Meme Kanserinde Hedefe Yönelik Tedavilerde Güncel Gelişmeler

Dr. Ö. Berna Öksüzoğlu
Ankara Onkoloji Eğt ve Arş Hastanesi
Tıbbi Onkoloji Kliniği

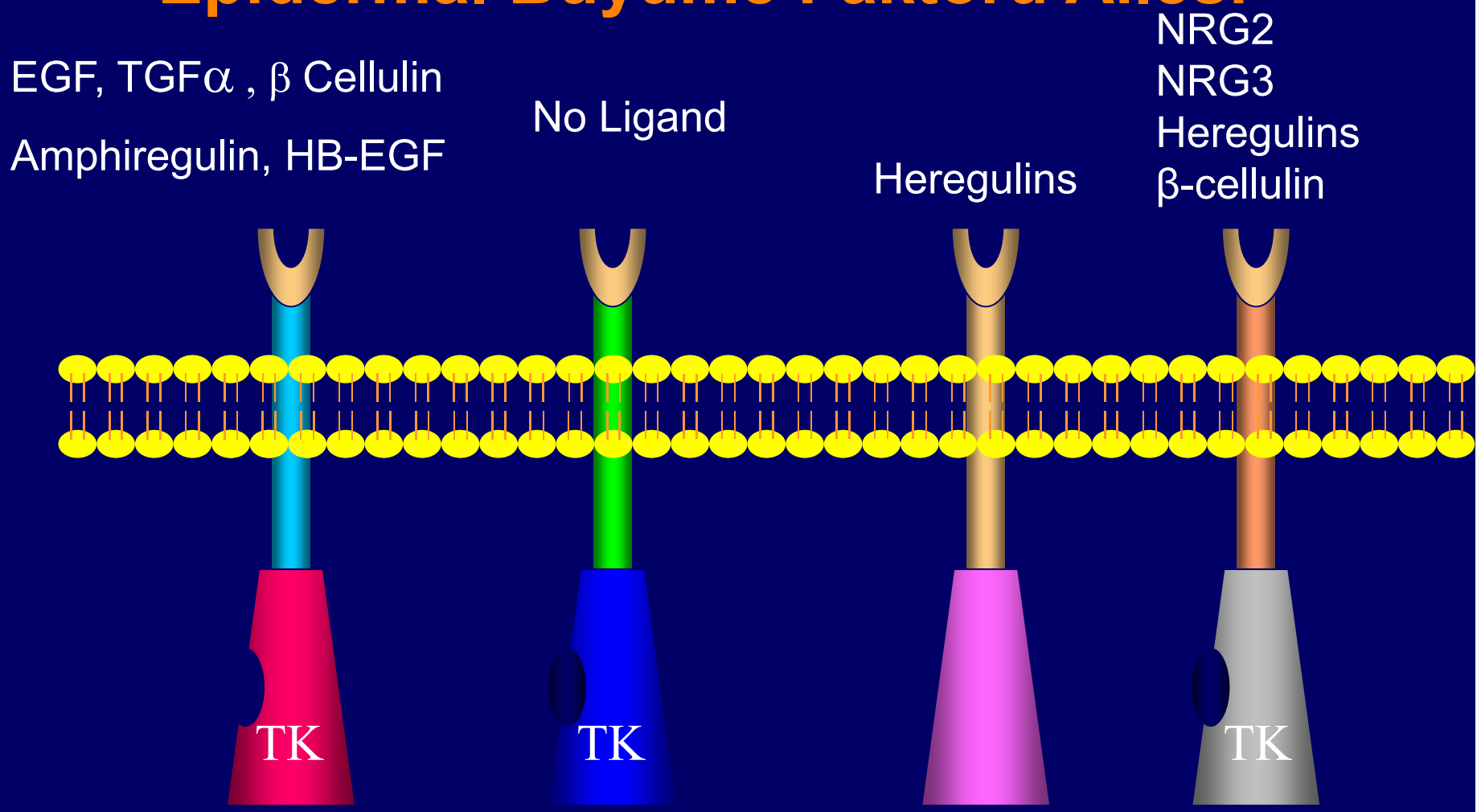
Sunum Planı

- Meme Kanseri Hedef Moleküller
- Standard Tedavi ve NCCN Kılavuzu
- HER2 hedefli kliniğe yansıyan ?yeni ilaçlar
  - Pertuzumab (Perjeta®)
  - Trastuzumab DM1 (Kadcyla®)
- 2014 yılı yaygın hastalık (neo)adjuvan tedaviler
- Sonuçlar

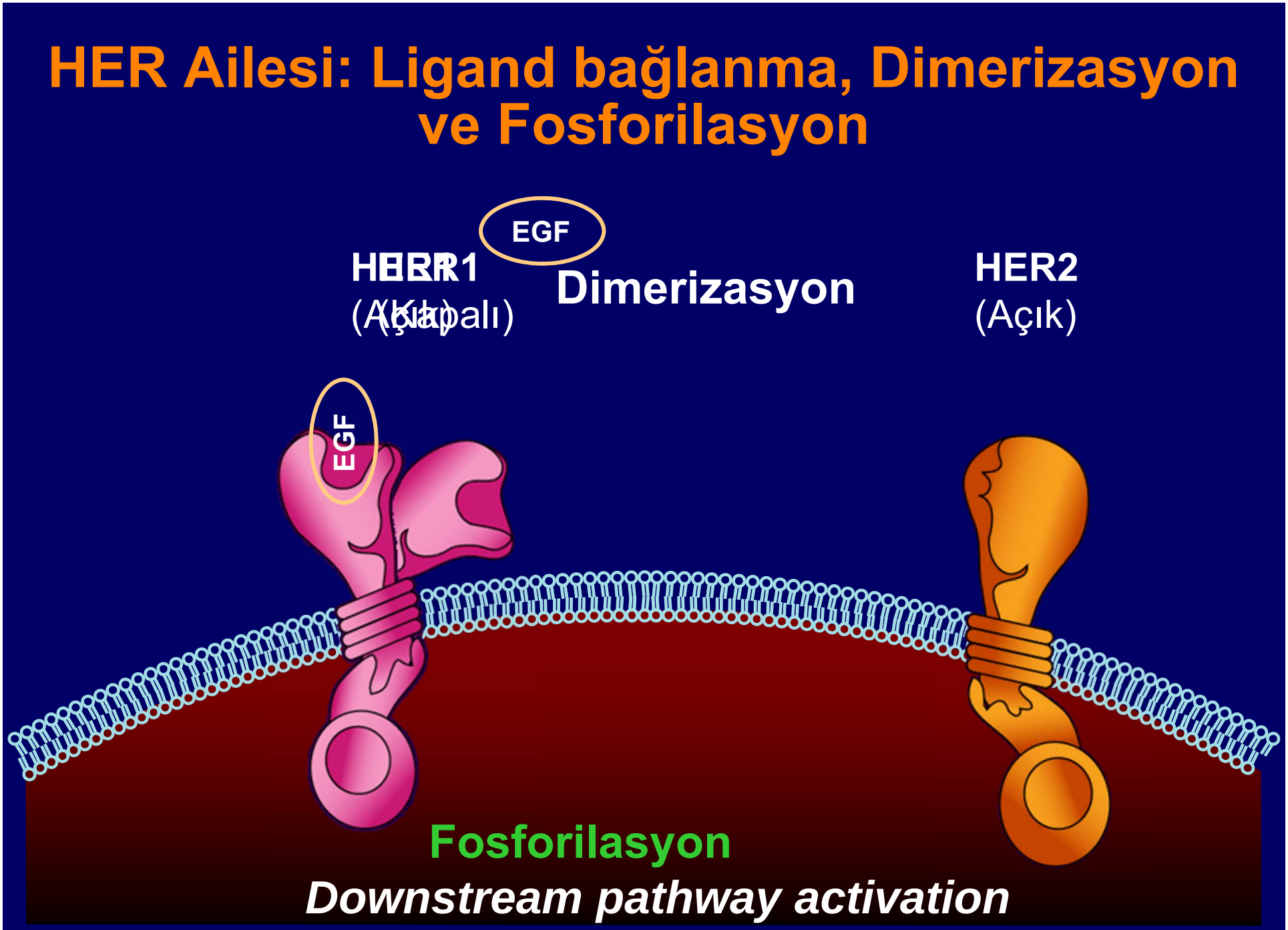
Meme Kanserinde Hedef Moleküller

- **HER-2**
- **VEGF**
- **PARP**
- mTOR
- EGFR
- IGFR
- SRC
- c-kit

Epidermal Büyüme Faktörü Ailesi

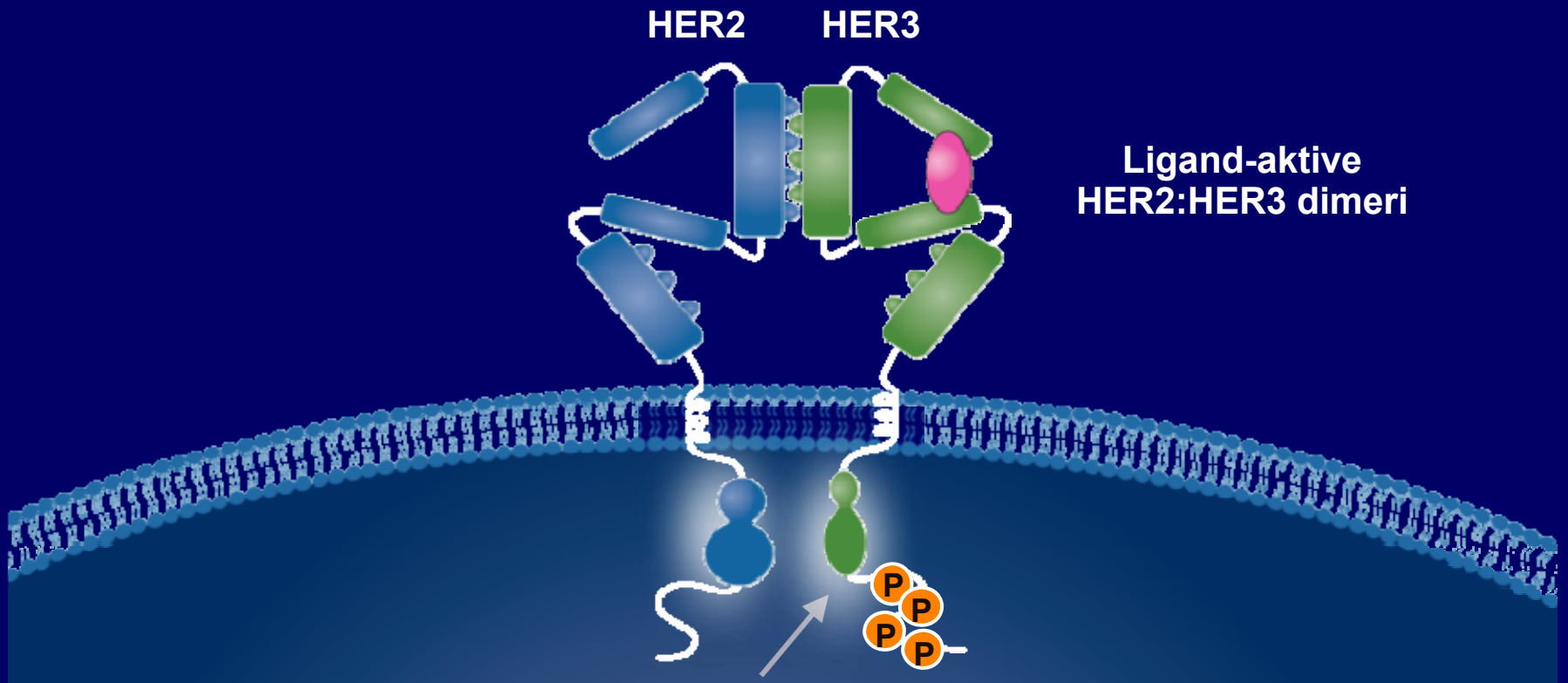


HER Ailesi: Ligand bağlanma, Dimerizasyon ve Fosforilasyon



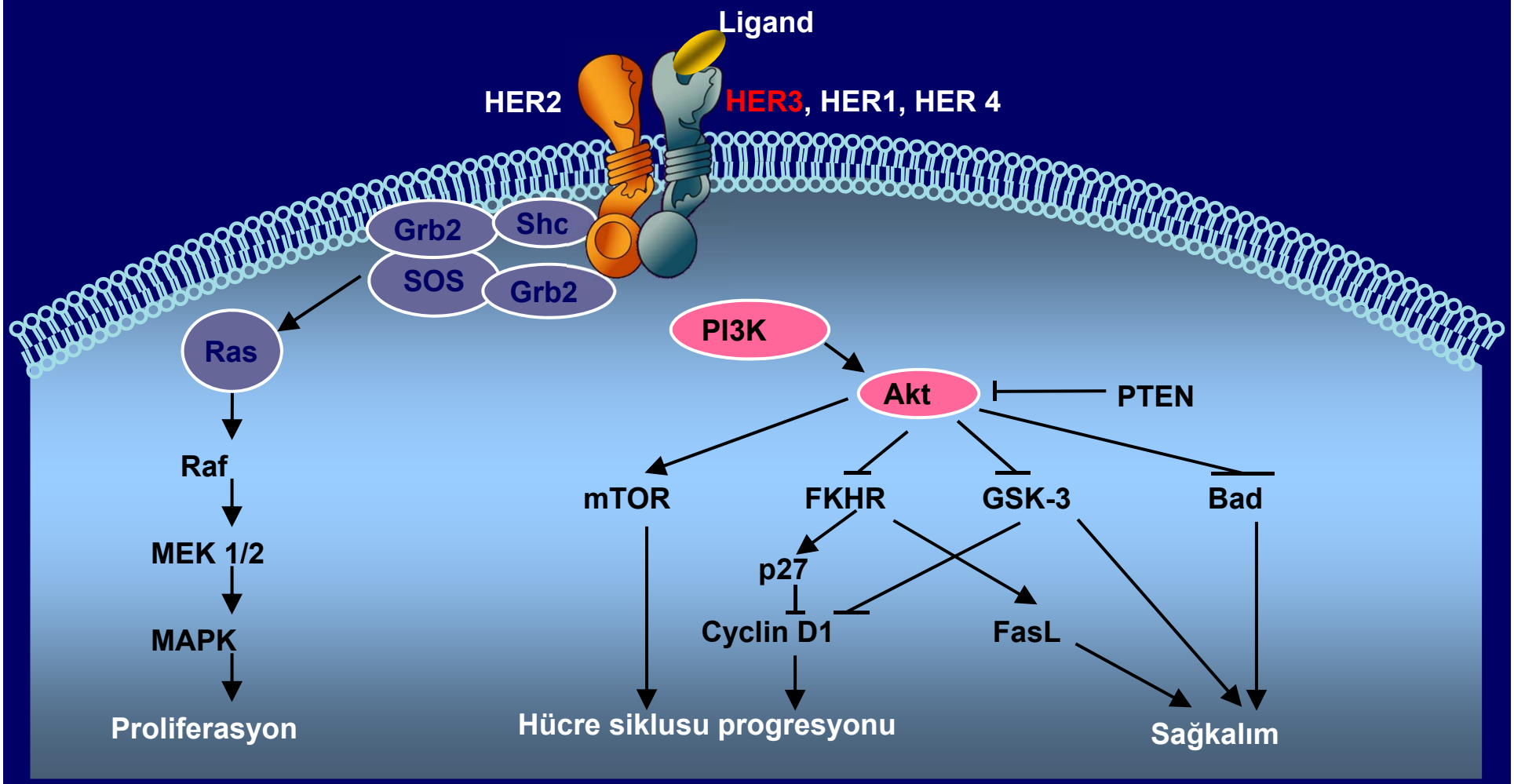
Roskoski. *Biochem Biophys Res Commun*. 2004;319:1; Herbst. *Int J Radiat Oncol Biol Phys*. 2004;59(suppl):21.

HER2 Dimerizasyonu



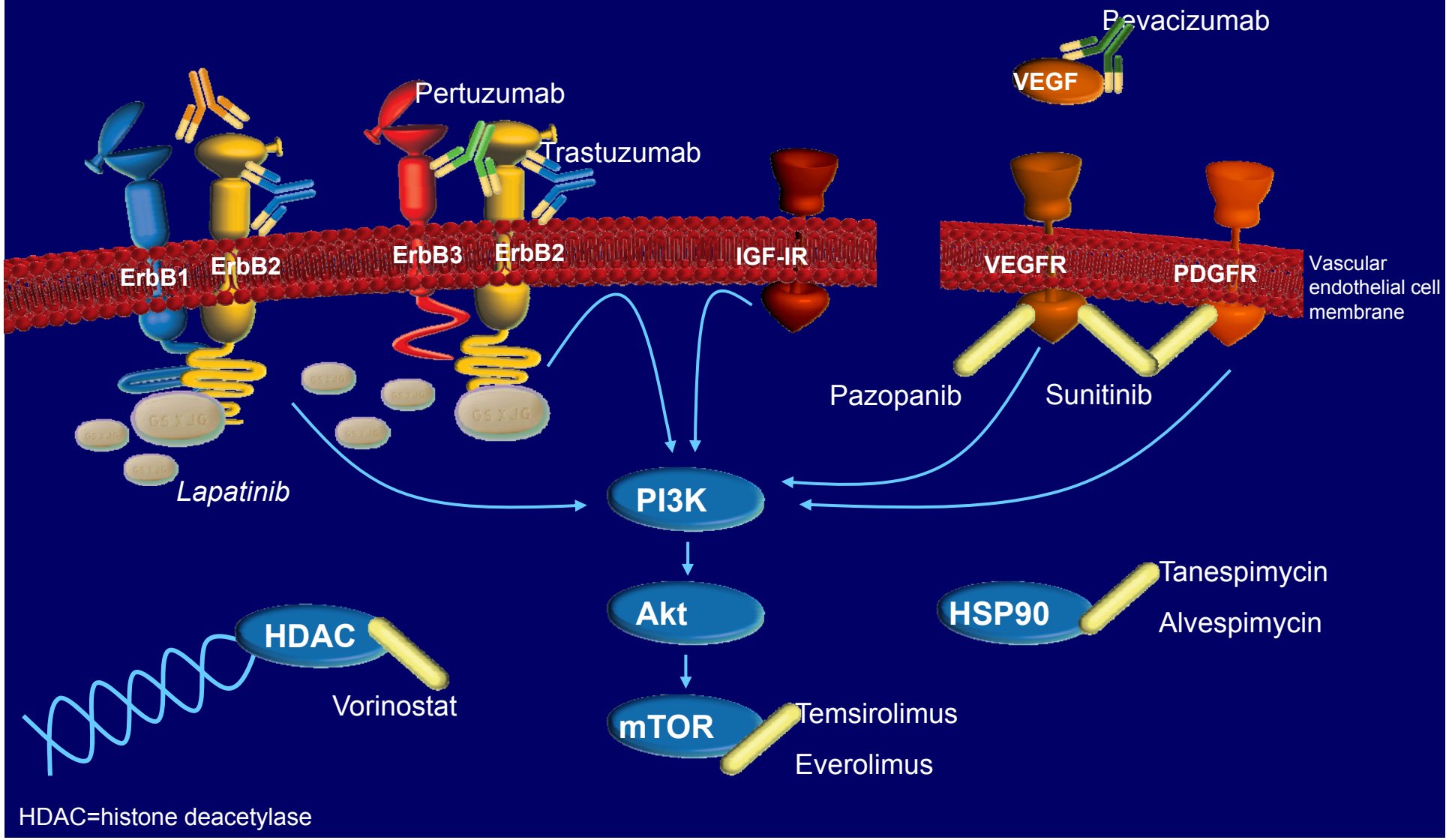
Ferguson KM, et al. Mol Cell. 2003;11:507-517. Olayioye MA, et al. EMBO J. 2000;19:3159-3167.
Hynes NE, et al. Nat Rev Cancer. 2005;5:341-354. Rowinsky EK. Annu Rev Med. 2004;55:433-457.

HER ailesi: Proliferasyon ve Sağkalım Sinyalizasyon Yolakları



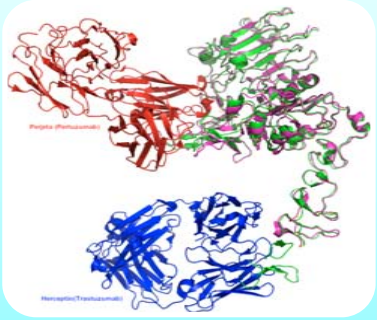
Lin and Winer. *Breast Cancer Res.* 2004;6:204.

Meme Kanserinde Hedefli Tedaviler



HDAC=histone deacetylase

HER2'yi hedefleyen ajanlar:

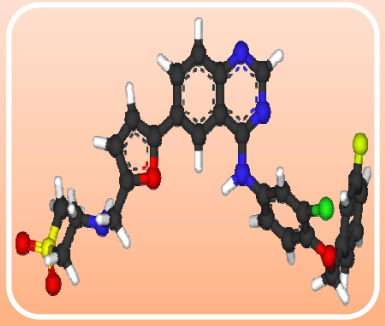


Monoklonal Antikorlar

- Trastuzumab
- Pertuzumab

Antikor-İlaç Konjugatları

- Trastuzumab-DM1



Küçük moleküllü inhibitörler

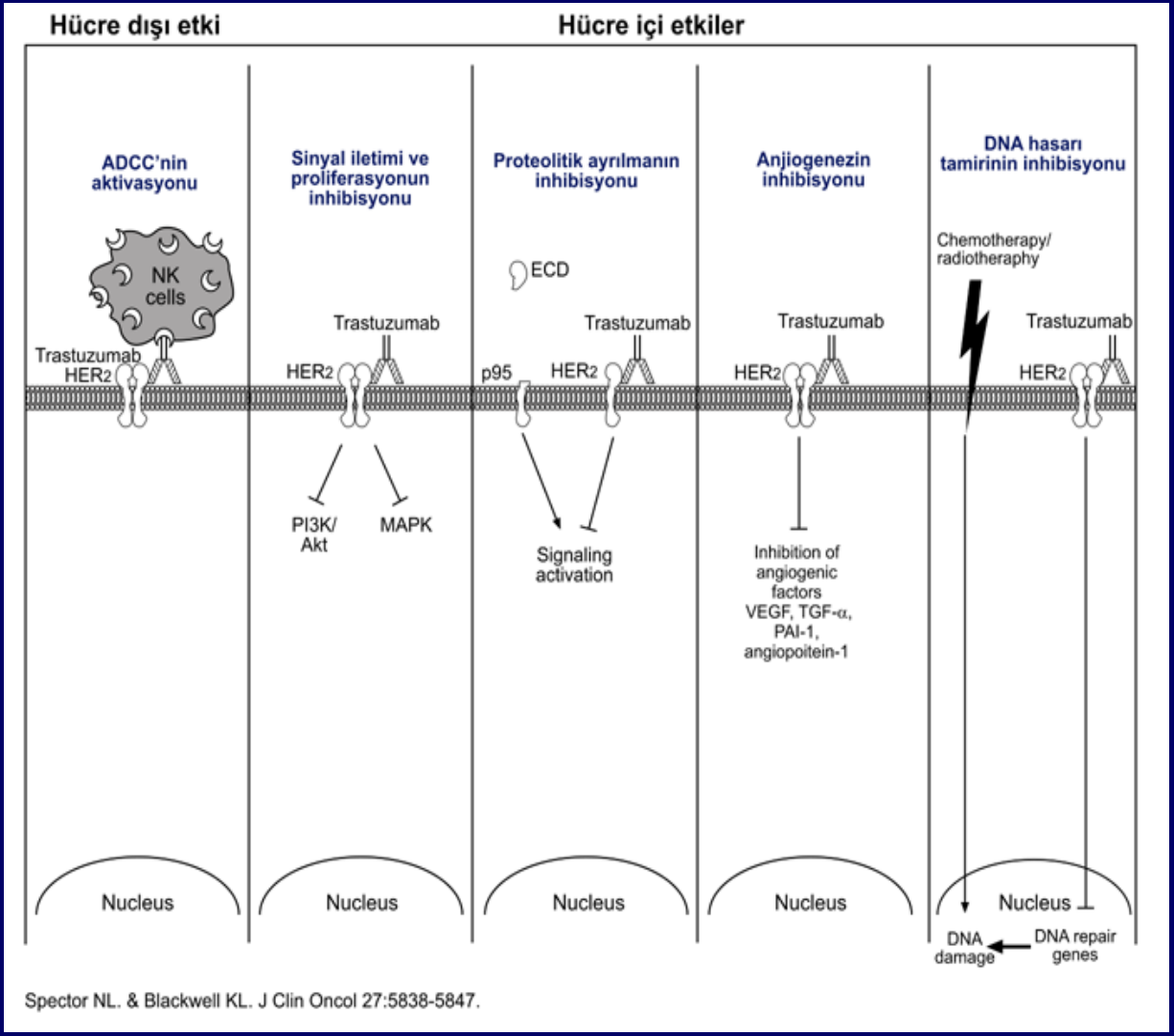
- Lapatinib
- Afatinib,Neratinib

Trastuzumab: Etki Mekanizmaları

Humanize kimerik monoklonal antikor trastuzumab

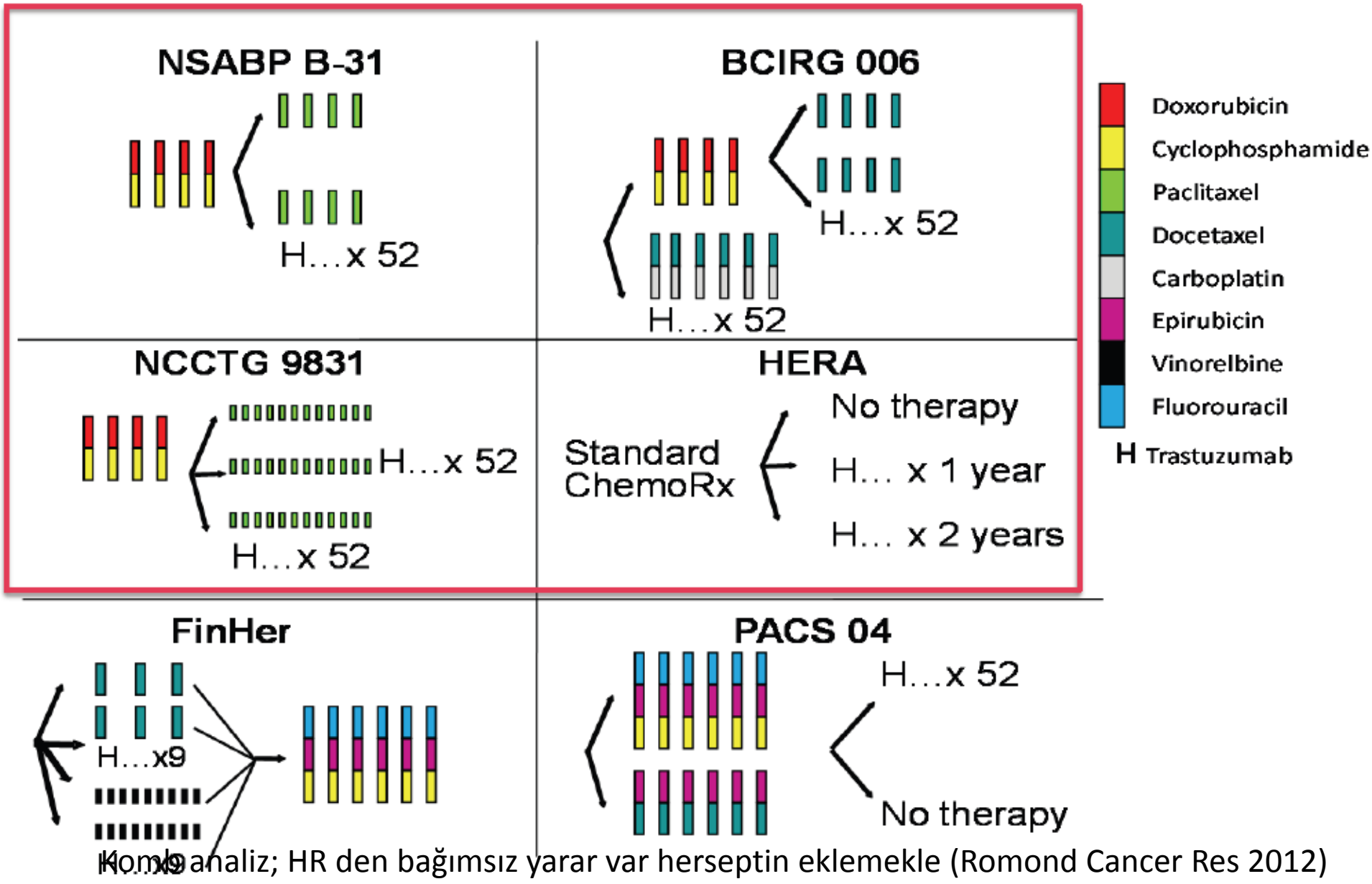
MMK için onay;
FDA 1998
Türkiye 2003

Adjuvan için onay;
FDA 2006
Türkiye 2008



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

Adjuvan Trastuzumab Çalışmaları



Komb analiz; HR den bağımsız yarar var herseptin eklemekle (Romond Cancer Res 2012)

9831 kombine > ardışık (Perez 2011)

Trastuzumab Plus Adjuvant Chemotherapy for Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Planned Joint Analysis of Overall Survival From NSABP B-31 and NCCTG N9831

Edith A. Perez, Edward H. Romond, Vera J. Suman, Jong-Hyeon Jeong, George Sledge, Charles E. Geyer Jr, Silvana Martino, Priya Rastogi, Julie Gralow, Sandra M. Swain, Eric P. Winer, Gerardo Colon-Otero, Nancy E. Davidson, Efstratios Mamounas, Jo Anne Zujewski, and Norman Wolmark

Results

Median time on study was 8.4 years. Adding trastuzumab to chemotherapy led to a 37% relative improvement in OS (hazard ratio [HR], 0.63; 95% CI, 0.54 to 0.73; $P < .001$) and an increase in 10-year OS rate from 75.2% to 84%. These results were accompanied by an improvement in DFS of 40% (HR, 0.60; 95% CI, 0.53 to 0.68; $P < .001$) and increase in 10-year DFS rate from 62.2% to 73.7%. All patient subgroups benefited from addition of this targeted anti-HER2 agent.

Conclusion

The addition of trastuzumab to paclitaxel after doxorubicin and cyclophosphamide in early-stage HER2-positive breast cancer results in a substantial and durable improvement in survival as a result of a sustained marked reduction in cancer recurrence.

Net yarar
DFS %11.5 (%62.2→73.7)
OS %8.8 (%75.2→%84)

JCO 2014

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JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Sharon H. Giordano, Sarah Temin, Jeffrey J. Kirshner, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Ana M. Gonzalez-Angulo, Ian Krop, Jennifer Levinson, Nancy U. Lin, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Naren Ramakrishna, and Eric P. Winer

Sharon H. Giordano and Ana M. Gonzalez-Angulo, University of Texas MD Anderson Cancer Center, Houston; Debra A. Patt, Texas Oncology, Austin, TX; Sarah Temin, American Society of Clinical Oncology, Alexandria, VA; Jeffrey J. Kirshner, Hematology/Oncology Associates of Central New York, East Syracuse; Sarat Chandarlapaty and Shanu Modi, Memorial Sloan Kettering Cancer Center; Francisco J. Esteva, New York University Cancer Institute, New York, NY; Jennie R. Crews, PeaceHealth St Joseph Cancer Center, Bellingham, WA; Nancy E. Davidson, University of Pittsburgh Cancer Institute and University of Pittsburgh Medical Center Cancer Center, Pittsburgh, PA; Ian Krop, Nancy U. Lin, and Eric P. Winer, Dana-Farber Cancer Institute, Boston, MA; Jennifer Levinson, Ponte Vedra Beach; Edith A. Perez, Mayo Clinic, Jacksonville; Naren Ramakrishna,

See accompanying article on page 2100

A B S T R A C T

Purpose
To provide evidence-based recommendations to practicing oncologists and others on systemic therapy for patients with human epidermal growth factor receptor 2 (HER2) –positive advanced breast cancer.

Methods
The American Society of Clinical Oncology convened a panel of medical oncology, radiation oncology, guideline implementation, and advocacy experts and conducted a systematic literature review from January 2009 to October 2012. Outcomes of interest included overall survival, progression-free survival (PFS), and adverse events.

Kanıta Dayalı Öneriler-Kanıt düzeyi

ER/PR (+) seçilmiş hasta dışında Her2+ hastada 1. basamak tedavide klinisyenlere Her2 hedefli tedavi önerilmelidir (kanıt derecesi yüksek, öneri gücü yüksek)

1.basamak tedavide taksana kontrendikasyon yoksa taksan trastuzumab pertuzumab önerilmelidir (kanıt derecesi yüksek, öneri gücü yüksek)

HER2 hedefli tedavi sırasında veya sonrasında progrese ise T-DM1 önerilmelidir (kanıt derecesi yüksek, öneri gücü yüksek)

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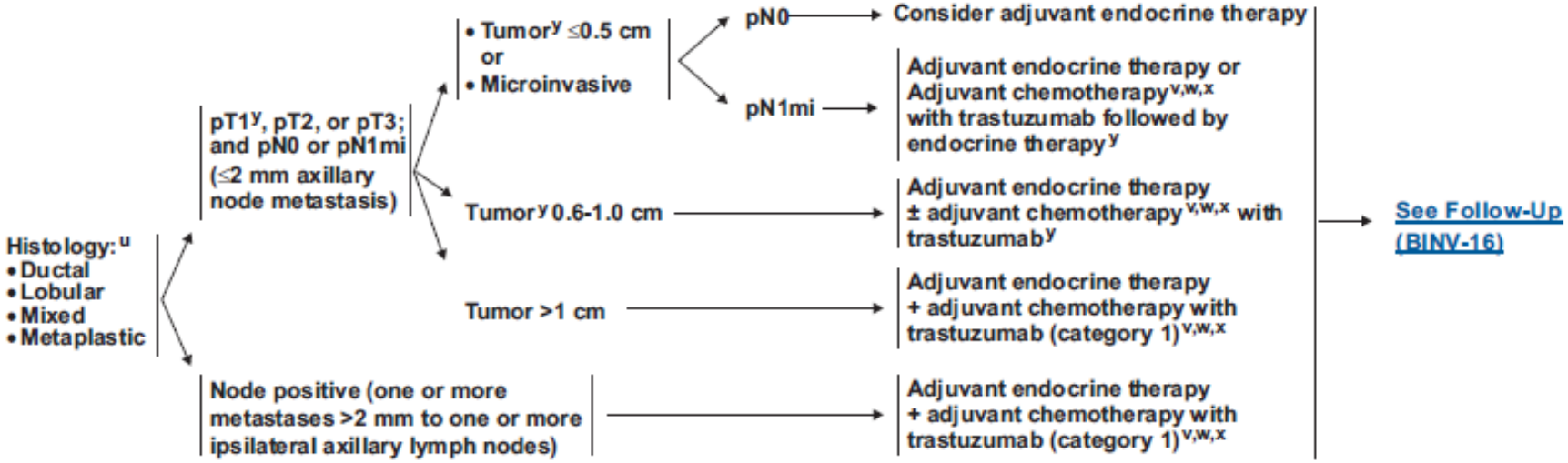
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE[b]



See Adjuvant Endocrine Therapy (BINV-J) and Neoadjuvant/Adjuvant Chemotherapy (BINV-K)

[b] See Principles of HER2 Testing (BINV-A).

[u] Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

[v] Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

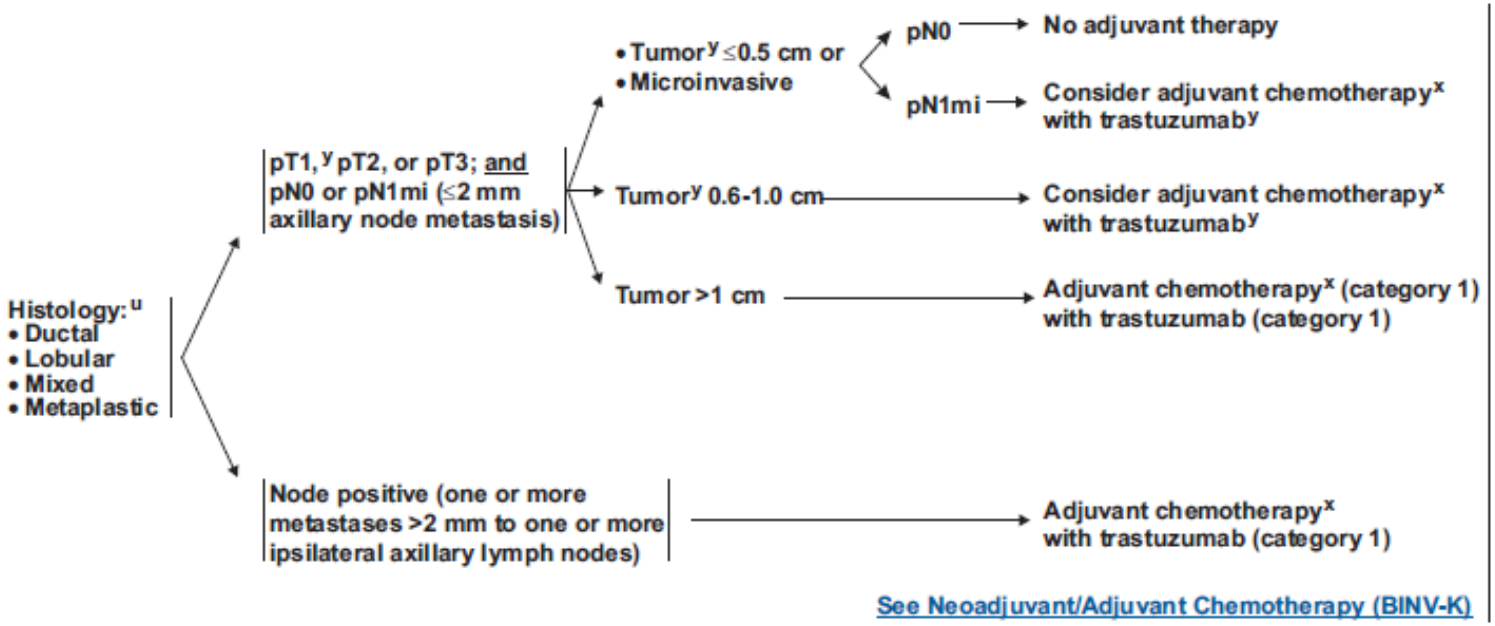
[w] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable.

[x] There are limited data to make chemotherapy recommendations for those >70 y old. Treatment should be individualized with consideration of comorbid conditions.

[y] The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or over-expressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE[b]



[b] See Principles of HER2 Testing (BINV-A).

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[y] The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

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NEOADJUVANT/ADJUVANT CHEMOTHERAPY[1,2,3,4]

Regimens for HER2-negative disease (all category 1)[5]

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)
- FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- AC followed by weekly paclitaxel
- EC (epirubicin/cyclophosphamide)
- FEC/CEF followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) or (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)
- FAC followed by T (fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:

- AC followed by T + trastuzumab ± pertuzumab[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

- AC followed by docetaxel + trastuzumab ± pertuzumab[9]
- FEC followed by docetaxel + trastuzumab + pertuzumab[9]
- FEC followed by paclitaxel + trastuzumab + pertuzumab[9]
- Paclitaxel + trastuzumab[10]
- Pertuzumab + trastuzumab + docetaxel followed by FEC[9]
- Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]

[1] Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.

[2] Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

[3] CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.

[4] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.

[5] The regimens listed for HER2-negative disease are all category 1 when used in the adjuvant setting.

[6] In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥1 cm (category 1).

[7] Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for one year total duration.

[8] A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer. Patients who have not received a neoadjuvant pertuzumab-containing regimen can receive adjuvant pertuzumab.

[9] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

[10] Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

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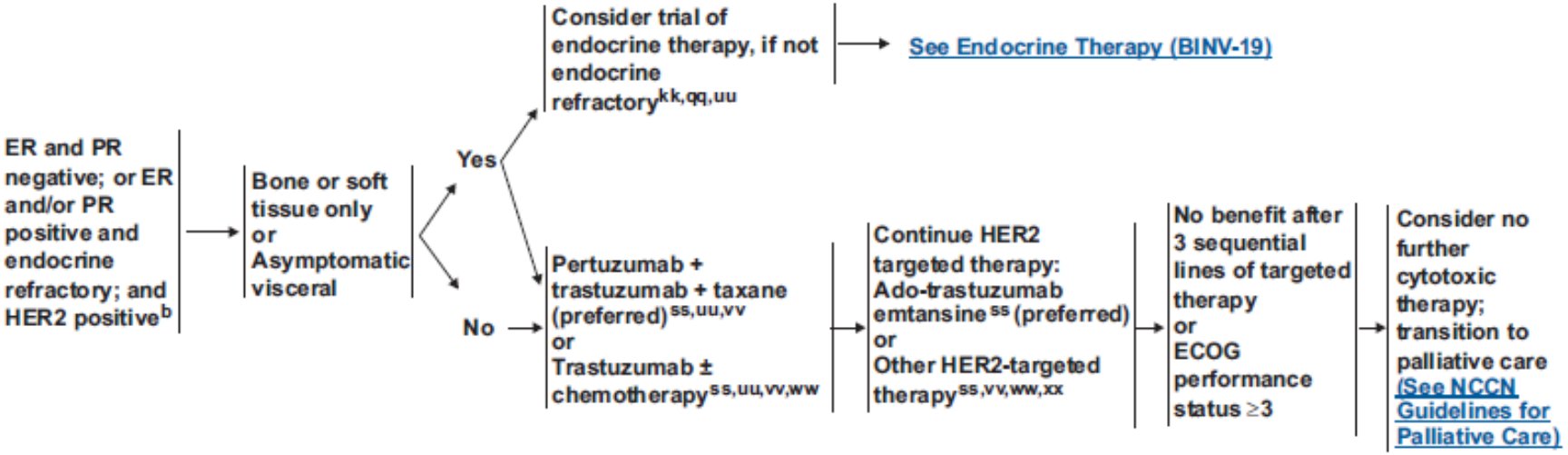
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and PR NEGATIVE; or ER and/or PR POSITIVE and ENDOCRINE REFRACTORY; and HER2 POSITIVE



[b] See Principles of HER2 Testing (BINV-A).

[kk] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

[qq] See Subsequent Endocrine Therapy for Systemic Disease (BINV-N).

[ss] See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-O).

[uu] See Principles of Monitoring Metastatic Disease (BINV-M).

[vv] Continue trastuzumab following progression on first-line trastuzumab-containing chemotherapy for metastatic breast cancer. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.

[ww] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

[xx] Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

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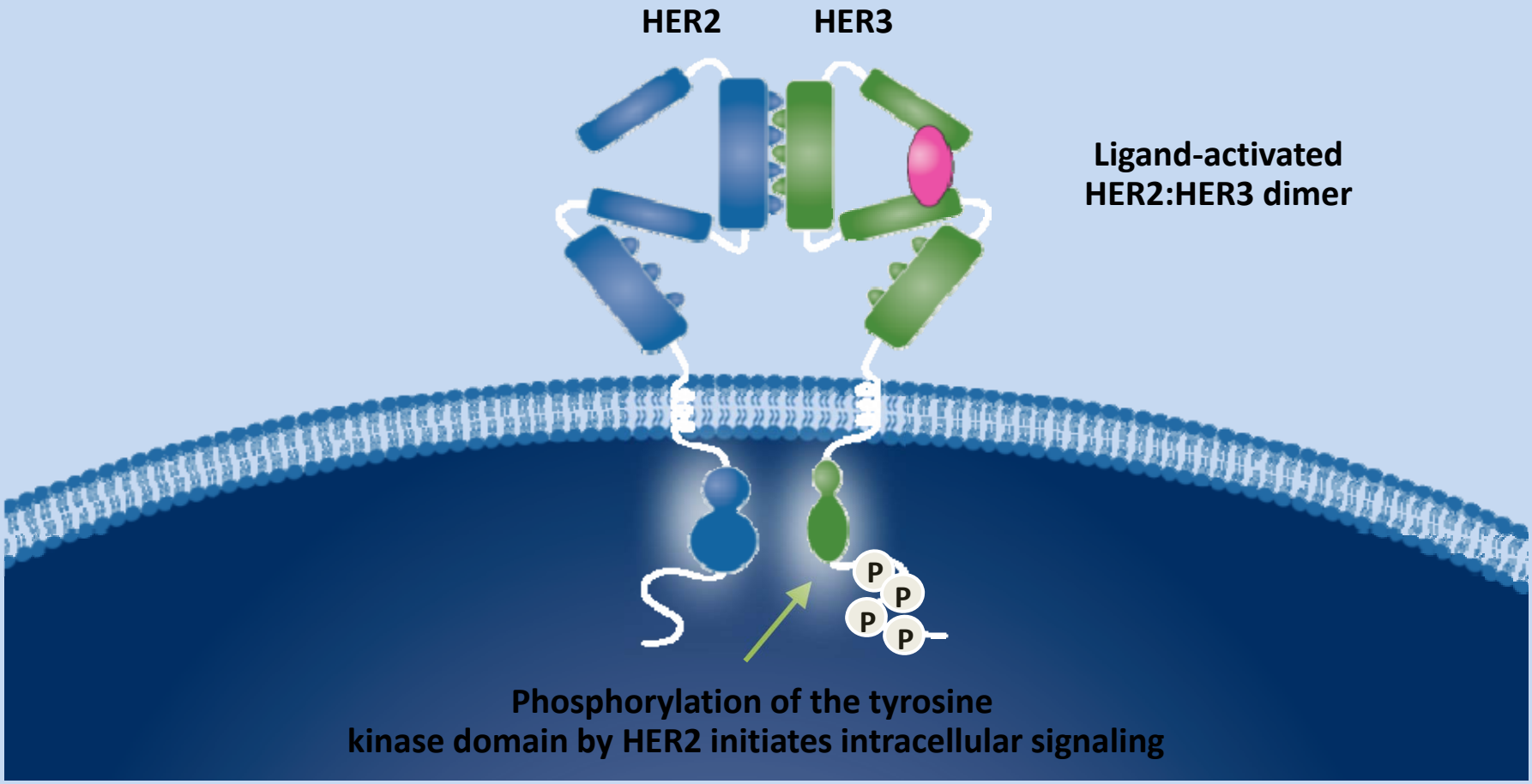
HER2 Dimerizasyonunun Anahtar Rolü



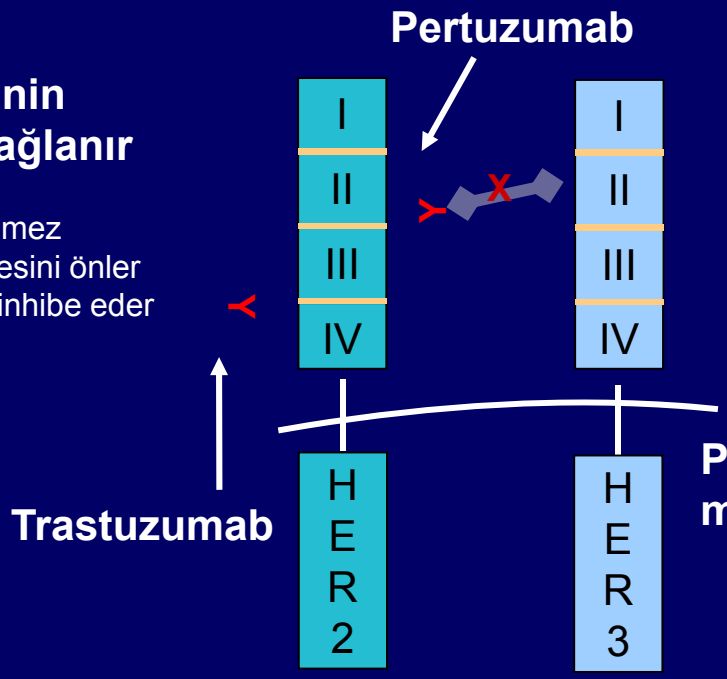
Ferguson KM, et al. Mol Cell. 2003;11:507-517. Olayioye MA, et al. EMBO J. 2000;19:3159-3167.
Hynes NE, et al. Nat Rev Cancer. 2005;5:341-354. Rowinsky EK. Annu Rev Med. 2004;55:433-457.

Pertuzumab

- Trastuzumab and pertuzumabın HER2 üzerinde farklı bağlanma bölgeleri var ve sinerjistik aktiviteleri olabilir

Trastuzumab HER2nin altdomain IV'üne bağlanır

HER2 dimerizationunu önlemez
- HER2 reseptör dökülmesini önler
- ER2 signalizasyonunu inhibe eder
- ADCC



Pertuzumab HER2nin dimerizasyon kısmına bağlanır
- HER2nin dimer oluşumunu engeller
- ADCC aktive eder
- HER2 reseptör dökülmesini engellemez

- Önceden trastuzumab tedavisi almış hastalarda pertuzumab + trastuzumab (n: 66)
  ORR: 24%; CBR: 50%

Baselga J, et al. J Clin Oncol. 2010;28:1138-1144.

CLEOPATRA

- Primer Sonlanım: PFS (bağımsız)
- İkincil sonlanım: PFS (araştırıcı), ORR, OS, güvenlik

coğrafi bölge ve önceki (neo)adjuvan kemoterapiye göre tabakalandırma

Önceden tedavi görmemiş (kemo-naif), HER2-pozitif lokal ileri/metastatik meme kanseri

(N = 808)

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

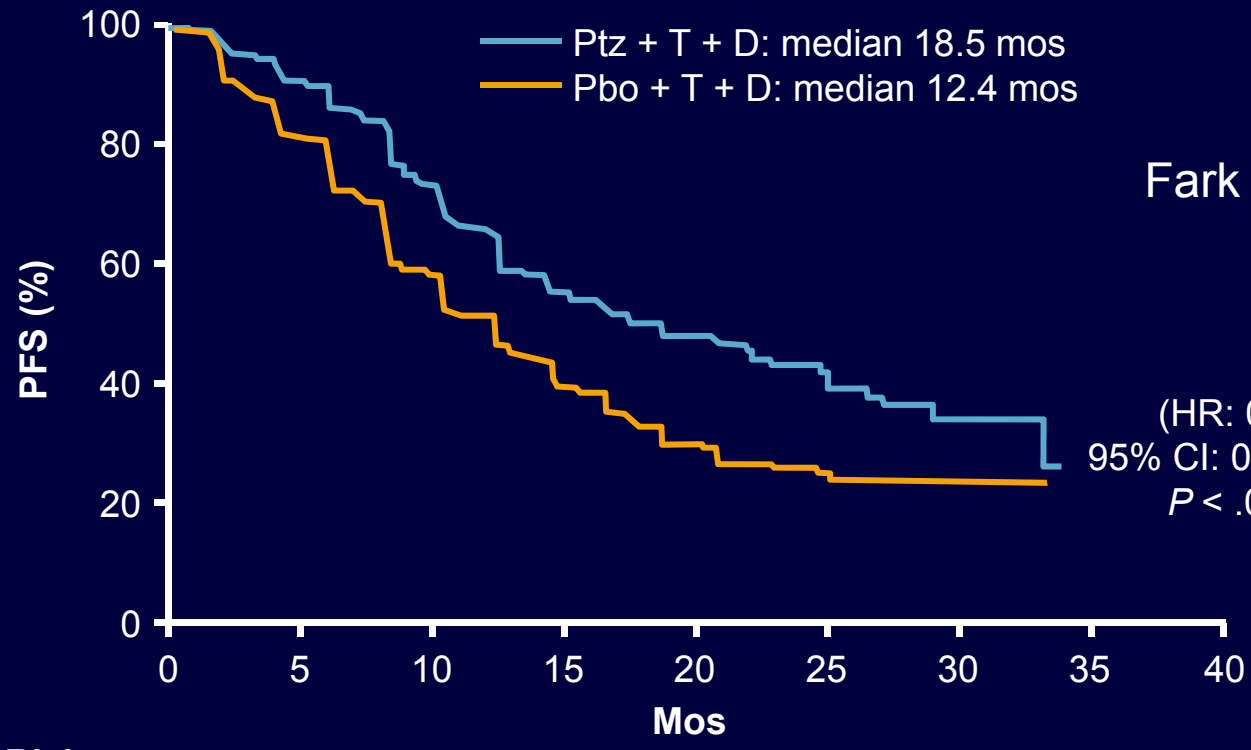
Trastuzumab 6 mg/kg q3w* +
Docetaxel 75-100 mg/m^2 q3w† +
Placebo q3w
(n = 406)

Progresyona veya kabul edilemez toksisiteye dek

*Trastuzumab 8-mg/kg yükleme.
†Minimum 6 siklus docetaxel önerildi; < 6 siklus kabul edilemez toksiste veya PD durumunda izin verildi.
‡Pertuzumab 840-mg yükleme dozu verildi.

Baselga J, et al. N Engl J Med. 2012;366:109-119.

CLEOPATRA: PFS (bağımsız)



Fark : 6.1 ay

(HR: 0.62;
95% CI: 0.51-0.75;
P < .001)

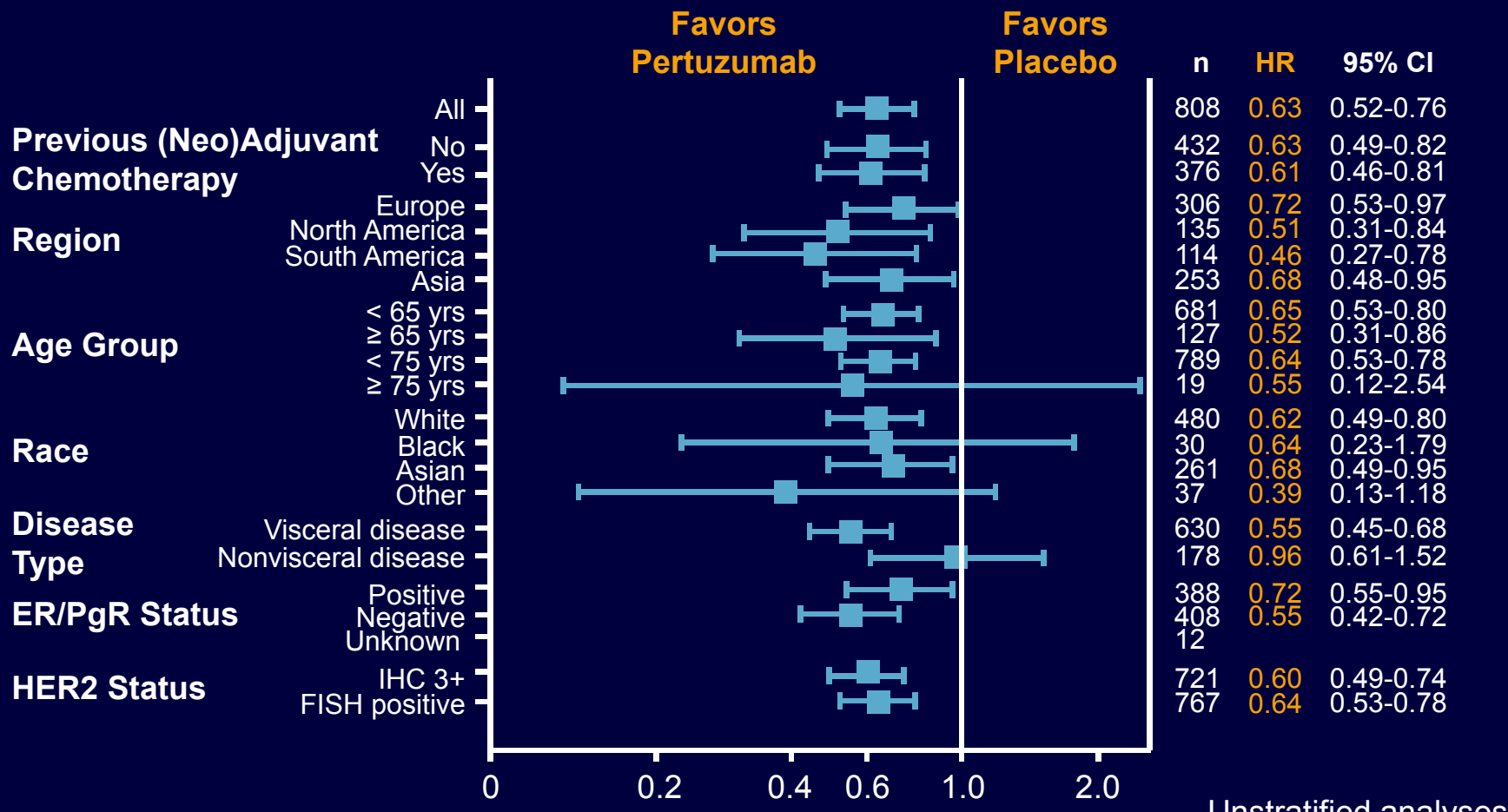
Pts at Risk, n

Ptz + T+ D	402	345	267	139	83	32	10	0	0
Pbo + T + D	406	311	209	93	42	17	7	0	0

Stratified by previous treatment status and region

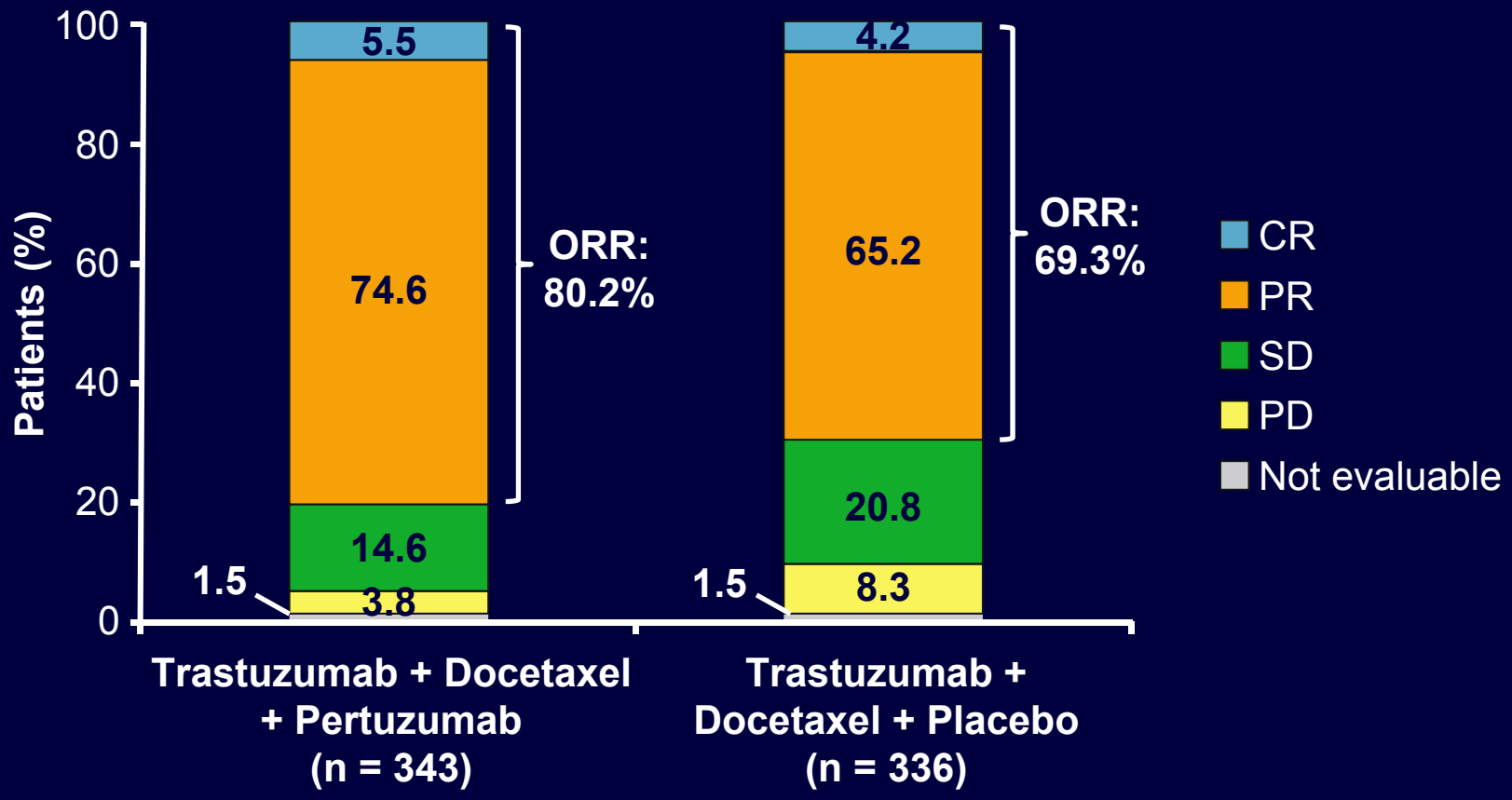
Baselga J, et al. N Engl J Med. 2012;366:109-119.

CLEOPATRA: PFS Altgrupları (bağımsız)



Baselga J, et al. N Engl J Med. 2012;366:109-119.

CLEOPATRA: Yanıt Oranları



Baselga J, et al. N Engl J Med. 2012;366:109-119.

CLEOPATRA: Güvenlik

Adverse Events, %	Trastuzumab + Docetaxel + Pertuzumab (n = 407)		Trastuzumab + Docetaxel (n = 397)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Diarrhea	66.8	7.9	46.3	5.0
Alopecia	60.9	NR	60.5	NR
Neutropenia	52.8	48.9	49.6	45.8
Nausea	42.3	NR	41.6	NR
Fatigue	37.6	2.2	36.8	3.3
Rash	33.7	NR	24.2	NR
Decreased appetite	29.2	NR	26.4	NR
Mucosal inflammation	27.8	NR	19.9	NR
Asthenia	26.0	2.5	30.2	1.5
Peripheral edema	23.1	NR	30.0	NR
Constipation	15.0	NR	24.9	NR
Febrile neutropenia	13.8	13.8	7.6	7.6
Dry skin	10.6	NR	4.3	NR
Leukopenia	NR	12.3	NR	14.6

Baselga J, et al. N Engl J Med. 2012;366:109-119.

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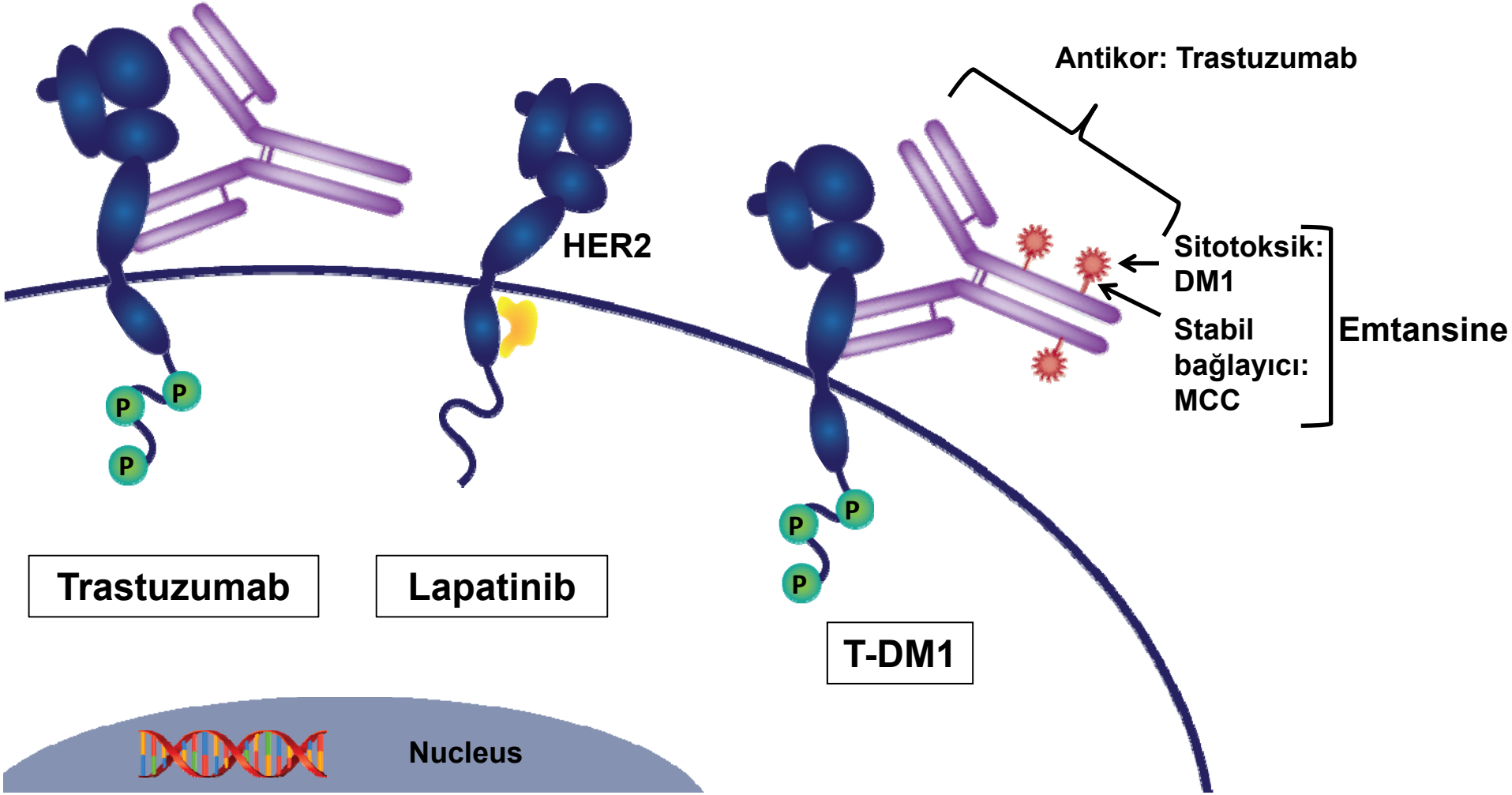
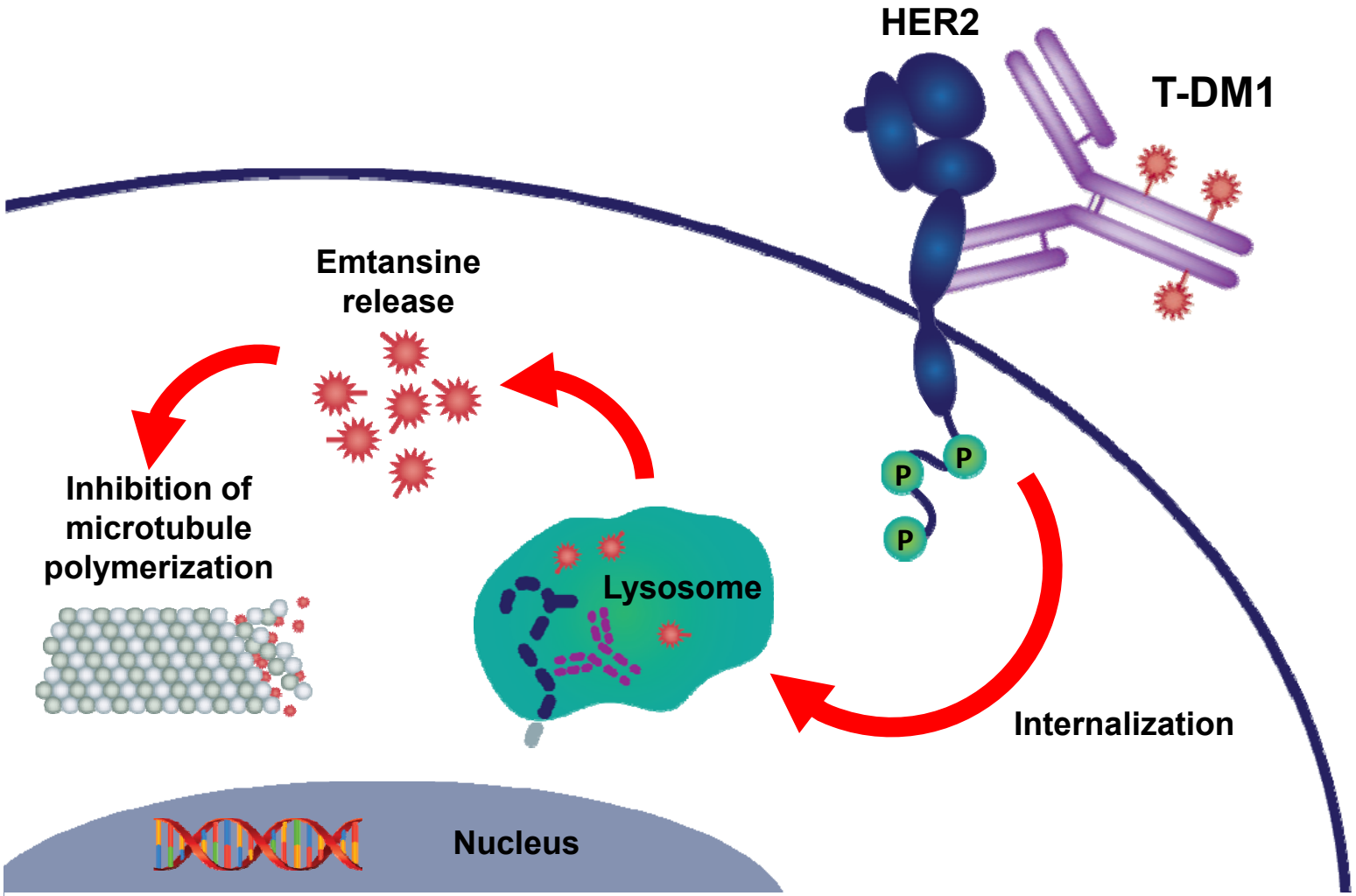
HER2+ Meme Kanserinde Hedefli Tedaviler : Trastuzumab, Lapatinib ve T-DM1



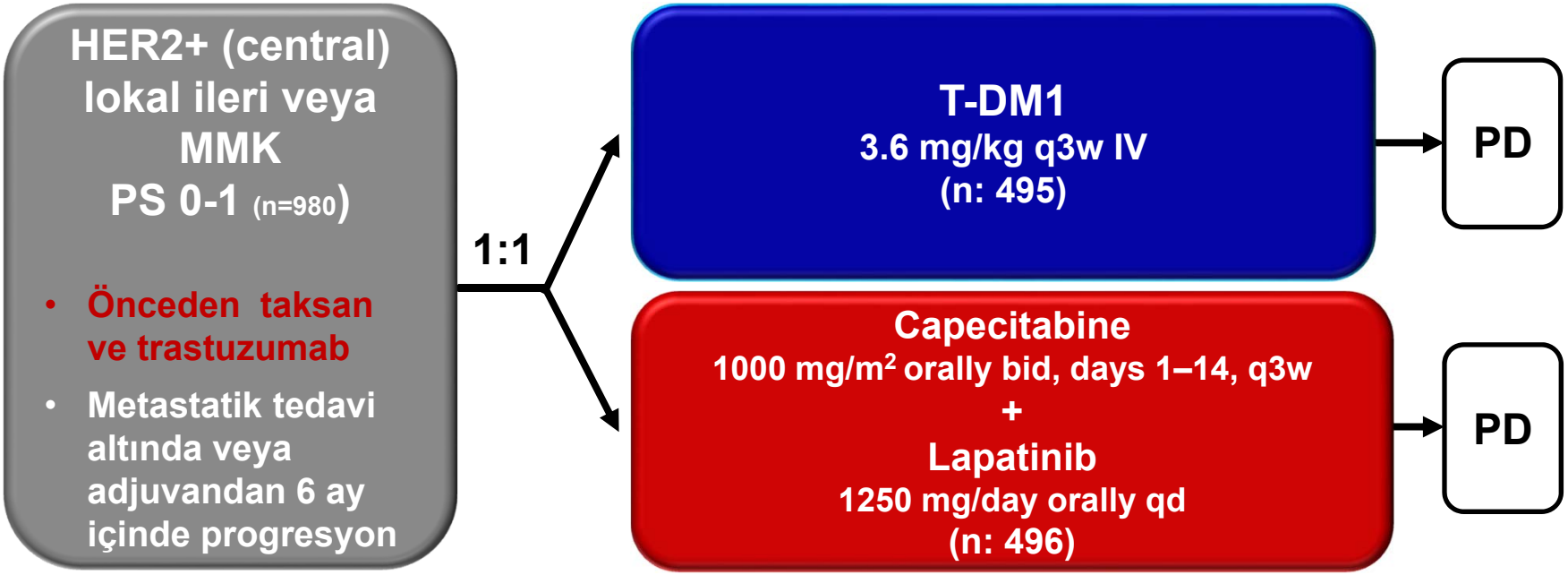
Spector NL, Blackwell KL. *J Clin Oncol* 2009; Nelson MH, et al. *Ann Pharmacother* 2006; Lewis Phillips GD, et al. *Cancer Res* 2008.

T-DM1: Etki Mekanizması



Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

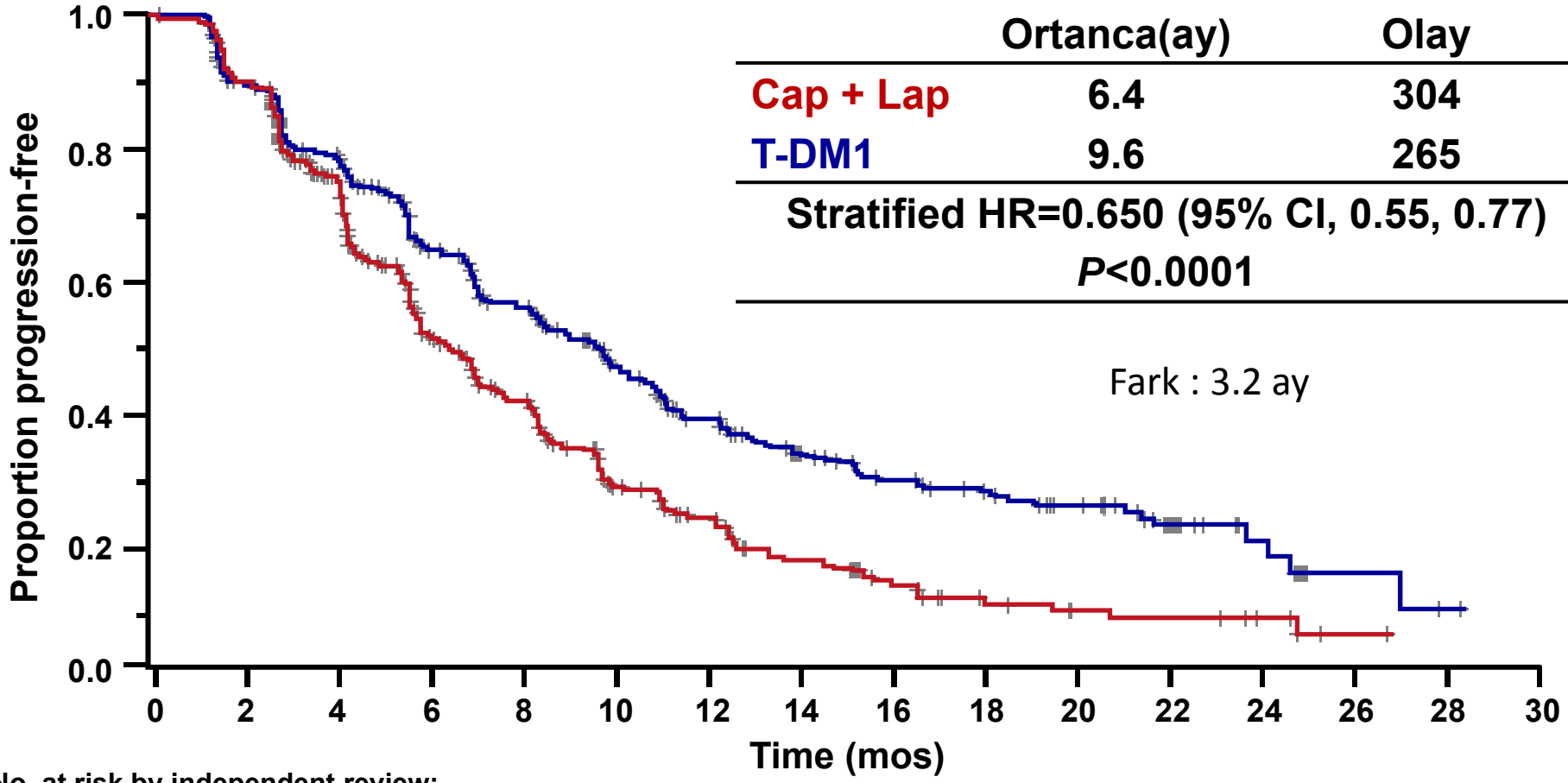
EMILIA



- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

2009 Şubat ile 2012 Ocak arası
%68 viseral metastatik, %53 hormon responsif, %62 <3 metastatik bölge, önceden antrasiklin alan %61, önceden endokrin tedavi %41
herseptin <1 yıl alan %43

Progresyonsuz Sağkalım (PFS)
(Bağımsız Gözlemci)



	Ortanca(ay)	Olay
Cap + Lap	6.4	304
T-DM1	9.6	265

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

***P*<0.0001**

Fark : 3.2 ay

No. at risk by independent review:

Cap + 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

Blackwell, ASCO 2012

EMILIA Sonuçlar

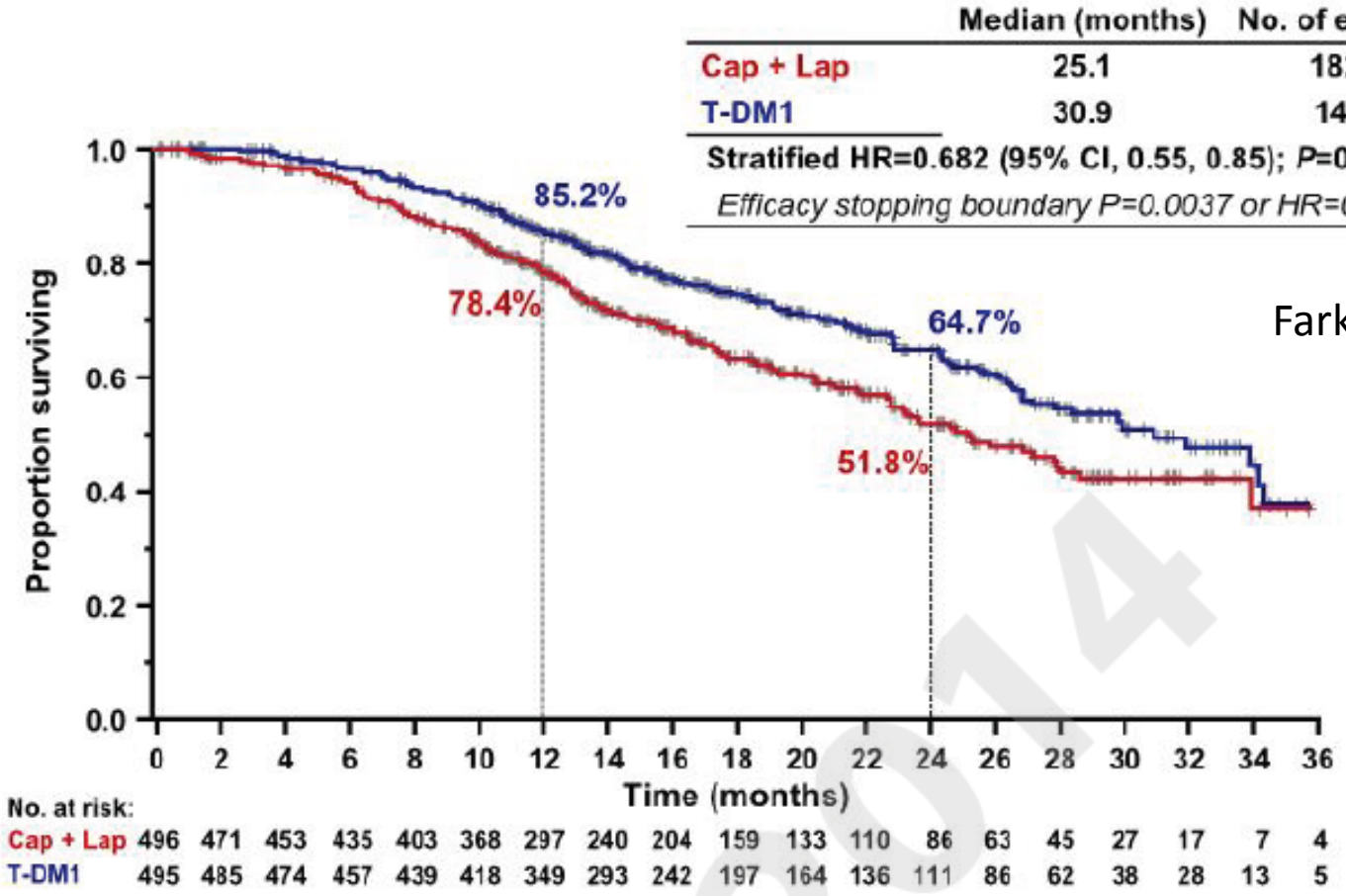
T-DM1, kapesitabin + lapatinibe göre etkinlik olarak daha üstün

- **T-DM1 ile PFS üstünlüğü**
  - **HR=0.650; *P*<0.0001**
- **Interim OS analizi de T-DM1 lehine ancak çalışmayı durdurma sınırında değil**
  - **HR=0.621; *P*=0.0005**
- **Güvenlik ve ikincil etkinlik analizi de T-DM1 i desteklemekte**

T-DM1, HER2-pozitif metastatik meme kanseri tedavisinde önemli bir tedavi opsiyonudur

	Cap (n=487)	Lap (n=488)	T-DM1 (n=490)
Median dose intensity, %	77.2	93.4	99.9
Pts with dose reduction, n (%)	260 (53.4)	133 (27.3)	80 (16.3)
T-DM1 decreased to 3.0 mg/kg, n (%)	—	—	58 (11.8)
T-DM1 decreased to 2.4 mg/kg, n (%)	—	—	22 (4.5)

Overall Survival: Confirmatory Analysis

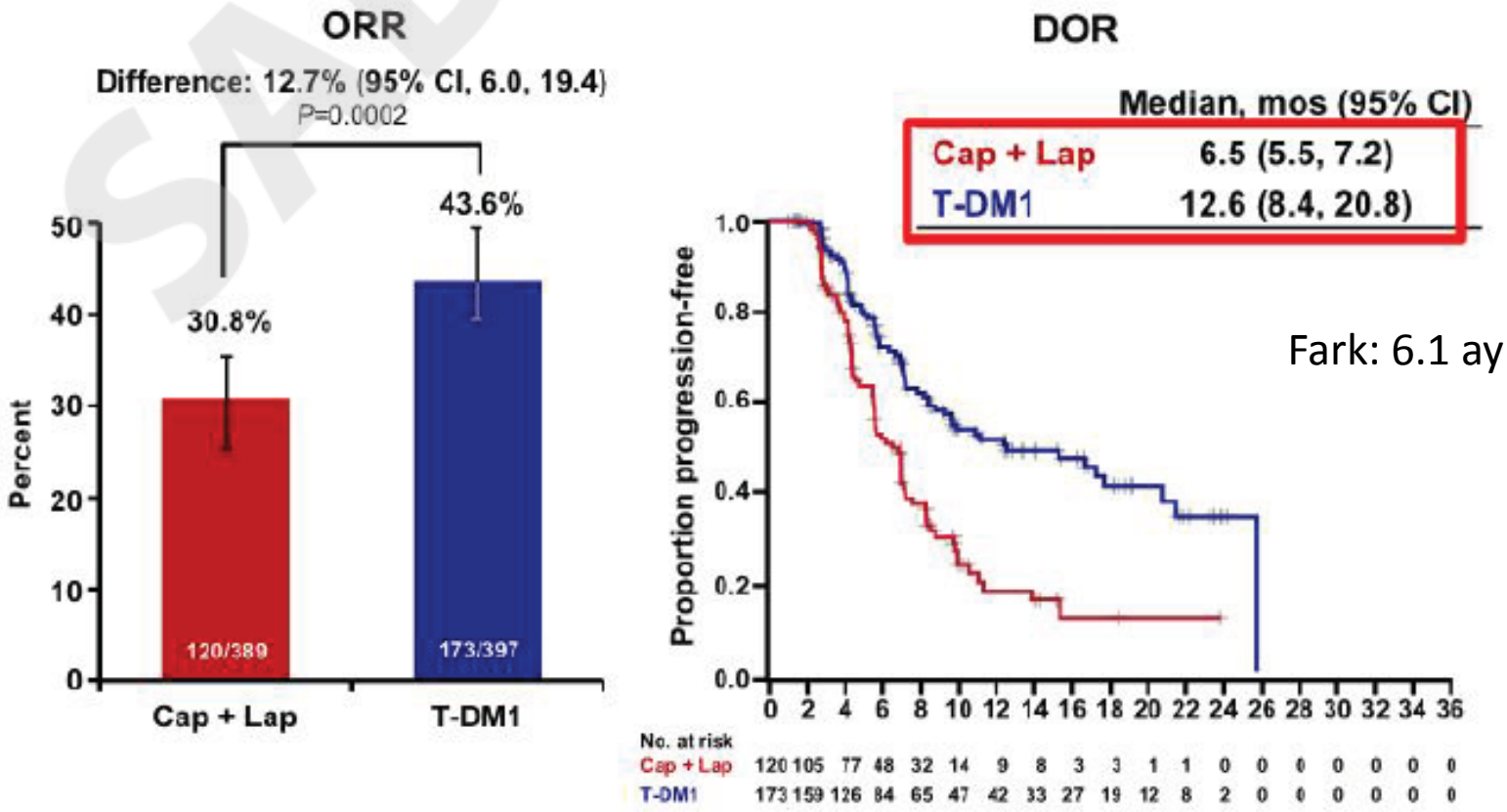


Fark: 5.8 ay

Data cut-off July 31, 2012; Unstratified HR=0.70 (*P*=0.0012).

Verma et al, ESMO 2012

Objective Response Rate (ORR) and Duration of Response (DOR) in Patients with Measurable Disease



Fark: 6.1 ay

Verma et al, ESMO 2012

Adverse Events

Grade ≥3 AEs With Incidence ≥2%

	Cap + Lap (n=488)		T-DM1 (n=490)	
Adverse Event	All Grades, %	Grade ≥3, %	All Grades, %	Grade ≥3, %
Diarrhea	79.7	20.7	23.3	1.6
Hand-foot syndrome	58.0	16.4	1.2	0.0
Vomiting	29.3	4.5	19.0	0.8
Neutropenia	8.6	4.3	5.9	2.0
Hypokalemia	8.6	4.1	8.6	2.2
Fatigue	27.9	3.5	35.1	2.4
Nausea	44.7	2.5	39.2	0.8
Mucosal inflammation	19.1	2.3	6.7	0.2
Thrombocytopenia	2.5	0.2	28.0	12.9
Increased AST	9.4	0.8	22.4	4.3
Increased ALT	8.8	1.4	16.9	2.9
Anemia	8.0	1.6	10.4	2.7

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

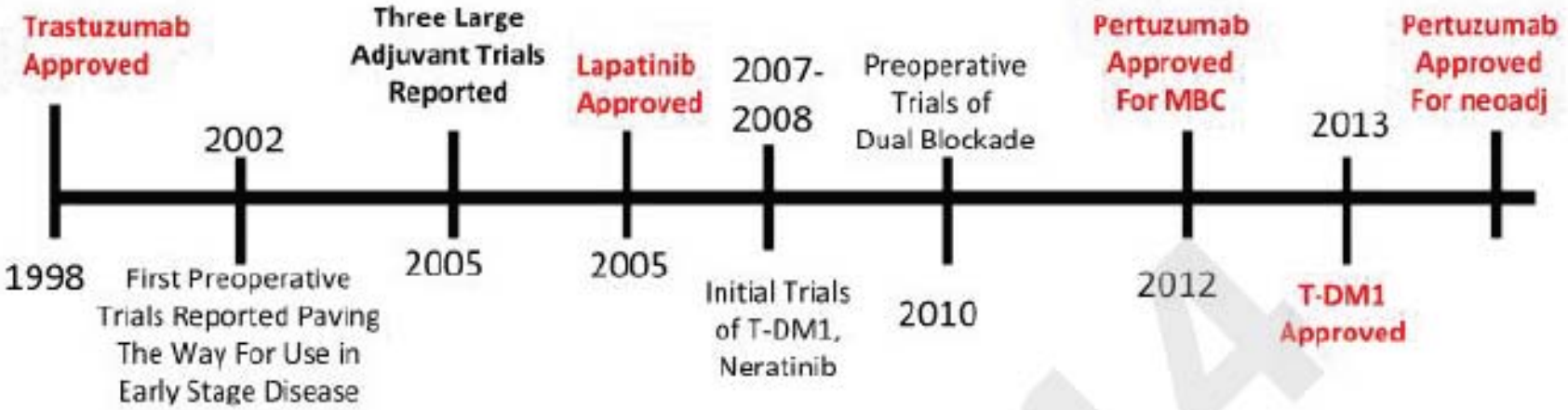
Verma et al, ESMO 2012

Trombositopeni kümülatif değil, doz azaltımı ile yönetilebilir, nadir 8. gün, ciddi kanama nadiren

Sunum Planı

- Meme Kanseri Hedef Moleküller
- Standard Tedavi ve NCCN Kılavuzu
- HER2 hedefli kliniğe yansıyan ?yeni ilaçlar
  - Pertuzumab (Perjeta®)
  - Trastuzumab DM1 (Kadcyla®)
- 2014 yılı yaygın hastalık ve (neo)adjuvan tedaviler
- Sonuçlar

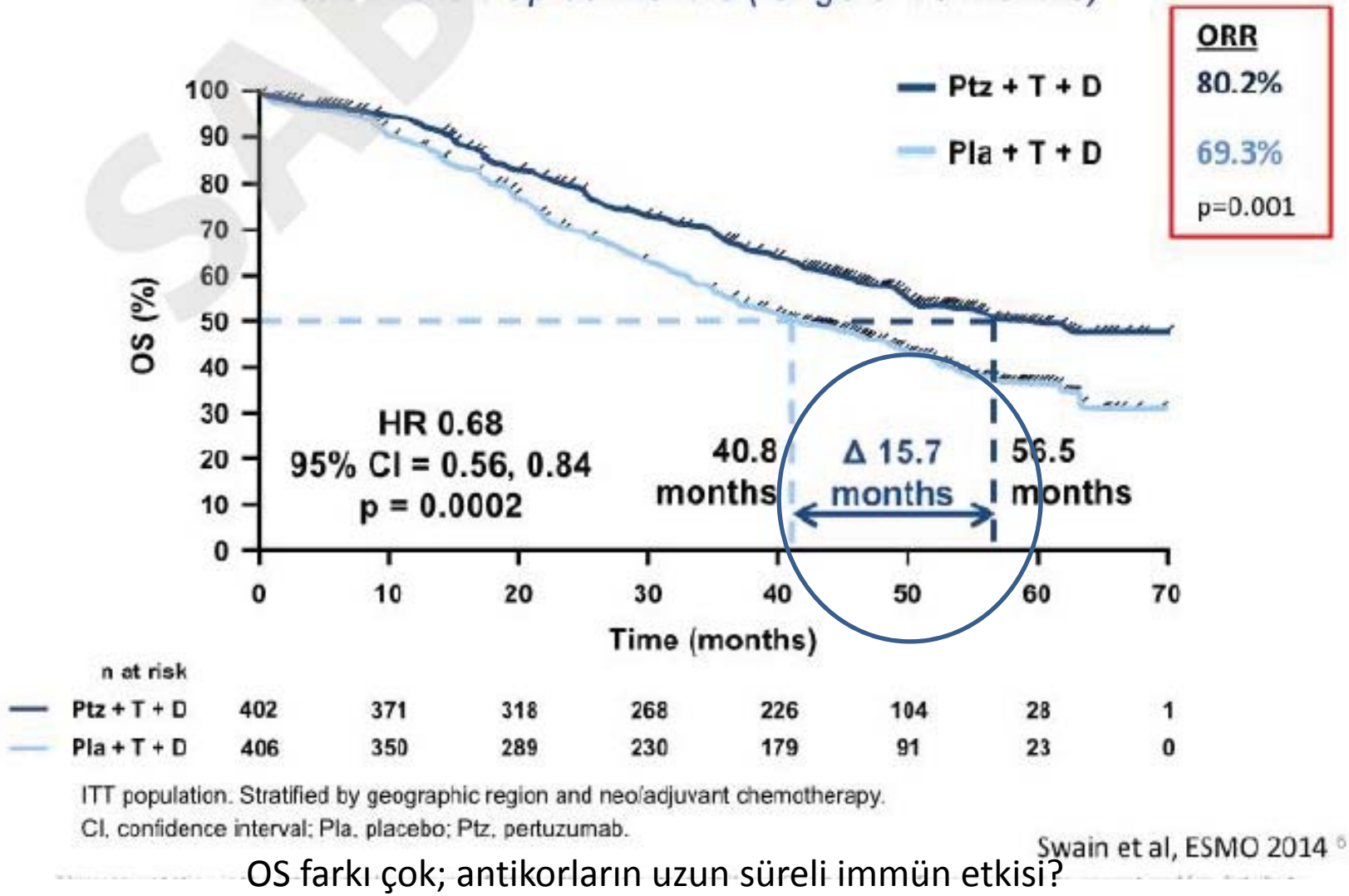
HER2+ Disease: Major Clinical Advances



San Antonio Breast Cancer Symposium – December 9-13, 2014

CLEOPATRA: Final OS Analysis

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



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

Swain et al, ESMO 2014

OS farkı çok; antikorların uzun süreli immün etkisi?

Pertuzumab: Key Clinical Questions

- Is the use of pertuzumab standard in the first-line setting?
  - **YES**
    - What chemotherapy partners are acceptable?

Vinorelbine with trastuzumab, and pertuzumab: VELVET study

- Single arm, phase 2 study in 1st line HER2+ MBC (n=213)
  - Vinorelbine 25mg/m^2 on day 1 and 8 cycle 1 then 35mg/m^2 subsequent cycles
- Common AE's: Diarrhea, neutropenia, nausea
  - Gr 3 AE's: Neutropenia (28%), diarrhea (5.7%)
- Efficacy (interim)
  - ORR 62.9%
  - PFS 14.3 mo

Andersson et al, ESMO 2014

Faz II- 1. veya 2. basamak MMK tedavisinde trast-hf pakl-pertuzumab ile RR %34

Datko F San Antonio 2012

Pertuzumab: Key Clinical Questions

- Is the use of pertuzumab standard in the first-line setting?
  - **YES**
- What chemotherapy partners are acceptable?
  - **For now, docetaxel or paclitaxel, vinorelbine (?)**
- Should pertuzumab be given beyond progression on P?

NO, but an important question to test in clinical trial(s)

- What about the patient who missed out on first-line pertuzumab?

San Antonio Breast Cancer Symposium – December 9-13, 2014

Clinical Activity Of Pertuzumab + Trastuzumab

- *Phase II single arm study of HER2+ MBC with progression on trastuzumab*

Best response	No Pts (Total 66)	%	80% CI (%)
Complete response	**5**	**7.3**	**3.7 - 13.6**
Partial response	**11**	**16.7**	**10.9 – 24.1**
Stable disease > 6 m	**17**	**25.8**	**18.8 – 33.9**
Progressive disease	**33**	**50**	**41.5 – 58.5**

SUMMARY

Overall RR: 24%

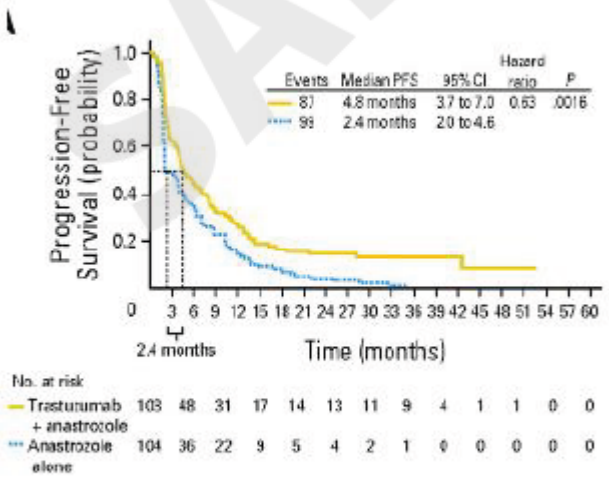
Clin Benefit Rate: 50%

Median PFS: 5.5 m

Baselga et al. JCO 2010

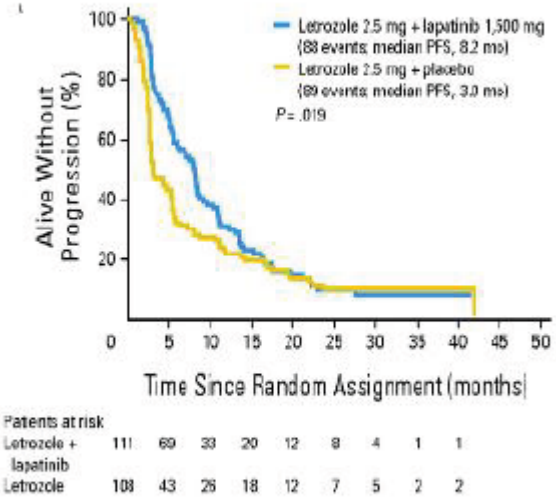
– Probably reasonable, but label is currently restricted to the first line setting

HER2 targeted therapy adds modestly to endocrine therapy



Anastrozole vs
Anastrozole + Trastuzumab

Kaufman et al, JCO 2008



Letrozole vs
Letrozole + Lapatinib

Johnston et al, JCO 2009

- Addition of HER2-directed therapy improves PFS but not OS

- Endocrine therapy + HER2-directed therapy can be considered for select 1st line pts with MBC (e.g. asymptomatic, low burden disease, pts at increased risk of toxicity from chemotherapy)

Her-2 (+) Hastalıkta 2. ve Sonraki Basamak Tedaviler

- EMILIA çalışması
  - Is the use of T-DM1 standard in the second-line setting (e.g. after trastuzumab)?
    - yes
  - Should T-DM1 only be used in the second line setting?

Th3RESA: Study Schema

HER2 positive
(Centrally confirmed)

Unresectable locally advanced/recurrent or Metastatic breast cancer

Prior trastuzumab, lapatinib and taxane,

2
1

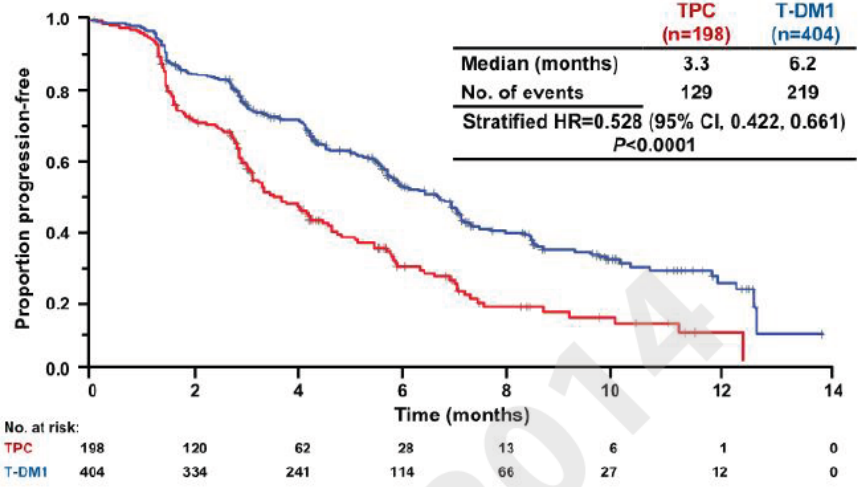
T-DM1 q3w

Treatment of physician's choice

Study treatment continues until disease progression or unmanageable toxicity

N = 600
2:1 randomization

PFS by Investigator Assessment



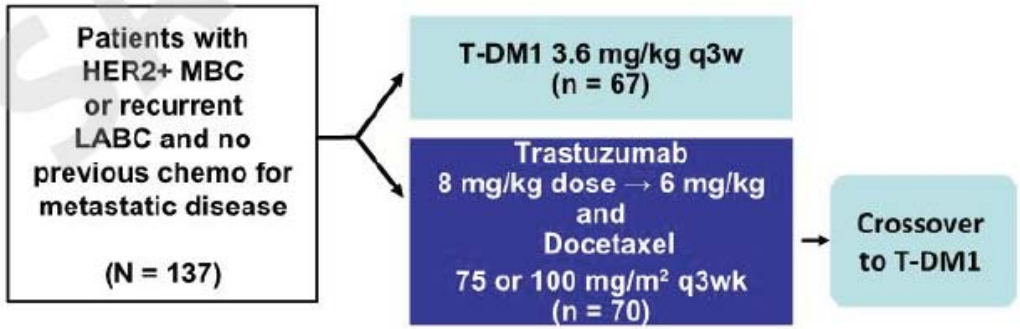
	TPC (n=198)	T-DM1 (n=404)
Median (months)	3.3	6.2
No. of events	129	219

Stratified HR=0.528 (95% CI, 0.422, 0.661)
P<0.0001

Median follow-up: TPC, 6.5 months; T-DM1, 7.2 months.
Unstratified HR=0.521 (P<0.0001).

Krop et al, Lancet Oncology In press
Wildiers et al, ECC-ESMO 2013

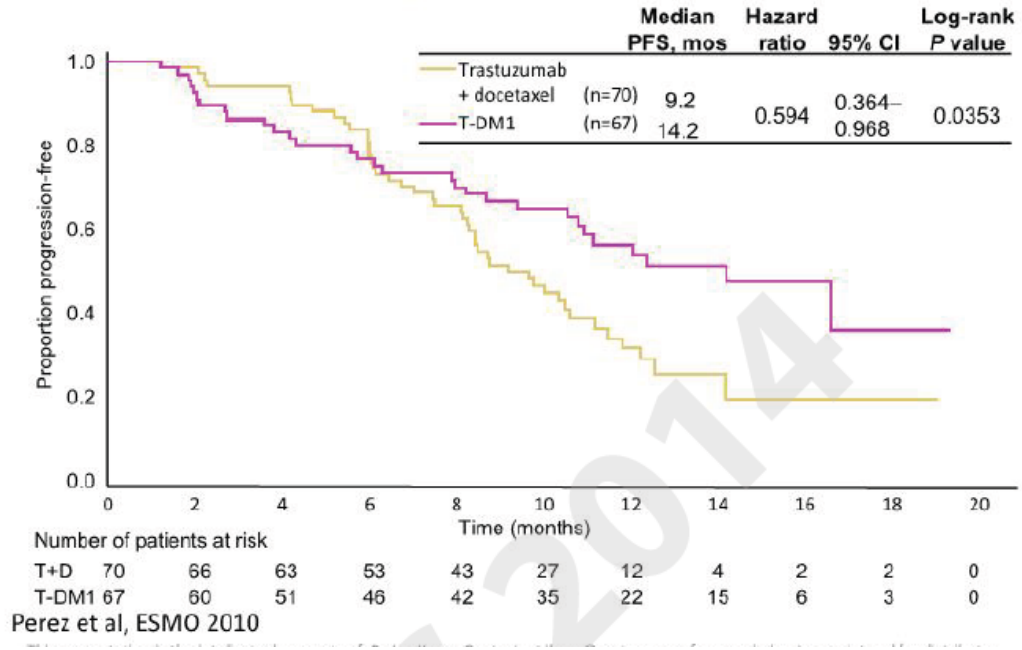
Phase II Study of First-line T-DM1 vs. Trastuzumab/Docetaxel in HER2+ MBC



- 1:1 randomization
- Primary endpoint: Progression-free surviva
- Secondary endpoints: ORR, CBR, OS, Qo
- Patients in trastuzumab/docetaxel arm allc T-DM1 on progression

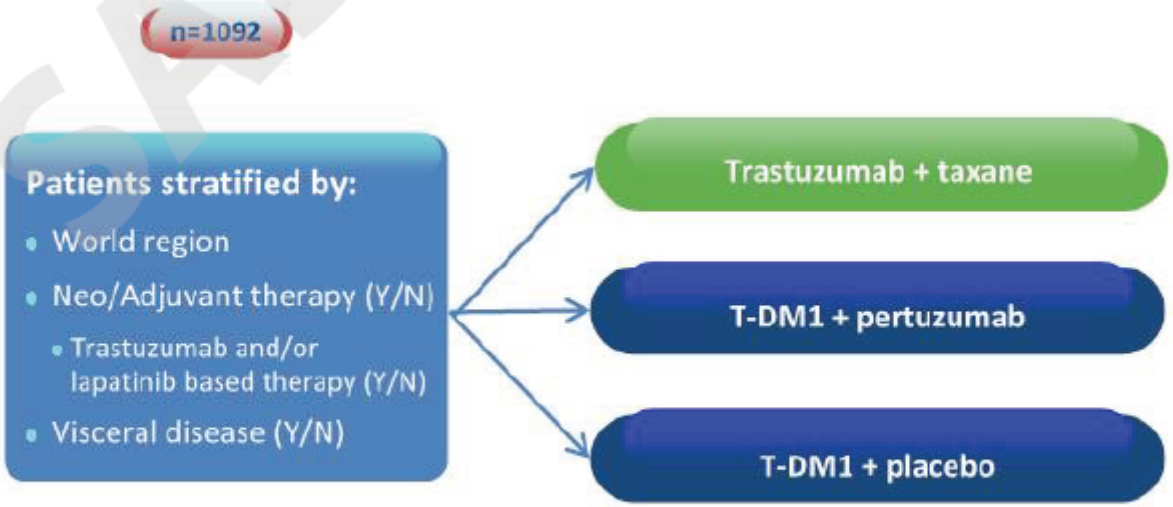
Perez EA, et al. *ESMO 2010.* Abstract LBA3.

Phase II Study of First-line T-DM1 vs. Trastuzumab/Docetaxel in HER2+ MBC



Perez et al, ESMO 2010

1st Line Phase III MARIANNE Study



Patients with HER2 positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer

- **Primary endpoints:** PFS as assessed by IRF; Safety
- **Secondary endpoints:** OS; PFS by investigator; PRO analyses; Biomarkers
- Superiority design with a Non-inferiority analysis between each of the experimental arms and the control arm
- **Interim futility analysis:** Option to drop experimental arm

Treatment Approach For Patient Presenting With HER2+ MBC in 2014

First Line: Taxane + Trastuzumab + Pertuzumab

Second Line: TDM-1

<u>Third, Fourth, Fifth, Sixth Line:</u>

Capecitabine + Lapatinib

Capecitabine + Trastuzumab

Vinorelbine + Trastuzumab

Lapatinib + Trastuzumab

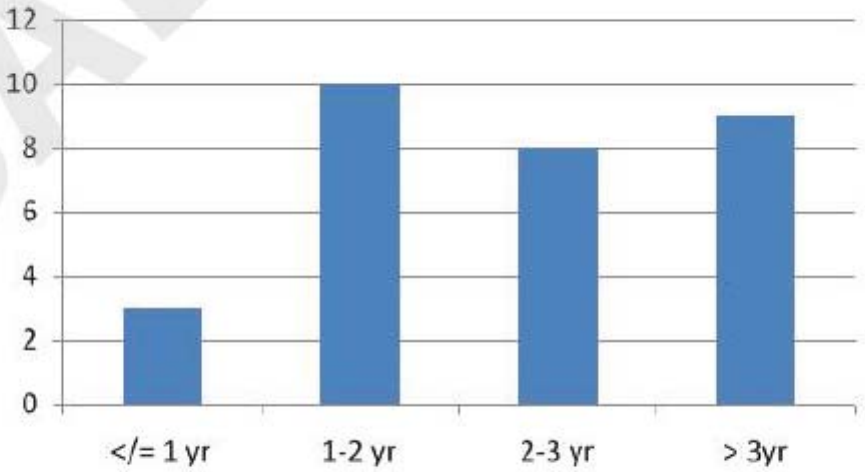
Pertuzumab + Trastuzumab (?? if no prior Pertuzumab)

Other chemotherapy + Trastuzmab

Endocrine Therapy + Trastuzumab

Her2 (+) Hastalıkta
Beyin Metastazları

Risk of CNS Metastases Continues Over Time



- Of N=64 patients alive >/= 3 yrs from HER2+ MBC diagnosis, the number of patients who developed new brain metastases in each time interval

Olson et al, Ann Oncol. 2013, 24(6):1526

Survival after CNS diagnosis by subtype

Study	HER2+*	TN
Bendell et al, 2003	**13 mo**	
Gori et al, 2007	**23 mo**	
Eichler et al, 2008	**17.1 mo**	4.0 mo
Nam et al, 2008		3.4 mo
Park et al, 2009	**14.9 mo**	
Dawood et al, 2008	**11.6 mo**	
Lin et al, 2008		4.9 mo
Melisko et al, 2008	**23.1 mo**	
Niwinska et al, Ann Oncol 2010	**11 mo**	3-4 mo
Anders et al, Cancer 2010	**14-15 mo**	2.9 mo
Olson et al, unpublished	**18 mo**	

*treated with trastuzumab

CNS Disease is Frequent in HER2+ MBC

- 30-50% incidence—risk continues over time
- Radiation typically first line therapy
- Lapatinib monotherapy
  - CNS ORR 2-6% in pretreated pts
- Lapatinib + capecitabine
  - CNS ORR 18-36%, PFS 3.6-5.1 months in pre-treated pts
  - CNS ORR 67%, PFS 5.5 months in up-front setting (Faz II ,LANDSCAPE)

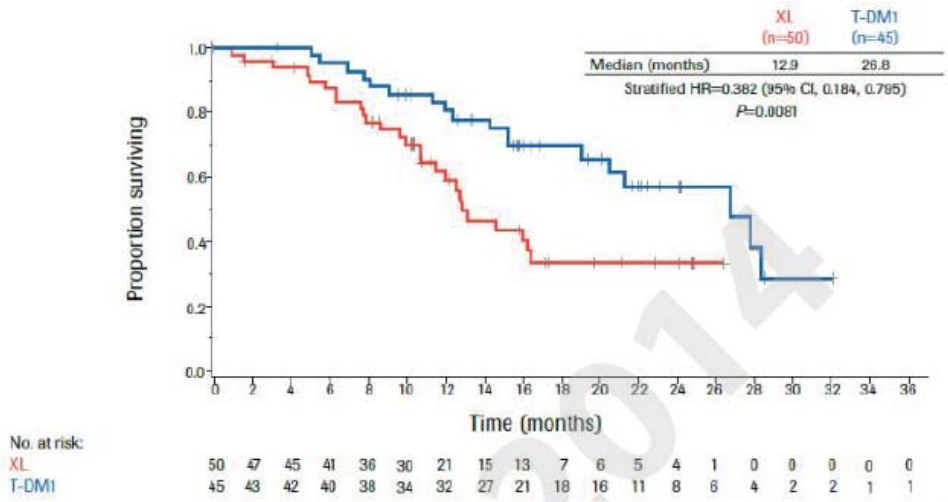
Current DFCI trials for HER2+ CNS disease

- Neratinib + capecitabine
- ARRY-380 + trastuzumab
- KD019 and trastuzumab

Rate of CNS progression was low in both arms of EMILIA

	Capecitabine/lapatinib N=446	T-DM1 N=450
Rate of CNS progression*	0.6%	1.8%

In patients with treated CNS mets, T-DM1 was associated with improved survival



Krop et at, SABCS 2013

VOLUME 32 · NUMBER 19 · JULY 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Recommendations on Disease Management for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: American Society of Clinical Oncology Clinical Practice Guideline

Naren Ramakrishna, Sarah Temin, Sarat Chandarlapaty, Jennie R. Crews, Nancy E. Davidson, Francisco J. Esteva, Sharon H. Giordano, Ana M. Gonzalez-Angulo, Jeffrey J. Kirshner, Ian Krop, Jennifer Levinson, Shanu Modi, Debra A. Patt, Edith A. Perez, Jane Perlmutter, Eric P. Winer, and Nancy U. Lin

Naren Ramakrishna, University of Florida Health Cancer Center at Orlando Health,

Key Recommendations

- For patients with a favorable prognosis for survival and a single brain metastasis, treatment options include surgery with postoperative radiation, stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT; ± SRS), fractionated stereotactic radiotherapy (FSRT), and SRS (± WBRT), depending on metastasis size, resectability, and symptoms. After treatment, serial imaging every 2 to 4 months may be used to monitor for local and distant brain failure.
- For patients with a favorable prognosis for survival and limited (two to four) metastases, treatment options include resection for large symptomatic lesion(s) plus postoperative radiotherapy, SRS for additional smaller lesions, WBRT (± SRS), SRS (± WBRT), and FSRT for metastases > 3 to 4 cm. For metastases < 3 to 4 cm, treatment options include resection with postoperative radiotherapy. In both cases, available options depend on resectability and symptoms.
- For patients with diffuse disease/extensive metastases and a more favorable prognosis and those with symptomatic leptomeningeal metastasis in the brain, WBRT may be offered.
- For patients with poor prognosis, options include WBRT, best supportive care, and/or palliative care.
- For patients with progressive intracranial metastases despite initial radiation therapy, options include SRS, surgery, WBRT, a trial of systemic therapy, or enrollment onto a clinical trial, depending on initial treatment. For patients in this group who also have diffuse recurrence, best supportive care is an additional option.
- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched.
- For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer.
- If a patient does not have a known history or symptoms of brain metastases, routine surveillance with brain magnetic resonance imaging (MRI) should not be performed.
- Clinicians should have a low threshold for performing diagnostic brain MRI testing in the setting of any neurologic symptoms suggestive of brain involvement.

Asemptomatik hastalarda rutin MRI ile surveyans önerilmemekte

Beyin metastazı sırasında sistemik hastalığı progrese olmayanlarda sistemik tedavi değişimine gerek yok

Beyin metastazı sırasında sistemik hastalığı progrese olanlarda HER2hedefli tedavi MMK tedavi kurallarına göre yapılmalıdır

Sunum Planı

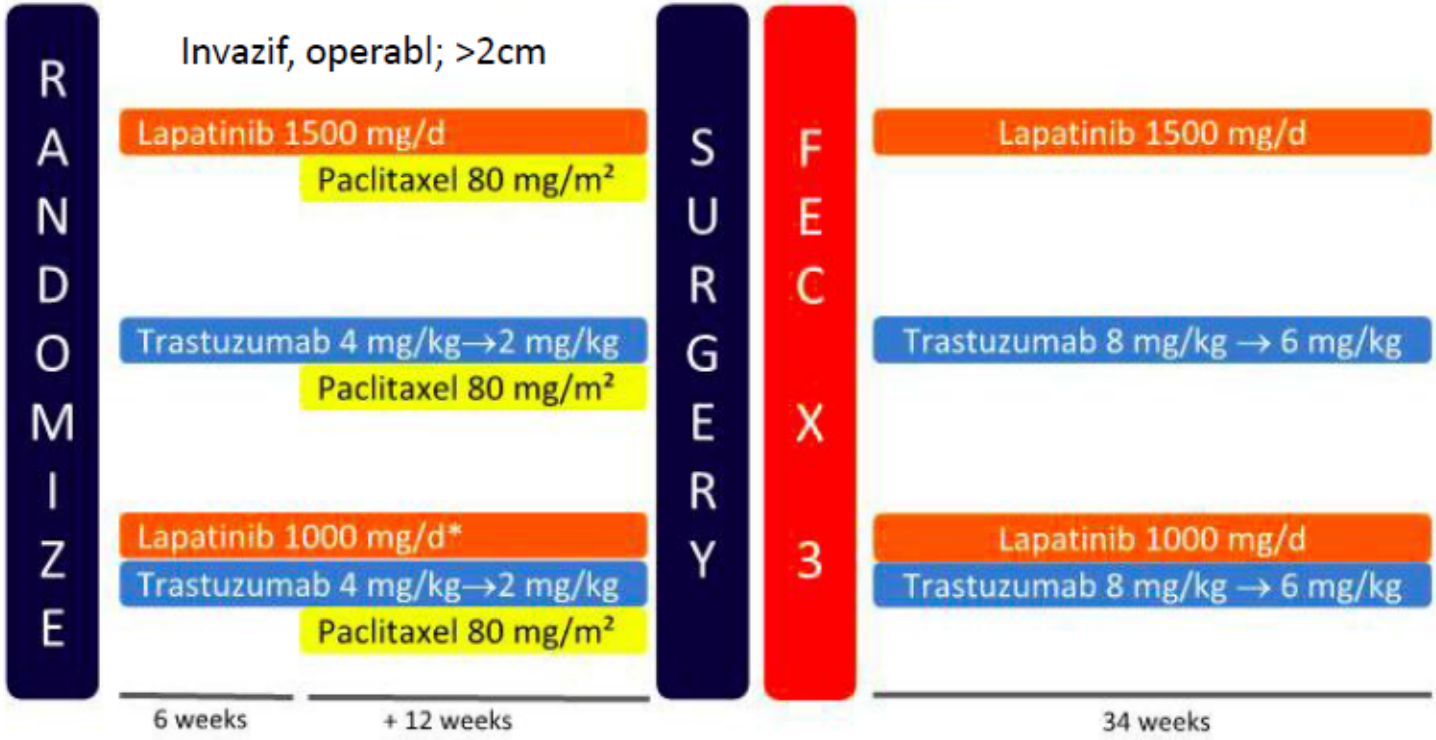
- Meme Kanseri Hedef Moleküller
- Standard Tedavi ve NCCN Kılavuzu
- HER2 hedefli kliniğe yansıyan ?yeni ilaçlar
  - Pertuzumab (Perjeta®)
  - Trastuzumab DM1 (Kadcyla®)
- 2014 yılı yaygın hastalık ve (neo)adjuvan tedaviler
- Sonuçlar

HER2 + Meme Kanseri

- Neoadjuvan Tedaviler (Adjuvan Tedaviler)
  - Dual blokaj >? Tekli Blokaj
    - 2013 San Antonio Neo Altto
    - 2014 ASCO Altto
  - PI3K mutasyonları
  - Postneoadjuvan Tedaviler

S1-01

The association between event-free survival and pathological complete response to neoadjuvant lapatinib, trastuzumab or their combination in HER2-positive breast cancer. Survival follow-up analysis of the NeoALTTO study (BIG 1-06)



**Amendment-2 October 2008, reduced dose of lapatinib to 750 mg/d with paclitaxel 54/152 had protocol-driven reduction*

Baselga J et al; SABCS 2010; Lancet 2012

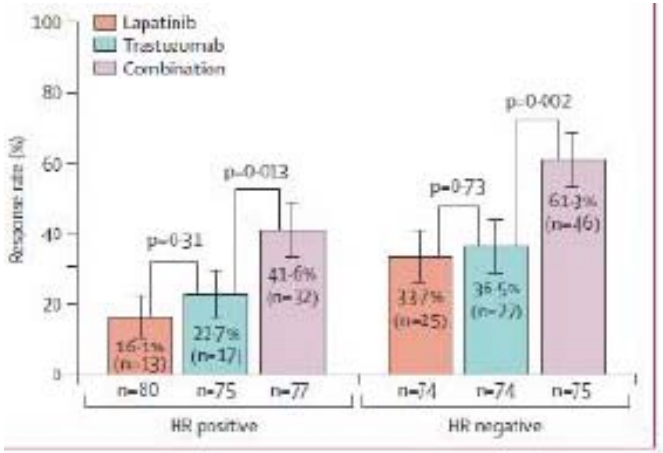
Piccart-Gebhart ve ark.

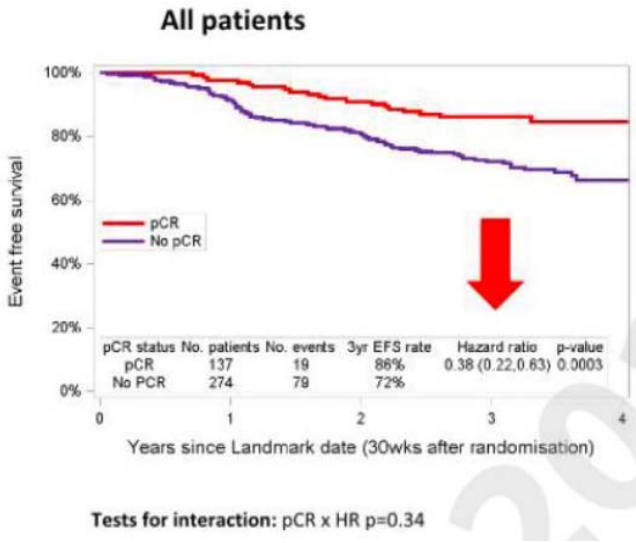
Pathological complete response rates (breast and LN) with trastuzumab (H) and/or lapatinib (L)

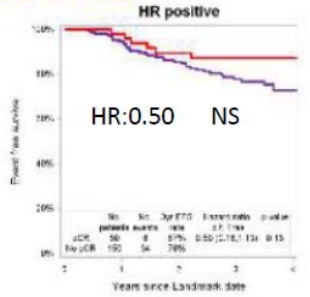
Study/ neoadjuvant regimen	Total pCR Trastuzumab	Total pCR Lapatinib	Total pCR H+L
NeoALTTO[1] (6 weeks H and/or L → (WP) x 12 plus H and/or L) **N=455**	**27.6%**	**20.0%**	**46.8%**
NSABP B-41[2] (ACx4→ WPx12 plus H and/or L) **N=519**	**49.4%**	**47.4%**	**60.2%**
CALGB 40601[3] (WPx16 plus H and/or L) **N-299**	**43%**	**29%**	**52%**
CHER-LOB[4] (WP x 12→FEC x 4 plus H and/or L throughout) **N=121**	**25%**	**26.3%**	**46.7%**

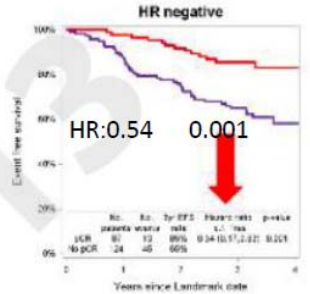
30 wk

LANDMARK ANALYSIS: EFS BY PCR





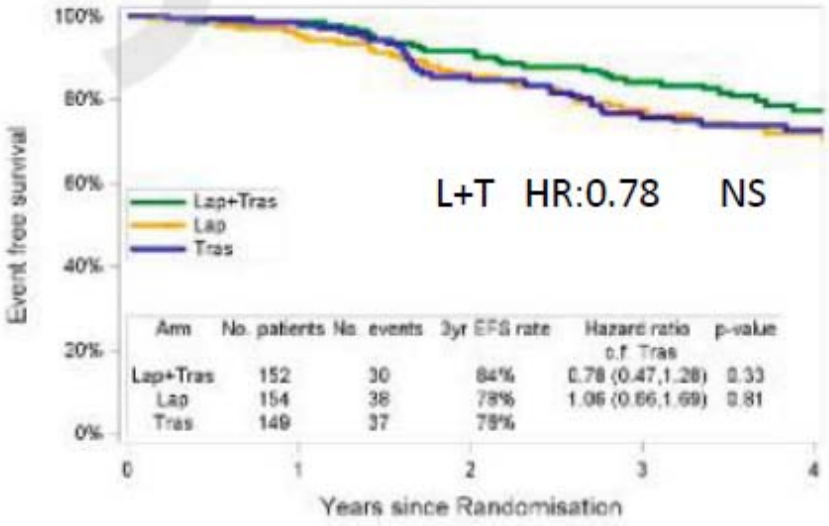




Baselga Lancet 2012
Piccart SanAntonio 2013

EVENT-FREE SURVIVAL (EFS) ANALYSIS

All patients

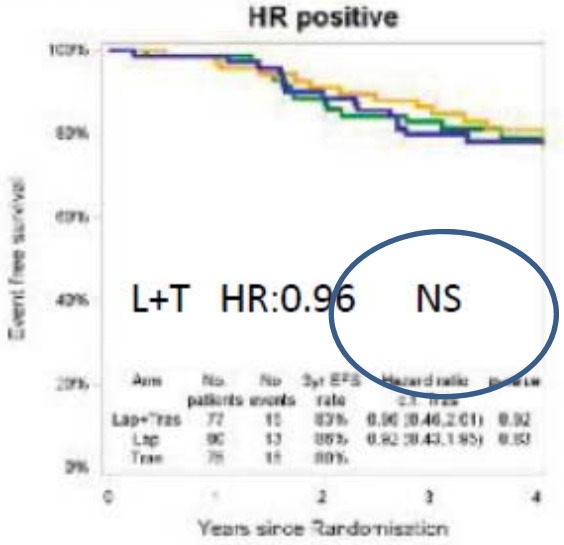


Tests for interaction according to HR status

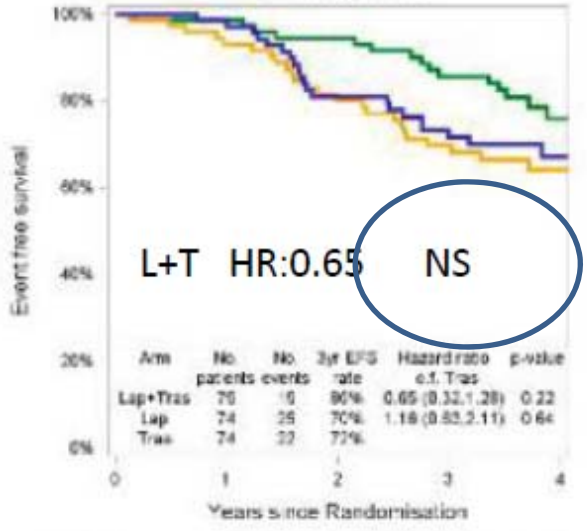
Lap + Tras vs. Tras p=0.48

Lap vs. Tras p=0.56

HR positive



HR negative



- 4 yıllık takibe göre dual HER2 hedefli tedavi anlamlı pCR avantajı sağlar
  - HR+ ve HR- hastalıklar ayrı biyolojik özellikler taşır
  - EFS ve GS farkı yok (tüm grupta) (gücü yeterli değil)
- pCR olanlar tedavi kolundan bağımsız anlamlı EFS ve OS avantajına sahip
- NeoALTTO sağkalım farklarını gösterecek güce sahip değil, bu konudaki kesin veriler ALTTO sonuçlanınca elde edilecek

BIG
Breast International Group

ALTTO
Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial

Alliance
for Clinical Trials
in Oncology

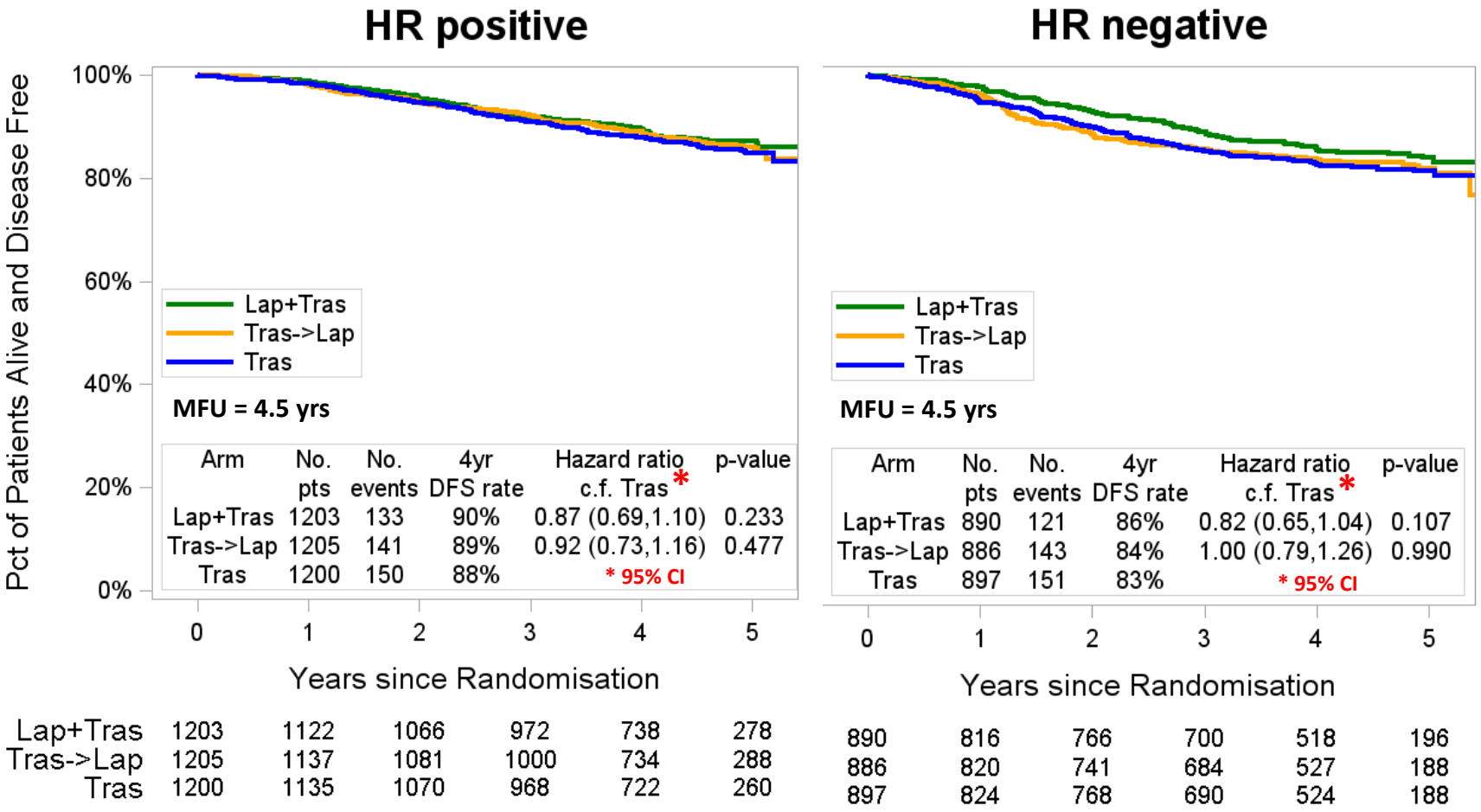
First results from the phase III ALTTO trial (BIG 02-06; NCCTG 063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L) or their combination (L + T) in the adjuvant treatment of HER2-positive early breast cancer (EBC)

Martine Piccart-Gebhart, Andrew P. Holmes, José Baselga, Evandro de Azambuja, Amylou Dueck, Giuseppe Viale, Jo Anne Zujewski, Aron Goldhirsch, Sergio Santillana, Kathleen Pritchard, Antonio C. Wolff, Christian Jackisch, Istvan Lang, Michael Untch, Ian Smith, Frances Boyle, Binghe Xu, Henry Gomez, Richard D. Gelber and Edith A. Perez

On behalf of the ALTTO Study Team

gsk

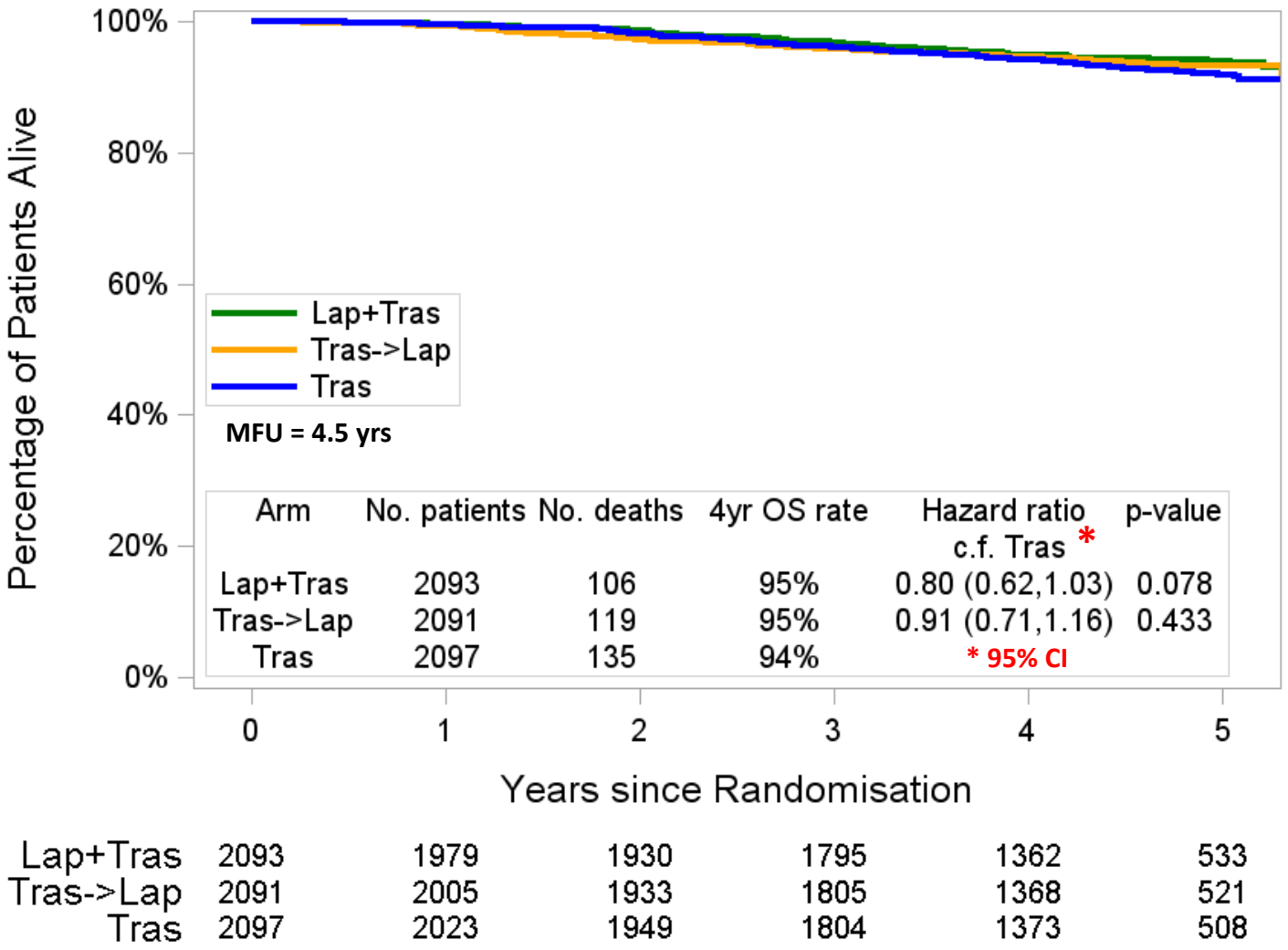
DFS BY HORMONE RECEPTOR STATUS



Interaction tests p = 0.70 L + T

p = 0.60 T → L

OVERALL SURVIVAL (OS) ANALYSIS



Arm	No. patients	No. deaths	4yr OS rate	Hazard ratio c.f. Tras *	p-value
Lap+Tras	2093	106	95%	0.80 (0.62,1.03)	0.078
Tras->Lap	2091	119	95%	0.91 (0.71,1.16)	0.433
Tras	2097	135	94%		

* 95% CI

ALTTO CONCLUSIONS (I)

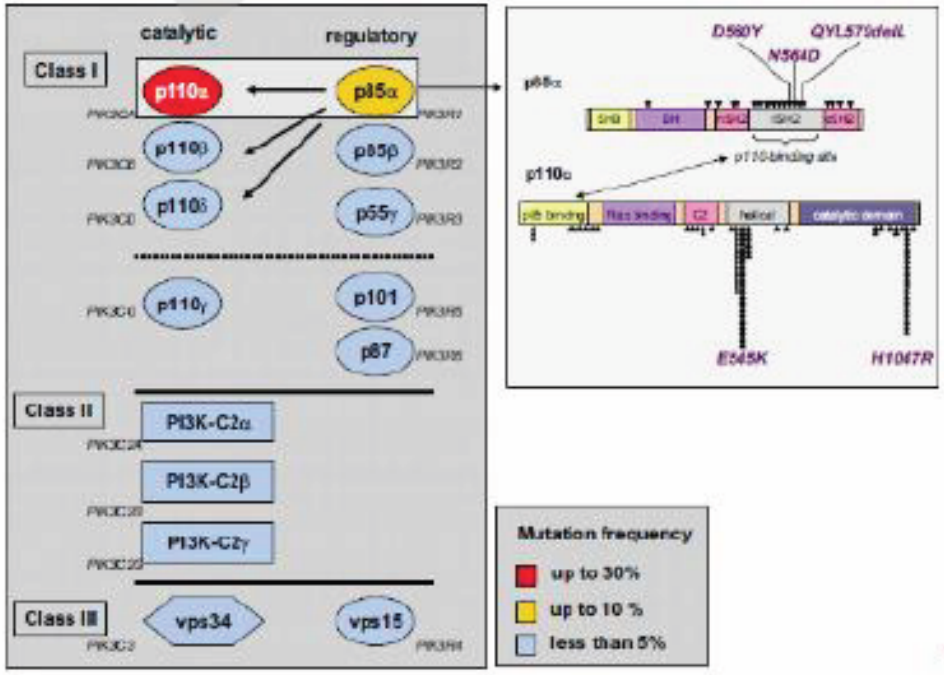
- **The event rate was lower than anticipated: 555 DFS events for the L + T vs. T comparison at 4.5 years median follow-up instead of 850 target.**
- **The ALTTO trial did not meet its endpoints (DFS): Neither the L + T vs. T comparison nor the T → L vs. T comparison.**
  - **4-year DFS 88% vs. 86% for L + T vs. T (HR 0.84; 97.5%CI 0.70-1.02)**
  - **4-year DFS 87% vs. 86% for T → L vs. T (HR 0.93; 97.5%CI 0.76-1.13)**
- **The doubling in pCR observed with L + T in NeoALTTO did not translate into improved survival outcomes in ALTTO at 4.5 years median follow-up.**

ALTTO CONCLUSIONS (II)

- **Lapatinib is associated with significant increase in AEs of special interest compared with trastuzumab alone: diarrhoea, hepatobiliary, and rash or erythema.**
  - **60-78% of patients in the lapatinib-containing arms received at least 85% of protocol specified L dose.**
- **Cardiac toxicity remained low in all treatment arms.**
- **Follow-up in ALTTO will continue – a protocol-specified updated efficacy analysis is planned in 2 years.**

High Frequency of Mutations of the *PIK3CA* Gene in Human Cancers

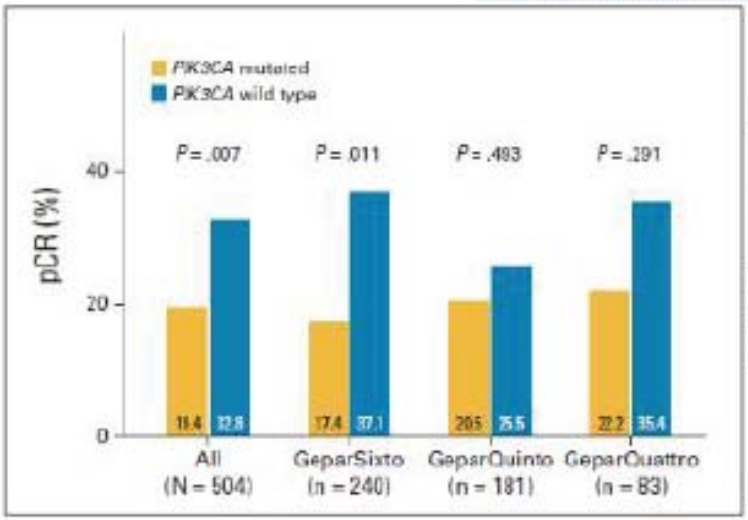
Yardena Samuels,[1] Zhenghe Wang,[1] Alberto Bardelli,[1] Natalie Silliman,[1] Janine Ptak,[1] Steve Szabo,[1] Hai Yan,[2] Adi Gazdar,[3] Steven M. Powell,[4] Gregory J. Riggins,[1] James K. V. Willson,[5] Sanford Markowitz,[5] Kenneth W. Kinzler,[1] Bert Vogelstein,[1] Victor E. Velculescu[1]*



Tissue type- PIK3CA mt	%
breast	26%
endometrium	23%
ovary	11%
CRC	13%
Lung	3%
urinary tract	20%
gastric	10%

Martin-Berenjano et al. Cancer cell 2009

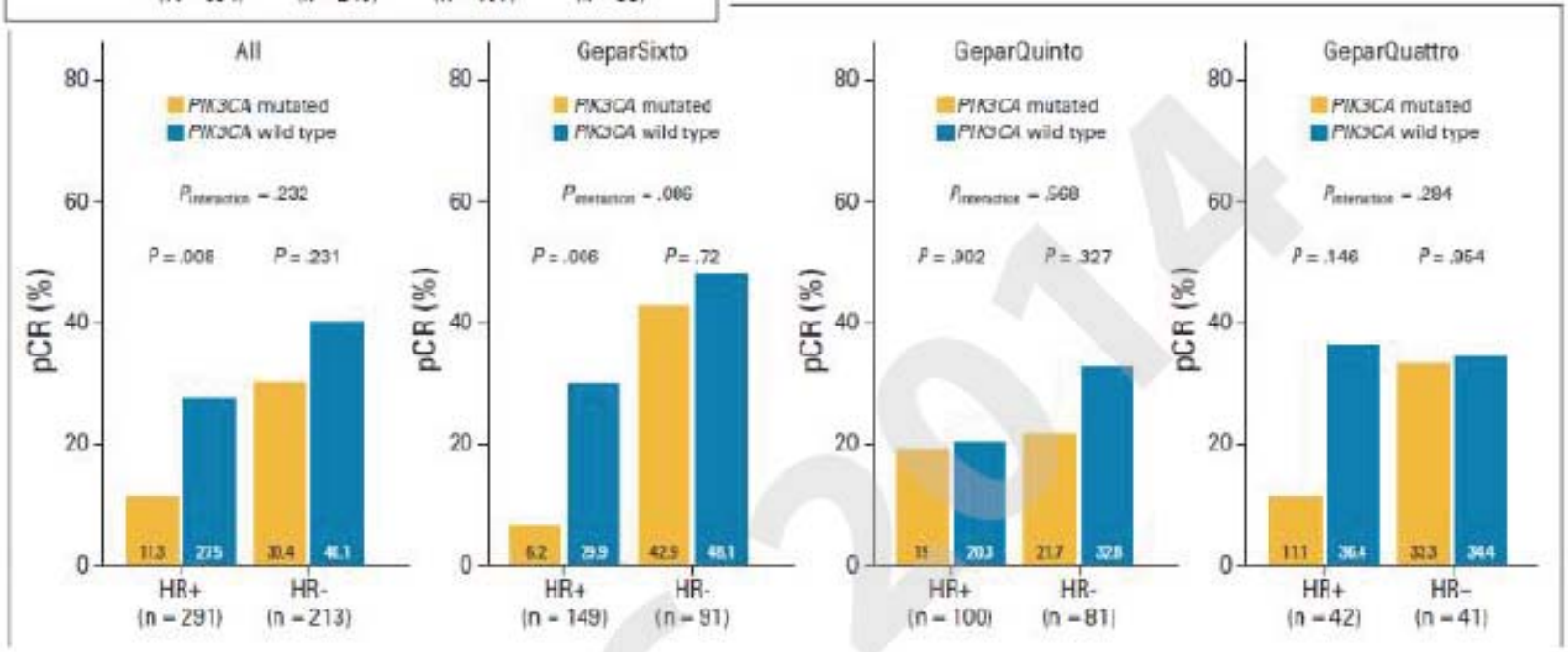
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT



PIK3CA Mutations Are Associated With Lower Rates of Pathologic Complete Response to Anti–Human Epidermal Growth Factor Receptor 2 (HER2) Therapy in Primary HER2-Overexpressing Breast Cancer

Sibylle Loibl, Gunter von Minckwitz, Andreas Schneeweiss, Stefan Paepke, Annika Lehmann, Mahdi Rezai, Dirk M. Zahm, Peter Sinn, Fariba Khandan, Holger Eidtmann, Karel Dohnal, Clemens Hilfrich, Jens Huober, Bern Pfitzner, Peter A. Fasching, Fabrice Andre, Judith L. Lindner, Christos Sotiriou, August Dykgers Sanxing Gua, Stephan Gade, Valentina Nekljudova, Sherene Lei, Michael Untch, and Carsten Denkert

See accompanying editorial doi: 10.1200/JCO.2014.57.8132



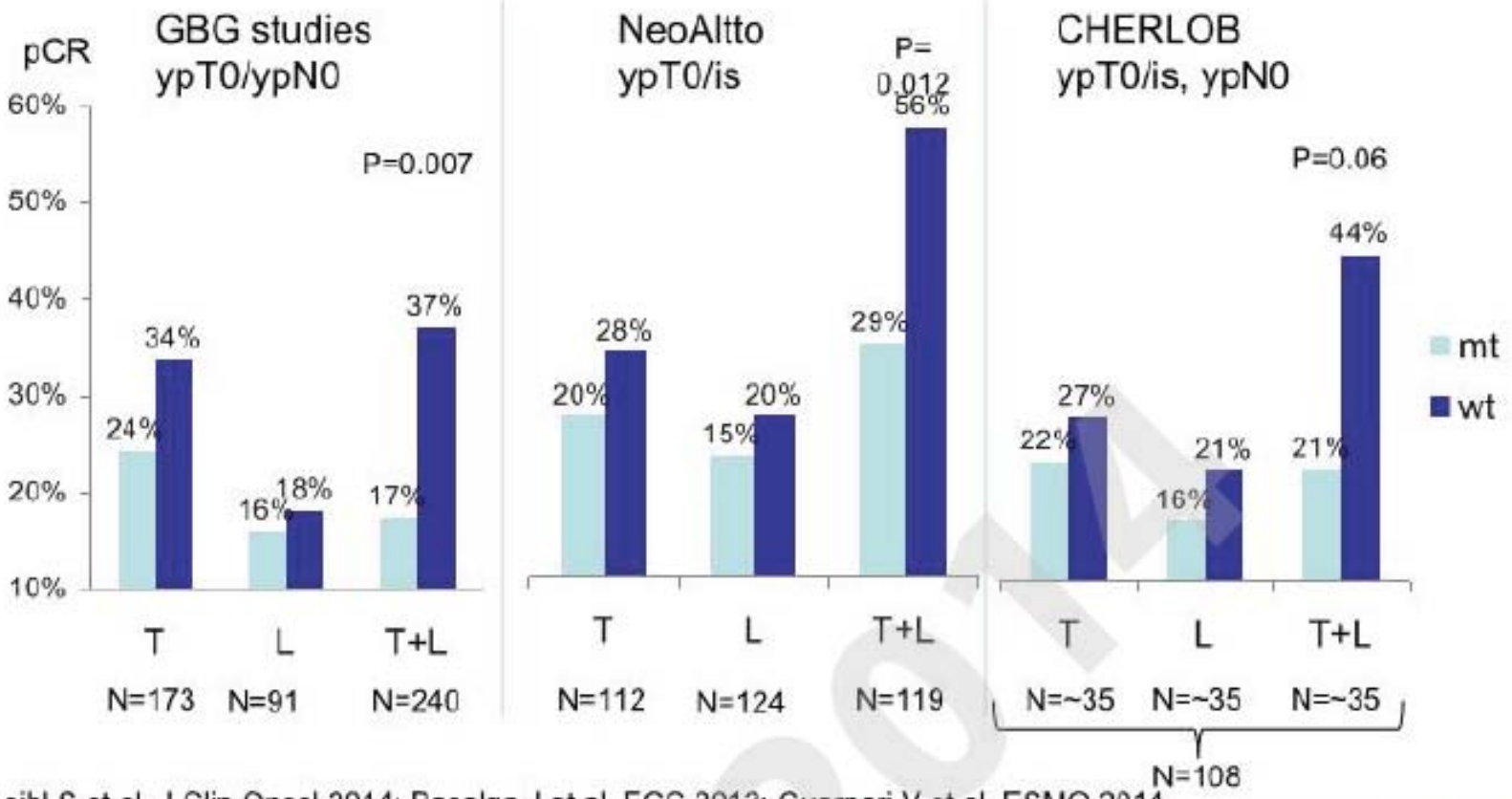
Multivariable Analysis* for Prediction of pCR in HER2+ Breast Cancer

		Odds ratio	95% CI	P-value
PIK3CA	wt	1.00		0.01
	mut	0.49	0.29-0.85	
Hormone receptor status	neg	1.00		0.001
	pos	0.50	0.33-0.75	

* adjusted for therapy, age, tumour and nodal status, histotype and grading, study and anti-HER2 therapy

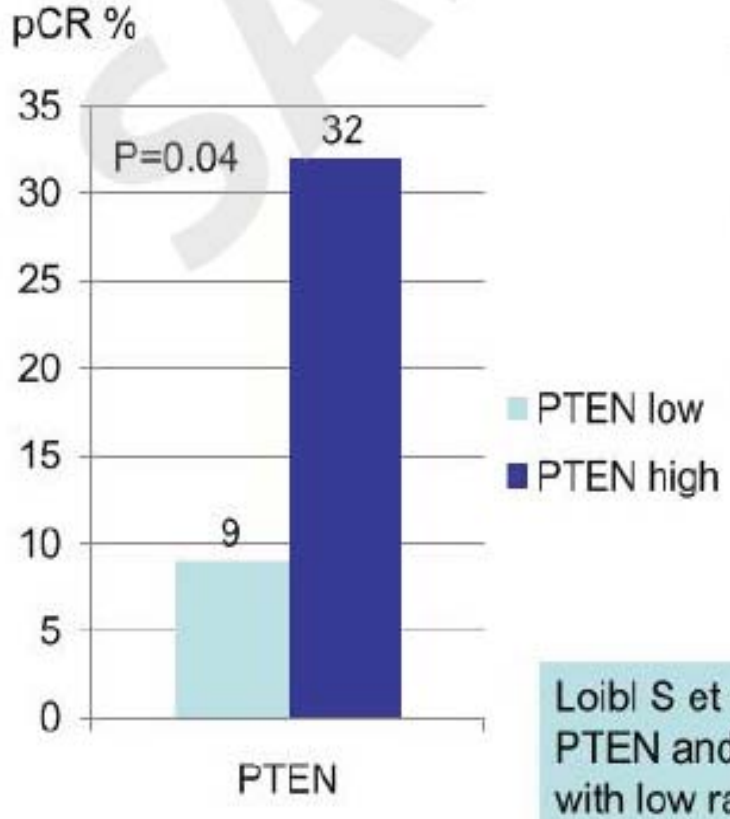
Loibl S et al. J Clin Oncol 2014

PIK3CA mut status and pCR



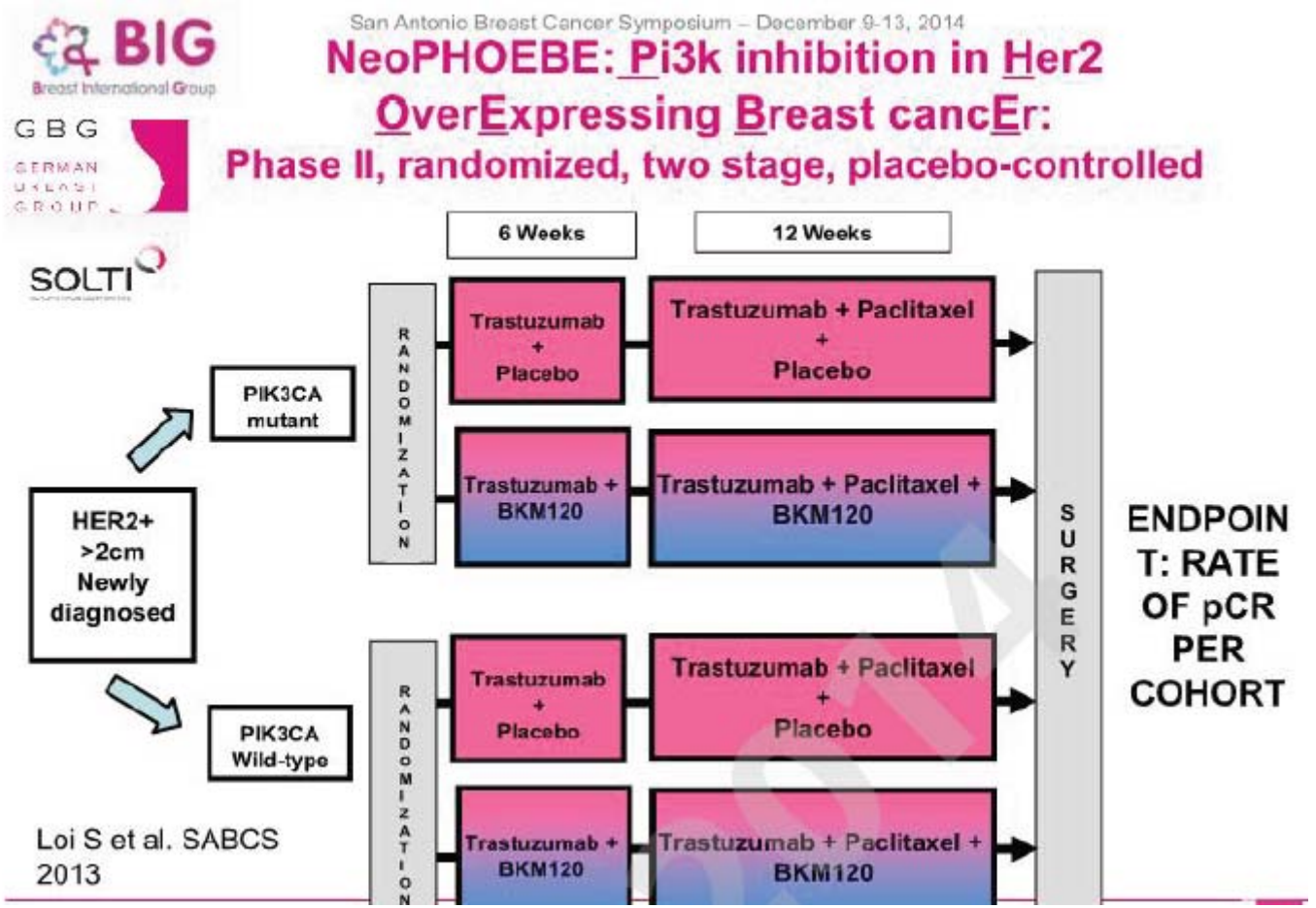
Loibl S et al. J Clin Oncol 2014; Baselga J et al. ECC 2013; Guarneri V et al. ESMO 2014

PIK3CA and PTEN as predictor in HER2+ w/o CHT

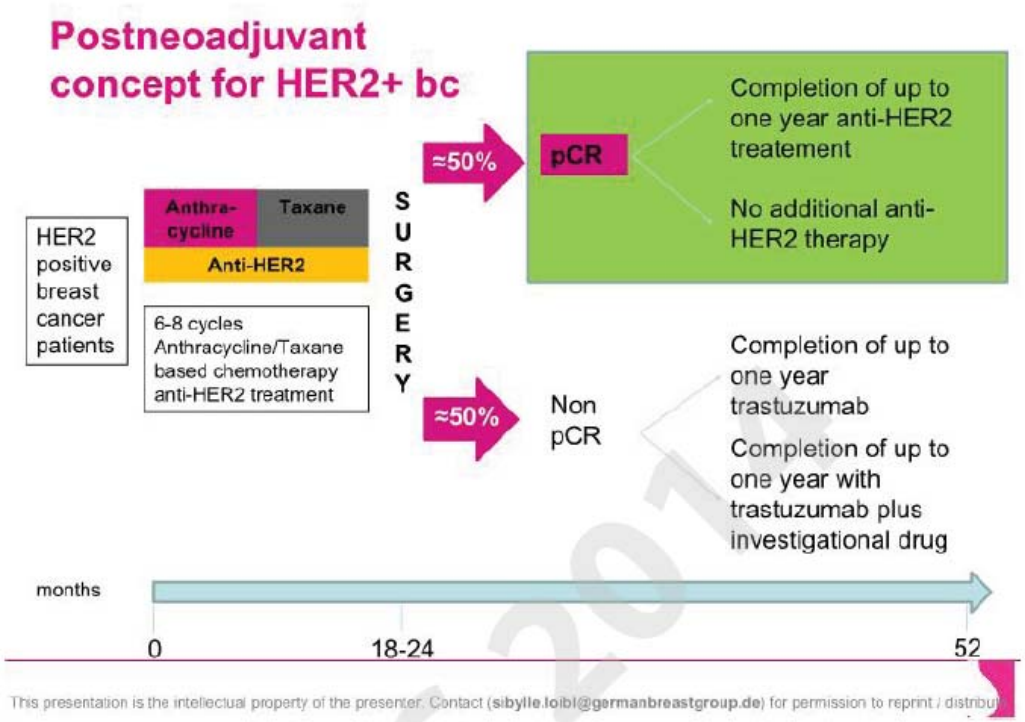


- **None of the patients whose tumors harbored a *PIK3CA* mutation achieved pCR (p=0.06).**
- There was no association between PTEN status and *PIK3CA* mutation (p=0.44).
- 0/17 cases (0%) with a mutation and/or PTEN low expression (<100 H score) had a pCR compared to 5/14 cases (36%) with *PI3KCA* wild type and high PTEN levels (p=0.01).

Loibl S et al. PD5-7
PTEN and *PIK3CA* but not p4EBP1 are associated with low rates of pathological complete response (pCR) to trastuzumab



BKM120 (buparlisib) –oral class I pan PIK3 inhibitörü



Geyer C et al. SABCS 2013

Sunum Planı

- Meme Kanseri Hedef Moleküller
- Standard Tedavi ve NCCN Kılavuzu
- HER2 hedefli kliniğe yansıyan ?yeni ilaçlar
  - Pertuzumab (Perjeta®)
  - Trastuzumab DM1 (Kadcyla®)
- 2014 yılı yaygın hastalık (neo)adjuvan tedaviler
- Sonuçlar

2015'e doğru HER2(+) Meme Kanseri Yenilikler

- İlerlemiş Hastalıkta;
  - Dual blokaj (CLEOPATRA- trast+pert) ile sağkalım yararı
  - Salvaj tedavide T-DM1 ile anti-HER2 tedavi devamı (birinci basamak?)
  - Beyin metastazları ileri araştırma konusudur

- (Neo)adjuvan Tedavide;
  - Sağkalım pCR ile ilişkili
    - HR durumu ve stromal TIL yüksek pCR göstergesi
  - Dual blokaj (NeoALTTO- tras+lap) pCR arttırır ancak sağkalıma yararsız (üstelik adjuvan çalışmalarda (ALTTO) dual blokajın sağkalım yararı gösterilememiş)
  - PIK3CA genotipi daha düşük pCR sağlamakta
  - Postneoadjuvan rezidü kalan hastalarda çalışmalar devam ediyor

.

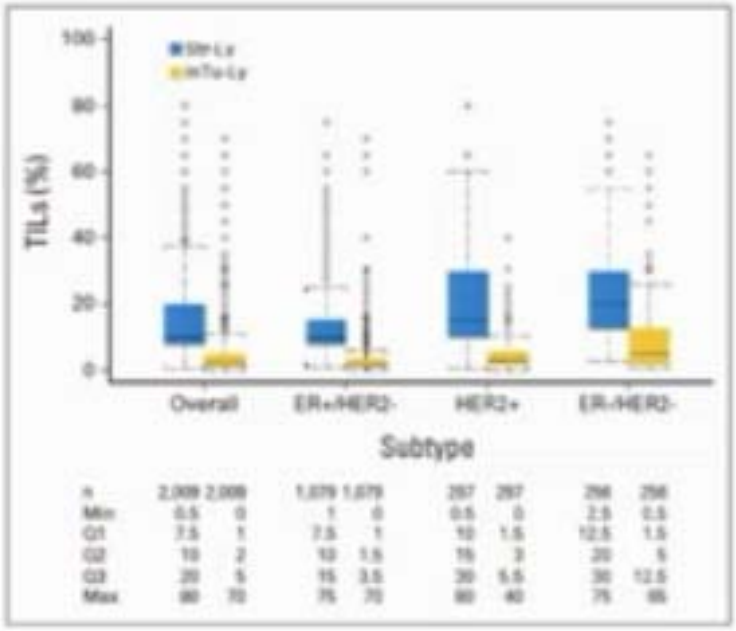

BU ARALAR BAYAĞI UNUTKAN OLDUM.
ALLAH ALLAH... NEDEN ACABA?
NE NEDEN?
GAGRI GEBECI

Teşekkür ederim

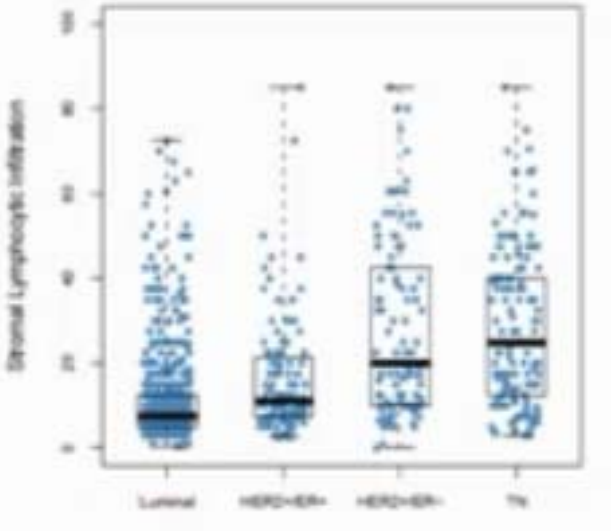
What has happened 2013-2014?

Clinical Strategy	Clinical Implication
Bevacizumab: Maintenance/Progression	Nothing changes
Overcoming Trastuzumab Resistance	Incremental
Endocrine	
1st line fulvestrant	Promising
Targeting cdk 4/6	Promising
Targeting PI3K	Very preliminary
TNBC: platinums	Only BRCA1/2; non-mutation not standard
Immune Checkpoint Inhibitors	Very preliminary

TILs
Higher levels in HER2+ and TNBC



	Overall		ER+/HER2-		HER2+		ER-/HER2-	
n	2,009	2,009	1,079	1,079	257	257	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	2.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65



	Luminal	HER2+/ER+	HER2+/ER-	TN
n	591	103	106	134
Min	0.5	2.5	0	3
Q1	5	7.5	10	12.5
Q2	7.5	11	20	25
Q3	12.5	21.2	42.5	40
Max	72.5	85	85	85

Loi et al, JCO 2013; Ann Oncol 2014

sTIL as Predictor in HER2+

San Antonio Breast Cancer Symposium, December 10-14, 2013

TILs associated with higher rates of pCR

Variable	P Value	Odds Ratio (95%CI)
Stromal TILs (per 10% increment)	0.038#	1.16 (1.01-1.32)
Age (<50 vs >50yrs)	0.24	1.53 (0.76-3.11)
Nodal status (pos vs neg)	0.87	1.06 (0.53-2.16)
Histologic Grade (1,2 vs 3)	0.44	0.76 (0.38-1.53)
Tumor stage (T4 vs T1-3)	0.43	1.47 (0.57-3.76)
ER status (neg vs pos)	0.03	2.14 (1.07-4.28)

Multivariate model is stratified by chemotherapy type;
likelihood ratio P=0.038 and chi-square (Δx^2) = 12.1 for the comparison of the analysis with and without the stromal TILs variable; CI: confidence interval.

Loi S, et al. SABCS 2013

BOLERO-3: Study Design

N = 572*

- Locally advanced or metastatic HER2+ breast cancer
- Prior taxane required
- TRAS resistance
  - Adjuvant: progression on or within 12 months of TRAS
  - Metastatic: progression within 4 weeks of TRAS
- Measurable disease only

Randomize 1:1

Everolimus (5 mg PO daily) + Vinorelbine (25 mg/m² weekly) + TRAS (2 mg/kg week¹) (n = 284)

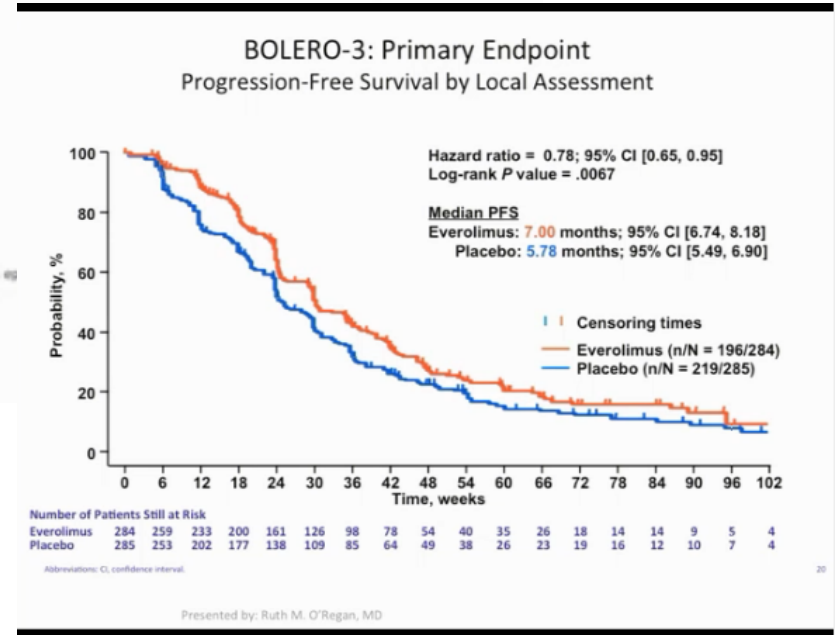
Placebo (PO daily) + Vinorelbine (25 mg/m² weekly) + TRAS (2 mg/kg weekly*) (n = 285)

Therapy until PD or intolerable toxicity

- Stratification by prior lapatinib use (yes/no)

Endpoints:
Primary: PFS
Secondary: OS, ORR, time to deterioration of ECOG PS, safety, DoR, CBR, and QoL

* Actual enrollment was 569.
¹Following a 4-mg/kg loading dose on day 1, cycle 1 (1 cycle = every 21 days).
Abbreviations: CBR, clinical benefit rate; DoR, Duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human ep
survival; PD, progressive disease; PFS, progressive-free survival; PO, oral; PS, performance status; QoL, quality of life.
http://www.clinicaltrials.gov/ct2/show/NCT01007942?term=BOLERO3&rank=1



BOLERO-1/TRIO 019: Trial Design

N = 719

- Locally advanced or metastatic HER2+ breast cancer
- No prior therapy for advanced or metastatic disease (except endocrine therapy)
- Prior (neo)adjuvant TRAS and/or chemotherapy allowed[1]
- Measurable disease or presence of bone lesions (lytic or mixed)

Randomized 2:1

- Everolimus (10 mg PO daily) + Paclitaxel[2] + Trastuzumab[3]
- Placebo + Paclitaxel[2] + Trastuzumab[3]

Stratification factors:
- Prior neo/adjuvant TRAS
- Visceral metastases

Therapy until disease progression or intolerable toxicity[4]

Endpoints

- **Primary: PFS (investigator-assessed)**
  - **Overall population and**
  - **HR- subpopulation**
- Secondary:
  - OS, ORR, CBR, Time to response, Safety, Duration of response

[1]Discontinued > 12 mo before randomization;
[2]Paclitaxel: 80 mg/m² weekly;
[3]Trastuzumab: 4 mg/kg loading dose on day 1 at cycle 1 followed by 2 mg/kg weekly doses
[4]Patients could discontinue any study treatment due to AEs; other study treatments continued until disease progression or intolerable toxicity

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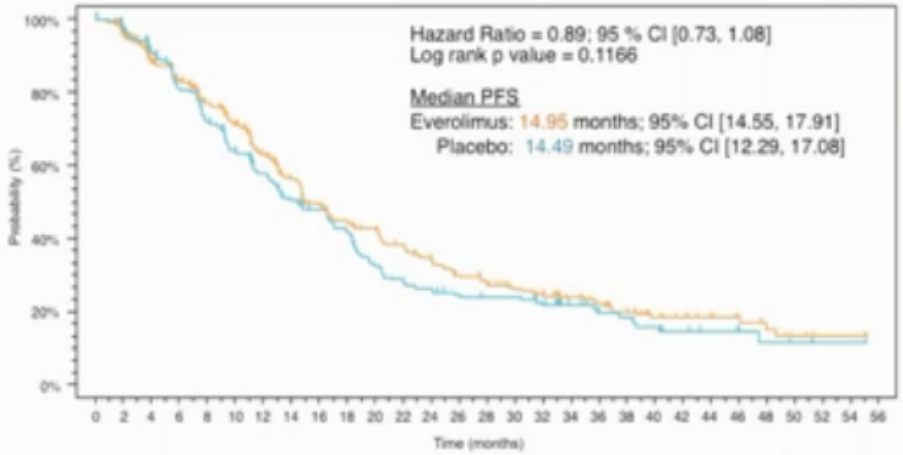
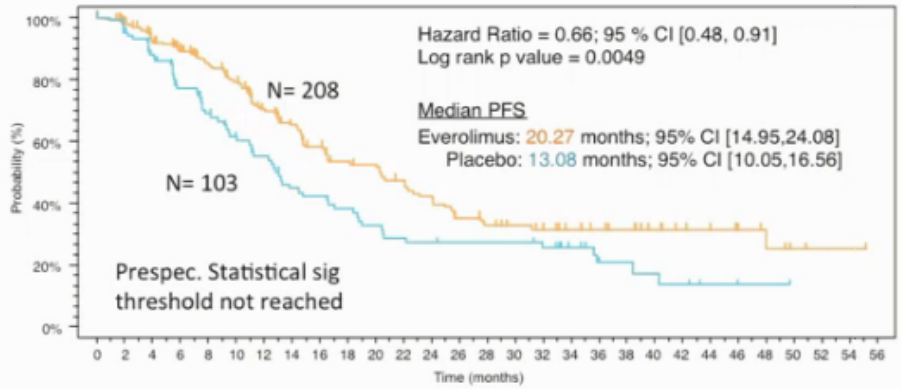
Hurvitz 2014, SABCS

BOLERO-1/TRIO 019: PFS by Investigator Assessment (Full Study Population)



BOLERO-1/TRIO 019: PFS by Investigator Assessment (HR- Subpopulation)



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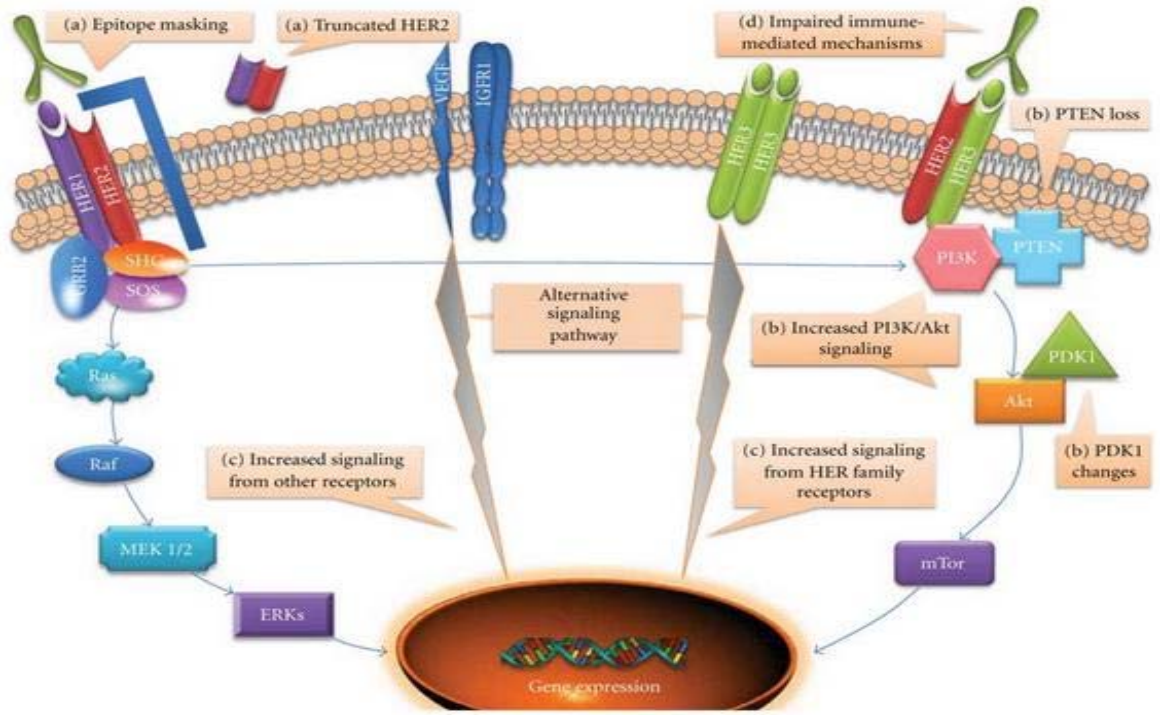
Hurvitz SABCS 2014

Trastuzumab direnci



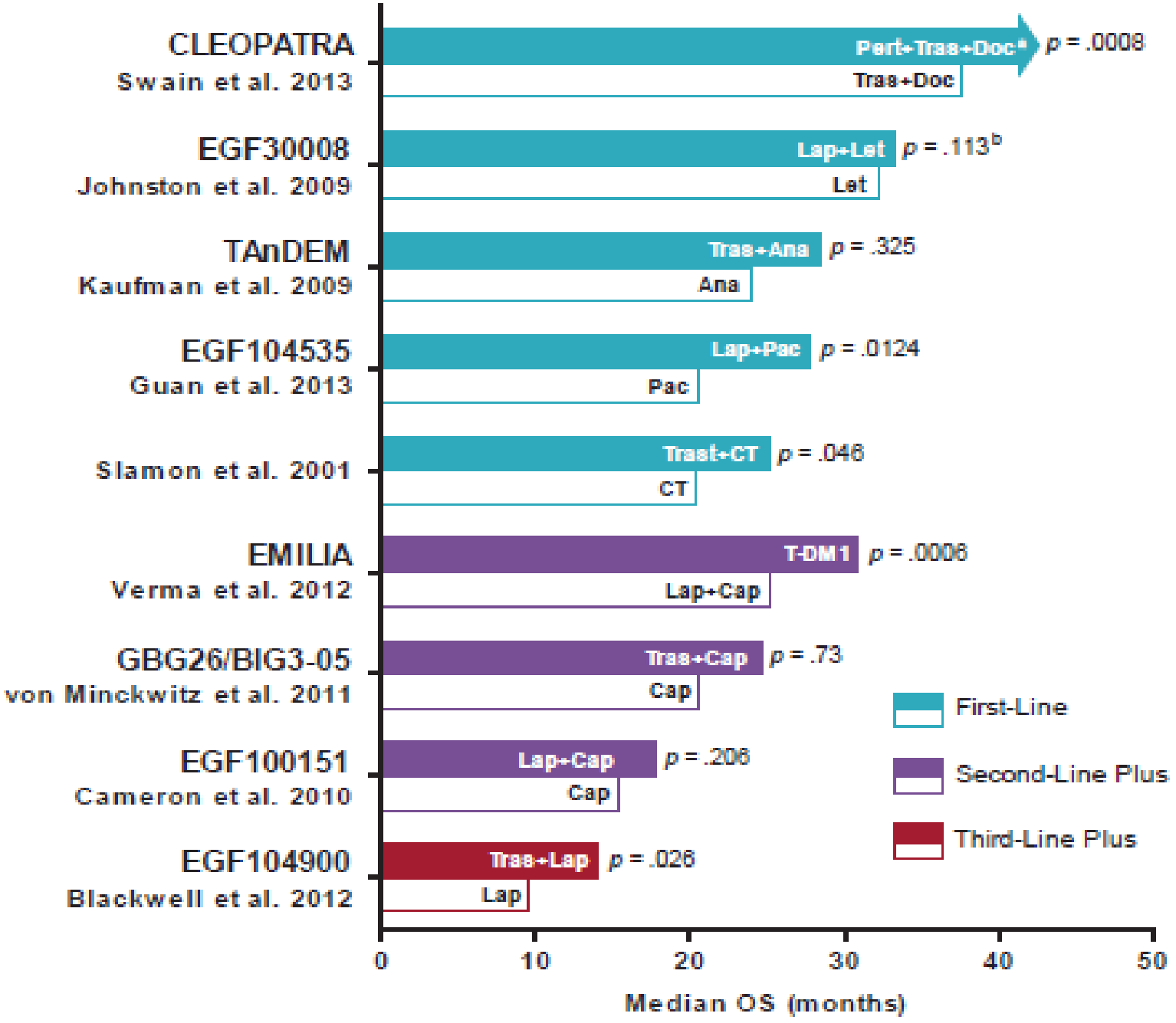
Trastuzumab direnci:

(a) HER2 bağlanması bozulur: trunkat HER2 ve epitop maskelenmesi(MUC4)

(b) HER2 ilişkili aşağı sistem yolaklarının upregülasyonu: PTEN kaybı, PI3K/Akt aktivite artışı ve PDK1 değişiklikleri

(c) Alternatif yolakların aktivasyonu/ diğer reseptörlerin aktivasyonu IGFRIGF 1R sinyalizasyonu veya HER2/IGF 1R heterodimerizasyonu MET reseptör: trastuzumaba bağlı p27 indüksiyonunu engeller HER ailesi ligandlarında overekspresyon; mutant TGFbeta-1 reseptör TACE/ADAM17 fosforilasyonuna ve ligand saçılmasına neden olur. Artmış ligandlar HER ailesi heterodimerlerinin artmasına neden olur

(d) İmmun aracılı sistem patolojileri


CLEOPATRA
Swain et al. 2013
Pert+Tras+Doc[a]
Tras+Doc
p = .0008
EGF30008
Johnston et al. 2009
Lap+Let
Let
p = .113[b]
TAnDEM
Kaufman et al. 2009
Tras+Ana
Ana
p = .325
EGF104535
Guan et al. 2013
Lap+Pac
Pac
p = .0124
Slamon et al. 2001
Trast+CT
CT
p = .046
EMILIA
Verma et al. 2012
T-DM1
Lap+Cap
p = .0006
GBG26/BIG3-05
von Minckwitz et al. 2011
Tras+Cap
Cap
p = .73
EGF100151
Cameron et al. 2010
Lap+Cap
Cap
p = .206
EGF104900
Blackwell et al. 2012
Tras+Lap
Lap
p = .026
First-Line
Second-Line Plus
Third-Line Plus
0
10
20
30
40
50
Median OS (months)


ASLINDA Bİ SORUNUNUZ YOK GİBİ AMA EN İYİSİ KAFANIZI KARIŞTIRMAK İÇİN Bİ SÜRÜ TEST YAPALIM...
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