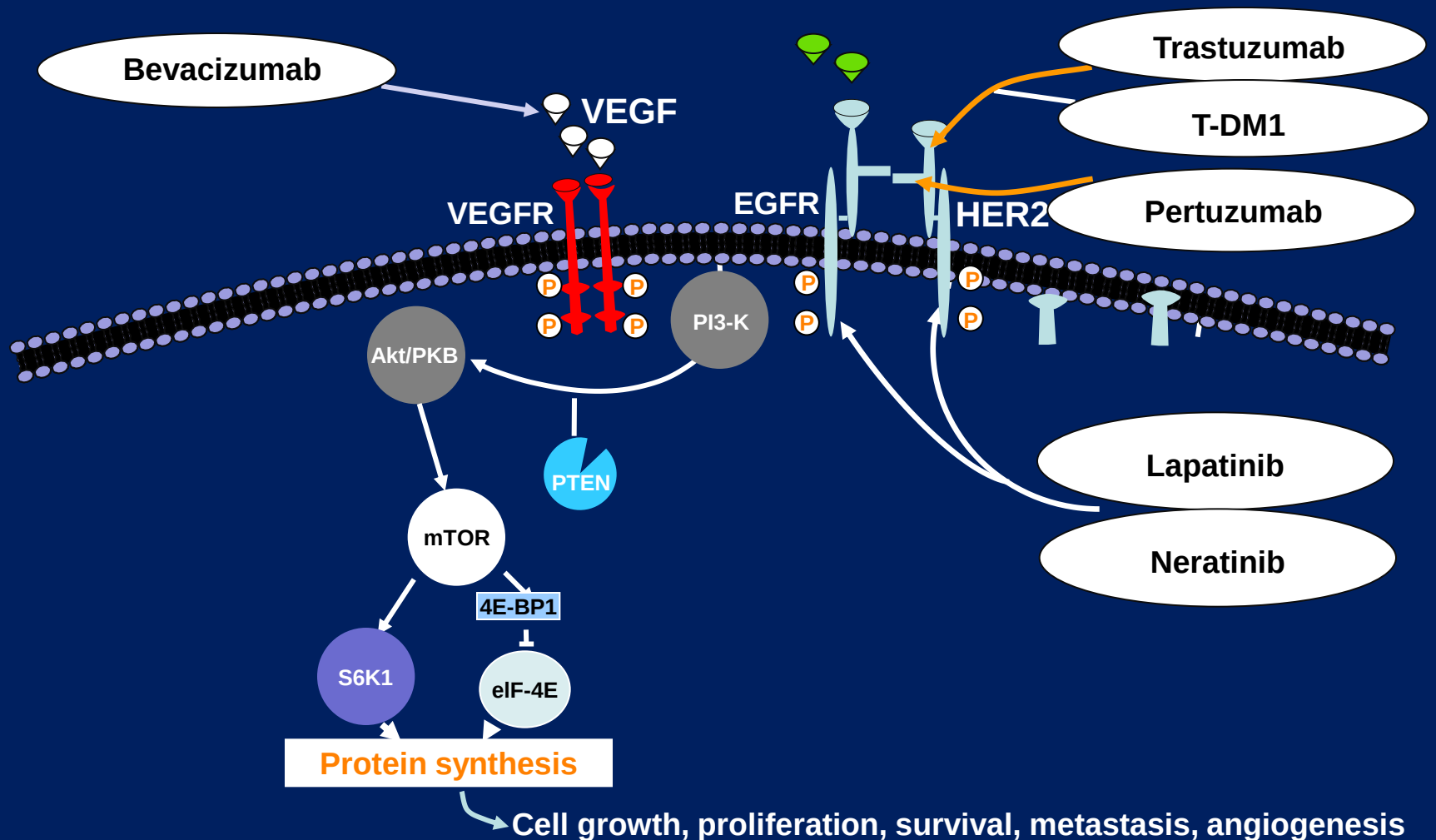
MEME KANSRİNDE HEDEFE YÖNELİK TEDAVİLERDE KOMPLİKASYONLAR

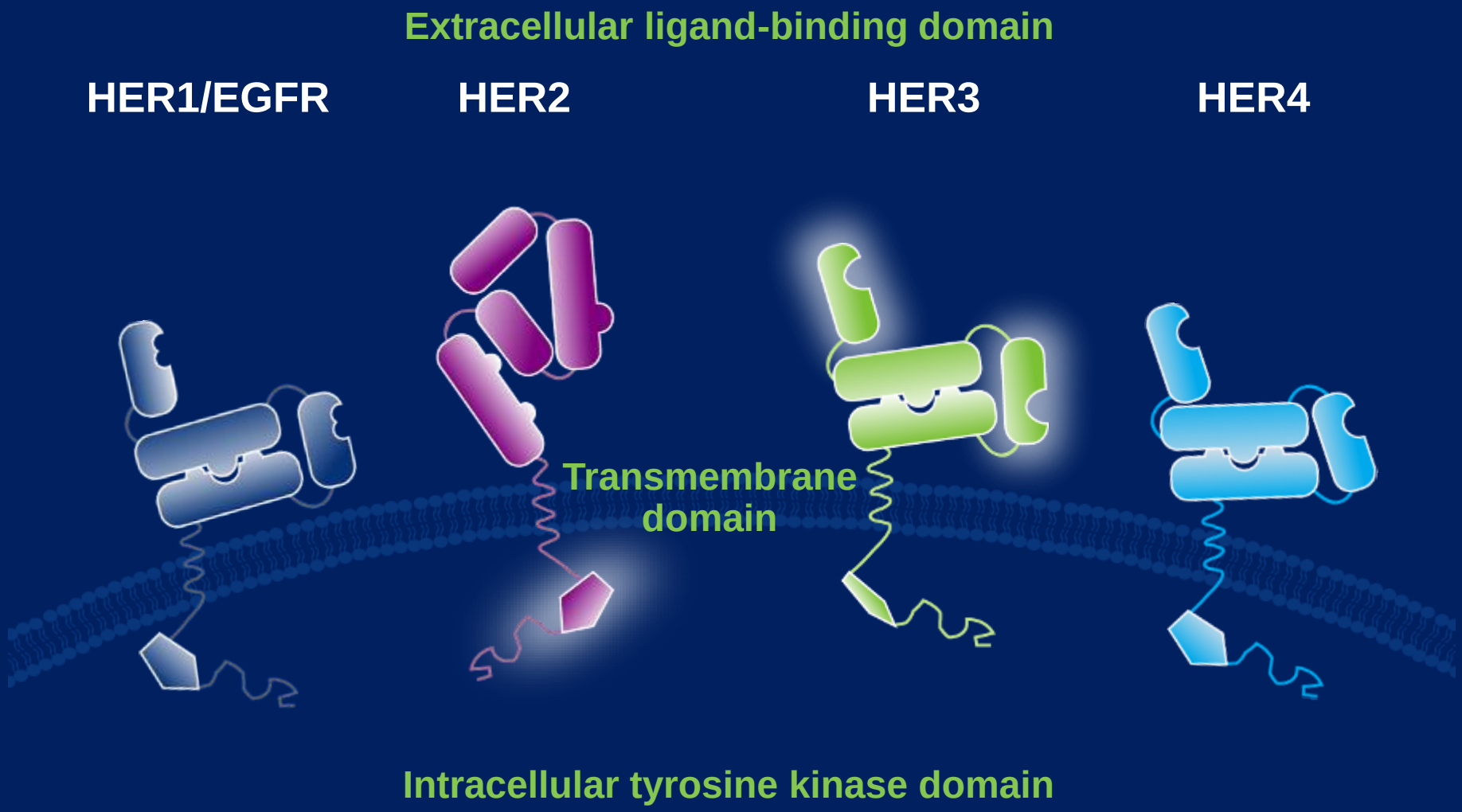
Prof. Dr. Uğur COŞKUN
Gazi Üniversitesi Tıp Fakültesi
Tıbbi Onkoloji ABD

HER2+ Meme Kanserinde Hedef Tedaviler



TRASTUZUMAB

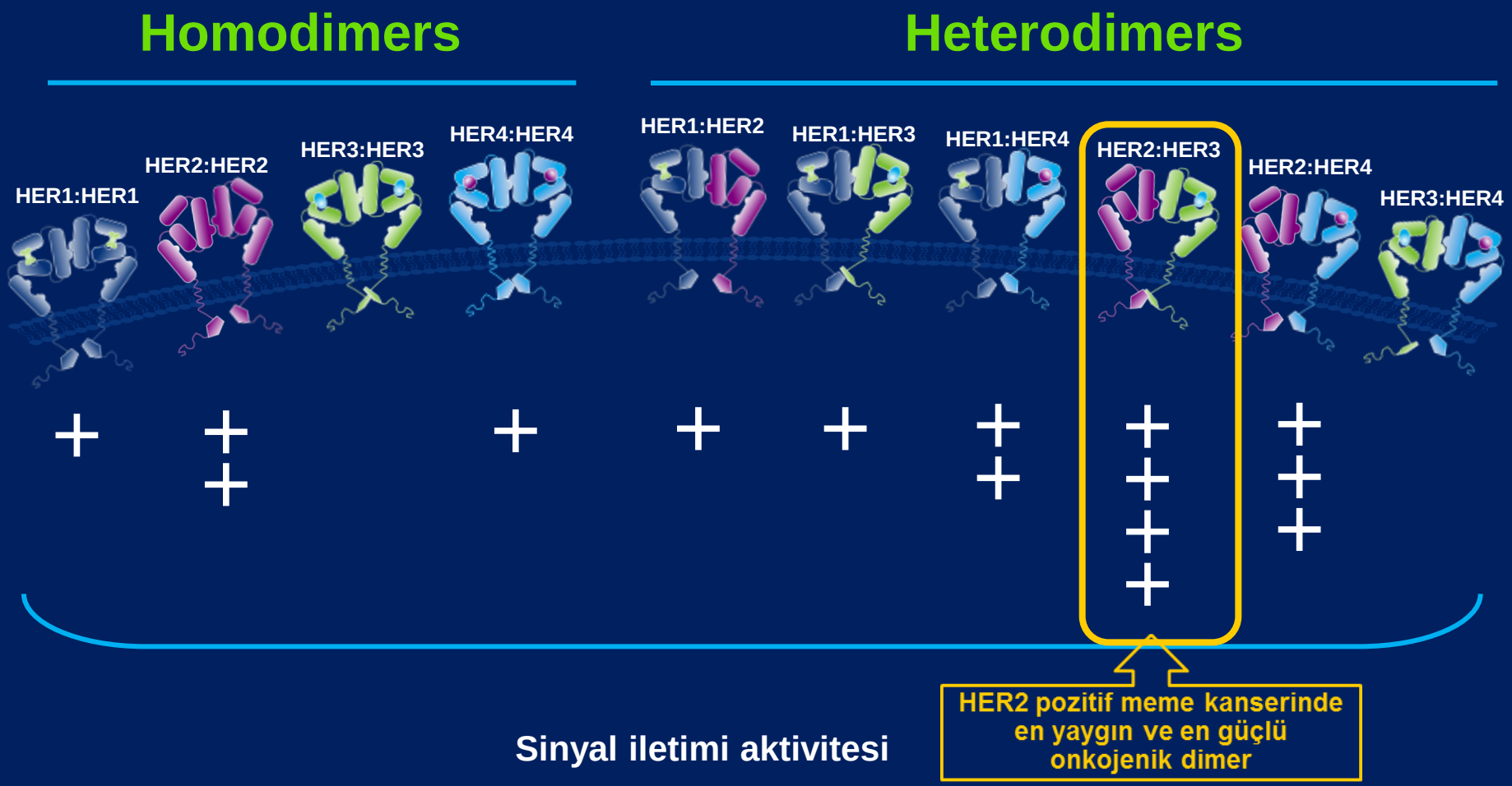
HER signaling: The network begins with the 4 HER receptors



HER=human epidermal growth factor receptor; EGFR=epidermal growth factor receptor.

Rowinsky EK. *Oncologist*. 2003;8:5-17. Yarden Y, Sliwkowski MX. *Nat Rev Mol Cell Biol.* 2001;2:127-137.

HER2 içeren dimerler hücre sağkalımı ve proliferasyonuna yol açan, güçlü mitojenik sinyal iletimini indükleyebilir



HER2 bu nedenle anti kanser tedavide akılcı bir hedeftir

Tzahar E., et al. *Mol Cell Biol*. 1996. Sergina NV, et al. *Nature*. 445:437-441.

Trastuzumab meme kanserinde sağkalımı arttırır

- **First demonstration of clinical benefit with HER2 targeting: the addition of trastuzumab to chemotherapy***

	Chemotherapy + Trastuzumab (n=236)	Chemotherapy Alone (n=234)	*P* value
Median time to disease progression	7.4 months	4.6 months	HR=0.51 *P*<.001
Median TTF	6.9 months	4.5 months	HR=0.58 *P*<.001
Median OS	25.1 months	20.3 months	HR=0.80 *P*=.046

*Either anthracycline + cyclophosphamide or paclitaxel

HR = hazard ratio; OS = overall survival; TTF= time to treatment failure

Slamon DJ, et al. *N Engl J Med*. 2001;344(11):783-792.

Medscape EDUCATION

8-Yr HERA Results, 1 Yr vs 2 Yrs of Trastuzumab: DFS

DFS, %	Trastuzumab for 1 Yr (n = 1552)	Trastuzumab for 2 Yrs (n = 1553)	HR (95% CI)	*P* Value
All patients			0.99 (0.85-1.14)	.86
▪ 3 yrs	86.7	89.1		
▪ 5 yrs	81.0	81.6		
▪ 8 yrs	76.0	75.8		
Hormone receptor–positive patients*			1.05 (0.85-1.29)	.67
▪ 3 yrs	89.6	90.3		
▪ 5 yrs	82.9	83.1		
▪ 8 yrs	77.2	76.1		
Hormone receptor–negative patients†			0.93 (0.76-1.14)	.51
▪ 3 yrs	83.8	87.8		
▪ 5 yrs	78.9	80.1		
▪ 8 yrs	74.7	75.4		

- No difference in OS between 1-yr and 2-yr trastuzumab arms through 8 yrs of median follow-up

Goldhirsch A, et al. SABCS 2012. Abstract S5-2.

8-Yr HERA Results: Survival

OS, %	Trastuzumab for 1 Yr (n = 1552)	Trastuzumab for 2 Yrs (n = 1553)	HR (95% CI)	*P* Value
All patients			1.05 (0.86-1.28)	.63
▪ 3 yrs	96.5	97.4		
▪ 5 yrs	91.4	92.6		
▪ 8 yrs	87.6	86.4		

- Benefits of 1-yr trastuzumab (52.1% of patients crossed over to receive trastuzumab beginning in 2005) vs observation proved durable through 8 yrs of median follow-up, with benefits seen in both hormone receptor–positive and hormone receptor–negative subpopulations
- Rates of grade 3/4 adverse events higher in trastuzumab arms compared with observation arm

Goldhirsch A, et al. SABCS 2012. Abstract S5-2.

TRASTUZUMAB - AKUT TOKSİSİTE

- İnfüzyon reaksiyonları
- Başağrısı
- Öksürük
- Myalji
- Ateş
- İnfeksiyon
- Myelosupresyon (kemoterapi ile birlikte
- Döküntü
- Nefrotik sendrom

KARDİYOTOKSİSİTE

Table 1. Anticancer therapy and cardiovascular toxicity [135–138] [a]

	Arrhythmia	Long QT	Myocardial ischemia	Thromboembolism	Systolic dysfunction	Hypertension
Anthracyclines (ANTHs)						
DOX	+++	NE	+	NE	+++	+
DOX (liposomal)	+	NE	++	NE	+	+
Epirubicin	+	NE	+	NE	+	+
Daunorubicin	++	NE	+	NE	+	+
Idarubicin	+++	NE	+	NE	++	+
Mitoxantrone	+++	NE	++	NE	++	++
Monoclonal antibody						
Trastuzumab (TRZ)	++	NE	+	++	+++	++
Bevacizumab	++	NE	++	+++	++	++
Cetuximab	++	NE	+	+	NE	++
Brentuzimab	+	NE	+	+	+	+
Ipilimumab	+	NE	+	+	NE	NE
Panitumumab	+	NE	++	++	NE	++
Pertuzumab	+	NE	+	+	++	+
Rituximab	+	NE	++	+++	+	++
Tyrosine kinase inhibitors						
Dasatinib	+++	++	++	++	++	++
Nilotinib	++	++	NE	+	++	+++
Vermurafenib	++	NE	++	++	+	++
Sorafenib	+	NE	++	++	++	+++
Sunitinib	+	+	++	++	+++	+++
Erlotinib	NE	NE	++	++	NE	NE
Gefitinib	NE	NE	++	++	NE	NE
Imatinib	NE	NE	+++	++	++	NE
Lapatinib	NE	+++	++	+	++	NE
Pazopanib	NE	NE	++	++	+	+++

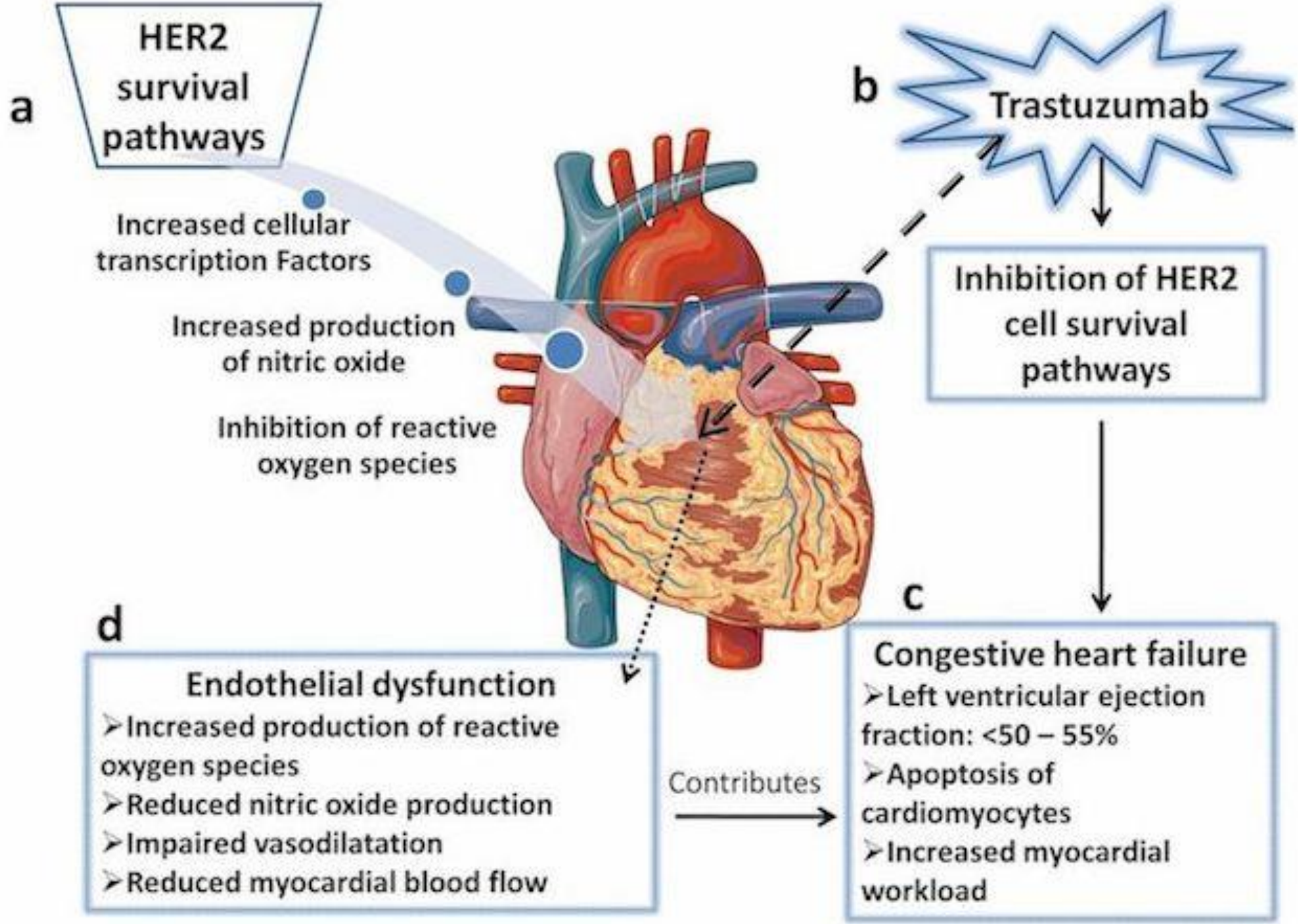

a
HER2 survival pathways
Increased cellular transcription Factors
Increased production of nitric oxide
Inhibition of reactive oxygen species
b
Trastuzumab
Inhibition of HER2 cell survival pathways
c
Congestive heart failure
➢Left ventricular ejection fraction: <50 – 55%
➢Apoptosis of cardiomyocytes
➢Increased myocardial workload
Contributes
d
Endothelial dysfunction
➢Increased production of reactive oxygen species
➢Reduced nitric oxide production
➢Impaired vasodilatation
➢Reduced myocardial blood flow

Table 2. Cardiotoxicity reported in control and trastuzumab arms of clinic trials.

Clinical trial	Reference	Control arm			Trastuzumab arm			
		N	Total cardiotoxicity	Symptomatic heart failure	*N*	Total cardiotoxicity	Symptomatic heart failure	Trastuzumab discontinued*
B31	Tan-Chiu *et al.* [2005]	814	13 (1.6%)	5 (0.6%)	850	74 (8.7%)	31 (3.6%)	133 (15.6%)
BCIRG006	Slamon *et al.* [2011], Verma *et al.* [2010]	1050	115 (10.9%)	7 (0.7%)	2124	298 (14.0%)	25 (1.2%)	NR
FinHer	Joensuu *et al.* [2006]	116	4 (3.4%)	2 (1.7%)	117	7 (6.0%)	1 (0.8%)	NR
HERA	Smith *et al.* [2007], Procter *et al.* [2010]	1698	12 (0.7%)	3 (0.2%)	1703	97 (5.7%)	46 (2.7%)	72 (4.2%)
N9831	Romond *et al.* [2005], Perez *et al.* [2008]	664	81 (12.2%)	3 (0.4%)	1280	230 (18.0%)	38 (3.0%)	218 (17.0%)
NOAH	Gianni *et al.* [2010]	118	19 (16.1%)	1 (0.8%)	117	26 (22.2%)	4 (3.4%)	NR
PACS-04	Spielmann *et al.* [2009]	268	38 (14.2%)	11 (4.1%)	260	92 (35.4%)	37 (14.2%)	41 (15.8%)

*Discontinued for cardiac-related reasons.
NR, not reported.

Table 3. Prevalence of trastuzumab-induced cardiotoxicity reported in community practice-based observational studies.

Reference	Country	Patients	Cardiotoxicity definition	Total cardiotoxicity*	Symptomatic heart failure	Trastuzumab discontinued
Bowles *et al.* [2012]	USA	554	Heart failure or cardiomyopathy defined by ICD9-based algorithm¶	63 (11.4%)	NR	NR
Tarantini *et al.* [2012]	Italy	499	LVEF decline >10% or to <50%	133 (26.6%)	16 (3.2%)	9 (1.8%)
Naumann *et al.* [2013]	UK	388	LVEF decline ≥10% to <50% or Reduction in NYHA cardiac function	61 (15.7%)	0 (0%)	NR
Piotrowski *et al.* [2012]	Poland	253	LVEF decline >15% or ≥10% to <50%	52 (20.5%)	6 (2.4%)	7 (2.8%)
Lemieux *et al.* [2013]	Canada	237	LVEF decline ≥10% to <50% or any decline to <45%	32 (13.5%)	16 (6.7%)	18 (7.6%)
Farolfi *et al.* [2013]	Italy	179	LVEF decline ≥ 15% or LVEF <50%	78 (43.6%)	4 (2.2%)	14 (7.8%)
Cochet *et al.* [2011]‖	France	118	LVEF decline ≥10%	18 (15.2%)	0 (0%)	3 (2.5%)
Tanz *et al.* [2011]	Morocco	53	LVEF measurements, NOS	11 (20.7%)	2 (3.8%)	9 (17%)
Onitilo *et al.* [2012b]	USA	49	LVEF decline ≥15% or to <50%	14 (28.6%)	0 (0%)	1 (2.0%)
Dent *et al.* [2012]‡	Canada	48	LVEF decline ≥ 10% or to <50%	NA	NA	7 (14.6%)
Serrano *et al.* [2012]§	Spain	45	LVEF decline ≥10% to <50% or >20%	12 (26.7%)	4 (8.9%)	3 (6.7%)

*Includes both symptomatic and asymptomatic cardiotoxicity.
‡Included only patients referred to cardiology department for concerns regarding treatment-related cardiotoxicity.
§Included only patients ≥ 60 years of age.

Table. Cumulative Incidence of CHF and/or Cardio -myopathy with Select Chemotherapeutic Agents

Cumulative Incidence (%)	Year After Treatment 1	2	3	4	5
Anthracycline	1.2	2.0	2.7	3.5	4.3
Trastuzumab	3.6	5.8	7.8	9.9	12.1
Anthracycline + Trastuzumab	6.2	9.8	13.2	16.5	20.1
Other agents	1.3	2.1	2.9	3.7	4.5
None	0.9	1.4	1.9	2.5	3.1

(Reproduced, with permission, from Journal of the National Cancer Institute 2012;104:1293-1305.)

Table 1: Risk Factors for Trastuzumab-Induced Cardiotoxicity

Strongly associated

- Old age
- Concurrent or prior exposure to anthracycline

Suspected

- Previous cardiac disease
- NYHA class II symptoms. (Slight, mild limitation of activity; patients are comfortable with rest or with mild exertion.)

NYHA = New York Heart Association. Based on information from References 8, 16, and 20.

8-Yr HERA Results: Cardiac Events

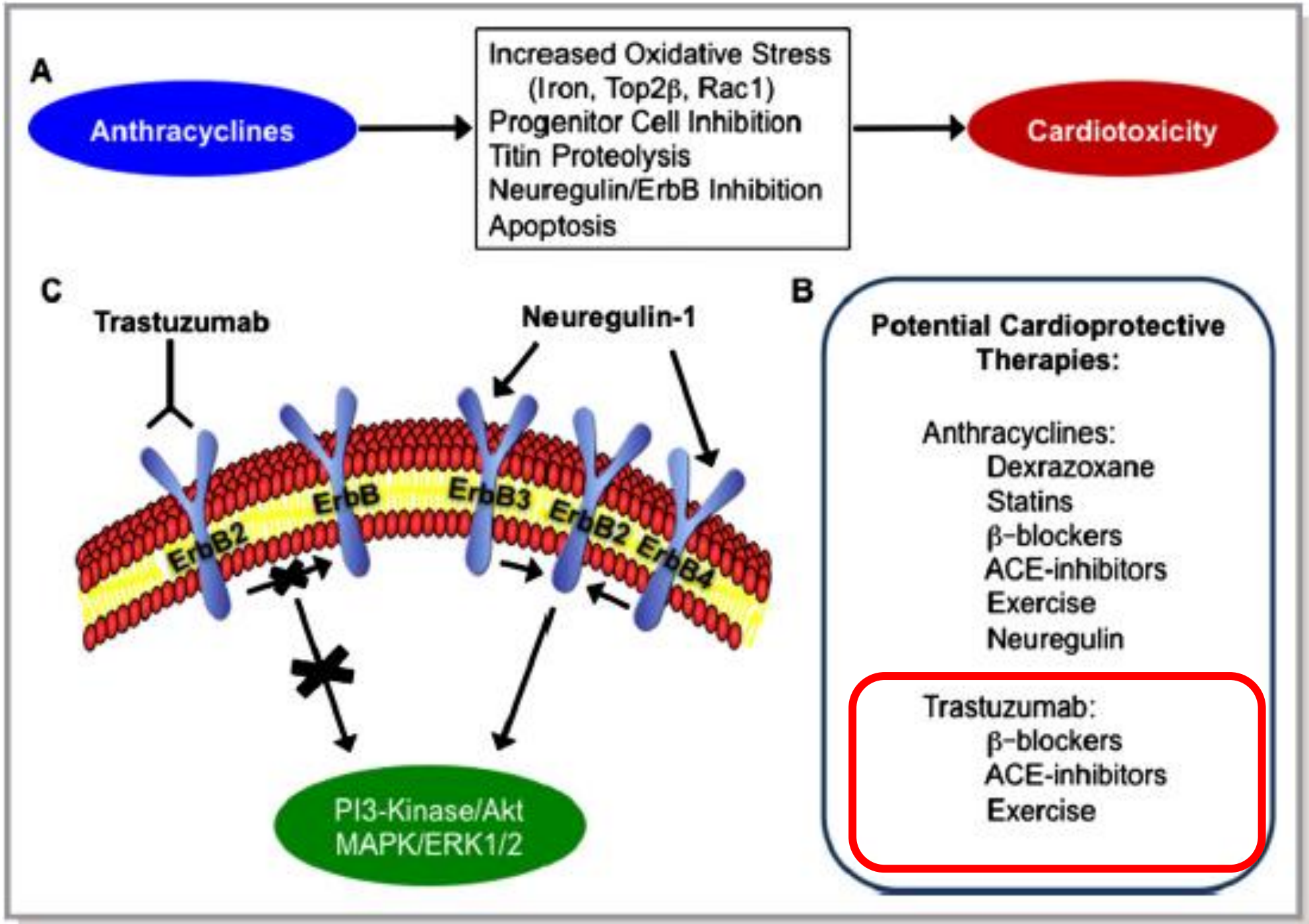
- Rates of grade 3/4 adverse events higher in trastuzumab arms compared with observation arm
- Rates of primary cardiac events comparable between 1-yr and 2-yr trastuzumab arms (0.8 and 1.0%, respectively), but rate of secondary cardiac events higher with 2 yrs vs 1 yr of trastuzumab (7.2% vs 4.1%, respectively)
  - Majority of cardiac events occurring during trastuzumab therapy reversible upon discontinuation

Goldhirsch A, et al. SABCS 2012. Abstract S5-2.

Anthracyclines, Trastuzumab and Cardiotoxicity

- Within 1 year of therapy
- Reflects progressive injury and loss of cardiac myocites
- Life-Threatening, related to cumulative doses, rapid onset and progression, may be resistant to treatment
- Treatment with anthracyclines should be stopped

- During trastuzumab therapy
- The pathophysiology of cardiac dysfunction is nor clear defined
- No dose related
- It is almost always responsive to medical management
- Treatment with trastuzumab may be continued


A
Anthracyclines
Increased Oxidative Stress
(Iron, Top2β, Rac1)
Progenitor Cell Inhibition
Titin Proteolysis
Neuregulin/ErbB Inhibition
Apoptosis
Cardiotoxicity
C
Trastuzumab
Neuregulin-1
ErbB2
ErbB
ErbB3
ErbB2
ErbB4
PI3-Kinase/Akt
MAPK/ERK1/2
B
Potential Cardioprotective Therapies:
Anthracyclines:
Dexrazoxane
Statins
β-blockers
ACE-inhibitors
Exercise
Neuregulin
Trastuzumab:
β-blockers
ACE-inhibitors
Exercise

Guidelines for stopping treatment in the event of reduced function based on Herceptin Adjuvant (HERA) trial protocol is as follows:

Asymptomatic patients			
LVEF	**Absolute decrease of <10%**	**Absolute decrease of 10–15%**	**Absolute decrease of ≥16%**
Within normal limits	Continue	Continue	Hold*
1–5% below normal limits	Continue	Hold*	Hold*
>6% below normal limits	Continue*	Hold*	Hold*

*Repeat LVEF assessment after four weeks. If criteria for continuation are met resume trastuzumab. If two consecutive 'holds' or total of three 'holds' occur, discontinue trastuzumab. **Key:** LVEF = left ventricular ejection fraction

Symptomatic patients

Patients who develop symptomatic cardiac dysfunction should have trastuzumab discontinued and be referred to a cardiologist

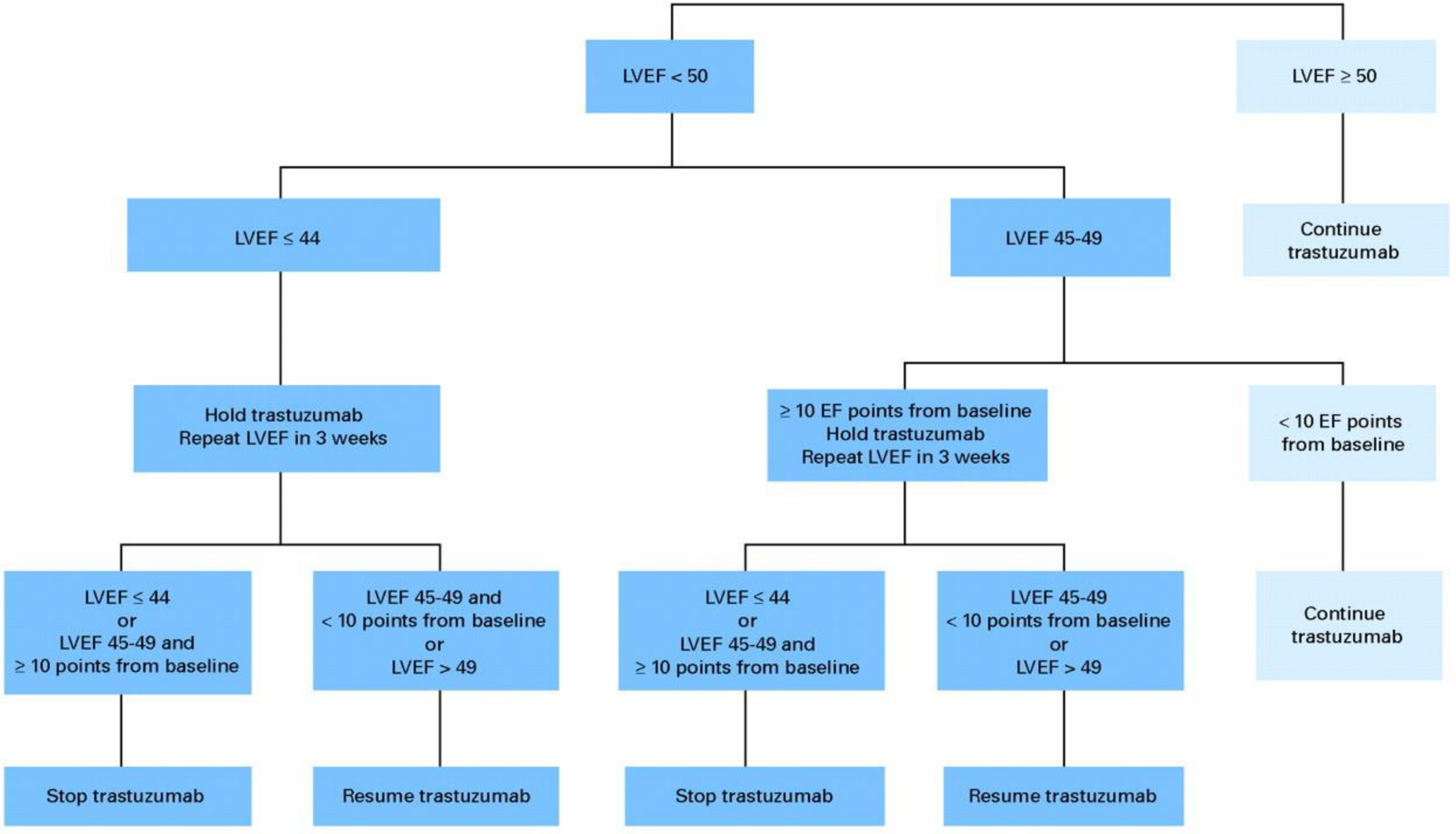
Table 6. Proposal for the evaluation and treatment of heart failure in patients undergoing treatment with trastuzumab.

Physical status	LVEF	Trastuzumab	Monitor LVEF	Therapeutic guidelines
Asymptomatic	>50%	Continue	Repeat in 4 weeks	
	↓ >10 points but normal	Continue	Repeat in 4 weeks	Consider ⊠B
	↓ 10-20 points and LVEF >40%	Continue	Repeat in 2-4 weeks	Treat CF
	↓>20 points or LVEF <30%	Suspend	If improved: surveillance	Treat CF
			If not improved/no change: stop	
			Repeat in 2 weeks	
			If improved (>45%): restart	
			If not improved/no change: stop	
Symptomatic	↓ <10 points	Continue		NC?
	↓ <10 points and LVEF >50%	Continue	Repeat in 2-4 weeks.	Anemia?
	↓ <30 points	Stop	If improved/no change:	Treat CF
			surveillance	Treat CF
			If not improved: stop	

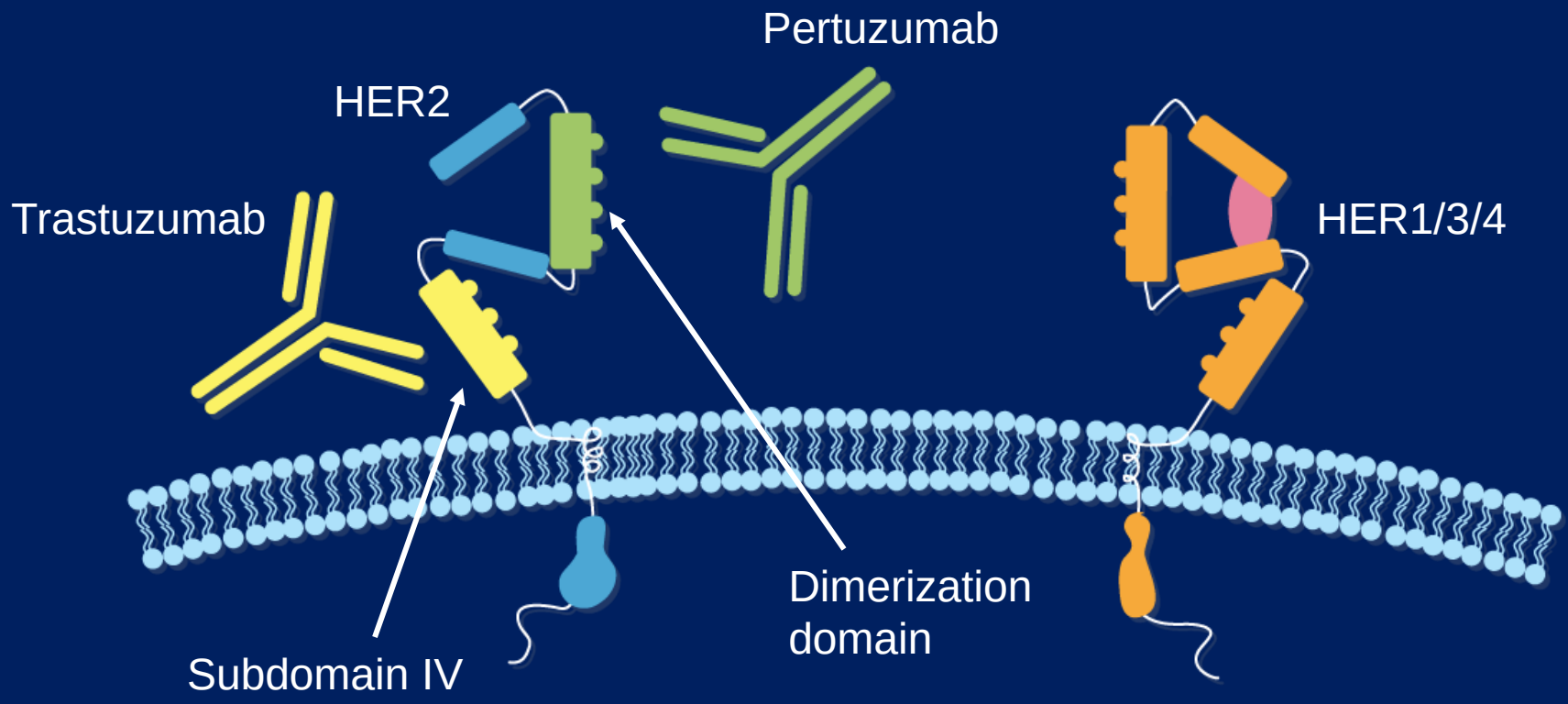
Adapted with permission from Keefe DL. Trastuzumab-associated cardiotoxicity. Cancer. 2002;95:1592-1600.
↓=decrease; ⊠B=beta-blockers; CF=cardiac failure; LVEF=le⊠ ventricular ejection fraction; NC=noncardiac pathology.

Table 7. Heart failure therapy in patients undergoing treatment with trastuzumab.

Diagnosis	Therapy	Details
Systolic dysfunction	ACE I/ARA-II	↓ LVEF
	Diuretics	↓ LVEF symptomatic
	Digoxin	↓ LVEF symptomatic
	Beta-blockers	↓ LVEF stable
	Aldosterone antagonists	↓ LVEF symptomatic and serious
Diastolic dysfunction	Diuretics	Symptomatic with normal LVEF
	Nitrates	
	Calcium antagonists	
	Beta-blockers	
	ACE I/ARA-II	


LVEF < 50
LVEF ≥ 50
LVEF ≤ 44
LVEF 45-49
Continue trastuzumab
Hold trastuzumab
Repeat LVEF in 3 weeks
≥ 10 EF points from baseline
Hold trastuzumab
Repeat LVEF in 3 weeks
< 10 EF points from baseline
LVEF ≤ 44
or
LVEF 45-49 and
≥ 10 points from baseline
LVEF 45-49 and
< 10 points from baseline
or
LVEF > 49
LVEF ≤ 44
or
LVEF 45-49 and
≥ 10 points from baseline
LVEF 45-49
< 10 points from baseline
or
LVEF > 49
Continue trastuzumab
Stop trastuzumab
Resume trastuzumab
Stop trastuzumab
Resume trastuzumab

PERTUZUMAB



Trastuzumab:

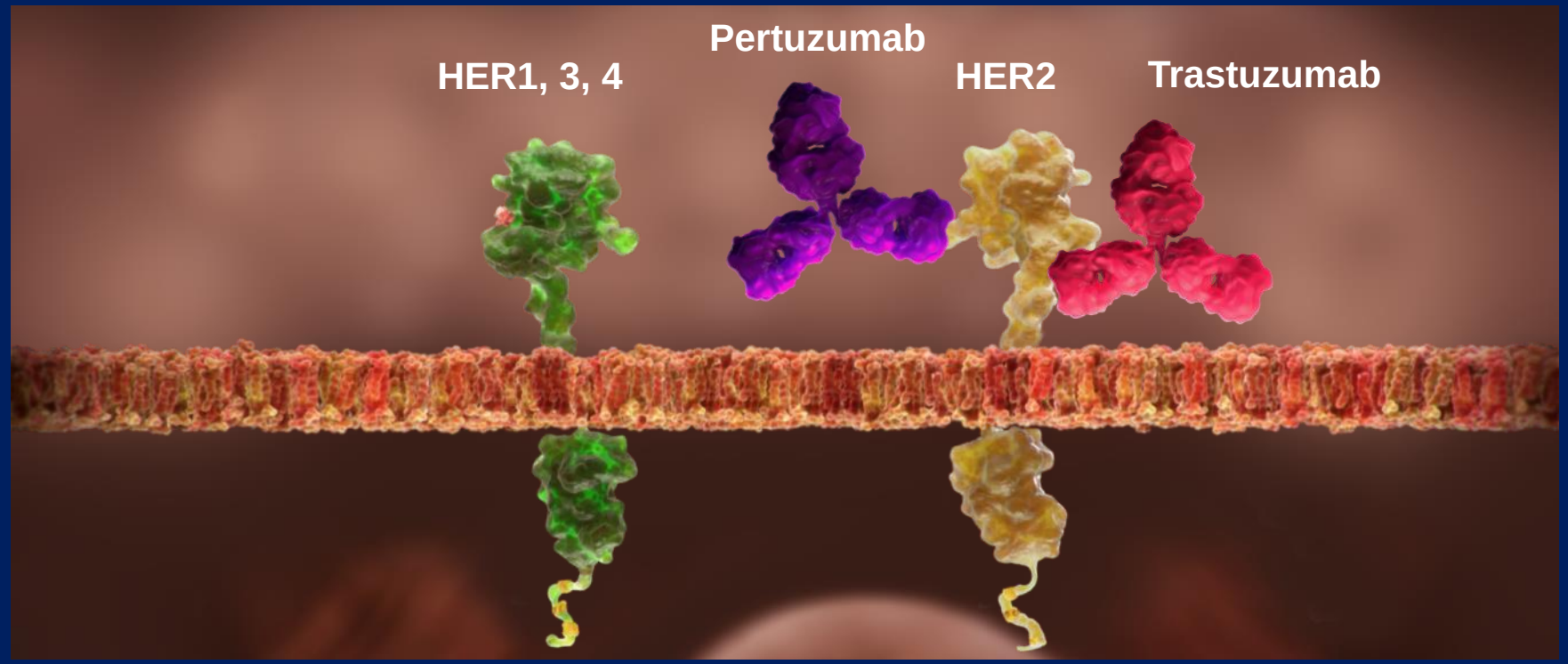
- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Pertuzumab:

- Inhibits ligand-dependent HER2 dimerization and signaling
- Activates ADCC

ADCC = antibody-dependent cell-mediated cytotoxicity; ECD = extracellular domain

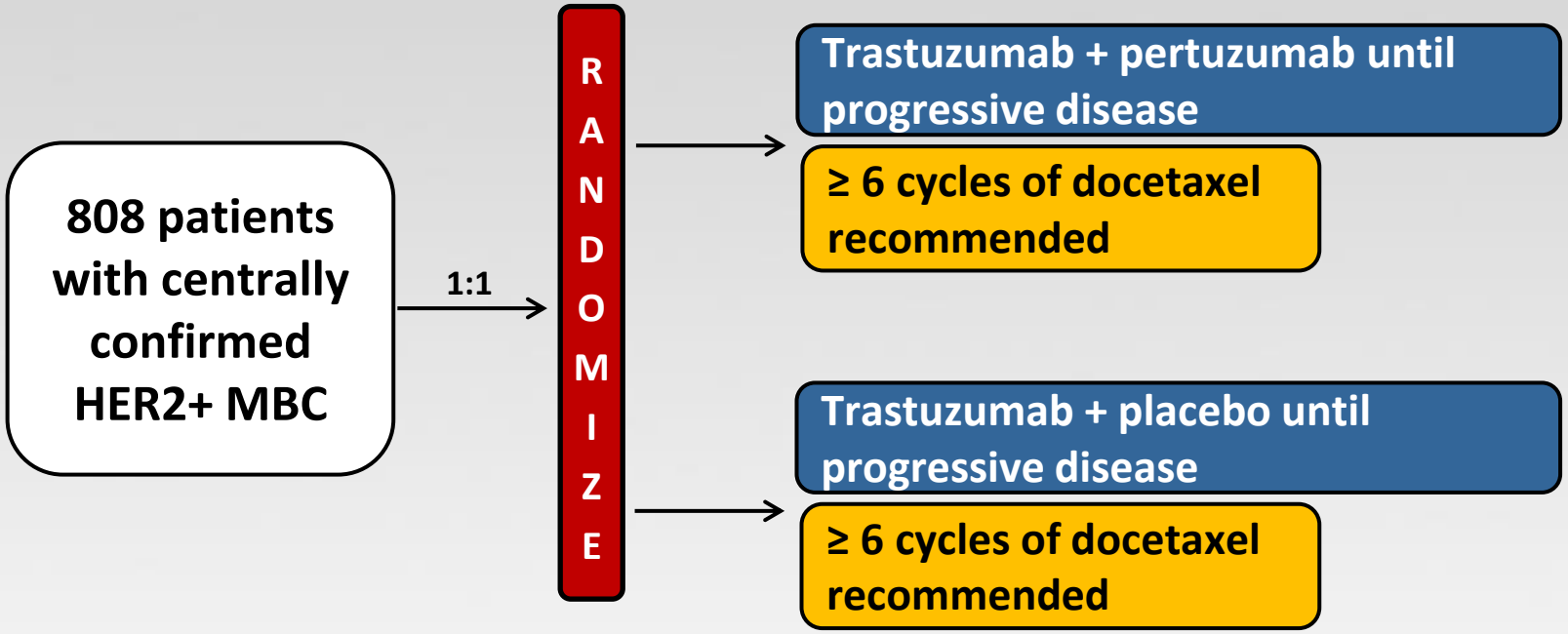
Pertuzumab ve trastuzumab (ya da T-DM1) HER2'de farklı alanlara bağlanır ve tamamlayıcı etki mekanizması gösterir



- Pertuzumab alt alan II'ye bağlanır ve liganda bağımlı sinyal iletimini inhibe eder[1]
- Trastuzumab alt alan IV'e bağlanır ve liganda bağımlı hücre içi sinyal iletimini inhibe eder
- **Pertuzumab–trastuzumab kombinasyonu daha kapsamlı HER2 blokajı sağlar[3,4]**
  - Pertuzumab–T-DM1 kombinasyonunda aynı etki mekanizması prensipleri geçerlidir[5]

1. Franklin MC, *et al. Cancer Cell* 2004; **5**:317–328; 2. Junttila TT, *et al. Cancer Cell* 2009; **15**:429–440; 3. Nahta R, *et al. Cancer Res* 2004; **64**:2343–2346; 4. Scheuer W, *et al. Cancer Re*
5. Fields C, *et al*. AACR 2010. Abstract 5607.

CLEOPATRA: Trastuzumab + Docetaxel + Pertuzumab or Placebo



Study dosing every 3 weeks

- **Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance**
- **Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance**
- **Docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated**

Medscape EDUCATION

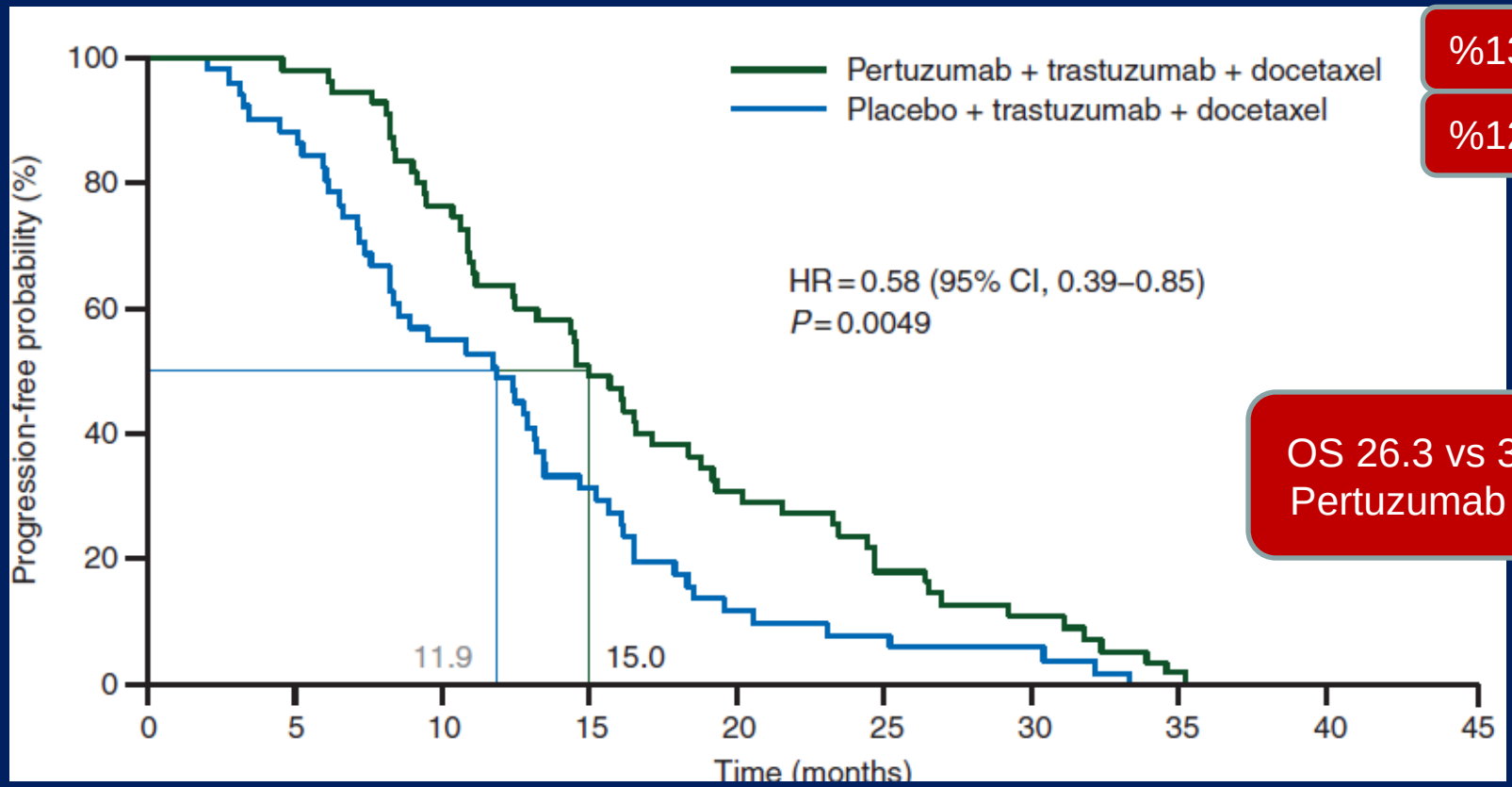
Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119.

original articles

Annals of Oncology 25: 1116–1121, 2014
doi:10.1093/annonc/mdu133
Published online 31 March 2014

Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA

S. M. Swain[1*], J. Baselga[2], D. Miles[3], Y.-H. Im[4], C. Quah[5], L. F. Lee[5] & J. Cortés[6]



%13.7

%12.6

OS 26.3 vs 34.4 ay
Pertuzumab lehine

CLEOPATRA: Updated Survival Results

	Pertuzumab + Trastuzumab + Docetaxel (n=402)	Placebo + Trastuzumab + Docetaxel (n=406)	*P* value
Median PFS	18.7 months	12.4 months	HR=0.68 *P*<.0001
	Improvement: 6.3 months		
Median OS	56.5 months	40.8 months	HR=0.68 *P*<.0002
	Improvement: 15.7 months		

PFS = progression-free survival

Swain SJ, et al. ESMO 2014. Abstract 350O_PR.

CLEOPATRA: Tedavi kollarında ≥%25 insidans ya da ≥%5 farkla ortaya çıkan advers olaylar (tüm gradlar)

Advers olay, n (%)	HT (n = 397)	PHT (n = 407)
Diyare	**184 (46.3)**	**272 (66.8)**
Alopesi	240 (60.5)	248 (60.9)
Nötropeni	197 (49.6)	215 (52.8)
Bulantı	165 (41.6)	172 (42.3)
Halsizlik	146 (36.8)	153 (37.6)
Döküntü	**96 (24.2)**	**137 (33.7)**
İştahta azalma	105 (26.4)	119 (29.2)
Mukoza inflamasyonu	**79 (19.9)**	**113 (27.8)**
Asteni	120 (30.2)	106 (26.0)
Periferik ödem	**119 (30.0)**	**94 (23.1)**
Konstipasyon	**99 (24.9)**	**61 (15.0)**
Febril nötropeni	**30 (7.6)**	**56 (13.8)**
Deride kuruluk	**17 (4.3)**	**43 (10.6)**

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

CLEOPATRA: Adverse Events

	Pertuzumab + Trastuzumab + Docetaxel (n=408)	Placebo + Trastuzumab + Docetaxel (n=396)
Grade 3/4 hematologic AEs		
Leukopenia	12.3%	14.9%
Neutropenia	49.0%	46.2%
Febrile neutropenia	13.7%	7.6%
Diarrhea (grade 3/4)	9.3%	5.1%
LVEF decline to < 50% and by ≥ 10% points from baseline	6.1%	7.4%

AE = adverse event; LVEF = left ventricular ejection fraction

Swain SJ, et al. ESMO 2014. Abstract 350O_PR.

LAPATİNİB

EGF104900: Trastuzumab + Lapatinib

- 296 patients previously treated with trastuzumab and a taxane randomly assigned (1:1) to lapatinib ± trastuzumab

	Lapatinib	Lapatinib + Trastuzumab	*P* value
Median PFS	8.1 weeks	11.1 weeks	HR=0.74 *P*=.011
Median OS	9.5 months	14.0 months	HR=0.74 *P*=.026
12-month survival rate	80%	56%	
24-month survival rate	70%	41%	

Blackwell K, et al. *J Clin Oncol.* 2012;30(21):2585-9252.

GEYER Çalışması

ErbB2+
Metastatik , veya lokal ileri meme kanseri

Daha önce antrasiklin, taksan ve trastuzumab* ile tedavi edilmiş

Daha önce kapesitabin kullanmamış

RECIST ile ölçülebilir hastalık

LVEF ≥ kurum LLN (normalin alt limiti)

*Trastuzumab metastatik hastalık için verilmişti.

RANDOMİZASYON

Hedef N=528

Lapatinib 1250 mg po 1x1 sürekli + Kapesitabin 2000 mg/m2/gün po 1.-14. gün, 3 haftada bir

Kapesitabin 2500 mg/m2/gün po 1-14. gün, 3 haftada bir

7-Geyer (EGF100151) C et al. *NEJM*. 2006;355:2733-2743.

YAN ETKİLER

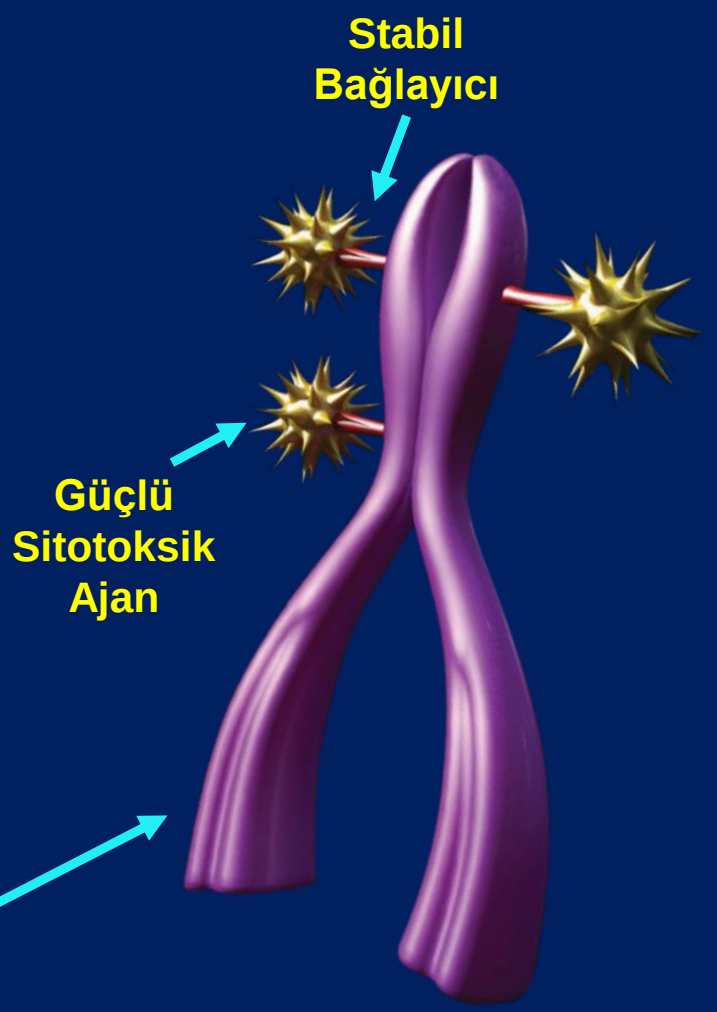
- Karaciğer fonksiyon bozukluğu
- Ciddi diyare
- Döküntü
- Hipokalemi
- Hipomagnezemi
- Uzamış QT riski
- Sıvı kaybı
- Interstisyel akciğer hastalığı veya pnömonitis

T-DM1

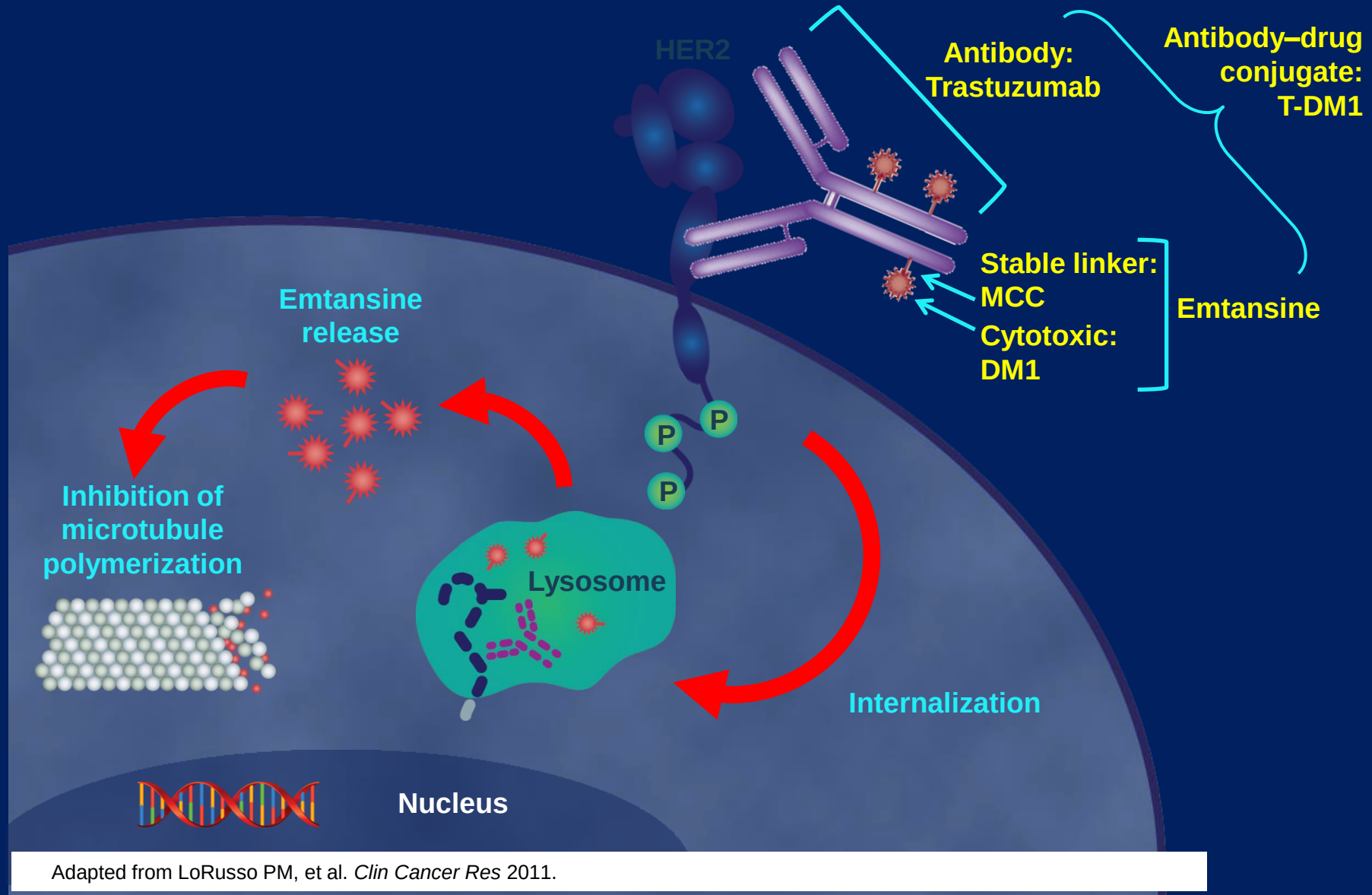
Trastuzumab emtansin

Antikor–İlaç Konjugatları (ADC)

- ADC'ler, kanser hücrelerini hedeflerken, normal doku üzerindeki etkileri minimum düzeye indirmek üzere tasarlanmaktadır
  - Sitotoksik ajan için terapötik pencerenin geliştirilmesi
- ADC, aşağıdakilerden oluşan benzersiz bir kombinasyondur:
  - Hedefe yönelik monoklonal antikor (mAb)
  - Stabil bir bağlayıcı
  - Güçlü bir sitotoksik ajan



Trastuzumab Emtansine (T-DM1): Mechanism of Action



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

TH3RESA: T-DM1 in Heavily Pretreated MBC

- 600 patients previously treated with ≥ 2 prior therapies (trastuzumab, lapatinib, taxane) randomly assigned (2:1) to T-DM1 or treatment of physician's choice*

	T-DM1	Physician's choice	*P* value
ORR	31.3%	8.6%	*P*<.0001
Median PFS	6.2 months	3.3 months	HR=0.528 *P*<.0001
Median OS (interim analysis)	NE	14.9 months	HR=0.552 *P*=.0034

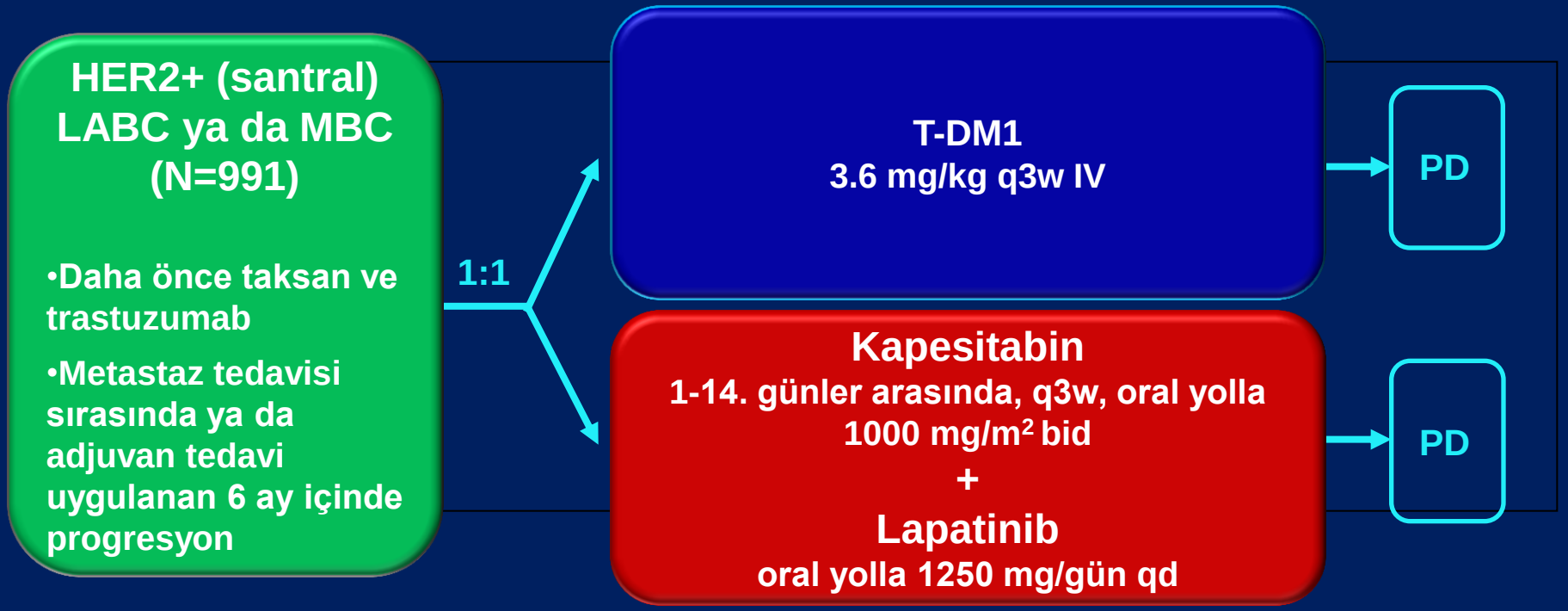
*Single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.

NE = not estimable

Medscape EDUCATION

Krop IE, et al. *Lancet Oncol.* 2014 ;15(7):689-699.

EMILIA Araştırmasının Tasarımı



- **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.

Advers Olayların Özeti

	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;
[a]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.

Hematolojik Olmayan Advers Olaylar

İnsidansı ≥%2 Olan Evre ≥3 Advers Olaylar

	Kap + Lap (n=488)		T-DM1 (n=490)	
Advers Olay	**Tüm Evreler, %**	**Evre ≥3, %**	**Tüm Evreler, %**	**Evre ≥3, %**
Diyare	79.7	**20.7**	23.3	1.6
El-ayak sendromu	58.0	**16.4**	1.2	0.0
Kusma	29.3	**4.5**	19.0	0.8
Hipokalemi	8.6	**4.1**	8.6	2.2
Yorgunluk	27.9	**3.5**	35.1	2.4
Bulantı	44.7	**2.5**	39.2	0.8
Mukoza enflamasyonu	19.1	**2.3**	6.7	0.2
AST artışı	9.4	0.8	22.4	**4.3**
ALT artışı	8.8	1.4	16.9	**2.9**

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

Hematolojik Advers Olaylar

	Kap + Lap (n=488)			T-DM1 (n=490)		
Advers Olay	**Tüm Evreler, %**	**Evre 3, %**	**Evre 4, %**	**Tüm Evreler, %**	**Evre 3, %**	**Evre 4, %**
Nötropeni	8.6	**3.5**	**0.8**	5.9	1.6	0.4
Febril nötropeni	1.0	**0.4**	**0.6**	0.0	0.0	0.0
Anemi	8.0	1.6	0.0	10.4	**2.7**	0.0
Trombositopeni	2.5	0.0	0.2	28.0	**10.4**	**2.4**

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

DİĞER AJANLAR

Trastuzumab/Paclitaxel ± Everolimus in HER2+ Advanced BC (BOLERO-1): Toxicity

Adverse Event, %	Everolimus/Trastuzumab/Paclitaxel (n = 472)			Placebo/Trastuzumab/Paclitaxel (n = 238)		
	Any*	Grade 3	Grade 4	Any	Grade 3	Grade 4
Stomatitis	67	13	0	32	1	0
Diarrhea	57	9	0	47	4	0
Alopecia	47	< 1	0	53	0	0
Rash	40	1	0	21	< 1	0
Cough	40	< 1	0	33	1	0
Pyrexia	39	2	0	27	1	0
Fatigue	35	5	0	36	3	0
Epistaxis	33	0	0	18	0	0
Peripheral edema	33	1	0	24	< 1	0
Nausea	33	1	0	35	1	0
Neutropenia	38	21	4	25	11	4
Anemia	31	9	1	16	3	0

Hurvitz S, et al. SABCS 2014. Abstract S6-01.

*3.6% of pts in everolimus arm died due to AEs (eg, pneumonitis, PE, respiratory failure, pneumonia).