HER2 Pozitif Meme Kanseri Optimal Adjuvan Tedavi

Dr Ö Berna ÖKSÜZOĞLU
Erzincan Üniversitesi Tıp Fakültesi
SB Dr AYurtaslan Ankara Onkoloji Eğt ve Arş Hastanesi

Sunum Planı

- Giriş (HER ailesi, trast, MMK de trast)
- Adjuvan Trastuzumab Çalışmaları
- Direnci Yenme için Artırma Çabaları
- Azaltma Çabaları
- Neoadjuvan Tedavi Öğretileri
- Adjuvan anti-Her2 Tedavi Terziliği
- Sonuçlar

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- Meme Kanseri %15-20 sinde HER2 pozitifliği
  - gen amplifikasyonu ve/veya protein ekspresyonu

- HER2 pozitifliği tümörün saldırganlığı ve azalmış sağkalım ile birliktelik gösterir
  - daha fazla viseral ve beyin metastazı

Epidermal Büyüme Faktör Reseptörü Ailesi

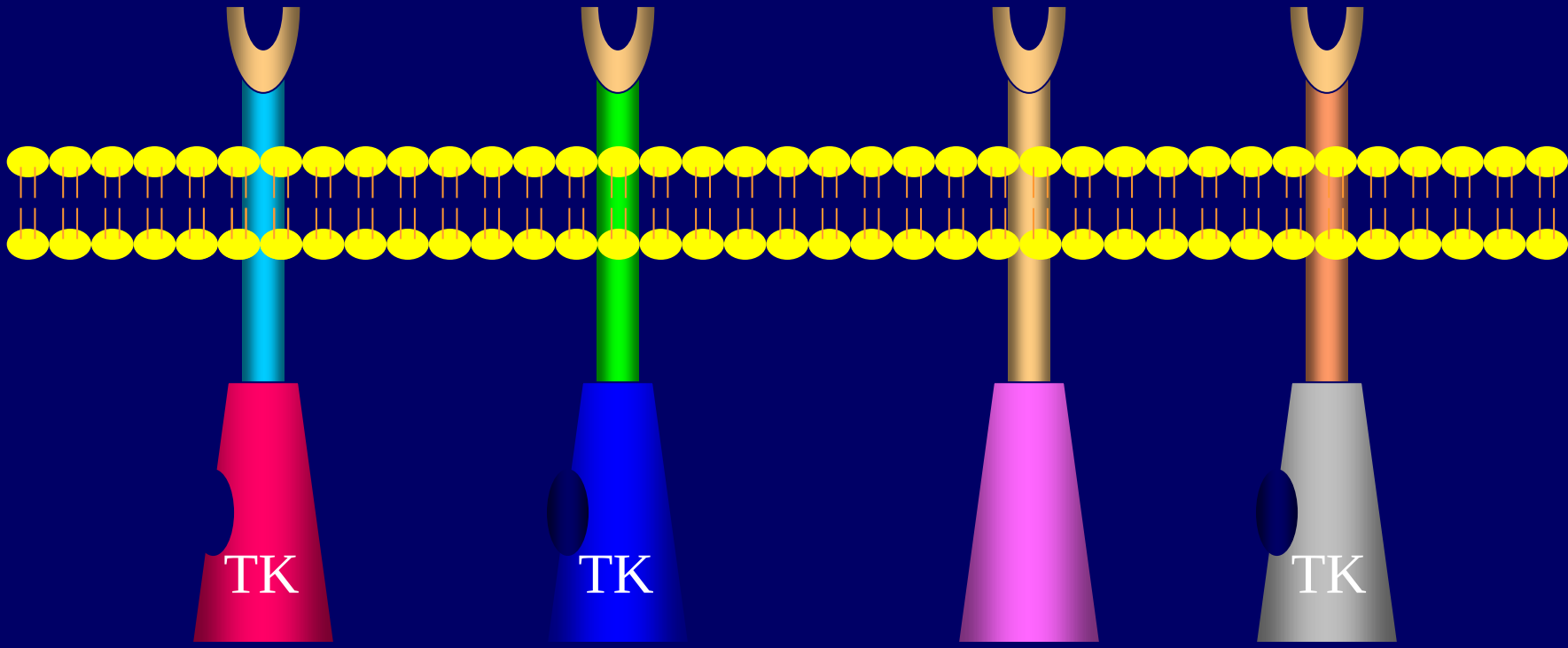
EGF, TGFα , β Cellulin

Amphiregulin, HB-EGF

No Ligand

Heregulins

NRG2
NRG3
Heregulins
β-cellulin



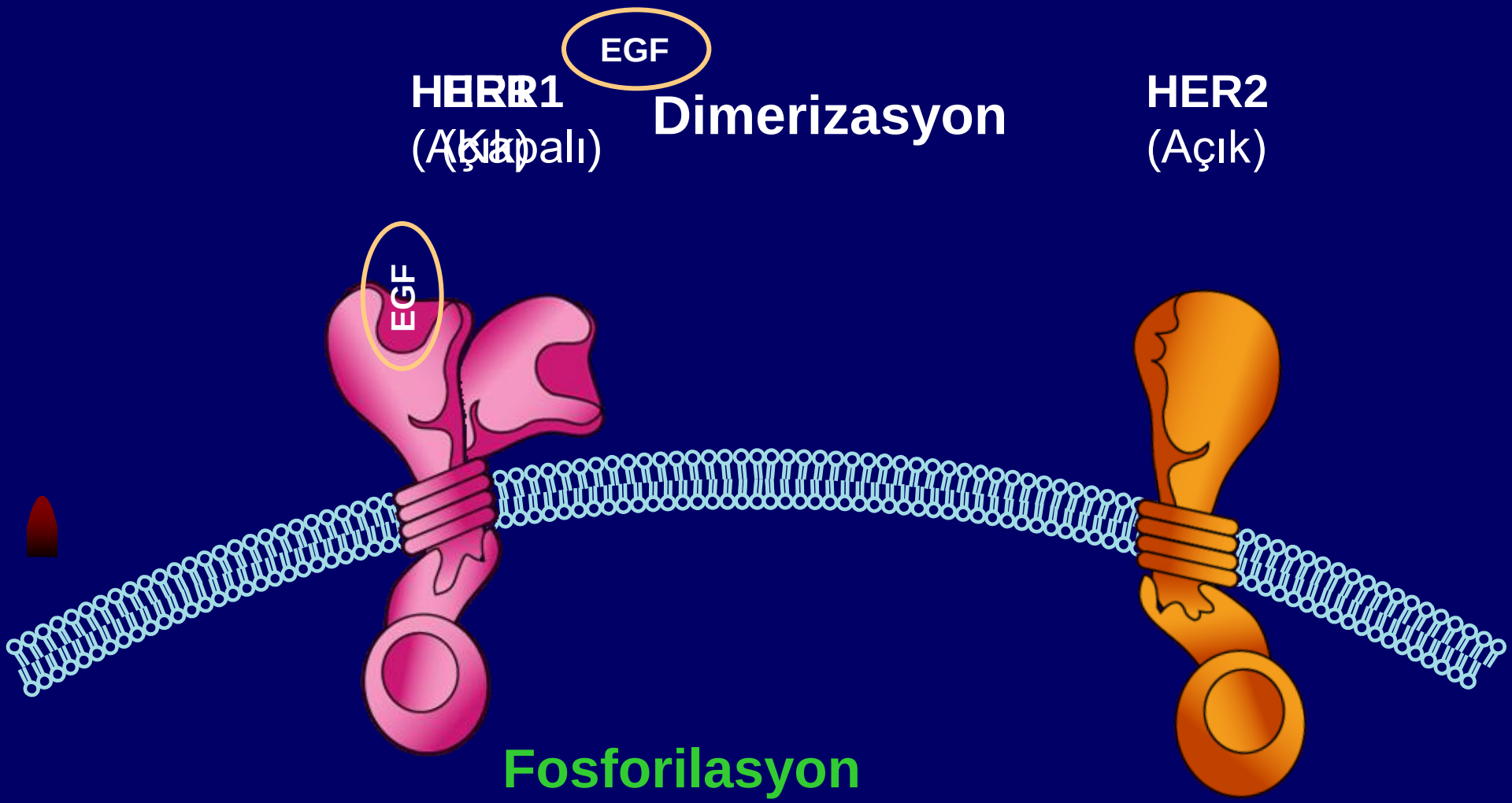
erbB1
HER1
EGFR

erbB2
HER2
neu

erbB3
HER3

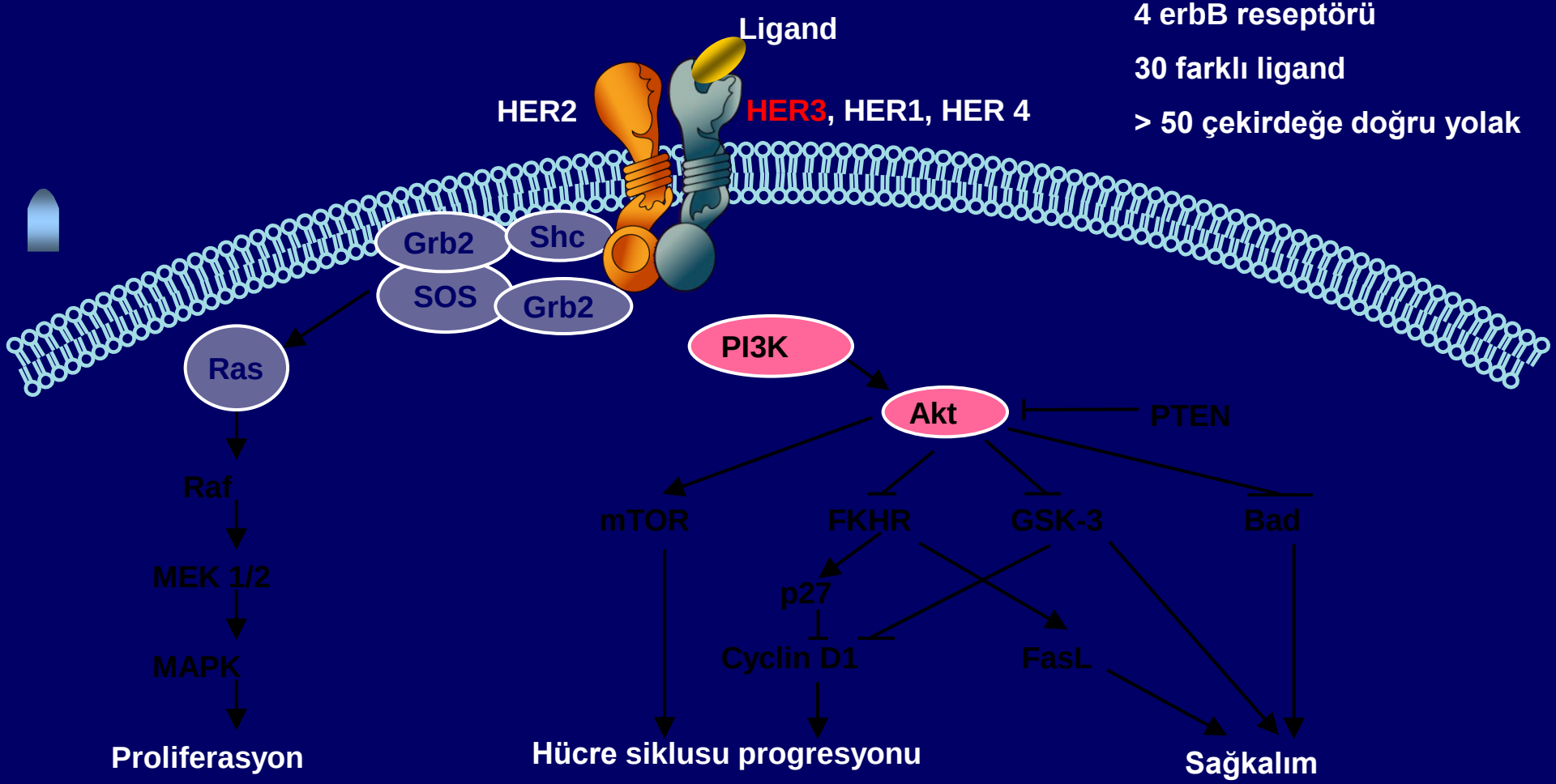
erbB4
HER4

HER Ailesi: Ligand bağlanma, Dimerizasyon ve Fosforilasyon



Roskoski. *Biochem Biophys Res Commun.* 2004;319:1; Herbst. *Int J Radiat Oncol Biol Phys*. 2004;59(suppl):21.

HER ailesi: Proliferasyon ve Sağkalım Sinyalizasyon Yolakları

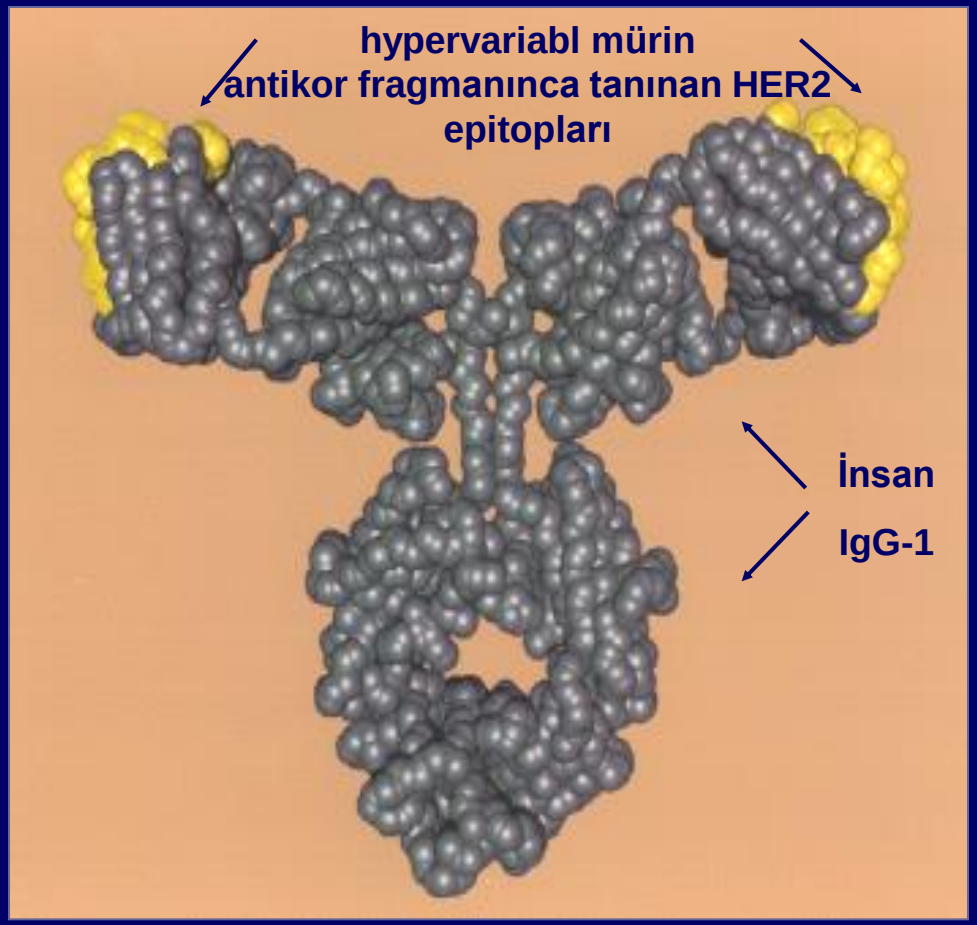


Lin and Winer. *Breast Cancer Res.* 2004;6:204.

Meme Kanserinde ErbB2 Hedeflenmesi

1987/88	gene amplification & protein overexpression found in ~ 20-30% primary breast tumors; correlation with poor prognosis
1989	growth inhibitory ErbB2 specific mAbs described
1991	Phase I clinical trial with murine mAb 4D5
1992	Phase I clinical trial with "humanized" 4D5 - Herceptin
1996	Phase II trial results published
1997	Phase III trials with published
1998	Herceptin approval in the USA for treatment of ErbB2^{+++}, metastatic breast cancer

Trastuzumab (Herceptin®)

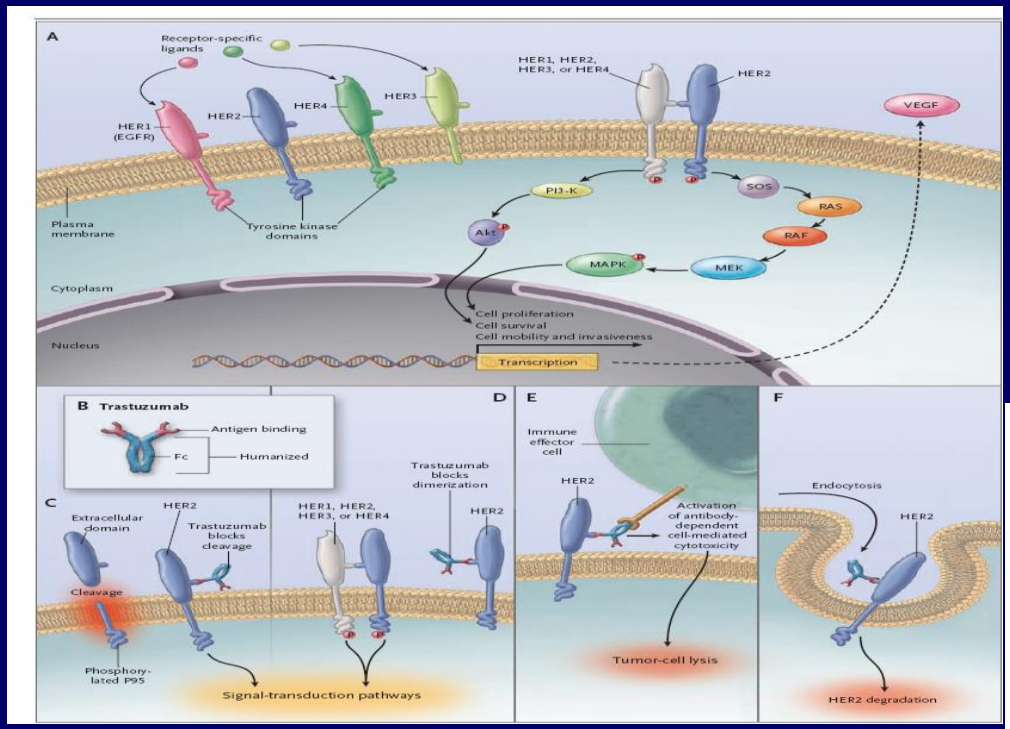


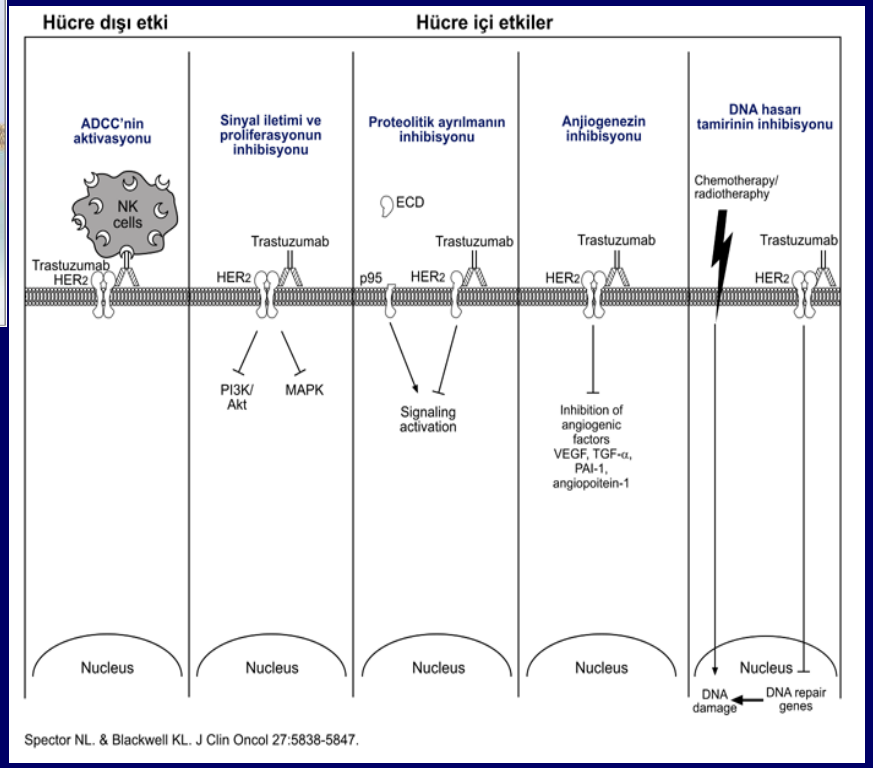
- Humanize monoklonal antikor
  - 95% insan, 5% mürin
  - Akut hipersensitivite < %10
  - HAMA (human anti-mouse antikor)
  - Myelosupr, bulantı-kusma nadir
  - Kardiyotoksisite
    - yaş,HT,bazal EF, antrasikl kullanma
    - LVEF ↓ %7.1-18.6 class III-IV KKY %0.4-4.1

MMK için onay;
FDA 1998
Türkiye 2003

Adjuvan için onay;
FDA 2006
Türkiye 2008

Trastuzumab: Etki Mekanizmaları





Spector NL. & Blackwell KL. J Clin Oncol 27:5838-5847.

MMK Trastuzumab Monoterapi

Table 1. Results of Studies of Trastuzumab as Monotherapy for Metastatic Breast Cancer.

Study	No. of Patients	Immunohistochemical Staining Grade (Assay)	Dose		No. of Previous Chemotherapy Regimens	Overall Response Rate	Median Treatment Duration (range)
			Loading	Maintenance		%	*wk*
Baselga et al.[41]	46	2–3+ (4D5)	250 mg	100 mg weekly	0 to 5	11	20 (4–240)
Cobleigh et al.[42]	222	2–3+ (4D5 or CB11)	4 mg/kg	2 mg/kg weekly	1 or 2	15	12 (0–118)
Vogel et al.[43]	114	2–3+ (4D5 or CB11)	4 mg/kg or 8 mg/kg	2 mg/kg weekly or 4 mg/kg weekly	0	26	15 (13–21)

Hudis C. N Engl J Med 2007;357:39-51

MMK : KT vs KT+ Trastuzumab

Table 2. Randomized Trials Comparing Chemotherapy Alone with Chemotherapy plus Trastuzumab for Metastatic Disease.

Trial and End Result	Chemotherapy	Chemotherapy plus Trastuzumab	P Value
Slamon et al.[46]			
No. of patients	234 (doxorubicin and cyclophosphamide or paclitaxel)	235 (doxorubicin and cyclophosphamide or paclitaxel)	
Time to disease progression (mo)	4.6	7.4	<0.001
Response rate (%)	32	50	<0.001
Median overall survival (mo)	20	25	0.046
Marty et al.[47]			
No. of patients	94 (docetaxel)	92 (docetaxel)	
Time to disease progression (mo)	6.1	10.7	0.001
Response rate (%)	34	61	0.001
Median overall survival (mo)	23	31	0.032

Hudis C. N Engl J Med 2007;357:39-51

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JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Prognosis of Women With Metastatic Breast Cancer by *HER2* Status and Trastuzumab Treatment: An Institutional-Based Review

Shaheenah Dawood, Kristine Broglio, Aman U. Buzdar, Gabriel N. Hortobagyi, and Sharon H. Giordano

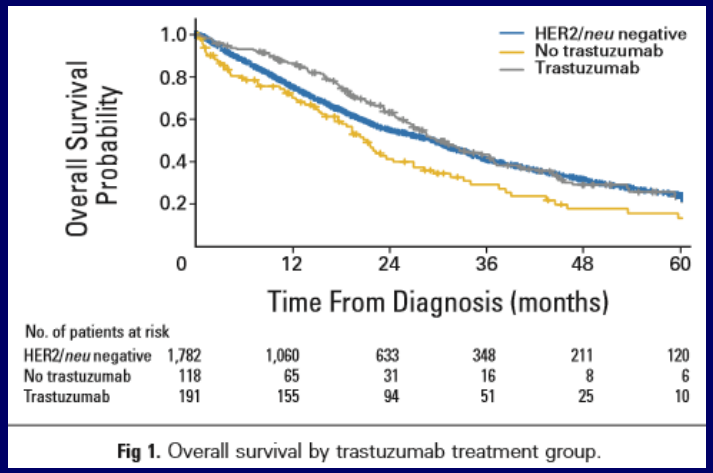
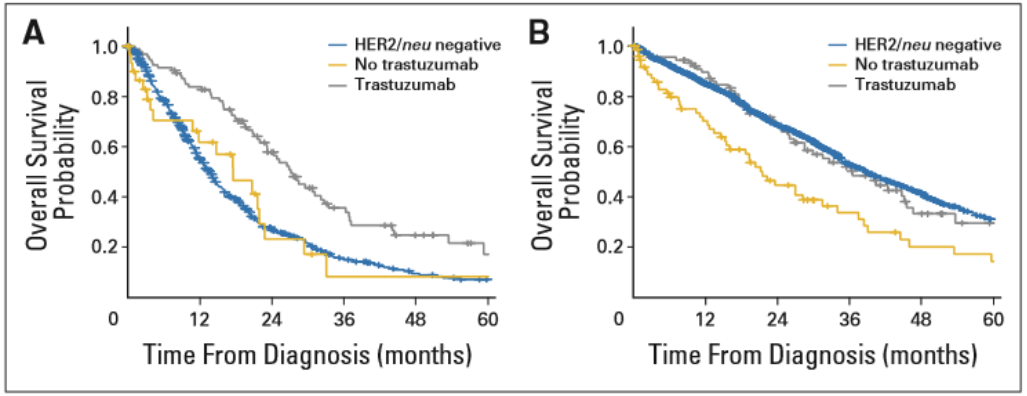


Fig 1. Overall survival by trastuzumab treatment group.

ER negatif

ER pozitif



1997-2007 arası her2 durumu bilinen 2091 MMK kadın izlem (MD Anderson)
118 (%5.6) her2+ ve trast almamış
191 (%9.1) her2+ ve trast almış
1782 (%85.3) her2 –
16.9 aylık izlemde 1 yıllık sağkalım % 70.2, 86.6 ve 75.1
Çalışma Sonucu: her2+trast alanlar (her2- kadınlara kıyasla) %44 daha uzun sağkalım (HR 0.56) ilk 24 ayda fark belirgin sonra kayboluyor
SONUÇ: Trastuzumab ile MMK seyri değişmiştir

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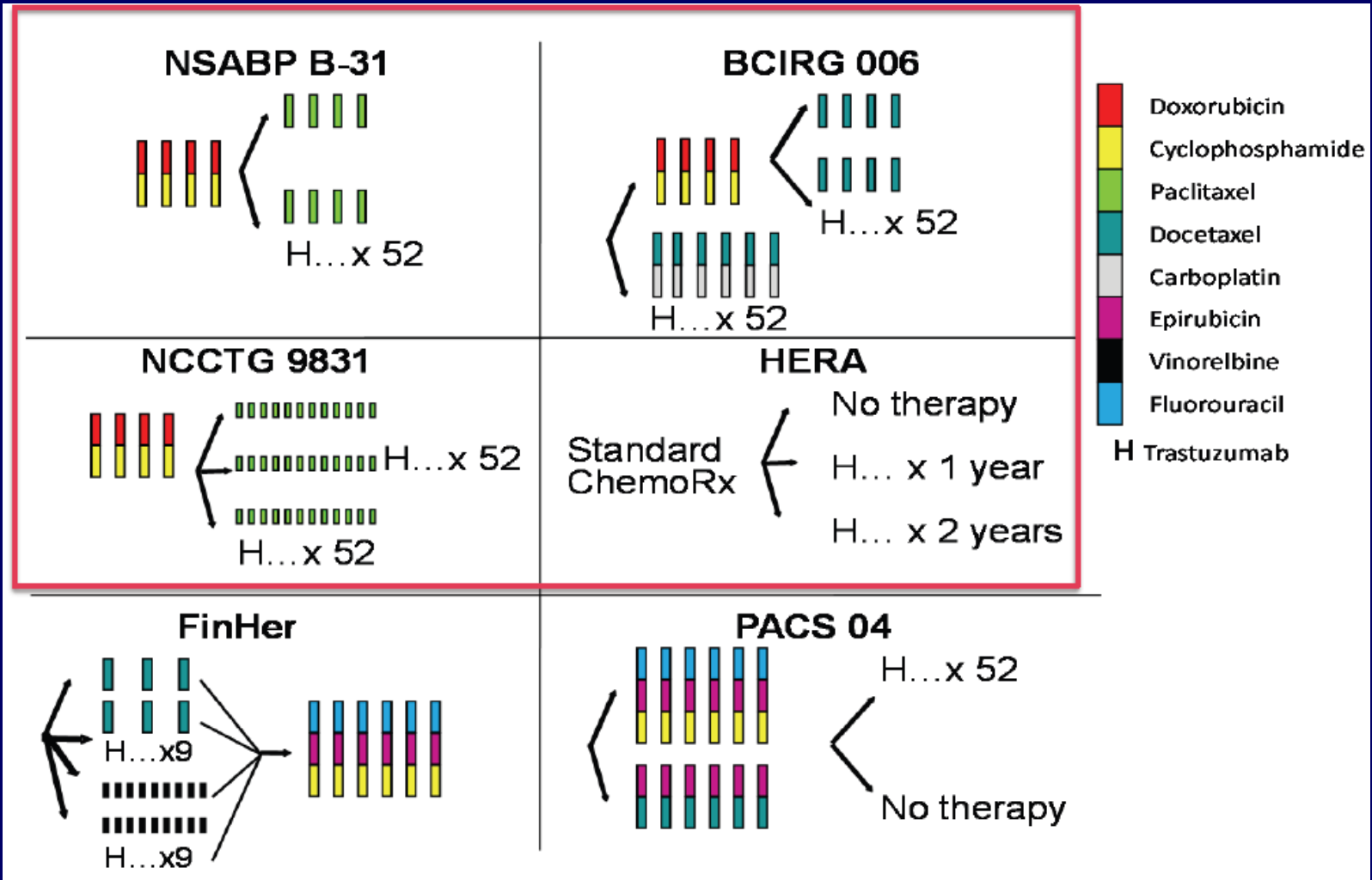
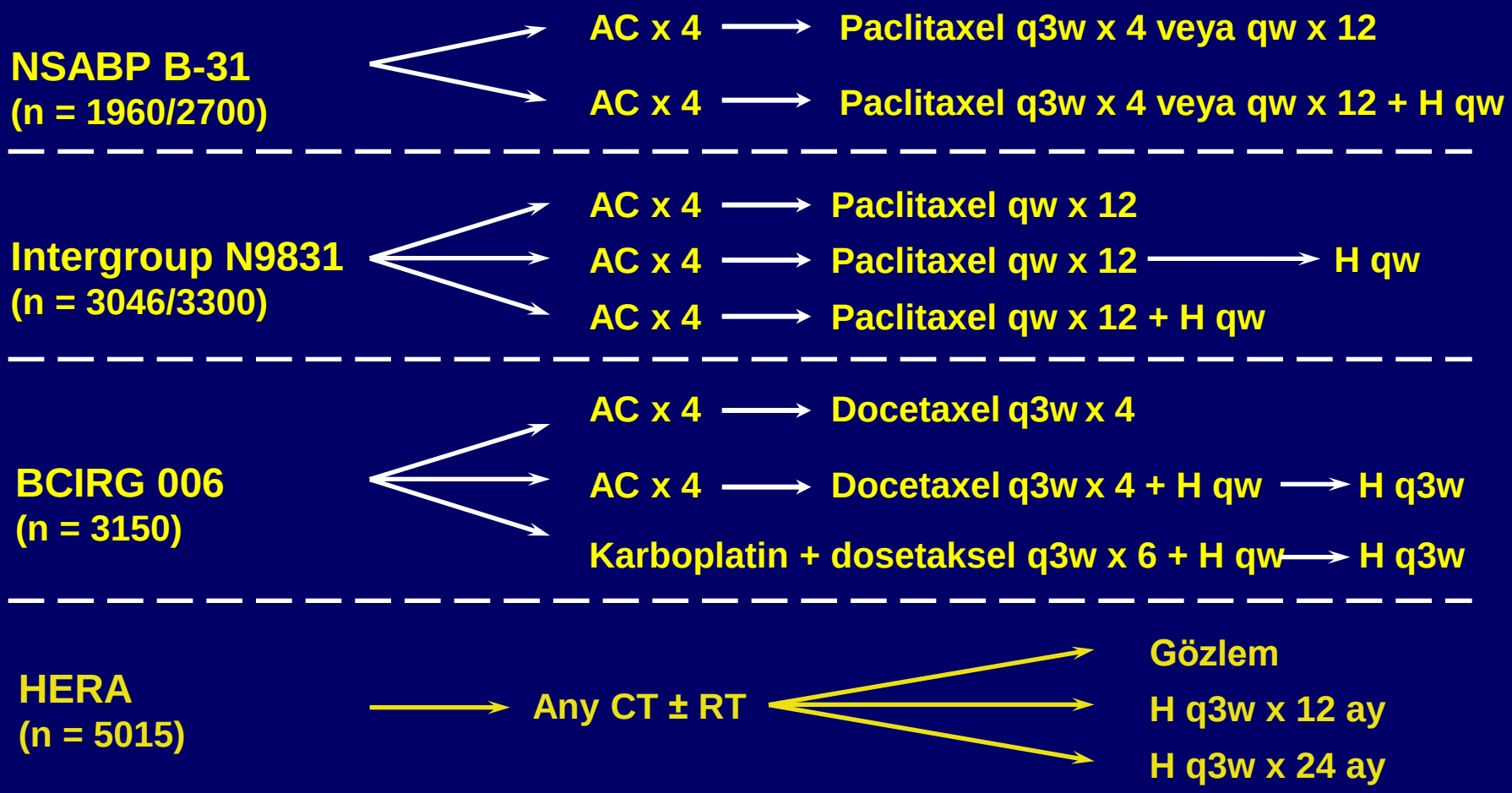
Herceptin®: Adjuvan Pivotal 4 Çalışma (>13,000 erken evre hasta)



Herceptin®: Adjuvan Pivotal 4 Çalışma (>13,000 erken evre hasta)

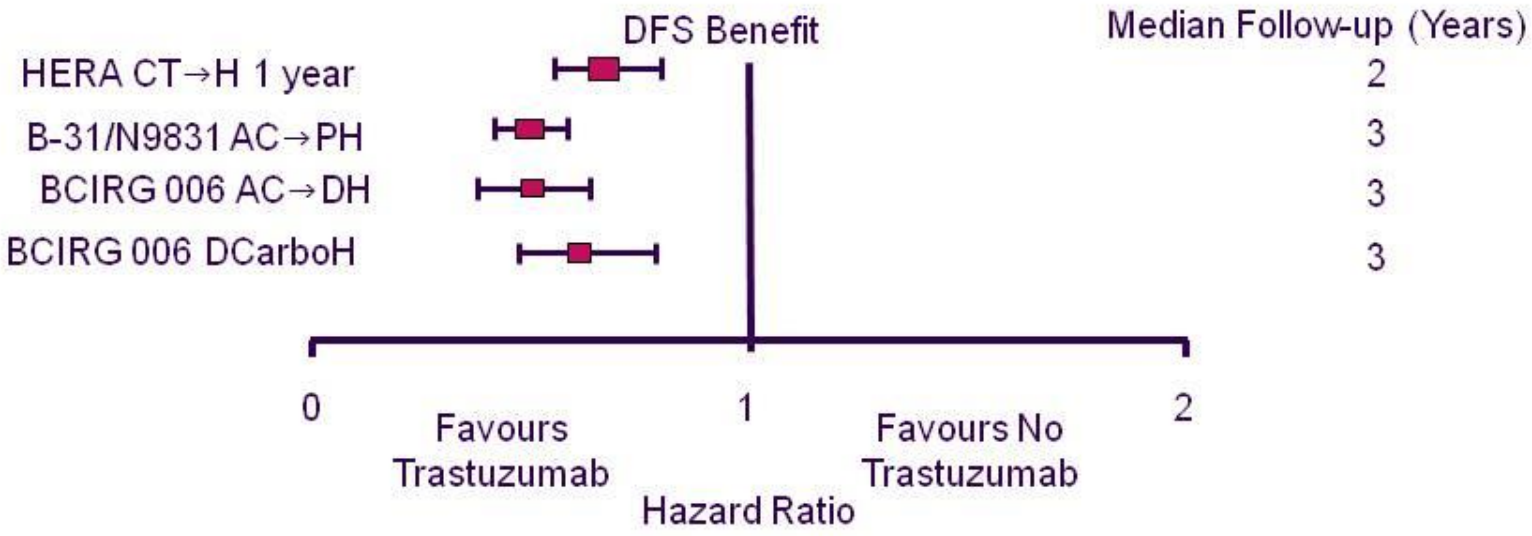


2000-2001 başlamış
2005 ilk sonuçlar açıklandı

Adjuvan Anti-Her 2 Çalışmaları

Trial	Number HER2+	Open	Original Reference	Updated Reference
HERA	5,102	2001-2005	Piccart-Gebhart NEJM 2005	Goldhirsch Lancet 2013
NCCTGN9831	3,505	2000-2005	Romond NEJM 2005	Perez JCO 2013
BCIRG 006	3,222	2001-2004	Slamon NEJM 2011	Slamon NEJM 2011
NSABP B31	2,101	2000-2005	Romond NEJM 2005	Romond JCO 2012
PACS-04	528	2003-2006	Spielmann JCO 2009	Spielmann JCO 2009
FinHER	232	2000-2003	Joensuu NEJM 2006	Joensuu JCO 2009

Trastuzumab Improves DFS by 40-50%

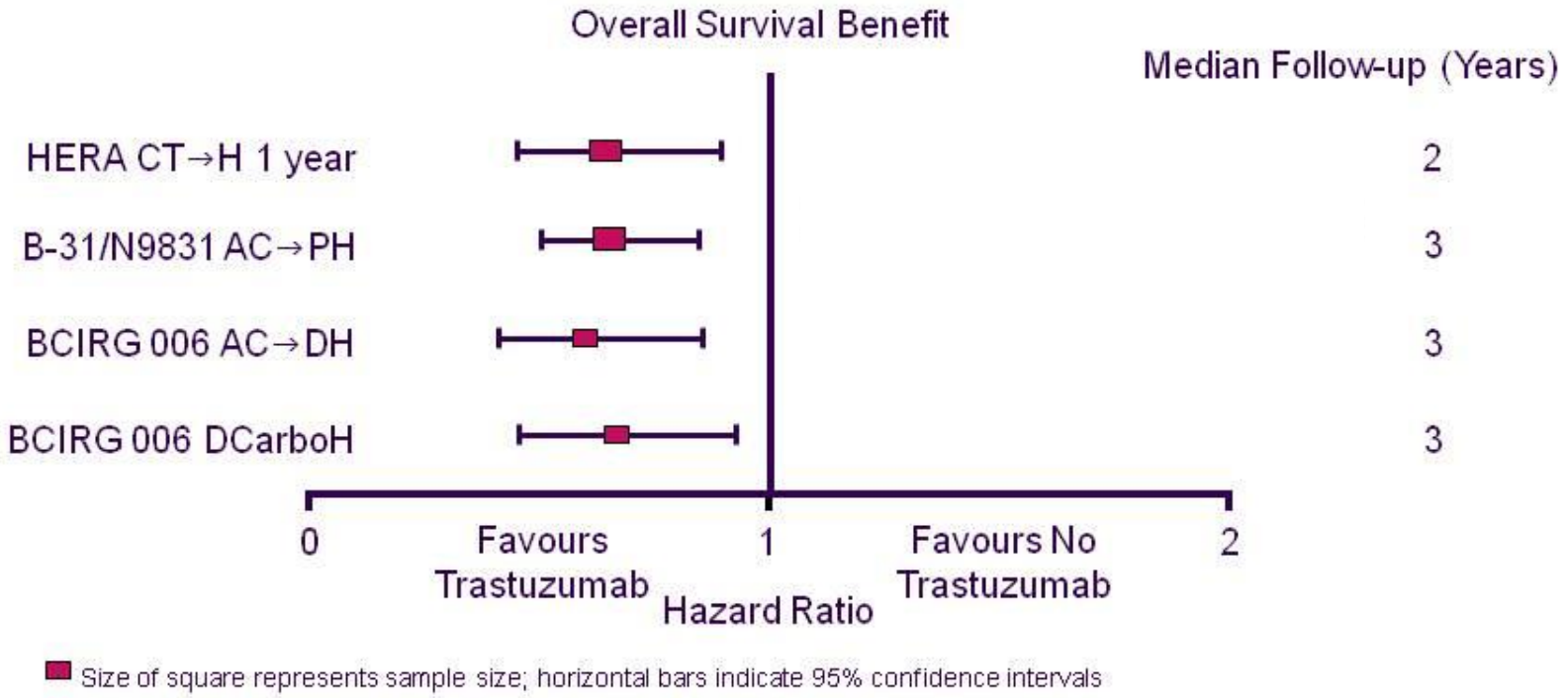


Size of square represents sample size; horizontal bars indicate 95% confidence intervals

CT = chemotherapy; H = trastuzumab; AC = doxorubicin, cyclophosphamide; P = paclitaxel; D = docetaxel; Carbo = carboplatin

Joensuu et al. N Engl J Med 2006; Perez et al. ASCO 2007, Abstract #512; Slamon et al. SABCS 2006; Smith et al. Lancet 2007; Spielmann et al 2007

Trastuzumab Improves OS by 33%



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Perez et al. ASCO 2007, Abstract #512; Slamon et al. SABCS 2006; Smith et al. Lancet 2007

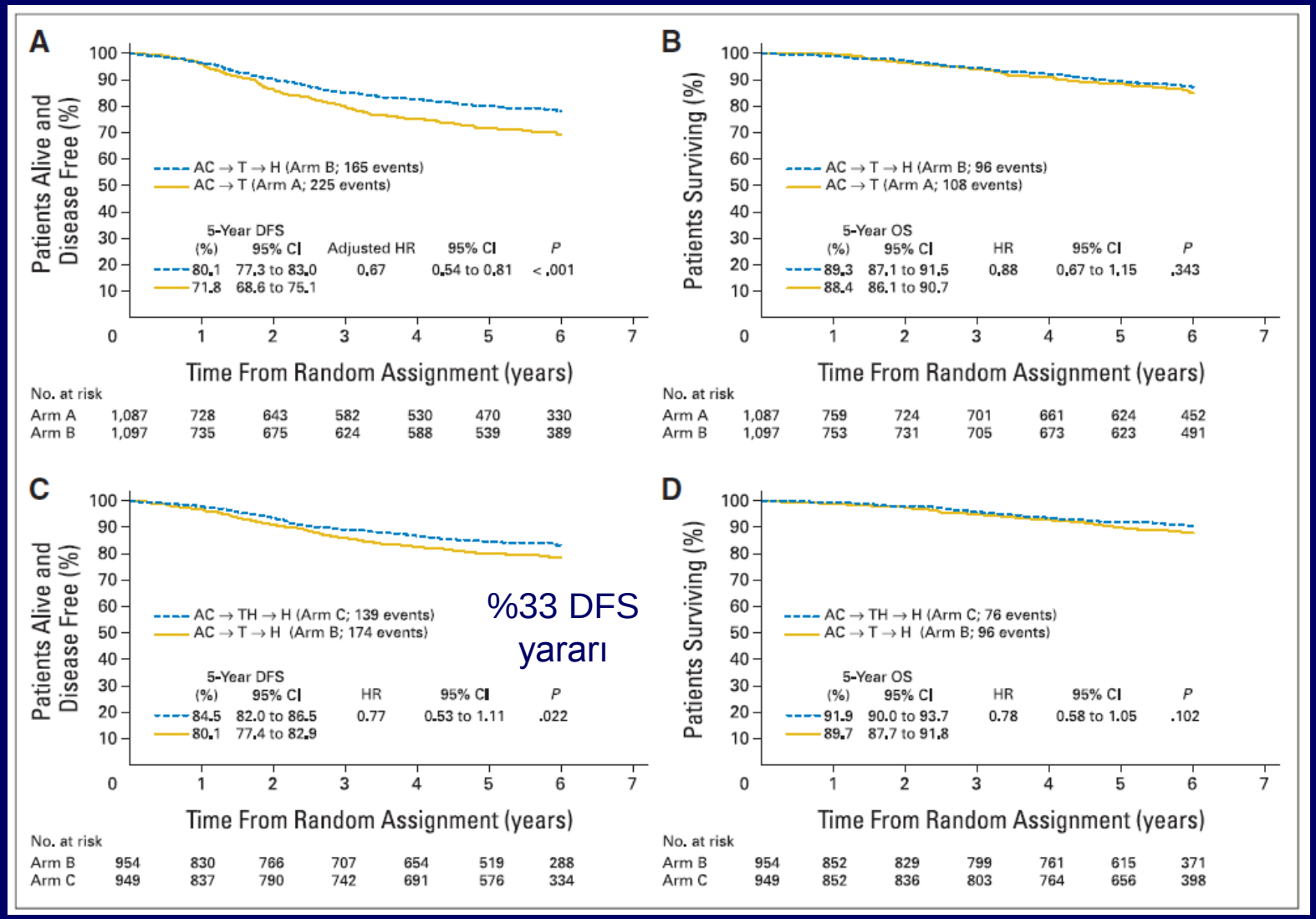
Randomized clinical trials assessing trastuzumab in the adjuvant setting.

Study	Treatment arms	Trastuzumab duration (weeks)	Timing of trastuzumab	Number of patients	Median follow-up	DFS (HR, 95% CI)	OS (HR, 95% CI)
HERA	CT	0	NA	1698	8 years	(0.76, 95% CI: 0.67–0.86)	(0.76, 95% CI: 0.65–0.88)
	CT T	52	Sequential	1703			
	CT T	104	Sequential	1701			
NSABP-B31 and NCCTG N9831 joint analysis	AC P	0	NA	2018	3.9 years	(0.52, 95% CI: 0.45–0.60)	(0.61, 95% CI: 0.50–0.75)
	AC PT T	52	Concurrent	2028			
BCIRG 006	AC D	0	NA	1073	65 months	DFS at 5 years is 84%	OS at 5 years 91%
	AC DT T	52	Concurrent	1074		(HR = 0.64, $P < 0.001$)	(HR = 0.77, $P = 0.04$).
	DCarboT T	52	Concurrent	1075			
FinHER	D/V FEC	0	NA	116	62 months	DDFS	(0.55, 95% CI, 0.27–1.11)
	D/V T FEC	9	Concurrent	115		(0.65, 95% CI: 0.38–1.12)	
PACS004	FEC ED	0	NA	268	47 months	3-year DFS	NA
	FEC ED T	52	Sequential	206		78% (95% CI, 72.3–82.5)	
						81% (95% CI, 75.3–85.4)	
ALTTO	L + T	52	2 designs: sequential (1)	8381	4.5 years	L + T vs. T	NA
	T→ L	12	Concurrent (2A, 2B)			(0.84, 97.5% CI: 0.70–1.02)	
	T	52				T→ L vs. T	
	L	NA				(0.93, 97.5% CI, 076–1.13)	
PHARE	T	26	Sequential	1691	42.5 months	2-year DFS	NA
	Observation	NA	NA	1693		(HR 1.28, 95% CI 1.05–1.56, p = 0.29 for a non-inferiority HR of 1.15)	

Özet Sonuç:
Aksilla LN pozitif ve yüksek riskli negatif hastalarda kemoterapiye trastuzumab eklenmesi DFS ve OS yararı

NSABP 9831 başabaş ardışık ve eşzamanlı karşılaştırılmış
6 yıllık izlemde eşzamanlı > ardışık (DFS) (%84 vs 80, HR 0.77, p .02)
Perez EA , JCO 2011; 29: 4491

N9831: Ardışık ve Eş Zamanlı Trastuzumab



Perez E et al. J Clin Oncol 2011;4491-4497

- Adjuvan trastuzumab ile tüm başarılara rağmen erken evre her2+ meme kanserli hastaların %10-15'i nüks etmekte (DİRENÇ)
- Direnci yenmek için
  - Artırma çabaları
  - Azaltma çabaları
  - Neoadjuvan tedavi öğretileri
  - Adjuvan antiHer2 tedavi terziliği

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Direnci Yenmek İçin Artırma Çabaları

- Daha uzun süreli trastuzumab
  - HERA çalışması 8 yıllık izlem
    - 2 yıl trast vermek 1 yıldan üstün değil (HR0.99, p.086)
    - gr 3-4 yanetki (%16.3→20.4) LVEF düşüş (%4.1→7.2) artmış

Goldhirsch A, ESMO 2012 ve Lancet 2013; 382: 1021

- Dual her2 blokajı
  - metastatik olgularda işe yaramış
    - EGF104900 trast dirençli MMK lapat +/- trast
      - trast eklemek PFS ve OS yararı (HR 0.74, 0.74)

Blackwell KL, JCO 2012; 30: 2585

Direnci Yenmek İçin Artırma Çabaları

- Dual her2 blokajı
  - ALTTO adjuvan lap and/or trast treatm optimisation
    - 4 kollu, n: 8381, KT sonra veya eşzamanlı antiher2
      - Trats vs Lap vs Trast+Lap vs ardışık 12w Trast→6hf boş→34 hf Lap
    - 4.5 yıllık izlemde eşzamanlı dual her2 blokajı, trast mono göre istatis anlamsız %16 DFS yararı (p 0.048)
      - Lap alanlarda ishal, döküntü, hepatotoks daha sık
  - ExteNET (n: 2840) uzatılmış adjuvan antiher2 tedavi
    - Adjuvan (KT ve) 1 yıl trast tamamlamış neratinib 1 yıl (irreversibl panHER TKİ)
    - %33 iDFS yararı (%91.6→93.9, HR0.67, p .004)
    - 2015 SanAntonio 3 yıllık iDFS yararı devam (%89.9→92, HR0.74)
    - HR + yarar daha fazla

Direnci Yenmek İçin Artırma Çabaları

- Dual her2 blokajı
  - ALTTO adjuvan lap and/or trast treatm optimisation
  - ExteNET neratinib ile uzatılmış tedavi
  - APHINITY trast +/- pertuzumab (devam ediyor)
  - BETH adj trast +/- bevasizumab (DFS yararı yok)
  - KATHARINE neoadj sonrası rezidü hast.da trast vs TDM1 (antikor-ilaç konjugatı) devam ediyor

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Azaltma Çabaları

- Standard adj trast temelli tedavi süre azaltma
  - FinHER (n:232) doset/vinorelbx3 +/- 9hf trast→3xCEF90
    - Trast eklenince 3 yıllık nükssüz sağkalım (RFS) yararı (%78→89, p .01)
    - Final analiz 62 ay izlem uzak DFS yarar trendi
  - PHARE (n:3381) optimal adj trast süresi 6 ay vs 12 ay
    - Non-inferiorite karşılanmadı (2 yıl DFS %91.1vs 93.8, p0.29)
    - Kardiyak olaylar 6 ay grubunda daha az (p <.0001)
  - Optimal trast süresini araştıran devam eden çalışmalar

Trials exploring shorter durations of adjuvant trastuzumab : status as of December 2015

Trial	N° of pts	Time needed	Pt charact	CTX/Trast	Non inf mar-gins	Results
6 months vs 12 months						
PHARE	3380	4(+2)Y	N- 55% HR+ 58%	A/T with trast concom or seq	1.15	HR 1.28 (1.05-1.56) (mostly driven by ER- sequential CTX group)
HELLENIC	481	8 Y (!)	N- 17% HR+ 69%	A/T with trast concomitant	1.53	DFS events : 13% vs 10.4% HR 1.58 (0.86-2.10)
PERSEPHONE	4089	8 Y (!)	?	?	?	?
3 months vs 12 months						
SHORT-HER	1250	≈ 5 Y	N- 51% ER+ 67%	Conv A->T+H for 12m TH->A for 3m arm	1.29	?
SOLD	2176	≈ 6 Y	?	TH->A->Tx9m(12m) TH->A (3m)	Superior OS by 4%	?

Azaltma Çabaları

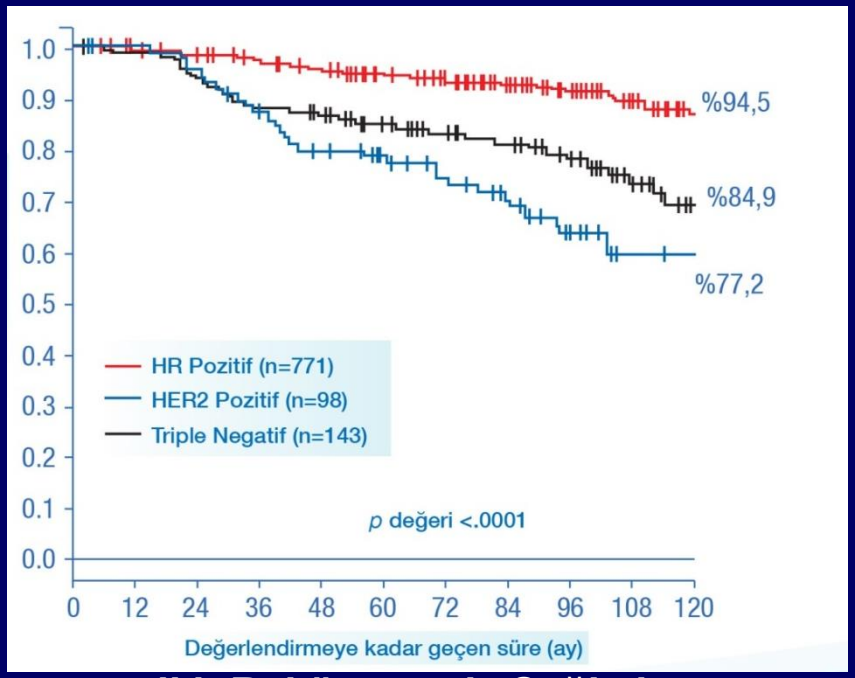
- Standard adj trast temelli tedavi süre azaltma
- Küçük her2+ meme kanserinde optimal tx arayış

Age and Survival Estimates in Patients Who Have Node-Negative T1ab Breast Cancer by Breast Cancer Subtype

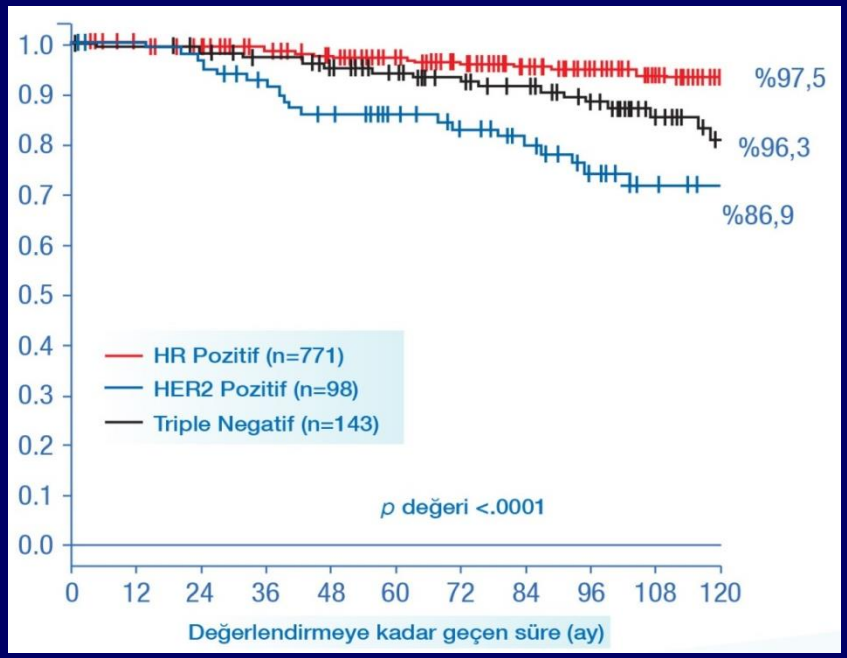
Rachel L. Theriault[1], **Jennifer K. Litton**[2], **Elizabeth A. Mittendorf**[3], **Huiqin Chen**[2], **Funda Meric-Bernstam**[3], **Mariana Chavez-MacGregor**[2], **Phuong K. Morrow**[2], **Wendy A. Woodward**[4], **Aysegul Sahin**[5], **Gabriel N. Hortobagyi**[2], and **Ana M. Gonzalez-Angulo**[2]

[1]Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

KT ve trastuzumab almayan T1a,b N0 hasta (n: 1020)



5 yıllık Rekürrenssiz Sağkalım

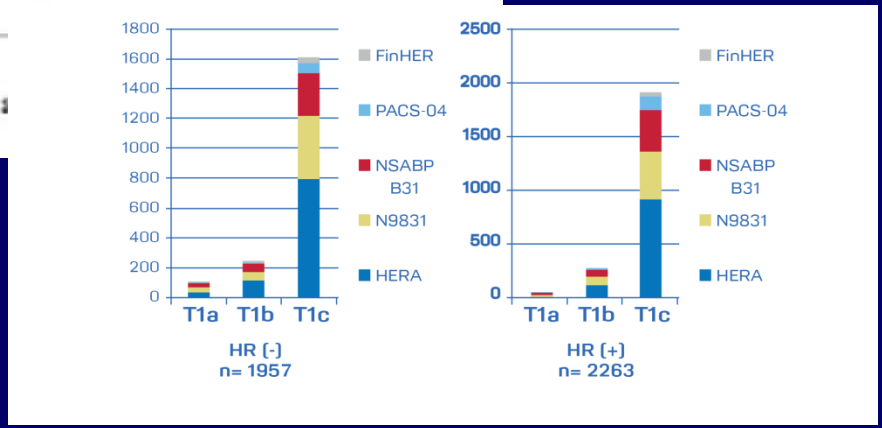


5 yıllık Uzak Rekürrenssiz Sağkalım

Clin Breast Cancer. 2011 October ; 11(5): 325–33

Her2 Pozitif Meme Kanserinde Adjuvan Tedavi

Trial	Eligibility Requirements
NSABP B-31	• Node-positive disease
N-9831	• Node-positive disease OR • High-risk node-negative disease: tumor ≥2 cm and ER- or PR-positive, or tumor ≥1cm and ER- and PR-negative
HERA	•Node-positive disease OR •Node-negative disease with tumor ≥1cm
BCIRG 006	•Node-positive disease OR •Node-negative disease AND one of the following risk factors: tumor >2cm, ER- and PR-negative, grade 2-3, or age <35
FinHER	•Node-positive disease OR •Node-negative disease with tumor ≥2 cm



Azaltma Çabaları

- Standard adj trast temelli tedavi süre azaltma
- Küçük her2+ meme kanserinde optimal tedavi arayış
  - Küçük (≤ 2cm) her2+ 4220 hasta retrosp meta-analizi
    - 8 yıllık izlemde HR + ve – lerde trast ekleme ile
      - **DFS (%17.3→24.3, p < 0.001 ve %24→33, p<0.0001)**
      - **OS yararı (7.8→11.6, p 0.005 ve %12.4→21.2, p 0.0001)**
      - Sonuç: HR pozitif ve < 2 LN tutulumu olanlar için daha az agresif tedavi çalışmaları için aday
        - O'Sullivan C, JCO 2015; 33: 2600

APT Çalışması
Çalışma Dizaynı

HER2+
ER+ ya da ER-
Nod Negatif
≤3 cm

Planlanan n=400

Dahil olma

Paklitaksel 80 mg/m2 + Trastuzumab 2mg/kg x12

Ardından 3 haftada bir trastuzumab dozu uygulaması
13 kez (6mg/kg)*

Tek kollu, çok merkezli, faz II çalışma

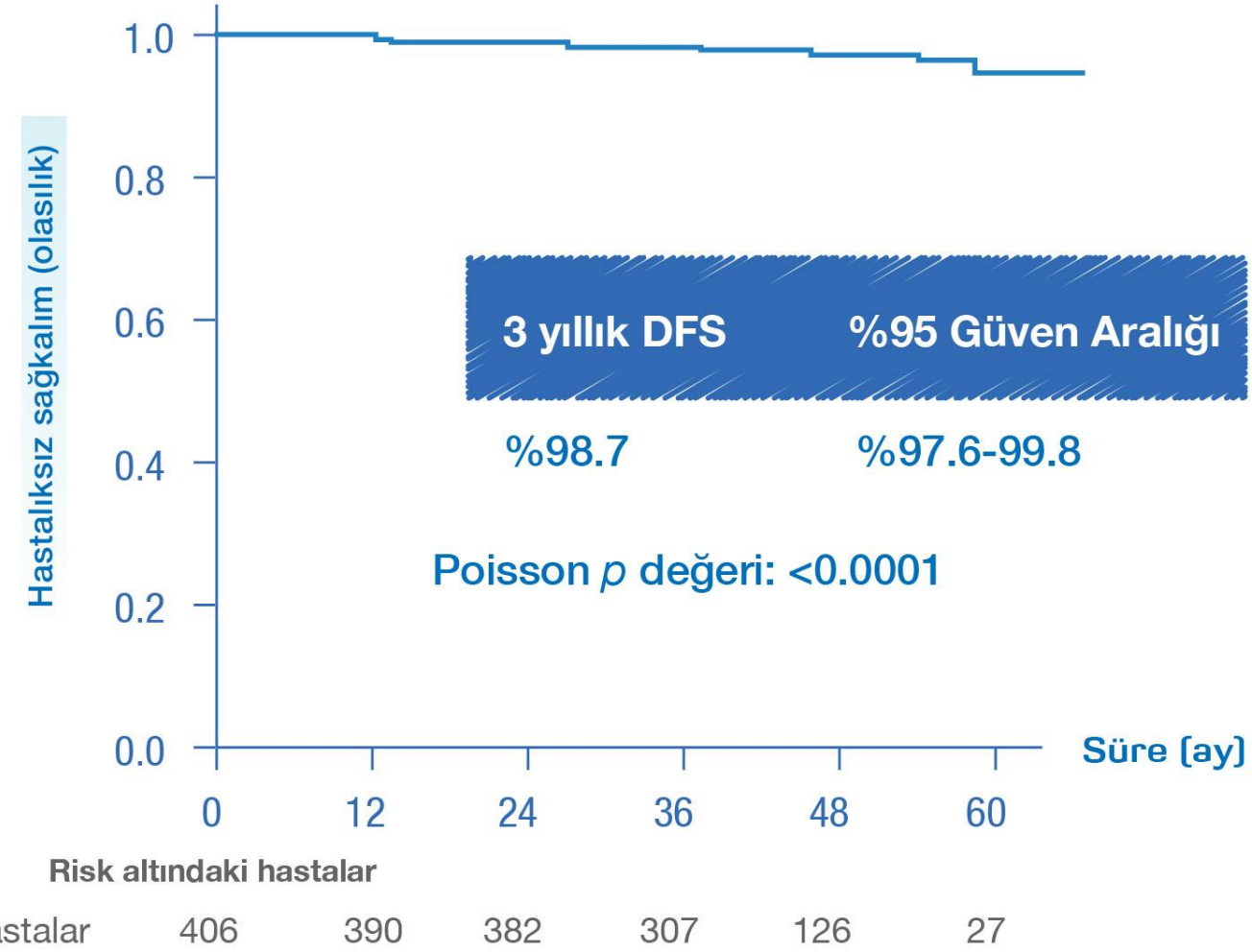
Primer sonlanım noktası: DFS

Tolaney et al, NEJM 2015

APT Çalışması

	n	%	
Yaş			
<50	132	33	
50-70	233	57	
≥70	10	10	
Primer tümör boyutu			
T1a ≤0.5cm	77	19	%50
T1b >0.5-≤1.0	124	31	
T1c >1.0-≤2.0	169	42	%50
T2 >2.0-≤3.0	36	9	
Histolojik Grad			
I İyi diferansiye	44	11	
II Orta derecede diferansiye	131	32	
III Kötü diferansiye	228	56	
HR Durumu (ER ve/veya PR			
Pozitif	272	67	
Negatif	134	33	

APT Çalışması
DFS Analizi - ITT Popülasyon



Tolaney et al, SABCS 2013

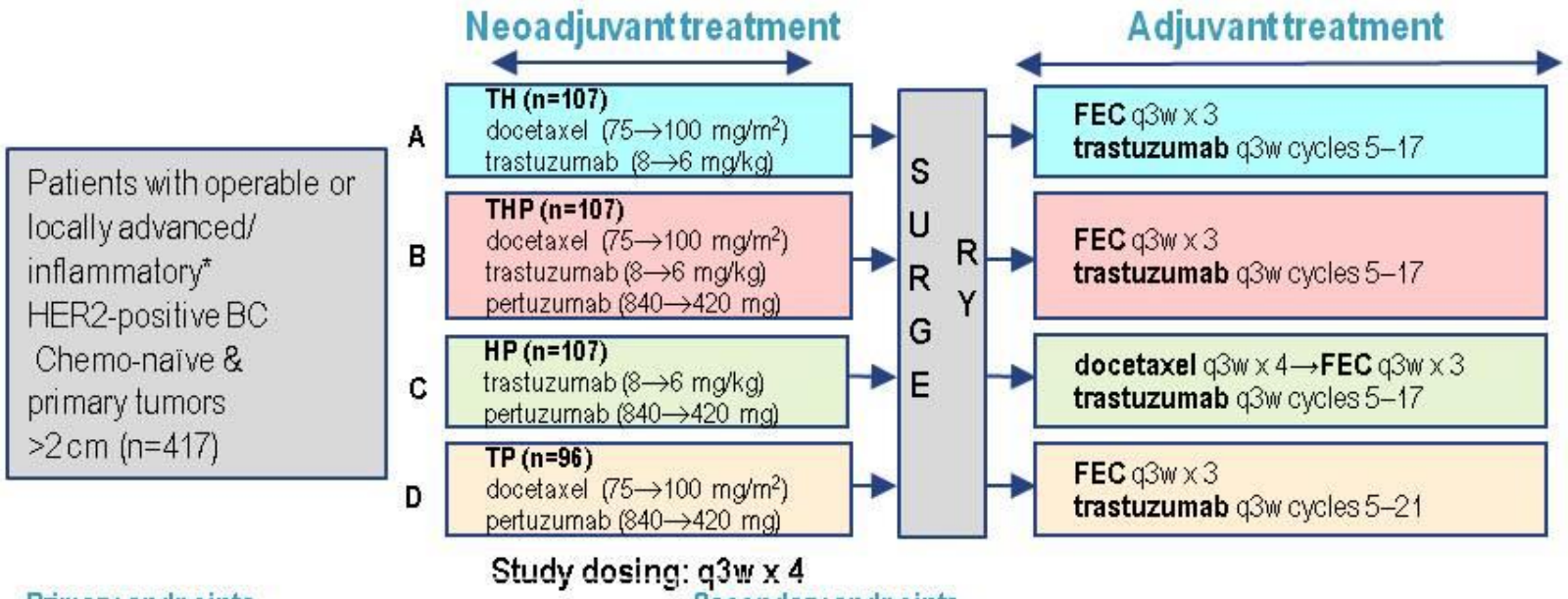
Sunum Planı

- Giriş (HER ailesi, trast, MMK de trast)
- Adjuvan Trastuzumab Çalışmaları
- Direnci Yenme için Artırma Çabaları
- Azaltma Çabaları
- Neoadjuvan Tedavi Öğretileri
- Adjuvan anti-Her2 Tedavi Terziliği
- Sonuçlar

Neoadjuvan Tedavi Öğretileri

- MD Anderson neoadj çalışması
  - KTye trast eklemekle pCR artmış (%26→65, p 0.01)
- NOAH çalışması benzer sonuçlar (Ktye trast ekleme)
  - pCR ve bağlantılı EFS yararı (5 yıl EFS %43→58 p .01)
    - çaprazgeçişe rağmen OS sayısal yarar
      - Gianni L, Lancet Oncol 2014; 15: 640
- NeoSphere (faz 2 n 417)trast ve pertuz ile dual blokaj
  - Pertuz eklenmesi (KT olmasa bile) pCR artmış
    - ER negatif tm.de daha belirgin
      - Gianni L, Lancet Oncol 2012; 13: 25

NeoSphere: Neoadjuvant Phase II Trial



Study dosing: q3w x 4

Primary endpoints

- Comparison of pCR (ypT0is) rates with:
  - TH vs. THP
  - TH vs. HP
  - THP vs. TP

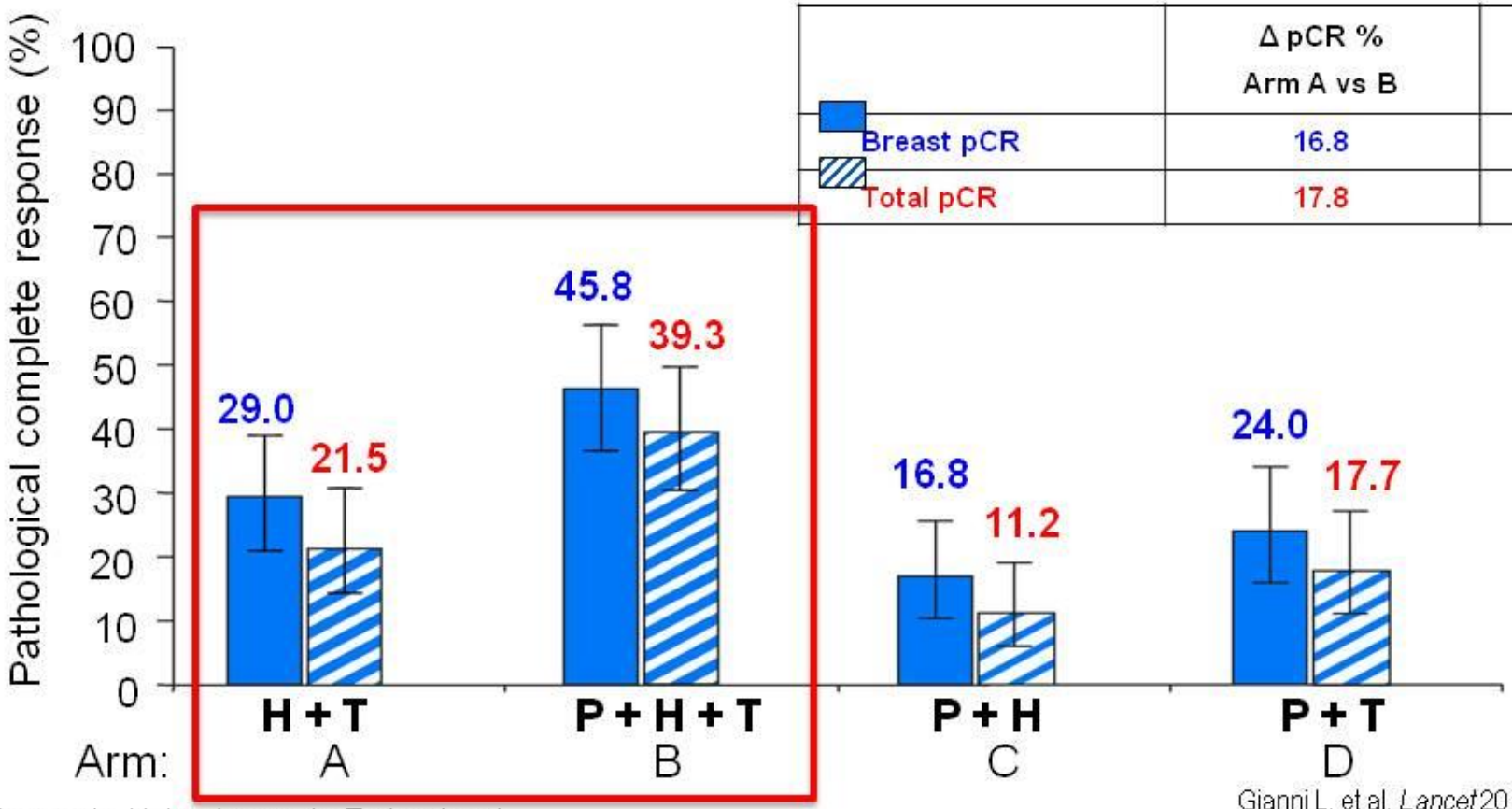
Secondary endpoints

- Clinical response
- DFS
- Breast conservation rate
- Biomarker evaluation

*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0
BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel

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

NeoSphere: pCR rates

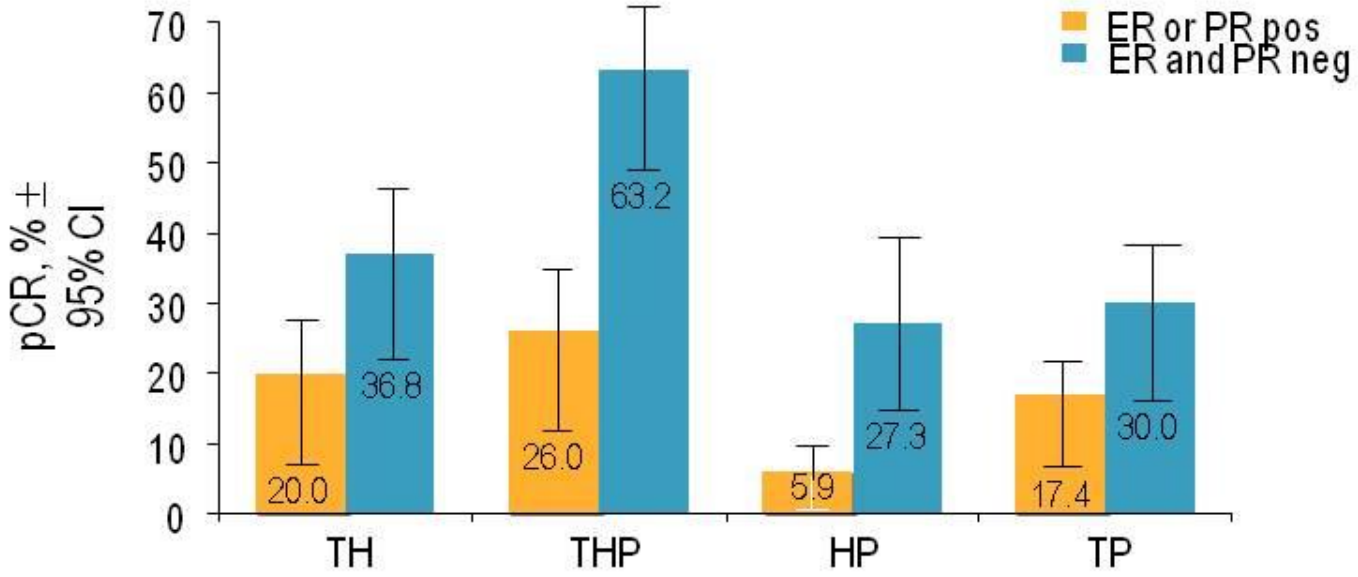


	Δ pCR % Arm A vs B	*p*
Breast pCR	16.8	0.0141
Total pCR	17.8	0.0063

P, pertuzumab; H, trastuzumab; T, docetaxel.

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

NeoSphere: pCR and Hormone Receptor Status



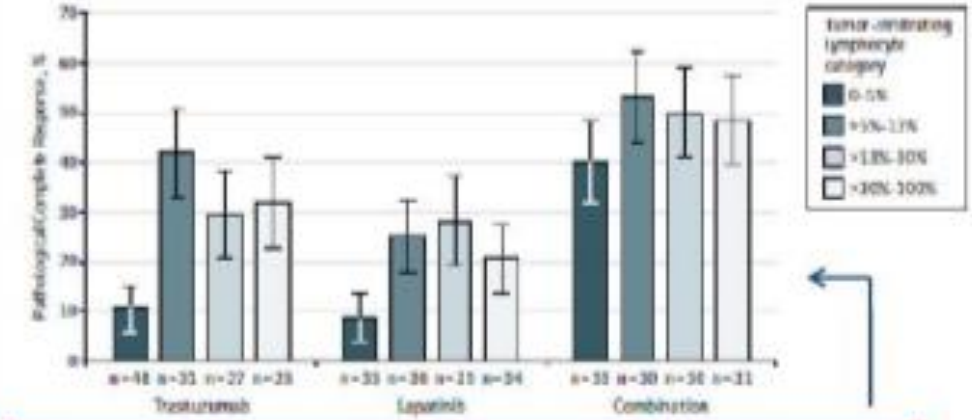
ER, estrogen receptor, H, trastuzumab; pCR, pathological complete response; P, pertuzumab; PR=progesterone receptor; T, docetaxel

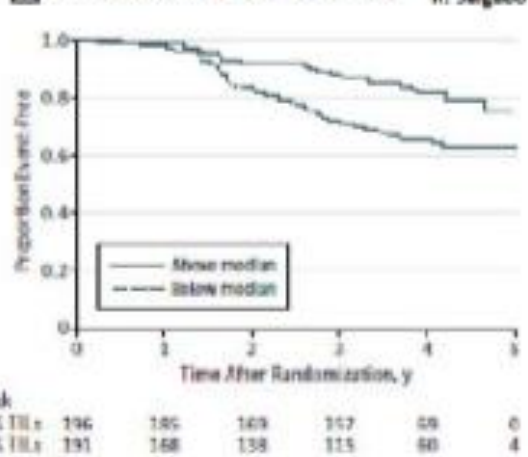
Gianni L et al. *Lancet* 2012;13:25-32

Neoadjuvan Tedavi Öğretileri

- MD Anderson neoadj çalışması
- NOAH çalışması benzer sonuçlar
- NeoSphere trast ve pertuz ile dual blokaj
- NeoALTTO trast ve lapat ile dual blokaj
  - Neoadj 6hf antiher2 (lap vs trast vs lap+trast) → neoadj12 hf hf.lık pakl+antiher2 →4hf ara→S→adj 3FEC100→34hf antiher2 (n 455)
  - Dual blokaj ile pCR artışı var ama EFS/OS farkı yok ve adjuvanda dual blokaj da işe yaramamış (ALTTO)
    - Eleştiri: neoadj çalışmalarda adj çalışmayı predikte etmesi için tüm sistemik tx cerr öncesi verilmelidir
      - DeAzambuja E, Lancet Oncol 2014; 15: 1137

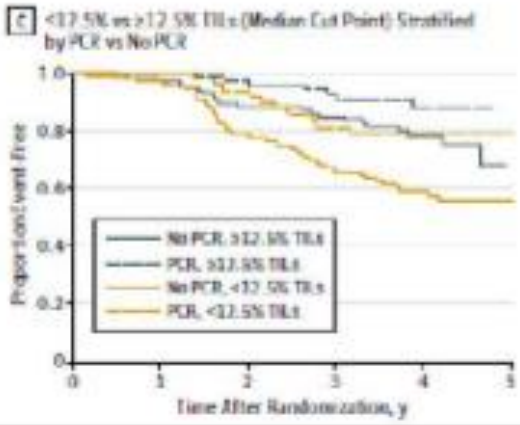
The association between TILs and pCR/EFS in NeoALTTO (n = 387/455 patients)





Higher TILs (> 5%) mean higher pCR rates, independent of treatment group

TILs retain strong prognostic value for EFS, independent of pCR



R. Salgado et al, JAMA Oncol 2015(4):488-455

Sunum Planı

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- Sonuçlar

Adjuvan Anti-HER2 Tedavi Terziliği

- PIK3CA mutasyonu veya PTEN kaybı ile gerçekleşen PI3K yolağı aktivasyonu, trastuzumab direnciyle ilişkilendirilmiş
  - Metastatik ve adjuvan (FinHER) çalışmalarda PIK3CA mutasyonlarının ve PTEN kaybının (N9831) adj trast yararı için prediktif olmadığı
- TIL (tümör infilltre eden lenfosit)
  - Trast yararını predikte eden biyobelirteç mi?
    - Evet (FinHER Loi S, Ann Oncol 2014)
    - Hayır (9831 Perez EA, SanAntonio 2014) ama bu çalışmada TIL kemoterapi yararını predikte etmekte
  - TIL rolü, immün gen imzaları çalışmaları devam

Association between TILS and RFS/OS in the adjuvant trastuzumab trials

S. Loi

FinHER: (N = 209)

Only *LPBC* benefit from addition of trastuzumab

↑

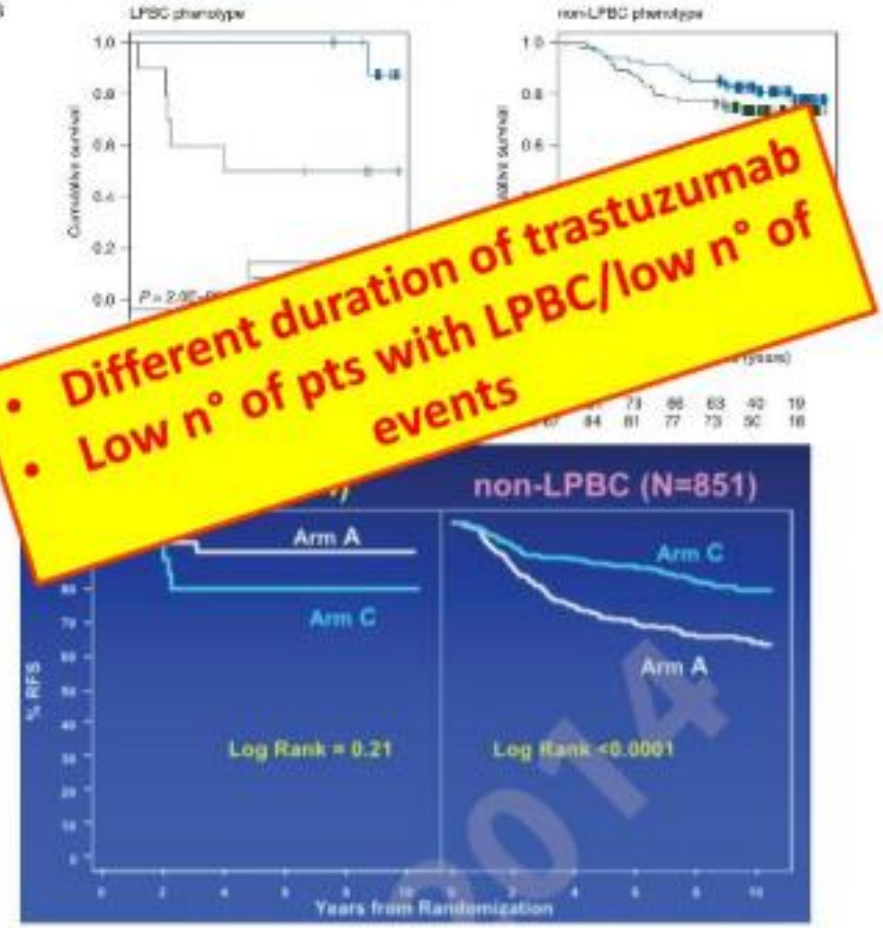
Conflicting results

↓

E. Perez

N9831: (N = 945)

Only *non-LPBC* benefit from addition of trastuzumab



Most promising "tools" for improved anti HER2 treatment tailoring

Advanced HER2+ BC	Early HER2+ BC
• Molecular imaging (HER2-PET/FDG-PET) • HER2 mRNA / PIK3CA • ? PDL-1	• TILs • Tumor exome sequencing • Immune / stroma gene expression signatures • CTC? ctDNA?

Need for ↑↑↑ collaboration, earlier and more comprehensive data sharing, multi-dimensional data analysis!

special articles

Annals of Oncology 26: 1533–1546, 2015
doi:10.1093/annonc/mdv221
Published online 4 May 2015

Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

A. S. Coates[1], E. P. Winer[2], A. Goldhirsch[3*], R. D. Gelber[4], M. Gnant[5], M. Piccart-Gebhart[6], B. Thürlimann[7], H.-J. Senn[8] & Panel Members[†]

Annals of Oncology 26: 1533–1546, 2015
doi:10.1093/annonc/mdv221
Published online 4 May 2015

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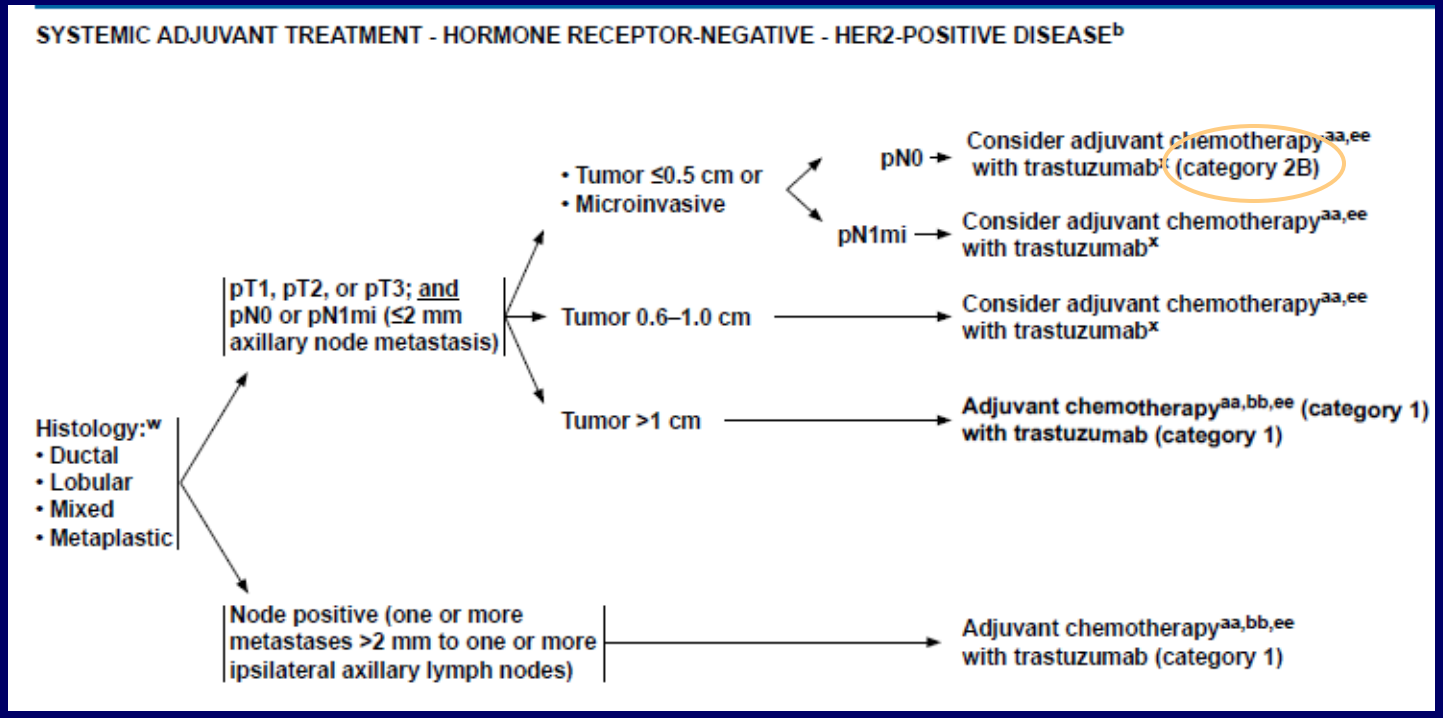
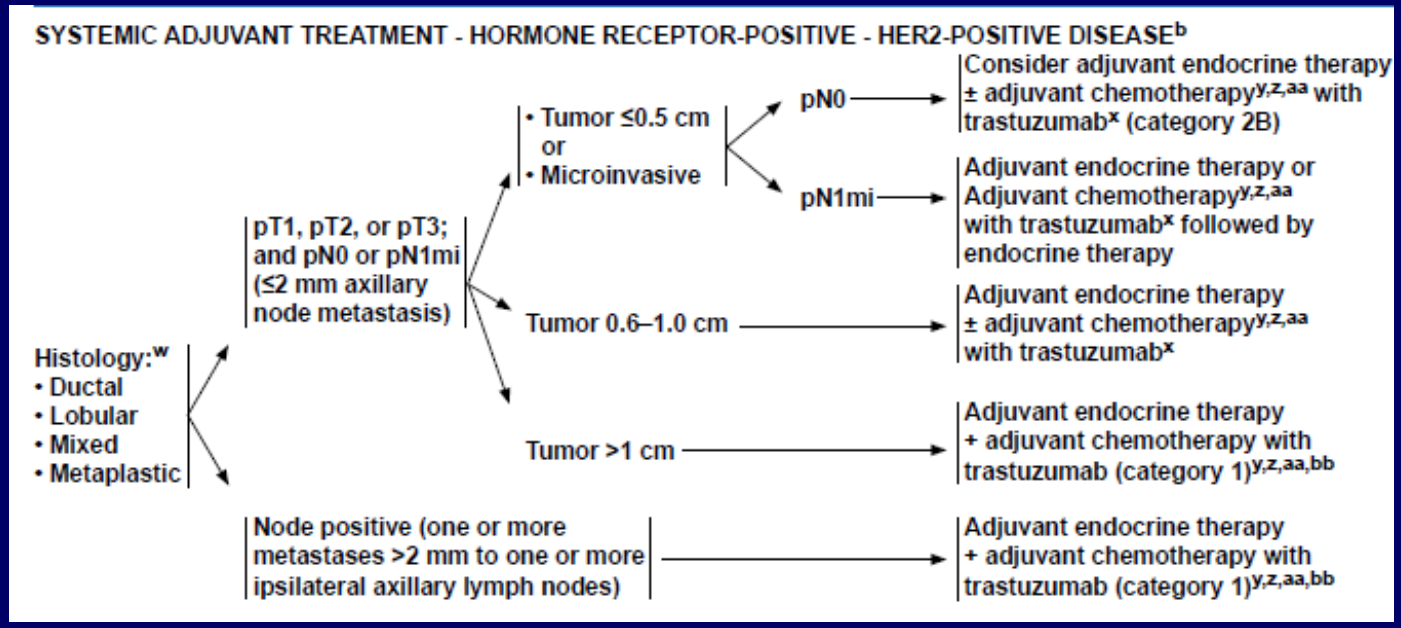
Table 3. Postoperative adjuvant systemic treatment recommendations

Clinical grouping	Type of therapy	Notes on therapy
Triple-negative	Cytotoxic chemotherapy including anthracycline and taxane	Platinum-based chemotherapy may be considered in patients with known BRCA mutation, see text
ER negative and HER2-positive		
T1a node negative	No systemic therapy	
T1 b,c node negative	Chemotherapy plus trastuzumab	Consider paclitaxel plus 12 months trastuzumab without anthracycline
Higher T or N stage	Anthracycline → taxane with concurrent trastuzumab continued to 12 months	Patients unsuitable for anthracycline may be treated with TCH regimen, though cardiac contraindications to anthracycline may also argue against trastuzumab [115]
ER positive and HER2-positive	As above plus endocrine therapy appropriate to menopausal status as below	
ER positive and HER2-negative (luminal disease)		
Without markers of less endocrine responsiveness (luminal A-like)	Endocrine therapy alone according to menopausal status	See Table 2. Consider chemotherapy if four or more nodes involved
Premenopausal low risk	Tamoxifen 5 years	
Premenopausal other	Tamoxifen 5–10 years or OFS plus tamoxifen or OFS plus exemestane	See criteria in papers [3, 4, 116]
Postmenopausal low risk	Tamoxifen 5 years	
Postmenopausal other	AI preferably up front; extended adjuvant therapy (see text)	No evidence on the safety or efficacy of more than 5 years of an AI
With markers suggesting lesser endocrine responsiveness (luminal B-like)	Endocrine therapy as above plus adjuvant cytotoxic chemotherapy in many cases	See Table 2
Factors supporting omission of cytotoxic chemotherapy despite 'luminal B-like' phenotype		'good' result of multiparameter molecular test if available


SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE[b]
Histology:[w]
• Ductal
• Lobular
• Mixed
• Metaplastic
pT1, pT2, or pT3; and pN0 or pN1mi (≤2 mm axillary node metastasis)
• Tumor ≤0.5 cm or
• Microinvasive
pN0
Consider adjuvant chemotherapy[aa,ee] with trastuzumab[t] (category 2B)
pN1mi
Consider adjuvant chemotherapy[aa,ee] with trastuzumab[x]
Tumor 0.6–1.0 cm
Consider adjuvant chemotherapy[aa,ee] with trastuzumab[x]
Tumor >1 cm
Adjuvant chemotherapy[aa,bb,ee] (category 1) with trastuzumab (category 1)
Node positive (one or more metastases >2 mm to one or more ipsilateral axillary lymph nodes)
Adjuvant chemotherapy[aa,bb,ee] with trastuzumab (category 1)

NCCN 2016 v1

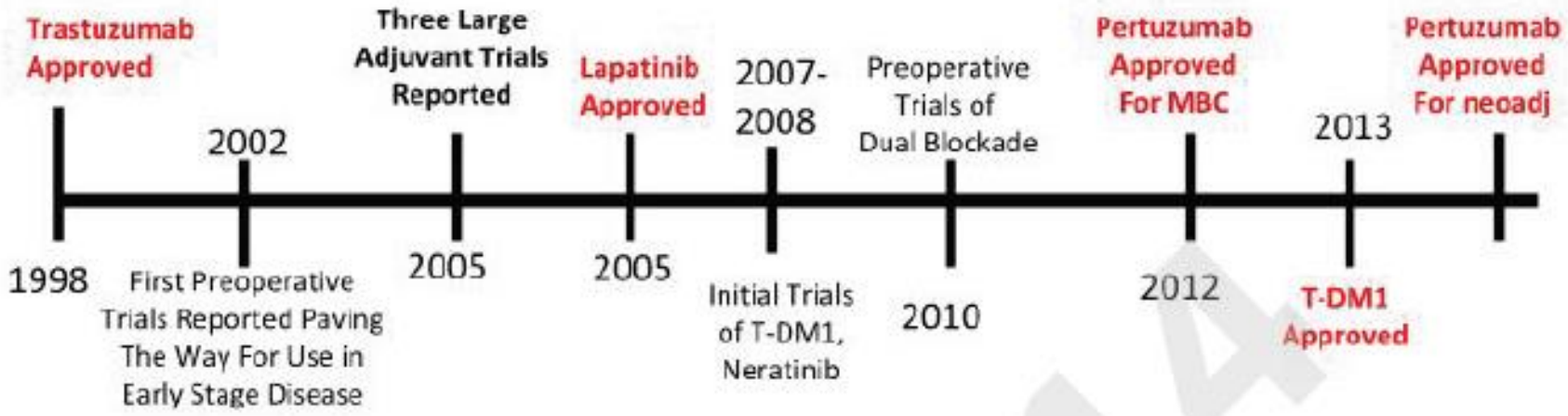

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE[b]
Histology:[w]
• Ductal
• Lobular
• Mixed
• Metaplastic
pT1, pT2, or pT3; and pN0 or pN1mi (≤2 mm axillary node metastasis)
• Tumor ≤0.5 cm or
• Microinvasive
pN0
Consider adjuvant endocrine therapy ± adjuvant chemotherapy[y,z,aa] with trastuzumab[x] (category 2B)
pN1mi
Adjuvant endocrine therapy or Adjuvant chemotherapy[y,z,aa] with trastuzumab[x] followed by endocrine therapy
Tumor 0.6–1.0 cm
Adjuvant endocrine therapy ± adjuvant chemotherapy[y,z,aa] with trastuzumab[x]
Tumor >1 cm
Adjuvant endocrine therapy + adjuvant chemotherapy with trastuzumab (category 1)[y,z,aa,bb]
Node positive (one or more metastases >2 mm to one or more ipsilateral axillary lymph nodes)
Adjuvant endocrine therapy + adjuvant chemotherapy with trastuzumab (category 1)[y,z,aa,bb]

Sonuçlar

- Erken evre her2+ meme kanserinde adj trast temelli tedaviler sağkalımı arttırmıştır
  - Standart tedavi adjuvant kemoterapi (taksan+/-antrasiklin) + 12 ay (1 yıl) trastuzumab
  - Taksan ile trastuzumabın eş zamanlı verilmesi hem daha etkili hem daha pratik
  - Nod negatif yüksek riskli olmayan hasta grubunda prognoz (trastuzumab kullanımı ile) çok iyi olduğundan kısa kemoterapi (4 kür, tercihen antrasiklinsiz) + 12 ay trastuzumab
- Artırma (dual blokaj) ve azaltma (daha kısa süre veya daha az yoğun KT ile) çalışma devam
- HER2 ekspresyon durumu dışında trast yararını öngördüren prediktif biyomarker saptanamamış

Teşekkür Ederim

HER2+ Disease: Major Clinical Advances



Selected studies assessing the potential predictive information linked to effectors of the PI3K pathway for trastuzumab-based treatment.

Study	Setting	Study Design	Treatment arms	Predictive	Magnitude of effect
NCT00133796 NCT00206427	Neoadjuvant	2 × Phase II studies	T → D L → TD	YES	OR: 0.11 0.02 to 0.65
GeparQuattro, GeparQuinto, GeparSixto	Neoadjuvant	3 × Phase III studies	T + CT L + CT T + L + CT	YES	OR: 0.49; 95% CI 0.29 to 0.83
NeoALTTO	Neoadjvuant	Phase III	L vs. T L + T vs. T	YES	OR: 0.45 0.23 to 0.85 .015
NCCTG N9831	Adjuvant	Phase III	CT CT → T CT + T	No	NA
NSABP-B31	Adjuvant	Phase III	AC P AC PT T	No	NA
FinHER	Adjuvant	Phase III	D/V FEC D/V T FEC	No	NA
Antoni van Leeuwenhoek Hospital and M.D. Anderson Cancer Center	Metastatic	Case series from 2 centers	Various trastuzumab containing regimens	YES (borderline)	HR: 1.9 (1.0–3.6)

Abbreviations: CI: Confidence Interval, CT: Chemotherapy, D: Docetaxel, FEC: 5-Fluorouracil, Epirubicin, Cyclophosphamide, L: Lapatinib, NA: Not available, OR: Odds Ratio, T: Trastuzumab, TD: Trastuzumab, Docetaxel.

Cancer Chemother Pharmacol (2005) 56: 361–369
DOI 10.1007/s00280-005-1026-z

ORIGINAL ARTICLE

Rene Bruno · Carla B. Washington · Jian-Feng Lu
Grazyna Lieberman · Ludger Banken · Pamela Klein

Population pharmacokinetics of trastuzumab in patients With HER2+ metastatic breast cancer

Received: 26 October 2004 / Accepted: 12 January 2005 / Published online: 3 May 2005

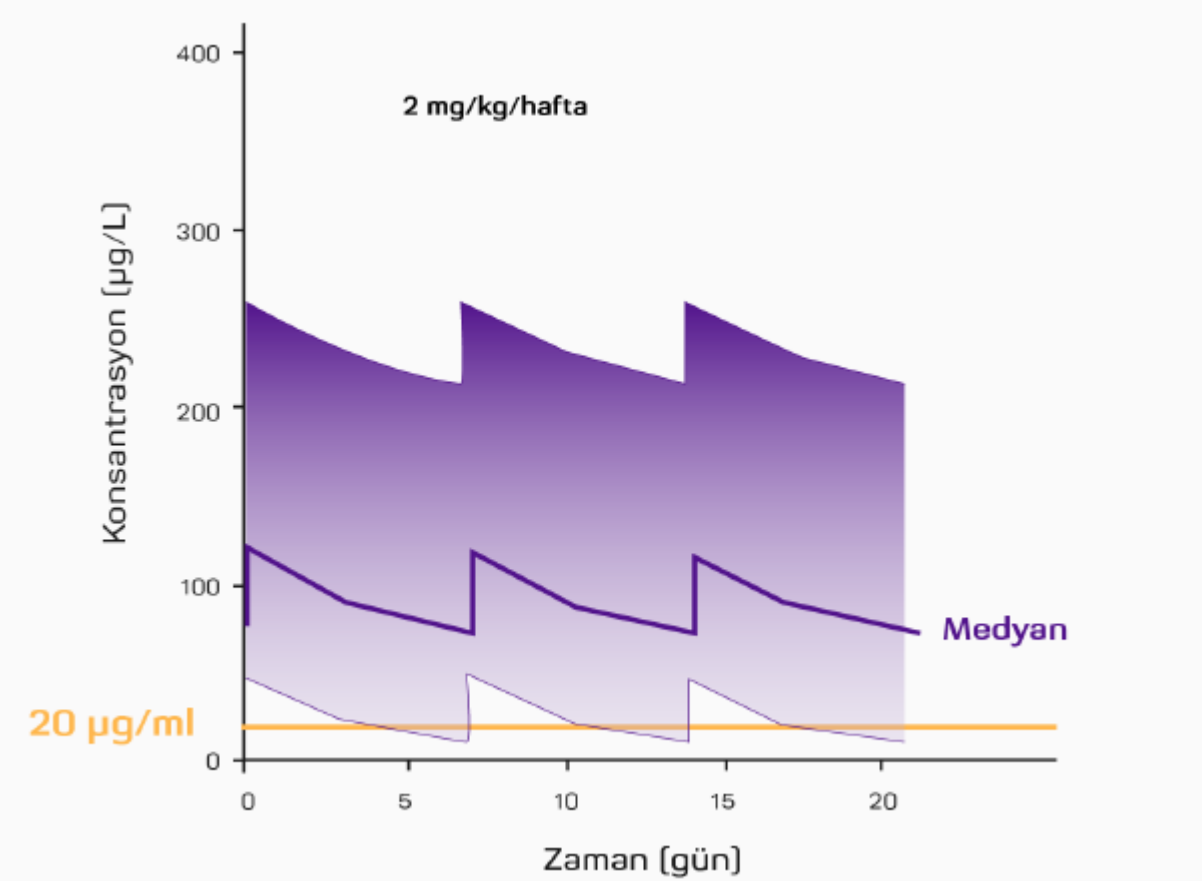
Abstract *Purpose*: To characterize the population pharmacokinetics of trastuzumab in patients with metastatic breast cancer. *Methods*: A nonlinear mixed effect model was based on pharmacokinetic data from phase I, II, and III studies of 476 patients. The phase I study enrolled patients with advanced solid tumors. The phase II and III studies enrolled patients with HER2-positive metastatic breast cancer. Patients in the pivotal phase II and III studies were treated with a 4 mg/kg loading dose of trastuzumab followed by 2 mg/kg weekly for up to 840 days. The model adequately predicted observed trastuzumab concentrations. Model stability and performance were verified using bootstrap simulations. Percentiles, mean, and standard deviation of observed levels were compared with their distributions from 100 replicates of datasets simulated under the model. *Results*: A two-compartment linear pharmacokinetic model best described the data and accounted for the long-term accumulation observed following weekly administration of trastuzumab. Population estimates from the base model for clearance (CL) and volume of distribution of the central compartment (V_1) of trastuzumab were 0.225 L/day, and 2.95 L, respectively. Estimated terminal halflife ($t_{1/2}$) based on the population estimate was 28.5 days. Interpatient variabilities in clearance and volume were 43 and 29%, respectively. The number of metastatic sites, plasma level of extracellular domain of the HER2 receptor, and patient weight were significant baseline covariates for clearance, volume, or both ($P < 0.005$). However, these covariate effects on trastuzumab exposure were modest and not clinically important in comparison with the large inter-patient variability of CL. Concomitant chemotherapy (anthracycline plus cyclophosphamide, or paclitaxel) did not appear to influence clearance. *Conclusion*: This population pharmacokinetic model can predict trastuzumab exposure in the long-term treatment of patients with metastatic breast cancer and provide comparison of alternative dosage regimens via simulation.

Keywords Pharmacokinetics · Trastuzumab · Metastatic breast cancer · HER2

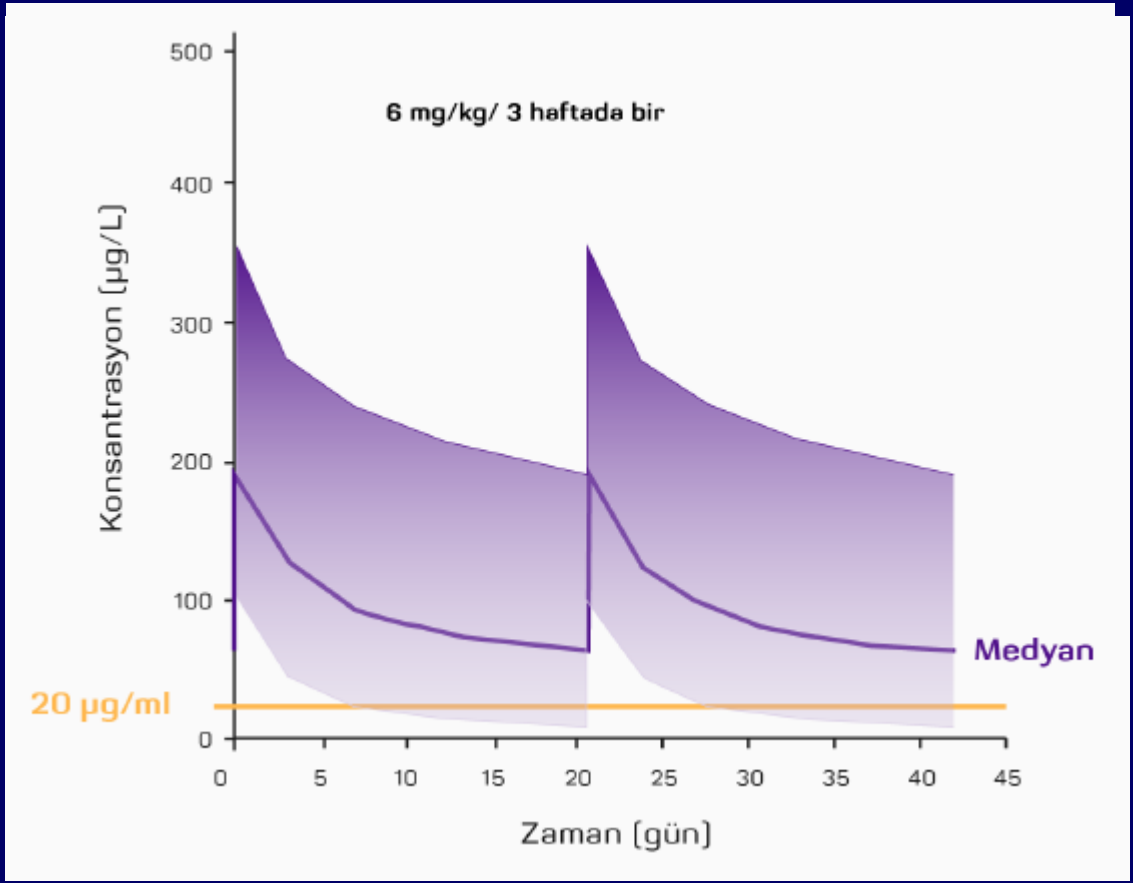
Introduction

Trastuzumab (Herceptin Genentech, Inc., South San Francisco, CA, USA), a recombinant, humanized anti-HER2 monoclonal antibody, is approved for the treatment of women with HER2-positive metastatic breast cancer (MBC) as a single agent or in combination with chemotherapy.

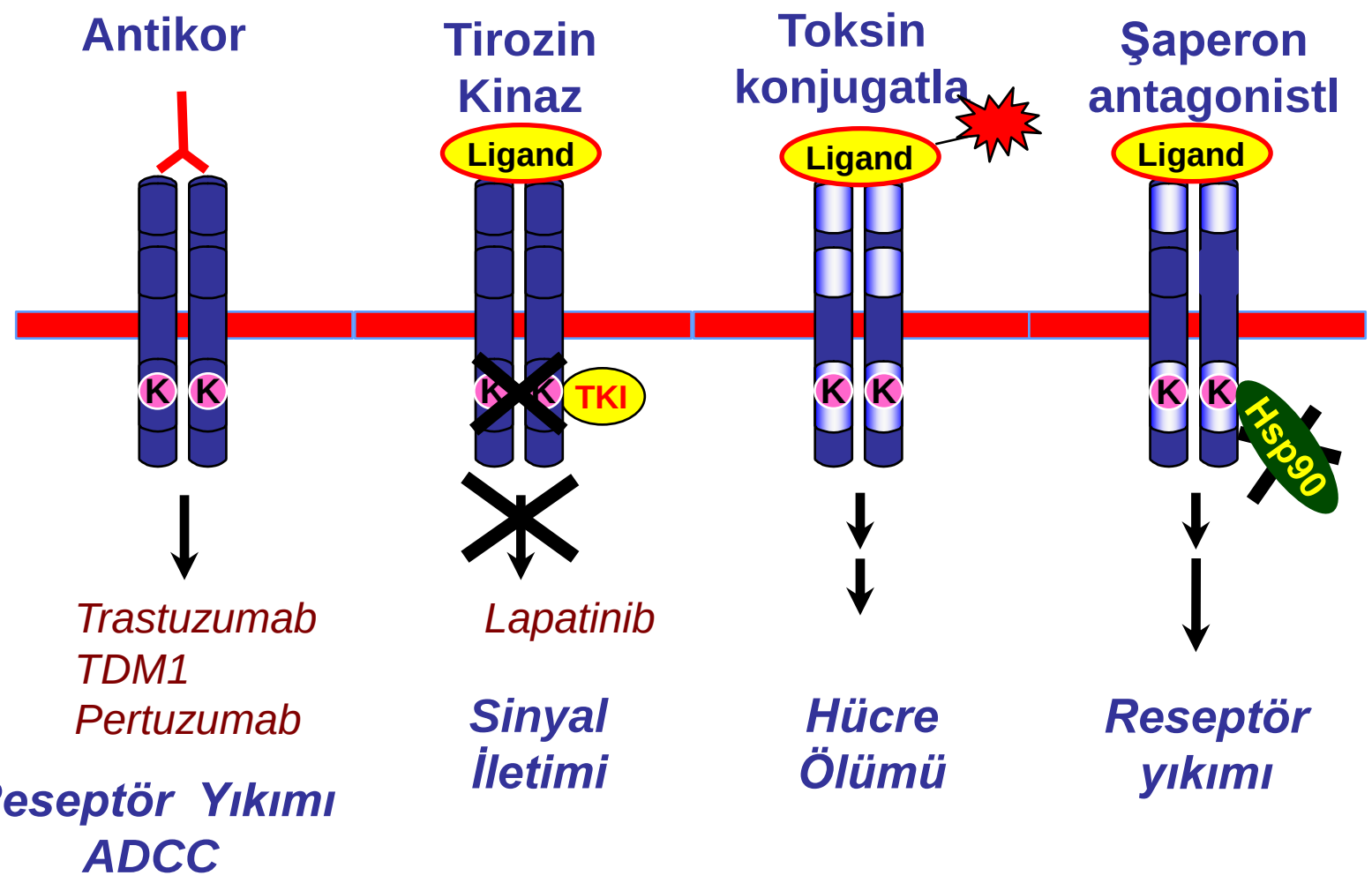
Haftalık uygulamada serum trastuzumab konsantrasyonu



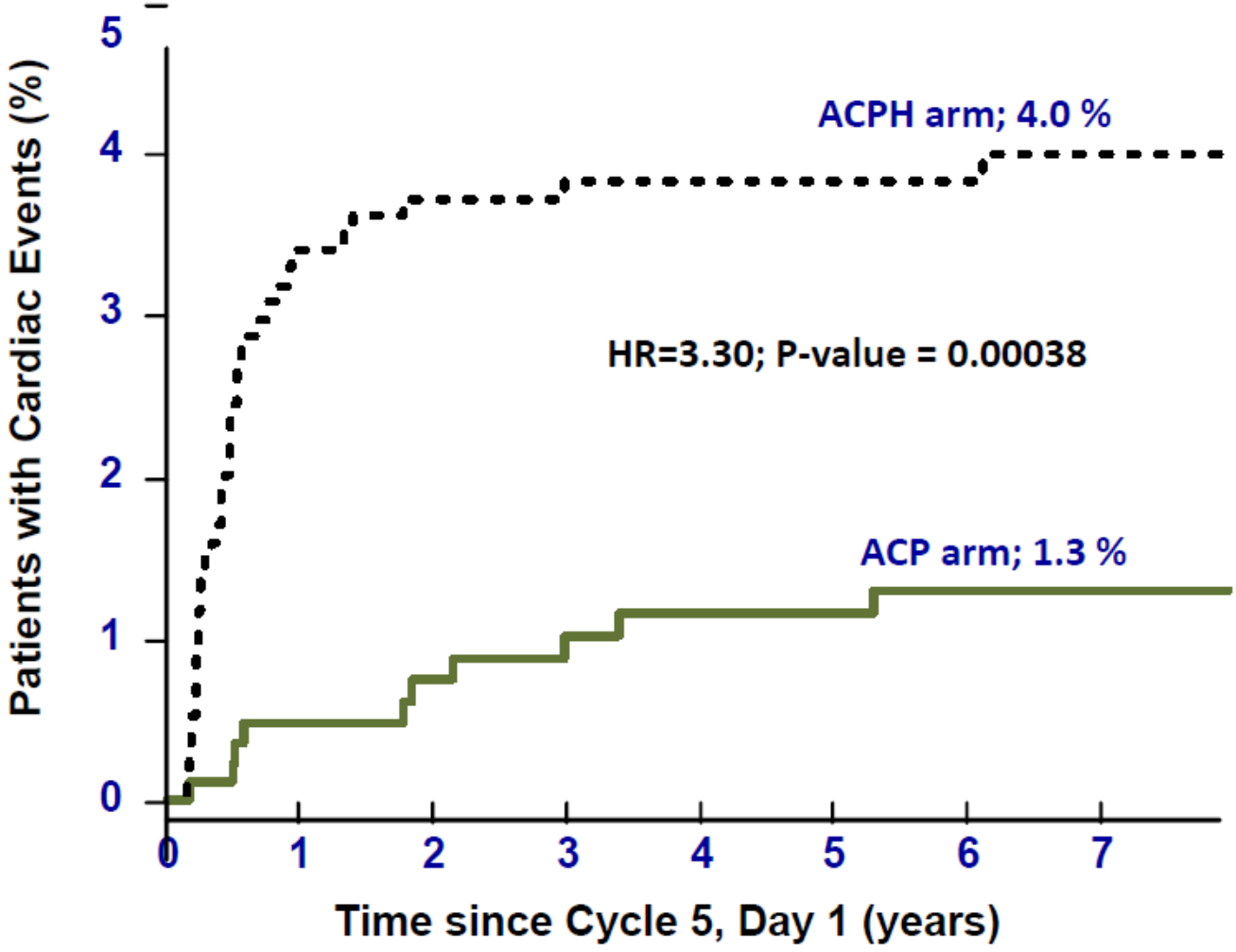
3 haftalık uygulamada serum trastuzumab konsantrasyonu



HER2 Hedefleyen Tedaviler



NSABP B-31: 7 yr FU
Cumulative Incidence of Cardiac Events
(Cardiac death or CHF with ↓ in EF – different from HERA)



Romond et al. JCO 9-2012

HERA Adverse Events (Safety Analysis Population)

	Observation Only N=1744	Trastuzumab 1 Year N=1682	Trastuzumab 2 Years N=1673
≥ 1 grade 3 or 4 AE	8.2%	16.3%	20.4%
Fatal adverse event	0.4%	1.1%	1.2%
Primary Cardiac[1]	0.1%	0.8%	1.0%
Secondary Cardiac[2]	0.9%	4.1%	7.2%

[1] NYHA class III or IV, confirmed by a cardiologist, and LVEF < 50% and ≥ 10% below baseline, OR cardiac death.

[2] LVEF < 50% and ≥ 10% below baseline confirmed by repeat assessment, excluding patients with a primary cardiac endpoint.

Goldhirsch et al. ESMO 2012; Oral Abstract #LBA6