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EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna
IRCCS Istituto di ricovero e cura a carattere scientifico

POLICLINICO DI SANT'ORSOLA

Focus on

Terapia neoadiuvante nella malattia HER2 positiva

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Direttore Oncologia medica senologica e ginecologica
IRCCS Azienda Ospedaliero-universitaria
Policlinico di Sant'Orsola, Bologna

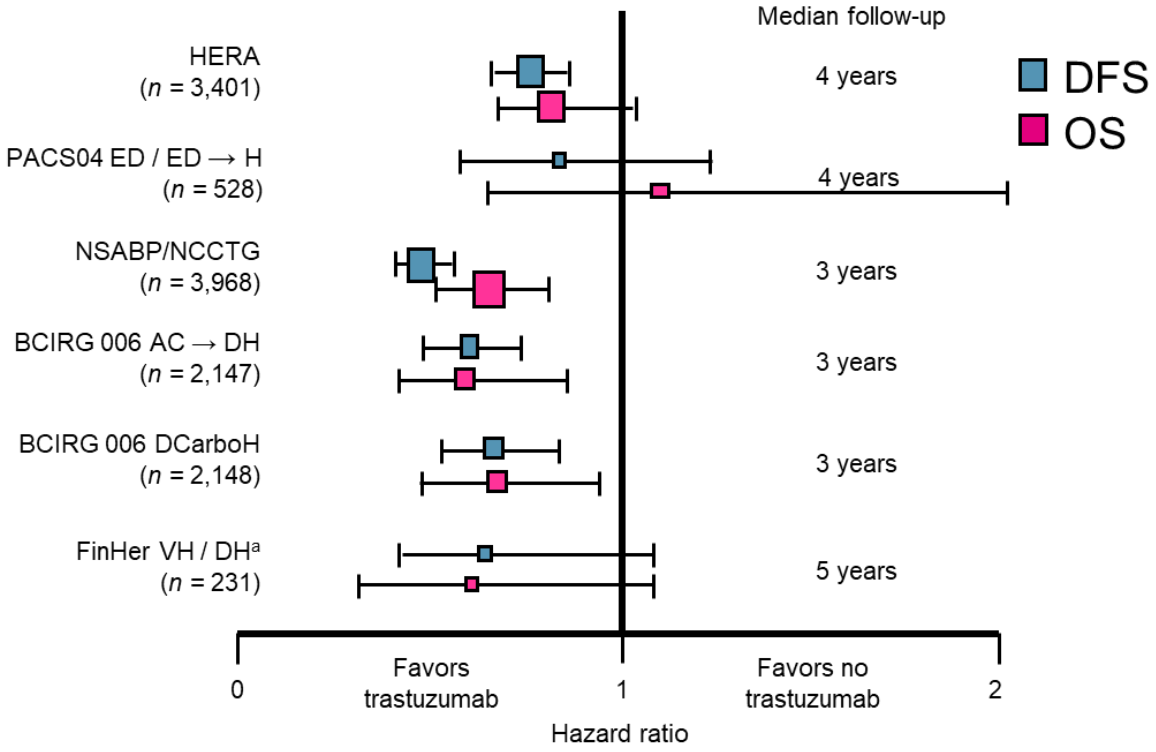
Tappe fondamentali della terapia anti HER-2

1998 l'inizio

2005 la rivoluzione

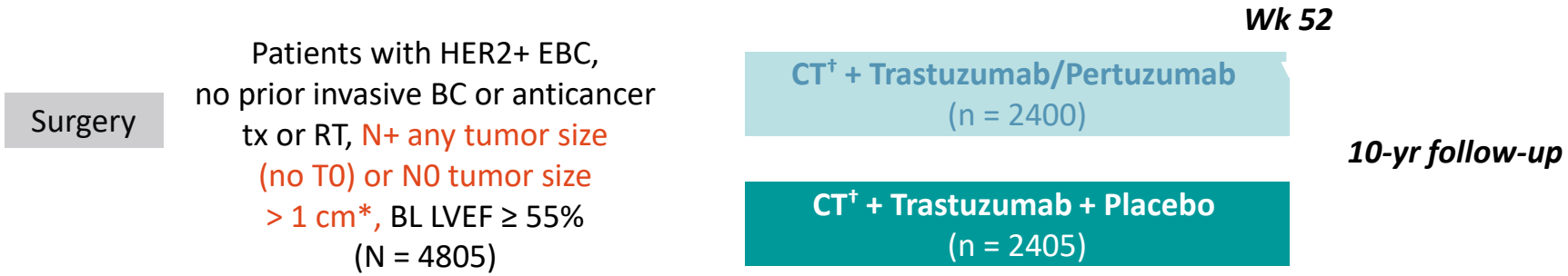
Adjuvant Trastuzumab Trials >14,000 pts

pT1a-b N0 esclusi



APHINITY: Study Design

- International, randomized, double-blind, placebo-controlled phase III trial [1]

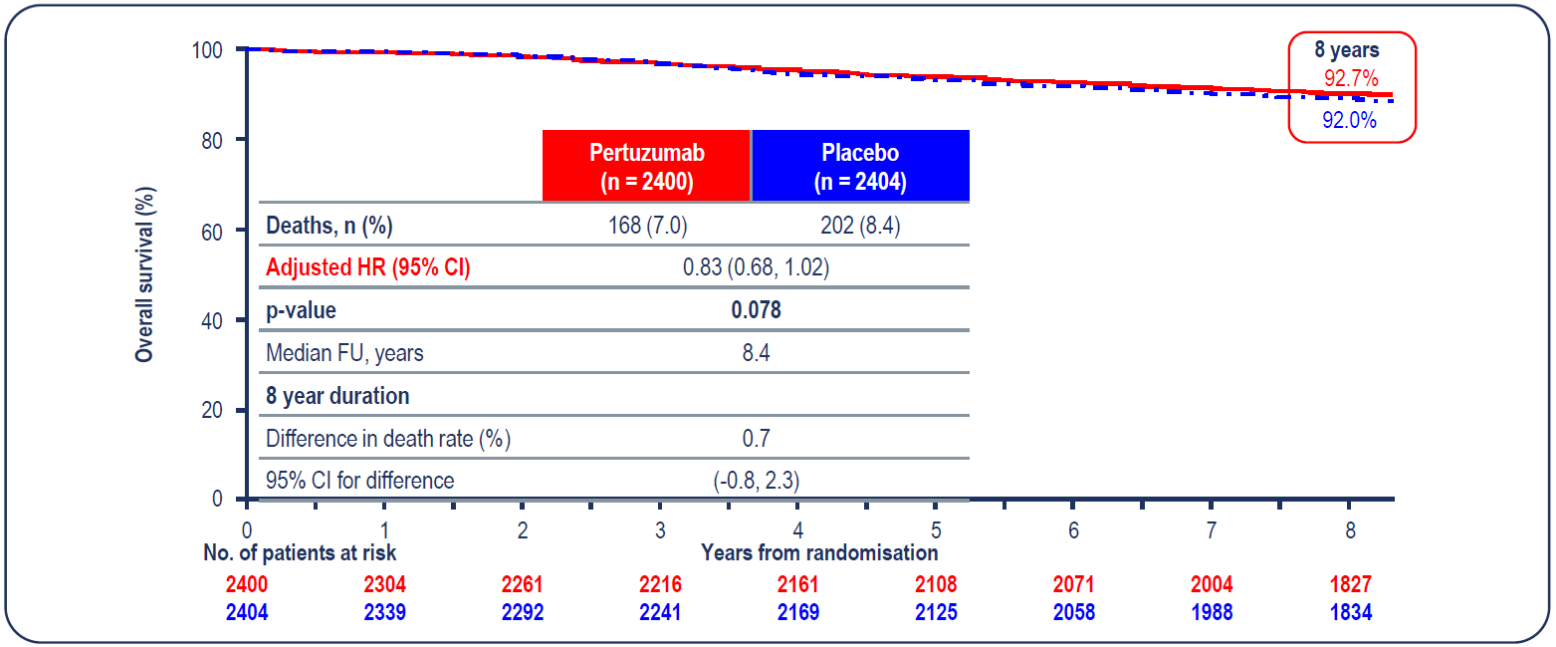


- Primary endpoint: IDFS per modified STEEP definition[2] (excludes second primary non-BC as event)
- Secondary endpoints: IDFS per STEEP definition,[2] OS, distant recurrence-free survival, DFS, recurrence-free interval, safety, cardiac safety, health-related QoL

*Or node negative with tumors > 0.5 to ≤ 1 cm + at least 1 of following: G3; ER and PgR neg; aged < 35 yrs. Node-negative enrollment capped after first 3655 patients randomized.
†Tx initiated ≤ 8 wks post surgery. Permitted CT: standard anthracycline or nonanthracycline regimens (FEC x 3-4 → TH x 3-4; AC x 4 → TH x 4; or TCH x 6, followed by HER2-targeted therapy for total of 1 yr). Endocrine and/or radiotherapy. could be started at end of adjuvant CT.

1. von Minckwitz. NJEM. 2017;377:122.
2. Hudis. JCO. 2007;25:2127.

APHINITY Interim Overall Survival Analysis at 8.4 years Median FU by Treatment Regimen (ITT Population)



Node-positive Cohort

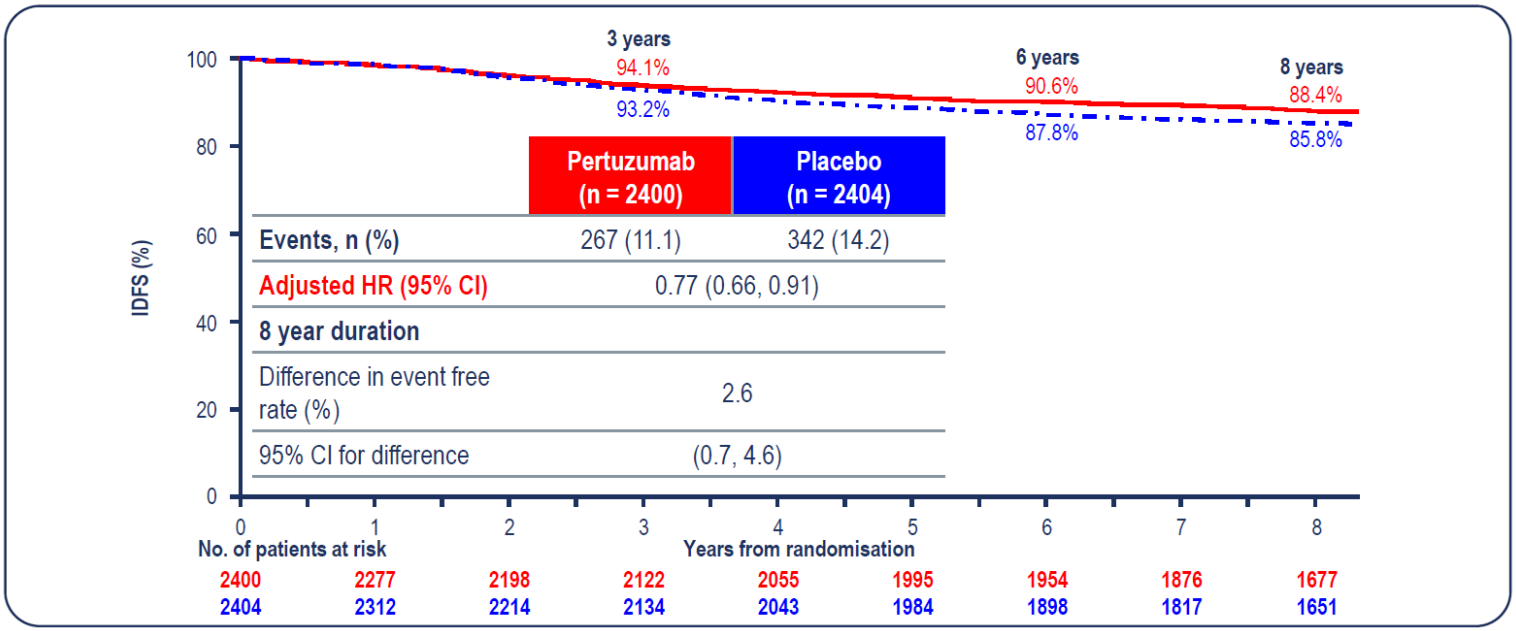
	Pertuzumab (n = 1503)	Placebo (n = 1502)
Deaths, n (%)	130 (8.6)	163 (10.9)
Unadjusted HR (95% CI)	0.80 (0.63, 1.00)	
8 year duration		
Difference in death rate (%)	1.9	
95% CI for difference	(-0.4, 4.1)	

Node-negative Cohort

	Pertuzumab (n = 897)	Placebo (n = 902)
Deaths, n (%)	38 (4.2)	39 (4.3)
Unadjusted HR (95% CI)	0.99 (0.64, 1.55)	
8 year duration		
Difference in death rate (%)	-0.9	
95% CI for difference	(-2.8, 1.0)	

Loibl S et al ESMO Virtual Plenary 2022

APHINITY Updated Descriptive IDFS Analysis at 8.4 Years Median FU by Treatment Regimen - ITT population



Node-positive Cohort

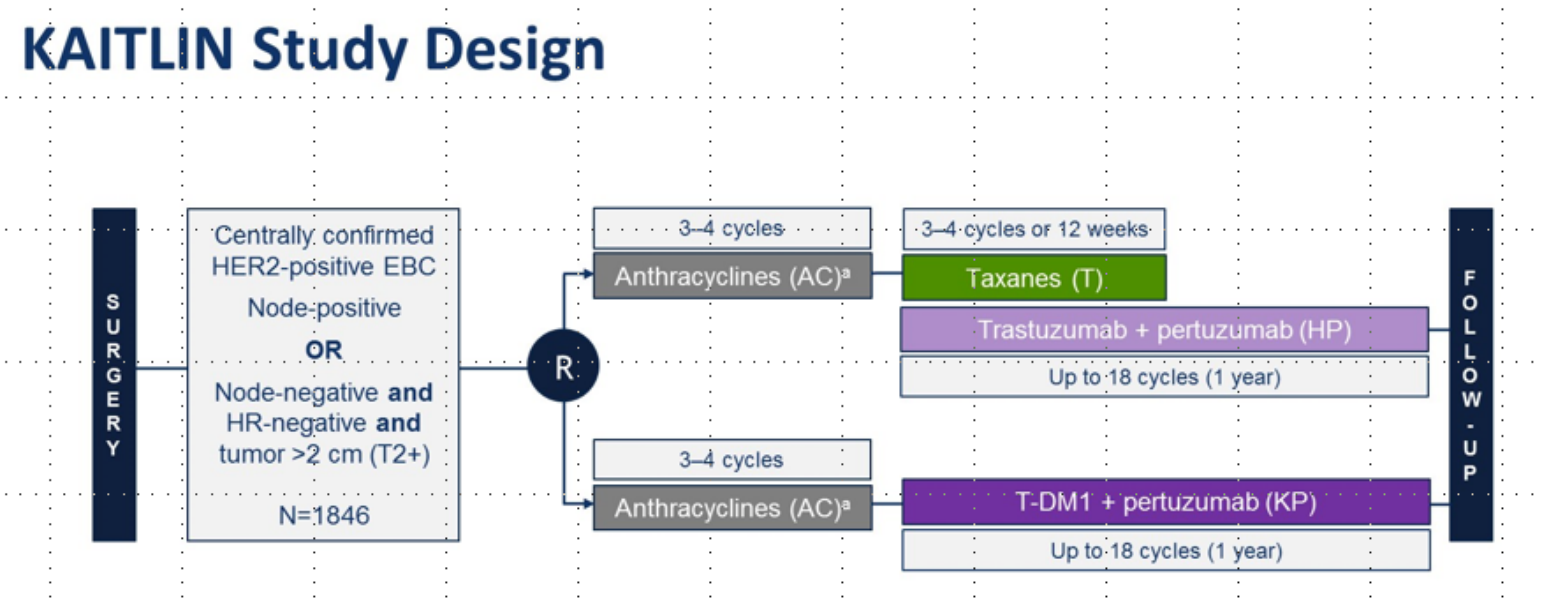
	Pertuzumab (n = 1503)	Placebo (n = 1502)
Events, n (%)	202 (13.4)	276 (18.4)
Unadjusted HR (95% CI)	0.72 (0.60, 0.87)	
8 year duration		
Difference in event free rate (%)	4.9	
95% CI for difference	(2.2, 7.6)	

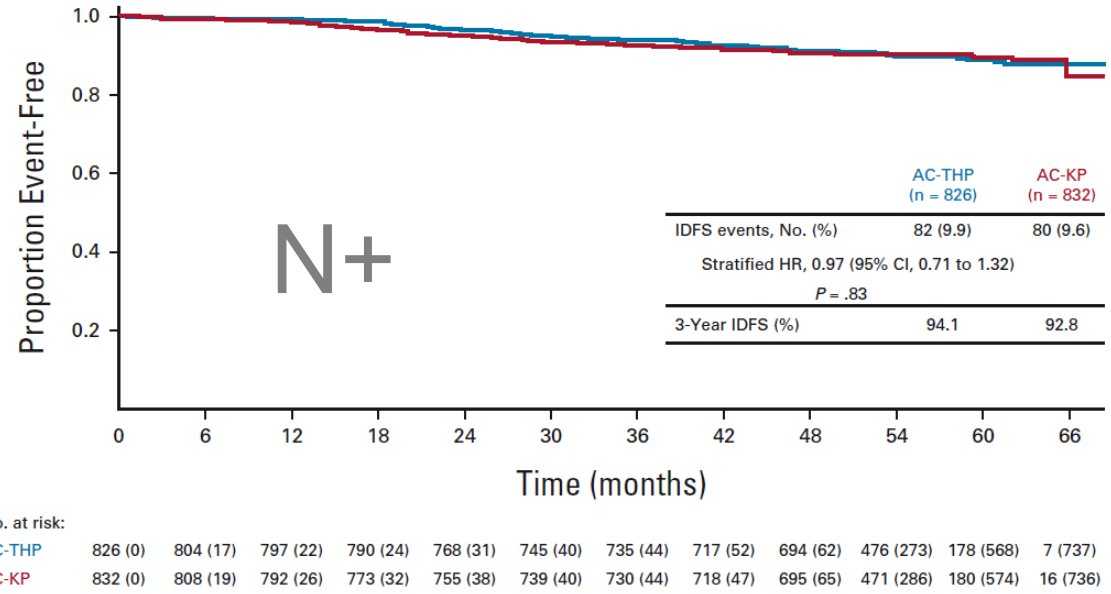
Node-negative Cohort

	Pertuzumab (n = 897)	Placebo (n = 902)
Events, n (%)	65 (7.2)	66 (7.3)
Unadjusted HR (95% CI)	1.01 (0.72, 1.42)	
8 year duration		
Difference in event free rate (%)	-1.0	
95% CI for difference	(-3.5, 1.5)	

Loibl S et al ESMO Virtual Plenary 2022

T-DM1 vs trastuzumab adjuvant?





Co-primary endpoints IDFS in N+ and ITT population

Krop IE et al J Clin Oncol 2022

eBC HER2+
Terapia adiuvante 2023

Chemio + 1 anno trastuzumab* (+ pertuzumab in N+)
(+/- ormonoterapia)

- **concomitante > sequenziale**
- **6 mesi sono un'opzione possibile in casi selezionati (Earl HR et al Meta-analisi ESMO 2021)**

Quale chemioterapia?

$E_{90}C$ x 4 → paclitaxel 80 mg/m2/w x 12

Platino/taxani

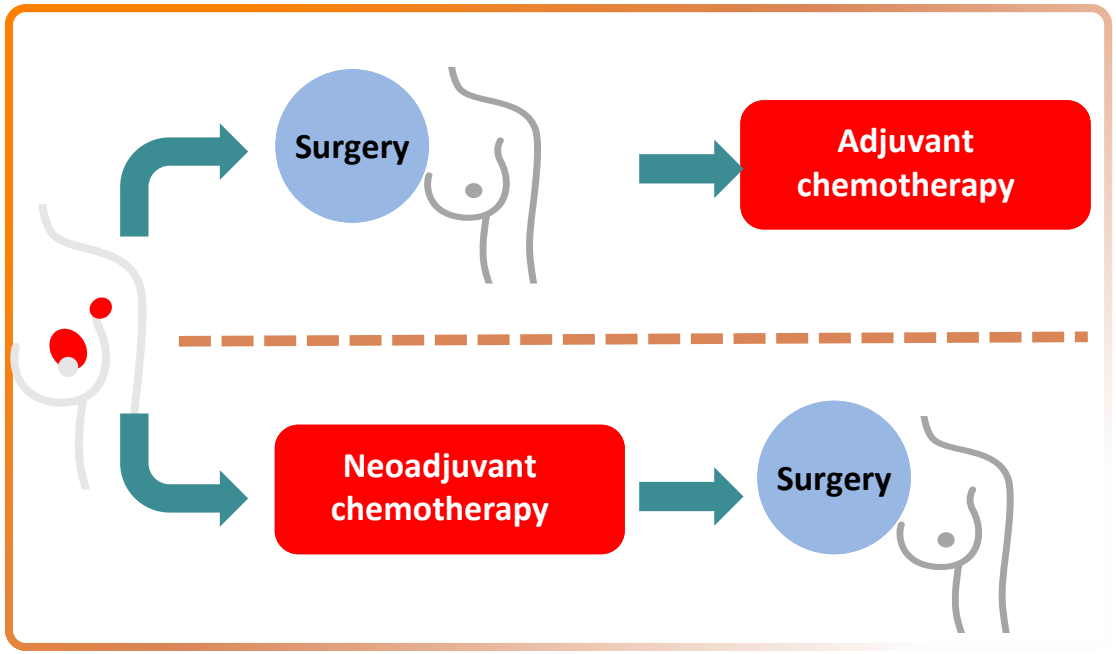
Paclitaxel 80 mg/m2/w x 12 in pT1 pN0 (compresi i pT1mi diffusi)

(St Gallen 2023 panelist 84.6%)

eBC HER2+

Adiuvante *vs* Neoadiuvante

Terapia adiuvante vs neoadiuvante: efficacia a lungo termine analoga



Ad eccezione dei tumori localmente avanzati o comunque non passibili di chirurgia conservativa la chirurgia seguita dalla terapia sistemica adiuvante è rimasta lo standard per molti anni, indipendentemente dal bioprofilo

Adiuvante *vs* Neoadiuvante

- **Consentire Chirurgia**
  (non operabile → operabile)

- **Consentire chirurgia conservative**
  (mastectomia → quadrantectomia)

- **Anticipare la terapia sistemica per migliorare la sopravvivenza?**

[CANCER RESEARCH 39, 3861–3865, October 1979]
0008-5472/79/0039-0000$02.00

Effect of Surgical Removal on the Growth and Kinetics of Residual Tumor[1]

Nurten Gunduz, Bernard Fisher,[2] and Elizabeth A. Saffer

Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261

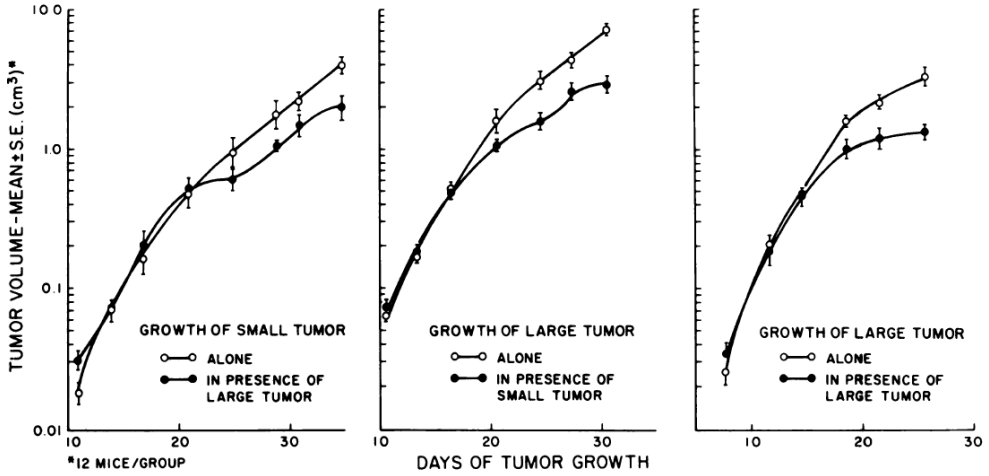


Chart 1. Effect of the presence of a distant tumor focus on tumor growth.

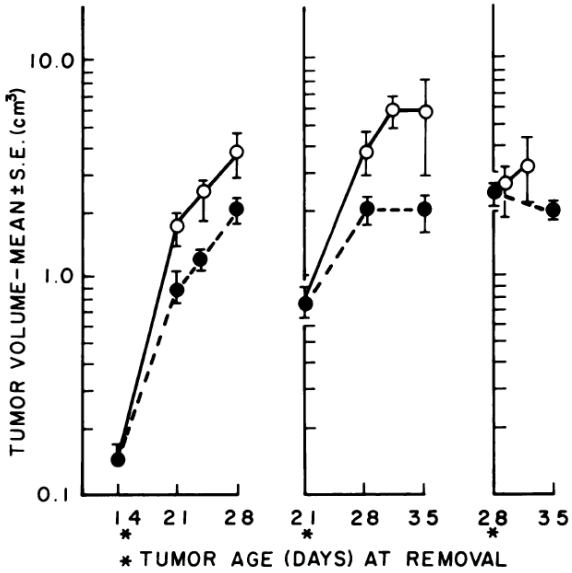
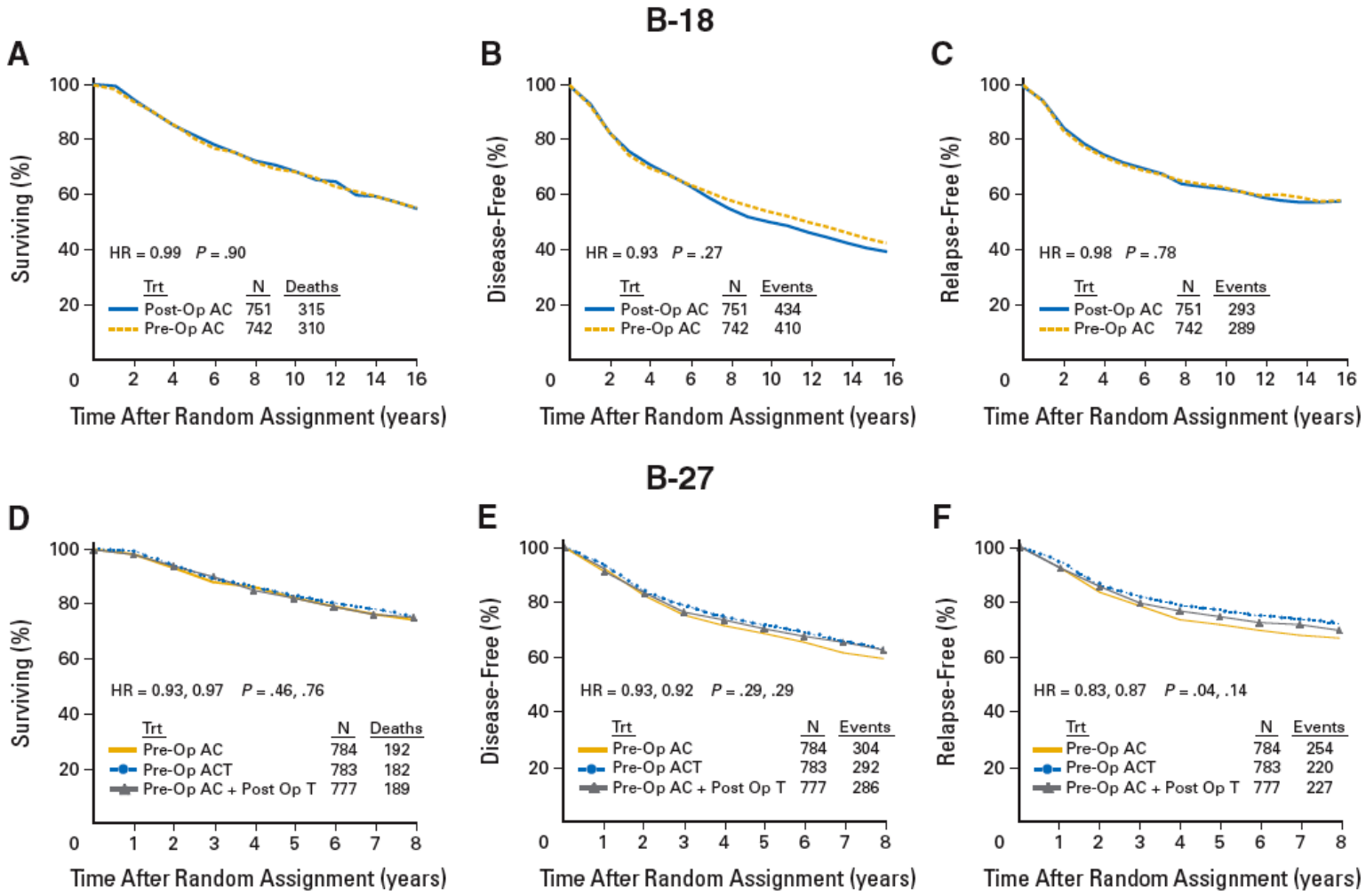


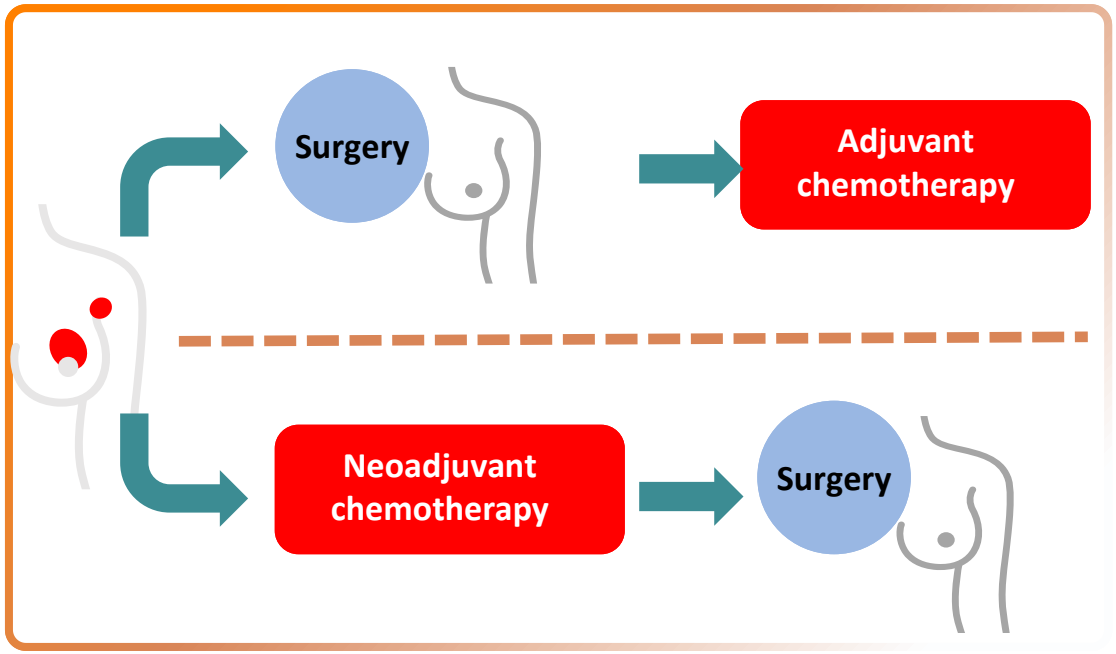
Chart 3. Effect of the removal of a distant tumor focus on tumor growth. ●, presence of distant focus; ○, after removal of distant focus (12 to 15 mice/group).

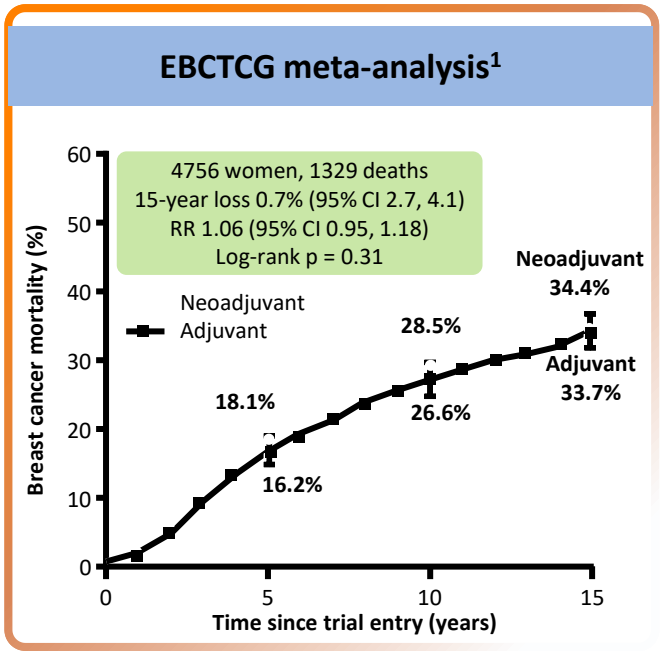
Efficacy in NSABP B-18 and B-27 after a long follow-up



Rastogi P et al, JCO 2008

Terapia adiuvante vs neoadiuvante: efficacia a lungo termine analoga





Ad eccezione dei tumori localmente avanzati o comunque non passibili di chirurgia conservativa la chirurgia seguita dalla terapia sistemica adiuvante è rimasta lo standard per molti anni, indipendentemente dal bioprofilo

[1] Early Breast Cancer Trialists' Collaborative Group (EBCTCG); *Lancet Oncol* 2018

Adiuvante *vs* Neoadiuvante

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  (non operabile → operabile)
- **Consentire chirurgia conservative**
  (mastectomia → quadrantectomia)
- **Anticipare la terapia sistemica per migliorare la sopravvivenza?**
- **Fornire informazioni prognostiche**
- **Anticipare risultati che richiedono migliaia di Pazienti in fase adiuvante (approvazione accelerata di farmaci)?**
  Quindi pCR come end-point surrogato di outcome?

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]; Luca Gianni, MD[6]; Andreas Schneeweiss, MD, PhD[7]; Pierfranco Conte, MD[8]; Martine Piccart, MD[9]; Herve Bonnefoi, MD[10]; Christian Jackisch, MD[11]; Valentina Nekljudova, PhD[2]; Gong Tang, MD[12]; Pinuccia Valagussa, MD[13]; Colin Neate, PhD[14]; Richard Gelber, MD[15]; Coralie Poncet, MD[16]; Pierre Squifflet, PhD[4]; Everardo D. Saad, PhD[4]; Dominik Heinzmann, PhD[17]; Carsten Denkert, MD, PhD[18]; Priya Rastogi, MD[5]; Javier Cortes, MD[19]; Valentina Guarneri, MD[8]; Evandro de Azambuja, MD[9]; David Cameron, MD[20]; Gustavo Ismael, MD[21]; Norman Wolmark, MD[5]; and Patricia Cortazar, PhD[22]; on behalf of the CTNeoBC project

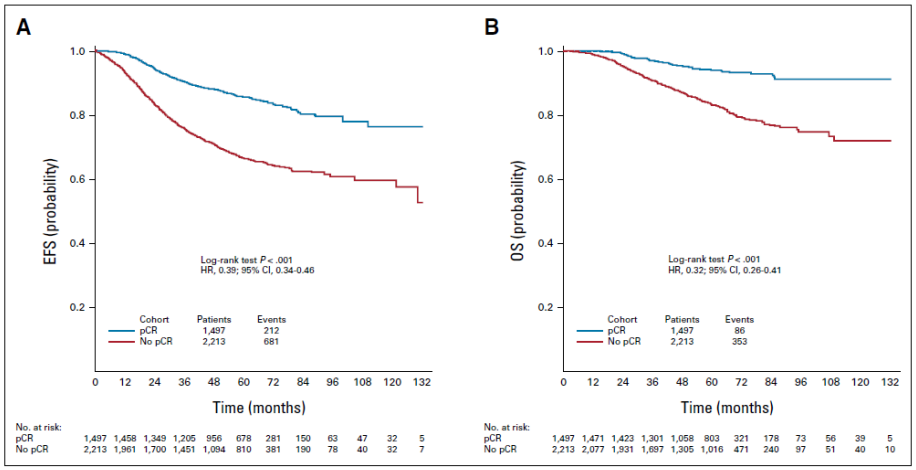
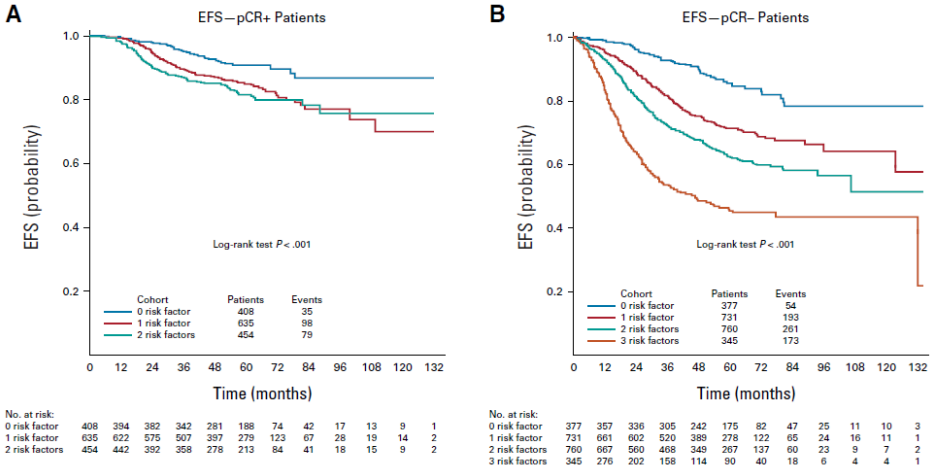


FIG A1. (A) EFS and (B) OS according to pCR in all patients. EFS, event-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response.

Beyond pCR:

- cT
- cN
- HR (no pCR only)



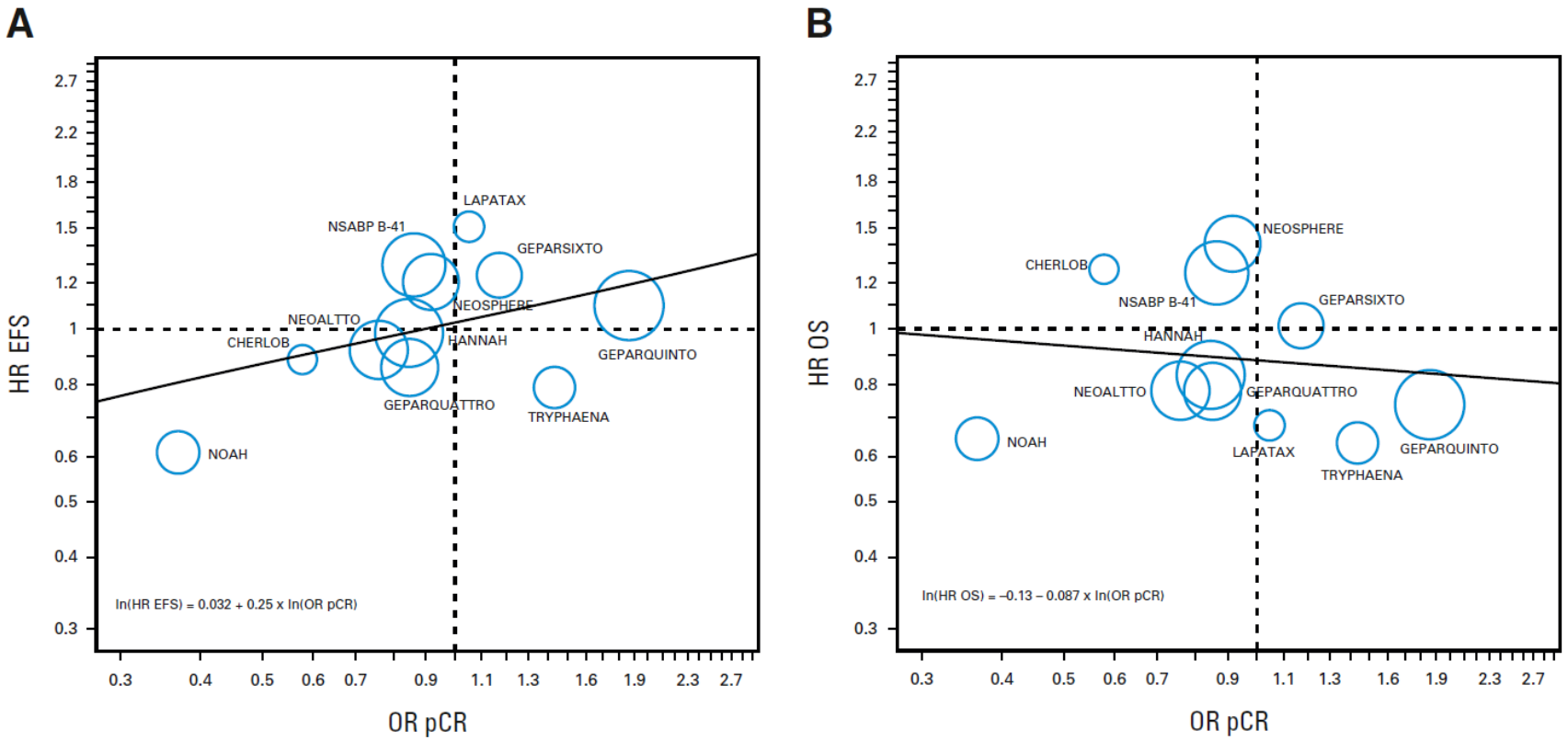
J Clin Oncol 41:2998-3008. © 2023

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]; Priya Rastogi, MD[4]; Luca Gianni, MD[5]; Andreas Schneeweiss, MD[6]; Pierfranco Conte, MD[7]; Martine Piccart, MD[8]; Hervé Bonnefoi, MD[9]; Christian Jackisch, MD[10]; Valentina Nekljudova, PhD[1]; Gong Tang, PhD[11]; Pinuccia Valagussa, MD[12]; Colin Neate, MD[13]; Richard Gelber, PhD[14]; Coralie Poncet, PhD[15]; Dominik Heinzmann, MD[16]; Carsten Denkert, MD[17]; Charles E. Geyer Jr, MD[18]; Javier Cortes, MD[19]; Valentina Guarneri, MD[7]; Evandro de Azambuja, MD[8]; David Cameron, MD[20]; Gustavo Ismael, MD[21]; Norman Wolmark, MD[18]; Patricia Cortazar, MD[22]; Marc Buyse, ScD[1,23]; and on behalf of the CTNeoBC Project

pCR & surrogacy:

- clear at patient level
- poor at trial level



J Clin Oncol 41:2988-2997. © 2023

Adiuvante *vs* Neoadiuvante

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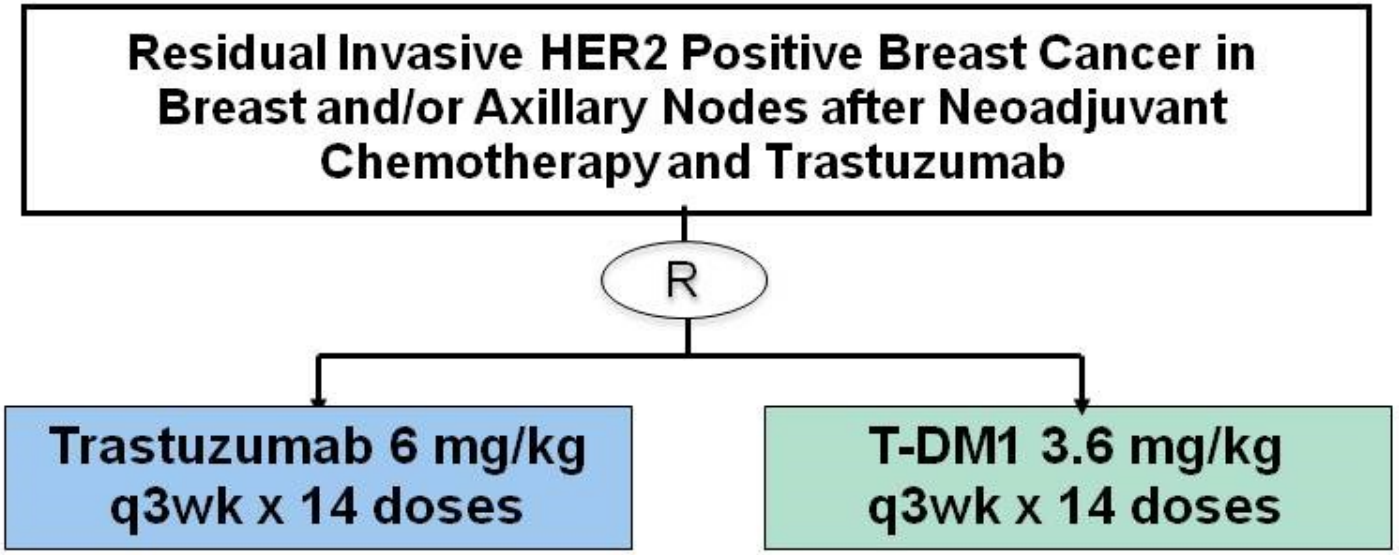
- **Fornire informazioni prognostiche**
- **Anticipare risultati che richiedono migliaia di Pazienti in fase adiuvante (approvazione accelerata di farmaci)**
  Quindi pCR come end point surrogate di outcome?
- **Modulare (personalizzare) la terapia post-operatoria e migliorare l'outcome**

NSABP B-50-I/GBG 77/Roche BO27938
Katherine: Study Schema



Radiation per standard guidance; hormone therapy if ER or PR pos
Accrual goal - 1484 patients
Primary Endpoint: DFS

PRESENTED AT: ASCO Annual '15 Meeting

von Minckwitz G et al ASCO 2015
von Minckwitz G et al NEJM 2019

The NEW ENGLAND JOURNAL of MEDICINE

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

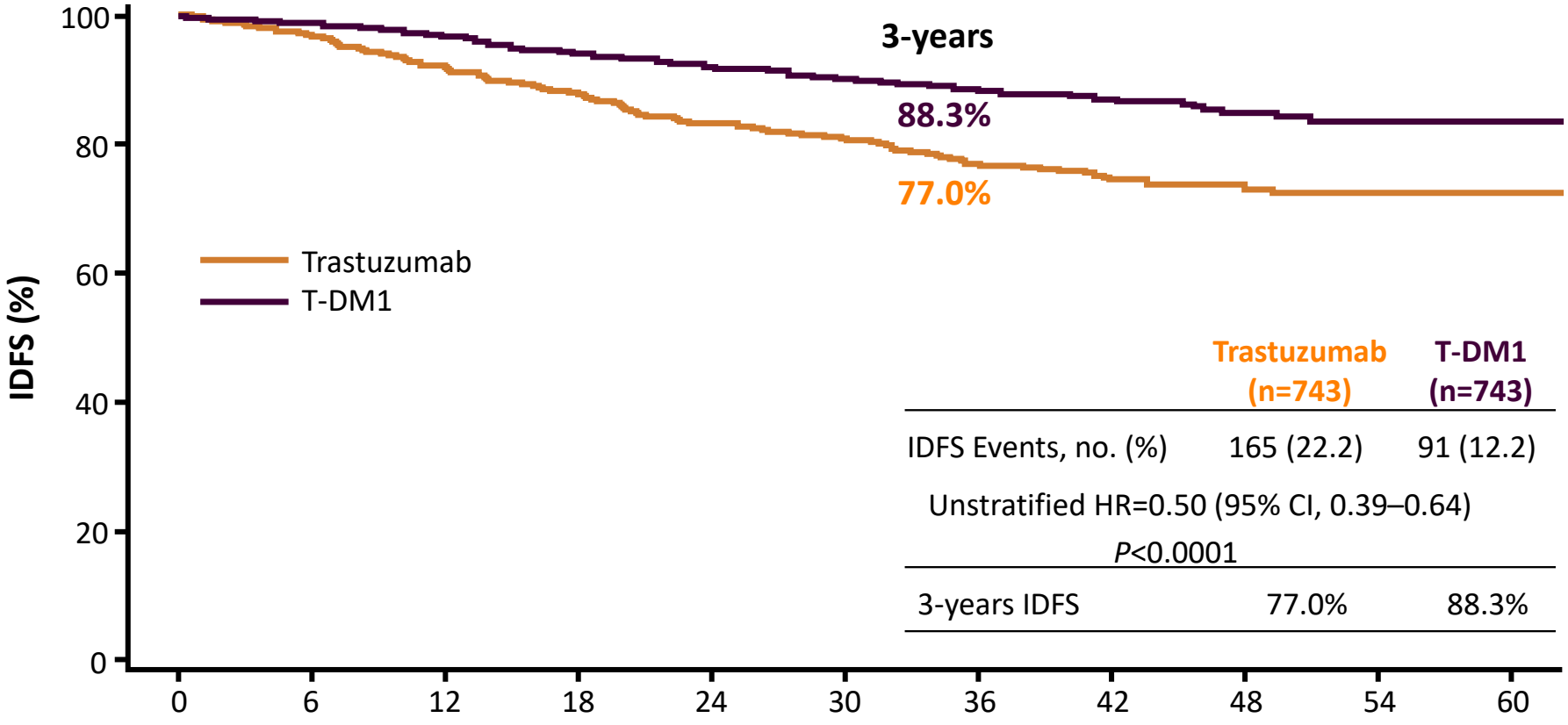
Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

T1-4, N0-3, M0 (T1a/bN0 not eligible)
Preoperative systemic treatment consisting of at least 6 cycles with a total duration of at least 16 weeks, including at least 9 weeks of trastuzumab and at least 9 weeks of taxane-based chemotherapy

Note: HER2-directed therapy and chemotherapy may be given concurrently; patients may have received more than one HER2-directed therapy.; Patients may have received an anthracycline as part of preoperative therapy

KATHERINE: Kaplan-Meier Plot of IDFS (ITT)

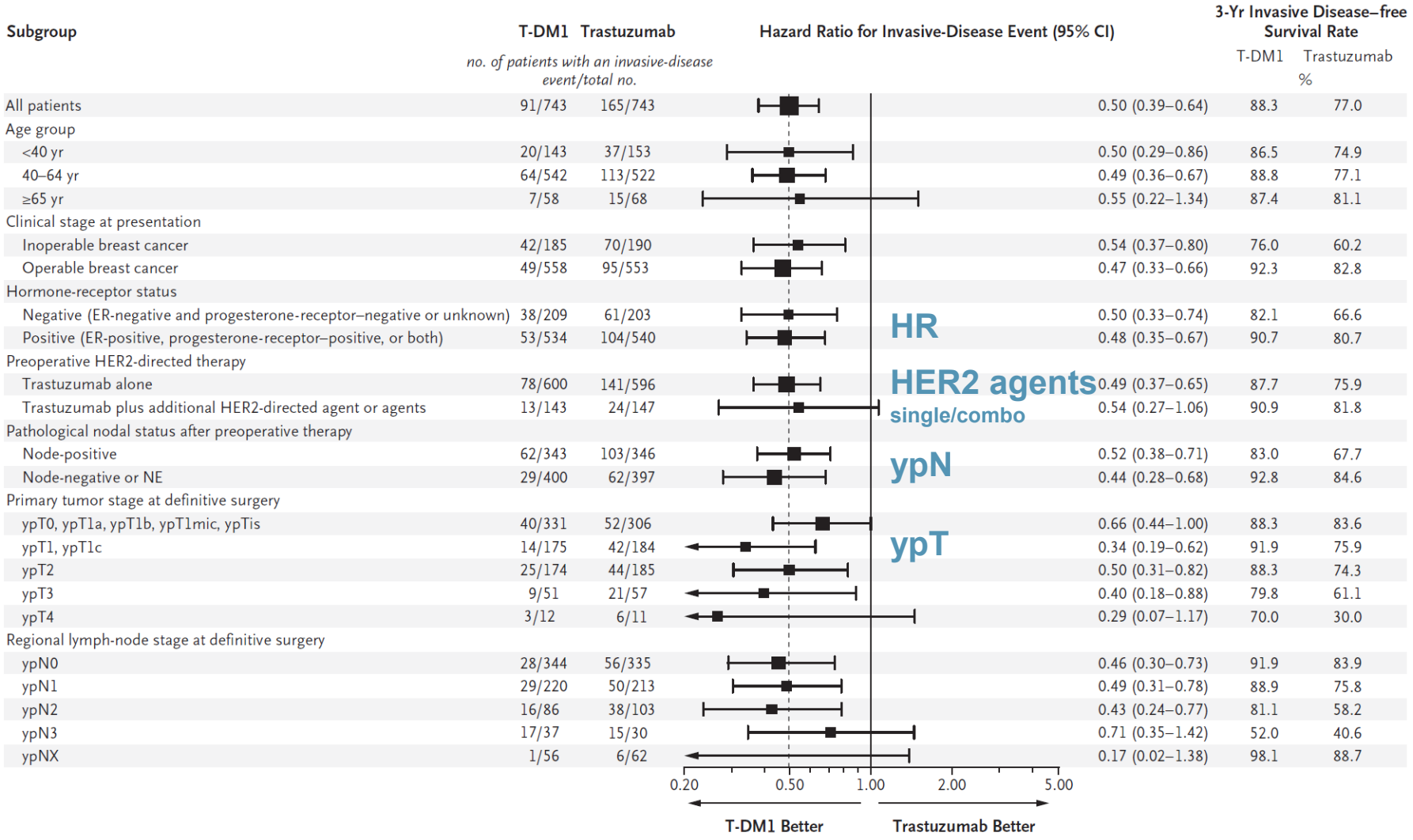


	Trastuzumab (n=743)	T-DM1 (n=743)
IDFS Events, no. (%)	165 (22.2)	91 (12.2)
Unstratified HR=0.50 (95% CI, 0.39–0.64) *P*<0.0001		
3-years IDFS	77.0%	88.3%

Trastuzumab	743	676	635	594	555	501	342	220	119	38	4
TDM-1	743	707	681	658	633	561	409	255	142	44	4

Geyer CE et al SABCS 2018,
von Minckwitz G et al NEJM 2019

Subgroup Analysis of iDFS



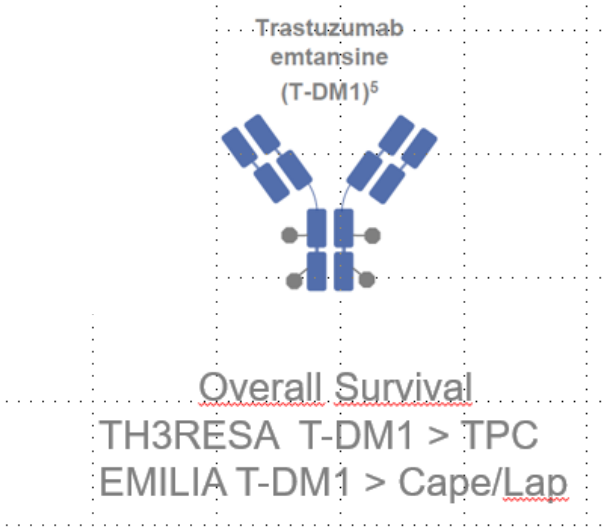
von Minckwitz G et al NEJM 2019

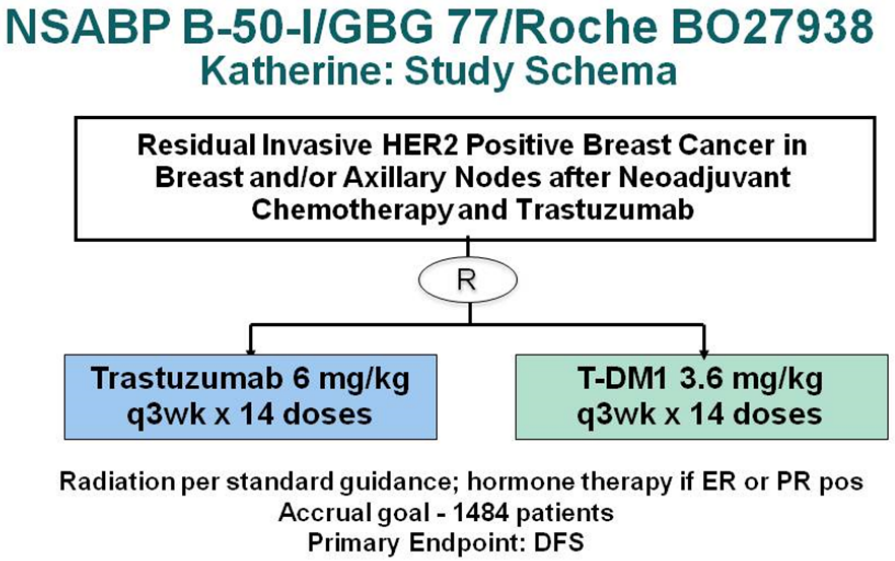
Tappe fondamentali della terapia anti HER-2

1998 l'inizio

2005 la rivoluzione

2019 il nuovo paradigma

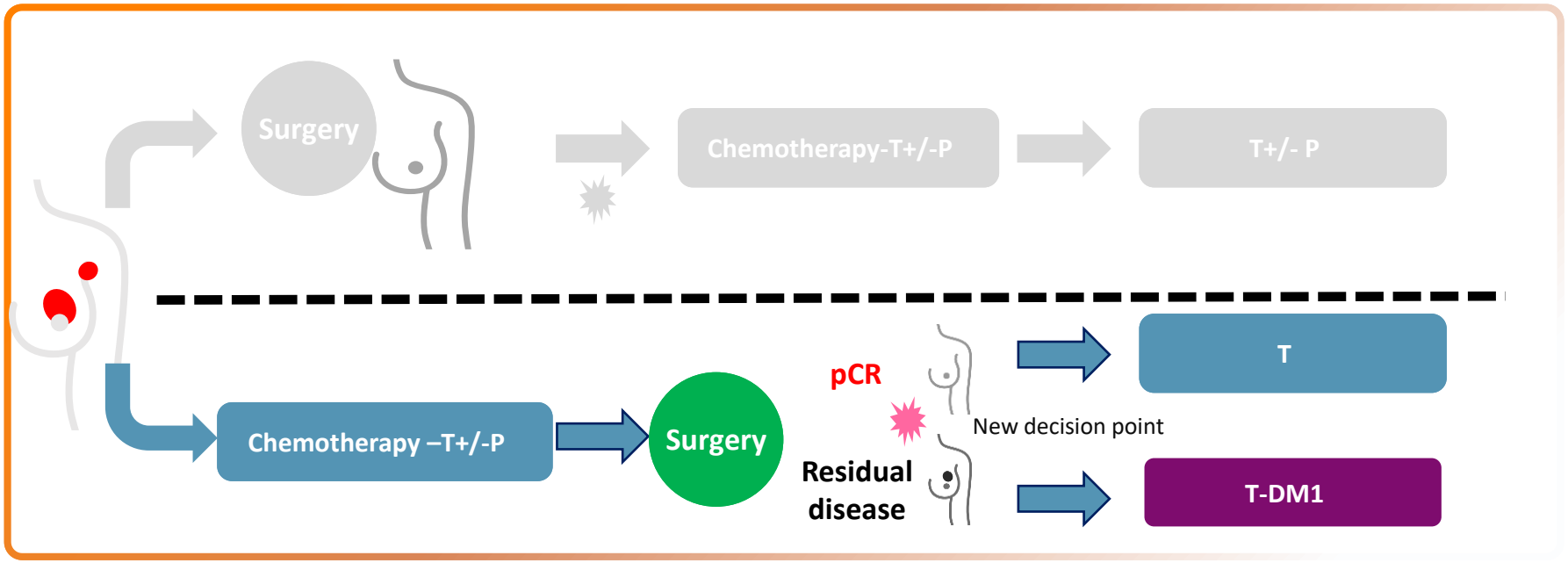




von Minckwitz G et al ASCO 2015
von Minckwitz G et al NEJM 2019

L’ottenimento della pCR assume quindi importanza di per sé, indipendentemente dal suo valore come end-point surrogato di outcome

Carcinoma mammario HER2+ in fase precoce



All patients should be given the opportunity to optimise treatment after surgery according to their response to neoadjuvant therapy

eBC HER2+ nel 2023

Approccio **neoadiuvante** in tutti gli stadi (esclusi cT1N0?)

Tutta la chemioterapia* prima dell'intervento

*EC/AC→ taxani *oppure* Platino/taxani

Trastuzumab e pertuzumab° in neoadiuvante

Trastuzumab adiuvante nelle pCR; TDM1 se malattia residua (T e/o N)

° attualmente indicato (on label) ma non rimborsabile

NeoSphere: Study design and main results

TH (n=107)
docetaxel (75→100 mg/m^2)
trastuzumab (8→6 mg/kg)

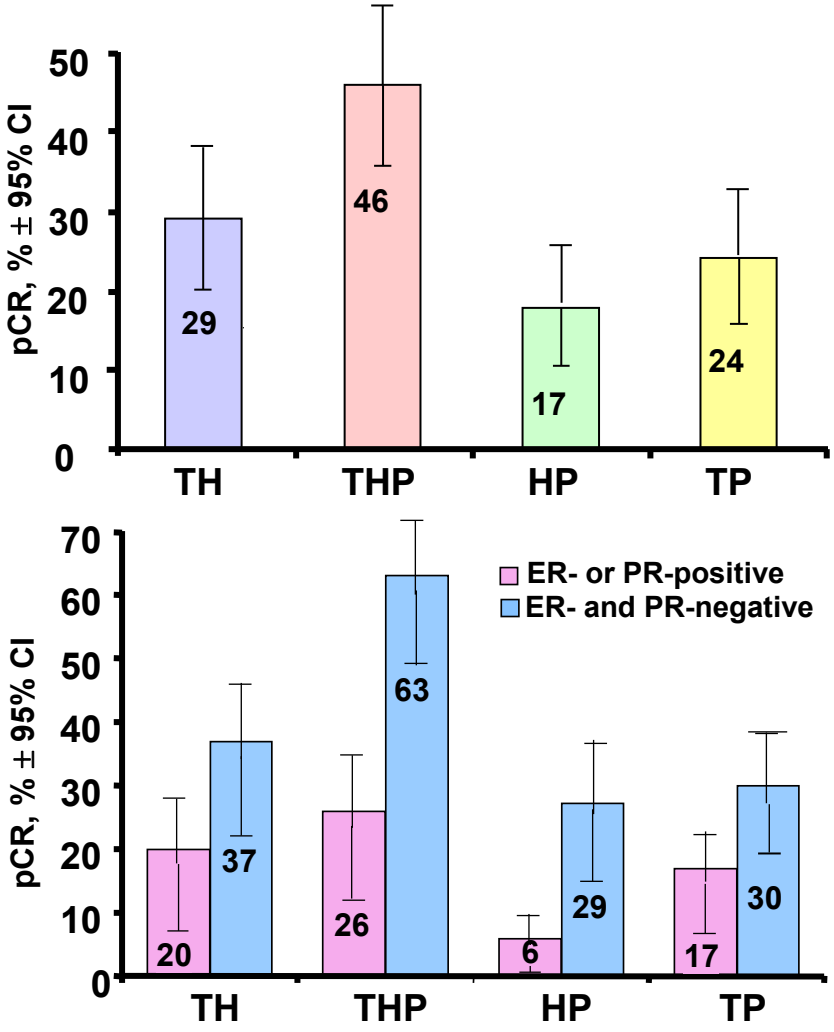
THP (n=107)
docetaxel (75→100 mg/m^2)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

HP (n=107)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

TP (n=96)
docetaxel (75→100 mg/m^2)
pertuzumab (840→420 mg)

Study dosing: q3w x 4

→ **SURGERY**



Gianni L, *et al. Lancet Oncol* 2012; **13**:25–32

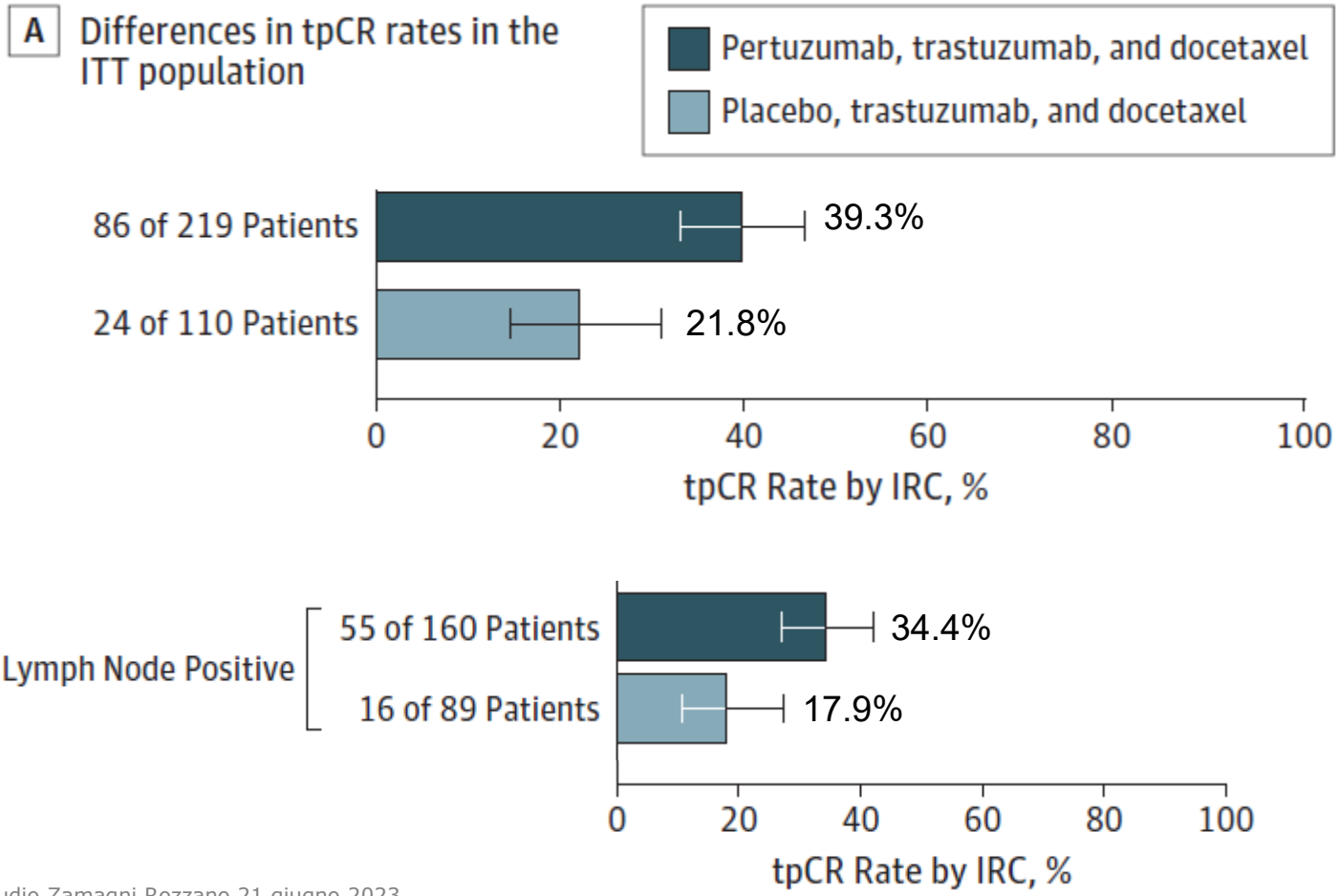
JAMA Oncology | Brief Report

Efficacy, Safety, and Tolerability of Pertuzumab, Trastuzumab, and Docetaxel for Patients With Early or Locally Advanced ERBB2-Positive Breast Cancer in Asia

The PEONY Phase 3 Randomized Clinical Trial

Zhimin Shao, MD; Da Pang, MD; Hongjian Yang, MD; Wei Li, MD; Shusen Wang, MD; Shude Cui, MD; Ning Liao, MD; Yongsheng Wang, MD; Chuan Wang, MD; Yuan-Ching Chang, MD; Hweichung Wang, MD; Seok Yun Kang, MD; Jae Hong Seo, MD; Kunwei Shen, MD; Suphawat Laohawiriyakamol, MD; Zefei Jiang, MD; Junjie Li, MD; Julian Zhou, PhD; Betsy Althaus, PharmD; Yixiang Mao, MD; Jennifer Eng-Wong, MD

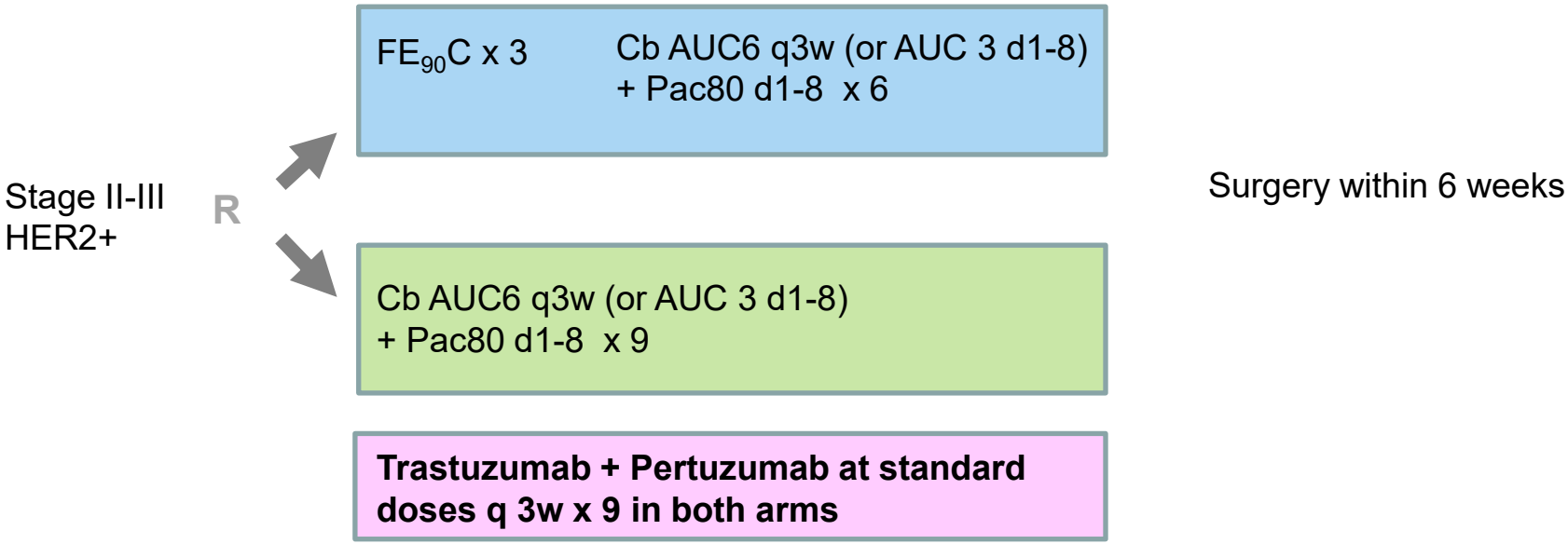
Figure 2. Efficacy Data



Shao Z et al JAMA Oncol 2020

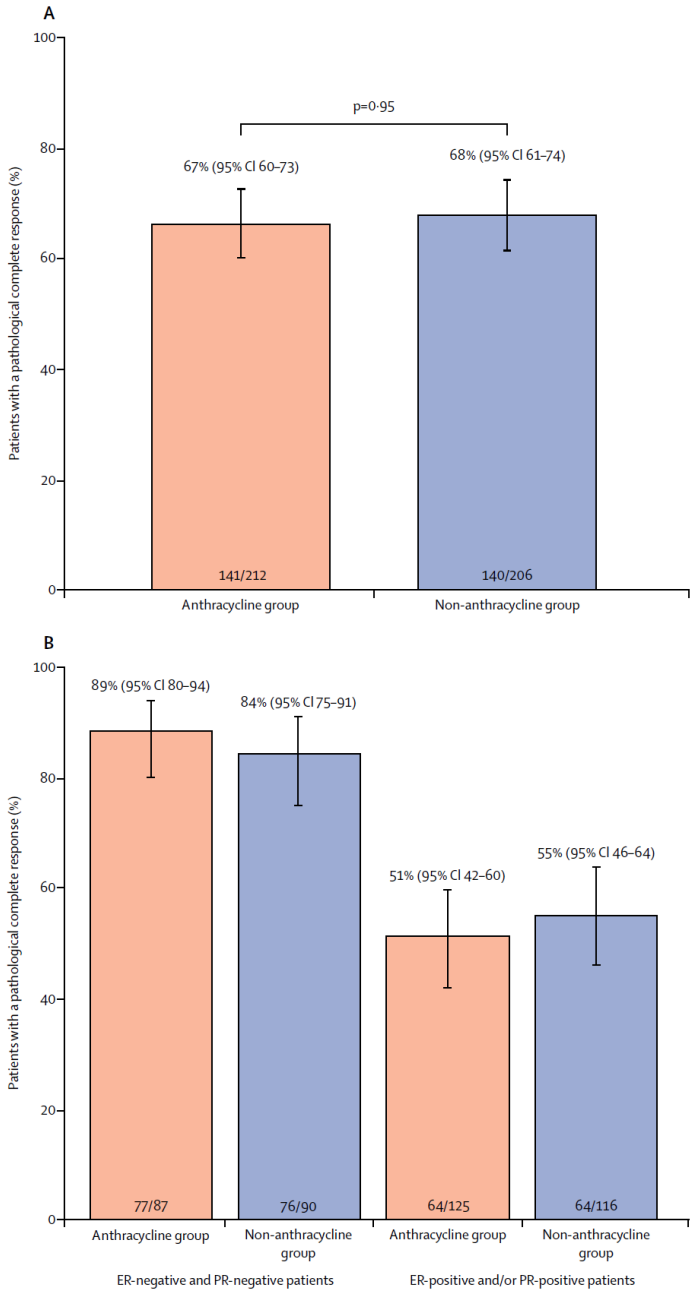
Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial

Mette S van Ramshorst, Anna van der Voort, Erik D van Werkhoven, Ingrid A Mandjes, Inge Kemper, Vincent O Dezentjé, Irma M Oving, Aafke H Honkoop, Lidwine W Tick, Agnes J van de Wouw, Caroline M Mandigers, Laurence J van Warmerdam, Jelle Wesseling, Marie-Jeanne T Vrancken Peeters, Sabine C Linn, Gabe S Sonke, on behalf of the Dutch Breast Cancer Research Group (BOOG)



Lancet Oncol 2018; 19: 1630–40

TRAIN-2 Trial: pCR (ypT0/is ypN0) according to treatment and ER-PR status



van Ramshorst MS et al Lancet Oncol 2018

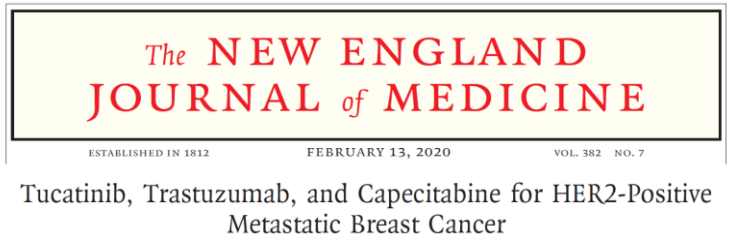
Tappe fondamentali della terapia anti HER-2

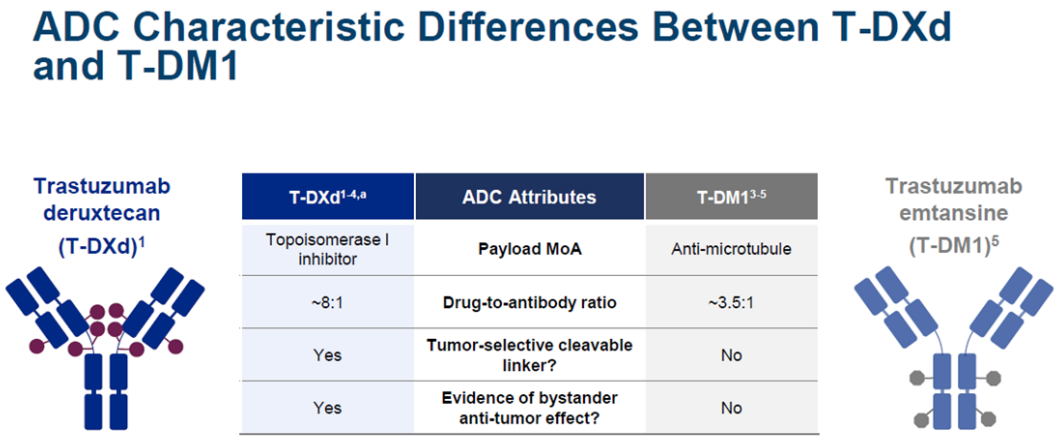
1998 l'inizio

2005 la rivoluzione

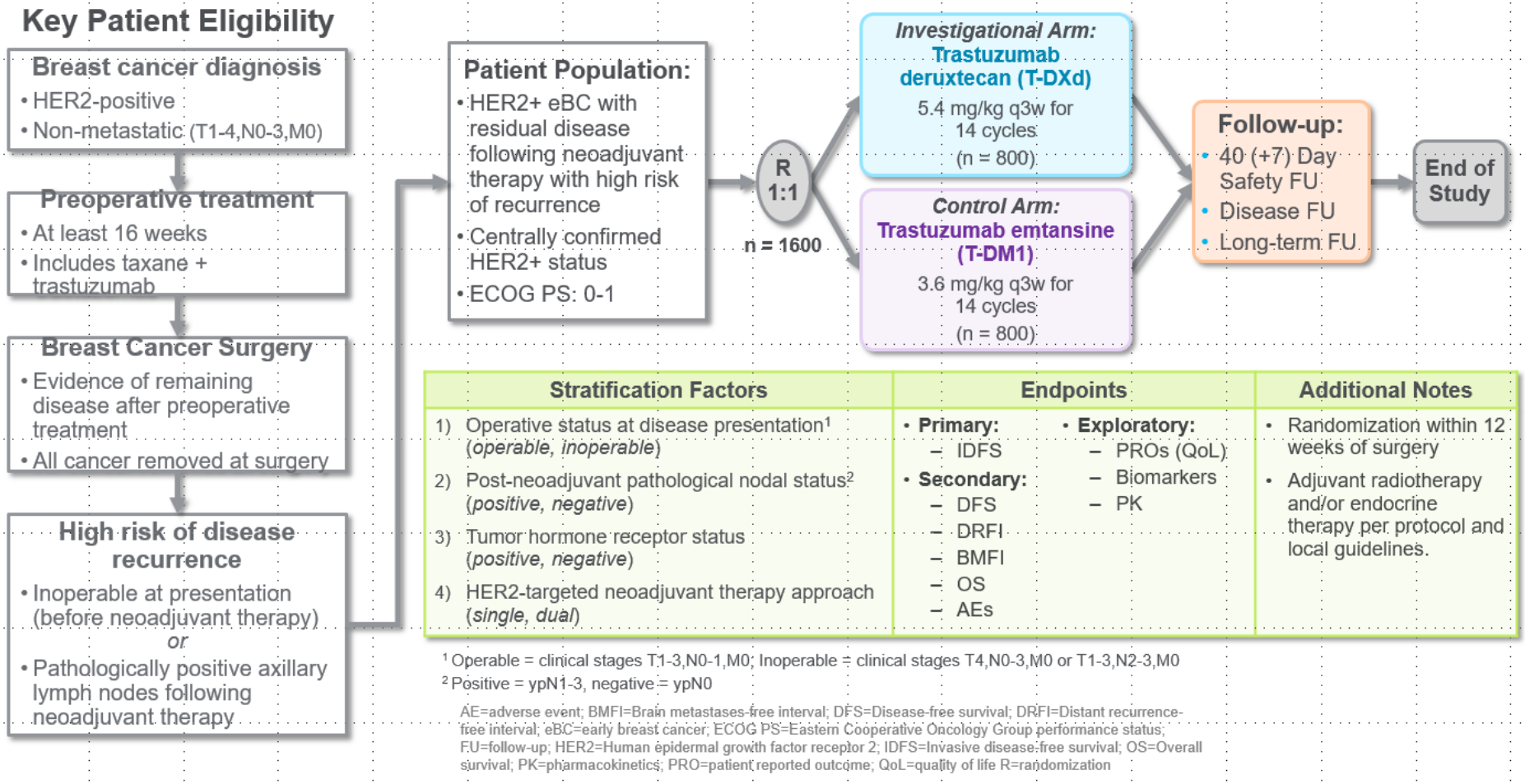
2019 il nuovo paradigma

2020 l'evoluzione della specie





DS8201-A-U305 (DESTINY-Breast05) Study Design



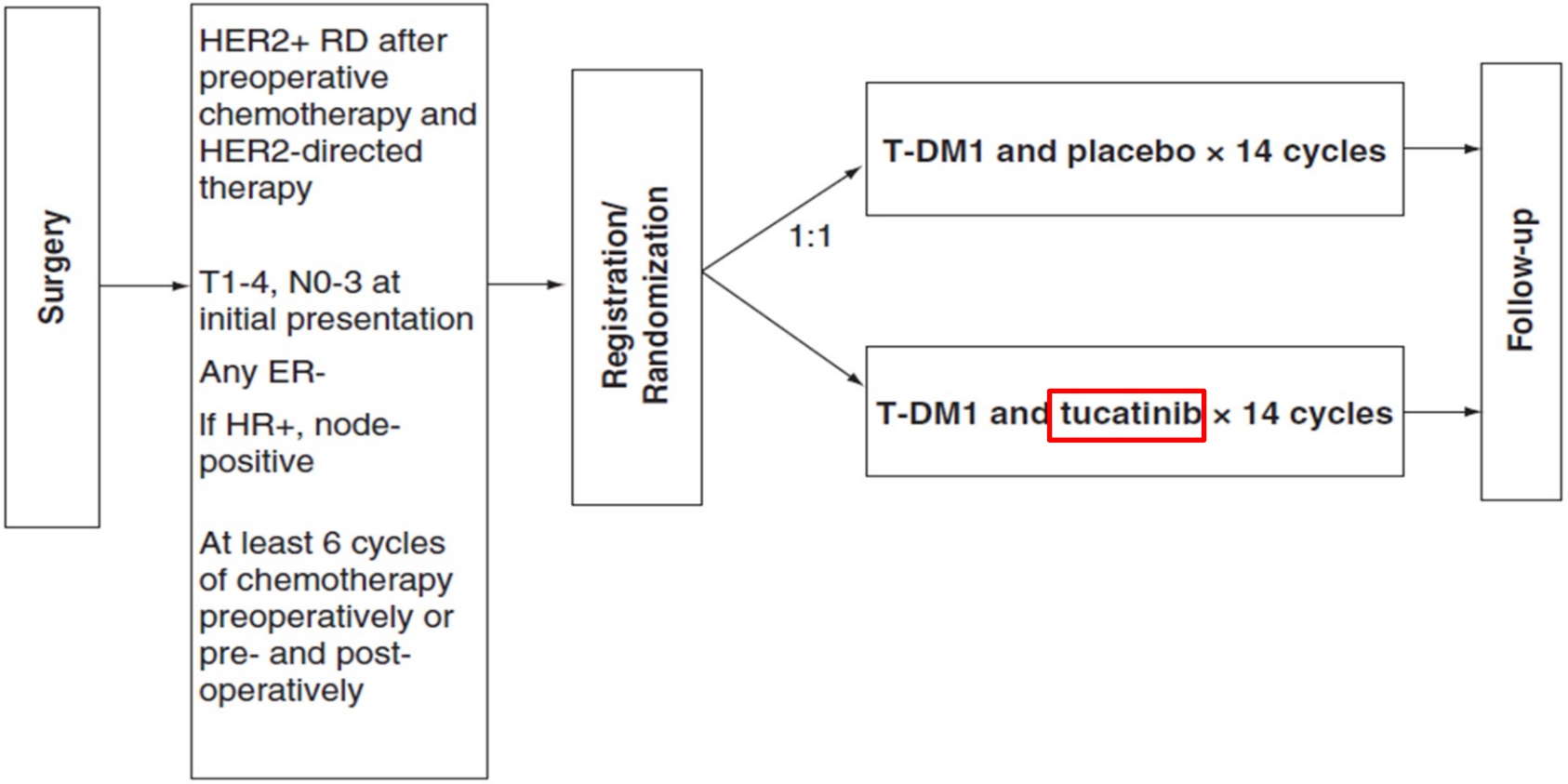
Stratification Factors	Endpoints	Additional Notes
1) Operative status at disease presentation[1] (*operable, inoperable*) 2) Post-neoadjuvant pathological nodal status[2] (*positive, negative*) 3) Tumor hormone receptor status (*positive, negative*) 4) HER2-targeted neoadjuvant therapy approach (*single, dual*)	• **Primary:** – IDFS • **Secondary:** – DFS – DRFI – BMFI – OS – AEs • **Exploratory:** – PROs (QoL) – Biomarkers – PK	• Randomization within 12 weeks of surgery • Adjuvant radiotherapy and/or endocrine therapy per protocol and local guidelines.

[1] Operable = clinical stages T1-3,N0-1,M0; Inoperable = clinical stages T4,N0-3,M0 or T1-3,N2-3,M0

[2] Positive = ypN1-3, negative = ypN0

AE=adverse event; BMFI=Brain metastases-free interval; DFS=Disease-free survival; DRFI=Distant recurrence-free interval; eBC=early breast cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; FU=follow-up; HER2=Human epidermal growth factor receptor 2; IDFS=Invasive disease-free survival; OS=Overall survival; PK=pharmacokinetics; PRO=patient reported outcome; QoL=quality of life R=randomization

CompassHER2 RD study design



O'Sullivan CC et al Future Oncol 2021

Destiny B11- Study Design: Phase 3, open-label 3-arm Neoadjuvant Study

Population

HER2+ EBC

HR+ or HR-

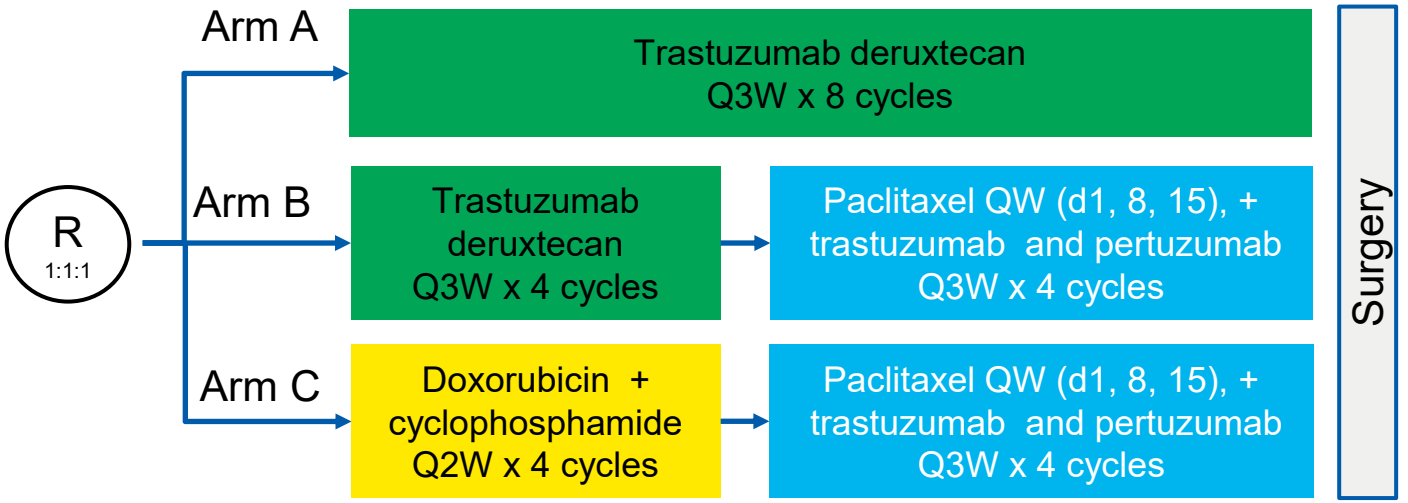
High-risk defined as one of the following:

- $T_xN_{1-3}M_0$
- $T_{3-4}N_xM_0$
- Inflammatory BC

Stratification factors:

- HR Status
  - HR+ vs HR-
- HER2 IHC
  - IHC3+ vs Other

Study Design



Post-neoadjuvant therapy will be determined by investigator and administered as per local SOC

Primary Endpoint:

- pCR (ypT0/Tis ypN0)

Secondary Endpoints:

- pCR (ypT0 ypN0)
- EFS
- IDFS
- OS
- HRQoL
- Safety
- PK and immunogenicity

Key Design Features:

- Study powered for pCR; SOC pCR benchmark 56%; Target pCR Δ15% for both experimental arms
- Cap HR-negative patients at 30% (natural prevalence)
- N+ or large tumor only eligible

Key Message
eBC HER2+ nel 2023

Approccio **neoadiuvante** in tutti gli stadi (esclusi cT1N0?)

Tutta la chemioterapia* prima dell'intervento

*EC/AC→ taxani *oppure* platino/taxani (solo taxani nei T1N0?)

Trastuzumab e pertuzumab° in neoadiuvante
Trastuzumab adiuvante nelle pCR; TDM1 se malattia residua (T e/o N)

° attualmente indicato (on label) ma non rimborsabile