

Riunione Annuale
GIM GRUPPO
ITALIANO
MAMMELLA

26-27 SETTEMBRE 2025 BERGAMO
HOTEL EXCELSIOR SAN MARCO
PIAZZA DELLA REPUBBLICA, 6

L'innovazione nella ricerca sul carcinoma mammario
**Lo stadio precoce di malattia
Sottotipo HER-2 positivo**

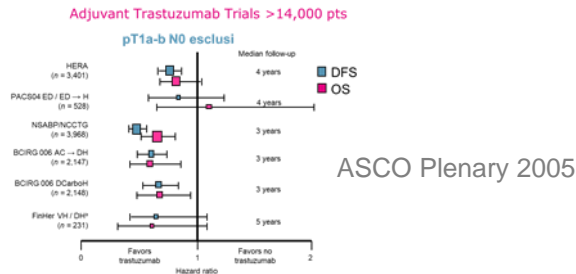
Claudio Zamagni
Direttore Oncologia Medica senologica e ginecologica & Breast Unit
IRCCS Azienda Ospedaliero-universitaria di Bologna
Ospedale di Sant'Orsola

Tappe fondamentali della terapia anti HER-2

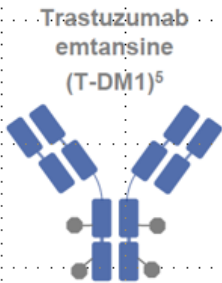
1998 l'inizio



2005 la rivoluzione



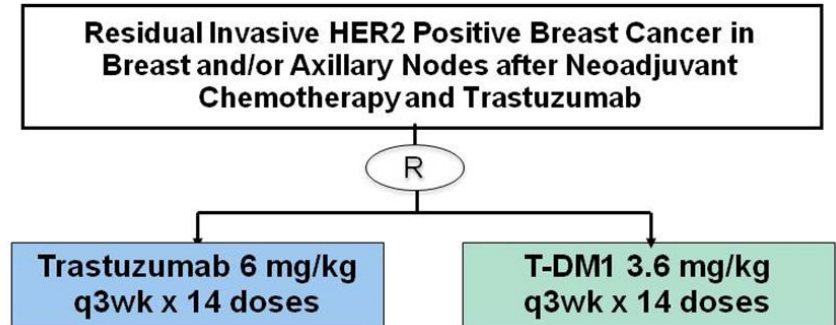
2019 il nuovo paradigma



Overall Survival

TH3RESA T-DM1 > TPC
 EMILIA T-DM1 > Cape/Lap

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

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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

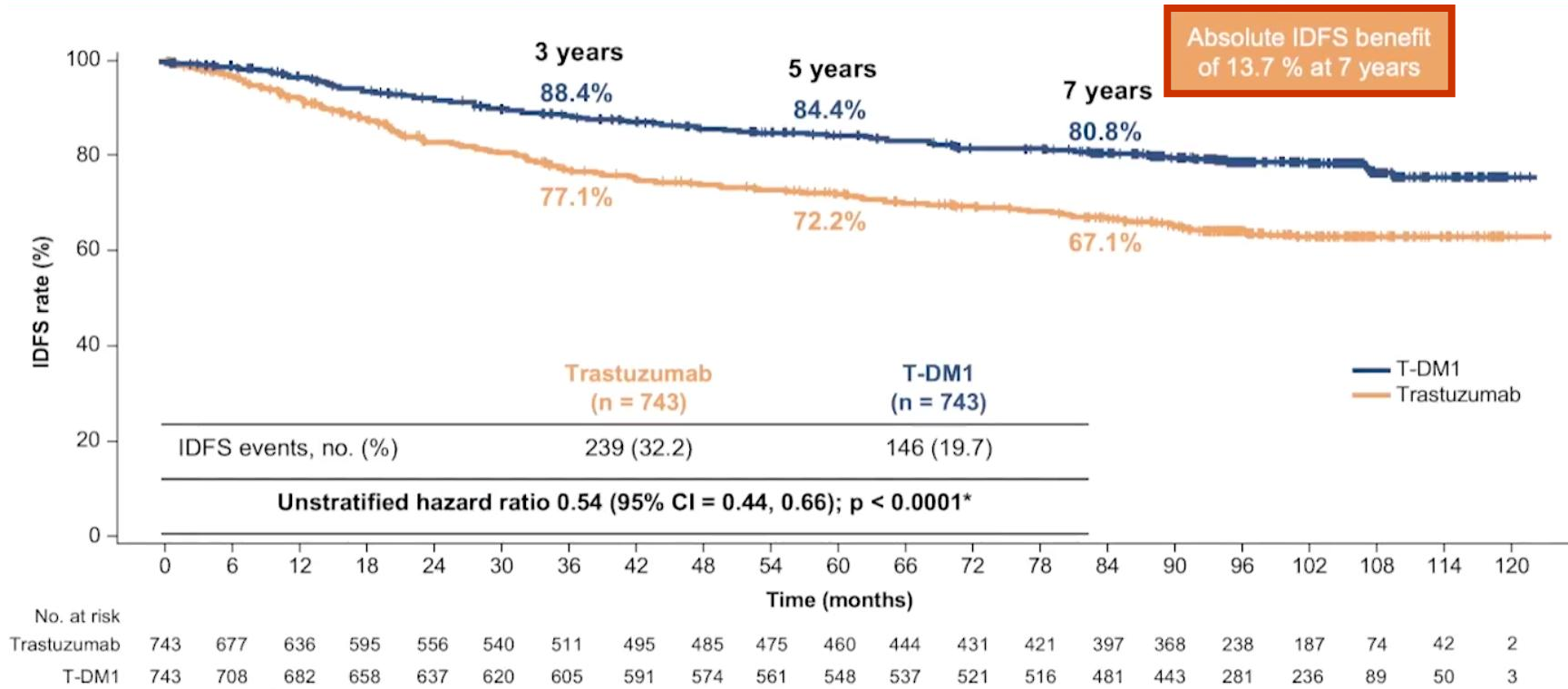
G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. 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)

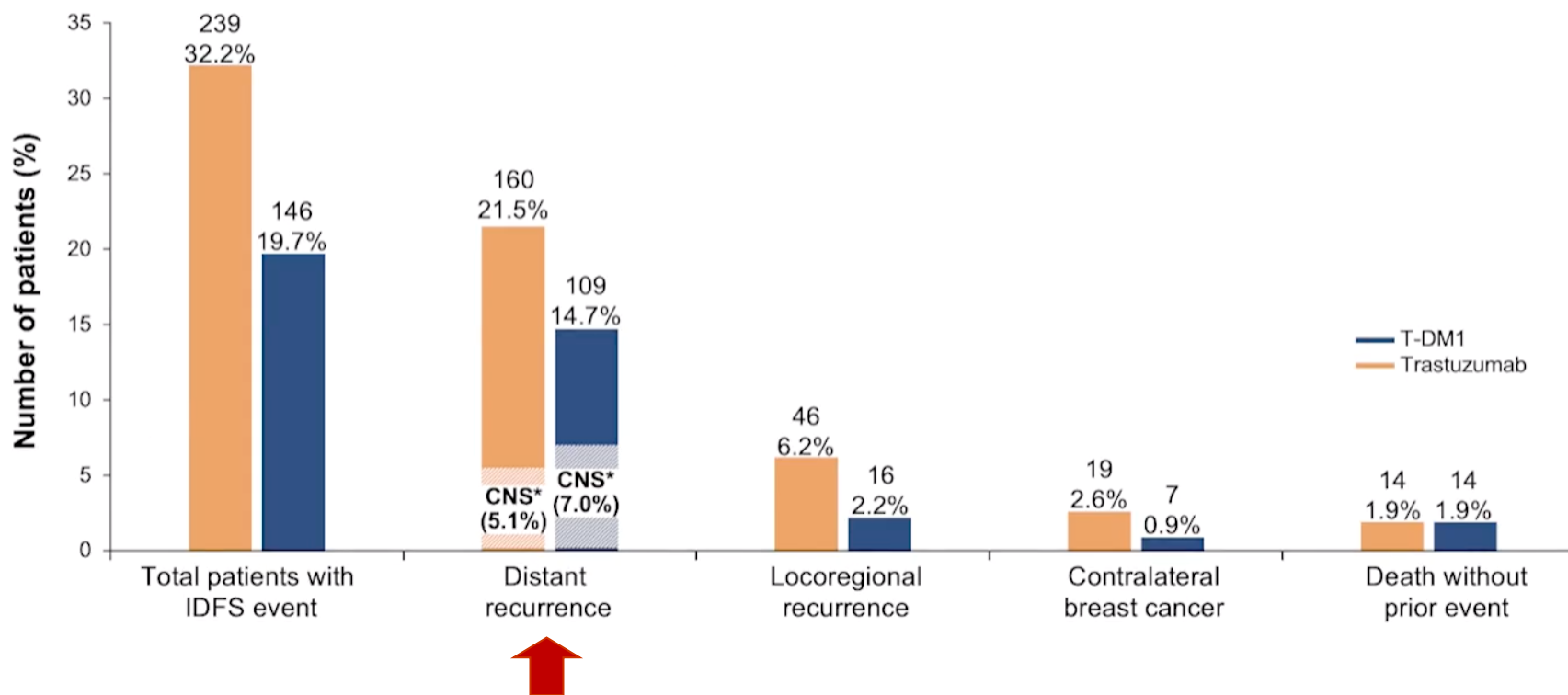
Preoperative systemic treatment consisting of at least 6 cycles with a total duration of at least 16 weeks, including at least 9 weeks of trastuzumab and at least 9 weeks of taxane-based chemotherapy

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

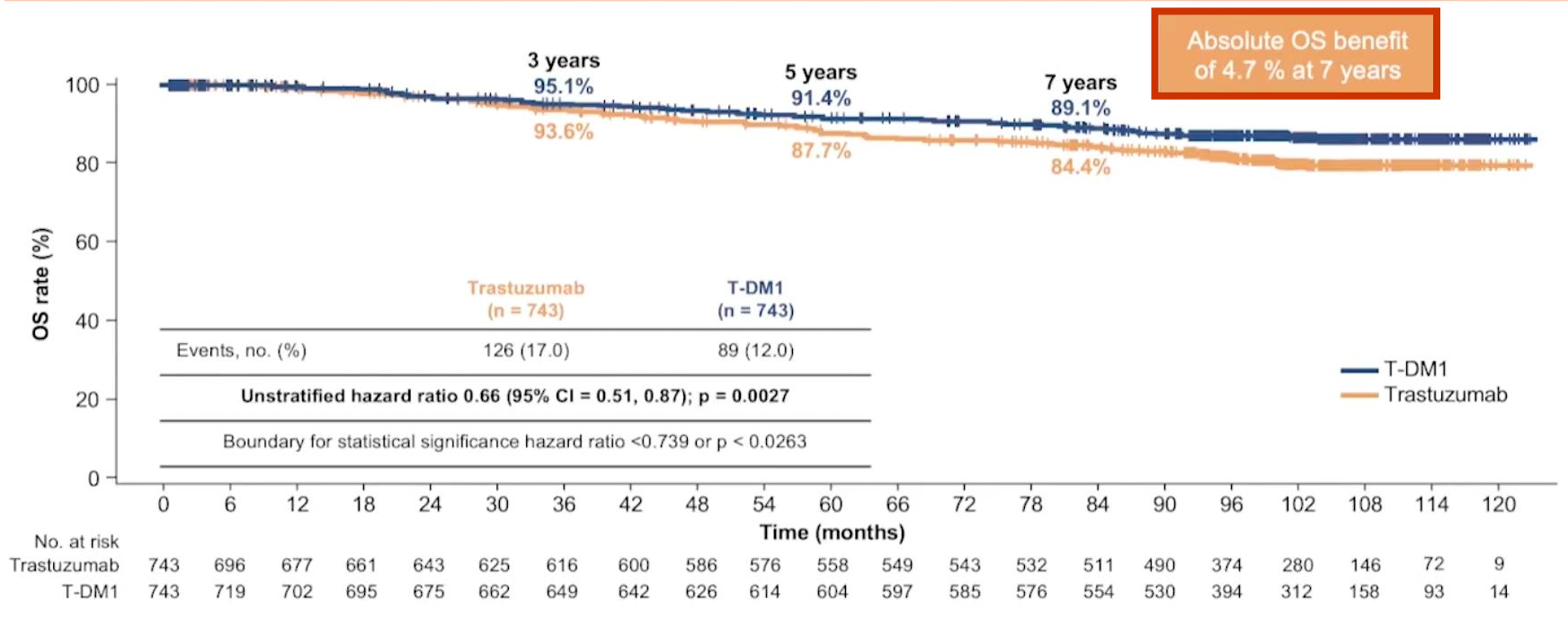
KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)

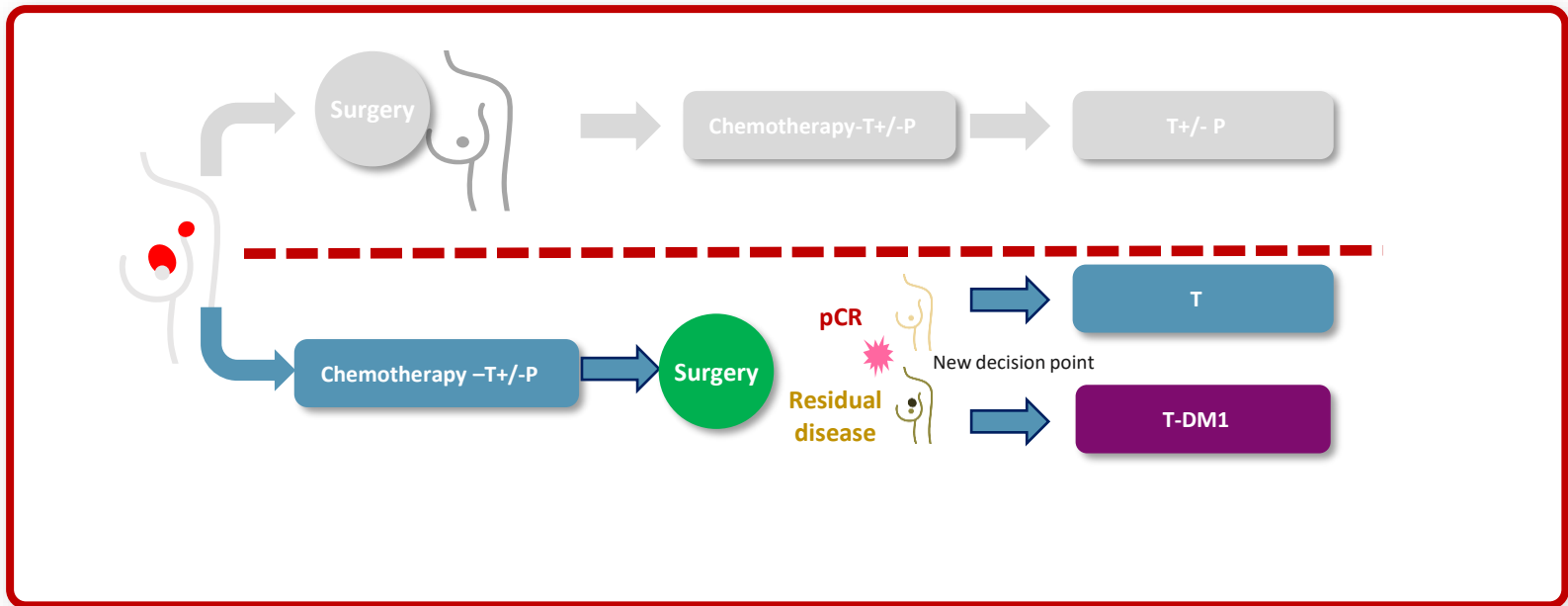


Site of first occurrence of an IDFS event



KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)





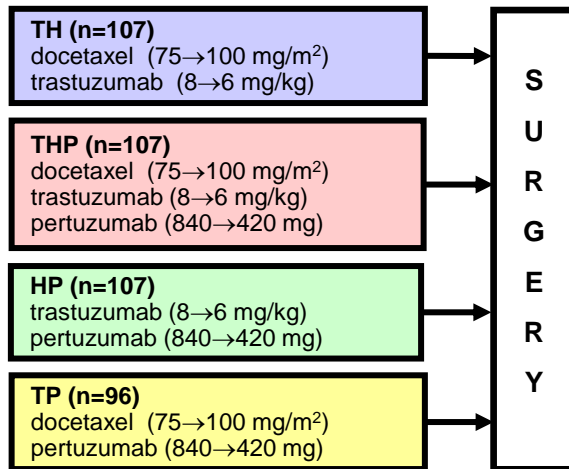
A tutte le pazienti va offerta l'opportunità di modulare il trattamento post-operatorio in funzione della risposta patologica alla terapia neoadiuvante

1

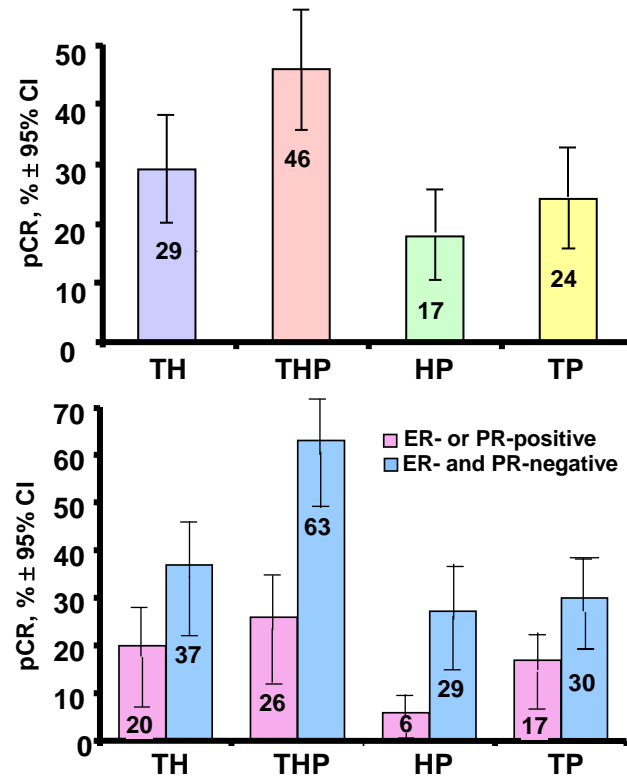
Quindi:

La terapia neoadiuvante è lo standard nel ca. mammario HER2+ in fase precoce esclusi cT1a,b

NeoSphere: Study design and main results

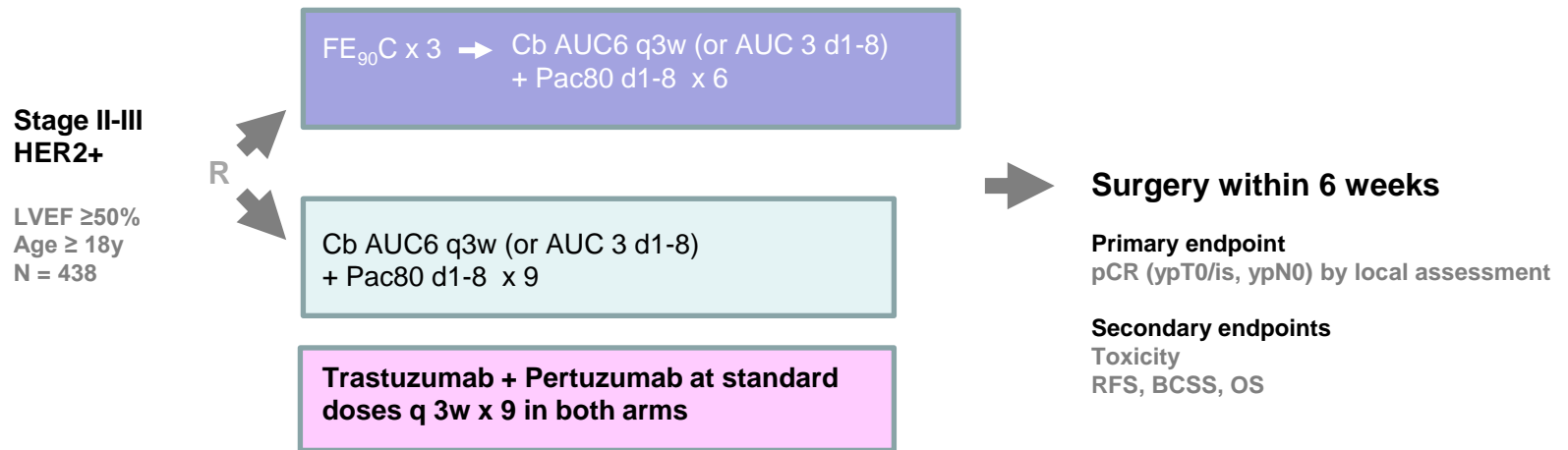


Study dosing: q3w x 4

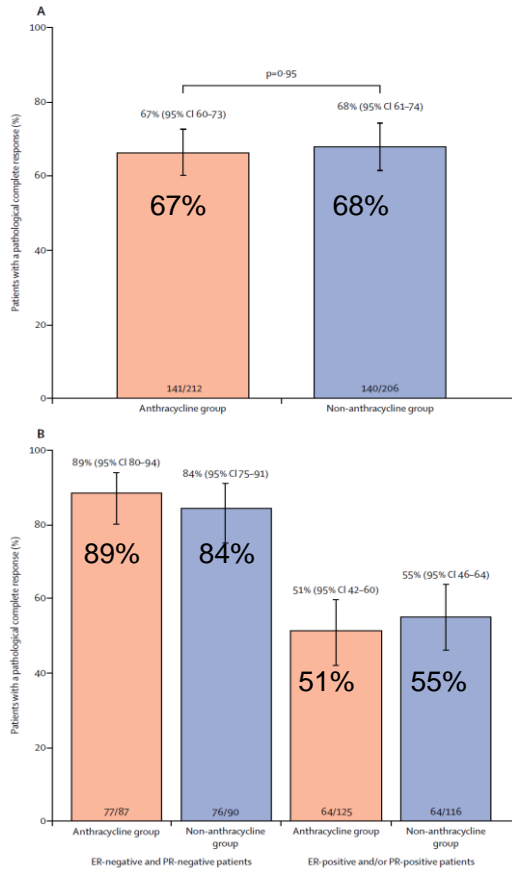


Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial

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)

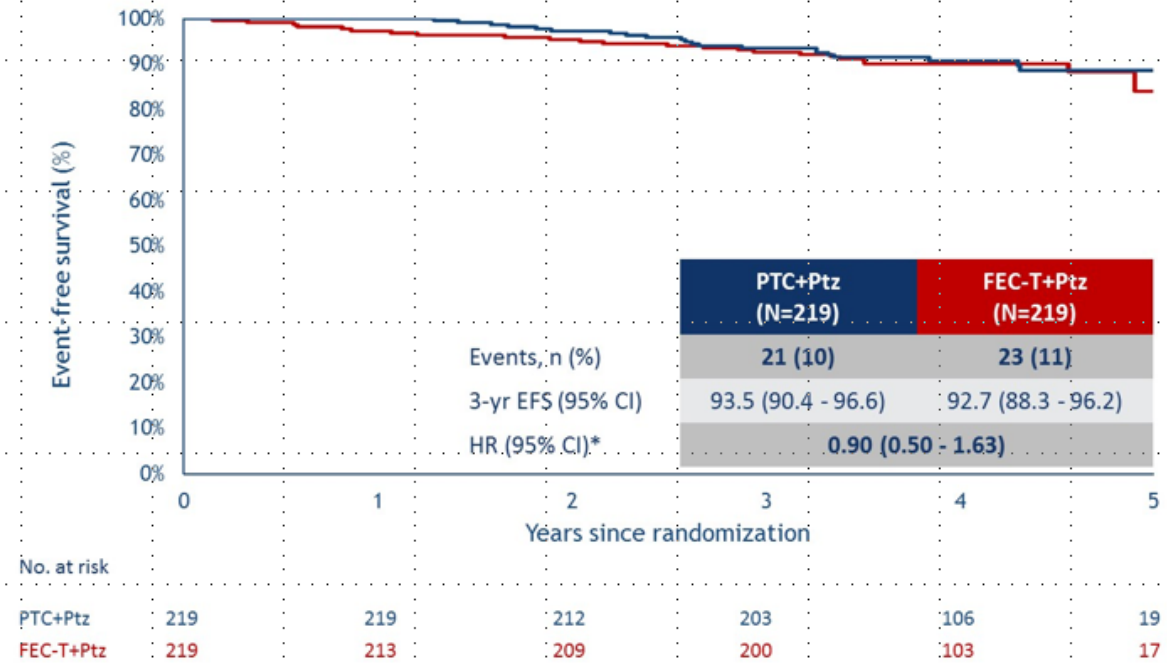


TRAIN-2 Trial: pCR (ypT0/is ypN0) according to treatment and ER-PR status, and EFS



van Ramshorst MS et al Lancet Oncol 2018

Event-free survival

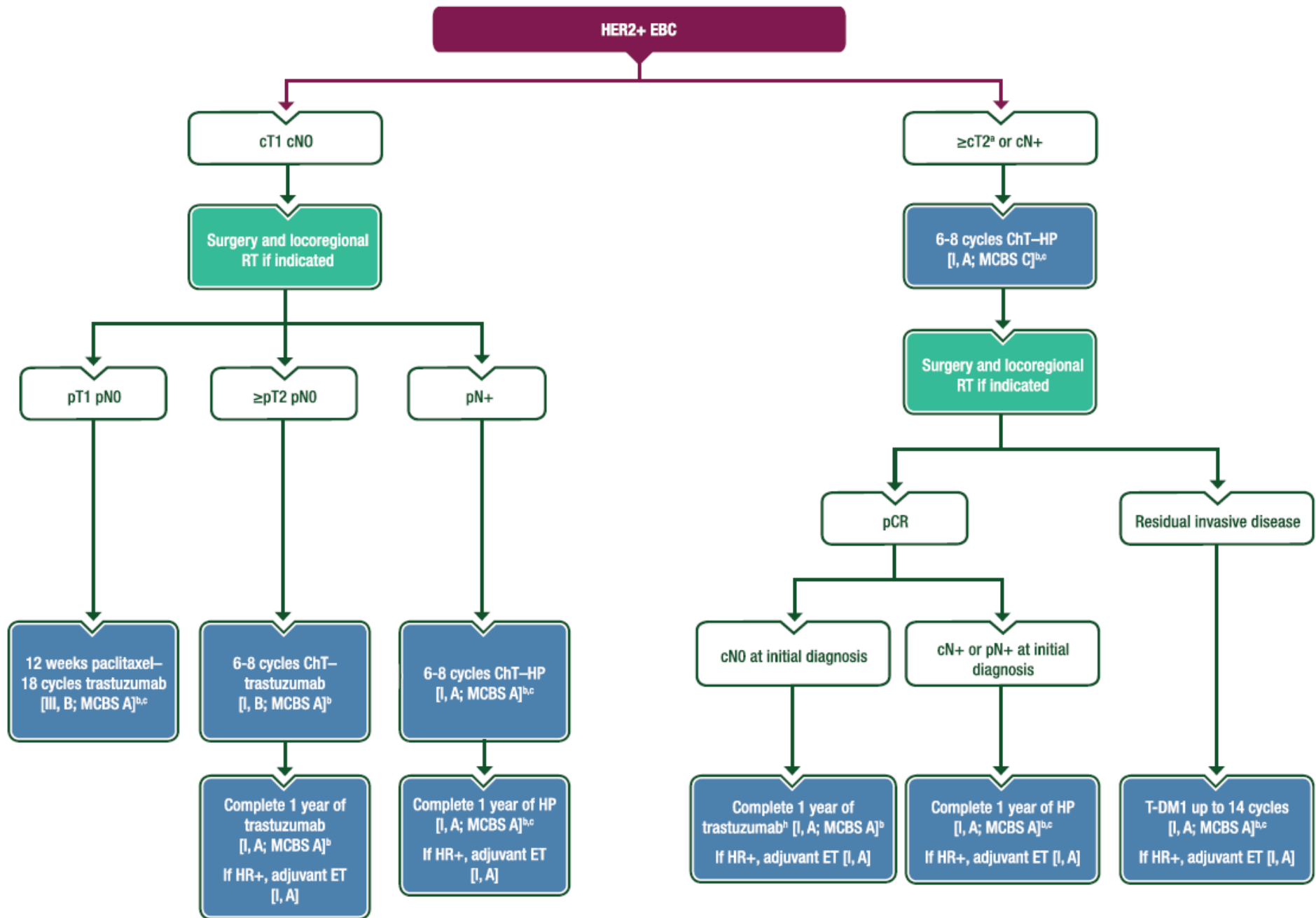


Anna van der Voort ASCO 2020

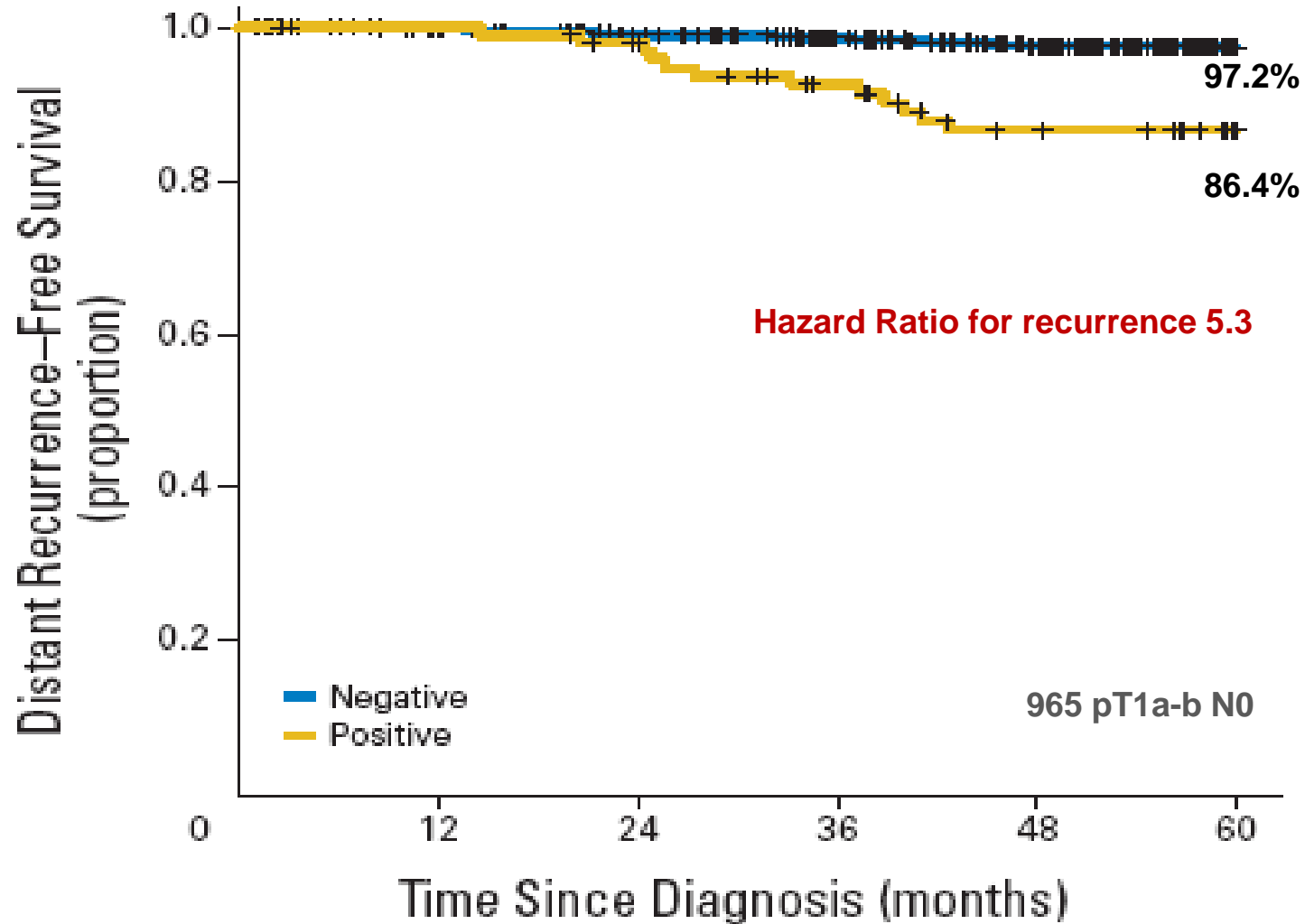
2

Quindi:

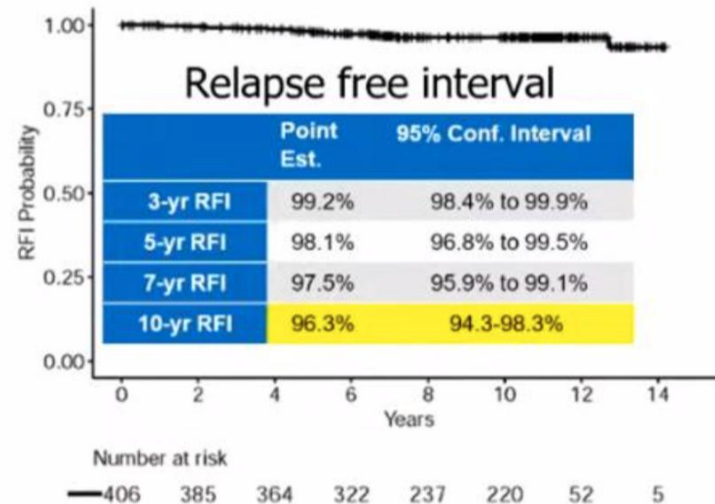
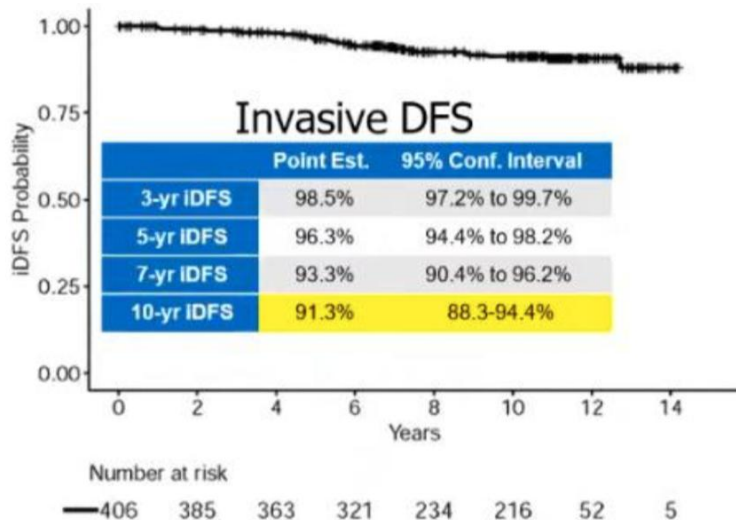
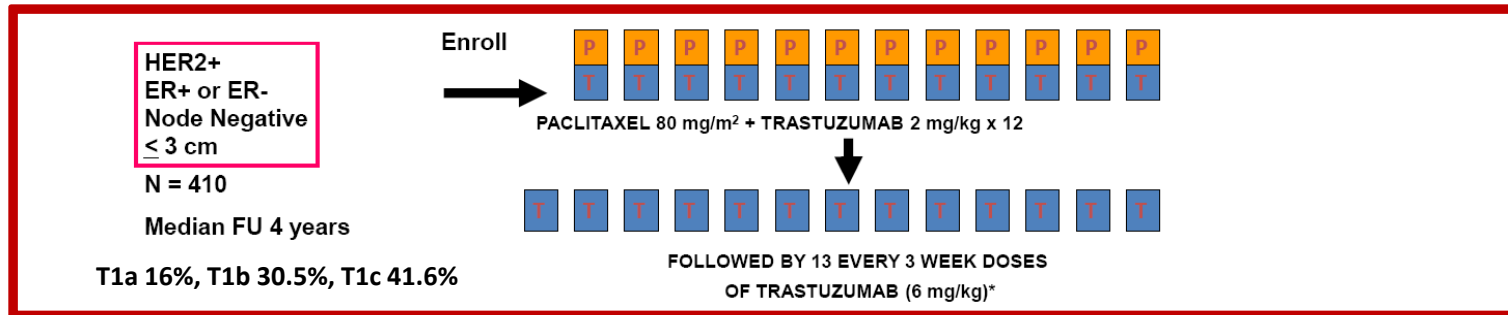
La migliore terapia neoadiuvante nei tumori HER2 positivi prevede l'associazione di chemioterapia con trastuzumab e pertuzumab e possiamo omettere le antracicline



Trastuzumab and chemo untreated pT1a-b N0



10y results of APT Chemotherapy de-escalated strategy



3

Quindi:

La terapia standard nei tumori HER2 positivi T1N0 è paclitaxel/trastuzumab in adiuvante

La neoadiuvante può essere proposta nei casi T1cN0

Il futuro prossimo

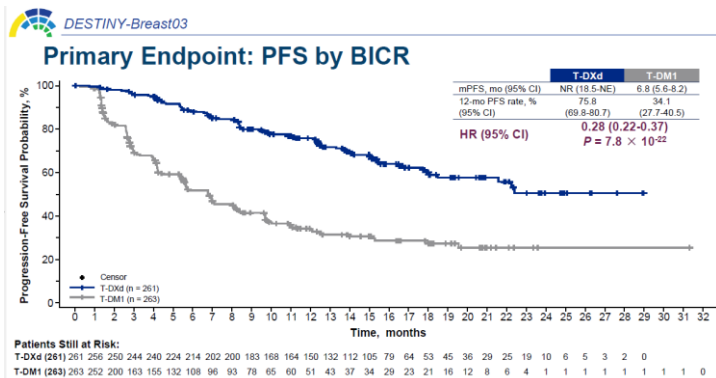
Tappe fondamentali della terapia anti HER-2

1998 l'inizio

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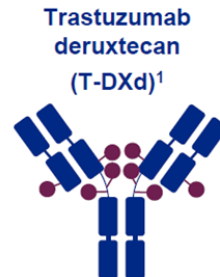
2019 il nuovo paradigma

2020 l'evoluzione della specie

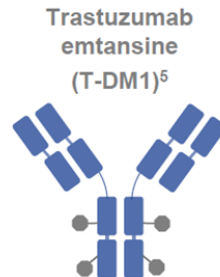


Cortès J et al ESMO 2021

ADC Characteristic Differences Between T-DXd and T-DM1



| T-DXd ^{1-4,a} | ADC Attributes | T-DM1 ³⁻⁵ |
|---------------------------|--|----------------------|
| Topoisomerase I inhibitor | Payload MoA | Anti-microtubule |
| ~8:1 | Drug-to-antibody ratio | ~3.5:1 |
| Yes | Tumor-selective cleavable linker? | No |
| Yes | Evidence of bystander anti-tumor effect? | No |



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

Study Design

Population

HER2+ EBC

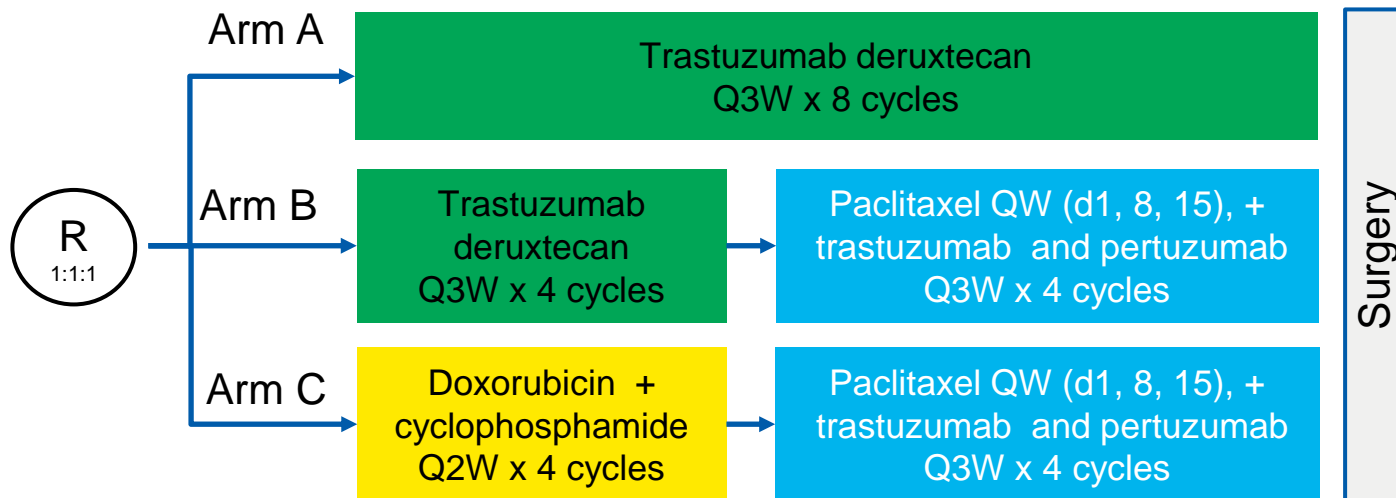
HR+ or HR-

High-risk defined as one of the following:

- $T_x N_{1-3} M_0$
- $T_{3-4} N_x M_0$
- Inflammatory BC

Stratification factors:

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



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

Primary Endpoint:

- pCR (ypT0/Tis ypN0)

Secondary Endpoints:

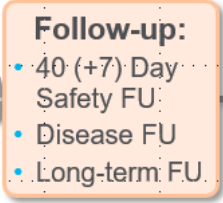
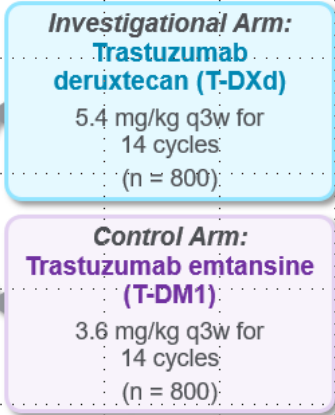
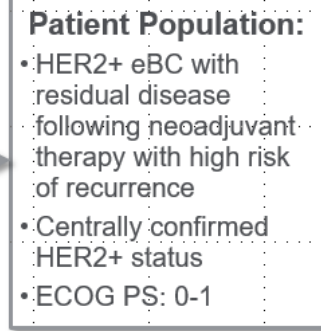
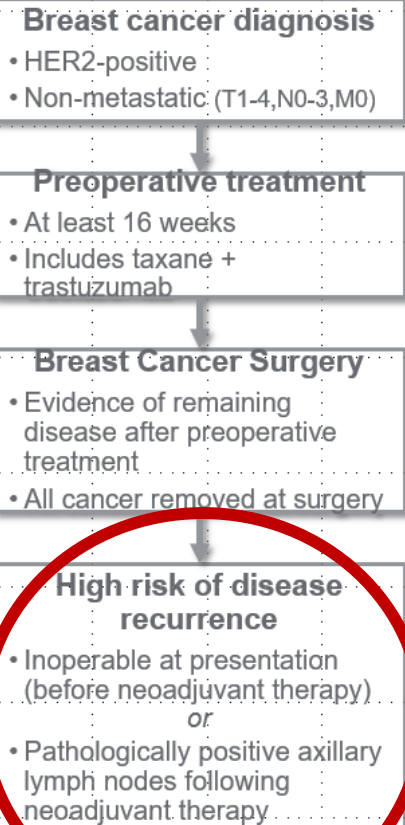
- pCR (ypT0 ypN0)
- EFS
- IDFS
- OS
- HRQoL
- Safety
- PK and immunogenicity

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

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

Key Patient Eligibility



| Stratification Factors | Endpoints | Additional Notes |
|--|--|---|
| 1) Operative status at disease presentation ¹ (<i>operable, inoperable</i>) | <ul style="list-style-type: none"> • Primary: <ul style="list-style-type: none"> - IDFS • Secondary: <ul style="list-style-type: none"> - DFS - DRFI - BMFI - OS - AEs | <ul style="list-style-type: none"> • Exploratory: <ul style="list-style-type: none"> - PROs (QoL) - Biomarkers - PK |
| 2) Post-neoadjuvant pathological nodal status ² (<i>positive, negative</i>) | | <ul style="list-style-type: none"> • Randomization within 12 weeks of surgery • Adjuvant radiotherapy and/or endocrine therapy per protocol and local guidelines. |
| 3) Tumor hormone receptor status (<i>positive, negative</i>) | | |
| 4) HER2-targeted neoadjuvant therapy approach (<i>single, dual</i>) | | |

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

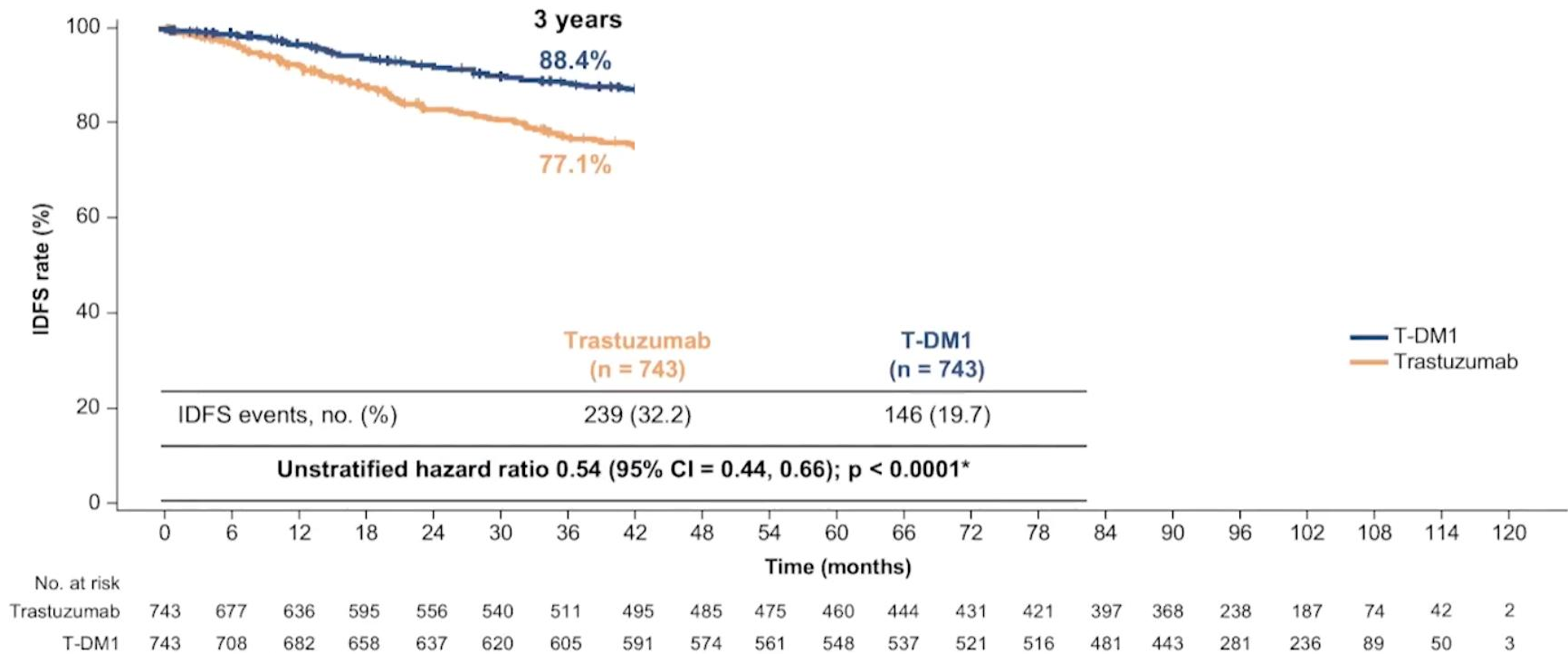
² Positive = ypN1-3, negative = ypN0

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

Final IDFS analysis: Subgroups (1/2)

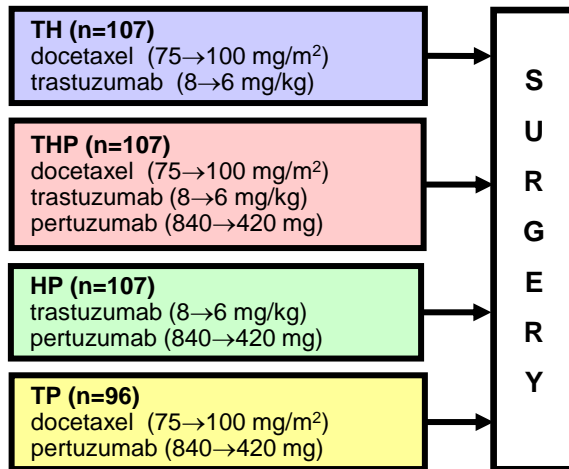
| Baseline risk factors | Trastuzumab (n = 743) | | | | T-DM1 (n = 743) | | | | Hazard ratio | 95% CI | T-DM1 better | Trastuzumab better |
|---|-----------------------|--------------------|----------|-------------|--------------------|----------|-------------|------|--------------|--------|--------------|--------------------|
| | Total n | Patients per group | n events | 7-year IDFS | Patients per group | n events | 7-year IDFS | | | | | |
| All | 1486 | 743 | 239 | 67.1 | 743 | 146 | 80.8 | 0.54 | (0.44, 0.66) | | | |
| Clinical stage at presentation | | | | | | | | | | | | |
| Inoperable | 375 | 190 | 87 | 51.3 | 185 | 62 | 66.7 | 0.63 | (0.45, 0.87) | | | |
| Operable | 1111 | 553 | 152 | 72.3 | 558 | 84 | 85.4 | 0.48 | (0.37, 0.63) | | | |
| Hormone receptor status | | | | | | | | | | | | |
| Negative (ER-negative and PgR-negative/-unknown) | 412 | 203 | 75 | 59.4 | 209 | 53 | 75.0 | 0.55 | (0.39, 0.78) | | | |
| Positive (ER- and/or PgR-positive) | 1074 | 540 | 164 | 69.8 | 534 | 93 | 83.1 | 0.52 | (0.40, 0.67) | | | |
| Preoperative HER2-directed therapy | | | | | | | | | | | | |
| Trastuzumab alone | 1196 | 596 | 198 | 66.4 | 600 | 128 | 79.5 | 0.56 | (0.45, 0.70) | | | |
| Trastuzumab plus additional HER2-directed agent(s) | 290 | 147 | 41 | 69.8 | 143 | 18 | 87.2 | 0.42 | (0.24, 0.72) | | | |
| Pathologic nodal status after preoperative therapy | | | | | | | | | | | | |
| Node-positive | 688 | 345 | 142 | 57.7 | 343 | 96 | 71.6 | 0.56 | (0.43, 0.72) | | | |
| Node-negative/not done | 798 | 398 | 97 | 74.8 | 400 | 50 | 88.8 | 0.47 | (0.34, 0.66) | | | |
| Central HER2 status by IHC | | | | | | | | | | | | |
| 0/1+ | 25 | 13 | 4 | 67.1 | 12 | 1 | 100.0 | 0.25 | (0.03, 2.22) | | | |
| 2+ | 326 | 168 | 52 | 68.8 | 158 | 44 | 72.4 | 0.84 | (0.56, 1.25) | | | |
| 3+ | 1132 | 559 | 183 | 66.5 | 573 | 101 | 82.8 | 0.47 | (0.37, 0.60) | | | |
| Unknown | 3 | 3 | 0 | 100.0 | | | | NE | (NE, NE) | | | |
| Race | | | | | | | | | | | | |
| White | 1081 | 530 | 158 | 69.3 | 551 | 110 | 80.7 | 0.59 | (0.46, 0.75) | | | |
| Black or African American | 40 | 19 | 11 | 51.3 | 21 | 2 | 88.9 | 0.13 | (0.03, 0.59) | | | |
| Asian | 129 | 64 | 22 | 62.9 | 65 | 16 | 75.3 | 0.65 | (0.34, 1.23) | | | |
| American Indian or Alaska Native | 86 | 50 | 25 | 50.2 | 36 | 8 | 75.8 | 0.40 | (0.18, 0.88) | | | |
| Other or multiple or unknown | 150 | 80 | 23 | 71.0 | 70 | 10 | 86.8 | 0.45 | (0.22, 0.95) | | | |

KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)

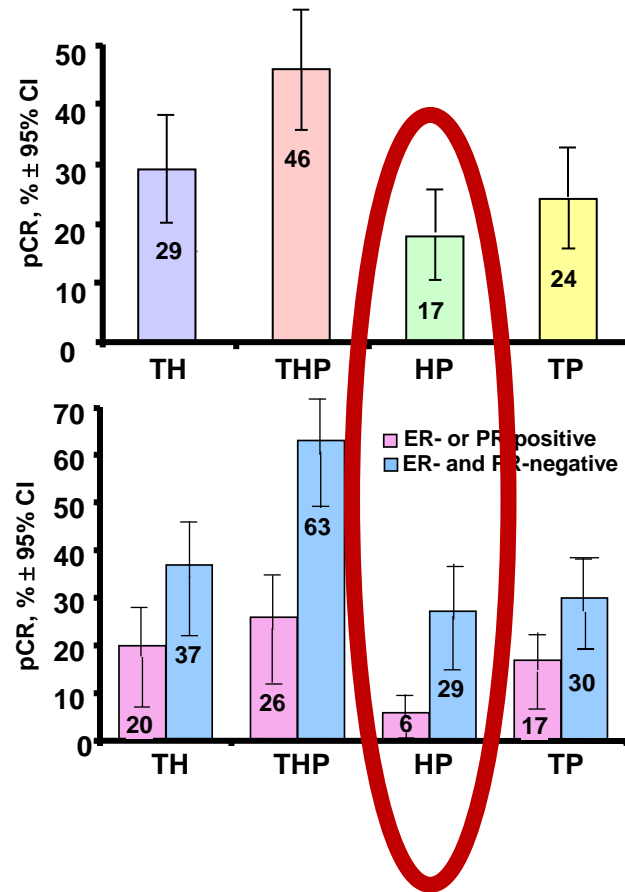


Loibl S et al SABCS 2023

NeoSphere: Study design and main results



Study dosing: q3w x 4

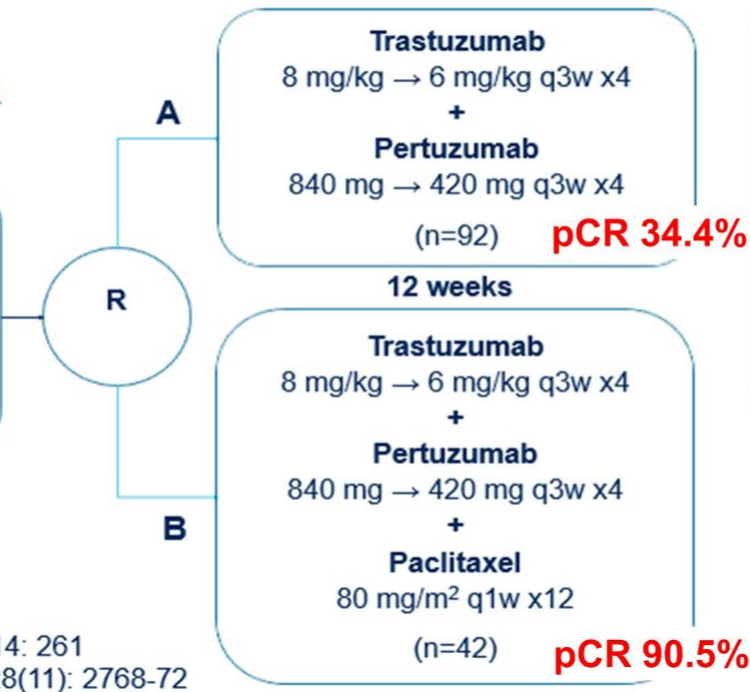


Could pCR be achieved with T+P even without CT?

WSG-ADAPT HER2+/HR-

Study Design

- HER2+, ER- and PR-
 - M0
 - ECOG ≤1 or KPS ≥80%
- (n=134)



Surgery within 3 weeks

In histologically confirmed non-pCR: standard neoadjuvant therapy followed by surgery

Adjuvant therapy according to national guidelines; if pCR was achieved after 12 weeks of study therapy, additional chemotherapy could be omitted at investigator's discretion

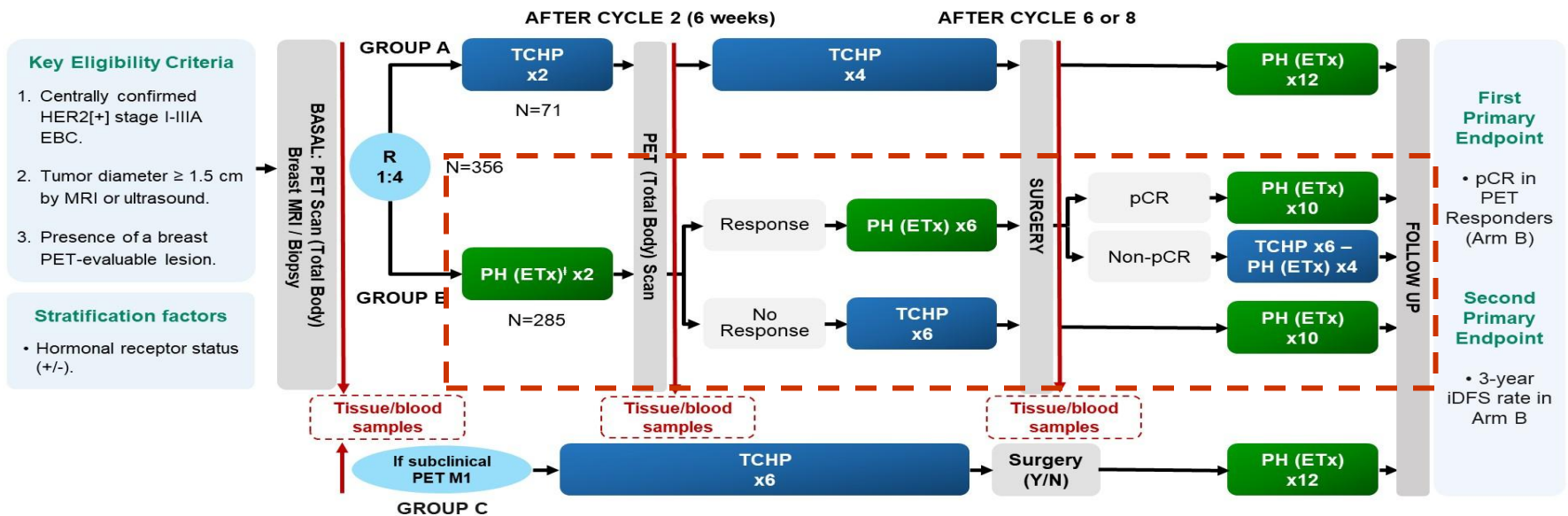
- Endpoints:
- pCR (ypT0/is ypN0; ypT0 ypN0)
 - **iDFS, dDFS, OS**, safety
 - Translational research: (DNA, RNA, IHC/Immune panel)

Hofmann et al, *Trials* 2013; 14: 261
Nitz et al, *Ann Oncol* 2017; 28(11): 2768-72

Stage I 40%; Stage II 52%; stage III 8%

Early response evaluation to modulate the treatment strategy

PHERGain Study Design

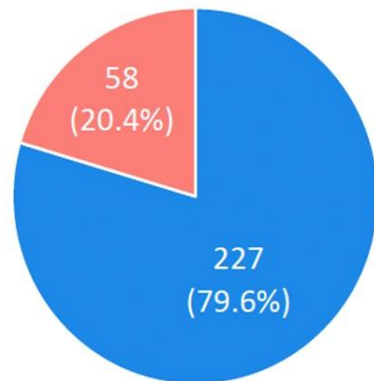


C: Carboplatin; D: Docetaxel; EBC: Early breast cancer; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal), Adjuvant ETx up to 3 years from surgery; PET: ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth Factor Receptor 2; iDFS: Invasive disease-free survival; MRI: Magnetic resonance imaging; P: Pertuzumab IV; R: Randomization; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin. [†] All hormonal receptor-positive patients received ETx concomitantly with PH (except on chemotherapy).

- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction $\geq 40\%$.
- pCR, Pathological complete response (ypT0/isN0)

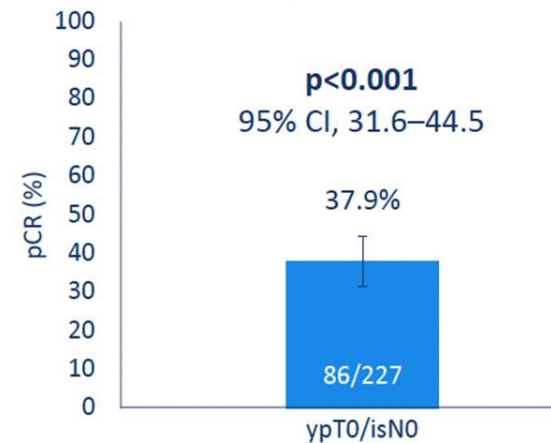
Primary Endpoint: pCR in ¹⁸F-FDG-PET responders in group B

PET Responders and Non-Responders



■ PET Responder ■ PET Non-Responder

pCR rate



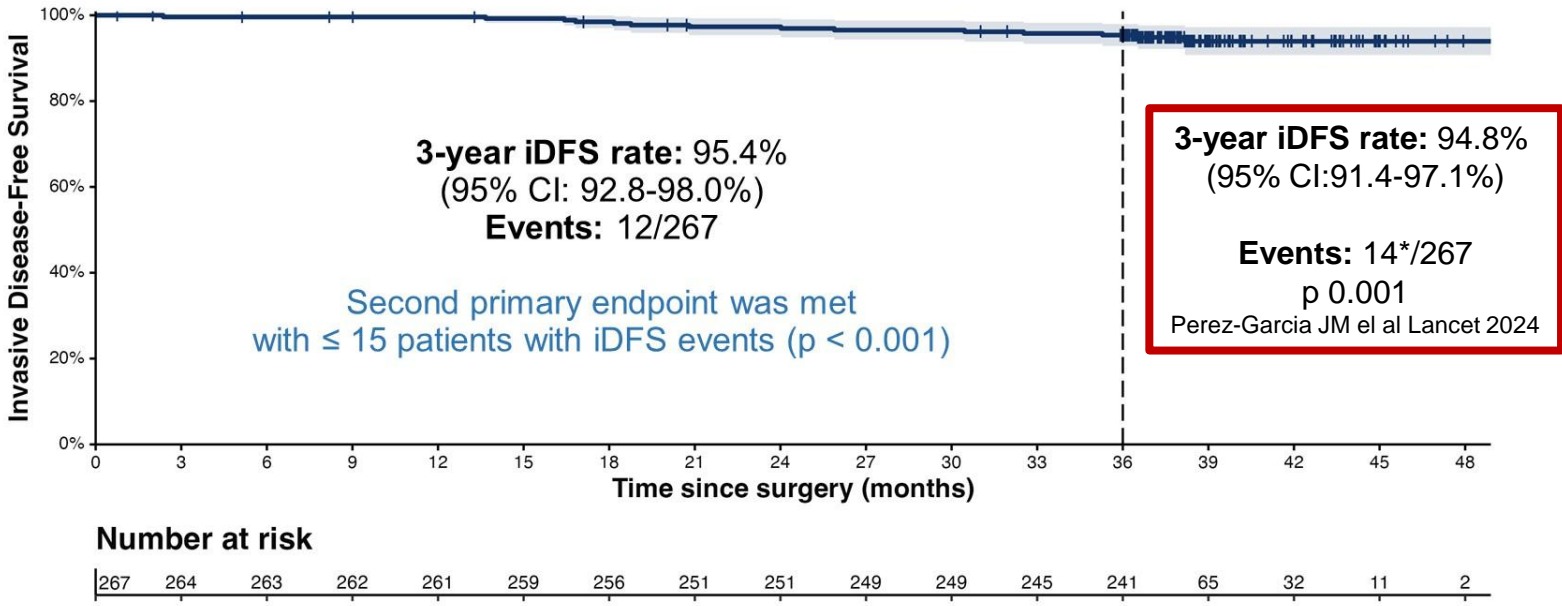
Null hypothesis: pCR ≤ 20%

pCR was observed in patients with both HER2++ and HER2+++; pts with stage II and stage III, and pts ER+ and ER-.

Pérez-García, JM, et al. (2021). *Lancet Oncol*, 22(6), 858-871.

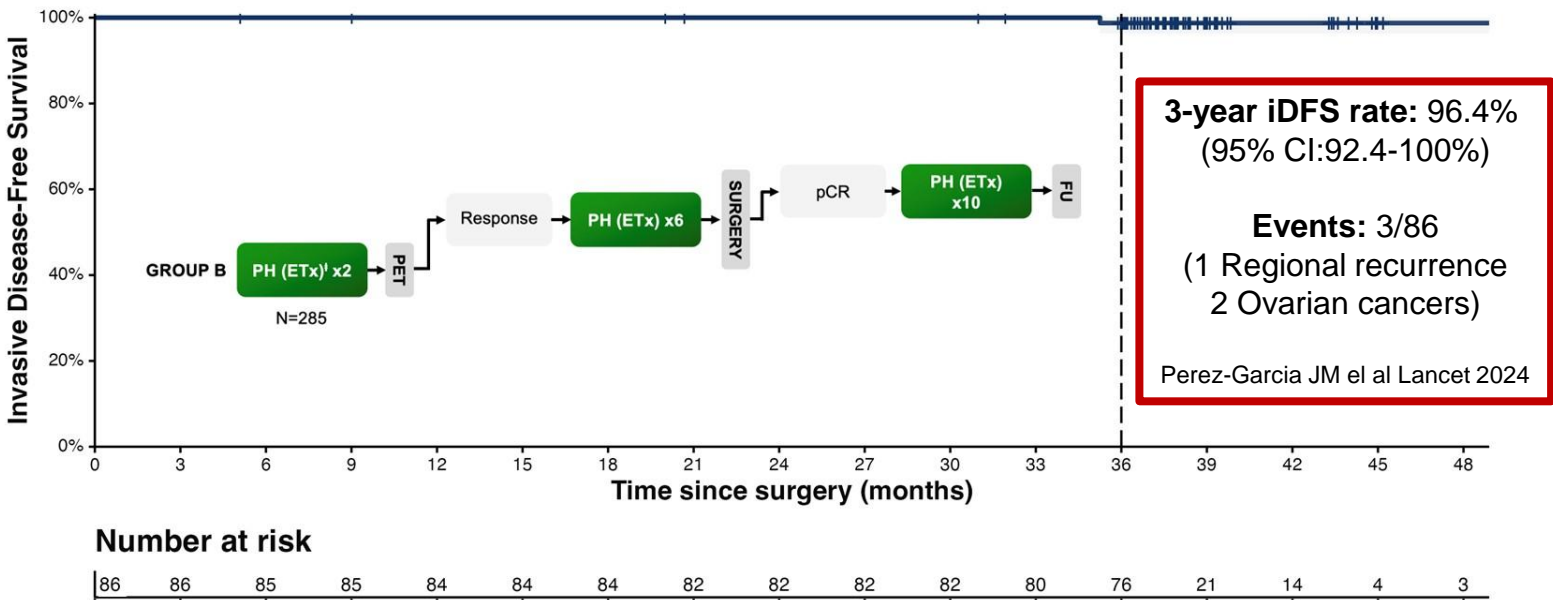
CI: Confidence interval; PET: ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response (ypT0/isN0).

Primary Endpoint: 3-year iDFS rate in group B ITT population



* (8 distant recurrence
3 Regional recurrence
2 Ovarian cancers
1 non-cancer death)

Subgroup analysis: 3-year iDFS rate without CT in PET responders with pCR (n=86)



How to move toward escalated or de-escalated strategy at single patient level?

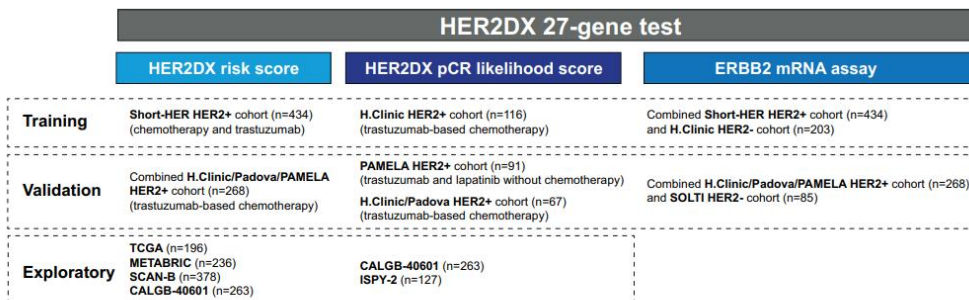
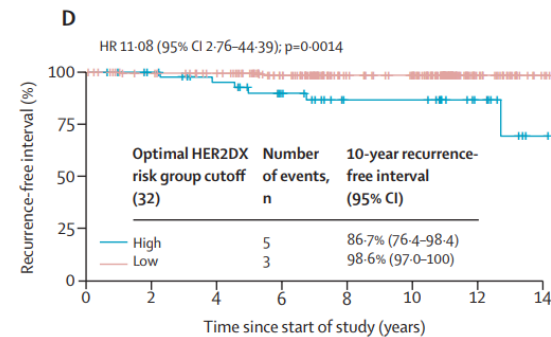
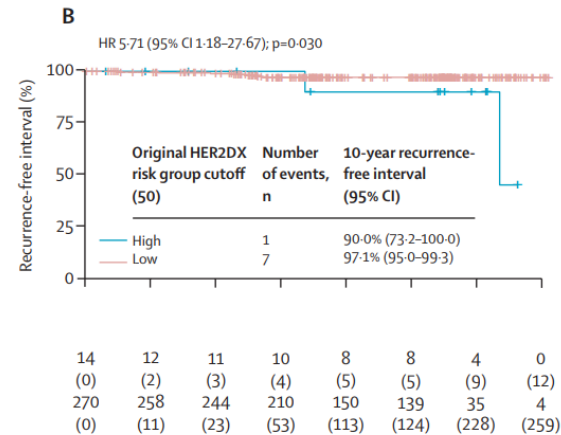
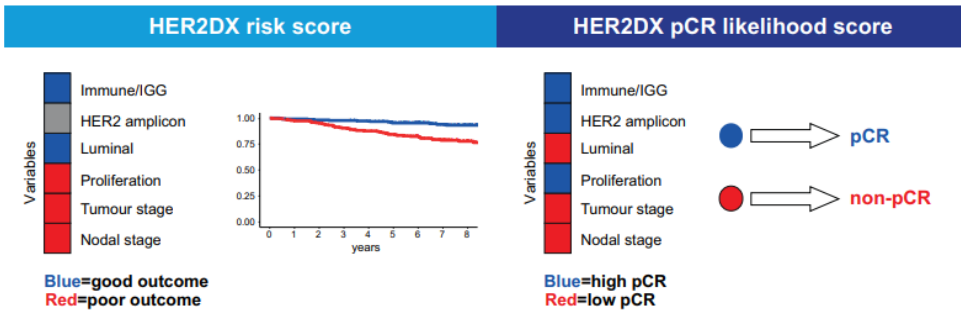


Figure 1. Summary of the different cohorts of patients evaluated during HER2DX development and validation.

APT trial 10-year recurrence free survival (B, D), stratified by HER2DX risk group



Tolaney S et al, Lancet Oncol 2023

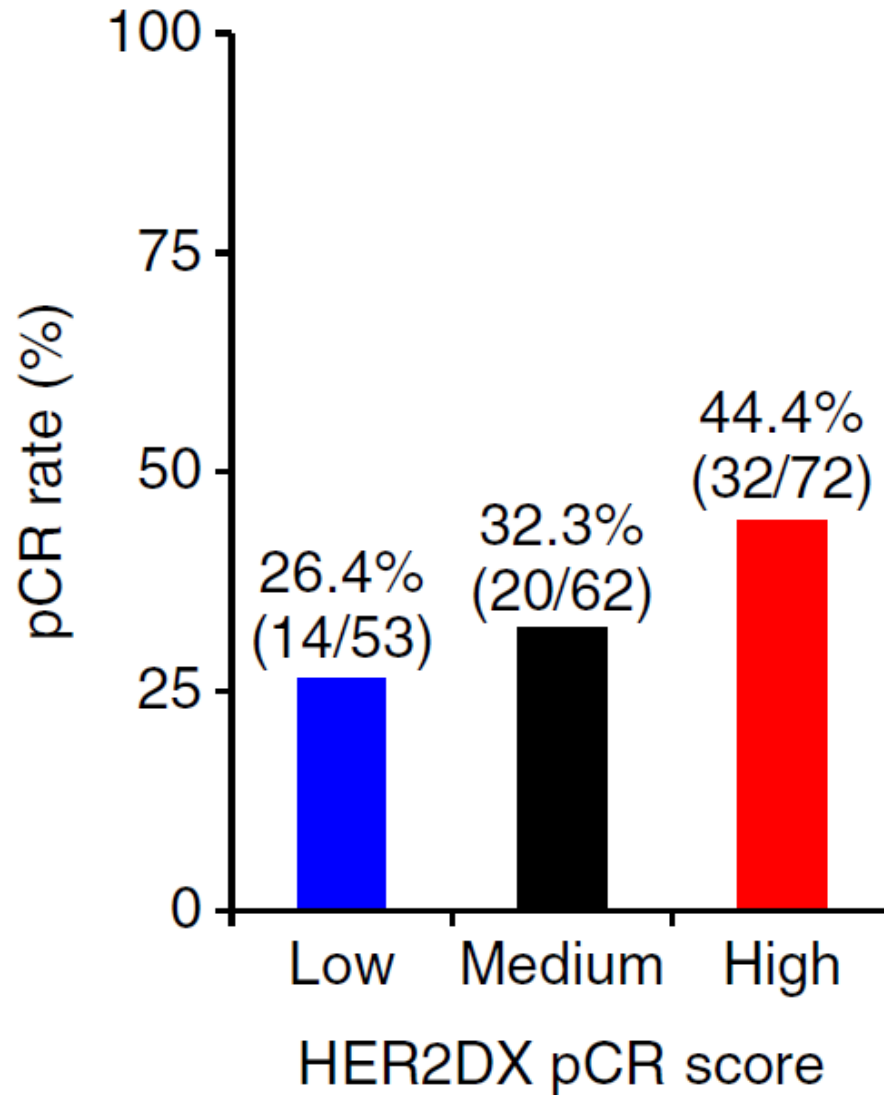


Prat A, et al. Ebiomedicine 2021; Prat A, et al. Lancet Oncol 2020

PHERGAIN Study

pCR rates across HER2DX pCR score groups

Patients in group B with a 18F-FDG-PET response

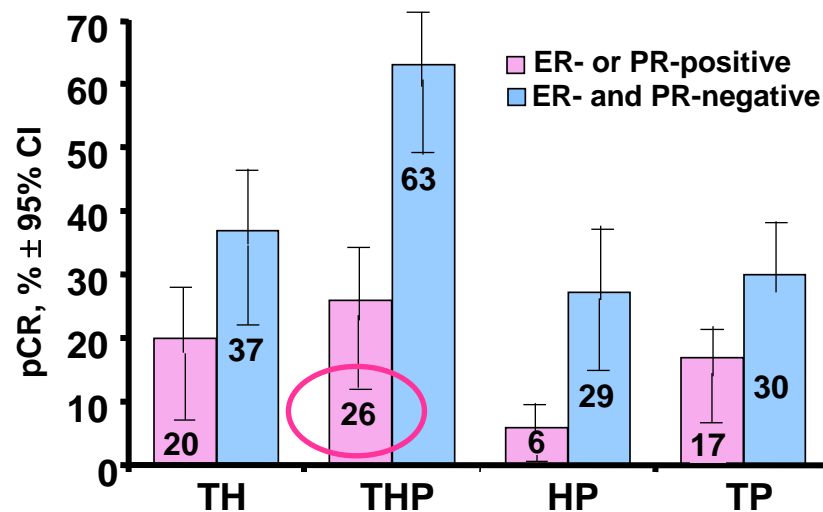


NA-PHER2 Clinical And Pathological Response

| | Eligible patients (n=30) |
|---|--------------------------|
| Overall clinical response | 29 (97% [83-100]) |
| Complete clinical response | 15 (50% [31-69]) |
| Partial clinical response | 14 (47% [28-64]) |
| Stable disease | 1 (3% [0-17]) |
| Pathological complete response (no invasive cells in breast and axillary lymph nodes) | 8 (27% [12-46]) |

Data are n (% [95% CI]).

Table 2: Clinical and pathological response



Gianni L, *et al.* Lancet Oncol 2018

Ricerca / Innovazione

vs

Pratica Clinica

Neoadjuvant chemotherapy for breast cancer in Italy: A Senonet network analysis of 37,215 patients treated from 2017 to 2022

A. De Luca^a, M.I. Amabile^{a,*}, F. Santori^{b,c}, S. Di Matteo^{b,d}, M. Tomatis^e, A. Ponti^e, F. Frusone^a, M. Taffurelli^f, C. Tinterri^g, L. Marotti^h, M. Calabreseⁱ, C. Marchiò^{j,k}, F. Puglisi^{l,m}, I. Palumboⁿ, L. Fortunato^b, the Senonet Collaborative Group*

Received 1 July 2024; Received in revised form 16 August 2024; Accepted 23 August 2024
Available online 30 August 2024

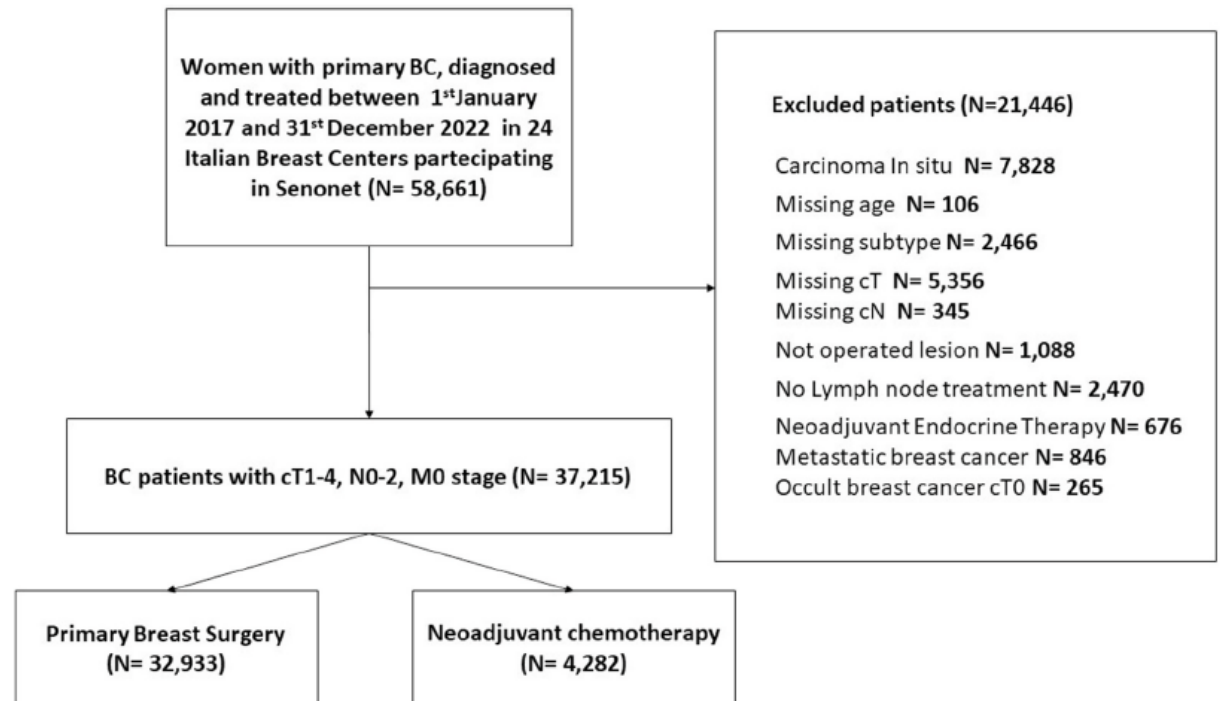
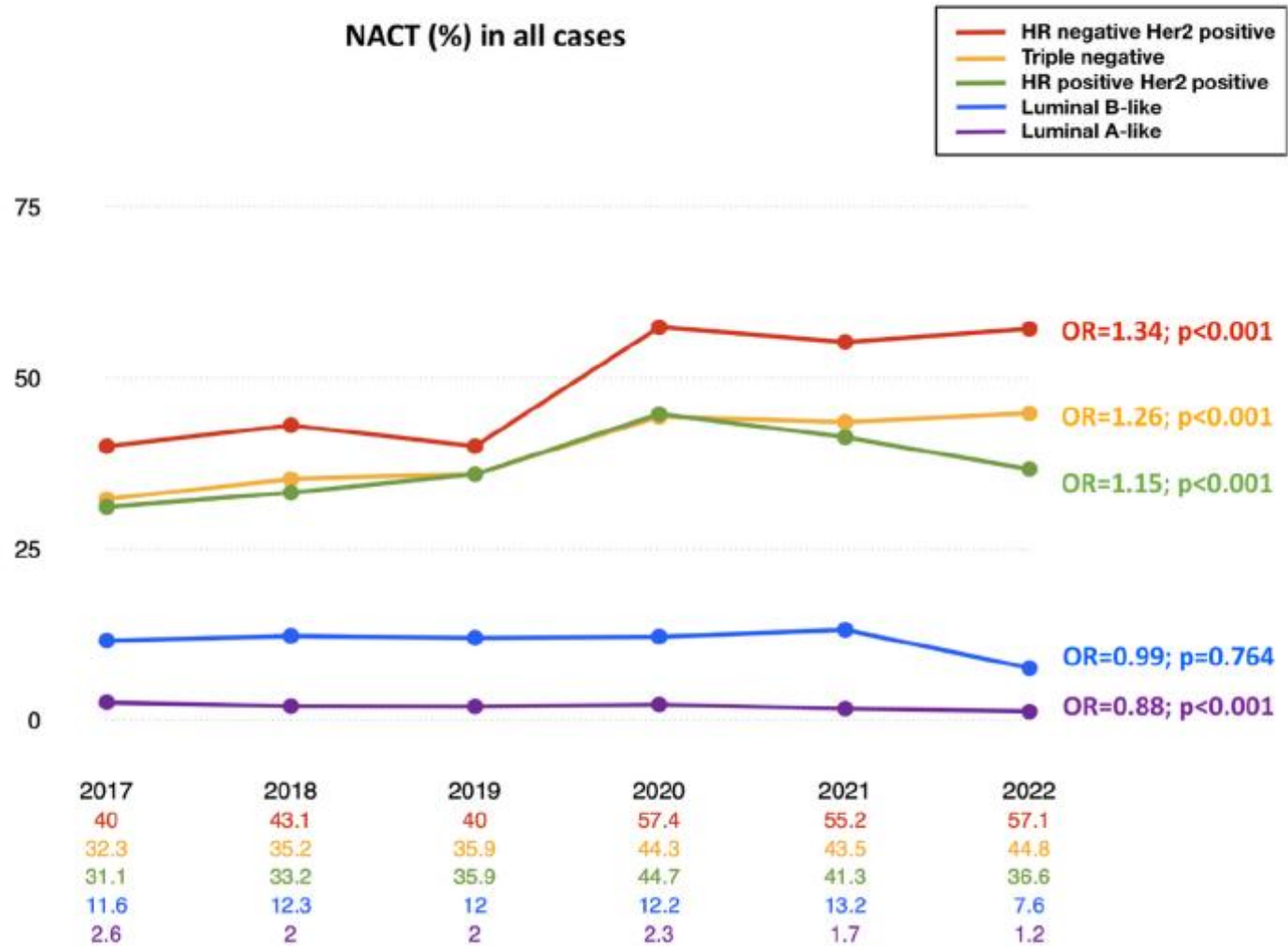
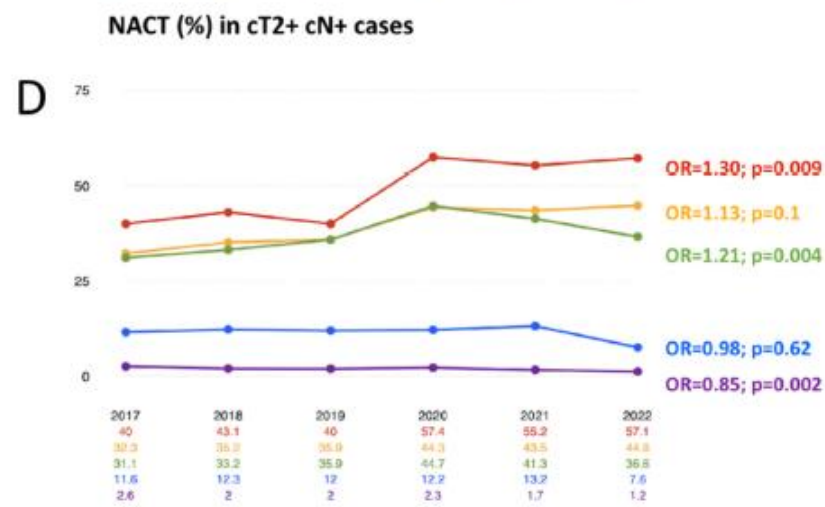
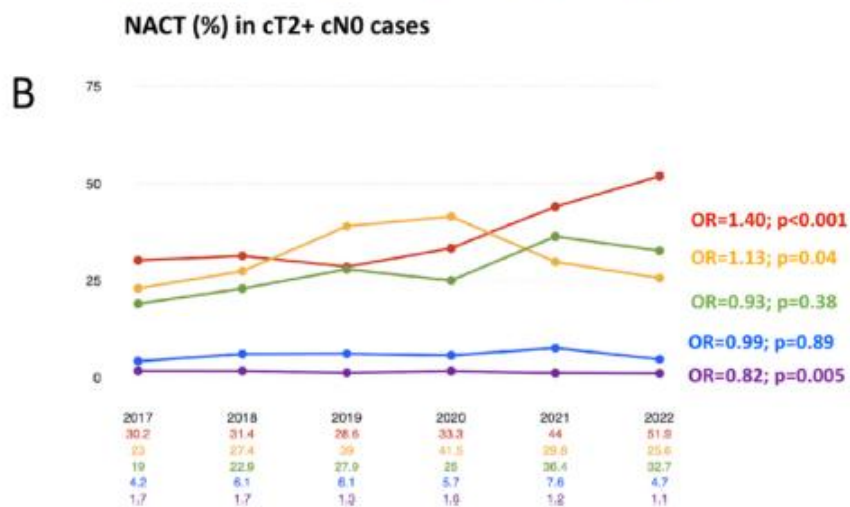
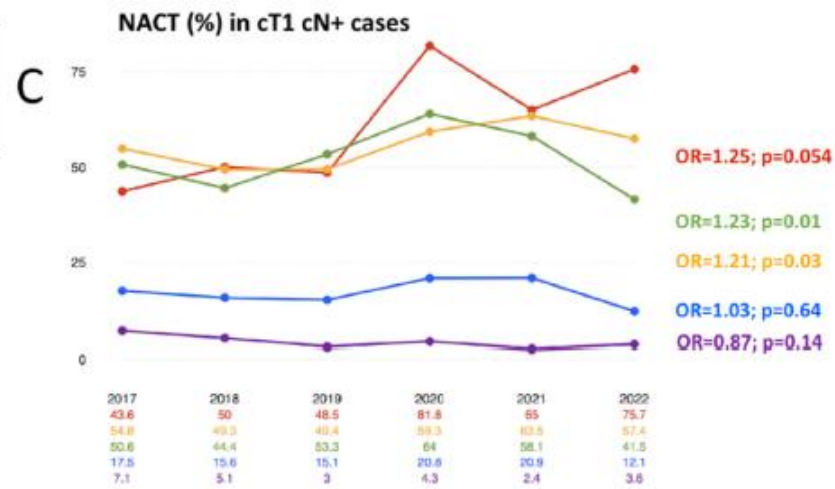
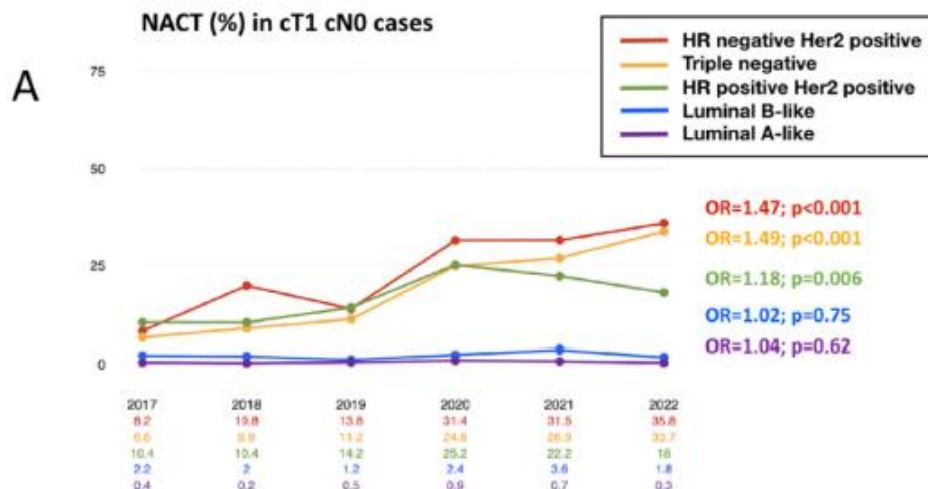


Fig. 1. Flowchart of patients selection.

% NACT per year from 2017 to 2022 by molecular subtypes in 24 Senonetwork high-volume centers



% NACT per year from 2017 to 2022 by molecular subtypes in 24 Senonetwork high-volume centers



ADVANCES

IN

BREAST

CANCER

THE

DEBATE

UDINE 19-20 SETTEMBRE 2025

La terapia **neoadiuvante** è lo **standard di trattamento** nel carcinoma mammario **HER2 positivo** in stadio precoce*

*Dati insufficienti per i cT1a-b N0

Non proporre la terapia neoadiuvante significa negare un'importante opportunità terapeutica

Il problema è clinico-scientifico, ma anche organizzativo. La capacità di mettere in atto un percorso corretto di terapia neoadiuvante è il vero banco di prova di un team multidisciplinare