HER-2 Pozitif Metastatik Meme Kanseri Tedavisinde Gelişmeler

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TTOD Sanal Kongresi, Pandemi Gölgesinde Geçen 2020 Yılında Ne değişti? 13-15 Kasım 2020

PLAN

- ✓ Son döneme kadar bilinenler
- ✓ Son dönemde öğrendiklerimiz

PLAN

- ✓ Son döneme kadar bilinenler
- ✓ Son dönemde öğrendiklerimiz

The Horizon of Precision Medicine in Breast Cancer: Fragmentation, Alliance, or Reunification?

Fabrice Andre, MD, PhD, Cecile Vicier, MD, and Suzette Delaloge, MD

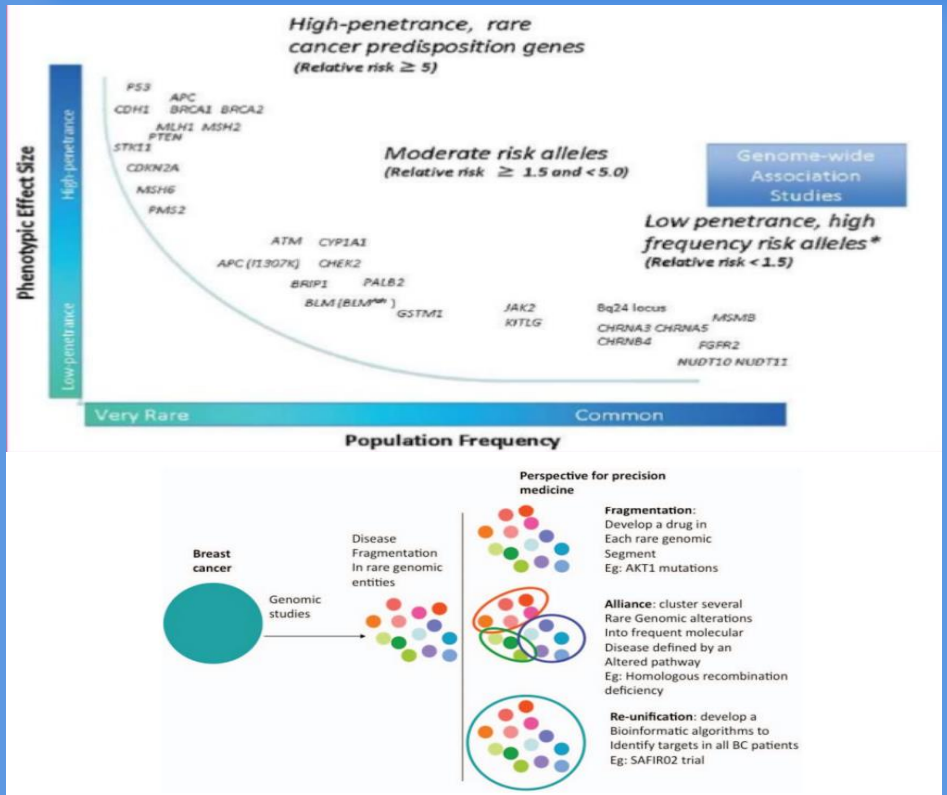


FIG 2. Fragmentation, alliance, or reunification: the three scenarios for precision medicine in metastatic breast cancers.

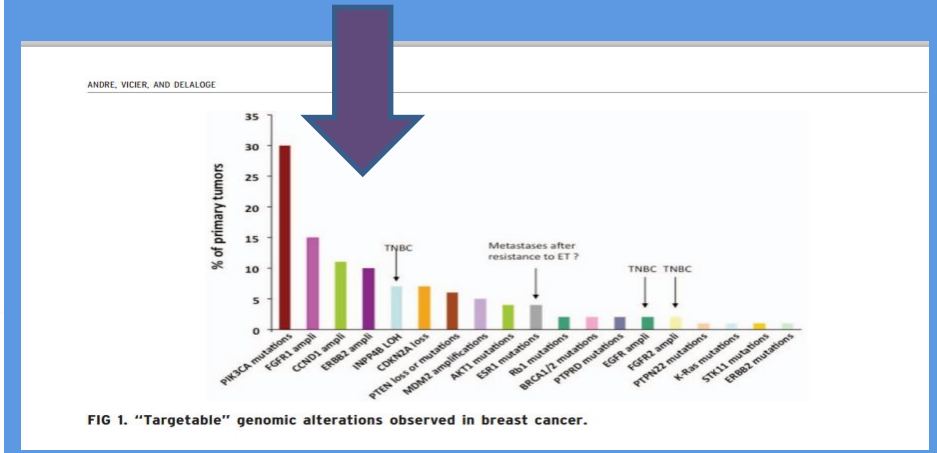
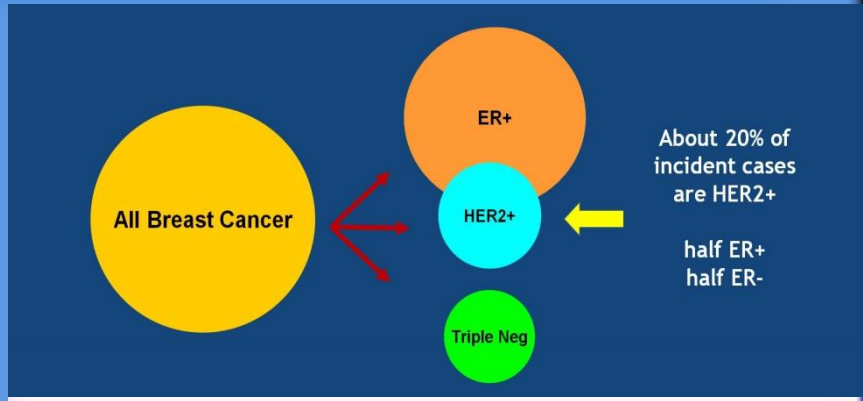
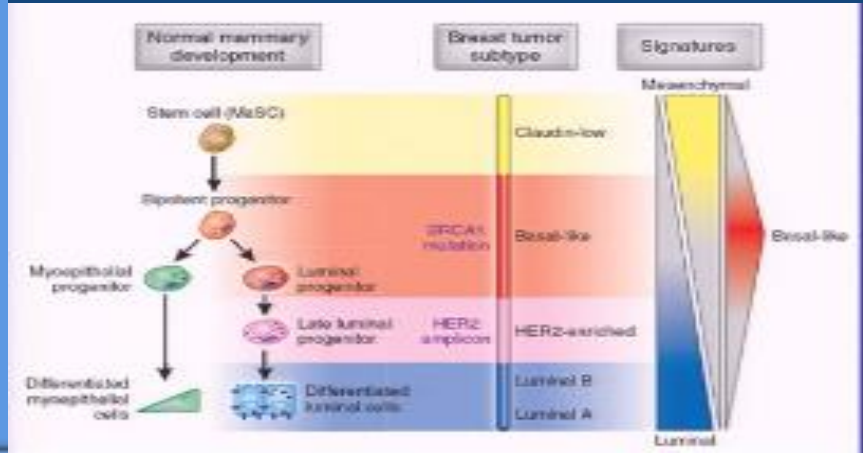


FIG 1. "Targetable" genomic alterations observed in breast cancer.

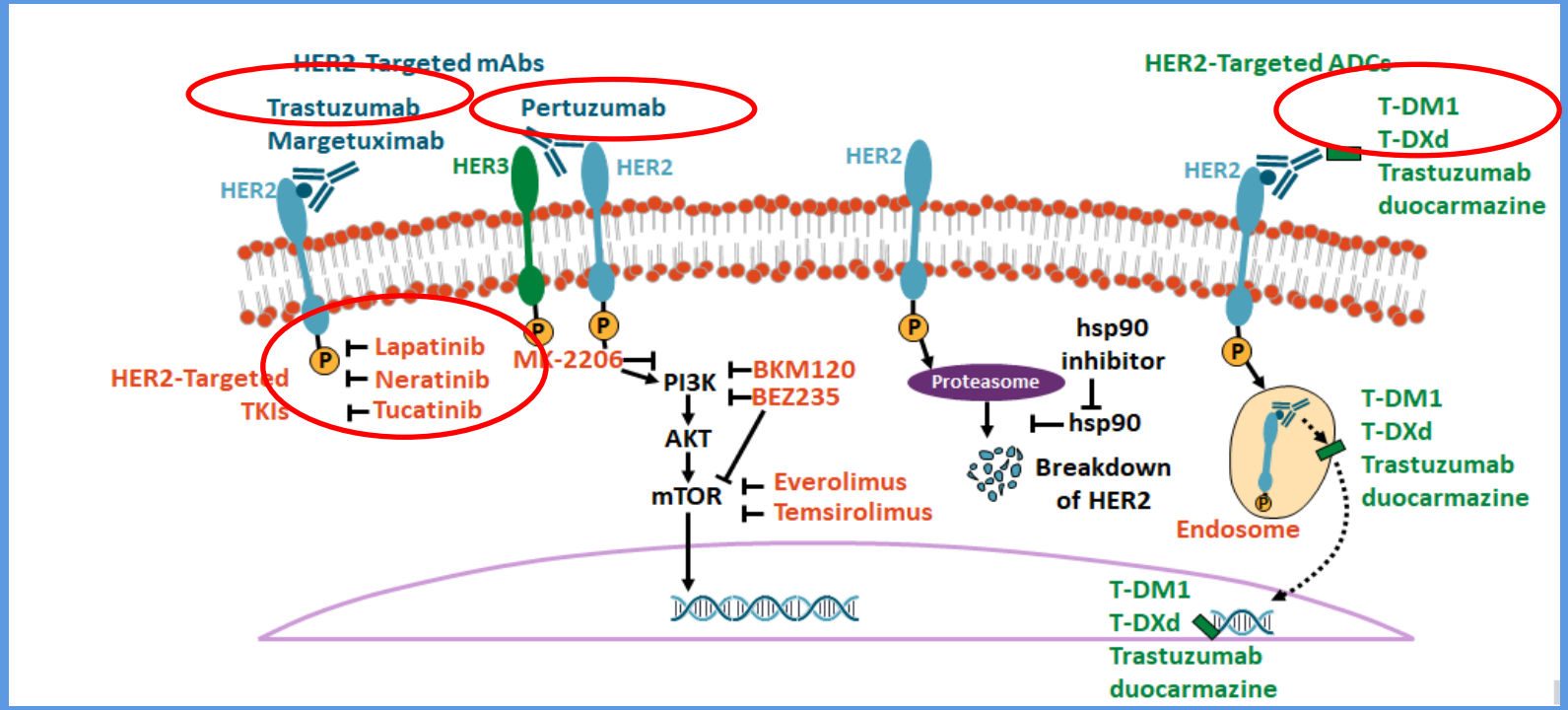
HER2+ hastalık

- ✓%20
- ✓Prognozu kötü
- ✓HER 2 + vs HER2 – meme Ca (n=1928)
  - ✓Daha sık LN met, daha büyük tm
  - ✓Grade 3, yüksek mitoz, lenfoid infiltrasyon, çoğu premenopozal
  - ✓Daha az hormon res +
- ✓Gen expresyon paterni:
  - ✓Bazal ve luminalden farklı

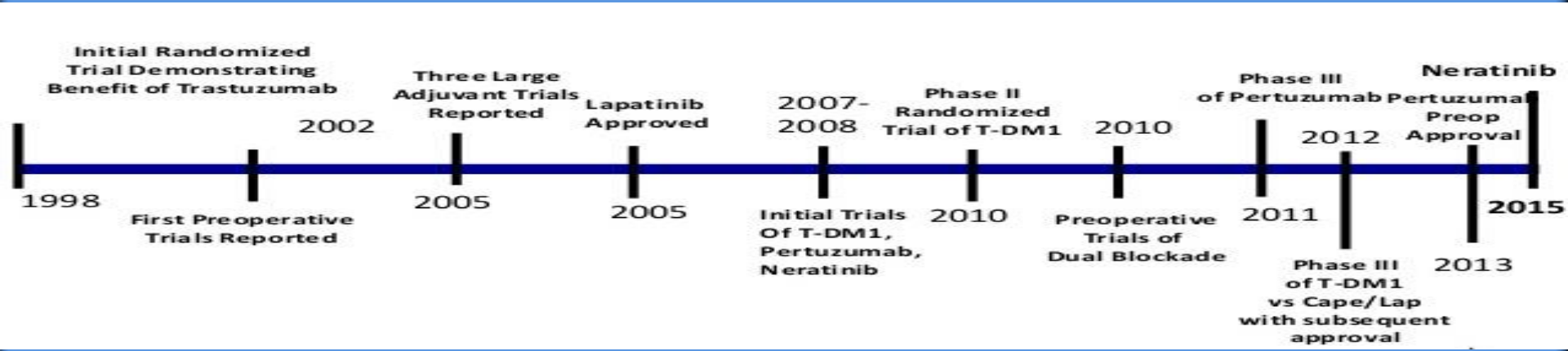


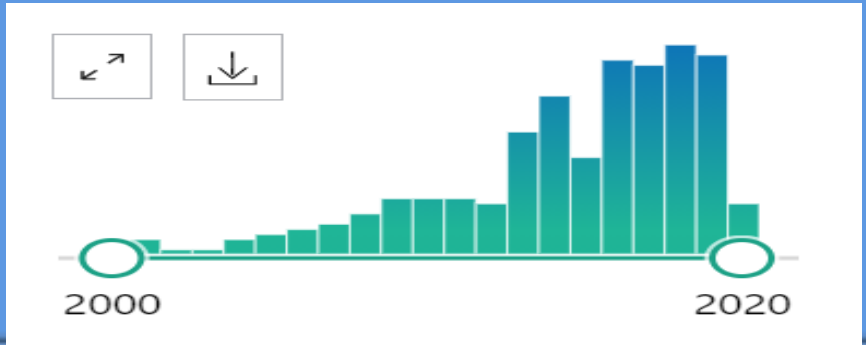


HER 2 Hedefli Tedaviler



Yıllar içerisinde Anti-HER2 tedaviler





HER 2 Hedefli Tedaviler

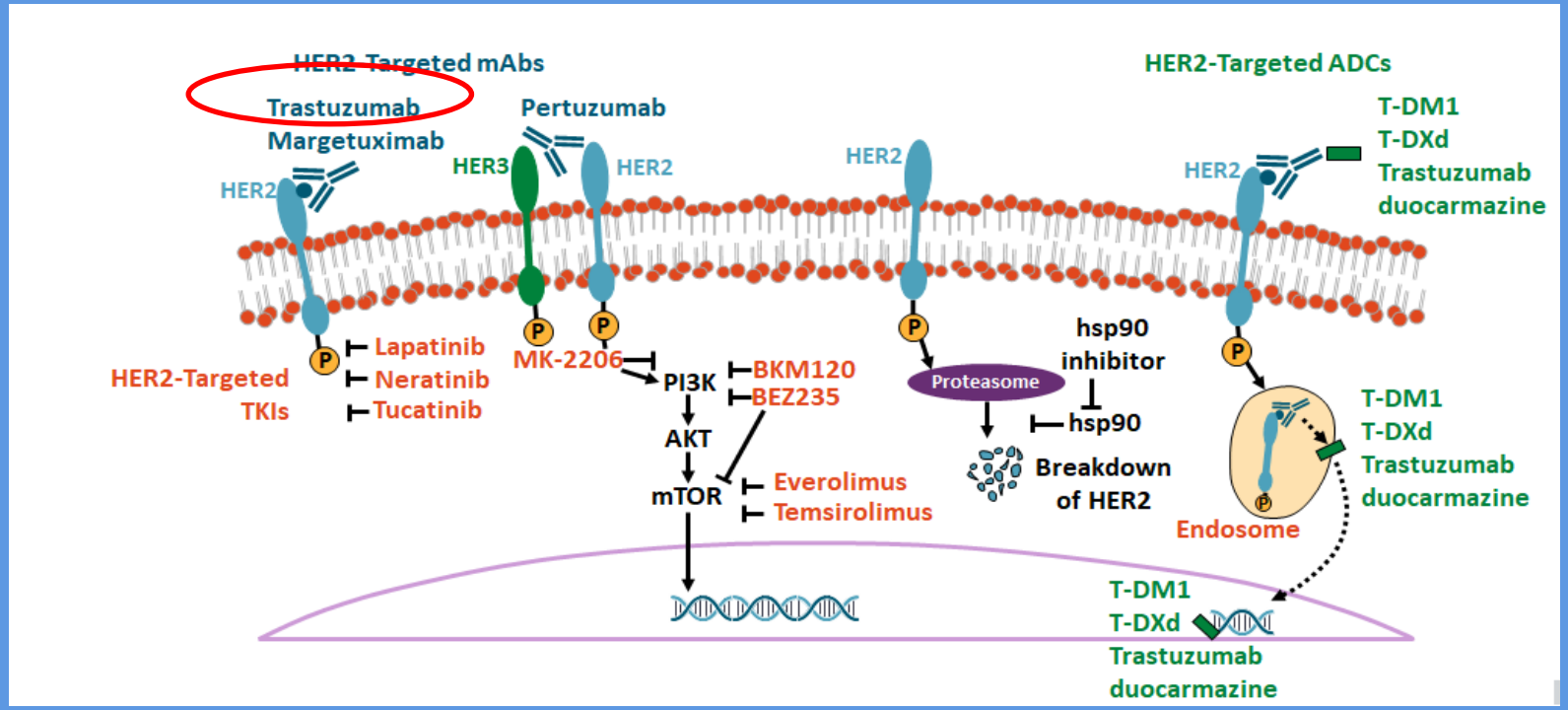


TABLE 1 First-line phase III trials incorporating anti-HER2 therapy and chemotherapy for HER2-p

Reference (study name)	Pts (n)	Treatment arms			
Slamon *et al.*, 2001[10]	469	Chemotherapy (various) with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly)			
		Chemotherapy (various)			
Robert *et al.*, 2006[11]	196	Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with paclitaxel 175 mg/m² and carboplatin AUC 6 every 3 weeks	[illegible] (p=0.03)	35.7 (p=0.76)	52 (p=0.04)
		Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with paclitaxel 175 mg/m² every 3 weeks	7.1	32.2	36
Burstein *et al.*, 2007[12]	81	Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with paclitaxel 80 mg/m² weekly OR docetaxel 35 mg/m² weekly for 7 weeks every 8 weeks	6.0 (p=0.09)	NR	58
		Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with vinorelbine 25 mg/m² weekly	8.5	NR	66
Andersson *et al.*, 2011[13] (HERNATA)	284	Trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), with docetaxel 100 mg/m² every 3 weeks	12.4 (p=0.67)	35.7 (p=0.98)	59 (p=1.00)
		Trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), with vinorelbine 30–35 mg/m² days 1 and 8 every 3 weeks	15.3	38.8	59
Valero *et al.*, 2011[14] (BCIRG 007)	263	Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with docetaxel 75 mg/m² and carboplatin AUC 6 every 3 weeks	10.4 (p=0.57)	37.4 (p=0.99)	72 (p=0.97)
		Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with docetaxel 100 mg/m² every 3 weeks	10.4	37.1	72
Gelmon *et al.*, 2012[15] (NCIC MA.31)	652	Paclitaxel 80 mg/m² weekly OR docetaxel 75 mg/m² every 3 weeks, with lapatinib 1500 mg daily	8.8 (p=0.01)	NR	NR
		Paclitaxel 80 mg/m² weekly OR docetaxel 75 mg/m² every 3 weeks, with trastuzumab 2 mg/kg weekly OR trastuzumab 6 mg/kg every 3 weeks with chemotherapy, then 6 mg/kg every 3 weeks	11.4	NR	NR
Guan *et al.*, 2013[16]	444	Paclitaxel 80 mg/m² weekly for 3 weeks every 4 weeks, with lapatinib 1500 mg daily	9.7 (p<0.001)	27.8 (p=0.012)	69 (p<0.001)
		Paclitaxel 80 mg/m² weekly for 3 weeks every 4 weeks, with placebo daily	6.5	20.5	50
Baselga *et al.*, 2012[5] and Swain *et al.*, 2014[17] (CLEOPATRA)	808	Docetaxel 75–100 mg/m² every 3 weeks, with trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), and pertuzumab 840 mg loading dose, then 420 mg every 3 weeks	18.5 (p<0.001)	56.5 (p<0.001)	80 (p=0.001)
		Docetaxel 75–100 mg/m² every 3 weeks, with trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), and placebo every 3 weeks	12.4	40.8	69

HER2 = human epidermal growth factor receptor 2; Pts = patients; TTP = time to progression; PFS = progression-free survival; OS = overall survival; BCIRG = Breast Cancer International Research Group; NR = not reported; NCIC = National Cancer Institute of Canada.

Taksanlara trastuzumab eklenmesi ORR, PFS ve OS artışı sağlar

TABLE 1 First-line phase III trials incorporating anti-HER2 therapy and chem

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Burstein *et al.*, 2007[12]	81	Trastuzumab (4 mg/kg loading dose, then 2 mg/kg with paclitaxel 80 mg/m² weekly OR docetaxel 35 mg/m² for 7 weeks every 8 weeks		(p=0.09)	
		Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with vinorelbine 25 mg/m² weekly	8.5	NR	66
Andersson *et al.*, 2011[13] (HERNATA)	284	Trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), with docetaxel 100 mg/m² every 3 weeks	12.4 (p=0.67)	35.7 (p=0.98)	59 (p=1.00)
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Baselga *et al.*, 2012[5] and Swain *et al.*, 2014[17] (CLEOPATRA)	808	Docetaxel 75–100 mg/m² every 3 weeks, with trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), and pertuzumab 840 mg loading dose, then 420 mg every 3 weeks	18.5 (p<0.001)	56.5 (p<0.001)	80 (p=0.001)
		Docetaxel 75–100 mg/m² every 3 weeks, with trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), and placebo every 3 weeks	12.4	40.8	69

HER2 = human epidermal growth factor receptor 2; Pts = patients; TTP = time to progression; PFS = progression-free survival; OS = overall survival; BCIRG = Breast Cancer International Research Group; NR = not reported; NCIC = National Cancer Institute of Canada.

- ✓ 2'li KT + trastuzumab kullanımı ORR ve PFS katkısı sağlar
- ✓ OS katkısı sağlamaz
- ✓ Bu katkı dosetaxel e karboplatin eklenmesiyle elde edilemedi

TABLE I First-line phase III trials incorporating anti-HER2 therapy and chemotherapy for HER2-positive metastatic breast cancer

Reference (study name)	*Pts (n)*	*Treatment arms*	*Median*		*Response rate (%)*
			TTP or PFS (months)	*OS (months)*	
Slamon *et al.*, 2001[10]	469	Chemotherapy (various) with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly)	7.4 ($p<0.001$)	50 ($p<0.001$)	25.1 ($p=0.046$)
		Chemotherapy (various)	4.6	20.3	32
Robert *et al.*, 2006[11]	196	Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with paclitaxel 175 mg/m^2 and carboplatin AUC 6 every 3 weeks			
		Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with paclitaxel 175 mg/m^2 every 3 weeks			
Burstein *et al.*, 2007[12]	81	Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with paclitaxel 80 mg/m^2 weekly OR docetaxel 35 mg/m^2 weekly for 7 weeks every 8 weeks			
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HER2 = human epidermal growth factor receptor 2; Pts = patients; TTP = time to progression; PFS = progression-free survival; OS = overall survival; BCIRG = Breast Cancer International Research Group; NR = not reported; NCIC = National Cancer Institute of Canada.

Trastuzumab+ Vinorelbin sonuçları Trastuzumab + taxan sonuçlarıyla benzer.

Trastuzumab + Endokrin Tedavi

TABLE II First-line phase III trials incorporating anti-HER2 therapy and endocrine therapy for metastatic hormone receptor–positive, HER2-positive breast cancer

Reference (study name)	*Pts (n)*	*Treatment arms*	*Median*		*Response*
Johnston *et al.*, 2009[18] (EGF30008)	263	Letrozole 2.5 mg with lapatinib 1500 mg daily			
		Letrozole 2.5 mg with placebo daily			
Kaufman *et al.*, 2009[19] (TANDEM)	207	Anastrozole 1 mg daily, with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly)	4.8 (p=0.002)	28.5 (p=0.325)	21 (p=0.018)
		Anastrozole 1 mg daily	2.4	23.9	7
Huober *et al.*, 2012[20] (ELECTRA)	92	Letrozole 2.5 mg daily, with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly)	14.1 (p=0.23)	NR	27 (p=0.002)
		Letrozole 2.5 mg daily	3.3	NR	13

HER2 = human epidermal growth factor receptor 2; Pts = patients; TTP = time to progression; PFS = progression-free survival; OS = overall survival; NR = not reported.

Hormonal tedaviye Trastuzumab eklenmesi ORR ve PFS katkısı sağlar

Trastuzumab Direnci

Trastuzumab Progresyon Sonrası Kullanım

1. Seri trastuzumab sonrası kapesitabine trastuzumab eklenmesi ORR ve PFS katkısı sunar

VOLUME 27 · NUMBER 12 · APRIL 20 2009

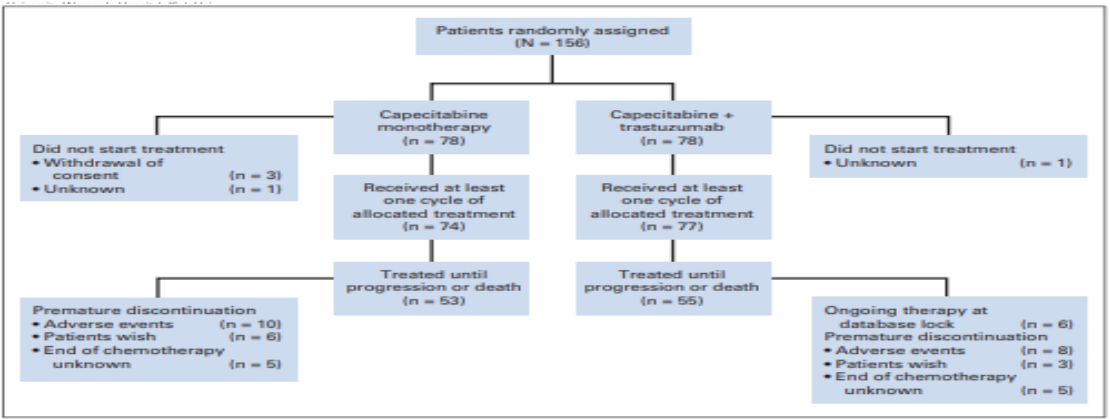
JOURNAL OF CLINICAL ONCOLOGY

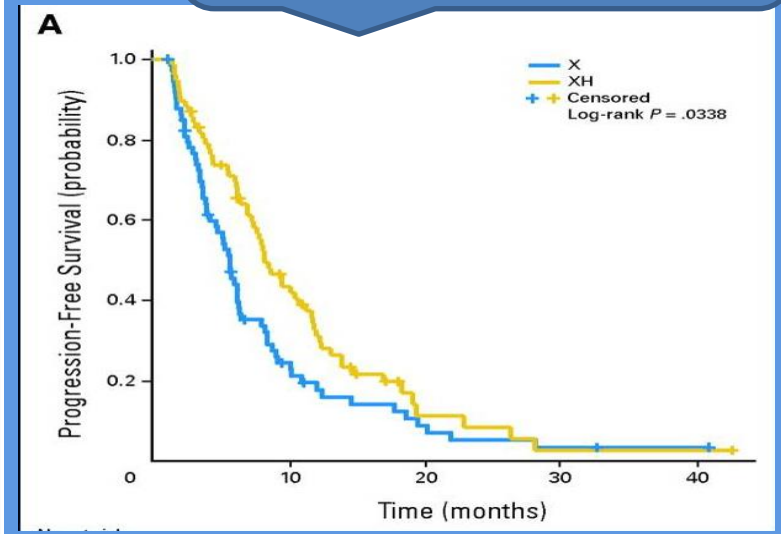
ORIGINAL REPORT

Trastuzumab Beyond Progression in Human Epidermal Growth Factor Receptor 2–Positive Advanced Breast Cancer: A German Breast Group 26/Breast International Group 03-05 Study

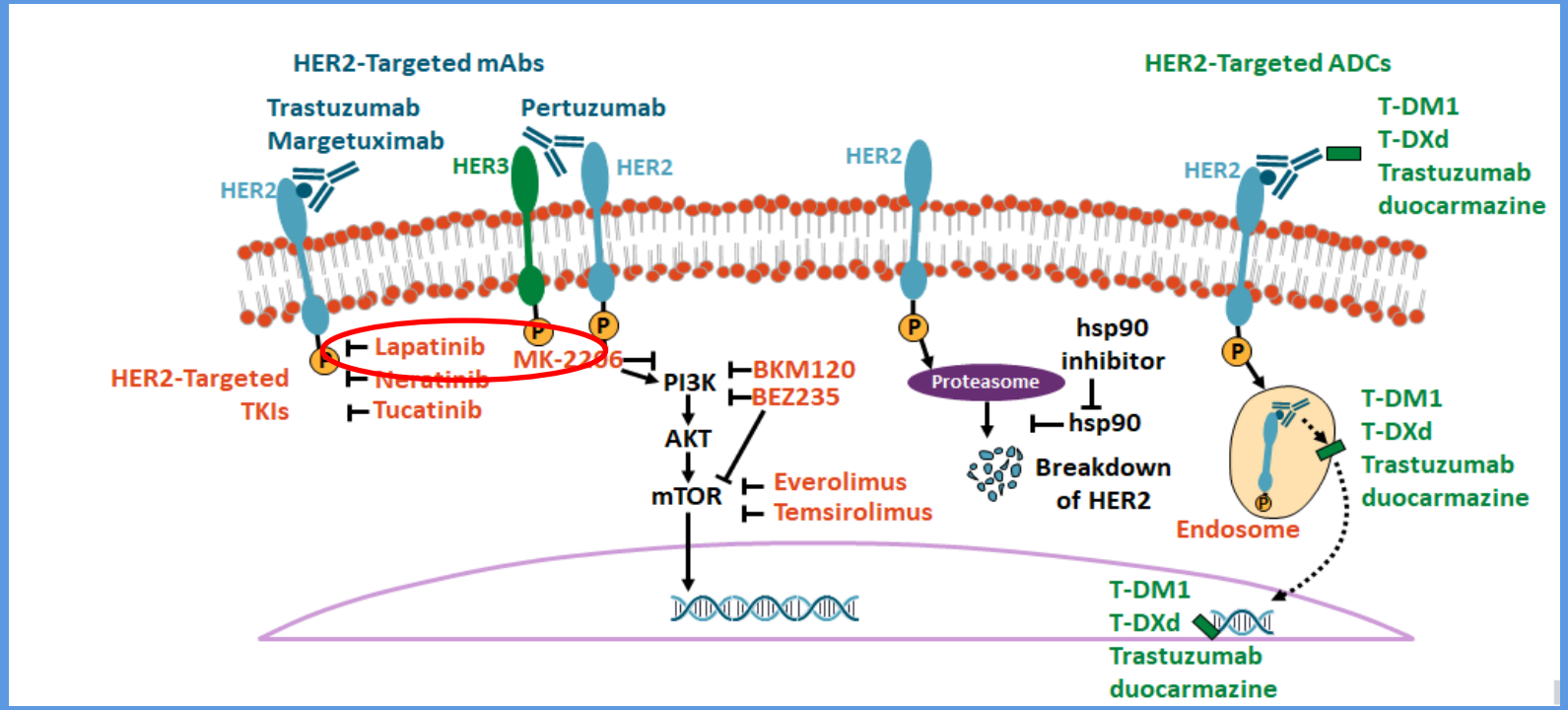
Gunter von Minckwitz, Andreas du Bois, Marcus Schmidt, Nicolai Maass, Tanja Cufer, Felix E. de Jongh, Eduard Maartense, Christoph Zielinski, Manfred Kaufmann, Wolfgang Bauer, Klaus H. Baumann, Michael R. Clemens, Ralph Duerr, Christoph Uleer, Michael Andersson, Robert C. Stein, Valentina Nekljudova, and Sibylle Loibl

From the GBG Forschungs GmbH, Neu-Isenburg; Dr.-Horst-Schmidt-Kliniken, Breast Unit, Wiesbaden; University Women's Hospital, Mainz;





HER 2 Hedefli Tedaviler



Lapatinib 2. basamak tedavi

1. Seri trastuzumab sonrası kapesitabine Lapatinib eklenmesi ORR ve PFS katkısı sunar

EGF100151 Phase III Study: Lapatinib + Capecitabine in Advanced Breast Cancer

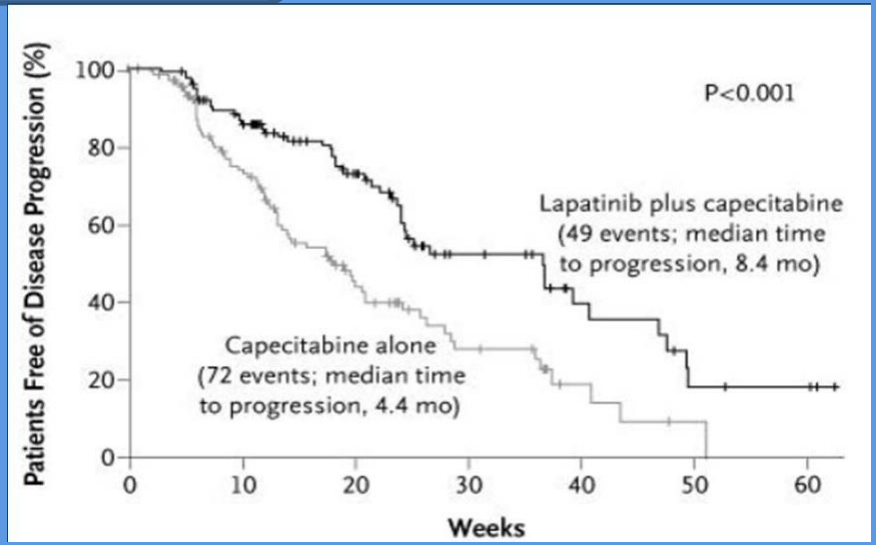
Patients with HER2+ progressive MBC or stage IIIB/IIIC LABC with T4 lesion and unlimited previous therapies*

→ **Lapatinib** 1250 mg/day PO + **Capecitabine** 2000 mg/m²/day on Days 1-14 every 21 days

→ **Capecitabine** 2500 mg/m²/day **on** Days 1-14 every 21 days

- **Primary endpoint: TTP**
- **Secondary endpoints: OS, PFS, ORR**

Geyer C, et al. N Engl J Med. 2006;355:2733-2743.



Lapatinib + Endokrin Tedavi

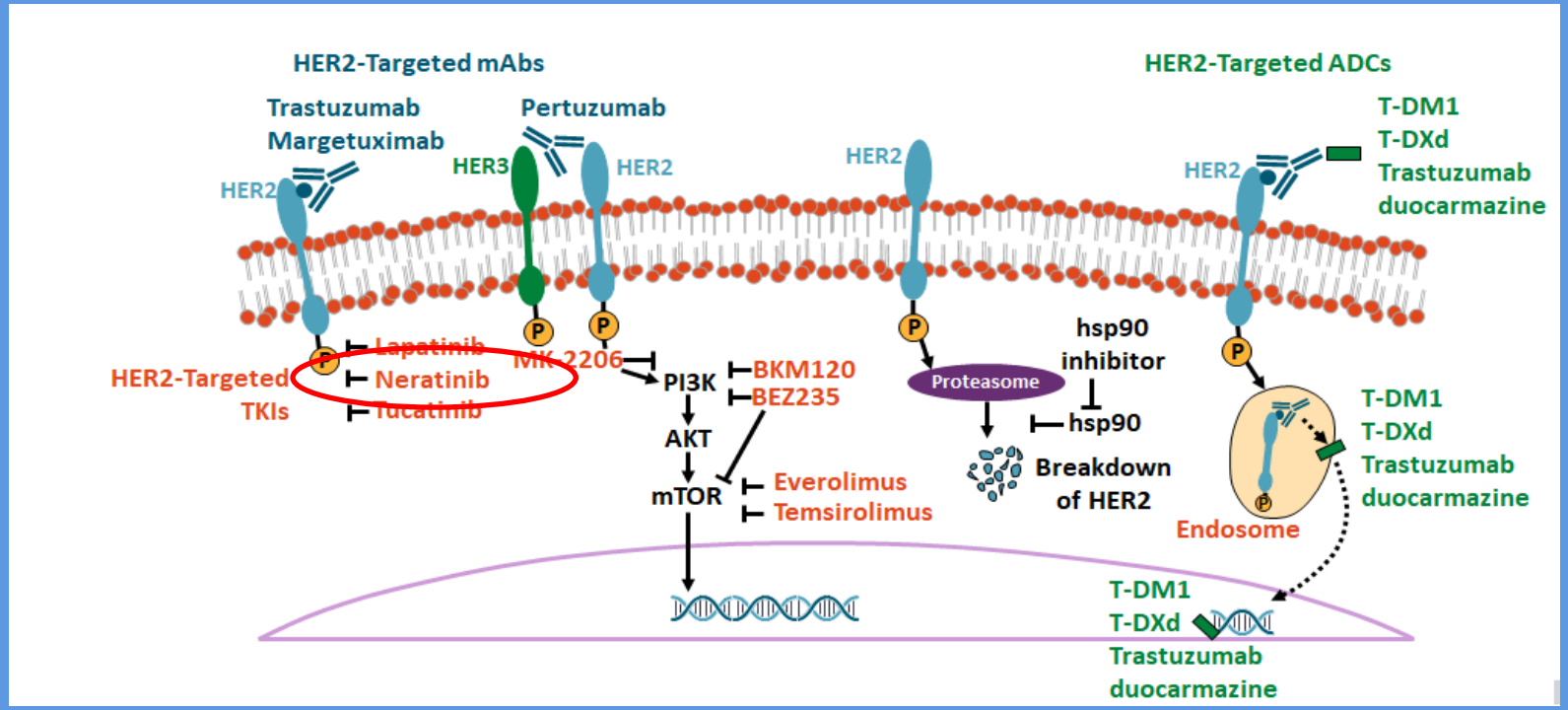
Hormonal tedaviye Lapatinib eklenmesi ORR ve PFS katkısı sağlar

TABLE II First-line phase III trials incorporating anti-HER2 therapy and endocrine therapy for met positive breast cancer

Reference (study name)	*Pts (n)*	*Treatment arms*			
Johnston *et al.*, 2009[18] (EGF30008)	263	Letrozole 2.5 mg with lapatinib 1500 mg daily	8.2 (p=0.019)	33.3 (p=0.113)	28 (p=0.021)
		Letrozole 2.5 mg with placebo daily	3.0	32.3	15
Kaufman *et al.*, 2009[19] (TANDEM)	207	Anastrozole 1 mg daily, with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly)	4.8 (p=0.002)	28.5 (p=0.325)	21 (p=0.018)
		Anastrozole 1 mg daily	2.4	23.9	7
Huober *et al.*, 2012[20] (ELECTRA)	92	Letrozole 2.5 mg daily, with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly)	14.1 (p=0.23)	NR	27 (p=0.002)
		Letrozole 2.5 mg daily	3.3	NR	13

HER2 = human epidermal growth factor receptor 2; Pts = patients; TTP = time to progression; PFS = progression-free survival; OS = overall survival; NR = not reported.

HER 2 Hedefli Tedaviler

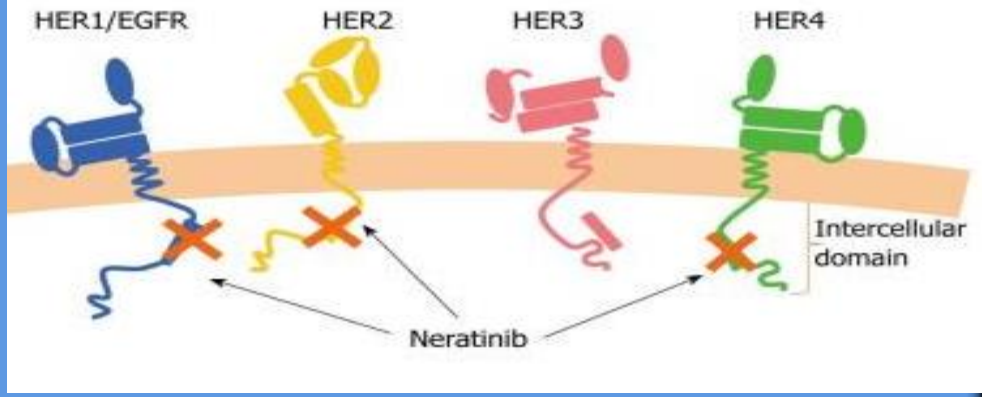


Daha önce tedavi almış, HER2-pozitif lokal ileri veya metastatik meme kanseri

(N = 233)

Neratinib 240 mg/gün devamlı
(n = 117)

Lapatinib 1250 mg/gün devamlı +
Kapesitabin 2000 mg/m²/gün 1-14. günler
21-gün arayla
(n = 116)

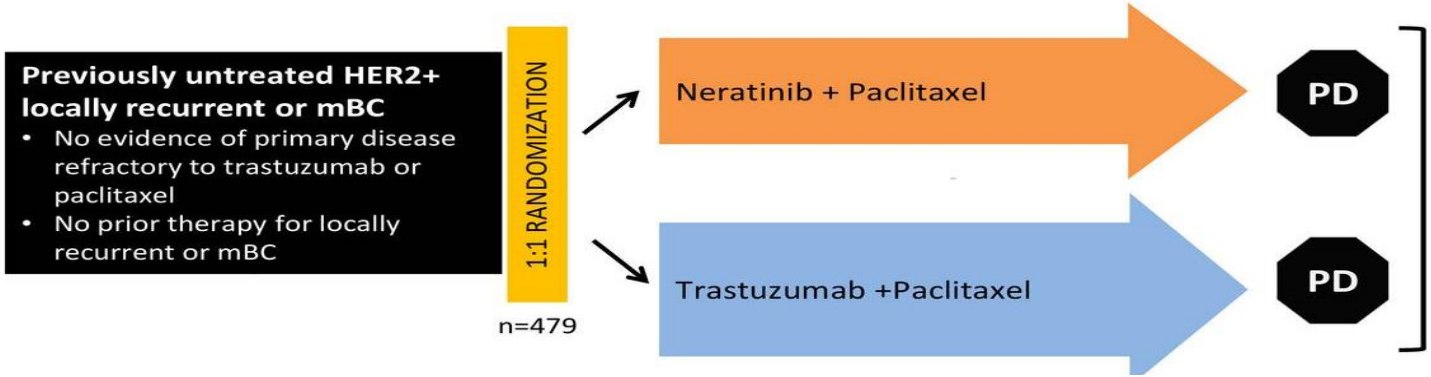


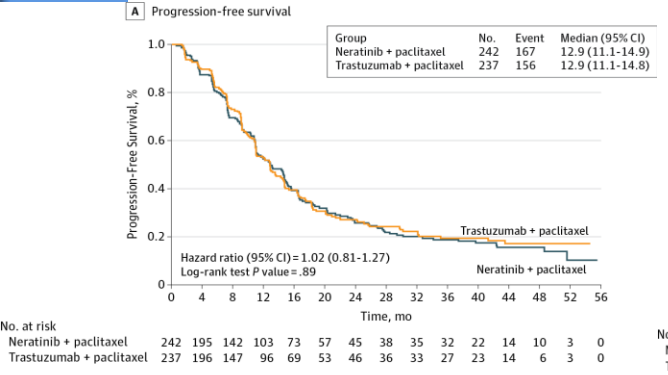
Sonuçlar, Ay	Neratinib (n = 117)	Lapatinib + Kapesitabin (n = 116)	*P* değeri
Medyan PFS	4.5	6.8	.231
Medyan OS	19.7	23.6	.280

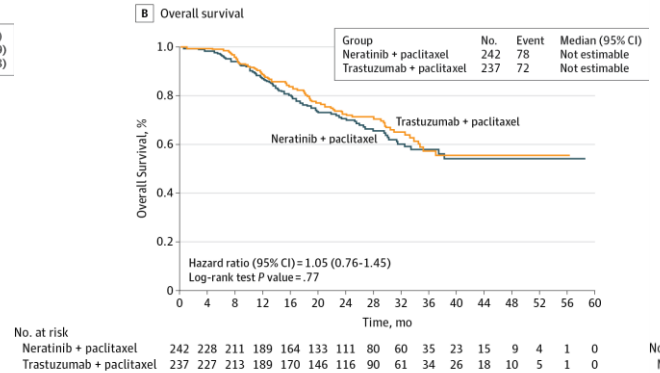
Original Investigation

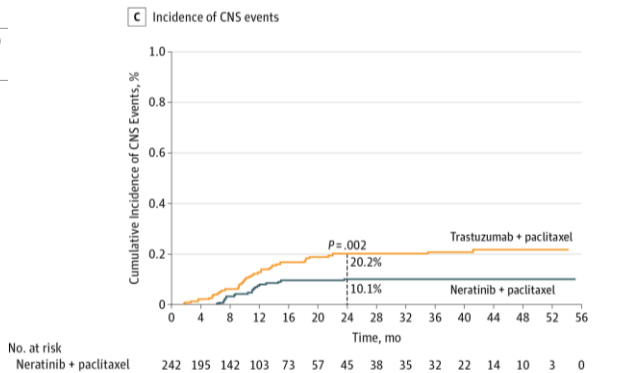
Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer

The NEfERT-T Randomized Clinical Trial

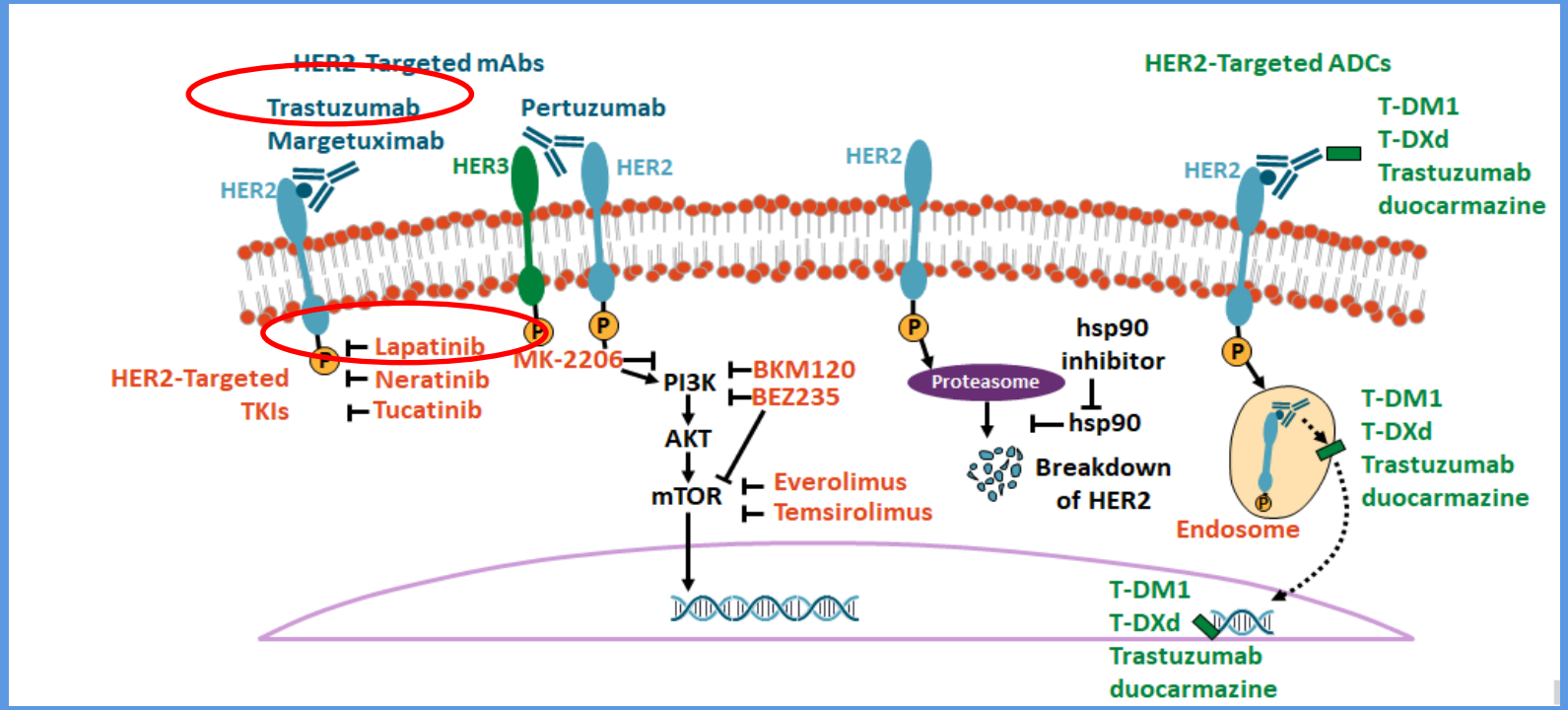








HER 2 Hedefli Tedaviler



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Study of Lapatinib Alone or in Combination With Trastuzumab in Women With ErbB2-Positive, Trastuzumab-Refractory Metastatic Breast Cancer

Patients with HER2+ (FISH/IHC3+) MBC and progression on anthracycline, taxane, and trastuzumab

→ **Lapatinib** 1500 mg/day PO (n = 148)

→ **Lapatinib** 1000 mg/day PO + **Trastuzumab** 4 mg/kg → 2 mg/kg IV weekly (n = 148)

Fig 2. Kaplan-Meier estimates of progression-free survival (PFS) in the intent-to-treat population. L, lapatinib; L+T, lapatinib plus trastuzumab.

1. Seri trastuzumab sonrası lapatinip e trastuzumab eklenmesi PFS ve OS katkısı sağlar

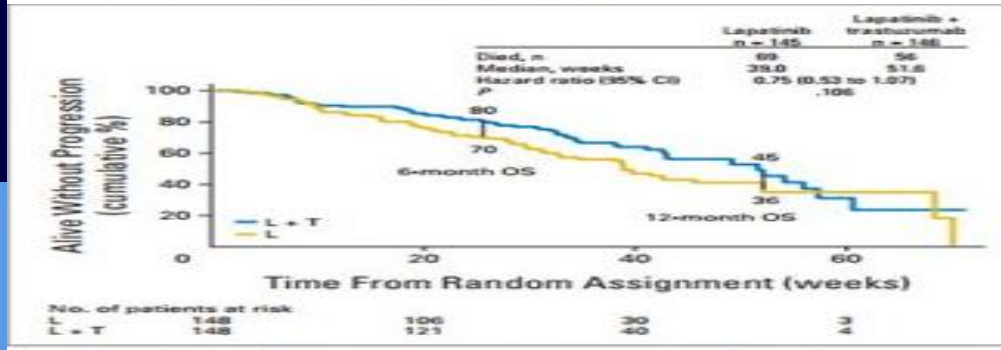
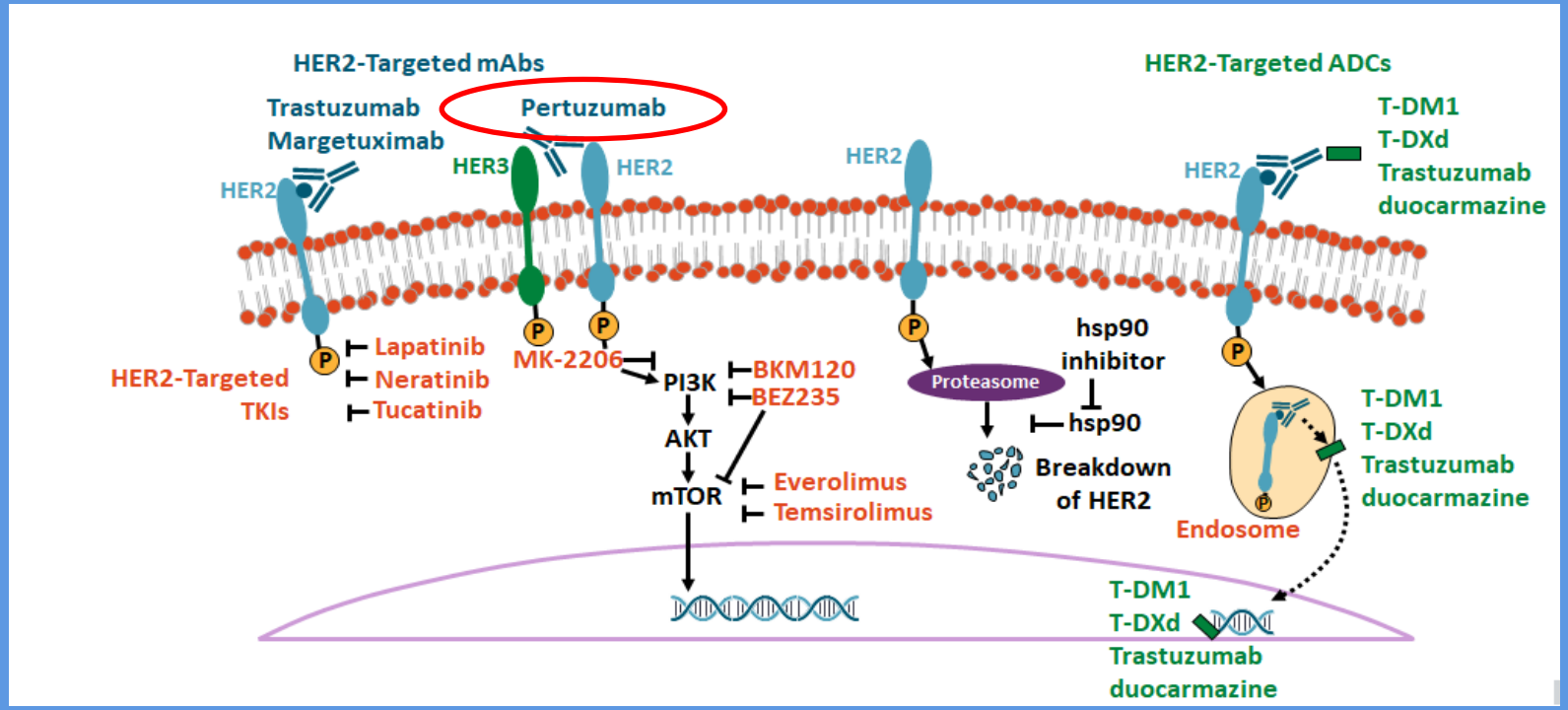


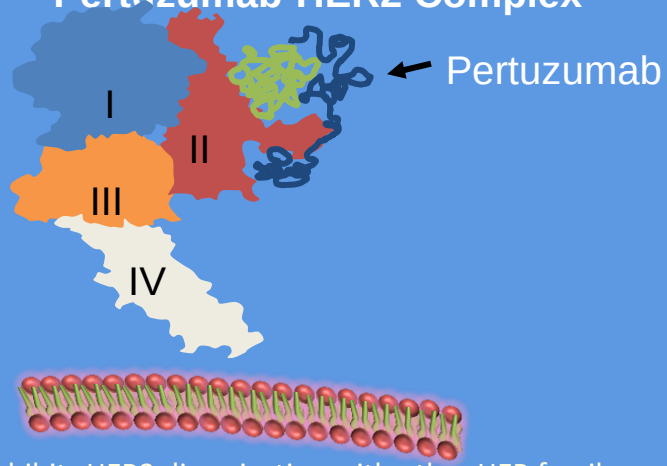
Fig 3. Kaplan-Meier estimates of overall survival (OS) in the intent-to-treat population. L, lapatinib; L+T, lapatinib plus trastuzumab.

HER 2 Hedefli Tedaviler



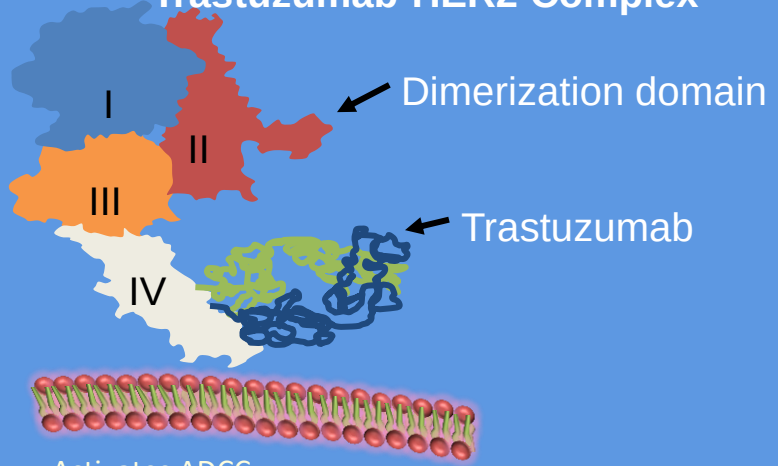
Pertuzumab

Pertuzumab-HER2 Complex



- Inhibits HER2 dimerization with other HER family receptors (particularly HER3)
- Activates ADCC
- Inhibits multiple HER-mediated signaling pathways

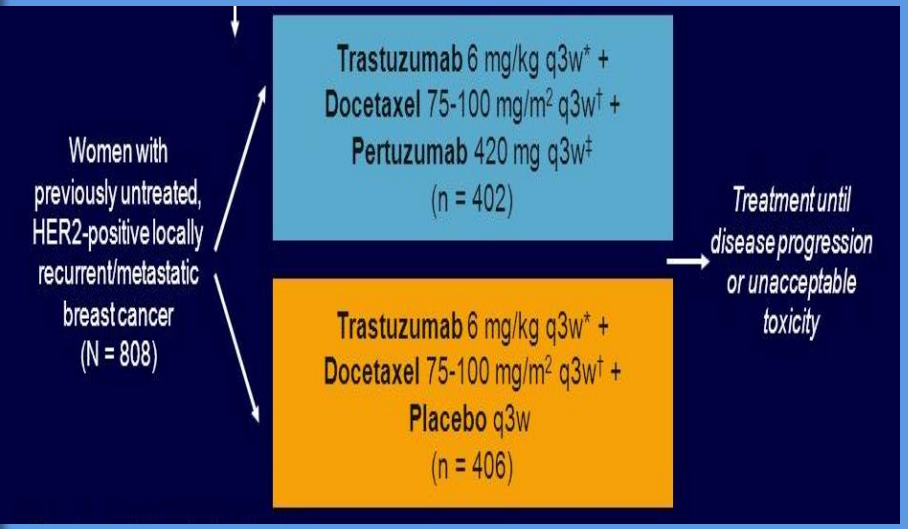
Trastuzumab-HER2 Complex

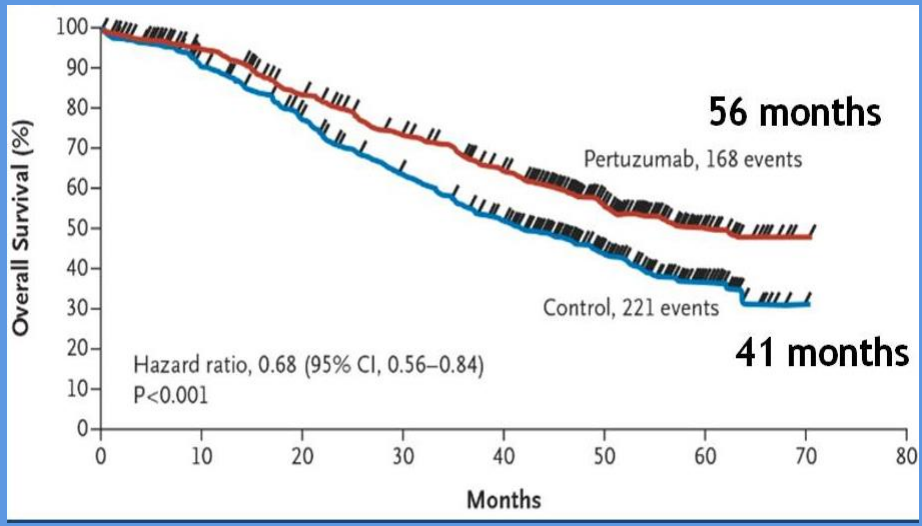


- Activates ADCC
- Inhibits HER-mediated signaling pathways
- Prevents HER2 domain cleavage

Hubbard SR. Cancer Cell. 2005;7:287-288.

Cleopatra Çalışması



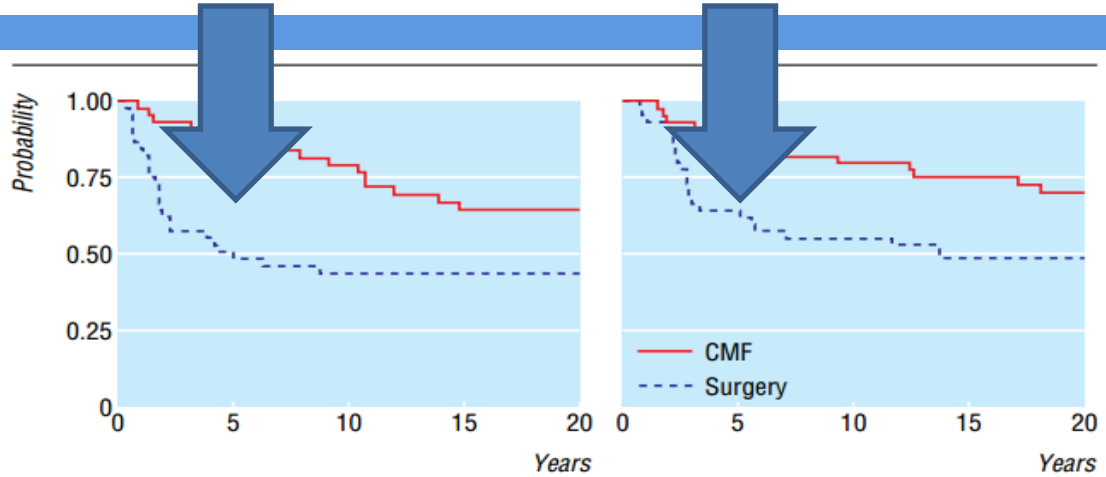


Cite this article as: BMJ, doi:10.1136/bmj.38314.622095.8F (published 13 January 2005)

Papers

30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study

Gianni Bonadonna, Angela Moliterni, Milvia Zambetti, Maria Grazia Daidone, Silvana Pilotti, Luca Gianni, Pinuccia Valagussa



PERUSE: First-line Pertuzumab, Trastuzumab Plus Investigator's Choice of Taxane Therapy

- Ongoing multicenter phase 3b study

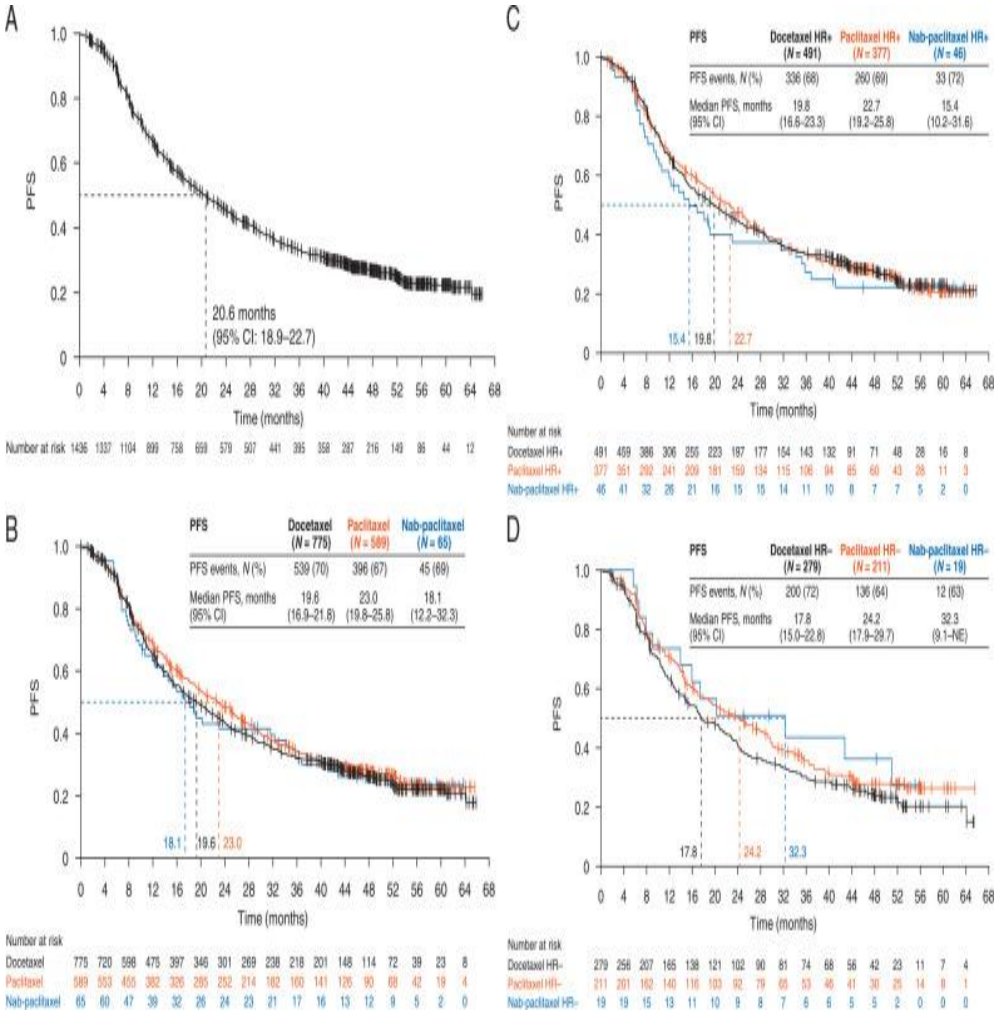
HER2-positive locally recurrent/ metastatic breast cancer N=1500

→ **Pertuzumab 840→420 mg every 3 weeks + Trastuzumab 8→6 mg/kg every 3 weeks + Taxane (D, PAC, or nab-PAC)**

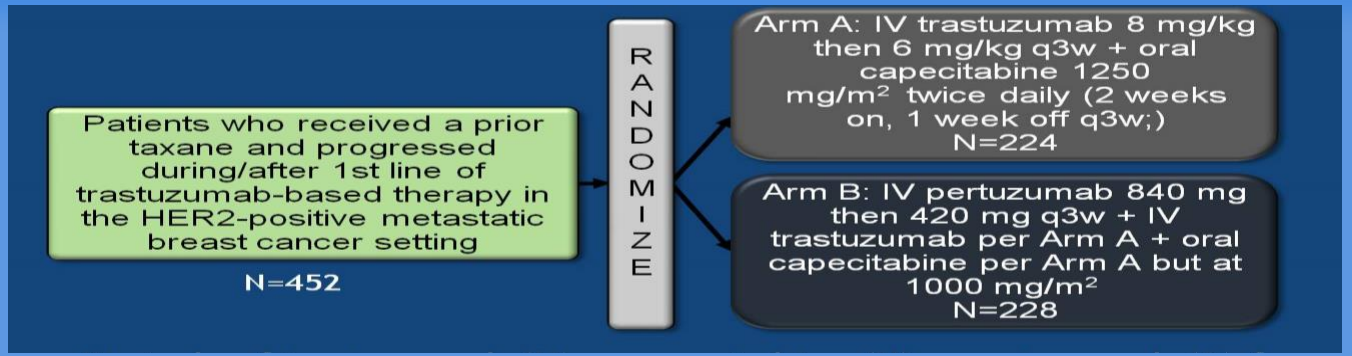
→ **PD**

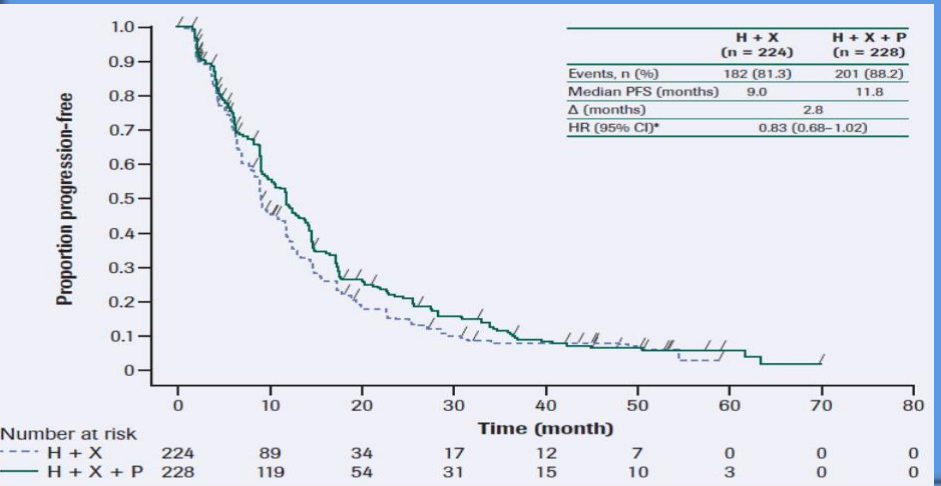
- Primary endpoint: Safety
- Secondary endpoints: PFS, OS, objective response, QoL
- Prespecified interim analysis of 704 patients showed initial taxane was D in 304 (45%) patients, PAC in 331 (47%) patients, and nab-PAC in 45 (6%) patients
- Safety profile of pertuzumab + trastuzumab + any taxane was consistent with previous clinical experience of pertuzumab + trastuzumab + docetaxel

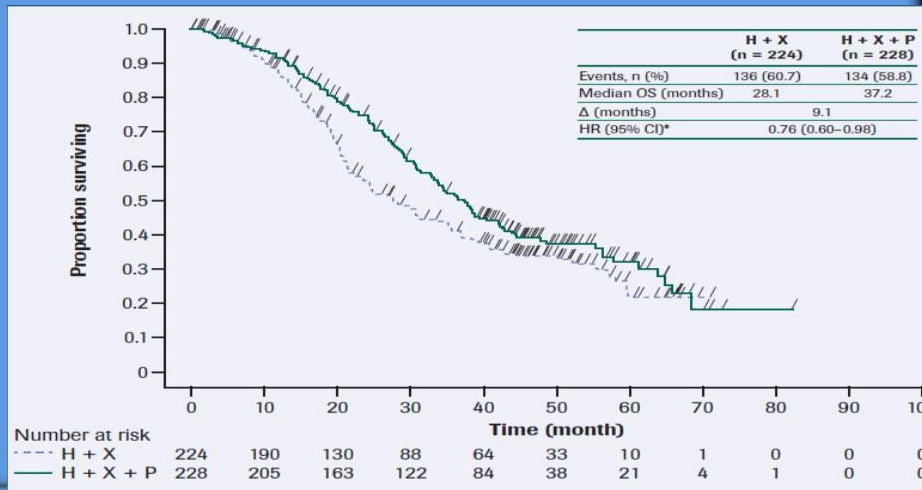
Bachelot TD, et al. ASCO 2015. Abstract 548.



PHREXA çalışması







PERTAIN Study Design (Phase II Trial)

Postmenopausal patients with HER2-positive and hormone receptor-positive LA/MBC, not previously treated with systemic non-hormonal anticancer therapy in the advanced setting (N = 258)*

Choice of chemotherapy must be specified before randomization

R

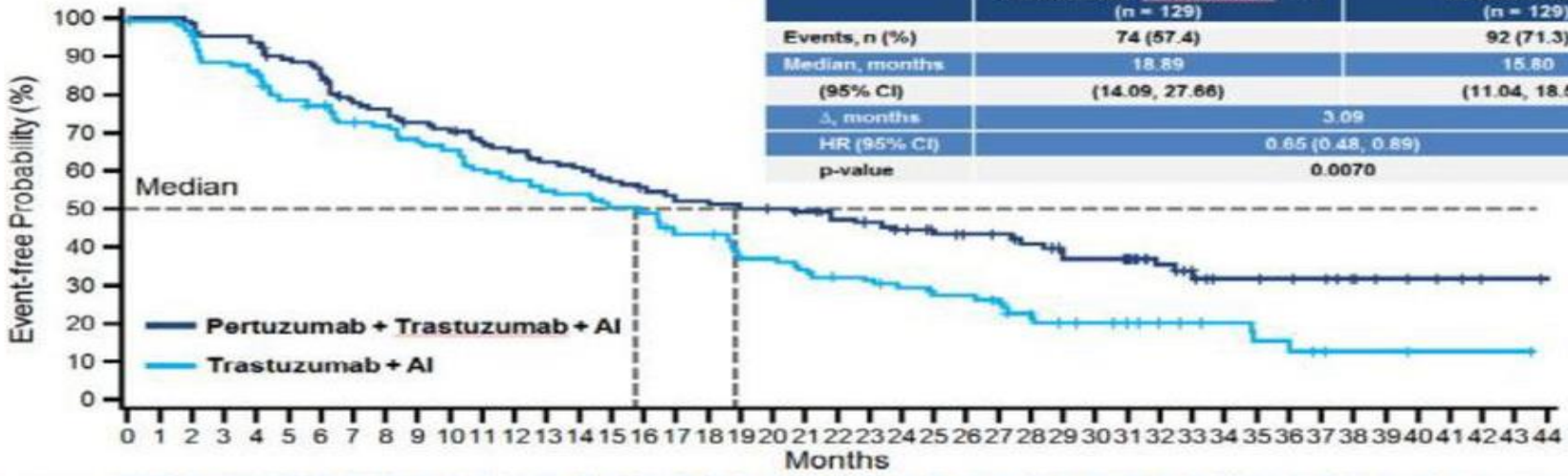
Pertuzumab + Trastuzumab
+
Aromatase Inhibitor
OR
Docetaxel or Paclitaxel (18–24 weeks)† → **Aromatase Inhibitor**

Trastuzumab
+
Aromatase Inhibitor
OR
Docetaxel or Paclitaxel (18–24 weeks)† → **Aromatase Inhibitor**

Stratification factors:
- Chemotherapy (yes/no)
- Time since adjuvant hormone therapy (<12 months/≥12 months/no prior therapy)

* 165 events to detect significant improvement in PFS from 7 months to 10.8 months (i.e. HR 0.645) with 80% power and a 2-sided log-rank test at an alpha level of 0.05.
† Choice of chemotherapy must be specified before randomization; administered per product labelling. LA, locally advanced; R, randomization.

	Pertuzumab + Trastuzumab + AI (n = 129)	Trastuzumab + AI (n = 129)
Events, n (%)	74 (57.4)	92 (71.3)
Median, months	18.89	15.80
(95% CI)	(14.09, 27.66)	(11.04, 18.56)
Δ, months	3.09	
HR (95% CI)	0.65 (0.48, 0.89)	
p-value	0.0070	



Perez et al. Breast Cancer Research (2016) 18:126
DOI 10.1186/s13058-016-0773-6

Breast Cancer Research

RESEARCH ARTICLE Open Access

Safety and efficacy of vinorelbine in combination with pertuzumab and trastuzumab for first-line treatment of patients with HER2-positive locally advanced or metastatic breast cancer: VELVET Cohort 1 final results

Edith A. Perez[1*], José Manuel López-Vega[2], Thierry Petit[3], Claudio Zamagni[4], Valerie Easton[5], Julia Kamber[5], Eleonora Restuccia[5] and Michael Andersson[6]

Table 3 Sensitivity analyses of best overall response, progression-free survival, and time to progression, intent-to-treat population

	Cohort 1: pertuzumab, trastuzumab, and vinorelbine	
	Sensitivity analyses	
	Excluding tumor assessments after intake of any new anticancer therapy N = 106	Including progressive disease due to symptomatic deterioration N = 106
Best overall response		ND[a]
Patients with measurable disease at baseline	89 (84.0%)	
Overall response rate	57 (64.0%) [53.2–73.9]	
Complete response	10 (11.2%) [5.5–19.7]	
Partial response	47 (52.8%) [41.9–63.5]	
Stable disease	17 (19.1%) [11.5–28.8]	
Progressive disease	5 (5.6%) [1.8–12.6]	
Not evaluable	10 (11.2%) [5.5–19.7]	
Progression-free survival		
Median	12.5 months [10.4–16.8]	13.8 months [11.0–17.3]
Number of patients with events	65 (61.3%)	74 (69.8%)
Number of patients censored	41 (38.7%)	32 (30.2%)
Time to progression		
Median	12.9 months [10.5–16.8]	14.3 months [11.2–17.5]
Number of patients with events	62 (58.5%)	72 (67.9%)
Number of patients censored	44 (41.5%)	34 (32.1%)

Data are reported number (%) [95% CI] for best overall response and median number of months [95% CI] or number (%) for progression-free survival and time to progression. Best overall response was assessed only in patients of the intent-to-treat population with measurable disease at baseline. Progression-free survival and time to progression were assessed in the intent-to-treat population

[a]A sensitivity analysis including progressive disease due to symptomatic deterioration was not performed for best overall response

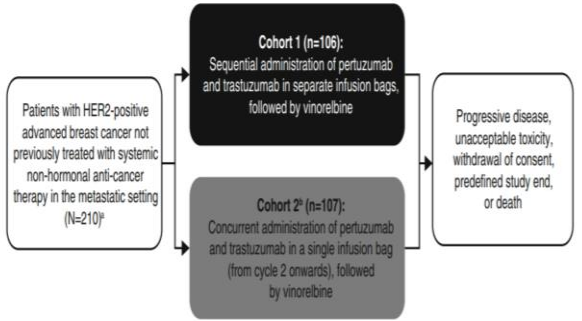


Fig. 1 Study design. [a] Sample size was based on assuming a best overall response of 70–80% in each cohort. [b] Recruitment into Cohort 2 began after Cohort 1 had finished enrolling patients

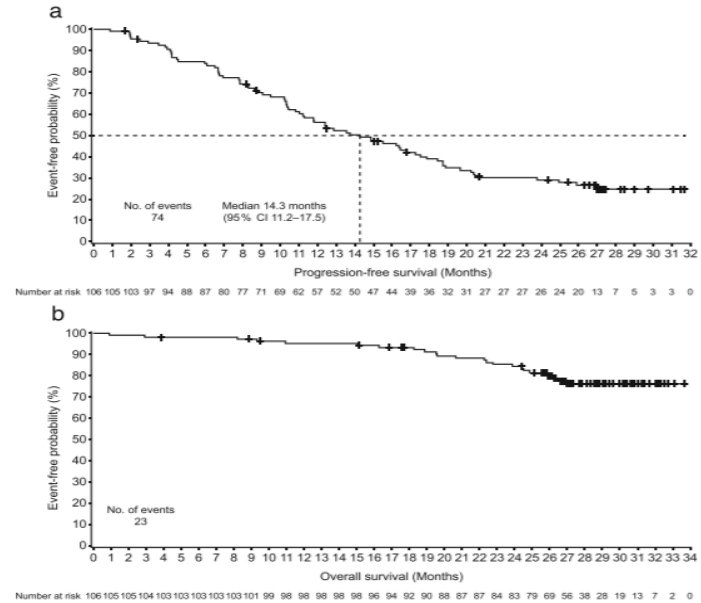
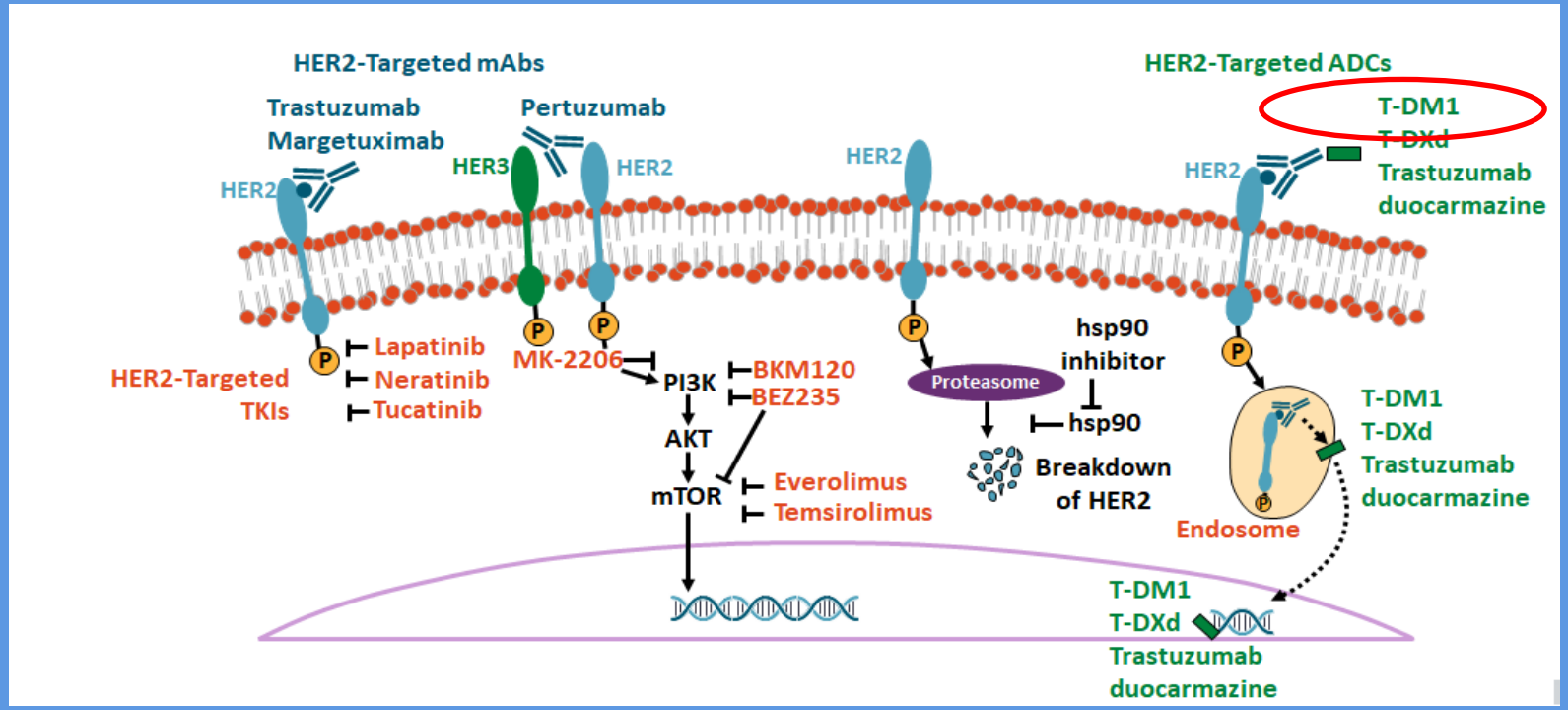


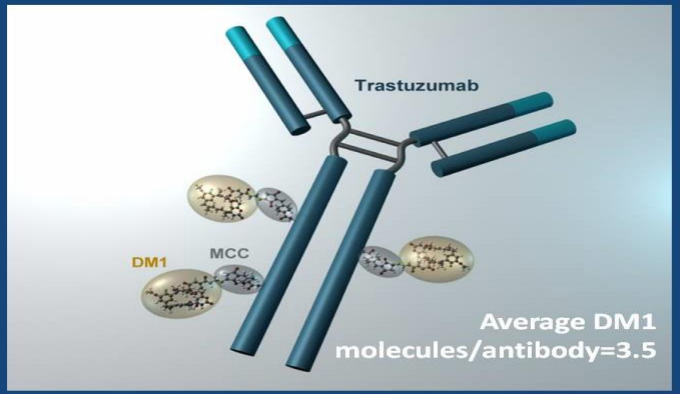
Fig. 4 Progression-free survival (**a**) and overall survival (**b**), intent-to-treat population (Cohort 1). Median overall survival was not reached. The *tick* marks indicate censoring events

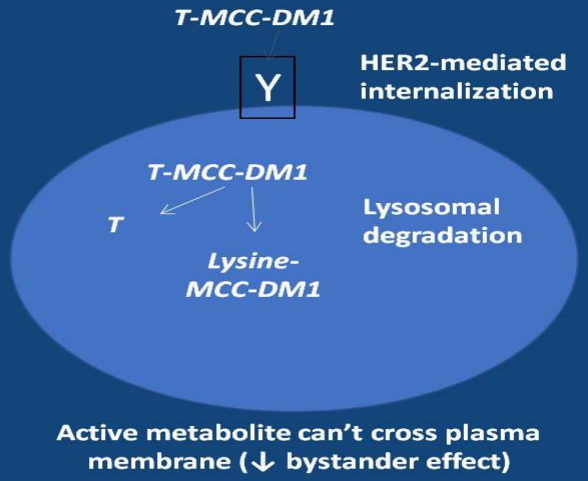
HER 2 Hedefli Tedaviler



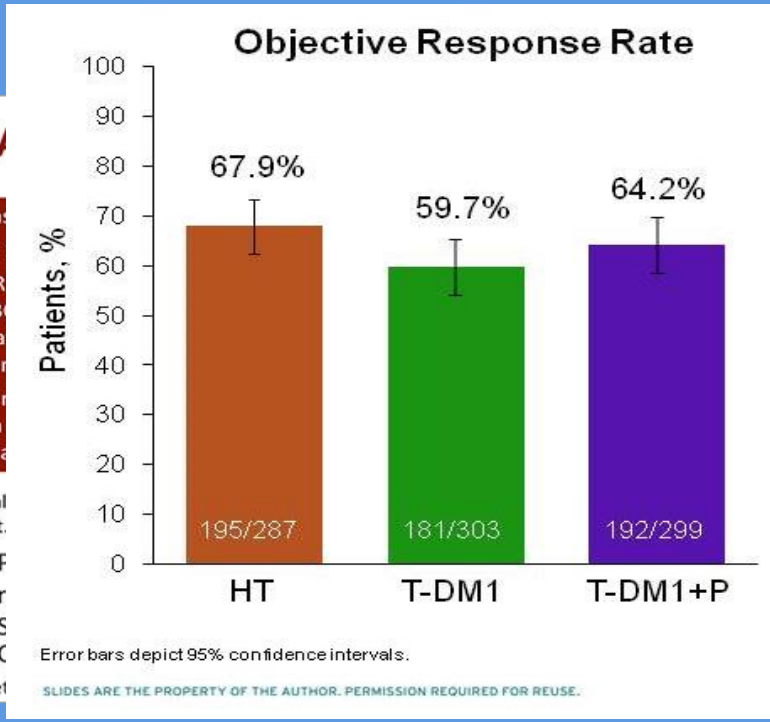
Trastuzumab-DM1

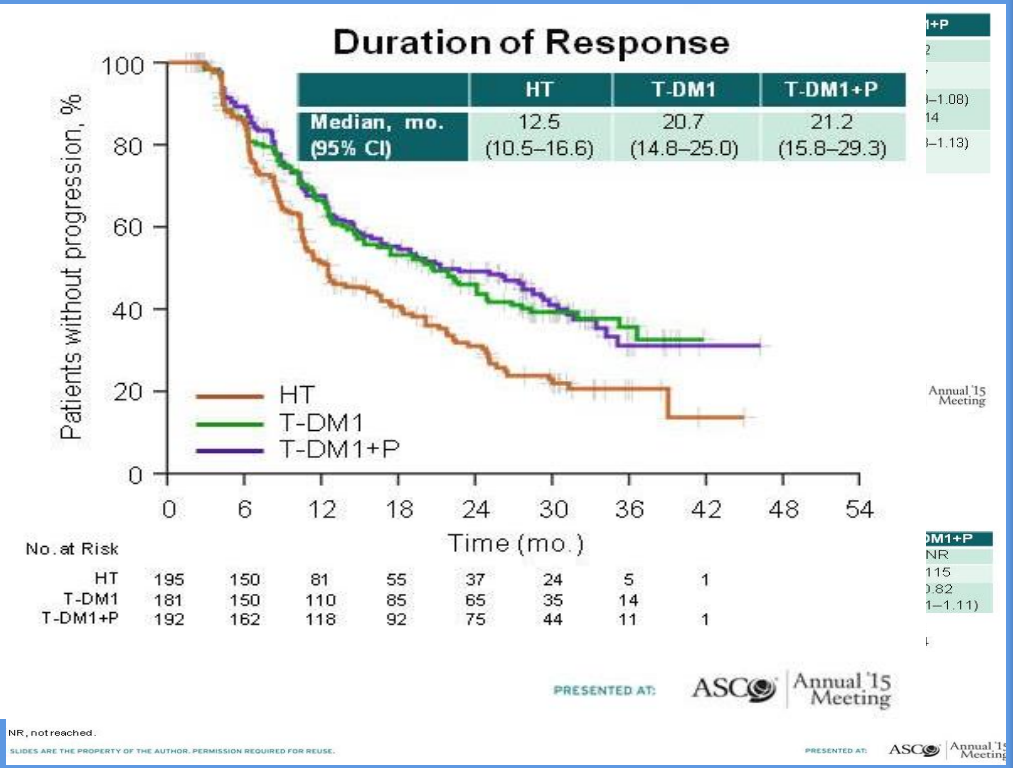
- Maytansine analogue DM1 (antitubule akin to vincas) conjugated to trastuzumab -
- Omission of separate cytotoxic





MARIENNE çalışması (1. sıra)





TDM1 vs Lapatinib + Kapesitabin :EMİLİA çalışması (2. sıra)

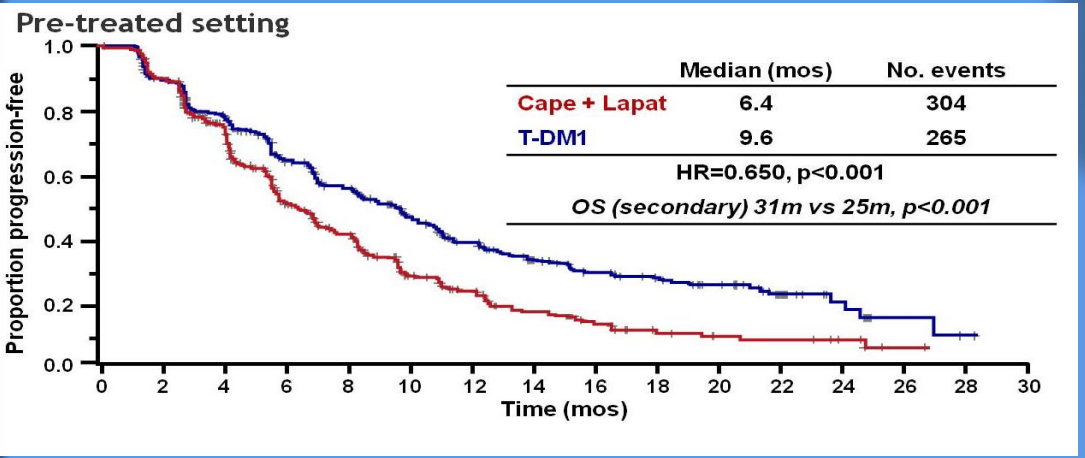
HER2+ (santral) LIMK ya da MMK
(N=980)

- Daha önce taksan ve trastuzumab
- Metastaz tedavisi sırasında ya da adjuvan tedavi uygulanan 6 ay içinde progresyon

1:1

T-DM1 (3.6 mg/kg) q3w

Lapatinib (1250 mg/day, days 1–21)**+ Kapesitabin** (1000 mg/m^2, days 1–14) q3w



Verma S, et al. N Eng J Med 2012.

TH3RESA Study: 3. basamak

HER2-positive (central) advanced BC[a]

(N=600)

≥2 prior HER2-directed therapies for advanced BC

Prior treatment with trastuzumab, lapatinib, and a taxane

2

1

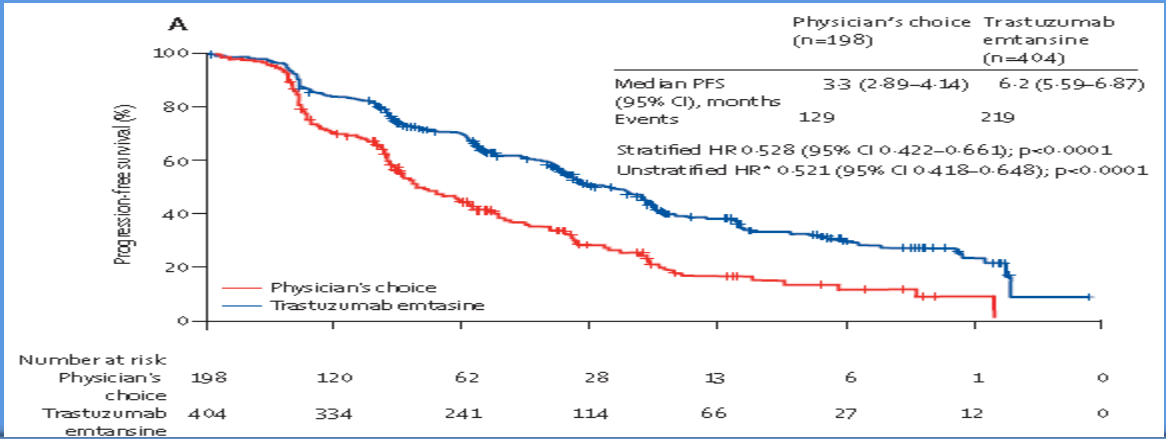
T-DM1
3.6 mg/kg q3w IV
(n=400)

PD

Treatment of physician's choice (TPC)[b]
(n=200)

PD

T-DM1[c]
(optional crossover)



VOLUME 34 · NUMBER 29 · OCTOBER 10, 2016

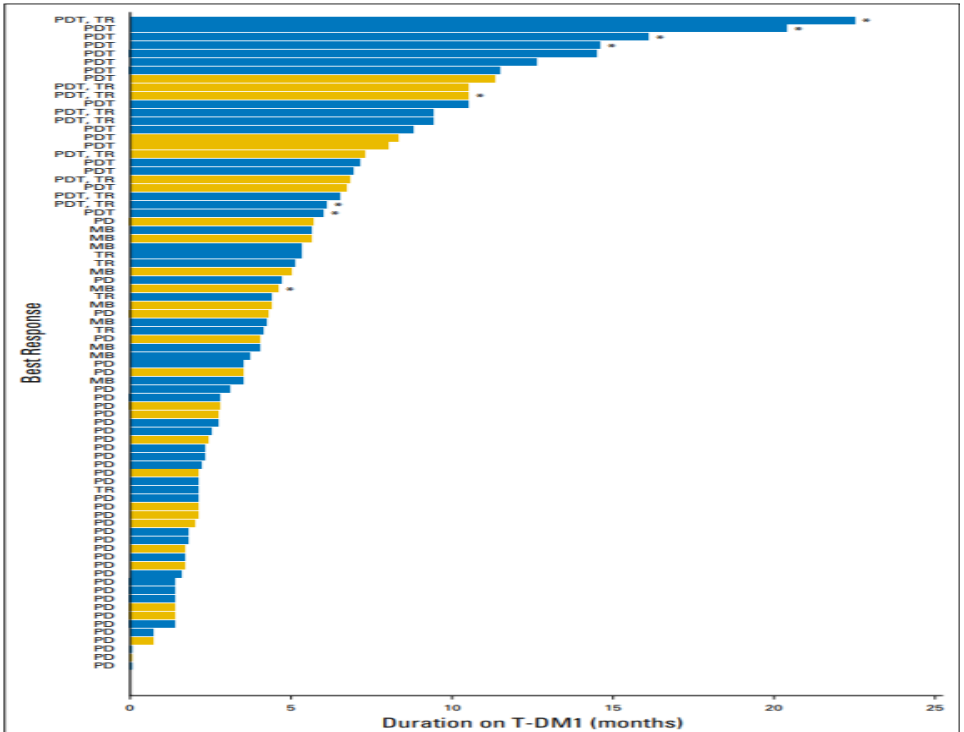
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

T-DM1 Activity in Metastatic Human Epidermal Growth Factor Receptor 2–Positive Breast Cancers That Received Prior Therapy With Trastuzumab and Pertuzumab

Hannah Dzimitrowicz, Michael Berger, Craig Vargo, Annette Hood, Osama Abdelghany, Akshara Singareeka Raghavendra, Debu Tripathy, Vicente Valero, Christos Hatzis, Lajos Pusztai, and Rashmi Murthy

See accompanying editorial on page 3492



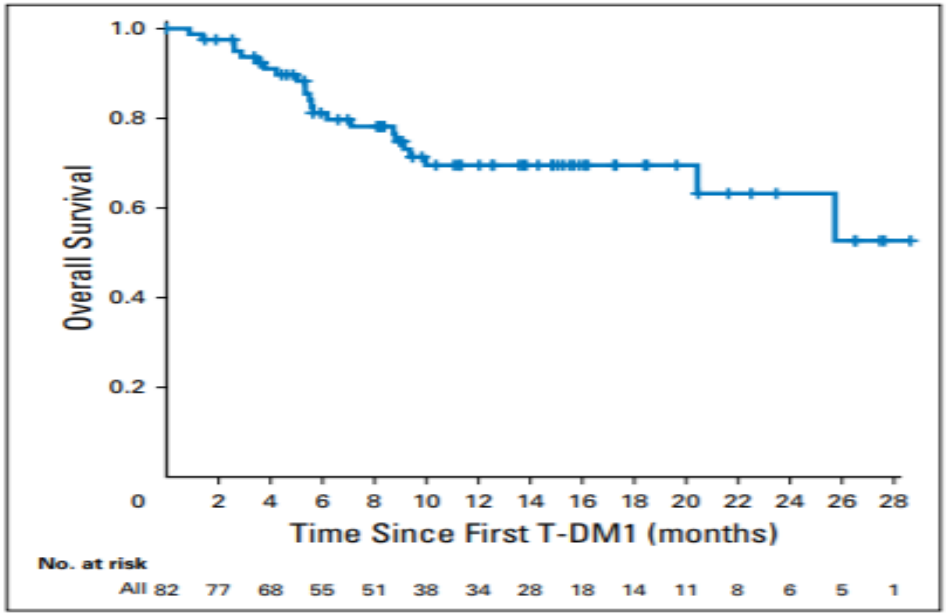
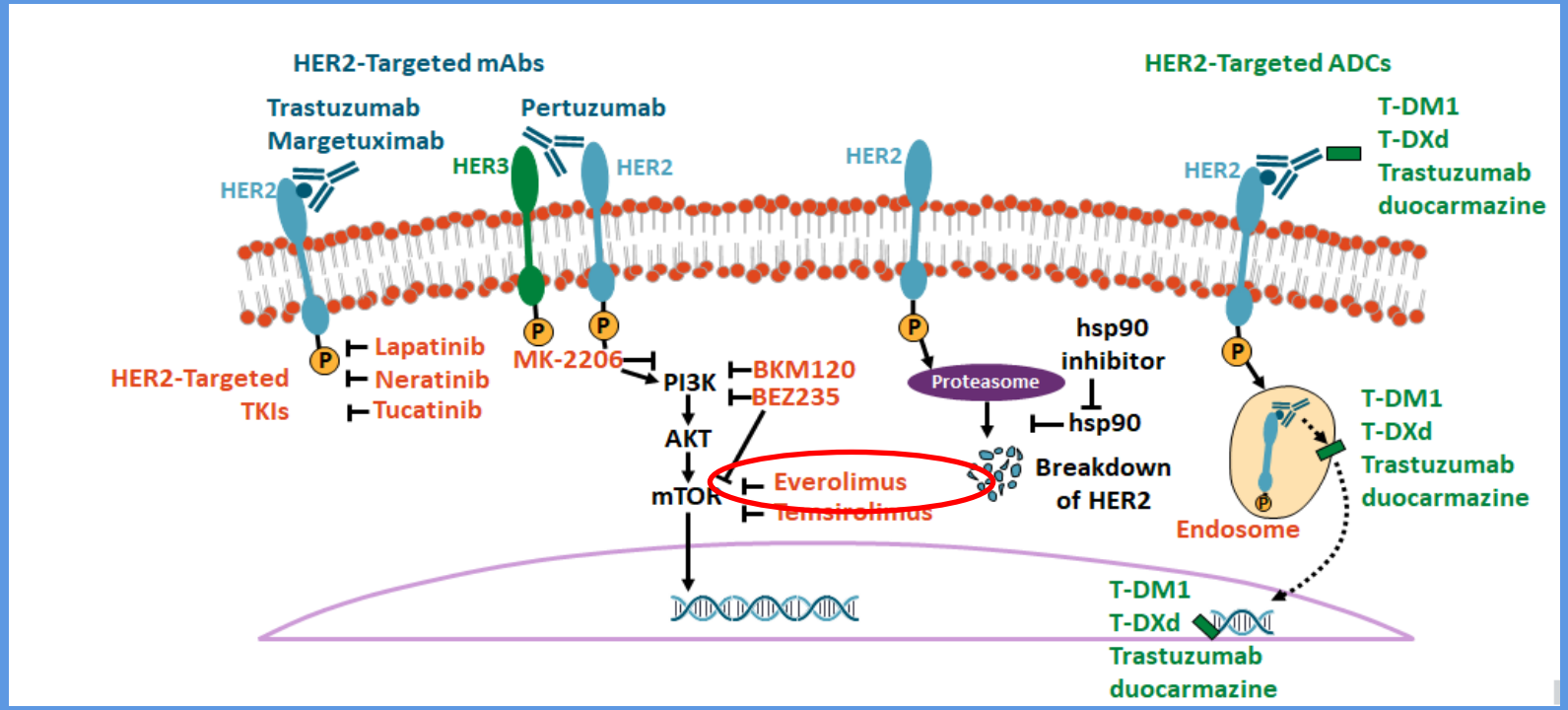


Fig 2. Overall survival. Kaplan-Meier estimates of overall survival from time of first dose of ado-trastuzumab emtansine (T-DM1) for all patients who received at least one dose of T-DM1 (82 patients).

HER 2 Hedefli Tedaviler



BOLERO-1/TRIO 019: Study 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]

Phase III trial: BOLERO-3 (advanced breast cancer, pretreated)

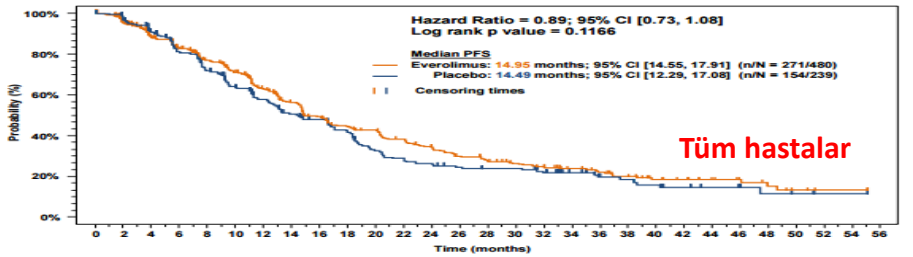
RANDOMIZATION

- **Everolimus** 10.0 mg orally daily
  Vinorelbine 25 mg/m² weekly
  Trastuzumab 2 mg/kg I.V.
  on days 1, 8, 15, and 22
- **Placebo** orally daily
  Vinorelbine 25 mg/m² weekly
  Trastuzumab 2 mg/kg I.V.
  on days 1, 8, 15, and 22

Assessment every 8 weeks
PFS
Response
Survival
Safety

N = 572

Available at: http://www.clinicaltrials.gov/ct2/show/NCT01007942. Accessed April 1, 2013

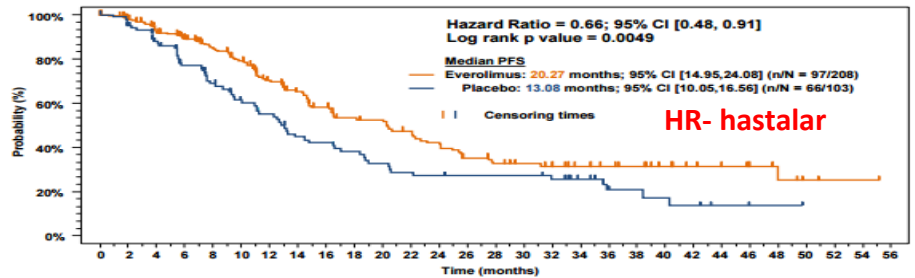


Tüm hastalar

No. of patients still at risk

Everolimus	480	416	365	324	289	260	217	178	151	130	122	107	94	80	72	63	58	48	42	35	26	21	17	13	10	5	3	3	0
Placebo	239	221	199	166	144	123	106	91	80	69	53	47	43	38	36	36	31	24	17	15	12	9	7	6	4	3	1	1	0

- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.

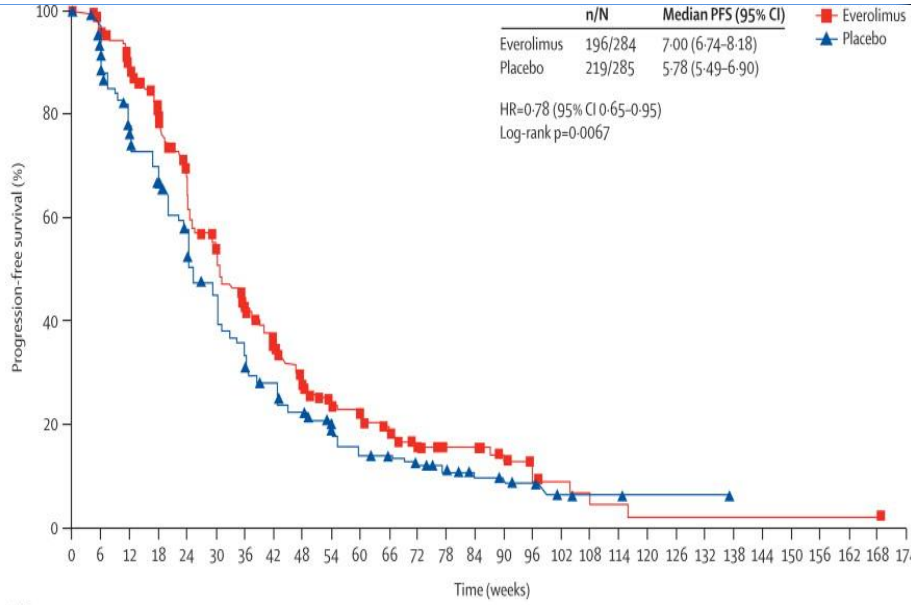


HR- hastalar

No. of patients still at risk

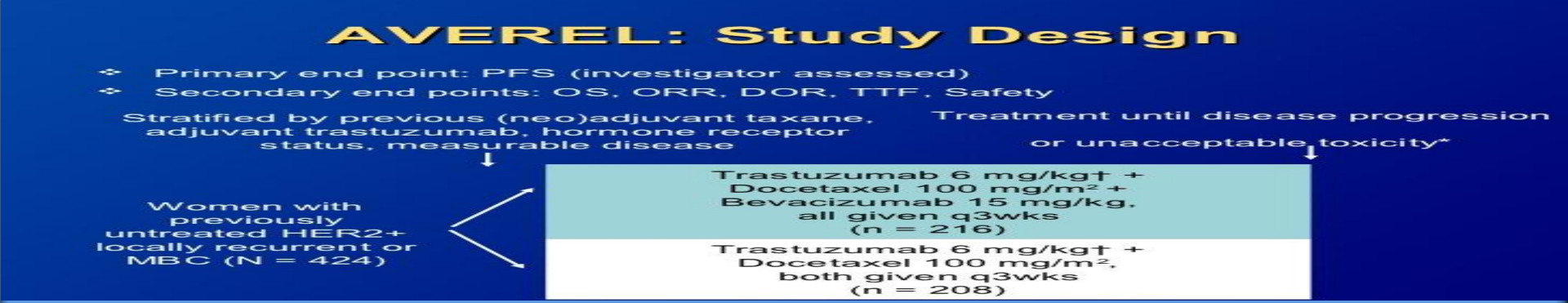
Everolimus	208	183	166	151	138	125	100	84	73	64	62	55	49	40	35	32	30	24	21	19	15	11	10	7	5	2	1	1	0
Placebo	103	96	83	68	58	49	43	34	32	28	24	21	20	19	19	19	17	13	7	6	5	4	2	1	1	0	0	0	0

- One-sided p-value is obtained from the log-rank test stratified by prior use of trastuzumab (Y/N) and Visceral metastasis (Y/N) from IWRS.



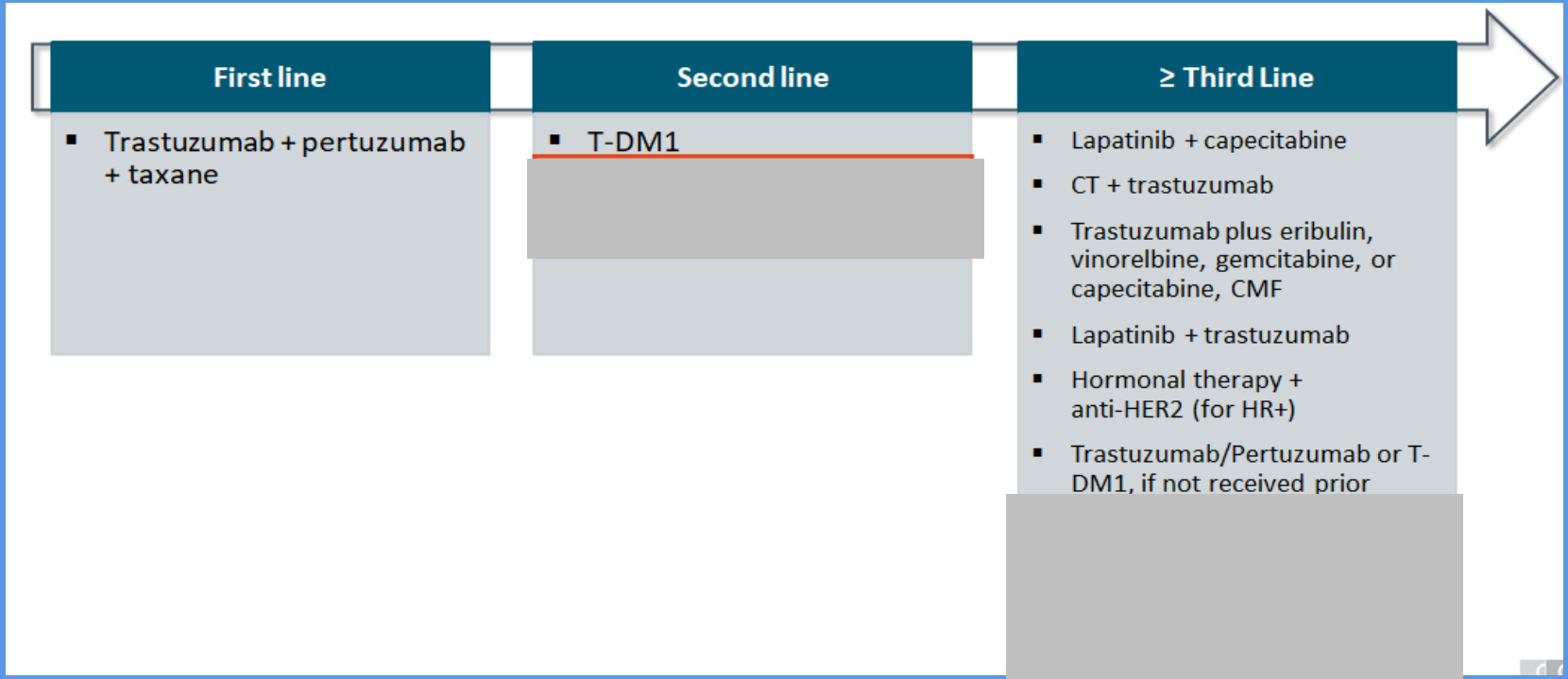
Number at risk

Everolimus	284	259	233	200	161	126	98	78	54	40	35	26	18	14	14	9	5	4	2	2	1	1	1	1	1	1	1	1	0
Placebo	285	253	202	177	138	109	85	64	49	38	26	23	19	16	12	10	7	4	3	3	1	1	1	0	0	0	0	0	0



Sonuç, Ay	T + Doc + Bev (n = 216)	T + Doc (n = 208)	HR (95% CI)	*P* değeri
Medyan PFS (Araştırıcı değerlendirmesi)	16.5	13.7	0.82 (0.65-1.02)	.0775
Medyan PFS (IRC değerlendirmesi)	16.8	13.9	0.72 (0.54-0.94)	.0162
Medyan OS	38.5	38.3	1.01 (0.74-1.38)	.9543
			0.94 (0.68-1.30)	.7078

Tedavi Sıralaması

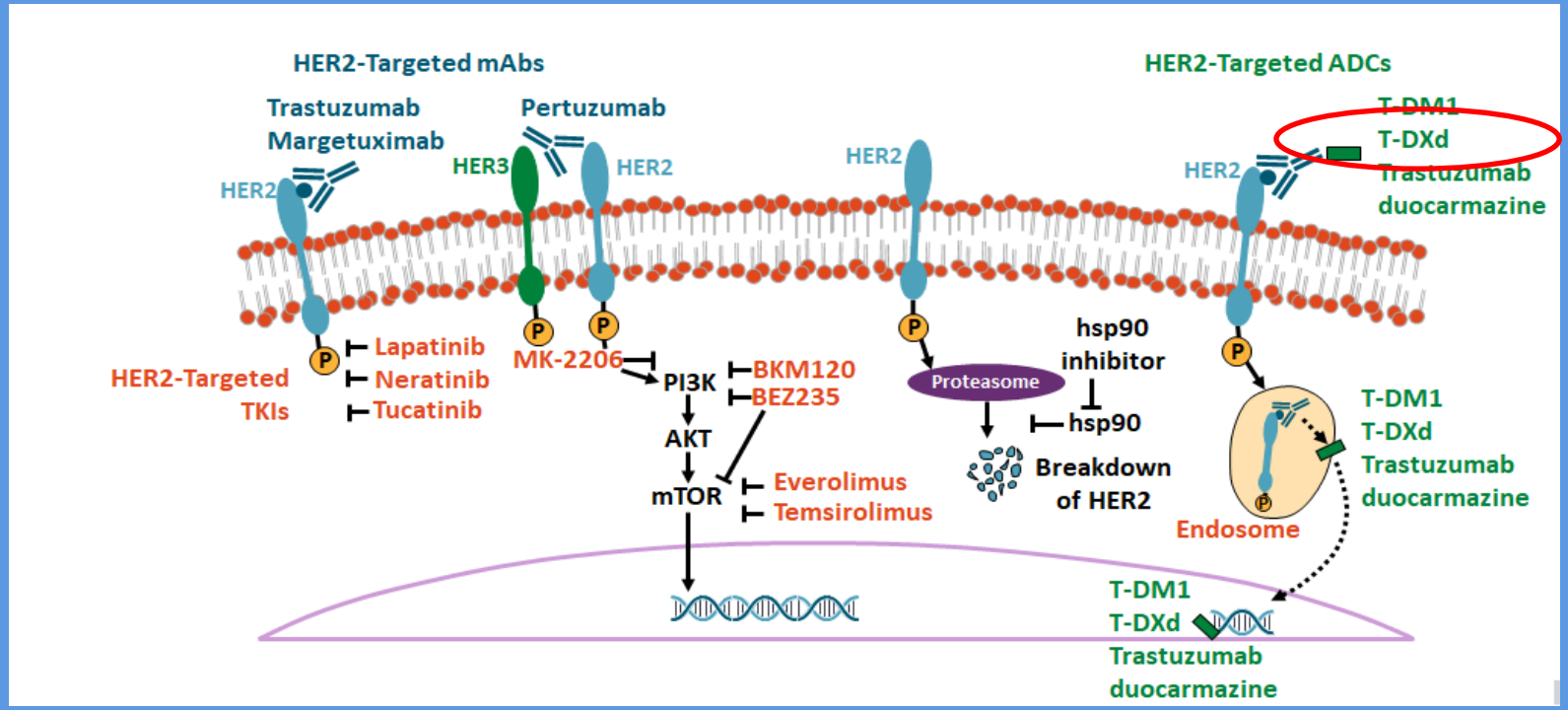


1. Giordano. JCO. 2018;36:2736. 2. NCCN. Breast Cancer. V5.2020. July 15, 2020.

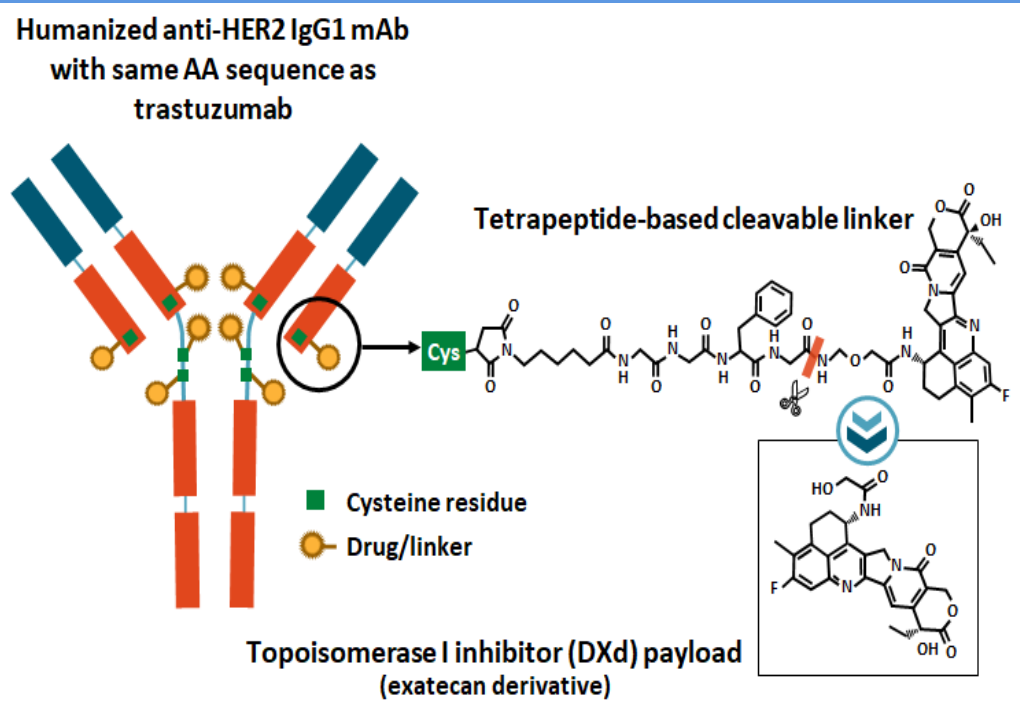
PLAN

- ✓ Son döneme kadar bilinenler
- ✓ Son dönemde öğrendiklerimiz

HER 2 Hedefli Tedaviler



Trastuzumab Deruxtecan (DS-8201)



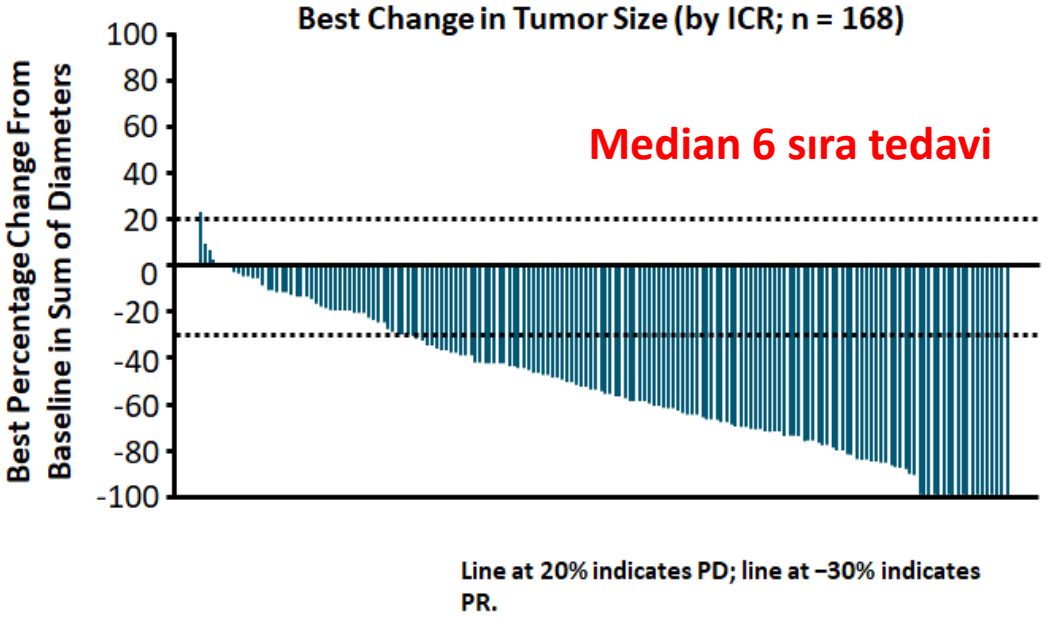
- High drug:antibody ratio: ~ 8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

DESTINY-Breast01: Phase II Trial of Trastuzumab Deruxtecan (T-DXd) in Advanced HER2+ Breast Cancer

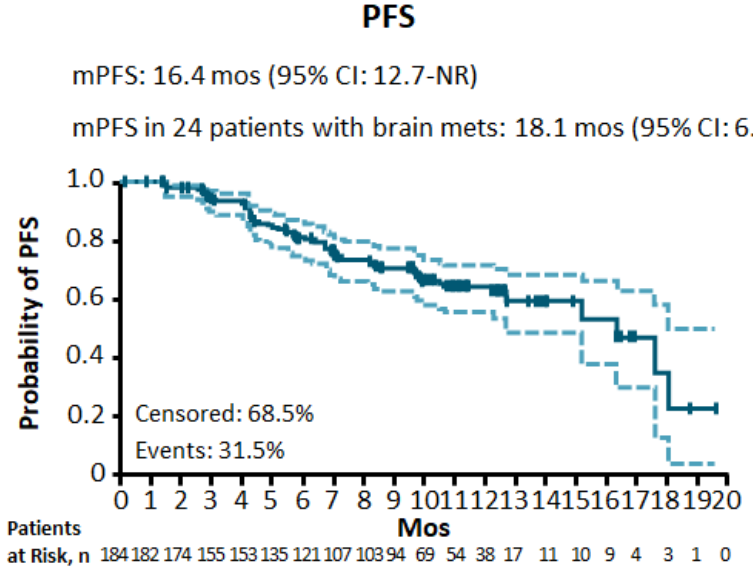
Response (ITT)	T-DXd 5.4 mg/kg (N = 184)
ORR* (by ICR; n = 112), % (95% CI)	60.9 (53.4-68.0)
▪ CR (n = 11)	6.0
▪ PR (n = 101)	54.9
▪ SD (n = 67)	36.4
▪ PD (n = 3)	1.6
▪ Not evaluable (n = 2)	1.1
DCR, % (95% CI)	97.3 (93.8-99.1)
6-mo CBR, % (95% CI)	76.1 (69.3-82.1)
Median DoR, mos (95% CI)	14.8 (13.8-16.9)
Median time to response, mos (95% CI)	1.6 (1.4-2.6)

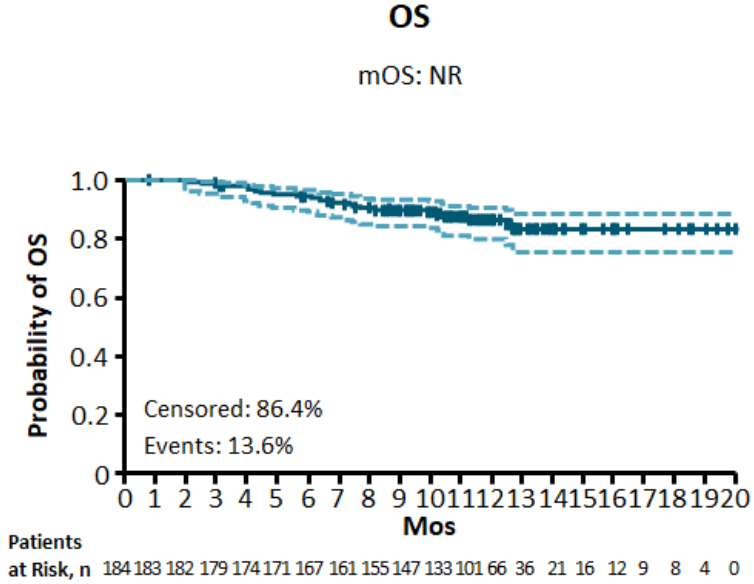
*Patients who received T-DXd 5.4 mg/kg.



Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2020;382:610.

DESTINY-Breast01: Survival





- Median follow-up: 11.1 mos (range: 0.7-19.9)

Modi. NEJM. 2020;382:610. Jerusalem. ESMO Breast 2020. Abstr 1380.

DESTINY-Breast01: Interstitial Lung Disease

AE, n (%)	T-DXd 5.4 mg/kg (N = 184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	25 (13.6)

Monitor

Suspected ILD

Interrupt drug

Rule out ILD if the patient exhibits:

- Radiographic changes suggesting ILD
- Acute onset of new/worsening pulmonary or related symptoms (eg, cough, dyspnea, fever)

Confirm

Assessments should include:

- High-resolution CT
- Pulmonologist consultation and, if indicated, ID consultation
- Blood culture and CBC; other blood tests as needed
- Consider bronchoscopy and BAL if indicated and feasible
- PFTs and pulse oximetry
- Arterial blood gasses, if indicated
- As soon as ILD suspected, collect 1 blood sample for PK assessment, if feasible

All ILD events should be followed until resolution and after drug discontinuation.

Manage

Hold drug for any ILD events independent of grade

- **Grade 1:** Hold until fully resolved, then:
  - *If resolved ≤ 28 d from onset:* maintain dose
  - *If resolved > 28 d after onset:* reduce dose by 1 level
  - *If grade 1 ILD occurs beyond cycle Day 22 and has not resolved within 49 d from last infusion:* discontinue drug
- **Grades 2-4:** permanently discontinue treatment and follow toxicity management guidelines for trastuzumab deruxtecan

Krop. SABCS 2019. Abstr GS1-03. Modi. NEJM. 2020;382:610.

Trastuzumab Deruxtecan Approval

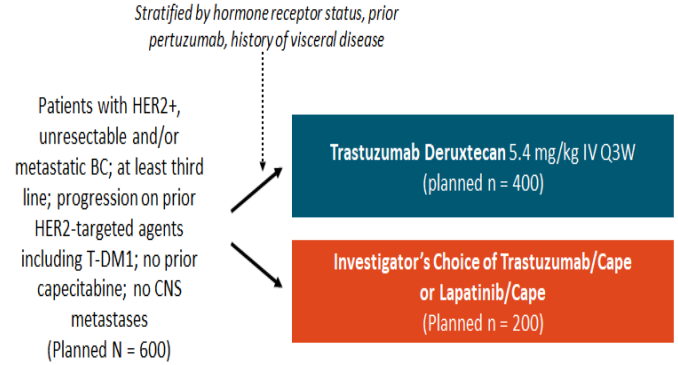
- On December 20, 2019, the FDA approved fam-trastuzumab deruxtecan-nxki for treatment of patients with unresectable or metastatic HER2+ BC who have received ≥ 2 previous HER2-targeted therapies in the metastatic setting
  - Administration/dose: IV 5.4 mg/kg QW3
  - Monitor CBC prior to each administration; assess LVEF prior to initiation and at regular intervals during treatment as clinically indicated; monitor for ILD and pneumonitis during treatment
  - Management of AEs may require temporary interruption, dose reduction, or discontinuation
- Based on ORR and DoR data from randomized phase II DESTINY-Breast01 trial
  - CNS progression was noted in only 8% of patients; including 2 of 40 patients with no baseline CNS lesions

Fam-trastuzumab deruxtecan-nxki PI. Jerusalem. ESMO Breast 2020. Abstr 1380.

Devam eden çalışmalar

DESTINY-Breast02: T-DXd vs Trastuzumab/Cape or Lapatinib/Cape in HER2+ MBC With Prior T-DM1

- Randomized, open-label, active-controlled phase III trial



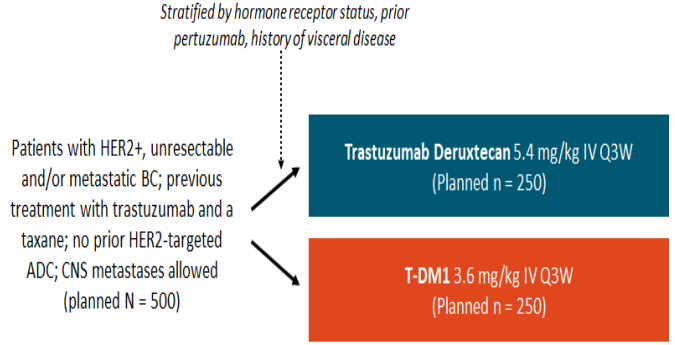
- Primary endpoint: PFS (RECIST v 1.1 by BICR)
- Secondary endpoints: OS, PFS by investigator assessment, ORR, DoR, CBR

NCT03523585.

Slide credit: clinicaloptions.com

DESTINY-Breast03: Second-line T-DXd vs T-DM1 in HER2+ MBC After Progression on Trastuzumab/Taxane

- Randomized, open-label phase III trial at ~ 160 sites in North America and Europe

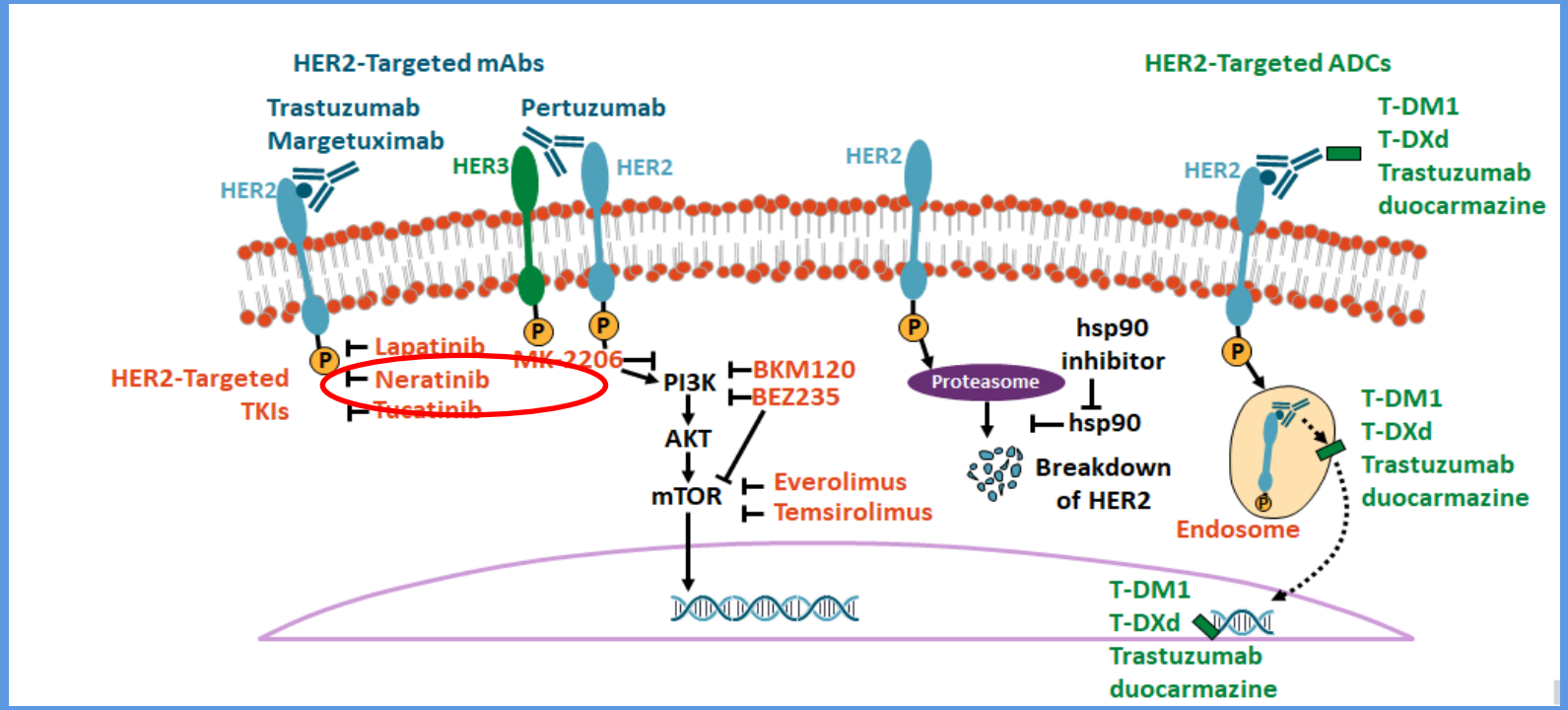


- Primary endpoint: PFS (RECIST v 1.1 by BICR)
- Secondary endpoints: OS, ORR, DoR, CBR, PFS (investigator assessment)

NCT03529110.

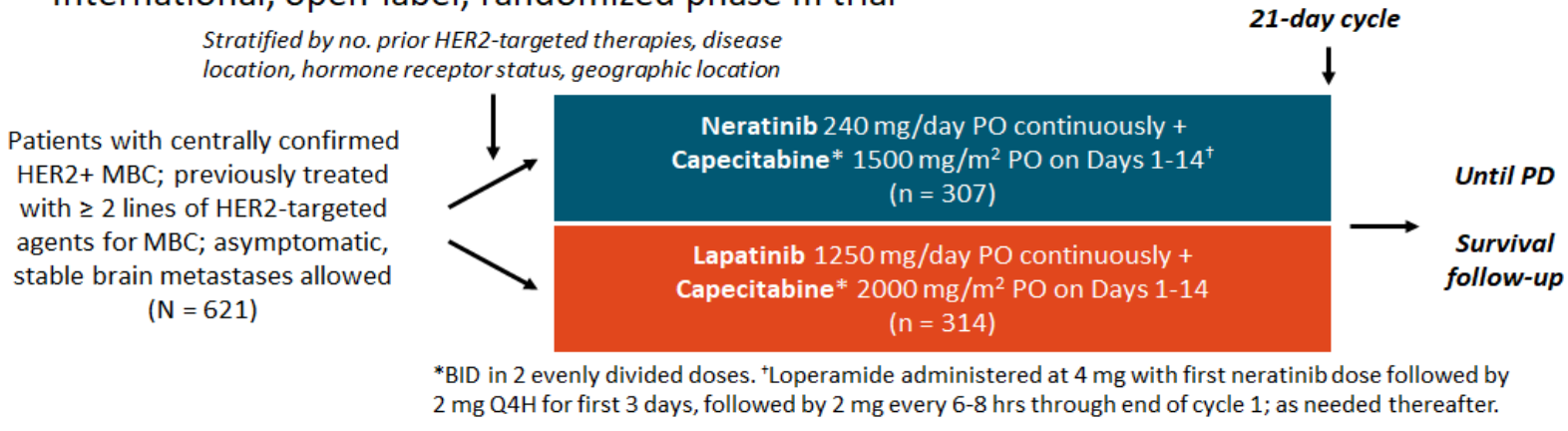
Slide credit: clinicaloptions.com

HER 2 Hedefli Tedaviler



NALA: Neratinib/Cape vs Lapatinib/Cape in HER2+ MBC With ≥ 2 Prior Lines of HER2-Targeted Agents

- International, open-label, randomized phase III trial

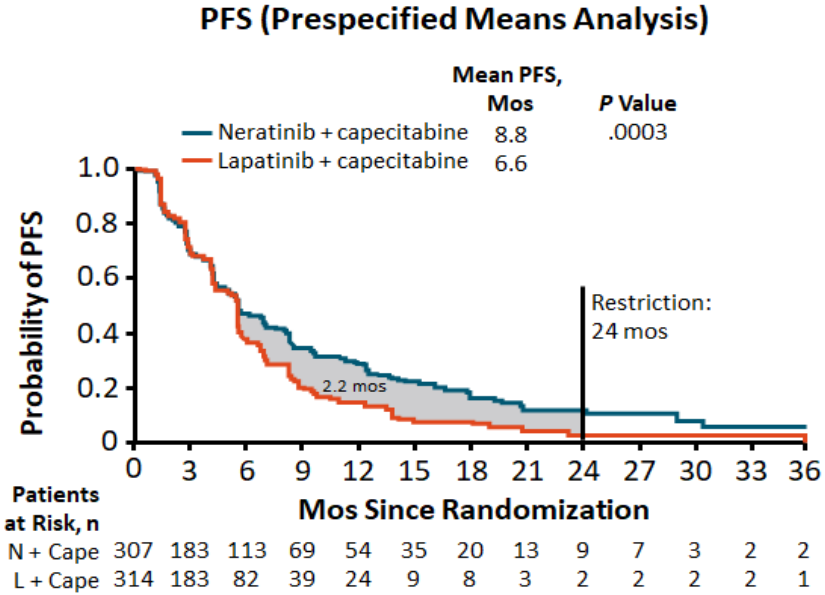


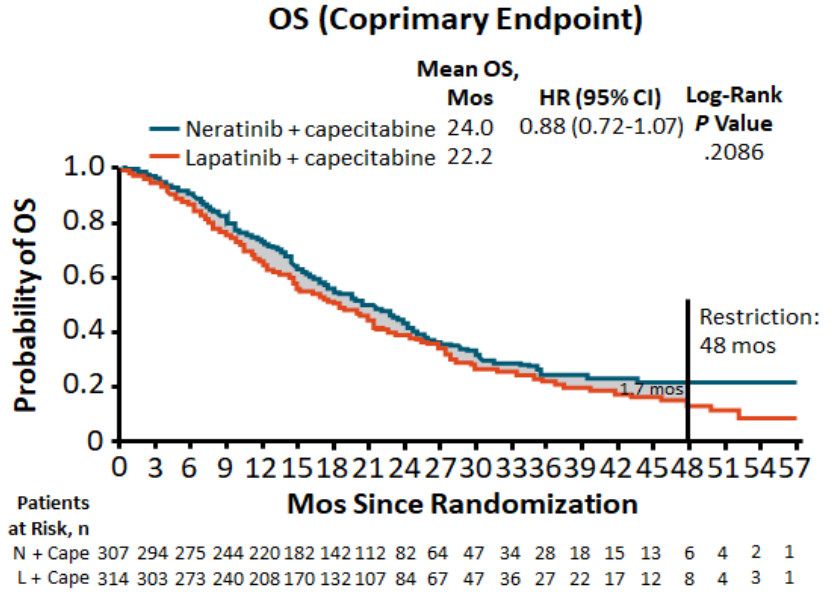
*BID in 2 evenly divided doses. †Loperamide administered at 4 mg with first neratinib dose followed by 2 mg Q4H for first 3 days, followed by 2 mg every 6-8 hrs through end of cycle 1; as needed thereafter.

- Coprimary endpoints: OS, PFS (centrally confirmed)
  - Study positive if either endpoint statistically significant (OS, $P < .04$; PFS, $P < .01$)
- Secondary endpoints: PFS (locally determined), ORR, DoR, CBR, intervention for CNS metastases, safety, PRO
- No endocrine therapy permitted

Saura. JCO. 2020. [Epub]. NCT01808573.

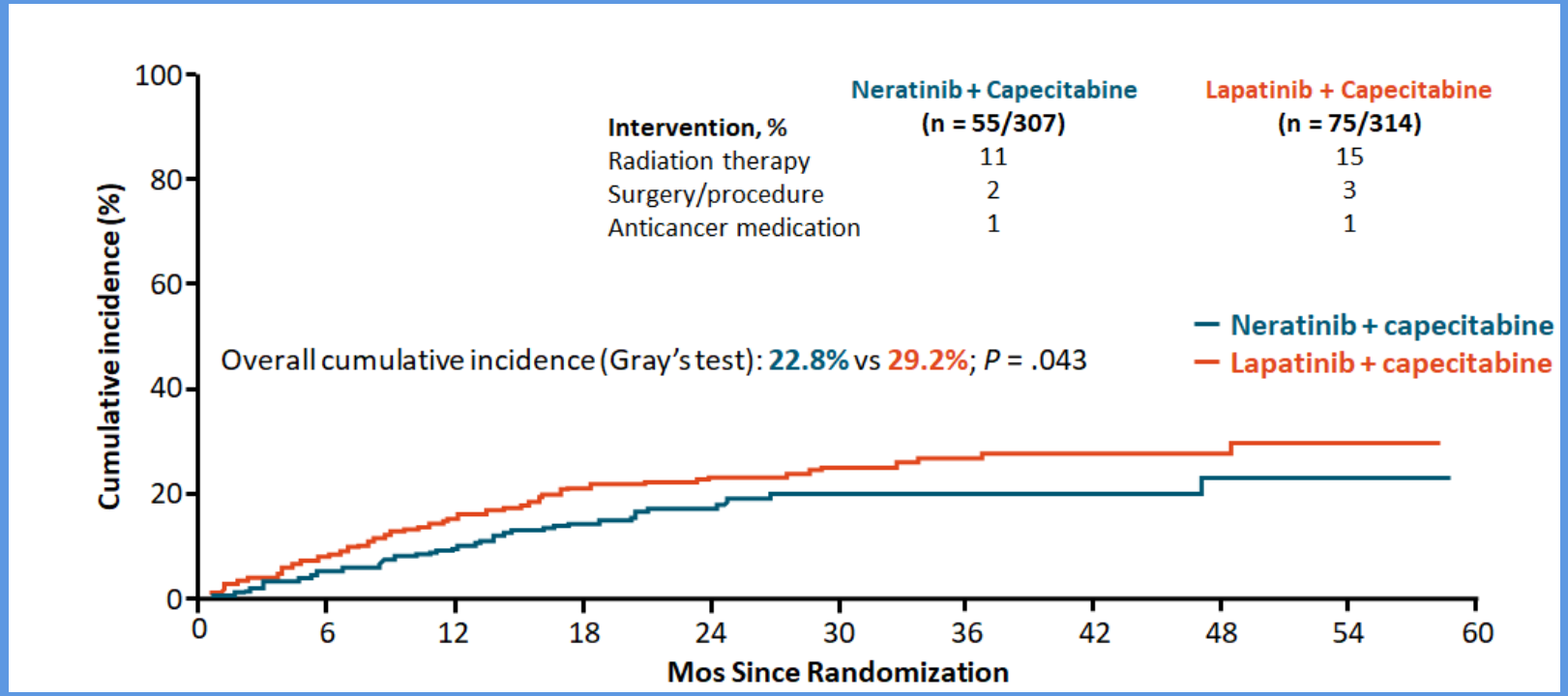
NALA: PFS and OS





Saura. JCO. 2020. [Epub].

NALA: Time to Intervention for CNS Metastases

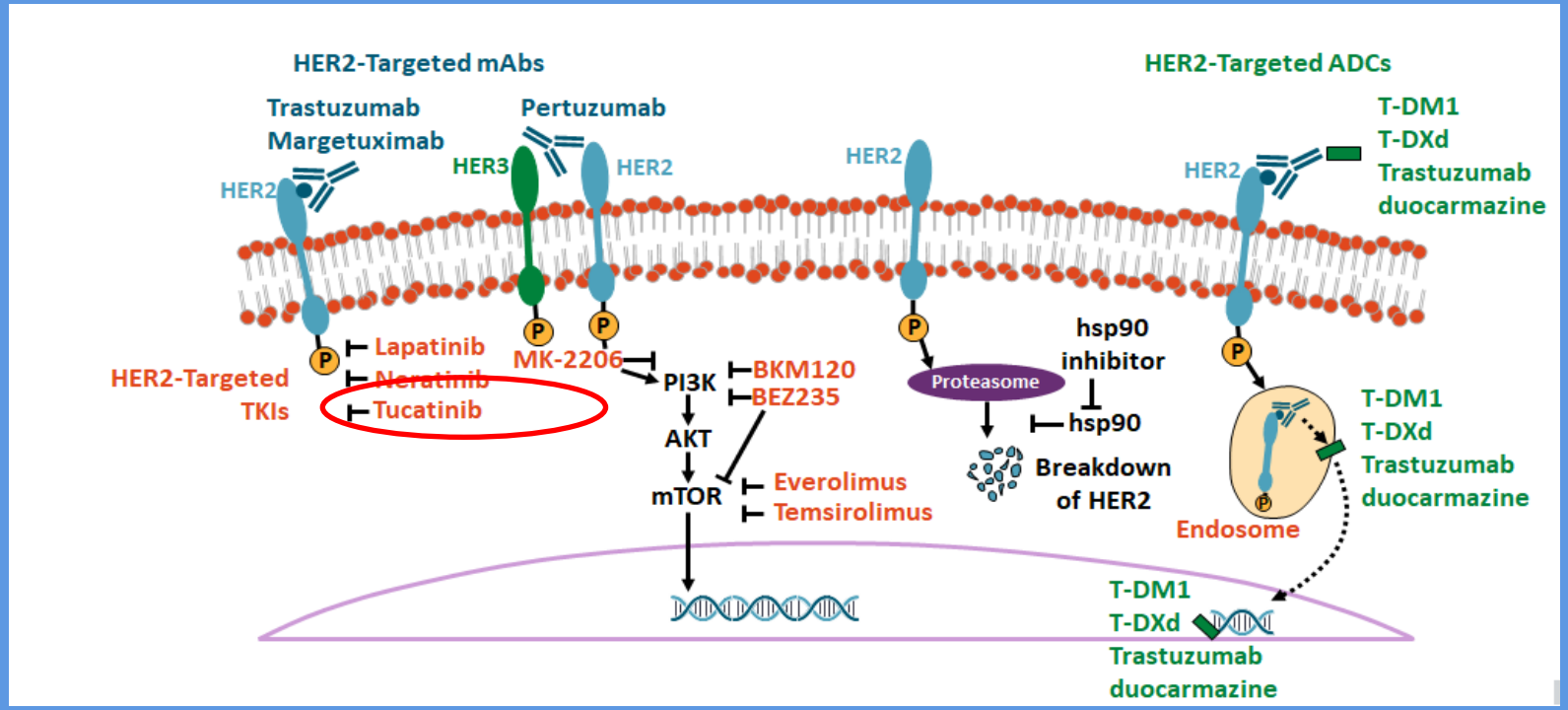


Saura. JCO. 2020. [Epub].

Neratinib Approval - 2.25.2020

- Neratinib approved in combination with capecitabine for adult patients with advanced or metastatic HER2-positive breast cancer *who have received 2 or more prior anti-HER2 based regimens in the metastatic setting*.

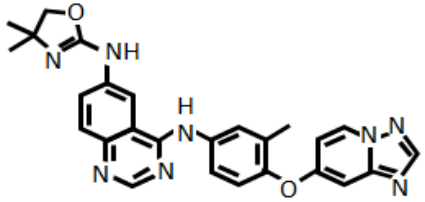
HER 2 Hedefli Tedaviler



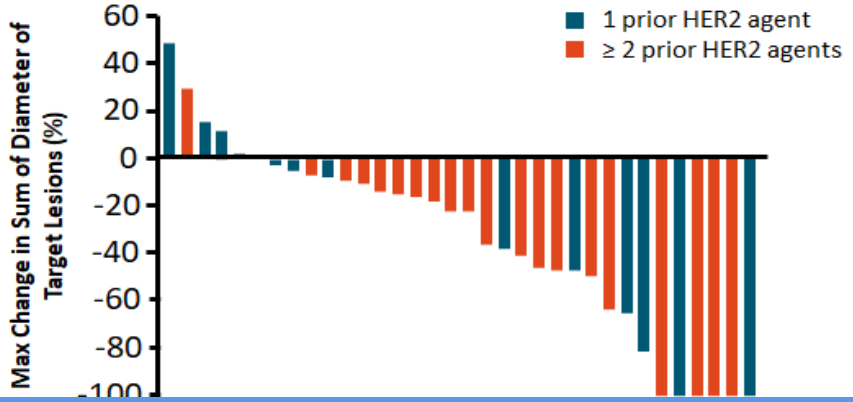
Tucatinib: HER2-Selective TKI

- Less EGFR-associated toxicity than other HER2-targeted TKIs
- CNS penetration
- Well tolerated and active in combinations (eg, with T-DM1, capecitabine, or trastuzumab)

Agent	Cellular Selectivity, IC_{50} (nM)	
	HER2	EGFR
Tucatinib	8	4000
Neratinib	7	8
Lapatinib	49	31



Phase Ib: Tucatinib + T-DM1 in HER2+ MBC



Borges. ASCO 2016. Abstr 513. Borges. JAMA Oncol. 2018;4:1214.

HER2CLIMB: Phase II Study Design

- Randomized, double-blind, placebo-controlled, active comparator phase II trial at 155 sites in 15 countries (February 2016 to May 2019); data cutoff: September 4, 2019; median f/u: 14.0 mos

Stratified by brain mets (yes vs no), ECOG PS (0 vs 1), and region (US or Canada vs rest of world)

21-day cycles

Patients with HER2+ MBC; prior trastuzumab, pertuzumab, and T-DM1; ECOG PS 0/1; brain mets allowed* (N = 612)

*Including previously treated stable mets, untreated mets not needing immediate local therapy, and previously treated progressing mets not needing immediate local therapy.

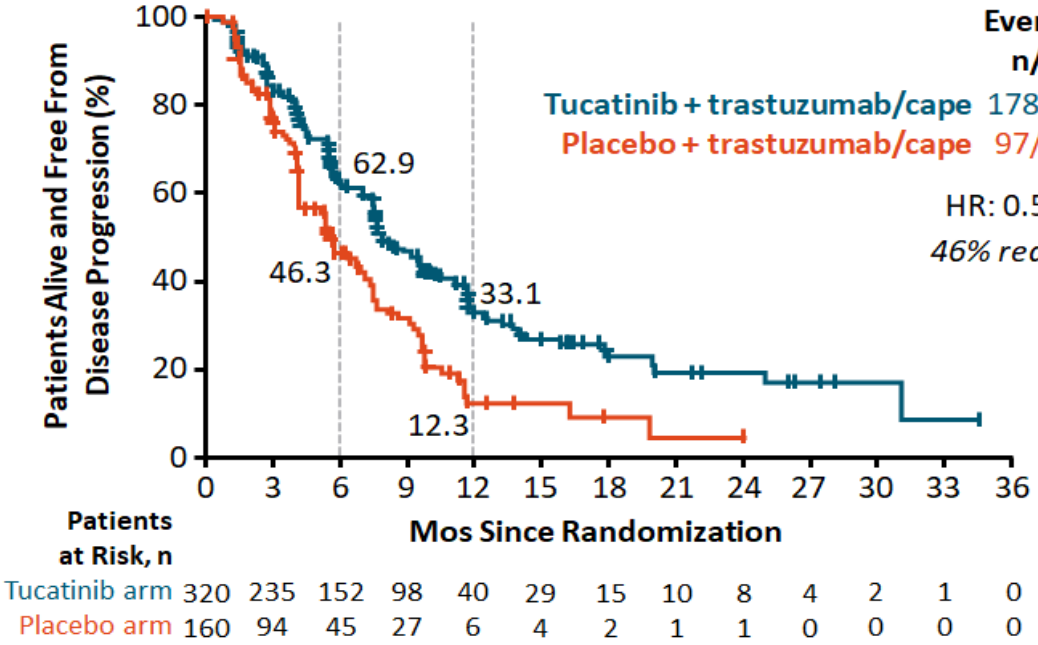
Tucatinib 300 mg PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
(n = 410)

Placebo PO BID +
Trastuzumab 6 mg/kg Q3W (loading dose: 8 mg/kg C1D1) +
Capecitabine 1000 mg/m^2 PO BID on Days 1-14
(n = 202)

- Primary endpoint: PFS (RECIST v 1.1 by BICR) among first 480 randomized patients
  - 90% power with 288 events at α = 5%, HR: 0.67
- Secondary endpoints (total population): OS, PFS in patients with brain mets, ORR in patients with measurable disease, safety in patients who received ≥ 1 dose of study tx

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;382:597.

HER2CLIMB: PFS (Primary Endpoint Population)



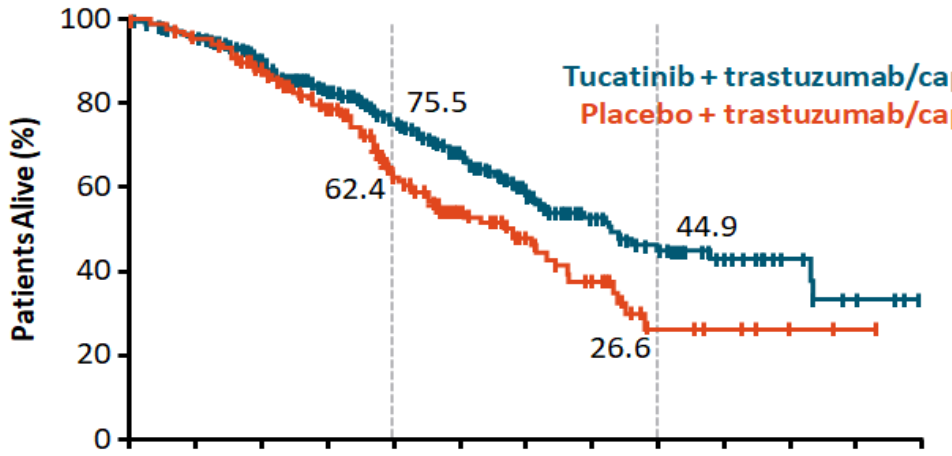
	Events, n/N	Median PFS, Mos (95% CI)	1-Yr PFS, % (95% CI)
Tucatinib + trastuzumab/cape	178/320	7.8 (7.5-9.6)	33 (27-40)
Placebo + trastuzumab/cape	97/160	5.6 (4.2-7.1)	12 (8-21)

HR: 0.54 (95% CI: 0.42-0.71; $P < .00001$)

46% reduction in risk of disease progression

Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;382:597.

HER2CLIMB: OS (Total Population)



Patients at Risk, n												
Tucatinib arm	410	388	322	245	178	123	80	51	34	20	10	4	0
Placebo arm	202	191	160	119	77	48	32	19	7	5	2	1	0

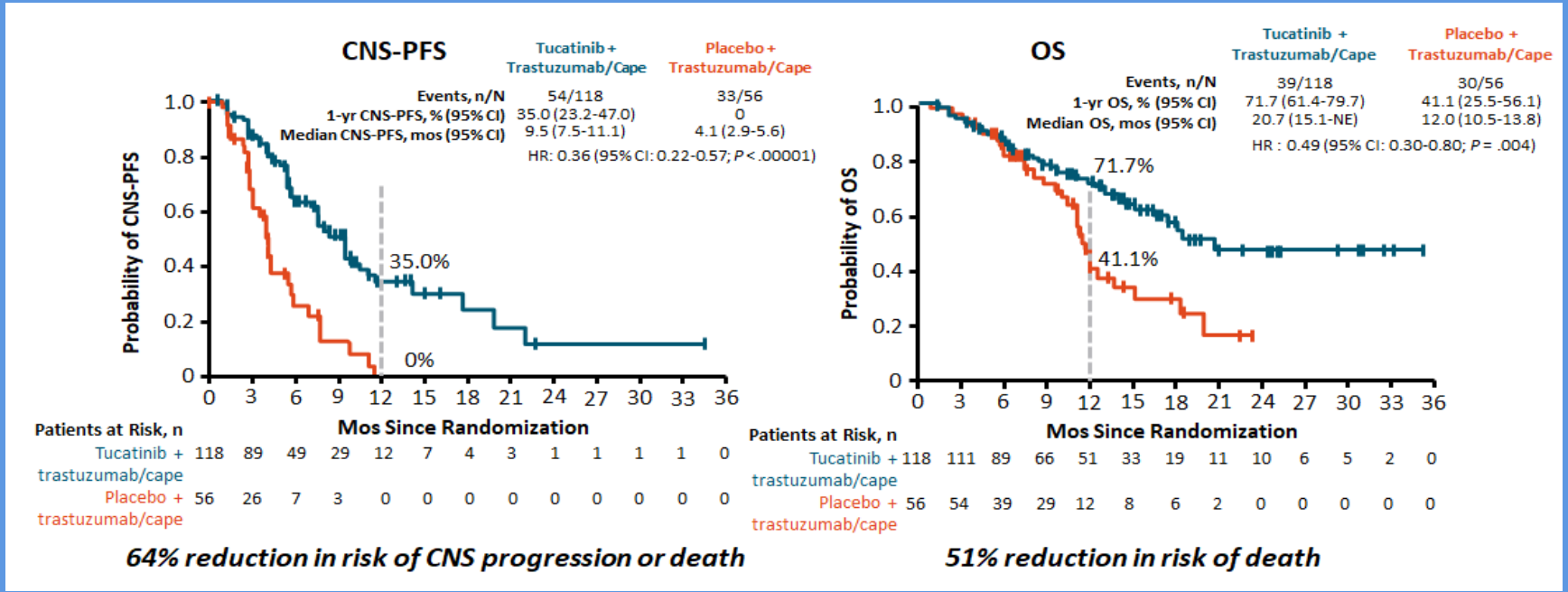
	Events, n/N	Median OS, Mos (95% CI)	2-Yr OS, % (95% CI)
Tucatinib + trastuzumab/cape	130/410	21.9 (18.3-31.0)	45 (37-53)
Placebo + trastuzumab/cape	85/202	17.4 (13.6-19.9)	27 (16-39)

HR: 0.66 (95% CI: 0.50-0.88; *P* = .0048)

34% reduction in risk of death

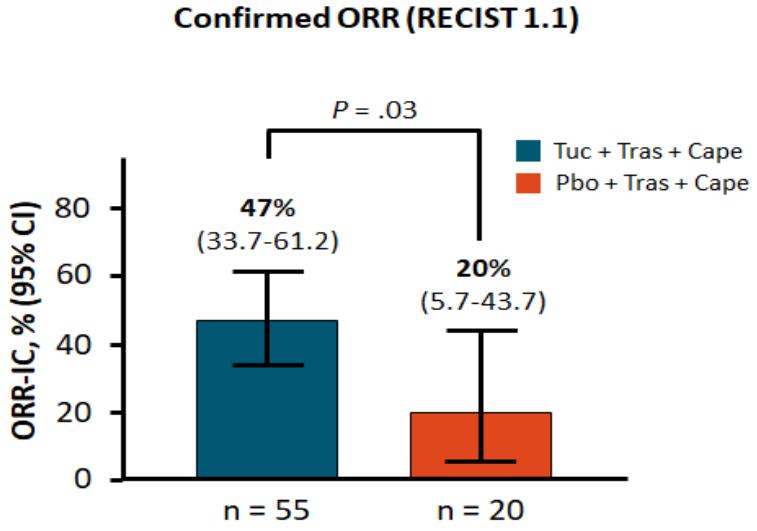
Murthy. SABCS 2019. Abstr GS1-01. Murthy. NEJM. 2019;382:597.

HER2CLIMB Intracranial Activity: CNS-PFS and OS in Patients With Active Brain Metastases



Lin. JCO. 2020;38:2610.

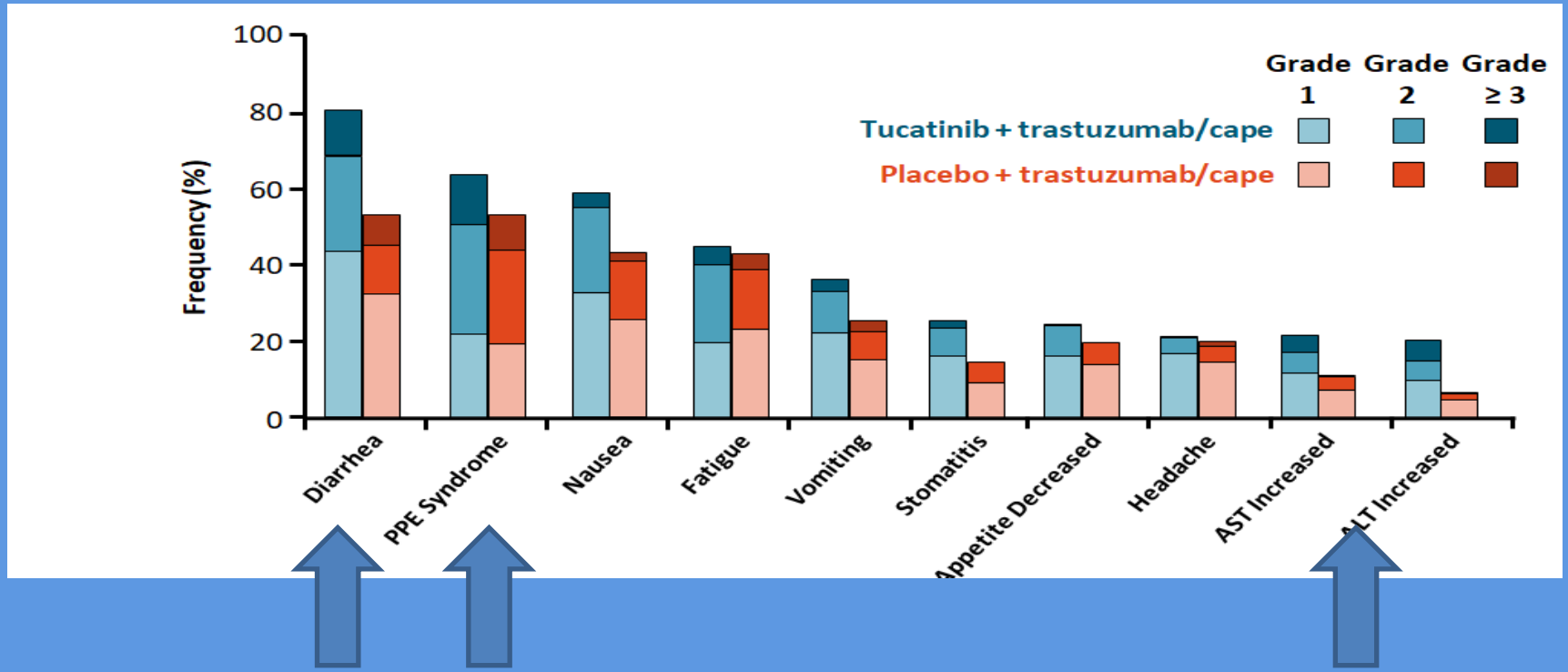
HER2CLIMB Intracranial Response Rate



Response	TUC+Tras+Cape (n = 55)	Pbo+Tras+Cape (n = 20)
Best overall intracranial response, n (%)		
▪ CR	3 (5.5)	1 (5.0)
▪ PR	23 (41.8)	3 (15.0)
▪ SD	24 (43.6)	16 (80.0)
▪ PD	2 (3.6)	0
▪ Not available	3 (5.5)	0
ORR, n	26	4
DoR of intracranial response, mos (95% CI)	6.8 (5.5-16.4)	3.0 (3.0-10.3)

Lin. JCO. 2020;38:2610.

HER2CLIMB: Most Common Adverse Events (≥ 20% in Tucatinib Arm)



Murthy. SABCS 2019. Abstr GS1-01.

Tucatinib Approval

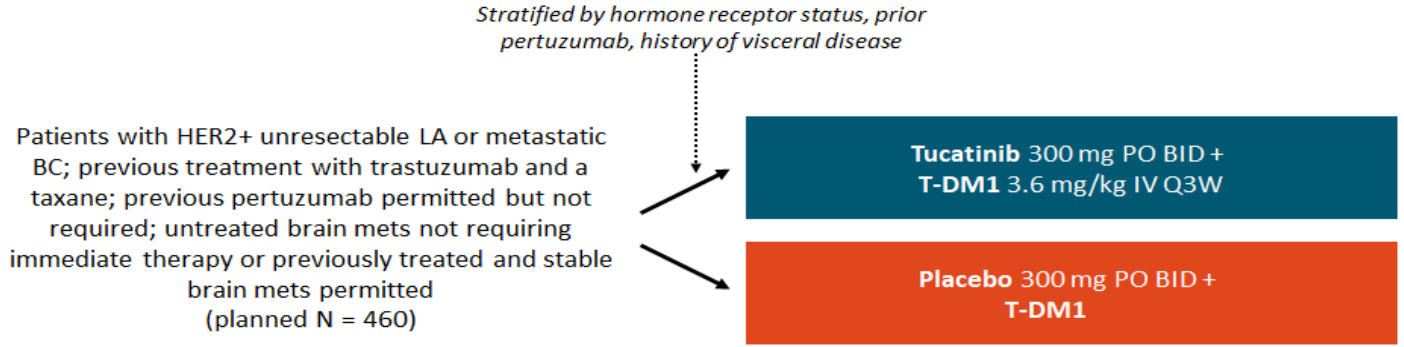
- On April 17, 2020, the FDA approved tucatinib in combination with trastuzumab/capecitabine for treatment of advanced, unresectable or metastatic HER2+ BC, including patients with brain metastases, who have received ≥ 1 previous HER2-targeted therapy in the metastatic setting
  - Administration: 300 mg taken orally twice daily with or without food
    - Reduce dose to 200 mg orally twice daily for patients with severe hepatic impairment
  - Tucatinib can cause severe diarrhea; administer antidiarrheal treatment as clinically indicated
  - Tucatinib can cause severe hepatotoxicity; monitor ALT, AST, and bilirubin prior to starting tucatinib, every 3 weeks during treatment, and as clinically indicated
  - Management of AEs may require temporary interruption, dose reduction, or discontinuation
- Approval based on efficacy data from randomized phase II HER2CLIMB trial

Tucatinib PI.

Devam Eden Çalışmalar

HER2CLIMB-02: Tucatinib or Placebo + T-DM1 in Unresectable HER2-Positive Breast Cancer

- Randomized, double-blind, phase III trial

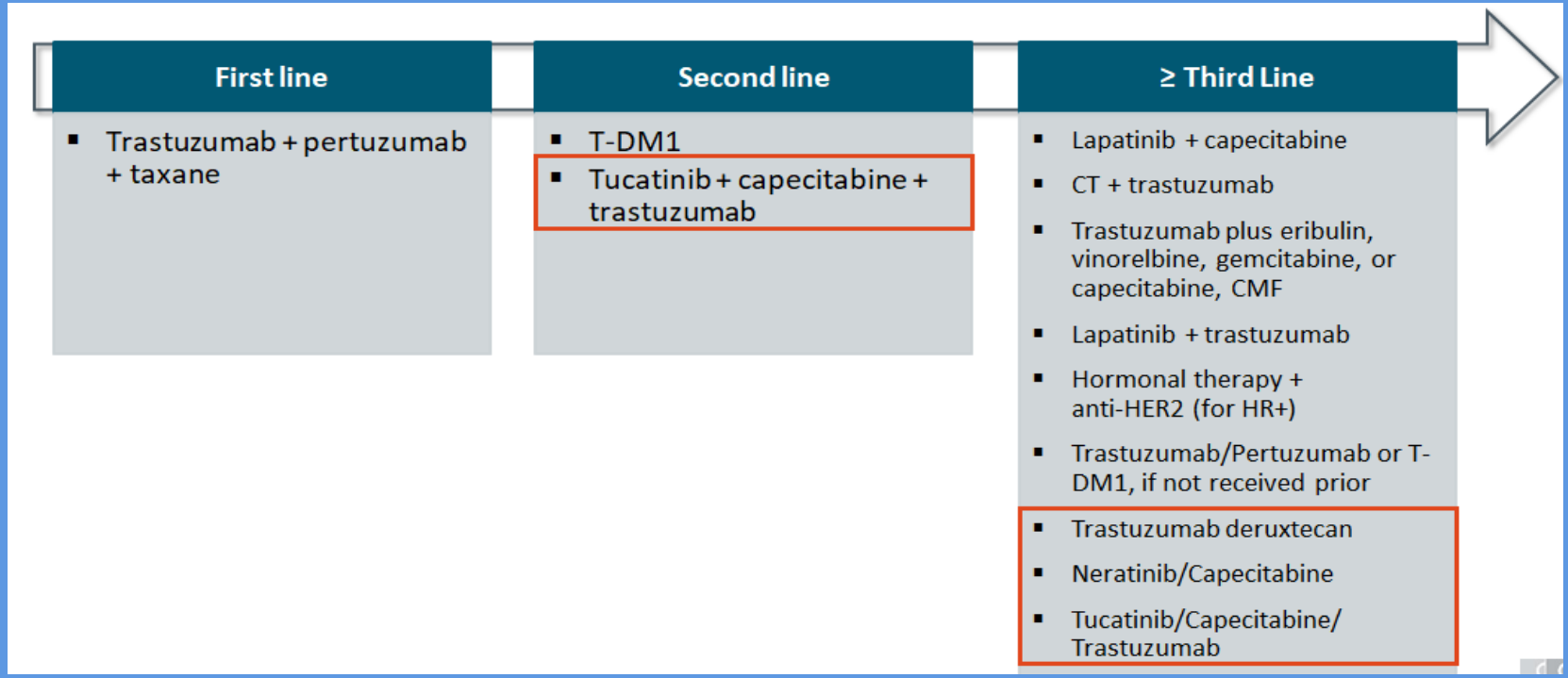


- Primary endpoint: PFS (RECIST v 1.1 by investigator assessment)
- Secondary endpoints: OS, PFS (BICR), ORR, DoR, CBR, rate of AEs

NCT03975647.

Slide credit: clinicaloptions.com

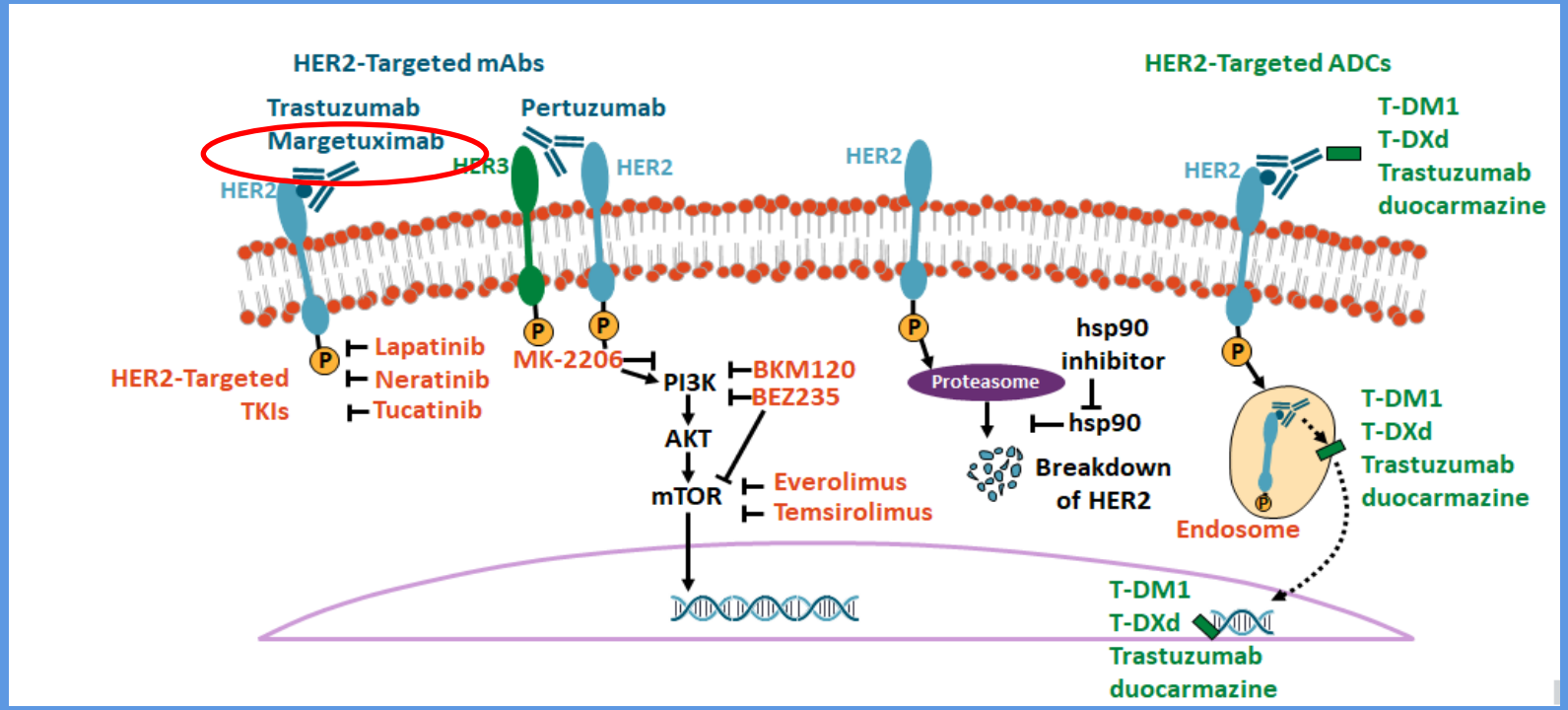
Tedavi Sıralaması



1. Giordano. JCO. 2018;36:2736. 2. NCCN. Breast Cancer. V5.2020. July 15, 2020.

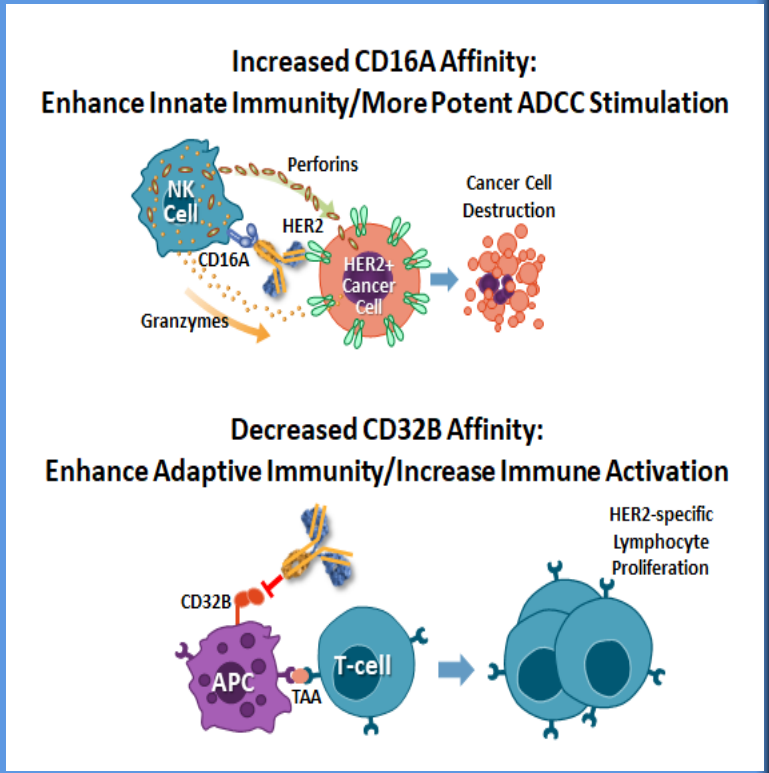
✓ Yeni Geliştirilen Tedaviler

HER 2 Hedefli Tedaviler



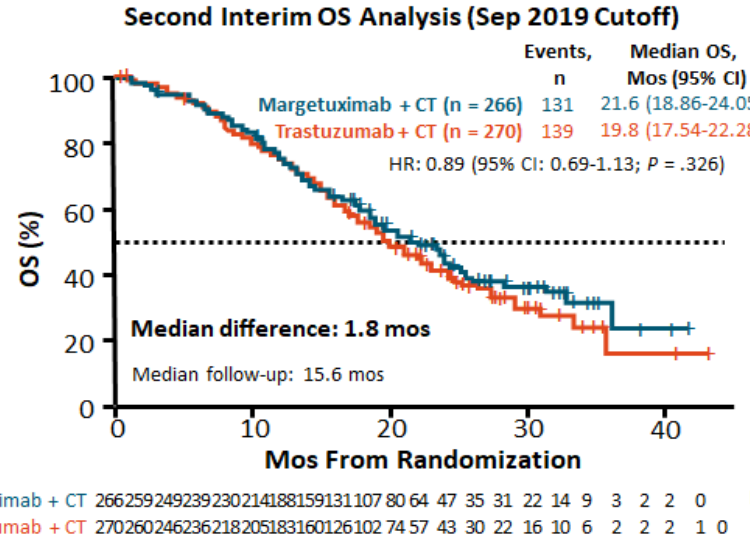
Margetuximab: Novel HER2-Targeted Monoclonal Antibody

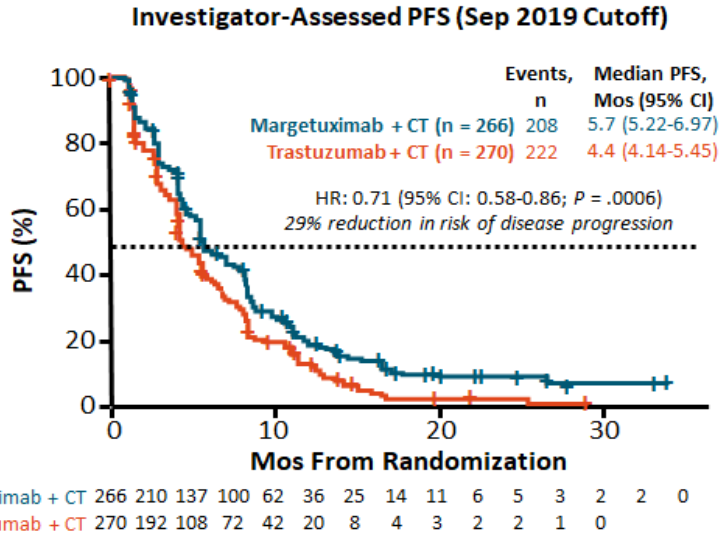
- Margetuximab has the same specificity, affinity to HER2 as trastuzumab with similar ability to disrupt signaling
- However, via Fc engineering with intent to activate immune responses, margetuximab has altered Fc receptor affinity
  - Trastuzumab: WT IgG1 effector domains; binds and activates immune cells
  - Margetuximab: Increased affinity for activating Fcγ RIIIA (CD16A) and decreased affinity for inhibitory Fcγ RIIB (CD32B)



Nordstrom. Breast Cancer Res. 2011;13:R123. Nordstrom. ASCO 2019. Abstr 1030.

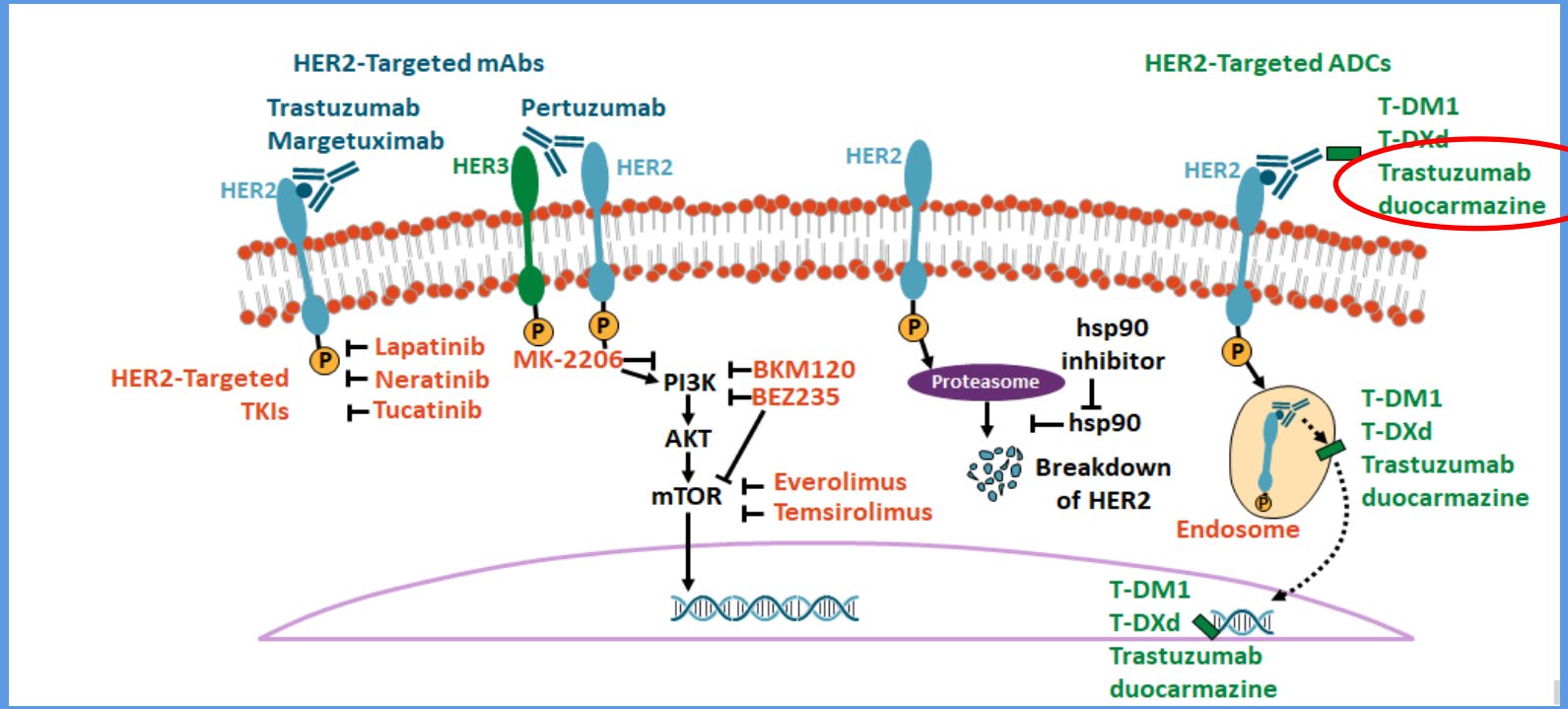
SOPHIA: Investigator-Assessed OS and PFS



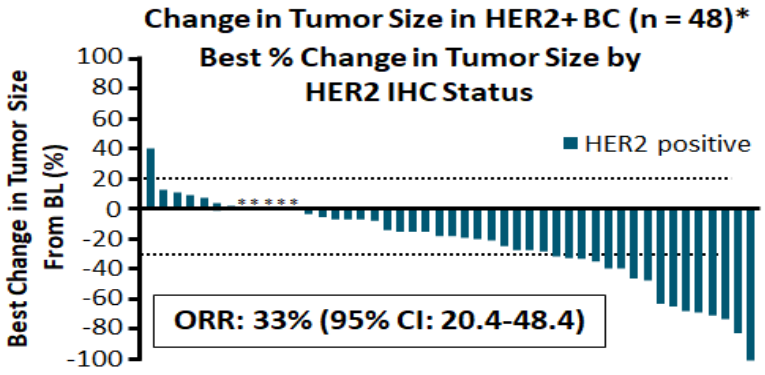


Rugo. SABCS 2019. Abstr GS1-02.

HER 2 Hedefli Tedaviler



Phase I Study: Trastuzumab Duocarmazine in Locally Advanced or Metastatic HER2+ Breast Cancer



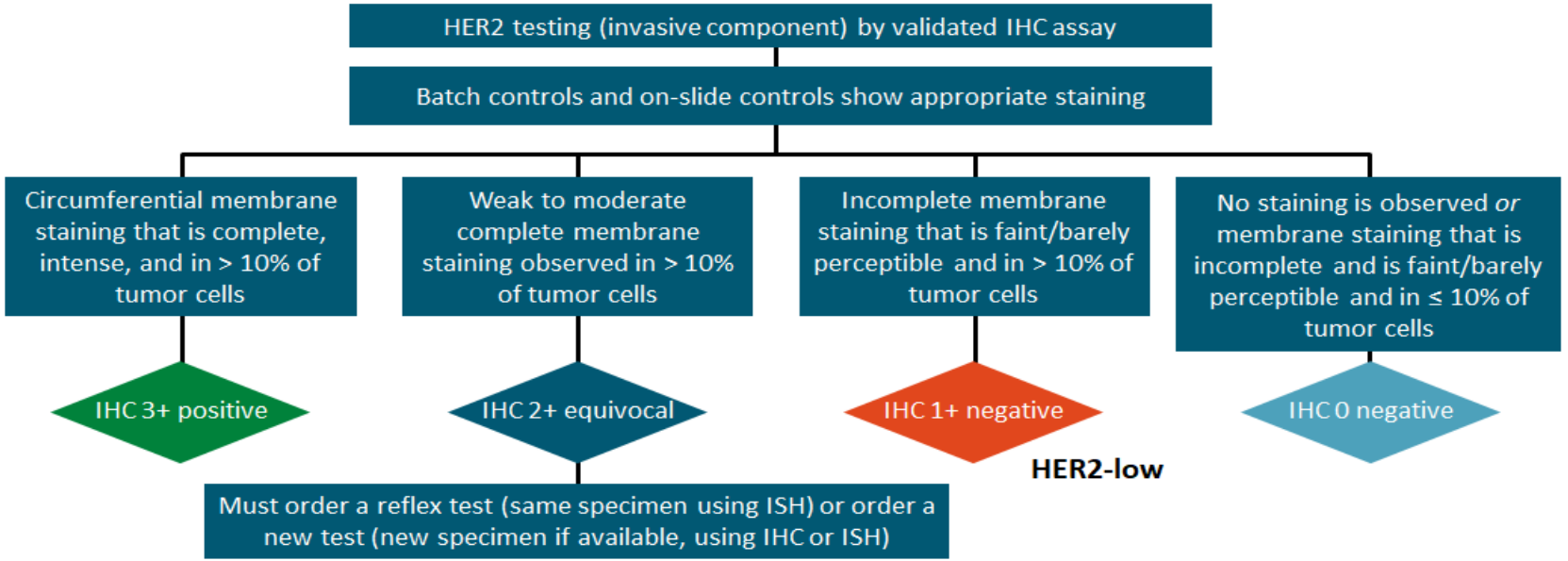
- Trastuzumab duocarmazine: ADC with trastuzumab linked to duocarmycin prodrug
- Most drug-related TEAEs mild to moderate
- Ocular toxicity reported in 2/3 of patients; most common reason for treatment discontinuation/dose modification

Drug-Related AE, n (%)	Dose-Expansion Cohorts (n = 146)	
	Grade 1/2	Grade 3
Fatigue	43 (29)	5 (3)
Conjunctivitis	41 (28)	4 (3)
Dry eye	44 (30)	1 (1)
Increased lacrimation	29 (20)	0
Dry skin	26 (18)	0
Decreased appetite	27 (18)	2 (1)
Alopecia	26 (18)	0
Nausea	27 (18)	0
Stomatitis	24 (16)	0
Neutropenia	14 (10)	9 (6)
Vomiting	17 (12)	0
Anemia	13 (9)	2 (1)
Pyrexia	9 (6)	0

Banerji. Lancet Oncol. 2019;20:1124.

✓ HER2-low: Yeni bir alt grup mu?

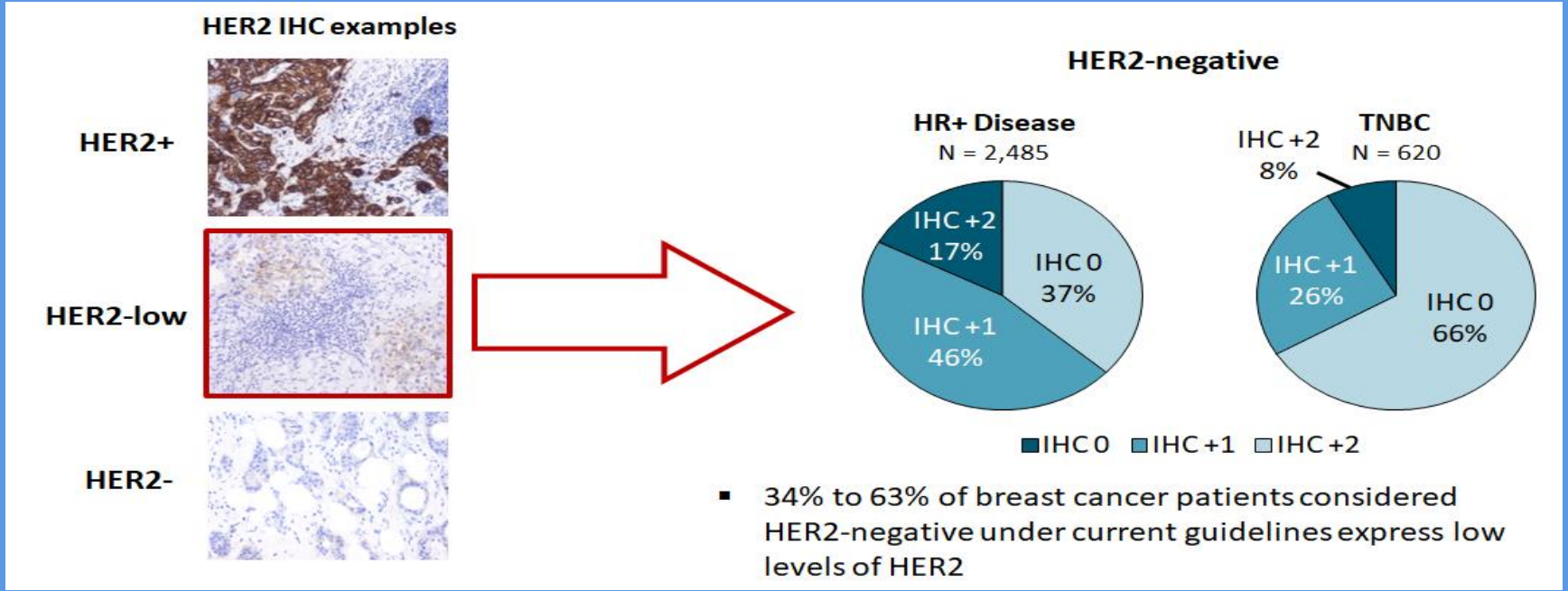
HER2 Testing by IHC: 2018 ASCO/CAP Guidelines



- 2007, 2013/2014, and 2018 guidelines largely ignore both the IHC 0/1+ false-negative and the IHC 3+ false-positives

Wolff. Arch Pathol Lab Med. 2018;142:1364.

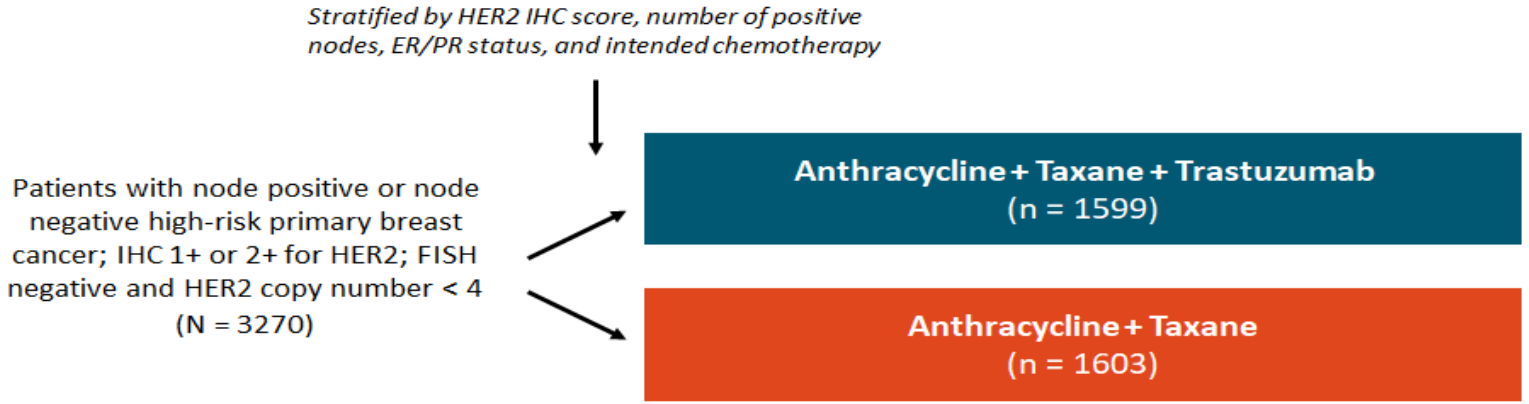
Prevalence of HER2-low by HR-status



Schettini. ESMO Breast Cancer Virtual Meeting 2020. Abstr 23P. Slide courtesy of Aleix Prat.

- ✓ HER2-low: Yeni bir alt grup mu?
- ✓ Anti-HER2 tedaviler bu grupta etkili mi?

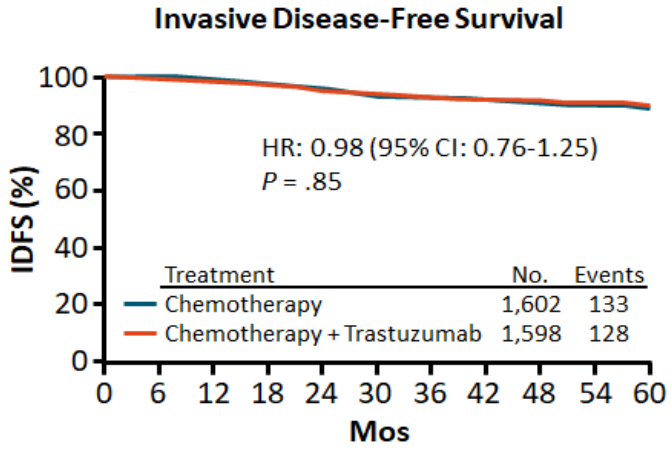
NSABP B-47: Adjuvant Trastuzumab in Patients With Normal/Low HER2 Expression Breast Cancer

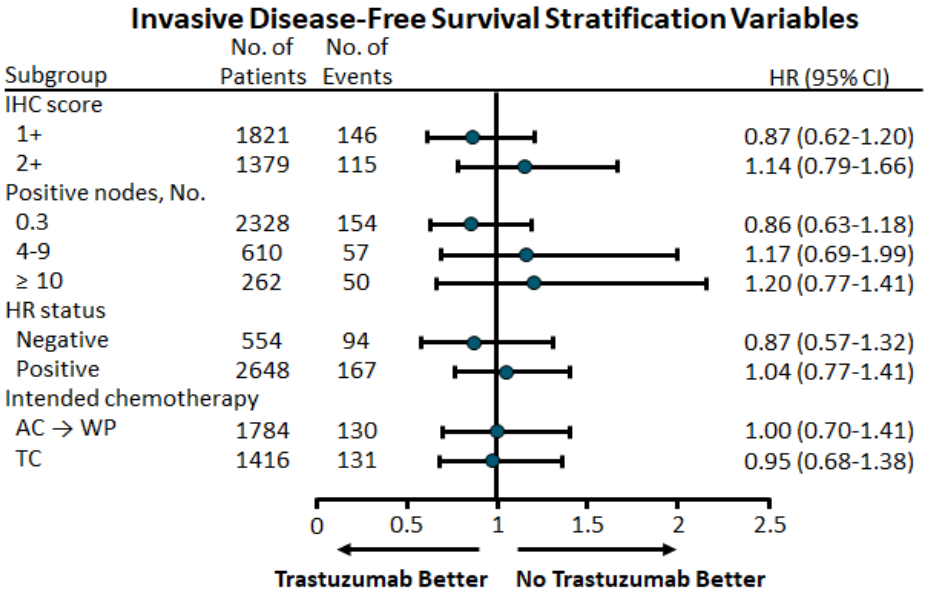


- Chemotherapy options: docetaxel/cyclophosphamide (6 cycles) or doxorubicin/cyclophosphamide (4 cycles) followed by paclitaxel

Fehrenbacher. SABCS 2017. Abstr GS1-02. Fehrenbacher. JCO. 2020;38:444.

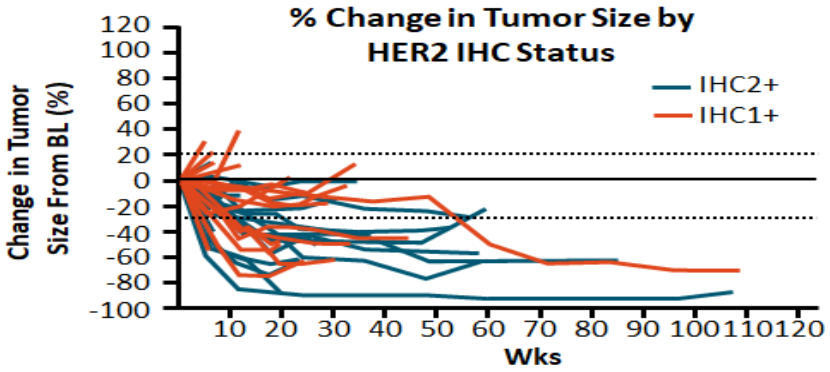
NSABP B-47: Invasive Disease-Free Survival

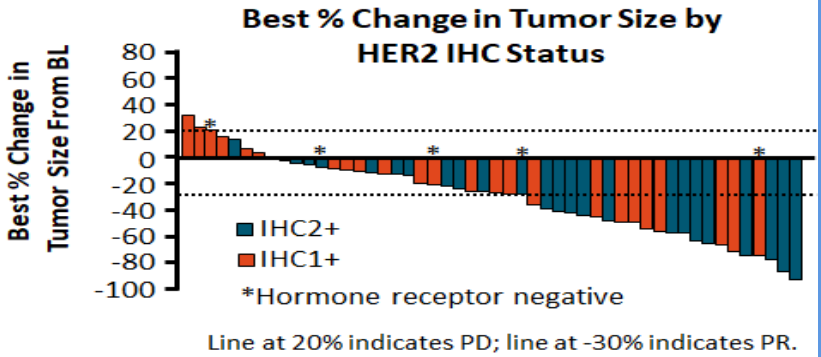




Fehrenbacher. JCO. 2020;38:444.

Efficacy of Trastuzumab Deruxtecan in HER2-Low MBC





Line at 20% indicates PD; line at -30% indicates PR.

Efficacy in HER2-Low MBC	Confirmed ORR, %	Median DoR, Mos	Median PFS, Mos
All (N = 51)	44.2	9.4	7.6
IHC 2+ (n = 24)	**54.5**	11.0	**13.6**
IHC 1+ (n = 27)	**33.3**	7.9	**5.7**
HR+ (n = 45)	47.4	11.0	7.9
Prior CDK4/6 inhibitor (n = 15)	33.3	NR	7.1

Modi. SABCS 2018. Abstr P6-17-02.

HER2-low Trastzumab Deruxtecan
Devam eden çalışmalar

- Randomized, open-label, active-controlled phase III trial

Stratified by HER2 IHC status, no. of prior lines of CT, HR status (HR+ without previous CDK4/6i vs HR+ with previous CDKi vs HR-)

Patients with HER2-low (IHC1+ or IHC2+/ISH-), unresectable and/or metastatic BC; progression on endocrine therapy; 1 to 2 prior lines chemo/adjuvant in metastatic setting; no prior findings of high HER2 expression; no prior anti-HER2 treatment
(planned N = 540)

Trastuzumab Deruxtecan 5.4 mg/kg IV Q3W
(planned n = 360)

Physician's Choice of CT:
Capecitabine, Eribulin, Gemcitabine, Paclitaxel or nab-Paclitaxel
(planned n = 180)

- Primary endpoint: PFS (RECIST v 1.1 by BICR)
- Secondary endpoints: OS, PFS (investigator assessment), ORR, DoR

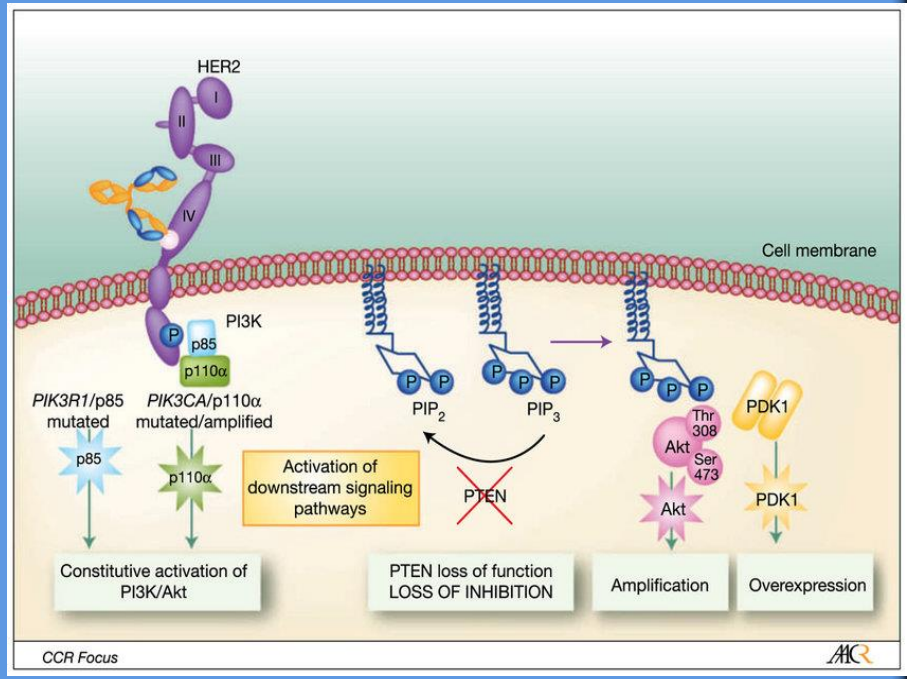
NCT03734029.

✓ HER2 hedefli tedavilerde direnç

Resistance to HER2 Targeted Therapy

Proposed mechanisms of resistance

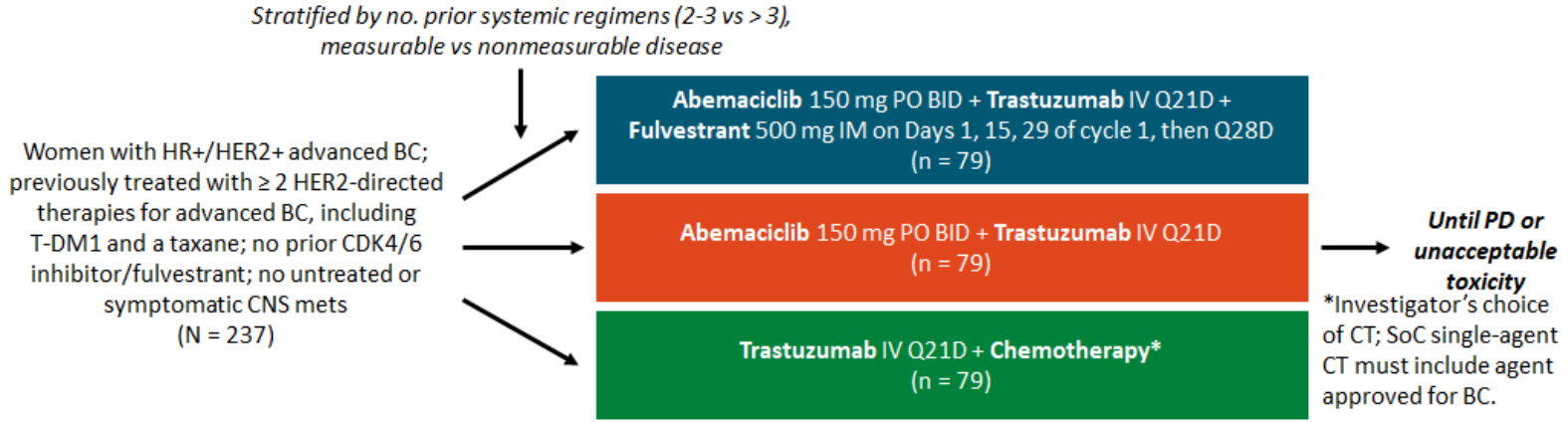
- ✓ Alterations in the HER2 receptor [1]
- ✓ Hyperactivation of the downstream signaling pathways (PI3K-AKT, EGFR, IGFR, mTOR and MAPK/ERK)[1-3]
- ✓ Variations in host-tumor immune interactions[4]
- ✓ Cyclin D1/CDK4/6/pRB pathway: a downstream signal activated by HER2 ligand-receptor interaction[5]



1. Vernieri. Crit Rev Oncol Hematol. 2019;139:53. 2. Berns. Cancer Cell. 2007;12:395. 3. Nagata. Cancer Cell. 2004;6:117.
4. Wang. Asian Pac J Cancer Prev. 2015;16:2591. 5. Goel. Cancer Cell. 2016;29:255.

monarcHER: Abemaciclib in Previously Treated HR+/HER2+ Advanced BC—Study Design

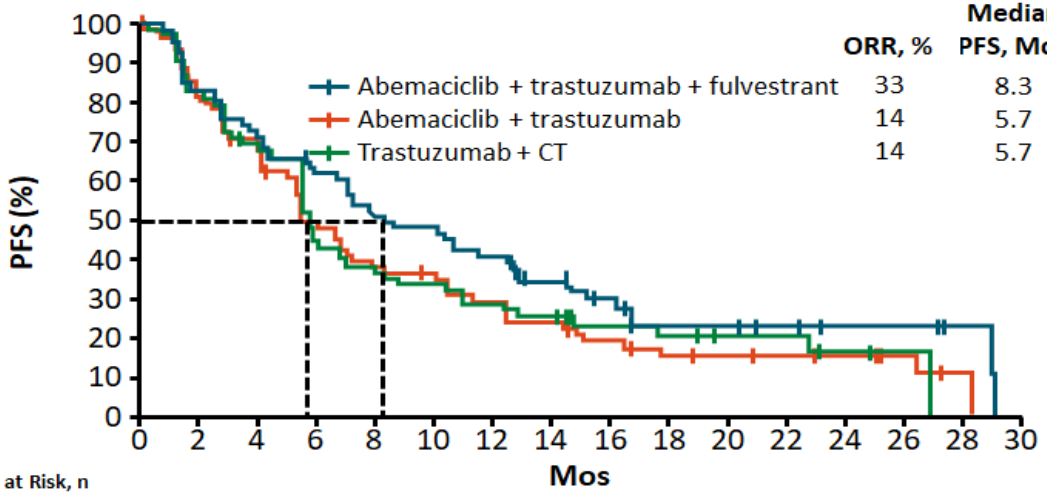
- International, open-label, randomized phase II trial



- Primary endpoint: investigator-assessed PFS for abemaciclib + trastuzumab + fulvestrant vs trastuzumab + CT, then abemaciclib + trastuzumab vs trastuzumab + CT if positive
  - Study designed to achieve 80% power and 2-sided $\alpha = 0.2$ with 165 PFS events, assuming hazard ratio of 0.667
- Secondary endpoints: ORR, OS, PRO, PK, safety

Tolaney. Lancet Oncol. 2020;21:763.x

monarcHER: Investigator-Assessed PFS (Primary Endpoint)



	ORR, %	Median PFS, Mos	HR	*P* Value (vs Trastuzumab + CT)
Abemaciclib + trastuzumab + fulvestrant	33	8.3	0.673	.051
Abemaciclib + trastuzumab	14	5.7	0.94	.77
Trastuzumab + CT	14	5.7	---	---

2-sided log-rank test

Patients at Risk, n															
Abemaciclib + trastuzumab + fulvestrant	79	63	53	44	36	34	29	21	14	8	8	6	4	4	2
Abemaciclib + trastuzumab	79	60	49	33	25	23	18	15	11	8	7	6	5	3	1
Trastuzumab + CT	79	54	44	27	22	20	17	15	8	7	5	5	2	1	0

- Median PFS significantly prolonged by 2.6 mos with abemaciclib + trastuzumab + fulvestrant (prespecified 2-sided $\alpha = 0.2$); no PFS benefit for abemaciclib + trastuzumab vs trastuzumab + CT

Tolaney. Lancet Oncol. 2020;21:763.

Other Selected Clinical Trials for HER2-Positive MBC

Study	Agents	Ph/N	Population	Results
PATRICIA[1]	Palbociclib + tras ± letrozole	I/II 15/31	ER- or ER+ HER2+ MBC w/ ≥ 2 but < 6 prior tx	6-mo PFS: ER-: 33.3%, ER+: 40%, 53.3% (w/letrozole)
PATINA[3]	Anti-HER2 + endo tx ± palbociclib	III 496	HER2+ HR+ MBC, no prior tx for adv disease beyond induction	NR
EPIK-B2[4]	Tras + pertuzumab ± alpelicib	III 448 (pl)	Adv HER2+, *PIK3CA* mut BC, prior tx w/ taxane/tras/pert 4-6 cycles	NR
PANACEA[5]	Pembrolizumab + tras	Ib/II 58	Adv BC, HER+, progression on tras or T-DM1, sample for PD-L1 screen	PD-L1+ vs PD-L1- (median, mos): PFS: 2.7 v 2.5; OS: NR v 7.0
KATE2[6]	TDM-1 ± atezolizumab	II 202	HER2+ LABC or MBC, prior tx w/ taxane and tras, no prog on met tx or w/in 6 mos adj tx	Median PFS, mos, TDM-1 + atezolizumab v TDM-1 + pbo: 8.2 v 6.8 (ITT); 8.5 v 4.1 (PD-L1 IC)

1. Ciruelos. SABCS 2018. Abstr PD3-03. 2. Tolaney. Lancet Oncol. 2020;21:763. 3. Metzger. SABCS 2018. Abstr OT3-02-07.
4. NCT04208178. 5. Loi. Lancet Oncol. 2019;20:371. 6. Emens. ESMO 2019. Abstr 3050. NCT02924883.

✓ Kılavuz Önerileri

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 6.2020 — September 8, 2020

SYSTEMIC THERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Positive[i,j,k]	
Preferred regimens	**Other recommended regimens**
• Pertuzumab + trastuzumab + docetaxel (category 1)[l] • Pertuzumab + trastuzumab + paclitaxel	• Tucatinib + trastuzumab + capecitabine (category 1)[m] • Ado-trastuzumab emtansine (T-DM1) • Fam-trastuzumab deruxtecan-nxki[n] • Trastuzumab + paclitaxel ± carboplatin • Trastuzumab + docetaxel[l] • Trastuzumab + vinorelbine[l] • Trastuzumab + capecitabine • Lapatinib + capecitabine • Trastuzumab + lapatinib (without cytotoxic therapy) • Trastuzumab + other agents[l,o,p] • Neratinib + capecitabine • See additional targeted therapy options (BINV-R)[e]

ABC5 | Bridging the Gap

Guideline statement	LoE/GoR	Consensus
✓Anti-HER2 tedavi, HER2-pozitif tüm hastalara erkenden başlanmalı (1. sıra)	I/A	98%
✓Anti-HER2 tedavi altında progrese hastalarda kontrendikasyon yoksa anti-HER2 tedaviye devam edilmeli. Tercih; ✓Ülkede ulaşılabilirlik ✓Daha önceki anti-HER2 tedaviler ve RFS ✓Optimal sıralama bilinmiyor ✓Optimal süre (ne zaman kesilecek) bilinmiyor	I/A	91%
✓CR elde edilmiş hastalarda optimal süre bilinmiyor; ✓Toksisite ,Bölge,Fiyat ,Hasta ile tartışılabilir ✓Uzun CR sonrası (rechallenge imkanı varsa) tedavi kesilebilir	Expert opinion/C	93%
Patients who have received any type of (neo)adjuvant anti-HER2 therapy should not be excluded from clinical trials for HER2-positive ABC. These patients remain candidates for anti-HER2 therapies.	I/B	100%

ABC5 | Bridging the Gap

✓Seçilmiş ER+ hastalarda 1. sırada anti-HER2+ET, dual blokaj tercih edilebilir.	I/B	80%
✓ER+ hastalıkta KT+AntiHER2 tedavi seçildiyse ve yarar sağlandıysa tedaviye ET+antiHER2 tedavi ile progresyona kadar devam edilebilir (her ne kadar randomize çalışması olmasa da). ✓İdame ET ile tek mi dual anti-HER2 mi sorusunun cevabı yok.	n/a/B	80%
In the first-line setting, for HER2-positive ABC previously treated (in the adjuvant setting with DFI >12 months) or untreated with trastuzumab, combinations of ChT + trastuzumab are superior to combinations of ChT + lapatinib in terms of PFS and OS.	I/A	95%
✓1. basamakta taksan+trastuzumab+pertuzumab (özellikle daha önce anti-HER2 tedavi almamış olanlarda) önerilen tedavi seçeneğidir ✓Neo(adjuvan) anti-HER2 tedavi almış hastalarda KT+trastuzumab+pertuzumab 1. sırada en önemli opsiyon (CLEOPATRA çalışmasında az hasta adjuvan trastuzmab kullanmış idi.	I/A I/A	86% 76%

Few (88) of these patients were treated in the CLEOPATRA trial and all with a trastuzumab-free interval >12 months.		
✓Progresyon sonrası Trastuzumab+pertuzumab dual blokajın devamı ile ilgili data yok ve kullanımı önerilmez. 1. sırada kullanılmamışsa 1. sıradan sonra kullanılabilir.	I/E	86%
	II/B	76%
✓Trastuzumab içerikli tedavi sonrası progresyonda en iyi seçenek T-DM1,	I/A	88%
✓Trastuzumab temelli tedavi sonrası Tratuzumab+lapatinib bir opsiyon. Pertuzumab ve TDM1 sonrası veri yok.	I/B	84%
✓Neratinib+Kapesitabin rutin kullanımı için yeterli veri yok	I/D	90%

ABC5 | Bridging the Gap

recommended for routine clinical practice. **ESMO-MCBS: No manuscript publication; precludes scoring.** Additional studies are needed to clearly establish the potential role of this combination in the treatment of brain metastases, as well as the role of neratinib for ABC.		
✓Trastuzumab Derukstekan çoklu basamak tedavi alan hastalarda aktif. Pulmoner toksisiteye dikkat!!!	II/B	98%
✓Pertuzumab+trastuzumab+TDM1 kullanmış hastalarda Trastuzumab+capesitabine Tucatinib eklemenin mütevazi yararı var. Ve bu aşamada kullanılabilir.	II/B	98%
Margetuximab + ChT showed only a small PFS benefit (1 month) when compared with trastuzumab + ChT for patients pretreated with pertuzumab and T-DM1, and cannot therefore be recommended for routine clinical practice. **ESMO-MCBS: No manuscript publication; precludes scoring.** The role of *CD16A* genotype as a predictor of anti-HER2 antibody efficacy and selection of anti-HER2 agent should be further explored.	I/D	95%
Regarding the ChT component of HER2-positive ABC treatment:	I/A	88%

ABC5 | Bridging the Gap

✓Pertuzumab verilmeyecek ise 1. sırada trastuzumab ile vinorelbin yada taksan kulalnılabilir. Diğer KT ajanları ile çalışmalar yetersiz olduğundan tercih edilmez.		
✓İleri basamaklarda Trastuzumab, ✓capecitabine, eribulin, liposomal anthracyclines, platinum, gemcitabine yada metronomic KT ile kullanılabilir.	II/A	91%
✓Trastuzumab + Pertuzumab ile kombine olacak KT ajanı docetaxel [I/A] or paclitaxel [I/B]dir. Vinorelbine [II/A], nabpaclitaxel [II/B] and capecitabine [I/A] ve metronomik KT de (II/B) olabilir.	See in statement	86%

UpToDate®

- ✓ Adjuvan trastuzumab almışsa;
  - ✓ > 6 ay TFI var ise P+H+T (dosetaxel/pakl)
  - ✓ <6 ay ise TDM-1 (ulaşılamıyorsa H+KT veya L+X)
- ✓ Daha önce tedavi almamış hastalarda P+H+T öneriliyor
- ✓ En iyi cevap alındıktan sonra (6-12 ay) T±P ile devam edilmesi (optimal süre??)
- ✓ HR+ ise KT kesildikten sonra hormonal tedavi eklenebilir

COVID-19 Pandemic Breast Cancer Consortium: Recommendations for Advanced-Stage Invasive BC

- Adjust dose/schedule of systemic therapy to reduce visits, bloodwork, and serious AEs
- Defer routine staging scans in patients without PD
- Risks of palliative CT may outweigh possible gains in some cases

ER+ BC	HER2+ BC
▪ Consider potential toxicity risks of oral targeted therapy (CDK4/6, mTOR, and PIK3CA inhibitors) ▪ Dose reduction may reduce toxicity ▪ First- or second-line CDK4/6 inhibitors can be delayed in patients likely to maintain tumor control with ET alone	▪ Dosing intervals may be increased for trastuzumab, pertuzumab, and antibody–drug conjugates ▪ Consider interrupting trastuzumab-based maintenance in patients with > 2 yrs of tumor control and minimal disease burden

Dietz. Breast Cancer Res Treat. 2020;181:487.