HER2 Pozitif Metastatik Hastalıkta Sistemik Tedavi Yaklaşımları

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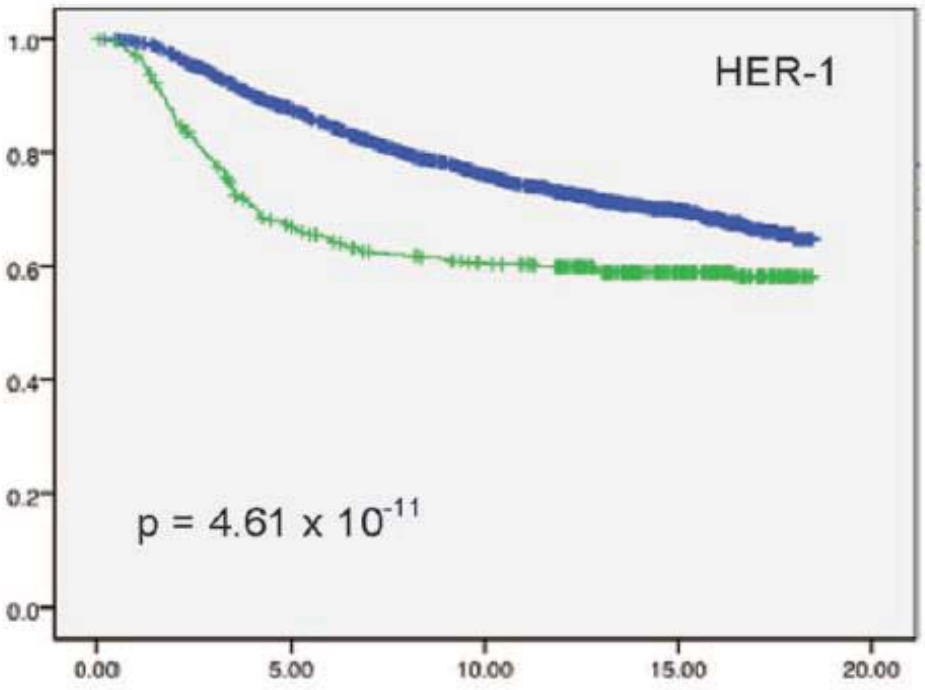
Meme Kanseri Moleküler Sınıflama

Alt Grup	*% Görülme*	*5yıl DDFS %*	*5 yıl OS %*	*Standart IHK*
Luminal A	51-61	75	90	ER+,PR+,HER2-
Luminal B	14-16	47	40	ER+ ve/veya PR+, HER2+
HER2	*7-9*	*34*	*31*	*ER ve PR-,HER2+*
Basal	11-20	18	0	ER,PR,HER2-; Sitokeratin5/6 ve EGFR+
Sınıflandırılamayan	2-6	----	----	Tüm Markırlar Negatif

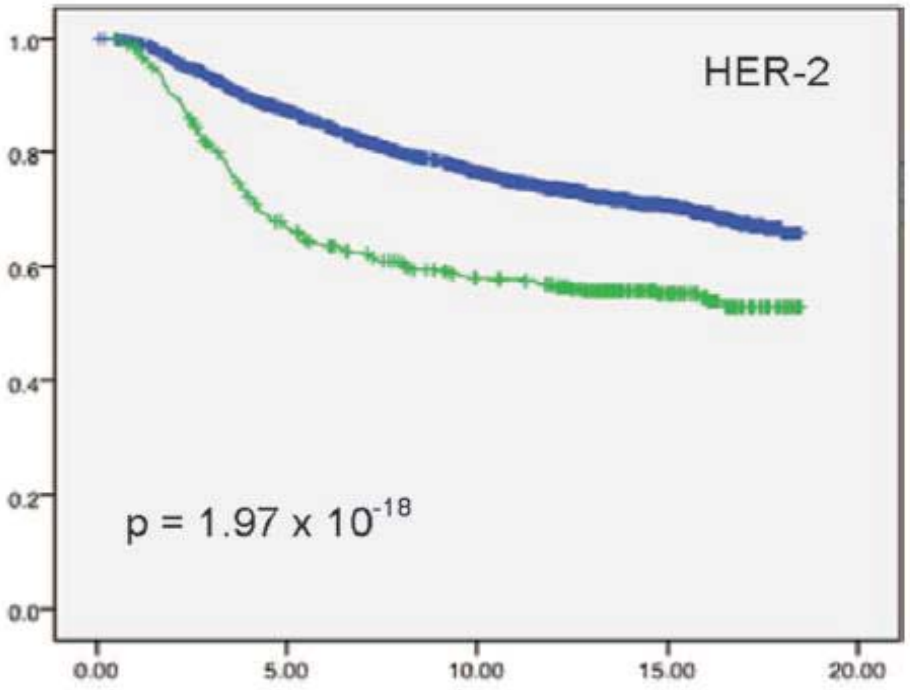
The Breast 2009; s:239

EGFR Ekspresyonu- Meme Kanseri

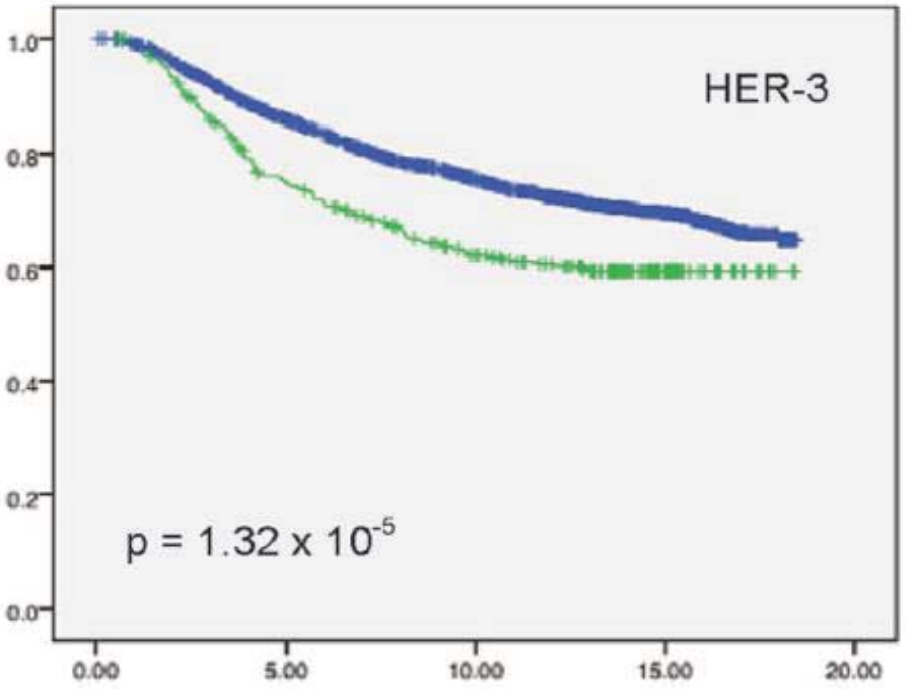
- N=4046 hasta
- Ortanca takip süresi 12.5 yıl
- HER-1, HER-2, HER-3, ve HER-4 IHK
- HER-2 durumu FISH
- **HER-1** %13.3
- **HER-2** %13.0
- **HER-3** **%10.0**
- **HER-4** **%** 78.2


HER-1
p = 4.61 x 10-11
1.0
0.8
0.6
0.4
0.2
0.0
0.00
5.00
10.00
15.00
20.00
Number of Years

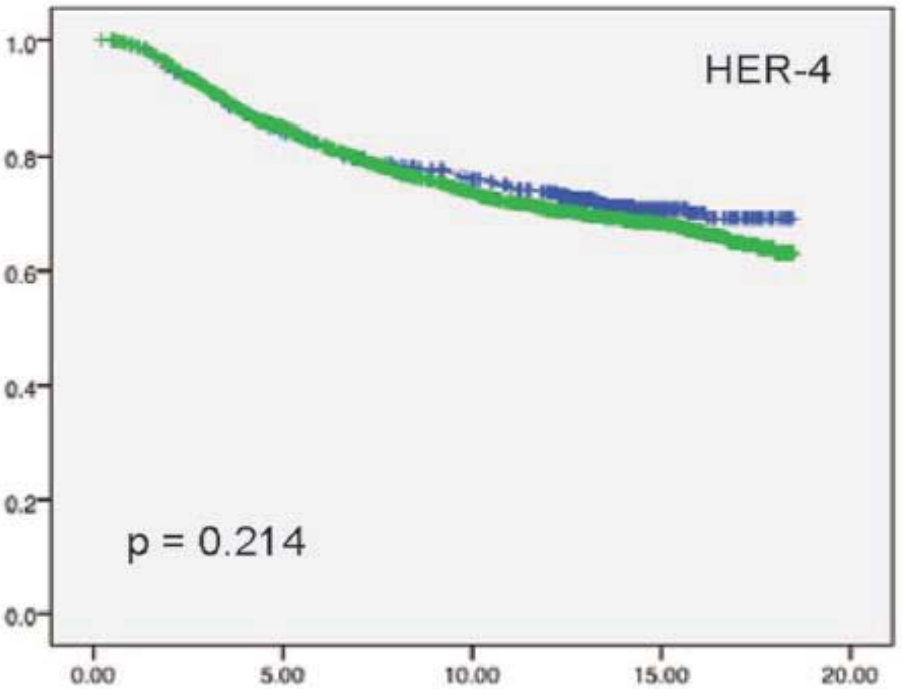
A


HER-2
p = 1.97 x 10-18
1.0
0.8
0.6
0.4
0.2
0.0
0.00
5.00
10.00
15.00
20.00
Number of Years

B


HER-3
p = 1.32 x 10-5
1.0
0.8
0.6
0.4
0.2
0.0
0.00
5.00
10.00
15.00
20.00
Number of Years

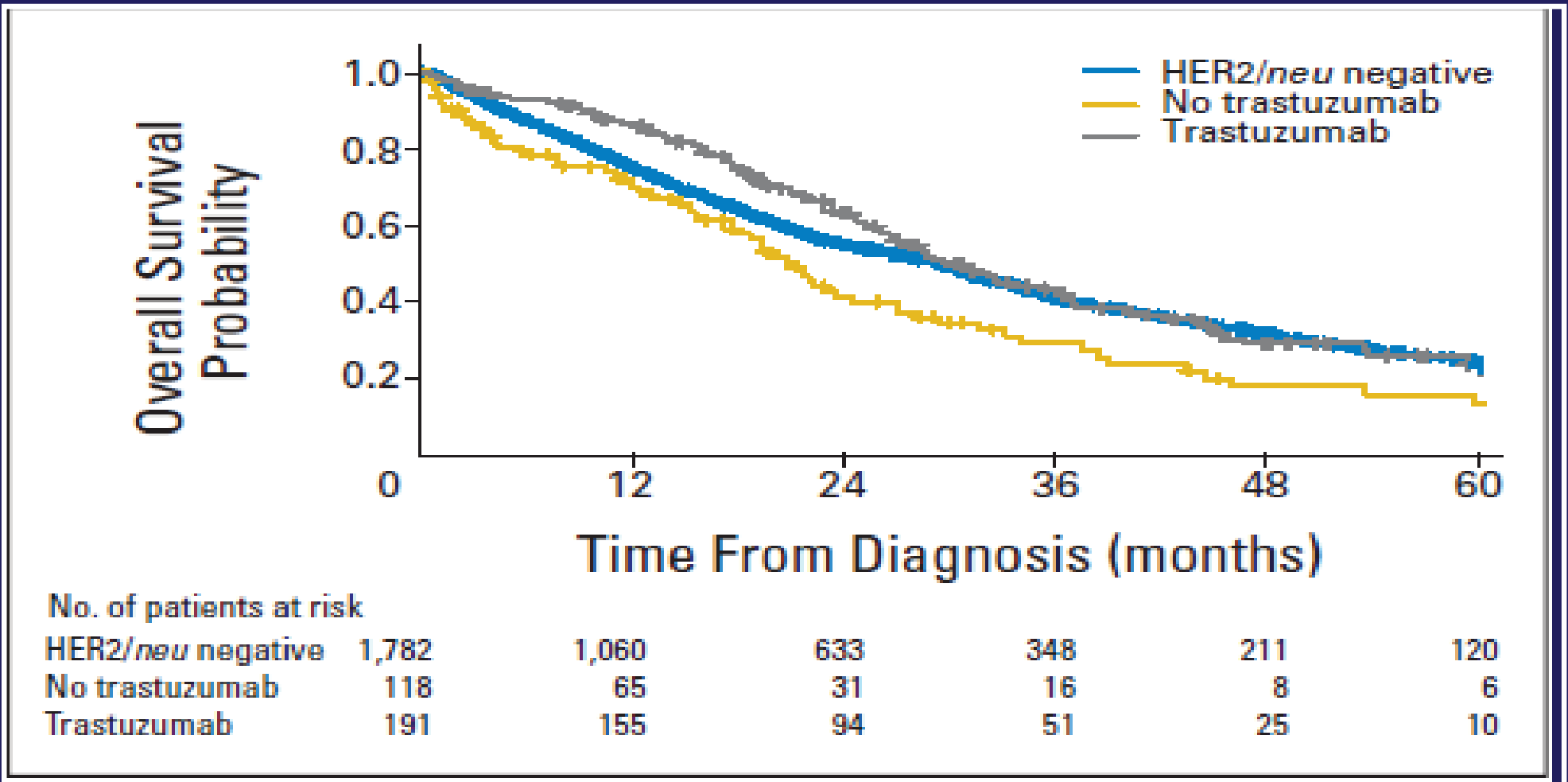
C


HER-4
p = 0.214
1.0
0.8
0.6
0.4
0.2
0.0
0.00
5.00
10.00
15.00
20.00
Number of Years

D

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

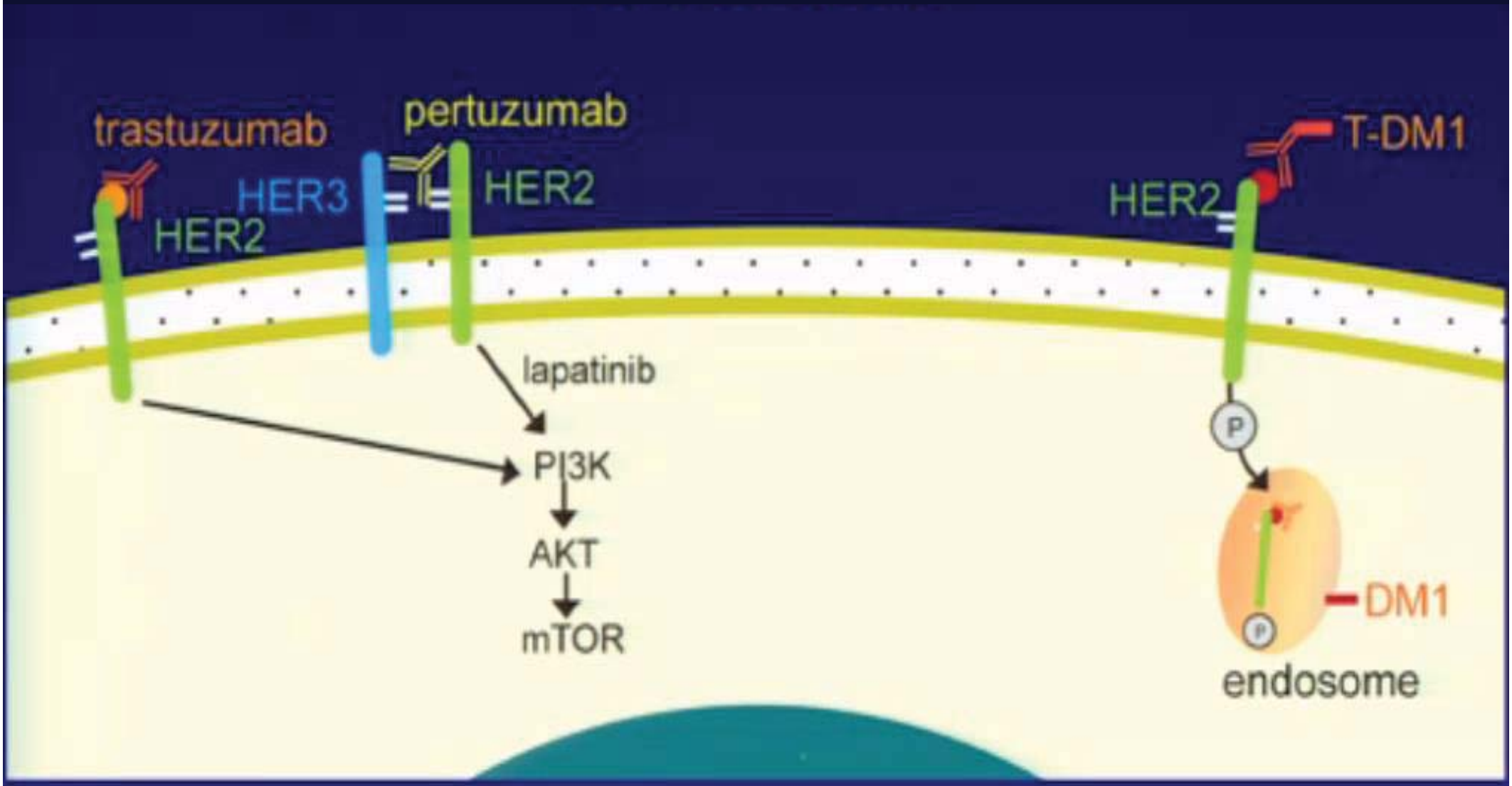


No. of patients at risk

HER2/*neu* negative	1,782	1,060	633	348	211	120
No trastuzumab	118	65	31	16	8	6
Trastuzumab	191	155	94	51	25	10

Fig 1. Overall survival by trastuzumab treatment group.

Anti-HER2 Tedavinin Etki Mekanizması



T-DM1 = trastuzumab emtansine

Gajria D. et al. *Expert Rev Anticancer Ther.* 2011;11:263-275

HER2: Hedefe Yönelik Tedaviler

1985: insan cDNA klonlaması

1987: Hastalıkla ilişki (Slamon et al)

1990: MAb 4D5

1998: *Trastuzumab*'ın metastatik meme kanserinde kullanılması onaylandı (FDA)
(Türkiye 2003)

2005: *Trastuzumab* Her 2 pozitif erken evre meme kanserinin adjuvan tedavisinde etkili bulundu ; Kasım 2006:FDA onayı
(Türkiye:2007 Eylül 9 hafta kullanım; 2008 ortaları 1 yıl kullanım)

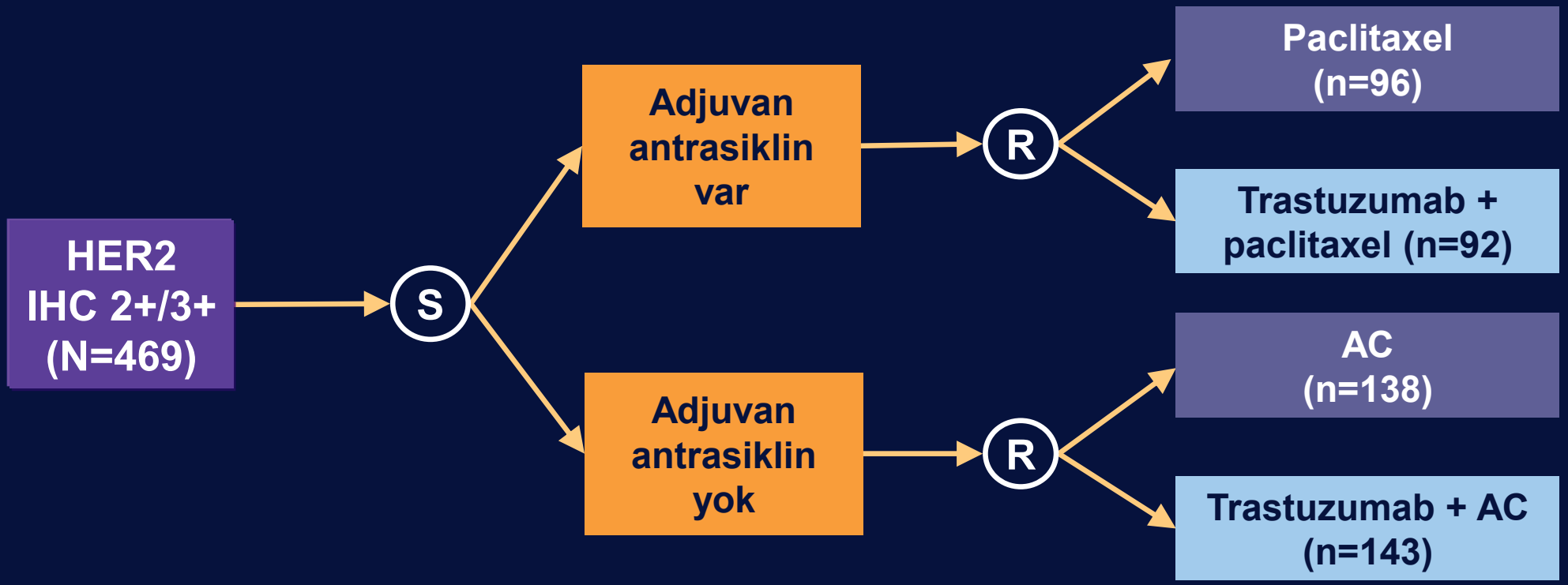
2007: *Lapatinib*

2012: Pertuzumab

2013: TDM1 (Taksan-Trastuzumab sonrası)

Birinci Basamak Tedavi

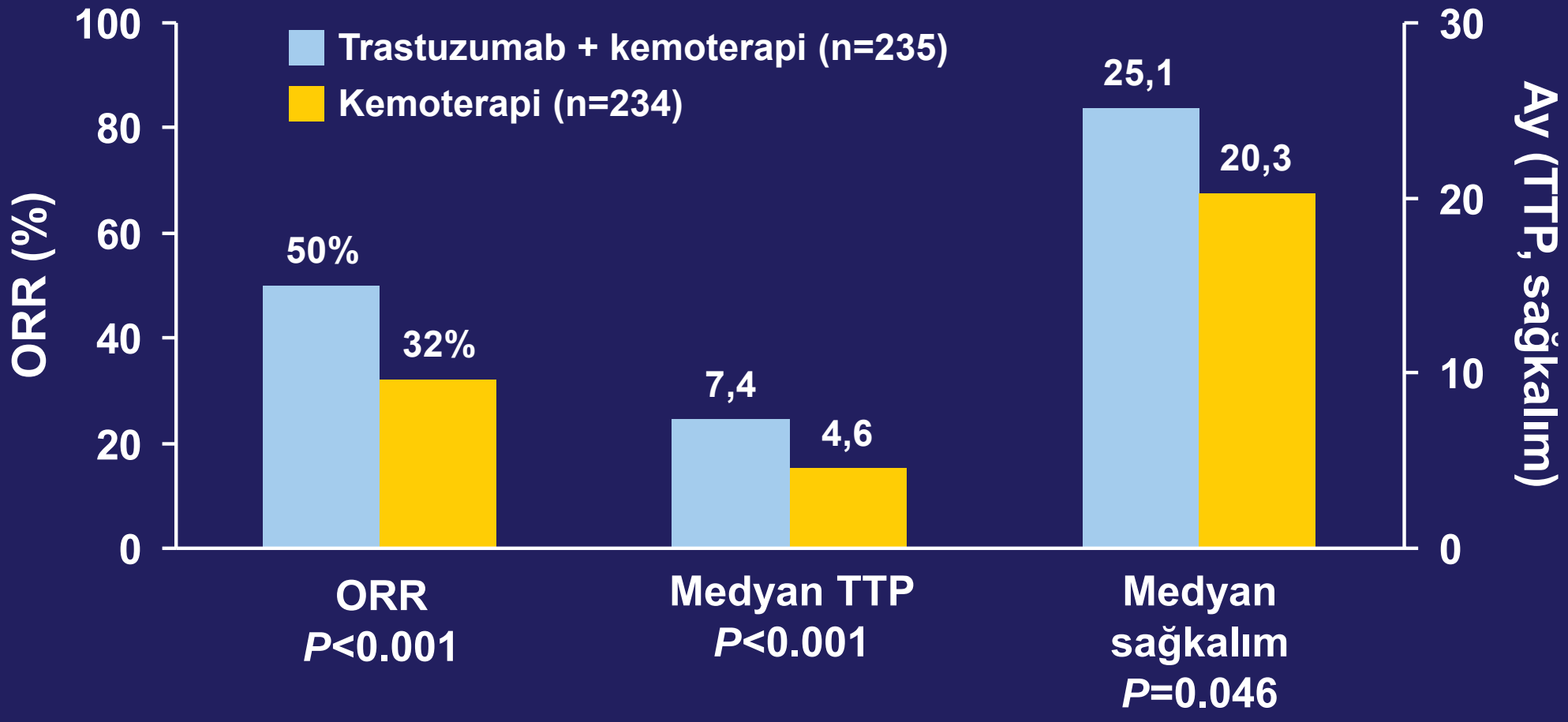
MMK de Birinci Basamak Tedavide Kemoterapi ± Trastuzumab
Pivotal Çalışma



AC = doksorubisin 60 mg/m^2 (veya epirubisin 75 mg/m^2) + siklofosfamid 600 mg/m^2; q3hafta × 6. Paclitaxel 175 mg/m^2 q3hafta × 6.
Trastuzumab 4 mg/kg yükleme dozu, sonra 2 mg/kg haftada bir progresyona kadar.

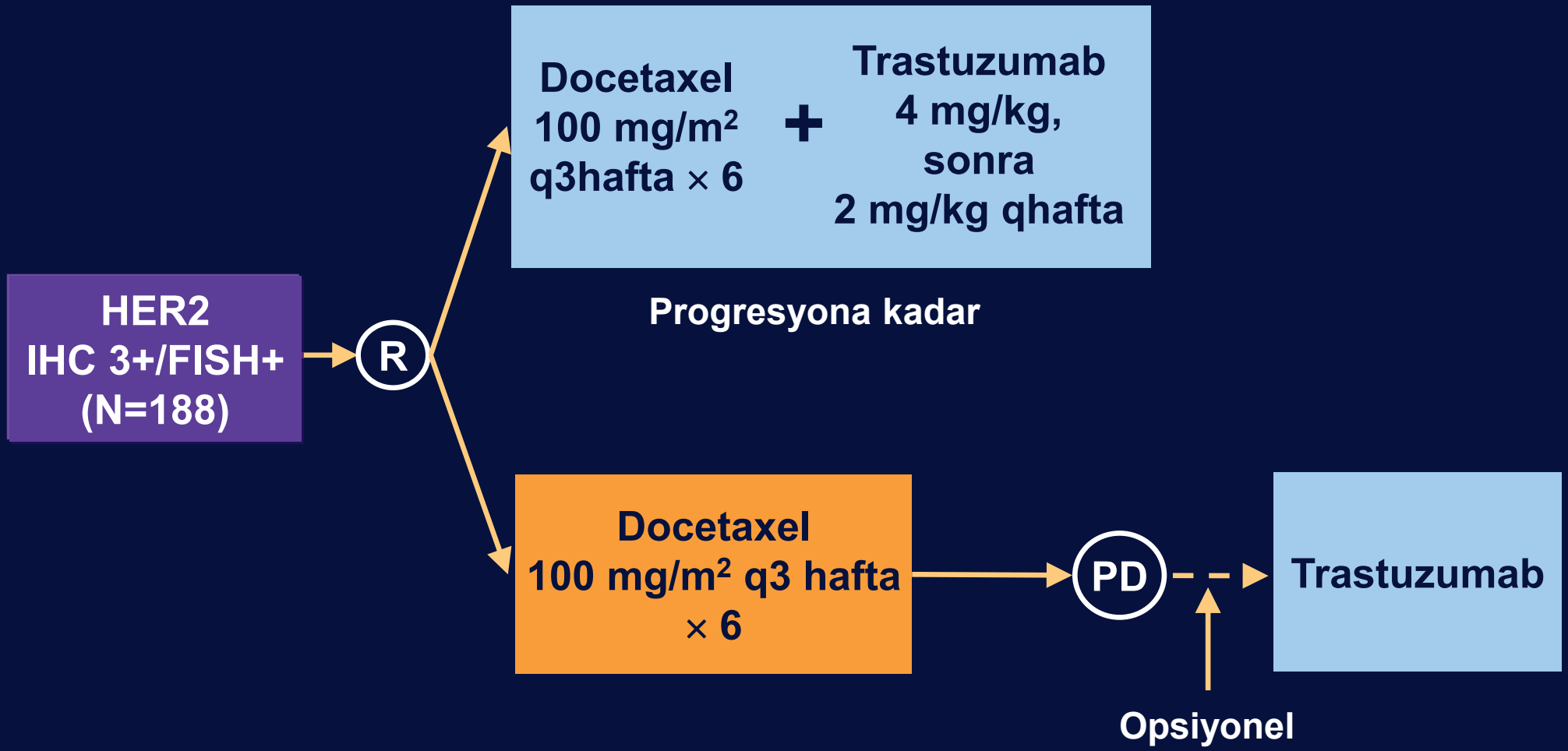
Slamon et al. *N Engl J Med.* 2001;344:783

MMK de Birinci Basamak Tedavide Kemoterapi ± Trastuzumab Pivotal Çalışma: Etkinlik



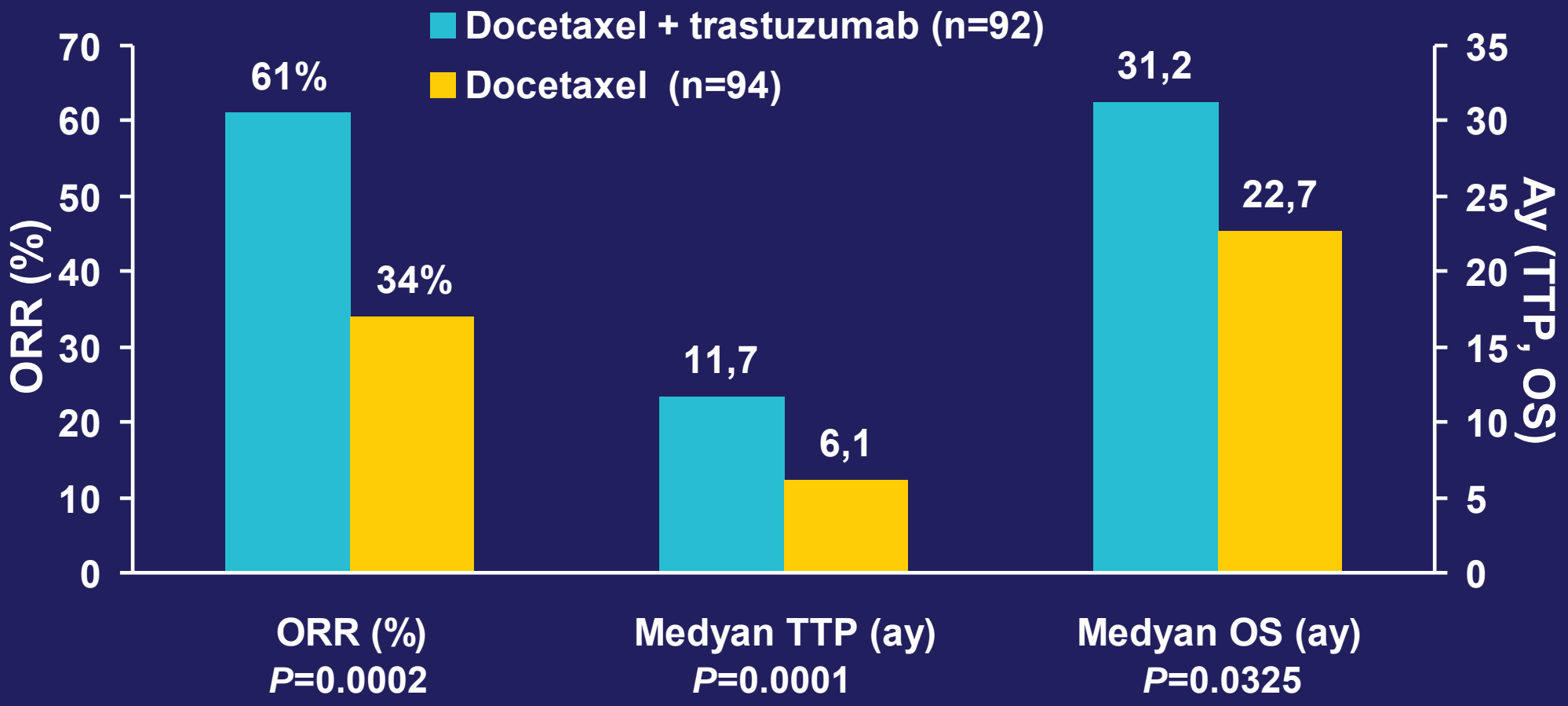
Slamon et al. N Engl J Med. 2001;344:783.

MMK de Birinci Basamak Docetaxel ± Trastuzumab (M77001) Randomize Faz II Çalışma



Extra et al. *J Clin Oncol.* 2005;23(16S):17s. Abstract 555;
Marty et al. *J Clin Oncol*. 2005;23:4265.

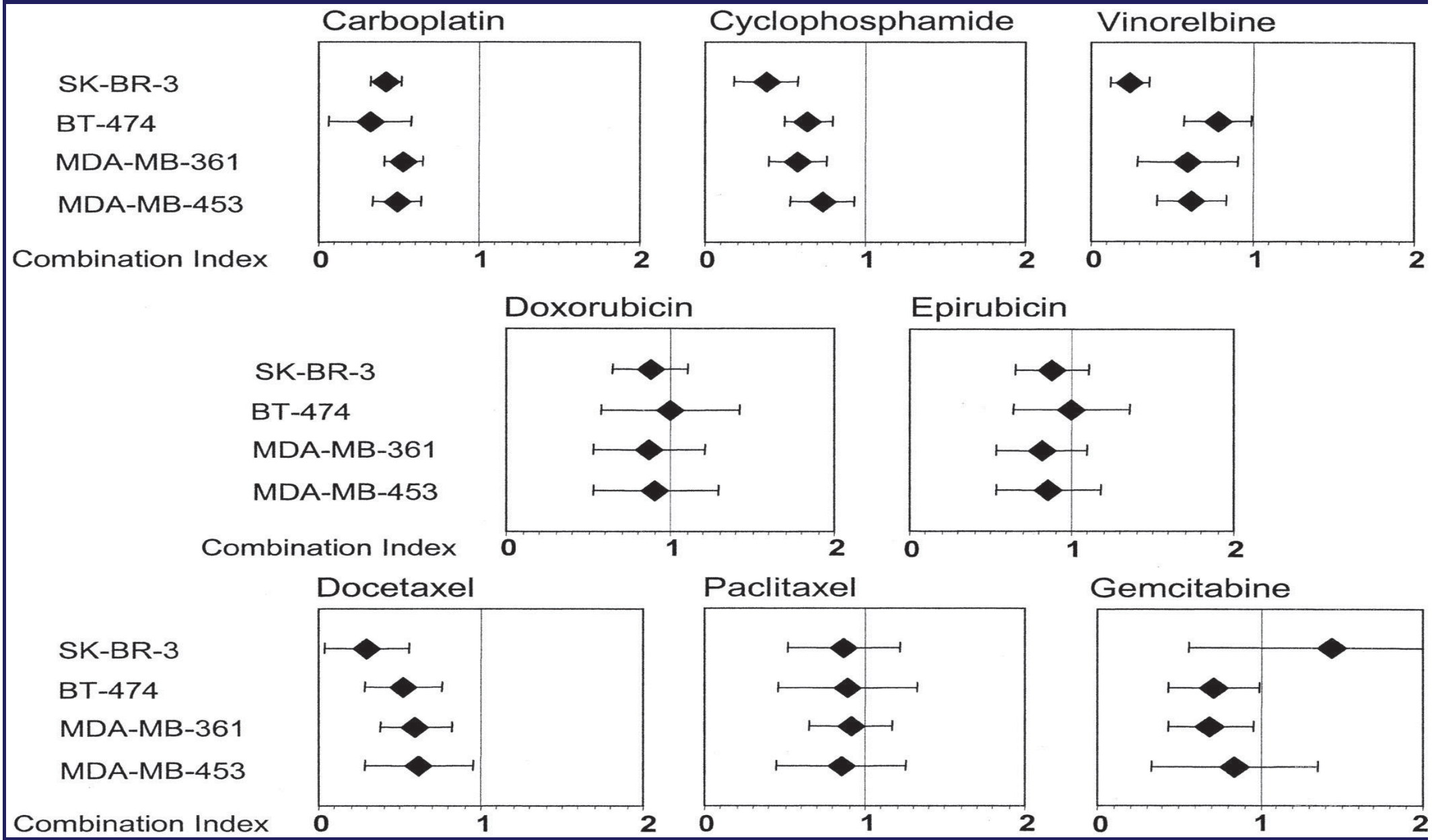
MMK de Birinci Basamak Docetaxel ± Trastuzumab : Etkinlik



- **45** "Uzun süreli yaşayan" hastanın (≥ 3 y), 41'i trastuzumabı başlangıc rejimi olarak veya crossover da aldı

Marty et al. *J Clin Oncol*. 2005;23:4265.

İn Vitro Trastuzumab + Kemoterapi Kombinasyonları



Pegram M et. al. JNCI 2004

Trastuzumab + Kemoterapi Kombinasyonlarının Etkinliği

• Docetaxel	61-70%
• Vinorelbine	42-78%
• Capecitabine	56%
• Liposomal Dox	52-58%
• Gemcitabine	38%
• Cisplatin	24%
• Pac/Carbo	52%
• Pac/Gem	67%
• Pac/Dox	88%
• Doc/Carbo	58%
• Dox/Cis	79%

Hudis et al, NEJM 2007

Birinci Basamak
Trastuzumab- Kemoterapi Tedavisi

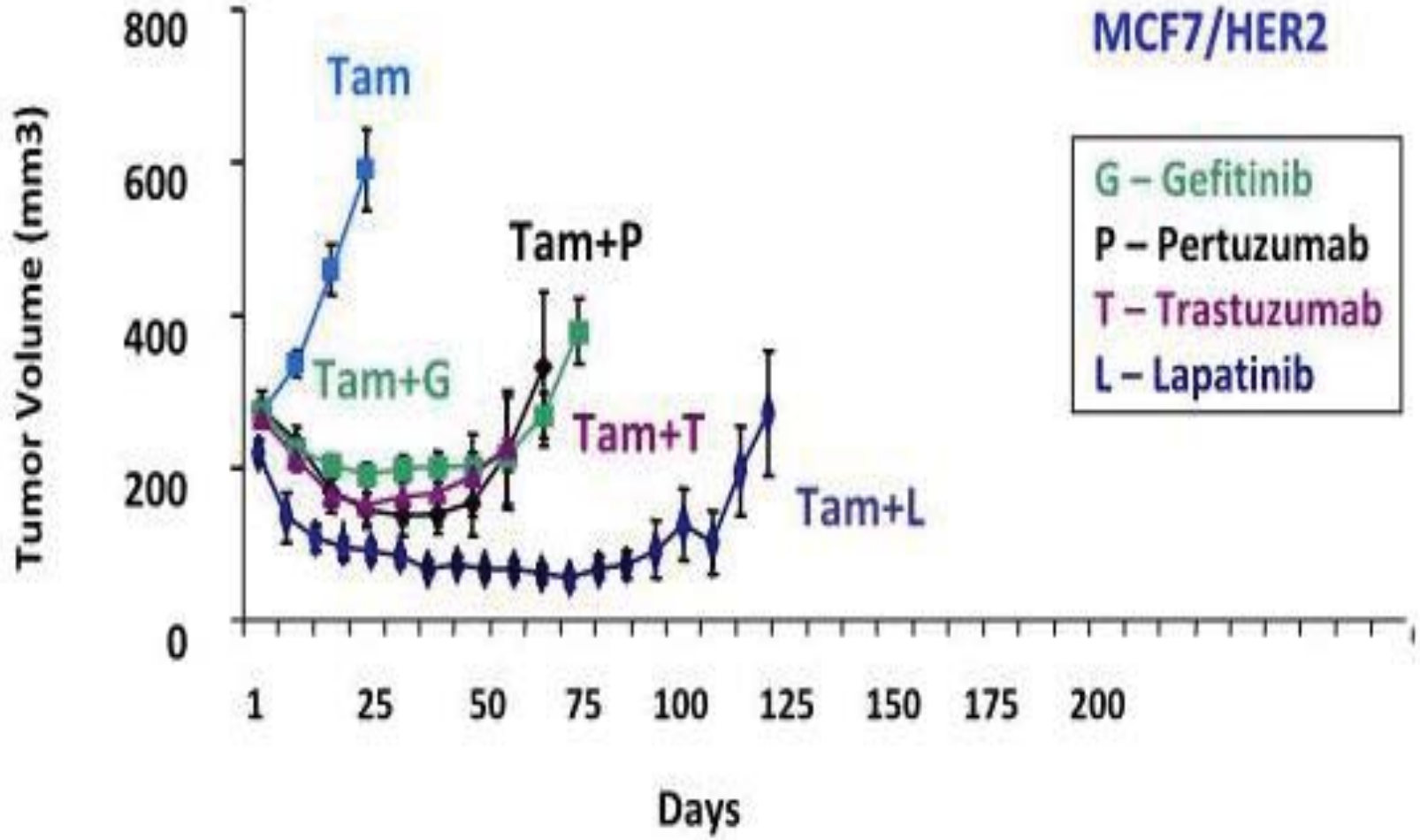
- Trastuzumab birçok kemoterapötik ajanla etkindir (paklitaksel, vinorelbine, dosetaksel, kapesitabine)
- Karşılaştırmalı çalışmalar tüm kombinasyonların benzer şekilde etkin ve kemoterapötiklere trastuzumab eklenmesi sağkalıma olumlu etkisi vardır.

ABC3 Konsensusu

- Anti-HER2 tedavi kullanmasında kontraendikasyon olmayan ileri evre meme kanserleri hastalarına erken dönemde (Birinci Basamak olarak) Anti-HER2 tedavi önerilmelidir.

Kanıt Düzeyi: 1A

Xenograft Modellerde Tekli Anti HER2 Tedavi



Arpino et al, JNCI 2007
Rimawi et al, CCR 2011

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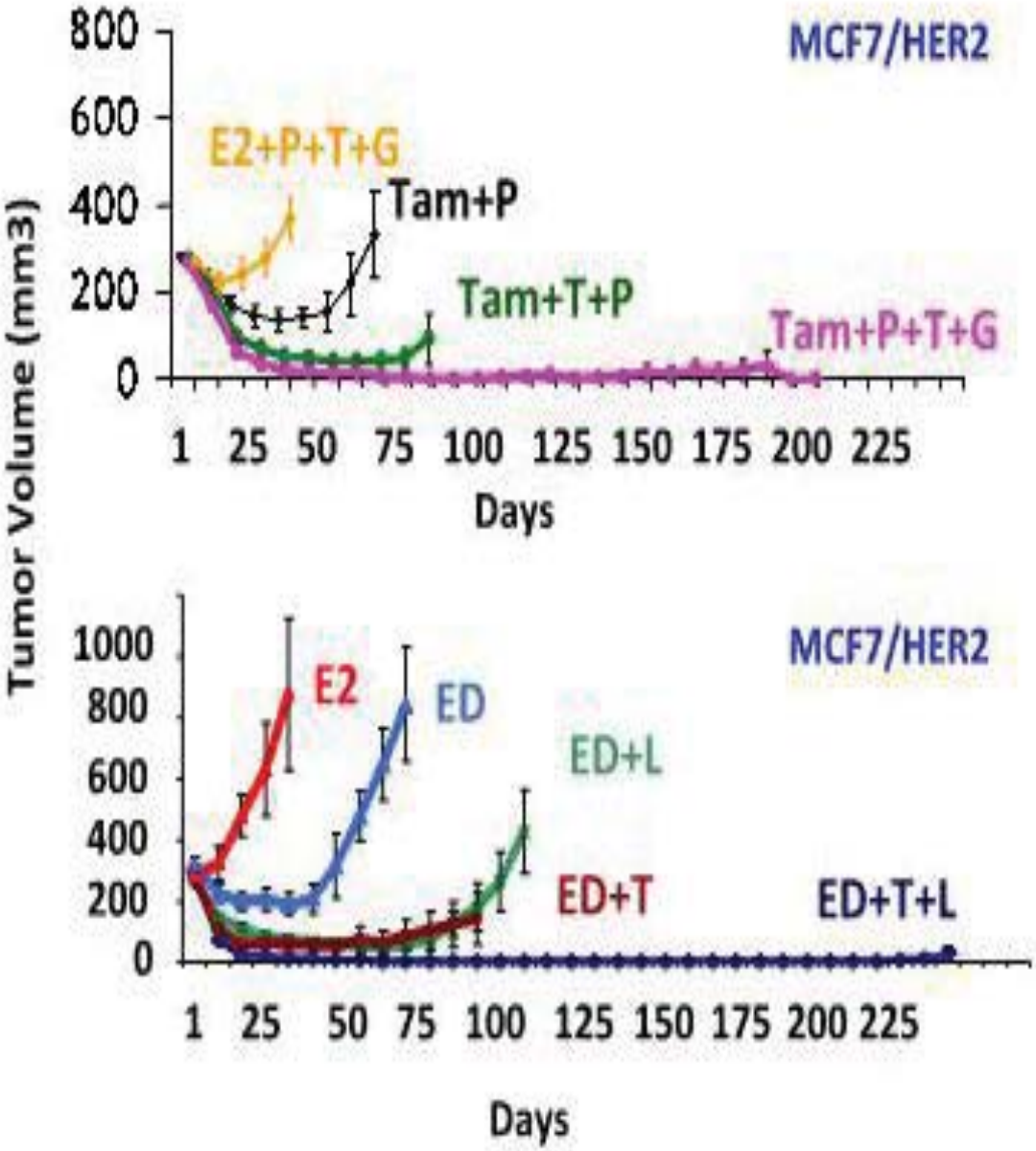
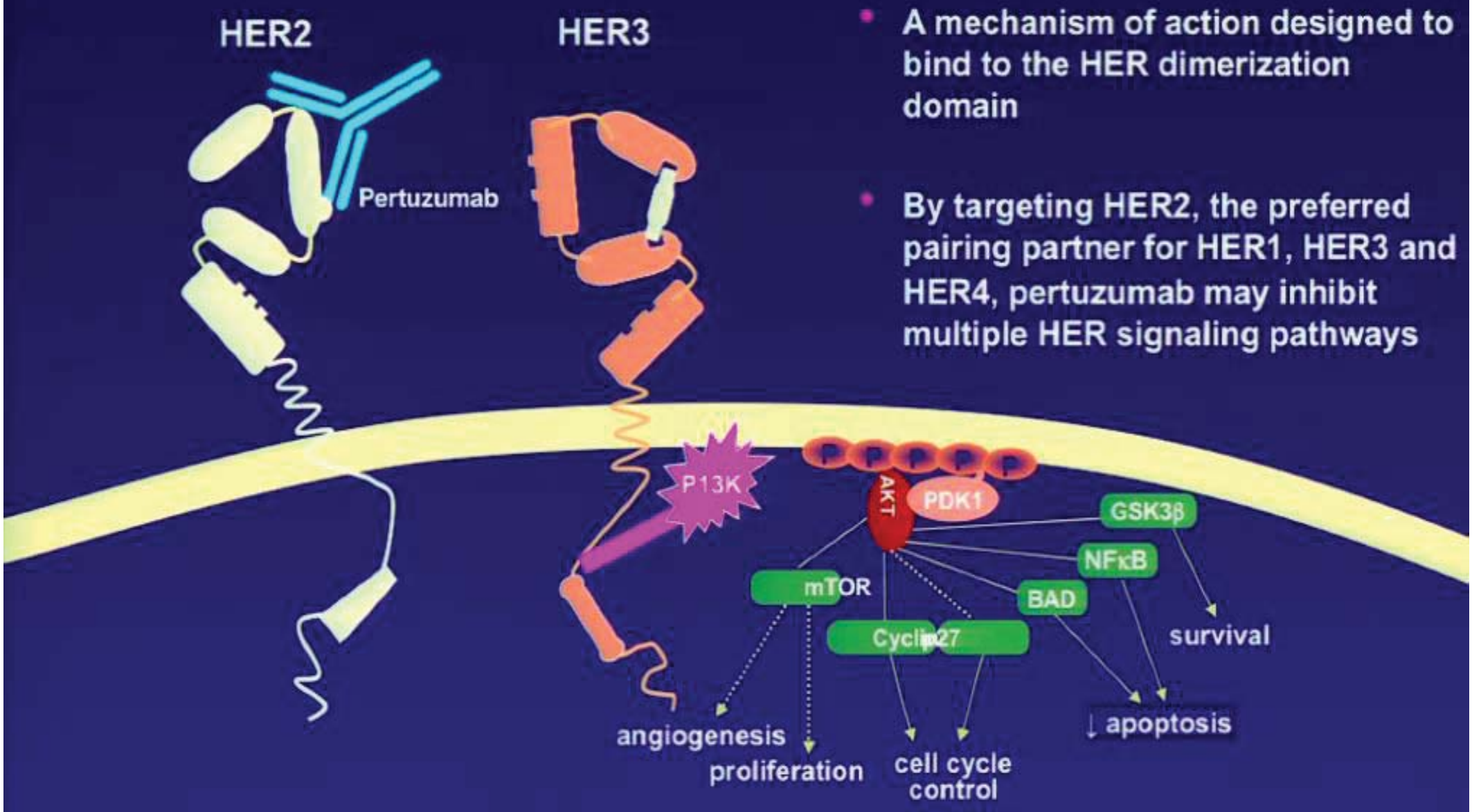
Xenograft Modellerde Çoklu Anti HER2 Tedavi



E2 - Estrogen
ED - Estrogen deprivation
Tam- Tamoxifen
T - Trastuzumab
L - Lapatinib
P- Pertuzumab
G- Gefitinib

Arpino, JNCI, 2007
Rimawi, CCR, 2011

Pertuzumab: a HER dimerization inhibitor



- A mechanism of action designed to bind to the HER dimerization domain
- By targeting HER2, the preferred pairing partner for HER1, HER3 and HER4, pertuzumab may inhibit multiple HER signaling pathways

Phase III CLEOPATRA study

(Neo)adjuvant systemic breast cancer chemotherapy including trastuzumab and/or taxanes allowed if followed by a disease-free interval of ≥12 months

- **Primary endpoint: PFS (independently assessed)**
- **Secondary endpoints: PFS (investigator assessment), ORR, OS, Safety**

Stratified by geographic region and previous (neo)adjuvant chemotherapy

Women with **previously untreated**, HER2-positive locally recurrent/metastatic breast cancer (N = 808)

Trastuzumab 6 mg/kg q3w* + Docetaxel 75-100 mg/m^2 q3w† + Pertuzumab 420 mg q3w‡ (n = 402)

Trastuzumab 6 mg/kg q3w* + Docetaxel 75-100 mg/m^2 q3w† + Placebo q3w (n = 406)

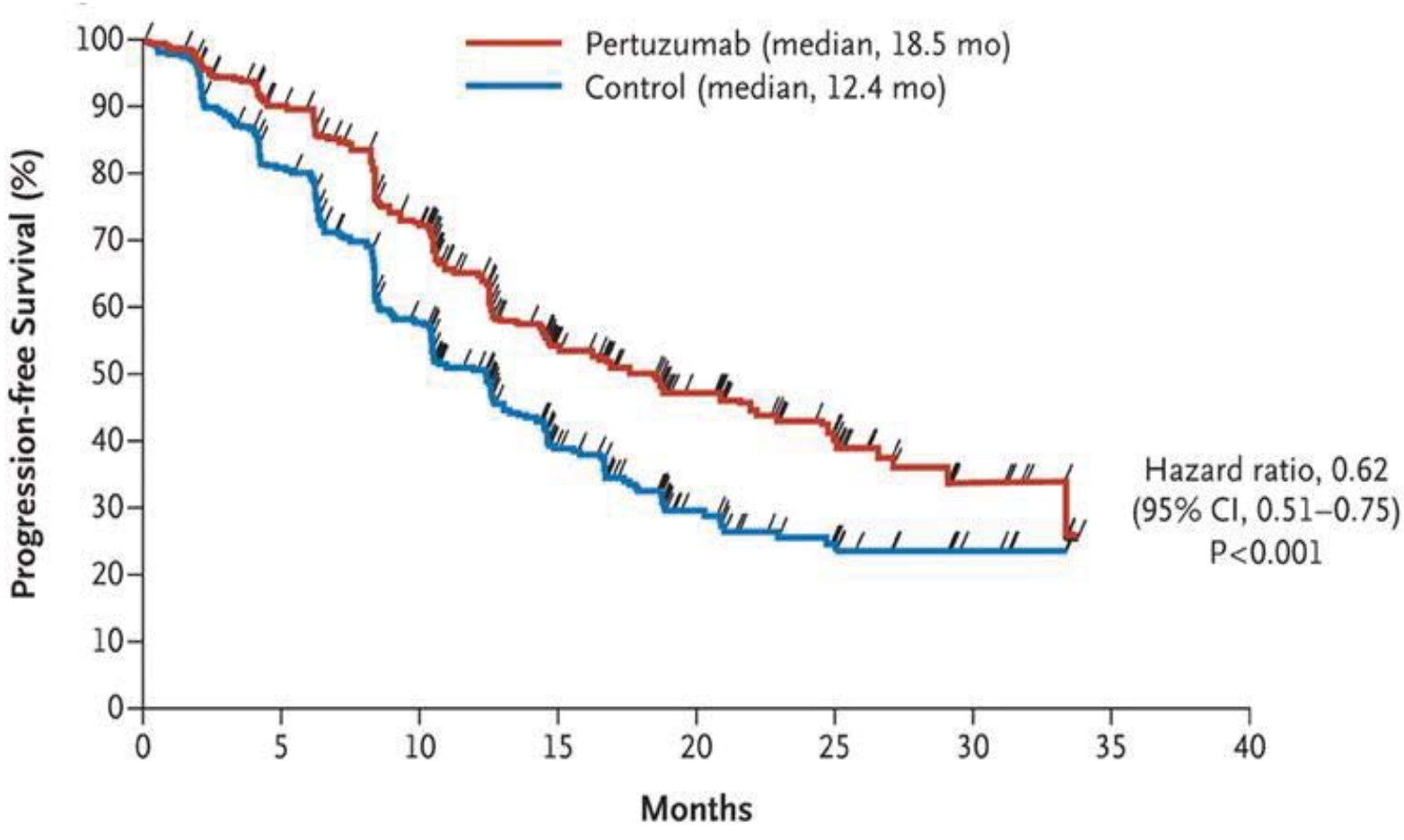
Treatment until disease progression or unacceptable toxicity

*Trastuzumab 8-mg/kg loading dose.
†Minimum of 6 docetaxel cycles recommended; < 6 cycles permitted for unacceptable toxicity or PD.
‡Pertuzumab 840-mg loading dose.

Baselga J et al. N Engl J Med 2012

CLEOPATRA
Pertuzumab plus Trastuzumab plus Docetaxel for MBC

PFS (Independent review)



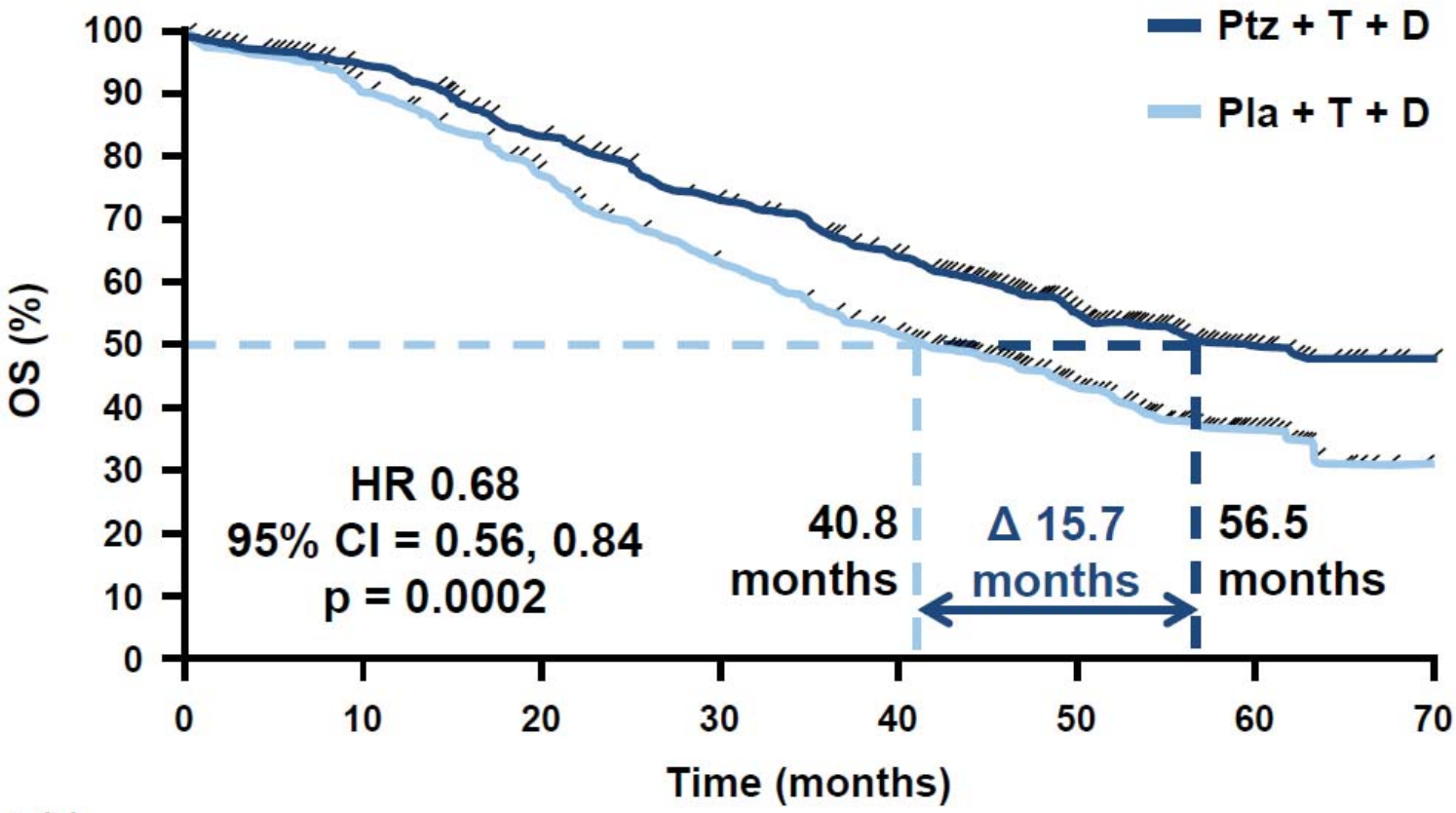
No. at Risk									
Pertuzumab	402	345	267	139	83	32	10	0	0
Control	406	311	209	93	42	17	7	0	0

Baselga J et al. New Engl J Med 2012

CLEOPATRA

Final OS Analysis

Median follow-up 50 months (range 0–70 months)

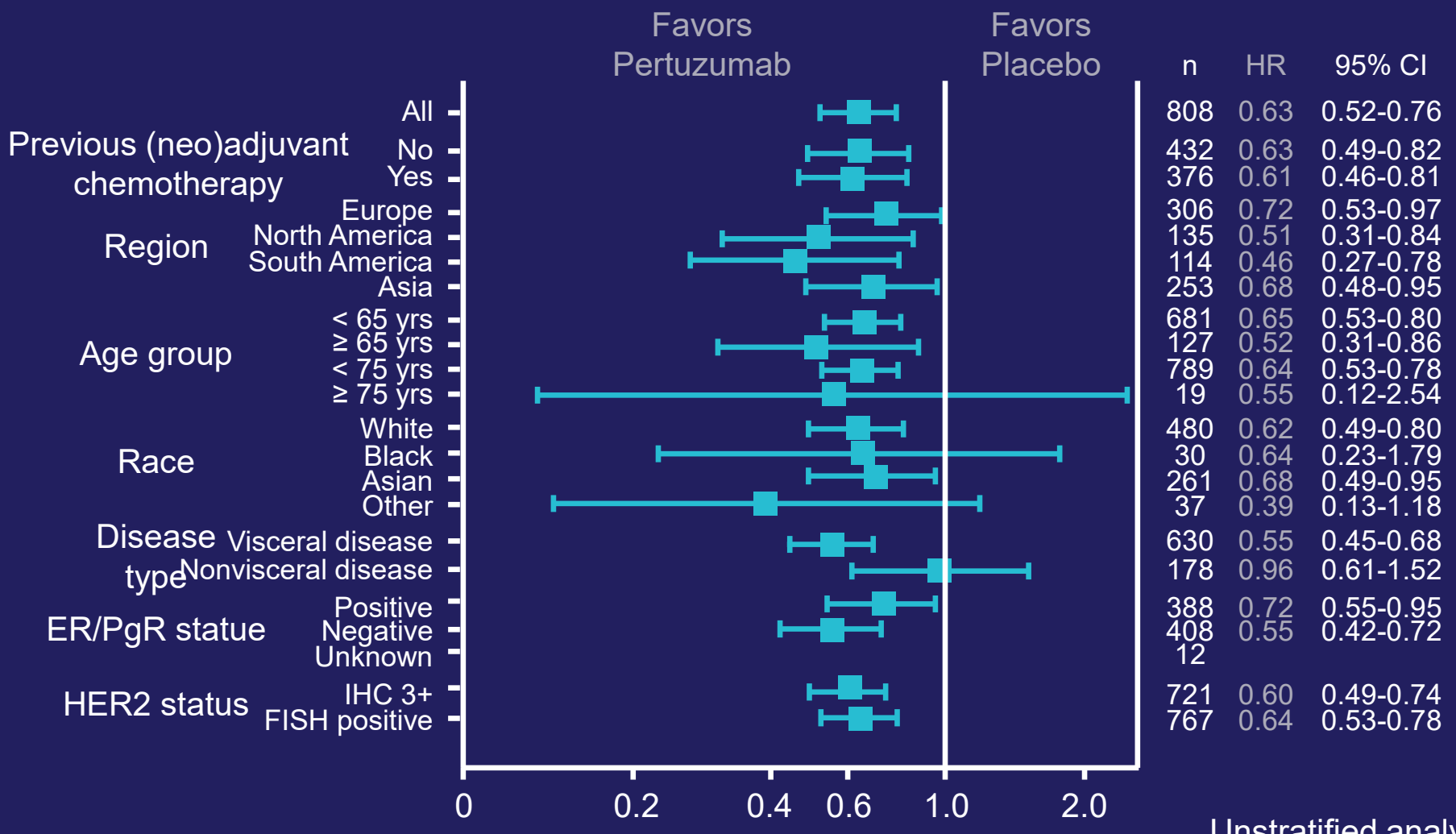


n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain SM et al, ESMO 2014

CLEOPATRA: Independently Assessed PFS by Predefined Subgroups



Baselga J, et al. SABCS 2011. Abstract S5-5.

CLEOPATRA - Toxicities

toxicity	Plac + T + Doc (n=397)	P + T + Doc (n=407)
Neutropenia G≥3	46.2%	49%
Febrile Neutropenia	7.6%	**13.8%**
Diarrhea any G	48.7%	**68.4%**
Rush any G	24%	**37.5%**
Mucositis any G	19.9%	**27.2%**
sLV systolic disfunction	**1.8%**	**1.5%**

Baselga J et al. New Engl J Med 2012; Swain S et al, ESMO 2014

CLEOPATRA
Selected patient characteristics

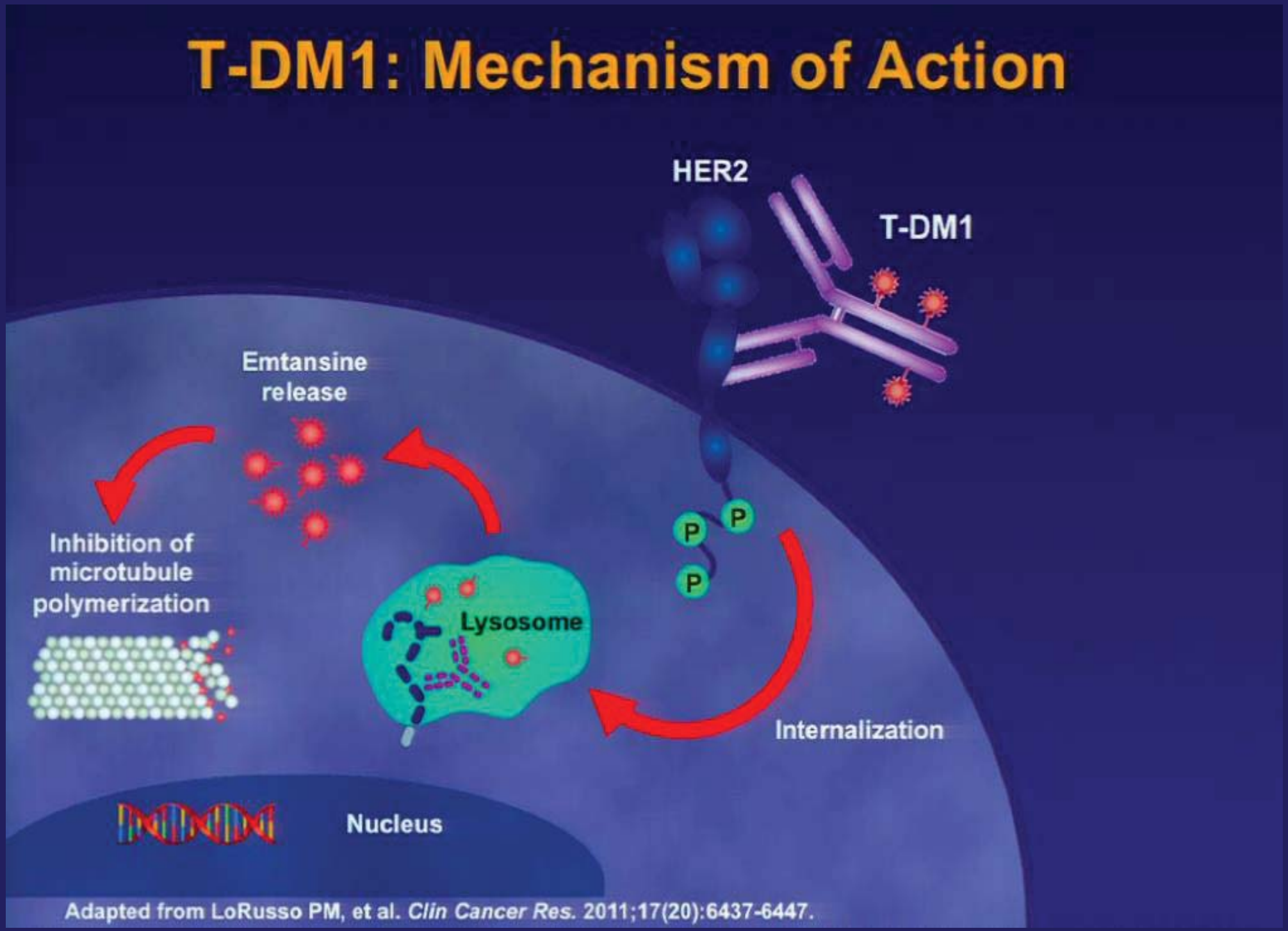
	Trast + Doc	Pert + trast + Doc
#	406	402
HR+ %	49	47
Visceral mets %	77.8	78.1
Prior adj ET %	23.9	26.4
Prior adj chemo %	47.3	45.8
Prior taxane %	23.2	22.6
Prior trastuzumab*	10.1	11.7

* Completed since > 12 months

Adapted from Baselga J et al. New Engl J Med 2012

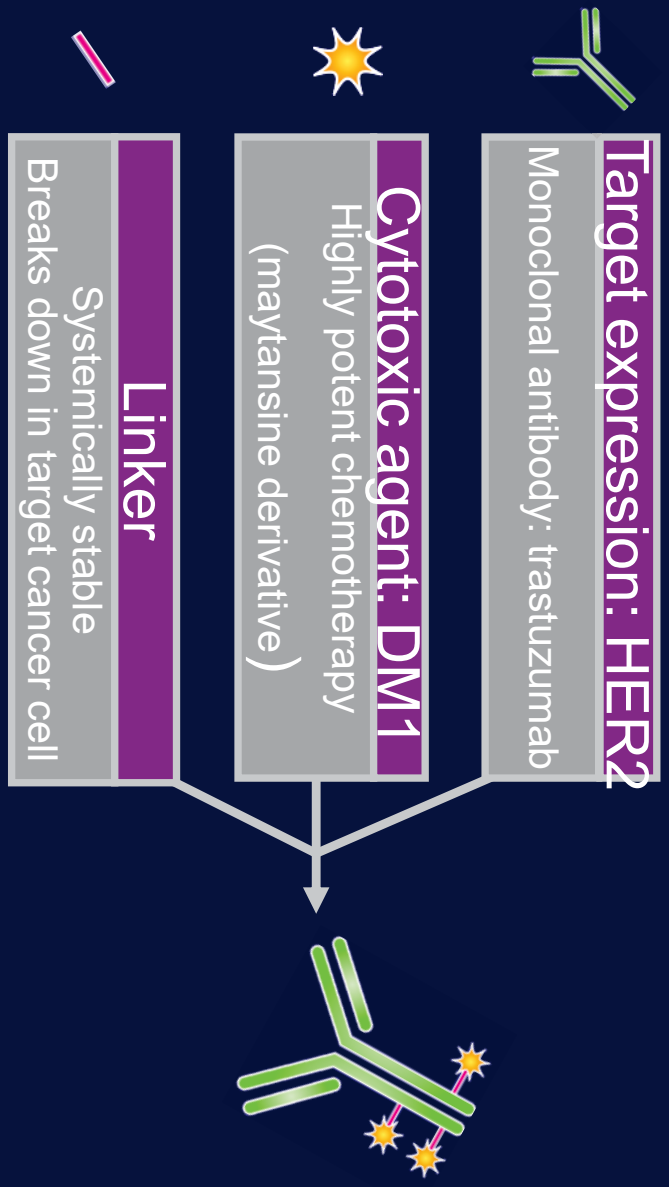
Trastuzmab-DM1

T-DM1: Mechanism of Action



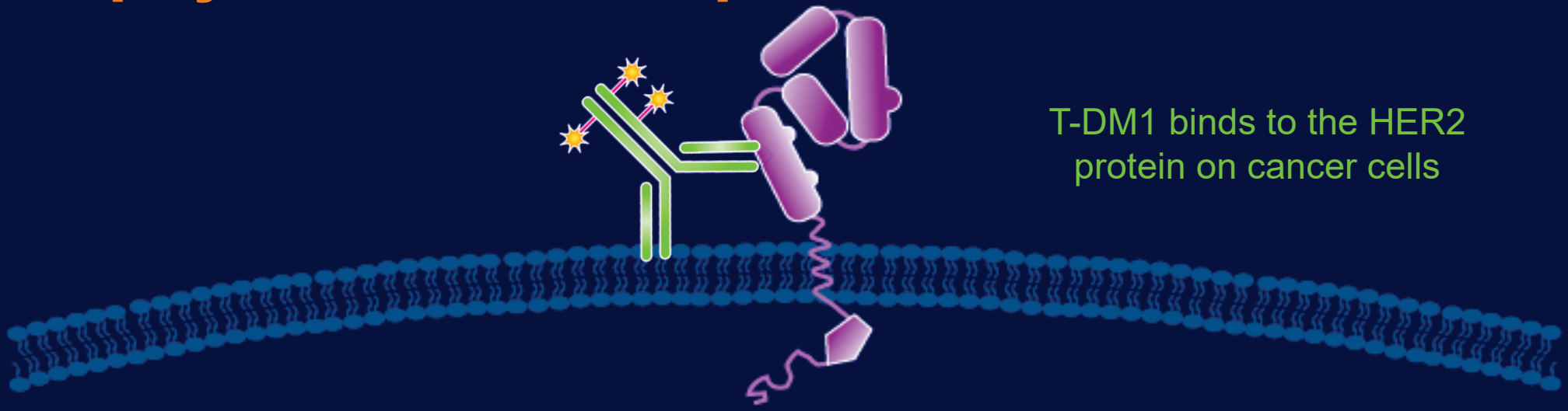
Adapted from LoRusso PM, et al. *Clin Cancer Res.* 2011;17(20):6437-6447.

T-DM1: 1st-in-class HER2 antibody-drug conjugate (ADC)



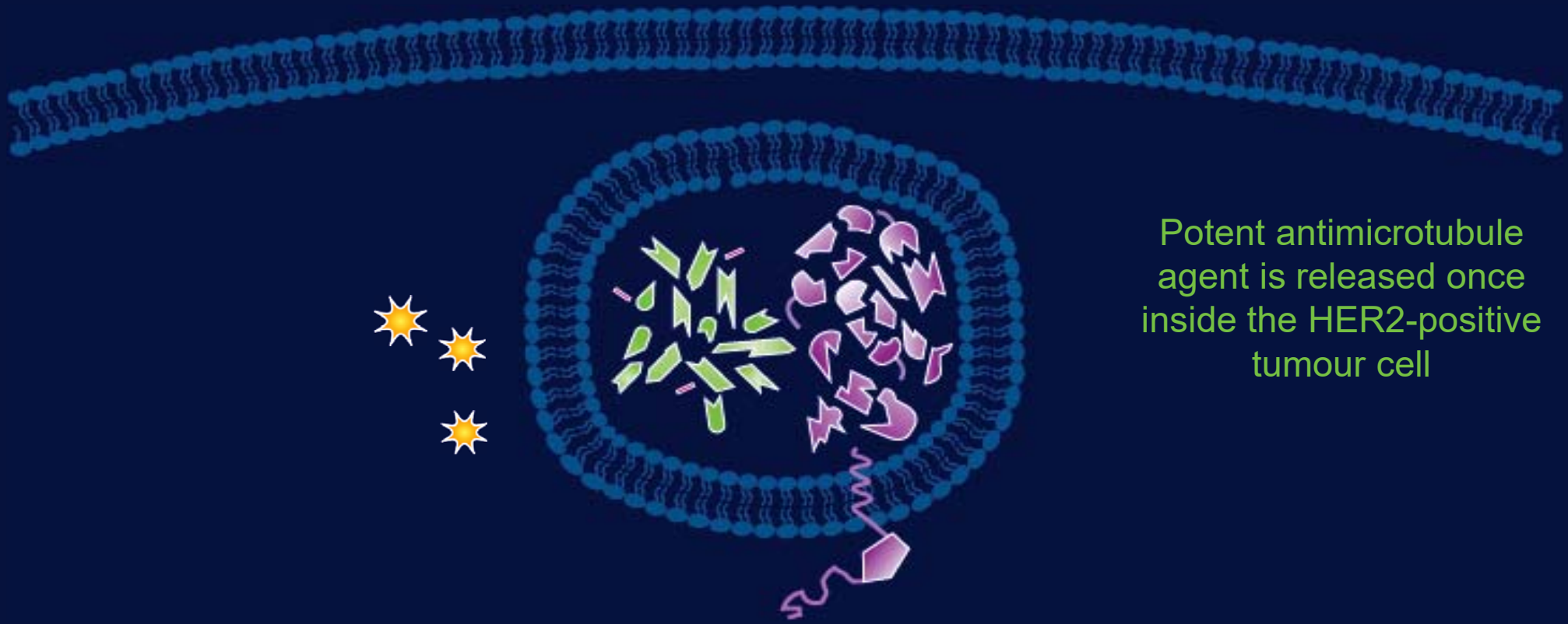
- Trastuzumab Emtansine (T-DM1)
- DM1, maytansine derivesi microtubule inhibitorü
- 20-100x vincristine etkinliği
- T-DM1, HER2 afinitesi trastuzumaba benzer

T-DM1 selectively delivers a highly toxic payload to HER2-positive tumour cells



T-DM1 binds to the HER2 protein on cancer cells

T-DM1 selectively delivers a highly toxic payload to HER2-positive tumour cells



Potent antimicrotubule agent is released once inside the HER2-positive tumour cell

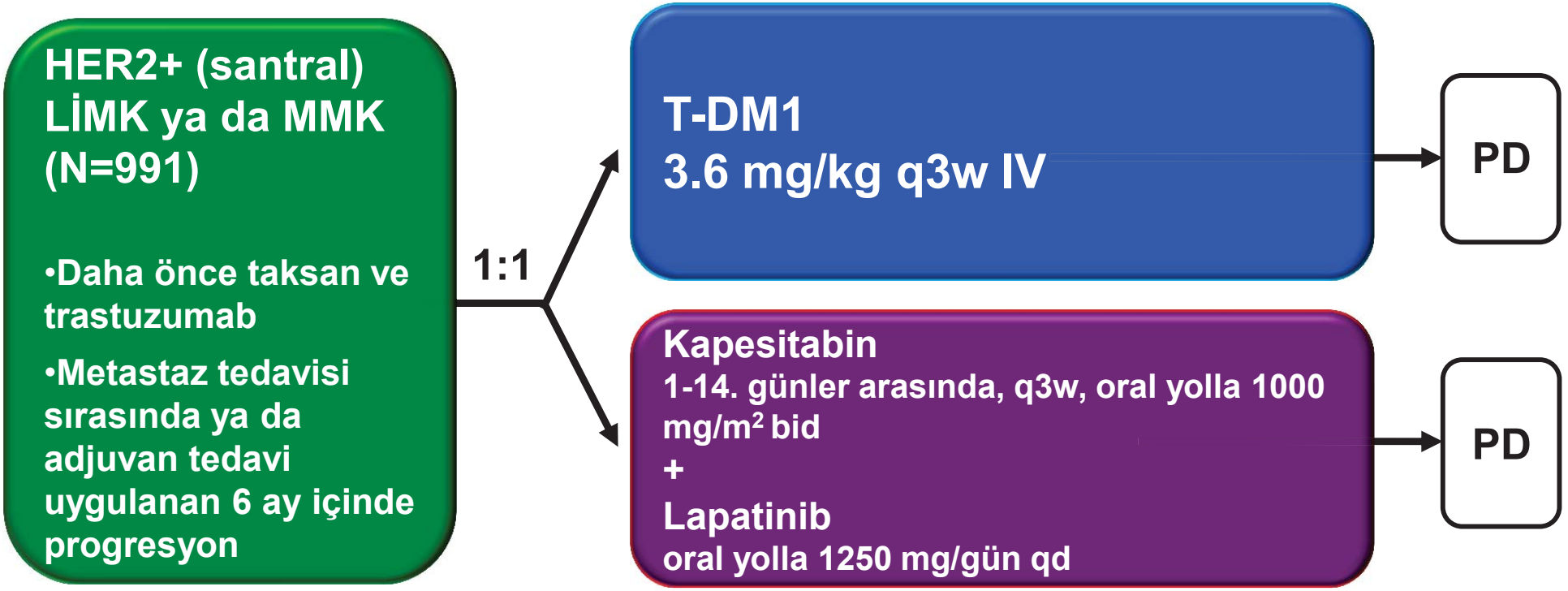
Çoklu Basamak Tedavi Edilmiş Hastalarda TDM1 Etkinliği

Tumour response	Independent review (n=110)	Investigator assessed (n=110)
ORR, % (95% CI)	32.7 (24.1, 42.1)	30.0 (22.0, 39.4)
CR	0	1.8
PR	32.7	28.2
SD[a]	46.4	52.7
PD	18.2	13.6
Unevaluable	1.8	0.9
Missing	0.9	2.7
CBR, % (95% CI)	44.5 (35.1, 54.3)	40.0 (31.1, 49.3)
Median PFS, months (range)	7.3 (0-11.7)	n/a

[a]Including unconfirmed PRs
CI, confidence interval; n/a, not assessed

Krop et al. SABCS 2009

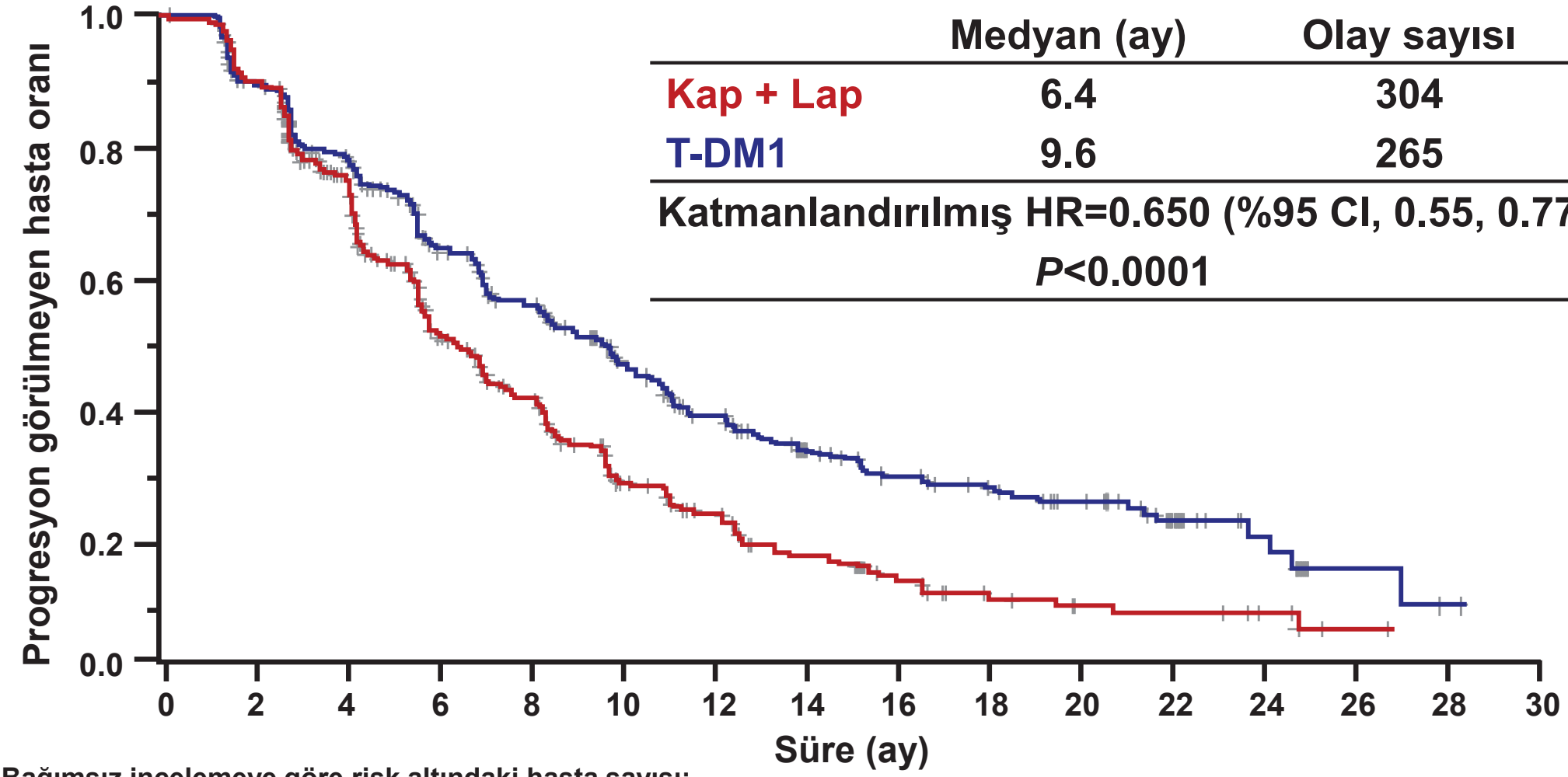
EMILIA Çalışmasının Tasarımı



- **Stratifikasyon faktörleri:** Yerleşim bölgesi, daha önce MMK ya da rezeke edilemeyen LİMK nedeniyle uygulanan kemoterapi rejimlerinin sayısı, viseral hastalık varlığı
- **Birincil sonlanım noktaları:** Bağımsız incelemeye göre PFS, OS ve güvenilirlik
- **Önemli ikincil sonlanım noktaları:** Araştırmacıya göre PFS, OFF, yanıt süresi, semptom progresyonuna kadar geçen süre

Verma S, *et al. N Engl J Med* 2012; 367:1783–1791.

Bağımsız İncelemeye Göre
Progresyonsuz Sağkalım



	Medyan (ay)	Olay sayısı
Kap + Lap	6.4	304
T-DM1	9.6	265

Katmanlandırılmış HR=0.650 (%95 CI, 0.55, 0.77)

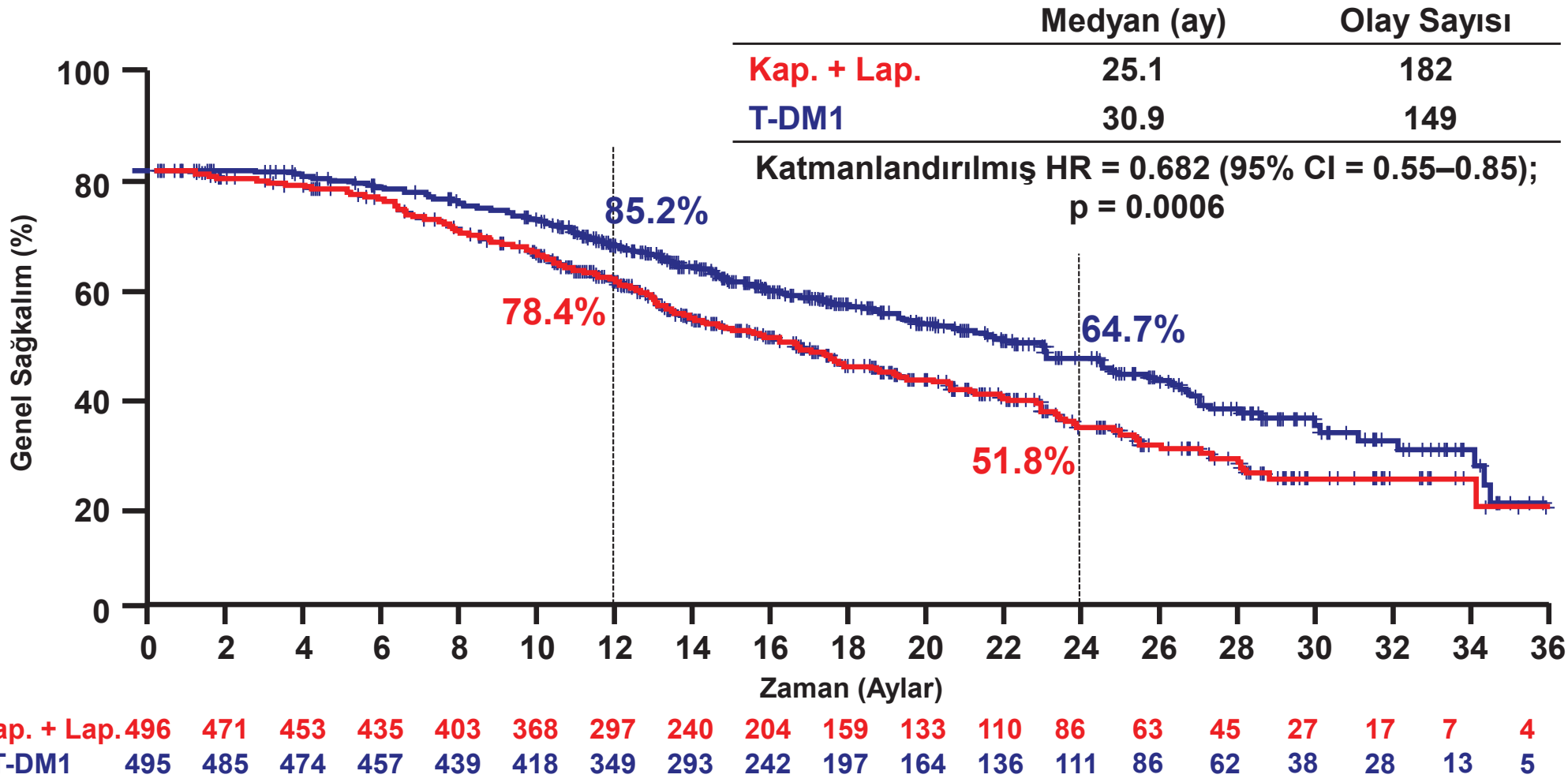
P<0.0001

Bağımsız incelemeye göre risk altındaki hasta sayısı:

Kap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

Verma S, *et al. N Engl J Med* 2012; **367:**1783–1791.

EMILIA: Genel Sağkalım (Doğrulayıcı Analiz)



T-DM1: trastuzumab emtansin, Kap.: Kapesitabin, Lap.: Lapatinib, HR:risk oranı

Verma S, *et al*. *N Engl J Med* 2012; **367:**1783–1791 (supplementary material available with the publication online); Verma S, et al. ESMO 2012 (Abstract LBA12; oral presentation).

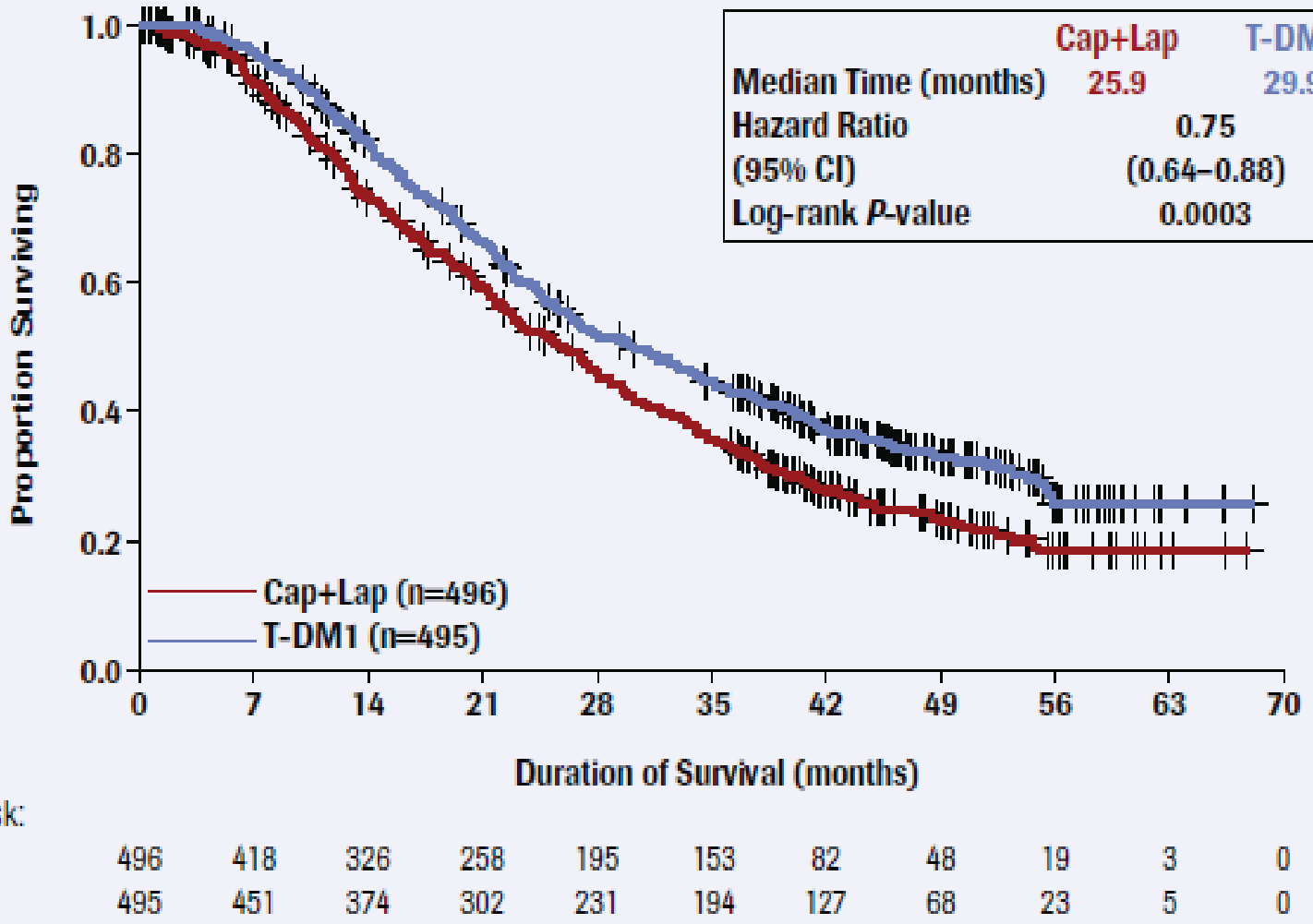
Genel Sağkalım Sonuçları

- Çalışmada ikinci interim OS analizi sonrası yapılan değişiklik ile lapatinib+kapesitabin kolundaki hastaların T-DM1 koluna çapraz geçişine izin verildi.

- Bu değişiklik sonrası lapatinib+kapesitabin kolundaki hastalardan **136**'sı **(%27.4) T-DM1 tedavisine geçiş yapmıştır.**

Véronique Diéras et al. Final Results From the Phase 3 EMILIA Study.
San Antonio Breast Cancer Symposium December 8–12, 2015 (Poster Presentation)

Figure 3. Final overall survival in the intent-to-treat population



Number at Risk:

Cap+Lap	496	418	326	258	195	153	82	48	19	3	0
T-DM1	495	451	374	302	231	194	127	68	23	5	0

Cap+Lap, capecitabine plus lapatinib; CI, confidence interval; T-DM1, trastuzumab emtansine.

Hastaların **%27.4'ünde çapraz geçiş** olmasına rağmen kontrol koluna karşı **T-DM1 ile sağlanan sağkalım faydası korunmuştur.**

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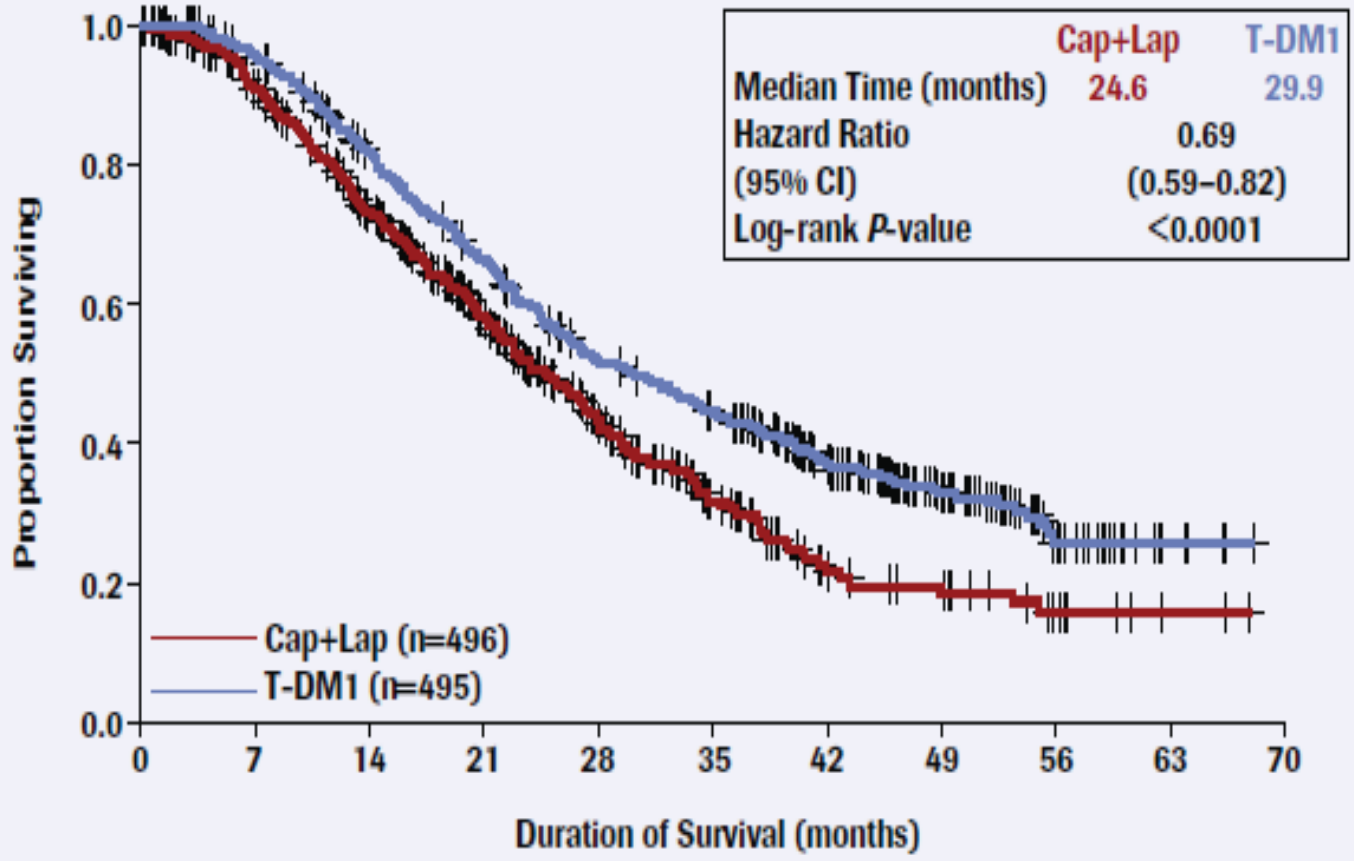
Figure 4. Sensitivity analysis: Overall survival with crossover patients censored



Number at Risk:

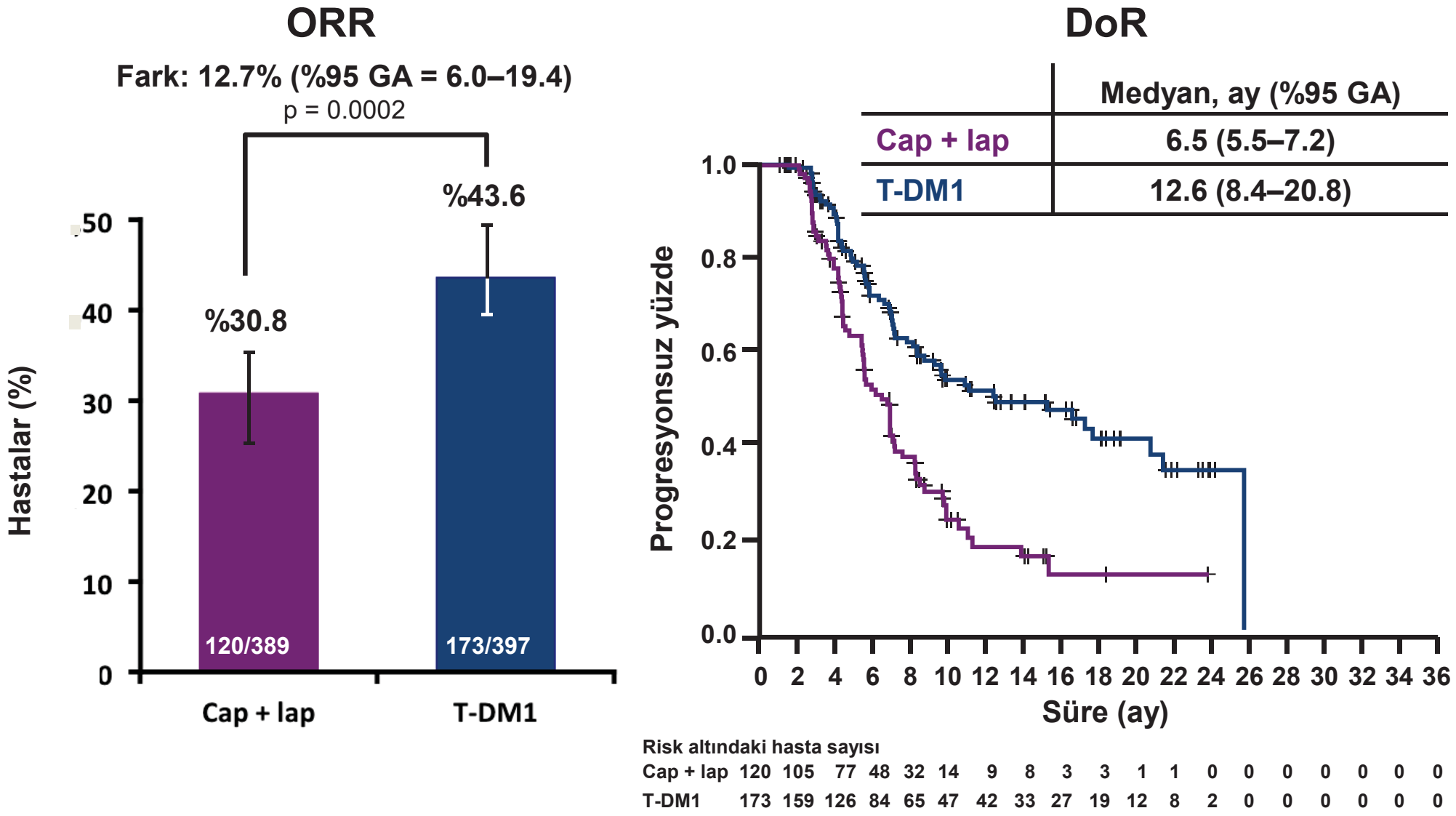
Cap+Lap	496	418	312	208	119	64	24	17	8	2	0
T-DM1	495	451	374	302	231	194	127	68	23	5	0

Cap+Lap, capecitabine plus lapatinib; CI, confidence interval; T-DM1, trastuzumab emtansine.

Çapraz geçiş yapan hastalar dışlanarak ortaya konulan sonuçlarda **Lapatinib+kapesitabin** kolu medyan **24.6 ayda** kalırken **HR: 0.69** olarak saptandı.

Véronique Diéras et al. Final Results From the Phase 3 EMILIA Study.
San Antonio Breast Cancer Symposium December 8–12, 2015 (Poster Presentation)

EMILIA : Değerlendirilebilir hastalık olan hastalarda ORR ve DoR



GA, güven aralığı; DoR, yanıt süresi; ORR, objektif yanıt oranı.

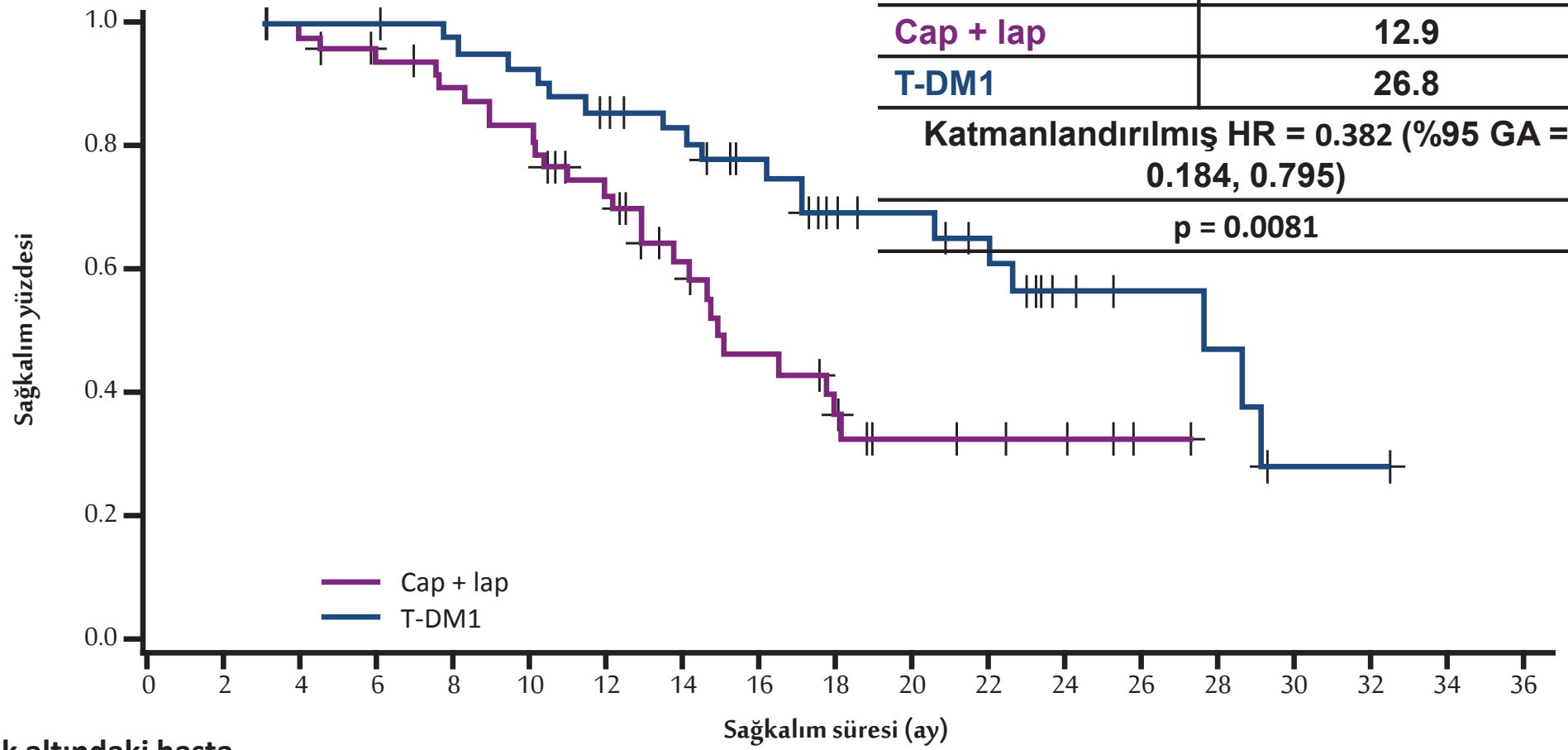
Verma S, *et al*. *N Engl J Med* 2012; **367:**1783–1791 (supplementary material available with the publication online); Blackwell KL, *et al*. ASCO 2012 (Abstract LBA1; oral presentation).

EMILIA : Başlangıçta MSS Hastalığı Olan Hastalarda Genel Sağkalım

	Medyan (ay)
Cap + lap	12.9
T-DM1	26.8

Katmanlandırılmış HR = 0.382 (%95 GA = 0.184, 0.795)

p = 0.0081



Risk altındaki hasta sayısı:

Cap + lap	50	47	45	41	36	30	21	15	13	7	6	5	4	1	0	0	0	0	0
T-DM1	45	43	42	40	38	34	32	27	21	18	16	11	8	6	4	2	2	1	1

Cap, kapesitabin; GA, güven aralığı; MSS, merkezi sinir sistemi; HR, hazard ratio; lap, lapatinib.

Krop I, *et al*. SABCS 2013 (P4-12-27; poster presentation).

Yan Etkiler

	Kap + Lap (n=488)	T-DM1 (n=490)
Tüm evrelerdeki AE, n (%)	477 (97.7)	470 (95.9)
Evre ≥3 AE, n (%)	278 (57.0)	200 (40.8)
Tedavinin bırakılmasına yol açan AE'ler (herhangi bir araştırma ilacı için), n (%)	52 (10.7)	29 (5.9)
Tedavi sırasında ölüme yol açan AE'ler, n (%)[a]	5 (1.0)	1 (0.2)
LVEF <%50 ve başlangıca göre ≥15 puan düşüş, %[b]	7 (1.6)	8 (1.7)

[a]Kap + Lap: CAD, çoğul organ yetersizliği, koma, hidrosefali, ARDS; T-DM1: metabolik ensefalopati.
[b]Değerlendirilebilen hastalar: 445 (Kap + Lap); 481 (T-DM1).

Verma S, *et al. N Engl J Med* 2012; 367:1783–1791.

EMILIA - Hasta Özellikleri

	Lapatinib+capecitabine	T-DM1
#	496	495
HR+ %	53	57
Visceral mets %	68	68
Prior therapy for mets %	88	88
Prior trastuzumab for EBC only %	16	16
Median time since last T mos.	1.5 (0-98)	1.5 (0-63)

- Verma et al. N Engl J Med 2012;367:1783.

EMILIA- Sonuç

- Genel Sağkalım analizi ile T-DM1'ın çapraz geçişe rağmen sağkalımı arttırdığı ortaya konmuş.

- Daha önce HER2 + metastatik meme kanseri için tedavi almış hastalarda yüksek düzeyde etkili ve tolere edilebilir bir tedavi seçeneğidir.

Phase III, randomized study of trastuzumab emtansine ± pertuzumab vs trastuzumab + taxane for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study

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PRESENTED AT: ASCO Annual '15 Meeting

MARIANNE Study Design

- **HER2-positive (central) LABC[a] or MBC**
- **No prior chemotherapy for LABC/MBC**
- **>6 months from prior neo-/adjuvant vinca alkaloid or taxane chemotherapy**

N = 1095

Trastuzumab + docetaxel
(8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m² q3w) **OR**
Trastuzumab + paclitaxel
(4 mg/kg LD then 2 mg/kg + 80 mg/m² qw)

T-DM1 + placebo[b]
(3.6 mg/kg + 840 mg LD then 420 mg q3w)

T-DM1 + pertuzumab
(3.6 mg/kg + 840 mg LD then 420 mg q3w)

- **Stratification factors:** World region, Prior neo-/adjuvant therapy (if Yes: prior trastuzumab/lapatinib), Visceral disease
- **Primary end point:** PFS by independent review facility (IRF), non-inferiority and superiority assessed
- **Key secondary end points:** OS, PFS by investigator, ORR, Safety, Patient-reported outcomes

LD, Loading dose. [a]Locally progressive or recurrent and not amenable to resection with curative intent; [b]Pertuzumab placebo.

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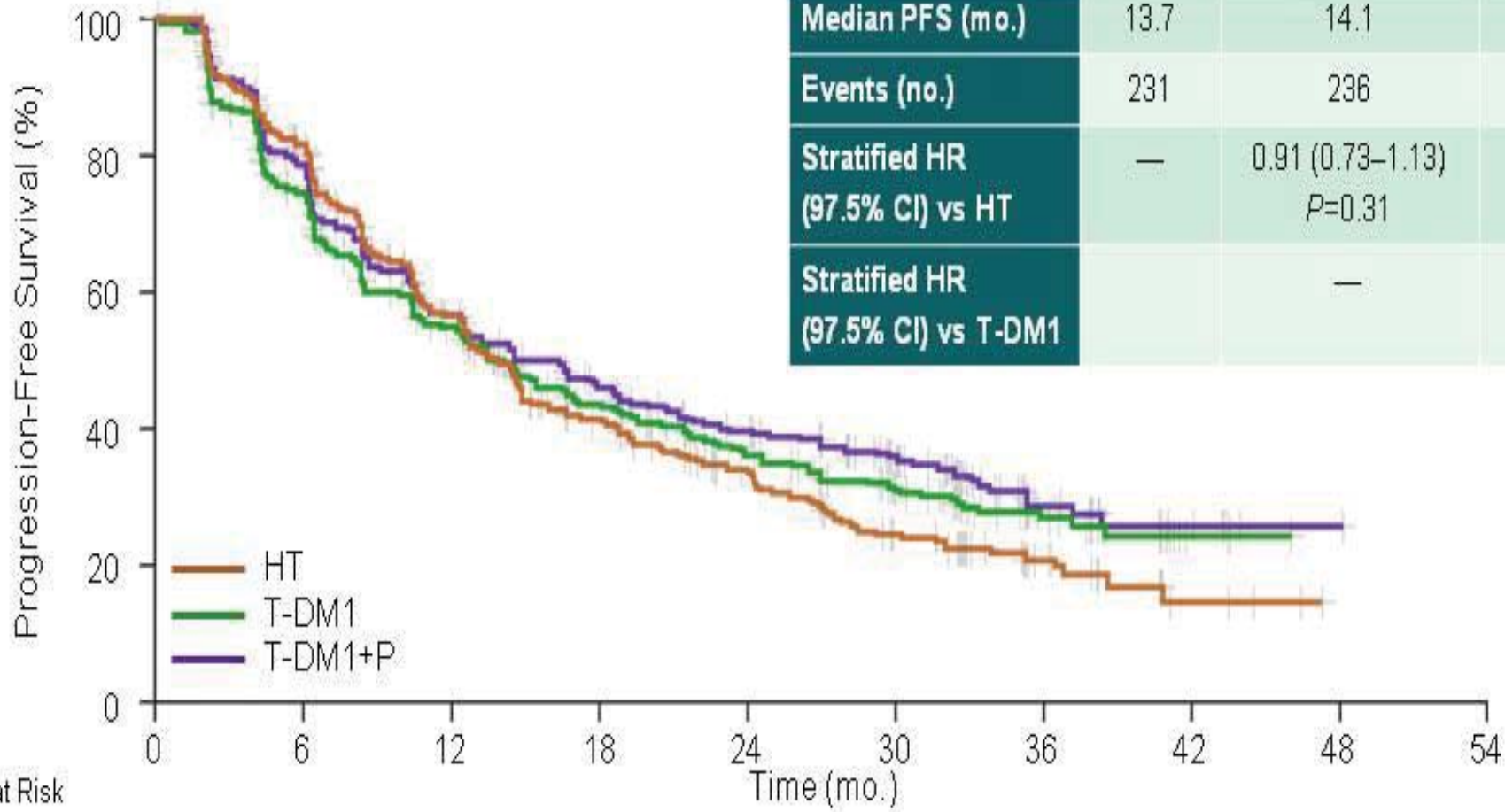
Prior Systemic Anti-Cancer Therapy

	HT (n = 365)	T-DM1 (n = 367)	T-DM1+P (n = 363)
Prior neo-/adjuvant therapy, %			
None	44	45	44
HER2-directed (trastuzumab/lapatinib)	31	31	32
Taxane	33	29	36
Anthracycline	42	44	46
Hormonal	24	23	25
Median time since prior neo-/adjuvant trastuzumab, mo. (range)	13 (0.4–118)	17 (0.8–64)	19 (1–62)
Prior LABC/MBC therapy, %	8	7	6
Hormonal	7	6	6
HER2-directed	2	2	2

Progression-Free Survival by IRF

	HT	T-DM1	T-DM1+P
Median PFS (mo.)	13.7	14.1	15.2
Events (no.)	231	236	217
Stratified HR (97.5% CI) vs HT	—	0.91 (0.73–1.13) *P*=0.31	0.87 (0.69–1.08) *P*=0.14
Stratified HR (97.5% CI) vs T-DM1		—	0.91 (0.73–1.13)



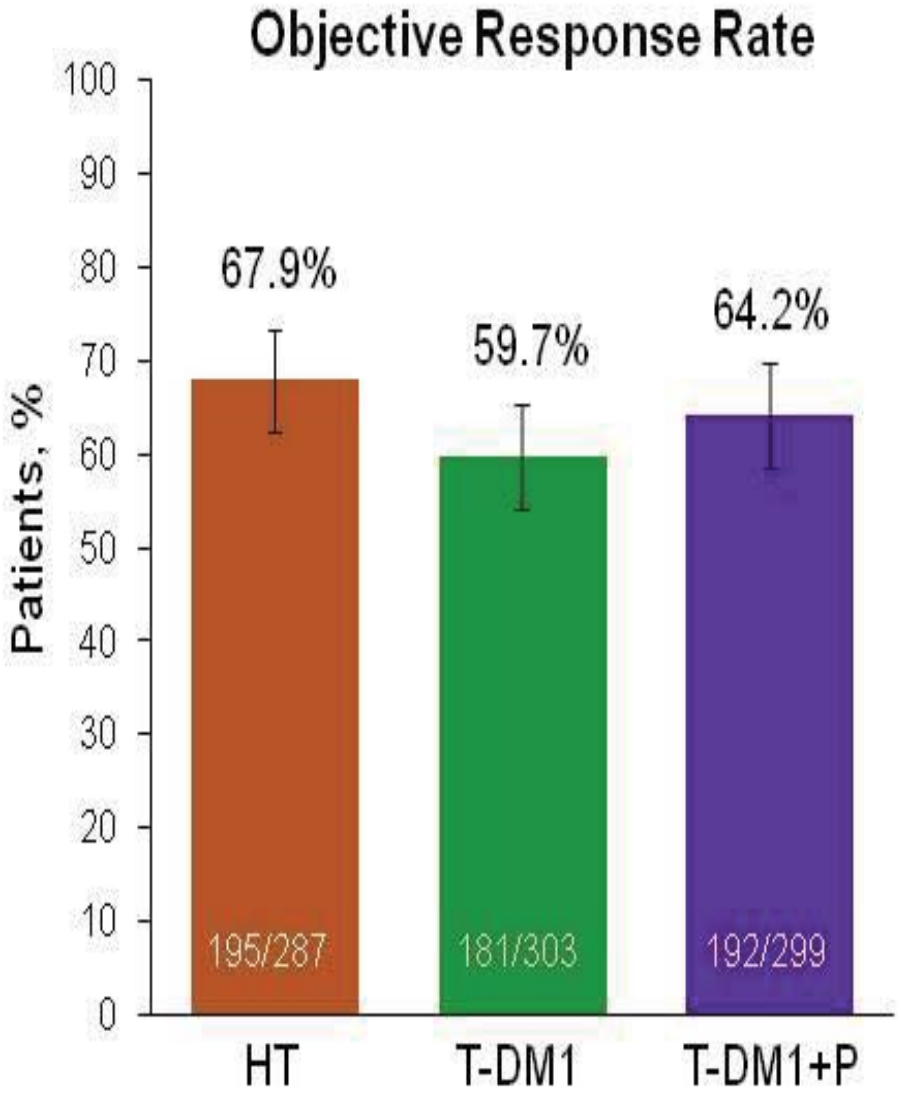
No. at Risk

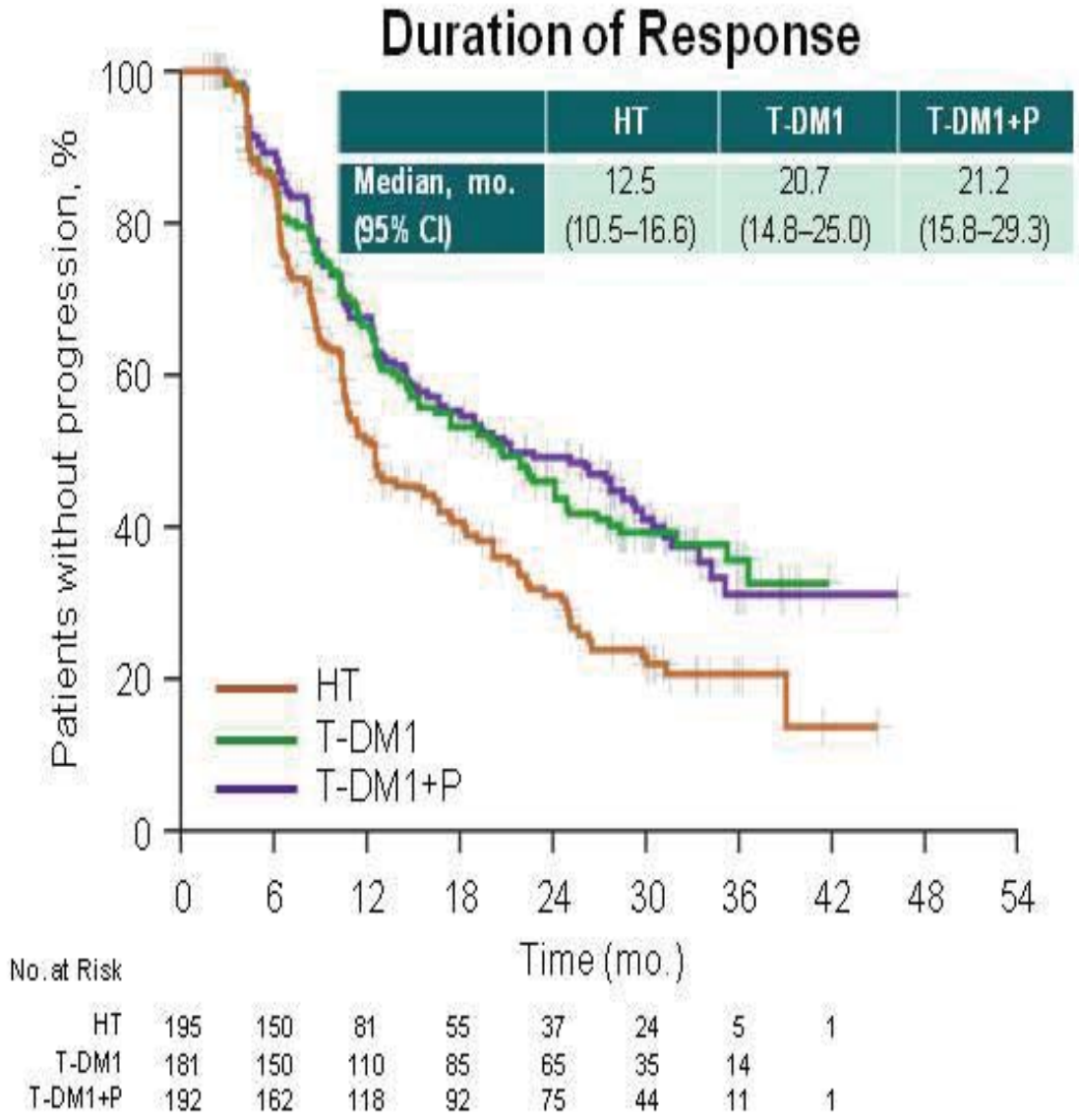
HT	365	265	163	107	75	50	21	5
T-DM1	367	257	176	133	104	67	28	3
T-DM1+P	363	261	177	135	109	75	25	5	1

Non-inferiority: Established if the upper limit of the 97.5% CI for the HR is below 1.1765 (non-inferiority margin).

PRESENTED AT: ASCO Annual '15 Meeting

Objective Response and Duration of Response by IRF





	HT	T-DM1	T-DM1+P
Median, mo. (95% CI)	12.5 (10.5–16.6)	20.7 (14.8–25.0)	21.2 (15.8–29.3)

Error bars depict 95% confidence intervals.

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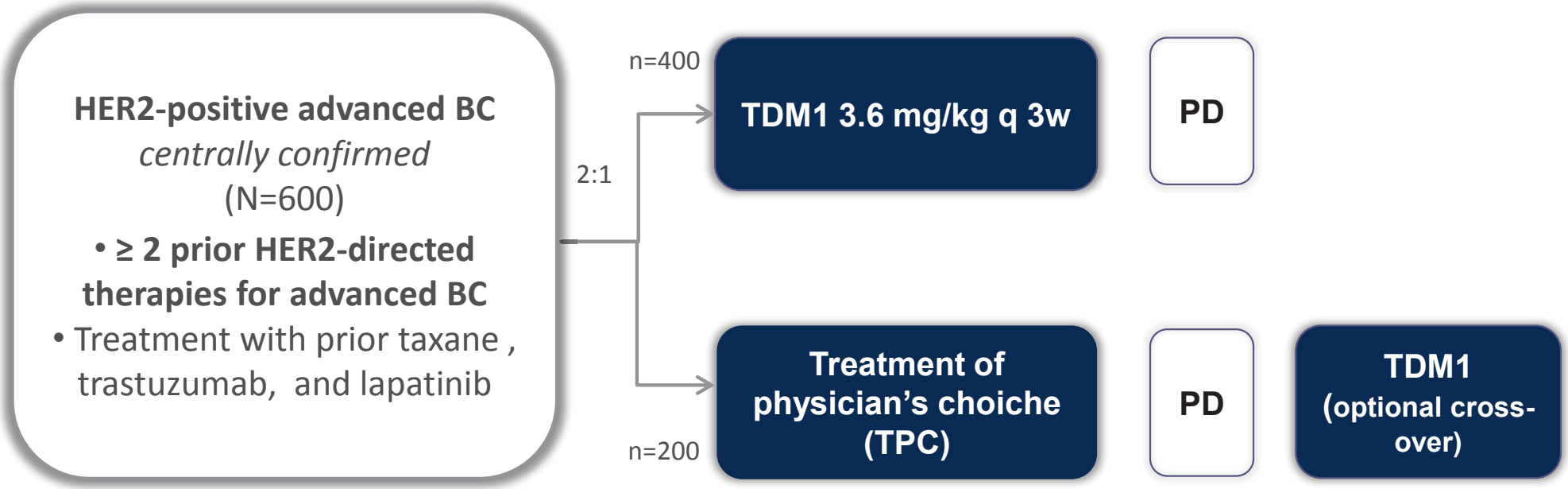
Phase III TH3RESA study



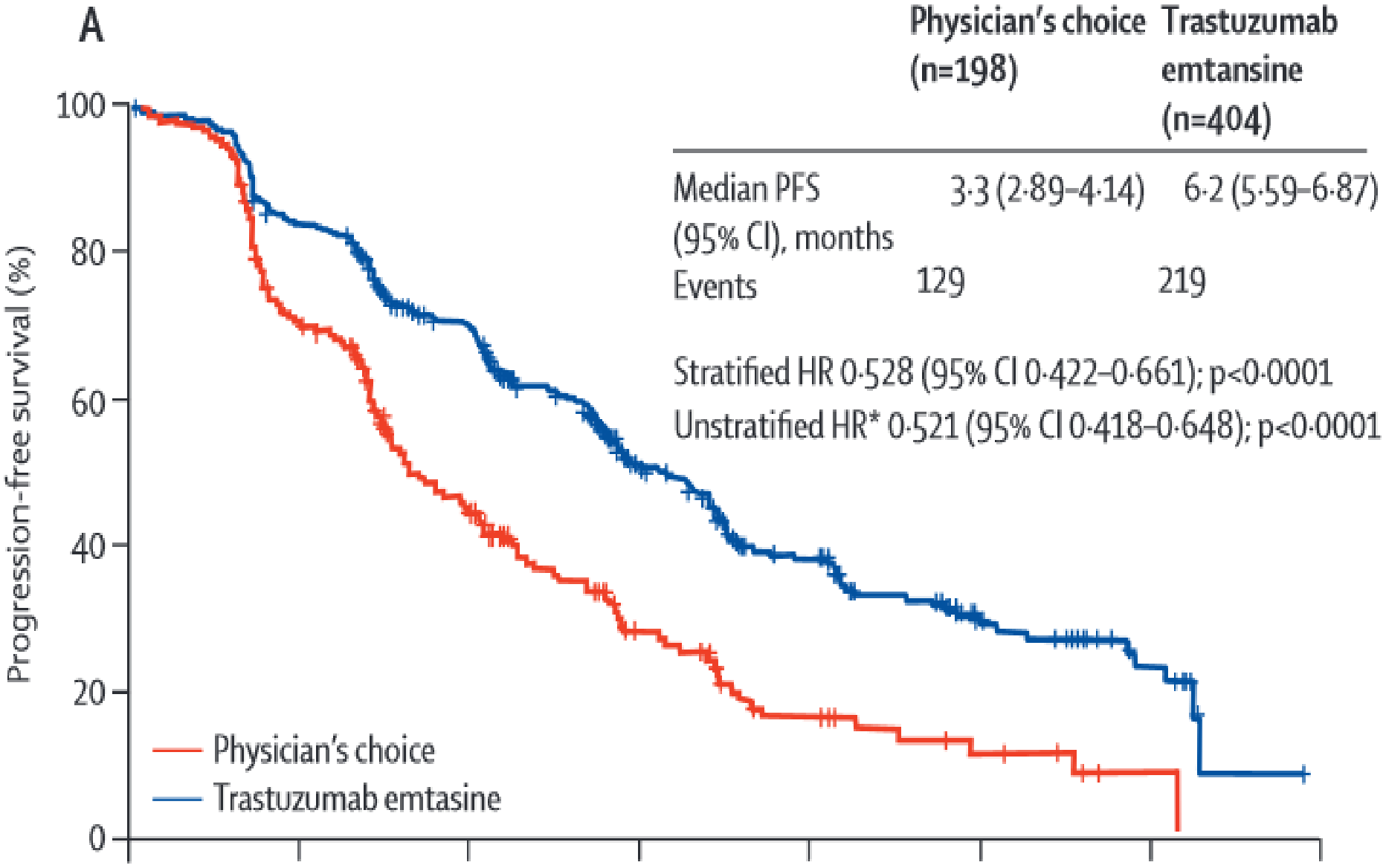
- **Stratification factors:** World region, number of prior regimens for advanced BC, presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

Phase III TH3RESA study: patients

Characteristic	TPC # 198	T-DM1 # 404
ER and/or PR-positive, %	52.0	51.5
Visceral involvement, %	75.8	74.8
Disease extent at study entry Metastatic unresectable LABC/recurrent BC	 94.4 5.6	 96.8 3.2
# of prior regimes for advanced BC, median (range) ≤3 4-5 >5	4 (1-19) 39.4 32.8 27.8	4 (1-14) 32.6 37.1 30.3
Brain metastases at baseline, %	13.8	9.9

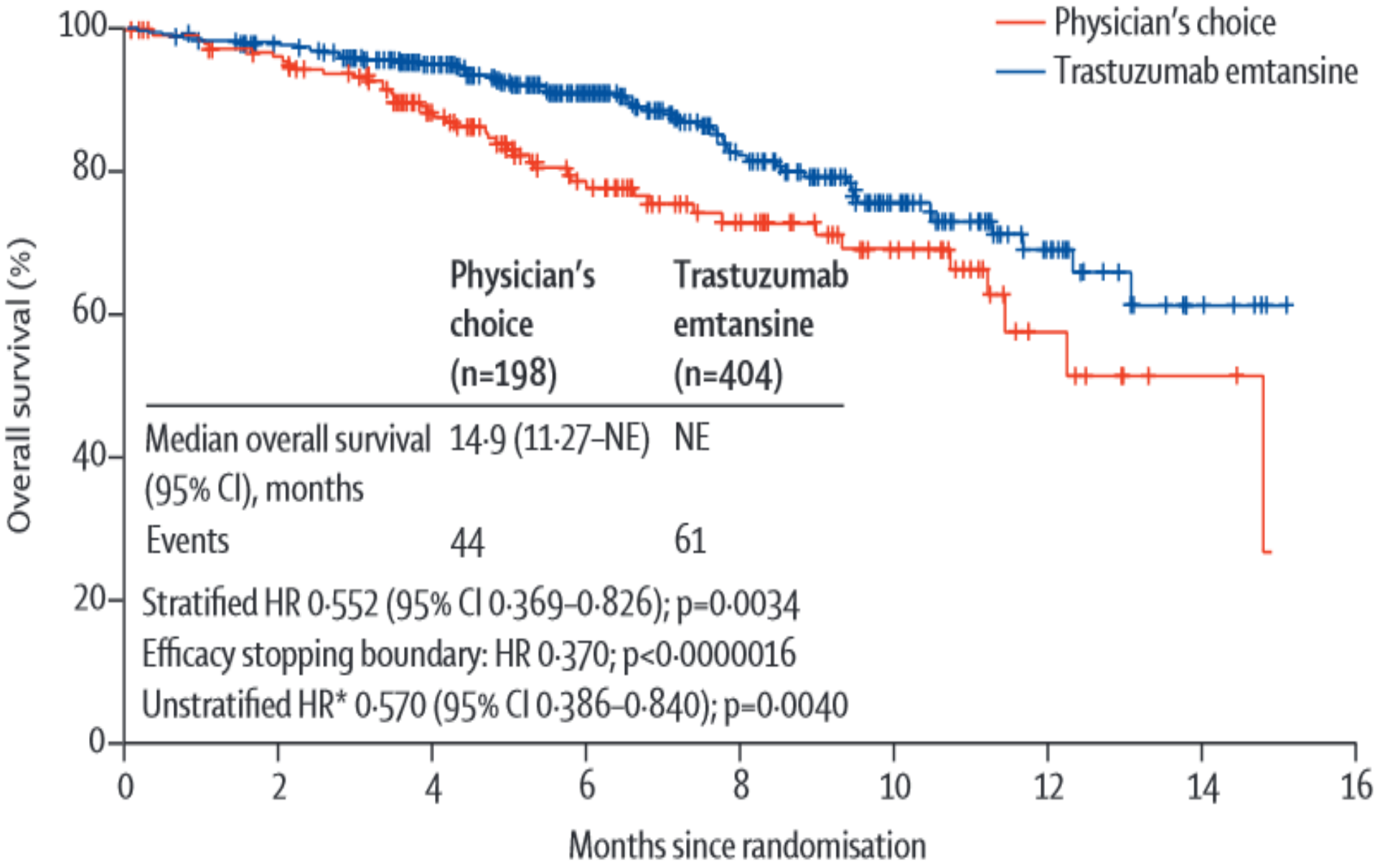
- *Krop I, Lancet Oncol 2014*

TH3RESA : PFS by investigator assessment



- *Krop I, Lancet Oncol 2014*

TH3RESA: first interim OS analysis



- *Krop I, Lancet Oncol 2014*

HER2 Metastatik Hastalıkta Hormonal Tedavi Seçenekleri

Regimen	ORR, %	Median PFS, months
Trastuzumab (N = 114; HER2 positive, n = 79)[1]	26	3.5-3.8
Anastrozole/trastuzumab (n = 103)[2]	20	4.8
Anastrozole (n = 104)[2]	7	2.4
Lapatinib/letrozole (n = 642)[3]	28	8.2
Letrozole (n = 644)[3]	15	3.0
Lapatinib (N = 138)[4]	24	NA

ORR, overall response rate; PFS, progression-free survival

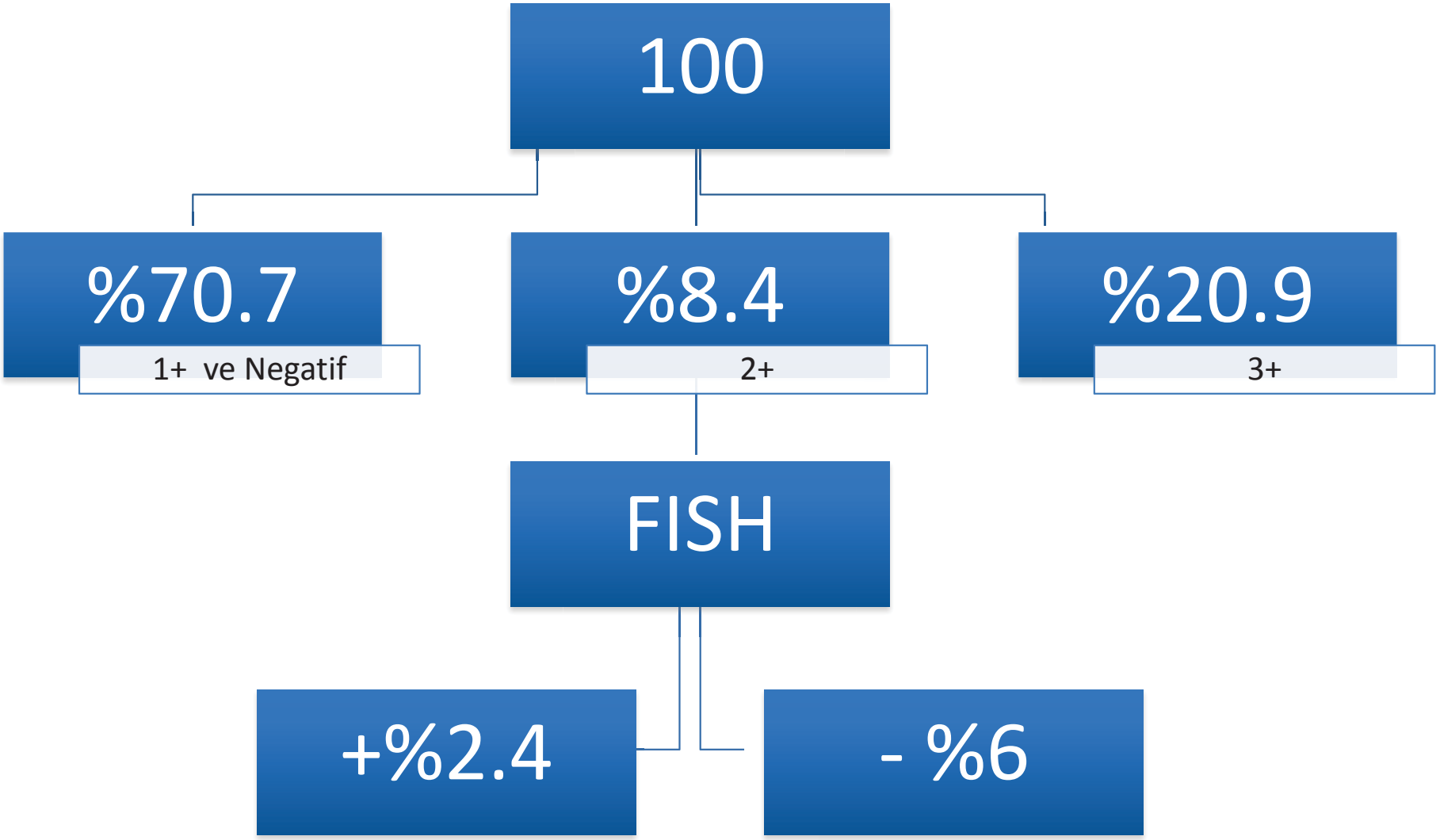
1. Vogel C, et al. *J Clin Oncol*. 2002;20(3):719-726. 2. Kaufman B, et al. *J Clin Oncol*. 2009;27(33):5529-5537.
3. Johnston S, et al. *J Clin Oncol*. 2009;27(33):5538-5546. 4. Gomez HL, et al. *J Clin Oncol*. 2008;26:2999-3005.

Co-Targeting HER2 and HR in Luminal B/HER2+ ABC

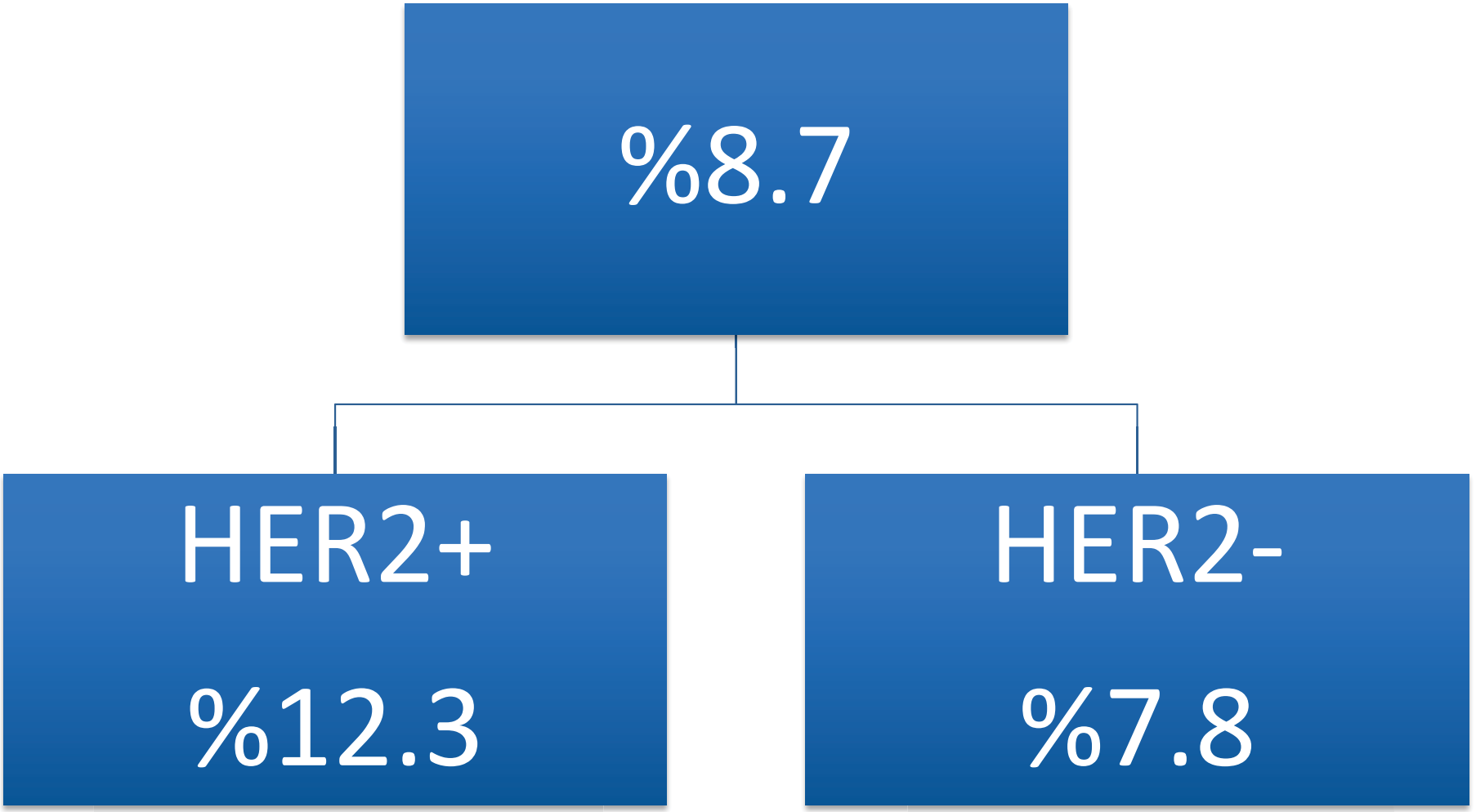
	TAnDEM [1] # 208		eLEcTRA[2] # 57		Johnston et al [3] # 219	
	Anastrozole	Anastrozole + trastuzumab	Letrozole	Letrozole + trastuzumab	Letrozole + placebo	Letrozole + Lapatinib
CBR %	27.9	**42.7 p 0.026**	39.0	**65.0 p 0.0001**	29	48 p 0.003
Median PFS (m)	2.4	**4.8 HR 0.63**	3.3	**14.1 HR 0.44**	3.0	8.2 HR 0.71
Median OS (m)	23.9	**28.5**	NR	**NR**	32.3	33.3

[1] Kaufman B, et al. JCO 2009; [2] Huober J et al. Breast 2012; [3] Johnston S et al. JCO 2009

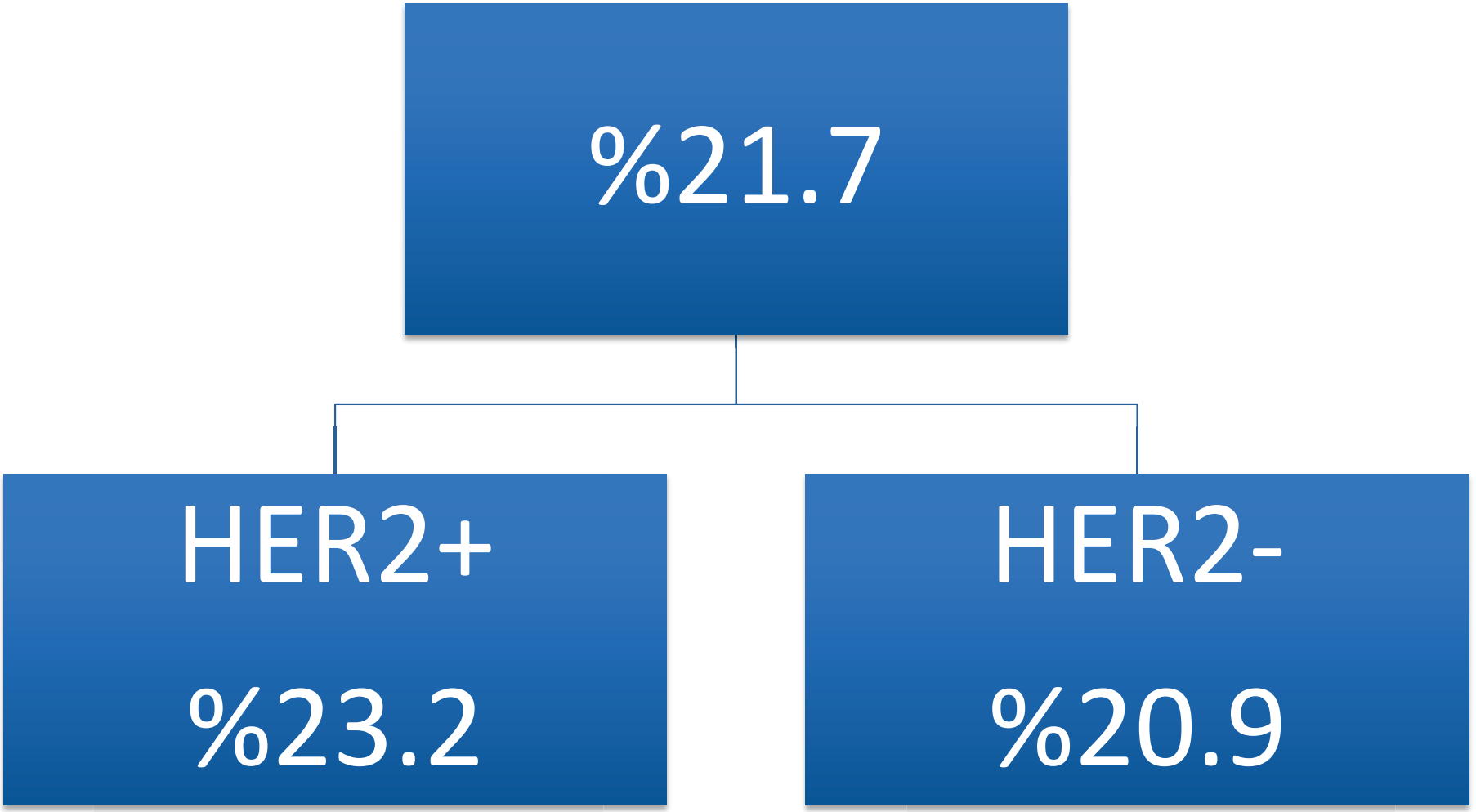
Hacettepe Üniversitesi-HER2



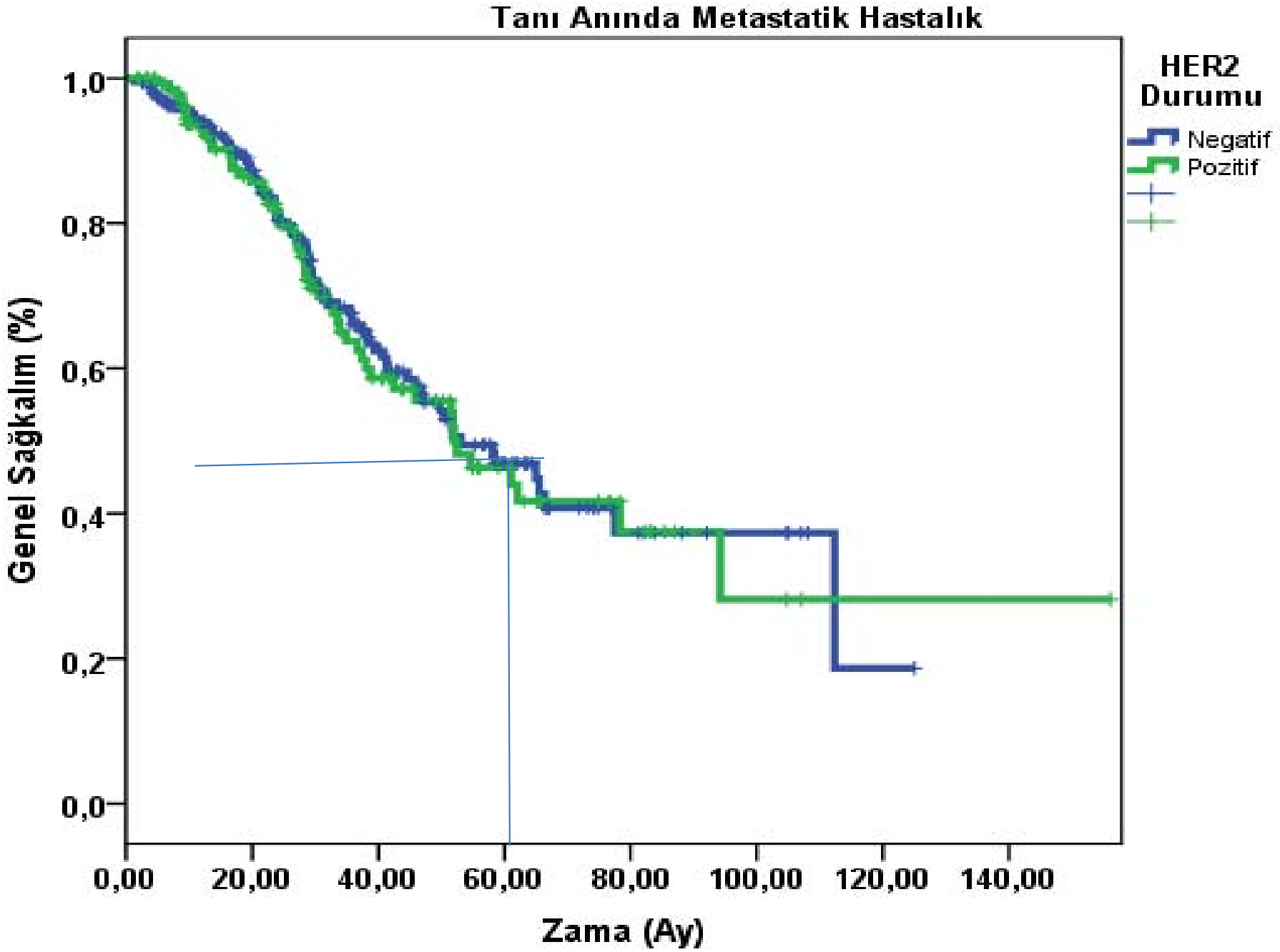
Tanı Anında Metastaz Durumu



Takipte Metastaz Durumu



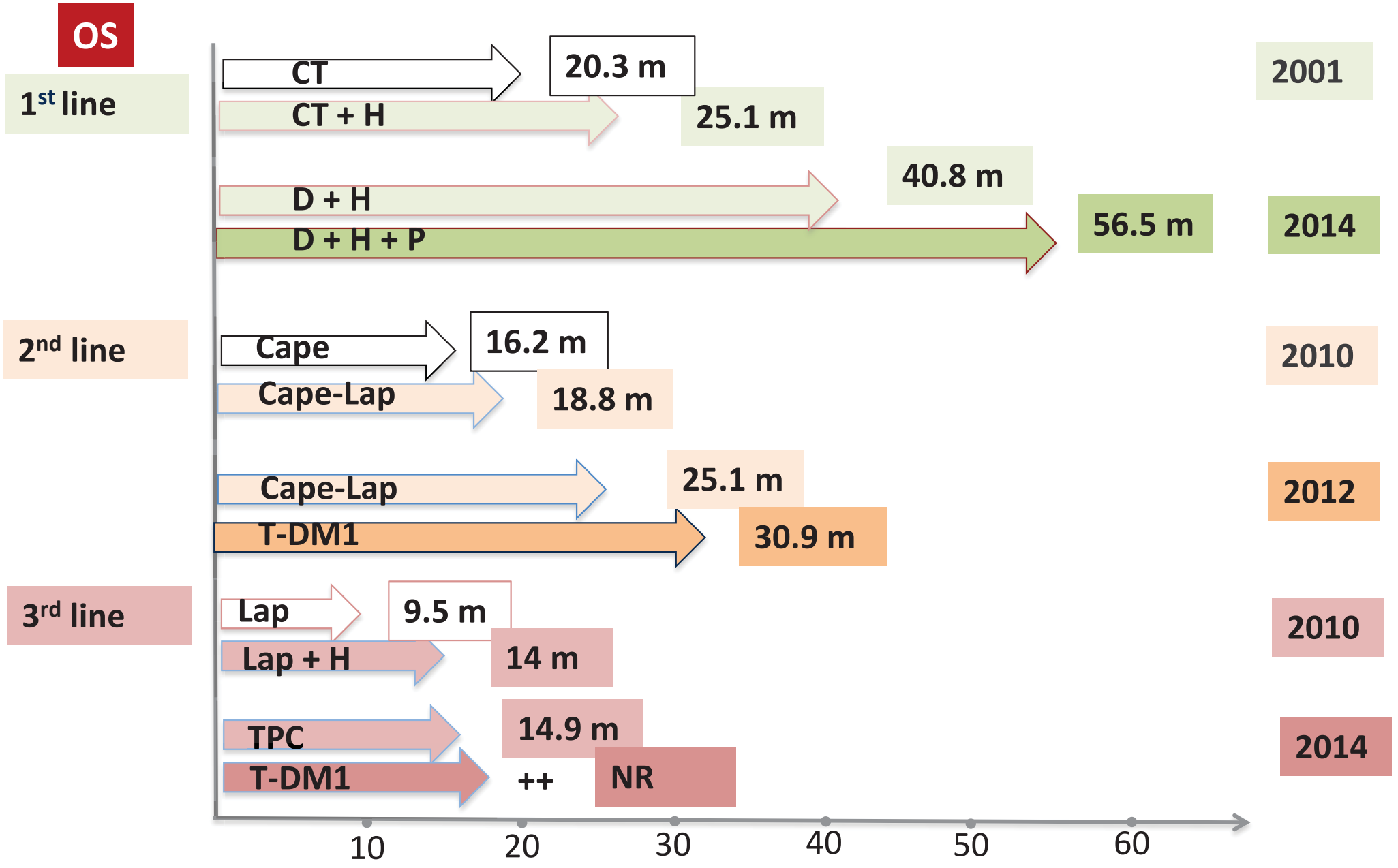
48 Ay Takipte


Tanı Anında Metastatik Hastalık
Genel Sağkalım (%)
1,0
0,8
0,6
0,4
0,2
0,0
0,00
20,00
40,00
60,00
80,00
100,00
120,00
140,00
Zama (Ay)
HER2 Durumu
Negatif
Pozitif

Sonuç

- Birinci basamak tedavide taksan ve trastuzumab kombinasyonuna pertuzumab eklenmesi yanıt oranlarını ve genel sağkalımı arttırmaktadır.
- İkinci Basamak tedavide T-DM1
- Sonraki Basamaklarda Trastuzumab ile birlikte farklı sitotoksiklerin kullanılması bir seçenektir.

Metastatik HER2+ Hastalıkta Sağkalım



Slamon, NEJM 2001
Swain ESMO 2014

Cameron, Oncologist 2010
Verma, NEJM 2012

Blackwell, JCO 2010
Krop, Lancet Oncol 2014