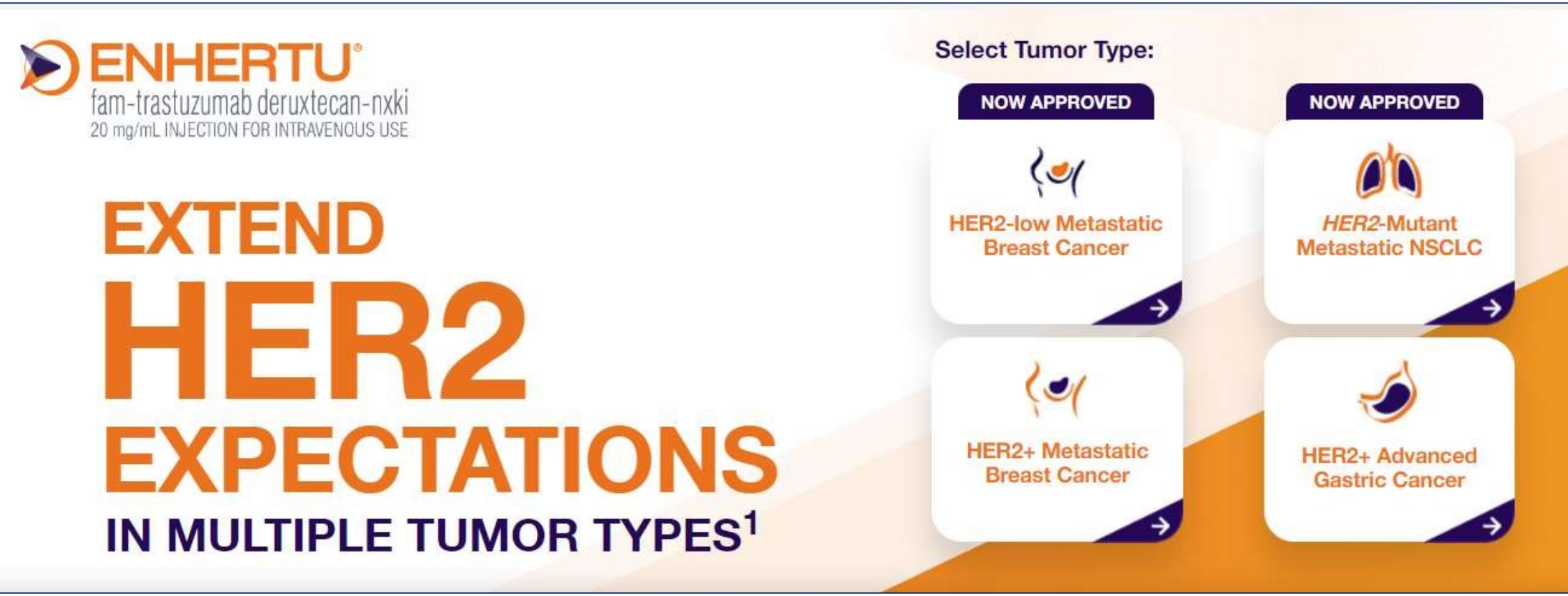
“HER2 low” expressie in borstkanker

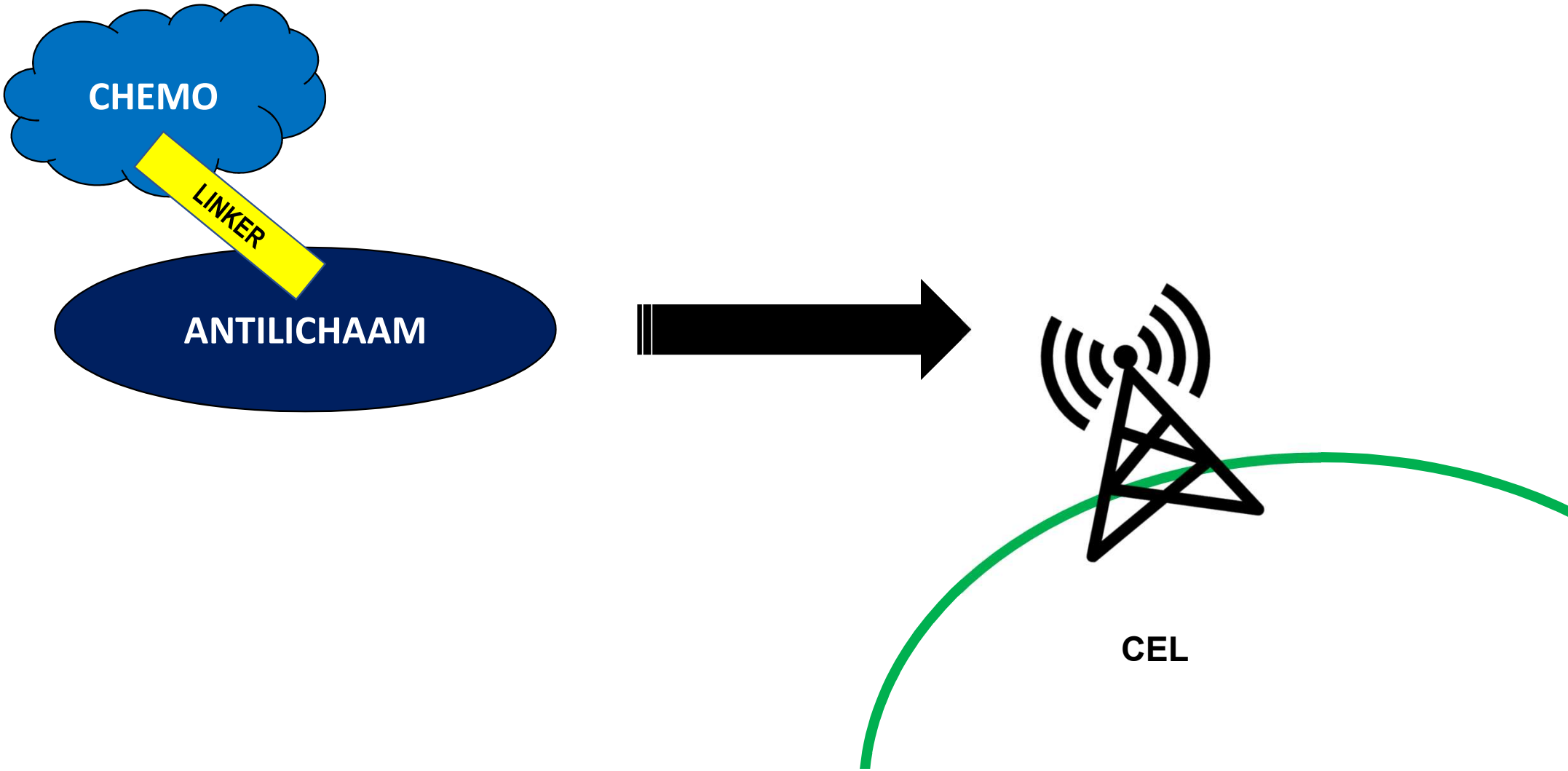
16/12/2022

Mieke Van Bockstal, MD PhD

Cliniques universitaires Saint-Luc, Brussels, Belgium



Nieuw medicijn ➔ nieuwe test?


CHEMO
LINKER
ANTILICHAAM
CEL

Antibody-drug conjugates (ADCs)

Trastuzumab emtansine (T-DM1)

- Eerste FDA-goedgekeurd anti-HER2 ADC
- Trastuzumab gekoppeld aan mertansine, een krachtige inhibitor van microtubuli, via een **onsplitsbare** thioether linker
- Behandeling van gevorderde **HER2-positieve** borstkanker
- Vroeg stadium hoog-risico patiënten met residuele ziekte na NAC.
- Trials: EMILIA, TH3RESA, KATHERINE

Trastuzumab deruxtecan (T-Dxd)

- Tweede FDA-goedgekeurd ADC voor gevorderde HER2-positieve borstkanker met minstens 2 voorafgaande lijnen van anti-HER2 gerichte therapie.
- Trastuzumab gekoppeld aan deruxtecan, afgeleid van exatecan, een potente topoisomerase I inhibitor, met een **splitsbare** linker (cathepsines!)
- Payload is membraandoorlaatbaar ➔ **bystander effect** ➔ laat activiteit toe in tumoren met **lage HER2 expressie**

Table 1 Ongoing clinical trials with T-Dxd including breast cancer patients

NCT identifier	Trial name	Phase	Experimental arm	Control arm	Setting	Population	Primary endpoint
NCT03523585	DESTINY-Breast02	III	T-DXd	Investigator's choice	Prior T-DM1	HER2+ MBC	PFS
NCT03529110	DESTINY-Breast03	III	T-DXd	T-DM1	Prior taxane +trastuzumab	HER2+ MBC	PFS
NCT03734029	DESTINY-Breast04	III	T-DXd	Investigator's choice	1 or 2 prior chemotherapies. POD on ET if HR+	HER2-low MBC	PFS
NCT04132960	DAISY	II	T-DXd	-	≥ 2nd line	MBC C1: HER2 over-expressing C2: HER2 low expressing C3: non expressing [d]	BOR
NCT04752059	TUXEDO-1	II	T-DXd	-	≥ 2nd line	Newly diagnosed or progressing BM HER2+MBC	CNS ORR
NCT04784715	DESTINY-Breast09	III	T-DXd+/− P	THP	1st line	No prior chemo or POD ≤ 6 mo from adj therapy HER2+ MBC	PFS
NCT04622319	DESTINY-Breast05	III	T-DXd	T-DM1	Post-neoadjuvant	Primary BC with residual invasive disease	IDFS
NCT04420598	DEBBRAH	II	T-DXd	-	≥ 2nd line	BM or LMD in HER2+or HER2-low MBC	CNS ORR, 16w PFS and OS of T-DXd
NCT04494425	DESTINY-Breast06	III	T-DXd	treatment of Investigator's Choice	≥ 3rd line	HR+ HER2-low MBC	PFS
NCT04257162	HER2-PREDICT	-	T-DXd	-	-	Patients treated with T-DXd+	ERBB2 mRNA cut-point predictive of T-DXd response
NCT04042701	-	Ib/II	T-DXd+ pembrolizumab	-	≥ 2nd line	HER2+ or low MBC and HER2+ or mut NSCLC	DLT and ORR
NCT04553770	-	II	T-DXd+/− ANA	-	Neoadjuvant setting	HR+ HER2-low EBC	pCR rate
NCT04556773	DESTINY-Breast 08	Ib	T-DXd+ Durva or T or Capi or ANA or Fulv or Cape	-	≥ 2nd line	HER2-low MBC	Safety
NCT04294628	-	I	T-DXd	-	≥ 2nd line	Any advanced solid tumor, HER2+	Effect of T-DXd on Top1cc
NCT04539938	HER2CLIMB-04	II	T-DXd+ tucatinib	-	≥ 2nd line	HER2+MBC	ORR
NCT04704661	DASH	I/Ib	T-DXd and AZD6738[a]	-	≥ 2nd line	HER2+/low/ mutant solid tumors	DLT and RP2D
NCT03742102	BEGONIA	Ib/II	Durvalumab + T-DXd or Capi or Ole[b] or T or DS-1062[c]	-	1st line	TNBC	Safety and ORR

Ferraro *et al. Breast Cancer Research* (2021) 23:84
https://doi.org/10.1186/s13058-021-01459-y

Breast Cancer Research

REVIEW Open Access

Implementing antibody-drug conjugates (ADCs) in HER2-positive breast cancer: state of the art and future directions

Emanuela Ferraro[1], Joshua Z. Drago[1,2] and Shanu Modi[1,2*]

Ferraro et al. Breast Cancer Research (2021) 23:84
https://doi.org/10.1186/s13058-021-01459-y

Breast Cancer Research

REVIEW Open Access

Implementing antibody-drug conjugates (ADCs) in HER2-positive breast cancer: state of the art and future directions

Emanuela Ferraro[1], Joshua Z. Drago[1,2] and Shanu Modi[1,2*]

Table 2 Pharmacological properties of anti-HER2 ADCs undergoing clinical trials

ADC name	Ab	Linker	Payload	DAR	Ongoing clinical trials[a]
SYD985	Trastuzumab	Valine-citrulline linker (cleavable)	Seco-DUBA (DNA-alkylating)	2.8	NCT03262935 NCT04602117 NCT04235101 NCT01042379
ZW49	ZW25	Cleavable	N-acyl sulfonamide auristatin (microtubule inhibitor)	N.A.	NCT03821233
PF-06804103	Trastuzumab-derived Ab	Maleimidocaproyl-valine-citrulline linker (cleavable)	Aur-06380101	4	NCT03284723
MRG002	Anti-HER2 IgG1	N.A.	Monomethyl auristatin E	NA	CTR20181778 NCT04492488, NCT04742153
GQ1001	Anti-HER2 IgG	NA	NA	NA	NCT04450732
ARX788	Modified heavy chain Ala114 of anti-HER2 mAb	Amberstatin (AS269) (non-cleavable)	Dolastatin monomethyl auristatin F (microtubule inhibitor)	1.9	NCT03255070
A166	Trastuzumab	Valine citrulline peptide (cleavable linker)	Duostatin-5 (microtubule inhibitor)	N.A.	NCT03602079
XMT-1522	HT-19 (anti-HER2 IgG1)	Cleavable hydrophilic polymer	AF-HPA (microtubule inhibitor)	12	NCT02952729
RC48-ADC	Hertuzumab (anti-HER2 humanized Ab)	Valine citrulline peptide (cleavable linker)	Monomethyl auristatin E (microtubule inhibitor)	4	NCT04329429 NCT04280341 NCT04311034 NCT04714190 NCT04073602 NCT04264936 NCT03556345 NCT03500380 NCT03052634
BDC-1001	Trastuzumab	Non cleavable linker	TLR7/8 inhibitor	NA	NCT04278144
FS-1502	Trastuzumab	NA	Monomethyl Auristatin F	NA	NCT03944499
GQ1001	NA	NA	NA	NA	NCT04450732
ALT-P7	Trastuzumab biobetter HM2	Cysteine-containing peptide	Monomethyl auristatin E (microtubule inhibitor)	NA	NCT03281824

Abbreviations: *AF-HPA* auristatin F-hydroxypropylamide, *NA* non- available
[a]https://clinicaltrials.gov/ April 2021

Table 3 Anti-HER2 ADCs treatment-related grade ≥ 3 adverse events occurring in > 2% of patients

Toxic effect	ADCs	Frequency	Possible mechanism
Thrombocytopenia	T-DM1 [7] T-DXd [15]	14.3% 4.3%	DM1-induced impairment of megakaryocytes differentiation Bone marrow toxicity of payload
Neutropenia	T-DM1 [7] T-DXd [15] SYD985 [18] RC48-ADC [23] ALT-P7 [24]	2.4% 20% 14% 10% 14%	Bone marrow toxicity of payloads
Anemia	T-DM1 [7] T-DXd [15]	3.8% 8.6%	Bone marrow toxicity of payloads
Leukopenia	RC48-ADC [23]	6.7%	Bone marrow toxicity of payloads
Decreased lymphocyte count	T-DXd [15]	8.1%	Bone marrow toxicity of payloads
Fatigue	T-DM1 [7] T-DXd [15] SYD985 [18] PF-06804103 [28]	2.4% 6% 3% 5.7%	Unknown
Arthralgia	PF-06804103 [28]	5.7%	Unknown
Increased ALT Increased ALT	T-DM1 [7] RC48-ADC [23] RC48-ADC [23]	15% 3.3% 3.3%	Cytotoxic activity on the hepatocytes (clearance of T-DM1 depends mainly on the hepatobiliary and gastrointestinal route)
Nausea	T-DXd [15]	7.6%	Off-target effect of the payload
Vomiting	T-DXd [15]	4.3%	Off-target effect of the payload
Diarrhea	T-DXd [15]	2.7%	Off-target effect of the payload
Peripheral neuropathy	T-DM1 [49] PF-06804103 [28]	13% 5.7%	Degeneration of the axons, time-dependent, due to the DM1 component Systemic release of payload

This table includes all the ADCs discussed in this review (approved and under development) for which toxicity data were available at the time of the last editing (April 2021)

Ferraro et al. Breast Cancer Research 2021; 23: 84

Phase Ib trial

original reports

Antitumor Activity and Safety of Trastuzumab Deruxtecan in Patients With HER2-Low–Expressing Advanced Breast Cancer: Results From a Phase Ib Study

Shanu Modi, MD[1]; Haeseong Park, MD, MPH[2]; Rashmi K. Murthy, MD, MBE[3]; Hiroji Iwata, PhD, MD[4]; Kenji Tamura, MD, PhD[5]; Junji Tsurutani, MD, PhD[6]; Alvaro Moreno-Aspitia, PhD[7]; Toshihiko Doi, MD, PhD[8]; Yasuaki Sagara, MD[9]; Charles Redfern, MD[10]; Ian E. Krop, MD, PhD[11]; Caleb Lee, MD, PhD[12]; Yoshihiko Fujisaki, MS[13]; Masahiro Sugihara, PhD[13]; Lin Zhang, MD, PhD[12]; Javad Shahidi, MD[12]; and Shunji Takahashi, MD[14]

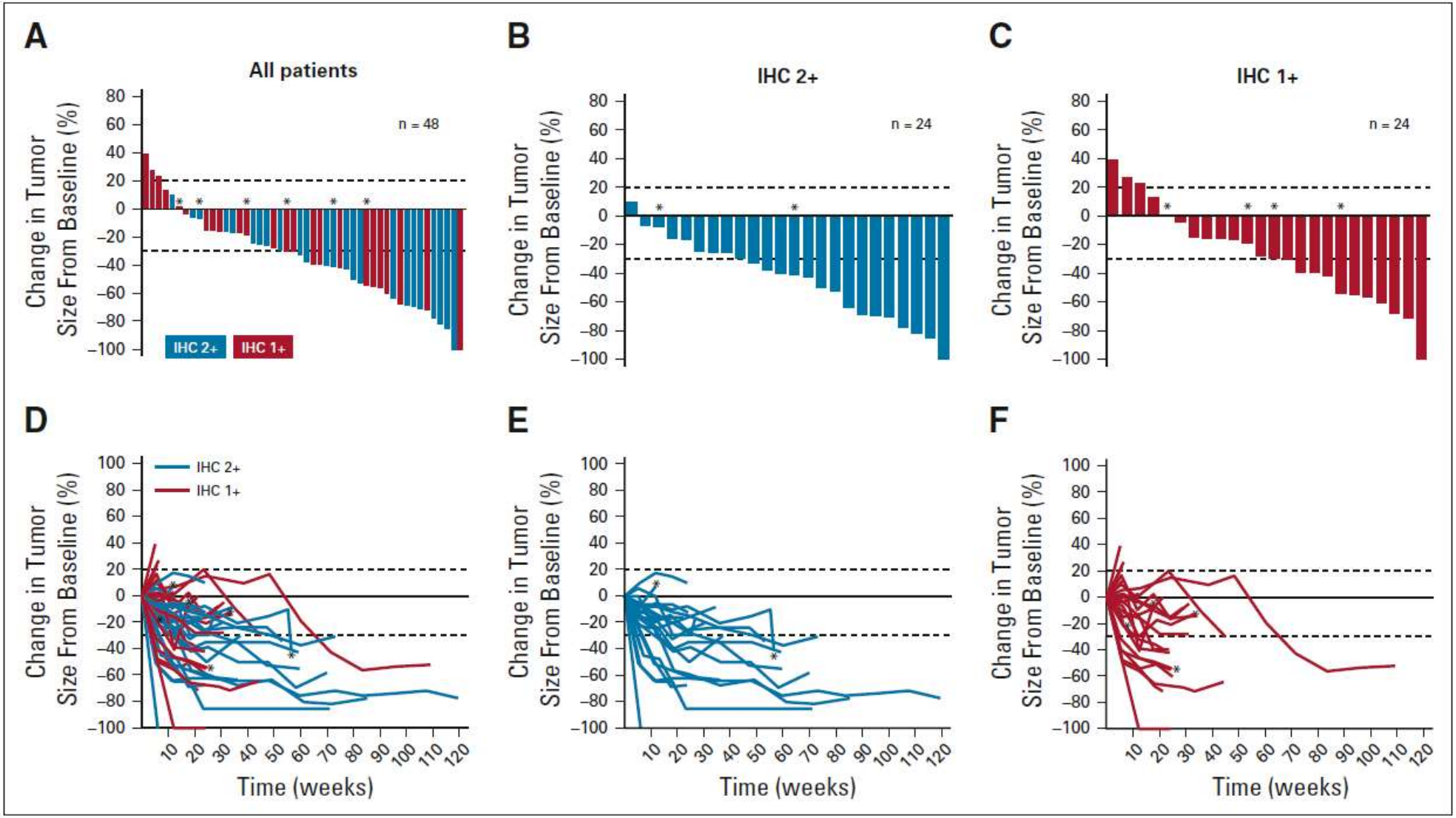
Veelbelovende preliminaire antitumor activiteit in patiënten met HER2 low borstkanker

CAVE : toxiciteit!

➔ Meestal gastro-intestinaal en hematologisch

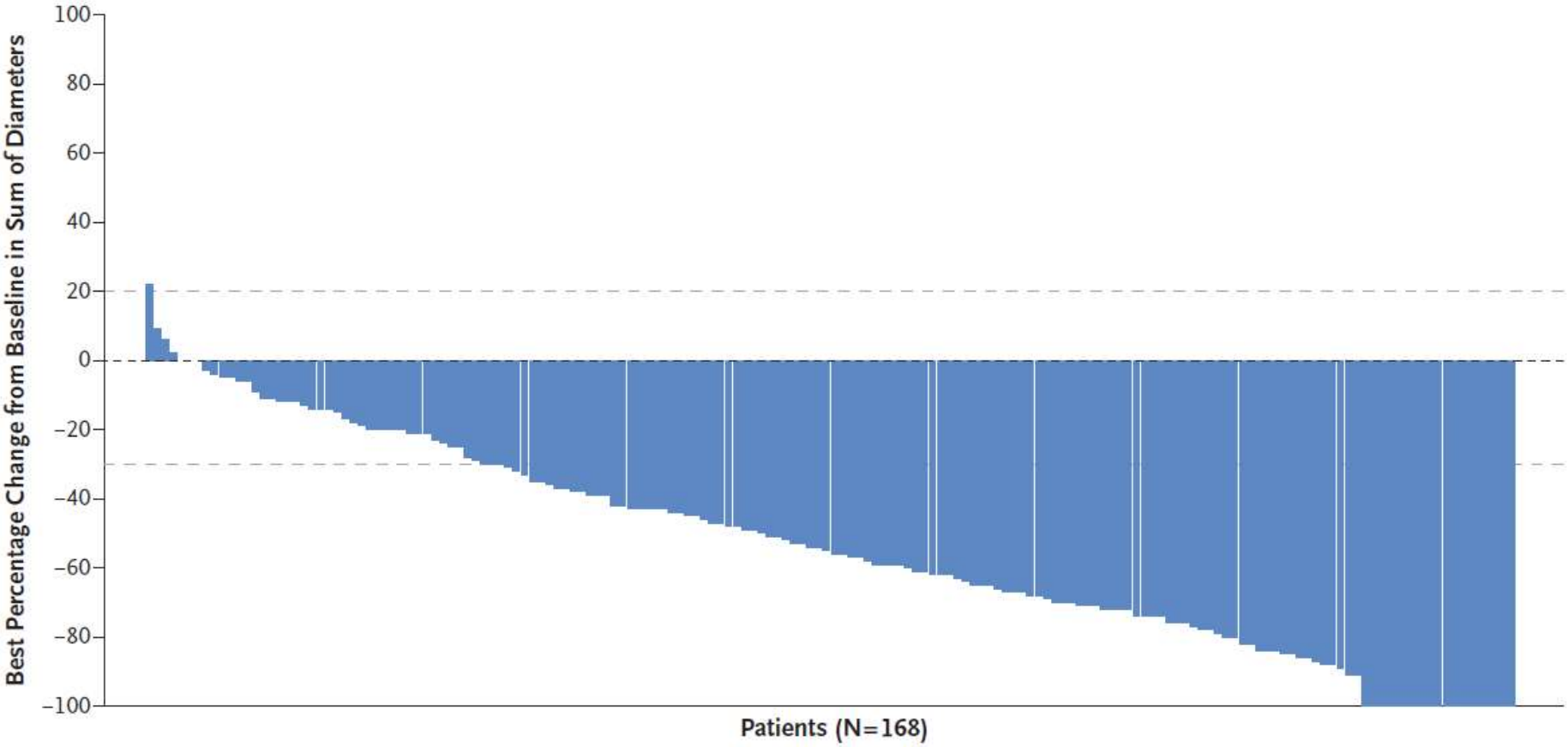
➔ Interstitiële longziekte: zeldzaam maar potentieel dodelijk!

Modi et al. J Clin Oncol 2020; 38:1887-1896



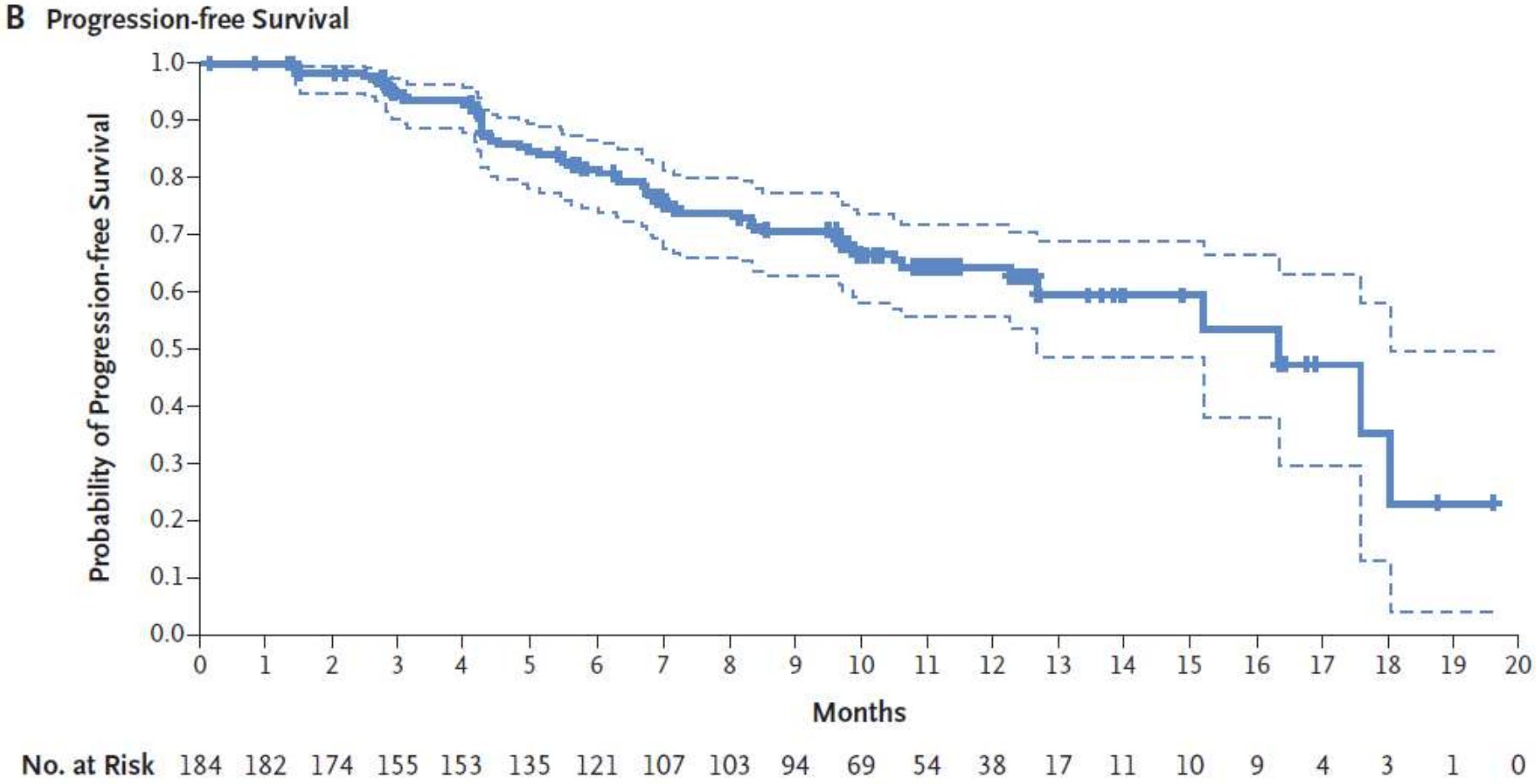
Modi et al. J Clin Oncol 2020; 38:1887-1896

Phase 2 study : DESTINY-Breast01



Modi et al. N Engl J Med 2020; 382:7

Phase 2 study : DESTINY-Breast01



Modi et al. N Engl J Med 2020; 382:7

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 7, 2022 VOL. 387 NO. 1

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

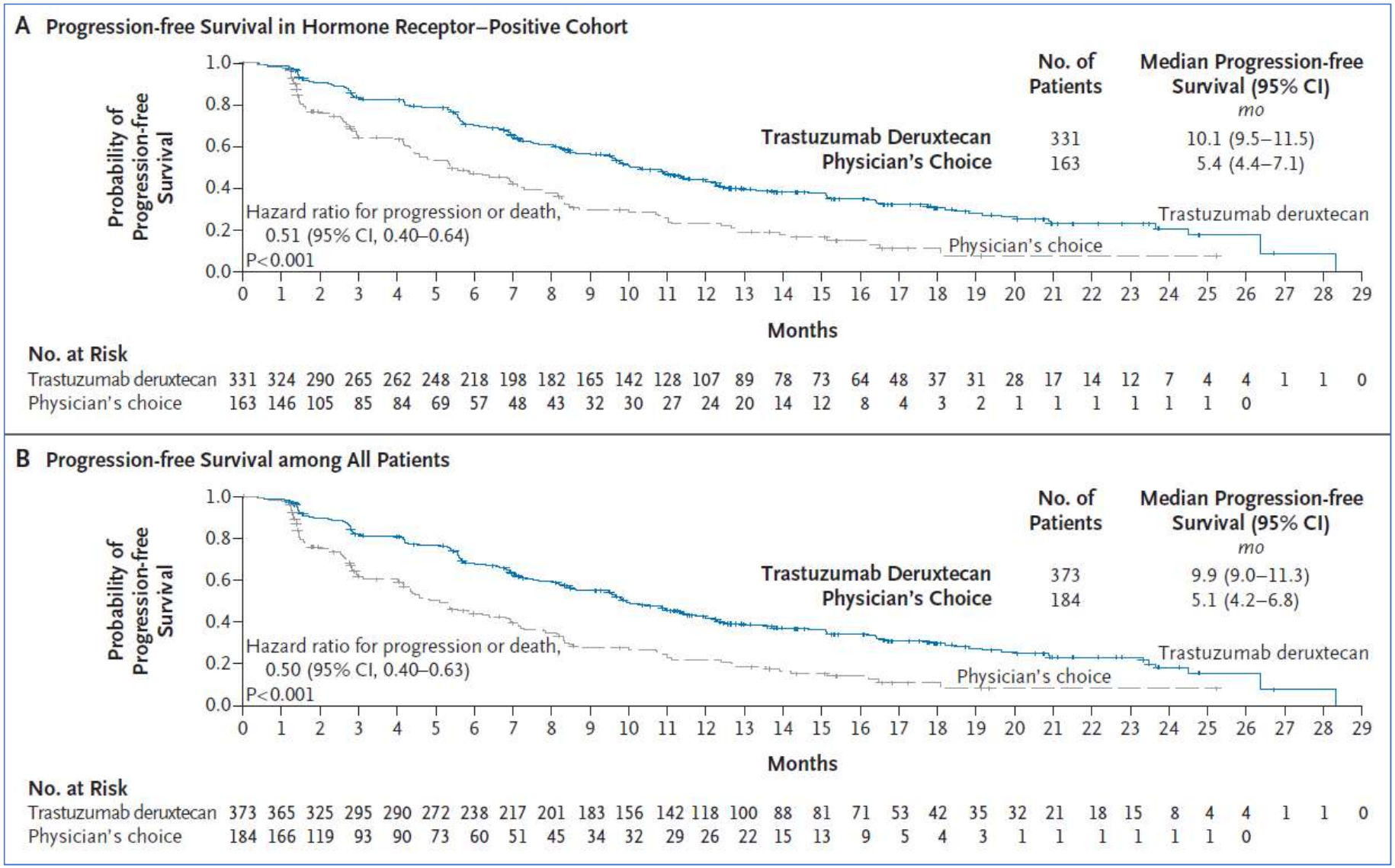
ABSTRACT

BACKGROUND

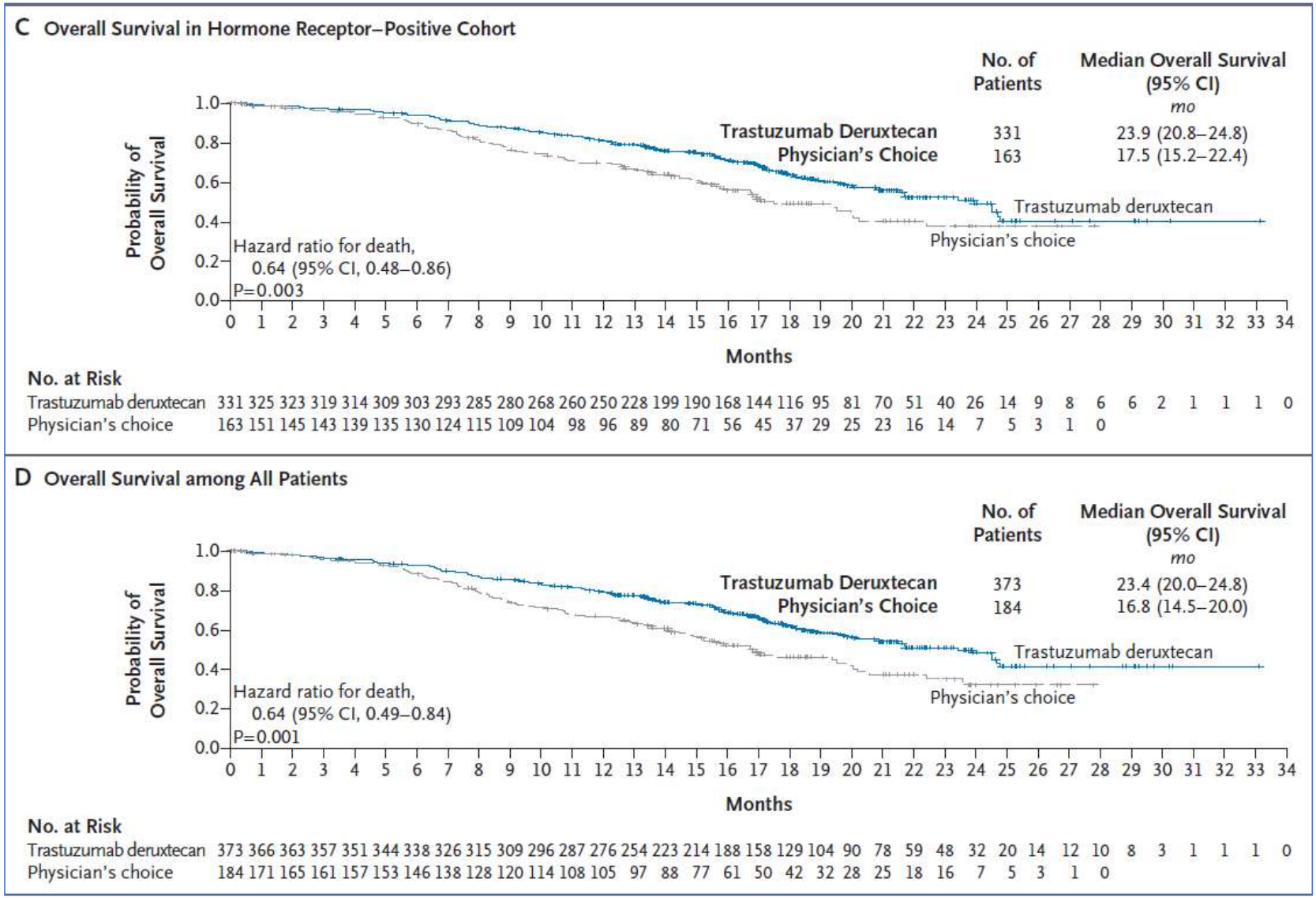
Among breast cancers without human epidermal growth factor receptor 2 (HER2) amplification, overexpression, or both, a large proportion express low levels of HER2 that may be targetable. Currently available HER2-directed therapies have been ineffective in patients with these "HER2-low" cancers.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Modi can be contacted at modis@mskcc.org or at the Memorial Sloan Kettering Cancer Center, 1275 York

Modi et al. N Engl J Med 2022; 387(1):9-20



Modi et al. N Engl J Med 2022; 387(1):9-20



Modi et al. N Engl J Med 2022; 387(1):9-20

Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials

Carsten Denkert, Fenja Seither, Andreas Schneeweiss, Theresa Link, Jens-Uwe Blohmer, Marianne Just, Pauline Wimberger, Almuth Forberger, Hans Tesch, Christian Jackisch, Sabine Schmatloch, Mattea Reinisch, Erich F Solomayer, Wolfgang D Schmitt, Claus Hanusch, Peter A Fasching, Kristina Lübbe, Christine Solbach, Jens Huober, Kerstin Rhiem, Frederik Marmé, Toralf Reimer, Marcus Schmidt, Bruno V Sinn, Wolfgang Janni, Elmar Stickeler, Laura Michel, Oliver Stötzer, Eric Hahnen, Jenny Furlanetto, Sabine Seiler, Valentina Nekljudova, Michael Untch, Sibylle Loibl

Summary

Background The development of anti-HER2 antibody–drug conjugates opens new therapeutic options for patients with breast cancer, including patients with low expression of HER2. To characterise this new breast cancer subtype, we have compared the clinical and molecular characteristics of HER2-low-positive and HER2-zero breast cancer, including response to neoadjuvant chemotherapy and prognosis.

Lancet Oncol 2021; 22: 1151–61

Published Online
July 9, 2021
https://doi.org/10.1016/S1470-2045(21)00301-6

Denkert et al. Lancet Oncol 2021; 22:1151-1161

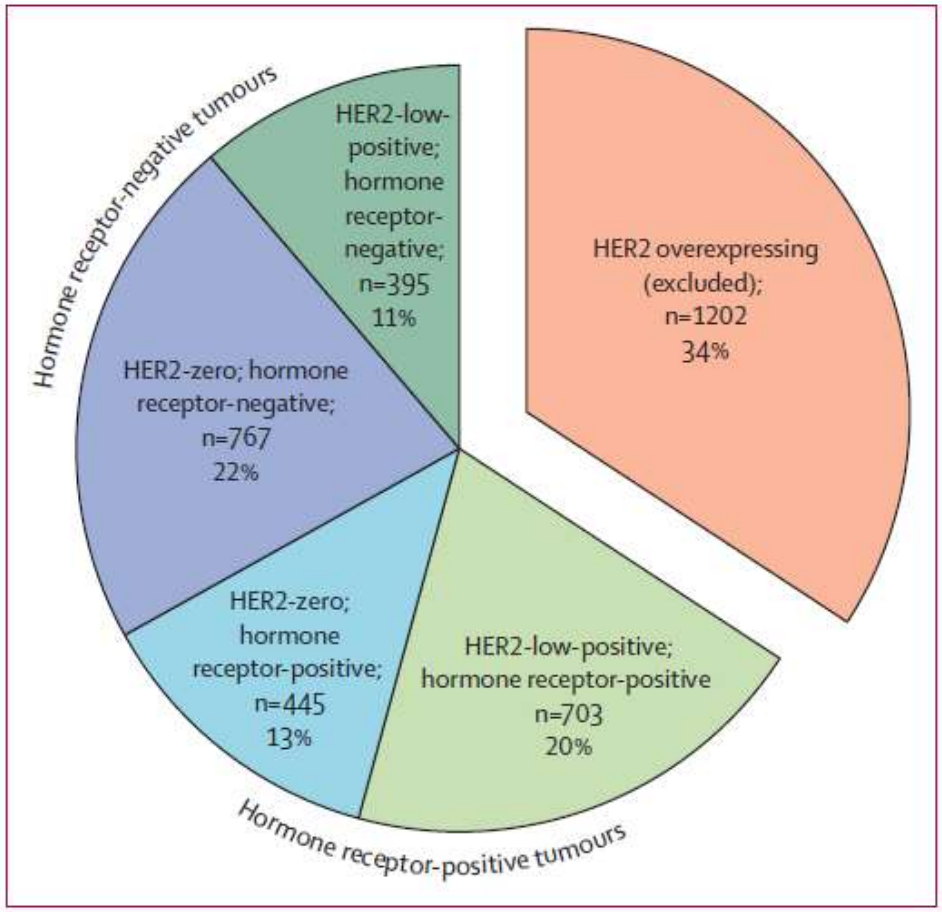


Figure 1: Modified classification of breast cancer based on a combination of hormone-receptor expression and HER2 expression

Denkert et al. Lancet Oncol 2021; 22:1151-1161

Patiënten uit 4 studies :

- GeparSepto
- GeparOcto
- GeparX
- Gain-2 neoadjuvant

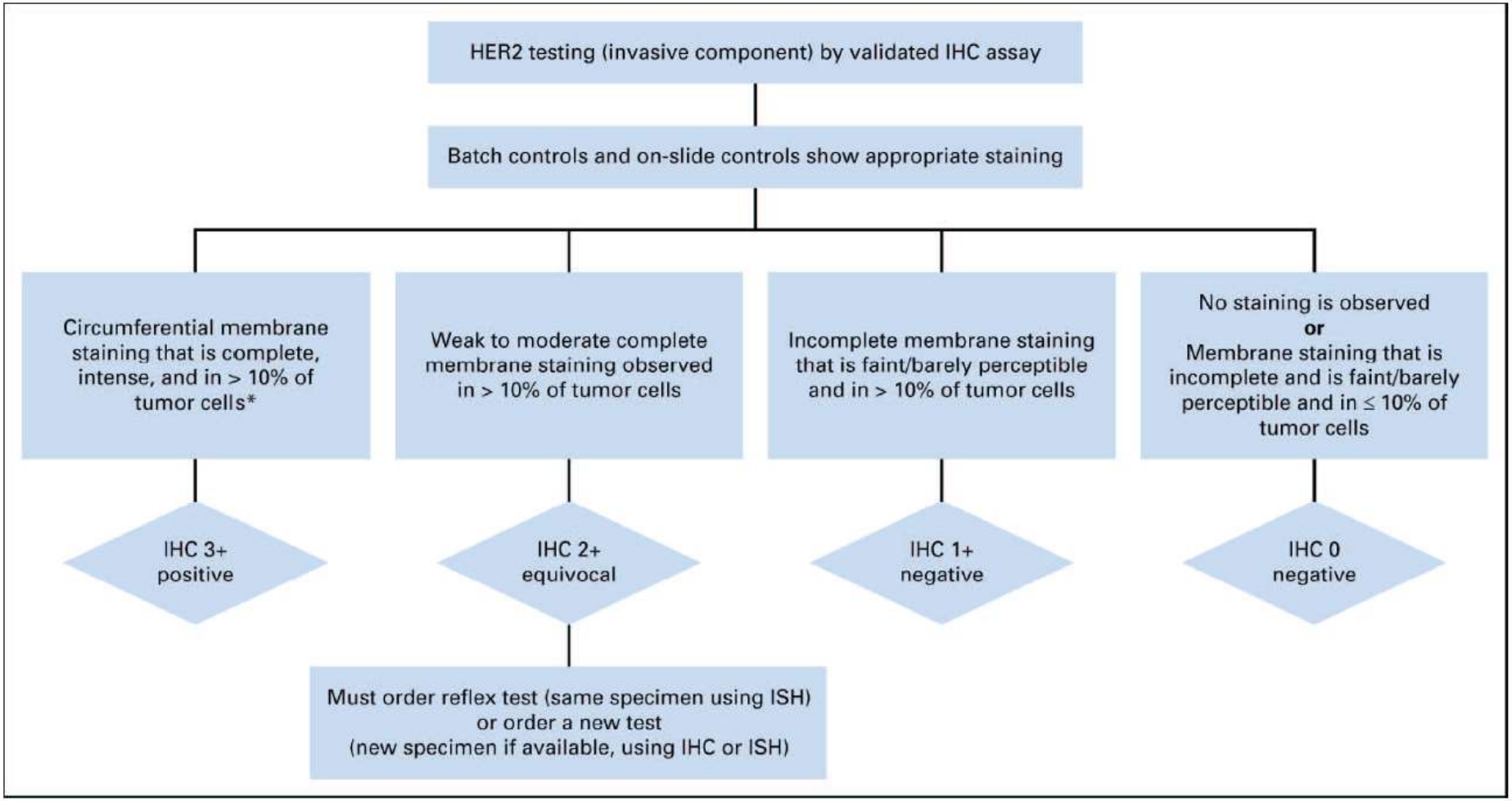
pCR was significant lager in HER2-low tumoren versus HER2-zero tumoren in de hormoonreceptor-positieve subgroep, maar niet in de hormoonreceptor-negatieve subgroep.

Retrospectieve analyse

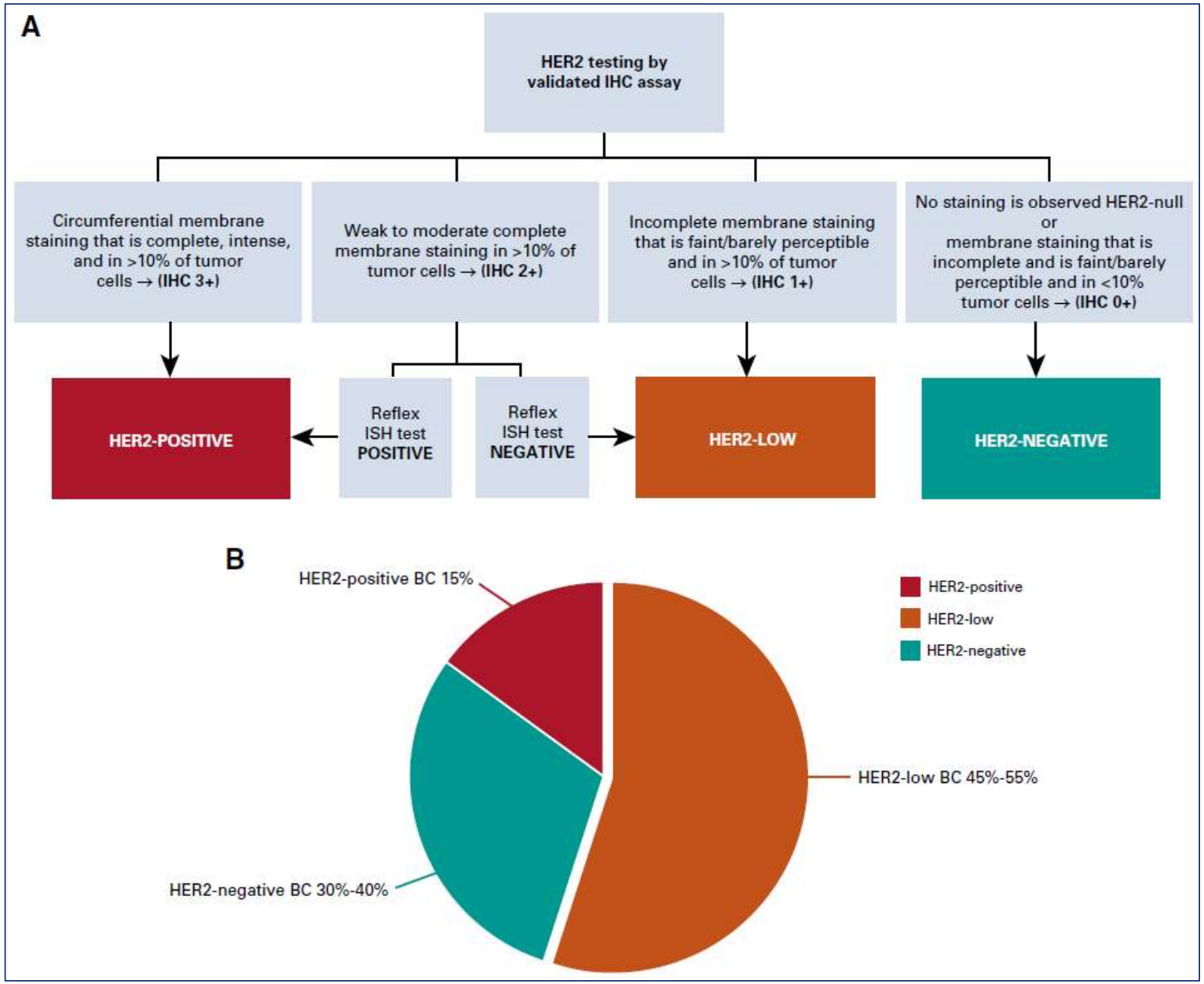
	HER2-zero	HER2-low
Mediane leeftijd (jaar)	48	49
Hormoonreceptor status	*63% negatief*	*36% negatief*
Nottingham graad	*72% graad 3*	*60% graad 3*
No special type carcinoom	85%	84%
Mediane Ki-67 (%)	*51%*	*40%*
Mediane TILs	20%	15%
cN0 stadium	65%	60%

Patiënten met HER2-low tumoren hadden een significant langere overleving dan patiënten with HER2-zero tumoren: 3-jaar ziektevrije overleving 83% versus 76%.

Denkert et al. Lancet Oncol 2021; 22:1151-1161



Arch Pathol Lab Med 2018; 142: 1364-1382



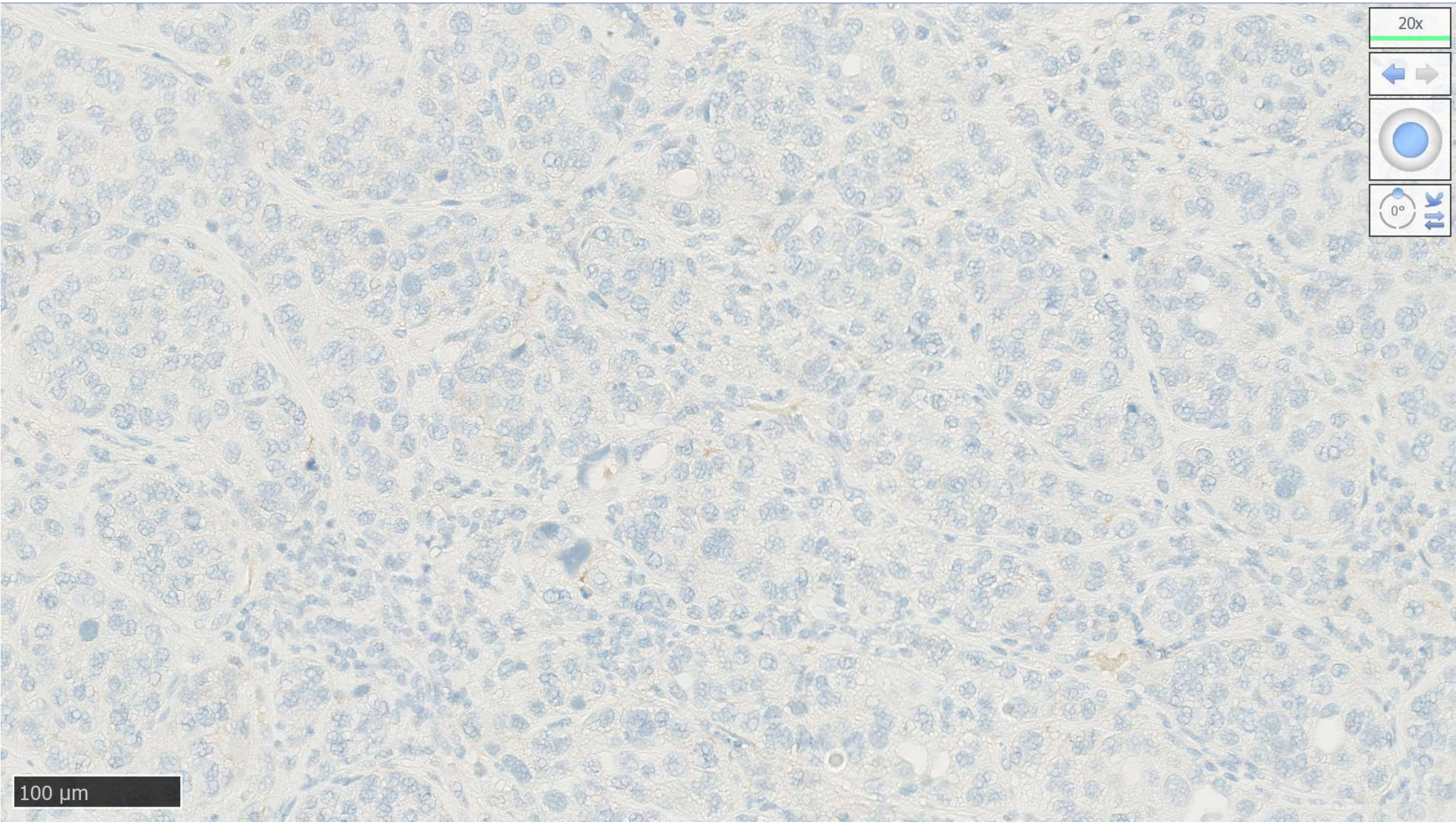
Tarantino et al. J Clin Oncol 2020; 38(17):1951-1962

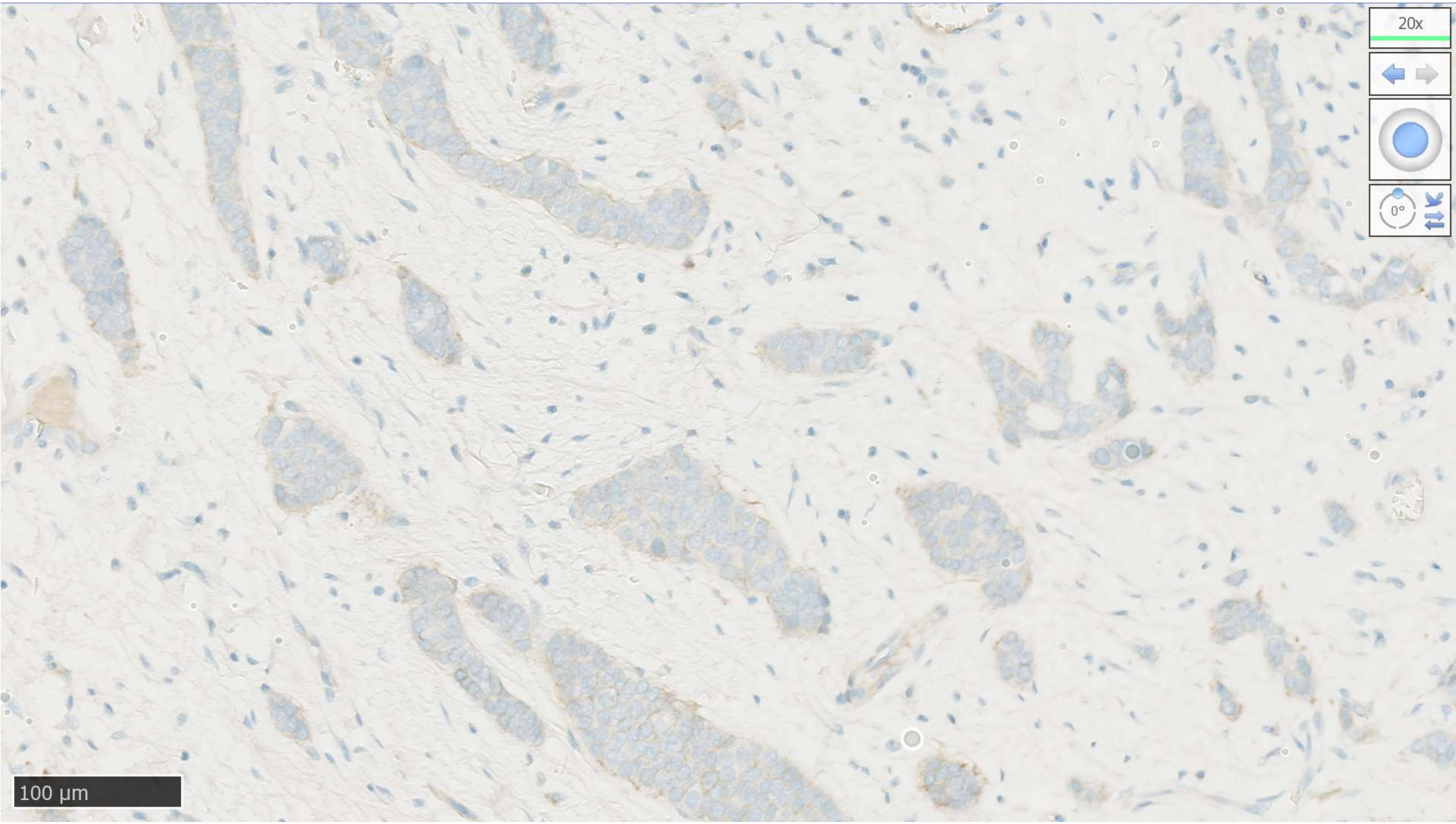
2013 verandering in definitie van score 0 versus 1+

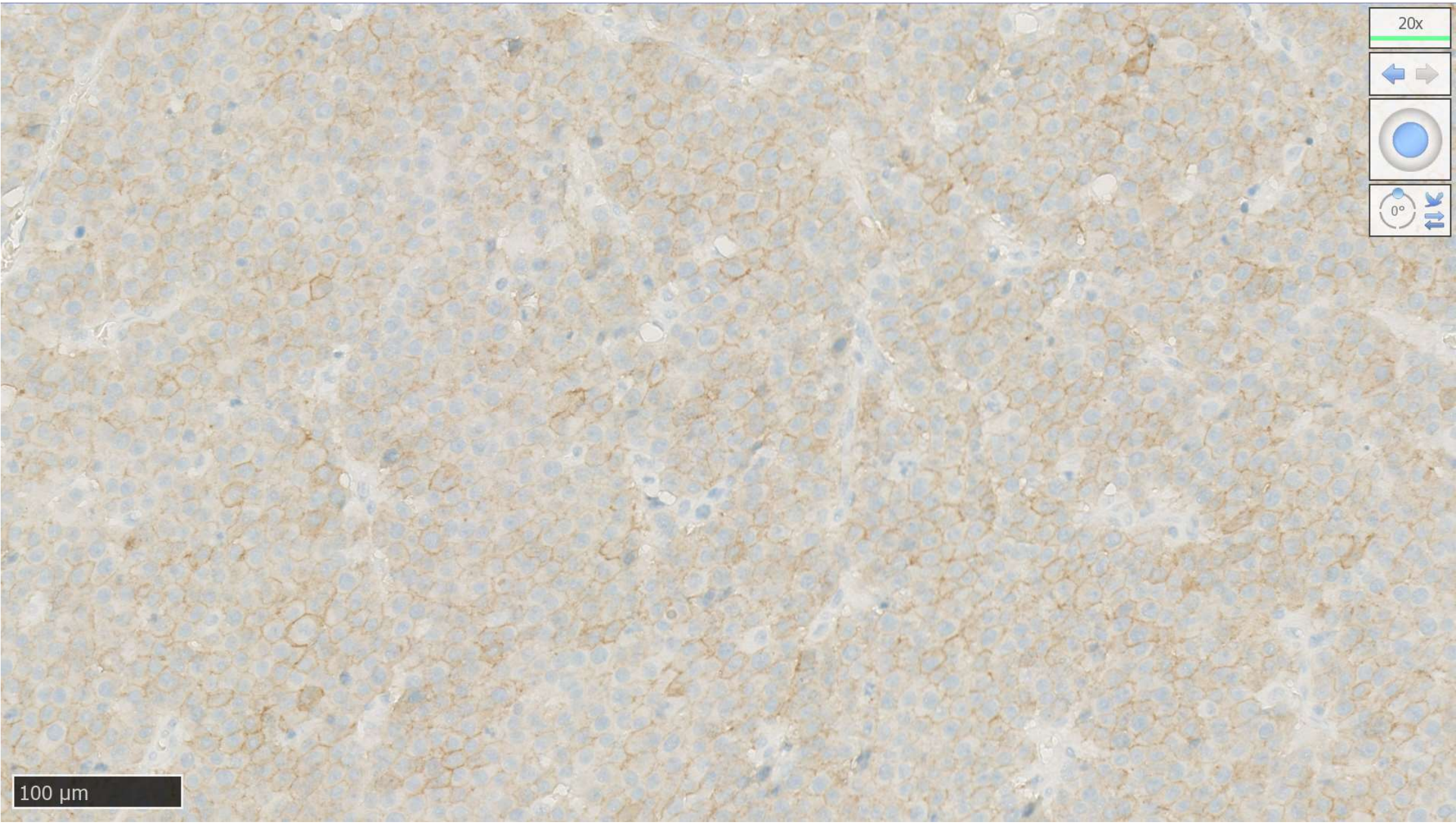
cap

ASCO GUIDELINES

Topic	2007 Recommendation	2013 Recommendation
	Negative for HER2 is defined as: • IHC HER2 0: no staining • IHC HER2 1+: Weak incomplete membrane staining in any proportion of tumor cells or weak, complete membrane staining in <10% of cells • FISH *HER2*/CEP17 ratio of < 1.8 or average *HER2* gene copy number of < 4 signals/nucleus for test systems without an internal control probe	Must report a **HER2 test result as negative** if a single test (or both tests) performed show:[a,b] • IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cells[d] • IHC 0 as defined by no staining observed[d] or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumor cells[d] • ISH negative based on: Single-probe average *HER2* copy number <4.0 signals/cell Dual-probe *HER2*/CEP17 ratio <2.0 with an average *HER2* copy number <4.0 signals/cell


20x
0°
100 µm

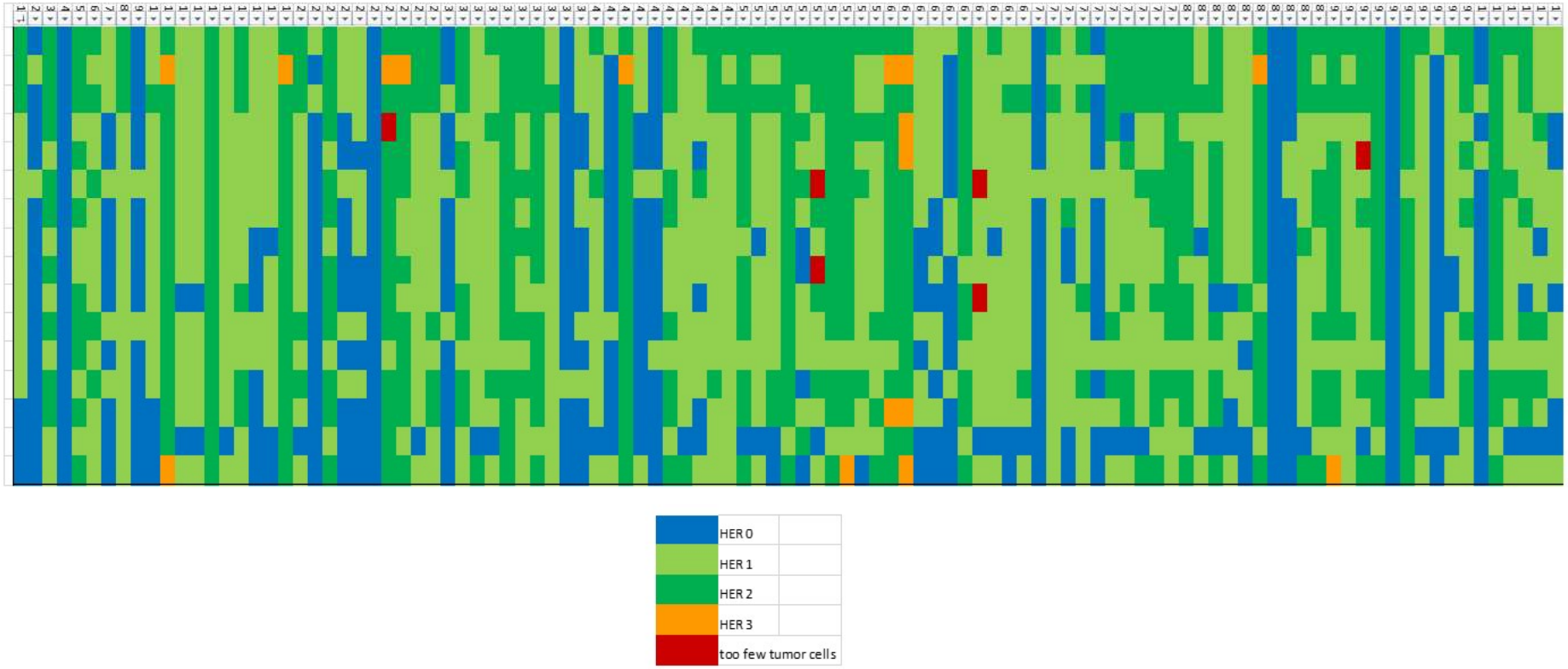

20x
0°
100 µm


20x
0°
100 µm

ROUND 1

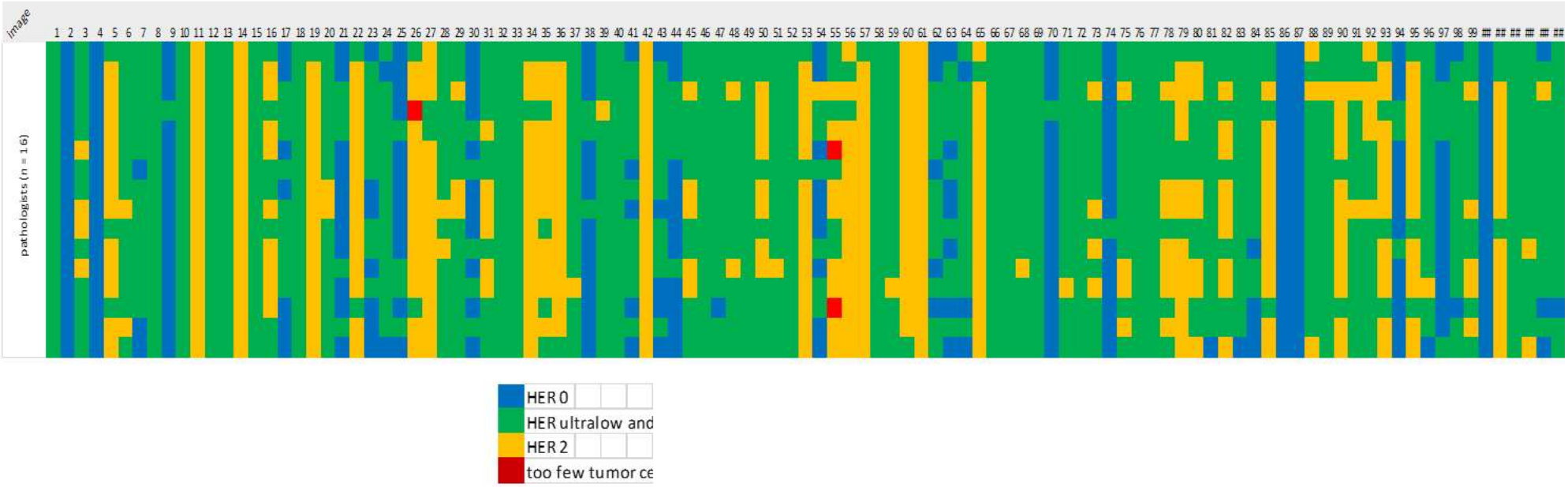
Houston, we have a problem!

Accepted for publication in Modern Pathology – by Ximena Baez et al.



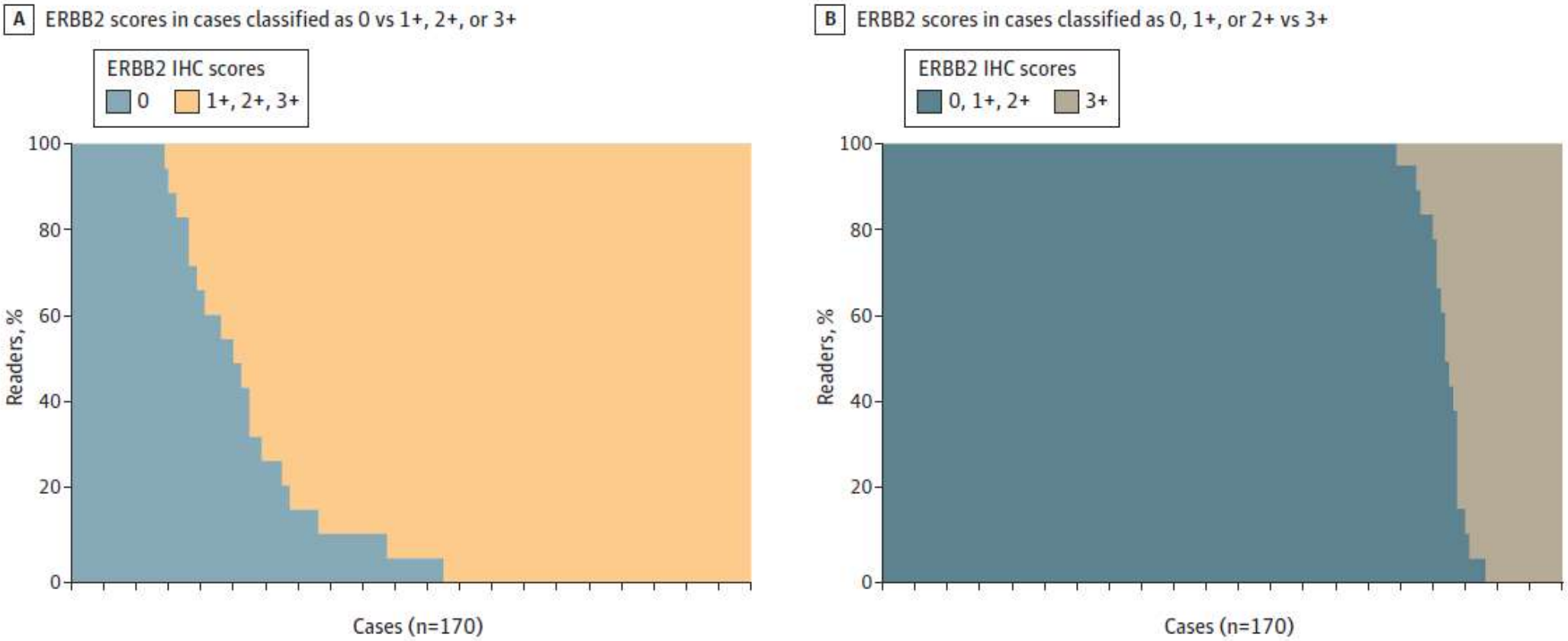
ROUND 2

Heatmap pathologist x case score (ultralow and 1+ together)



Moeten we overstappen naar de 2007 IHC guidelines?

Erasmus MC



A, Each case (on the x-axis) is shown as the percentage of observers who called the case ERBB2 0 vs ERBB2 1+, 2+, or 3+. B, Each case (on the x-axis) is shown as the percentage of observers who called the case ERBB2 3+ vs ERBB2 0, 1+, or 2+.

Fernandez et al. JAMA Oncology 2022; 8(4): 607-610

Oplossingen voor inter-observer variabiliteit

1. Meer training?
2. Strengere criteria ivm wie HER2 IHC mag aflezen?
3. Overstap naar de ‘oude’ 2007 IHC guidelines voor score 0 versus 1+ ?
4. Evaluatie door meerdere pathologen / panel?
5. Hoeveel discordantie is te tolereren?
6. Switch naar andere test voor bepaling van HER2-low status?
7. Artificiële intelligentie?

DESTINY BREAST-06 trial

- 2 onafhankelijke ‘open label’ therapie-armen:
  - Trastuzumab deruxtecan
  - Investigator's choice chemotherapie (paclitaxel, nab-paclitaxel or capecitabine).

- Primair eindpunt : progressie-vrije overleving
- Studie startdatum : 24 juli 2020
- Geschat einde van de studie : 19 juni 2026

- Inclusie:
  - Patiënten met ziekteprogressie tijdens minstens 2 voorafgaande lijnen van endocriene therapie voor metastatische ziekte.
  - Ziekteprogressie binnen 6 maanden na de start van een eerste lijn therapie voor metastatische ziekte met endocriene therapie in combinatie met een CDK4/6 inhibitor.

Aanpak op de werkvloer

- Moet er opnieuw getest (= gekleurd) worden?
- Is een historisch HER2-low resultaat voldoende bij een recente HER2-score 0 metastase?
- Op hoeveel stalen moeten we HER2 IHC uitvoeren?
- Cave HER2 heterogeniteit?

Samenvatting

Onderscheid tussen score 0, score 1+ en score 2+ is belangrijk!

Rapporteer HER2 status niet als ‘positief’ versus ‘negatief’.

➔ Vermeld de precieze HER2 IHC score.

Nog veel onbeantwoorde vragen over beoordeling van HER2 low status in de dagelijkse praktijk ➔ nood aan praktische richtlijnen!