New Data for HER2 Driven Metastatic Breast Cancer

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Overview

- New mechanisms of Trastuzumab and Lapatinib Resistance
- New Therapies and Combinations

New Mechanisms of Resistance

Mechanisms of Action and Biological Significance of HER2 Mutations in HER2-Overexpressing Breast Cancer

Delphine R. Boulbes, Quanri Jin, Stefan T. Arold, John E. Ladbury, Dihua Yu, Francisco J. Esteva

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MD Anderson Cancer Center

Background

- The *her2* gene is amplified in 20% of invasive breast cancers
- *Her2* amplification is a predictive marker of response to trastuzumab and lapatinib therapy
- Response to trastuzumab and lapatinib is heterogeneous
  - 15-20% of patients with early-stage breast cancer develop metastatic disease despite adjuvant trastuzumab
  - Most patients with HER2 positive metastatic breast cancer develop progressive disease and die despite trastuzumab- and lapatinib-based therapy

Background

- Identification of molecular mechanisms of resistance to HER2-targeted therapy is an area of active investigation
- EGFR and HER2 mutations are predictive of response to tyrosine kinase inhibitors in lung cancer cells
- Limited data on *her2* mutations in breast cancer

Hypothesis: mutations in the *her2* kinase domain predict response to targeted therapy in HER2-positive breast cancers

Methods

78 HER2-positive primary invasive breast cancers from patients who subsequently received trastuzumab for metastatic disease

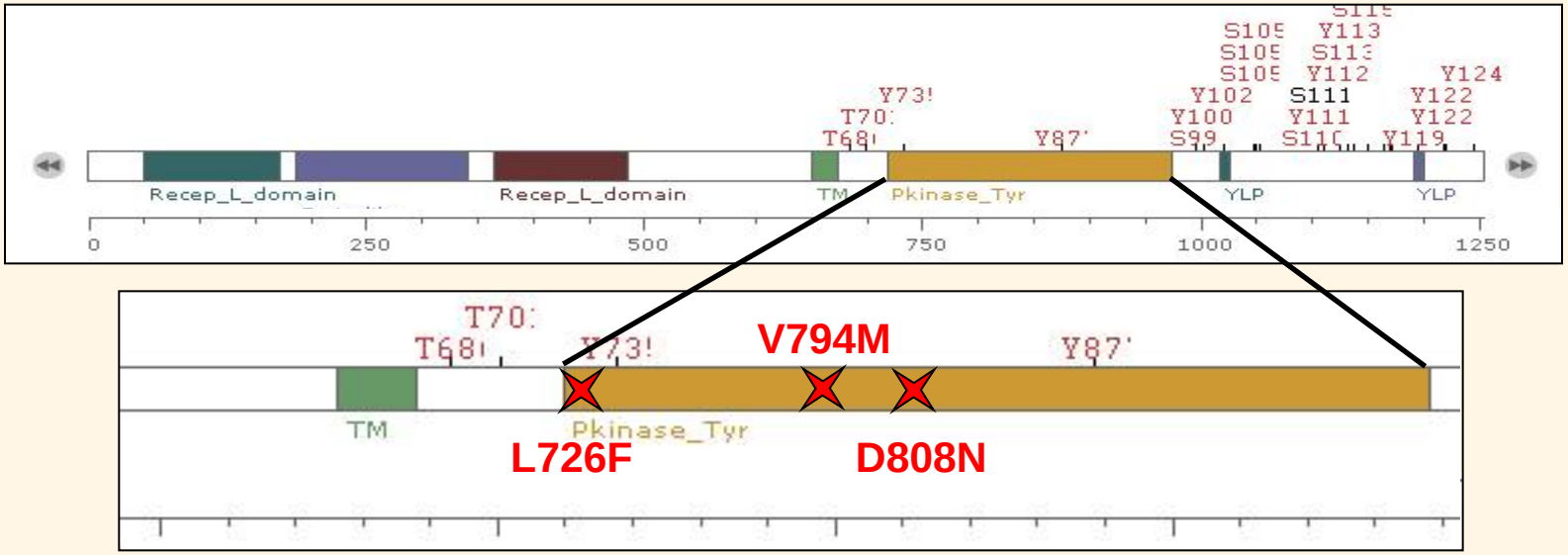
↓

Sequenced kinase domain of *her2* using the Sanger method

↓

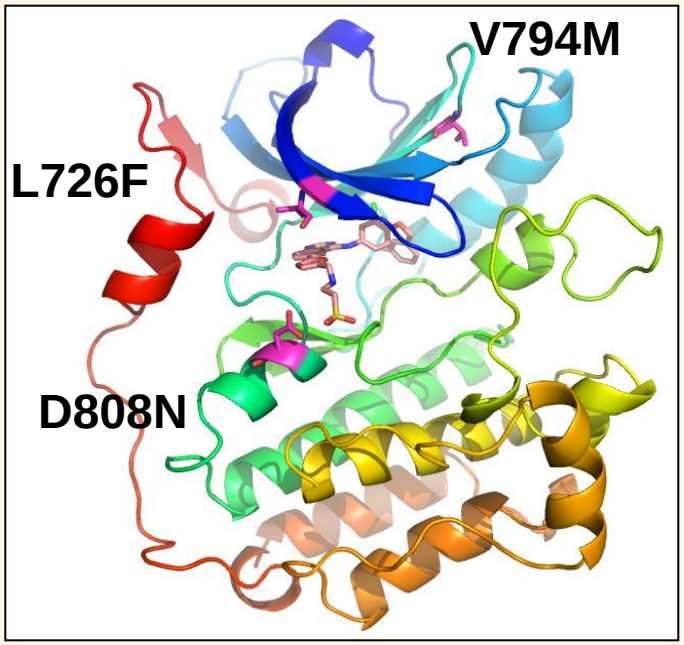
Identified 3 mutations: D808N, V794M, L726F (each mutation on a different tumor)

Localization of HER2 mutations



L726F is located at the entrance of the ATP binding cleft.

D808N is close to nucleotide binding site.

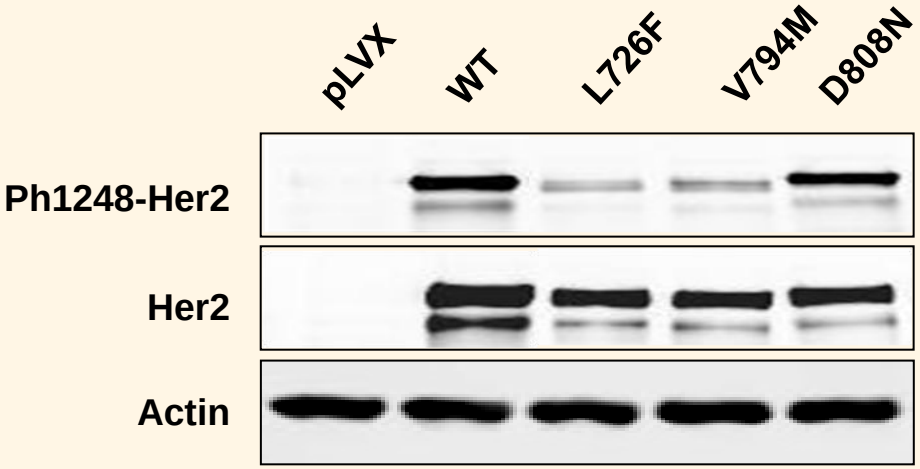


V794M is at the interface between 'activator' and 'acceptor' molecules.

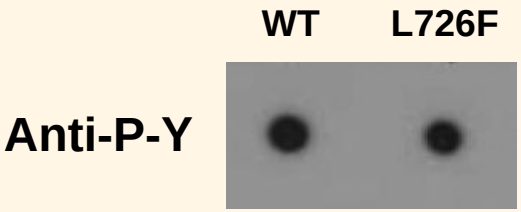
Methods (Cont.)

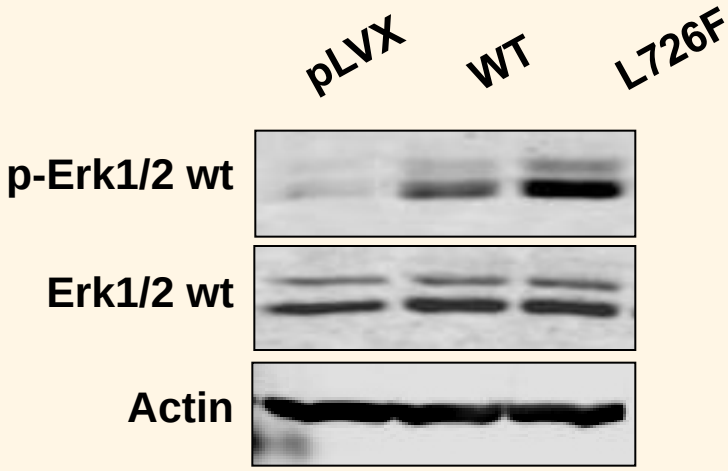
- Site-directed mutagenesis
- Cell Lines
  - MCF10A: non-tumorigenic
  - MDA-MB-175: HER2 overexpressed
  - SKBR3 and BT474: Her2 gene amplified
- Anchorage-independent growth (soft-agar)
- Mammosphere formation
- Invasion assay (matrigel)
- Cell survival during drug incubation

L726F & V794M show a dramatic lack of phosphorylation



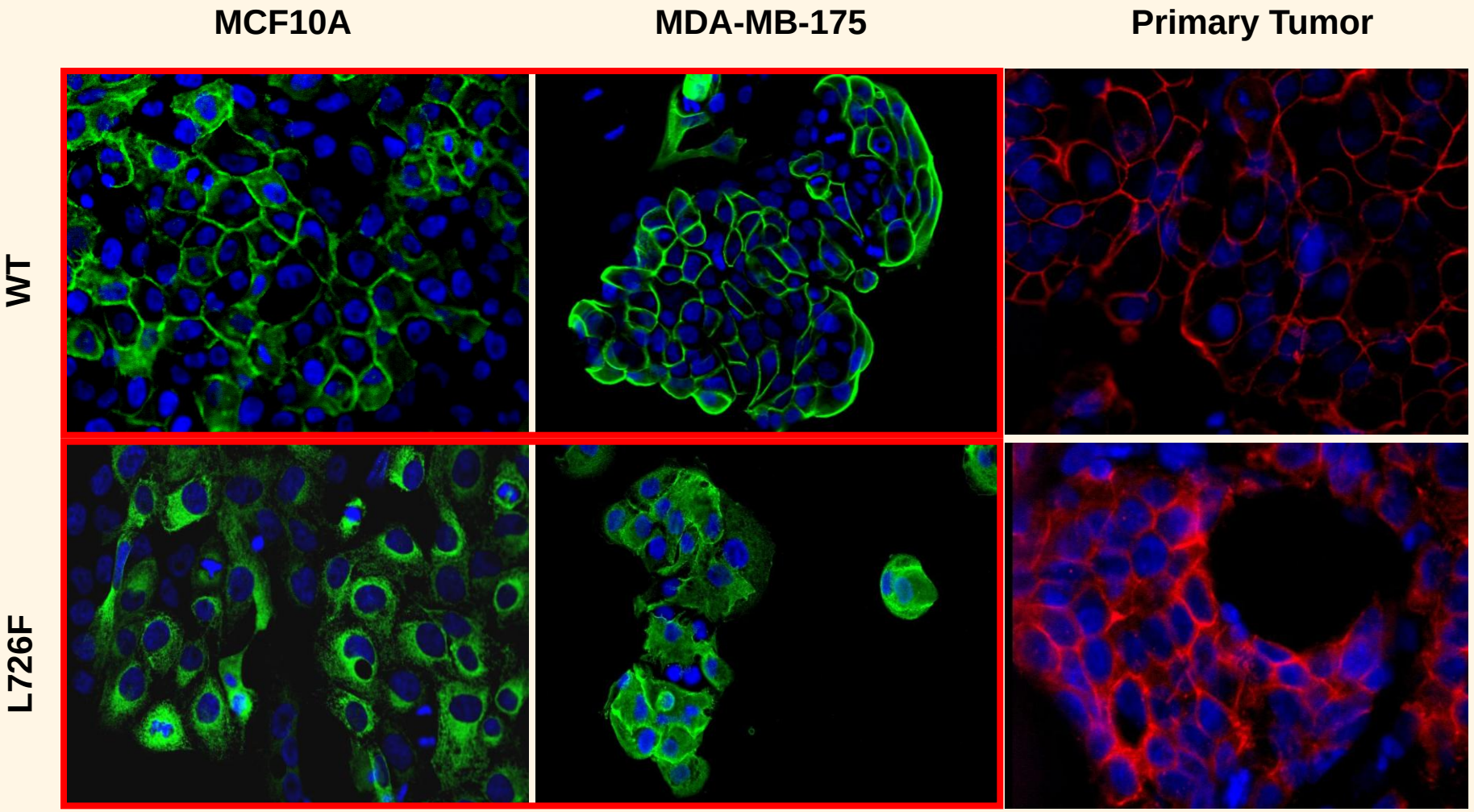
IP: HER2
Kinase assay



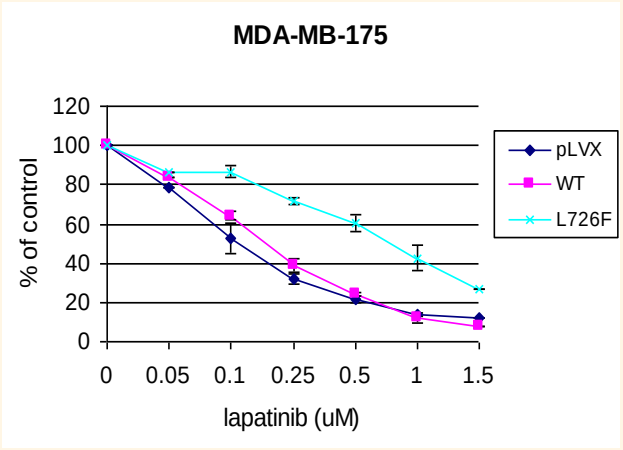


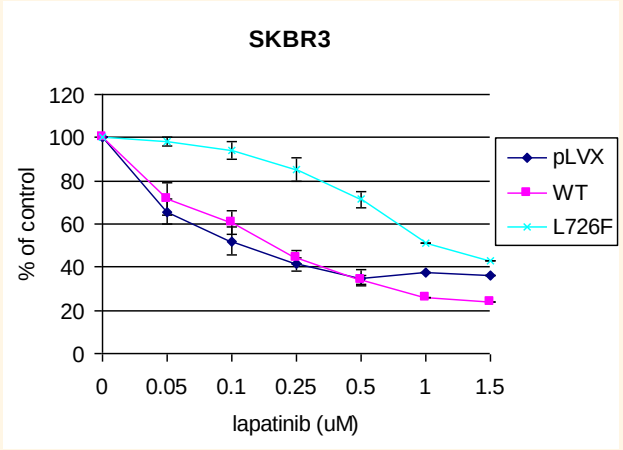
Impaired Cellular Localization of the L726F mutant in Primary Breast Cancer Tissue

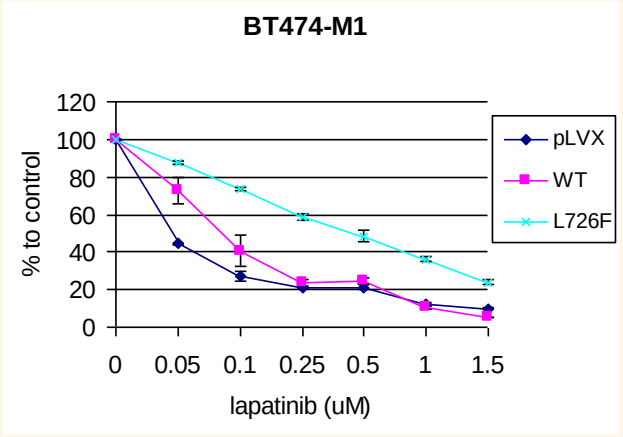
➢ Y1248 altered phosphorylation status has been shown to be involved in intracellular localization (Ramsauer VP et al., *J Biol Chem* 278, 30142-7)

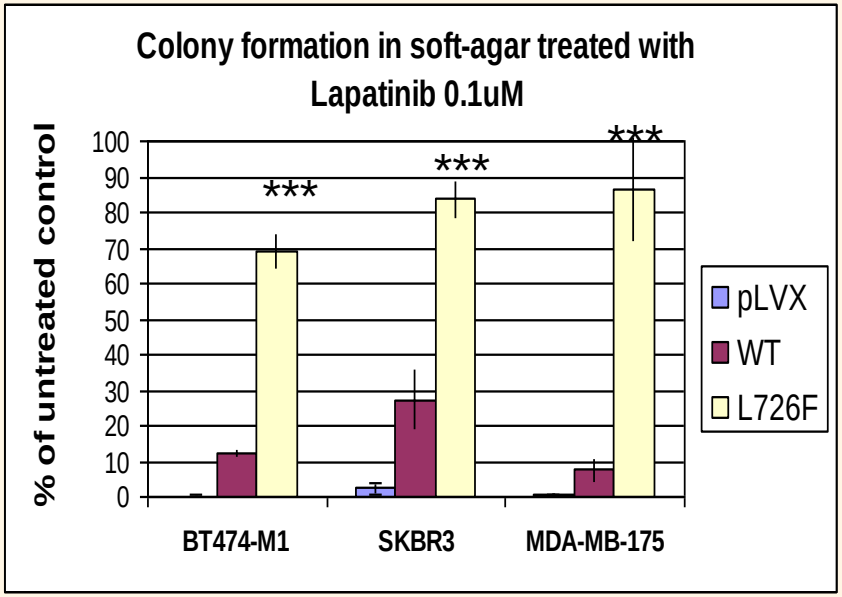


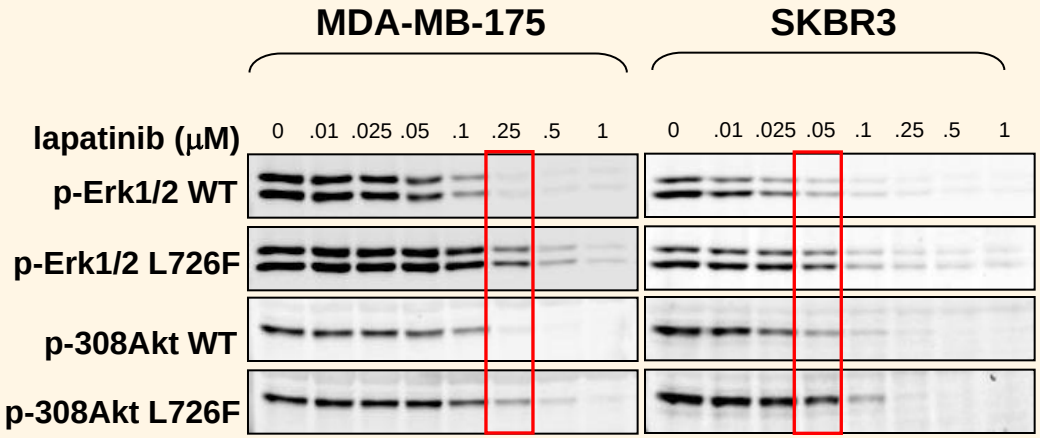
L726F mutation confers lapatinib resistance



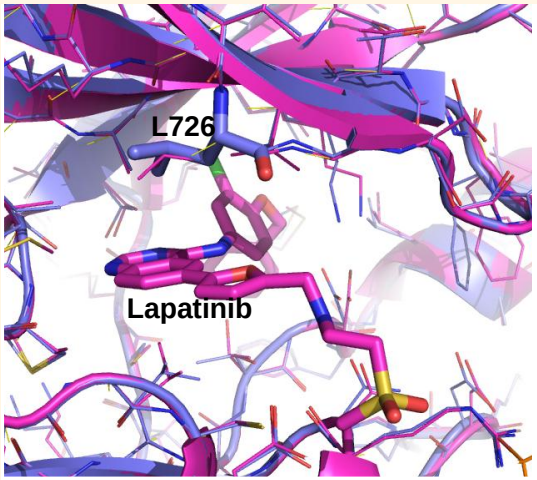




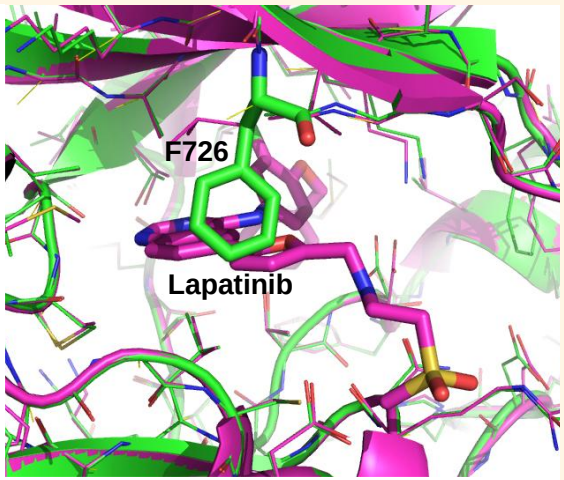




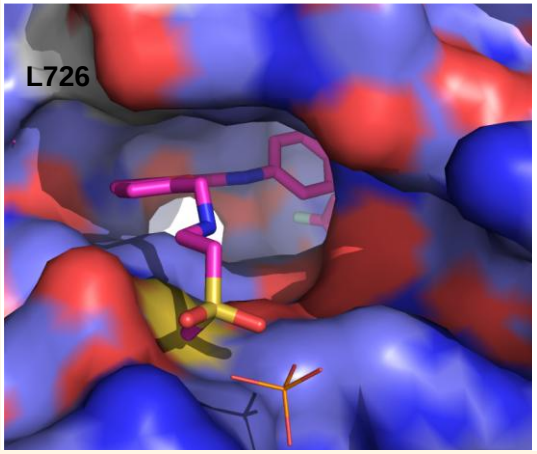
L726F interferes with binding of lapatinib to HER-2

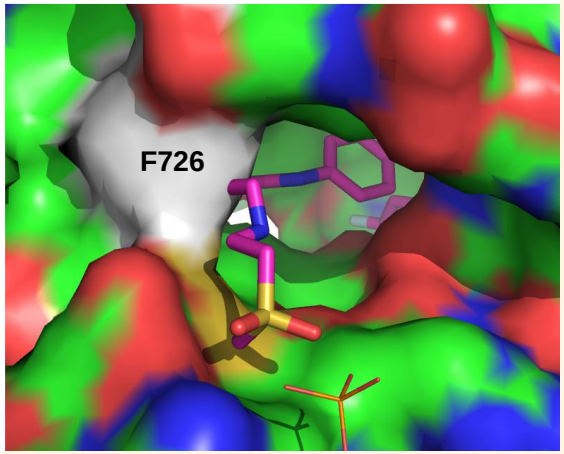


Herb2 wt model vs 1XKK



Herb2 L726F model vs 1XKK





Models based on EGFR / ErbB-1 in complex with Lapatinib

L726F location at the entrance of the ATP binding cleft probably hamper binding of lapatinib and similar drugs.

Conclusions

- **All three HER2 kinase mutations are associated with aggressive phenotypes**
  - D808N: promotes anchorage independence, invasion and impairs formation of normal acini
  - V794M: promotes invasion and mammosphere formation and impairs formation of normal acini
  - L726F: promotes invasion and mammosphere formation and impairs formation of normal acini

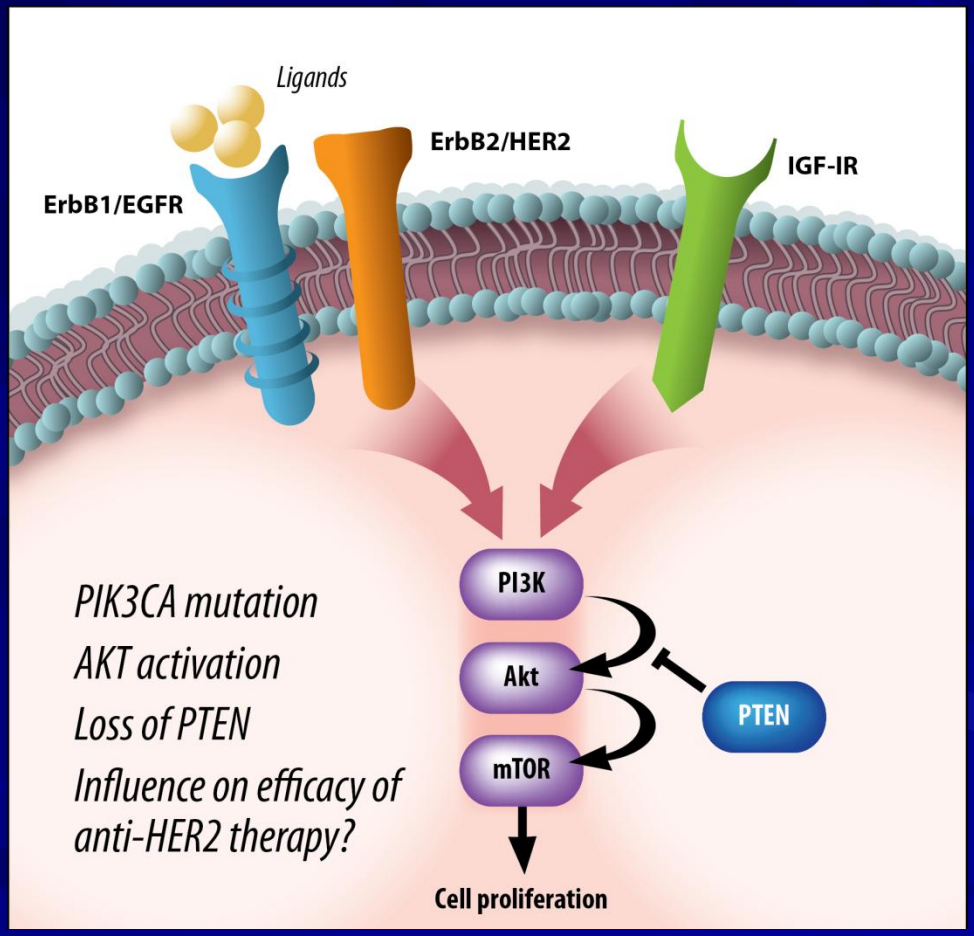
- **L726F mutation confers resistance to lapatinib in HER2-Overexpressing breast cancer cell lines**

Association of PTEN Loss and PIK3CA Mutations on Outcome in HER2+ Metastatic Breast Cancer Patients Treated With First-Line Lapatinib Plus Paclitaxel or Paclitaxel Alone

Bing-he Xu[1], Zhong-zhen Guan[2], Zhen-zhou Shen[3], Zhong-shen Tong[4], Ze-fei Jiang[5], Jun-lan Yang[6], Michelle DeSilvio[7], Meggan Leigh[7], Catherine Ellis[7]

[1]Cancer Hospital, CAMS & PUMC, Beijing, China; [2]Sun Yat-Sen Medical University Cancer Center, Guangzhou, China; [3]Shanghai Cancer Center, Fudan University, Shanghai, China; [4]Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; [5]Hospital affiliated to Military Medical Science, Beijing, China; [6]Beijing 301 PLA Hospital, Beijing, China; [7]GlaxoSmithKline Oncology, Collegeville, PA, USA

Predictive Relevance of Biomarkers Downstream of HER2 Not Proven



EGFR=epidermal growth factor receptor; HER2=human epidermal growth factor receptor 2; mTOR=mammalian target of rapamycin PI3K=phosphoinositide-3-kinase; PTEN=phosphatase and tensin homolog. Adapted from Vogel C et al. Management of HER2-positive breast cancer with lapatinib. *Japanese Journal of Clinical Oncology*. 2010;40:1-9.

Effect of PTEN Loss/PIK3CA Mutations on Lapatinib Efficacy

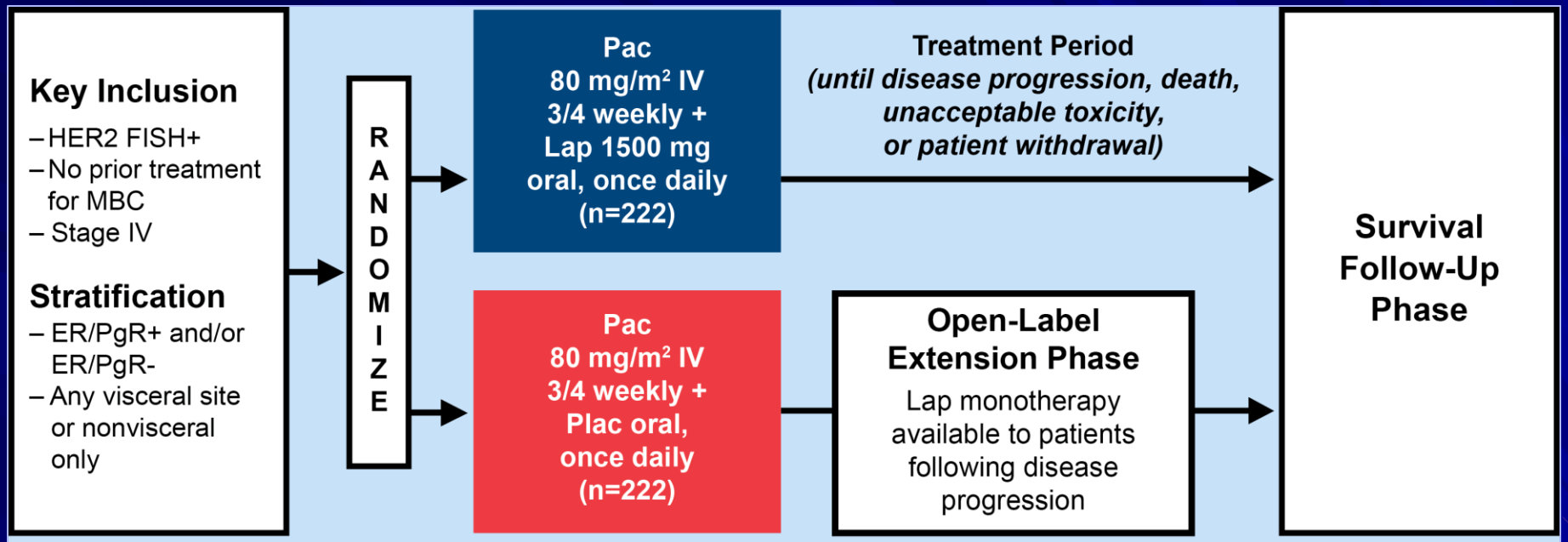
Articles	Study Population	Patient No.	Treatment	PTEN Loss	PIK3CA Mutation	AKT or PTEN Loss/PIK3CA Mutation
Spector et al, 2008	HER2+ IBC	45	Lap	○	–	○
Toi et al, 2009	HER2+ MBC	100	Lap	○	○	–
Chang et al, 2011	HER2+ BC/HER2+ cell lines	49	Lap→Tra/Dox Tra→Dox	○	○	○
Xu et al, 2011	HER2+ MBC	38	Lap + Cap	–	○	–
Hu et al, 2011	HER2+ MBC	57	Lap + Cap	–	–	⊘
Baselga et al, 2008	HER2+ BC cell lines	N/A	Lap	⊘	⊘	–
Slamon et al, 2010	HER2+ BC cell lines	N/A	Lap or Tra	○	○	○

○ No impact on Lap efficacy ⊘ Impact on Lap efficacy

Biomarker Study Aim

Evaluate the predictive and prognostic value of PIK3CA mutations or PTEN loss in HER2+ metastatic breast cancer patients receiving first-line treatment with paclitaxel alone or in combination with lapatinib.

EGF104535 Study Schema

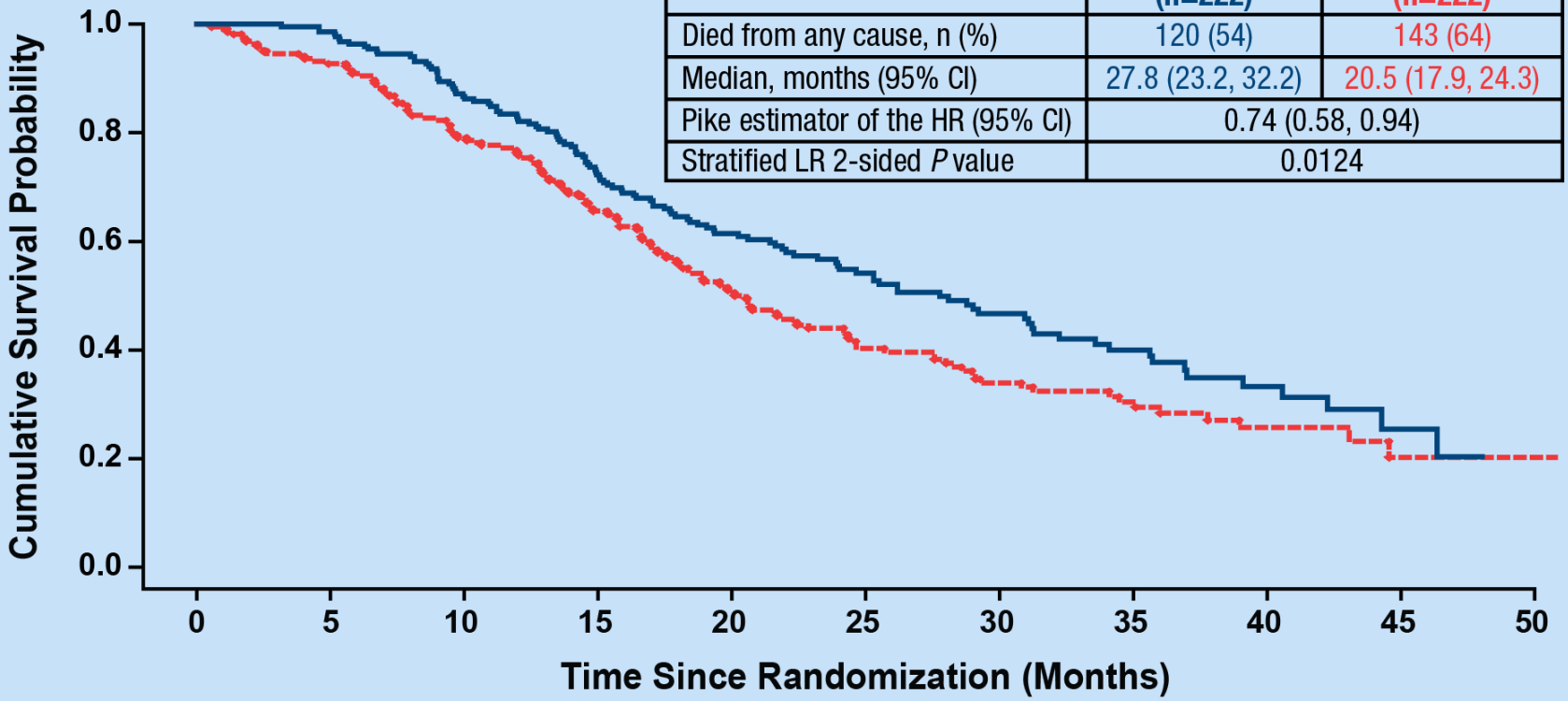


Efficacy assessments: every 8 weeks
Safety assessments: every 4 and 8 weeks
Laboratory assessments: weekly

Primary endpoint	OS
Secondary endpoints	PFS, ORR, CBR, biomarker assessment, safety

Primary Endpoint: OS (ITT Population)

	Lap + Pac (n=222)	Plac + Pac (n=222)
Died from any cause, n (%)	120 (54)	143 (64)
Median, months (95% CI)	27.8 (23.2, 32.2)	20.5 (17.9, 24.3)
Pike estimator of the HR (95% CI)	0.74 (0.58, 0.94)	
Stratified LR 2-sided *P* value	0.0124	



Patients at Risk

Lap + Pac	222	216	189	153	113	79	54	38	18	7
Plac + Pac	222	204	173	139	97	63	45	31	16	6	1

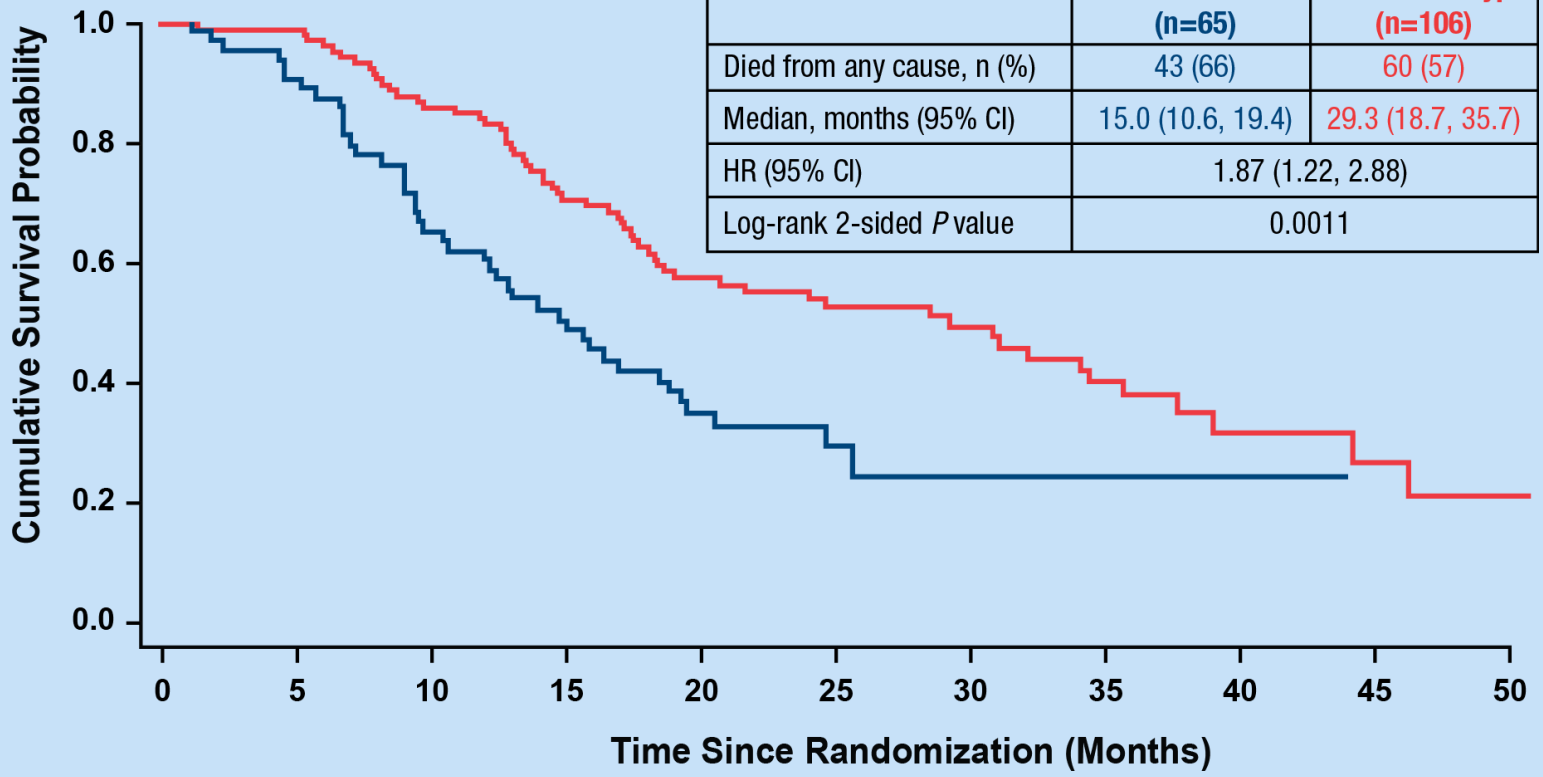
Abbreviations: CI=confidence interval; HR=hazard ratio; LR=log rank

Secondary Efficacy Endpoints (ITT Population)

	Lap + Pac (n=222)	Plac + Pac (n=222)
Median PFS (95% CI), months	9.7 (9.2, 11.1)	6.5 (5.5, 7.3)
HR (95% CI)	0.52 (0.42, 0.64)	
Stratified LR *P* value	<0.0001	
ORR,[a] n (%)	154 (69)	110 (50)
Odds ratio (95% CI)	2.30 (1.54, 3.47)	
P value	<0.0001	
CBR,[b] n (%)	166 (75)	124 (56)
Odds ratio (95% CI)	2.34 (1.54, 3.58)	
P value	<0.0001	

[a]Confirmed CR or PR.
[b]Confirmed CR or PR, or SD ≥24 weeks.
Abbreviations: CR=complete response; PR=partial response; SD=stable disease.

PIK3CA Mutations: Prognostic of Worse Survival Outcome



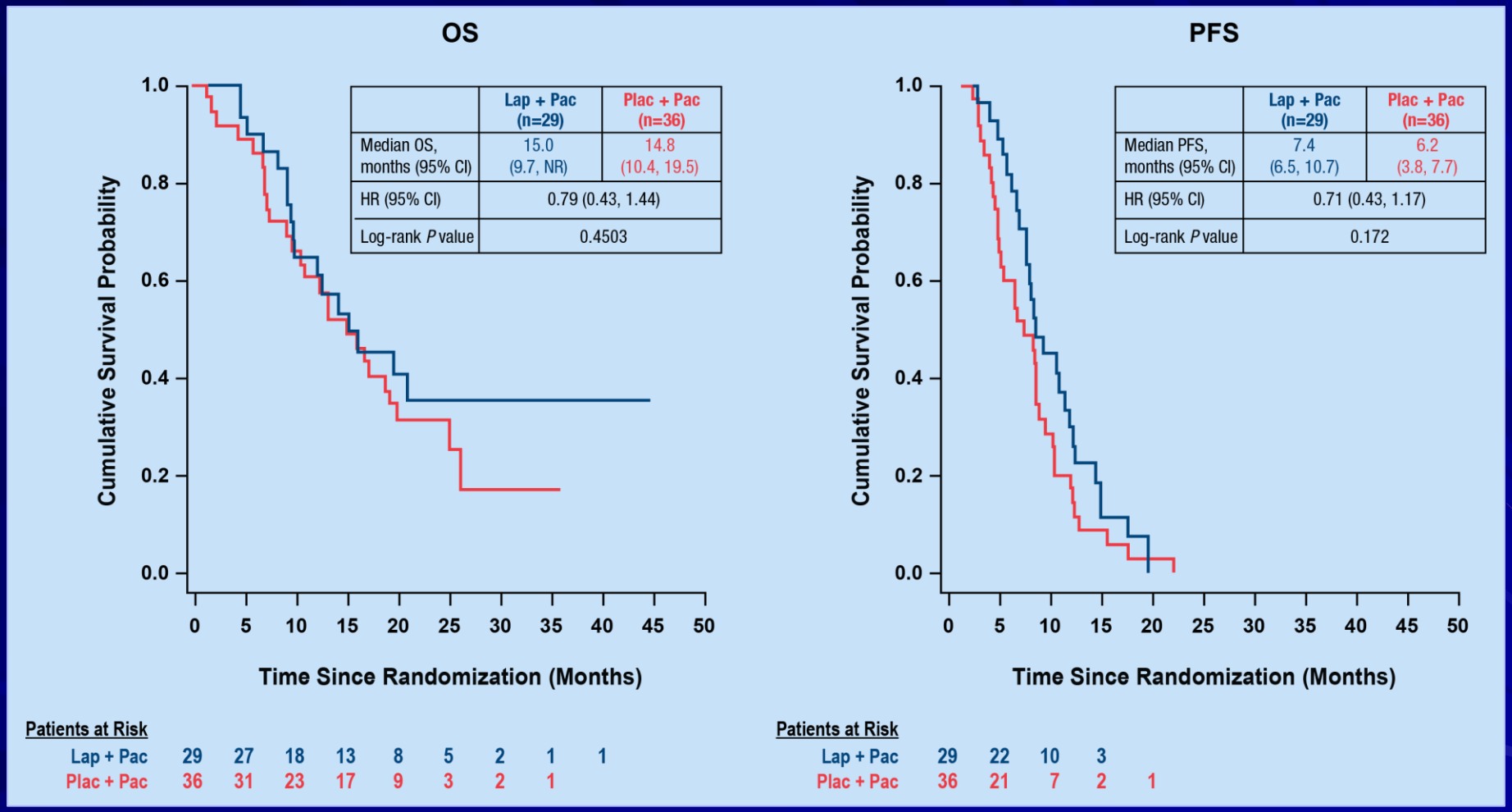
	PIK3CA Mutation (n=65)	PIK3CA Wildtype (n=106)
Died from any cause, n (%)	43 (66)	60 (57)
Median, months (95% CI)	15.0 (10.6, 19.4)	29.3 (18.7, 35.7)
HR (95% CI)	1.87 (1.22, 2.88)	
Log-rank 2-sided *P* value	0.0011	

Patients at Risk

PIK3CA Mutation	65	58	41	30	17	8	4	2	1		
PIK3CA Wildtype	106	105	91	73	53	39	30	20	9	5	1

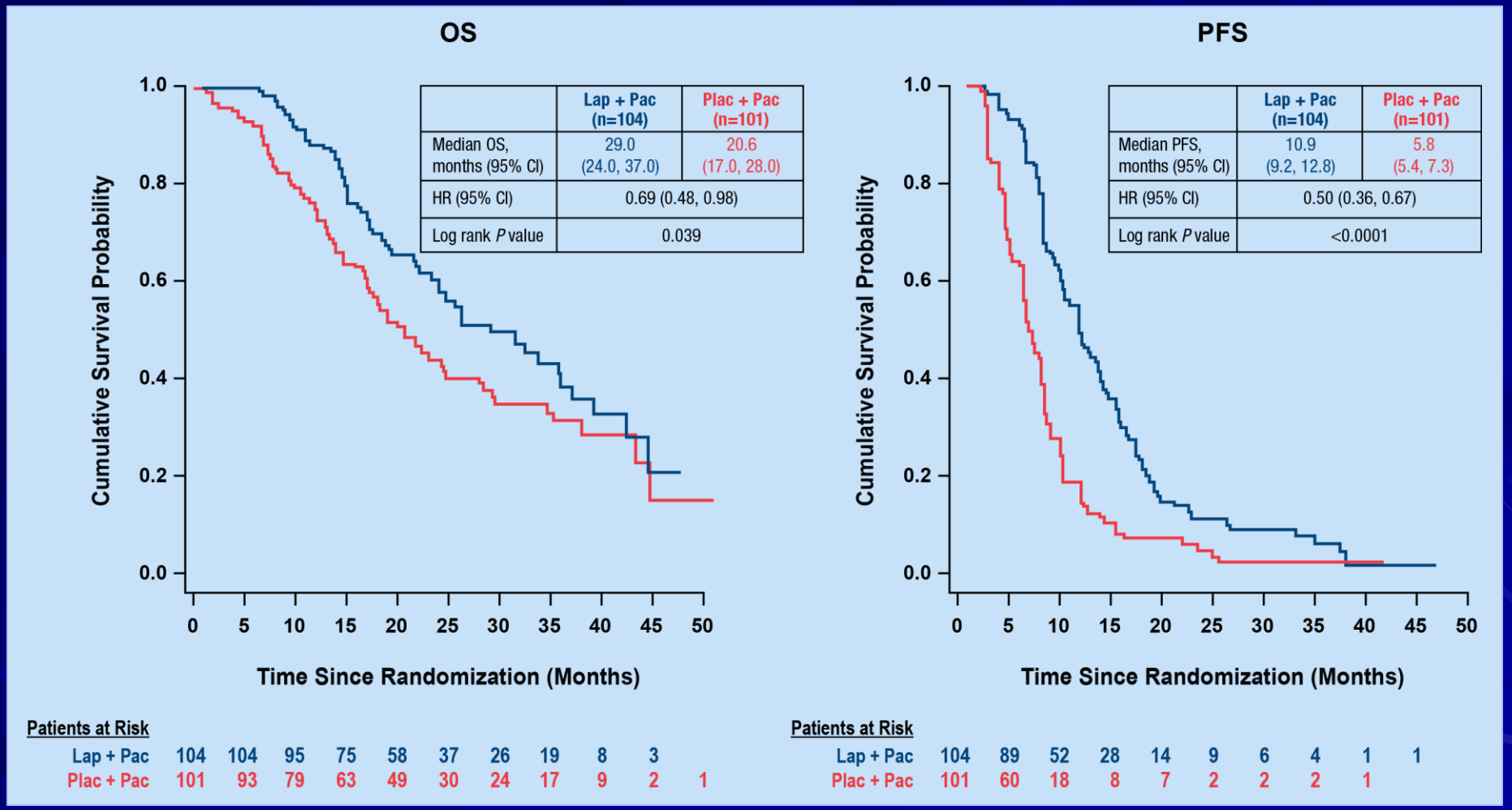
- **PTEN expression was not prognostic in this population, *P*>0.47**

Effect of PIK3CA Mutations on Lapatinib Efficacy



- **In the PIK3CA wild-type subgroup, treatment with Lap+Pac reduced the risk of progression compared with Pac alone (n=106; HR=0.44; 95% CI=0.28, 0.69; *P*<0.0001); OS was not significant (*P*>0.7)**

Effect of PTEN Loss on Lapatinib Efficacy

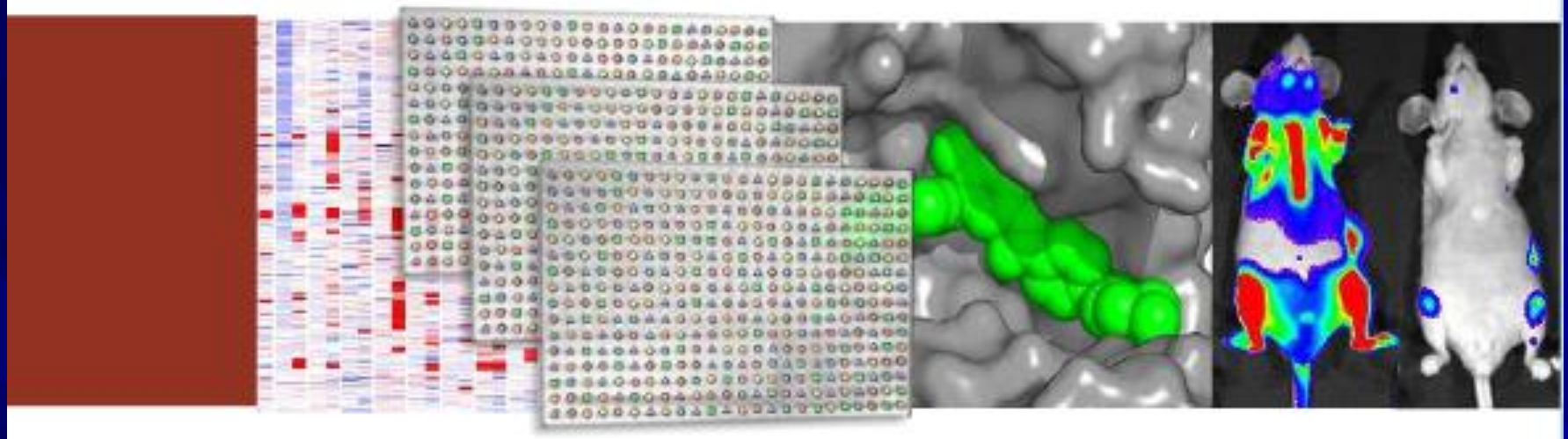


- **In both PTEN subgroups, patients treated with Lap+Pac had significant improvement in PFS in compared with Pac alone (*P* <0.05)**

Summary and Conclusions

- In a randomized phase III study with prospective tumor sample collection
  - Prevalence of PIK3CA mutations was consistent with other reports (30.1%, reported ~25%)
  - Prevalence of PTEN IHC 0 cases was lower than reported (12.4%, reported ~30%-40%)
- PIK3CA mutation
  - PIK3CA mutations were significantly associated with worse survival in this HER2+ breast cancer population
  - A trend in PFS improvement was observed in the PIK3CA mutation subgroup with the addition of lapatinib
- Loss of PTEN
  - OS was significantly improved in the PTEN loss group with addition of lapatinib
  - PFS was significantly improved in patients treated with Lap+Pac regardless of PTEN status

New Therapies and Combinations



Targeting cancer with a novel anti-HER3 antibody

An anti-HER3 antibody that stabilizes the inactive conformation inhibits both HER2 and ligand driven tumor growth.

Andy Garner

SABCS 2011

NOVARTIS

Genomics Institute of the Novartis Research Foundation

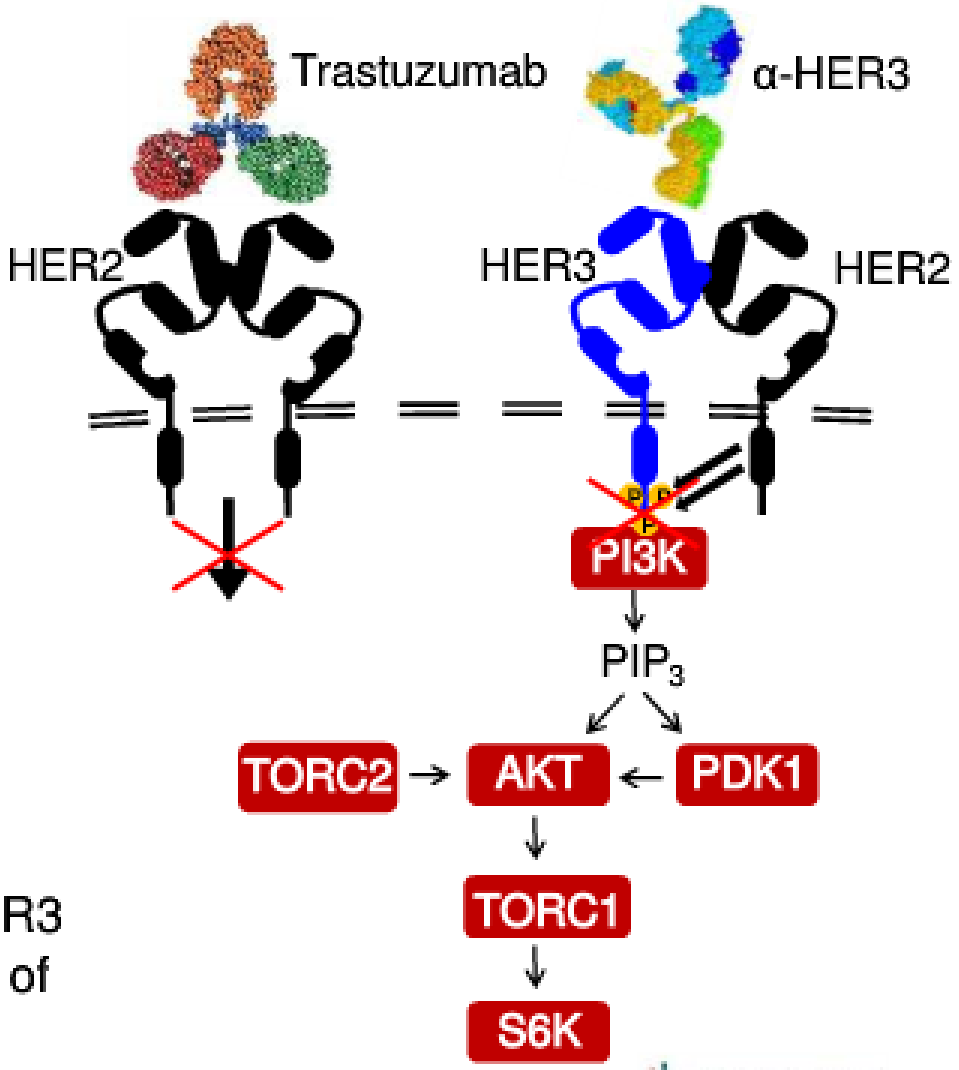
morphosys

HER3 is a key signaling node in HER2+ cancer

- HER3 is activated by ligands such as Neuregulin (NRG)
- HER2 preferentially dimerizes with HER3
- In HER2+ cancer, assembly of HER2/ HER3 heterodimers is ligand-independent
- Persistent HER3 signaling is a common mechanism of therapeutic resistance

Therapeutic Hypothesis

Targeting ligand-independent HER3 signaling will improve the activity of trastuzumab in HER2+ cancer



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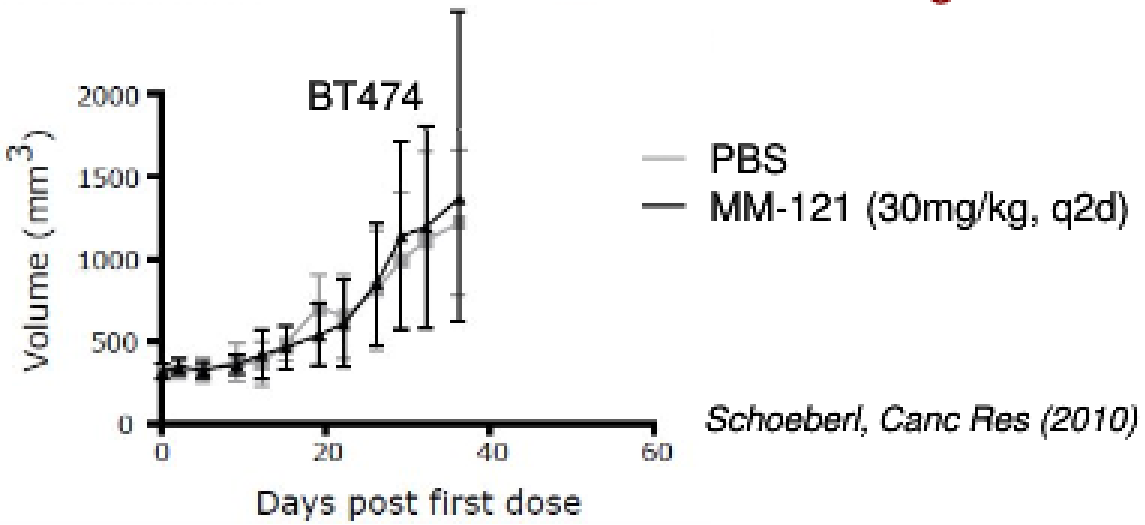
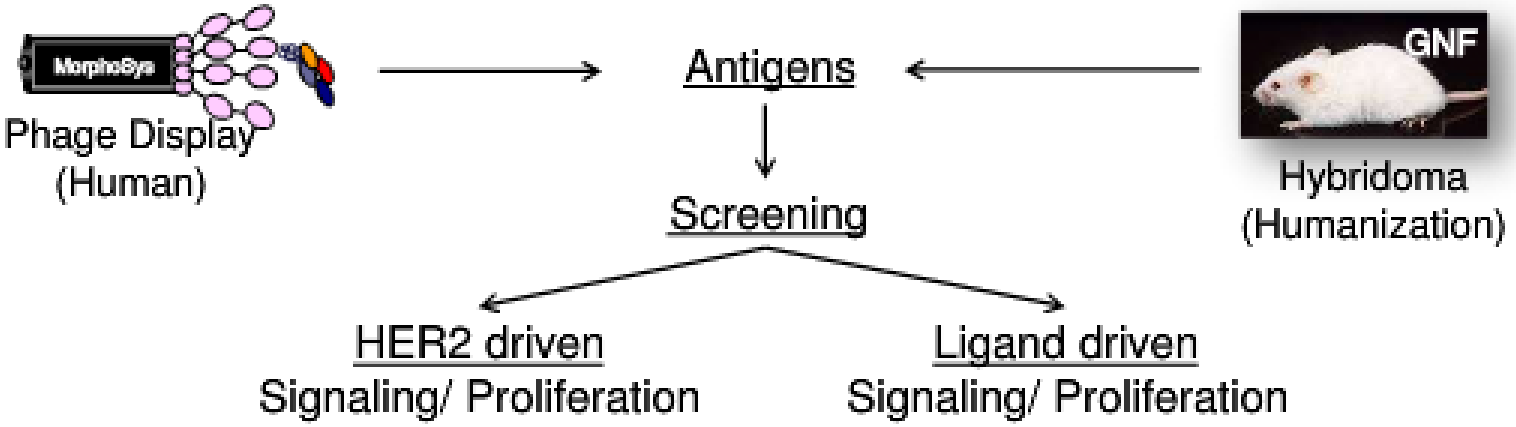
Targeting the HER2/ HER3 oncogenic signaling complex

Goal: Inhibition of ligand-independent HER3 signaling

Ligand blocking antibodies do not inhibit HER2/ HER3 driven growth



Novartis Approach: Target ligand-independent HER3 signaling



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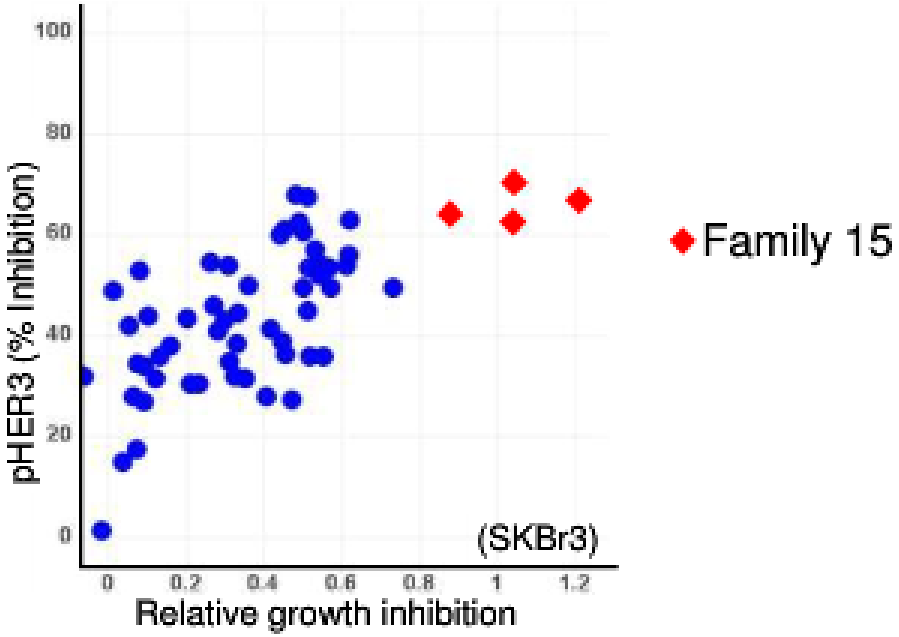
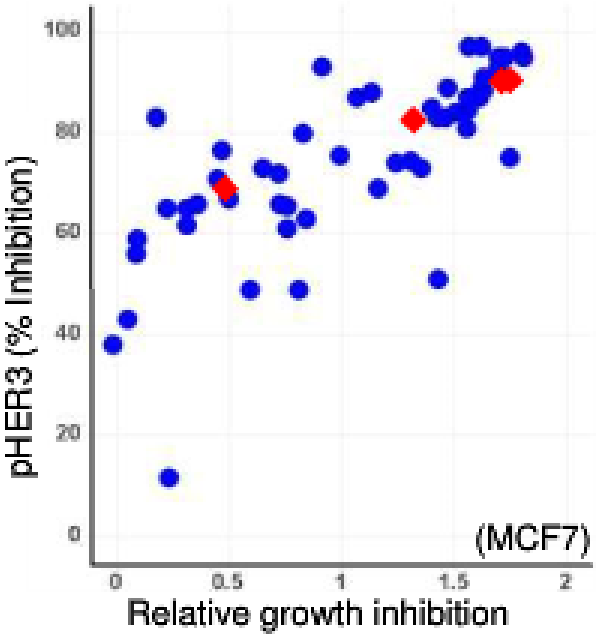
The identification of dual-blocking HER3 antibodies

Ligand-independent signaling/ growth



Ligand-dependent signaling/ growth



	HER3 SET K_D (nM)			
	Human	Cyno	Mouse	Rat
α-HER3	0.032	0.043	0.037	0.057

Conclusion:

- Family 15 antibodies uniquely target multiple mechanisms of HER3 activation

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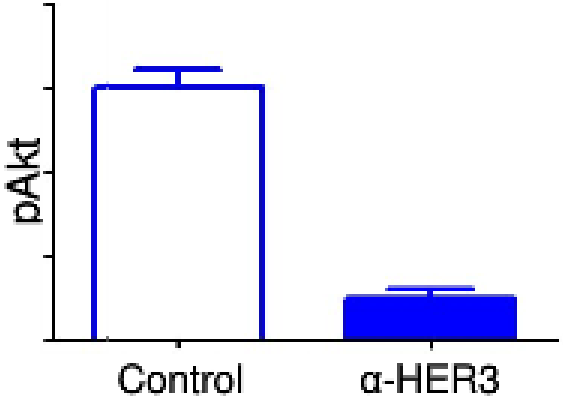
Can a HER3 antibody inhibit HER3 signaling *in vivo*?

Single dose (20mg/kg) pharmacodynamic study

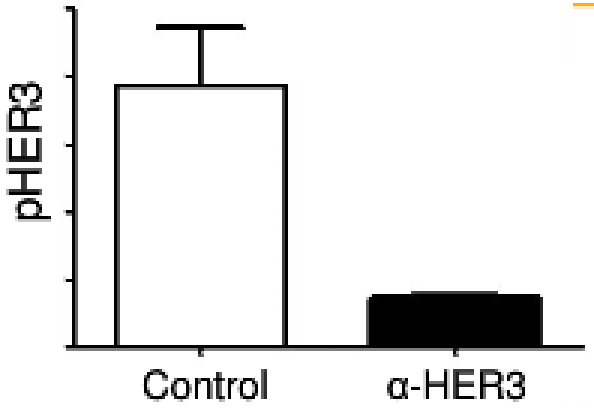
Ligand-independent

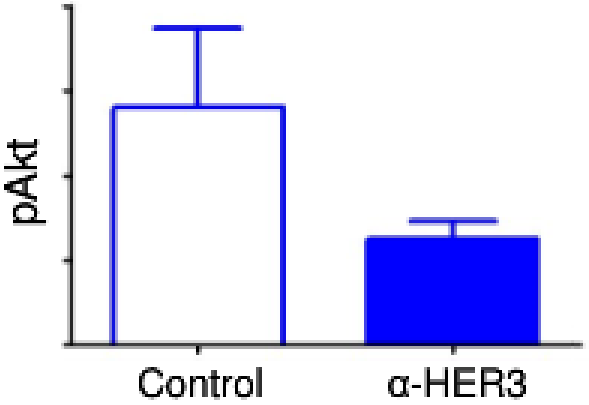
(BT474, *HER2* amp)



Ligand-dependent

(BxPC3)





Conclusion:

- α-HER3 inhibits HER2 & NRG driven HER3 signaling *in vivo*

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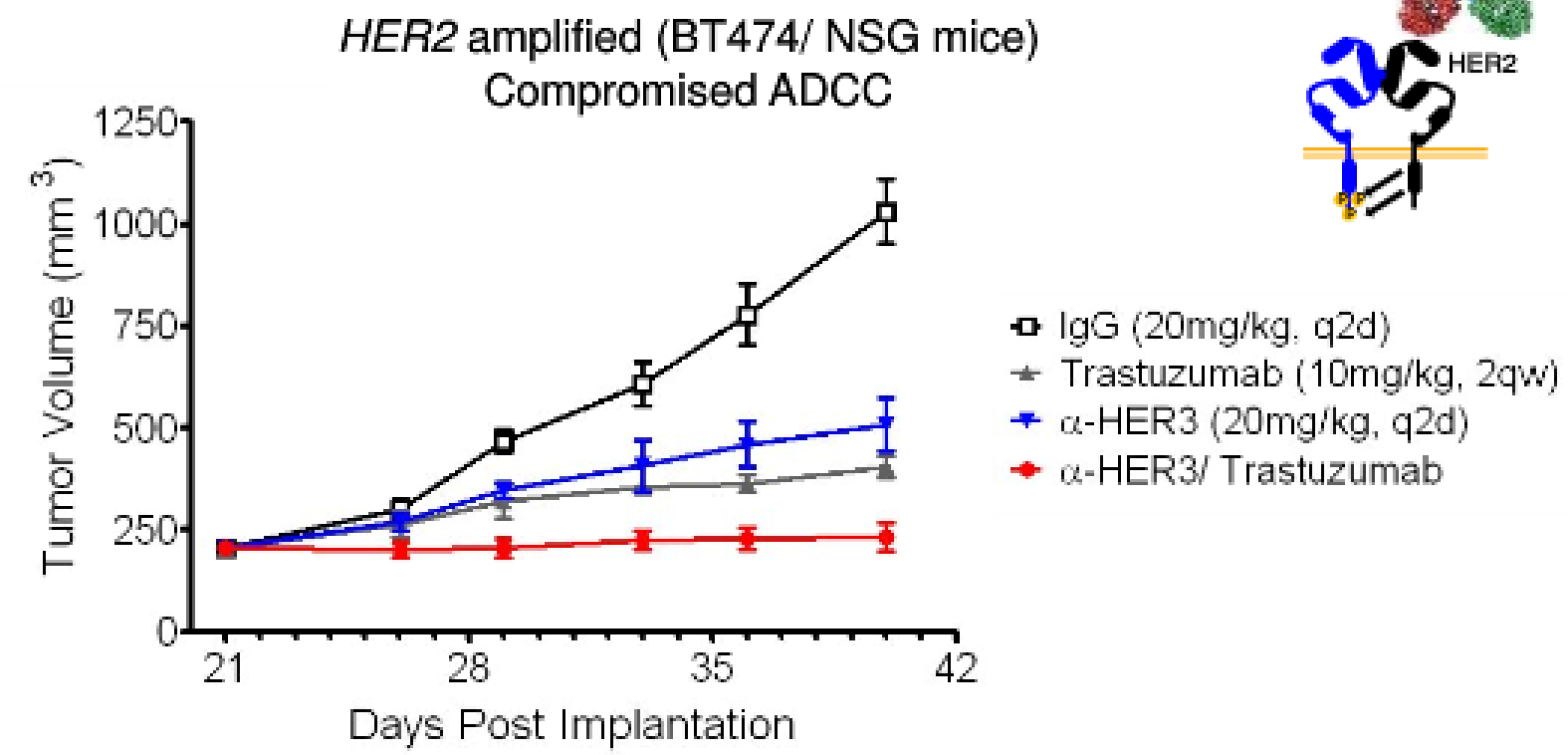
Saxena, Li, Chen

HER2/ HER3 combinations are efficacious *in vivo*



Conclusions:

- HER3 antibodies can combine with trastuzumab to improve efficacy in trastuzumab resistant models

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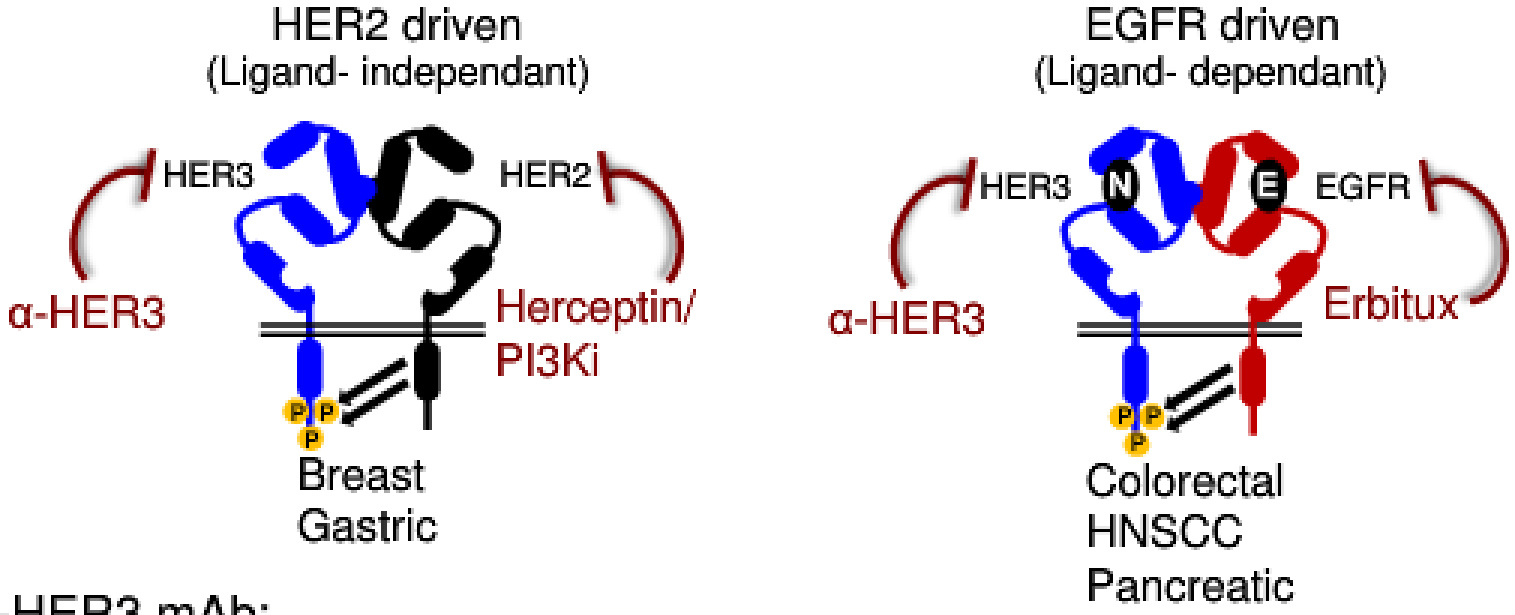
Chen

Summary



α-HER3 mAb:

- Stabilizes the inactive conformation of HER3
- Targets both HER2 & NRG driven HER3 activation
- First anti-HER3 mAb to demonstrate efficacy in *HER2* amplified models
- Active in combination with trastuzumab and PI3Ki

α-HER3 mAb exhibits a unique profile and will shortly enter the clinic

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AVEREL, a randomized phase III trial to evaluate bevacizumab in combination with trastuzumab + docetaxel as first-line therapy for HER2-positive locally recurrent/ metastatic breast cancer

L Gianni[1], G Romieu[2], M Lichinitser[3], S Serrano[4], M Mansutti[5], X Pivot[6], I Smirnova[7], A Moliterni[8], F Andre[9], A Chan[10], O Lipatov[11], S Chan[12], A Wardley[13], R Greil[14], L Provencher[15], N Moore[16], S Prot[16], V Semiglazov[17]

[1]Ospedale San Raffaele, Milan, Italy; [2]Centre Régionale de Lutte contre le Cancer, Val d'Aurelle, Montpellier, France; [3]N N Blokhin Russian Oncology Research Center, Moscow, Russian Federation; [4]Fundação Pio XII Hospital de Câncer de Barretos, Barretos, Brazil; [5]University Hospital of Udine, Udine, Italy; [6]University Hospital Jean Minjoz, Besançon, France; [7]Medical Radiological Science Center, Obninsk, Russian Federation; [8]Fondazione IRCCS, Istituto Nazionale Tumori, Milan, Italy; [9]Gustave Roussy Institute, Villejuif, France; [10]Mount Hospital, Perth, Australia; [11]Republican Clinical Oncology Dispensary, Ufa, Russian Federation; [12]Nottingham University Hospitals NHS Trust, Nottingham, UK; [13]The Christie, Manchester, UK; [14]III Medizinische Universitätsklinik Salzburg, Salzburg, Austria; [15]CHA-Hôpital du Saint Sacrement, Québec, Canada; [16]F Hoffmann-La Roche Ltd, Basel, Switzerland; [17]N N Petrov Research Institute of Oncology, St Petersburg, Russian Federation

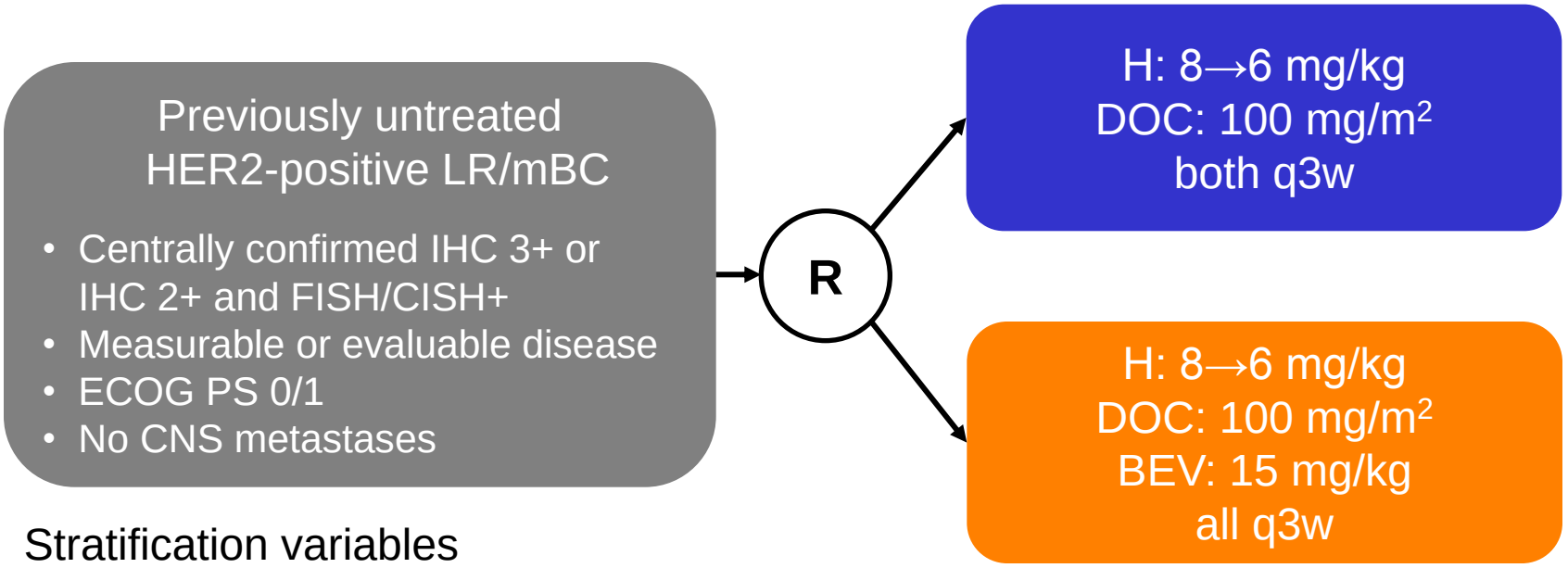
Background

- Strong preclinical rationale for combining trastuzumab (H) and bevacizumab (BEV):
  - VEGF expression is positively regulated by HER2[1,2]
  - VEGF levels correlate with HER2 overexpression[3,4]
  - H and BEV are synergistic in *in vivo* models[5]
- Single-arm phase II studies of H + BEV (± chemotherapy) in LR/mBC showed encouraging activity[6,7]

LR/mBC = locally recurrent/metastatic breast cancer; VEGF = vascular endothelial growth factor

1. Klos et al. Cancer Res 2008; 2. Loureiro et al. Biochem Biophys Res Commun 2005; 3. Yang et al. Cancer 2002
4. Konecny et al. Clin Cancer Res 2004; 5. Pegram et al. SABCS 2004; 6. Hurvitz et al. SABCS 2009; 7. Tjulandin et al. ASCO 2011

Study schema



Stratification variables

- Prior (neo)adjuvant taxane (yes vs no [no chemotherapy/relapse <12 months vs ≥12 months since last chemotherapy])
- Adjuvant H (yes vs no)
- ER/PgR status (positive vs negative)
- Measurable disease (yes vs no)

- H and BEV continued to PD or unacceptable toxicity
- DOC given until PD or unacceptable toxicity (planned minimum of 6 cycles)

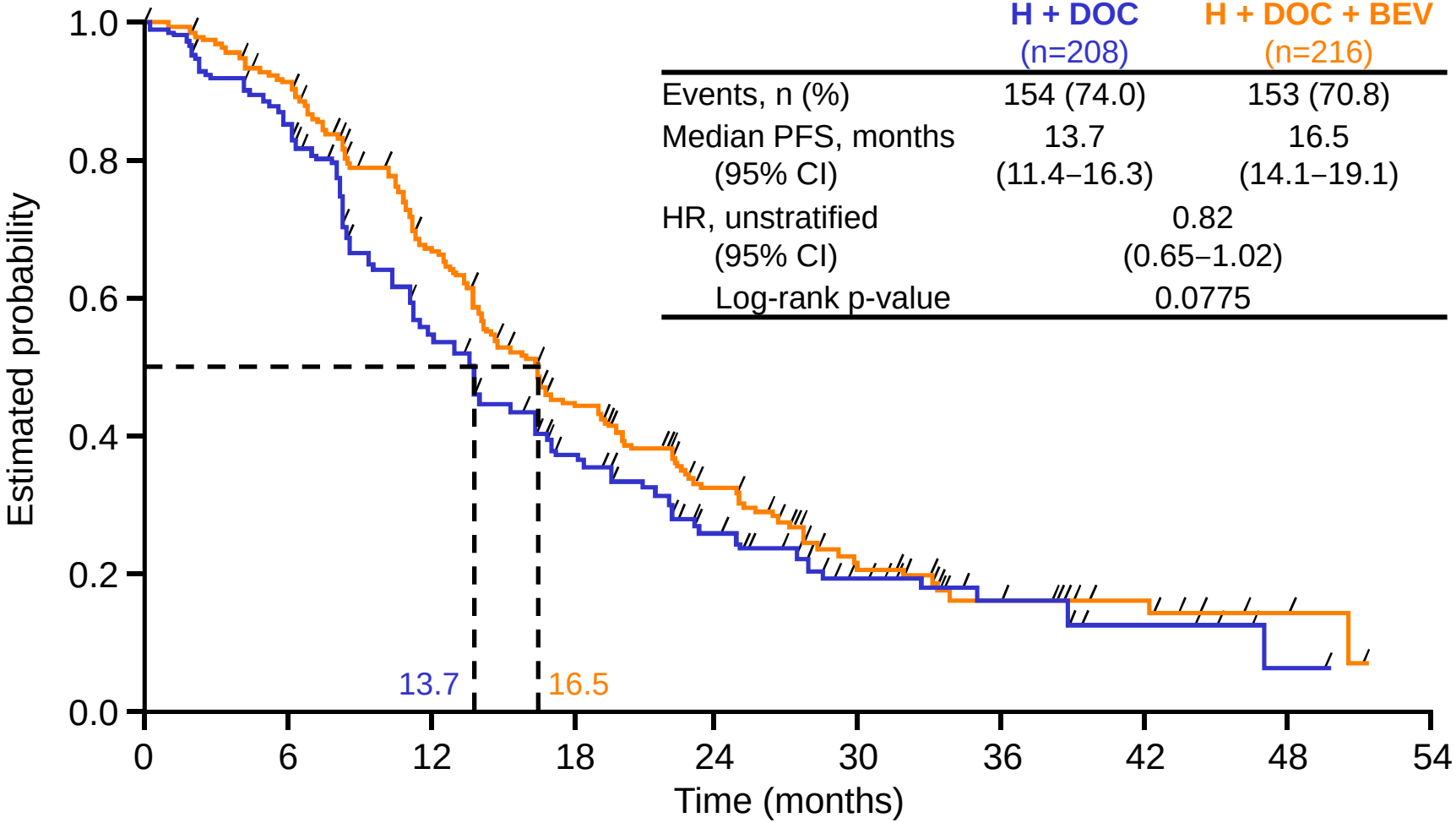
CISH = chromogenic in situ hybridization; DOC = docetaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; ER = estrogen receptor; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; PD = progressive disease; PgR = progesterone receptor

Study endpoints

- Primary: Investigator-assessed PFS
- Secondary:
  - Efficacy (OS, ORR [RECIST v1.0], duration of response, time to treatment failure)
  - Safety (NCI CTCAE v3.0)
  - Quality of life (FACT-B)
- Exploratory:
  - IRC-assessed PFS (for US regulatory purposes)
  - Translational research (participation optional; blood and tumor biomarker assessment)

IRC = Independent Review Committee; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Investigator-assessed PFS (unstratified[a])

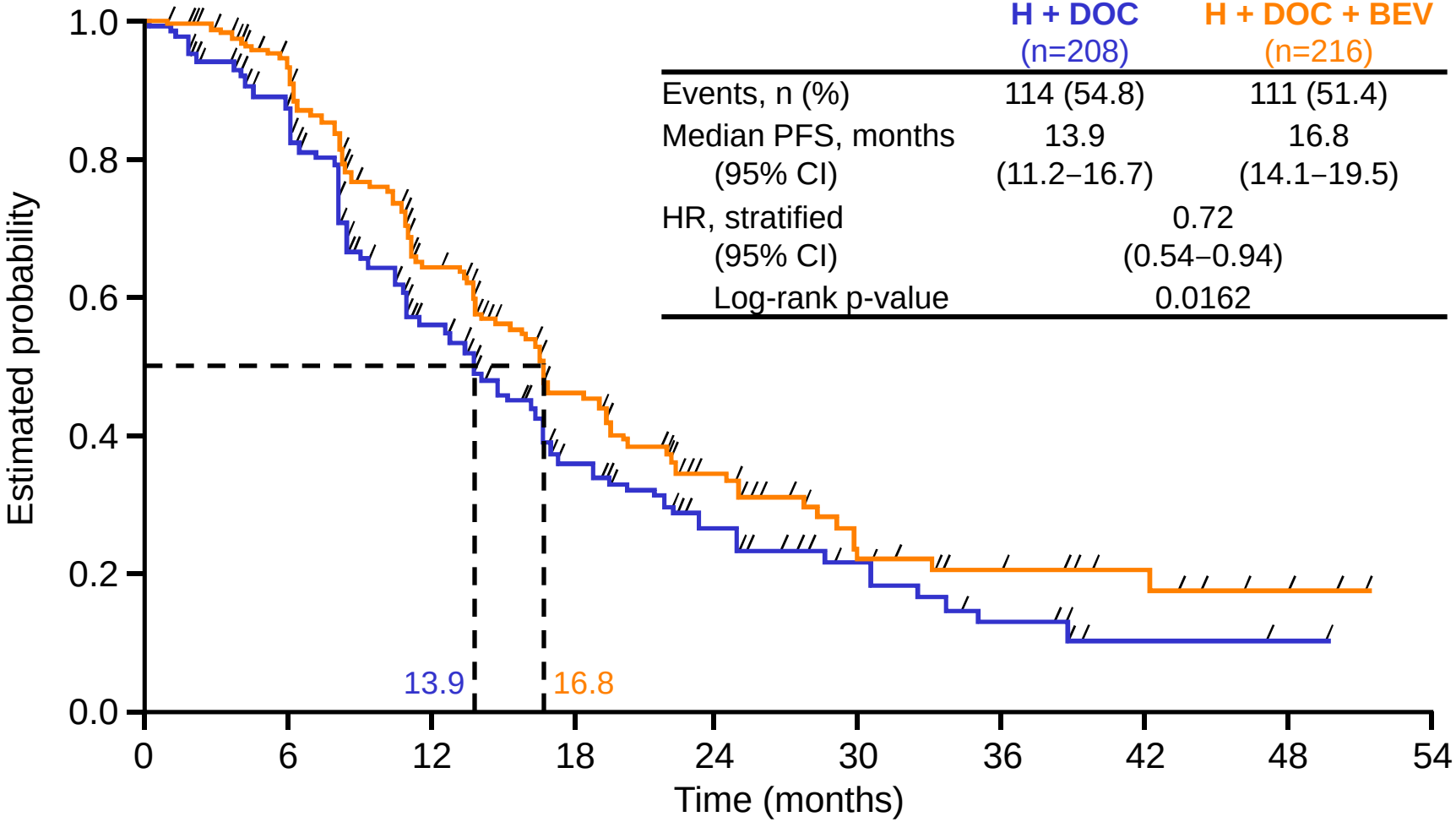


	H + DOC (n=208)	H + DOC + BEV (n=216)
Events, n (%)	154 (74.0)	153 (70.8)
Median PFS, months (95% CI)	13.7 (11.4–16.3)	16.5 (14.1–19.1)
HR, unstratified (95% CI)	0.82 (0.65–1.02)	
Log-rank p-value	0.0775	

No. at risk:										
H + DOC	208	173	106	65	38	18	10	5	1	0
H + DOC + BEV	216	192	134	82	48	22	12	8	2	0

[a]Primary analysis per protocol

IRC-assessed PFS[a] (stratified, censored for non-protocol therapy)

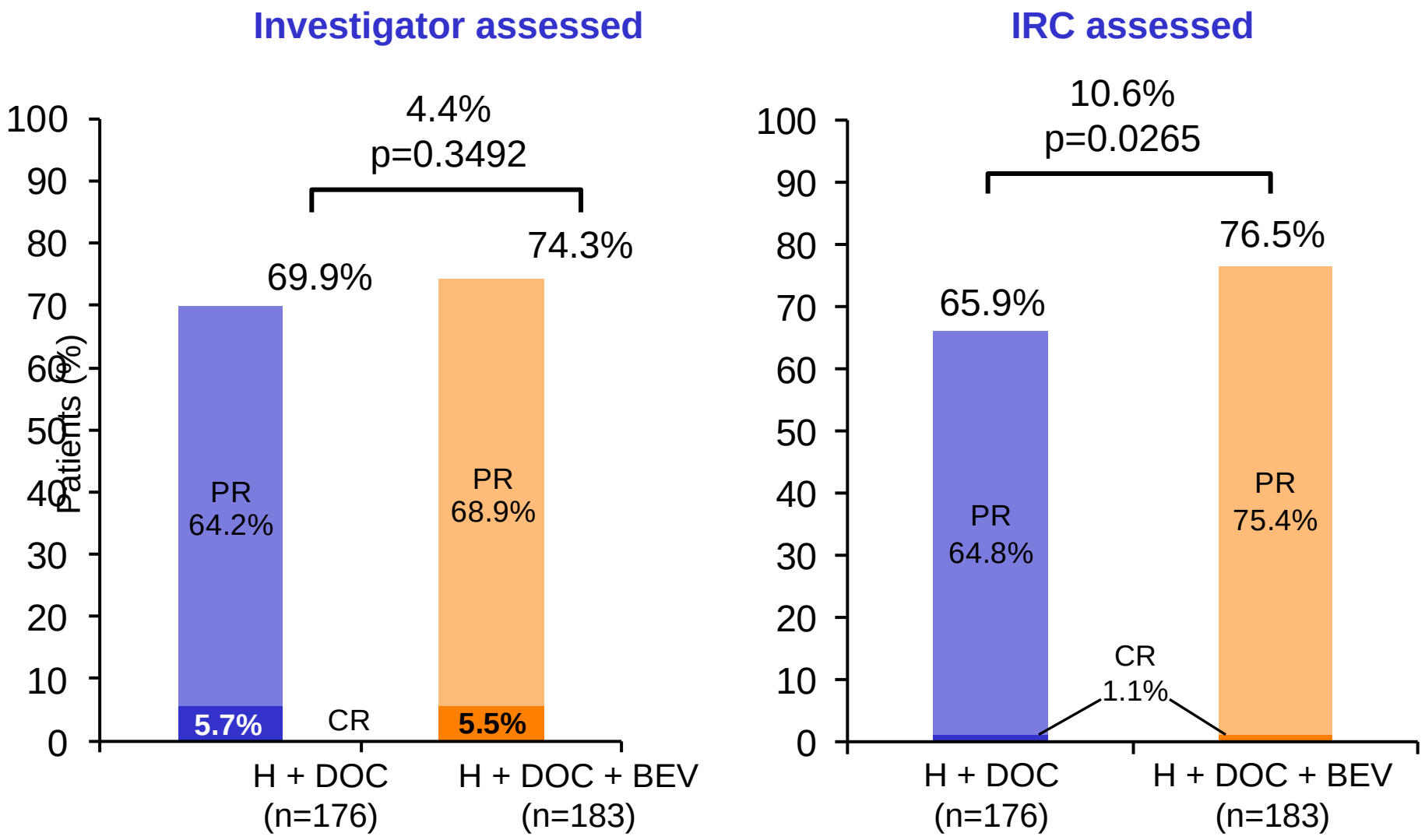


	H + DOC (n=208)	H + DOC + BEV (n=216)
Events, n (%)	114 (54.8)	111 (51.4)
Median PFS, months (95% CI)	13.9 (11.2–16.7)	16.8 (14.1–19.5)
HR, stratified (95% CI)	0.72 (0.54–0.94)	
Log-rank p-value	0.0162	

No. at risk:									
H + DOC	208	149	75	39	24	14	7	2	1	0
H + DOC + BEV	216	173	101	58	32	15	10	7	2	0

[a]Prespecified in the statistical analysis plan for US regulatory purposes

Objective response rates[a]



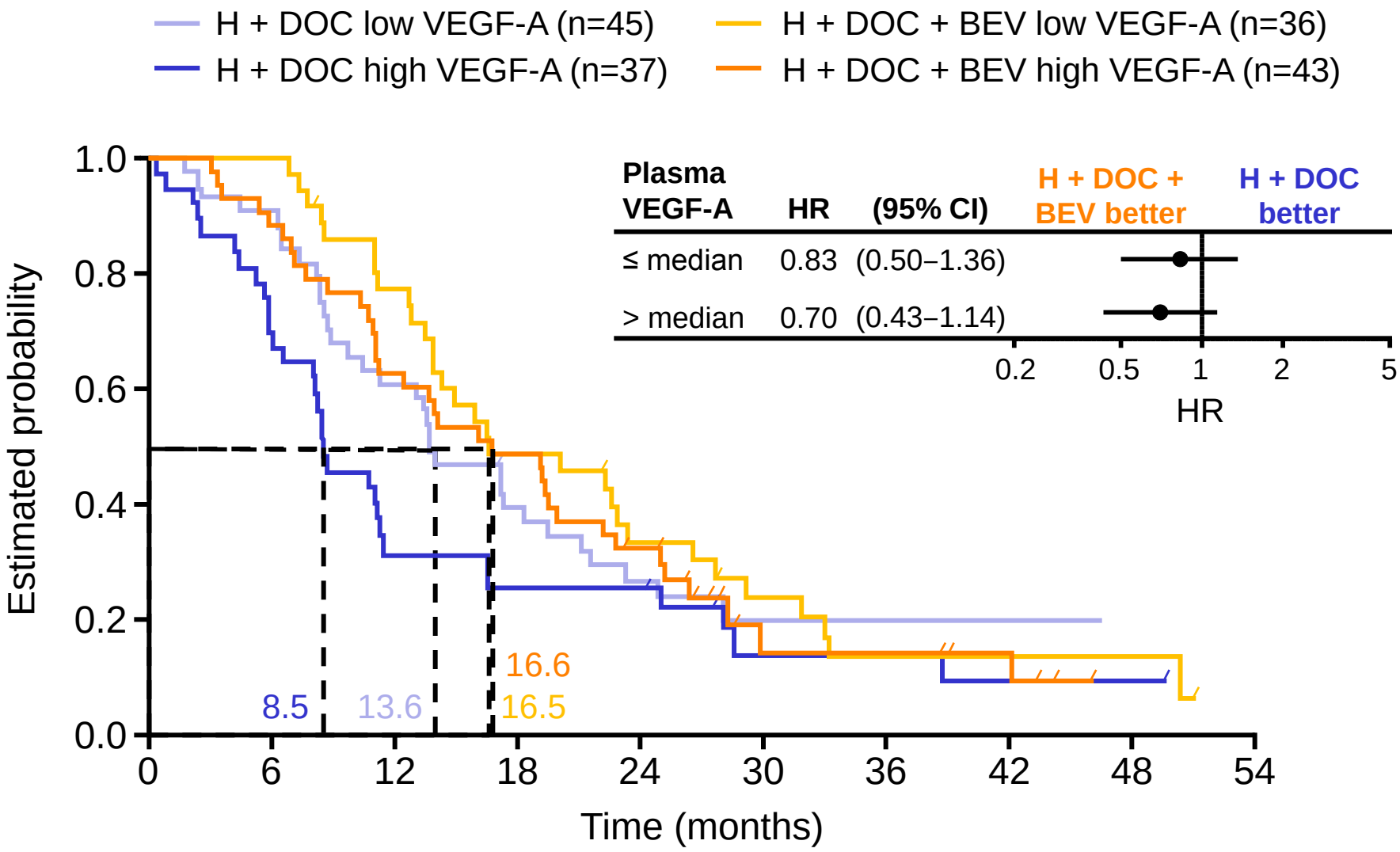
[a]Patients with measurable disease at baseline

Exploratory biomarker study

- In HER2-negative LR/mBC (AVADO):
  - High baseline plasma VEGF-A levels were associated with poorer prognosis in the control (DOC monotherapy) arm[1]
  - Patients with high baseline plasma VEGF-A levels derived a more pronounced PFS improvement from BEV in combination with DOC than those with low plasma VEGF-A levels[1]
- In AVEREL, an exploratory analysis of PFS according to baseline plasma VEGF-A levels was conducted

1. Miles et al. SABCS 2010

PFS according to baseline plasma VEGF-A



Conclusions

- AVEREL demonstrated longer median PFS when BEV was combined with H + DOC in patients with HER2-positive LR/mBC
  - Investigator-assessed PFS (**primary endpoint**) HR 0.82 (p=0.0775)
  - IRC-assessed PFS HR 0.72 (p=0.0162)
- No difference in OS (immature data)
- No new safety signals were observed

Perspectives

- In AVEREL, exploratory analyses of plasma VEGF-A suggest a potentially predictive effect (greater benefit with high VEGF-A levels), consistent with observations in HER2-negative LR/mBC
  - Global biomarker study GO25632 (MERiDiAN) is planned: BEV + paclitaxel with stratification by plasma VEGF-A level
- The BETH adjuvant trial will provide further data on BEV in patients with HER2-positive breast cancer

A Phase 2, Randomized, Open-label Study of Neratinib (HKI-272) Versus Lapatinib Plus Capecitabine for 2nd/3rd-line Treatment of HER2+ Locally Advanced or Metastatic Breast Cancer

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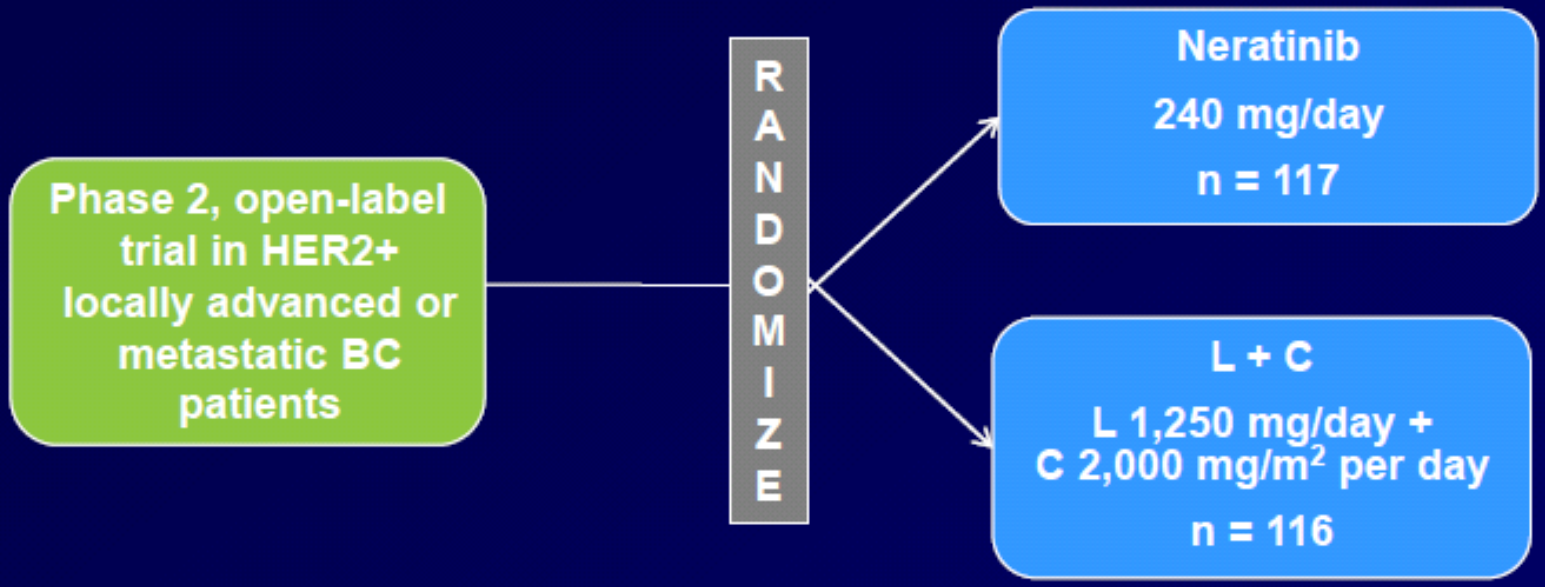
**This author was employed at Pfizer during the conduct of this study, but has since become employed at another company.*

Background

- Neratinib is an orally active, irreversible pan-ErbB receptor tyrosine kinase inhibitor with activity against HER1, -2, and -4
- As a single agent, neratinib showed clinical activity in patients with advanced and metastatic HER2+ breast cancer (BC)
  - In trastuzumab-naive patients, the objective response rate (ORR) was 56% and the median progression-free survival (PFS) was 39.6 weeks[1]
  - In pretreated patients, the ORR was 24%, and the median PFS was 22.3 weeks[2]
  - The most common adverse event was diarrhea

1. Wong KK, et al. *Clin Cancer Res*. 2009;15(7):2552-2558.
2. Burstein HJ, et al. *J Clin Oncol*. 2010;28(8):1301-1307.

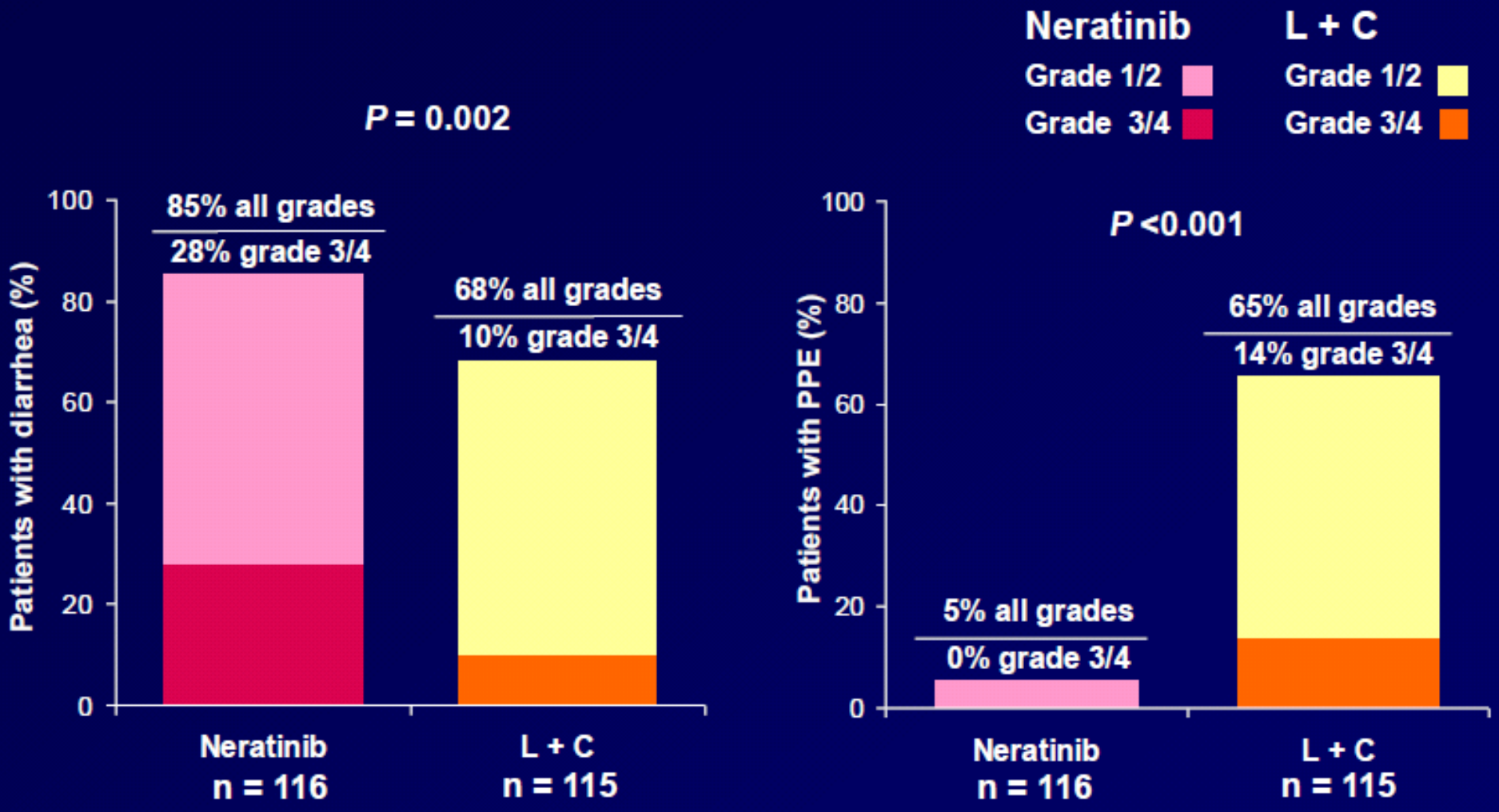
Study Design (cont)



Randomization is stratified based on geographical regions.

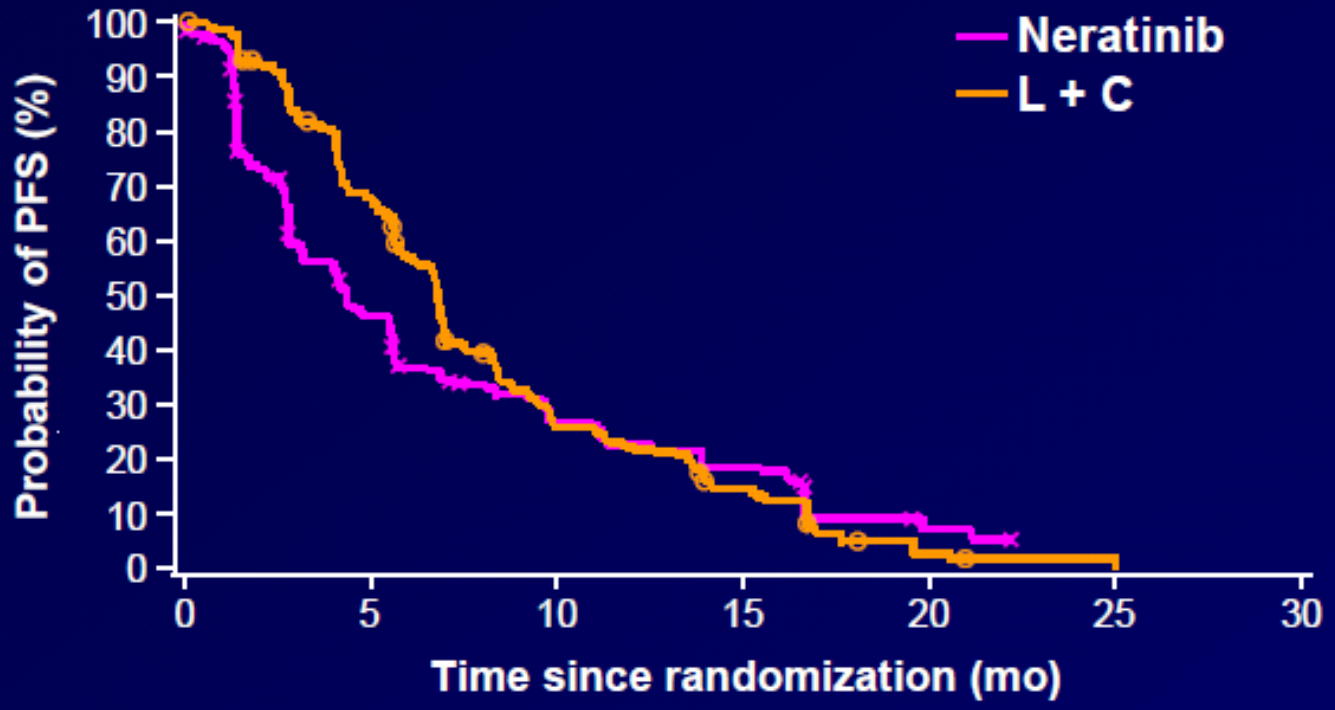
- Patients were randomized 1:1 to neratinib or L + C
  - Neratinib was administered orally at 240 mg/day continuously
  - L 1,250 mg/day was administered orally continuously; C 2,000 mg/m^2 was administered orally on Days 1 to 14 of each 21-day cycle

Incidences of Diarrhea and PPE: Safety Population



PPE, palmar-plantar erythrodysesthesia syndrome; L, lapatinib; C, capecitabine.

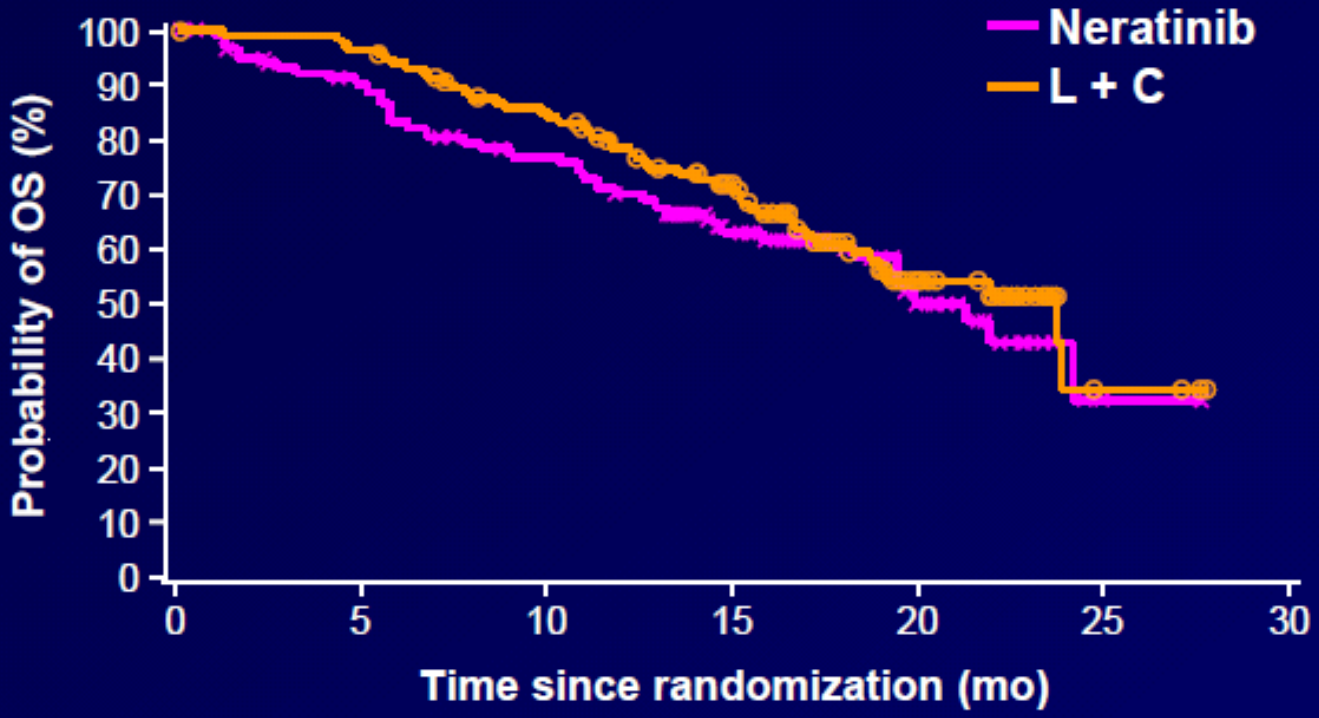
PFS: ITT Population



	n	Median PFS	95% CI	*P* value
Neratinib	117	4.5 mo	3.1–5.7 mo	0.231
L + C	116	6.8 mo	5.9–8.2 mo	

L, lapatinib; C, capecitabine; PFS, progression-free survival; CI, confidence interval.

Overall Survival: ITT Population



	n	Median OS	95% CI	*P* value
Neratinib	117	19.7 mo	18.2 mo–NE	0.280
L + C	116	23.6 mo	18.0 mo–NE	

L, lapatinib; C, capecitabine; OS, overall survival; CI, confidence interval; NE, not estimable.

Conclusions

- Neratinib did not demonstrate non-inferiority versus L + C in terms of PFS
- The median PFS was numerically, but not statistically, superior in L + C (4.5 mo for neratinib vs 6.8 mo for L + C)
- In addition, the antitumor activity of neratinib monotherapy in heavily pretreated patients with advanced or metastatic HER2+ BC was robust (ORR of 29%) and consistent with results from the preceding single-arm trial[1]

1. Burstein HJ, et al. *J Clin Oncol.* 2010;28(8):1301-1307.

San Antonio Breast Cancer Symposium – Cancer Therapy and
Research Center at UT Health Science Center – December 6-10, 2011

A Phase III, Randomized, Double-Blind, Placebo-Controlled Registration Trial to Evaluate the Efficacy and Safety of Placebo + Trastuzumab + Docetaxel vs. Pertuzumab + Trastuzumab + Docetaxel in Patients with Previously Untreated HER2-Positive Metastatic Breast Cancer (CLEOPATRA)

J Baselga,[1] S-B Kim,[2] S-A Im,[3] R Hegg,[4] Y-H Im,[5] L Roman,[6] J L Pedrini,[7] J Cortés,[8] A Knott,[9] E Clark,[9] G Ross[9] and S M Swain[10]

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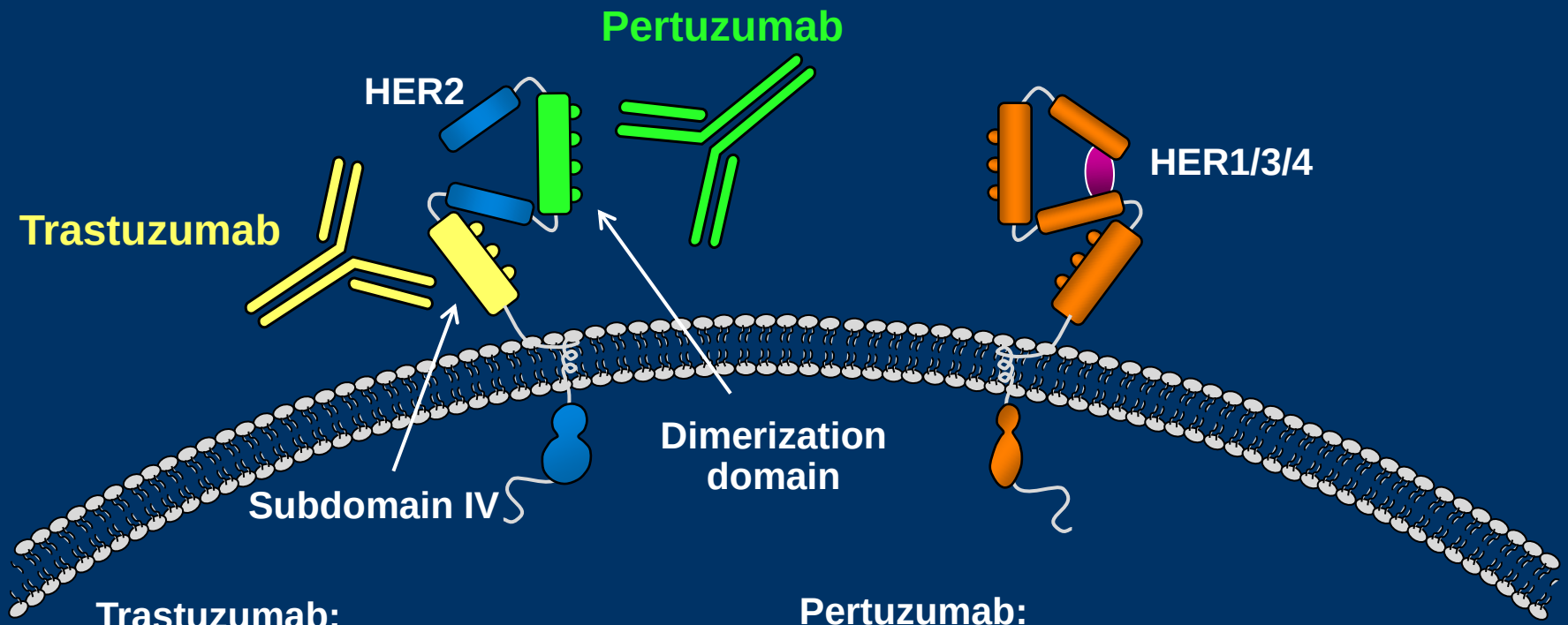
Introduction

- **Trastuzumab-based therapy improves progression-free and overall survival in HER2-positive MBC.[1] However, disease progression still occurs in a majority of patients[2]**
- **Pertuzumab is a humanized monoclonal antibody and HER2 dimerization inhibitor that binds HER2 at a different epitope from trastuzumab[3]**
- **Phase II trials in patients with HER2-positive breast cancer have shown improved activity, and a good safety profile with pertuzumab-trastuzumab-based therapy[4,5]**

HER2, human epidermal growth factor receptor 2;
MBC, metastatic breast cancer

**1. Slamon et al. *N Engl J Med* 2001; 2. Nahta and Esteva *Oncogene* 2007;
3. Franklin et al. *Cancer Cell* 2004; 4. Baselga et al. *J Clin Oncol* 2010;
5. Gianni et al. *Lancet Oncol* 2011**

Pertuzumab and trastuzumab have complementary mechanisms of action



Trastuzumab:

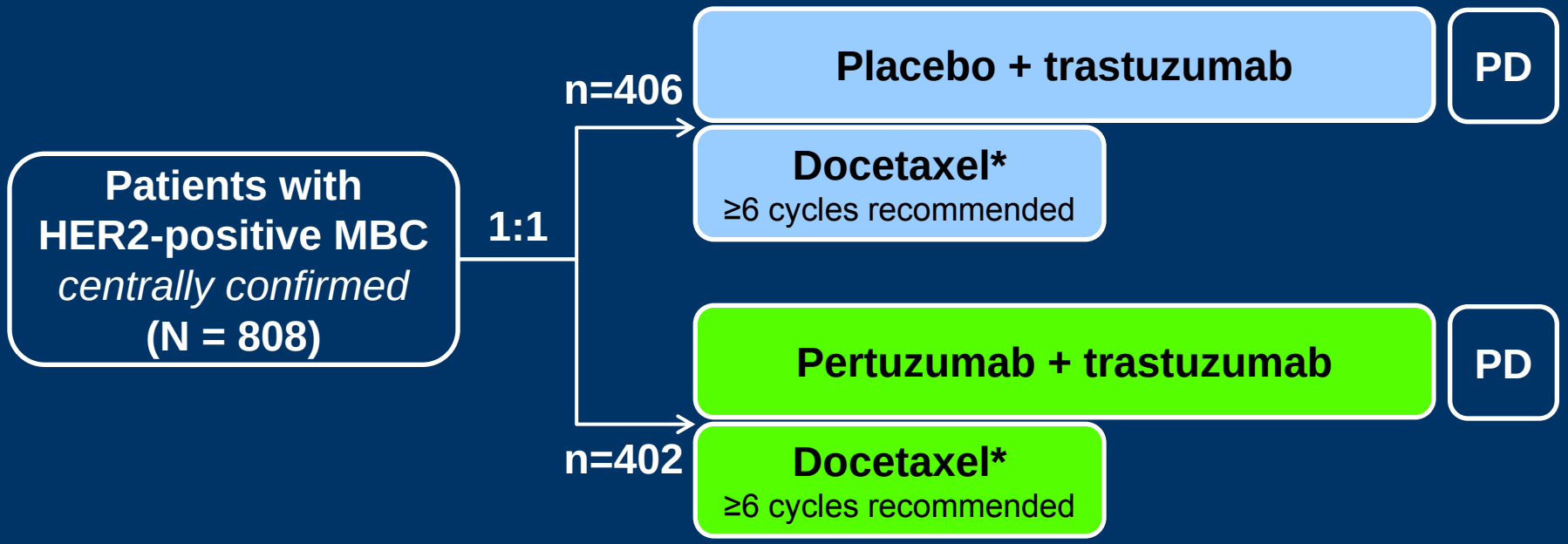
- Inhibits ligand-independent HER2 signaling
- Activates ADCC
- Prevents HER2 ECD shedding

Pertuzumab:

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

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

Study design



- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - 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

*** <6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion**

MBC, metastatic breast cancer; PD, progressive disease

Key patient eligibility criteria

- Centrally confirmed HER2-positive (IHC 3+ and/or FISH-positive; ratio ≥2.0) locally recurrent, unresectable, or metastatic breast cancer
- Measurable and/or non-measurable disease
- No more than one hormonal regimen for MBC prior to randomization
- Prior (neo)adjuvant systemic breast cancer chemotherapy including trastuzumab and/or taxanes allowed if followed by a disease-free interval of ≥12 months
- LVEF ≥50% at baseline; no history of CHF or LVEF decline to <50% during or after prior trastuzumab therapy

CHF, congestive heart failure; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer

Prior therapy for breast cancer

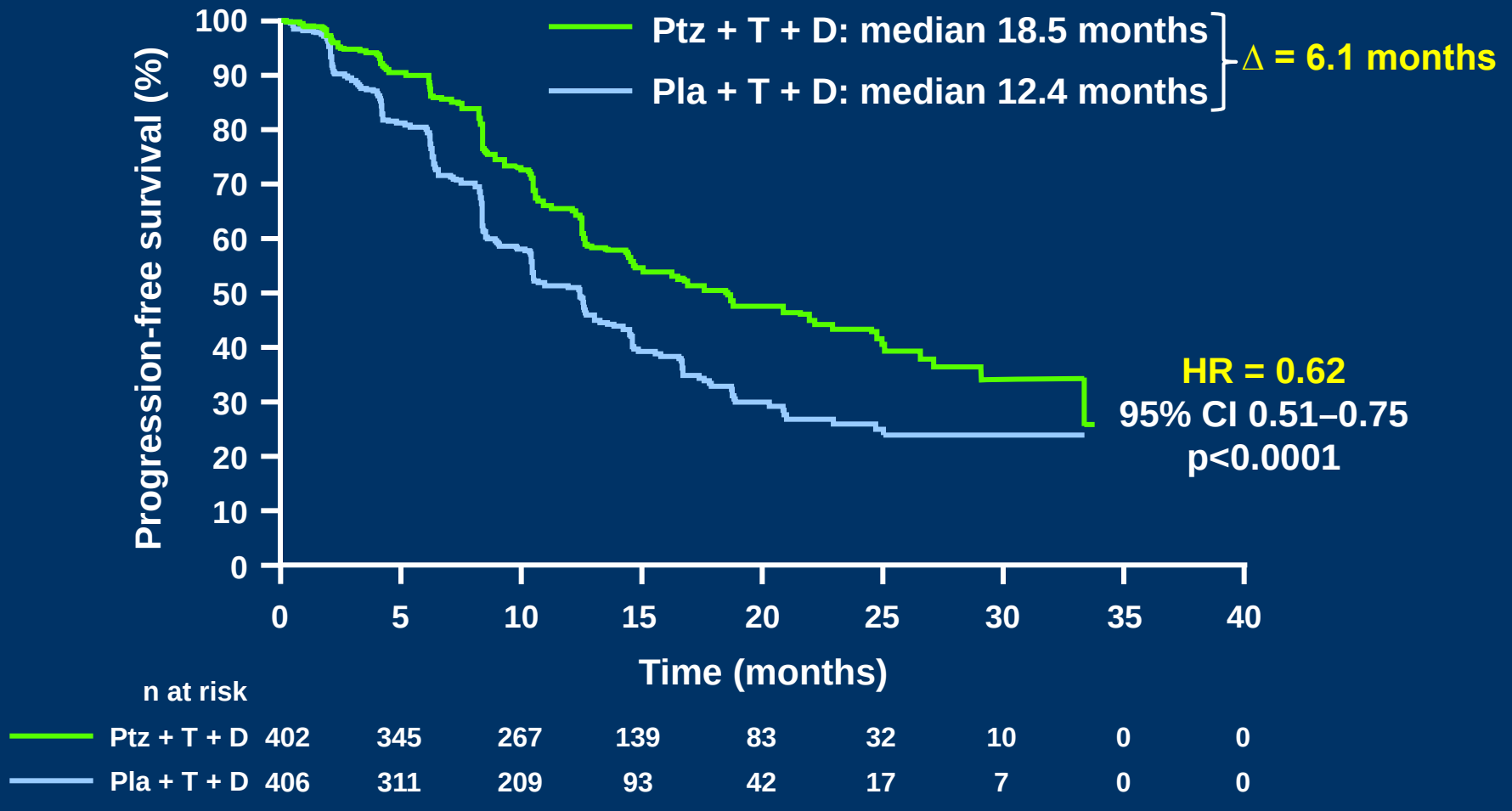
	Placebo + trastuzumab + docetaxel (n = 406)	Pertuzumab + trastuzumab + docetaxel (n = 402)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	192 (47.3)	184 (45.8)
No	214 (52.7)	218 (54.2)
Components of (neo)adjuvant therapy*, n (%)		
Anthracycline	164 (40.4)	150 (37.3)
Hormones	97 (23.9)	106 (26.4)
Taxane	94 (23.2)	91 (22.6)
Trastuzumab	41 (10.1)	47 (11.7)

* Numbers add up to more than 100% because patients could have received more than one therapy

Efficacy results

Primary endpoint: Independently assessed PFS

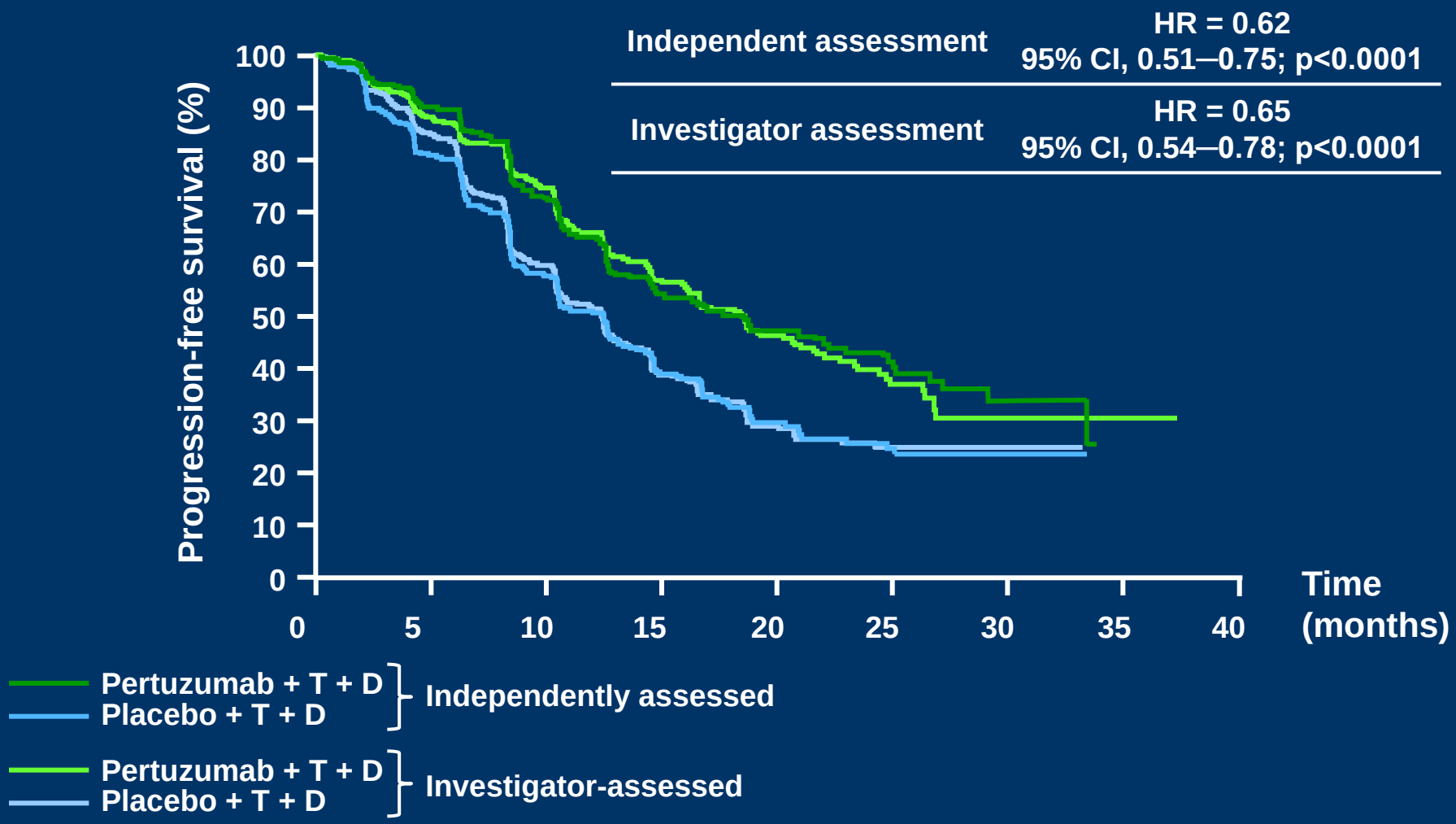
n = 433 PFS events



Stratified by prior treatment status and region

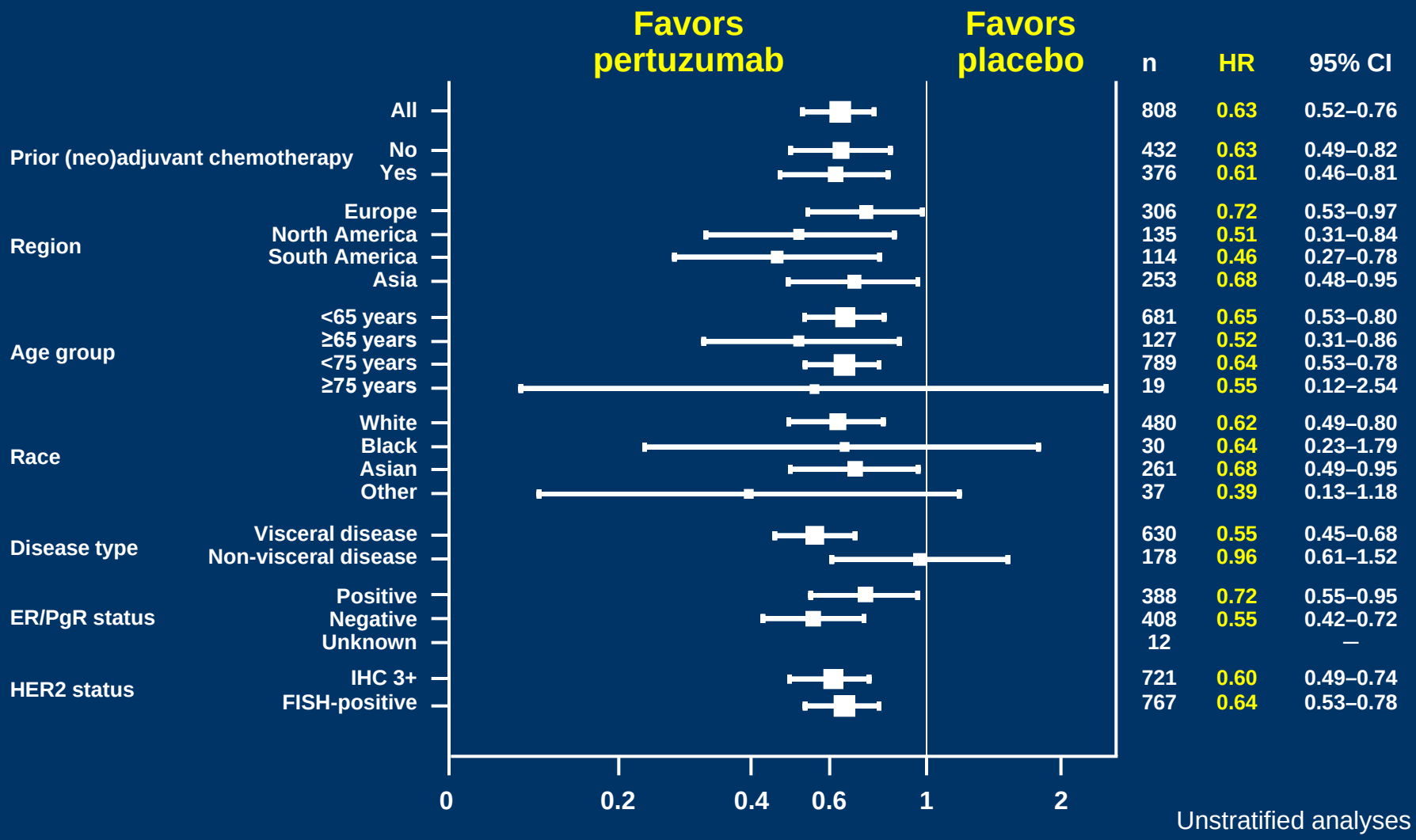
D, docetaxel; PFS, progression-free survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Independently and investigator-assessed PFS



D, docetaxel; PFS, progression-free survival; T, trastuzumab

Independently assessed PFS in predefined subgroups



Unstratified analyses

ER, estrogen receptor; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; PgR, progesterone receptor; PFS, progression-free survival

Independently assessed PFS by prior trastuzumab therapy in patients with (neo)adjuvant therapy

	Placebo + trastuzumab + docetaxel Median PFS, months	Pertuzumab + trastuzumab + docetaxel Median PFS, months	Hazard ratio (CI)
Prior (neo)adjuvant trastuzumab treatment (n = 88)	10.4	16.9	0.62 (0.35–1.07)
No prior (neo)adjuvant trastuzumab treatment (n = 288)	12.6	21.6	0.60 (0.43–0.83)

PFS, progression-free survival

Independently reviewed objective response

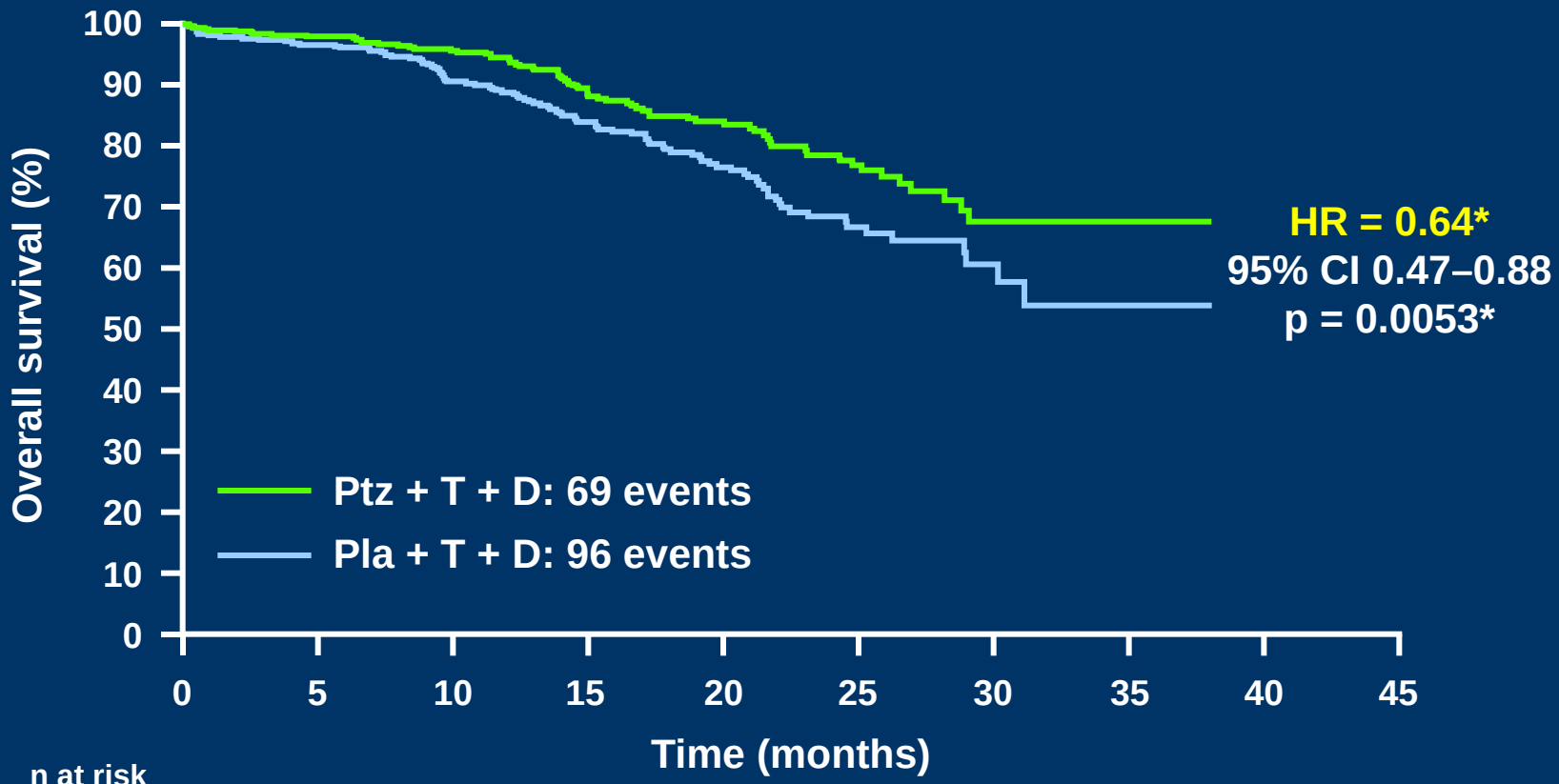
In patients with measurable disease at baseline

	Placebo + trastuzumab + docetaxel (n = 336)	Pertuzumab + trastuzumab + docetaxel (n = 343)
Objective response rate, n (%)	233 (69.3)	275 (80.2)
Complete response rate, n (%)	14 (4.2)	19 (5.5)
Partial response rate, n (%)	219 (65.2)	256 (74.6)
	p = 0.0011*	
Stable disease, n (%)	70 (20.8)	50 (14.6)
Progressive disease, n (%)	28 (8.3)	13 (3.8)
Unable to assess or no assessment, n (%)	5 (1.5)	5 (1.5)

* The statistical test result is deemed exploratory

Overall survival: Predefined interim analysis

Median follow-up: 19.3 months, n = 165 OS events



n at risk										
Pertuzumab + T + D	402	387	367	251	161	87	31	4	0	0
Placebo + T + D	406	383	347	228	143	67	24	2	0	0

*** The interim OS analysis did not cross the pre-specified O'Brien-Fleming stopping boundary (HR ≤0.603; p ≤0.0012)**

D, docetaxel; OS, overall survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab

Safety results

Cardiac tolerability

	Placebo + trastuzumab + docetaxel (n = 397)	Pertuzumab + trastuzumab + docetaxel (n = 407)
Investigator-assessed symptomatic LVSD*	1.8%	1.0%
Independently adjudicated symptomatic LVSD*	1.0%	1.0%
Fall in LVEF to <50% and by ≥10 percentage points from baseline	6.6%	3.8%

* LVSD was defined as NYHA class III/IV

LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction

Adverse events (all grades) ≥25% incidence or ≥5% difference between arms

Adverse event, n (%)	Placebo + trastuzumab + docetaxel (n = 397)	Pertuzumab + trastuzumab + docetaxel (n = 407)
Diarrhea	184 (46.3)	272 (66.8)
Alopecia	240 (60.5)	248 (60.9)
Neutropenia	197 (49.6)	215 (52.8)
Nausea	165 (41.6)	172 (42.3)
Fatigue	146 (36.8)	153 (37.6)
Rash	96 (24.2)	137 (33.7)
Decreased appetite	105 (26.4)	119 (29.2)
Mucosal inflammation	79 (19.9)	113 (27.8)
Asthenia	120 (30.2)	106 (26.0)
Peripheral edema	119 (30.0)	94 (23.1)
Constipation	99 (24.9)	61 (15.0)
Febrile neutropenia	30 (7.6)	56 (13.8)
Dry skin	17 (4.3)	43 (10.6)

Summary and conclusions

- CLEOPATRA met its primary endpoint and demonstrated a statistically significant and clinically meaningful improvement in PFS (HR = 0.62) in patients with HER2-positive MBC
  - Median PFS increased by 6.1 months from 12.4 to 18.5 months
  - The PFS improvement was consistent across subgroups and supported by the secondary endpoints of ORR and OS (immature)
- The combination of pertuzumab and trastuzumab plus docetaxel increased rates of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin
  - These adverse events were primarily grades 1–2, manageable, and occurred during docetaxel therapy
  - There was no increase in cardiac adverse events or LVSD
- This new regimen may be practice-changing in HER2-positive first-line MBC

Take Home Messages

- New predictive markers of trastuzumab and lapatinib response and resistance have been defined- PI3K mutations and PTEN loss.
- New therapies should become rapidly available
  - Ab to HER3
  - Neratinib
  - Pertuzumab
  - DM-1