Lokal İleri Evre Meme Kanserinde Neoadjuvant Hedefe Yönelik Tedaviler

Prof. Dr. Handan Onur

Ankara, 07.04.2018

Kime Neoadjuvan tedavi verilmeli?

- **Mutlak endikasyon: Lokal ileri inoperable**
  - **Evre IIIA (N2)**
  - **Evre IIIB (T4)**
  - **Evre IIIC (N3)**

AMAÇ
Inoperabl → Operabl
Neoadjuvan: Standart tedavi

- **Rölatif endikasyon: Neoadjuvan veya adjuvan farketmez**
  - **Lokal ileri operabl: T3N1M0 (Evre IIIA)**
  - **Adjuvan tedavi gerektiren tüm evreler**
    - **>2 cm tüm tümörlerde**

AMAÇ
- **Mastektomi → MKC**
- **DFS ve OS açısından Neoadjuvan = Adjuvan**

Operabl hastaya adjuvan yerine niye neoadjuvan?

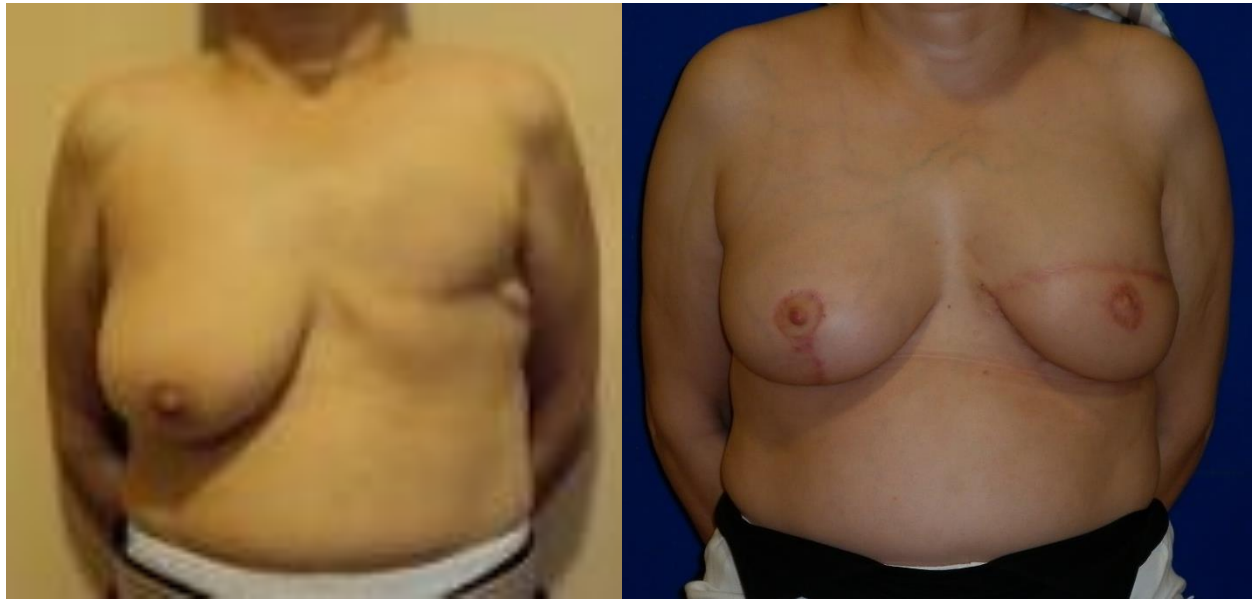
- **Sağkalım benzer**
  - **14 randomize çalışma (n: 5500 hasta) → Benzer OS HR 0.98 (%95 CI 0.87-1.09)**

- **Daha az cerrahi**

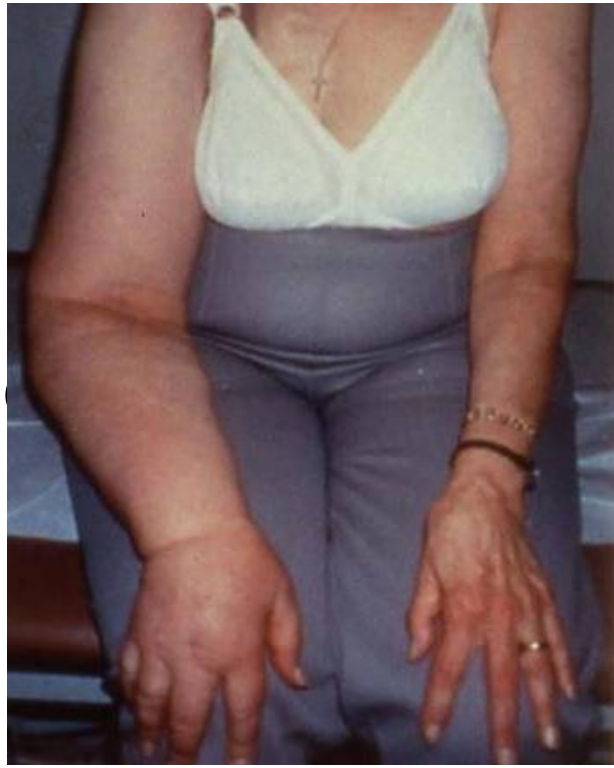
Mieog JS et al;. Cochrane Database Syst Rev 2007

Neoadjuvan tedavi downstaging yapar

- **Tümörde küçülme → Seçilmiş hastada meme koruyucu cerrahi**



%10-15 daha fazla MKC



- **Aksiller downstaging→ ~ %40 hasta (tümör subtipine göre**
  - **Tedavi öncesi nod (+) hastada aksiller diseksiyon ihtiyacı azalabilir**
  - **Lenfödem riski azalır→Artmış hayat kalitesi**

Operabl hastaya adjuvan yerine niye neoadjuvan?

- Sağkalım benzer
  - 14 randomize çalışma (n: 5500 hasta) → Benzer OS HR 0.98 (%95 CI 0.87-1.09)
- Daha az cerrahi
- **Tedaviye yanıtın in vivo değerlendirmesi ve genel sağkalım için erken belirteç (pCR)**

Mieog JS et al;. Cochrane Database Syst Rev 2007

Neoadjuvan Tedavi
Klinik çalışmalardaki yeri

Neoadjuvan tedavilerin araştırıldığı klinik çalışmalarda

- **Sonuçların daha hızlı gözlenebilmesi**
- **Daha az sayıda hastaya ihtiyaç duyulması**
- **Biyomarker analizleri için rutin doku örneklemelerine olanak tanıması**

açısından adjuvan çalışmalara göre daha avantajlıdır

Adjuvan çalışma:

Neoadjuvan çalışma:

Amos, et al. Int J Breast Cancer 2012

Hedef nedir?

Patolojik tam yanıt (pCR)

↓

Sağkalım artar

↓

Bunu sağlamak için en etkin tedavi verilmeli

Definitions of pCR

Breast pCR	Total pCR	GBG pCR
ypT0/is	ypT0/is ypN0	ypT0 ypN0
• No invasive tumor in the breast	• No invasive tumor in the breast • Node negative at definitive surgery	• No invasive tumor in the breast • Node negative at definitive surgery • No remaining *in situ* disease

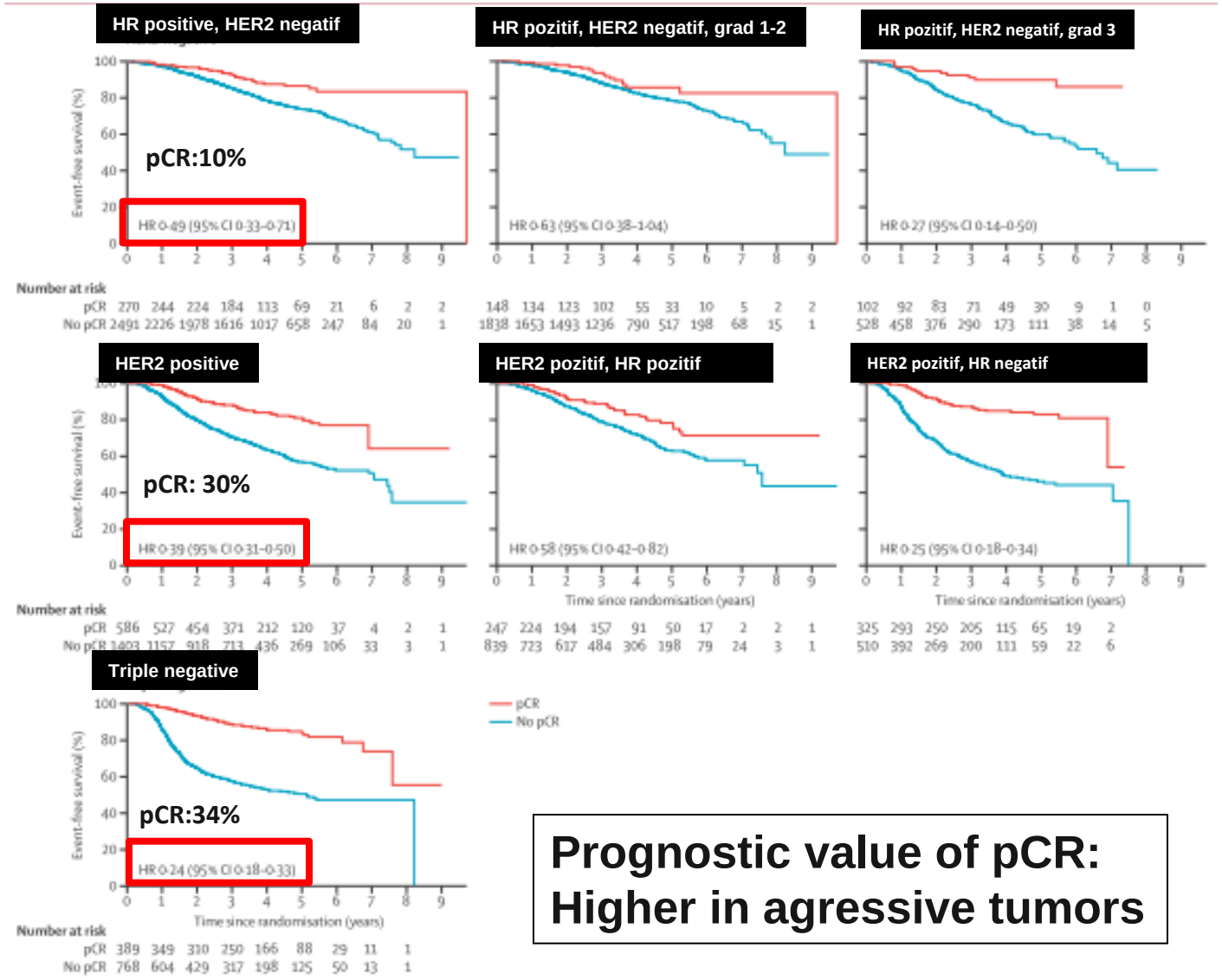
TNM (tumor, nodes, metastasis) classification; y=status post initial therapy; p=confirmed by pathology after initial treatment; T=tumor; N=nodes; is=in situ; GBG=German Breast Group.

pCR: Tüm altgruplarda sağkalımı predikte eder

HR+, HER2(-)

HER2 positive

TNBC



Prognostic value of pCR: Higher in agressive tumors

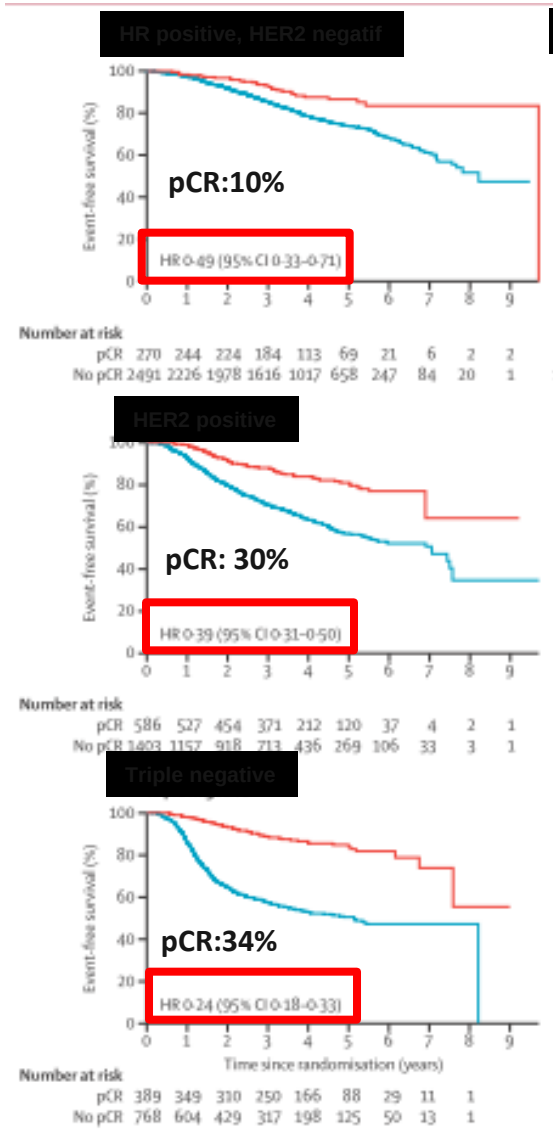
Cortazar P, et al. Lancet. 2014;384:164-172.

pCR: Tüm altgruplarda sağkalımı predikte eder

HR+, HER2(-)

HER2 positive

TNBC



Moleküler alttip önemli

pCR oranı farklı: Daha agresif tm→ ⇑ pCR

pCR'ın sağkalım üzerine etkisi farklı

HER2+ ve Triple neg. MK'da pCR çok önemli

Cortazar P, et al. Lancet. 2014;384:164-172.

Operabl olan her hastaya neoadjuvan tedavi verelim mi?

- **Adjuvan tedavi verilecek her hasta neoadjuvan tedavi alabilir**

- **Hedef meme ve aksiller downstaging ise:**

Tedaviye yanıt olasılığı yüksek olan hastalar seçilmeli

	pCR
✓ Triple negatif	%35-45
✓ HER2+	% 45-60
✓ Luminal B	%28
✗ Luminal A	%10

4 cm tümör
Aksillada 1 adet LN

Rouzier, Clin CancRes' 05;Carey, Clin Canc Res'07

PATOLOJİK TAM YANIT (pCR)

Breast pCR
ypT0/is

Duktal in situ karsinomdan ve aksiller lenf nodlarından bağımsız olarak memede invaziv kanser olmaması

Total pCR
ypT0/is ypN0

Duktal in situ karsinomdan bağımsız olarak meme ve aksiller lenf nodlarında invaziv kanser olmaması

GBG* pCR
ypT0 ypN0

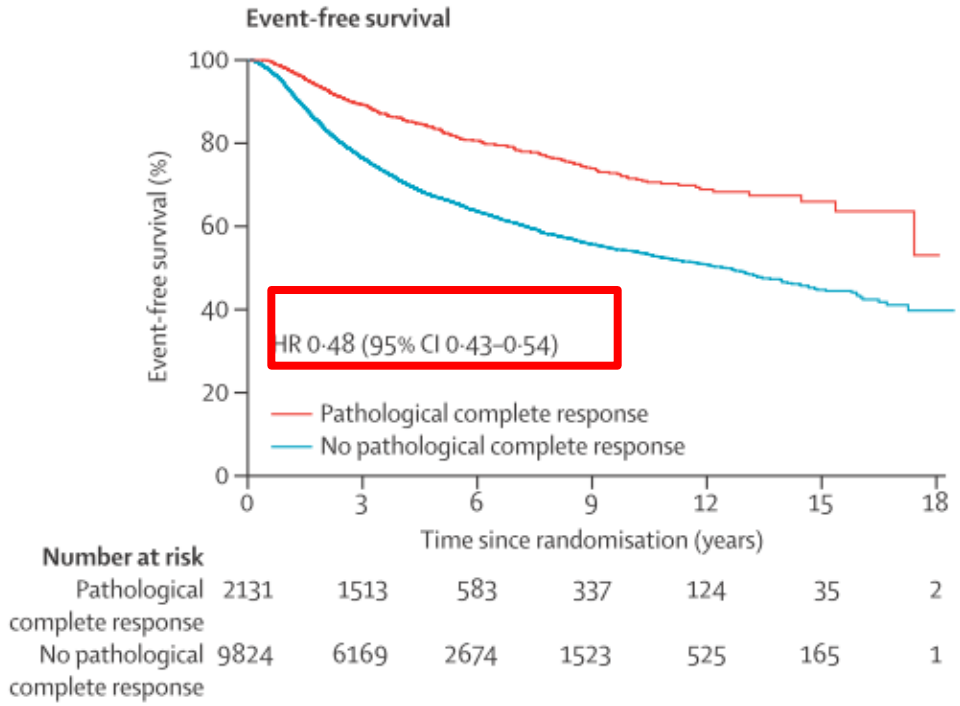
Aksiller lenf nodları ve memede in situ ve invaziv kanser olmaması

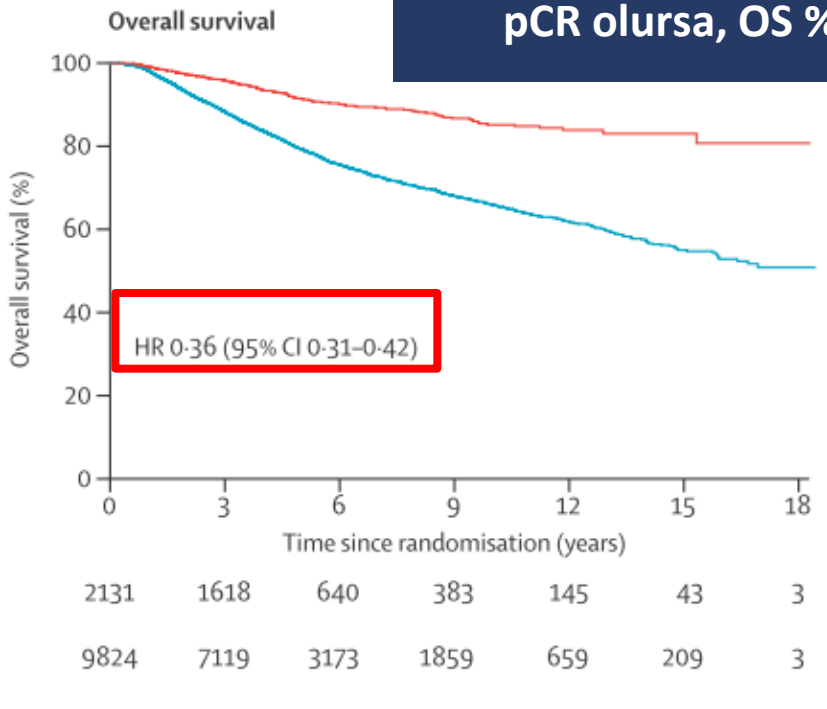
*GBG: German Breast Group

Ogston, et al. The Breast 2003;
Cortazar, et al. Lancet 2014;
von Minckwitz, et al. J Clin Oncol 2012

Sağkalımı belirleyen en önemli parametre: Patolojik tam yanıt (pCR)

pCR olursa, OS %64 daha iyi



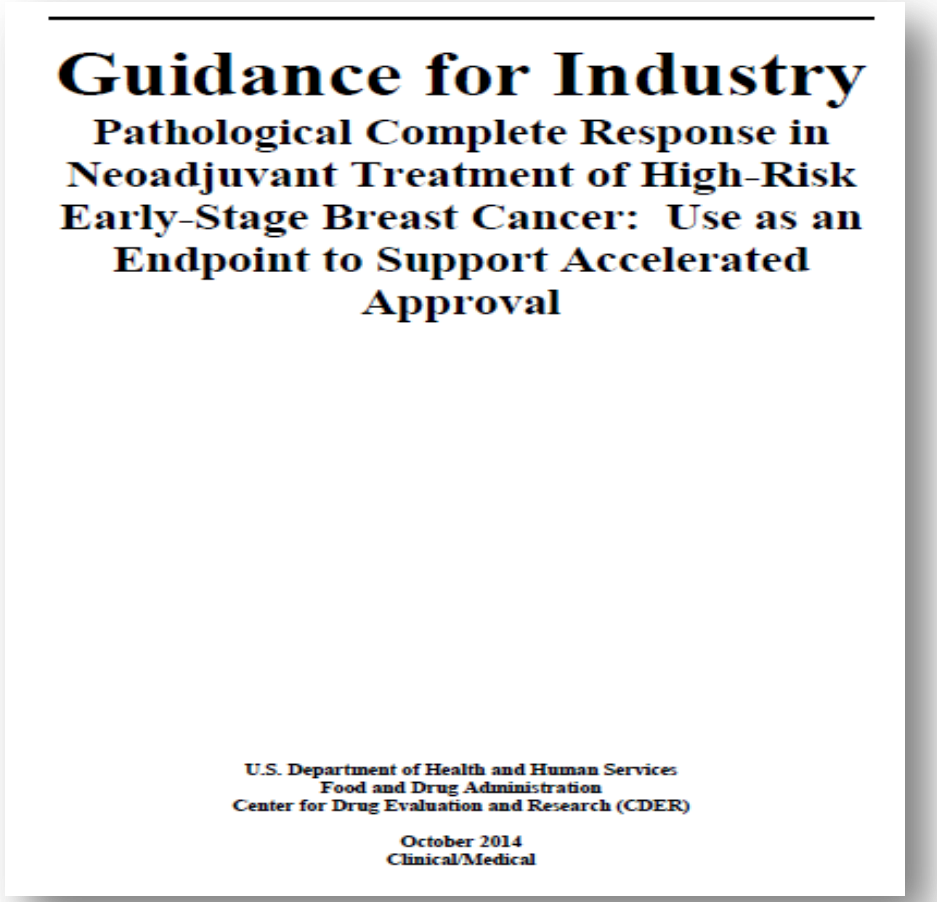


- **Metanaliz**
- **12 klinik çalışma**
- **n: 11.955**

pCR tanımı:
ypT0 ypN0 or ypT0/is ypN0

Cortazar P, et al. Lancet. 2014;384:164-172.

Bir sonlanım noktası olarak PCR



Guidance for Industry

Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2014
Clinical/Medical

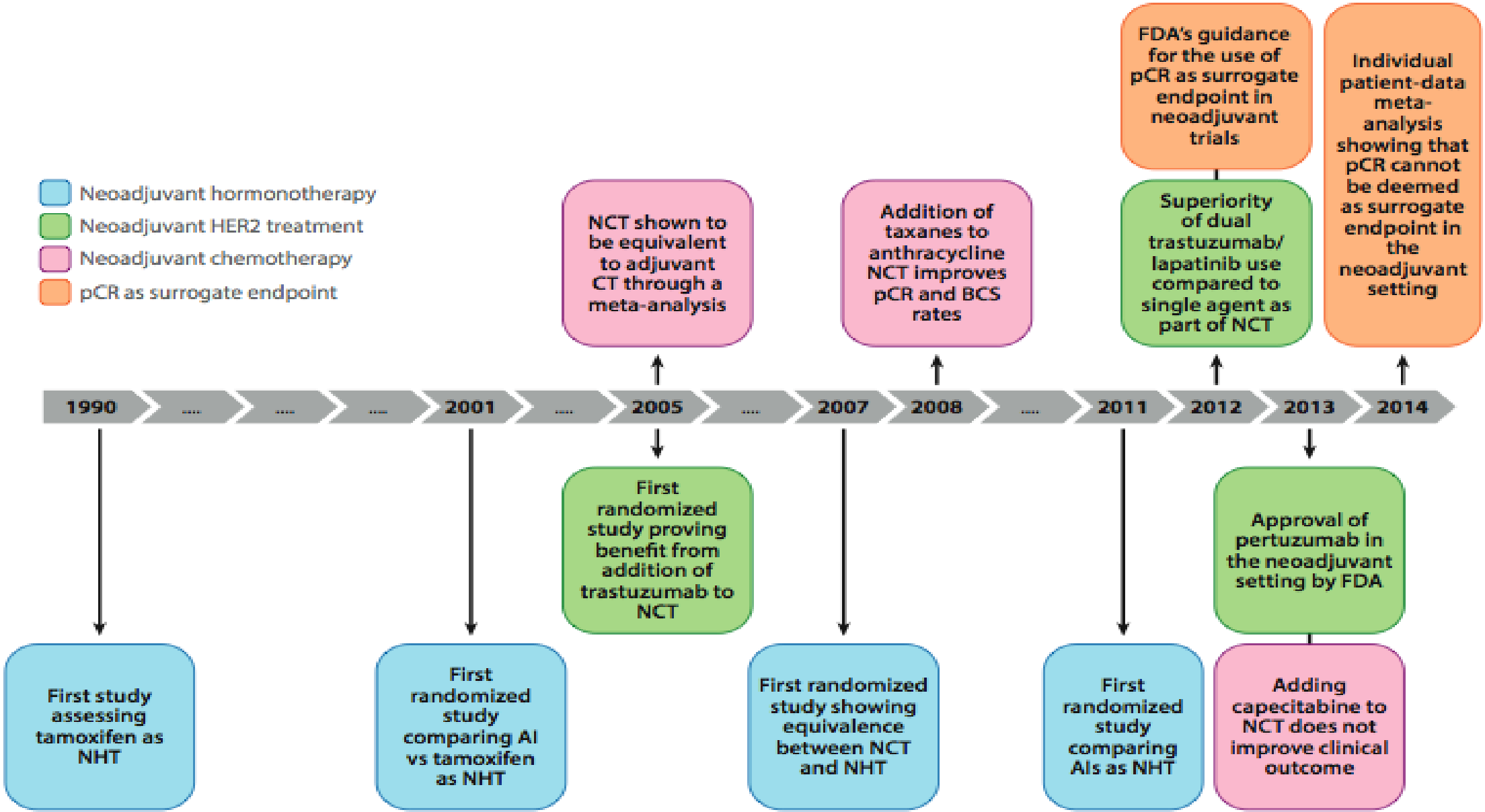
- **FDA pCR'i neoadjuvan çalışmalar için geçerli bir ''vekil/surrogate'' sonlanım noktası olarak kabul etmektedir.**

- **Ayrıca neoadjuvan çalışmalarda uzun dönem sağkalım faydasının ölçümünün ise EFS (olaysız sağkalım) ile ölçülmesi gerektiğini belirtmiştir.**

Cortazar, et al. Lancet 2014, FDA Guidance For Industry 2014

PERJETA PI, PERJETA SmPC

Neoadjuvant tx for BC



KEMOTERAPİ ROLÜNÜ KAYBETTİ Mİ..?

YIL < 2000

YIL 2000-2015

YIL >2015

Neoadjuvant Therapy

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, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Eleftherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz

Summary

Background Pathological complete response has been proposed as a surrogate endpoint for prediction of long-term clinical benefit, such as disease-free survival, event-free survival (EFS), and overall survival (OS). We had four key objectives: to establish the association between pathological complete response and EFS and OS, to establish the definition of pathological complete response that correlates best with long-term outcome, to identify the breast cancer subtypes in which pathological complete response is best correlated with long-term outcome, and to assess whether an increase in frequency of pathological complete response between treatment groups predicts improved EFS and OS.

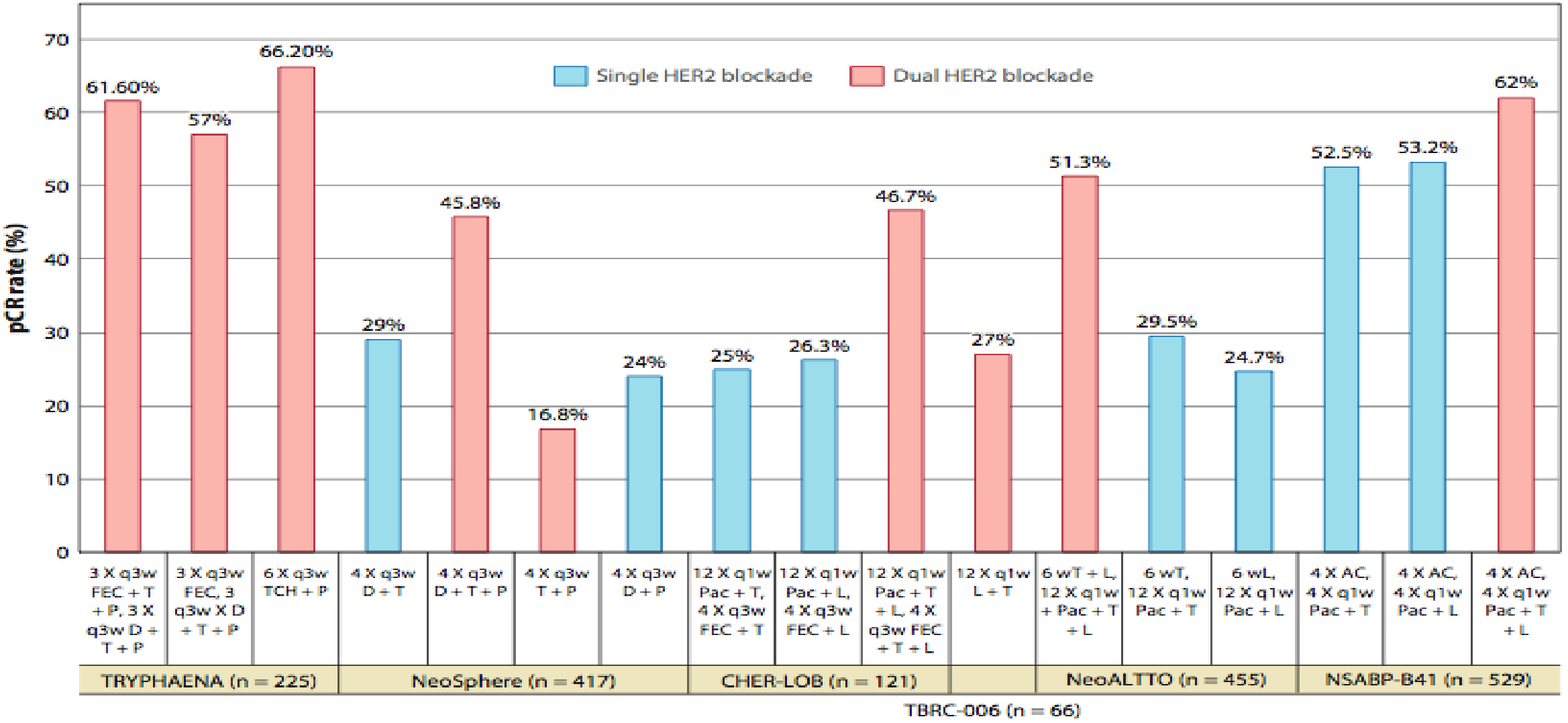
Methods We searched PubMed, Embase, and Medline for clinical trials of neoadjuvant treatment of breast cancer. To be eligible, studies had to meet three inclusion criteria: include at least 200 patients with primary breast cancer treated with preoperative chemotherapy followed by surgery; have available data for pathological complete response, EFS, and OS; and have a median follow-up of at least 3 years. We compared the three most commonly used definitions of pathological complete response—ypT0 ypN0, ypT0/is ypN0, and ypT0/is—for their association with EFS and OS in a responder analysis. We assessed the association between pathological complete response and EFS and OS in various subgroups. Finally, we did a trial-level analysis to assess whether pathological complete response could be used as a surrogate endpoint for EFS or OS.

Findings We obtained data from 12 identified international trials and 11955 patients were included in our responder analysis. Eradication of tumour from both breast and lymph nodes (ypT0 ypN0 or ypT0/is ypN0) was better associated with improved EFS (ypT0 ypN0: hazard ratio [HR] 0·44, 95% CI 0·39–0·51; ypT0/is ypN0: 0·48, 0·43–0·54) and OS (0·36, 0·30–0·44; 0·36, 0·31–0·42) than was tumour eradication from the breast alone (ypT0/is; EFS: HR 0·60, 95% CI 0·55–0·66; OS 0·51, 0·45–0·58). We used the ypT0/is ypN0 definition for all subsequent analyses. The association between pathological complete response and long-term outcomes was strongest in patients with triple-negative breast cancer (EFS: HR 0·24, 95% CI 0·18–0·33; OS: 0·16, 0·11–0·25) and in those with HER2-positive, hormone-receptor-negative tumours who received trastuzumab (EFS: 0·15, 0·09–0·27; OS: 0·08, 0·03, 0·22). In the trial-level analysis, we recorded little association between increases in frequency of pathological complete response and EFS (R^2=0·03, 95% CI 0·00–0·25) and OS (R^2=0·24, 0·00–0·70).

Interpretation Patients who attain pathological complete response defined as ypT0 ypN0 or ypT0/is ypN0 have improved survival. The prognostic value is greatest in aggressive tumour subtypes. Our pooled analysis could not validate pathological complete response as a surrogate endpoint for improved EFS and OS.

ypT0 ypN0> ypT0 a/w EFS
pCR & EFS was stongest in TN and Her-2 pos H treated pts

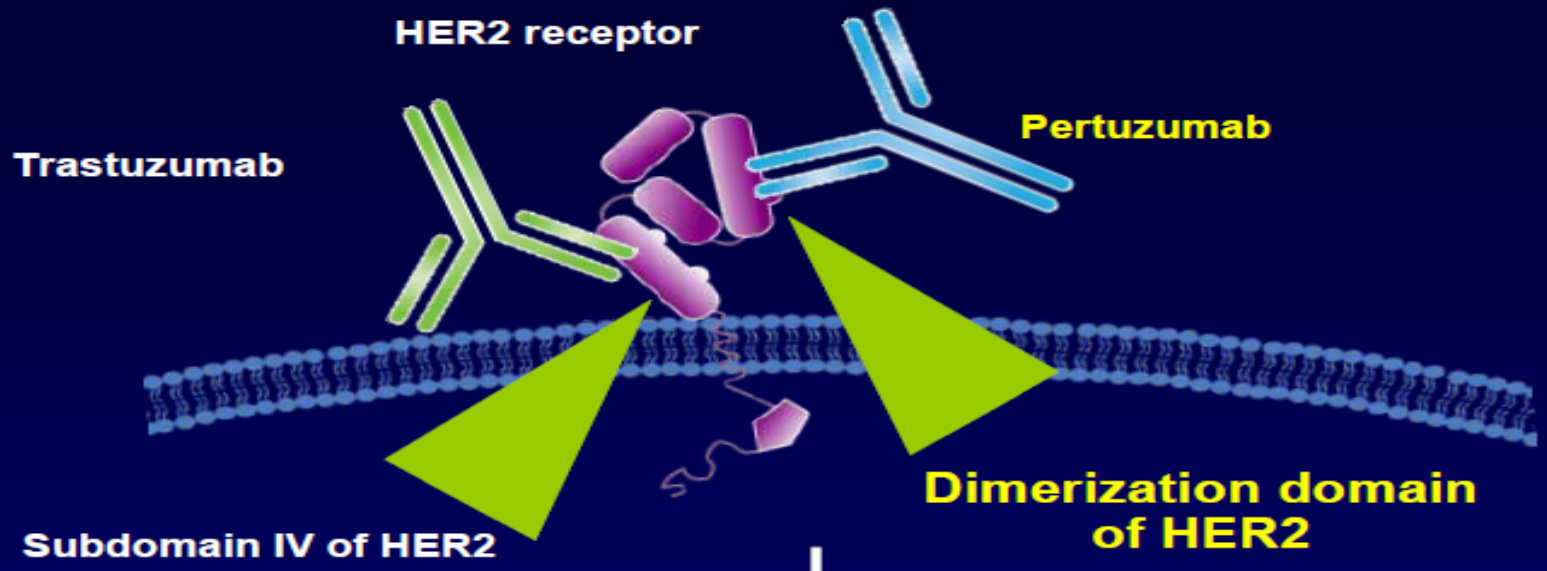
pCR could not be validated as a surrogate endpoint for improved EFS and OS



- **Dual block increases pCR, can safely be combined with CT**
- **Some pts achieve pCR w/o addition of CT**
- **High pCR isn te HR neg group**

HER2+ Meme Kanserinde Neoadjuvan Tedavi ve Pertuzumab

Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity



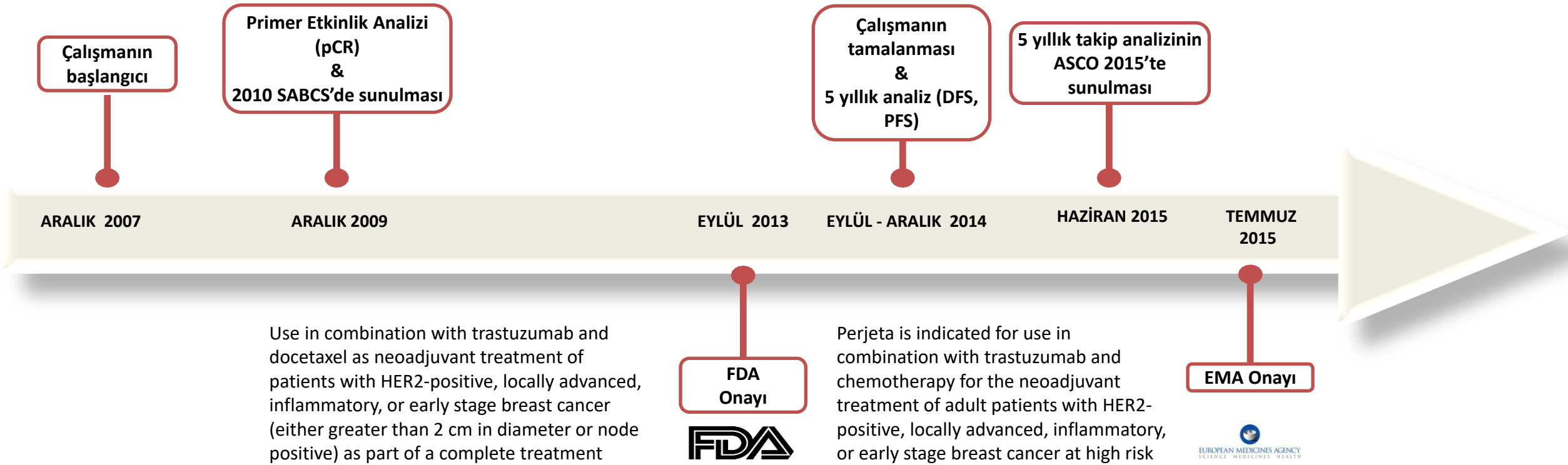
- Trastuzumab continually suppresses HER2 activity
- Flags cells for destruction by the immune system
  - Activates ADCC

- Pertuzumab inhibits HER2 forming dimer pairs
- Suppresses multiple HER signaling pathways
- Flags cells for destruction by the immune system
  - Activates ADCC

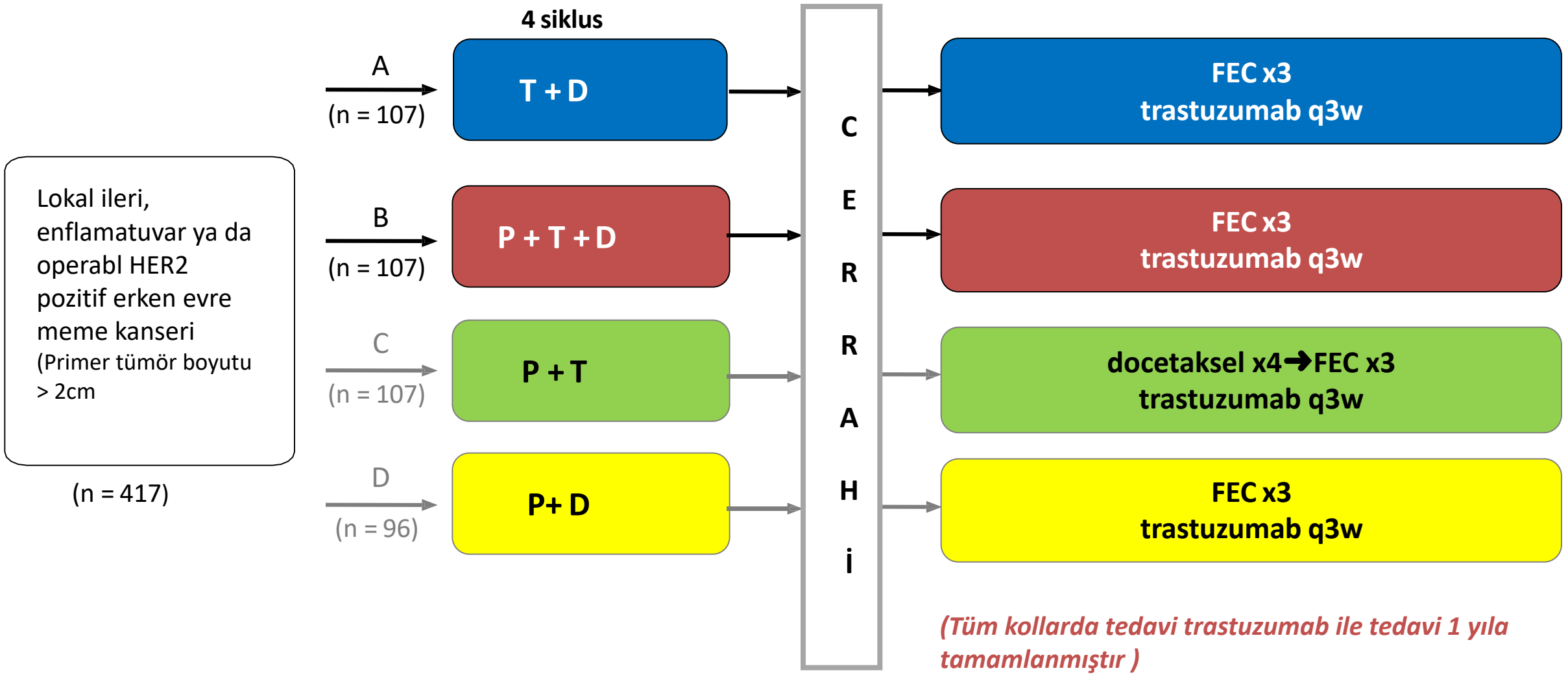
Faz II-trast dirençli 66 hastada ---trast+pertuzumab ile RR %18 (Gelmon ASCO 2008)

NeoSphere

Neoadjuvant study of pertuzumab and Herceptin in an early regimen evaluation



NeoSphere
Çalışma Tasarımı

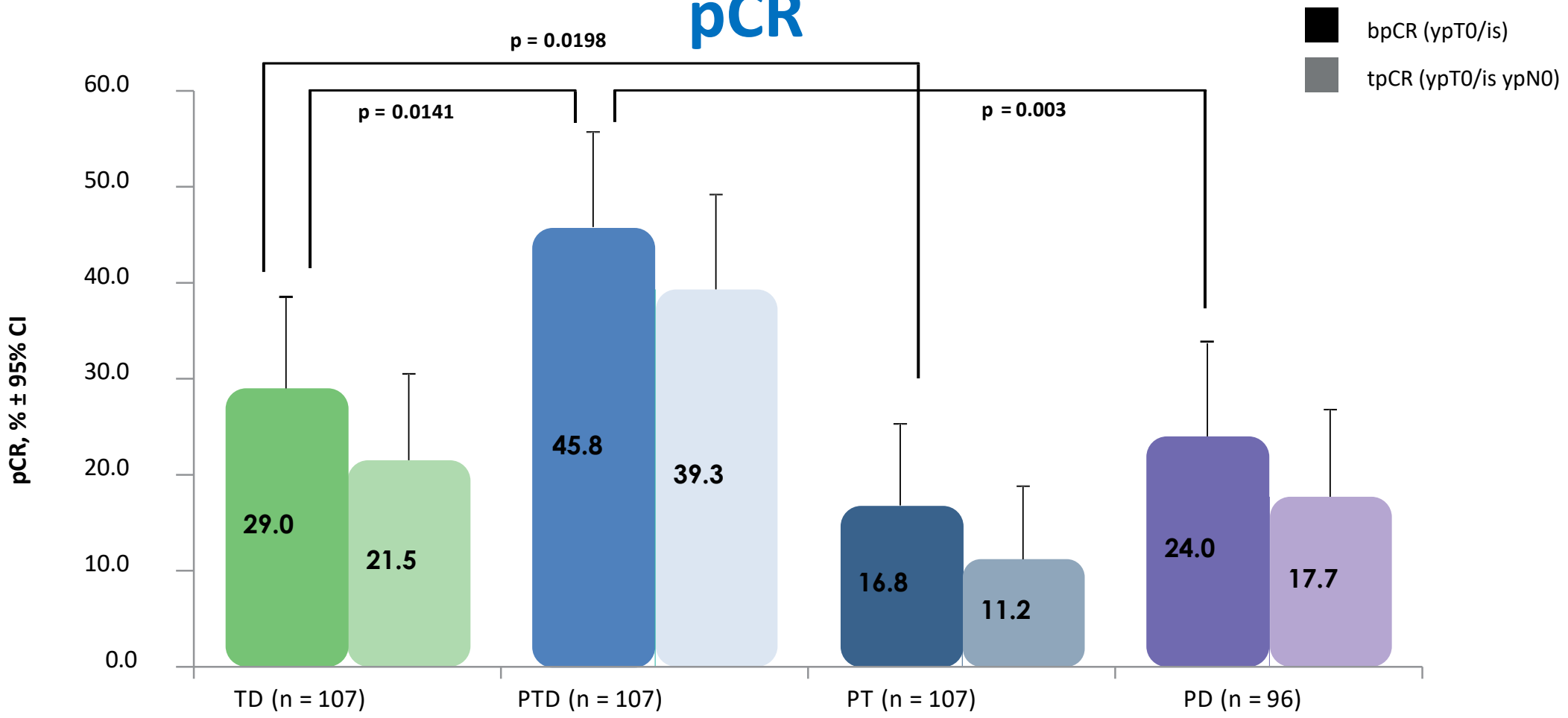


(Tüm kollarda tedavi trastuzumab ile tedavi 1 yıla tamamlanmıştır)

P: Pertuzumab T:Trastuzumab D: Dosetaksel FEC: Florourasil, Epirubisin, Siklofosfamid

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

NeoSphere
pCR



TD:Trastuzumab + Dosetaksel
PTD: Pertuzumab + Trastuzumab + Dosetaksel
PT: Pertuzumab + Trastuzumab
PD: Pertuzumab + Dosetaksel

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

NeoSphere
pCR

	TD (n=107)	PTD (n=107)	PT (n=107)	PD (n=96)
bpCR (ypT0/is)	%29.0	%45.8	%16.8	%24.0
P-değeri*		0.0094 (vs T+D)	0.0198 (vs T+D)	0.0010 (vs Ptz+T+D)
P-değeri**		0.0141 (vs T+D)	0.0198 (vs T+D)	0.0030 (vs Ptz+T+D)
tpCR (ypT0/is ypN0)	%21.5	%39.3	%11.2	%17.7
GBG pCR (ypT0 ypN0)	%12.1	%32.7	%5.6	%13.5

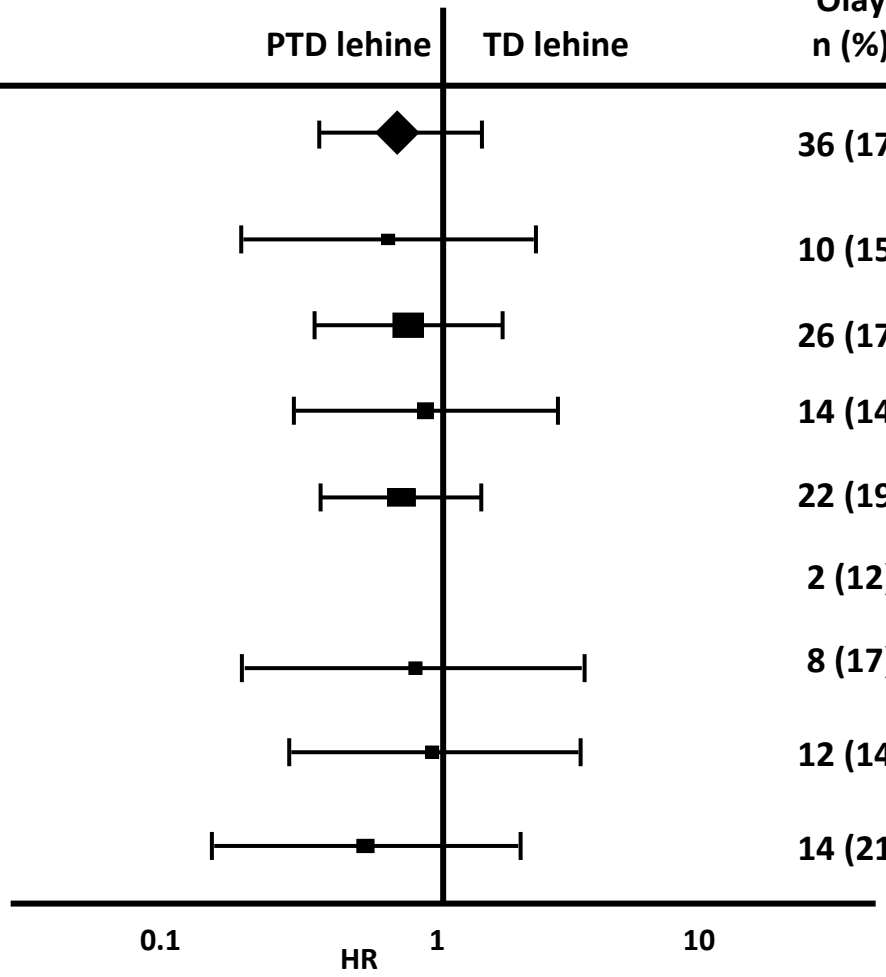
GBG pCR (ypT0 ypN0) : Memedeki tüm invaziv tümörün eradike edilmesi (in-situ hastalık dahil) ve cerrahi esnasında nod negatif olması

* *CMH Testi*

** *Simes düzenlemesi ile CMH Testi*

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

NeoSphere
5 yıllık takipte PFS – Altgrup analizleri (PTD vs TD kolları)



Altgrup	Olay n (%)	HR (95% CI)	5-yıllık PFS oranı, % PTD	5-yıllık PFS oranı, % TD
Genel populasyon (N = 214)	36 (17)	0.69 (0.34–1.40)	86	81
tpCR var(n = 65)	10 (15)	0.63 (0.17–2.38)	88	81
tpCR yok (n = 149)	26 (17)	0.74 (0.32–1.70)	84	81
HR-pozitif (n = 100)	14 (14)	0.86 (0.27–2.75)	86	87
HR-negatif (n = 114)	22 (19)	0.60 (0.24–1.48)	85	75
tpCR var/HR-pozitif (n = 17)	2 (12)	–	91	80
tpCR var/HR-negatif (n = 48)	8 (17)	0.78 (0.17–3.47)	87	81
tpCR yok/HR-pozitif (n = 83)	12 (14)	0.93 (0.26–3.34)	85	88
tpCR yok /HR-negatif (n = 66)	14 (21)	0.51 (0.13–1.97)	83	73

Gianni L, *et al.* ASCO 2015 (Abstract 505; oral presentation).

NeoSphere Study: pCR for Neoadjuvant Pertuzumab, Trastuzumab, Docetaxel

Pts With pCR, n (%)	Trastuzumab, Docetaxel (n = 107)	Pertuzumab, Trastuzumab, Docetaxel (n = 107)	Pertuzumab, Trastuzumab (n = 107)	Pertuzumab, Docetaxel (n = 96)
ITT population	31 (29.0)	49 (45.8)	18 (16.8)	23 (24.0)
N- at surgery	23 (21.5)	42 (39.3)	12 (11.2)	17 (17.7)
N+ at surgery	8 (7.5)	7 (6.5)	6 (5.6)	6 (6.3)
ER and/or PgR positive	10/50 (20.0)	13/50 (26.0)	3/51 (5.9)	8/46 (17.4)
ER and PgR negative	21/57 (36.8)	36/57 (63.2)	15/55 (27.3)	15/50 (30.0)

Long-term outcomes for neoadjuvant trastuzumab + pertuzumab??

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

NeoSphere Study: Safety for Neoadjuvant Pertuzumab, Trastuzumab, Docetaxel

Grade ≥ 3 AEs, n	Trastuzumab, Docetaxel (n = 107)	Pertuzumab, Trastuzumab, Docetaxel (n = 107)	Pertuzumab, Trastuzumab (n = 107)	Pertuzumab, Docetaxel (n = 96)
Pts with ≥ 1 SAE	18	11	4	16
CHF	0	0	1	0
Drug hypersensitivity	0	1	2	0
Fulminant hepatitis*	0	1	0	0

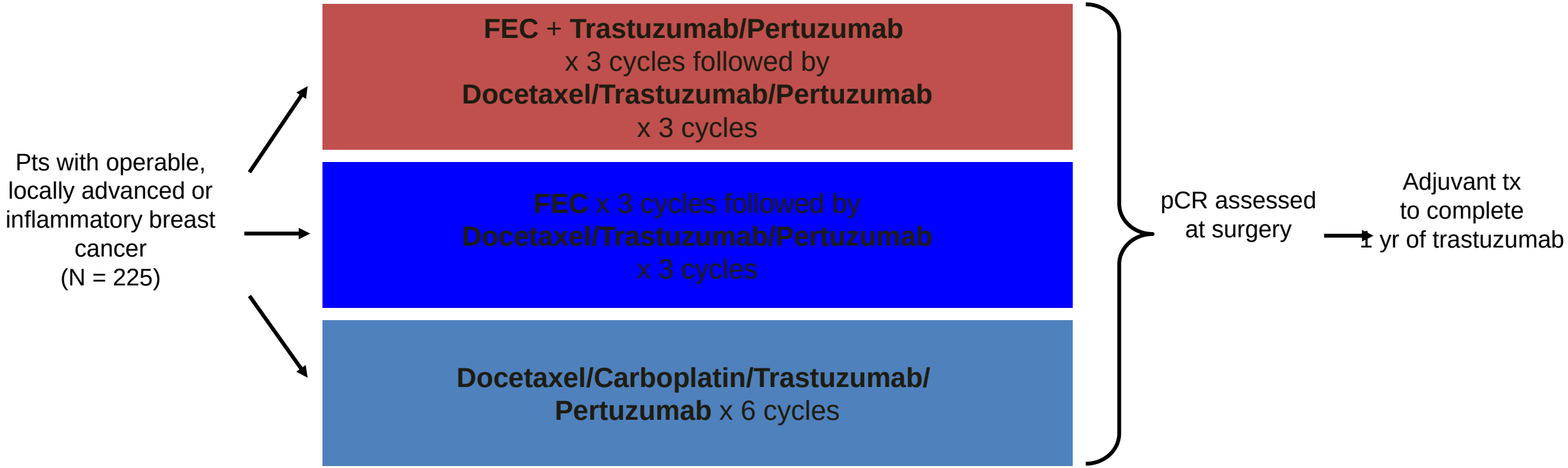
*Hepatitis related to death.

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

NEOadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation

TRYPHAENA

Phase II TRYPHAENA Cardiac Safety Study: Dual HER2 Targeting ± Anthracycline Tx



- Primary endpoint: cardiac safety
- Secondary endpoint: pCR

Schneeweiss A, et al. Ann Oncol. 2013;24:2278-2284.

TRYPHAENA

Klinik yanıt oranları

(n,%)	FEC + PT x3 → PTDx3	FEC x3 → PTD x3	PTDC x6
Objektif yanıt oranı	67 (91.8)	71 (94.7)	69 (89.6)
Tam yanıt oranı	37 (50.7)	21 (28.0)	31 (40.3)
Parsiyel yanıt oranı	30 (41.1)	50 (66.7)	38 (49.4)
Stabil hastalık	3 (4.1)	1 (1.3)	5 (6.5)
Progresif hastalık	0 (0.0)	1 (1.3)	0 (0.0)
Değerlendirme yapılamadı	3 (4.1)	2 (2.7)	3 (3.9)

Schneeweiss A, Ann Oncol 2013; 24:2278–2284.

TRYPHAENA
3 yıllık sağkalım sonuçları

- **SABCS 2016'da açıklanan 3 yıllık sağkalım sonuçlarının NeoSphere'deki 5 yıllık sonuçlar ile uyumlu olduğu görülmüştür.**

% (%95 GA)	FEC + PT x3 → PTDx3	FEC x3 → PTD x3	PTDC x6
DFS	87 (79–95)	88 (80–96)	90 (82–97)
PFS	89 (81–96)	89 (81–96)	87 (80–95)
OS	94 (89–100)	94 (89–100)	93 (87–99)

SABCS 2016 Poster Presentation P4–21–02 , Schneeweiss A. et al European Journal of Cancer 89 (2018) 27-35

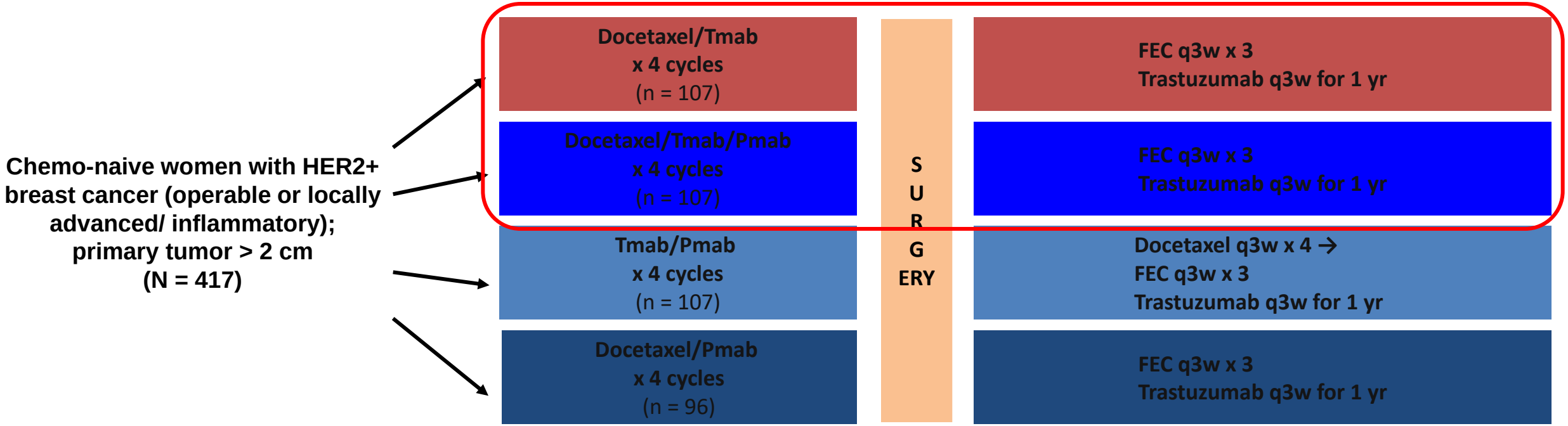
TRYPHAENA Cardiac Safety Study of Dual HER2 Targeting ± Anthracycline Tx: Results

Cardiac Events During Neoadjuvant Tx, n	Arm A FEC + HP → THP (n = 73)	Arm B FEC → THP (n = 75)	Arm C TCHP (n = 77)
Symptomatic LVSD	0	2	0
≥ 10% decline in LVEF	4	4	3

- **Conclusion: The combination of pertuzumab with trastuzumab and standard chemotherapy resulted in low rates of symptomatic LVSD**

Schneeweiss A, et al. Ann Oncol. 2013;24:2278-2284.. Schneeweiss, et al. SABCS 2011. Abstract S5-6.

Open-Label Phase II NeoSphere Study: Neoadjuvant Pertuzumab/Trastuzumab



- Primary endpoint: pCR in breast (ITT pop)
- pCR defined as absence of invasive neoplastic cells at microscopic examination of the primary tumor at surgery

Trastuzumab 8 mg/kg loading dose, then 6 mg/kg q3w; pertuzumab 840 mg loading dose, then 420 mg q3w; docetaxel 75 mg/m^2 escalating, if tolerated, to 100 mg/m^2 q3w

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

TRYPHAENA
Sonuç

- **TRYPHAENA çalışmasından elde edilen sonuçlara göre, neoadjuvan ya da adjuvan dönemlerde tüm kollarda semptomatik ve asemptomatik LVSD insidansı düşüktür.**
  - **Pertuzumab, trastuzumab ve epirubisinin eş zamanlı uygulanması, antrasiklinsiz rejimlerin sıralı uygulanmasıyla benzer kardiyak tolerabilite sergilemiştir.**

- **Nötropeni, febril nötropeni, lökopeni ve diyare tüm kollarda en sık bildirilen advers olaylar olmuştur. (Grade ≥3)**

- **Seçilen kemoterapiden bağımsız olarak, neoadjuvan koşulda pertuzumabın trastuzumabla kombinasyonu yüksek pCR oranları sağlamıştır.(%57–66)**

Schneeweiss A, Ann Oncol 2013; 24:2278–2284.

Pertuzumab Approved as NeoAdj Tx for HER2+ BC Based on NeoSphere Results

Study	pCR Rates, % (95% CI)		
	Trastuzumab	Additional HER2 Agent*	Combination
NeoALTTO[1]	30	24	51
NeoSphere[2]	29 (21-39)	24 (16-34)	46 (36-56)

*NeoALTTO: lapatinib; NeoSphere: pertuzumab

- **Pertuzumab (NeoSphere)**
  - Indication: in combination with trastuzumab and docetaxel for HER2+ BC
  - Caution (per PI): "No data are available demonstrating improvement in event-free survival or overall survival"
- **Lapatinib (NeoALTTO)**
  - Indication: in combination with letrozole or capecitabine for metastatic disease
  - No indication for use with trastuzumab

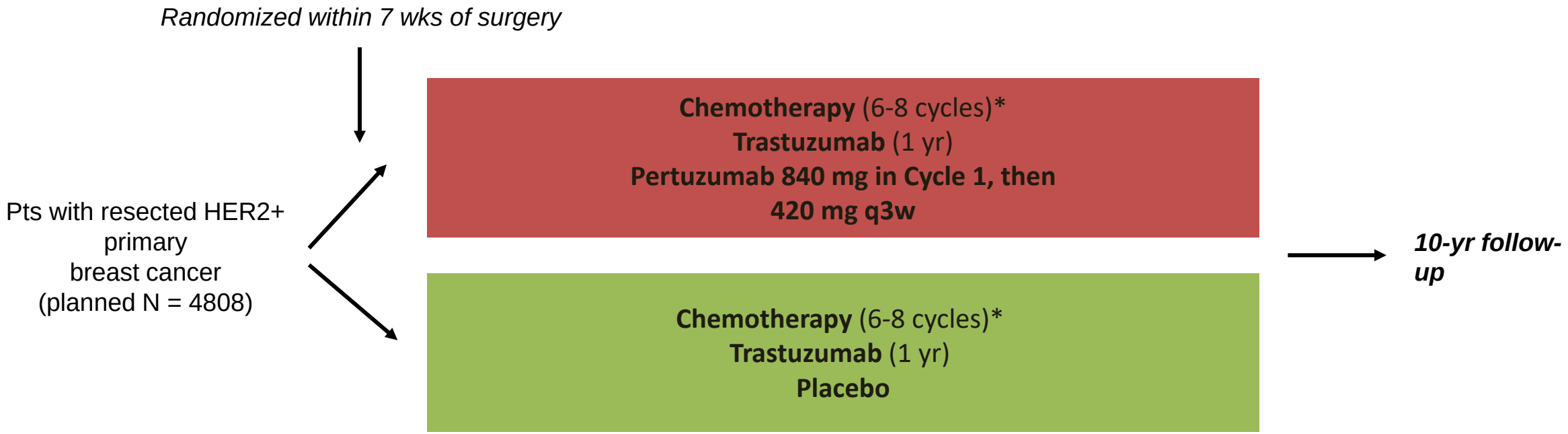
1. Baselga J, et al. Lancet. 2012;379:633-640. 2. Gianni L, et al. Lancet Oncol. 2012;13:25-32.

Pertuzumab: Approval for Neoadjuvant Therapy in Early Breast Cancer

- **Pertuzumab prescribing information[1]**
  - **Indication: Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of pts with HER2+ locally advanced, inflammatory, or early-stage breast cancer (either > 2 cm in diameter or node positive)**
  - **Caution: "No data are available demonstrating improvement in event-free survival or overall survival"**
- **NCCN: more aggressive stand on addition of pertuzumab to neoadjuvant or adjuvant therapy for pts with early breast cancer[2]**
  - **"A pertuzumab-containing regimen can be administered to pts with ≥ T2 or ≥ N1, HER2-positive, early stage breast cancer"**

1. Pertuzumab [package insert]. 2012. 2. NCCN. Clinical practice guidelines in oncology: breast cancer v.2.2015.

Phase III APHINITY: Dual HER2 Targeting in Adjuvant Therapy of EBC



*Anthracycline or nonanthracycline. Radiotherapy and/or endocrine therapy may be started after completion of adjuvant chemotherapy.

- Primary endpoint: invasive DFS
- Secondary endpoints: invasive DFS, including second non-breast cancer, DFS, OS, RFI, distant RFI, safety, QoL

ClinicalTrials.gov. NCT01358877.

Should Pts With HER2+ EBC Receive Neoadj and Adj Tx With Tras or Tras/Pmab?

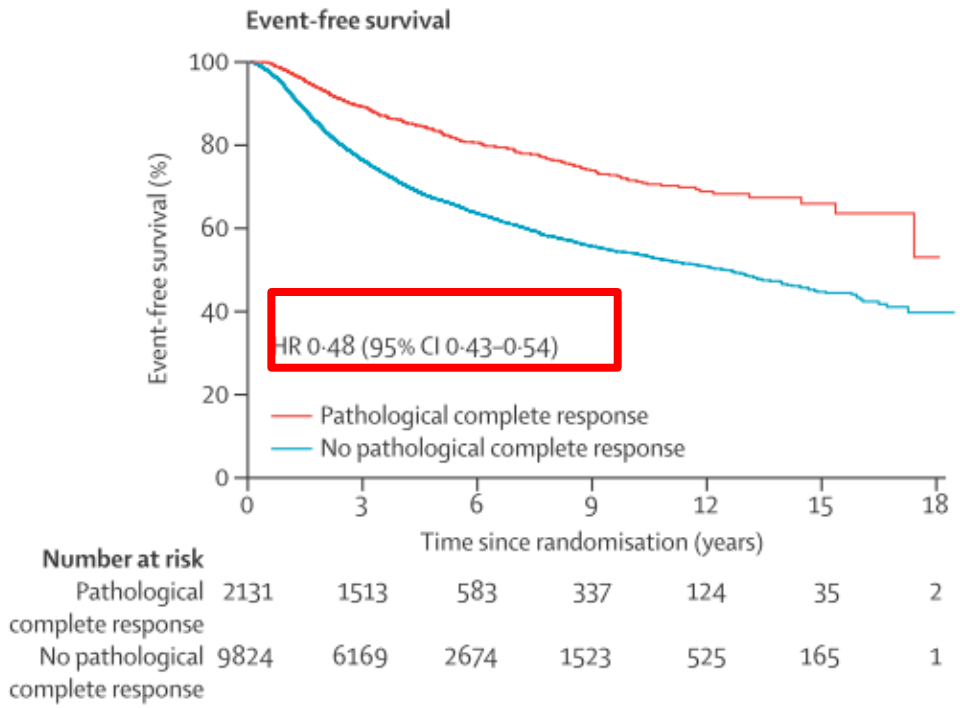
- If the major goal is a better preoperative response, add pertuzumab to trastuzumab
  - Pertuzumab approved based on improvement in pCR
- If the goal is longer survival, there is no definitive evidence yet that pertuzumab provides a survival benefit
- Caveats
  - Pertuzumab does add to expense, but not in a unprecedented way[1]
  - Pertuzumab slightly increases risk of toxicity but does not seem to worsen cardiac effects

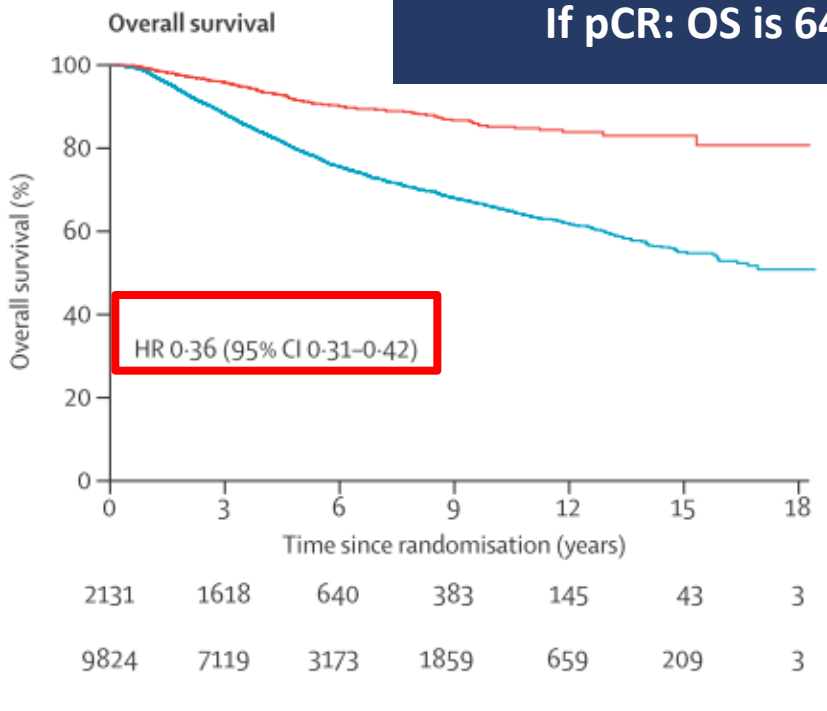
1. Babigumira JB, et al. ASCO 2014. Abstract 642.

Molecular subtypes of breast cancer

			Luminal	
	Triple negative	HER2 (+)	Luminal A	Luminal B
ER	-	-	+++	++/+
PR	-	-	+++	+/-
HER2	-	+++	-	-/+
Ki-67	↑↑↑	↑↑↑	<%15	>%15
Relapse risk	+++	+++	+	++
Mortality	+++	+++	+	++
Chemosensitivity	+++	+++	-	++

CTNeoBC pooled analysis:
Best prognostic factor for survival: Pathological complete response (pCR)





If pCR: OS is 64% better

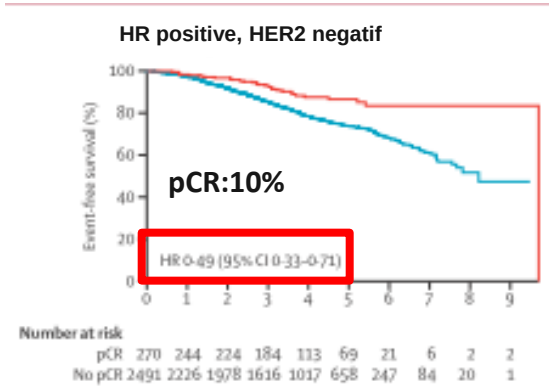
- **12 neoadjuvant clinical trials**
- **n: 11.955**
- **pCR: %18**

pCR definition
ypT0 ypN0 or
ypT0/is ypN0

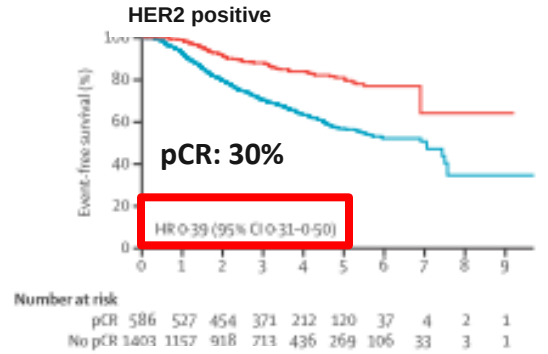
Cortazar P, et al. Lancet. 2014;384:164-172.

pCR: Predicts EFS in all subtypes

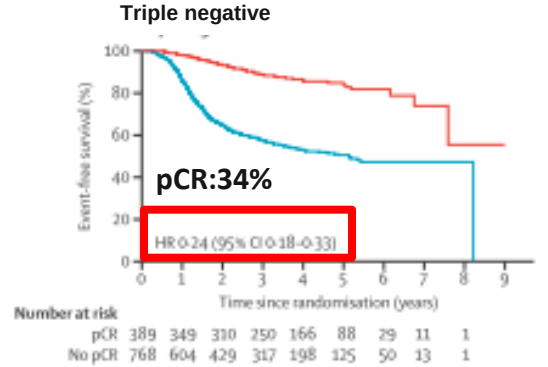
HR+, HER2(-)



HER2 positive



TNBC



Molecular subtype is important

Rate of pCR differs: More agressive tm→ ⇑ pCR

	pCR
Triple negatif	%35-45
HER2+	% 45-60
Luminal B	%28
Luminal A	%10

Cortazar P, et al. Lancet. 2014;384:164-172.

When should we consider neoadjuvant treatment in operable patients?

- **If the goal is downstaging the tumor and axilla:**

Give neoadjuvant treatment if the probability of pCR is high

	pCR
Triple negative	%35-45
HER2+	% 45-60
Luminal B	%28
Luminal A	%10

3 cm tumor
Clinically 1 axillary LN
T2N1

Rouzier, Clin CancRes' 05;Carey, Clin Canc Res'07

Primary analysis of BERENICE: A phase II cardiac safety study of pertuzumab, trastuzumab, and neoadjuvant anthracycline-based chemotherapy in patients with locally advanced, inflammatory, or early-stage, unilateral, and invasive HER2-positive breast cancer

Sandra M. Swain, Michael S. Ewer, Giuseppe Viale, Suzette Delaloge, Jean Marc Ferrero, Mark Verrill, Ramon Colomer, Cláudia Vieira, Theresa L. Werner, Hannah Douthwaite, Denise Bradley, Maeve Waldron-Lynch, Jennifer Eng-Wong, Chau Dang

Data presented at SABCS 2016
Abstract P4-21-41

https://clinicaltrials.gov/ct2/show/NCT02132949

BERENICE

Gerekçe

- **Pertuzumabın trastuzmab ve dosetaksel ile birlikte HER2 pozitif meme kanserinin 1. basamak tedavisindeki PFS ve OS faydası CLEOPATRA çalışmasında gösterilmiştir.[1,2]**
- **Anti-HER2 ilaçların özellikle antrasiklinlerle kombine kullanımı kardiyak toksisite riskini arttırabilmektedir.[3–5]**
- **NeoSphere, TRYPHAENA and GeparSepto çalışmalarında neoadjuvan tedavide trastuzuam ve taksanlı rejimlere pertuzumabı eklemenin yüksek pCR sonuçları sağladıüğı görülmüştür.[5–7] NeoSphere çalışmasında bu 3 lü kombinasyonun tolerabiliteyi eklmediği görülürken, TRYPHAENA'da da düşük LVSD oranları gözlenmiştir. [5,6]**
- **Neoadjuvan tedavide trastuzumab + pertuzumaba FEC + taksanlı kemoterapinin eklenmesinin güvenliliği konusunda sınırı bilgi mevcuttur.[5]**
- **Ayrıca ddAC'yik takibek pakliteksel ile birlikte trastuzumab + pertuzumab kombinasyonunun etkilik ve günvenliliği ilgili veriler de ksıtılıdır.**

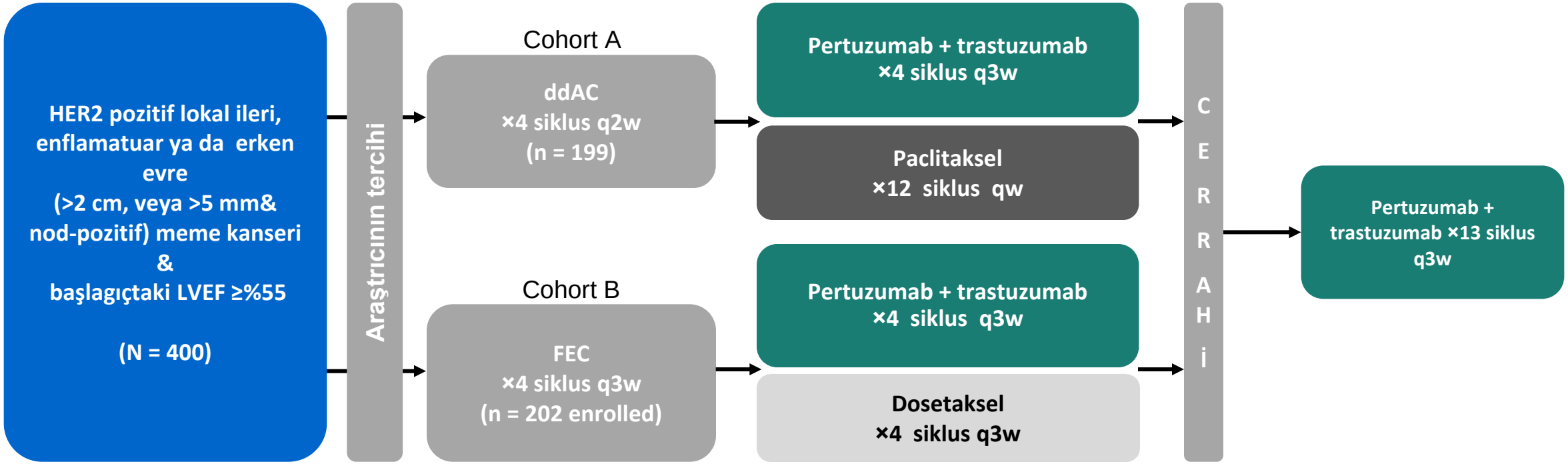
Bu veriler ışığında, HER2 pozitif meme kanserinin neoadjuvan tedavisinde ddAC'yi takiben paklitaksel ya da FEC'i takiben doestakselin kardiyak güvenliliğini değerlendirmek için BERENICE çalışması dizayn edilmiştir.

ddAC, dose-dense doxorubicin plus cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival.

1. Baselga J, *et al. N Engl J Med* 2012; 366:109–119;
2. Swain SM, *et al. N Engl J Med* 2015; 372:724–734;
3. Seidman A, *et al. J Clin Oncol* 2002; 20:1215–1221;
4. Slamon DJ, *et al. N Engl J Med* 2011; 365:1273–1283;
5. Schneeweiss A, *et al. Ann Oncol* 2013; 24:2278–2284;
6. Gianni L, *et al. Lancet Oncol* 2012; 13:25–32;
7. Untch M, *et al. Ann Oncol* 2016; 17:345–356.

Çalışma Tasarımı

- **BERENICE çok merkezli,non-randomize,açık etiketli, Phase II kardiyak güvenlilik çalışmasıdır. 12 ülkede 75 merkezde gerçekleşmiştir.**



ITT populasyonu: 199 (Cohort A) ve 201 patients (Cohort B)
Safety populations were 199 (Cohort A) and 198 (Cohort B)

ddAC (A: 60 mg/m^2; C: 600 mg/m^2); FEC (F: 500 mg/m^2, E: 100 mg/m^2, C: 600 mg/m^2); docetaxel (75 mg/m^2 escalating to 100 mg/m^2 if no dose-limiting toxicity); paclitaxel (80 mg/m^2); pertuzumab (840 mg→420 mg); trastuzumab (8 mg/kg→6 mg/kg).

SABCS 2016, Abstract P4-21-41

Primer sonlanım noktası 2:
Neoadjuvan tedavi esnasında LVEF düşüşü

	Cohort A: ddAC→TPH, n=199	Cohort B: FEC→DPH, n=198
Patients with at least one LVEF decline	13 (6.5%; 95% CI 3.5%, 10.9%)	4 (2.0%; 95% CI 0.6%, 5.1%)
Number of events	19	5
Onset prior to neoadjuvant HER2-targeted therapy, patients (Cycles 1–4)	0	1 (0.5%)
Onset during neoadjuvant HER2-targeted therapy, patients (Cycles 5–8)	13 (6.5%)	3 (1.5%)
Patients with at least one confirmed LVEF decline	2 (1.0%; 95% CI 0.1%, 3.6%)	1 (0.5%; 95% CI 0%, 2.8%)

95% CIs of were calculated with the use of the Clopper-Pearson method.
Includes events with onset from the first dose of pertuzumab or trastuzumab prior to surgery through the day before the first dose of any study drug after surgery. If a patient withdrew without entering the adjuvant period, the table includes all AEs with onset from first dose of pertuzumab or trastuzumab through 42 days after last dose of any study drug or on the day of target surgery, whichever is later. Multiple occurrences of the same events in one individual are counted only once in the patient frequency counts.
Confirmed LVEF declines are defined as at least two consecutive readings of declines in LVEF, and single LVEF declines are defined as only one reading of significant declines (no consecutive readings) in LVEF.

SABCS 2016, Abstract P4-21-41

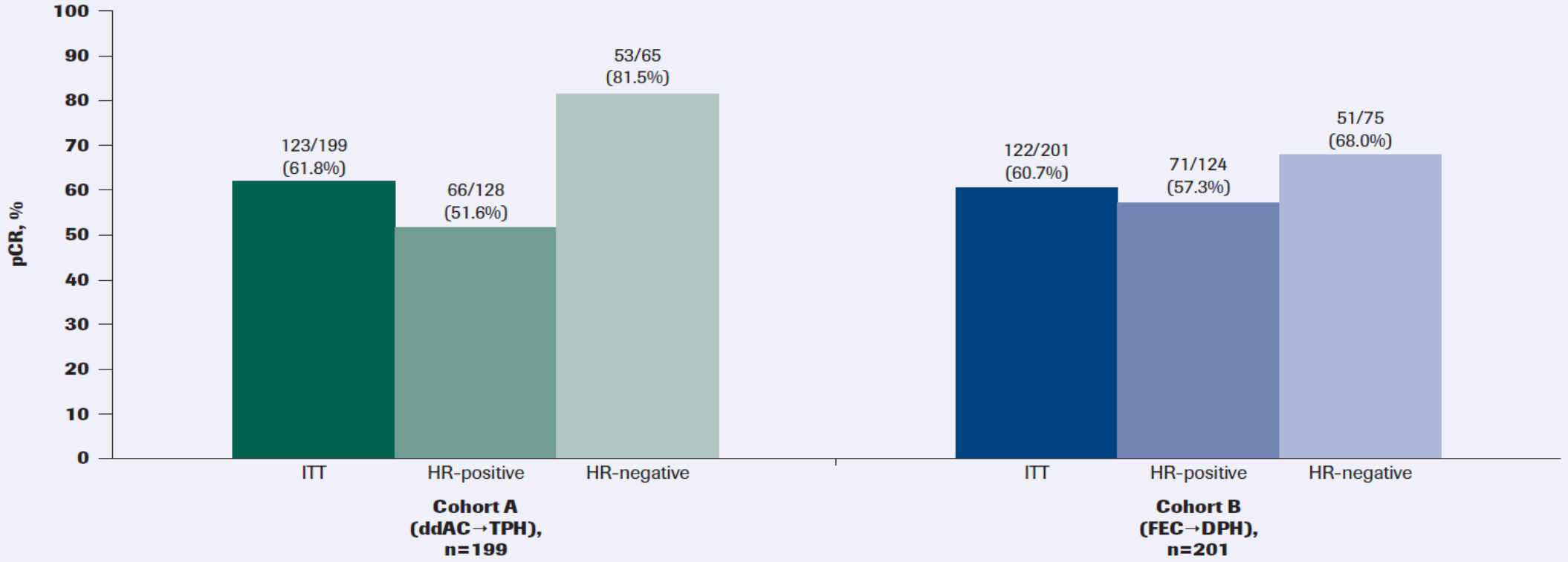
Sekonder sonlanım noktası:Güvenlilik

	Kohort A ddAC → PHpac (n = 199)	Kohort B FEC → PHT (n = 198)
≥1 advers olau (herhangi bir grade), n (%)	198 (99.5)	198 (100)
Most common AEs (all grades), n (%) Mide bulantısı Diyare Alopesi	 141 (70.9) 133 (66.8) 124 (62.3)	 137 (69.2) 137 (69.2) 116 (58.6)
≥1 Grade 3–5 advers olay , n (%)	99 (49.7)	108 (54.5)
Most common grade 3–5 AEs, n (%) Febrile neutropenia* Neutropenia Diarrhoea	 14 (7.0) 24 (12.1) 6 (3.0)	 34 (17.2) 17 (8.6) 20 (10.1)
≥1 ciddi advers olay (SAE), n (%)	45 (22.6)	52 (26.3)
Trastuzumab ya da pertuzumab tedavisini bırakmaya neden olan ≥1 advers olay, n (%)	10 (5.0)	4 (2.0)
Ölüm, n (%)	0	0

SABCS 2016, Abstract P4-21-41

Sekonder sonlanım noktası:

pCR *ITT populasyonu*



Araştırıcılar, sonuç kısımında, bu pCR sonuçlarının NeoSphere ve TRYPHAENA çalışmalardaki pertuzumab + trastuzumab ile elde edilen pCR sonuçları ile uyumlu olduğunu bildirmiştir.

SABCS 2016, Abstract P4-21-41

Safety of adjuvant treatment with pertuzumab plus trastuzumab after neoadjuvant anthracycline-based chemotherapy in patients with HER2-positive localized breast cancer: Updated results from the BERENICE study

Chau Dang, Michael S. Ewer, Suzette Delaloge, Jean-Marc Ferrero, Mark Verrill, Ramon Colomer, Cláudia Vieira, Luis de la Cruz Merino, Jennifer Lucas, Theresa L. Werner, Hannah Douthwaite, Denise Bradley, Maeve Waldron-Lynch, Jennifer Eng-Wong, Sandra M. Swain

Data presented at SABCS 2017

Abstract P5-20-04

https://clinicaltrials.gov/ct2/show/NCT02132949

BERENICE Güncellenmiş Güvenlilik Verileri Sonuç

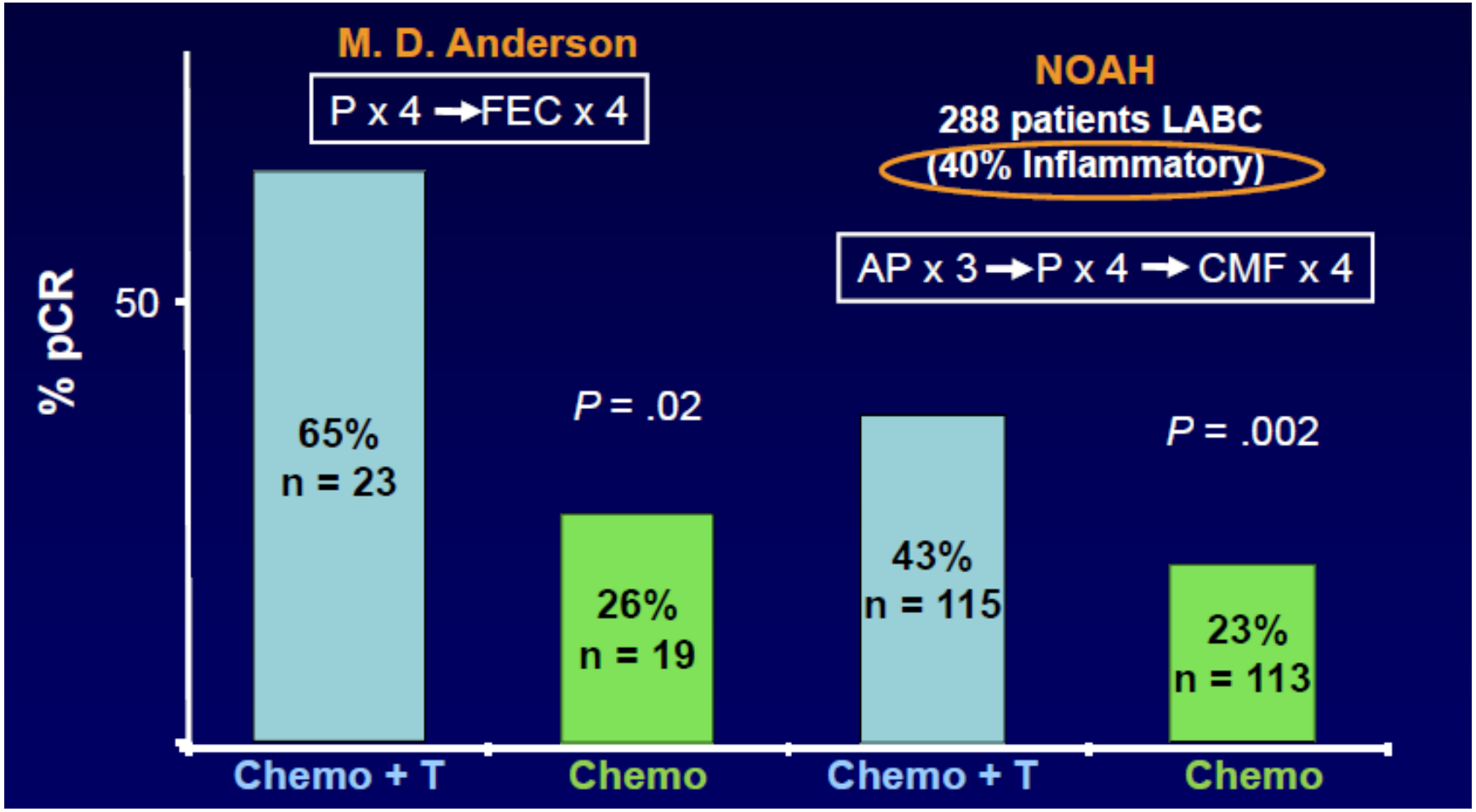
- **Antrasiklin ya da taksan bazlı rejim + pertuzumab ve trastuzumabı takiben adjuvan pertuzumab ve trastuzumab ile tedavide kardiyak advers olay insidansı düşük olarak gözlenmiştir.**

- **Bu veriler pertuzumab ve trastuzumab kombinasyonu ile yapılan diğer çalışmalardaki güvenlilik verileri ile uyumludur ve adjuvan tedavide pertuzumab ve trastızumab ile birlikte kadiyak toksisite riskinin artmadığını işaret etmektedir.**

- **≥ 3 advers olay sıklığı özellikle kemoterapinin kesilmesinden sonra belirgin bir şekilde azalmıştır ve yeni bir güvenlilik sinyali ortaya çıkmamıştır.**

SABCS 2017, Abstract P5-20-04

HER2+ MK: Neoadjuvan kemoterapi + Trastuzumab

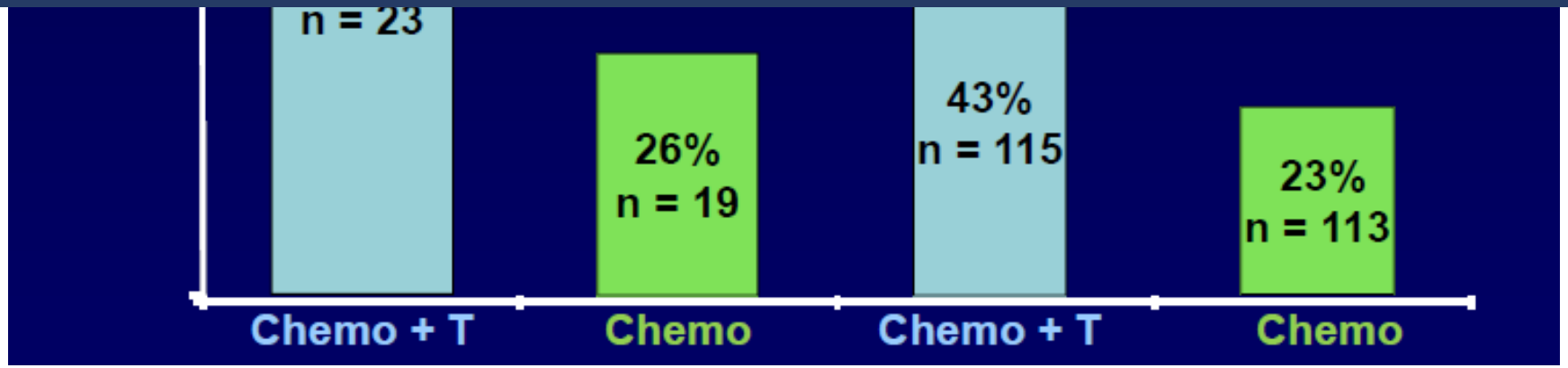


Buzdar A, et al. Clin Cancer Res. 2007;13(1):228-233, Gianni L, et al. Lancet. 2010;375(9712):377-384, Petrelli F et al. Anticancer Drugs 2011; 22: 128 .

HER2+ MK: Neoadjuvan kemoterapi + Trastuzumab

METANALİZ
Kemoterapiye trastuzumab eklemenin sonucu

pCR artar (%20 → %43)
Relaps azalır (%39→ %26, RR: 0.67)
Mortalite azalma eğilimi (%20→ %13, RR: 0.67)



Buzdar A, et al. Clin Cancer Res. 2007;13(1):228-233, Gianni L, et al. Lancet. 2010;375(9712):377-384, Petrelli F et al. Anticancer Drugs 2011; 22: 128 .

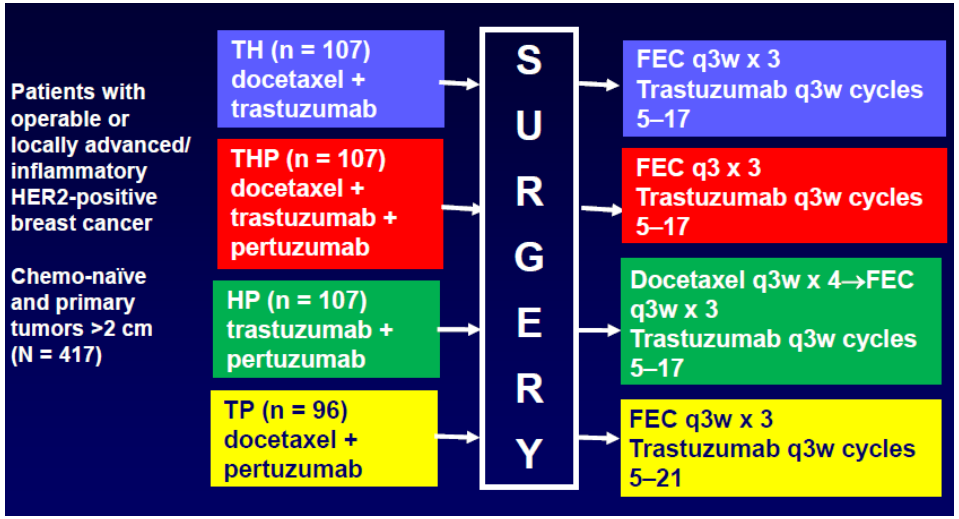
HER2+ MK'da pCR artırılabilir mi? Kombine antiHER2 tedaviler

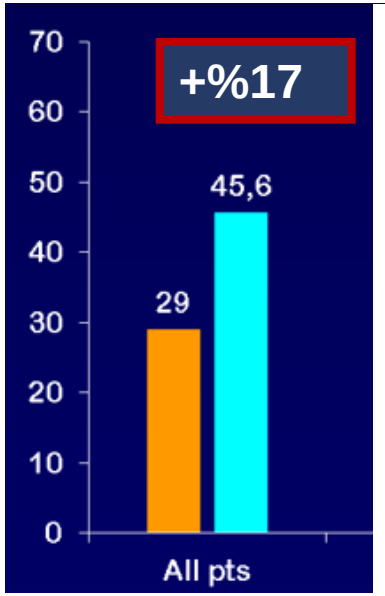
- **Standard:** Kemoterapi (Antrasiklin+taksan bazlı) + trastuzumab

- **Kombine HER2 blokajı**
  - Trastuzumab + lapatinib: Neoadjuvan ve adjuvanda önerilmiyor
  - Trastuzumab +pertuzumab:
    - Metastatik HER2 hastalıkta: Sağkalımda **NET 16 AYLIK AVANTAJ**

HER2+ MK: Trastuzumab+Pertuzumab

- **NeoSphere Çalışması**

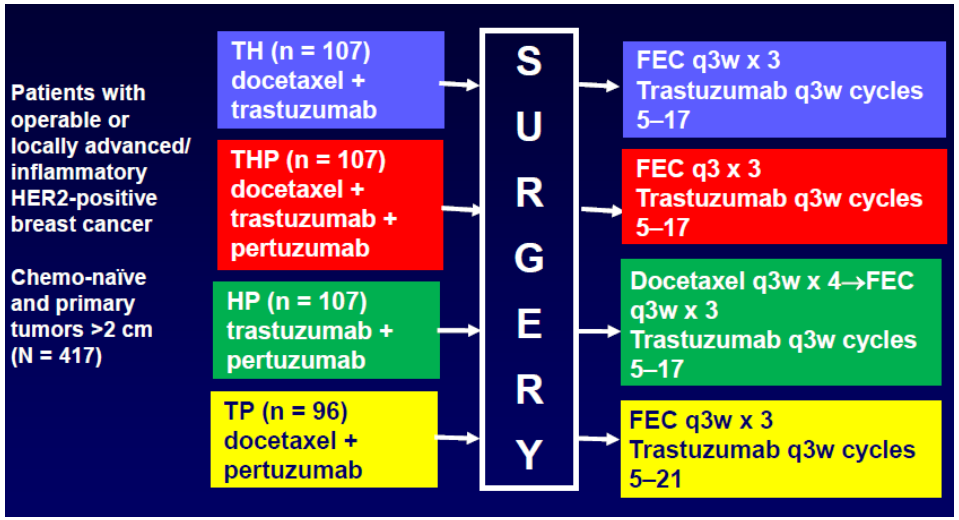


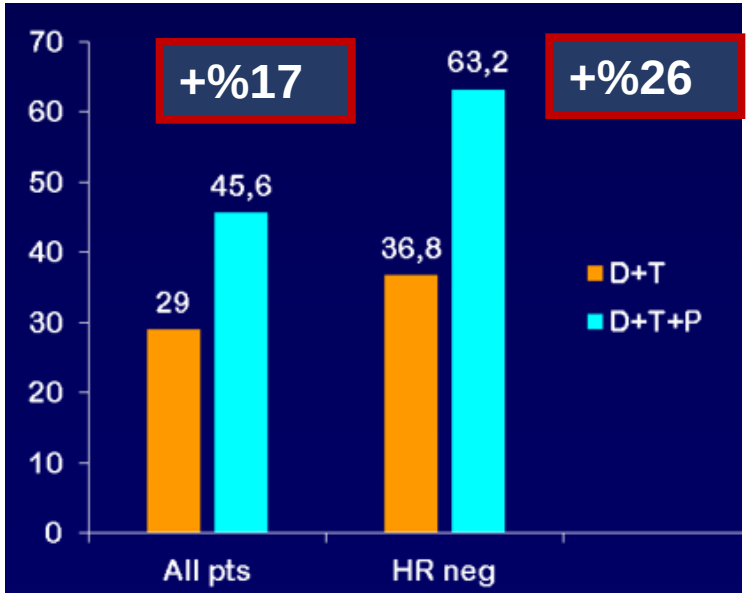


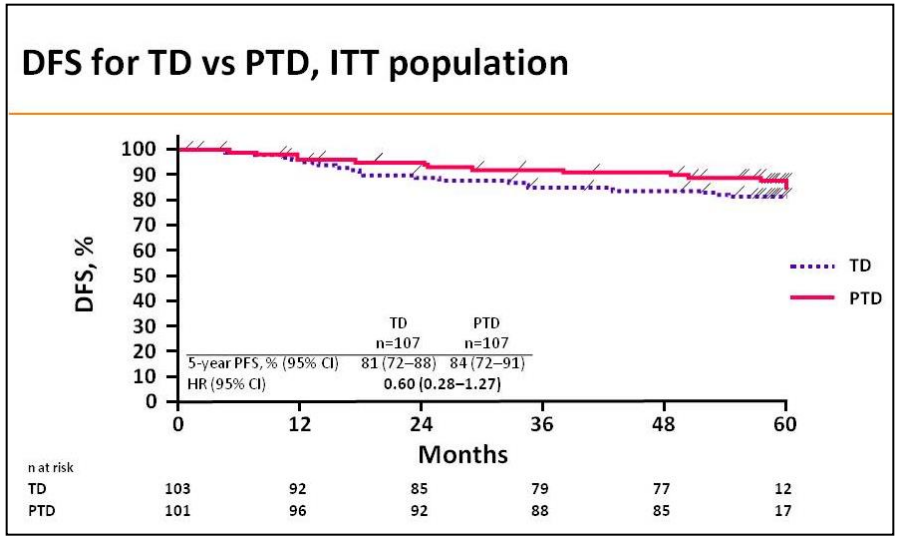
Gianni L. Lancet Oncol. 2012 Jan;13:25, Gianni ASCO 2015

HER2+ MK: Trastuzumab+Pertuzumab

- **NeoSphere Çalışması**







Hastalıksız sağkalımda anlamlı artış yok

ÇALIŞMANIN GÜCÜ YETERSİZ

Gianni L. Lancet Oncol. 2012 Jan;13:25, Gianni ASCO 2015

HER2+ MK: Trastuzumab+Pertuzumab

Pertuzumab için adjuvan verisi var (APHINITY çalışmasının yüksek riskli olgularda öneriliyor)

Erken evre meme kanserinde Pertuzumab: neoadjuvan dönemde veri var

⇑ pCR → Sağkalımı artırması beklenir

FDA onayı var

- **Lokal ileri ve erken evre meme kanseri (> 2 cm veya LN pozitif)**
- **Yalnız cerrahi öncesi**

TD	103	92	85	79	77	12
PTD	101	96	92	88	85	17

Gianni L. Lancet Oncol. 2012 Jan;13:25, Gianni ASCO 2015

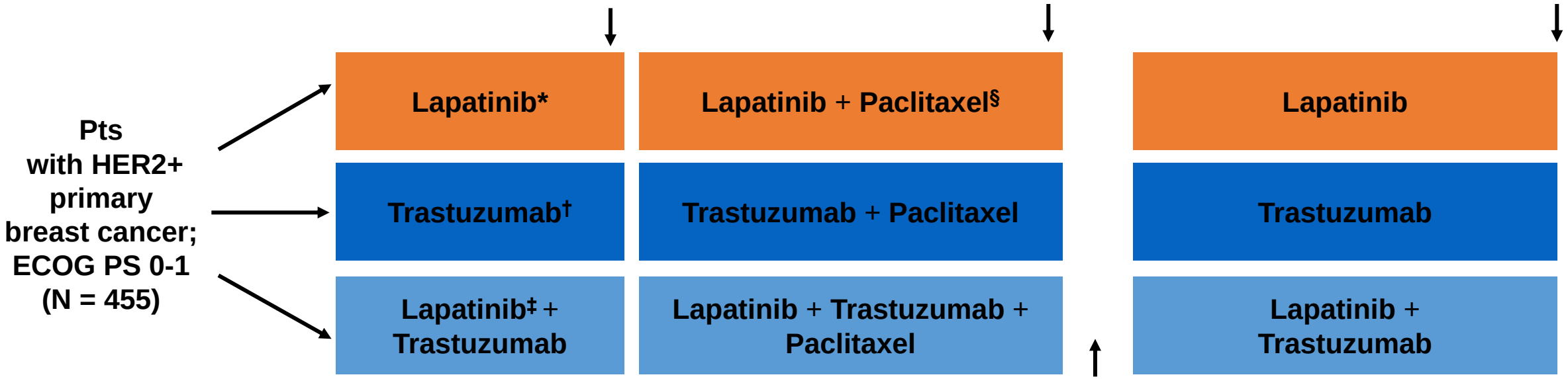
Neoadjuvant Combined Regimens (Tras + Lapatinib) Usually Better Than Tras Alone

Study and Regimen, %	Total pCR: Trastuzumab	Total pCR: Lapatinib	Total pCR: Both Agents
NeoALTTO[1] (N = 455) L and/or H (paclitaxel added after first 6 wks)	27.6	20.0	46.8
NSABP B-41[2] (N = 519) AC → paclitaxel + H and/or L	49.4	47.4	60.2
CALGB 40601[3] (N = 299) Paclitaxel + H and/or L	43.0	29.0	52.0
CHER-LOB[4] (N = 121) Paclitaxel → FEC with H and/or L	25.0	26.3	46.7
TRIO B07[5] (N = 128) H and/or L → docetaxel/ carboplatin + H and/or L	47.0	25.0	51.0

1. Baselga J, et al. Lancet. 2012;379:633-640. 2. Robidoux A, et al. Lancet Oncol. 2013;14:1183-1192.
3. Carey, et al. ASCO 2013. Abstract 500. 4. Guarneri V, et al. J Clin Oncol. 2012;30:1989-1995.
5. Hurvitz S, et al. SABCS 2013. Abstract S1-02.

NeoALTTO/BIG 1-06: Neoadjuvant Tx With Lapatinib and/or Trastuzumab

- **Randomized, multicenter, open-label phase III trial**

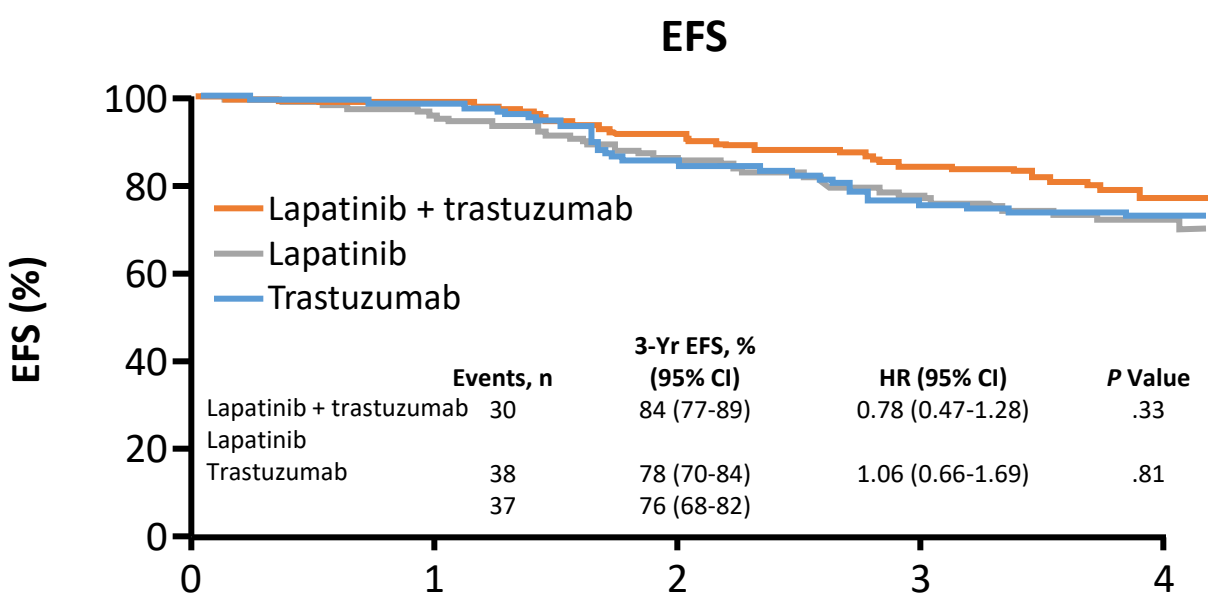


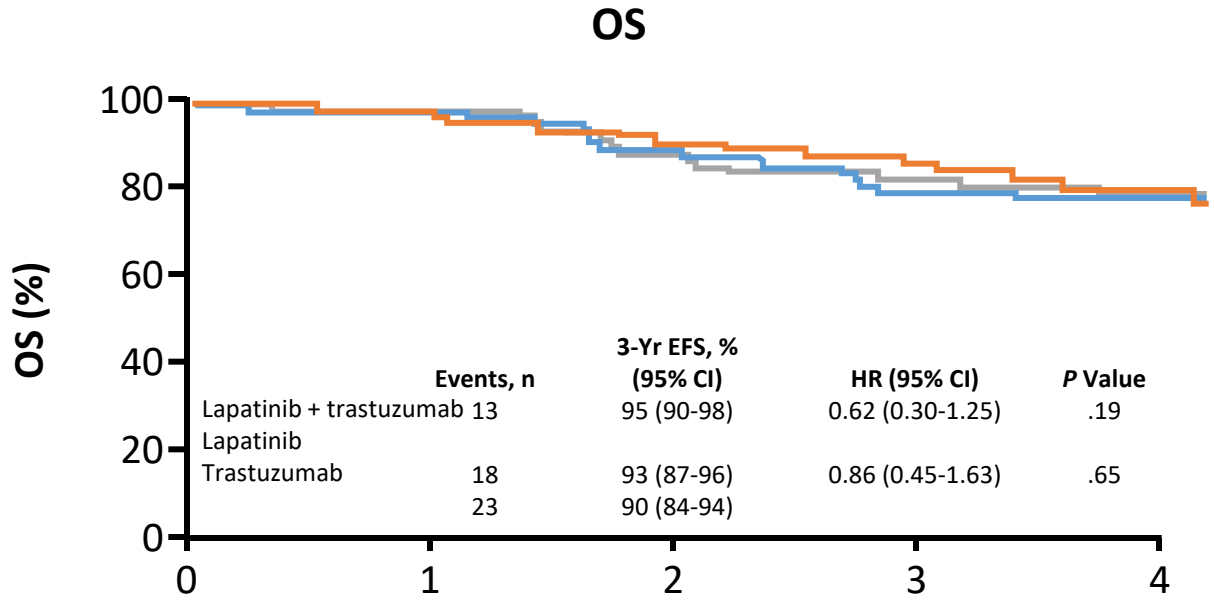
Lapatinib 1500 mg/day. †Trastuzumab 4 mg/kg, then 2 mg/kg weekly. ‡Lapatinib 1000 mg/day, reduced to 750 mg/day with paclitaxel. §Paclitaxel 80 mg/m^2/wk.

Baselga J, et al. Lancet 2012;379:633-640. Piccart-Gebhart M, et al. SABCS 2013. Abstract S1-01.

NeoALTTO: Improved pCR Rate Not Associated With Improved EFS and OS

- pCR rate increased with dual HER2-targeted therapy (46.8% vs 27.6%, 20.0% with single HER2-targeted agents)
- EFS and OS did not differ between treatment groups
  - Caveat: small trial (N = 455); very short follow-up





de Azambuja E, et al. Lancet Oncol. 2014;15:1137-1146.

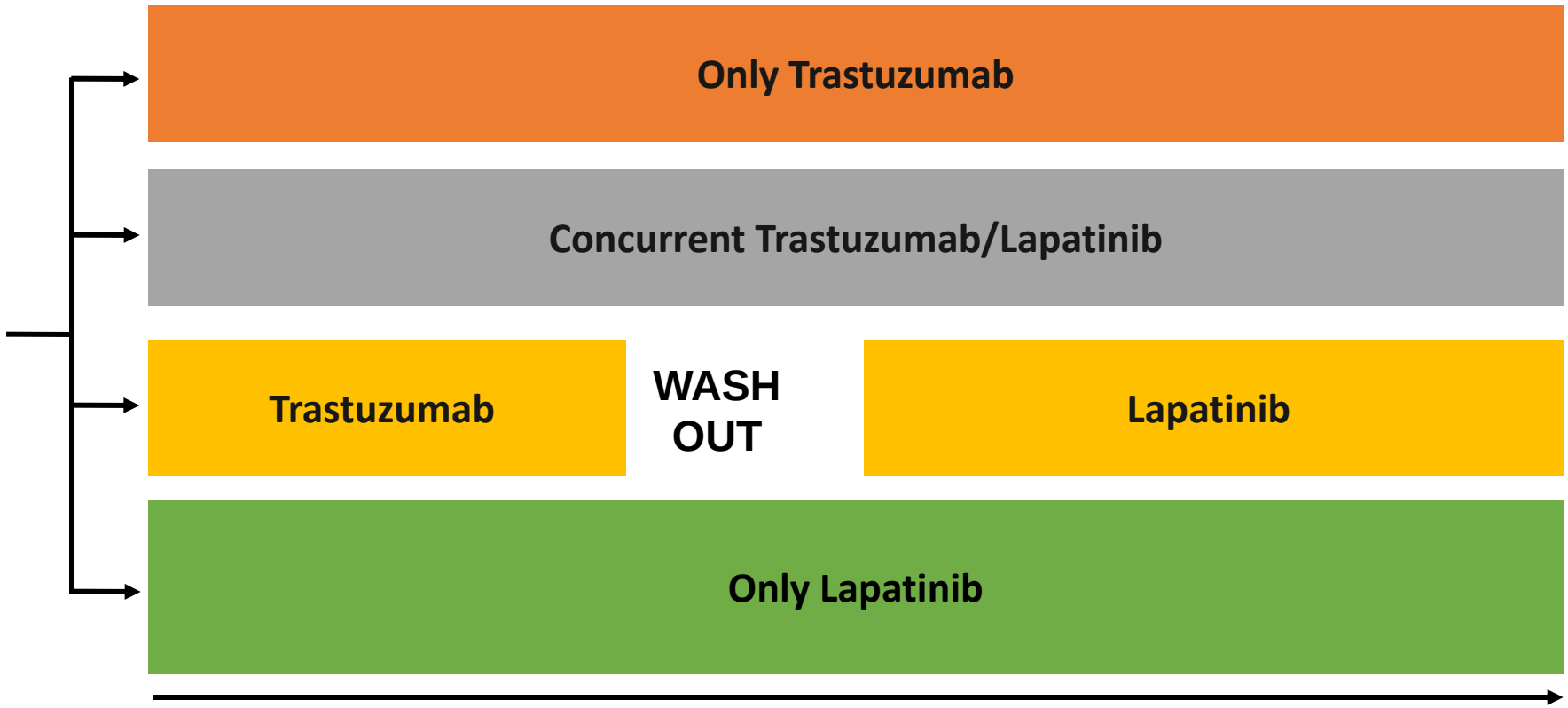
ALTTO Trial: An Adjuvant Trial Comparing Lapatinib, Trastuzumab, the Combination

HER2+ breast cancer pts in 3 groups:

Sequential:
(Neo)adjuvant chemotherapy prior to anti-HER2 treatment
(N = 4613)

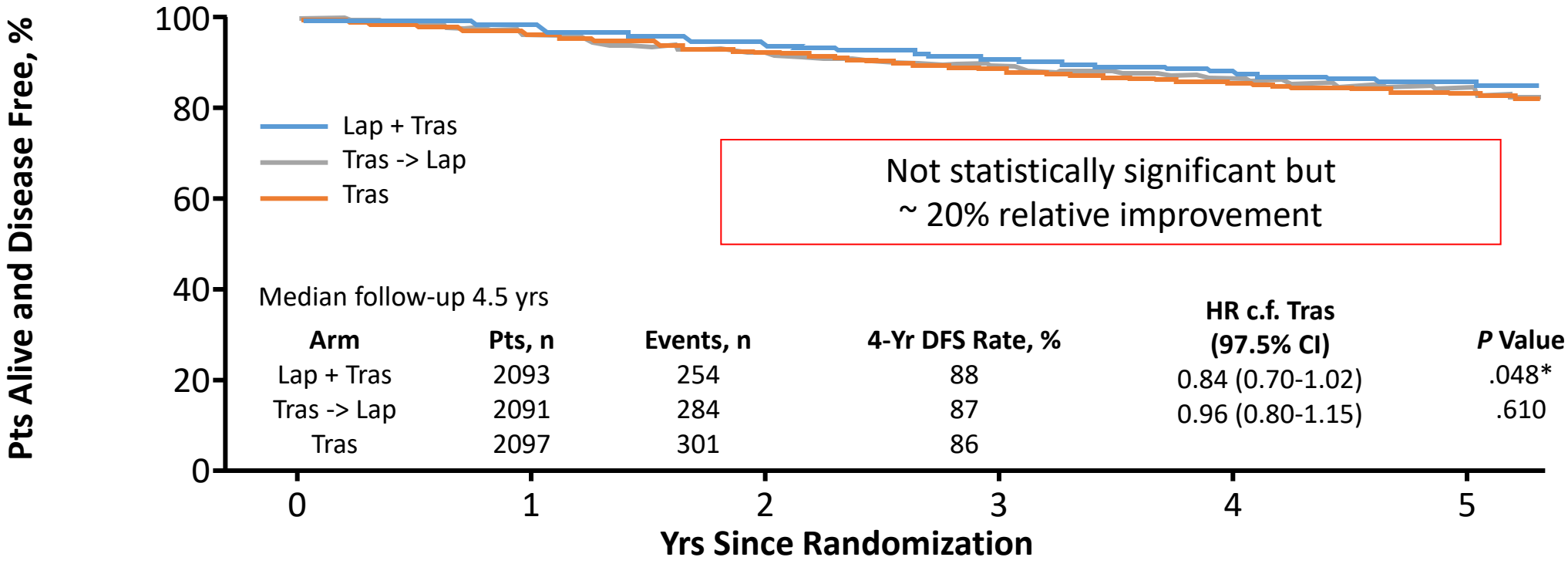
Concurrent Anti-HER2+
12 wks of anthracycline-based chemotherapy
(paclitaxel or docetaxel)
(N = 3337)

Concurrent Anti-HER2+
18 wks of nonanthracycline-based chemotherapy
(docetaxel + carboplatin)
(N = 431)



Piccart-Gebhart M, et al. ASCO 2014. Abstract LBA4.

ALTTO Trial: DFS With Adjuvant Lapatinib, Trastuzumab, or Both in HER2+ BC



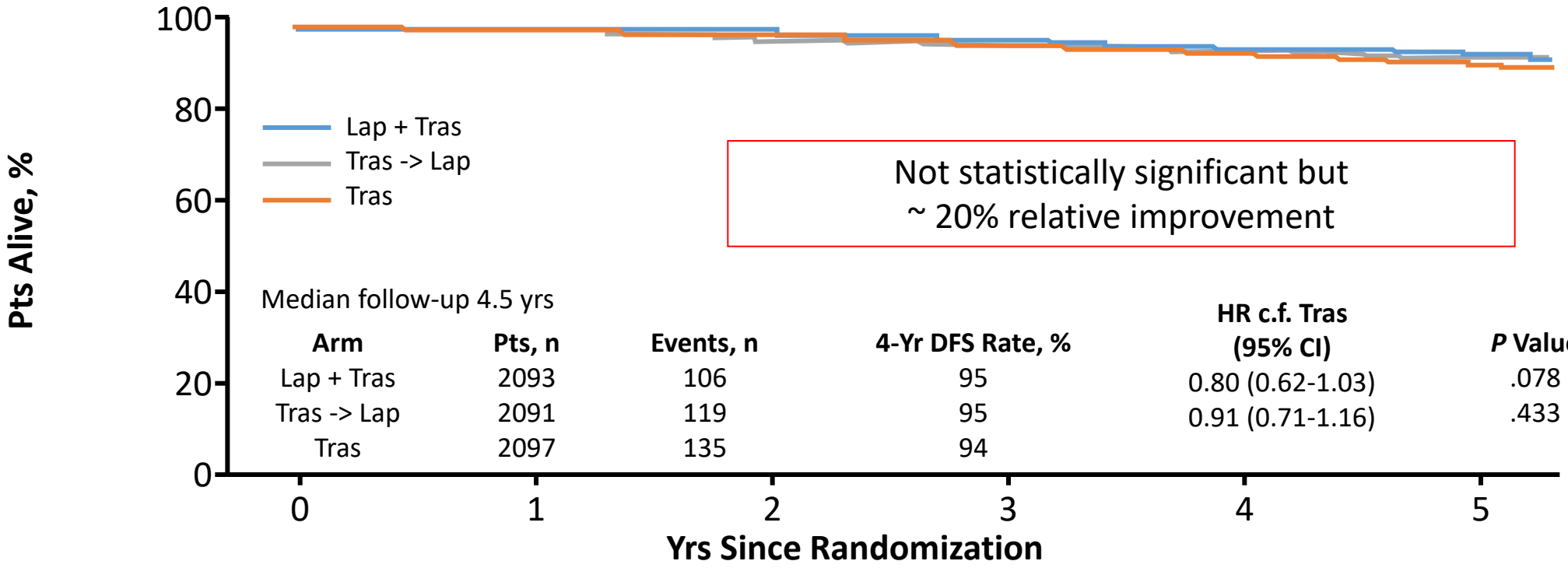
Median follow-up 4.5 yrs

Arm	Pts, n	Events, n	4-Yr DFS Rate, %	HR c.f. Tras (97.5% CI)	*P* Value
Lap + Tras	2093	254	88	0.84 (0.70-1.02)	.048*
Tras -> Lap	2091	284	87	0.96 (0.80-1.15)	.610
Tras	2097	301	86		

**P* value ≤ 0.025 required for statistical significance.

Piccart-Gebhart M, et al. ASCO 2014. Abstract LBA4.

ALTTO Trial: OS With Adjuvant Lapatinib, Trastuzumab, or Both in HER2+ BC



Median follow-up 4.5 yrs

Arm	Pts, n	Events, n	4-Yr DFS Rate, %	HR c.f. Tras (95% CI)	*P* Value
Lap + Tras	2093	106	95	0.80 (0.62-1.03)	.078
Tras -> Lap	2091	119	95	0.91 (0.71-1.16)	.433
Tras	2097	135	94		

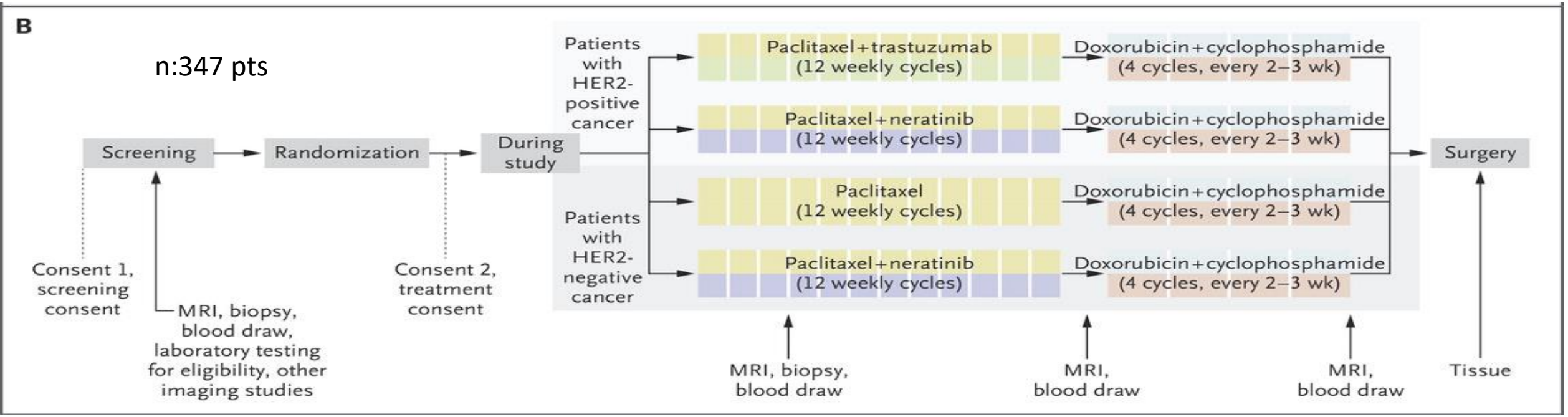
Piccart-Gebhart M, et al. ASCO 2014. Abstract LBA4.

NeoALTTO and ALTTO: pCR to Neoadj Tx Not Predictive of Adjuvant Results

- **NeoALTTO and ALTTO results dealt blow to strategy of using pCR in neoadjuvant trials to predict adjuvant results**
- **However, trends are in the right direction, and follow-up is short**
- **Counterpoint argument[1]**
  - **There may be theoretical reasons the effect on DFS is smaller than on pCR; the effect is real but smaller**
  - **ALTTO trial was actually confirmatory**

1. DeMichele A, et al. Clin Cancer Res. 2015;[Epub ahead of print].

I-SPY2 Trial



Park JW et al. N Engl J Med 2016;375:11-22.

Final Posterior and Predictive Probabilities of Neratinib Efficacy with Regard to Biomarker Signatures.

Table 2. Final Posterior and Predictive Probabilities of Neratinib Efficacy with Regard to 10 Biomarker Signatures.

Biomarker Signature	Estimated Rate of Pathological Complete Response (95% Probability Interval)		Probability of Neratinib Being Superior to Control	Predictive Probability of Success in Phase 3 Trial
	Neratinib	Control		
		percent		
Any	33 (24–40)	23 (14–33)	93	48
Hormone-receptor positive	23 (13–33)	16 (6–28)	81	40
Hormone-receptor negative	44 (30–55)	31 (17–45)	92	58
HER2 positive	39 (28–51)	23 (8–38)	95	73
HER2 negative	28 (15–37)	24 (13–35)	69	25
High-risk category 2 on 70-gene profile*	48 (30–60)	29 (11–48)	93	72
HER2 positive, hormone-receptor positive	30 (18–44)	17 (3–32)	91	65
HER2 positive, hormone-receptor negative	56 (37–73)	33 (11–54)	95	79
HER2 negative, hormone-receptor positive	14 (3–25)	16 (5–27)	42	14
HER2 negative, hormone-receptor negative	38 (22–50)	31 (15–46)	77	40

* The status of high-risk category 2 on the 70-gene profile was determined with the use of the MammaPrint assay (see the Supplementary Appendix).

Park JW et al. N Engl J Med 2016;375:11-22.

I-SPY3 Neoadjuvant Phase 3 Trial

- Trastuzumab+pertuzumab+taxane

vs

- Neratinib+trastuzmab+pertuzumab+taxane

vs

- neratinib+trastuzumab+taxane

All followed by ACX4 and surgery

Neoadjuvant therapy

Yesterday's strategy

Use the same regimens you would use adjuvantly

→

DFS and OS similar to adjuvant strategy

Today's and future strategy

More Patient-centric treatment depending on:

- Molecular subtype (add)
- Response during treatment (change)
- Residual disease and its characteristics (consolidate)

→

DFS and OS may be better

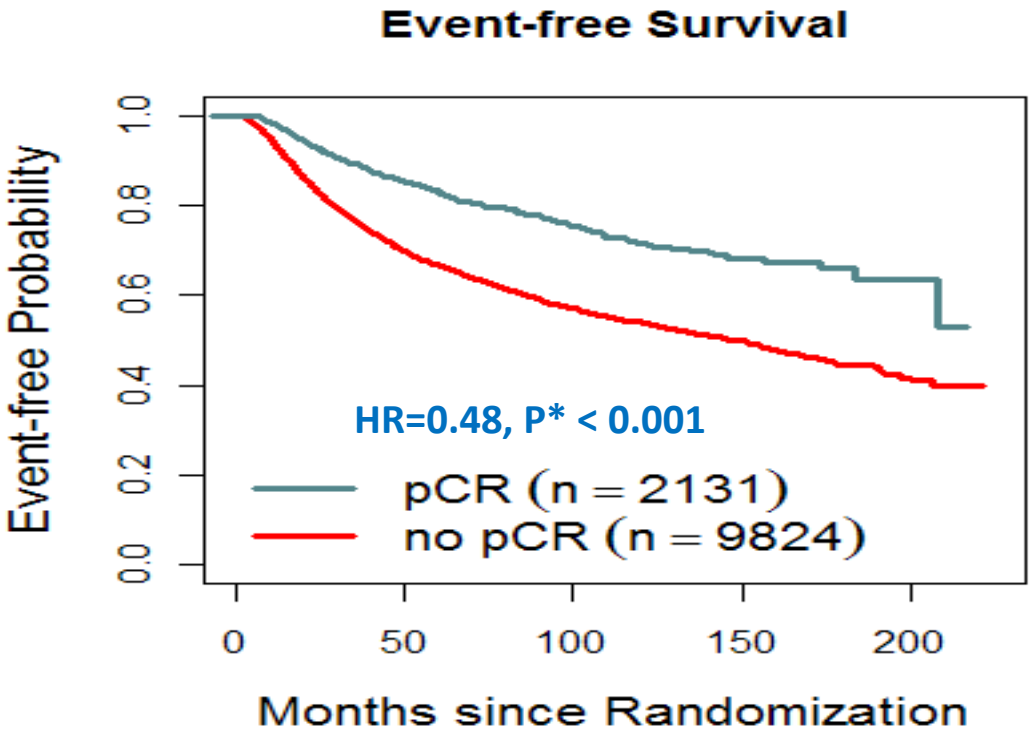
May allow <u>treatment de-escalation</u>

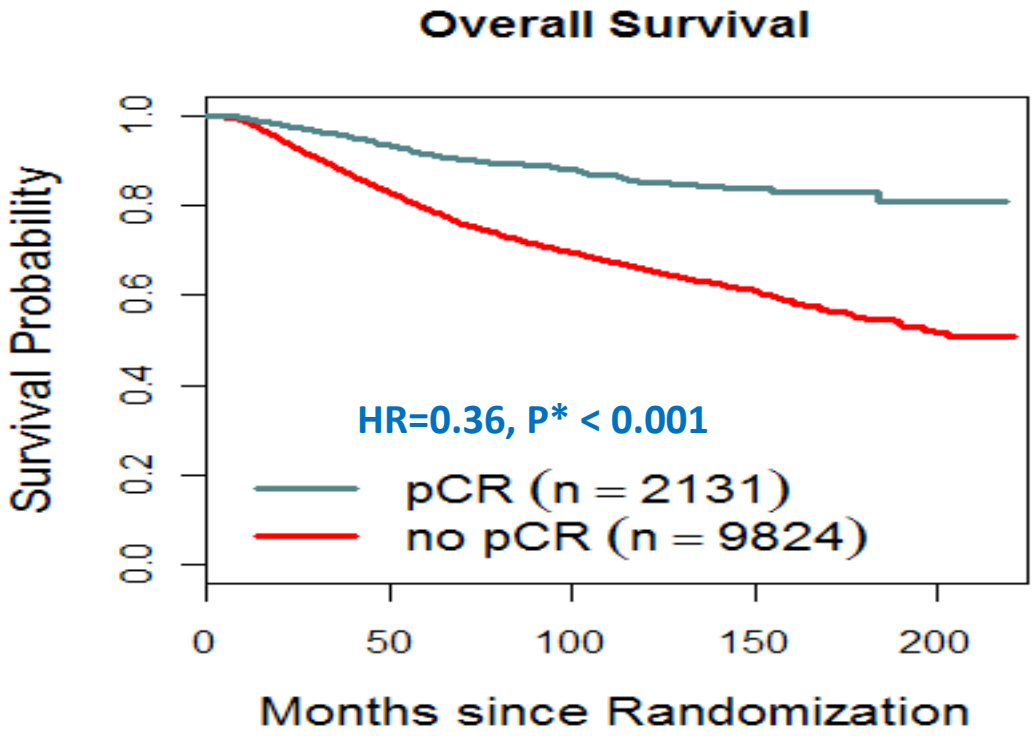
- No chemotherapy in some patients (Some HER2+ or HR+)
- Shorter duration of therapy

Neoadjuvant Chemo for Operable BC Loco-Regional Endpoints

- **High clinical response rates (80-90%)**
- **Increasing pathologic complete response rates:**
  - **10-15% with anthracyclines**
  - **25-30% with anthracyclines/taxanes**
  - **40-50% with chemo + trastuzumab in HER-2 (+)**
  - **50-60% with chemo + two anti-HER agents**
- **Increase in the rate of lumpectomy in RCTs**
- **Decrease in the rate of axillary positivity in RCTs**
  - **30% with anthracyclines**
  - **Up to 40% with anthracyclines/taxanes**
  - **Probably > 50% with chemo + anti-HER-2 therapies**

Association of pCR with EFS and OS





pCR=ypT0/is ypN0

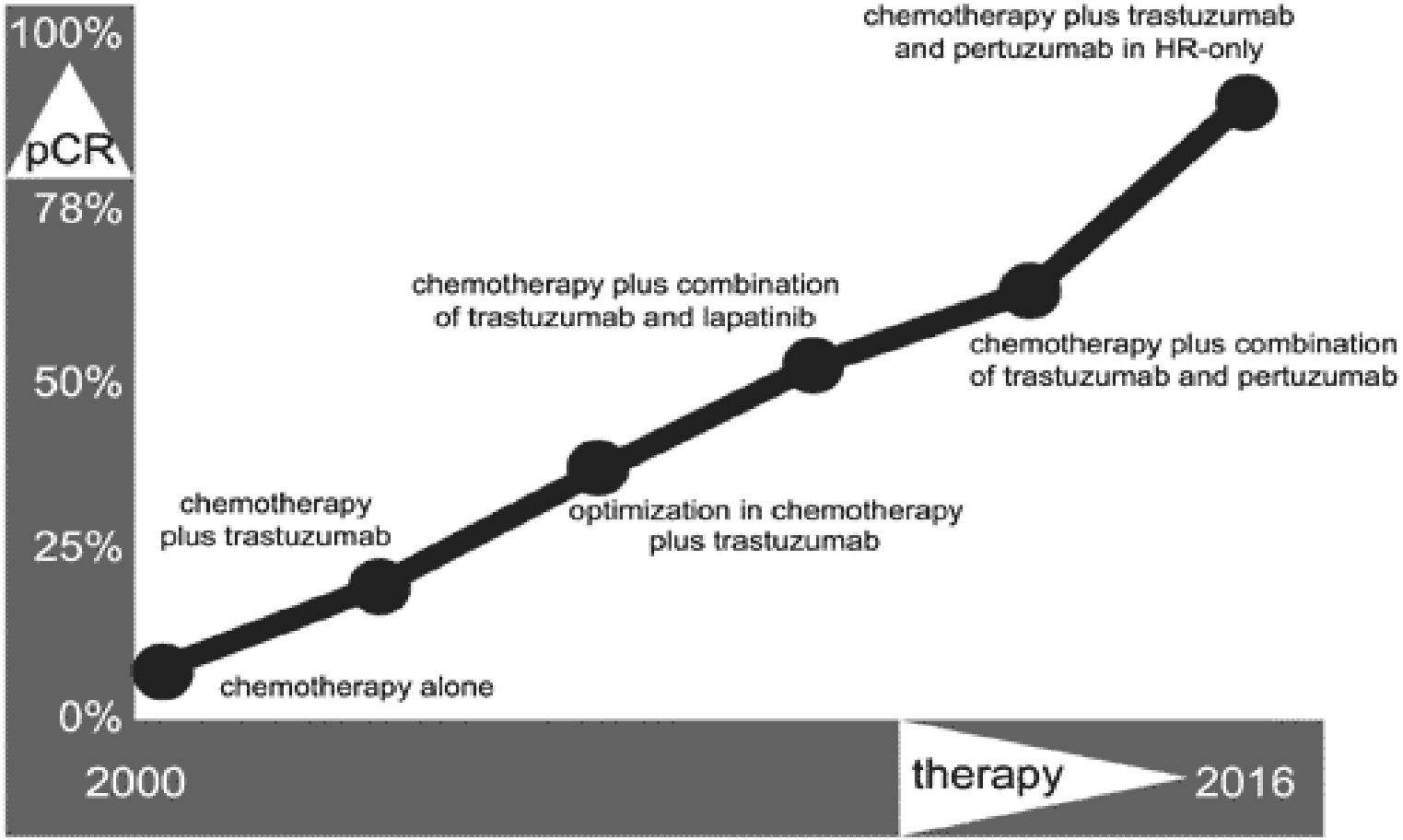
*** Nominal p-value**

Cortazar P, et al: SABCS 2012

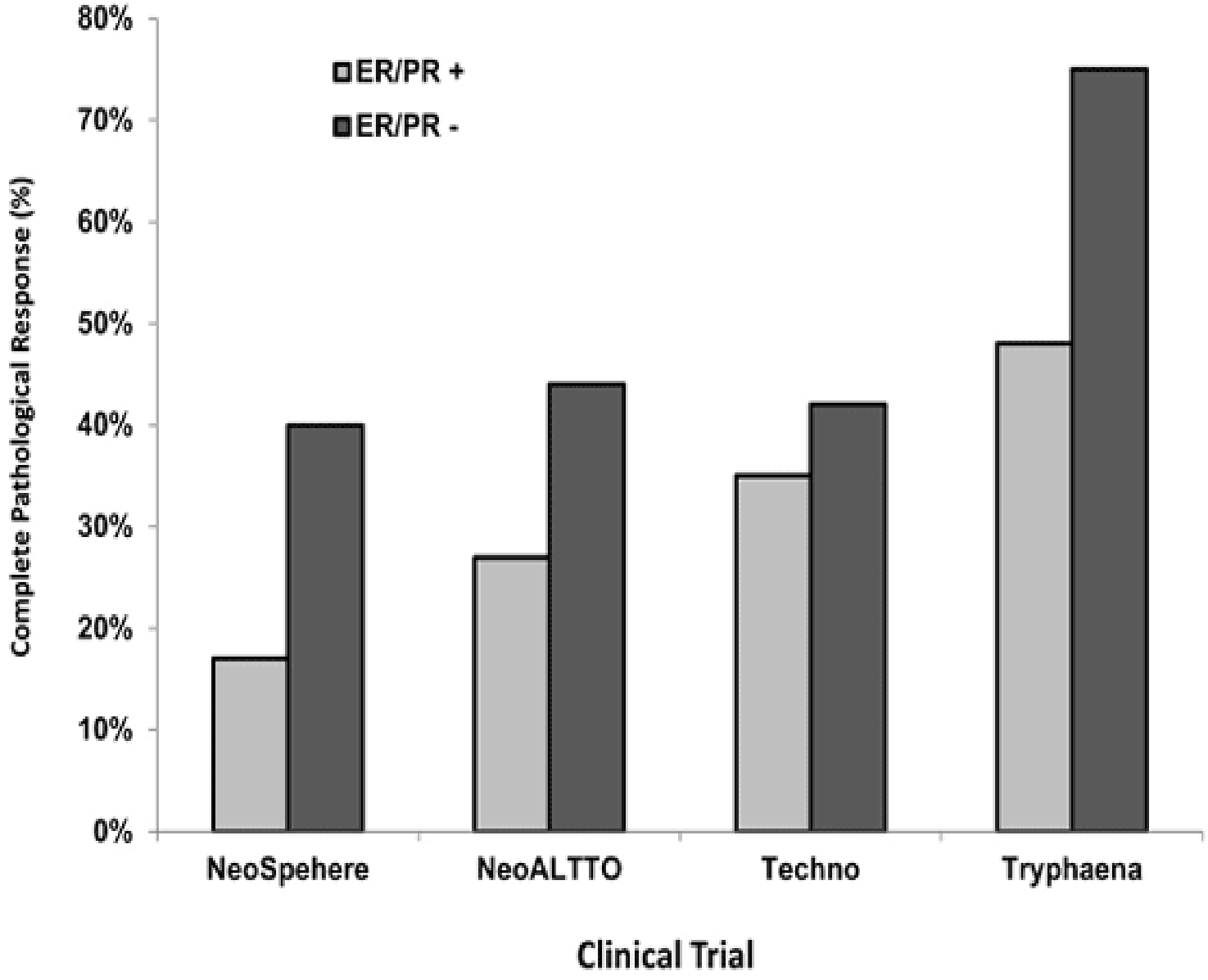
Neoadjuvant Therapy for HER2-positive Breast Cancer.

Rachel Wuerstlein*, Nadia Harbeck.

Reviews on Recent Clinical Trials ***Volume 12 , Issue 2 , 2017***
DOI *: 10.2174/1574887112666170202165049*



Over the last 10 year, pCR in HER2-positive early breast cancer has been improved by optimizing and individualizing neoadjuvant systemic therapy.

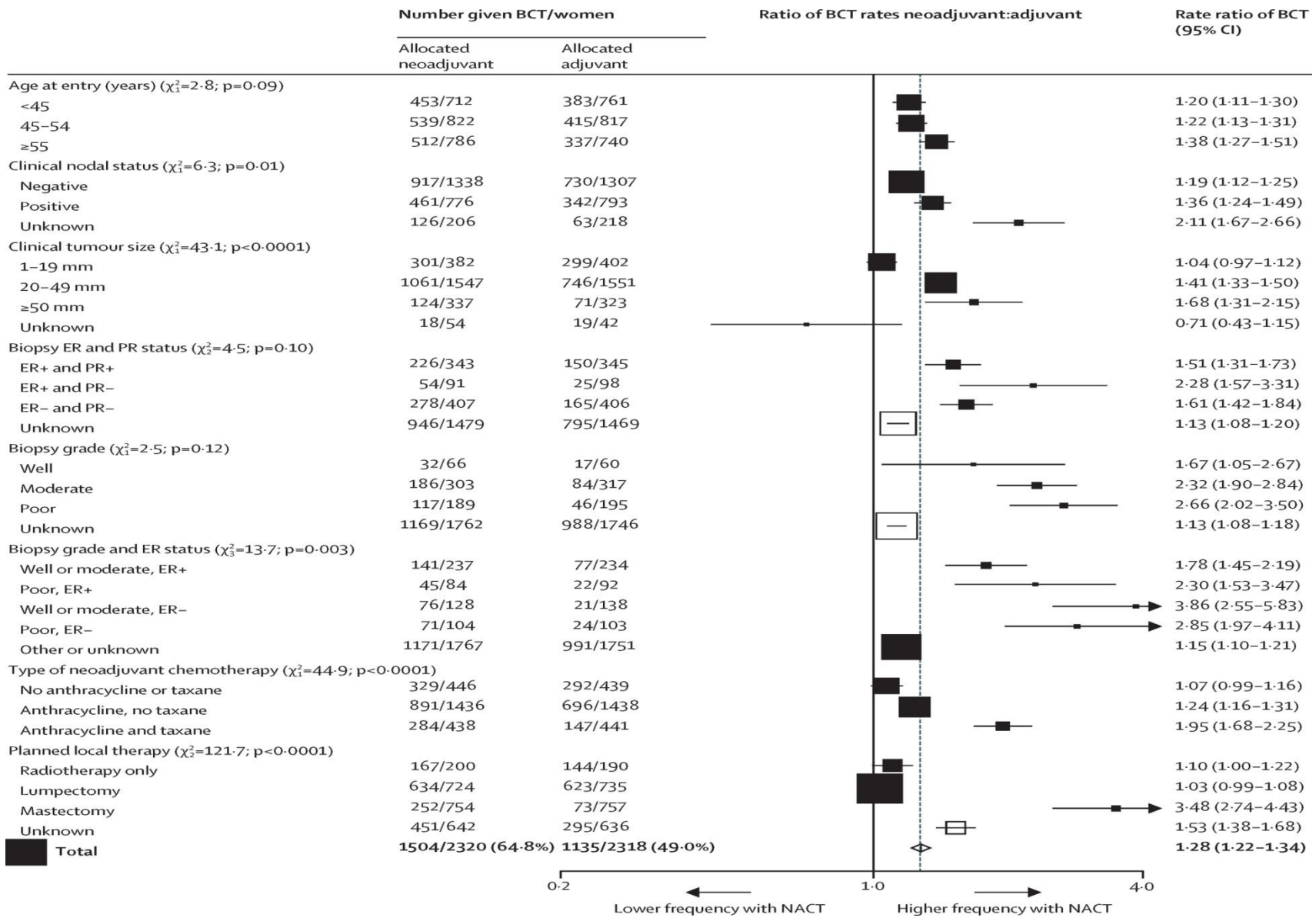

80%
70%
60%
50%
40%
30%
20%
10%
0%
ER/PR +
ER/PR -
Complete Pathological Response (%)
NeoSpehere
NeoALTTO
Techno
Tryphaena
Clinical Trial

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

Bernard Asselain, William Barlow, John Bartlett, Jonas Bergh, Elizabeth Bergsten-Nordström, Judith Bliss, Francesco Boccardo, Clare Boddington, Jan Bogaerts, Gianni Bonadonna, Rosie Bradley, Etienne Brain, Jeremy Braybrooke, Philippe Broet, John Bryant, Julie Burrett, David Cameron, Mike Clarke, Alan Coates, Robert Coleman, Raoul Charles Coombes, Candace Correa, Joe Costantino, Jack Cuzick, David Danforth, Nancy Davidson, Christina Davies, Lucy Davies, Angelo Di Leo, David Dodwell, Mitch Dowsett, Fran Duane, Vaughan Evans, Marianne Ewertz, Bernard Fisher, John Forbes, Leslie Ford, Jean-Claude Gazet, Richard Gelber, Lucy Gettins, Luca Gianni, Michael Gnant, Jon Godwin, Aron Goldhirsch, Pamela Goodwin, Richard Gray, Daniel Hayes, Catherine Hill, James Ingle, Reshma Jagsi, Raimund Jakesz, Sam James, Wolfgang Janni, Hui Liu, Zulian Liu, Caroline Lohrisch, Sibylle Loibl, Liz MacKinnon, Andreas Makris, Eleftherios Mamounas, Gurdeep Mannu, Miguel Martín, Simone Mathoulin, Louis Mauriac, Paul McGale, Theresa McHugh, Philip Morris, Hirofumi Mukai, Larry Norton, Yasuo Ohashi, Ivo Olivotto, Soon Paik, Hongchao Pan, Richard Peto, Martine Piccart, Lori Pierce, Philip Poortmans, Trevor Powles, Kathy Pritchard, Joseph Ragaz, Vinod Raina, Peter Ravdin, Simon Read, Meredith Regan, John Robertson, Emiel Rutgers, Suzy Scholl, Dennis Slamon, Lidija Sölkner, Joseph Sparano, Seth Steinberg, Rosemary Sutcliffe, Sandra Swain, Carolyn Taylor, Andrew Tutt, Pinuccia Valagussa, Cornelis van de Velde, Jos van der Hage, Giuseppe Viale, Gunter von Minckwitz, Yaochen Wang, Zhe Wang, Xiang Wang, Tim Whelan, Nicholas Wilcken, Eric Winer, Norman Wolmark, William Wood, Milvia Zambetti, Jo Anne Zujewski Bernard Asselain, William Barlow, John Bartlett, Jonas Bergh, Elizabeth Bergsten-Nordström, Judith Bliss, Francesco Boccardo, Clare Boddington, Jan Bogaerts, Gianni Bonadonna, Rosie Bradley, Etienne Brain, Jeremy Braybrooke, Philippe Broet, John Bryant, Julie Burrett, David Cameron, Mike Clarke, Alan Coates, Robert Coleman, Raoul Charles Coombes, Candace Correa, Joe Costantino, Jack Cuzick, David Danforth, Nancy Davidson, Christina Davies, Lucy Davies, Angelo Di Leo, David Dodwell, Mitch Dowsett, Fran Duane, Vaughan Evans, Marianne Ewertz, Bernard Fisher, John Forbes, Leslie Ford, Jean-Claude Gazet, Richard Gelber, Lucy Gettins, Luca Gianni, Michael Gnant, Jon Godwin, Aron Goldhirsch, Pamela Goodwin, Richard Gray, Daniel Hayes, Catherine Hill, James Ingle, Reshma Jagsi, Raimund Jakesz, Sam James, Wolfgang Janni, Hui Liu, Zulian Liu, Caroline Lohrisch, Sibylle Loibl, Liz MacKinnon, Andreas Makris, Eleftherios Mamounas, Gurdeep Mannu, Miguel Martín, Simone Mathoulin, Louis Mauriac, Paul McGale, Theresa McHugh, Philip Morris, Hirofumi Mukai, Larry Norton, Yasuo Ohashi, Ivo Olivotto, Soon Paik, Hongchao Pan, Richard Peto, Martine Piccart, Lori Pierce, Philip Poortmans, Trevor Powles, Kathy Pritchard, Joseph Ragaz, Vinod Raina, Peter Ravdin, Simon Read, Meredith Regan, John Robertson, Emiel Rutgers, Suzy Scholl, Dennis Slamon, Lidija Sölkner, Joseph Sparano, Seth Steinberg, Rosemary Sutcliffe, Sandra Swain, Carolyn Taylor, Andrew Tutt, Pinuccia Valagussa, Cornelis van de Velde, Jos van der Hage, Giuseppe Viale, Gunter von Minckwitz, Yaochen Wang, Zhe Wang, Xiang Wang, Tim Whelan, Nicholas Wilcken, Eric Winer, Norman Wolmark, William Wood, Milvia Zambetti, Jo Anne Zujewski

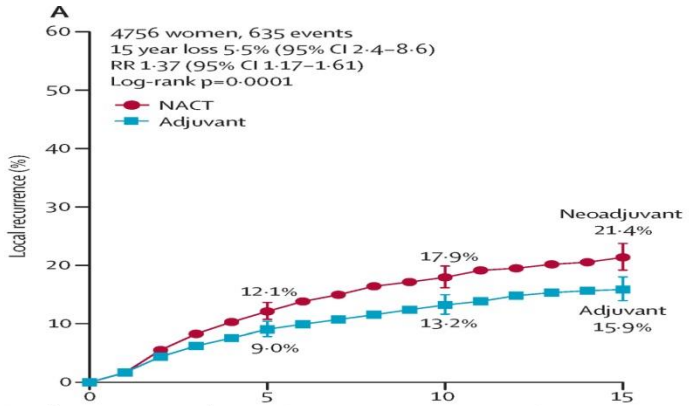
The Lancet Oncology
Volume 19, Issue 1, Pages 27-39 (January 2018)
DOI: 10.1016/S1470-2045(17)30777-5

BCT=breast-conserving therapy rate ratios.



Effect of neoadjuvant versus adjuvant chemotherapy on recurrence and mortality

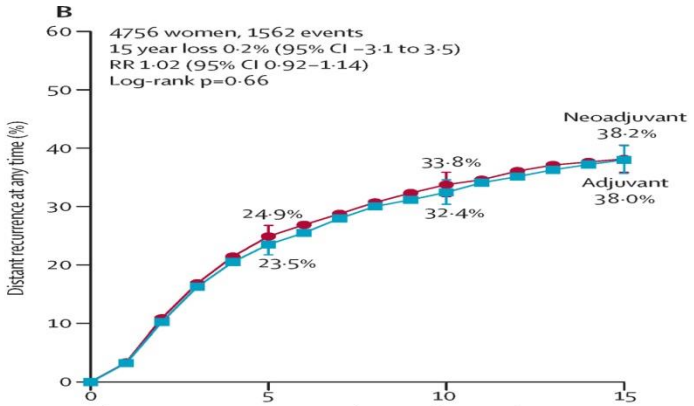
Local recurrence



Local recurrence crude rates (events per woman-years) and log-rank analyses

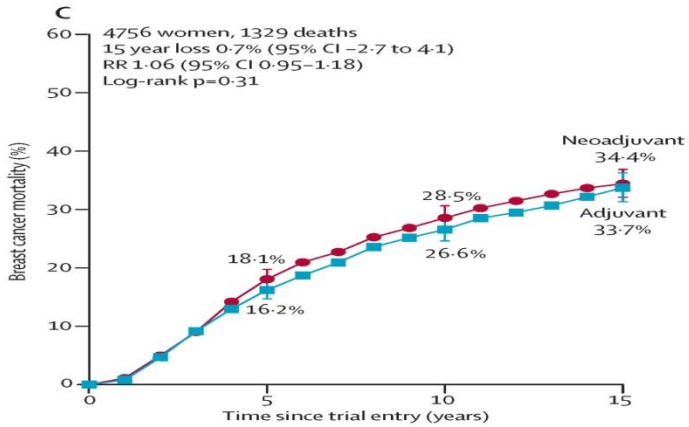
	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	2·58 (245/9493)	1·43 (79/5528)	0·93 (26/2784)	2·16 (16/740)
Adjuvant	1·95 (185/9477)	0·96 (54/5618)	0·69 (19/2769)	1·42 (11/772)
Rate ratio	1·35 (1·11–1·64)	1·53 (1·08–2·17)	1·29 (0·70–2·38)	1·11 (0·48–2·57)
(95% CI) from (O–E)/V	30·4/102·0	13·6/31·8	2·7/10·3	0·6/5·4

distant recurrence



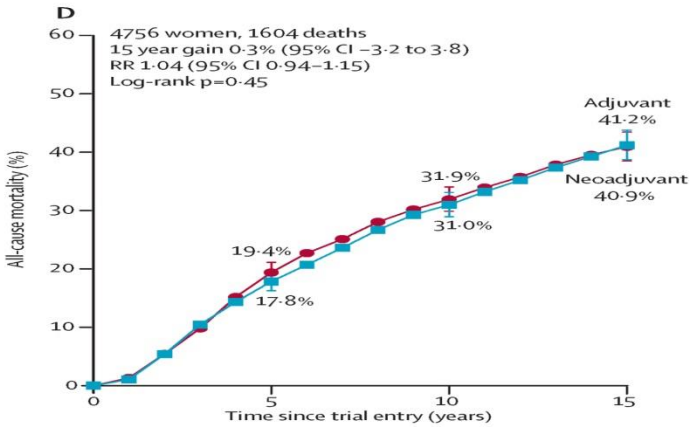
Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
5·69 (568/9983)	2·58 (162/6291)	1·49 (50/3351)	1·44 (14/974)
5·44 (535/9840)	2·54 (157/6187)	1·84 (60/3270)	1·74 (16/919)
1·07 (0·94–1·21)	0·99 (0·79–1·24)	0·80 (0·55–1·18)	0·75 (0·35–1·61)
16·5/251·5	−0·6/75·5	−5·7/25·8	−1·9/6·7



Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	3·90 (412/10567)	2·82 (191/6785)	1·93 (69/3570)	1·24 (13/1050)
Adjuvant	3·49 (364/10432)	2·81 (190/6771)	2·19 (78/3559)	1·18 (12/1014)
Rate ratio	1·12 (0·97–1·30)	1·03 (0·84–1·27)	0·88 (0·63–1·21)	0·90 (0·41–1·97)
(95% CI) from (O–E)/V	20·5/179·6	2·8/91·6	−4·8/36·6	−0·7/6·2



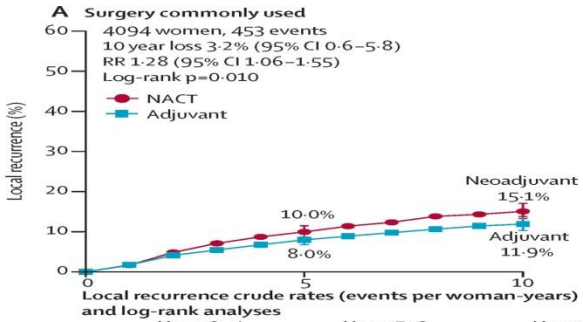
Any death crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
4·22 (446/10567)	3·51 (238/6785)	2·91 (104/3570)	3·52 (37/1050)
3·86 (403/10432)	3·56 (241/6771)	3·20 (114/3559)	2·07 (21/1014)
1·09 (0·95–1·25)	0·98 (0·81–1·17)	0·90 (0·68–1·18)	1·69 (0·95–2·99)
16·7/196·6	−2·7/112·2	−5·6/51·3	6·1/11·7

breast cancer mortality

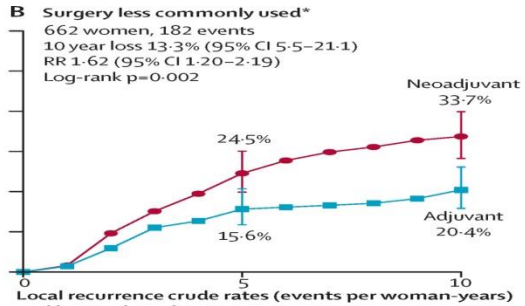
death from any cause

Time to recurrence and breast cancer mortality



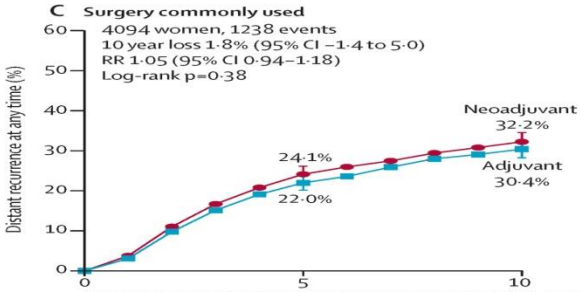
Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Neoadjuvant	2·12 (173/8164)	1·21 (57/4721)	0·85 (22/2577)
Adjuvant	1·73 (142/8200)	0·94 (45/4778)	0·55 (14/2547)
Rate ratio (95% CI)	1·26 (1·00–1·58)	1·35 (0·91–2·01)	1·32 (0·65–2·69)
from (O–E)/V	17·3/75·2	7·3/24·3	2·1/7·5



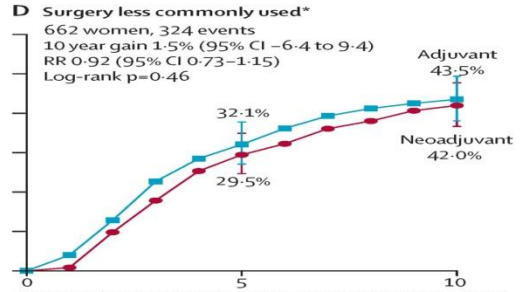
Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
	5·42 (72/1329)	2·73 (22/806)	2·11 (20/947)
	3·37 (43/1277)	1·07 (9/840)	1·61 (16/994)
	1·63 (1·12–2·39)	2·30 (1·13–4·70)	1·15 (0·58–2·27)
	13·2/26·8	6·3/7·5	1·1/8·2



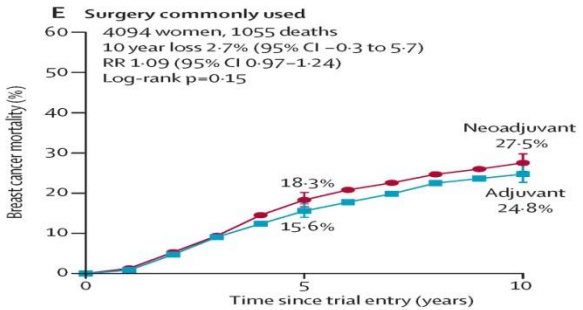
Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Neoadjuvant	5·50 (470/8545)	2·29 (121/5284)	1·30 (40/3078)
Adjuvant	5·07 (431/8496)	2·32 (122/5262)	1·77 (54/3050)
Rate ratio (95% CI)	1·12 (0·97–1·28)	0·98 (0·75–1·26)	0·74 (0·49–1·13)
from (O–E)/V	22·8/205·9	−1·4/58·0	−6·6/21·8



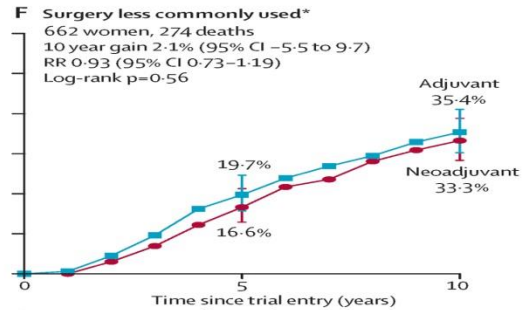
Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
	6·81 (98/1438)	4·07 (41/1007)	1·92 (24/1248)
	7·74 (104/1344)	3·78 (35/926)	1·93 (22/1139)
	0·87 (0·65–1·17)	1·05 (0·66–1·68)	0·91 (0·50–1·66)
	−6·3/45·6	0·8/17·5	−1·0/10·7



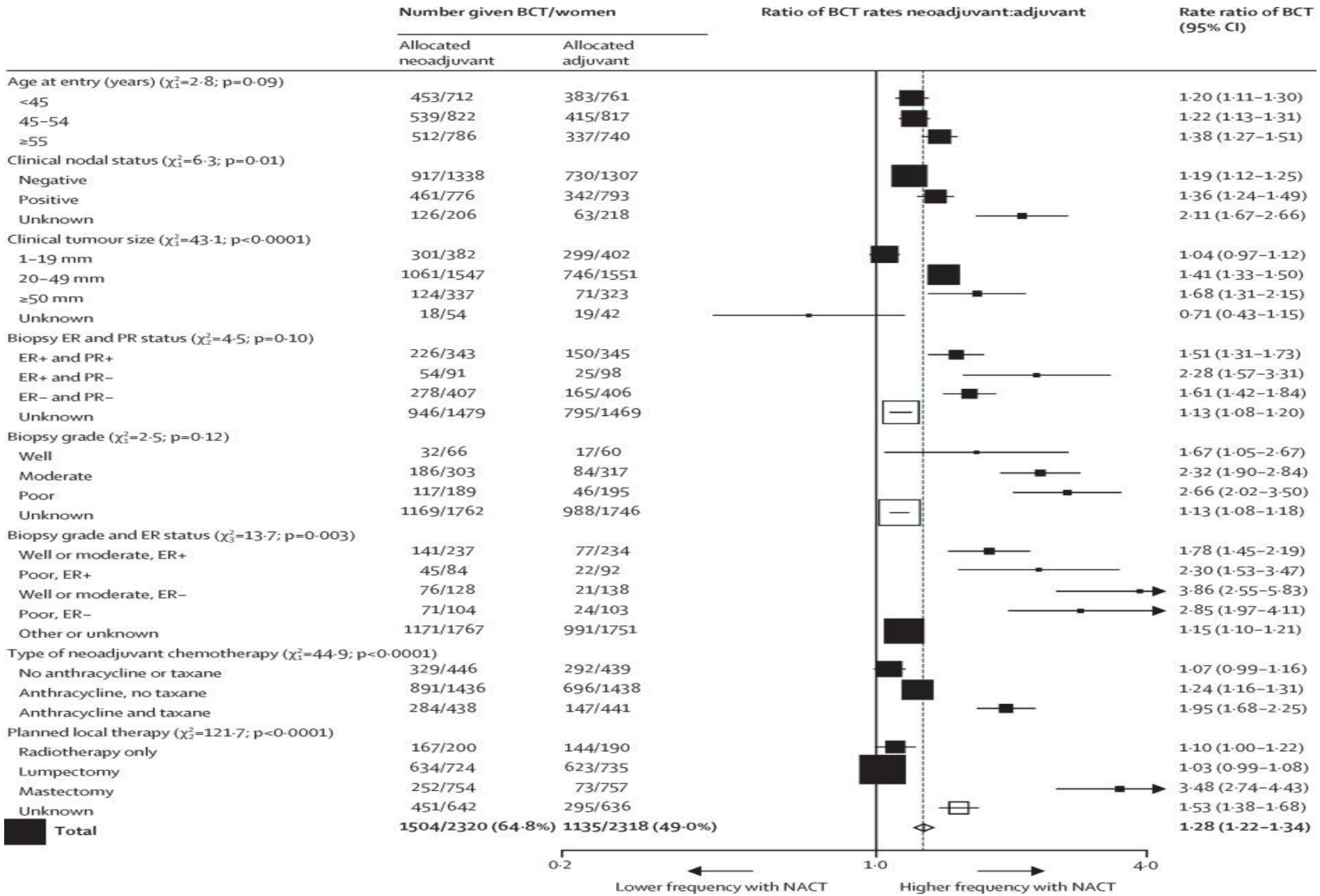
Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

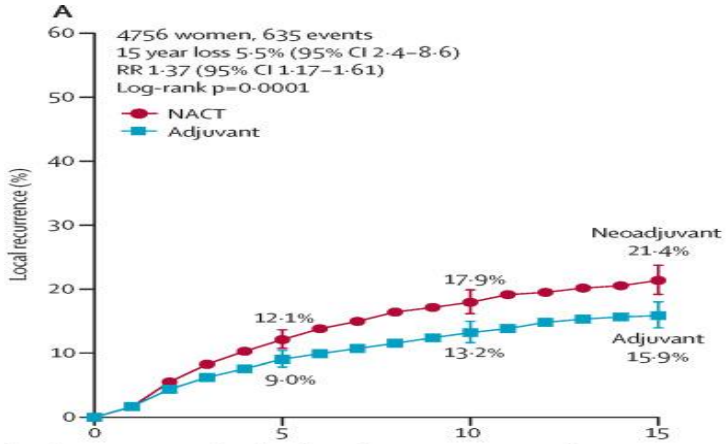
	Years 0–4	Years 5–9	Years ≥10
Neoadjuvant	3·95 (356/9007)	2·48 (139/5610)	1·65 (53/3206)
Adjuvant	3·37 (301/8944)	2·49 (141/5662)	2·01 (65/3237)
Rate ratio (95% CI)	1·19 (1·01–1·39)	1·03 (0·81–1·31)	0·82 (0·57–1·17)
from (O–E)/V	26·4/152·1	2·1/67·4	−6·0/30·0



Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

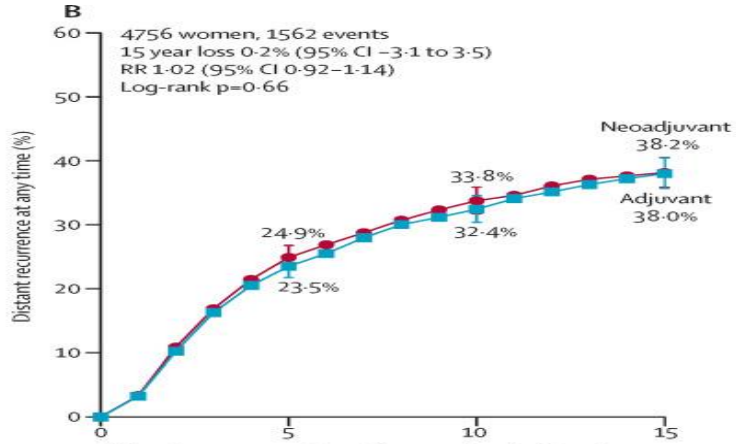
	Years 0–4	Years 5–9	Years ≥10
	3·59 (56/1560)	4·43 (52/1175)	2·05 (29/1414)
	4·23 (63/1488)	4·42 (49/1109)	1·87 (25/1336)
	0·81 (0·56–1·18)	1·03 (0·69–1·53)	1·03 (0·60–1·79)
	−5·8/27·6	0·7/24·2	0·4/12·9


Number given BCT/women
Allocated neoadjuvant
Allocated adjuvant
Ratio of BCT rates neoadjuvant:adjuvant
Rate ratio of BCT (95% CI)
Age at entry (years) (χ²₁=2·8; p=0·09)
<45 453/712 383/761 1·20 (1·11–1·30)
45–54 539/822 415/817 1·22 (1·13–1·31)
≥55 512/786 337/740 1·38 (1·27–1·51)
Clinical nodal status (χ²₁=6·3; p=0·01)
Negative 917/1338 730/1307 1·19 (1·12–1·25)
Positive 461/776 342/793 1·36 (1·24–1·49)
Unknown 126/206 63/218 2·11 (1·67–2·66)
Clinical tumour size (χ²₁=43·1; p<0·0001)
1–19 mm 301/382 299/402 1·04 (0·97–1·12)
20–49 mm 1061/1547 746/1551 1·41 (1·33–1·50)
≥50 mm 124/337 71/323 1·68 (1·31–2·15)
Unknown 18/54 19/42 0·71 (0·43–1·15)
Biopsy ER and PR status (χ²₂=4·5; p=0·10)
ER+ and PR+ 226/343 150/345 1·51 (1·31–1·73)
ER+ and PR– 54/91 25/98 2·28 (1·57–3·31)
ER– and PR– 278/407 165/406 1·61 (1·42–1·84)
Unknown 946/1479 795/1469 1·13 (1·08–1·20)
Biopsy grade (χ²₁=2·5; p=0·12)
Well 32/66 17/60 1·67 (1·05–2·67)
Moderate 186/303 84/317 2·32 (1·90–2·84)
Poor 117/189 46/195 2·66 (2·02–3·50)
Unknown 1169/1762 988/1746 1·13 (1·08–1·18)
Biopsy grade and ER status (χ²₃=13·7; p=0·003)
Well or moderate, ER+ 141/237 77/234 1·78 (1·45–2·19)
Poor, ER+ 45/84 22/92 2·30 (1·53–3·47)
Well or moderate, ER– 76/128 21/138 3·86 (2·55–5·83)
Poor, ER– 71/104 24/103 2·85 (1·97–4·11)
Other or unknown 1171/1767 991/1751 1·15 (1·10–1·21)
Type of neoadjuvant chemotherapy (χ²₁=44·9; p<0·0001)
No anthracycline or taxane 329/446 292/439 1·07 (0·99–1·16)
Anthracycline, no taxane 891/1436 696/1438 1·24 (1·16–1·31)
Anthracycline and taxane 284/438 147/441 1·95 (1·68–2·25)
Planned local therapy (χ²₃=121·7; p<0·0001)
Radiotherapy only 167/200 144/190 1·10 (1·00–1·22)
Lumpectomy 634/724 623/735 1·03 (0·99–1·08)
Mastectomy 252/754 73/757 3·48 (2·74–4·43)
Unknown 451/642 295/636 1·53 (1·38–1·68)
Total 1504/2320 (64·8%) 1135/2318 (49·0%) 1·28 (1·22–1·34)
0·2
1·0
4·0
Lower frequency with NACT
Higher frequency with NACT



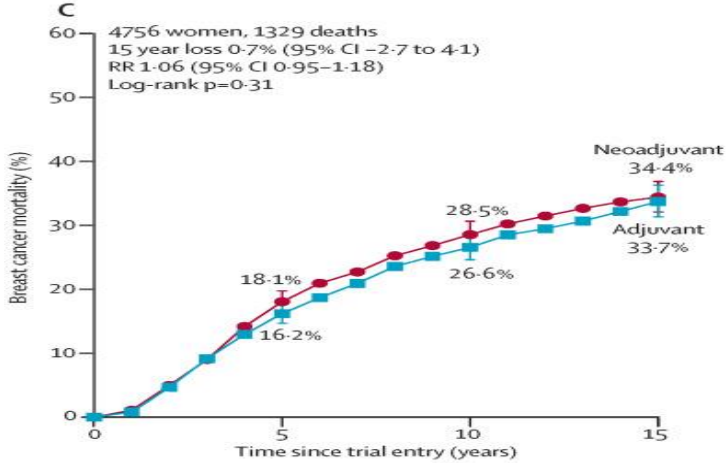
Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	2·58 (245/9493)	1·43 (79/5528)	0·93 (26/2784)	2·16 (16/740)
Adjuvant	1·95 (185/9477)	0·96 (54/5618)	0·69 (19/2769)	1·42 (11/772)
Rate ratio	1·35 (1·11–1·64)	1·53 (1·08–2·17)	1·29 (0·70–2·38)	1·11 (0·48–2·57)
(95% CI) from (O–E)/V	30·4/102·0	13·6/31·8	2·7/10·3	0·6/5·4



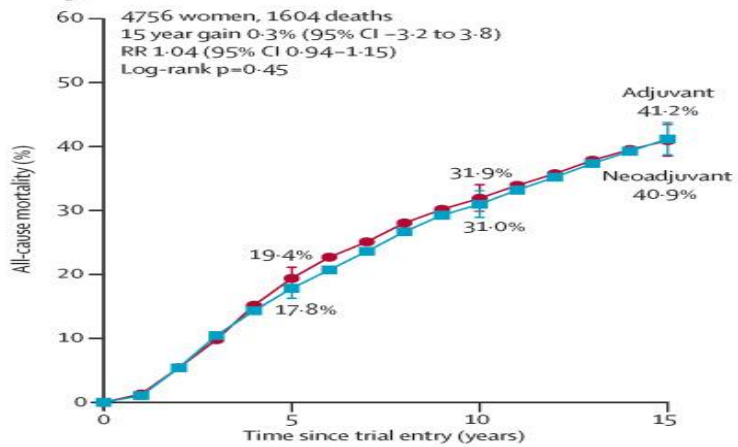
Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
5·69 (568/9983)	2·58 (162/6291)	1·49 (50/3351)	1·44 (14/974)
5·44 (535/9840)	2·54 (157/6187)	1·84 (60/3270)	1·74 (16/919)
1·07 (0·94–1·21)	0·99 (0·79–1·24)	0·80 (0·55–1·18)	0·75 (0·35–1·61)
16·5/251·5	−0·6/75·5	−5·7/25·8	−1·9/6·7



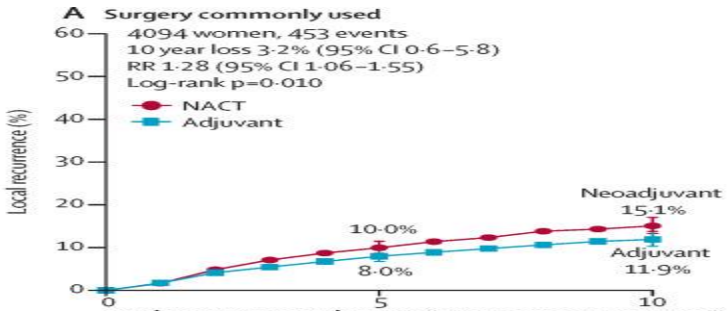
Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	3·90 (412/10567)	2·82 (191/6785)	1·93 (69/3570)	1·24 (13/1050)
Adjuvant	3·49 (364/10432)	2·81 (190/6771)	2·19 (78/3559)	1·18 (12/1014)
Rate ratio	1·12 (0·97–1·30)	1·03 (0·84–1·27)	0·88 (0·63–1·21)	0·90 (0·41–1·97)
(95% CI) from (O–E)/V	20·5/179·6	2·8/91·6	−4·8/36·6	−0·7/6·2



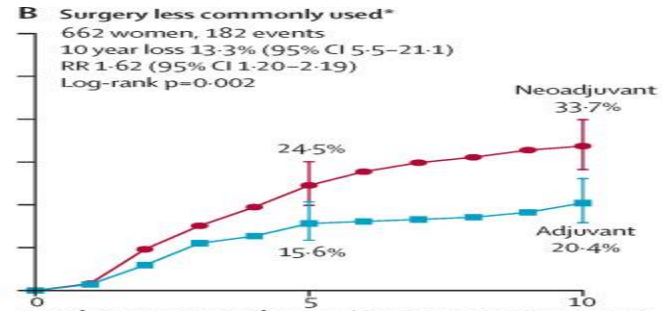
Any death crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
4·22 (446/10567)	3·51 (238/6785)	2·91 (104/3570)	3·52 (37/1050)
3·86 (403/10432)	3·56 (241/6771)	3·20 (114/3559)	2·07 (21/1014)
1·09 (0·95–1·25)	0·98 (0·81–1·17)	0·90 (0·68–1·18)	1·69 (0·95–2·99)
16·7/196·6	−2·7/112·2	−5·6/51·3	6·1/11·7



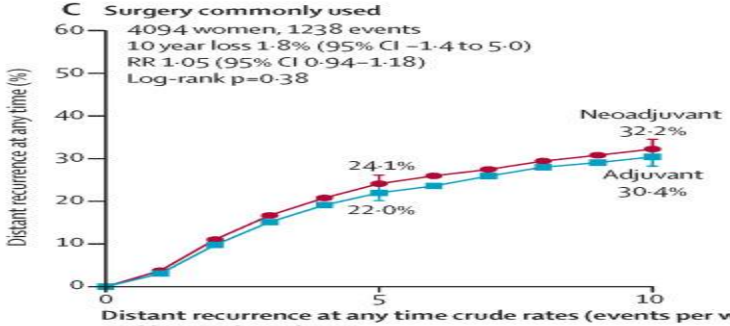
Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Neoadjuvant	2·12 (173/8164)	1·21 (57/4721)	0·85 (22/2577)
Adjuvant	1·73 (142/8200)	0·94 (45/4778)	0·55 (14/2547)
Rate ratio (95% CI)	1·26 (1·00–1·58)	1·35 (0·91–2·01)	1·32 (0·65–2·69)
from (O–E)/V	17·3/75·2	7·3/24·3	2·1/7·5



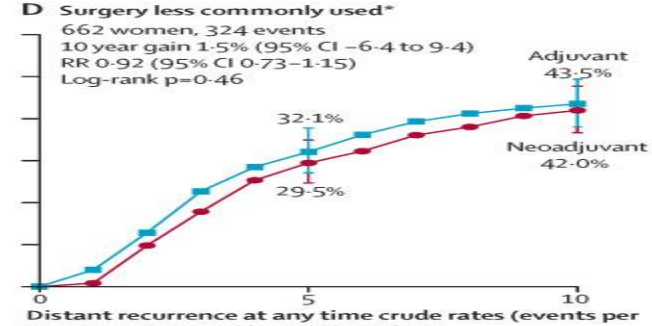
Local recurrence crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
5·42 (72/1329)	2·73 (22/806)	2·11 (20/947)
3·37 (43/1277)	1·07 (9/840)	1·61 (16/994)
1·63 (1·12–2·39)	2·30 (1·13–4·70)	1·15 (0·58–2·27)
13·2/26·8	6·3/7·5	1·1/8·2



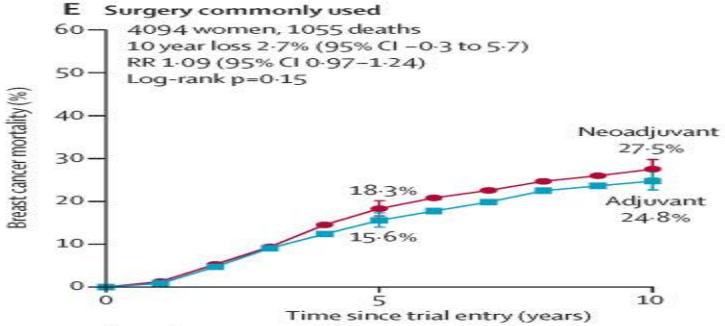
Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Neoadjuvant	5·50 (470/8545)	2·29 (121/5284)	1·30 (40/3078)
Adjuvant	5·07 (431/8496)	2·32 (122/5262)	1·77 (54/3050)
Rate ratio (95% CI)	1·12 (0·97–1·28)	0·98 (0·75–1·26)	0·74 (0·49–1·13)
from (O–E)/V	22·8/205·9	−1·4/58·0	−6·6/21·8



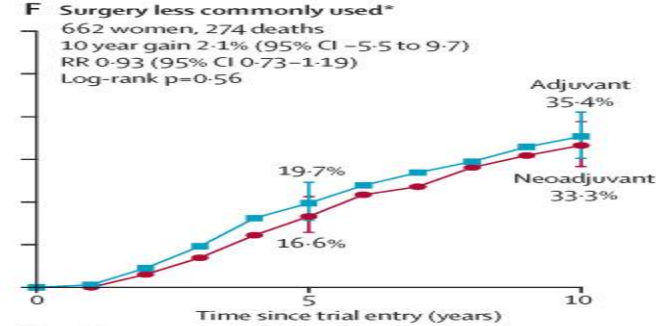
Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
6·81 (98/1438)	4·07 (41/1007)	1·92 (24/1248)
7·74 (104/1344)	3·78 (35/926)	1·93 (22/1139)
0·87 (0·65–1·17)	1·05 (0·66–1·68)	0·91 (0·50–1·66)
−6·3/45·6	0·8/17·5	−1·0/10·7



Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Neoadjuvant	3·95 (356/9007)	2·48 (139/5610)	1·65 (53/3206)
Adjuvant	3·37 (301/8944)	2·49 (141/5662)	2·01 (65/3237)
Rate ratio (95% CI)	1·19 (1·01–1·39)	1·03 (0·81–1·31)	0·82 (0·57–1·17)
from (O–E)/V	26·4/152·1	2·1/67·4	−6·0/30·0



Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
3·59 (56/1560)	4·43 (52/1175)	2·05 (29/1414)
4·23 (63/1488)	4·42 (49/1109)	1·87 (25/1336)
0·81 (0·56–1·18)	1·03 (0·69–1·53)	1·03 (0·60–1·79)
−5·8/27·6	0·7/24·2	0·4/12·9

A

	Events/women			Neoadjuvant events	
	Preoperative *vs* postoperative chemotherapy*	Allocated neoadjuvant	Allocated adjuvant	Log-rank O−E	Variance of O−E
Trials where preoperative chemotherapy included neither anthracyclines nor taxanes					
BCCA Vancouver[17]	1C600M40F600	10/42	3/39	3·2	2·1
St George's London[12]	4Mz7M35Mit7	11/53	8/50	1·5	4·3
RMH London[11]	4Mz7M35Mit7	7/155	8/150	−1·4	3·5
Austrian BCSG VII[8]	3C600×2M40×2F600×2	16/142	12/137	1·6	6·8
Austrian BCSG VII[8]	3C600×2M40×2F600×2	11/74	4/76	3·8	3·5
Subtotal		55/466 (11·8%)	35/452 (7·7%)	8·8	20·2
Trials using anthracyclines but not taxanes					
IB Bordeaux[14]	3E50Vc1000M20; 3Mit10Tt20Vd4000	39/134	18/138	11·1	13·6
Institut Curie S6[15]	4F500A25C500	75/200	50/190	9·5	28·9
NSABP B-18[9]	4A60C600	124/760	105/763	9·0	55·1
NCI Bethesda[16]	5F400×3Fol500×3A15×3C600	2/26	1/27	0·1	0·5
EORTC 10902[10]	4F600E60C600	33/350	30/348	3·9	14·9
Subtotal		273/1470 (18·6%)	204/1466 (13·9%)	33·5	113·0
Trials using anthracyclines and taxanes					
ECTO Italy[13]	4E60P200; 4C600×2M40×2F600×2	38/451	30/451	4·9	16·4
Subtotal		38/451 (8·4%)	30/451 (6·7%)	4·9	16·4
Total		**366/2387 (15·3%)**	**269/2369 (11·4%)**	**47·2**	**149·5**

99% CI 95% CI

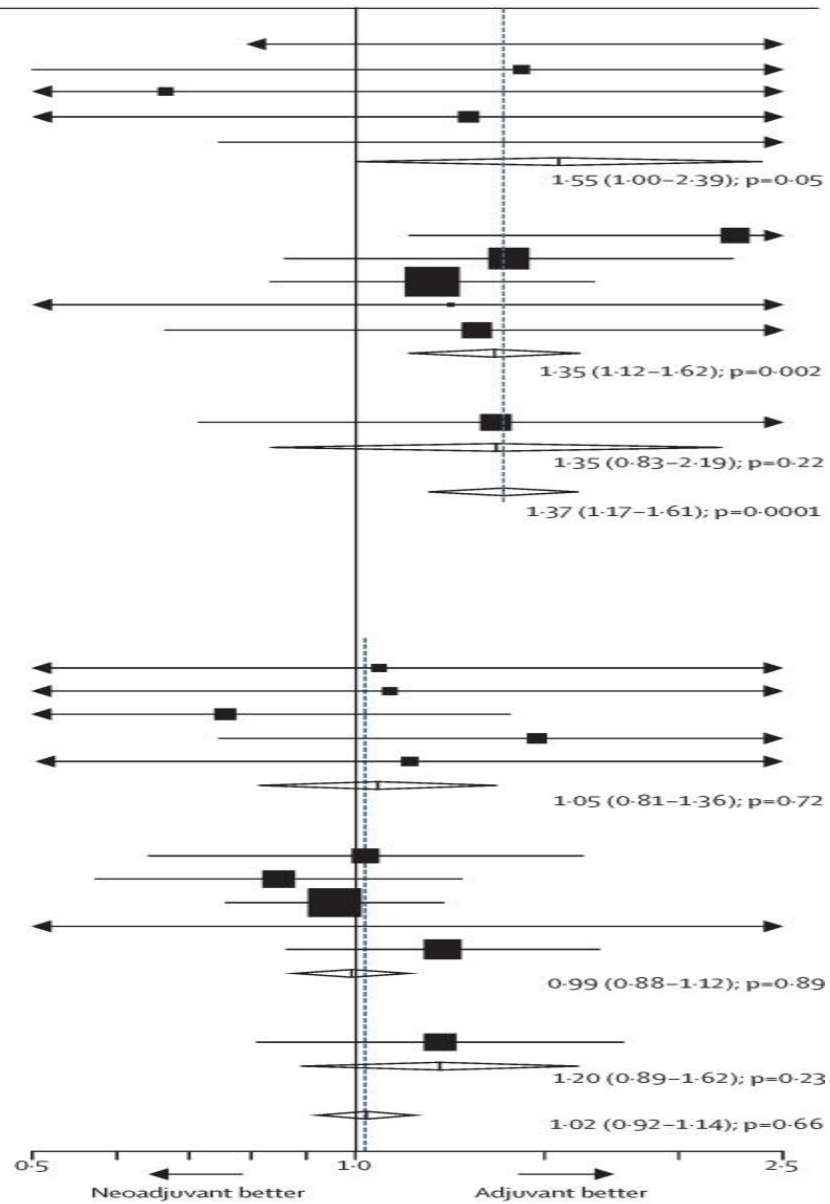
Heterogeneity between three subtotals: χ^2_2=0·3; p=0·85
Heterogeneity within subtotals: χ^2_8=11·5; p=0·18
Heterogeneity between 11† trials: χ^2_{10}=11·8; p=0·30

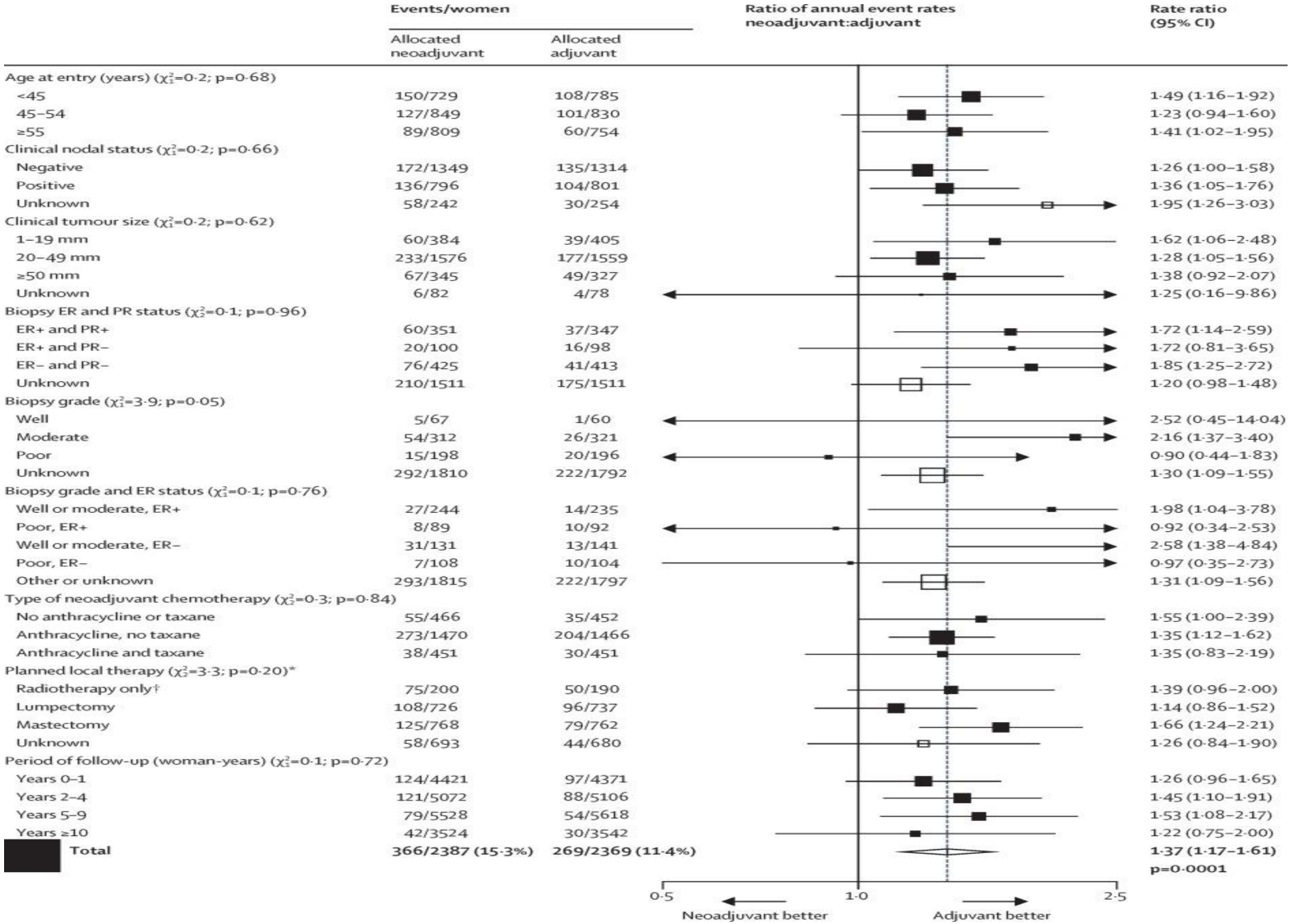
B

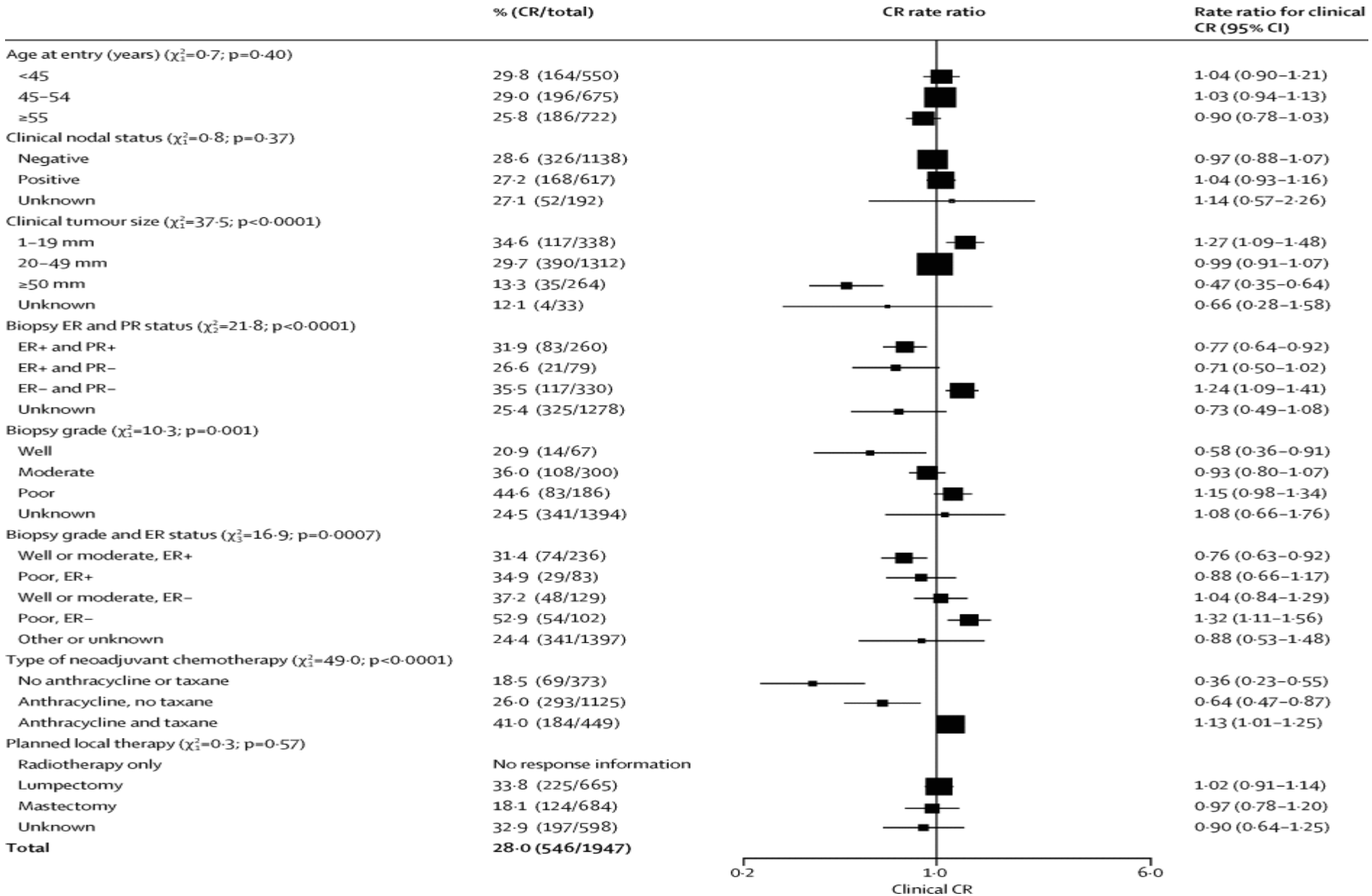
Trials where preoperative chemotherapy included neither anthracyclines nor taxanes					
BCCA Vancouver[17]	1C600M40F600	20/42	20/39	0·4	8·0
St George's London[12]	4Mz7M35Mit7	19/53	17/50	0·6	8·0
RMH London[11]	4Mz7M35Mit7	37/155	41/150	−5·0	17·8
Austrian BCSG VII[8]	3C600×2M40×2F600×2	37/142	25/137	5·6	14·3
Austrian BCSG VII[8]	3C600×2M40×2F600×2	23/74	23/76	1·2	10·3
Subtotal		136/466 (29·2%)	126/452 (27·9%)	2·8	58·4
Trials using anthracyclines but not taxanes					
IB Bordeaux[14]	3E50Vc1000M20; 3Mit10Tt20Vd4000	66/134	65/138	0·7	30·7
Institut Curie S6[15]	4F500A25C500	97/200	96/190	−7·1	43·1
NSABP B-18[9]	4A60C600	256/760	264/763	−5·4	122·7
NCI Bethesda[16]	5F400×3Fol500×3A15×3C600	3/26	7/27	−1·5	2·1
EORTC 10902[10]	4F600E60C600	139/350	122/348	11·1	59·3
Subtotal		561/1470 (38·2%)	554/1466 (37·8%)	−2·2	258·0
Trials using anthracyclines and taxanes					
ECTO Italy[13]	4E60P200; 4C600×2M40×2F600×2	97/451	88/451	7·8	43·2
Subtotal		97/451 (21·5%)	88/451 (19·5%)	7·8	43·2
Total		**794/2387 (33·3%)**	**768/2369 (32·4%)**	**8·4**	**359·5**

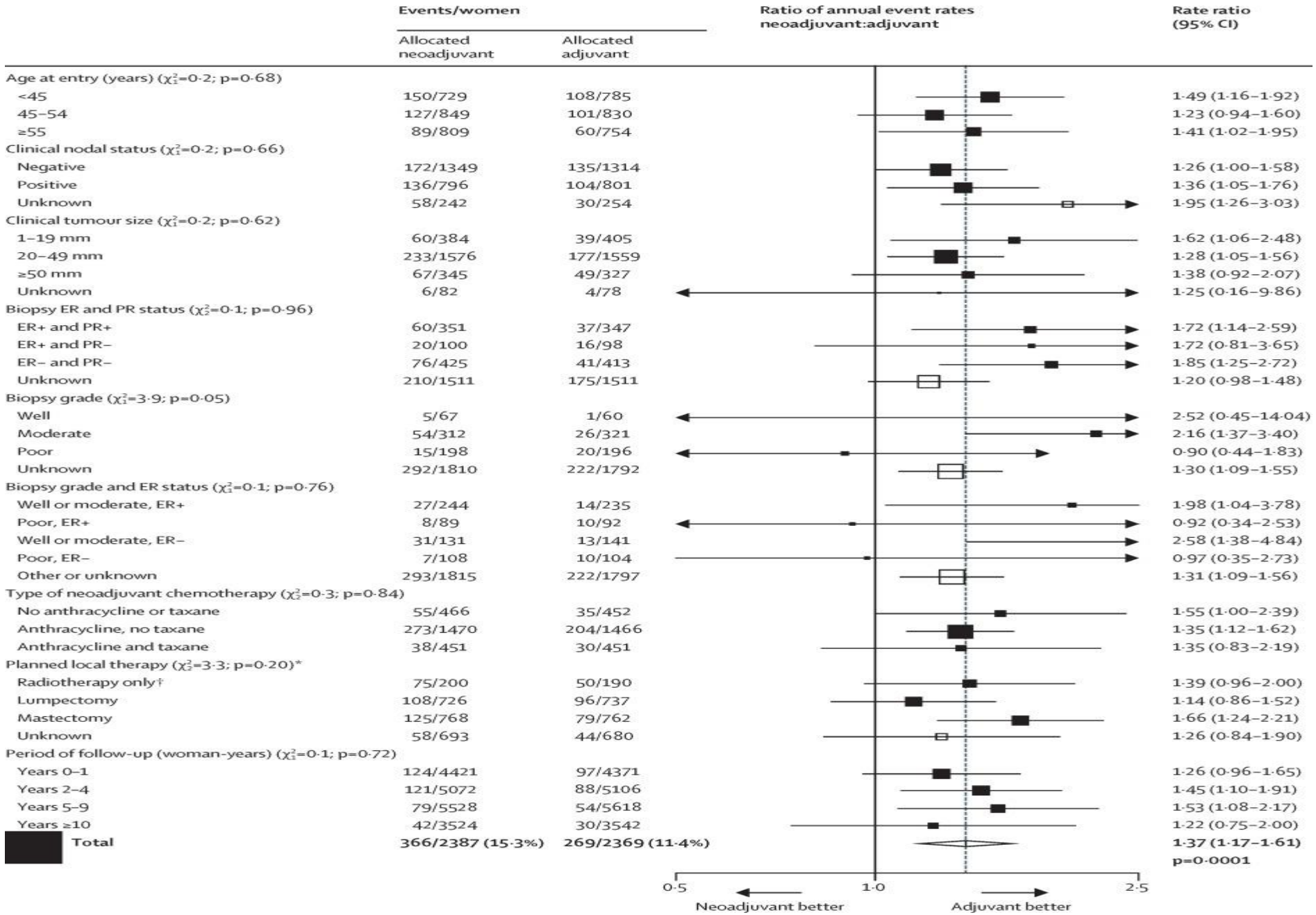
99% CI 95% CI

Heterogeneity between three subtotals: χ^2_2=1·4; p=0·50
Heterogeneity within subtotals: χ^2_8=8·2; p=0·42
Heterogeneity between 11† trials: χ^2_{10}=9·5; p=0·48




Events/women
Allocated neoadjuvant
Allocated adjuvant
Ratio of annual event rates neoadjuvant:adjuvant
Rate ratio (95% CI)
Age at entry (years) (χ^2_1=0·2; p=0·68)
<45 150/729 108/785 1·49 (1·16–1·92)
45–54 127/849 101/830 1·23 (0·94–1·60)
≥55 89/809 60/754 1·41 (1·02–1·95)
Clinical nodal status (χ^2_1=0·2; p=0·66)
Negative 172/1349 135/1314 1·26 (1·00–1·58)
Positive 136/796 104/801 1·36 (1·05–1·76)
Unknown 58/242 30/254 1·95 (1·26–3·03)
Clinical tumour size (χ^2_1=0·2; p=0·62)
1–19 mm 60/384 39/405 1·62 (1·06–2·48)
20–49 mm 233/1576 177/1559 1·28 (1·05–1·56)
≥50 mm 67/345 49/327 1·38 (0·92–2·07)
Unknown 6/82 4/78 1·25 (0·16–9·86)
Biopsy ER and PR status (χ^2_3=0·1; p=0·96)
ER+ and PR+ 60/351 37/347 1·72 (1·14–2·59)
ER+ and PR– 20/100 16/98 1·72 (0·81–3·65)
ER– and PR– 76/425 41/413 1·85 (1·25–2·72)
Unknown 210/1511 175/1511 1·20 (0·98–1·48)
Biopsy grade (χ^2_2=3·9; p=0·05)
Well 5/67 1/60 2·52 (0·45–14·04)
Moderate 54/312 26/321 2·16 (1·37–3·40)
Poor 15/198 20/196 0·90 (0·44–1·83)
Unknown 292/1810 222/1792 1·30 (1·09–1·55)
Biopsy grade and ER status (χ^2_4=0·1; p=0·76)
Well or moderate, ER+ 27/244 14/235 1·98 (1·04–3·78)
Poor, ER+ 8/89 10/92 0·92 (0·34–2·53)
Well or moderate, ER– 31/131 13/141 2·58 (1·38–4·84)
Poor, ER– 7/108 10/104 0·97 (0·35–2·73)
Other or unknown 293/1815 222/1797 1·31 (1·09–1·56)
Type of neoadjuvant chemotherapy (χ^2_2=0·3; p=0·84)
No anthracycline or taxane 55/466 35/452 1·55 (1·00–2·39)
Anthracycline, no taxane 273/1470 204/1466 1·35 (1·12–1·62)
Anthracycline and taxane 38/451 30/451 1·35 (0·83–2·19)
Planned local therapy (χ^2_3=3·3; p=0·20)*
Radiotherapy only† 75/200 50/190 1·39 (0·96–2·00)
Lumpectomy 108/726 96/737 1·14 (0·86–1·52)
Mastectomy 125/768 79/762 1·66 (1·24–2·21)
Unknown 58/693 44/680 1·26 (0·84–1·90)
Period of follow-up (woman-years) (χ^2_1=0·1; p=0·72)
Years 0–1 124/4421 97/4371 1·26 (0·96–1·65)
Years 2–4 121/5072 88/5106 1·45 (1·10–1·91)
Years 5–9 79/5528 54/5618 1·53 (1·08–2·17)
Years ≥10 42/3524 30/3542 1·22 (0·75–2·00)
Total 366/2387 (15·3%) 269/2369 (11·4%) 1·37 (1·17–1·61)
p=0·0001
0·5
1·0
2·5
Neoadjuvant better
Adjuvant better


% (CR/total)
CR rate ratio
Rate ratio for clinical CR (95% CI)
Age at entry (years) (χ^2_1=0·7; p=0·40)
<45 29·8 (164/550) 1·04 (0·90–1·21)
45–54 29·0 (196/675) 1·03 (0·94–1·13)
≥55 25·8 (186/722) 0·90 (0·78–1·03)
Clinical nodal status (χ^2_1=0·8; p=0·37)
Negative 28·6 (326/1138) 0·97 (0·88–1·07)
Positive 27·2 (168/617) 1·04 (0·93–1·16)
Unknown 27·1 (52/192) 1·14 (0·57–2·26)
Clinical tumour size (χ^2_1=37·5; p<0·0001)
1–19 mm 34·6 (117/338) 1·27 (1·09–1·48)
20–49 mm 29·7 (390/1312) 0·99 (0·91–1·07)
≥50 mm 13·3 (35/264) 0·47 (0·35–0·64)
Unknown 12·1 (4/33) 0·66 (0·28–1·58)
Biopsy ER and PR status (χ^2_2=21·8; p<0·0001)
ER+ and PR+ 31·9 (83/260) 0·77 (0·64–0·92)
ER+ and PR– 26·6 (21/79) 0·71 (0·50–1·02)
ER– and PR– 35·5 (117/330) 1·24 (1·09–1·41)
Unknown 25·4 (325/1278) 0·73 (0·49–1·08)
Biopsy grade (χ^2_1=10·3; p=0·001)
Well 20·9 (14/67) 0·58 (0·36–0·91)
Moderate 36·0 (108/300) 0·93 (0·80–1·07)
Poor 44·6 (83/186) 1·15 (0·98–1·34)
Unknown 24·5 (341/1394) 1·08 (0·66–1·76)
Biopsy grade and ER status (χ^2_3=16·9; p=0·0007)
Well or moderate, ER+ 31·4 (74/236) 0·76 (0·63–0·92)
Poor, ER+ 34·9 (29/83) 0·88 (0·66–1·17)
Well or moderate, ER– 37·2 (48/129) 1·04 (0·84–1·29)
Poor, ER– 52·9 (54/102) 1·32 (1·11–1·56)
Other or unknown 24·4 (341/1397) 0·88 (0·53–1·48)
Type of neoadjuvant chemotherapy (χ^2_2=49·0; p<0·0001)
No anthracycline or taxane 18·5 (69/373) 0·36 (0·23–0·55)
Anthracycline, no taxane 26·0 (293/1125) 0·64 (0·47–0·87)
Anthracycline and taxane 41·0 (184/449) 1·13 (1·01–1·25)
Planned local therapy (χ^2_2=0·3; p=0·57)
Radiotherapy only No response information
Lumpectomy 33·8 (225/665) 1·02 (0·91–1·14)
Mastectomy 18·1 (124/684) 0·97 (0·78–1·20)
Unknown 32·9 (197/598) 0·90 (0·64–1·25)
Total 28·0 (546/1947)
0·2
1·0
6·0
Clinical CR


Events/women
Allocated neoadjuvant
Allocated adjuvant
Ratio of annual event rates neoadjuvant:adjuvant
Rate ratio (95% CI)
Age at entry (years) (χ^2_1=0·2; p=0·68)
<45 150/729 108/785 1·49 (1·16–1·92)
45–54 127/849 101/830 1·23 (0·94–1·60)
≥55 89/809 60/754 1·41 (1·02–1·95)
Clinical nodal status (χ^2_1=0·2; p=0·66)
Negative 172/1349 135/1314 1·26 (1·00–1·58)
Positive 136/796 104/801 1·36 (1·05–1·76)
Unknown 58/242 30/254 1·95 (1·26–3·03)
Clinical tumour size (χ^2_1=0·2; p=0·62)
1–19 mm 60/384 39/405 1·62 (1·06–2·48)
20–49 mm 233/1576 177/1559 1·28 (1·05–1·56)
≥50 mm 67/345 49/327 1·38 (0·92–2·07)
Unknown 6/82 4/78 1·25 (0·16–9·86)
Biopsy ER and PR status (χ^2_2=0·1; p=0·96)
ER+ and PR+ 60/351 37/347 1·72 (1·14–2·59)
ER+ and PR– 20/100 16/98 1·72 (0·81–3·65)
ER– and PR– 76/425 41/413 1·85 (1·25–2·72)
Unknown 210/1511 175/1511 1·20 (0·98–1·48)
Biopsy grade (χ^2_1=3·9; p=0·05)
Well 5/67 1/60 2·52 (0·45–14·04)
Moderate 54/312 26/321 2·16 (1·37–3·40)
Poor 15/198 20/196 0·90 (0·44–1·83)
Unknown 292/1810 222/1792 1·30 (1·09–1·55)
Biopsy grade and ER status (χ^2_1=0·1; p=0·76)
Well or moderate, ER+ 27/244 14/235 1·98 (1·04–3·78)
Poor, ER+ 8/89 10/92 0·92 (0·34–2·53)
Well or moderate, ER– 31/131 13/141 2·58 (1·38–4·84)
Poor, ER– 7/108 10/104 0·97 (0·35–2·73)
Other or unknown 293/1815 222/1797 1·31 (1·09–1·56)
Type of neoadjuvant chemotherapy (χ^2_2=0·3; p=0·84)
No anthracycline or taxane 55/466 35/452 1·55 (1·00–2·39)
Anthracycline, no taxane 273/1470 204/1466 1·35 (1·12–1·62)
Anthracycline and taxane 38/451 30/451 1·35 (0·83–2·19)
Planned local therapy (χ^2_2=3·3; p=0·20)*
Radiotherapy only† 75/200 50/190 1·39 (0·96–2·00)
Lumpectomy 108/726 96/737 1·14 (0·86–1·52)
Mastectomy 125/768 79/762 1·66 (1·24–2·21)
Unknown 58/693 44/680 1·26 (0·84–1·90)
Period of follow-up (woman-years) (χ^2_1=0·1; p=0·72)
Years 0–1 124/4421 97/4371 1·26 (0·96–1·65)
Years 2–4 121/5072 88/5106 1·45 (1·10–1·91)
Years 5–9 79/5528 54/5618 1·53 (1·08–2·17)
Years ≥10 42/3524 30/3542 1·22 (0·75–2·00)
Total 366/2387 (15·3%) 269/2369 (11·4%) 1·37 (1·17–1·61)
p=0·0001
0·5
1·0
2·5
Neoadjuvant better
Adjuvant better

Ongoing clinical trials with immune checkpoint inhibitors including HER2-positive tumors

Phase	Clinical Trial Gov	Disease setting	Type of disease	Breast cancer subtype	Anti-PD1/PDL1	Combined treatments
I	NCT02639026	Metastatic	Multiple solid	All	Durvalumab	Tremelimumab and Radiotherapy
I/II	NCT02643303	Metastatic	Multiple solid	All	Durvalumab	Poly-ICLC +/- Tremelimumab
I	NCT02914470	Metastatic	Multiple solid	All	Atezolizumab	Carboplatin and cyclophosphamide
I/II	NCT02318901	Metastatic	Multiple solid	HER2-pos	Pembrolizumab	Trastuzumab or T-DM1
I	NCT01975831	Metastatic	Multiple solid	HER2-pos and ER+/HER2-	Durvalumab	Tremelimumab
I/II	NCT02403271	Metastatic	Multiple solid	HER2-pos and TNBC	Durvalumab	Ibrutinib
II/III	NCT02725489	Metastatic	Only BC	All	Durvalumab	Autologous Tumor Cell" Immunotherapy (Vigil™)
II	NCT01042379	Neoadjuvant	Only BC	All	Pembrolizumab	Paclitaxel
II	NCT01502592	Pre-surgical	Only BC	All	Ipilimumab	Cryoablation
II	NCT02833233	Pre-surgical	Only BC	All	Nivolumab	Ipilimumab and cryoablation
I	NCT02303366	Metastatic	Only BC	All	Pembrolizumab	Stereotactic Ablative Body Radiosurgery
I/II	NCT02129556	Metastatic	Only BC	HER2-pos	Pembrolizumab	Trastuzumab
I	NCT02649686	Metastatic	Only BC	HER2-pos	Durvalumab	Trastuzumab
II	NCT02924883	Metastatic	Only BC	HER2-pos	Atezolizumab	T-DM1
I	NCT02605915	Metastatic and neoadjuvant	Only BC	HER2-pos	Atezolizumab	Trastuzumab/pertuzumab or T-DM1 or Trastuzumab/Pertuzumab/Carboplatin/Docetaxel

Table 1. Ongoing clinical trials with combinations of immunotherapy and anti-HER2 agents.

STUDY	PHASE	SETTING	TREATMENT
PANACEA NCT02129556	Phase Ib/II	Advanced disease	MK-3475 (mAb against PD-1) + Trastuzumab
NCT02605915	Ib	Locally advanced and metastatic disease	Atezolizumab + trastuzumab + pertuzumab or Atezolizumab + T-DM1
PembroMab NCT02318901	II	Metastatic disease	Pembrolizumab + T-DM1

Source: www.clinicaltrials.gov. Accessed November 20, 2015.

Widening therapeutic option in HER2-positive disease

What's next?

HER2-positive (HR+)

- T + P + ET (?)
- CDK4/6 inhibitors + ET
- CDK4/6 inhibitors + T + ET
- CDK4/6 inhibitors + T + P + ET

HER2-positive (HR+ and HR-)

HER2 mutant

- Neratinib
- Paused

- Anti-PD1/PDL1 + T
- Anti-PD1/PDL1 + T + CT
- Anti-PD1/PDL1 + T + P+ CT
- Anti-PD1/PDL1 + T-DM1

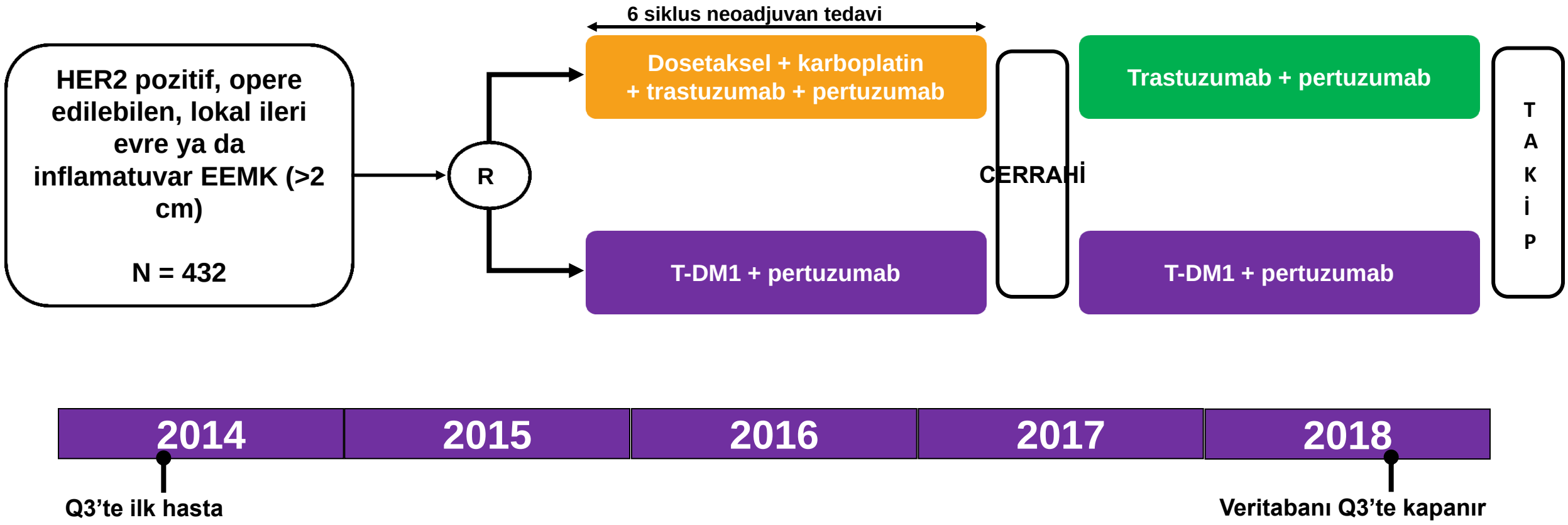
HER2-positive (HR-)

PI3K activation

- Everolimus + T + CT
- PIK3CA inhibitors + T + CT

T=Trastuzumab
P=Pertuzumab
L=Lapatinib
CT=Chemotherapy
ET=Endocrine therapy

BO28408 (KRISTINE): Faz III, iki kollu, neoadjuvan etiket tabanlı çalışma



www.clinicaltrials.gov/ct2/show/NCT02131064.

The updated network meta-analysis of neoadjuvant therapy for HER2-positive breast cancer

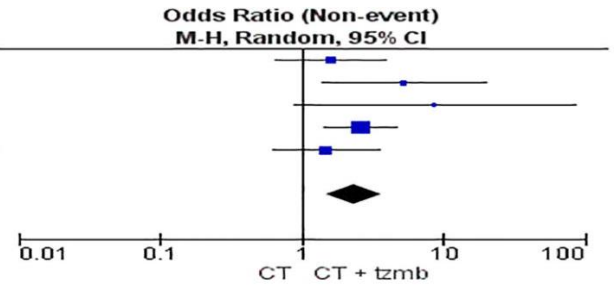
Ayako Nakashoji, Tetsu Hayashida, Takamichi Yokoe, Hinako Maeda, Tomoka Toyota, Masayuki Kikuchi, Rurina Watanuki, Aiko Nagayama, Tomoko Seki, Maiko Takahashi, Takayuki Abe, Yuko Kitagawa

Cancer Treatment Reviews
Volume 62, Pages 9-17 (January 2018)
DOI: 10.1016/j.ctrv.2017.10.009

A

Study or Subgroup	CT Events	CT Total	CT + tzmb Events	CT + tzmb Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
ABCSG-24 2013	12	49	15	44	21.2%	1.59 [0.65, 3.93]
Buzdar 2005	5	19	15	23	10.4%	5.25 [1.38, 19.93]
Chang 2006	1	14	6	15	3.7%	8.67 [0.89, 84.84]
NOAH 2010	23	118	45	117	42.2%	2.58 [1.43, 4.65]
Pierga 2010	11	58	16	62	22.6%	1.49 [0.62, 3.54]
Total (95% CI)		**258**		**261**	**100.0%**	**2.32 [1.49, 3.62]**
Total events	52		97			

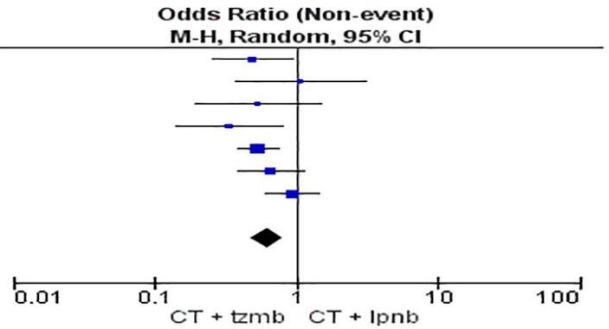
Heterogeneity: Tau² = 0.03; Chi² = 4.53, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 3.70 (P = 0.0002)



B

Study or Subgroup	CT + tzmb Events	CT + tzmb Total	CT + lpnb Events	CT + lpnb Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
CALBG40601 2015	51	117	17	62	11.9%	0.49 [0.25, 0.95]
CHER-LOB 2012	9	36	10	38	5.5%	1.07 [0.38, 3.04]
EORTC 10054 2014	27	52	8	22	5.7%	0.53 [0.19, 1.47]
GEICAM 2006-2014	23	48	12	51	7.7%	0.33 [0.14, 0.79]
GeparQuinto 2012	137	307	93	308	29.9%	0.54 [0.39, 0.75]
NeoALTTO 2012	40	149	30	154	16.4%	0.66 [0.38, 1.13]
NSABP B-41 2013	87	177	81	171	22.9%	0.93 [0.61, 1.42]
Total (95% CI)		**886**		**806**	**100.0%**	**0.62 [0.48, 0.81]**
Total events	374		251			

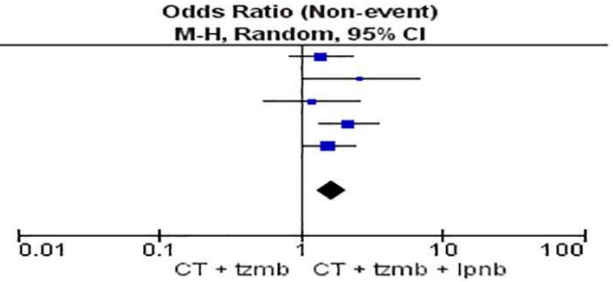
Heterogeneity: Tau² = 0.03; Chi² = 7.97, df = 6 (P = 0.24); I² = 25%
Test for overall effect: Z = 3.61 (P = 0.0003)



C

Study or Subgroup	CT + tzmb Events	CT + tzmb Total	CT + tzmb + lpnb Events	CT + tzmb + lpnb Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
CALBG40601 2015	51	117	60	116	23.1%	1.39 [0.83, 2.32]
CHER-LOB 2012	9	36	21	45	6.7%	2.63 [1.01, 6.82]
EORTC 10054 2014	27	52	27	48	9.9%	1.19 [0.54, 2.62]
NeoALTTO 2012	40	149	67	152	26.3%	2.15 [1.32, 3.48]
NSABP B-41 2013	87	177	103	171	34.0%	1.57 [1.02, 2.40]
Total (95% CI)		**531**		**532**	**100.0%**	**1.67 [1.30, 2.14]**
Total events	214		278			

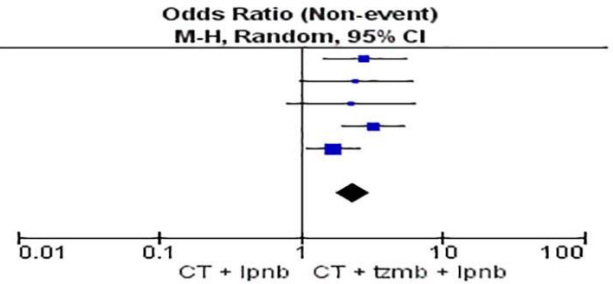
Heterogeneity: Tau² = 0.00; Chi² = 3.20, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.04 (P < 0.0001)



D

Study or Subgroup	CT + lpnb Events	CT + lpnb Total	CT + tzmb + lpnb Events	CT + tzmb + lpnb Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
CALBG40601 2015	17	62	60	116	17.1%	2.84 [1.46, 5.52]
CHER-LOB 2012	10	38	21	45	9.0%	2.45 [0.97, 6.21]
EORTC 10054 2014	8	22	27	48	7.2%	2.25 [0.80, 6.36]
NeoALTTO 2012	30	154	67	152	28.1%	3.26 [1.95, 5.43]
NSABP B-41 2013	81	171	103	171	38.7%	1.68 [1.10, 2.58]
Total (95% CI)		**447**		**532**	**100.0%**	**2.34 [1.76, 3.10]**
Total events	146		278			

Heterogeneity: Tau² = 0.01; Chi² = 4.21, df = 4 (P = 0.38); I² = 5%
Test for overall effect: Z = 5.91 (P < 0.00001)



HER2+, HR+ meme kanseri:

Neoadjuvan kemoterapiye, hormonal tedavi eklenmesi yanıtı artırır mı?

NSABP B-52: Neoadjuvan kemoterapi±hormonal tedavi

Rasyonel:

- **ER+/HER2+ tümör: ER-/HER2+ tümöre göre ikili anti-HER2 tedaviye daha az yanıt verir.**
- **ER yolağı: Anti-HER2 tedaviye dirence yol açabilir**
- **Kemoterapi+Endokrin tedavi: Antagonistik (eski çalışmalarda)**

Hipotez:

- **Kemoterapi+Anti-HER2 tedavi+endokrin tedavi: Antagonistik değildir, direnci yenebilir→ ⇑ pCR**

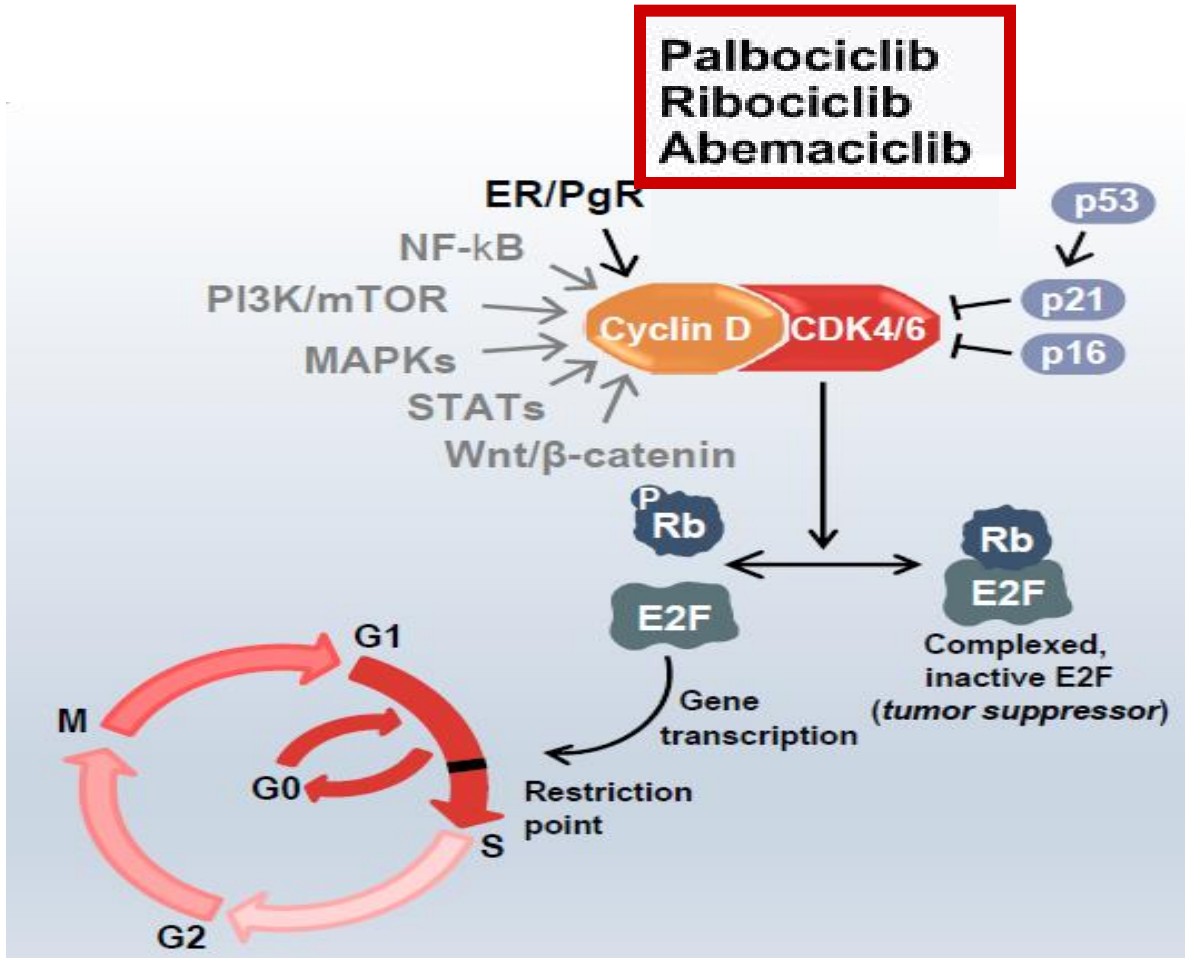
HER2-, HR+ meme kanseri:
Neoadjuvan abemaciclib (CDK4/6 inhibitörü)'in klinik ve biyolojik etkileri

Faz II NeoMONARCH çalışması: Postmenopozal HR+, HER2- meme kanserinde abemaciclibin biyolojik ve klinik etkileri

- **Endokrin direnç önemli bir klinik problem**
- **Abemaciclib: CDK4/6 inhibitörü**

Hurvitz Set al. SABCS 2016: S04.06

Meme kanserinde CDK4/6



Estrojen

↓

Cyclin D'nin uyarılması

↓

CDK4 ve CDK 6'nin aktivitesinde artış

↓

RB, transkripsiyon faktörü E2F'den ayrılır

↓

Hücre siklusunda G1'den S fazına geçiş

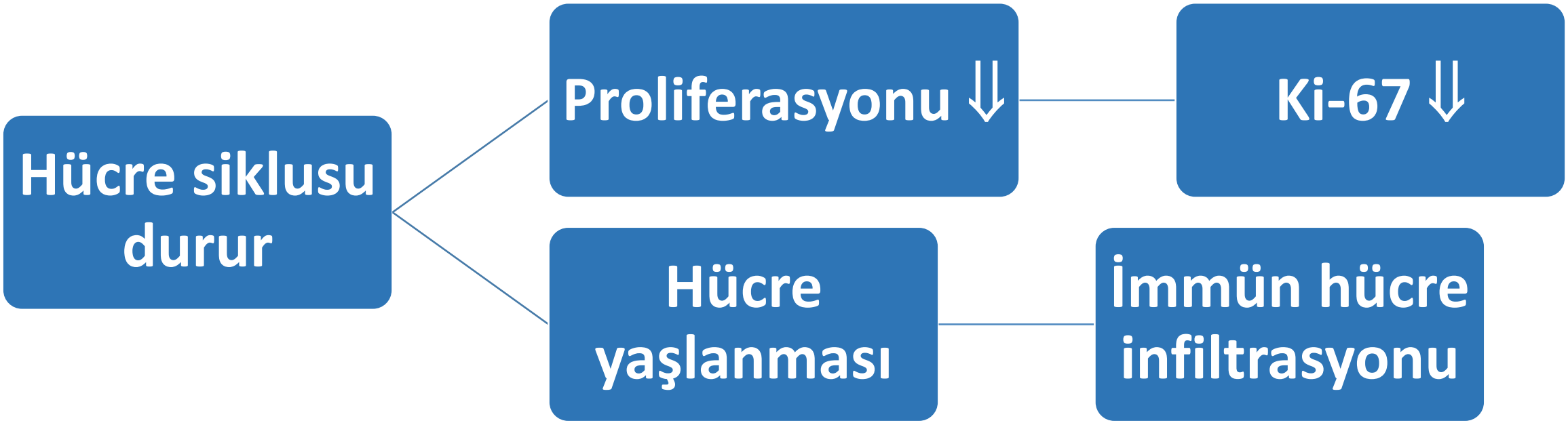
↓

Proliferasyon

Artmış Ki-67

Nat Rev Drug 2015; 14: 130

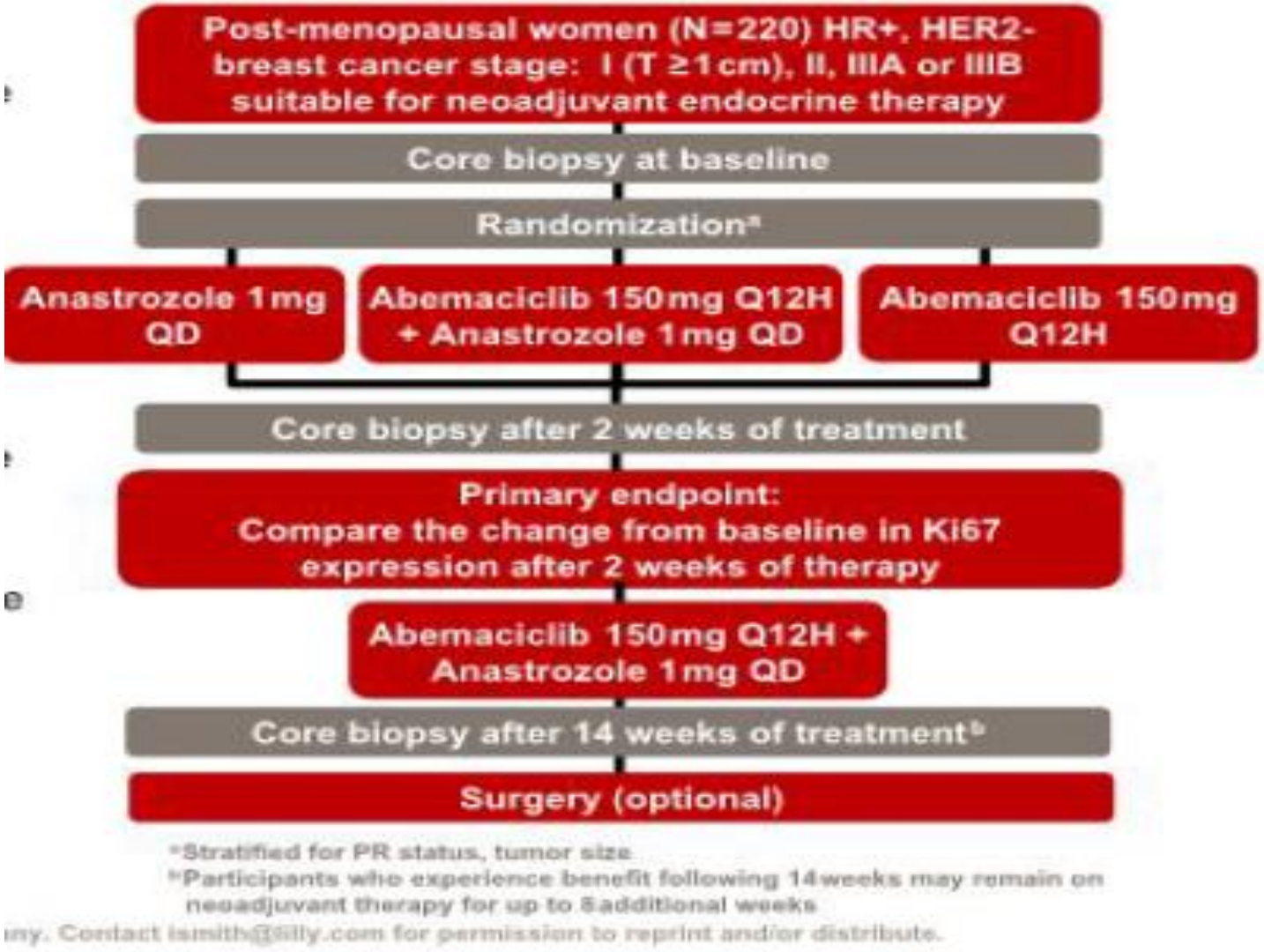
CDK4/6 inhibisyonu



HR+ metastatik meme kanserinde CDK4/6 inhibitörleri

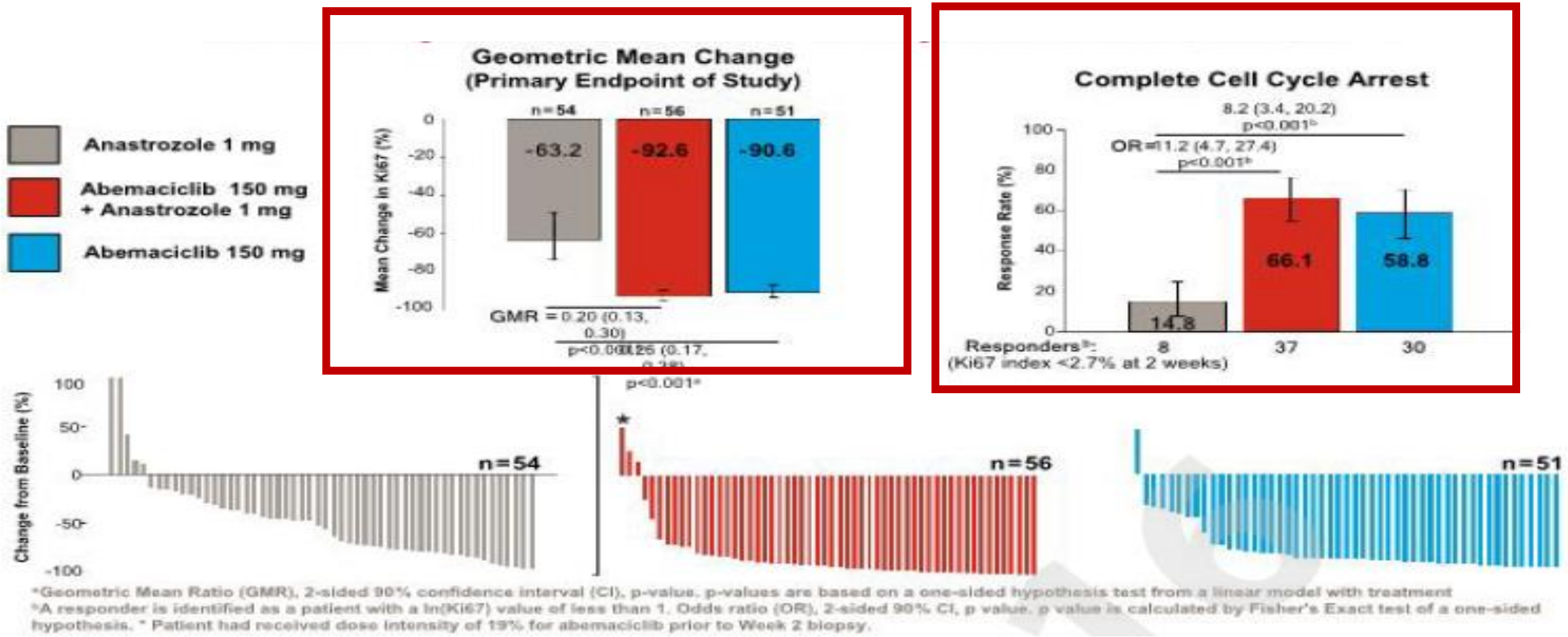
	1. Basamak	>1. basamak
Palbociclib	**PALOMA-2** (letrozole ± palbo.) PFS: 24.8 ay vs. 14.5 ay	**PALOMA-3** (fulvestrant± palbo.) PFS: 9.5 ay vs. 4.6 ay
Ribociclib	**MONALEESA-2** (letrozole ± ribo.) PFS: NR vs. 14.7 ay	
Abemaciclib	**MONARCH-3** (Anas/letro± abema)	**MONARCH-1 (faz 2) Abemaciclib tek ajan** **MONARCH-2 (faz III)** (fulvestrant± abema.)

Faz II neoMONARCH



- **Rasyonel:**
- **Neoadjuvan tedavinin 2.haftasında Ki-67 değerinde değişiklik, adjuvan tedavilerde DFS farkını predikte edebilir**

2 haftalık kullanım: ⇓ Ki-67 ekspresyonu ve hücre siklusunda durma

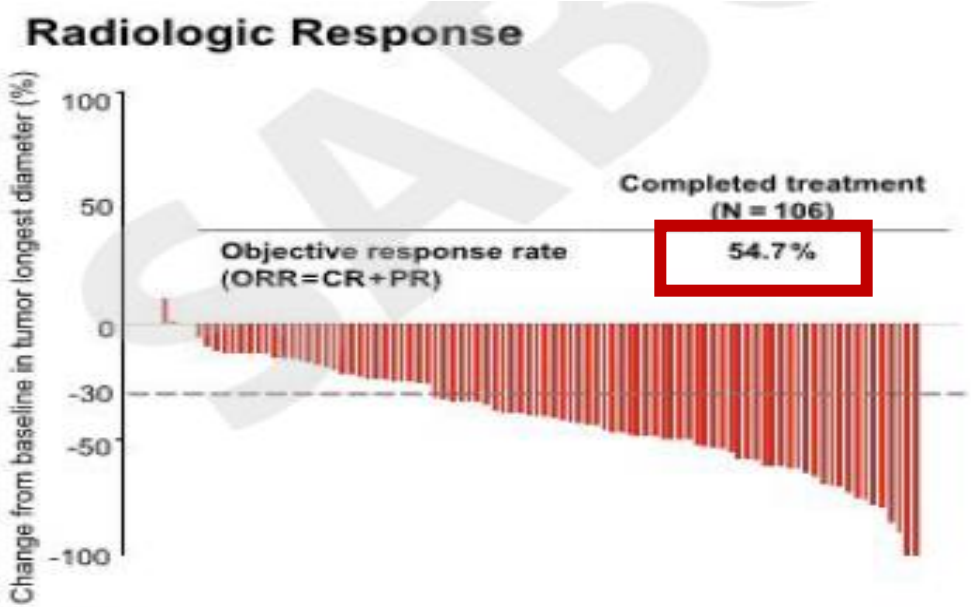


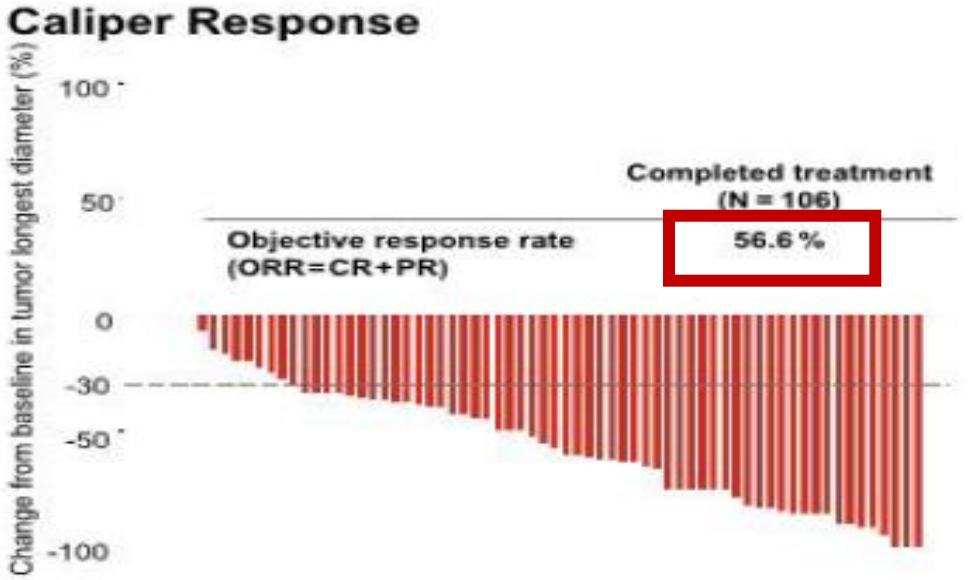
- **Abemaciclib ile Ki-67'de daha fazla azalma**
  - **>%90 hastada azalma var**

16 haftalık tedavi sonunda ki-67 ekspresyonunda azalma

- **İlk 2 hafta: Anastrazole vs. Anast+abema vs. Abemaciclib**
- **-16. hafta: Tüm hastalar anastrazole+abemaciclib**

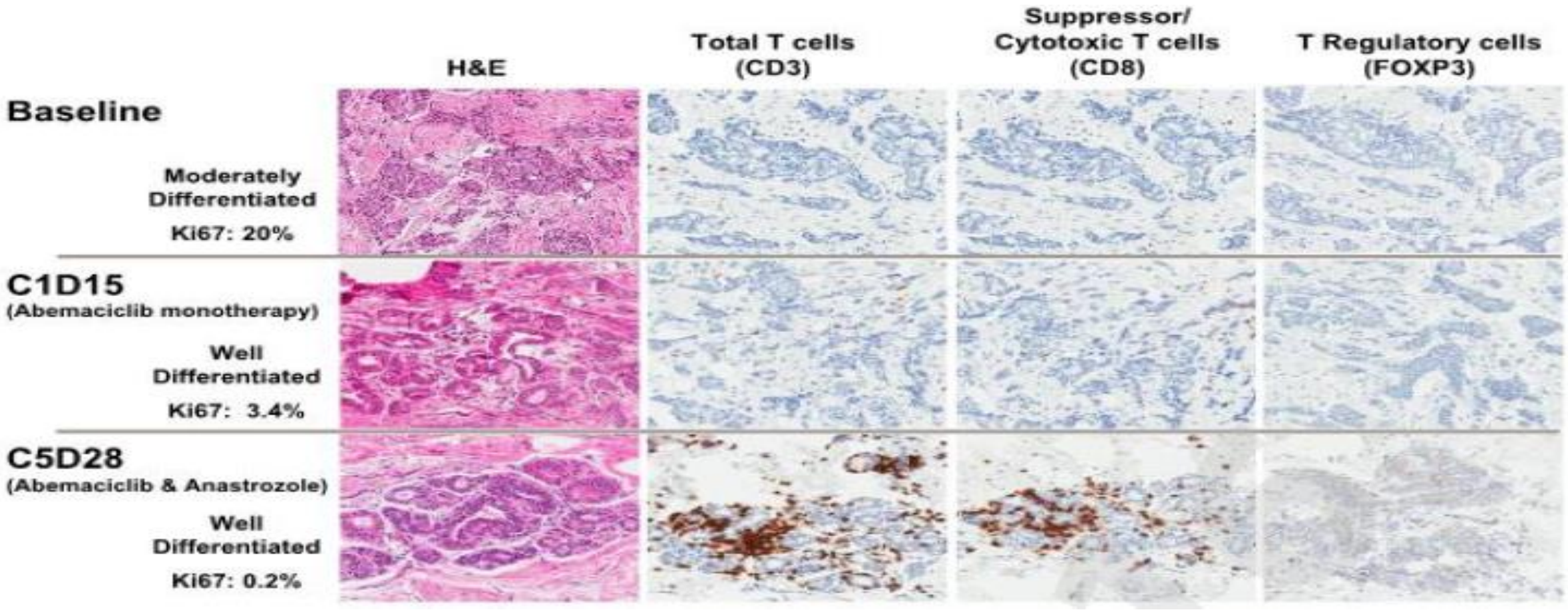
RECİST yanıtı





- At time of analysis:
  - Complete pathologic response in three (3.2%) of 95 patients that underwent surgery.
  - One patient discontinued therapy for progressive disease (20.7% change from baseline in tumor size at week 12).

Zaman içinde tümör diferensiasyonu ve immün infiltrasyonda artış



Sonuç

- **Abemaciclib, tek başına veya anastrozole ile kombine olarak 2 haftalık tedavi sonunda**
  - **⇓ Ki-67 (ki-67 <%2.7)**
  - **Hücre siklusunda durma**
- **Hücre siklusunun baskılanması → morfolojik değişiklikler (tümör diferensiasyonu)**
- **Abemaciclib + anastrozole:**
  - **İmmün hücre infiltrasyonunu indükler**
  - **Artmış yanıt:**
    - **Klinik yanıt: %56.6**
    - **Radyolojik yanıt: %54.7**
- **Sonuçlar, abemaciclibin erken evre meme kanserinde çalışılmasını destekliyor**

Yorum

- **Alınan yanıt iyi mi?**

	Neoadj. aromataz inhibitörü	Neoadj. Anast+abemaciclib
Klinik yanıt	%40-50	%56.6
Radyolojik yanıt	%30-35	%54.7

- **Sonuçlar ümit verici**

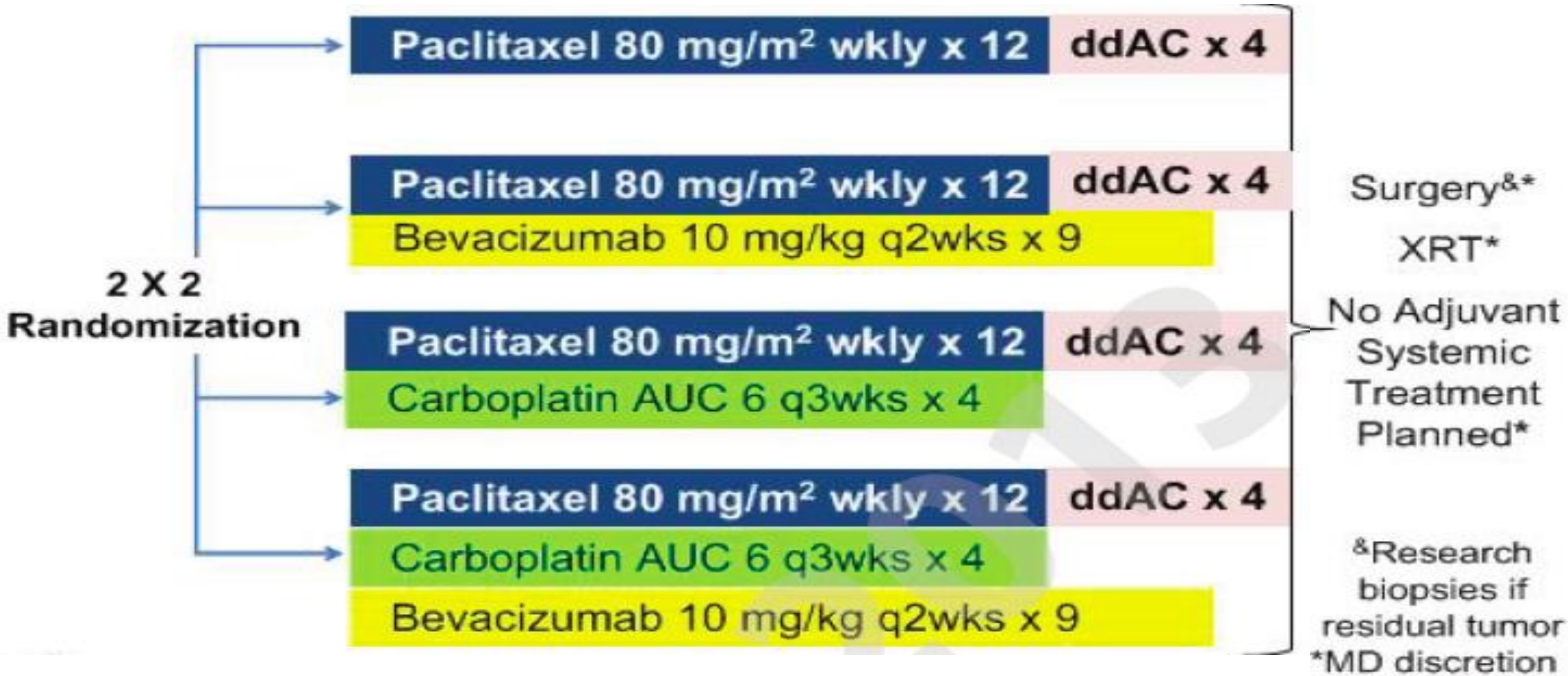
- **HR+ meme kanserinde immün kontrol noktası inhibitörlerine yanıt az.**
- **Abemaciclib→ İmmün hücre infiltrasyonunu artırıyor**

Metastatik hastalıkta, immünoterapi öncesi kullanılarak, immün yanıt artırılabilir mi?

S5-01

Impact of the addition of carboplatin (Cb) and/or bevacizumab (B) to neoadjuvant weekly paclitaxel (P) followed by dose-dense AC on pathologic complete response (pCR) rates in triple-negative breast cancer (TNBC): CALGB 40603 (Alliance)

Sikov ve ark.



Neoadjuvan tedavi süresi

- Evre IIIA, IIIB, IIIC
  - 6-8 kür
- Evre I ve II
  - Adjuvan tedavide verilen her rejim, neoadjuvan için de uygun
  - 4-8 kür
- Neoadjuvan hormonal tedavi
  - En az 4 ay
- Planlanan tedavi cerrahi öncesi tamamlanmalı

Neoadjuvan tedavi sonrası pCR elde edilmeyen hastada ne yapılmalı?

Postop adjuvan kemoterapinin yeri var mı?

Neoadjuvan tedavi sonrası rezidü

	pCR	Rezidünün sağkalımı etkisi	Cerrahi sonrası tedavi
HR+ tümörler	Düşük: %7-20	Az	Hormonal tedavi
HER2+ tümör	%45-60	Rezidü→ Nüks ⇑⇑⇑	Trastuzumab
Triple negatif	%35-45	Rezidü→ Nüks ⇑⇑⇑	-

- Rezidü en çok hangi tümörlerde önemli? **TRİPLE NEGATİF TÜMÖRLER**

Neoadjuvan ve adjuvan rejimler gerçekten benzer mi?

Operabl hastada neoadjuvan tedavi: Güncel yaklaşım

Cerrahi

ADJUVAN

Antrasiklin ve taksan bazlı

± Trastuzumab

TNBC: -

ER+: Hormonal tedavi

HER2+: Trastuzumab 1 yıl

NEOADJUVAN

Antrasiklin ve taksan bazlı± Trastuzumab

Surgery

TNBC: -

ER+: Hormonal tedavi

HER2+: Trastuzumab 1 yıl

Tek fark: Zamanlama

Aynı ajanlar, benzer DFS and OS

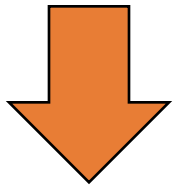
Cerrahi öncesi veya sonrası

Neoadjuvan ve adjuvan tedaviler artık benzer değildir

- **Adjuvan:** Antrasiklin ve taksan bazlı rejimler ± trastuzumab

- **Neoadjuvan:**
  - TNBC: Karboplatin düşünülmeli
  - HER2+: Pertuzumab eklenmesi düşünülmeli (özellikle HR negatif)

  - pCR olmazsa: 6 ay capecitabine (özellikle TNBC)



Bu değişiklikler sağkalımı etkileyecek mi?
ÇOK BÜYÜK OLASILIKLA

SONUÇ

Neoadjuvan kemoterapi

Kişiselleştirilmiş tedavi dönemi olan günümüzde

Adjuvan ≠ Neoadjuvan

Neoadjuvan tedavide yeni yaklaşım

TNBC

NEOADJUVAN
Antrasiklin ve taksan bazlı
+Karboplatin

→

Cerrahi

ALND'siz cerrahi

→

Residü varsa:
Kapesitabin x8 kür

GELECEK: PARP inhibitörü
Immünoterapi

HER2 (+)

NEOADJUVANT
Antrasiklin ve taksan bazlı
Trastuzumab+
Pertuzumab

→

Cerrahi

ALND'siz cerrahi

→

HER2+: Trastuzumab 1 yıl
ER+: Hormonal tedavi

GELECEK:
Rezidü varsa: TDM1?
Adjuvan pertuzumab?

HR+

NEOADJUVANT
Antrasiklin ve taksan bazlı

→

Cerrahi

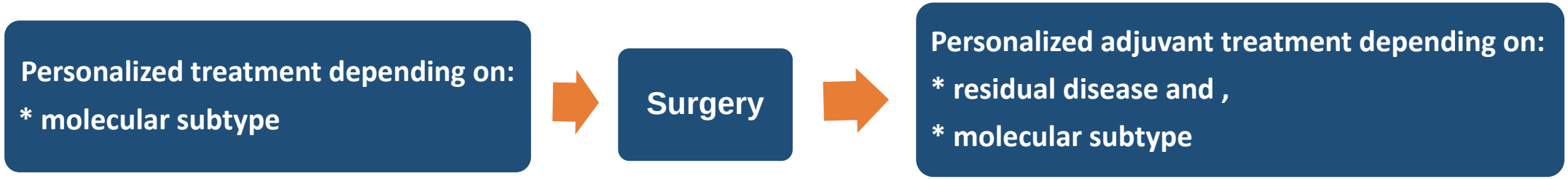
ALND'siz cerrahi

→

Hormonal tedavi

GELECEK:
Rezidü varsa: + CDK4/6 inhibitörleri (ör. palbociclib)

Neoadjuvant Treatment



Enables individualization of treatment at 2 points:

1. Pre-surgery: Choosing treatment agents acc. to molecular subtypes
2. Post-surgery: According to presence of residual disease

Should be preferred in:

- Triple negative, >1-2 cm
- HER-2 positive, > 2 cm
- Luminal B, LN +
- Luminal A → Locally advanced inoperable

TEŞEKKÜR EDERİM