Neoadjuvan Meme Kanseri Tedavisi ve Reziduel Hastalığa Yaklaşım

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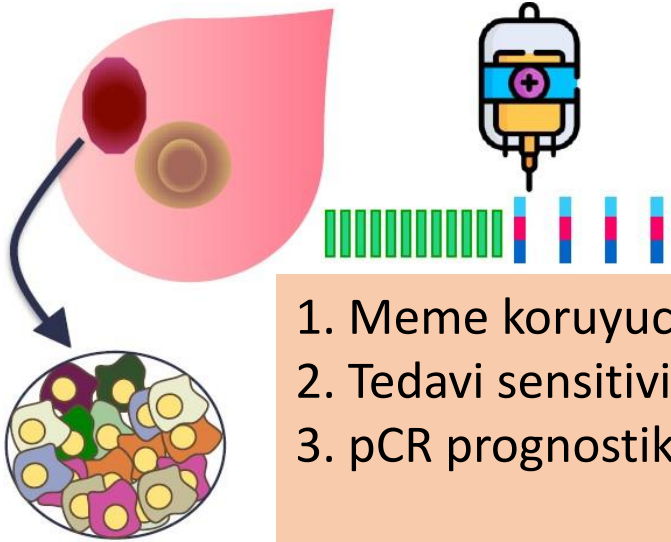
ANADOLU H

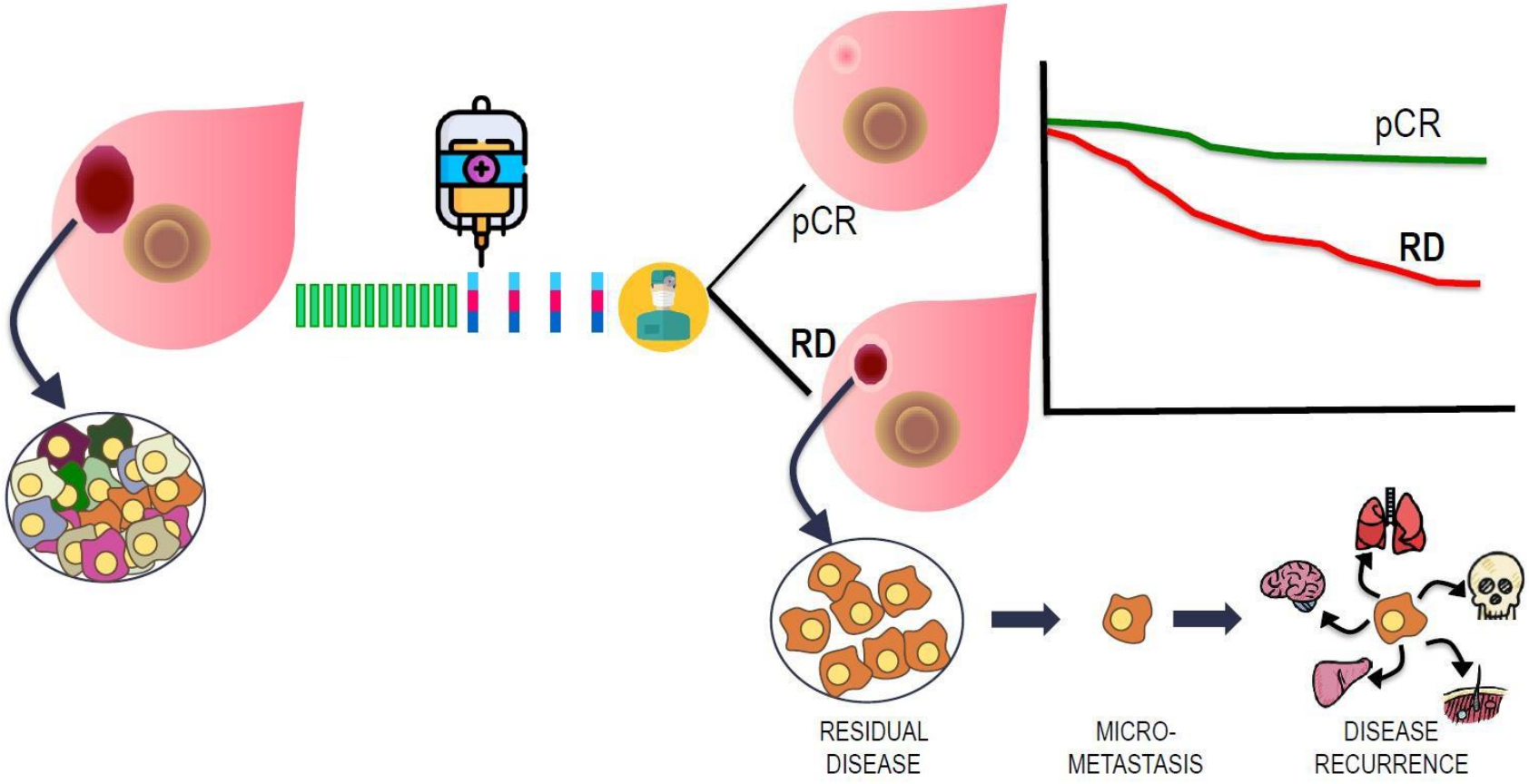
In Affiliation with
JOHNS HOPKINS MEDICINE

NEOADJUVANT TEDAVI: Kişiselleştirilmiş kanser tedavisi platformu



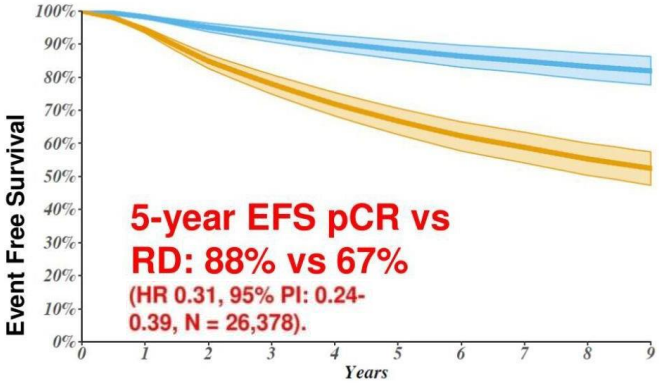
1. Meme koruyucu cerrahi
2. Tedavi sensitivitesi
3. pCR prognostik bilgi

NEOADJUVANT TEDAVI:Kişiselleştirilmiş kanser tedavisi platformu

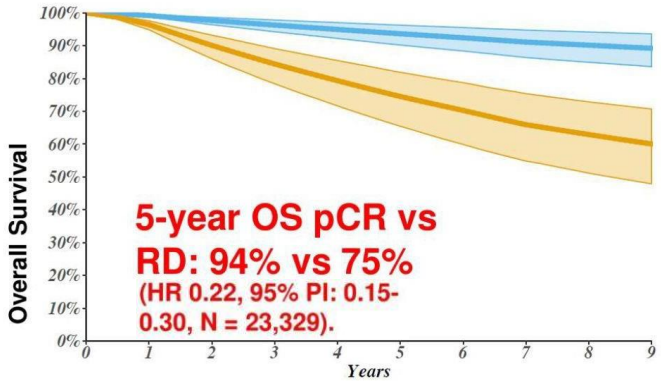


Meta-analysis: pCR ile EFS - OS ilişkisi (N=27.895, 52 studies)

Event free survival (EFS)



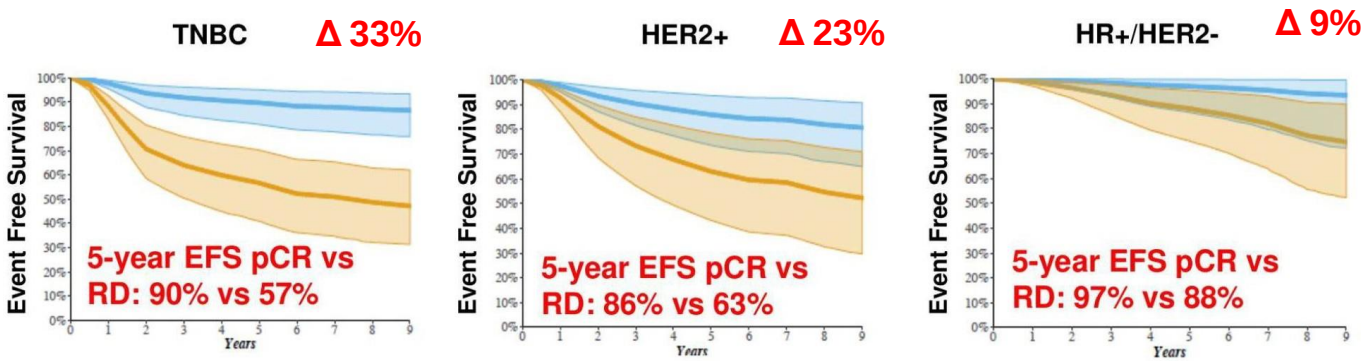
Overall survival (OS)



Blue: pCR group
Orange: Residual disease (RD) group

Spring LM, et al. SABCS 2018 (GS2-03)

Meta-analysis: pCR ile EFS ve OS ilişkisi (N=27.895, 52 çalışma)



Blue: pCR group
Orange: Residual disease (RD) group

Similar results seen with OS

TNBC > HER2+ > HR+/HER2-

Spring LM, et al. SABCS 2018 (GS2-03)

ARTTIRILMIŞ YAKLAŞIM

HER2 pozitif

Arttırılmış yaklaşım: TRASTUZUMAB (MDACC) eklenmesi

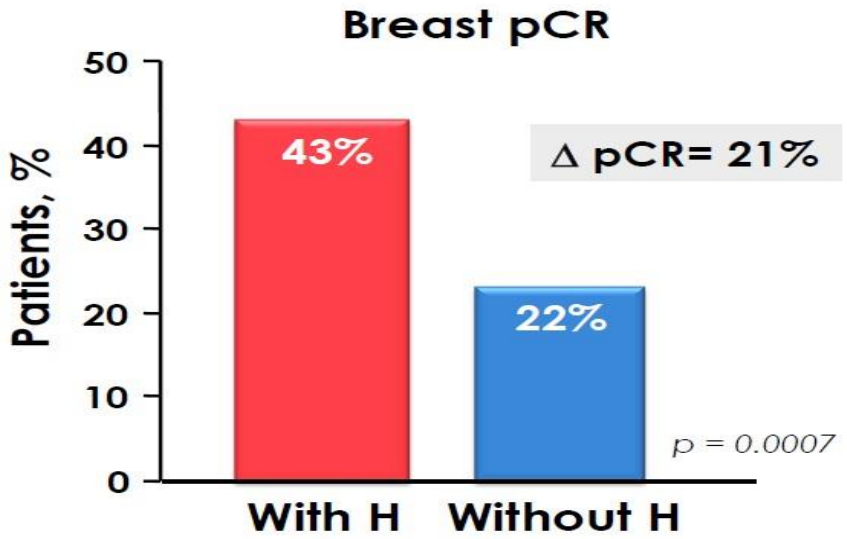
	P-FEC 19 pts	P-FEC + T 23 pts
pCR	26.3%	65.2%
pCR ER pos	27%	61%
pCR ER neg	25%	70%
pN0	78.9%	86.9%

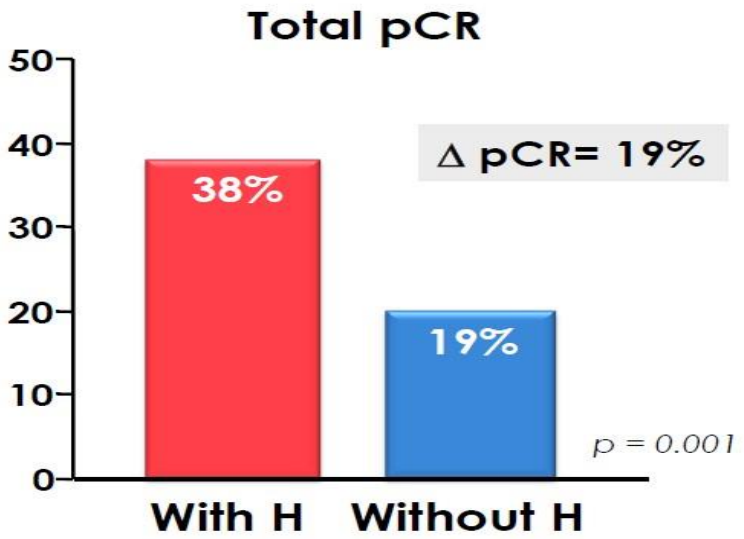
Trastuzmab bazlı tedavinin belirgin etkisinden sonra
Çalışma erken sonlandırıldı.

Buzdar AU, et al. J Clin Oncol 2005

Neoadjuvan Trastuzumab NOAH

Tekli HER2 blokaj

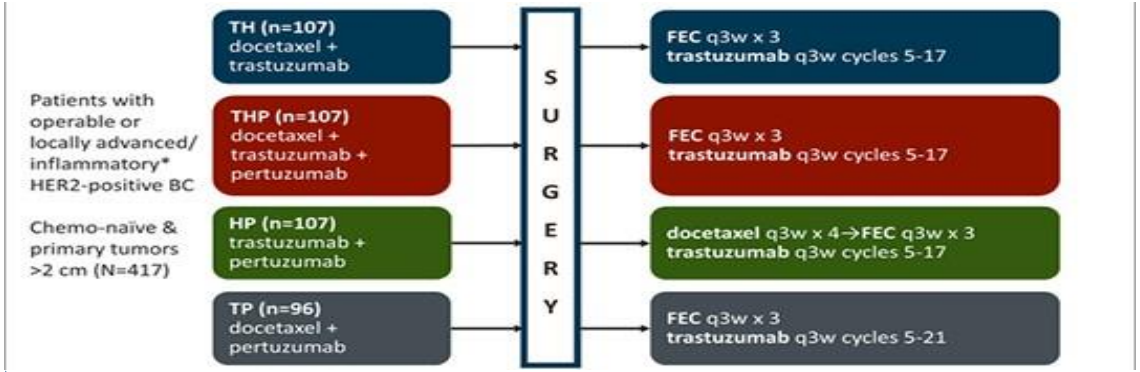




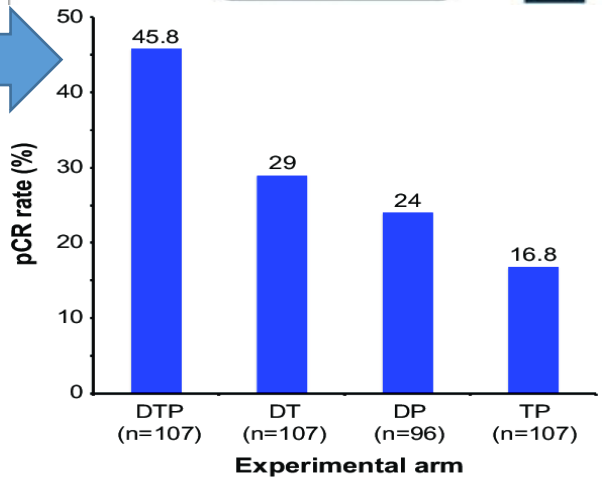
Gianni L et al, Lancet Oncol, 2010

Arttırılmış yaklaşım: **Dual Blokaj**

Pertuzumab Neosphere



İkili HER2 blokaj



Gianni L et al, Lancet Oncol, 2012
Gollamudi J et al, Cancer Management and Research, 2016

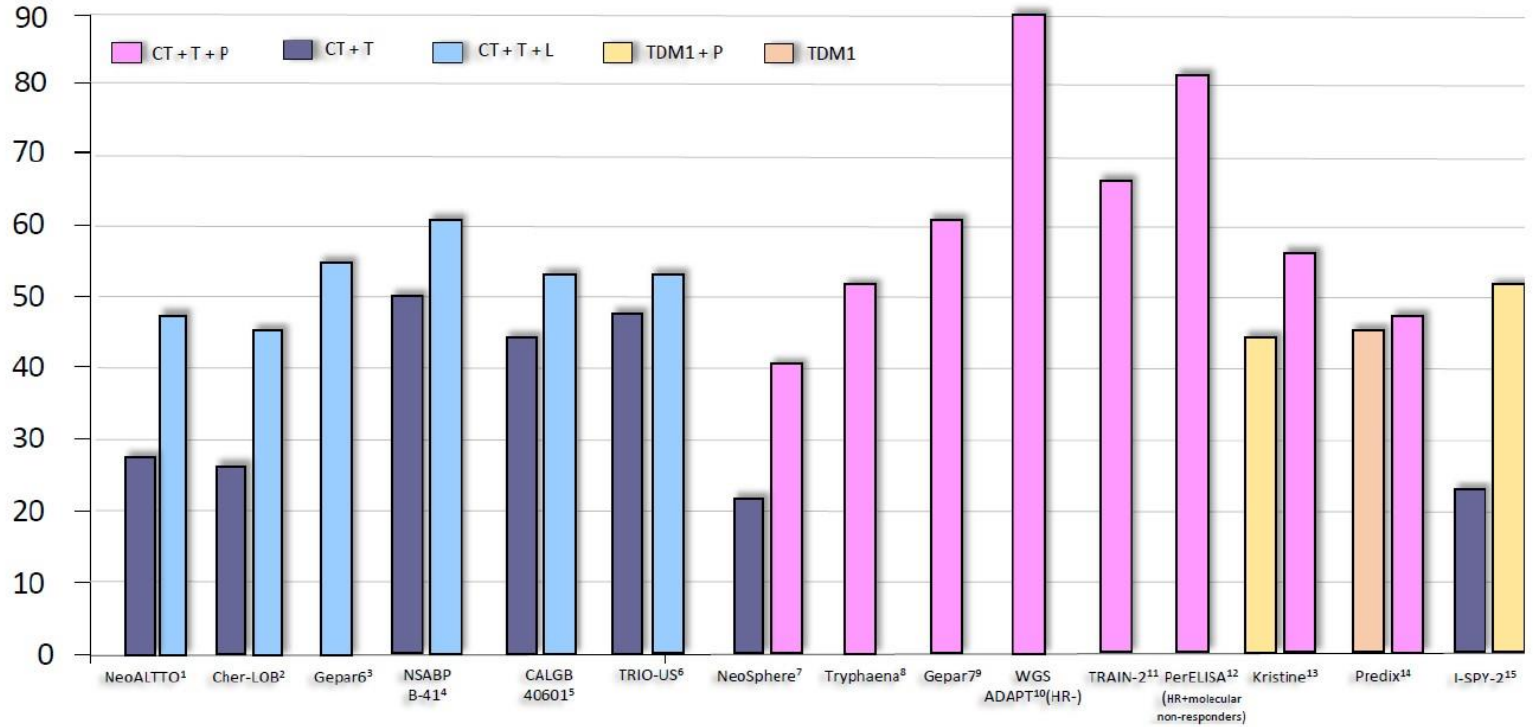
NEOADJUVANT PERTUZUMAB/TRASTUZUMAB

(FDA ONAYLI 3 REJIM 9/2013)

	NEOSPHERE[1]	TRYPHAENA[2]	TRYPHAENA[2]
Treatment	Pertuzumab, Trastuzumab, Docetaxel THP x 4 FEC x 3 post-op)	Docetaxel/Carbo/ Trastuzumab/ Pertuzumab TCHP x 6	FEC x 3 → THP x 3
N	107	77	75
ypT0/is ypN0 (%)	39.3	63.6	54.6

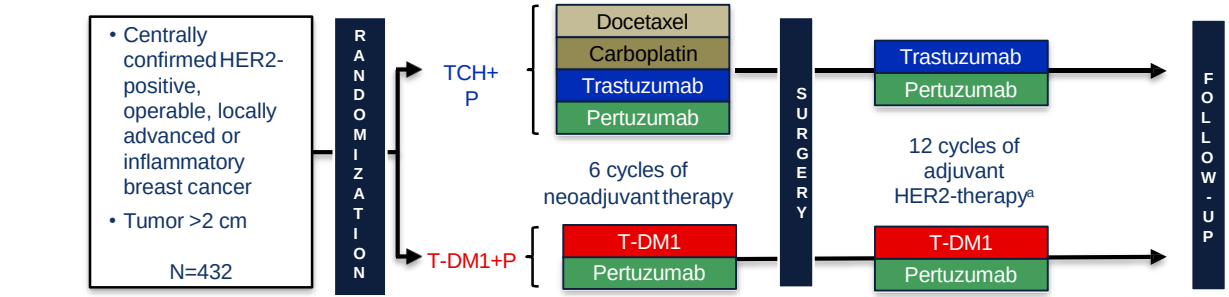
1. Gianni L, et al. Lancet Oncol. 2012
2. Schneeweiss A, et al. Ann Oncol. 2013

ARTTIRILMIS YAKLASIM: DUAL BLOKAJ, pCR



1. Baselga J. Lancet 2012; 2. Guarneri V. J Clin Oncol 2012; 3. von Minckwitz. Lancet Oncol 2014; 4. Robidoux A. Lancet Oncol 2013; 5. Carey L .ASCO 2013; 6. Hurvitz S SABCS 2013 7. Gianni L . Lancet Oncol 2012; 8. Schneeweiss A . Ann Oncol 2013 ; 9 Untch M. 10. Nitz UA Ann Oncol 2017; 11. Ramshorst MS The Lancet 2018; 13. 12. Guarneri V. Ann Oncol 2019; 13. Hurvitz SA The Lancet 2017; 14. Bergh J ASCO 2019; 15. press release

T-DM1 neoadjuvanda yeri?
KRISTINE ÇALIŞMASI:



Neoadjuvan TCH+P daha pCR sağlıyor T-DM1+P'e göre
56% vs 44%, *P*=0.0155

[a]Adjuvant chemotherapy was permitted for any patient in the T-DM1+P arm but was recommended for those with residual disease in lymph node(s) or in the breast (>1cm) Apx 33% with residual disease received adjuvant chemotherapy

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

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

Secondary endpoints: EFS, IDFS, OS, Safety, PROs

Hurvitz S et al, ASCO 2016

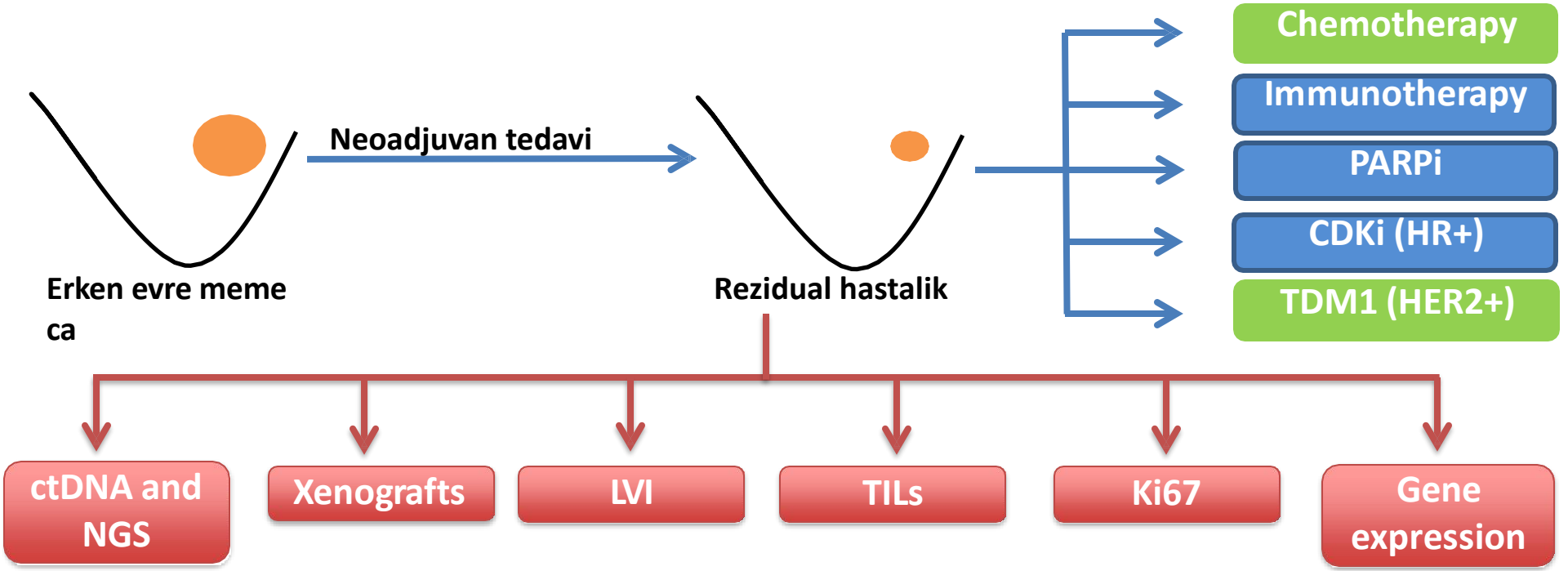
Post-neoadjuvan tedavi

REZIDU HASTALIKTA EK TEDAVI GEREKLI MI?

Preoperatif tedavi yanıtına göre DFS

Trial Name	Therapy	pCR	Non-pCR
Techno (tpCR) 3-yr DFS	EC → T + H	88%	73%
GeparQuinto GBG-44 (tpCR) 3-yr DFS	EC → T + H EC → T + L	90%	83%
NeoALTTO (breast pCR only) 3-yr EFS	L → L + T → surgery → FEC + L H → H + T → surgery → FEC + H H/L → H/L + T → surgery → FEC + H/L	86%	72%
NSABP B-41 (breast pCR only) 5-yr RFI	AC → T + H AC → T + L AC → T + H/L	90%	81%
NeoSphere (tpCR) 5-yr PFS	H + T → surgery → FEC + H H/P + T → surgery → FEC + H H/P → surgery → T → FEC + H P + T → surgery → FEC + H	85%	76%

Post-neoadjuvan tedavi



Caparica R et al, Ther adv Med Oncol 2019

Post-neoadjuvant: TDM1
KATHERINE

- Erken evre HER2+ meme ca
- Pertuzumab kullanimina izin

- Neoadj Kemo+Trastuzumab sonrasi rezidu hastalik

R
1:1

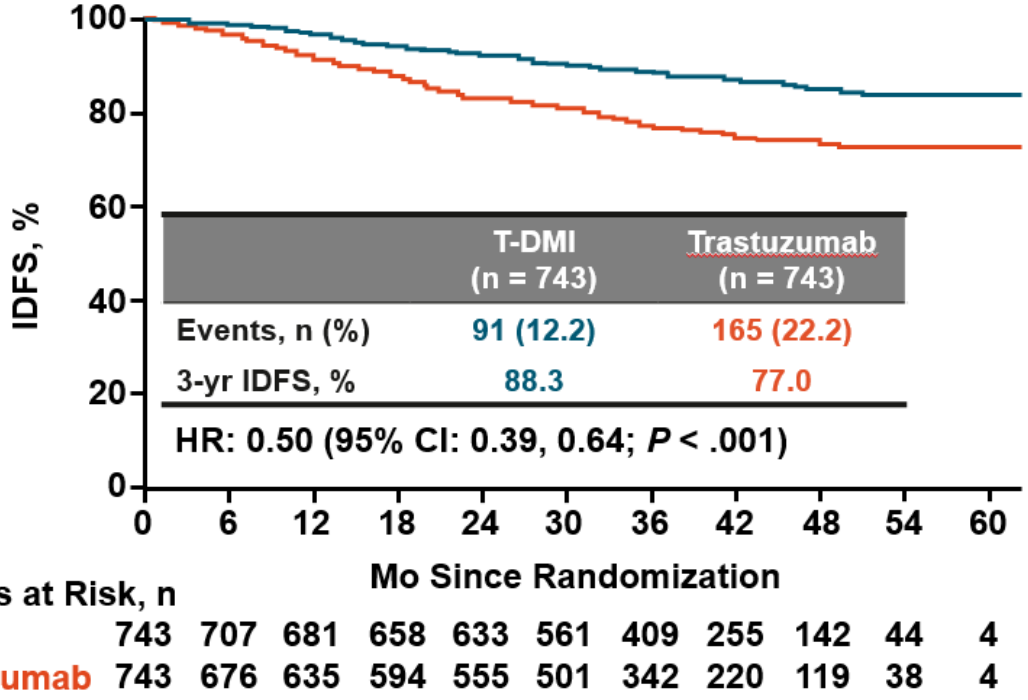
N=1,486

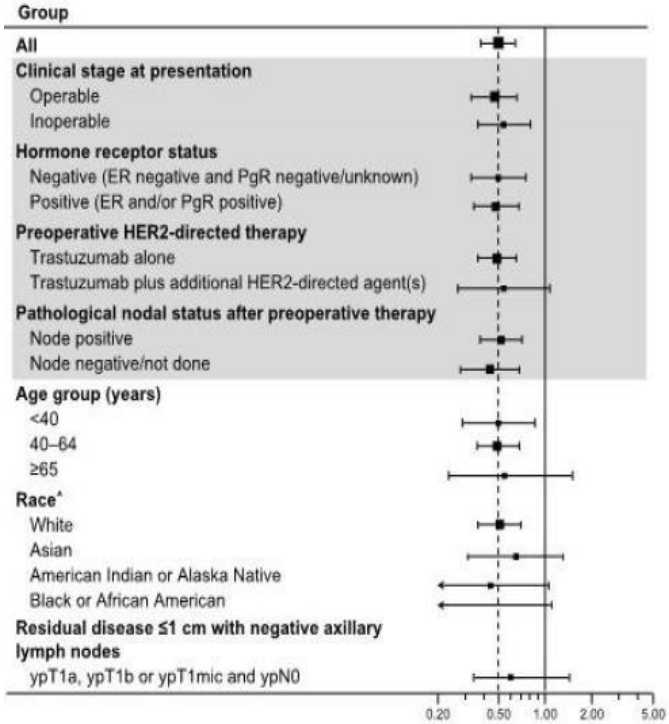
T-DM1
3.6mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

RT ve endokrin tedavi klavuzlara uygun olarak verilmis___

NEOADJUVAN TEDAVİYE YANIT YÜKSEK RiSKLİ HASTA GRUBUNU BELİRLİYOR: (KATHERINE)





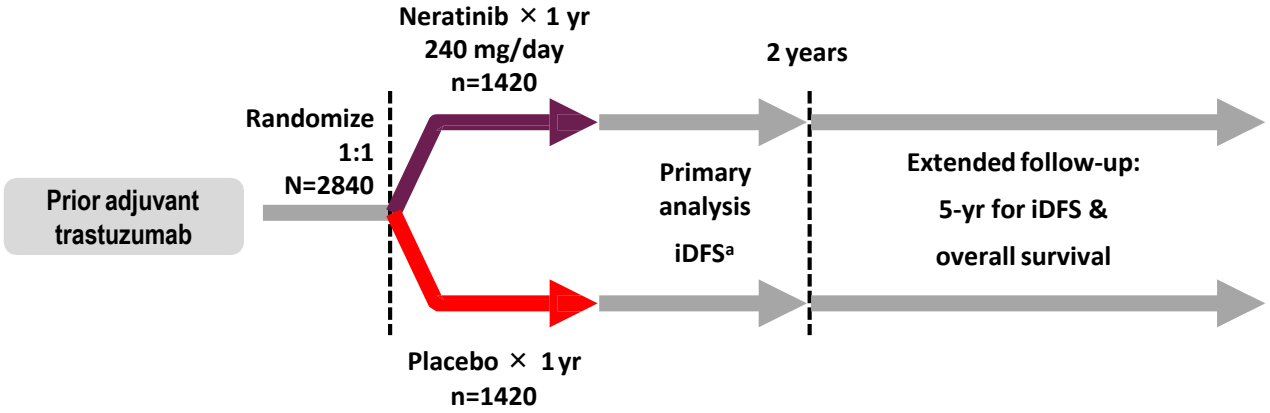
CNS events: *5.9% vs †4.3%.

Geyer C, et al. SABCS 2018
von Minckwitz G, et al. *N Engl J Med.* 2019

KATHERINE: Sorular.. Sorular..

- **Eğer T-DM1 H-P ile karşılaştırılsaydı aynı yanıtlar alınır mıydı?**
- **Dual HER2 alan hastalarda durum ne olurdu?**
- ~% 20 hasta dual HER2 aldı, onlarda da etkin..
- **Optimal süre ne olmalı?**
- ~%71% hasta 14 kürü tamamlamış, %18 yan etki nedeniyle devam edememiş.

EXTENET Çalışması: Neratinib



Primary endpoint: invasive disease-free survival (iDFS)[a]

Secondary endpoints: overall survival, DFS-DCIS, distant DFS, time to distant recurrence, CNS metastases, safety,

Stratification: nodes 0, 1-3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

Study blinded: Until primary analysis; OS remains blinded

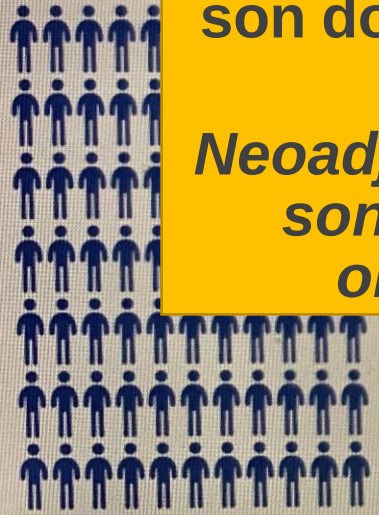
Neratinib for Early-Stage HER2-Positive Breast Cancer

International, Randomized, Phase 3 ExteNET Trial

Intention-to-treat population

2840 patients

HER2+ early-[illegible] cancer after [illegible]



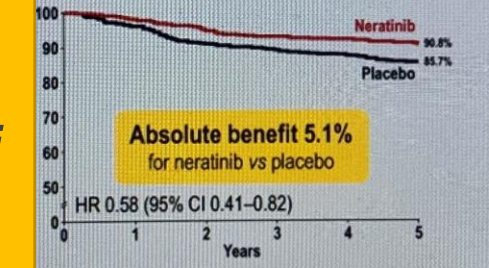
Overall survival at 8 years' follow-up

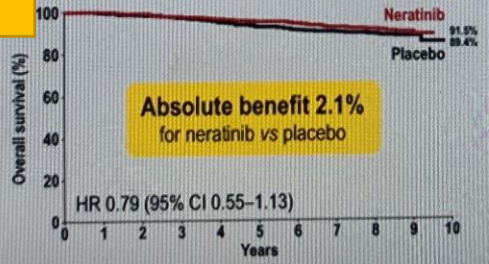
HR+, trastuzumabin son dozundan< 1y ve *Neoadjuvan tedavi sonrasi pCR olmamis*

HER2+/HR+ early-stage breast cancer within 1 year of prior trastuzumab*

1334 patients

[illegible]/HR+ early-stage breast cancer [illegible] year of prior trastuzumab

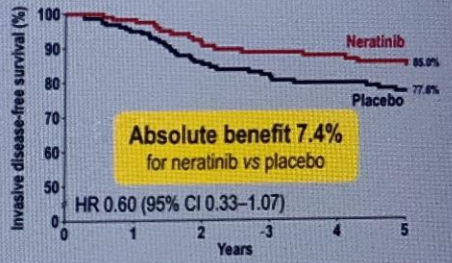


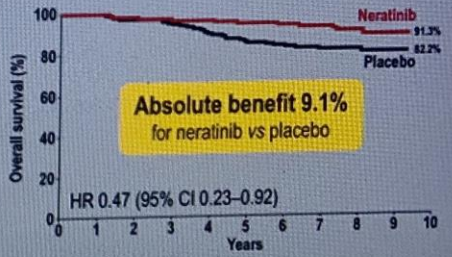


Patients with residual disease after neoadjuvant therapy

295 patients

HER2+/HR+ early-stage breast cancer within 1 year of prior trastuzumab with residual disease after neoadjuvant therapy





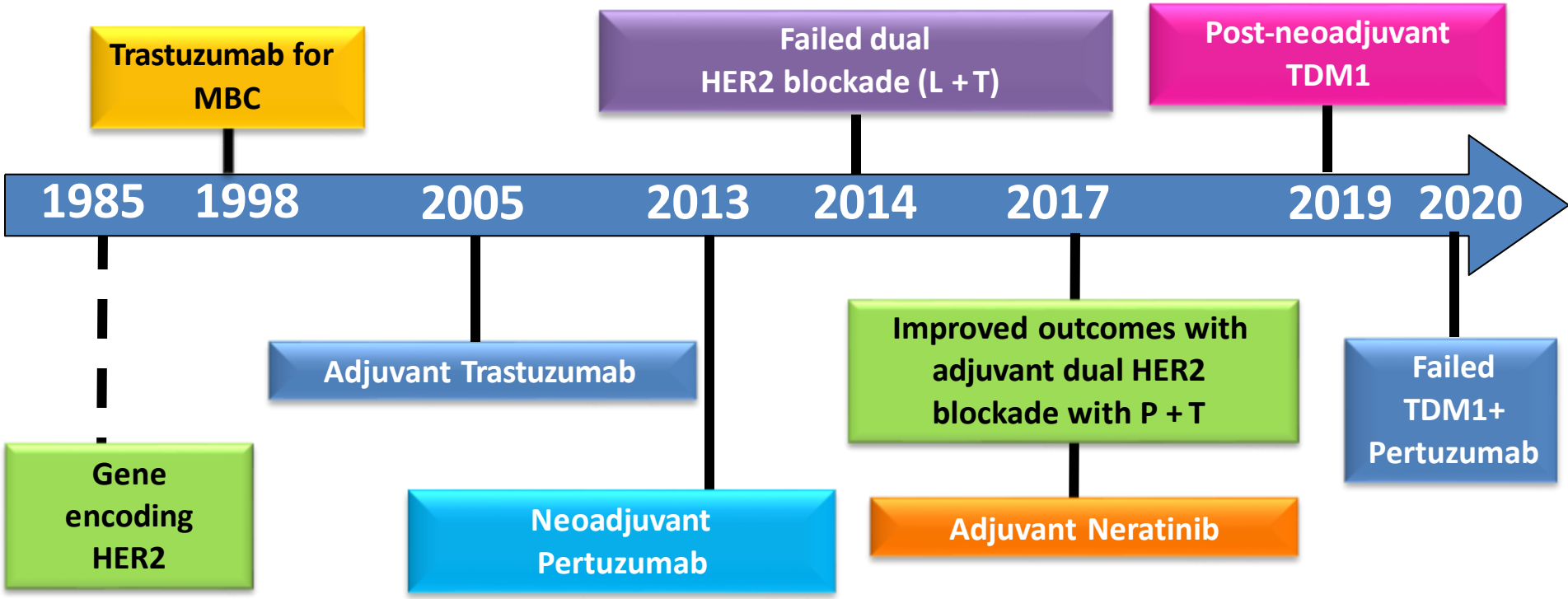
*According to labelling in the European Union and other countries

Ne zaman neratinib düşünülebilir?

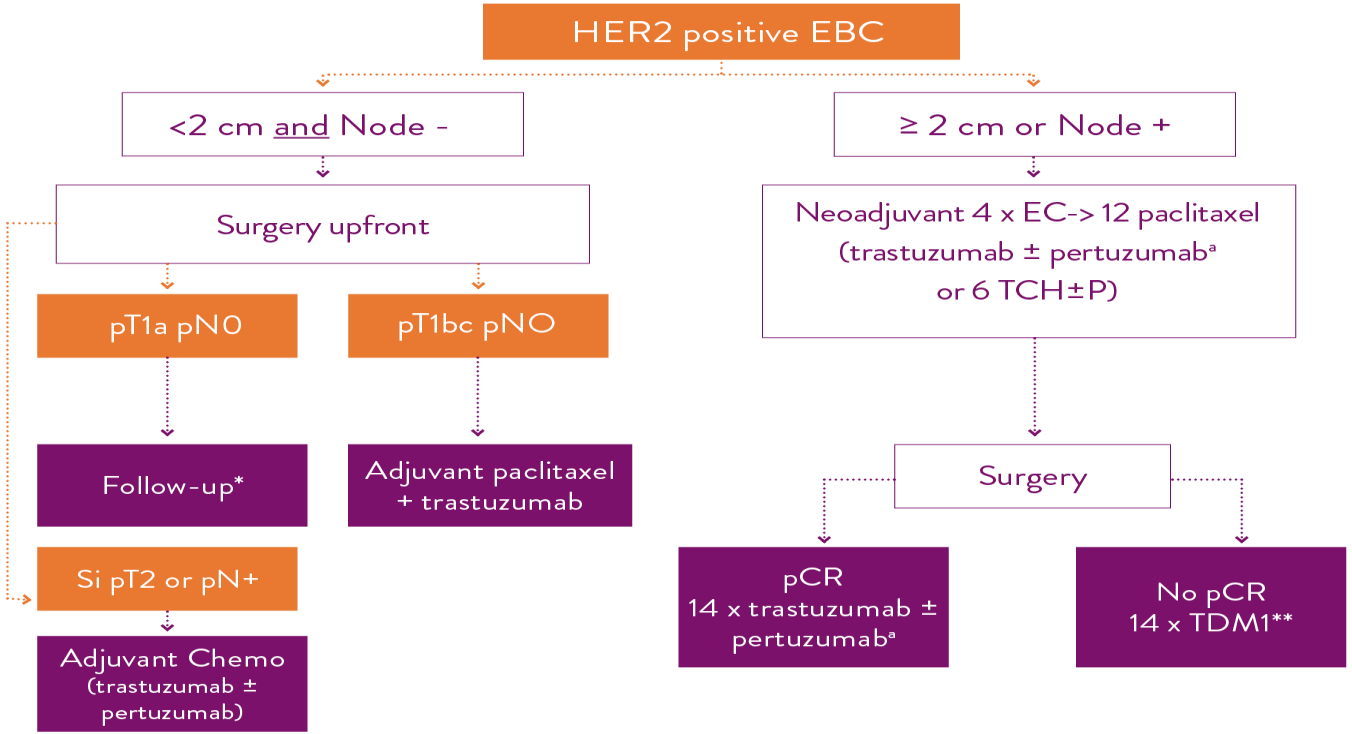
- Yarar genellikle yüksek riskli rezidual hastalığı olan HR+ HER+
- Hasta daha önce pertuzumab yada TDM1 almışa yararı olur mu?

- Toksisitesi unutulmamalı (diyare ~40% greyd 3/4)

HER2-pozitif Meme Kanserinde :



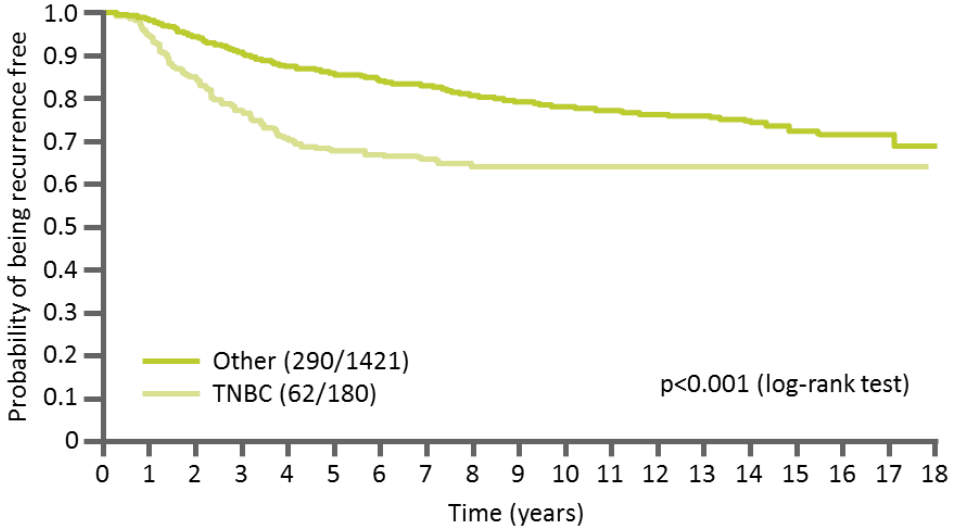
HER2-positive early breast cancer in **2020** Expert Opinion



* adjuvant therapy may be considered in selected cases (e.g. 4-5 mm and very young patients). ** TDM1 is not yet approved in Belgium.
[a] Pertuzumab is reimbursed in Belgium for node-positive patients only.
Endocrine therapy for all hormone positive receptor tumors.

TNBC

TNBC nüks riski



Results from a study of 1601 patients with breast cancer (180 with TNBC) diagnosed between January 1987 and December 1997 at Women's College Hospital in Toronto

In patients treated with ACT, invasive-disease events were experienced by:[2]

HER2−/HR+	TNBC
7.8%	10.6%
(n=110/1408)	(n=69/654)

The studies included in this analysis had follow-up times of 6.3 years, 4.8 years, 2.2 years, and 3.3 years

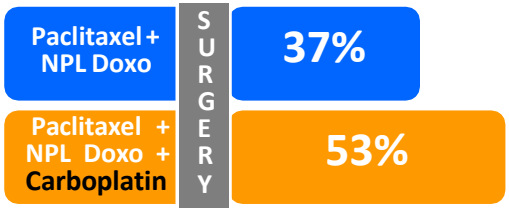
ACT, doxorubicin + cyclophosphamide + taxane; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer

1. Dent, et al. Clin Cancer Res 2007; 2. Blum, et al. J Clin Oncol 2017

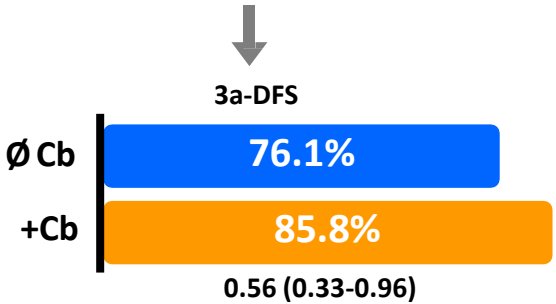
Neoadjuvan Carboplatin – Evet mi Hayır mı?

Carboplatinsiz pCR % 35
Carboplatinli pCR >% 50%
DFS /EFS etkisi?

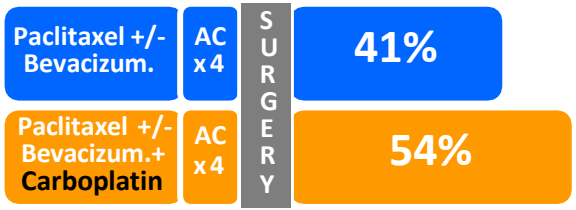
GeparSixto



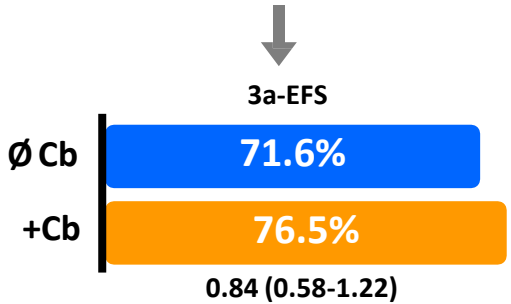
Paclitaxel 80 mg/m² q1w x18 + NPLD 20 mg/m² q1w x18 + Carboplatin AUC 1.5 q1w



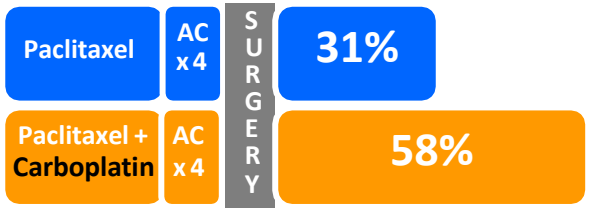
CALGB 40603



Paclitaxel 80 mg/m² q1w x 12 + Carboplatin AUC 6 q3w x 4



BrighTNess

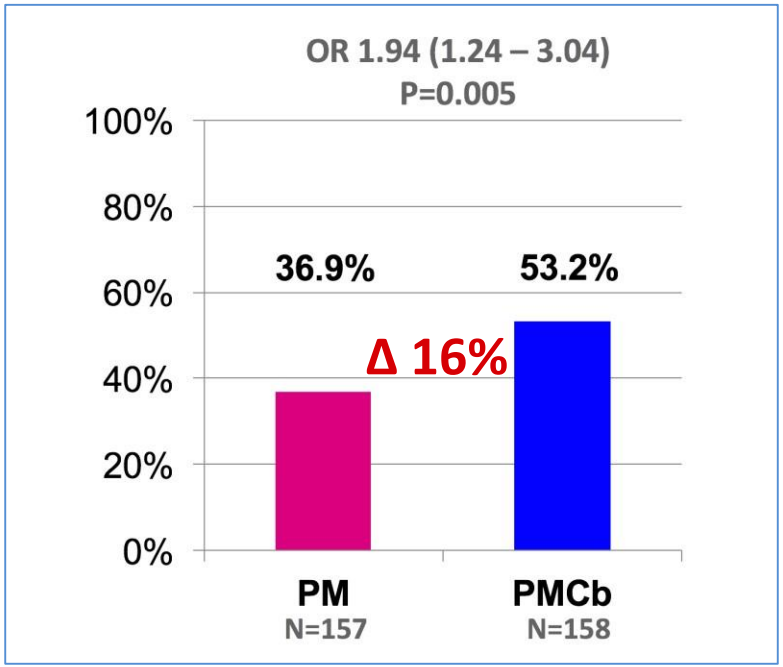


Paclitaxel 80 mg/m² q1w x 12 + Carboplatin AUC 6 q3w x 4

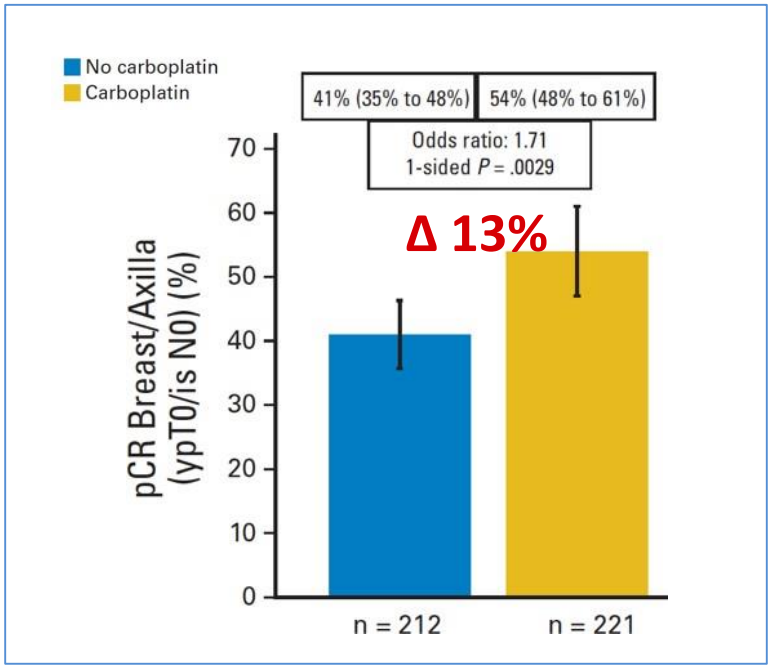
von Minckwitz G, SABCS 2015. #S2-04, von Minckwitz G. Lancet Oncol. 2014; Sikov, JCO 2015, Sikov, SABCS 2015 S2-05; Loibl, S, et al. Lancet Oncol 2018.

carboplatin .. TNBC

GeparSixto (G6)



CALGB 40603 (Alliance)

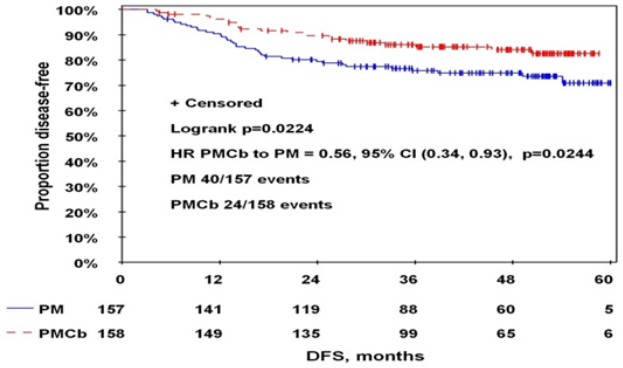


Von Minckwitz G et al. Lancet Oncol 2014

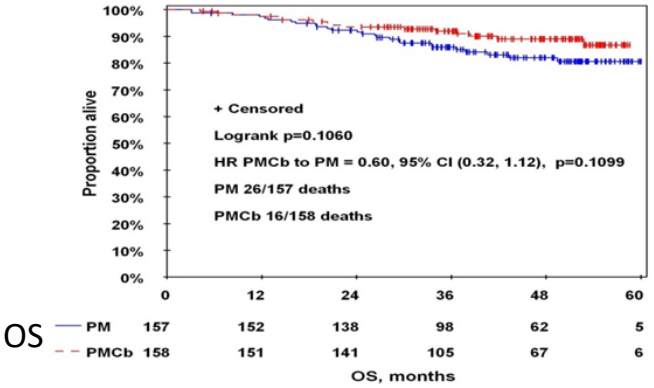
Sikov et al., J Clin Oncol. 2014 Aug 4

Carbo eklenmesi sağ kalıma etkili mi?

GeparSixto

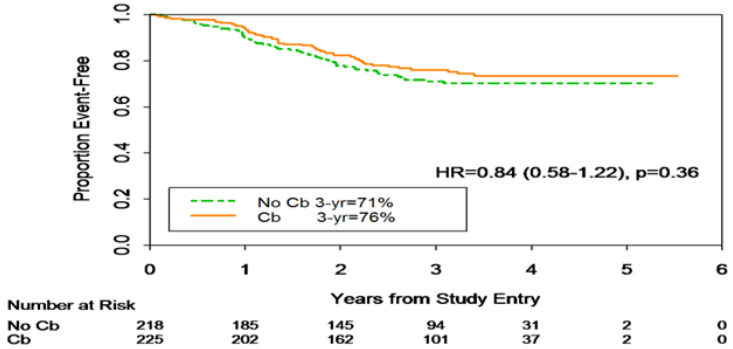


DFS



OS

CALGB 40603



Sikov et al. SABCS 2015

Loibl S et al. Annals Oncol 2018

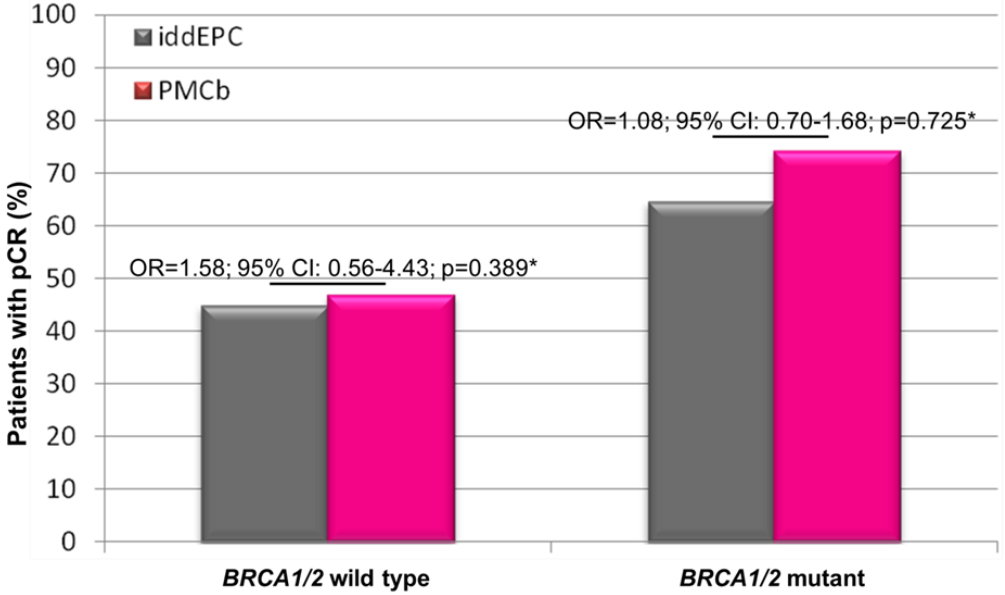
GeparSixto: PCR GBRCA durumu ve carboplatin kullanimina gore

Type of Treatment	pCR[a] Yes	pCR[a] No	Mutant vs Wild-type *BRCA* OR (95% CI)	Mutant vs Wild-type *BRCA* *P* Value	pCR[b] Yes	pCR[b] No	Mutant vs Wild-type *BRCA* OR (95% CI)	Mutant vs Wild-type *BRCA* *P* Value
Noncarboplatin arm, No. (%)								
Overall (n = 145)	60 (41.4)	85 (58.6)			52 (35.9)	93 (64.1)		
Mutant (n = 24)	16 (66.7)	8 (33.3)	3.50 (1.39-8.84)	.008	12 (50.0)	12 (50.0)	2.03 (0.84-4.91)	.12
Wild-type (n = 121)	44 (36.4)	77 (63.6)			40 (33.1)	81 (66.9)		
Carboplatin arm, No. (%)								
Overall (n = 146)	83 (56.8)	63 (43.2)			77 (52.7)	69 (47.3)		
Mutant (n = 26)	17 (65.4)	9 (34.6)	1.55 (0.64-3.74)	.33	16 (61.5)	10 (38.5)	1.55 (0.65-3.68)	.32
Wild-type (n = 120)	66 (55.0)	54 (45.0)			61 (50.8)	59 (49.2)		

Type of Treatment in Cb vs NonCb Arm	pCR[a] OR (95% CI)	pCR[a] *P* Value	pCR[b] OR (95% CI)	pCR[b] *P* Value
Cb vs nonCb, overall	1.87 (1.17-2.97)	.009	2.00 (1.25-3.19)	.004
Cb vs nonCb, mutant	0.94 (0.29-3.05)	.92	1.29 (0.46-3.56)	.63
Cb vs nonCb, wild-type	2.14 (1.28-3.58)	.004	2.23 (1.31-3.80)	.003

Hahnen E et al. JAMA Oncol 2017; 3, 1378–1385

IDDDEPC VS PLATIN içeren kemo: PCR GBRCA mutant vs wild tip

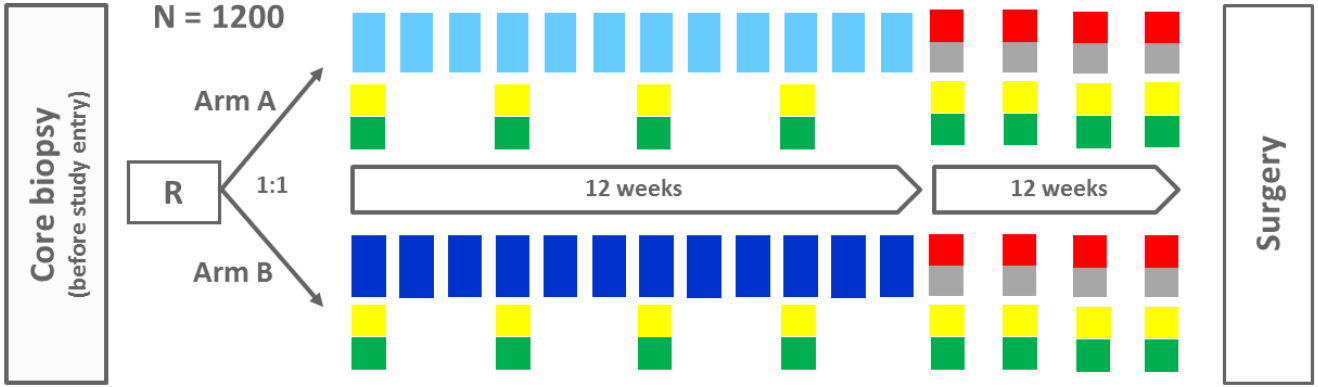


g*BRCA* predicts higher pCR

g*BRCA* does not predict higher benefit from platinum in eBC

Esther Pohl-Rescigno et al. JAMA Oncol 2020

GEPARSEPTO: Nab-paklitaxel



STRATIFICATION FACTORS:

- HER2+/HR- vs. HER2+/HR+ vs. HER2-/HR- vs. HER2-/HR+
- Ki67 (≤20% vs. >20%)
- SPARC (positive vs. negative)

Paclitaxel
80 mg/m^2 weekly

Nab-paclitaxel 150 mg/m^2 weekly
The dose was reduced to 125 mg/m^2 after recruitment of 464 patients

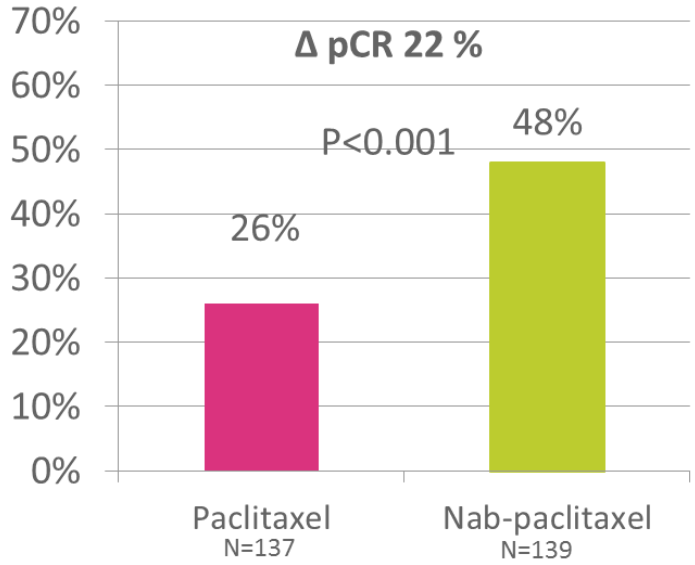
Epirubicin 90 mg/m^2
Cyclophosphamide 600 mg/m^2

HER2 positive patients:
Trastuzumab 8 mg/kg (loading dose) → 6 mg/kg
Pertuzumab 840 mg (loading dose) → 420 mg

Untch et al. Lancet Oncol 2016

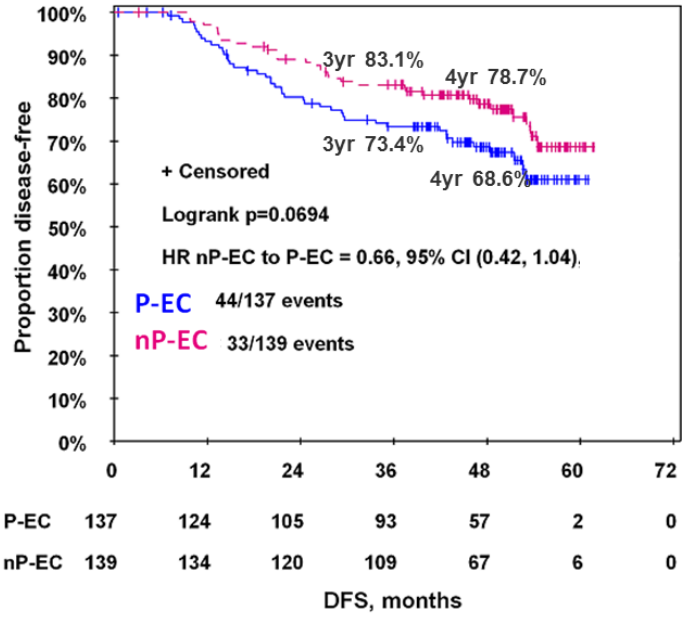
GEPARSEPTO: pCR DFS

pCR for TNBC



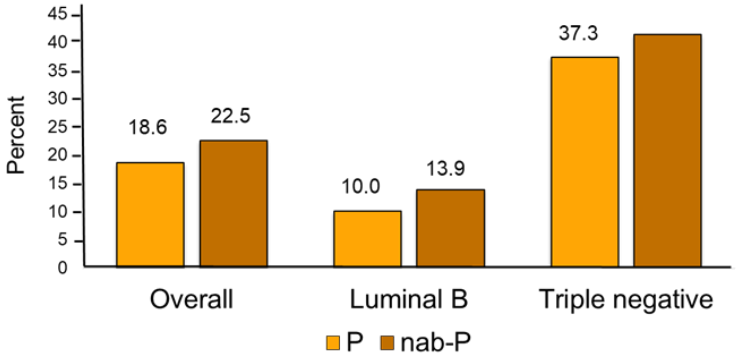
Untch et al. Lancet Oncol 2016

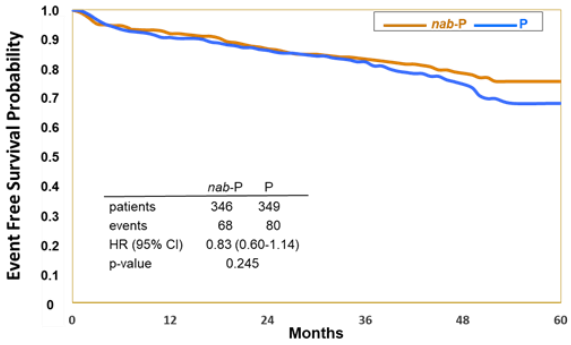
DFS in TNBC

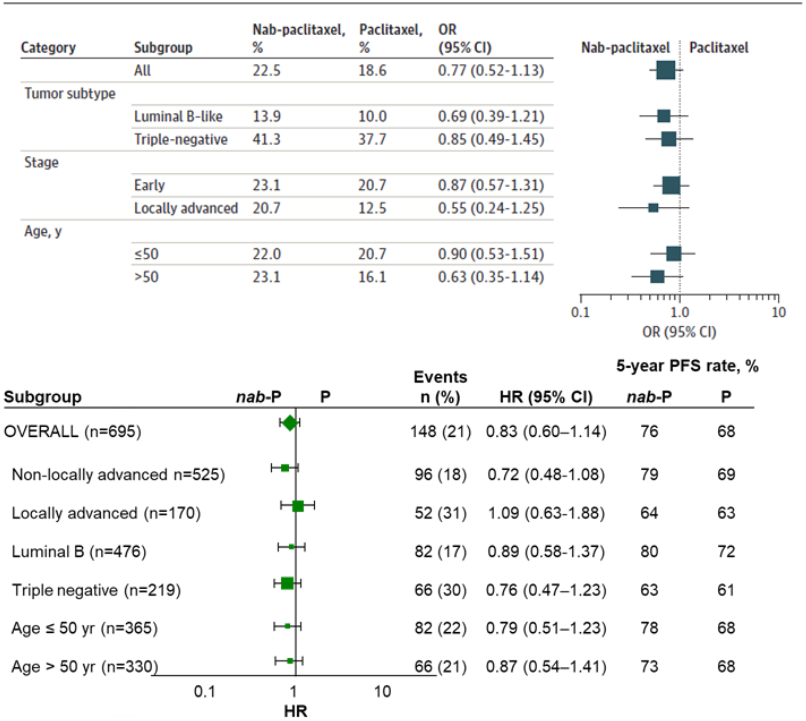


Untch et al. J Clin Oncol 2019

ETNA CALISMASI:

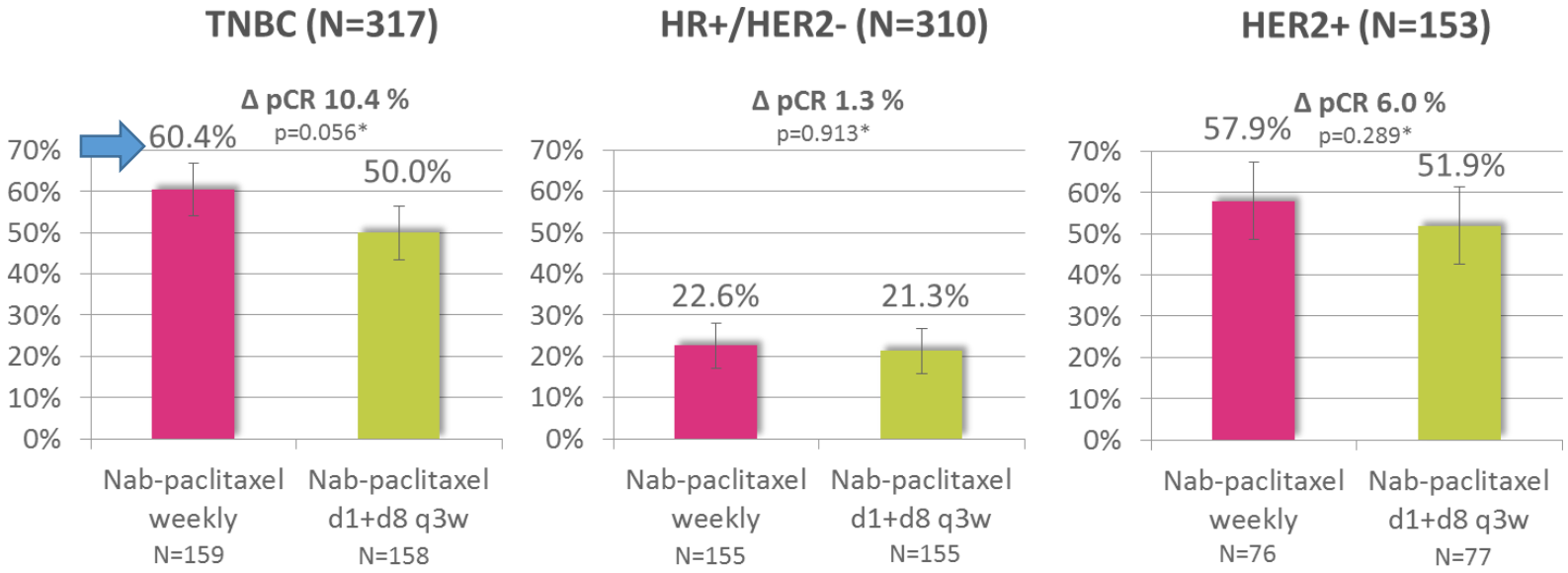






Gianni L, et al. JAMA Oncol 2018

GEPARSEPTO: Nab-paklitaxel haftalık daha etkin



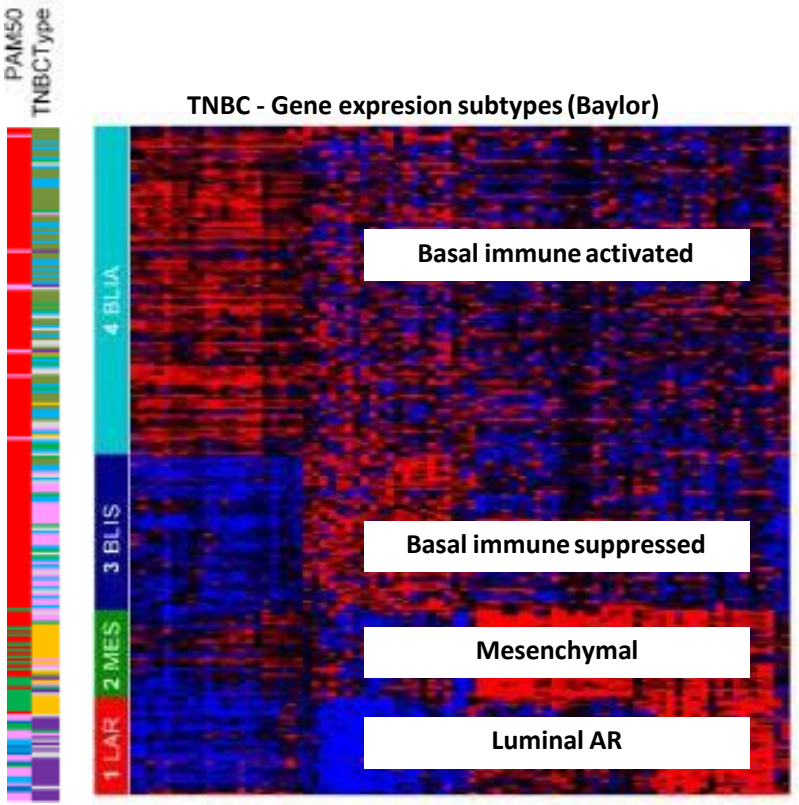
Blohmer J et al. SABCS 2019

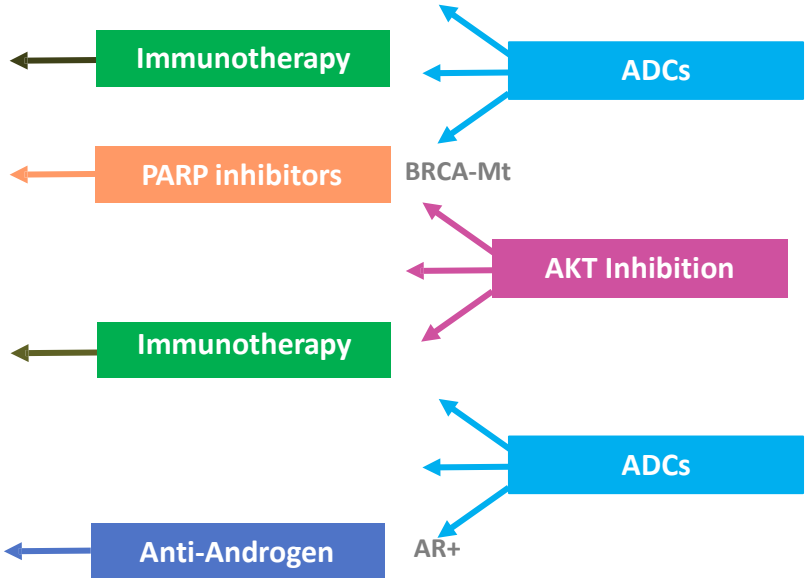
*p-value stratified test; stratified by sTILs, subtype, EC schedule and denosumab

Nab-paklitaxelle G7'da DFS ve pCR artmiş ancak ETNA çalışması negatif

Paklitaxel allerjisi olanlarda

TNBC heterojenitisine gore nasil bir strateji izlenmeli ?

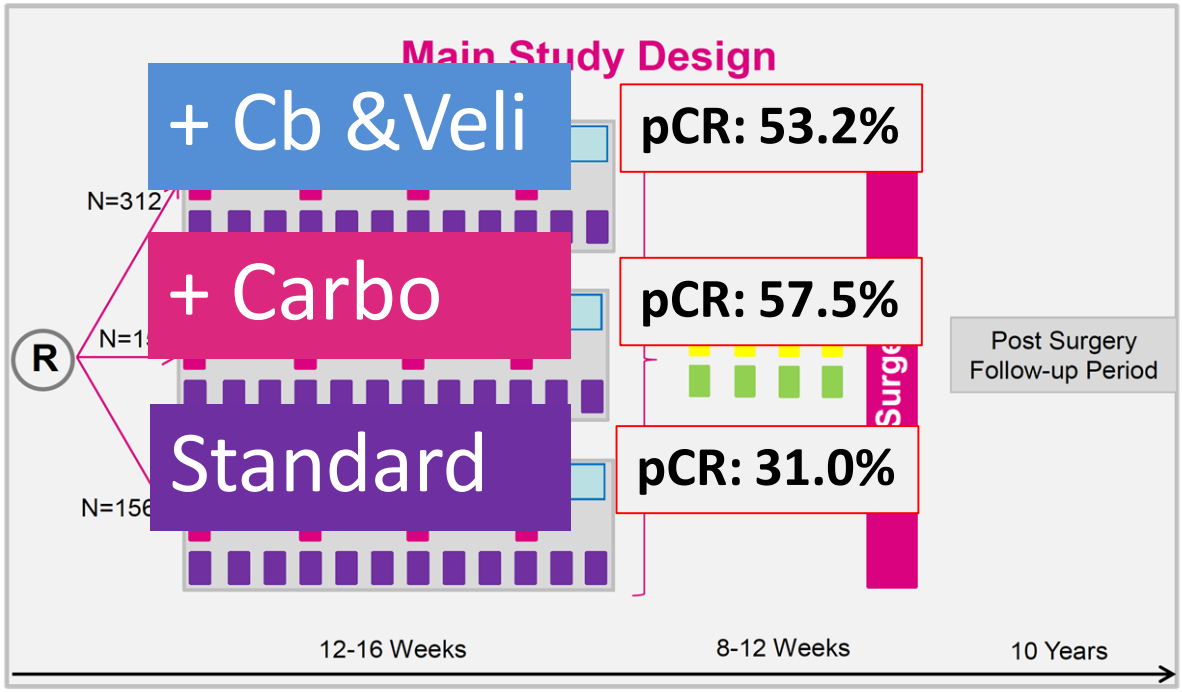




Adapted from Burstein et al, CCR 2014

NEOADJUVAN PARPİ:
BRIGHTNESS ÇALIŞMASI

TNBC
BRCA^{wt}
&
BRCA^{mt}



Veliparib or Placebo
50 mg BID, daily

Paclitaxel
80 mg/m^2 , q1w

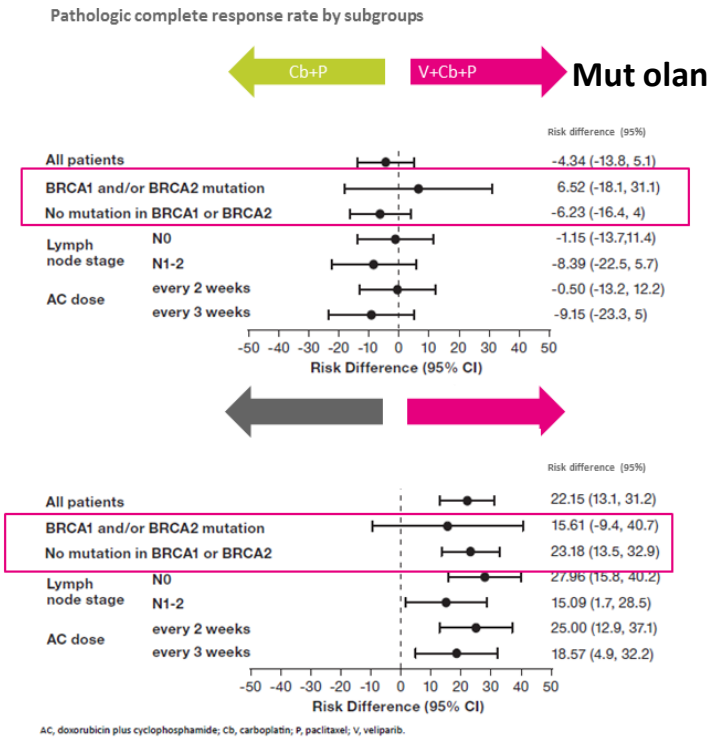
Carboplatin or Placebo
AUC 6, q3w

Doxorubicin
60 mg/m^2 q2w or q3w

Cylcophosphamide
600 mg/m^2 , q2w or q3w

Geyer CE et al., ASCO 2017 © M. Thill

NEOADJUVAN BRIGHTNESS:ETKINLIK

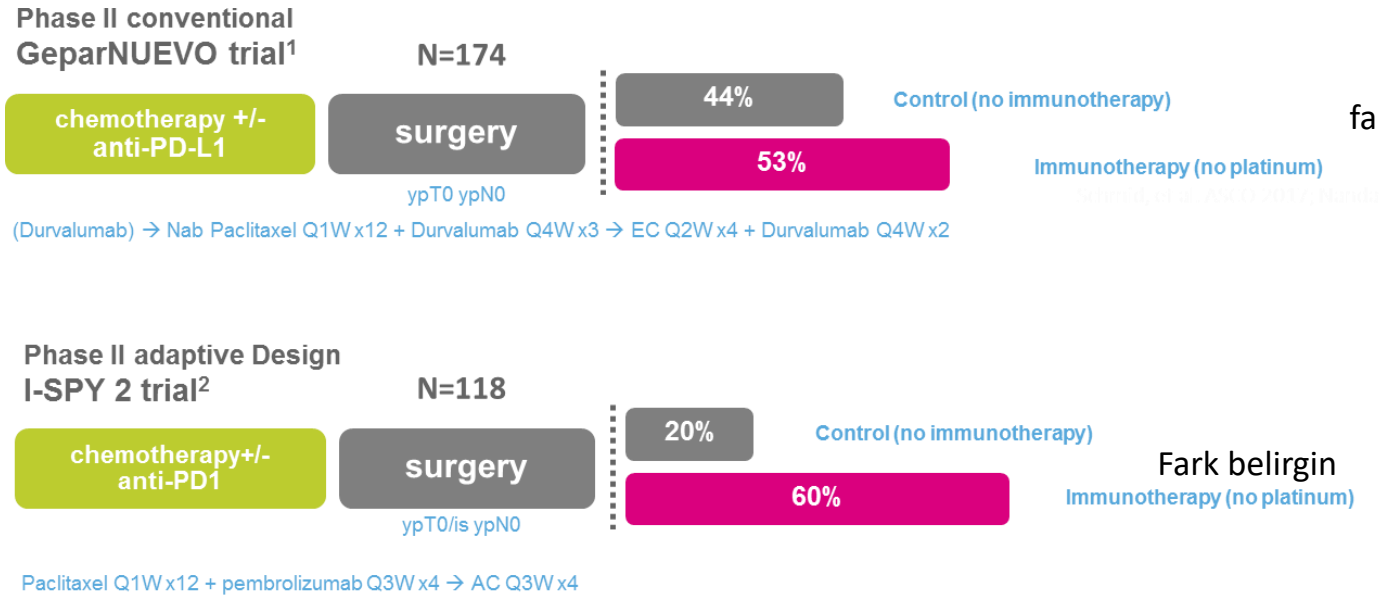


Mut olan ve olmayanlar arasinda fark yok

A/C, doxorubicin plus cyclophosphamide; Cb, carboplatin; P, paclitaxel; V, veliparib

Loibl S et al. Lancet Oncol 2018 in press

NEOADJUVAN KEMO-İMMUNOTERAPİ
Faz II calismalar



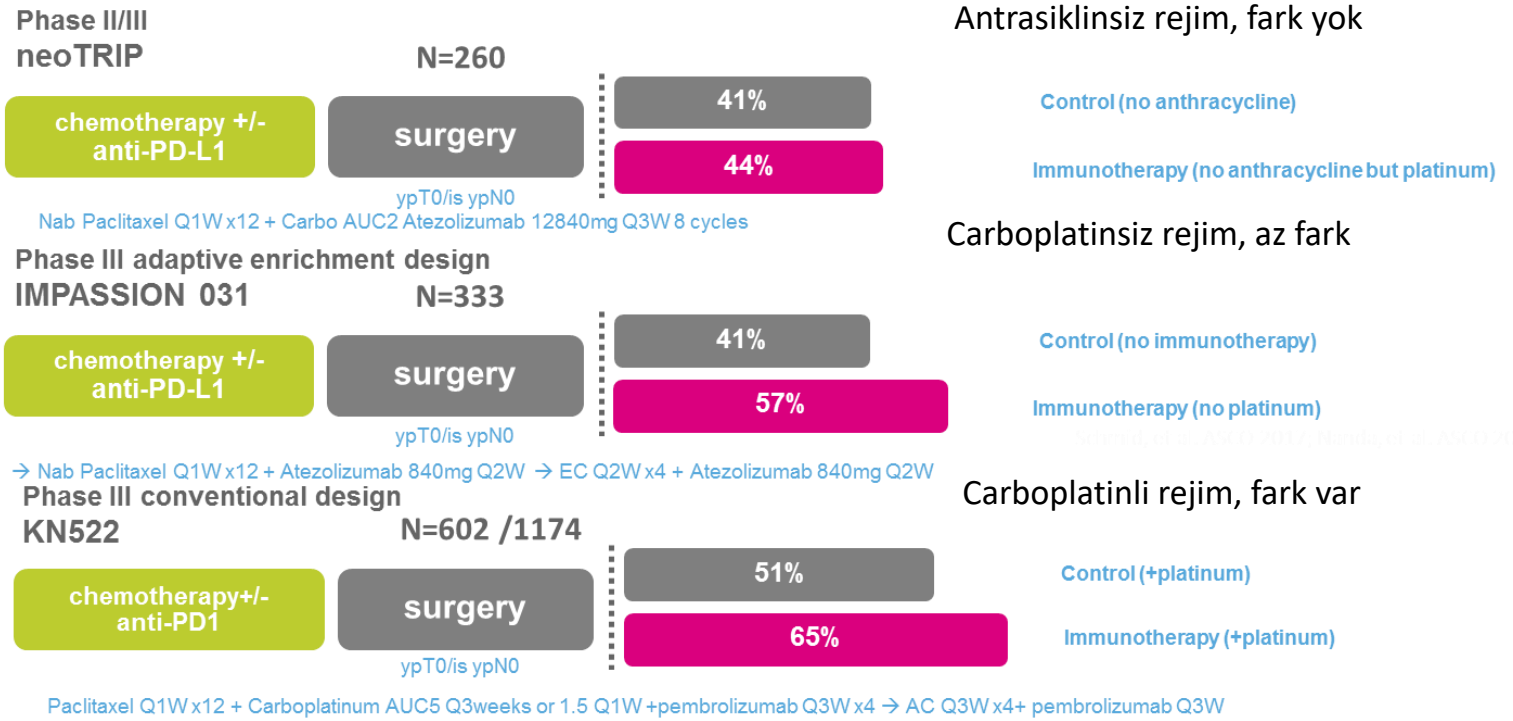
fark yok

Fark belirgin

[1]Loibl S et al. Annals Oncol 2019

[2]Nanda R et al. JAMA Oncol 2020

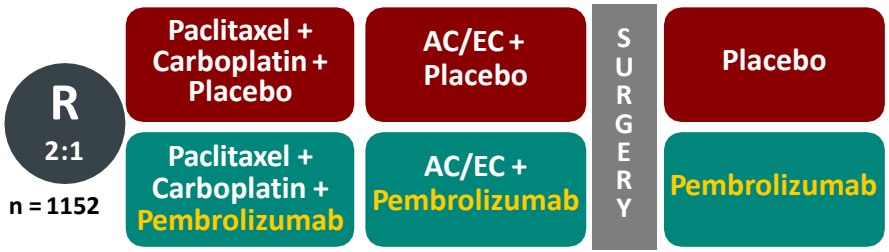
NEOADJUVAN KEMO-İMMUNOTERAPİ
Faz II/III calismalar



Gianni L et al. SABCS 2019 GS3-02 Harbeck N et al. Lancet 2020 Schmidt P et al. New Engl Journal 2019

Evre II/III TNBC Faz 3 immunoterapi çalışmaları

Keynote 522



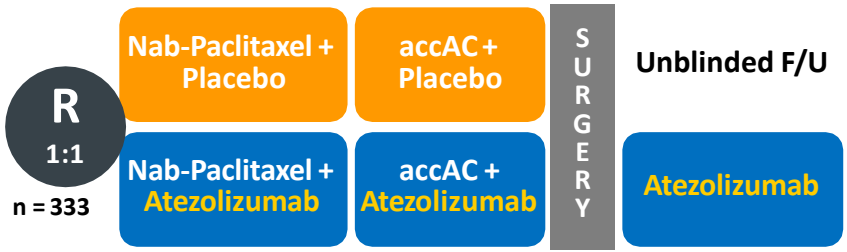
- PDL1+ (22C3 CPS1) 82%
- N+ 52%, T3/4 26%
- Carbo QW 41%

Co-primary endpoints:

- pCR (ypT0/Tis ypN0)
- Event-free Survival

Pembrolizumab: 200 mg given IV q3w
Paclitaxel: 80 mg/m² given IV qw for 12 weeks;Carboplatin: AUC5 q3w x 4 or AUC1.5 qw x 12
Doxorubicin: 60 mg/m² given IV q2w/Cyclophosphamide: 600 mg/m² given IV q2w

Impassion 031



- PDL1+ (SP142≥1%) 53%
- N+ 38% (34% Ate; 43% Pla)
- T3/4 28%

Primary endpoint:

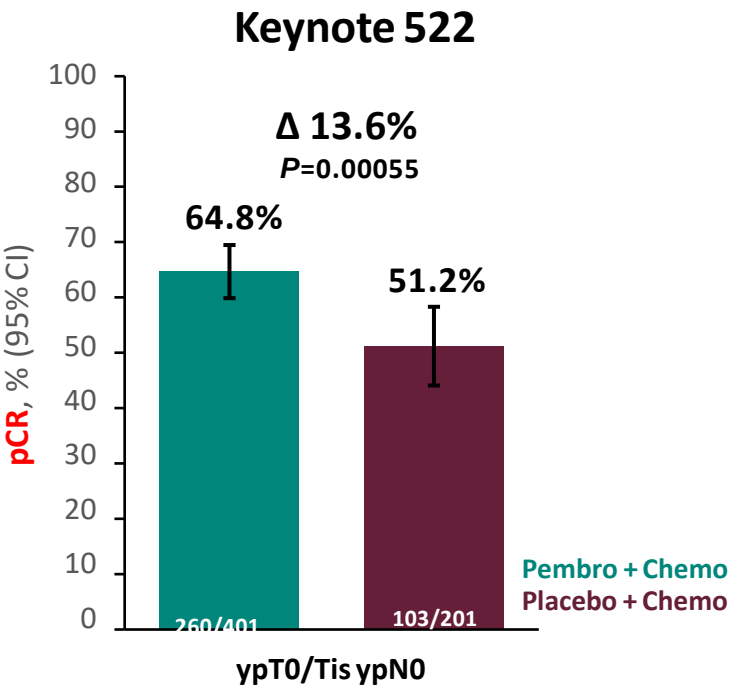
- pCR (ypT0/Tis ypN0) in ITT & PD-L1+

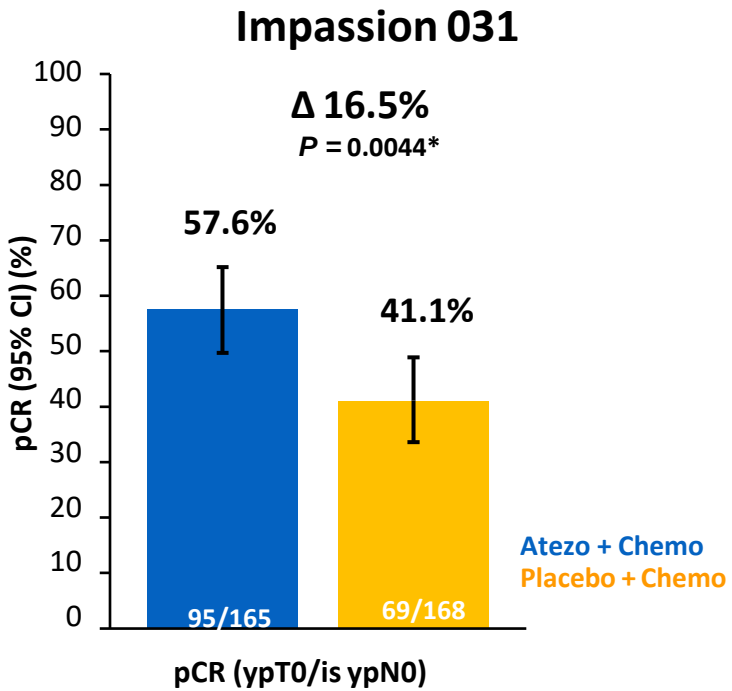
Atezolizumab: 840 mg given IV q2w (neoadjuvant); 1200 mg IV q3w x 11(adjuvant)
Nab-paclitaxel: 125 mg/m² given IV qw for 12 weeks
Doxorubicin: 60 mg/m² given IV q2w/Cyclophosphamide: 600 mg/m² given IV q2w

Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Harbeck et al, ESMO 2020

Neoadjuvant kemo-immuno TNBC: pCR

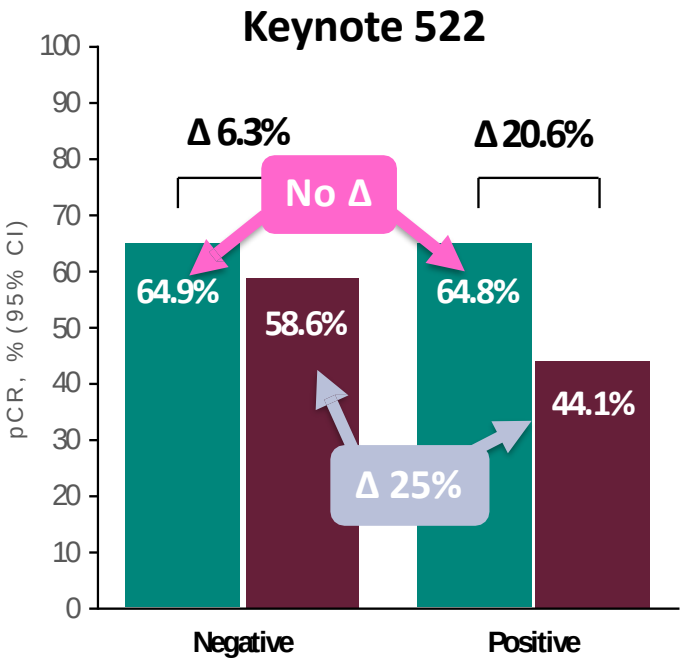
pCR (ITT Population)

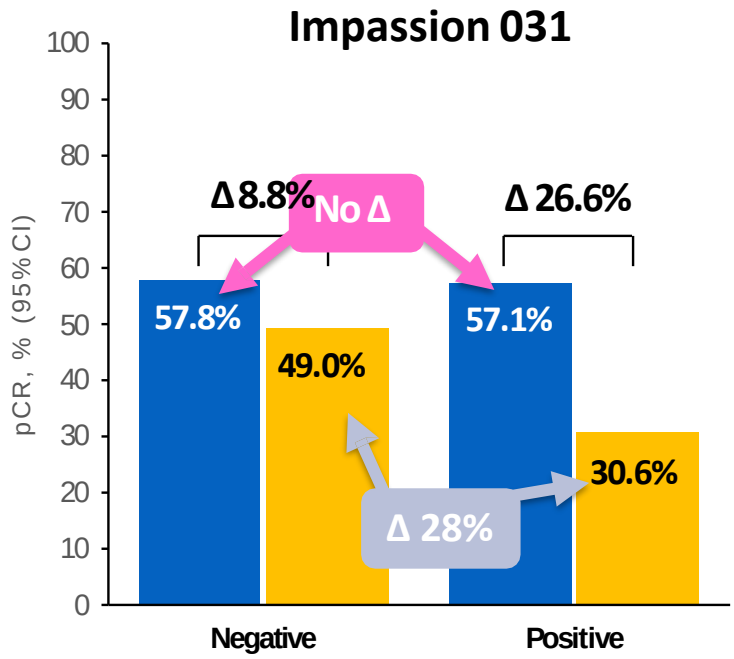




Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Harbeck et al, ESMO 2020

Nodal Durum ve pCR

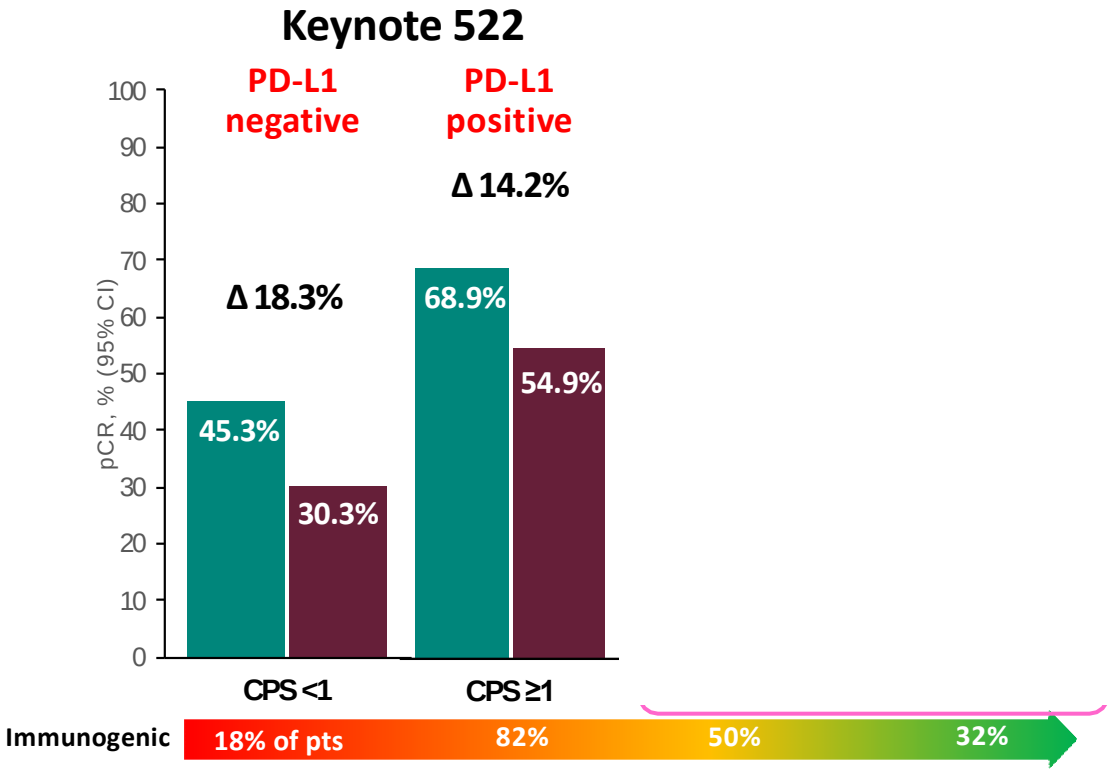


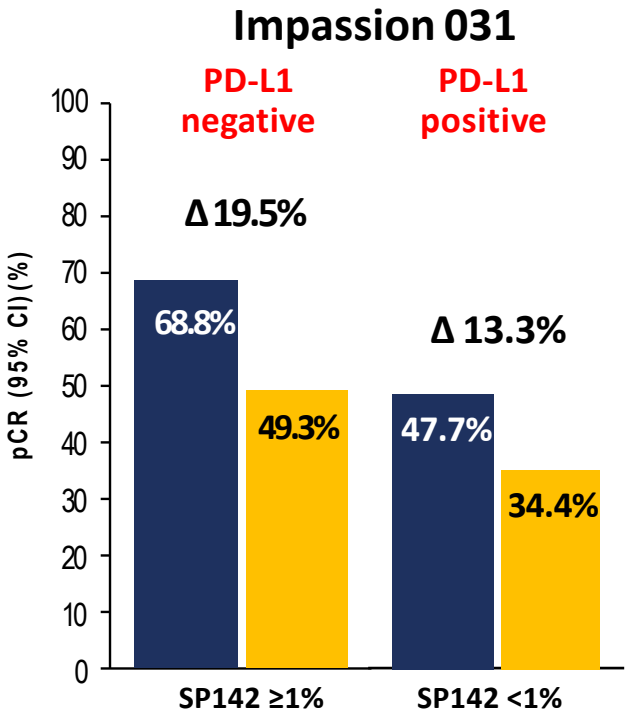


Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Harbeck et al, ESMO 2020

Neoadjuvant kemo-immuno TNBC: pCR, PD-L1 expression

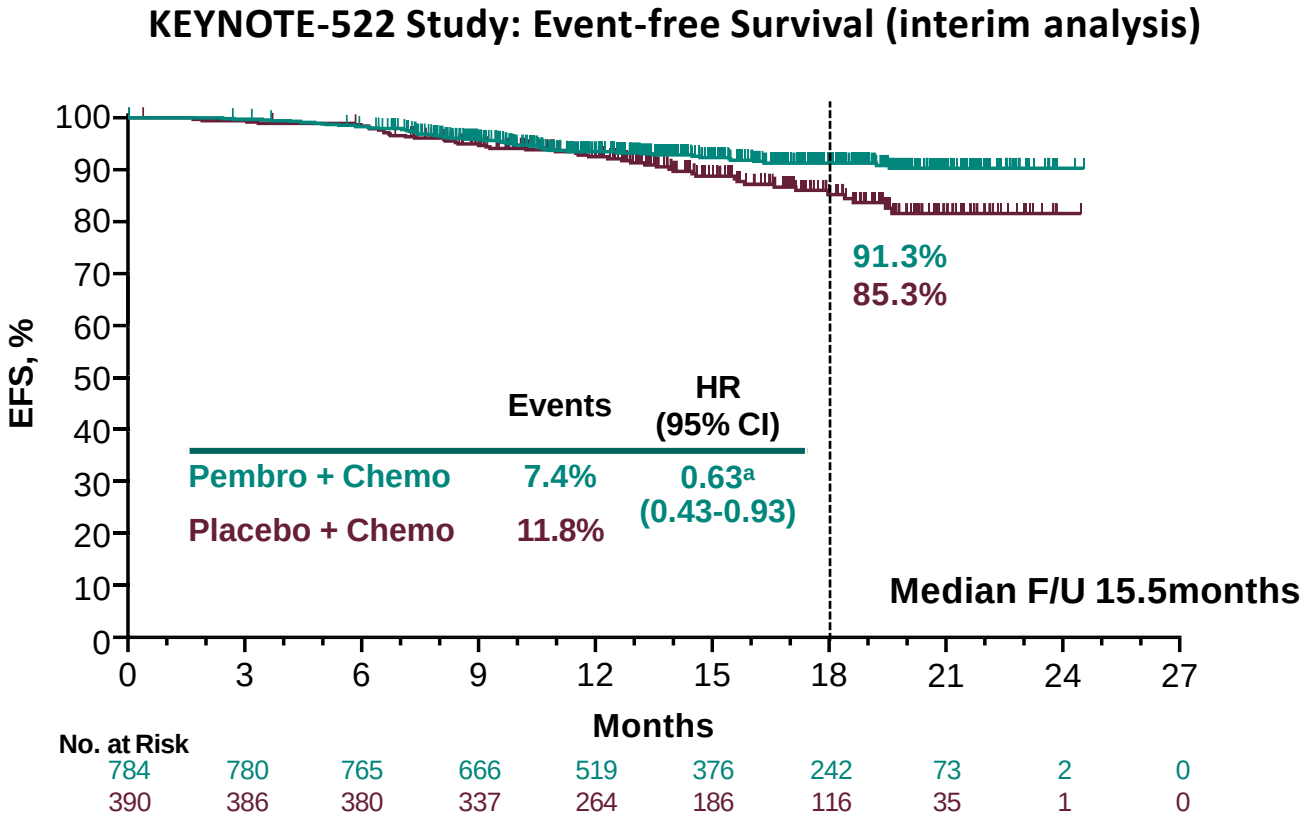
Her iki grupta da etkin ! PDL-1 bakmaya gerek yok!





Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Harbeck et al, ESMO 2020

pCR-faydası sağ kalıma yansıdı mı?



[a]Prespecified *P* value boundary of 0.000051 not reached at this first interim analysis of EFS.
Data cutoff April 24, 2019.

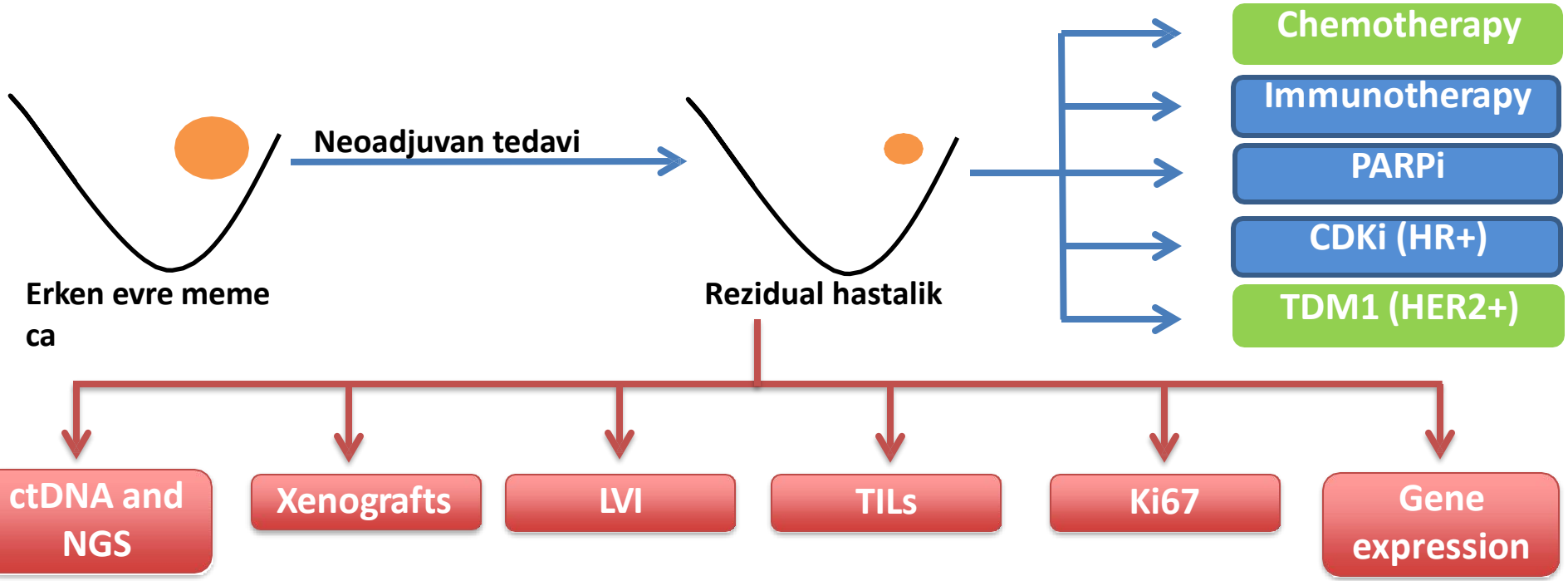
Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020

Neoadjuvant TNBC
carbo/ nab paklitaxel/ immuno TNBC

- Carboplatin pCR arttiriyor (BRCA durumundan bagimsiz)
- Nab-paklitaxel pCR'i arttiriyor gorunuyor DFS daha iyi, paklitaxel allerji varsa
- PARPi: Veliparib etkisiz
- Immunoterapi:
  - %14-17 pCR artiyor
  - pCR etkisi PDL1 durumundan bagimsiz
  - Yuksek riskli grupta muhtelen daha etkin (N+ △20-27%)
  - Takip suresi kisa (F/U o15 ay)

Post-neoadjuvan tedavi

Post-neoadjuvan tedavi



Caparica R et al, Ther adv Med Oncol 2019

Preoperatif vs Postoperatif Kemoterapi TNBC?

RCTs confirm same outcome with adjuvant/neo-adjuvant therapy (eg NSABP18)

Adjuvant Treatment

OP → Chemo

Neoadjuvant Treatment

Historically if inoperable

Chemo → OP

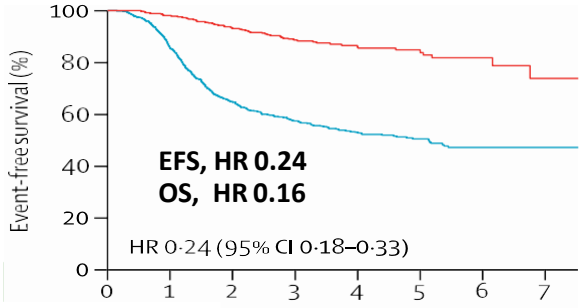
Downstaging
Facilitates less invasive surgery (BCS, SLN, TAD)

Path CR
ypT0/is ypN0

Residual Disease

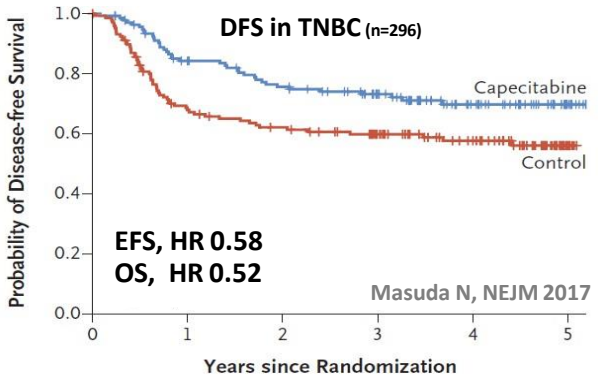
CREATE-X

Metaanalysis: pCR predictive of good outcome



Cortazar, Lancet 2014

Adjuvant Capecitabine improves outcome



HR + /HER2 -

NEOADJUVAN ENDOKRIN TEDAVI KIME ve NEDEN ?

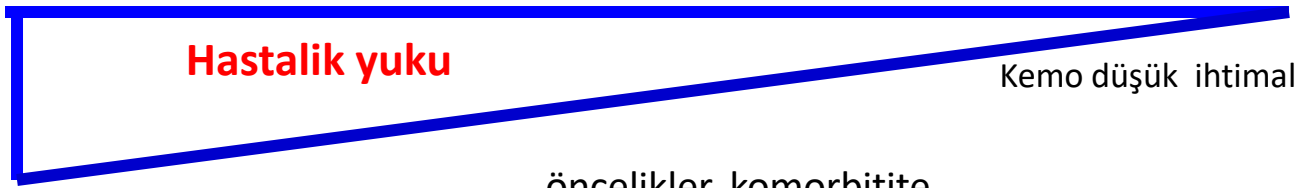
POSTMENOPOZAL

- Cerrahiye tedaviye uygun degilse (T4, N2, inflamtuar olanlar haric)
- Meme koruyucu cerrahiye ilk etapta uygun degilse
- Ko-morbitide durumunda, yasam kalitesi icin

- PREMENOPOZAL KADINLAR[illegible]IK CALISMA HARICINDE NEOADJ ENDOKRIN TEDAVI KULLA[illegible]MAMA[illegible]DIR!

Neoadjuvant kemo …. ER + grup

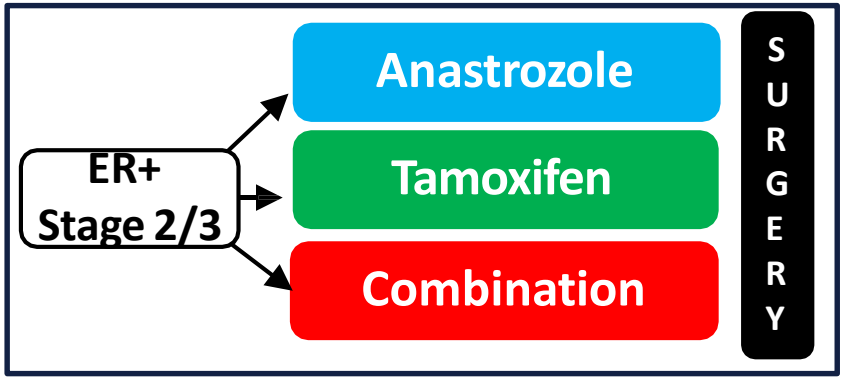
Genelde evet	**BELKI**	***Genelde Hayir***
Yuksek greyd		Dusuk greyd
Yuksek Ki67		Dusuk Ki67
Zayıf ER and PR		Kuvvetli ER and PR
Unfavorable signature		Favorable signature
Luminal B		Luminal A
Erken nüks riski		Geç nüks riski



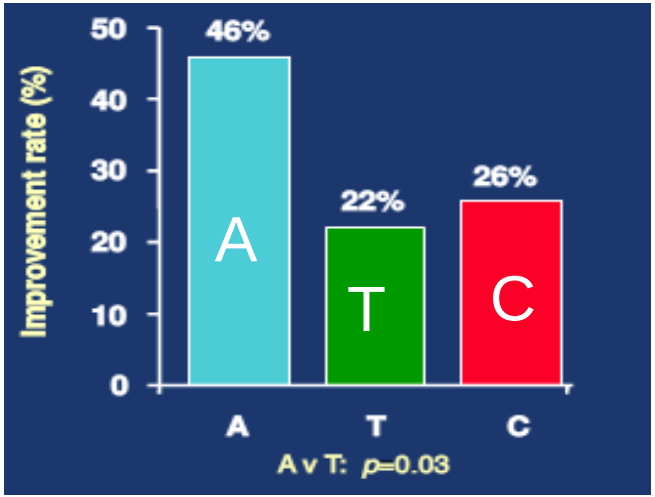
Neoadjuvan Endokrin Tedavi

Meme koruyucu cerrahi (MKC) oranını arttirir

IMPACT



MKC imkanı



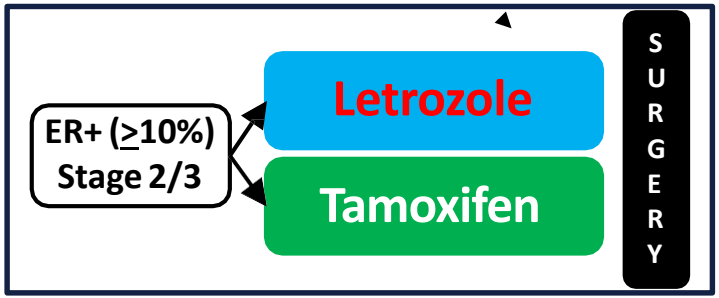
Başlangıçta 124 hasta (330 hasta içinde) MKC için uygun değildi.

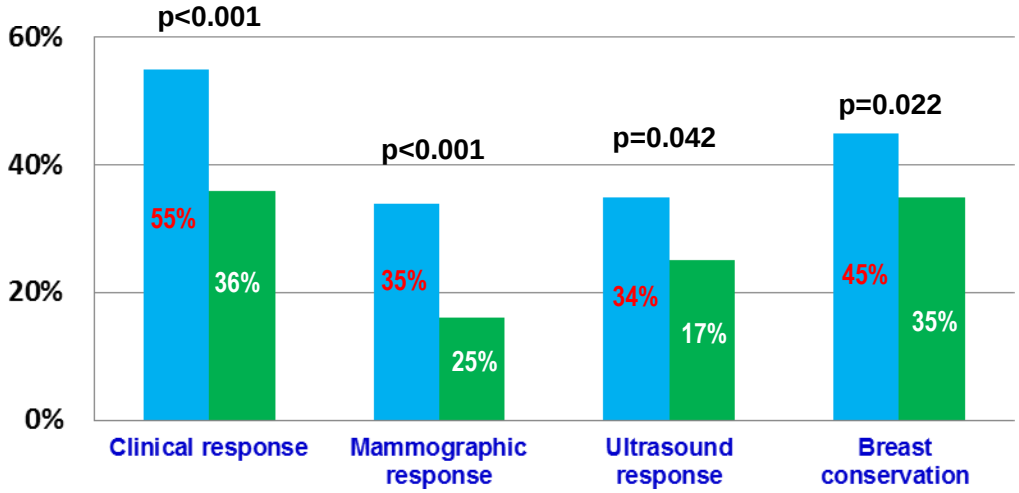
Smith IE, et al, J Clin Oncol 23:5108-16, 2005

Neoadjuvan Endokrin Tedavi

Meme koruyucu cerrahi oranını arttırır

P024

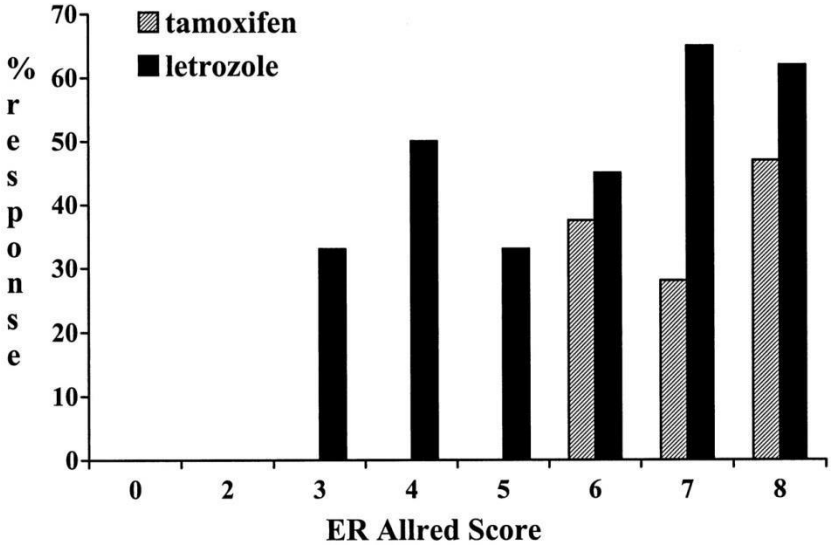




Baslangıçta hiç bir hasta MKC için uygun degildi.

Eiermann W, et al, Ann Oncol 12:1527-32, 2001

Clinical Response by ER Allred Score

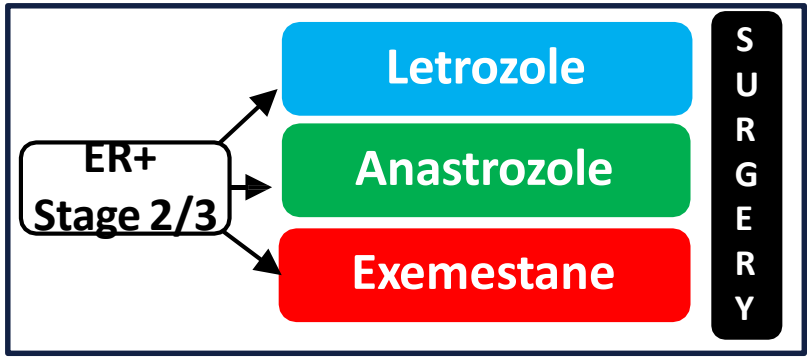


Ellis, MJ, et al, J Clin Oncol 19: 3808-3816, 2001

P024-IMAPCT-PROCAT: Meta-analiz: AI tamoksifene gore daha etkin MKC acisindan

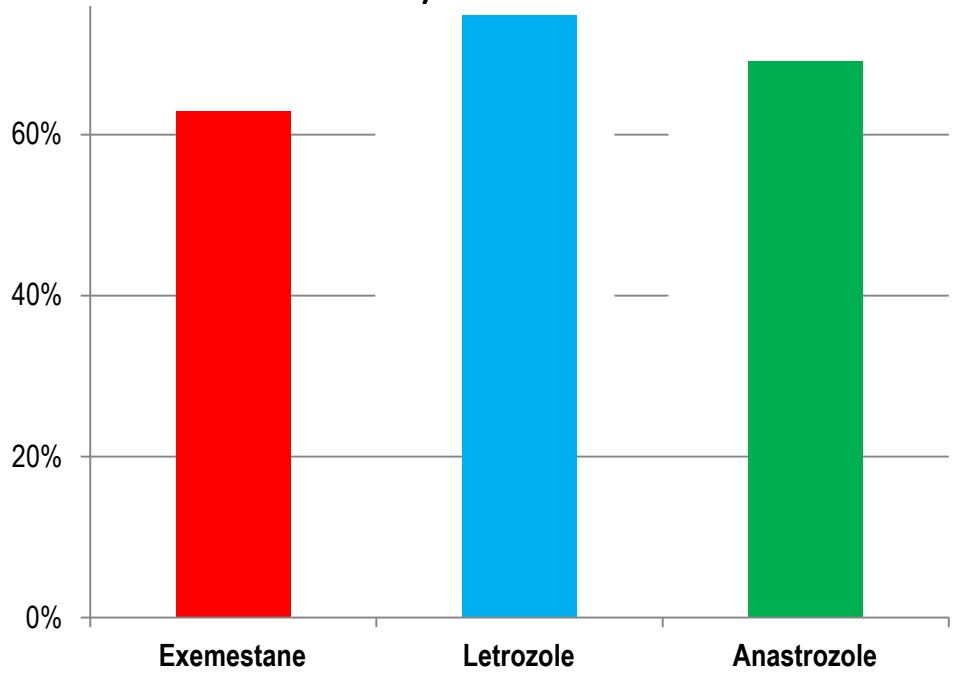
AI klinik yanitlar benzer etkili

Z1031



Ellis, MJ, et al, J Clin Oncol 29:2342-2349, 2011

Ki 67 yanitlari da benzer!



Neoadjuvan Endokrin Tedavi: Ne kadar süre?

- Postmenapozal
- Letrozole yanıt vermiş hastalarda 3-4 aydan daha uzun kullanıldığında tümör boyutunda azalmalar daha da devam ediyor
- OR medyan zaman: 3.9 (95% CI, 3.3–4.5) ay
- Medyan zaman- max yanıt : 4.2 (95% CI, 4.0–4.5) ay
- Tedavi uzadıkça pCR artıyor

Neoadjuvant Endokrin Tedavi (ET) vs Kemo (CT)

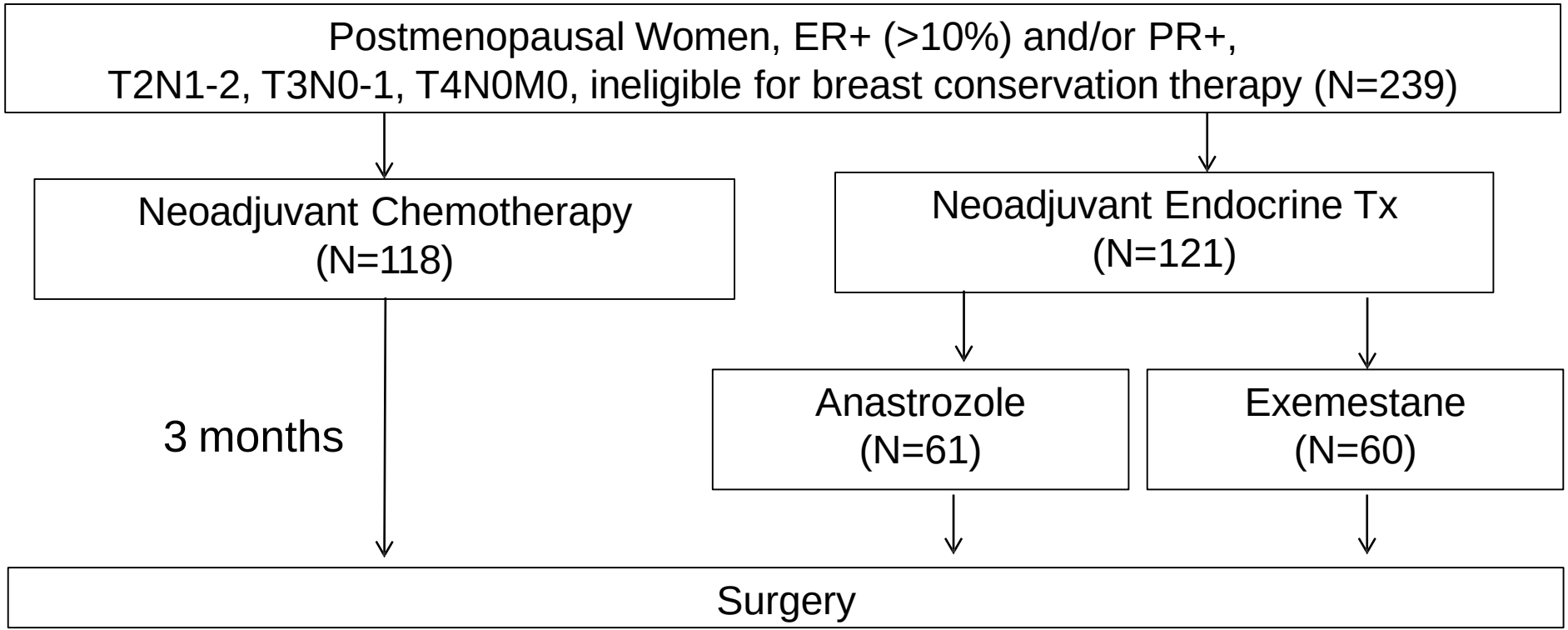
Author Year	Endocrine therapy (ET)		Chemotherapy (CT)		Sample Size (n)	Clinical Response (ET vs CT)	P Value
	Agents	Duration	Agents	Duration			
Semiglazov 2007	Anastrozole or exemestane	12 wks	Doxorubicin and Paclitaxel Q3wk x 4	12 wks	239	65% vs 64%	>0.5
Alba 2012	Exemestane plus goserelin if premenopausal	24 wks	EC-T (Epirubicin plus Cytoxan Q3w x 4 then Docetaxel Q3w x 4	24 wks	95	48% vs 66%	0.075
Palmieri 2014	Letrozole	18-23 wks	FEC x 6 or FEC x3 then T x3 if SD or PD	18 wks	44	91% vs 77%	0.32

Semiglazov VF, et al. *Cancer. 2007;110(2):244-254.*

Alba E, et al; GEICAM. *Ann Oncol. 2012;23(12):3069-3074.*

Palmieri C, et al. *Breast Cancer Res Treat. 2014;148(3):581-590.*

Neoadjuvant Endokrin Tedavi mi (ET) Kemoterapi mi (CT)



Semiglazov VF, et al, Cancer 110:244-54, 2007

Neoadjuvant (ET) vs Kemo (CT)

	Endocrine Therapy (N=121)	Chemotherapy (N=118)
Clinical Response	65%	64%
pCR	3%	6%
Breast conservation	33%	24%

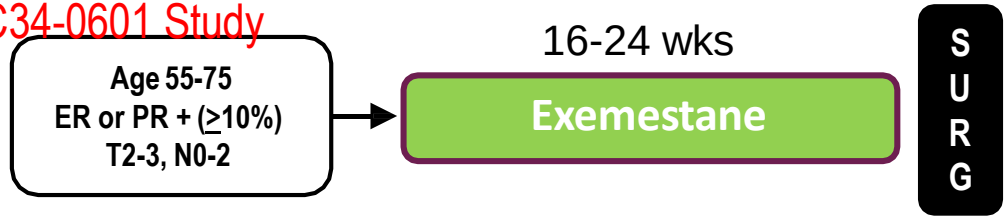
ER Allred ≥ 6	Endocrine Therapy (N=70)	Chemotherapy (N=63)	p
Clinical Response	70%	60%	0.07
Breast conservation	43%	24%	0.05

Semiglazov VF, et al, Cancer 110:244-54, 2007

Hangi Hastalar Neodaj Endokrin Tedaviye uygun?

Neoadjuvan ET Oncotype Rekurrens Skoruna göre yanıtı:

JFMC34-0601 Study



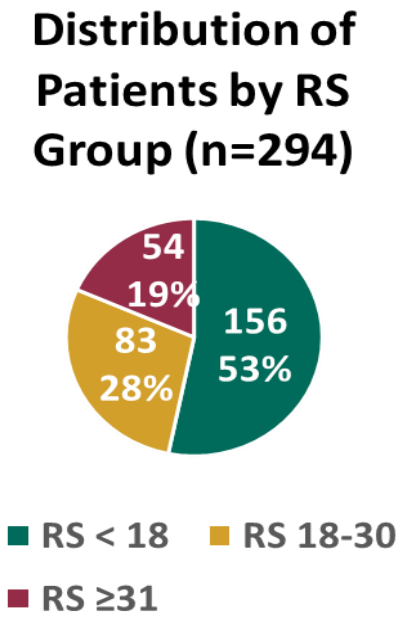
RS Risk Group	N	Clinical Response			Breast-Conserving Surgery (BCS)		
		Response Rate (%)	Odds ratio (95 % CI)	*P* value	BCS Rate (%)	Odds ratio (95 % CI)	*P* value
Low (RS <18)	32	59.4%	1	n/a	90.6%	1	n/a
Intermediate (RS 18–30)	17	58.8%	0.977 (0.296, 3.233)	0.970	76.5%	0.336 (0.066, 1.722)	0.19
High (RS ≥31)	15	20.0%	0.171 (0.040, 0.728)	0.017	46.7%	0.091 (0.019, 0.432)	0.003

Ueno T. et al Int J Clin Oncol (2014)19 (4): 607-613

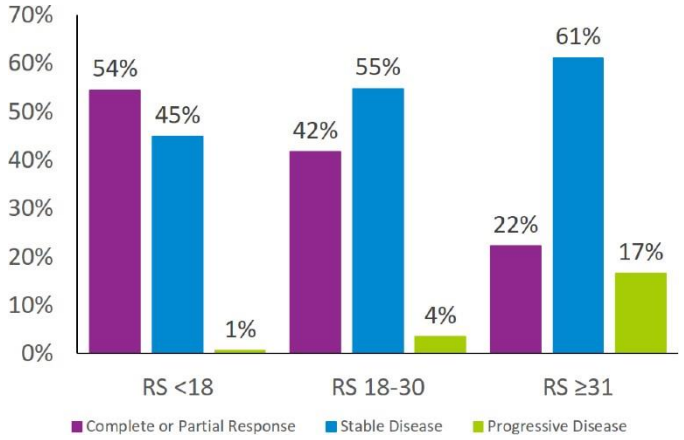
TransNEOS: Neoadjuvan Al'nun Onkotip skoruna gore Klinik yanit oranlarini belirleme

24-28 hafta neoadjuvan LET

Postmenopausal
cT2N0M0
ER+, HER2-



Klinik yanit %* RS Grup (N=294)

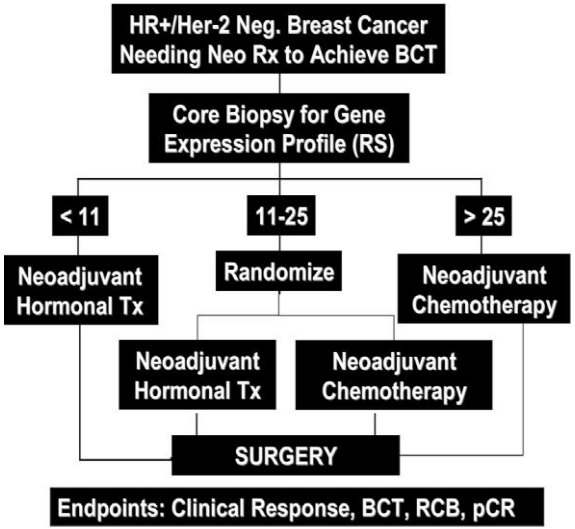


chi-square test, p<0.001

***MRI ya da CT ile yanit degerlendirme, RECIST criteria**

Hiroji Iwata, et al. SABCS 2017

Oncotype RS Neoadjuvan Tedavi secimi ER+ HER2-

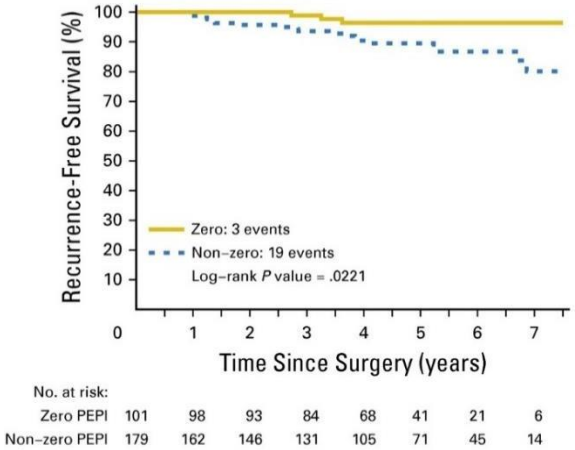


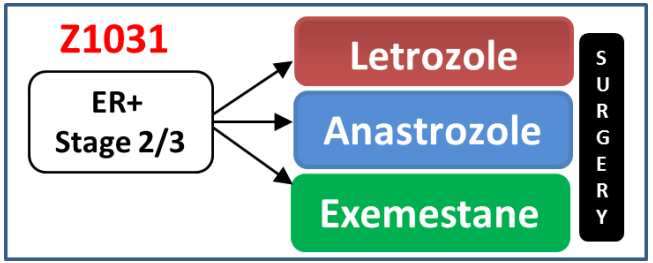
Treatment group	Group A RS < 11 NHT *N* = 12 (%)	Group B RS = 11-25 NHT *N* = 18 (%)	Group C RS = 11-25 NCT *N* = 11 (%)	Group D RS ≥ 26 NCT *N* = 14 (%)	Overall *P*-value
cCR	8.3	22.2	36.4	28.6	0.0422
cPR	75.0	27.8	36.4	64.3	
cCR + cPR	**83.3**	**50.0**	**72.7**	**92.9**	**0.0490**
pCR breast	8.3	6.0	0	21.4	NS
pCR breast + nodes	0	0	0	14.3	NS
Successful BCS	**75.0**	**72.2**	**63.6**	**57.1**	**NS**

Bear, et al. J Surg Oncol. 2017;115:917–923.

Preoperatif Endokrin Prognostik Index (PEPI) 3-4 ay Neoadj ET

Pathology, Biomarkers Factors		RFS		BCS	
		HR	Points	HR	Points
Tumor size	T1/2	-	0	-	0
	T3/4	2.8	3	4.4	3
Node status	No	-	0	-	0
	Yes	3.2	3	3.9	3
Ln Ki67 level	0 -1	-	0	-	0
	1+ -2	1.3	1	1.4	1
	2+ -3	1.7	1	2.0	2
	3+ -4	2.2	2	2.7	3
	4+	2.9	3	3.8	3
ER Allred	0-2	2.8	3	7.0	3
	3-8	-	0	-	0





Ellis MJ, et al., J Natl Cancer Inst 100:1380-8, 2008

Ellis, JCO 2017

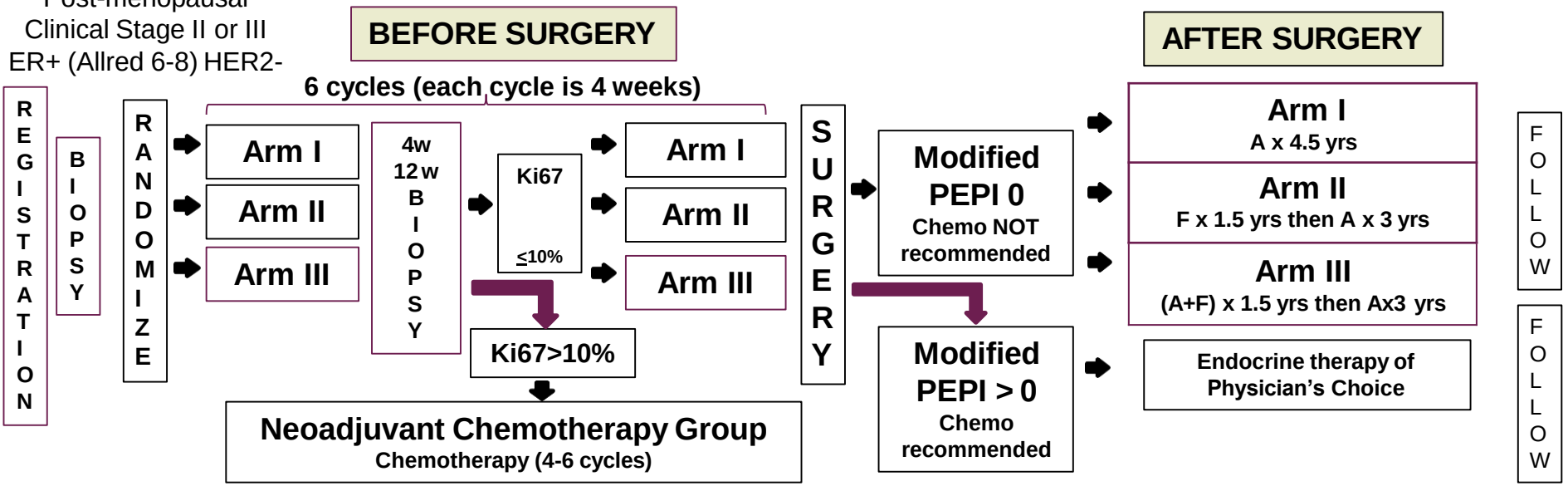
N=1,455

ALTERNATE Trial (A011106)

NCT01953588

Eligibility

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

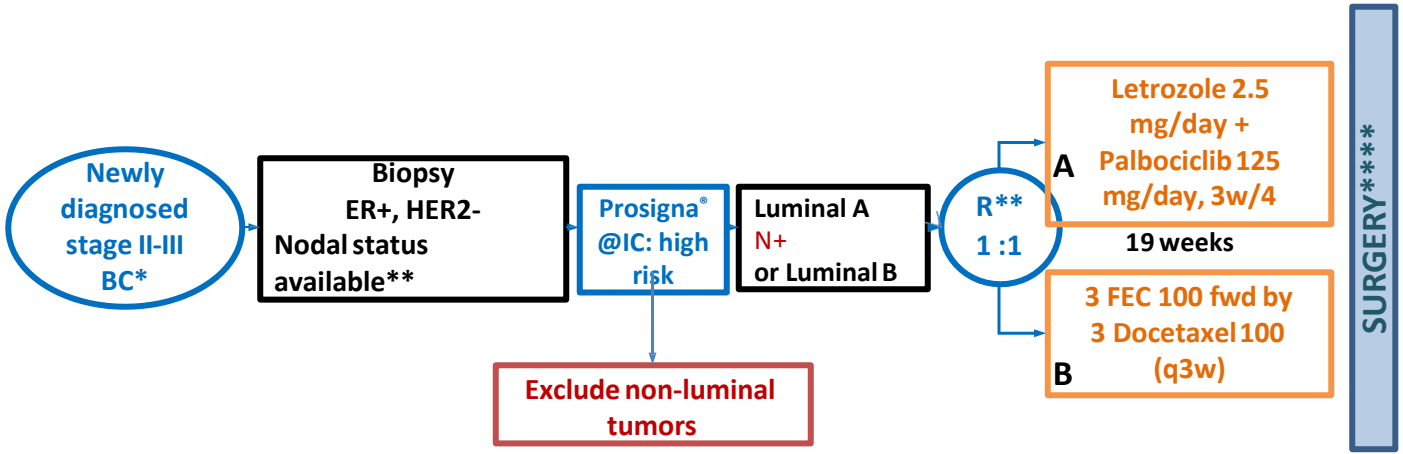


Primary Endpoints:

1st Phase: Modified PEPI 0 rate
2nd Phase: RFS in Modified PEPI0

Arm I: Anastrozole (A)
Arm II: Fulvestrant (F)
Arm III: Anastrozole + Fulvestrant

Yeni Jenerasyon Neoadjuvan Endokrin Tedavi
NEOPAL CALISMASI



- *DAHIL EDILME KRITERI: post menopausal ; ER Allred ≥ 4; meme koruyucu cerrahiye uygun olmayan
- ***T2 vs T3; Luminal A vs luminal B
- ****Cerrahi 24. hafta sonrasi

Primer sonlanma noktası: Rezidu kanser yükü (RCB)

Lokal ve santral değerlendirmede benzerlik

	LETPALBO (n=52)	KEMO (n=51)
Local 0-I	4 (7.7%)	8 (15.7%)
Central	3 (5.7%)	7 (14.6%)
Local II-III	48 (92.3%)	43 (84.3%)
Central	49 (94.2%)	44 (85.4%)

Son RCB 0 (pCR) and RCB III kollar arasında benzer

		LET PALBO (n=52)	KEMO (n=51)
RCB class	0	**2 (3.8%)**	**3 (5.9%)**
	I	2 (3.8%)	5 (9.8%)
	II	27 (51.9%)	19 (37.3%)
	III	**21 (40.4%)**	**24 (47.1%)**

NEOPAL	PALLET	CORRALEN
FAZ II	FAZ II	FAZ II
KT vs LET-+AL	Let vs LET+PAL Let.. Let+PAL PAL.. Let+ Let+PAL	KT vs Ribo

Yeni Jenerasyon Neoadjuvan Endokrin Tedavi Calismalari

Trial/Target	Treatment	Duration	N	Primary Endpoint	pCR	Radiology Response	Comments
Neo Orb **(PI3K)**	Letrozole/placebo	24 wks	126	pCR and ORR	3% (mut): 2/67 1.7% (WT): 1/59	45% (PIK3CA Mut): 30/67 61% (PIK3CA WT): 36/59	Alpelisib did not improve the pCR, ORR or Ki67 suppression in PIK3CA mutant or WT cohort.
	Letrozole/alpelisib		131		1.7% (mut): 1/60 2.8% (WT): 2/71	43% (PIK3CA mut): 26/60 63% (PIK3CA WT): 45/71	
LORELEI **(PI3K)**	Letrozole/placebo	16 wks	168	pCR and ORR	No difference	39% by MRI 40% (PIK3CA WT)	Taselisib improved ORR in PIK3CA mutant cohort.
	Letrozole/taselisib		16			46% (PIK3CA WT) 56% (PIK3CA Mut)	
Everolimus **(mTOR)**	Letrozole/placebo	16 wks	132	ORR by palpation	0.8% : 1/132	47% by ultrasound	Everolimus improved clinical ORR and Ki67 suppression.
	Letrozole/ everolimus		138		1.4%: 2/138	58% by ultrasound	
NeoMonarch **(CDK4/6)**	Anastrozole/ abemaciclib	16 wks	224	Ki67 suppression at 2 wk comparing to baseline	3.7%; 7/190	46.4% by ultrasound	Abemaciclib improved Ki67 suppression.
PALLET **(CDK4/6)**	Letrozole	14 wks	87	Ki67 suppression at 14 wk and ORR	0%: 0/87	49.5%	Palbociclicb improved Ki67 suppression but not ORR.
	Letrozole/palbo (concurrent or after 2 wks of monotherapy)		180		1.1%: 2/180	54.3%	

OZETLE: yeni mollekuler ORR arttirmiyor

Post-neoadjuvan tedavi

PENELOPE-B: Yuksek riskli meme ca Faz 3 palbociclib + adjuvan endokrin tedavi

- Pre- and post-menopausal women with **HR+/HER2-** early breast cancer
- CPS-EG ≥3 or 2 if ypN+
- **Completed taxane-based neoadjuvant therapy, surgery, radiotherapy**

N=1250

R

Palbociclib 125 mg QD, 3/1 schedule (1 year) + SOC (≥5 years)

Placebo QD, 3/1 schedule (1 year) + SOC (≥5 years)

Primary endpoint: iDFS

Secondary endpoints:

- DDFS
- OS
- Safety and compliance
- PRO
- QALY

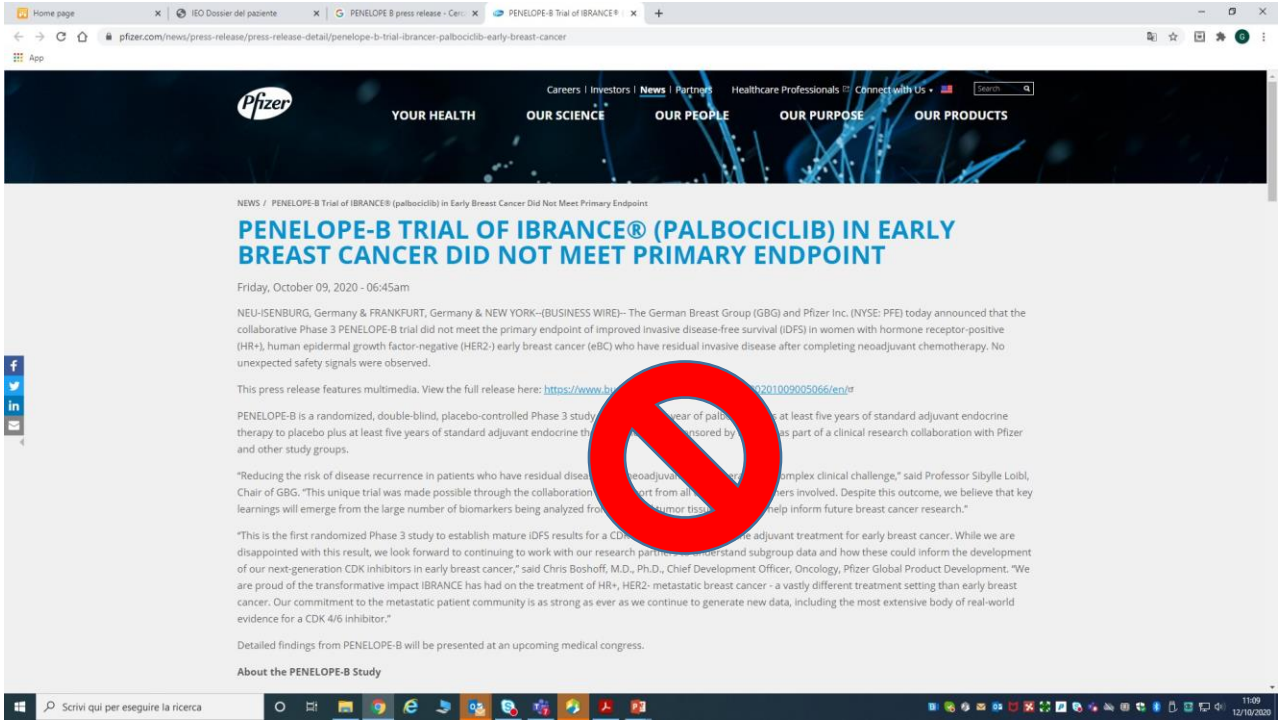
Status: Active, not recruiting
Primary completion date: December 2020

Palbociclib is not approved for the treatment of eBC.

CPS-EG, clinical pathological stage-oestrogen grade; DDFS, distant disease-free survival; eBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; OS, overall survival; PRO, patient-reported outcomes; QALY, quality-adjusted life years; QD, once-daily; SOC, standard of care; ypN, axillary lymph node.

ClinicalTrials.gov NCT01864746.

PENELOPE-B: Yuksek riskli meme ca Faz 3 palbociclib + adjuvan endokrin tedavi



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pfizer.com/news/press-release/press-release-detail/penelope-b-trial-ibrancer-palbociclib-early-breast-cancer

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NEWS / PENELOPE-B Trial of IBRANCE® (palbociclib) in Early Breast Cancer Did Not Meet Primary Endpoint

PENELOPE-B TRIAL OF IBRANCE® (PALBOCICLIB) IN EARLY BREAST CANCER DID NOT MEET PRIMARY ENDPOINT

Friday, October 09, 2020 - 06:45am

NEU-ISENBURG, Germany & FRANKFURT, Germany & NEW YORK--(BUSINESS WIRE)-- The German Breast Group (GBG) and Pfizer Inc. (NYSE: PFE) today announced that the collaborative Phase 3 PENELOPE-B trial did not meet the primary endpoint of improved invasive disease-free survival (iDFS) in women with hormone receptor-positive (HR+), human epidermal growth factor-negative (HER2-) early breast cancer (eBC) who have residual invasive disease after completing neoadjuvant chemotherapy. No unexpected safety signals were observed.

This press release features multimedia. View the full release here: https://www.b...

PENELOPE-B is a randomized, double-blind, placebo-controlled Phase 3 study ... at least five years of standard adjuvant endocrine therapy to placebo plus at least five years of standard adjuvant endocrine th... as part of a clinical research collaboration with Pfizer and other study groups.

"Reducing the risk of disease recurrence in patients who have residual disea... complex clinical challenge," said Professor Sibylle Loibl, Chair of GBG. "This unique trial was made possible through the collaboration ... ers involved. Despite this outcome, we believe that key learnings will emerge from the large number of biomarkers being analyzed fro... help inform future breast cancer research."

"This is the first randomized Phase 3 study to establish mature iDFS results for a CD... adjuvant treatment for early breast cancer. While we are disappointed with this result, we look forward to continuing to work with our research pa... stand subgroup data and how these could inform the development of our next-generation CDK inhibitors in early breast cancer," said Chris Boshoff, M.D., Ph.D., Chief Development Officer, Oncology, Pfizer Global Product Development. "We are proud of the transformative impact IBRANCE has had on the treatment of HR+, HER2- metastatic breast cancer - a vastly different treatment setting than early breast cancer. Our commitment to the metastatic patient community is as strong as ever as we continue to generate new data, including the most extensive body of real-world evidence for a CDK 4/6 inhibitor."

Detailed findings from PENELOPE-B will be presented at an upcoming medical congress.

About the PENELOPE-B Study

Scrivi qui per eseguire la ricerca

11:09 12/10/2020

• monarchE: çalışma dizaynı

HR+, HER2-, high risk early breast cancer

High risk defined as:

- ≥4 positive axillary lymph nodes (ALN) OR
- 1-3 ALN and at least 1 of the below:
  - Tumor size ≥5 cm
  - Histologic grade 3
  - Centrally tested Ki67 ≥20%

N = 5637[a]

R
1:1

Abemaciclib (150mg twice daily for up to 2 years[b])
+ Standard of Care Endocrine Therapy
(5 to 10 years as clinically indicated)

Standard of Care Endocrine Therapy[b]
(5 to 10 years as clinically indicated)

Stratified for:
- Daha once kemo
- (neodj%37; adjuvan %56)
- Menopausal status
- Region

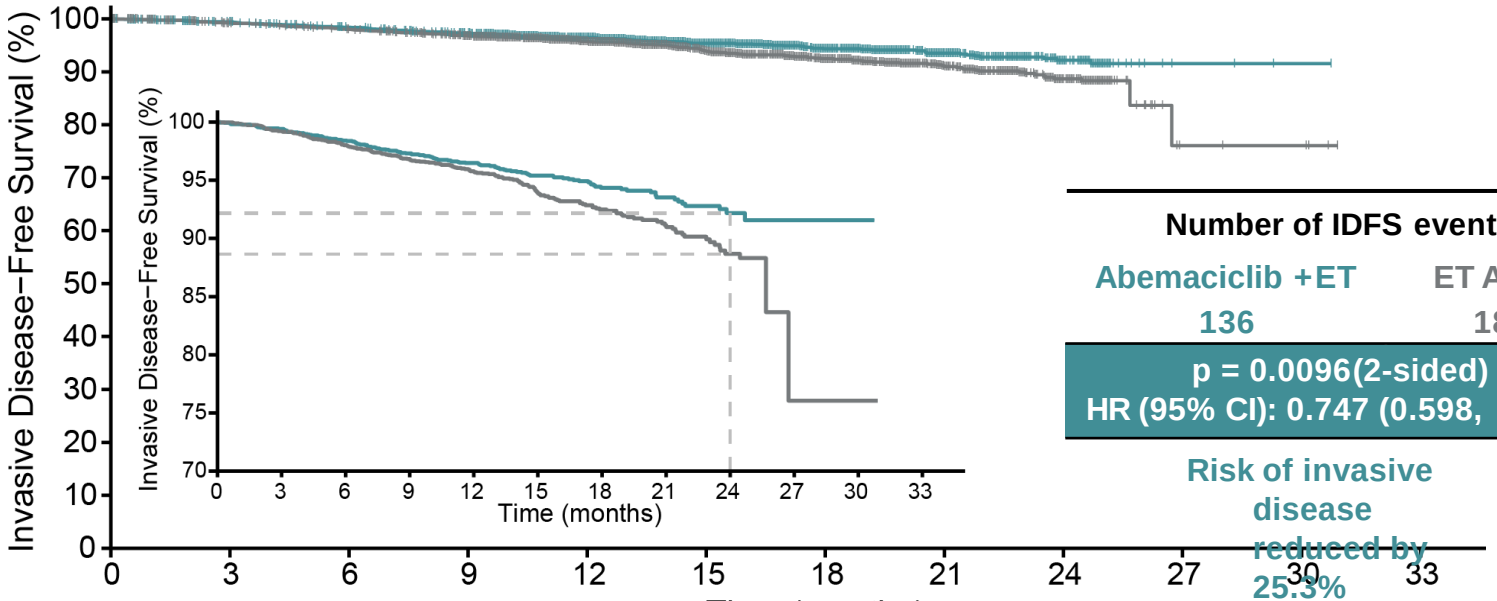
Endocrine therapy of physician's choice

Other criteria:
- Women or men
- Pre-/ postmenopausal
- With or without prior adjuvant/neoadjuvant chemotherapy
- No distant metastases

Primary Objective: Invasive disease-free survival (STEEP criteria)
Key Secondary Objectives: Distant relapse-free survival, Overall survival, Safety, Patient reported outcomes, and Pharmacokinetics

[a] Recruitment from July 2017 to August 2019; [b] Treatment period = first 2 years on study treatment after randomization

• Invasive Disease-Free Survival



Number of IDFS events

Abemaciclib +ET	ET Alone
136	187

p = 0.0096(2-sided)
HR (95% CI): 0.747 (0.598, 0.932)

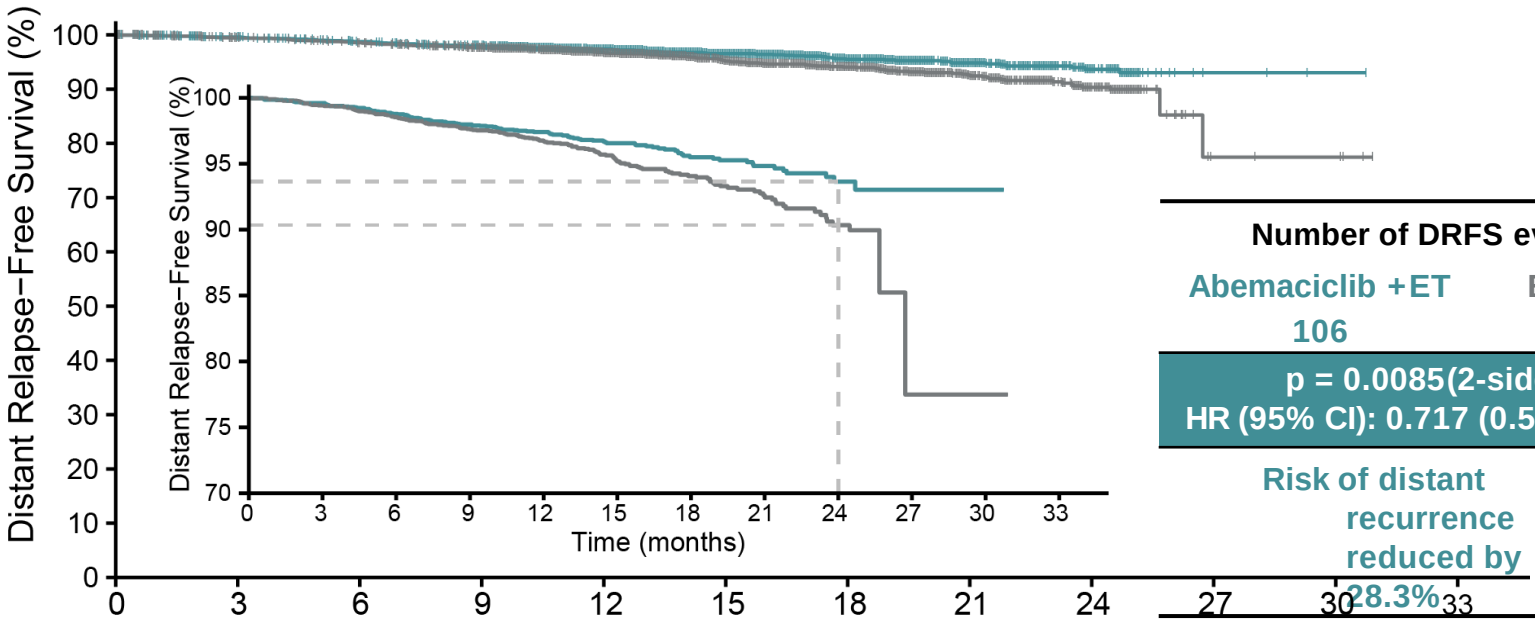
Risk of invasive disease reduced by 25.3%

Number at risk

Abemaciclib + ET	2808	2676	2613	2543	1996	1371	918	566	245	3	1	0
ET Alone	2829	2699	2649	2562	2013	1405	932	586	262	7	6	0

Two-year IDFS rates were 92.2% (abemaciclib + ET arm) and 88.7% (ET arm) – 3.5% absolute difference

• Distant Relapse-Free Survival



Number of DRFS events

Abemaciclib +ET	ET Alone
106	152

p = 0.0085(2-sided)
HR (95% CI): 0.717 (0.559, 0.920)

Risk of distant recurrence reduced by 28.3%

Number at risk

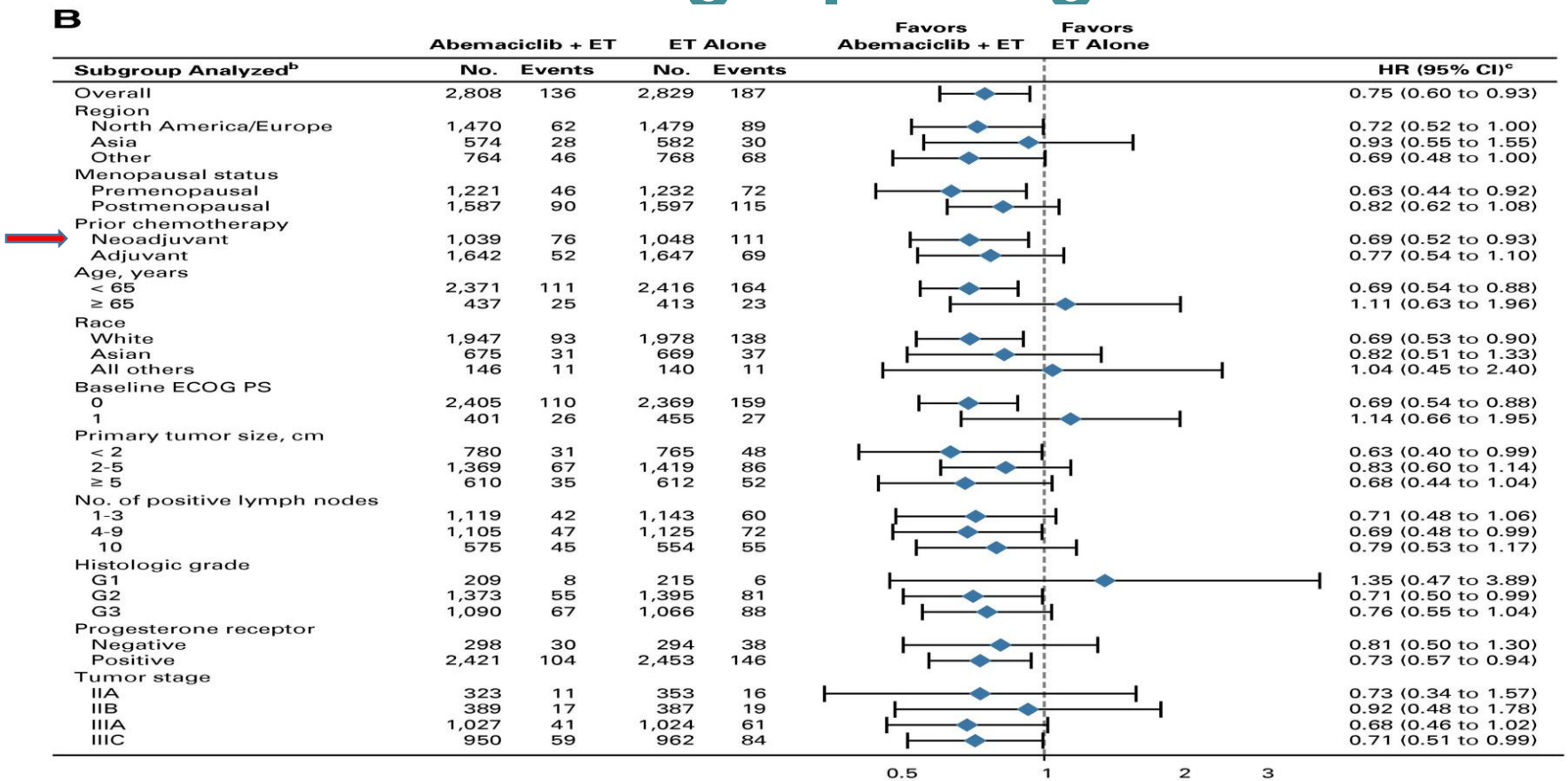
Time (months)

Abemaciclib + ET	2808	2680	2619	2555	2005	1378	925	573	247	3	1	0
ET Alone	2829	2704	2659	2576	2026	1417	941	590	263	7	6	0

T2 yıllık DRFS 93.6% (abemaciclib + ET) ve 90.3% (ET) –
3.3% absolut fark DRFS yararı tüm alt gruplarda

monarchE: Alt gruplara gore IDFS

B



Subgroup Analyzed[b]	Abemaciclib + ET No.	Abemaciclib + ET Events	ET Alone No.	ET Alone Events	HR (95% CI)[c]
Overall	2,808	136	2,829	187	0.75 (0.60 to 0.93)
Region					
North America/Europe	1,470	62	1,479	89	0.72 (0.52 to 1.00)
Asia	574	28	582	30	0.93 (0.55 to 1.55)
Other	764	46	768	68	0.69 (0.48 to 1.00)
Menopausal status					
Premenopausal	1,221	46	1,232	72	0.63 (0.44 to 0.92)
Postmenopausal	1,587	90	1,597	115	0.82 (0.62 to 1.08)
Prior chemotherapy					
Neoadjuvant	1,039	76	1,048	111	0.69 (0.52 to 0.93)
Adjuvant	1,642	52	1,647	69	0.77 (0.54 to 1.10)
Age, years					
< 65	2,371	111	2,416	164	0.69 (0.54 to 0.88)
≥ 65	437	25	413	23	1.11 (0.63 to 1.96)
Race					
White	1,947	93	1,978	138	0.69 (0.53 to 0.90)
Asian	675	31	669	37	0.82 (0.51 to 1.33)
All others	146	11	140	11	1.04 (0.45 to 2.40)
Baseline ECOG PS					
0	2,405	110	2,369	159	0.69 (0.54 to 0.88)
1	401	26	455	27	1.14 (0.66 to 1.95)
Primary tumor size, cm					
< 2	780	31	765	48	0.63 (0.40 to 0.99)
2-5	1,369	67	1,419	86	0.83 (0.60 to 1.14)
≥ 5	610	35	612	52	0.68 (0.44 to 1.04)
No. of positive lymph nodes					
1-3	1,119	42	1,143	60	0.71 (0.48 to 1.06)
4-9	1,105	47	1,125	72	0.69 (0.48 to 0.99)
10	575	45	554	55	0.79 (0.53 to 1.17)
Histologic grade					
G1	209	8	215	6	1.35 (0.47 to 3.89)
G2	1,373	55	1,395	81	0.71 (0.50 to 0.99)
G3	1,090	67	1,066	88	0.76 (0.55 to 1.04)
Progesterone receptor					
Negative	298	30	294	38	0.81 (0.50 to 1.30)
Positive	2,421	104	2,453	146	0.73 (0.57 to 0.94)
Tumor stage					
IIA	323	11	353	16	0.73 (0.34 to 1.57)
IIB	389	17	387	19	0.92 (0.48 to 1.78)
IIIA	1,027	41	1,024	61	0.68 (0.46 to 1.02)
IIIC	950	59	962	84	0.71 (0.51 to 0.99)

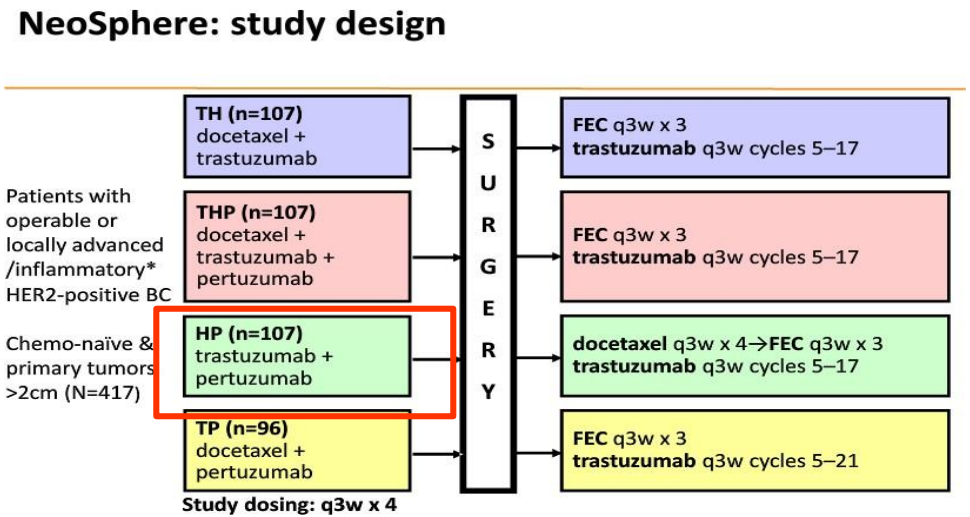
Sonuc:

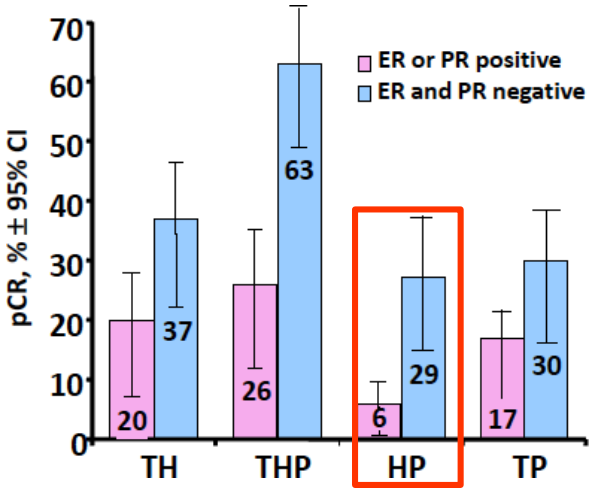
- Abemaciclib-ET yuksek riksli grupra IDFS arttiriyor.
- Relaps riksini % 25.3 azaltiyor (HR = 0.747; 95% CI, 0.598 to 0.932; p = 0.0096)
  - % 3.5% absolute ikazanc 2-yillik IDFS: 92.2% vs 88.7%
- Erken nuks ve uzak met onleme klinik olarak anlamli:% 28.3
  - Ozellikle karaciger ve kemik

Abemaciclib HR+ HER2- yuksek riksli hastalikta ET ile kombine edildiginde ET gore IDFS arttiran ilk CDKi

AZALTILMIS YAKLASIM

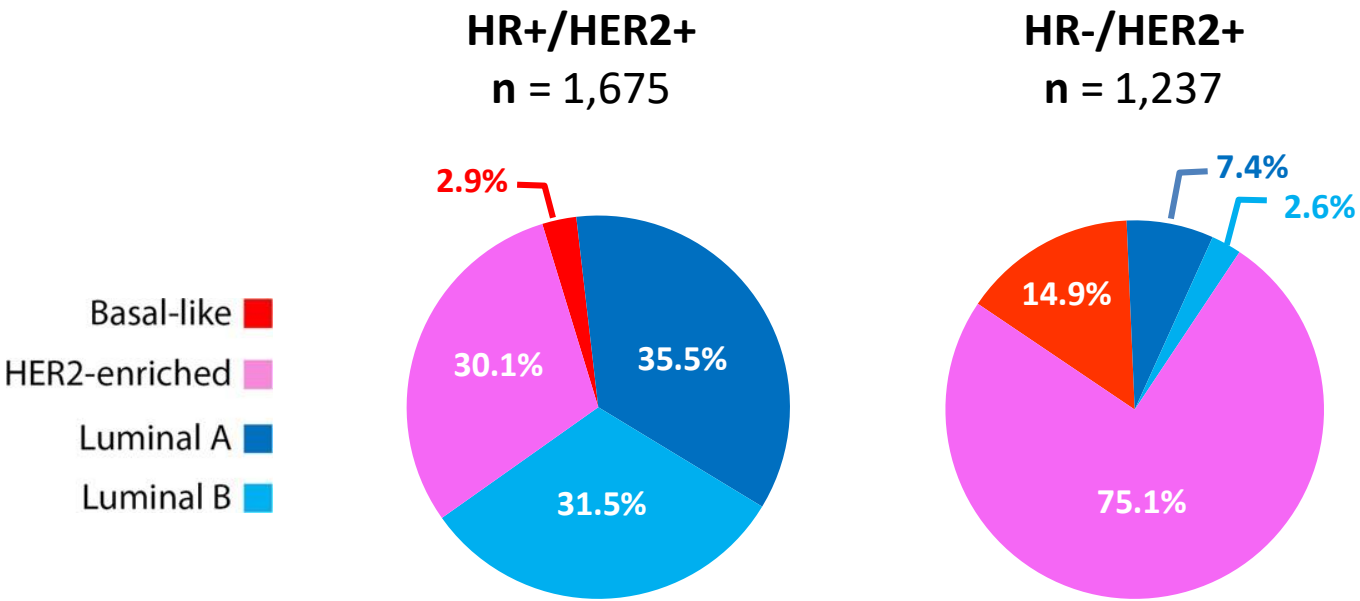
Azaltılmış Yaklaşım: daha az tedavi ile pCR elde etme





Gianni L, et al. Lancet Oncol 2012

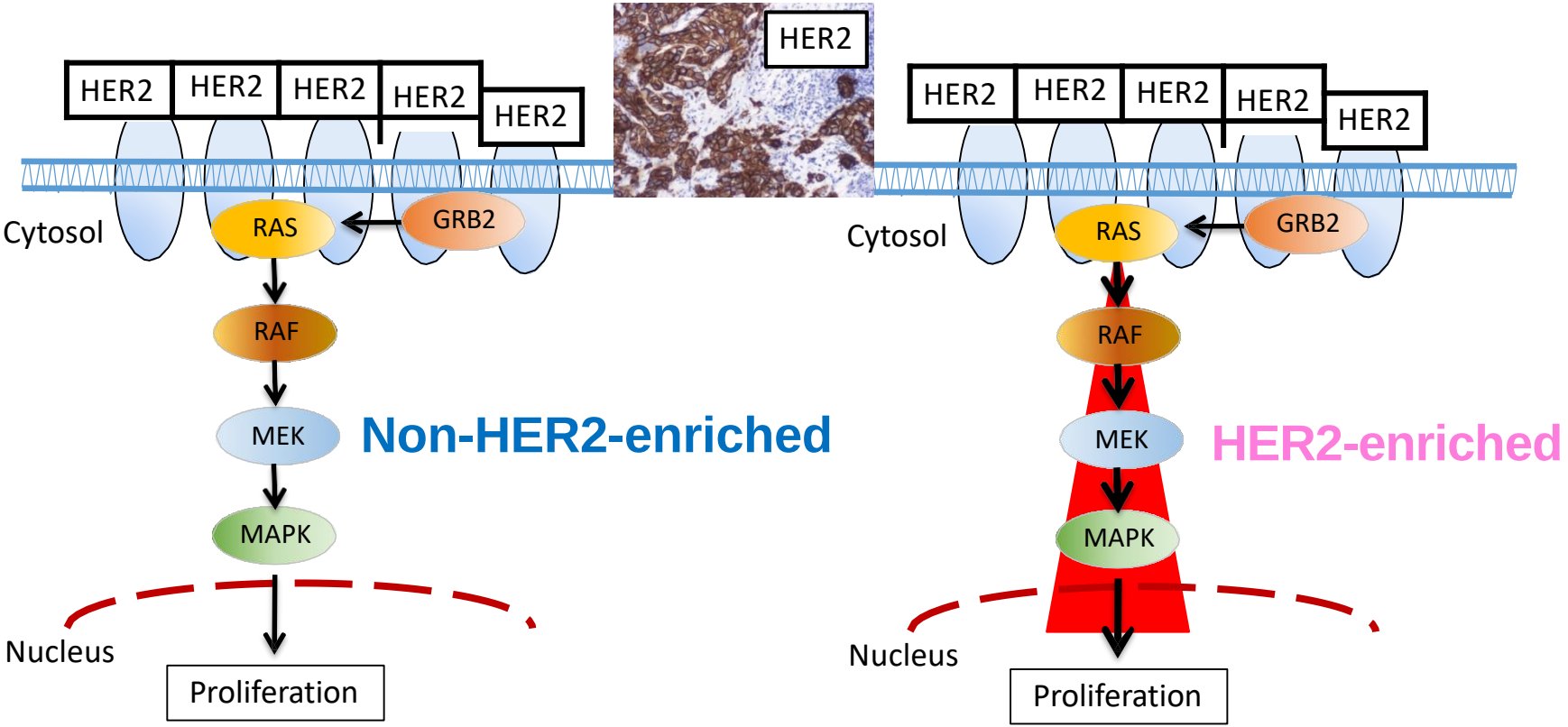
HER2+ subtipler



HER2-E subtip tüm HER tümorlerin %50-60%

1. Cancer Genome Atlas Network Nature 2012; 490:61–70
2. Prat et al. J Natl Cancer Inst. 2014;106 (8)
3. Cejalvo et al. Cancer Treat Rev 2018
4. Cejalvo JM, et al. Ann Oncol. 2017 vol 28 suppl 5

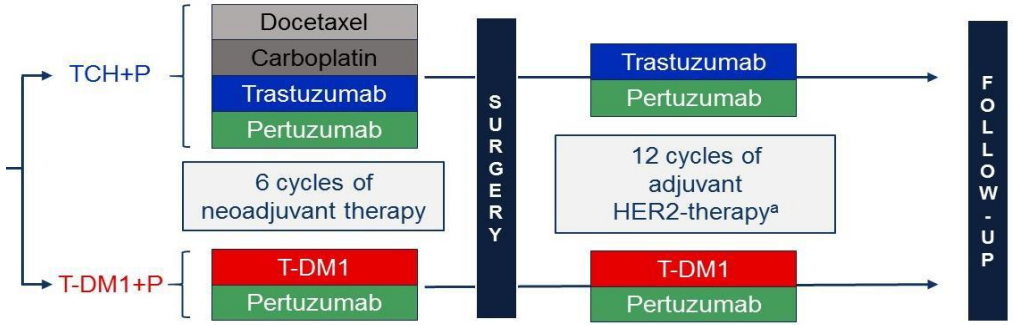
HER2 sinyal yolağı HER2+ Meme ca

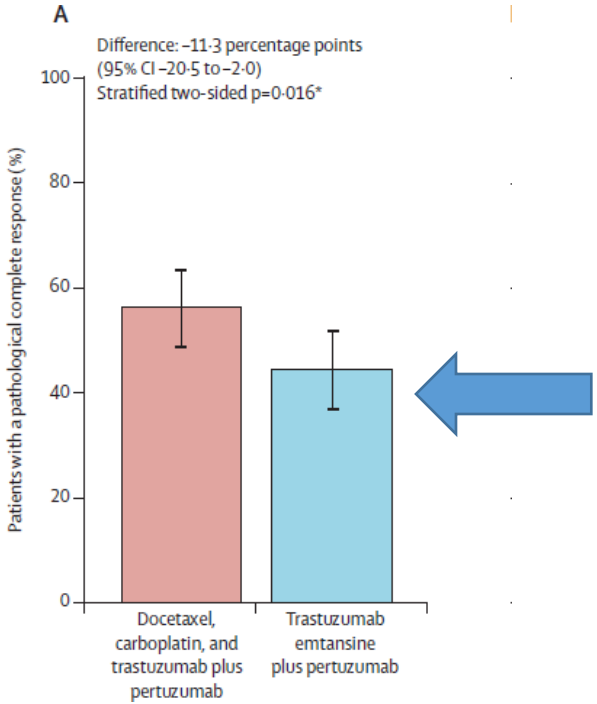


Adapted from Prat et al. JNCI 2019

Azaltılmış Yaklaşım: daha az tedavi ile pCR

KRISTINE trial



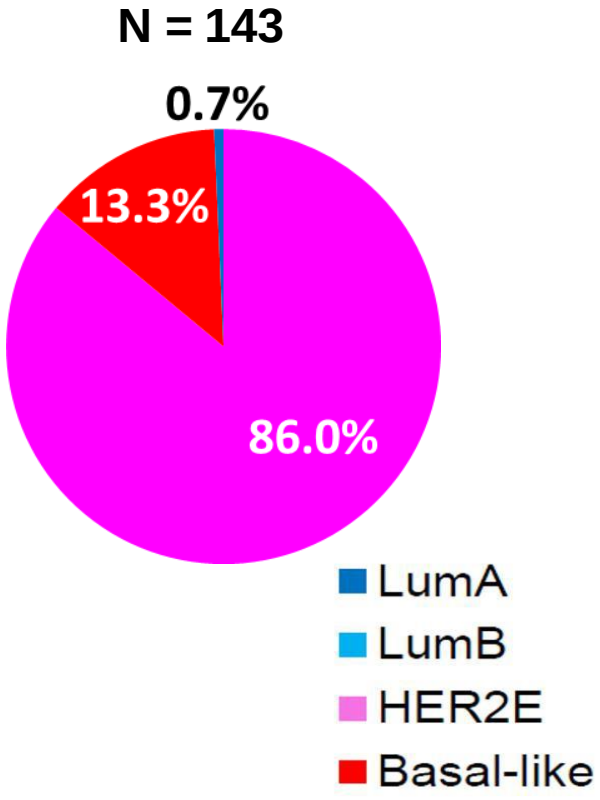


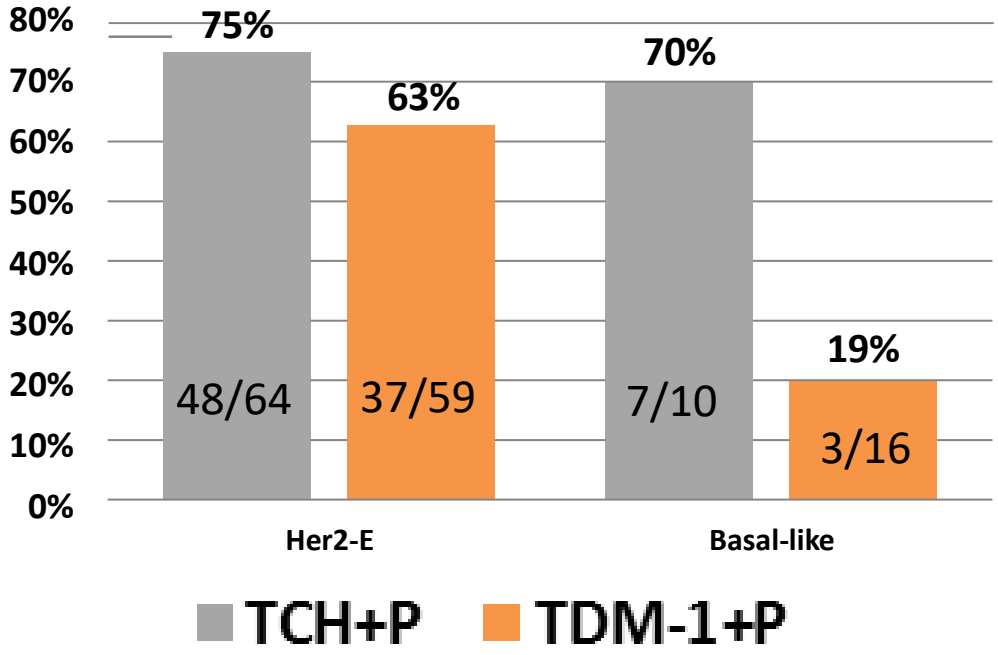
More favourable toxicity profile of T-DM1 + p vs TC-HP

Hurvitz S, et al. Lancet Oncol 2018

PAM50 vs. pCR in HER2+/HR-negatif

KRISTINE calismasi

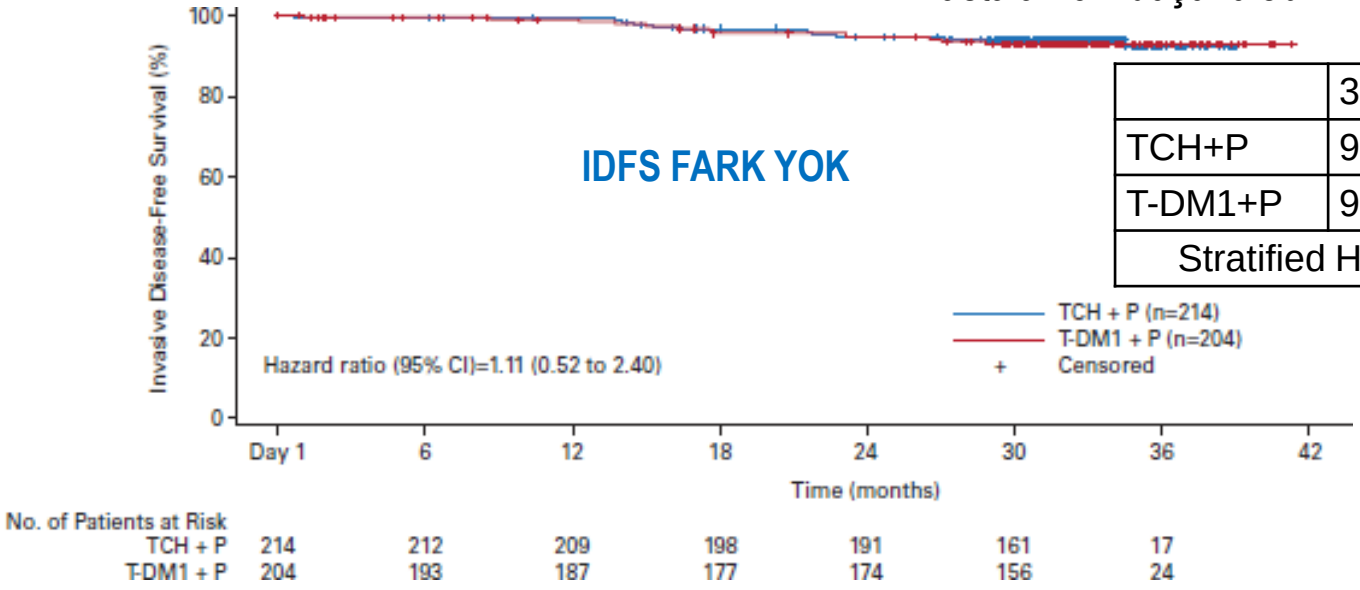




Prat et al. SABCS 2017

KRISTINE: IDFS (INVASIVE DISEASE-FREE SURVIVAL)

- T-DM1+ P belki COVID döneminde HER2 hastalar icin düşünülebilir.

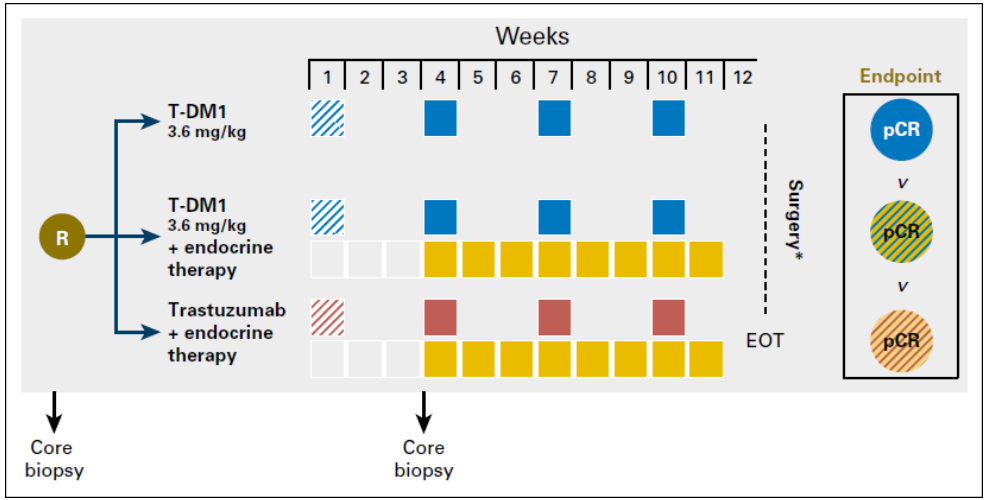


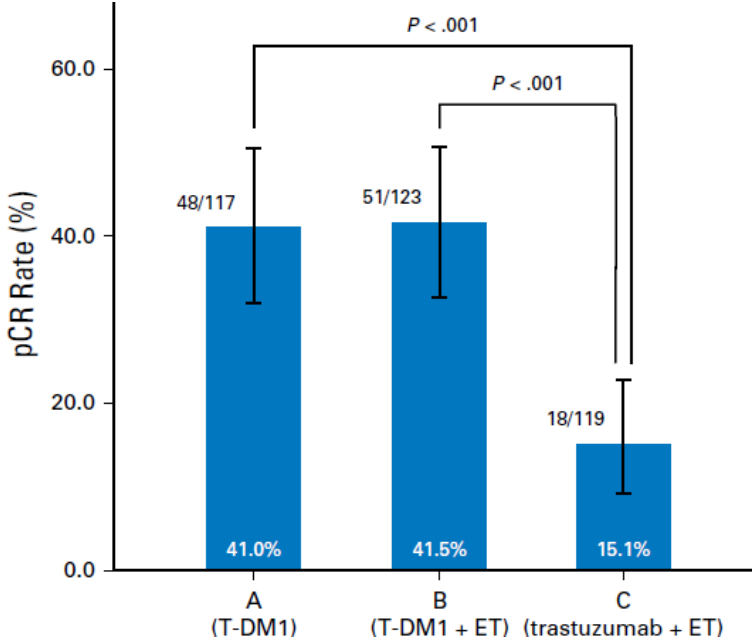
	3-Year IDFS (95% CI)
TCH+P	92.0% (86.7–97.3)
T-DM1+P	93.0% (89.4–96.7)
Stratified HR=1.11 (0.52–2.40)	

Hurvitz S et al, JCO 2020

Azaltılmış Yaklaşım: daha az tedavi ile pCR

ADAPT-TPçalışması (HER2+/HR+): T-DM1 (+/- endokrin tedavi) vs trastuzumab + endokrin tedavi





Harbeck N, et al. J Clin Oncol 2017

Azaltılmış Yaklaşım: daha az tedavi ile pCR

PAMELA calismasi: HER2-enriched subtip, kemoterapi olmadan trastuzumab- lapatinib tedavisi pCR icin bir prediktordur.

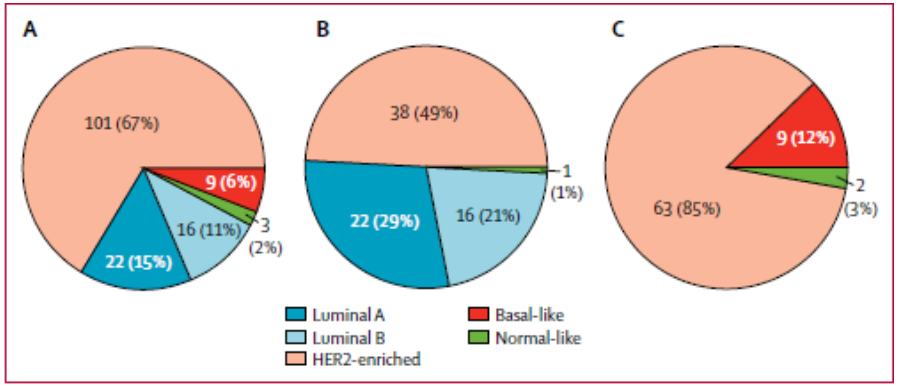


Figure 2: Distribution of intrinsic molecular subtypes at baseline

	Number of patients with molecular subtype at baseline	Number of patients achieving pathological complete response	Pathological complete response (95% CI)
Total	151	46	30% (23–39)
Luminal A	22	0	0%
Luminal B	16	2	13% (4–36)
HER2-enriched	101	41	41% (31–51)
Basal-like	9	1	11% (2–44)
Normal-like	3	2	67% (21–94)

Table 2: Pathological complete response at the time of surgery, by intrinsic molecular subtype assessed at baseline

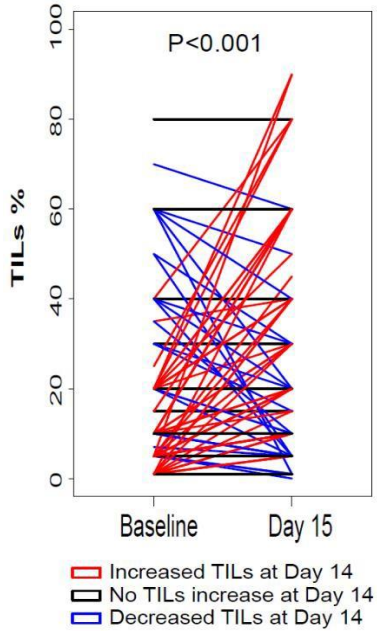
Llombart-Cussac A, et al. Lancet Oncol 2017

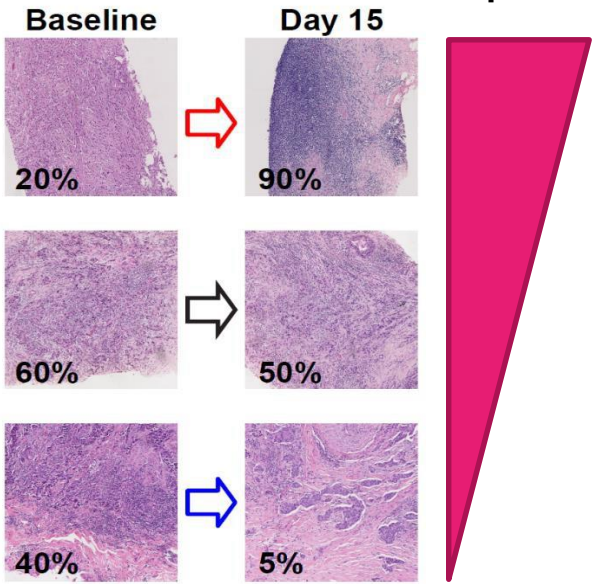
HER2+ MC, erken TILs ve Tümör selülarite değişikliği

Pamela

Retrospective Analysis from PAMELA trial (n=134/151)

Lapatinib + Trastuzumab (+ ET if HR+) for 18 weeks





CelTIL score D15

=

Tumor cellularity

+

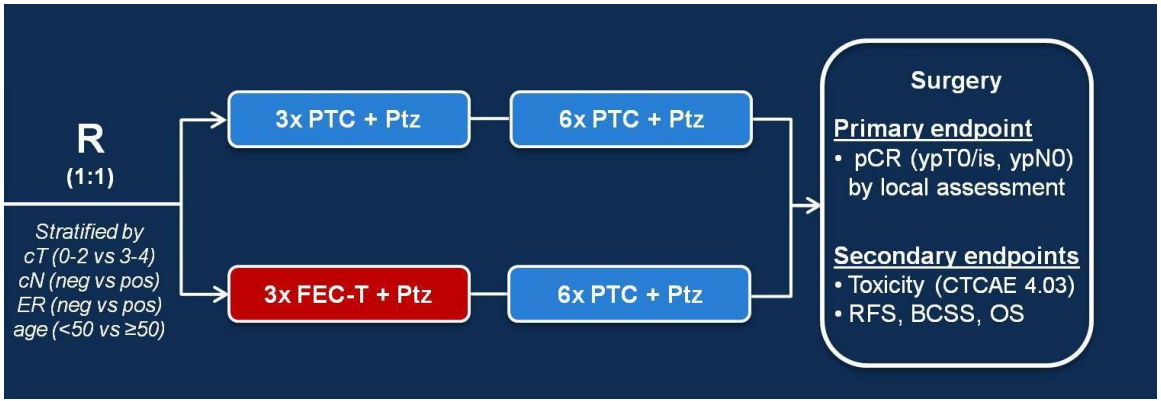
TILs

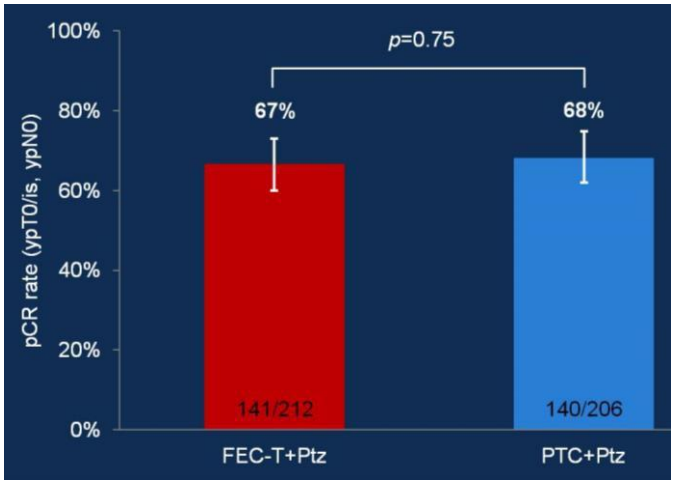
Nuciforo et al. Ann Oncol 2017

Azaltılmış Yaklaşım: daha az tedavi ile pCR

Antrasiklinsiz olur mu?

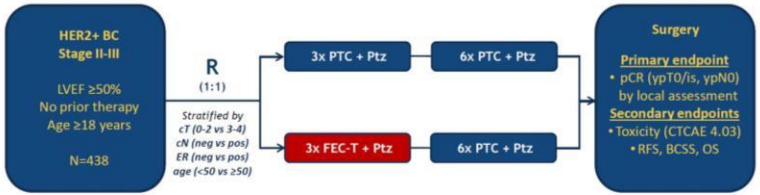
TRAIN-2 trial





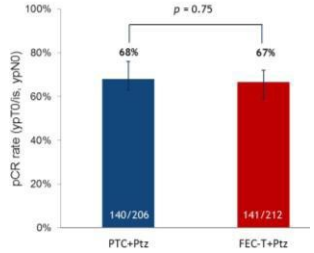
Van Ramshorst MS, et al. ASCO 2017, Lancet Oncol 2018

TRAIN-2 çalışması

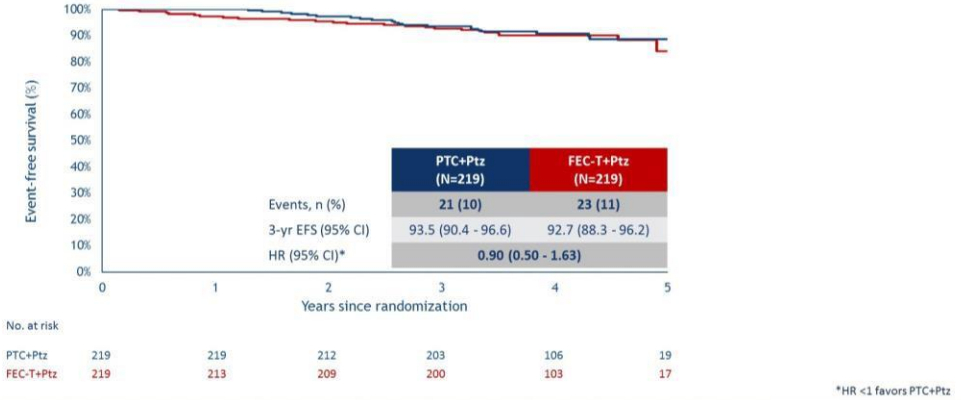


- PTC+Ptz cycle of 3 weeks, day 1 PTC+Ptz, day 8 only P: P = paclitaxel 80mg/m²; T = trastuzumab 6mg/kg (loading dose 8mg/kg); C = carboplatin AUC = 6mg-min/ml; Ptz = pertuzumab, 420mg (loading dose 840mg)
- FEC-T+Ptz cycle of 3 weeks: F = 5-fluorouracil 500mg/m²; E = epirubicin 90mg/m²; C = cyclophosphamide 500mg/m²;T = trastuzumab 6mg/kg (loading dose 8mg/kg); Ptz = pertuzumab, 420mg (loading dose 840mg)
- Adjuvant trastuzumab to complete one year of treatment and endocrine therapy for ER+ and/or PR+ tumors

van Ramshorst et al, *Lancet Oncol* 2018; van Ramshorst et al, *Eur J Cancer* 2017 — ClinicalTrials.gov identifier: NCT01996267



Event-Free Survival



*HR <1 favors PTC+Ptz

Anthracycline-bazli kemo:

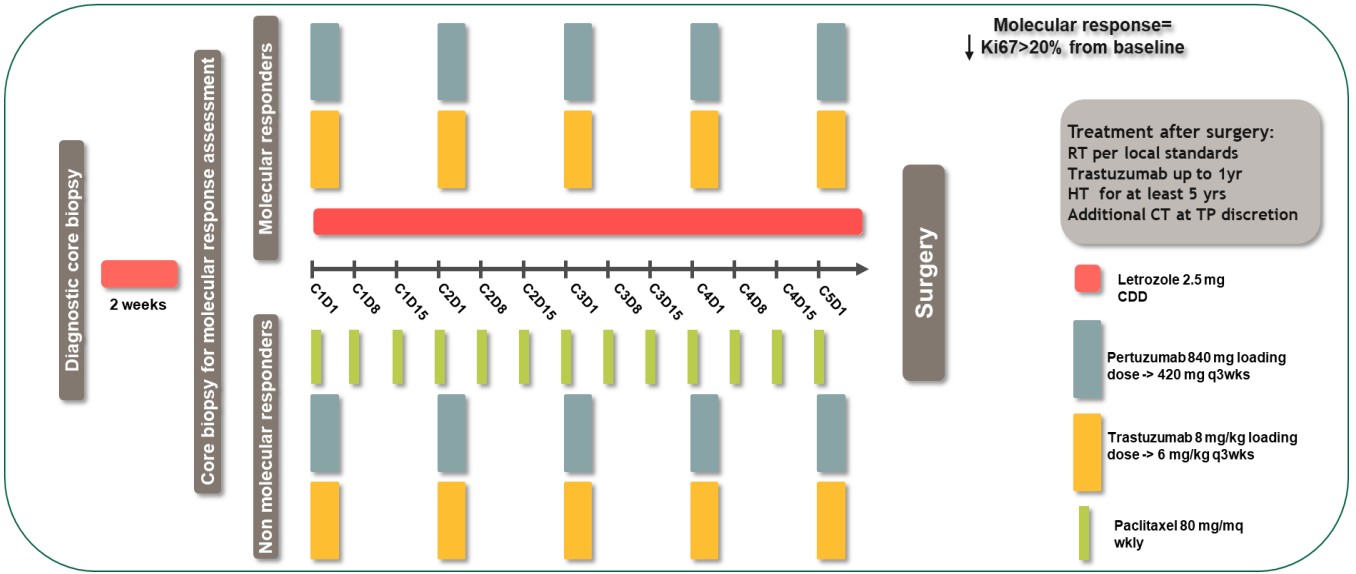
- Daha cok febril notropeni (10% vs. 1%)
- Daha cok kardiyak toksisite : LVEF decrease ≥10% and LVEF <50% (8% vs. 3%, p 0.044)
- Daha cok 2.cil kanser
- Daha az neuropati (5% vs. 7%)

van der Voort et al, ASCO 2020

Azaltilmis Yaklasim: daha az tedavi ile pCR

Kemoterapisiz olur mu?

PerELISA: HER2+/HR+ hastalar 2 haftalik Letrazol Ki67 yanitina gore gruplandirildi:

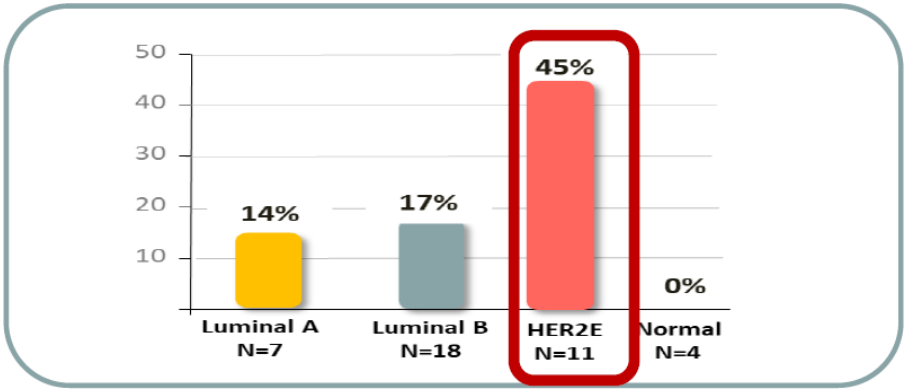


Guarneri V et al. Ann Oncol 2019

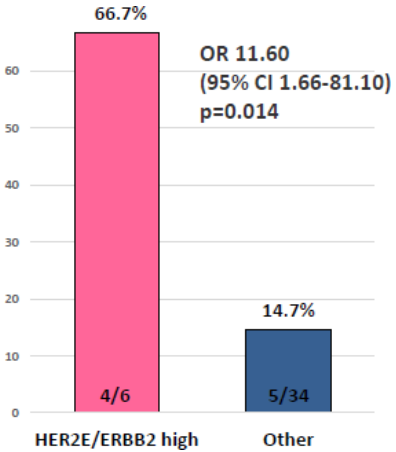
Azaltılmış Yaklaşım: daha az tedavi ile pCR

PerELISA: pCR oranlari molekular yaniti olanlarda letrozole, trastuzumab-pertuzumabla tedavi (KEMOTERAPISIZ)

pCR rate according to PAM50



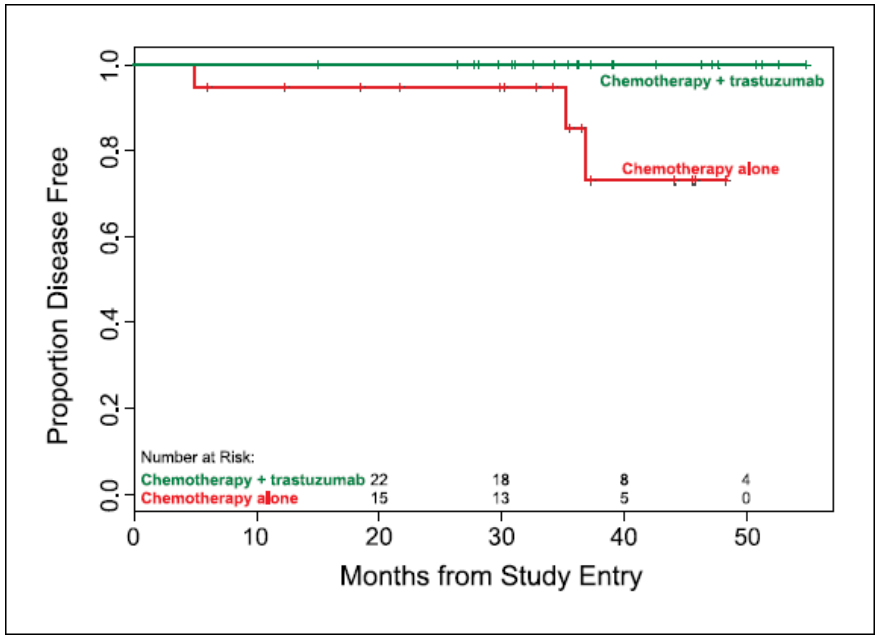
kombine biomarkırlara göre pCR
(HER2E/ERBB2 high mRNA)



Guarneri V, et al. ASCo 2018, Ann Oncol 2019; Prat A, et al. JNCI 2019

Azaltılmış Yaklaşım: pCR varsa daha az tedavi?

Indirek kanit MDACC calismasi (trastuzumab + kemo sadece neoadjuvan fazda verilmis)

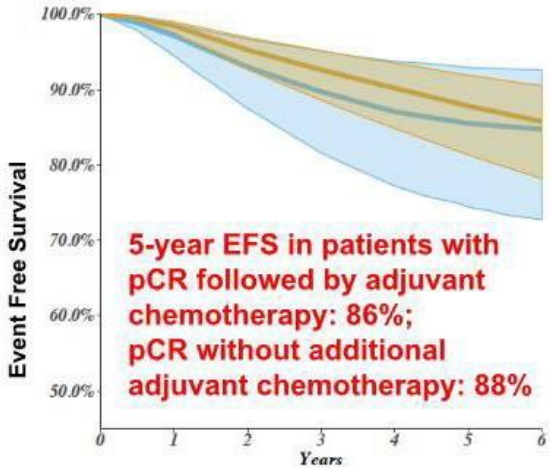


DFS of randomized patients, irrespectively of pCR

Buzdar AU, et al. Clin Cancer Res 2007

Azaltilmis Yaklasim: pCR varsa daha az tedavi?

27.000 hastanin metaanalizi, adjuvan kemoterapinin pCR ve EFS'ye etkisi



Blue: pCR without adjuvant chemotherapy
Orange: pCR with adjuvant chemotherapy

Adjuvant Chemotherapy	Hazard Ratio (pCR and EFS)	95% PI
Yes[1]	0.36	0.19-0.67
No[2]	0.36	0.27-0.54

pCR was associated with significantly improved EFS in both groups, and there was no significant difference in Hazard Ratios between the two groups[3].

[1] >90% of patients received adjuvant chemotherapy
[2] No more than 10% of patients received adjuvant chemotherapy
[3] Paired T-test (difference in log-HR: 0.02, 95% PI: -0.75-0.73; p = 0.60)

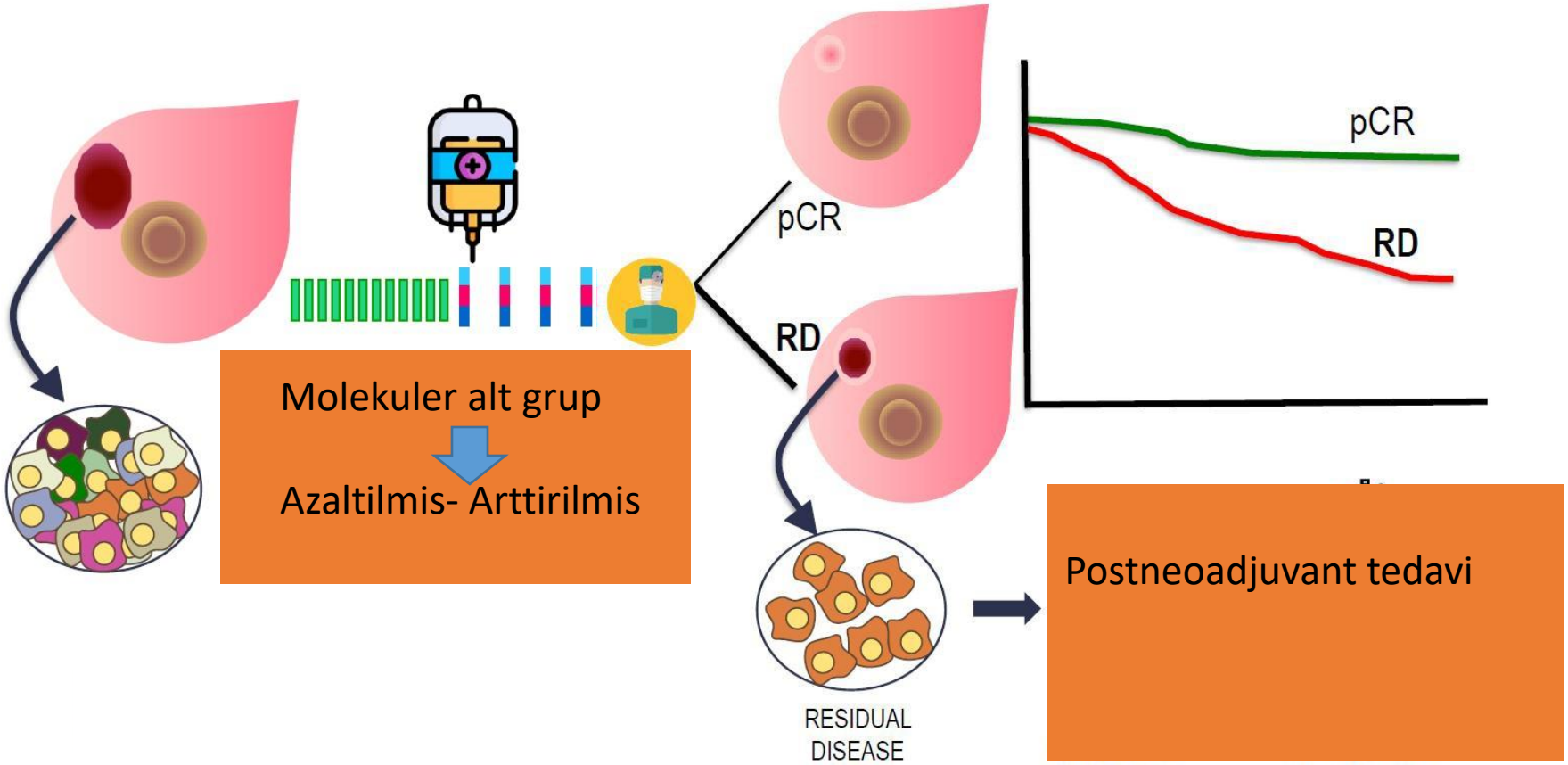
Randomizasyon yok, tum meme kanseri subtipleri

L. Spring, SABCS 2018

AZALTILMIŞ NEOADJUVAN TEDAVİ YAKLAŞIMI

- Daha geniş analizlere ihtiyaç var.
- Daha iyi prediktorler gerekir.
- Ancak COVID pandemisi döneminde uygun hastalar için düşünülebilir.

NEOADJUVANT TEDAVI:
Kisisellestirilmis kanser tedavisi platformudur



Teşekkürler

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