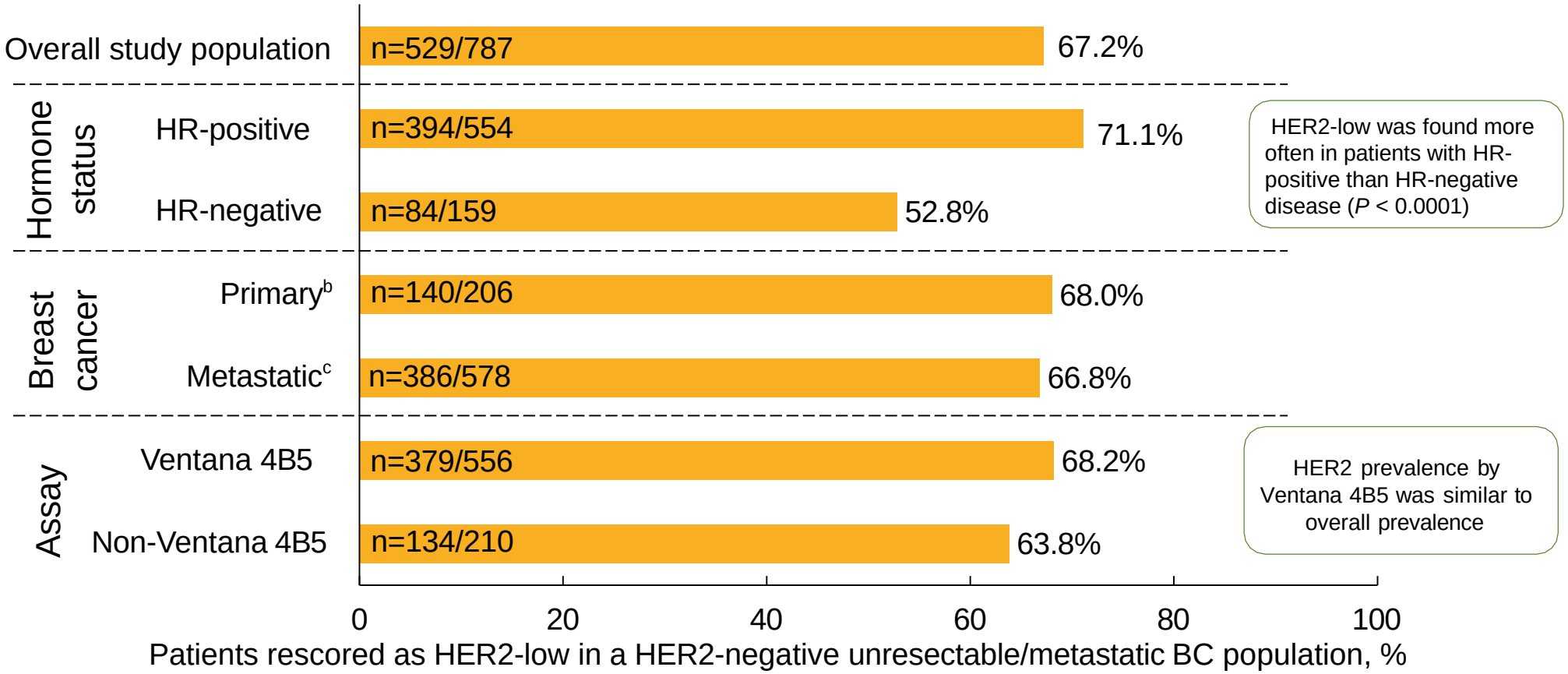




Open questions

- 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]



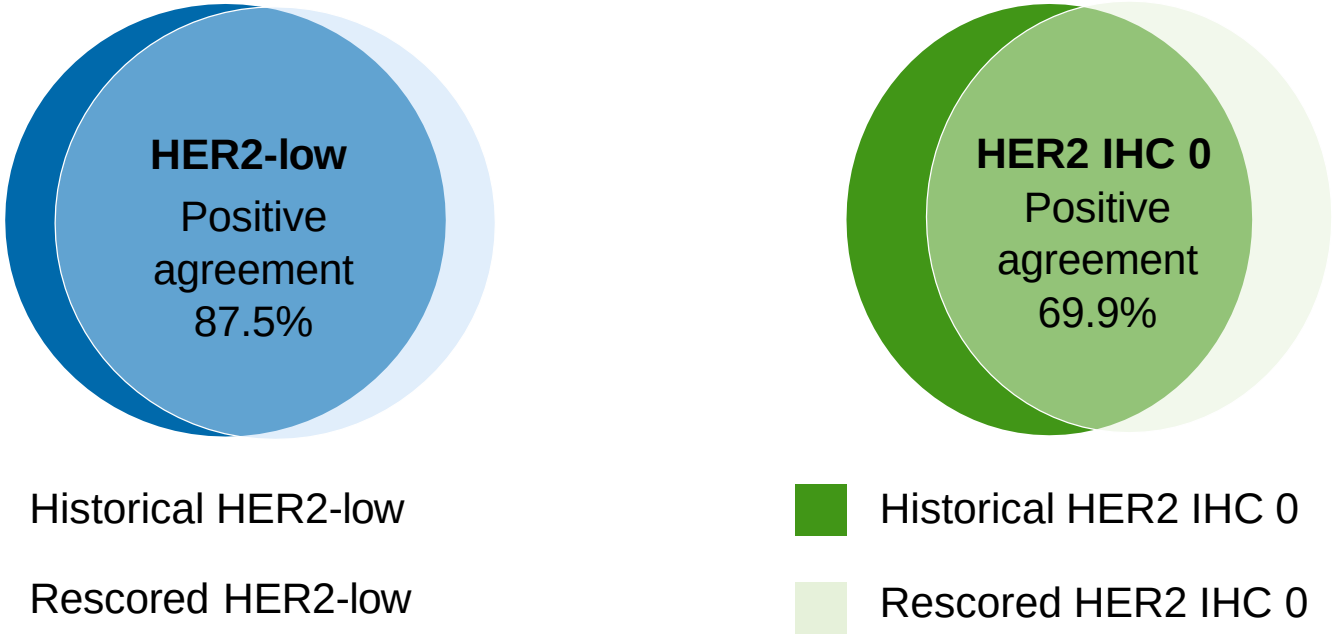
BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

[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.

Viale G et al. San Antonio Breast Cancer Symposium 2022

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]

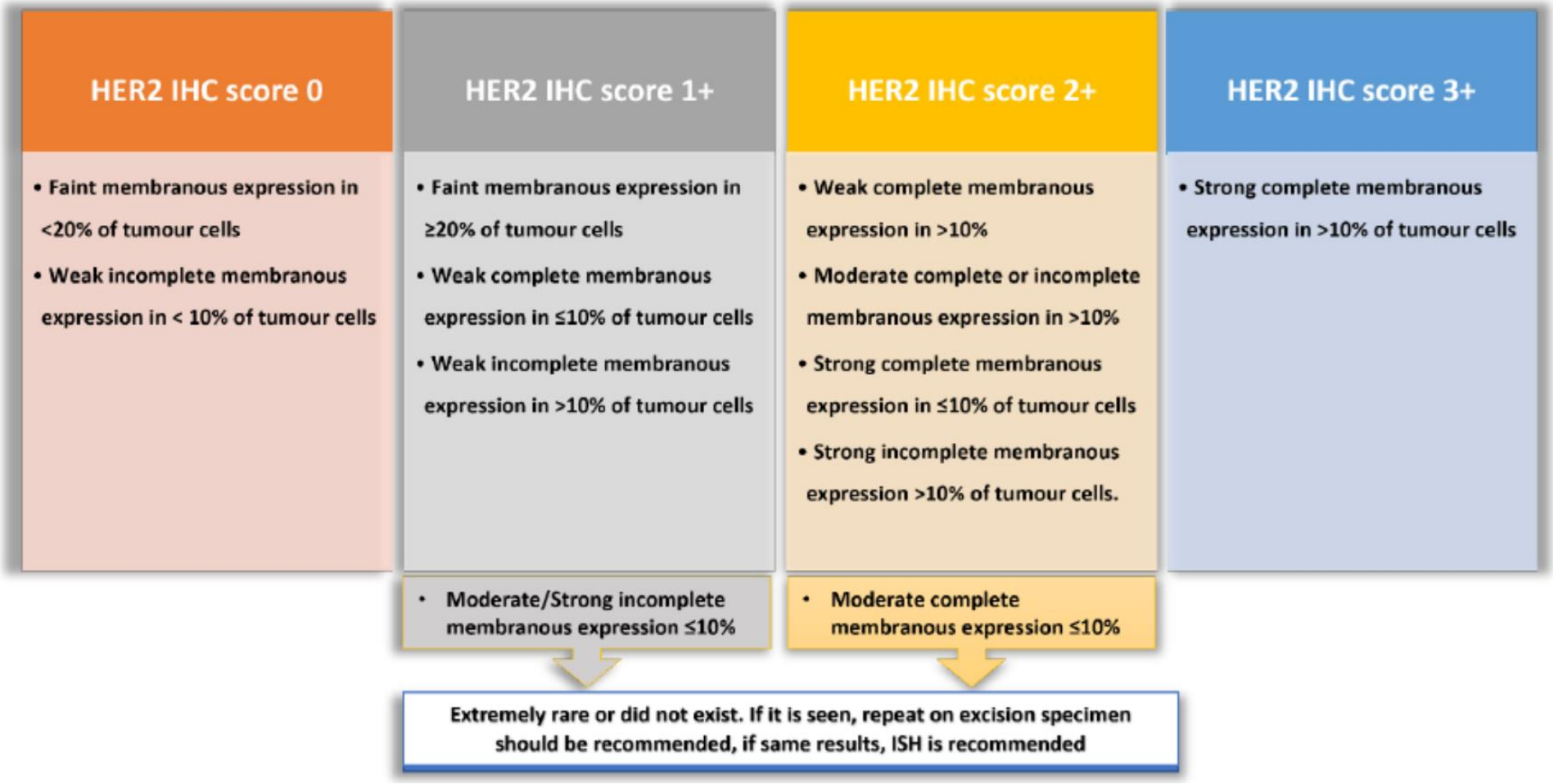


[a] Concordance includes only patients with both historical and rescored IHC scores available. [b] Indicates moderate agreement (defined as κ 0.4 to ≤ 0.6).[2]
BC, breast cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
1. Viale G et al. San Antonio Breast Cancer Symposium 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

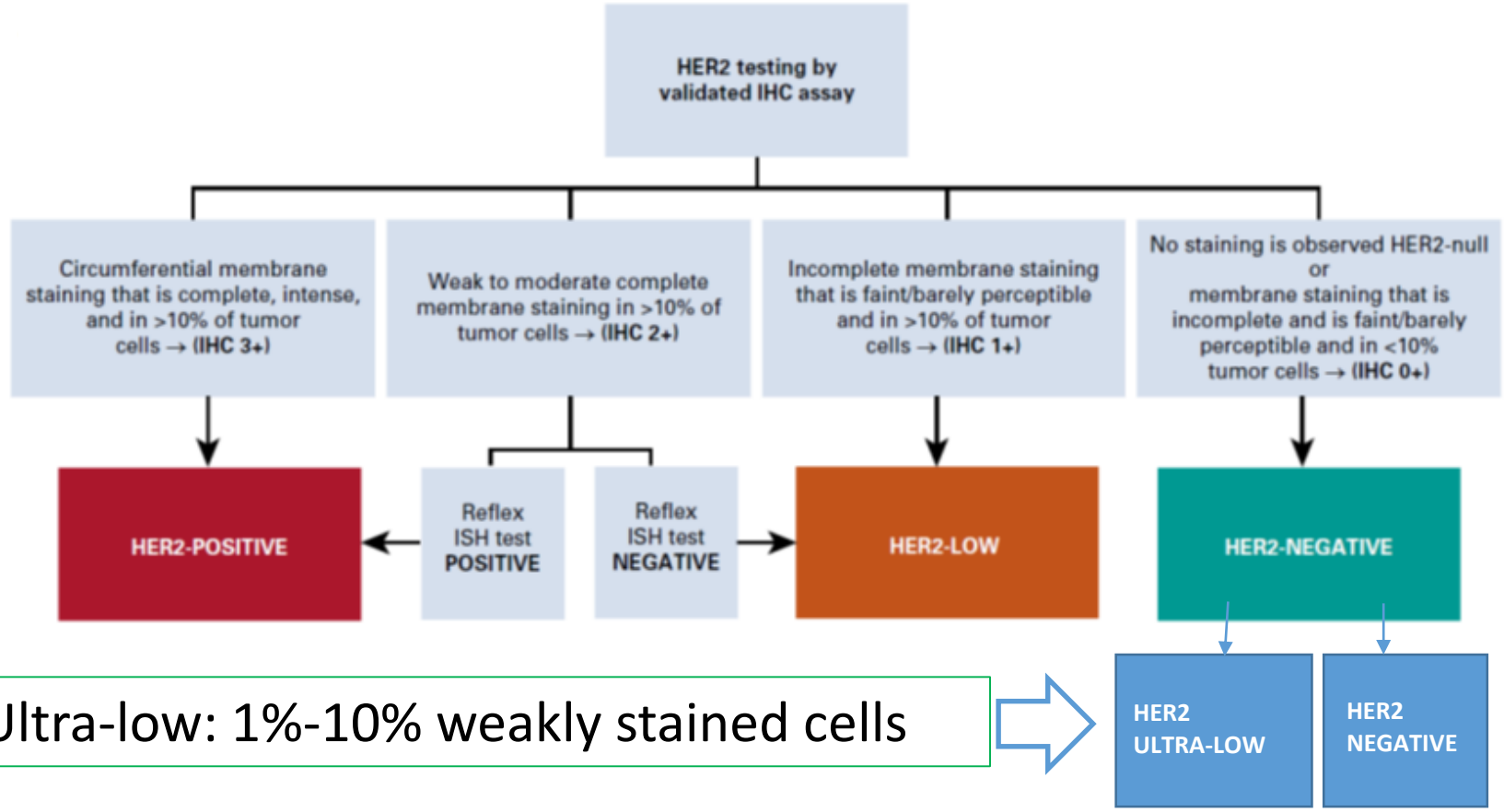
- The exciting results of the clinical studies for HER2-low disease were obtained by selecting patients with an usual IHC test (4B5, Ventana) and with the ASCO/CAP scoring system
- Neither the test nor the scoring system were developed to identify tumors with low HER2 expression
- Many want to change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



Atallah NM, et al. Histopathology 2022

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?