Phase III CORRECT trial of regorafenib in metastatic colorectal cancer (mCRC)

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On behalf of:

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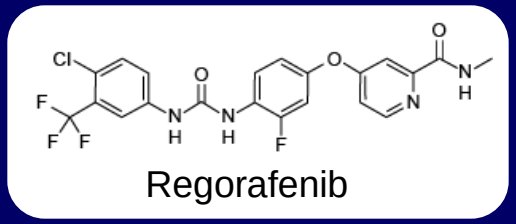
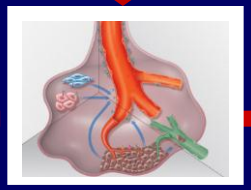
Metastatic CRC: a major problem

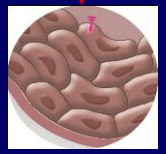
- Globally, 1.2 million new CRC cases and over 600,000 deaths each year[1,2]
- ≈ 50% of patients develop metastases[3,4]
- Current standard medical treatments include:[3,4]
  - Chemotherapy (fluoropyrimidines, oxaliplatin, irinotecan)
  - Monoclonal antibodies (bevacizumab, cetuximab or panitumumab)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

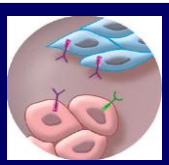
1. GLOBOCAN. Cancer fact sheets: colorectal cancer. 2008.
2. American Cancer Society. Cancer Facts and Figures 2012.
3. NCCN Guidelines. Colon cancer. v.2.2012.
4. Van Cutsem E *et al*. ESMO Guidelines 2010.

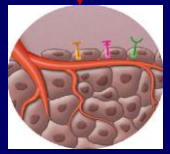
Regorafenib (BAY 73-4506), an oral multikinase inhibitor targeting multiple tumor pathways[1-3]











Inhibition of proliferation

KIT
PDGFR
RET

Inhibition of tumor microenvironment signaling

PDGFR-β
FGFR

Inhibition of neoangiogenesis

VEGFR1-3
TIE2

Biochemical 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)

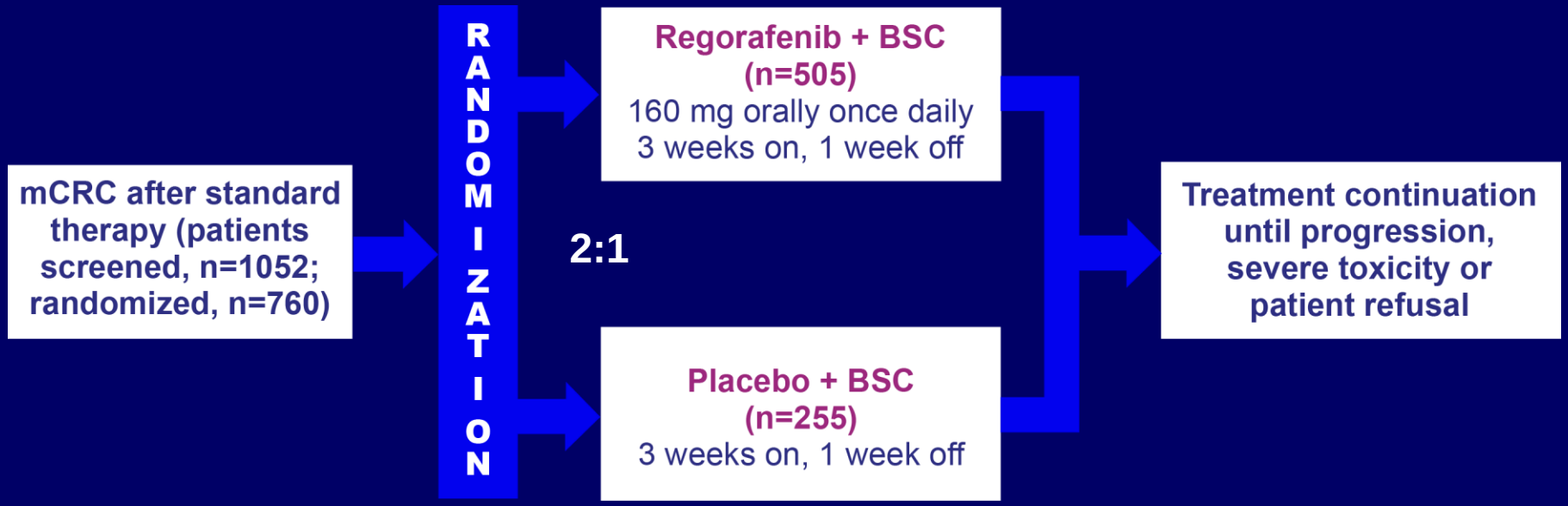
1. Wilhelm SM *et al. Int J Cancer* 2011.
2. Mross K *et al. Clin Cancer Research* 2012.
3. Strumberg D *et al. Expert Opin Invest Drugs* 2012.

Clinical rationale for regorafenib in mCRC: phase I experience[1,2]

- 38 patients with CRC:
  - Dose-escalation phase: n=15
    - Regorafenib doses ranging from 60 to 220 mg/day (3 weeks on, 1 week off)
  - Expansion phase: n=23
    - At recommended dose of 160 mg/day (3 weeks on, 1 week off)
- All treatment-related adverse events grade ≤3 apart from one grade 4 thrombocytopenia
  - Most common adverse events: skin toxicity (hand–foot skin reaction, rash), diarrhea, fatigue and voice change
- 27 patients evaluable for response:
  - Disease control rate (DCR): 74%
    - Partial response (PR): 4% (n=1); stable disease (SD): 70% (n=19)
  - Progression-free survival (PFS): median 107 days (95% CI, 66-161)
  - Decrease in tumor perfusion by dynamic contrast-enhanced magnetic resonance imaging

1. Strumberg D *et al. Br J Cancer* 2012.
2. Mross K *et al. Clin Cancer Research* 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
  - Stratification: prior anti-VEGF therapy, time from diagnosis of metastatic disease, geographical region
- Global trial: 16 countries, 114 centers
- Recruitment: May 2010 to March 2011

CORRECT endpoints

- Primary endpoint: overall survival (OS)
  - 90% power to detect 33.3% increase (hazard ratio [HR]=0.75), 1-sided overall α=0.025
  - Planned sample size: 690
  - Interim analyses:
    - ≈ 30% of events (for futility only)
    - ≈ 70% of events (for futility and efficacy)
- Secondary endpoints: PFS, overall response rate (ORR), DCR
- Tertiary endpoints: duration of response/SD, quality of life (QoL), PK, biomarkers

Patient eligibility: key inclusion criteria

- Histological or cytological documentation of adenocarcinoma of the colon or rectum
- Disease progression during/within 3 months after last administration of or intolerance to approved standard therapies, which had to include:
  - Fluoropyrimidine, oxaliplatin, irinotecan
  - Bevacizumab
  - Cetuximab or panitumumab (if KRAS wild-type)
- Measurable or nonmeasurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Age ≥18 years, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, life expectancy ≥3 months
- Adequate bone marrow, liver and renal function
- Signed informed consent

Patient eligibility: key exclusion criteria

- Previous or concurrent cancer (different site or histology) within 5 years before randomization
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study
- Cardiovascular dysfunction including:
  - Myocardial infarction within 6 months
  - Uncontrolled hypertension
  - Unstable or new-onset angina
- Arterial or venous thrombotic or embolic events within 6 months

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, %	White	77.6	78.8
	Black	1.2	3.1
	Asian	15.0	13.7
ECOG, %	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

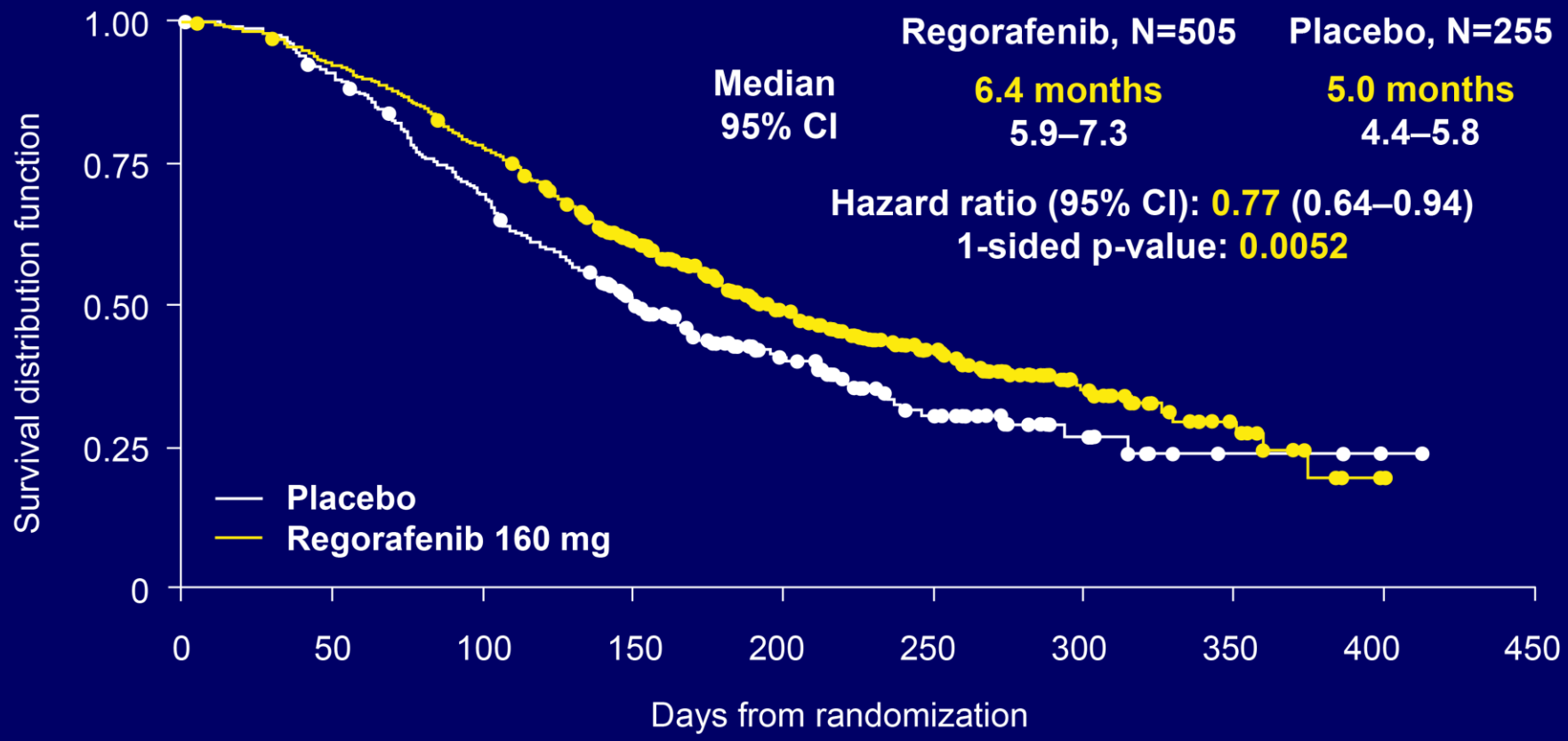
Baseline disease characteristics

		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

Overall survival (primary endpoint)

Primary endpoint met prespecified stopping criteria at interim analysis (1-sided p<0.009279 at approximately 74% of events required for final analysis)

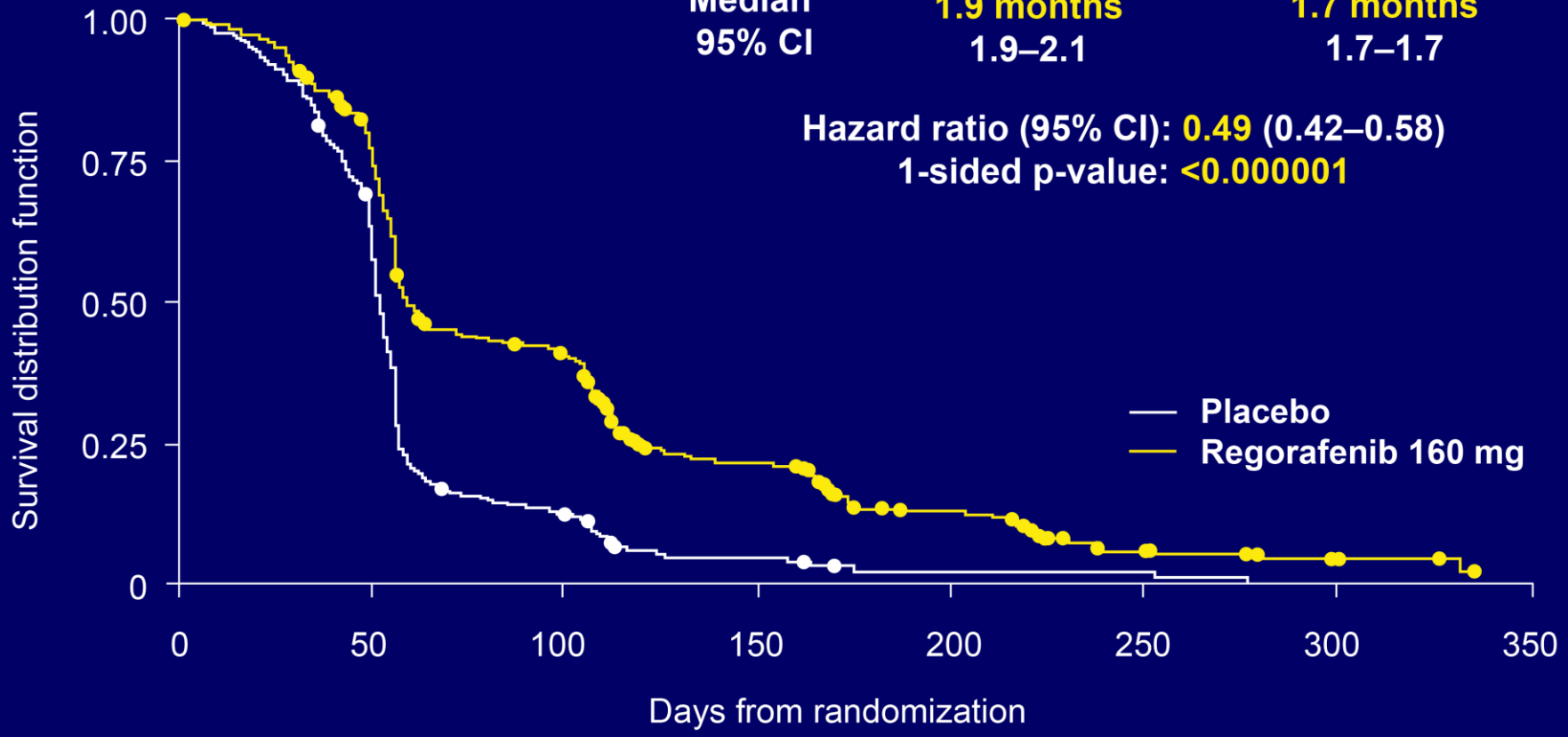


Progression-free survival (secondary endpoint)

Regorafenib significantly improves PFS compared to placebo

	Regorafenib, N=505	Placebo, N=255
Median	1.9 months	1.7 months
95% CI	1.9–2.1	1.7–1.7

Hazard ratio (95% CI): 0.49 (0.42–0.58)
1-sided p-value: <0.000001



Overall response and disease control rates (secondary endpoints)

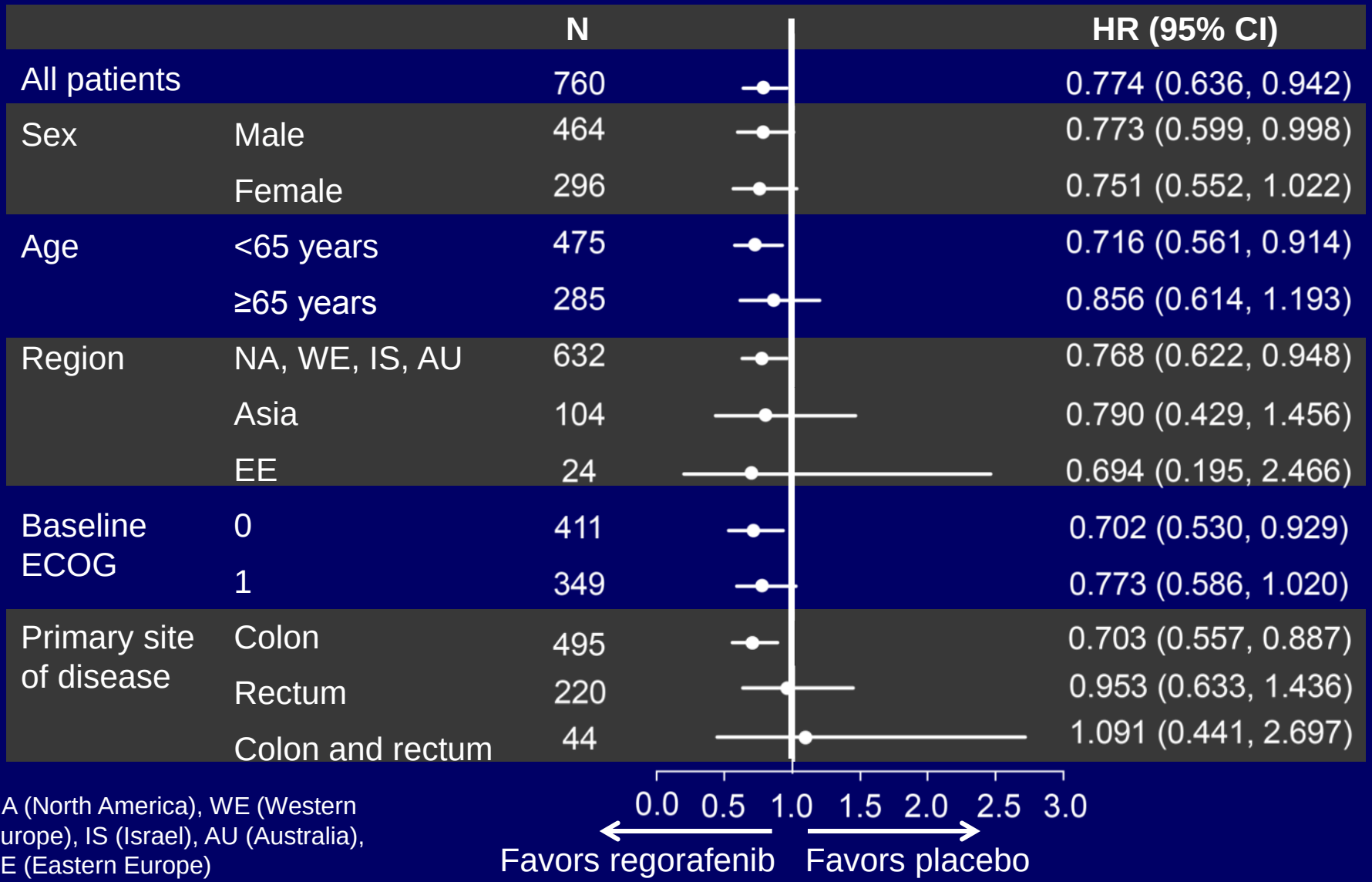
Regorafenib significantly improves DCR compared to placebo

Best response, %	Regorafenib N=505	Placebo N=255
Complete response	0	0
PR	1.0	0.4
SD	42.8	14.5
Progressive disease	49.5	80.0
DCR*	**41.0**	**14.9**

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

Subgroup analysis of overall survival

Regorafenib benefit *vs* placebo is achieved across subgroups

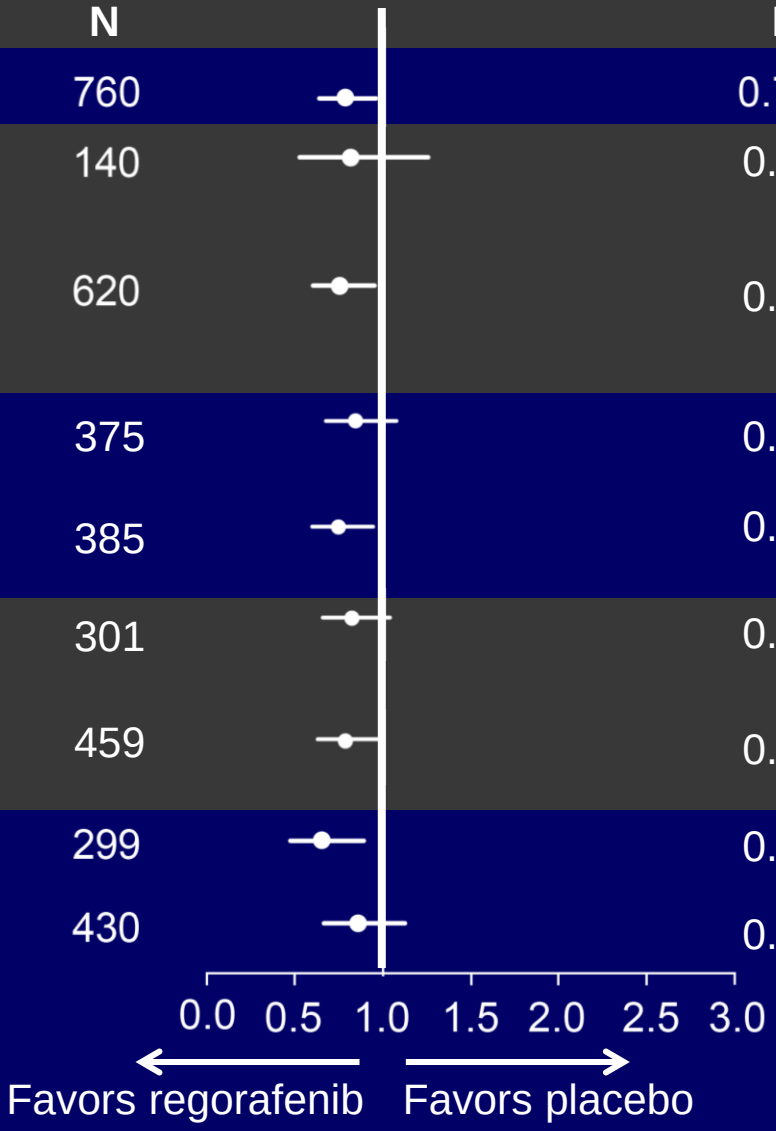


NA (North America), WE (Western Europe), IS (Israel), AU (Australia), EE (Eastern Europe)

Subgroup analysis of overall survival

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	301	0.709 (0521, 0.967)
	>3	459	0.804 (0.624, 1.038)
KRAS mutation status (historical)	N	299	0.653 (0.476, 0.895)
	Y	430	0.867 (0.670, 1.123)



F (fluoropyrimidine), Ox (oxaliplatin), Iri (irinotecan), Bev (bevacizumab)

Subgroup analysis of PFS

Regorafenib benefit *vs* placebo is achieved across subgroups

Subgroup	N	Hazard ratio (regorafenib/placebo)	
		Estimate	95% CI
All patients	760	0.494	0.419-0.582
Age			
< 65 years	475	0.418	0.340-0.514
≥ 65 years	285	0.651	0.496-0.855
Region			
NA, WE, IS, AU	632	0.500	0.418-0.599
Asia	104	0.433	0.277-0.679
Eastern Europe	24	0.576	0.199-1.664
Primary site of disease			
Colon	495	0.550	0.450-0.671
Rectum	220	0.454	0.332-0.620
Colon and rectum	44	0.348	0.163-0.745
Prior line of Tx			
≤ 3	301	0.523	0.404-0.676
>3	459	0.478	0.387-0.592
KRAS mutation			
N	299	0.475	0.362-0.623
Y	430	0.525	0.425-0.649

NA (North America), WE (Western Europe), IS (Israel), AU (Australia)

KRAS subgroup analysis

		Regorafenib N=505	Placebo N=255	HR (95% CI)
***KRAS* mutation, %**	No	40.6	36.9	NA
	Yes	54.1	61.6	NA
Median OS, months	*KRAS* wild-type	7.3	5.0	0.653 (0.476-0.895)
	KRAS mutant	6.2	5.1	0.867 (0.670-1.123)
Median PFS, months	*KRAS* wild-type	2.0	1.8	0.475 (0.362-0.623)
	KRAS mutant	1.9	1.7	0.525 (0.425-0.649)

- Regorafenib shows OS and PFS benefit in both KRAS-wild-type and KRAS-mutant subgroups
- KRAS mutational status was not prognostic nor predictive in the study population

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 AEs: 1.0% in regorafenib arm vs 0% in placebo arm

Health-related QoL analyses:
time-adjusted area under the curve

No significant difference in health-related QoL with regorafenib *vs* placebo

	Treatment group	Least-squares mean	(95% CI)
EORTC QLQ-C30	Placebo	58.13	(55.72, 60.53)
	Regorafenib	56.93	(54.79, 59.08)
EQ-5D index	Placebo	0.67	(0.64, 0.70)
	Regorafenib	0.67	(0.64, 0.70)
EQ-5D VAS	Placebo	61.84	(59.59, 64.09)
	Regorafenib	60.62	(58.62, 62.63)

VAS, visual analog scale

Summary of CORRECT results

- The study met its primary endpoint at the preplanned interim analysis
- Regorafenib *vs* placebo:
  - **OS: 6.4 *vs* 5.0 months, HR=0.77, p=0.0052**
    - Crossed prespecified boundary (1-sided p<0.009279)
  - PFS: 1.9 *vs* 1.7 months, HR=0.49, p<0.000001
  - DCR (PR + SD): 41.0% *vs* 14.9%, p<0.000001
- Subgroup analyses:
  - Regorafenib showed OS and PFS benefit across prespecified subgroups
  - Efficacy of regorafenib was independent of KRAS mutation status
- No new or unexpected safety findings:
  - Most frequent grade 3 events related to regorafenib were hand–foot skin reaction, fatigue, diarrhea, hypertension and rash

Conclusions

- Regorafenib is the first oral multikinase inhibitor with proven activity in mCRC
- Regorafenib increases OS and PFS in patients with mCRC who have failed current standard therapies
  - Benefit is shown across prespecified subgroups (including KRAS)
- Side effects are 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

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