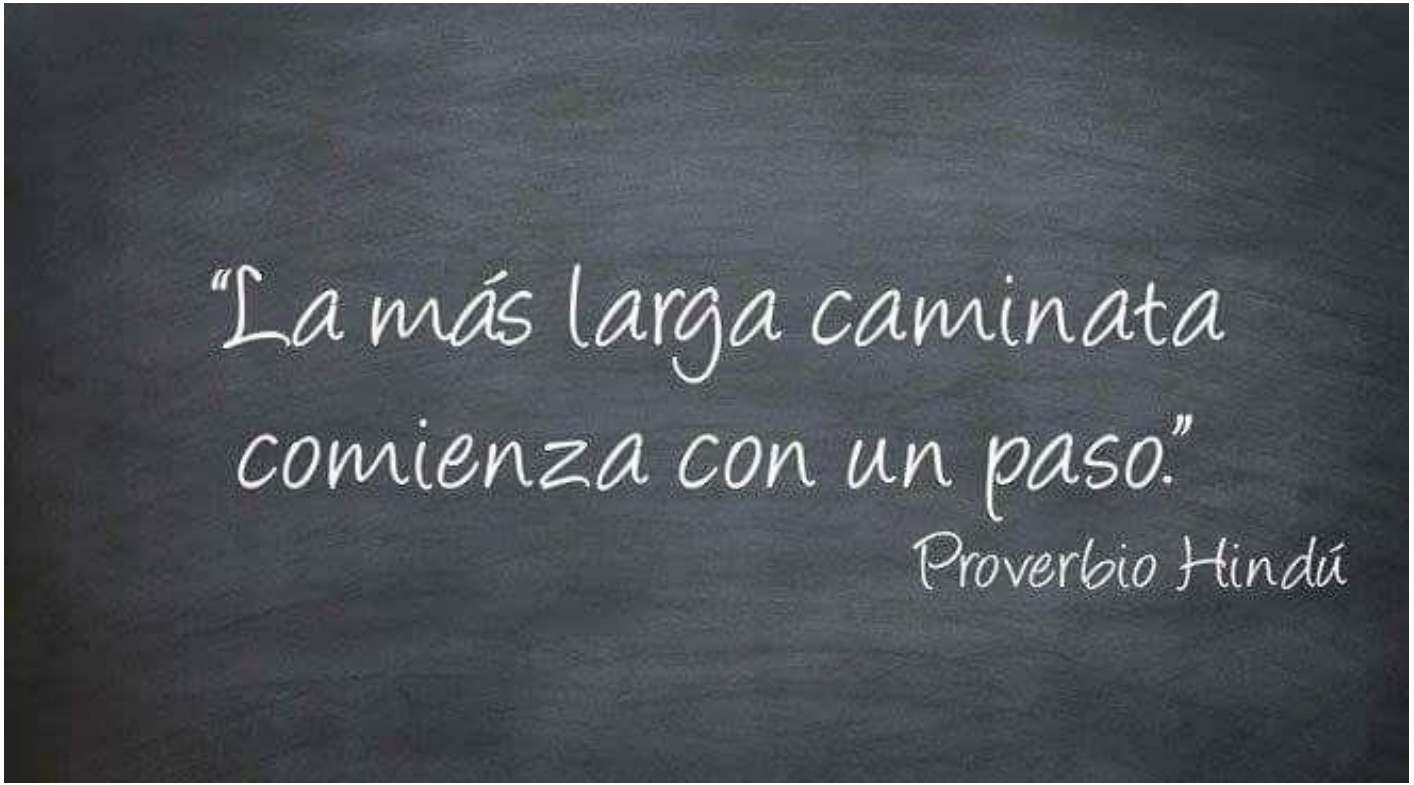
XV SIMPOSIUM
BASES BIOLÓGICAS DEL CÁNCER
E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

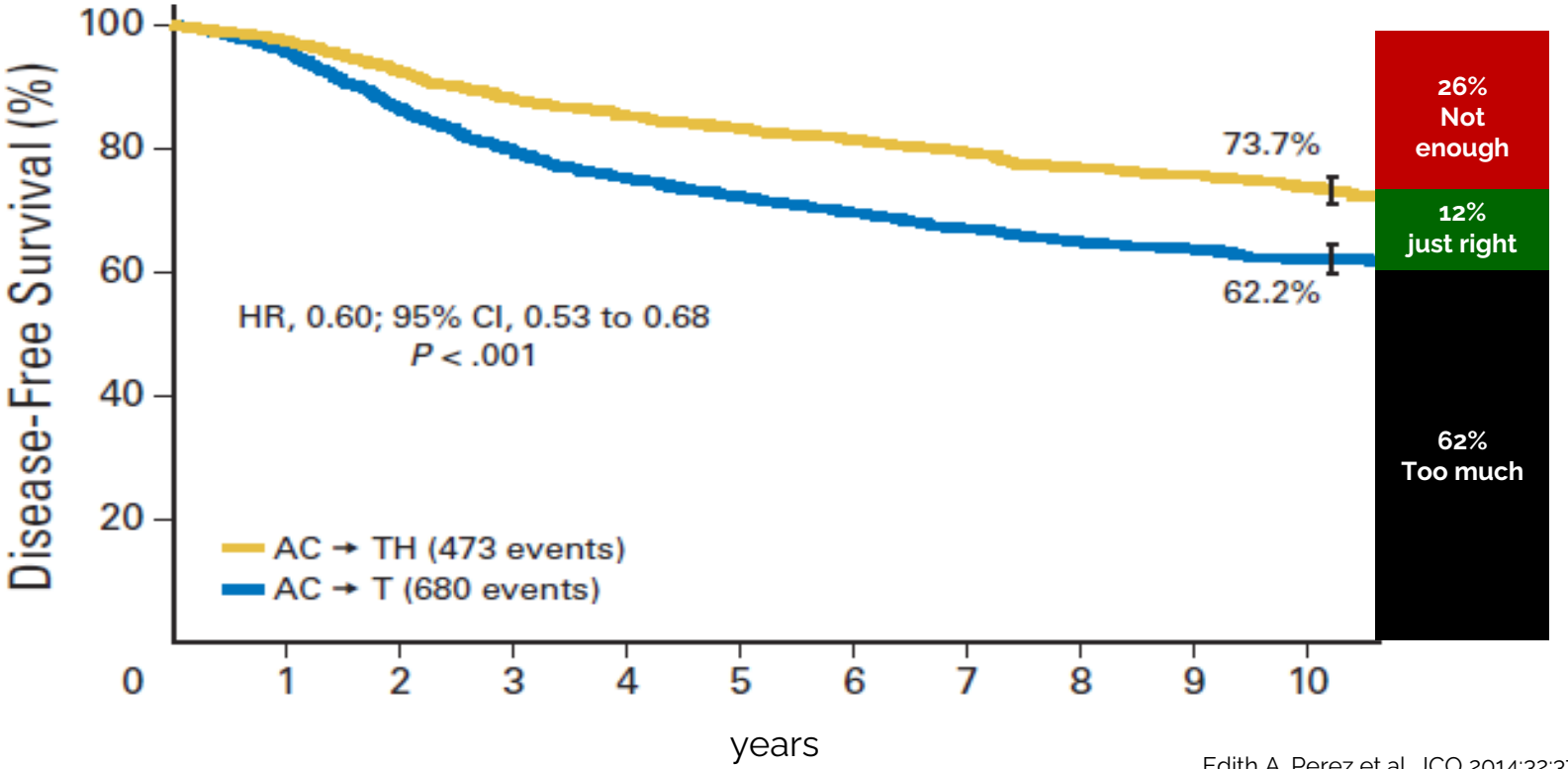
17, 18 Y 19 DE MAYO DE 2023

Optimizando el tratamiento del cáncer de mama Her2 positivo en estadios tempranos. ¿A quiénes más y a quiénes menos?

Fernando Moreno Antón
Servicio de Oncología Médica
Hospital Clínico San Carlos


"La más larga caminata
comienza con un paso."
Proverbio Hindú

Unmet Medical Need Remains in HER2+ EBC



Edith A. Perez et al. JCO 2014;32:3744-3752

De-escalation of treatment (reducing toxicity)

- Shortening adjuvant trastuzumab
- Less toxic chemotherapy
- Avoiding treatment of “low risk” patients
- Optimizing trastuzumab administration
- Economic toxicity (biosimilars)

Escalation (increasing efficacy)

- Increasing duration of trastuzumab
- Addition of lapatinib
- Addition of neratinib
- Addition pertuzumab
- Addition of T-DM1

De-escalation of treatment (reducing toxicity)

- **Shortening adjuvant trastuzumab**
- **Less toxic chemotherapy**
- Avoiding treatment of “low risk” patients
- **Optimizing trastuzumab administration**
- **Economic toxicity (biosimilars)**

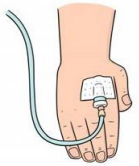
Escalation (increasing efficacy)

- Increasing duration of trastuzumab
- Addition of lapatinib
- **Addition of neratinib**
- **Addition pertuzumab**
- **Addition of T-DM1**

- **Definition of risk is critical in clinical decission & in the success of escalation and de-escalation clinical trials**

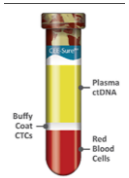
Standard Clinical & Pathological features

Response to neoadjuvant therapy



Biology

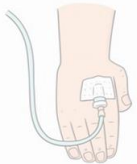
Posible role of ctDNA



- **Definition of risk is critical in clinical decission & in the success of escalation and de-escalation clinical trials**

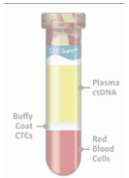
Standard Clinical & Pathological features

Response to neoadjuvant therapy



Biology

Posible role of ctDNA



HER2 + stage I-III Breast Cancer

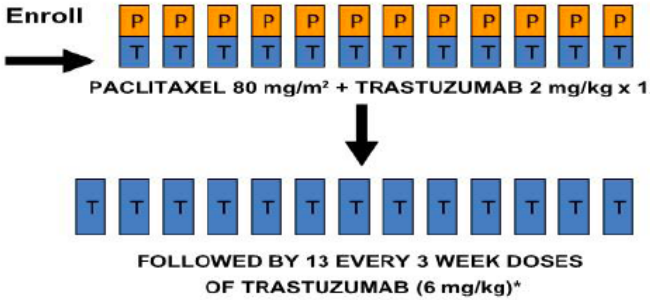
Surgery

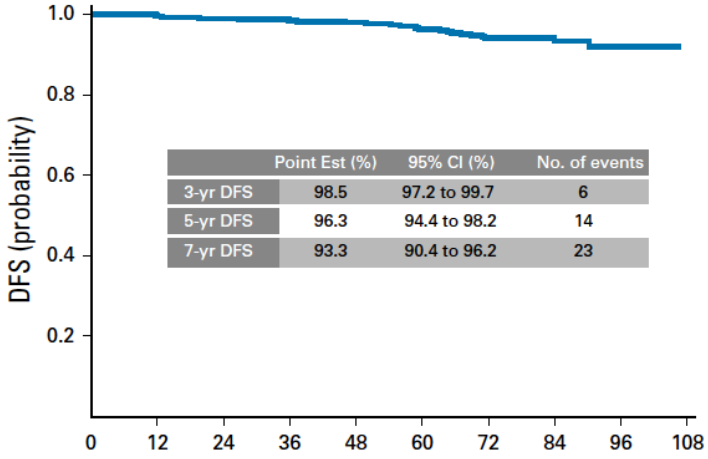
pT1N0

APT Trial: Study Design

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400





	Point Est (%)	95% CI (%)	No. of events
3-yr DFS	98.5	97.2 to 99.7	6
5-yr DFS	96.3	94.4 to 98.2	14
7-yr DFS	93.3	90.4 to 96.2	23

Tolaney S, JCO 2019

HER2 + stage I-III Breast Cancer

Surgery

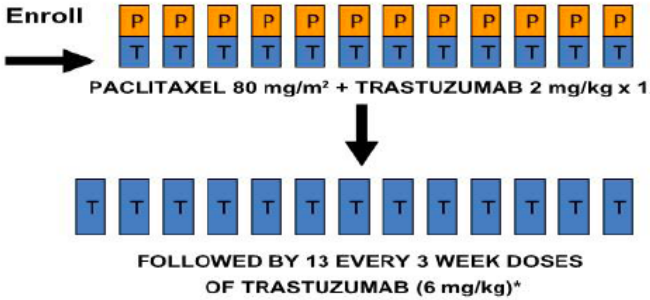
pT1N0

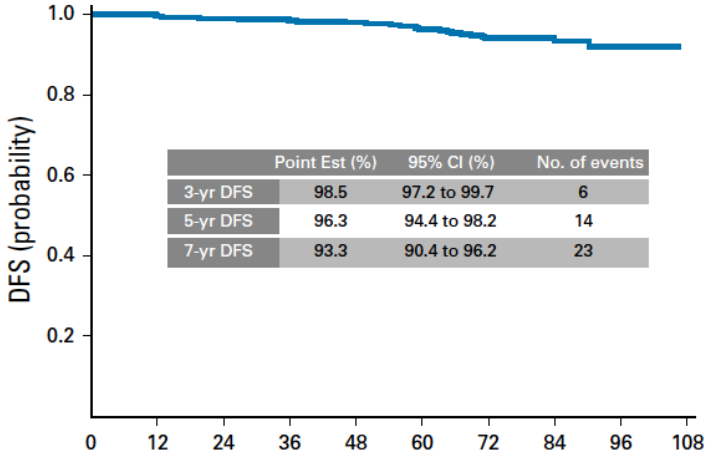
T + paclitaxel

APT Trial: Study Design

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

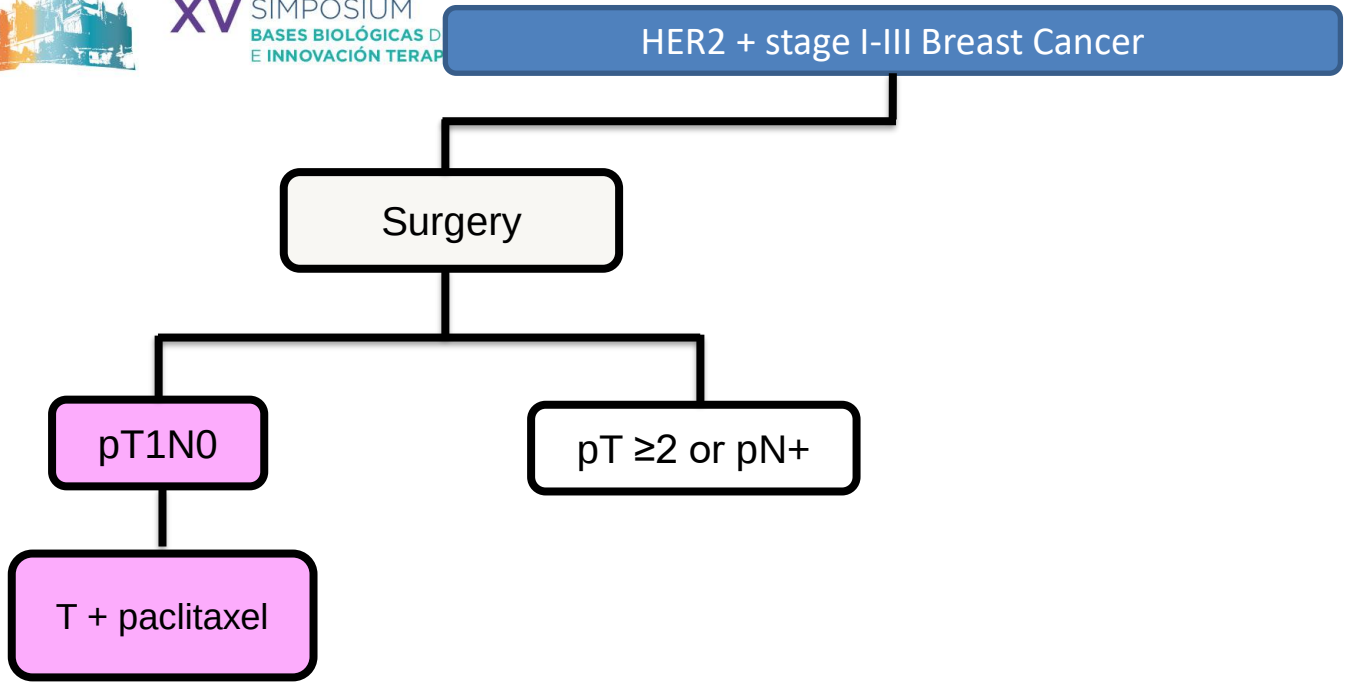
Planned N=400



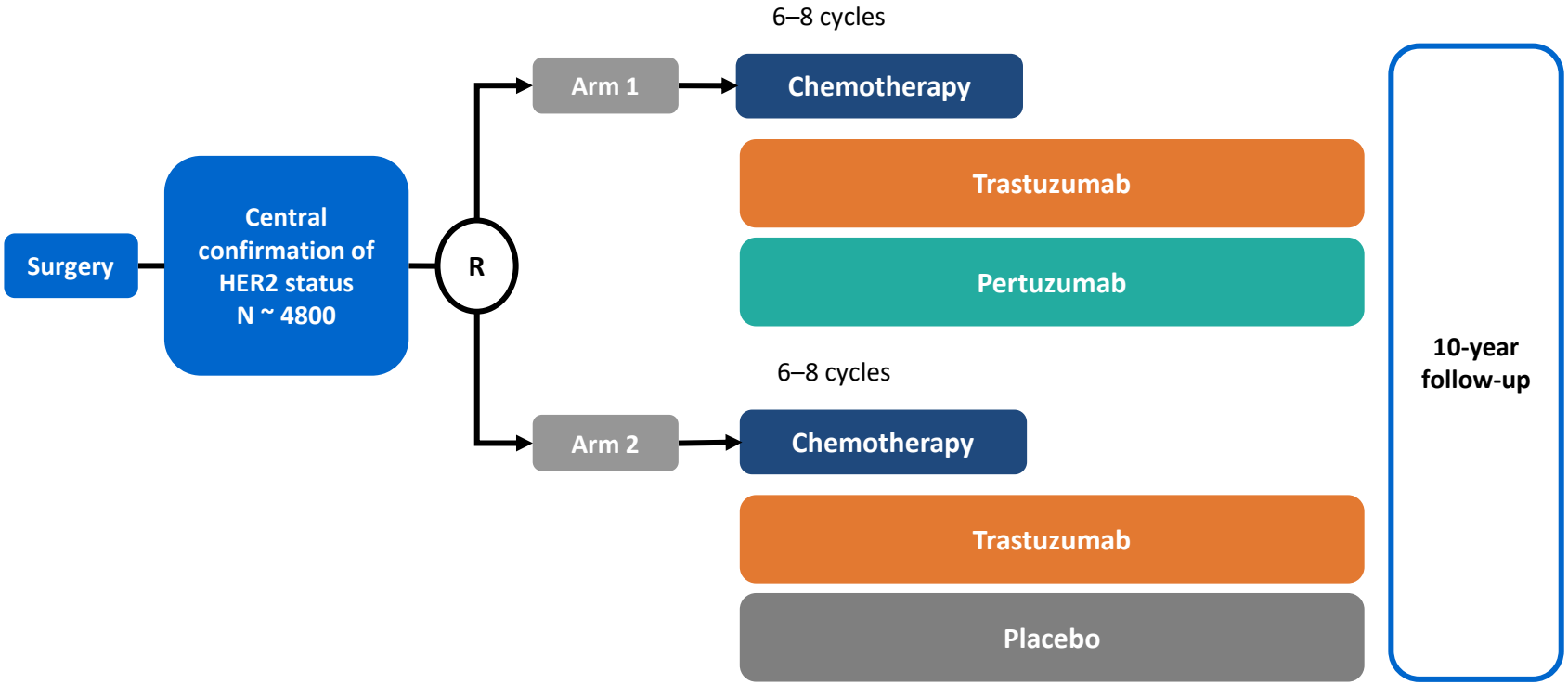


	Point Est (%)	95% CI (%)	No. of events
3-yr DFS	98.5	97.2 to 99.7	6
5-yr DFS	96.3	94.4 to 98.2	14
7-yr DFS	93.3	90.4 to 96.2	23

Tolaney S, JCO 2019


HER2 + stage I-III Breast Cancer
Surgery
pT1N0
pT ≥2 or pN+
T + paclitaxel

Aphinity Trial: Design

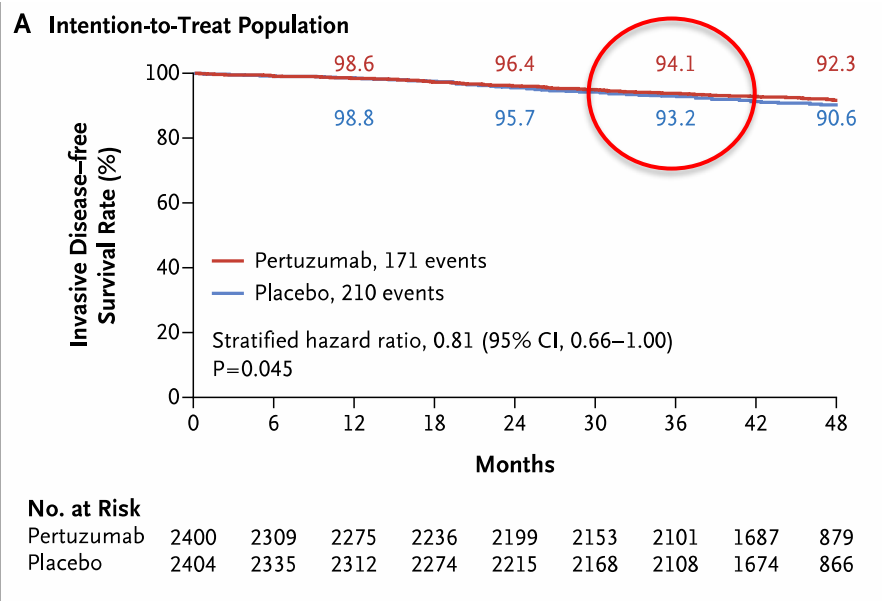


Anti-HER2 therapy for a total of 1 year (18 cycles)

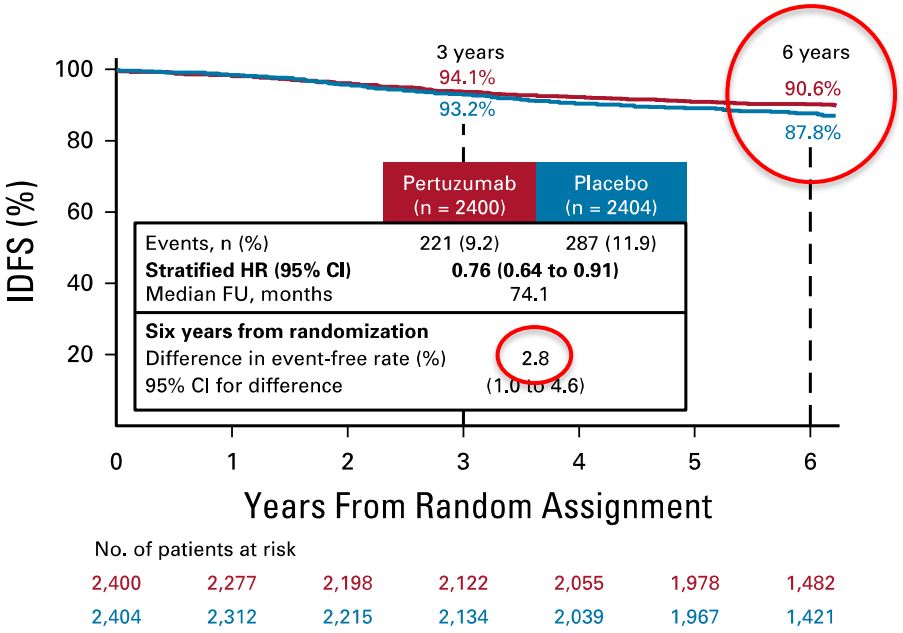
- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS including second non-breast cancer, DFS, OS, recurrence-free interval, distant recurrence-free interval, cardiac and overall safety, HRQoL

Aphinity Trial: Results

iDFS after 45.2 months of FU (2017)



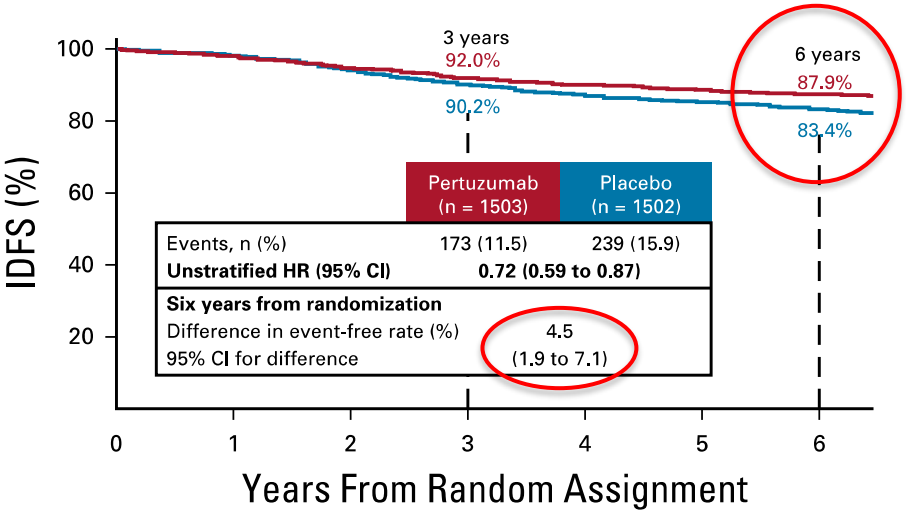
Updated descriptive iDFS analysis after 74.1 months of FU (2019)



von Minckwitz G, NEJM 2017; Piccart M, JCO 2021

Aphinity Trial: Results

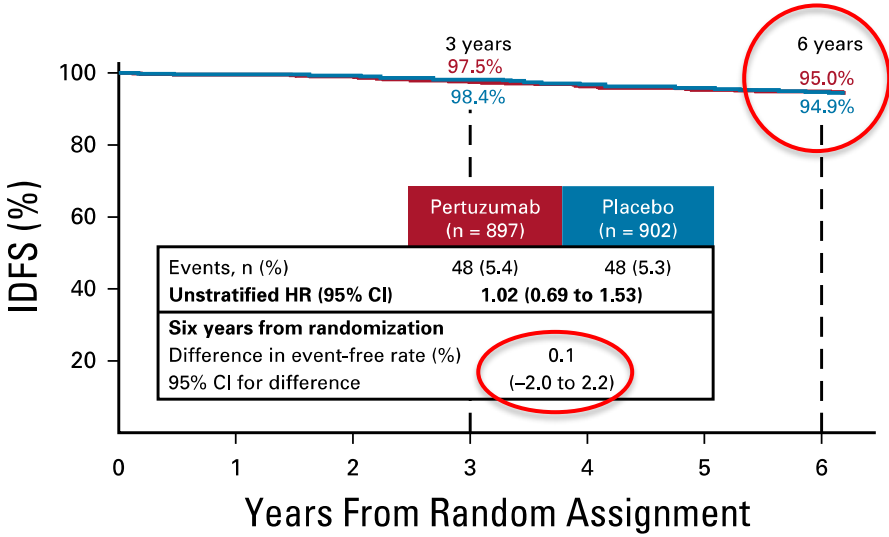
IDFS in the node-positive cohort



No. patients at risk

1,503	1,420	1,357	1,301	1,257	1,205	814
1,502	1,439	1,359	1,288	1,223	1,176	741

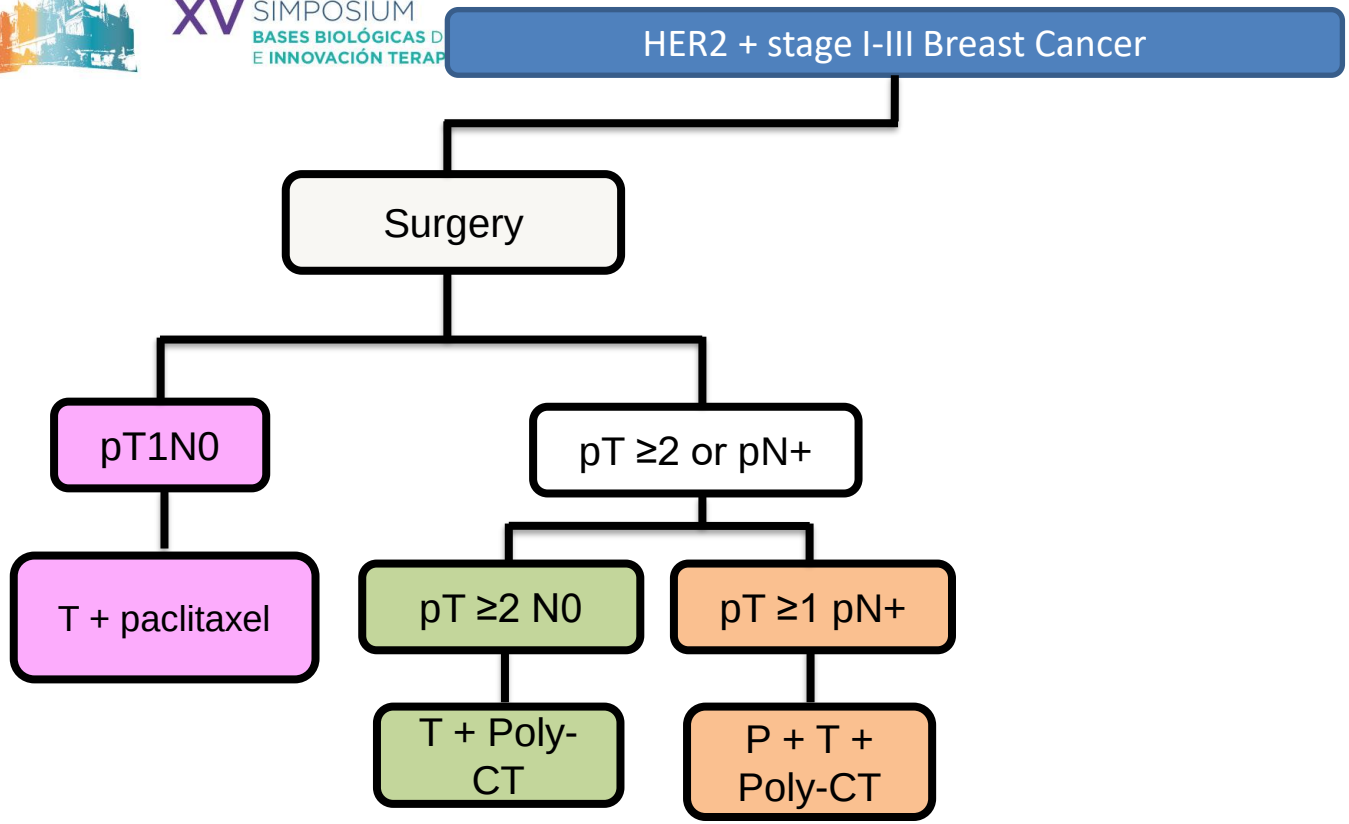
IDFS in the node-negative cohort



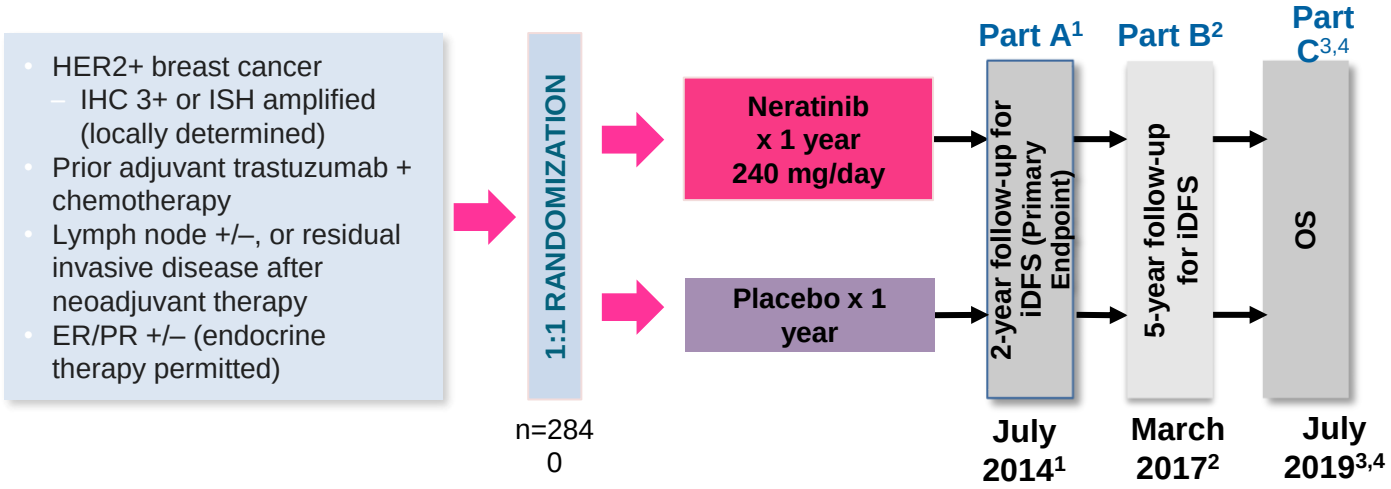
No. patients at risk

897	857	841	821	798	773	668
902	873	856	846	816	791	680

Piccart M, JCO 2021


HER2 + stage I-III Breast Cancer
Surgery
pT1N0
pT ≥2 or pN+
T + paclitaxel
pT ≥2 N0
pT ≥1 pN+
T + Poly-CT
P + T + Poly-CT

ExteNET phase III trial: Study design

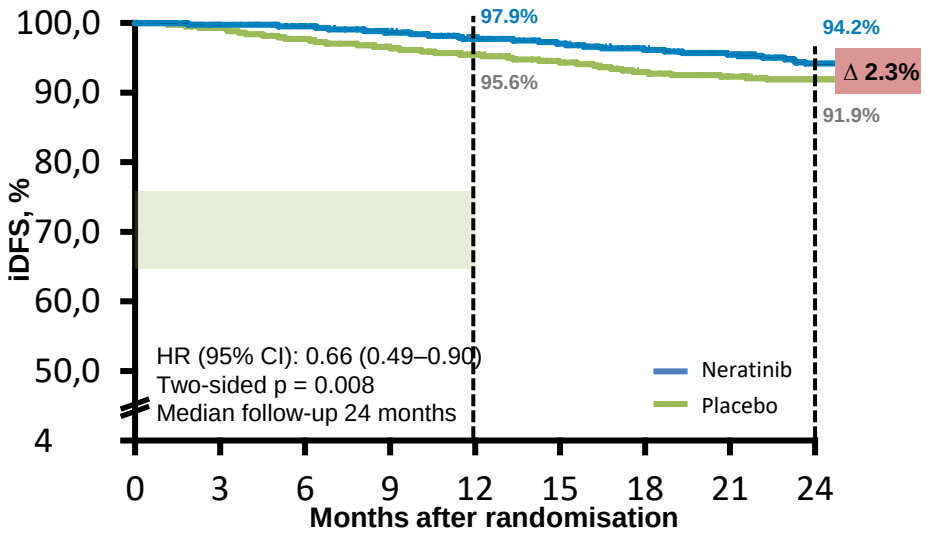


- **Primary endpoint:** invasive disease-free survival (iDFS)
- **Secondary endpoints:** DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, OS, safety
- **Other analyses:** biomarkers, health outcome assessment (FACT-B, EQ-5D)
- **Stratified by:** nodes 0, 1–3 *vs.* 4+, ER/PR status, concurrent *vs.* sequential trastuzumab
- Study blinded: Until primary analysis; OS remains blinded

1. Chan et al. Lancet Oncology 201.
2. Martin et al. Lancet Oncology 2017.
3. Chan et al. Clinical Breast Cancer 2020.
4. Holmes et al. SABCS 2020 PD3-03

ExteNET Primary Endpoint: iDFS Intention-to-treat Population 2-Year Analysis and 5-Year Analysis

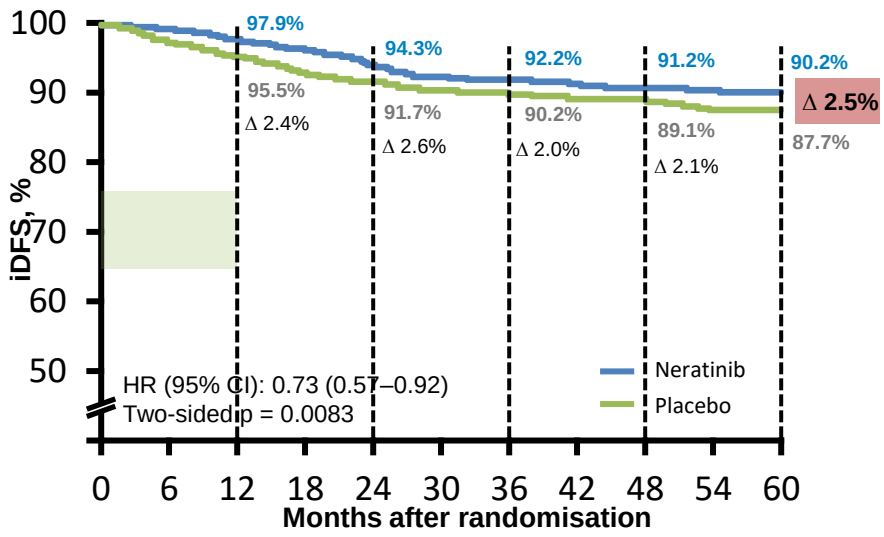
ITT iDFS 2-year analysis[1]



No. at risk

Neratinib	1420	1288	1257	1227	1188	1150	1108	1033	662
Placebo	1420	1367	1323	1291	1242	1206	1161	1089	704

ITT iDFS 5-year analysis[2]



No. at risk

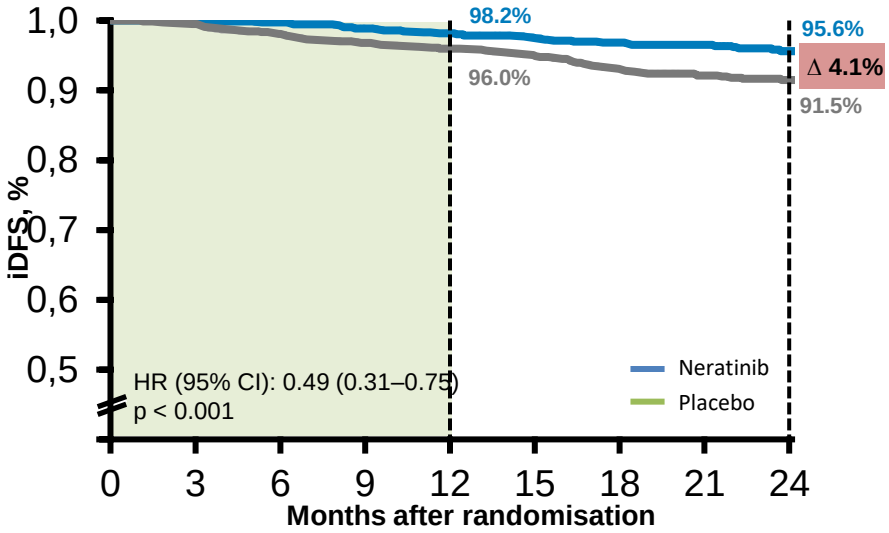
Neratinib	1420	1316	1272	1225	1106	978	965	949	938	920	885
Placebo	1420	1354	1298	1248	1142	1029	1011	991	978	958	927

CI, confidence interval; HR, hazard ratio;
iDFS, invasive disease-free survival; ITT, intention to treat.

1. Nerlynx (neratinib) EPAR Public Assessment Report. European Medicines Agency. 13 July 2018. EMA/CHMP/525204/2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/nerlynx-epar-public-assessment-report_en.pdf; 2. Martin M, et al. Lancet Oncol. 2017;18:1688–1700.

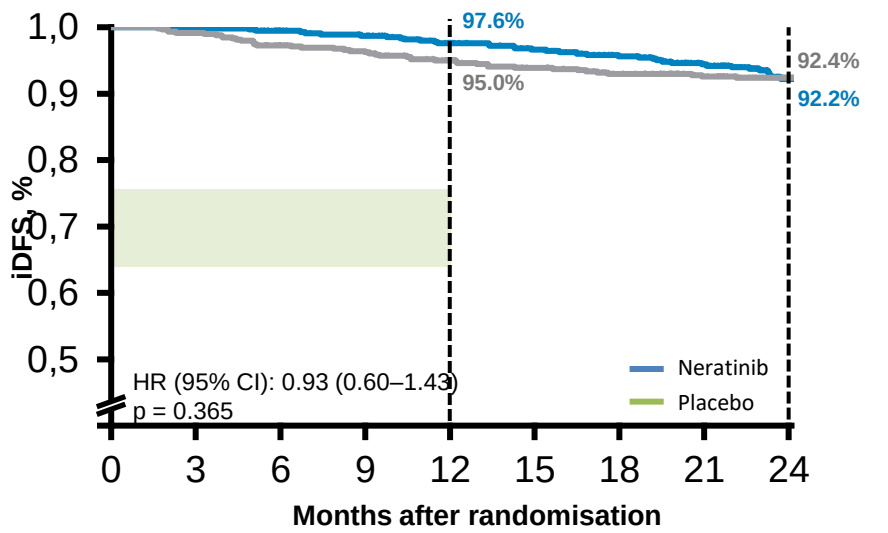
ExteNET 2-year Analysis: the absolute iDFS advantage with neratinib in the HR+ subgroup is up to 4.1%

HR+



No. at risk									
Neratinib	816	735	719	697	677	653	629	591	380
Placebo	815	784	760	740	715	697	668	621	401

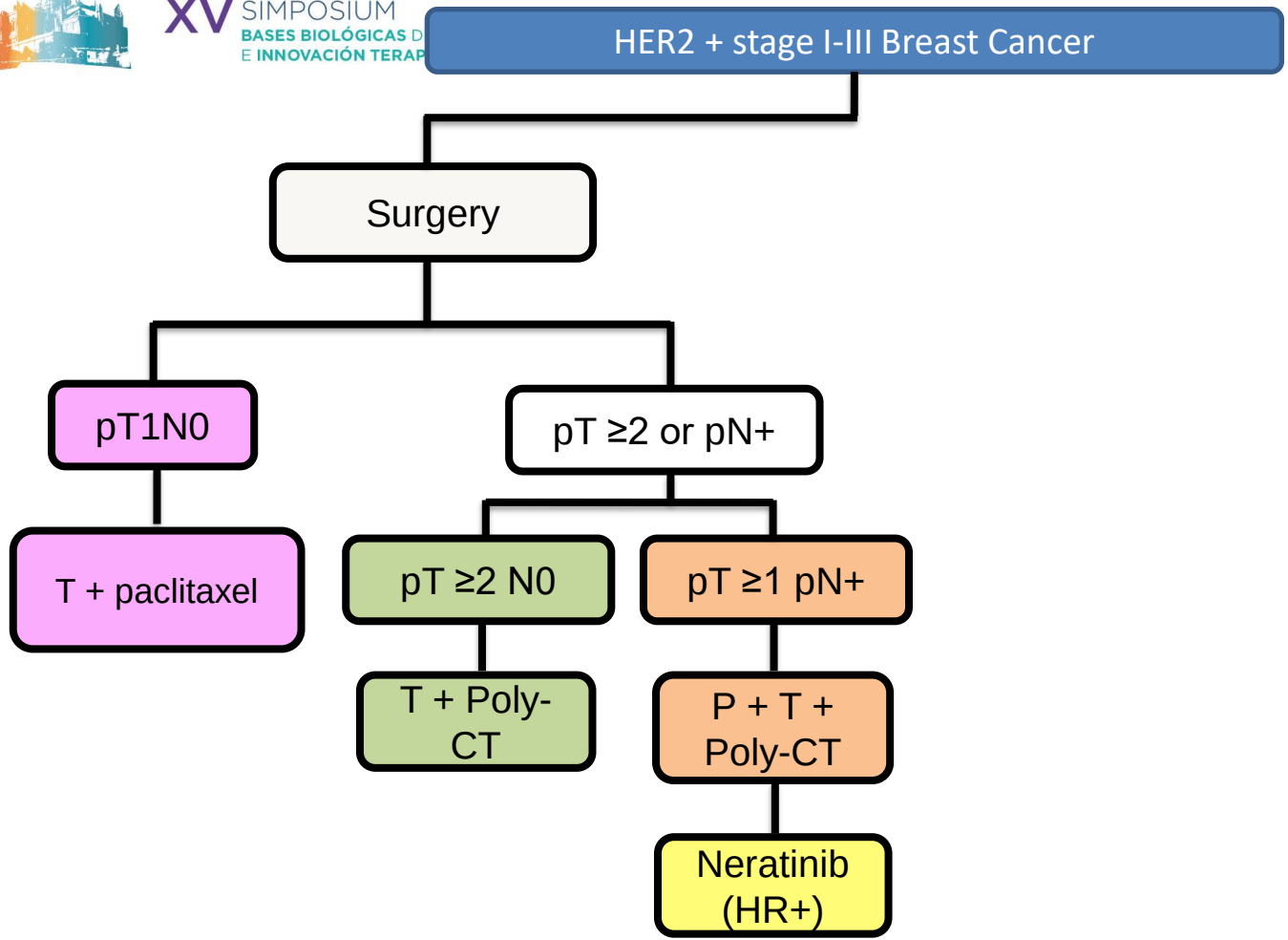
HR-



No. at risk									
Neratinib	604	553	538	530	511	497	479	442	282
Placebo	605	583	563	551	527	509	493	468	303

CI, confidence interval; HR, hazard ratio; HR+, hormone receptor positive; HR-, hormone receptor negative; iDFS, invasive disease-free survival.

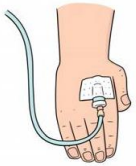
Nerlynx EPAR Public Assessment Report. European Medicines Agency. 13 July 2018. EMA/CHMP/525204/2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/nerlynx-epar-public-assessment-report_en.pdf;


HER2 + stage I-III Breast Cancer
Surgery
pT1N0
pT ≥2 or pN+
T + paclitaxel
pT ≥2 N0
pT ≥1 pN+
T + Poly-CT
P + T + Poly-CT
Neratinib (HR+)

- **Definition of risk is critical in clinical decission & in the success of escalation and de-escalation clinical trials**

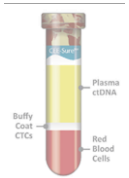
Standard Clinical & Pathological features

Response to neoadjuvant therapy

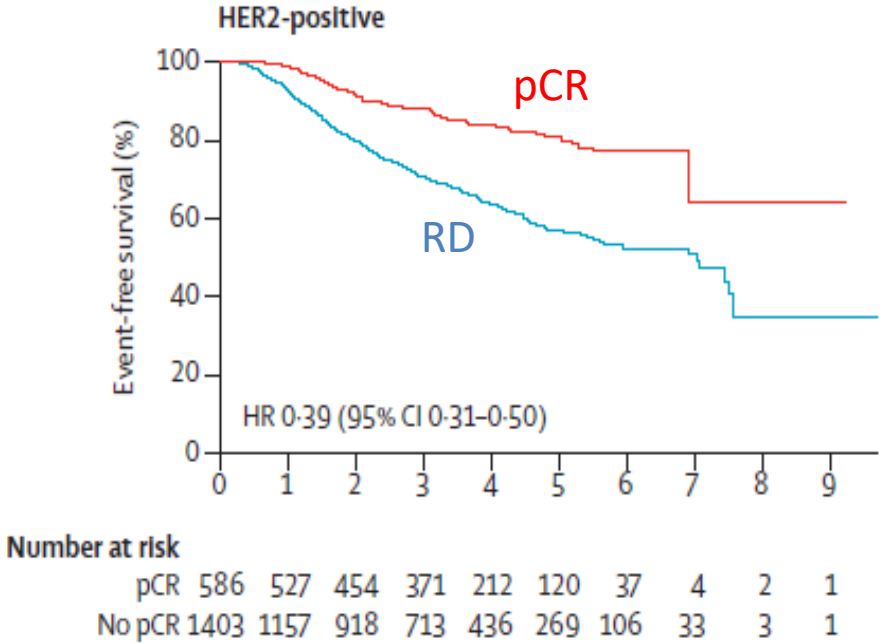


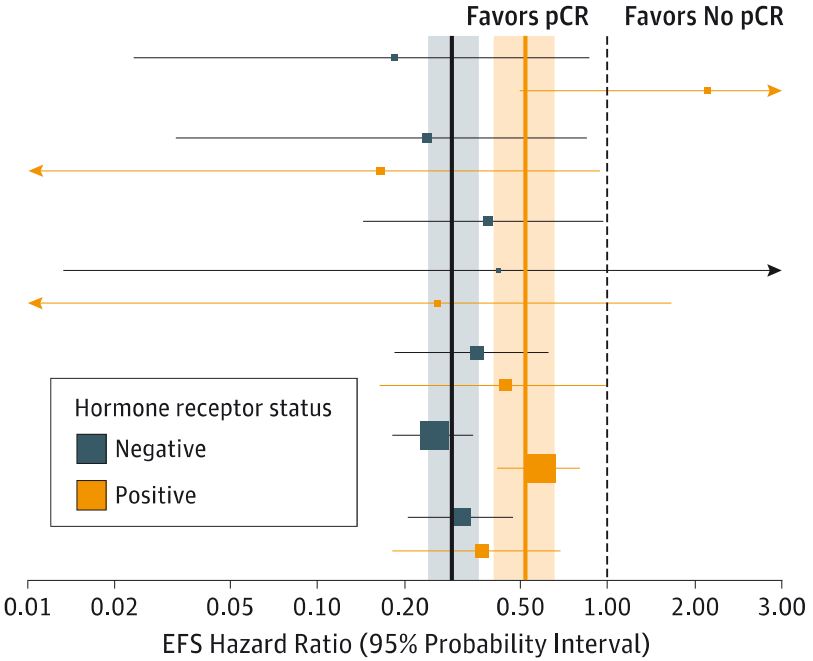
Biology

Posible role of ctDNA



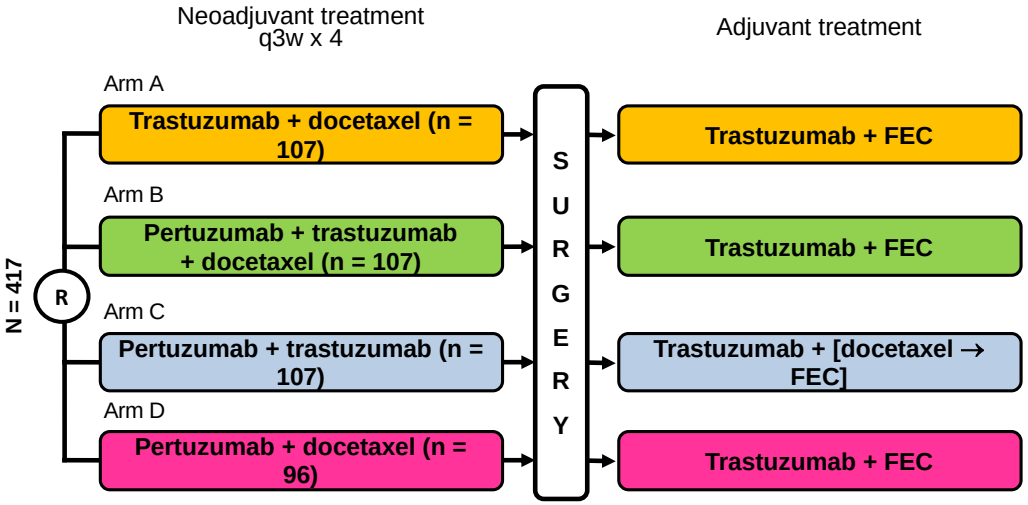
Association between pCR and EFS (patient level)



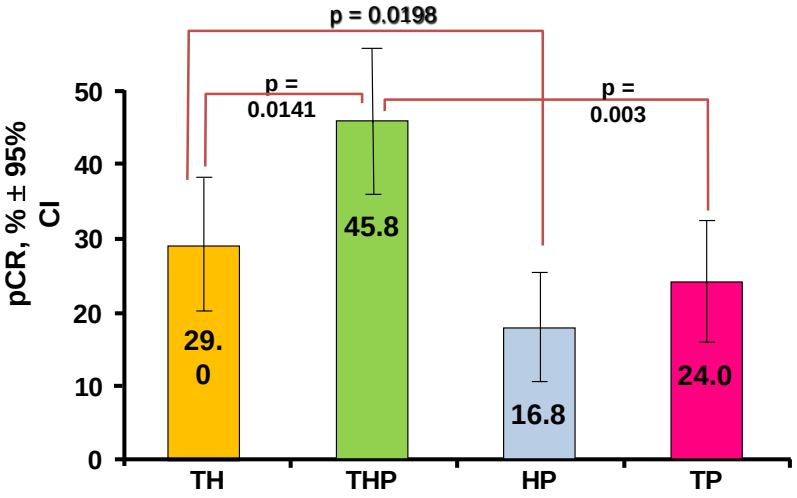


HR negative: HR 0.29 (0.24-0.36) **HR positive:** HR 0.52 (0.40-0.66)

NeoSphere: Design

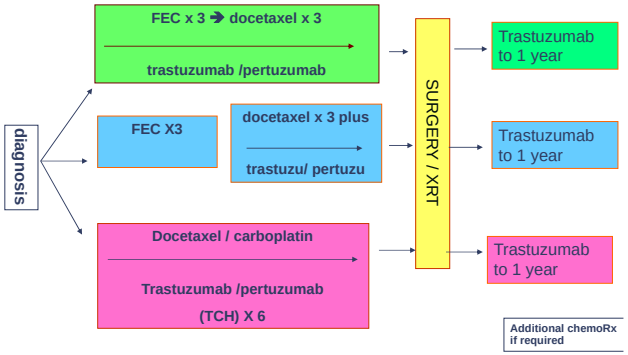


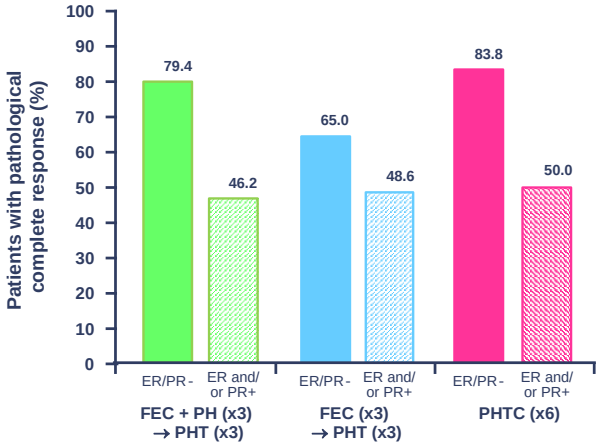
Neosphere: pCR rate (breast)



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

TRYPHAENA trial





BERENICE trial

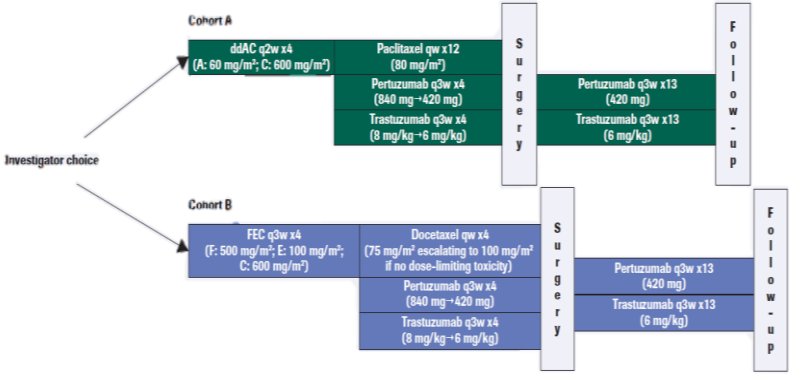
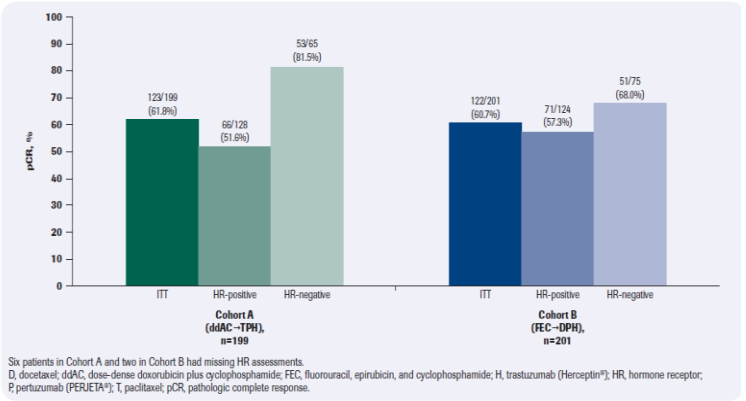
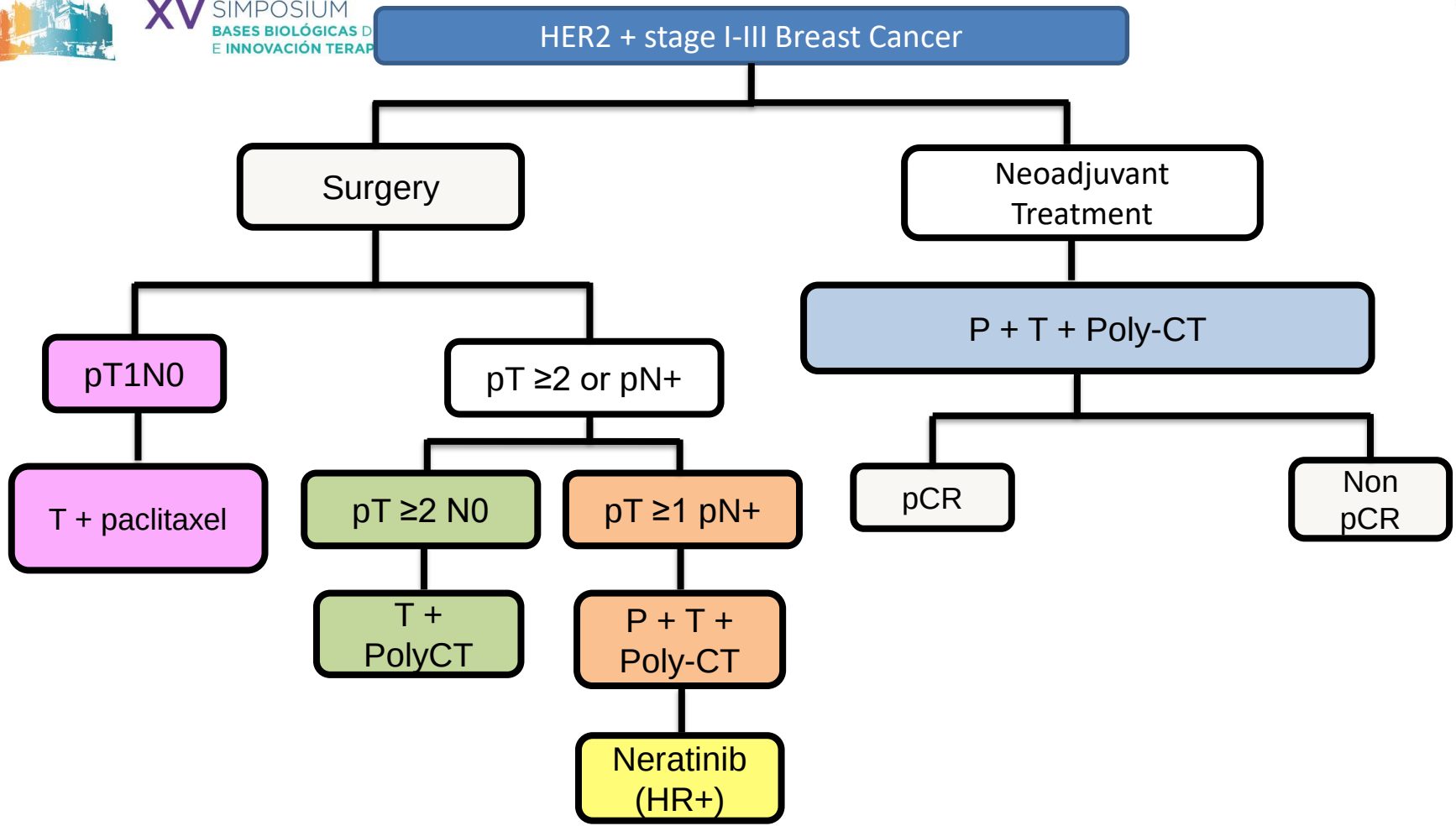


Figure 3. pCR (ypT0/is ypN0, intent-to-treat population)



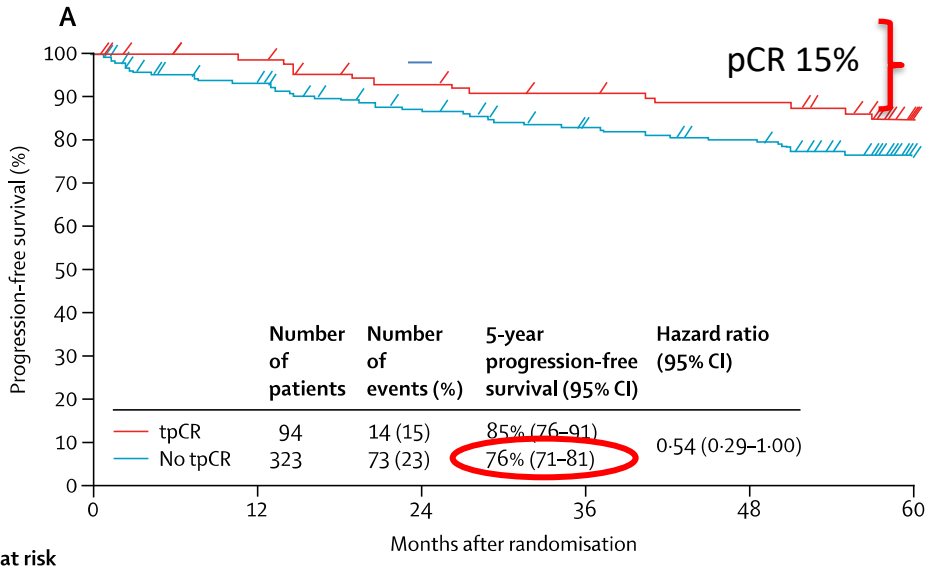
Six patients in Cohort A and two in Cohort B had missing HR assessments.
D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab (Herceptin®); HR, hormone receptor; P, pertuzumab (PERJETA®); T, paclitaxel; pCR, pathologic complete response.

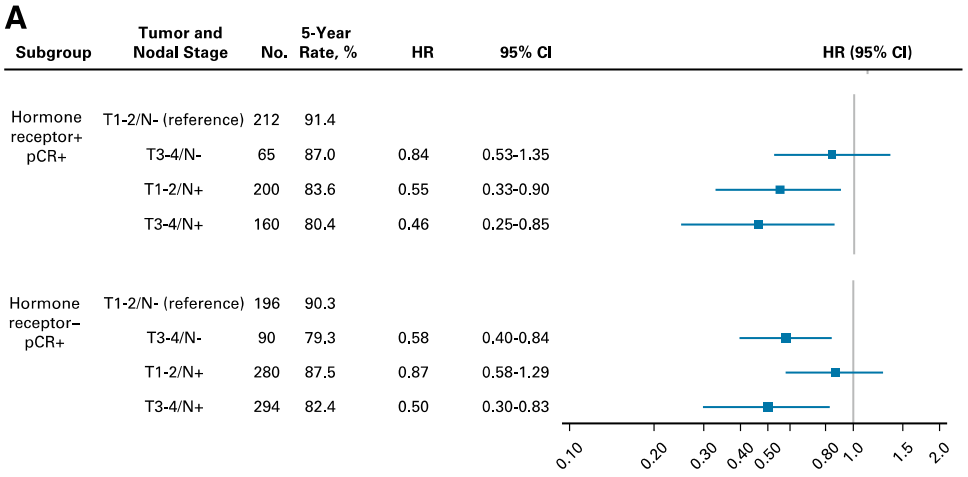
Sandra M. Swain et al., Primary analysis of Berenice, SABCS 2016; Schneeweiss, et al. SABCS 2011


HER2 + stage I-III Breast Cancer
Surgery
Neoadjuvant Treatment
pT1N0
pT ≥2 or pN+
P + T + Poly-CT
T + paclitaxel
pT ≥2 N0
pT ≥1 pN+
pCR
Non pCR
T + PolyCT
P + T + Poly-CT
Neratinib (HR+)

HER2+ EBC: Which factors predict relapse after pCR ?

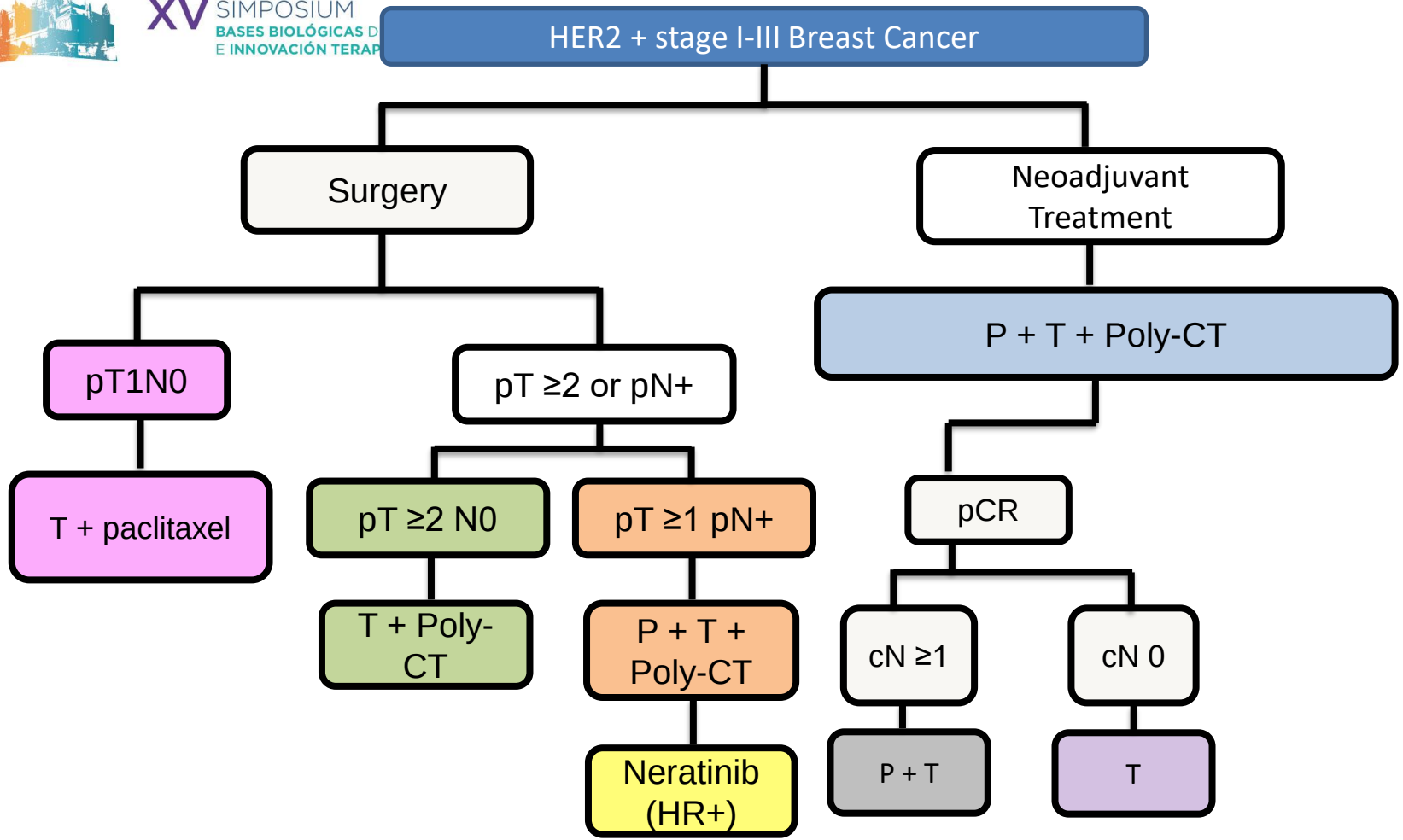
NeoSphere: DFS according pCR (No adjuvant pertuzumab)



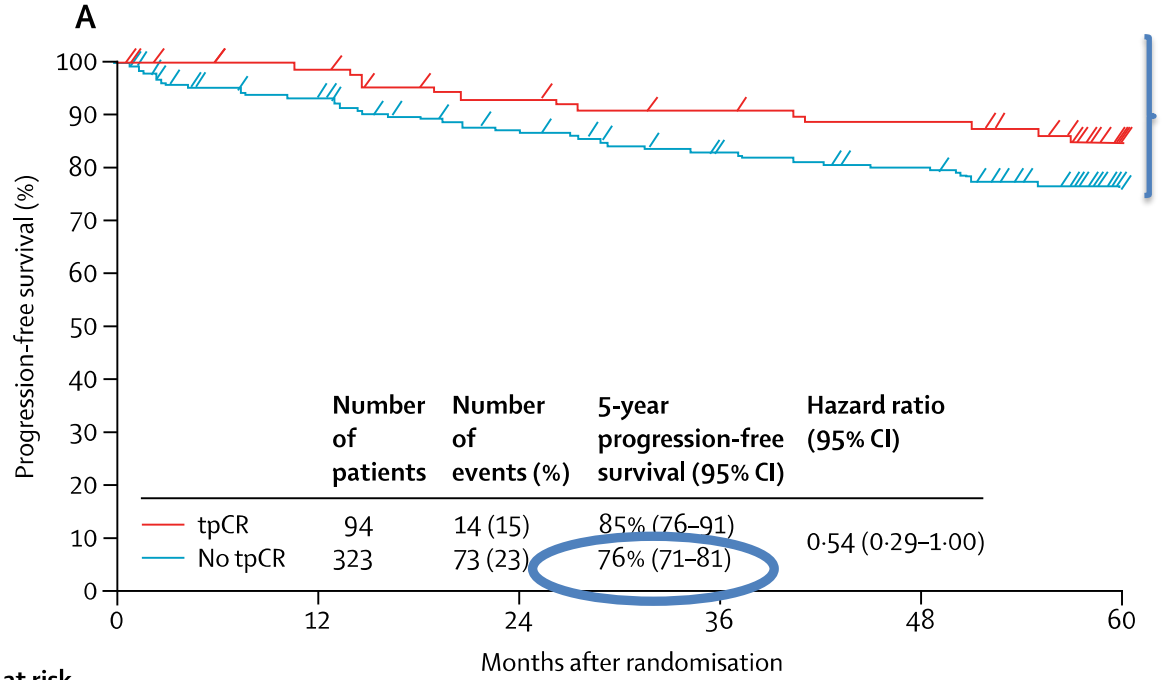


In pCR+ patients, cT and cN were significant independent prognostic factors for EFS

Gianni L et al. Lancet Oncol 2016; van Mackelenbergh MT. JCO 2023


HER2 + stage I-III Breast Cancer
Surgery
Neoadjuvant Treatment
pT1N0
pT ≥2 or pN+
P + T + Poly-CT
T + paclitaxel
pT ≥2 N0
pT ≥1 pN+
pCR
T + Poly-CT
P + T + Poly-CT
cN ≥1
cN 0
Neratinib (HR+)
P + T
T

NeoSphere: DFS according pCR

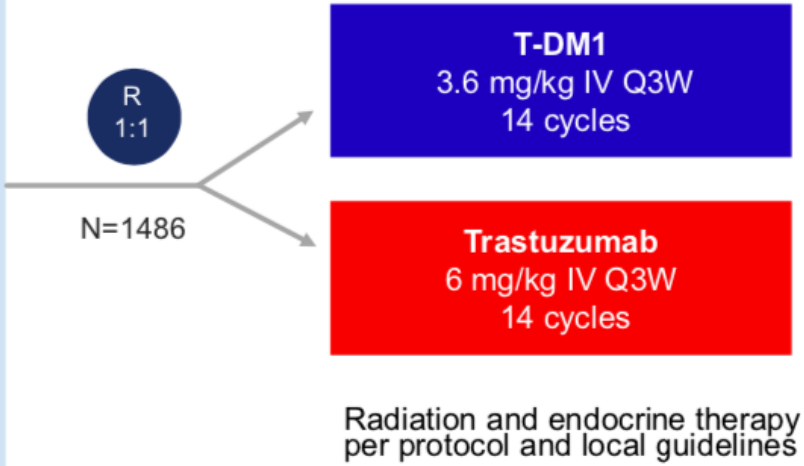


Non-pCR 24%

Gianni L et al. Lancet Oncol 2016.

KATHERINE: Study Design

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

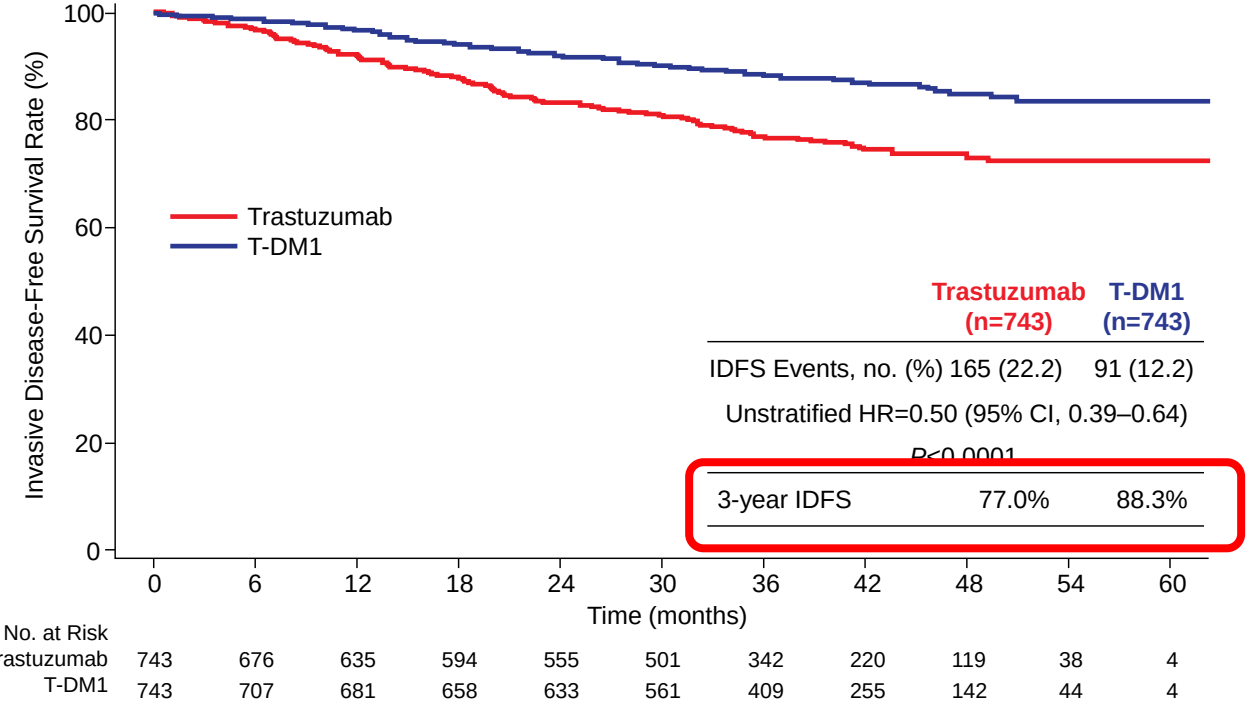


Stratification factors:

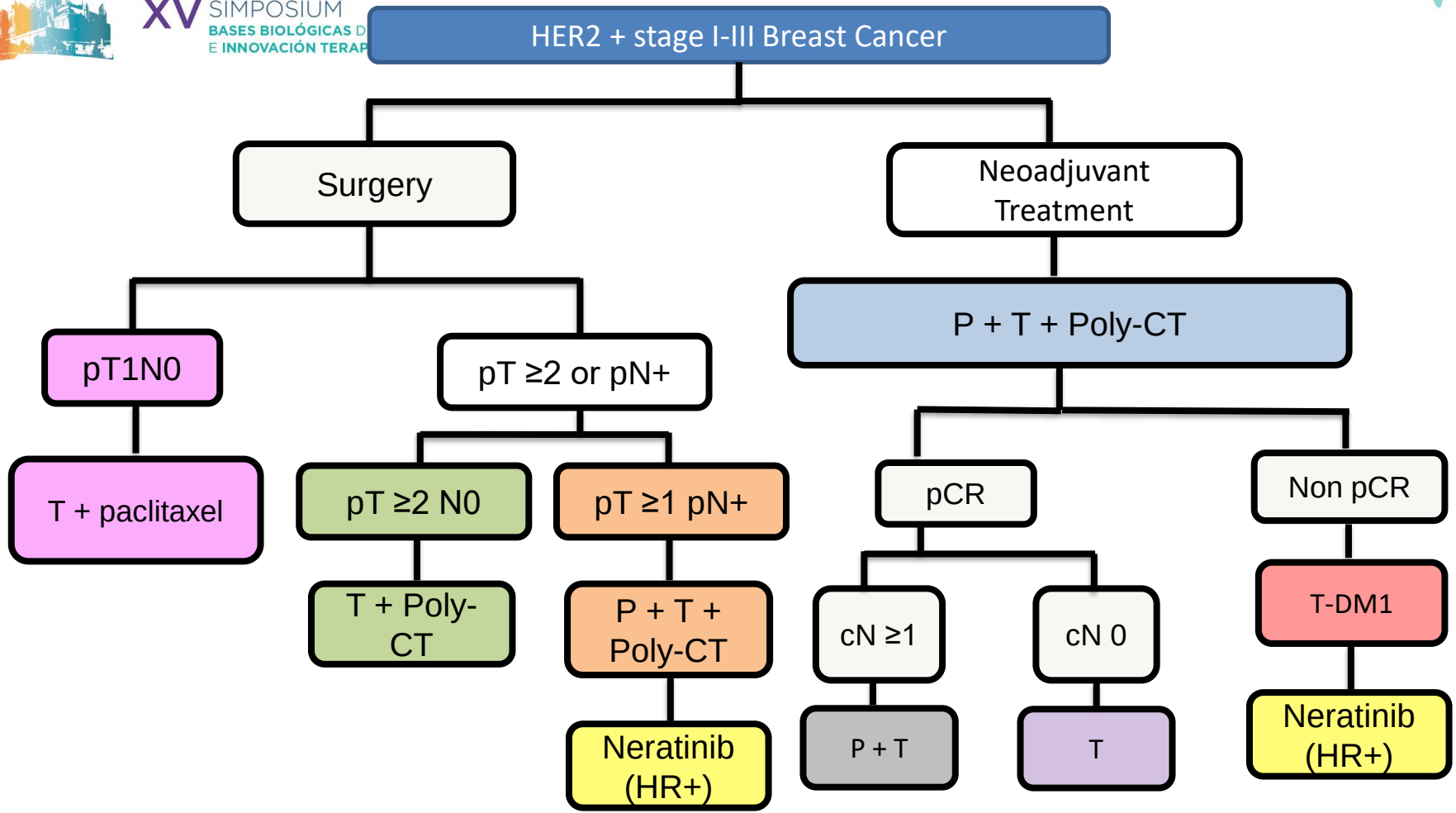
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: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

Geyer CE. ASCO 2018

KATHERINE Invasive Disease-Free Survival



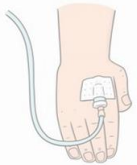
Geyer CE. ASCO 2018


HER2 + stage I-III Breast Cancer
Surgery
Neoadjuvant Treatment
pT1N0
pT ≥2 or pN+
P + T + Poly-CT
T + paclitaxel
pT ≥2 N0
pT ≥1 pN+
pCR
Non pCR
T + Poly-CT
P + T + Poly-CT
cN ≥1
cN 0
T-DM1
Neratinib (HR+)
P + T
T
Neratinib (HR+)

- **Definition of risk is critical in clinical decission & in the success of escalation and de-escalation clinical trials**

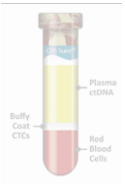
Standard Clinical & Pathological features

Response to neoadjuvant therapy

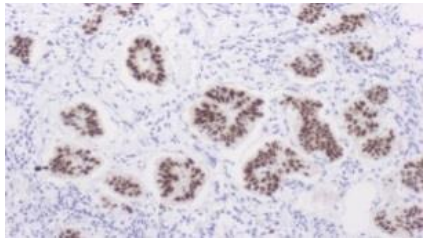


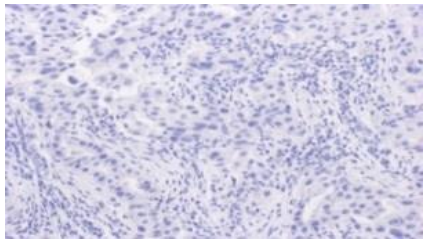
Biology

Posible role of ctDNA

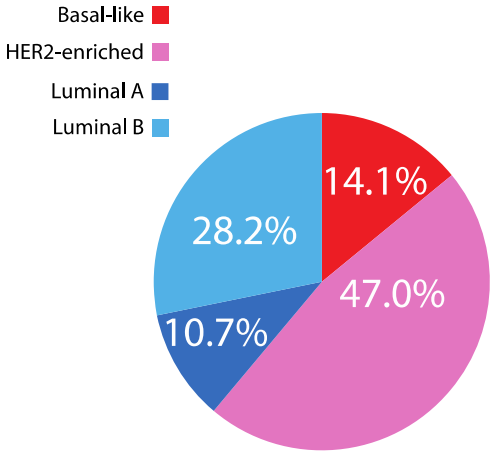


ER/PR expression

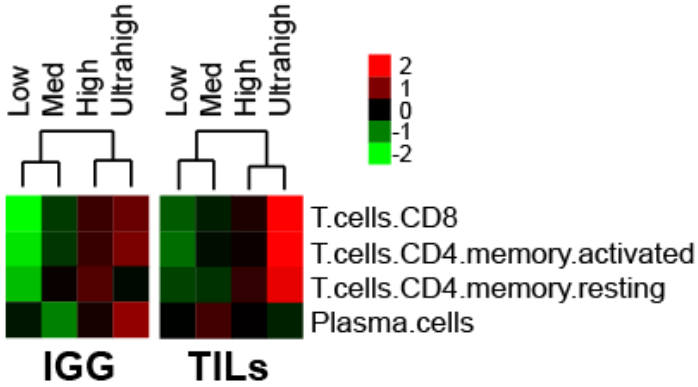




Gene expression PAM 50

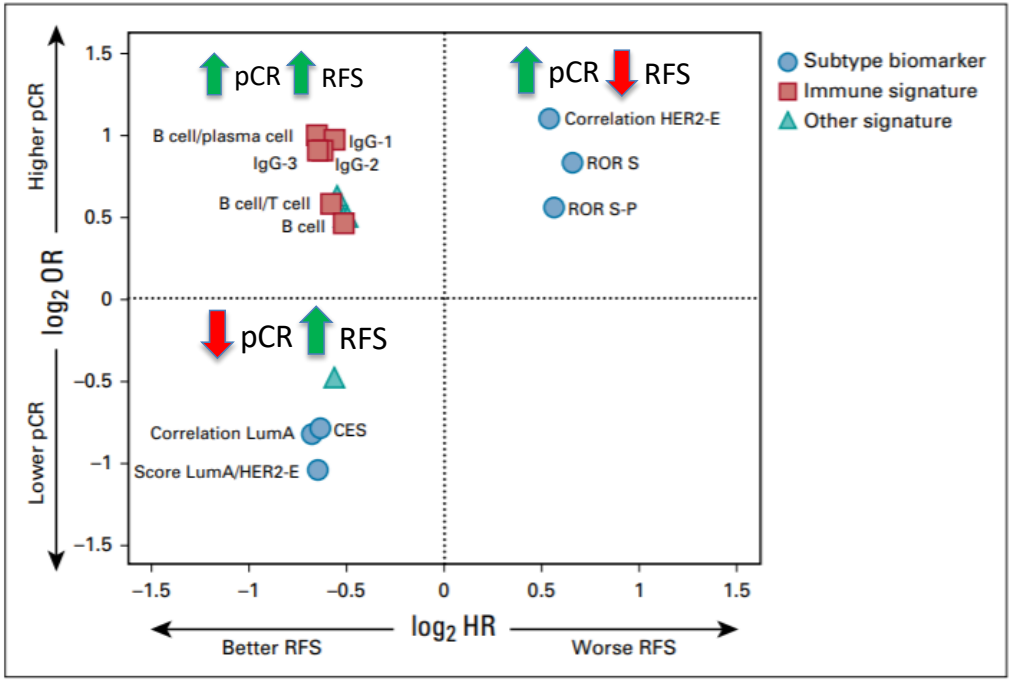


Immune signatures & TILs



Prat A, JNCI 2014; CIBERSORT from PAMELA RNAseq data, unpublished

Predicting pCR vs prognosis in CALGB40601 trial



Among **688 RNA biomakers**:

215 (31%) were associated with pCR
45 (7%) were associated with RFS*
22 (3%) were associated with both

Easier to predict pCR than RFS

Predictors of pCR do not have to predict RFS and vice-versa

*Relapse-free survival

Fernandez-Martinez et al. JCO 2020

HER2DX genomic test for early-stage HER2+ disease

- T size
- Nodal status
- 27 genes
- 4 gene signatures
  - IGG/B-cell/plasma (14 genes)
  - Proliferation
  - luminal differentiation
  - HER2 amplicon expression
- **HER2DX risk-score**
- **HER2DX pCR-score**
- **HER2DX ERBB2-score**

Prat et al,Lancet Oncol 2020; Prat et al, EBioMedicine 2022; Guarneri et al, EBioMedicine 2022; Brasó-Maristany et al., JNCI 2022

HER2DX clinical validation

HER2DX risk score

7 Studies → 1,812 patients

- Clinic-Padova-PAMELA phase II
- APT phase II trial
- ATEMPT phase II trial
- CALGB40601 phase III
- SCAN-B
- TCGA
- METABRIC

1 Gene list association study

- N9831 phase III: 849 patients

HER2DX pCR likelihood score

7 Studies → 872 patients

- Clinic-Padova
- PAMELA phase II
- CALGB40601 phase III
- ISPY-2 phase II
- PER-ELISA phase II
- DAPHNe phase II trial
- MADRID/GOM observational trial
- BiOnHER phase II trial

Prat et al. EBioMedicine 2022
Fara Brasó-Maristany ESMO Breast 2022
PER-ELISA presented at ESMO Paris 2022 and published in EBioMedicine 2022
DAPHNe and GOM studies: JAMA Oncol 2023 In Press
APT and ATEMPT: SABCS 2022 and ESMO Breast 2023
BiOnHER phase II trial: To be presented at ESMO Breast 2023

Should we change this algorithm depending on HER2DX test results?

HER2 + stage I-III Breast Cancer

Surgery

pT1N0

T + paclitaxel

APT trial (n=406)

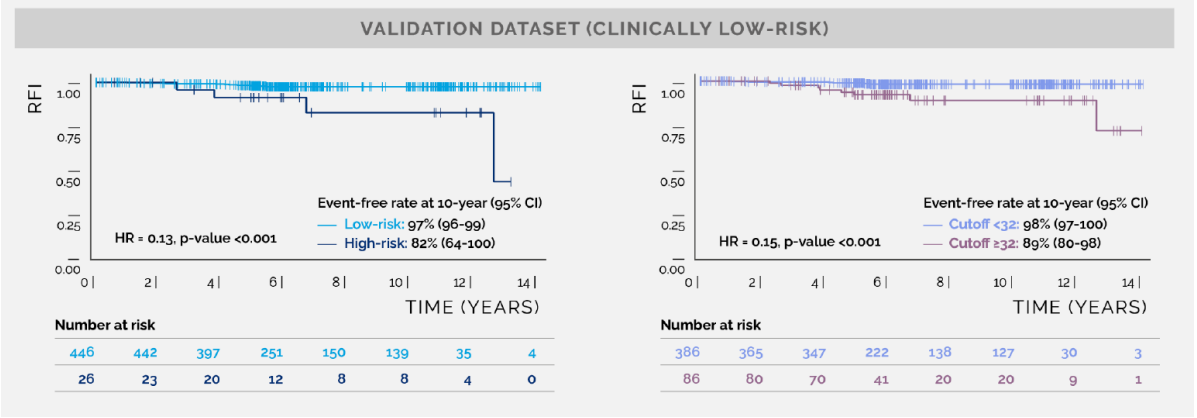
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

ATEMPT trial (n=497)

Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial



5-20% of clinically low-risk tumors may be undertreated

Tolaney NEJM 2015; Tolaney JCO 2019; Tolaney Lancet Oncol 2023; Tolaney JCO 2021

HER2 + stage I-III Breast Cancer

Surgery

pT1N0

T + paclitaxel

T +/- P poly-CT

HER2DX low-risk

HER2DX high-risk

APT trial (n=406)

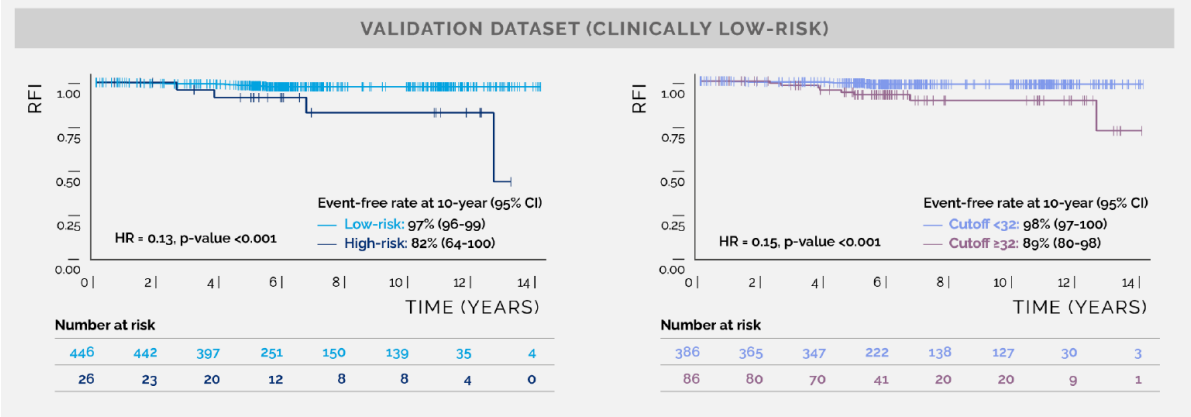
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

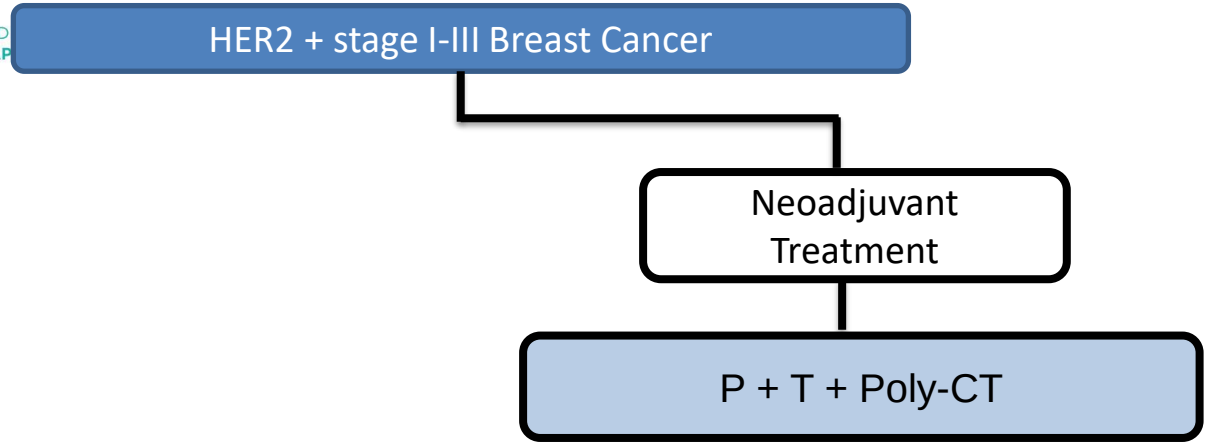
Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

ATEMPT trial (n=497)

Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial



Tolaney NEJM 2015; Tolaney JCO 2019; Tolaney Lancet Oncol 2023; Tolaney JCO 2021



Bueno-Muiño C, JAMA Oncol 2023

HER2 + stage I-III Breast Cancer

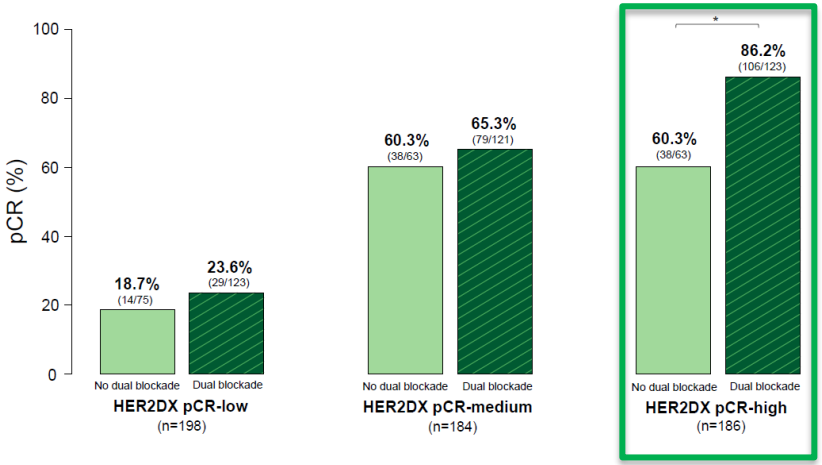
- Combined analysis of 4 neoadjuvant cohorts (CALGB 40601, ISPY-2, DAPHNe, GOM-HGUGM-2018-05)
- n=568 patients
- pCR rates +/- dual blockade (44.8% vs 58.3%)
- HER2DX-pCR-high benefits from dual HER2 blockade (OR 4,10 p< 0.001)

Neoadjuvant Treatment

HER2DX pCR high

P + T + Taxane

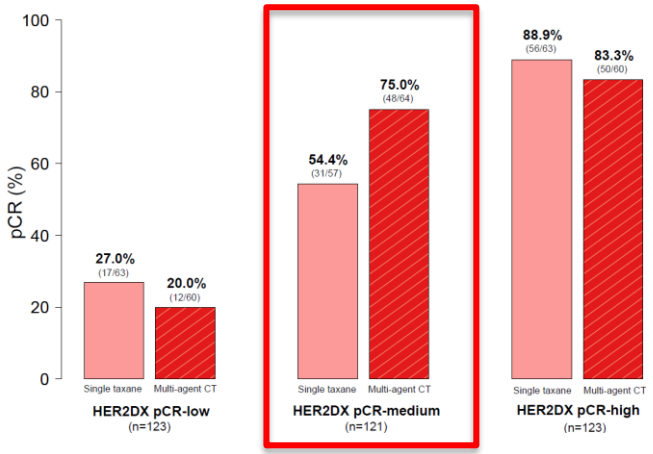
Who needs neoadjuvant pertuzumab?

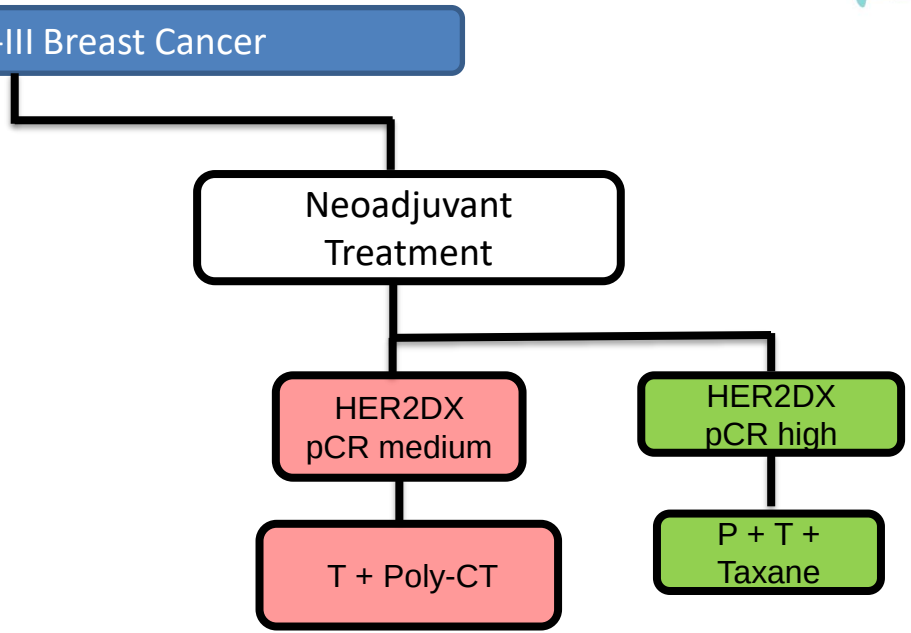


Bueno-Muiño C, JAMA Oncol 2023; Waks A, ESMO breast 2023

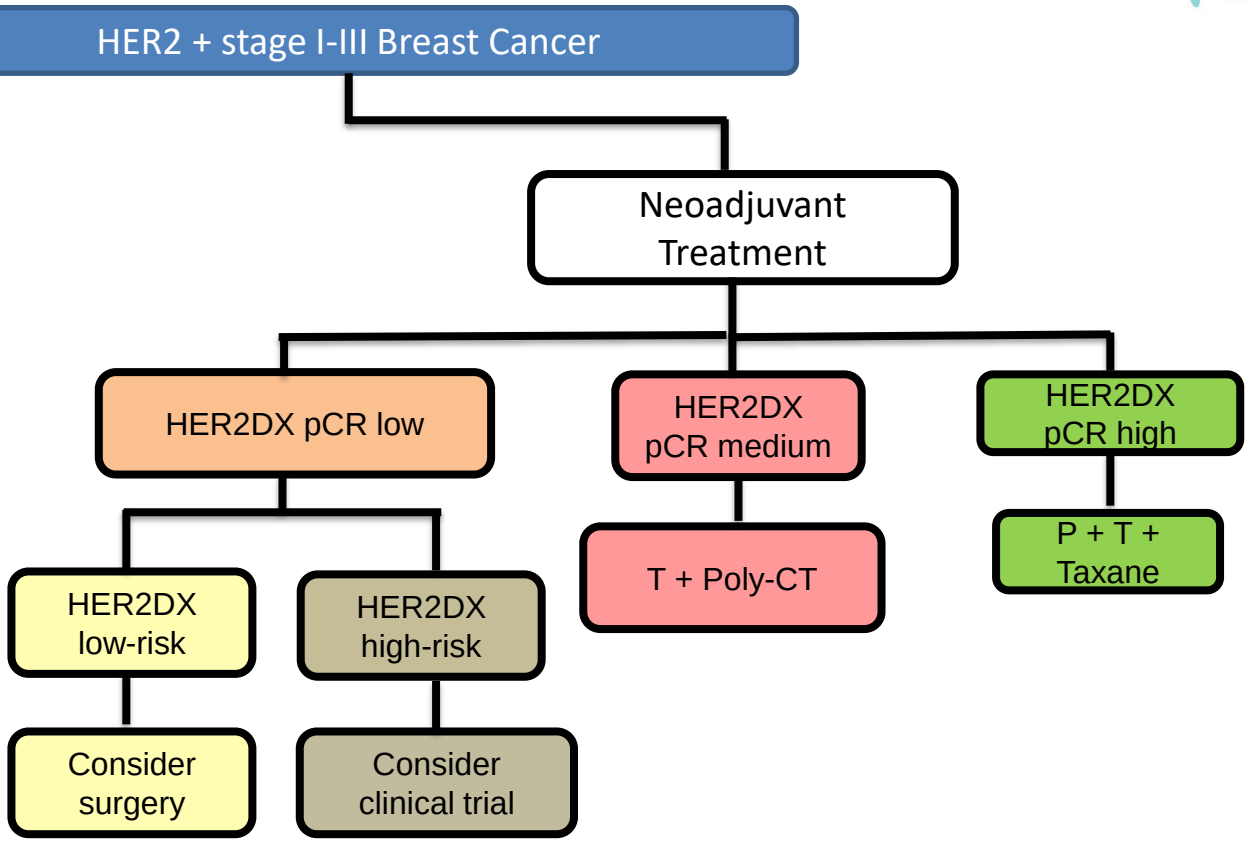
- Combined analysis of 4 neoadjuvant cohorts (CALGB 40601, ISPY-2, DAPHNe, GOM-HGUGM-2018-05)
- n=568 patients
- Poly-CT (n=282; 49.6%) Single taxane (n=286; 50.4%
- pCR rates poly-CT single taxane (59.8% vs 56.6%)
- HER2DX-pCR-medium benefits from multi-agent CT

Who needs neoadjuvant poly-CT?

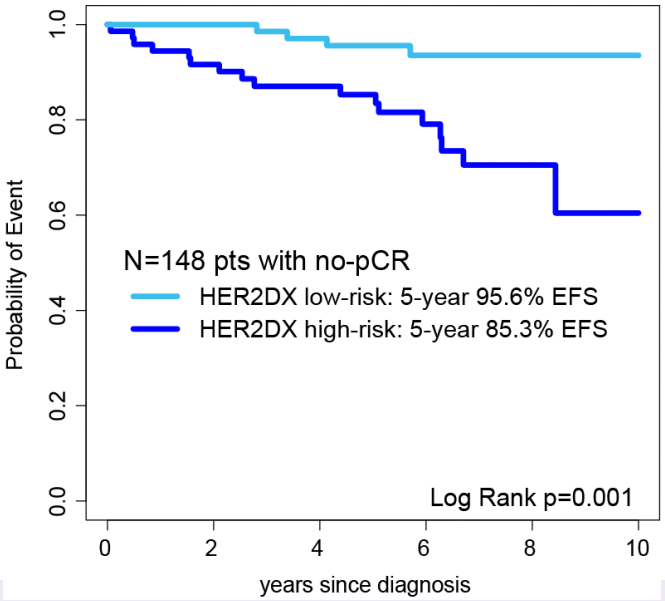


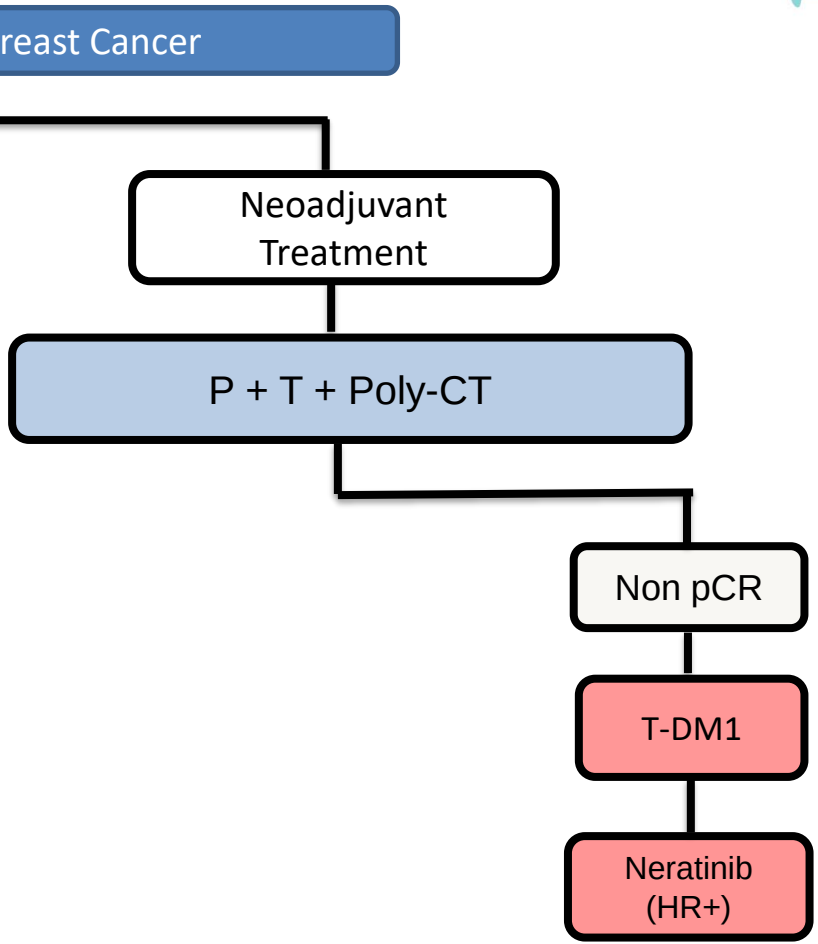


Waks et al. ESMO Breast 2023

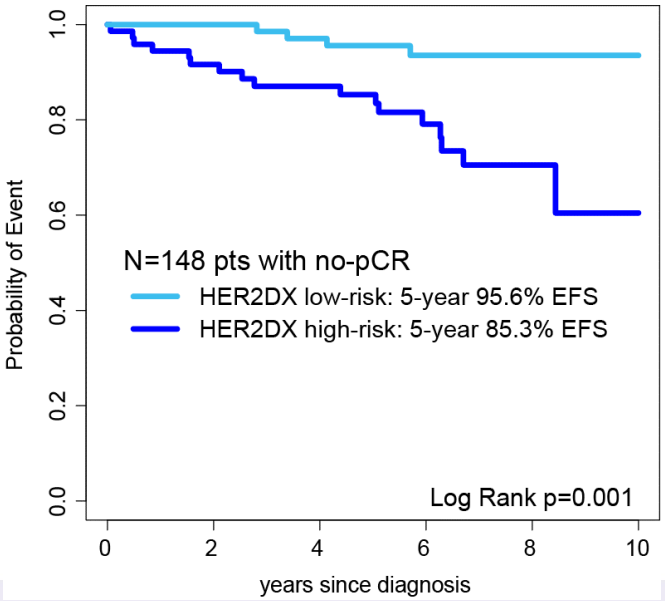

HER2 + stage I-III Breast Cancer
Neoadjuvant Treatment
HER2DX pCR low
HER2DX pCR medium
HER2DX pCR high
HER2DX low-risk
HER2DX high-risk
T + Poly-CT
P + T + Taxane
Consider surgery
Consider clinical trial

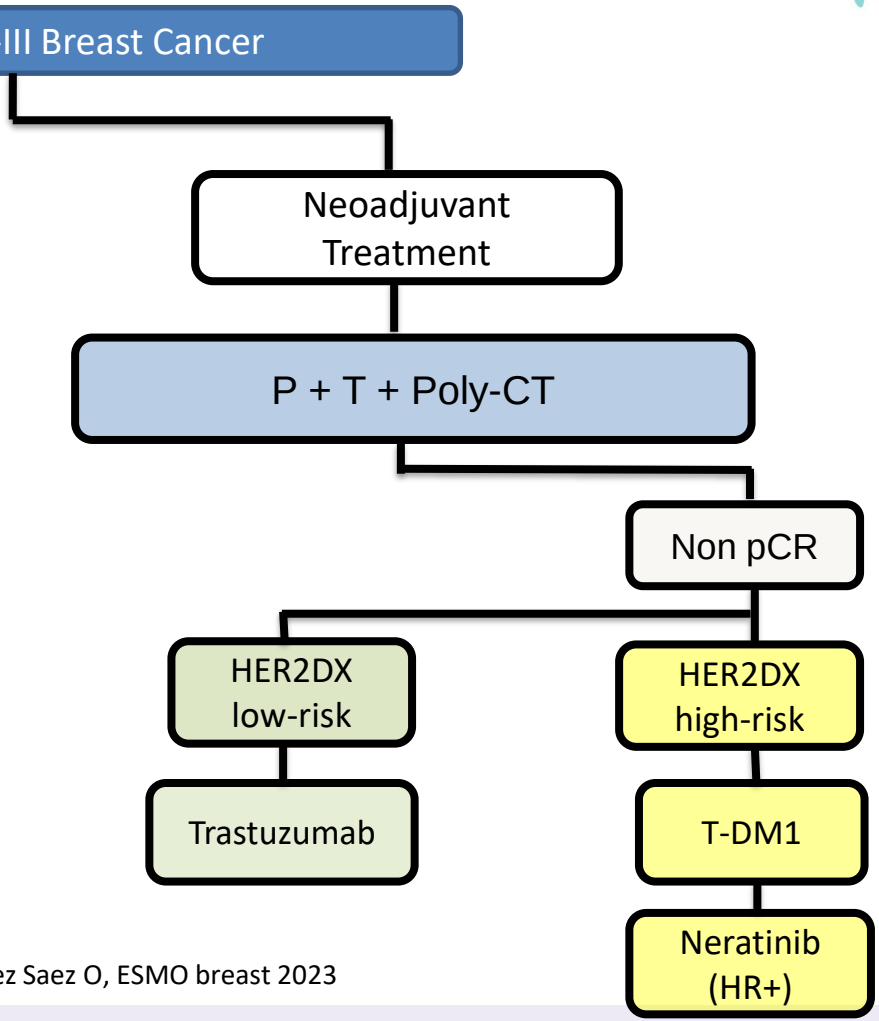
- **Validation cohort** with more median follow-up (73.2 months)
- **N=148 pts did not achieve a pCR**
- **The HER2DX low-risk group had longer DFS than high-risk (7-year 94.6%vs. 77.5%; HR=0.40, p=0.002).**





- **Validation cohort** with more median follow-up (73.2 months)
- **N=148 pts did not achieve a pCR**
- **The HER2DX low-risk group had longer DFS than high-risk (7-year 94.6%vs. 77.5%; HR=0.40, p=0.002).**



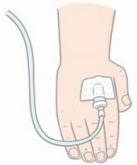


Martínez Saez O, ESMO breast 2023

- **Definition of risk is critical in clinical decission & in the success of escalation and de-escalation clinical trials**

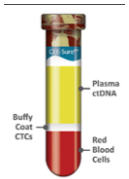
Standard Clinical & Pathological features

Response to neoadjuvant therapy

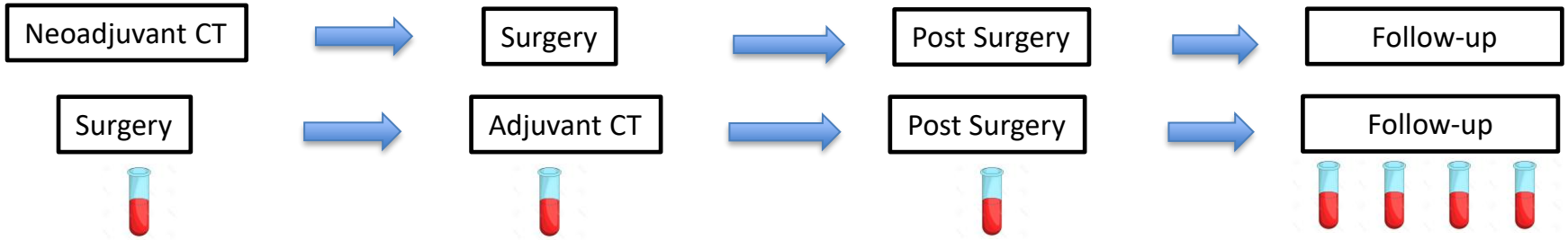


Biology

Posible role of ctDNA

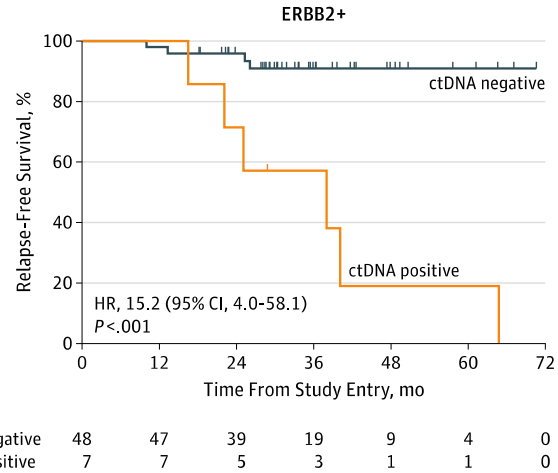


ctDNA in risk stratification



- Prospective, multicenter, sample collection, validation study conducted at 5 UK medical centers (2011-2016)
- N=170 eBC with NACT→surgery OR surgery→adjuvant CT
- Personalized digital (dPCR) assays designed to track individual somatic muts in plasma samples
- 165 muts identified: 78 pts (77.2%) with 1 mut and 23 pts (22.8%) with multiple muts (median allele frequency of 26%)
- Validated personalized dPCR assays developed for 150 muts (90.9%) from 101 pts

Mutation tracking in HER2 + BC



Garcia Murillas I. JAMA Oncol 2019

Conclusions

- **Clinicopathologic features & pathologic response** are the main factors to stratify patients on the basis of their risk of recurrence and guide us in making treatment recommendations
- **Biologic heterogeneity** within HER2-positive disease modulates treatment response and prognosis
- Strategies to escalate or de-escalate treatment in HER2-positive early-stage BC should consider **other biomarkers**, beyond HER2 and HR-status, including **molecular intrinsic subtype, immune infiltration, levels of HER2**
- **HER2DX integrates this information and could be useful to select (neo)adjuvant treatment.** However, clinical utility should be confirmed in randomized clinical trials.