IEO
Istituto Europeo di Oncologia

(Neo)-Adjuvant Chemotherapy in triple negative early breast cancer

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IBCSG

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

BIG against breast cancer

Outline

- Neoadjuvant treatment in triple negative early breast cancer
- Picking optimal adjuvant chemotherapy for TN early breast cancer

(Neo)Adjuvant therapy in TN EBC

- Who needs more treatment?
- Addition of carboplatin
- Nab-paclitaxel ready for prime time?
- Tumor infiltrating lymphocytes
- Post-neoadjuvant setting

Treatment-oriented classification of sub-groups of breast cancer

Clinical grouping	Notes
Hormone receptor-positive & HER2– a spectrum	ER and/or PgR positive >= 1%[1]
• **high receptor, low proliferation, low burden ("luminal A-like")**	Multi-parameter molecular marker "good" if available. High ER/PgR and clearly low Ki-67. Low or absent nodal involvement (N 0-3), smaller T size (T1 T2)
• **intermediate**	Among multi-parameter molecular markers, only the 21 gene RS reports an intermediate value. Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies.
• **low receptor, high proliferation, high burden ("luminal B-like")**	Multi-parameter molecular marker "bad" if available. Lower ER/PgR with clearly high Ki-67. More extensive nodal involvement, histological grade 3, extensive lymphovascular invasion, larger T size (T3)

Treatment-oriented classification of sub-groups of breast cancer

- ER values between 1% and 9% were considered equivocal. Thus endocrine therapy alone cannot be relied upon for patients with these values.

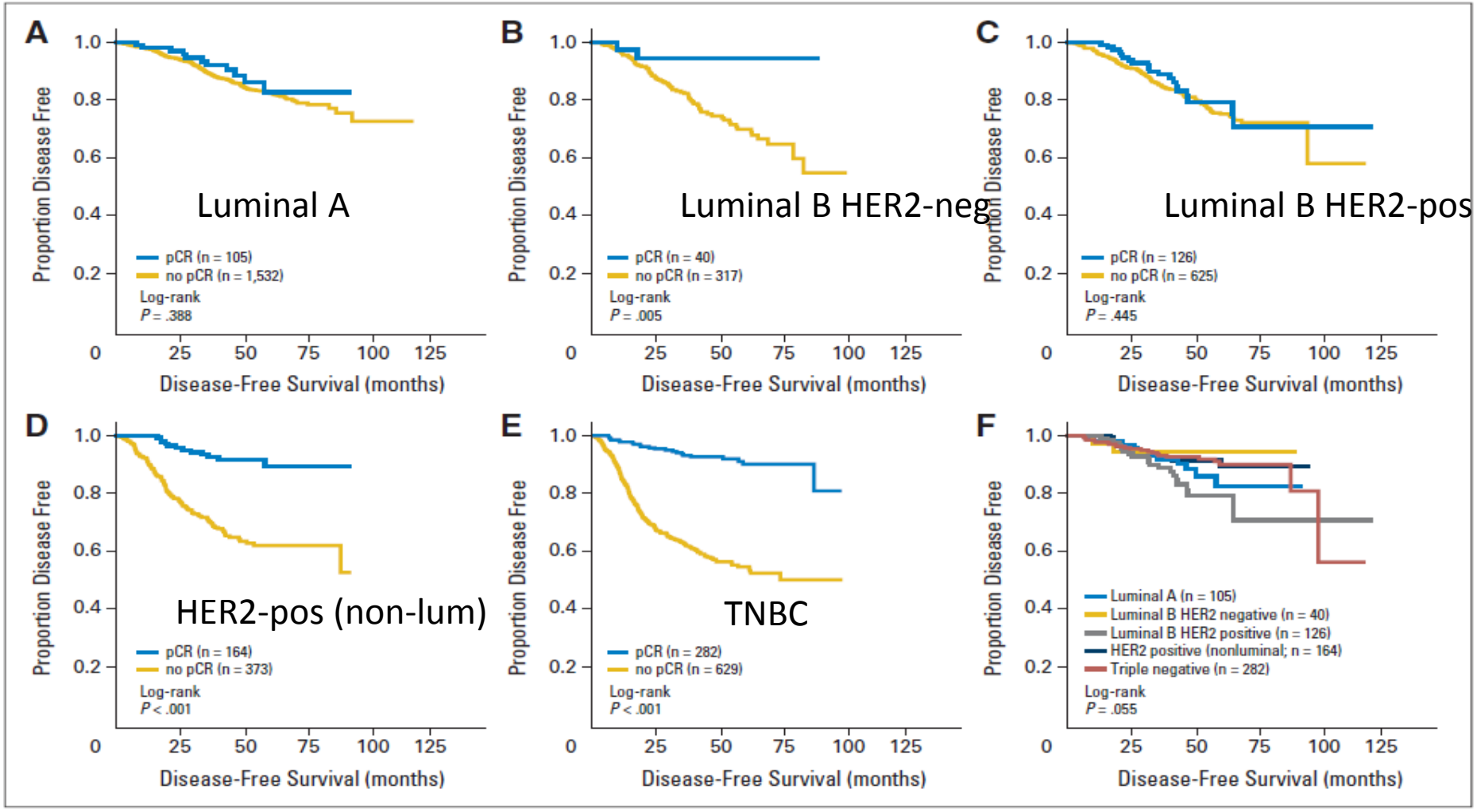
News and Progress Neoadjuvant

Field or Treatment	Status of research/implications for patient care
Neoadjuvant systemic therapies	An improved pCR rate was observed with carboplatin for patients with triple negative disease. Such improvement was not observed for HER2-positive disease. An improved pCR was also observed in triple negative breast cancer using nab-paclitaxel instead of solvent-based paclitaxel. pCR rates were higher in patients with lymphocyte predominant breast cancer, either triple negative or HER2-positive, who were treated with carboplatin.

FDA statement on pCR

- The absence of any residual invasive cancer on H&E evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of neoadjuvant systemic therapy (i.e., ypT0 ypTis ypN0 in the current AJCC staging system).
- This definition resumes the current understanding of major features of the intrinsic biology of early-stage breast cancer

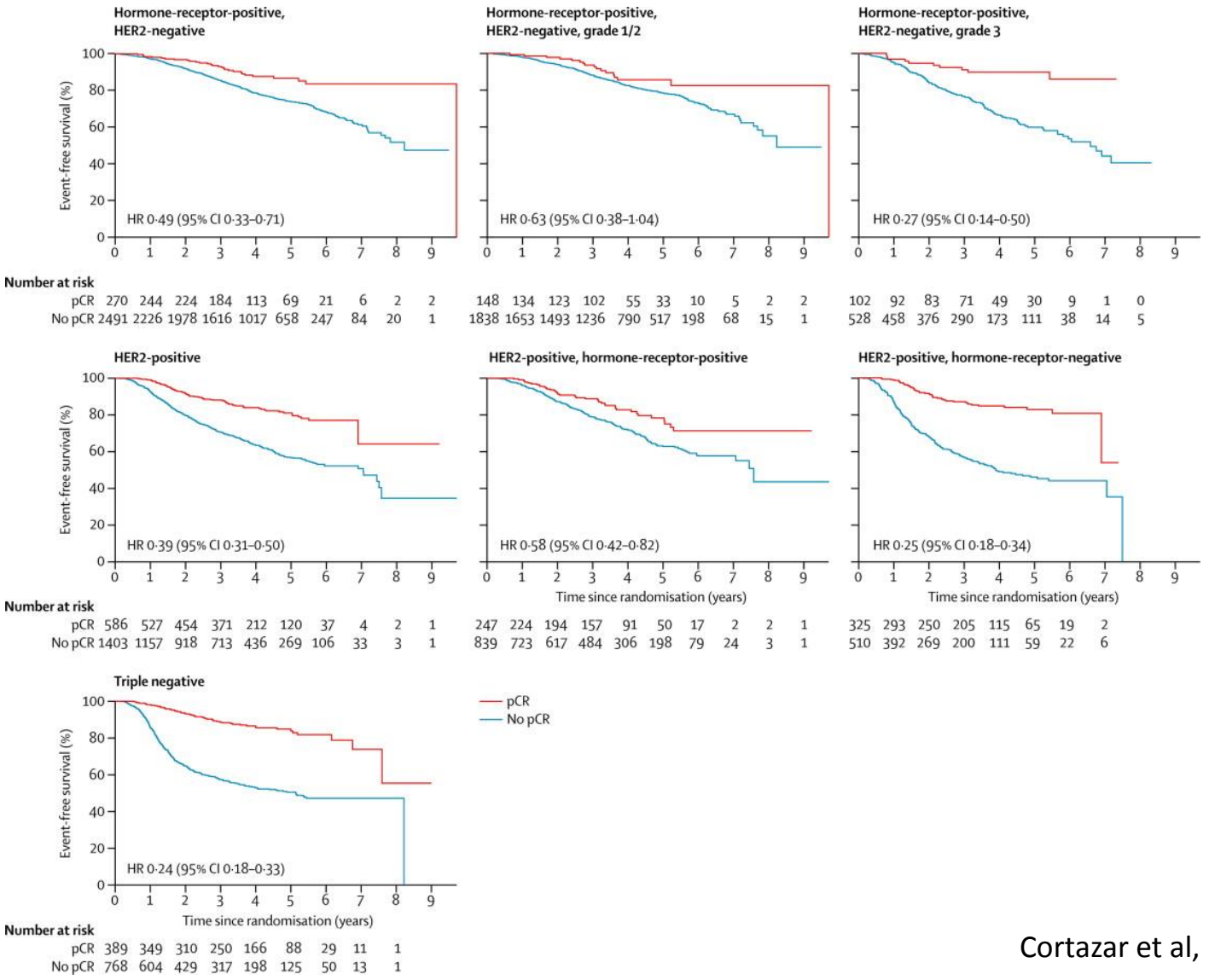
pCR as surrogate for survival



von Minckwitz G et al, J Clin Oncol 2012

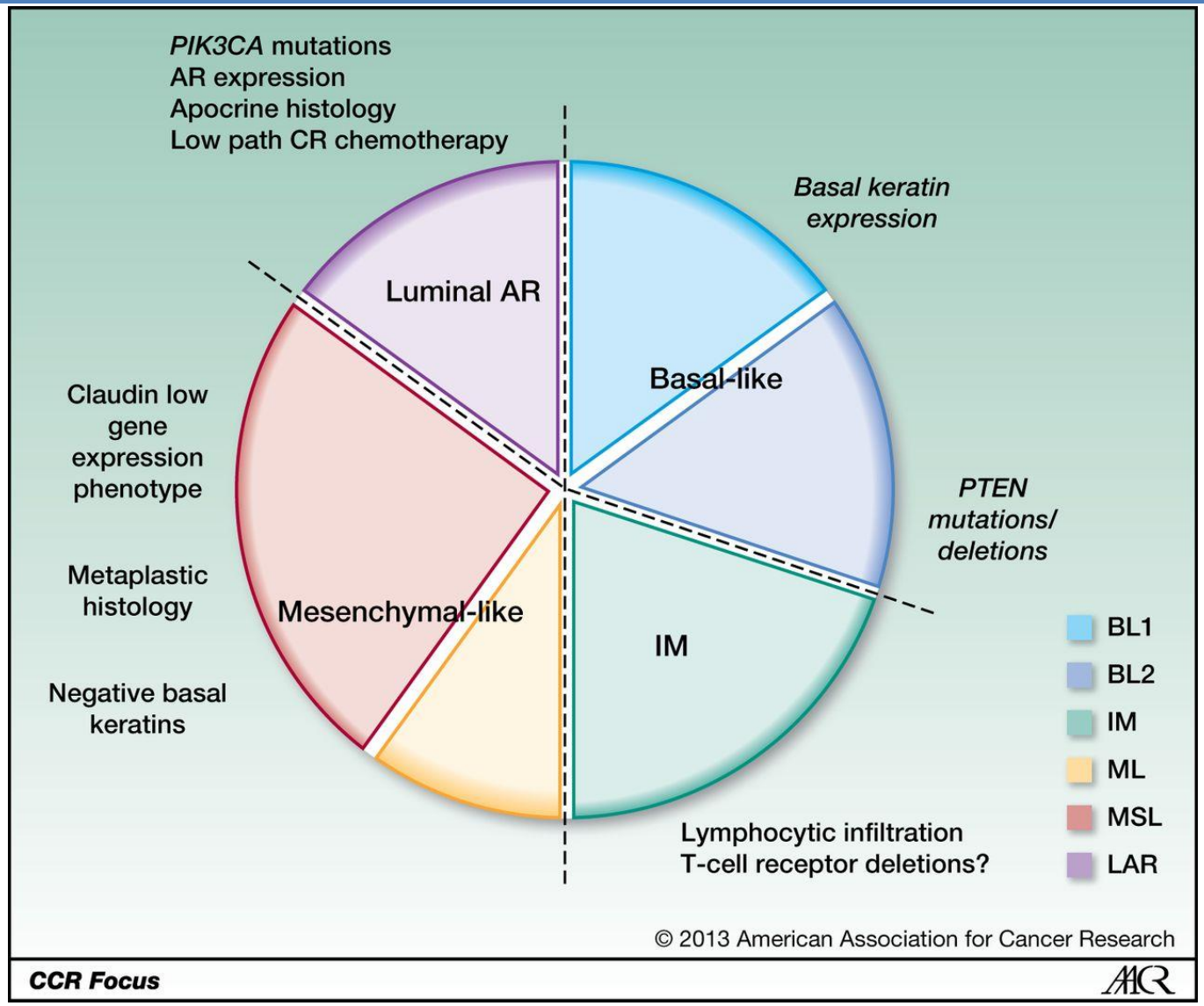
pCR as surrogate for survival

(N=11,955)



Cortazar et al, Lancet 2014

Targeting heterogeneity of TNBC



BL1, basal-like 1;
BL2, basal-like 2;
IM, immunomodulatory;
ML, mesenchymal-like;
MSL, mesenchymal stem-like;
LAR, luminal androgen receptor;
AR, androgen receptor;

Nicholas C. Turner, and Jorge S. Reis-Filho Clin Cancer Res 2013;19:6380-6388

Outcome of Neoadjuvant Therapy in Patients with BRCA Mutations

n = 90 treated with non-platinum regimens
Approximately 85% triple negative

Group	# path CR/# total	%
Overall	14/90	16%
CMF	1/14	7%
Adria/Docetaxel	2/25	8%
AC or FAC	11/51	22%

- MD Anderson retrospective series demonstrated path CR of 46% (26/57) in BRCA carriers.

Byrski et al, JCO 2010 and Arun et al JCO 2011

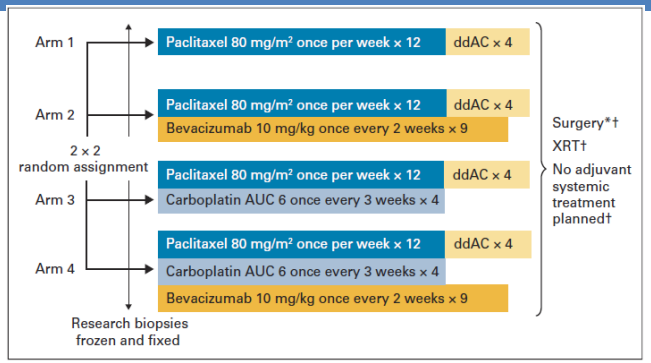
What About Tumors in Patients with Inherited BRCA Mutation?

- 107 patients with *BRCA1* mutations
- Stage I-III disease
- Treatment:
  - Preoperative Cisplatin 75 mg/m^2 q 3 weeks x 4
  - Mastectomy
- Path CR defined as no invasive tumor in breast/nodes

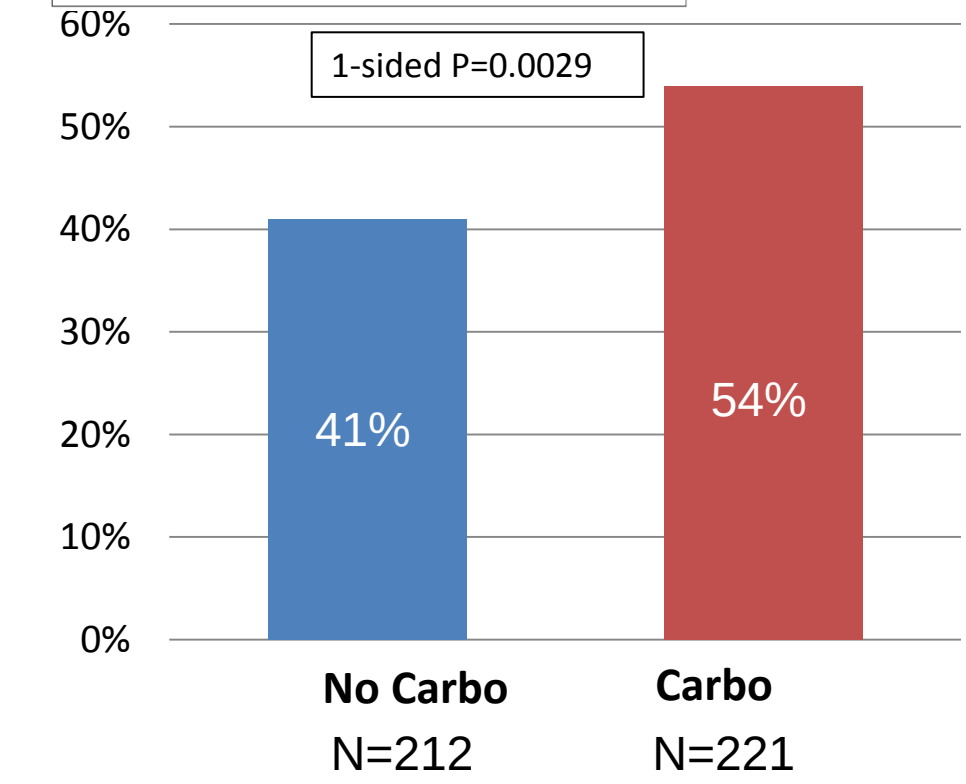
Pathologic complete response = 61%

Byrski et al. Breast Cancer Research and Treatment 2014 and Arun et al, JCO 2011

Platinum-based neoadjuvant chemotherapy for triple-negative breast cancer

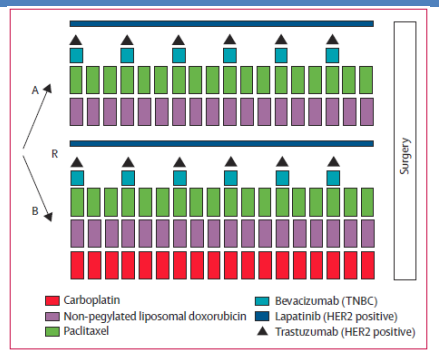


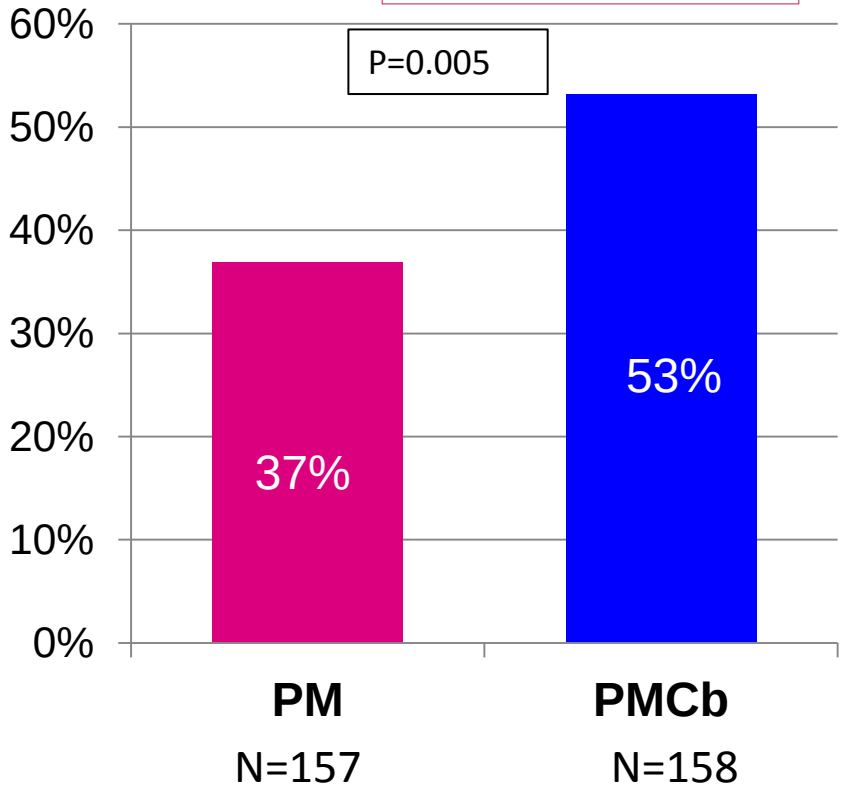
CALGB 40603



Sikov W, et al. J Clin Oncol 2014

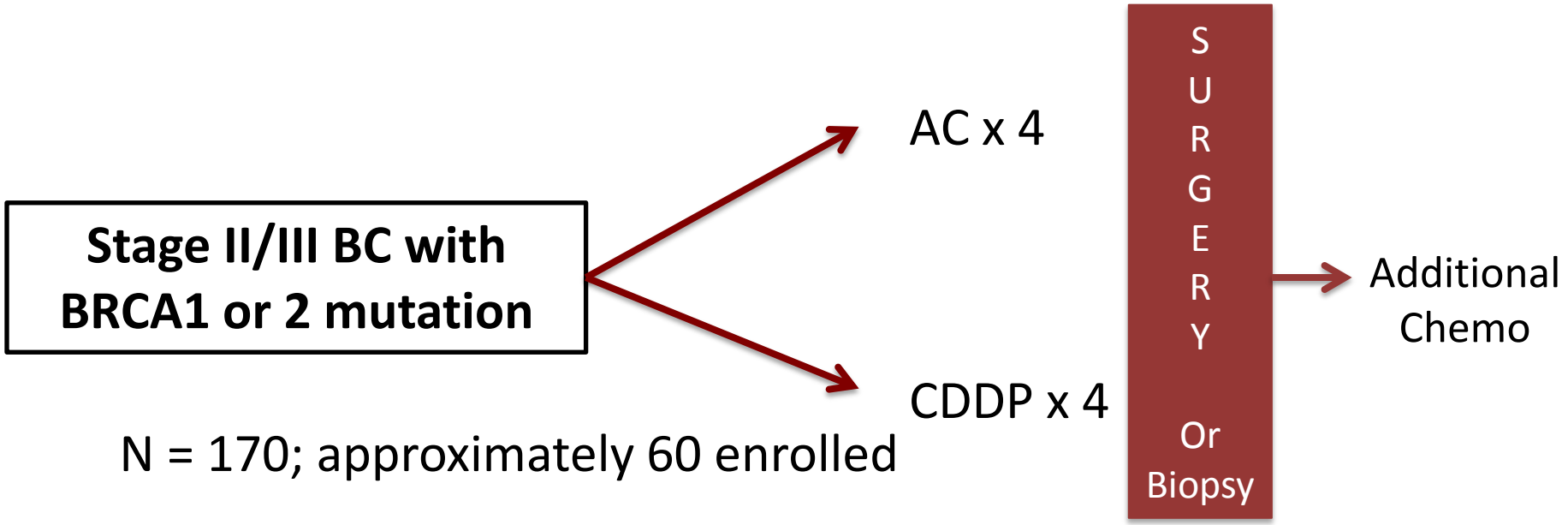
GeparSixto





von Minckwitz G, et al. Lancet Oncol 2014

INFORM: preop cisplatin vs AC for BRCA 1/2 carriers



N = 170; approximately 60 enrolled

- Multicenter study
- Designed to show 20% improvement in pCR with cisplatin over AC

Principal Investigators:
Nadine Tung and Judy Garber
TBCRRC and other sites

Do We Have Sufficient Data To Incorporate Platinum in Treatment of BRCA Carriers with TNBC?

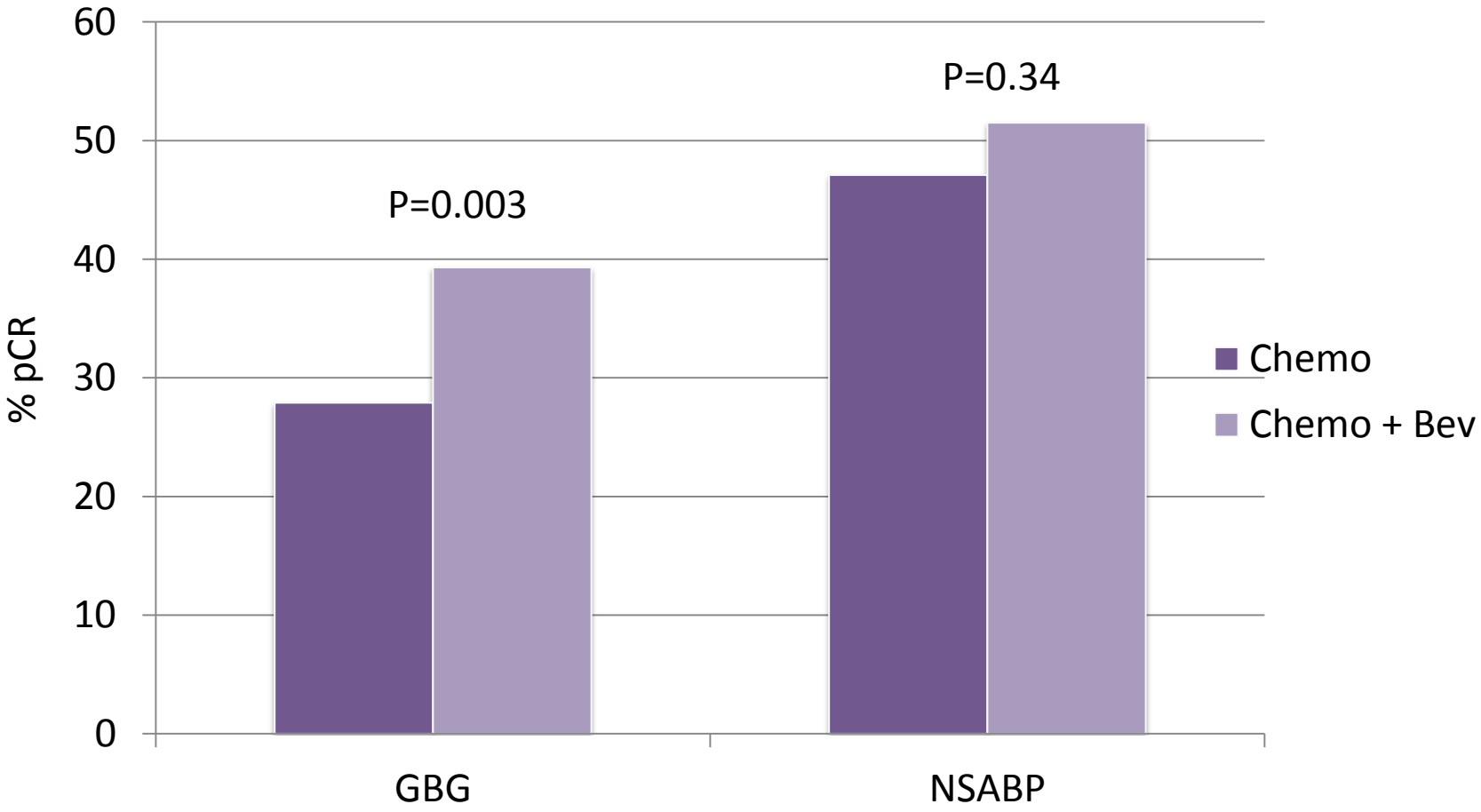
- May never have large, definitive trial
- Mounting evidence in neoadjuvant and metastatic settings
- Biology is consistent with clinical observations
- Probably ready or close to it – ideally would like to see results of neoadjuvant INFORM trial
- How do we do it? Add to standard? Substitute for one or more agents?

Is Carboplatin Ready for Primetime in Unselected TNBC in the Adjuvant or Neoadjuvant Setting?

NO

- Need definitive study showing improvement in DFS and/or OS
- If platinum is ultimately used, should it be added to standard therapy or substituted for one or more drugs?
- Are there triple negative subtypes that are particularly sensitive to platinum salts?

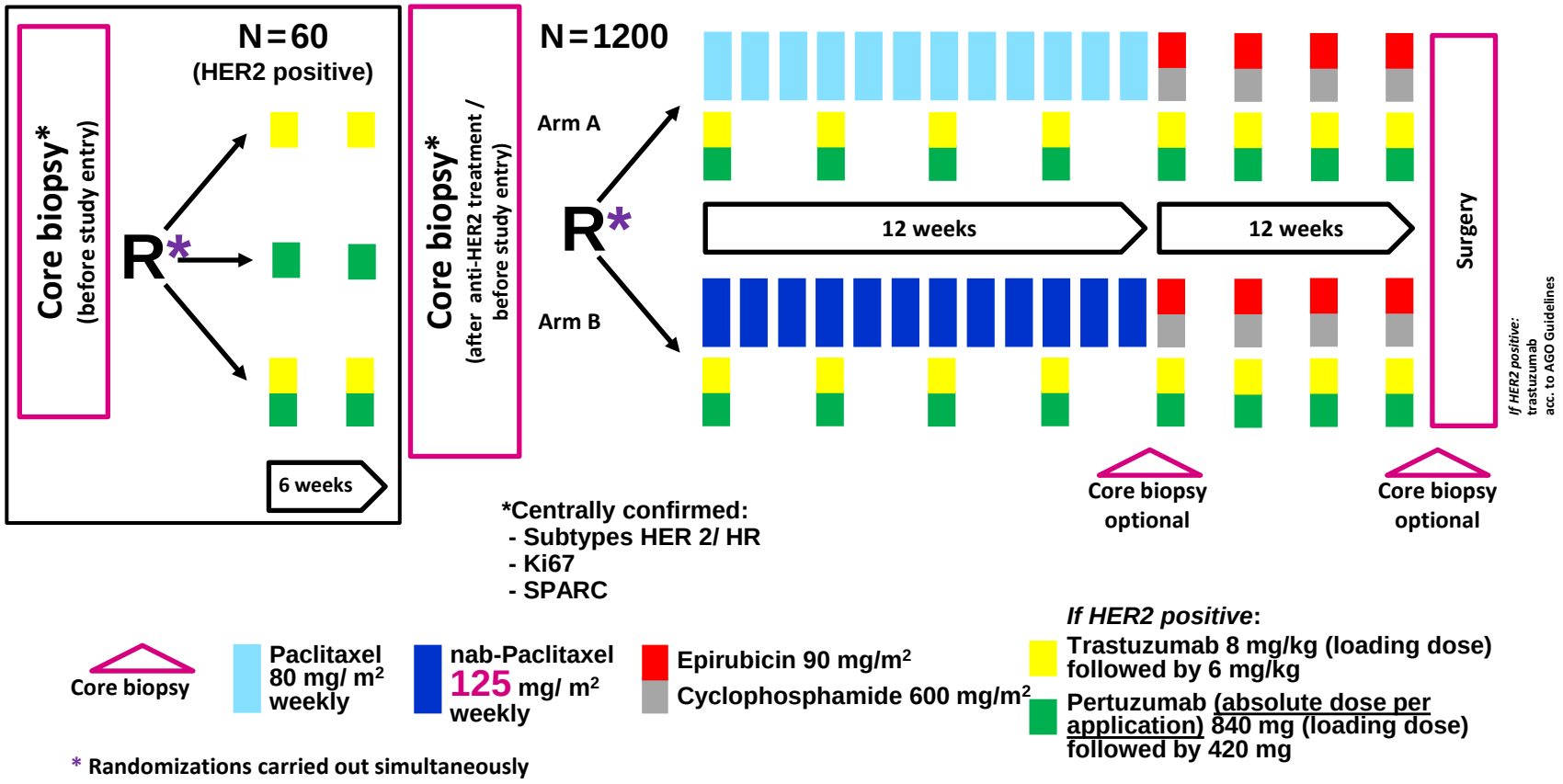
Neoadjuvant chemotherapy plus bevacizumab for triple-negative breast cancer



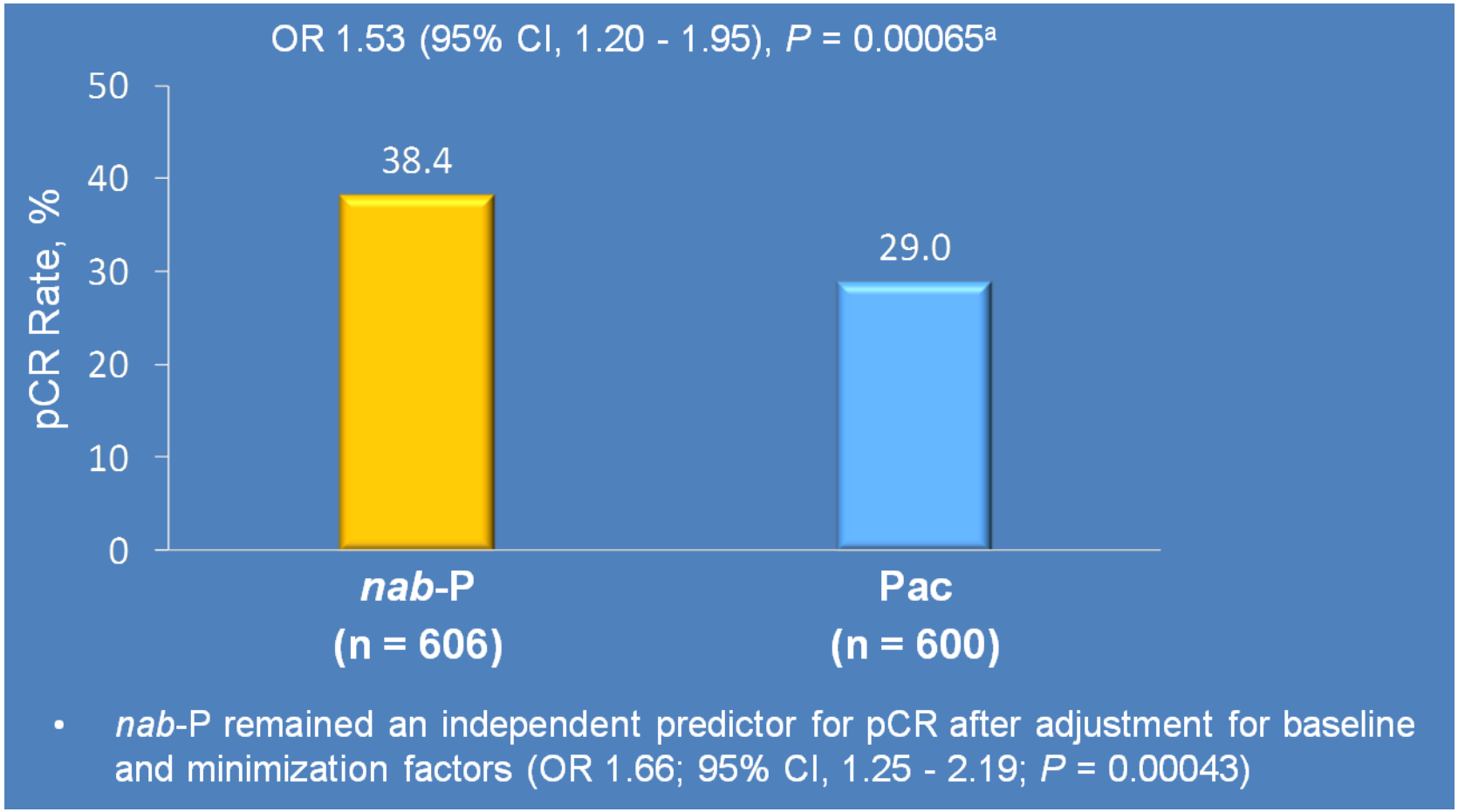
Von Minckwitz G, et al. NEJM 2012:366;299-309

Bear HD, et al. NEJM 2012:366;310-320

Neoadjuvant nabpaclitaxel for triple-negative breast cancer Geparsepto



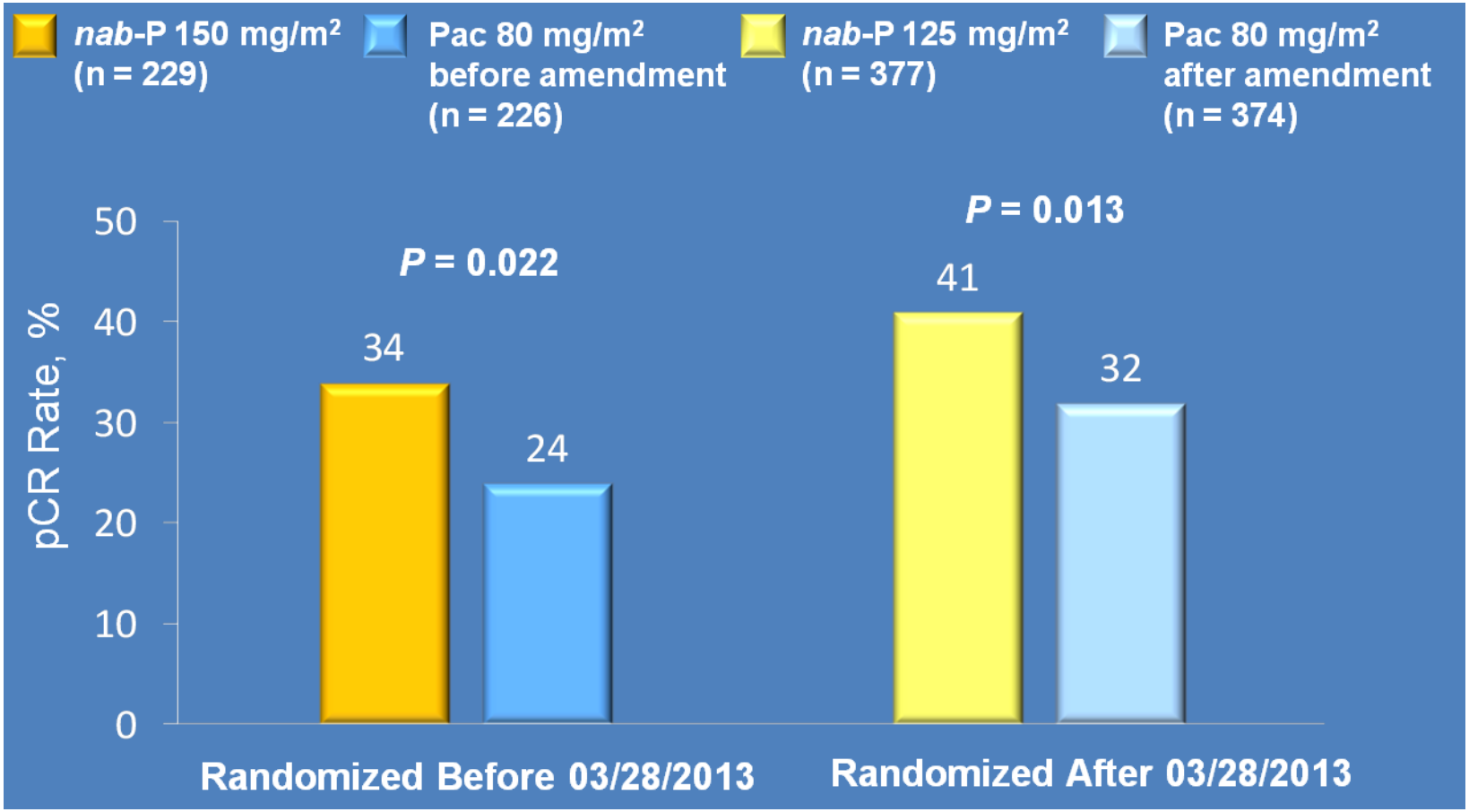
Neoadjuvant nabpaclitaxel for triple-negative breast cancer Geparsepto



- *nab*-P remained an independent predictor for pCR after adjustment for baseline and minimization factors (OR 1.66; 95% CI, 1.25 - 2.19; *P* = 0.00043)

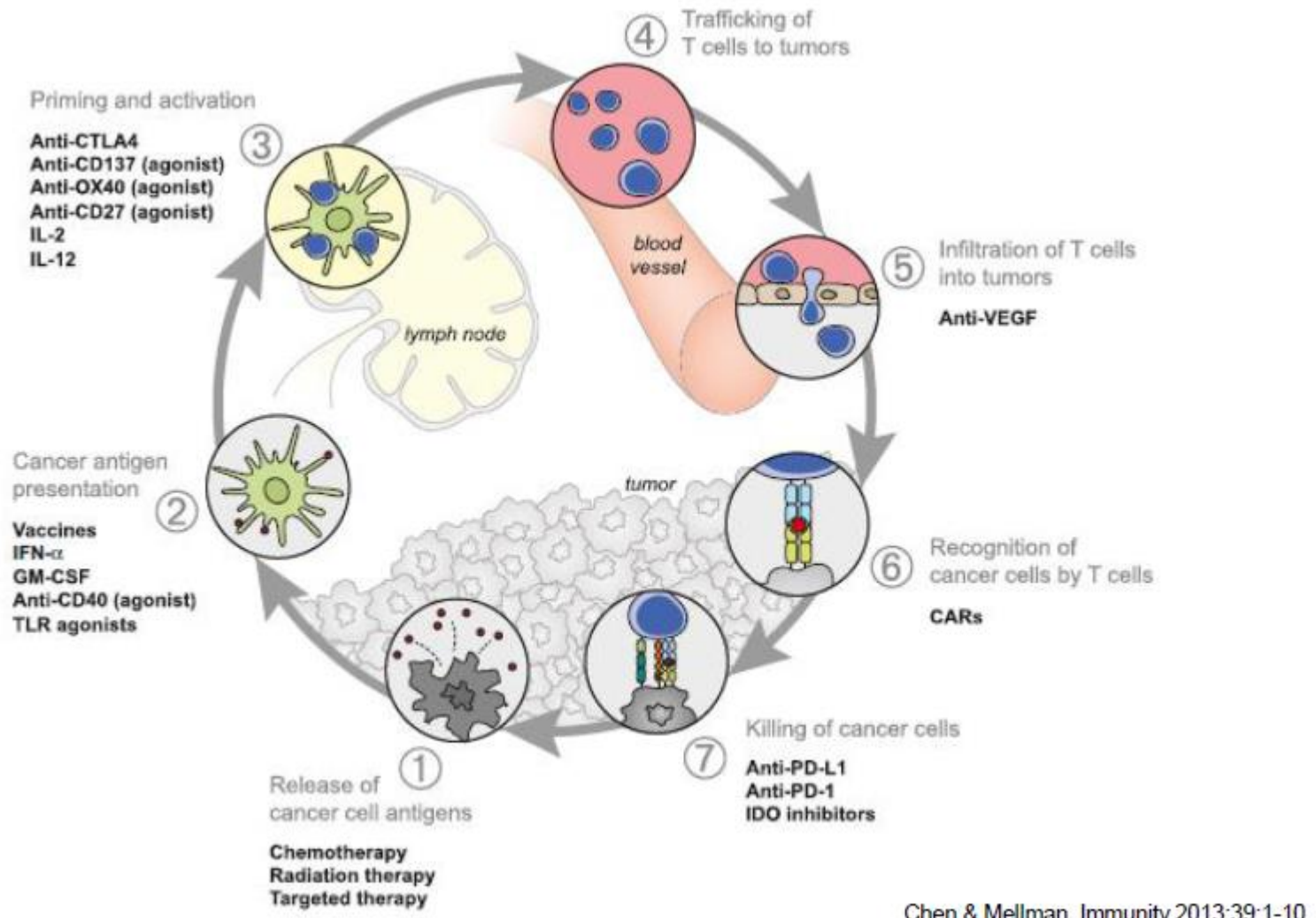
Untch M, et al. Lancet Oncol. 2016. Epub ahead of print.

Neoadjuvant nabpaclitaxel for triple-negative breast cancer Geparsepto



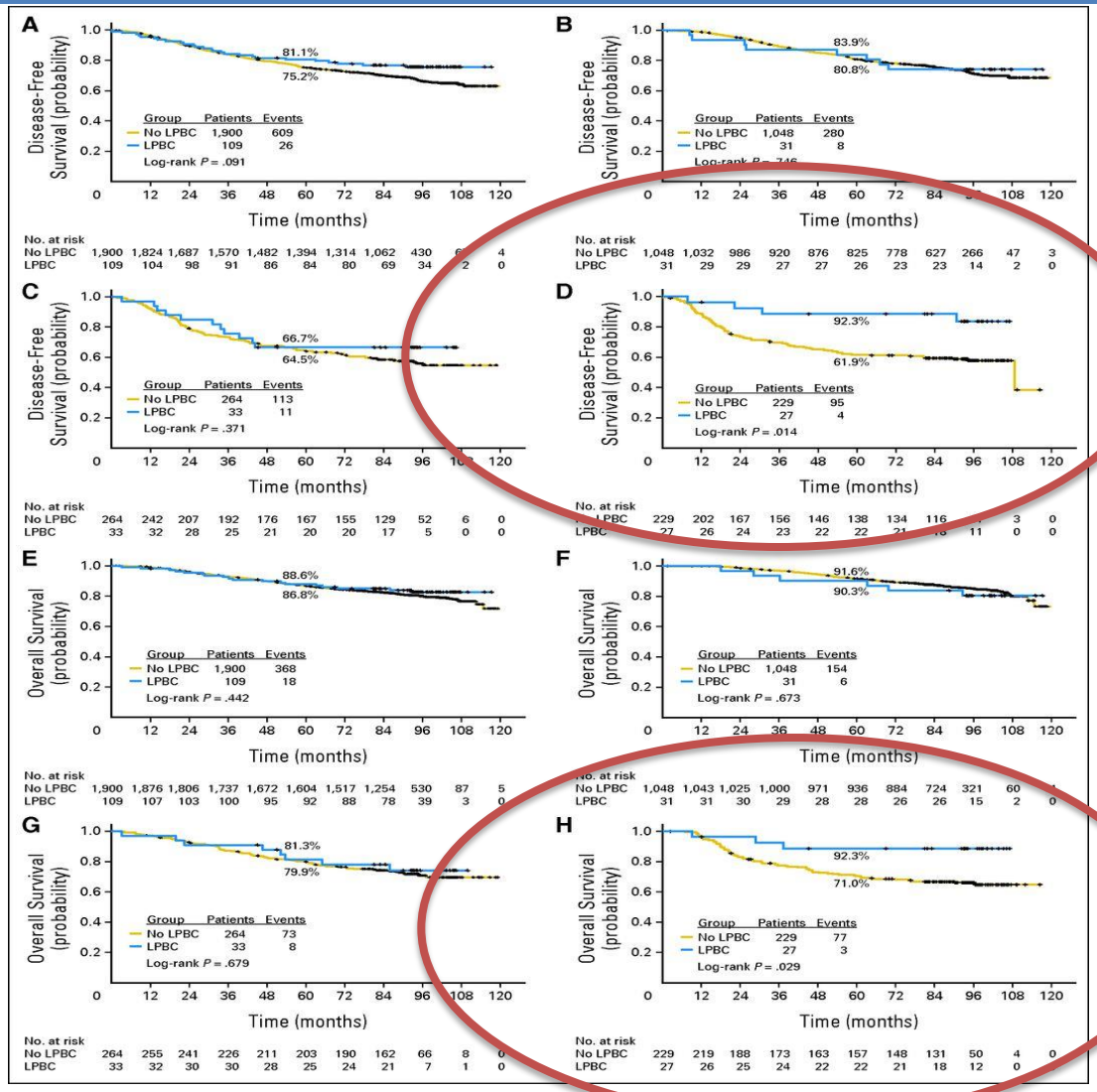
Untch M, et al. Lancet Oncol. 2016. Epub ahead of print.

New prognostic factors and new targets



Chen & Mellman. Immunity 2013;39:1-10

Prognostic Ability of the Lymphocyte-predominant Breast Cancer (LPBC) Phenotype.



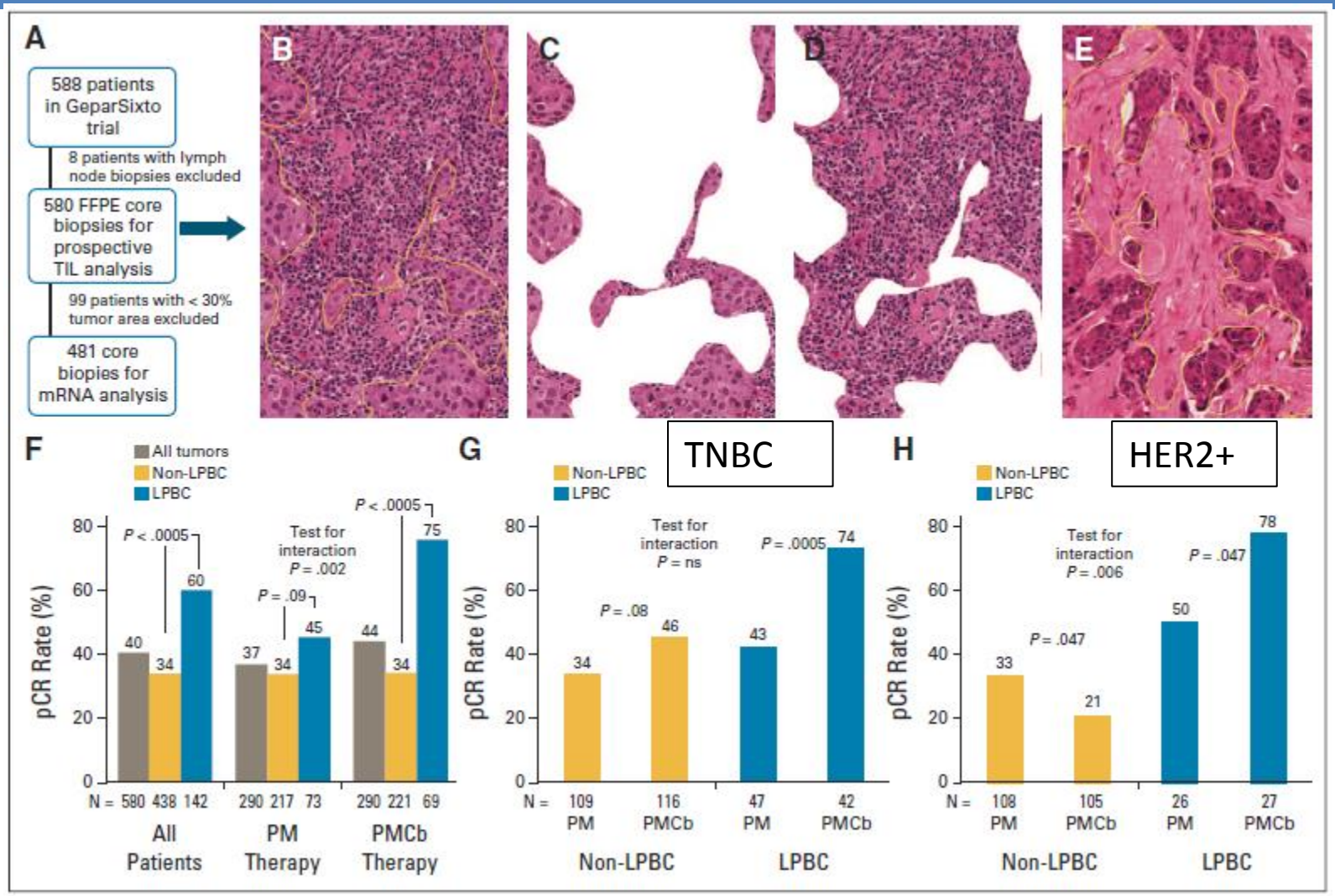
TNBC DFS

TNBC OS

Sherene Loi et al. JCO 2013;31:860-867

JOURNAL OF CLINICAL ONCOLOGY ASCO

TILs in HER2 positive and TN breast cancer

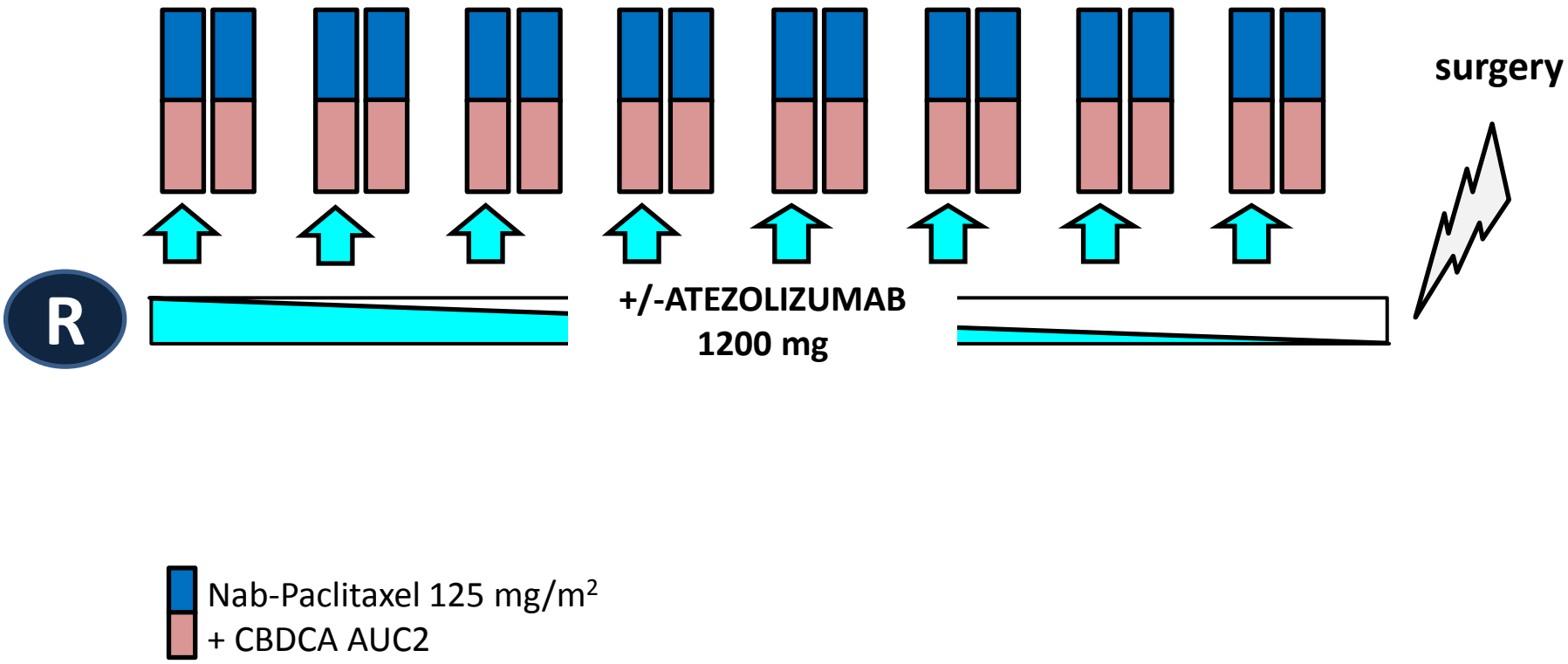


Denkert C et al. J Clin Oncol Dec 2014; epub ahead of print

Neoadjuvant I-O for triple-negative breast cancer

N=272

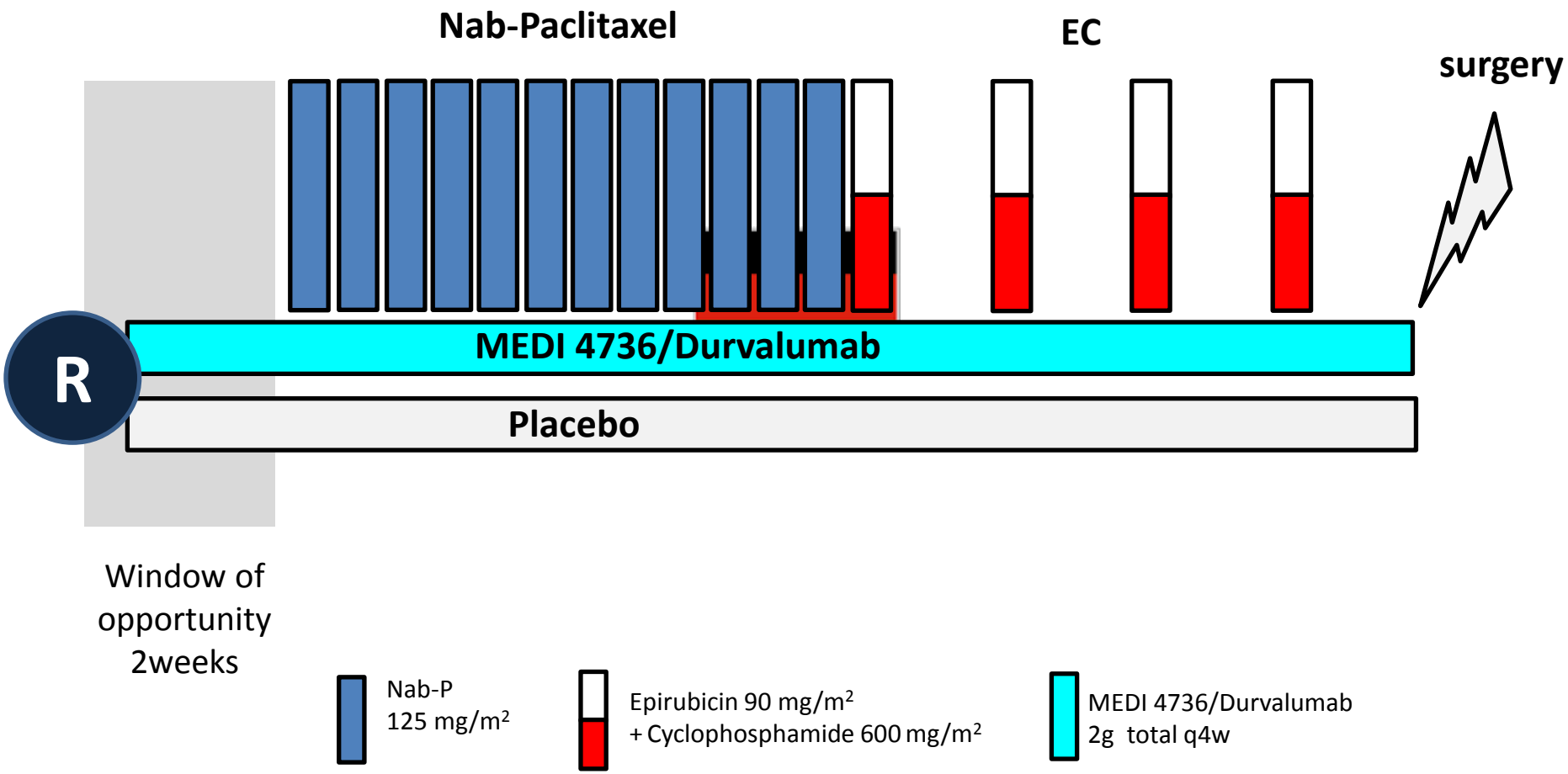
Primary endpoint: EFS
Secondary endpoint: pCR (ypT0-ypTis ypN0)



NEOTRIP Trial, PI L. Gianni

Neoadjuvant I-O for triple-negative breast cancer

N=174 **Primary endpoint: pCR (ypT0 ypN0)**



GEPARNUEVO

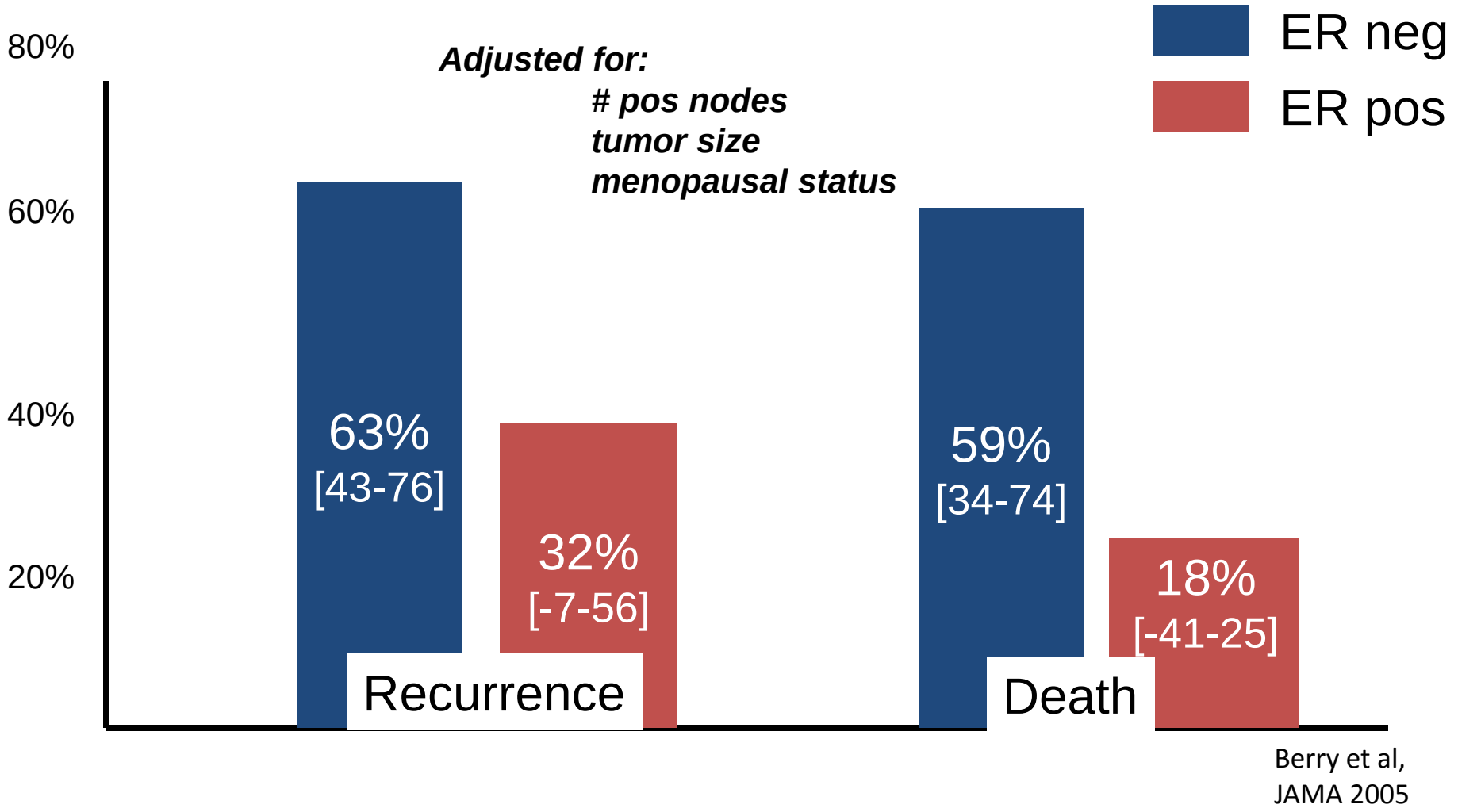
Summary for Neo Adjuvant

- pCR increased in TNBC to around 55%
- Adding Carboplatin increased the pCR rate in TNBC
- Do TILs predict Carboplatin benefit in HER2+ patients?
- Should we combine Carboplatin and nab-Paclitaxel to further increas the pCR inTNBC?
- TILs seem to select patients with better response to NAT

Adjuvant CT in TN EBC

Triple-negative Breast Cancer:
Is there an optimal adjuvant treatment?

Benefit from CT in TN EBC



Berry et al,
JAMA 2005

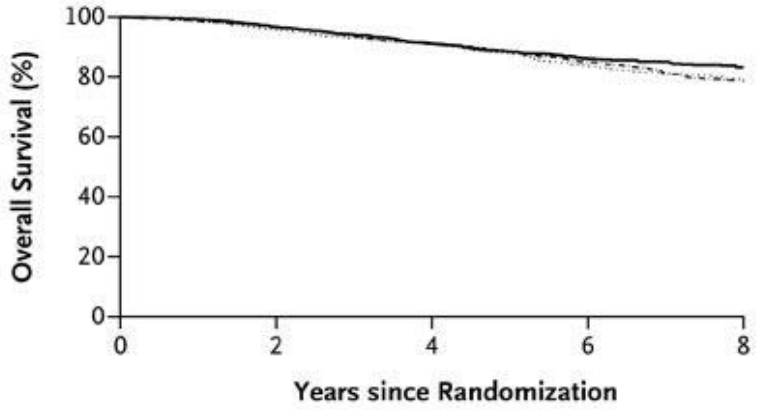
Criteria to define optimal regimens

- Biological
  - Intrinsic heterogeneity within TNBC
  - Lack of targeted therapies
- Clinical
  - Epidemiological links to younger age and heredity
  - Higher risk means lower stage threshold for treatment
  - Chemo question is not “yes/no?” but “which?”
  - Trade-offs still include consideration of short-term and long-term side effects but balanced by tumor risk and treatment needs
- Analytical
  - Few trials specifically for TNBC
  - Subset analyses with familiar limitations, including post hoc analyses and lack of power/events

NSABP B-30. $AC_4 \rightarrow T_4$ vs TAC_4 vs AT_4 Overall Survival and Disease-free Survival.

A

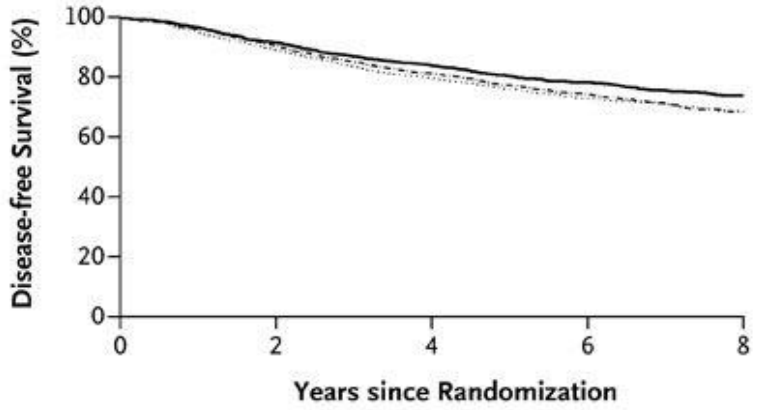
	No. of Patients	No. of Events	Hazard Ratio	P Value
Sequential ACT	1753	240	0.86 vs. concurrent ACT	0.09
			0.83 vs. doxorubicin–docetaxel	0.03
Doxorubicin–docetaxel	1753	285		
Concurrent ACT	1758	278	0.96 vs. doxorubicin–docetaxel	0.67



No. at Risk					
Total	5264	5042	4620	2300	779
Sequential ACT	1753	1685	1533	775	271
Doxorubicin–docetaxel	1753	1668	1531	752	253
Concurrent ACT	1758	1689	1556	773	255

B

	No. of Patients	No. of Events	Hazard Ratio	P Value
Sequential ACT	1753	388	0.83 vs. concurrent ACT	0.01
			0.80 vs. doxorubicin–docetaxel	0.001
Doxorubicin–docetaxel	1753	468		
Concurrent ACT	1758	457	0.96 vs. doxorubicin–docetaxel	0.58



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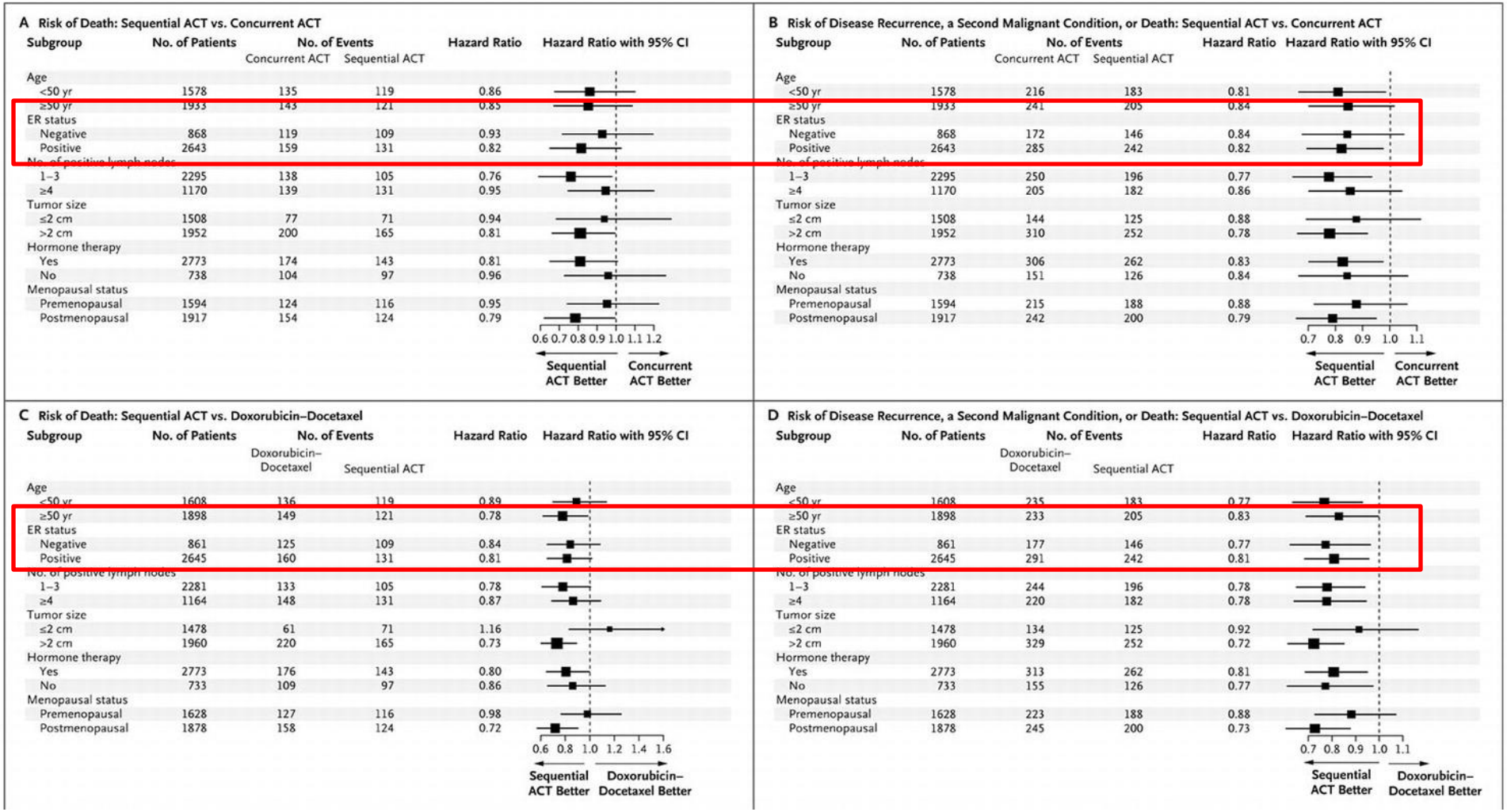
Total	5264	4743	4158	2021	679
Sequential ACT	1753	1600	1414	709	242
Doxorubicin–docetaxel	1753	1557	1349	652	222
Concurrent ACT	1758	1586	1395	660	215

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

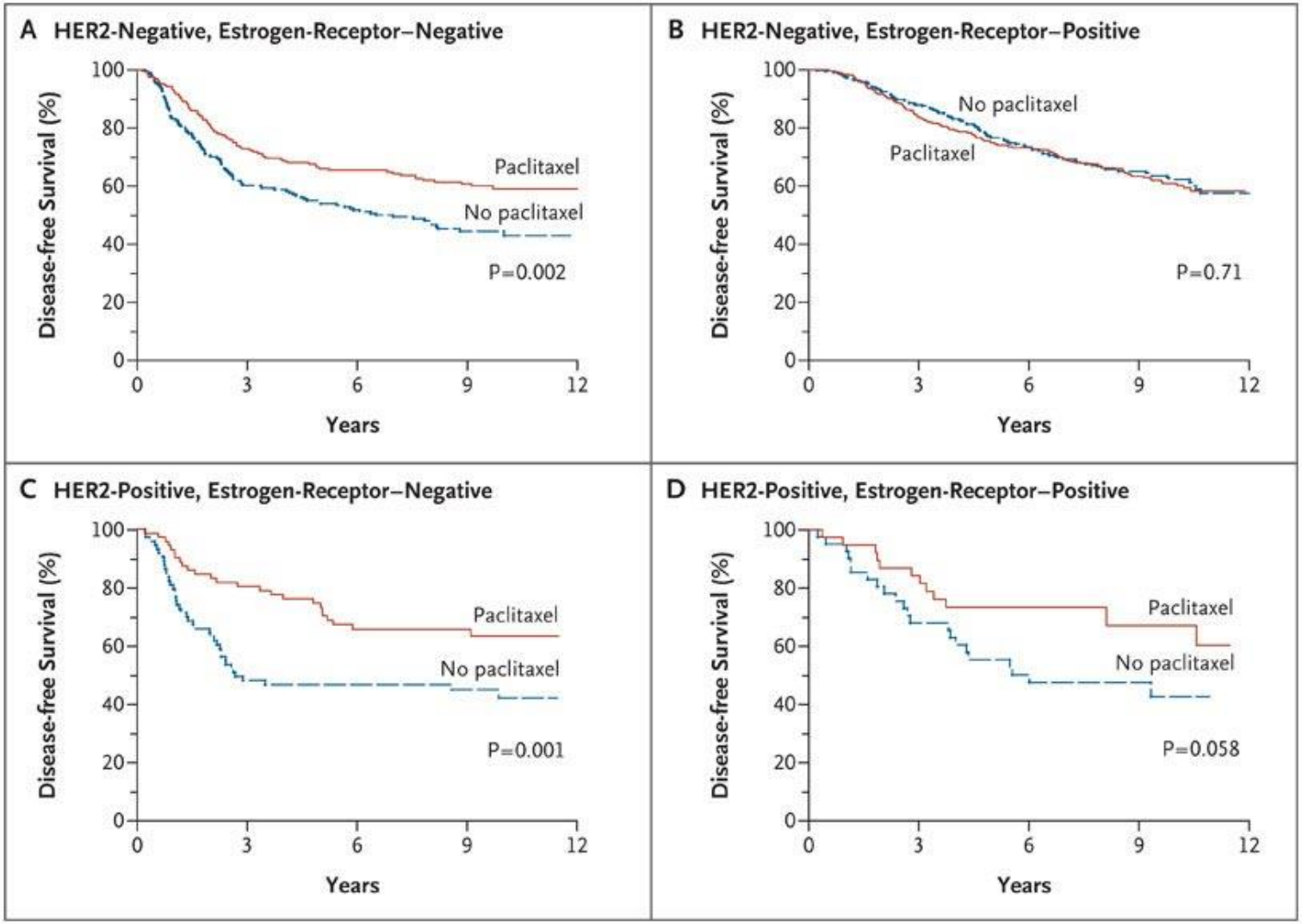
NSABP B-30

OS DFS



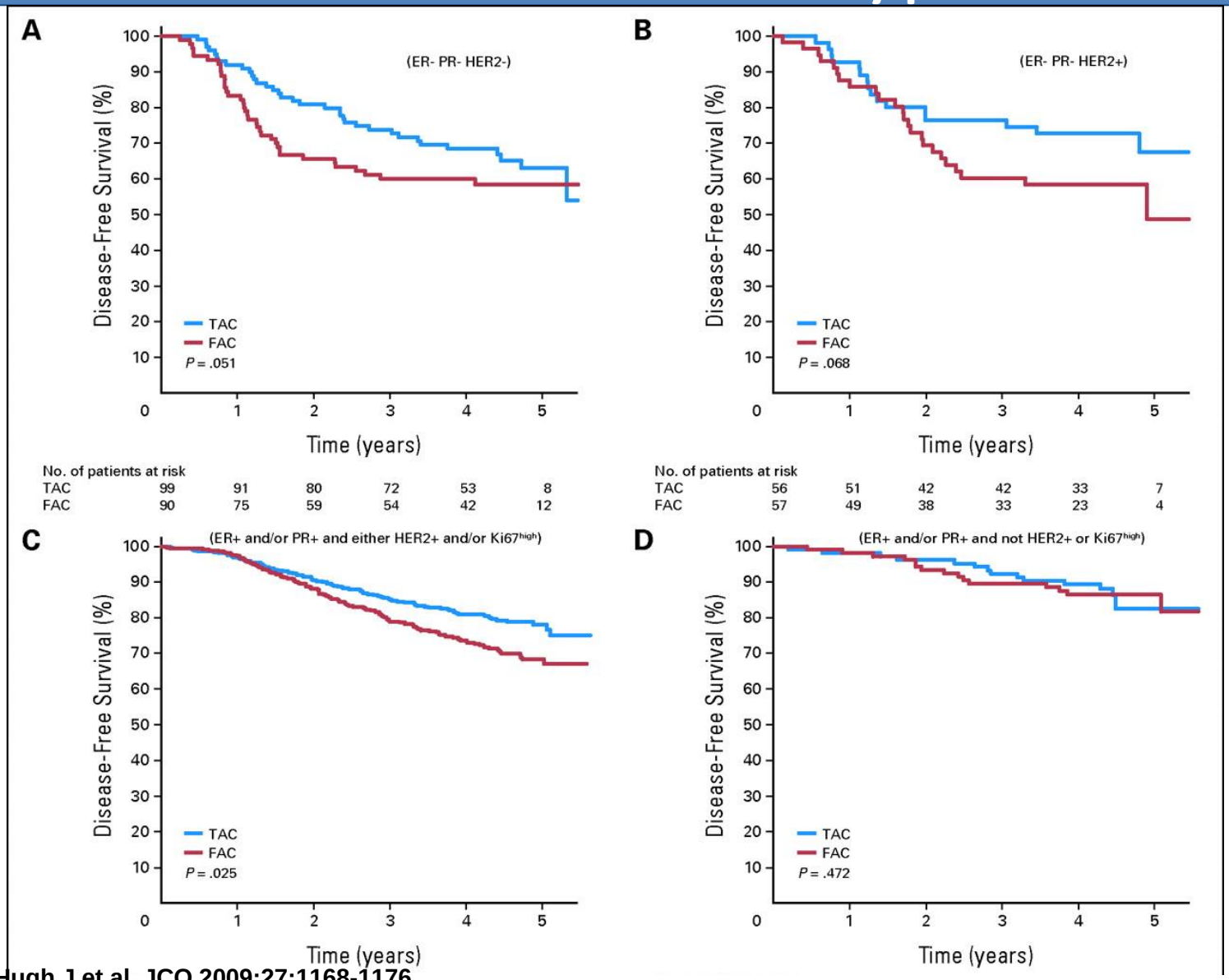
Swain SM et al. N Engl J Med 2010;362:2053-2065.

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



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

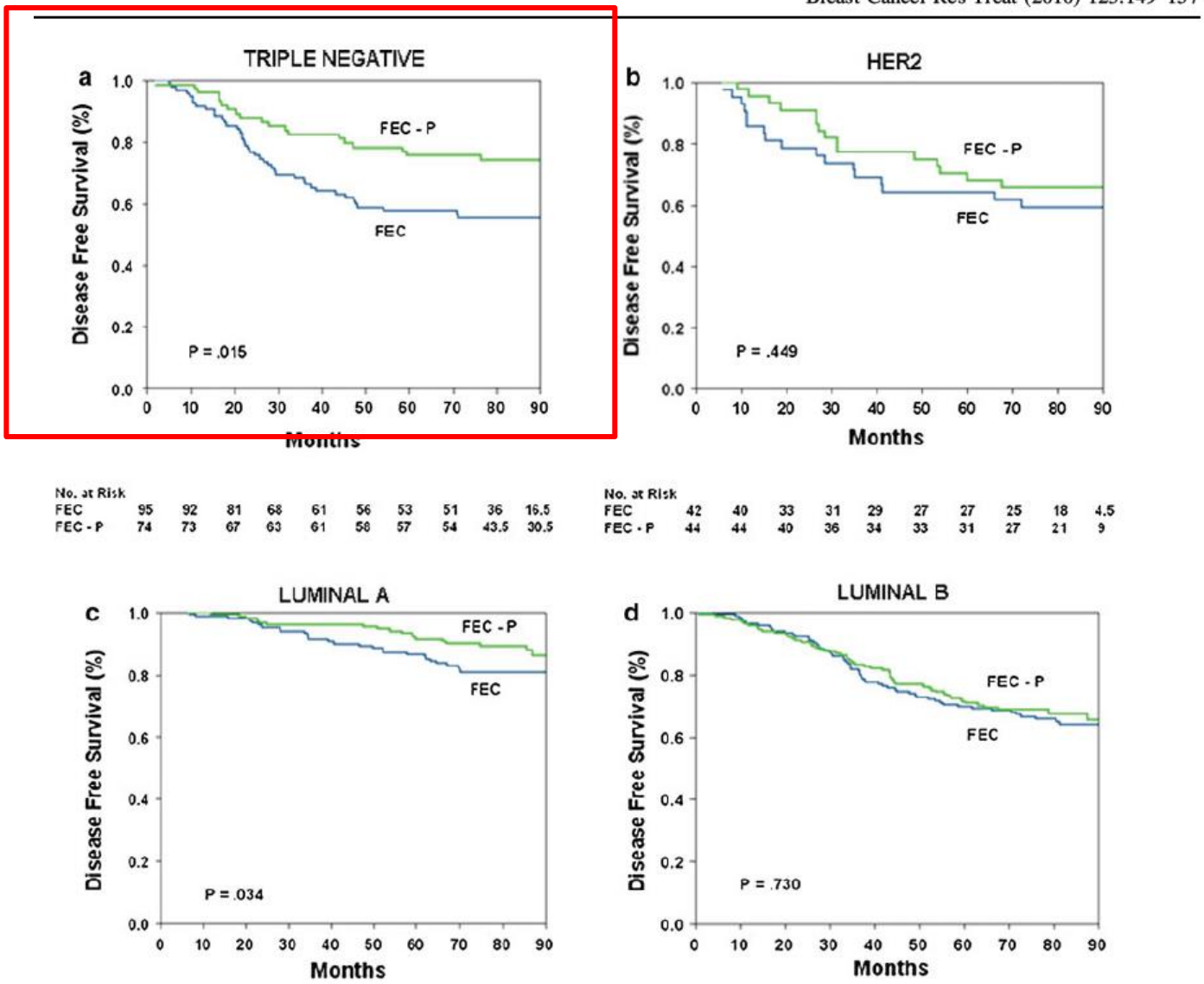
BCIRG 001: TAC vs FAC Outcome for Subtypes



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

GEICAM 9906: FEC vs FEC/P Outcomes by Subtypes

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



Adjuvant therapy in TN EBC

NSABP-B30

AC-T x 8 vs AT x 4 vs TAC x 6

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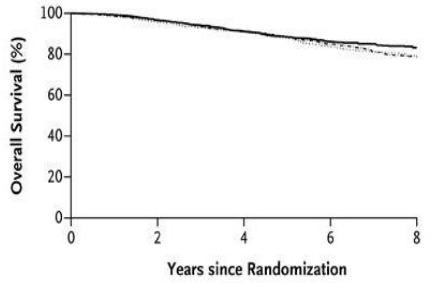

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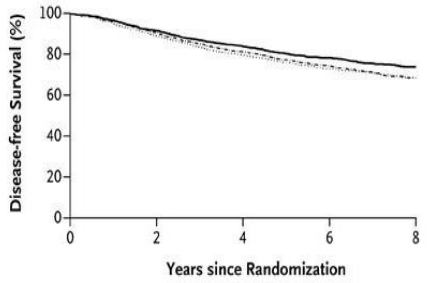

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Swain SM et al. N Engl J Med 2010;362:2053-2065

POSSIBLE REGIMENS

- AC-paclitaxel (dose dense)
- AC-weekly paclitaxel
- AC-docetaxel (every 3 weeks)
- FEC-docetaxel

Adjuvant therapy in TN EBC

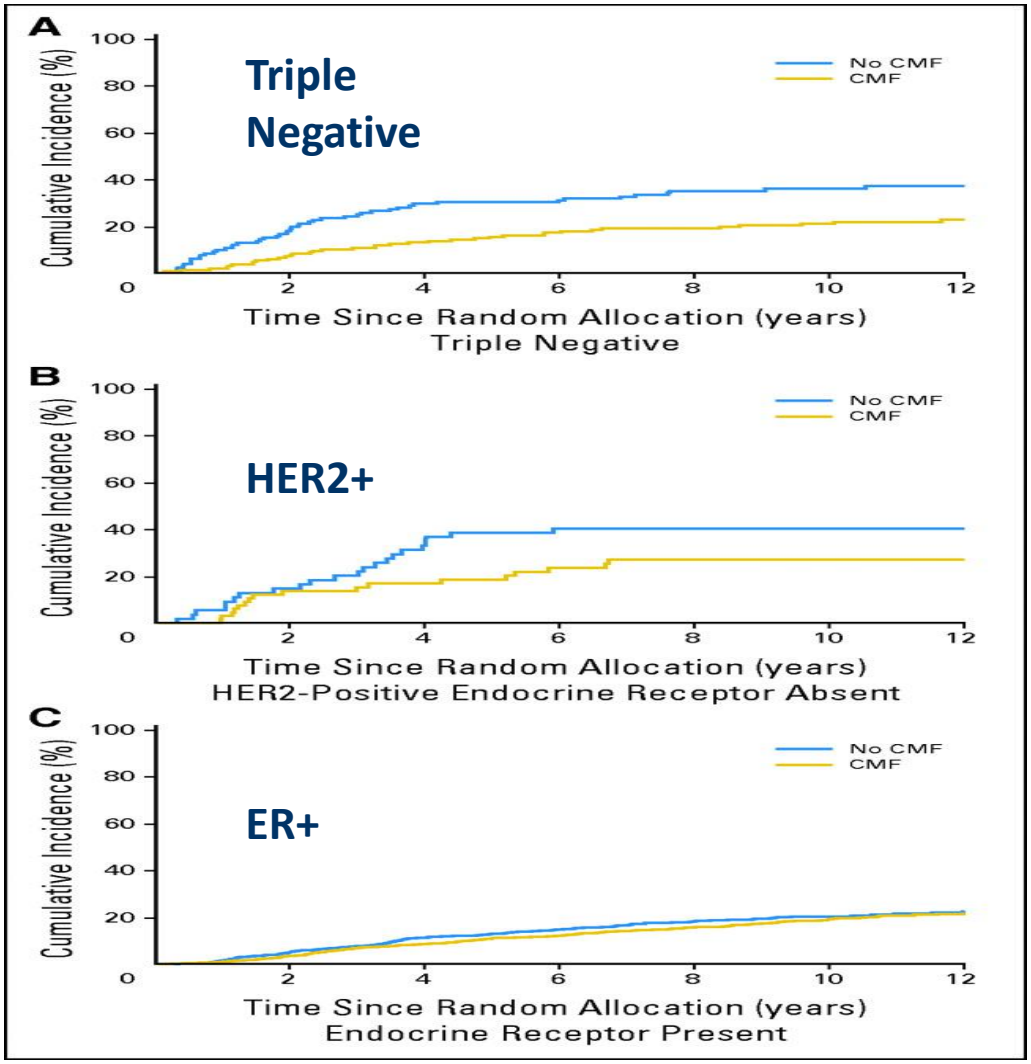
- Standard chemotherapy agents are effective adjuvant therapy, particularly in TNBC
- Enhancements to adjuvant chemotherapy (addition of taxanes, sequential therapy, schedule) are valuable, particularly in TNBC
- While anthracyclines are standard components of modern adjuvant regimens, questions persist about their importance, particularly in TNBC

Should Stage Affect the Choice of of a Treatment Regimen?

Year of diagnosis	Percent of adjuvant chemotherapy (±trastuzumab) (%)							
	HR+HER2-		HR+HER2+		HR-HER2+		Triple-negative	
	T1a	T1b	T1a	T1b	T1a	T1b	T1a	T1b
2003	3%	10%	13%	36%	50%	76%	18%	70%
2005	1%	11%	25%	50%	38%	77%	31%	50%
2009	2%	13%	47%	100%	56%	100%	50%	69%

IEO Data

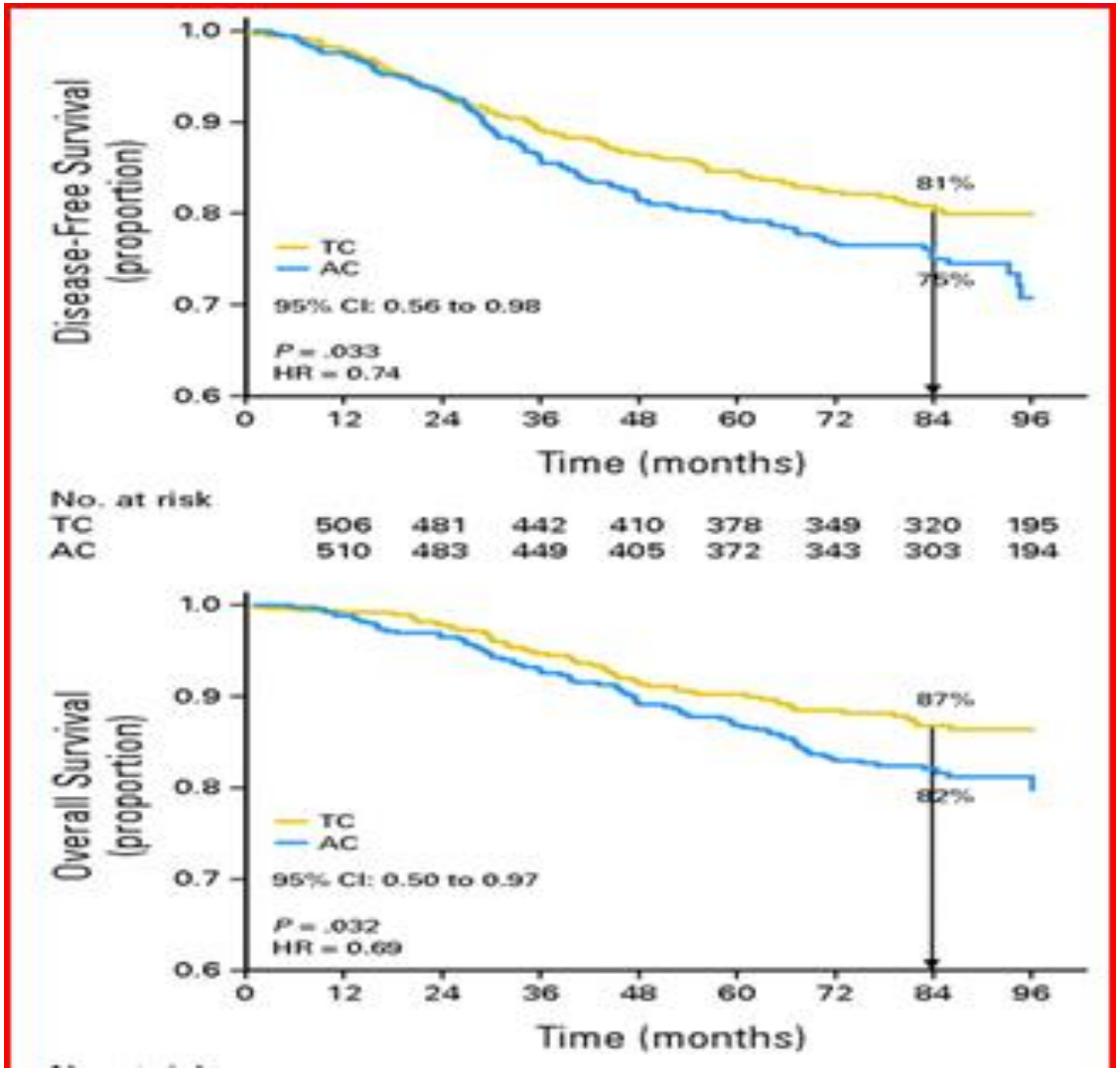
CMF



Retrospective analysis of MA-5 suggested CMF marginally more effective than CEF in basal-like BC (Cheang et al Clin Can Res 2012)

Colleoni M et al. JCO. 2010;28:2966-2973

Docetaxel/Cyclophosphamide (TC)



TC appeared superior to AC in one relatively small trial

Probably at least as good as AC

Would be hesitant about using TC in BRCA mutation carriers

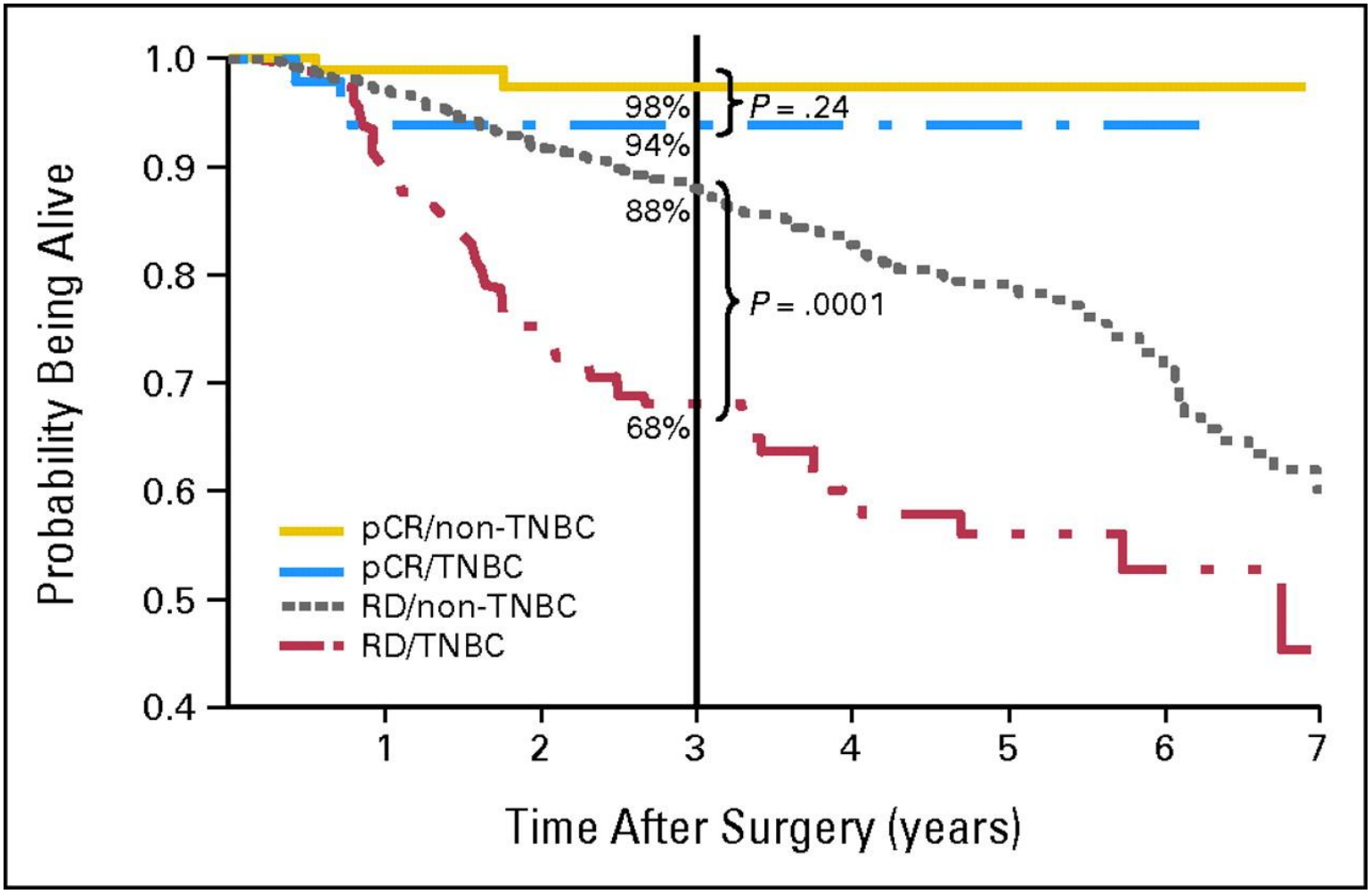
From: Jones, S. et al. J Clin Oncol; 27:1177-1183 2009

Options for Stage I Disease

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

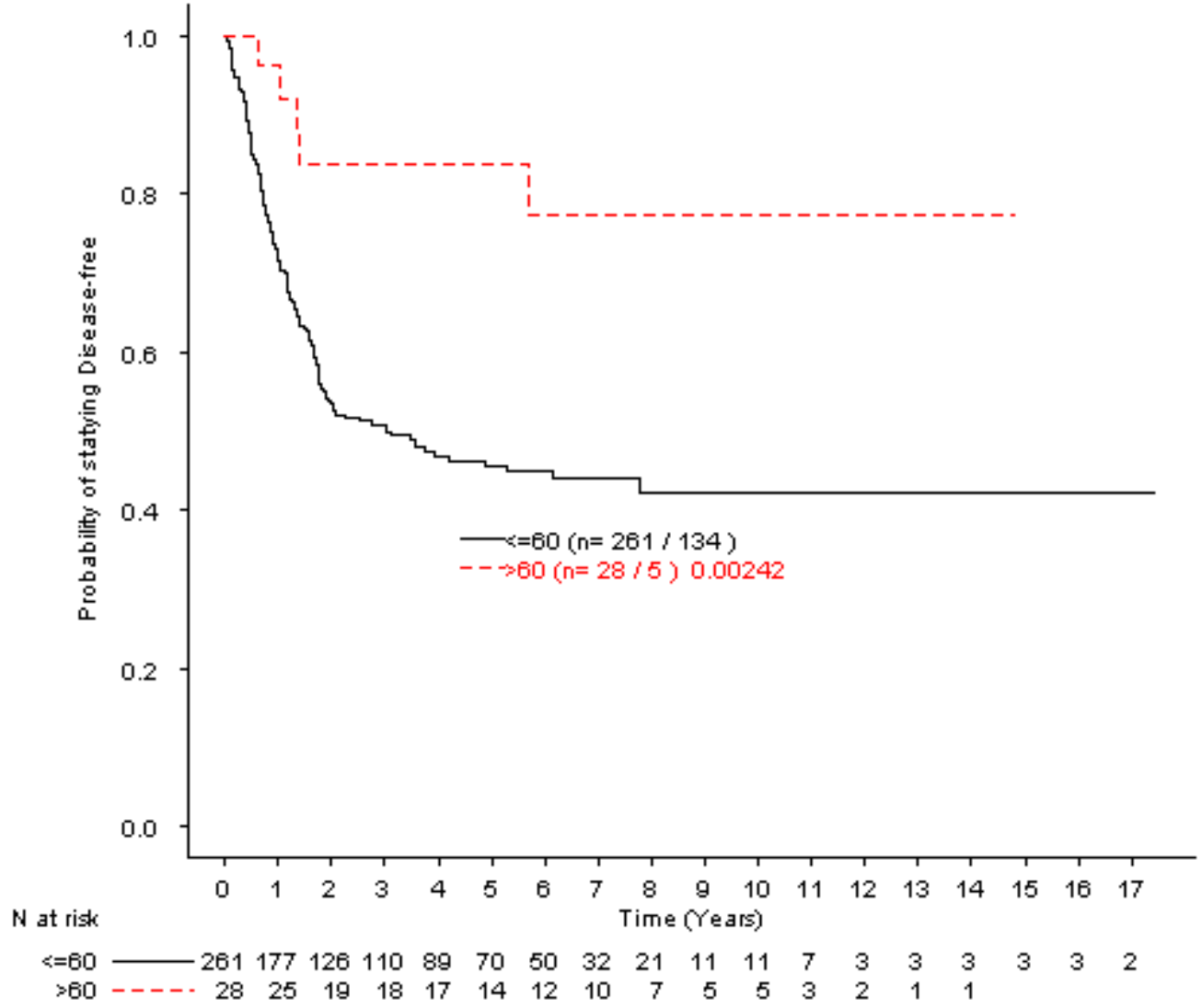
	Enthusiasm for Chemotherapy	Possible Regimens
Microinvasion only	**Virtually none**	**---**
T1a	**Low to moderate**	**Simple**
T1b	**Moderate to high**	**Simple**
T1c	**High**	**Simple or selectively sequential approach**

Post-Neoadjuvant setting

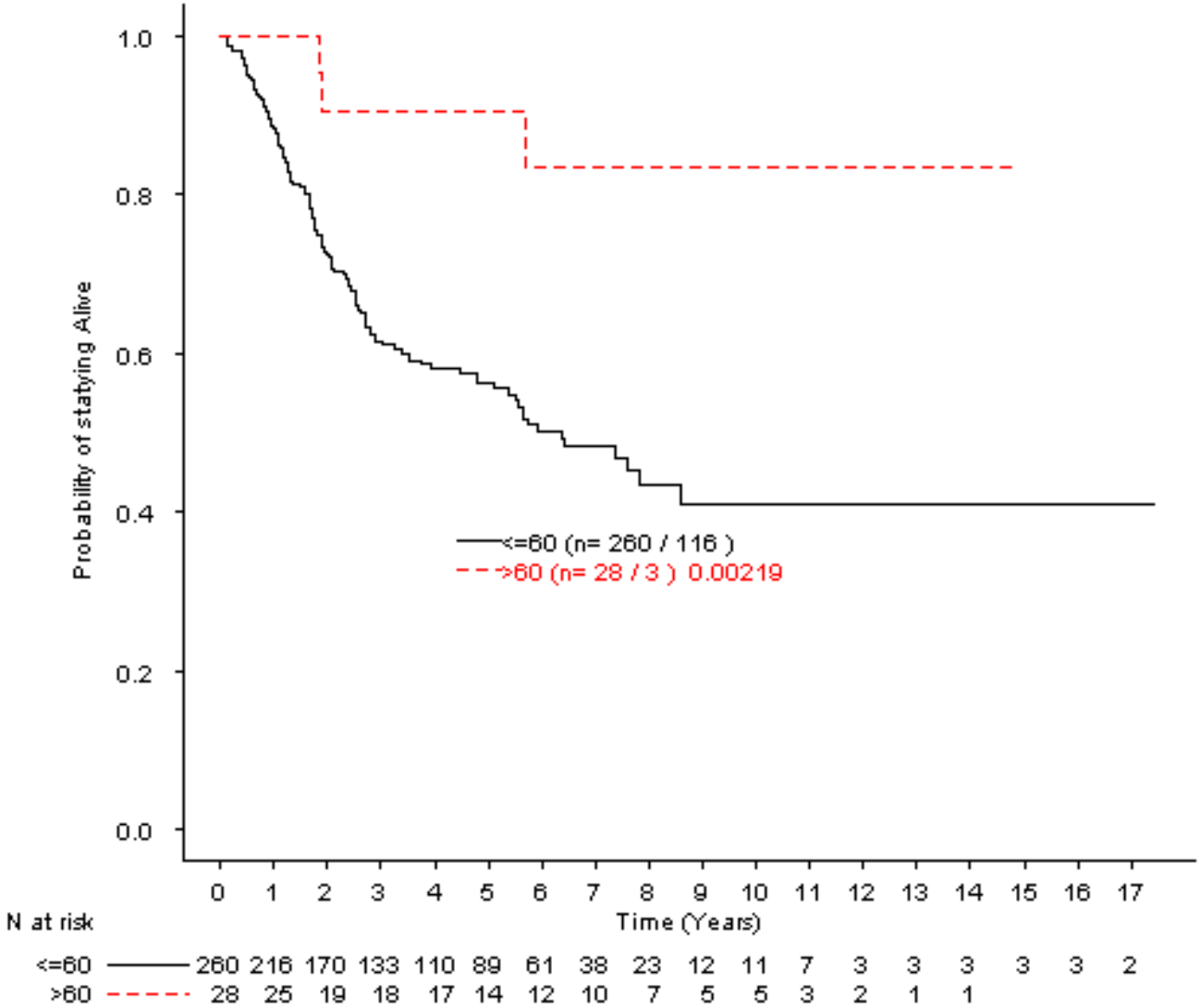


C. Liedtke JCO, 26, 8, 2008: pp. 1275-1281

TILs in residual disease: DFS

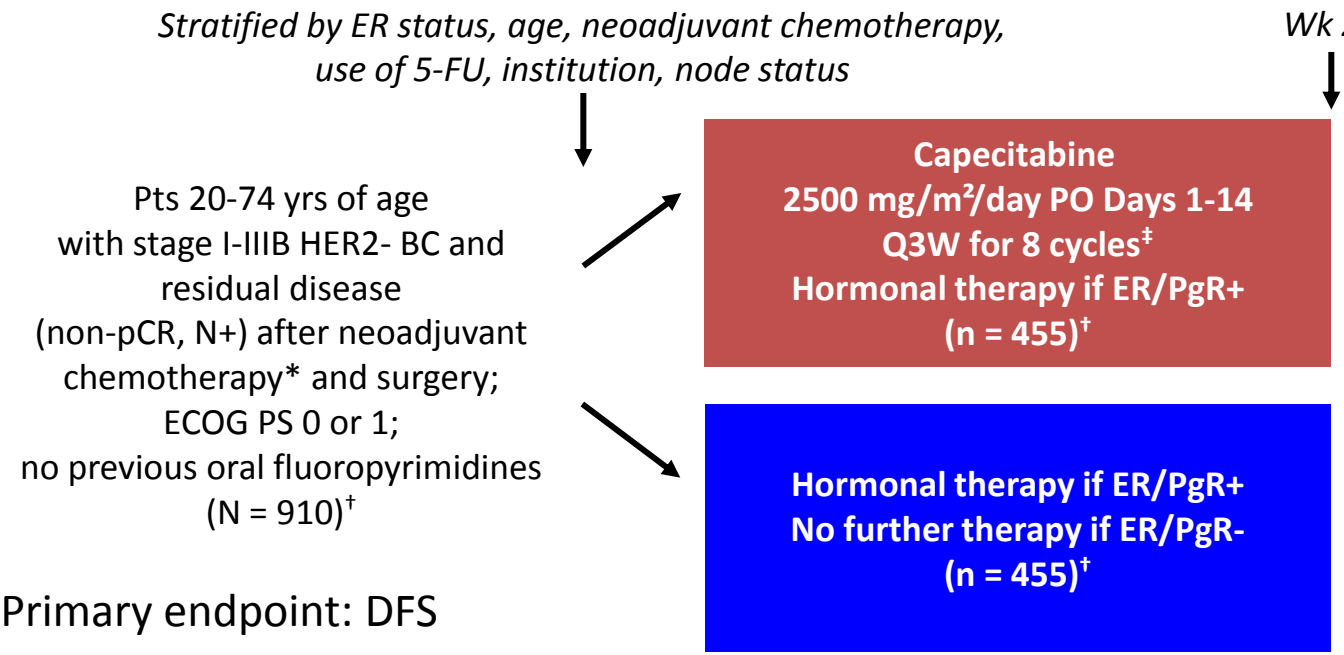


TILs in residual disease: OS



Post-Neoadjuvant setting

- Preplanned interim analysis of a randomized, open-label phase III study[1]



- Primary endpoint: DFS
- Secondary endpoints: OS, time from first day of preoperative chemotherapy to recurrence or death, safety, cost-effectiveness

*Anthracycline/taxane, anthracycline containing, or docetaxel/cyclophosphamide.
†25 pts were removed from treatment (n = 10) and control (n = 15) arms due to failure to meet eligibility criteria.
‡IDMC recommended extension to 8 cycles following interim safety analysis of first 50 pts receiving 6 cycles.[2]

1. Toi M, et al. SABCS 2015. Abstract S1-07.
2. Ohtani S, et al. SABCS 2013. Abstract P3-12-03.

Post-Neoadjuvant setting

Characteristic	Capecitabine (n = 440)	No Capecitabine (n = 445)
Age, median yrs (range)	48 (25-74)	48 (25-74)
Menopausal status, %		
▪ Pre	59.3	56.0
▪ Post	40.7	44.0
Stage, %		
▪ I, IIA, IB	58.9	62.0
▪ IIIA, IIIB	40.5	37.5
Hormonal receptor status, %		
▪ ER+ or PgR+	63.9	62.9
▪ ER- and PgR-	33.4	33.5
Lymph nodes with metastatic disease, %		
▪ 0	39.3	38.7
▪ 1-3	37.5	39.1
▪ ≥ 4	22.7	22.2
Histologic effect grading by NAC, %		
▪ 0, 1a, 1b	56.4	52.6
▪ 2, 3	41.6	45.4

Toi M, et al. SABCS 2015. Abstract S1-07.

Post-Neoadjuvant setting

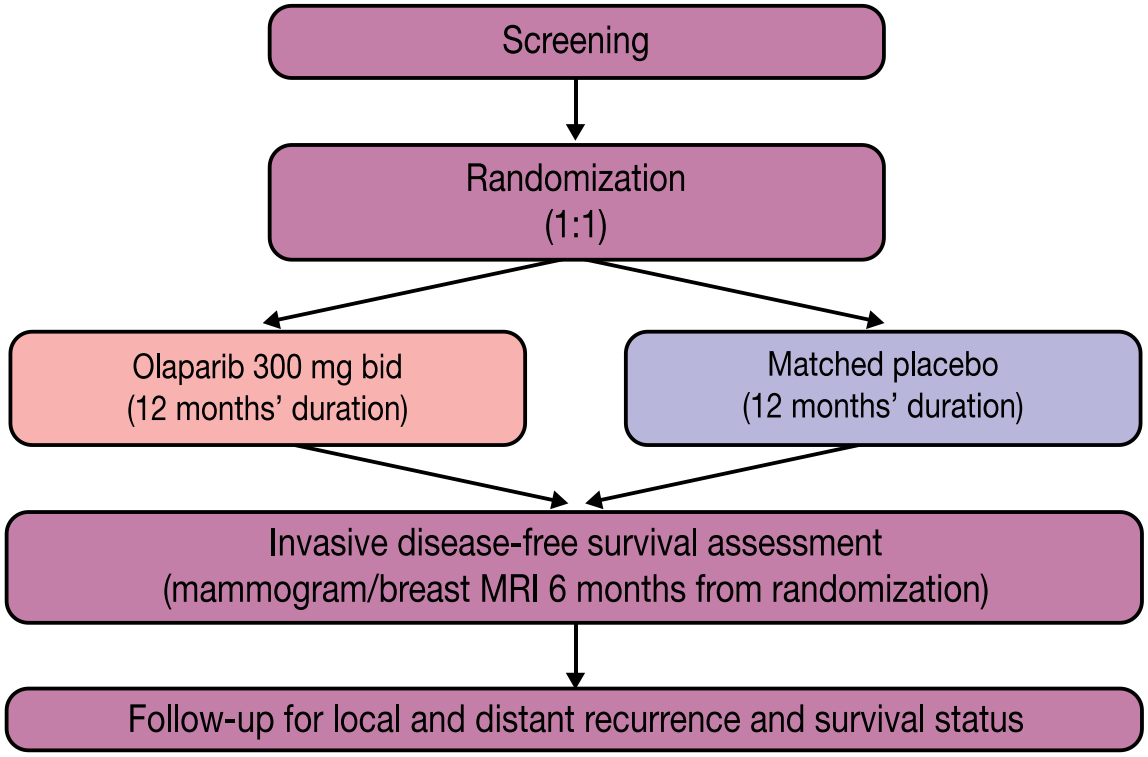
- Capecitabine achieved significantly higher 5-yr DFS and OS in HER2- BC pts with residual disease

Characteristic, %	Capecitabine (n = 440)	No Capecitabine (n = 445)	HR (95% CI)	*P* Value
5-yr DFS	74.1	67.7	0.70 (0.53-0.93)	.00524
5-yr OS	89.2	83.9	0.60 (0.40-0.92)	< .01

Toi M, et al. SABCS 2015. Abstract S1-07.

Triple negative BRCA mutated

Figure 1. OlympiA study design



Adjuvant therapy in TN

- Because of the lack of targeted therapy, the intrinsic recurrence risk, and the efficacy of chemotherapy, thresholds for adjuvant chemotherapy treatment for TNBC are low (~ 0.5 cm, node-negative) despite the familiar side effects of chemotherapy treatment
- Data suggest “optimal” regimens should include cyclophosphamide, taxanes, and anthracyclines
- Data are insufficient and/or negative for additional treatments such as:
  - Capecitabine
  - Gemcitabine
  - Platinum-based chemotherapy
  - Bevacizumab

Adjuvant therapy in TN

- **Standard of Care**
  - based on direct comparisons, subset analyses and considerations of toxicity/tolerability
  - **sequential anthracycline, cyclophosphamide and taxane-based therapy**
  - **arguably ddAC → paclitaxel**
- Alternative regimens
  - Preferred regimen without anthracyclines: TC
  - Preferred regimen without taxanes: AC or CMF
- Neoadjuvant regimens = adjuvant regimens

Research priorities

- Event rates in TNBC enable familiar adjuvant trial designs
- Design & power studies specifically for TNBC outcomes
- Define role of anthracyclines [NSABP B-49] in modern era
- Molecular / genomic correlatives
- Innovative neoadjuvant FDA accelerated approval pathway exists for potent, novel agents studied through add-on design trials with adequate sample size and planned long-term follow-up for EFS / OS, but the relationship of change in pCR and change in EFS remains unclear

Thank you