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HER2-LOW BREAST CANCER: EVOLUTION FROM PRIMARY BREAST CANCER TO RD AFTER NACT

F. Miglietta, G. Griguolo, M. Bottosso, T. Giarratano, M. Lo Mele, M. Fassan, M. Cacciatore, E. Genovesi, D. De Bartolo, G. Vernaci, PF. Conte, V. Guarneri, and MV. Dieci

UNIVERSITÀ DEGLI STUDI DI PADOVA

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ARTICLE OPEN

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HER2-low-positive breast cancer: evolution from primary tumor to residual disease after neoadjuvant treatment

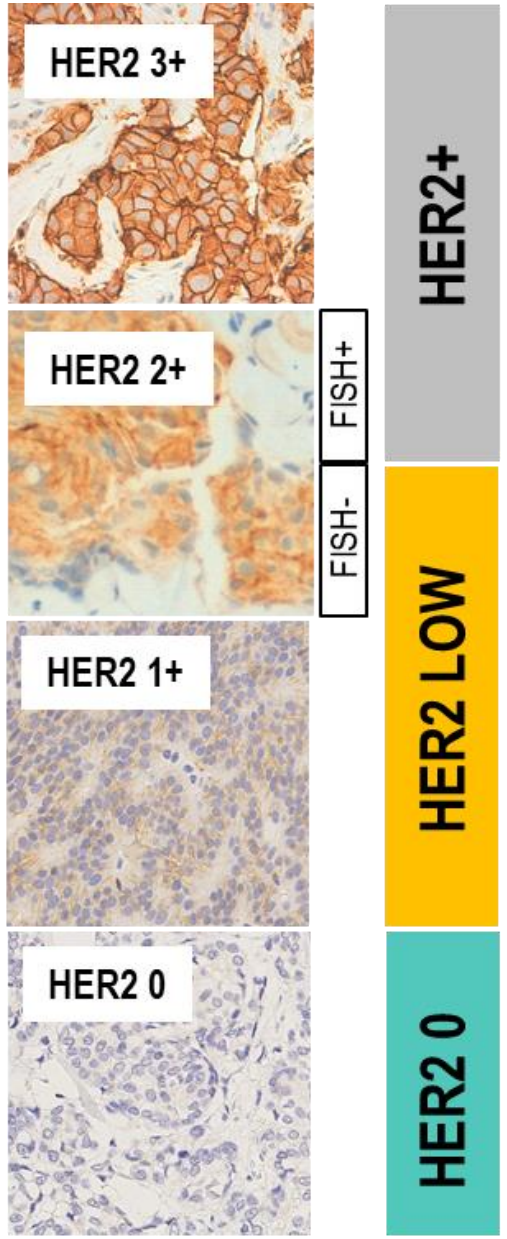
Federica Miglietta[1,2], Gaia Griguolo[1,2], Michele Bottosso[1,2], Tommaso Giarratano[2], Marcello Lo Mele[3], Matteo Fassan[4,5], Matilde Cacciatore[6], Elisa Genovesi[1,2], Debora De Bartolo[4], Grazia Vernaci[1,2], Ottavia Amato[1,2], Francesca Porra[1,2], PierFranco Conte[1,2], Valentina Guarneri[1,2]✉ and Maria Vittoria Dieci[1,2]

BACKGROUND

- In the past decades access to anti-HER2 drugs has been driven by the **dichotomy between HER2-positive and HER2-negative** breast cancer established in the context of pivotal trials of trastuzumab
  - HER2+ BC: defined as IHC score 3+ and/or HER2 gene amplification by ISH[1].

- Results from the **phase III DESTINY-Breast04 trial[2]** revolutionized this dogma by demonstrating a high efficacy of T-DXd in patients traditionally classified as HER2-negative but showing low levels of HER2 expression
  - HER2-low BC: defined as IHC score 1+ or 2+ in the absence of gene amplification by ISH

- It has been consistently reported that **HER2-low expression is highly unstable from primary to recurrent BC[3,4]**
  - No data is available regarding the evolution of HER2-low expression under neoadjuvant treatment exposure



Courtesy of *Dr M. Lo Mele, MD*, Pathology Unit Padova Hospital, Italy

1. Wolff et al, 2018; 2. Modi et al, NEJM 2022; 3. Miglietta et al, NPJ BC 2021; 4. Tarantino et al, EJC 2022

METHODOLOGY

AIM

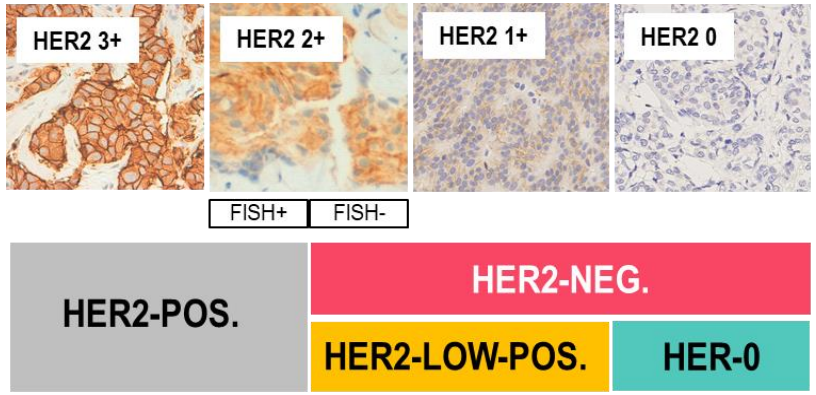
- **To describe the evolution of HER2-LOW expression from baseline biopsy to residual disease (RD) in patients undergoing neoadjuvant chemotherapy (NACT).**

METHODS

- Patients with samples of **primary BC and matched RD** were included.

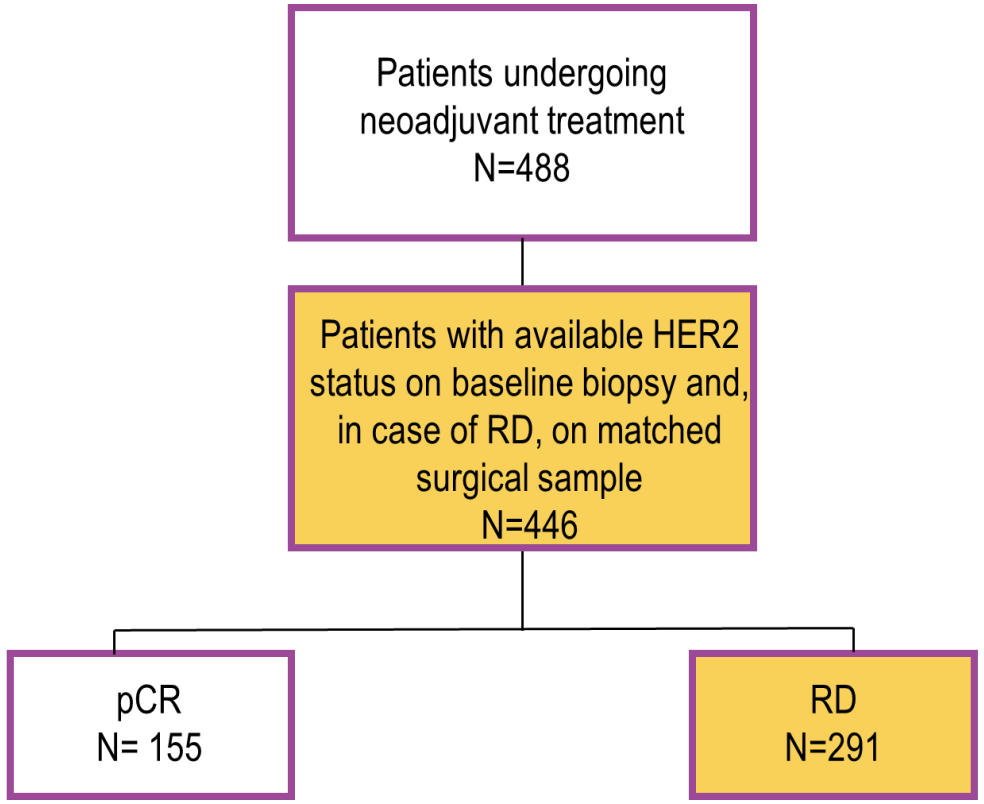
- **HER2 status was evaluated according to ASCO/CAP recommendations** in place at the time of diagnosis, with 10% cutoff for IHC applied (cases diagnosed between 2007-2013 reviewed to comply with this cutoff)

- HER2-neg cases were sub-classified as:
  - **HER2-LOW**: IHC 1+ or IHC 2+ and ISH NOT-amplified
  - HER2 0: score 0 by IHC.



RESULTS

Patients' features

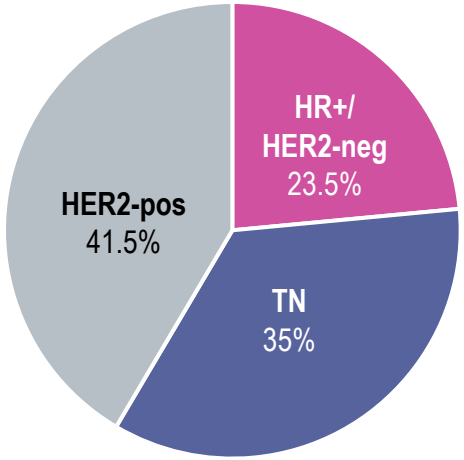


Age, median	50.2 (Q1-Q3: 42.7-60.2)		
Histology	**Ductal of No Special Type**	397	89.0%
	Lobular	28	6.3%
	Other/NA	21	4.7%
Grading	**1**	4	0.9%
	2	89	20.0%
	3	316	70.9%
	NA	37	8.2%
Clinical TNM	**I**	21	4.7%
	II	259	58.1%
	III	159	35.7%
	NA	7	1.5%
Neoadj. CT	**Anthra-Tax**	354	79.4%
	Tax	68	15.2%
	Anthra	9	2.0%
	Other/NA	15	3.4%
Neoadj. anti-HER2	**Trastuzumab**	160	35.9%
Pathologic response	**pCR**	155	34.8%
	RD	291	65.2%

RESULTS

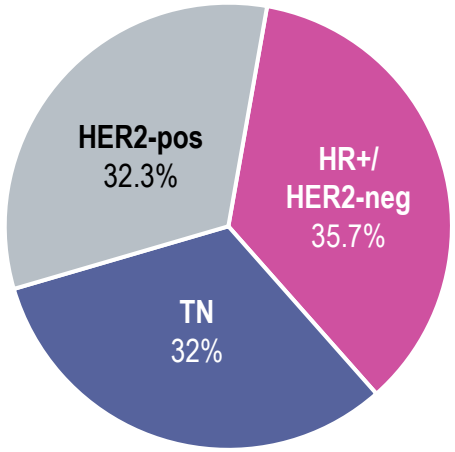
Tumor phenotype

PRIMARY BC



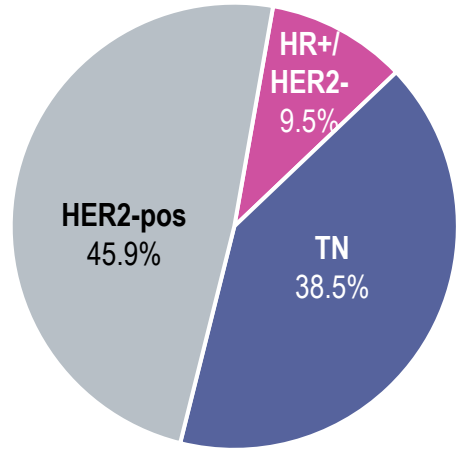
HER2-LOW+ 55.6%*	*p*
68.6%	*0.001*
46.8%	

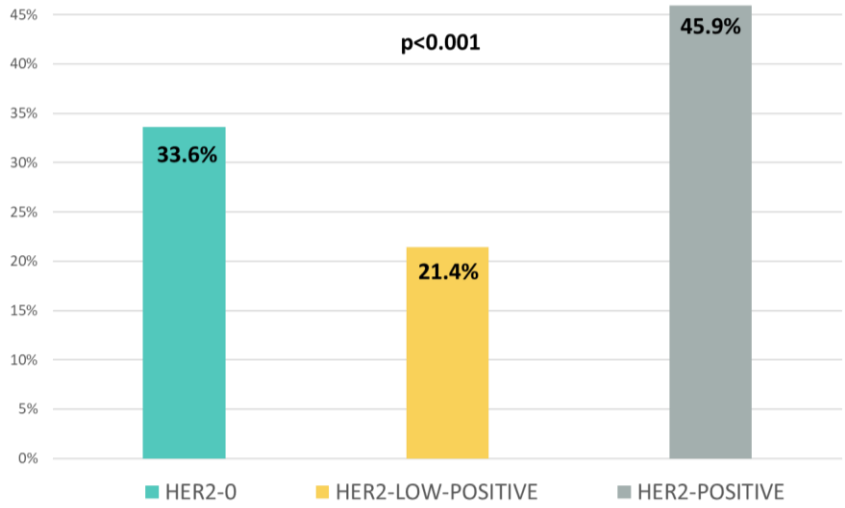
RD



HER2-LOW+ 52.3%*	*p*
65.4%	*<0.001*
36.6%	

pCR rates





RESULTS

HER2-low high-risk subgroup

TNBC

		HER2-0, n (%)	HER2-LOW, n(%)	p-value
Pathologic response	pCR	42.2%	34.2%	0.327
	RD	58.8%	**65.8%**	

HR+/HER2- BC

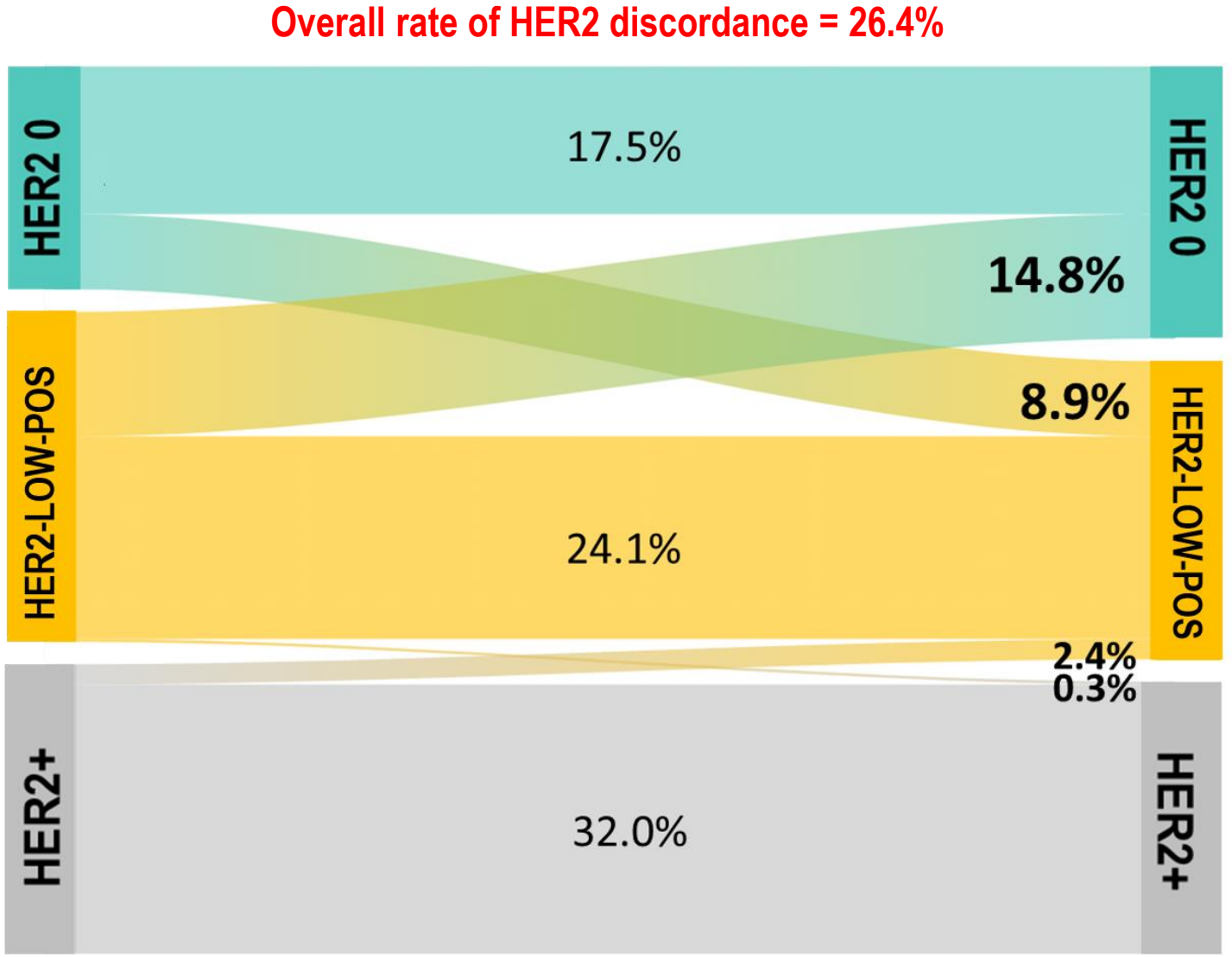
		HER2-0, n (%)	HER2-LOW, n(%)	p-value
RPCB[1,2]	Class<3	20.0%	48.6%	1,00
	Class=3	8.6%	**22.9%**	
CPS-EG[3]	<3	13.1%	28.6%	0,81
	≥3	20.2%	**38.1%**	

RPCB: residual proliferative cancer burden

1. Sheri et al, Ann Oncol 2015; 2. Miglietta et al, The Oncologist 2018; 3. Marmé et al, EJC 2016

RESULTS

HER2-low BC evolution



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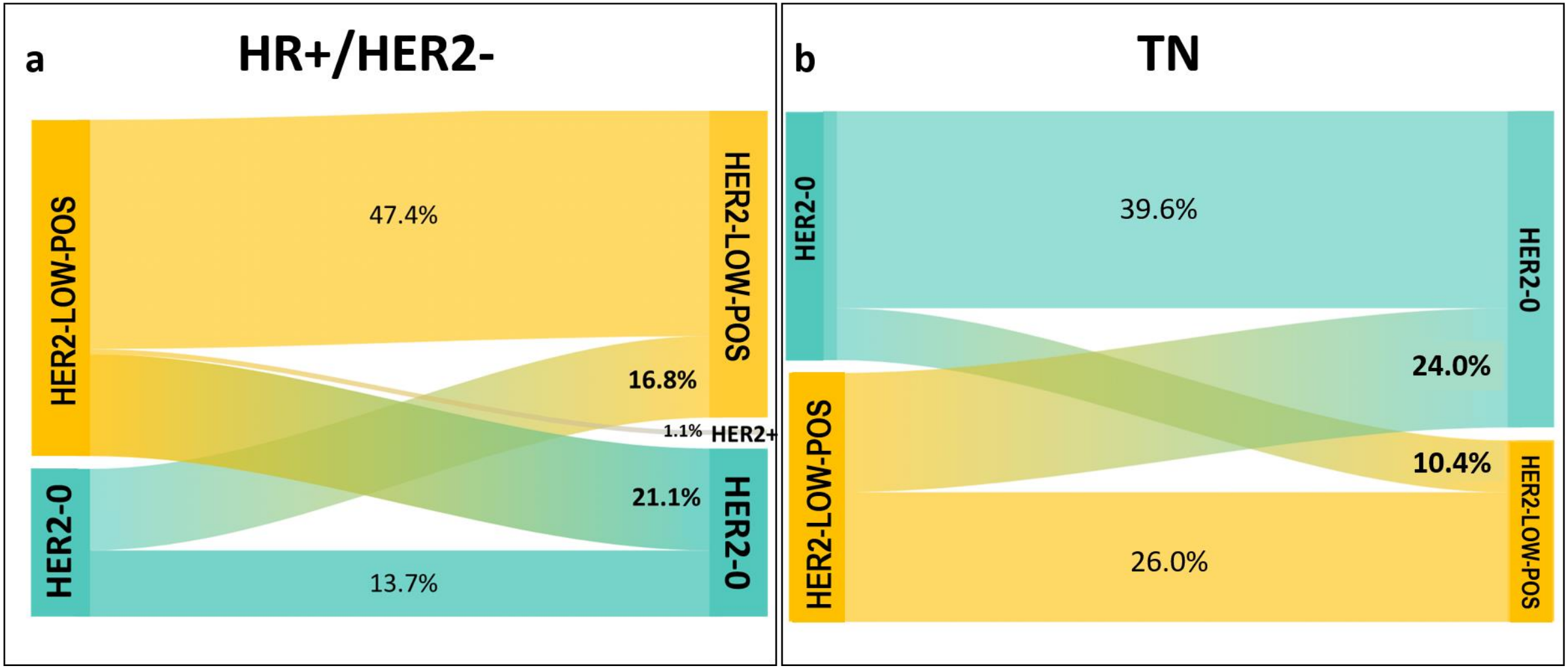
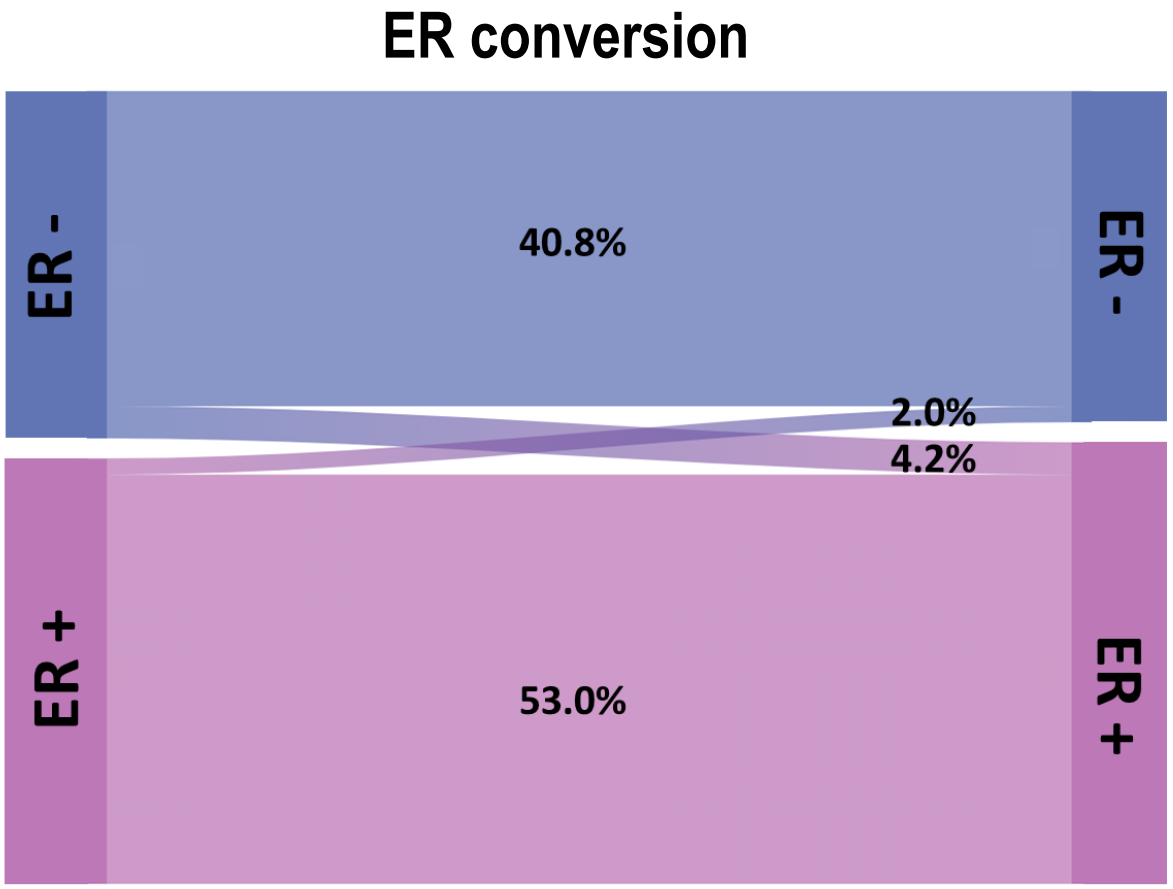
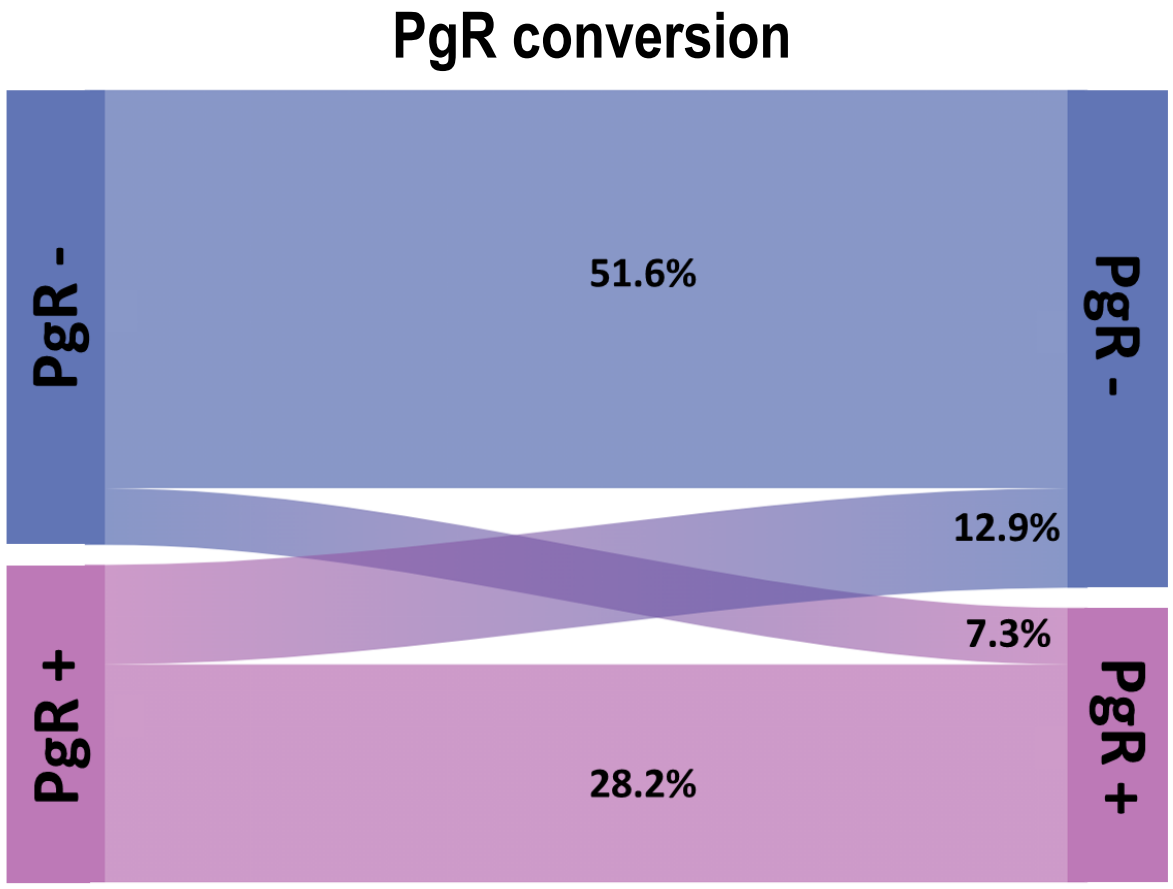
HER2-low BC evolution



RESULTS

HR status evolution

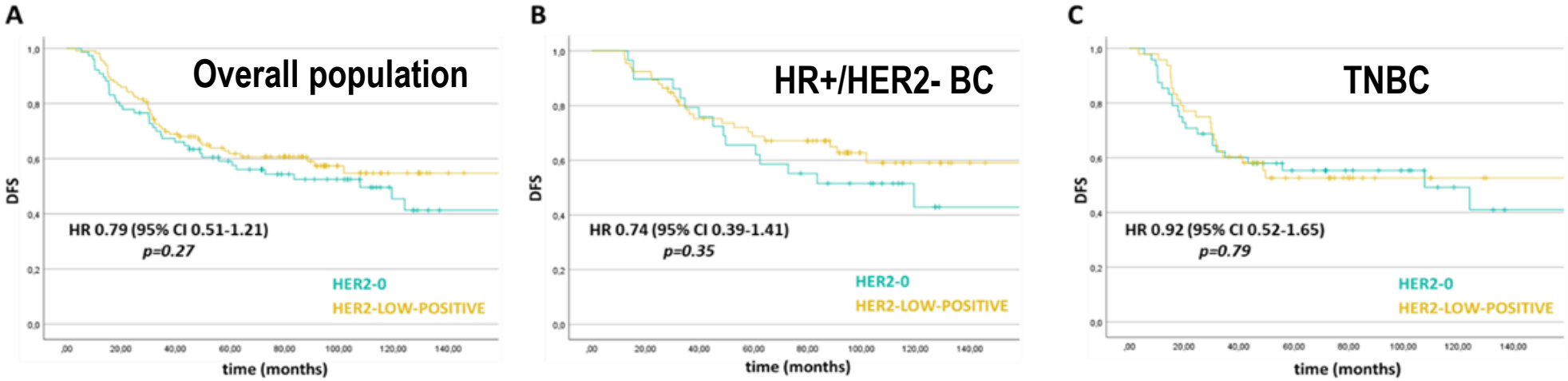




RESULTS

Exploratory survival analysis

DFS according to baseline HER2



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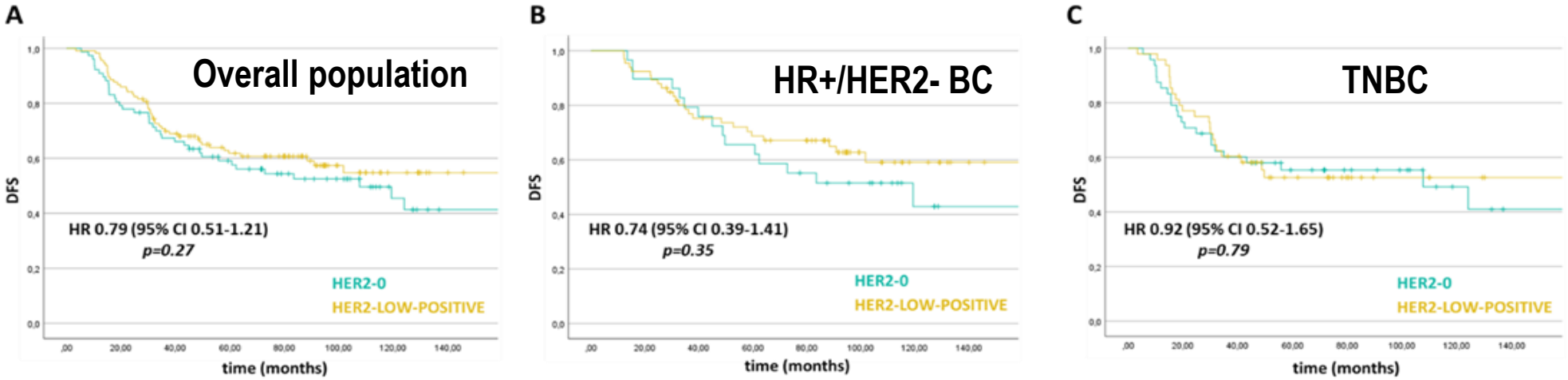
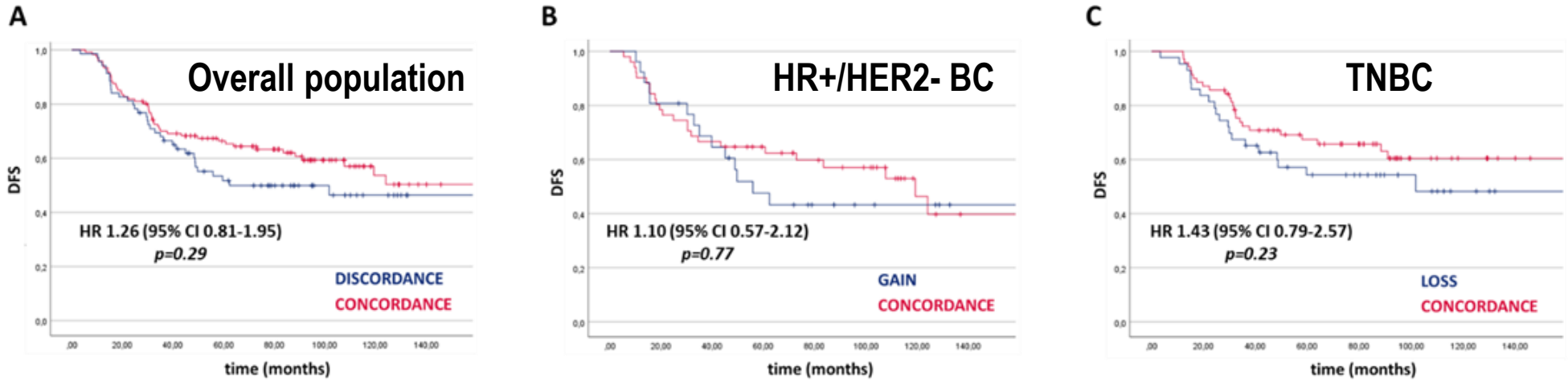


DFS according to HER2 evolution



DISCUSSION

We confirmed the **strong relationship between HER2-low breast cancer and HR-positive status.**

Possible crucial role or ER signaling in shaping HER2-low BC biology

Significantly **lower pCR rates in patients with HER2-low phenotype** as compared to HER-0 driven by HR status.

The major determinant of chemo-sensitivity was HR status rather than HER2 expression

26.4% overall rate of HER2 discordance from baseline biopsies to RD samples and this phenomenon mostly reflected the conversion to or from HER2-low expression.

This solidifies the **great instability of HER2-low expression** in a different setting

Our findings emphasize the **importance of re-assess HER2 status on residual disease**, supporting the inclusion of the HER2-low BC in this evaluation

DISCUSSION

7% of HER2+ BC patients at diagnosis exhibited **HER2-loss**

It is currently largely unknown whether those maintaining some level of HER2 expression (HER2-low-positive subgroup) may derive greater advantage by the administration of novel anti-HER2 ADCs given post-neoadjuvantly with respect to TDM1

An exploratory survival analysis did not reveal **any significant DFS difference** between HER2-0 vs HER2-low BC

Our results strengthen the notion that HER2-low BC should NOT be considered as a distinct clinical entity from a prognostic point of view

CONCLUSIONS

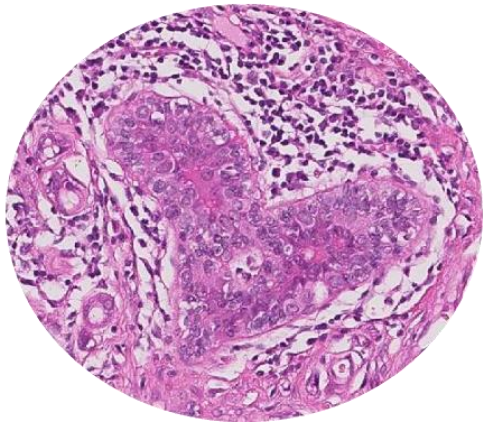
1. The positive results of the DB04 trial will probably drive a rapid **transfer of this experimental scenario in the early setting**

2. The **post-neoadjuvant setting** will probably be given priority

3. **Our findings anticipate the forthcoming and, at that point, imperative need to broaden the pool of patients who may get access to anti-HER2 blockade** as well as proper selecting those who may potentially derive the greatest benefit from these novel strategies

Grazie

Federica Miglietta



federica.miglietta@unipd.it

@FedeMiglietta