SCIENTIFIC BITES®

Cancer research
e-learning platform

Unmet medical needs in HER2+ breast cancer

Eva Ciruelos: Hospital Universitario 12 de Octubre de Madrid
Maria Vidal: Hospital Clínic de Barcelona

Medical OncologyDeparment
Breast Cancer Unit
12 de octubre Hospital, Madrid
HM CIOCC, Madrid
Complutense University, Madrid

by SOLTI

Early breast cancer

Overview of eBC outcomes according to risk

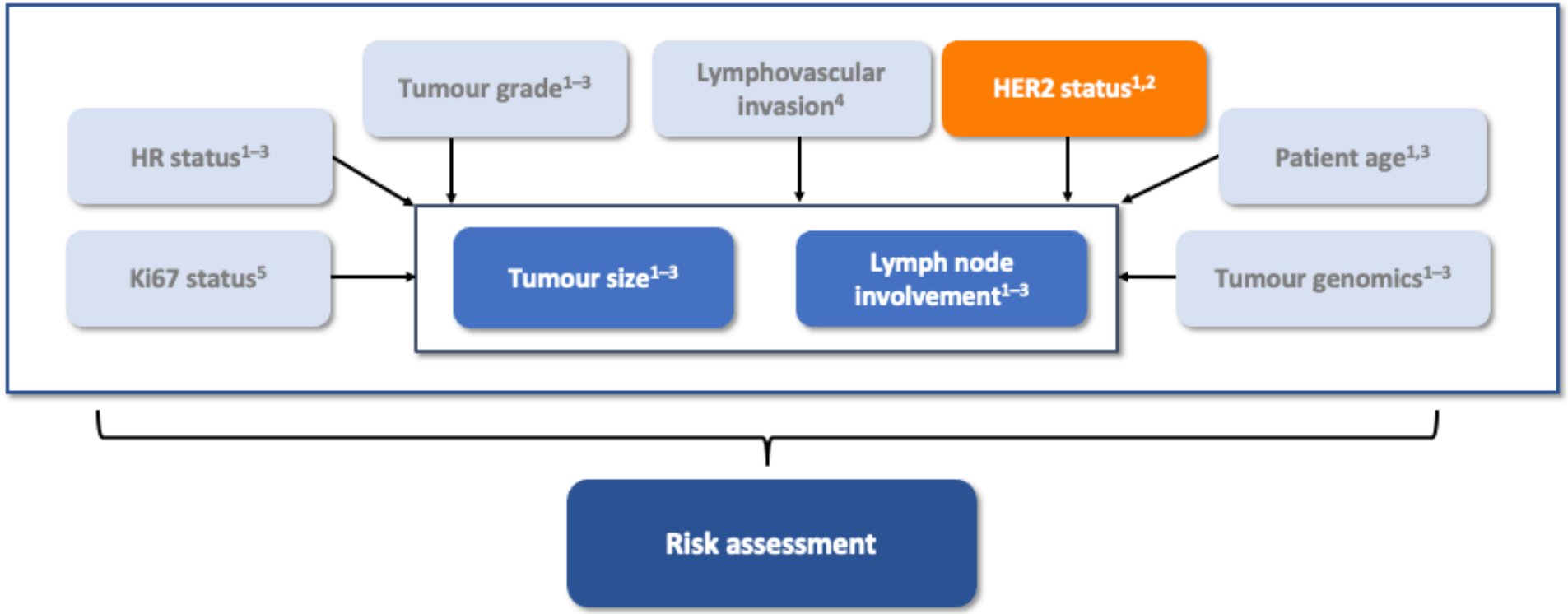
	5-year EFS (%)			
	Stage II		Stage III	
	Grade II	Grade III	Grade II	Grade III
HR-positive HER2-negative	83	71	63	51
HR-positive HER2-positive	81	69	50	48
HR-negative HER2-positive	61	66	58	46
Triple-negative	66	72	38	37

EFS, event-free survival.

Cortazar, P. Presented at FDA Public Workshop, Innovations in Breast Cancer Drug Development – Neoadjuvant Breast Cancer Workshop, March 22, 2013

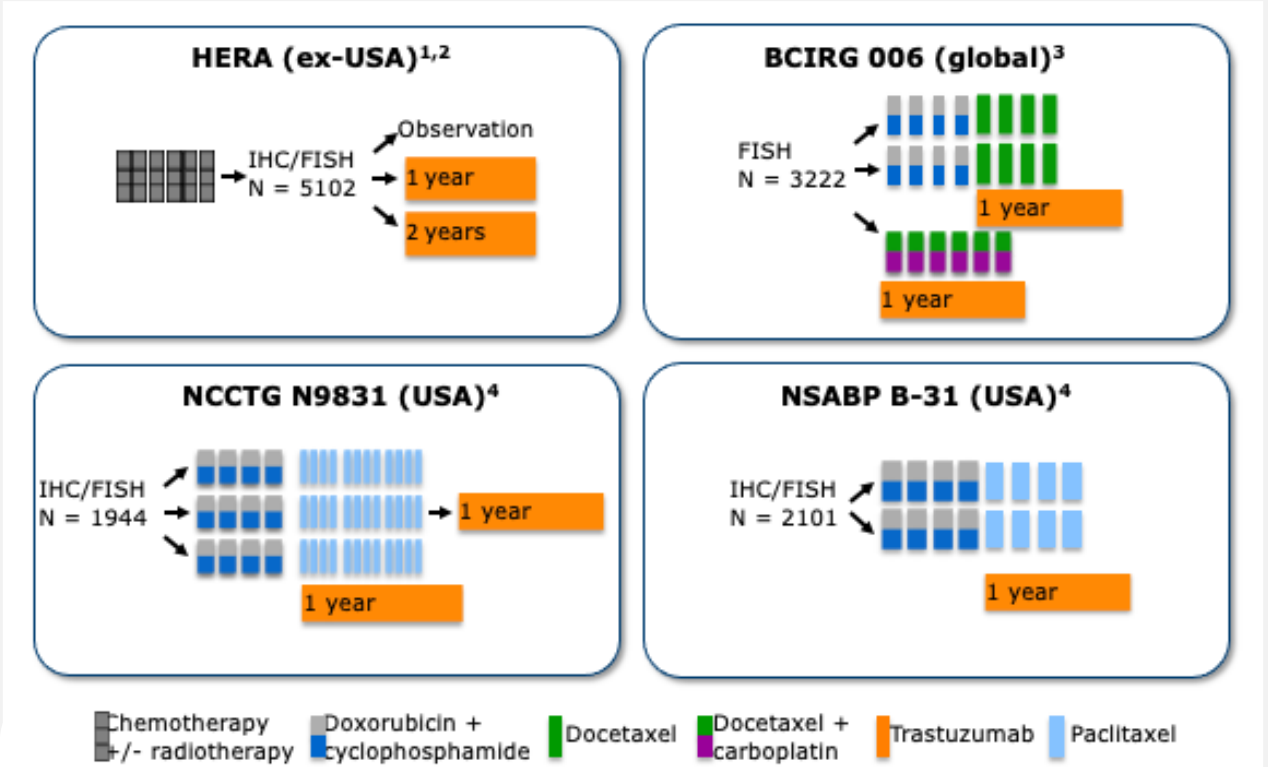
Tumour biology and prognosis in trastuzumab-treated HER2-positive eBC patients is determined by a number of different risk factors

Biological factors



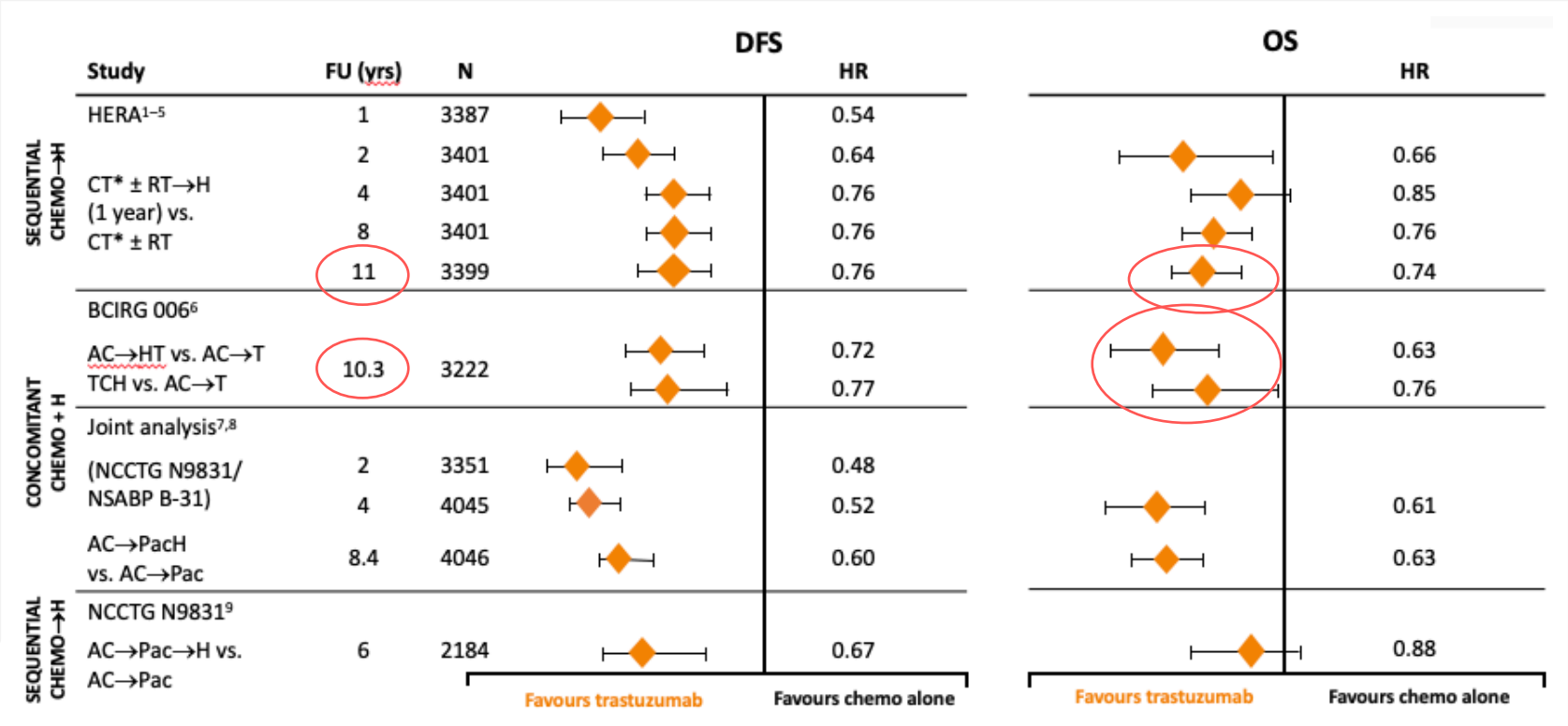
1. Martei YM & Matro JM. Breast Cancer (Dove Med Press) 2015; 7:337–343;
2. Sparano JA, et al. N Engl J Med 2015; 373:2005–2014; 3. Drukker CA, et al. Int J Cancer 2013; 133:929–936;
4. Zhang S, et al. BMC Cancer 2017; 17:335; 5. Inwald EC, et al. Breast Cancer Res Treat 2013; 139:539–552

Tumour biology and prognosis in trastuzumab-treated HER2-positive eBC patients is determined by a number of different risk factors



Piccart-Gebhart MJ, et al. N Engl J Med 2005; 353:1659–1672; 2. Gianni L, et al. Lancet Oncol 2011; 12:236-244;
3. Slamon D, et al. N Engl J Med 2011; 365:1273-1283; 4. Perez EA, et al. J Clin Oncol 2011; 29:3366-3373

Adjuvant trials : consistent DFS and OS benefit over time with 1 year of trastuzumab

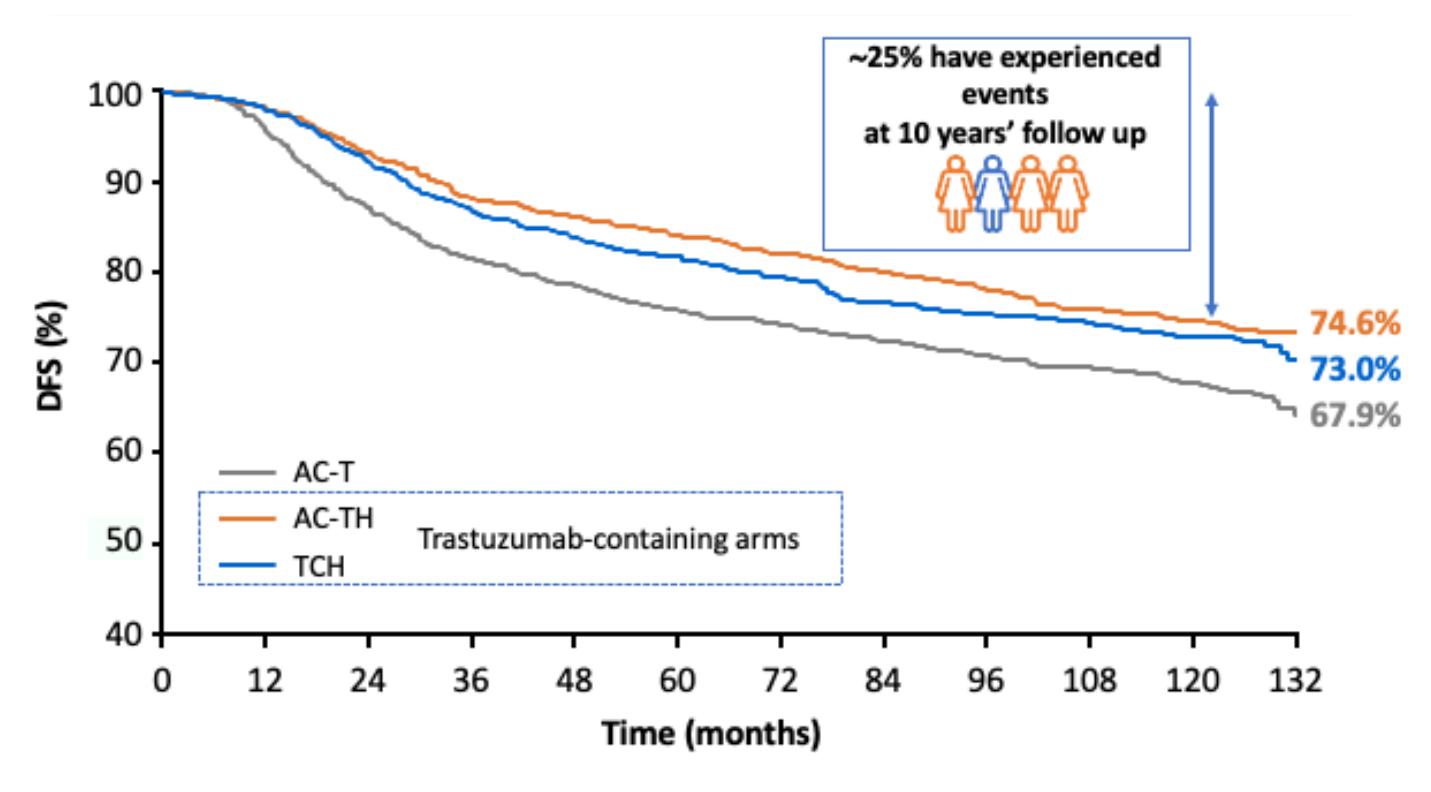


AC, doxorubicin + cyclophosphamide; C, carboplatin; CT, chemotherapy; DFS, disease-free survival; FU, follow-up; H, trastuzumab; OS, overall survival; Pac, paclitaxel; RT, radiotherapy; T, docetaxel.
* Selected from a list of approved regimens consisting of ≥4 cycles.

1. Piccart-Gebhart MJ, et al. N Engl J Med 2005; **353**:1659–1672; 2. Smith I, et al. Lancet 2007; **369**:29–36; 3. Gianni L, et al. Lancet Oncol 2011; 12:236–244; 4. Goldhirsch A, et al. Lancet 2013; 382:1021–1028; 5. Cameron D, et al. Lancet 2017; **389**:1195–1205; 6. Slamon D, et al. SABCS 2015 (Abstract S5-04; oral presentation); 7. Perez EA, et al. J Clin Oncol 2011; **29**:3366–3373; 8. Perez EA, et al. J Clin Oncol 2014; **32**:3744–3752; 9. Perez EA, et al. J Clin Oncol 2011; **29**:4491–4497.

BCIRG 006: Relapse rates in HER2-positive eBC remain high

DFS final analysis (10.3 years' median follow-up)



1 in 4 patients will still experience recurrence or death

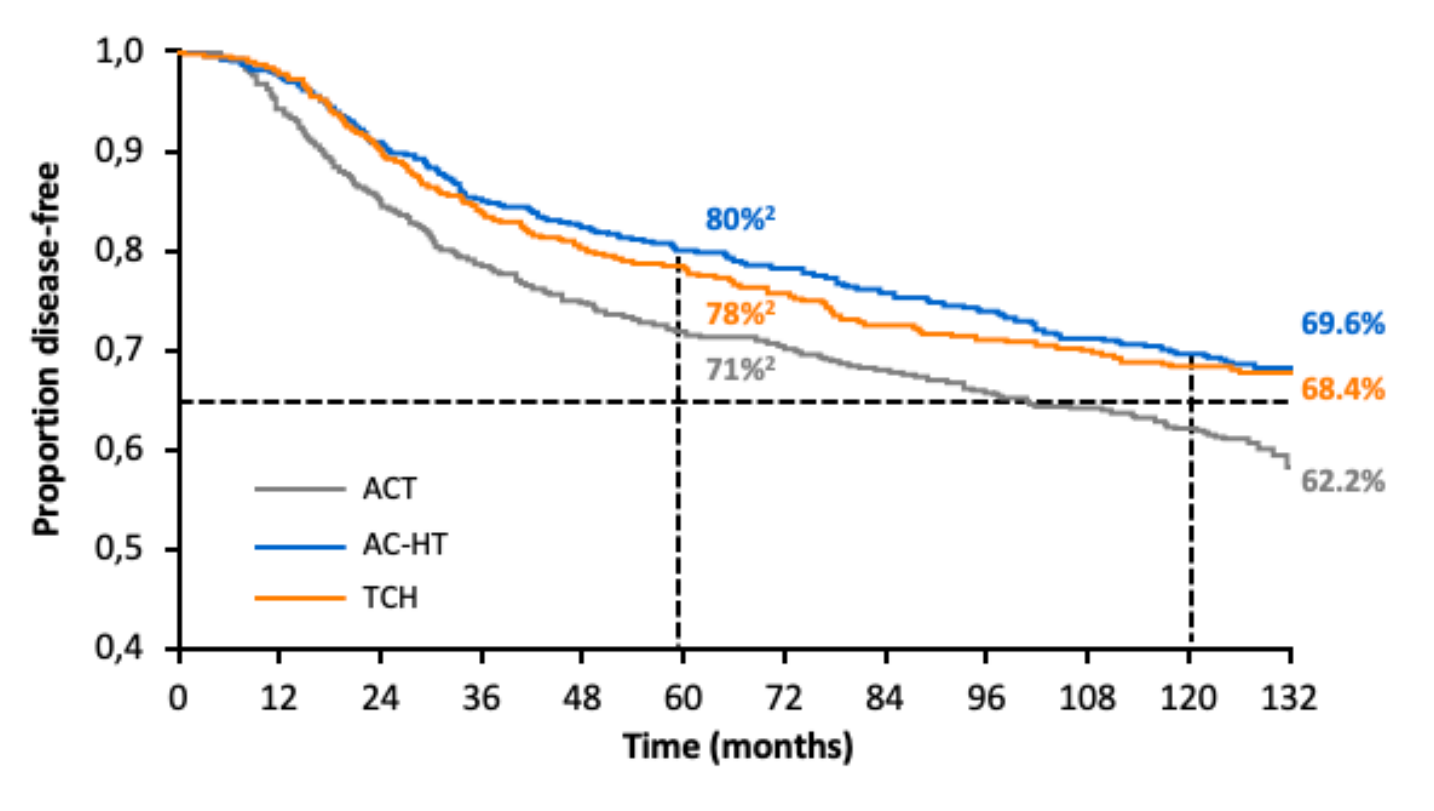
despite 1 year of adjuvant trastuzumab-based therapy

AC, doxorubicin + cyclophosphamide; C, carboplatin; CT, chemotherapy; DFS, disease-free survival; FU, follow-up; H, trastuzumab; OS, overall survival; Pac, paclitaxel; RT, radiotherapy; T, docetaxel.
* Selected from a list of approved regimens consisting of ≥4 cycles.

Slamon D, et al. SABCS 2015 (Abstract S5-04; oral presentation).

BCIRG 006: after 1 year of adjuvant trastuzumab, ~30% of node-positive patients still relapse

BCIRG 006: DFS in node-positive disease after 10 years' follow-up[1]

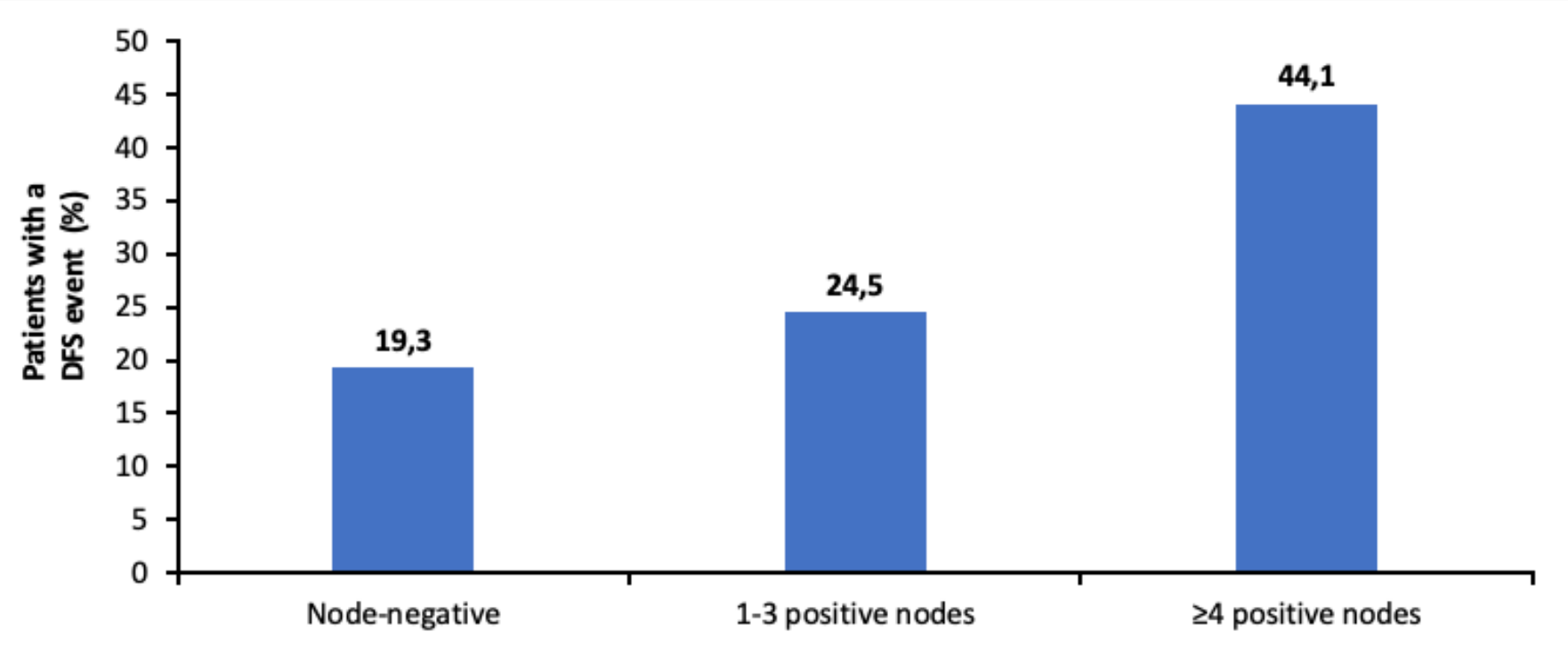


AC, doxorubicin + cyclophosphamide; C, carboplatin; CT, chemotherapy; DFS, disease-free survival; FU, follow-up; H, trastuzumab; OS, overall survival; Pac, paclitaxel; RT, radiotherapy; T, docetaxel.
* Selected from a list of approved regimens consisting of ≥4 cycles.

1. Slamon D, et al. SABCS 2015 (Abstract S5-04; oral presentation);
2. Slamon D, et al. N Engl J Med 2011; **365**:1273–1283.

HERA: DFS event rate increases with increasing numbers of positive nodes

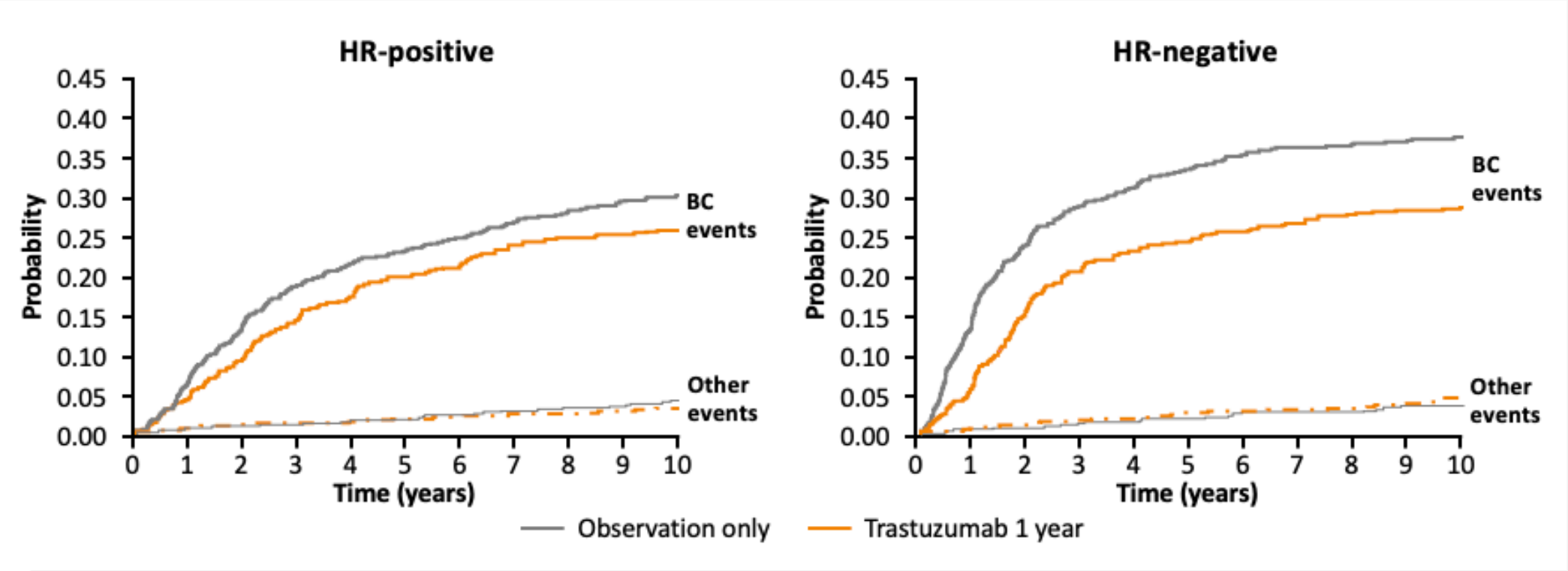
HERA 11-year FU: DFS events by nodal status with 1 year of adjuvant trastuzumab



Cameron D, et al. Lancet 2017; 389:1195–1205 (Supplementary information).

HERA: HR-negative status confers a higher risk for early relapse, and within a shorter timeframe

HERA 11-year FU: Cumulative incidence of type of DFS event with 1 year of adjuvant trastuzumab



Cameron D, et al. Lancet 2017; 389:1195–1205 (Supplementary information).

How to improve long-term results:

- 2 vs 1 year trastuzumab adjuvant therapy

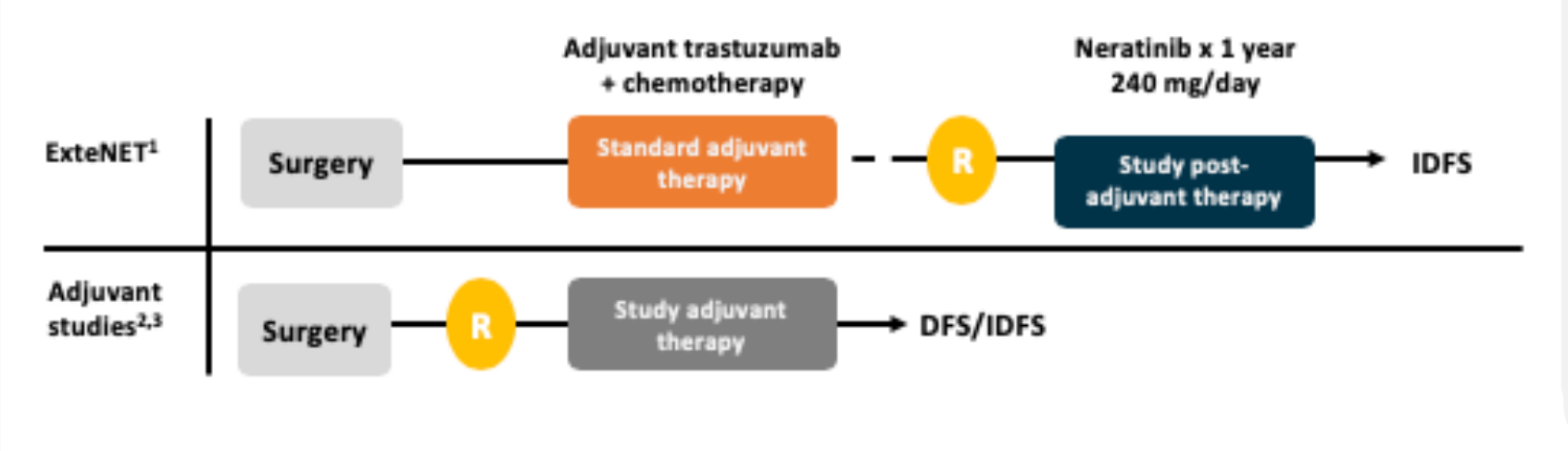
  HERA: negative trial

- Adding a second antiHER2 targeted agent

  ALTTO: negative trial
  BETH: negative trial

  Extenet: positive trial
  Aphinity: positive trial

ExteNET: Neratinib in the extended ‘post-adjuvant’ setting

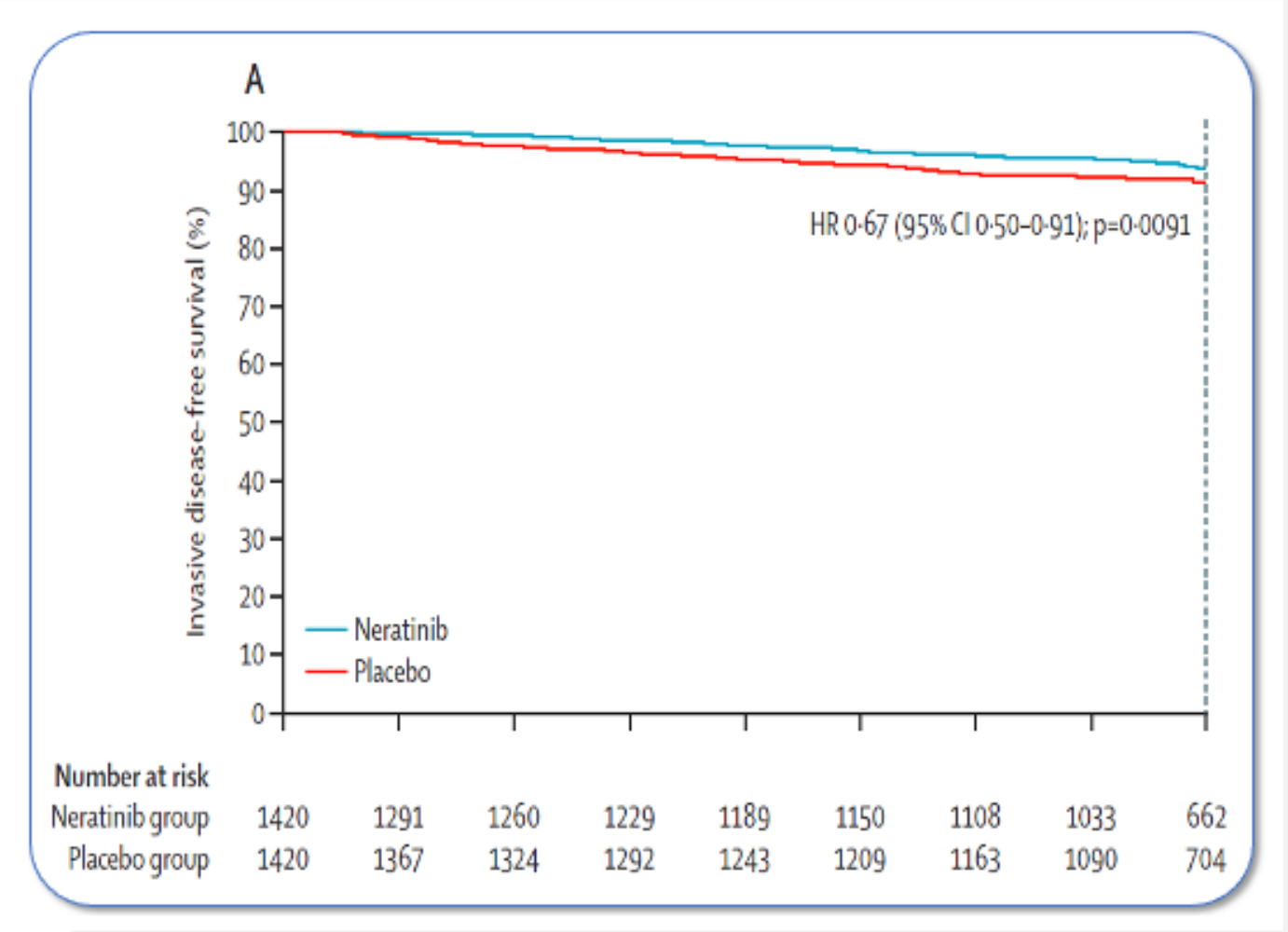


- Pendpoint: IDFS at 2 years
- Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- Other analyses: Biomarkers, health outcome assessment (FACT-B, EQ-5D)
- Stratified by: Nodes 0, 1–3 vs. 4+, ER/PR status, concurrent vs. sequential trastuzumab

DCIS, ductal carcinoma in situ.

1. Chan A, et al. Lancet Oncol 2016; **17**:367–377;
2. Goldhirsch A, et al. Lancet 2013; **382**:1021–1028;
3. von Minckwitz G, et al. SABCS 2011 (Abstract OT1-02-04).

ExteNET: 2-year IDFS (ITT population) with extended ‘post-adjuvant’ neratinib

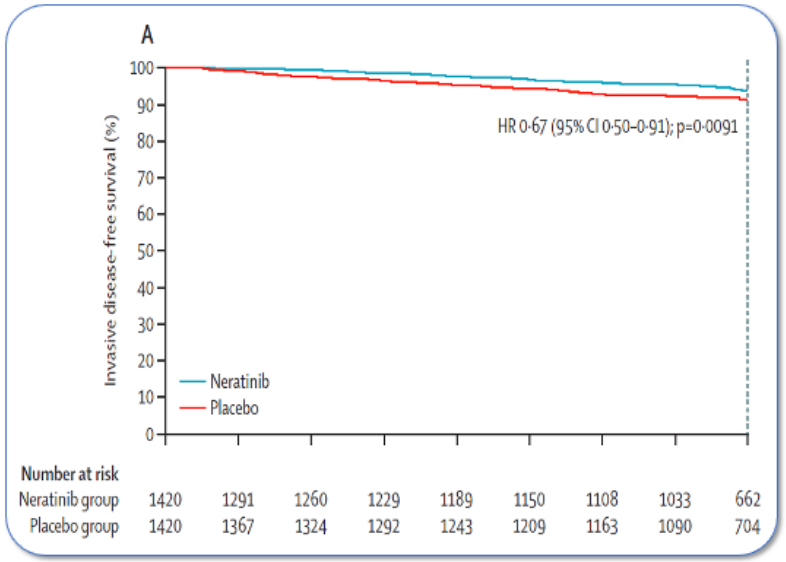


ITT, intention-to-treat.

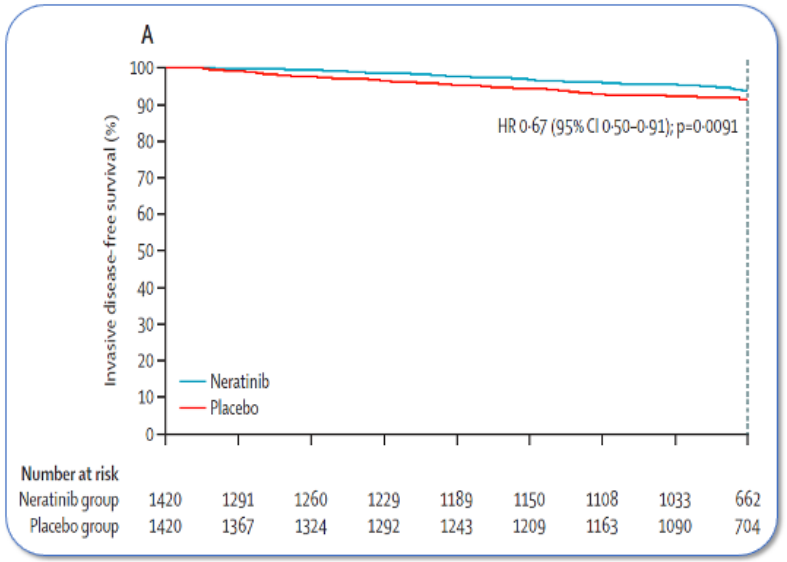
Chan A, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016; **17**:367–377.

ExteNET: Treatment effect in ITT according to hormone receptor status

Hormone receptor-positive



Hormone receptor-negative



Chan A, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016; 17:367–377 (supplementary information).

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA approves neratinib for extended adjuvant treatment of early stage HER2-positive breast cancer

On July 17, 2017, the U.S. Food and Drug Administration approved neratinib (NERLYNX, Puma Biotechnology, Inc.) for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.

Approval was based on the ExteNET trial (NCT00878709), a multicenter, randomized, double-blind, placebo-controlled trial of neratinib following adjuvant trastuzumab treatment. Women (n=2,840) with early-stage HER2-positive breast cancer and within two years of completing adjuvant trastuzumab were randomized to receive either neratinib (n=1420) or placebo (n=1420) for one year.

The major efficacy outcome measure was invasive disease-free survival (iDFS) defined as the time between the randomization date to the first occurrence of invasive recurrence (local/regional, ipsilateral or contralateral breast cancer), distant recurrence, or death from any cause, within two years and 28 days of follow-up. After two years, iDFS was 94.2% in patients treated with neratinib compared with 91.9% in those receiving placebo (HR 0.66; 95% CI: 0.49, 0.90, p=0.008).

Press Office

EMA Recommends Granting a Marketing Authorisation for Neratinib After Re-examining Its Negative Opinion for This Medicine

It is indicated in extended adjuvant treatment of adult patients with early stage, hormone receptor positive, HER2-overexpressed/amplified breast cancer

Date: 02 Jul 2018
Topic: **Breast cancer** / **Anticancer agents & Biologic therapy**

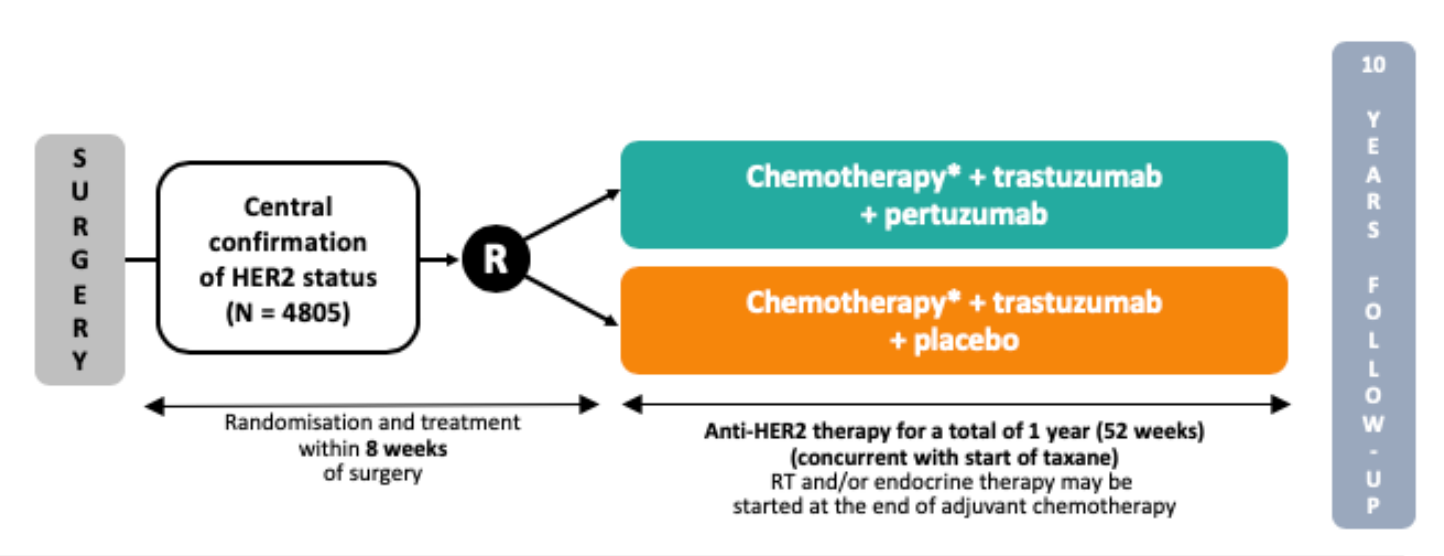
On 28 June 2018, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP), following a re-examination procedure, adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product **neratinib** (Nerlynx), intended for the adjuvant treatment of adult patients with breast cancer.

The applicant for this medicinal product is Puma Biotechnology Limited.

On 22 February 2018, the CHMP had originally adopted a negative opinion for Nerlynx for broader use in HER2-positive early breast cancer. At the request of the applicant, the CHMP started a re-examination of its opinion. Following the re-examination, the CHMP adopted a final positive opinion on 28 June 2018, but in a restricted patient population.

Nerlynx will be available as 40-mg film-coated tablets. The active substance of Nerlynx is neratinib, an irreversible pan-ERBB tyrosine kinase inhibitor (ATC code: L01XE45). It blocks mitogenic growth factor signal transduction through covalent, high-affinity binding to the ATP binding site of 3 epidermal growth factor receptors resulting in sustained inhibition of these growth promoting pathways in breast cancers

APHINITY: Phase III study to assess pertuzumab plus trastuzumab in the adjuvant setting



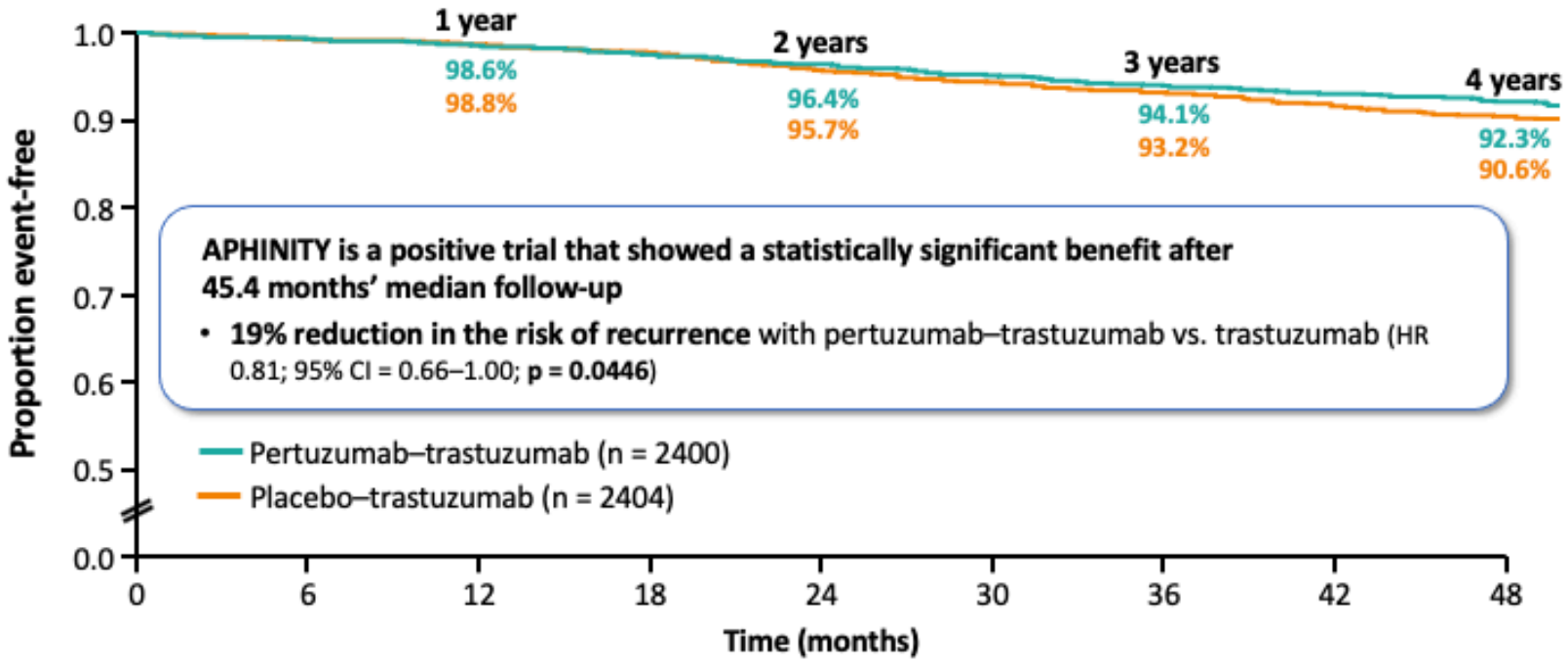
* Standard anthracycline or non-anthracycline (TCH) regimens were allowed

- Primary endpoint: IDFS
- Secondary endpoints: IDFS with second non-breast primary cancers included, DFS, OS, RFI, DRFI, safety and HRQoL
- Predefined stratification factors: Chemotherapy regimen, HR status, nodal status, geographic region and protocol version (A vs. B)

DRFI, distant relapse-free interval; HRQoL, health-related quality of life; IDFS, invasive DFS; RFI, relapse-free interval.

von Minckwitz G, et al. N Engl J Med 2017; **377**:122–131.

APHINITY: Pertuzumab–trastuzumab plus chemotherapy significantly increased IDFS rates for HER2-positive eBC in the adjuvant setting



Stratification factors are: nodal status and protocol version, intended adjuvant chemotherapy and central hormone receptor status.
Hazard ratio was estimated by Cox regression.

von Minckwitz G, et al. N Engl J Med 2017; **377**:122–131.

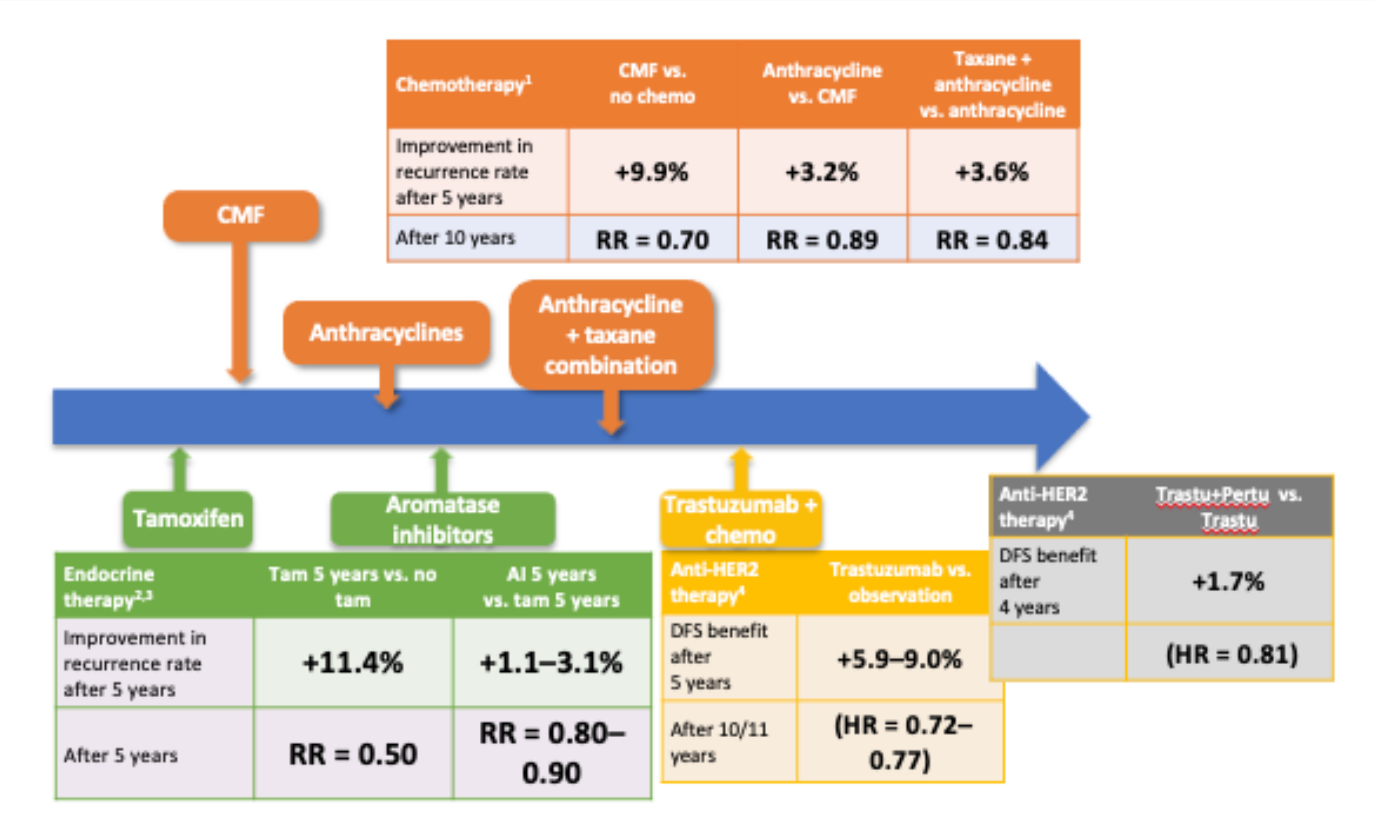
APHINITY: Clinical Benefit in Primary vs Secondary Analysis

HR for IDFS (95% CI)	Primary Analysis (mFU: 45.4 Mos)	Updated Analysis (mFU: 74.1 Mos)
ITT population	0.81 (0.66-1.00)	**0.76 (0.64-0.91)**
Lymph node positive	0.77 (0.62-0.96)	**0.72 (0.59-0.87)**
Lymph node negative	1.13 (0.68-1.86)	1.02 (0.69-1.53)
Hormone receptor positive	0.86 (0.66-1.13)	0.73 (0.59-0.92)
Hormone receptor negative	0.76 (0.56-1.04)	0.83 (0.63-1.10)

IDFS at 6-Yr	Pertuzumab, %	Placebo, %	Absolute Benefit, % (95% CI)
ITT population	90.6	87.8	**2.8 (1.0-4.6)**
Lymph node positive	87.9	83.4	**4.5 (1.9-7.1)**
Lymph node negative	95.0	94.9	0.1 (-2.0-2.2)
Hormone receptor positive	91.2	88.2	3.0 (0.8-5.2)
Hormone receptor negative	89.5	87.0	2.5 (-0.7-5.6)

Piccart. SABCS 2019. Abstr GS1-04

Introduction of new treatment modalities over time has improved recurrence outcomes in the ADJUVANT setting



Chemotherapy[1]	CMF vs. no chemo	Anthracycline vs. CMF	Taxane + anthracycline vs. anthracycline
Improvement in recurrence rate after 5 years	+9.9%	+3.2%	+3.6%
After 10 years	RR = 0.70	RR = 0.89	RR = 0.84

Endocrine therapy[2,3]	Tam 5 years vs. no tam	AI 5 years vs. tam 5 years
Improvement in recurrence rate after 5 years	+11.4%	+1.1–3.1%
After 5 years	RR = 0.50	RR = 0.80–0.90

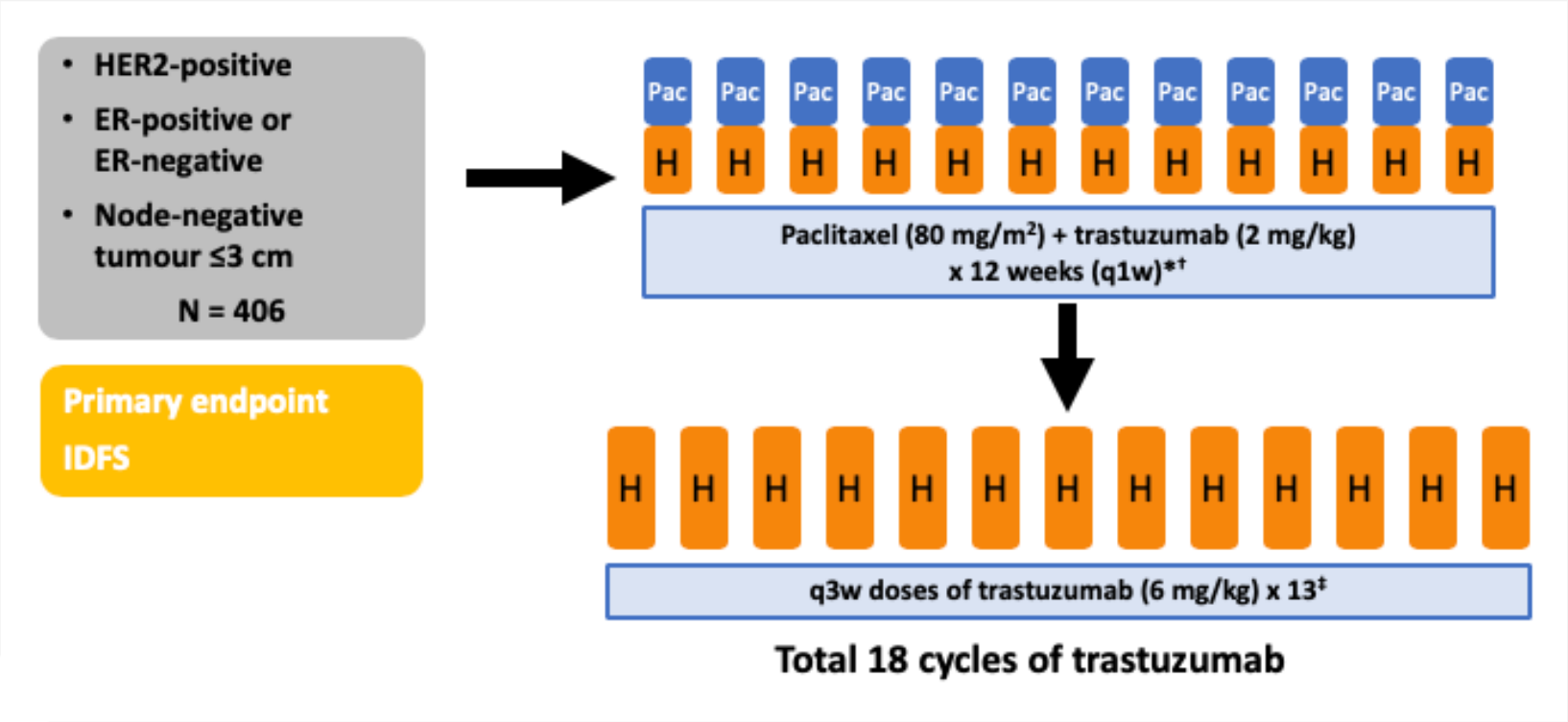
Anti-HER2 therapy[4]	Trastuzumab vs. observation
DFS benefit after 5 years	+5.9–9.0%
After 10/11 years	(HR = 0.72–0.77)

Anti-HER2 therapy[4]	Trastu+Pertu vs. Trastu
DFS benefit after 4 years	+1.7%
	(HR = 0.81)

.
AI, aromatase inhibitor; CMF, cyclophosphamide, methotrexate and fluorouracil; HR, hazard ratio; RR, risk ratio.

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet 2012; 379:432–444;
2. EBCTCG. Lancet 2015; 386:1341–1352; 3. EBCTCG. Lancet 2005; 365:1687–1717;
4. Jackisch C, et al. SABCS 2015 (Abstract PD5-01); 5. Slamon D, et al. SABCS 2015 (Abstract S5-04);
6. Slamon D, et al. N Engl J Med 2011; 365:1273–1283.

APT (Tolaney) trial: Adjuvant paclitaxel and trastuzumab for HER2-positive breast cancer at lower risk of recurrence



NOTE: This is a single-arm, single-centre study, so is unable to provide definitive data on treatment benefit

q1w, weekly; q3w, every 3 weeks.
* Loading dose of 4 mg/kg intravenous trastuzumab on Day 1.
† Radiation and hormonal therapy were initiated after completion of paclitaxel.
‡ Dosing could alternatively be 2 mg/kg intravenous q1w for 40 weeks.

Tolaney SM, et al. N Engl J Med 2015; 372:134–141.

APT (Tolaney) trial: Trastuzumab plus paclitaxel is effective in the treatment of patients at low risk of recurrence

TABLE 1. Patient Baseline Characteristics From the Overall Cohort and From Patients With PAM50 Data

Characteristic	All Treated Patients (N = 406)	Patients With PAM50 Assessed (n = 278)	Patients Without PAM50 Assessed (n = 128)	P*
Age group, years				
< 50	132 (33)	79 (28)	53 (41)	.02
50-59	137 (34)	101 (36)	36 (28)	
60-69	96 (24)	64 (23)	32 (25)	
≥ 70	41 (10)	34 (12)	7 (5)	
Sex				
Female	405 (100)	277 (100)	128 (100)	1.00
Male	1 (< 1)	1 (< 1)	0 (0)	
Race				
White	351 (86)	242 (87)	109 (85)	.88
Black or African American	28 (7)	17 (6)	11 (9)	
Asian	11 (3)	8 (3)	3 (2)	
Other	16 (4)	11 (4)	5 (4)	
Size of primary tumor, cm				
T1mi (≤ 0.1)	9 (2)	1 (< 1)	8 (6)	< .001
T1a (0.1 to ≤ 0.5)	68 (17)	29 (10)	39 (30)	
T1b (> 0.5 to ≤ 1.0)	124 (31)	81 (29)	43 (34)	
T1c (> 1.0 to ≤ 2.0)	169 (42)	137 (49)	32 (25)	
T2 (> 2.0 to ≤ 3.0)	36 (9)	30 (11)	6 (5)	
Histologic grade				
I: Well differentiated	44 (11)	26 (9)	18 (14)	.02
II: Moderately differentiated	131 (32)	88 (32)	43 (34)	
III: Poorly differentiated	228 (56)	164 (59)	64 (50)	
Unknown	3 (1)	0 (0)	3 (2)	
ER status				
Positive	260 (64)	188 (68)	72 (56)	.03
Negative	141 (35)	88 (32)	53 (41)	
Borderline	5 (1)	2 (1)	3 (2)	
PR status				
Positive	201 (50)	150 (54)	51 (40)	.02
Negative	196 (48)	123 (44)	73 (57)	
Borderline	8 (2)	5 (2)	3 (2)	
Unknown	1 (< 1)	0 (0)	1 (1)	
HR status				
Positive	272 (67)	196 (70)	76 (59)	.03
Negative	134 (33)	82 (30)	52 (41)	

Tolaney SM, et al. JCO 2019.

APT (Tolaney) trial: Trastuzumab plus paclitaxel is effective in the treatment of patients at low risk of recurrence

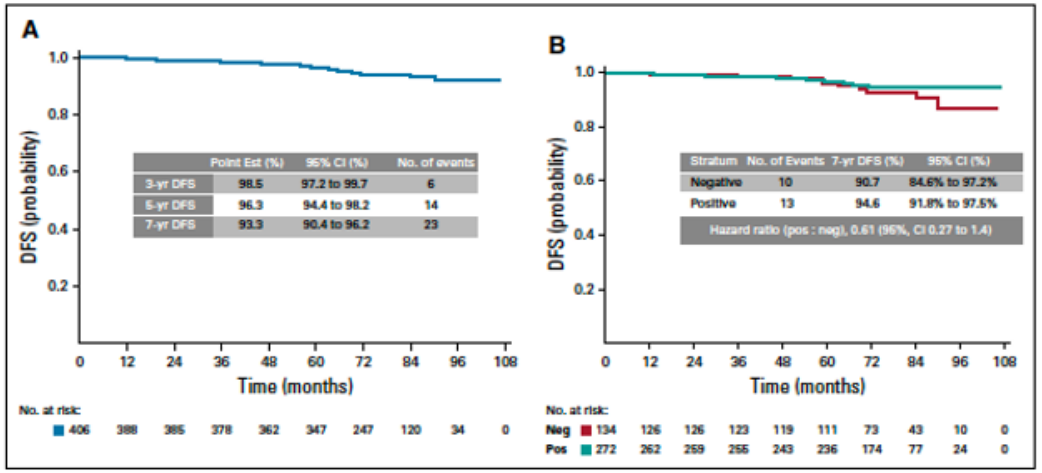


FIG 2. Disease-free survival (DFS). (A) Kaplan-Meier plot of DFS in the intention-to-treat population. (B) DFS according to hormone-receptor status. Abbreviations: neg, negative; Point est, point estimate; pos, positive.

TABLE 3. Estimated 3-Year, 5-Year, and 7-Year Rates for RFI, BCSS, and OS

	RFI			BCSS			OS		
Time (years)	No. of Events	No. at Risk	Rate (95% CI)	No. of Events	No. at Risk	Rate (95% CI)	No. of Events	No. at Risk	Rate (95% CI)
3	3	378	99.2 (98.4 to > 99.9)	0	386	—	1	386	99.7 (99.2 to > 99.9)
5	7	347	98.1 (96.8 to 99.5)	1	362	99.7 (98.1 to > 99.9)	5	362	98.7 (97.5 to 99.8)
7	9	120	97.5 (95.9 to 99.1)	3	127	98.6 (97.0 to > 99.9)	14	127	95.0 (92.4 to 97.7)

Abbreviations: BCSS, Breast Cancer-Specific Survival; OS, overall survival; RFI, Recurrence-Free Interval.

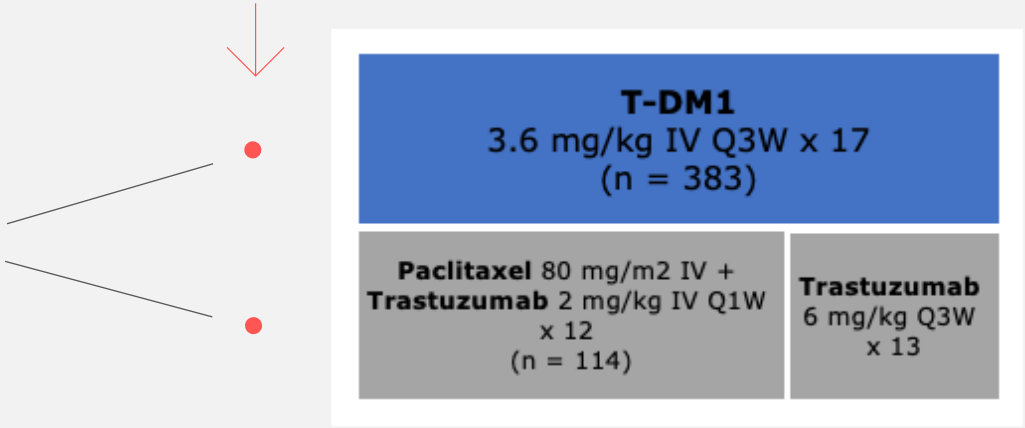
Tolaney SM, et al. JCO 2019.

ATEMPT: Study Design

A randomized (3:1), open-label phase II study

Stratified by age (<55, ≥ 55), planned radiation therapy (Y/N), planned hormonal therapy (Y/N)

Women with stage I HER2+ BC with N0 or N1mic disease; LVEF ≥ 50%; no prior invasive BC surgery; ≤ 90 days from last surgery (N = 497)



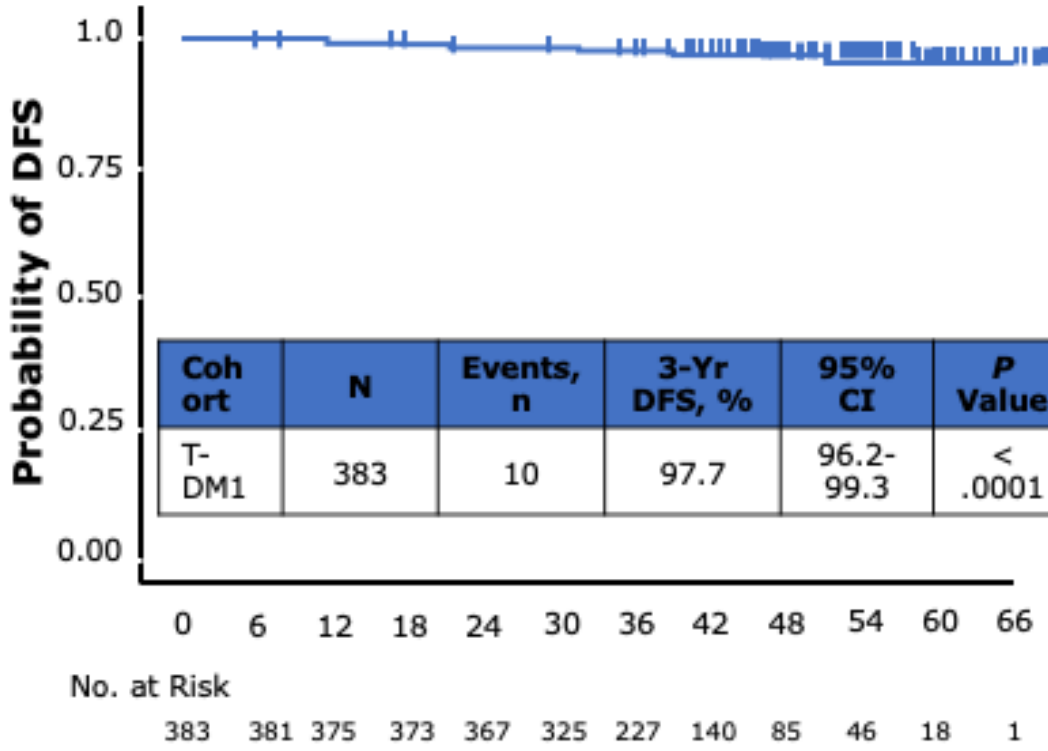
Follow-up for 5 yrs after final dose of T-DM1 or TH

Study not powered to assess efficacy of TH or to compare efficacy of T-DM1 to TH

Coprimary endpoints: 3-yr DFS in T-DM1; comparison of incidence of clinically relevant toxicities with T-DM1 vs TH, including: grade ≥ 3 non-hematologic AEs, grade ≥ 2 neurotoxicity, grade ≥ 4 hematologic AEs, febrile neutropenia, and any AE requiring dose delay or discontinuation of protocol therapy

Tolaney. SABCS 2019. Abstr GS1-05.

ATEMPT: T-DM1 DFS in ITT and by Hormone Receptor Status and Tumor Size



Cohort	N	Events, n	3-Yr DFS, %	95% CI	*P* Value
T-DM1	383	10	97.7	96.2-99.3	< .0001

HR Status	Events, n	3-Yr DFS, % (95% CI)
HR+ (n = 289)	8	97.5 (95.6-99.3)
HR- (n = 94)	2	98.5 (95.6-100)

Tumor Size, cm	Events, n	3-Yr DFS, % (95% CI)
< 1 (n =163)	2	98.5 (96.5-100)
≥ 1 (n = 22)	8	97.1 (94.9-99.4)

Tolaney. SABCS 2019. Abstr GS1-05.

ATEMPT: Grade ≥ 2 treatment-related AEs

Characteristic, n (%)	T-DM1 (n = 383)	TH (n = 114)
Fatigue	84 (22)	26 (23)
Neuropathy	44 (11)	27 (24)
Neutropenia	13 (3)	15 (13)
Thrombocytopenia	43 (11)	1 (1)
Nausea	39 (10)	8 (7)
Hypertension	35 (9)	7 (6)
ALT increase	33 (9)	5 (4)
Headache	24 (6)	4 (4)
Bilirubin increase	21 (5)	1 (1)
Infusion related reaction	19 (5)	12 (11)
Arthralgia	18 (5)	2 (2)
Anemia	18 (5)	2 (2)
Congestive heart failure, symptomatic	*3 (0.8)*	*1 (0.9)*
Asymptomatic decline in LVEF of ≥ 15%	*5 (1.3)*	*7 (6.1)*

Tolaney. SABCS 2019. Abstr GS1-05.

Neoadjuvant therapy

Defining pCR

pCR in breast cancer

- pCR is the absence of cancerous cells in resected breast tissue or lymph node specimens[1]
- tpCR is the most widely accepted definition of pCR in clinical practice[3,4]

The definition of pCR can vary[1]

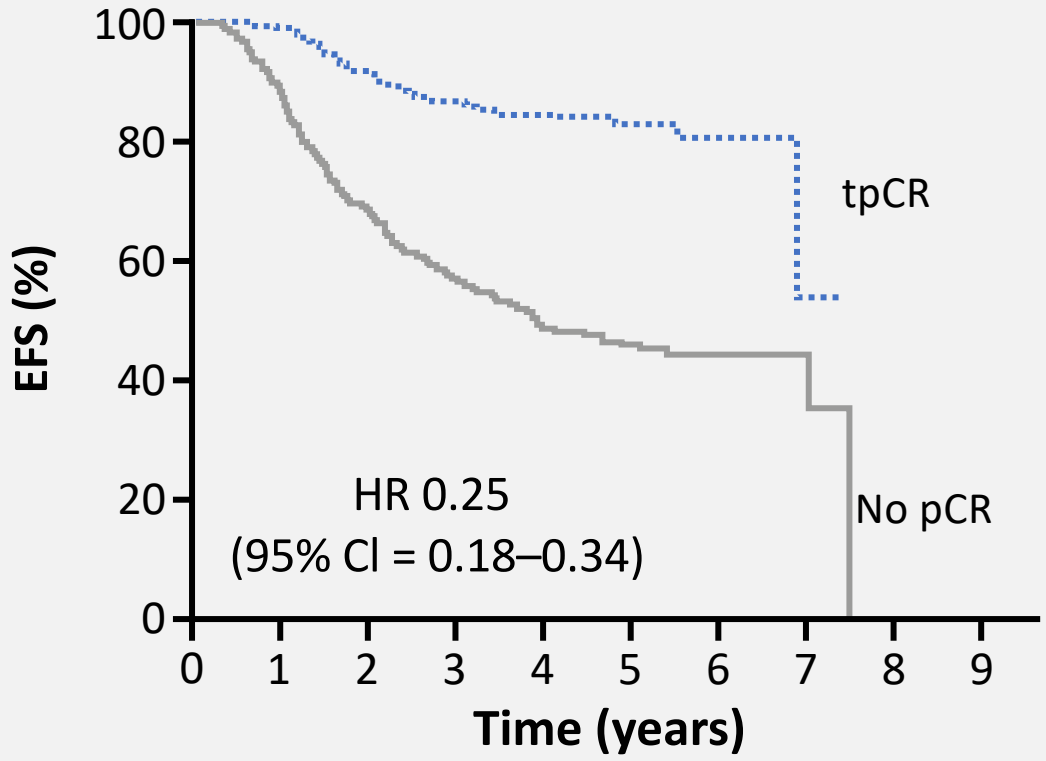
Commonly called	TMN code	Definition
Breast pCR (bpCR)	ypT0/is ypN0/+	Absence of invasive cancer in breast (irrespective of ductal carcinoma *in situ*). Invasive disease in lymph nodes is permitted
Total pCR (tpCR)	ypT0/is ypN0	Absence of invasive cancer in breast and axillary nodes (irrespective of ductal carcinoma *in situ*)
German Breast Group (GBG) pCR	ypT0 ypN0	Absence of invasive cancer and *in situ* cancer in breast and axillary nodes

1. von Minckwitz G, et al. J Clin Oncol 2012; 30:1796–1804; 2. Roche. Data on file. Protocol BO27938 (KATHERINE) – version 6; 3. Cortazar P, et al. Lancet 2014; 384:164–172;
4. Stebbing J, et al. Expert Rev Anticancer Ther 2018; 18:531-541.

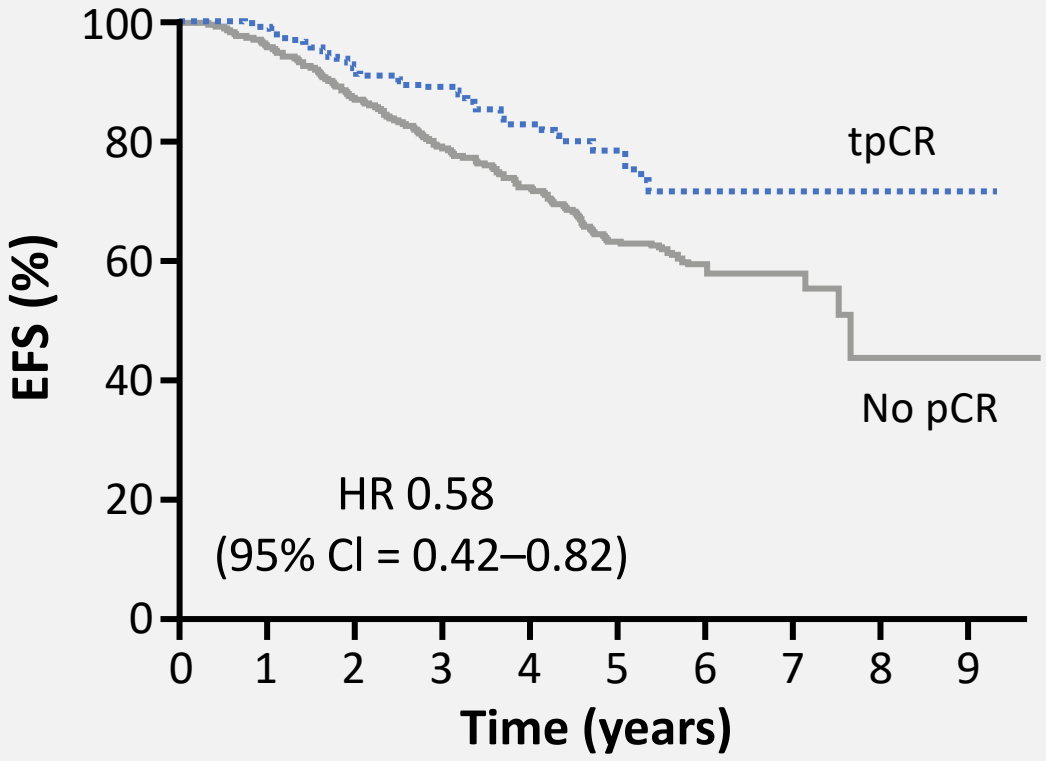
pCR, pathological complete response

CTNeoBC meta-analysis: EFS benefit after pCR was more pronounced in HER2-positive, HR-negative tumours

HER2-positive, HR-negative



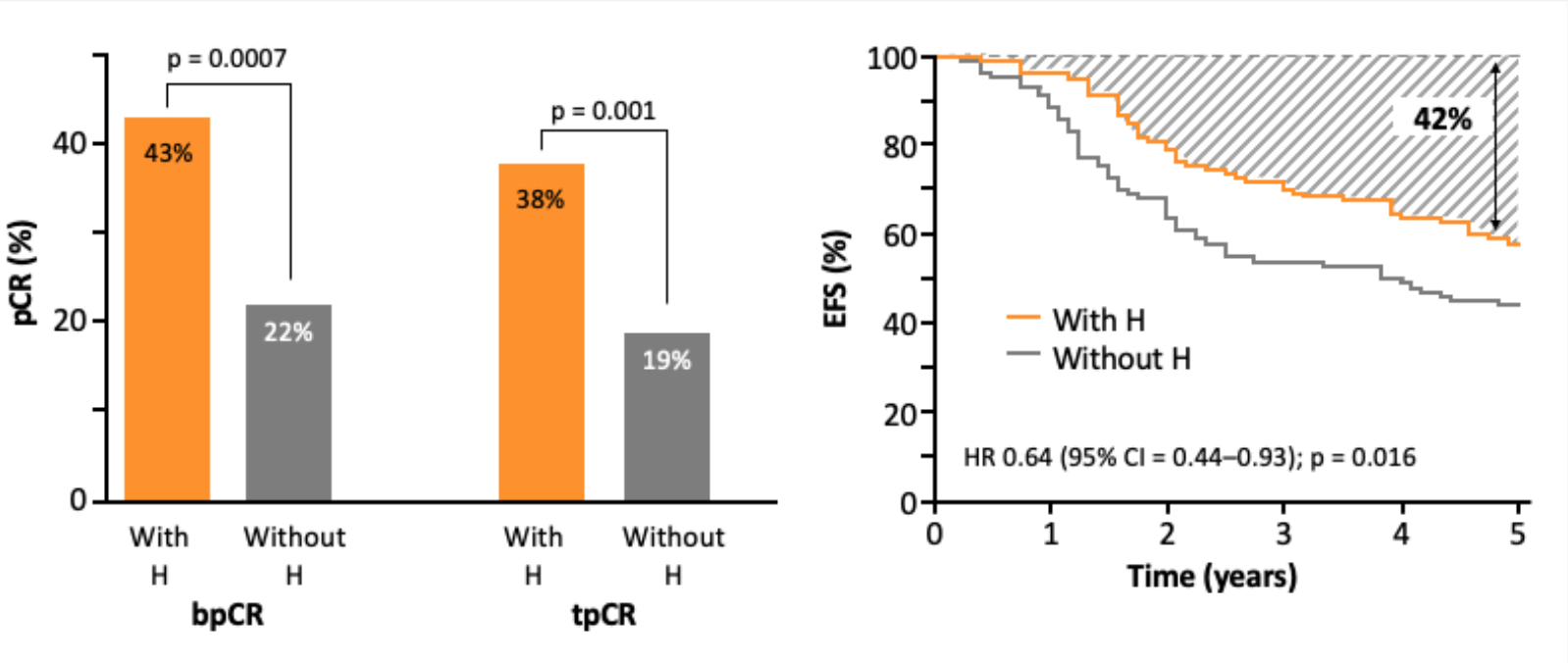
HER2-positive, HR-positive



Cortazar P, et al. Lancet 2014; **384**:164–172.

NOAH: Trastuzumab increased both pCR and EFS, but many patients still experience relapse

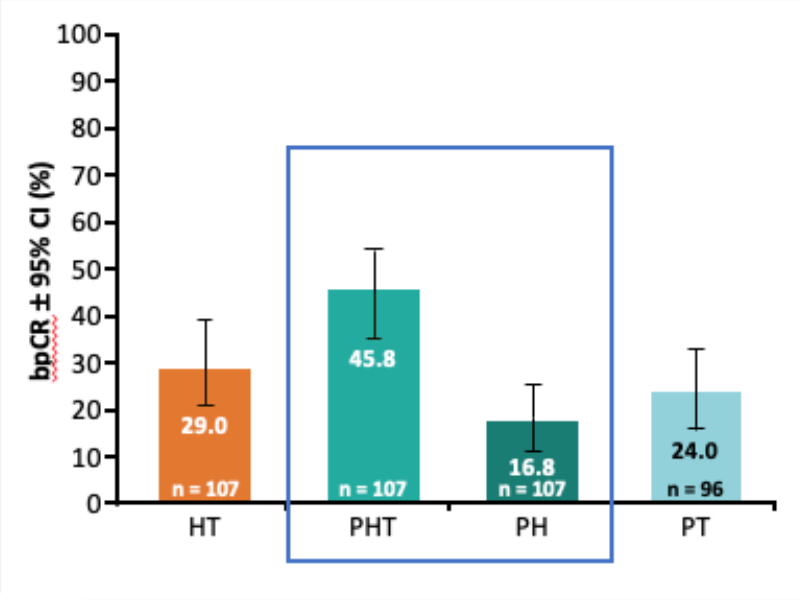
Increased pCR rates with trastuzumab added to chemotherapy resulted in improved EFS, but 42% of patients had relapsed at 5 years



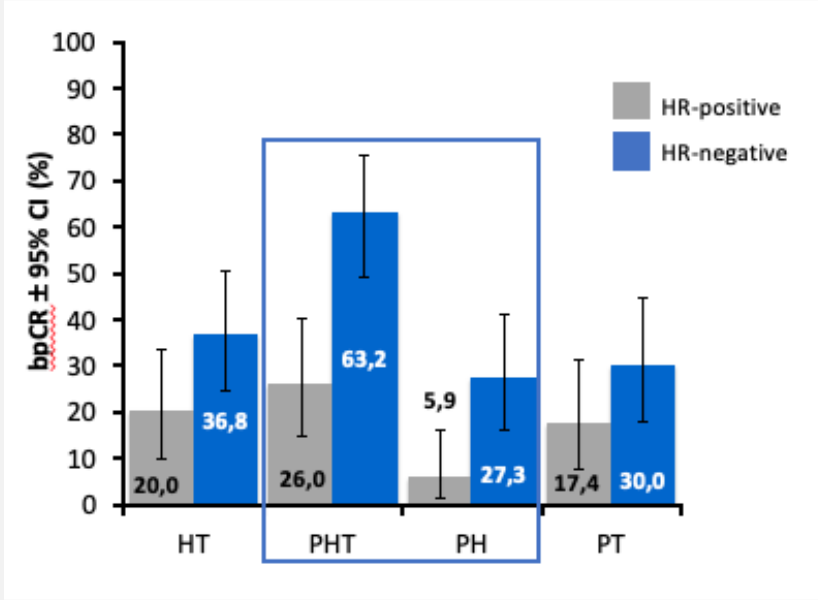
Gianni L, et al. Lancet 2010; 375:377–384; Gianni L, et al. Lancet Oncol 2014; 15:640–647.

NeoSphere: PHT improved pCR regardless of HR status

pCR in the breast*



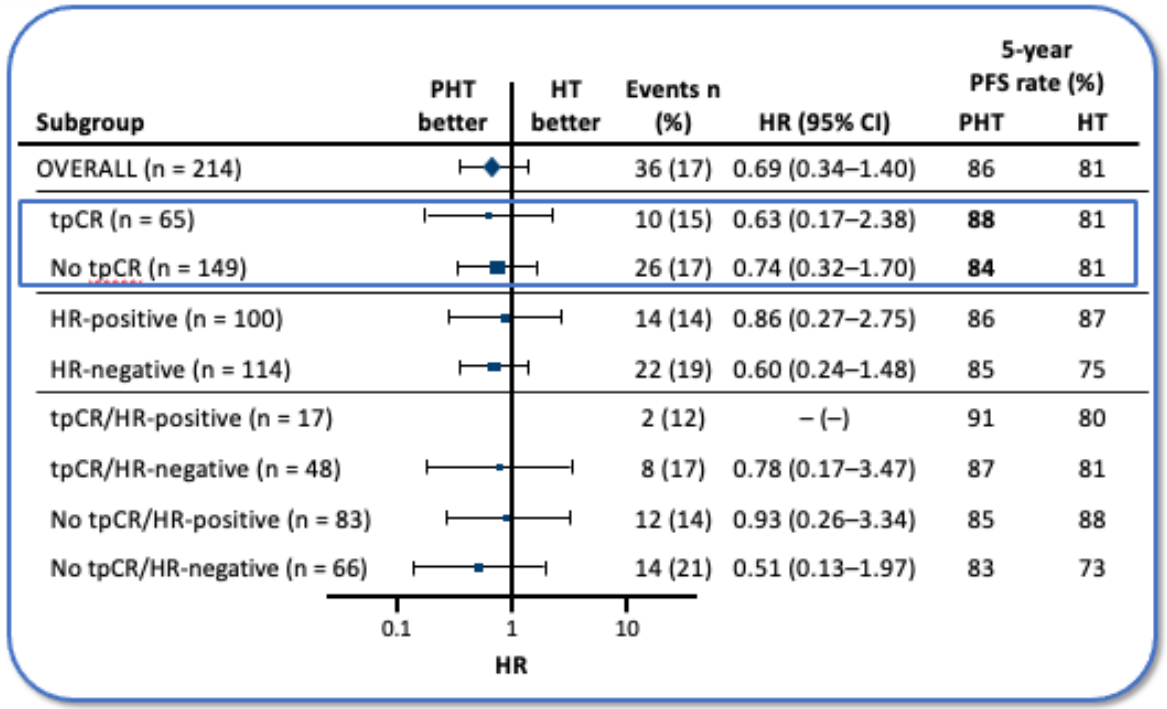
pCR in the breast by HR status*



bpCR, pathological complete response in the breast;
CI, confidence interval; P, pertuzumab; pCR, pathological complete response.
* NeoSphere: chemotherapy was given following surgery.

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

NeoSphere: All patients are at risk of disease recurrence, whether or not they achieve a pCR



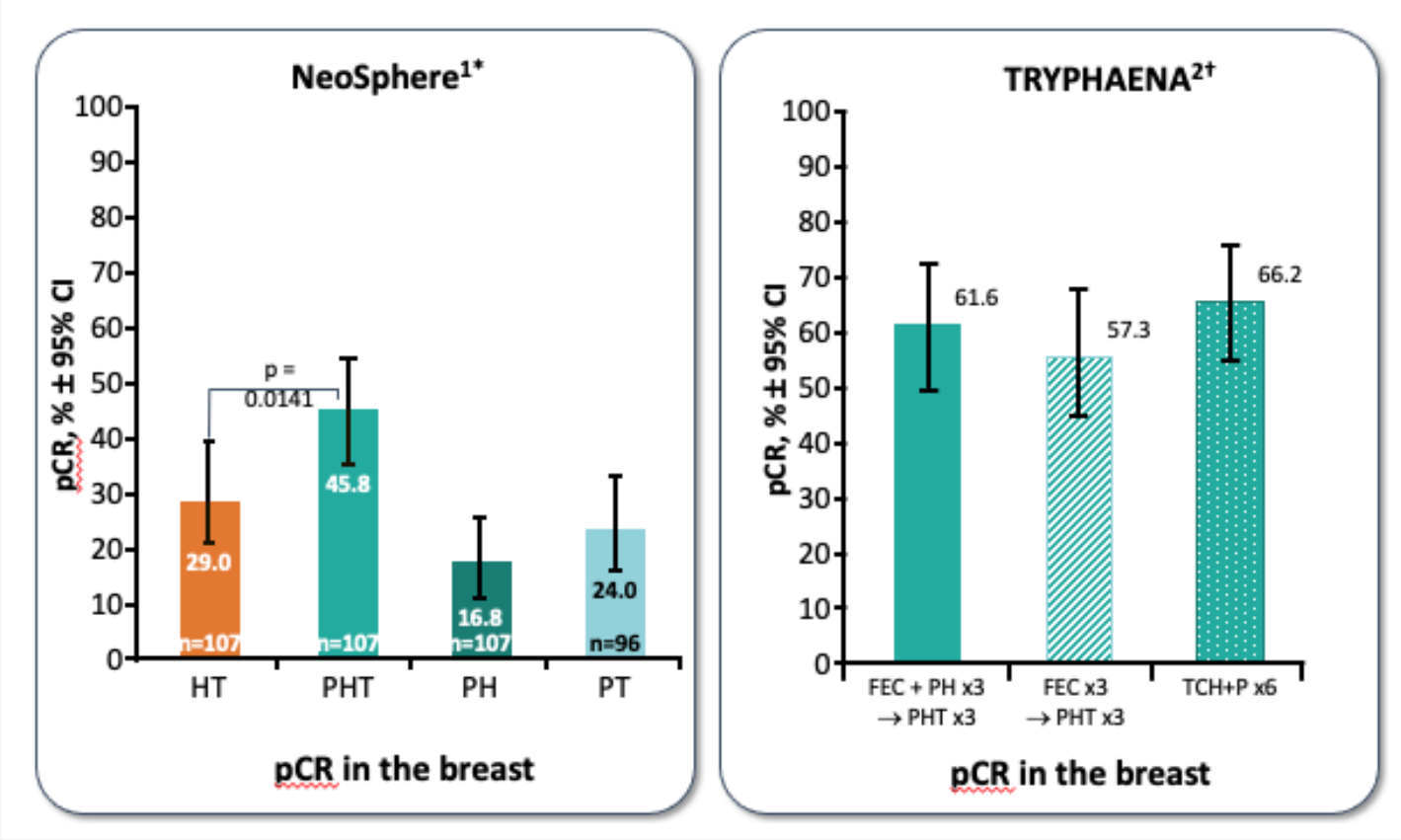
Subgroup	Events n (%)	HR (95% CI)	5-year PFS rate (%) PHT	HT
OVERALL (n = 214)	36 (17)	0.69 (0.34–1.40)	86	81
tpCR (n = 65)	10 (15)	0.63 (0.17–2.38)	**88**	81
No tpCR (n = 149)	26 (17)	0.74 (0.32–1.70)	**84**	81
HR-positive (n = 100)	14 (14)	0.86 (0.27–2.75)	86	87
HR-negative (n = 114)	22 (19)	0.60 (0.24–1.48)	85	75
tpCR/HR-positive (n = 17)	2 (12)	– (–)	91	80
tpCR/HR-negative (n = 48)	8 (17)	0.78 (0.17–3.47)	87	81
No tpCR/HR-positive (n = 83)	12 (14)	0.93 (0.26–3.34)	85	88
No tpCR/HR-negative (n = 66)	14 (21)	0.51 (0.13–1.97)	83	73

Both tpCR and
non-tpCR patients are at risk of relapse:

- In patients with no tpCR following PHT, 16% had relapsed after 5 years vs. 12% in those who did achieve tpCR

Gianni L, et al. Lancet Oncol 2016; 6:791–800 (Supplementary information).

NeoSphere; TRYPHAENA: Improved neoadjuvant outcomes with dual anti-HER2 therapy with pertuzumab plus trastuzumab

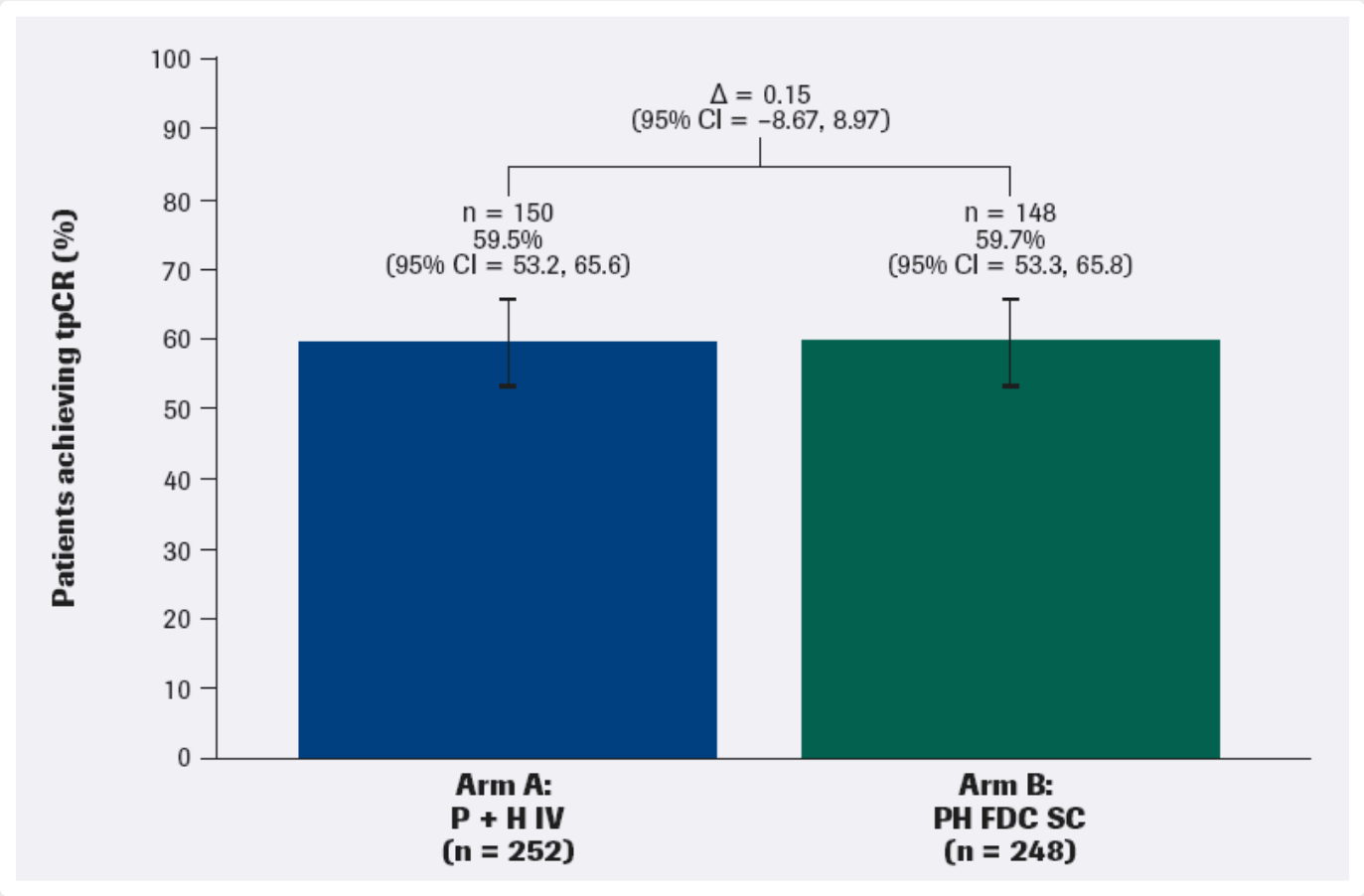


NeoSphere: chemotherapy was given following surgery; † TRYPHAENA was a safety study and pCR was a secondary endpoint.
FEC, 5-fluorouracil, epirubicin, cyclophosphamide; pCR, pathological complete response

1. Gianni L, et al. Lancet Oncol 2012; **13**:25–32;
2. Schneeweiss A, et al. Ann Oncol 2013; **24**:2278–2284

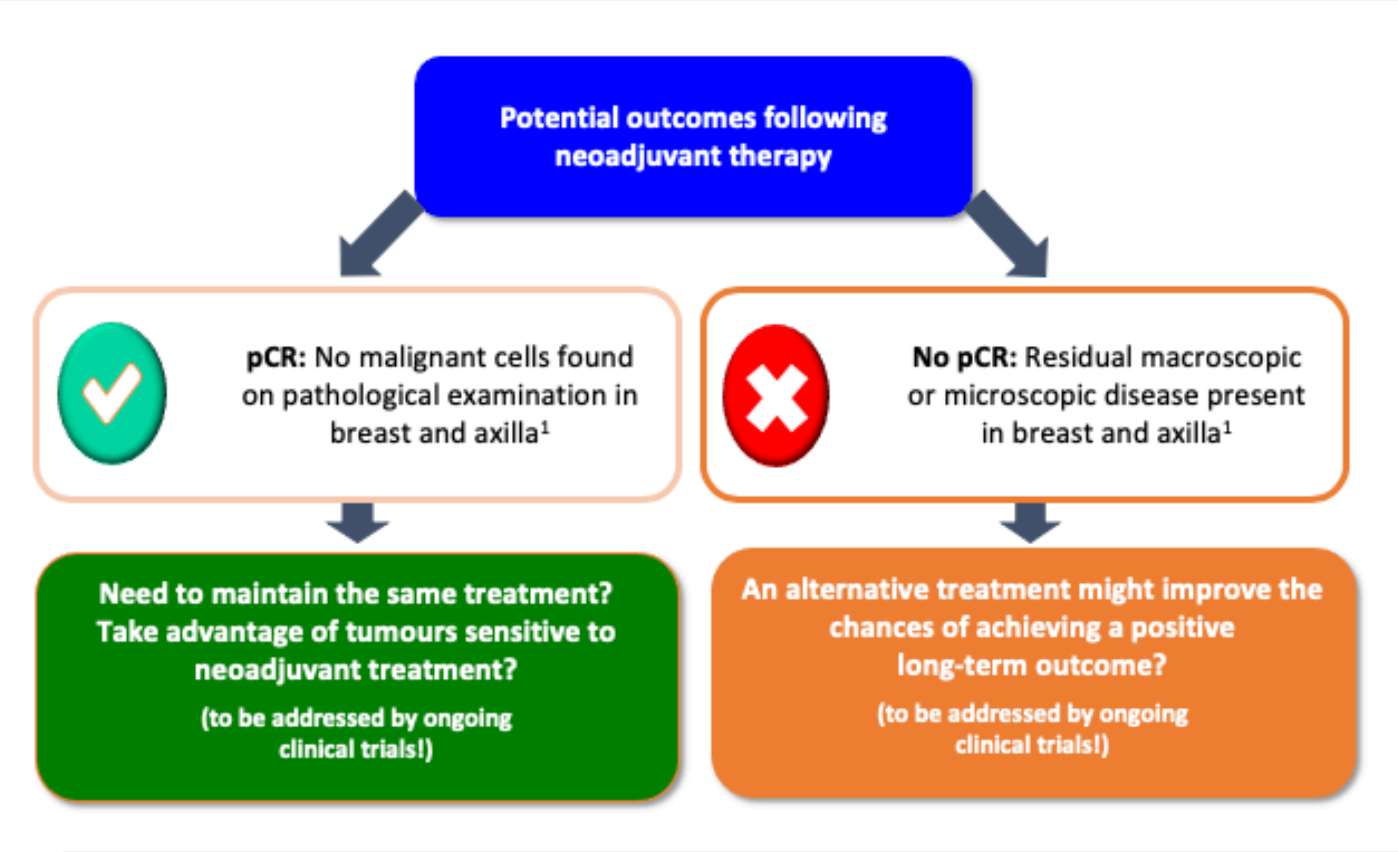
SC TP: FeDeriCa: tpCR

FDA approved. 29th June 2020



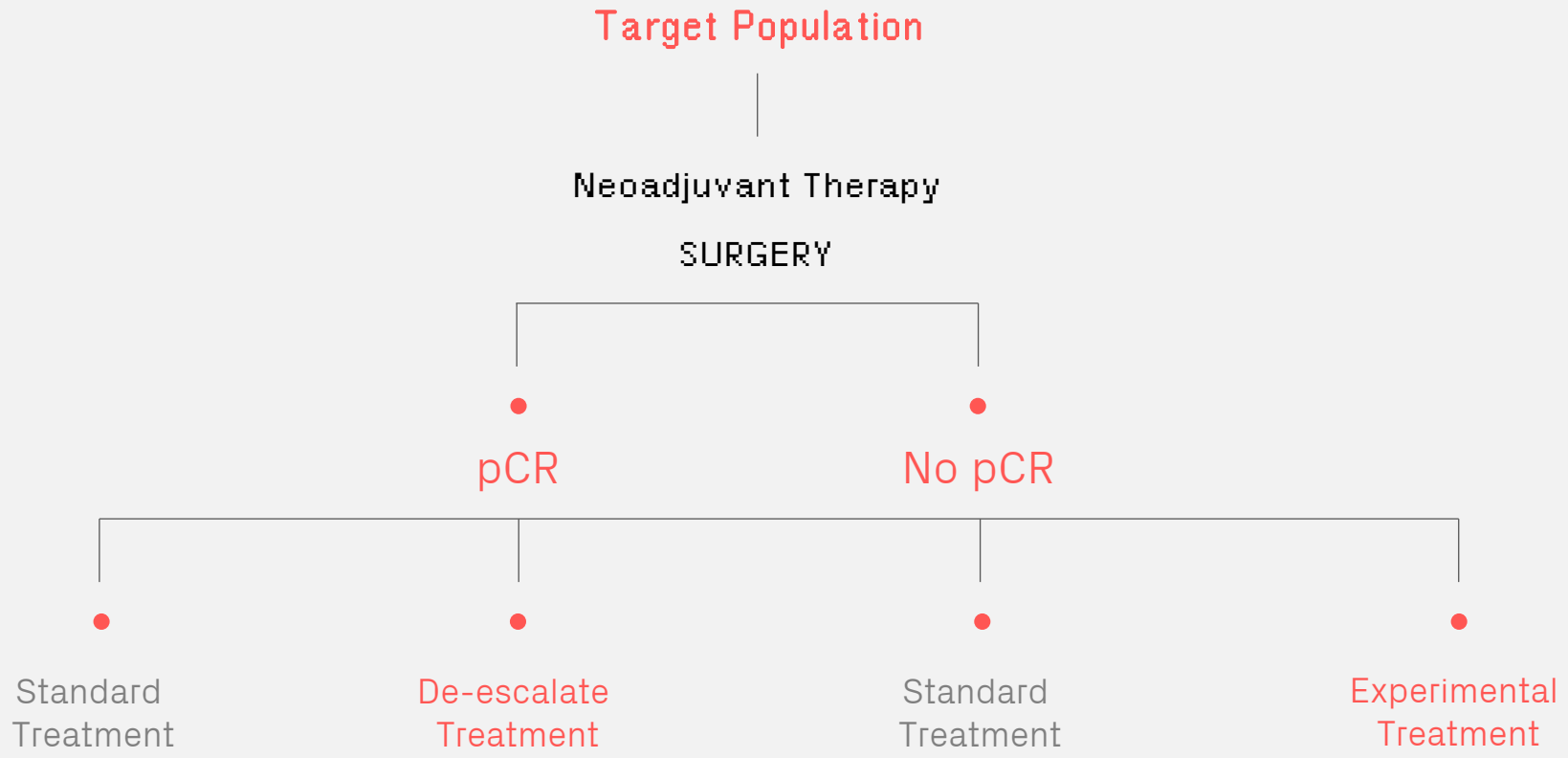
Tan. SABCS 2019. Abstr PD4-07

The outcome of neoadjuvant therapy may still influence subsequent treatment decisions

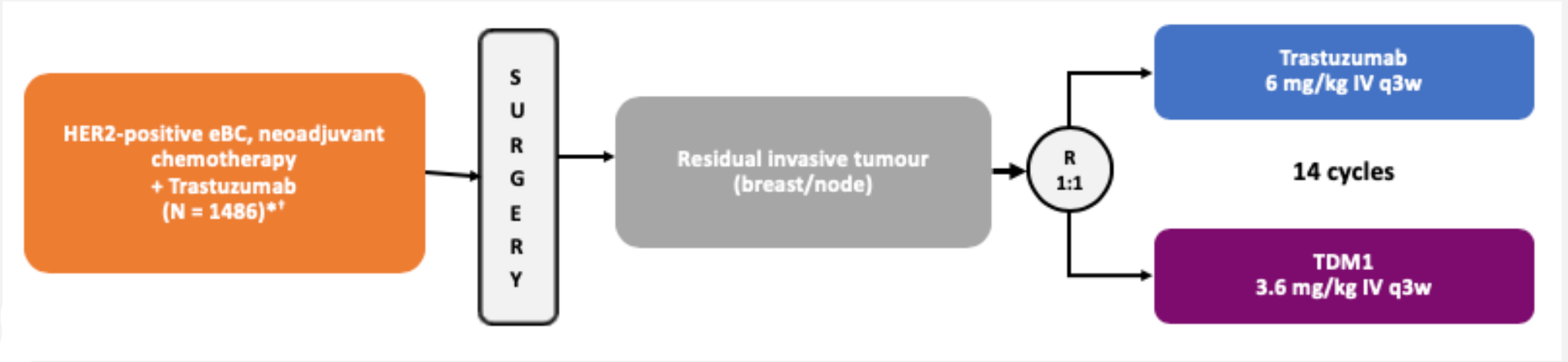


1. FDA Guidance for Industry. https://www.fda.gov/downloads/drugs/guidances/ucm305501.pdf.

Designs based on response to therapy



KATHERINE (BO27938/NSABP B-50-I/GBG 77) Phase III randomised, open-label adjuvant study[1,2]

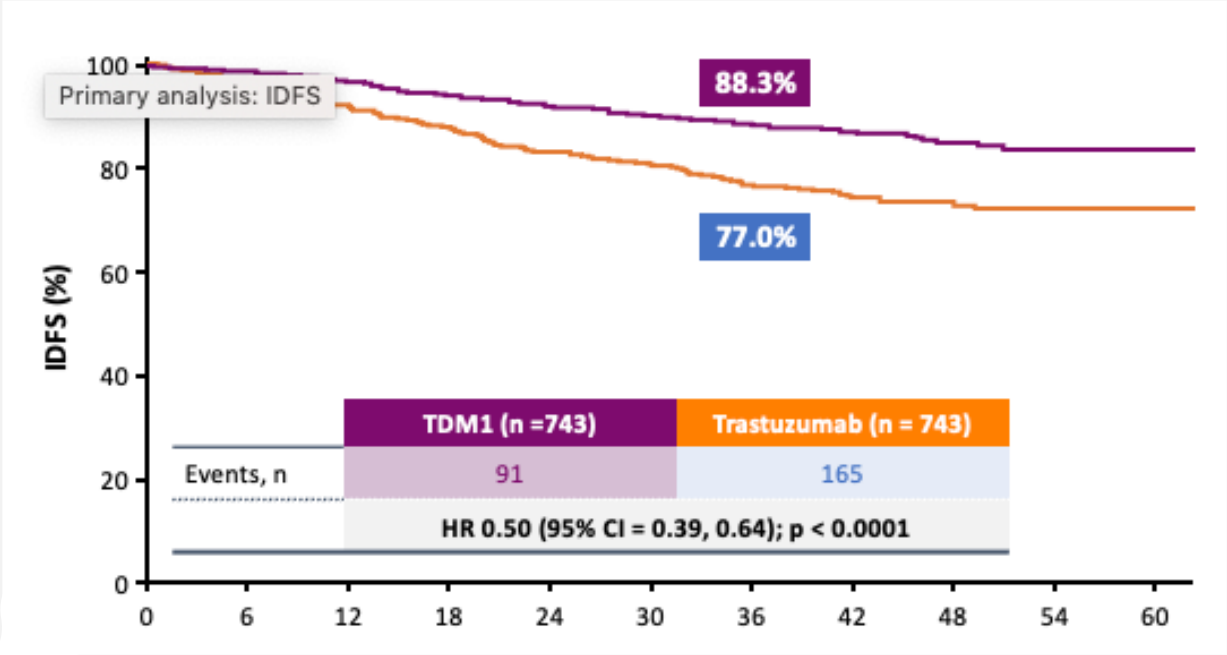


* Neoadjuvant systemic treatment was given for at least 6 cycles, with a total duration of at least 16 weeks, including at least 9 weeks of anti-HER2 therapy and at least 9 weeks of taxane-based chemotherapy (or, if receiving dose-dense chemotherapy regimens, at least 8 weeks of taxane-based therapy and at least 8 weeks of anti-HER2 therapy).
† Dual anti-HER2 therapy was also permitted in the neoadjuvant setting.

1. Roche. Data on File. Protocol BO27938 (KATHERINE) – version 6;
2. von Minckwitz G, et al. N Engl J Med; submitted.

Primary analysis: IDFS

3 years



TDM1 reduced the risk of an IDFS event by 50% compared with Trastuzumab at a median follow-up of 41 months:

TDM1 increased the
3-year IDFS rate from 77.0% to 88.3%

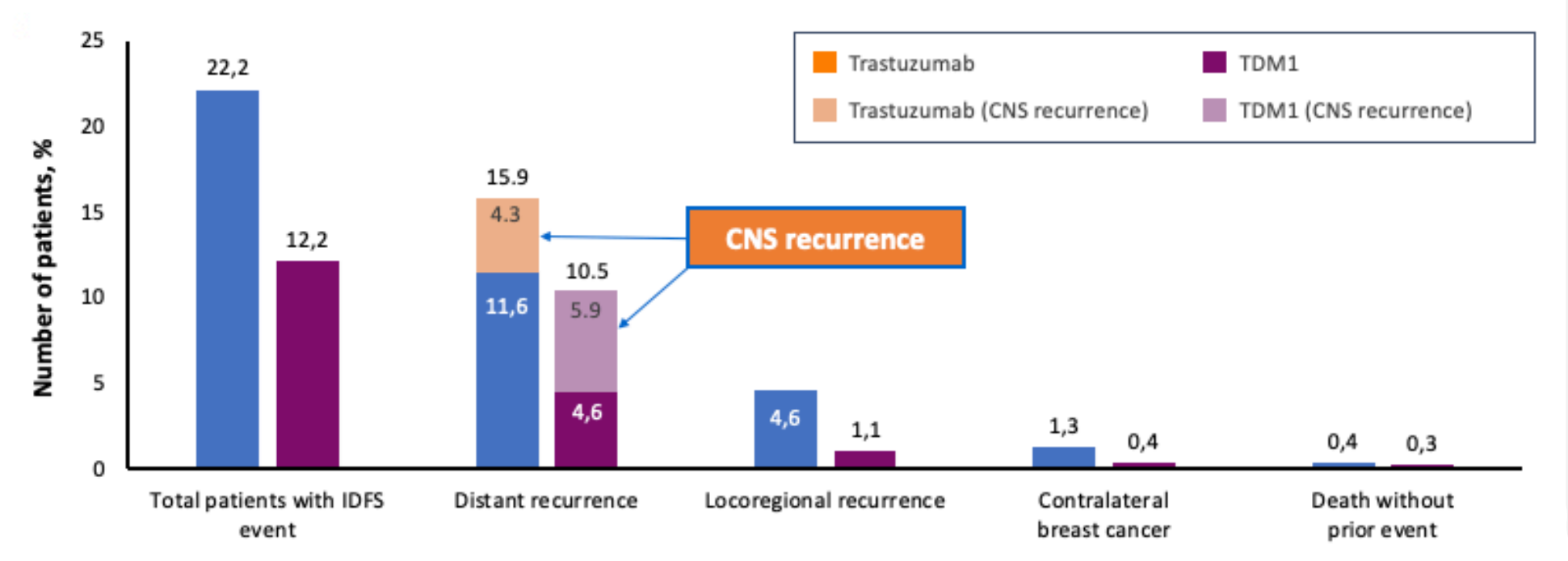
Time (months)

No. At risk

TDM1	743	707	681	658	633	561	409	255	142	44	4
Trastuzumab	743	676	635	594	555	501	342	220	119	38	4

von Minckwitz G, et al. N Engl J Med; submitted.
TolaCI, confidence interval; HR, hazard ratio IDFS, invasive disease-free survival.

First occurrence of an IDFS event

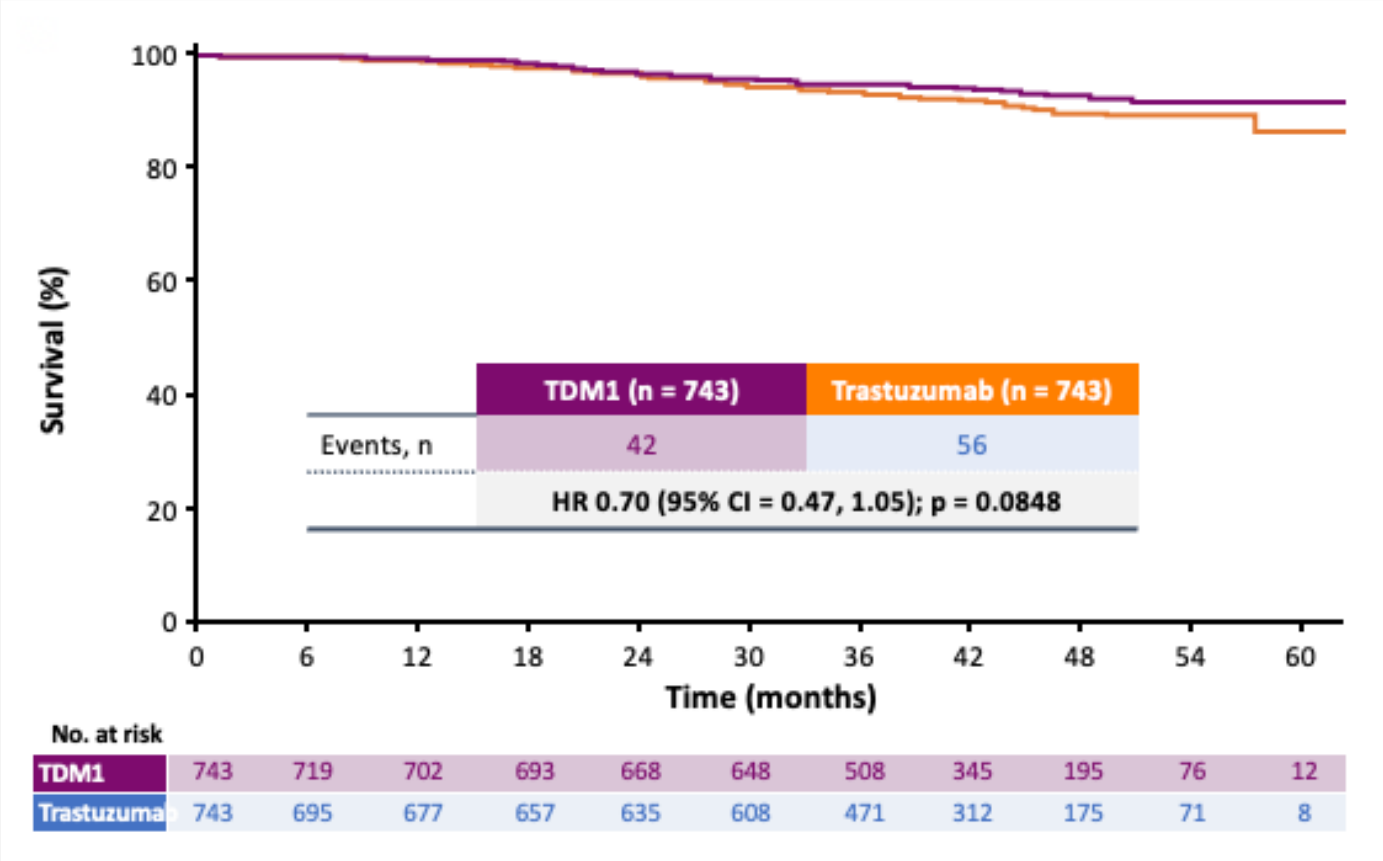


The majority of recurrences were distant, with a reduced incidence in the TDM1 arm

* Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy: 1. Distant recurrence; 2. Locoregional recurrence; 3. Contralateral breast cancer; 4. Death without prior event.CNS, central nervous system; IDFS, invasive disease-free survival.

von Minckwitz G, et al. N Engl J Med; submitted.

First interim analysis OS results



OS data are immature

* Up to three formal interim OS analyses and one final OS analysis are planned. Data here represent the first interim OS analysis; the final OS analysis will be performed at the end of 10 years of follow-up.

CI, confidence interval; HR, hazard ratio; OS, overall survival.

von Minckwitz G, et al. N Engl J Med; submitted.

IDFS by neoadjuvant PERJETA

	Trastuzumab n = 743	TDM1 n = 743
	IDFS events, % (number of patients)	
Prior Trastuzumab only	23.7 (141/596)	13.0 (78/600)
	HR 0.489 (95% CI = 0.371, 0.645)	
	3-year IDFS, %	
	75.9	**87.7**
Prior Pertuzumab–Trastuzumab	IDFS events, % (number of patients)	
	17.3 (24/139)	9.0 (12/133)
	HR 0.498 (95% CI = 0.249, 0.995)	
	3-year IDFS, %	
	80.9	**91.4**

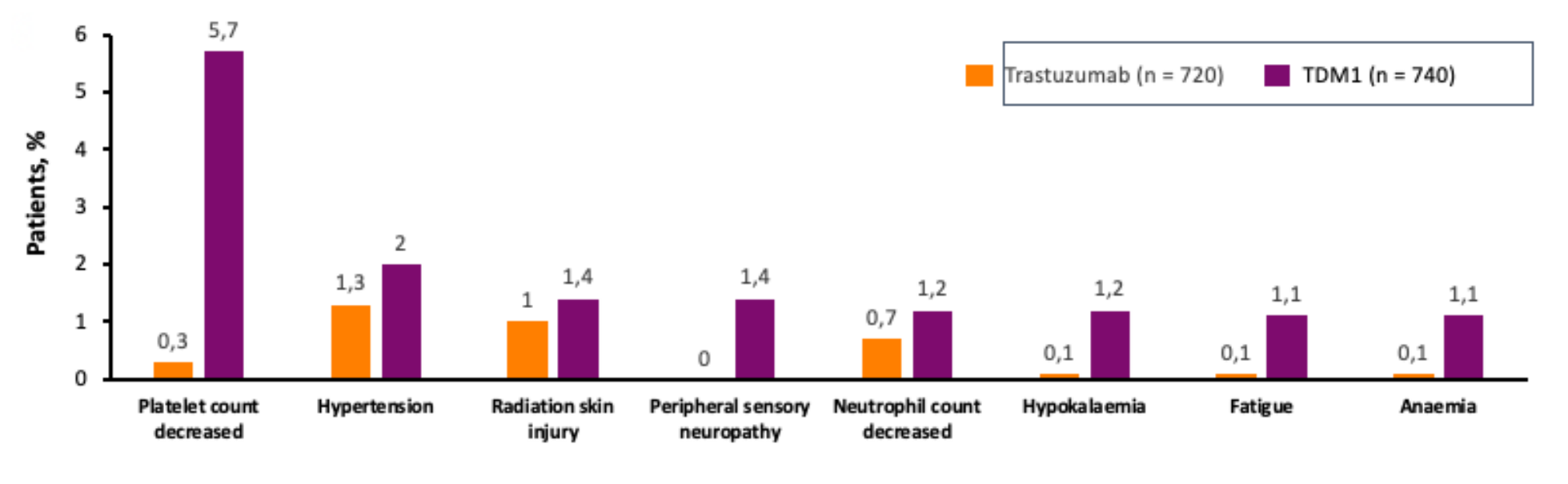
This exploratory analysis shows that TDM1 gave a consistent magnitude of IDFS benefit regardless of prior HER2-directed therapy*

* Caution must be exercised as this exploratory analysis involves low patient numbers and the study is not powered to determine the statistical significance of these data.

CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival.

von Minckwitz G, et al. N Engl J Med; submitted.

Grade ≥3 AEs with ≥1% incidence in either arm



Higher incidence of toxicities in TDM1 arm

* Grade ≥3 haemorrhage rates: 0.4% Kadcyla arm, 0.3% Herceptin arm. One fatal intracranial haemorrhage was reported in the Kadcyla arm.
AE, adverse event.

Geyer Jr. CE, et al. SABCS 2018; abstract GS1-10.

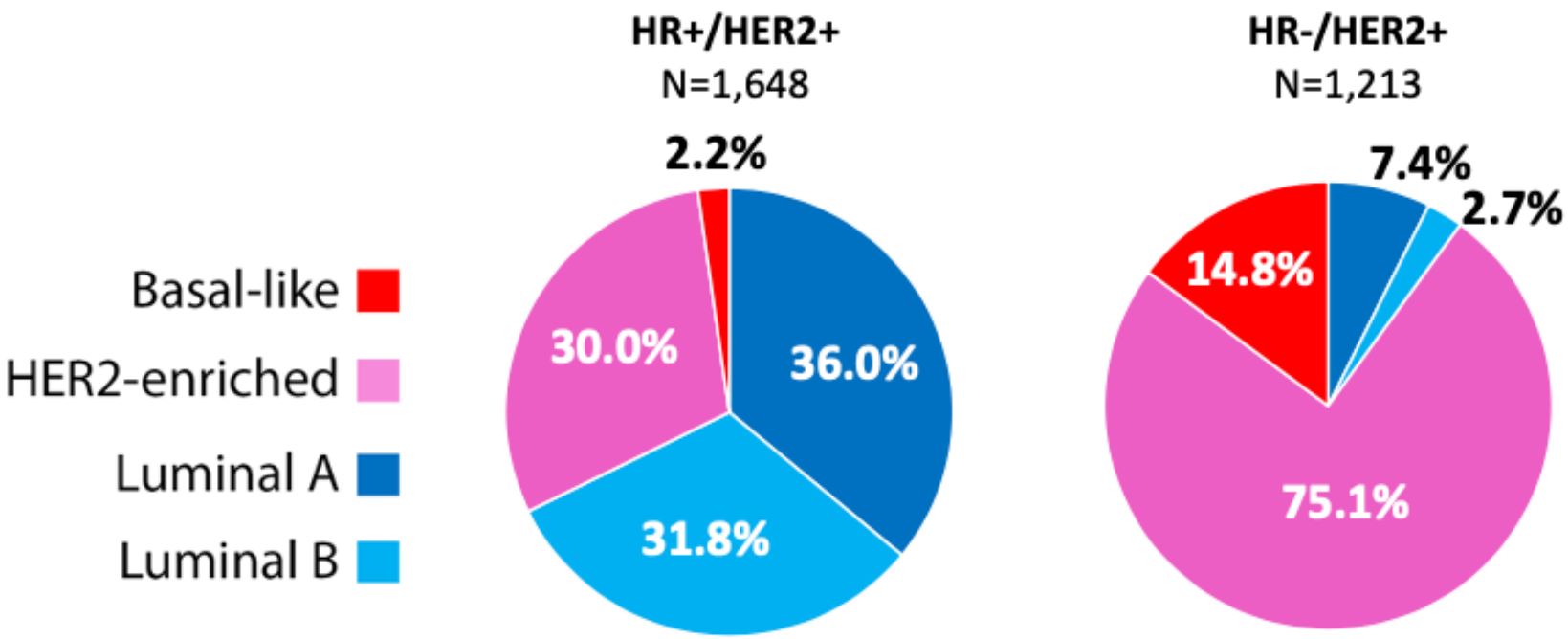
De-escalating neoadjuvant therapy: Biological heterogeneity

pCR rates lower for HR+ HER2+ disease

Trial	HER2 Inhibition	pCR in ER-positive	pCR in ER-negative
NeoSphere[1]	Per/Tras	26%	63%
NeoALTTO[2]	Lap/Tras	42%	61%
CALGB 40601[3]	Lap/Tras	42%	77%
NSABP B-41[4]	Lap/Tras	56%	73%
TRYPHAENA[5]	Per/Tras	46-50%	65-84%
TRAIN-2[6]	Per/Tras	51-55%	84-89%

1. Gianni L, et al. Lancet Oncol 2012. 2. Baselga J, et al. Lancet 2012 and de Azambuja E, et al. Lancet Oncol 2014. 3. Carey LA, et al. J Clin Oncol 2016. 4. Robidoux A, et al. Lancet Oncol 2013. 5. Schneeweiss A, et al. Ann Oncol 2013. 6. van Ramshorst MS, et al. ASCO 2017 Abstract 507

HER2-E subtype is not recapitulated by hormone receptor status



SOLTI: innovative breast cancer research
Cejalvo et al. ESMO 2017 #1727P

HER2-enriched subtype vs. pCR following anti-HER2-based neoadjuvant treatment

(13 studies – 2,087 patients)

	NOAH[1] (Prat, CCR 2014)	NeoALTTO[2] (Fumagalli, JAMA Oncol 2016)	CALGB[3] 40601 (Carey, JCO 2016)	CherLOB[4] (Dieci, Ann Oncol 2018)	ICO+CLINIC[5] (Pernas, SABCS 2017)	OPTIHER[6] (Gavilá, BMC Med 2019)	KRISTINE[7] (Prat, SABCS 2017)	KRISTINE[7] (Prat, SABCS 2017)	BERENICE[8] (Swain, Oncol 2018)	B41[9] (Swain, ASCO 2018)	PAMELA[10] (Llombart-Cussac, Lancet Oncol 2017)	TBCRC[11] 006/023 (Prat, ASCO 2018)	PER-ELISA[12] (Guarneri, ASCO 2018)
Therapy	AT +H	T +L/H/LH	T +L/H/LH	AT +L/H/LH	AT +H	AT +H+P	T-DM1 +P	DC +H+P	AT +H+P	AT +L/H/LH	L+H (18w)	L+H/L+H (12w/12 vs 24w)	H+P+Le
N	63	254	265	64	154	58	183	171	294	276	151	114	40
Variable	pCR_{BA}	pCR_{B}	pCR_{B}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{B}	pCR_{B}	pCR_{BA}
pCR in HER2-E	52.9%	52.0%	65.8%	50.0%	63.4%	83.3%	62.2%	72.1%	74.2%	60.9%	41%	27.4%	45.5%
pCR in non-HER2-E	34.5%	21.5%	31.1%	17.0%	26.2%	46.43%	26.9%	32.8%	26.9%	25.7%	10%	9.8%	13.8%
P-value	0.014	<0.001	<0.001	0.008	<0.001	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	0.034	0.042

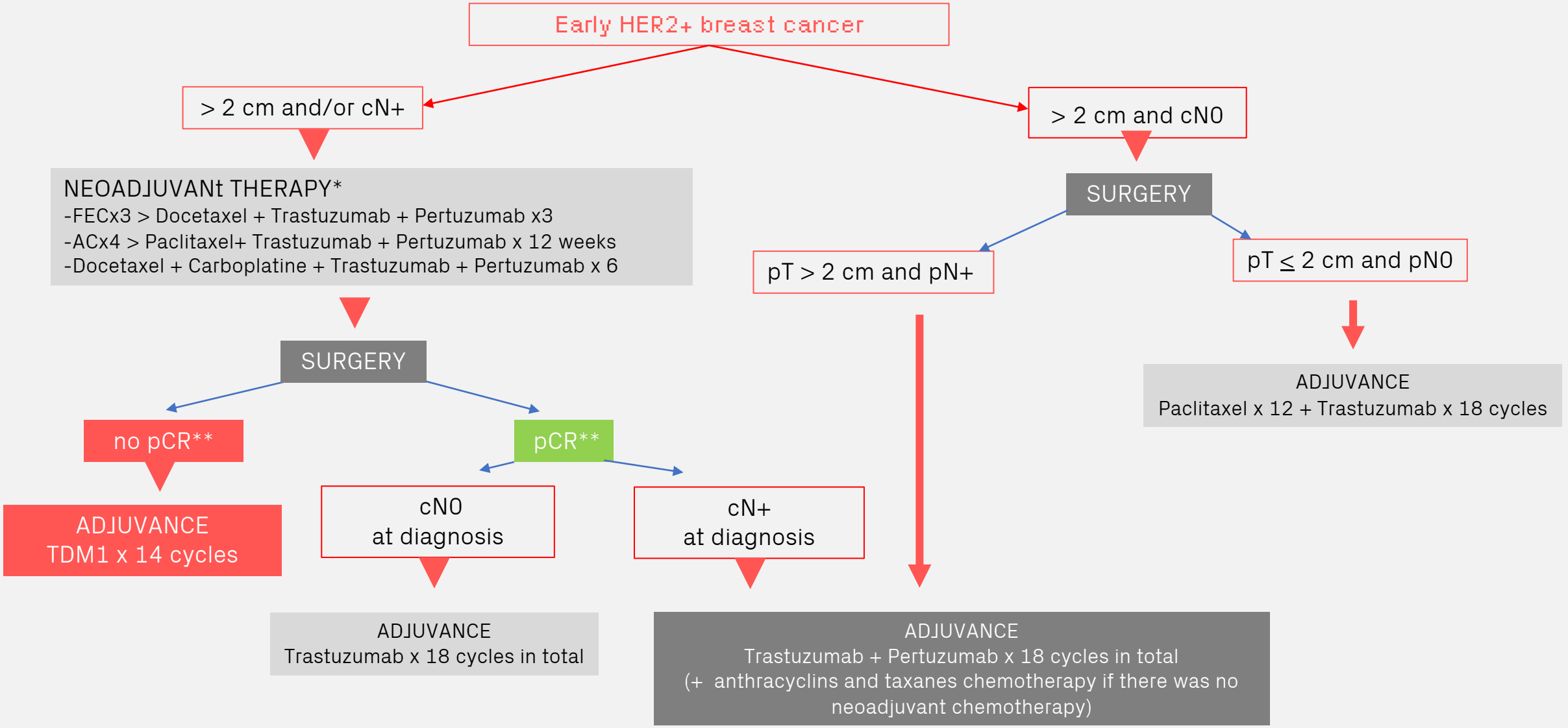
No Chemo

Mean pCR in HER2-E 57.7%

Mean pCR in non-HER2-E 24.8%

NOAH: Prat et al. Clin Cancer Res. 2014 Jan 15;20:511-21
NeoALTTO: Fumagalli et al. JAMA Oncol. 2016.3824
CALGB: Carey et al. J Clin Oncol. 2016;34:542-9
CherLOB: Dieci et al. Ann Oncol. 2016;27:1867-73
ICO+CLINIC: Pernas et al. San Antonio Breast Cancer Symposium 2017; P2-09-11
OPTIHER: Gavilá et al. San Antonio Breast Cancer Symposium 2017; P2-09-04
KRISTINE: Prat et al. San Antonio Breast Cancer Symposium 2017; PD3-06
BERENICE: Swain et al. Annals of Oncology 29: 646–653
PAMELA: Llombart-Cussac et al. Lancet Oncol. 2017;18:545–54
TBCRC006/023: Prat et al. J Clin Oncol 2018;36 (Supplement abstract 509)
Per-ELISA: Guarneri et al. J Clin Oncol 2018;36 (Supplement; abstract 507)

AT, anthracycline/taxane; C, carboplatin; D, docetaxel;
H, herceptin; L, lapatinib; P, pertuzumab; T, paclitaxel; Le, letrozole



*Consider Trastuzumab + Pertuzumab with anthracyclins and taxanes in high risk tumors
** pCR: absence of infiltrating carcinoma in breast and lymph nodes
Add endocrine adjuvant therapy and radiotherapy according to standard indications

Unmet medical needs in HER2+ breast cancer

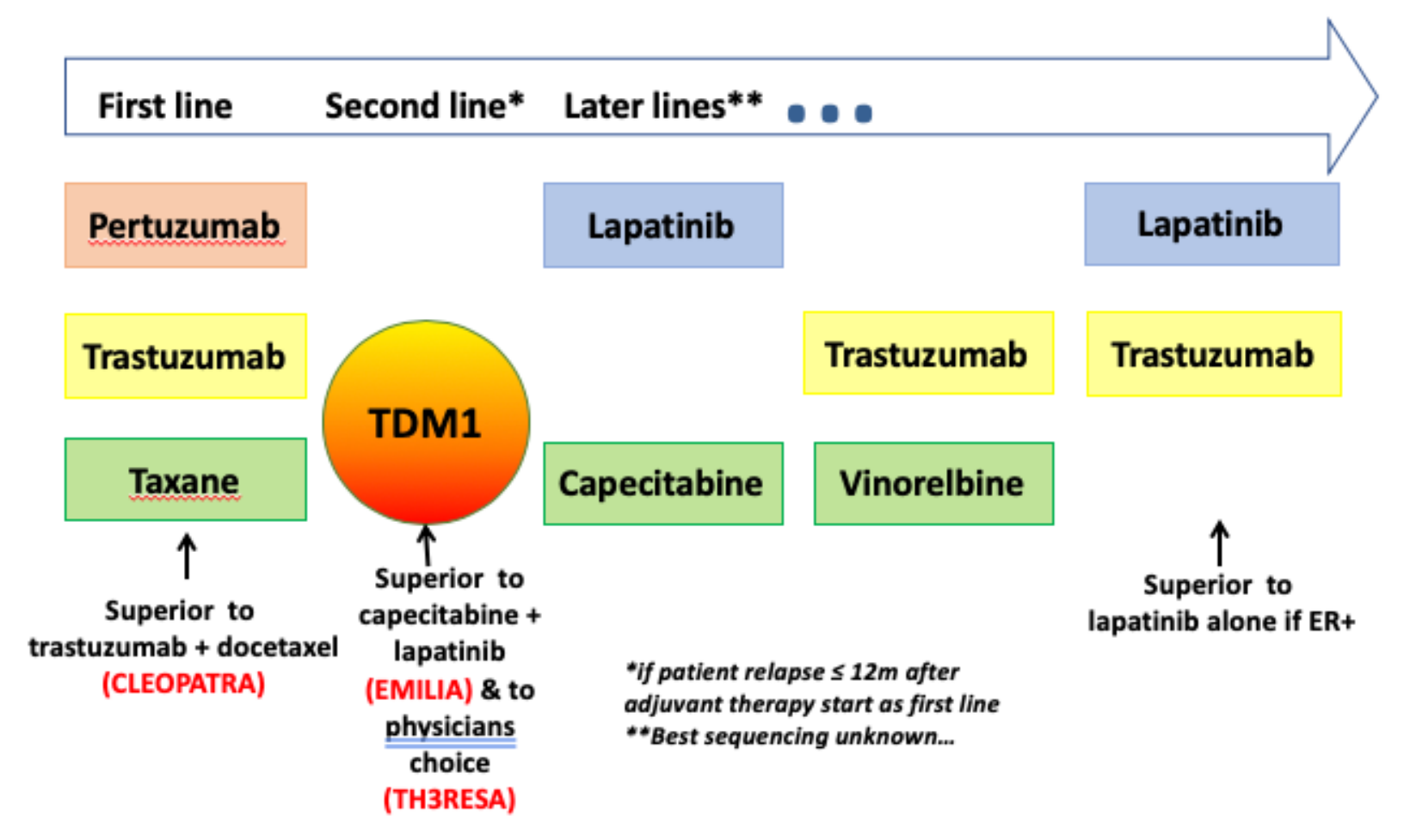
- Around 20% of patients will relapse despite adjuvant treatment
- There are NOT “chemo-free” schemes for fragile population
- Identify high risk populations candidate for a more intensive treatment
- Biological Heterogeneity: diversity of response to neoadjuvant treatment

  - identify populations with a different sensitivity
  - adapt adjuvant treatment

    * in pCR
    * in residual disease

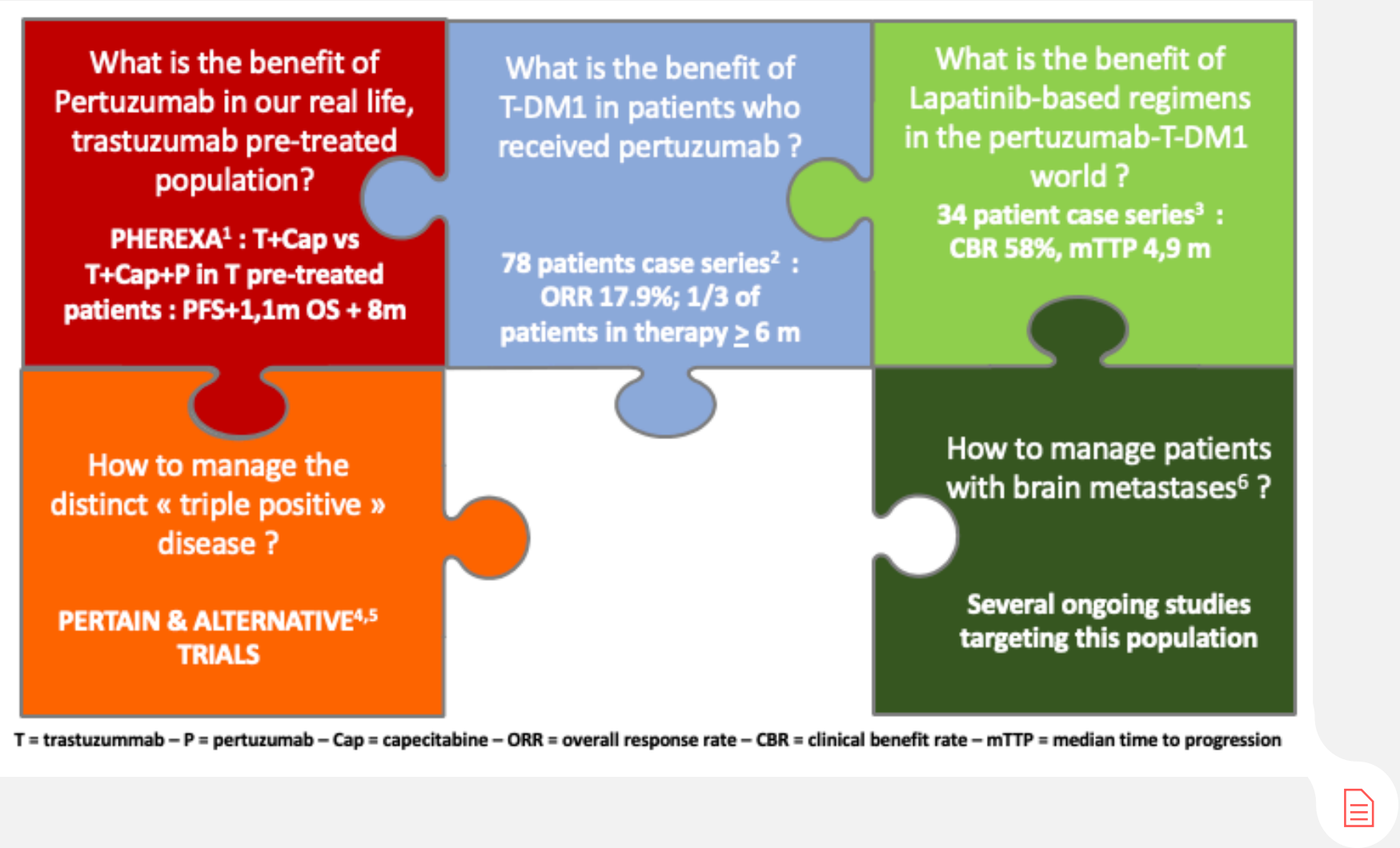
Advanced breast cancer

Advanced HER2+ Breast Cancer : Current Standards of Care in 2020



Giordano S. et al; JCO 32(19) 2014; 2078-2099

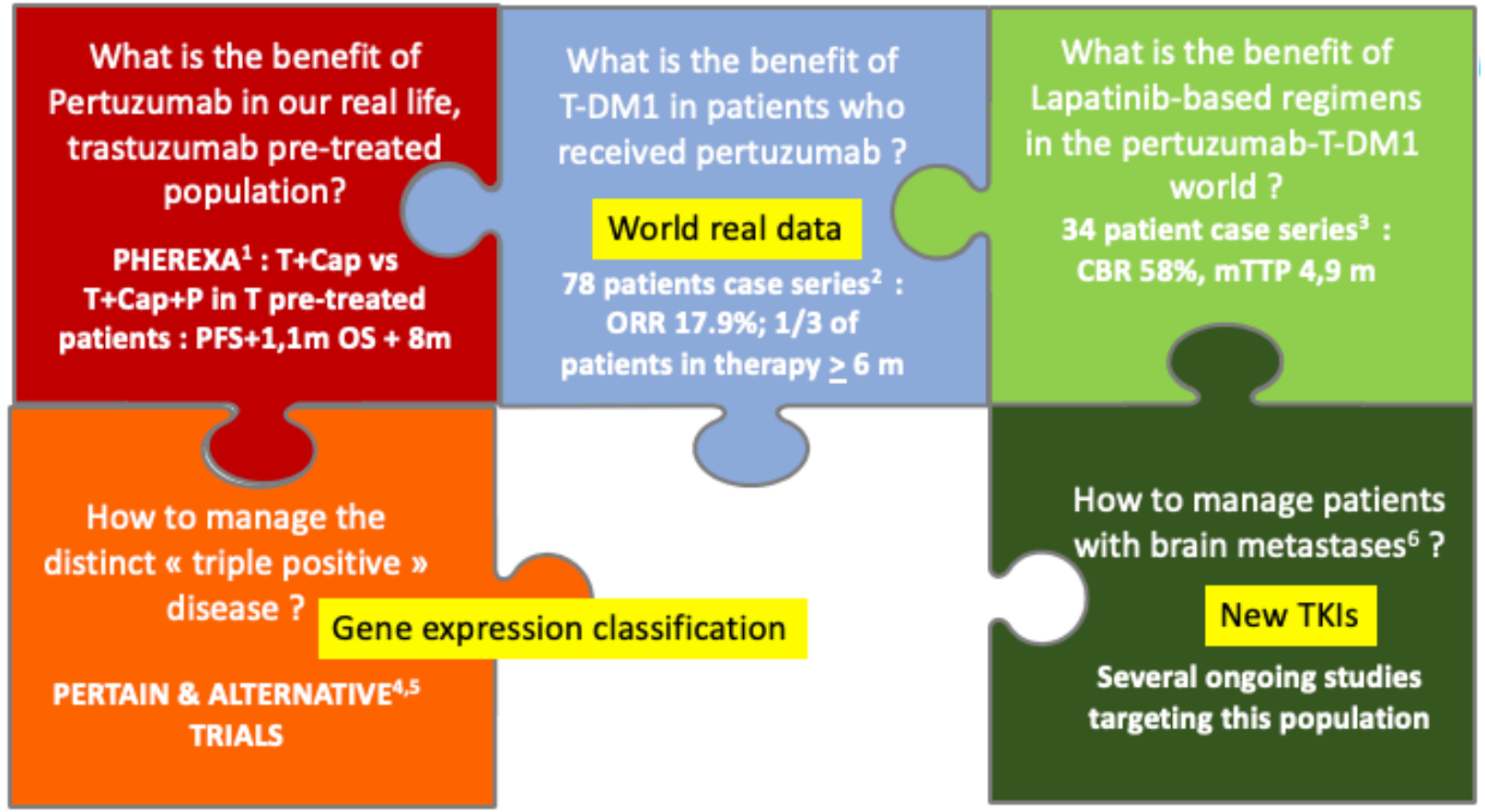
Current Standards of care pending questions



T = trastuzummab – P = pertuzumab – Cap = capecitabine – ORR = overall response rate – CBR = clinical benefit rate – mTTP = median time to progression

1. Urriticoechea A et al; JCO 2017 35, (26) 3030-3038; 2. Dzimitrowicz H. et al; JCO 2016; 34(29):3511-3517; 3.Báez-Vallecillo L et al SABCS 2016 P4-21-20; 4. Arpino G et al SABCS 2016 abstract S3-04; 5. Gradishar et al ASCO 2017 abstract 1004

Current Standards of care pending questions



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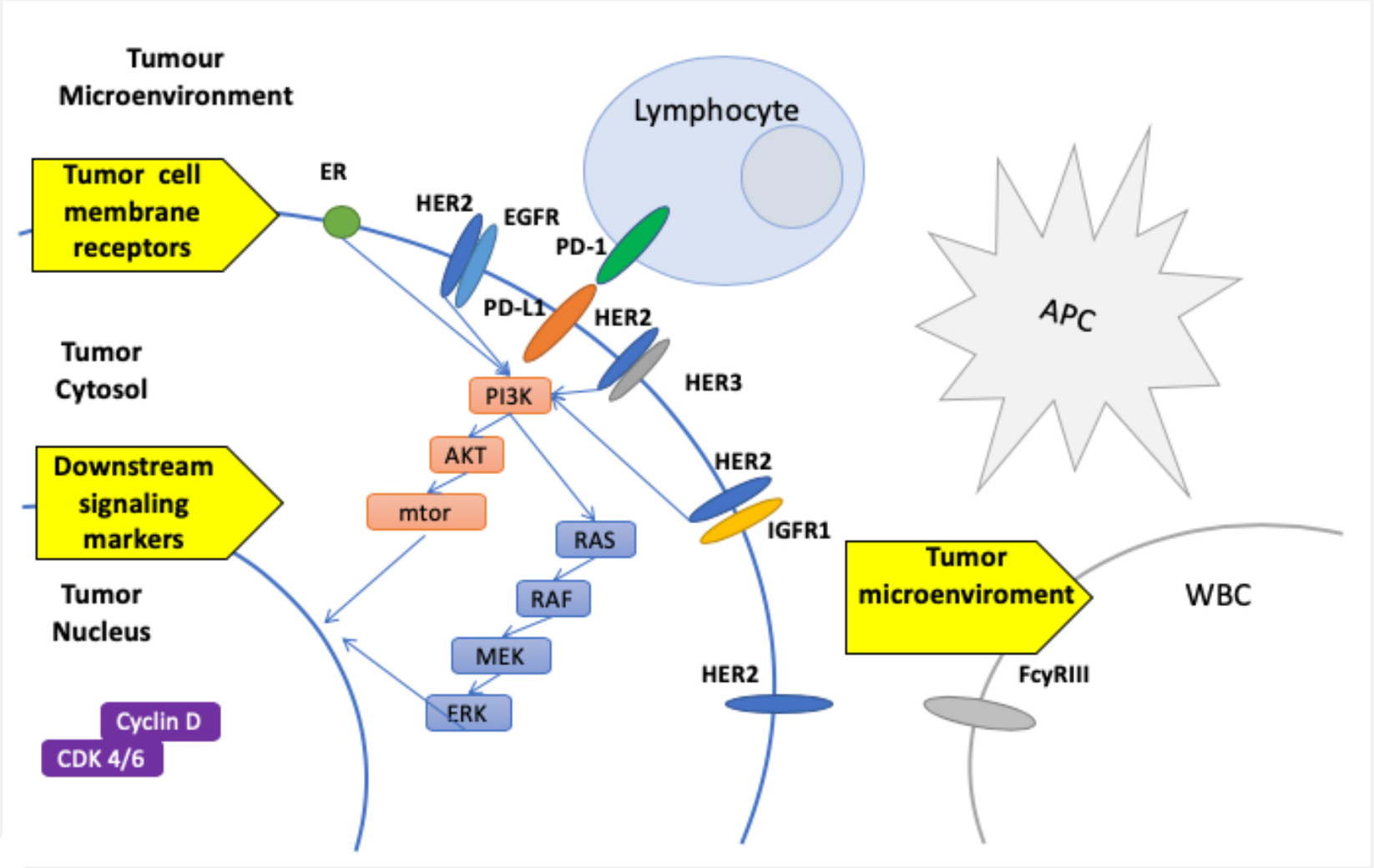
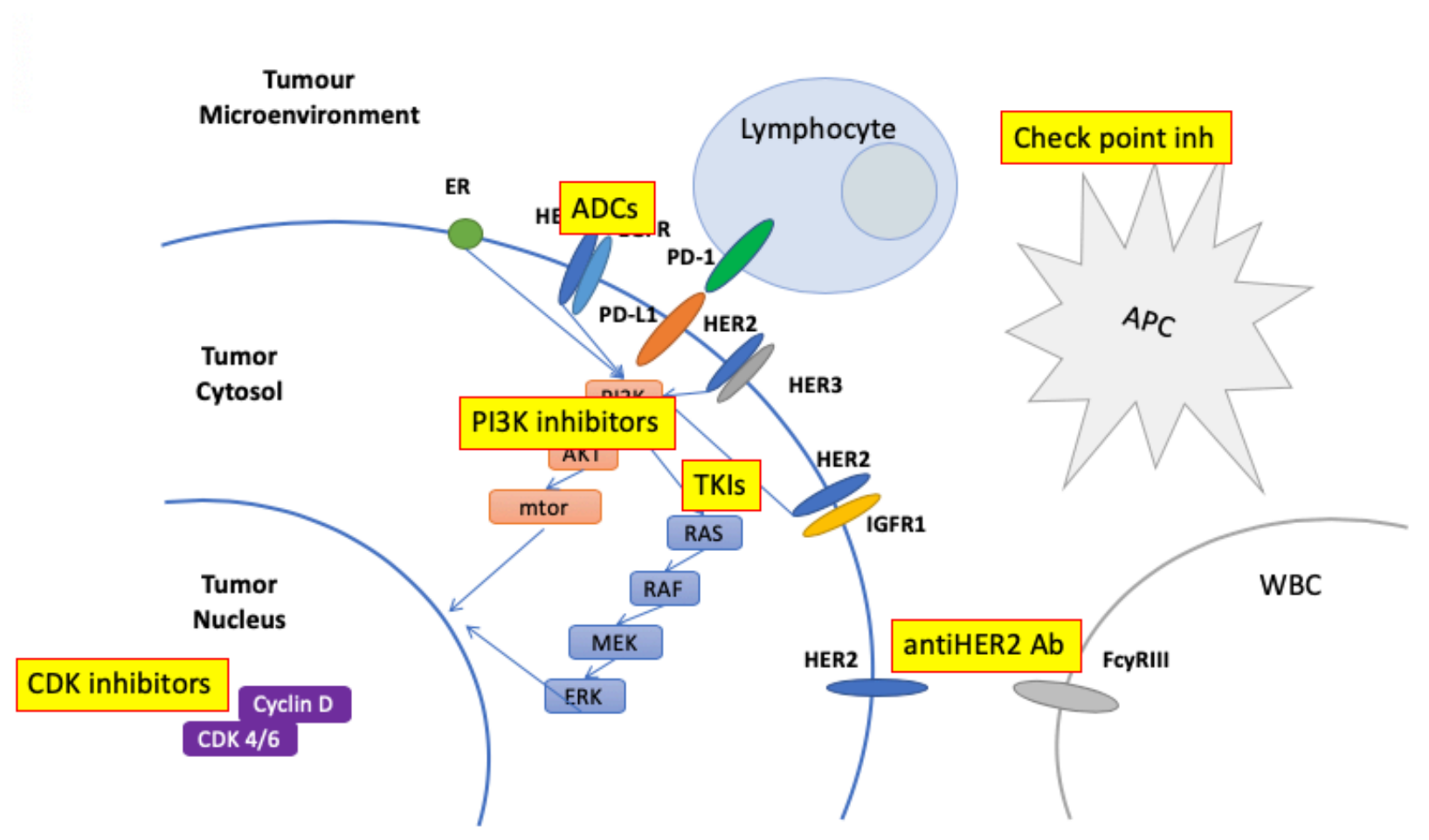
Advanced HER2+ Breast Cancer : Predictive Biomarkers ?



Adapted from Gingras I et al; Nature Reviews clinical Oncology 2017

Advanced HER2+ Breast Cancer : Predictive Biomarkers ?



Adapted from Gingras I et al; Nature Reviews clinical Oncology 2017

Unmet medical needs in HER2+ breast cancer

- Around 20% of patients will relapse despite adjuvant treatment
- There are NOT “chemo-free” schemes for fragile population
- Identify high risk populations candidate for a more intensive treatment
- Biological Heterogeneity: diversity of response to neoadjuvant treatment

  - identify populations with a different sensitivity
  - adapt adjuvant treatment

    * in pCR
    * in residual disease

Unmet medical needs in HER2+ breast cancer

ADVANCED BREAST CANCER

- IT IS STILL AN INCURABLE DISEASE
- There are NOT “chemo-free” schemes for fragile population / luminal subtype / de-escalating
- Lack of evidence in phase III studies according to previous treatment
- Special clinical situations: metastasis in CNS
- Toxicity: Cardiac
- Biological Heterogeneity

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Thank you

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