FOLLOW UP OF EARLY BREAST CANCER: WORKING FOR A 2023 CONSENSUS

Previsione del rischio di recidiva nei diversi sottotipi di carcinoma mammario in fase precoce: è possibile?

Tumori HR-positivi/HER2-negativi e Tumori HER2-positivi

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ROMA - 31/03/2023

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DISCLOSURE INFORMATIONS

Luca Arecco:

- Nessun conflitto d’interesse

OUTLINE

- **Introduzione**
- **Rischio di recidiva nei tumori HR-positivi**
- **Rischio di recidiva nei tumori HER2-positivi**
- **Conclusioni**

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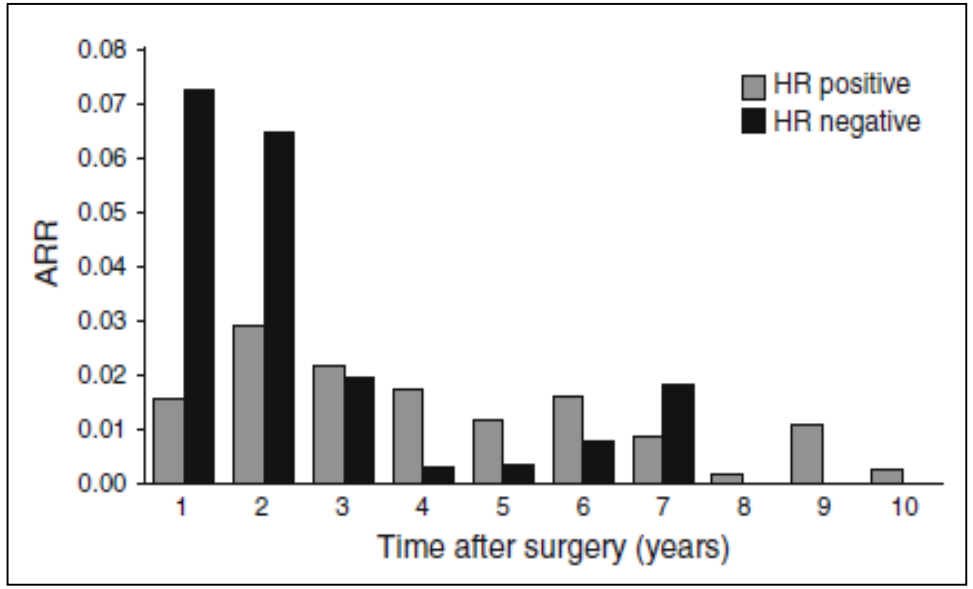
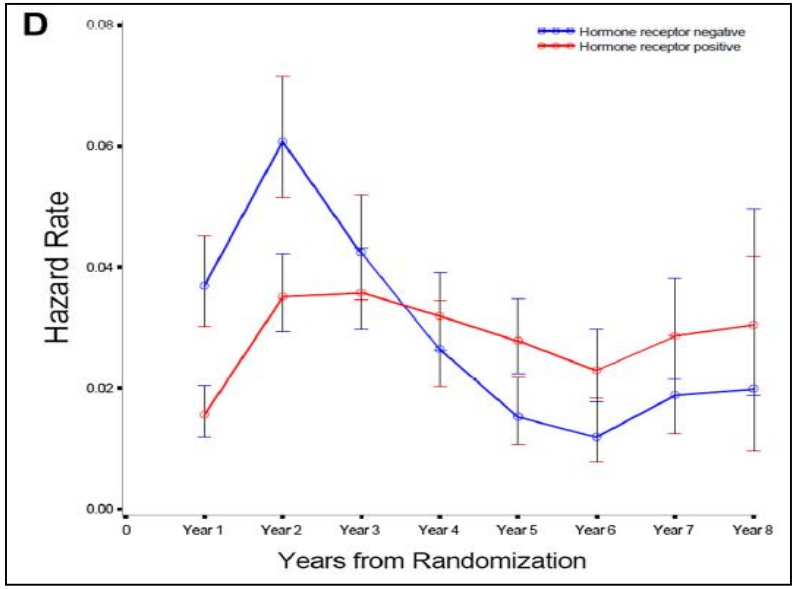
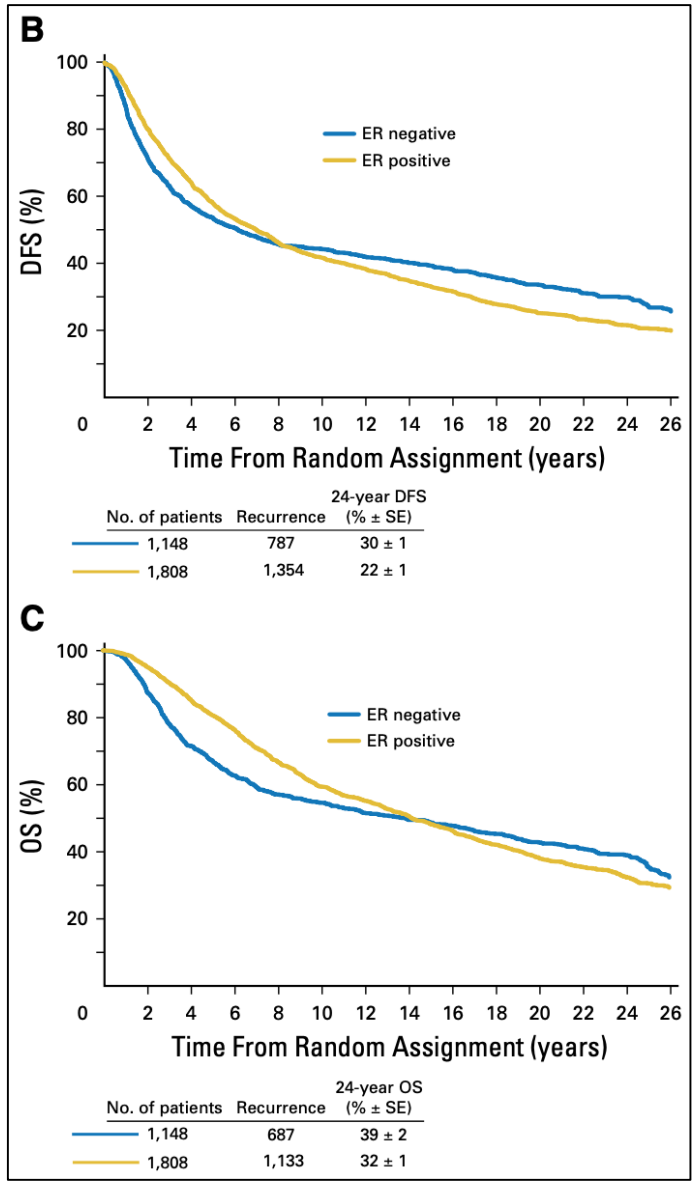
- Rischio di recidiva nei tumori HR-positivi
- Rischio di recidiva nei tumori HER2-positivi
- Conclusioni

RISCHIO DI RECIDIVA NEI TUMORI HR+ E HER2+







- Nei pazienti HR-, il tasso di di recidive raggiunge un picco entro 2 anni dall'intervento e successivamente cala gradualmente.

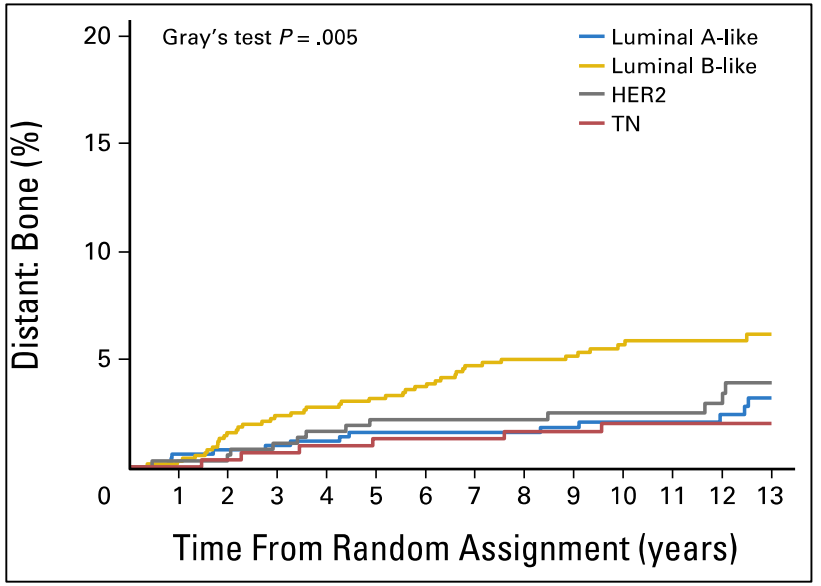
- Nei pazienti HR+, il tasso di recidive raggiunge un picco 2 anni dopo l'intervento e poi rimane quasi costante.

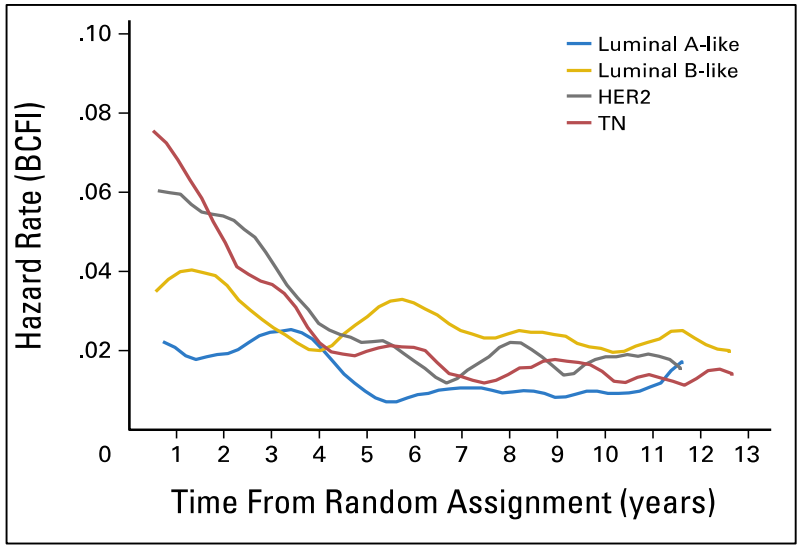
Kimura M et al, Breast Cancer Res Treat 2007;106:407-11 | Lambertini M et al, Breast Cancer Res Treat 2019;177(1):103-14 | Metzger-Filho O et al, J Clin Oncol 2013;31(25)

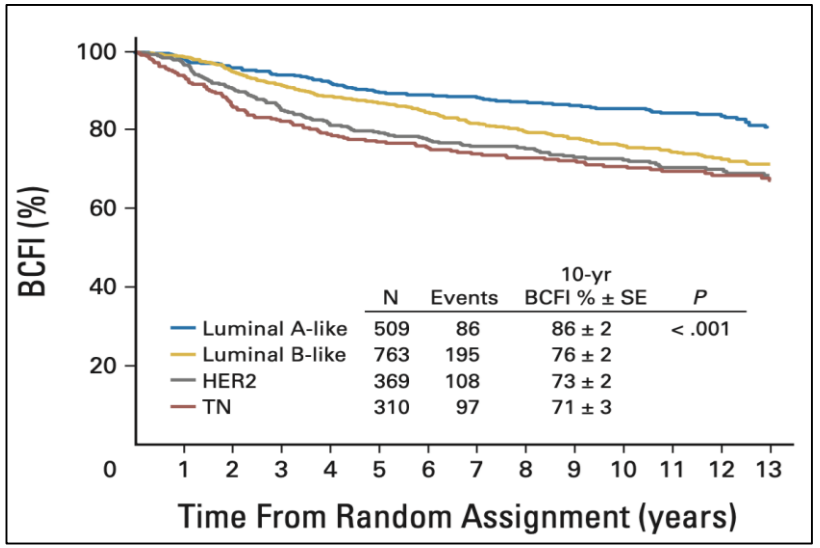
RISCHIO DI RECIDIVA NEI TUMORI HR+ E HER2+

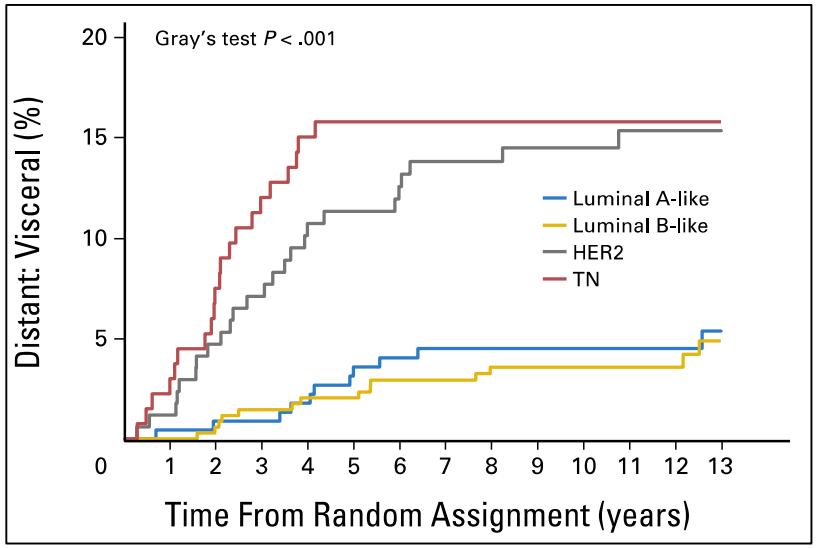
- **Il sottotipo LuminalA-like** ha un BCFI a 10 anni più alto (86%) rispetto ai sottotipi LB-like (76%), HER2+ (73%) e TN (71%) (P<.001).

- **Nel sottogruppo HER2+,** la malattia **HR-** ha tassi di BCFI peggiori rispetto alla malattia HR+, ma la differenza tende ad attenuarsi con il follow-up a lungo termine.









Metzger-Filho O et al, J Clin Oncol 2013;31(25):3083-90

RISCHIO DI RECIDIVA NEI TUMORI HR+ E HER2+

Saper identificare il rischio di recidiva nei diversi sottotipi di carcinoma mammario permette di personalizzare i trattamenti (neo)adiuvanti

BASSO RISCHIO DI RECIDIVA

ALTO RISCHIO DI RECIDIVA

De-escalation dei trattamenti

Riduzione effetti collaterali

Escalation dei trattamenti

Aumento effetti collaterali

OUTLINE

- Introduzione
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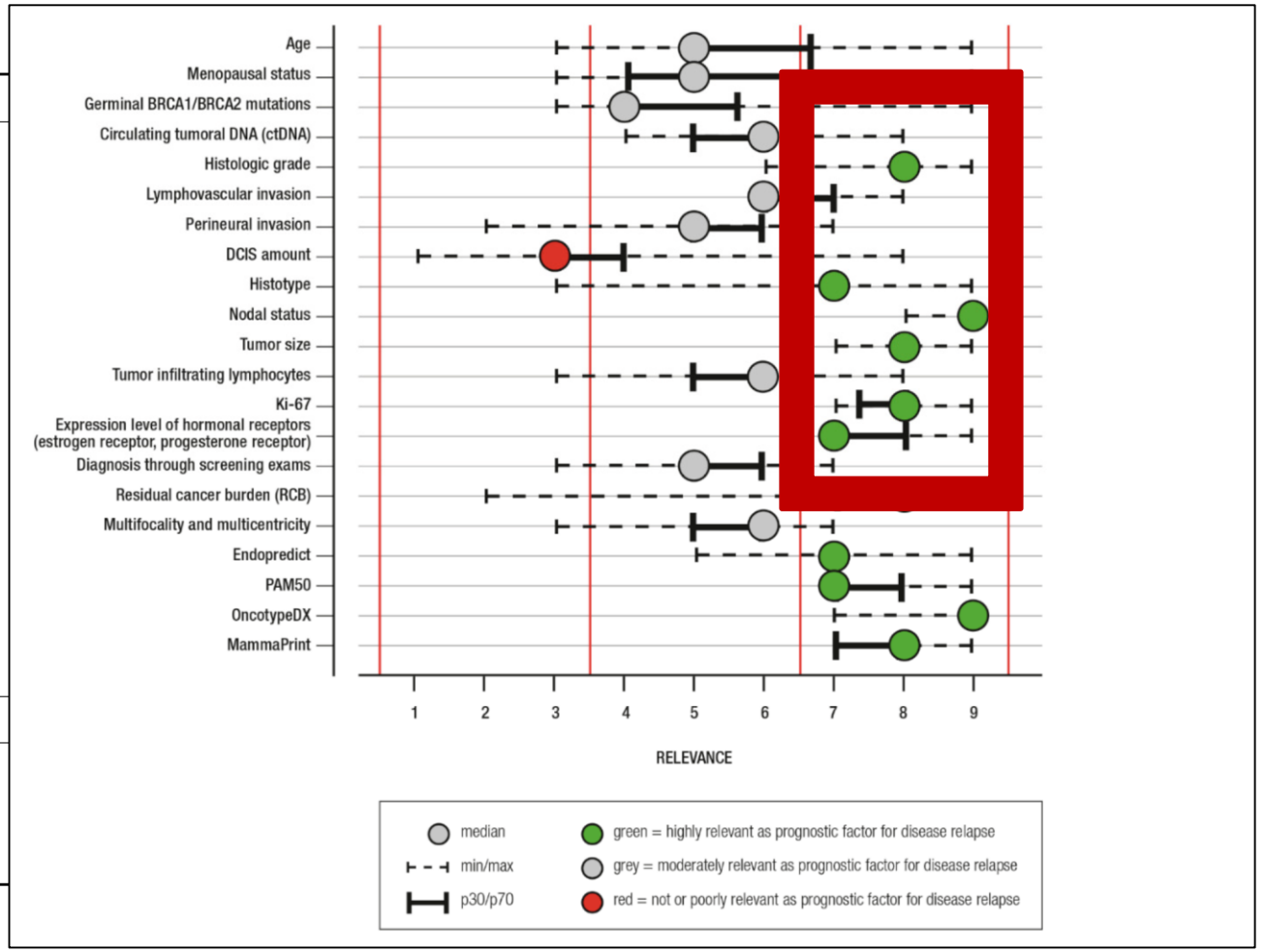
- Rischio di recidiva nei tumori HER2-positivi
- Conclusioni

CRITERI DI STRATIFICAZIONE DEL RISCHIO DI RECIDIVA

Quali fattori sono più rilevanti nello stratificare il rischio di recidiva delle pazienti con malattia luminale?

Clinical, Pathological, and Morphological Factors
• Age
• Menopausal status
• Germinal *BRCA1/BRCA2* mutations
• Circulating tumoral DNA
• Histological grade
• Lymphovascular invasion
• Perineural invasion
• DCIS amount
• Histotype
• Nodal status (N)
• Tumor size (T)
• Tumor-infiltrating lymphocytes
• Ki-67
• Expression level of hormonal receptors (ER, PgR)
• Diagnosis through screening exams
• Residual cancer burden
• Multifocality and multicentricity
Genomic Factors
• EndoPredict®
• PAM50
• Oncotype DX
• MammaPrint®



Garutti M, et al. Cancers (Basel). 2022;14(8):1898.

PROGNOSTIC TOOLS

Nottingham **P**rognostic **I**ndex

NPI= (0.2 x **T**)+ **N** + **Grade**

Stage Biology

Age, T, N, grade, ER, PR, HER2, Ki67

Prognostic information

SOFT & TEXT TRIALS

Absolute Benefit of Adjuvant Endocrine Therapies for Premenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Early Breast Cancer: TEXT and SOFT Trials

Meredith M. Regan, Prudence A. Francis, Olivia Pagani, Gini F. Fleming, Barbara A. Walley, Giuseppe Viale, Marco Colleoni, István Láng, Henry L. Gómez, Carlo Tondini, Graziella Pinotti, Karen N. Price, Alan S. Coates, Aron Goldhirsch, and Richard D. Gelber

ORIGINAL ARTICLE

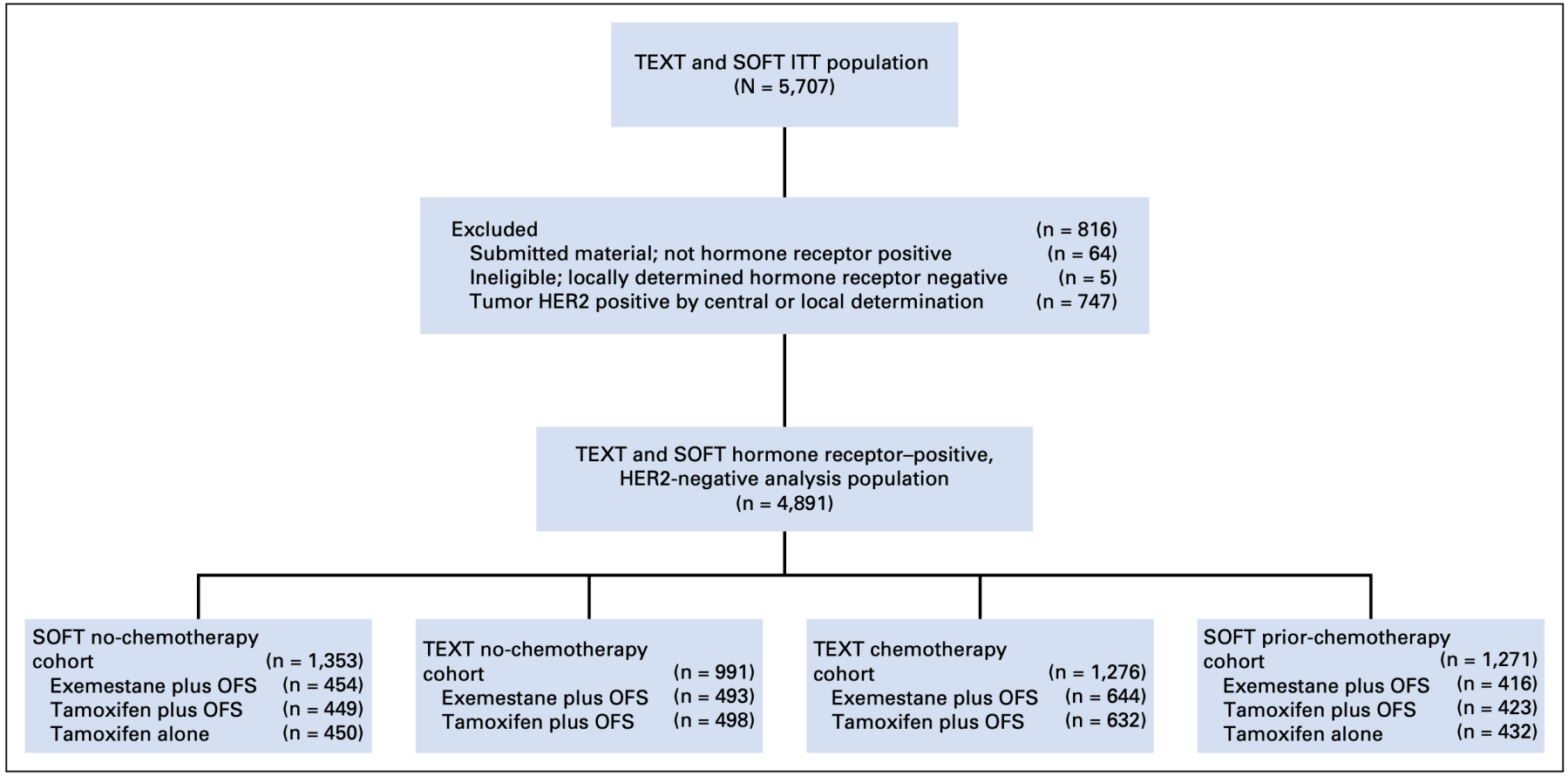
Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

P.A. Francis, O. Pagani, G.F. Fleming, B.A. Walley, M. Colleoni, I. Láng, H.L. Gómez, C. Tondini, E. Ciruelos, H.J. Burstein, H.R. Bonnefoi, M. Bellet, S. Martino, C.E. Geyer, Jr., M.P. Goetz, V. Stearns, G. Pinotti, F. Puglisi, S. Spazzapan, M.A. Climent, L. Pavesi, T. Ruhstaller, N.E. Davidson, R. Coleman, M. Debled, S. Buchholz, J.N. Ingle, E.P. Winer, R. Maibach, M. Rabaglio-Poretti, B. Ruepp, A. Di Leo, A.S. Coates, R.D. Gelber, A. Goldhirsch, and M.M. Regan, for the SOFT and TEXT Investigators and the International Breast Cancer Study Group*

original reports

Absolute Improvements in Freedom From Distant Recurrence to Tailor Adjuvant Endocrine Therapies for Premenopausal Women: Results From TEXT and SOFT

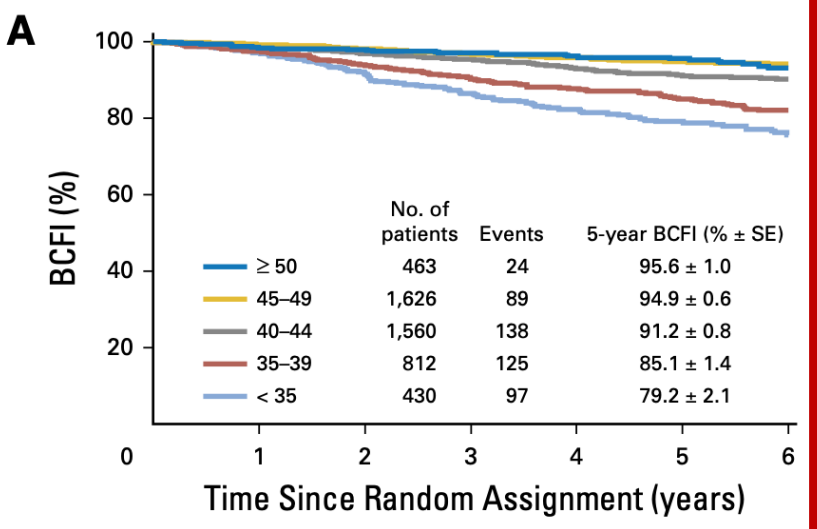
Olivia Pagani, MD[1]; Prudence A. Francis, MD[2]; Gini F. Fleming, MD[3]; Barbara A. Walley, MD[4]; Giuseppe Viale, MD[5]; Marco Colleoni, MD[6]; István Láng, MD, PhD[7]; Henry L. Gómez, MD, PhD[8]; Carlo Tondini, MD[9]; Graziella Pinotti, MD[10]; Angelo Di Leo, MD, PhD[11]; Alan S. Coates, MD[12]; Aron Goldhirsch, MD[6]; Richard D. Gelber, PhD[13]; and Meredith M. Regan, ScD[14] for the SOFT and TEXT Investigators and International Breast Cancer Study Group



Regan MM et al, J Clin Oncol 2016;34(19):2221-31. | Pagani O et al, J Clin Oncol 2020;38(12):1293-1303

SOFT & TEXT TRIALS

ETA’



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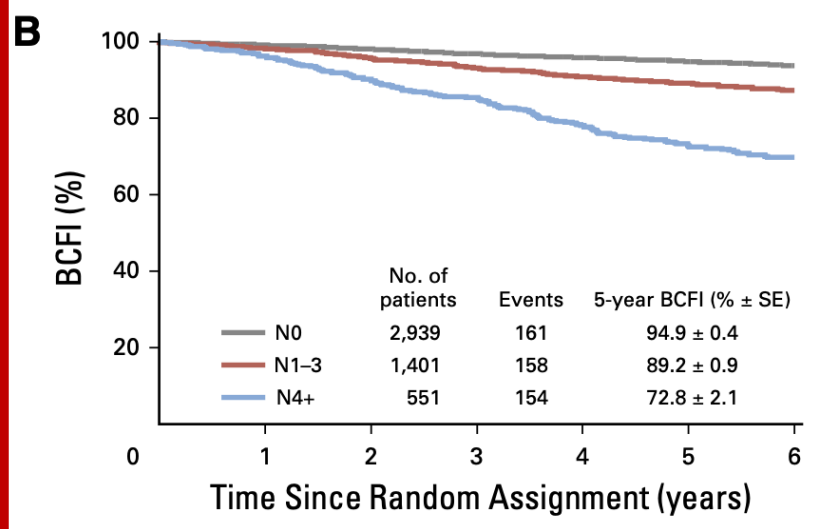

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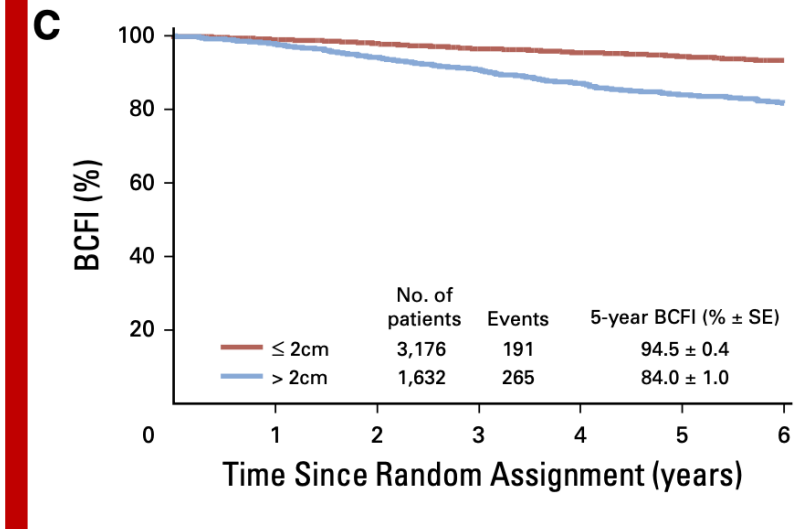
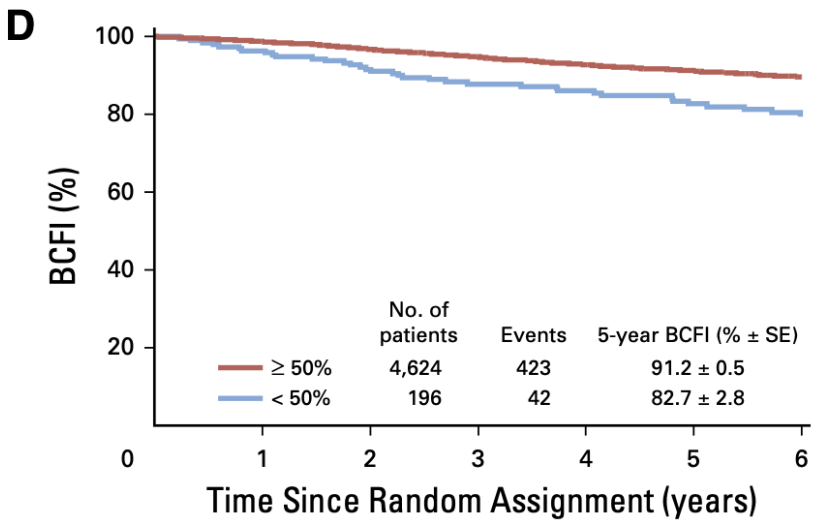
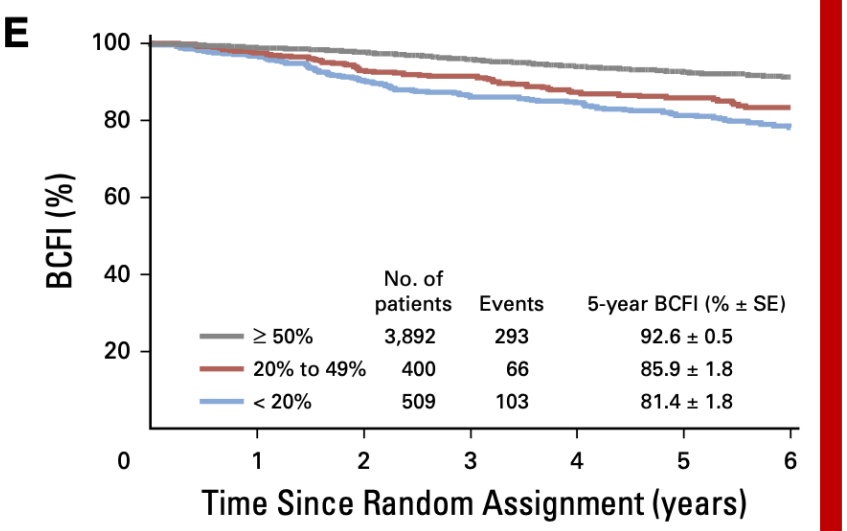


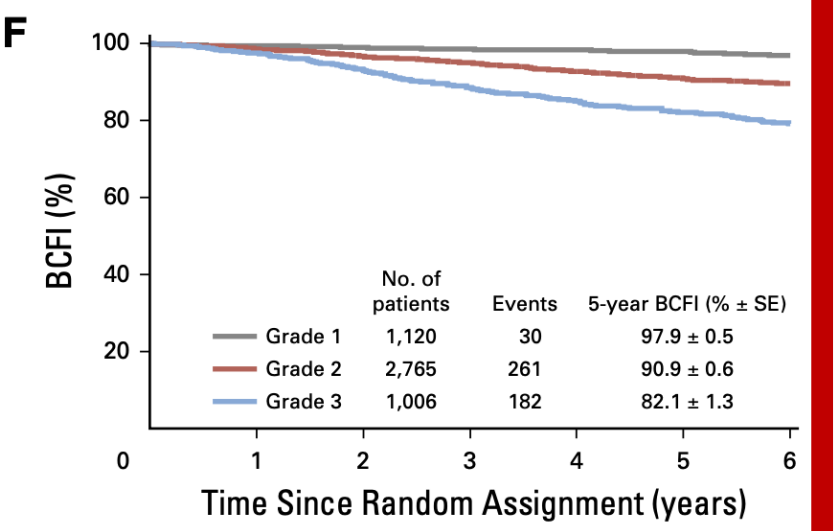
ESTROGENI



KI67



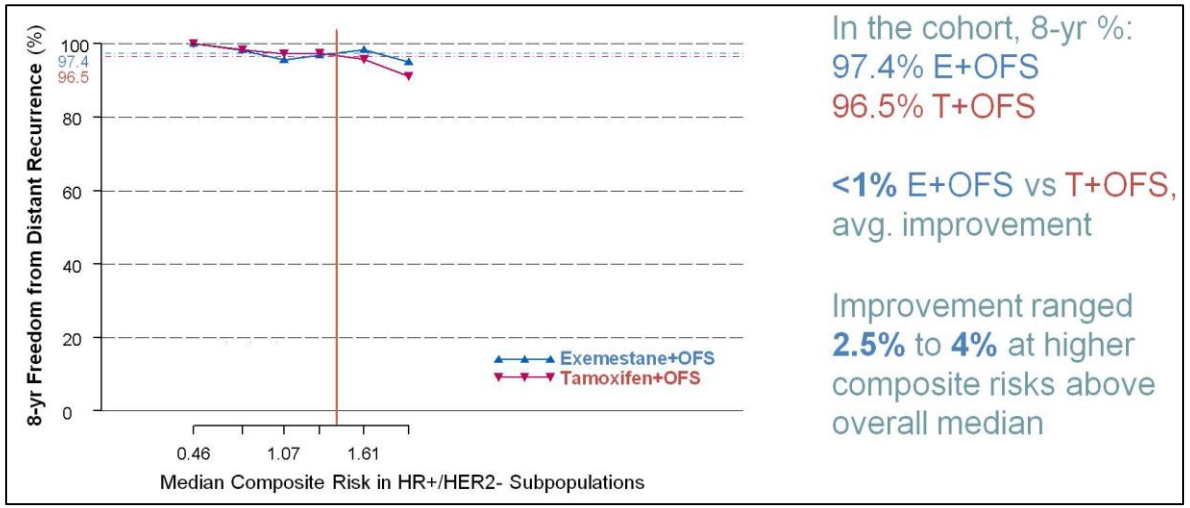
GRADING



Regan MM et al, J Clin Oncol 2016;34(19):2221-31.

SOFT & TEXT TRIALS

TEXT – No chemioterapia

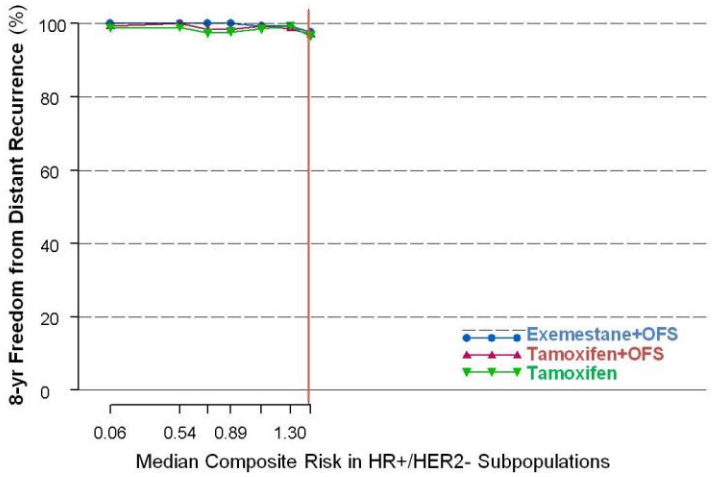


In the cohort, 8-yr %:
97.4% E+OFS
96.5% T+OFS

<1% E+OFS vs T+OFS, avg. improvement

Improvement ranged **2.5%** to **4%** at higher composite risks above overall median

SOFT – No chemioterapia

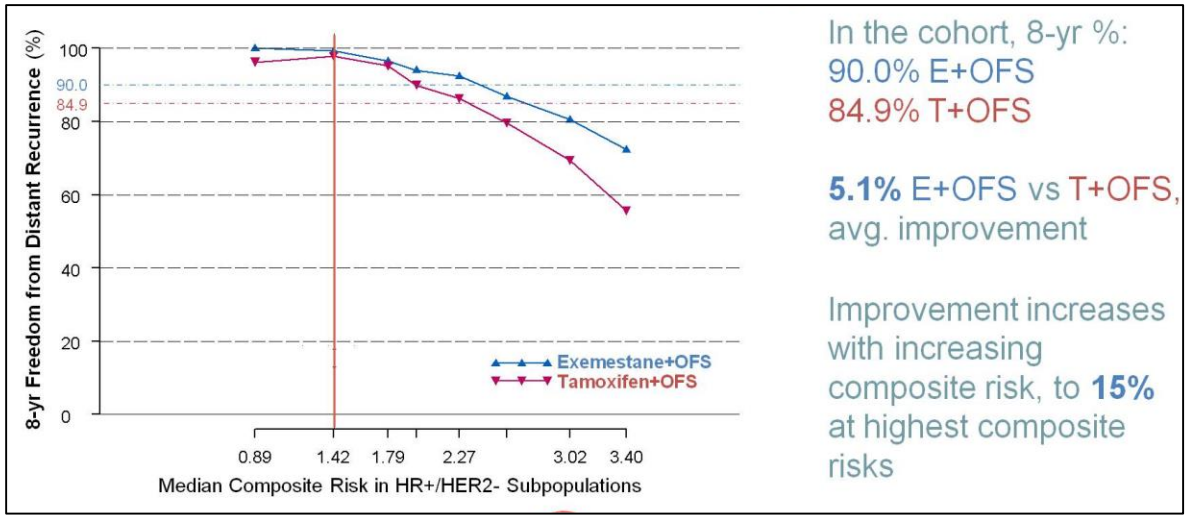


In the cohort, 8-yr %:
99.3% E+OFS
98.3% T+OFS
98.0% T

1.3% E+OFS vs T, avg. improvement ranged **1** to **2.5%**

<1% avg. improvement T+OFS vs T

TEXT – Precedente chemioterapia

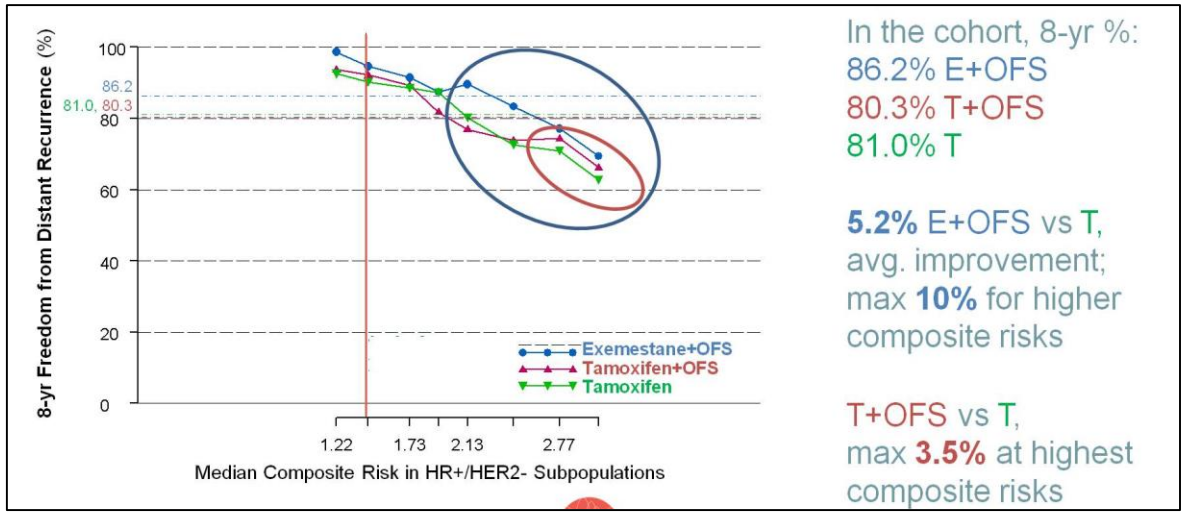


In the cohort, 8-yr %:
90.0% E+OFS
84.9% T+OFS

5.1% E+OFS vs T+OFS, avg. improvement

Improvement increases with increasing composite risk, to **15%** at highest composite risks

SOFT – Precedente chemioterapia



In the cohort, 8-yr %:
86.2% E+OFS
80.3% T+OFS
81.0% T

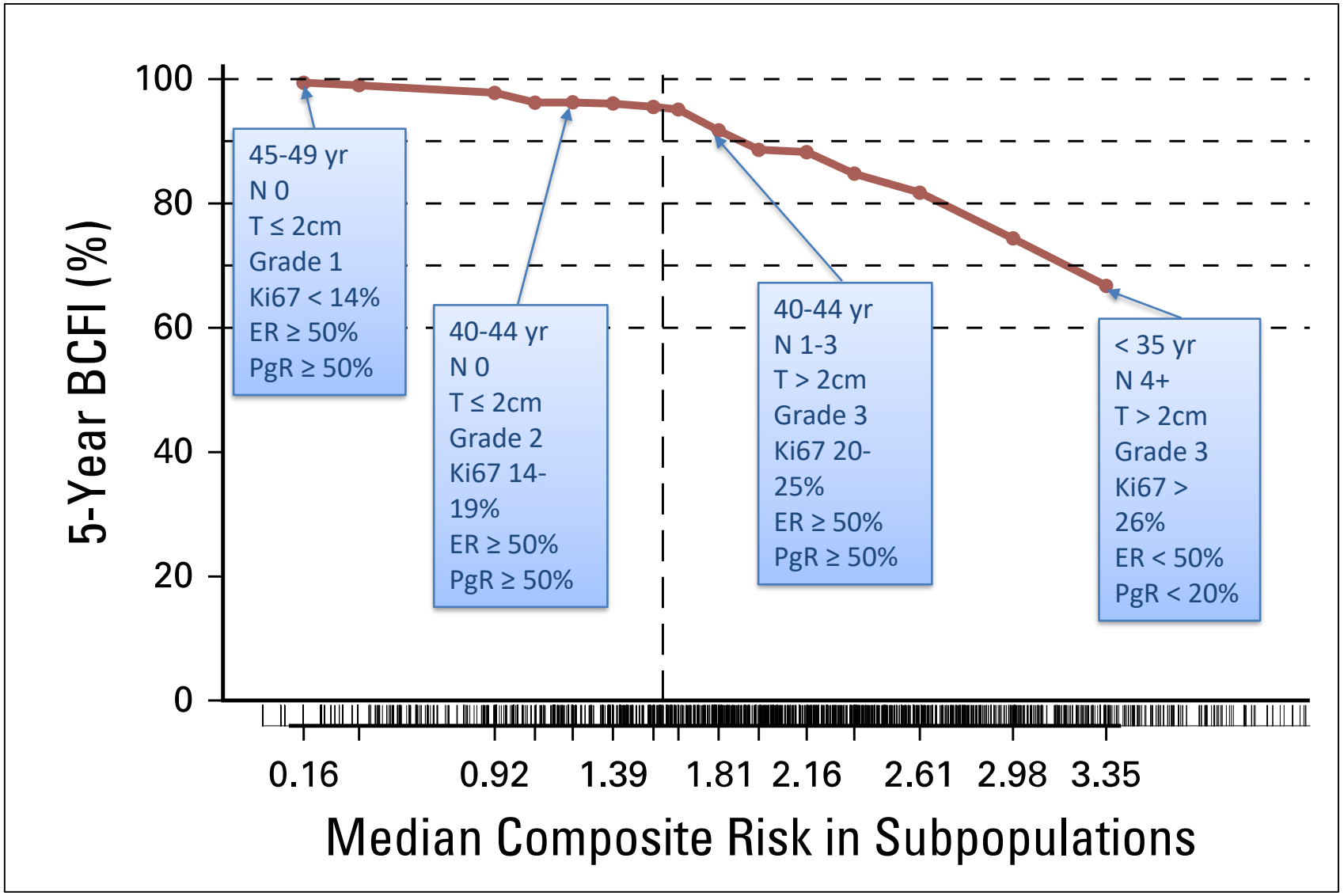
5.2% E+OFS vs T, avg. improvement; max **10%** for higher composite risks

T+OFS vs T, max **3.5%** at highest composite risks

Regan MM et al, J Clin Oncol 2016;34(19):2221-31. Pagani O et al, J Clin Oncol 2020;38(12):1293-1303

RISCHIO DI RECIDIVA NEI TUMORI HR+

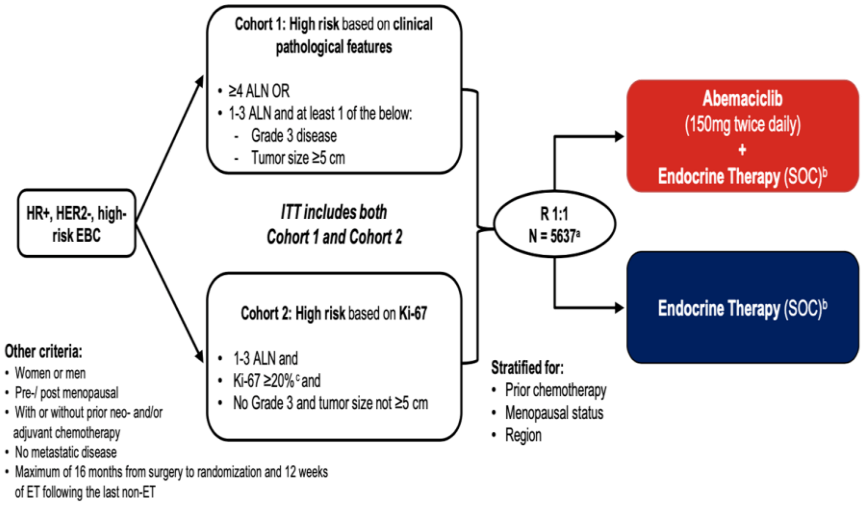
https://rconnect.dfci.harvard.edu/CompositeRiskSTEPP/

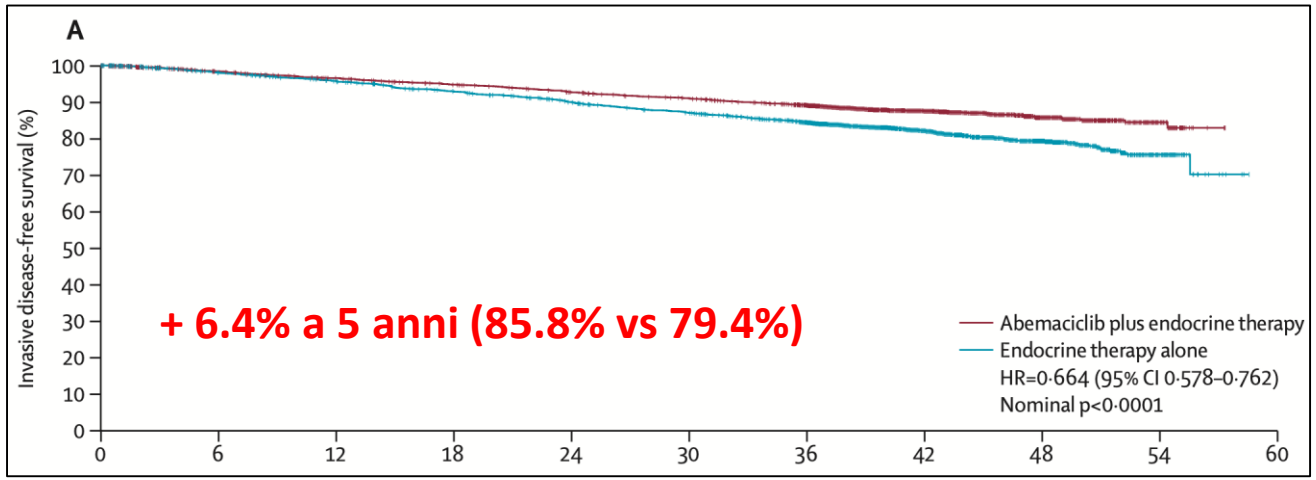


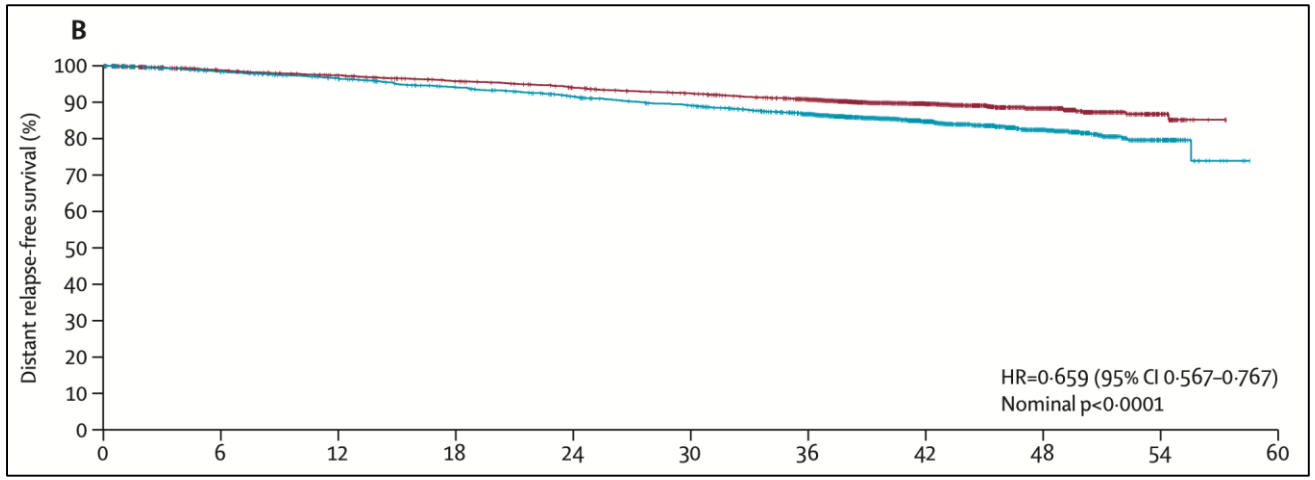
Regan MM et al, J Clin Oncol 2016;34(19):2221-31. Pagani O et al, J Clin Oncol 2020;38(12):1293-1303

MonarchE

Pazienti con carcinoma mammario HR+ ad alto rischio di recidiva (+/- CT) randomizzate all'aggiunta di Abemaciclib per due anni o a trattamento endocrino standard







Prescrivibile sulla base del rischio clinico:

- **≥ 4 linfonodi positivi**
- **1-3 linfonodi positivi in presenza di: G3 e/o T≥ 5 cm**

Johnston SRD et al.,. *Lancet Oncol*. 2023;24(1):77-90.

Quante sono le pazienti HR+ ad alto rischio?

- Più di 4,000 pazienti con diagnosi di EBC in stadio IA-IIIC HR+, HER2-.
- Follow-up di 40 mesi.

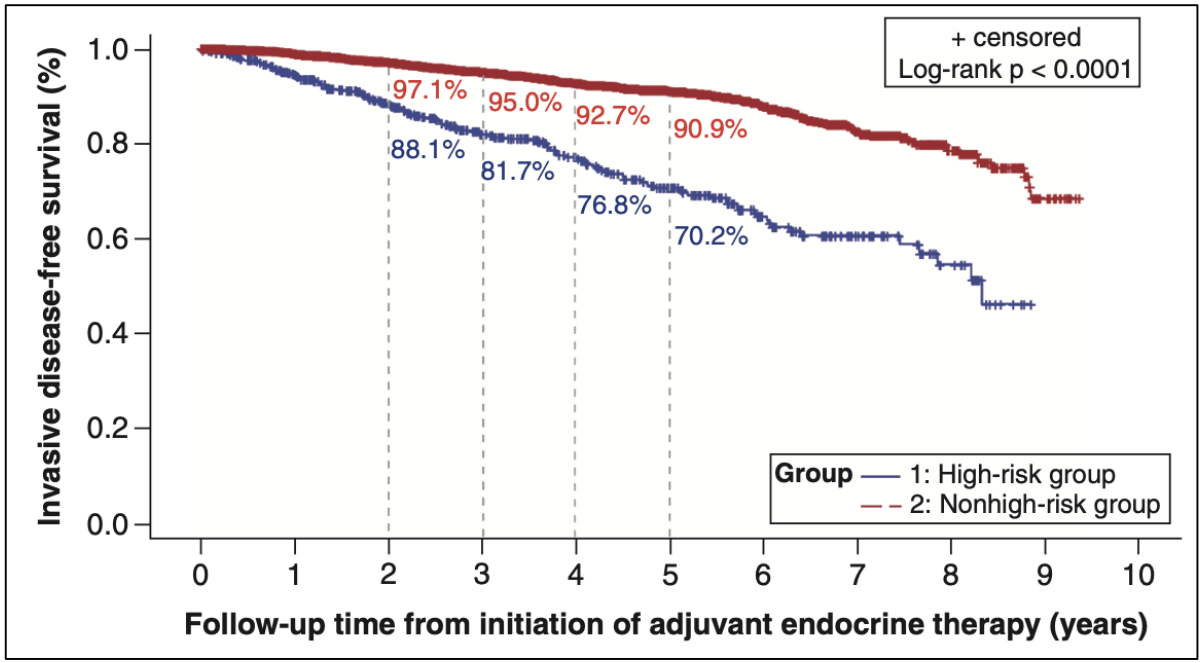
- **557 (13,8%)** pazienti nel gruppo ad **alto rischio** (≥4nodi, o 1–3 nodi e G3, T ≥5 cm o Ki-67 ≥20%).
- **3471 (86,2%)** nel gruppo a **basso rischio.**

- Il tasso di IDFS a 2 anni è:
  - 88,1% nel gruppo ad **alto rischio**
  - 97,1% del gruppo a **basso rischio**

- **Il 12% dei pazienti nel gruppo ad alto rischio ha avuto una recidiva o un decesso entro 2 anni**, rispetto a solo il **3%** dei pazienti nel gruppo a basso rischio.

A real-world US study of recurrence risks using combined clinicopathological features in HR-positive, HER2-negative early breast cancer

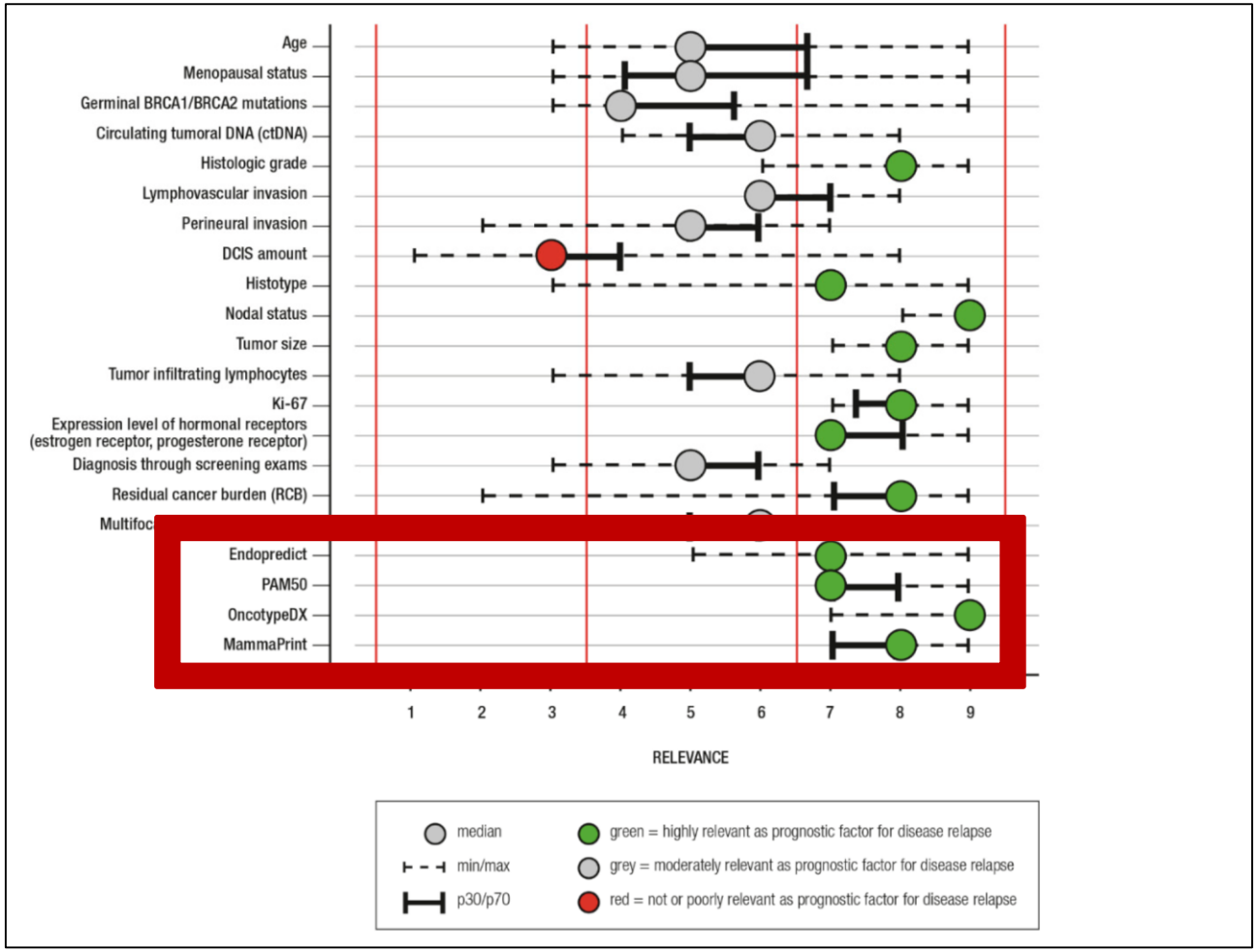
Kristin M Sheffield*[,1], Jessica R Peachey[1], Michael Method[1,4], Brenda R Grimes[1], Jacqueline Brown[1], Kim Saverno[1,5], Tomoko Sugihara[2], Zhanglin Lin Cui[1] & Kimberley T Lee[3]



Sheffield KM et al., *Future Oncol*. 2022;18(21):2667-2682.

CRITERI DI STRATIFICAZIONE DEL RISCHIO DI RECIDIVA

Quali fattori sono più rilevanti nello stratificare il rischio di recidiva delle pazienti con malattia luminale?



Garutti M, et al. Cancers (Basel). 2022;14(8):1898.

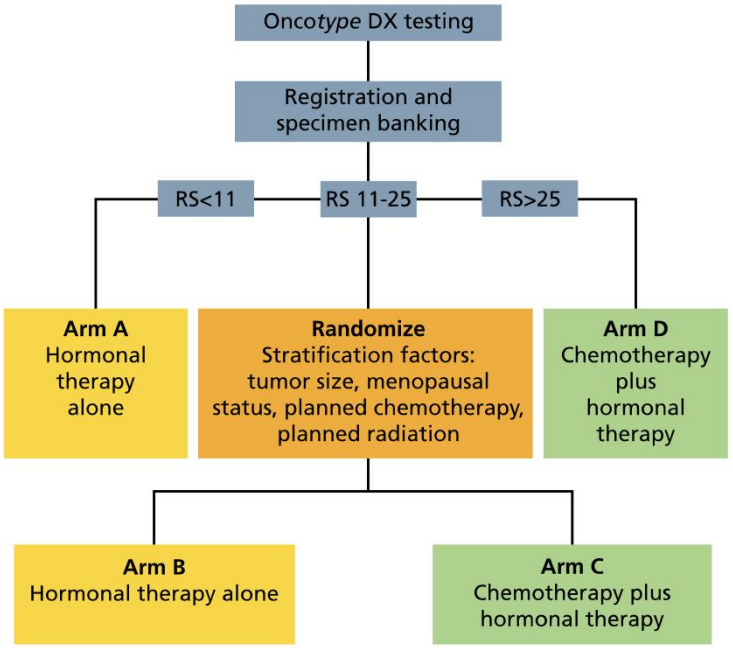
TEST GENOMICI

QUALI SONO I PRINCIPALI TEST GENOMICI ATTUALMENTE UTILIZZABILI IN PRATICA CLINICA?

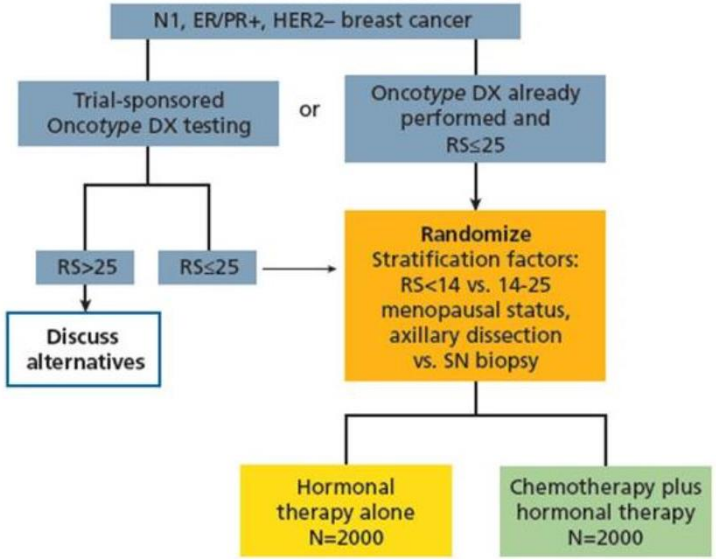
Test	Description	Site	Risk classification
Oncotype	21-gene signature on paraffin sample	Central	Low, intermediate, high
Mammaprint	70-gene signature on both frozen and paraffine sample	Central	Low, High
Endopredict	11-gene signature	Local labs	Low, high
Prosigna	50-gene signature	Local labs	Low, intermediate, high

RUOLO DEI TEST GENOMICI

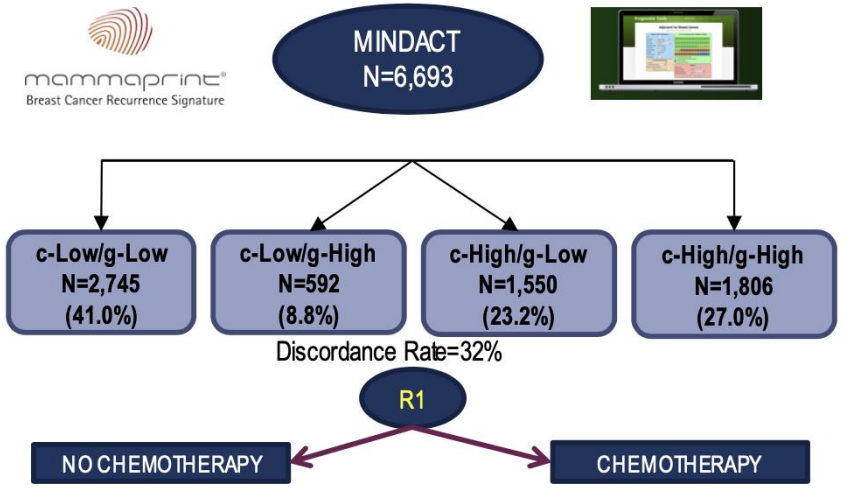
TAILORx
Node negative
All ER+/HER2-
N=9719



RxPONDER
Node positive (**1-3 N+**)
All ER+/HER2-
N=5083



MINDACT
Node negative/positive
(**1-3 N+ 21%**)
81% ER+/HER2-
N=6693



21,459 PAZIENTI

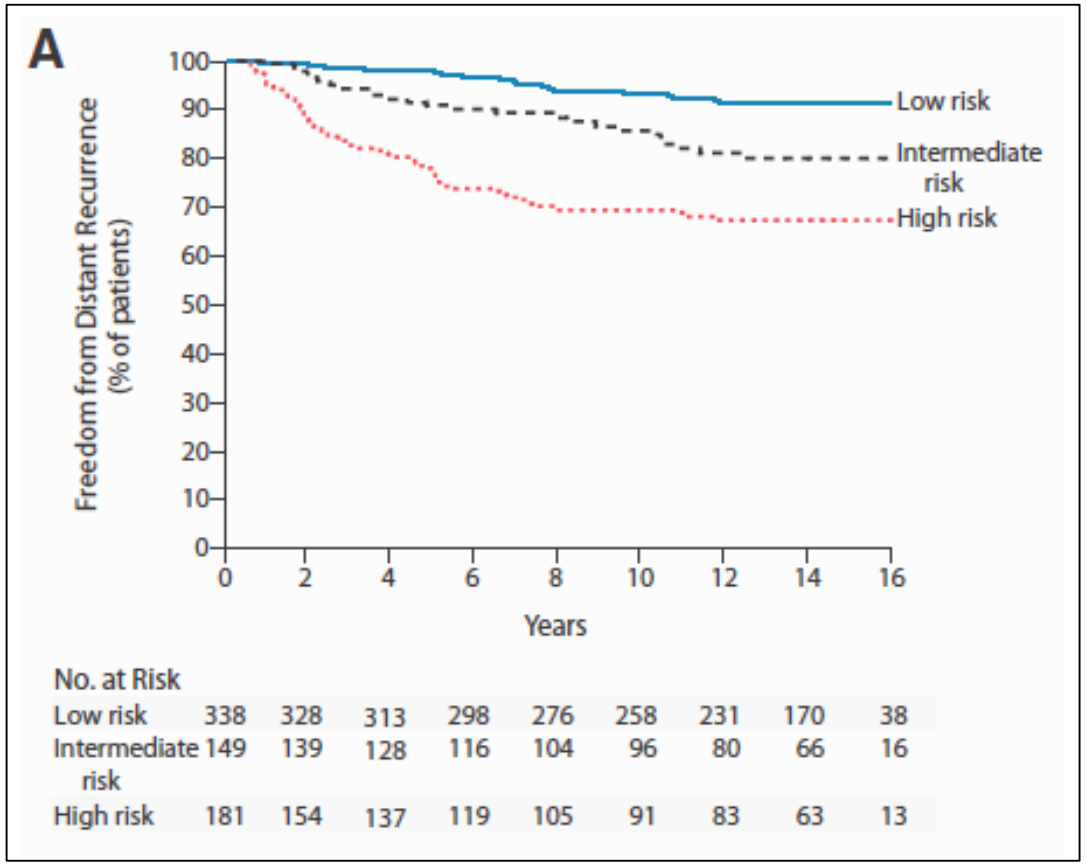
TEST GENOMICI

BASSO RISCHIO	ALTO RISCHIO
Le seguenti 5 caratteristiche	Almeno 4 delle seguenti caratteristiche
G1	G3
T1 (a-b)*	T3 T4
Ki 67 <20%	Ki 67>30%
ER>80%	ER<30%
N Negativo	N Positivo (>3 linfonodi non indicazione al test)
*In caso di T1a non e' indicato l'accesso al test in presenza di almeno altri 2 parametri favorevoli	

RUOLO DEI TEST GENOMICI

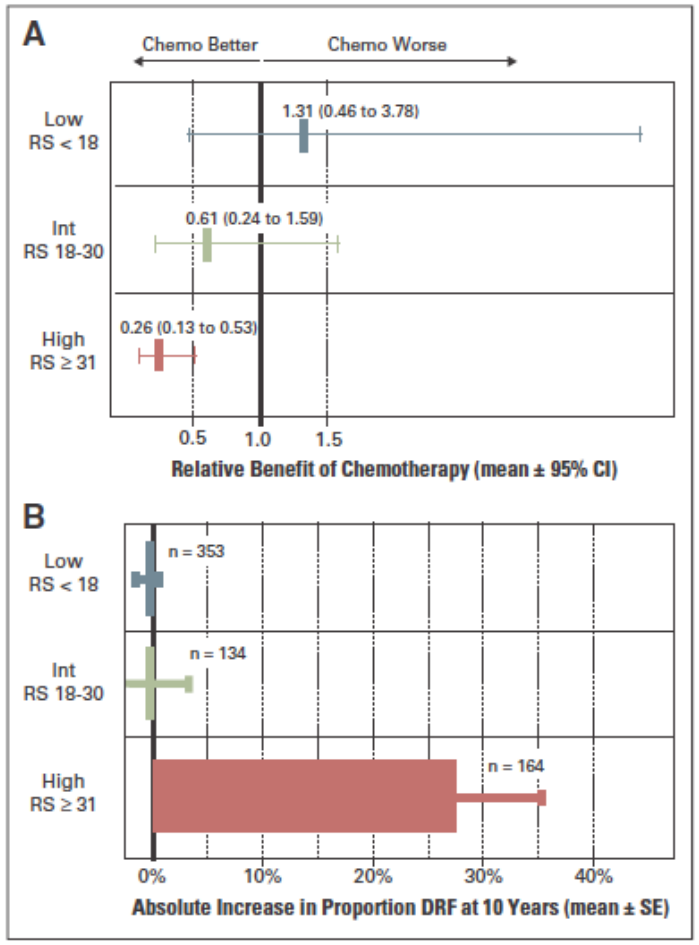
Definire ulteriormente il rischio di recidiva:

ruolo prognostico



Fornire uno strumento nella decisione sui successive trattamenti:

ruolo predittivo

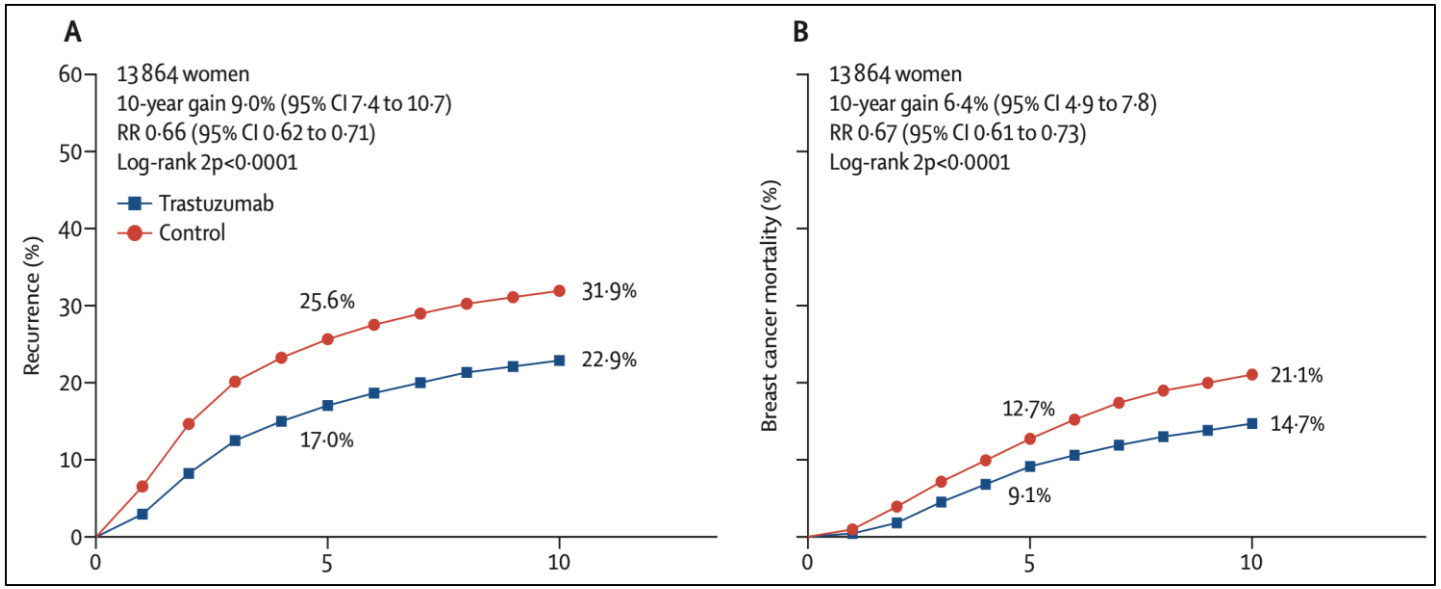


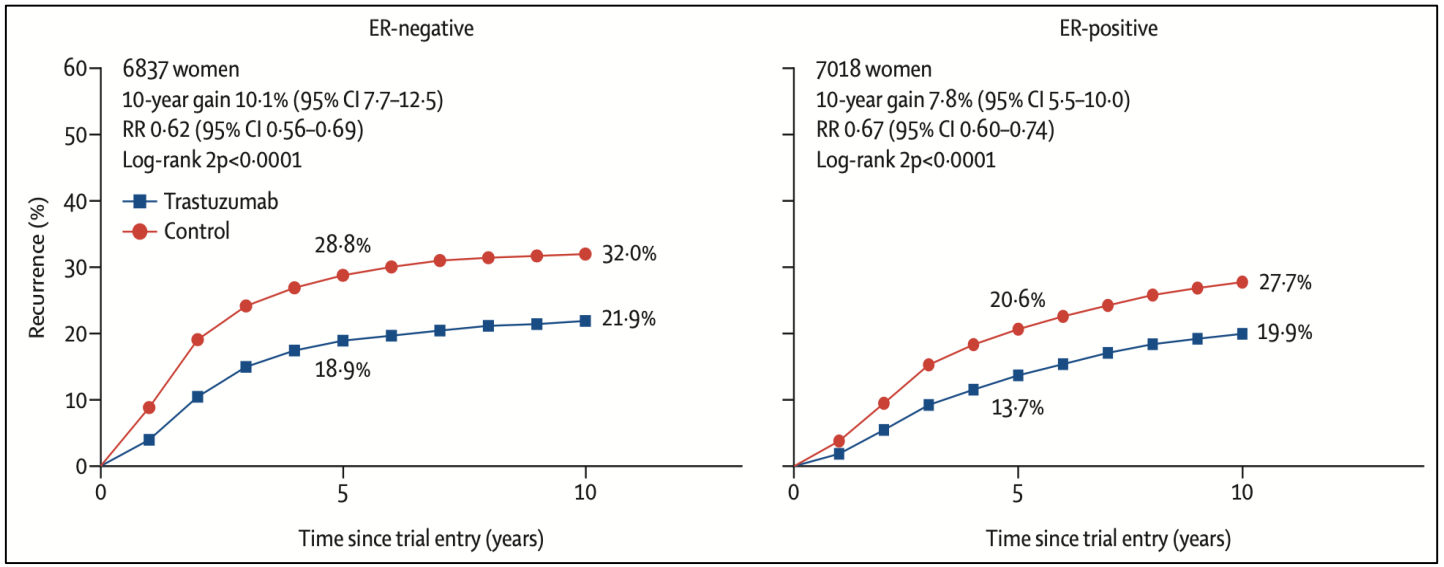
Sparano et al., JCO 2008

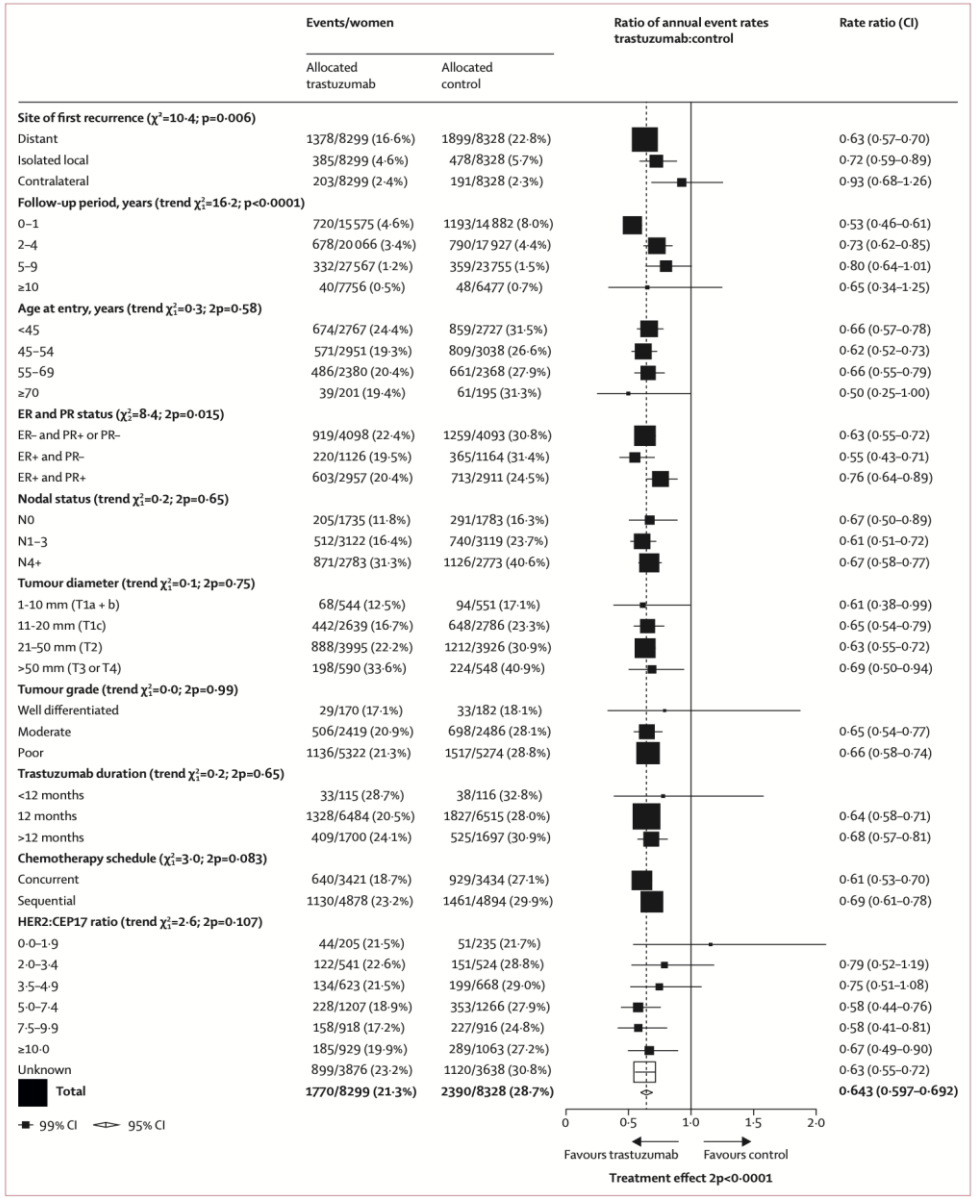
OUTLINE

- Introduzione
- Rischio di recidiva nei tumori HR-positivi
- **Rischio di recidiva nei tumori HER2-positivi**
- Conclusioni

RISCHIO DI RECIDIVA NEI TUMORI HER2+





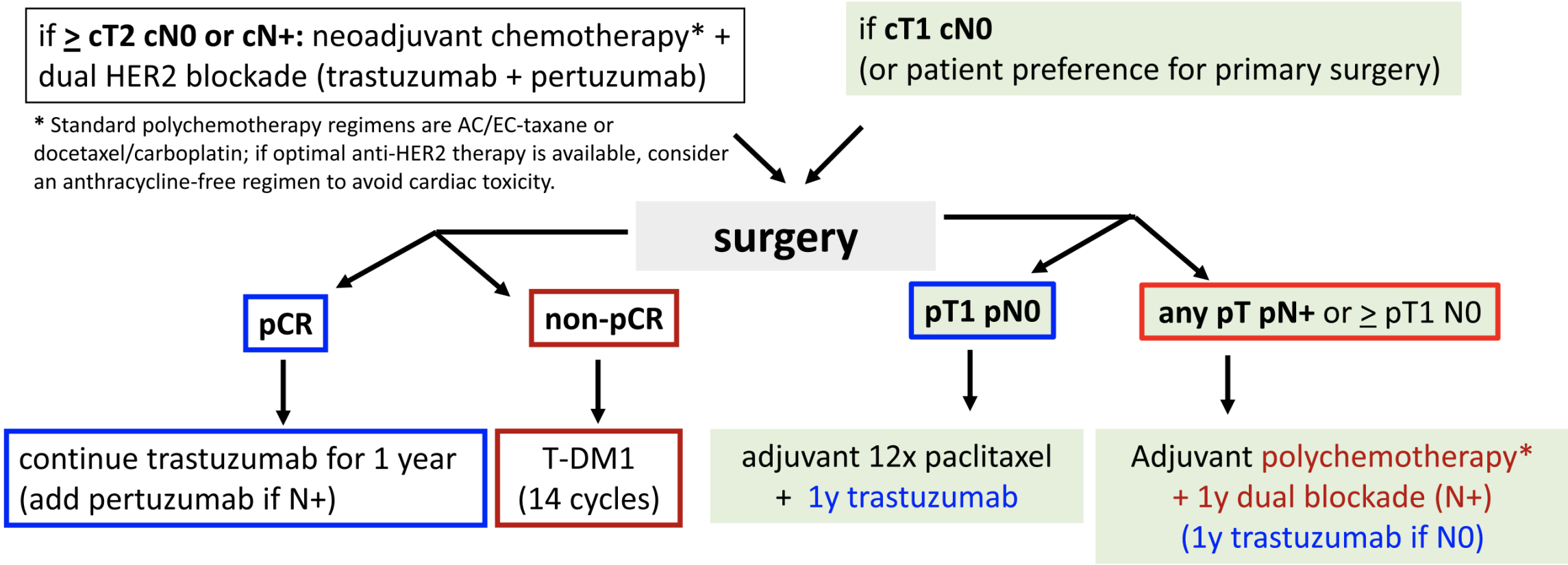


	Events/women		Ratio of annual event rates trastuzumab:control	Rate ratio (CI)
	Allocated trastuzumab	Allocated control		
Site of first recurrence (χ^2=10·4; p=0·006)				
Distant	1378/8299 (16·6%)	1899/8328 (22·8%)		0·63 (0·57–0·70)
Isolated local	385/8299 (4·6%)	478/8328 (5·7%)		0·72 (0·59–0·89)
Contralateral	203/8299 (2·4%)	191/8328 (2·3%)		0·93 (0·68–1·26)
Follow-up period, years (trend χ^2_1=16·2; p<0·0001)				
0–1	720/15 575 (4·6%)	1193/14 882 (8·0%)		0·53 (0·46–0·61)
2–4	678/20 066 (3·4%)	790/17 927 (4·4%)		0·73 (0·62–0·85)
5–9	332/27 567 (1·2%)	359/23 755 (1·5%)		0·80 (0·64–1·01)
≥10	40/7756 (0·5%)	48/6477 (0·7%)		0·65 (0·34–1·25)
Age at entry, years (trend χ^2_1=0·3; 2p=0·58)				
<45	674/2767 (24·4%)	859/2727 (31·5%)		0·66 (0·57–0·78)
45–54	571/2951 (19·3%)	809/3038 (26·6%)		0·62 (0·52–0·73)
55–69	486/2380 (20·4%)	661/2368 (27·9%)		0·66 (0·55–0·79)
≥70	39/201 (19·4%)	61/195 (31·3%)		0·50 (0·25–1·00)
ER and PR status (χ^2_1=8·4; 2p=0·015)				
ER– and PR+ or PR–	919/4098 (22·4%)	1259/4093 (30·8%)		0·63 (0·55–0·72)
ER+ and PR–	220/1126 (19·5%)	365/1164 (31·4%)		0·55 (0·43–0·71)
ER+ and PR+	603/2957 (20·4%)	713/2911 (24·5%)		0·76 (0·64–0·89)
Nodal status (trend χ^2_1=0·2; 2p=0·65)				
N0	205/1735 (11·8%)	291/1783 (16·3%)		0·67 (0·50–0·89)
N1–3	512/3122 (16·4%)	740/3119 (23·7%)		0·61 (0·51–0·72)
N4+	871/2783 (31·3%)	1126/2773 (40·6%)		0·67 (0·58–0·77)
Tumour diameter (trend χ^2_1=0·1; 2p=0·75)				
1–10 mm (T1a + b)	68/544 (12·5%)	94/551 (17·1%)		0·61 (0·38–0·99)
11–20 mm (T1c)	442/2639 (16·7%)	648/2786 (23·3%)		0·65 (0·54–0·79)
21–50 mm (T2)	888/3995 (22·2%)	1212/3926 (30·9%)		0·63 (0·55–0·72)
>50 mm (T3 or T4)	198/590 (33·6%)	224/548 (40·9%)		0·69 (0·50–0·94)
Tumour grade (trend χ^2_1=0·0; 2p=0·99)				
Well differentiated	29/170 (17·1%)	33/182 (18·1%)		
Moderate	506/2419 (20·9%)	698/2486 (28·1%)		0·65 (0·54–0·77)
Poor	1136/5322 (21·3%)	1517/5274 (28·8%)		0·66 (0·58–0·74)
Trastuzumab duration (trend χ^2_1=0·2; 2p=0·65)				
<12 months	33/115 (28·7%)	38/116 (32·8%)		
12 months	1328/6484 (20·5%)	1827/6515 (28·0%)		0·64 (0·58–0·71)
>12 months	409/1700 (24·1%)	525/1697 (30·9%)		0·68 (0·57–0·81)
Chemotherapy schedule (χ^2_1=3·0; 2p=0·083)				
Concurrent	640/3421 (18·7%)	929/3434 (27·1%)		0·61 (0·53–0·70)
Sequential	1130/4878 (23·2%)	1461/4894 (29·9%)		0·69 (0·61–0·78)
HER2:CEP17 ratio (trend χ^2_1=2·6; 2p=0·107)				
0·0–1·9	44/205 (21·5%)	51/235 (21·7%)		
2·0–3·4	122/541 (22·6%)	151/524 (28·8%)		0·79 (0·52–1·19)
3·5–4·9	134/623 (21·5%)	199/668 (29·0%)		0·75 (0·51–1·08)
5·0–7·4	228/1207 (18·9%)	353/1266 (27·9%)		0·58 (0·44–0·76)
7·5–9·9	158/918 (17·2%)	227/916 (24·8%)		0·58 (0·41–0·81)
≥10·0	185/929 (19·9%)	289/1063 (27·2%)		0·67 (0·49–0·90)
Unknown	899/3876 (23·2%)	1120/3638 (30·8%)		0·63 (0·55–0·72)
Total	**1770/8299 (21·3%)**	**2390/8328 (28·7%)**		**0·643 (0·597–0·692)**

99% CI 95% CI
0 0·5 1·0 1·5 2·0
Favours trastuzumab Favours control
Treatment effect 2p<0·0001

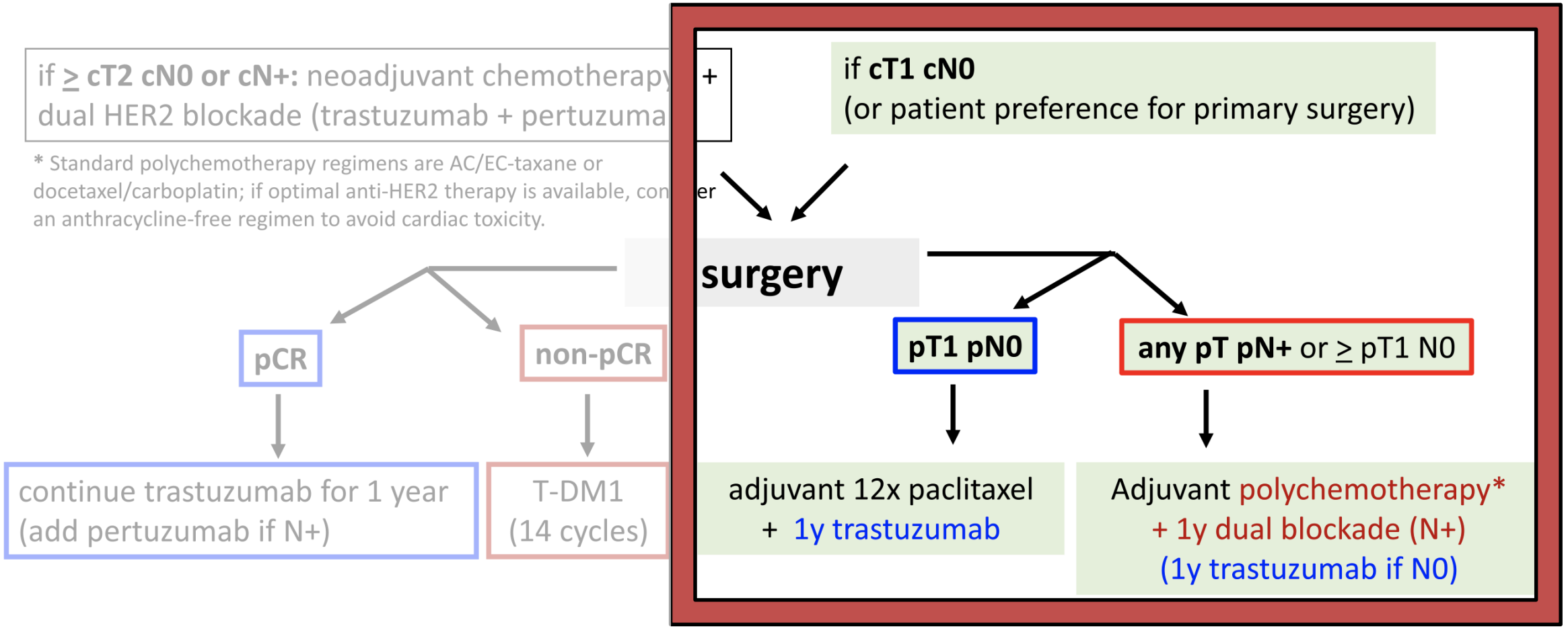
Early Breast Cancer Trialists' Collaborative group (EBCTCG). *Lancet Oncol*. 2021;22(8):1139-1150.

ALGORITMO TERAPEUTICO TUMORI HER2+



Harbeck N. *Breast*. 2022;62:S12-S16.

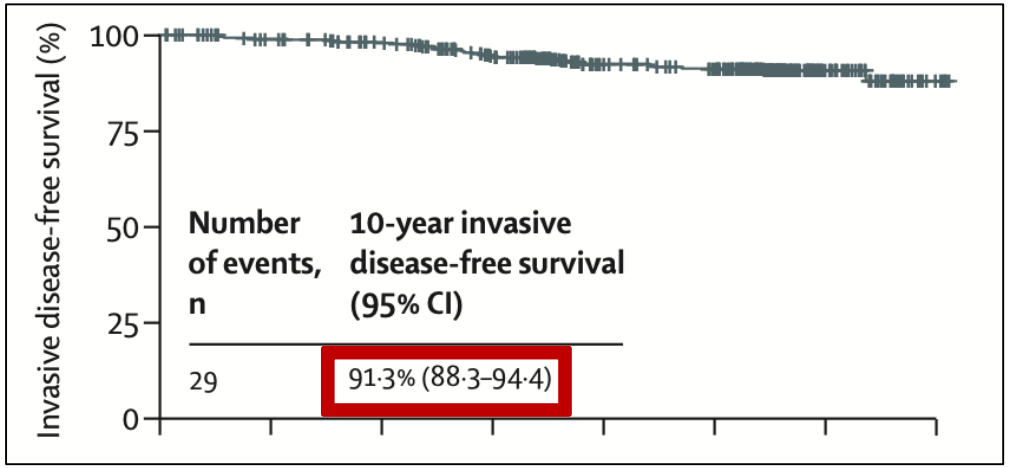
ALGORITMO TERAPEUTICO TUMORI HER2+

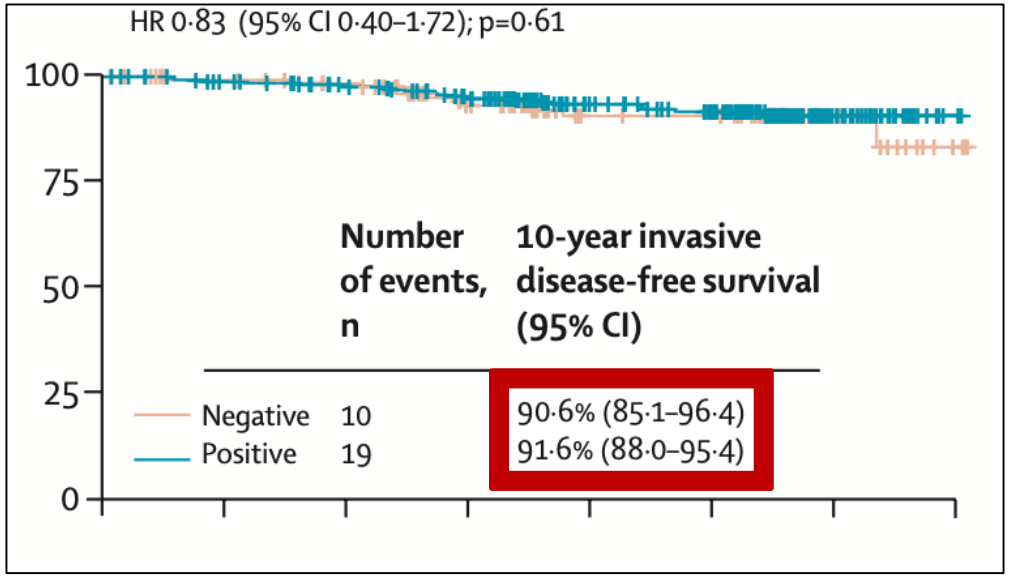


Harbeck N. *Breast*. 2022;62:S12-S16.

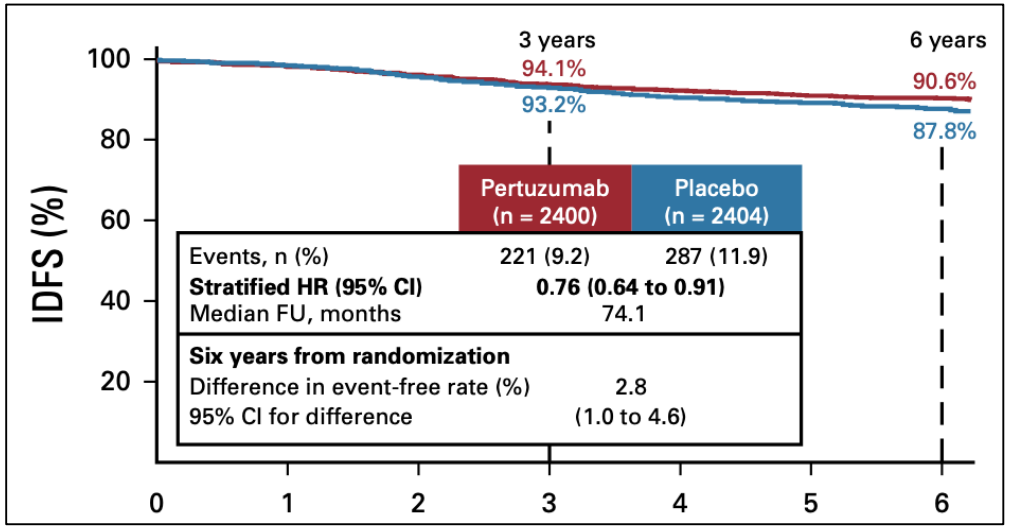
TRIAL ADIUVANTE HER2+ IN BASE AL RISCHIO CLINICO

Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial

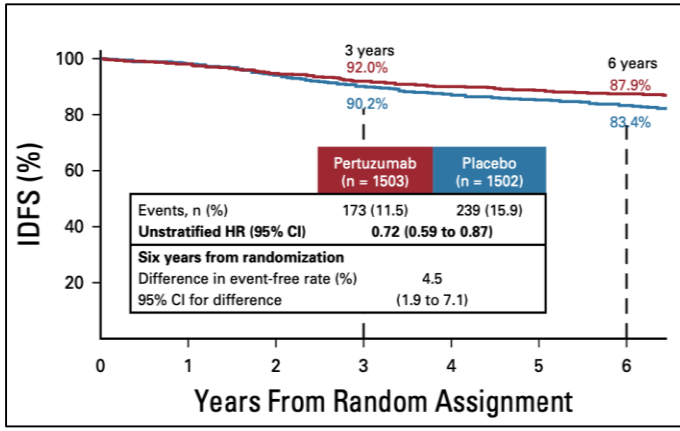




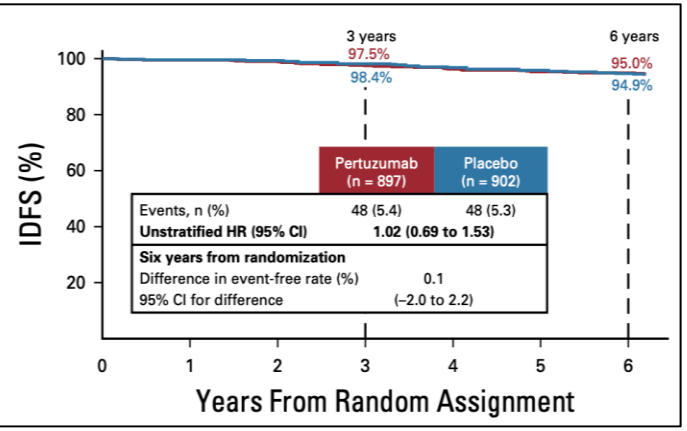
Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up



LINFONODI +



LINFONODI -



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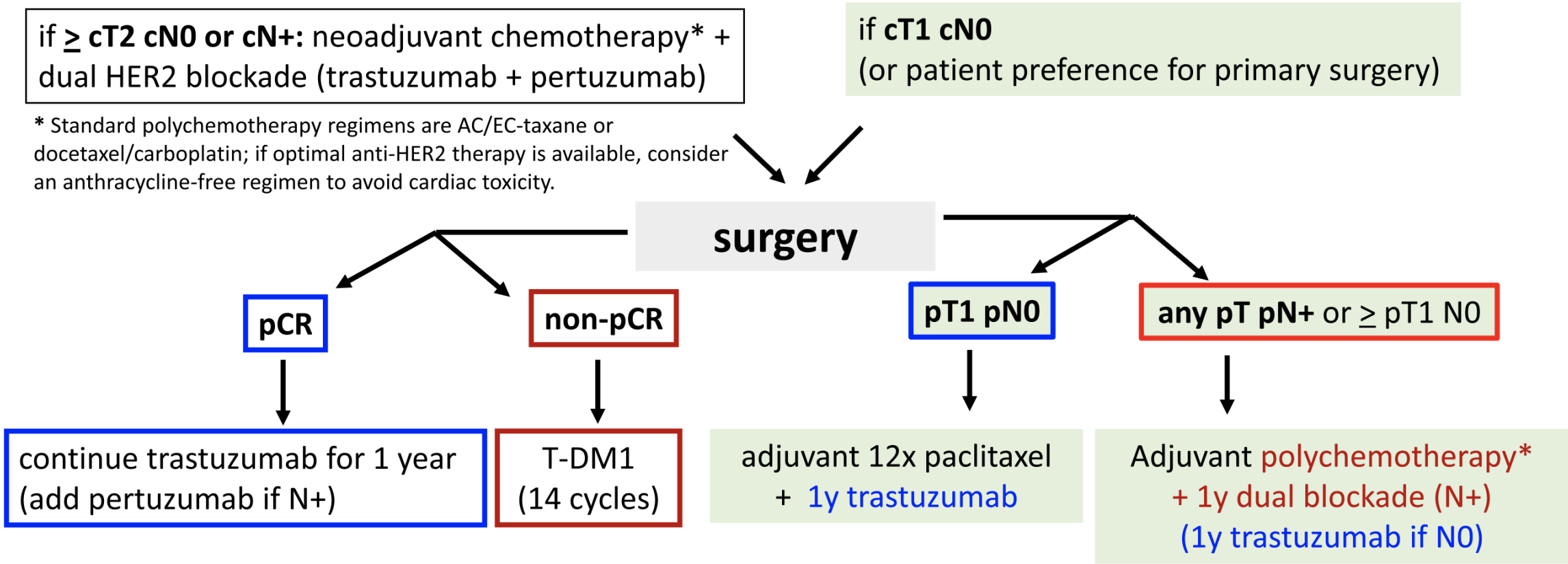
ALGORITMO TERAPEUTICO TUMORI HER2+



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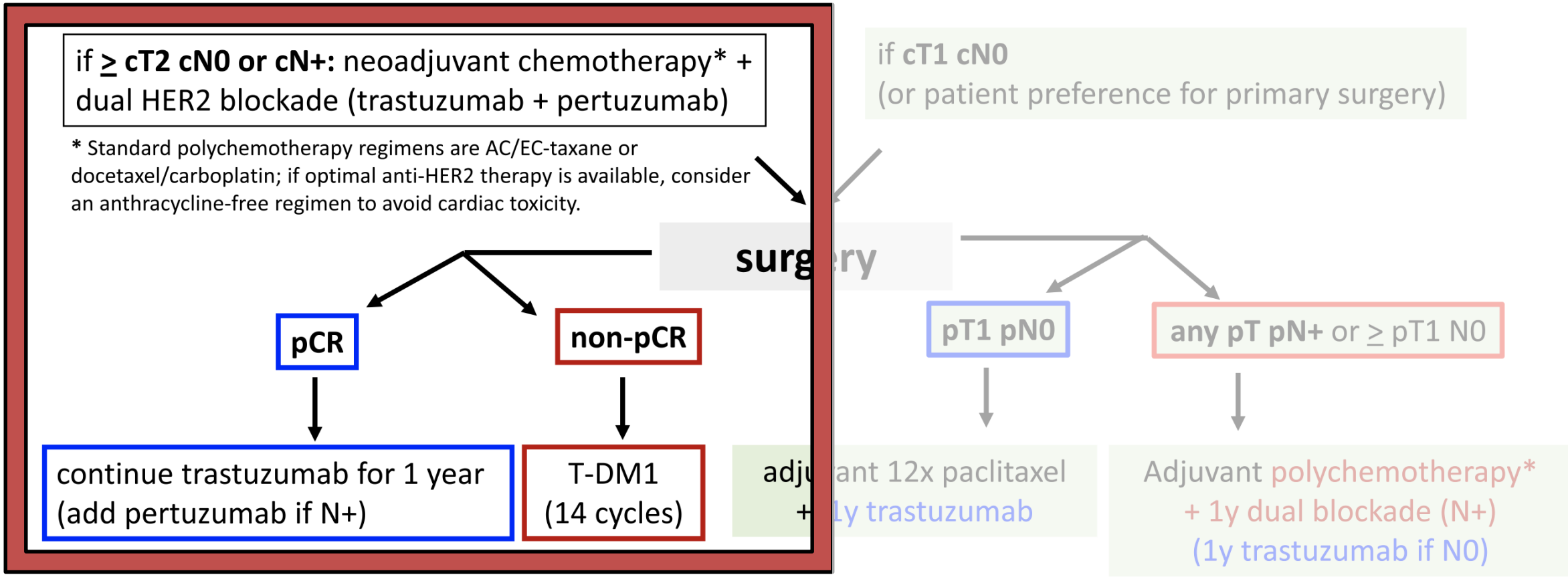
ALGORITMO TERAPEUTICO TUMORI HER2+



Harbeck N. *Breast*. 2022;62:S12-S16.

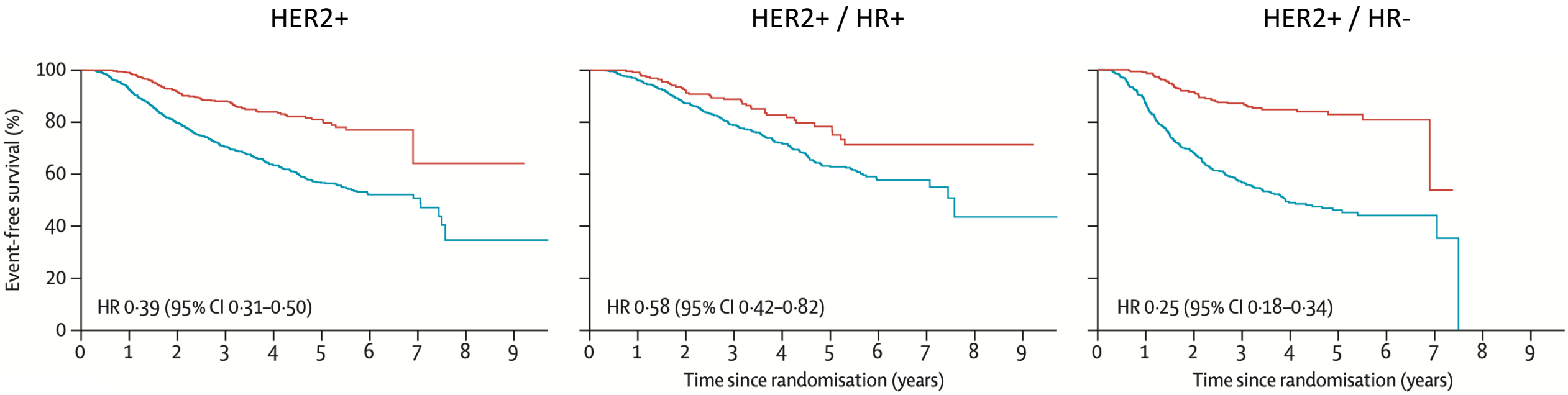
RUOLO PROGNOSTICO DELLA pCR DOPO CT NEOADIUVANTE

- L'associazione tra pCR ed esiti a lungo termine è stata più forte nelle pazienti con carcinoma mammario triplo-negativo e HER2+.

- Nelle pazienti HER2+, il massimo beneficio dalla pCR è ottenuto nelle pazienti HR- che abbiano ricevuto trastuzumab.

Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

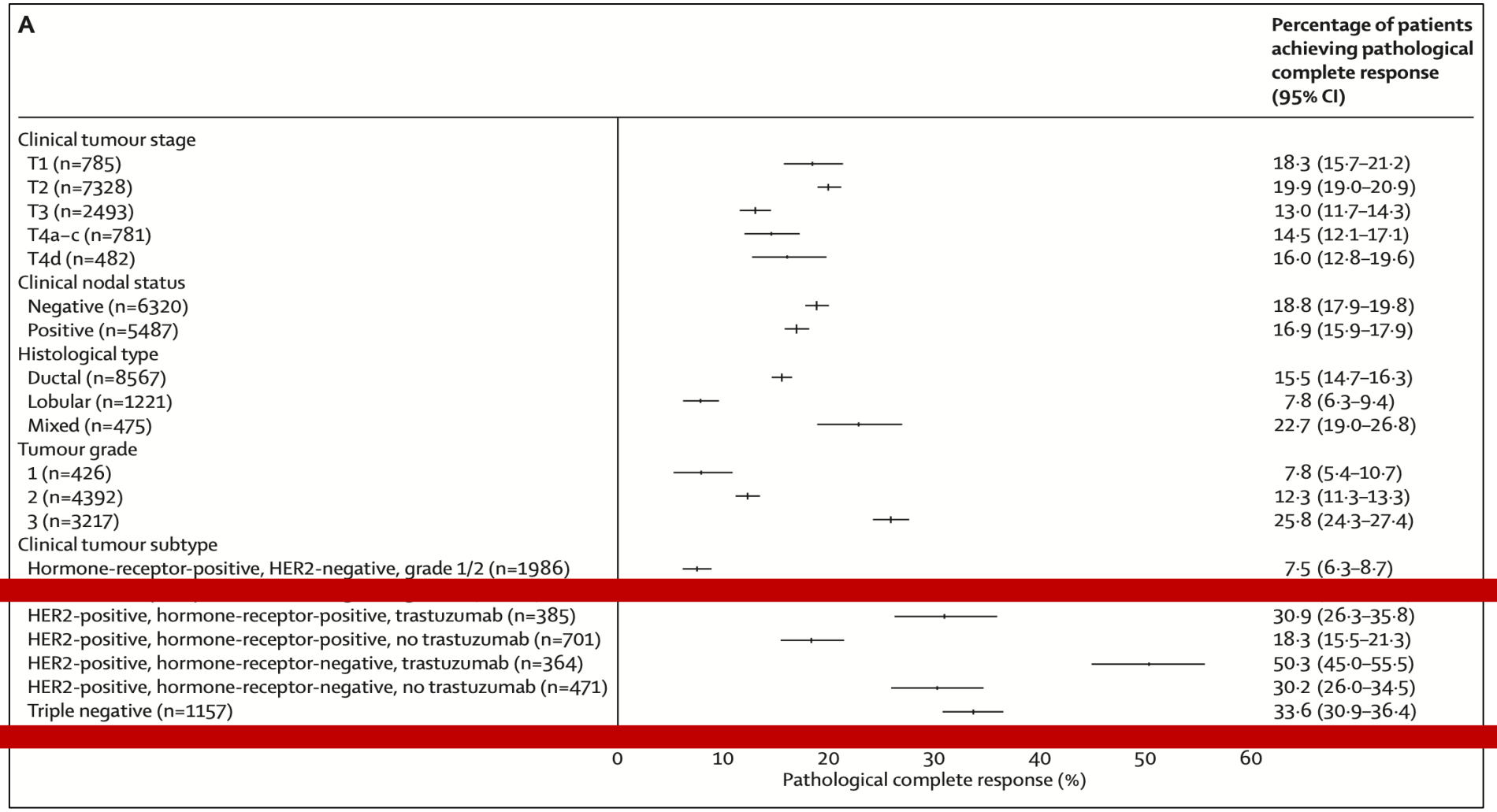
Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz



Cortazar P, et al, *Lancet*. 2014;384(9938):164-172.

RUOLO PROGNOSTICO DELLA pCR DOPO CT NEOADIUVANTE

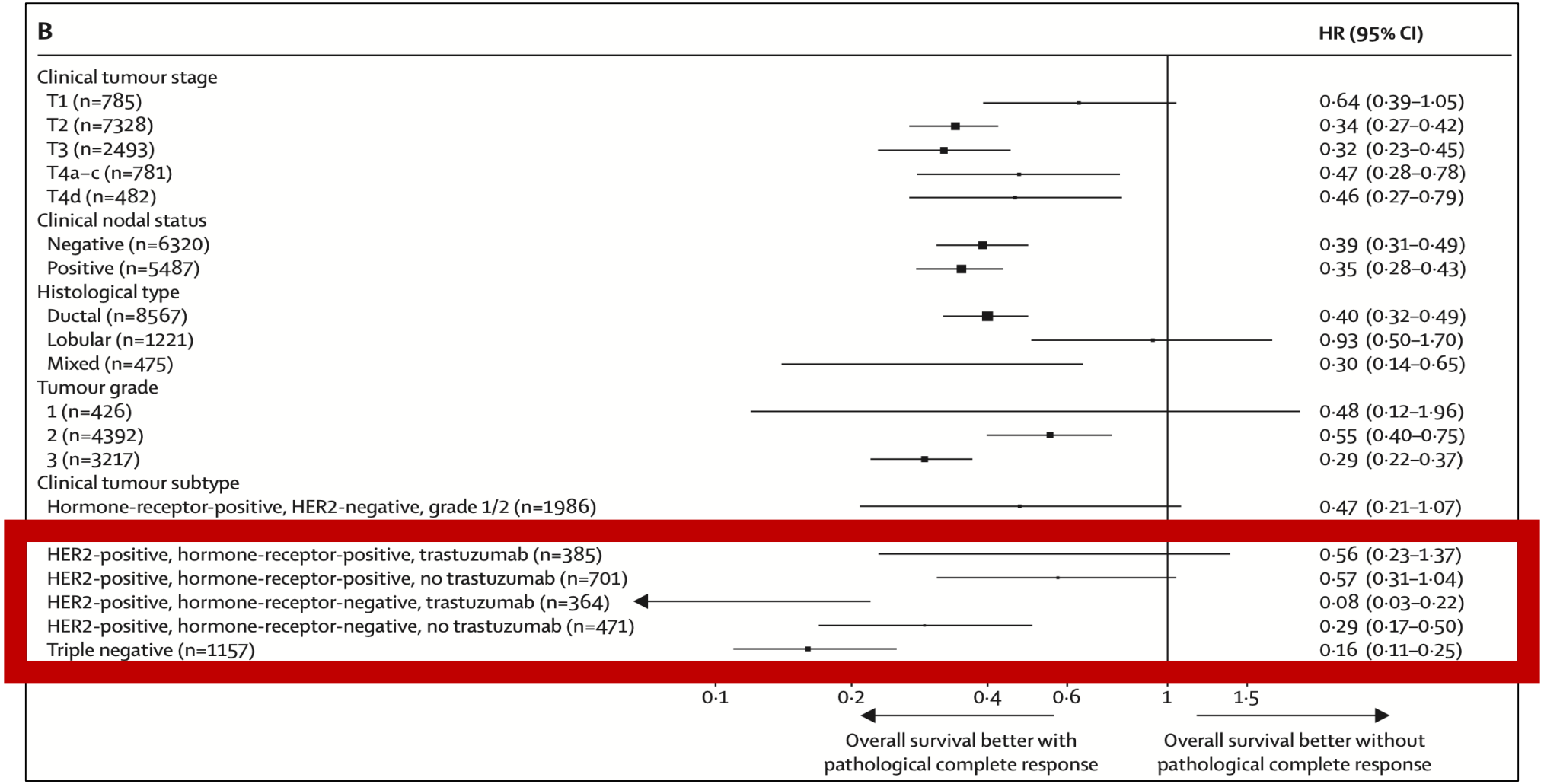
Percentuale di pazienti che ottengono una risposta patologica completa in base alle caratteristiche della patologia



Cortazar P, et al, *Lancet*. 2014;384(9938):164-172.

RUOLO PROGNOSTICO DELLA pCR DOPO CT NEOADIUVANTE

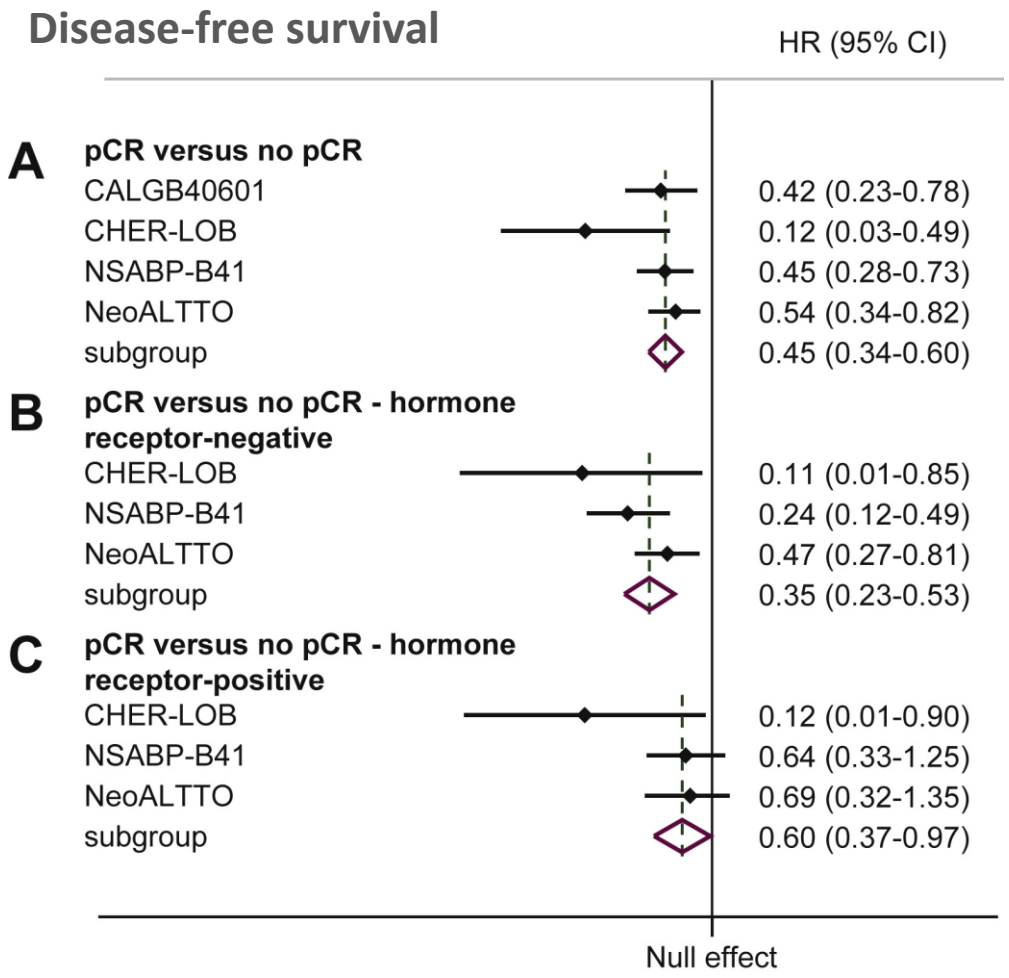
HR di overall survival (OS) divisi per sottogruppo di patologia

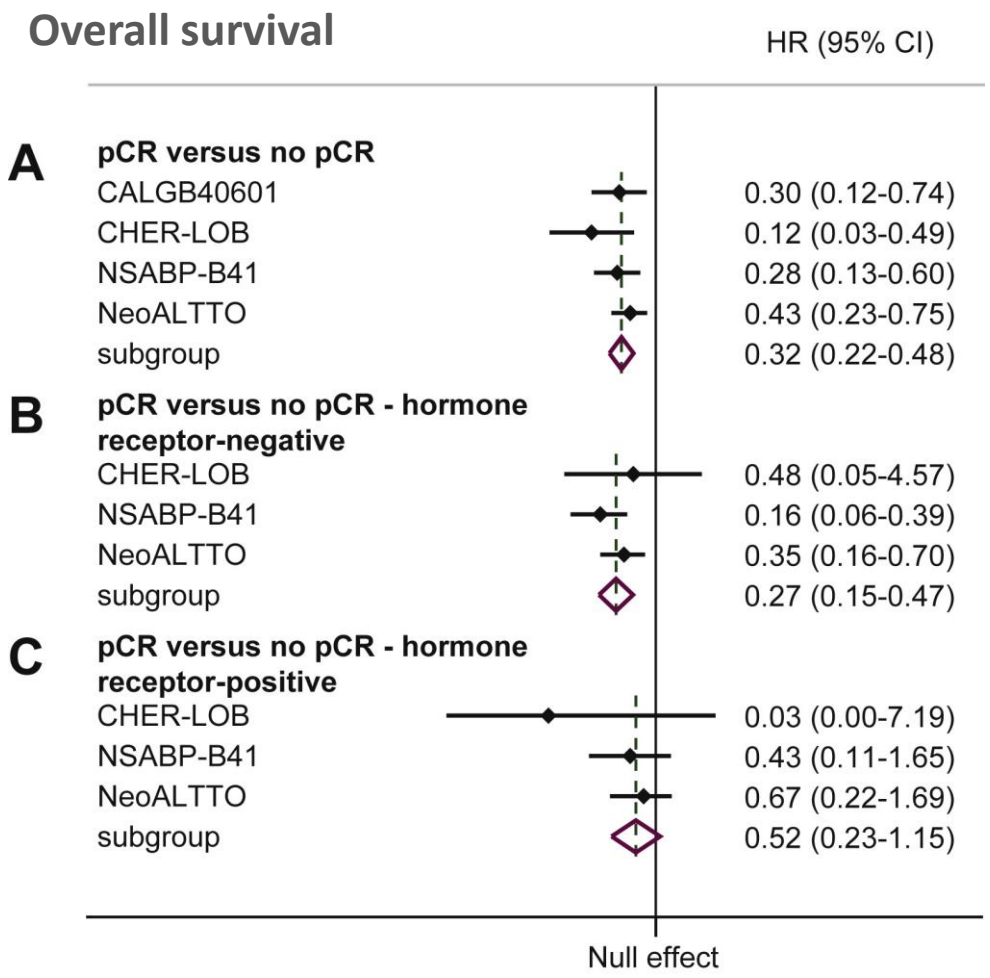


Cortazar P, et al, *Lancet*. 2014;384(9938):164-172.

RUOLO PROGNOSTICO DELLA pCR DOPO CT NEOADIUVANTE

La pCR dopo chemioterapia neoadiuvante è un fattore prognostico fondamentale sia per la disease-free survival (DFS) che per l'overall survival (OS)





Guarnieri et al. ESMO Open, 2022

RUOLO PROGNOSTICO DELLA pCR DOPO CT NEOADIUVANTE

P5-06-02

Pathologic complete response (pCR) and prognosis following neoadjuvant chemotherapy plus anti-HER2 therapy of HER2-positive early breast cancer (EBC)

Loibl S[1], Untch M[2], Buyse M[3], Robidoux A[4], Gianni L[5], Schneeweiss A[6], Conte P[7], Piccart M[8], Bonnefoi H[9], Jackisch C[10], Nekljudova V[1], Costantino J[11], Valagussa P[12], Neate C[13], Gelber R[14], Poncet C[15], Squifflet P[3], Saad E[3], Heinzmann D[16], Denkert C[17], Geyer, Jr. CE[18], Cortes J[19], Guarneri V[7], de Azambuja E[20], Cameron D[21], Ismael G[22], von Minckwitz G[1], Wolmark N[23], Cortazar P[24], on behalf of the CTNeoBC project

[1]German Breast Group, Neu-Isenburg, Germany; [2]Helios Kliniken Berlin-Buch, Germany; [3]International Drug Development Institute (IDDI), Louvain-la-Neuve, Belgium; [4]Centre Hospitalier Université de Montréal, Montreal, Quebec, Canada; [5]San Raffaele Scientific Institute, Milan, Italy; [6]Nationales Centrum für Tumorerkrankungen, Heidelberg, Germany; [7]Department of Surgery, Oncology and Gastroenterology, University of Padova and Medical Oncology 2, Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy; [8]Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium; [9]Institut Bergonié and Université de Bordeaux INSERM U916, Bordeaux, France; [10]Sana Klinikum Offenbach, Germany; [11]University of Pittsburgh, USA; [12]Fondazione Michelangelo, Milan, Italy; [13]F. Hoffmann-La Roche Ltd., Basel, Switzerland; [14]Dana-Farber Cancer Institute, Harvard Medical School, Harvard TH Chan School of Public Health and Frontier Science and Technology Research Foundation, Boston, MA, USA; [15]European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium; [16]Product Development-Oncology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [17]Institut für Pathologie, Philipps-Universität Marburg und Universitätsklinikum Marburg, Germany; [18]Houston Methodist Cancer Center, Houston USA; [19]IOB Institute of Oncology, Quiron Group, Madrid & Barcelona and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [20]Institut Jules Bordet and l'Université Libre de Bruxelles (U.L.B), Brussels, Belgium; [21]Edinburgh Cancer Research Centre, University of Edinburgh and NHS Lothian, UK; [22]Fundação Doutor Amaral Carvalho, Jaú, Brazil; [23]Allegheny Health Network Cancer Institute, Pittsburgh, USA; [24]Genentech, Inc, South San Francisco, USA

Background

The achievement of pCR (breast and axilla) is strongly prognostic for event-free (EFS) and overall survival (OS) in EBC [1], and modulation of therapy improves long-term outcomes for patients with HER2-positive disease not achieving pCR [2].

We sought to investigate prognostic factors for invasive disease-free survival (iDFS) and OS among patients with and without pCR following neoadjuvant systemic treatment consisting of chemotherapy plus anti-HER2 therapy.

Patients and Methods

The current analysis contained individual data from 3,710 patients randomized in 11 neoadjuvant trials for HER2-positive EBC with N≥100 patients enrolled, available data for pCR, EFS, and OS, and follow-up ≥3 years: CHERLOB [3], GeparQuattro [4], GeparQuinto [5], GeparSixto [6], HANNAH [7], LAPATAX [8], NEOALTTO [9], NEOSPHERE [10], NOAH [11], NSABP B-41 [12], and TRYPHAENA [13]. The pCR was defined as ypT0/Tis ypN0.

Statistical considerations

A multivariate Cox proportional hazard model was used to assess the potential prognostic factors baseline clinical tumor size (cT), nodal (cN) and hormone receptor (HR) status for iDFS and OS among patients with pCR (pCR+) or without (pCR-). The prognostic role of baseline cT and cN was analyzed using stratified (by trial and treatment) Cox models separately for HR-positive vs. HR-negative disease, and for pCR+ patients vs. pCR- patients. The plots represent 5-year Kaplan-Meier estimates of iDFS and OS, and hazard ratios with 95% confidence intervals (CIs). A two-tailed level of significance of 0.05 was considered. No imputation of missing data was used.

Objectives

- **iDFS** defined as the time from randomization to occurrence of one of the following events (whichever came first): ipsilateral invasive breast tumor recurrence, local recurrence in the skin of the chest wall or the chest wall (after neoadjuvant therapy), regional recurrence, distant metastases, contralateral invasive breast cancer, death from any cause.
- **OS** defined as the time from randomization until death from any cause.

Results

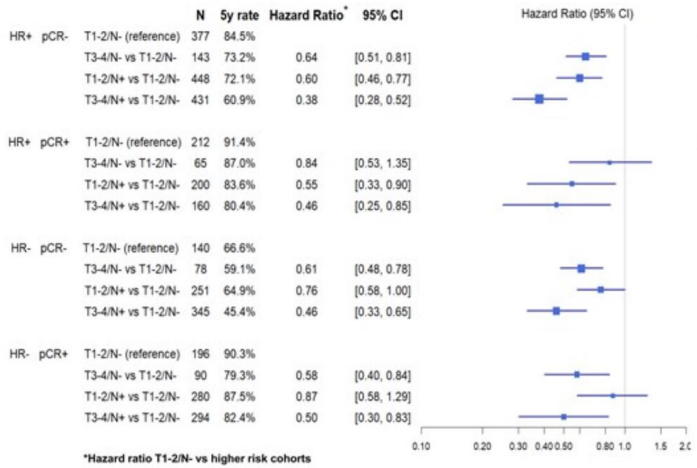
Table 1. Frequency of risk factors in patients without and with pCR

Potential prognostic factors for iDFS/OS	pCR- N (%)	pCR+ N (%)	Total N
Clinical tumor stage at study entry			
T1-2	1216 (58%)	888 (42%)	2104
T3-4	997 (62%)	609 (38%)	1606
Clinical nodal stage at study entry			
negative (N-)	738 (57%)	563 (43%)	1301
positive (N+)	1475 (61%)	934 (39%)	2409
Hormone receptor status			
negative (HR-)	814 (49%)	860 (51%)	1674
positive (HR+)	1399 (69%)	637 (31%)	2036

Table 2. Multivariate Cox model for iDFS and OS according to pCR

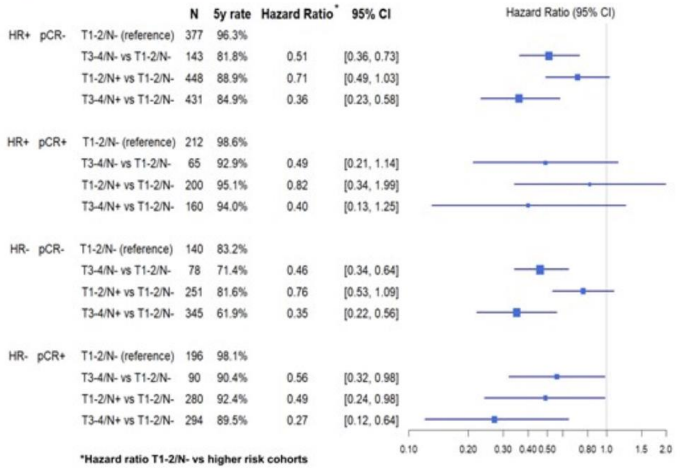
Prognostic factor	pCR- iDFS Hazard Ratio (95% CI)	pCR- iDFS p-value	pCR- OS Hazard Ratio (95% CI)	pCR- OS p-value	pCR+ iDFS Hazard Ratio (95% CI)	pCR+ iDFS p-value	pCR+ OS Hazard Ratio (95% CI)	pCR+ OS p-value
cT (cT1-2 vs cT3-4)	0.62 (0.53-0.73)	<0.001	0.47 (0.37-0.60)	<0.001	0.67 (0.50-0.90)	0.007	0.55 (0.34-0.87)	0.011
cN (cN- vs cN+)	0.66 (0.55-0.79)	<0.001	0.75 (0.58-0.96)	0.025	0.72 (0.53-0.98)	0.039	0.61 (0.36-1.03)	0.065
HR-status (HR+ vs HR-)	0.59 (0.50-0.68)	0.005	0.44 (0.36-0.55)	<0.001	0.97 (0.73-1.29)	0.842	0.76 (0.47-1.22)	0.251

Figure 1. iDFS according to hormone receptor status and pCR



*Hazard ratio T1-2/N- vs higher risk cohorts

Figure 2. OS according to hormone receptor status and pCR



*Hazard ratio T1-2/N- vs higher risk cohorts

- Overall, a median follow-up was 61 months for both iDFS and OS.
- Of the 3,710 evaluable patients, 40.4% had a pCR and 59.6% did not (Tab. 1).
- In pCR+ patients, cT and cN were significant independent prognostic factors for iDFS whereas only cT was significant predictor for OS. In pCR- patients cT, cN and HR status were significant independent predictors for both iDFS and OS (Tab. 2).
- Regardless of HR status, cT and cN, the 5y iDFS/OS rates were higher in pCR+ than pCR- patients. In most subsets with regards to HR and pCR status, cT and cN were independent prognostic factors for both iDFS and OS, including pCR+ patients (Fig. 1 and 2).

Conclusions

- **Our results confirm that patients with a documented pCR have far better long-term outcome than non-pCR patients.**
- **Patients with a pCR can still relapse. The traditional poor prognostic features at baseline namely tumor size and nodal status remain important even after a pCR, with no clear evidence that the relative impact of unfavorable (cT3-4 or cN+) features is different in patients who had a pCR than in those who did not.**

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RUOLO PROGNOSTICO DELLA pCR DOPO CT NEOADIUVANTE

P5-06-02

Pathologic complete response (pCR) and prognosis following neoadjuvant chemotherapy plus anti-HER2 therapy of HER2-positive early breast cancer (EBC)

Loibl S[1], Untch M[2], Buyse M[3], Robidoux A[4], Gianni L[5], Schneeweiss A[6], Conte P[7], Piccart M[8], Bonnefoi H[9], Jackisch C[10], Nekljudova V[1], Costantino J[11], Valagussa P[12], Neate C[13], Gelber R[14], Poncet C[15], Squifflet P[3], Saad E[3], Heinzmann D[16], Denkert C[17], Geyer, Jr. CE[18], Cortes J[19], Guarneri V[7], de Azambuja E[20], Cameron D[21], Ismael G[22], von Minckwitz G[1], Wolmark N[23], Cortazar P[24], on behalf of the CTNeoBC project

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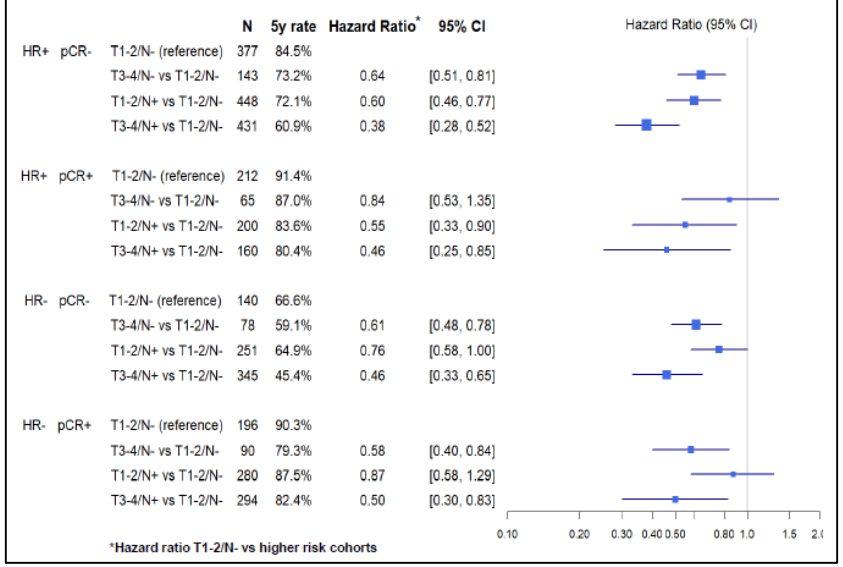
- **Obbiettivo**: Valutare fattori prognostici nelle pazienti HER2+ che abbiano ottenuto o meno pCR dopo chemioterapia neoadiuvante.

- **Risultati**:
  - 3,710 pazienti da 11 studi di neoadiuvante.
  - Le pazienti che ottengono pCR hanno IDFS e OS migliori.
  - **Anche le pazienti con pCR possono recidivare.**
  - Nelle pazienti **senza pCR**: cT, cN e stato recettori ormonali sono fattori prognostici indipendenti per IDFS e OS.
  - Nelle pazienti **con pCR**: cT e cN sono fattori prognostici per IDFS, mentre solo cT è prognostico per l'OS.

- **Conclusioni**:
  1. Pazienti con **pCR hanno una prognosi migliore**.
  2. Pazienti con pCR possono comunque ricadere e **questo rischio di recidiva si basa sui fattori prognostici classici alla diagnosi**.

Stadio clinico alla diagnosi	Invasive disease-free survival (follow-up mediano di 5 anni)
T1-2 N-	91.4
T3-4 N-	87.0
T1-2 N+	83.6
T3-4 N+	80.4

Figure 1. iDFS according to hormone receptor status and pCR



Loibl S et al, SABCS 2019

Test genomici per terapie personalizzate: HER2DX

27 genes

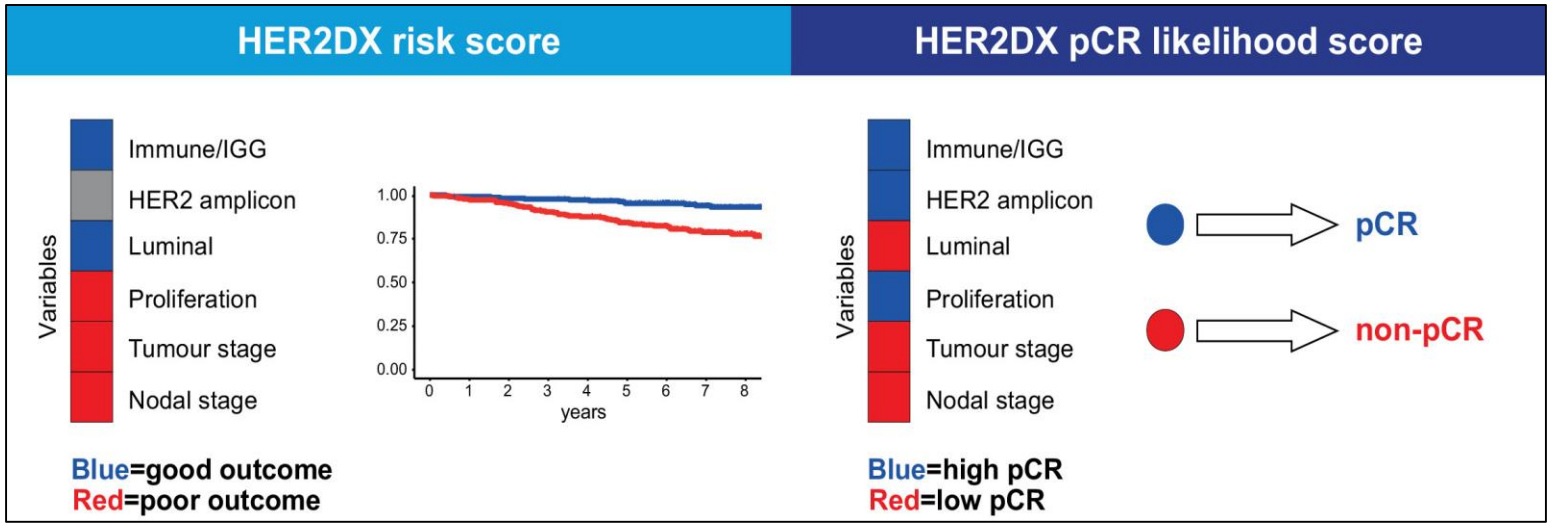
4 gene signatures + T + N:

- Immune
- HER2 amplicon
- Proliferation
- Luminal differentiation

HER2DX risk-score (0-100)
HER2DX pCR-score (0-100)

HER2DX 27-gene test

	HER2DX risk score	HER2DX pCR likelihood score	ERBB2 mRNA assay
Training	**Short-HER HER2+** cohort (n=434) (chemotherapy and trastuzumab)	**H.Clinic HER2+** cohort (n=116) (trastuzumab-based chemotherapy)	Combined **Short-HER HER2+** cohort (n=434) and **H.Clinic HER2-** cohort (n=203)
Validation	Combined **H.Clinic/Padova/PAMELA HER2+** cohort (n=268) (trastuzumab-based chemotherapy)	**PAMELA HER2+** cohort (n=91) (trastuzumab and lapatinib without chemotherapy) **H.Clinic/Padova HER2+** cohort (n=67) (trastuzumab-based chemotherapy)	Combined **H.Clinic/Padova/PAMELA HER2+** cohort (n=268) and **SOLTI HER2-** cohort (n=85)
Exploratory	**TCGA** (n=196) **METABRIC** (n=236) **SCAN-B** (n=378) **CALGB-40601** (n=263)	**CALGB-40601** (n=263) **ISPY-2** (n=127)	



Prat A. et al, EBioMedicina 2022

OUTLINE

- Introduzione
- Rischio di recidiva nei tumori HR-positivi
- Rischio di recidiva nei tumori HER2-positivi
- **Conclusioni**

CONCLUSIONI

- Stabilire il rischio di recidiva della carcinoma della mammella è **fondamentale per pianificare** il migliore percorso terapeutico di ogni paziente.

- Nella malattia HR+/HER2- sono soprattutto I **fattori di rischio "classici"** a guidare ancora oggi nella decisione del programma terapeutico.

- **I test genomici** negli ultimi anni hanno aiutato a personalizzare le terapie nelle pazienti con **rischio clinico intermedio** per le quali non sempre la chemioterapia è risultato essere il migliori trattamento.

- Nella malattia HER2+, la **pCR è ad oggi il fattore prognostico principale** in grado di stratificare efficacemente le pazienti dopo la chemioterapia neoadiuvante.

- Le pazienti con pCR possono ricadere e i tassi di recidiva dipendono dai fattori clinici classici, in particolare dal **coinvolgimento linfonodale**.

GRAZIE PER L'ATTENZIONE!