Phase 3 CORRECT trial of regorafenib in metastatic colorectal cancer (mCRC): overall survival update

Eric Van Cutsem, MD, PhD
University Hospitals Gasthuisberg/Leuven,
Leuven, Belgium

On behalf of 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, Axel Grothey, and the CORRECT Investigator Group

Presenter conflict of interest

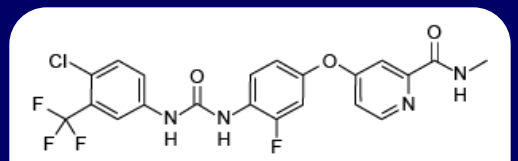
- EVC has received research funding from Bayer paid at his institution

Metastatic CRC: a major problem

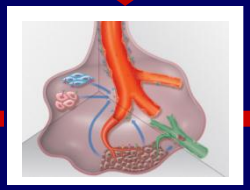
- Globally, 1.2 million new CRC cases and over 600,000 deaths each year[1,2]
- ≈ 50% of patients develop metastases[3,4]
- Current standard medical treatments include:[3,4]
  - Chemotherapy (fluoropyrimidines, oxaliplatin, irinotecan)
  - Monoclonal antibodies (bevacizumab, cetuximab, or panitumumab)
- No standard salvage therapy available, although many patients retain good performance status[3,4]
- High unmet clinical need for treatment options for mCRC

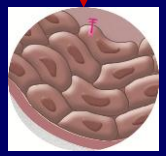
1. GLOBOCAN. Cancer fact sheets: colorectal cancer. 2008.
2. American Cancer Society. Cancer Facts and Figures 2012.
3. NCCN Guidelines. Colon cancer. v.2.2012.
4. Schmoll H, Van Cutsem E *et al*. ESMO consensus 2012.

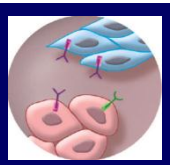
Regorafenib (BAY 73-4506), an oral multikinase inhibitor targeting multiple tumor pathways[1-3]

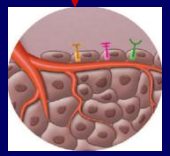


Regorafenib









Inhibition of proliferation

KIT
PDGFR
RET

Inhibition of tumor microenvironment signaling

PDGFR-β
FGFR

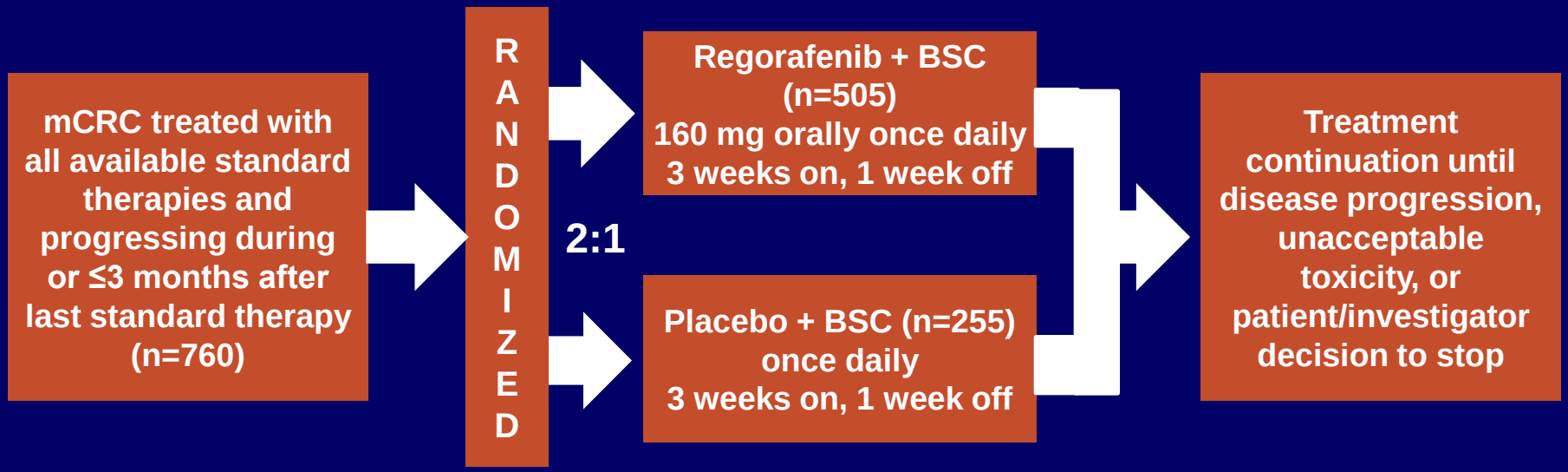
Inhibition of neoangiogenesis

VEGFR1-3
TIE2

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.

CORRECT: Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy

- Multicenter, randomized, double-blind, placebo-controlled, phase III trial
  - 16 countries, 114 centers
  - Recruitment: May 2010 to March 2011
- Stratification: prior anti-VEGF therapy, time from diagnosis of metastasis, geographical region



Primary endpoint: overall survival (OS)

90% power to detect 33.3% increase (HR=0.75), 1-sided overall α=0.025

Patient demographics

		Regorafenib N=505	Placebo N=255
Age, median years (range)		61 (22-82)	61 (25-85)
Sex, %	Male	61.6	60.0
	Female	38.4	40.0
Race, %	Caucasian	77.6	78.8
	Black	1.2	3.1
	Asian	15.0	13.7
ECOG PS, %	0	52.5	57.3
	1	47.5	42.7
Region, %	North America, Western Europe, Israel, Australia	83.2	83.1
	Asia	13.7	13.7
	Eastern Europe	3.2	3.1

Baseline disease characteristics

		Regorafenib N=505	Placebo N=255
Primary site of disease, %	Colon	64.0	67.5
	Rectum	29.9	27.1
	Colon and rectum	5.9	5.5
KRAS* mutation, %	No	40.6	36.9
	Yes	54.1	61.6
	Unknown	5.3	1.6
Histology, %	Adenocarcinoma	98.0	97.3
	Other (adenosquamous or unspecified carcinoma)	2.0	2.8
Number of prior lines of therapy for metastatic disease, %	1-2	26.7	24.7
	3	24.8	28.2
	≥4	48.5	47.1
Prior bevacizumab, %		100	100

**KRAS* status based on historical patient record

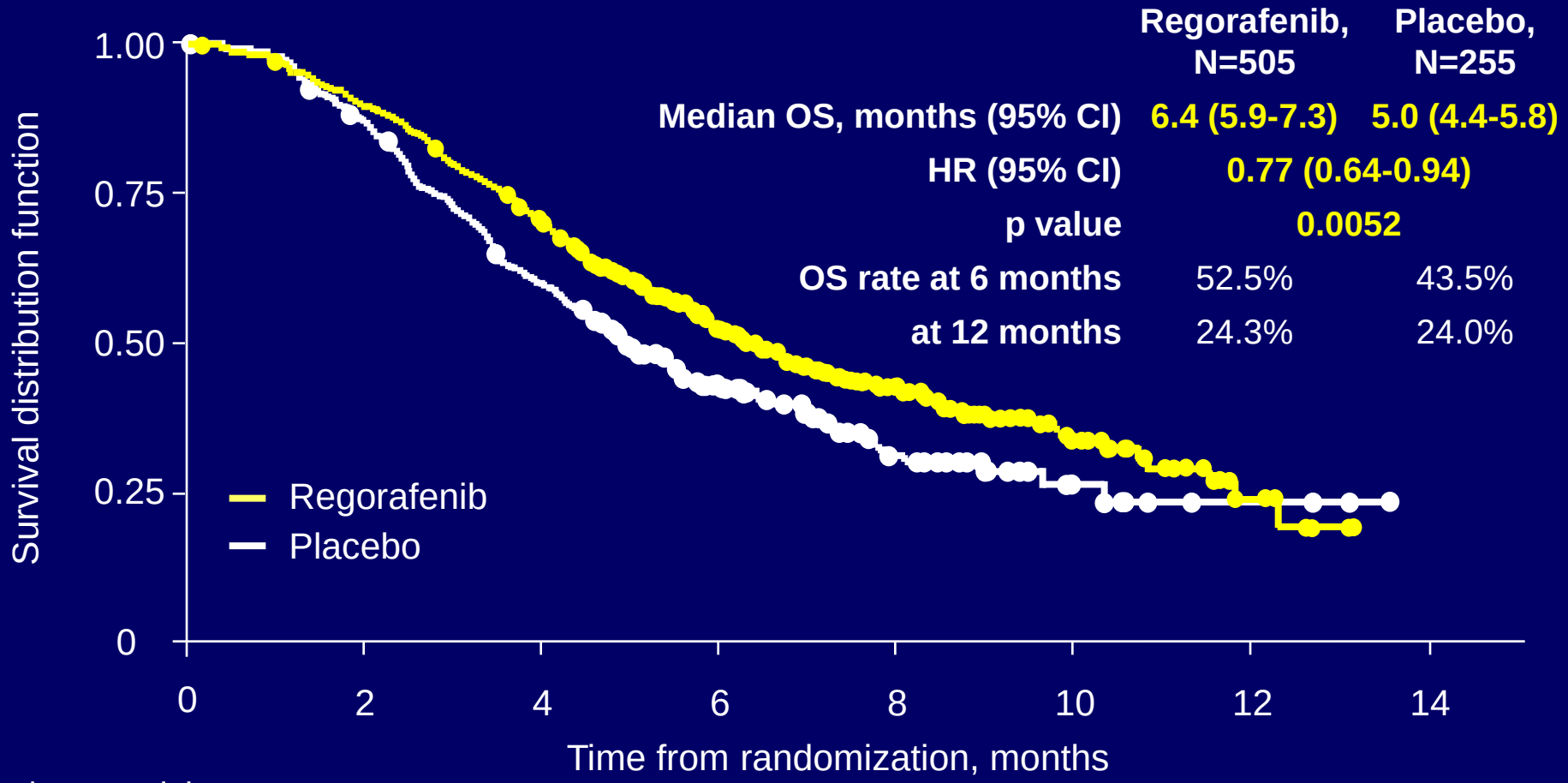
Drug exposure

	Regorafenib N=505	Placebo N=255
Duration of treatment, weeks		
Mean ± SD	12.1 ± 9.7	7.8 ± 5.2
Median (range)	7.3 (0.3-47.0)	7.0 (0.6-38.6)
Dose received		
Mean ± SD daily dose, mg	147.2 ± 18.6	159.3 ± 4.9
Proportion of planned dose received, %	78.9	90.2
Dose modifications		
Patients requiring ≥1 dose reduction, %	20.0	3.2
Patients requiring ≥1 treatment interruption, %	70.4	37.5

Overall survival (interim analysis)

Primary endpoint met prespecified stopping criteria at interim analysis

(1-sided p<0.009279 at 74% of events [432] required for final analysis)



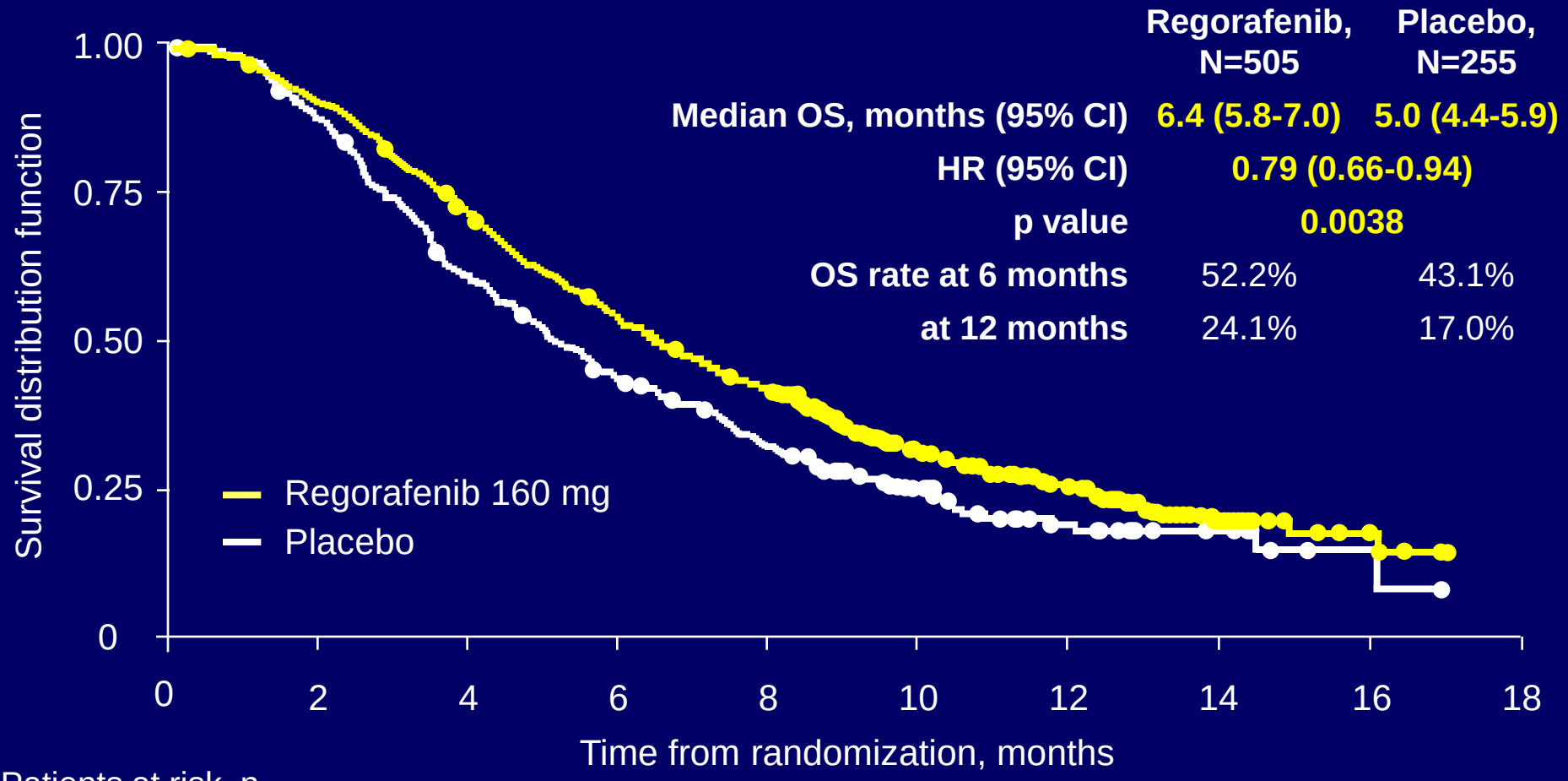
	Regorafenib, N=505	Placebo, N=255
Median OS, months (95% CI)	6.4 (5.9-7.3)	5.0 (4.4-5.8)
HR (95% CI)	0.77 (0.64-0.94)	
p value	0.0052	
OS rate at 6 months	52.5%	43.5%
at 12 months	24.3%	24.0%

Patients at risk, n

Regorafenib	452	352	187	93	33	7
Placebo	221	150	75	32	9	3

Overall survival (updated analysis)

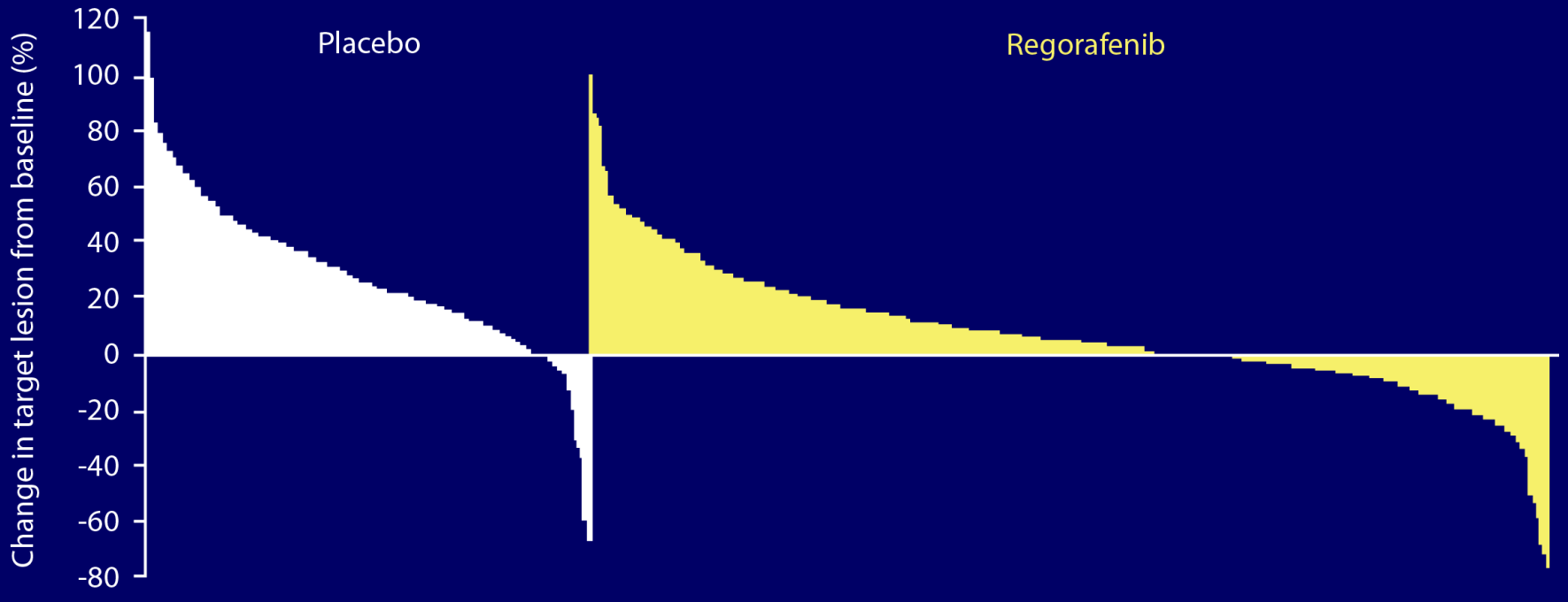
Extended analysis shows that significant benefit is maintained after 566 events (97% of planned total)



Patients at risk, n

Regorafenib	452	353	259	199	99	59	18	5
Placebo	221	150	106	74	38	17	8	2

Objective response and disease control rates



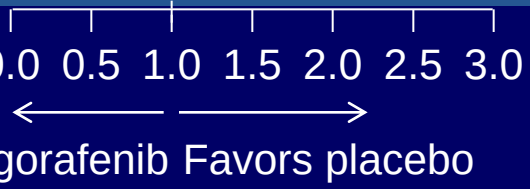
	Regorafenib N=505	Placebo N=255
Best response, %		
Complete response	0	0
Partial response	1.0	0.4
Stable disease	42.8	14.5
Progressive disease	49.5	80.0
Disease control rate*	**41.0**	**14.9**

*DCR = PR + SD ≥6 weeks after randomization; $p<0.000001$

Subgroup analysis of overall survival (interim analysis)

Regorafenib benefit *vs* placebo is achieved across subgroups

		N	HR (95% CI)
All patients		760	0.774 (0.636-0.942)
Sex	Male	464	0.773 (0.599-0.998)
	Female	296	0.751 (0.552-1.022)
Age	<65 years	475	0.716 (0.561-0.914)
	≥65 years	285	0.856 (0.614-1.193)
Region	NA, WE, IS, AU	632	0.768 (0.622-0.948)
	Asia	104	0.790 (0.429-1.456)
	EE	24	0.694 (0.195-2.466)
Baseline ECOG PS	0	411	0.702 (0.530-0.929)
	1	349	0.773 (0.586-1.020)
Primary site of disease	Colon	495	0.703 (0.557-0.887)
	Rectum	220	0.953 (0.633-1.436)
	Colon and rectum	44	1.091 (0.441-2.697)

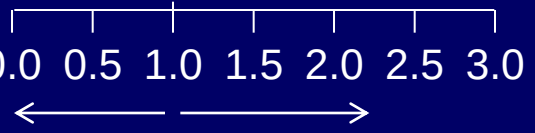


NA: North America, WE: Western Europe, IS: Israel, AU: Australia, EE: Eastern Europe

Subgroup analysis of overall survival (interim analysis)

Regorafenib benefit *vs* placebo is achieved across subgroups

		N	HR (95% CI)
All patients		760	0.774 (0.636-0.942)
Time from first diagnosis of metastatic disease to randomization	<18 months	140	0.816 (0.532-1.251)
	≥18 months	620	0.760 (0.609-0.948)
Prior anticancer treatment	F, Ox, Iri, Bev	375	0.825 (0.625-1.089)
	F, Ox, Iri, Bev, anti-EGFR	385	0.710 (0.538-0.938)
Prior treatment lines for metastatic disease	≤3	395	0.788 (0.599-1.038)
	>3	365	0.747 (0.564-0.988)
***KRAS* mutation (based on historical patient record)**	No	299	0.653 (0.476-0.895)
	Yes	430	0.867 (0.670-1.123)



F: fluoropyrimidine; Ox: oxaliplatin; Iri: irinotecan; Bev, bevacizumab

Drug-related treatment-emergent adverse events occurring in ≥10% of patients

Adverse event, %	Regorafenib N=500				Placebo N=253			
	All grades	Grade 3	Grade 4	Grade 5*	All grades	Grade 3	Grade 4	Grade 5*
Hand-foot skin reaction	46.6	16.6	0	0	7.5	0.4	0	0
Fatigue	47.4	9.2	0.4	0	28.1	4.7	0.4	0
Hypertension	27.8	7.2	0	0	5.9	0.8	0	0
Diarrhea	33.8	7.0	0.2	0	8.3	0.8	0	0
Rash/desquamation	26.0	5.8	0	0	4.0	0	0	0
Anorexia	30.4	3.2	0	0	15.4	2.8	0	0
Mucositis, oral	27.2	3.0	0	0	3.6	0	0	0
Thrombocytopenia	12.6	2.6	0.2	0	2.0	0.4	0	0
Fever	10.4	0.8	0	0	2.8	0	0	0
Nausea	14.4	0.4	0	0	11.1	0	0	0
Bleeding	11.4	0.4	0	0.4	2.8	0	0	0
Voice changes	29.4	0.2	0	0	5.5	0	0	0
Weight loss	13.8	0	0	0	2.4	0	0	0

*Grade 5 drug-related adverse events: 1.0% in regorafenib arm *vs* 0% in placebo arm

Key drug-related treatment-emergent adverse events by subgroup

			Grade ≥3 adverse events (regorafenib group only), %				
		n	HFSR	Fatigue	Hypertens	Diarrhea	Rash/desq
Total		500	16.6	9.2	7.2	7.0	5.8
Age	<65	307	18.6	9.4	4.9	6.8	5.2
	≥65	193	13.5	9.8	10.9	7.8	6.7
Sex	Female	193	18.7	12.4	4.7	5.2	13.5
	Male	307	15.3	7.8	8.8	8.4	1.0
Race	Caucasian	389	13.1	9.8	7.2	7.8	6.7
	Asian	74	28.4	9.5	9.5	4.1	2.7
	Black	6	0	0	16.7	0	16.7
	Not known/other	31	35.5	9.7	0	9.7	0
ECOG PS	0	263	18.6	8.0	8.0	7.6	6.5
	1	237	14.3	11.4	6.3	6.7	5.1
Baseline kidney function	Moderately impaired*	21	19.0	9.6	9.5	14.3	4.8
	Normal/mildly impaired†	479	16.5	9.6	7.1	6.9	5.8
Baseline hepatic function	AST/ALT ≤1.5 × ULN	453	17.0	9.7	7.5	7.5	5.3
	AST/ALT >1.5 but ≤3 × ULN	44	13.6	9.1	4.5	4.5	11.4
	AST/ALT >3 × ULN	2	0	0	0	0	0

HFSR: hand-foot skin reaction; Hypertens: hypertension; Rash/desq: rash/desquamation; ECOG PS: Eastern Cooperative Oncology Group performance status; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal; estimated glomerular filtration rate *< or †≥60 ml/min/1.73 m^3

Summary of CORRECT results

- Updated survival data showed sustained OS benefit with regorafenib *vs* placebo:
  - **Median OS: 6.4 *vs* 5.0 months, respectively**
    - **HR=0.79, p=0.0038**
  - Benefit achieved across prespecified subgroups
- No new or unexpected safety findings:
  - Subgroup analysis shows few differences in the rate of drug-related adverse events between groups

Conclusions

- Regorafenib is the first oral multikinase inhibitor with proven activity in mCRC
- Regorafenib increases OS in patients with mCRC that has progressed following all current standard therapies
  - Benefit is sustained over time and across prespecified subgroups
- Side effects are tolerable and manageable in this patient population
- Regorafenib is a new potential standard of care for patients with chemorefractory mCRC

Thanks to the investigating centers and study participants

CORRECT lead investigators:

AUSTRALIA:	Philip Beale, Kathryn Field, Peter Gibbs, Nick Pavlakis, Timothy Price;
BELGIUM:	Eric Van Cutsem, Hans Prenen, Jochen Decaestecker, Alain Hendlisz, Yves Humblet, Marc Peeters, Jean-Luc Van Laethem;
CANADA:	Mary Mackenzie, Wilson Miller, Mark Rother, Rafal Wierzbicki, Asif Shaik, Scott Berry;
CHINA:	Jianming Xu;
CZECH REPUBLIC:	Vladimira Stahalova, Ilona Kocakova, Bohuslav Melichar, Eugen Kubala;
FRANCE:	Marc Ychou, Olivier Bouche, Thierry Andre, Antoine Adenis, Mohamed Hebbar, Olivier Dupuis, Jean-Francois Seitz, Laurent Mineur, Christian Borel;
GERMANY:	H.-J. Schmoll, Martin Becker, Claudio Denzlinger, Volker Heinemann, Meinolf Karthaus, Claus-Henning Koehne, Nicolas Ziegenhagen, Hendrik Kroening, Wolfgang Schepp, Tanja Trarbach, Michael Clemens, Gunnar Folprecht, Ulrich Hacker, Ralf-Dieter Hofheinz, Arndt Vogel;
HUNGARY:	Janos Szanto, Laszlo Thurzo;
ISRAEL:	Adi Shani, Eina Shaham-Shmueli, Alex Beny, Ayala Hubert, Sofia Man, Baruch Brenner;
ITALY:	Alberto Sobrero, Giacomo Carteni, Gabriele Luppi, Alfredo Falcone, Salvatore Siena, Alberto Zaniboni, Carlo Barone, Fortunato Ciardiello, Corrado Boni;
JAPAN:	Hideo Baba, Eishi Baba, Tadamichi Denda, Hirofumi Fujii, Junji Furuse, Etsuko Warita, Yoshito Komatsu, Nobuyuki Mizunuma, Tomohiro Nishina, Wataru Okamoto, Yasutsuna Sasaki, Hiroya Takiuchi, Kazuma Kobayashi, Hiroyuki Uetake, Takashi Ura, Yasuhide Yamada, Kensei Yamaguchi, Kentaro Yamazaki, Takayuki Yoshino, Hideyuki Mishima;
NETHERLANDS:	A. J. Gelderblom, D. H. Verheul;
SPAIN:	Josep Tabernero, Rocio Garcia-Carbonero, Carles Pericay Pijaume, Cristina Gravalos, Manuel Benavides, Javier Sastre, Jaime Feliu, Mercedes Martinez Villaca;
SWITZERLAND:	Arnaud Roth;
TURKEY:	Mustafa Benekli, Faruk Aykan;
USA:	Axel Grothey, Billy Clowney, Martin Hyzinski, Ali Khojasteh, Marc Saltzman, Heinz-Josef Lenz, Udit Verma, John Kugler, Jyotsna Fuloria, Kenneth Nahum, George Kim, Rex Mowat, Philip Stella, Martin Wiesenfeld, Brian Dicarlo, George Geils, Youram Nassir

The CORRECT trial was sponsored by Bayer HealthCare AG, Leverkusen, Germany