Results from the large, open-label phase 3b CONSIGN study of regorafenib in patients with previously treated metastatic colorectal cancer (mCRC)

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Oral # 140O

ESMO Asia 2015 Congress, December 18–21, 2015, Singapore

Disclosures ESMO Asia 2015
Eric Van Cutsem

- I have received research funding from Bayer HealthCare
- The CONSIGN (NCT01538680) trial was sponsored by Bayer HealthCare Pharmaceuticals

Background

- Regorafenib is an oral multikinase inhibitor that blocks the activity of multiple protein kinases involved in angiogenesis, oncogenesis, and the tumor microenvironment[1]
- Regorafenib was approved for patients with previously treated mCRC based on the results of the phase 3 CORRECT trial (NCT01103323; N=760):[2]
  - Median OS was 6.4 months with regorafenib vs 5.0 months with placebo (HR 0.77 [95% CI 0.64, 0.94]; one-sided P=0.0052)
  - Median PFS was 1.9 months with regorafenib vs 1.7 months with placebo (HR 0.49 [95% CI 0.42, 0.58]; one-sided P<0.0001)
  - The most common grade ≥3 treatment-emergent regorafenib-related adverse events were hand–foot skin reaction, fatigue, diarrhea, hypertension, and rash or desquamation
- The phase 3b CONSIGN trial (NCT01538680) was designed to further characterize the safety of regorafenib while allowing patients with mCRC to receive regorafenib prior to market authorization

HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

1. Wilhelm SM, et al. *Int J Cancer* 2011;129:245–255. 2. Grothey A, Van Cutsem E, et al. *Lancet* 2013;381:303–312.

Objectives

- To provide access to regorafenib prior to market authorization for patients with mCRC who had failed standard therapies
- To further characterize the safety of regorafenib in a large cohort of patients with treatment-refractory mCRC
- To estimate PFS (the only efficacy variable assessed)

Methods

CONSIGN: Open-label, phase 3b study of regorafenib in previously treated mCRC

- **mCRC**
- **Progression during/ within 3 months of approved standard therapies***
- **ECOG PS 0–1**
- **N=2872**

→ **Regorafenib (oral)** **160 mg once daily 3 weeks on/ 1 week off** → **Treatment until PD (or longer at the discretion of the investigator)** → **Safety follow-up 30 days after last dose**

Primary endpoint: Safety

Efficacy endpoint: PFS (investigator-assessed)†

- Prospective, single-arm
- Conducted at 186 sites across 25 countries; planned enrollment approximately 3000 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

*Must have included fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and cetuximab/panitumumab (if *KRAS* wild-type). †Per investigator using radiological and/or clinical tumor assessment according to local standards (tumor measurements performed at intervals and with methods that comply with each institution's best standard of care). ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PS, performance status.

Results

- A total of 2872 patients were assigned to treatment with regorafenib between April 2012 and December 2013
- Safety analysis includes 2864 patients who received treatment
- The cut-off date for this analysis was January 2, 2015
- As of April 7, 2015, 10 patients remained on treatment at 10 sites across 6 countries

Baseline characteristics

	Regorafenib (N=2872)
Median age, years (range)	62 (19–89)
Male, %	59
Race, %	
White	83
Black	2
Asian	1
Other/not reported	15
Median body mass index, kg/m^2	26
Primary site of disease, %	
Colon	64
Rectum	28
Colon and rectum	8
ECOG PS, %	
0/1	47/53
KRAS mutation status, %	
Wild-type	45
Mutant	51
Unknown	4
Prior treatment regimens on or after diagnosis of metastatic disease, %	
0	<1
1–2	26
3	27
≥4	46

ECOG PS, Eastern Cooperative Oncology Group performance status.

Treatment duration and dosing

	Regorafenib (n=2864)
Duration of treatment*, months	
Median (range)	2.5 (0–30)
Mean (SD)	3.6 (3.8)
Median number of cycles* (range)	3 (1–33)
Patients who started	
≥3 cycles, n (%)	1645 (57)
≥6 cycles, n (%)	606 (21)
≥9 cycles, n (%)	286 (10)
Daily dose, mg	
Median (range)	160 (74–166)
Mean (SD)	146 (19)
Mean percentage of planned dose (SD)	75 (20)

*Includes time off drug/interruptions.
SD, standard deviation.

Treatment modifications

	Regorafenib (n=2864)
Any treatment modification*, n (%)	2497 (87)
Treatment interruptions/delays, n (%)	2401 (84)
Duration of interruption/delay, days†	
Median (range)	5.0 (1–54)
Mean (SD)	5.8 (4.8)
Interruption/delay >5 days, n (%)	1724 (60)
Dose reductions, n (%)	1394 (49)
Duration of dose reduction, days†	
Median (range)	14.0 (1–45)
Mean (SD)	13.0 (7.4)
Dose reduction >5 days, n (%)	1210 (42)

*Modifications include reductions, interruptions/delays, and re-escalations. †Based on the total number of events.
SD, standard deviation.

Treatment-emergent adverse events*†

n (%)	Regorafenib (n=2864)	
	Treatment-emergent drug-related	Treatment-emergent regardless of relation to study drug
Any grade	2613 (91)	2847 (99)
Grade ≥3	1629 (57)	2294 (80)
Serious	251 (9)	1251 (44)
Grade 5	13 (<1)	404 (14)

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

Treatment-emergent adverse events in CORRECT and CONSIGN*

%	CORRECT		CONSIGN
	Placebo (n=253)	Regorafenib (n=500)	Regorafenib (n=2864)
Any grade, **drug-related**	61	93	91
Grade ≥3	14	55	57
Serious	4	12	9
Grade 5	0	1	<1
Any grade, **regardless of relation to study drug**	97	100	99
Grade ≥3	49	78	80
Serious	40	44	44
Grade 5	15	13	14

*Adverse events were graded using the NCI-CTC for Adverse Events version 3.0 for CORRECT and version 4.0 for CONSIGN.

Treatment-emergent adverse events leading to treatment modifications*†

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

*During treatment or up to 30 days post treatment. †Adverse events were graded using the NCI-CTC for Adverse Events version 4.0.
‡Modifications include reductions, interruptions/delays, and re-escalations.
NE, not evaluated.

Treatment-emergent drug-related grade ≥3 adverse events occurring in ≥5% of patients*

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)

*Adverse events were graded using the NCI-CTC for Adverse Events version 4.0.

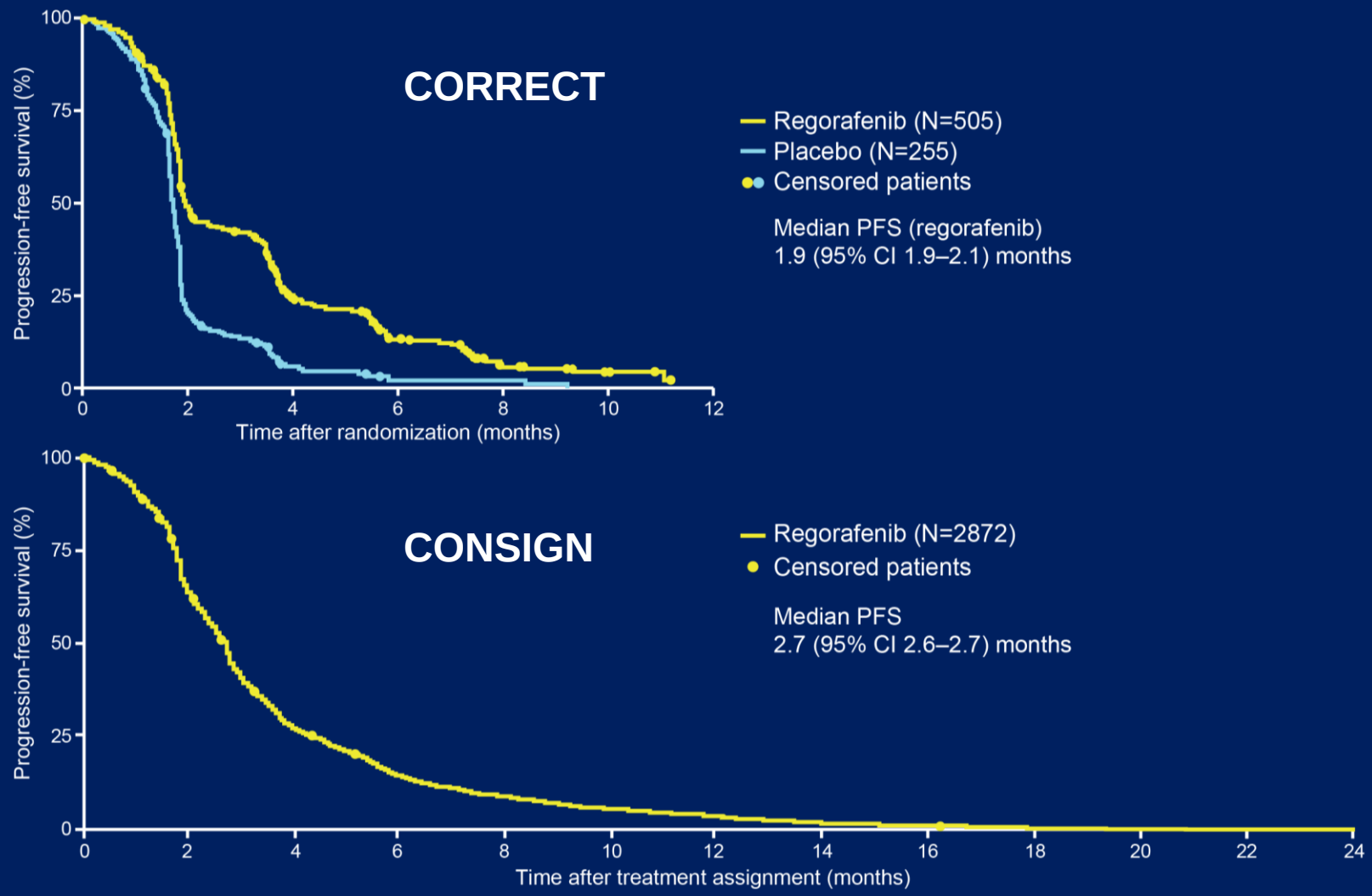
Treatment-emergent grade ≥3 hepatic and hematologic laboratory values of interest, regardless of relation to study drug

	Regorafenib (n=2864)	
	n/N	%
Blood bilirubin increased	374/2815	13
AST increased	193/2808	7
ALT increased	156/2809	6
Anemia	101/2786	4
Thrombocytopenia	57/2788	2
Neutropenia	23/2357	1

- One non-fatal case of severe drug-induced liver injury* was identified by ongoing monitoring

N, number of patients with measurements for the given parameter.
*According to International DILI Working Group criteria in Aithal GP, et al. *Clin Pharmacol Ther* 2011;89:806–815.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

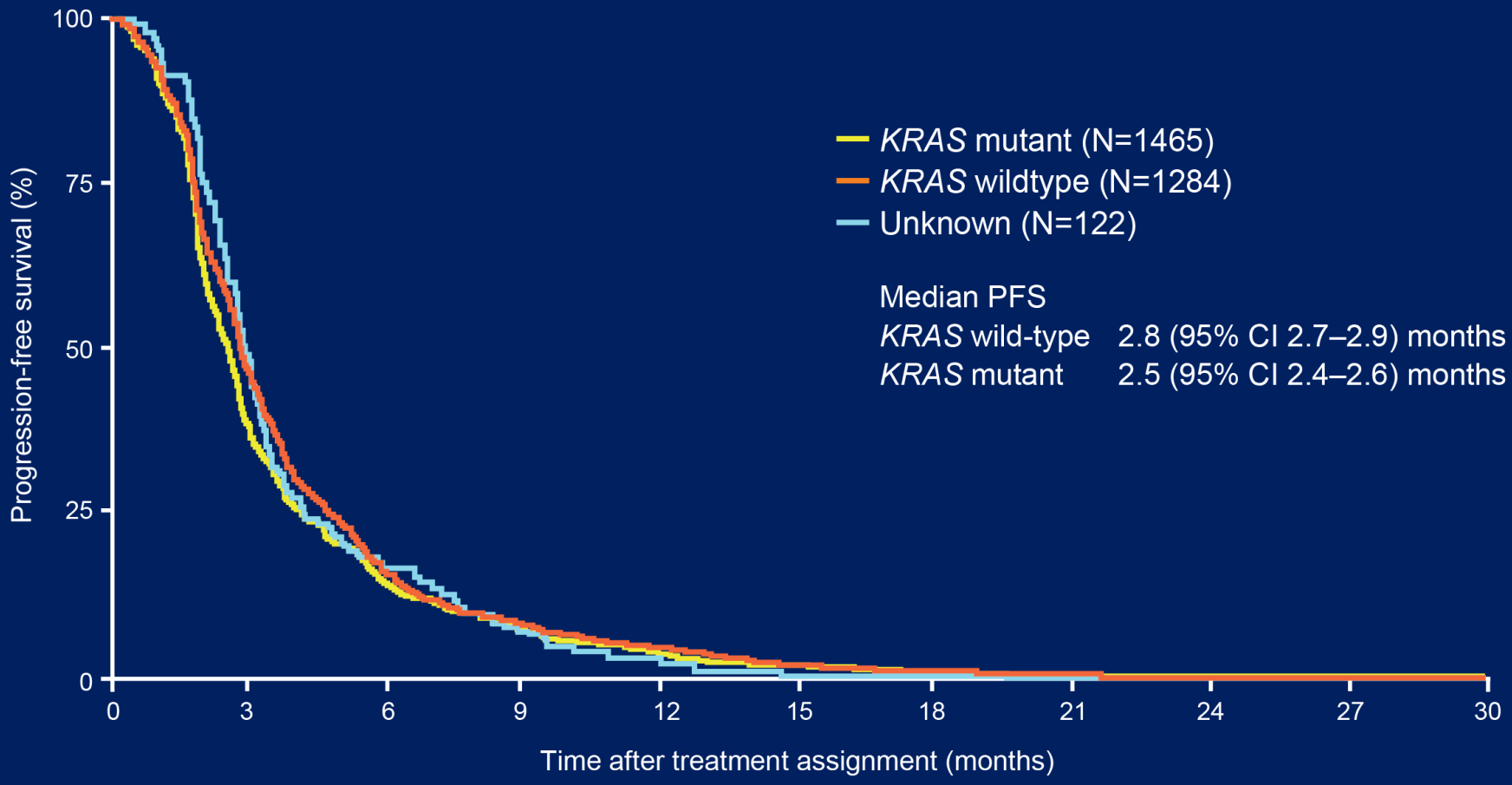
Progression-free survival (PFS)*



*In CONSIGN, intervals for radiological assessments were not pre-determined as they were in CORRECT. PFS in CONSIGN was by investigator assessment using radiological and/or clinical tumor assessment according to local standards; tumor assessments were not as rigorous as in a confirmatory study with a PFS endpoint.

Grothey A, Van Cutsem E, *et al. Lancet* 2013;381:303–312.

PFS by *KRAS* mutation status



Conclusions

- In this large, prospective study in patients with mCRC who have been previously treated with standard therapy, the adverse event profile of regorafenib was consistent with that reported in the randomized phase 3 CORRECT trial[1]
- PFS was in the range of that reported with regorafenib in this setting and was similar across *KRAS* wild-type and mutant subgroups
- The rate of dose reductions and interruptions highlights the importance of optimal patient selection, adverse event management, and dose modification

1. Grothey A, Van Cutsem E, et al. *Lancet* 2013;381:303–312.

Thanks to the investigating centers and study participants (CONSIGN)

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AUSTRALIA: Philip Beale, Nick Pavlakis, Jeanne Tie, Peter Gibbs, Timothy Price; AUSTRIA: Wolfgang Eisterer, Werner Scheithauer, Hellmut Samonigg, Josef Thaler; BELGIUM: Yves Humblet, Jochen Decaestecker, Eric Van Cutsem, Alain Hendlisz, Marc Peeters, Jean-Luc Van Laethem; CANADA: Jeffrey Rothenstein, Scott Berry, Mark Rother, Adrian Langleben, Felix Couture, Andrew Scarfe, Scot Dowden, Wendy Lam; CZECH REPUBLIC: Vladimira Stahalova, Ilona Kocakova; DENMARK: René Kroejgaard Olesen, Lone Noergaard Petersen; FINLAND: Riikka Huuhtanen, Tuomo Alanko; FRANCE: Antoine Adenis, Aziz Zaanan, Caroline Petorin, Christian Borel, Denis Smith, Eric Francois, Jean Baptiste Bachet, Jean-François Seitz, Jean-Yves Douillard, Laurent Mineur, Marc Ychou, Mohamed Hebbar, Olivier Bouché, Olivier Dupuis, Rosine Guimbaud, Thierry André; GERMANY: Andrea Heider, Andreas Block, Arndt Vogel, Claus-Henning Koehne, Dirk Strumberg, Friedrich Overkamp, Gunnar Folprecht, Hans-Joachim Schmoll, Hendrik Kroening, Henning Schulze-Bergkamen, Jan Kuhlmann, Klaus Mross, Martin Becker, Meinolf Karthaus, Michael Clemens, Michael Geissler, Ralf-Dieter Hofheinz, Stefan Kasper, Thomas Seufferlein, Thomas Zander, Ullrich Graeven, Ulrich Keilholz, Volker Heinemann, Wolff Schmiegel, Wolfgang Schepp; GREECE: Epaminondas Samantas, Vassilis Georgoulias; HUNGARY: Gyorgy Bodoky; IRELAND: Seamus O'Reilly, Sean Raymond McDermott; ISRAEL: Alex Beny, Ayala Hubert, Baruch Brenner, Ravit Geva, Sofia Man; ITALY: Alberto Sobrero, Alberto Zaniboni, Alfredo Falcone, Antonio Russo, Armando Santoro, Carlo Barone, Corrado Boni, Evaristo Maiello, Fortunato Ciardiello, Francesco Di Costanzo, Gabriele Luppi, Giacomo Cartenì, Maria Di Bartolomeo, Salvatore Siena, Stefano Cascinu, Vittorina Zagonel; MEXICO: Carlos Hernandez, Fidel Huitzil, Froylan Lopez, Gabriel Tellez, German Calderillo, Maria Enriquez, Paulino Alfaro, Rafael Rodriguez, Raquel Gerson; NETHERLANDS: André Johan Gelderblom, C.J.A. Punt, Henk Verheul; NORWAY: Rune Smaaland, Tormod Kyrre Guren; POLAND: Marek Wojtukiewicz, Piotr Tomczak; PORTUGAL: Anabela Sá, Cristina Sarmento; RUSSIA: Boris Berdov, Georgy Manikhas, Irina Davidenko, Marina Sekacheva, Nadezhda Mikhailova, Vadim Shirinkin, Vladimir Moiseenko; SPAIN: Carles Pericay, Carmen Guillén, Cristina Nadal, Enrique Aranda, Fernando Rivera Herrero, Jaime Feliu Batle, Javier Sastre, Jose Luis Manzano, Josep Tabernero, Laura Lema, Manuel Benavides, Manuel Valladares, Maria José Safont, Mercedes Martínez Villacampa, Pilar García Alfonso, Rocio Garcia Carbonero; SWEDEN: Maria Albertsson, Peter Nygren; SWITZERLAND: Andreas Wicki, Anna Dorothea Wagner, Arnaud Roth, Martin Berger, Panagiotis Samaras, Roger von Moos; UNITED KINGDOM: Anne Thomas, Mark Saunders; USA: Ahmed Zakari, Alec Goldenberg, Ali Khojasteh, Allen Cohn, Amit Panwalker, Andre Liem, Andrew Pippas, Andrew Poklepovic, Billy Clowney, Bobby Wilkerson, Brad Somer, Brian Mannion, Catherine Chodkiewicz, Charles Henderson, Crystal Denlinger, Dale Shepard, Darren Sigal, Deborah Wilbur, Donald Wender, Fadi Braiteh, Francis Arena, Gamini Soori, Gazala Khan, George Geils, Gina Vaccaro, Heinz-Josef Lenz, Howard Hochster, J Stuart Salmon, J. Marc Pipas, John Marshall, Jordan Berlin, Joseph Pizzolato, Jyotsna Fuloria, Lloyd Shabazz, Maged Khalil, Manish Shah, Marc Saltzman, Marisa Siebel, Mark Taylor, Navkiranjit Gill, Peter Enzinger, Peter Kozuch, Philip Gold, Philip Philip, Philip Stella, Rex Mowat, Ritesh Rathore, Robert Dichmann, Sanjay Goel, Tannaz Armaghany, Theresa Ryan, Thomas Cartwright, Vincent Chung, Yull Arriaga

The CONSIGN trial was sponsored by Bayer HealthCare Pharmaceuticals.