Riccardo Giampieri, MD, PhD
Università Politecnica delle Marche
Ospedali Riuniti di Ancona

Antiangiogenic therapy in GI cancer: current status and future directions

Before starting…

Ministero della Salute

ErCongressi

E.C.M.

Programma nazionale per la formazione continua degli operatori della Sanità

Premesso che la ***Commissione Nazionale per la Formazione Continua*** *ha* accreditato quale attività di formazione continua l'evento formativo n. **361-8015693** denominato **FIRST INTERNATIONAL CONFERENCE "TRANSLATIONAL RESEARCH IN ONCOLOGY"** organizzato da **E.R. Congressi – Gruppo Triumph** e tenutosi a Forlì il 14-16 maggio 2008, *assegnando all'evento stesso*

N. 15 (quindici) Crediti Formativi E.C.M.
(Determinazione della Commissione del 22 Novembre 2001)

il sottoscritto
Elisabetta Tura
Responsabile dell'evento, su delega del rappresentante legale dell'Organizzatore

Verificato l'apprendimento del partecipante

CERTIFICA
che

Dott/Dott.ssa/Prof/Proff.ssa ***RICCARDO GIAMPIERI*** in qualità di MEDICO CHIRURGO
nato a _____ il _____, ha conseguito:

N. 15 (quindici) Crediti formativi per l'anno 2008

Bologna, li 23 giugno 2008

IL RESPONSABILE DELL'EVENTO,
su delega del Rappresentante legale dell'Organizzatore

The First International Conference "Translational Research in Oncology" Forlì, Italy, 14-16 May 2008

Summary

- Antiangiogenesis in colorectal cancer: a “continuous history”

- Antiangiogenesis in gastric cancer: a “promising benchmark”

Colon Cancer

Why continuous?

Cancer Treatment Reviews 40 (2014) 934–941

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

The "angiogenetic ladder", step-wise angiogenesis inhibition in metastatic colorectal cancer

Riccardo Giampieri [1], Mario Scartozzi *, Michela Del Prete [1], Agnese Fulli [1], Luca Faloppi [1], Maristella Bianconi [1], Elena Maccaroni [1], Stefano Cascinu [1]

Department of Clinical Oncology, Translational Oncology Unit, Università Politecnica delle Marche, AOU "Ospedali Riuniti", Via Conca 71, 60020 Ancona, Italy

Critical Reviews in Oncology/Hematology 100 (2016) 99–106

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Second-line angiogenesis inhibition in metastatic colorectal cancer patients: Straightforward or overcrowded?

Riccardo Giampieri [a], Marta Caporale [b], Filippo Pietrantonio [b], Filippo De Braud [b], Francesca V. Negri [c], Francesco Giuliani [d], Valeria Pusceddu [e], Laura Demurtas [e], Angelo Restivo [f], Caterina Fontanella [g], Giuseppe Aprile [g], Stefano Cascinu [a], Mario Scartozzi [e,*]

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[b] *Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
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[e] *Medical Oncology,University Hospital, University of Cagliari, Cagliari, Italy*
[f] *Colorectal Cancer Surgery, University Hospital, University of Cagliari, Cagliari, Italy*
[g] *Medical Oncology, University Hospital, Udine, Italy*

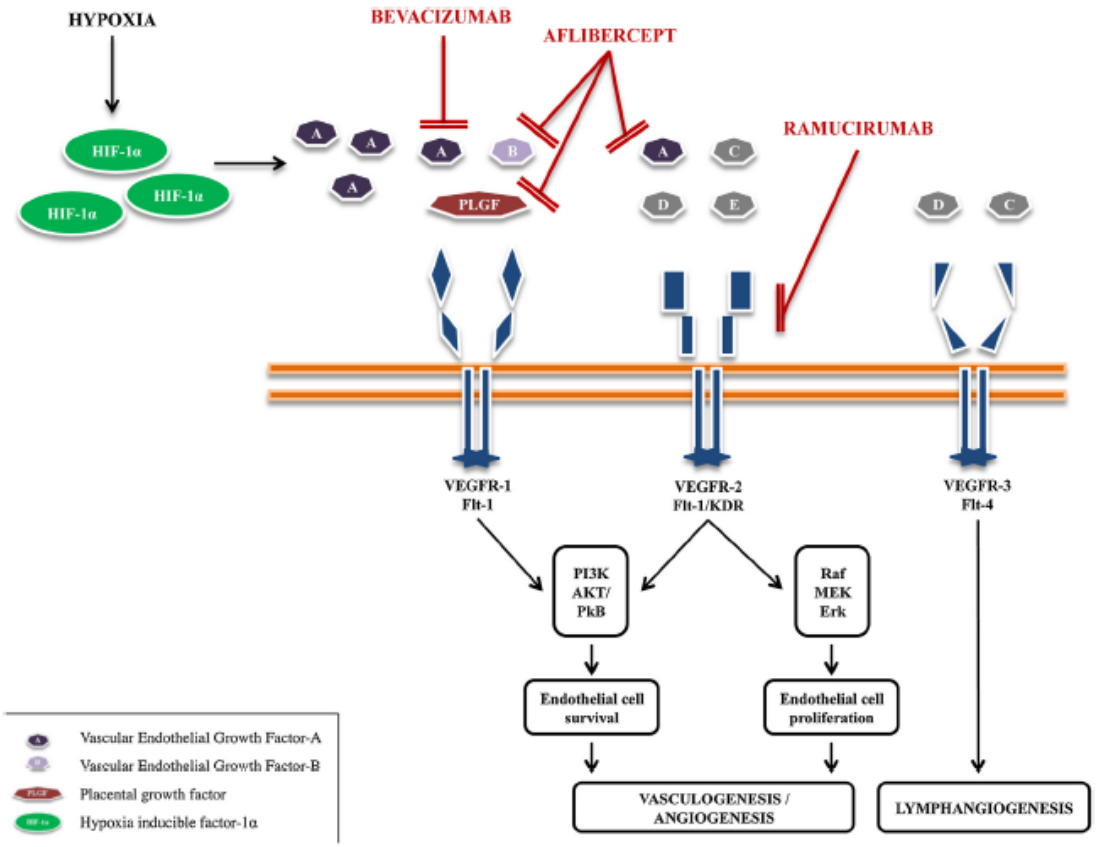
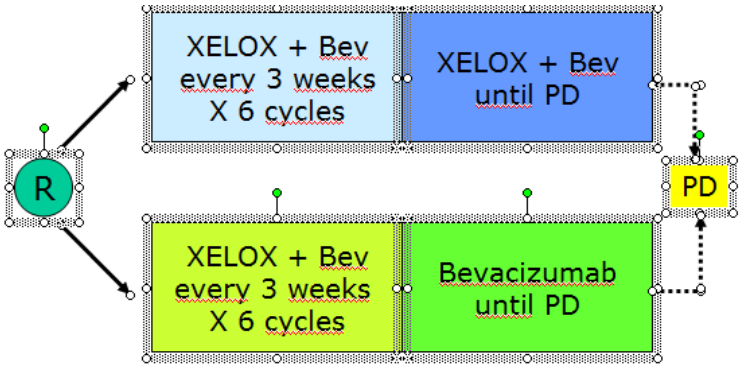


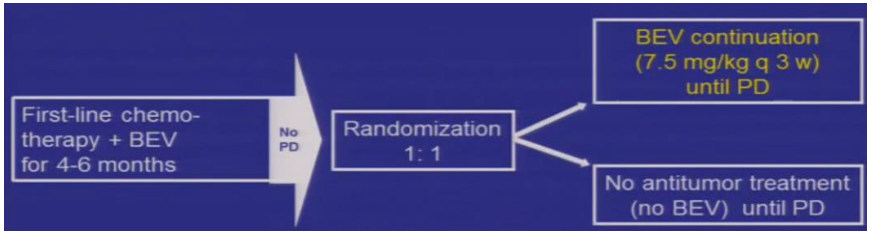
Fig. 1. Main angiogenic pathways and related therapeutic options in colorectal cancer.

Continuous angiogenesis inhibition? Maintenance trials

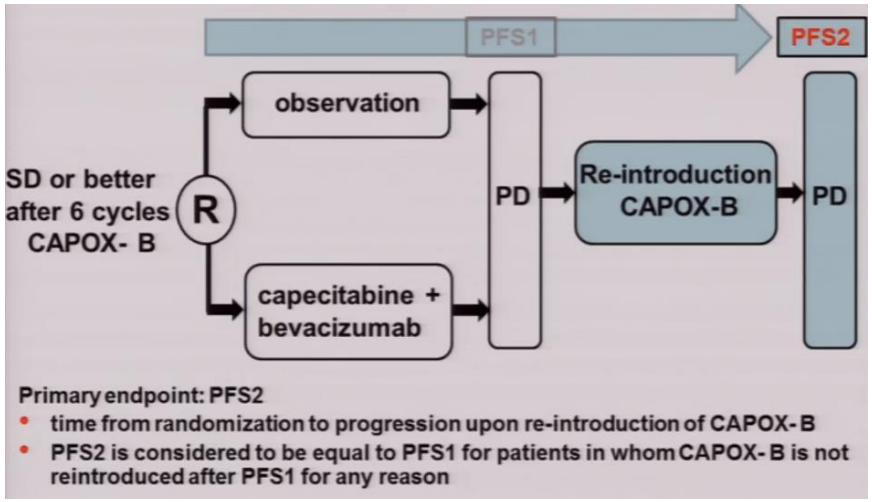
MACRO



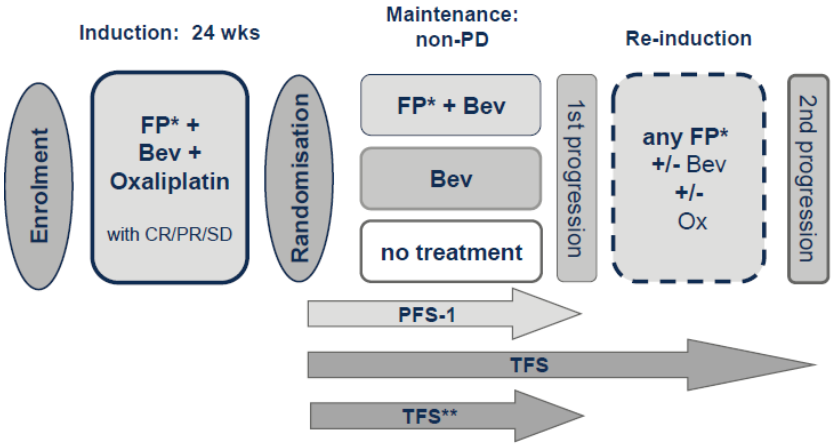
SAKK



CAIRO-3



AIO-0207



*FP= any fluoropyrimidine in a standard protocol (e.g.mFOLFOX6, FOLFOX4, Cape/Ox, LV5FU2; Cape 2x1000)

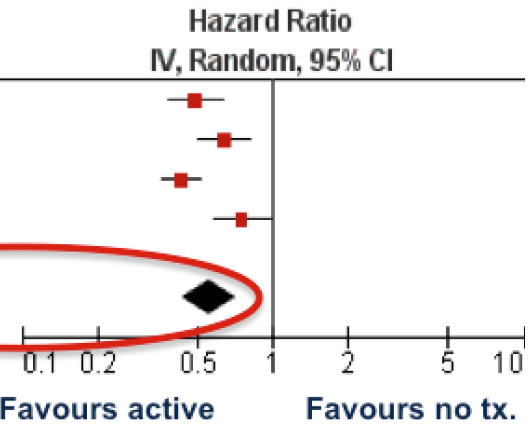
** TFS = PFS-1 for patients not receiving re-induction

Maintenance trials: combined results

PFS

Study or Subgroup		log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
AIO 0207	FP/bev	-0.71334989	0.12971368	24.1%	0.49 [0.38, 0.63]
AIO 0207	bev	-0.4462871	0.12595133	24.5%	0.64 [0.50, 0.82]
CAIRO-3	cape/bev	-0.84397007	0.09065533	27.4%	0.43 [0.36, 0.51]
SAKK	bev	-0.28768207	0.13114787	24.0%	0.75 [0.58, 0.97]
Total (95% CI)				**100.0%**	**0.56 [0.43, 0.72]**

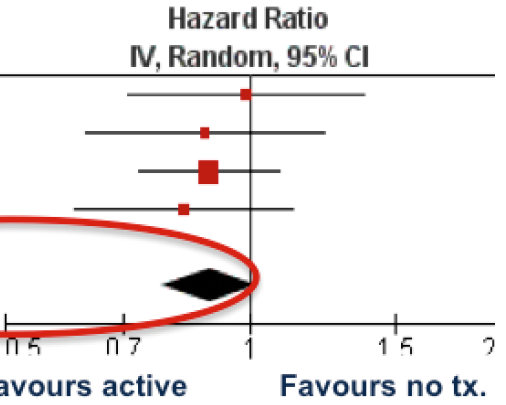
Heterogeneity: Tau² = 0.05; Chi² = 14.92, df = 3 (P = 0.002); I² = 80%
Test for overall effect: Z = 4.42 (P < 0.00001)



OS

Study or Subgroup		log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
AIO 0207	FP/bev	-0.01005034	0.16961535	16.8%	0.99 [0.71, 1.38]
AIO 0207	bev	-0.12783337	0.1705144	16.6%	0.88 [0.63, 1.23]
CAIRO-3	cape/bev	-0.11653382	0.10111254	47.1%	0.89 [0.73, 1.09]
SAKK	bev	-0.18632958	0.15712878	19.5%	0.83 [0.61, 1.13]
Total (95% CI)				**100.0%**	**0.89 [0.78, 1.02]**

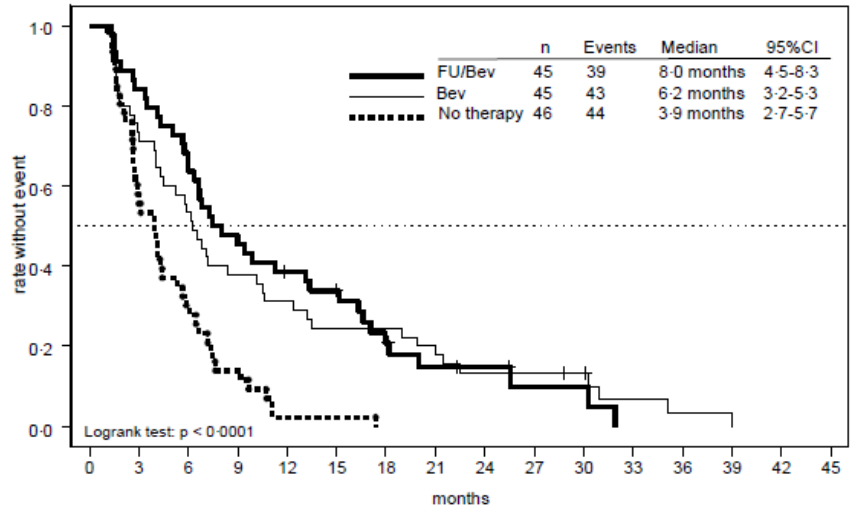
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)



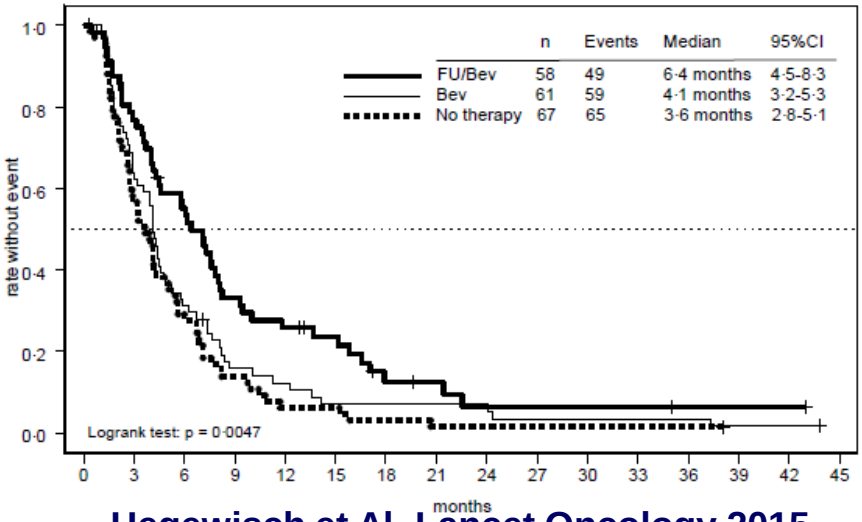
Arnold et Al, ASCO 2014

Perhaps prolonged VEGF-A inhibition is not enough…

RAS/BRAF WT



RAS/BRAF MUT



Hegewisch et Al, Lancet Oncology 2015

THE LANCET Oncology

Comment

Maintenance therapy for metastatic colorectal cancer

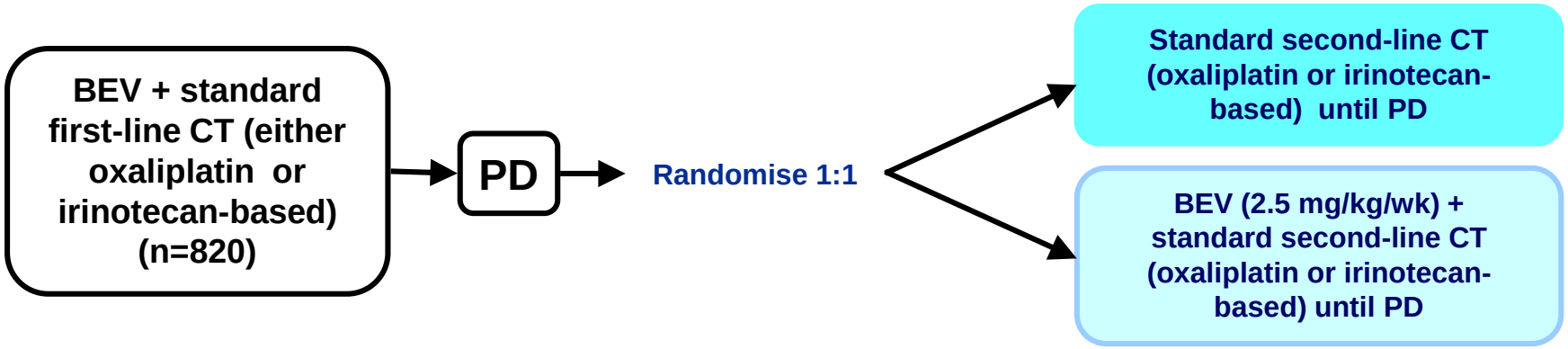
In an unselected population the "gain" of maintenance treatment is somehow counteracted by other factors but in a population of patients with "poor" prognostic features (RAS/RAF mutants) maintenance treatment might have greater activity.

Giampieri & Cascinu, Lancet Oncology 2015

Angiogenesis inhibition after 1° line?

- Bevacizumab again!
- Aflibercept (only FOLFOX-based 1° line pts)
- Ramucirumab (only FOLFOX-based 1° line pts)

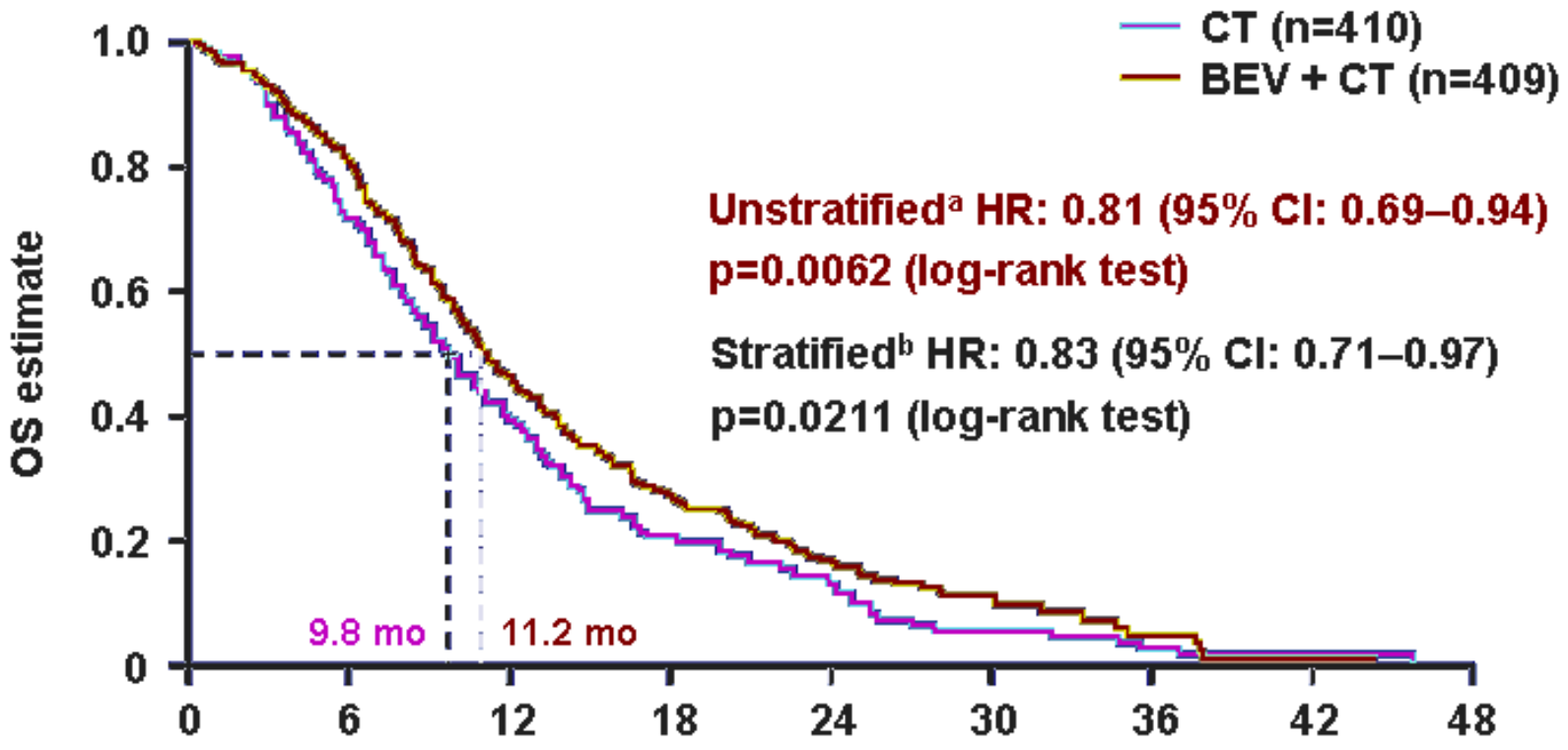
Bevacizumab maintenance after PD: TML trial



Primary endpoint	• Overall survival (OS) from randomisation
Secondary endpoints included	• Progression-free survival (PFS) • Best overall response rate • Safety
Stratification factors	• First-line CT (oxaliplatin-based, irinotecan-based) • First-line PFS (≤9 months, >9 months) • Time from last BEV dose (≤42 days, >42 days) • ECOG PS at baseline (0/1, 2)

Study conducted in 220 centres in Europe and Saudi Arabia

TML (ML18147) : OS



Unstratified[a] HR: 0.81 (95% CI: 0.69–0.94)
p=0.0062 (log-rank test)

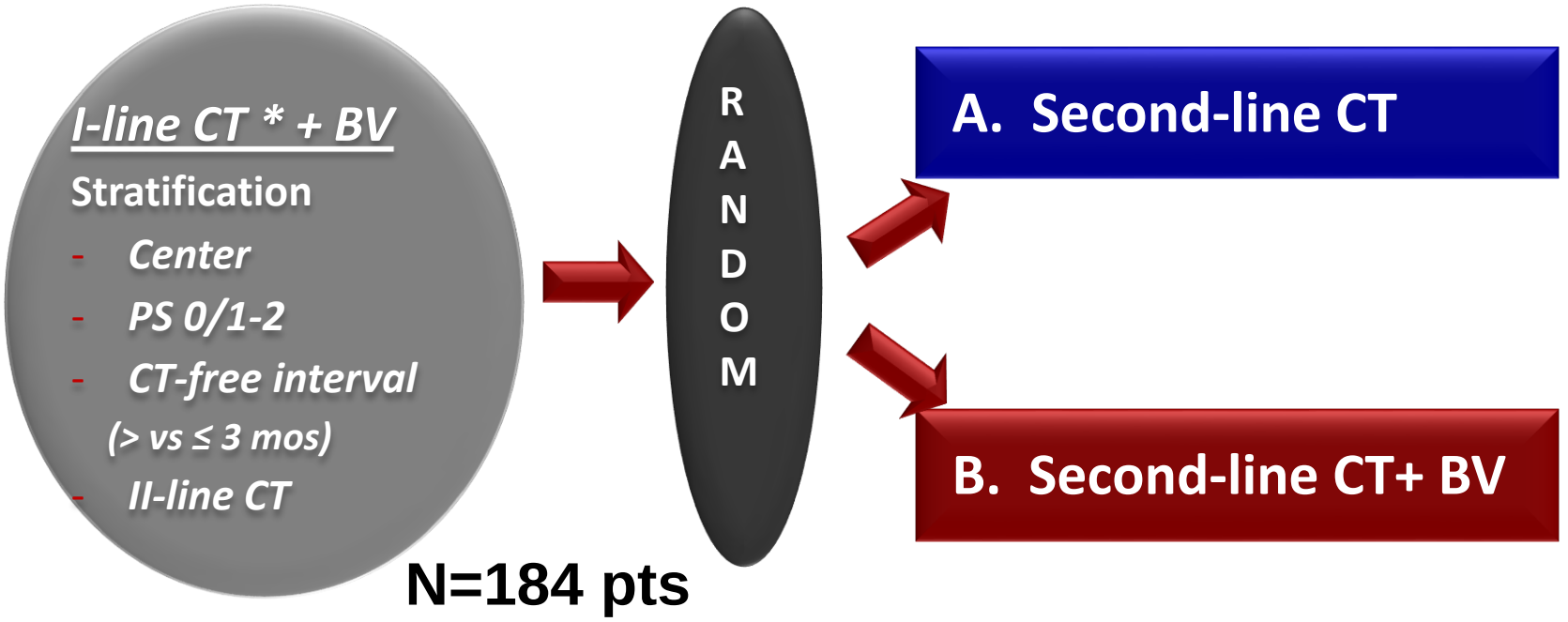
Stratified[b] HR: 0.83 (95% CI: 0.71–0.97)
p=0.0211 (log-rank test)

No. at risk								
CT	410	293	162	51	24	7	3	2
	0							
BEV + CT	409	328	188	64	29	13	4	1

Median follow-up: CT, 9.6 months (range 0–45.5); BEV + CT, 11.1 months (range 0.3–44.0)

[a]Primary analysis method; [b]Stratified by first-line CT (oxaliplatin-based, irinotecan-based), first-line PFS (≤9 months, >9 months), time from last dose of BEV (≤42 days, >42 days), ECOG performance status at baseline (0, ≥1)

Bevacizumab maintenance after PD: BEBYP trial



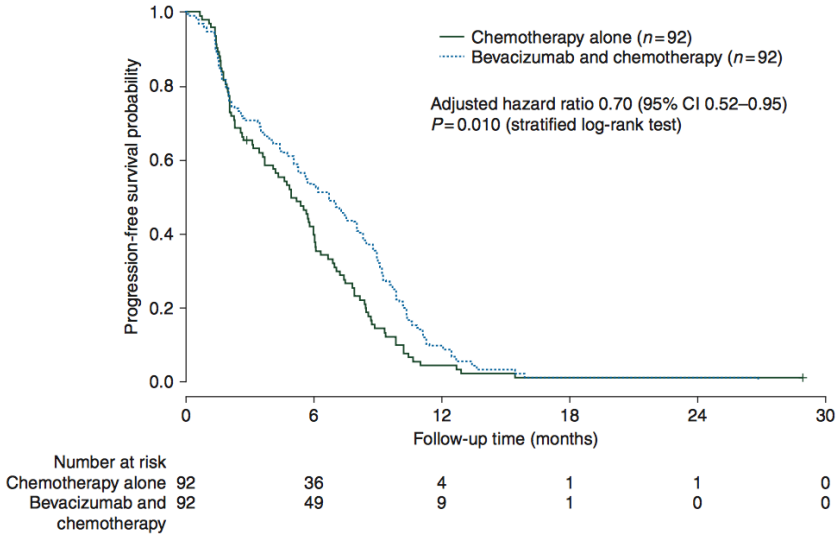
N=184 pts

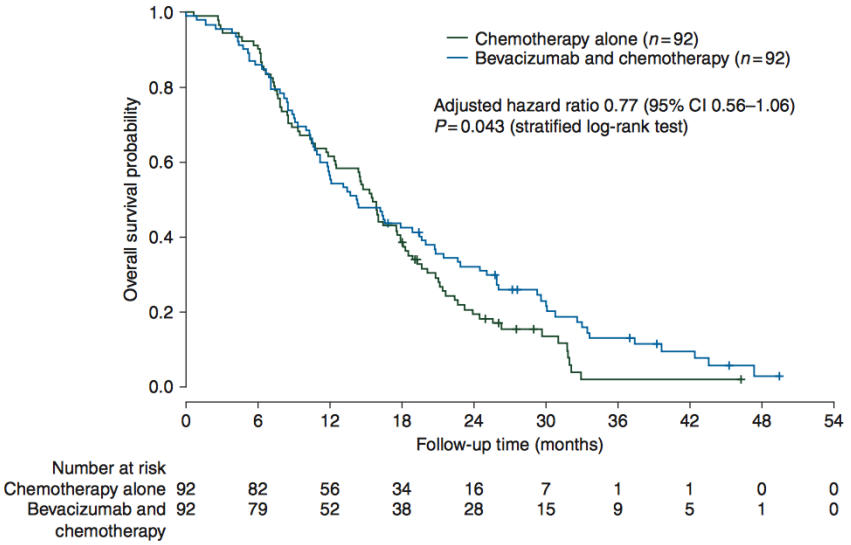
- **FOLFIRI**
- **FOLFOX**
- **FOLFOXIRI**
- **Fluoropyrimidine mono-tx**

- **FOLFIRI** (34% in both arms)
- **mFOLFOX-6** (66% in both arms)

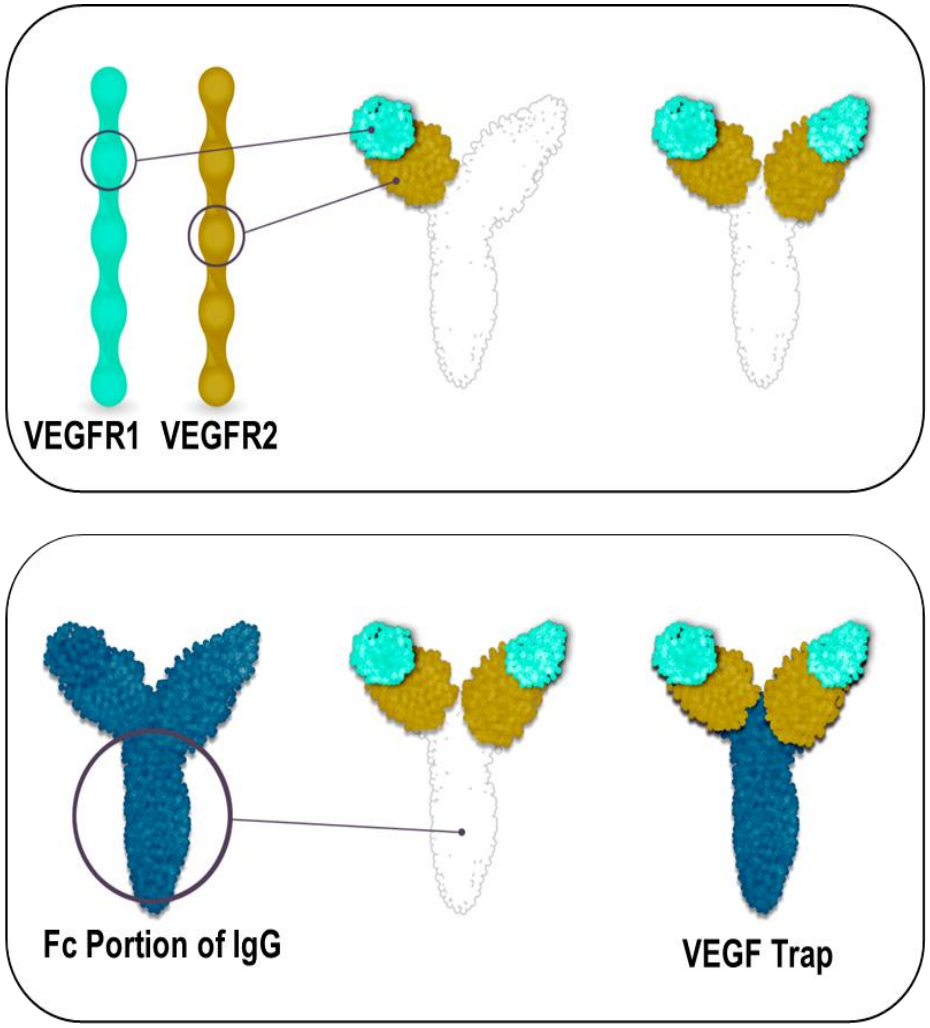
Masi GL et al, Ann Oncol 2015

BEBYP : RESULTS





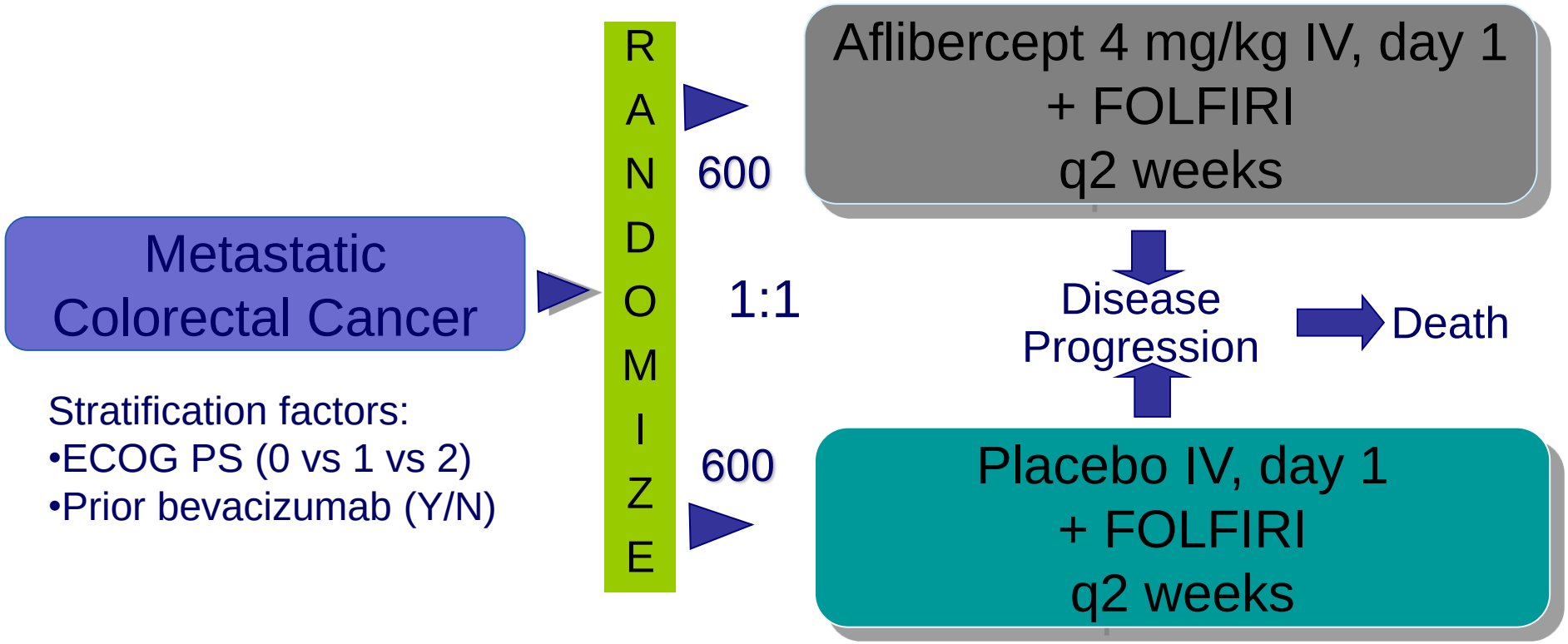
Aflibercept: Structure



- Fusion protein of key domains from human VEGF receptors 1 and 2 with human IgG Fc[1]
- Blocks all human VEGF-A isoforms, VEGF-B, and placental growth factor (PlGF)[2]
- High affinity – binds VEGF-A and PlGF more tightly than native receptors

1. Holash J et al. *Proc Natl Acad Sci USA*. 2002;99:11393-11398.
2. Tew WP et al. *Clin Cancer Res*. 2010;16:358-366.

VELOUR study design

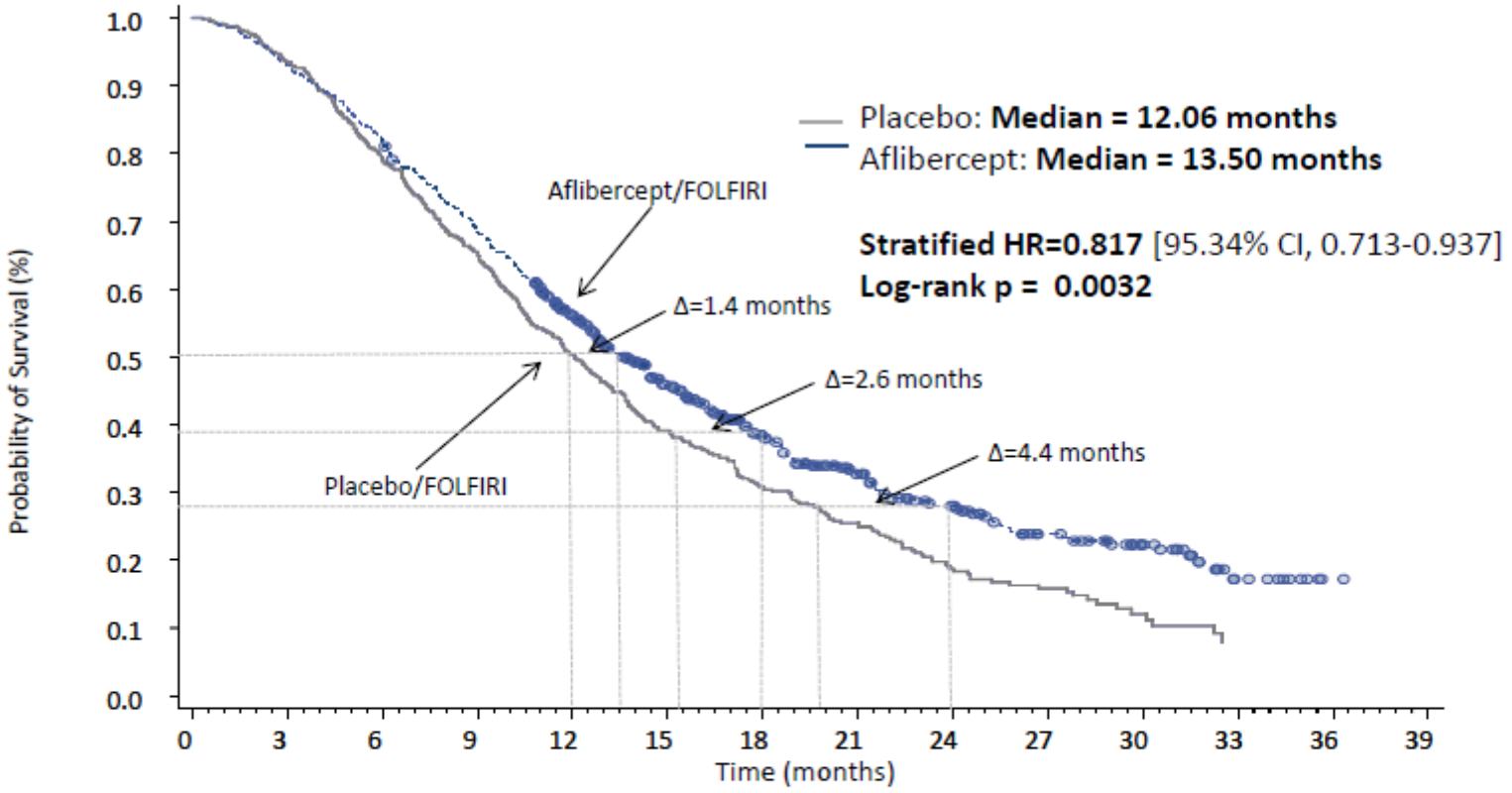


Primary endpoint: overall survival

Sample size: HR=0.8, 90% power, 2-sided type I error 0.05

Final analysis of OS: analyzed at 863rd death event using a 2-sided nominal significance level of 0.0466 (α spending function)

VELOUR: OS



Number At Risk	614	485	286	131	51	14	
	612	498	311	148	75	33	
Survival Probability		79.1%	50.3%	30.9%	18.7%	12.0%	
		81.9%	56.1%	38.5%	28.0%	22.3%	

Median follow-up = 22.28 months

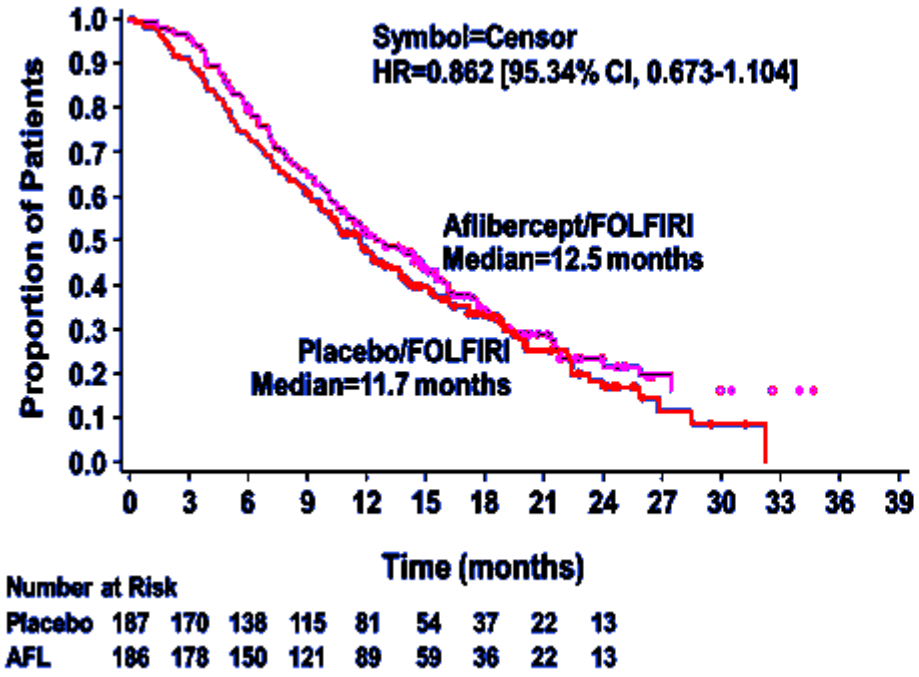
Van Cutsem E et al. *JCO* 2012;30:3499-3506

VELOUR: RR

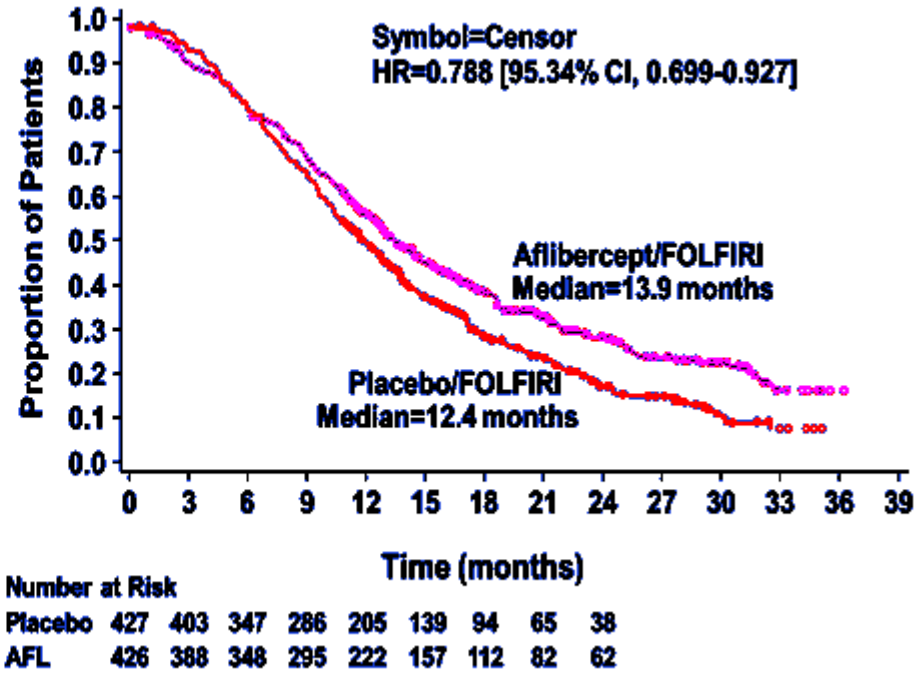
	FOLFIRI + Placebo (n = 612)	FOLFIRI + Aflibercept (n = 614)	Treatment effect (HR, P-value)
ORR	11.1 %	19.8 %	0.0001
PFS	4.7 mos	6.9 mos	0.76 (0.00007)
OS	12.06 mos	13.5 mos	0.82 (0.0032)

OS by prior Bevacizumab

Prior Bevacizumab

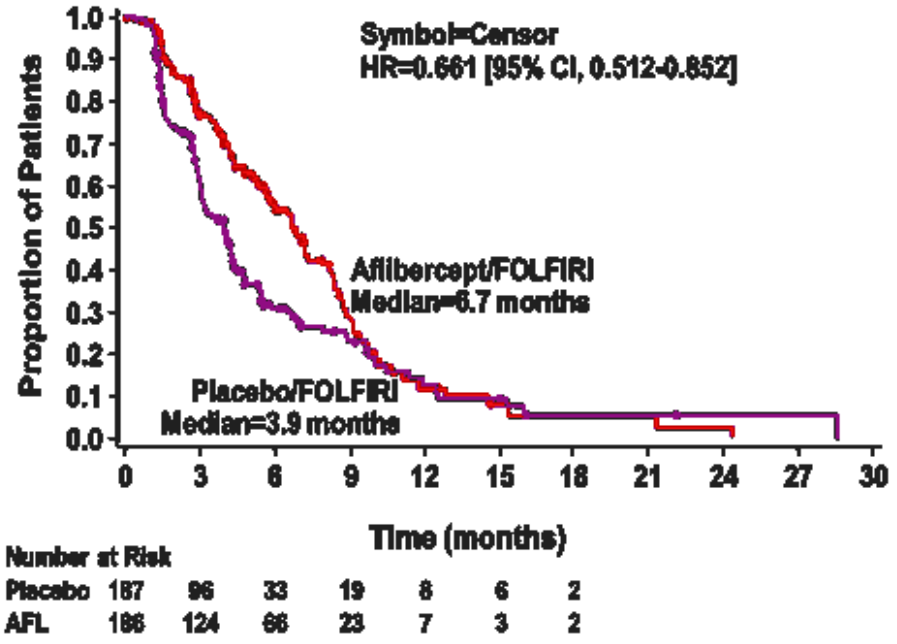


No Prior Bevacizumab

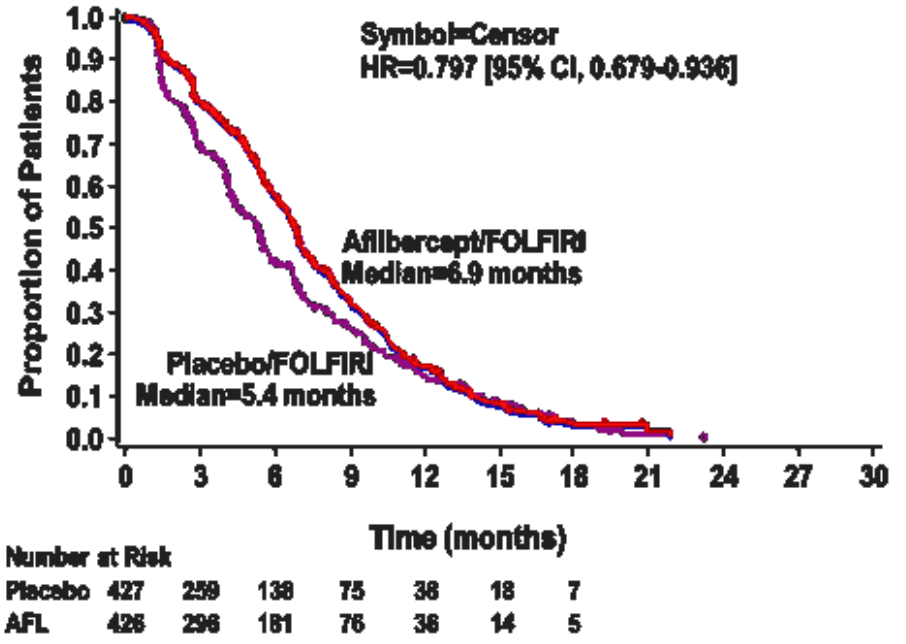


PFS by prior Bevacizumab

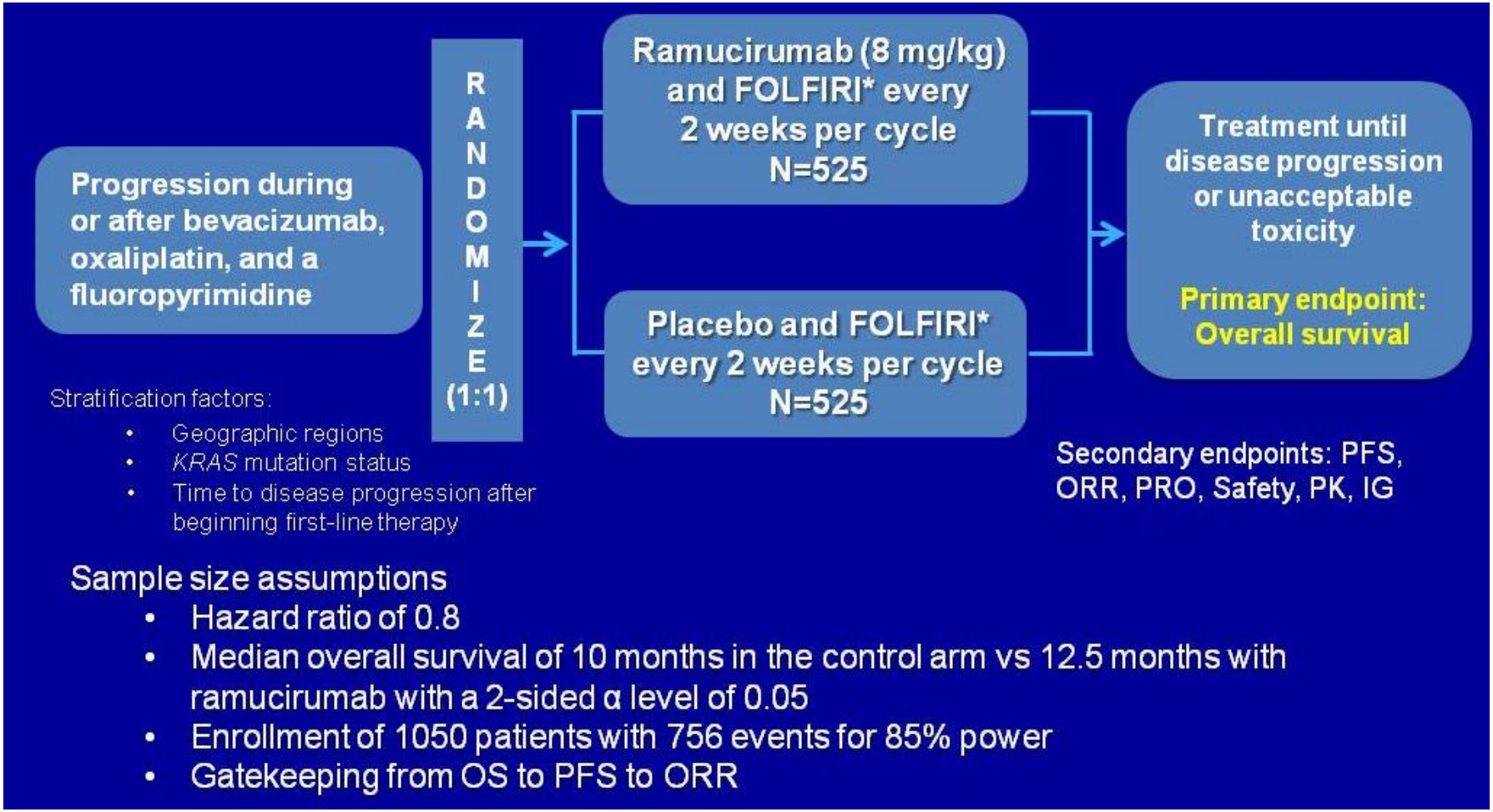
Prior Bevacizumab



No Prior Bevacizumab

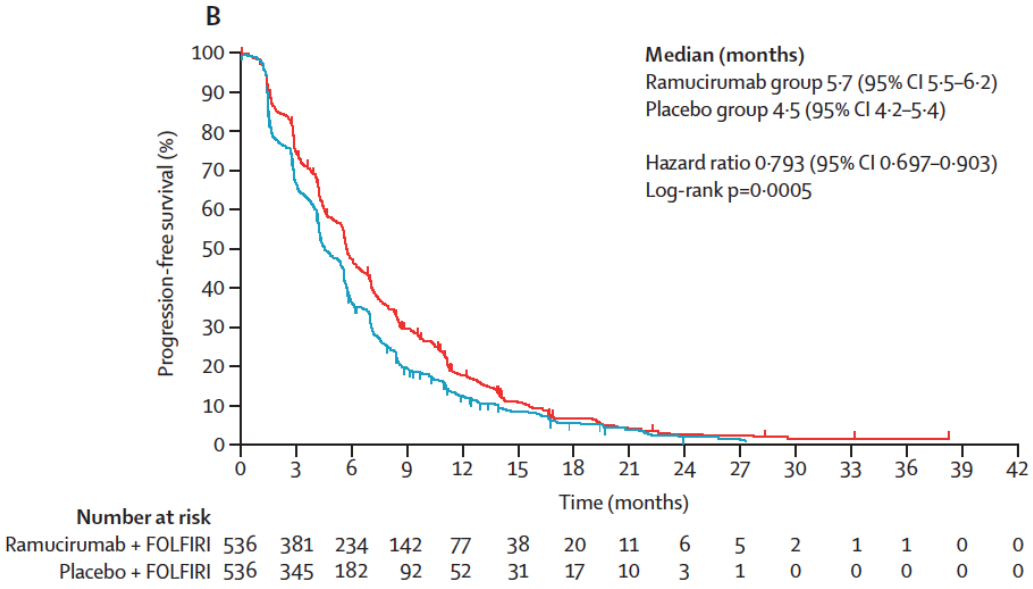


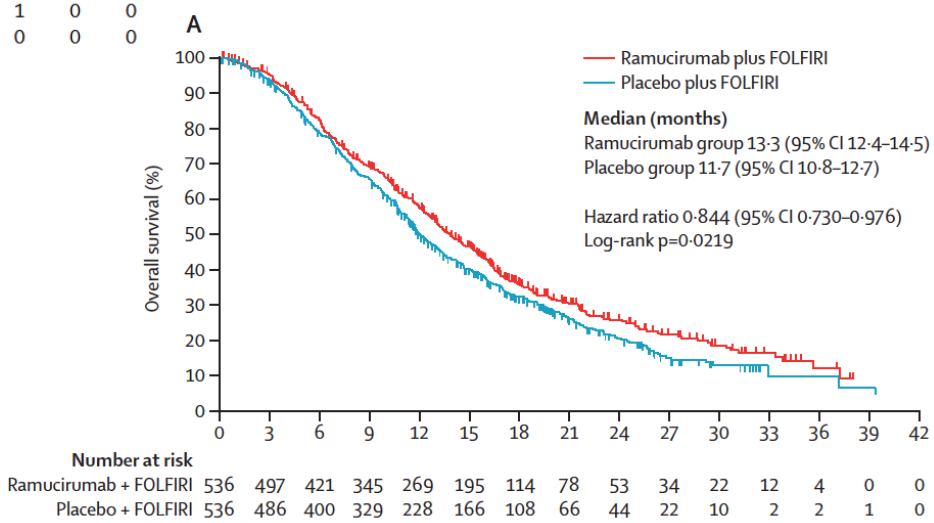
Ramucirumab: RAISE



Tabernero J et Al, Lancet Oncology 2015

RAISE: OS & PFS





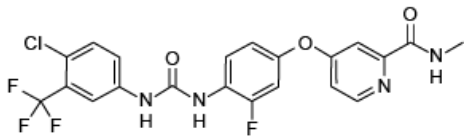
Tabernero J et Al, Lancet Oncology 2015

SUMMARY of 2° lines

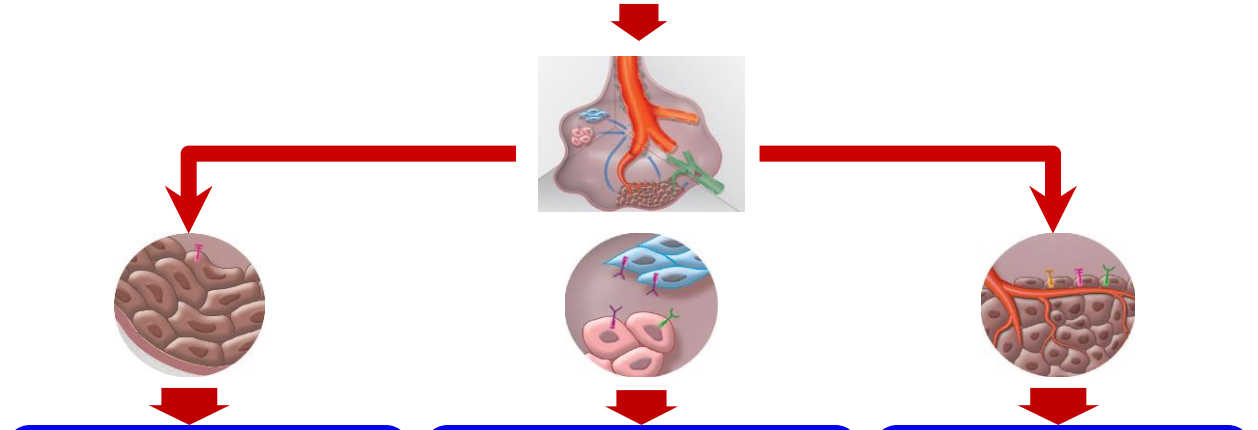
Trial	OS (HR)	PFS (HR)	RR (%)	Toxicity
ML18147 (BEV)	HR=0.81 *p=0.0062*	HR=0.68 *p<0.0001*	5.4 vs. 3.9 *p=ns*	No unexpected AEs
BEBYP (BEV)	HR=0.77 *p=0.04*	HR=0.70 *p=0.001*	20 vs. 15 *p=ns*	No unexpected AEs
VELOUR (AFL)	HR=0.81	HR=0.75	19.8 vs. 11.1 *< 0.001*	Increased CT-related AEs
RAISE (RAM)	HR=0.84 *p=0.0005*	HR=0.79 *p=0.0005*	13 vs. 12.5 *p=ns*	Increased CT-related AEs

Giampieri R et Al, CROH 2016

Regorafenib: not just antiangiogenic…



Regorafenib



Inhibition of proliferation

•KIT

•PDGFR

–RET

Inhibition of tumor microenvironment signaling

PDGFR-β

FGFR

Inhibition of neoangiogenesis

VEGFR1-3

TIE2

Biochemic activity	Regorafenib IC_{50} mean ± SD nmol/l (n)	
VEGFR1	13 ± 0.4	(2)
Murine VEGFR2	4.2 ± 1.6	(10)
Murine VEGFR3	46 ± 10	(4)
TIE2	311 ± 46	(4)
PDGFR-β	22 ± 3	(2)
FGFR1	202 ± 18	(6)
KIT	7 ± 2	(4)
RET	1.5 ± 0.7	(2)
RAF-1	2.5 ± 0.6	(4)
B-RAF	28 ± 10	(6)
$B\text{-}RAF^{V600E}$	19 ± 6	(6)

1. Wilhelm SM *et al. Int J Cancer* 2011.
2. Mross K *et al. Clin Cancer Research* 2012.
3. Strumberg D *et al. Expert Opin Invest Drugs* 2012.

Regorafenib in CRC: CORRECT

Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial

Axel Grothey*, Eric Van Cutsem*, Alberto Sobrero, Salvatore Siena, Alfredo Falcone, Marc Ychou, Yves Humblet, Olivier Bouché, Laurent Mineur, Carlo Barone, Antoine Adenis, Josep Tabernero, Takayuki Yoshino, Heinz-Josef Lenz, Richard M Goldberg, Daniel J Sargent, Frank Cihon, Lisa Cupit, Andrea Wagner, Dirk Laurent, for the CORRECT Study Group†

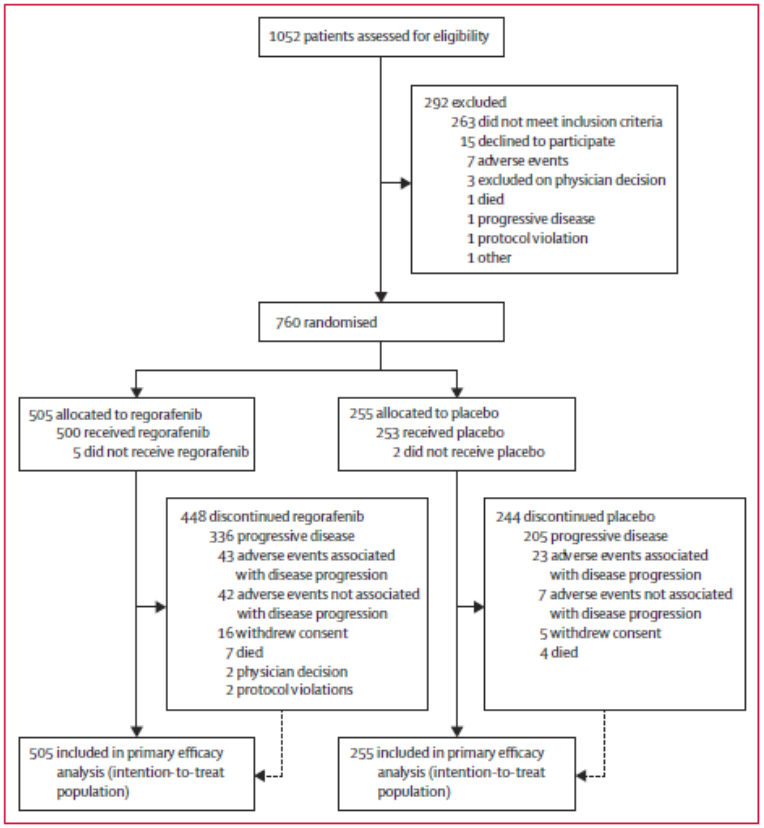
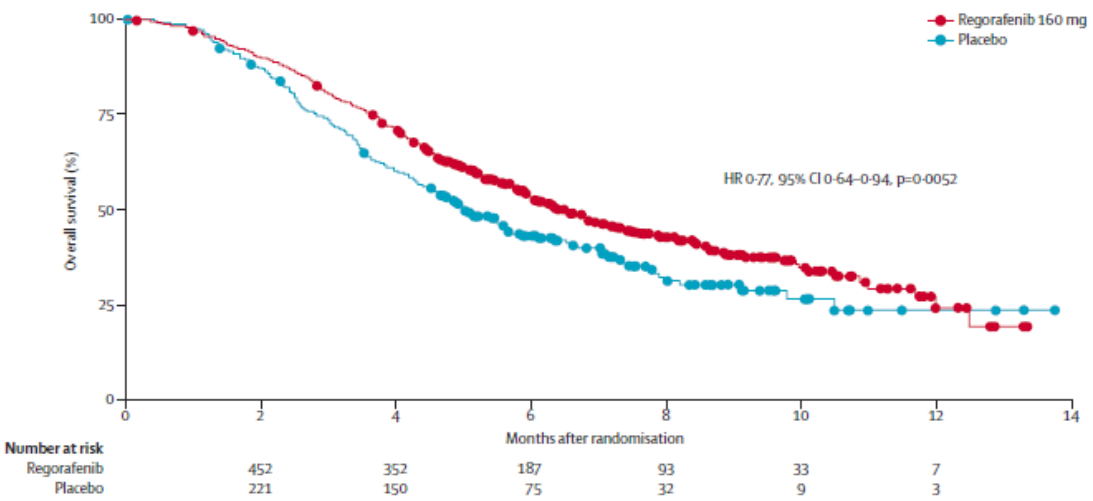


Figure 1: Trial profile



Regorafenib in Asia: CONCUR

Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial

Jin Li, Shukui Qin*, Ruihua Xu*, Thomas C C Yau, Brigette Ma, Hongming Pan, Jianming Xu, Yuxian Bai, Yihebali Chi, Liwei Wang, Kun-Huei Yeh, Feng Bi, Ying Cheng, Anh Tuan Le, Jen-Kou Lin, Tianshu Liu, Dong Ma, Christian Kappeler, Joachim Kalmus, Tae Won Kim*, on behalf of the CONCUR Investigators†*

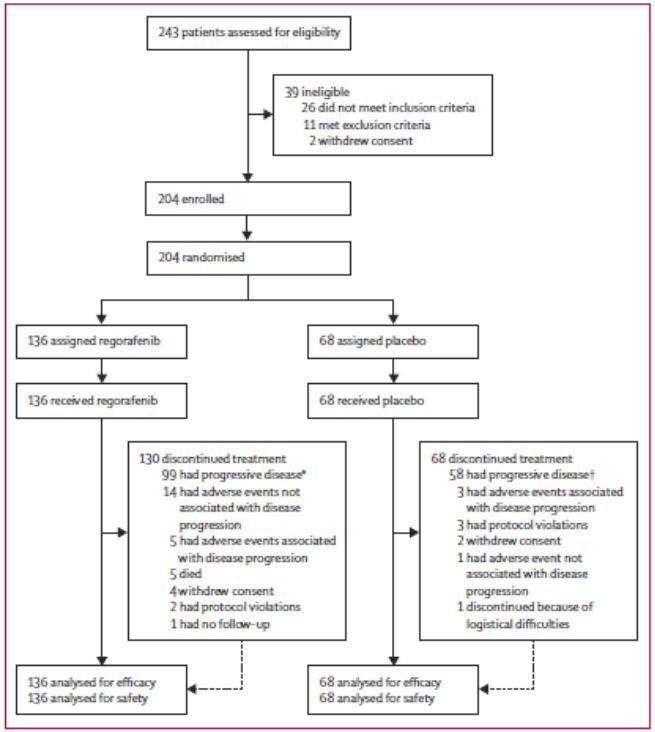
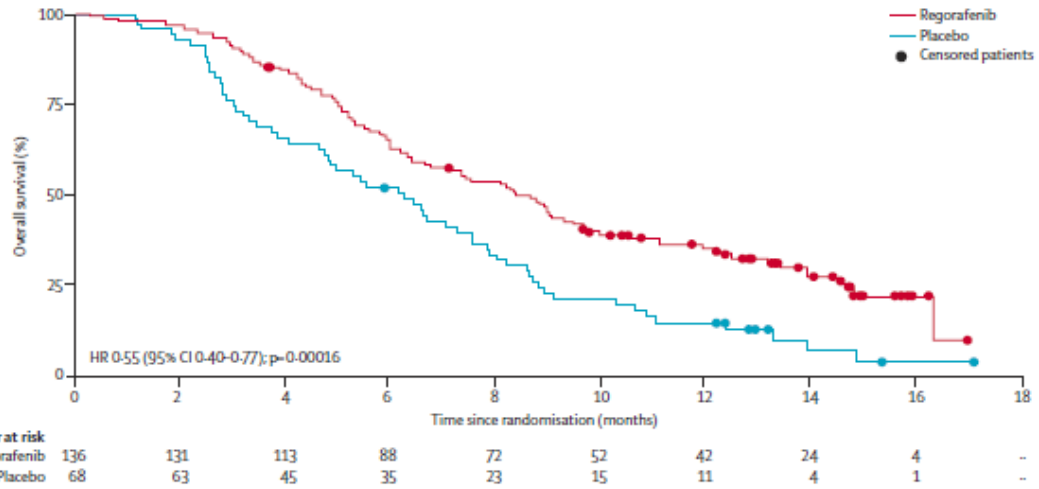
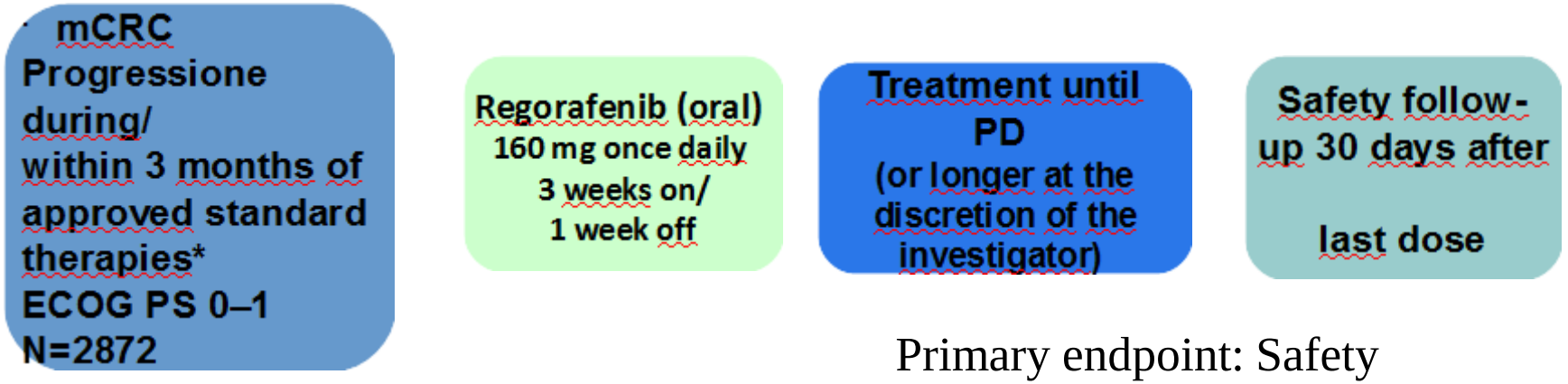


Figure 1: Trial profile

*95 patients had radiological disease progression and four had clinical progression. †56 patients had radiological progression and two had clinical progression.



Regorafenib to “many”: CONSIGN



Primary endpoint: Safety
Efficacy endpoint: PFS (investigator-assessed)

Prospective, single-arm
Conducted at 188 sites across 25 countries; planned enrollment approximately 3,000 patients
Treatment with regorafenib until one of the following:
PD by radiological assessment or clinical progression
Death
Unacceptable toxicity
Withdrawal of consent
Determination by the treating physician that discontinuation is in the best interest of the patient

Tossicità CONSIGN

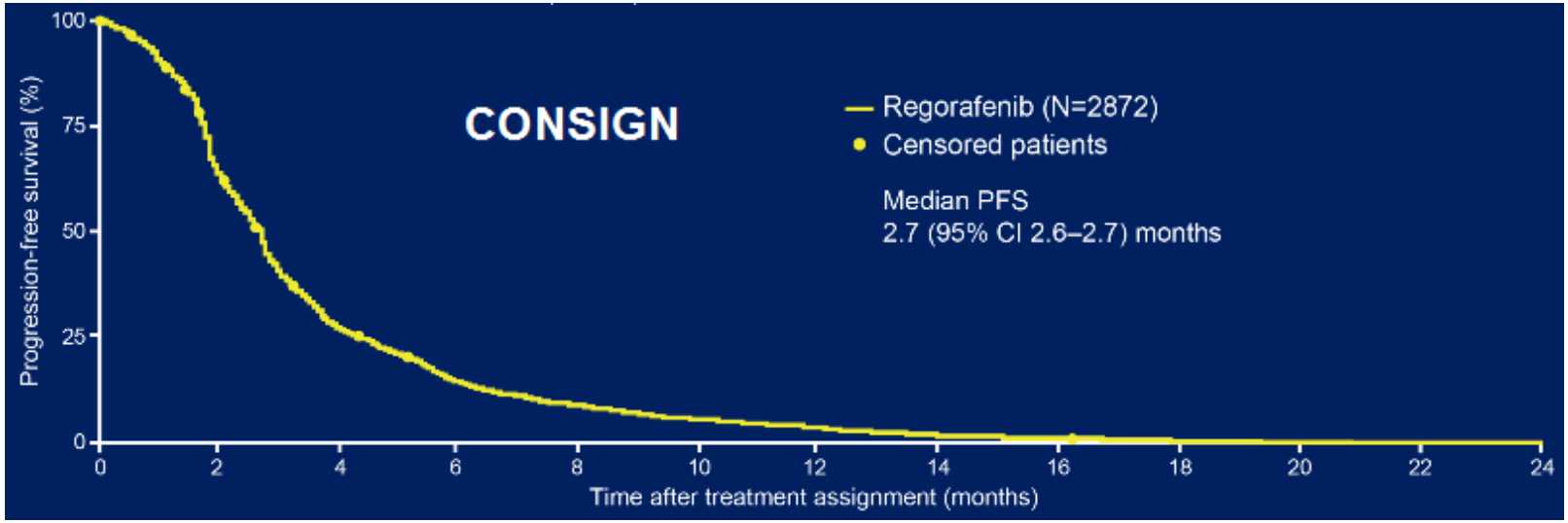
n (%)	Regorafenib (n=2864)
Grade ≥3, drug-related	1629 (57)
Hypertension	435 (15)
Hand–foot skin reaction	396 (14)
Fatigue	376 (13)
Diarrhea	135 (5)
Hypophosphatemia	149 (5)

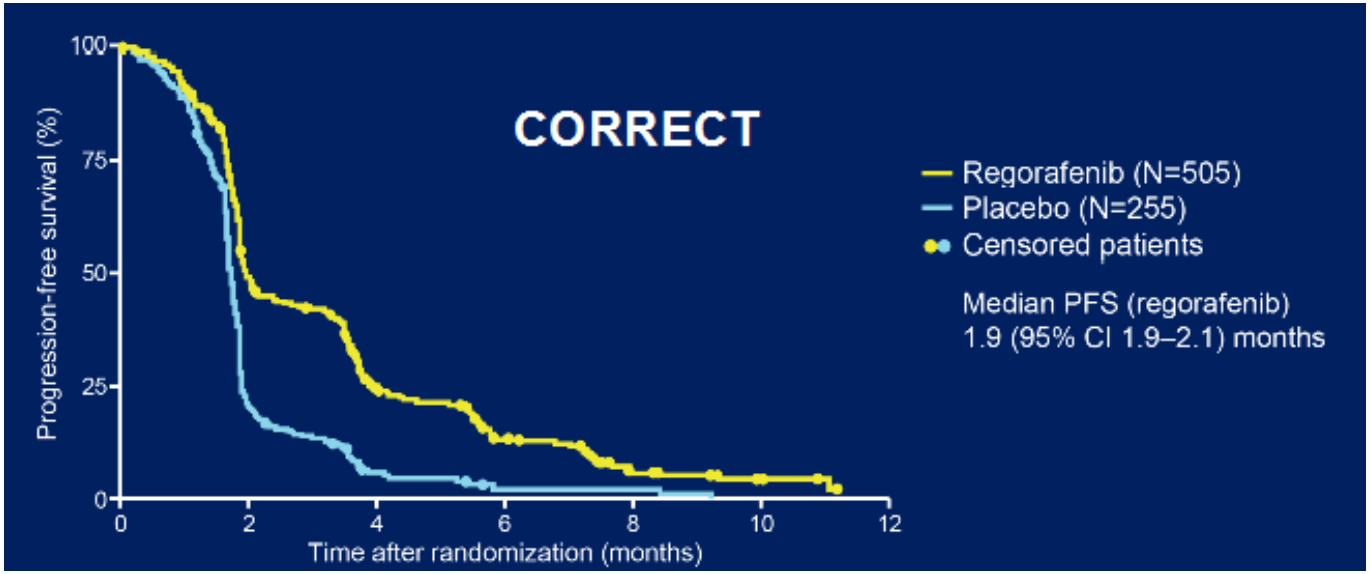
	Regorafenib (n=2864)	
n (%)	Treatment-emergent regardless of relation to study drug	Treatment-emergent drug-related
Leading to treatment discontinuation	720 (25)	266 (9)
Leading to treatment modification‡	2129 (74)	1732 (60)
Leading to dose reduction	1321 (46)	NE
Leading to treatment interruption/delay	1934 (68)	NE

	Regorafenib (n=2864)
n (%)	Treatment-emergent drug-related
Any grade	2613 (91)
Grade ≥3	1629 (57)
Serious	251 (9)
Grade 5	13 (<1)

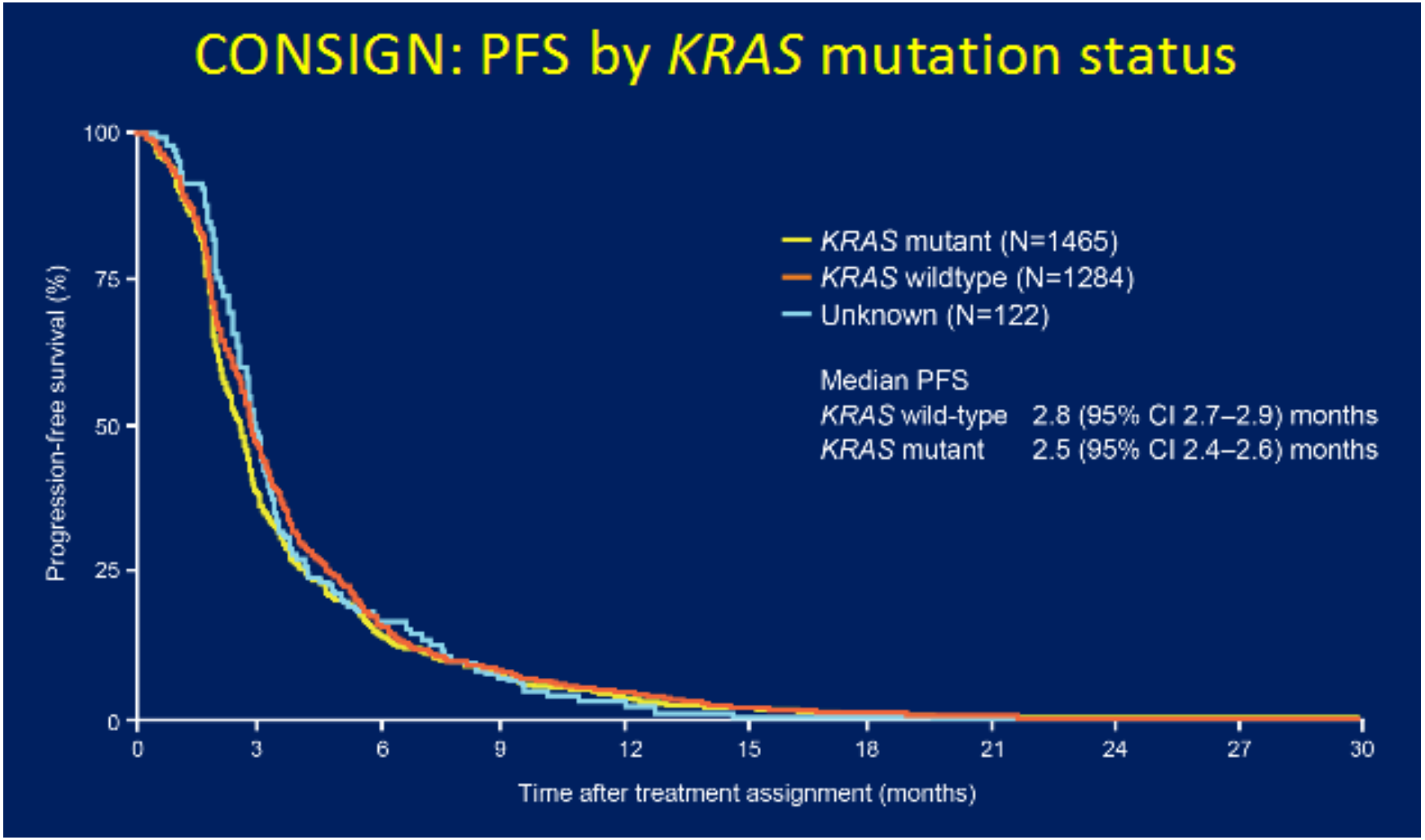
*During treatment or up to 30 days post treatment. †Adverse events were graded using the NCI-CTC for Adverse Events version 4.0.

CONSIGN PFS


CONSIGN
Regorafenib (N=2872)
Censored patients
Median PFS
2.7 (95% CI 2.6–2.7) months
Progression-free survival (%)
100
75
50
25
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time after treatment assignment (months)


CORRECT
Regorafenib (N=505)
Placebo (N=255)
Censored patients
Median PFS (regorafenib)
1.9 (95% CI 1.9–2.1) months
Progression-free survival (%)
100
75
50
25
0
0
2
4
6
8
10
12
Time after randomization (months)

CONSIGN PFS x KRAS



Gastric Cancer

Angiogenesis inhibition in gastric adenocarcinoma: unsteady start

VOLUME 29 · NUMBER 30 · OCTOBER 20 2011

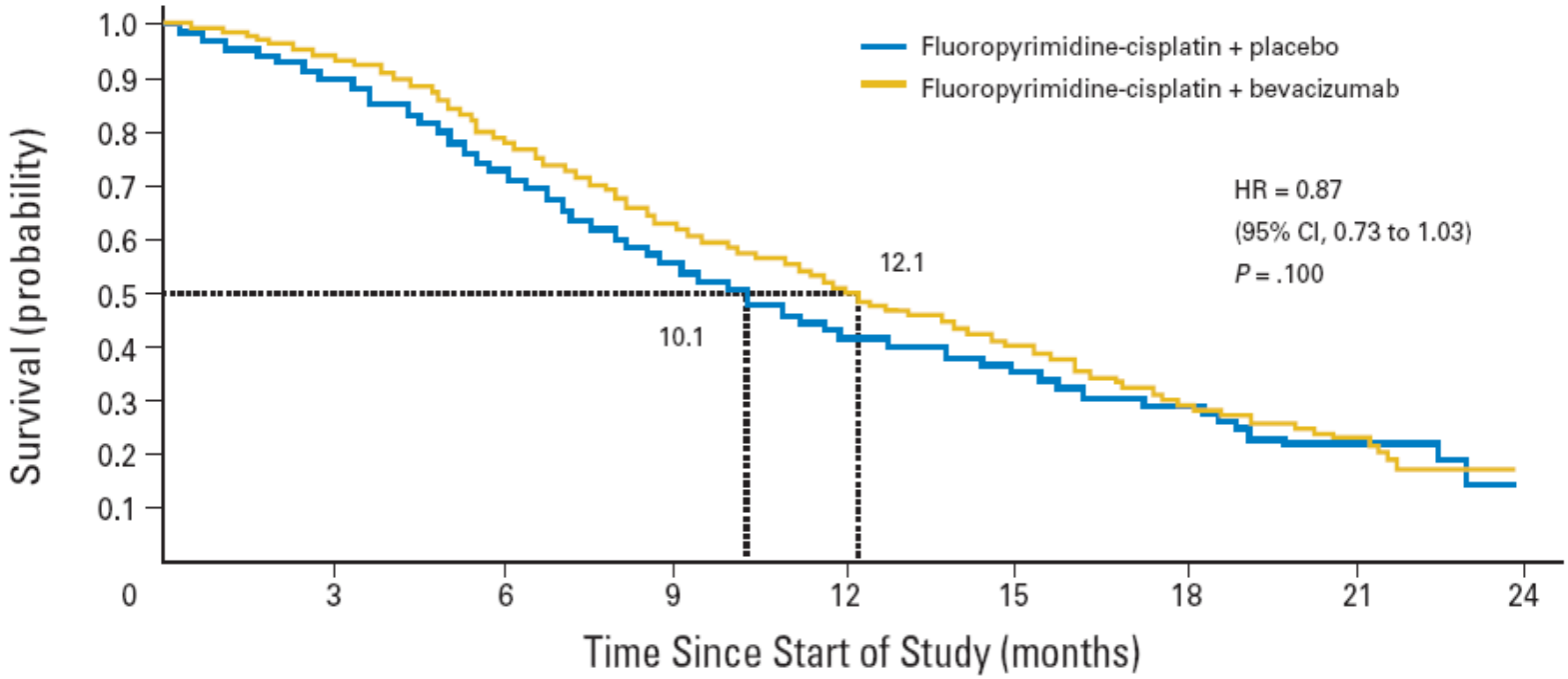
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study

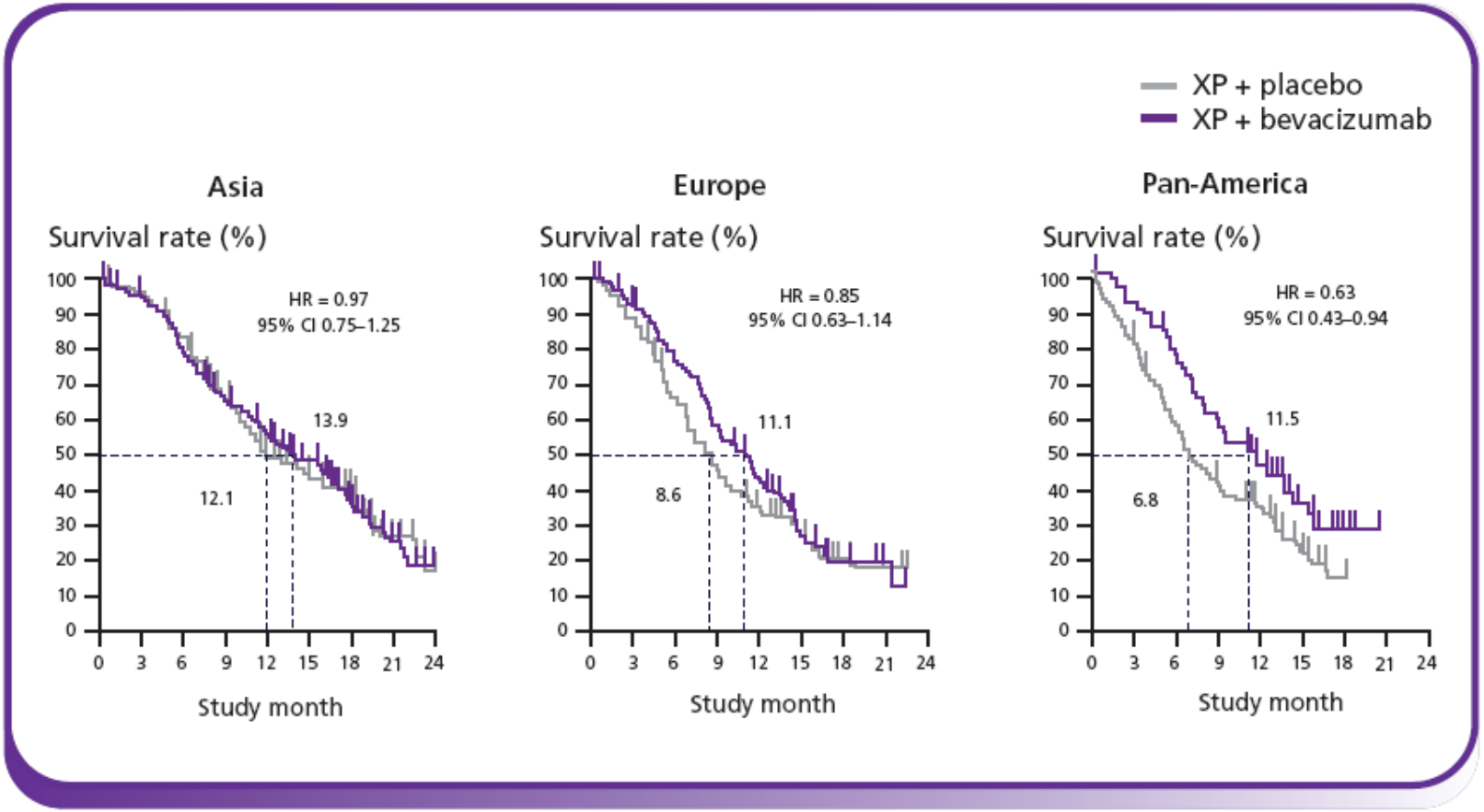
Atsushi Ohtsu, Manish A. Shah, Eric Van Cutsem, Sun Young Rha, Akira Sawaki, Sook Ryun Park, Ho Yeong Lim, Yasuhide Yamada, Jian Wu, Bernd Langer, Michal Starnawski, and Yoon-Koo Kang

Atsushi Ohtsu, National Cancer Center



Different countries = surrogate for efficacy?

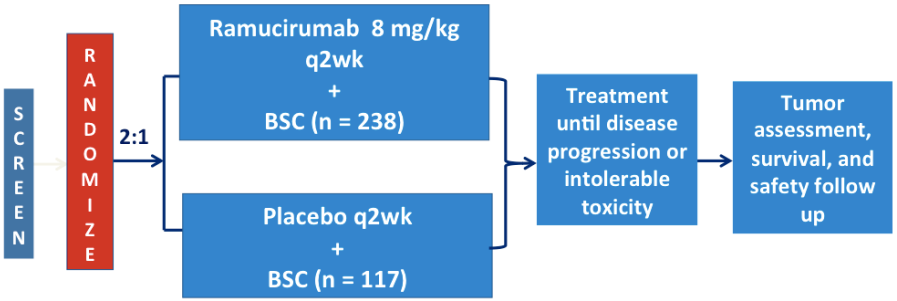
OS by region



- Analysis of OS by region found that the largest difference in OS was observed in the Pan-American patient population.

Angiogenesis inhibition in gastric cancer 2.0

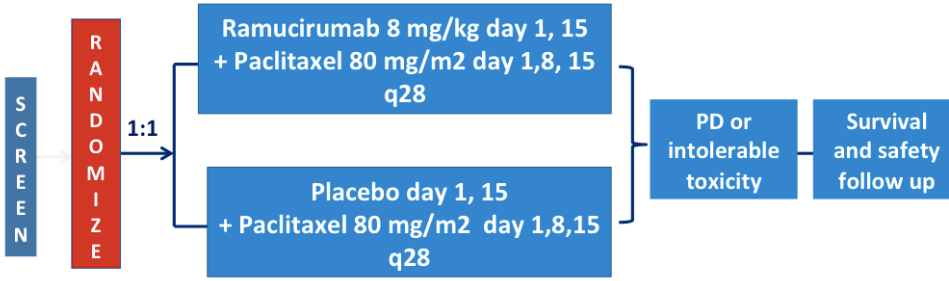
REGARD



- Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial
- **PS 0-1 Gastric or GEJ adenocarcinoma** with disease progression ≤4 months after first-line therapy or ≤6 months after adjuvant therapy
- Stratification factors: geographic region, weight loss (≥10% vs. <10% over 3 months), location of primary tumor (gastric vs. GEJ)

Fuchs et Al, Lancet Oncology 2014

RAINBOW



Important inclusion criteria:

- Metastatic or loc. adv. unresectable gastric or GEJ* adenocarcinoma
- Progression after 1st line platinum/fluoropyrimidine based chemotherapy

Stratification factors:

- Geographic region
- Measurable vs non-measurable disease,
- TTP on 1st line therapy (< 6 mos vs. ≥ 6 mos)

Wilke et Al, Lancet Oncology 2014

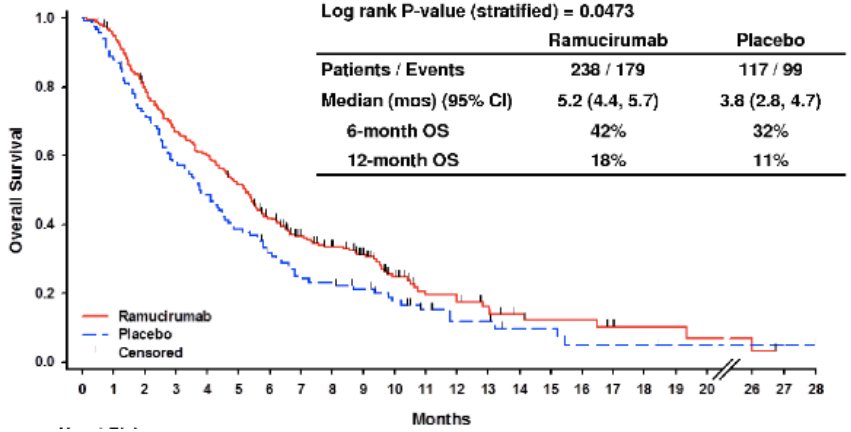
Ramucirumab II line: Results

REGARD

HR (95% CI) = 0.776 (0.603, 0.998)

Log rank P-value (stratified) = 0.0473

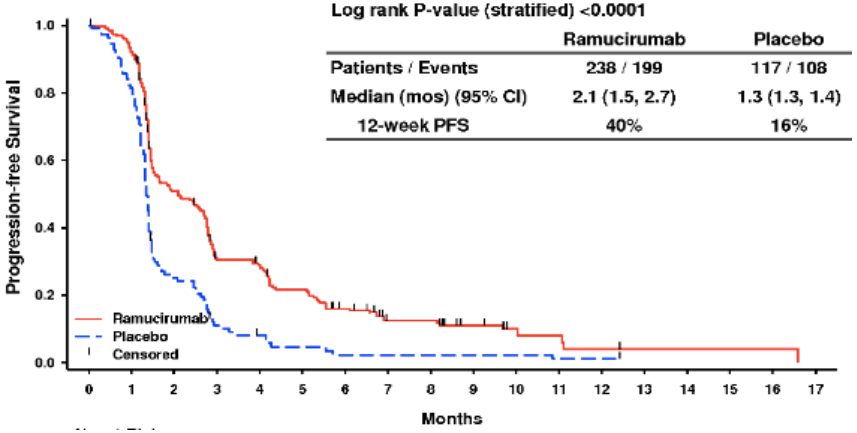
	Ramucirumab	Placebo
Patients / Events	238 / 179	117 / 99
Median (mos) (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)
6-month OS	42%	32%
12-month OS	18%	11%



HR (95% CI) = 0.483 (0.376, 0.620)

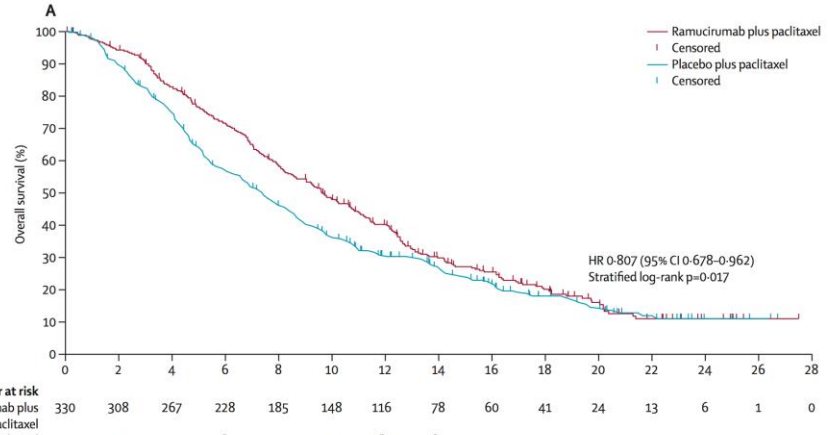
Log rank P-value (stratified) <0.0001

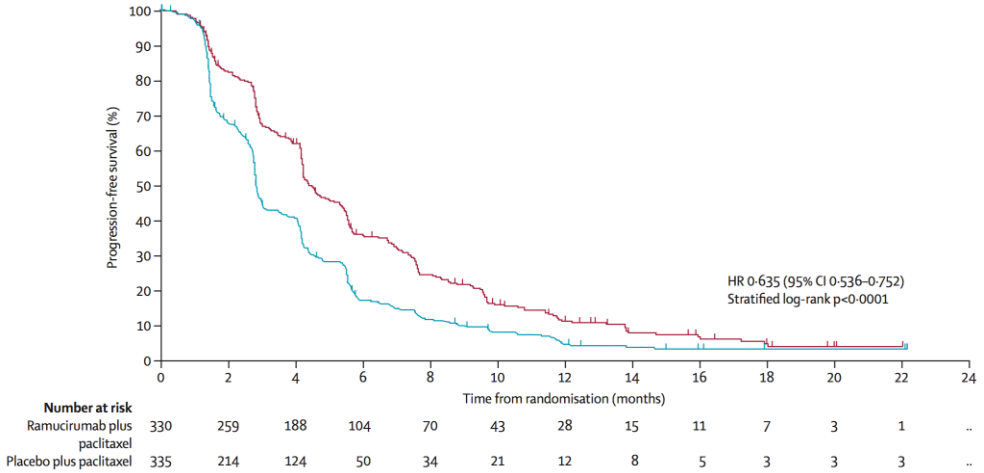
	Ramucirumab	Placebo
Patients / Events	238 / 199	117 / 108
Median (mos) (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)
12-week PFS	40%	16%



Fuchs et Al, Lancet Oncology 2014

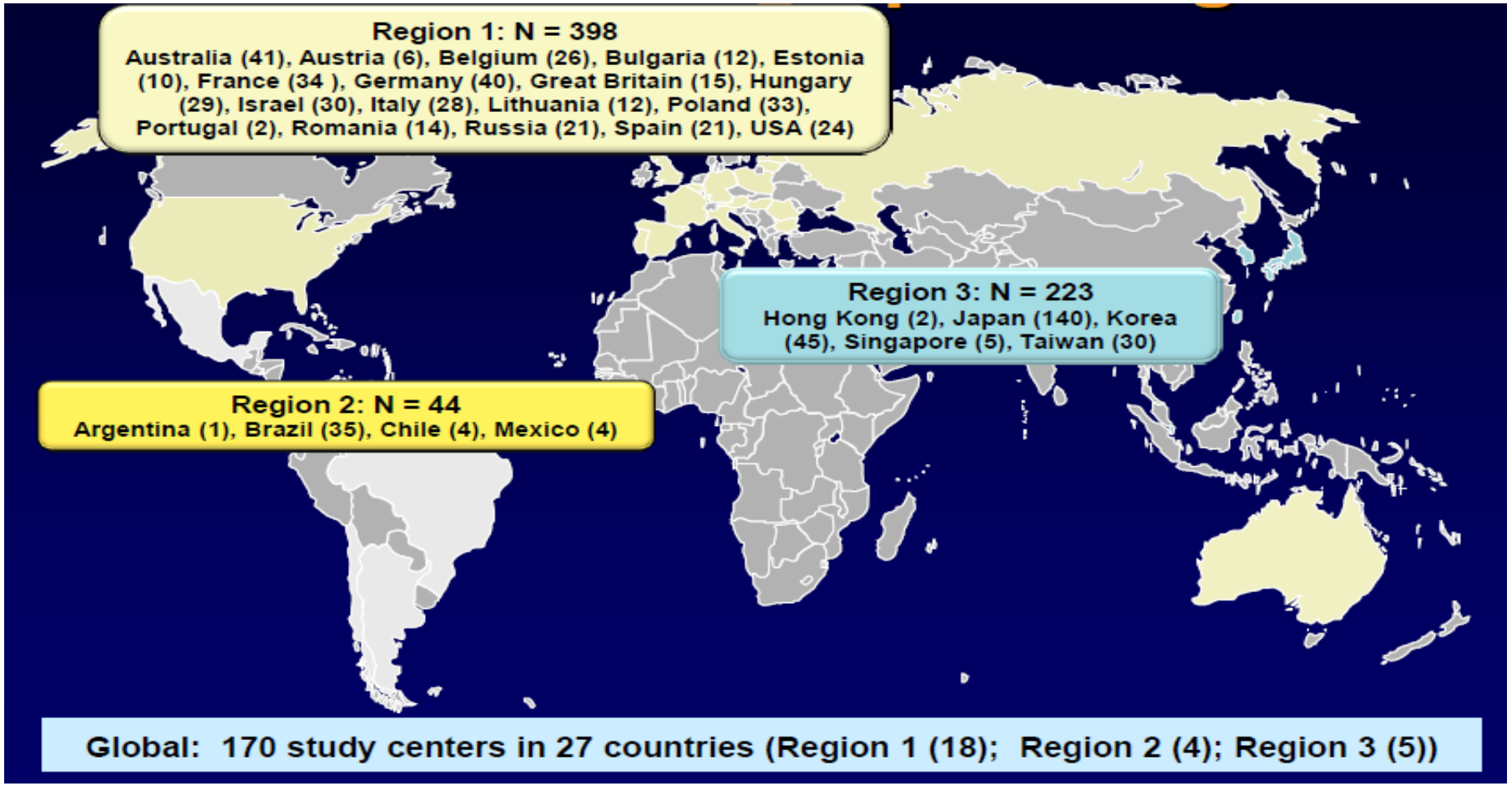
RAINBOW





Wilke et Al, Lancet Oncology 2014

RAINBOW:
Stratification by geographical area



•Wilke H et al. Lancet 2014

RAINBOW:
Effectiveness by geographical area

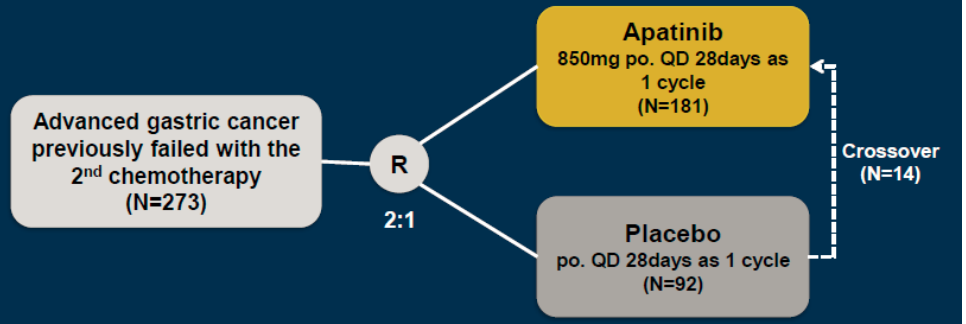
	Ramucirumab plus paclitaxel	Placebo plus paclitaxel	Hazard ratio (95% CI)	Odds ratio (95% CI)
Median overall survival				
Regions 1 (n=398) and 2 (n=44)	8·5 months (7·4–9·8)	5·9 months (5·2–7·1)	0·732 (0·591–0·907)	
Region 3 (n=223)	12·1 months (10·0–13·3)	10·5 months (7·8–14·1)	0·986 (0·727–1·337)	
Median progression-free survival				
Region 1 (n=398) and 2 (n=44)	4·2 months (3·9–4·9)	2·9 months (2·6–3·5)	0·639 (0·518–0·788)	
Region 3 (n=223)	5·5 months (4·2–5·7)	2·8 months (2·8–4·1)	0·628 (0·473–0·834)	
Proportion of patients achieving an objective response				
Regions 1 (n=398) and 2 (n=44)	55 (25%)	31 (14%)		2·087 (1·278–3·409)
Region 3 (n=223)	37 (34%)	23 (20%)		2·235 (1·177–4·244)

•Wilke H et al. Lancet 2014

Angiogenesis inhibition 2.0 – Asian Bootleg

Phase III Study design

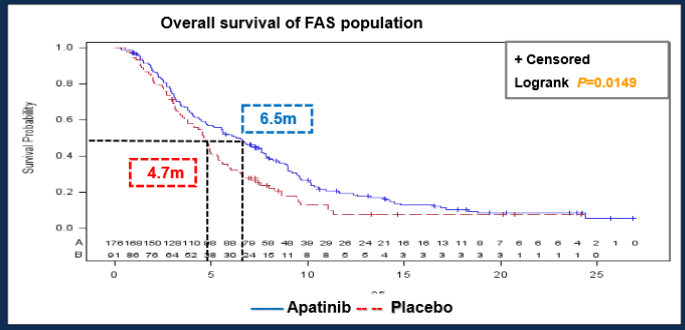
- Design: multicenter, randomized, double-blind, placebo-controlled clinical trial



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

PRESENTED AT: ASCO 50 ANNUAL MEETING

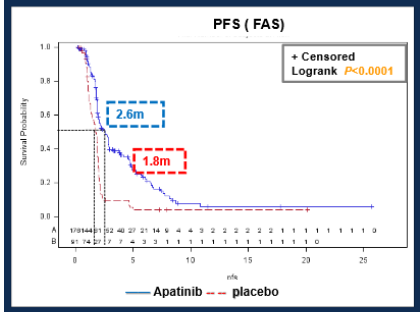
Primary end point – OS (FAS population)

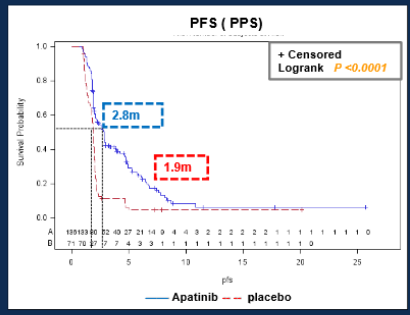


Group	n	mOS (95% CI), months	*P* value	HR(95%CI)
Apatinib	176	6.5(4.8-7.6)	*0.0149*	0.709 (0.537-0.937)
Placebo	91	4.7(3.6-5.4)		

PRESENTED AT: ASCO 50 ANNUAL MEETING

Secondary end point – PFS (FAS and PPS)





Group	n	mPFS (95% CI), months	*P* value	HR (95%CI)
Apatinib	176	2.6(2.0-2.9)	*<0.0001*	0.444 (0.331-0.595)
Placebo	91	1.8(1.4-1.9)		

Group	n	mPFS (95% CI), months	*P* value	HR (95%CI)
Apatinib	136	2.8(2.1-3.3)	*<0.0001*	0.455 (0.332-0.624)
Placebo	71	1.9(1.1-1.7)		

PRESENTED AT: ASCO 50 ANNUAL MEETING

Angiogenesis Inhibition 3.0


INTEGRATE

AGITG

INTEGRATE: A randomized, phase II, double-blind, placebo-controlled study of regorafenib in refractory advanced oesophagogastric cancer (AOGC): A study by the Australasian Gastrointestinal Trials Group (AGITG) Final overall and subgroup results

Pavlakis N*, Sjoquist KM*, Tsobanis E, Martin A, Kang YK, Bang YJ, O'Callaghan CJ, Tebbutt NC, Rha SY, Lee J, Cho JY, Lipton L, Burnell M, Alcindor T, Strickland AH, Kim JW, Yip S, Simes J, Zalcberg J, Goldstein D*.

ANZCTR 12612000239864

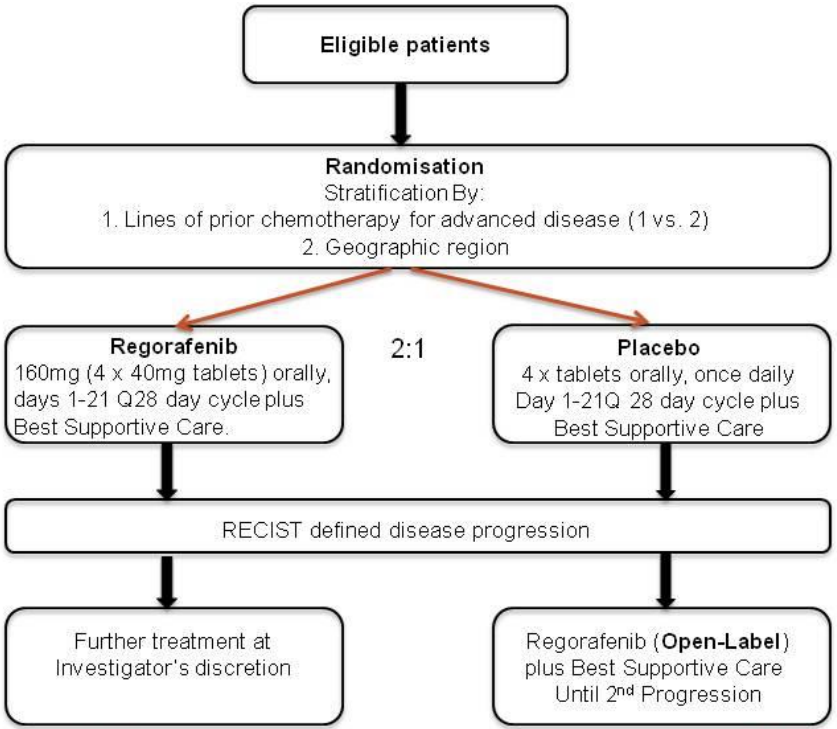
Primary endpoint: PFS

Secondary endpoints: OS,ORR,CBR, Safety

Prior CT lines
1: 42%
2: 58%

Study Schema

Nov 2012 - Feb 2014

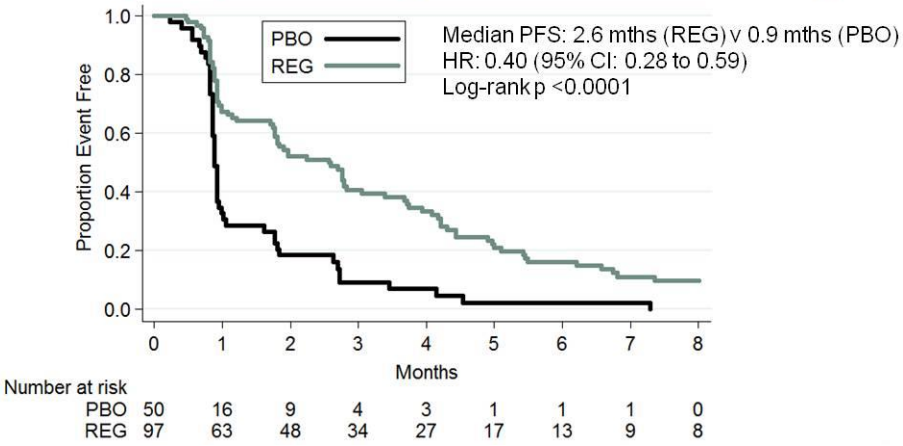


PRESENTED AT: ASCO Annual '15 Meeting

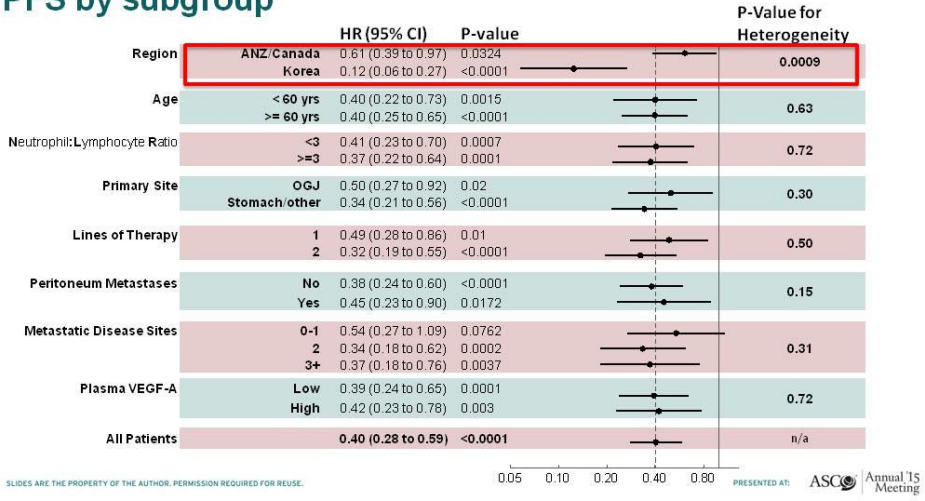
Pavlakis N ASCO 2015

INTEGRATE: results

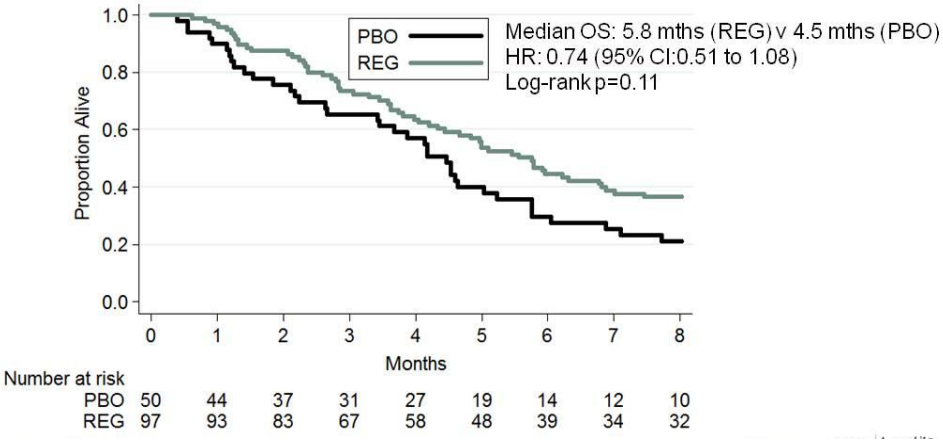
Primary endpoint: Progression-Free Survival (PFS)



PFS by subgroup



Secondary endpoint: Overall Survival (OS)



Pavlakis N ASCO 2015

INTEGRATE: toxicity

Toxicity: All AE's by worst grade - not drug specific

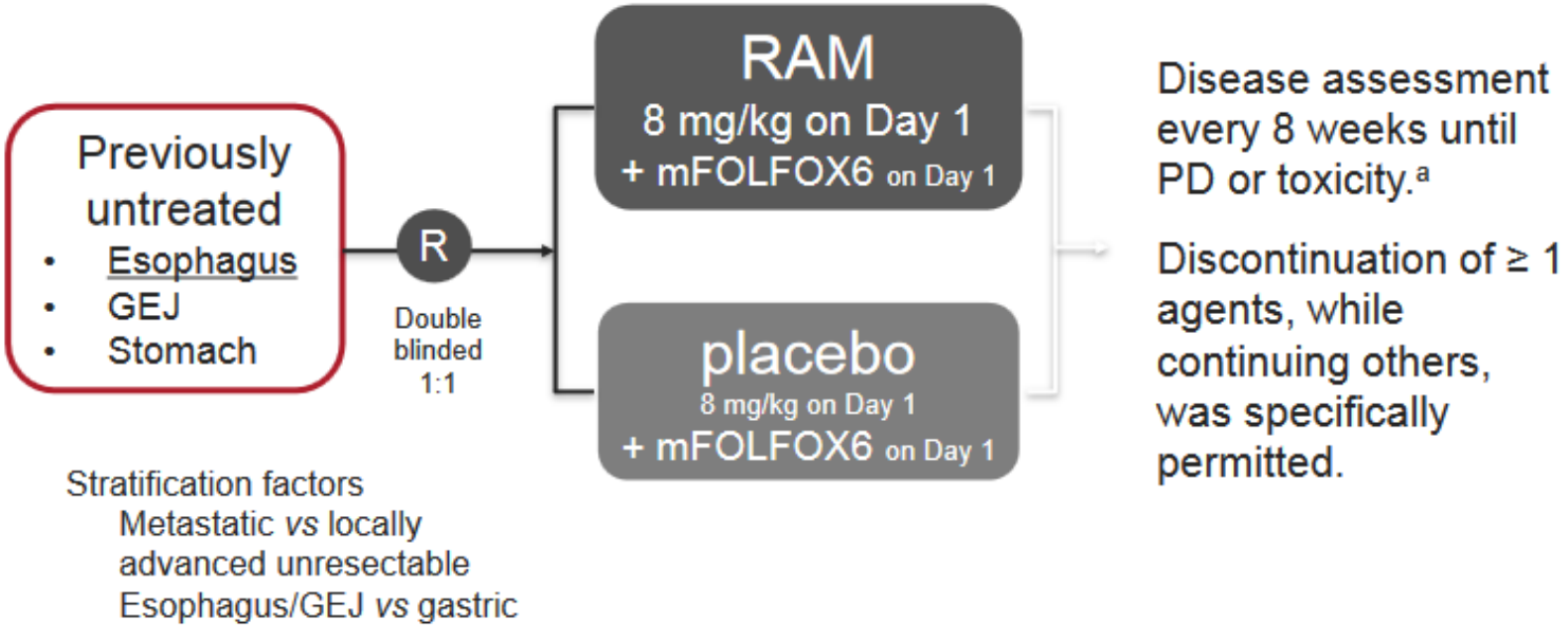
AEs with >15% incidence in Regorafenib Arm	INTEGRATE							
	Placebo (n=52)				Regorafenib (n=100)			
CTCAE Term	Grade 1-2		Grade 3-5		Grade 1-2		Grade 3-5	
Fatigue	19	(37%)	4	(8%)	44	(44%)	3	(3%)
Anorexia	17	(33%)	3	(6%)	31	(31%)	6	(6%)
Aspartate aminotransferase increased	6	(12%)	0	(0%)	19	(19%)	9	(9%)
Hypertension	0	(0%)	1	(2%)	17	(17%)	10	(10%)
Abdominal pain	7	(13%)	1	(2%)	1	(1%)	5	(5%)
Constipation	9	(17%)	0	(0%)	25	(25%)	0	(0%)
Nausea	12	(23%)	0	(0%)	23	(23%)	1	(1%)
Diarrhea	8	(15%)	0	(0%)	20	(20%)	1	(1%)
Palmar-plantar erythrodysesthesia syndrome	6	(12%)	1	(2%)	17	(17%)	3	(3%)
Alanine aminotransferase increased	3	(6%)	3	(6%)	11	(11%)	8	(8%)
Blood bilirubin increased	4	(8%)	0	(0%)	14	(14%)	2	(2%)
Vomiting	10	(19%)	3	(6%)	12	(12%)	1	(1%)

Pavlakis N ASCO 2015

Future developments?

Ramucirumab + Oxaliplatin 1° line?

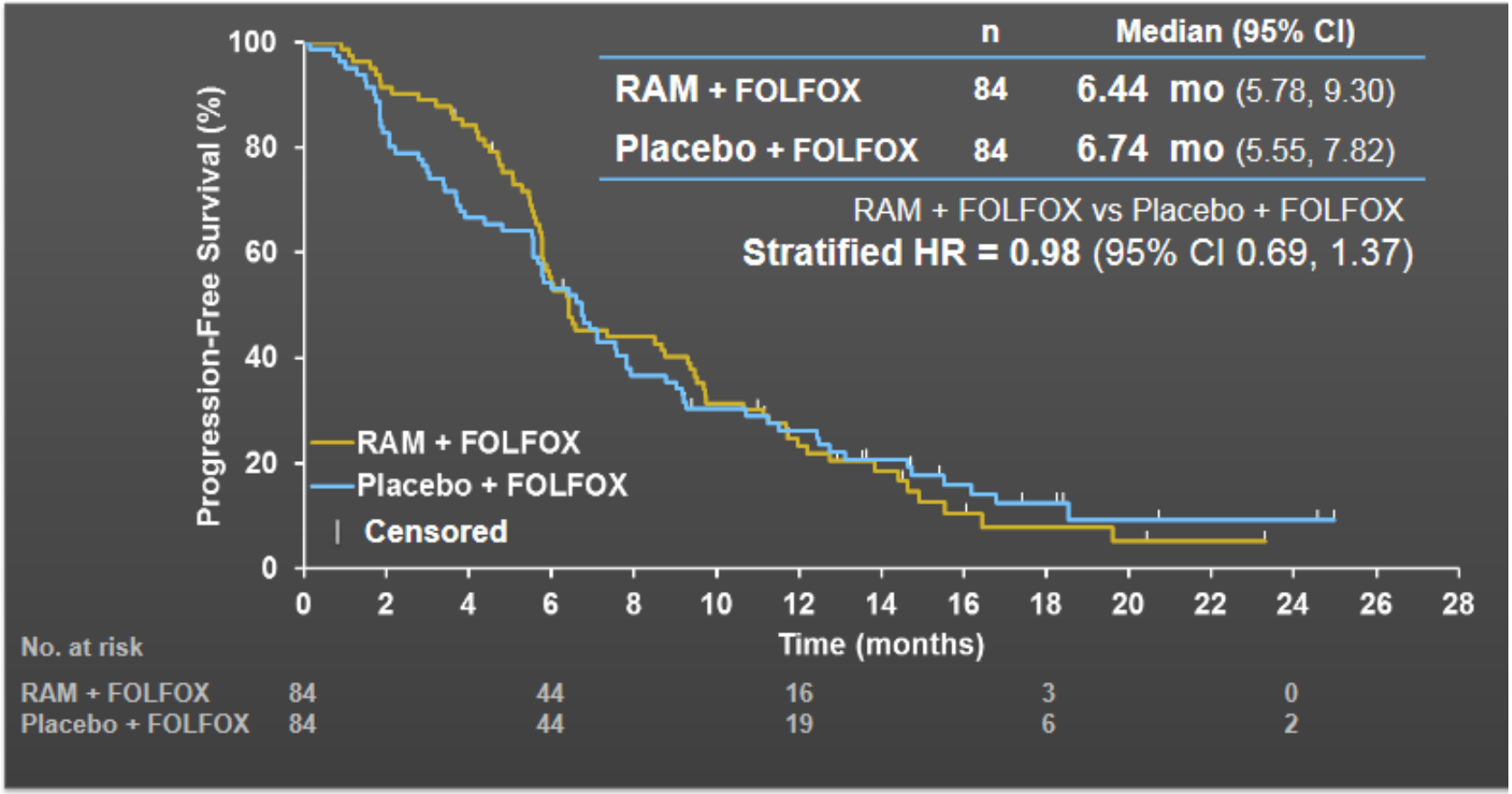
I4T-MC-JVBT (NCT01246960)



[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)

Maybe not

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

Yoon et al WGIC 2014

… and yet still…

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"
Search for studies: Search
Advanced Search | Help | Studies by Topic | Glossary

Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail

Text Size

A Study of Ramucirumab (LY3009806) in Combination With Capecitabine and Cisplatin in Participants With Stomach Cancer (RAINFALL)

This study is ongoing, but not recruiting participants.

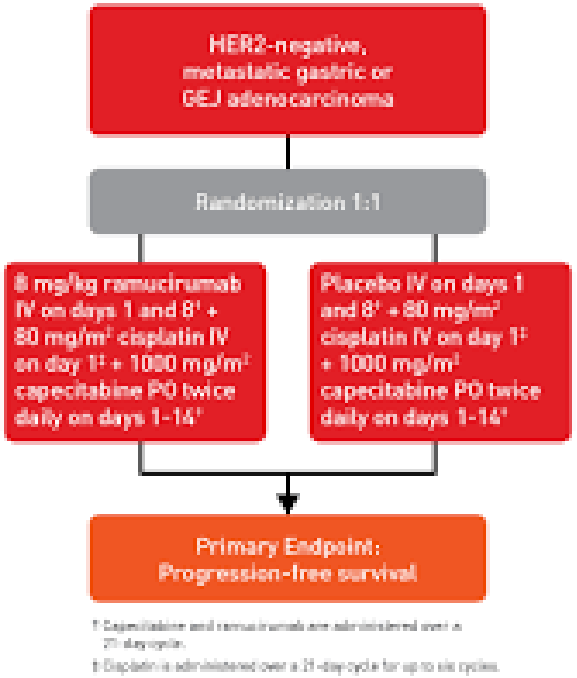
Sponsor:
Eli Lilly and Company

Information provided by (Responsible Party):
Eli Lilly and Company

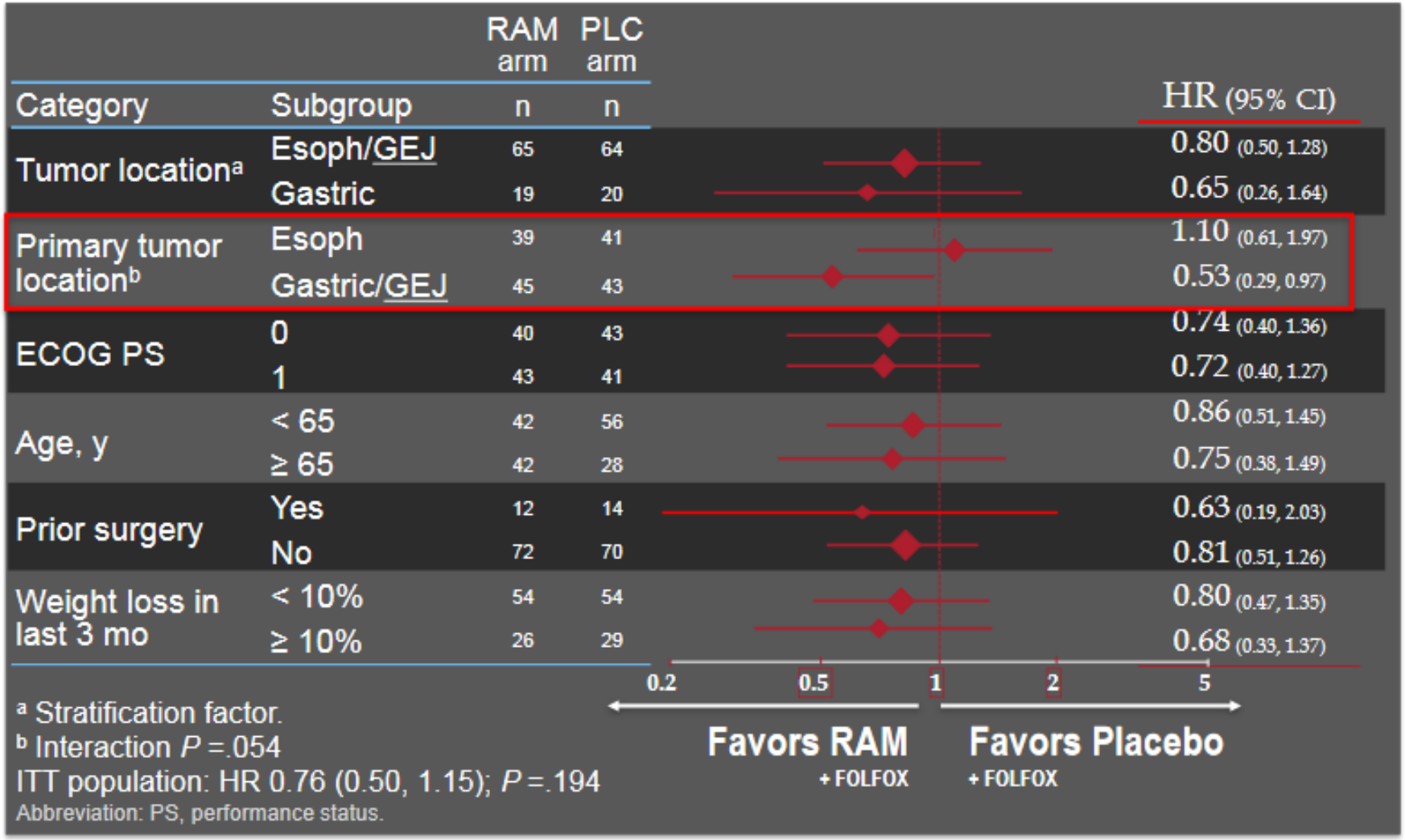
ClinicalTrials.gov Identifier:
NCT02314117

First received: December 8, 2014
Last updated: September 15, 2016
Last verified: September 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record



… perhaps it is a matter of ORIGIN



Yoon et al WGIC 2014

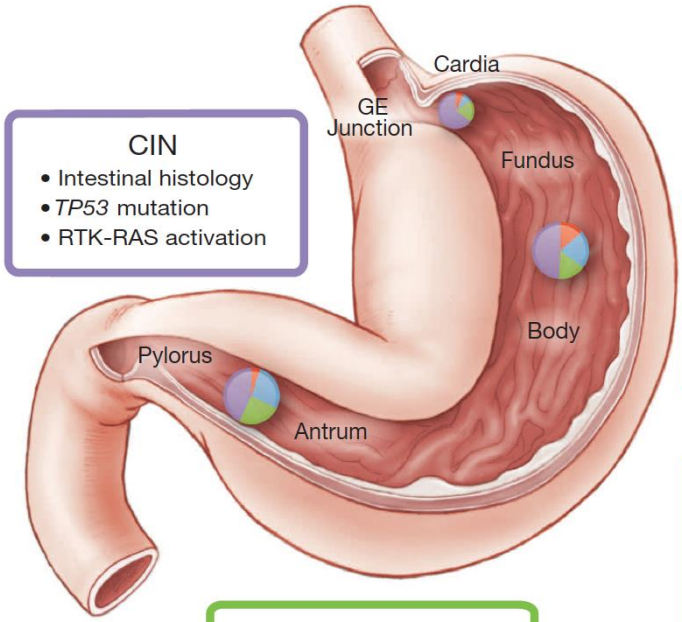
ORIGIN that is surrogate for biology

ARTICLE OPEN
doi:10.1038/nature13480

Comprehensive molecular characterization of gastric adenocarcinoma

The Cancer Genome Atlas Research Network*

50% GEJ



CIN
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

EBV
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

8%

MSI
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

22%

GS
- Diffuse histology
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

20%

Switch-maintenance in gastric cancer? ARMANI trial

Assessment of Ramucirumab Plus Paclitaxel as Switch MANtelnance Versus Continuation of First-line Chemotherapy in Patients With Advanced HER-2 Negative Gastric or Gastroesophageal Junction Cancers: the ARMANI Phase III Trial (ARMANI)

This study is not yet open for participant recruitment. (see Contacts and Locations)

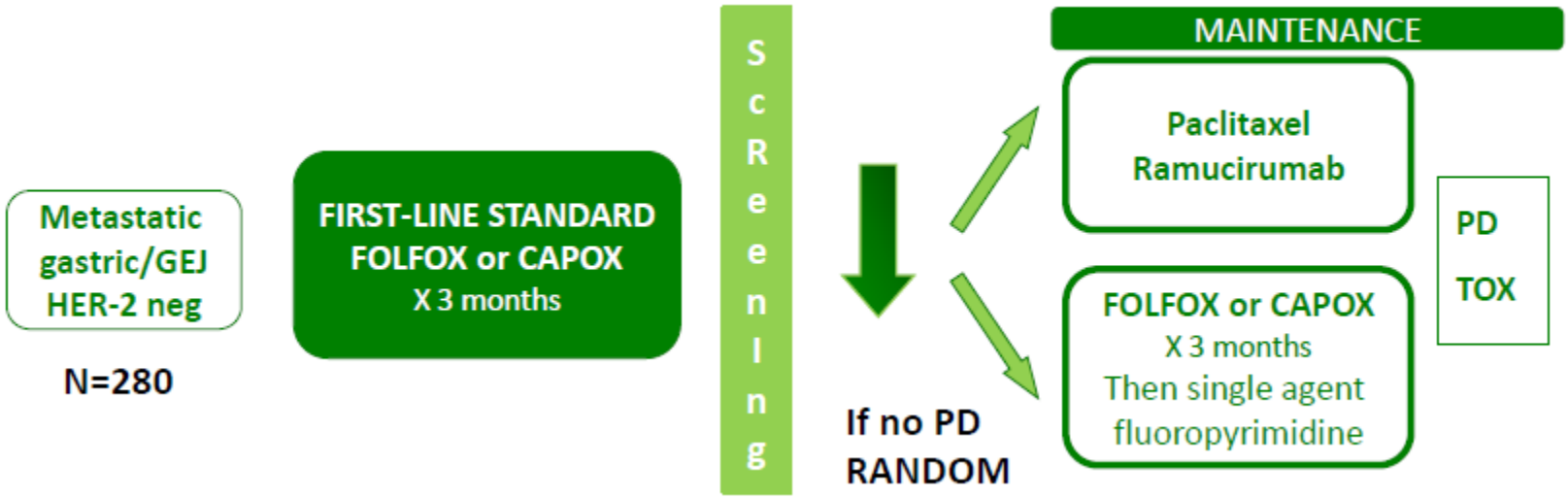
Verified October 2016 by Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Sponsor:
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Information provided by (Responsible Party):
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

ClinicalTrials.gov Identifier:
NCT02934464

First received: October 6, 2016
Last updated: October 13, 2016
Last verified: October 2016
History of Changes



Switch-maintenance in gastric cancer? MANTRA trial

A. Protocol Information		
A.1	Member State Concerned	Italy - Italian Medicines Agency
A.2	EudraCT number	2014-004395-28
A.3	Full title of the trial	Phase II randomized study of maintenance regorafenib vs placebo in no progression patients after first-line platinum and fluoropyrimidines based chemotherapy in HER2 negative locally advanced/metastatic gastric or gastroesophagel junction cancer. Studio randomizzato, di fase II, per la valutazione dell'efficacia di Regorafenib vs Placebo in pazienti con adenocarcinoma gastrico o adenocarcinoma della giunzione gastro-esofagea, HER2-negativo localmente avanzato/metastatico non in progressione di malattia dopo chemioterapia di prima linea contenente fluoro pirimidine o fluorofolati in associazione a composti del platino.
A.3.1	Title of the trial for lay people, in easily understood, i.e. non-technical, language	Regorafenib vs placebo as maintenance therapy in no progression patients after first-line platinum and fluoropyrimidines based chemotherapy in HER2 negative locally advanced/metastatic gastric or gastroesophagel junction cancer. Regorafenib vs placebo come terapia di mantenimento dopo una prima linea contenente fluoro pirimidine o fluorofolati in associazione a composti del platino in pazienti con adenocarcinoma gastrico o della giunzione gastro-esofagea HER2 negativo localmente avanzato o metastatico in risposta o stabilità di malattia.
A.3.2	Name or abbreviated title of the trial where available	MANTRA Study Protocollo MANTRA
A.4.1	Sponsor's protocol code number	MANTRA
A.7	Trial is part of a Paediatric Investigation Plan	No
A.8	EMA Decision number of Paediatric Investigation Plan	

Switch-maintenance in colorectal cancer? RAVELLO trial

Phase III study of regorafenib versus placebo as maintenance therapy in RAS wild type metastatic colorectal cancer (RAVELLO trial)

E. Martinelli[1], T. Troiani[1], F. Venturini[1], A. Cervantes[2], J. Douillard[3], A. Falcone[4], G. Folprecht[5], C. Köhne[6], J. Taïeb[7], J. Tabernero[8], C. Cardone[1], V. Sforza[1], G. Martini[1], S. Napolitano[1], A. Capuano[9], F. Auricchio[9], F. Ciardiello[1]

ABSTRACT

Background

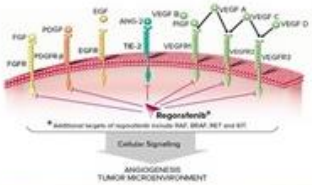
Treatment of metastatic colorectal cancer (mCRC) has improved due to the introduction of more active chemotherapies (CT) and novel targeted agents that have significantly increased response rate (RR), progression free survival (PFS) and overall survival (OS). Recently, CORRECT and CONCUR trials have demonstrated both activity and efficacy of regorafenib, a small multi-kinase inhibitor, as monotherapy in pretreated mCRC. The wide range of action of regorafenib makes it an ideal candidate for monotherapy in earlier disease treatment lines in which different pathways could be involved in the acquisition of resistance. To improve long term efficacy of first line therapy several therapeutic approaches of maintenance treatment have been explored in mCRC.

Methods

RAVELLO is an academic randomized, double-blind, placebo-controlled, multi-center, phase III study designed to evaluate efficacy and safety of regorafenib as maintenance treatment after first line therapy. Eligible patients: pathologically confirmed mCRC RAS wild type (KRAS and NRAS genes) treated with a first line fluoropyrimidine-based CT in combination with an anti-EGFR (epidermal growth factor receptor) monoclonal antibody for a minimum of 4 to a maximum of 8 months, with a stratification by response to the first line treatment (complete response/partial response or stable disease). 480 patients will be enrolled and randomly assigned in a 1:1 ratio to receive 160 mg regorafenib or placebo per os, every day for 3 weeks of every 4 weeks cycle, until disease progression or unacceptable toxicity. Primary endpoint is PFS. With a two-tailed alpha error of 0.05, the study will have 90% power to detect a 3-month prolongation of median PFS from randomization (corresponding to a hazard ratio of progression of 0.67 with 6-month median PFS expected in the control arm). Secondary endopoint are OS, safety, and biomarker correlative studies. Currently, one patient has been enrolled and is on treatment.

EudraCT number: 2013-005428-41.

BACKGROUND



Regorafenib is an ideal partner for a "switch maintenance" strategy, thanks to its broad spectrum of multi-kinase inhibitory activity against several pathways potentially responsible for secondary resistance, both in endothelial and in cancer cells

STUDY AIMS

Primary objective
- Progression Free Survival (PFS)

Secondary objectives

Efficacy, as assessed by:
- Overall survival (OS)
- Safety Profile

Other objectives
- Biomarker correlative studies

STUDY DESIGN

- First-line treatment course is given for a minimum of 4 months (8 cycles) to a maximum of 8 months (16 cycles) who are progression-free (i.e. have achieved PR, CR or SD) could be enrolled
- Stratification by response to 1st line chemotherapy (PR/CR vs SD)
- Treatment continues until disease progression, unacceptable toxicity, or other discontinuation criterion is met

MAIN INCLUSION CRITERIA

- Genetic diagnosis of RAS (hot spot mutations KRAS codon 2-3-4 and NRAS at least codon 2-3) wild type tumor
- Previous standard first line treatment defined as fluoropirimidine based chemotherapy (any variant) in combination with either cetuximab or panitumumab for a minimum of 4 months and a maximum of 8 months
- Patients that have achieved either partial response (PR), complete response (CR) or stable disease (SD) at the completion of the first line treatment after a minimum of 4 months (8 cycles) and a maximum of 8 months (16 cycles)
- Patients with PR/SD must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST criteria, version 1.1)
- Adequate bone marrow, liver and renal function conducted within 7 days of starting study treatment
- Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1

MAIN EXCLUSION CRITERIA

- Prior treatment with regorafenib
- Interruption of the first line treatment for progressive disease or in which progressive disease was diagnosed prior to entry into this study
- Congestive heart failure > New York Heart Association (NYHA) class 2
- Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before start of study medication
- Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
- Uncontrolled hypertension. (systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management)
- Unresolved toxicity higher than NCI-CTCAE (version 3.0) grade 1 attributed to any prior therapy/procedure excluding alopecia, oxaliplatin induced neurotoxicity and anti-EGFR Ab induced skin toxicity ≤ Grade 1

STUDY PROGRESS

- Number of Italian centers involved in the trial: 14
- Number of European centers involved in the trial: 21 (Germany, France, Spain)
- First patient (CC) enrolled on September 2014 at the Second University of Naples, currently at cycles 4.

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Conclusions

- Colorectal cancer: 4 different drugs (Bevacizumab 1°-2° line, Aflibercept 2° line FOLFOX 1° only, Ramucirumab 2° line FOLFOX 1° only, Regorafenib 2 or + line) with no molecularly driven selection

- Gastric cancer: 1 drug currently available (Ramucirumab 2° line alone or + Paclitaxel) + many to come! (Apatinib 2-3° line, Regorafenib 3° line) with a hint towards a histology/site of involvement selection

Thank you for your attention!

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