Progetto **CANOA**: quali novità per il 2024

Verona, 22-23 marzo 2024

Q#2. Quale impatto nella pratica clinica ?

Alberto Zambelli

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Rozzano (Mi)

Disclosure

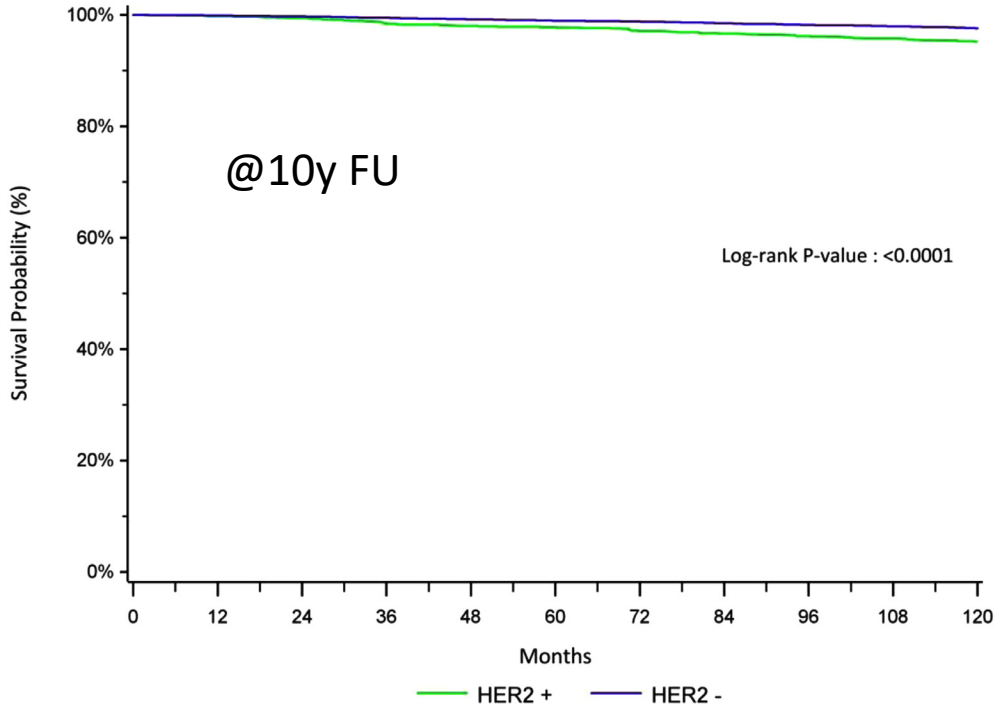
Honoraria for Consultancy and Advisory Board from:

Roche, Novartis, Lilly, AstraZeneca, Pfizer, MSD, Daiichi Sankyo, Gilead, Seagen, Exact Sciences.

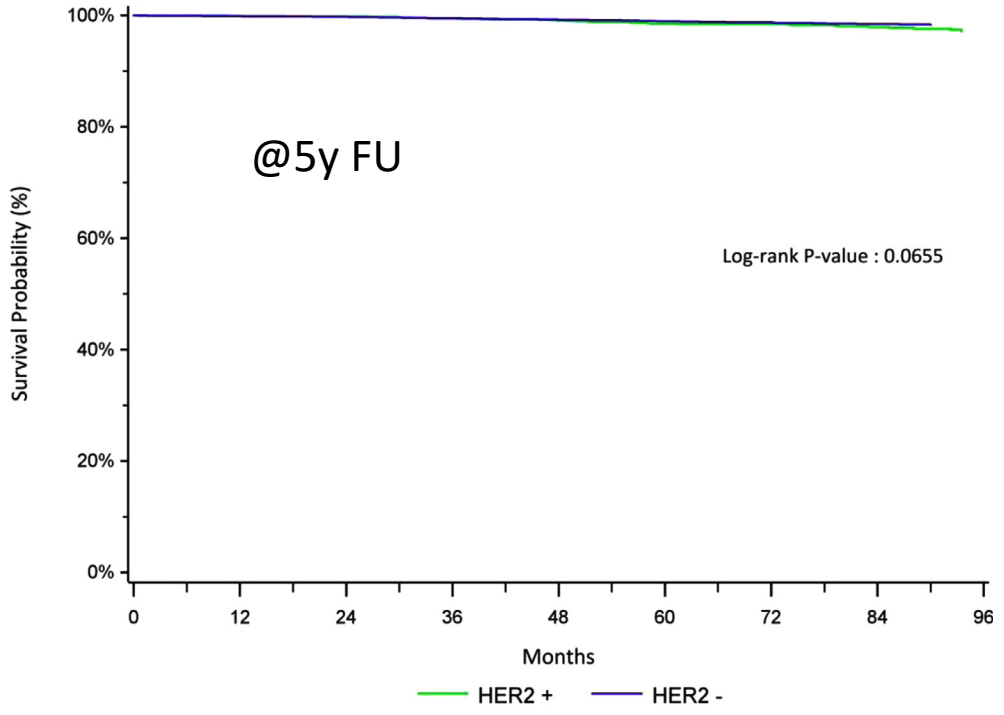
Outcomes in pT1a/b N0 eBC

BCSS in 45,346 women with T1a/b, N0 eBC b/w 2000-2012 (10% HER2-pos) by California Cancer Registry

Breast cancer-specific survival exceeding 95%



BCSS among T1a/b, N0 2000–2004 by HER2 status.



BCSS among T1a/b, N0 2005–2012 by HER2 status.

Parikh et al. CTRC, 2018

Outcomes in HER2-pos pT1a/b N0 eBC

Systematic review of 7-studies involving 1,181 patients with pT1a/b N0, HER2-pos eBC

Recurrence type	No. of studies	Total (n)	Trastuzumab, recur/total	Control, recur/total	Trastuzumab *vs*. control, odds ratio (95% CI)	P heterogeneity, I^2	P value
Overall recurrence	7	1,181	10/552 (1.8%)	55/629 (8.7%)	0.201 (0.100–0.404)	0.479, 0.0%	<0.001
Distant recurrence	5	673	0/237	16/436 (3.7%)	0.328 (0.082–1.311)	0.589, 0.0%	0.115

CI, confidence interval.

The adjuvant treatment including trastuzumab was shown to reduce overall recurrence.
Distant recurrence may also be reduced, as it did not occur among the 237 patients with trastuzumab treatment.

Yoon Lee Ann et al. Transl med 2020

Outcomes in HER2-pos pT1a/b N0 eBC (SEER)

Outcomes according to treatment received for small node-negative HER2+ breast tumors in the Surveillance, Epidemiology, and End Results (SEER) database, 2010-2019.

Adrienne Gropper Waks, Paolo Tarantino, Rachel A. Freedman, Nancy U. Lin, Nabihah Tayob, Carlos Teodoro Vallejo, Julieta Leone, Sara M. Tolaney, Jose Pablo Leone; Dana-Farber Cancer Institute, Boston, MA; Unidad Oncologica de Neuquen, Neuquen, Argentina; Cooperative Oncological Group of Sur, Neuquén, Argentina; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

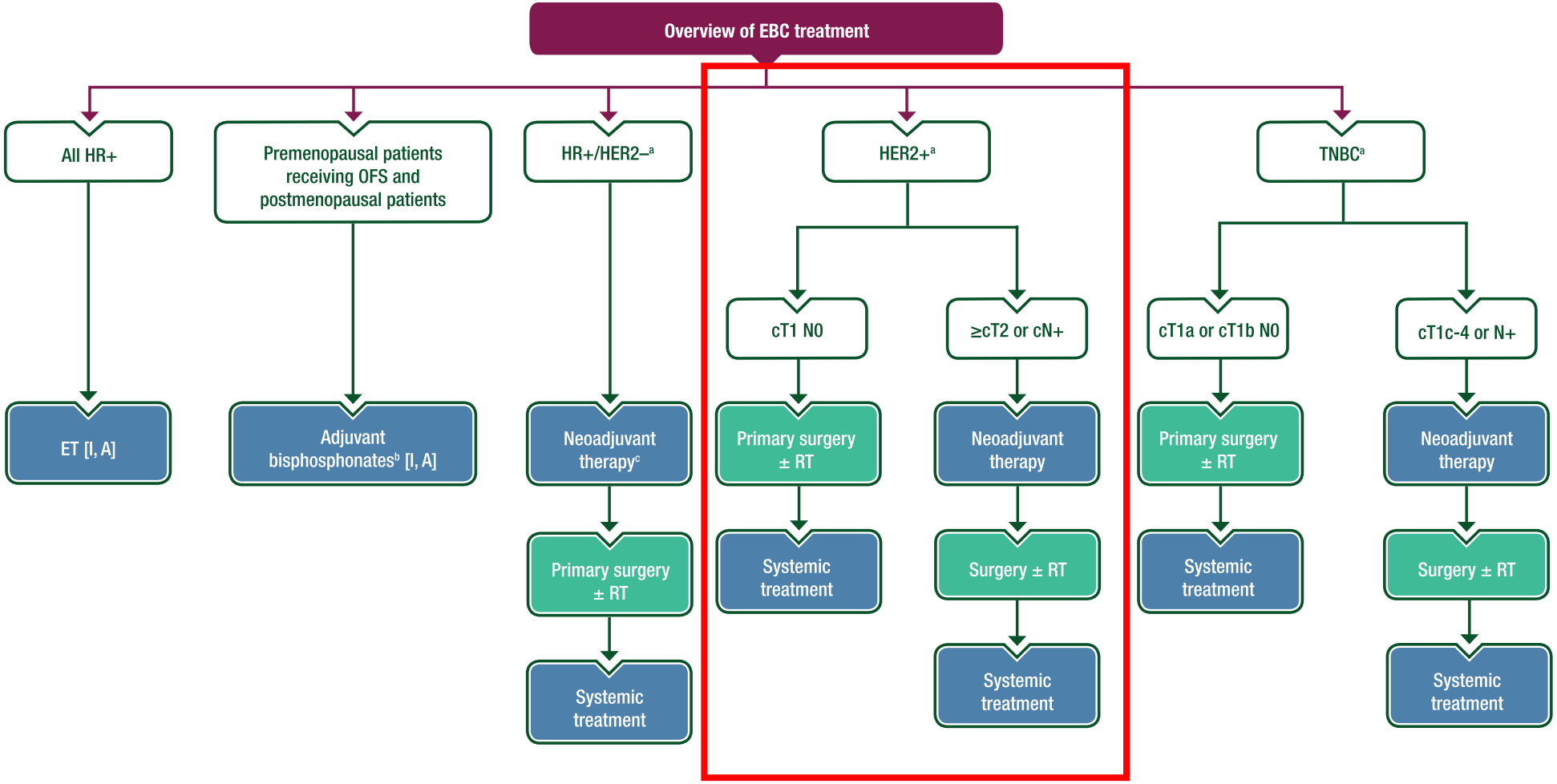
5 yr BCSS for stage IA HER2+ breast cancer.

HR+/HER2+	Overall N=9513	pT1mi N=503	pT1a N=1477	pT1b N=2439	pT1c N=5094
Chemo: yes	99.0%	100%	99.8%	99.3%	98.7%
Chemo: no/unk	97.5%	99.1%	98.9%	97.6%	95.9%
Adjusted HzR / p-value	0.60/0.009	-	-	0.67/0.421	0.60/0.02

HR-/HER2+	Overall N=3348	pT1mi N=492	pT1a N=729	pT1b N=712	pT1c N=1415
Chemo: yes	97.6%	100%	98.4%	98.9%	96.7%
Chemo: no/unk	97.3%	99.6%	98.3%	98.6%	92.1%
Adjusted HzR / p-value	0.70/0.19	-	-	-	0.61/0.137

A Gropper ASCO 2023

eBC ESMO Living Practice Guideline



Loibl S Ann Oncol 2024

HER2-pos eBC: an Italian consensus paper

Review Article

Risk-Based Therapeutic Strategies for HER2-Positive Early Breast Cancer: A Consensus Paper

Statement	QoE	Recommendation	Consensus
Neoadjuvant Therapy vs. Upfront Surgery			
1.3 Patients with cT1a/b cN0 HER2+ BC can be candidates for upfront surgery and then adjuvant therapy with paclitaxel-trastuzumab	High	Weak for	90%

Garutti et al., Clin Breast Cancer 2023

What do you do in cT1c N0 ?

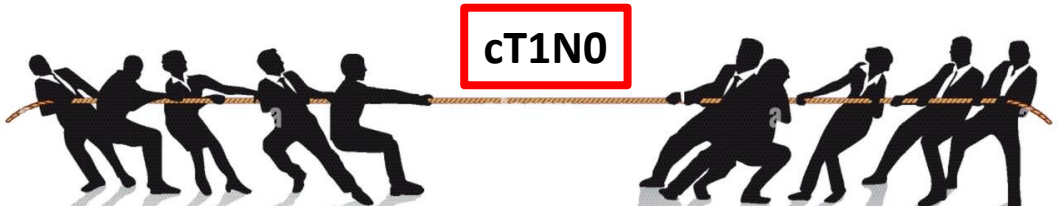
APT trial Phase2, SAT, non-RCT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

pT1-2 (<3cm) pN0

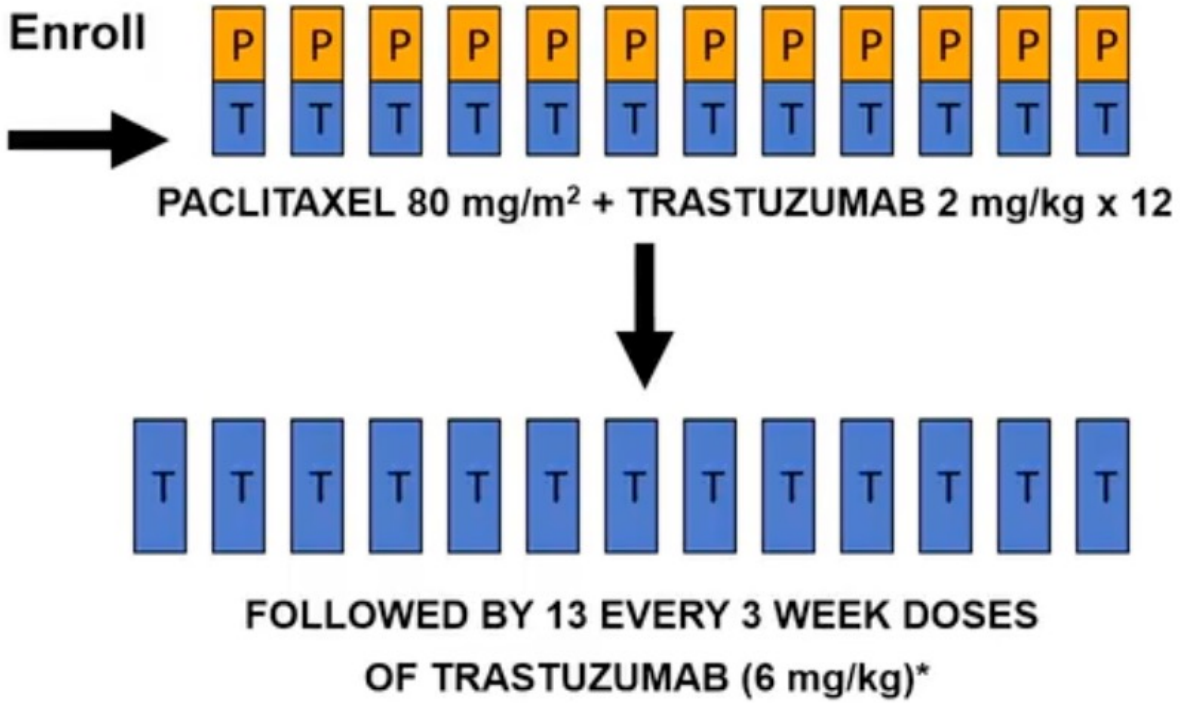


Sara M. Tolaney,

APT trial design (Ph2 SAT,not-RCT)

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

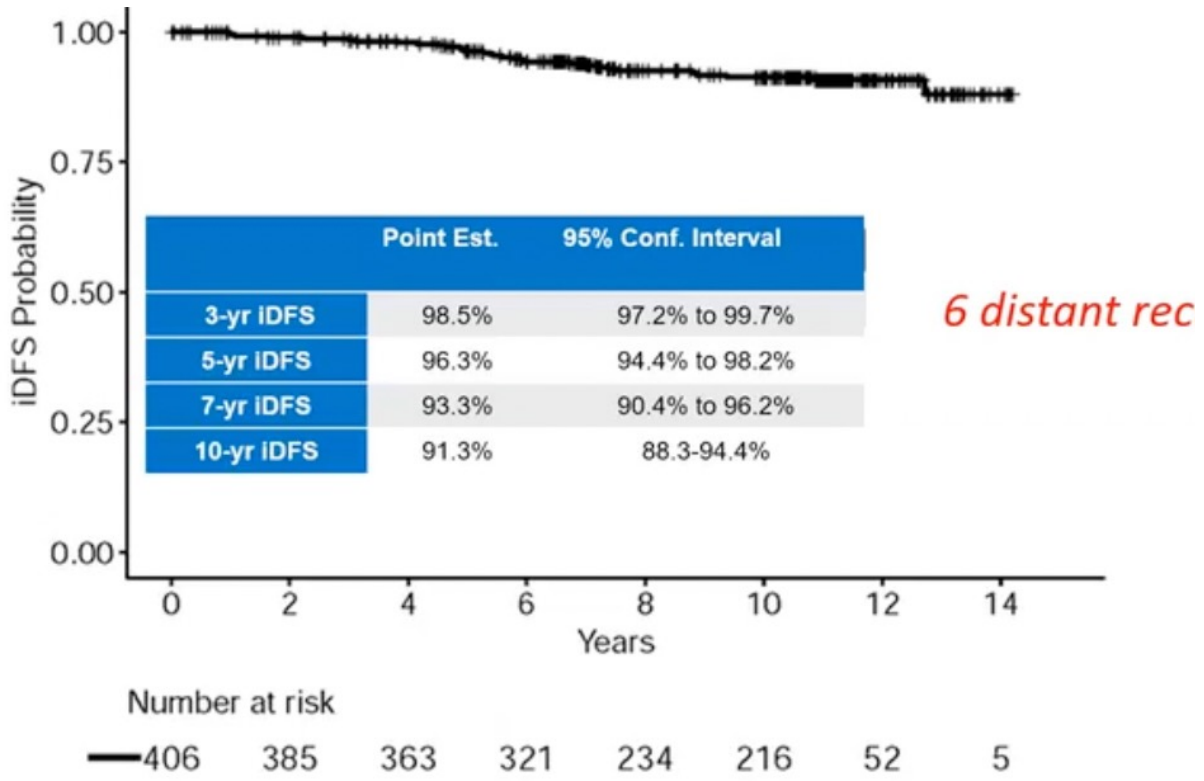
Planned N=400



Tolaney SM et al, NEJM 2015
Tolaney SM et al, JCO 2019

APT trial results

	N	%	
Age			
<50	132	33	
50-70	232	57	
≥70	40	10	
Size of Primary Tumor			
T1a ≤0.5 cm	78	19	~90%
T1b >0.5-≤1.0	123	30	
T1c >1.0-≤2.0	169	42	
T2 >2.0-≤3.0	36	9	
Histologic Grade			
I Well differentiated	44	11	
II Moderately differentiated	131	32	
III Poorly differentiated	228	56	
HR Status (ER and/or PR)			
Positive	272	67	
Negative	134	33	

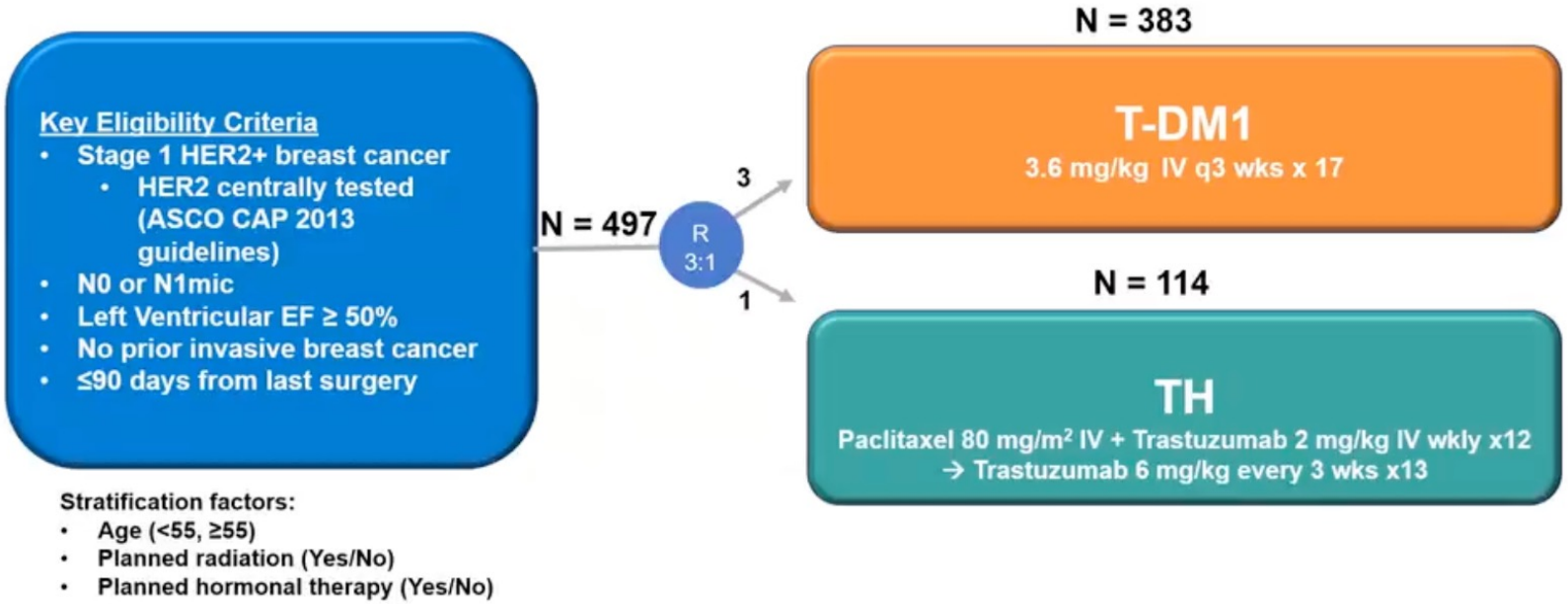


6 distant rec

31 IDFS events: 6 DR (19%), 6 ILRR (19%), 9 CLBC (29%, 8/9 HER2-neg), 10 all causes of death

Tolaney SM et al, NEJM 2015
Tolaney SM et al, JCO 2019

ATEMPT trial design



Two co-primary EP:

1. compare the incidence of CRTL
2. evaluate IDFS in pts with TDM-1

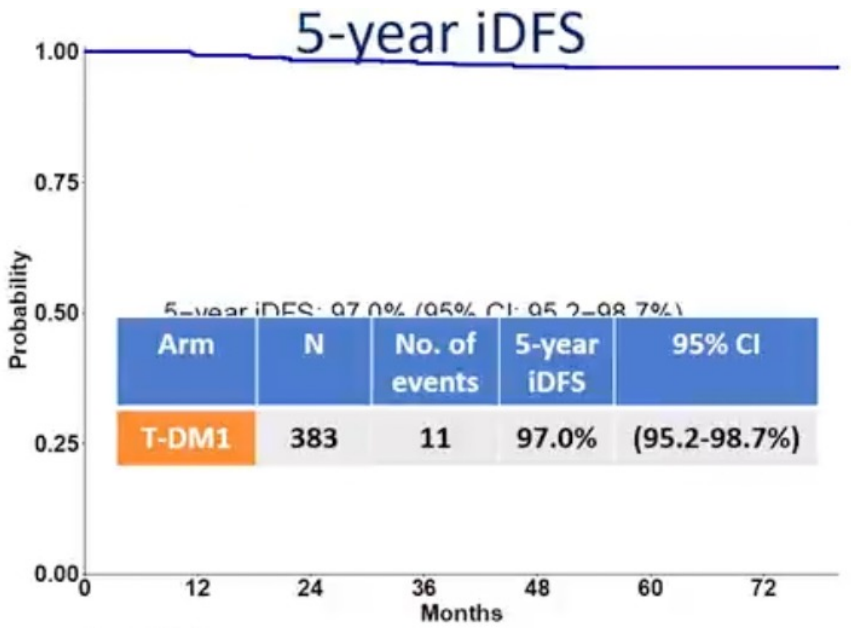
Tolaney SM et al, SABCS 2019
Tolaney SM et al, JCO 2021

ATEMPT trial results

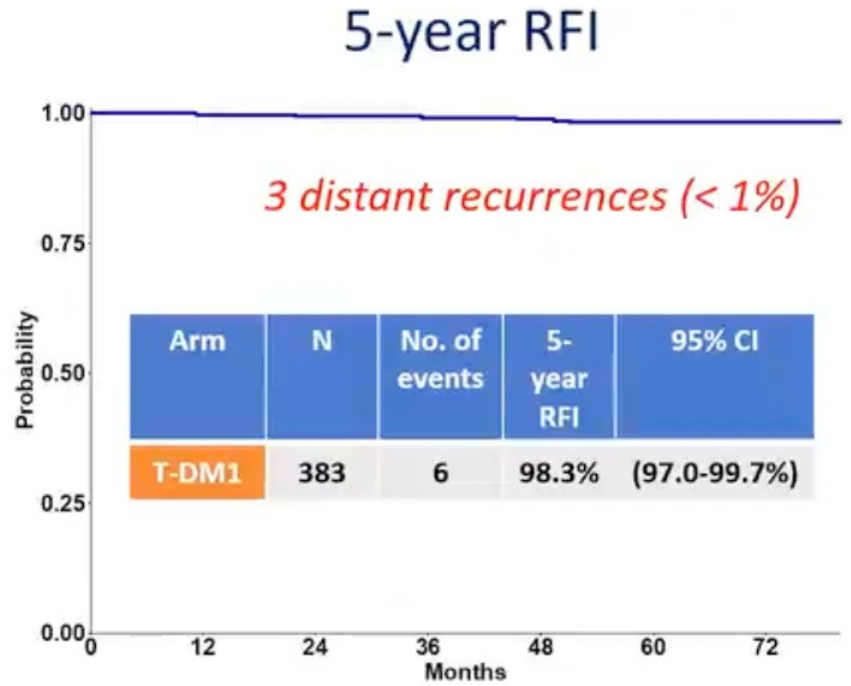
	T-DM1 (n = 383)	TH (n = 114)	All Patients (n = 497)
Median Age (Range)	56 (32-85)	55 (23-82)	56 (23-85)
Tumor Size			
<0.5 cm	42 (11%)	14 (12%)	56 (11%)
≥0.5-1.0 cm	121 (32%)	38 (33%)	159 (32%)
≥1.0-1.5 cm	118 (31%)	29 (25%)	147 (30%)
≥1.5-2.0 cm	102 (27%)	33 (29%)	135 (27%)
Histologic Grade			
Well Differentiated	11 (3%)	4 (4%)	15 (3%)
Moderately Differentiated	148 (39%)	46 (40%)	194 (39%)
Poorly Differentiated	219 (57%)	62 (54%)	281 (57%)
Unknown	5 (1%)	2 (2%)	7 (2%)
HR status			
Positive	289 (75%)	84 (74%)	373 (75%)
Negative	94 (25%)	30 (26%)	124 (25%)
HER2 Status (Central)			
1+	5 (1%)	1 (1%)	6 (1%)
2+	92 (24%)	25 (22%)	117 (24%)
3+	277 (72%)	87 (76%)	364 (73%)
Not done*	9 (2%)	1 (1%)	10 (2%)

Tolaney SM et al, SABCS 2019
Tolaney SM et al, JCO 2021

ATEMPT 2.0 is on-going (TDM-1 x 6c q3w)



Arm	N	No. of events	5-year iDFS	95% CI
T-DM1	383	11	97.0%	(95.2-98.7%)



3 distant recurrences (< 1%)

Arm	N	No. of events	5-year RFI	95% CI
T-DM1	383	6	98.3%	(97.0-99.7%)

HER2-pos eBC: an Italian consensus paper

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1.3 Patients with cT1a/b cN0 HER2+ BC can be candidates for upfront surgery and then adjuvant therapy with paclitaxel-trastuzumab	High	Weak for	90%
1.4 In patients with cT1c cN0 HER2+ BC, upfront surgery could represent a treatment option, although neoadjuvant therapy could be considered in selected cases	Low	Weak for	100%

Garutti et al., Clin Breast Cancer 2023

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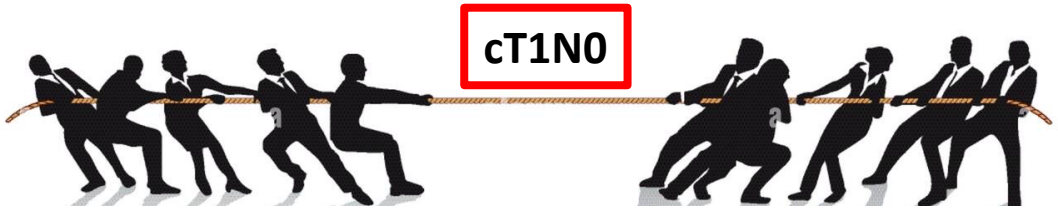
KATHERINE trial: Phase3, RCT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 14, 2019 VOL. 380 NO. 7

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

cT1-4, cN0-3, excluding T1abN0

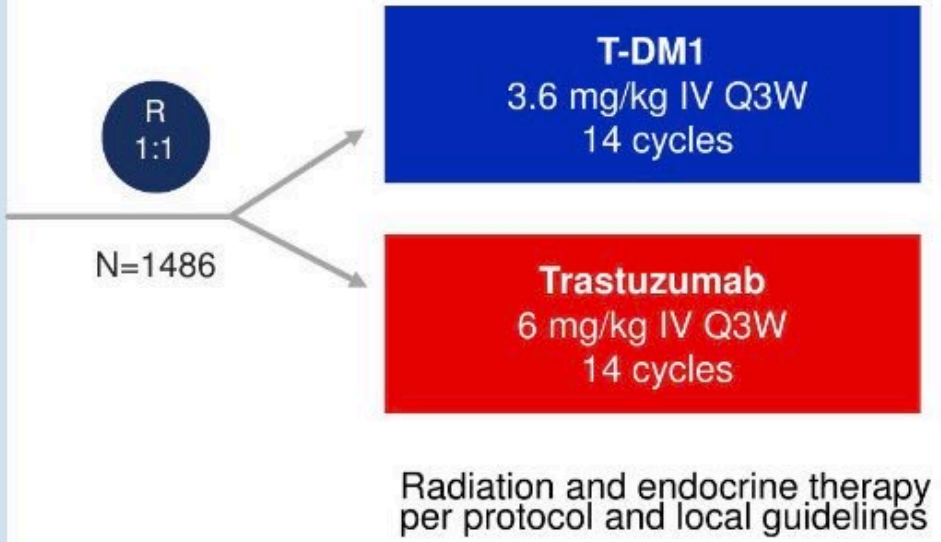


Sara M. Tolaney,

G. von Minckwitz,

KATHERINE trial design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

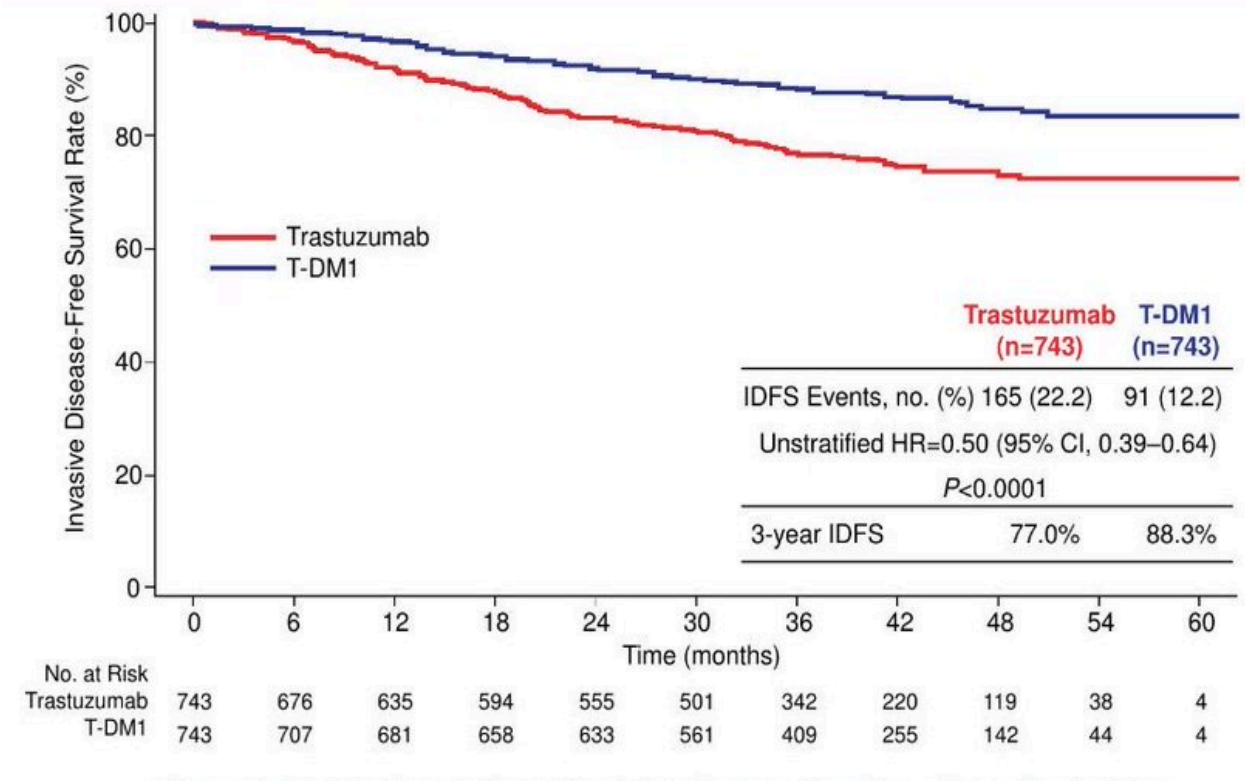
G. von Minckwitz et al. NEJM 2019

KATHERINE trial – results

The quote of pts w/o previous exposure to anthracicline is quite limited (24%)

Characteristics	AC-based NACT		Non-AC-based NACT	
	T-DM1 (*n*=579)	Trastuzumab (*n*=564)	T-DM1 (*n*=164)	Trastuzumab (*n*=179)
Median age (range), y	48 (24–73)	48 (23–80)	51 (25–79)	51 (28–78)
Primary tumor stage at initial diagnosis, *n* (%)				
cT1	72 (12.4)	56 (9.9)	27 (16.5)	25 (14.0)
cT2	288 (49.7)	281 (49.8)	77 (47.0)	108 (60.3)
cT3	135 (23.3)	148 (26.2)	42 (25.6)	37 (20.7)
cT4, cT4a, cT4b, cT4c	48 (8.3)	49 (8.7)	11 (6.7)	5 (2.8)
cT4d	36 (6.2)	30 (5.3)	7 (4.3)	4 (2.2)

N=180



In 77 pts with cT1cN0 and with RD at surgery **6 IDFS events were observed all of which occurred in the 32 trastuzumab recipients** (3 non-CNS mets, 2 CNS recurrences, and 1 contralateral BC).

None of the 45 pts with T-DM1 had an IDFS event.

G. von Minckwitz et al. NEJM 2019

KATHERINE in the context

The NeoCT FDA metanalysis

12 preop clinical trial (N 11.955)

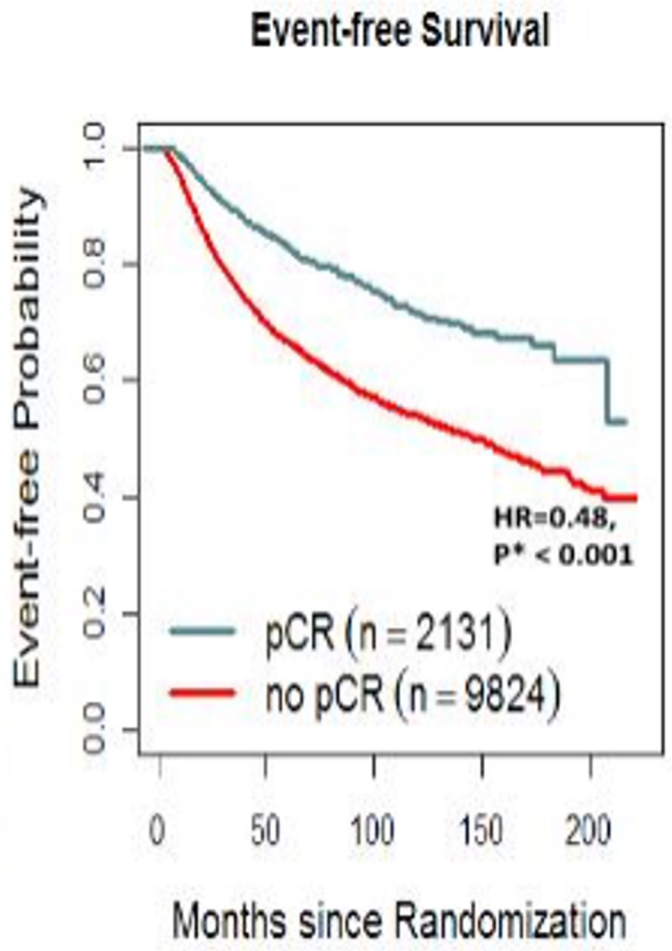
Inclusion criteria : >200pts/trial

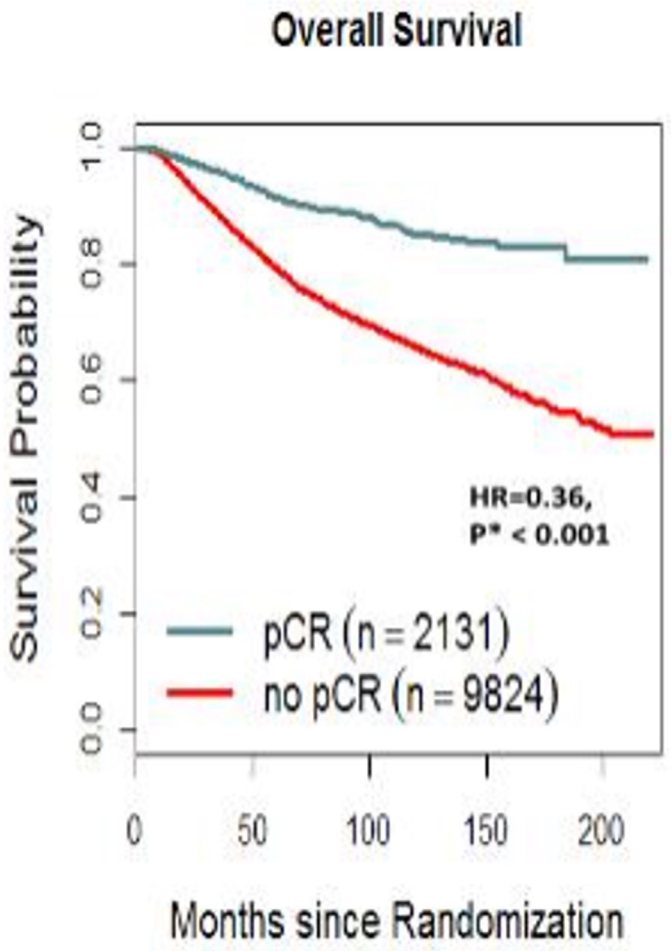
Available data for pCR) EFS/OS (at least 3yrs FU)

Metanalysis per individual data (pCR vs no pCR)

Analysis at patient level and at trial level

TRIALS	Patients (n)
GBG/AGO: 7	6377
NSABP: 2	3171
EORTC/BIG: 1	1856
ITA: 2	1589
Total # patients	12993





pCR=ypT0/is ypN0

Lancet. 2014 12;384:164-172

KATHERINE hidden clinical implication

RD after HER2-directed NAT defines a group of tumors enriched for relative resistance to trastuzumab and the same drug(s) should not continue as adjuvant after RD at surgery (peri-operative approach)

As a hidden implication of KATHERINE, we should maximize the chances of pCR during neoadjuvant treatment

After KATHERINE, the application of an adjuvant strategy to patients with high risk HER2+ eBC is suboptimal and in many of them detrimental.

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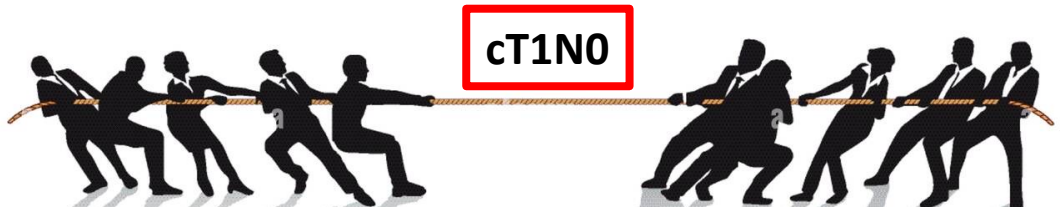
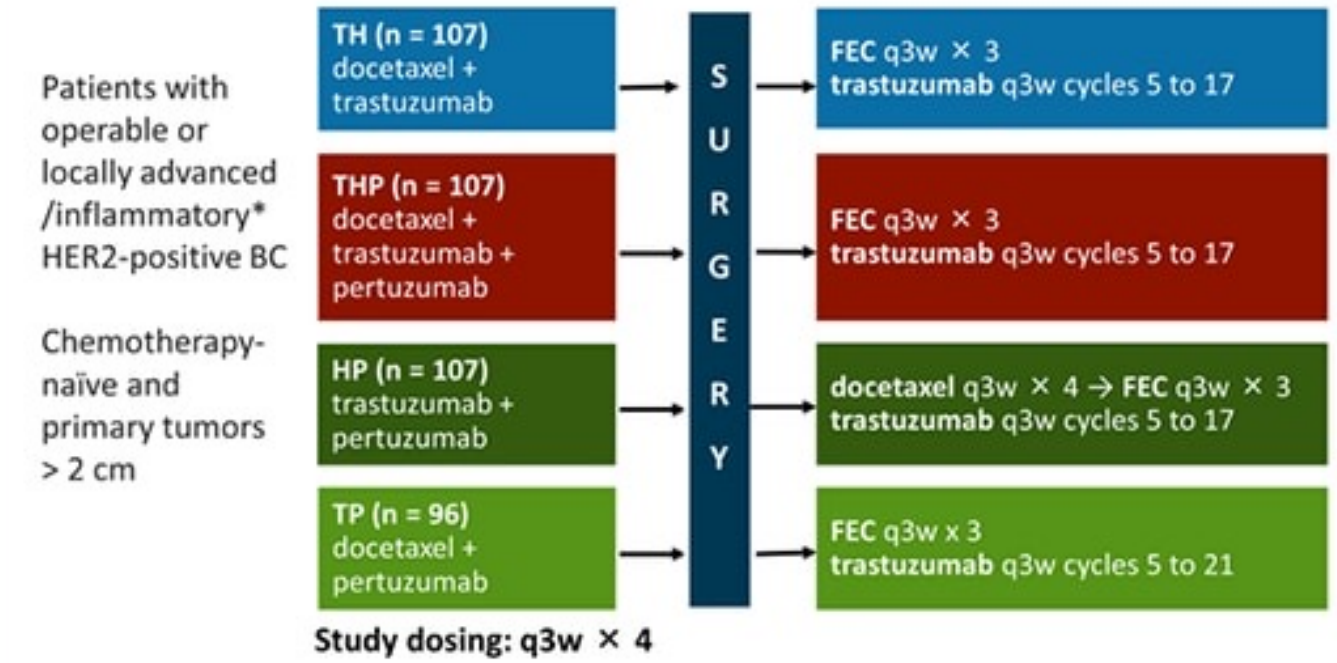
1.4 In patients with cT1c cN0 HER2+ BC, upfront surgery could represent a treatment option, although neoadjuvant therapy could be considered in selected cases	Low	Weak for	100%
3.6 In cT1N0 patients, wPx12 + trastuzumab may be considered as a preoperative approach in selected cases	Low	Weak for	100%



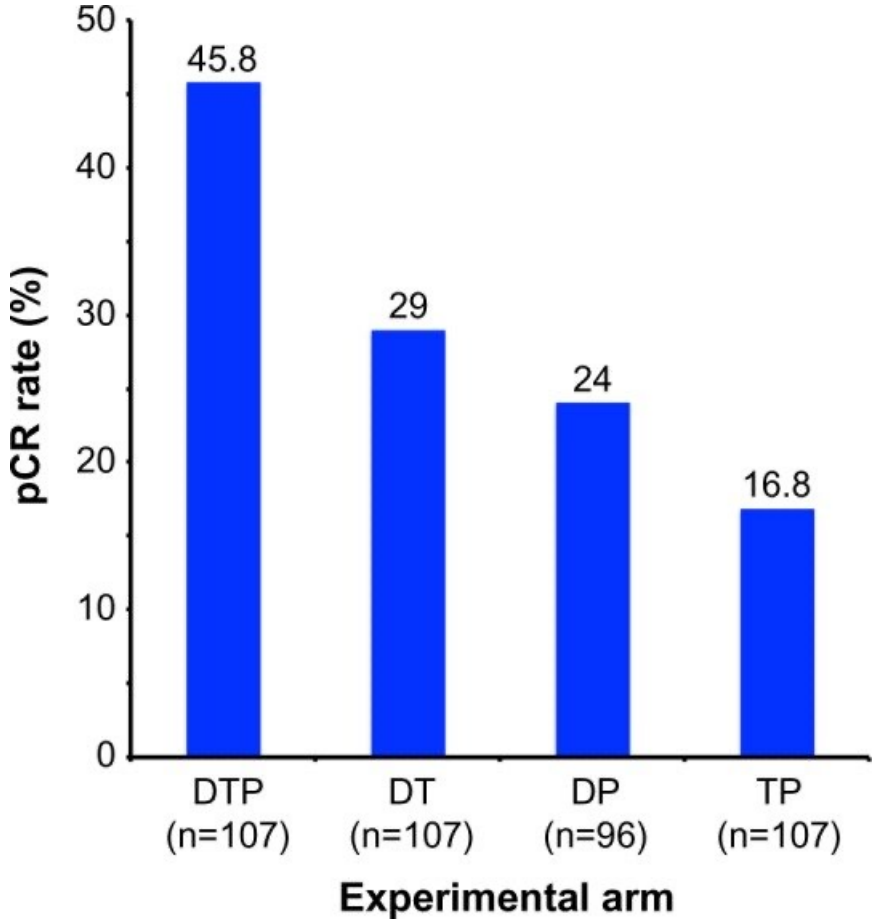
Garutti et al., Clin Breast Cancer 2023

(Neo)adj Tx : the max tolerated Tx

NeoSPHERE trial – pCR



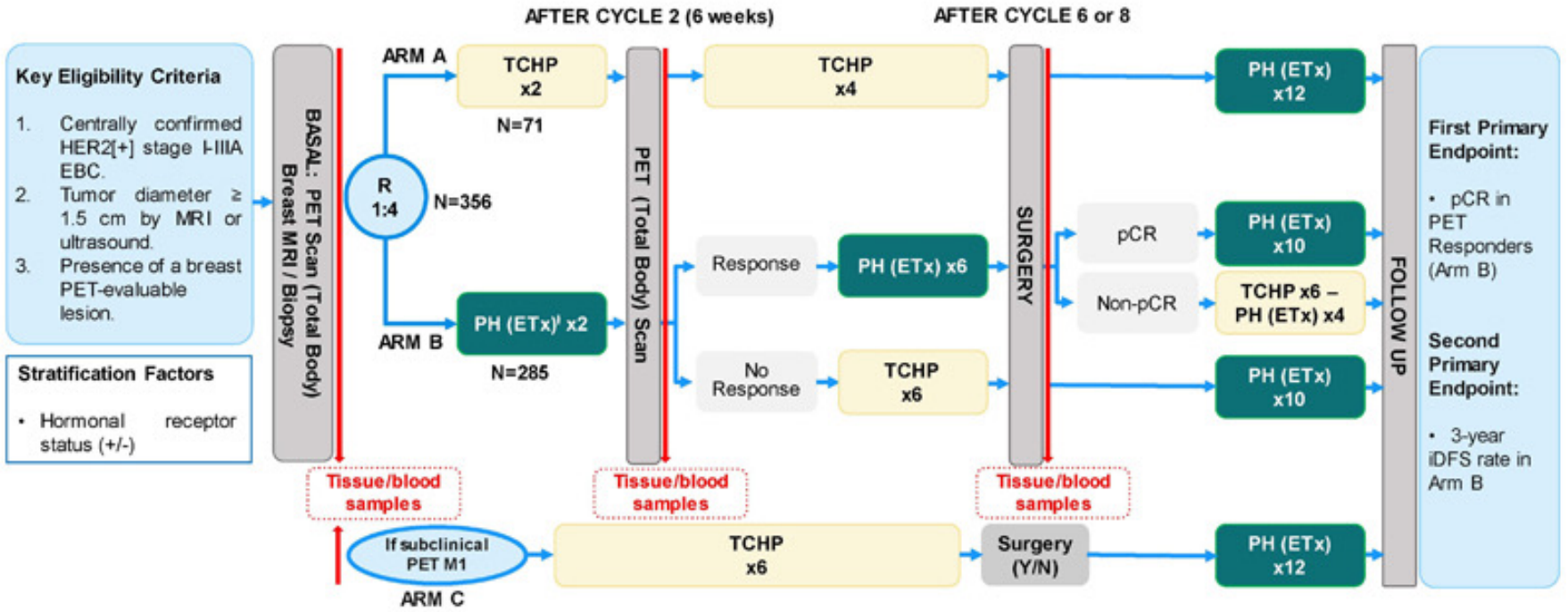
*Locally advanced = T2-3, N2-3, M0 or T4a-c, any N, M0; operable = T2-3, N0-1, M0; inflammatory = T4d, any N, M0



L Gianni, The Lancet et al. 2012

(Neo)adj: the min effective Tx

PHERGAIN trial design: a paradigm shift



ARM B (HP) : pCR in PET responders 37.9% (p<0.001, null hypothetsis <=20%)
IDFS @3y 95.4% (p<0.001, null hypothesis <90%)

J Cartes SABCS 2023

Re-appraisal of pCR in HER2

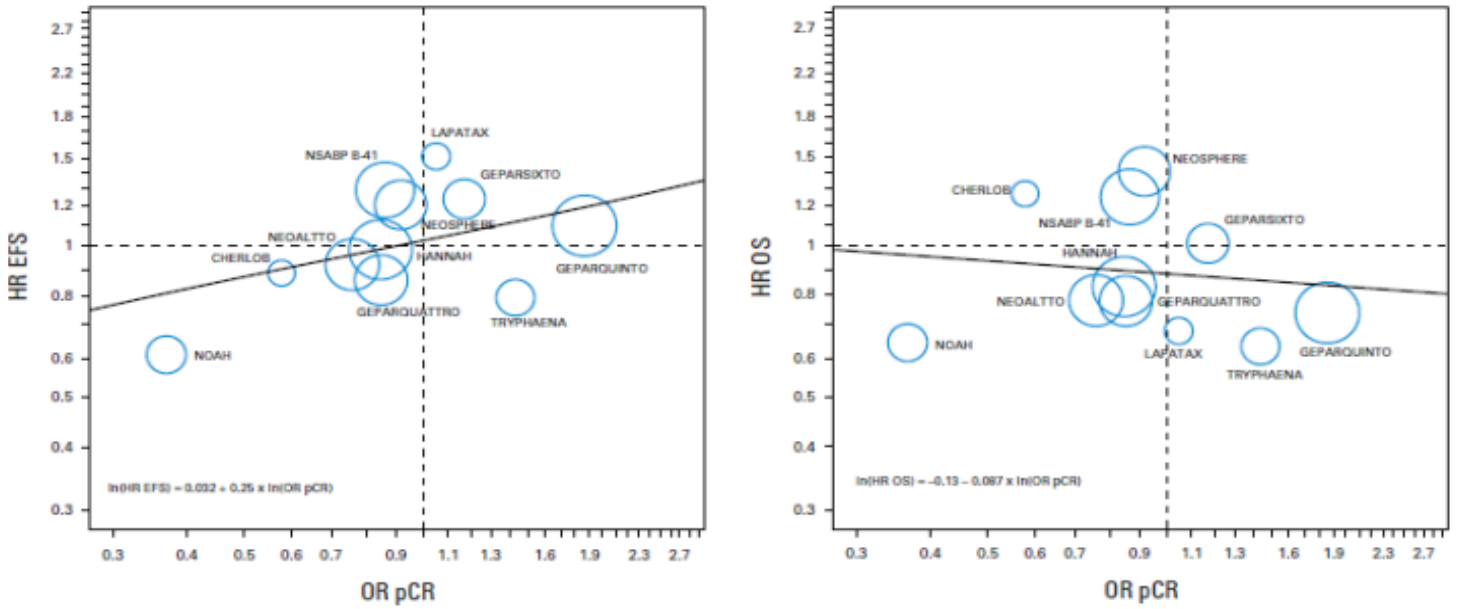
pCR surrogacy at patients level not at trial (CTneoBC)

Re-Evaluation of Pathologic Complete Response as a Surrogate for Event-Free and Overall Survival in Human Epidermal Growth Factor Receptor 2–Positive, Early Breast Cancer Treated With Neoadjuvant Therapy Including Anti–Human Epidermal Growth Factor Receptor 2 Therapy

Pierre Squifflet, MSc[1]; Everardo D. Saad, MD[1]; Sibylle Loibl, MD[2]; Marion T. van Mackelenbergh, MD[2]; Michael Untch, MD[3];

CONCLUSION

pCR cannot be used as a trial-level surrogate for either EFS or OS prognostic role



pCR & surrogacy:

- clear at patient level
- poor at trial level

IMPLICATION

Obtaining a pCR is good for individual patients, but the relationship between pCR and long-term outcome across trials is poor.
The use of pCR as a surrogate for early drug approval should be revisited

Pierre Squifflet, J Clin Oncol 2023

Disconnection between pCR and EFS/OS

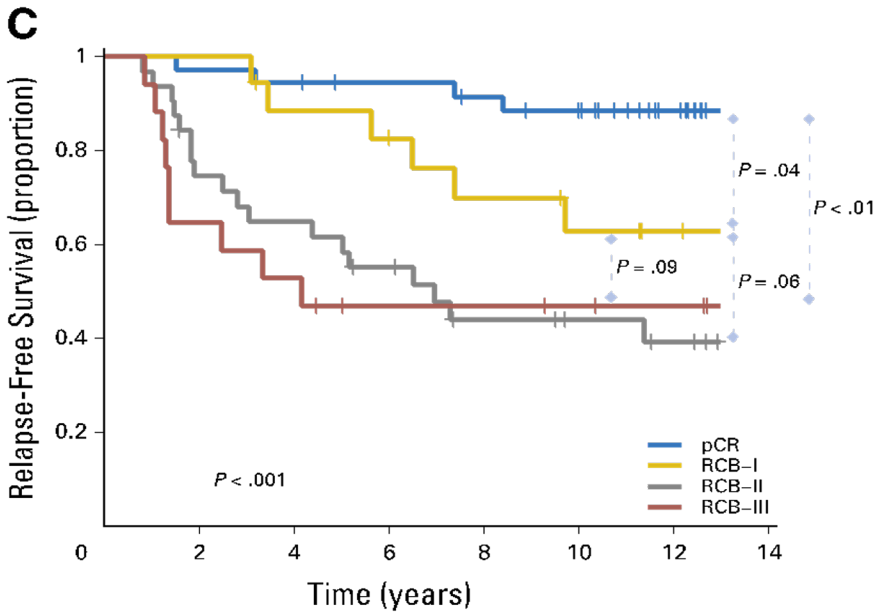
Clinical point of view: RCB

The long-term prognosis in each phenotypic subset of BC related to RCB after NAC

(N 1158 at MDACC)

HER2-pos

No Tras



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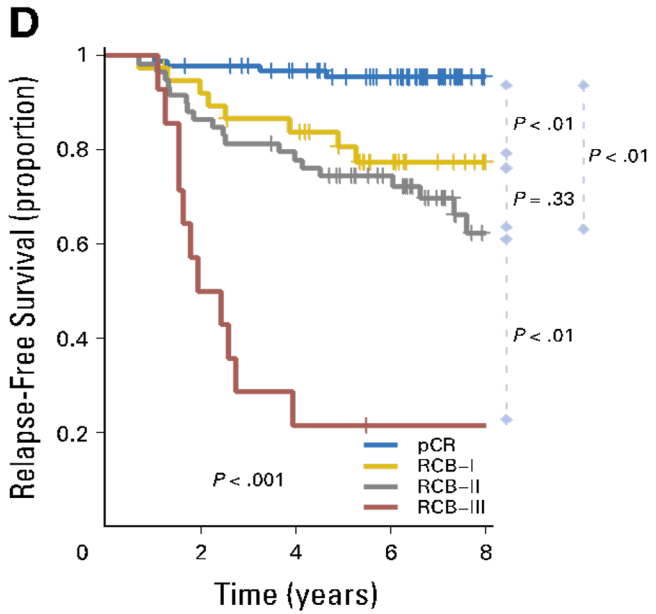


Symmans JCO 2017

Disconnection between pCR and EFS/OS

Cinical point pfview: the quality effect of pCR

Pathologic Complete Response and Individual Patient Prognosis After Neoadjuvant Chemotherapy Plus Anti–Human Epidermal Growth Factor Receptor 2 Therapy of Human Epidermal Growth Factor Receptor 2–Positive Early Breast Cancer

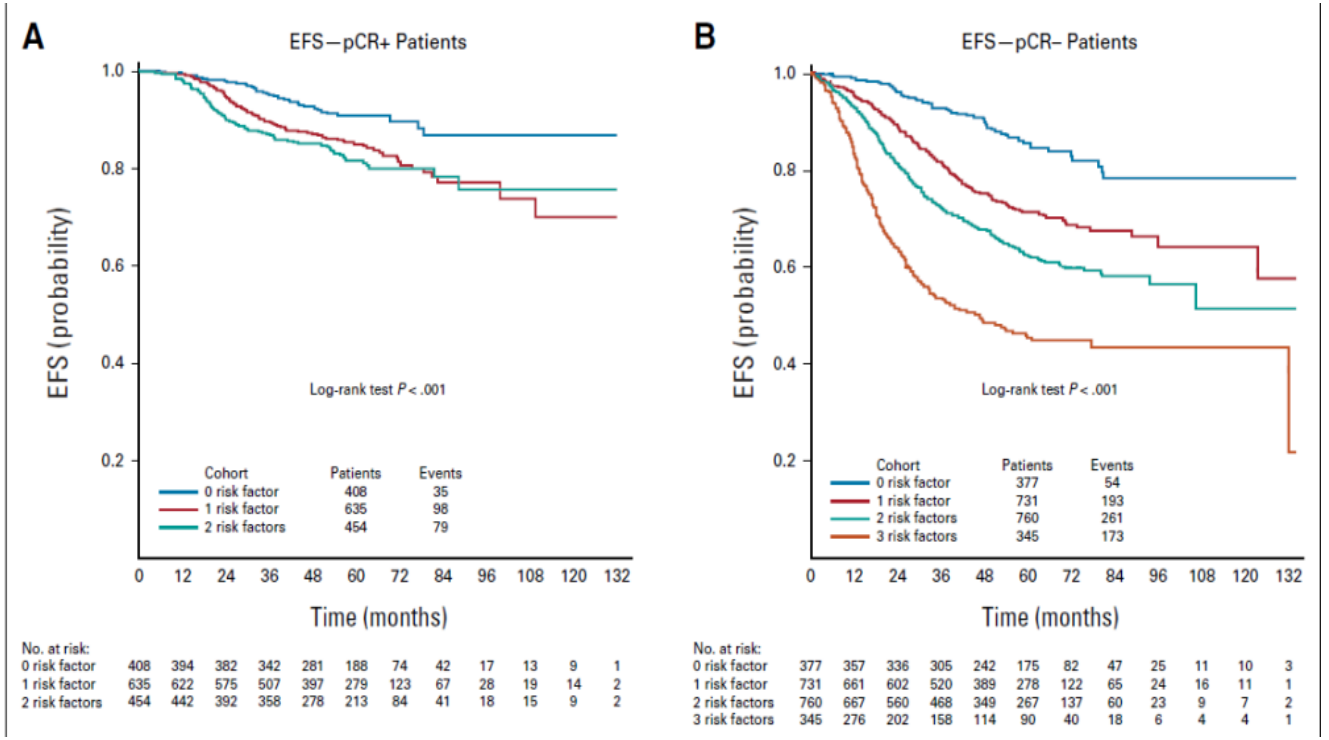
Marion T. van Mackelenbergh, MD, PhD[1]; Sibylle Loibl, MD[2]; Michael Untch, MD[3]; Marc Buyse, PhD[4]; Charles E. Geyer Jr, MD[5];

	pCR−				pCR+			
	EFS		OS		EFS		OS	
Prognostic Factor	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
cT (cT1-2 *v* cT3-4)	0.62 (0.53 to 0.73)	<.001	0.47 (0.37 to 0.60)	<.001	0.67 (0.50 to 0.90)	.007	0.55 (0.34 to 0.87)	.011
cN (cN− *v* cN+)	0.66 (0.55 to 0.79)	<.001	0.75 (0.58 to 0.96)	.025	0.72 (0.53 to 0.98)	.039	0.61 (0.36 to 1.03)	.065
Hormone receptor status (hormone receptor+ *v* hormone receptor−)	0.59 (0.50 to 0.68)	.005	0.44 (0.36 to 0.55)	<.001	0.97 (0.73 to 1.29)	.842	0.76 (0.47 to 1.22)	.251

Abbreviations: cN, clinical nodal status; cT, clinical tumor size; EFS, event-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response.

Beyond pCR:

- cT and cN
- HR (no pCR only)



IMPLICATION

Many had assumed that achieving a pCR was the great equalizer and that patients with a pCR had a low risk of recurrence regardless of the extent of disease at diagnosis. These results are sobering.

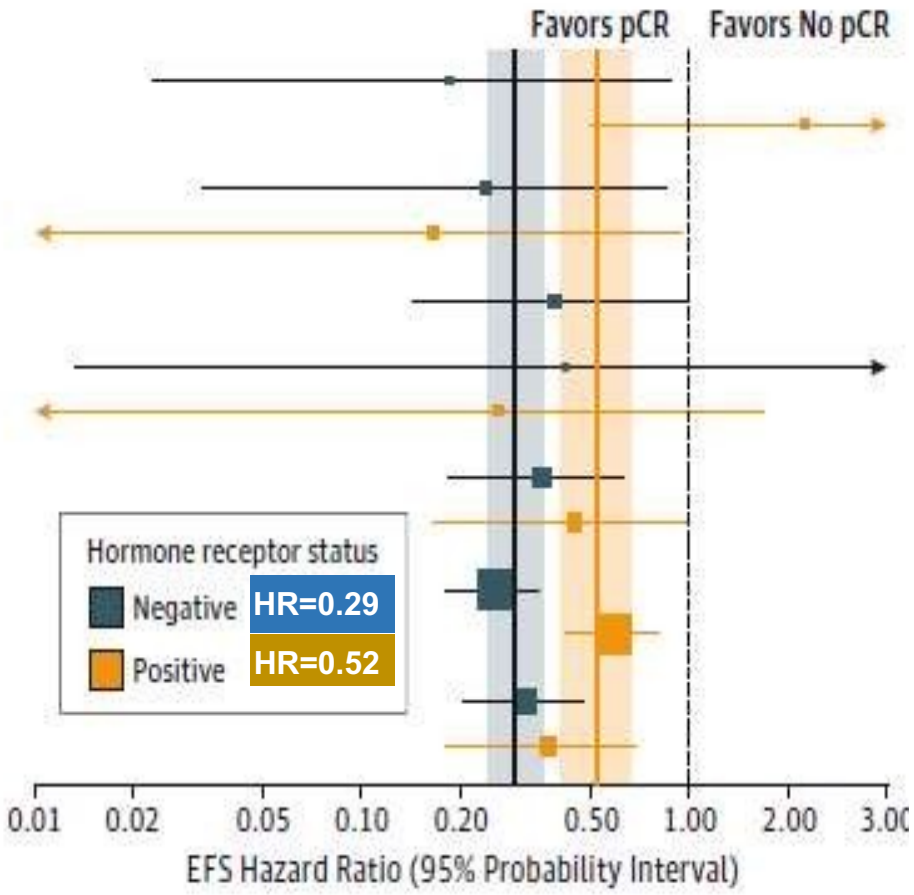
Marion T. van Mackelenbergh J Clin Oncol 2023

Disconnection between pCR and EFS/OS

Biological point of view: ER expression

A EFS by hormone receptor status groups

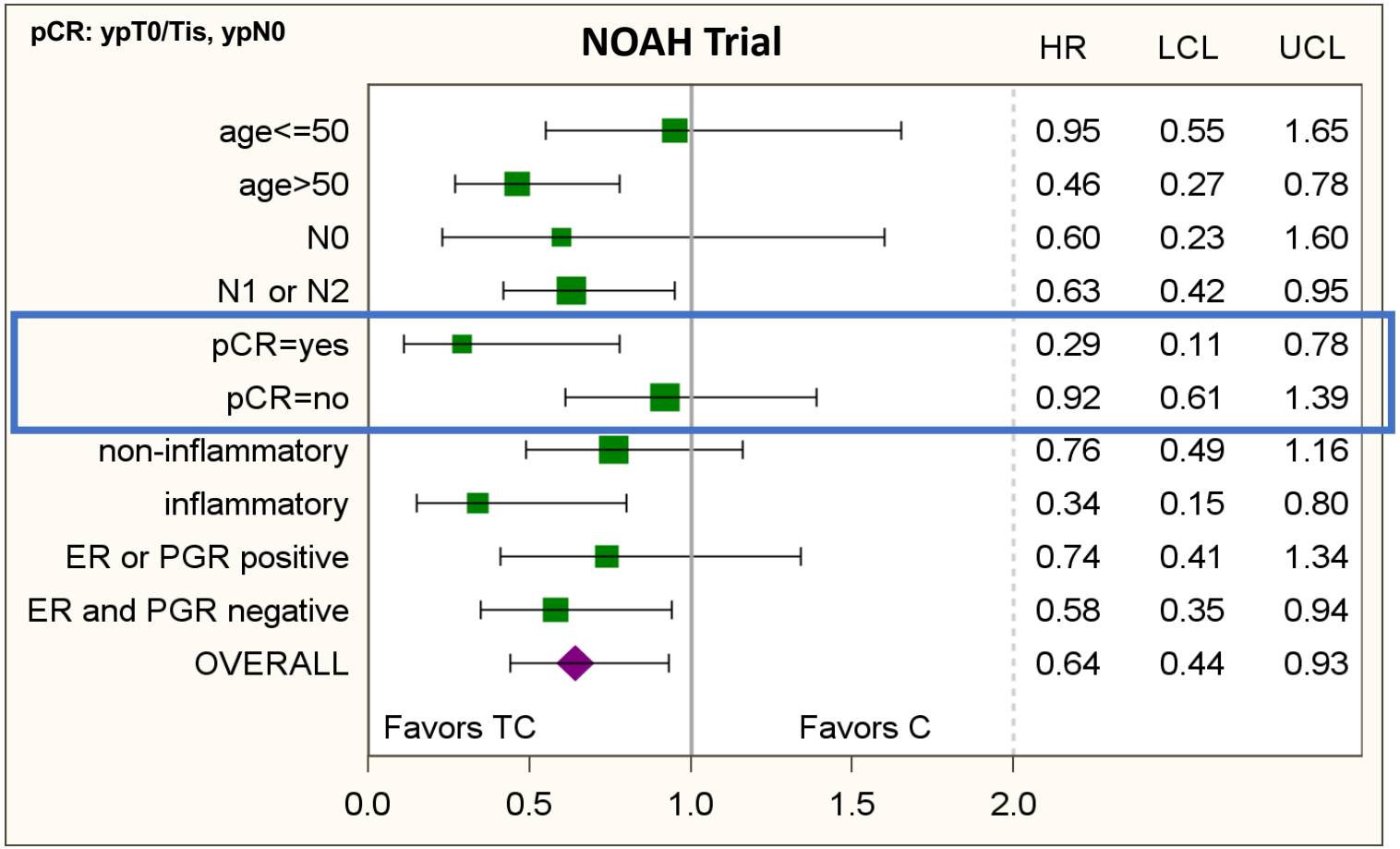
Source	pCR Events/N	No pCR Events/N
Esserman et al,[6] 2012	2/19	6/14
	4/11	4/22
Krishnan et al,[51] 2013	2/13	22/42
	1/9	17/38
Natoli et al,[33] 2013	7/44	13/36
Sánchez-Muñoz et al,[46] 2013	1/8	2/8
	1/5	9/17
de Azambuja et al,[53] 2014	14/87	47/124
	6/50	36/150
Cortazar et al,[5] 2014	48/325	223/510
	43/247	243/839
Takada et al,[30] 2014	35/281	62/158
	11/120	54/214



Broglio K, et al. JAMA Oncol 2016

Disconnection between pCR and EFS/OS

Clinical point of view: the quality of pCR by treatment

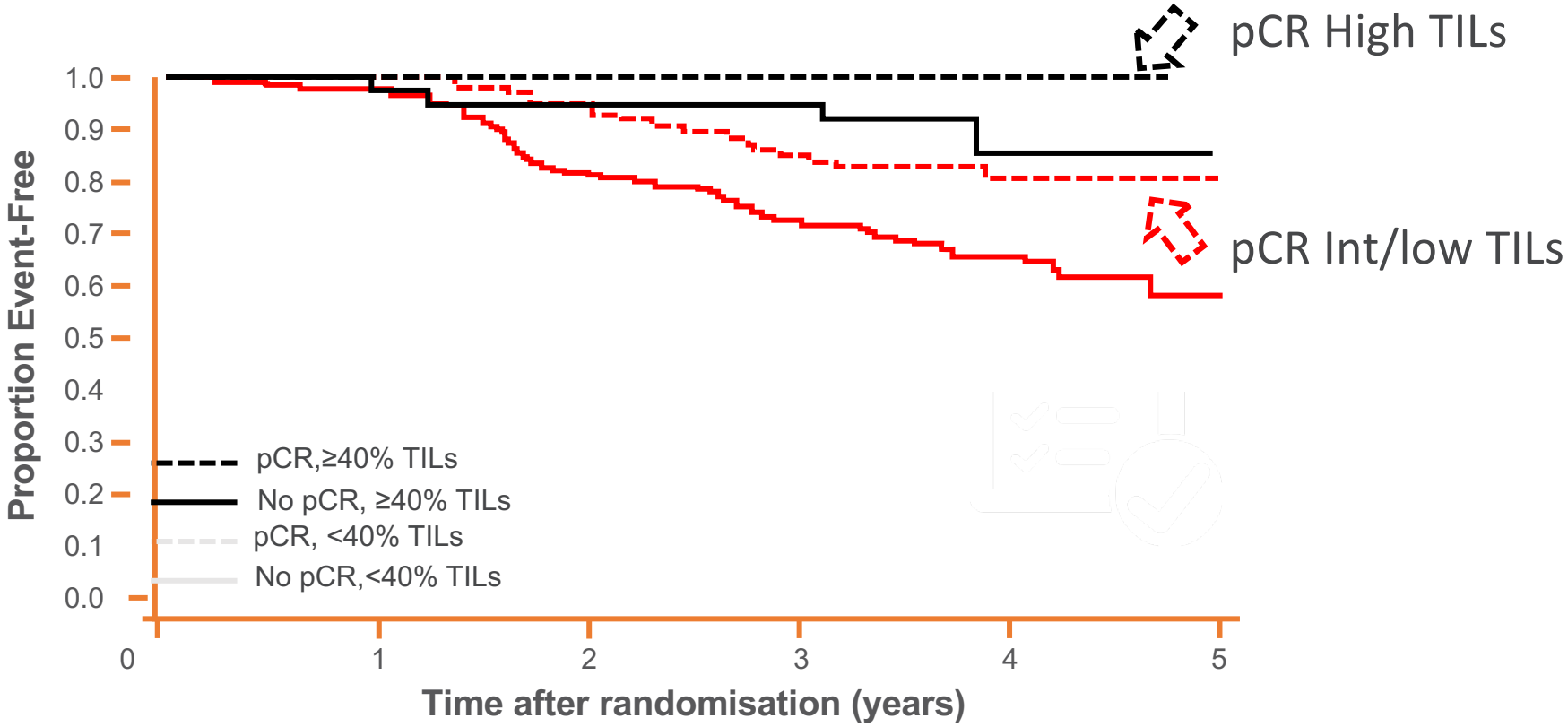


pCR with Trastuzumab+CT is better than pCR with CT only
Trastuzumab benefit over CT is weak to nil w/o pCR

Gianni L et al, Lancet Oncol 2014

Disconnection between pCR and EFS/OS

Biological point of view: Immune features



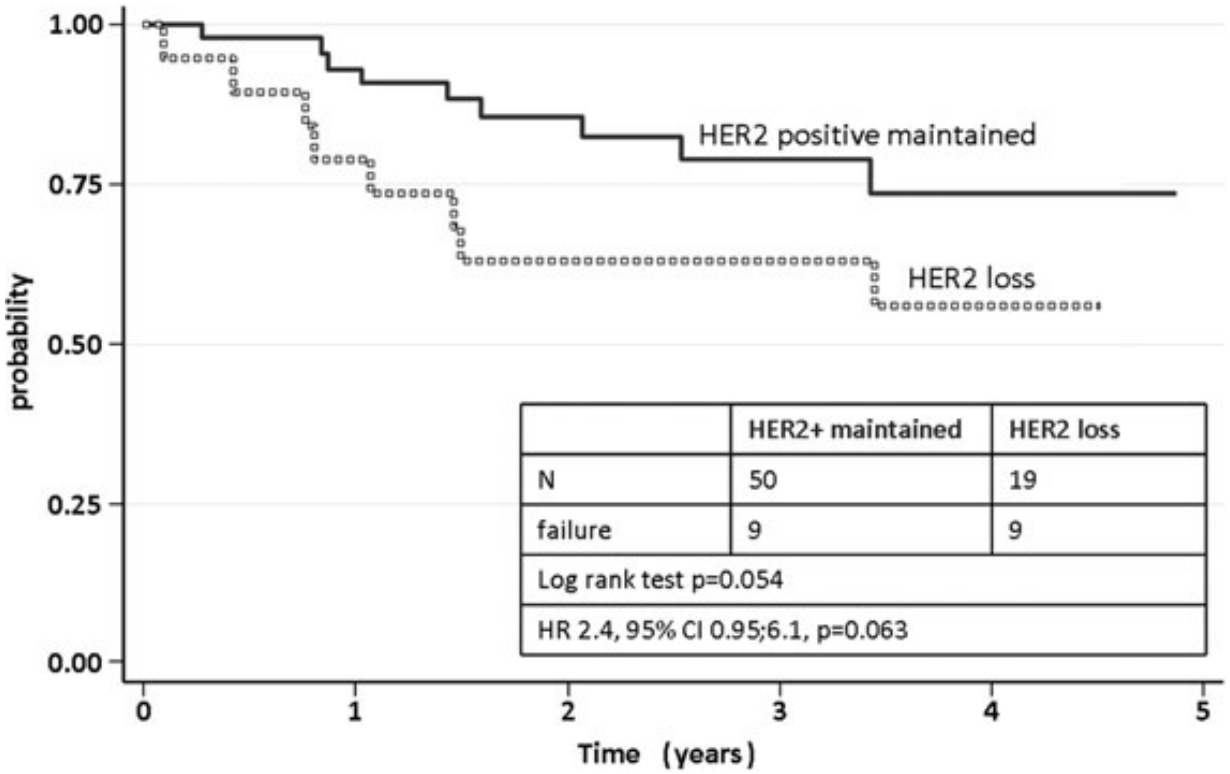
No. at risk						
pCR, ≥40% TILs	21	21	20	20	9	0
pCR, <40% TILs	98	97	89	75	33	3
No pCR, ≥40% TILs	39	36	33	33	13	0
No pCR, <40% TILs	218	188	155	134	69	1

Salgado R *JAMA Oncol* 2015

Disconnection between pCR and EFS/OS

Biological point of view: HER2 heterogeneity

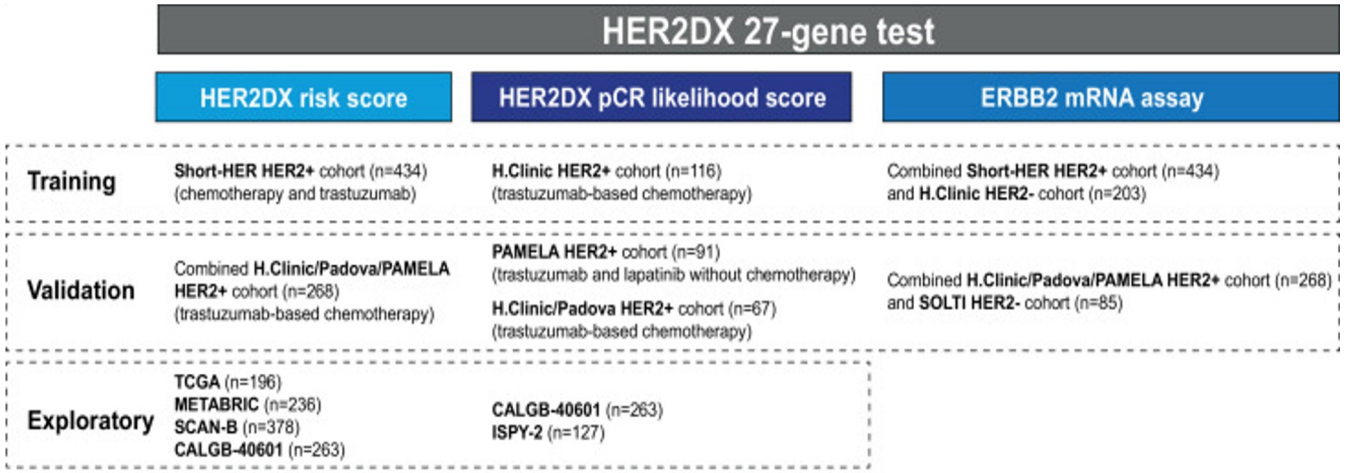
	Cohort A ($N = 40$) Chemotherapy	Cohort B ($N = 67$) Chemotherapy + anti-HER2	*P*-value
Median age (minimum–maximum)	49 yrs (29–76)	47 yrs (26–80)	
pCR, *n* (%)			
Yes	3 (7.5%)	29 (43.8%)	<0.001
No	37 (92.5%)	38 (56.7%)	
Breast-conserving surgery, *n* (%)			
Yes	15 (38.5%)	39 (58.2%)	0.050
No	24 (61.5%)	28 (41.8%)	
HER2 loss[a], *n* (%)			
Yes	14 (40%)	5 (14.7%)	0.019
No	21 (60%)	29 (85.3%)	

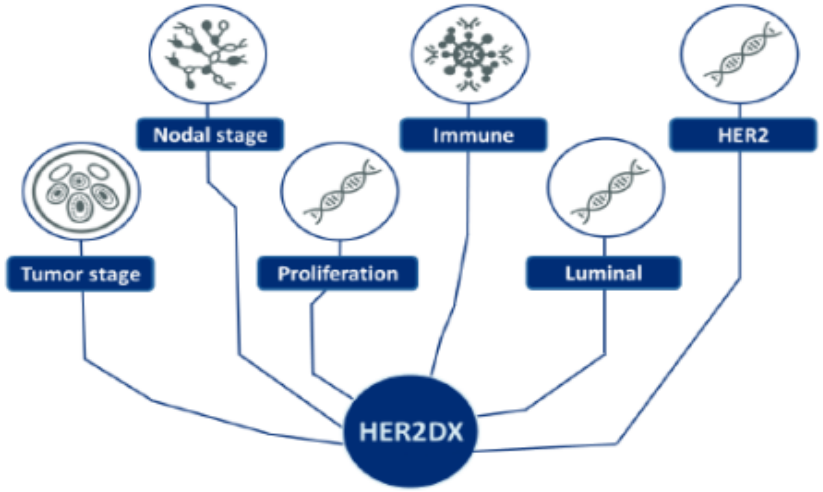


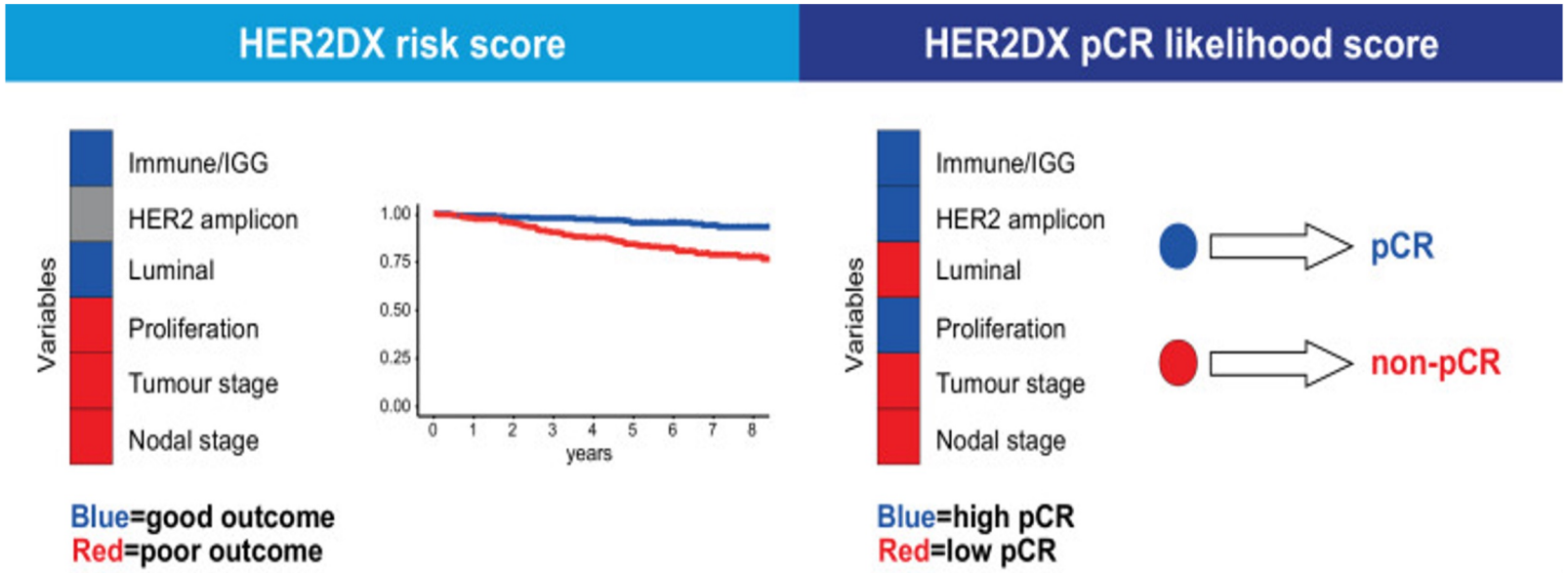
The rate of HER2 loss is higher in pats receiving NAT w/o anti-HER2 agents.
HER2 status on RD can be helpful in selecting different risk of relapse

Guarneri et al Ann Surg Oncol 2013

Disconnection between pCR and EFS/OS







HER2DX pCR-score and risk-score might help identify ideal candidates to receive neoadj HER2 blockade in combination with CT in HER2+eBC and defining individualized (de-)escalation strategies

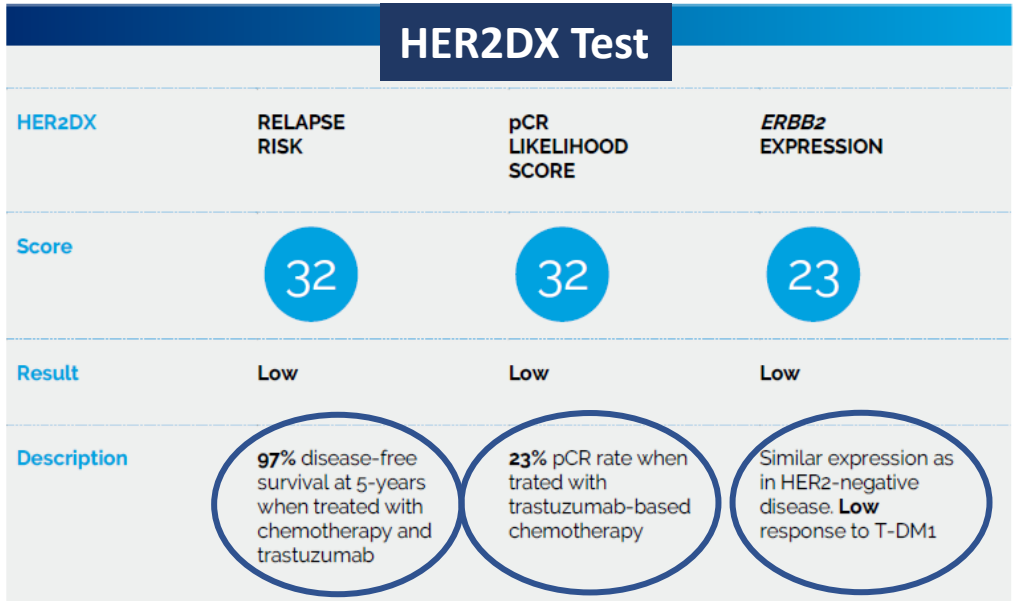
Prat A, et al. EBioMedicine. 2022

HER2DX exemples

Patient MR, 51 yrs old

2,6 cm nodule in right breast; cT2, cN0, M0

IDC, G3, ER 75%, PgR 80%, HER2 3+, Ki 67 75%



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April 27, 2023

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JAMA Oncol. Published online April 27, 2023. doi:10.1001/jamaoncol.2023.0181

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Annals of Oncology

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In Press, Journal Pre-proof | What's this?

Original Article

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Courtesy P Conte

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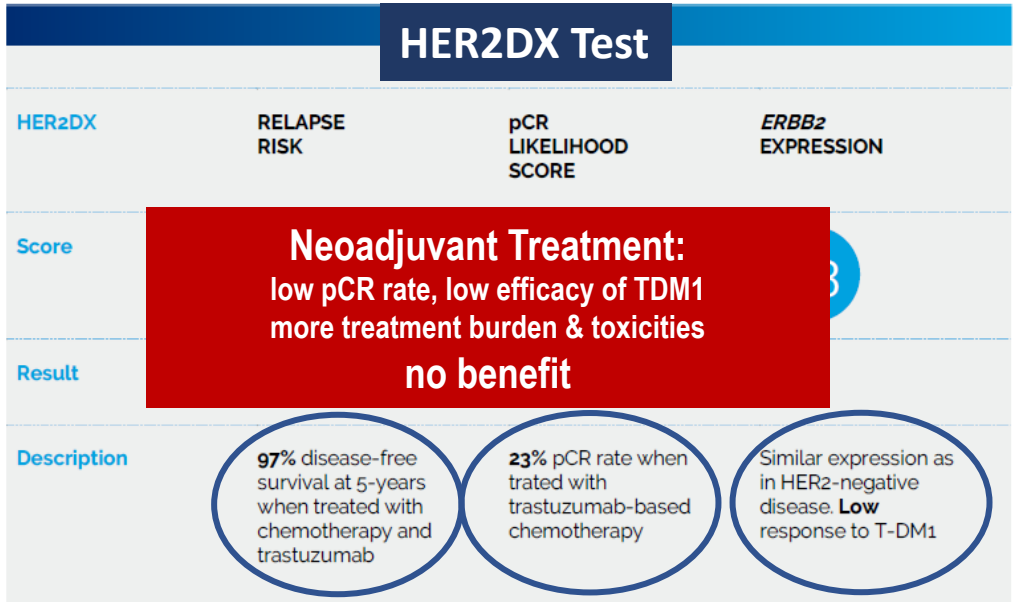

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Patient MR, 51 yrs old

2,6 cm nodule in right breast; cT2, cN0, M0

IDC, G3, ER 75%, PgR 80%, HER2 3+, Ki 67 75%

HER2DX Test

HER2DX	RELAPSE RISK	pCR LIKELIHOOD SCORE	*ERBB2* EXPRESSION
Score			
Result			
Description	**97%** disease-free survival at 5-years when treated with chemotherapy and trastuzumab	**23%** pCR rate when trated with trastuzumab-based chemotherapy	Similar expression as in HER2-negative disease. **Low** response to T-DM1

Neoadjuvant Treatment:
low pCR rate, low efficacy of TDM1
more treatment burden & toxicities
no benefit

Patient VA, 35 yrs old

1.5 cm nodule in right breast + palpable nodes; cT1c cN+, M0

IDC, G3, ER 75%, PgR 40%, HER2 3+, Ki 67 70%

HER2DX Test

HER2DX	RELAPSE RISK	pCR LIKELIHOOD SCORE	*ERBB2* EXPRESSION
Score	32	82	57
Result	**Low**	**High**	**High**
Description	**97%** disease-free survival at 5-years when treated with chemotherapy and trastuzumab	**73%** pCR rate when trated with trastuzumab-based chemotherapy	**High** response to T-DM1

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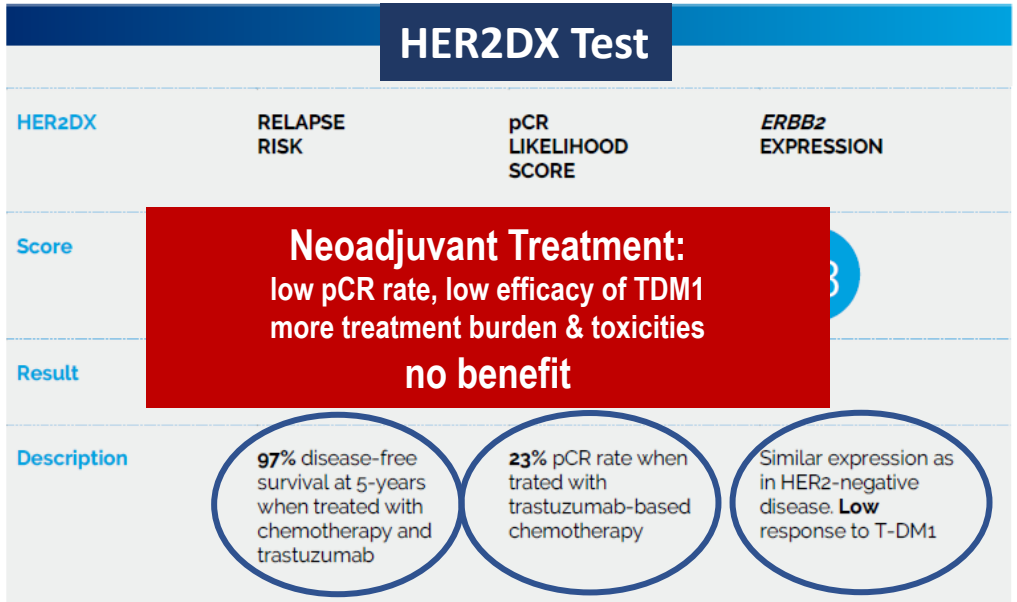

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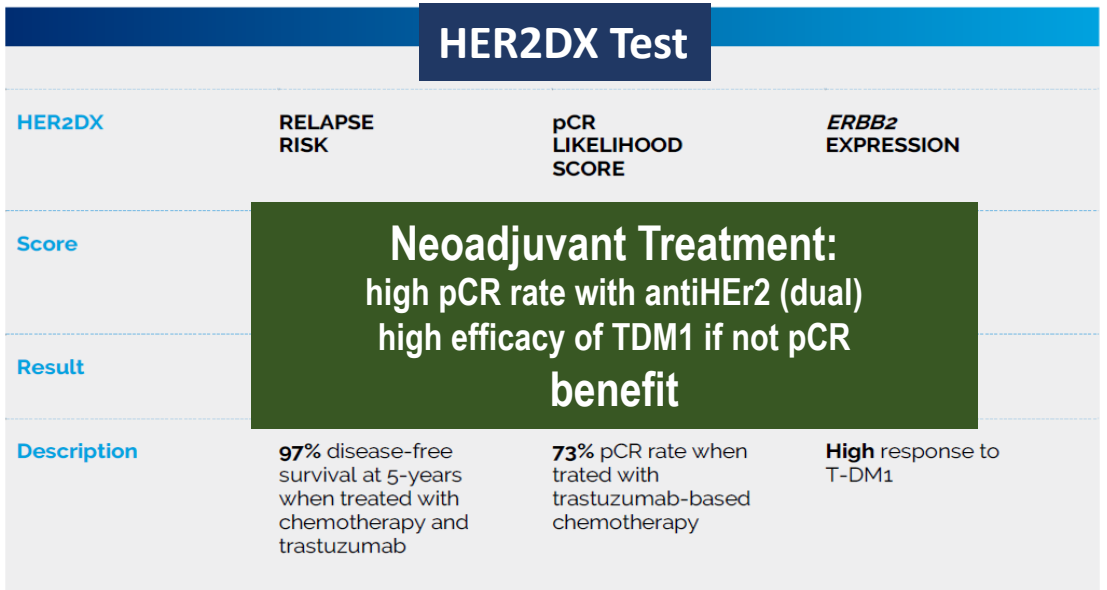

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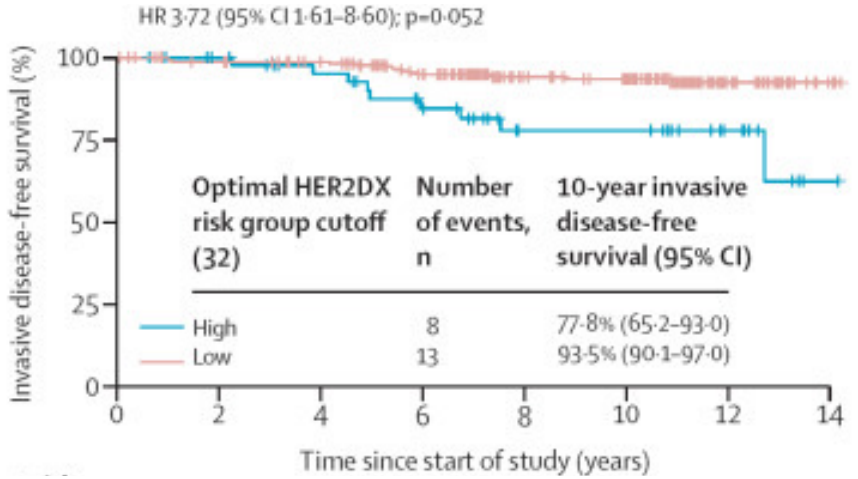
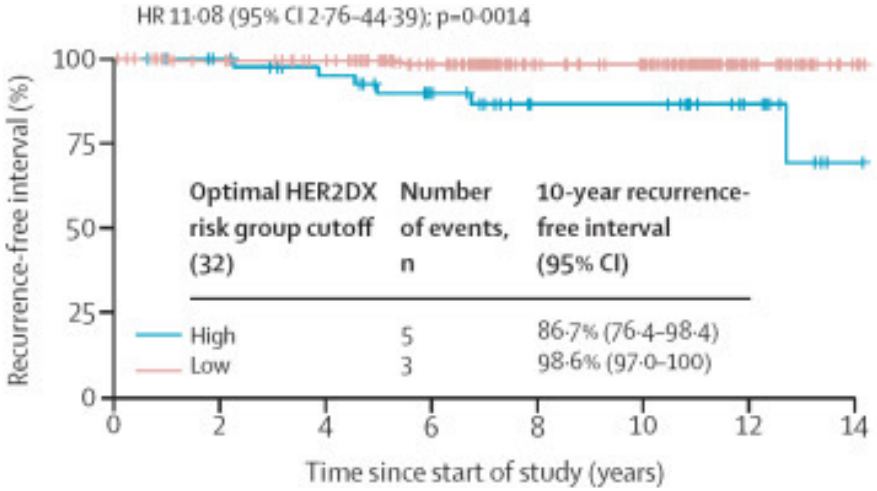
HER2DXin APT trial

(284/406 samples adequate for HER2DX genomic testing)





In univariate post-hoc analysis:

HER2DX @32 discriminates low vs. high risk pts (IDFS & RFS)

In multivariate no association b/w survival end-points and any of well-known CP prognostic factors

S Tolaney Lancet Oncol 2023

Conclusion

- T1a/b excellent prognosis with surgery alone
- T1c ER-pos excellent prognosis with TH adj + ET/H
- In selected cases (i.e. <50y, HR-ve), cT1c eBCs derserve the least toxic neoadj regimen and, in case of RD, the adj treatment escalation
- In selected cases, the use of MGA (i.e. HER2DX) could support the decision making process for optimal (neo)adjuvant treatment recommendation

Thank you

alberto.zambelli@hunimed.eu