Optimal approach in locally advanced disease: ESO-ESMO ABC Guidelines

Damir Vrbanec
Juraj Dobrila University of Pula
Croatia

Annals of Oncology 29: 1634–1657, 2018
doi:10.1093/annonc/mdy192
Published online 19 July 2018

SPECIAL ARTICLE

4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†

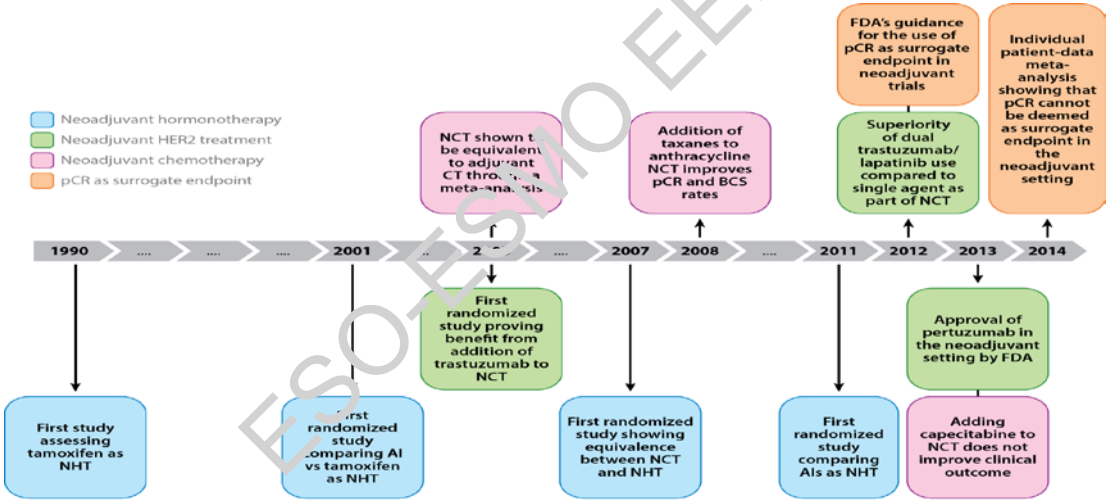
F. Cardoso[1*], E. Senkus[2], A. Costa[3], E. Papadopoulos[4], M. Aapro[5], F. André[6], N. Harbeck[7], B. Aguilar Lopez[8], C. H. Barrios[9], J. Bergh[10], L. Biganzoli[11], C. B. Boers-Doets[12], M. J. Cardoso[13], L. A. Carey[14], J. Cortés[15], G. Curigliano[16], V. Diéras[17], N. S. El Saghir[18], A. Eniu[19], L. Fallowfield[20], P. A. Francis[21], K. Gelmon[22], S. R. D. Johnston[23], B. Kaufman[24], S. Koppikar[25], I. E. Krop[26], M. Mayer[27], G. Nakigudde[28], B. V. Offersen[29], S. Ohno[30], O. Pagani[31], S. Paluch-Shimon[32], F. Penault-Llorca[33], A. Prat[34], H. S. Rugo[35], G. W. Sledge[36], D. Spence[37], C. Thomssen[38], D. A. Vorobiof[39], B. Xu[40], L. Norton[41] & E. P. Winer[42]

Section XI: LABC

Guideline statement	LoE/GoR	Consensus
Systemic therapy (not surgery or RT) should be the initial treatment.	III/A	100%

Neoadjuvant treatment for breast cancer :

- The concept of neoadjuvant chemotherapy for breast cancer was first evaluated more than 30 years ago for the treatment of locally advanced and inoperable breast cancer
- Neoadjuvant chemotherapy /NACT/, also called primary sistemic therapy, is a treatment option given after diagnosis, but before surgery for non-metastatic cancer



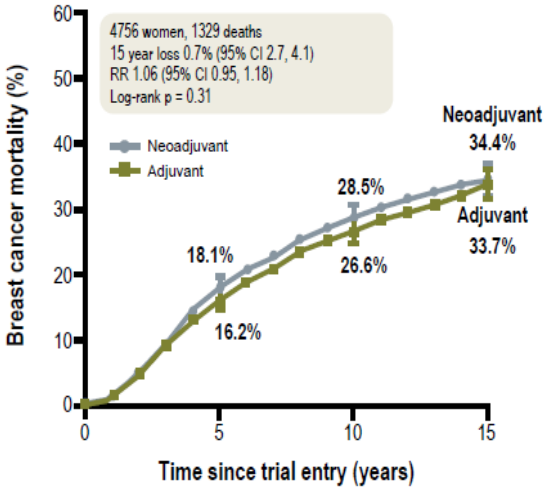
Zardavas D, Piccart M. 2015. Annu. Rev. Med. 66:31–48

Advantages of NAT :

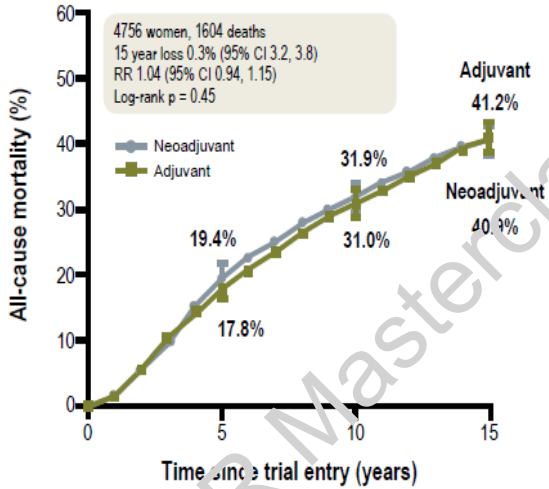
- increase opportunity for BCS and less radical axillary dissection
- avoiding the risk associated with surgery, improved cosmetic outcomes and reduced postoperative complications such as lymph edema
- permits an early evaluation of clinical efficacy of systemic therapy
- the surrogate endpoint, the presence or absence of residual invasive cancer after neoadjuvant therapy is a strong prognostic factor for risk of recurrence/especially in triple-negative and HER-2 positive breast cancer
- allows more time for genetic and other testing(surgical options)
- enables a second opportunity in patients with no pCR
- trials evaluating neoadjuvant therapies require smaller numbers of patients with inherent lower coast compared with larger adjuvant studies – supports faster regulatory approval of new drugs

Meta-analysis of neoadjuvant or adjuvant chemotherapy only

Breast cancer mortality



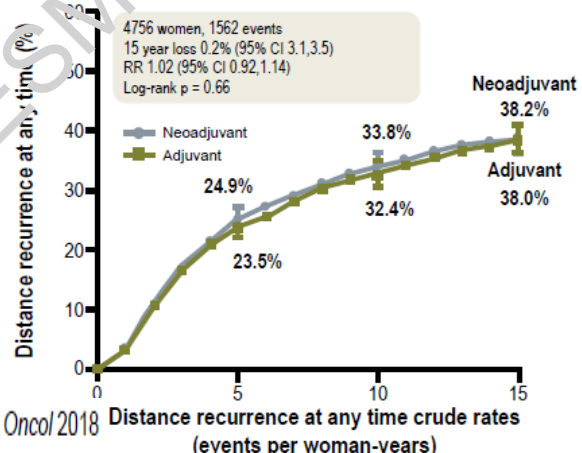
All-cause mortality



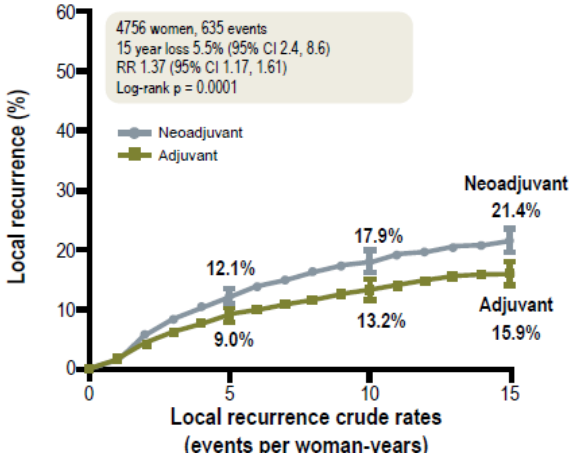
* All breast cancer subtypes included in the analysis; it was not an HER2-positive specific

Meta-analysis of neoadjuvant or adjuvant chemotherapy only

Distant recurrence



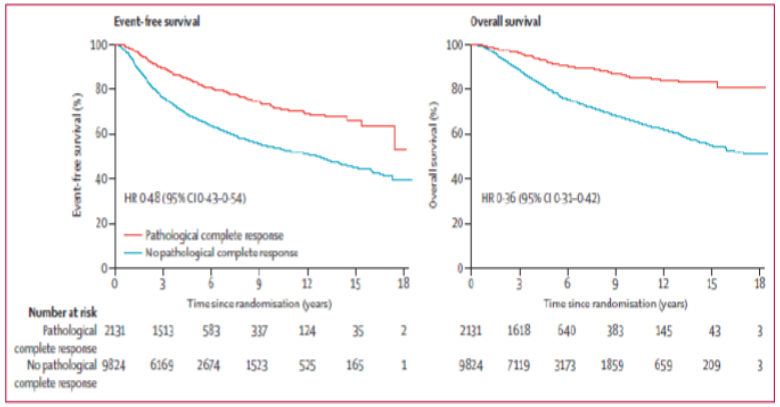
Local recurrence



Early Breast Cancer Trialists' Collaborative Group (EBCTCG); *Lancet Oncol* 2018

pCR and long term clinical benefit : the CTNeoBC pooled analysis

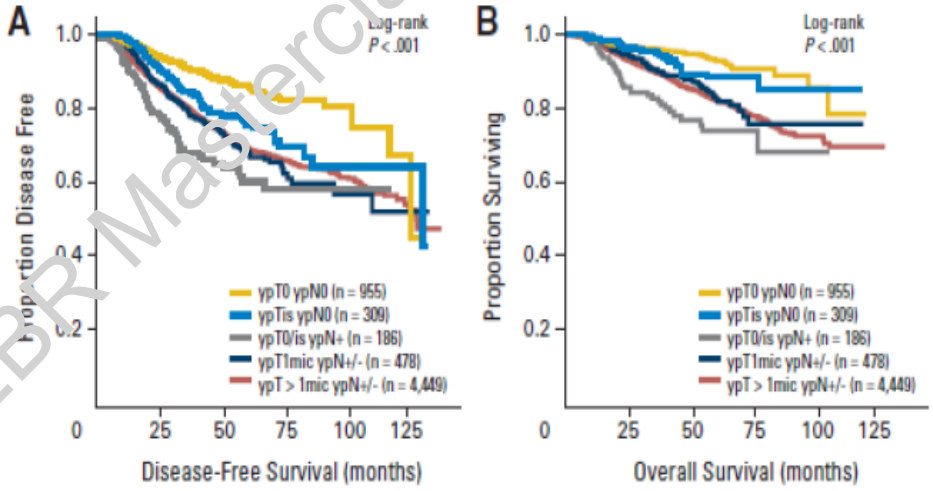
12 international clinical trials, N= 11,955 patients
Anthracycline – taxane based chemotherapy



Cortazar, et al Lancet 384:164-172, 2

Pathologic complete response (pCR) : Definition and prognostic implication

7 randomized clinical trials, N= 6,377 patients
Anthracycline – taxane based chemotherapy



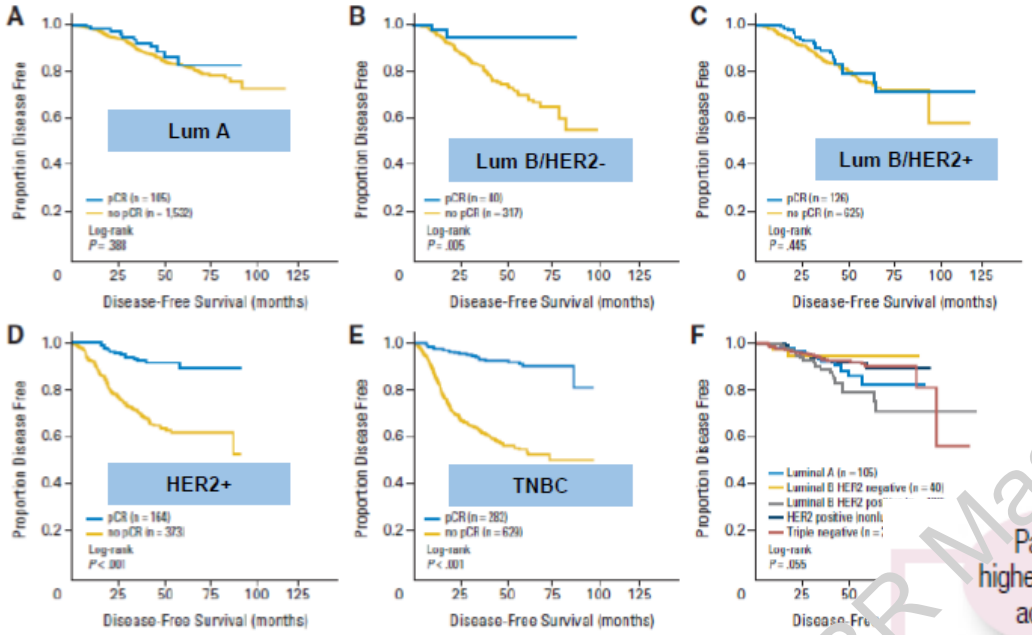
Von Minckwitz, et al JCO 30:1796-1804, 2012

The absence of any residual cancer cells in the breast and lymph nodes following preoperative therapy is called a pathological complete response (pCR).

In many neoadjuvant trial, patients with pCR showed a better long-term outcome.

Patients with residual invasive tumor in lymph nodes have the worst prognosis in terms of disease-free survival/DSF/ and overall survival/OS/

Clinical impact of pCR according to subtypes



any patients who is candidate for adjuvant therapy can be considered for neoadjuvant therapy

Patient selection

Von Minckwitz, et al J

Table 1. Patient selection criteria for neoadjuvant therapy in early breast cancer

Selection criteria	Level of evidence [reference]
Clinical lymph node involvement	A [1, 2]
Size >2 cm	B [1, 2]
Triple-negative	B [22, 23]
HER2-positive	B [24, 25]
High proliferative index	B [26]
Unresectable tumors	A [1, 2]
Inflammatory carcinoma	B [1–3]

The Oncologist 2019;24:1–9

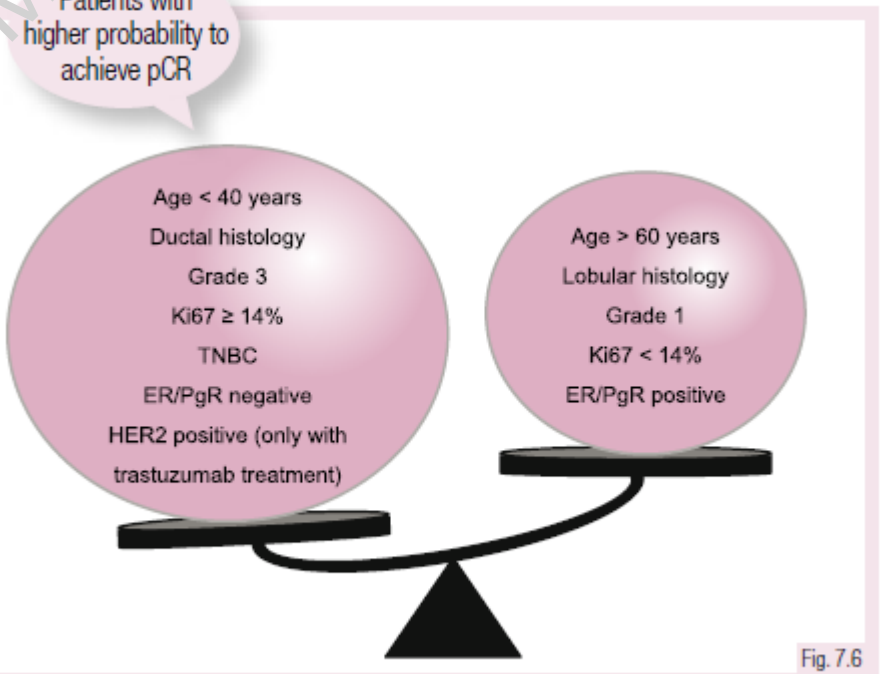


Fig. 7.6

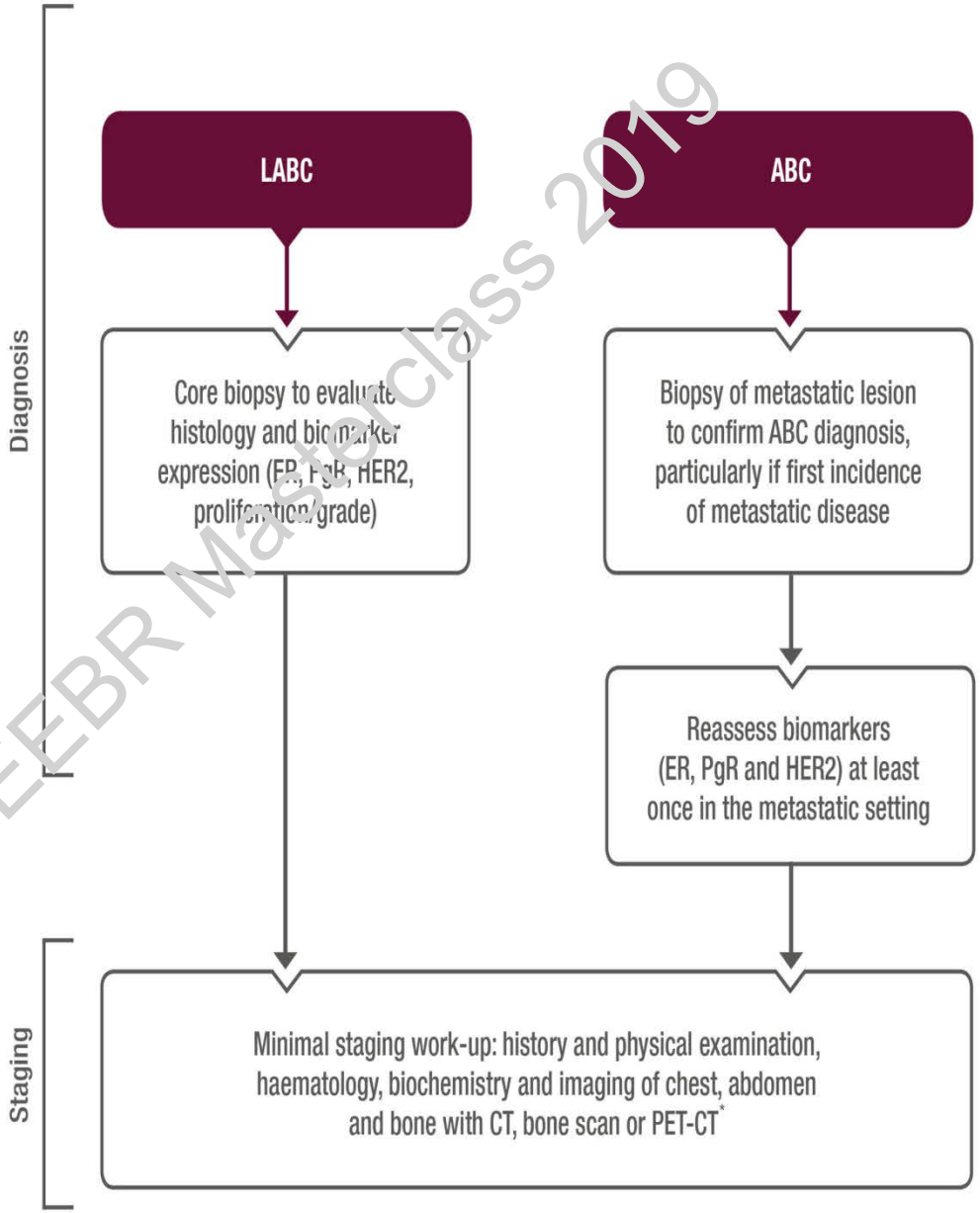
, Oestrogen receptor; HER2, human epidermal growth factor receptor 2; pCR, pathological mplete response; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

Section XI: LABC

Guideline statement	LoE/GoR	Consensus
Before starting any therapy, a core biopsy providing histology and biomarker (ER, PgR, HER2, proliferation/grade) expression is indispensable to guide treatment decisions.	I/A	97%
Since LABC patients have a significant risk of metastatic disease, a full staging work-up, including a complete history, physical examination, laboratory tests and imaging of chest and abdomen (preferably with CT scan) and bone, before initiation of systemic therapy is highly recommended.	I/A	100%
PET-CT, if available, may be used (instead of and not in addition to CT scans and bone scan).	II/B	100%
Systemic therapy (not surgery or RT) should be the initial treatment.	III/A	100%

CLINICAL PRACTICE GUIDELINES

ABC diagnostic work-up and staging



*Discuss indications. Brain MRI not indicated unless there are symptoms

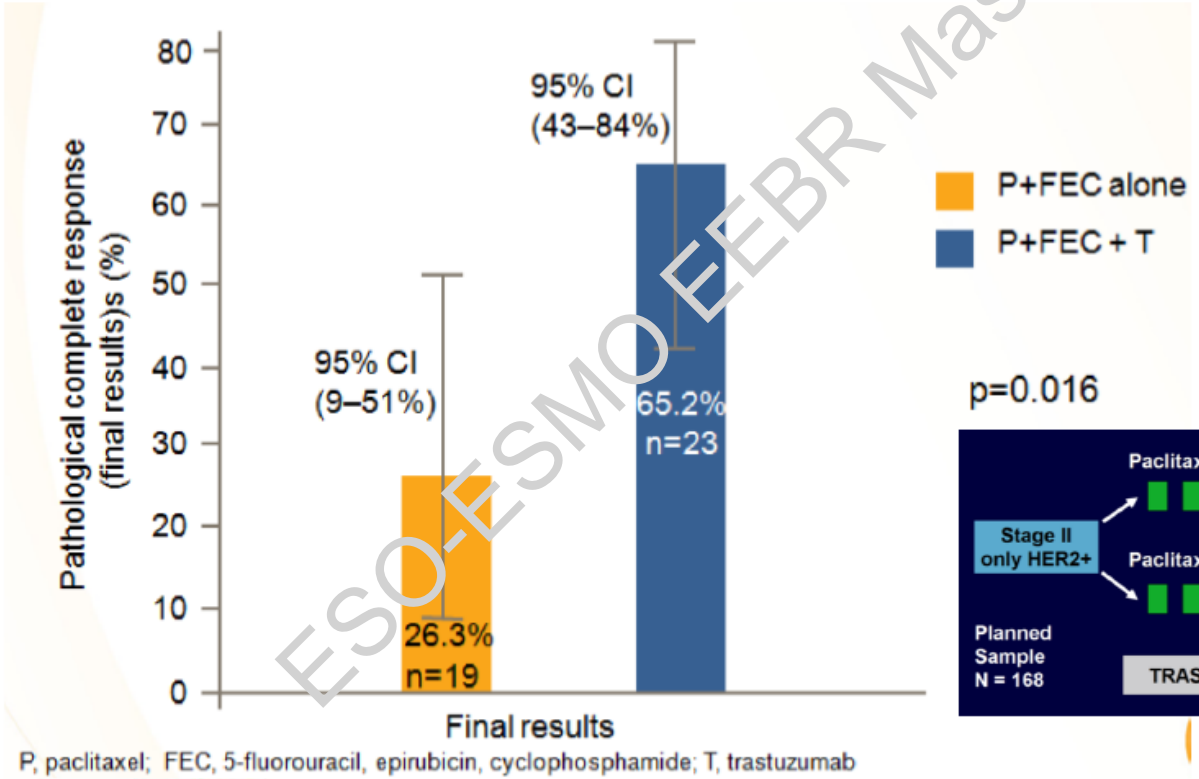
ESMO

Guideline statement	LoE/GoR	Consensus
A combined treatment modality based on a multidisciplinary approach (systemic therapy, surgery and RT) is strongly indicated in the majority of cases	IVA	100%

HER2-positive LABC

Double vs single anti-HER2 therapies

Neoadjuvant Trastuzumab significantly increases pCR rates



P, paclitaxel; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; T, trastuzumab

Buzdar A, et al. J Clin Oncol 2005

Meta-analysis: Neoadjuvant anthracyclines/taxanes with or without trastuzumab

All cooperative neoadjuvant trials in Germany between 1998 and 2006 using anthra/taxanes (N=4913) plus GeparQuattro and TECHNO trials (N=1721) using trastuzumab for HER2+ tumors

Von Minckwitz et al, SABCS 2008, Abstract 79

Total: 6634 pts

Goals:

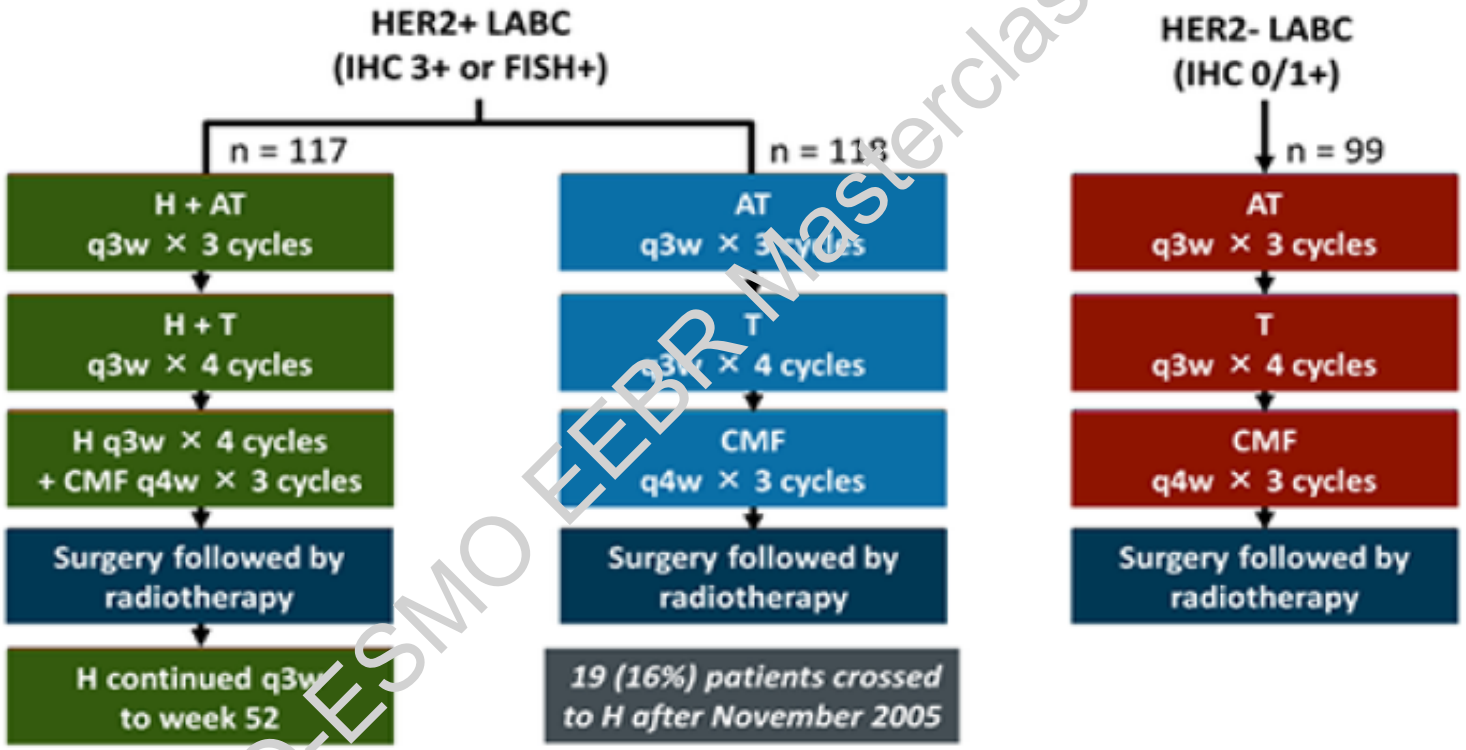
In patients with HER2+ tumors:

	Trastuzumab (N=671)	No Trastuzumab (N=736)	P-value
pCR rate	41%	23%	<.001

Other characteristics associated with high rate of pCR (multivariate analysis):

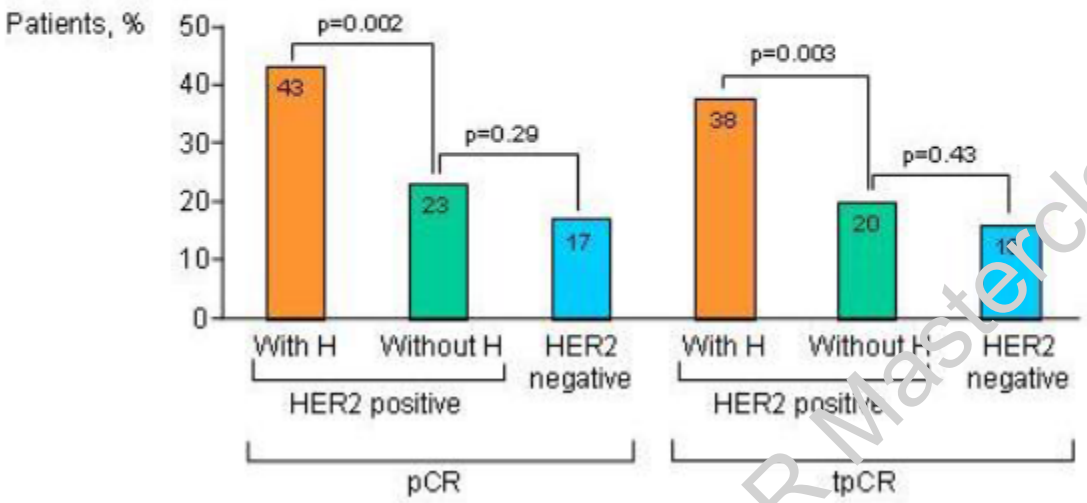
- Younger age (P<.001)
- Ductal (P<.001)
- Histological grade 3 (p<.001)
- Positive HER2 (P<.001)
- Negative HR (P<.001)
- Tumor size (P<.001)
- Conventional dosage (vs. dd) (P<.001)

NOAH : phase III, open label trial of neoadjuvant trastuzumab



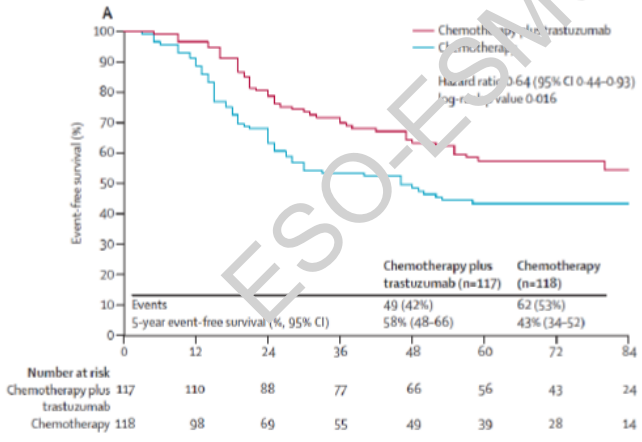
Gianni L, et al. Lancet 2010;375:377-384

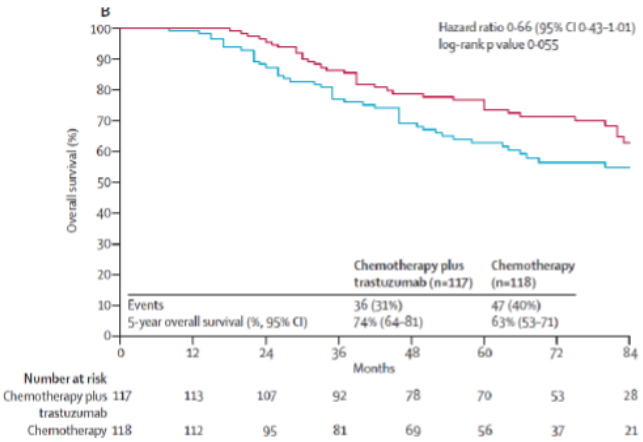
Cooperation of trastuzumab increased pCR & EFS : NOAH trial



Gianni L, et al. Lancet 2010;375:377-384

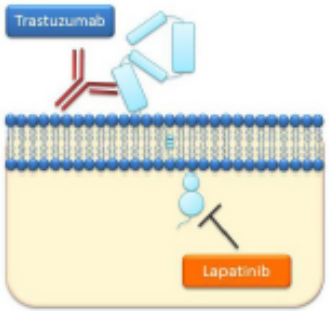
Neoadjuvant Trastuzumab
NOAH Study; similar EFS and OS than adjuvant



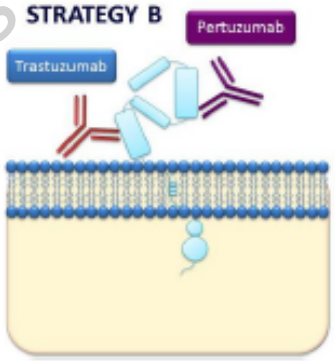


TRIALS EVALUATING DUAL HER2 BLOCKADE

STRATEGY A



STRATEGY B



Advanced Disease

EGF104900

Cleopatra
PERUSE
PHEREXA

Neoadjuvant setting

NeoALTTO
Cherlob
LPT 109096
NSABP B-41
CALGB 40601

NeoSPHERE
TRYPHAENA
WSG-ADAPT
KRISTINE

Adjuvant setting

ALTTO

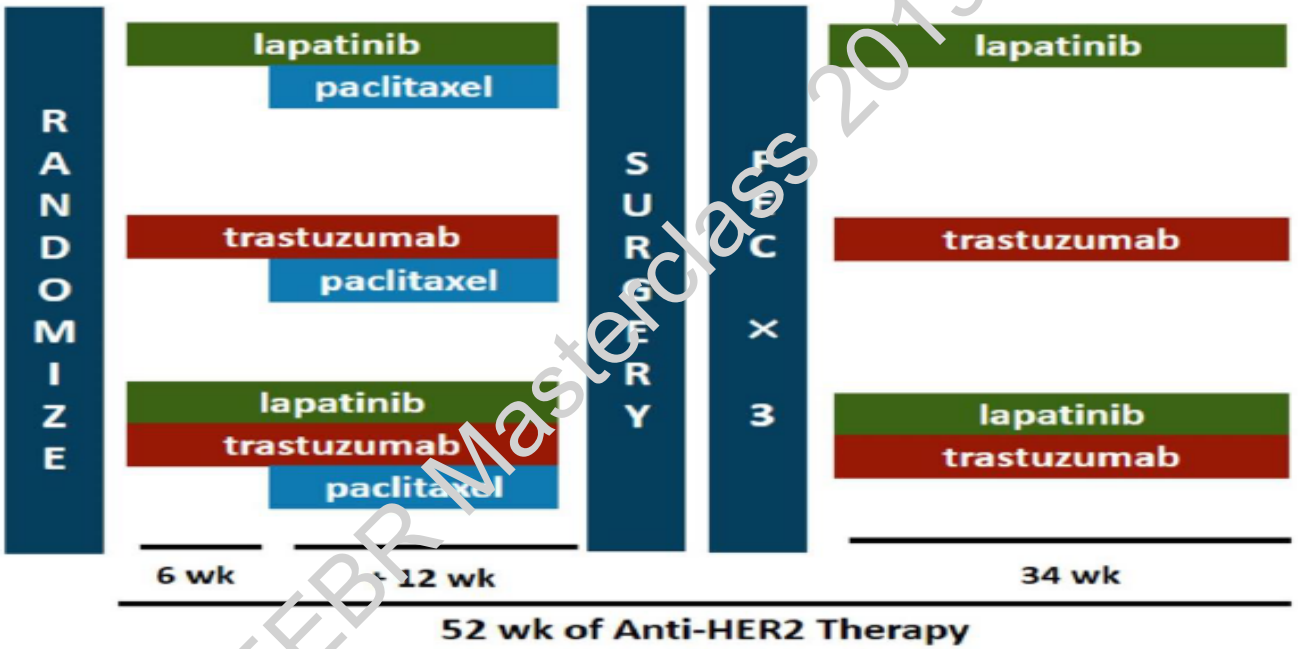
APHINITY

Alvaro Moreno-Aspitia et al, ASCO 2017

NeoALTTO : dual HER2 blockade with lapatinib/trastuzumab

Invasive operable HER2+ BC
Tumor > 2 cm
(inflammatory BC excluded)
LVEF ≥ 50%
N = 450

Stratification
- Tumor ≤ 5 cm vs Tumor > 5 cm
- ER- or PgR+ vs ER- and PgR-
- N 0-1 vs N ≥ 2
- Conservative surgery or not



Baselga J, et al. Lancet 2012;379:633-640

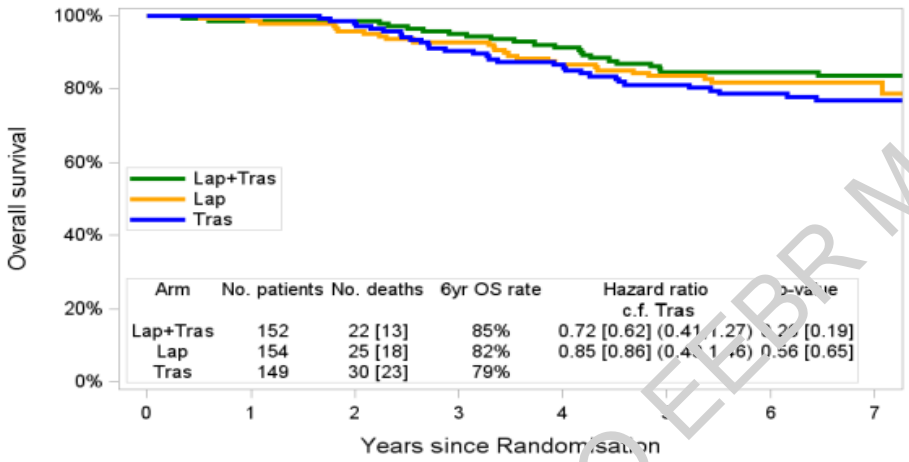
Study and regimen, %	Total pCR: T	Total pCR: L	Total pCR: T + L
NeoALTTO[1] (N = 455) L and/or T; paclitaxel added after first 6 weeks	27.6	20.0	46.8 *p=0.0007 c/w T
NSABP B-41[2] (N = 519) AC → paclitaxel + T and/or L	49.4	47.4	60.2 p=0.056 c/w T
CALGB 40601[3] (N = 299) Paclitaxel + H and/or L (*pCR in breast only)	46	32	56 p=NS c/w T or L
CHER-LOB[4] (N = 121) Paclitaxel → FEC with T and/or L	25.0	26.3	46.7 *p=0.019 c/w T and L arms
TRIO B07[5] (N = 128) H and/or L → docetaxel/ carboplatin + T and/or L	47	26	52 p=NS c/w T

L, lapatinib; T, trastuzumab

NeoALTTO trial
Overall Survival Analysis by treatment arm

MEDIAN FU: 6.7 years

Jens Huober et al, ESMO 2017



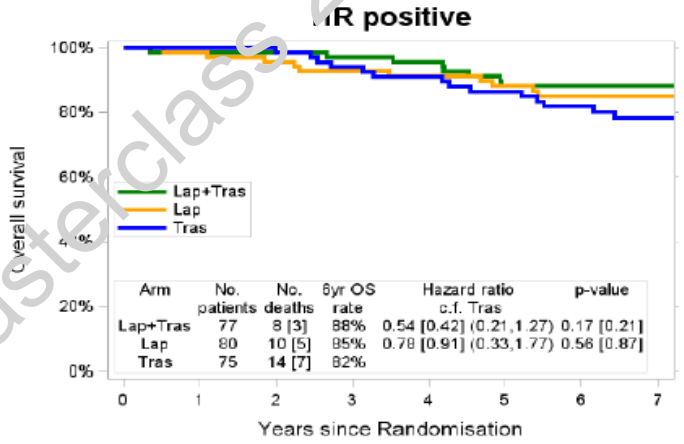
Tests for interaction:

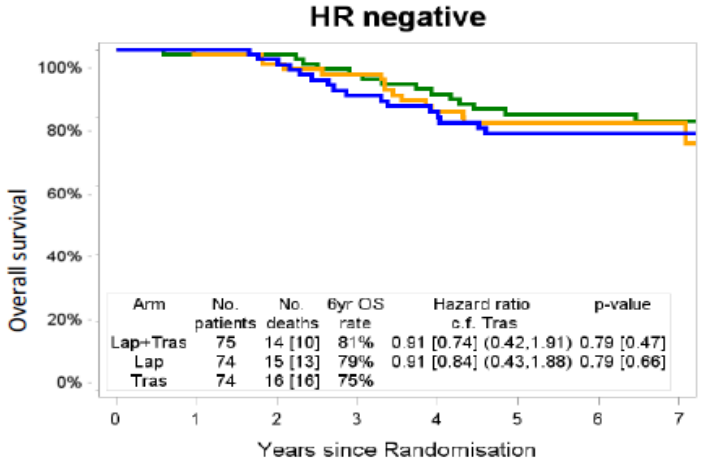
L + T vs T x HR p= 0.45

L vs T x HR p=0.72

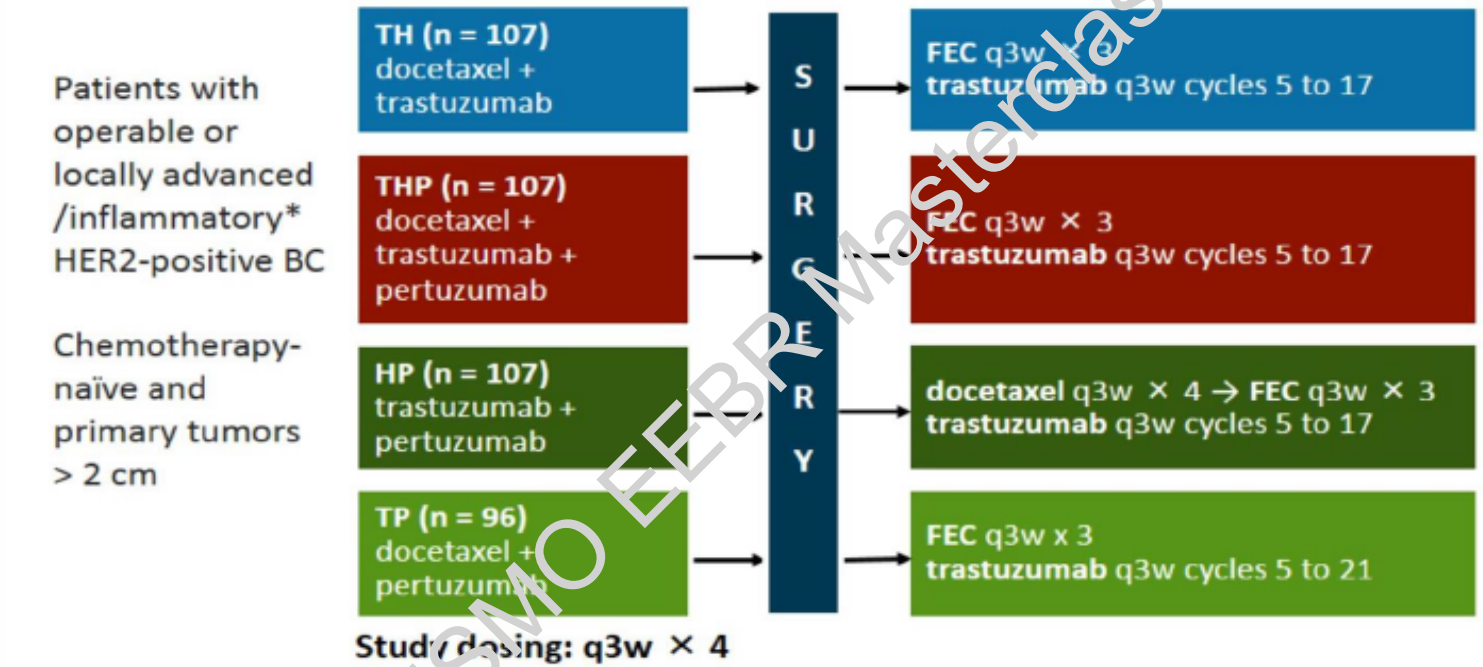
Results of first analysis of EFS/OS are shown in square brackets to provide comparison with this update

De Azambuja et al. Lancet Oncol 2014





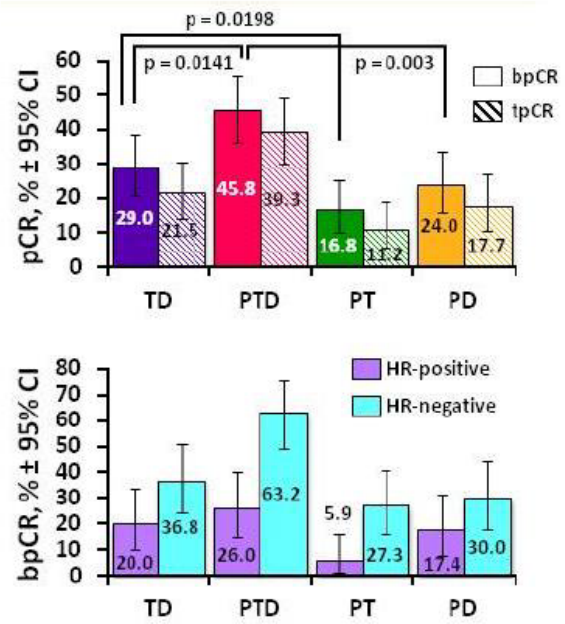
NeoSphere : dual HER2 blockade with pertuzumab and trastuzumab



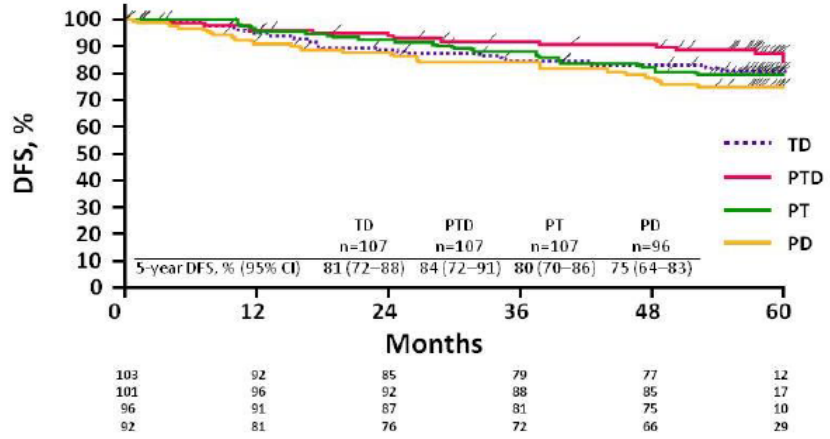
*Locally advanced = T2-3, N2-3, M0 or T4a-c, any N, M0; operable = T2-3, N0-1, M0; inflammatory = T4d, any N, M0

Gianni L et al. Lancet Oncol 2012;13:25-32

Higher pCR rate with dual HER2 blockade : NeoSphere trial



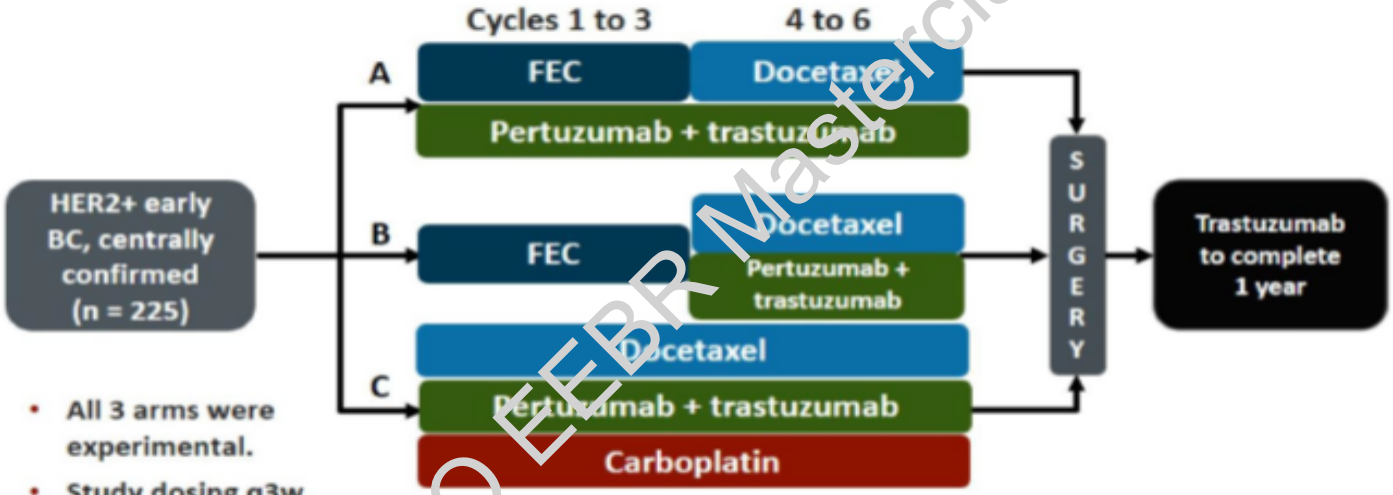
Gianni et al. Lancet Oncol 2012;13:25-32



Kaplan–Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up. Two late events occurred with PTD: one case of PD at 67 months, and one death due to an unrelated cerebrovascular accident without PD at 72 months

Presented By Luca Gianni at 2015 ASCO Annual Meeting

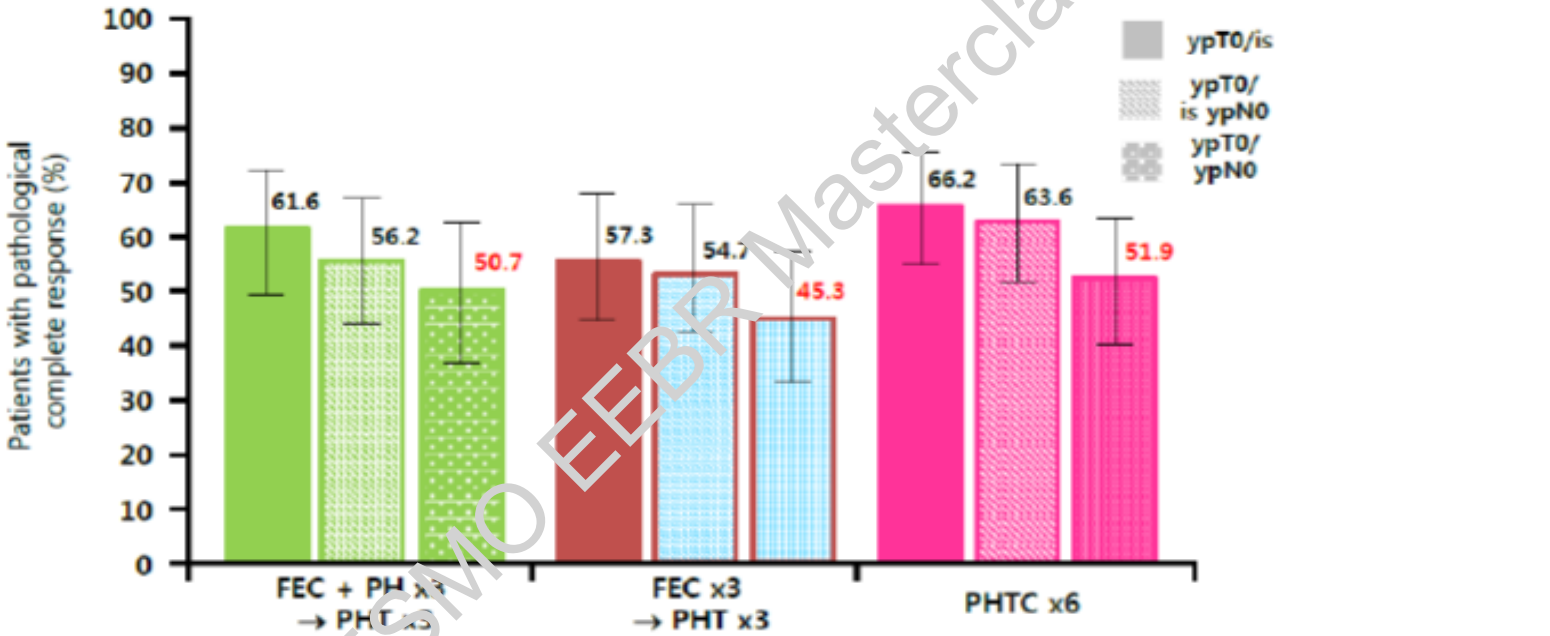
TRYPHAENA : phase II neoadjuvant trastuzumab and pertuzumab in HER2+ EBC



- All 3 arms were experimental.
- Study dosing q3w
  - FEC: 500 mg/m², 100 mg/m², 600 mg/m²
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m² (escalating to 100 mg/m² if tolerated, in arms A and B only)
- Stratification
  - Operable, locally advanced, and inflammatory BC
  - HR positivity

Schneeweiss A et al. Ann Oncol 2013;24:2278-84

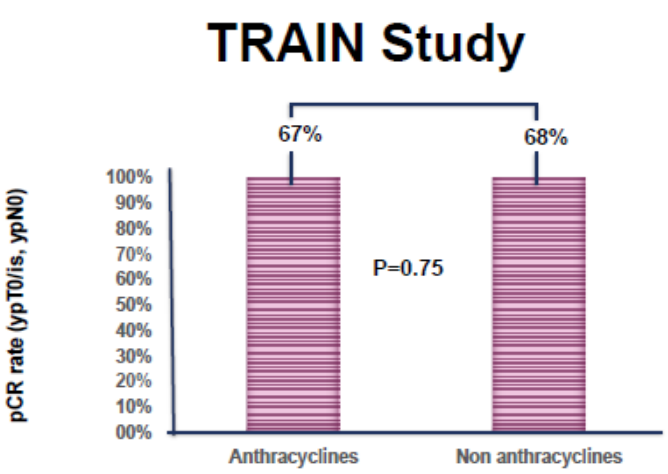
High pCR rates of regardless of chemotherapy backbone



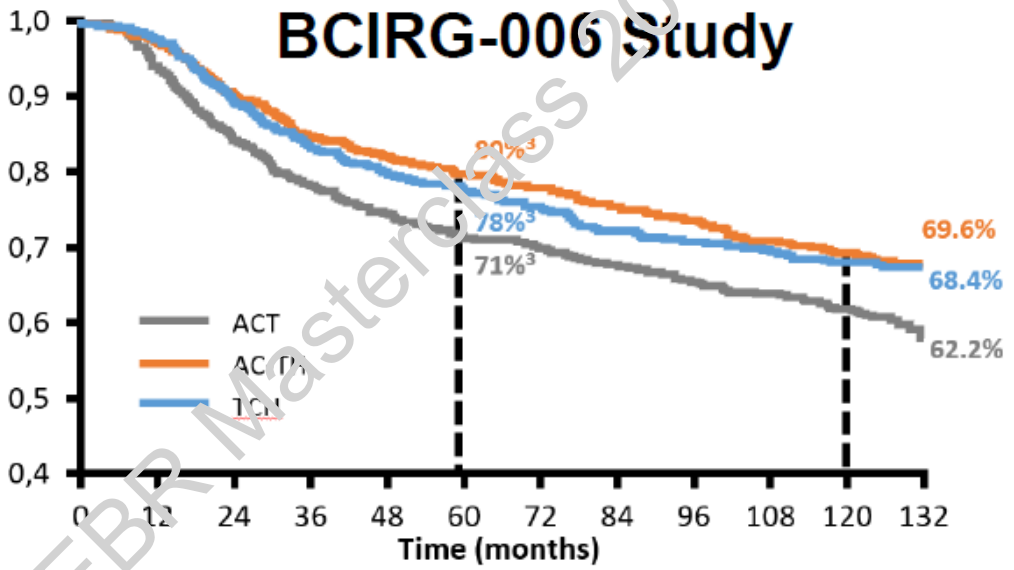
•C, carboplatin; FEC, 5-fluorouracil, epirubicin, cyclophosphamide;
•H, trastuzumab; P, pertuzumab; pCR, pathological complete response;
•T, docetaxel

Schneeweiss A et al. Ann Oncol 2013;24:2278-84

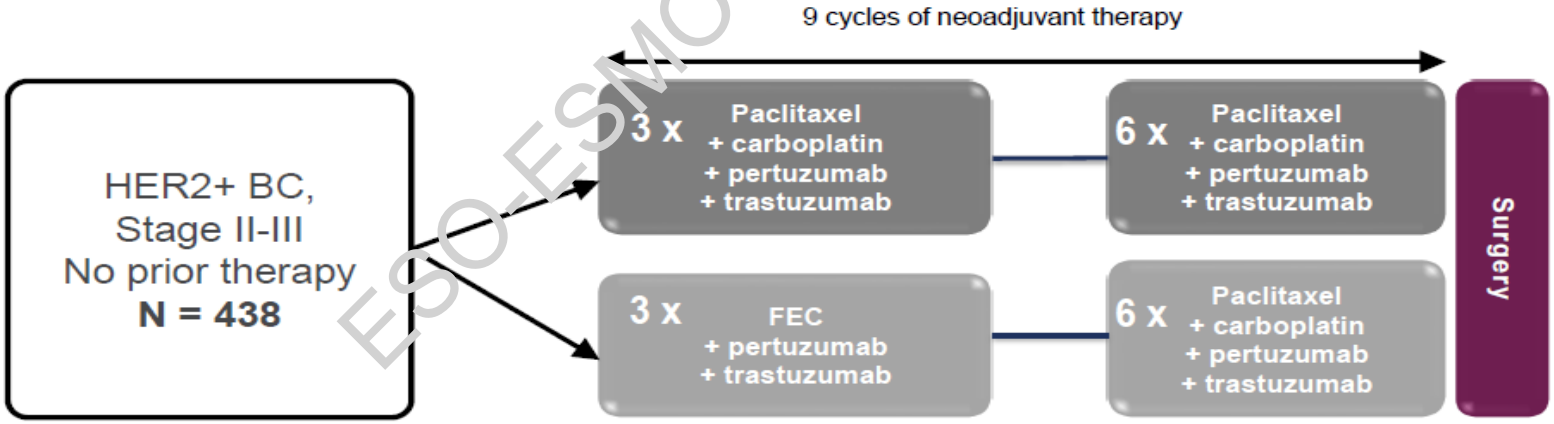
NAT with anthracyclines



Van Ramshorst M, at al. ASCO 2017

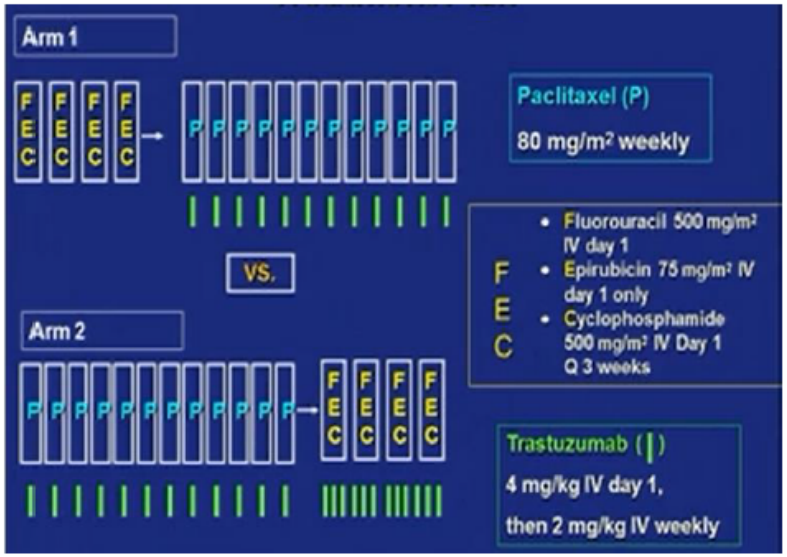


Slamon D, *et al.* SABCS 2015; Slamon D, *et al. N Engl J Med* 2011



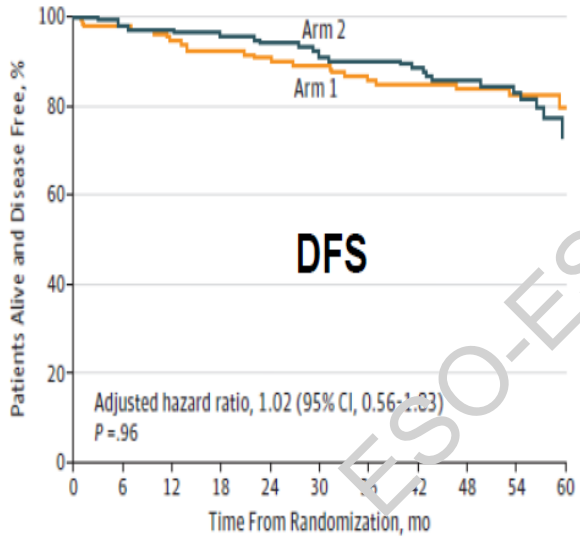
Van Ramshorst M, at al. ASCO 2017

ACOSOG Z1041 (Alliance)



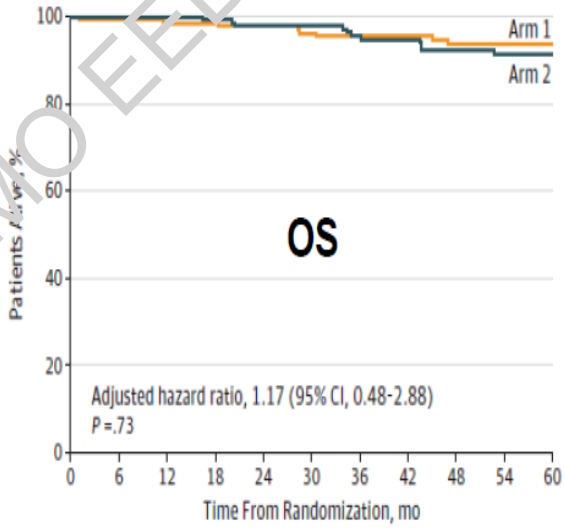
Regimen	No Trastu-Antras (n=138)	Trastu-Antras (n= 142)
pCR (Breast)	56.5%	54.2%

Regimen	No Trastu-Antras (n=138)		Trastu-Antras (n= 142)	
patients	RE[+]	RE[-]	RE[+]	RE[-]
pCR	45%	72%	38%	77%



No. at risk

Arm 1	138	130	120	116	113	107	100	96	83	58	23
Arm 2	142	136	128	125	120	117	112	99	83	60	16

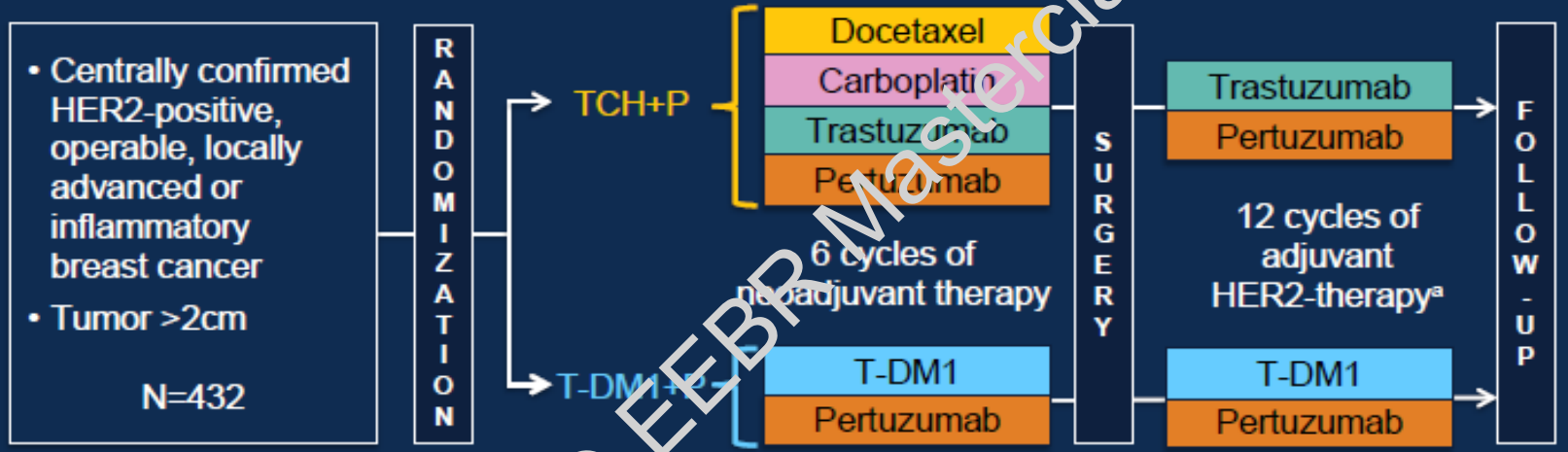


No. at risk

Arm 1	138	133	129	128	125	123	120	115	101	82	39
Arm 2	142	140	137	136	132	132	128	120	104	81	38

Buzdar A, at al. JAMA Oncol 2018

KRISTINE Study Design

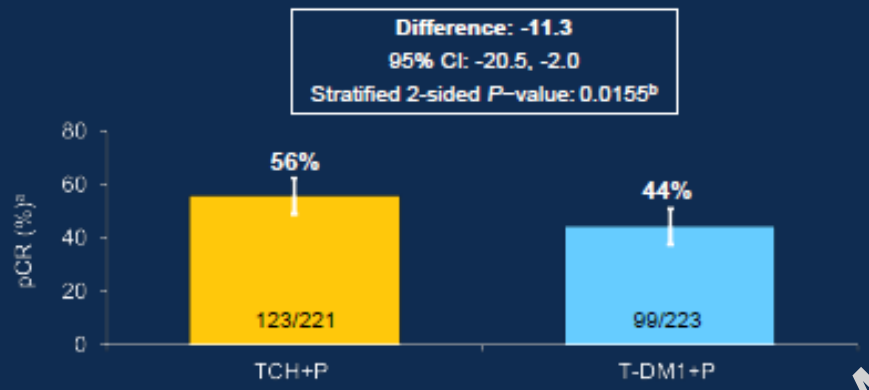


Primary endpoint: pCR by local assessment (ypT0/is, ypN0)

- **Stratification factors:** local HR status, geographic location, and clinical stage at presentation

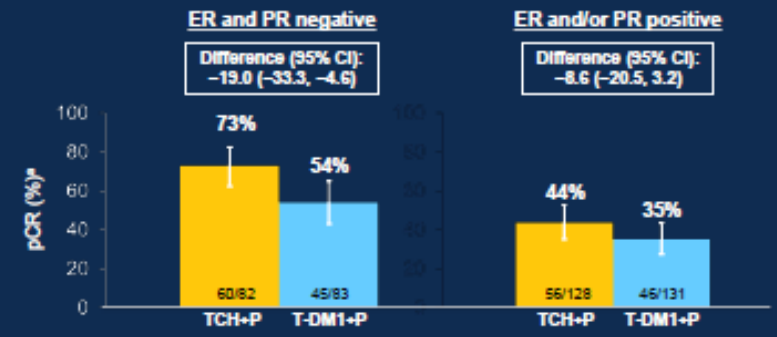
[a]Adjuvant chemotherapy was recommended for patients in the T-DM1+P arm who had residual disease in lymph node(s) or in the breast (>1cm).

Primary Endpoint: pCR (ypT0/is, ypN0)



[a]pCR rate and 95% CI are shown. Patients with missing or unevaluable pCR status were considered nonresponders: TCH+P, 7 (3.2%); T-DM1+P, 15 (6.7%). Treatment discontinuation in the neoadjuvant phase for progressive disease: TCH+P, 0% of patients; T-DM1+P, 7% of patients.
[b]Cochran-Mantel-Haenszel Chi-square.

pCR by Central ER/PR Receptor Status

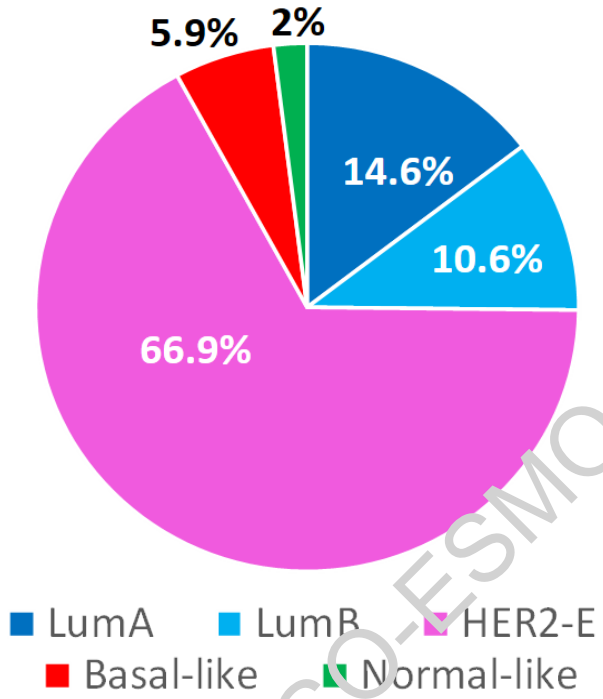


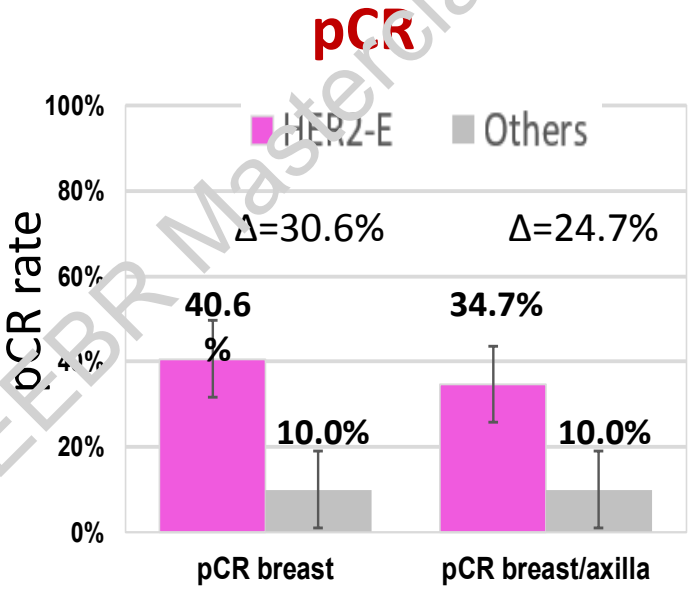
[a]ypT0/is, ypN0; patients with missing or unevaluable pCR status were considered nonresponders. Twenty patients had "unknown" ER/PR status by central analysis.

Presented by:

Intrinsic Subtype at Baseline vs. pCR in the Breast

Baseline samples (N=151)





Signatures	N	Breast pCR rate
HR status		
HR+	77	18.2%
HR-negative	74	43.2%
Intrinsic subtype		
nonHER2-E	50	10.0%
HER2-E	101	40.6%

Prat et al. SABCS 2016; Lancet Oncol 2017

- No other clinical-pathological variable was found associated with pCR.

Table 1. Pathological complete remission rates in neoadjuvant trials with anti-HER2 blockade on HR-positive breast cancers

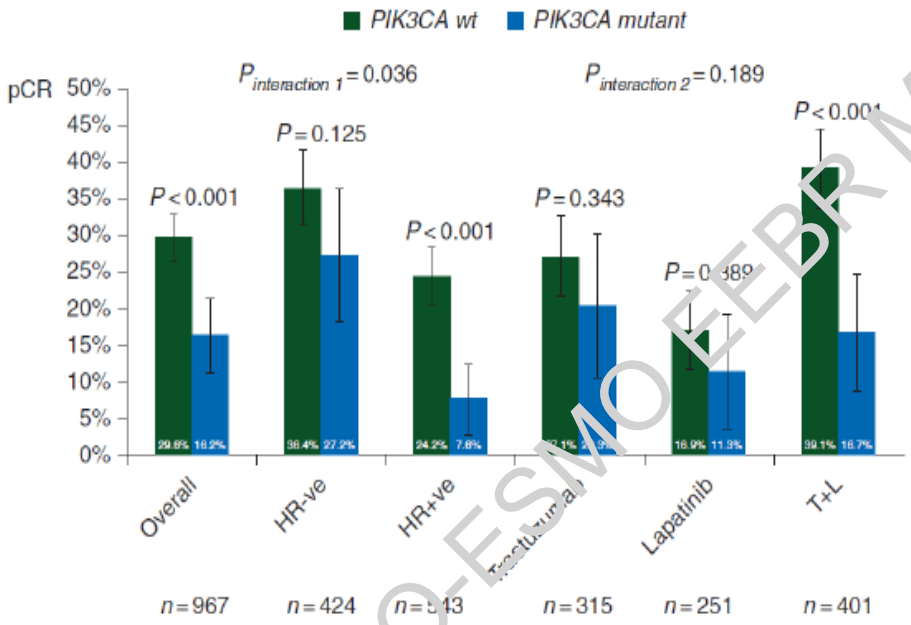
Type of neoadjuvant therapy	Therapy	Trial	pCR (%)*	pCR rates in pre-/post-menopausal patients (%)
Chemotherapy+trastuzumab	T-DM1	ADAPT (n=119) [53]	41	37.9/44.1
	Trastuzumab+docetaxel	CALGB40601 (n=70) [45]	41	
		NeoSphere (n=50) [43]	20	
Chemotherapy+dual HER2 blockade	T-DM1+pertuzumab	KRISTINE (n=138) [54]	35	
	Trastuzumab+docetaxel+carboplatin+pertuzumab	KRISTINE (n=128) [54]	44	
	Trastuzumab+docetaxel+lapatinib	CALGB40601 (n=69) [45]	41	
	Trastuzumab+docetaxel+pertuzumab	NeoSphere (n=50) [43]	26	
Chemotherapy+dual HER2 blockade+endocrine therapy	Trastuzumab+docetaxel+carboplatin+pertuzumab+aromatase inhibitor	NSABP B-52 (n=157) [49]	46	
Chemotherapy+trastuzumab+endocrine therapy	T-DM1+endocrine therapy	ADAPT (n=127) [53]	41.5	38.1/45
Trastuzumab+endocrine therapy	Trastuzumab+endocrine therapy	ADAPT (n=129) [53]	15.1	13.6/16.7
Dual HER2 blockade	Trastuzumab+pertuzumab	NeoSphere (n=51) [43]	6	

HER=human epidermal growth factor receptor 2; HR=hormonal receptor; pCR=pathological complete response; T-DM1=trastuzumab emtansine.
*pCR rate for HER2 positive and estrogen receptor positive tumours (pCR rate in %).

Biomarkers

- **Neosphere (neoadjuvant pertuzumab)**
  - HER2 expression (H-score) associated with sensitivity to pertuzumab
  - Exon 9 PI3K mutations linked to lack of sensitivity to HER2-directed Mab's (prognosis)
- **NeoALTO (neoadjuvant lapatinib)**
  - Lower rate of pCR in 23% with PIK3CA mutations
- **Across neoadjuvant trials**
  - Lower rate of pCR in ER+ disease
  - Higher pCR in HER2 enriched (and improved outcome in NSABP B-31)
    - 70% in HER2-E vs. 35% in luminal
- **Immune markers**
  - CALGB 40601 and N9831
    - Improved pCR and outcome correlates with immune signatures

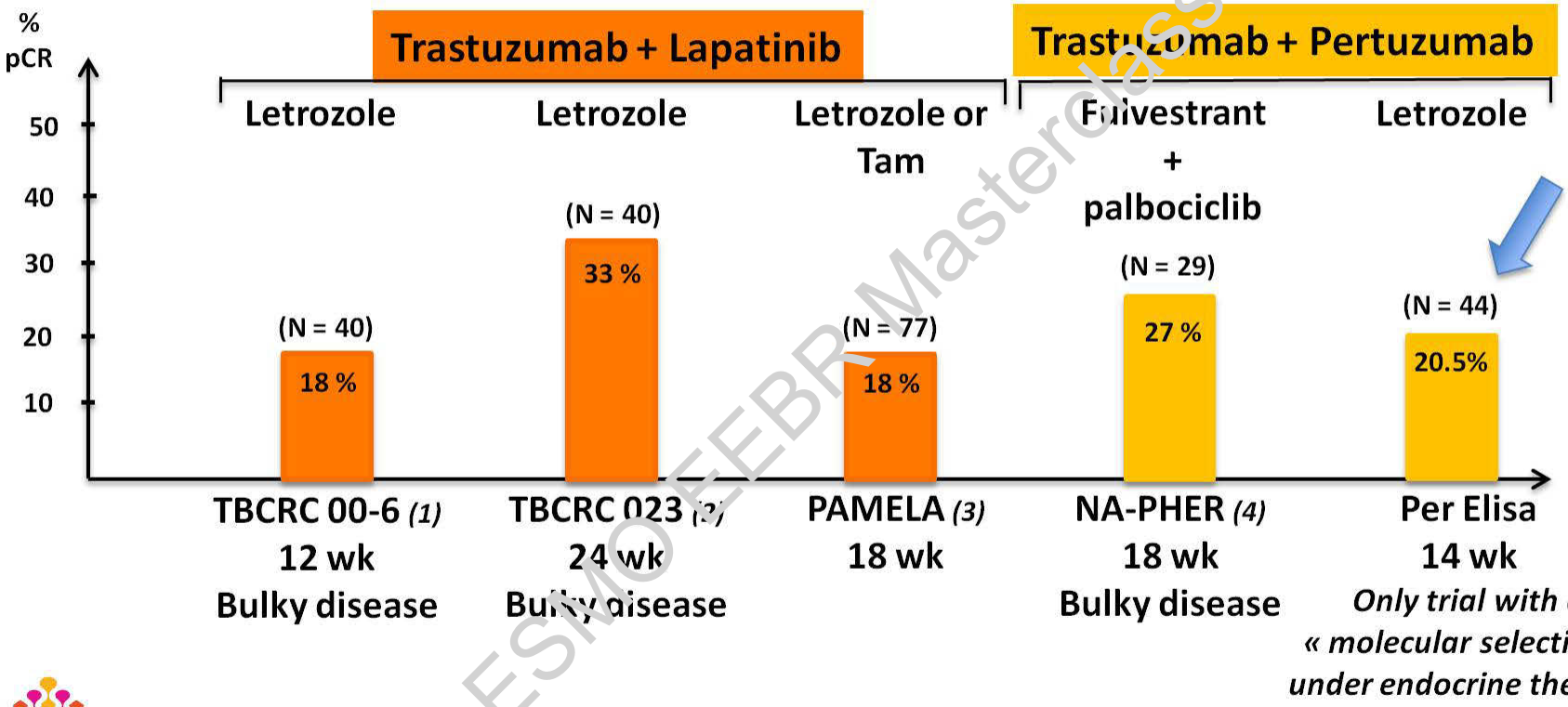
PIK3CA mutations are associated with reduced pathological complete response rates in HER2+ disease



- N=967 (GeparQuattro, GeparQuinto, GeparSixto, NeoALTTO, CHERLOB)
- Chemotherapy + antiHER2 (single vs. dual)
- Overall, the pCR rate was significantly lower in the PIK3CA mutant compared with the wild-type group (16.2% versus 29.6%; P<0.001).
- Within the HR+ subgroup, the PIK3CA mutant group had a pCR rate of only 7.6% compared with 24.2% in the wild-type group (P<0.001).

Loibl S, et al. Ann Oncol 2016

Single-arm Neoadjuvant trials of dual anti-HER2 blockade + endocrine therapy : pCR (YpT0/is YpN0) rates reported



(1) Rimawi M et al, JCO 2013 - (2) Rimawi M et al, SABCS 2014 - (3) Llombart-Cusac A et al, Lancet Oncol 2017- (4) Gianni L et al, Lancet Oncology 2018

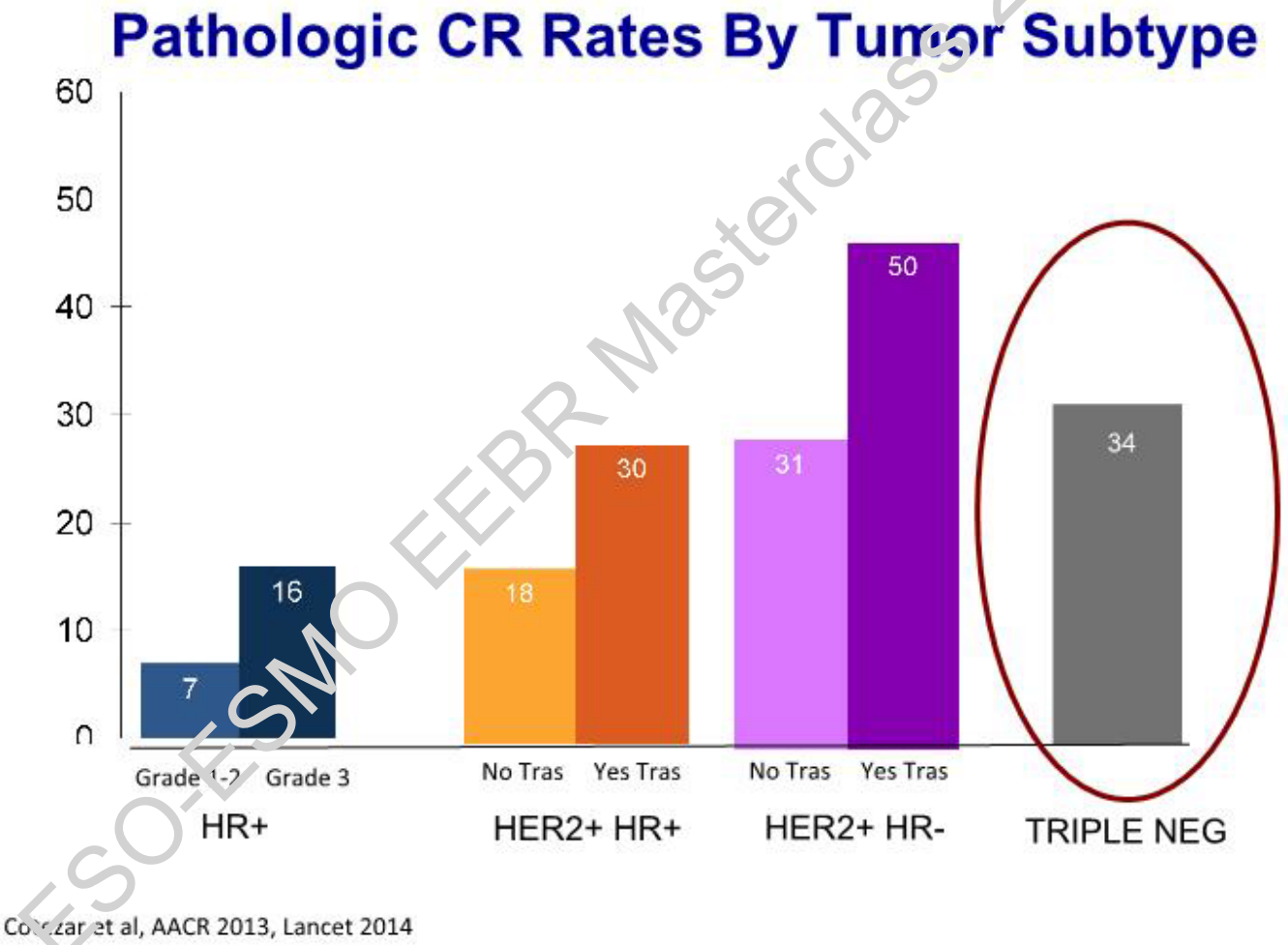
TABLE 3. Ongoing or Planned Trials Evaluating HER2-Directed Agents in the Preoperative Setting

Study Name	No. of Patients	ClinicalTrials.gov Identifier	Treatment Arms	Primary Objective
BOLD-1	1,366 (open)	NCT02625441	Taxane/trastuzumab/pertuzumab × 3 → FEC × 3 vs. taxane/trastuzumab × 3 → FEC × 3 → trastuzumab for 1 year	pCR
BRUOG308	30 (open)	NCT02789657	Paclitaxel/carboplatin/trastuzumab/pertuzumab × 4	pCR
			Paclitaxel/carboplatin/trastuzumab/pertuzumab × 4 → AC × 4	
			Paclitaxel/carboplatin/trastuzumab/pertuzumab × 6 → AC	
			Paclitaxel/carboplatin/trastuzumab/pertuzumab × 6	
			Paclitaxel/carboplatin/trastuzumab/pertuzumab × 4 → AC × 4	
GeparOcto	950 (open)	NCT02125344	PMCb vs. ETC if HER2+, also pertuzumab/ trastuzumab	pCR
NEOTOP	90	NCT02339532	If TOP2A amplified, FEC × 3 then docetaxel/trastuzumab/pertuzumab × 3 → 3 cycles of trastuzumab/pertuzumab/docetaxel	pCR
			If TOP2A not amplified, docetaxel, carboplatin/trastuzumab/pertuzumab × 6	
PALTAN	48	NCT02907918	Palbociclib + letrozole (+ goserelin if premenopausal) + trastuzumab × 16 weeks	pCR
Predix-HER2	200 (open)	NCT02568839	Docetaxel/sq trastuzumab/pertuzumab vs. T-DM1 therapy arms switched if no response after cycle 2	pCR
TEAL	30 (open)	NCT02073487	T-DM1/lapatinib → nanoparticle albumin-bound paclitaxel vs. trastuzumab/pertuzumab/paclitaxel	pCR
TP-II	259	NCT03272477	Paclitaxel/trastuzumab/ pertuzumab × 14 weeks vs. trastuzumab/pertuzumab/endocrine therapy × 14 weeks	pCR

Abbreviations: pCR, pathologic complete response; FEC, 5-FU, epirubicin, and cyclophosphamide; AC, adriamycin-cytoxan; P, paclitaxel; M, nonpegylated liposomal doxorubicin; Cb, carboplatin; ETC, epirubicin, taxane, cytoxan.

Guideline statement	LoE/GoR	Consensus
For **HER2-positive LABC**, concurrent taxane and anti-HER2 therapy is recommended since it increases the rate of pCR.	I/A	92%
For **HER2-positive LABC**, anthracycline-based ChT should be incorporated in the treatment regimen.	I/A	72%
When an anthracycline is given, it should be administered sequentially with the anti-HER2 therapy.	I/A	87%
For patients with **HER2-positive LABC** (inflammatory or non-inflammatory), without distant metastases, who are in complete remission after appropriate neoadjuvant systemic therapy and appropriate locoregional therapy, and being treated with a potential curative intent, the approved adjuvant duration of 1 year of anti-HER2 therapy should be used.	I/A	85%

HR-positive LABC

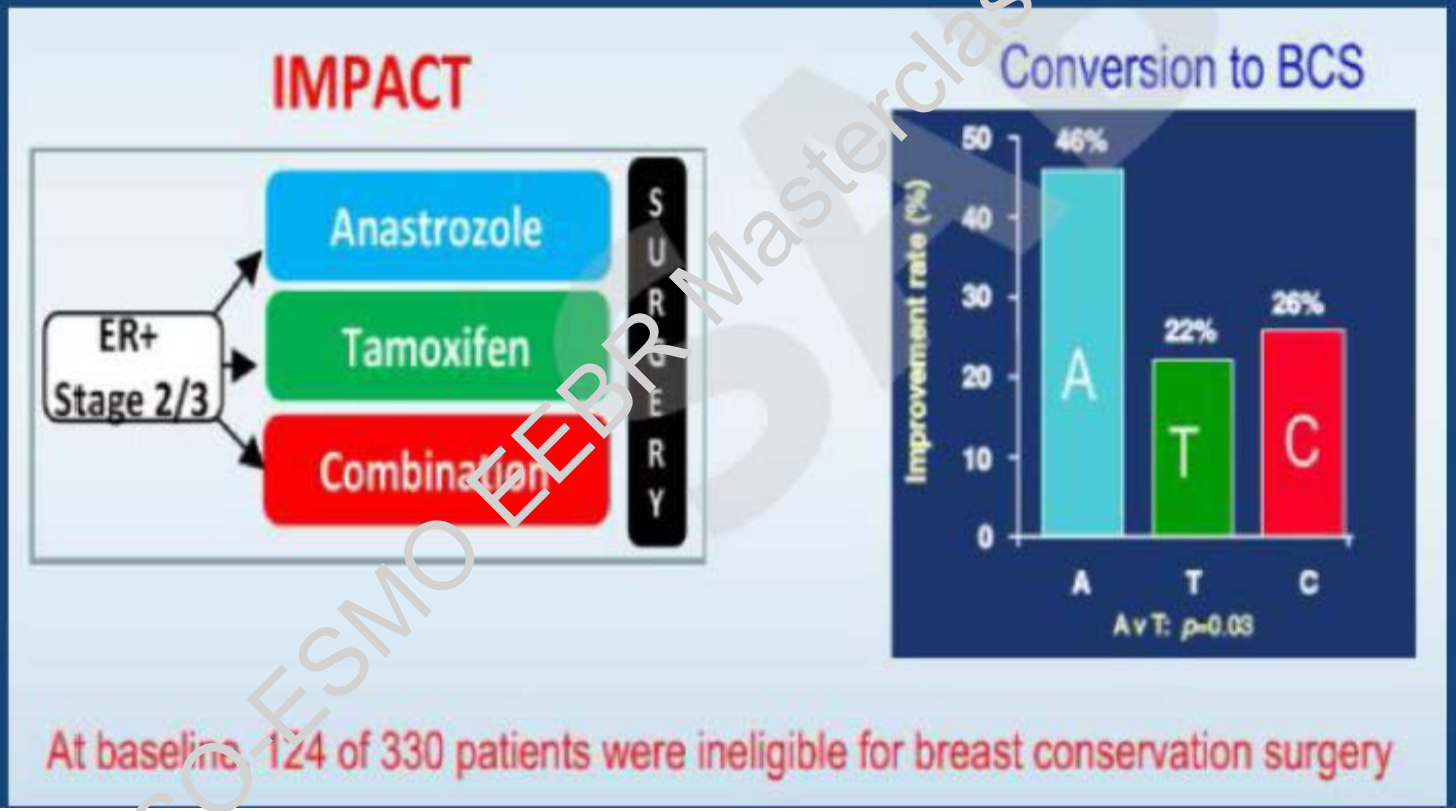


Cortazar et al, AACR 2013, Lancet 2014

Luminal EBC: Small neoadjuvant trials (n~800) with early response assessment predict outcome of large phase III trials (n~11,000)

Trial	IMPACT	ATAC	ACOSOG Z1031	EXCE	NEWEST	CONFIRM
Patients	158	9366	377	4136	211	736
Setting	neoadjuvant	adjuvant	neoadjuvant	adjuvant	neoadjuvant	palliative
Drugs	Tamoxifen / Anastrozole / Combination	Tam / Ana / Comb.	Ana / Letrozole / Exemestane	Let / Ana	Fulvestrant$_{500}$ / F$_{250}$	F$_{500}$ / F$_{250}$
Efficacy	**2-week Ki67 suppression**: ANA > TAM (p=0.004); TAM=combination	ANA vs. TAM DFS 0.87; p=0.01; Combination arm discontinued	**Geometr. mean % Ki67 change: surgery)** A -78, L-87.1, E-81.2% (biolog. equal)	5y DFS 84.8 vs. 82.9% (HR 0.93; 0.80-1.07) p=n.s.	**4-week Ki67 LI reduction** - 78.8 vs. -47.4% (p<0.0001)	Median OS 26.4 vs. 22.3 months (HR 0.81; nominal p=0.02)

NET increases BCS



At baseline 124 of 330 patients were ineligible for breast conservation surgery

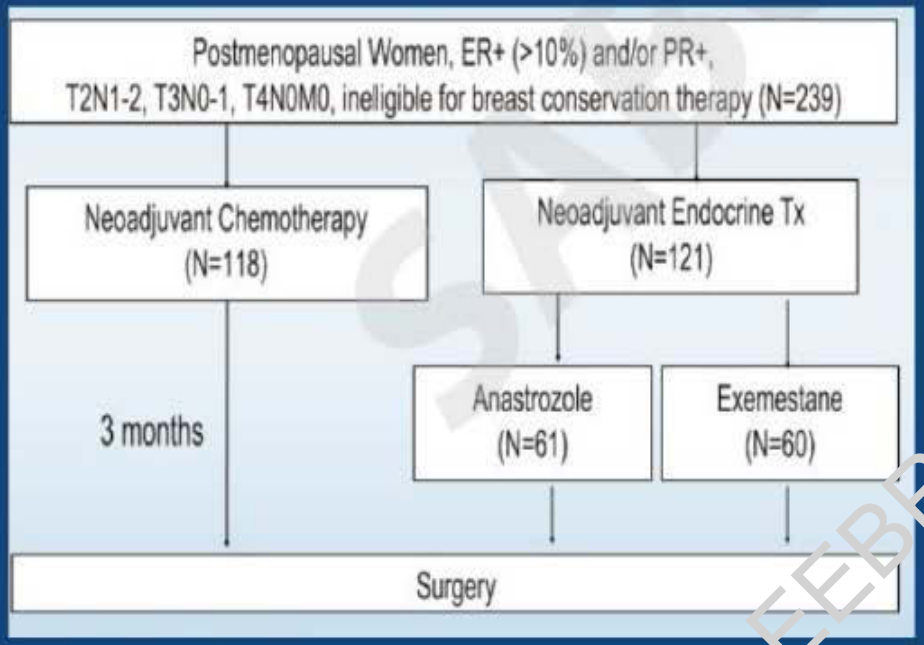
Smith et al, JCO 2005

NET vs. Chemotherapy

	NET	N	Duration	Clinical Response
Thomas (2007)	Letrozole	103	3 months	89% vs 85%
Semiglazov (2007)	Anastrazole or Exemestane	239	3 months	65% vs 64%
Generali (2011)	Letrozole	114	6 months	73% vs 88%
Alba (2011)	Exemestane +/- goserelin	95	6 months	48% vs 66%
Palmieri (2014)	Letrozole	44	18-23 weeks	59% vs 55%

Charehbili, Can Treat Rev 2014

NET vs. Chemotherapy



	NET N=121	Chemo N=118	
ORR	65%	64%	
pCR	3%	6%	
BCS	33%	24%	
Ki67 ≥ 6	**NET N=70**	**Chemo N=63**	***p***
ORR	70%	60%	0.07
BCS	43%	24%	0.05

Semiglazov, Cancer 2007

Putting NET into Practice

	Neo CT	NET
Ideal candidate	TNBC, HER2+	Allred ≥ 6, lobular
Duration of Rx	Defined # cycles	Prolonged and flexible
Follow-up	Each cycle	Recommend q4-6 weeks
pCR	30-50%, impacts DFS	Rare, no impact on PFS
Early biomarkers	Change in FDG uptake (?)	Ki-67, PEPI
Multiplex assays	Predictive	Predictive
Local therapy	Adjust based on response	Adjust based on response

Neoadjuvant Endocrine Therapy in Patients with Endocrine-responsive Breast Cancer

Guidelines Breast
Version 2018.1

	Oxford LoE	GR	AGO
▪ **Postmenopausal patients:**			
▪ Who are inoperable and cannot / will not receive chemotherapy	2a	B	+
▪ Optimizes the option for breast conserving therapy	1b	A	+
▪ Aromatase inhibitors (for > 3 months)	1a[a]	B	+
▪ Aromatase inhibitor + lapatinib (HER2+ BC)	2b	B	+/-
▪ **Premenopausal patients**			
▪ Who are inoperable and cannot / will not receive chemotherapy	5	C	+
▪ Tamoxifen	2b	C	+
▪ Aromatase inhibitors + LHRHa	1b	C	+/-
▪ **Concurrent chemo-endocrine therapy**	1b	A	-
▪ **Prognostic scores:**			
▪ PEPI: pTN-Stadium, ER expression and Ki-67 expression after neoadjuvant endocrine therapy	1b	B	+

[a] Optimal duration of neoadjuvant endocrine therapy is unknown.
No long term results for neoadjuvant endocrine therapy (vs. adjuvant endocrine therapy)

Preoperative Endocrine Predictive Index (PEPI)

Pathology, Biomarkers Factors		RFS		BCS	
		HR	Points	HR	Points
Tumor size	T1/2	-	0	-	0
	T3/4	2.8	3	4.4	3
Node status	No	-	0	-	0
	Yes	3.2	3	3.9	3
Ln Ki67 level	0 -1	-	0	-	0
	1+ -2	1.3	1	1.4	1
	2+ -3	1.7	1	2.0	2
	3+ -4	2.2	2	2.7	3
	4+	2.9	3	3.6	3
ER Allred	0-2	2.8	3	7.0	3
	3-8	-	0	-	0

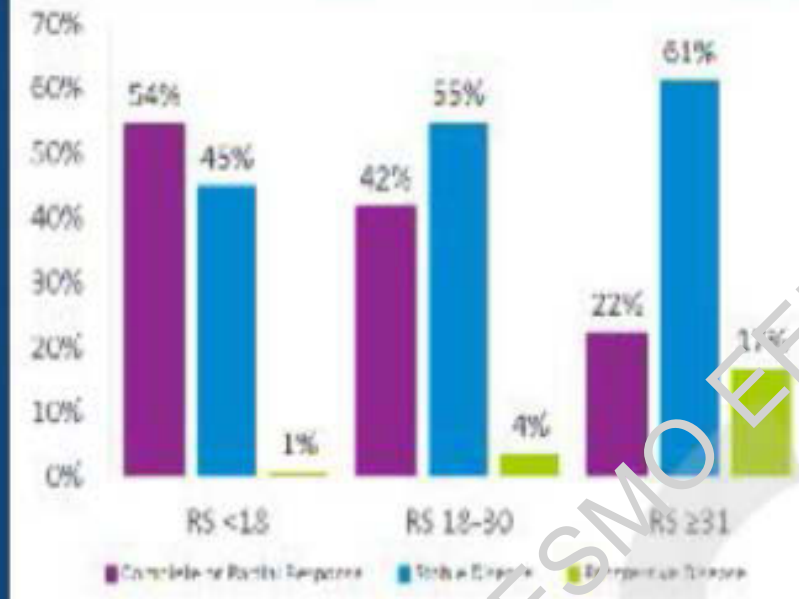
- Initially developed in P024 trial to predict recurrence
- Validated in Z1031

PEPI 0
pT1/2
pN0
Ki67 ≤ 2.7%
ER Allred 3-8

- *Modified* PEPI score excludes ER

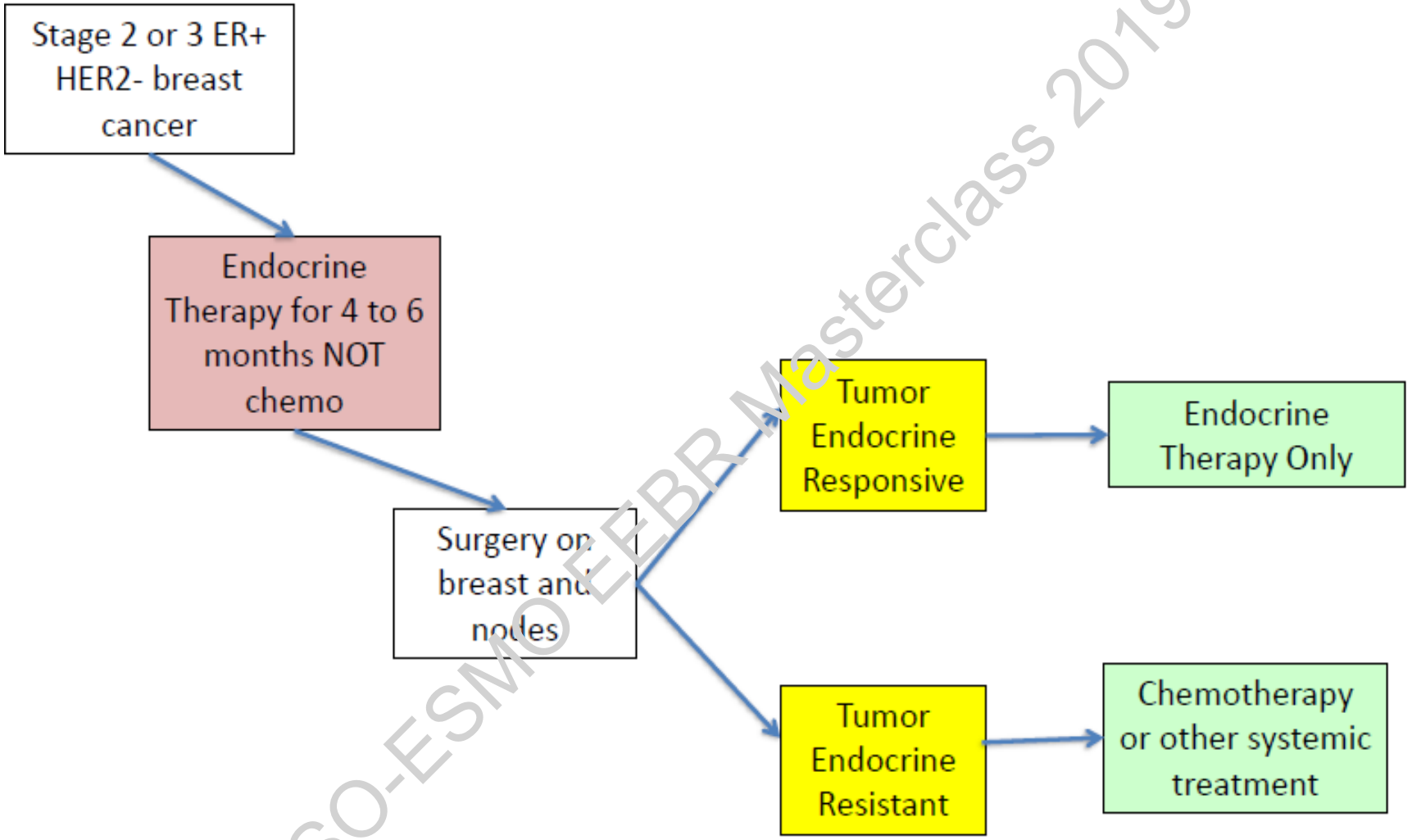
Ellis, JNCI 2008

Oncotype predicts response to NET

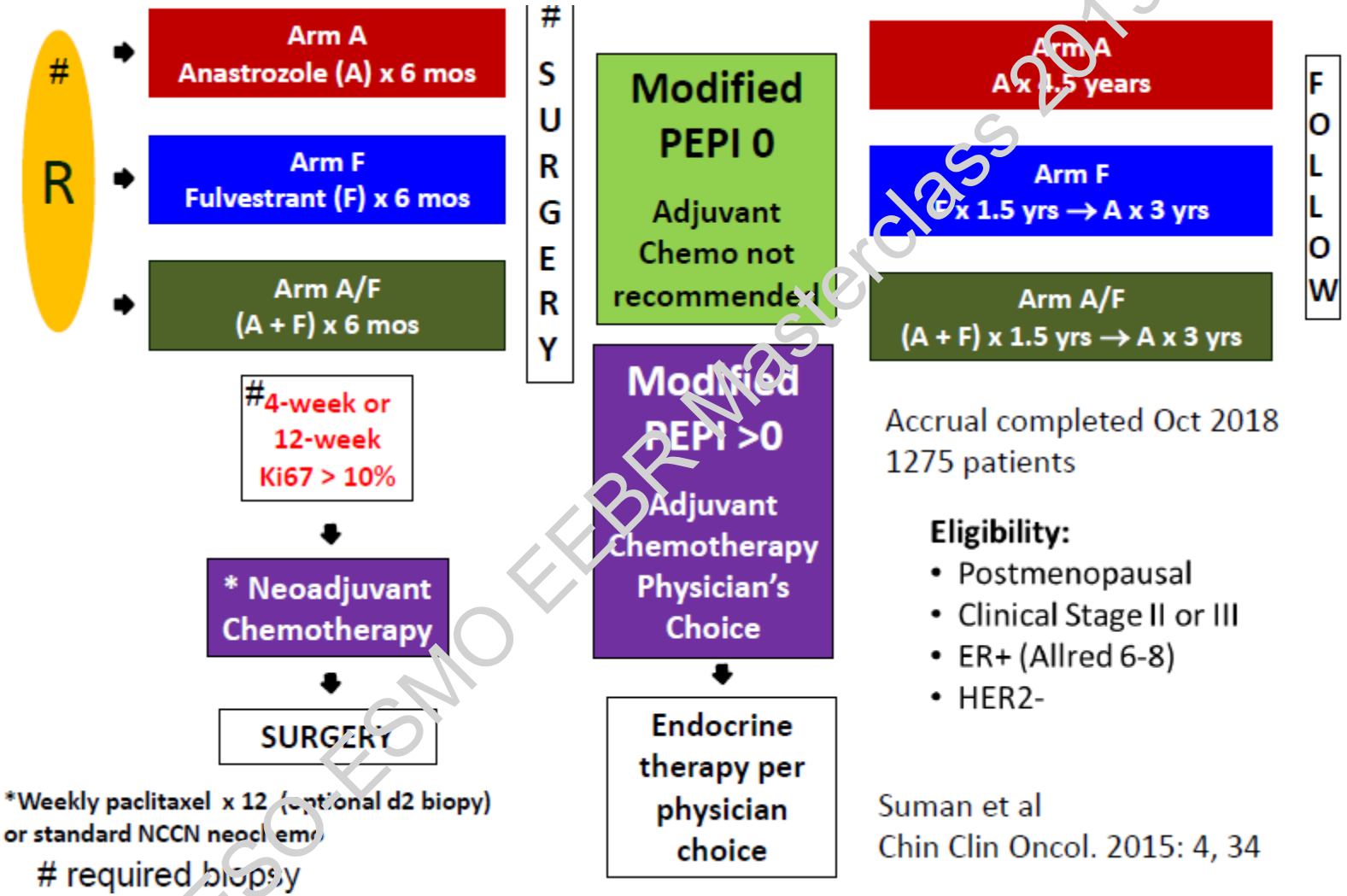


Clinical response, n	RS <18	RS 18-30	RS ≥31	Total
CR + PR	85	35	12	132
SD	70	46	33	149
PD	1	3	9	13
Total	156	84	54	294

Iwata et al, SABCS 2017



Ellis, M.J. Breast 2017:34, S104-107



*Weekly paclitaxel x 12 (optional d2 biopy)
or standard NCCN neoadjuvant

required biopsy

Accrual completed Oct 2018
1275 patients

Eligibility:

- Postmenopausal
- Clinical Stage II or III
- ER+ (Allred 6-8)
- HER2-

Suman et al
Chin Clin Oncol. 2015: 4, 34

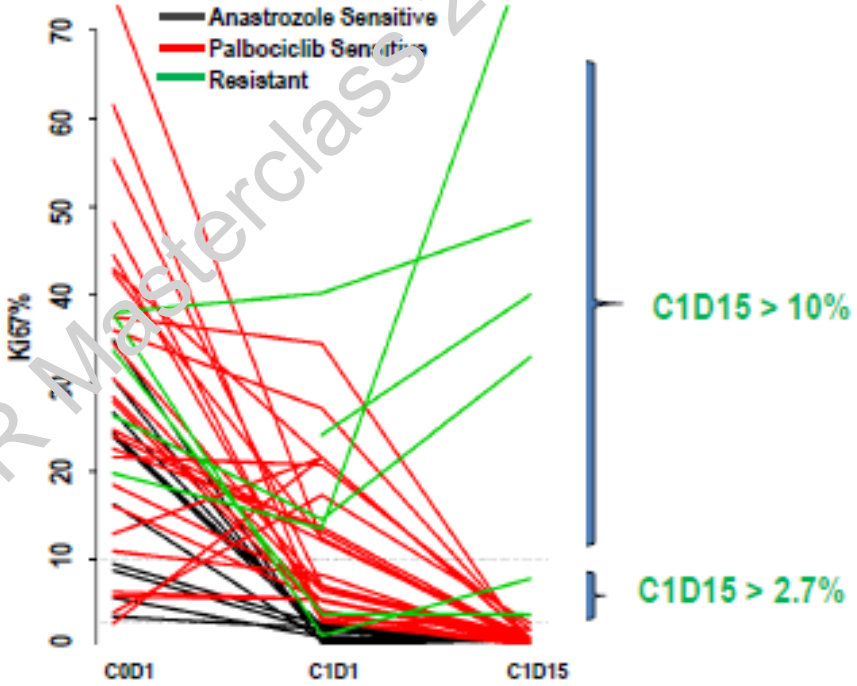
Ma, C et al Clin Cancer Res 2017: 23, 4055-4065

Anastrozole Sensitive
Anastrozole (A) Alone induced CCCA
n=12 (26%)

Palbociclib Sensitive
Adding P converted non-CCCA to CCCA
n=26 (60%)

Resistant
Persistent non-CCCA on Both A+P
n=6 (14%)

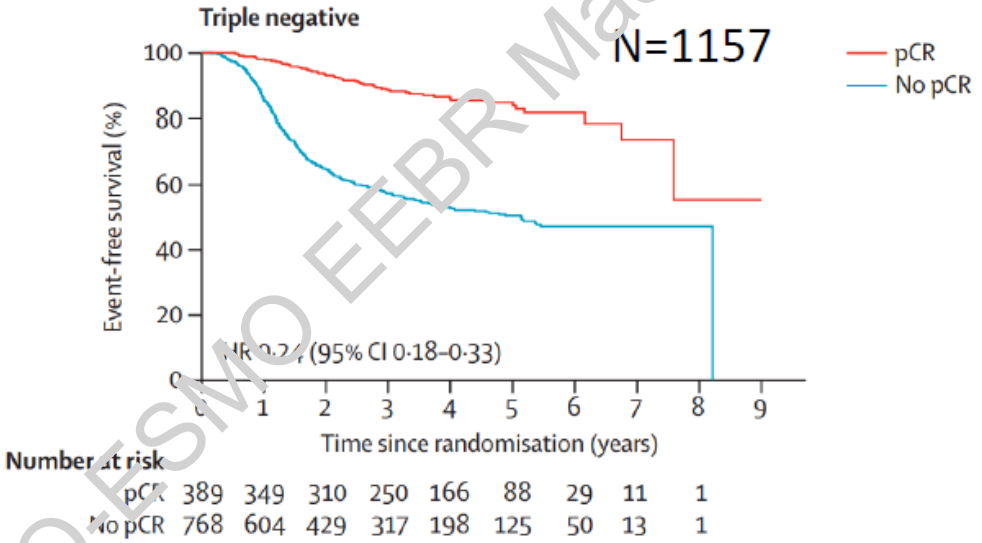
P: palbociclib; A: anastrozole



Guideline statement	LoE/GoR	Consensus
Options for **HR-positive LABC** include an anthracycline- and taxane-based ChT regimen, or ET.	I/A	85%
The choice of ChT versus ET, as initial treatment, will depend on tumour (grade, biomarker expression) and patient (menopausal status, PS, comorbidities, preference) considerations.	Expert opinion/ A	85%

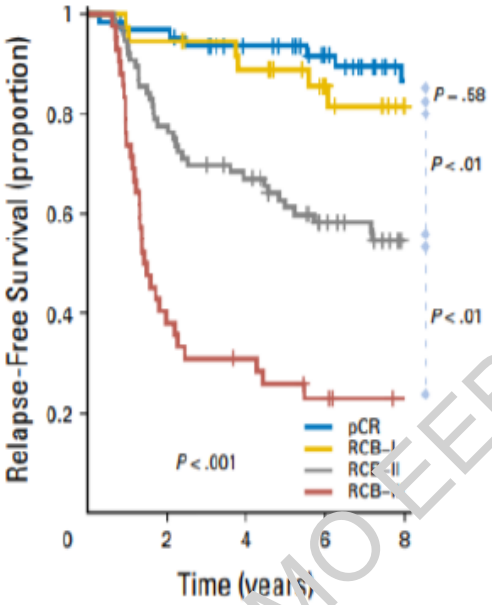
Triple-negative LABC

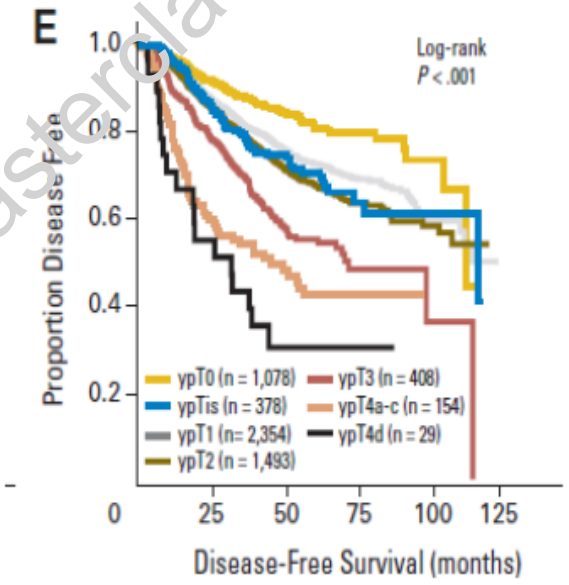
pCR is a strong Prognostic factor



Cortazar et al., Lancet 2014; 384: 164–72

Recurrence in TNBC correlates with volumen of residual disease

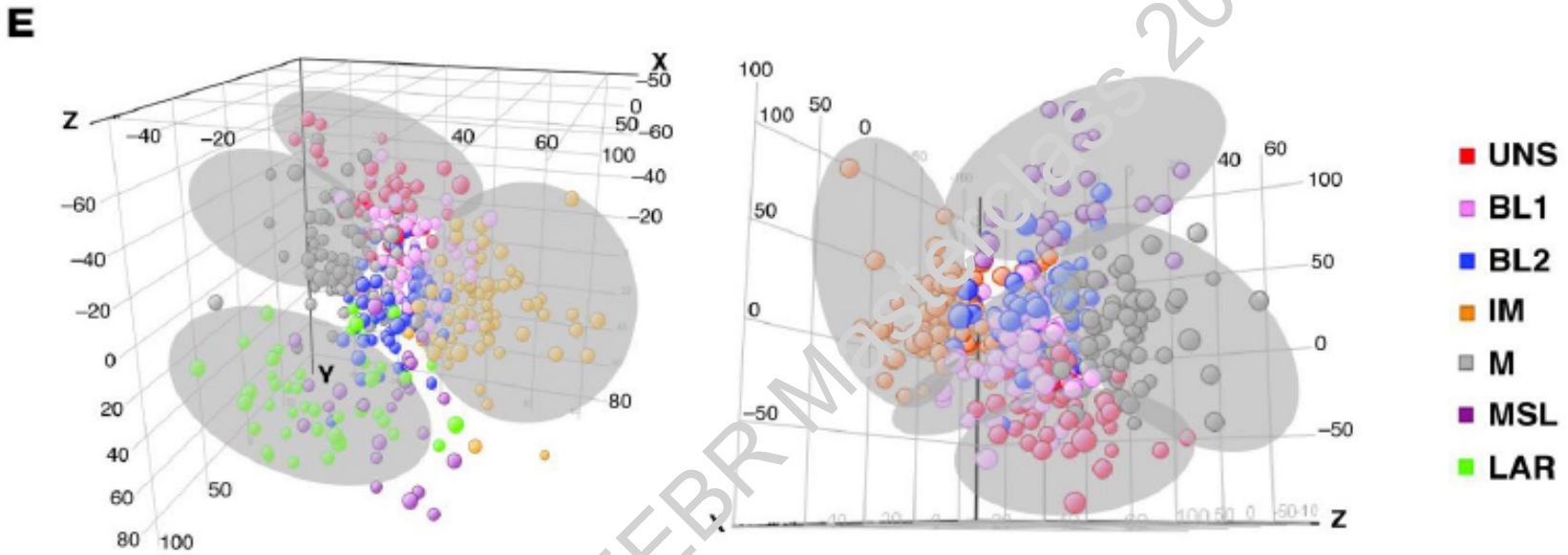




Estimates 10-year relapse-free survival rates: 86%, 81%, 55%, and 23%

W. Fraser Symmans et al., J Clin Oncol 35:1049-1060, 2017
von Minckwitz et al., J Clin Oncol 30:1796-1804.

Clinical Heterogeneity of TNBC



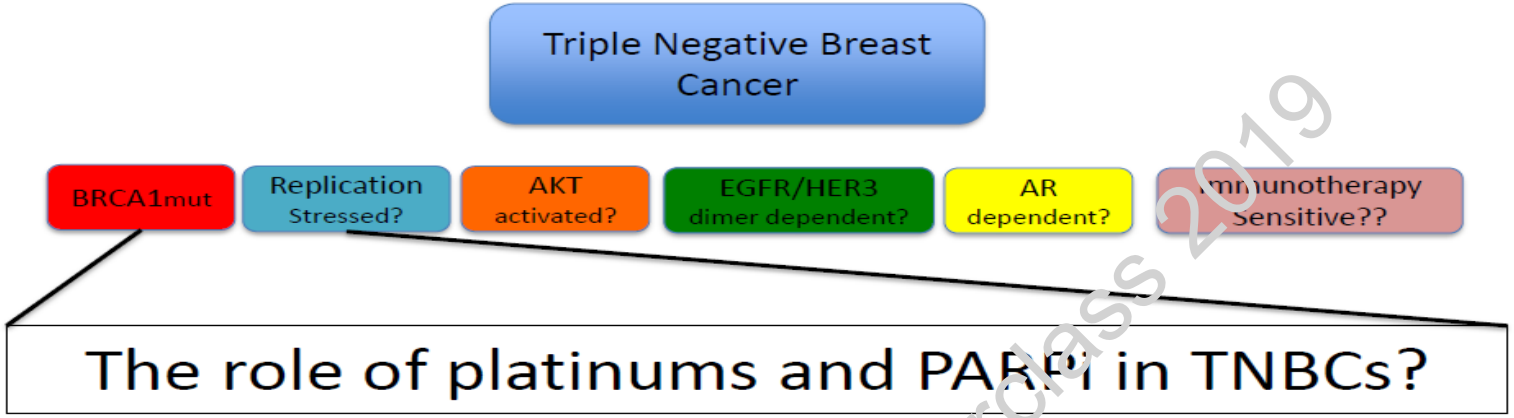
Subtype	Gene expression profile	Clinical
Basal-like 1	high Ki-67; DNA damage response	BRCA-associated
Basal-like 2	GF pathways	Higher pCR
Immunomodulatory	Immune genes	
Mesenchymal	Cell motility	Lower DDFS
Mesenchymal stem-like	Cell motility; claudin-low	
Luminal androgen receptor	Steroid pathways	Apocrine features, higher LRF; PI3Kmut

Lehman BD, et al. J Clin Invest 2011;121:2750-67.

TABLE 1. Efficacy of Standard Anthracycline-Taxane Chemotherapy in TNBC Subtypes[34,35]

Subtype	No. of Patients	pCR, %	95% CI
Basal-like 1	21	52	0.31–0.73
Basal-like 2	8	0	0.00–0.00
Mesenchymal	26	31	0.13–0.48
Mesenchymal stem cell–like	13	23	0.0001–0.45
Immunomodulatory	27	30	0.12–0.46
Luminal AR	20	10	0.03–0.23

Abbreviations: TNBC, triple-negative breast cancer; pCR, pathologic complete response; AR, androgen receptor.



The role of platinums and PARPi in TNBCs?

Adding platinum improves pCR

Table 1. Selected Cb NACT trials in TNBC.

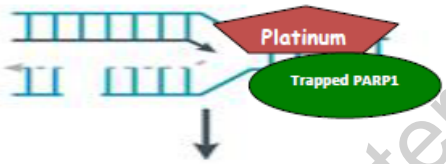
Study [reference]	Study design	Chemotherapy regimen	N	PCR definition used	PCR (%) Control	PCR (%) Platinum
GeparSixto[26]	Randomized phase II	wP + nPLD 20 mg/m² qw + B 15 mg/kg q 3w ± Cb AUC 1.5-2 qw x 18 w	315	ypT0 ypN0	37	53
CALGB 40603[28]	Randomized phase II	wP x 12 ± Cb AUC 6 q 3w x 4 → ddAC x 4 ± B 10 mg/kg q 2w x 9	433	ypT0/is ypN0	41	54
ISPY-2[30]	Randomized phase II	wP x 12 → Cb AUC 6 q 3w x 4 + veliparib → ddAC x 4	60	ypT0/is ypN0	26	51
ADAPT[31]	Randomized phase II	weekly nab-paclitaxel 125 mg/m² + Cb AUC 2 or gemcitabine 1, 000 mg/m² on day 1 and 8 q 3w x 4	336	ypT0/is ypN0	28.7	45.9
Sharma *et al.*[34]	Observational	Cb AUC 6 + Docetaxel 75 mg/m² 3w x 4-6 cycles	76	ypT0/is ypN0	na	66

Abbreviations: AC, doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²; ddAC, dose dense AC; Cb, carboplatin; AUC, area under the curve; B, Bevacizumab; wP, weekly paclitaxel 80 mg/m²; nPLD, non-pegylated-liposomal doxorubicin; pCR, complete pathologic response; na, not available; qw, every week; q 2w, every 2 weeks; q 3w, every 3 weeks; ypT0 ypN0, absence of invasive cancer and *in situ* cancer in the breast and axillary nodes; ypT0/is ypN0, absence of invasive cancer in the breast and axillary nodes, irrespective of carcinoma *in situ*.

Castrellon, A. B., et al. (2017). Oncology reviews, 11(1), 324.

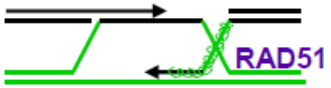
Platinum and PARPi form adducts that also arrest DNA replication forks and require BRCA1/2 for repair

Platinums and PARPi both cause Replication fork arrest and DSBs



DNA replication fork arrest and collapse

Normal BRCA1/BRCA2



HR-based repair

Fork Protection

Chromosome Stability

Cell Survival

BRCA1/BRCA2 failure

Impaired HR repair

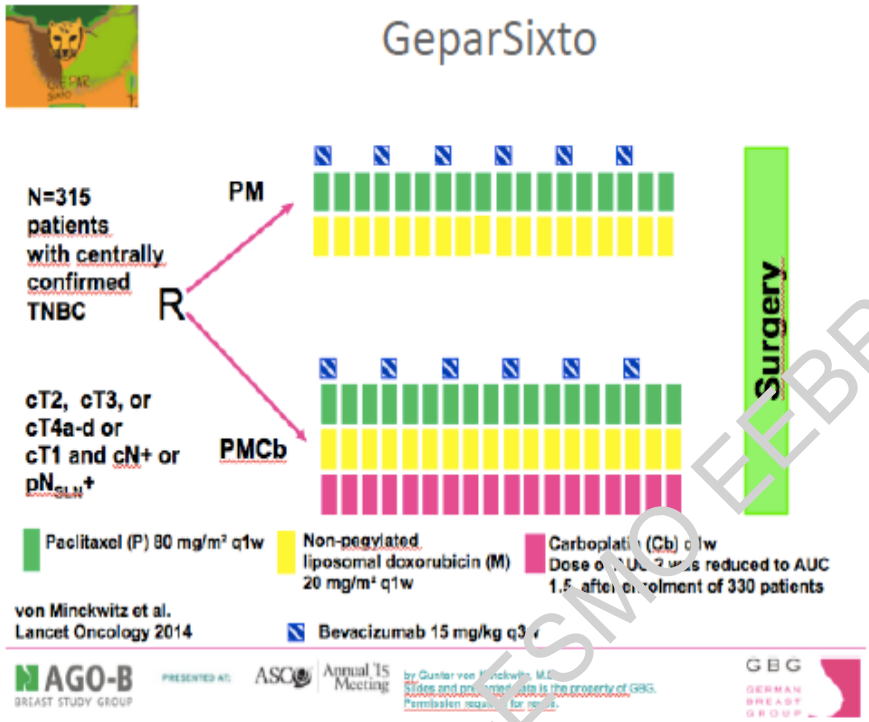
Loss Fork Protection

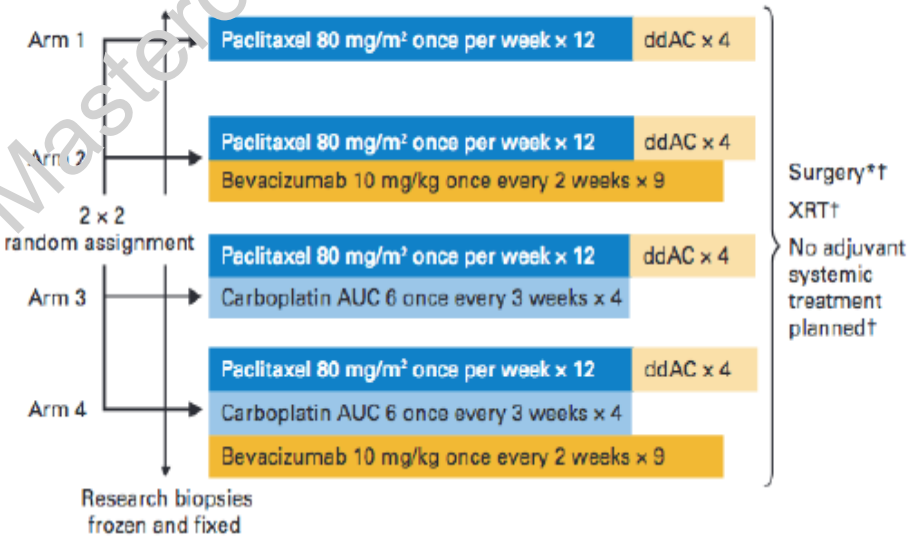
Alternative error prone repair

Chromosomal Instability

Cell Death

Use of platinum in Neoadjuvant therapy in TNBC



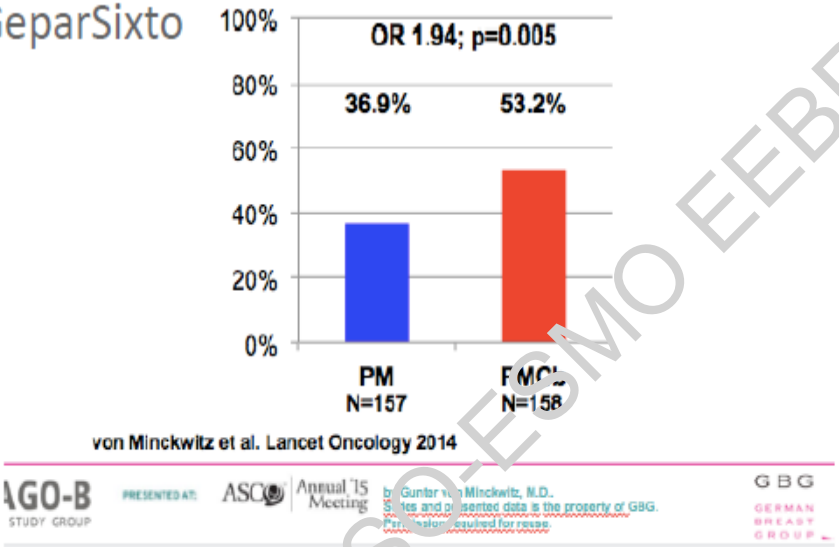


von Minckwitz G, et al. Lancet Oncol 2014

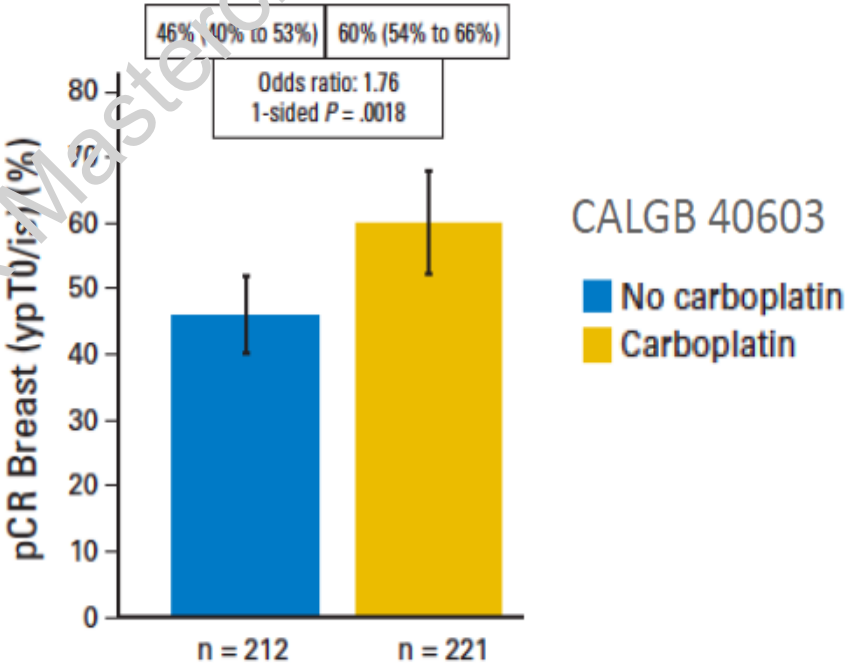
Sikov W, et al. JCO 2014

Carboplatin increases Path CR in TNBC in addition to anthracyclines and taxanes

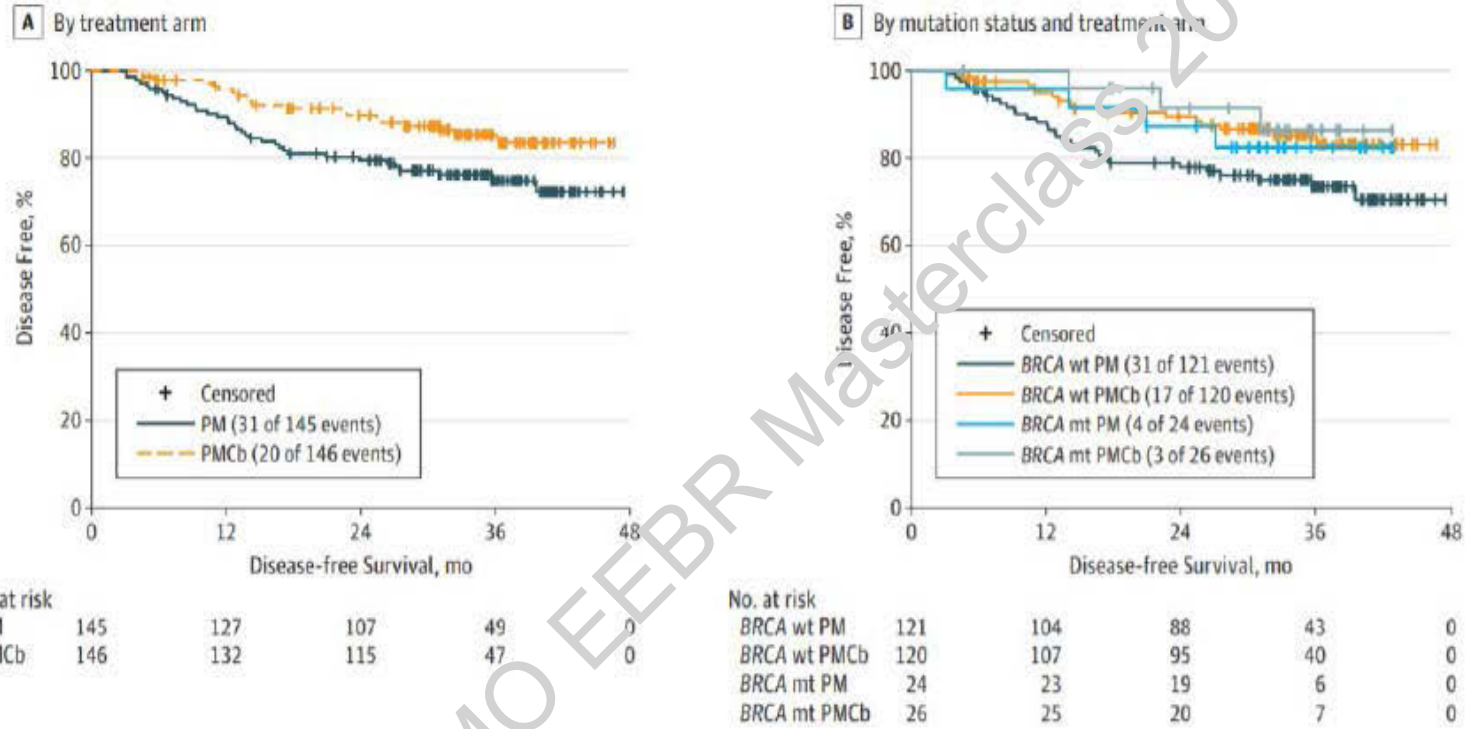
GeparSixto



von Minckwitz G, et al. Lancet Oncol 2014



Sikov W, et al. JCO 2014



A, Disease-free survival by treatment arm. B, Disease-free survival by *BRCA1* and *BRCA2* mutation status and treatment arm. mt Indicates mutant; PM, paclitaxel and myocet; PMCb, paclitaxel, myocet, and carboplatin; and wt, wild-type.

Hahnen et al., JAMA Oncol. 2017;3(10):1378-1385

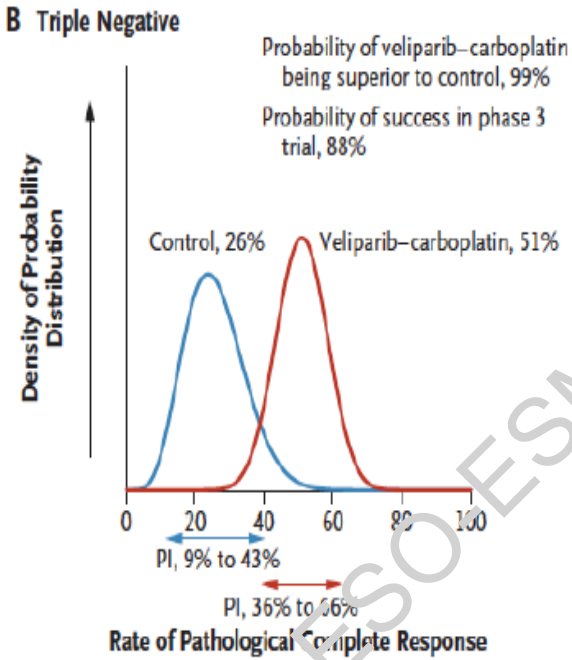
I-SPY2 trial

Paclitaxel then AC
vs
Paclitaxel/Veliparib/Carbo then AC

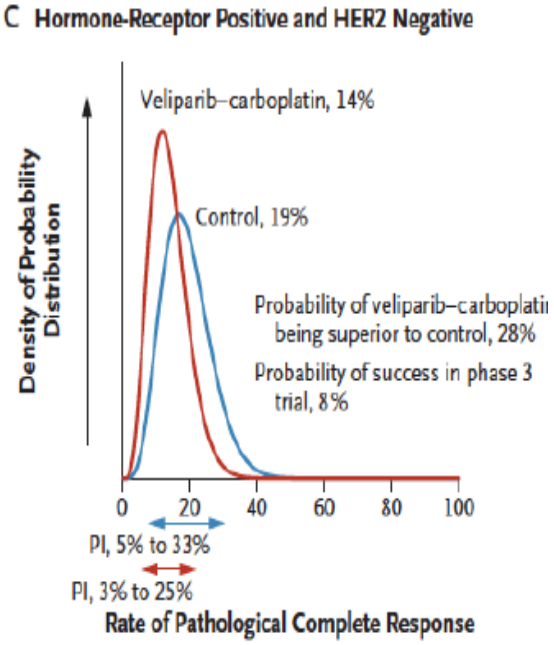
ORIGINAL ARTICLE

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

H.S. Rugo, O.I. Olopade, A. DeMichele, C. Yau, L.J. van 't Veer, M.B. Buxton, M. Hogarth, N.M. Hylton, M. Paoloni, J. Perlmutter, W.F. Symmans, D. Yee, A.J. Chien, A.M. Wallace, H.G. Kaplan, J.C. Boughey, T.C. Haddad, K.S. Albain, M.C. Liu, C. Isaacs, Q.J. Khan, J.E. Lang, R.K. Viscusi, L. Pusztai, S.L. Moulder, S.Y. Chui, K.A. Kemmer, A.D. Elias, K.K. Edmiston, D.M. Euhus, B.B. Haley, R. Nanda, D.W. Northfelt, P. Kunkel, W.C. Wood, C. Ewing, R. Schwab, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, D.A. Berry, and L.J. Esserman, for the I-SPY 2 Investigators*

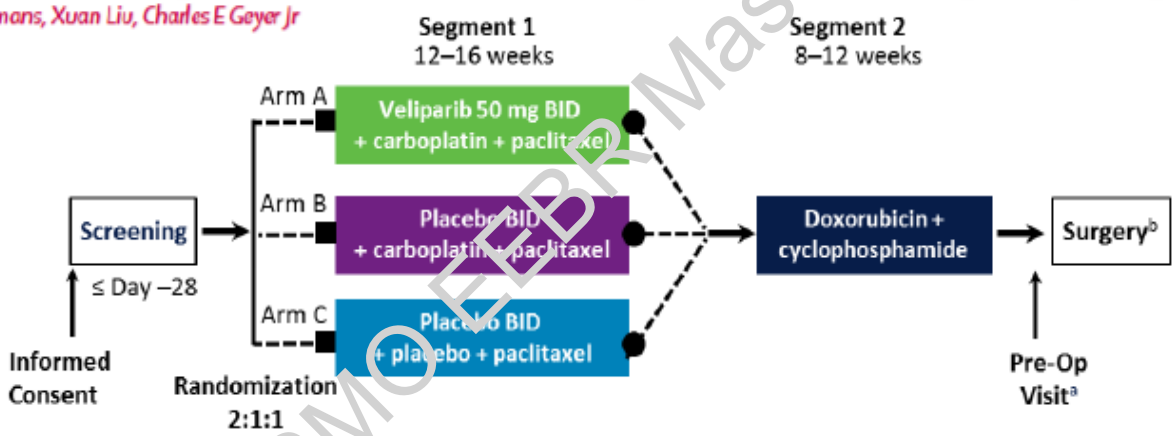


This PARPi (veliparib) / carboplatin regimen graduated I-SPY2 neoadjuvant platform with TNBC as the selection biomarker



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



634 pts 2:1:1 Carbo AUC6 Q21

15% gBRCA Paclitaxel 80mg/m2 wkly

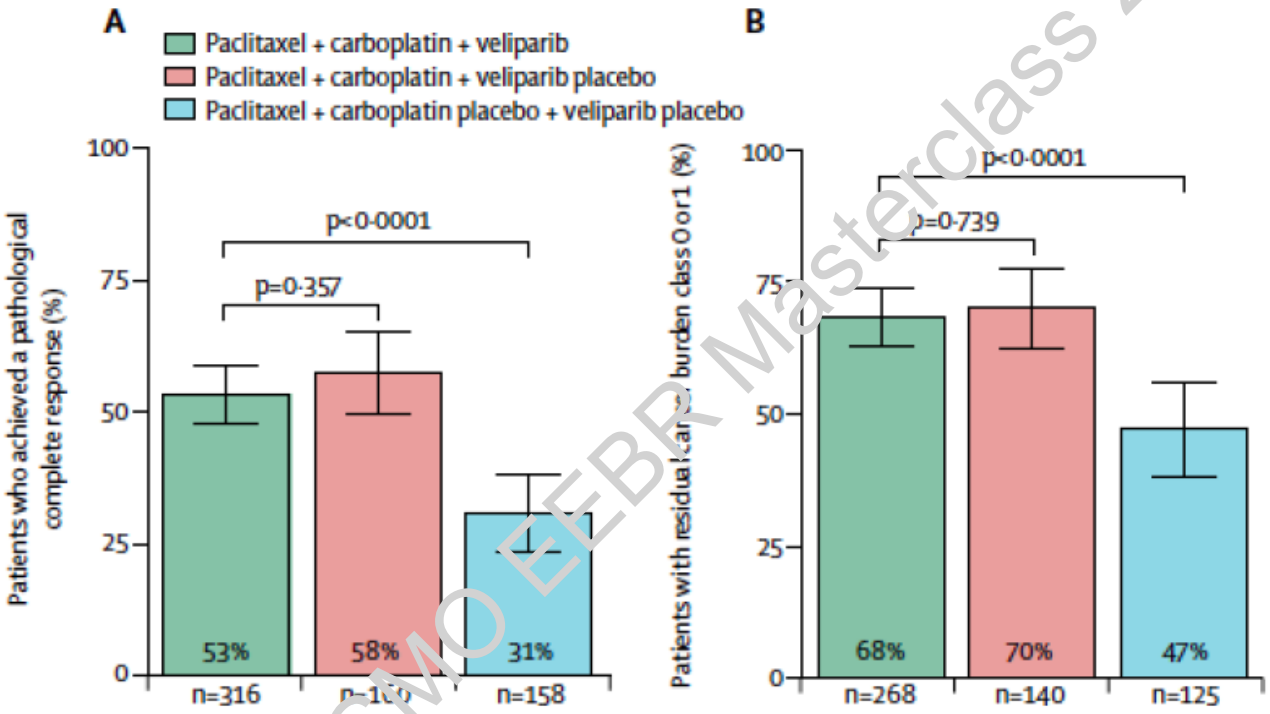
■ = first day of treatment with veliparib/placebo + carboplatin/placebo + paclitaxel

● = last dose of veliparib/placebo + carboplatin/placebo + paclitaxel

[a] Performed at least 2 weeks after last chemotherapy treatment.

[b] Surgery (+/- radiotherapy) was recommended approximately 2–8 weeks after last chemotherapy treatment.

Carboplatin is the main driver of increase in pathological response in I-SPY2 regimen



Neoadjuvant Talazoparib for Early Stage Breast Cancer Patients with a BRCA Mutation

JK Litton, M Scoggins, KR Hess, B Adrada, CH Barcenas, RK Murthy, S Damodaran, SM DeSnyder, AM Brewster, AM Thompson, GJ Whitman, NK Ibrahim, V Valero, SL Moulder, J Schwartz-Gomez, EA Mittendorf and BK Arun

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Study Design

*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

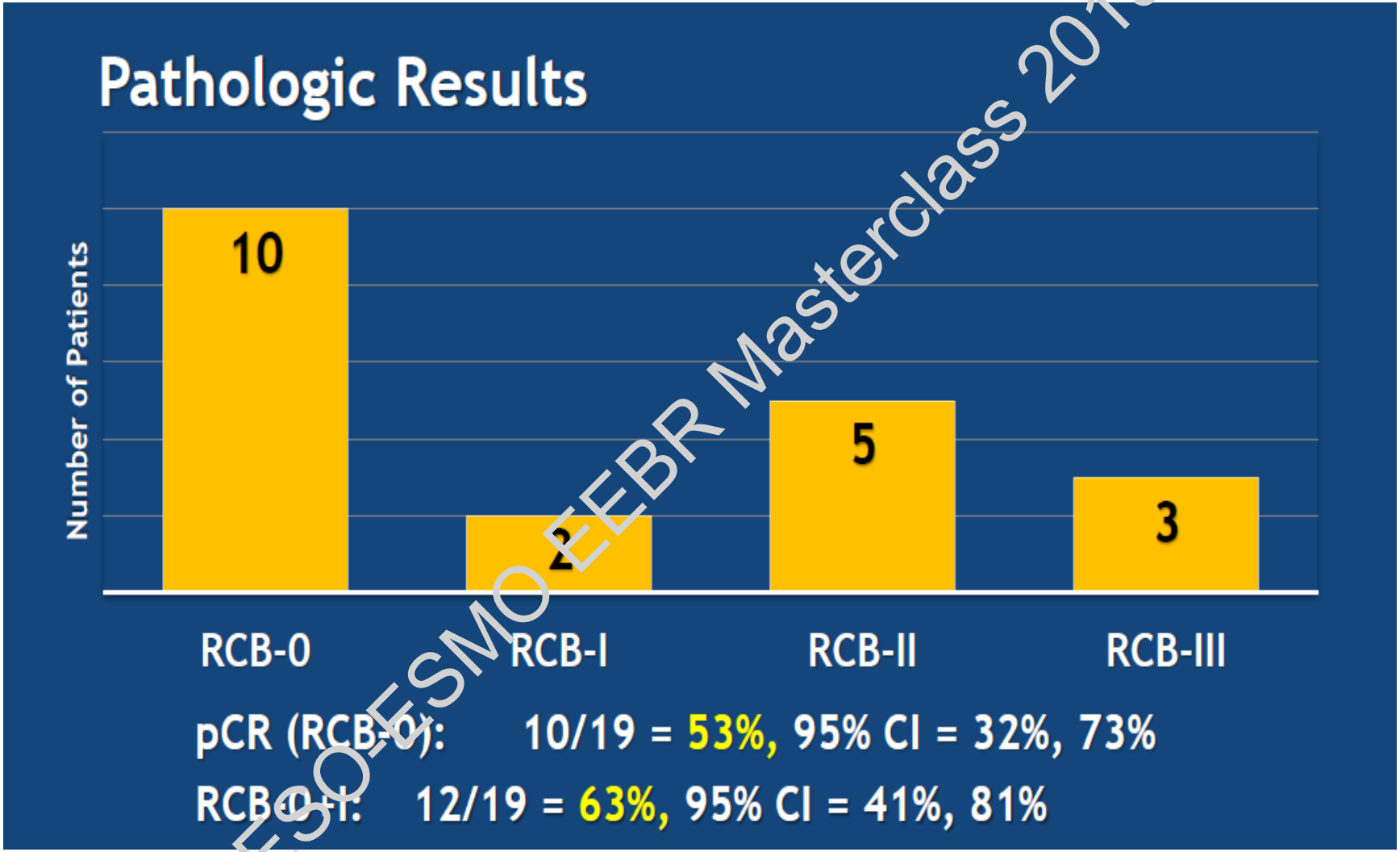
- HER2 positive

Primary Objectives

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

Secondary Objective

- Evaluate toxicity

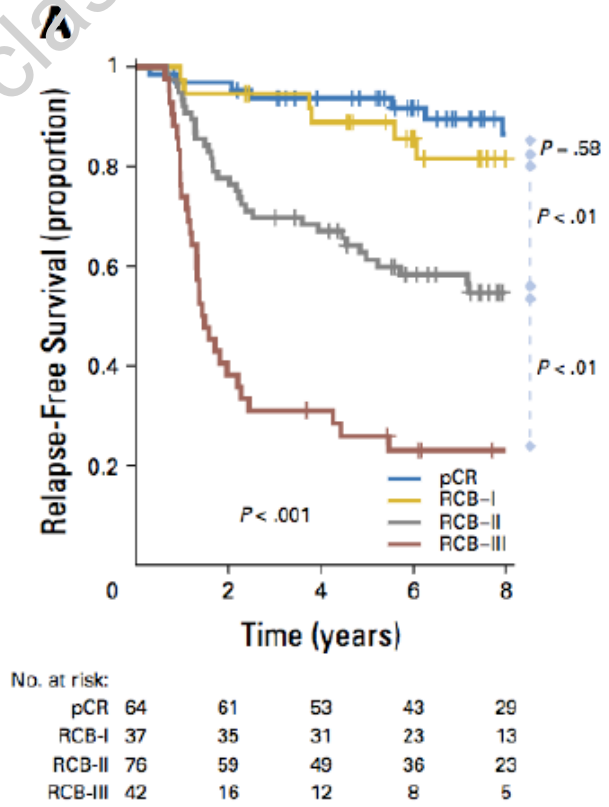


New Diagnosis

Neoadjuvant Rx

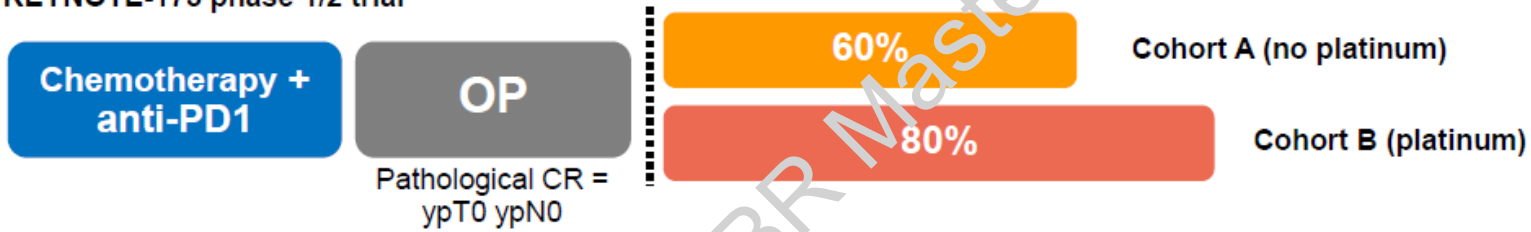
Post-Rx residual disease

Definitive Surgery



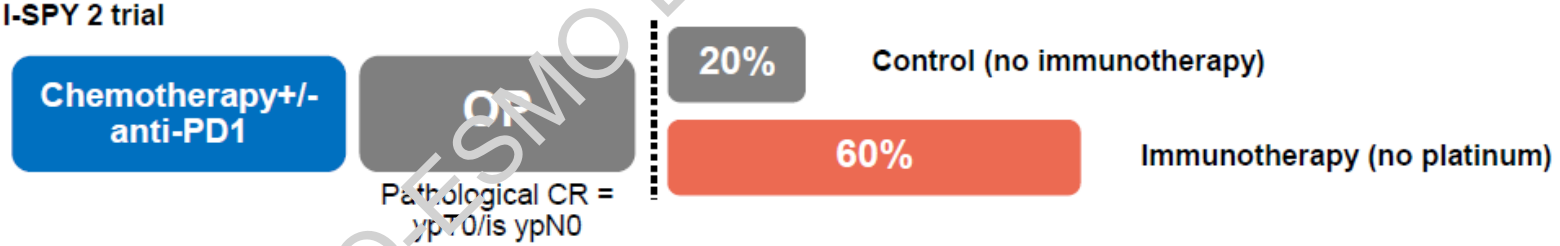
Neoadjuvant Chemo + anti-PDL1/anti-PD1 in TNBC

KEYNOTE-173 phase 1/2 trial



Paclitaxel Q1W x12 ± carboplatin Q1W x12 + pembrolizumab Q3W x4 → AC Q3W x4 + pembrolizumab Q3W x4

I-SPY 2 trial



Paclitaxel Q1W x12 + pembrolizumab Q3W x4 → AC Q3W x4

AC, doxorubicin + cyclophosphamide; CR, complete response; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; Q1W, every week; Q3W, every 3 weeks; ypT0/Tis ypN0, no invasive residual in breast or nodes - noninvasive breast residuals allowed; ypT0 ypN0, no invasive or noninvasive residual in breast or nodes

Schmid, et al. ASCO 2017;
Nanda, et al. ASCO 2017

TABLE 2. Selected Trials Evaluating the Efficacy of the Addition or Substitution of New Agents to Standard Anthracycline-Taxane Chemotherapy on pCR in TNBC

Trial	Arms	pCR	p Value
Calgb 40603[39] (443 Patients)	P → AC	41%	p = .0029
	PCb →AC	54%	
Geparsixto[40] (296 Patients)	PMB	36.9%	p = .005
	PMBCb	53.2%	
I-Spy 2: Veliparib-Carboplatin Arm[42] (116 Patients)	P → AC	26%	N/A
	PVCb → AC	51%	
I-Spy 2: Pembrolizumab Arm[43] (249 Patients)	P → AC	20%*	N/A
	PPemb → AC	60%*	
Geparsepto[37] (276 Patients With Tnbc)	P → EC	26%*	p < .001
	*nab*P → EC	48%*	
Etna[38] (219 Patients)	P → AC/EC/FEC	37.3%	NS
	*nab*P → AC/EC/FEC	41.3%	

*Estimated pCR.

Abbreviations: pCR, pathologic complete response; TNBC, triple-negative breast cancer; P, paclitaxel; AC, adriamycin-cytoxan; Cb, carboplatin; M, nonpegylated liposomal doxorubicin; B, bevacizumab; V, veliparib; pemb, pembrolizumab; nabP, nab paclitaxel; EC, epirubicin-cytoxan; FEC, 5-fluorouracil, epirubicin, cytoxan; N/A, nonapplicable; NS, nonsignificant.

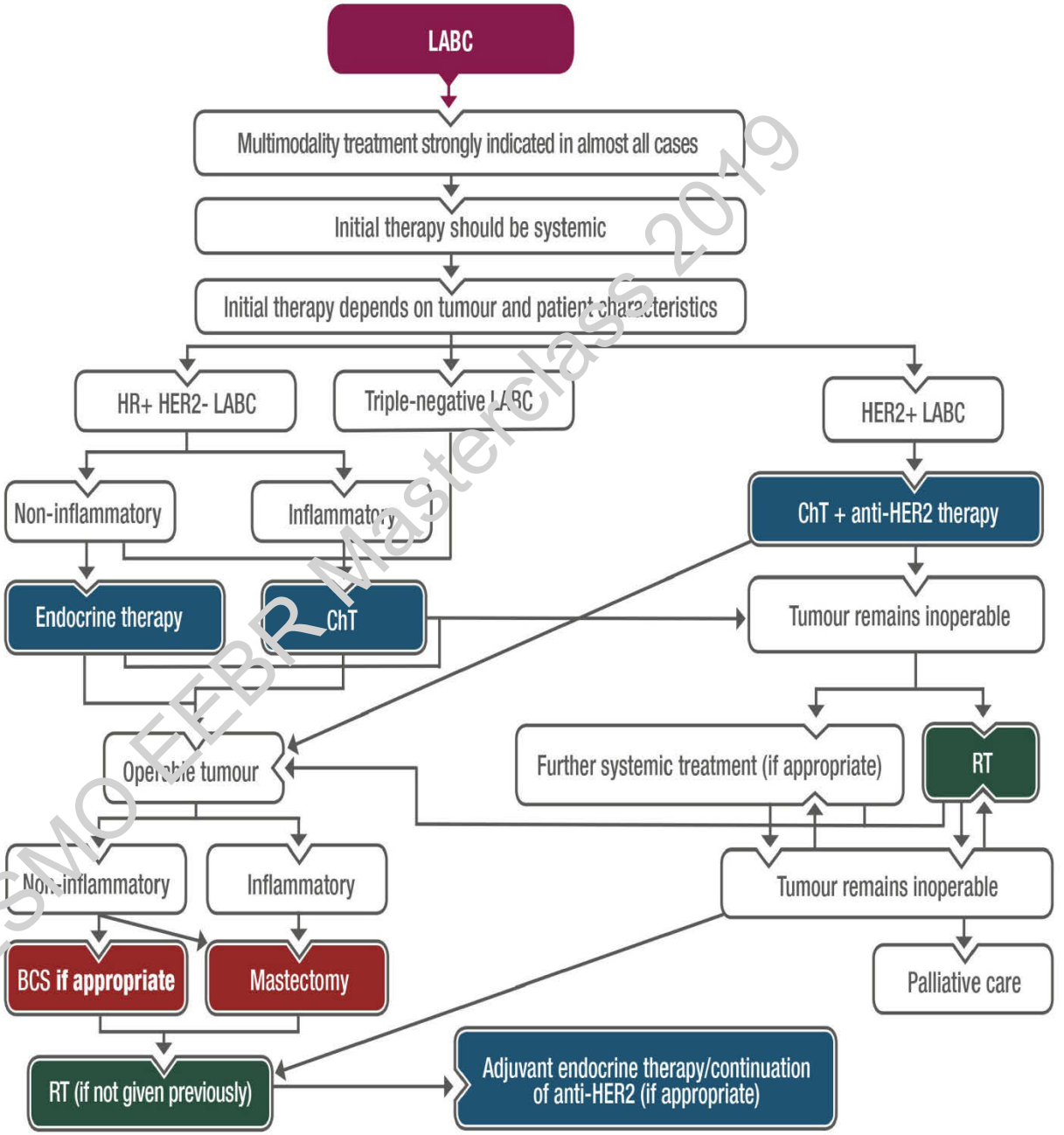
Guideline statement	LoE/GoR	Consensus
For **triple-negative LABC**, anthracycline- and taxane-based ChT is recommended as initial treatment.	I/A	85%

Guideline statement	LoE/GoR	Consensus
If LABC remains inoperable after systemic therapy and eventual RT, 'palliative' mastectomy should not be done, unless the surgery is likely to result in an overall improvement in QoL.	Expert opinion/ D	100%
Following effective neoadjuvant systemic therapy with or without RT, surgery will be possible in many patients. This will consist of mastectomy with axillary dissection in the majority of cases, but in selected patients with a good response, BCS may be possible.	II/A	98%
In patients with axillary low burden of disease at presentation (previously cN0-cN1) with complete response after systemic treatment (ycN0), sentinel lymph node biopsy can be an option, provided all the recommendations for sentinel node after primary systemic treatment are followed (i.e. dual tracer, clipping/marking positive nodes, minimum of three sentinel nodes).	III/B	62%

Guideline statement	LoE/GoR	Consensus
Inflammatory LABC		
For inflammatory LABC, overall treatment recommendations are similar to those for non-inflammatory LABC, with systemic therapy as first treatment.	I/A	93%
Mastectomy with axillary dissection is recommended in almost all cases, even when there is good response to primary systemic therapy.	I/A	95%
Immediate reconstruction is generally not recommended in patients with inflammatory LABC.	IV/E	95%
Locoregional RT (chest wall and lymph nodes) is required, even when a pCR is achieved with systemic therapy.	I/A	98%

CLINICAL PRACTICE GUIDELINES

Treatment of LABC



ESMO

Take home message

- Despite extensive clinical investigations, it has not yet been clarified whether preoperative systemic therapy would results in improved survival in comparison with the standard adjuvant therapy in any subgroup of patients. Randomized trials have demonstrated equivalent mortality for pre or postoperative application of systemic therapy
- Pateints with triple-negative/TNBC/, HER-2 positive, or ER/PgR positive/HER-2 negative(high-grade G3) breast cancer /depending on size, nodal status, comorbidity/ have the the highest probability of therapeutic response
- NAT can significantly impact surgical treatment and facilitates BCS
- pCR can be used as an endpoint for early drug approval
- NAT offers great advantages for new drug development in breast cancer and for individual investigations into the mechanism of action of drugs
- Sequential biopsies could help to identify biomarkers of treatment resistance/response
- Concernig chemotherapy an anthracycline/cyclophosphamide/taxane regimens is the standard of care. A dose-dense anthracycline regimen may be used in patients with high-grade or hormone receptor-negative tumors.

Further Reading:

Early Breast Cancer Trialists' Collaborative Group/EBCTCG/. Long-therm outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis in individual patients data from ten randomised trials. Lancet Oncol 2018;19:27-39.

Cortazar P, Zhang L, Untch M,et al.: Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384:164-172.

Denduluri N, Miller K, O'Regan R.M. Using Neoadjuvant Approach for Evaluating Novel Therapies for Patients with Breast Cancer. 2018: ASCO Educational Book 47-55.

Reyal F, Hamy A.S, Piccart M. Neoadjuvant treatment: the future of patients with breast cancer. ESMO Open 2018;3:e000371.doi:10.1136/esmoopen-2018-000371

Vaidya J.S, Massarut S, Vaidya H.J et al.: Rethinking neoadjuvant chemotherapy for breast cancer. BMJ 2018;360:j5913

Schneeweiss A, Chia s, Hickish T. Et al.Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol.2013:2278-2284,2013

Gianni L, Pienkowski T, Im J.H et al.:5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016 17(6):791-800.

Hahnen E, Lederer B, Hauke J. Et al. Germline mutation status, pathological complete response, and disease-free survival in triple-negative breast cancer: secondary analysis of tge GeparSixto randomised clinical trial. JAMA oncol.2017;3:1378-85

Sikov WM ,Berry DA ,Perou CM et al.Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance).*J Clin Oncol.* 2015; 33: 13-21

Colomber R, Saura C, Sanchez-Rovira P. et al.: Neoadjuvant Management of Early Breast Cancer: A Clinical and Investigational position statement. The Oncologist 2019;24:1-9.