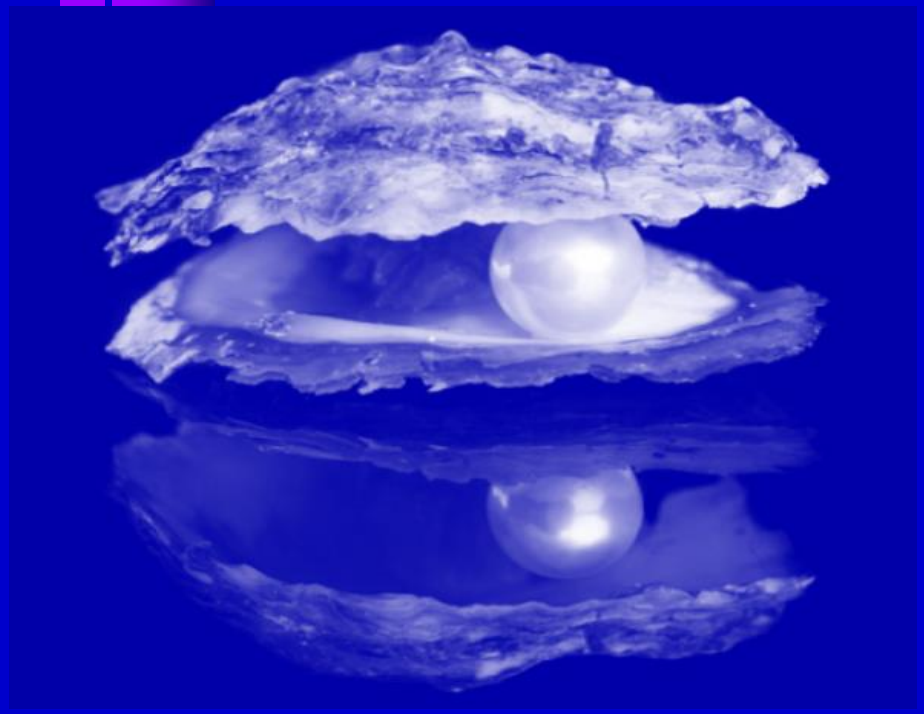
Meme Kanserinde Neoadjuvan Tedavi



Dr Arzu OĞUZ

Lokal İleri Evre Meme Kanseri Kursu,
07/04/2018

Lokal İleri Evre Meme Kanseri

Survival According to Treatment

Treatment	No. of Patients	5-Yr. Survival (%)
Surgery only	2,453	36
Radiation only	2,386	29
Surgery plus radiation	4,249	33
Chemotherapy, surgery, and radiation	1,923	63

Giordiano SH. *Oncologist*. 2003;8:521-530.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Invasive Breast Cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Inflammatory Breast Cancer

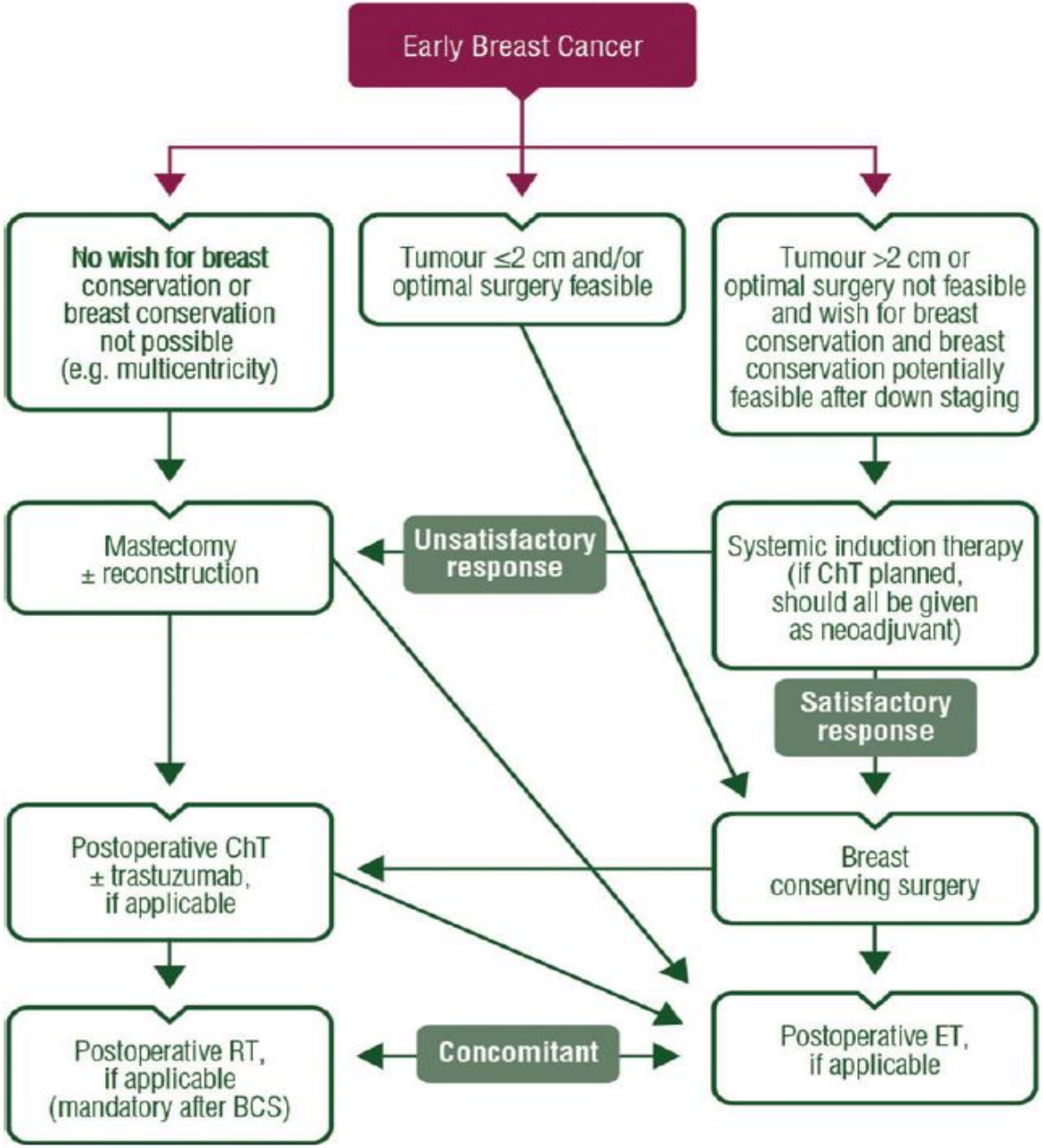
CLINICAL PRESENTATION[a]

Clinical pathologic diagnosis of inflammatory breast cancer (IBC)

WORKUP

- History and physical exam by multidisciplinary team
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Pathology review[b]
- Determination of tumor ER/PR status and HER2 status[c]
- Bilateral diagnostic mammogram, ultrasound as necessary
- Breast MRI (optional)
- Fertility counseling if premenopausal[d]
- Bone scan or sodium fluoride PET/CT (category 2B)[e]
- Chest/abdominal/pelvic diagnostic CT with contrast (category 2B)
- Chest diagnostic CT with contrast (if pulmonary symptoms are present)
- Genetic counseling if patient is high risk for hereditary breast cancer[f]
- FDG PET/CT[g,h] (optional)

Preoperative systemic therapy,[i] anthracycline + taxane (preferred).[i] If tumor HER2 positive, HER2-targeted therapy[j]


Early Breast Cancer
No wish for breast conservation or breast conservation not possible (e.g. multicentricity)
Tumour ≤2 cm and/or optimal surgery feasible
Tumour >2 cm or optimal surgery not feasible and wish for breast conservation and breast conservation potentially feasible after down staging
Mastectomy ± reconstruction
Unsatisfactory response
Systemic induction therapy (if ChT planned, should all be given as neoadjuvant)
Satisfactory response
Postoperative ChT ± trastuzumab, if applicable
Breast conserving surgery
Postoperative RT, if applicable (mandatory after BCS)
Concomitant
Postoperative ET, if applicable

Esmo

Neoadjuvan Kemoterapi

- Tümörün küçültülmesi
  - İnoperabl → Operabl
  - Mastektomi → MKC
    - MKC oranı artar
- Tedavi yanıtı ile önemli prognostik bilgi (TN, HER2+)
- Rekonstrüksiyon planlaması için zaman tanır
- Tedavi ile negatifleşen aksiller tutulum durumunda SLN şansı tanır

Neoadjuvant Kemoterapi

Avantajları

- İlaç duyarlılığının in vivo testi
- Etkisiz tedavi kullanımının engellemesi
- Kozmetik sonuçlar daha iyi
- Prediktif biyobelirteçler ve yeni tedaviler açısından bir araştırma platformu

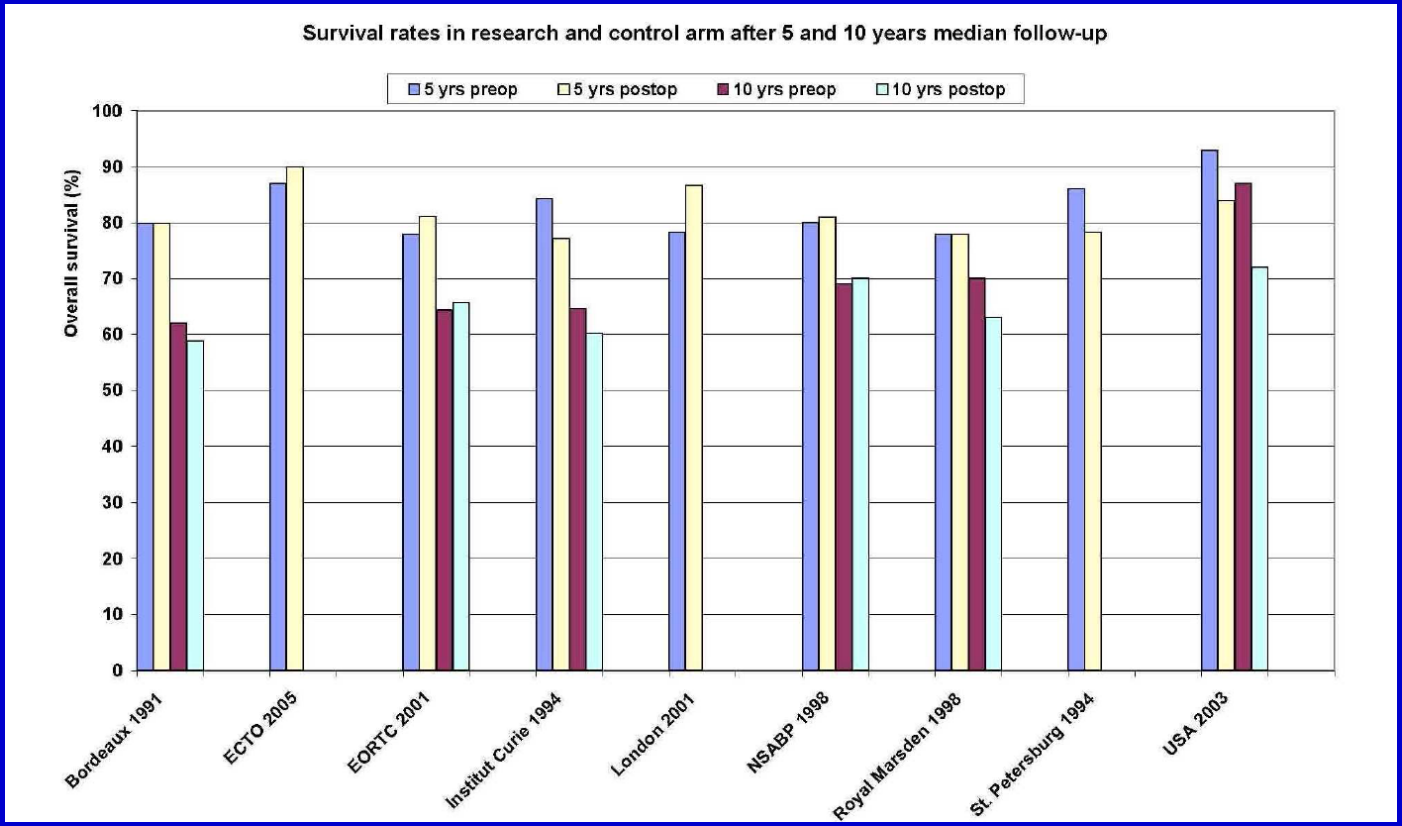
Dezavantajları

- Primer tümörün biyolojik özelliklerinde değişme
- Sistemik overtreatment
- Lokal rekürrensin artması (lokorejyonel undertreatment)
- Preop tedavi sürecinde hastalık progresyon riski açısından dikkatli takip
- Psikolojik bariyer

Preoperative chemotherapy for women with operable breast cancer (Review)

van der Hage JH, van de Velde CCJH, Mieog SJSD

14 çalışma ve 5500 hasta
MRM oranında neoadj ile %29 luk azalma
Lokal rekürens riskinde artış (HR:1.21)
DFS ve OS ler benzer (HR:0.97 ve 0.98)



2007

NSABP B-18(16 yıllık) ve B-27 (8,5 yıllık) update

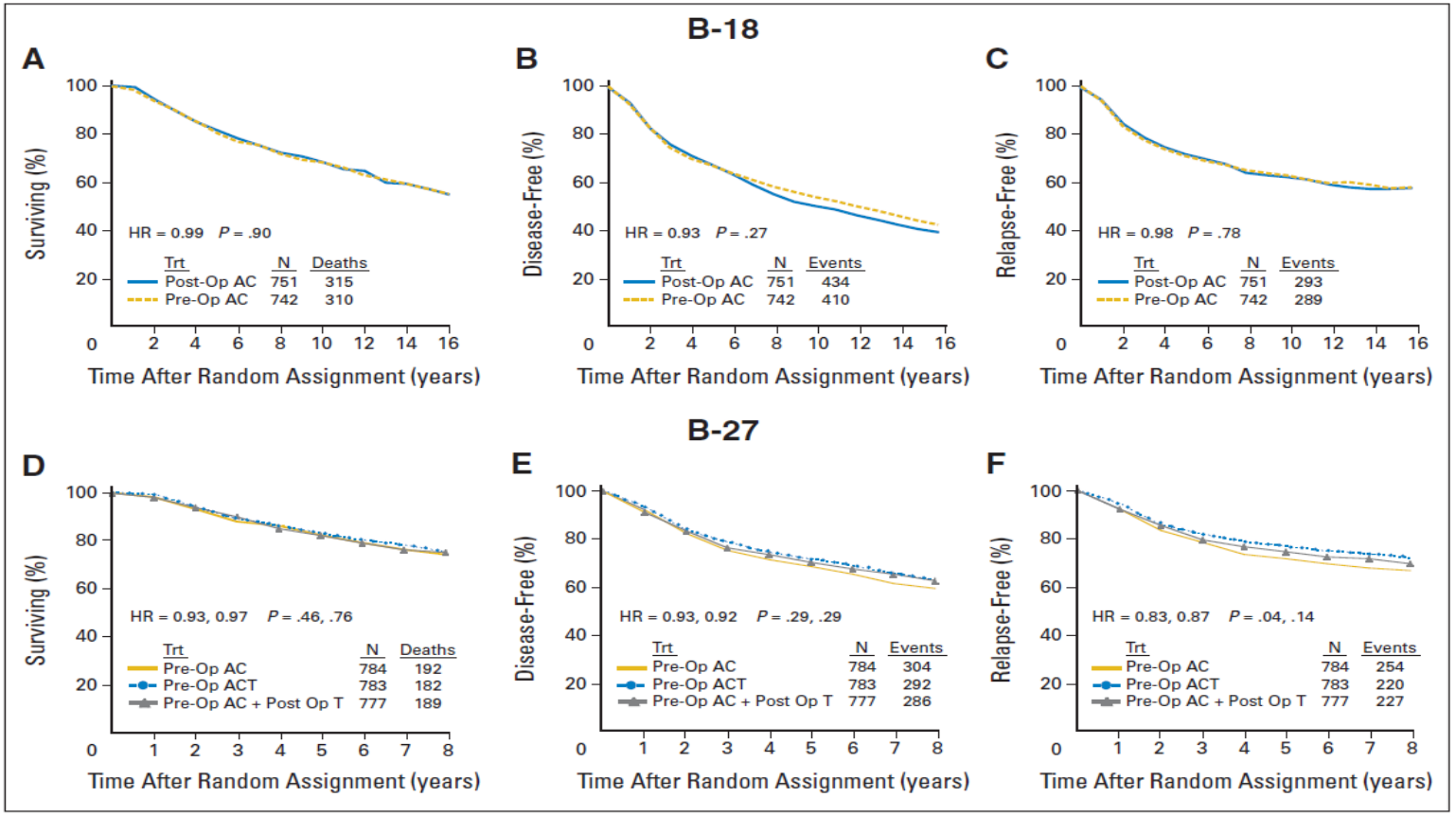
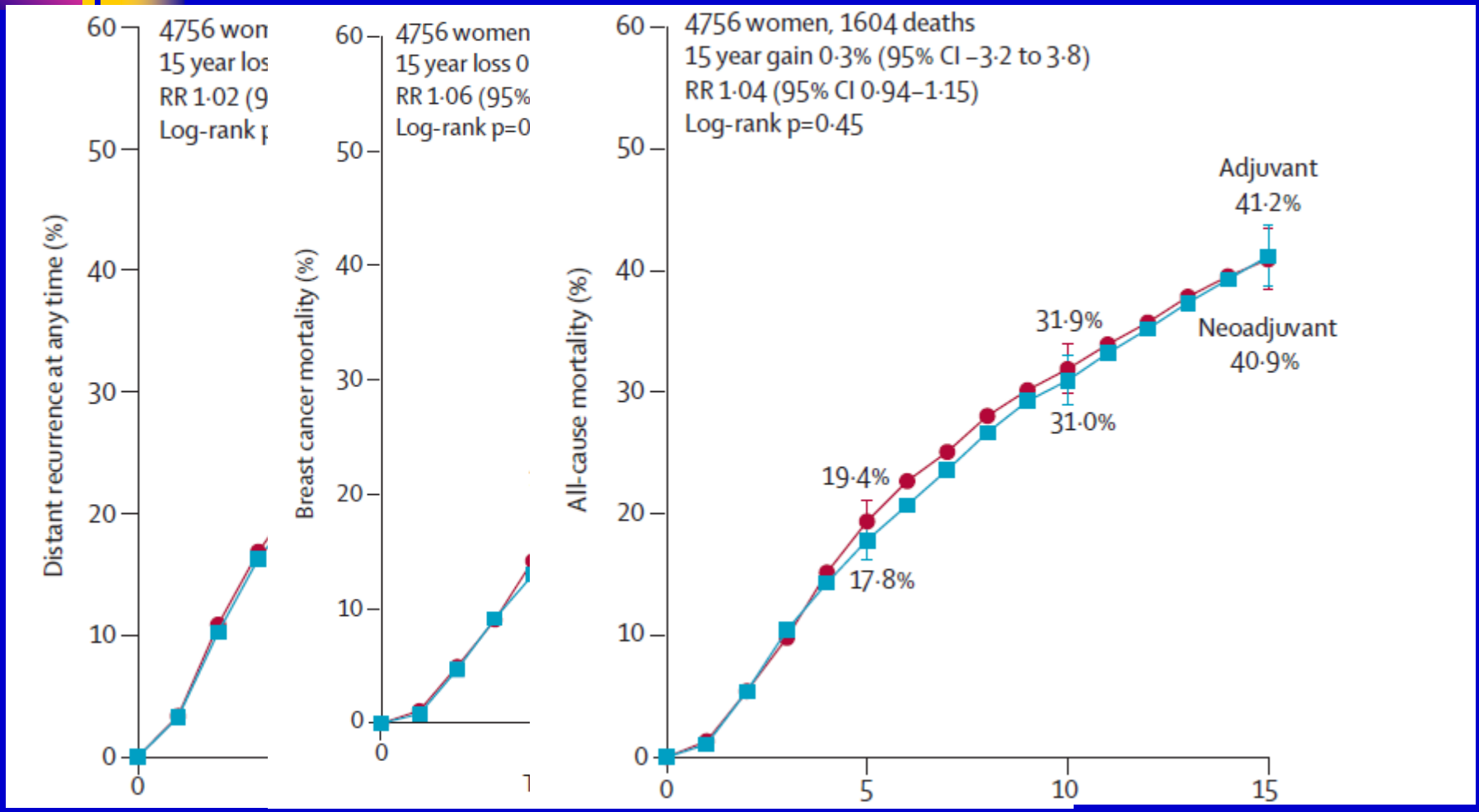


Fig 1. (A) Overall survival (OS) in National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18. (B) Disease-free survival (DFS) in NSABP Protocol B-18. (C) Relapse-free interval (RFI) in NSABP Protocol B-18. (D) OS in NSABP Protocol B-27. (E) DFS in NSABP Protocol B-27. (F) RFI in NSABP Protocol B-27. HR, hazard ratio; Post-Op, postoperative; Pre-Op, preoperative; AC, doxorubicin and cyclophosphamide; T, docetaxel.

Rastogi P, JCO, 2008

Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials

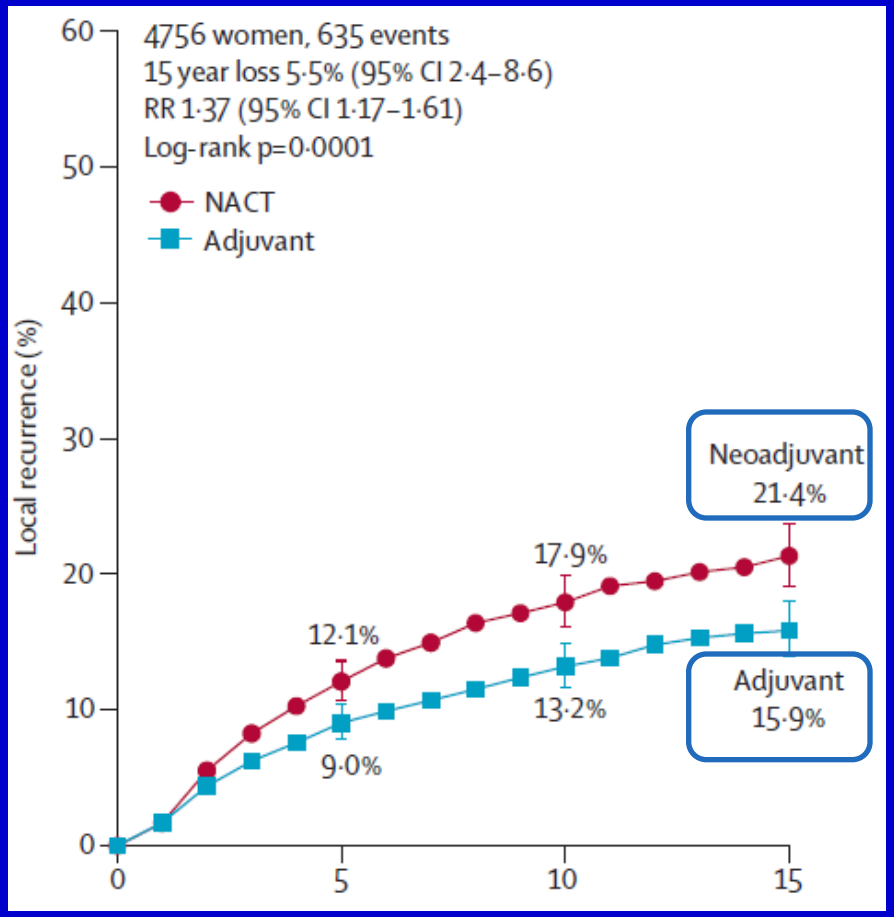
*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**



Lancet Oncol, 2018

Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**



Med f/u:9 yıl

MKC oranları %65 vs %49

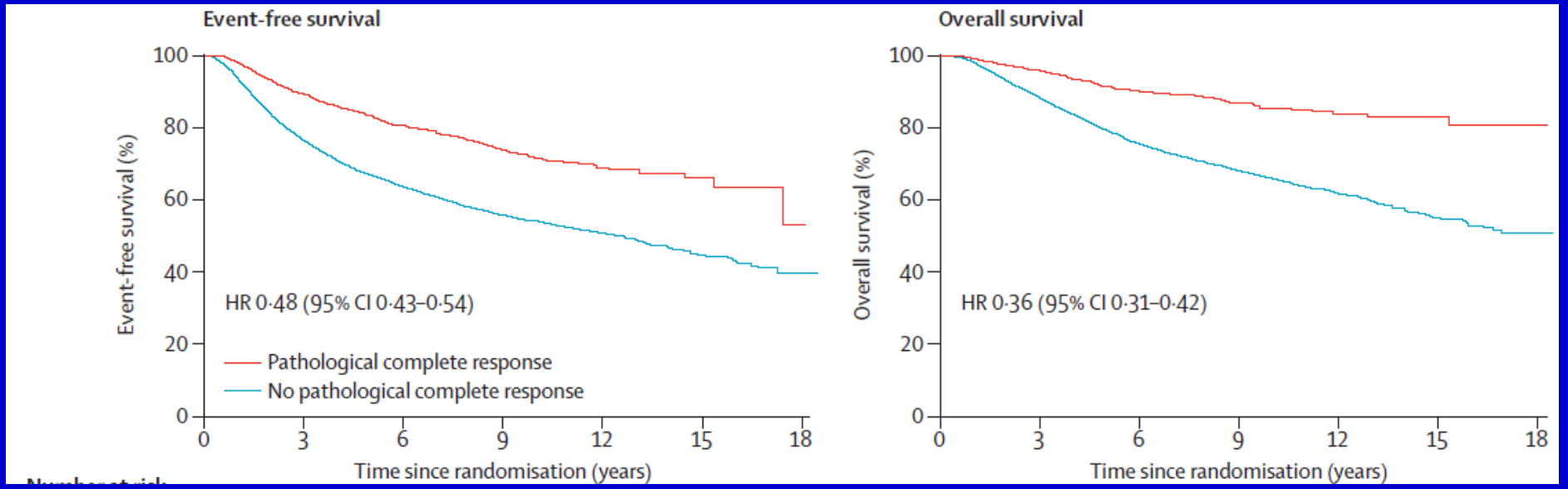
Neoadj tedavide %28 cCR; %41 cPR

Lancet Oncol, 2018

Neoadjuvan tedavide prognostik ve prediktif faktörler??

Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron,



Lancet, 2014

Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

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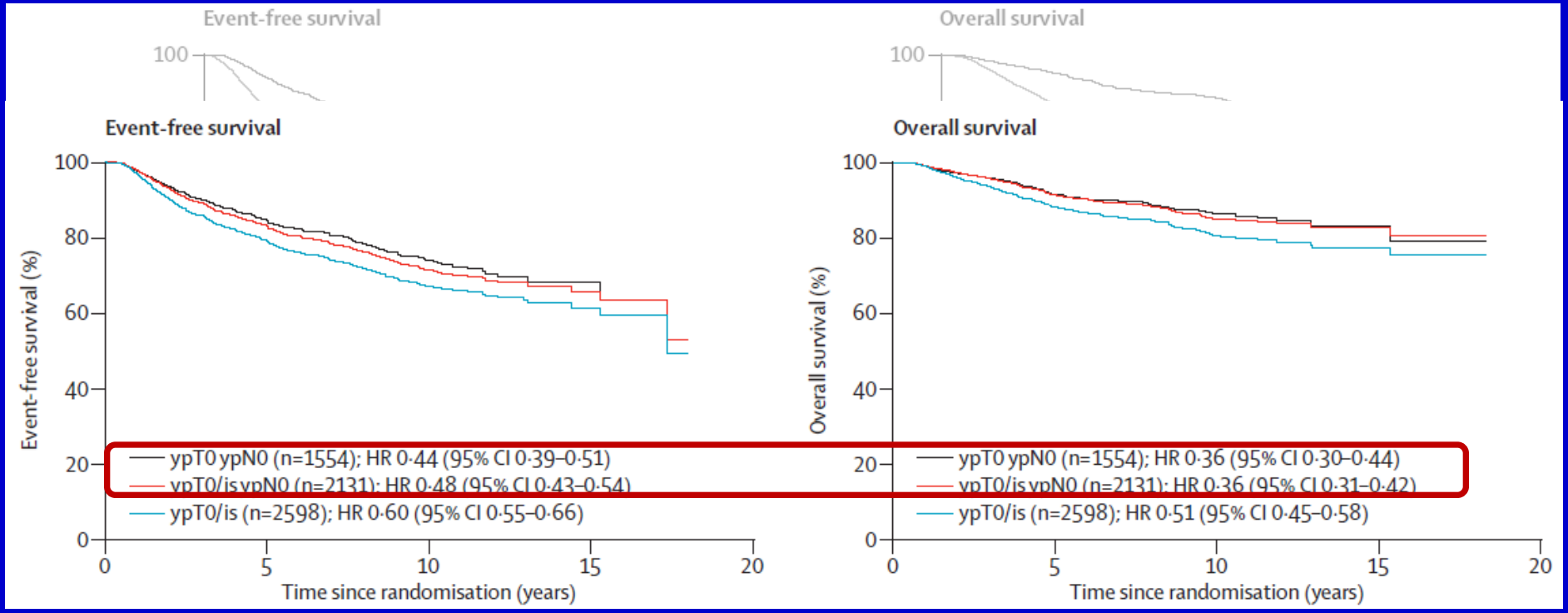


Lancet, 2014

VOLUME 26 · NUMBER 8 · MARCH 10 2008

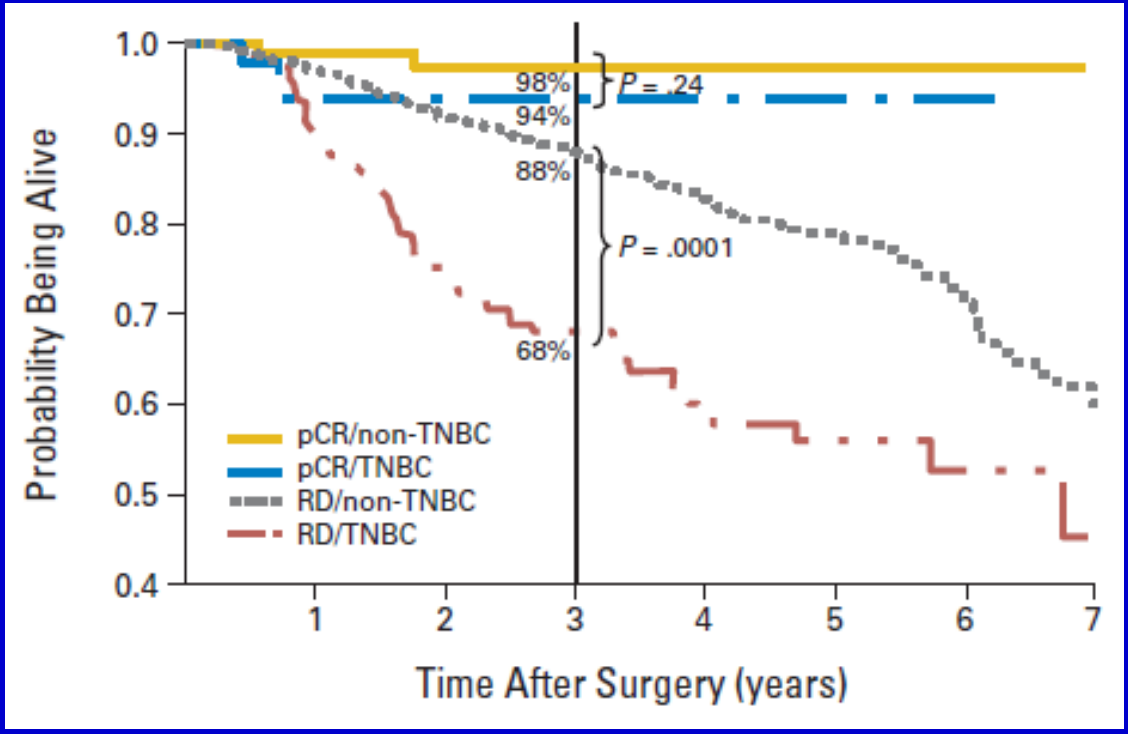
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer

Cornelia Liedtke, Chafika Mazouni, Kenneth R. Hess, Fabrice André, Attila Tordai, Jaime A. Mejia,

N:1118; neoadj KT almış evre I-III hastalar; 255'i TN



pCR oranları;
%22 vs %11 (p:0.034)

pCR durumunda;
rekürens ve ölüm oranları benzer(p:0.24)

Rezidüel hastalık+ ise;
TN %68 vs Non-TN %88 (p<0.0001)

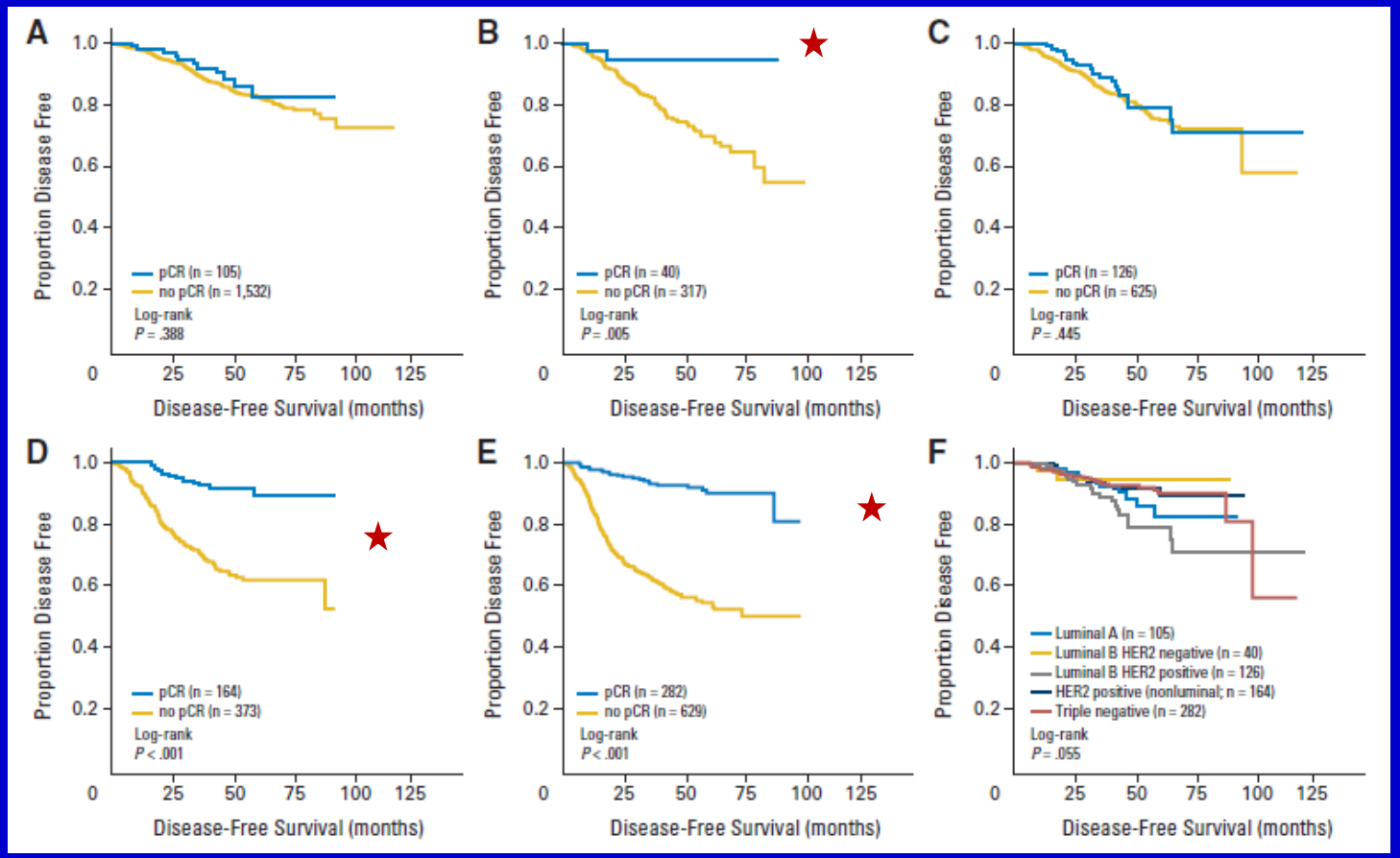
VOLUME 30 · NUMBER 15 · MAY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes

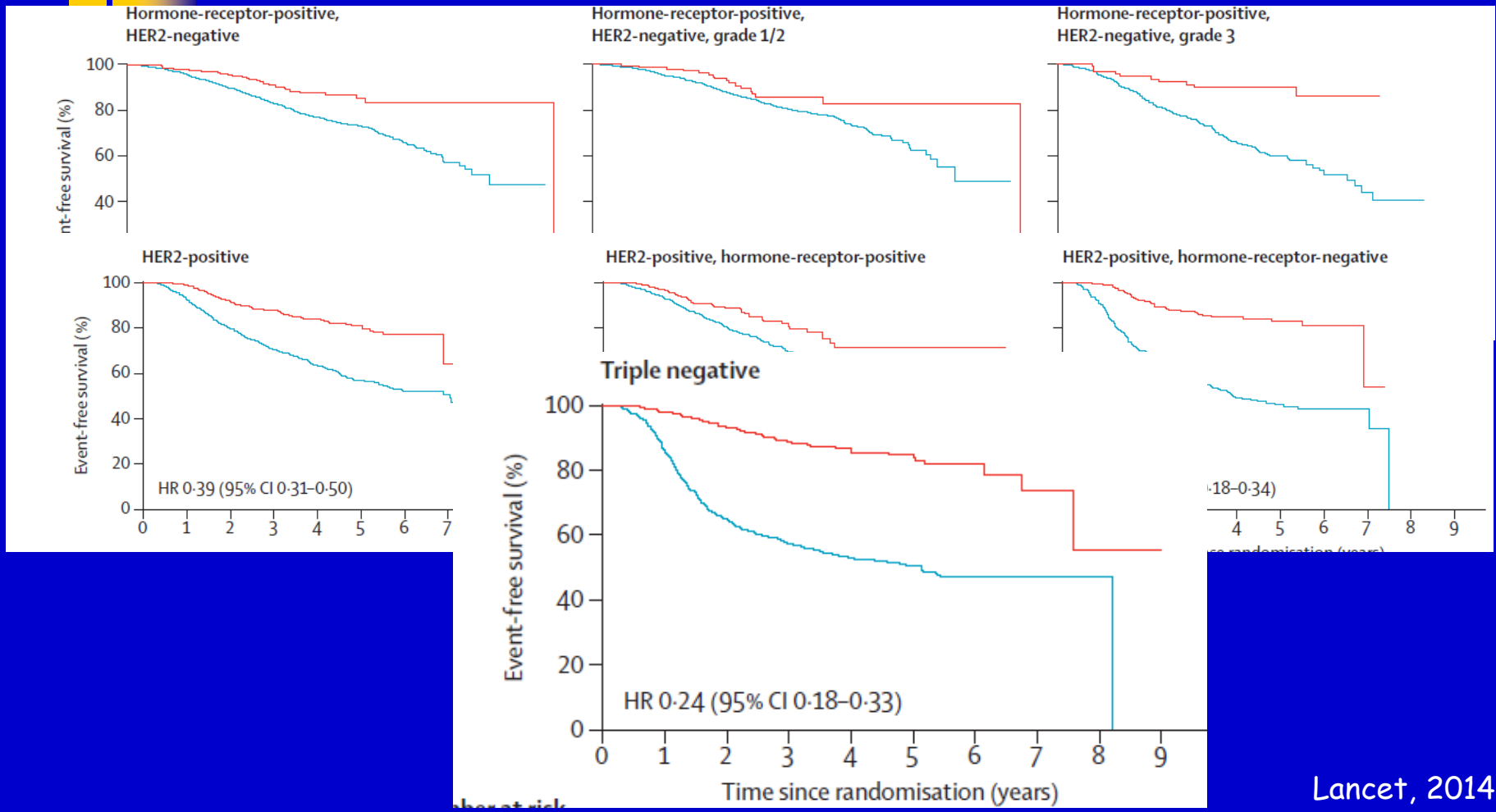
Gunter von Minckwitz, Michael Untch, Jens-Uwe Blohmer, Serban D. Costa, Holger Eidtmann, Peter A. Fasching,



Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron,

pCR
No pCR



Lancet, 2014

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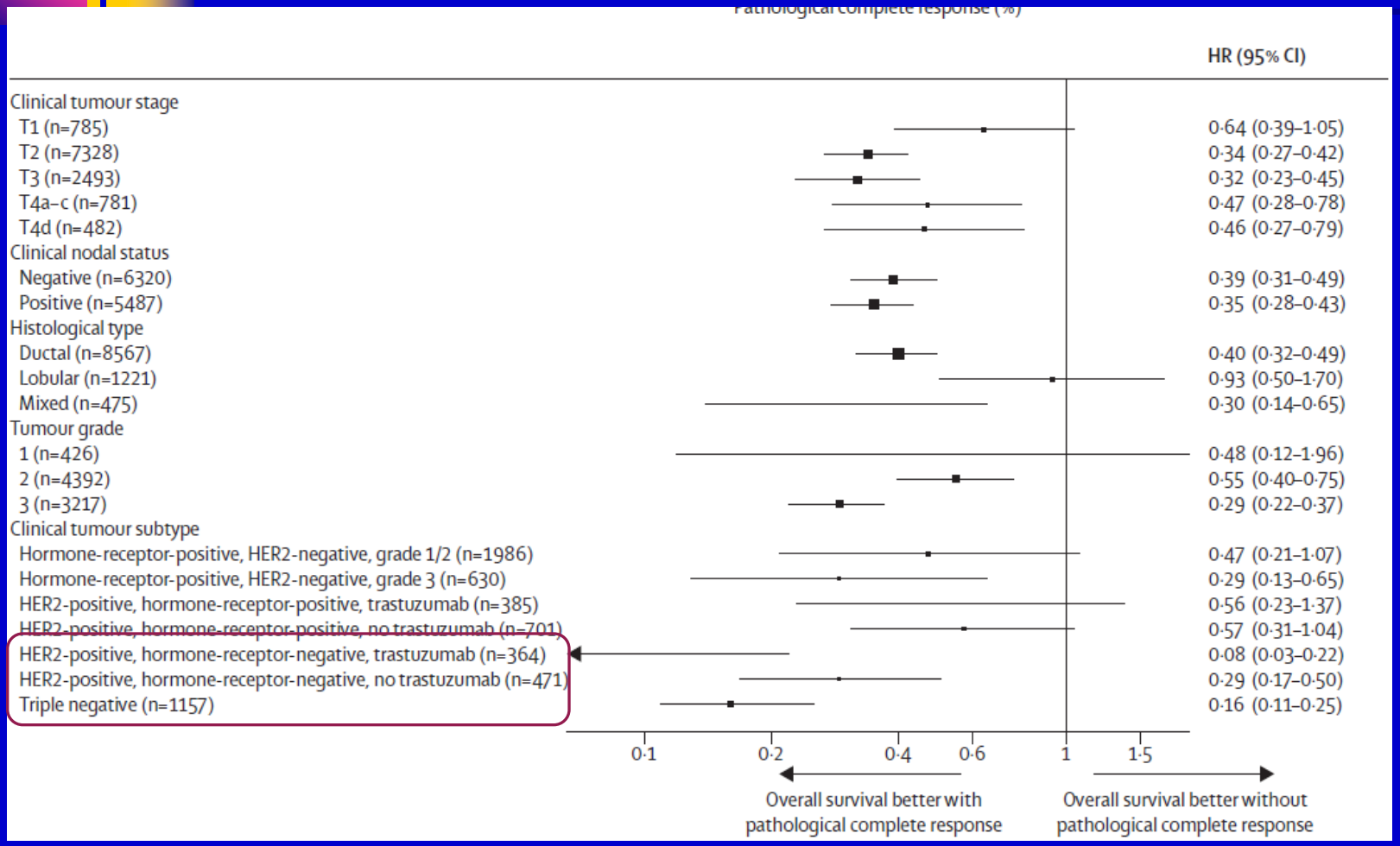
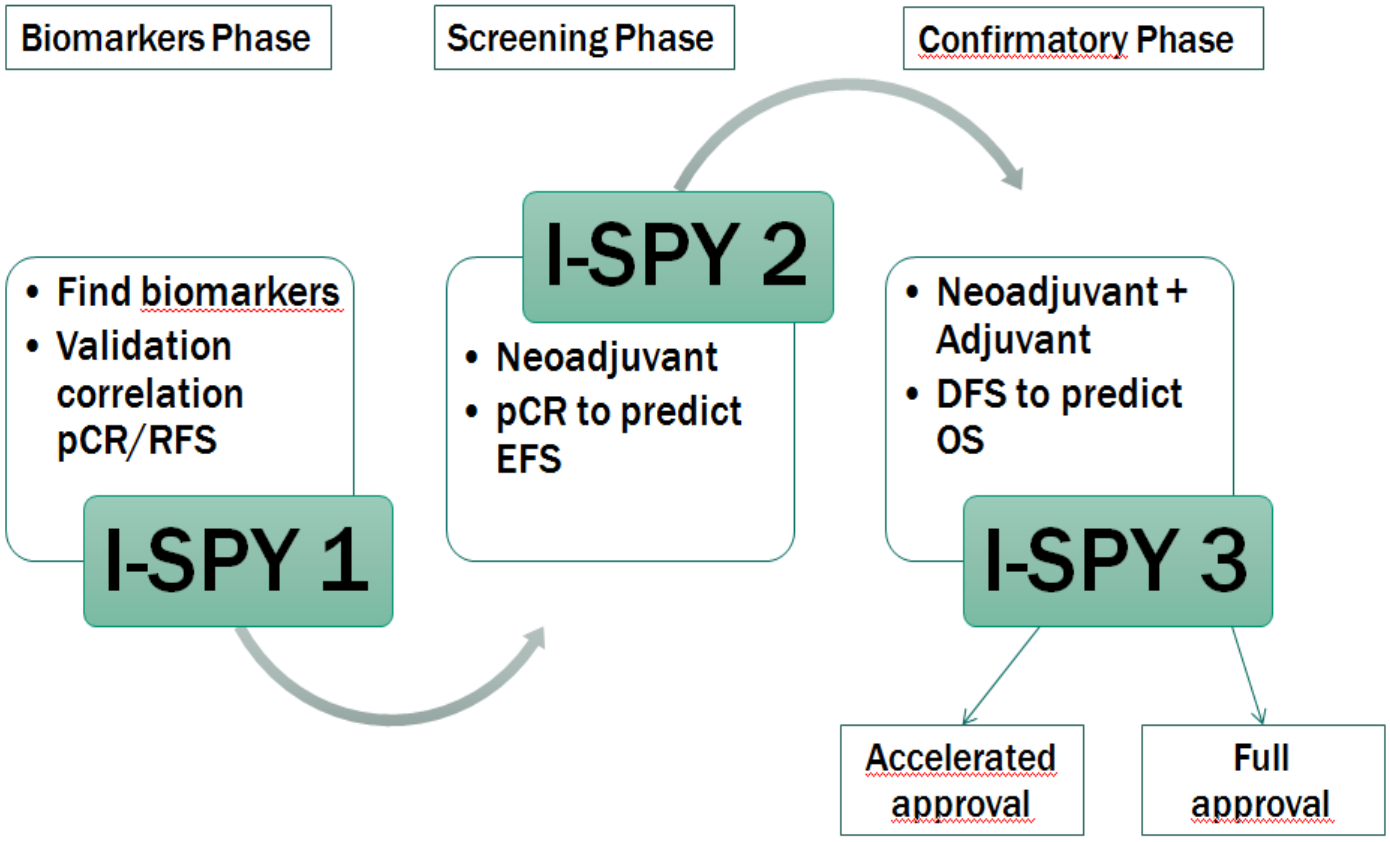
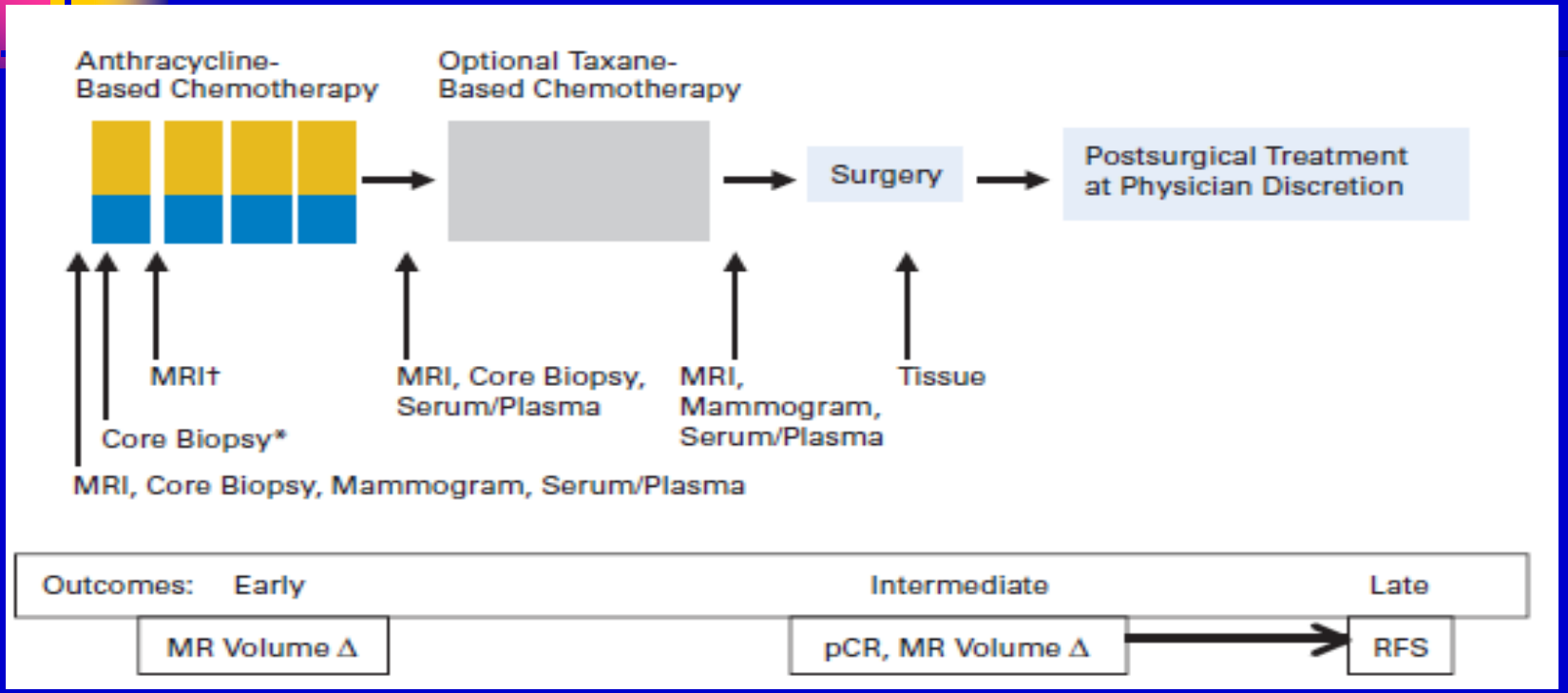


Lancet, 2014


Biomarkers Phase
Screening Phase
Confirmatory Phase
I-SPY 2
• Neoadjuvant
• pCR to predict EFS
• Find biomarkers
• Validation correlation pCR/RFS
I-SPY 1
• Neoadjuvant + Adjuvant
• DFS to predict OS
I-SPY 3
Accelerated approval
Full approval

Pathologic Complete Response Predicts Recurrence-Free Survival More Effectively by Cancer Subset: Results From the I-SPY 1 TRIAL—CALGB 150007/150012, ACRIN 6657

Laura J. Esserman, Donald A. Berry, Angela DeMichele, Lisa Carey, Sarah E. Davis, Meredith Buxton,



Neoadj tedavi alan ≥3 cm meme ca
pCR ve RFS açısından prediktif belirteçler (pCR/RCB??)
çok merkezli çalışma; N:221

JCO 2012

I-SPY Trial: pCR Rates According to IHC and Intrinsic Subtypes

	Distribution (n = 190)	pCR (n = 190)	*P* value
IHC			
HR+ HER2-	48%	10%	NR
HR+ HER2+	12%	32%	
HR- HER2-	28%	33%	
HR- HER2+	12%	50%	
Intrinsic Subtypes	**Distribution (n = 149)**	**pCR (n = 144)**	***P* value**
Luminal A	29%	2%	<.0001
Luminal B	19%	15%	
HER2-enriched	15%	52%	
Basal	32%	34%	
Normal-like	5%	43%	

Esserman et al. *J Clin Oncol* 2009; 27 (suppl): 18s (abstract LBA515).

I-SPY Trial: pCR Rates According to RNA Classifiers

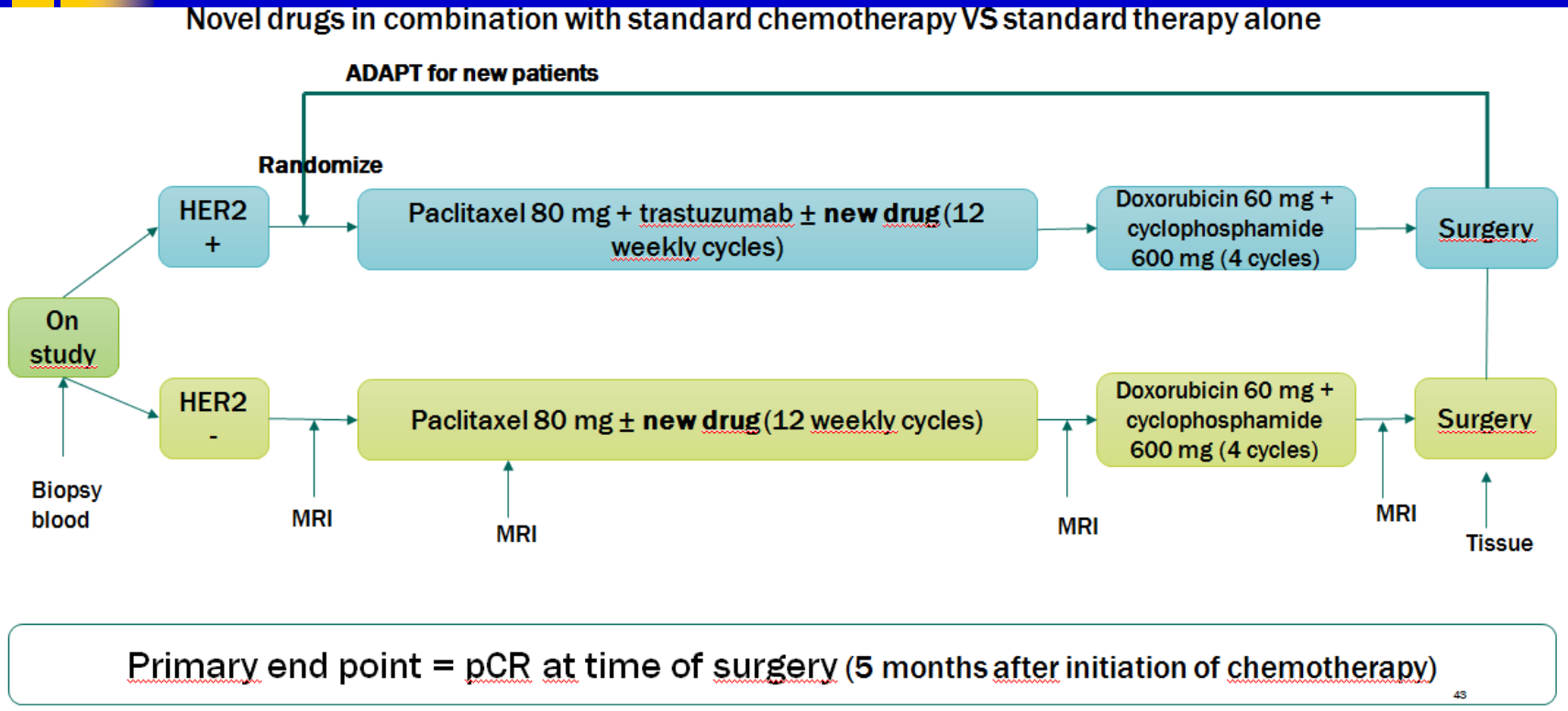
	Distribution (n = 149)	pCR (n = 144)	P value
21 Gene Recurrence Score			
Low	22%	3%	<.0001
Moderate	10%	0%	
High	68%	36%	
70-Gene Signature			
Good signature	9%	0%	.038
Poor signature	91%	27%	
Wound Healing Signature			
Quiescent	23%	6%	.0049
Activated	77%	30%	
p53 Mutation			
Wildtype	50%	11%	.0004
Mutation	50%	38%	

PER

Esserman et al. *J Clin Oncol* 2009; 27 (suppl): 18s (abstract LBA515).

I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy

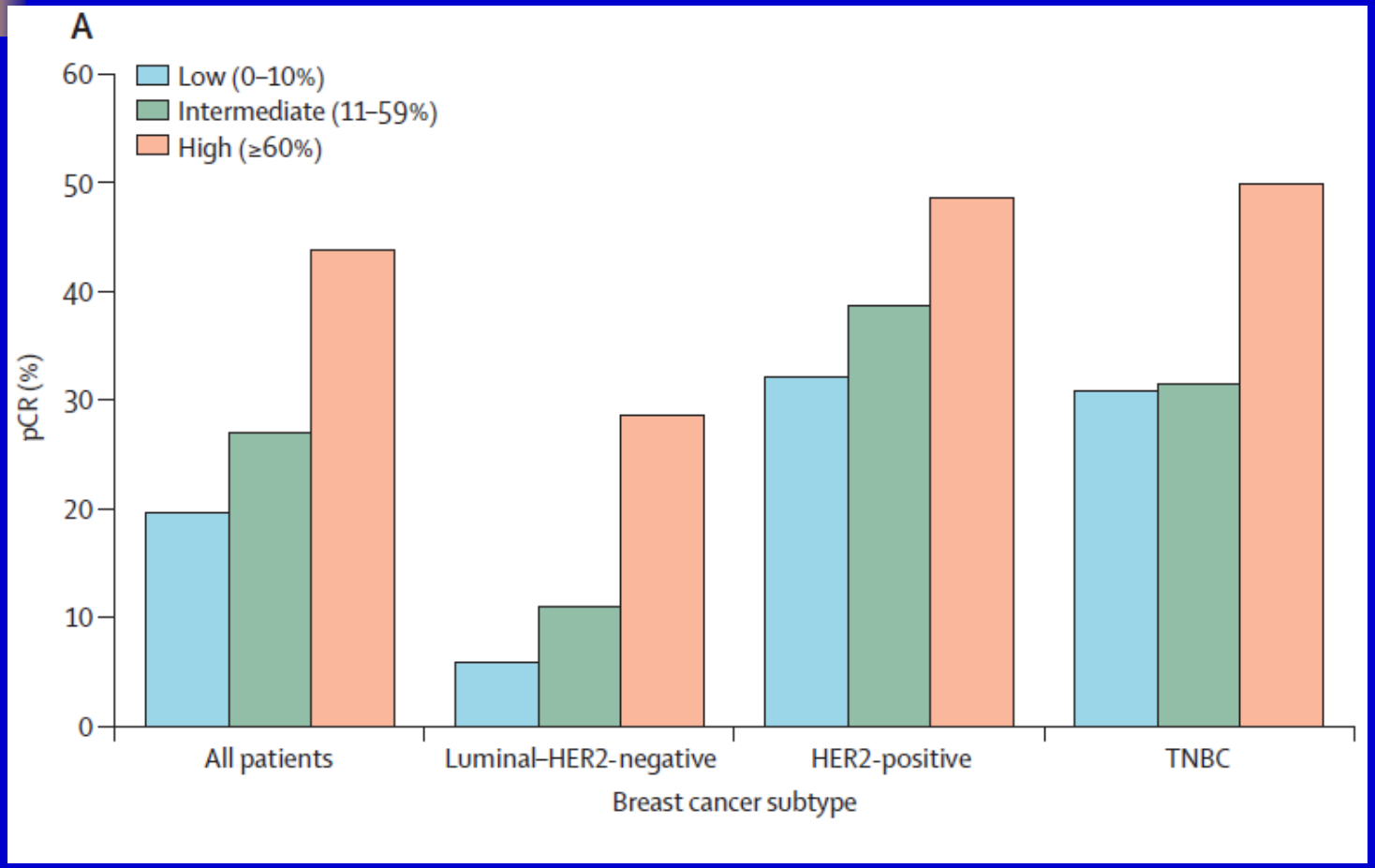
AD Barker[1], CC Sigman[2], GJ Kelloff[1], NM Hylton[3], DA Berry[4] and LJ Esserman[3]



Clin Pharmacol Therap, 2009

Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy

Carsten Denkert, Gunter von Minckwitz, Silvia Darb-Esfahani, Bianca Lederer, Barbara I Heppner, Karsten E Weber, Jan Budczies, Jens Huober,



TIL seviyeleri arttıkça bütün alttiplerde pCR da artıyor

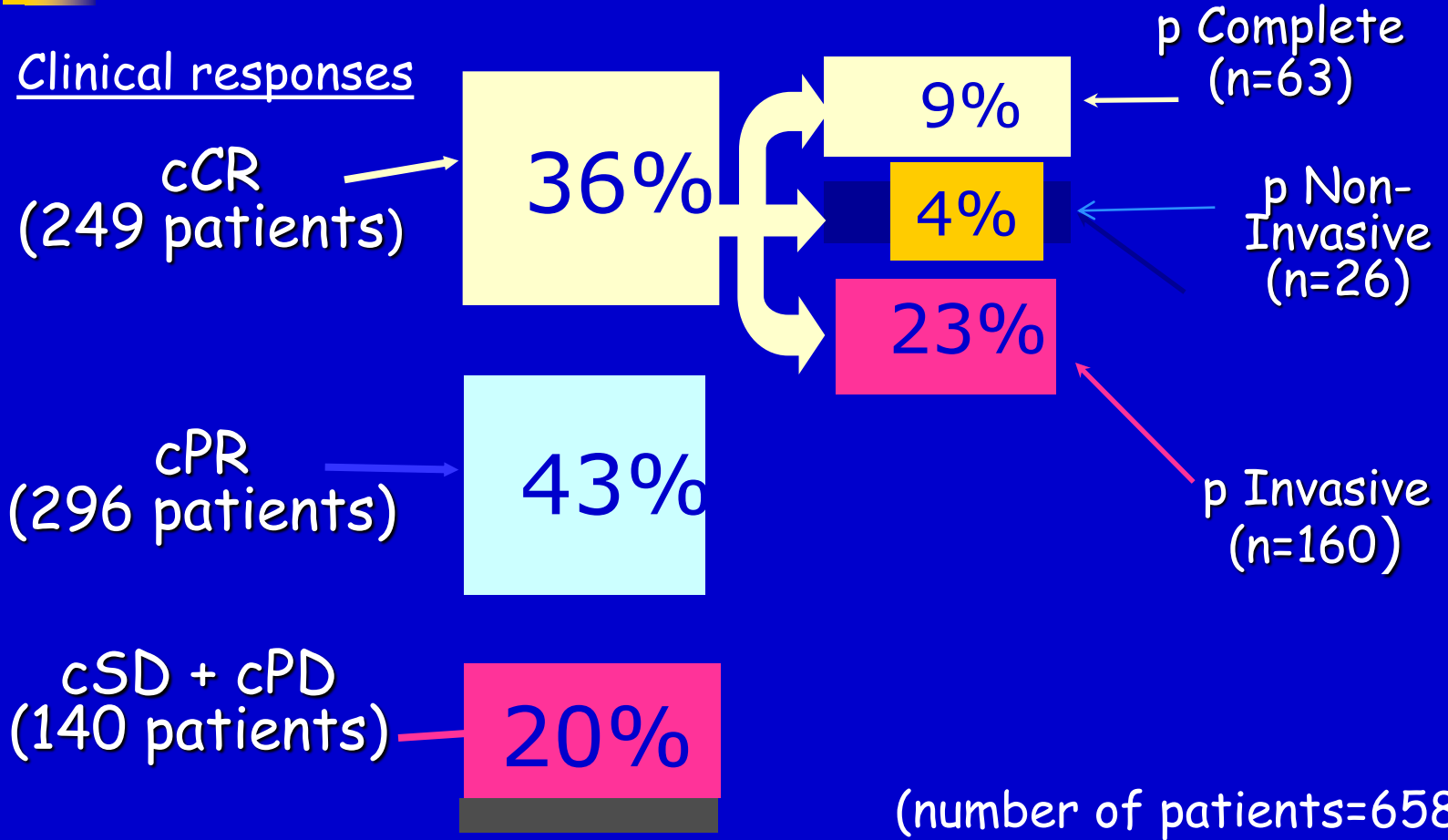
Lancet Oncology, 2018

NSABP B-18-Pivotal çalışma

- Evre I/II (T1-3N0-1M0) n=1523
- 50 yaş üstü Tamoksifen
  HR bakılmadan tüm hastalar

Fisher B, J Clin Oncol, 1998

NSABP B-18 neoadj group
Klinik ve patolojik yanıtlar



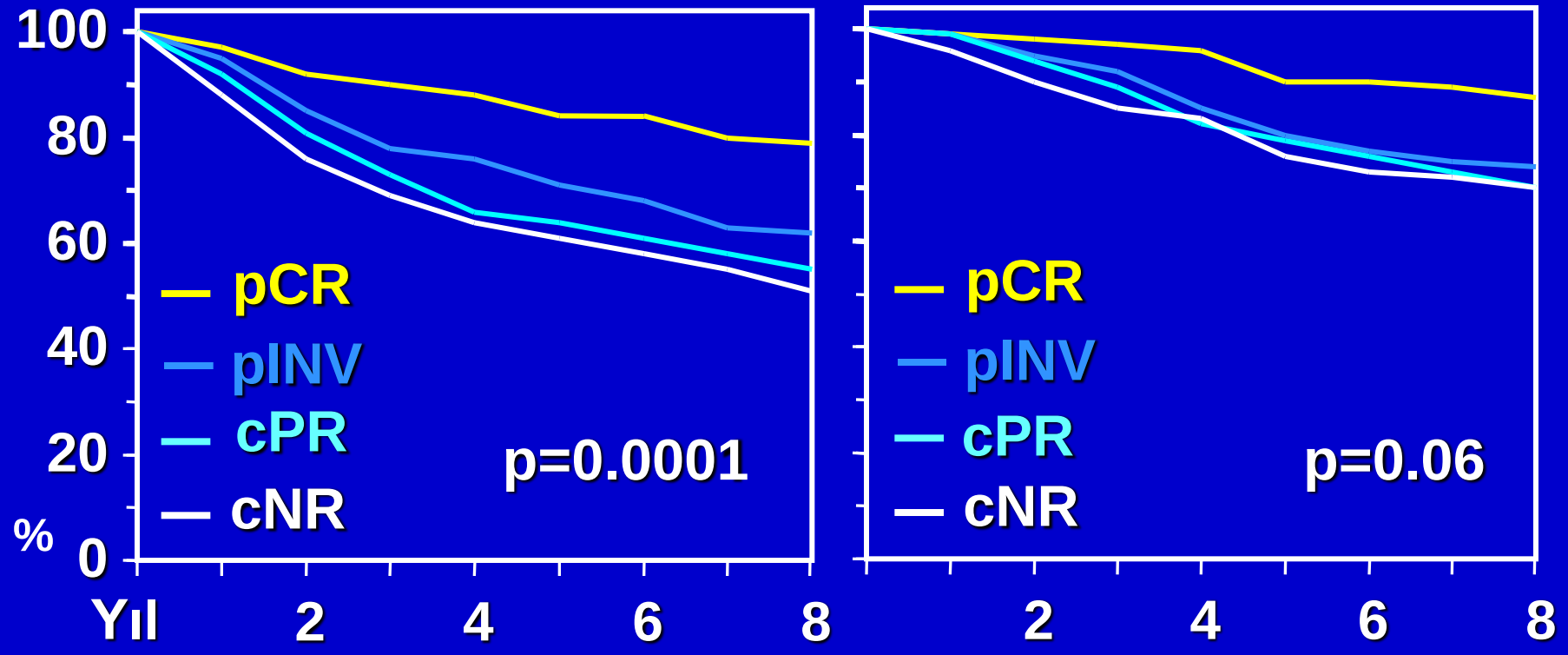
NSABP B-18

5Y Oran	Postop (n=752)	Preop (n=743)	p
GS	80	79.6	0.83
HS	67.3	66.7	0.99
Uzak HS	73.2	73.3	0.7
Lokal nüks	5.8	7.9	0.23
MKC	60	67	0.002

Preop KT vs postop KT'den kötü değil

Fisher B, J Clin Oncol, 1998

NSABP B-18
Cevaba Göre HS ve GS



Fisher B, J Clin Oncol, 1998

MD Anderson

Prospective Evaluation of Paclitaxel Versus Combination Chemotherapy With Fluorouracil, Doxorubicin, and Cyclophosphamide as Neoadjuvant Therapy in Patients With Operable Breast Cancer

By Aman U. Buzdar, S. Eva Singletary, Richard L. Theriault, Daniel J. Booser, Vicente Valero, Nuhad Ibrahim,

- T1-3N0-1M0 meme Ca (T1N0 grubu dahil değil)
- Neoadj 4 FAC(n:87) vs 4 paklitaksel(n:87); takiben cerrahi;

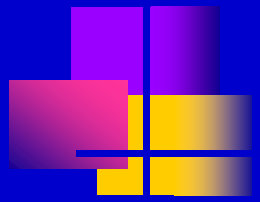
  adj 4 FAC ve RT;

  HR+ ise tamoksifen
- cCR+PR: %79 vs %80
- pCR: %17 vs %8
- MKC %35 vs %46

} Anlamlı fark yok

Buzdar AU, JCO 1999

Tax301 (Aberdeen) çalışması



Birinci evre

İkinci evre

Tüm hastalar

CVAP X4

Yanıt yok

Yanıt var

Randomizasyon

Dosetaksel X4

Dosetaksel X4

CVAP X4

Son Değerlendirme/ Cerrahi

T>3cm / T3-4, N2

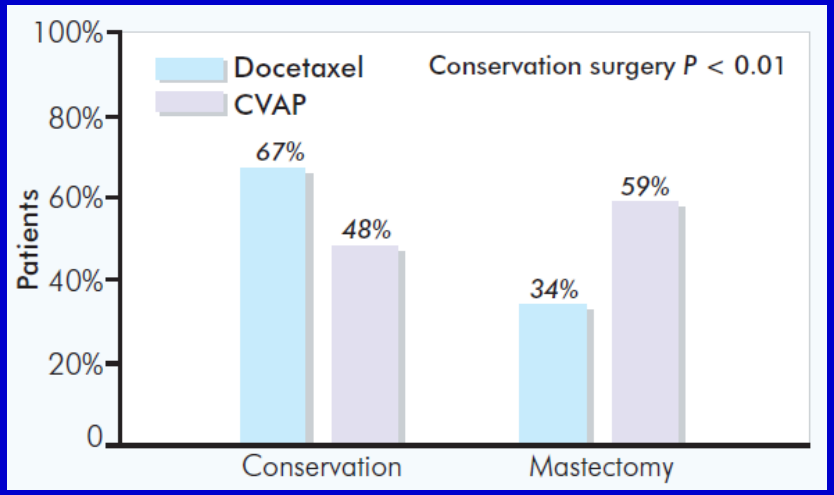
162 hasta

Smith AC. JCO 2002

Tax301 (Aberdeen) çalışması

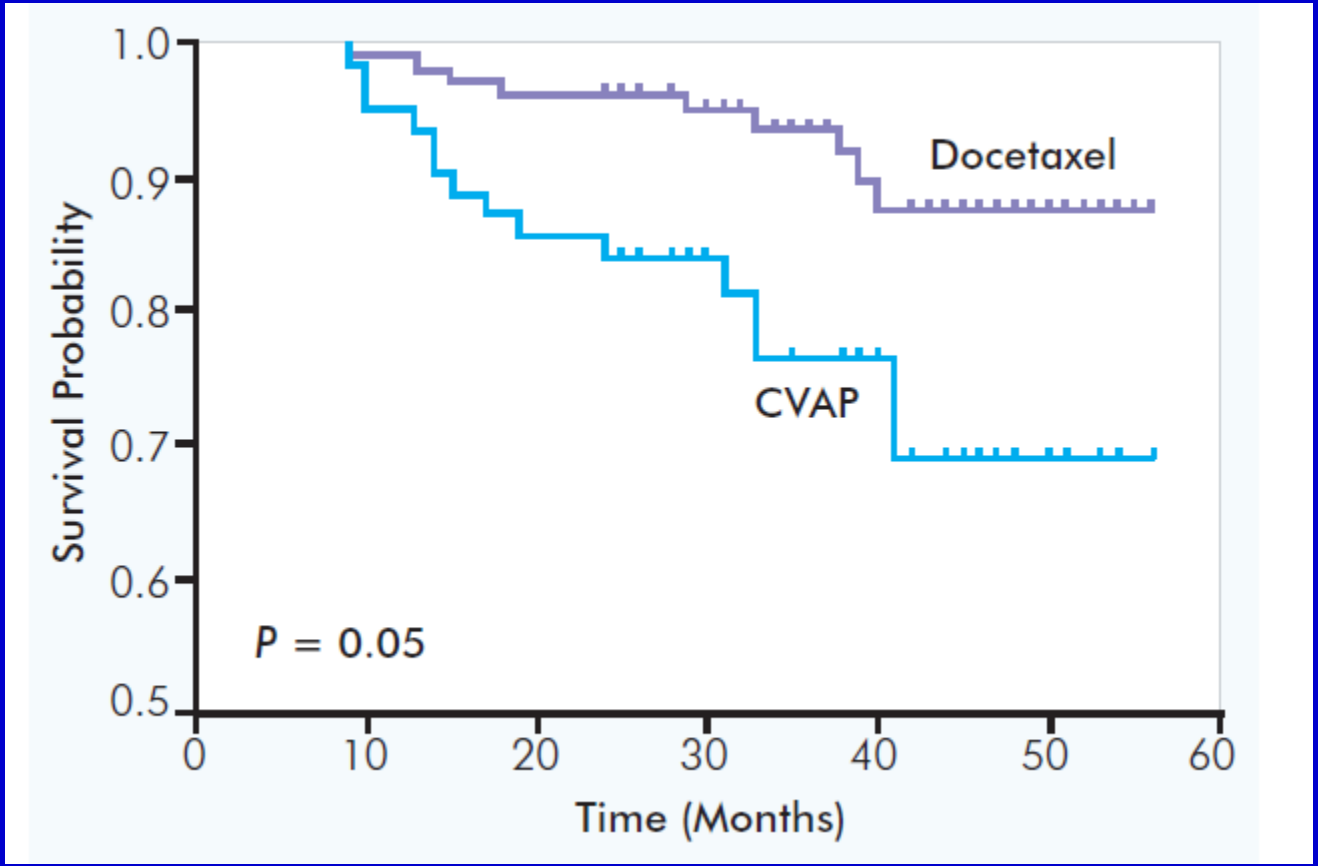
	Grade of Pathological Response*	CVAP (n = 50)	Docetaxel (n = 47)
Pathological Non-Response	1	22%	4%
	2	18%	20%
	3	28%	23%
Pathological Complete Response	4	16%	19%
	5	16%	34%

Miller&Payne Gradlama Sistemine göre



Heys SD; 2002

Tax301 (Aberdeen) çalışması



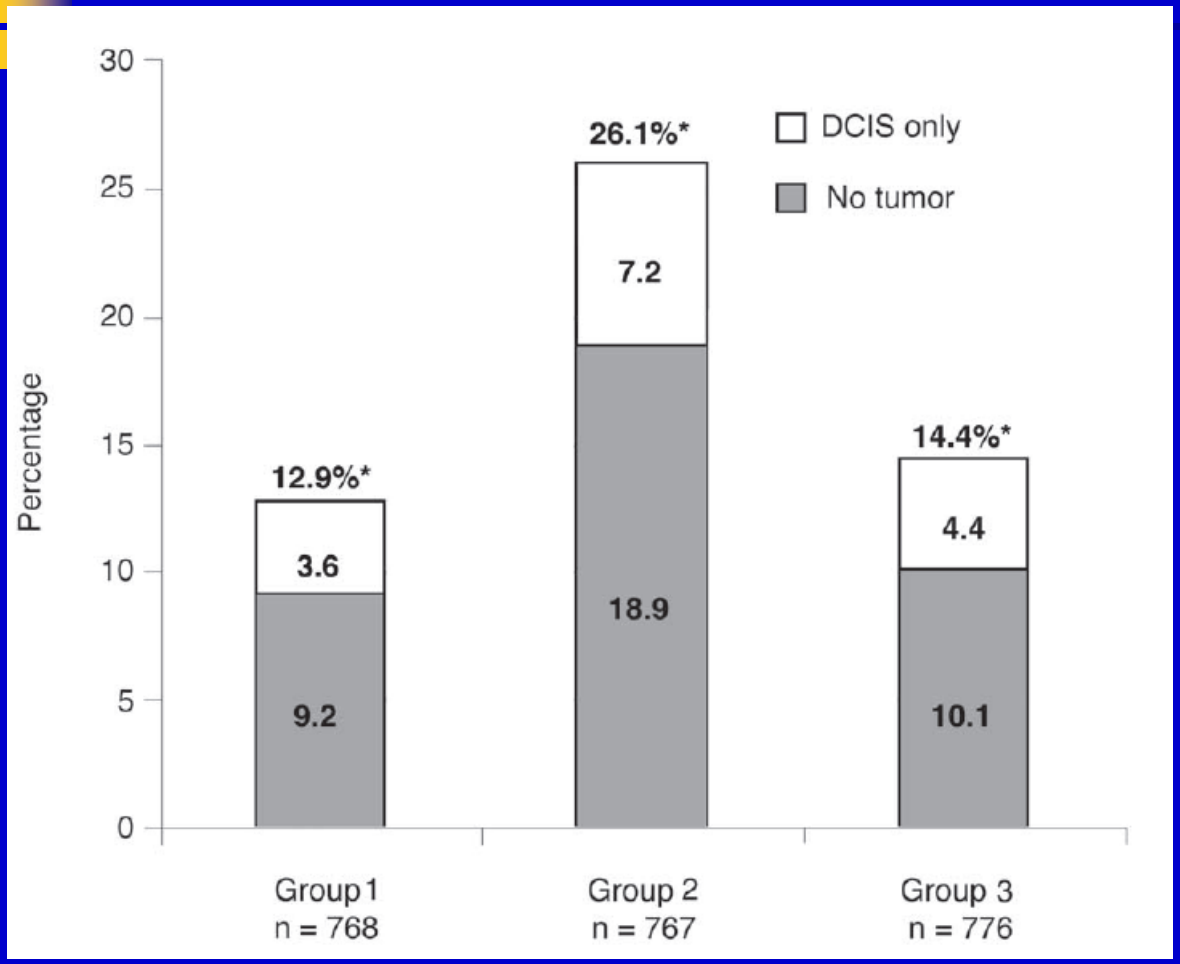
3 yıllık OS dosetaksel lehine anlamlı

Heys SD; 2002

Sequential Preoperative or Postoperative Docetaxel Added to Preoperative Doxorubicin Plus Cyclophosphamide for Operable Breast Cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27

Bear HD, JCO 2006

NSABP B-27

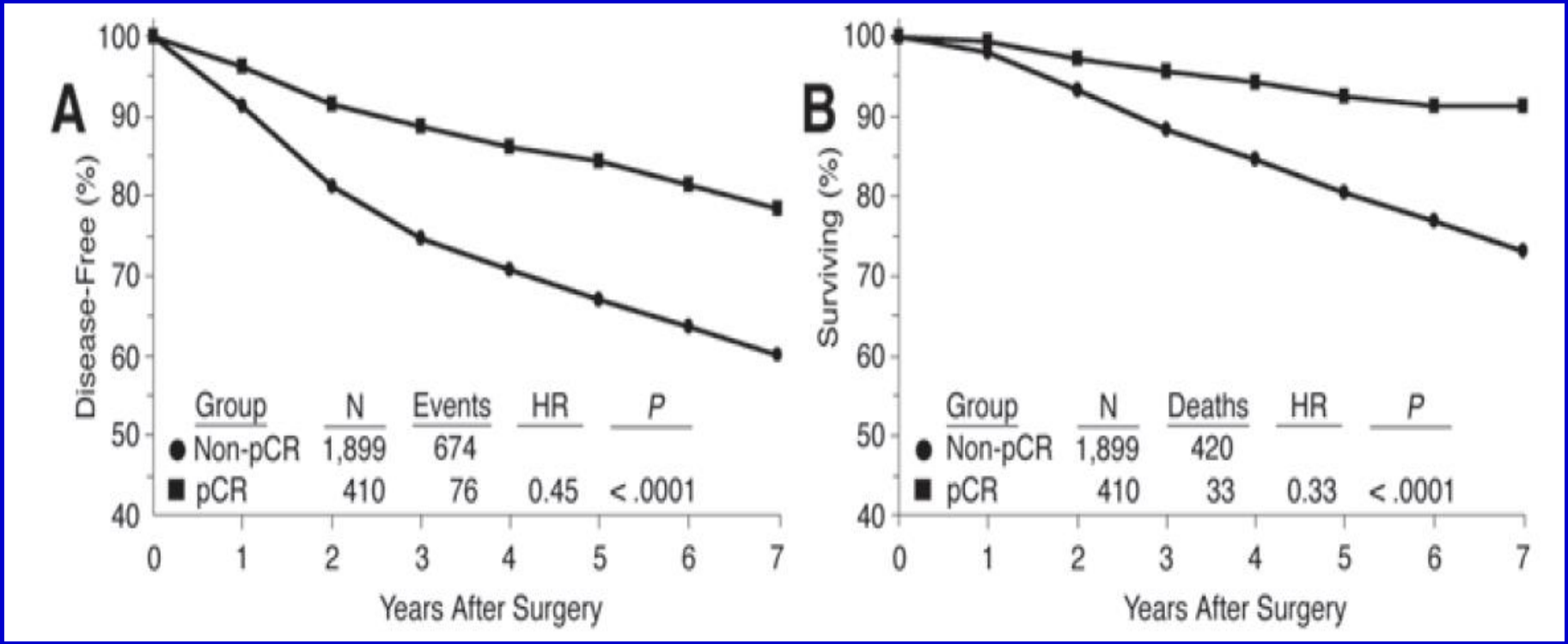


cRR: %91 vs %86

pCR oranları *p<0.001

Bear HD, JCO 2006

NSABP B-27; pCR a göre DFS ve OS



Bear HD, JCO 2006

NSABP B-18(16yıllık) ve B-27 (8,5 yıllık) update

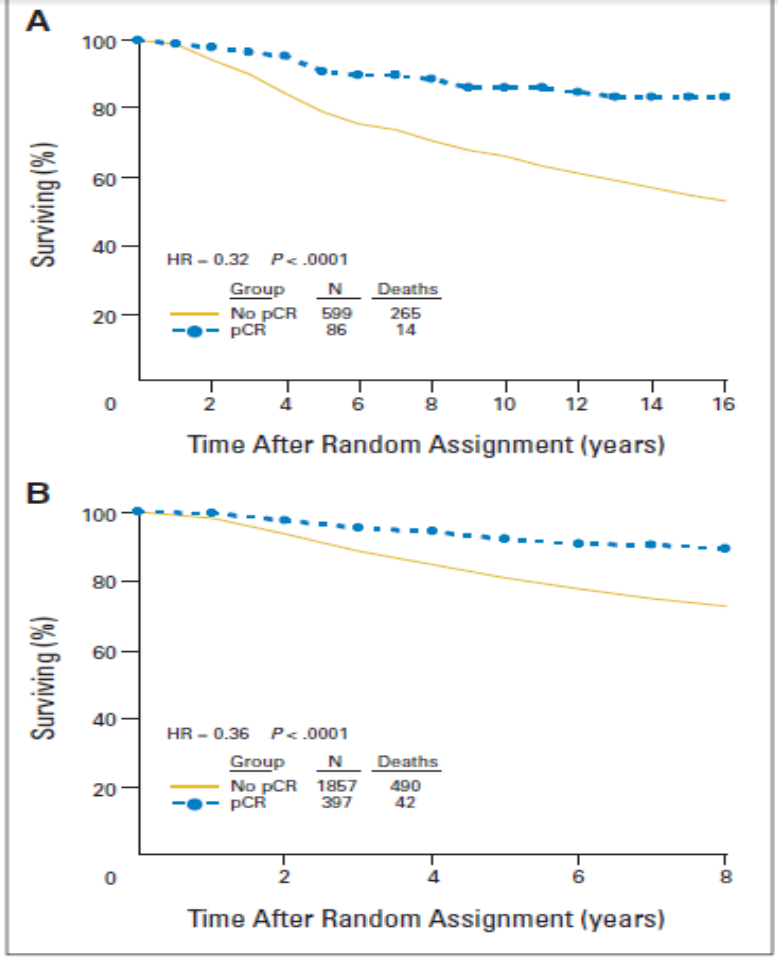


Fig 4. Survival by pathologic complete response (pCR) status in patients who received preoperative doxorubicin and cyclophosphamide. (A) National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18: group 2 patients. (B) NSABP Protocol B-27: all patients. HR, hazard ratio.

- Preop AC alan hastalarda pCR OS ve DFS açısından anlamlı

Rastogi P, JCO, 2008

Breast Cancer (2017) 24:63–68
DOI 10.1007/s12282-016-0666-7

ORIGINAL ARTICLE

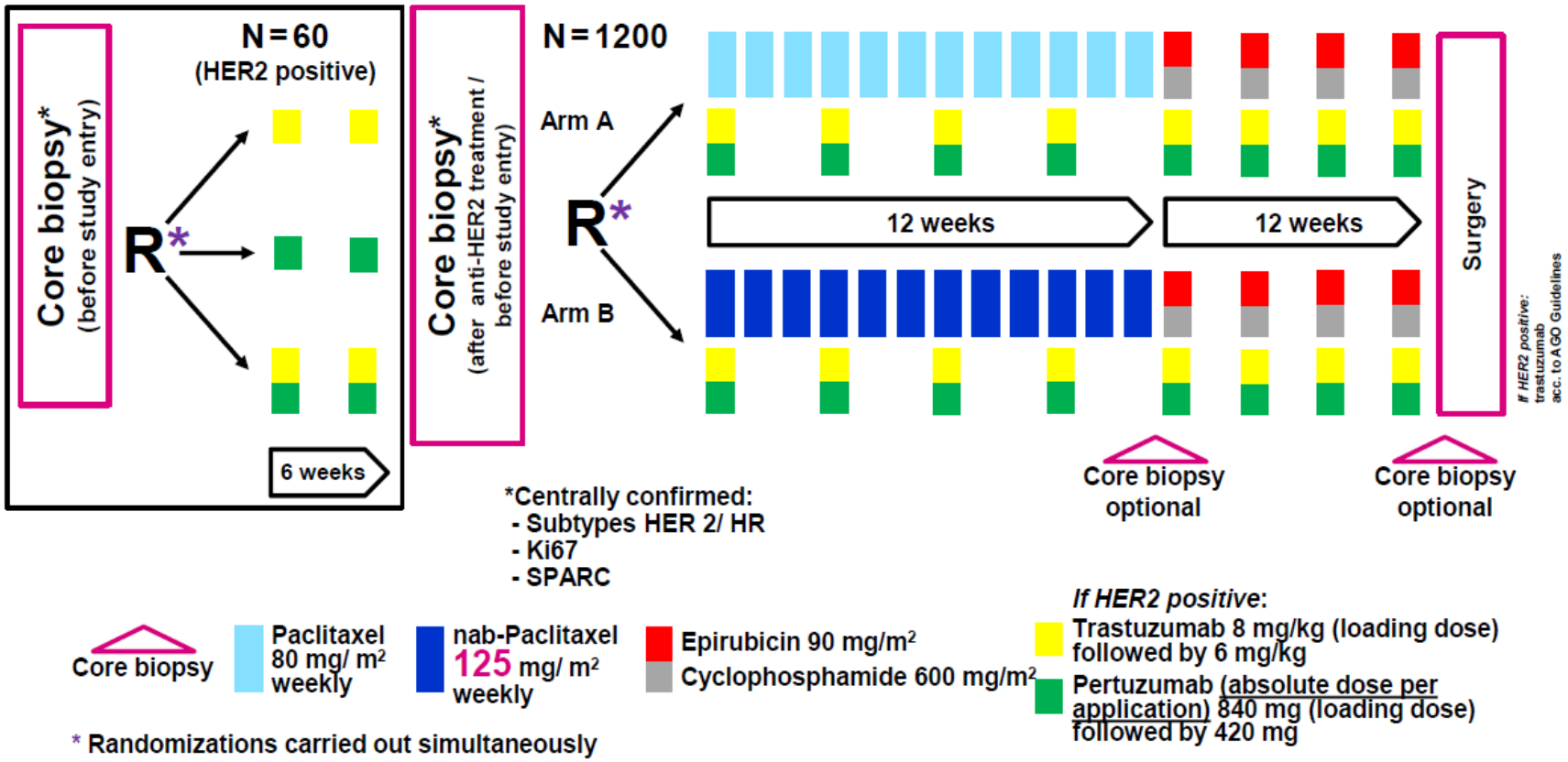
Docetaxel and cyclophosphamide as neoadjuvant chemotherapy in HER2-negative primary breast cancer

Katsuhiko Nakatsukasa[1] · Hiroshi Koyama[2] · Yoshimi Oouchi[2] · Seiichi Imanishi[2] ·

T1-3N0-1 HER2- meme ca(N:52)
TC (dose 75 mg/m2+siklofosfamid 600 mg/m2 q3wx4)
Tüm grupta pCR %16.3 ve 7/8 tanesi TN grupta

	Total ($n = 49$)	Luminal A-like ($n = 12$)	Luminal B-like ($n = 23$)	Triple-negative ($n = 14$)	p value*
pCR n (%)	8 (16.3)	0 (0 %)	1 (4.3 %)	7 (50.0 %)	0.017

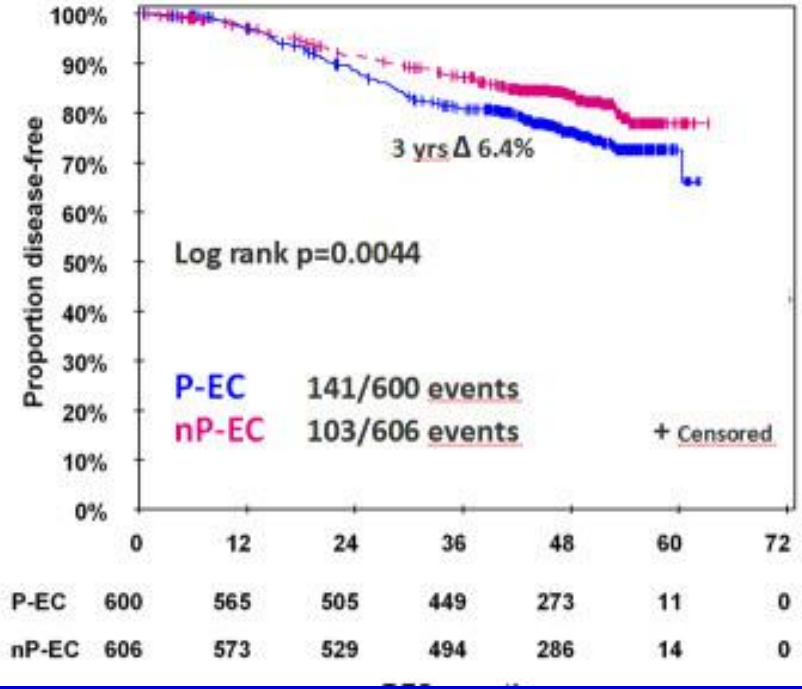
Final Study Design
(after 400 patients recruited)



pCR: %38 vs %29 nab-pakli lehine; TN kolda %48 vs%26

Untch M et al

[GS3-05] Survival analysis of the prospectively randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy with weekly nab-paclitaxel with solvent-based paclitaxel followed by anthracycline-cyclosphosphamide for patients with early breast cancer - GBG69



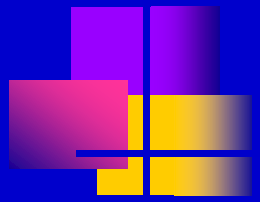
- Median follow-up of 49 months (IQR 44.6 - 52.9)
- HR (nP-EC vs. P-EC) = 0.69 (95% CI 0.54-0.89)
- Number needed to treat (NNT; 3yrs) = 16 pts

DFS rates (estimated):

Time	P-EC	95% CI, P-EC	nP-EC	95% CI, nP-EC
3 yrs	80.7%	(77.2-83.7)	87.1%	(84.1-89.6)
4 yrs	76.2%	(72.3-79.5)	83.5%	(80.2-86.4)

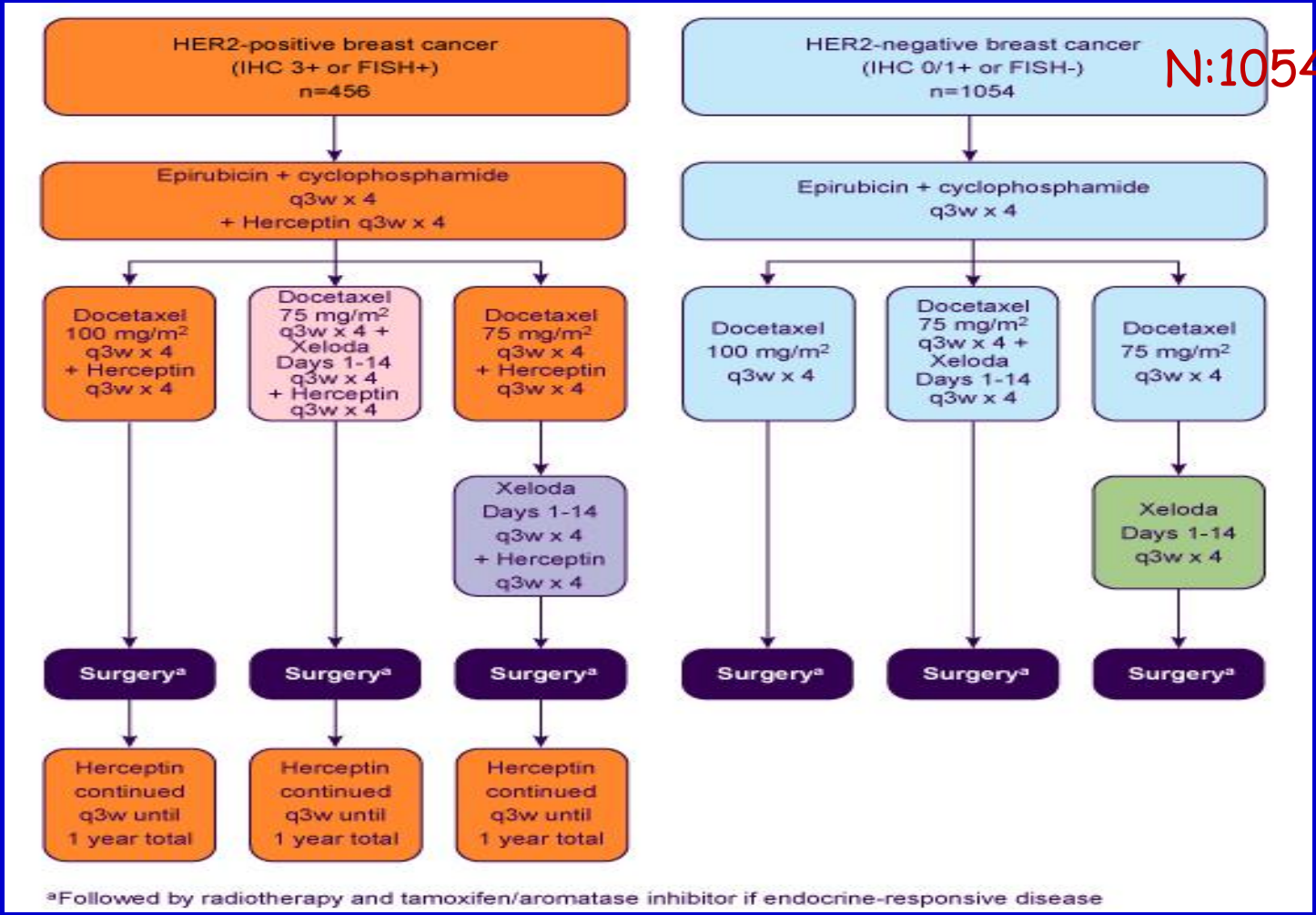
P:0.0044

OS verileri matür değil
Yan etki >grad 3 %26 vs %21



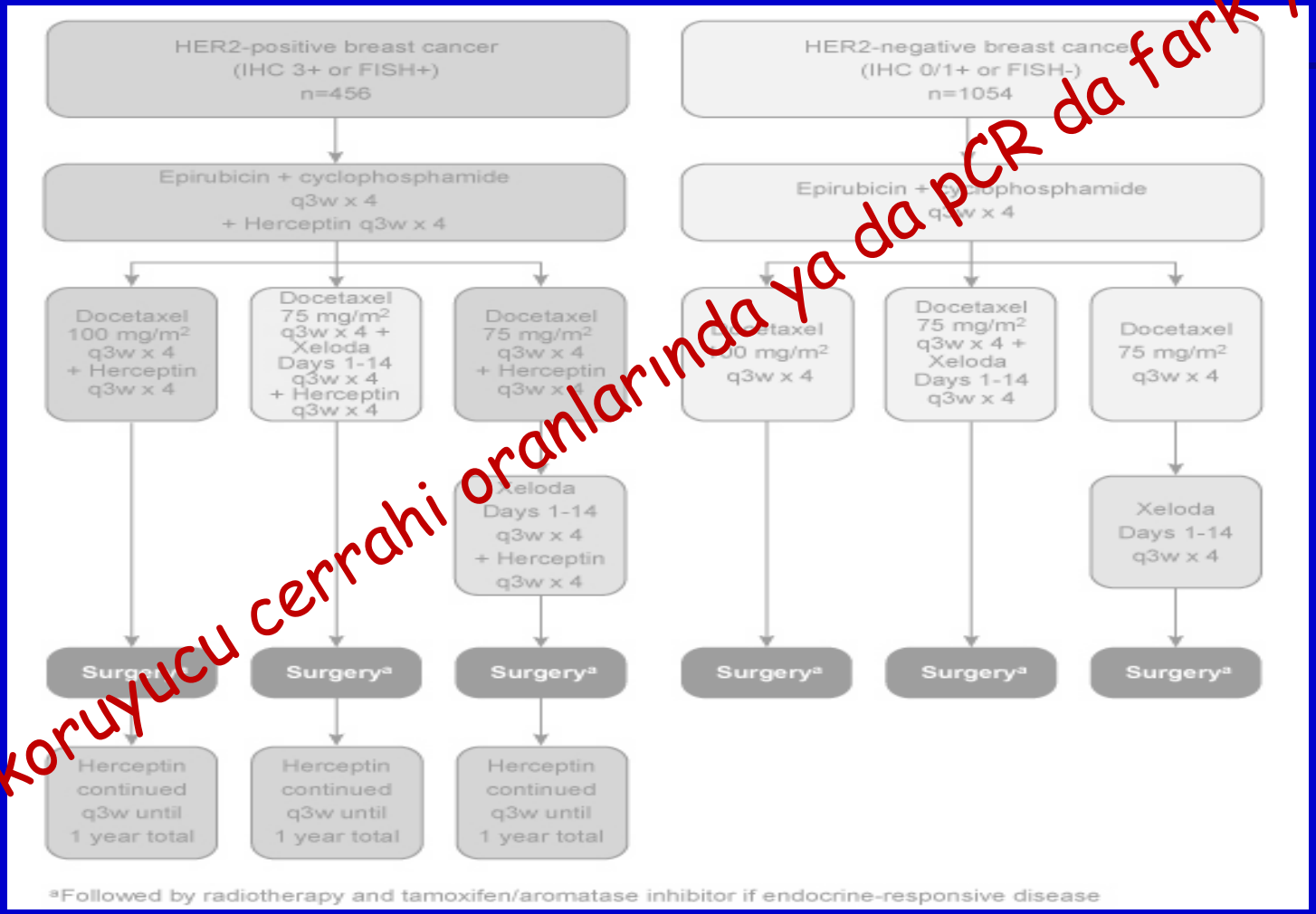
Antrasiklin ve taksan dışı ilaçlar??

GeparQuattro çalışması



Von Minckwitz G, JCO 2010

GeparQuattro çalışması



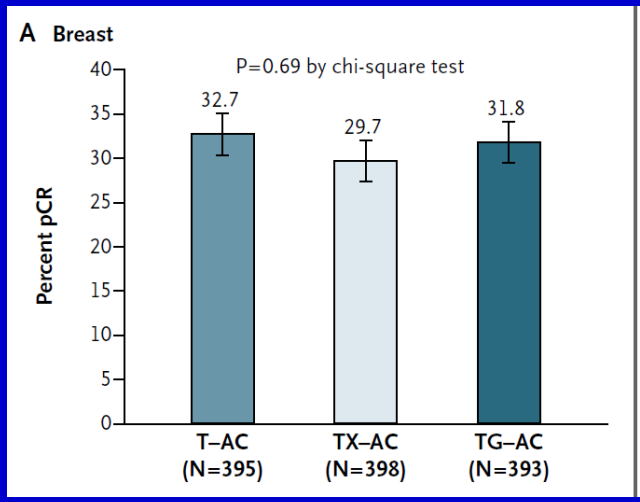
Meme koruyucu cerrahi oranlarında ya da pCR da fark yok

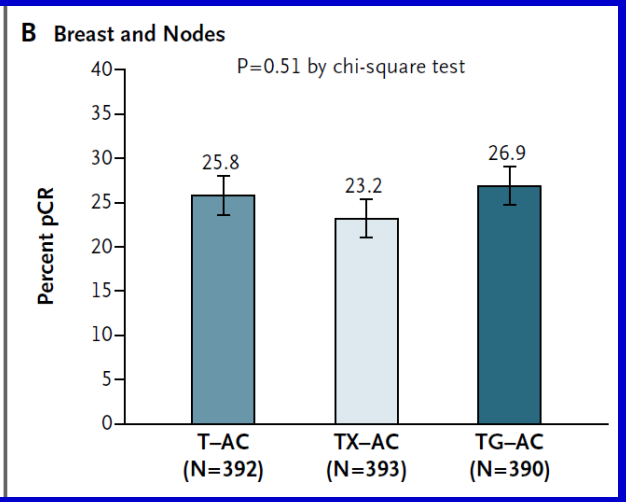
Von Minckwitz G, JCO 2010

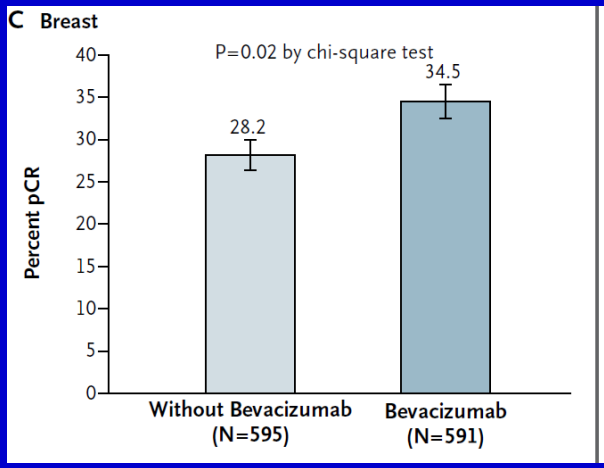
Bevacizumab Added to Neoadjuvant Chemotherapy for Breast Cancer

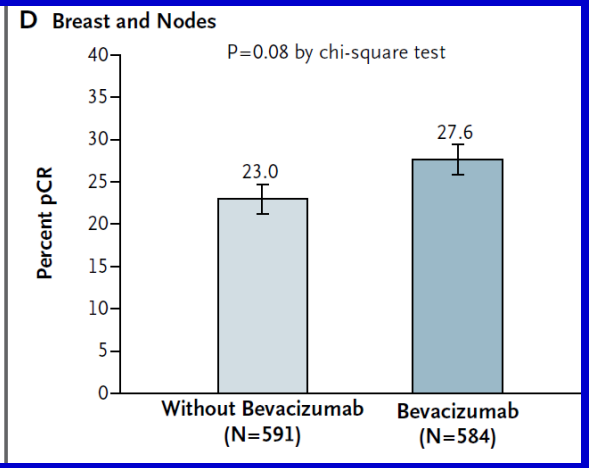
Harry D. Bear, M.D., Ph.D., Gong Tang, Ph.D., Priya Rastogi, M.D.,

Gem ve Cape eklemenin
- pCR
- DFS ve OS katkısı yok







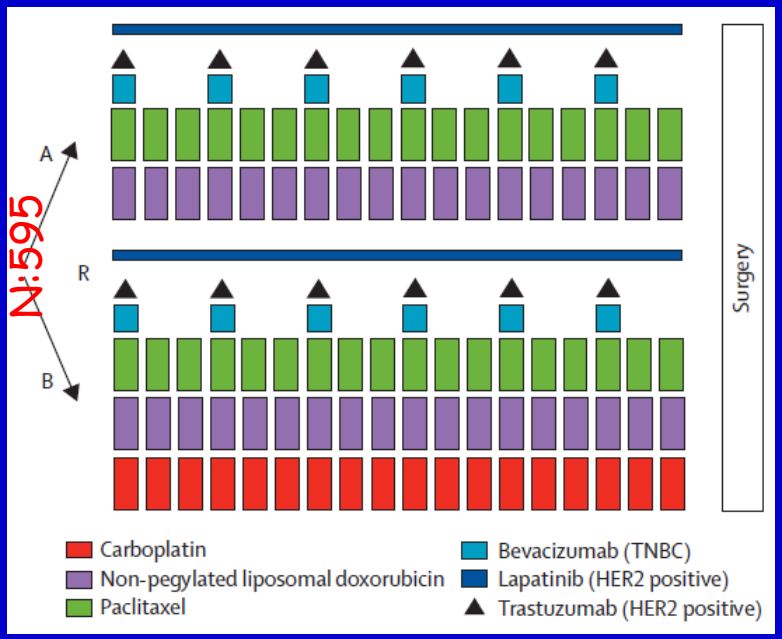


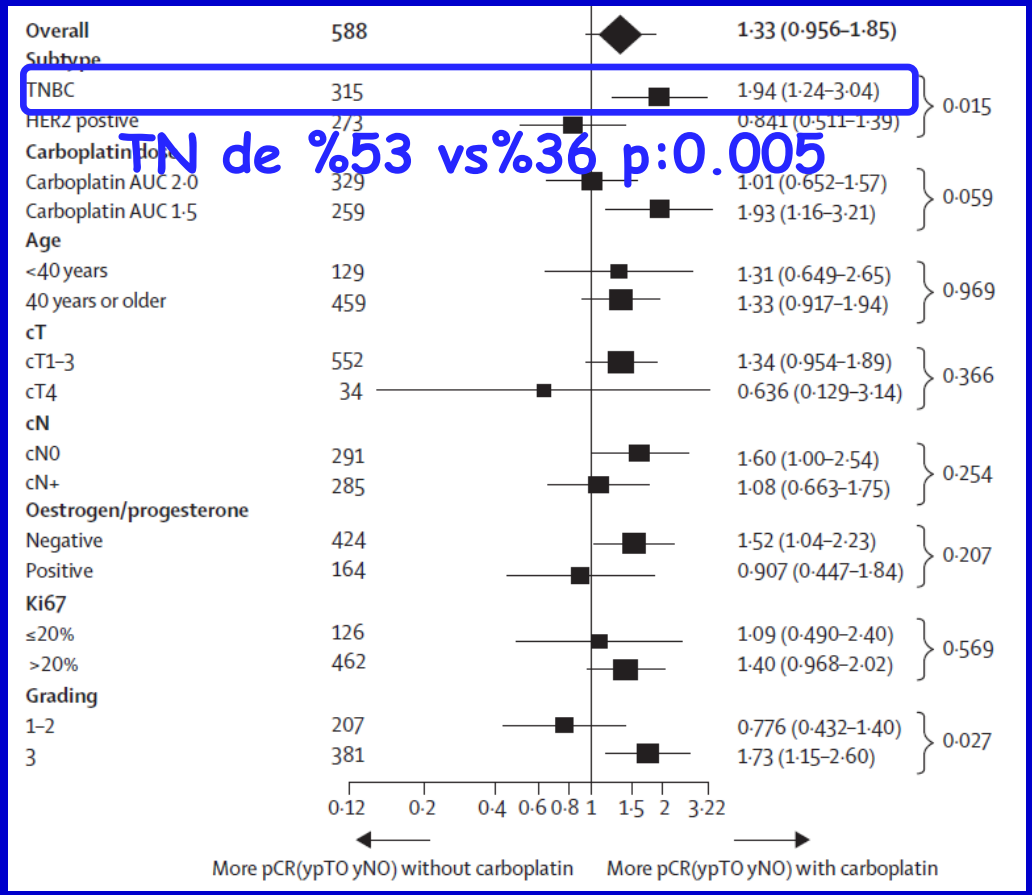
- Bev ile pCR da fark var; AMA
- Yan etki daha fazla
- Hangi hastalar?
- Adj da uzun dönem klinik katkı henüz yok

Bear HD, NSABP-B40, NEJM 2012

Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial

Gunter von Minckwitz, Andreas Schneeweiss, Sibylle Loibl, Christoph Salat, Carsten Denkert, Mahdi Rezai, Jens U Blohmer, Christian Jackisch,



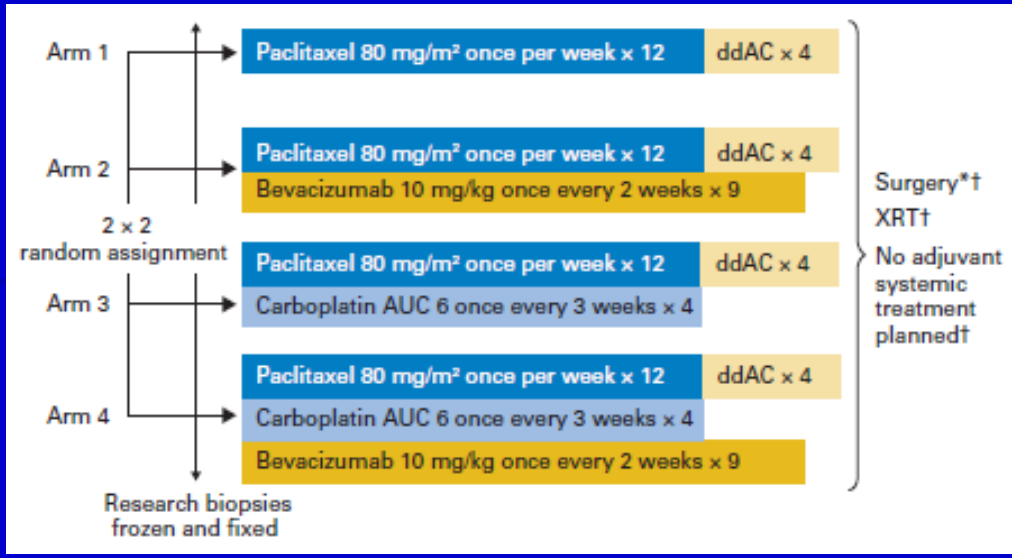


TN de %53 vs%36 p:0.005

Lancet Oncol, 2014

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)

William M. Sikov, Donald A. Berry, Charles M. Perou, Baljit Singh, Constance T. Cirrincione,



JCO 2015

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)

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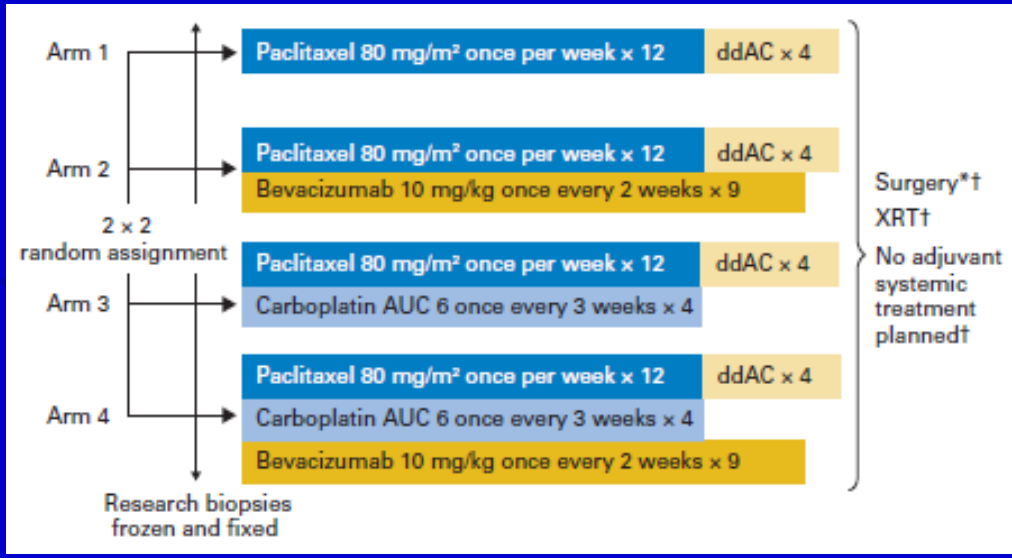

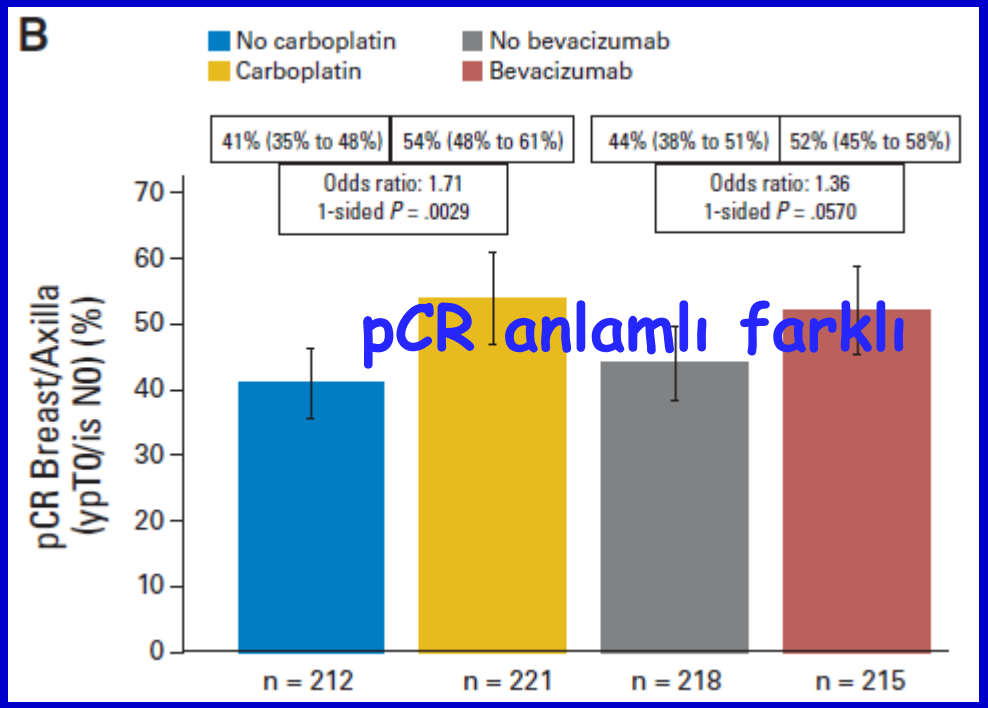

pCR anlamlı farklı

JCO 2015

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)

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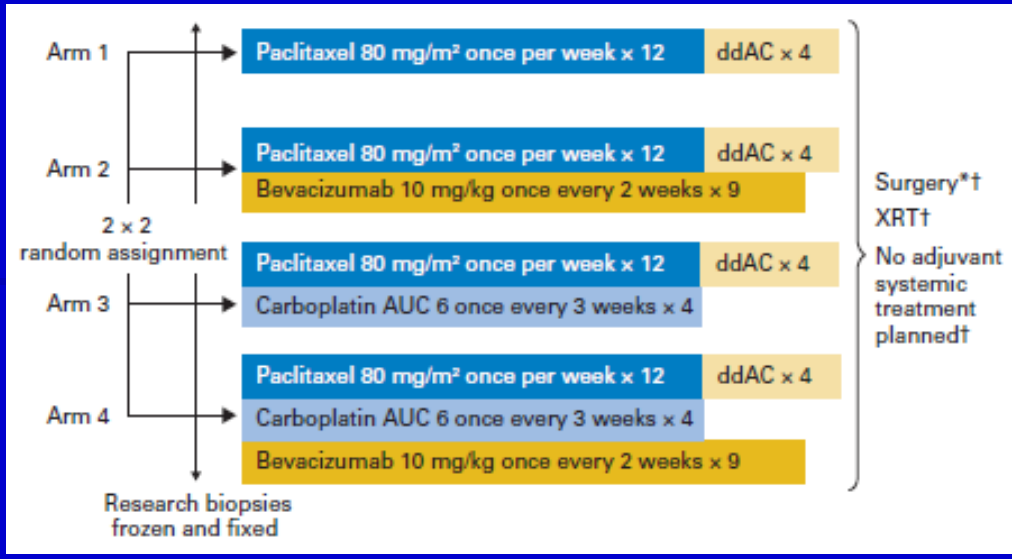
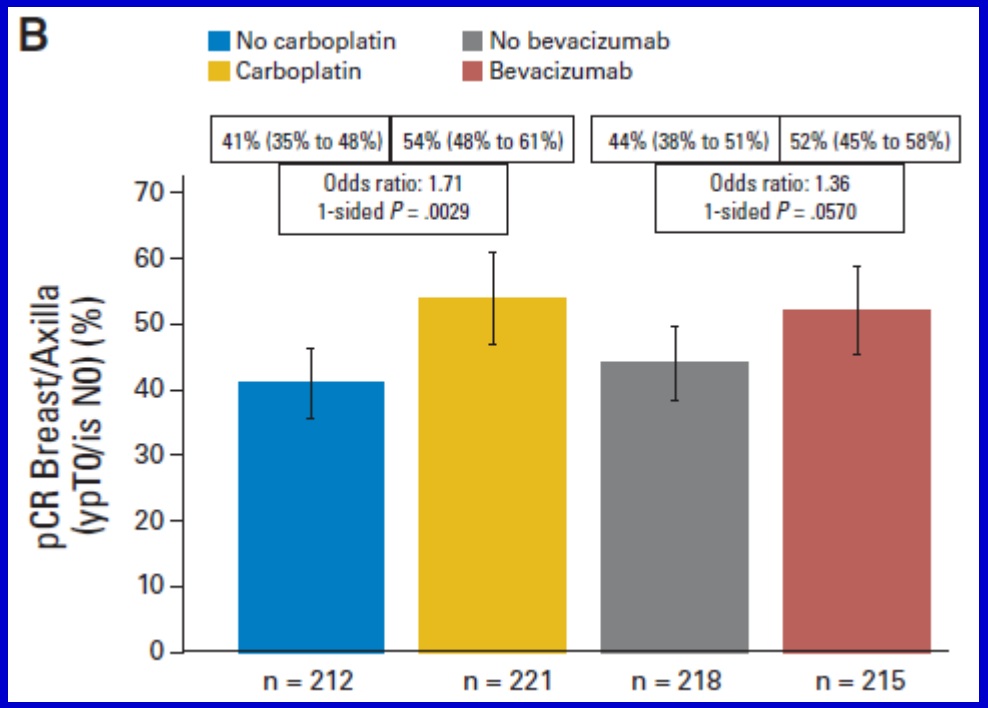


Table 3. Grade 3 to 4 Treatment-Related Toxicities

	Arm One: Control (%)	Arm Two: Control + Bev (%)	Arm Three: Control + Carbo (%)	Arm Four: Control + Bev and Carbo (%)
Leukopenia	12	13	13	**25**
Neutropenia	22	27	**56**	**67**
Thrombocytopenia	4	3	**20**	**26**
Hemoglobin	0	2	4	5
Febrile neutropenia	7	9	12	**24**
Nausea	4	4	3	8
Vomiting	2	2	2	4
Mucositis	2	0	1	4
Diarrhea	0	3	2	3
Hypertension	2	**12**	0	**10***
ALT elevation	0	3	0	3
Hypokalemia	3	1	6	2
Peripheral neuropathy	2	6	7	4
Fatigue	10	12	10	**20**
Pain	3	6	3	**11**



RFS ve OS verisi??

JCO 2015

Breast Cancer Res Treat (2014) 147:401–405
DOI 10.1007/s10549-014-3100-x

EPIDEMIOLOGY

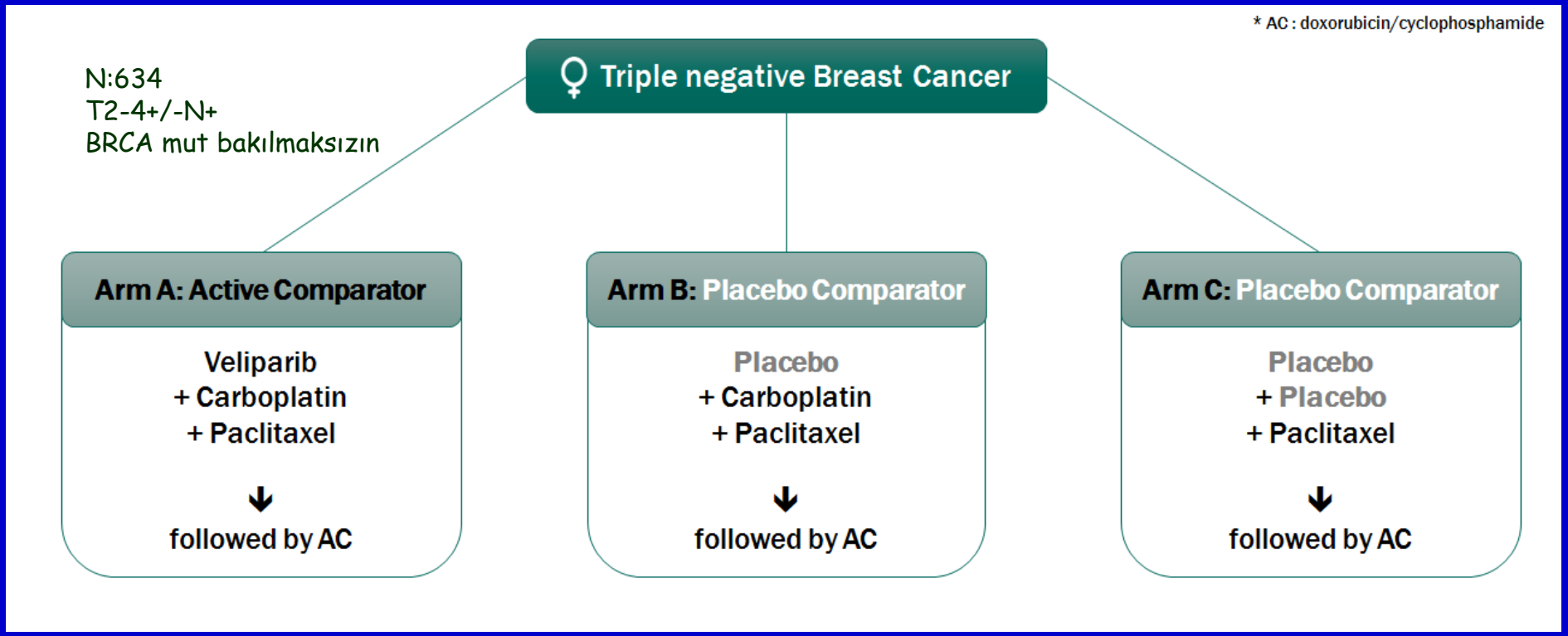
Pathologic complete response to neoadjuvant cisplatin in BRCA1-positive breast cancer patients

T. Byrski · T. Huzarski · R. Dent · E. Marczyk · M. Jasiowka ·

- N:107 evre *I-III BRCA* 1 mut+ olan meme ca
- %85 HR neg; % 98 HER2 neg
- Neoadjuvan Sisplatin 75 mg/m2 q3wx4 sonrası op ve konvansiyonel KT

pCR %61 fakat OS verileri sunulmadı

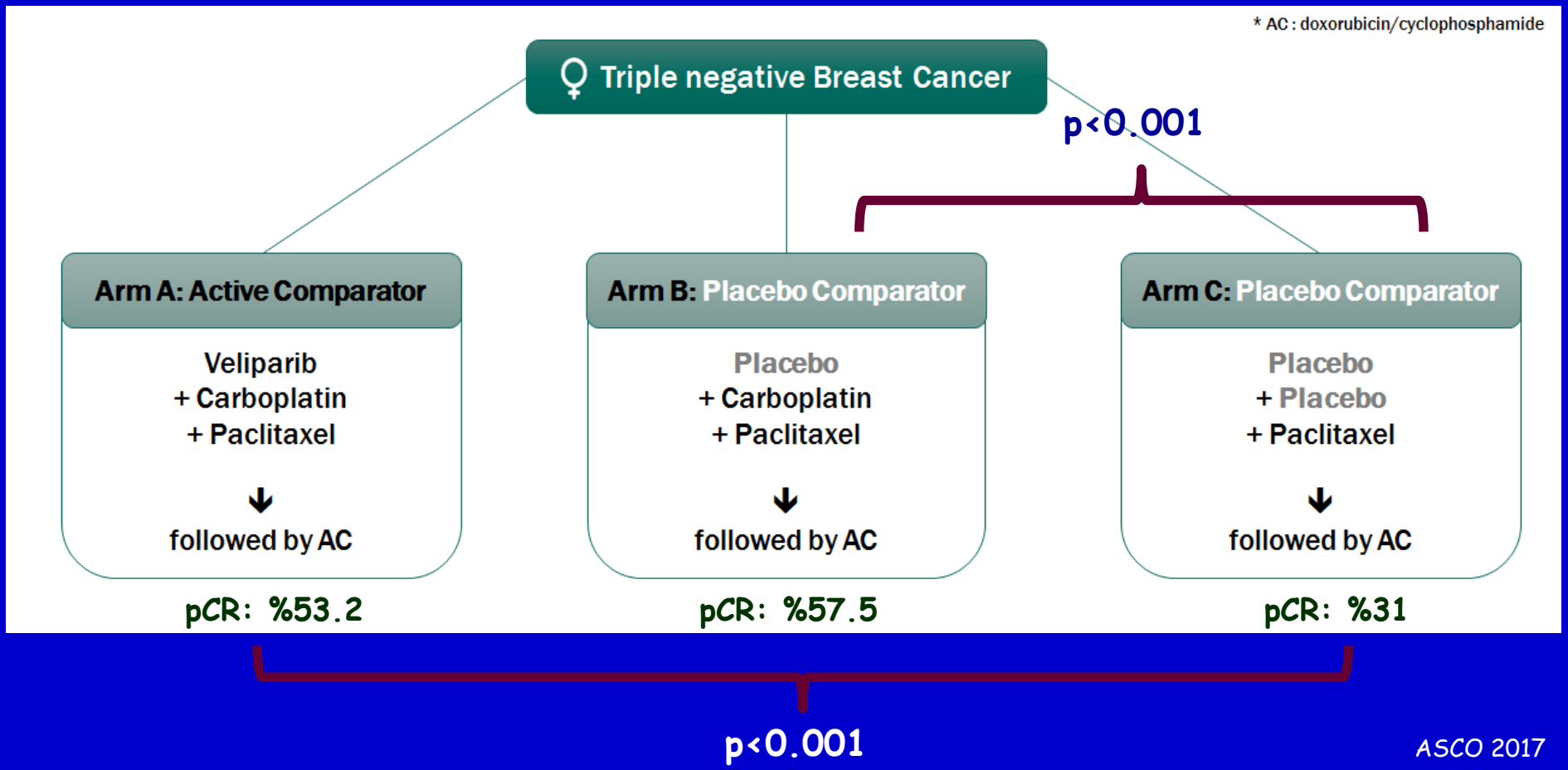
Veliparib : Brightness Study



Primer sonlanım pCR

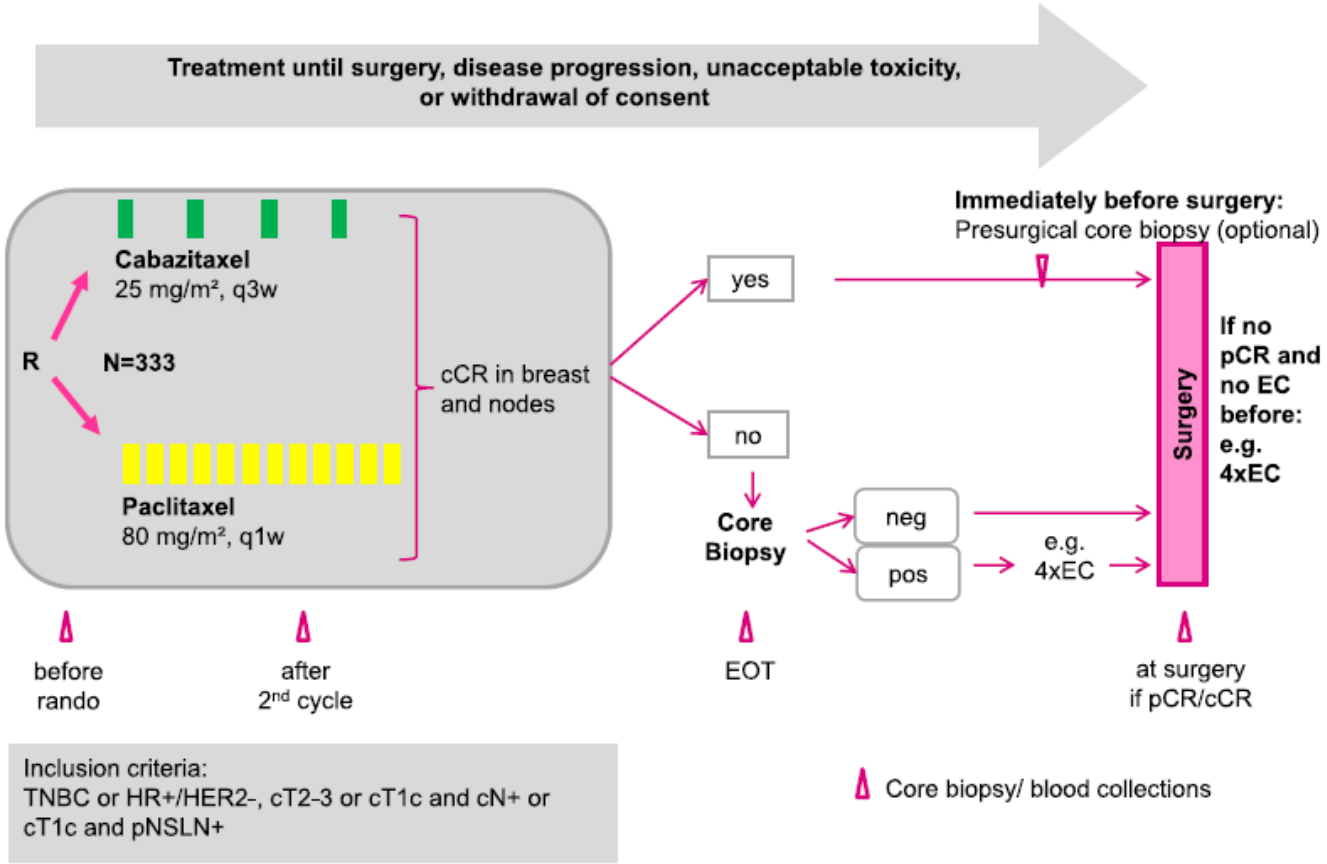
ASCO 2017

Veliparib : Brightness Study



Randomised, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neoadjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer (GENEVIEVE)

Sherko Kümmel [a,*], Stefan Paepke [b], Jens Huober [c], Christian Schem [d],



Eur J Cancer 2017

Randomised, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neoadjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer (GENEVIEVE)

Sherko Kümmel [a,*], Stefan Paepke [b], Jens Huober [c], Christian Schem [d],

Table 2
Comparison between different definitions of pathological complete responses and selected secondary end-points.

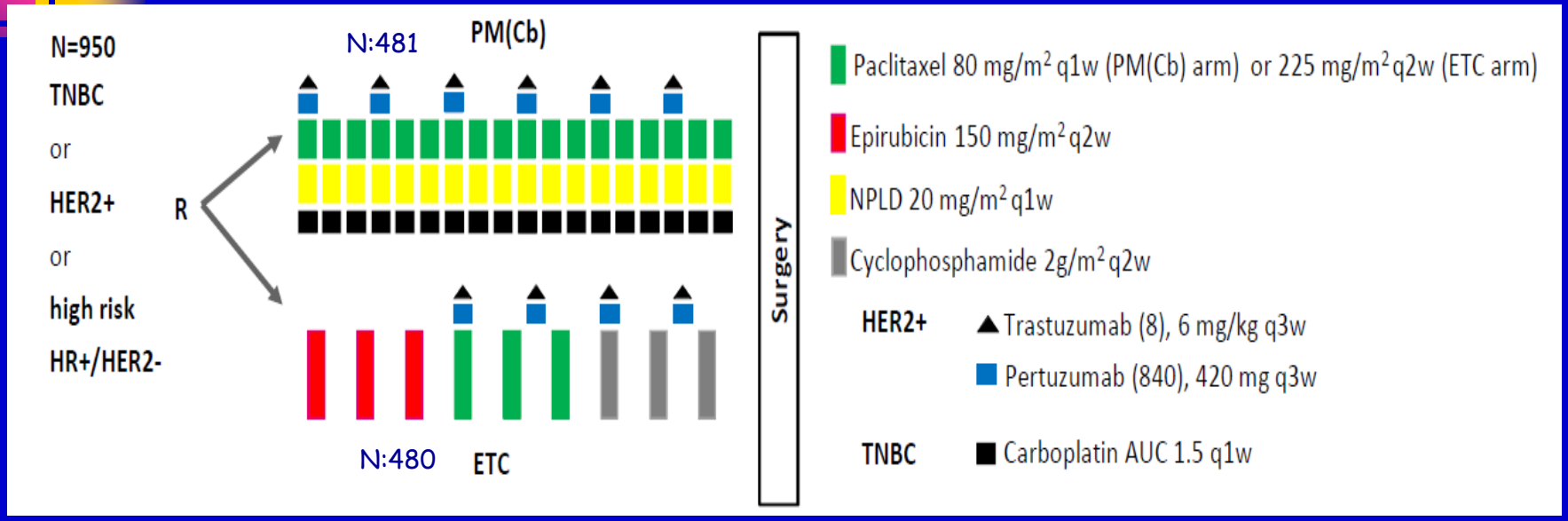
End-points	Cabazitaxel N (%; 95% CI)	Paclitaxel N (%; 95% CI)	Overall N (%; 95% CI)	p Value[a]
Primary end-point (pCR = ypT0/is ypN0/+)	**N = 166**	**N = 167**	**N = 333**	
Overall	2 (1.2; 0.0–2.9)	18 (10.8; 6.1–15.5)	20 (6.0; 3.5–8.6)	0.001[b]
ORR (CR or PR)	74 (59.2; 50.6–67.8)	112 (77.2; 70.4–84.1)	186 (68.9; 63.4–74.4)	0.002

Cabazitaxel adına Negatif çalışma

Eur J Cancer 2017

A randomised phase III trial comparing two intense dose-dense approaches (ETC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto)

Schneeweiss A[1], Möbus V[2], Tesch H[3], Hanusch C[4], Denkert C[5], Lübbe K[6], Huober J[7], Klare P[8], Kümmel S[9], Untch M[10], Kast K[11], Jackisch C[12], Thomalla J[13], Ingold Heppner B[5], Blohmer J U[5], Rezai M[14], Frank M[15], Nekljudova V[16], von Minckwitz G[16], Loibl S[16]

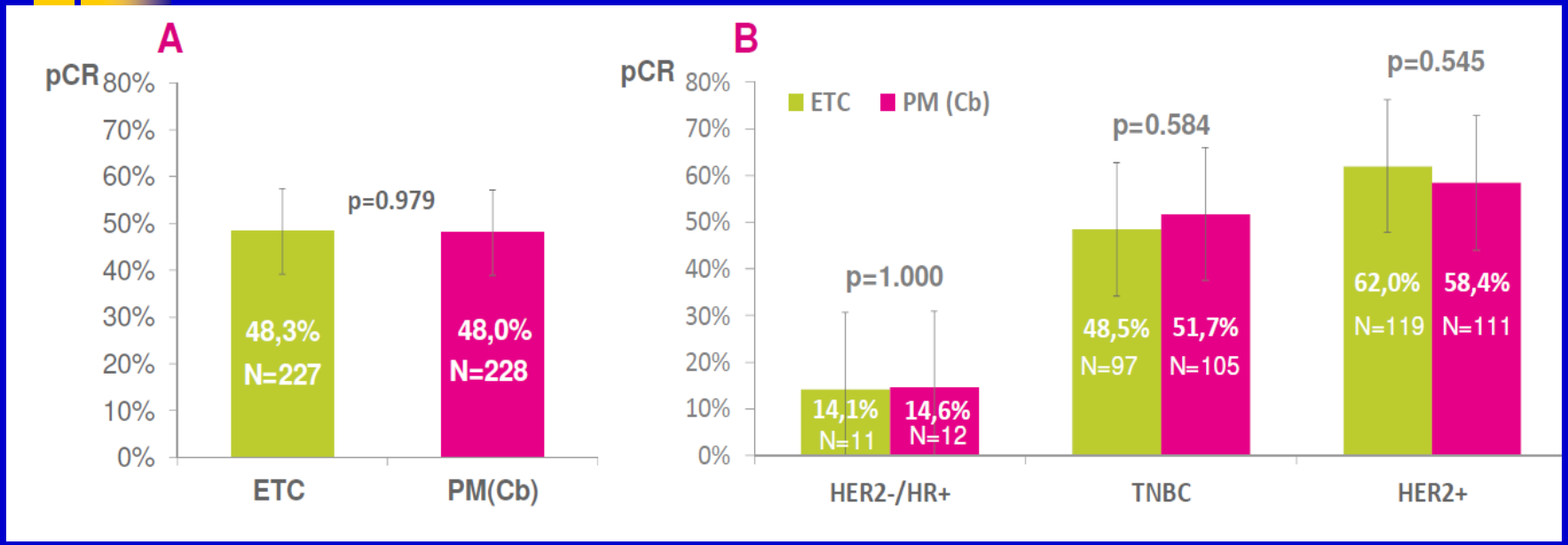


PM(Cb) açısından bir non-inferiorite çalışması (TN de carbo eklenmiş)
Primer sonlanım pT0/isN0 pCR oranları

ASCO 2017

A randomised phase III trial comparing two intense dose-dense approaches (ETC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer (GeparOcto)

Schneeweiss A[1], Möbus V[2], Tesch H[3], Hanusch C[4], Denkert C[5], Lübbe K[6], Huober J[7], Klare P[8], Kümmel S[9], Untch M[10], Kast K[11], Jackisch C[12], Thomalla J[13], Ingold Heppner B[5], Blohmer J U[5], Rezai M[14], Frank M[15], Nekljudova V[16], von Minckwitz G[16], Loibl S[16]



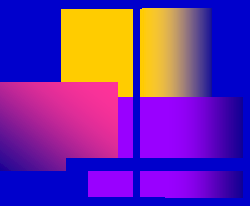
PM(Cb) de daha yüksek oranda pnomoni ve pnomonit
İstatistiki olarak non-inf gösterilemedi

Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): Results from I-SPY 2.

	Current raw data: pCR/n [total assigned]		Estimated pCR rate (95% prob interval) [equivalent n]	
Signature	Pembro	Control	Pembro	Control
HR+/HER2–	7/25	13/88	34.2%	13.6%
	(28.0%)	(14.8%)	(17-51%)	(6-21%)
	[40]	[99]	[29.4]	[72.4]
TNBC	15/21	16/83	62.4%	22.3%
	(71.4%)	(19.3%)	(45-80%)	(12-33%)
	[29]	[89]	[28.6]	[58.4]

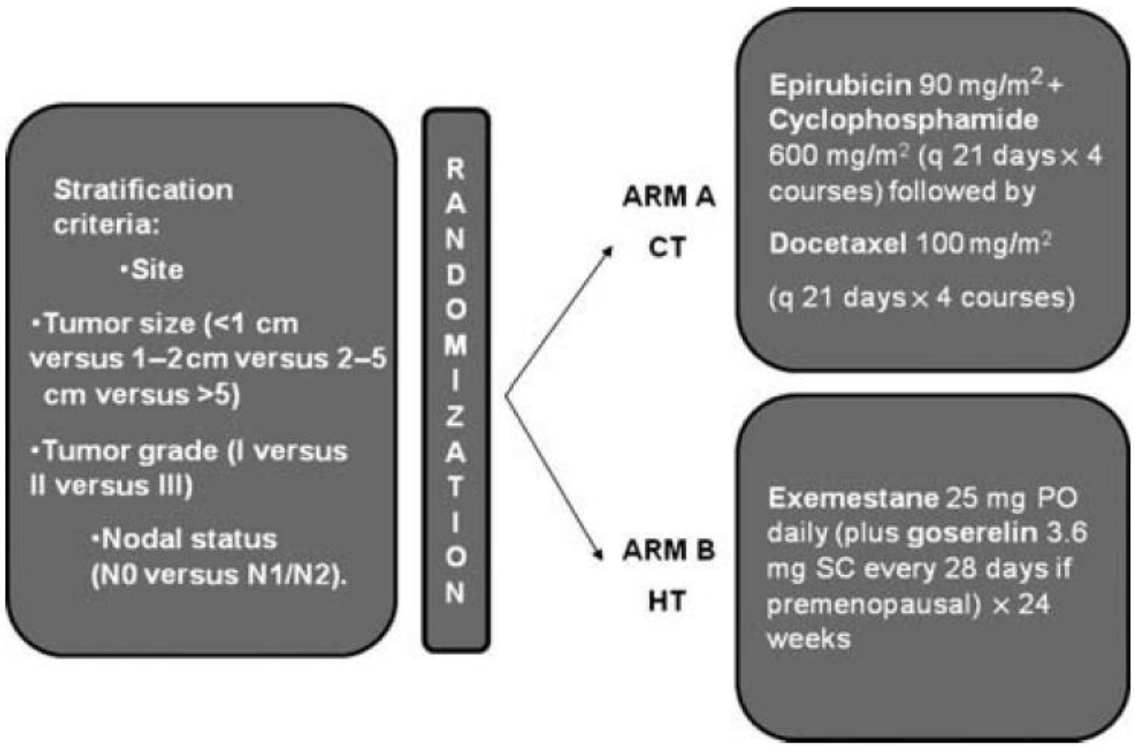
Rita Nanda et al, *ASCO 2017*

Neoadjuvan Endokrin Tedavi



Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study

E. Alba[1*], L. Calvo[2], J. Albanell[3], J. R. De la Haba[4], A. Arcusa Lanza[5], J. I. Chacon[6], P. Sanchez-



Yanıt oranları (KT vs ET)
%66 vs %48 (p:0.075)
Premen:
%75 vs %44 (p:0.027)
Postmen:
%57 vs %52 (p:0.78)

Faz II çok merkezli çalışma
Luminal meme ca
N:95 (51 premenapozal)

Ann Oncol 2012

Original Investigation

Neoadjuvant Endocrine Therapy for Estrogen Receptor–Positive Breast Cancer

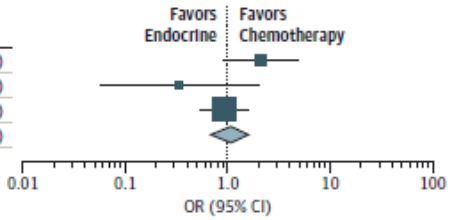
A Systematic Review and Meta-analysis

Laura M. Spring, MD; Arjun Gupta, MD; Kerry L. Reynolds, MD; Michele A. Gadd, MD; Leif W. Ellisen, MD, PhD;

A Clinical response

Source	OR (95% CI)
Alba et al,[30] 2012	2.11 (0.92-4.82)
Palmieri et al,[31] 2014	0.34 (0.06-1.98)
Semiglazov et al,[32] 2007	0.93 (0.55-1.57)
Total	1.08 (0.50-2.35)

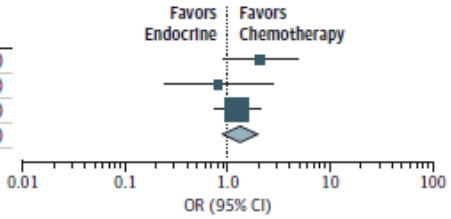
Heterogeneity: $\chi^2_2 = 4.47$ ($P = .11$), $I^2 = 55\%$
Test for overall effect: $z = 0.19$ ($P = .85$)



B Radiological response

Source	OR (95% CI)
Alba et al,[30] 2012	2.11 (0.92-4.82)
Palmieri et al,[31] 2014	0.83 (0.25-2.74)
Semiglazov et al,[32] 2007	1.28 (0.77-2.14)
Total	1.38 (0.92-2.07)

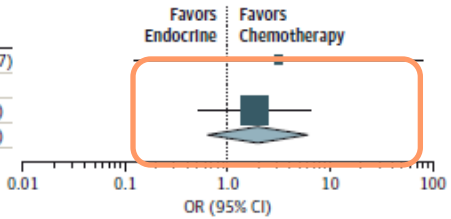
Heterogeneity: $\chi^2_2 = 1.77$ ($P = .41$), $I^2 = 0\%$
Test for overall effect: $z = 1.54$ ($P = .12$)



C Pathologic complete response

Source	OR (95% CI)
Alba et al,[30] 2012	3.13 (0.12-78.77)
Palmieri et al,[31] 2014	Not estimable
Semiglazov et al,[32] 2007	1.84 (0.53-6.47)
Total	1.99 (0.62-6.39)

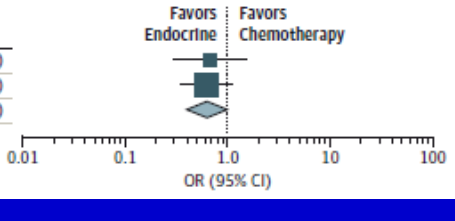
Heterogeneity: $\chi^2_2 = 0.09$ ($P = .76$), $I^2 = 0\%$
Test for overall effect: $z = 1.16$ ($P = .25$)



D Breast conservation surgery

Source	OR (95% CI)
Alba et al,[30] 2012	0.68 (0.30-1.54)
Semiglazov et al,[32] 2007	0.63 (0.36-1.11)
Total	0.65 (0.41-1.03)

Heterogeneity: $\chi^2_1 = 0.03$ ($P = .87$), $I^2 = 0\%$
Test for overall effect: $z = 1.83$ ($P = .07$)



Klinik yanıt oranları
Meme koruyucu cerrahi
Radyolojik yanıt oranları
BENZER FAKAT;

3 tane çalışma sadece
HT vs KT değerlendirmiş

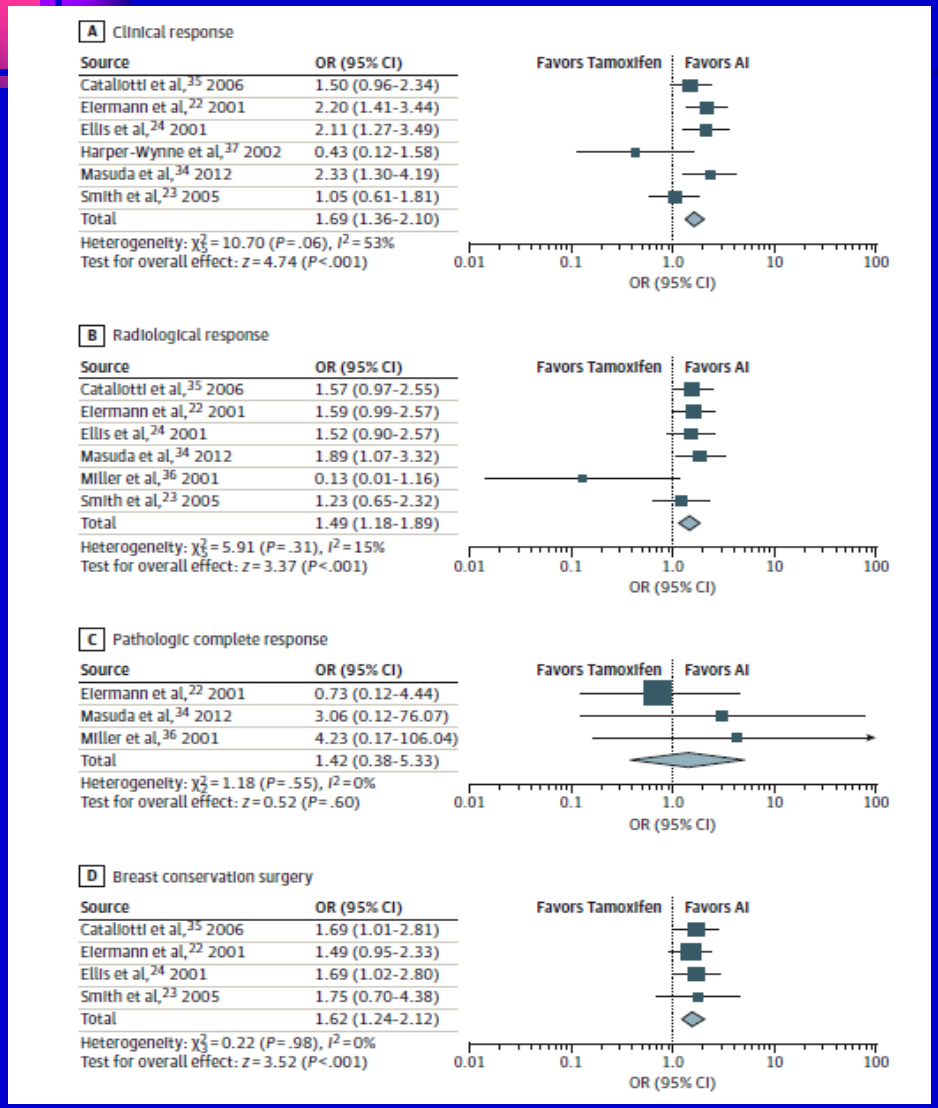
JAMA; 2016

Original Investigation

Neoadjuvant Endocrine Therapy for Estrogen Receptor–Positive Breast Cancer

A Systematic Review and Meta-analysis

Laura M. Spring, MD; Arjun Gupta, MD; Kerry L. Reynolds, MD; Michele A. Gadd, MD; Leif W. Ellisen, MD, PhD;



Klinik yanıt oranları
Meme koruyucu cerrahi
Radyolojik yanıt oranları

Aİ ile tmx e göre anlamlı üstün

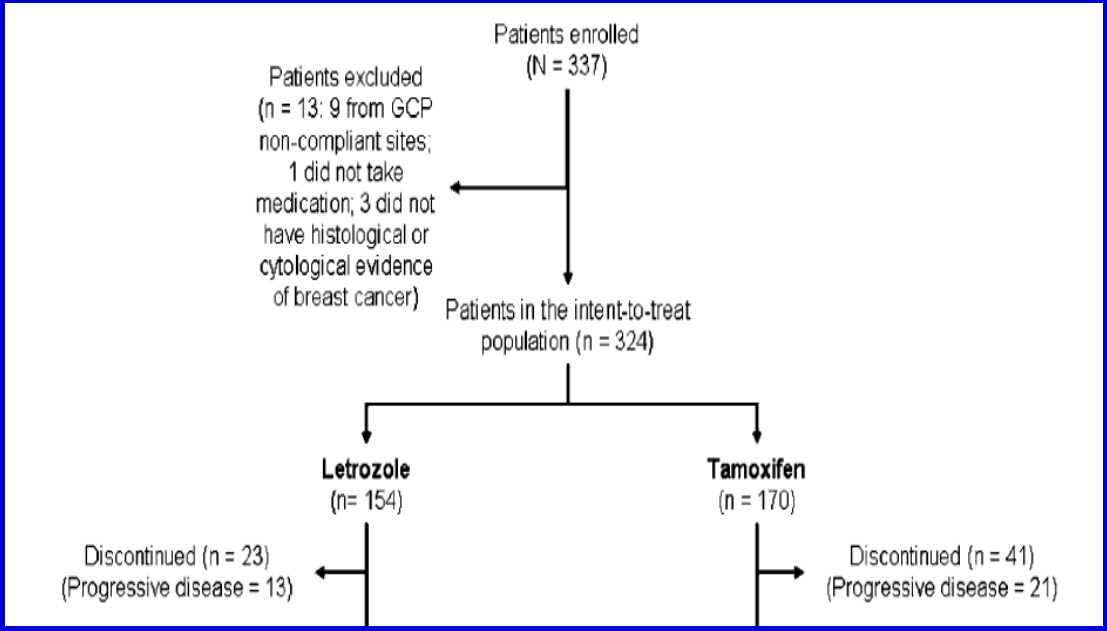
JAMA; 2016

Breast Cancer Res Treat (2007) 105:33–43
DOI 10.1007/s10549-007-9701-x

REVIEW

Letrozole in the neoadjuvant setting: the P024 trial

Matthew J. Ellis · Cynthia Ma



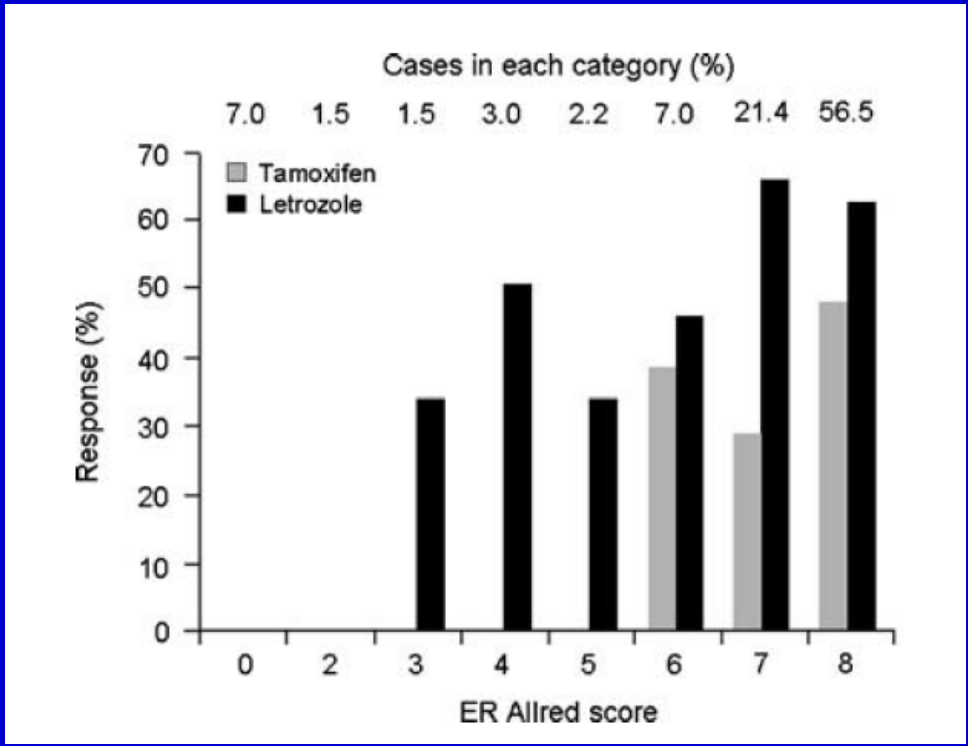
Cerrahi öncesi 4 ay tedavi
T2-4a-cN0-2
Primer sonlanım:ORR

Breast Cancer Res Treat (2007) 105:33–43
DOI 10.1007/s10549-007-9701-x

REVIEW

Letrozole in the neoadjuvant setting: the P024 trial

Matthew J. Ellis · Cynthia Ma



Letrozol vs tmx

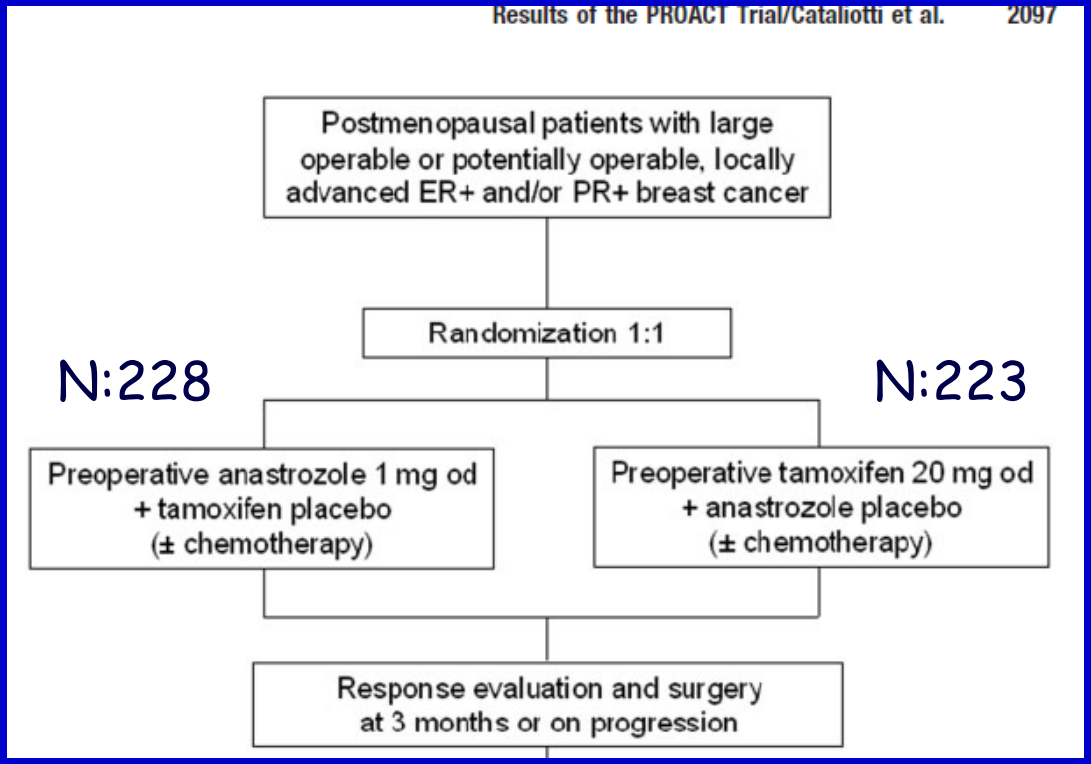
- ORR %55 vs %36*
- BCS %45 vs %35*

- ✓HER2+ grupta %88 vs %21*
- ✓HER2- grupta %55 vs %42

Comparison of Anastrozole versus Tamoxifen as Preoperative Therapy in Postmenopausal Women with Hormone Receptor-Positive Breast Cancer

The Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) Trial

Preop 12 hafta süre ile



T2-4bN0-2M0
ORR:
%40 vs%35 (NS)

Cancer 2006

Randomized Phase II Neoadjuvant Comparison Between Letrozole, Anastrozole, and Exemestane for Postmenopausal Women With Estrogen Receptor–Rich Stage 2 to 3 Breast Cancer: Clinical and Biomarker Outcomes and Predictive Value of the Baseline PAM50-Based Intrinsic Subtype—ACOSOG Z1031

Matthew J. Ellis, Vera J. Suman, Jeremy Hoog, Li Lin, Jacqueline Snider, Aleix Prat, Joel S. Parker, Jingqin Luo,

Evre II-III ER kuvvetli + meme ca; 16-18 hafta HT planlanmış

Table 1. Clinical Response Using WHO Criteria Based on ITT Population

Response	Exemestane (n = 124)		Letrozole (n = 127)		Anastrozole (n = 123)	
	No.	%	No.	%	No.	%
Clinical response at week 16 (WHO criteria with caliper measurements)						
Complete response	27	21.8	27	21.3	22	17.9
Partial response	51	41.1	68	53.5	63	51.2
No change	28	22.6	20	15.7	20	16.3
Disease progression	8	6.5	6	4.7	9	7.3
Off treatment because of toxicity/refusal	5	4.0	3	2.4	2	1.6
Measurements not done	5	4.0	3	2.4	7	5.7
ITT clinical response rate, %	62.9		74.8		69.1	

BCS oranları benzer

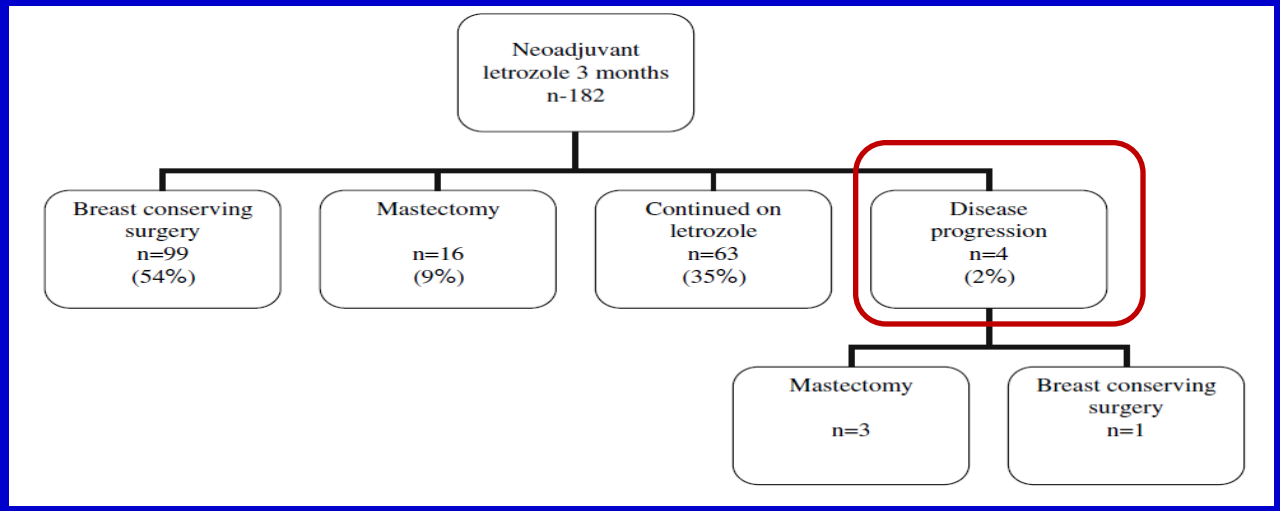
JCO 2011

Breast Cancer Res Treat (2009) 113:145–151
DOI 10.1007/s10549-008-9915-6

CLINICAL TRIAL

Increase in response rate by prolonged treatment with neoadjuvant letrozole

J. Michael Dixon · Lorna Renshaw · E. Jane Macaskill · Oliver Young ·



- 182 neoadj letrozol kullanan hasta; 63'ü 3 aydan uzun kullanım
- 24'ü 2 yıldan uzun kullanmış (med yaş 83)
- RR **%69.8 den %83.5**; MKC **%60 dan %72**

Original article

21-Gene expression profile assay on core needle biopsies predicts responses to neoadjuvant endocrine therapy in breast cancer patients

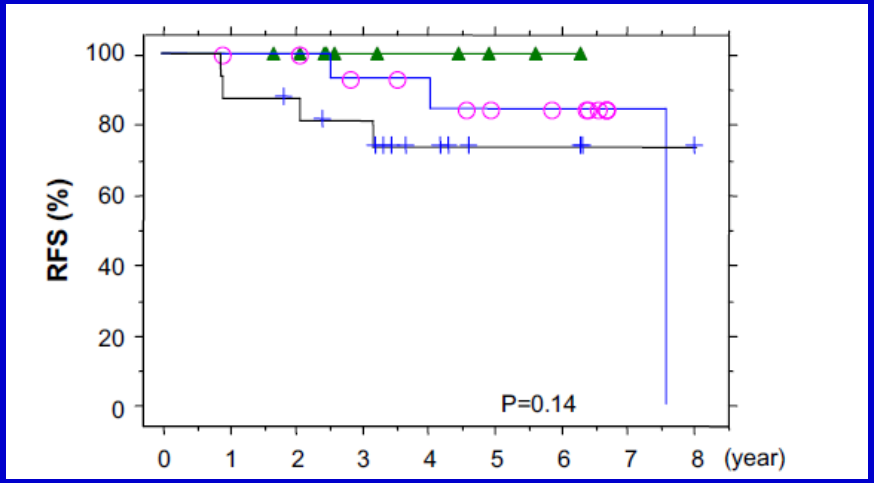
Sadako Akashi-Tanaka [a,*], Chikako Shimizu [b], Masashi Ando [b], Tatsuhiro Shibata [c], Noriyuki Katsumata [b],

87 postmen meme ca, HR+, tm>3 cm (T2-4N0-3),
neoadj tmx vs anastrazol (4 ay)
Core bx ten Oncotype Dx

Clinical response rates and 21-gene recurrence score by neoadjuvant treatment.

Neoadjuvant Treatment	*n*	Low (RS < 18)	Intermediate (18 < RS ≤ 30)	High (RS ≥ 31)	*p*-Value by trend test
Tamoxifen	14	67% (2/3)	33% (2/6)	40% (2/5)	0.53
Anastrozole	29	63% (5/8)	30% (3/10)	27% (3/11)	0.13
All	43	64% (7/11)	31% (5/16)	31% (5/16)	0.11

RFS %100 vs %84 vs %73



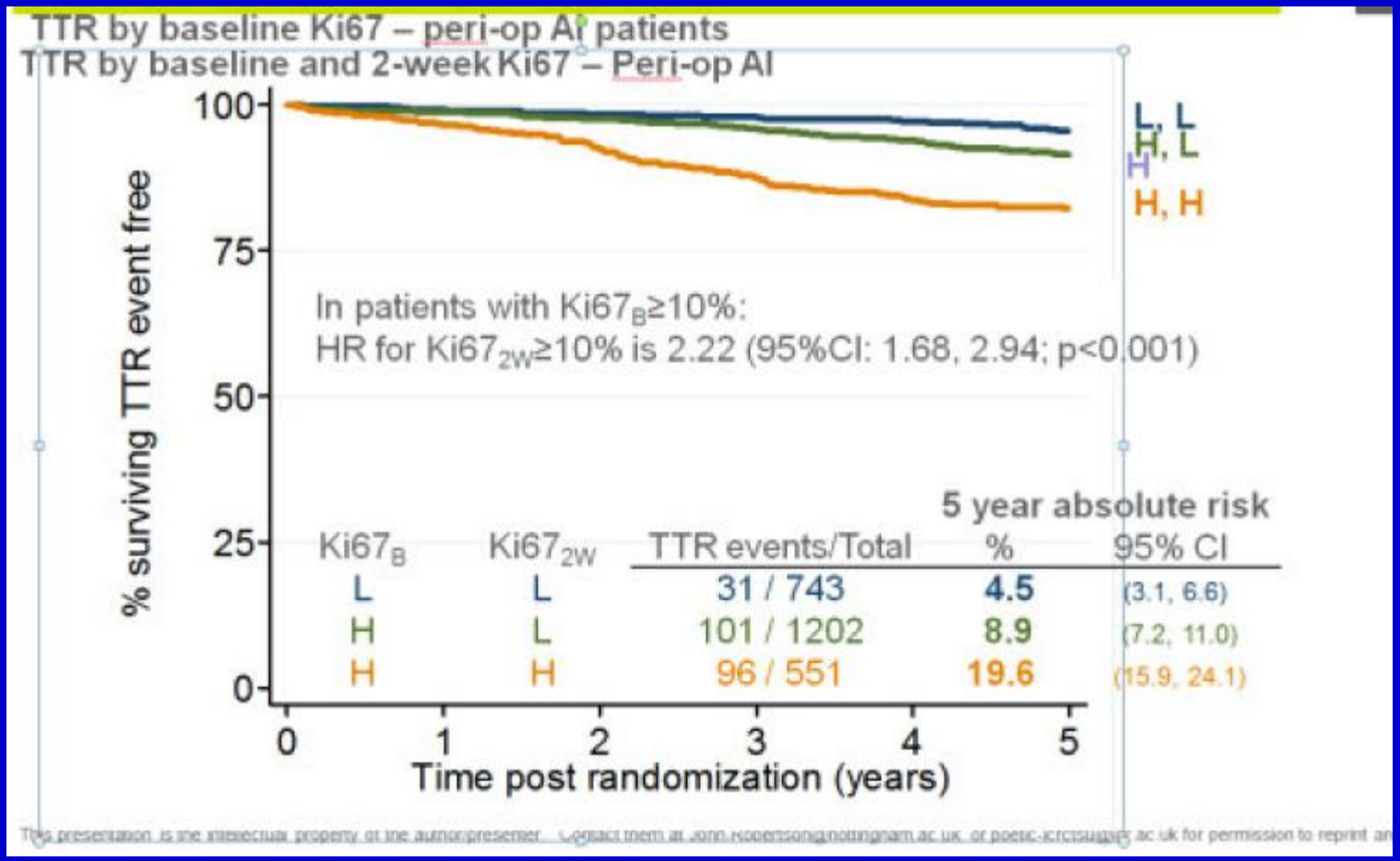
Breast 2009

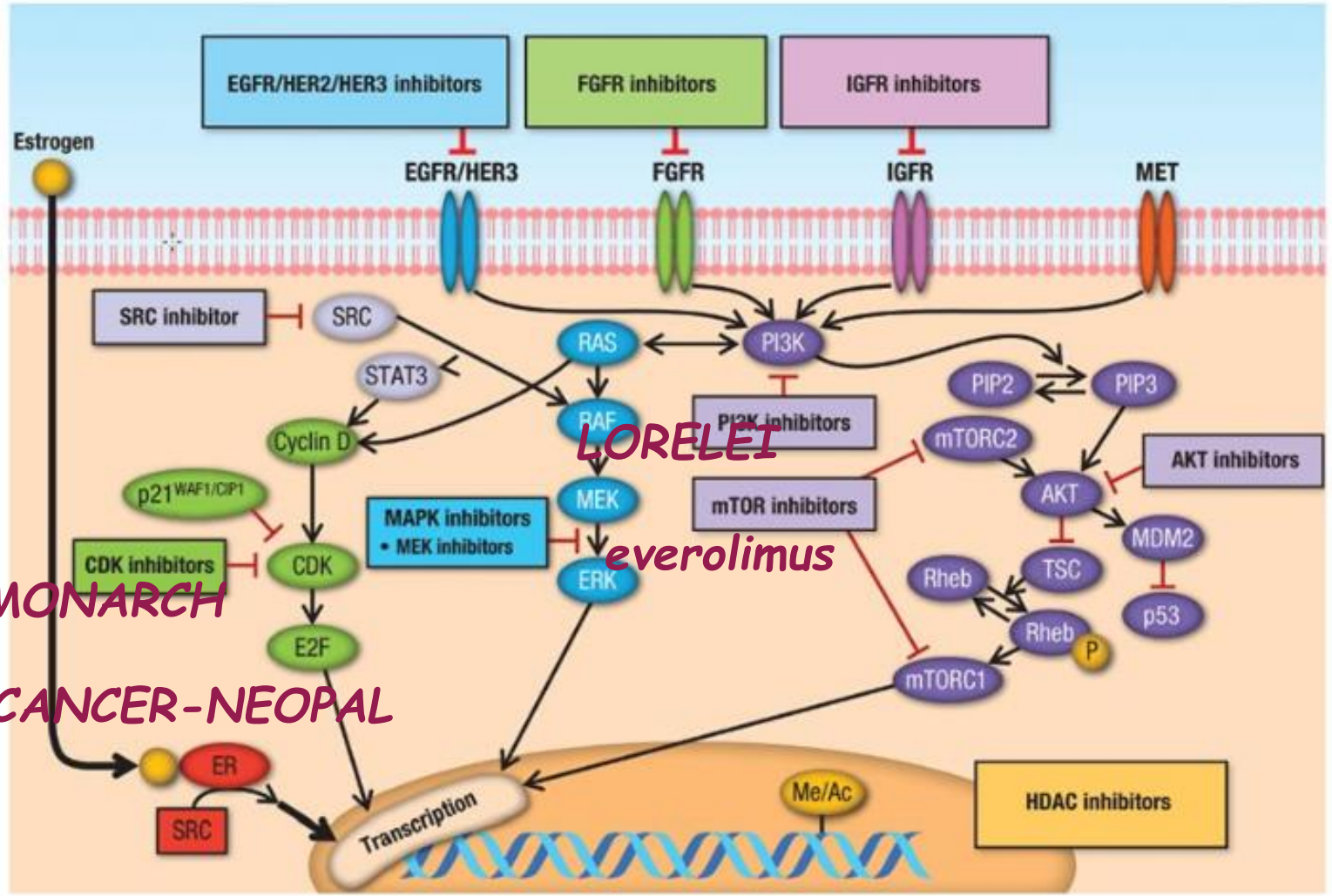
Ki67 prediktif olabilir mi?; IMPACT

- ER/PR (+), T2 (≥2cm)-T4b, N0-2 (n=330)
- Tamoksifen x 3 ay vs
- Anastrazole x 3 ay vs
- Anastrazole + Tamoksifen x 3 ay
- OR % 36.1 vs 37.2 vs 39.4 (fark Ø)
- 2. haftada Ki-67'deki azalma % 59 vs 76 vs 64 AMA YANITLA ANLAMLI İLİŞKİ GÖSTERİLEMEDİ

Dowsett M, J Natl Cancer Inst 2007

[GS1-03] Perioperative aromatase inhibitor treatment in determining or predicting long term outcome in early breast cancer – the POETIC trial.





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NCCN Guidelines Version 1.2018
Invasive Breast Cancer

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[1,2,3,4,5]

HER2-Negative[6]

- **Preferred regimens:**
  - Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks[7]
  - Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel[7]
  - TC (docetaxel and cyclophosphamide)
- **Useful in certain circumstances:**
  - Dose-dense AC (doxorubicin/cyclophosphamide)
  - AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
  - CMF (cyclophosphamide/methotrexate/fluorouracil)
  - AC followed by weekly paclitaxel
- **Other recommended regimens:**
  - AC followed by docetaxel every 3 weeks
  - EC (epirubicin/cyclophosphamide)
  - TAC (docetaxel/doxorubicin/cyclophosphamide)

HER2-Positive

- **Preferred regimens:**
  - AC followed by T + trastuzumab[8] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
  - AC followed by T + trastuzumab + pertuzumab[8] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab)
  - Paclitaxel + trastuzumab[9]
  - TCH (docetaxel/carboplatin/trastuzumab)
  - TCH (docetaxel/carboplatin/trastuzumab) + pertuzumab
- **Useful in certain circumstances:**
  - Docetaxel + cyclophosphamide + trastuzumab
- **Other recommended regimens:**
  - AC followed by docetaxel + trastuzumab[8] (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab)
  - AC followed by docetaxel + trastuzumab + pertuzumab[8] (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab plus pertuzumab)

[1]Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.
[2]Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.
[3]CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.
[4]Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.
[5]Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m^2.
[6]The regimens listed for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.
[7]It would be acceptable to change the administration sequence to paclitaxel followed by dose-dense AC.
[8]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[9]Paclitaxel + trastuzumab may be considered for patients with low-risk T1,N0,M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

- **Preoperative endocrine therapy alone may be considered for patients with ER-positive disease based on comorbidities or low-risk luminal biology.**

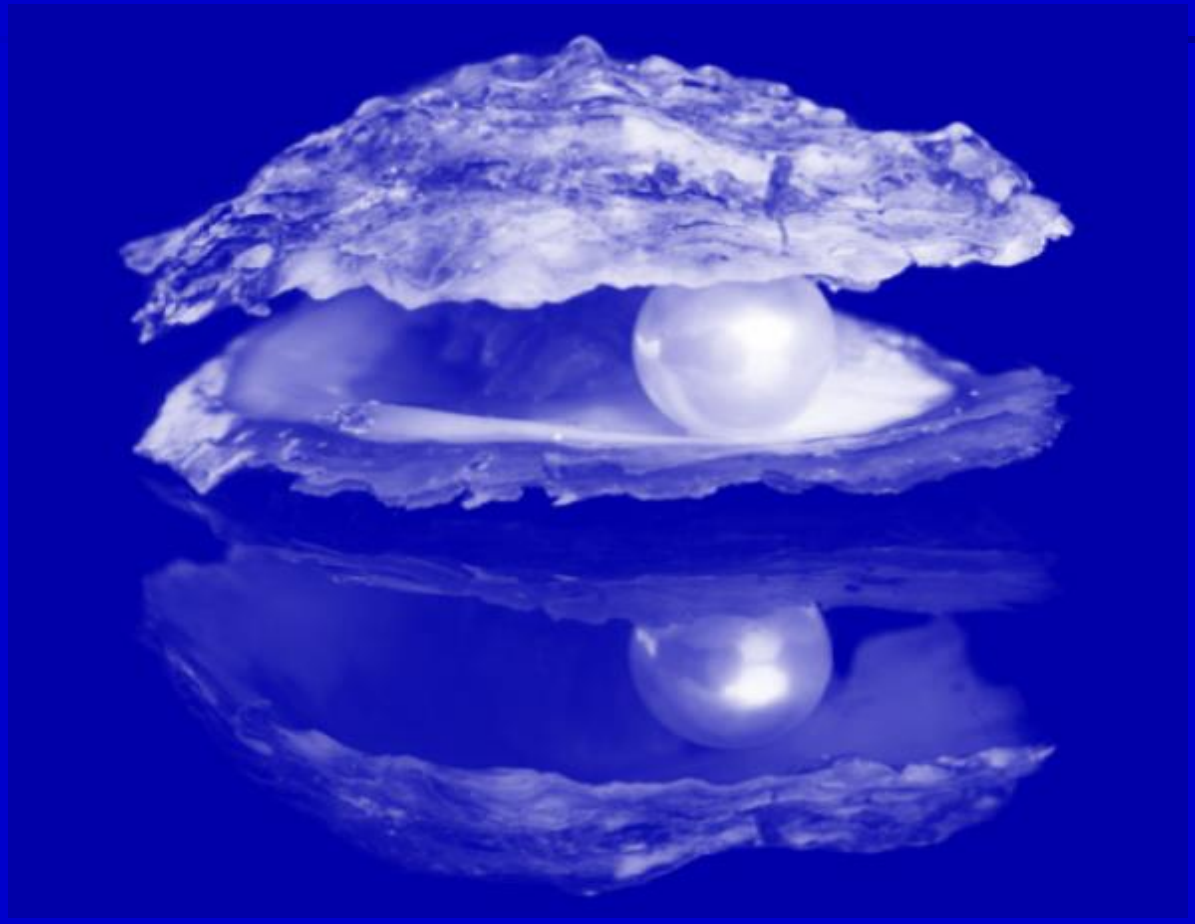
Take home..

- Lokal ileri, potansiyel operabl, MKC tercihi, genç hastalarda, özellikle TN ve HER2+ alt grupta neoadjuvan KT
- pCR elde edilirse OS katkısı
- Halen antrasiklin+taksanlı rejimler
- Postmen cerrahi yapılmayacak luminal tip neoadj HT (4-6 ay süre ile)
- Yeni gelişmeler devam etmekte...

Peki ya..

- HER2+ alt grup???
- Hedefe yönelik diğer tedaviler??

- pCR elde edilmeyen hastalarda tedavi???



Teşekkürler..