CARCINOMA MAMMARIO HER 2+

Novità sul trattamento (neo)adiuvante

Enna, 01/03/2019
Dott.ssa Cristina Raimondi

Evolution of neoadjuvant therapy

Reserved for patients with inoperable, locally advanced BC to enable surgery[1]

IChemotherapy

IEndocrine therapy

Used for patients with inoperable, locally advanced BC or for those with operable BC at high risk of recurrence[1,2]

ITargeted therapies

IChemotherapy

IEndocrine therapy

1.Cain H,et al. ClinOncol (RColl Radiol)2017; 2. TeshomeM & Hunt KK. SurgOncol ClinN Am2014.

Neoadjuvant treatment supports various aspects of eBC management

- Increases opportunity for BCS and less radical axillary dissection[1,2]
- Reduces surgical morbidity[1,2]
- Enables early response assessment[3]
- Complements assessment of prognosis together with other risk factors[4]
- Allows more time for genetic testing and consideration of surgical options[4,5]
- Supports faster regulatory approval of new drugs[5,6]

1.KaufmannM, et al.Ann SurgOncol2012; 2. Abt NB,et al. JAMASurg2014; 3. Prowell TM,et al. NEJM2012;4. Cain H, et al. ClinOncol2017;5.FDA 2014. Guidance for Industry: pCRin neoadjuvant treatment ofhigh-risk eBC; 6. EMA Anticancer Guidelines, 2014, Appendix4.

A multi-disciplinary approach is key to providing a comprehensive treatment plan for patients

Surgical, medical and radiation oncologists involved in treatment plan design

Discussions of the benefits of neoadjuvant vs. adjuvant treatment from each speciality's standpoint

Staging studies may be needed before treatment initiation

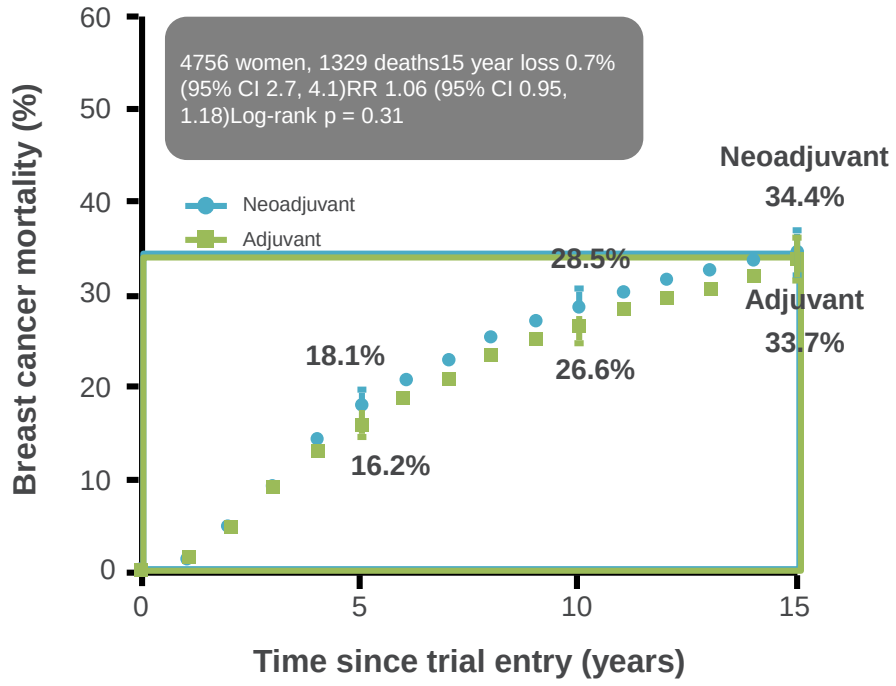
Additional imaging studies/interventions may be necessary to better define the extent of loco-regional disease and plan therapy

Early involvement of plastic surgeons and geneticists further facilitates the treatment plan

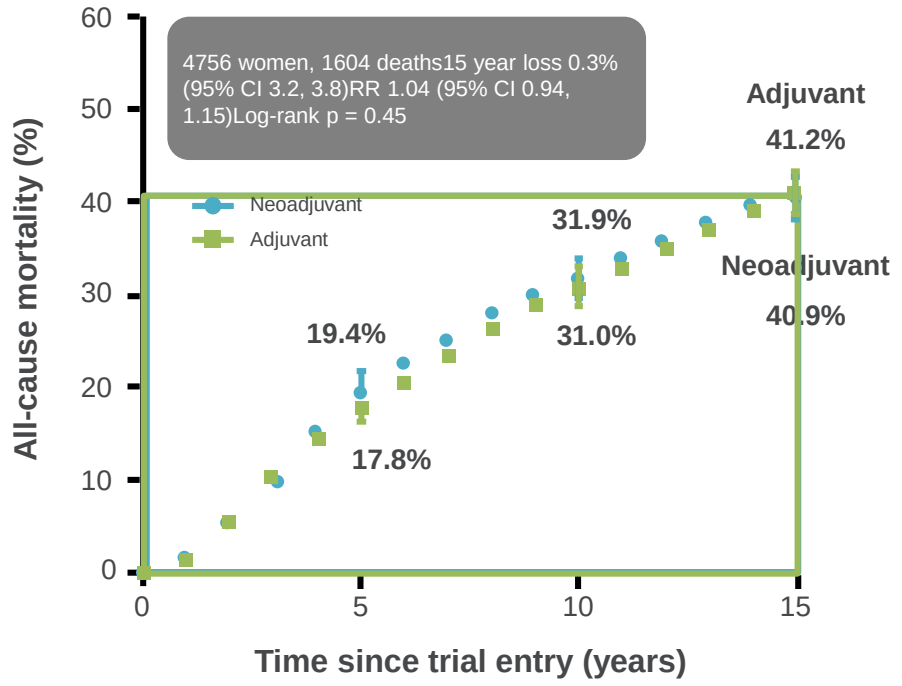
Chatterjee A & Erban JK. Gland Surg 2017.

EBCTCG Meta-analysis: mortality rates

Breast cancer mortality



All-cause mortality

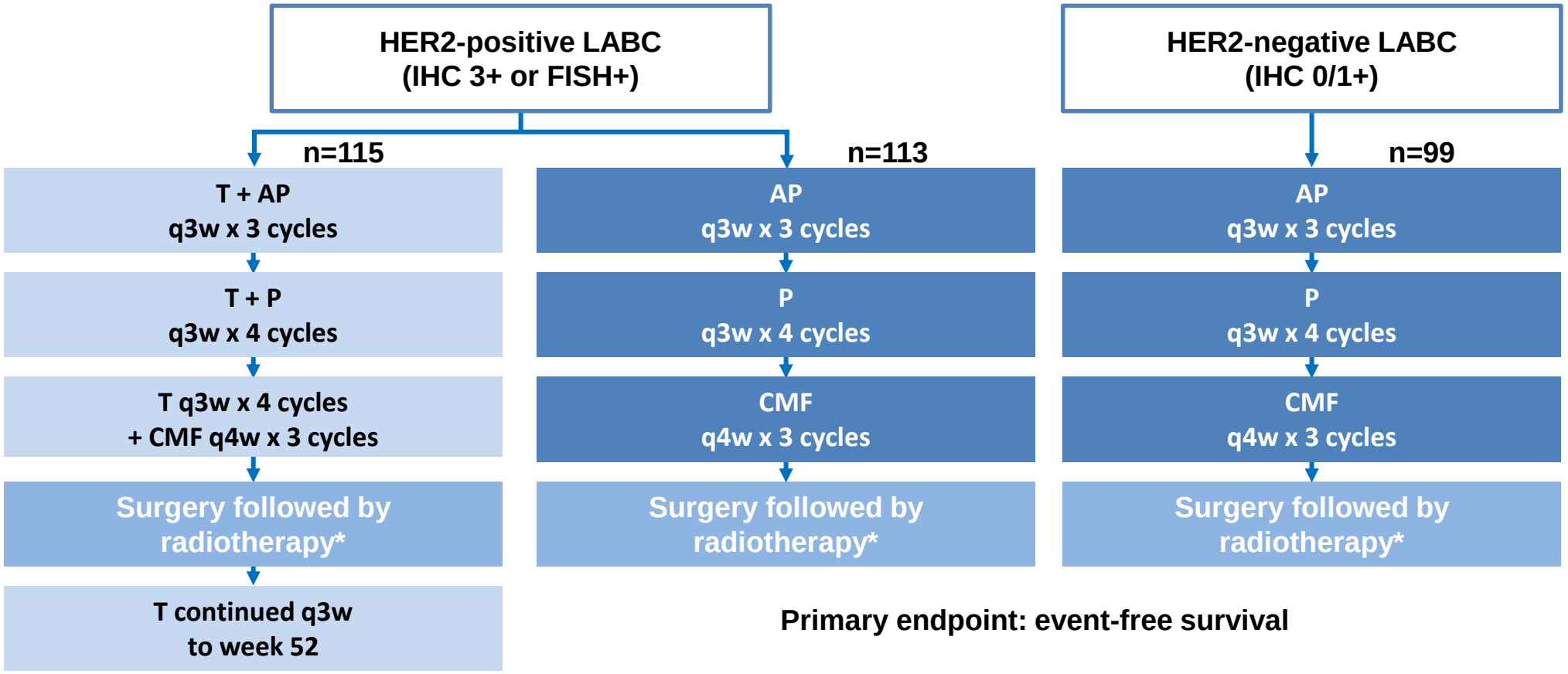


EBCTCG Meta-analysis of ten randomised trials (1983-2002)in BC* showed that mortality rates are similar with neoadjuvant or adjuvant chemotherapy only

Adapted from Early BreastCancer Trialists' Collaborative Group (EBCTCG);LancetOncol. 2018 Jan;19(1):27-39

** All breast cancer subtypes included in the analysis; it was not an HER2-positive specific analysis.NACT, neoadjuvantchemotherapy; RR, rate ratio.*

NOAH: study of neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone in HER2+ LABC or inflammatory BC



AP = doxorubicin (60 mg/m^2), paclitaxel (150 mg/m^2); T = trastuzumab (8 mg/kg loading dose then 6mg/kg); P = paclitaxel (175 mg/m^2).
**Hormone receptor-positive patients will receive adjuvant tamoxifen*
LABC = locally advanced breast cancer; CMF = cyclophosphamide, methotrexate and fluorouracil

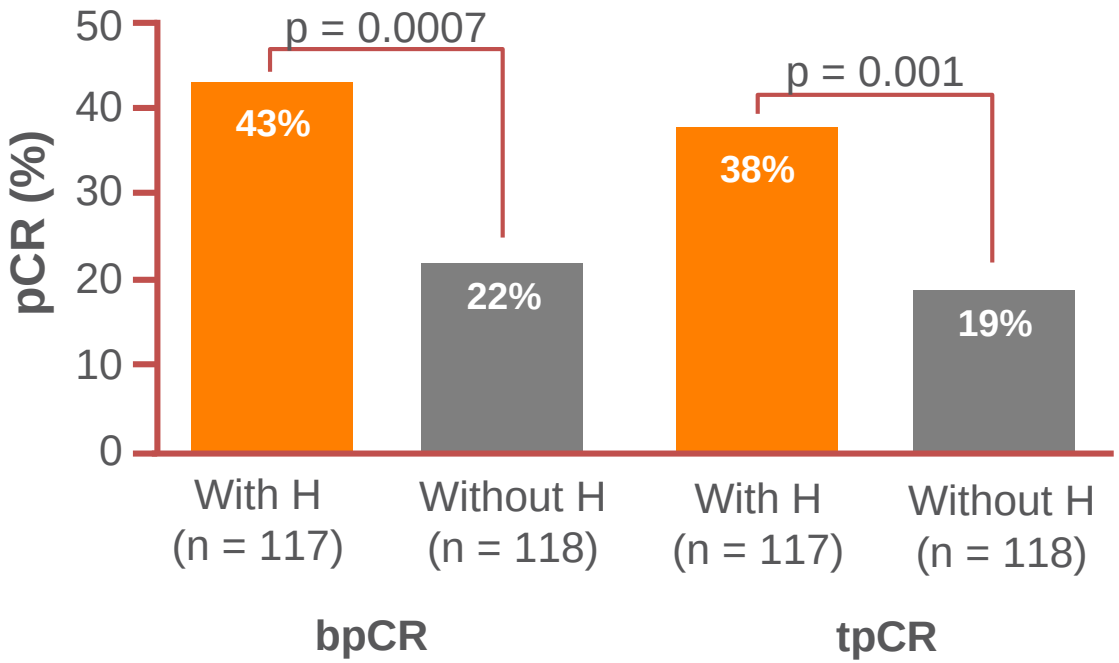
Graphical elaboration from text data Gianni L, *et al. Lancet* 2010; 375: 377-84

NOAH: Neoadjuvant outcomes improved with the addition of HER2-targeted therapy

Pathological responses to treatment

	HER2-positive disease		p value*	HER2-negative disease	p value †
	With trastuzumab (n=117)	Without trastuzumab (n=118)		Without trastuzumab (n=99)	
bpCR	50 (43%)	26 (22%)	0·0007	17 (17%)	0·37
tpCR	45 (38%)	23 (19%)	0·001	16 (16%)	0·52
OR‡	102 (87%)	87 (74%)	0·009	70 (71%)	0·62

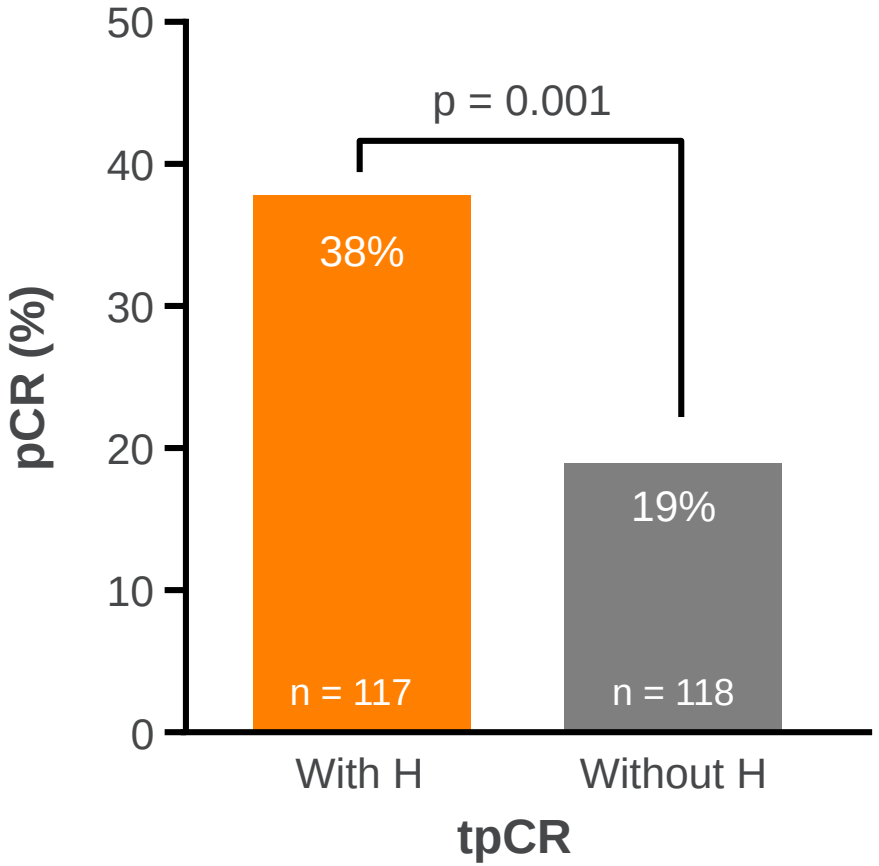
*Data are n (%). bpCR=pathological complete response in breast tissue. tpCR=total pathological complete response (in breast and axillary nodes). OR=overall response. *For comparison of HER2-positive disease groups. †For comparison of without trastuzumab groups. ‡Complete and partial clinical responses.*



Graphical elaboration from table data Gianni L, et al. Lancet 2010.
bpCR, pathological complete response in the breast; EFS, event-free survival; H, Herceptin; tpCR, total pathological complete response.

NOAH Long term outcomes

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



Graphical elaboration from table data Gianni L, et al. Lancet 2010; 375: 377–84.
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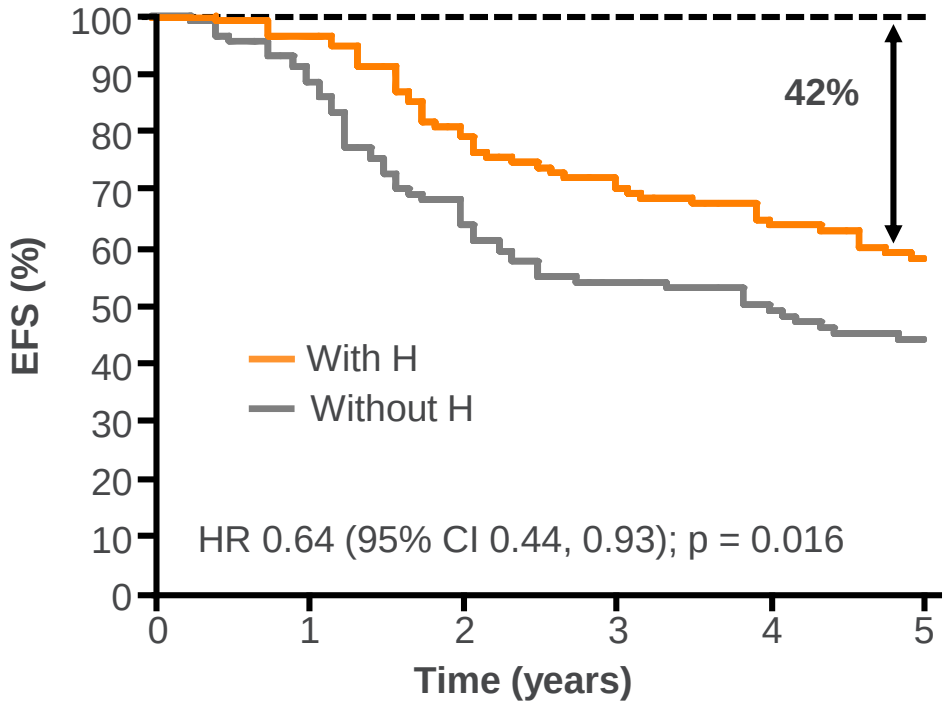
NOAH Long term outcomes

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

Summary of efficacy endpoints

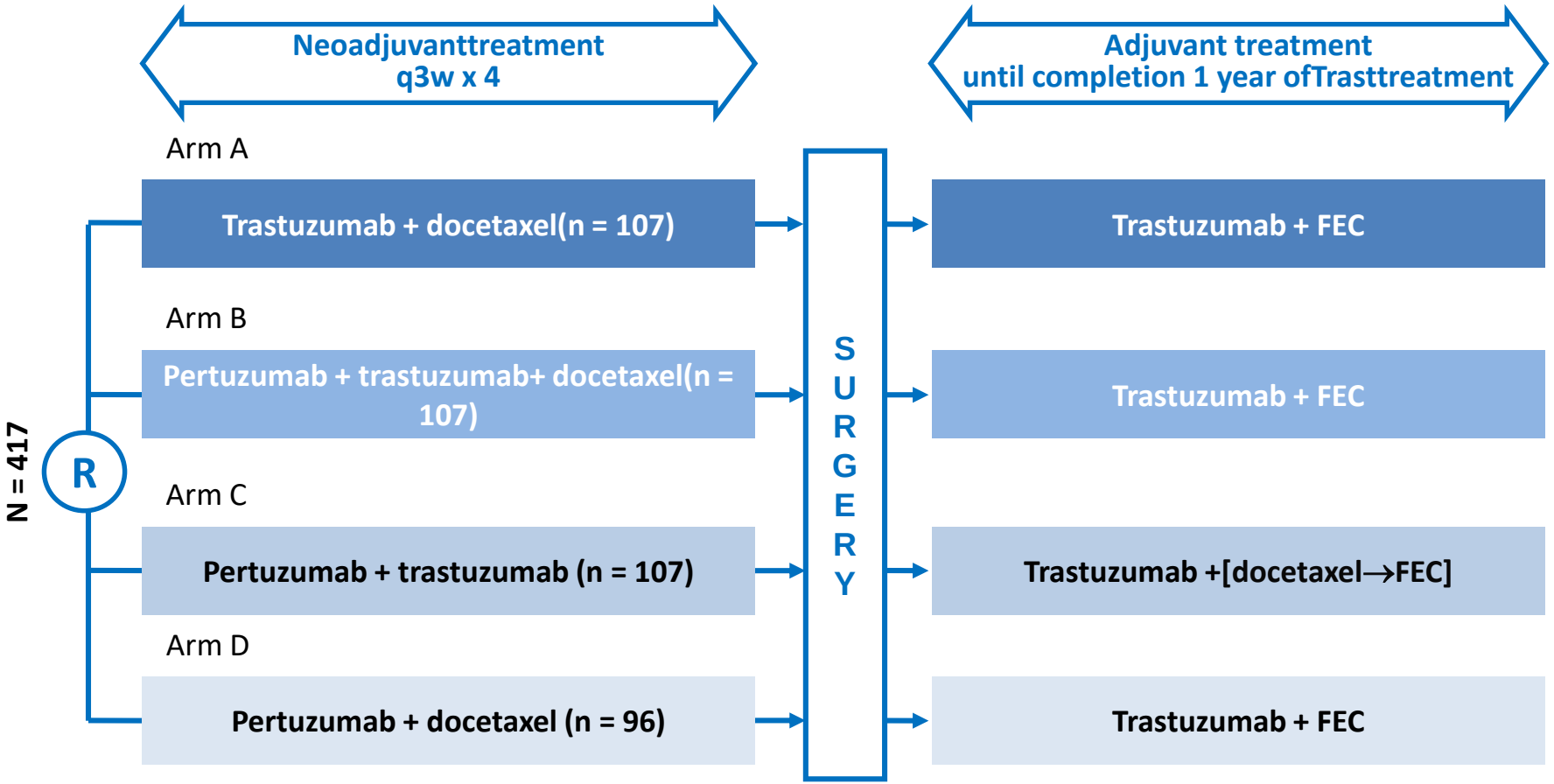
	HER2 Positive				HER2 Negative
	Trastuzumab plus chemotherapy (n=117)	Chemotherapy alone (n=118)	HR (95% CI)	P value	Chemotherapy alone (n=99)
5 year event-free survival	58% (48-66)	43% (34-52)	0·64 (0·44-0·93)	0·016	61% (50-70)
5 year overall survival	74% (64-81)	63% (53-71)	0·66 (0·43-1·01)	0·055	76% (66-84)
5 year relapse-free survival*	65% (54-73)	47% (36-57)	0·58 (0·38-0·90)	0·012	67% (56-77)
5 year breast cancer-specific survival	77% (69-85)	64% (55-73)	0-59 (0·37-0·92)	0·021	79% (70-86)

Data are % (95% CI). HR=hazard ratio. *in patients who had surgery after neoadjuvant systemic therapy (HER2-positive: trastuzumab plus chemotherapy n=98, chemotherapy alone n=90; HER2-negative: n=83).



Graphical elaboration from table data Gianni L, et al. Lancet Oncol 2014;15:640–47.
bpCR, pathological complete response in the breast; H, Herceptin; tpCR, total pathological complete response.

NeoSphere: Phase II study of efficacy and safety of neoadjuvant PH in women with locally advanced,inflammatory, or early HER2+ breast cancer



- **Inclusion criteria**
  - Femalepatients≥18 years of age
  - Operable*,locally advanced‡or inflammatory§breast cancer
  - HER2-positive (IHC 3+ or IHC 2+ and FISH+/CISH+)
  - Primarytumours>2 cm.
- **Exclusion criteria**
  - Metastaticdisease (stage IV), bilateral breast cancer or other malignancy
  - Previous anti-cancer therapy
  - Impaired cardiac, liver or renalfunction.

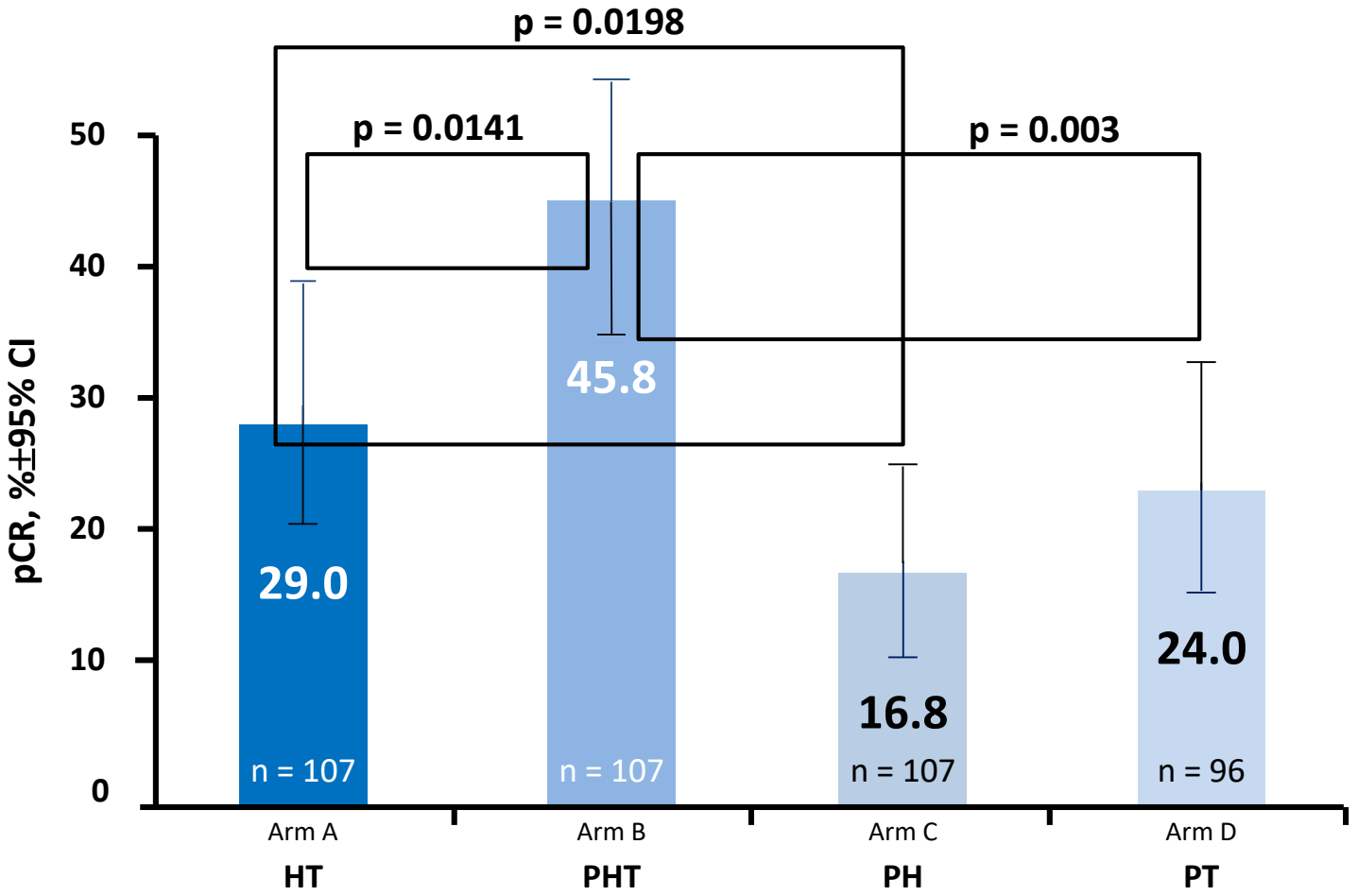
Gianni L, et al.Lancet Oncol2012; 13(1): 25-32. (study protocol available with the publication online).

NeoSphere: Objectives

- **Primary**
  - –To assess the pCR rate at the time of surgery
    - •Arm A (HT) vs. Arm B (PHT)
    - •Arm A (HT) vs. Arm C (PH)
    - •Arm B (PHT) vs. Arm D (PT).
- **Secondary**
  - –To evaluate the safety profiles of each regimen,including neoadjuvant and adjuvant treatment
  - –To determine the time to clinical response, time to response, disease-free survival and progression-free survival
  - –To evaluate biomarkers
  - –To compare the rate of breast-conserving surgery for all patients with T2–3 tumours for whom mastectomy was planned at diagnosis
  - –To make a preliminary assessment of the efficacy of neoadjuvant treatment with pertuzumab and docetaxel.

Gianni L, et al.Lancet Oncol2012; 13(1): 25-32. (study protocol available with the publication online).

NeoSphere: Pertuzumab and trastuzumab plus docetaxel significantly increased the pCR rate vs. other arms



H, trastuzumab; P, pertuzumab; pCR, pathological complete response; T, docetaxel.

Gianni et al. Oral presentation SABCS 2011- available at http://sabcs11.m2usa.com/sabcs.html- Last access October 2013; Gianni L, et al. Lancet Oncol 2012; 13(1): 25-32.

APPROCCI ALTERNATIVI ALLA CHEMIOTERAPIA

Neoadjuvant treatment with trastuzumab and pertuzumab plus palbociclib and fulvestrant in HER2-positive, ER-positive breast cancer (NA-PHER2): an exploratory, open-label, Phase 2 study

Gianni L. et al, Lancet Oncology 2018

First-Line Trastuzumab plus an Aromatasi Inhibitor, with or without Pertuzumab, in Human Epidermal growth factor receptor 2-positive and Hormone Receptor-positive metastatic or Locally advanced Breast cancer (PERTAIN): a randomized, open-label, phase II trial

Rimawi M. et al, J Clin Oncol 2018

Conclusioni: differenza di 3,1 mesi in PFS mediana(18.9 mesi per il braccio con P+T+AI vs 15.8 mesi)
In favore dell' associazione con doppio blocco anti-HER2

STRATEGIA CON DOPPIO BLOCCO (Lapatinib + Trastuzumab)

Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open –label, multicentre, phase 3 trial

Baselga J. et al, Lancet 2012

Preoperative chemoterapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study

Guarneri V. et al, J Clin Oncol 2012

STRATEGIA CON DOPPIO BLOCCO (Lapatinib +Trastuzumab)

Molecular Heterogenity and Response to Neoadiuvant Human Epidermal Growth Factor Receptor 2 targeting in CALGB 40601, a randomized, phase III trial of Pacltaxel plus trastuzumab with or without Lapatinib

Carey LA et al, J Clin Oncol 2016

Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial

Robidoux A. et al, Lancet Oncol 2013

Targeted neoadjuvant therapy in the HER-2-positive breast cancer patients: a systematic review and meta-analysis

Ma W et al., Onco Targets Ther 2019 Jan

CONCLUSION: Efficacy of lapatinib was less than that of trastuzumab, but incidence of adverse effect of lapatinib was higher than that of trastuzumab.
Combination of chemoterapy plus both lapatinib and trastuzumab could significantly increase PCR and tPCR in breast cancer patients, but rate of breast conservation, event-free survival, and overall survival was not significantly improved.
Incidence of diarrhea, hepatic toxicity and skin rash was significantly increased in the groups using lapatinib

Front Oncology 2018 may

Debiasi M et al

Efficacy Anti-HER2 agents in combination with adjuvant or neoadjuvant chemotherapy for early and locally advanced HER2-positive breast cancer patients: A Network Meta-Analysis

Conclusion: this network meta-analysis suggests that dual anti HER-2 blockade with trastuzumab plus either lapatinib or pertuzumab are probably the best treatment options in the (neo)adjuvant setting for HER2-positive breast cancer patients in terms of OS gain. Mature OS results are still expected for the Aphinity trial and for the sequantial use of Trastuzumab followed neratinib, the treatment that showed the best performance in terms of DFS in our analysis.

STRATEGIA CON DOPPIO BLOCCO CON ALTRI AGENTI ANTI HER2

Dual blockade with *Afatinib* and trastuzumab as neoadjuvant treatment for patients with Locally advanced or operable breast cancer receiving taxane-anthracycline containing Chemoterapy-DAFNE (GBG-70)

Hanusch C. et al, Clin Cancer Res 2015

Tassi di pCR pari al 49%

NSABP FB-07: A phase II randomized trial evaluating neoadiuvant therapy with weekly paclitaxel (P) plus *Neratinib* (N) or Trastuzumab (T) or neratinib and trastuzumab (N+T) Followed by doxorubicin and cyclophosphamide (AC) with postoperative T in women with Locally advanced HER2-positive breast cancer

Jacobs S. et al, Cancer Res 2016

Tassi di pCR pari al 50%

EFFICACIA di T-DM1 nel setting neoadiuvante

Neoadjuvant trastuzumab, pertuzumb and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomized, open-label, multicentre, phase 3 trial

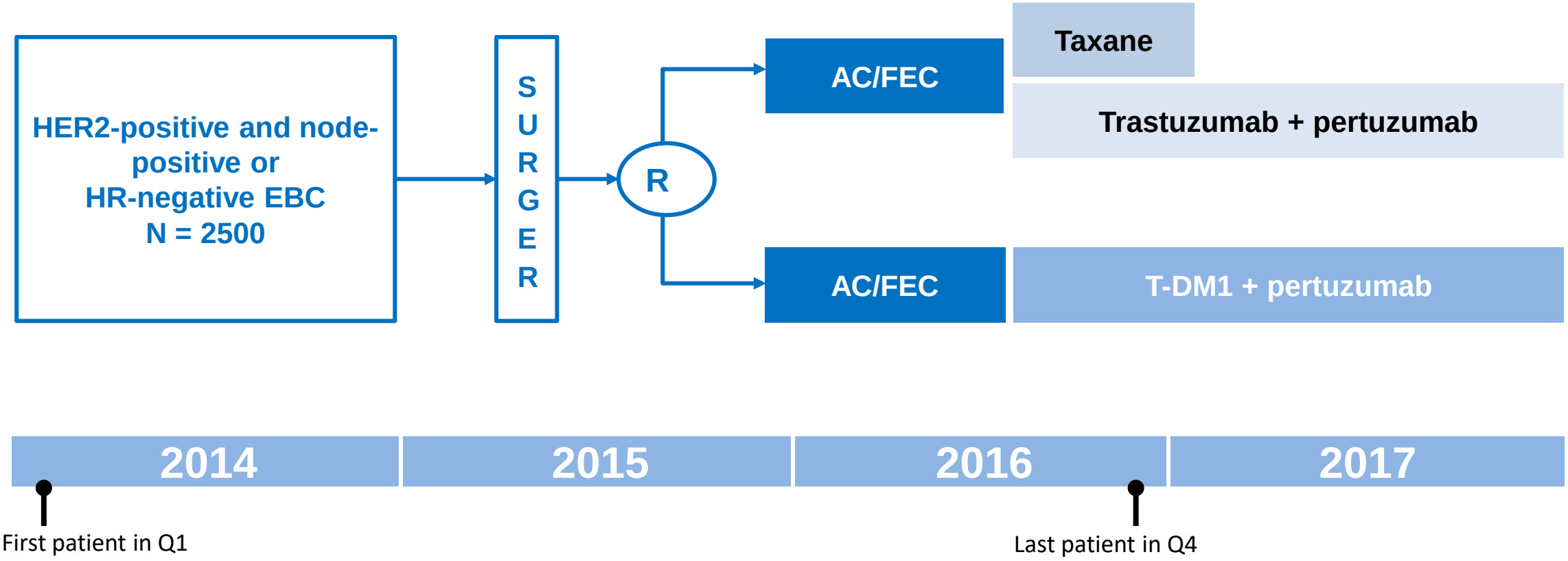
Hurvitz SA. et al, Lancet Oncol 2018

Lo studio ha randomizzato 444 pazienti con Ca mammario HER2-positivo a ricevere

- 6 cicli di T-DM1 in associazione a Pertuzumab
- 6 cicli di Trastuzumab + Pertuzumab + Docetaxel + Carboplatino

Conclusioni: sebbene la combinazione con T-DM1 sia complessivamente meglio tollerata, il tasso di pCR nel braccio con T-DM1 (44% vs 56%; p=0.016) è risultato inferiore al braccio di cht Associata al doppio blocco anti-HER2, arrestando lo sviluppo del farmaco in questo setting

BO28407 (KAITLIN): Phase III, two-arm adjuvant trial of trastuzumab + pertuzumab + taxane vs. T-DM1 + pertuzumab



AC, doxorubicin/cyclophosphamide; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; HR, hormone receptor.

www.clinicaltrials.gov/ct2/show/NCT01966471.

- Less pCR in HER2 + and HR+ disease after neoadjuvant chemo based therapy
- Efficacy of dual anti HER2 blockade can help reducing intensity of chemo
- Ki67 drop after short term endocrine therapy as a biomarker of endocrine sensitivity in HR+/HER2- disease

Primary objective: pCR rate (breast and axilla)
Secondary objective: Breast clinical objective RR (by US)
Breast conservative surgery rate
Safety
Biomarker analysis

Quali novità nel 2018?

- Escalation and De-Escalation trials

TARGET

1) To hit the target with more drugs **(escalation)** for **patients who need more**:

-Adjuvant TDM1 if no pCR (KATHERINE)

2) To hit the target with the hope to **de-escalate** therapy for **patients who need less**:

-De escalating or omitting CHT (PerELISA)
-De-escalating anti HER2 therapy (Persephone/ PHARE/ShortHer/SOLD)

Adjuvant trastuzumab: the pivotal phase III studies

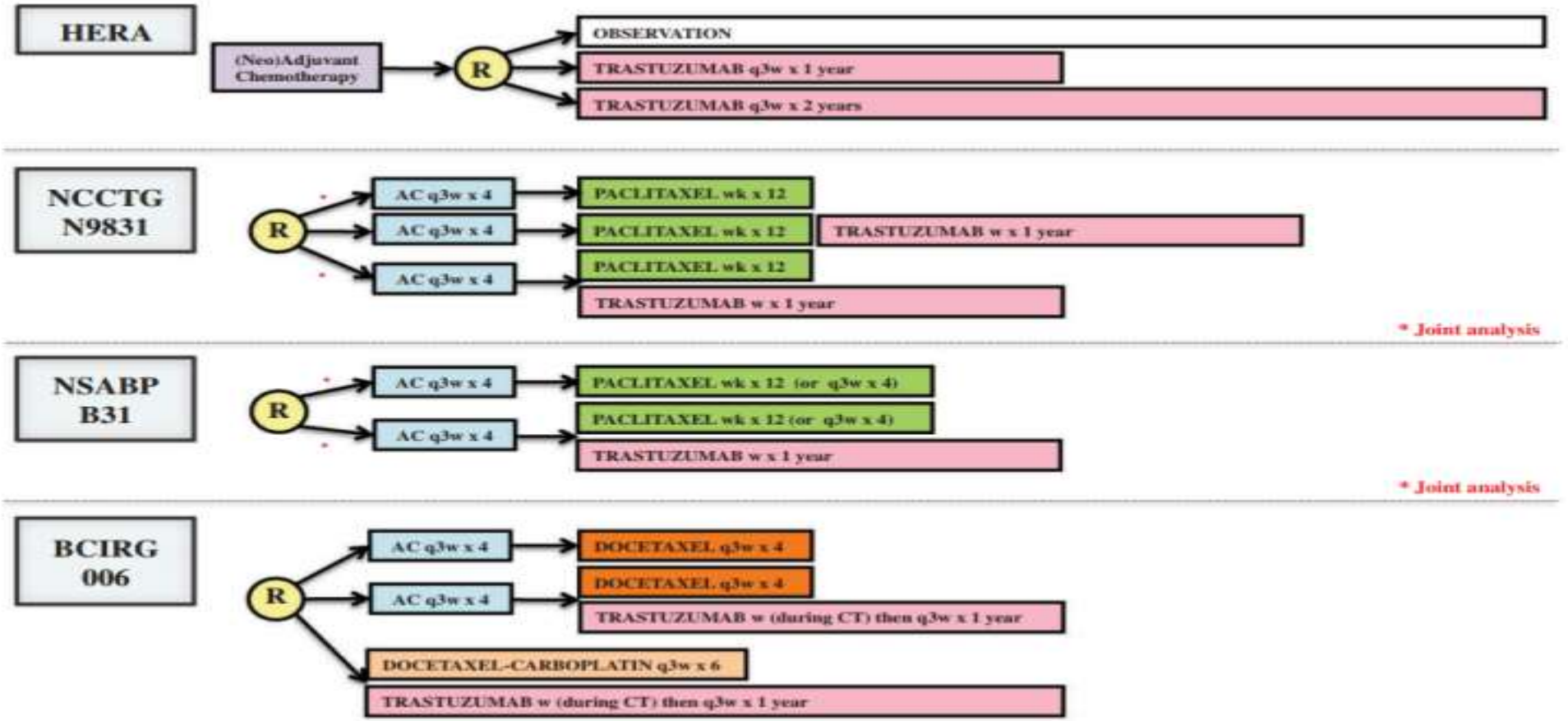
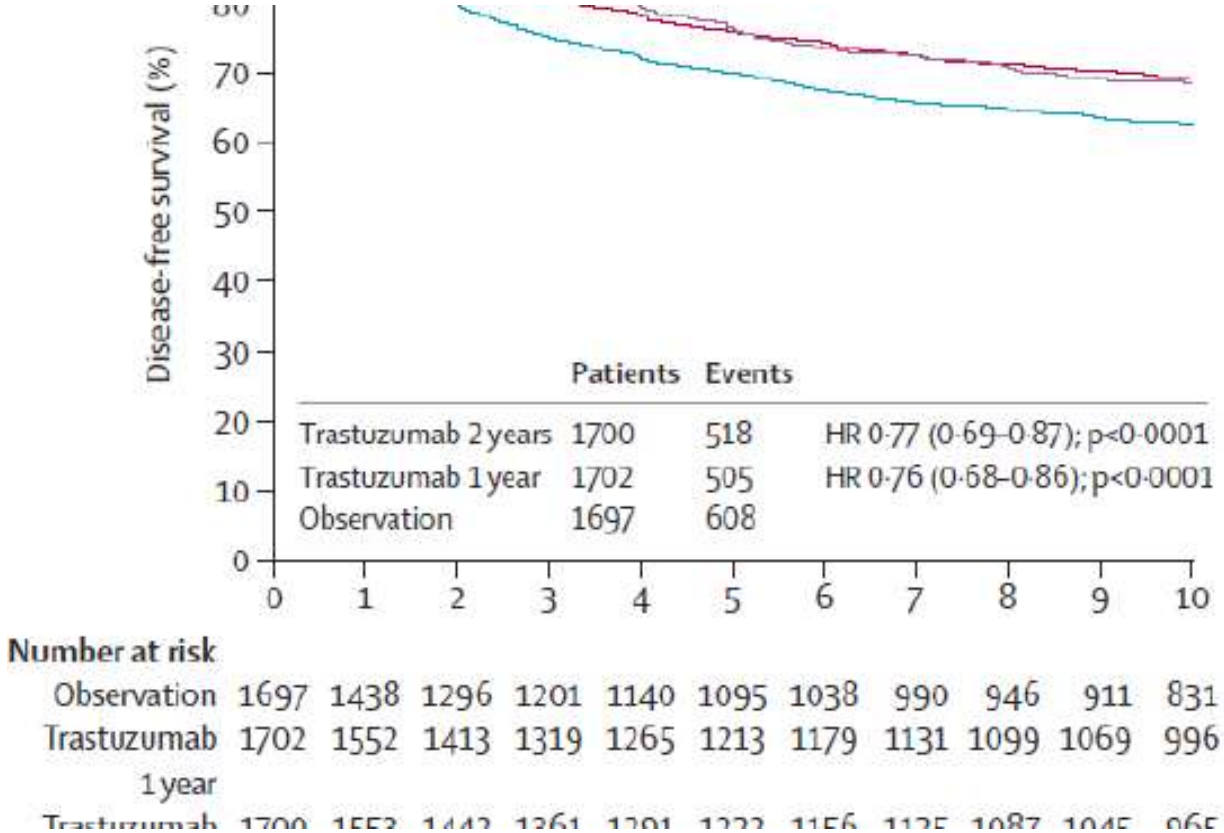
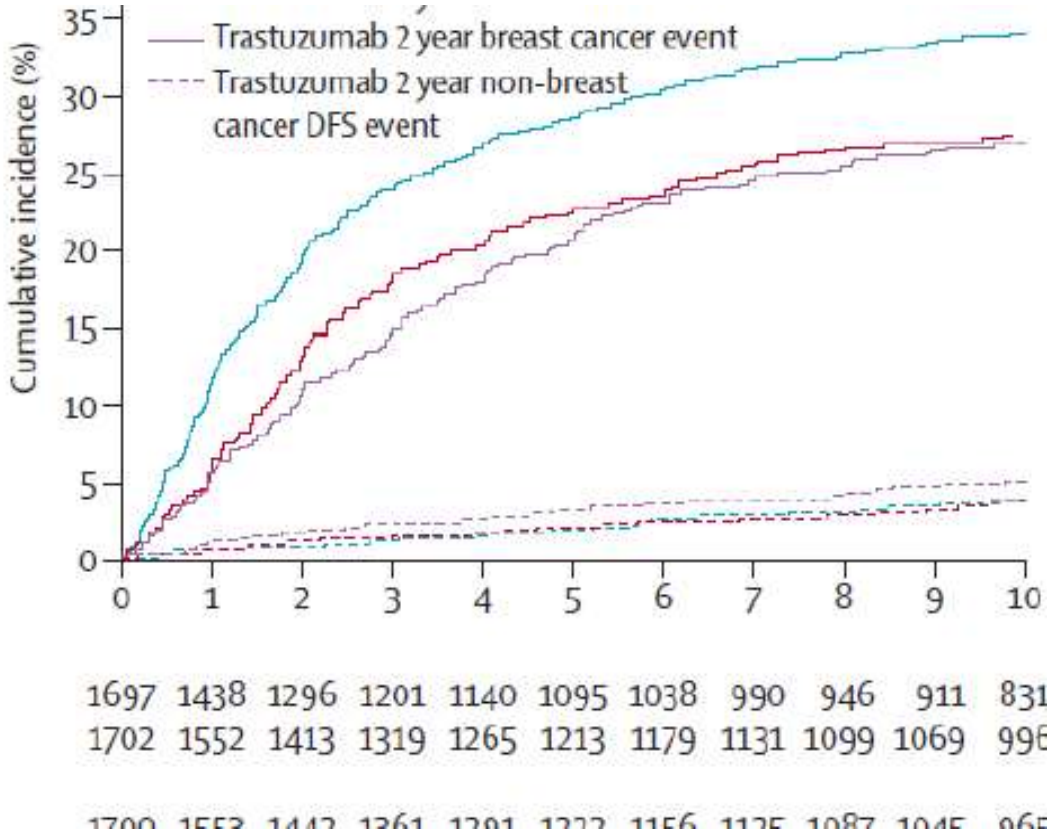


Figure 1. Adjuvant trastuzumab: the pivotal phase III studies.
AC: doxorubicin, cyclophosphamide; CT: chemotherapy; FEC: 5-fluoruracil, epirubicin, cyclophosphamide.

Adapted from Lambertini M et al Expert Rev Anticancer Ther 1 7(1):61-74

Adjuvant trastuzumab improves DFS (HERA 11 years follow up)





Adapted from D Cameron et al. Lancet 389 (10075), 1195-1205. 2017 Feb 17.

Chemotherapy Schemes in Trastuzumab trials

- Sequential (Post antrhacyclines +/- taxanes)

trastuzumab for 12 months following completion of chemotherapy (HERA trial)

- Concurrent post antrhacyclines chemotherapy –trastuzumab

for 12 months started in combination with a taxane following completion of antrhacyclines (NASBP B31, NCCTG N9831, BCIRG)

- Concurrent pre antrhacyclines chemotherapy-trastuzumab for 9-10 weeks

started in combination with a taxane prior to antrhacycline chemotherapy (FinHER)

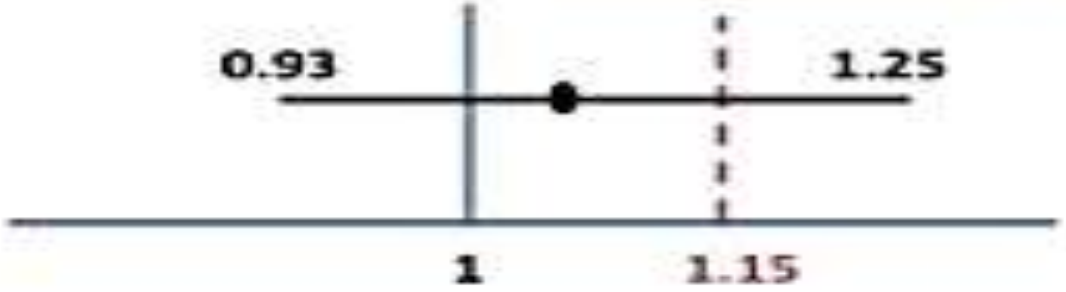
Ad un follow up mediano di 62 mesi in particolare nelle pts trattate con docetaxel l' aggiunta di T per 9 w ha mostrato significativa riduzione del rischio di recidiva a distanza

1. Smith I et al., Lancet. 2007 Jan 6;369(9555):29-36; 2. Piccart-Gebhart MJ et al., *N Engl J Med. 2005 Oct 20;353(16):1659-72; 3. Romond EH et al., *N Engl J Med. 2005 Oct 20;353(16):1673-84; 4. Slamon D et al, *N Engl J Med. 2011 Oct 6;365(14):1273-83; 5. Joensuu H et al, J Clin Oncol. 2009 Dec 1;27(34):5685-92.

Disegnato per valutare la non inferiorità di 6 vs 12 mesi di trattamento con T aggiunto alla CHT (approccio sequenziale o concomitante).
T per 6 mesi è risultata associata ad un incremento del 28% del rischio di ricaduta
I risultati consolidano i 12 mesi di T come standard di trattamento

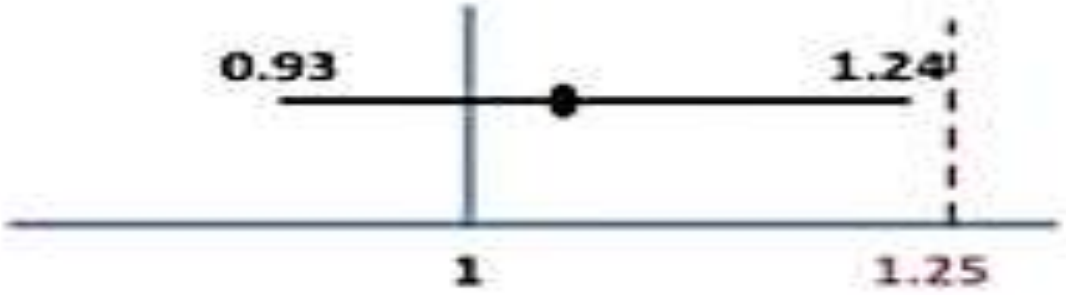
Conclusion

PHARE failed to show that 6 months of trastuzumab is non inferior to 12 months



HR: 1.08 (95%CI: 0.93-1.25) p=0.39

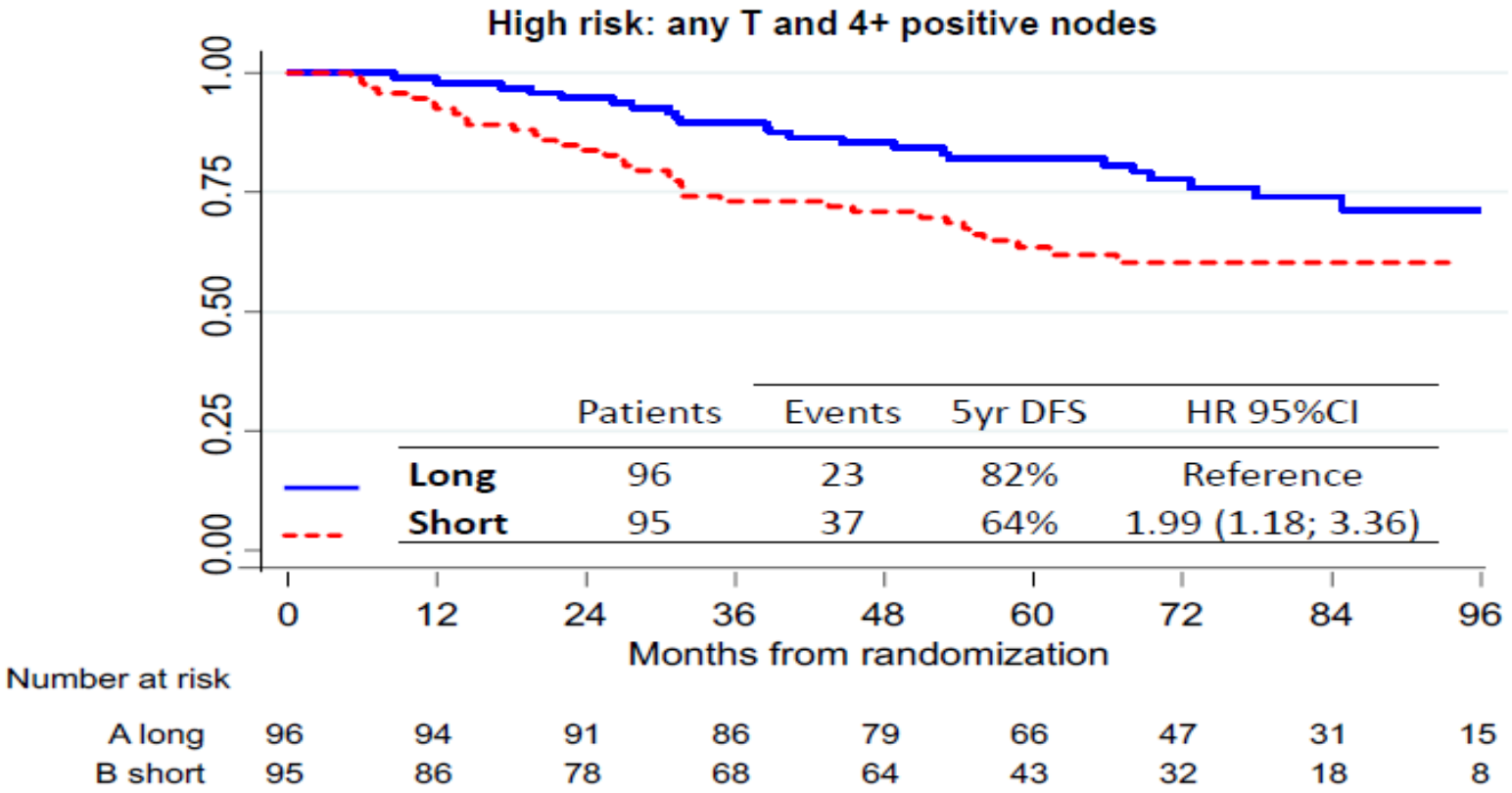
PERSEPHONE Showed that 6 months of trastuzumab is non inferior to 12 months



HR: 1.07 (90%CI: 0.93-1.24) p=0.01

ASCO 2017

ShortHER: subgroup analysis to identify patients for whom a shorter trastuzumab administration may have a favourable risk/benefit ratio



Conte P, ESMO 2018

Dal 2007 al 2013 ha arruolato 1254 pts (stadi I, IIA/B e III)
Studio di non inferiorità di T settimanale x 9 w vs 1 y
Incidenza di tossicità cardiaca significativamente più bassa nel braccio di trattamento breve

STUDIO SOLD

Joensuu H, Fraser J, Wildiers H, et al.

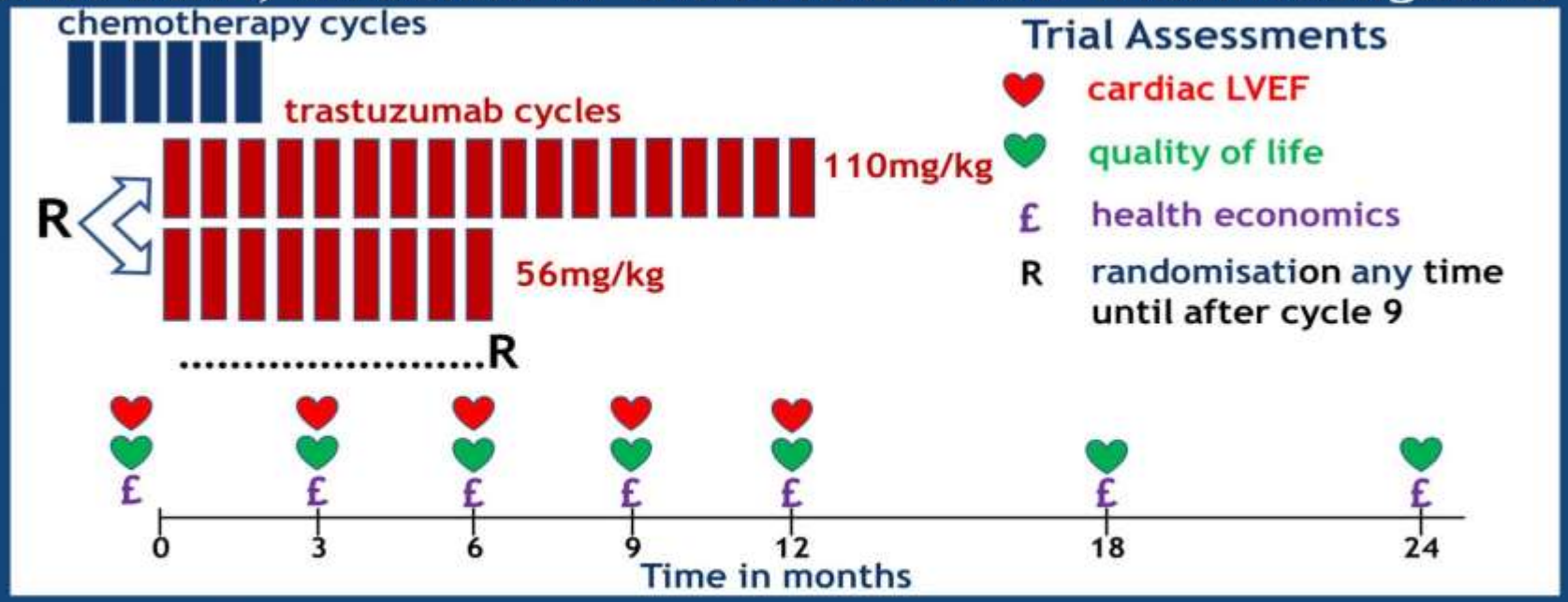
JAMA Oncol. 2018 May 31.

Effect of Adjuvant Trastuzumab for a Duration of 9 Weeks vs 1 Year With Concomitant Chemotherapy forEarly Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: The SOLD Randomized Clinical Trial.

Ha randomizzato 2174 pazienti a ricevere Docetaxel 3w+T weekly x 9w→ FEC x3 vs stesso regime CHT seguito da T x 1y
Pur dimostrando una differenza assoluta di DFS a 5 anni di solo il 2.5% tra i bracci (90.5% 1 anno vs 88% 9 settimane)
NON dimostra la NON INFERIORITA' DEL TRATTAMENTO BREVE

PERSEPHONE: 6 versus 12 months of adjuvant trastuzumab in patients with HER2 positive early breast cancer: Randomised phase 3 non-inferiority trial with definitive 4-year disease-free survival results

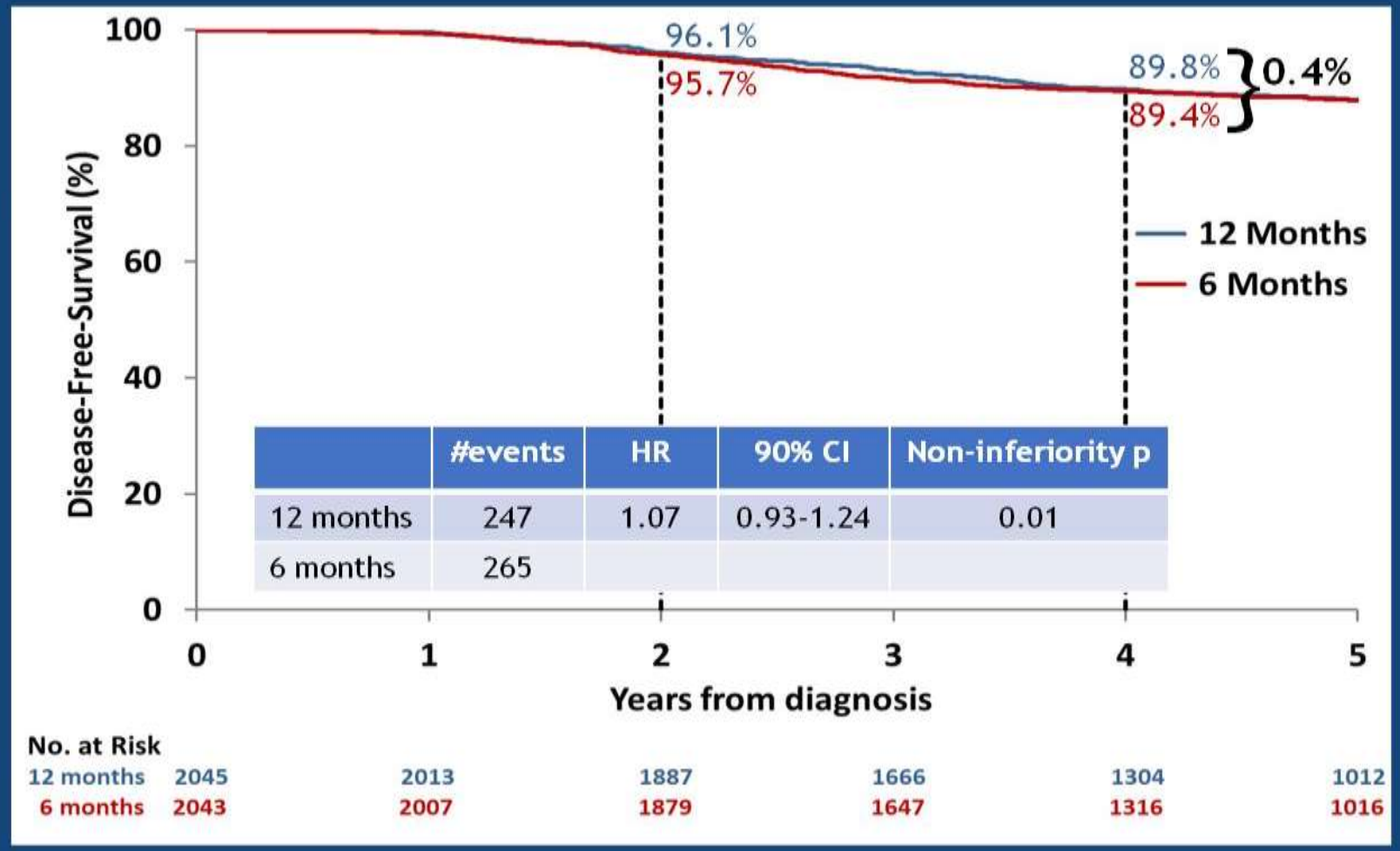
Helena Earl, Louise Hiller, Anne-Laure Vallier, Shrushma Loi, Donna Howe, Helen Higgins, Karen McAdam, Luke Hughes-Davies, Adrian Harnett, Mei-Lin Ah-See, Richard Simcock, Daniel Rea, Janine Mansi, Jean Abraham, Carlos Caldas, Claire Hulme, David Miles, Andrew Wardley, David Cameron, Janet Dunn, on behalf of the PERSEPHONE Trial Investigators



1° : DFS [Diagnosis to 1st relapse (local or distant) or death]

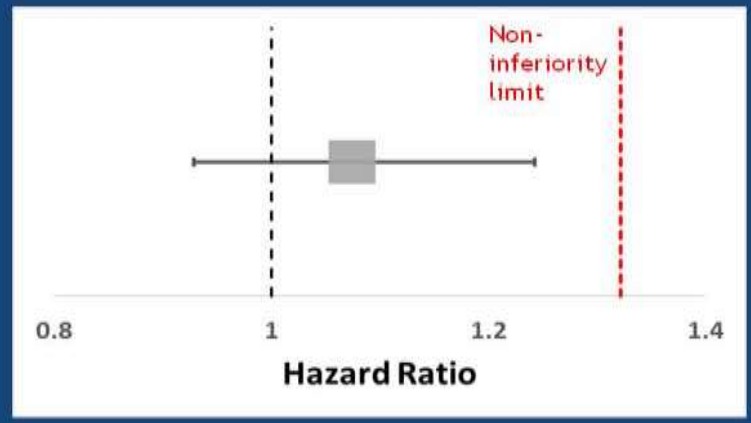
2° :OS ; Cost effectiveness ; Cardiac function

Disease-free survival



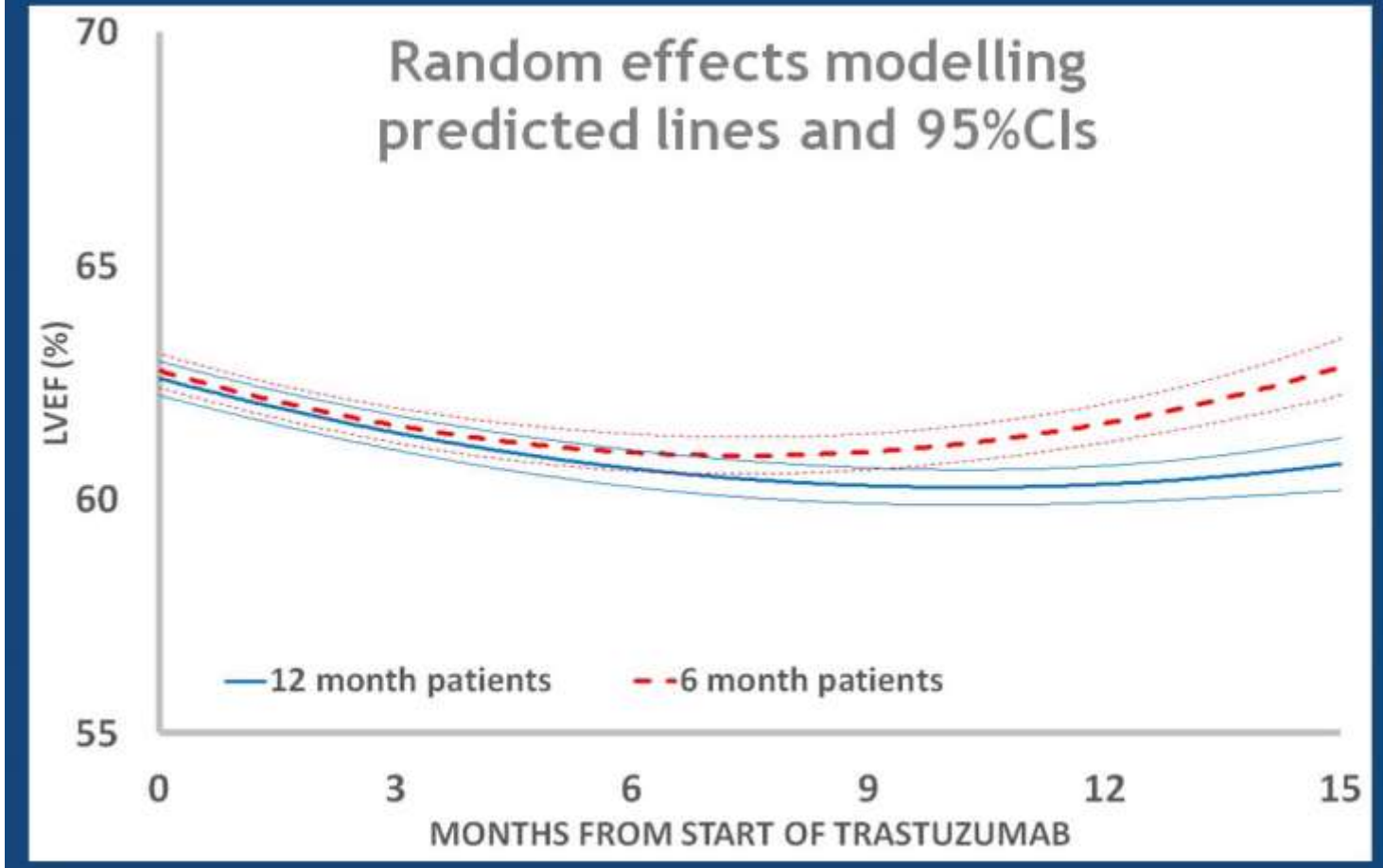
	#events	HR	90% CI	Non-inferiority p
12 months	247	1.07	0.93-1.24	0.01
6 months	265			

No. at Risk						
12 months	2045	2013	1887	1666	1304	1012
6 months	2043	2007	1879	1647	1316	1016



Follow up mediano di 5.4 mesi

Cardiotoxicity



Stopped trastuzumab because of cardiotoxicity
- in **8%** of 12-month patients
- in **4%** of 6-month patients

(p<0.0001)

- Cardiac function recovers post-trastuzumab (p<0.0001)
- 6-month patients had a more rapid recovery (p=0.02)

Ref: Earl et al. British Journal of Cancer (2016) 115, 1462–1470

Shorter adjuvant HER2 blockade?

- Less cardiotoxicity in all trials with less Trastuzumab

- The matter of «non inferiority margin»

→ which is the clinically acceptable loss of efficacy?

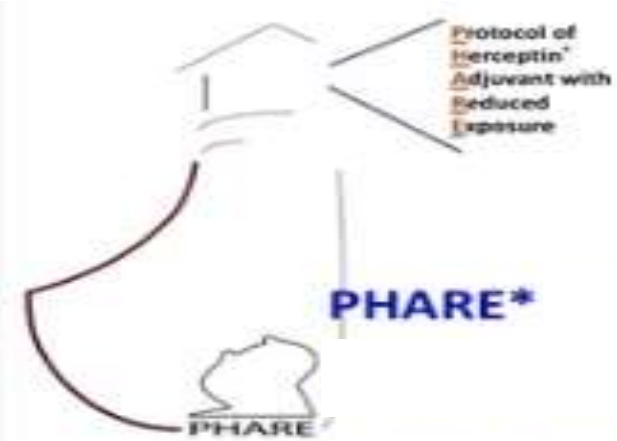
- Less relevant question today, we are more interested in reducing CHT

- It is not clear who benefits from reduced HER2 blockade

- Persephone trial reduces in someway anxiety for women who has to stop Trastuzumab early

ShortHER

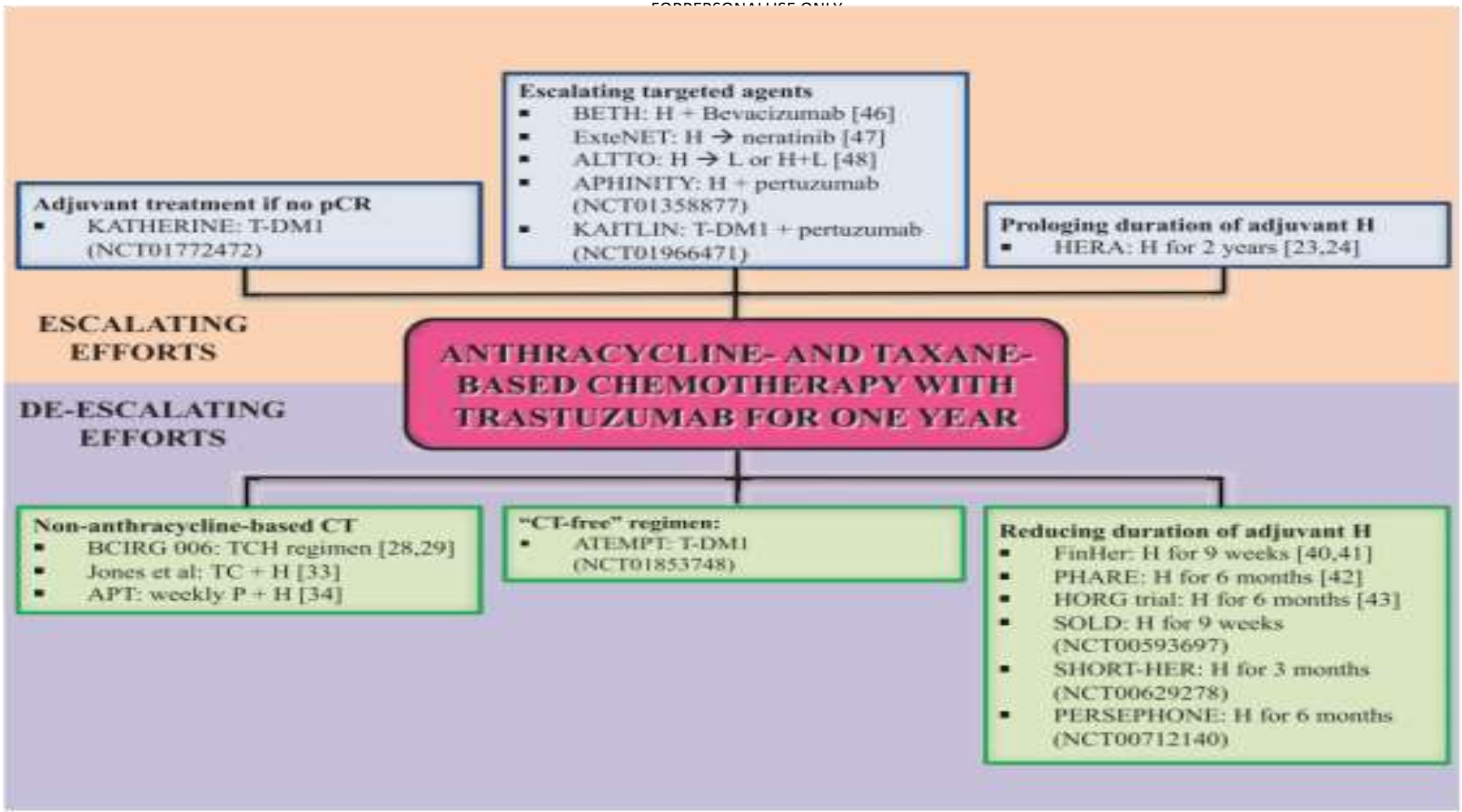
Persephone



Escalation

To hit the target with more drugs **(escalation)** for **patients who need more**:

- Adjuvant TDM1 if no pCR (KATHERINE)
- Studio ALTTO
- Studio APHINITY
- ExteNET
- KAITLIN



lating and de-escalating efforts in the adjuvant treatment of HER2-positive breast cancer.
ic complete response; T-DM1: trastuzumab emtansine; H: trastuzumab; L: lapatinib; CT: chemotherapy; TCH: docetaxel, carboplatin, t
cyclophosphamide; P: paclitaxel.

Phase III Study of Trastuzumab Emtansine (T-DM1) vs Trastuzumab as Adjuvant Therapy in Patients with HER2-Positive Early Breast Cancer with Residual Invasive Disease after Neoadjuvant Chemotherapy and HER2-Targeted Therapy Including Trastuzumab: Primary Results from KATHERINE (NSABP B-50-I, GBG 77 and Roche BO27938)

Charles E. Geyer, Jr., Chiun-Sheng Huang, Max S. Mano, Sibylle Loibl, Eleftherios P. Mamounas, Michael Untch, Norman Wolmark, Priya Rastogi, Andreas Schneeweiss, Andrés Redondo, Hans H. Fischer, William Jacot, Alison K. Conlin, Claudia Arce-Salinas, Irene L. Wapnir, Christian Jackisch, Michael P. DiGiovanna, Peter A. Fasching, John P. Crown, Pia Wülfing, Zhimin Shao, Elena Rota Caremoli, Haiyan Wu, Lisa H. Lam, David Tesarowski, Melanie Smitt, Hannah Douthwaite, Stina M. Singel, and Gunter von Minckwitz, on behalf of the KATHERINE investigators

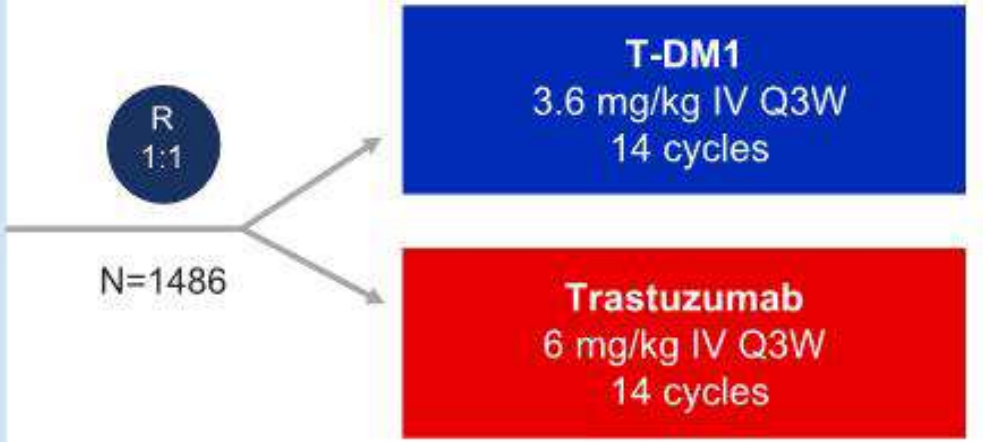
GBG GERMAN BREAST GROUP

NSABP Foundation, Inc. Partners in Cancer Research

Roche Genentech

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



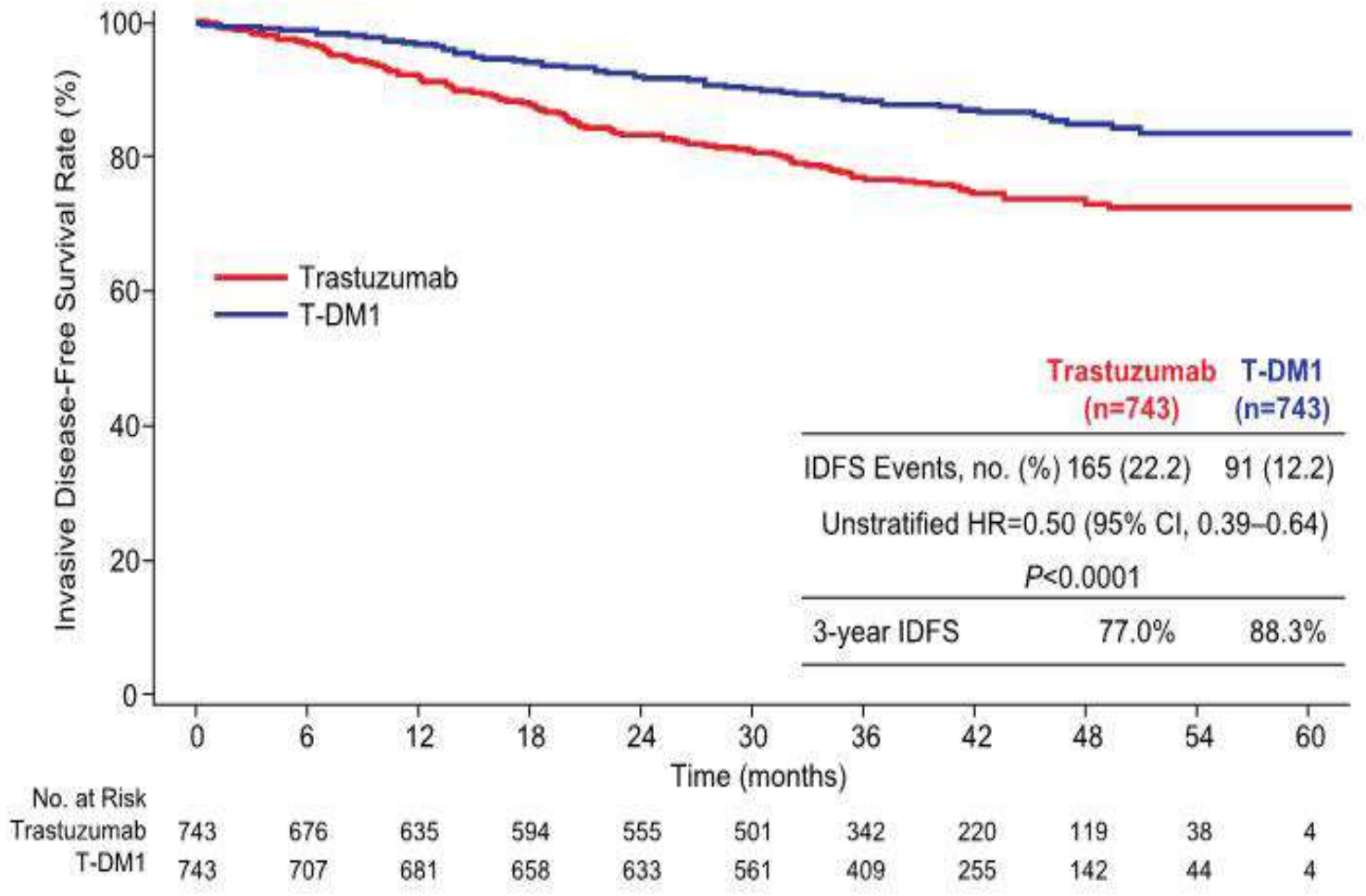
Radiation and endocrine therapy per protocol and local guidelines

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

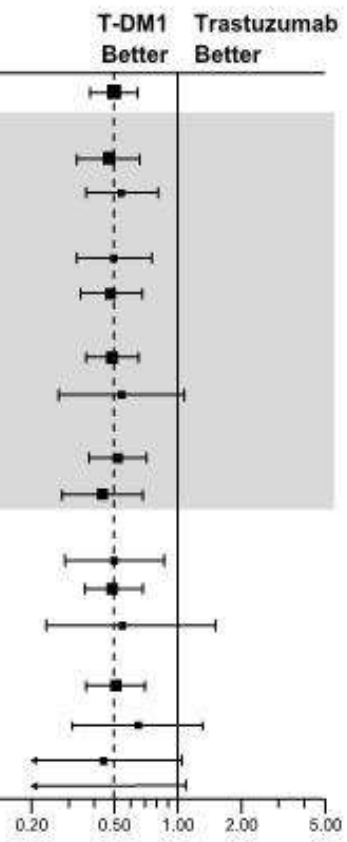
Primary Endpoint: IDFS

Invasive Disease-Free Survival



IDFS Subgroup Analysis (1)

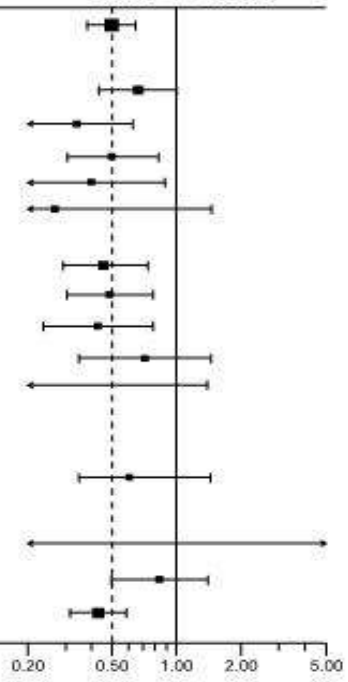
Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS	Hazard Ratio	95% CI
All	1486	77.0	88.3	0.50	(0.39–0.64)
Clinical stage at presentation					
Operable	1111	82.8	92.3	0.47	(0.33–0.66)
Inoperable	375	60.2	76.0	0.54	(0.37–0.80)
Hormone receptor status					
Negative (ER negative and PgR negative/unknown)	412	66.6	82.1	0.50	(0.33–0.74)
Positive (ER and/or PgR positive)	1074	80.7	90.7	0.48	(0.35–0.67)
Preoperative HER2-directed therapy					
Trastuzumab alone	1196	75.9	87.7	0.49	(0.37–0.65)
Trastuzumab plus additional HER2-directed agent(s)	290	81.8	90.9	0.54	(0.27–1.06)
Pathological nodal status after preoperative therapy					
Node positive	689	67.7	83.0	0.52	(0.38–0.71)
Node negative/not done	797	84.6	92.8	0.44	(0.28–0.68)
Age group (years)					
<40	296	74.9	86.5	0.50	(0.29–0.86)
40–64	1064	77.1	88.8	0.49	(0.36–0.67)
≥65	126	81.1	87.4	0.55	(0.22–1.34)
Race^					
White	1082	79.1	88.8	0.51	(0.37–0.69)
Asian	129	71.9	82.5	0.65	(0.32–1.32)
American Indian or Alaska Native	86	60.3	81.8	0.44	(0.18–1.03)
Black or African American	40	66.0	94.7	0.13	(0.02–1.10)



^149 were of multiple races or unknown race.

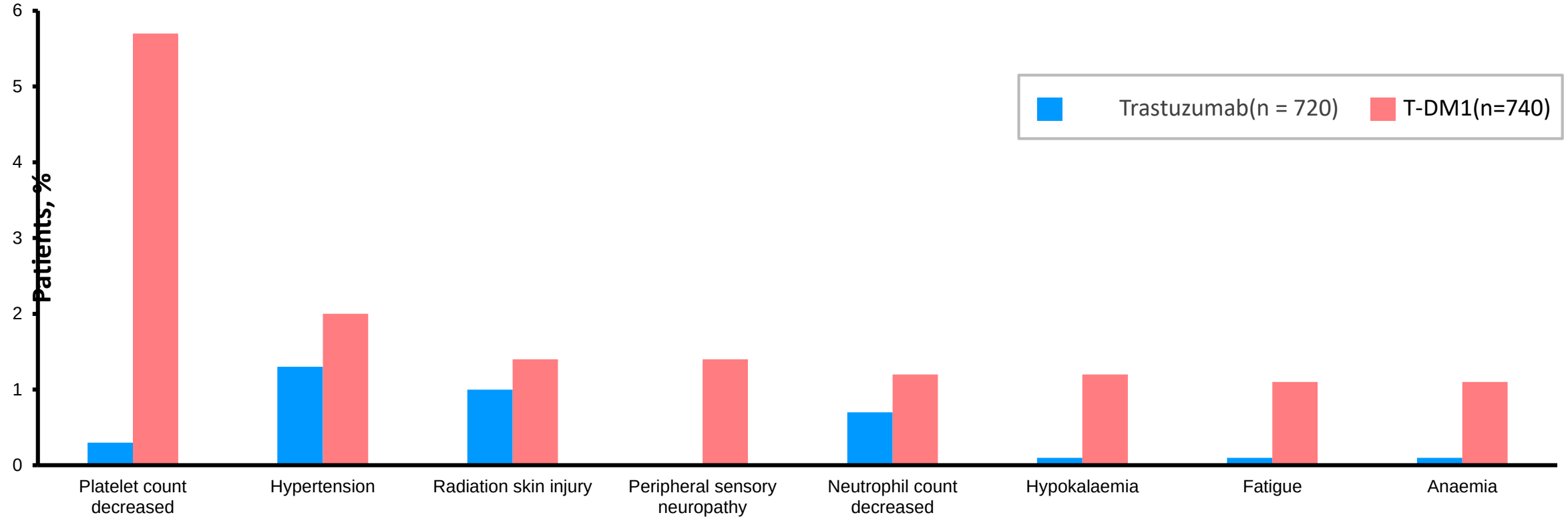
IDFS Subgroup Analysis (2)

Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS	Hazard Ratio	95% CI
All	1486	77.0	88.3	0.50	(0.39–0.64)
Primary tumor stage (at definitive surgery)					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	637	83.6	88.3	0.66	(0.44–1.00)
ypT1, ypT1c	359	75.9	91.9	0.34	(0.19–0.62)
ypT2	359	74.3	88.3	0.50	(0.31–0.82)
ypT3	108	61.1	79.8	0.40	(0.18–0.88)
ypT4*	23	30.0	70.0	0.29	(0.07–1.17)
Regional lymph node stage (at definitive surgery)					
ypN0	679	83.9	91.9	0.46	(0.30–0.73)
ypN1	433	75.8	88.9	0.49	(0.31–0.78)
ypN2	189	58.2	81.1	0.43	(0.24–0.77)
ypN3	67	40.6	52.0	0.71	(0.35–1.42)
ypNX	118	88.7	98.1	0.17	(0.02–1.38)
Residual disease ≤1 cm with negative axillary lymph nodes					
ypT1a, ypT1b or ypT1mic and ypN0	331	85.3	90.0	0.60	(0.33–1.12)
Central HER2 status by IHC†					
0/1+	25	83.9	100.0	<0.01	(0.00–NE)
2+	326	80.9	84.7	0.83	(0.50–1.38)
3+	1132	75.7	89.0	0.43	(0.32–0.58)



*Includes all ypT4 and 1 patient with ypTX; †Three patients had "unknown" HER2 IHC status.

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



Despite a higher incidence of decreased platelet count (thrombocytopenia) in theT-DM1arm, rates of Grade ≥3 haemorrhage were similar between groups*

* Grade≥3 haemorrhage rates: 0.4%T-DM1arm, 0.3%Trastuzumabarm. One fatal intracranial haemorrhage was reported in theT-DM1arm.

AE, adverse event.

vonMinckwitzG, et al. NEnglJ Med 2018 Dec 5. [Epubahead of print]

KATHERINE: Overall summary

KATHERINE is the first trial to demonstrate a significant benefit with a therapy optimisation by changing to targeted chemotherapy in patients with residual disease after neoadjuvant therapy in HER2-positive BC

Study met its primary objective, with a 50% reduction of the risk of an IDFS event withT-DM1vs.Trastuzumab(HR 0.50; 95% CI = 0.39, 0.64; p < 0.0001)

Safety profile of T-DM1 was consistent with previous trials

Magnitude of IDFS benefit was consistent across all subgroups, including HR status, nodal status and prior dual HER2 blockade

These results will likely form the foundation of a new SoC in this population

The benefit:risk of T-DM1 is transformative for patients with HER2-positive eBC who have residual disease following completion of neoadjuvant therapy

BC, breast cancer; CI, confidence interval; eBC, early breast cancer; HR, hazard ratio; IDFS, invasive disease-free survival.

vonMinckwitzG, et al. NEnglJ Med 2018 Dec 5. [Epubahead of print]

Safety Overview

	Trastuzumab n=720	T-DM1 n=740
Number of patients with at least one , n (%)		
Grade ≥3 AEs	111 (15.4)	190 (25.7)
Serio Ejection fraction decreased	10 (1.4%)	9 (1.2%)
AE leading to treatment discontinuation	15 (2.1)	133 (18.0)
AE with fatal outcome^	0	1 (0.1)

81% of pts completed Trastuzumab
71% of pts completed T-DM1

Malattia HER2 positive: Cosa fare in caso di malattia residua dopo chemioterapia neoadiuvante?

- T-DM1 adiuvante ha dimostrato una riduzione statisticamente significativa di IDFS rispetto al trastuzumab
- Unstratified HR=0.50; 95% CI 0.39–0.64; P<0.0001
- IDFS a 3 anni migliorato dal 77.0% all' 88.3%
- Beneficio di T-DM1 consistente in tutti i sottogruppi, anche in chi ha ricevuto dual blockade in setting neoadiuvante. Necessario il follow up per i dati di OS
- I dati del KATHERINE data ci fornicono un nuovo standard of care nei pazienti con malattia residua HER2 positive dopo trattamento neoadiuvante
- Messaggio: Terapia neoadiuvante standard in stadi II e III

- The residual disease was HER2 driven?
- Should T-DM1 be recommended after Pertuzumab?
- Should Pertuzumab be continued?
- The matter of toxicity: 14cyclesof T-DM1...
- What if we need to stop T-DM1?
- Who benefits more/less? Predictive biomarkers?
- Brain met?

- The residual disease was HER2 driven?

The risult demonstrates that residual disease was often still HER2-driven

- Should T-DM1 be recommended after Pertuzumab?

No direct data, and I would not continue pertuzumab with T-DM1 now BUT, inspite of Marianne results, Pertuzumab could possibly add to T-DM1

- Should Pertuzumab be continued?

If a patient does not have pCR inspite of pertuzumab,it is unlikely that continuing pertuzumab would be better than as witch,given modest improvement in Aphinity

- The matter of toxicity: 14 cyclesof T-DM1...

For some patients,this will mean more than a year of anti-HER2 treatment
HOWEVER, the results were achieved with 14cycle swhich should be the standard approach

- What if we need to stop T-DM1?

If a patient having trouble with toxicity, she may need to stop sooner but I woul push for at least one full year of anti HER2 treatment

- Brain met?
- Unfortunately,there was no impact whatsoever on the incidence of brain metastases

- Is there a role of Neratinib in pts with residual disease?

Data forT-DM1 in Katherine directly address residual disease setting are strong

No data for Neratinib after T-DM1

STUDIO ALTTO

Piccart-Gebhart M,et al. Optimization Trial. J Clin Oncol 2016;34:1034-1042

Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment

Braccio: T+CHT o T da solo
Braccio: lapatinib + CHT o L da solo
Braccio: T→L (sequenza dei 2 agenti)
Braccio T+L+CHT
Tra giugno 2007 e luglio 2011 sono state arruolate 8381 pts.
L' analisi prevista dopo un follow up mediano di 4.5 anni, ha evidenziato una riduzione del 16% del rischio di recidiva confrontando L+T vs T.
Una riduzione del 4% è stata osservata confrontando T→L vs T
Le pts trattate con L hanno sperimentato+effetti collaterali.Cardiotossicità in tutti i bracci
Lapatinib non è approvato per l'utilizzo nel setting adiuvante

STUDIO ExteNET

Martin M. et al. Lancet Oncol 2017

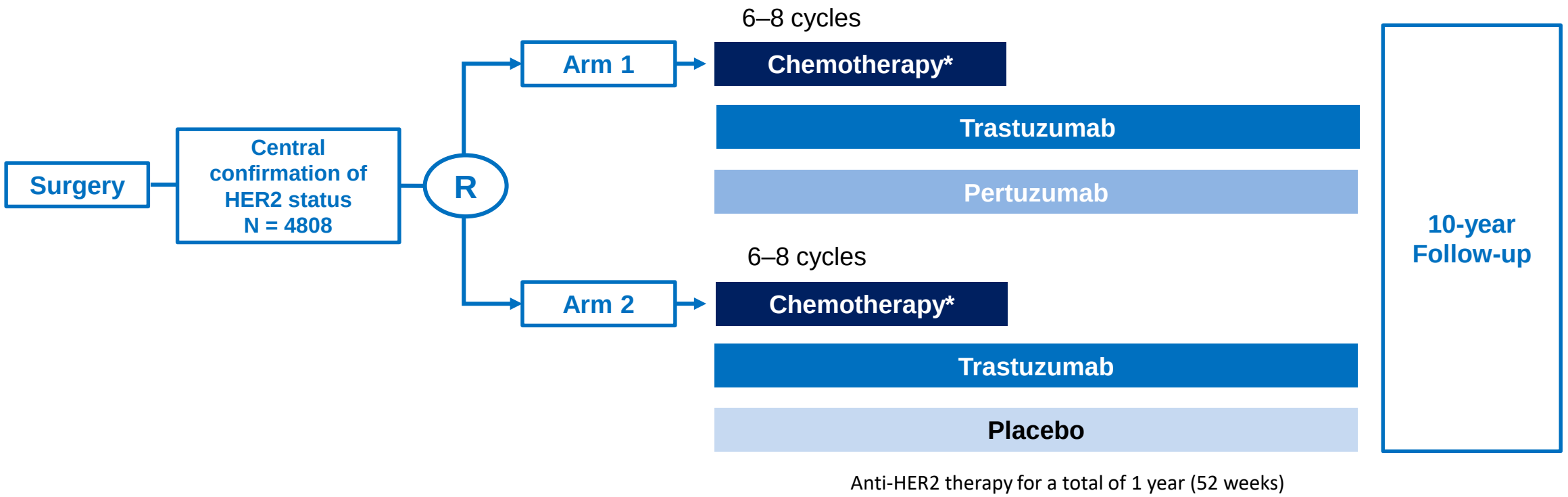
Neratinib after trastuzumab-based adjuvant therapy in HER2 positive breast cancer (ExteNET): 5-years analysis of a randomised, double-bind, placebo-controlled phase 3 trial

Lo studio ha analizzato l' aggiunta in successione al regime adiuvante con chemioterapia e trastuzumab di Neratinib (N), una piccola molecola con azione inibitrice irreversibile del dominio tirosinchinasico di HER2, HER1 e HER4.
Neratinib ha un profilo di farmacodinamica e farmacocinetica differente da Lapatinib
E' stato dimostrato un vantaggio signiticativo in termini di DFS
A giugno 2018 N è stato approvato da EMA per il carcinoma mammario operato ormono+ e HER2+ nel setting adiuvante, per 1 anno di terapia con N al termine del regime con Trastuzumab

APHINITY

Adjuvant **P**ertuzumab and **H**erceptin **IN** **I**nitial **T**herap**Y**
of breast cancer

APHINITY: Phase III trial of pertuzumab, trastuzumab and chemotherapy in the adjuvant setting



Graphical Elaboration from text data from References
1. www.clinicaltrials.gov/ct2/show/NCT01358877; 2. von Minckwitz G, Baselga et al. Cancer Res 2011; 71(15 December suppl.): Abstract OT1-02-04

APHINITY

ANTHRACYCLINE-BASED CHEMOTHERAPY	**3–4 FEC or FAC q3w → 3–4 T +H/+HP** – 5-FU 500-600 mg/m^2 – epirubicin 90–120 mg/m^2 (doxorubicin 50 mg/m^2 is acceptable) – cyclophosphamid 500–600 mg/m^2 – docetaxel 75–100 mg/m^2 q3w [oder paclitaxel 80 mg/m^2 weekly]	**4 AC or EC → 3–4 T +H/+HP** – AC (or EC) q3w or dosedense q2w with G-CSF support • doxorubicin 60 mg/m^2 (epirubicin 90–120 mg/m^2) • cyclophosphamid 500–600 mg/m^2 – docetaxel 75–100 mg/m^2 q3w [or paclitaxel 80 mg/m^2 weekly]
NON-ANTHRACYCLINE-BASED CHEMOTHERAPY	**6 TC q3w +H/+HP** – docetaxel 75 mg/m^2 – carboplatin AUC 6 (max. dose 900 mg)	

ER and/or PgR +: hormonal agents should be started at the end of chemotherapy consisting of tamoxifen or an aromatase inhibitor for post-menopausal patients; or tamoxifen with or without ovarian suppression *or an aromatase inhibitor with ovarian suppression* for pre-menopausal patients.
Hormonal therapy should be given for at least 5 years in accordance with the protocol recommendations.
Radiotherapy is to be given as clinically indicated at the end of chemotherapy in accordance with protocol recommendations

Graphical Elaboration from text data from www.clinicaltrials.gov/ct2/show/NCT01358877;

APHINITY: Study endpoints

- Primary endpoint:
  - Invasive disease-free survival (at 3 y) between treatment arms.
- Secondary endpoints:
  - Invasive disease-free survival including second non-breast cancer
  - Disease-free survival
  - Overall survival
  - Recurrence-free interval
  - Distant recurrence-free interval
  - Cardiac and overall safety
  - Health-related quality of life.

www.clinicaltrials.gov/ct2/show/NCT01358877; von Minckwitz G, et al. Cancer Res 2011; 71(15 December suppl.): Abstract OT1-02-04 (and associated poster presentation).

OVERVIEW

- The Phase III APHINITY study demonstrated that adjuvant PERJETA–Herceptin + chemo significantly improved IDFS compared with Herceptin-placebo + chemo, reducing the risk of recurrence or death by 19%; HR 0.81 (95% CI 0.66–1.00; p = 0.0446) in HER2-positive eBC[1]
- At the time of the primary analysis, treatment effect was driven by high-risk subgroups, defined as node-positive or hormone receptor-negative (la differenza a 3 anni è stata > evidente nel gruppo delle ptz N+)
- Diarrhoea (retrospective analysis of diarrhoea events in the safety population) was the most common AE reported

Bines J, et al. Abstract P1-13-07, Wed 6 Dec, 5:00–7:00 pm, Poster Session 1, Hall 1

CONCLUSIONS

- Pertuzumab adiuvante in associazione con chemioterpia e trastuzumab è stato approvato dall' EMA per le pazienti con carcinoma mammario HER2 positivo ad alto rischio di recidiva (linfonodi positivi e recettori ormonali negativi)
- In Italia attualmente è in classe Cnn

Bines J, et al. Abstract P1-13-07, Wed 6 Dec, 5:00–7:00 pm, Poster Session 1, Hall 1

INNOVAZIONE, ⇒ ***recenti trials***

ACCESSIBILITA' ⇒ ***farmaci già saggiati in altri setti***

SOSTENIBILITA' ⇒ ***depotenziamento terapie***

INFORMAZIONE IN ONCOLOGIA