Targeted Therapy for Gastric Cancer

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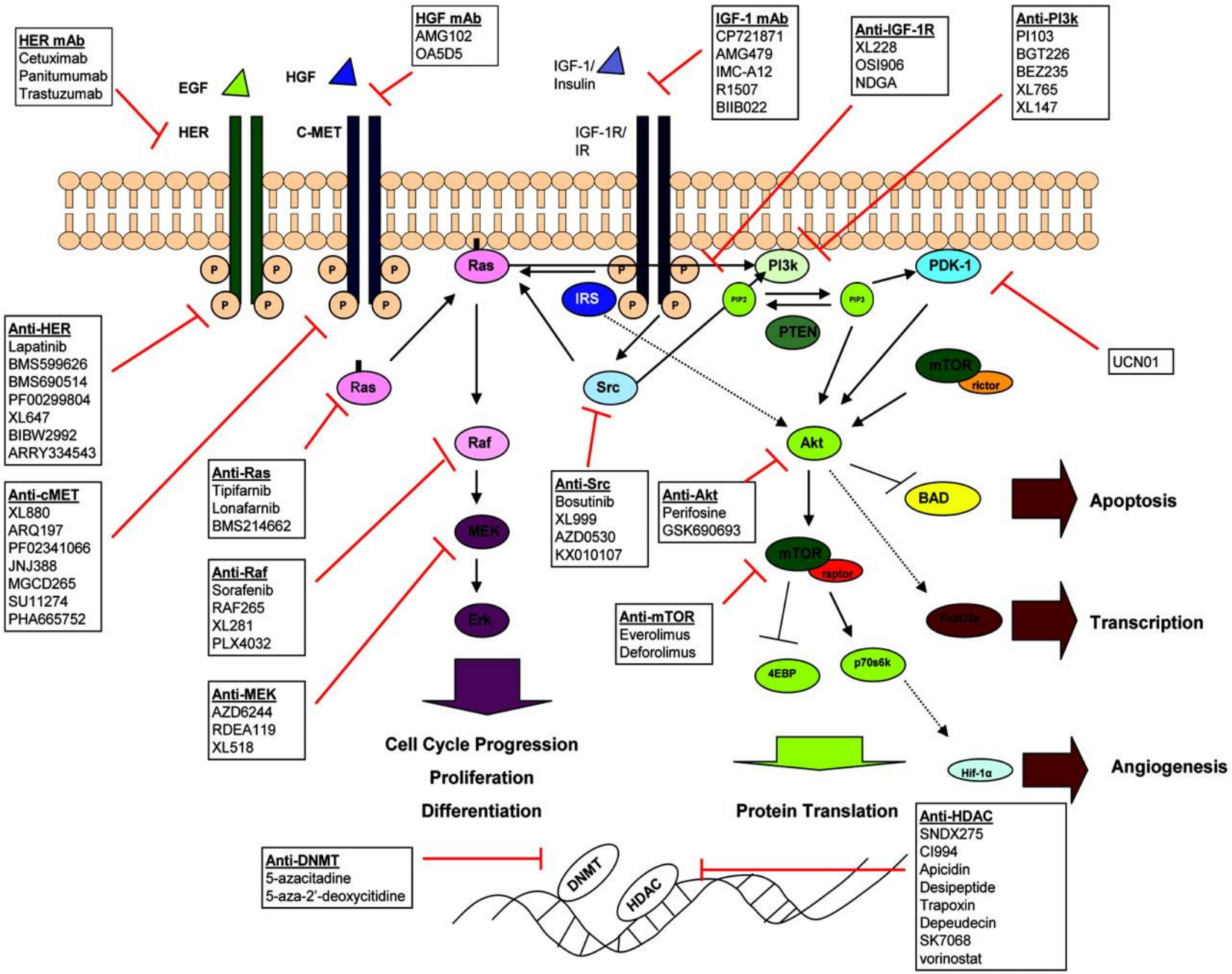
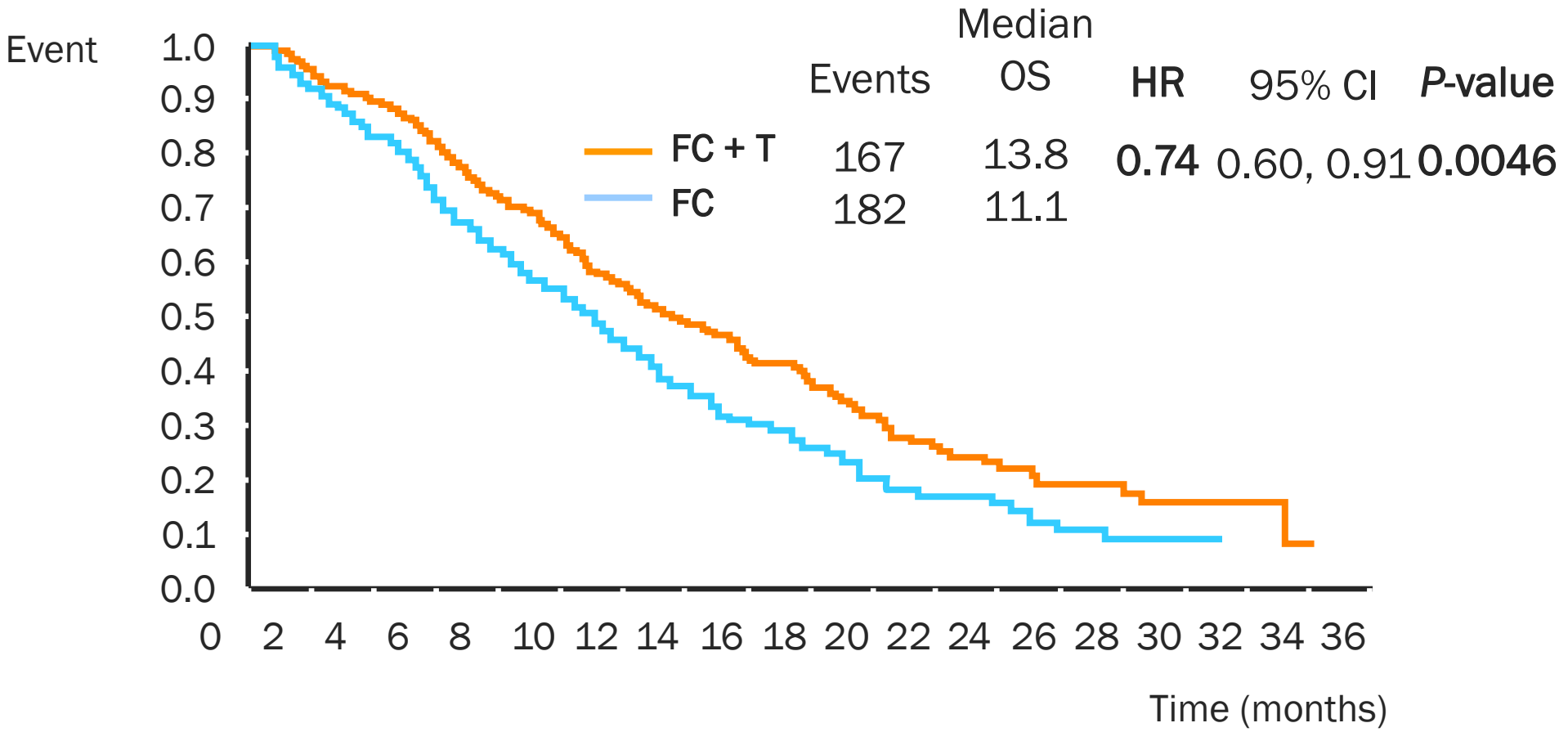
THE CELLULAR SIGNALLING PATHWAYS WITH THE TARGETS AMENABLE TO THERAPEUTIC INTERVENTIONS IN CANCER THERAPY



Ma, Adjei. CA Cancer J Clin 2009.

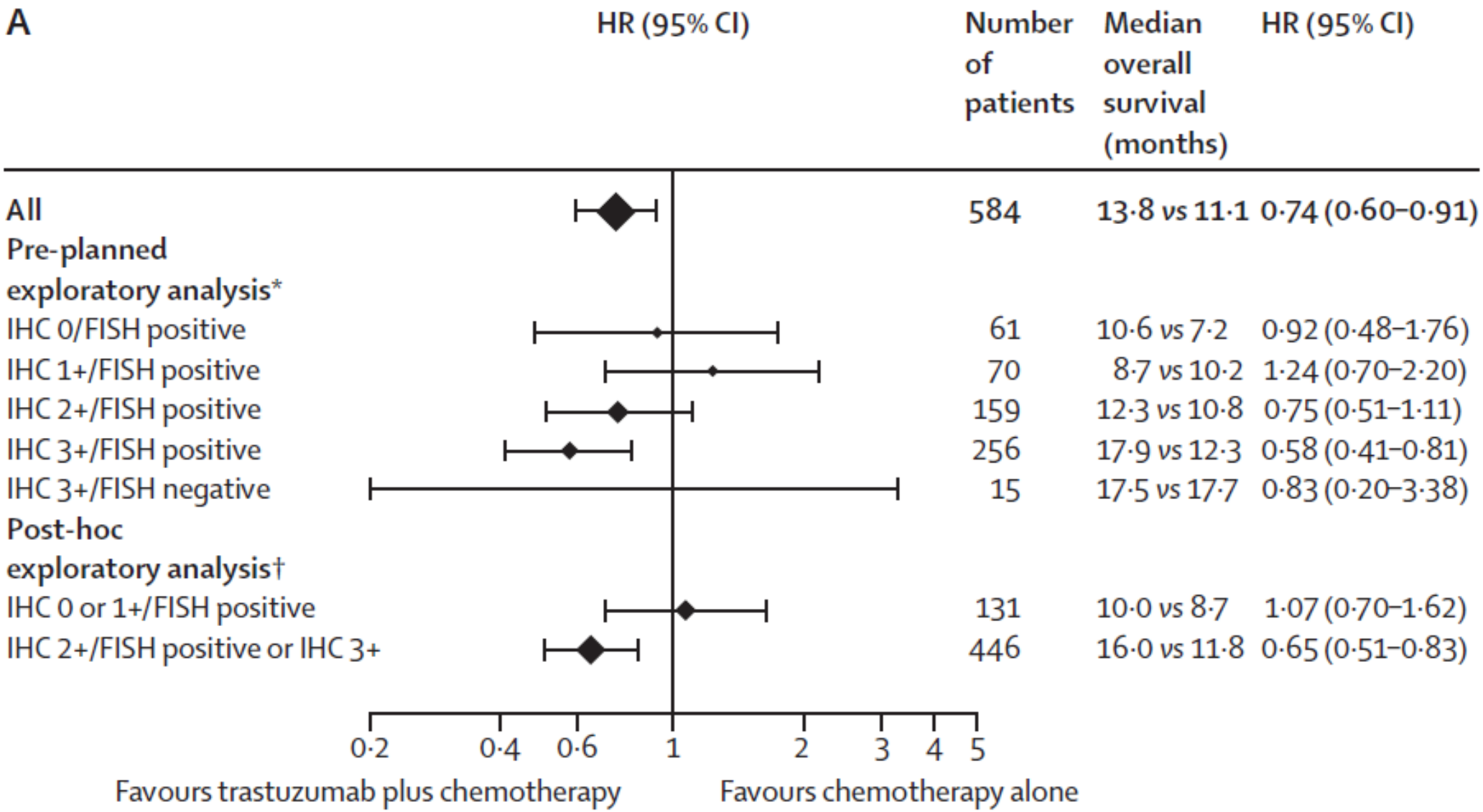
ToGA Primary Endpoint
Overall Survival



T, trastuzumab
FC, 5-FU or capecitabinea + cisplatin

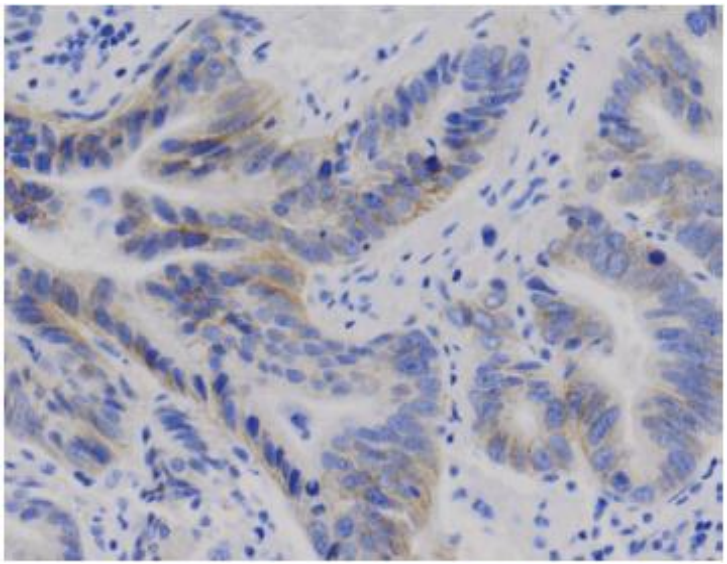
Bang YJ et al. *Lancet.* 2010;376:687-697.

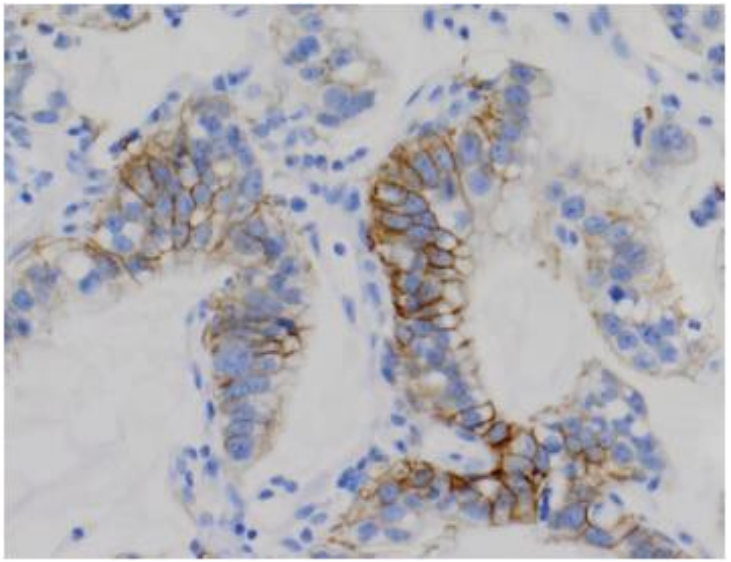
ToGA Efficacy
Overall Survival by HER2 Status



HER2 Immunohistochemistry of Gastroesophageal Cancers

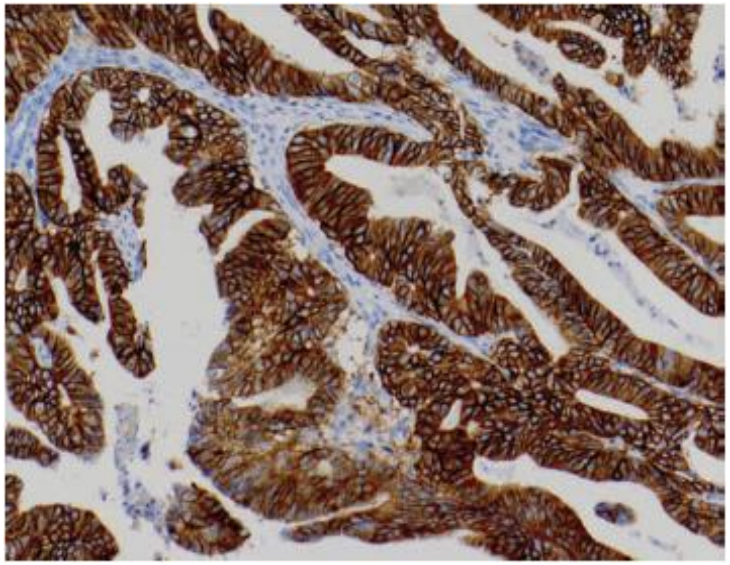
IHC 0





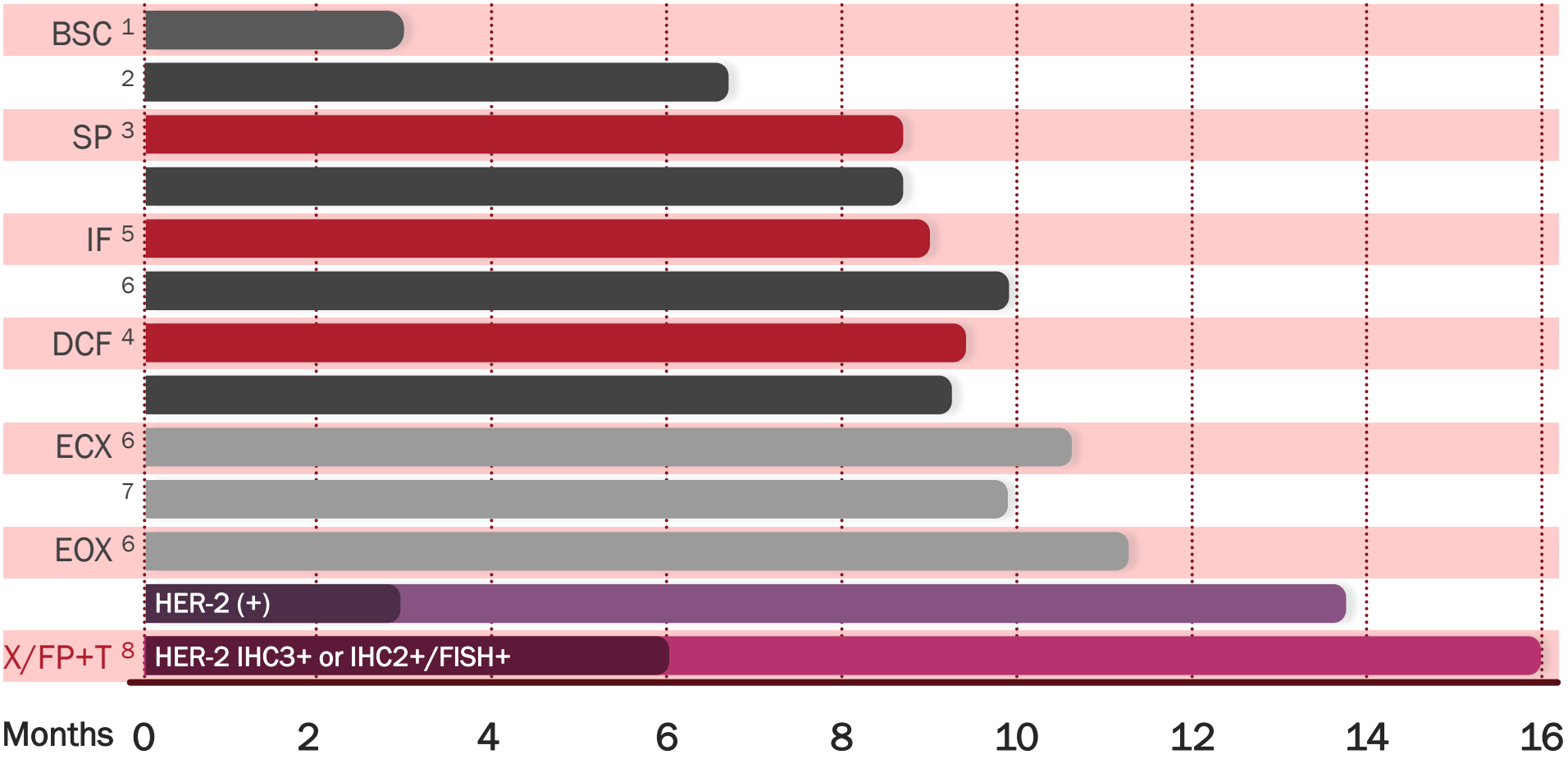
IHC2+

IHC3



Whitney-Miller CL, Hicks DG. *Connection.* 2010. Available at www.dako.com/28830_connection_15_her2_testing_in_gastric_and_esophageal_adenocarcinoma.pdf.

Median OS Observed in Trials of Current Therapies in Advanced GC

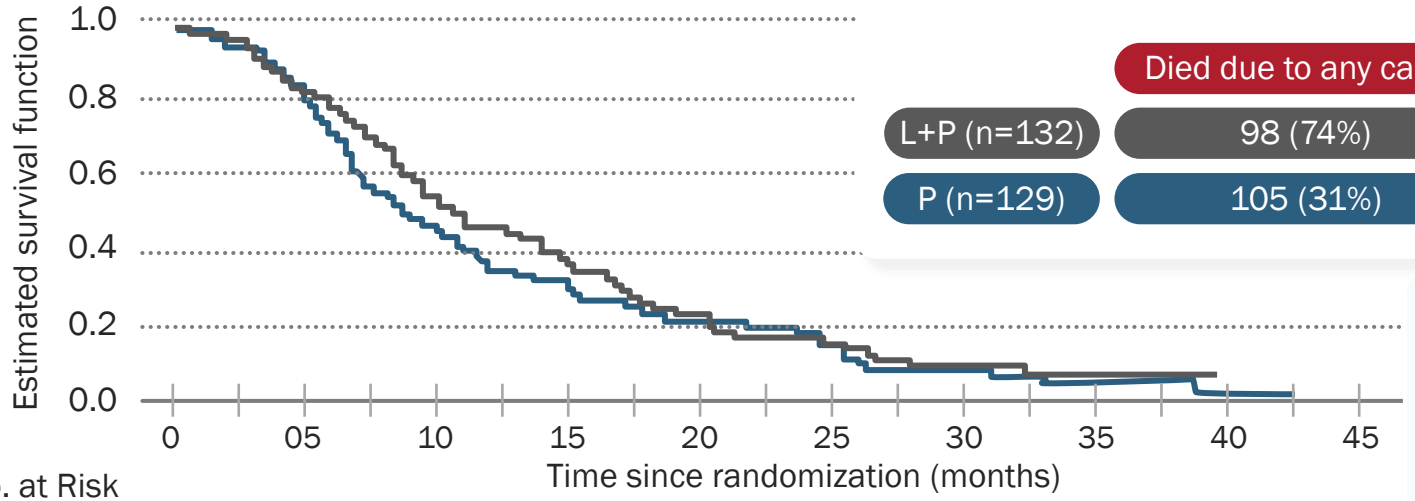


BSC = best supportive care; F = 5-FU; A = doxorubicin; MTX = methotrexate; S = S-1; C/P = cisplatin; I = irinotecan; E = epirubicin;
O = oxaliplatin; D = docetaxel

1. Murad AM et al. *Cancer.* 1993;72:37-41. 2. Vanhoefer U et al. *J Clin Oncol.* 2000;18:2648-2657. 3. Ajani JA et al. *J Clin Oncol.* 2009;27(15 suppl):abstract 4511. 4. Van Cutsem E et al. *J Clin Oncol.* 2006;24:4991-4997. 5. Dank M et al. *Ann Oncol.*2008;19:1450-1457. 6. Cunningham D et al. *N Engl J Med.* 2008;358:36-46. 7. Kang YK et al. *Ann Oncol.* 2009;20:666-673. 8. Bang Y et al. *J Clin Oncol.* 2009;27(15 suppl):abstract 4556.

TyTAN Study
Treatment Outcomes

OS

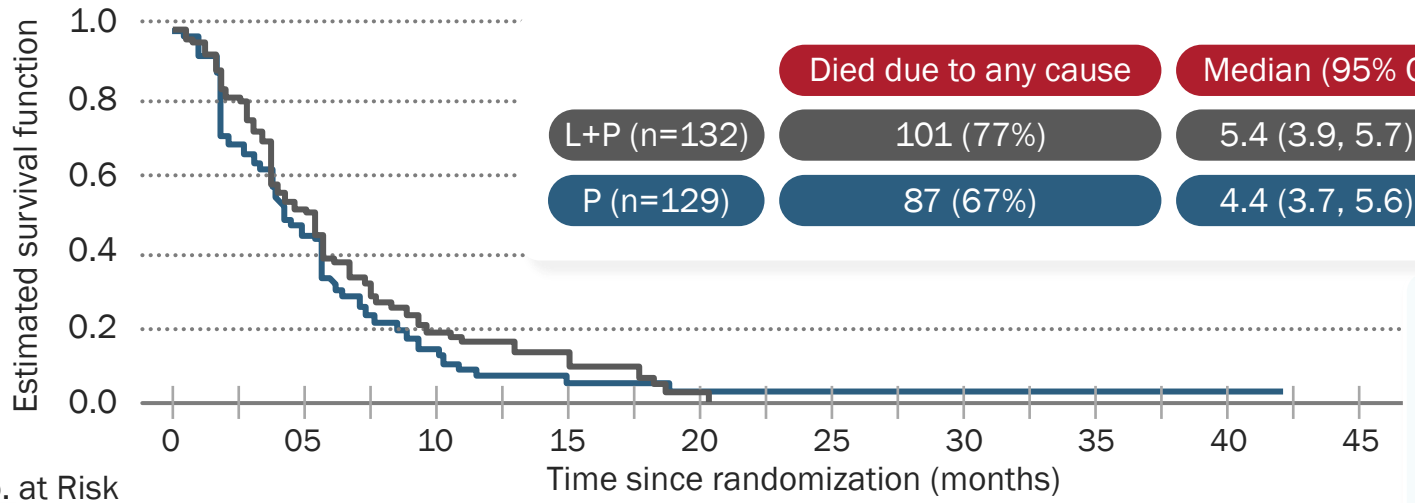


	Died due to any cause	Median (95% CI)
L+P (n=132)	98 (74%)	11.0 (9.5, 14.5)
P (n=129)	105 (31%)	8.9 (7.4, 11.1)

HR = 0.54
95% CI (0.54, 1.11)
p value = 0.2088

No. at Risk										
Lapatinib + Paclitaxel	132	110	63	37	19	9	6	1	0	0
Paclitaxel alone	129	106	56	33	19	10	5	3	1	0

PFS



	Died due to any cause	Median (95% CI)	Best OHH (95% CI)
L+P (n=132)	101 (77%)	5.4 (3.9, 5.7)	27% (19.2, 34.9)
P (n=129)	87 (67%)	4.4 (3.7, 5.6)	9% (4.3, 14.7)

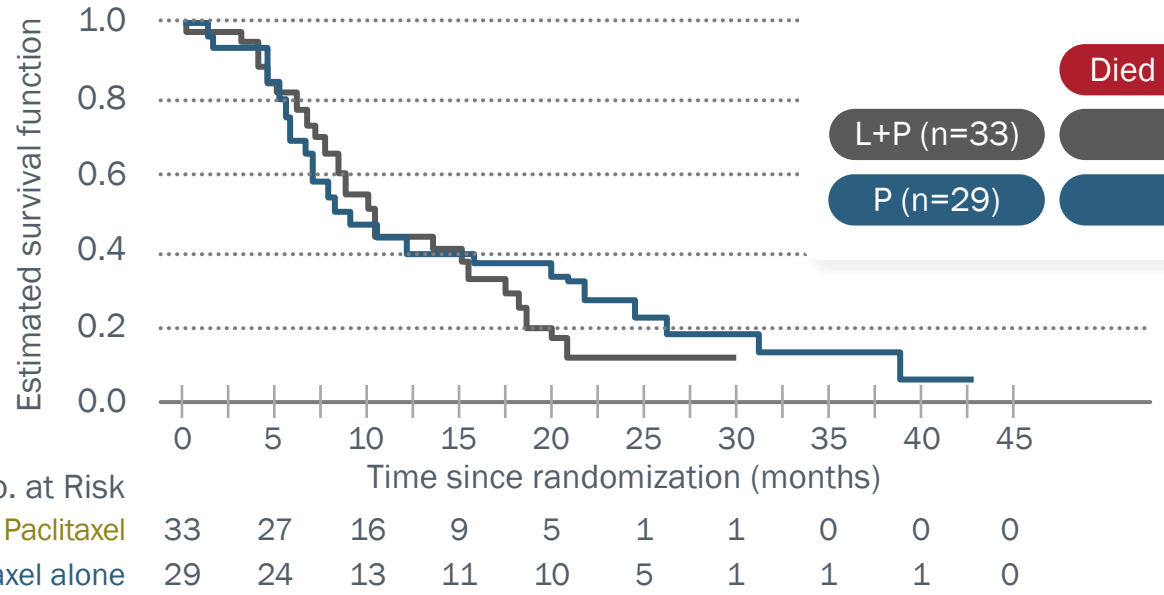
HR = 0.85
95% CI (0.53, 1.13)
p value = 0.2441

No. at Risk										
Lapatinib + Paclitaxel	132	59	15	6	1	0	0	0	0	0
Paclitaxel alone	129	40	9	3	1	1	1	1	1	0

Bang, et al. 2013 ASCO-GI

TyTAN Study Significant Efficacy in IHC3+
More patients with IHC 0 or 1+ (36% vs. 22% in ToGA)

IHC 0/1+

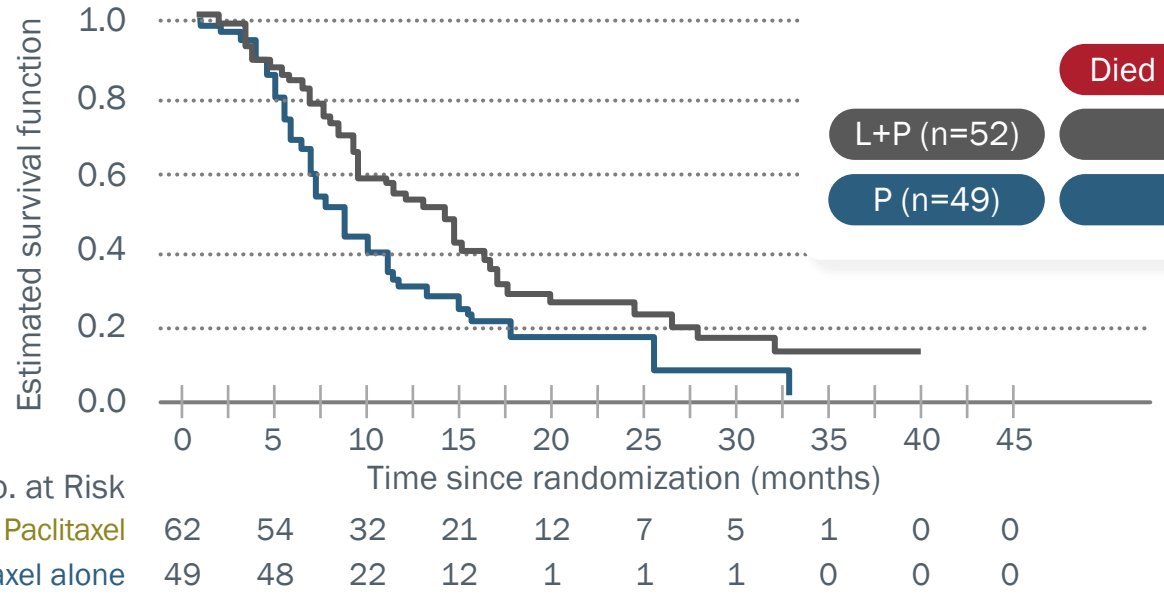


No. at Risk										
Lapatinib + Paclitaxel	33	27	16	9	5	1	1	0	0	0
Paclitaxel alone	29	24	13	11	10	5	1	1	1	0

	Died due to any cause	Median (95% CI)
L+P (n=33)	26 (79%)	10.1 (8.2, 15.3)
P (n=29)	24 (83%)	8.7 (6.0, 21.7)

HR = 1.16
95% CI (0.67, 2.02)
p value = 0.5851

IHC 3+



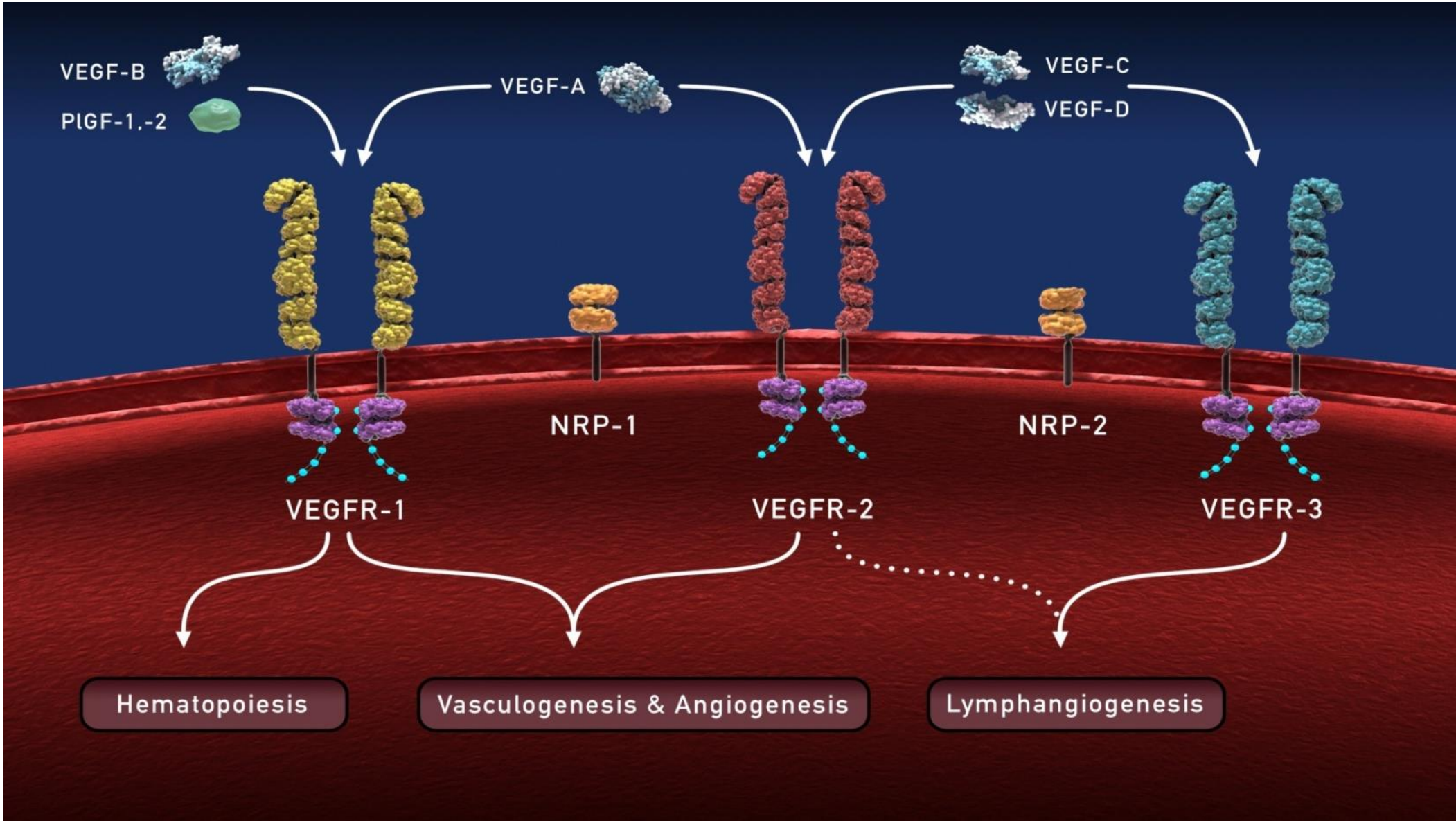
No. at Risk										
Lapatinib + Paclitaxel	62	54	32	21	12	7	5	1	0	0
Paclitaxel alone	49	48	22	12	1	1	1	0	0	0

	Died due to any cause	Median (95% CI)
L+P (n=52)	37 (71%)	14.0 (9.6, 15.7)
P (n=49)	40 (82%)	7.6 (6.8, 10.8)

HR = 0.59
95% CI (0.37, 0.93)
p value = 0.0176

Bang, et al. 2013 ASCO-GI

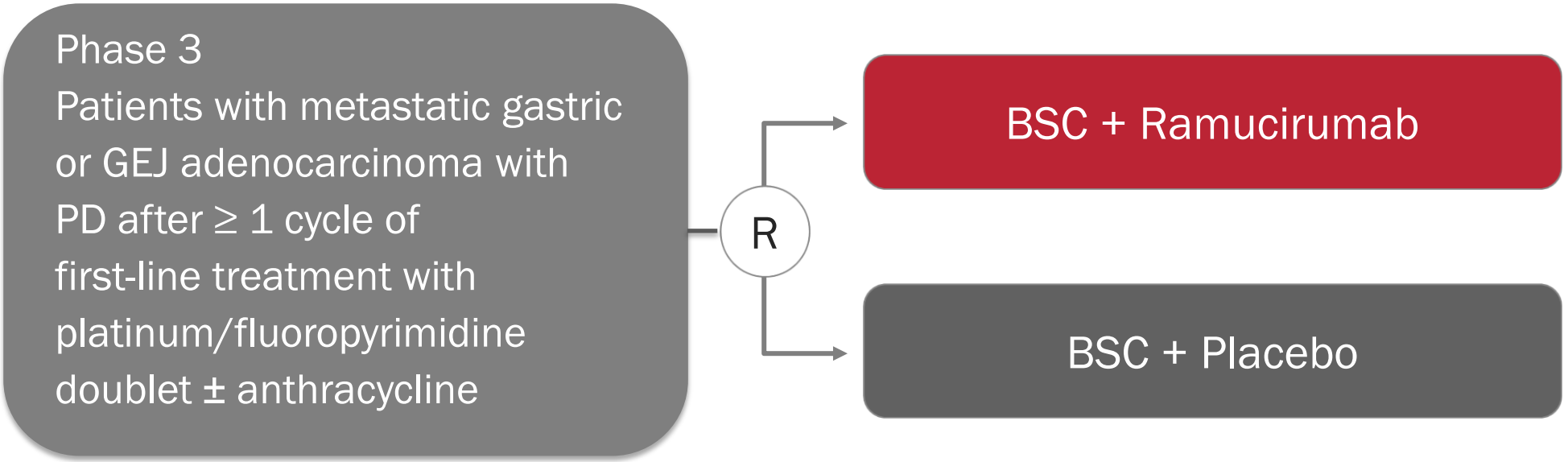
VEGF-Family of Ligands and Receptors



Hicklin DJ, Ellis LM. *J Clin Oncol.* 2005;23:1011-1027.
Holmes K et al. *Cell Signal*. 2007;19:2003-2012.

REGARD

BSC +/- Ramucirumab for Metastatic Gastric Cancer-Study Design

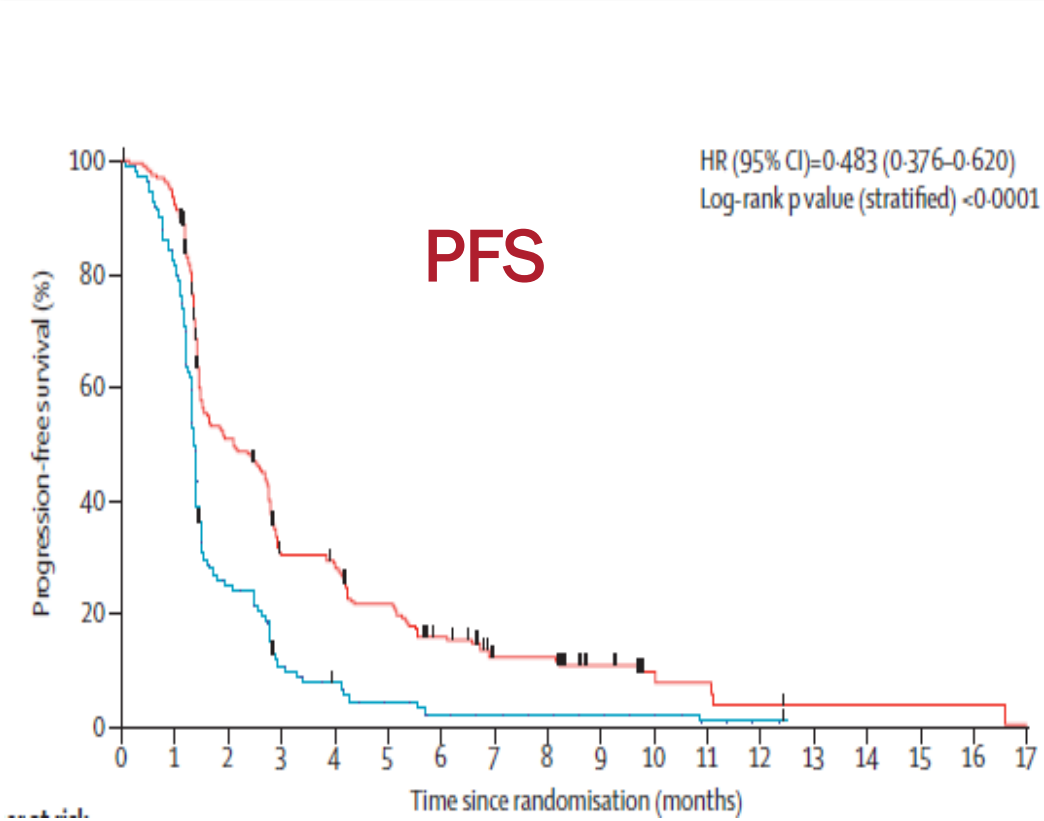


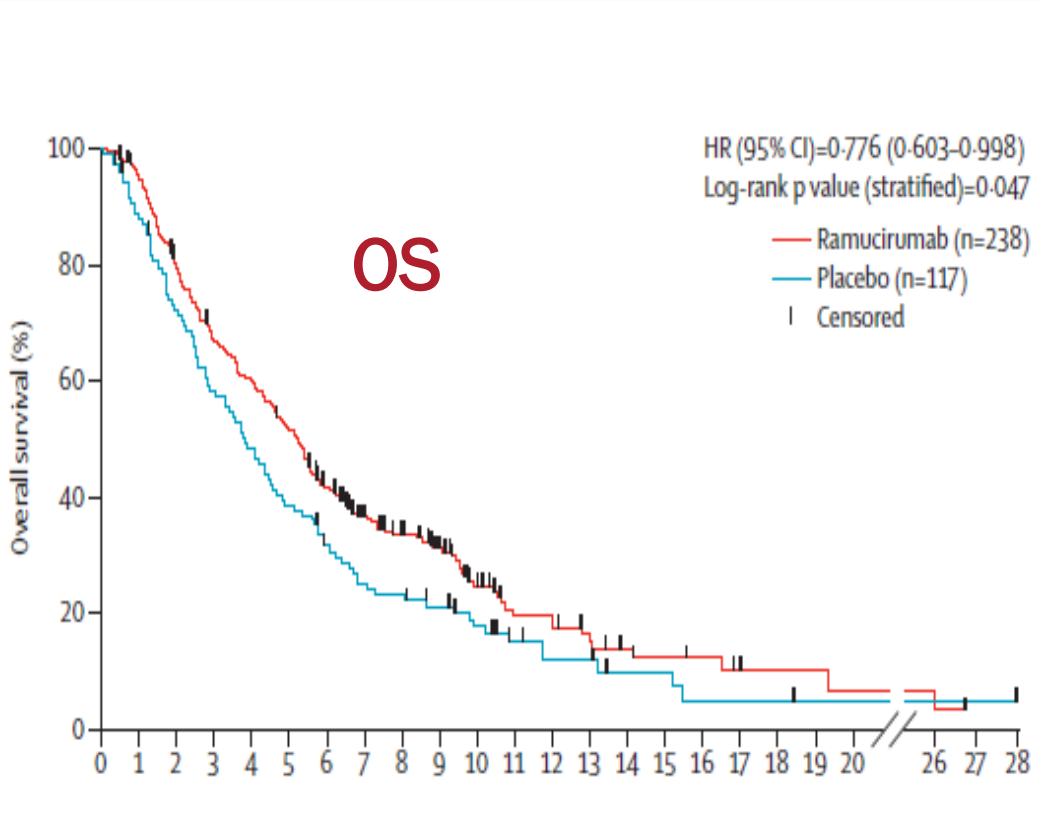
➔ primary endpoint: OS

Fuchs CS et al. *Lancet.* 2014;383:31-39.

REGARD

BSC +/- Ramucirumab for Metastatic Gastric Cancer-Results

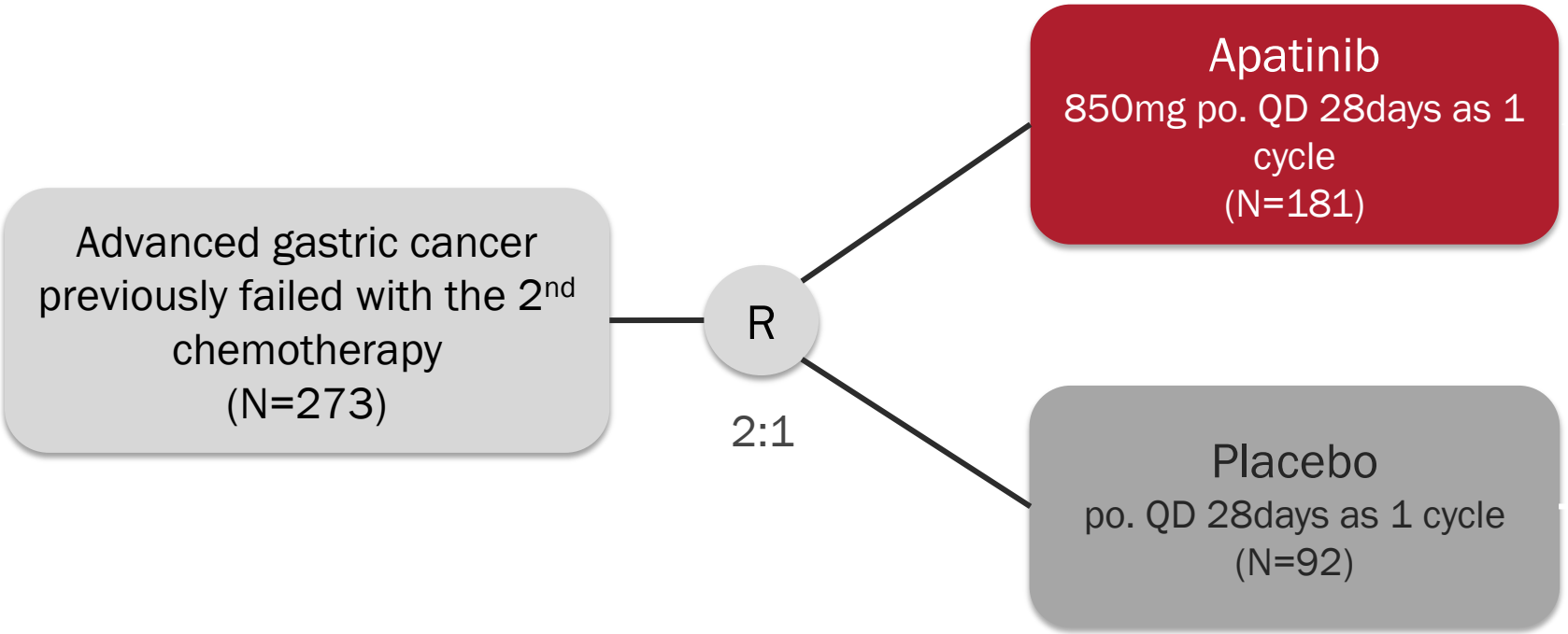




Fuchs CS et al. *Lancet.* 2014;383:31-39.

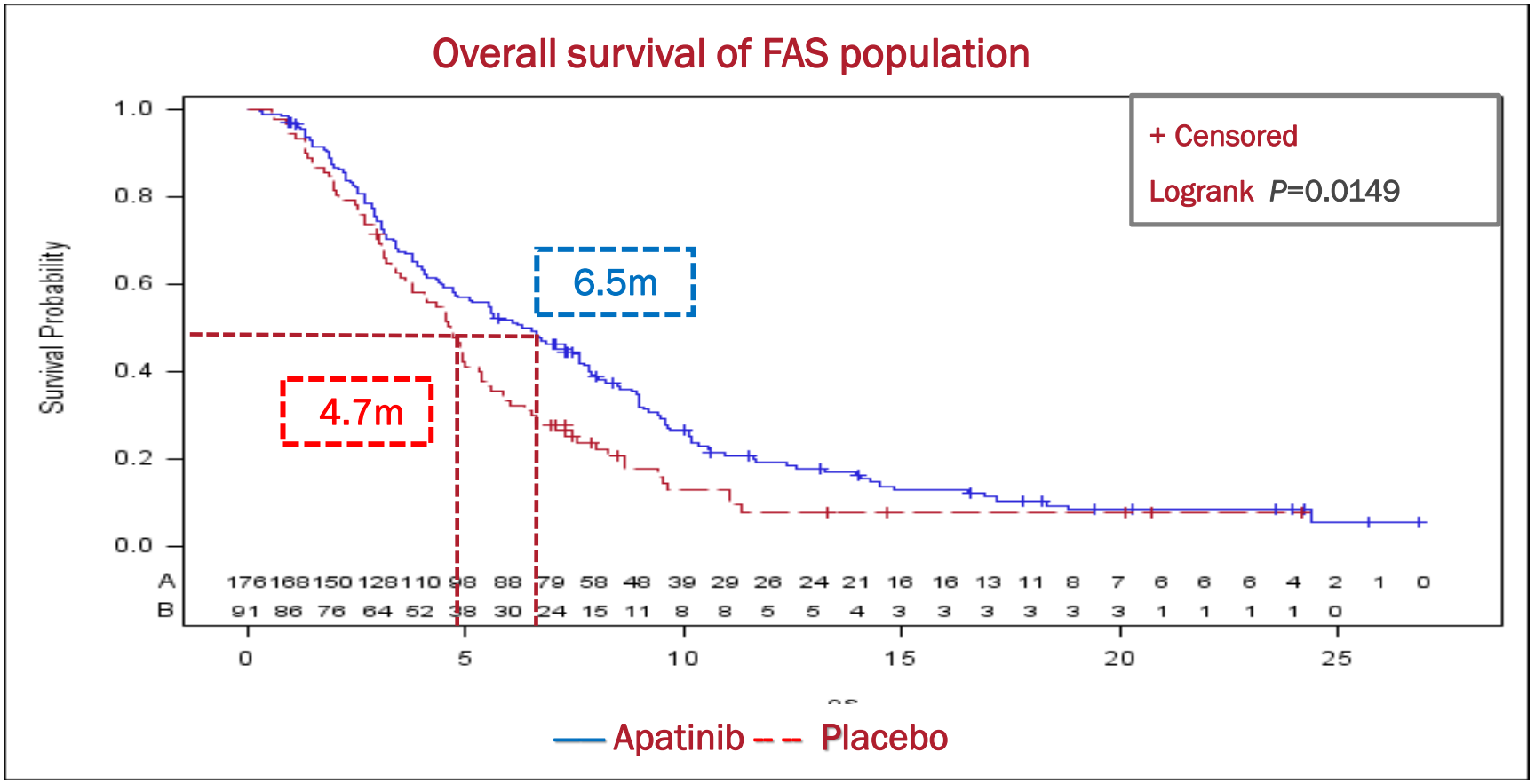
Apatinib Phase III Study design

- Oral tyrosine kinase inhibitor to VEGFR2
- Design: multicenter, randomized, double-blind, placebo-controlled clinical trial



- 1 treatment cycle = 28 days
- Stratification factor: the number of metastatic sites (≤ 2 *vs.* >2)

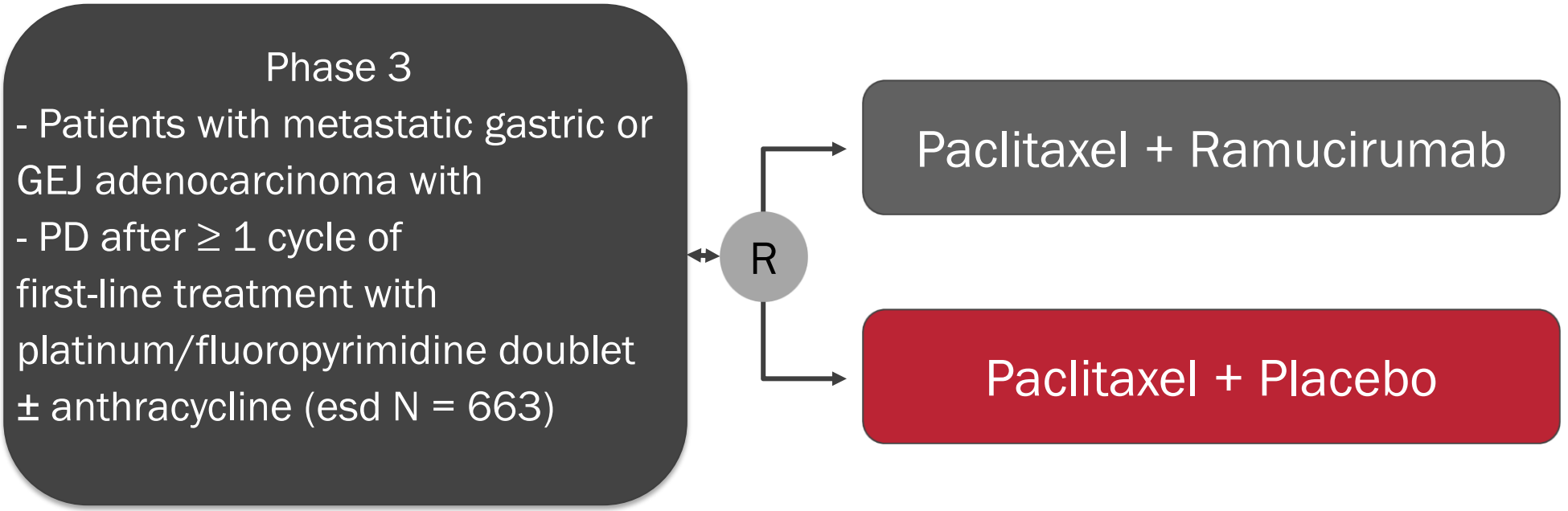
PRIMARY END POINT – OS



Group	n	mOS (95% CI), months	*P* value	HR(95%CI)
Apatinib	176	6.5(4.8-7.6)	*0.0149*	0.709 (0.537-0.937)
Placebo	91	4.7(3.6-5.4)		

RAINBOW

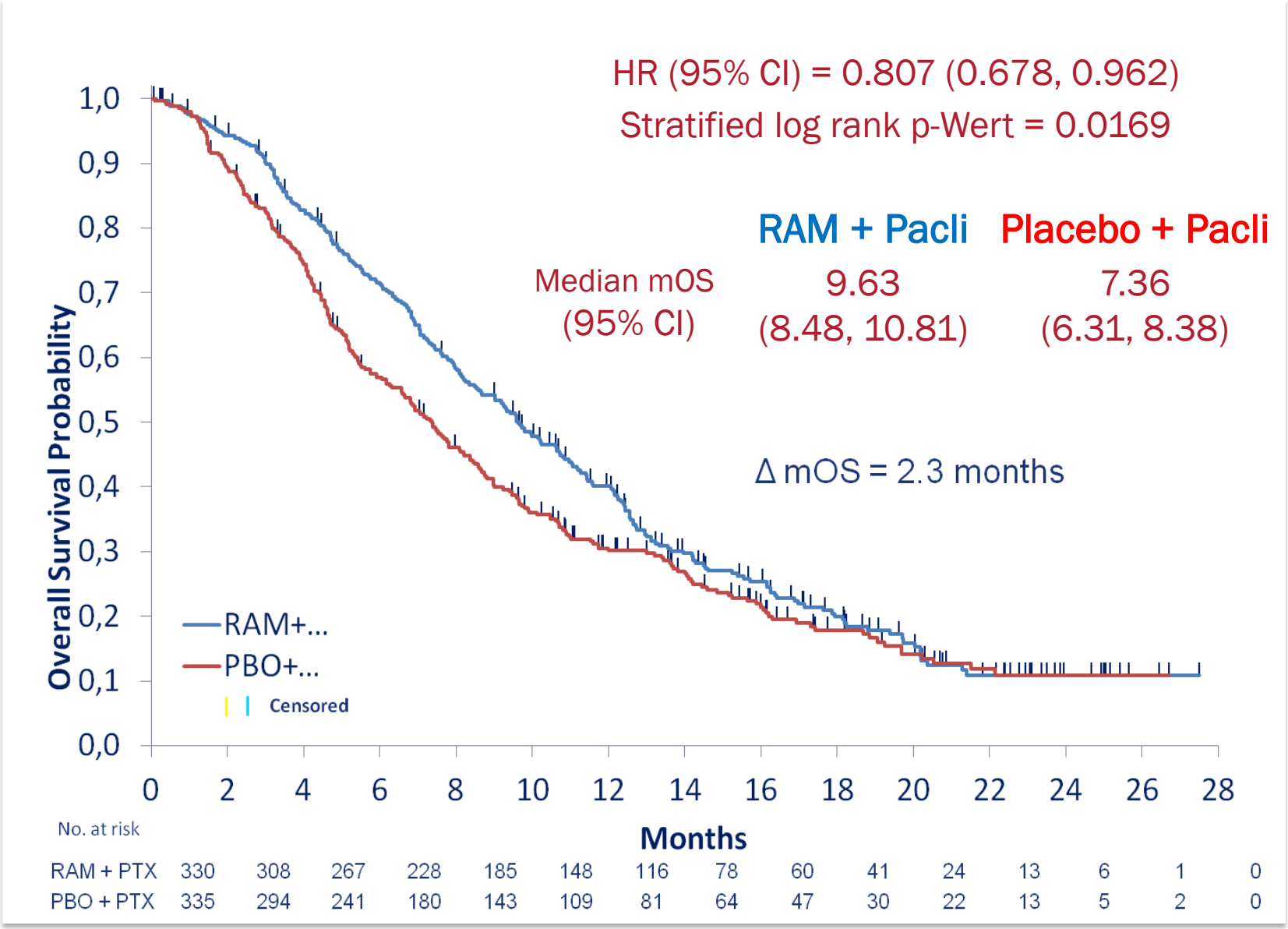
Ramucirumab + Paclitaxel for Metastatic Gastric Cancer



➔ primary endpoint: OS

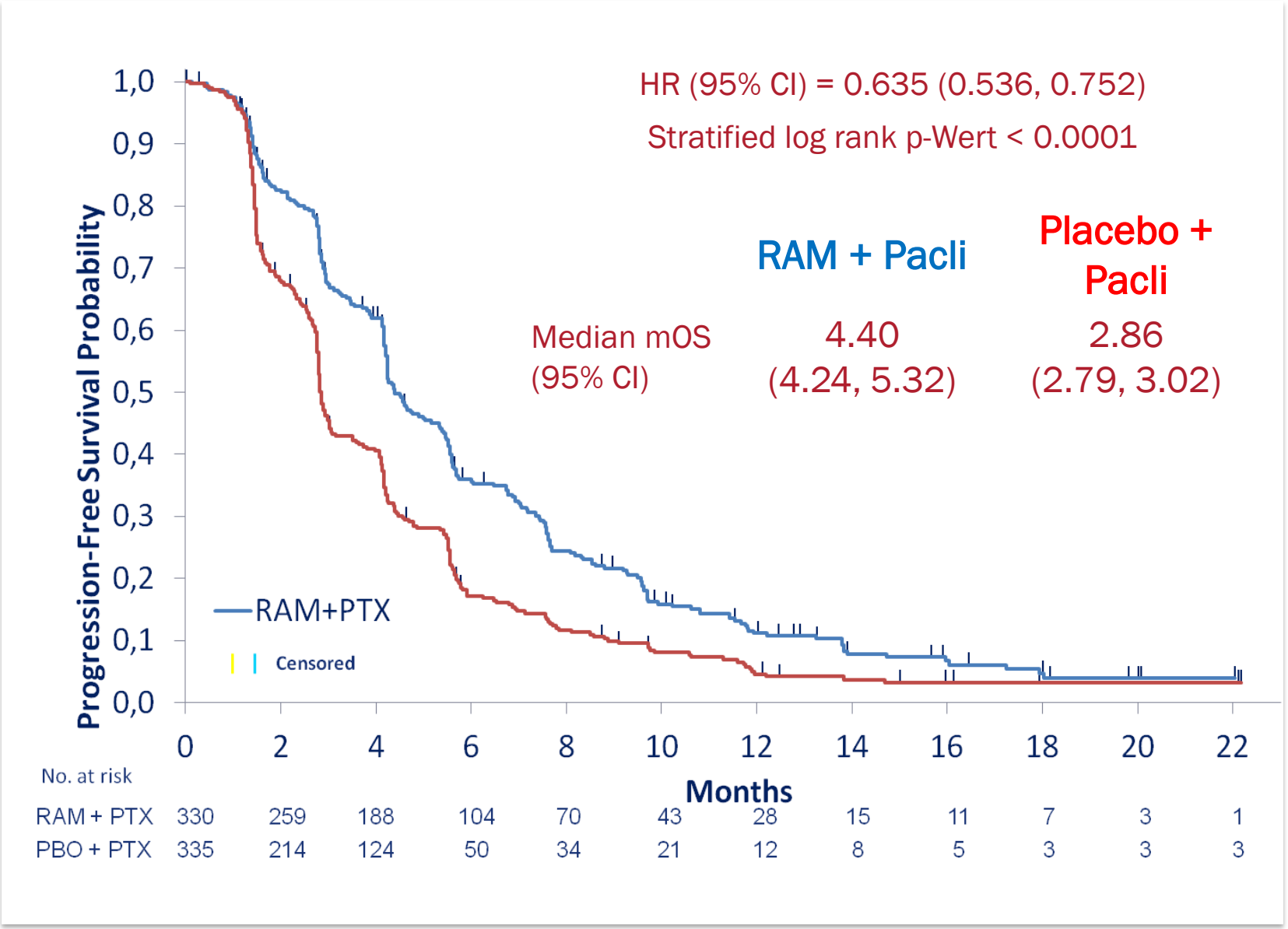
ClinicalTrials.gov. NCT01170663.

RAINBOW
Overall Survival



Wilke et al. ASCO GI 2014. Abstract LBA7

RAINBOW
PROGRESSION-FREE SURVIVAL



Wilke et al. ASCO GI 2014. Abstract LBA7

RAINBOW
EFFICACY SUMMARY

Efficacy Parameter	RAM + PTX	PBO + PTX	HR *P*-value	Delta
Response Rate	28%	16%	*P*=0.0001	+ 12%
Disease Control Rate	80%	64%	*P*<0.0001	+ 16%
PFS (med, mos) - at 6-months - at 9-months	4.40 36% 22%	2.86 17% 10%	HR 0.635 *P*<0.0001	+ 1.5 + 19% + 12%
OS (med, mos) - at 6-months - at 12-months	9.63 72% 40%	7.36 57% 30%	HR 0.807 *P*=0.0169	+ 2.3 + 15% + 10%

Wilke et al. ASCO GI 2014

Treatment-Emergent Adverse Events*

	RAM + PTX (N=327)		PBO + PTX (N=329)	
Preferred Term†	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
Fatigue†	56.9	11.9	43.8	5.5
Neutropenia†	54.4	40.7	31.0	18.8
Neuropathy†	45.9	8.3	36.2	4.6
Decreased appetite	40.1	3.1	31.9	4.0
Abdominal pain†	36.1	6.1	29.8	3.3
Leukopenia†	33.9	17.4	21.0	6.7
Diarrhea	32.4	3.7	23.1	1.5
Epistaxis	30.6	0	7.0	0
Vomiting	26.9	3.1	20.7	3.6
Hypertension†	25.1	14.7	5.8	2.7
Peripheral Edema	25.1	1.5	13.7	0.6

***Occurring in ≥ 20% of Patients and ≥ 5% Higher in the RAM + PTX Arm**

†Consolidated AE terms are comprised of synonymous MedDRA preferred terms: fatigue includes asthenia; neutropenia includes neutrophil count decreased; neuropathy includes peripheral sensory neuropathy; paraesthesia; neuropathy peripheral, polyneuropathy; hypoasethesia, neuralgia, dysaesthesia; abdominal pain includes abdominal pain upper and abdominal pain lower; leukopenia includes white blood cell decreased; hypertension includes blood pressure increased, hypertensive cardiomyopathy, procedural hypertension, systolic hypertension.

Wilke et al. ASCO GI 2014. Abstract LBA7

Adverse Events of Special Interest

	RAM + PTX (N=327)		PBO + PTX (N=329)	
Category of event†	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
Bleeding/Hemorrhage	41.9	4.3	17.9	2.4
Epistaxis	30.6	0	7.0	0
Hypertension	25.1	14.7	5.8	2.7
Proteinuria	16.8	1.2	6.1	0
GI hemorrhage	10.1	3.7	6.1	1.5
Renal failure	6.7	1.8	4.3	0.9
Infusion-related reaction	5.8	0.6	3.6	0
Venous thromboembolic	4.0	2.4	5.5	3.3
Cardiac failure	2.4	0.6	1.2	0.6
Arteriothromboembolic	1.8	0.9	1.5	0.9
GI perforation	1.2	1.2	0.3	0

†Each AESI category is comprised of consolidated synonymous MeDRA preferred terms.

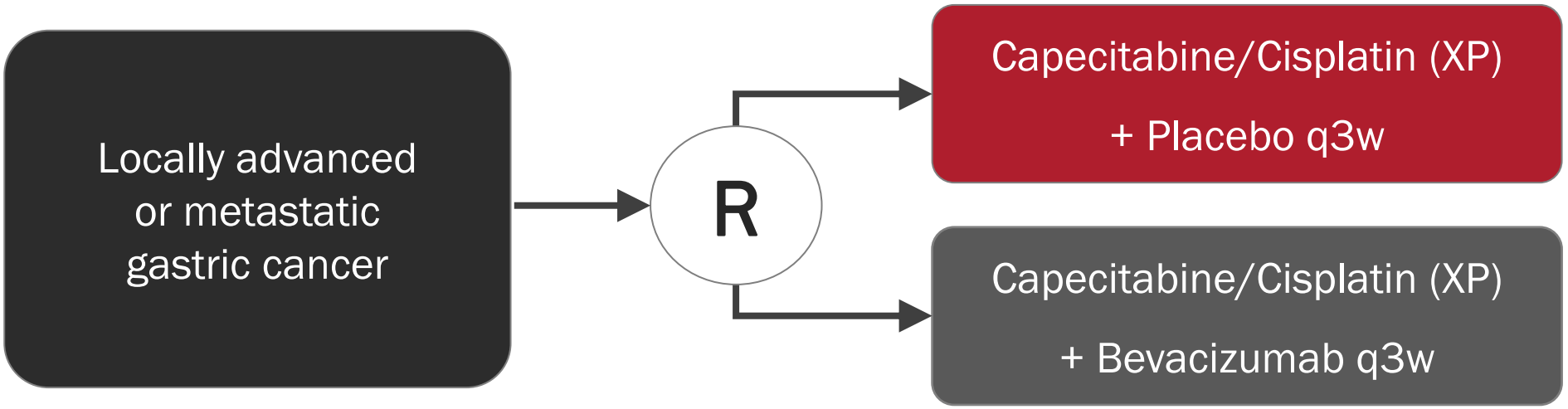
Wilke et al. ASCO GI 2014

Discussion

Why did ramucirumab work?

- 2nd line disease is easier to improve outcomes in?
- Disease heterogeneity?
- Ramucirumab or VEGFR2 targeting better than a VEGF-A inhibitor?

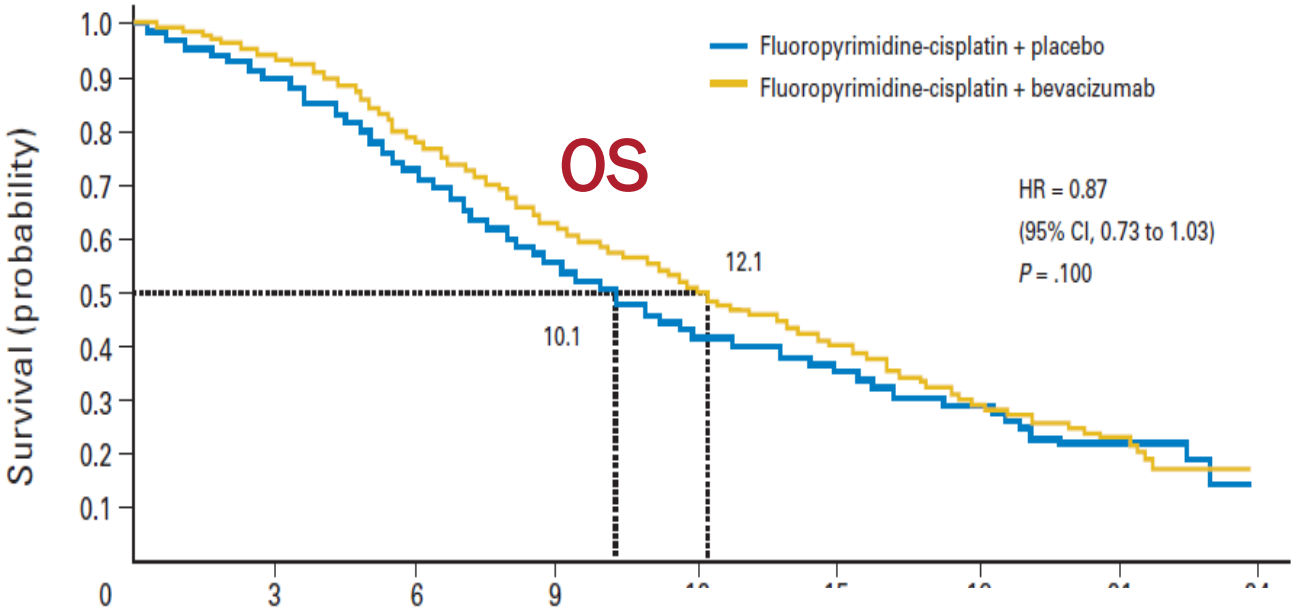
AVAGAST



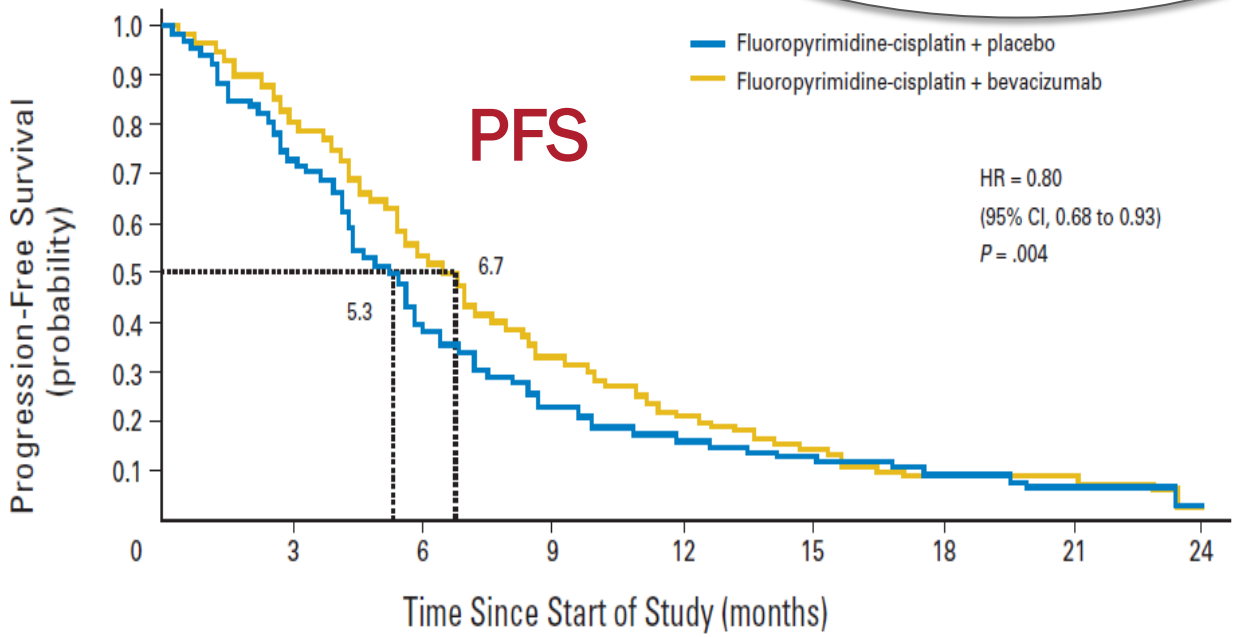
Primary endpoint overall survival
10 → 12.8 Months (HR 0.78)

Kang Y et al. *J Clin Oncol.* 2010;28(18 suppl):abstract LBA4007.

AVAGAST TRIAL



10% higher response rate !



Ohtsu A et al.
J Clin Oncol. 2011;29:3968-3976.

BEVACIZUMAB PLUS CT FOR ADVANCED GASTROESOPHAGEAL ADENOCARCINOMA (GC): COMBINED U.S. EXPERIENCE*

Tumor Characteristics					
	US cohort		AVAGAST Chemo + Bev arm		p value
	n	%	n	%	
Site					
Gastric	64	(41)	333	(86)	
GEJ	92	(59)	54	(14)	<0.0001
Lauren's Classification*					
Diffuse	42	(27)	176	(46)	
Intestinal	81	(52)	155	(40)	<0.0001**
Mixed			35	(9)	
Not reported	33	(21)			
Liver metastasis	81	(52)	130	(34)	<0.0001

*Data from 4 investigator initiated U.S. phase II studies of chemotherapy plus bevacizumab for the treatment of metastatic/unresectable gastric cancer were pooled. Sites involved were: 1) Memorial Sloan-Kettering Cancer Center, 2) Dana-Farber/Harvard Cancer Center, 3)Yale Cancer Center, and 4) Stanford Comprehensive Cancer Center.

Smyth, et al. ASCO 2011 (Abstract 4056)

AVAGAST VS. RAMUCIRUMAB

	Avagast	Rainbow
Study Design	1st line	2nd line
Backbone chemotherapy	Cisplatin/ capecitabine	Paclitaxel
Demographics	N = 774	N = 665
Asia	376 (49%)	223 (33.5%)
Non-Asia	398 (51%)	442 (66.5%)
Results OS		
Asia	12.1 → 13.9 mo **HR 0.97** (0.75-1.25)	10.5 → 12.1 mo **HR 0.99** (0.73-1.34)
Non-Asia	7.3 → 11.4 mo **HR 0.67** (0.52-0.88)	5.9 → 8.5 mo **HR 0.73** (0.59-0.91)
Results PFS		
Asia	5.6 → 6.7 (HR 0.92)	2.8 → 5.5 (HR 0.63)
Europe	4.4 → 6.9 (HR 0.71)	2.9 → 4.2 (HR 0.64)
Pan-America	4.4 → 5.9 (HR 0.65)	

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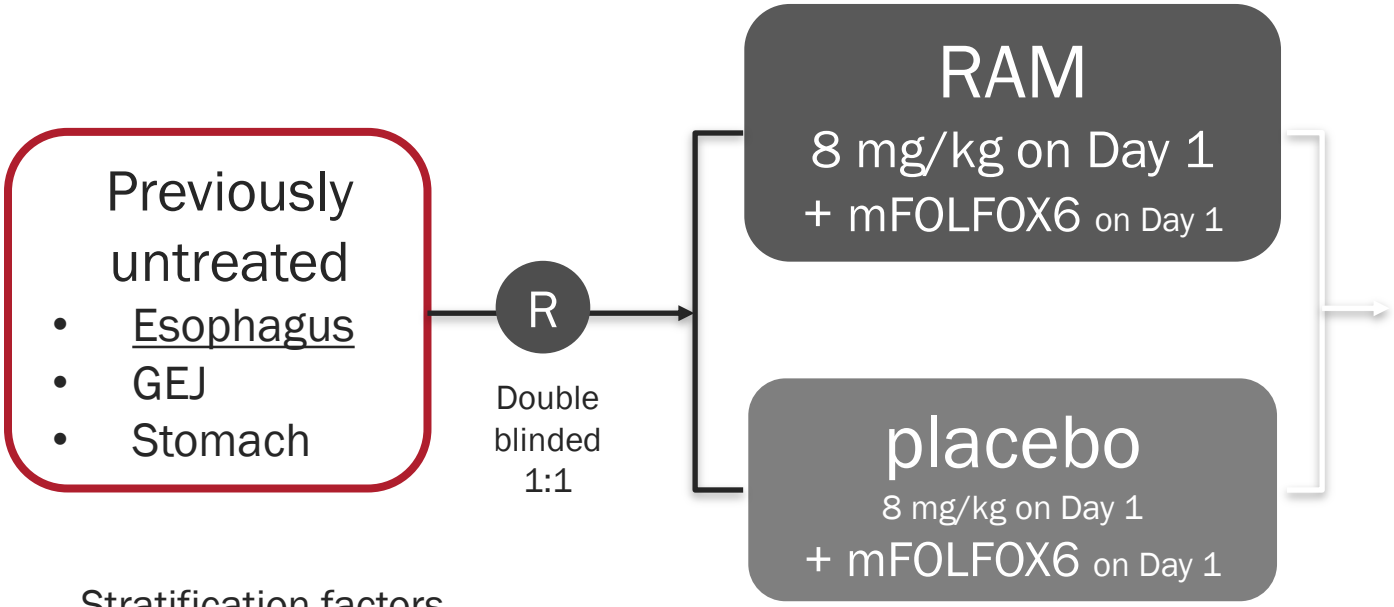
Study Design
I4T-MC-JVBT (NCT01246960)



Stratification factors
- Metastatic *vs* locally advanced unresectable
- Esophagus/GEJ *vs* gastric

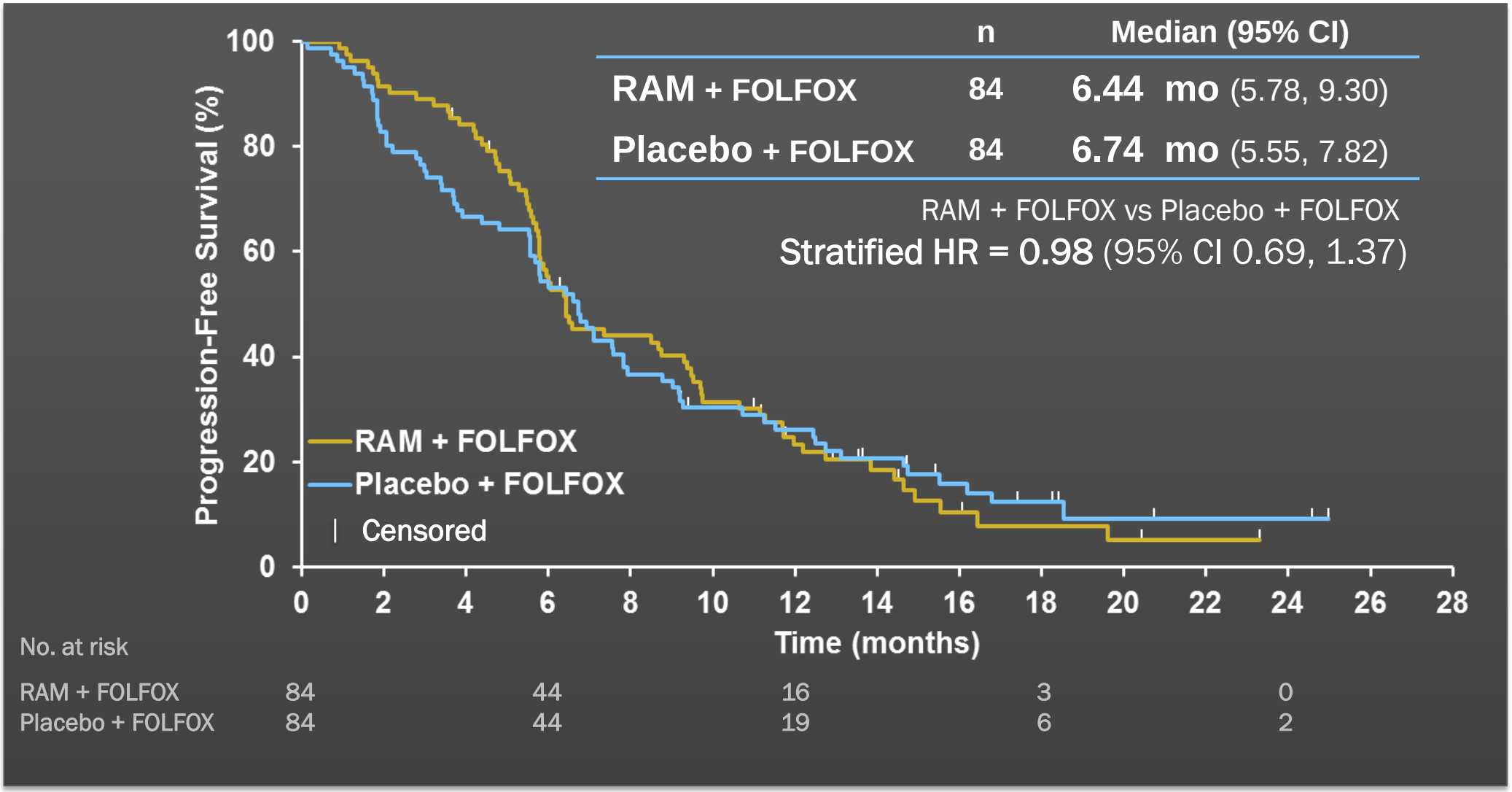
Disease assessment every 8 weeks until PD or toxicity.[a]

Discontinuation of ≥ 1 agents, while continuing others, was specifically permitted.

[a] Treatment continued until progressive disease (PD), unacceptable toxicity, patient or investigator decision.
mFOLFOX6 = 5-FU 400 mg/m2 bolus, leucovorin 400 mg/m^2, oxaliplatin 85 mg/m^2, then 5-FU continuous infusion 2,400 mg/m^2 (for 46-48 hr)

Presented by: Harry H. Yoon

Primary Endpoint
Progression-free survival in ITT population



Overall Survival: HR 1.08 (95% CI 0.73, 1.58), stratified; median 11.7 *vs* 11.5 mo

Exploratory Analysis: PFS

Censoring for Treatment Discontinuation for Reasons Other Than Progressive Disease

Category	Subgroup	RAM arm n	PLC arm n	HR (95% CI)
Tumor location[a]	Esoph/GEJ	65	64	0.80 (0.50, 1.28)
	Gastric	19	20	0.65 (0.26, 1.64)
Primary tumor location[b]	Esoph	39	41	1.10 (0.61, 1.97)
	Gastric/GEJ	45	43	0.53 (0.29, 0.97)
ECOG PS	0	40	43	0.74 (0.40, 1.36)
	1	43	41	0.72 (0.40, 1.27)
Age, y	< 65	42	56	0.86 (0.51, 1.45)
	≥ 65	42	28	0.75 (0.38, 1.49)
Prior surgery	Yes	12	14	0.63 (0.19, 2.03)
	No	72	70	0.81 (0.51, 1.26)
Weight loss in last 3 mo	< 10%	54	54	0.80 (0.47, 1.35)
	≥ 10%	26	29	0.68 (0.33, 1.37)

[a] Stratification factor.

[b] Interaction *P* =.054

ITT population: HR 0.76 (0.50, 1.15); *P* =.194

Abbreviation: PS, performance status.

Biomarkers- pVEGFA and NRP

Candidate Biomarkers for Bevacizumab Efficacy in Gastric Cancer

Biomarker	Subgroup*	Patients, n	Overall survival	
			HR (95% CI)‡	P value§
All patients		774	0.87 (0.73-1.03)	
VEGF-A	Low	357	1.01 (0.77-1.31)	0.07
	High	355	0.72 (0.57-0.93)	
Neuropilin-1	Low	350	0.75 (0.59-0.97)	0.06
	High	329	1.07 (0.81-1.40)	

Van Cutsem E [Shah MA]. JCO 2012;30:2119-2127

DAWN OF A NEW ERA?

NEWS & VIEWS

GASTROINTESTINAL CANCER

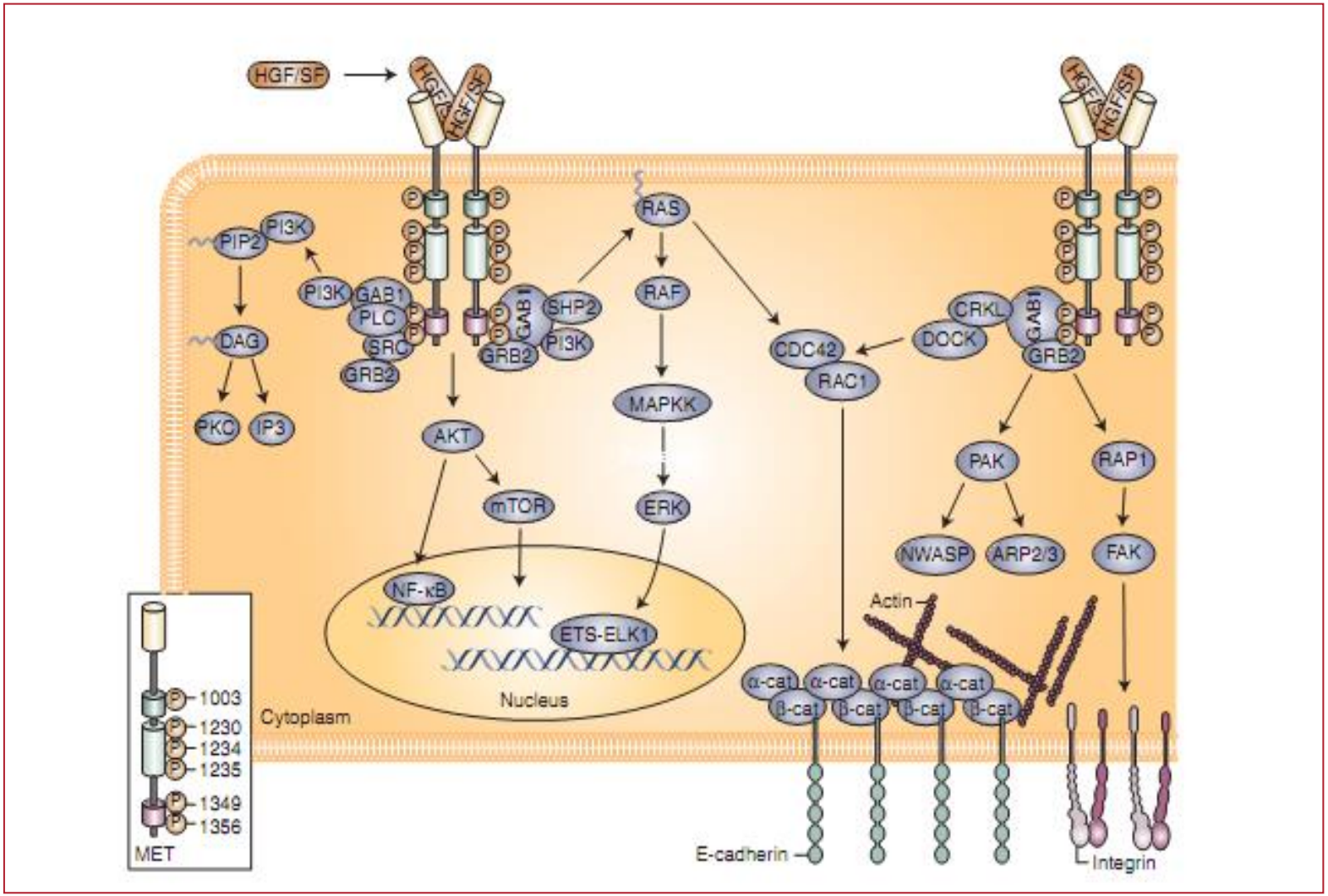
Targeted therapies in gastric cancer—the dawn of a new era

Manish A. Shah

The international phase III REGARD study demonstrated improved overall survival with ramucirumab as second-line therapy for patients with advanced-stage gastric and gastroesophageal junction adenocarcinoma. As a novel biological treatment, is ramucirumab also the harbinger of a

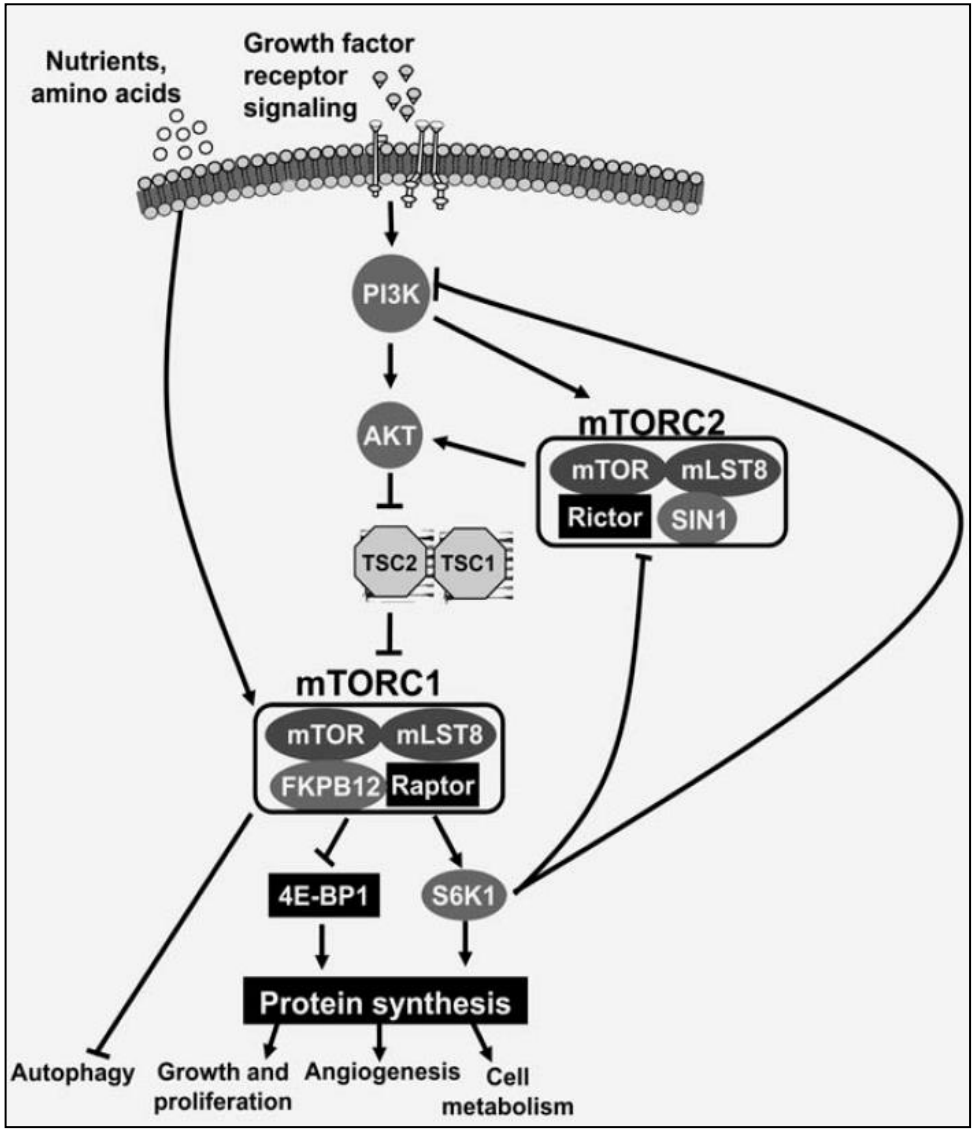
Shah MA. Nat Rev Clin Oncol 2014;11:10-11.

MET Signaling Pathway



Graveel CR et al. Cold Spring Harb Perspect Biol. 2013;5(7).

mTOR Pathway in Gastric Cancer



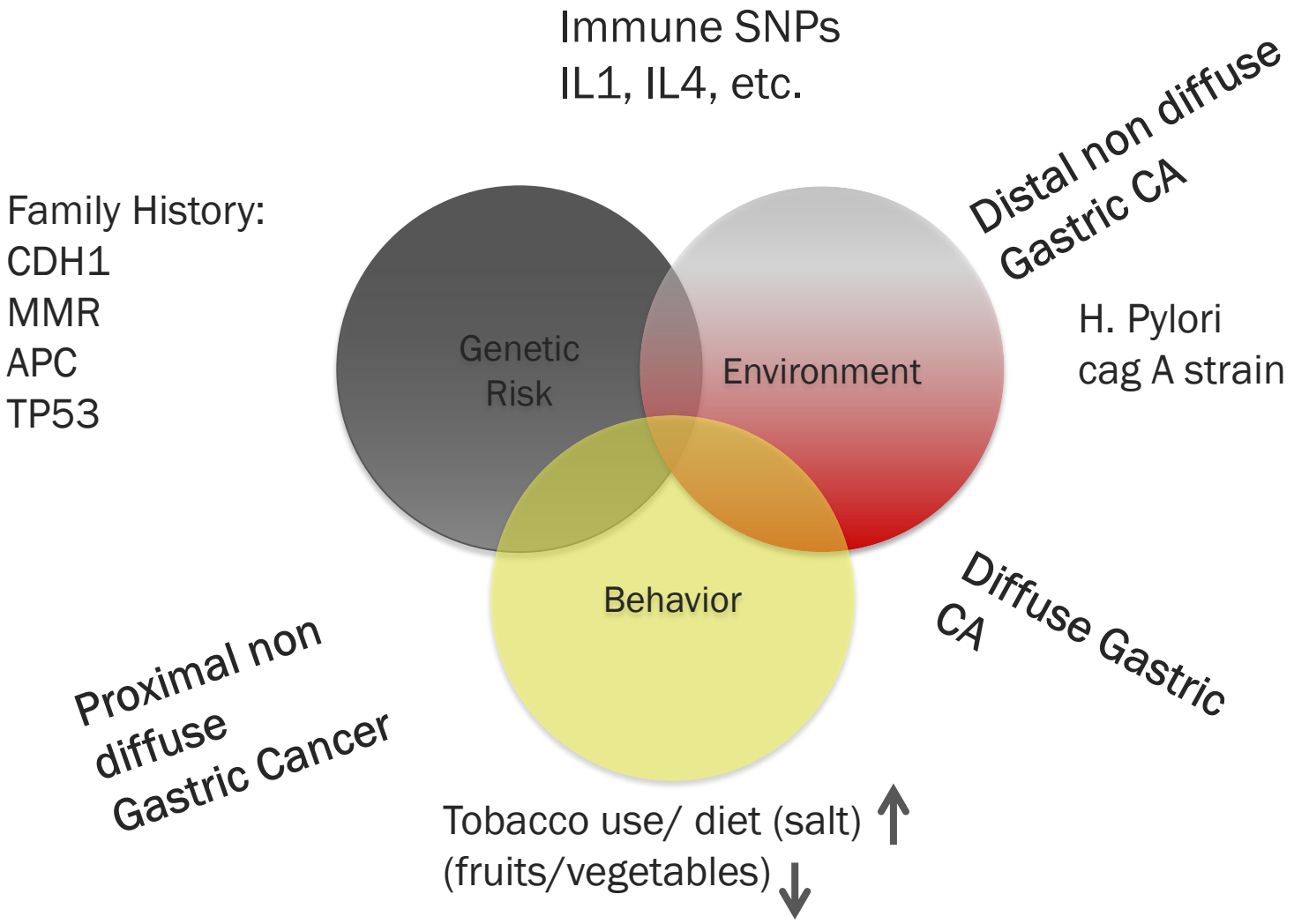
- Activation of mTOR or upstream signaling molecules is frequent in gastric cancer
- mTOR inhibitor Phase 2 trials: favorable disease control rates

mTOR, mammalian target of rapamycin

Al-Batran SE et al. *Int J Cancer*. 2012;130(3):491-496.

What have we learned

- Disease biology is important, as shown by gastric cancer heterogeneity.



SUMMARY

- HER2 is a validated target for 1st line GC.
- Targeting the angiogenesis pathway in gastric/ GEJ adenocarcinoma is now validated
- Ramucirumab + paclitaxel is a viable, safe, effective treatment option following 1st line therapy.
- We still need to learn who would benefit most from antiangiogenic therapy.
- Many new targets are being evaluated – we are in the *Dawn of a new Era*!

Thank you!

-Manish A. Shah, MD