IL CARCINOMA MAMMARIO HER2+: Quali novità nel setting (neo)-adiuvante?

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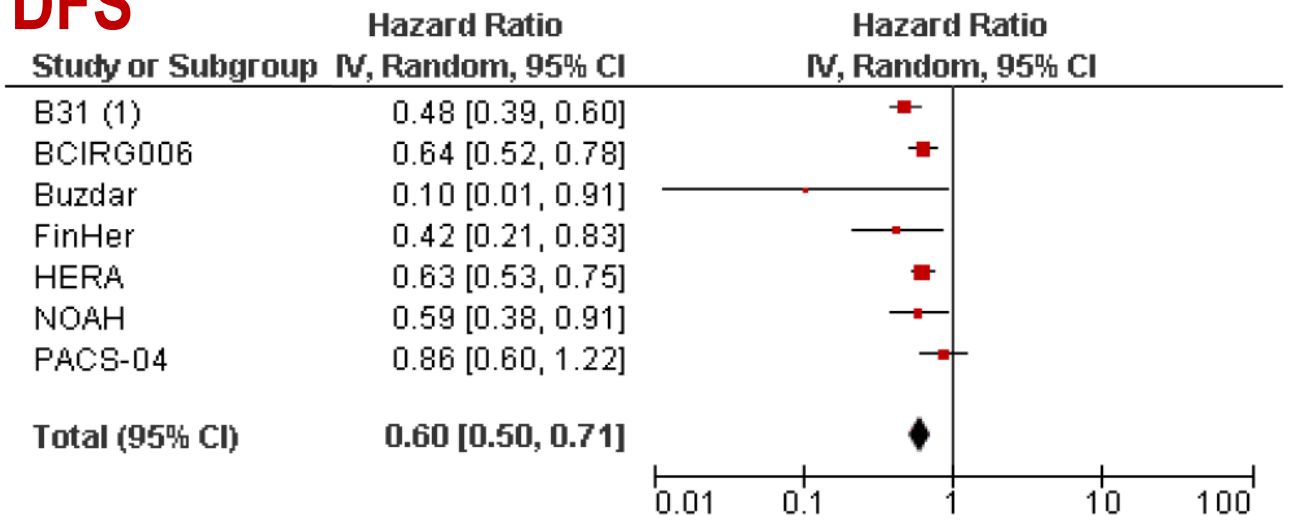
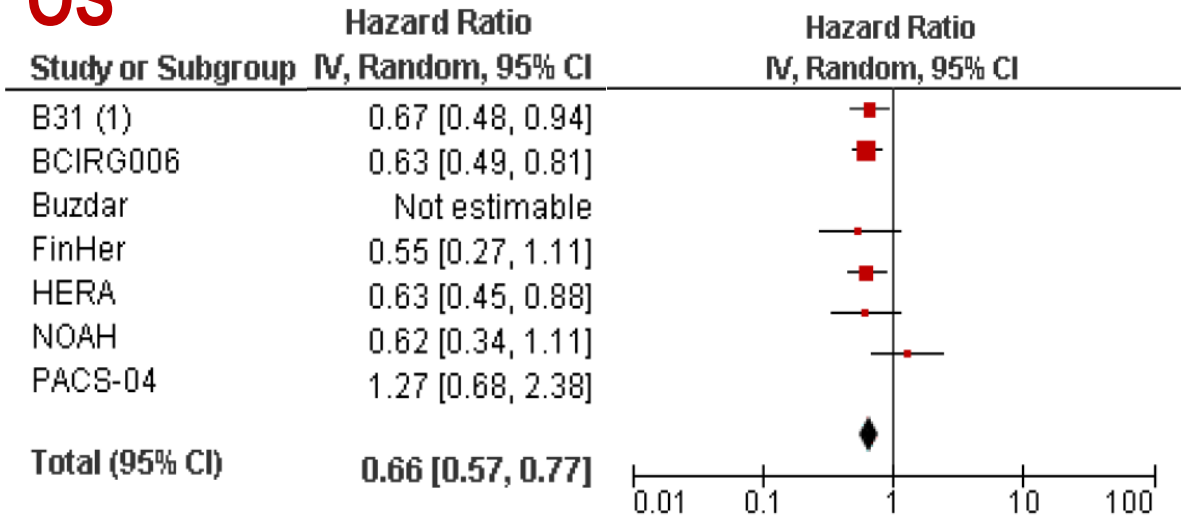
Trastuzumab for HER2+ early BC: a paradigmatic story of success

DFS



OS



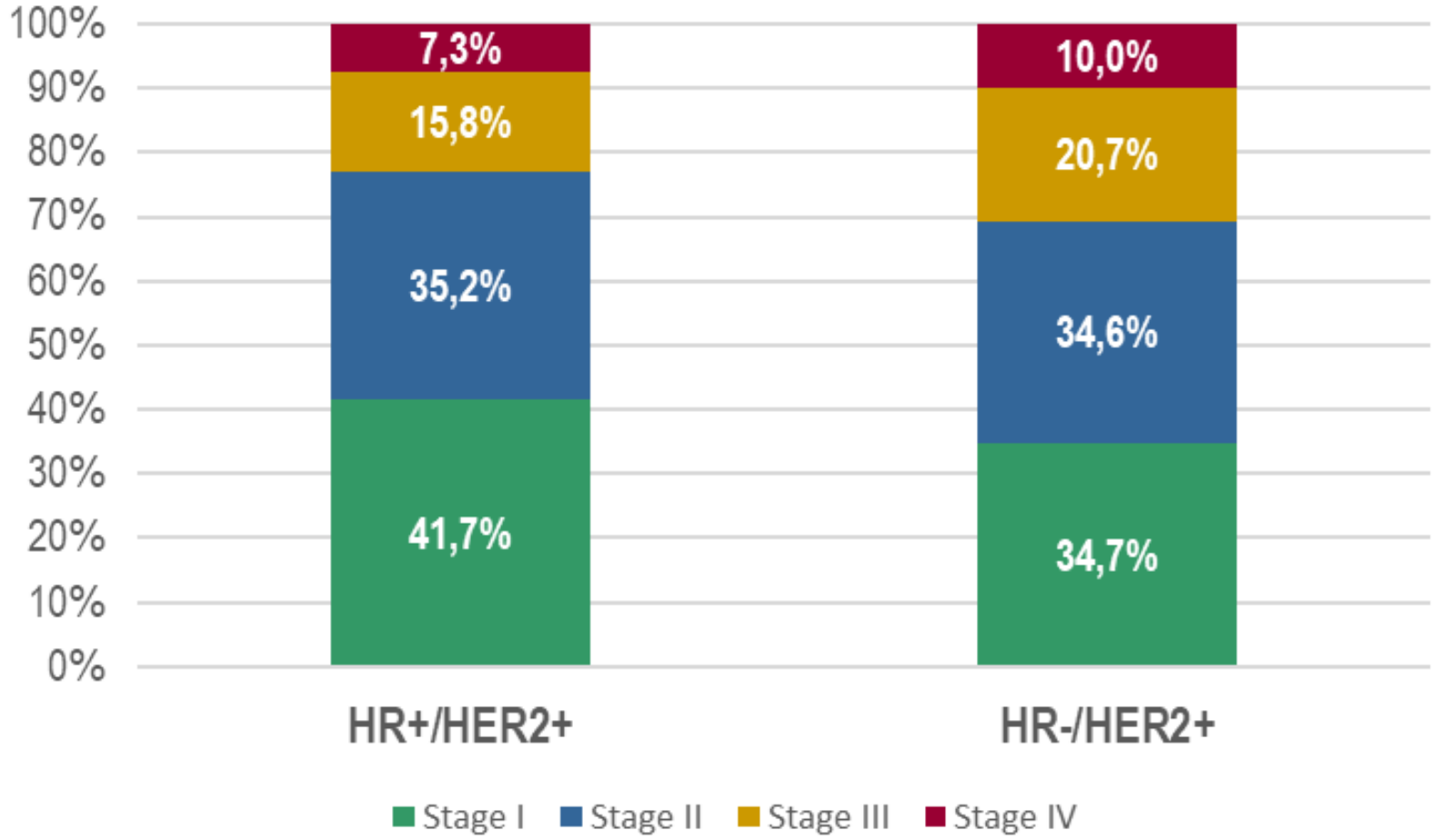
STANDARD: 1 year of trastuzumab concurrent with sequential A→T chemotherapy

THE COCHRANE COLLABORATION®

Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R

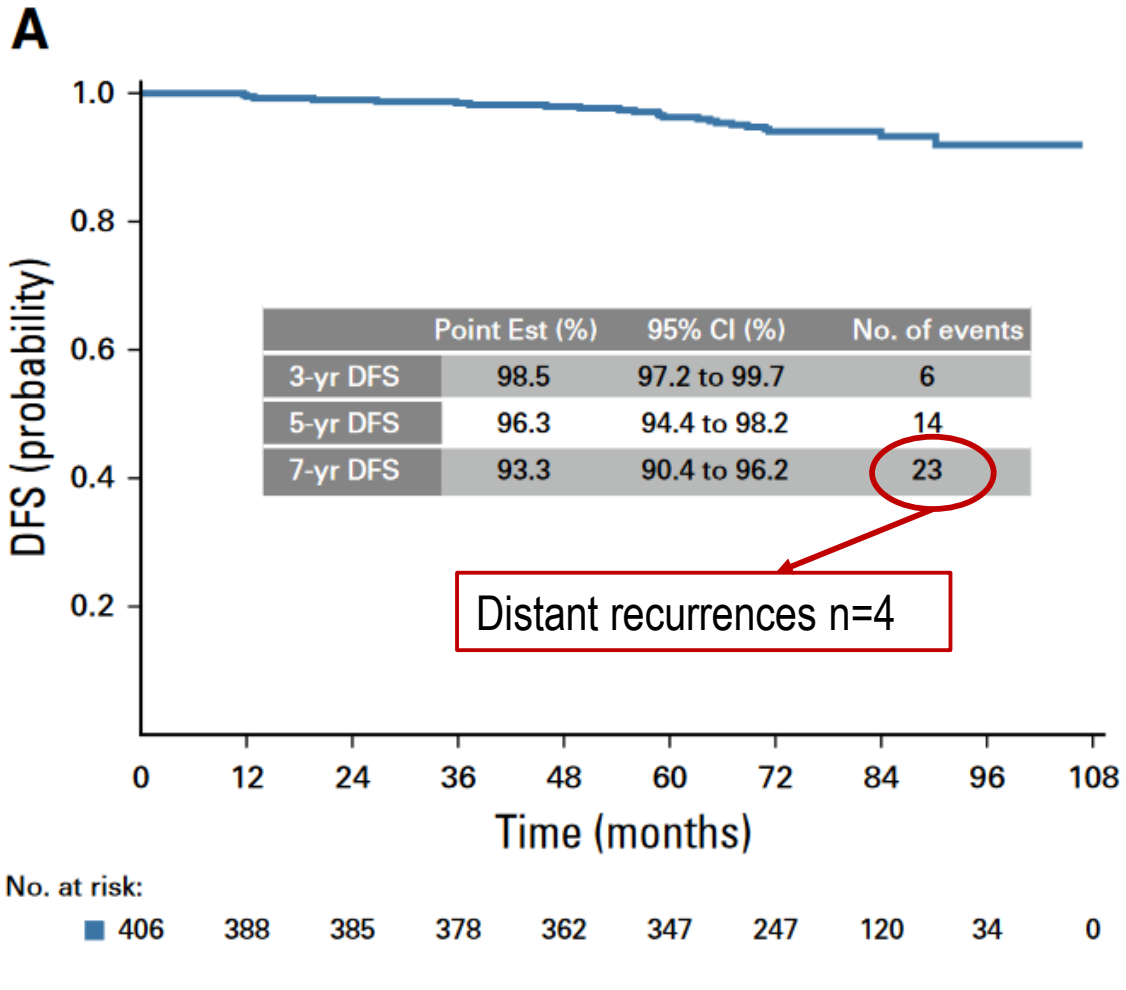
Stage of HER2+ BC at diagnosis

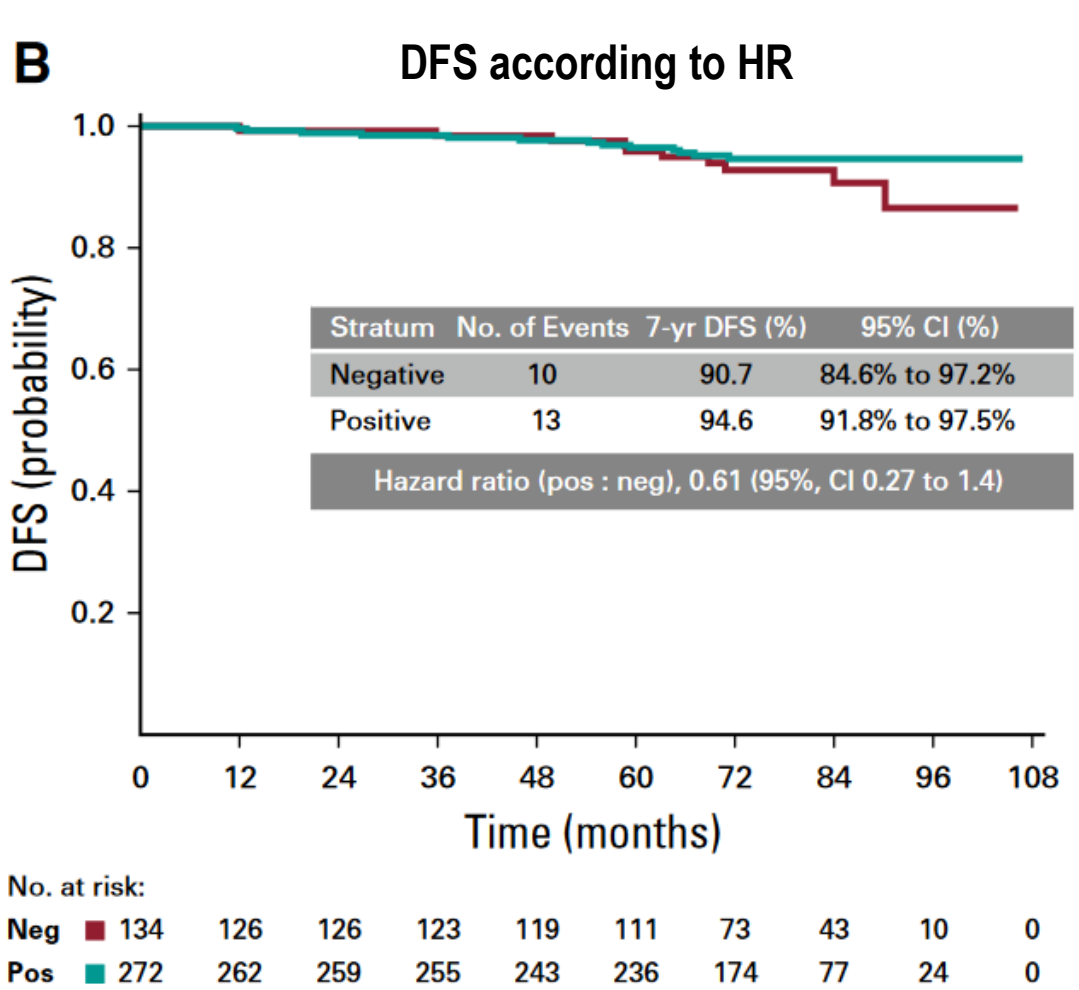
AJCC 7th Stage distribution at diagnosis in >7300 HER2+ BC patients from SEER database (year 2010)



Howlader N et al., JNCI 2014

Paclitaxel + trast x 12 wks → trast up to 1yr for T<3cm N0

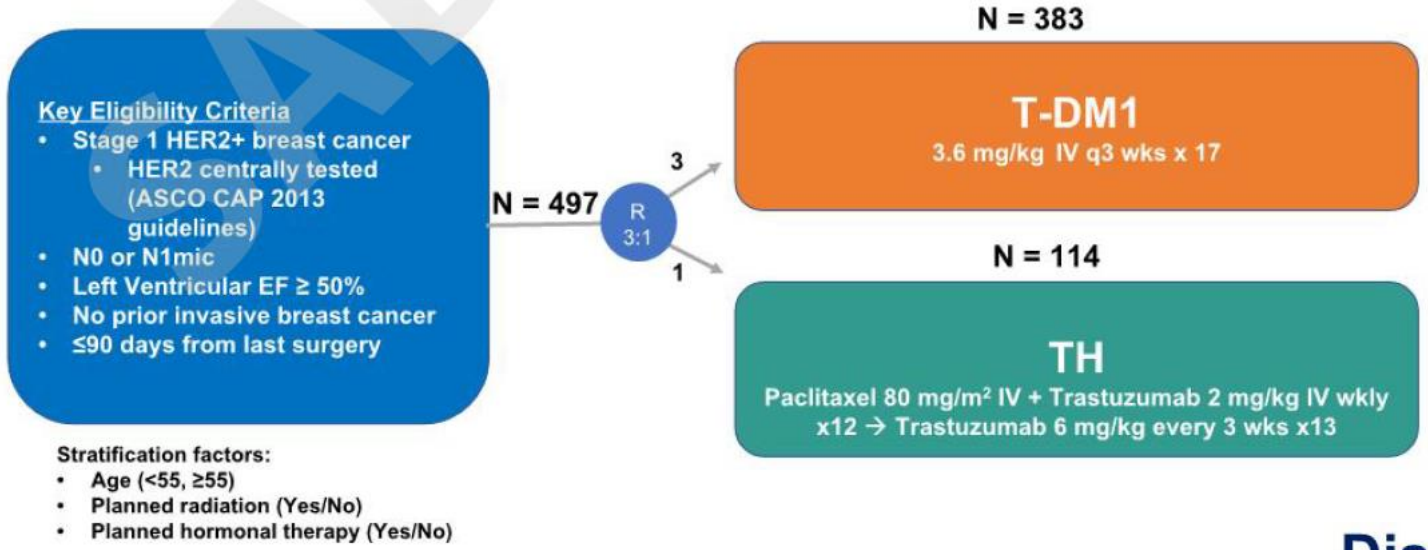




91% T≤2 cm (17% pT1a, 31% pT1b, 42% pT1c); 65% HR+; 11% G1, 32% G2

Tolaney SM, J Clin Oncol 2019

Study Design: ATEMPT Trial



Stratification factors:
- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

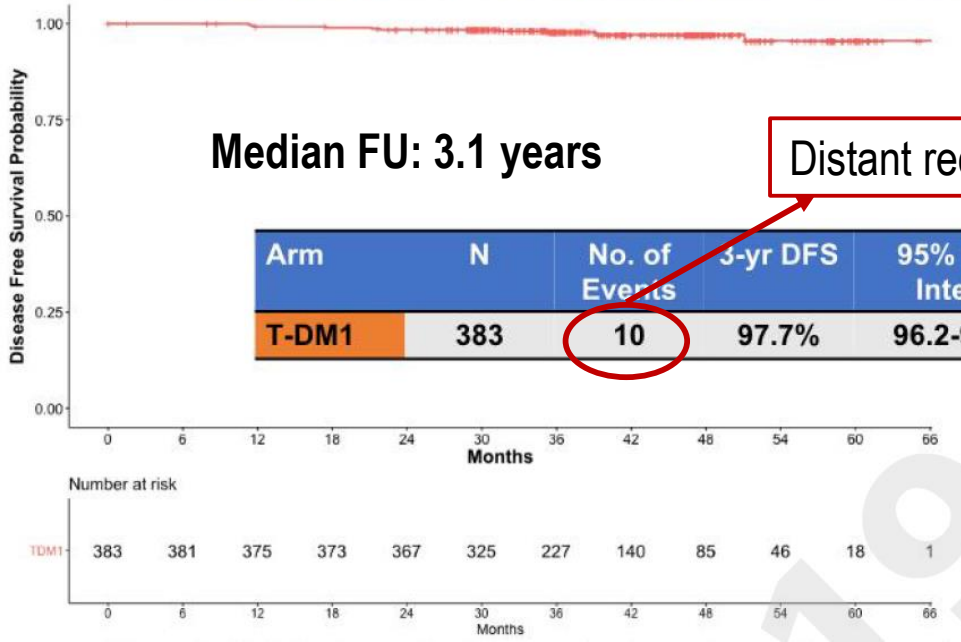
*Radiation and endocrine therapy could be initiated after 12 weeks on study therapy

Co-primary endpoints:
- 3-yr DFS with T-DM1
- Comparison of clinically relevant toxicities between arms

Pts characteristics:
- HR+ 75%
- T <1 cm 43%
- T 1-2 cm 57%
- HER2 IHC 3+ 73%

Safety:
- No signifcant difference in the incidence of clinically relevant toxicities between arms
- Worse neurotoxicity with paclitaxel-trastuzumab
- More AEs leading to discontinuation with T-DM1

Disease-Free Survival: T-DM1



Median FU: 3.1 years

Distant recurrences n=2

Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
T-DM1	383	10	97.7%	96.2-99.3%

p<0.0001

Tolaney SM, SABCS 2019

Escalation and de-escalation in HER2 positive early breast cancer

2018

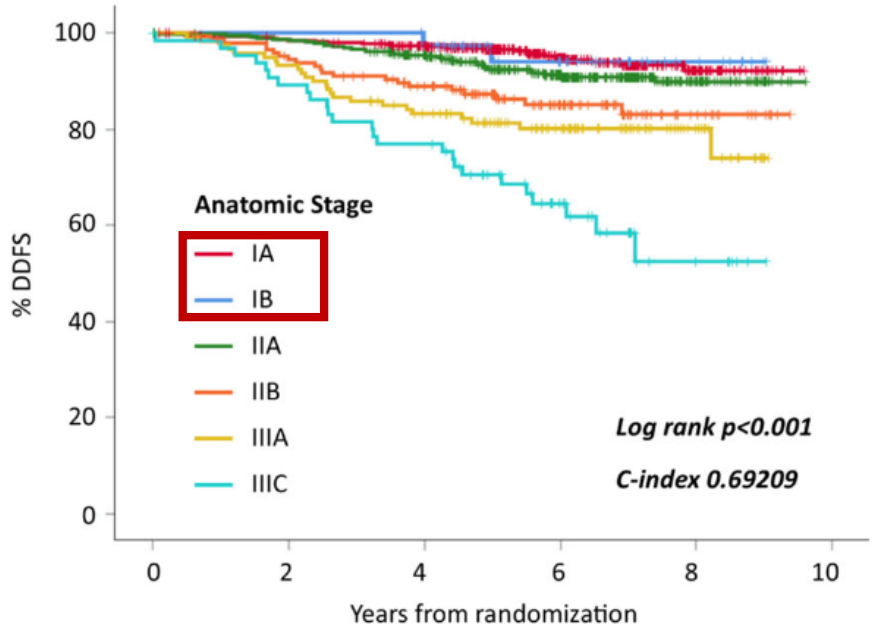
Maria Vittoria Dieci[a,b], *Grazia Vernaci*[a], *and Valentina Guarneri*[a,b]

Randomized noninferiority trials of short vs. 1 year adjuvant trastuzumab

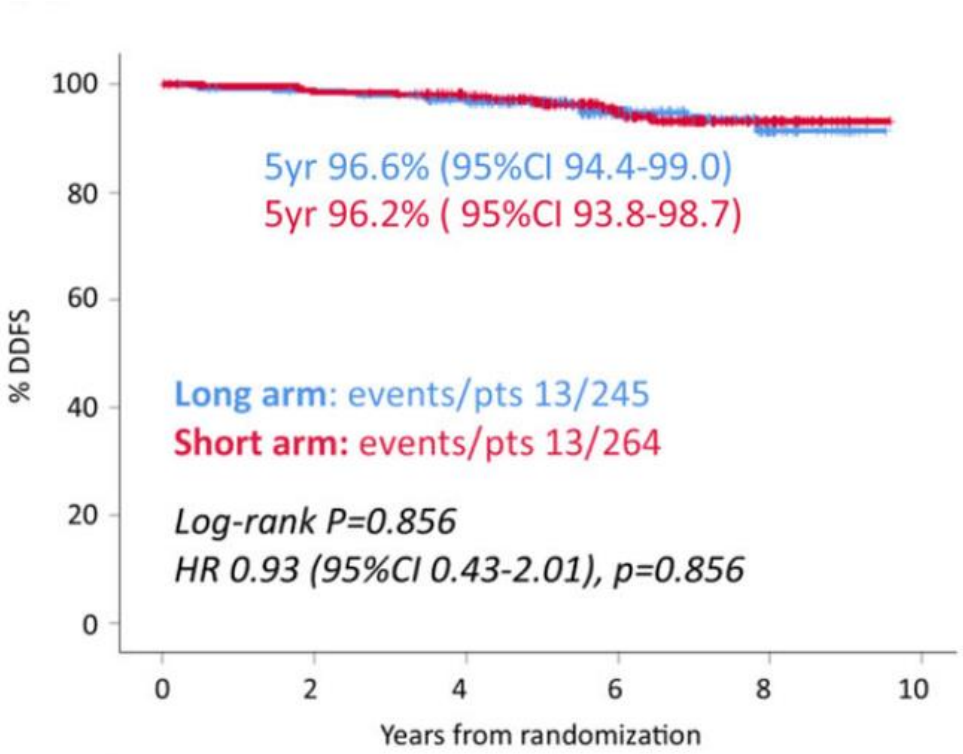
Study	N	Median FU (years)	Treatment arms	Efficacy		Cardiac events (according to protocol definition)	
				% DFS	HR 95% CI	% events	P
PERSEPHONE [30▪▪]	4088	4.9	CT (Center's choice) + H for 6 m CT (Center's choice) + H for 12 m	4 yrs 89.4% 4 yrs 89.8%	1.07 (0.93–1.24) [a]	4% [f] 8% [f]	<0.0001 [f]
PHARE [31,32]	3380	3.5	CT → H (6 m) CT → H (12 m)	2 yrs 91.1% 2 yrs 93.8%	1.28 (1.05–1.56) [b]	4.0% 6.6%	<0.001
SOLD [33▪]	2174	5.2	TH (9 w) →FEC TH (9 w) →FEC → H (up to 12 m)	5 yrs 88.0% 5 yrs 90.5%	1.39 (1.12–1.72) [c]	2% 4%	0.01
ShortHER [34▪]	1253	5.2	3 wT + wH (9 w) → FEC AC → 3 wTH →H (up to 12 m)	5 yrs 85.4% 5 yrs 87.5%	1.15 (0.91–1.46) [d]	5.2% 14.4%	<0.0001 [g]
HORG [35]	481	3.9–4.25	ddFEC → ddT + H (6 m) ddFEC → ddT + H (12 m)	3 yrs 93.3% 3 yrs 95.7%	1.57 (0.086–2.10) [e]	0.8% 0%	NA

Earl HM, ASCO 2018; Pivot X, Lancet Oncol 2013; Joensuu H, JAMA Oncol 2018; Conte P, Ann Oncol 2018; Mavroudis D, Ann Oncol 2015

Analysis of stage I pts in the ShortHER trial



N. at risk						
IA	469	455	410	227	63	0
IB	40	40	38	22	8	0
IIA	399	389	348	214	60	0
IIB	149	137	118	62	17	0
IIA	121	112	93	60	20	0
IIIC	66	58	50	26	6	0



N. at risk						
Long	245	238	215	120	33	0
Short	264	257	233	129	38	0

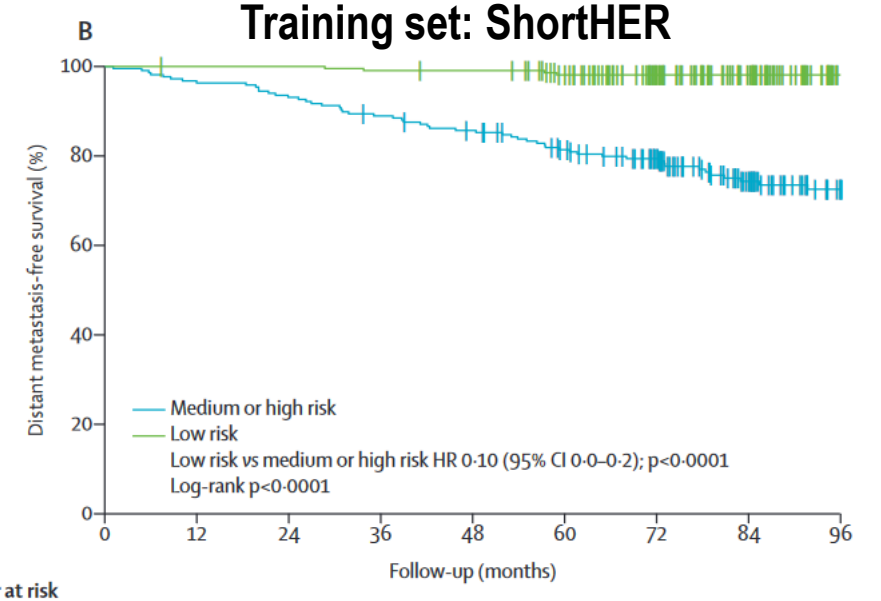
Dieci MV, BMC Medicine 2019

A multivariable prognostic score to guide systemic therapy in early-stage HER2-positive breast cancer: a retrospective study with an external evaluation

Lancet Oncol 2020; 21: 1455–64

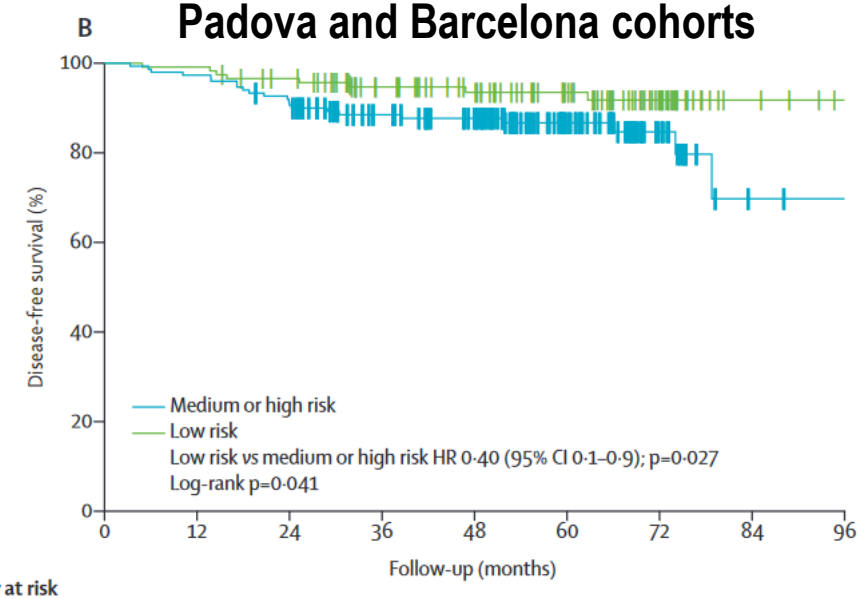
Aleix Prat, Valentina Guarneri, Laia Paré, Gaia Griguolo, Tomás Pascual, Maria V Dieci, Núria Chic, Blanca González-Farré, Antonio Frassoldati, Esther Sanfeliu, Juan M Cejalvo, Montserrat Muñoz, Giancarlo Bisagni, Fara Brasó-Maristany, Loredana Urso, Maria Vidal, Alba A Brandes, Barbara Adamo, Antonino Musolino, Federica Miglietta, Benedetta Conte, Mafalda Oliveira, Cristina Saura, Sònia Pernas, Jesús Alarcón, Antonio Llombart-Cussac, Javier Cortés, Luis Manso, Rafael López, Eva Ciruelos, Francesco Schettini, Patricia Villagrasa, Lisa A Carey, Charles M Perou, Federico Piacentini, Roberto D'Amico, Enrico Tagliafico, Joel S Parker, Pierfranco Conte

Training set: ShortHER



Number at risk (number censored)									
Medium or high risk	217 (0)	209 (0)	202 (0)	192 (1)	183 (3)	167 (10)	145 (28)	100 (65)	70 (93)
Low risk	218 (0)	217 (1)	217 (1)	215 (1)	214 (2)	203 (11)	173 (41)	137 (77)	92 (122)

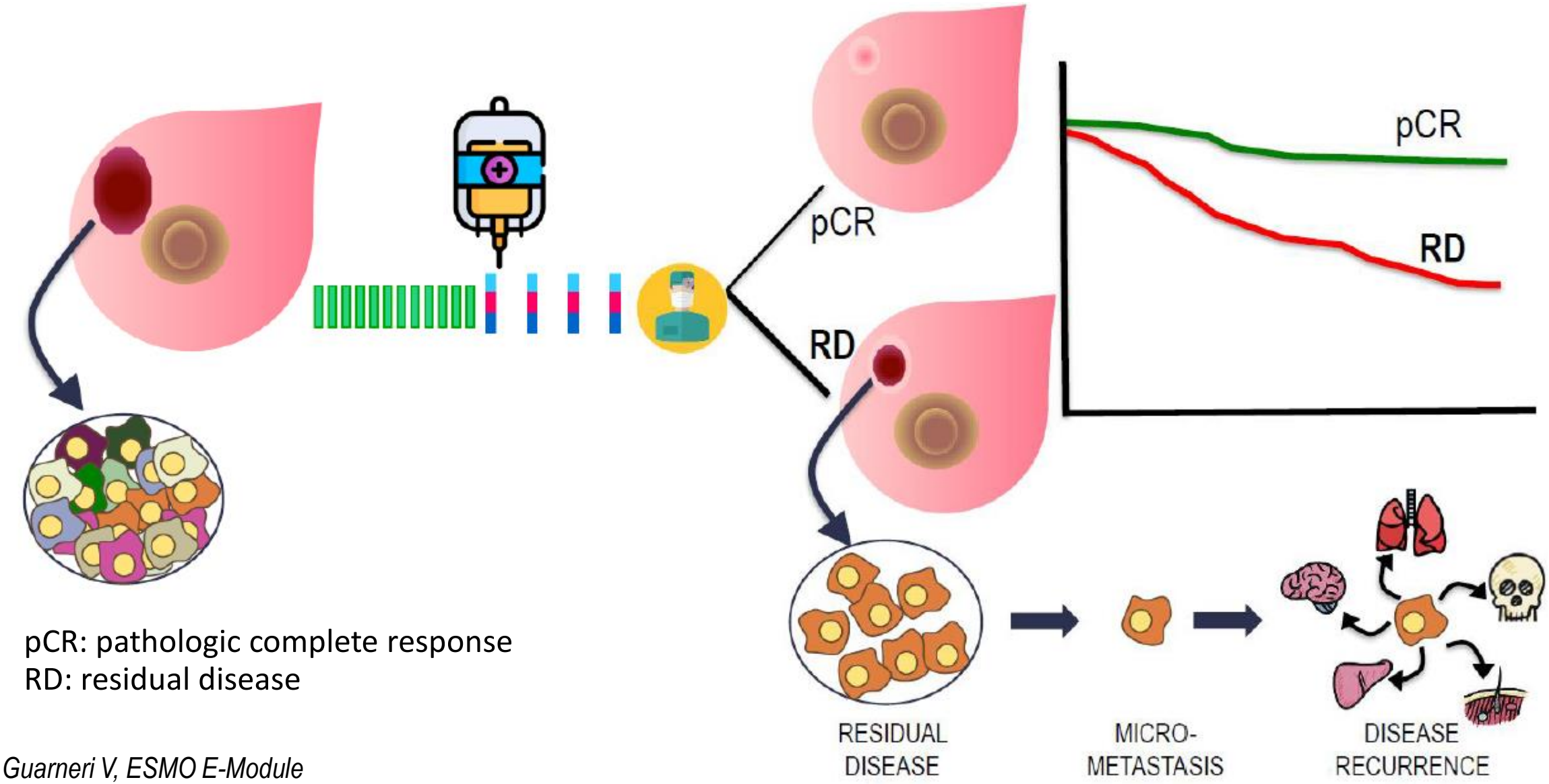
Evaluation set: CherLOB, PAMELA, Padova and Barcelona cohorts



Number at risk (number censored)									
Medium or high risk	150 (0)	146 (0)	135 (1)	113 (20)	99 (33)	60 (71)	22 (108)	5 (123)	4 (124)
Low risk	117 (0)	116 (0)	109 (4)	89 (22)	77 (33)	58 (52)	32 (77)	6 (103)	2 (107)

HER2DX score based on 17 variables: T (T1 vs others), nodal status (N0 vs others), TILs (continuous variable), PAM50 subtype (HER2-enriched and basal vs others), and 13 individual genes.

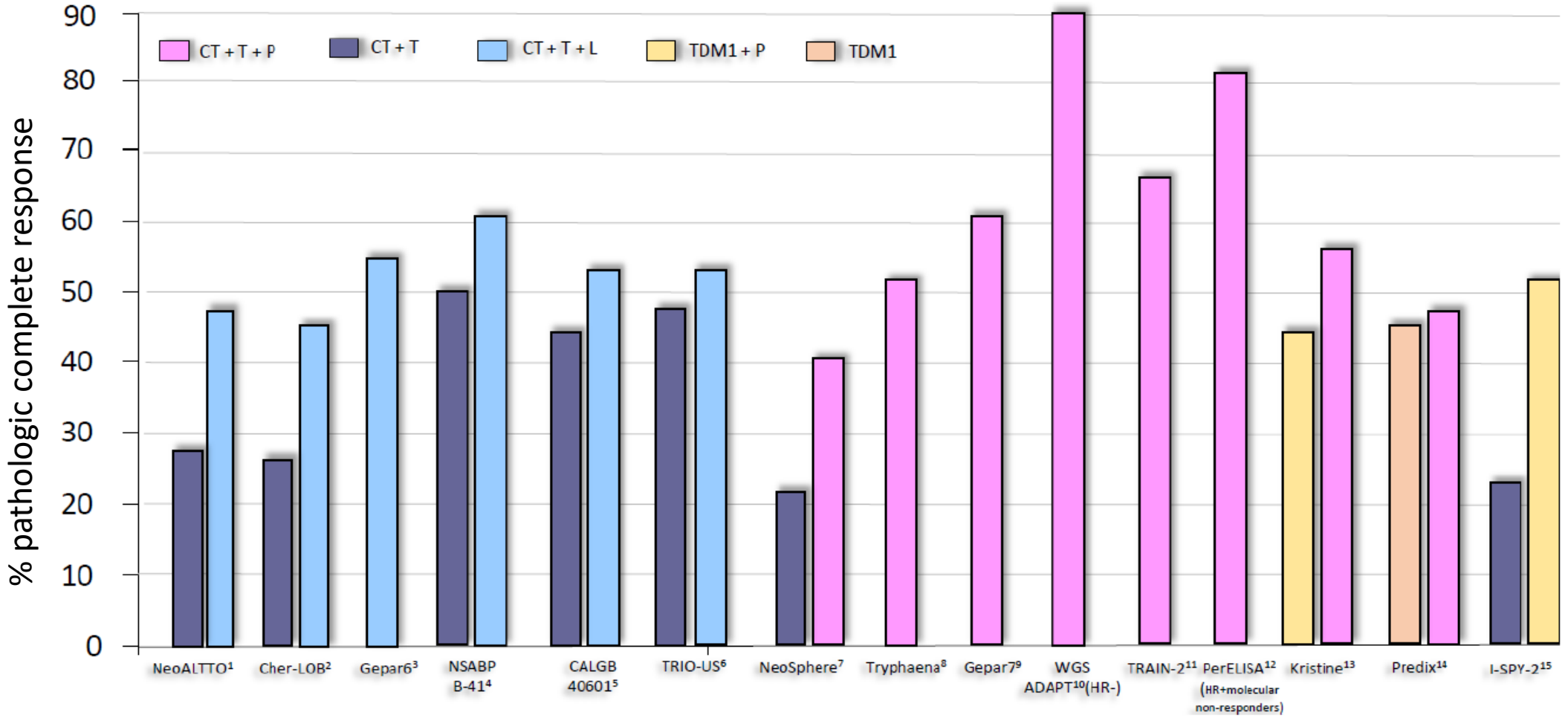
Neoadjuvant therapy: the prognostic value of pCR



pCR: pathologic complete response
RD: residual disease

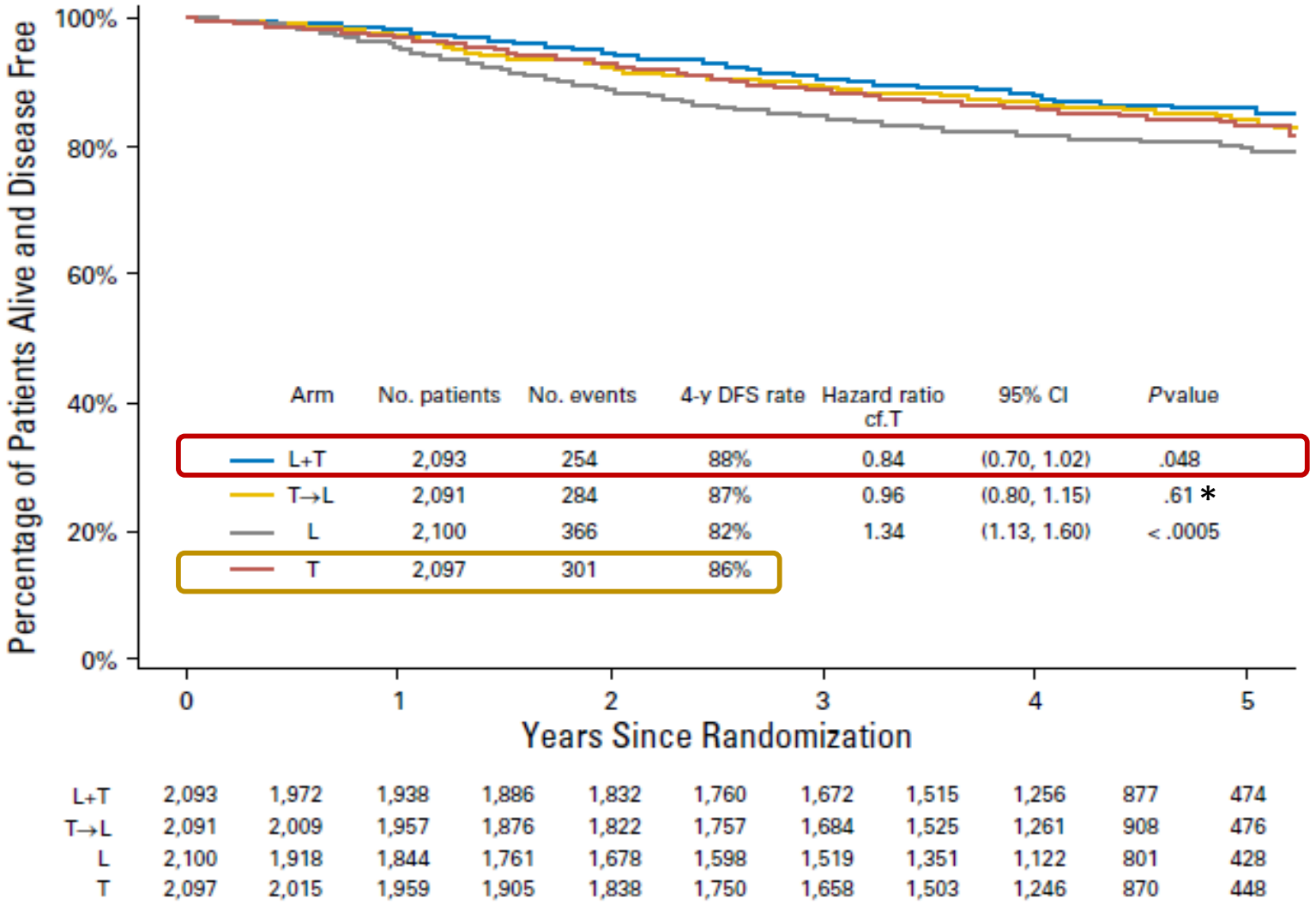
Guarneri V, ESMO E-Module

Escalating strategy in HER2 + BC: dual HER2 blockade



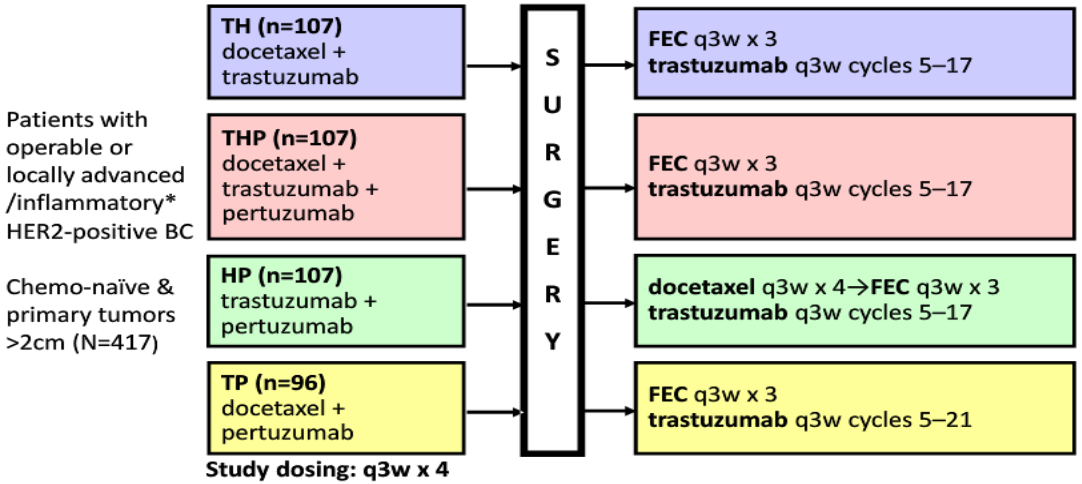
1. Baselga J. Lancet 2012; 2. Guarneri V. J Clin Oncol 2012; 3. von Minckwitz. Lancet Oncol 2014; 4. Robidoux A. Lancet Oncol 2013; 5. Carey L .ASCO 2013; 6. Hurvitz S SABCS 2013 7. Gianni L . Lancet Oncol 2012; 8. Schneeweiss A . Ann Oncol 2013 ; 9 Untch M. 10. Nitz UA Ann Oncol 2017; 11. Ramshorst MS The Lancet 2018; 13. 12. Guarneri V. Ann Oncol 2019; 13. Hurvitz SA The Lancet 2017; 14. Bergh J ASCO 2019; 15. press release

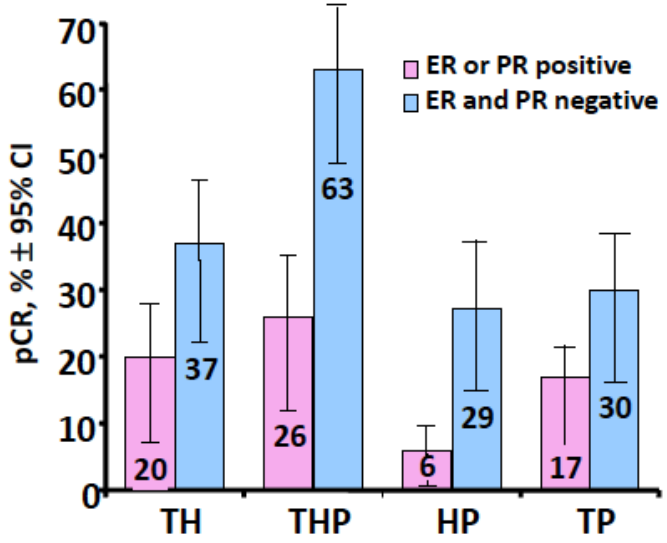
ALTTO trial: Primary DFS analysis

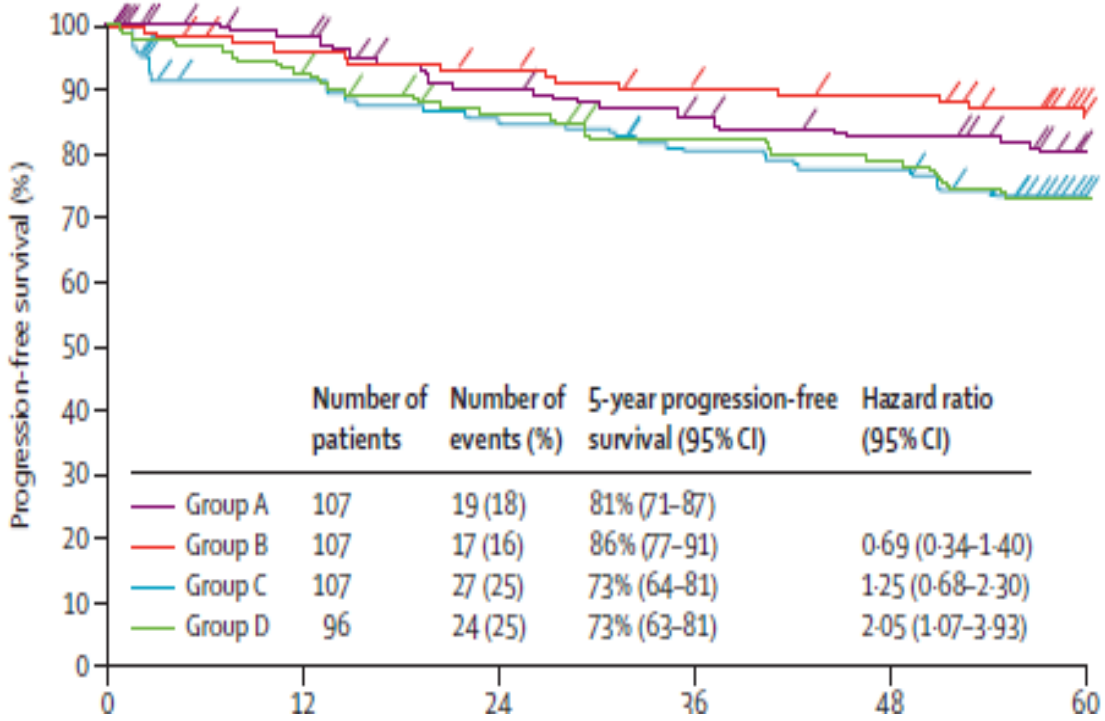


Piccart M et al., J Clin Oncol 2015

NeoSphere trial: pCR and survival data







	Number of patients	Number of events (%)	5-year progression-free survival (95% CI)	Hazard ratio (95% CI)
Group A	107	19 (18)	81% (71–87)	
Group B	107	17 (16)	86% (77–91)	0·69 (0·34–1·40)
Group C	107	27 (25)	73% (64–81)	1·25 (0·68–2·30)
Group D	96	24 (25)	73% (63–81)	2·05 (1·07–3·93)

Gianni L et al., Lancet Oncol 2012; Gianni L et al., Lancet Oncol 2016

APHINITY: primary and updated (descriptive) iDFS analysis

Population	Primary analysis, median FU 45.4 months				Updated descriptive analysis, median FU 74.1 months			
	3-yr iDFS P+T	3-yr iDFS T	Δ	HR (95% CI)	6-yr iDFS P+T	6-yr iDFS T	Δ	HR (95% CI)
ITT	94.1%	93.2%	0.9%	0.81 (0.66-1.00)	90.6%	87.8%	2.8%	0.76 (0.64-0.91)
N+	92.0%	90.2%	1.8%	0.77 (0.62-0.96)*	87.9%	83.4%	4.5%	0.72 (0.59-0.87)
N-	97.5%	98.4%	-0.9%	1.13 (0.68-1.86)	95.0%	94.9%	0.1%	1.02 (0.69-1.53)
HR+	94.8%	94.4%	0.4%	0.86 (0.66-1.13)	91.2%	88.2%	3.0%	0.73 (0.59-0.92)
HR-	92.8%	91.2%	1.6%	0.76 (0.56-1.04)*	89.5%	87.0%	2.5%	0.83 (0.63-1.10)

*negative interaction tests for N+/N- and HR+/HR- subgroups

Piccart M, SABCS 2019

APHINITY: primary and updated (descriptive) iDFS analysis

Population	Primary analysis, median FU 45.4 months				Updated descriptive analysis, median FU 74.1 months			
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*negative interaction tests for N+/N- and HR+/HR- subgroups

Questioning the EMA approval in high-risk pts defined as N+ or HR-

→ No significant difference in OS at the 2nd interim analysis (42.5% of events)

Piccart M, SABCS 2019

Escalating strategy: T-DM1 in patients with residual disease (KATHERINE)

- **N= 1486**
- **Centrally confirmed HER2-positive breast cancer**
- **Residual invasive tumor in breast or axillary nodes after PCT including:**
  - **Minimum of 6 cycles of CT**
  - **Minimum of 9 weeks of T**

1:1R

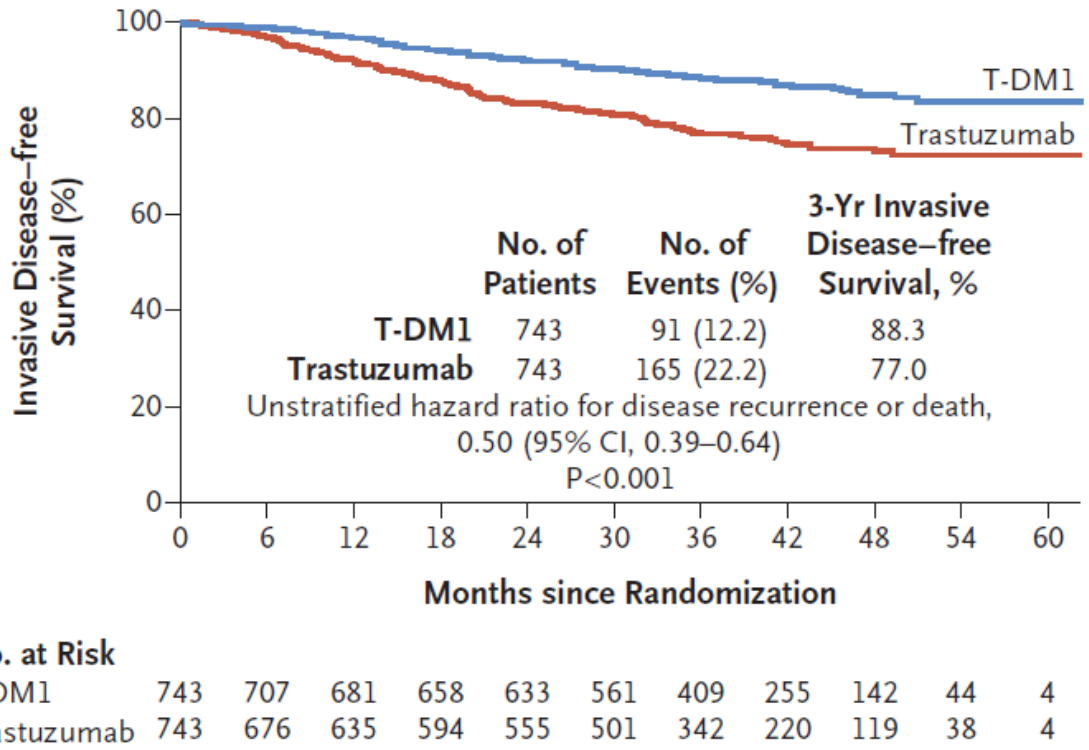
T-DM1
3.6 mg/kg IV Q3W, 14 cycles

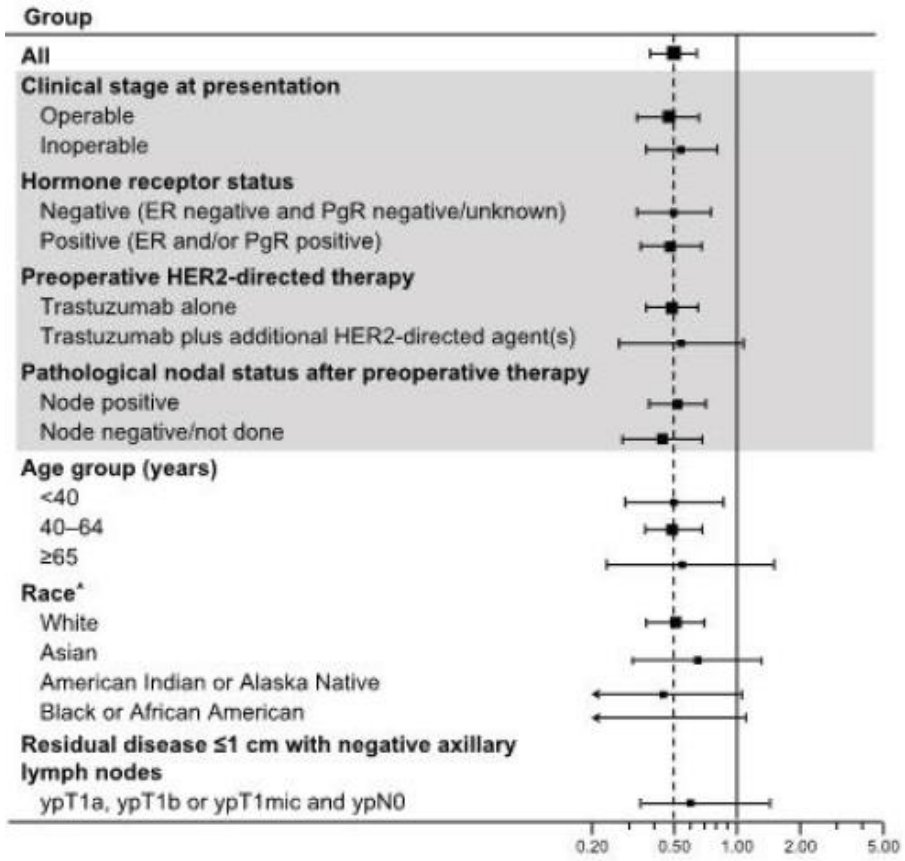
Trastuzumab
6 mg/kg IV Q3W, 14 cycles

75% of the patients with operable breast cancer
72% HR+
18% neoadjuvant pertuzumab+trastuzumab
76% neoadjuvant anthracyclines

von Minckwitz G, et al. NEJM 2018; Geyer C, SABCS 2018

Escalating strategy: T-DM1 in patients with residual disease (KATHERINE)





CNS as site of first recurrence in ~5% of pts in both arms

von Minckwitz G, et al. NEJM 2018; Geyer C, SABCS 2018

KATHERINE: summary of further subgroup analyses

- **Type of NACT**
  - Anthra: HR 0.51 (0.38–0.67)
  - no Anthra: HR 0.43 (0.22–0.82)

- **cT1cN0**
  - N=77; iDFS events: 6/32 Trastuzumab, 0/45 T-DM1

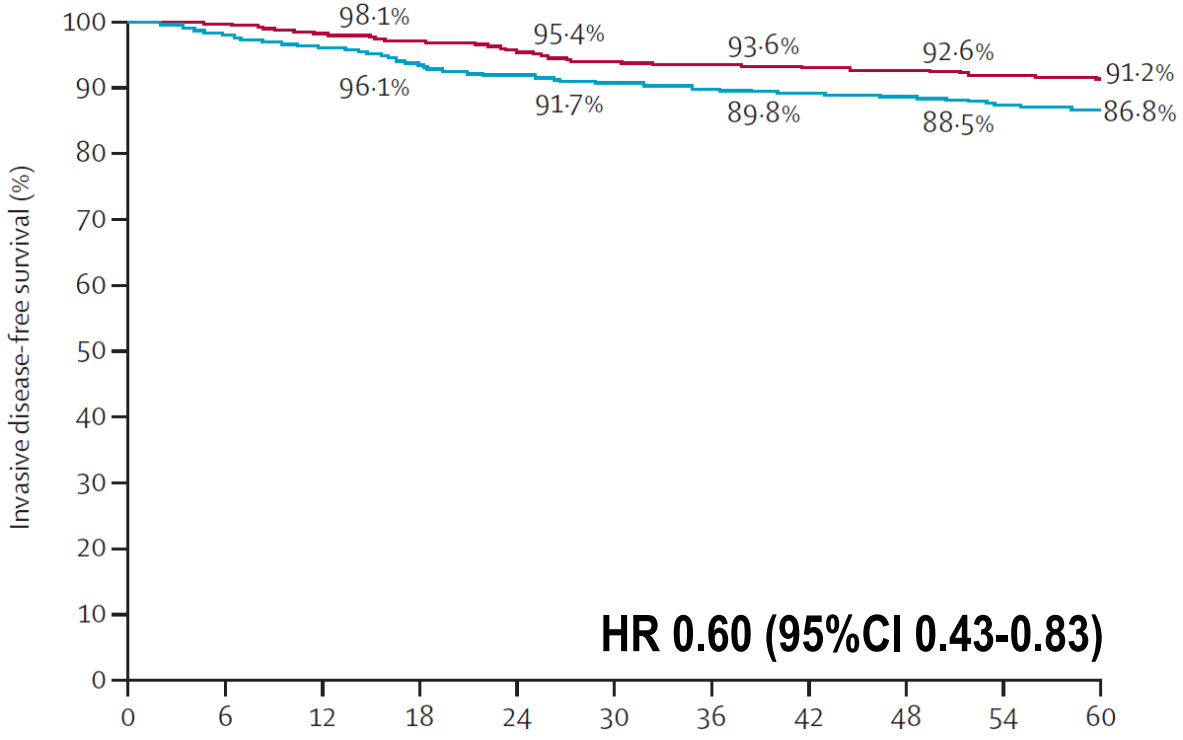
- **HER2-loss**
  - N=70
  - iDFS events: 11/42 Trastuzumab, 0/28 T-DM1

Mano MS et al., SABCS 2019; Loibl S et al., ESMO Breast Cancer 2020

ExteNET: iDFS at 5 yrs in HR+ patients

1 year Neratinib following 1 year Trastuzumab

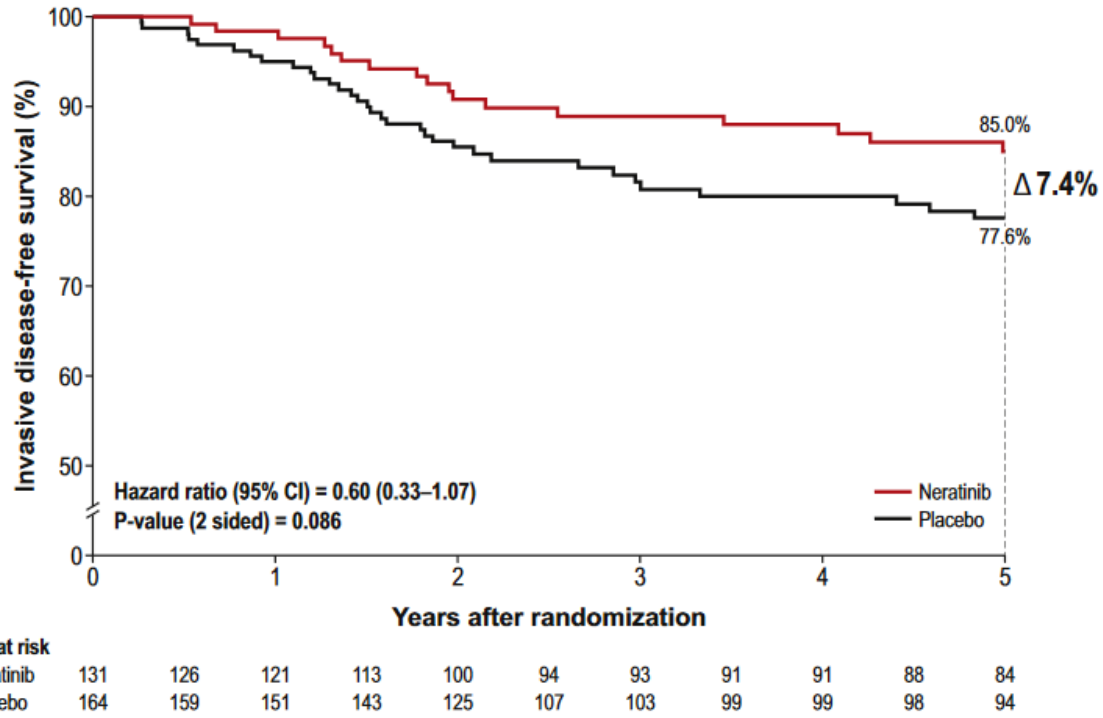
Subgroup: HR+



HR 0.60 (95%CI 0.43-0.83)

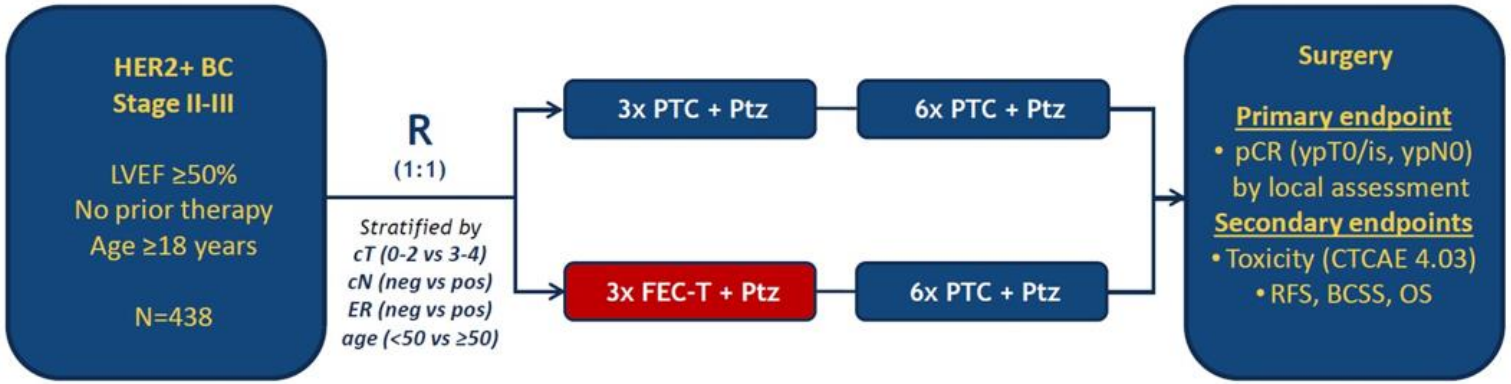
Main AE: diarrhea (G3 40%)

Subgroup: HR+, neratinib started ≤1 year from trastuzumab AND no pCR after NACT

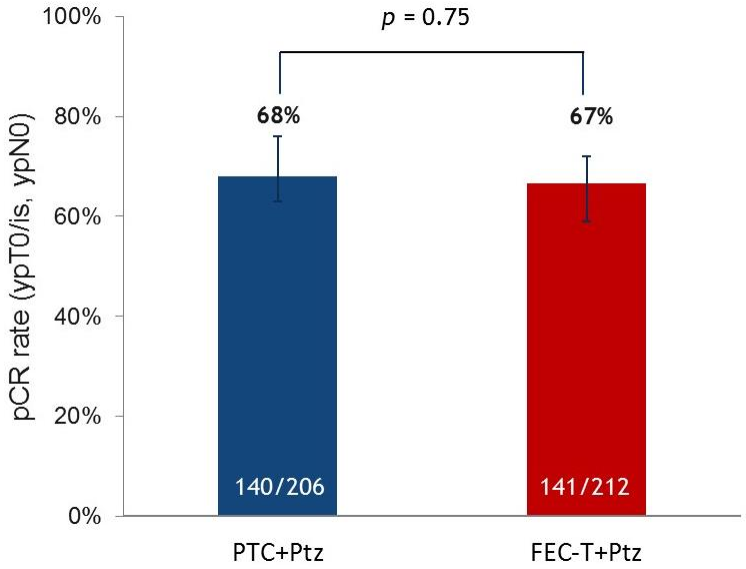


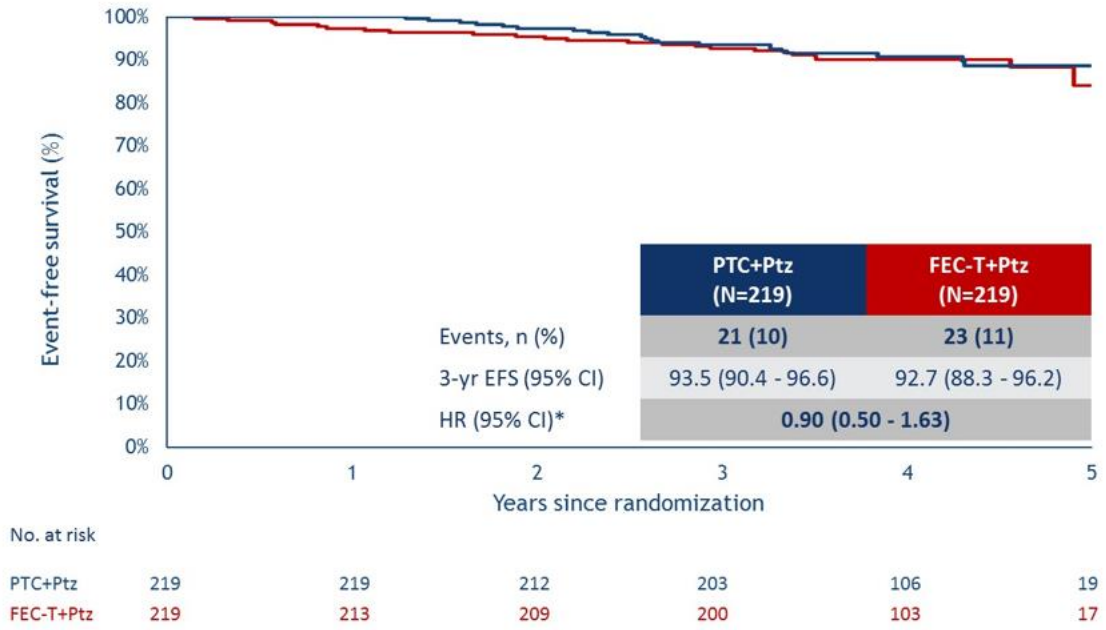
Martin M, Lancet Oncol 2017

Neoadjuvant anthracycline-free regimens for stage II-III: TRAIN-2



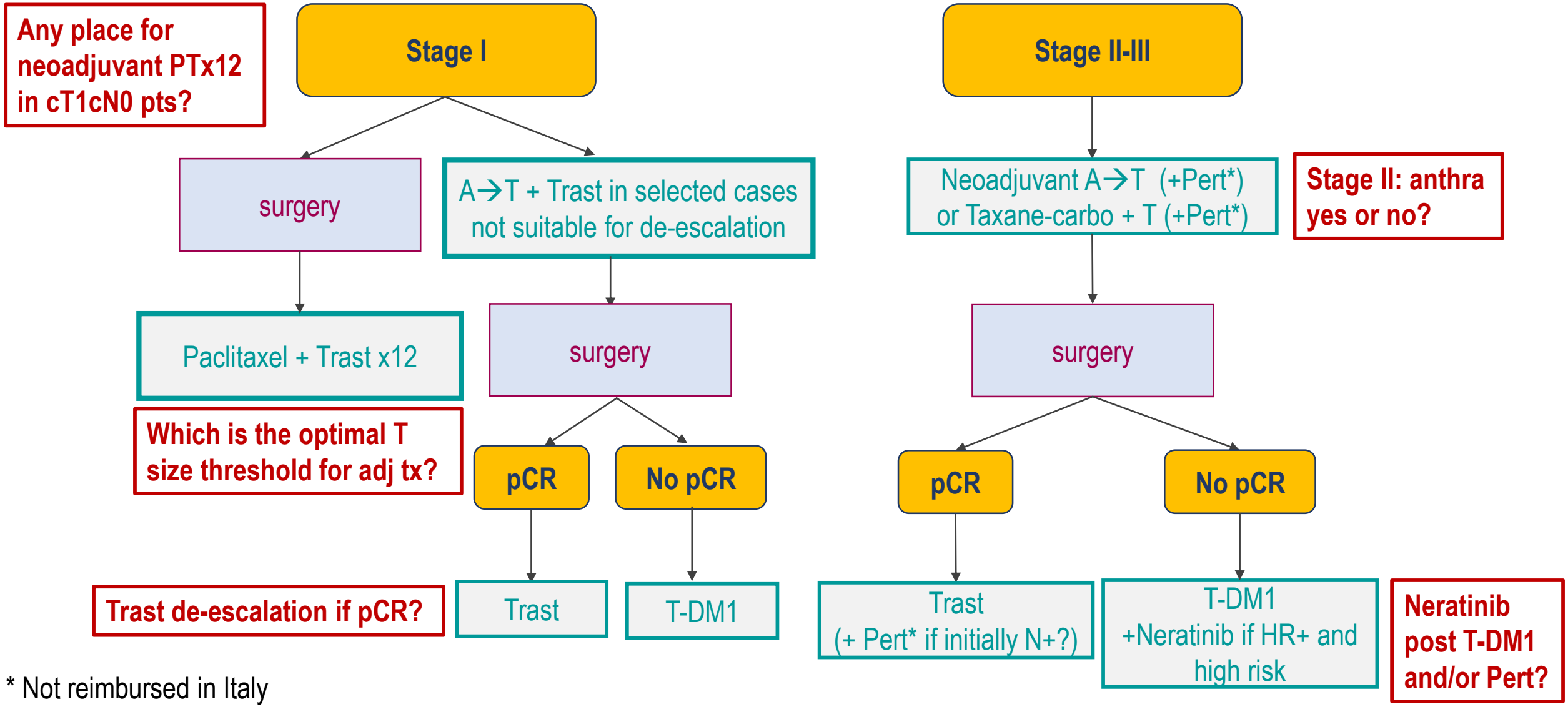
Stage II 65%!!
N+ 64%
HR+ 58%





Van Ramshorst MS et al, Lancet Oncol 2018; van der Voort A et al., ASCO 2020

Proposal of treatment algorithm



* Not reimbursed in Italy