bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

20 - 21 APRILE
2023 ROMA

THE HIVE HOTEL

Via Torino, 6

THE OXFORD DEBATE EDITION

Outline

✓The paper

✓The perspective

✓The author

The paper

npj | breast cancer

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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

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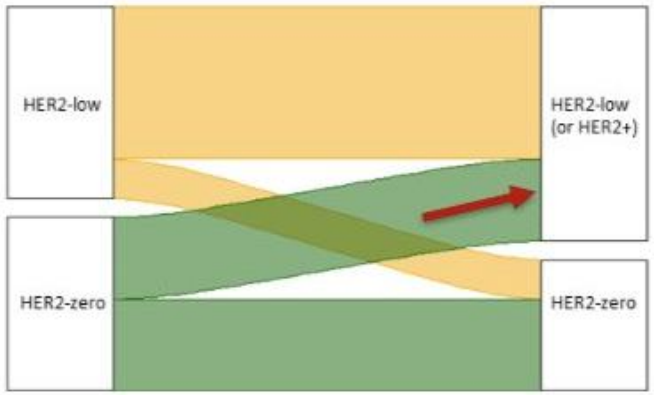
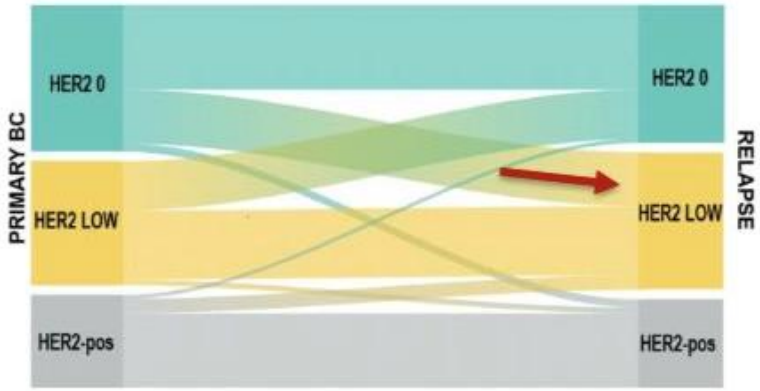
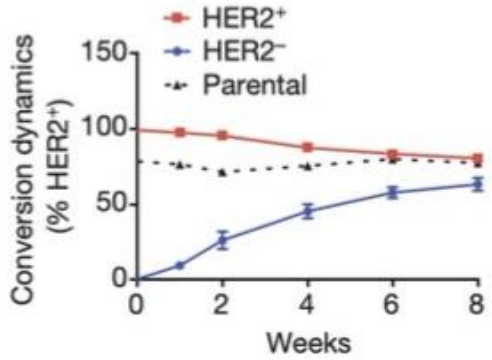
npj Breast Cancer (2022) 66

Backgroud: HER2-low is unstable

HER2-low expression status can change between the early and relapsed setting





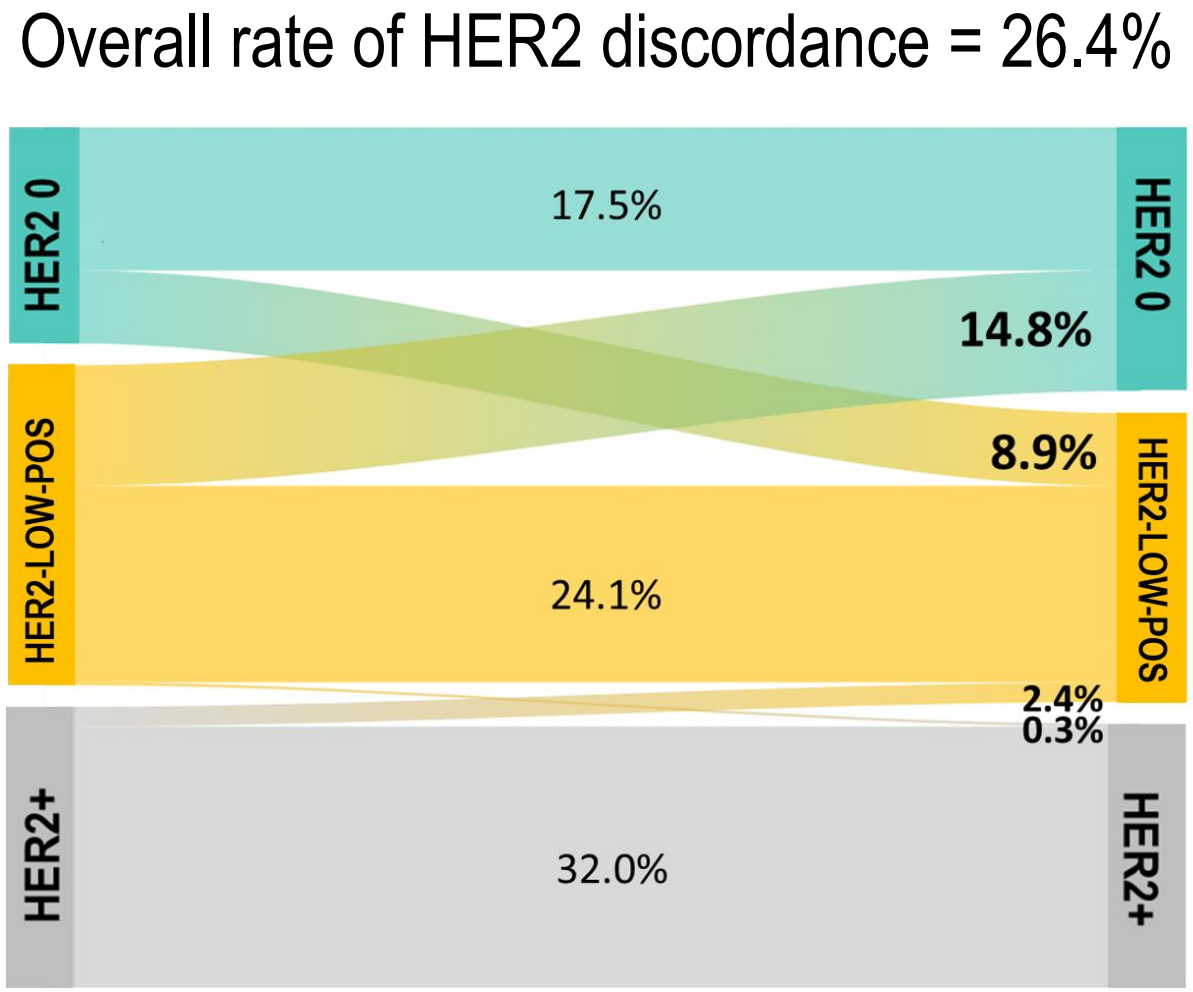


Also observed on liquid biopsy: HER2- CTCs can spontaneously convert into HER2-expressing CTCs and viceversa

Tarantino P et al Eur J Cancer 2022; Miglietta F et al. Breast NPJ 2021, Jordan NV, Bardia A et al. Nature 2016

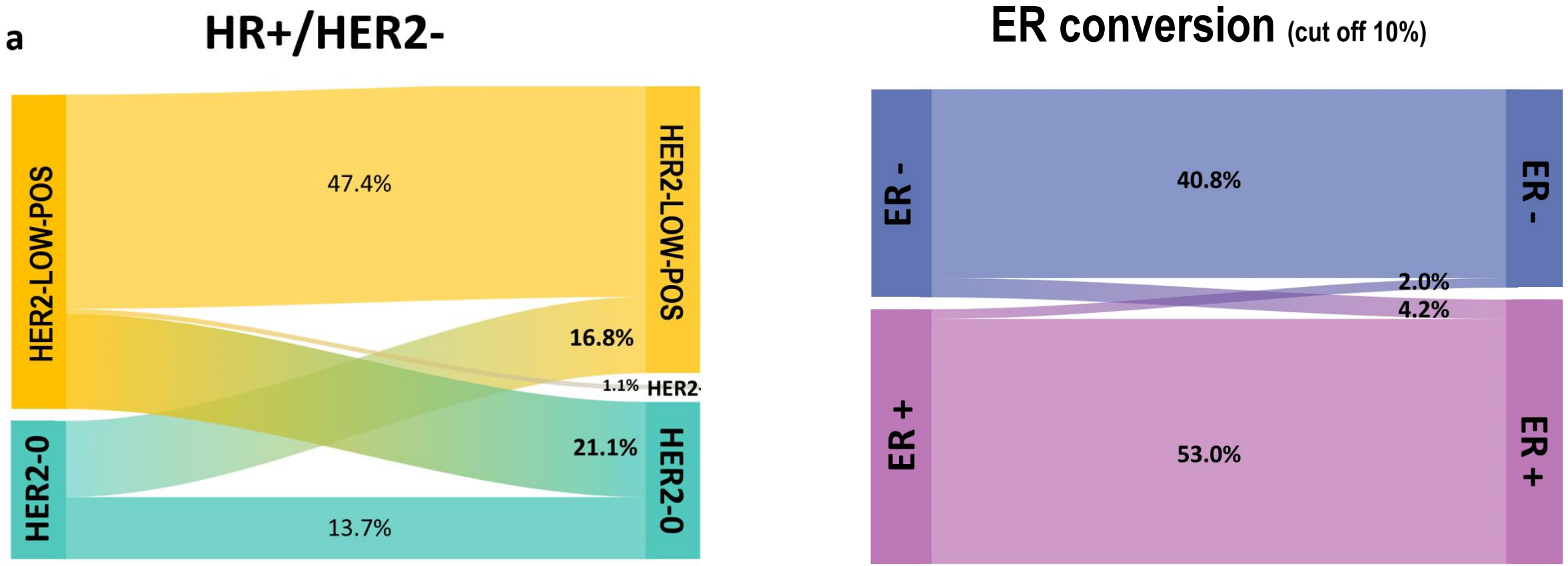
RESULTS

HER2-low BC evolution (N=446 eBC receiving NAC)



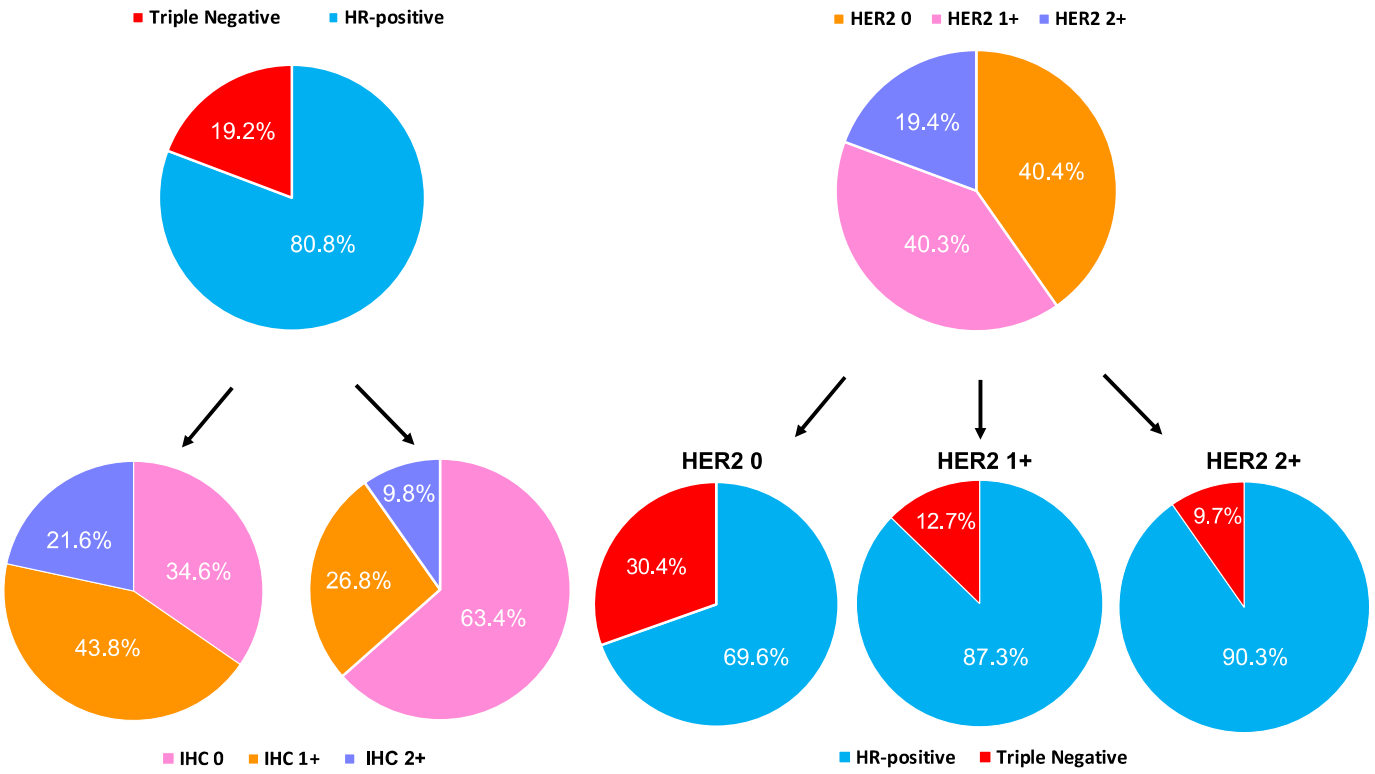
RESULTS

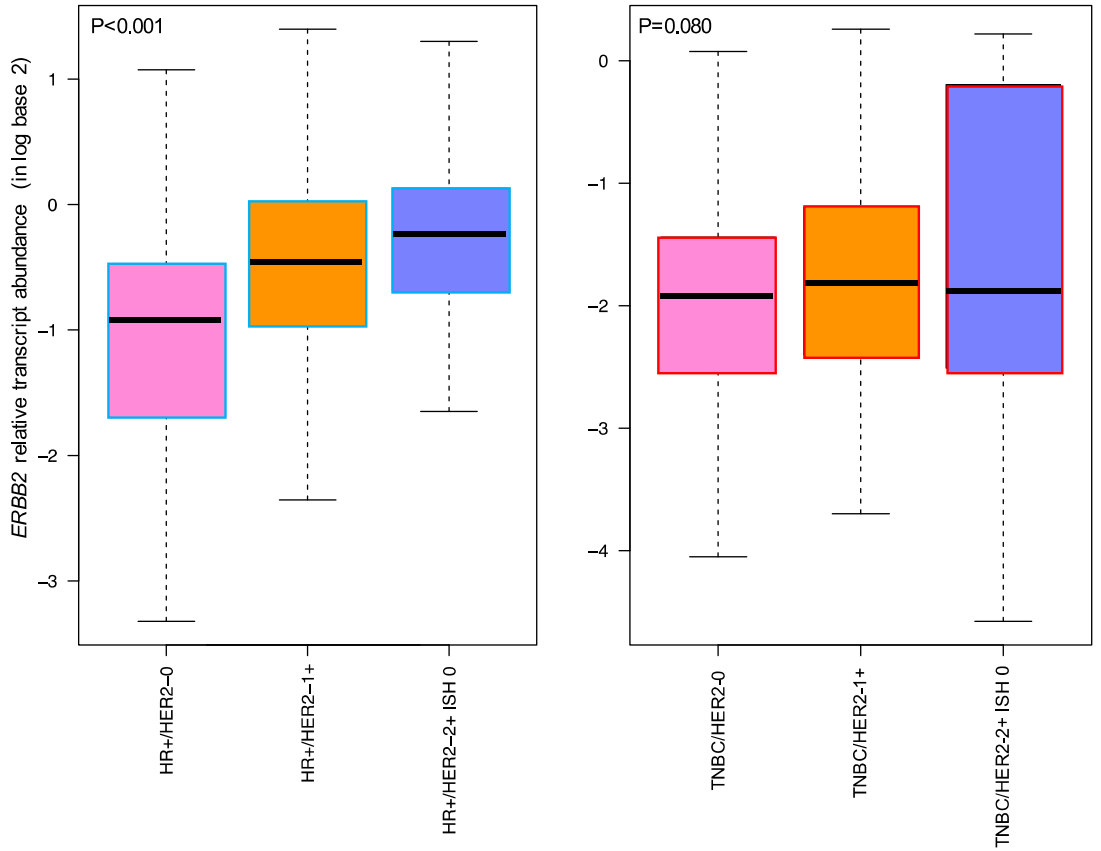
HER2 and HR status evolution



It’s unclear wether the instability of HER2-low expression reflects a genuine shift (CT, CB)

HER2-neg BC: HR/HER2-low status and IHC/mol distrib

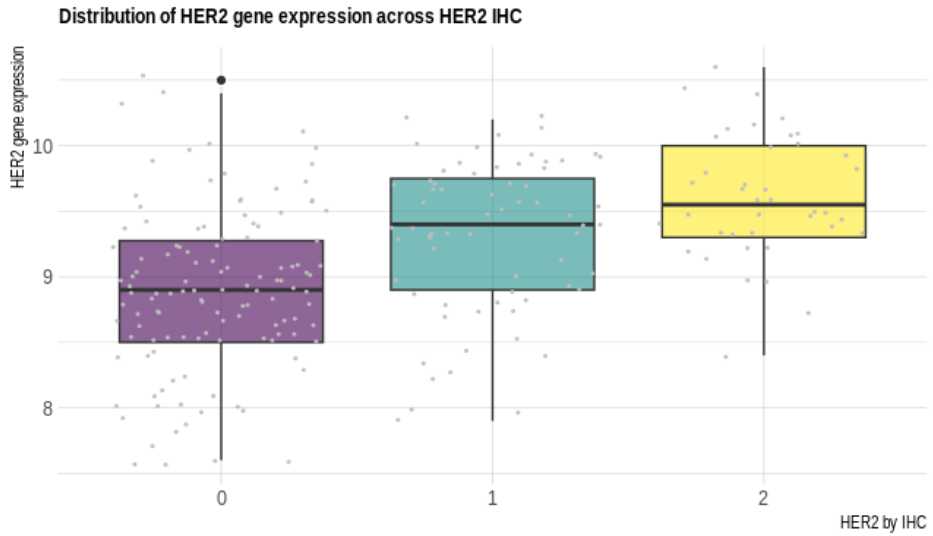




13 independent datasets for a total of 3,689 patients with HER2-neg BC

Schettini, npj Breast Cancer (2021)

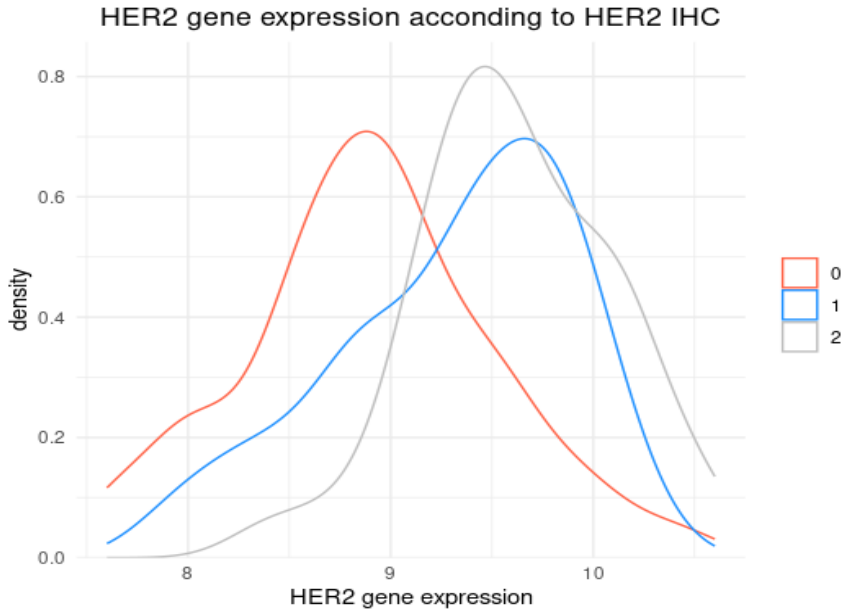
HR-pos/HER2-neg BC: ICH & gene-expression (ODX)



Graph 1. Distribution of HER2 gene expression across HER2 IHC categories.

HER2	n	Mean (SD)	Median (IQR)
Negative	74	8.89 (0.582)	8.9 (0.6)
Ultralow (1-10%)	47	8.91 (0.585)	8.9 (0.9)
Low (>10%)	108	9.41 (0.566)	9.5 (0.725)

Table 1. HER2 gene expression differences between negative, ultralow and low HER2 according to IHC.



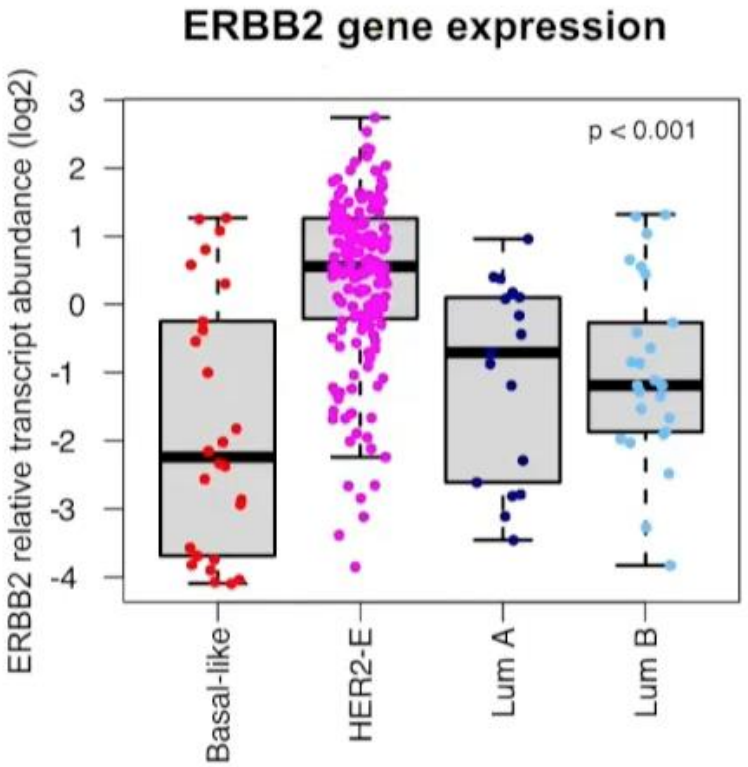
Graph 2. Density plot of HER2 gene expression according to HER2 IHC

Recurrence Score	41 (33.6)	22 (32.8)	15 (37.5)	0.875
>25	43 (35.2)	24 (35.8)	16 (40.0)	0.154
11-25	75 (61.5)	36 (53.7)	19 (47.5)	
<11	4 (3.3)	7 (10.4)	5 (12.5)	

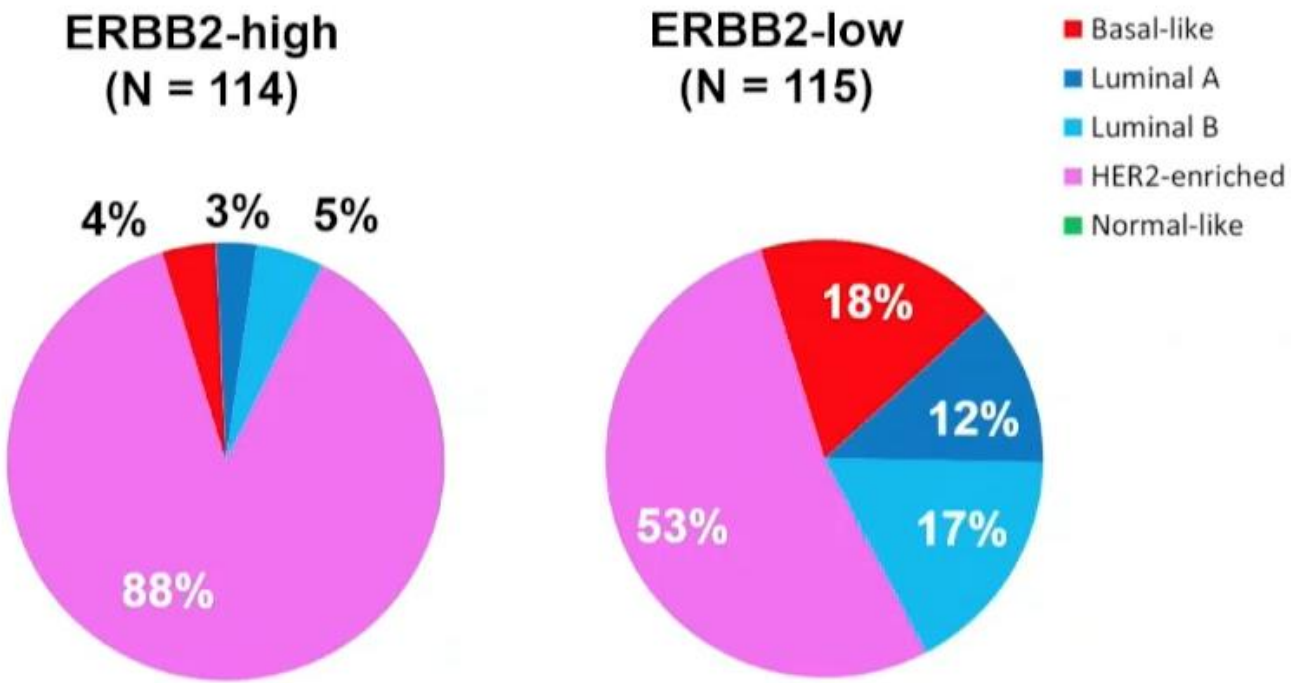
Table 2. RS differences across HER2 IHC categories.

M Gaudio, submitted 2023

HER2-pos BC: low ERBB2 enriches Luminal BC



ERBB2 gene expression by intrinsic subtype in CALGB 40601



Low ERBB2 → more luminal disease

ERBB2-high vs. ERBB2-low: median Split by mRNA

A Prat J Natl Cancer Inst, 2020

HER2-pos BC: the higher ERBB2, the more pCR rate

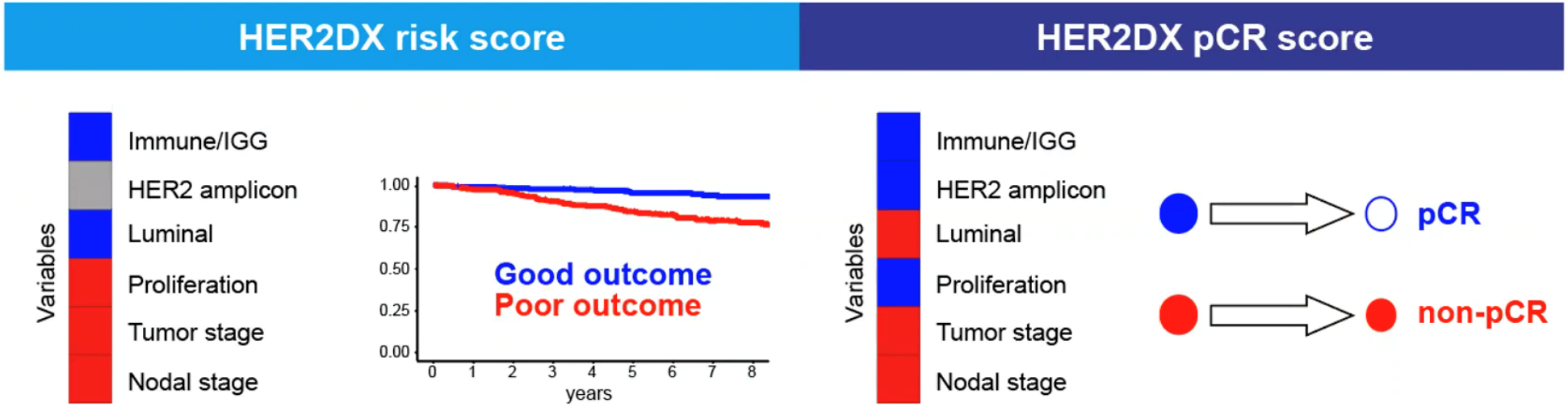
	OPTIHER (Gavilá BMC Med 2019)	ICO (Pernas Front. Oncol.2019)	NeoSphere (Bianchini BCR 2017)	CALGB40601 (Carey JCO 2016)	NeoSphere (Bianchini BCR 2017)	PAMELA (Llombart-Cussac Lancet Oncol 2017)
Treatment	**Chemo** H+P	**Chemo** +H	**Chemo** +anti-HER2	**Chemo** +anti-HER2	**No chemo** H+P	**No Chemo** L+H
N	58	89	285	265	102	151
Variable	pCR rate	pCR rate	pCR rate	pCR rate	pCR rate	pCR rate
ERBB2_high*	**79%**	**66%**	**42%**	**58%**	**23%**	**51%**
ERBB2_low*	**48%**	**44%**	**26%**	**34%**	**11%**	**11%**
P-value	0.025	0.019	0.004	0.0001	0.113	0.0001

H, herceptin; P; pertuzumab; L, lapatinib.

In HR+/HER2- eBCs experience a signidicantly lower pCR than the TN subgroup

HER2-pos BC: predictive biomarkers for PFS & pCR

HER2DX is based on 4 different gene signatures comprising 27 genes, which capture various biological processes: immune infiltration, tumour cell proliferation, luminal differentiation, and expression of the HER2 amplicon



- Immune is associated with better outcome and more pCR
- HER2 amplicon is not associated with outcome but is associated with more pCR
- Luminal is associated with better outcome and less pCR
- Proliferation is associated with worse outcome and more pCR

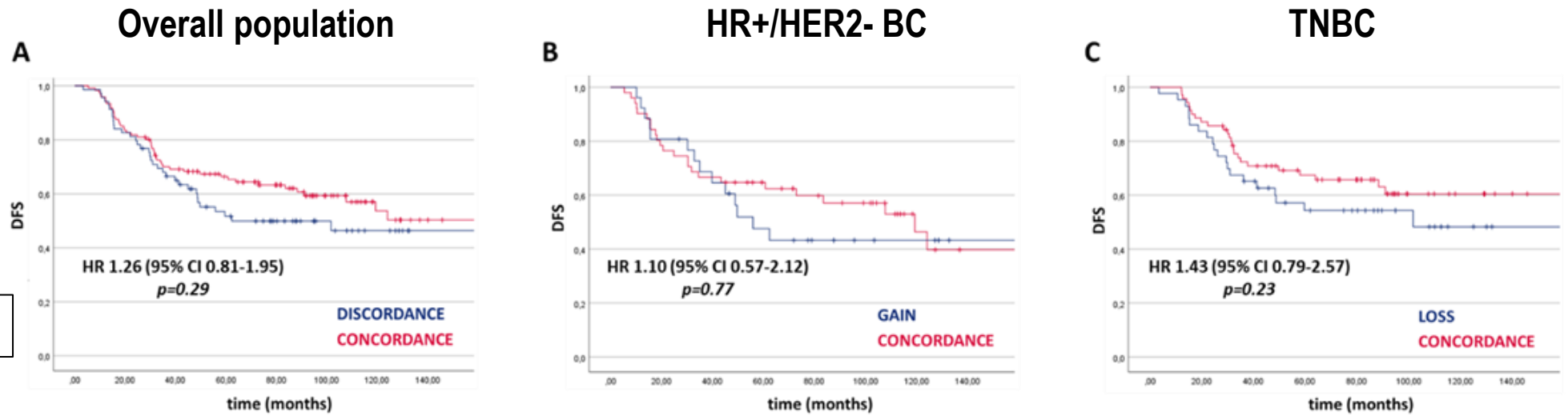
A Prat, The Lancet 2022

HER2-low-pos: conversion and survival

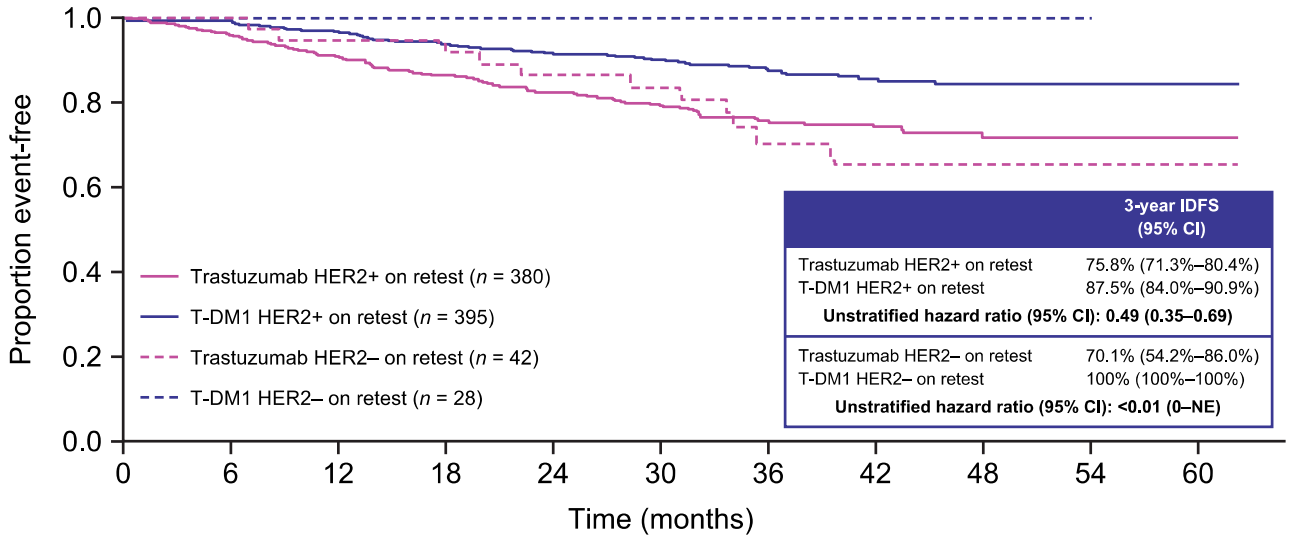
1/3 converted from HER2-0 to HER2-low-pos

DFS according to HER2 evolution

7% of HER2-pos->HER2-low

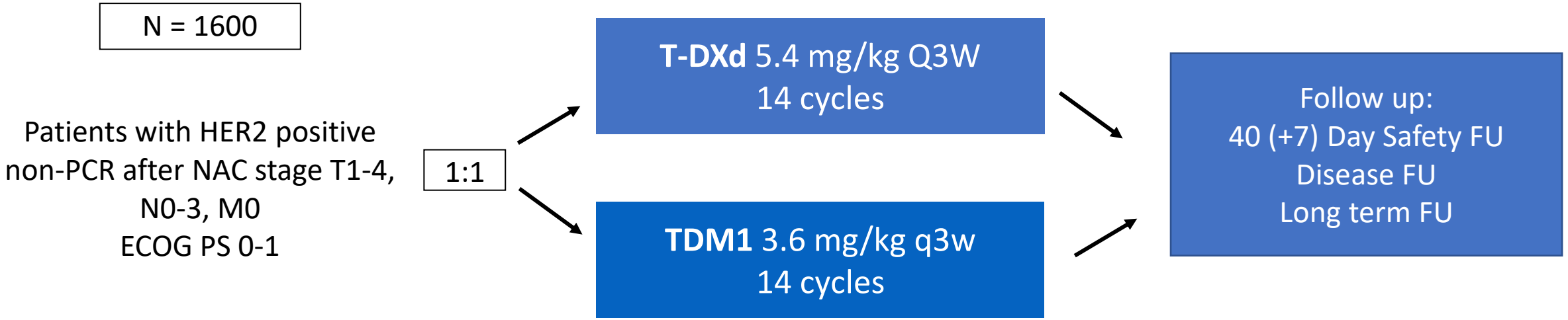


EFS in Katherine in HER2-neg evolution



Destiny BREAST 05

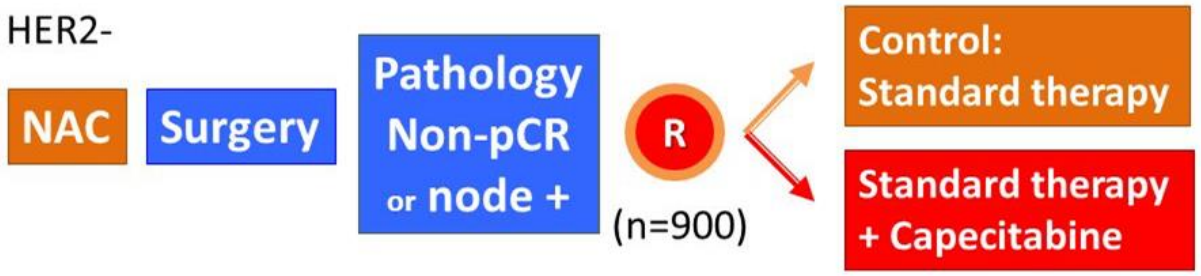
dedicated to HER2-pos, so far…



Create X

Adjuvant Capecitabine vs Control in residual disease after NAC

Study design

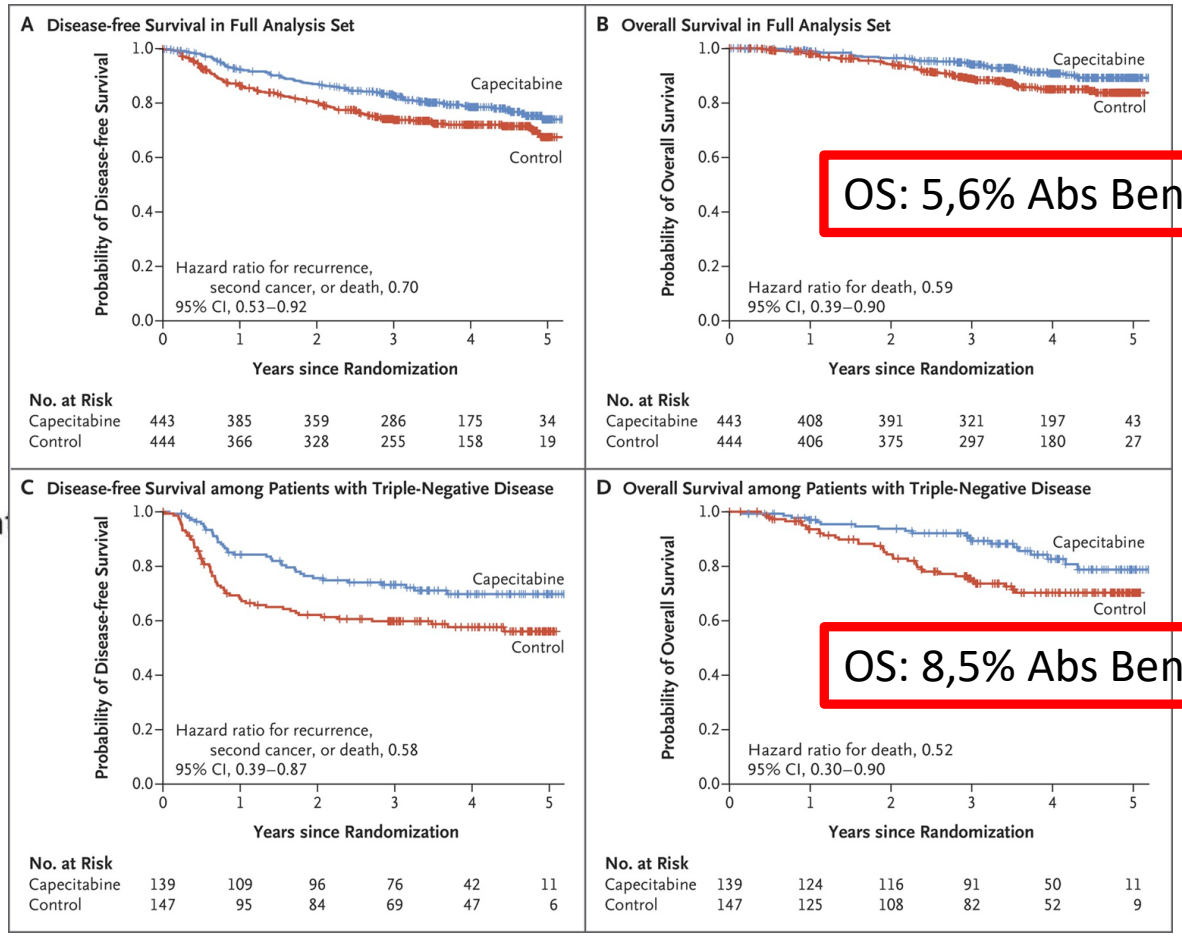


Stratification factors:
ER, Age, NAC, ypN,
5FU and institution

Standard therapy:
HR+: Hormone therapy
HR-: No further systemic treatmen

C: 1250mg po/bid
14d q3w for 6-8c

Survival outcomes



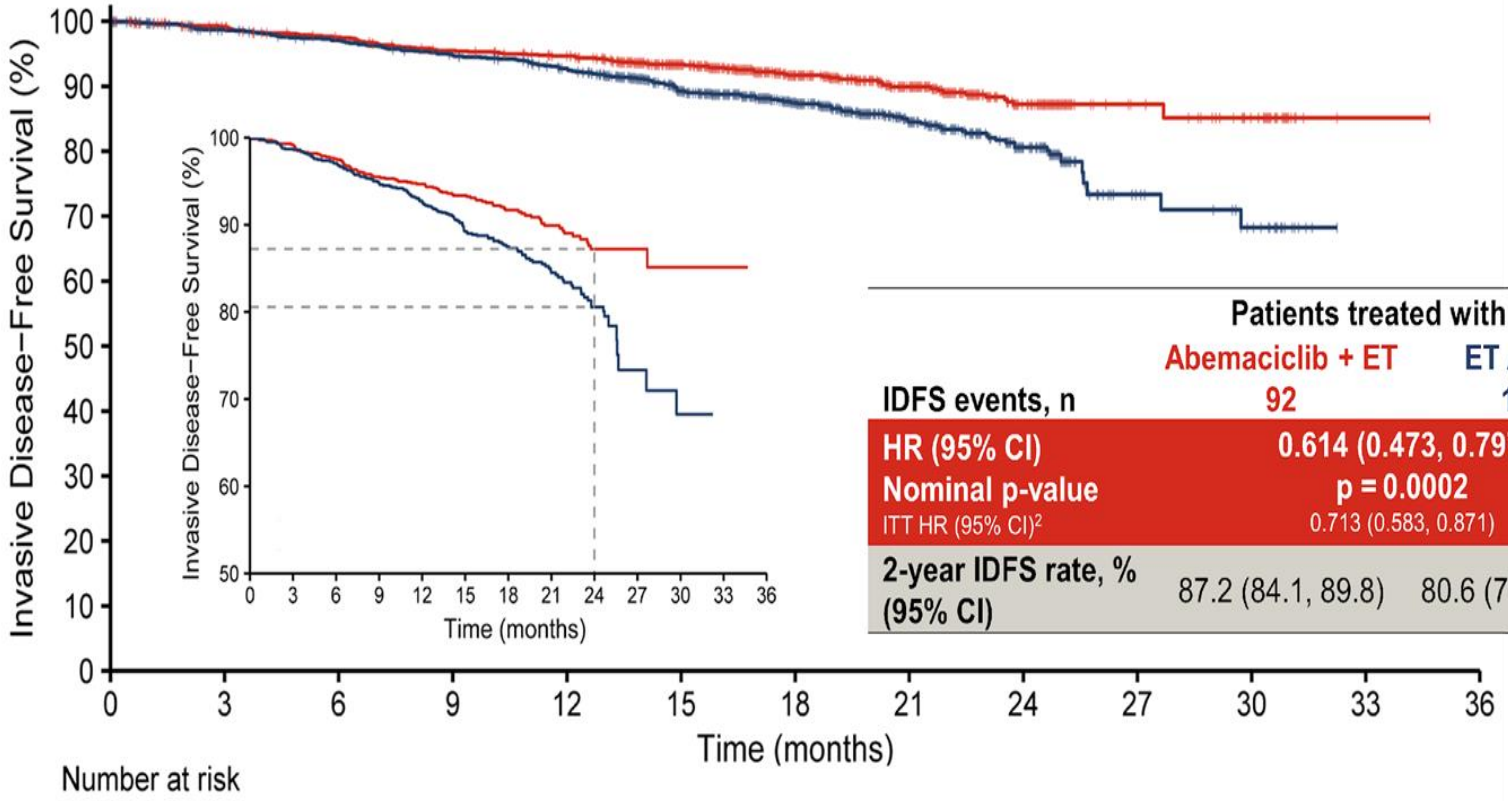
OS: 5,6% Abs Benefit

OS: 8,5% Abs Benefit

Masuda et al, NEJM 2017

MonarchE

IDFS in Patients Who Received NAC



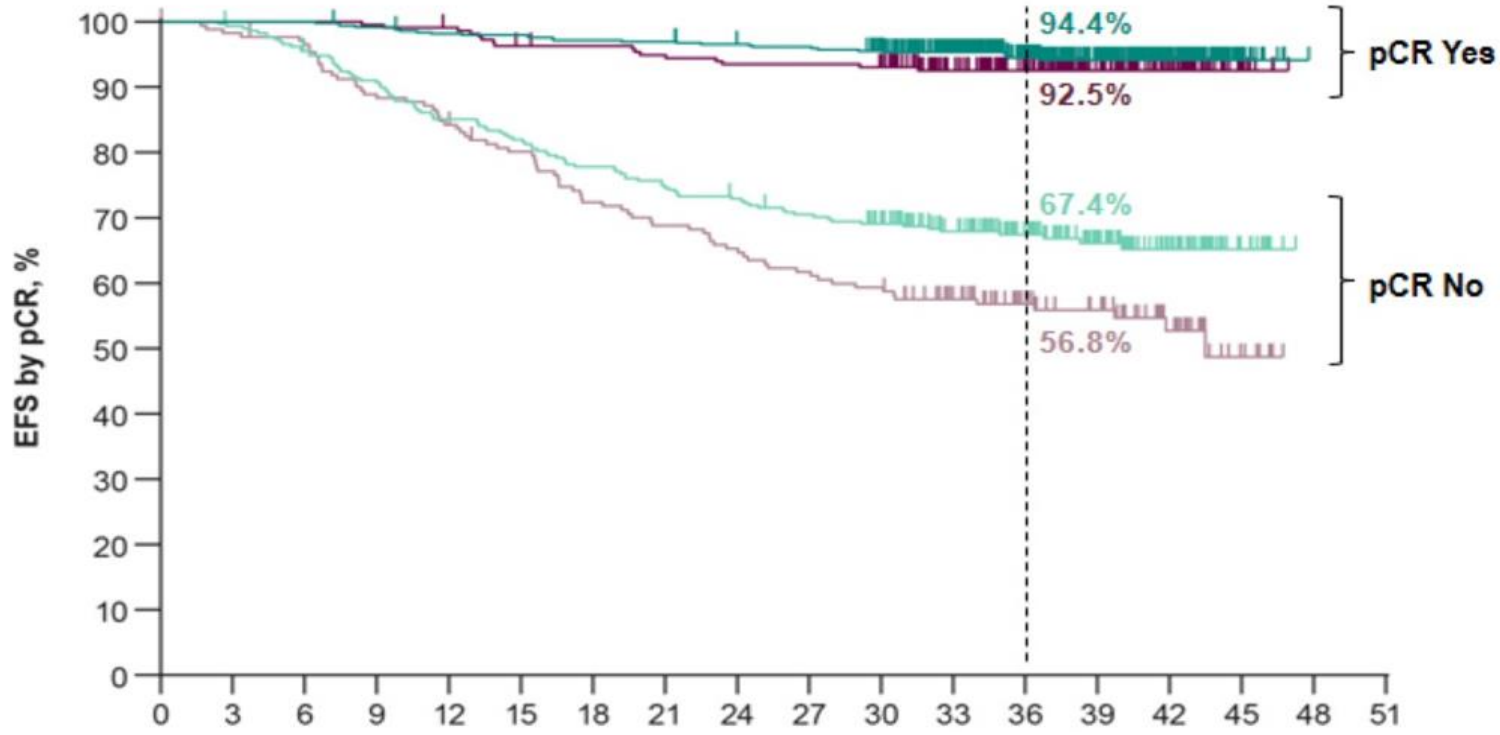
	Patients treated with NAC	
	Abemaciclib + ET	ET Alone
IDFS events, n	92	148
HR (95% CI)	0.614 (0.473, 0.797)	
Nominal p-value	p = 0.0002	
ITT HR (95% CI)[2]	0.713 (0.583, 0.871)	
2-year IDFS rate, % (95% CI)	87.2 (84.1, 89.8)	80.6 (77.0, 83.6)

Clinically meaningful improvement in IDFS – 38.6% reduction in the risk of developing an IDFS event
Two-year IDFS rates were 87.2% in the abemaciclib + ET arm and 80.6% in the ET arm – 6.6% difference

[2]Rastogi P. et al. SABCS 2020; presentation number GS1-01

KN-522

Update EFS by pCR vs no pCR

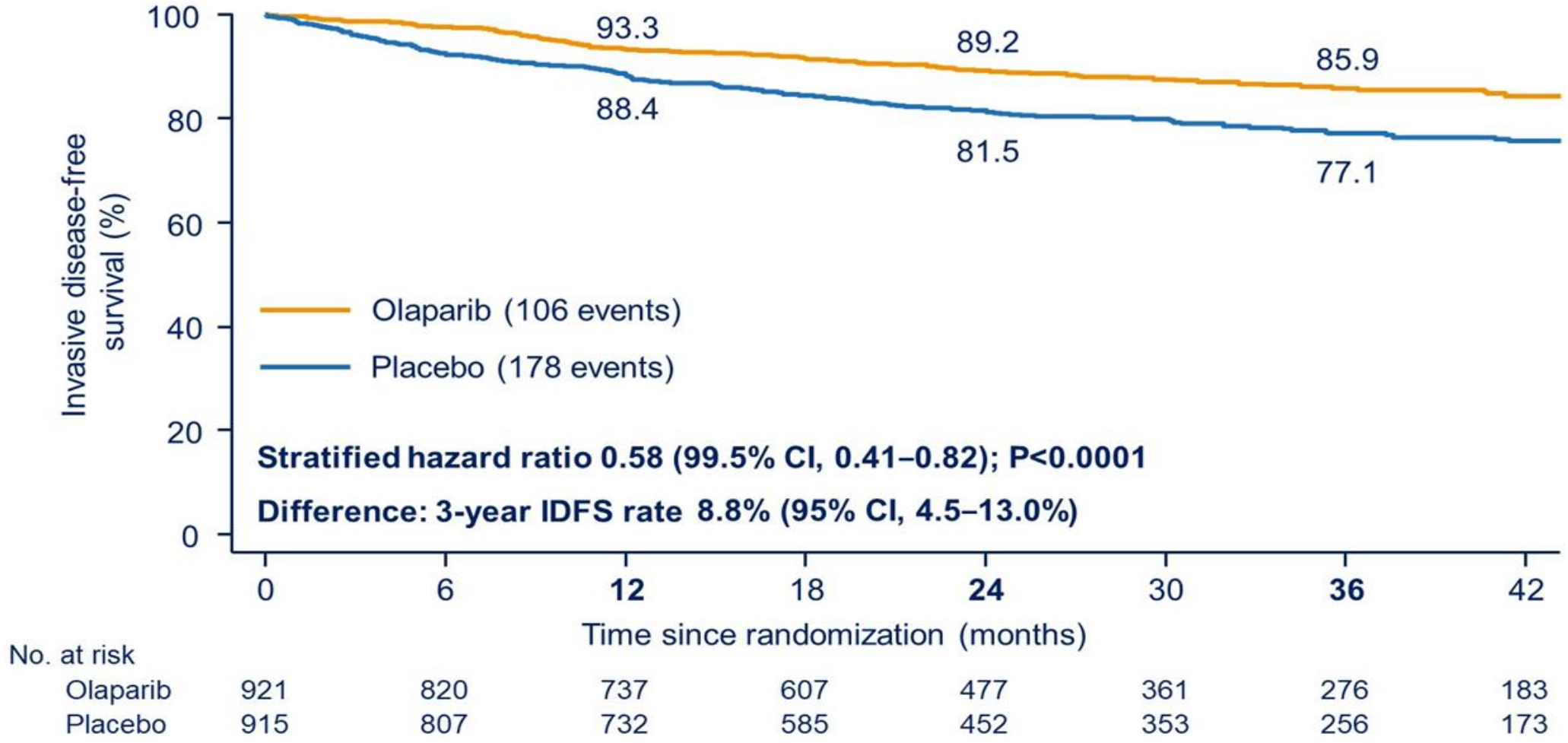


No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Schimd ESMO 2021

OlympiA

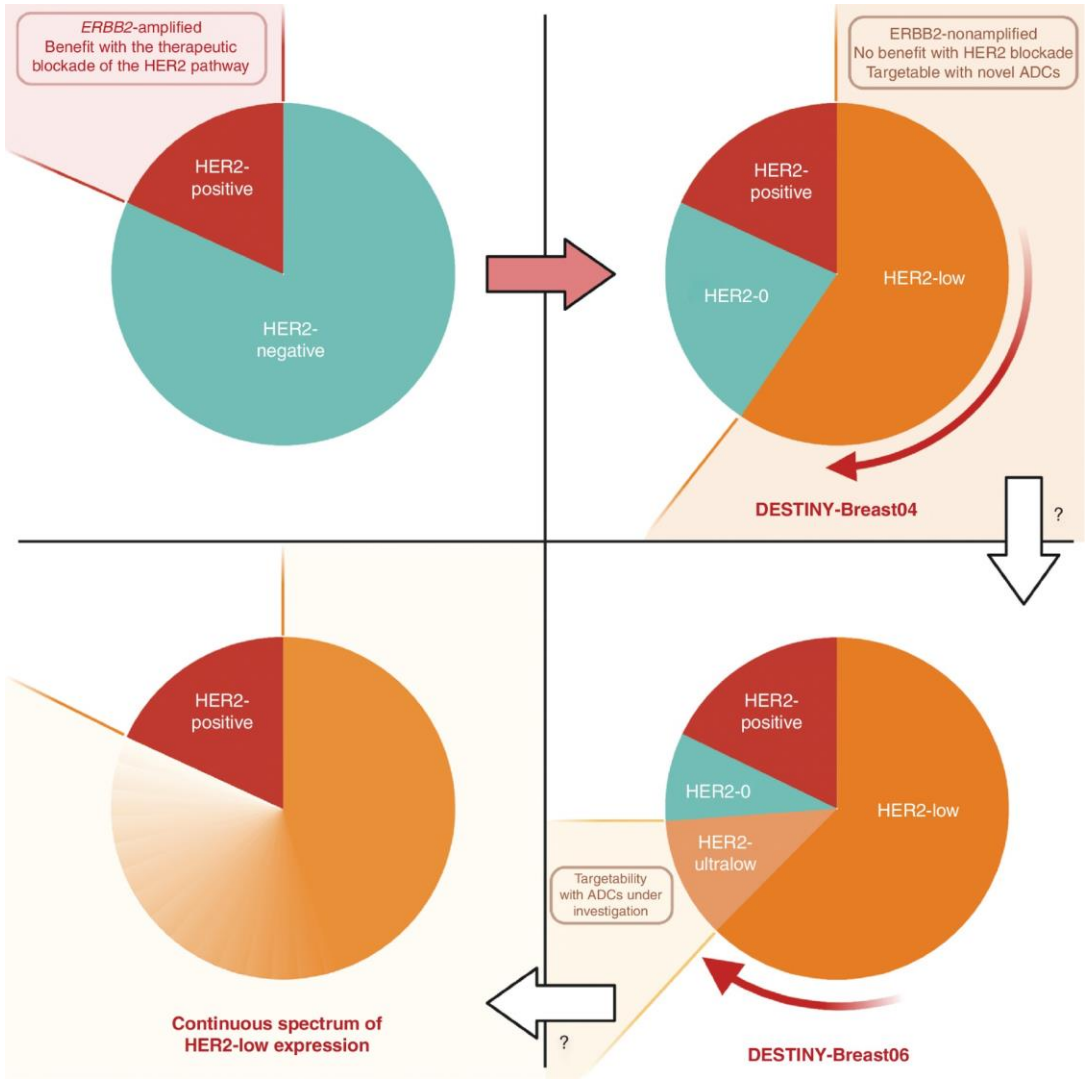
Results: IDFS in ITT



A Tutt ASCO 2021

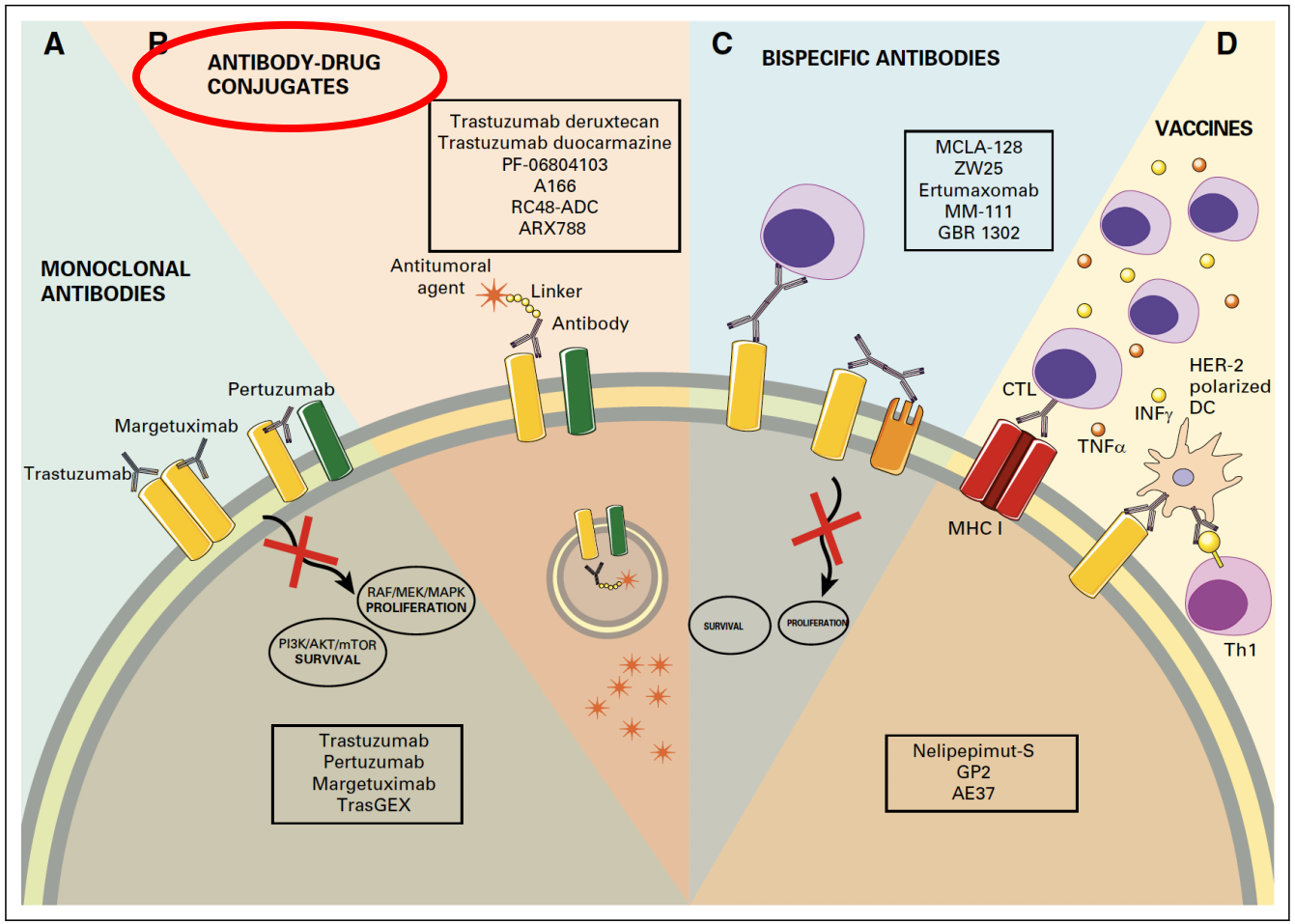
One size fits all ?

The evolving categorization of HER2

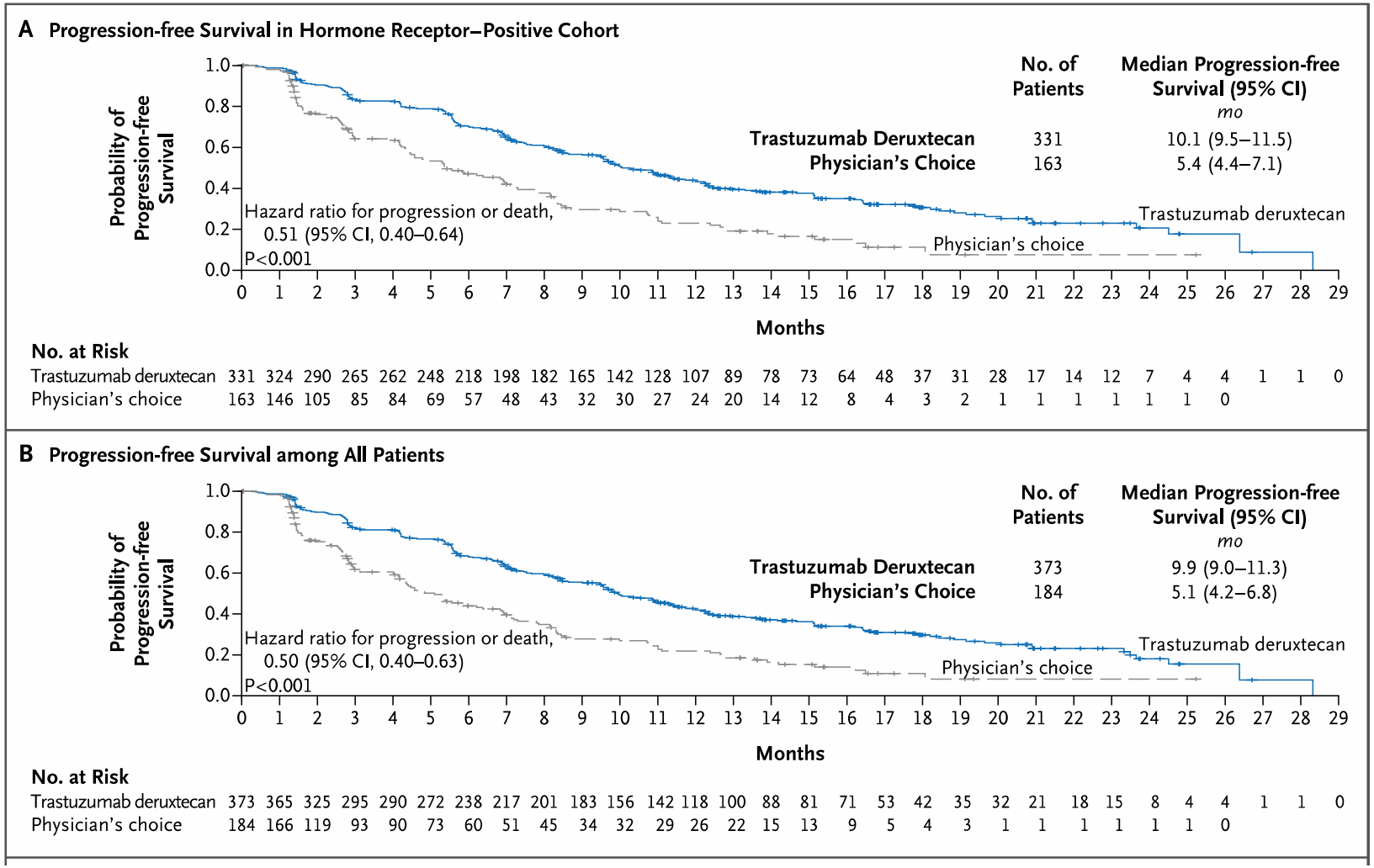


Tarantino Cancer Discov. 2022

The perspective (HER2-low-pos)

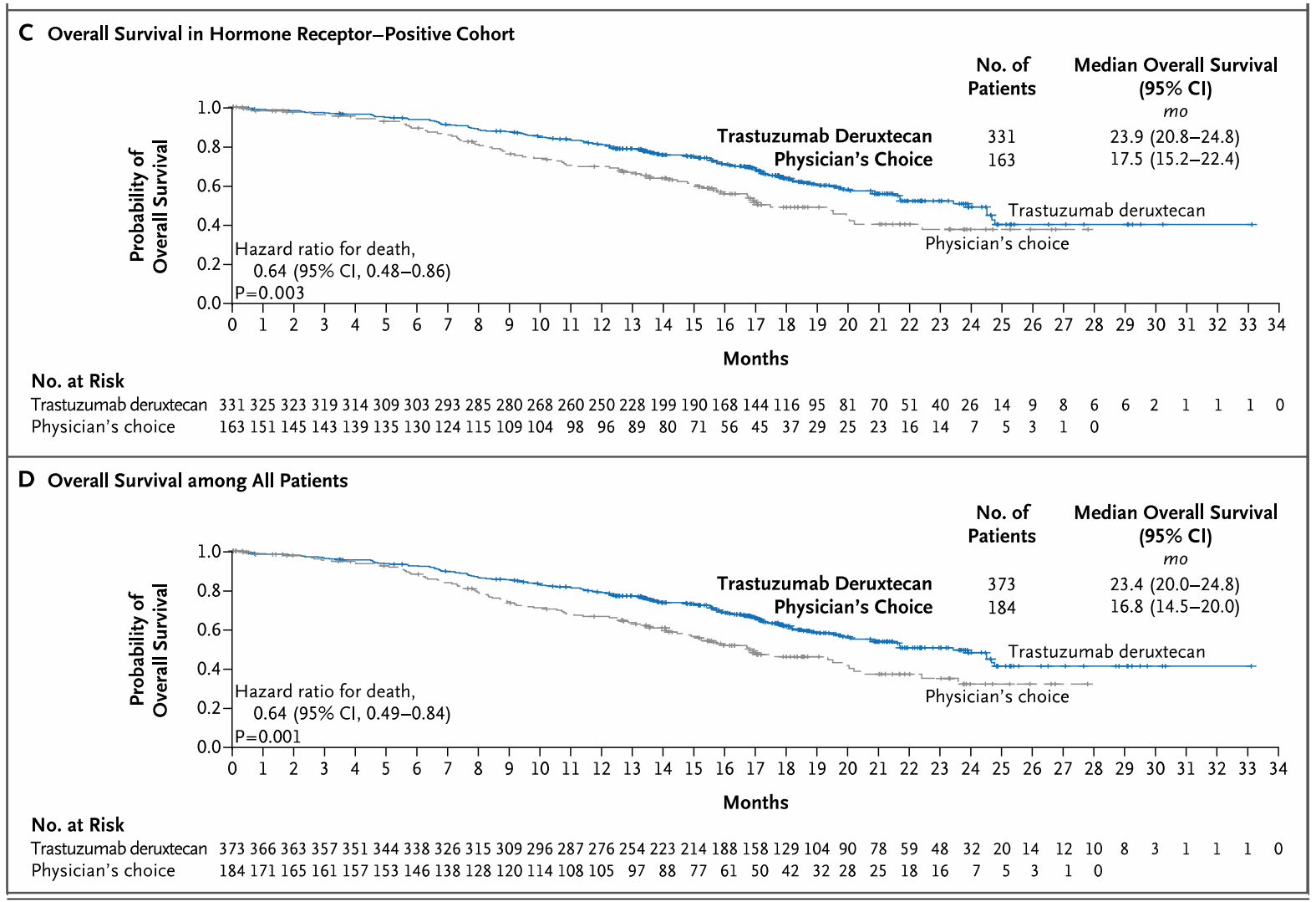


Destiny-BREAST 04 (PFS)



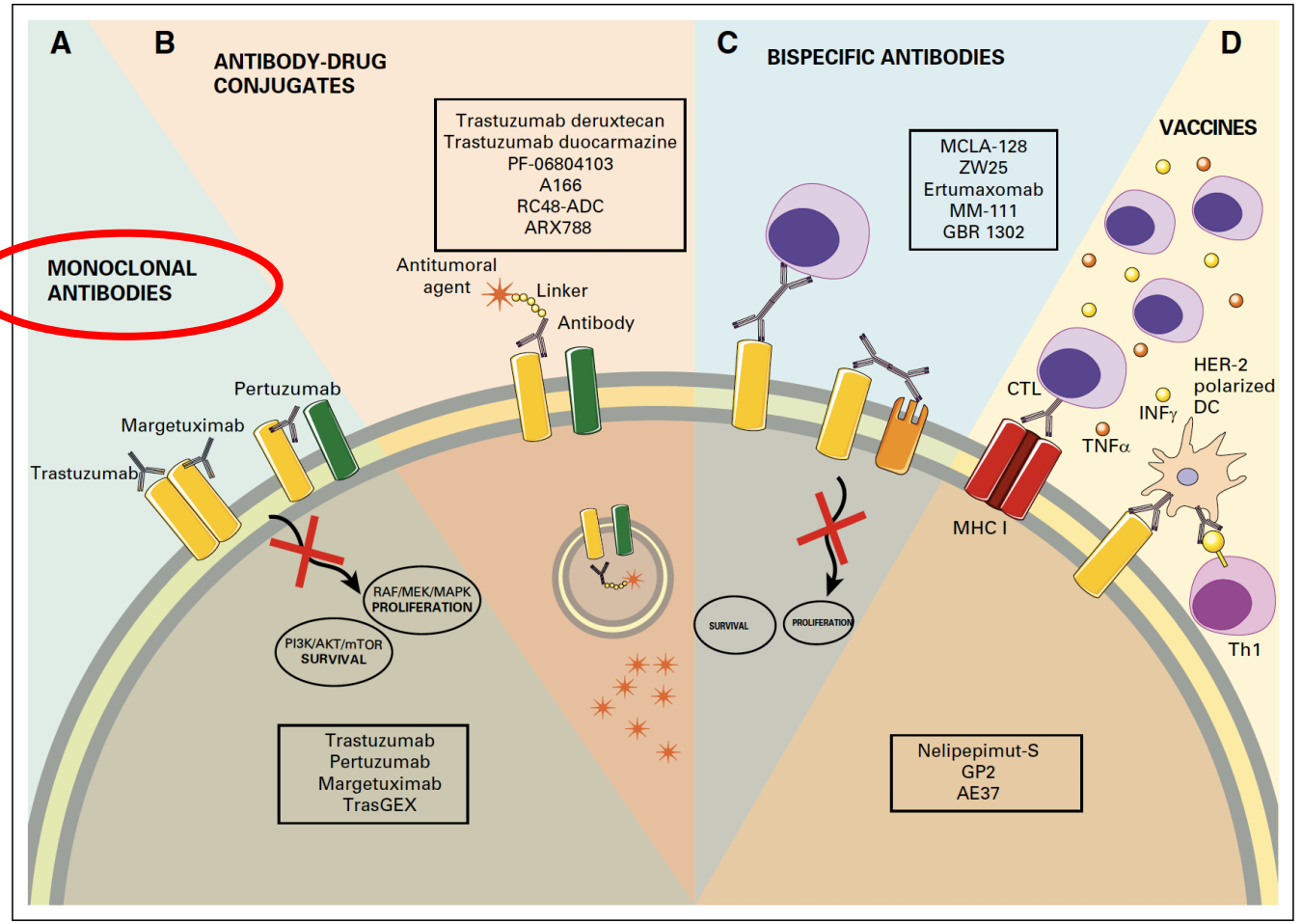
Modi NEJM 2022

Destiny-BREAST 04 (OS)



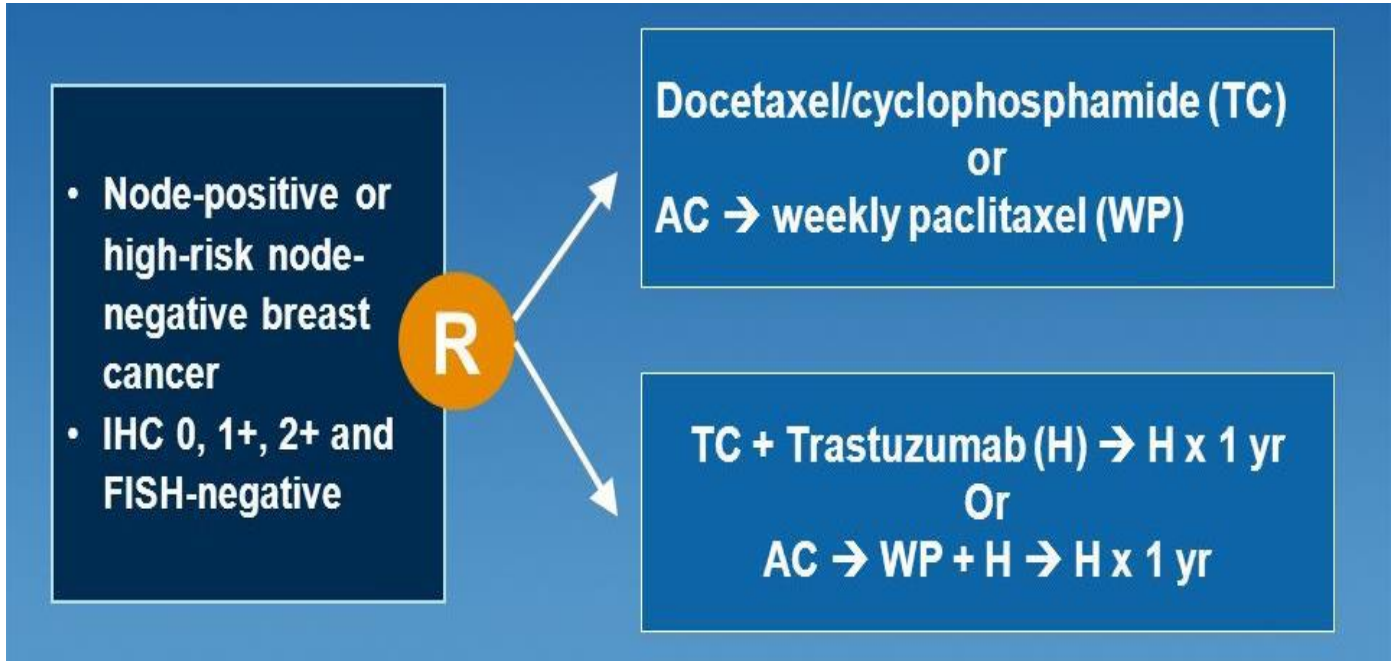
Modi NEJM 2022

mAB in HER2-low



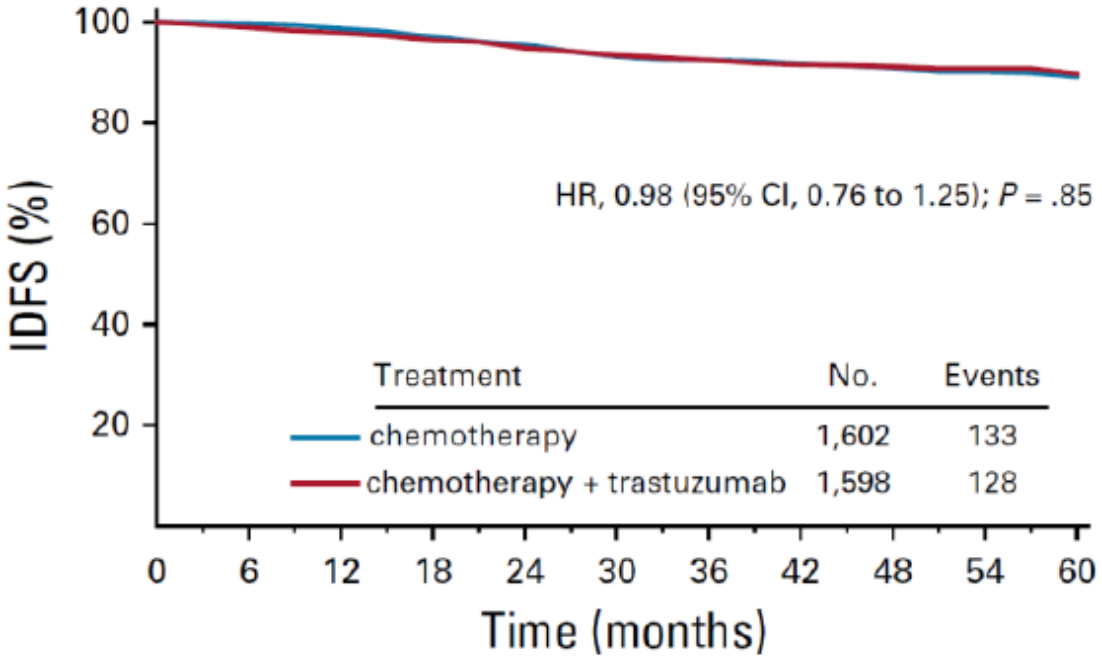
HER2-low-pos & Trastuzumab

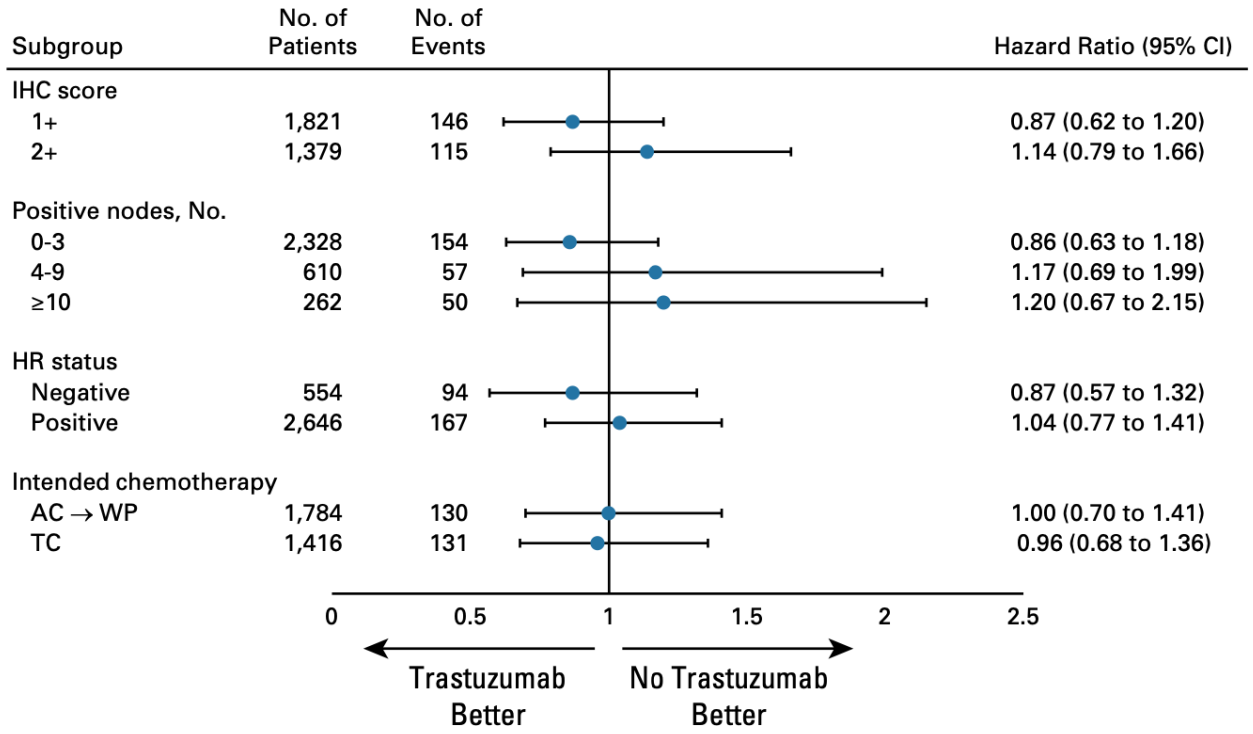
- NSABP B-31 HER2 central testing
  - 174/1,787 (9.7%) not IHC 3+ or gene amplified
  - Appeared to benefit from trastuzumab
    - Relative risk for DFS = 0.34



Paik S, et al. *N Engl J Med* 2008;358:16409-1411

HER2-low-pos & Trastuzumab (B-47)





Fehrenbacher L, et al. *J Clin Oncol* 2020;38:444-453

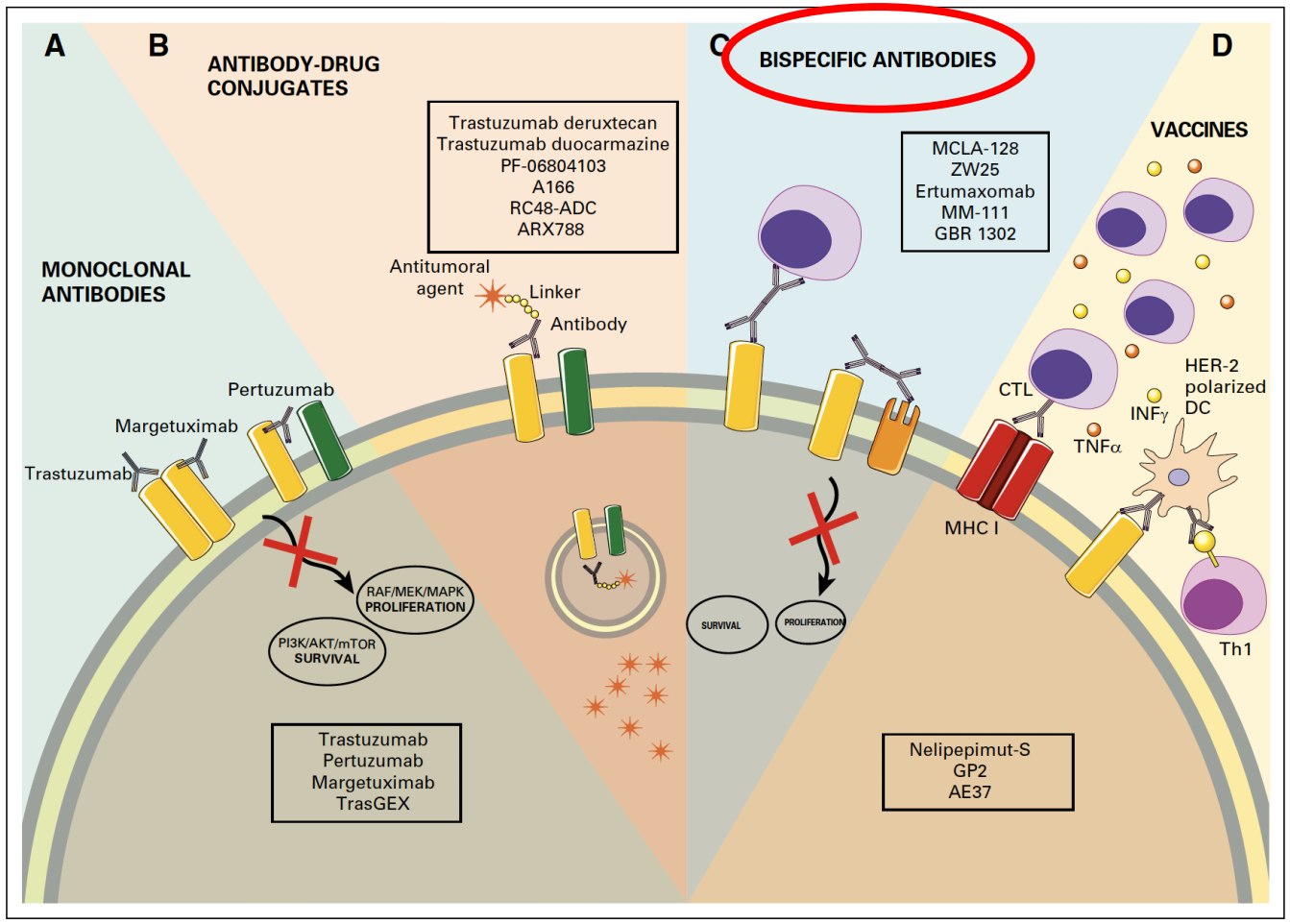
HER2-low-pos & Pertuzumab

- Phase II trial of pertuzumab in HER2- (majority HER2 low)
- 2 dosing cohorts (q3w 420mg or 1,050 mg)
- N=79
  - partial response in only 2 (2.5%)
  - Stable disease 24 mo in 4 (5.0%)

Variable	Arm A (n = 41)		Arm B (n = 37)	
	No.	%	No.	%
PR	2	4.9	0	
SD ≥ 12 weeks	18	43.9	14	37.8
SD ≥ 24 weeks	2	4.9	2	5.4
Progressive disease	21	51.2	22	59.5
Missing	0		1	2.7
Clinical benefit (CR + PR + SD ≥ 24 weeks)	4	9.8	2	5.4
Duration of clinical benefit, weeks				
Median	36.5		33.6	
Range	22.1-74.9		31.0-36.3	
Time to progression, weeks				
Median	6.1		6.1	
Range	2.0-37.0		2.7-36.3	

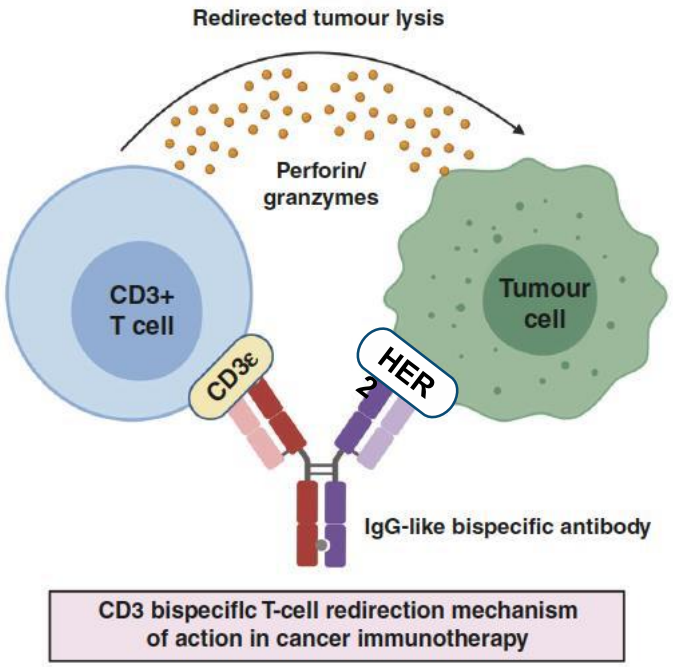
Gianni L, et al. *J Clin Oncol* 2010;28:19131-1137

Bispecific antibody



BSmAb

- Antibodies that bind 2 distinct epitopes, can:
  - Inhibit multiple oncogenic pathways
  - Force connection between cancer cells and immune cells
  - Deliver payload to the tumor microenvironment

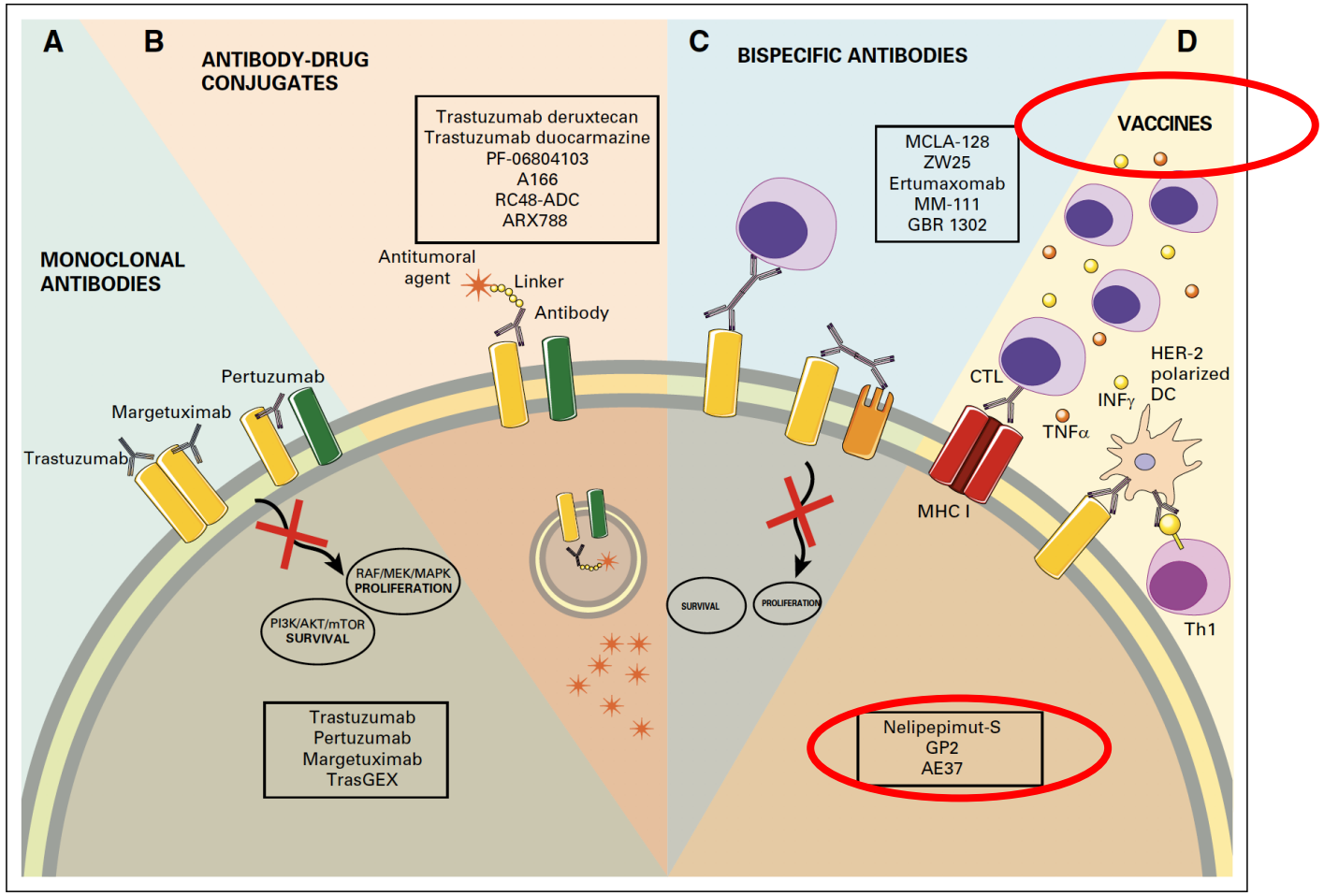


CD3 bispecifIc T-cell redirection mechanism of action in cancer immunotherapy

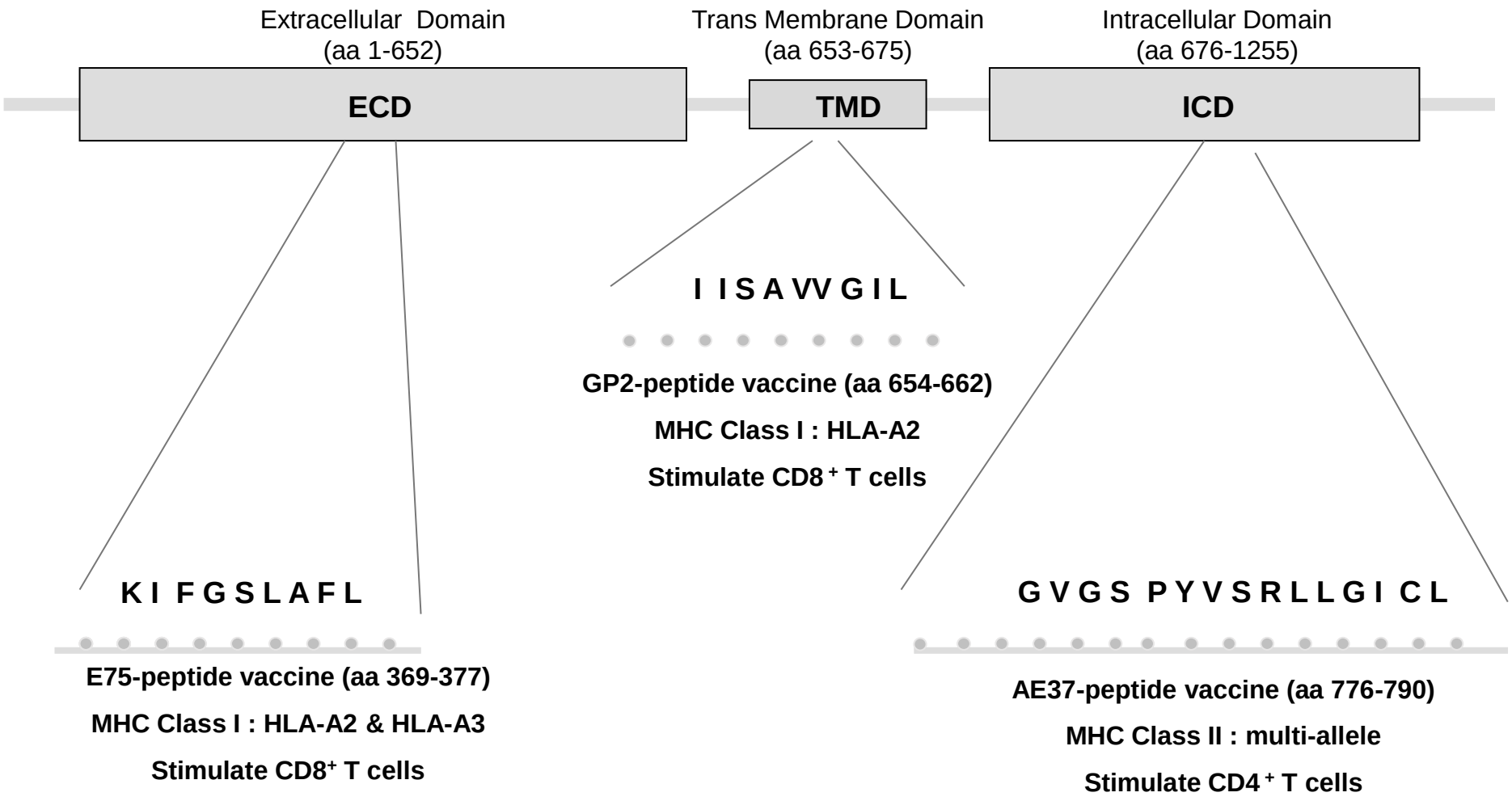
Trial with BSmAB in HER2-low-pos

Bispecific antibodies					
Ertumaxomab (Fresenius, Germany)	NCT00522457[87]	II	28	Pretreated HR+ HER2-low–expressing (IHC 1+ or 2+, FISH-negative) mBC, locally assessed	ORR, 0% DCR, 53.8%
GBR1302(Glenmark Pharmaceuticals, Mumbai, India)	NCT02829372[88]	I	19	Pretreated HER2-positive and HER2-low–expressing (2+, FISH-negative) solid tumors, including BC	ORR, 0% DCR, 10%
MCLA-128 (Merus, Utrecht, the Netherlands)	NCT03321981	II; R	120	Advanced, HR+, HER2-low–expressing BC (IHC 1+ or 2+), progressing during an endocrine treatment	MCLA-128 + endocrine treatment
ZW25 (Zymeworks, Vancouver, British Columbia, Canada)	NCT02892123	I; R	234	Pretreated advanced, HER2-expressing (HER2 1+, 2+, or 3+ by IHC) BC	ZW25
BTRC4017A (Genentech, San Francisco, CA)	NCT03448042	I; R	449	Pretreated HER2-expressing (not further specified) advanced BC, locally assessed	BTRC4017A
IBI315 (Innovent Biologics, Jiangsu, China)	NCT04162327	I; R	191	Pretreated HER2-expressing (not further specified) advanced solid tumors	IBI315

Vaccines


A
B
ANTIBODY-DRUG CONJUGATES
C
BISPECIFIC ANTIBODIES
D
VACCINES
MONOCLONAL ANTIBODIES
Trastuzumab deruxtecan
Trastuzumab duocarmazine
PF-06804103
A166
RC48-ADC
ARX788
MCLA-128
ZW25
Ertumaxomab
MM-111
GBR 1302
Antitumoral agent
Linker
Antibody
Pertuzumab
Margetuximab
Trastuzumab
RAF/MEK/MAPK PROLIFERATION
PI3K/AKT/mTOR SURVIVAL
SURVIVAL
PROLIFERATION
MHC I
CTL
INFγ
TNFα
HER-2 polarized DC
Th1
Trastuzumab
Pertuzumab
Margetuximab
TrasGEX
Nelipepimut-S
GP2
AE37

HER2-pos Vaccines platform



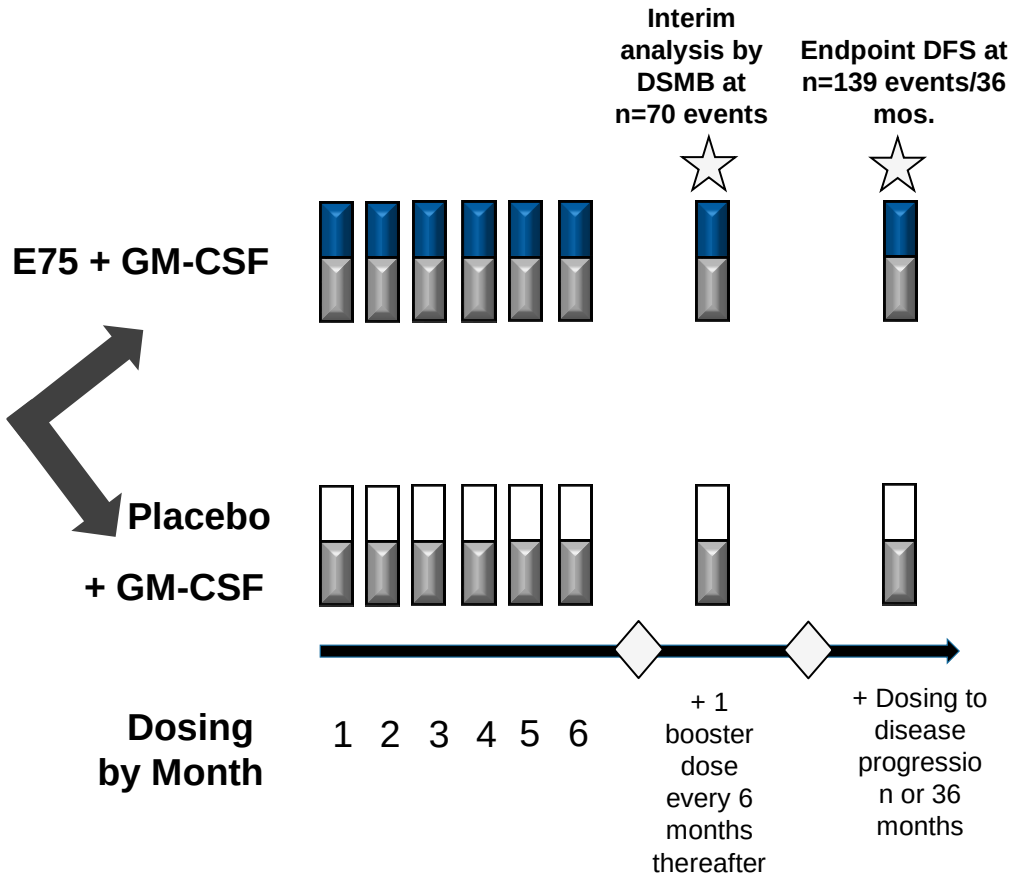
E75 Phase III Trial in HER2-low-pos eBC

PRESENT – **P**revention of **R**ecurrence in **E**arly-**S**tage Node Positive Breast Cancer with Low to Intermediate HER2 **E**xpression with **N**euVax **T**reatment

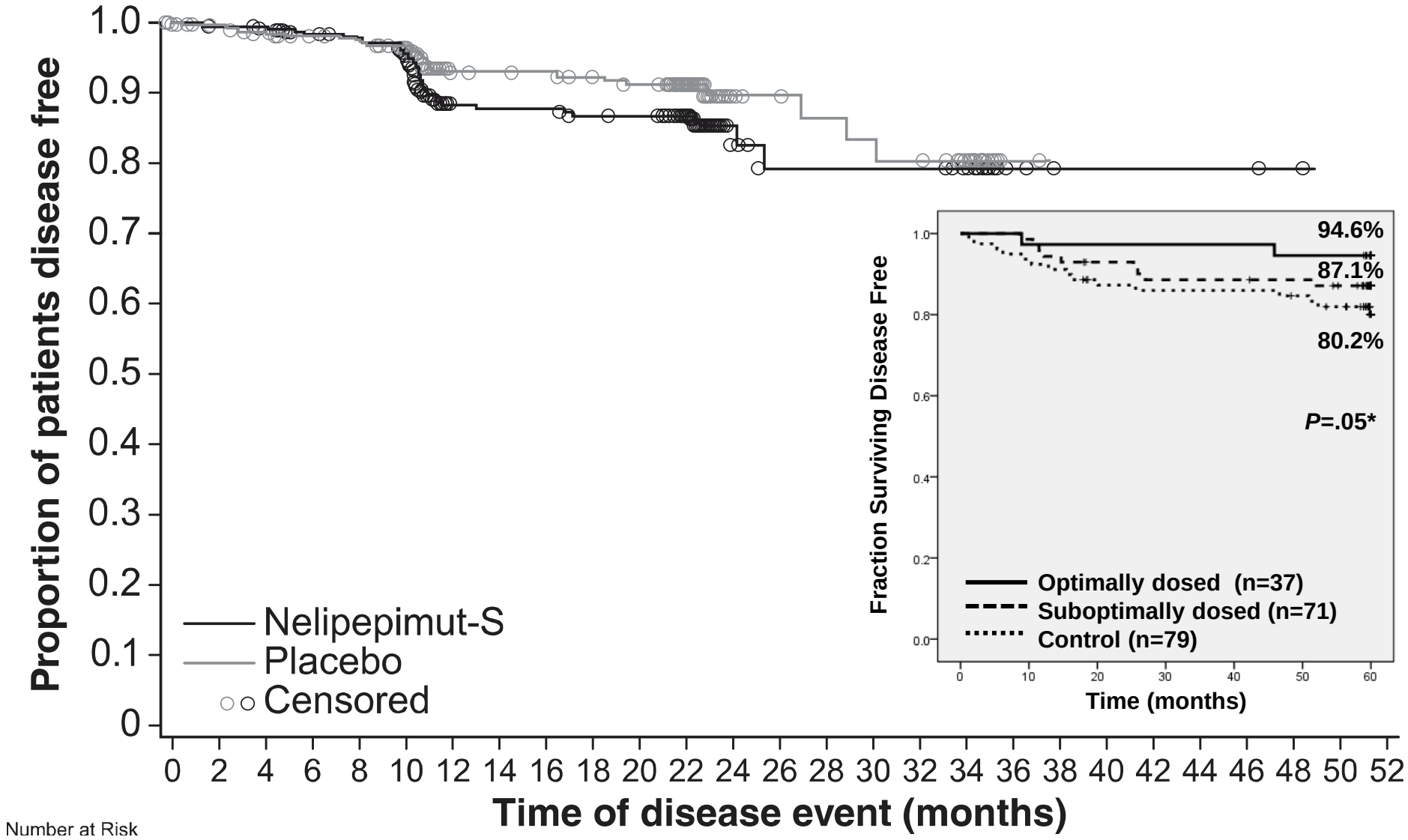
Study Population

Adjuvant Breast cancer (BC) patients, n=700, randomized 1:1

- Node positive (NP), HLA A2/A3+, low and intermediate HER2 expression
- Achieve CR with standard of care (SOC)
- Stratified by Stage (IIA-IIIA), Type of Surgery, Hormone Receptor and Menopausal status
- Single dose level of GM-CSF +/- E75

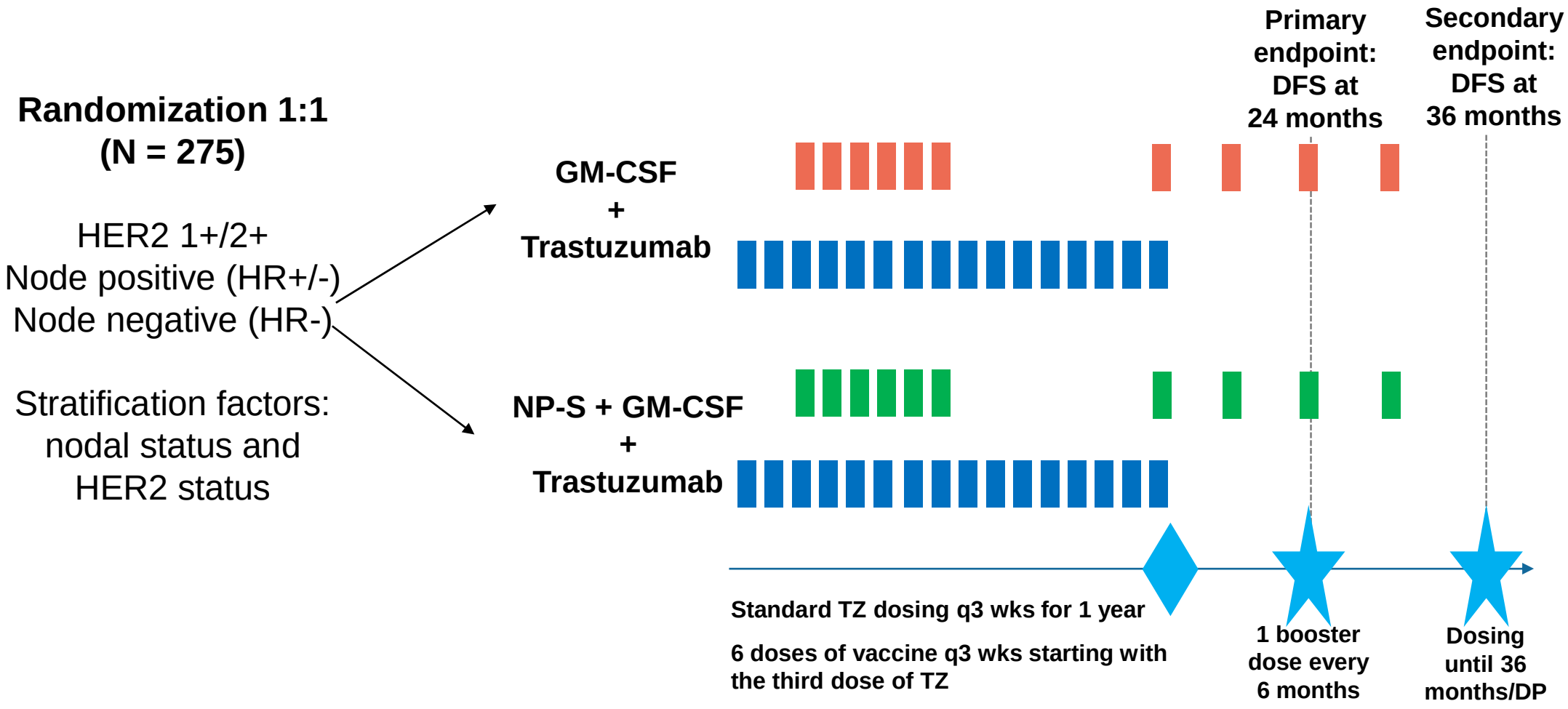


PRESENT

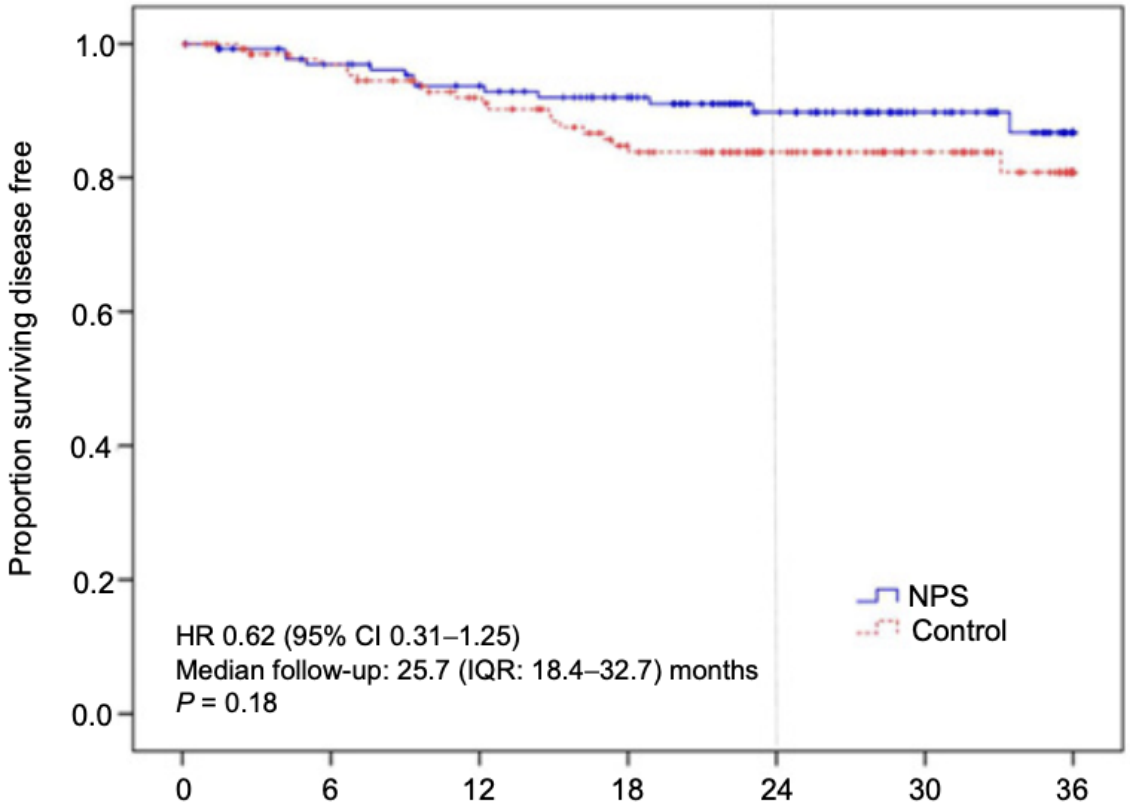


Mittendorf EA, et al. *Clin Cancer Res* 2019;25:540248-4254

PhII Trial E75 Vaccine + Trastuzumab in HER2-low-pos



DFS – All Randomized Patients



Number at risk

NPS	135	124	114	97	70	42	19
Control	137	122	106	88	63	41	19

24 month DFS

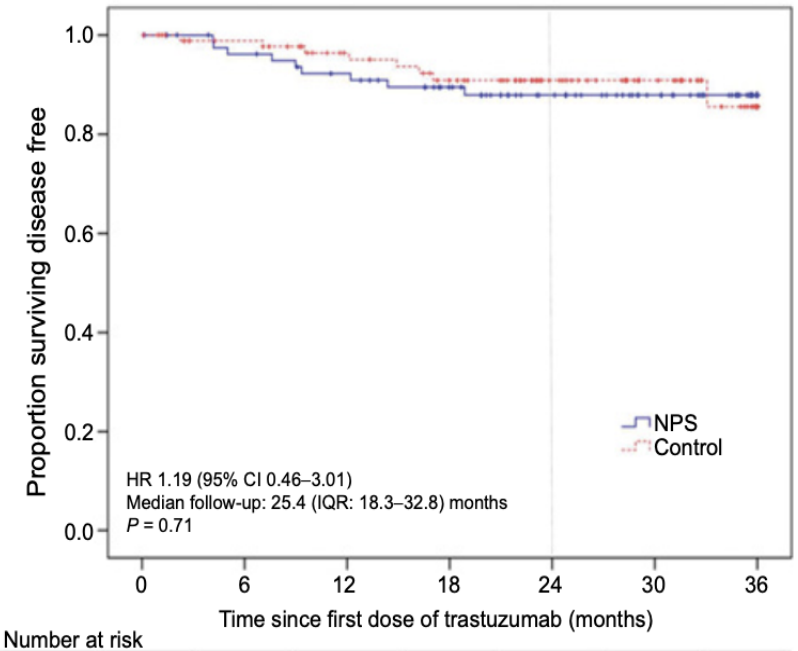
- Vaccinated 89.8%
- Control 83.8%

- HR 0.62 (95% CI: 0.31-1.25)

Clifton GT, Clin *Cancer Res* 2020;26:2515-2523

DFS – By HR Status

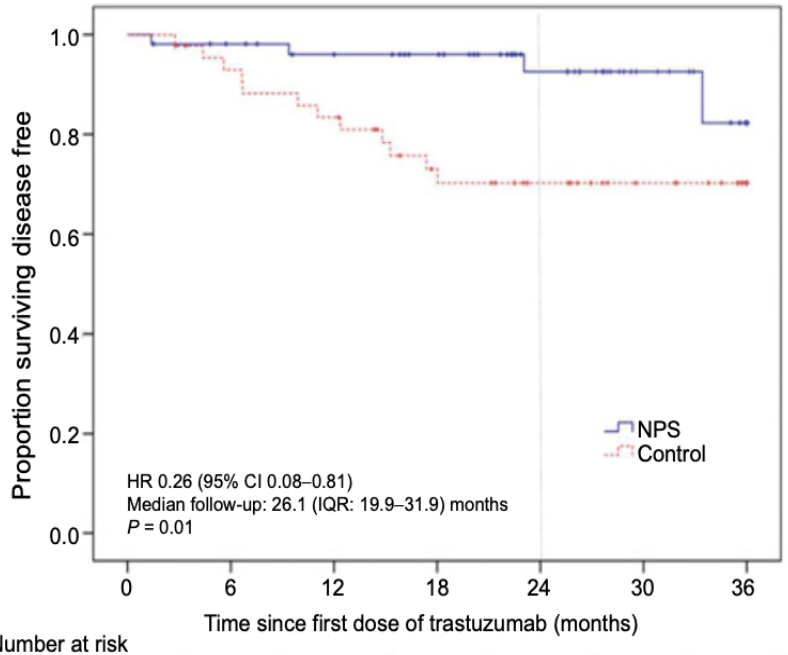
HR+/HER2 1+/2+



Number at risk

NPS	53	75	69	58	43	29	13
Control	44	83	71	62	43	28	12

HR-/HER2 1+/2+



Number at risk

NPS	53	49	45	40	27	13	7
Control	44	39	35	26	20	13	7

24 month DFS

- Vaccinated 92.6%
- Control 70.1%

- HR 0.26 (95% CI: 0.08-0.81)

Clifton GT, Clin *Cancer Res* 2020;26:2515-2523

Way Forward?

- NeuVax not being further developed
- Strong scientific rationale and encouraging phase II trial data to suggest synergy between vaccination and trastuzumab in HER2-low breast cancer
- Opportunity for improved vaccine strategies
  - Multi-epitope vaccine
  - Improved immunoadjuvant
  - Improved vaccine delivery system
- Is there a better partner than tratuzumab? (i.e. bispecific Ab with increased antigen release)

Ongoing Vaccine Trials in HER2-Low Breast

Vaccines					
HER-2/neu peptide vaccine (National Cancer Institute, Bethesda, MD)	NCT01355393	I/II; ANR	50	Stage II/III HER2-positive BC (IHC 1+ or 2+ or 3+ and/or ISH positive) or stage IV HER2-positive BC treated to NED or stable bone only disease	HER-2/neu peptide vaccine + rintatolimod *v* HER-2/neu peptide vaccine + sargramostim *v* HER-2/neu peptide vaccine + sargramostim + rintatolimod
AdHER2/neu DC vaccine (National Cancer Institute, Bethesda, MD)	NCT01730118	I; ANR	33	Advanced "anti-HER2-naïve" HER2-positive BC (IHC 1+ or 2+ or 3+ and/or FISH positive or equivocal)	AdHER2/neu DC vaccine monotherapy

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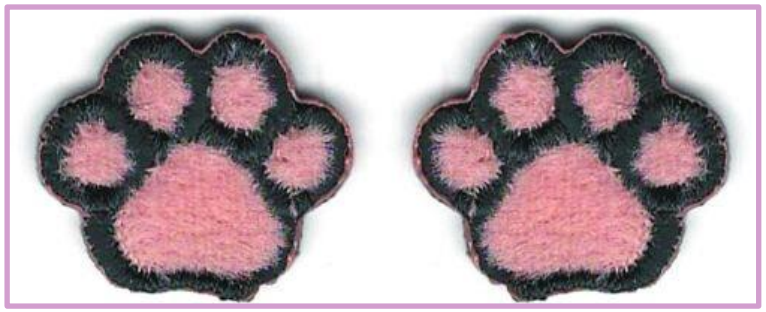


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