CONCUR: A randomized, placebo-controlled phase 3 study of regorafenib (REG) monotherapy in Asian patients with previously treated metastatic colorectal cancer (mCRC)

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on behalf of the CONCUR Investigators

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TW Kim disclosures

- Consultant or advisory role
  - Merck, Abbvie
- Research Funding
  - Bayer

Background

- CONCUR is the second phase 3 trial showing that regorafenib improves survival in patients with mCRC who progress after standard therapies
  - CONCUR: OS HR 0.55 (95% CI 0.40 – 0.77); *P* = 0.0002 (1-sided)[1]
  - CORRECT: OS HR 0.77 (95% CI 0.64 – 0.94); *P* = 0.0052 (1-sided)[2]
- In CONCUR, 40% of patients did not receive prior anti-VEGF or anti-EGFR targeted therapy before randomization
  - In contrast, 100% of patients in CORRECT had received prior bevacizumab and 51% received a prior anti-EGFR (cetuximab and/or panitumumab)[2]
- The aim of this planned subgroup analysis was to evaluate overall survival in the CONCUR trial by prior targeted therapy

[1] Li J, et al. *Ann Oncol* 2014; 25 (Suppl 2): ii114–ii115
[2] Grothey A, et al. *Lancet* 2013; 381: 303–12 (NCT01103323)

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CONCUR

Clinicaltrials.gov NCT01584830

Asian patients with mCRC who progressed after standard therapies

- **25 centers in mainland China, Hong Kong, Taiwan, South Korea, Vietnam**
- **Failed ≥2 prior standard regimens including oxaliplatin, fluoropyrimidine, irinotecan**
- **Progression within 3 months after last standard therapy or within 6 months after adjuvant oxaliplatin**
- **Prior anti-VEGF or anti-EGFR therapy allowed, but not mandatory**

R
2:1

Regorafenib

160 mg daily
3 weeks on / 1 week off
(4-week cycle)
***n* = 136**

Stratification

- Metastases: single *vs* multiple organs
- Time from mCRC diagnosis: ≥18 *vs* <18 months

Placebo

***n* = 68**

- All received best supportive care
- Treatment until progression, unacceptable toxicity, or withdrawal
- Tumor assessments (CT/MRI) every 8 weeks during the treatment period

Primary endpoint: overall survival (OS)

- One-sided alpha 0.2 and assumed 33.3% OS improvement (HR=0.75 favoring regorafenib) with 154 events had 80% power

Secondary endpoints: progression-free survival, response rate, disease control rate

Planned subgroup analysis by prior targeted therapy (anti-VEGF, anti-EGFR)

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Baseline characteristics

	Regorafenib (*n*=136)	Placebo (*n*=68)
Age, median years (range)	58 (31–79)	56 (30–84)
Male, *n* (%)	85 (62.5)	33 (48.5)
ECOG PS, *n* (%)		
0	35 (25.7)	15 (22.1)
1	101 (74.3)	53 (77.9)
***KRAS* status, *n* (%)**		
Wild-type	50 (36.8)	29 (42.6)
Mutant	46 (33.8)	18 (26.5)
Unknown	40 (29.4)	21 (30.9)
***BRAF* status, *n* (%)**		
Wild-type	28 (20.6)	14 (20.6)
Mutant	0	1 (1.5)
Unknown	108 (79.4)	53 (77.9)
No prior targeted therapy*	56 (41.2)	26 (38.2)
>3 prior treatment lines	73 (53.7)	35 (51.5)
>3 prior treatment lines for mCRC	52 (38.2)	27 (39.7)

Intent-to-treat population

*No prior anti-VEGF or anti-EGFR therapy

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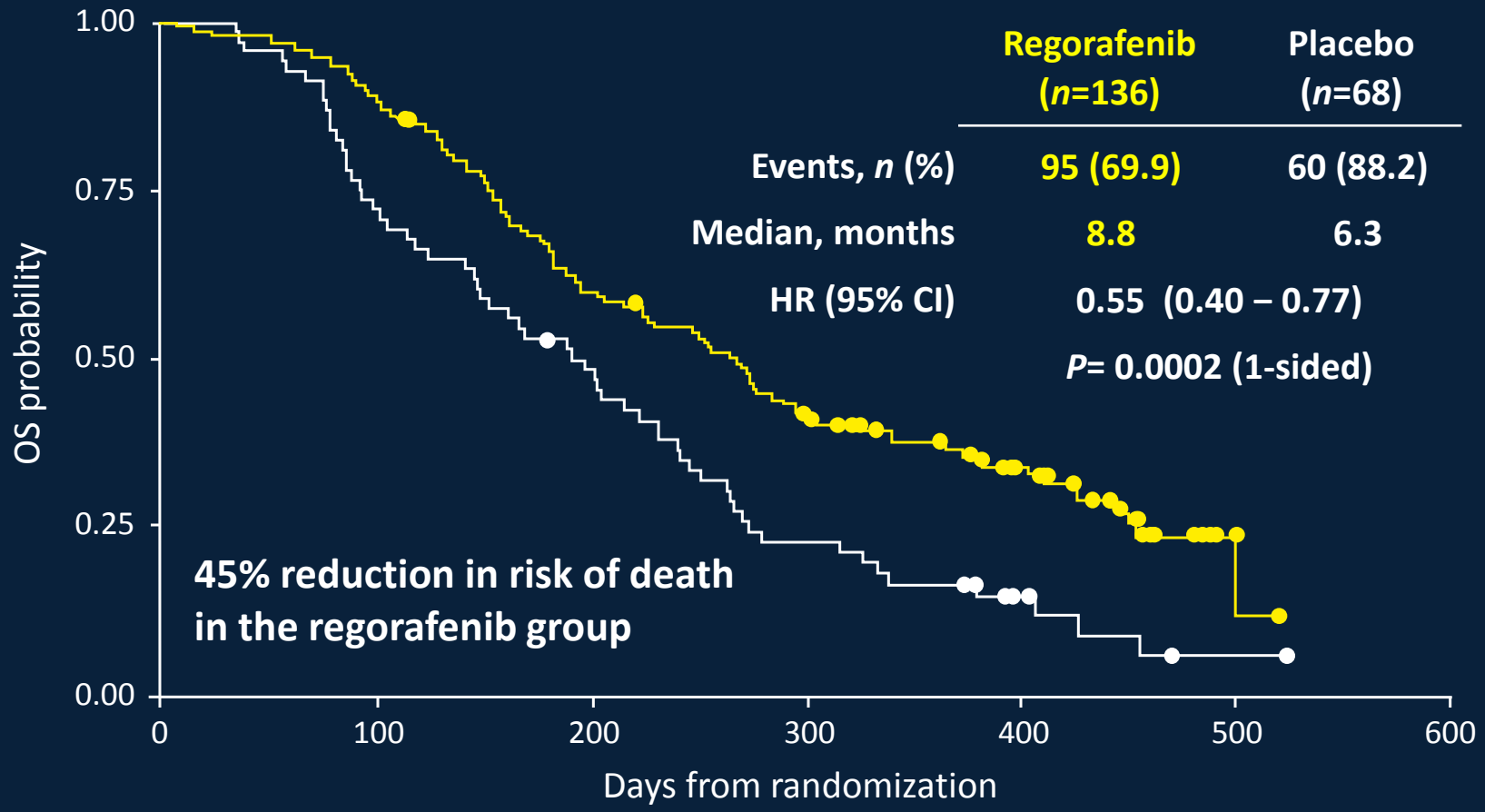
Overall survival (OS)

Primary endpoint



	Regorafenib (*n*=136)	Placebo (*n*=68)
Events, *n* (%)	95 (69.9)	60 (88.2)
Median, months	8.8	6.3
HR (95% CI)	0.55 (0.40 – 0.77)	
	P= 0.0002 (1-sided)	

Overall survival is defined as the time (days) from randomization to death due to any cause. Patients alive at the time of analysis will be censored at their last date known to be alive; closed circles represent censored observations

Comparison using a stratified log-rank test (single *vs* multiple organ metastases and ≥18 *vs* <18 months from mCRC diagnosis); one-sided alpha = 0.2

Cut-off date for the analysis was 29 November 2013

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Safety

- Adverse events (AE) were consistent with the known safety profile of regorafenib in mCRC
- Most frequent grade ≥3 AEs in regorafenib-treated patients included hand-foot skin reaction (16%), hypertension (12%), hyperbilirubinemia (12%), elevated liver enzymes (AST 10%, ALT 8%), hypophosphatemia (9%)
- There were no reports of liver failure or pancreatitis
- 14% of patients in the regorafenib group and 6% of patients in the placebo group permanently discontinued treatment due to AEs

Adverse events are irrespective of relationship to study drug as defined in NCI-CTCAE v 4.0
AST, aspartate aminotransferase; ALT, alanine aminotransferase

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Treatment with targeted therapies prior to randomization

n (%)	Regorafenib (*n*=136)	Placebo (*n*=68)
No prior targeted therapy *(No prior anti-VEGF or anti-EGFR)*	**56 (41.2)**	**26 (38.2)**
Any prior targeted therapy *(Prior anti-VEGF or anti-EGFR or both)*	**80 (58.8)**	**42 (61.8)**
Prior anti-VEGF only	**32 (23.5)**	**13 (19.1)**
Prior anti-EGFR only	**24 (17.6)**	**17 (25.0)**
Prior anti-VEGF and anti-EGFR	**24 (17.6)**	**12 (17.6)**

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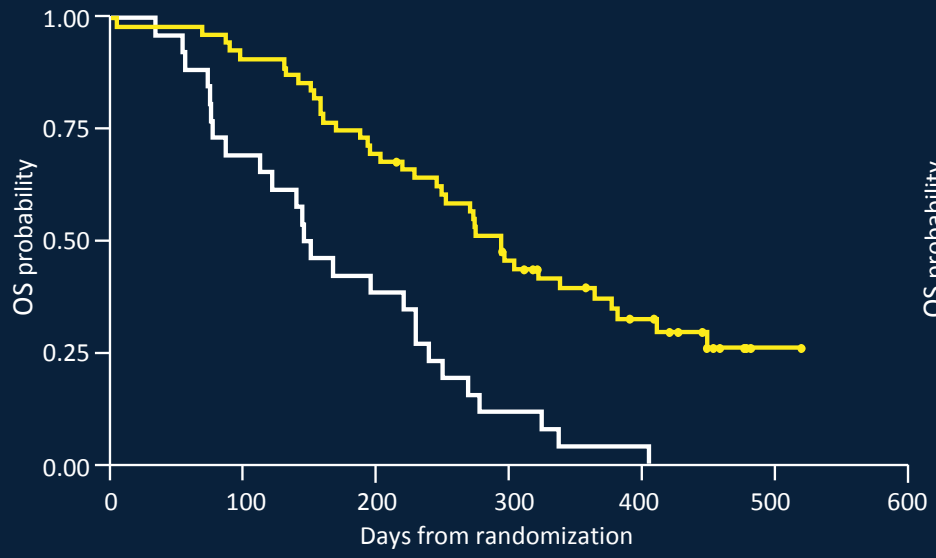
Subgroup analysis of OS by prior targeted therapy

No prior targeted therapy

(No prior anti-VEGF or anti-EGFR)

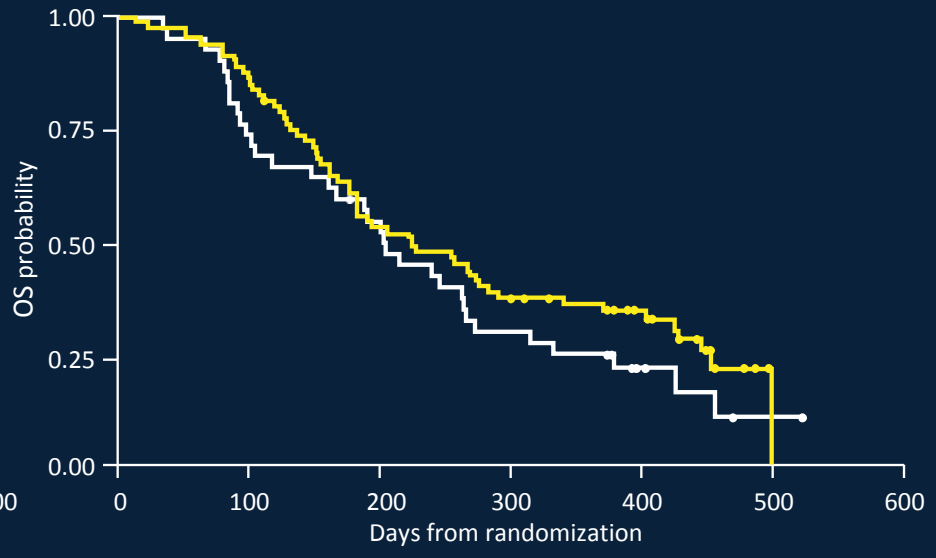
	Regorafenib (*n*=56)	Placebo (*n*=26)
Median, months	9.7	4.9
HR (95% CI)	0.31 (0.19 – 0.53)	



Any prior targeted therapy

(Prior anti-VEGF or anti-EGFR or both)

	Regorafenib (*n*=80)	Placebo (*n*=42)
Median, months	7.4	6.7
HR (95% CI)	0.78 (0.51 – 1.19)	



Closed circles represent censored observations

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Subgroup analysis of OS by prior targeted therapy

	Median OS (months)	HR (95% CI)	Had post-study anti-cancer treatment (% *n*)
All patients			
Regorafenib (*n*=136)	**8.8**	**0.55**	**30.9**
Placebo (*n*=68)	**6.3**	**(0.40 – 0.77)**	**42.6**
No prior targeted therapy*			
Regorafenib (*n*=56)	**9.7**	**0.31**	**28.6**
Placebo (*n*=26)	**4.9**	**(0.19 – 0.53)**	**23.1**
Any prior targeted therapy†			
Regorafenib (*n*=80)	**7.4**	**0.78**	**32.5**
Placebo (*n*=42)	**6.7**	**(0.51 – 1.19)**	**54.8**
Prior anti-VEGF only			
Regorafenib (*n*=32)	**5.5**	**0.99**	**18.8**
Placebo (*n*=13)	**8.1**	**(0.48 – 2.03)**	**53.8**
Prior anti-EGFR only			
Regorafenib (*n*=24)	**9.1**	**0.80**	**33.3**
Placebo (*n*=17)	**8.6**	**(0.38 – 1.68)**	**52.9**
Prior anti-VEGF and anti-EGFR			
Regorafenib (*n*=24)	**8.1**	**0.48**	**50.0**
Placebo (*n*=12)	**5.9**	**(0.22 – 1.08)**	**58.3**

- Greatest imbalance in post-study treatment in the anti-VEGF only group

*No prior anti-VEGF or anti-EGFR
†Prior anti-VEGF or anti-EGFR or both

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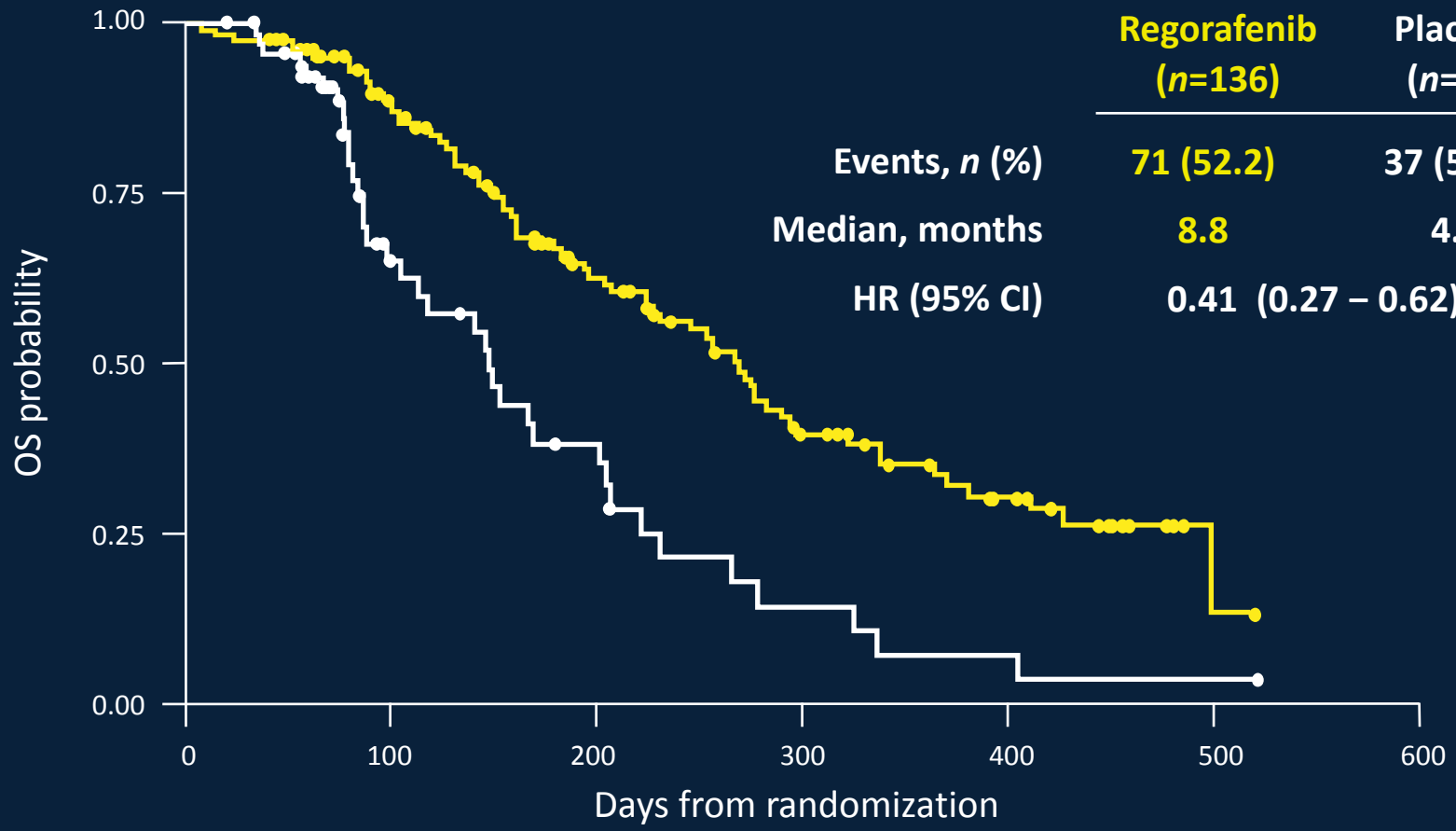
Exploratory post hoc analysis of OS (all patients)

*Patients censored at the start of post-study treatment**



	Regorafenib (*n*=136)	Placebo (*n*=68)
Events, *n* (%)	71 (52.2)	37 (54.4)
Median, months	8.8	4.8
HR (95% CI)	0.41 (0.27 – 0.62)	

*Results should be interpreted with caution due to non-random censoring of patients who received post-study treatment

Comparison using a stratified log-rank test (single *vs* multiple organ metastases and ≥18 *vs* <18 months from mCRC diagnosis)

Cut-off date for the analysis was 29 November 2013; closed circles represent censored observations

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Exploratory post hoc OS subanalysis by prior targeted therapy

Patients censored at the start of post-study treatment

		Median OS (months)		
	n	Regorafenib	Placebo	HR (95% CI)*
All patients	204	8.8	4.8	0.41 (0.27 – 0.62)
No prior targeted therapy *(No prior anti-VEGF or anti-EGFR)*	82	10.6	4.8	0.27 (0.15 – 0.49)
Any prior targeted therapy *(Prior anti-VEGF or anti-EGFR or both)*	122	7.4	4.9	0.57 (0.32 – 1.02)
Prior anti-VEGF only	45	5.3	3.5	0.41 (0.16 – 1.06)
Prior anti-EGFR only	41	8.4	6.6	0.59 (0.22 – 1.61)
Prior anti-VEGF and anti-EGFR	36	8.8	6.7	0.51 (0.16 – 1.61)

- Results should be interpreted with caution due to small sample size of some subgroups and non-random censoring of patients who received post-study treatment

*Subgroups were analyzed using an unstratified Cox regression model

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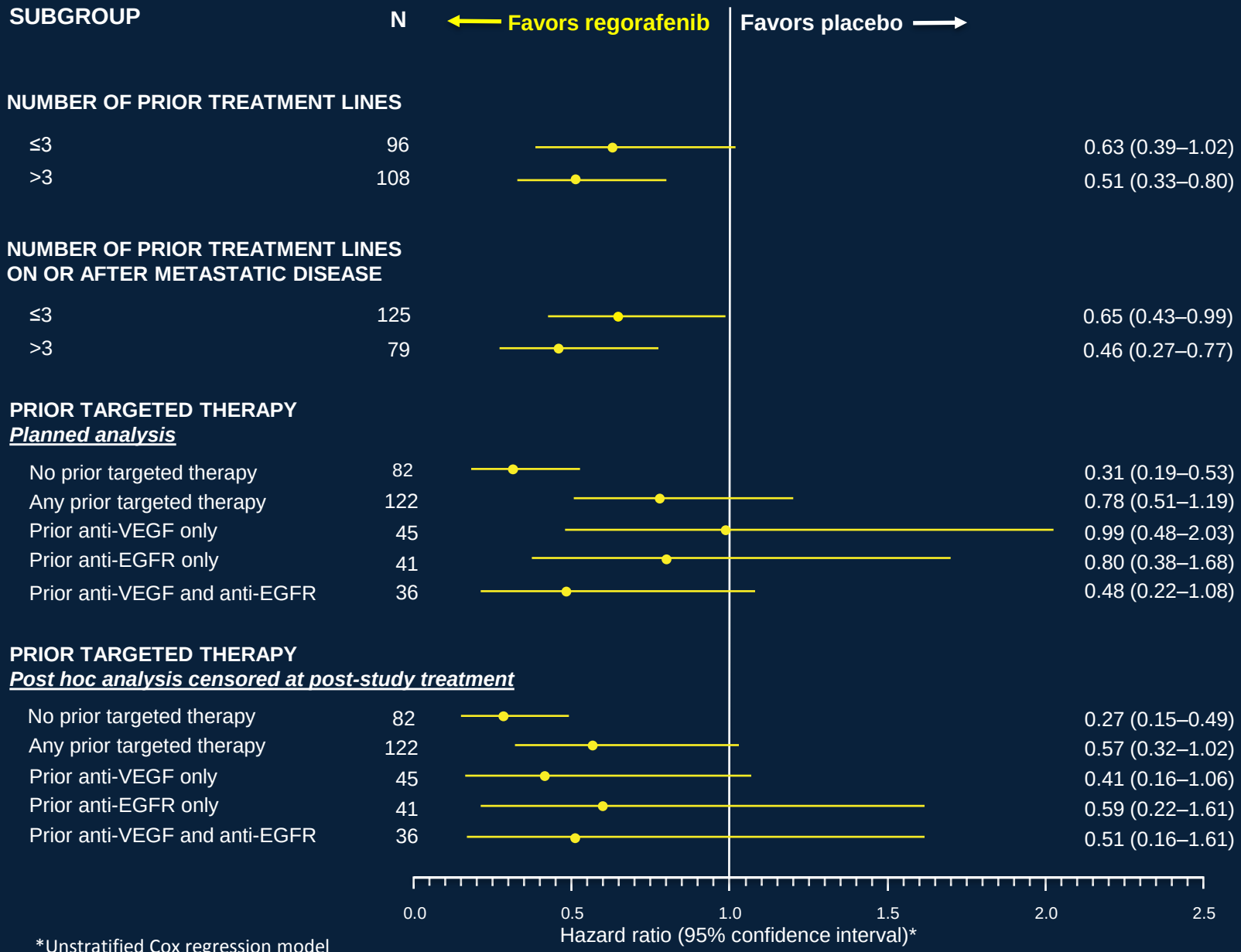
Subgroup analysis of OS



*Unstratified Cox regression model

Conclusions

- Regorafenib significantly improves OS in Asian patients with mCRC, reducing the risk of death by 45% (HR 0.55; 1-sided *P* =0.0002)
- OS was better in patients who had no prior anti-VEGF or anti-EGFR therapy than in patients who received at least one prior targeted drug
  - No prior targeted therapies: (n=82) HR 0.31 (0.19 – 0.53)
  - Any prior targeted therapy: (n=122) HR 0.78 (0.51 – 1.19)
- Subgroup analysis of OS by prior targeted therapy generally favored regorafenib, but may have been impacted by imbalances in post-study anti-cancer treatments
- An exploratory post hoc analysis of OS with censoring at the start of post-study treatment favored regorafenib irrespective of whether or not patients received prior anti-VEGF or prior anti-EGFR therapy

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