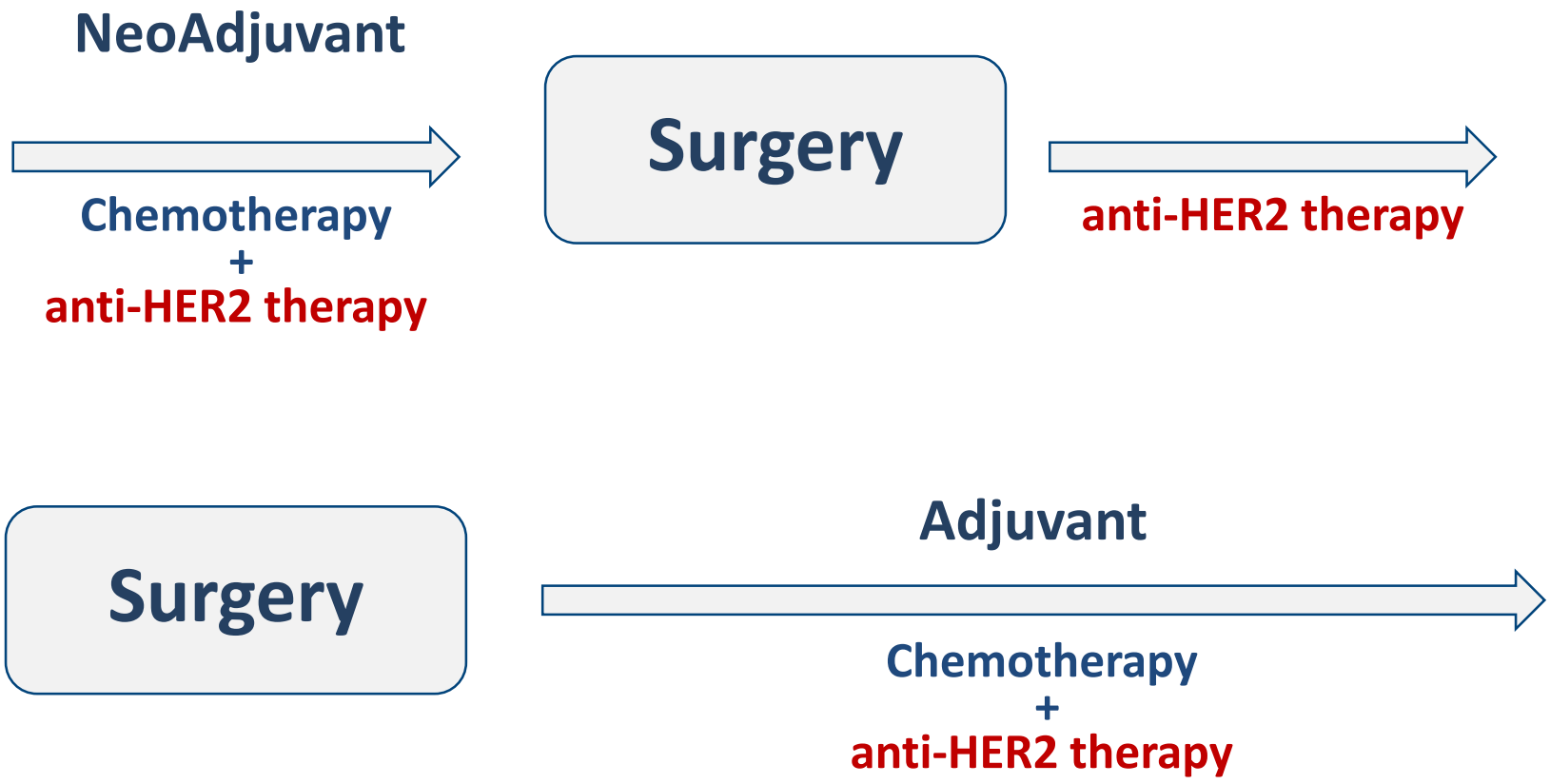
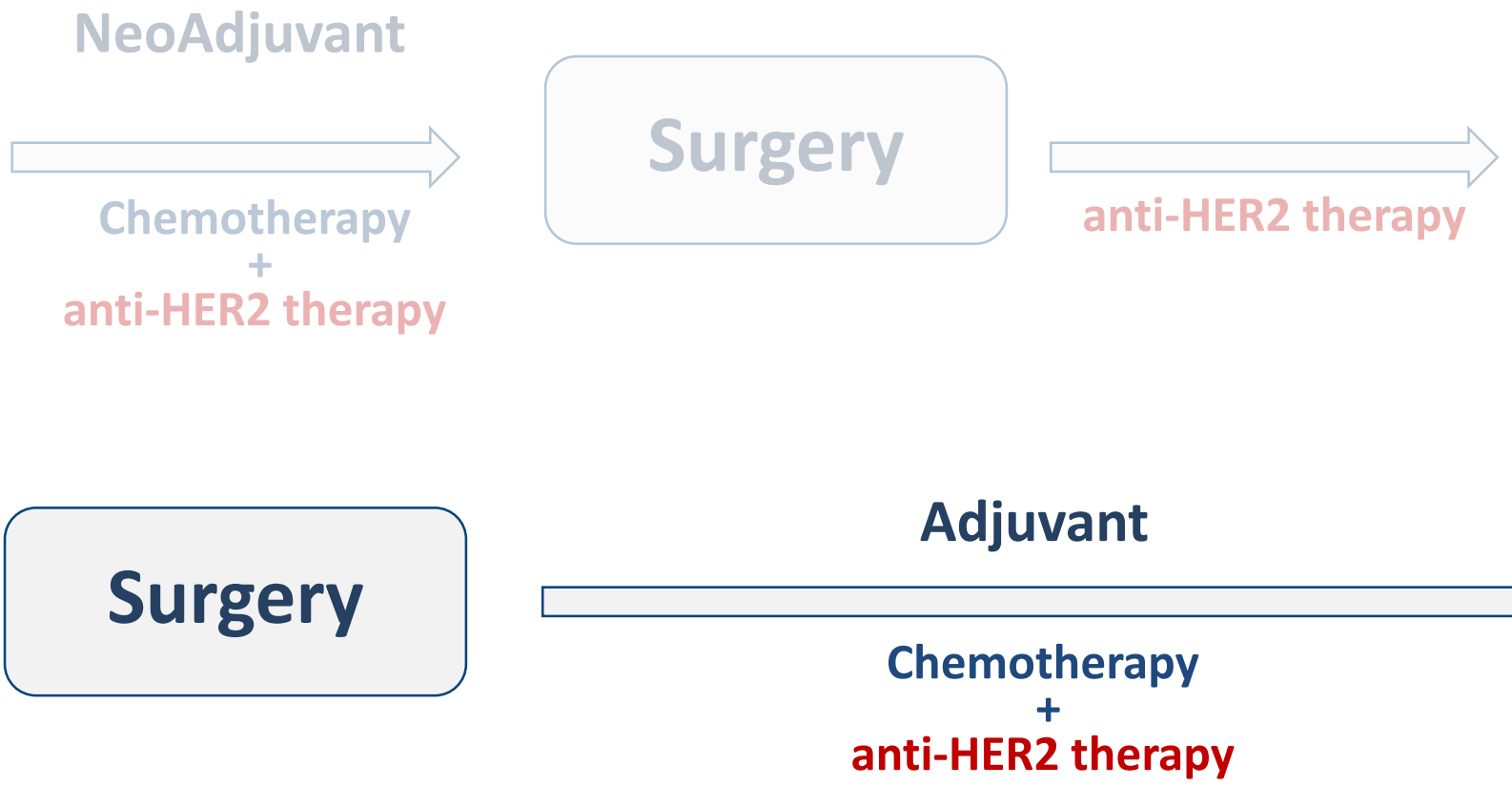
SOTTOGRUPPI HER2-POSITIVI E TRIPLE NEGATIVE IN STADIO PRECOCE

Lo Standard
G. ARPINO

HER2-positive BC-Adjuvant/Neo-adjuvant Setting



Adjuvant/Neo-adjuvant Setting



Benefit of adjuvant Trastuzumab

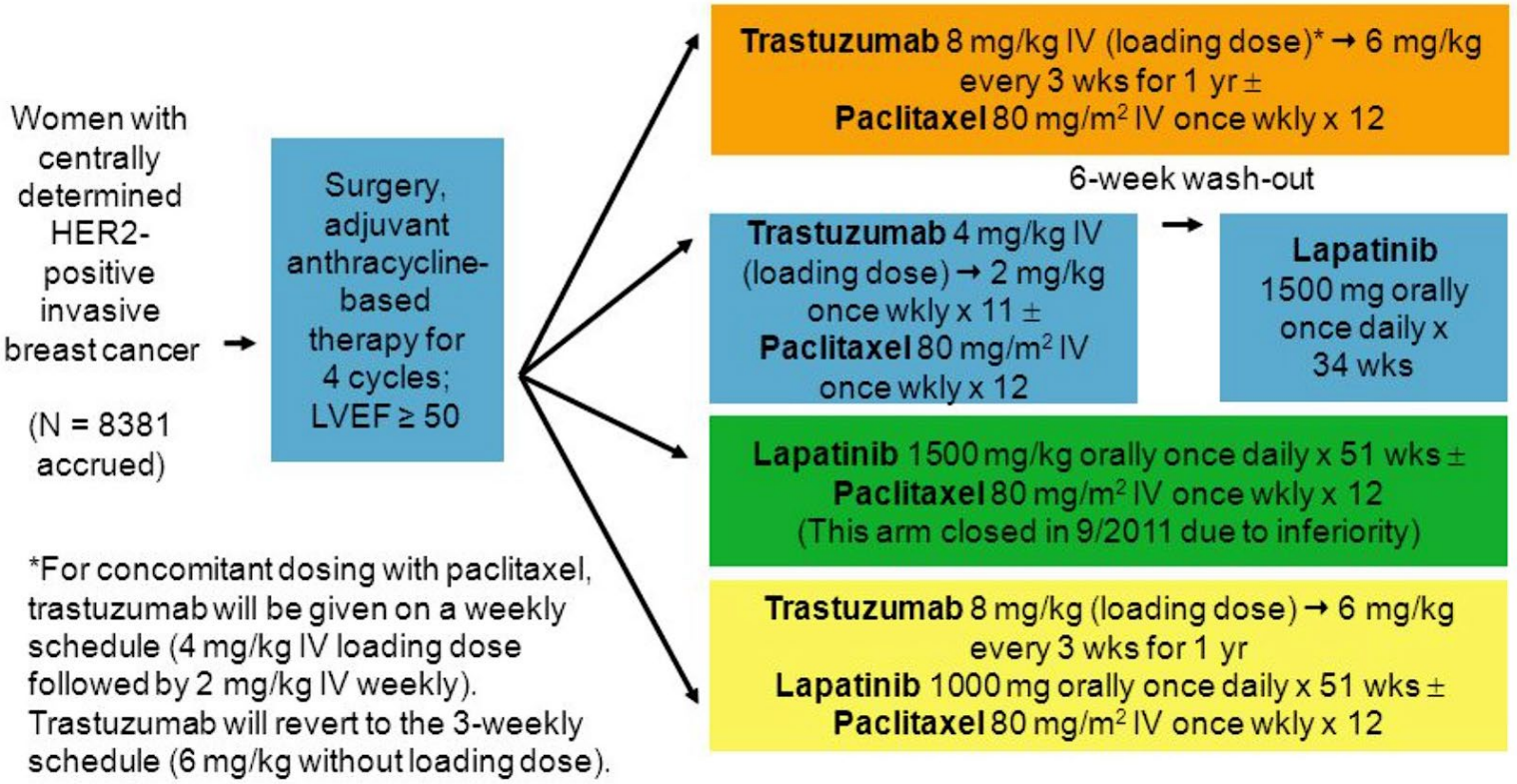
Trial	Treatment arms	Median Follow-up	DFS	OS
HERA[1]	Chemo Chemo -> H 1year Chemo-> H 2 year	11years	63% 69% 69%	73% 79% 80%
B-31[2]	ACT AC->TH-> H	8.4 years*	62,2% 73,7%	75,2% 84,0%
N9831[2]	AC-> wT AC -> wTH->H AC->wT->H	8.4 years*	62,2% 73,7%	75,2% 84,0%
BCIRG 006[3]	AC->D DCbH->H AC->DH->H	10 years	67,9% 73,0% 74,6%	78,7% 83,3% 85,9%

A=doxorubicin; C=cyclophosphamide; T=paclitaxel, D=docetaxel, Cb=carboplatin, H=trastuzumab
*combined analysis of B-31 and N9831

1. Cameron et al. Lancet 2017
2. Perez et al. JCO 2014
3. Slamon et al. SABCS2015

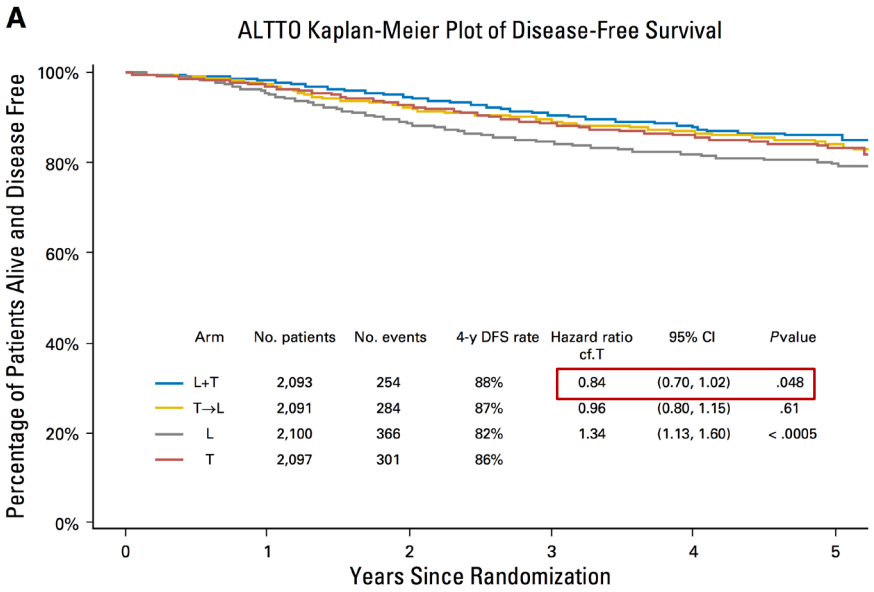
ALTTO

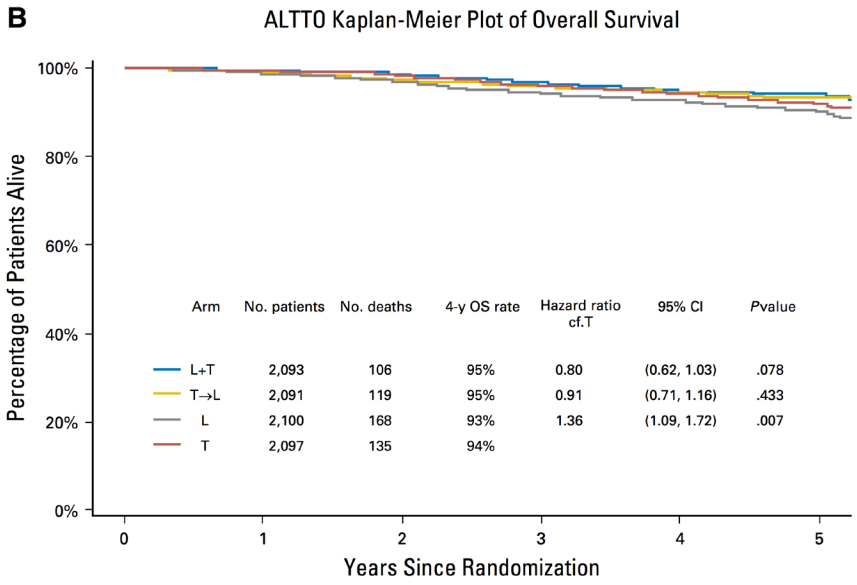
Study Design



ALTTO

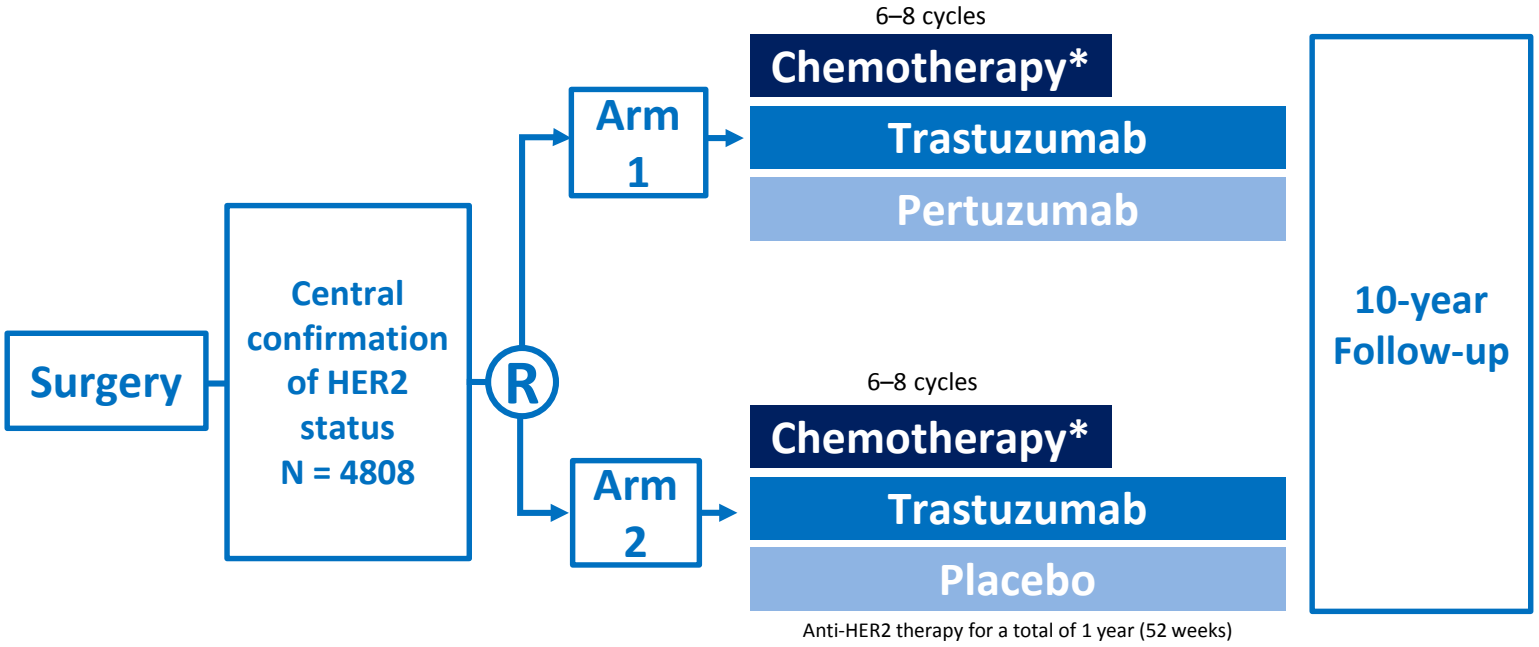
Results





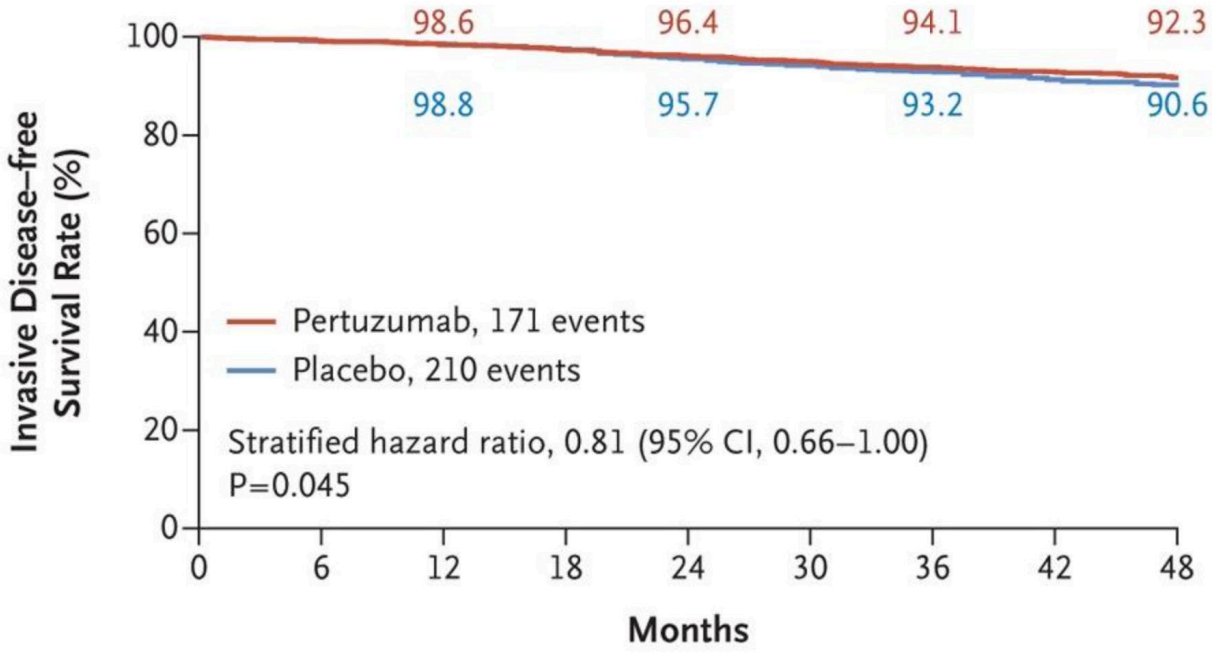
Piccart-Gebhart M et al, J Clin Oncol 2016

APHINITY



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

ITT POPULATION iDFS

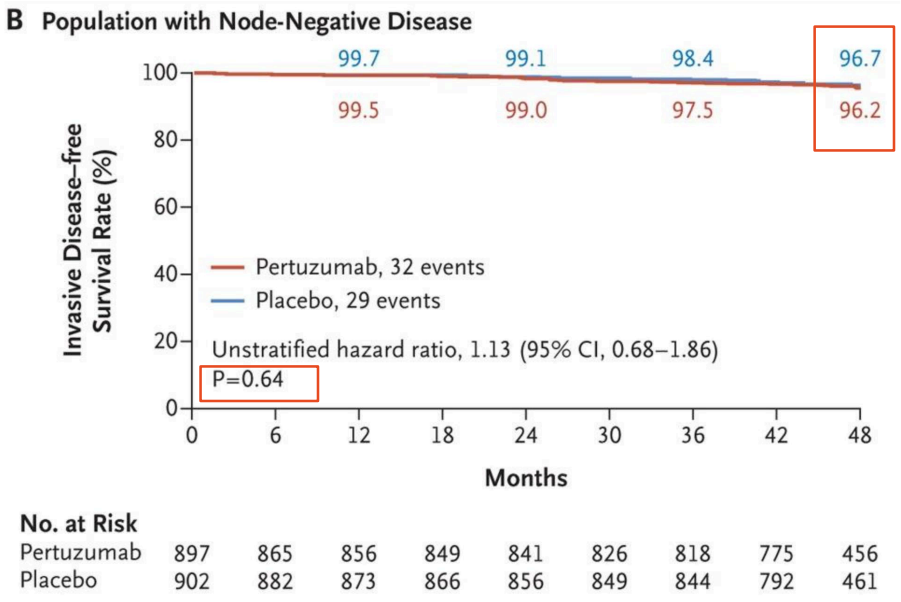


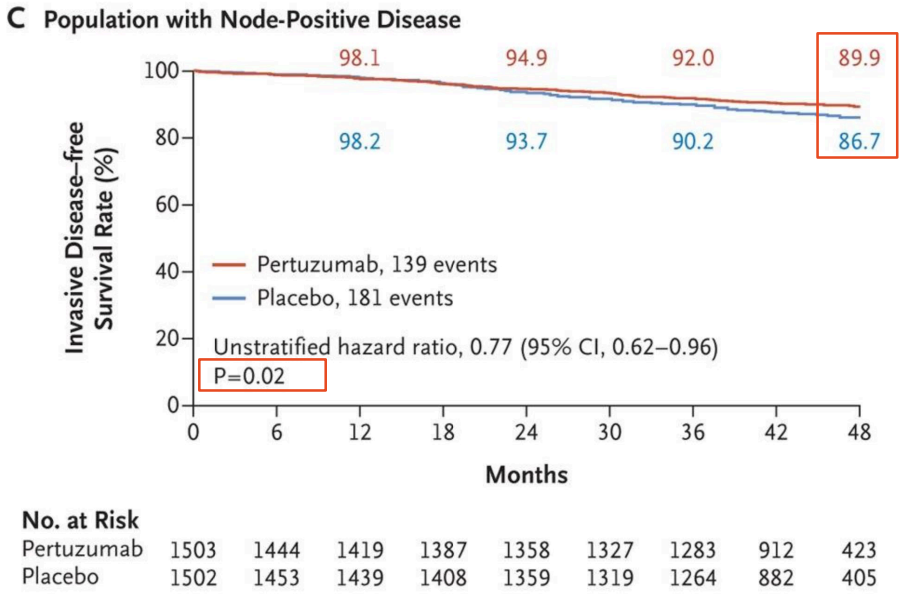
No. at Risk

Pertuzumab	2400	2309	2275	2236	2199	2153	2101	1687	879
Placebo	2404	2335	2312	2274	2215	2168	2108	1674	866

Von Minckwitz G, et al. N Engl J Med 2017 Jun 5.

iDFS for Node negative and node positive patients



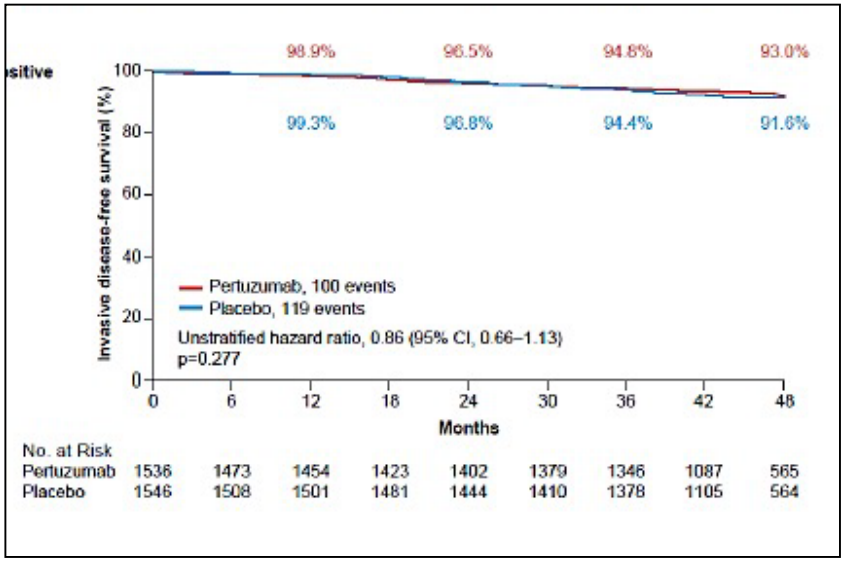


Increased rates of diarrhea (9.8 vs. 3.7%) and anemia (6.9 vs. 4.7%)
AND
Similar rates of cardiac toxicity (0.6% vs. 0.2%) with pertuzumab

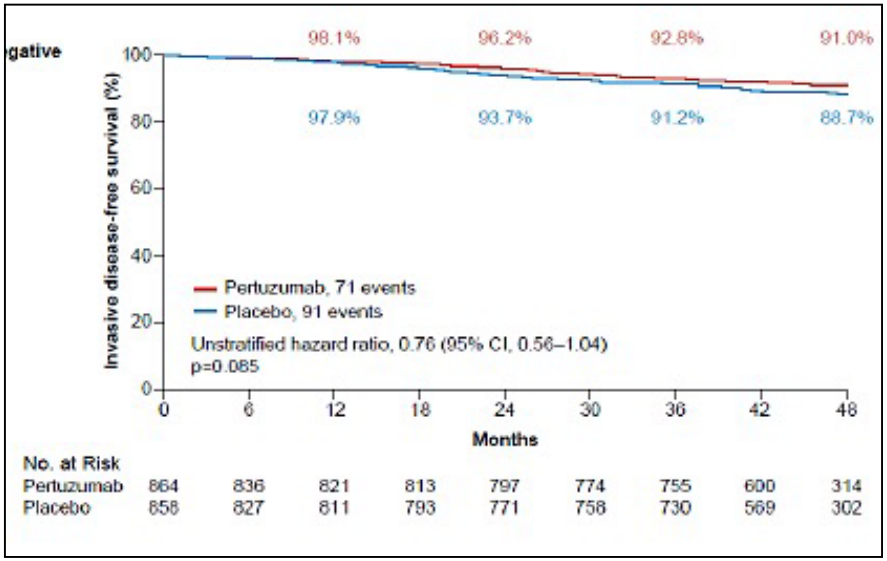
Von Minckwitz G, et al. N Engl J Med 2017 Jun 5.

iDFS for HR+ and HR- populations

Hormone receptor (HR) positive



Hormone receptor (HR) negative



Von Minckwitz G, et al. N Engl J Med 2017 Jun 5.

International guidelines support continuation of T + P from neoadjuvant to adjuvant in HER2-positive eBC

Pertuzumab PI[1]

Patients should continue to receive Pertuzumab and trastuzumab to **complete 1 year** of treatment (up to 18 cycles)

Pertuzumab SmPC 2018[2]

Pertuzumab should be administered in combination with trastuzumab for a **total of 1 year**…as part of a **complete regimen** for early breast cancer and regardless of the timing of surgery

NCCN Breast Cancer Guidelines[3]

Node positive or HR positive or HR-negative

Adjuvant systemic treatment recommendations after neoadjuvant therapy:
Complete up to 1 year of HER2-targeted therapy with trastuzumab ± pertuzumab

AGO Guidelines[4]

Node-positive or HR-negative disease

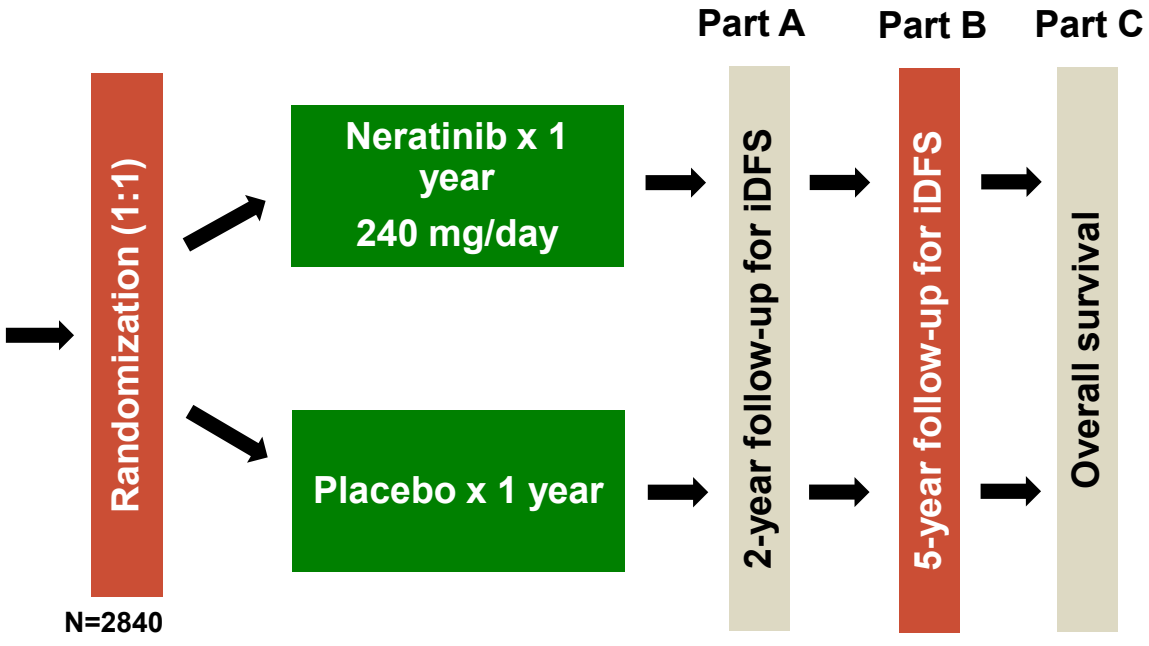
Continue using pertuzumab as adjuvant systemic therapy after neoadjuvant systemic therapy to **complete 1 year** of treatment

1. PERJETA US PI; 2017(Accessed Aug 2018); 2. PERJETA SmPC 2018 (Accessed Aug 2018);
3. NCCN Breast Cancer Guidelines. Version 1, 2018 – March 20, 2018; 4. AGO guidelines March 2018 (Accessed Aug 2018).

ExteNET Trial

Design

- **HER2+ breast cancer**
  - IHC 3+ or ISH amplified (locally determined)
  - Prior adjuvant trastuzumab + chemotherapy
  - Lymph node +/–, or residual invasive disease after neoadjuvant therapy
- **Stratified by:** nodal status, hormone receptor status, concurrent *vs* sequential trastuzumab



Primary endpoint: invasive disease-free survival (iDFS)

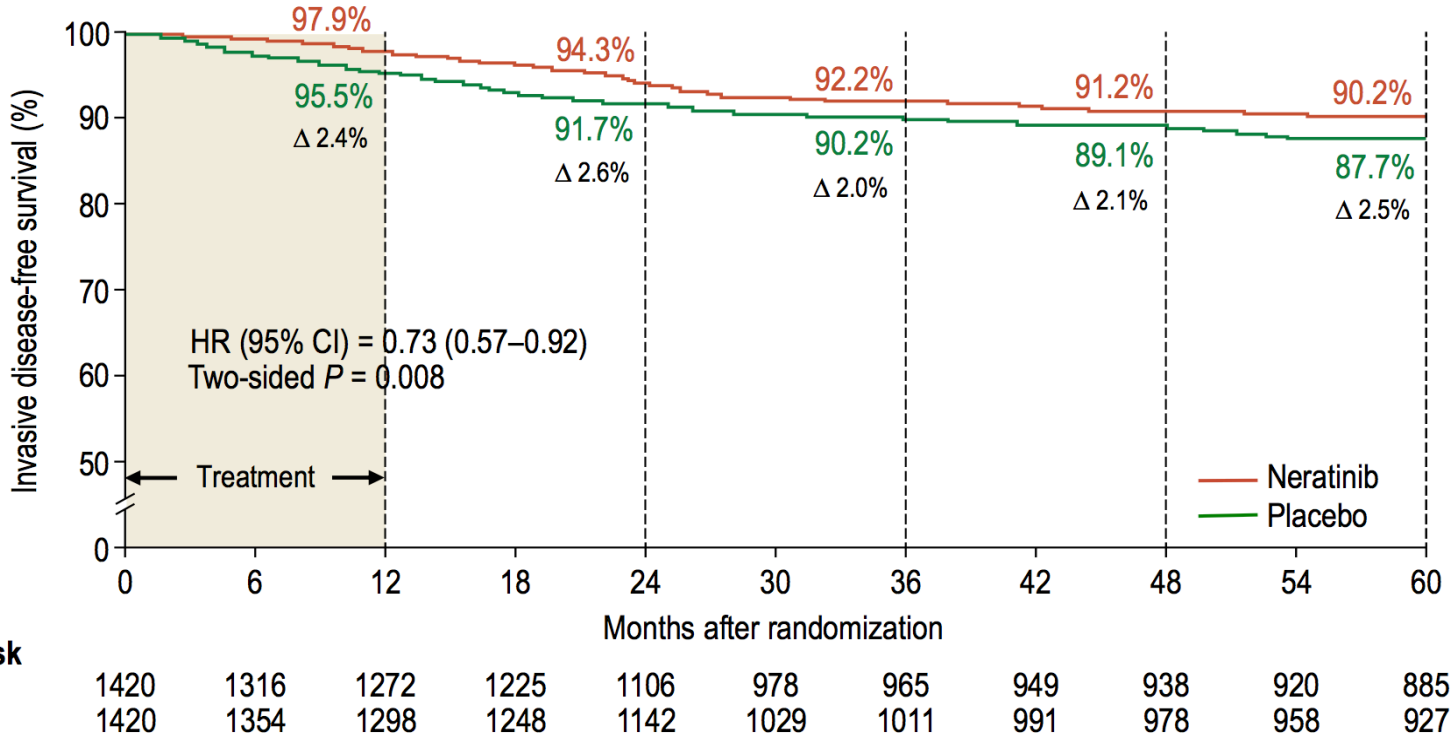
Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS recurrences, OS, safety

Other analyses: biomarkers, health outcome assessments (FACT-B, EQ-5D)

Endocrine adjuvant therapy given to patients with HR-positive tumors according to local practice

Chan et al, Lancet Onc 2016

ExteNET: 5-year analysis: iDFS

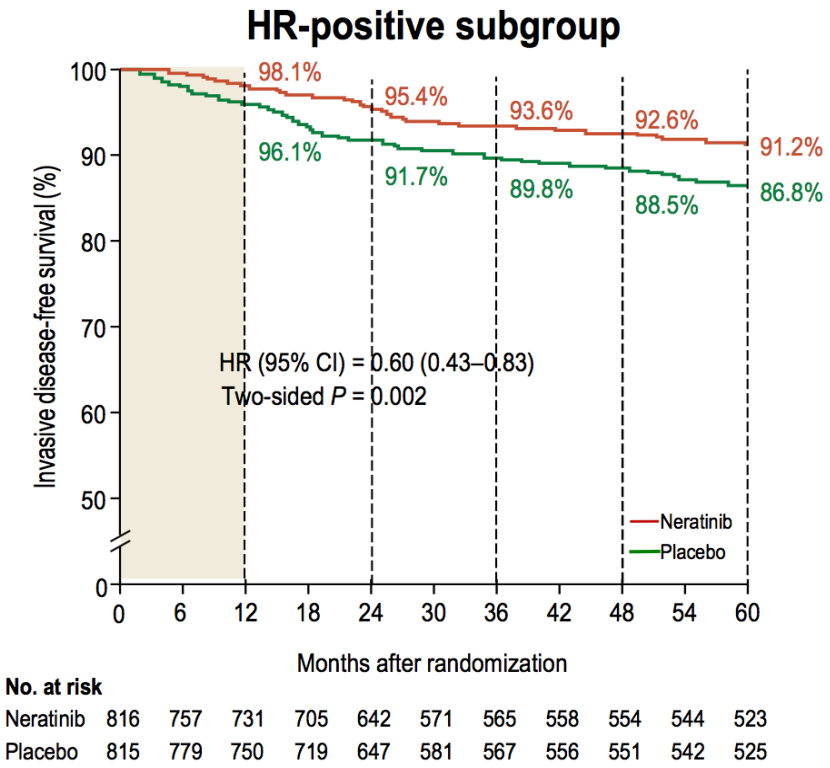


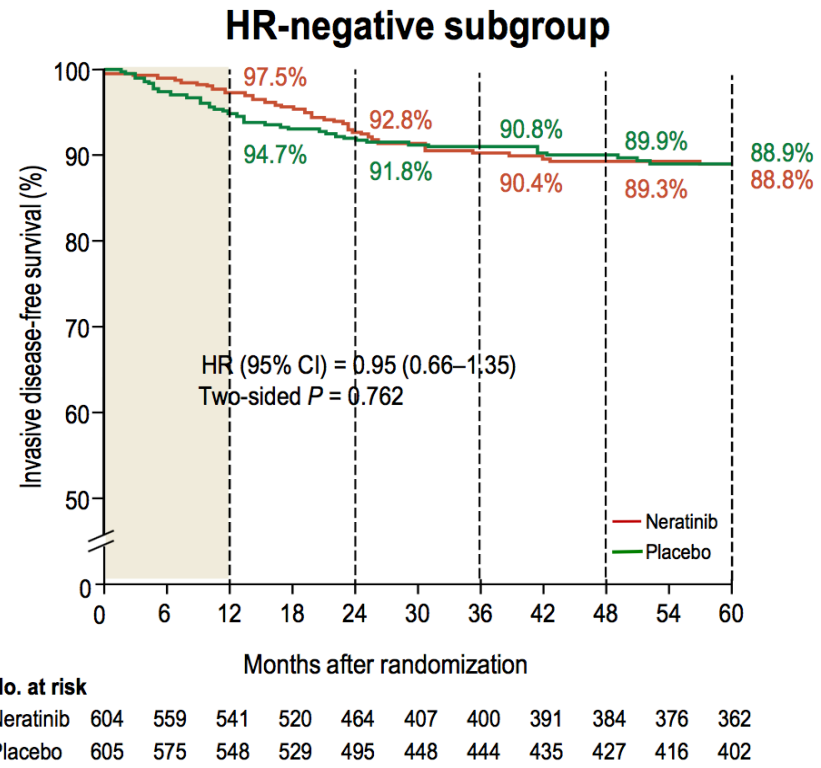
Diarrhea and rash were more frequent with neratinib
Grade 3 diarrhea 40% vs. 2%

Martin M et al, ESMO 2017

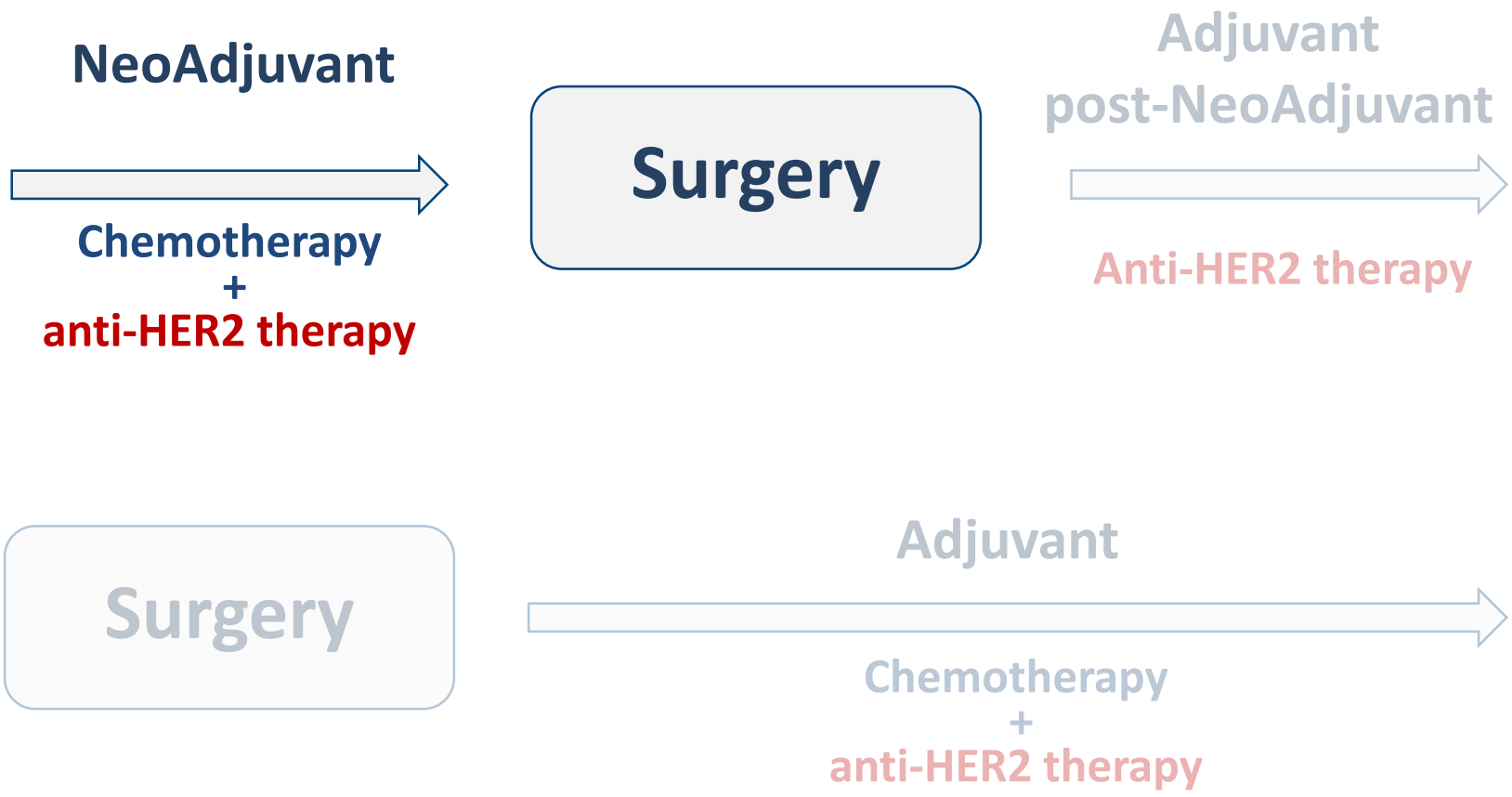
ExteNET Trial

Results according to HR status

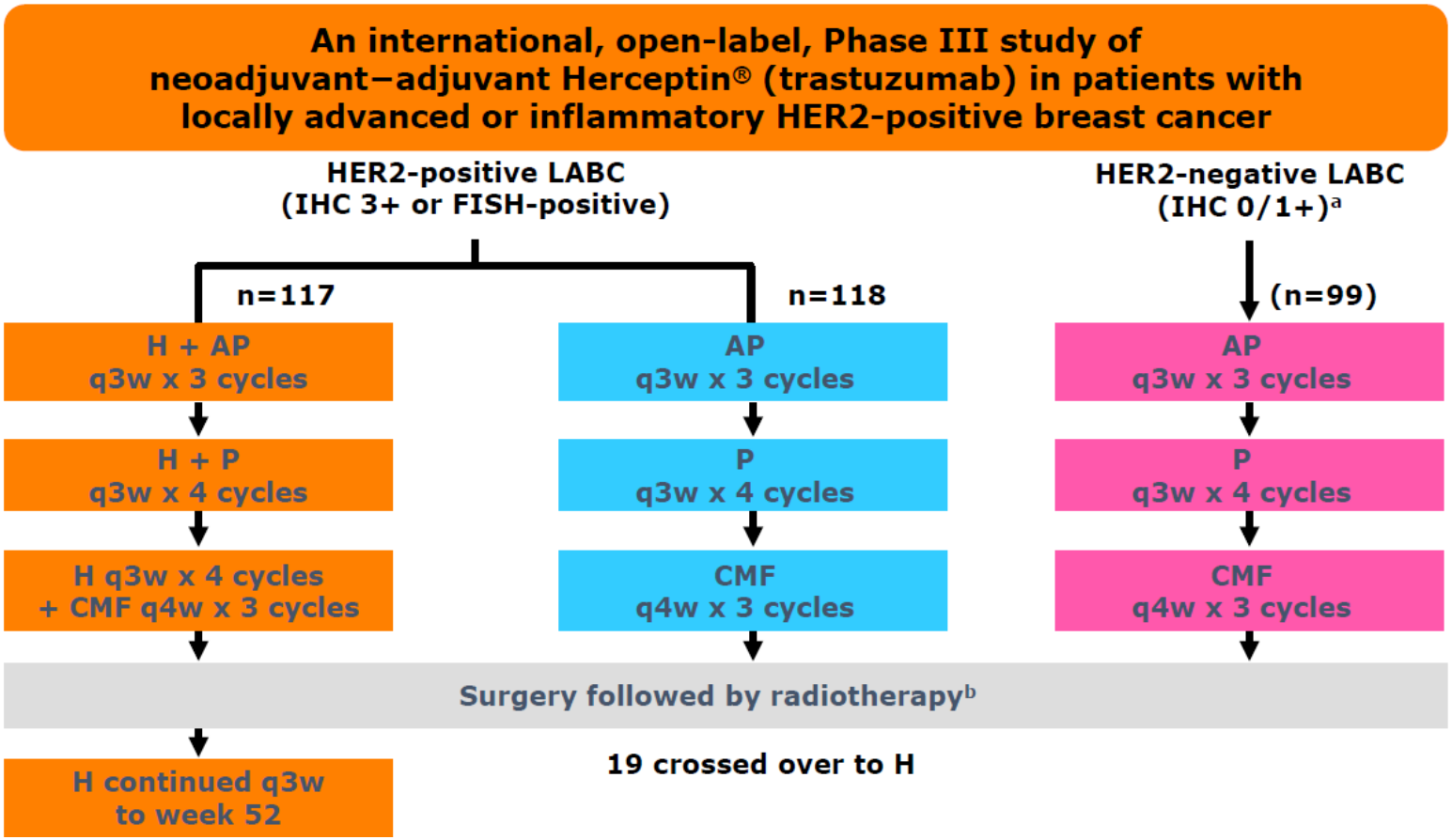




New treatment options for (neo)adjuvant treatment of HER2+ BC



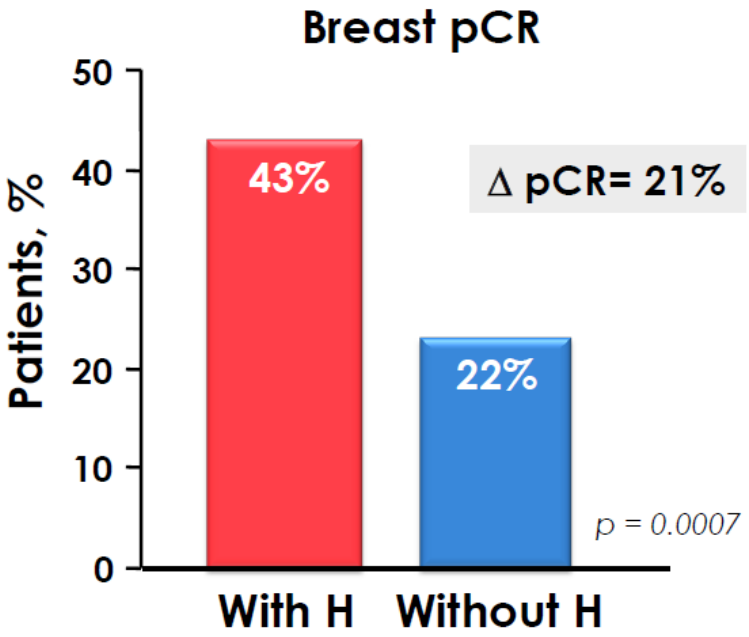
Neoadjuvant Trastuzumab - NOAH

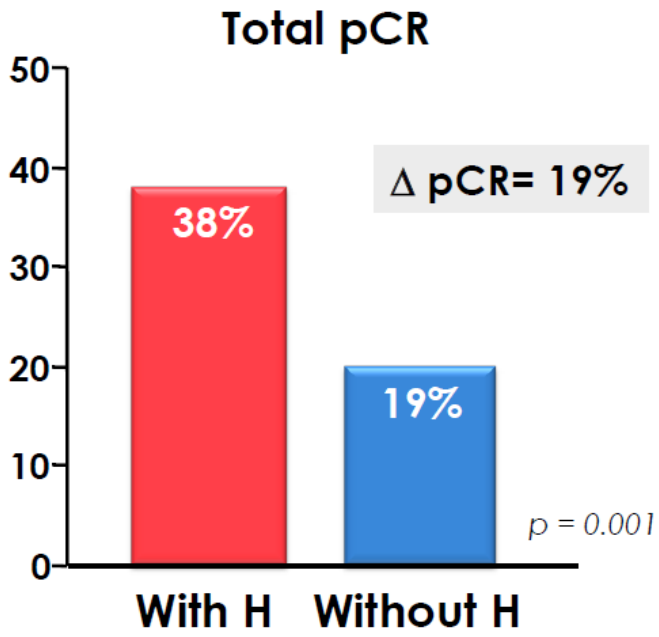


Gianni L et al, Lancet Oncol, 2010

Neoadjuvant Trastuzumab - NOAH

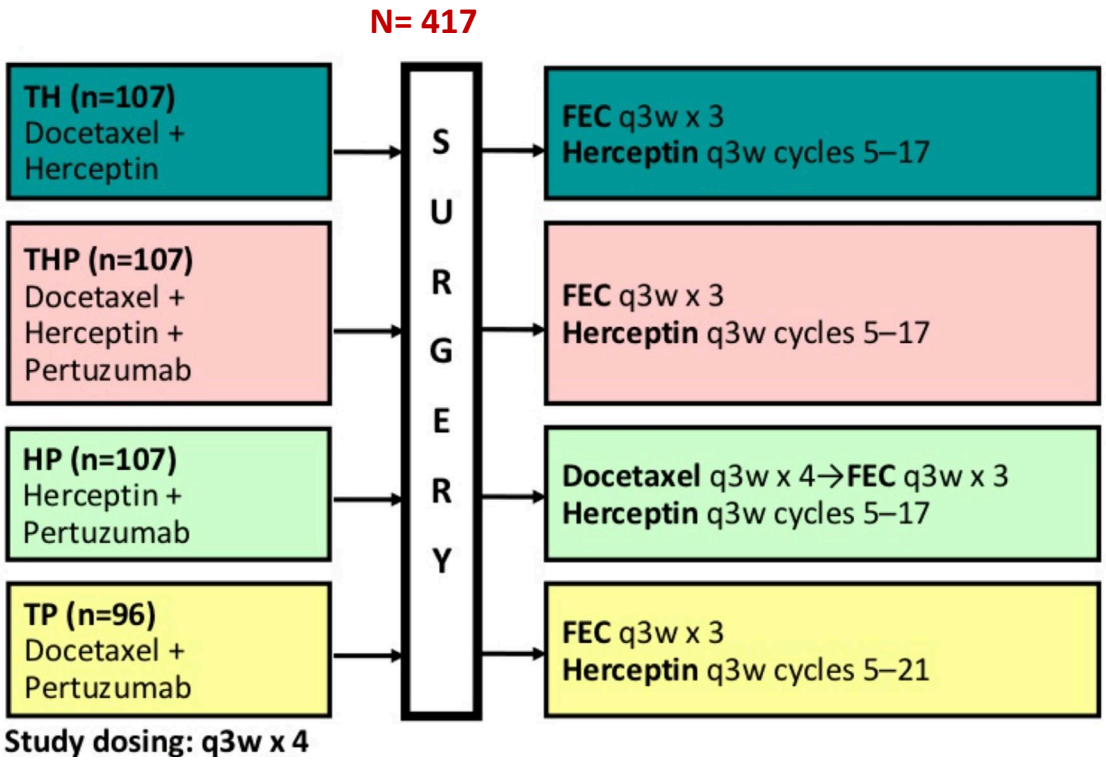
Single HER2 blockade





NeoSphere

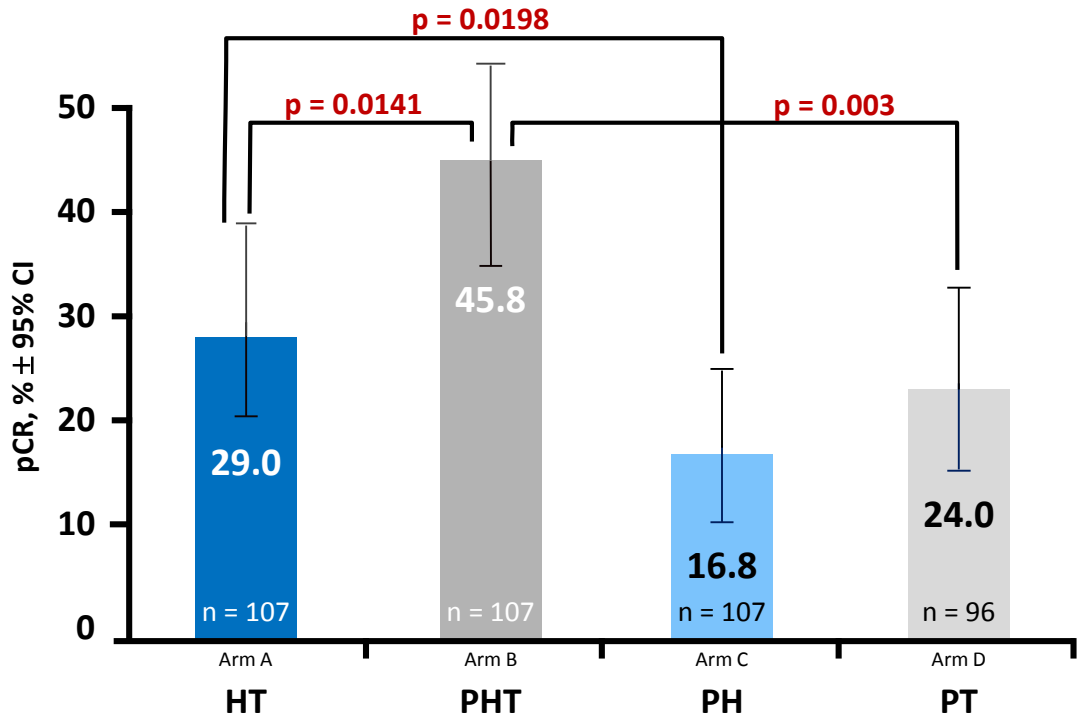
Phase II study of efficacy and safety of neoadjuvant PH in women with locally advanced, inflammatory, or early HER2+ breast cancer



- **Inclusion criteria**
  - Female patients ≥18 years of age
  - Operable*, locally advanced‡ or inflammatory§ breast cancer
  - HER2-positive (IHC 3+ or IHC 2+ and FISH+/CISH+)
  - Primary tumours >2 cm.
- **Exclusion criteria**
  - Metastatic disease (stage IV), bilateral breast cancer or other malignancy
  - Previous anti-cancer therapy
  - Impaired cardiac, liver or renal function.

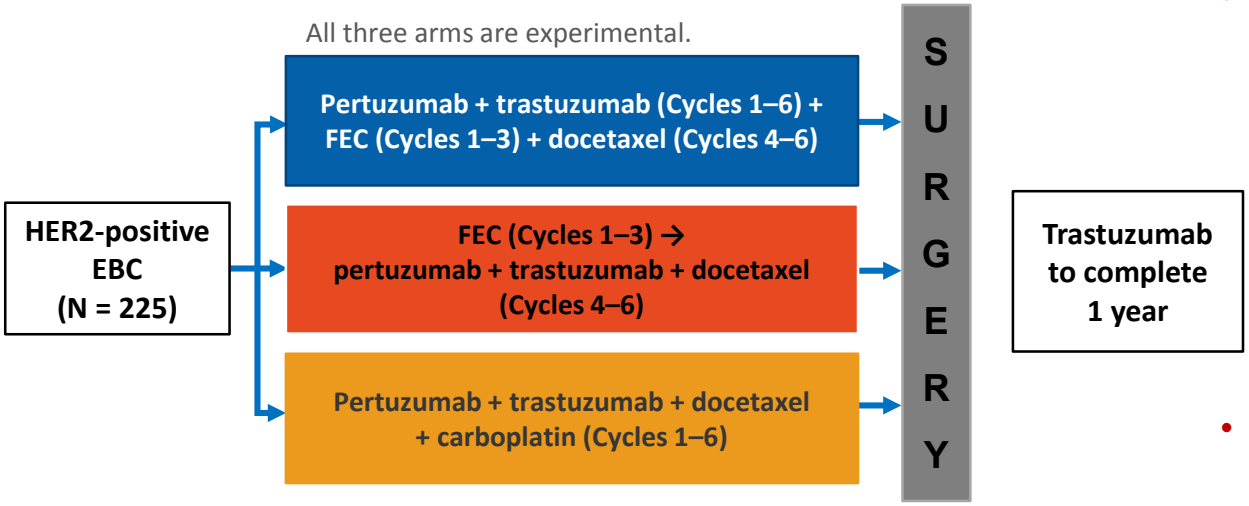
Gianni L, et al. Lancet Oncol 2012; 13(1): 25-32.

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 L, et al. Lancet Oncol 2012; 13(1): 25-32.

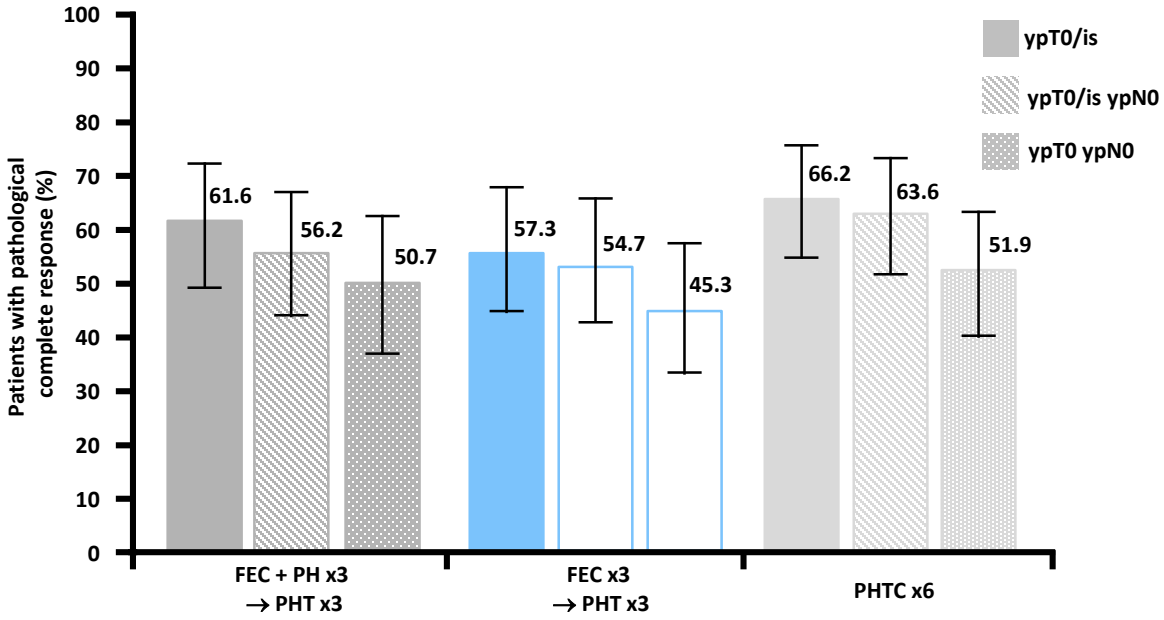
TRYPHAENA: phase II cardiac safety study assessing Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer



FEC, 5-fluorouracil, epirubicin, cyclophosphamide.
Schneeweiss A, et al. Ann Oncol 2013; 24(9): 2278-2284.

- **Inclusion criteria**
  - Female patients with centrally confirmed HER2-positive, locally advanced, inflammatory or early-stage breast cancer
  - Primary tumour ≥2 cm
  - Baseline LVEF ≥55%
  - ECOG PS 0 or 1.
- **Exclusion criteria**
  - Previous anti-cancer therapy or radiotherapy for any malignancy
  - Cardiac dysfunction, or inadequate bone marrow, liver or renal function.

TRYPHAENA: pCR rate

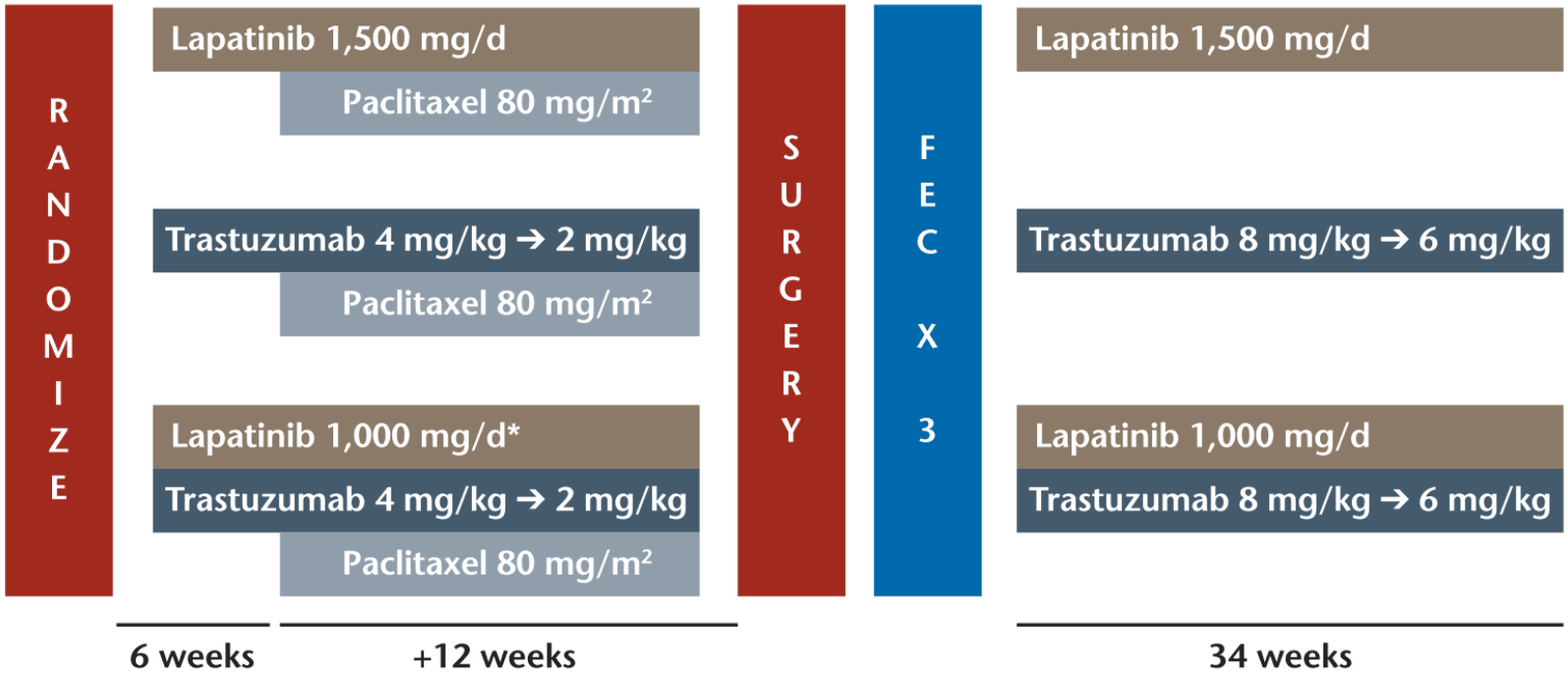


Pertuzumab and trastuzumab provide clinical benefit, regardless of chemotherapy partner

C, carboplatin; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; pCR, pathological complete response; T, docetaxel.

Adapted from Schneeweiss A, et al. Ann Oncol 2013; 24(9): 2278-2284.

NeoALTTO Trial



d = day; FEC = fluorouracil, epirubicin, cyclophosphamide
**Amendment: October 2, 2008, reduced dose of lapatinib to 750 mg/d with paclitaxel; 54/152 had protocol-driven reduction.*

Dual HER2 targeting
pCR rates

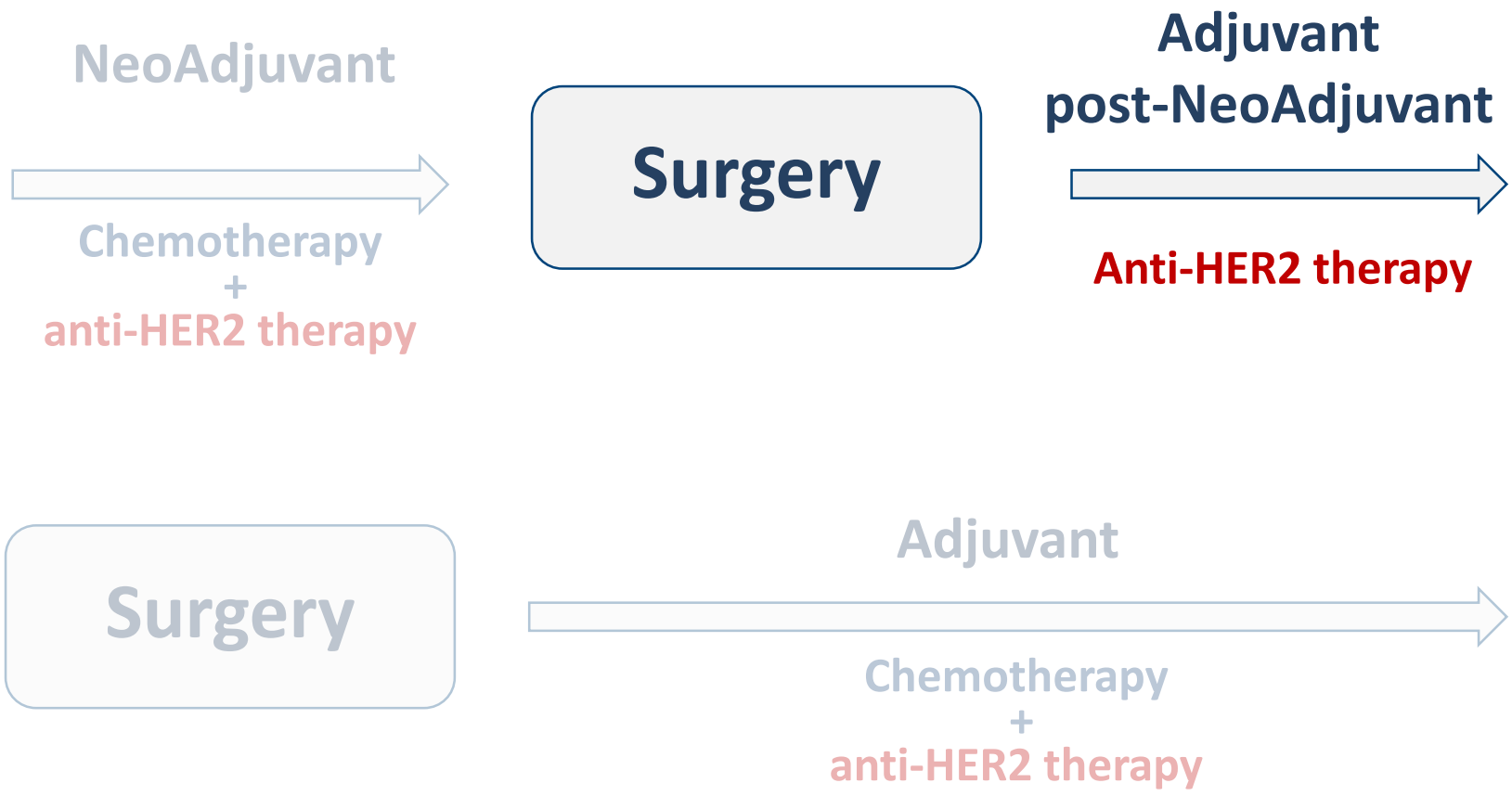
NEO-SPHERE

	Trastuzumab Docetaxel	Pertuzumab Docetaxel	Trastuzumab Pertuzumab Docetaxel	Trastuzumab Pertuzumab
ITT	29%	24%	46%	17%

NEO-ALTTO

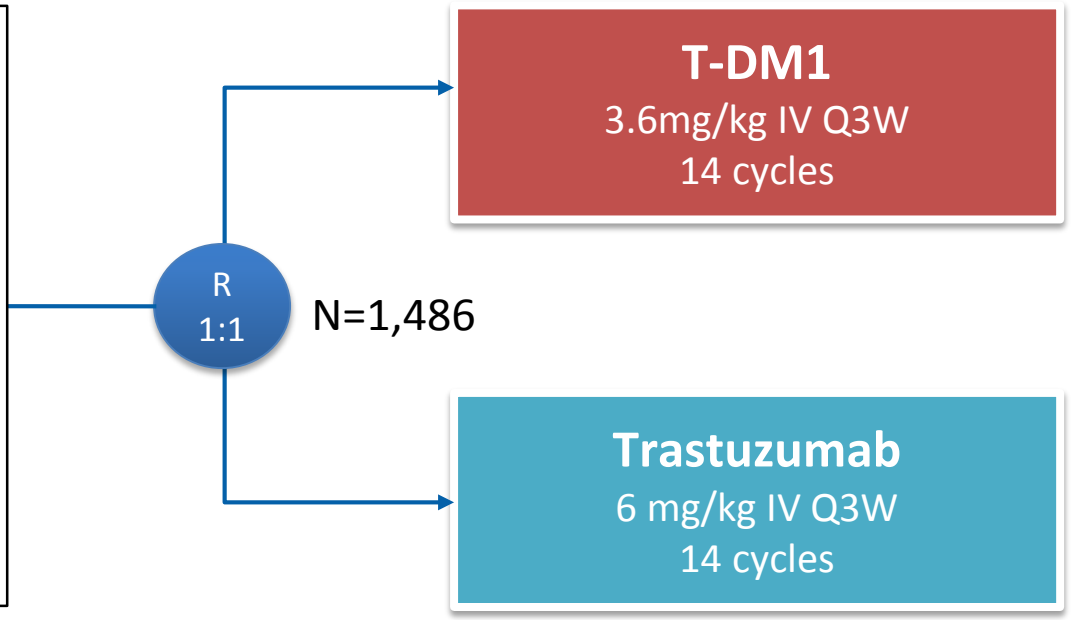
	Trastuzumab Paclitaxel	Lapatinib Paclitaxel	Trastuzumab Lapatinib Paclitaxel
ITT	29%	25%	51%

New treatment options for (neo)adjuvant treatment of HER2+ BC



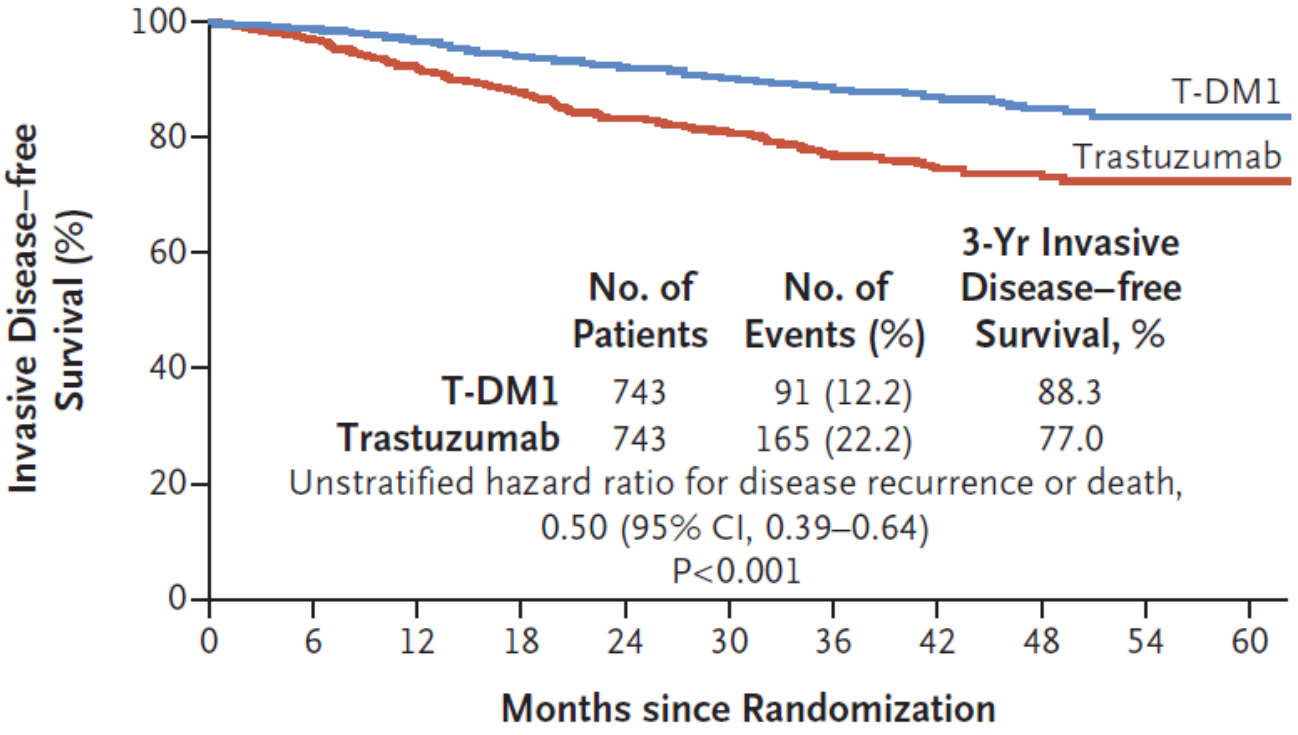
Post-neoadjuvant – TDM1
KATHERINE

- Early HER2+ breast cancer patients
- Pertuzumab use was allowed
- Residual disease after neoadjuvant treatment with chemotherapy and trastuzumab



Radiation and endocrine treatment were administered according to local guidelines

Post-neoadjuvant – TDM1



11.3%

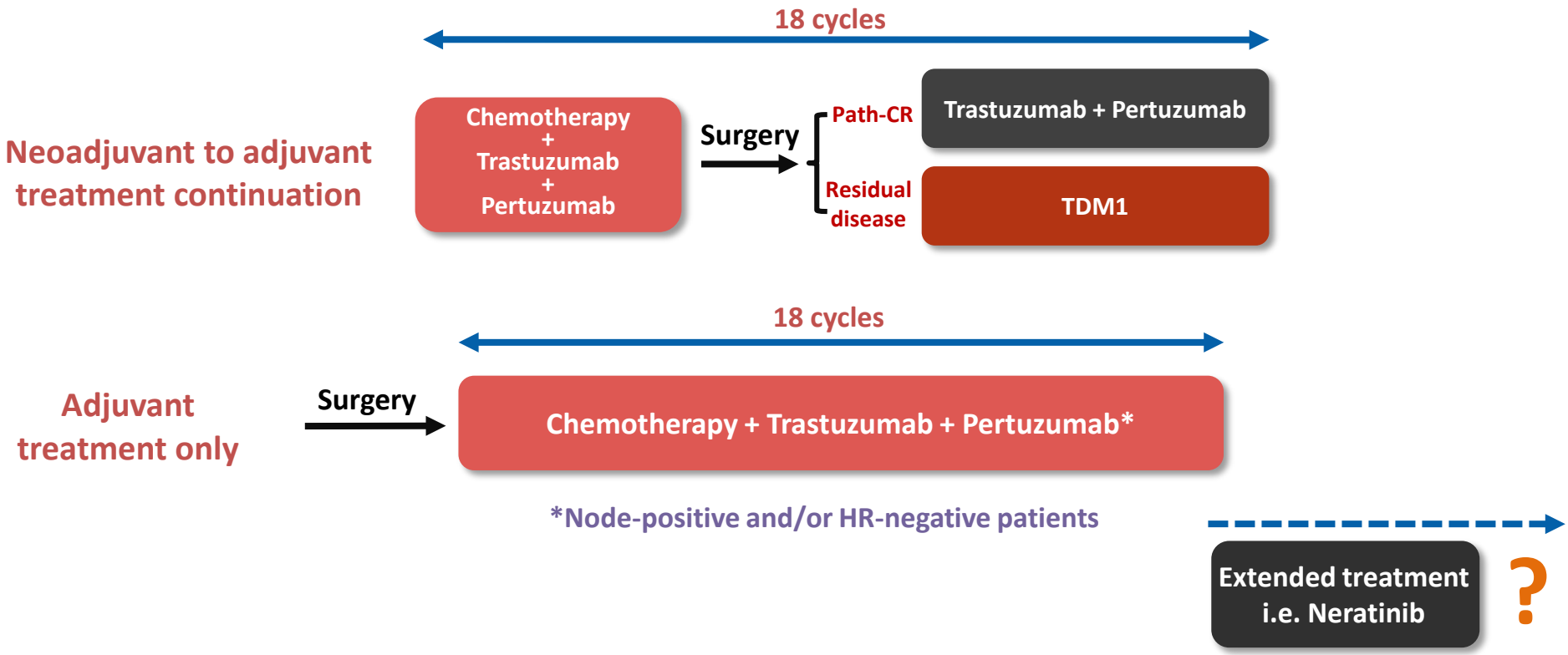
Von Minckwitz et al, NEJM 2019

T-DM1 gave a consistent magnitude of IDFS benefit regardless of prior HER2-directed therapy

	Trastuzumab n = 743	T-DM1 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**

Von Minckwitz et al, NEJM 2019

Potential treatment algorithm for the (neo)adjuvant setting



De-escalation Treatment in HER2+ disease

- *De-escalation strategies:*

  1. Shorter trastuzumab duration
  2. Reduction of chemotherapy backbone
  3. Chemo-free regimens

Shorter duration trials—results

Trial	Duration of trial	Timing of randomization	Patient characteristics	Chemotherapy with anthracyclines and taxanes	Concomitant trastuzumab with chemotherapy	Patients (*n*)	Efficacy (short arm versus long arm)[b]	Notable Subgroup analysis favoring 1 year	Cardiac events (short arm vs long arm)
6 months vs 12 months									
PERSEPHONE	8 years	Within first 6 months	N−: 59% ER+: 69%	48%	47%	4089	11.6% vs 11.2% 4-year DFS events HR 1.07 (0.93–1.24)	Taxane-only, concurrent chemotherapy and trend in ER-	9% vs 12%
PHARE	6 years	At 6 months	N−: 55% ER+: 60%	74%	56%	3380	8.9% vs 6.2% 3.5-year DFS events: HR 1.28 (1.05–1.56)	Tumour size >2 cm and sequential chemotherapy-trastuzumab	1.9% vs 5.7%
HORG	8 years	Previously to treatment	N−: 17% ER+: 69%	100%	100%	481	6.7% vs 4.3% 3-year DFS events: HR 1.57 (0.86–2.10)	No significant findings	0 vs 2 cases
9 weeks vs 12 months									
SOLD	9 years	Previously to treatment	N−: 60% ER+: 66%	100%	100%	2,176	12.0% vs 9.5% 5-year DFS events: HR 1.39 (1.12–1.72)	lower docetaxel dose, trend in ER- and LN1–3 of benefit in 1-year arm	2.0 vs 3.9%
SHORT-HER	9 years	Previously to treatment	N−: 51% ER+: 67%	100%	100%	1,253	14.6% vs 12.5% 5-year DFS events: HR 1.15 (0.91–1.46)	Stage III and N2/N3 significantly benefit from 1 year	5.1% vs 14.4%

a. From first patient in to initial presentation of results
b. The confidence intervals are, respectively, 95% (HORG, PHARE) and 90% (SOLD, SHORT-HER, PERSEPHONE)

De-escalation Treatment in HER2+ disease

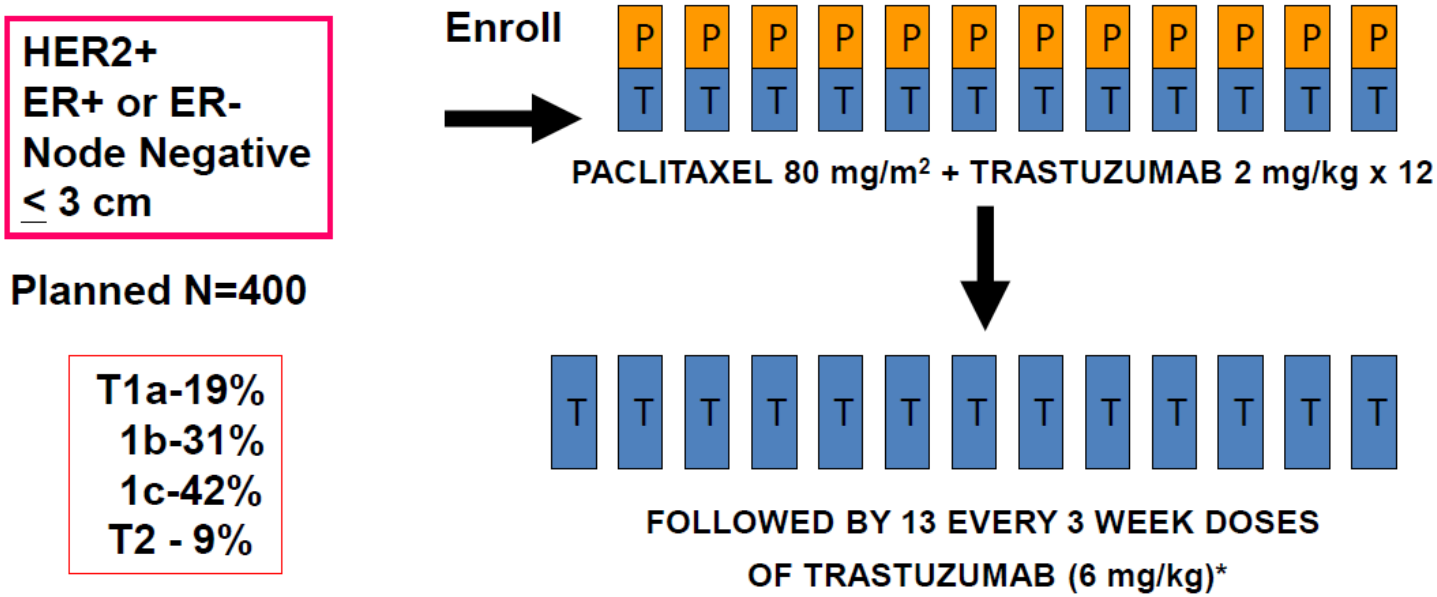
- *De-escalation strategies:*

  1. Shorter trastuzumab duration

  2. Reduction of chemotherapy backbone

  3. Chemo-free regimens

Adjuvant Paclitaxel and Trastuzumab (APT)



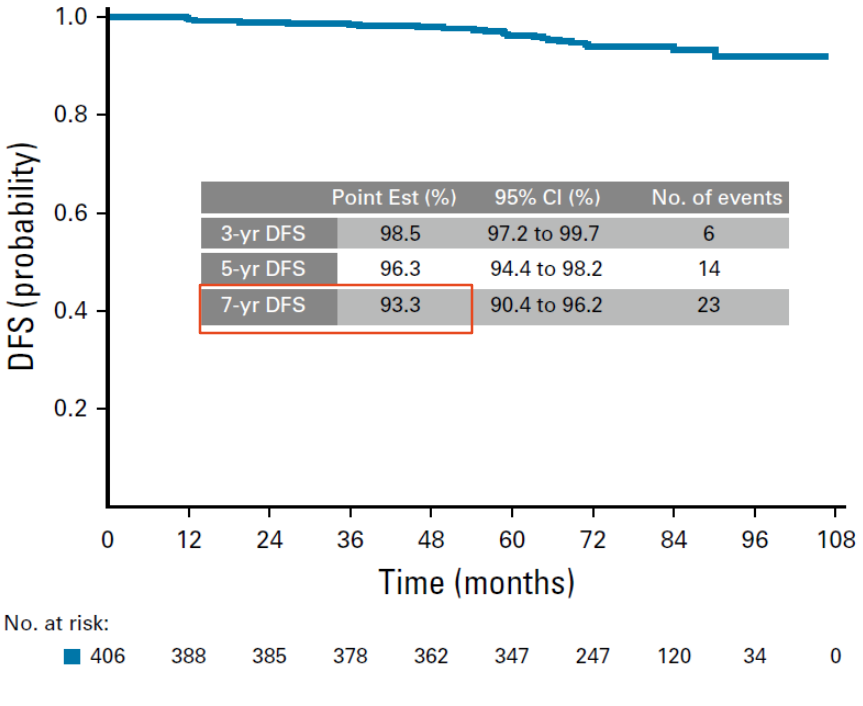
*Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks
** Radiation and hormonal therapy was initiated after completion of paclitaxel

Tolaney et al. NEJM 2015

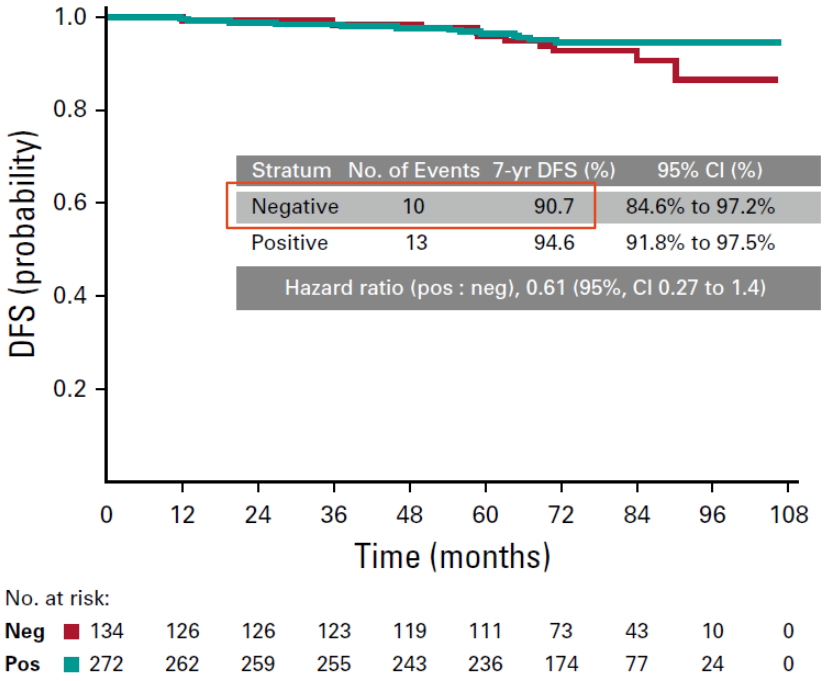
Tolaney et al, NEJM 2015

Adjuvant Paclitaxel and Trastuzumab (APT) Disease-free Survival

All patients



HR+ vs HR-



Tolaney S et al, JCO 2019

Phase II study of Docetaxel, cyclophosphamide and Trastuzumab

493 patients, median FU of 3 years

Node status:
- Positive = 20.7%
- Negative = 79,3%

Stage:
- I = 57,6%
- II = 41,2%
- III = 1,2%

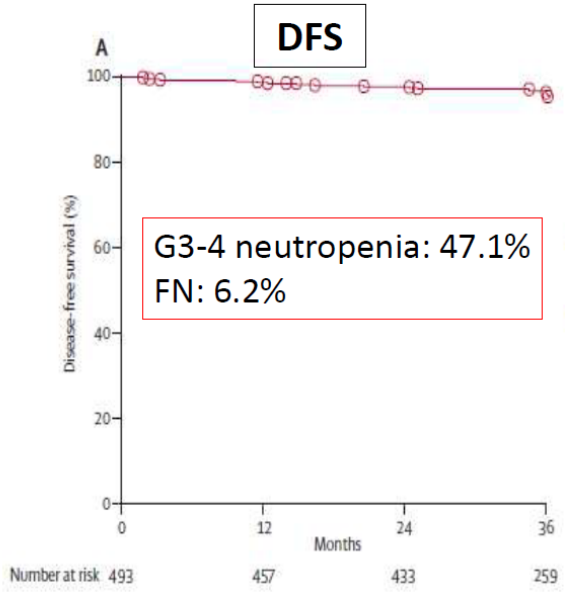
Outcome:
- *2 year DFS = 97.8%*
- *3 year DFS = 96,9%*
  - *Node - = 97.8%*
  - *Node + = 93.5%*

Symptomatic heart failure: 0.4%

Jones et al, Lancet Oncol 2014

Phase II Study of Docetaxel, Cyclophosphamide, and Trastuzumab

- N = 493, med FU of 3 yrs
- Node Status
  - Node (-): 79.3%
  - Node (+): 20.7%
- Stage: I (57.6%), II (41.2%)
  III (1.2%)
- Outcomes:
  - 2 year DFS: 97.8%
  - 3 year DFS: 96.9%
    - Node (-): 97.8%
    - Node (+): 93.5%
- Symptomatic heart failure: 0.4%

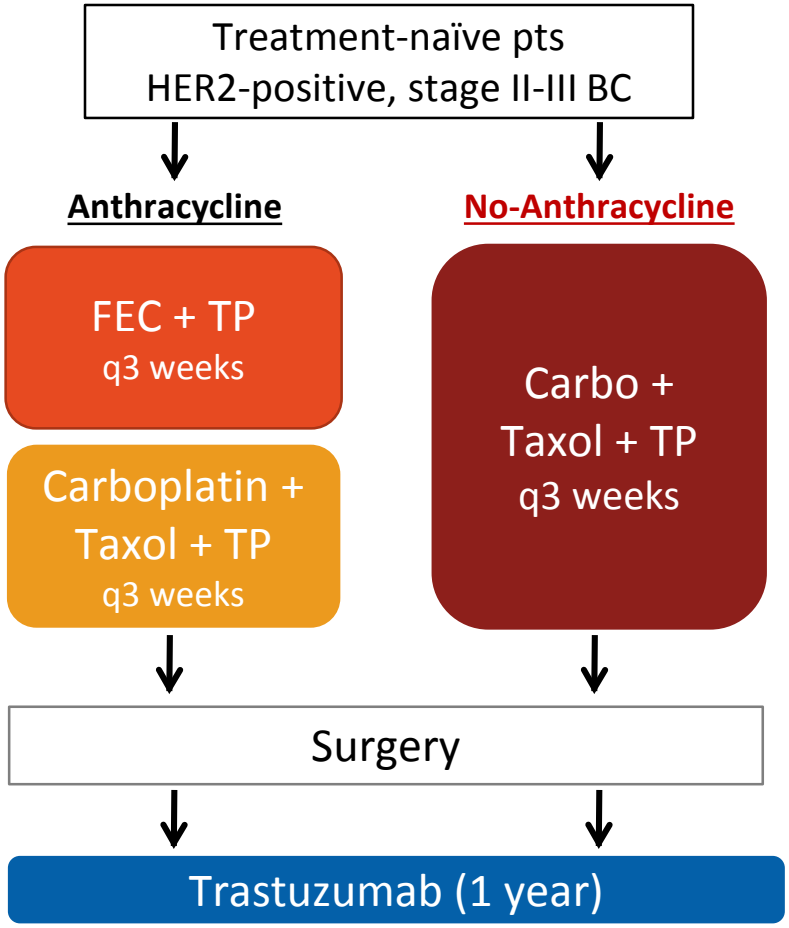


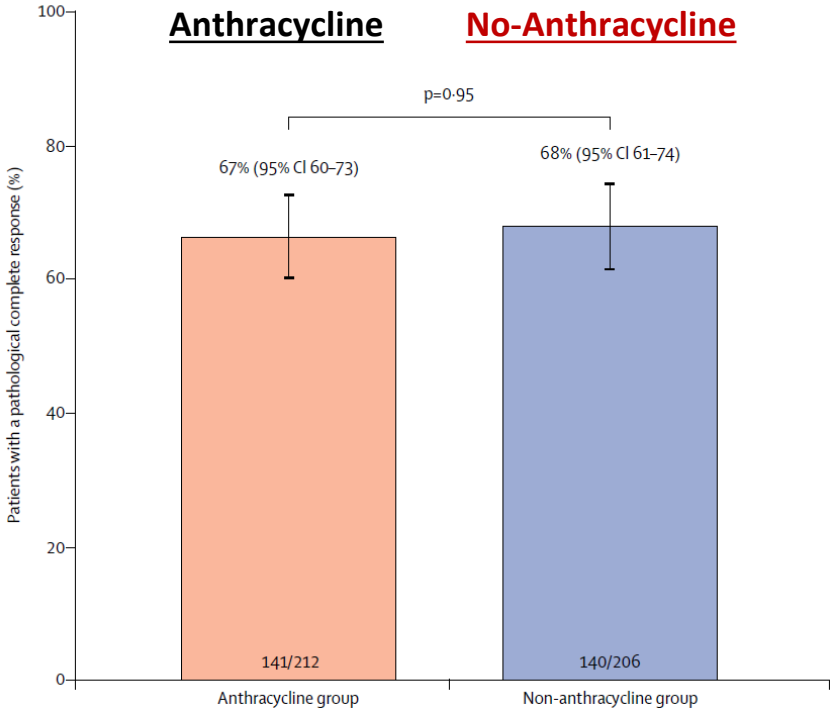
G3-4 neutropenia: 47.1%
FN: 6.2%

Jones et al. Lancet Oncol 2014

Non-anthracycline regimens

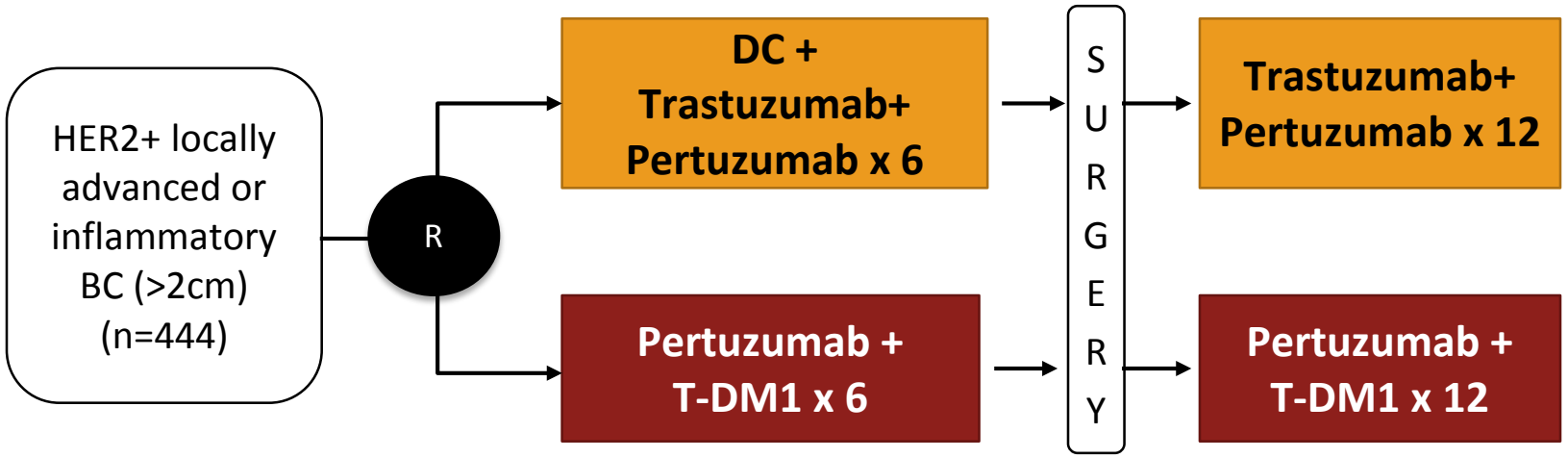
TRAIN II study





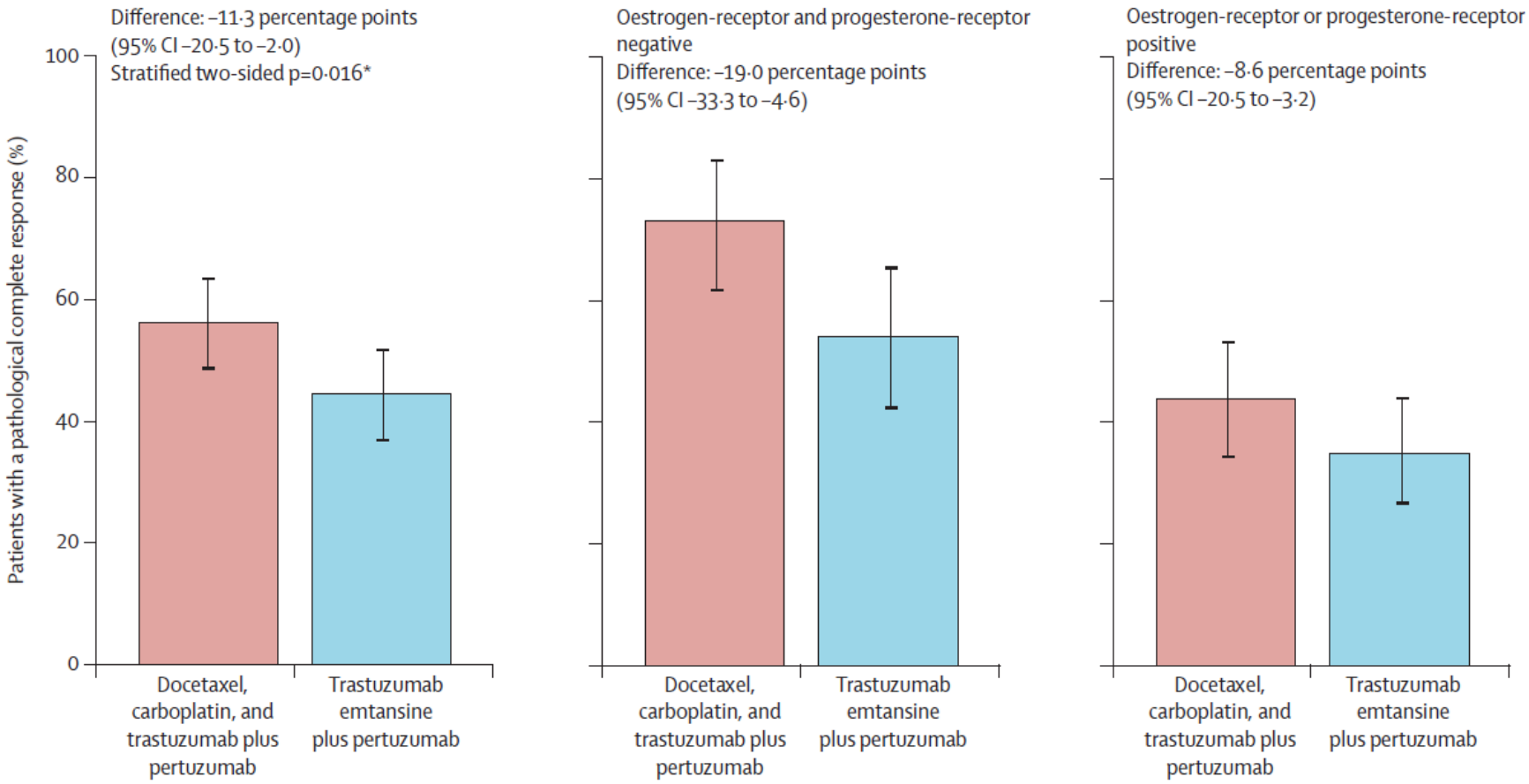
Van Ramshorst MS et al, Lancet Oncol 2019

KRISTINE study



Hurvitz S, Lancet Oncol 2018

KRISTINE study



Hurvitz S, Lancet Oncol 2018

De-escalation Treatment in HER2+ disease

- *De-escalation strategies:*

  1. Shorter trastuzumab duration

  2. Reduction of chemotherapy backbone

  3. Chemo-free regimens

TBCR006 study

Neoadjuvant treatment

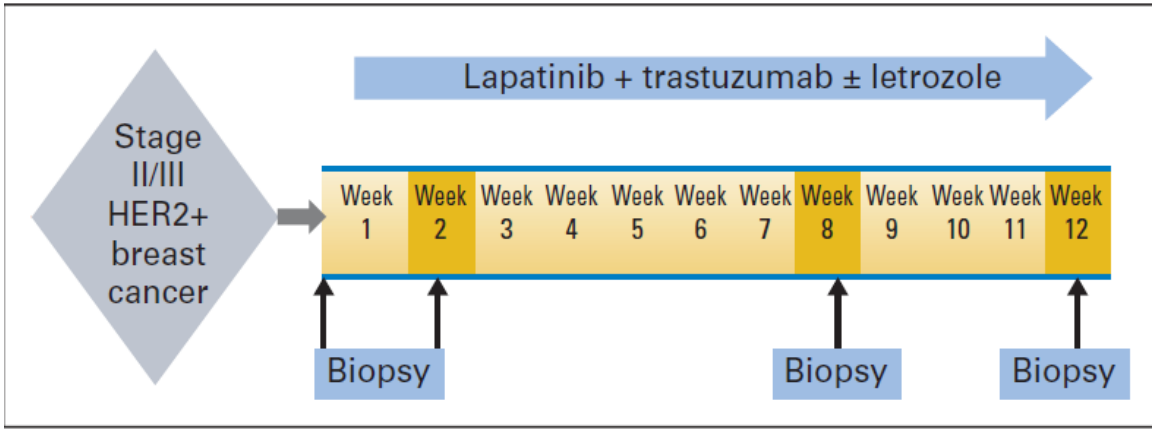


Table 2. Pathologic Response Rates

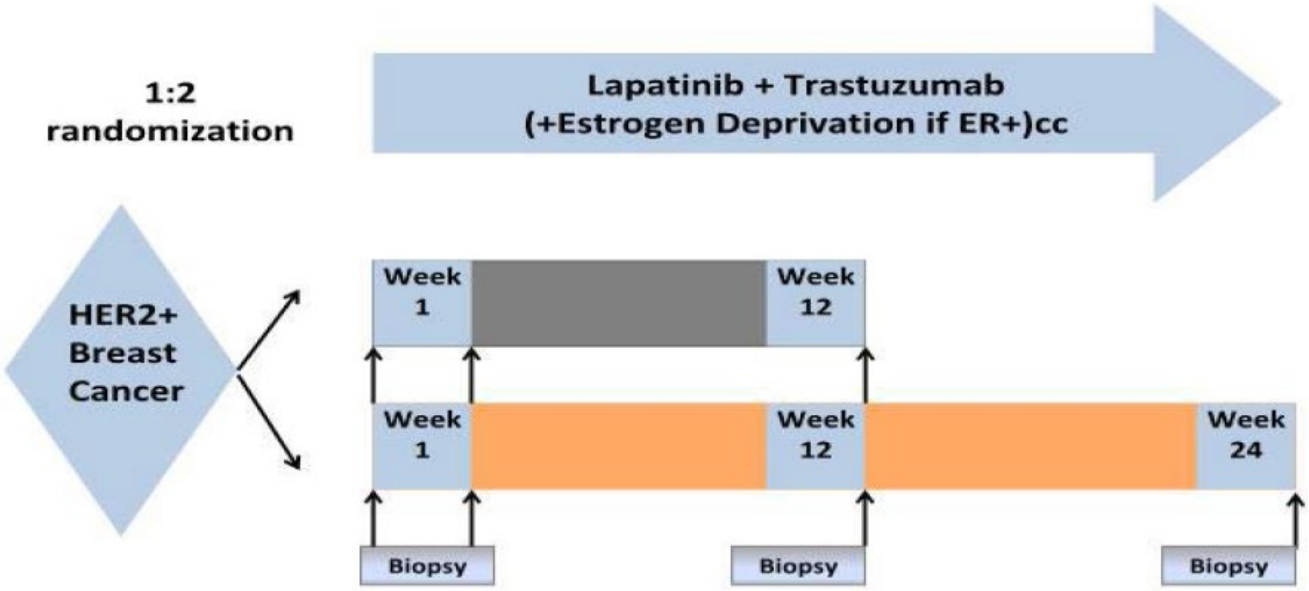
ER Status	pCR		ypT_{1a-b}		NR		Total No. of Patients
	No.	%	No.	%	No.	%	
Positive	8	21	13	33	18	46	39
Negative	9	36	1	4	15	60	25
Total	17	27	14	22	33	52	64

Abbreviations: ER, estrogen receptor; NR, nonpathologic response; pCR, pathologic complete response.

Rimawi M, JCO 2013

TBCR023 study

Neoadjuvant treatment

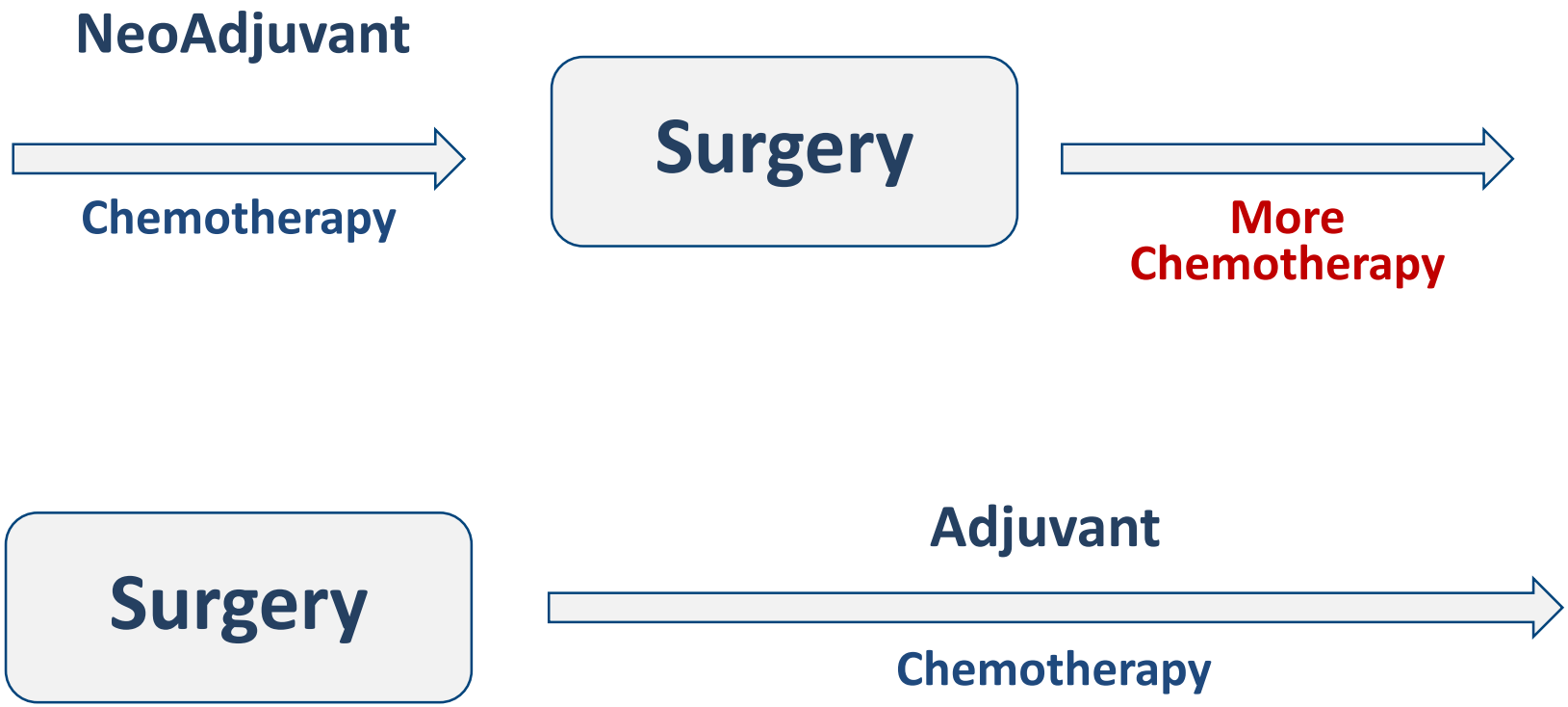


Hypothesis: a longer HER2/ER blockade would increase pCR rates

Path CR (ypT_{0-is})	12 weeks (n=33)	24 weeks (n=61)
Overall	4 (12%)	17 (28%)
ER-positive	2 (9%)	13 (33%)
ER-negative	2 (20%)	4 (18%)

Rimawi M, Clinical Cancer Research, 2019

Triple Negative BC-Adjuvant/Neo-adjuvant Setting

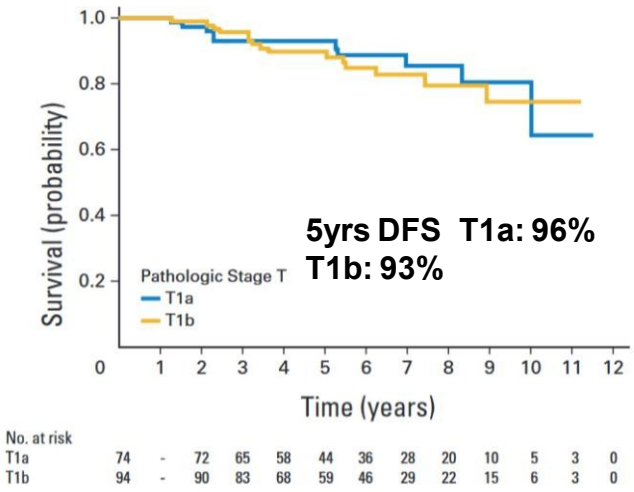


Adjuvant therapy in TNBC- Outline

- Small Tumor
- Addition of Taxanes
- High Dose Chemotherapy
- PARPi: narrowing target population to BRCA+
- Timing of chemotherapy
-

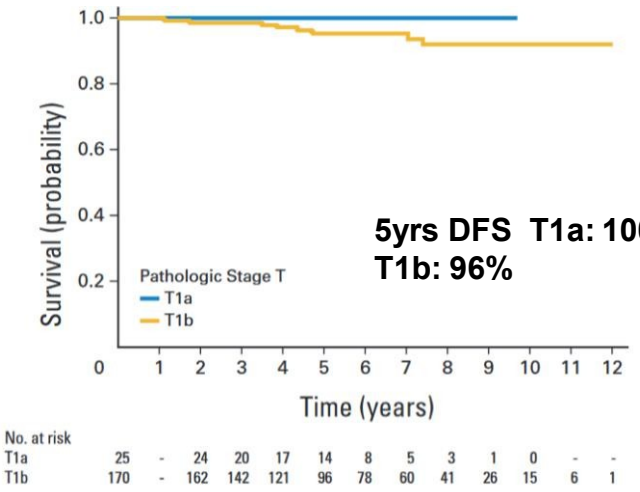
ADJUVANT CHEMOTHERAPY FOR PATIENTS WITH SMALL TNBC

No chemotherapy



5yrs DFS T1a: 96%
T1b: 93%

Chemotherapy



5yrs DFS T1a: 100%
T1b: 96%

Vaz-Luis I, *et al.,* J Clin Oncol 2014;32:2142–50.

Options for Stage I Disease

- Chemotherapy treatment options for low risk disease:
  - 1) simple regimen (AC, TC, CMF)
  - 2) sequential anthracycline/taxane

	Enthusiasm for Chemotherapy	Possible Regimens
Microinvasion only	Virtually none	---
T1a	Low to moderate	Simple
T1b	Moderate to high	Simple
T1c	High	Simple or selectively sequential approach

Adjuvant therapy in TNBC- Outline

- Small Tumor
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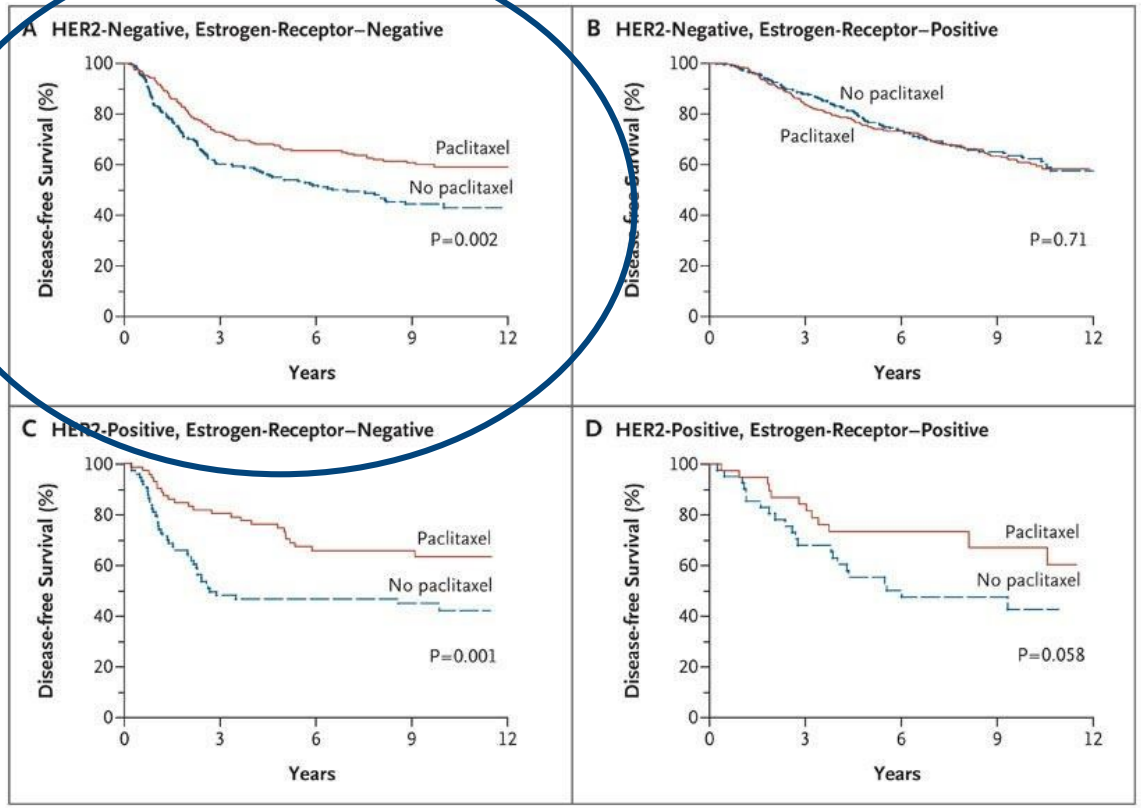
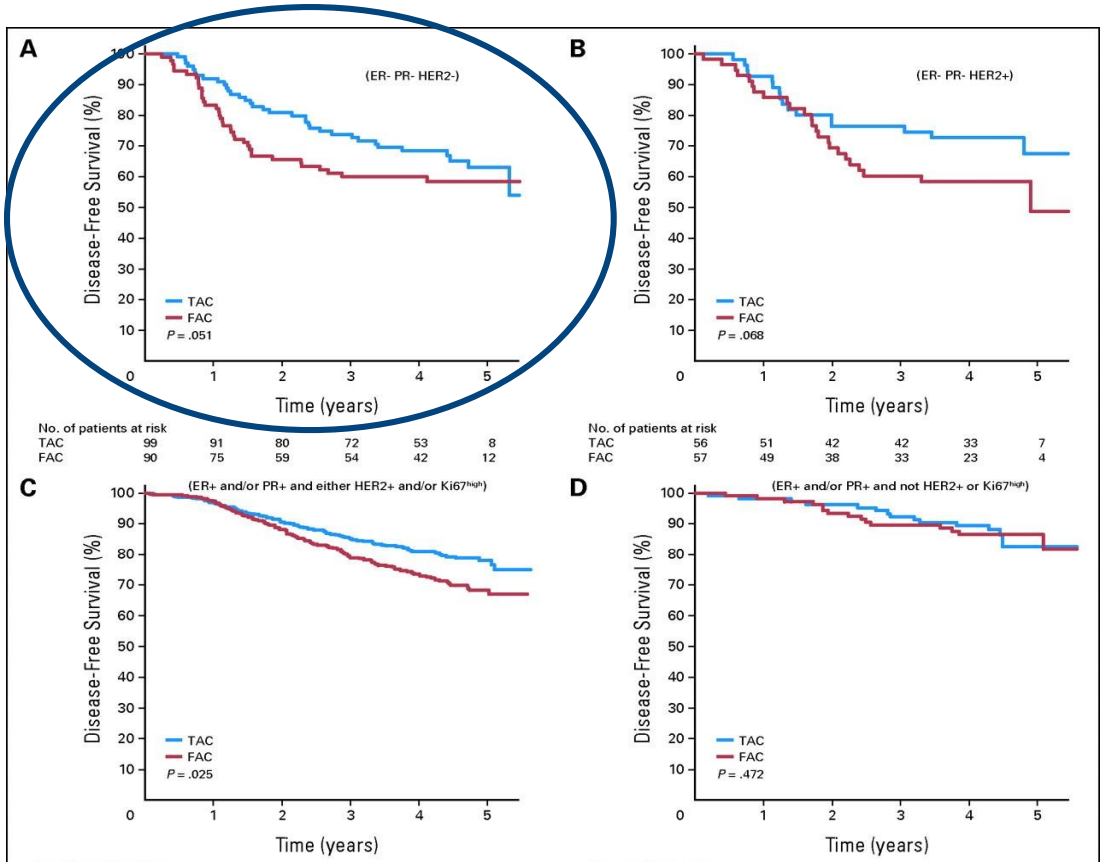
- Timing of chemotherapy
-

CALGB 9344: AC x 4 ± Paclitaxel x 4 Outcomes for Subtypes



Hayes D et al. N Engl J Med 2007;357:1496-1506

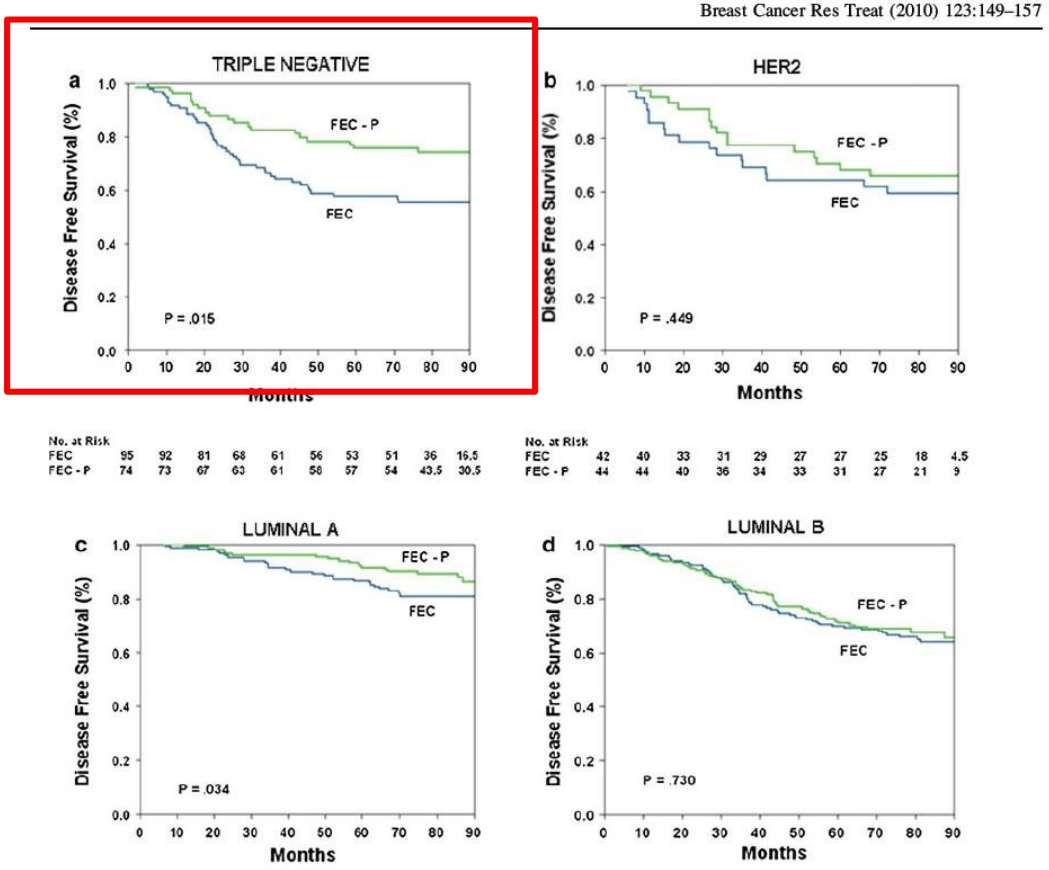
BCIRG 001: TAC vs FAC Outcome for Subtypes



Hugh J et al. JCO 2009;27:1168-1176

GEICAM 9906: FECvs FEC/P Outcomes by Subtypes

Breast Cancer Res Treat (2010) 123:149–157



Adjuvant therapy in TNBC- Outline

- Small Tumor
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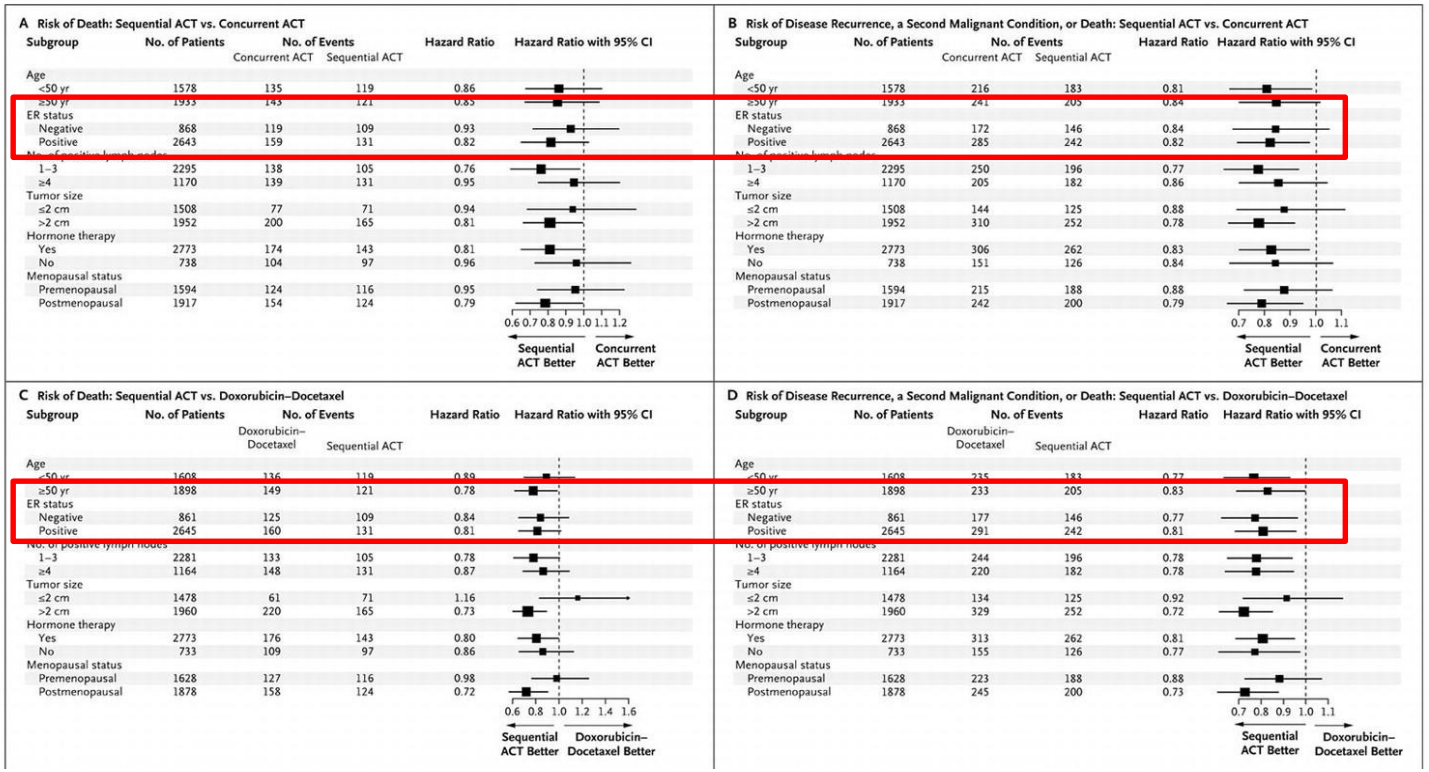
- PARPi: narrowing target population to BRCA+
- Timing of chemotherapy
-

NSABP B-30. AC_4-T_4 vs TAC_4 vs AT_4 TNBC subgroup

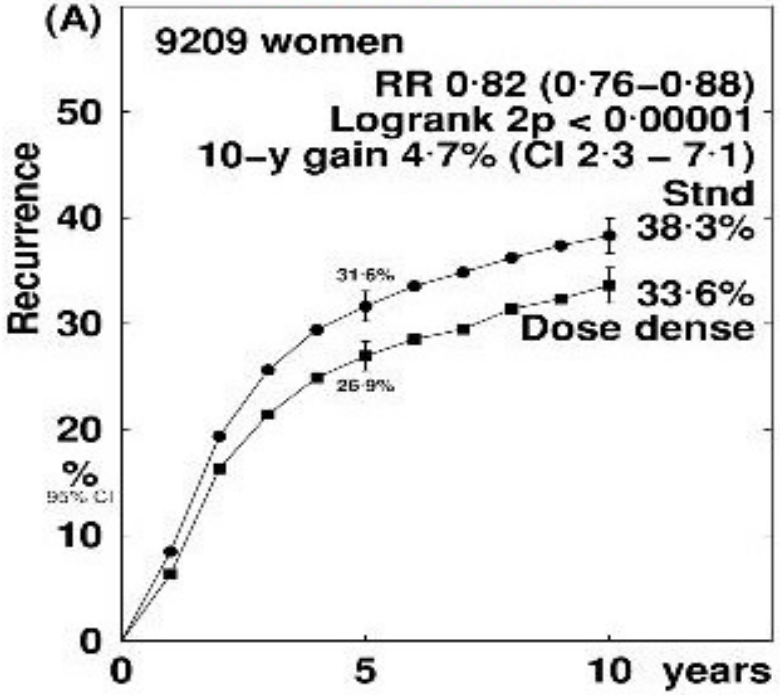
OS DFS



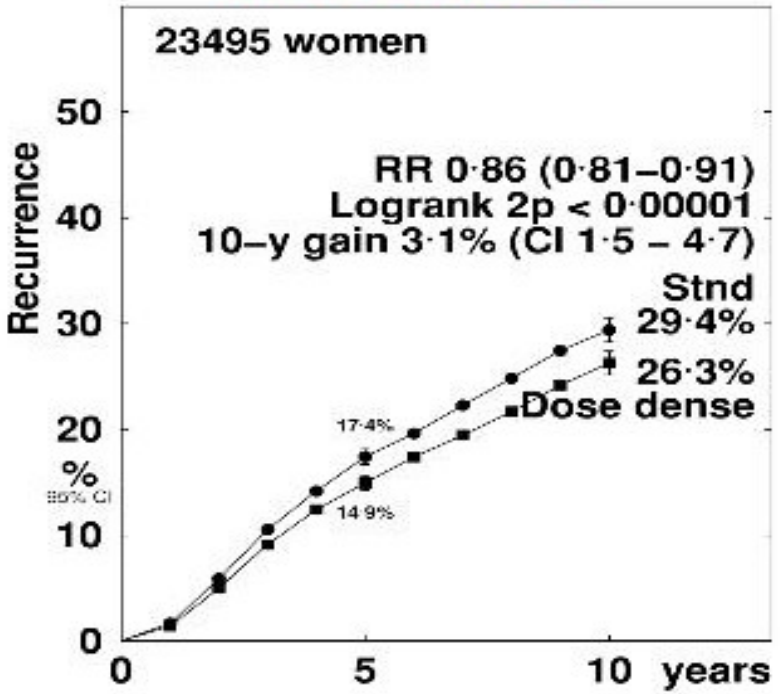
Swain SM et al. N Engl J Med 2010;362:2053-2065.

Pooled Analysis: recurrence by ER status

ER- Negative



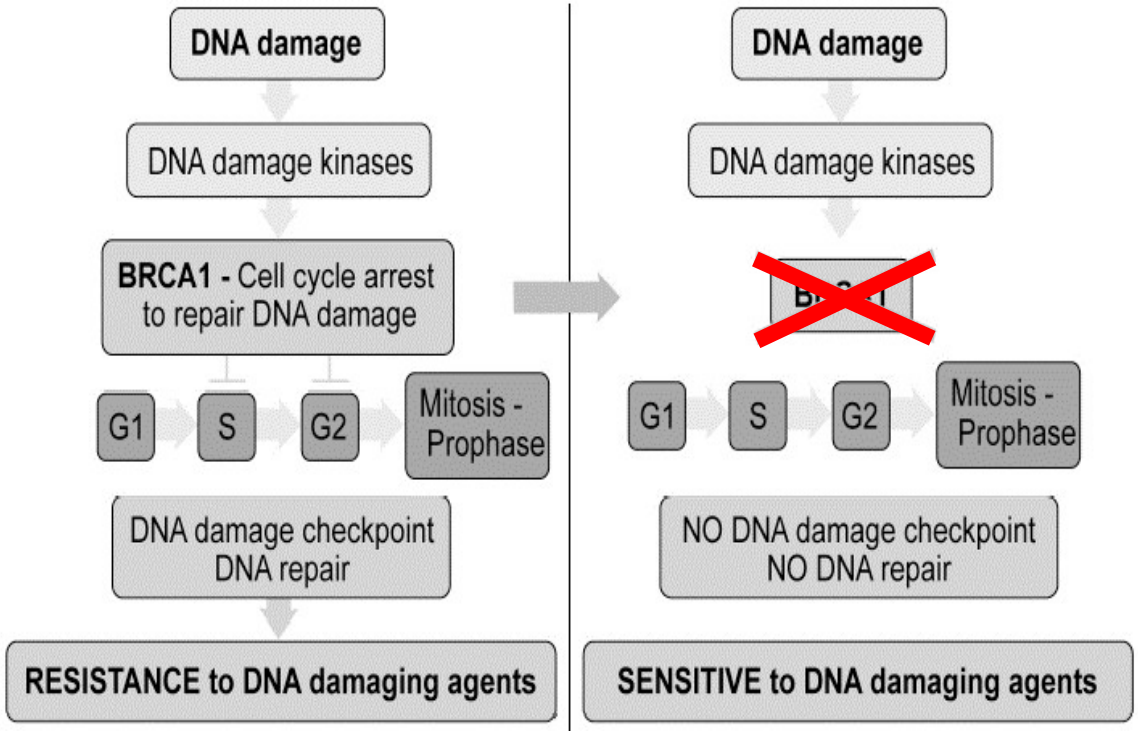
ER - Positive



Adjuvant therapy in TNBC- Outline

- Small Tumor
- Addition of Taxanes
- High Dose Chemotherapy
- PARPi: narrowing target population to BRCA+
- Timing of chemotherapy
-

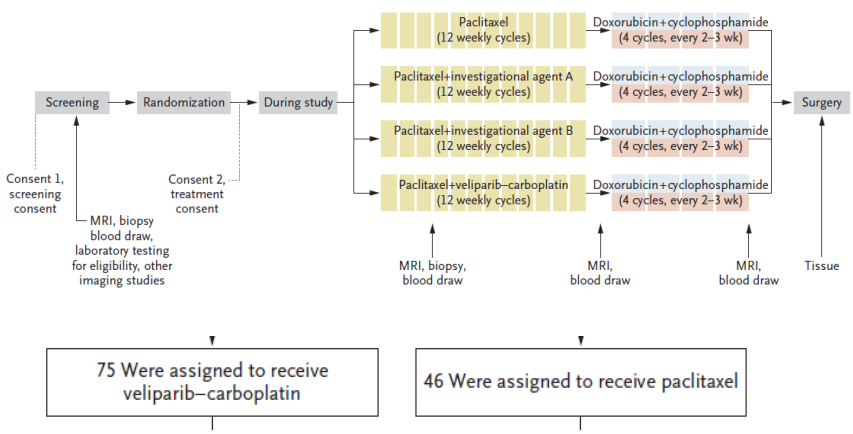
DRUG-SPECIFIC CHEMOTHERAPY FOR TNBC?

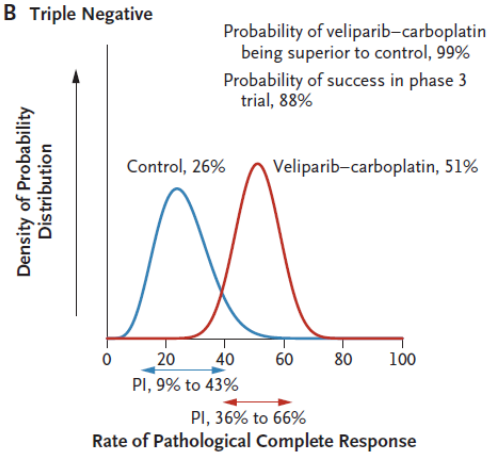


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

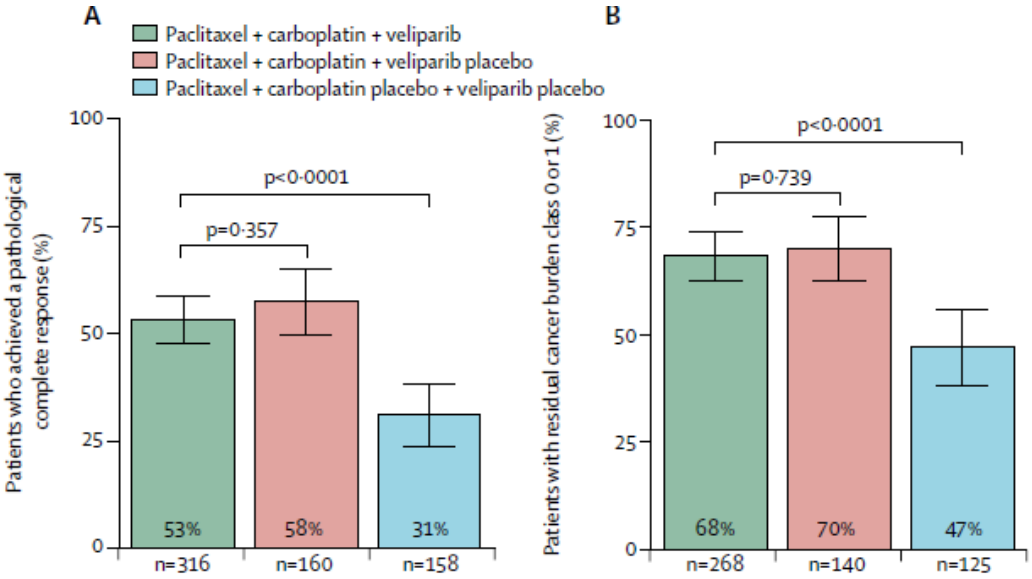
Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer





Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial

Sibylle Loibl, Joyce O'Shaughnessy, Michael Untch, William M Sikov, Hope S Rugo, Mark D McKee, Jens Huober, Mehra Golshan, Gunter von Minckwitz, David Maag, Danielle Sullivan, Norman Wolmark, Kristi McIntyre, Jose J Ponce Lorenzo, Otto Metzger Filho, Priya Rastogi, W Fraser Symmans, Xuan Liu, Charles E Geyer Jr



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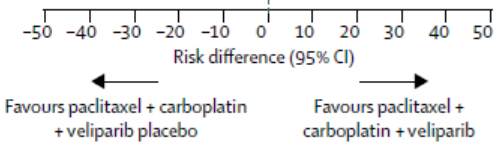
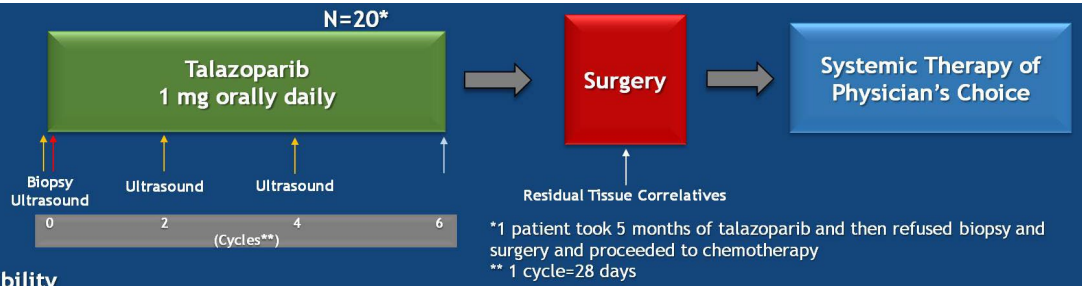
Lancet Oncol 2018; 19: 497–509

A

	n/N (%)		Risk difference (95% CI)
	Paclitaxel + carboplatin + veliparib placebo	Paclitaxel + carboplatin + veliparib	
All patients	92/160 (58%)	168/316 (53%)	−4·3 (−13·8 to 5·1)
BRCA1 or *BRCA2* mutation, or both	12/24 (50%)	26/46 (57%)	6·5 (−18·1 to 31·1)
No mutation in *BRCA1* or *BRCA2*	80/136 (59%)	142/270 (53%)	−6·2 (−16·4 to 4·0)
Lymph node stage N0	54/87 (62%)	106/174 (61%)	−1·2 (−13·7 to 11·4)
Lymph node stage N1–2	38/73 (52%)	62/142 (44%)	−8·4 (−22·5 to 5·7)
AC dose every 2 weeks	50/89 (56%)	98/176 (56%)	−0·5 (−13·2 to 12·2)
AC dose every 3 weeks	42/71 (59%)	70/140 (50%)	−9·2 (−23·3 to 5·0)



Neoadjuvant talazoparib for BRCA mut



*1 patient took 5 months of talazoparib and then refused biopsy and surgery and proceeded to chemotherapy
** 1 cycle=28 days

Eligibility

- Tumors > 1 cm
- Clinical Stage I-III
- Germline BRCA mutation
- No previous therapy for invasive breast cancer

Exclusion

- HER2 positive

Primary Objectives

- pCR (ypT0/is ypN0)
- RCB-0 + RCB-I

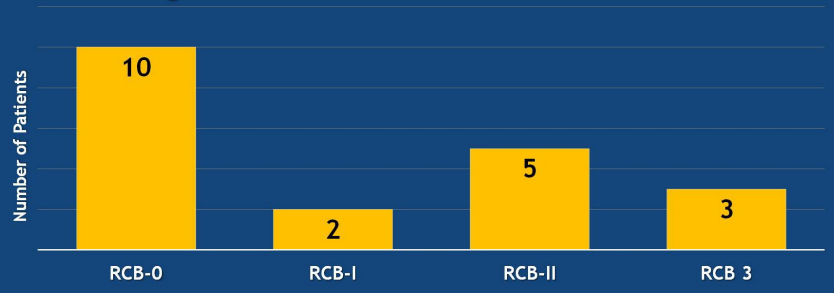
Secondary Objective

- Evaluate toxicity

Characteristics		Number of Patients
BRCA mutation	1	17
	2	3
Tissue Receptor Subtype	TNBC (<10% ER or PR)	15
	Hormone Receptor positive (≥10%)	5

Neoadjuvant talazoparib for BRCA mut

Pathologic Results

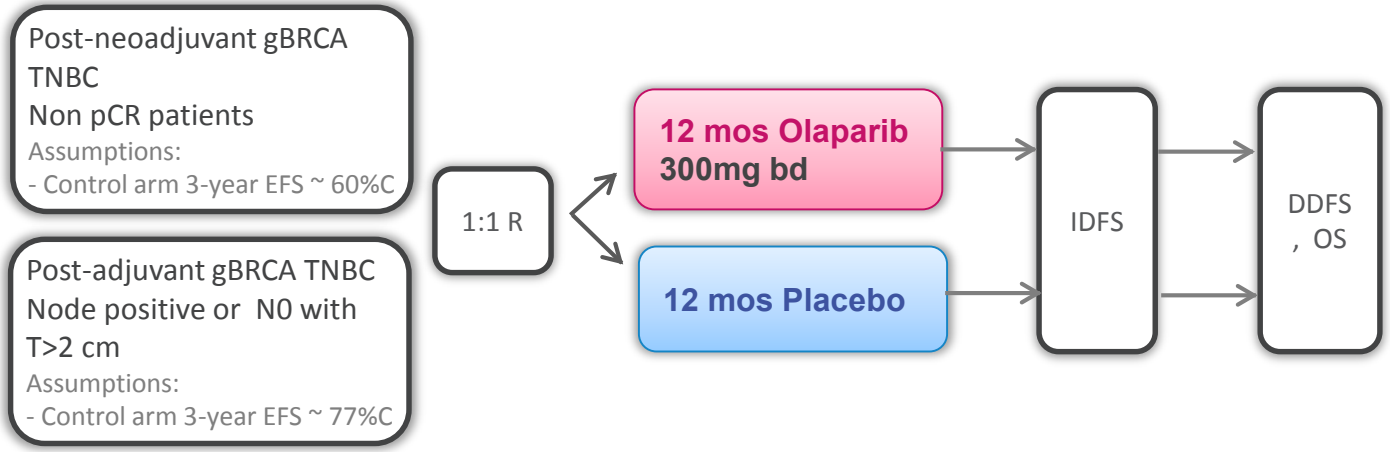


pCR (RCB-0): 10/19 = 53%, 95% CI = 32%, 73%

RCB-0+I: 12/19 = 63%, 95% CI = 41%, 81%

Variable	RCB-0	RCB-I	RCB-II	RCB-III
BRCA1 (n=16)	8	1	5	2
BRCA2 (n=3)	2	1	0	0
TNBC (n=14)	7	1	4	2
HR+ (n=5)	3	1	1	0
Stage 1 (n=5)	4	0	1	0
Stage 2 (n=12)	5	2	4	1
Stage 3 (n=2)	1	0	0	1

OlympiA



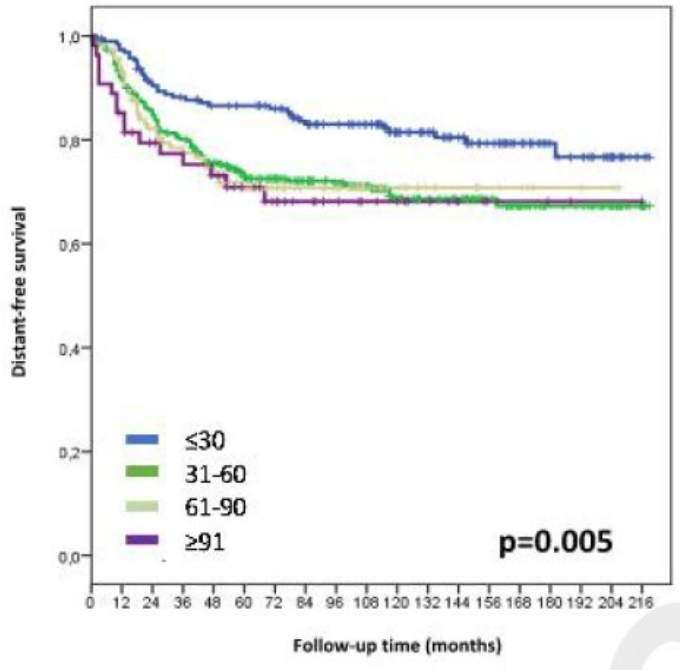
N=1,320

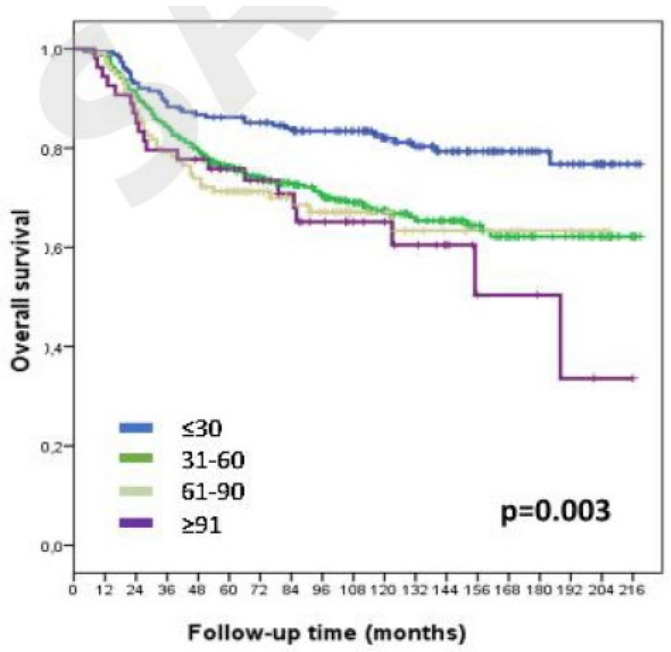
- **Study to start recruiting patients with TNBC; plan to add ER/PR+ patients once data available from PK/PD interactions (expected Mid 2014)**
- **Primary endpoint: IDFS (invasive disease-free survival; STEEP approach)**
  - **HR=0.7 (CV=0.81), 90% power, 5% significance level, approx 330 events required**
    - **Assumes consistent treatment effect (HR=0.7) across patient groups**
    - **N=1320 (25% maturity), assuming 4 years recruitment, IDFS analysis estimated approx. 5.5–6 years from FSI**

Adjuvant therapy in TNBC- Outline

- Small Tumor
- Addition of Taxanes
- High Dose Chemotherapy
- PARPi: narrowing target population to BRCA+
- Timing of chemotherapy
-

Impact of the delayed initiation of adjuvant CT in TNBC





Morante Z, et al. SABCS 2018

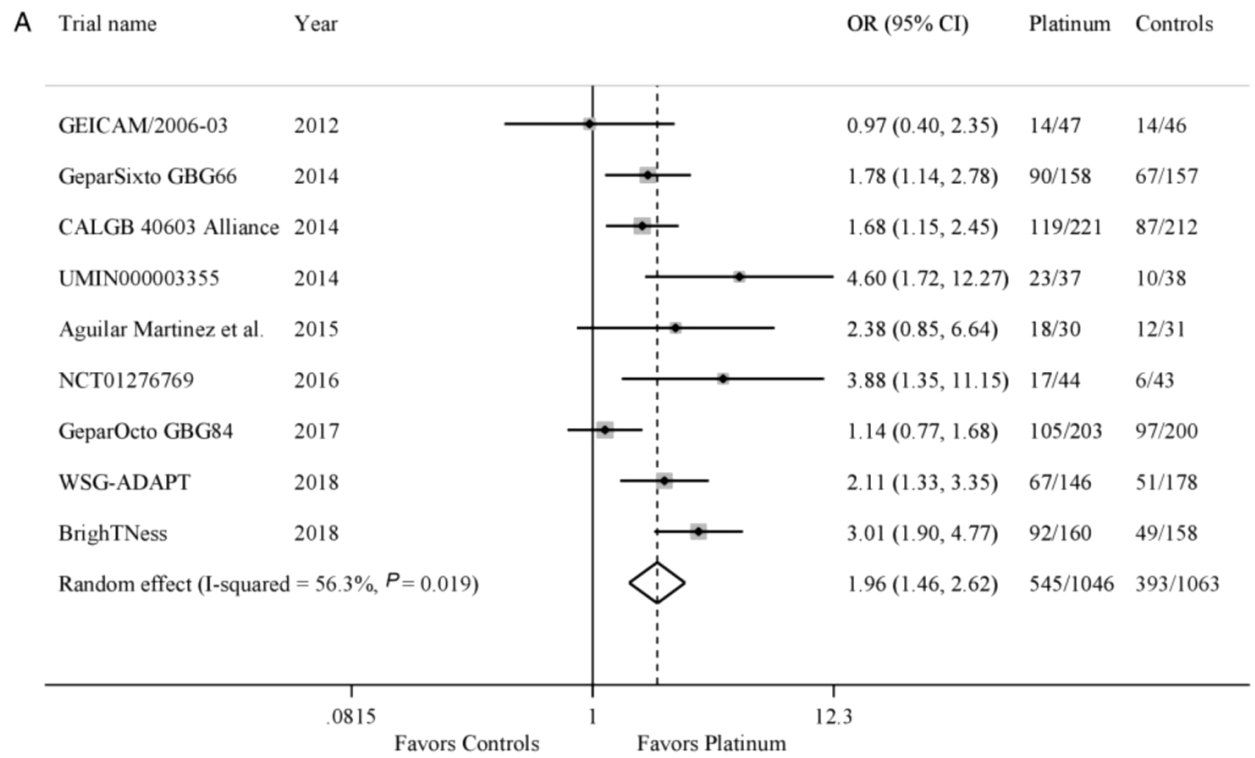
Adjuvant therapy in TN

- Low thresholds for adjuvant chemotherapy treatment for TNBC (~ 0.5 cm, node- negative)
- Standard chemotherapy agents are effective adjuvant therapy
- Enhancements to adjuvant chemotherapy (addition of taxanes, sequential therapy, dose dense schedule) should be considered
- Alternative regimens
  - Preferred regimen without anthracyclines: TC
  - Preferred regimen without taxanes: AC or CMF
- PARP inhibitors hold great promises for BRCA-mut patients
- Timing of adjuvant treatment matters!

(Neo)Adjuvant therapy in TNBC- Outline

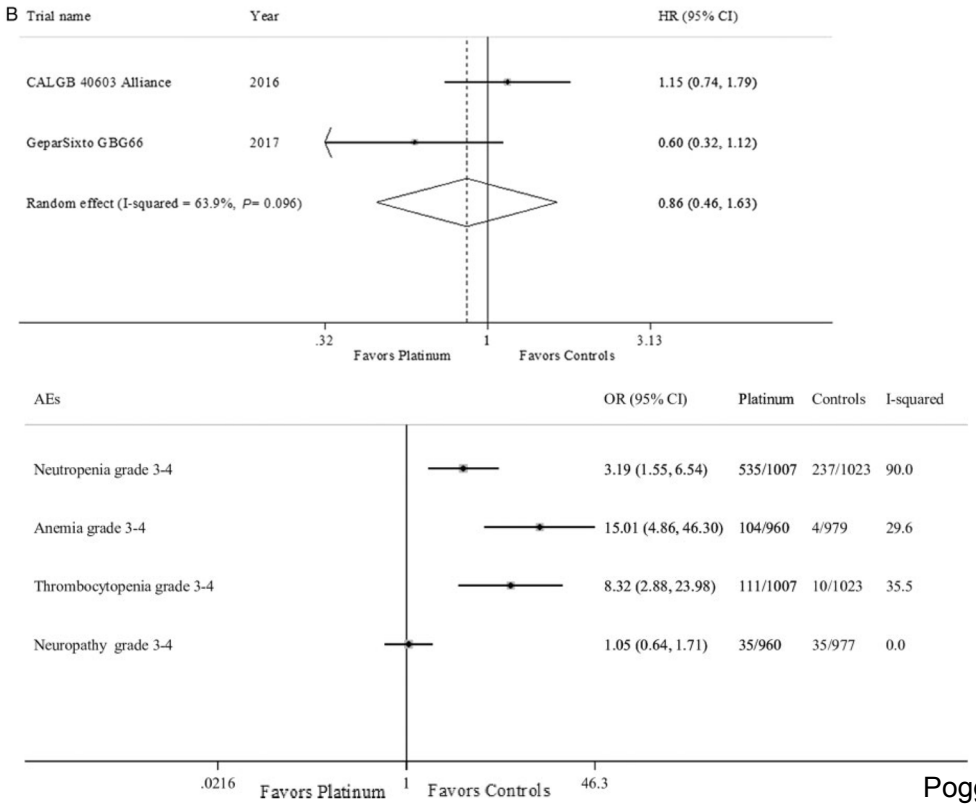
- Addition of carboplatin
- Addition of Bevacizumab
- Addition of Nab-paclitaxel
- Post-neoadjuvant setting

Adding platinum to neoadj CT increases pCR



Poggio F. et al. Ann Oncol 2018

Survival benefit is uncertain and adding platinum is more toxic



Hazard-ratios for overall survival

Safety profile

Poggio F. et al. Ann Oncol 2018

QUESITO GRADE n.5:
Platino nella terapia neoadiuvante per TNBC

QUESITO CLINICO N. 14 (RIFERIRSI AL quesito GRADE n. 5) (Figura n. 9)

Nelle donne con carcinoma mammario TRIPLO NEGATIVO (recettori ormonali negativi ed HER2-negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, è raccomandabile l'aggiunta del platino ad uno schema standard con antracicline e taxani rispetto alla sola chemioterapia a base di antracicline e taxani?

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle donne con carcinoma mammario triplo negativo (recettori ormonali negativi ed HER2 negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, l'aggiunta del platino ad uno schema standard con antracicline e taxani può essere preso in considerazione.	**Positiva debole**

Leggere capitolo 14- Raccomandazioni prodotte secondo metodologia GRADE

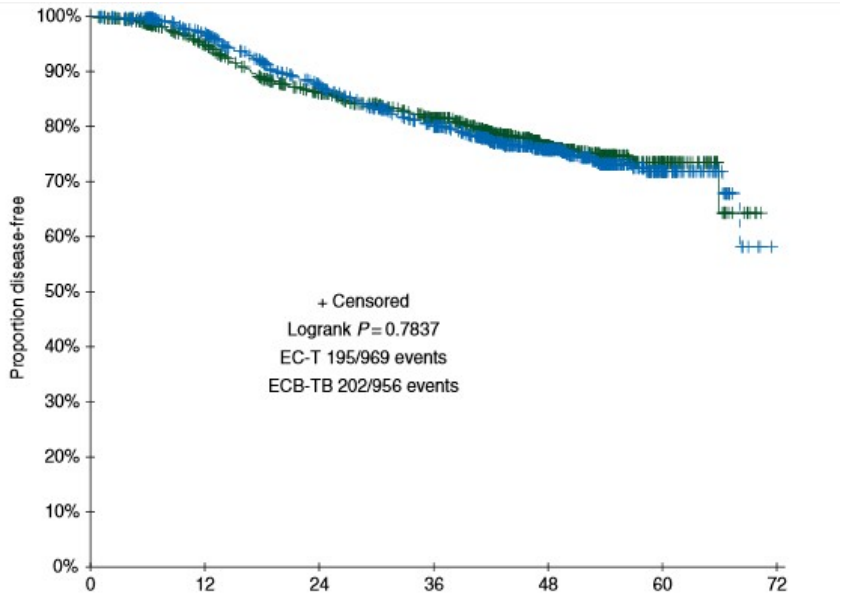
- Framework Evidence to Decision (EtD) utilizzato per supportare lo sviluppo della raccomandazione (allegato).
- Importanza degli effetti di beneficio: «MODERATE»
- Importanza degli effetti di danno: «SMALL»
- Qualità delle evidenze: «MODERATE»
- Valutazione rapporto beneficio/danno: «Incerto: favorevole» (10/11)

MV Dieci, AIOM 2018

(Neo)Adjuvant therapy in TNBC- Outline

- Addition of carboplatin
- Addition of Bevacizumab
- Addition of Nab-paclitaxel
- Post-neoadjuvant setting

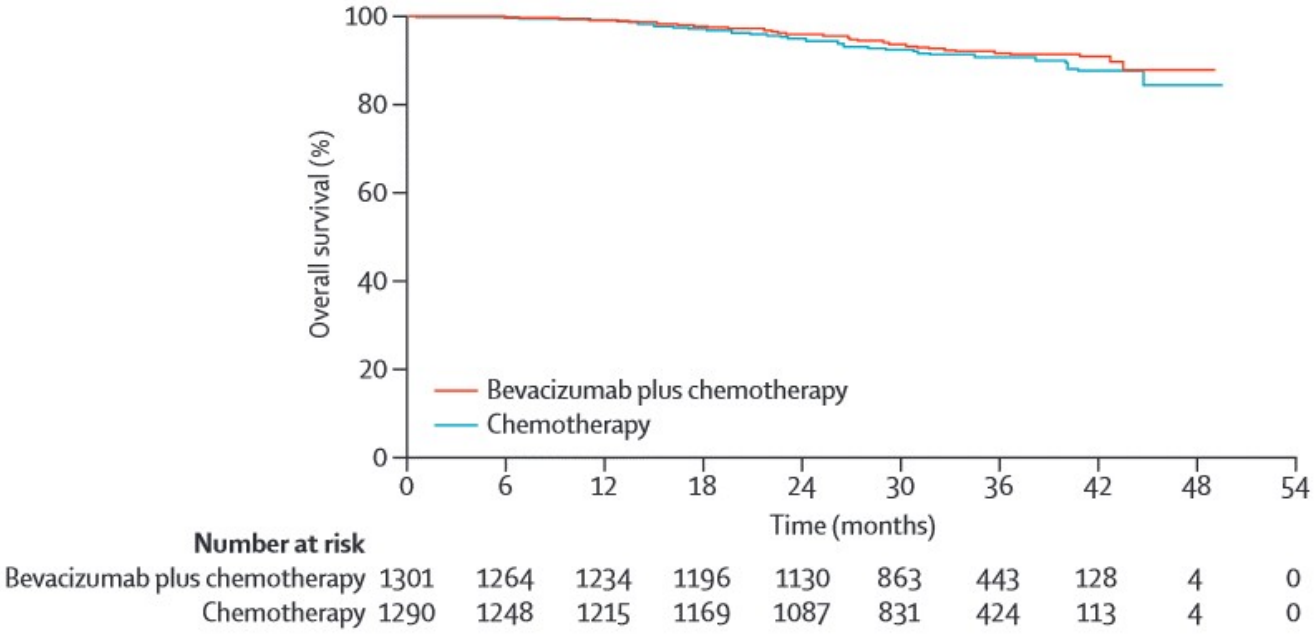
GEPARQUINTO: NEOADJUVANT BEVACIZUMAB AND SURVIVAL



Receptor status			.610
ER and/or PgR positive	1262	1.10 (.821, 1.47)	.527
ER and PgR negative	663	.990 (.757, 1.29)	.941

von Minckwitz G, *et al.,* Ann Oncol 2014;25:2363-72.

BEATRICE PHASE III ADJUVANT TRIAL



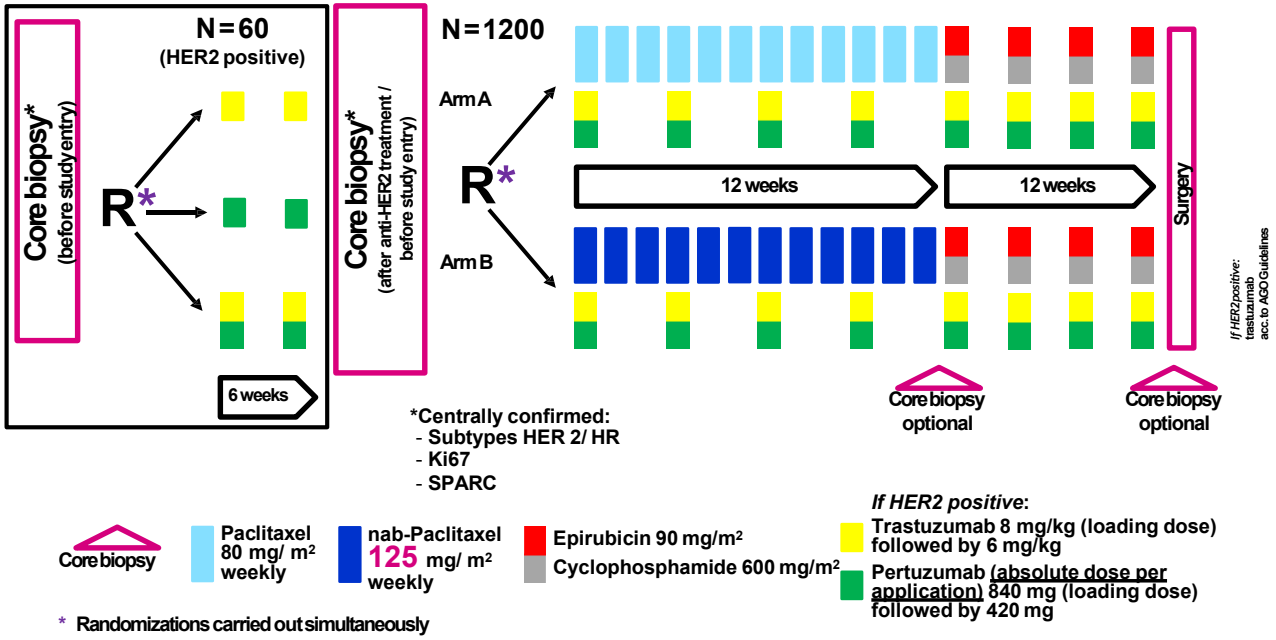
Number at risk										
Bevacizumab plus chemotherapy	1301	1264	1234	1196	1130	863	443	128	4	0
Chemotherapy	1290	1248	1215	1169	1087	831	424	113	4	0

Reprinted from Cameron D, Lancet 2013;14:933–42.

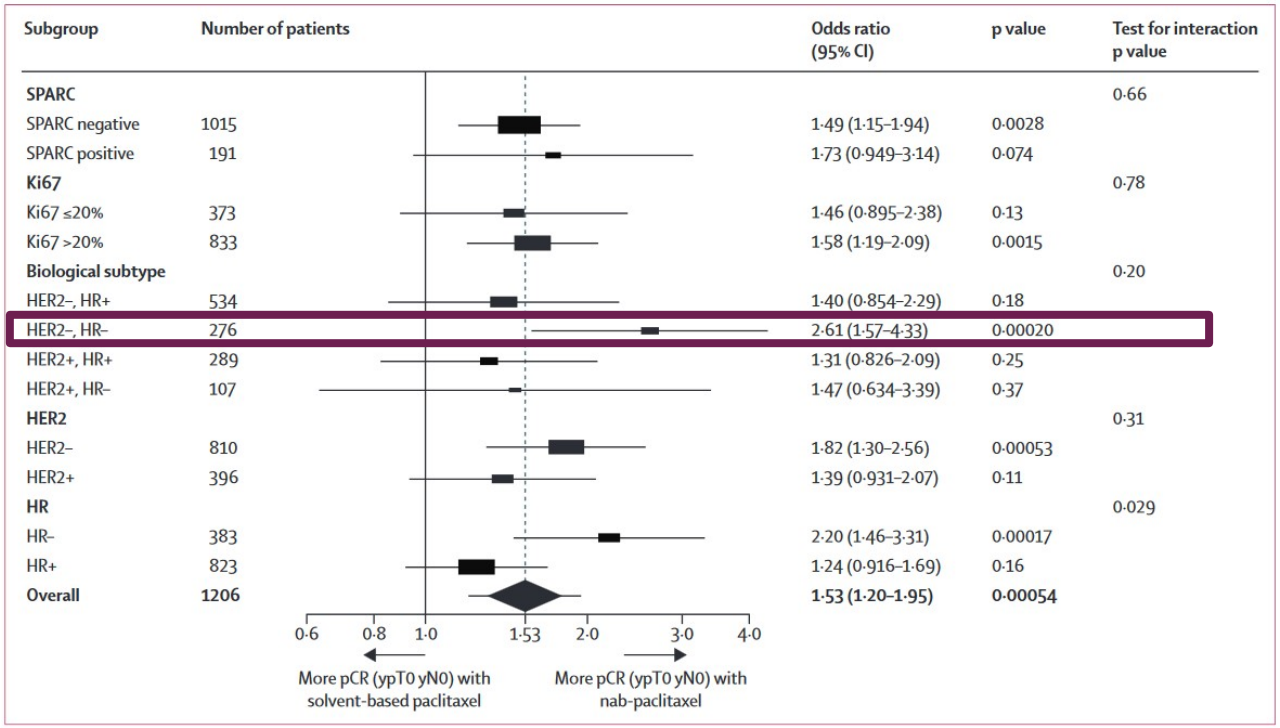
(Neo)Adjuvant therapy in TNBC- Outline

- Addition of carboplatin
- Addition of Bevacizumab
- Addition of Nab-paclitaxel
- Post-neoadjuvant setting

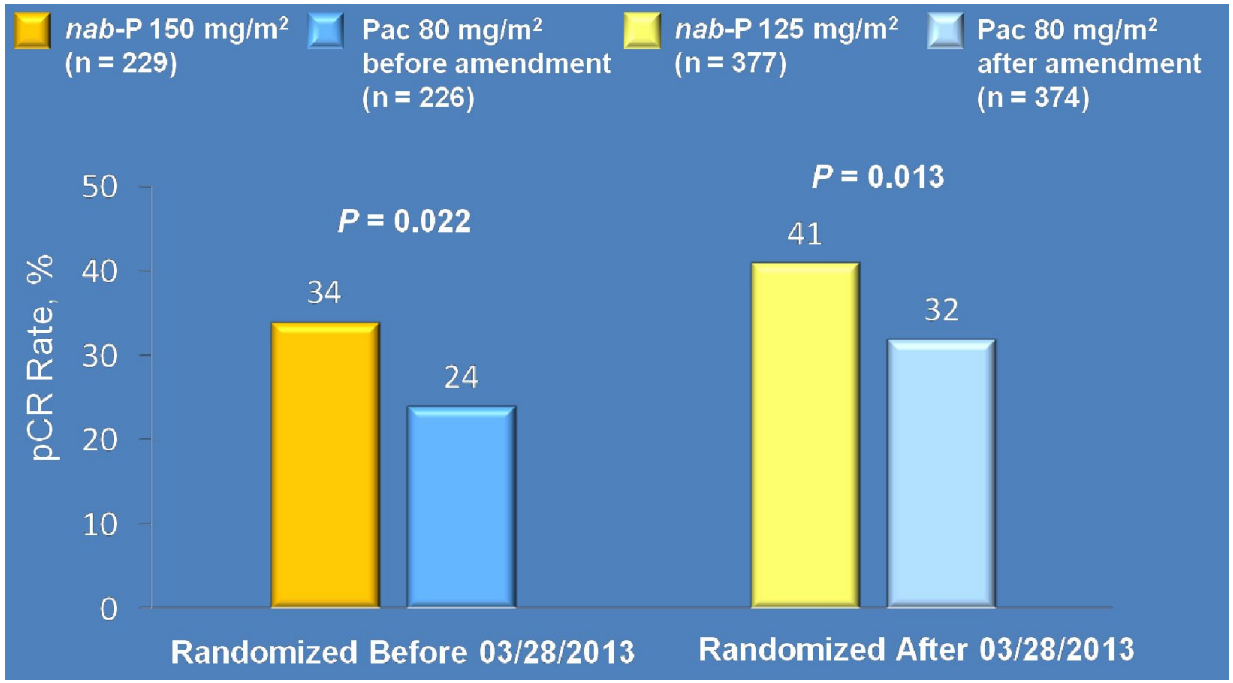
Neoadjuvant nabpaclitaxel for triple-negative breast cancer Geparsepto



GEPAR7: SUBGROUP ANALYSIS



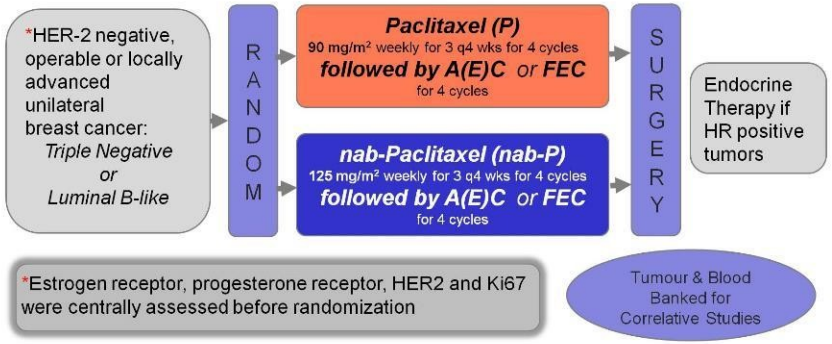
Neoadjuvant nabpaclitaxel for triple-negative breast cancer Geparsepto



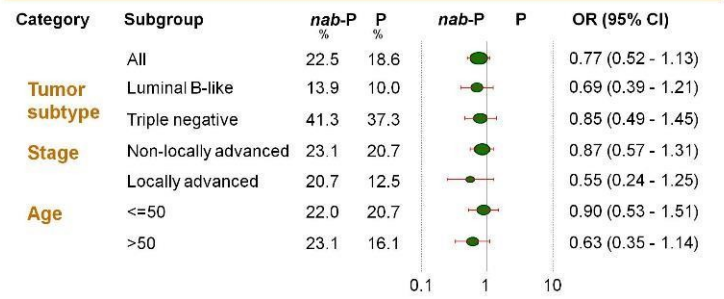
Untch M, et al. Lancet Oncol. 2016. Epub ahead of print.

PHASE III RANDOMISED ETNA TRIAL

Scheme of the Phase III randomized ETNA trial



Subgroup Analysis: pCR rate

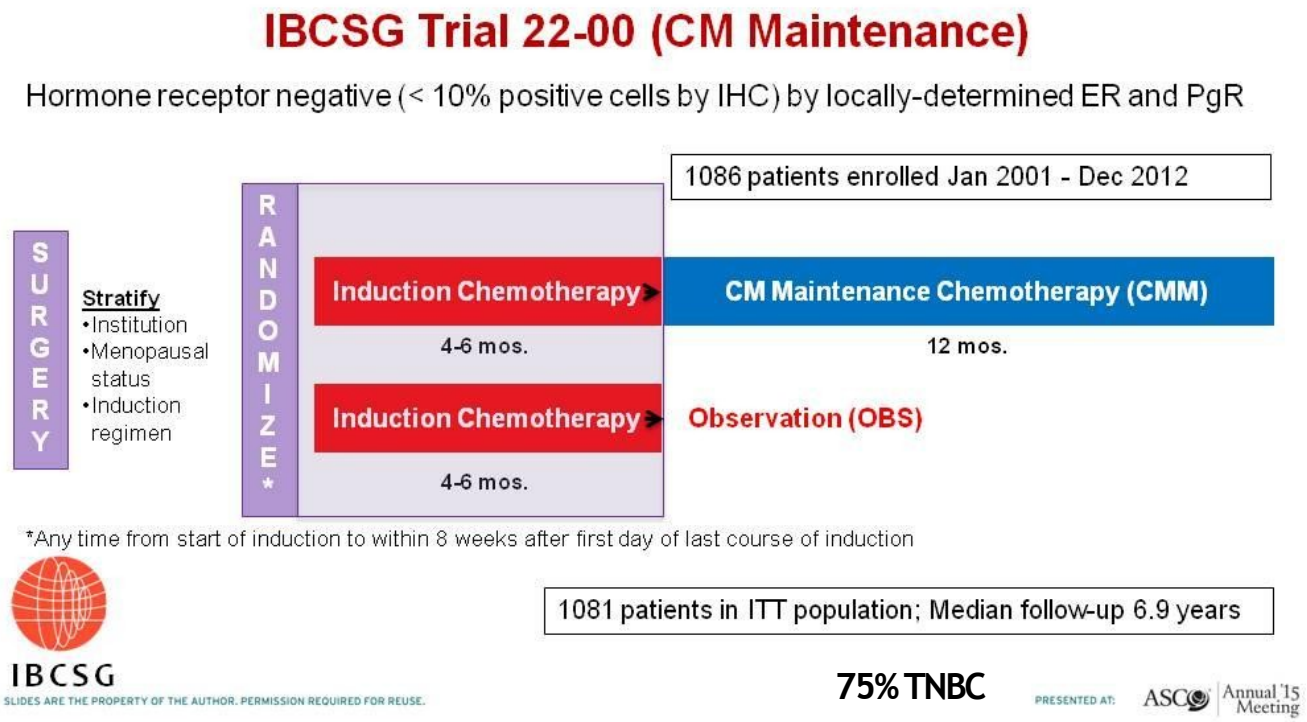


Gianni L, at 2016 ASCO Annual Meeting.

(Neo)Adjuvant therapy in TNBC- Outline

- Addition of carboplatin
- Addition of Bevacizumab
- Addition of Nab-paclitaxel
- Post-neoadjuvant setting

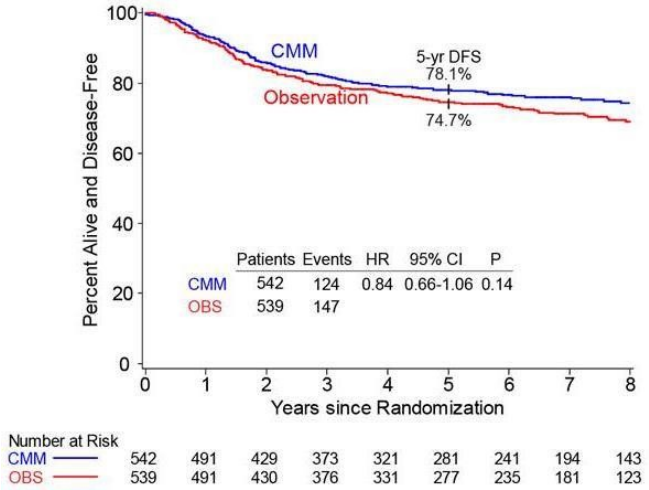
CMM MAINTENANCE AFTER ADJUVANT CHEMOTHERAPY



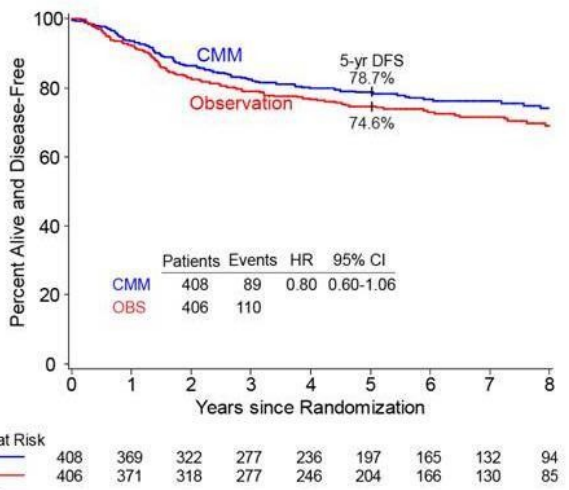
Colleoni M, at 2015 ASCO Annual Meeting.

CMM MAINTENANCE AFTER ADJUVANT CHEMOTHERAPY

All patients

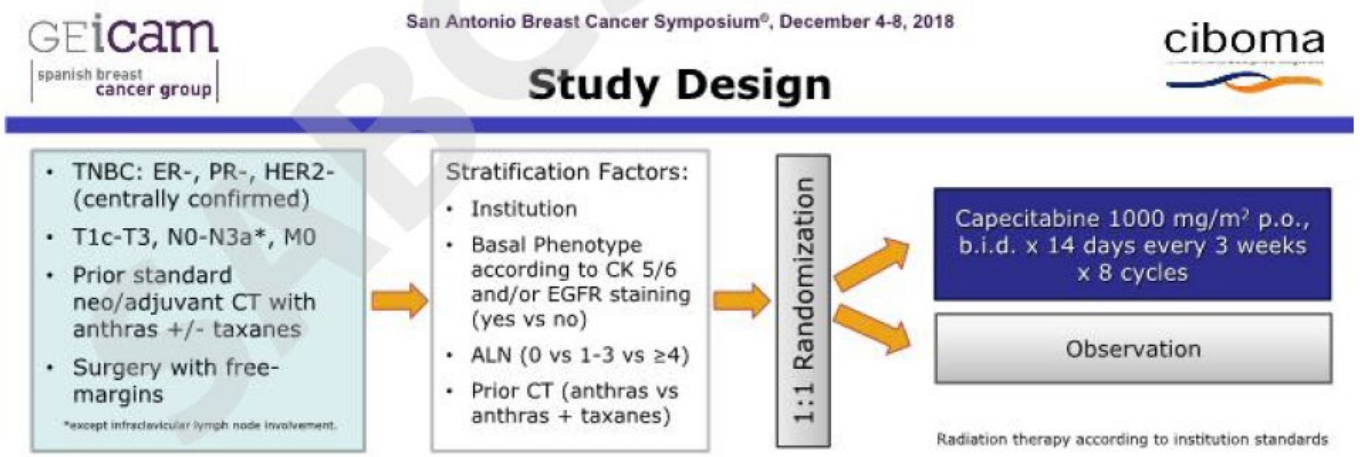


TN patients



Colleoni M, at 2015 ASCO Annual Meeting

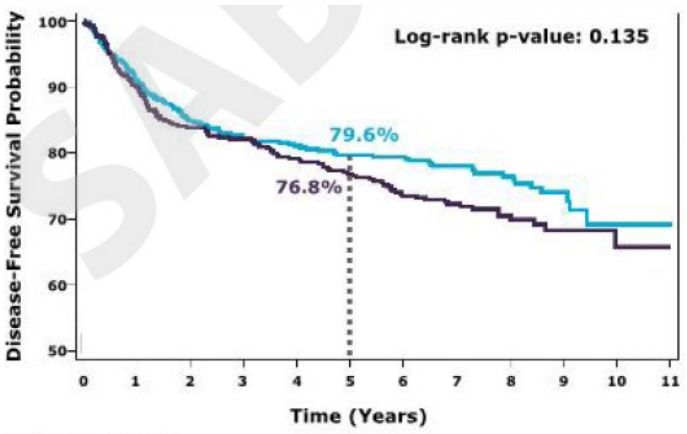
GEICAM/CIBOMA randomized phase III trial

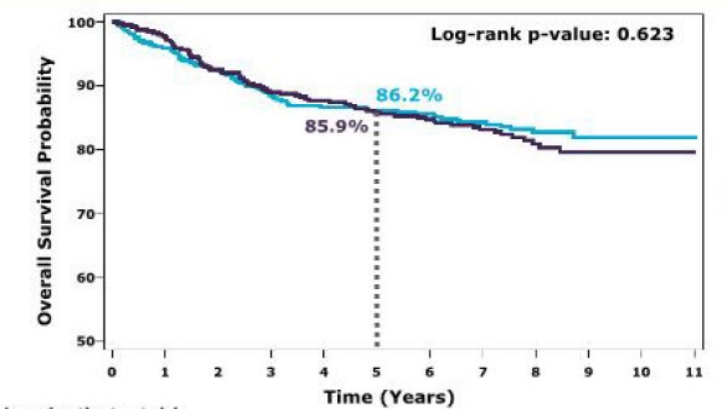


- 6 cy. of standard CT mandatory except for N0 tumors (4 cy. of AC admitted).
- Primary endpoint: Disease-Free Survival (DFS).
- Secondary endpoints: Overall Survival (OS), subgroup analyses, safety, biomarkers.

M. Martin, SABCS 2018

GEICAM/CIBOMA randomized phase III trial: DFS and OS in ITT population





Median follow-up: 7.34 years

Group	Events
Capecitabine	105
Observation	120
HR: 0.82 (95% CI: 0.63, 1.06, p=0.136)	
Adjusted HR*: 0.79 (95% CI: 0.61, 1.03, p=0.082)	

*Adjusted HR for stratification variables: Spain vs. LA, previous neo/adjuvant treatment (anthracyclines vs. anthracyclines and taxanes), number of involved nodes (0 vs. 1-3 vs. ≥4) and TN phenotype by IHC (basal vs. non-basal).

Median follow-up: 7.34 years

Group	Events
Capecitabine	71
Observation	73
HR: 0.92 (95% CI: 0.66, 1.28)	

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RCTs of Capecitabine in EBC

Study	Patients	RFS/DFS in TN	OS in TN
FinXX	1500 (202 TN)	**HR 0.53 (95%CI 0.31-0.92)**	**HR 0.55 (95%CI 0.31-0.96)**
GEICAM/2003-10	1384 N+(166 TN)	HR 1.19 (95%CI 0.70-2.04)	NR
GAIN	2994 N+ (421 TN)	HR 0.971 (95%CI 0.682-1.38)	NR
NCT00089479	2611 (780 TN)	HR 0.81 (95%CI 0.57-1.15)	**HR 0.62 (95%CI 0.41-0.94)**
Create-X	910 (286 TN) (post-neoadj)	**HR 0.58 (95%CI 0.39-0.87)**	**HR 0.52 (95%CI 0.30-0.90)**

Joensuu H et al, J Clin Oncol 2012 & JAMA Oncol 2018; Martin M et al, J Clin Oncol 2015; Mobus V et al, Ann Oncol 2017; O'Shaughnessy CCR 2015; NEJM 2017

(Neo)Adjuvant therapy in TNBC

Chemotherapy is the mainstay of treatment:

- Anthracycline+taxanes: first choice in the (neo)adjuvant setting
- BRCA-mut (or BRCAwt with BRCAness features?): chance for tailored- chemotherapy with platinum salts
- No role for bevacizumab-encouraging data for nab-paclitaxel
- If no pCR post neoadjuvant therapy may be a feasible and effective option