ESMO Open Cancer Horizons

Radiological imaging markers predicting clinical outcome in patients with metastatic colorectal carcinoma treated with regorafenib: post hoc analysis of the CORRECT phase III trial (RadioCORRECT study)

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To cite: Ricotta R, Verrioli A, Ghezzi S, *et al*. Radiological imaging markers predicting clinical outcome in patients with metastatic colorectal carcinoma treated with regorafenib: post hoc analysis of the CORRECT phase III trial (RadioCORRECT study). *ESMO Open* 2017;**1**:e000111. doi:10.1136/esmoopen-2016-000111

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Received 07 October 2016
Revised 02 December 2016
Accepted 06 December 2016

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ABSTRACT

Objective To identify imaging markers predicting clinical outcomes to regorafenib in metastatic colorectal carcinoma (mCRC).

Methods The RadioCORRECT study is a post hoc analysis of a cohort of patients with mCRC treated within the phase III placebo-controlled CORRECT trial of regorafenib. Baseline and week 8 contrast-enhanced CT were used to assess response by RECIST 1.1, changes in the sum of target lesion diameters (ΔSTL), lung metastases cavitation and liver metastases density. Primary and secondary objectives were to develop ex novo univariable and multivariable models to predict overall survival (OS) and progression-free survival (PFS), respectively.

Results 202 patients were enrolled, 134 (66.3%) treated with regorafenib and 68 (33.7%) with placebo. In the univariate analysis, PFS predictors were lung metastases cavitation at baseline (HR 0.50, 95% CI 0.27 to 0.92, p=0.03) and at week 8 (HR 0.58, 95% CI 0.36 to 0.93, p=0.02). Baseline cavitation (HR 0.23, 95% CI 0.08 to 0.66, p=0.007), RECIST 1.1 (HR 0.23, 95% CI 0.14 to 0.4, p <0.0001) and ΔSTL (HR 1.16, 95% CI 1.06 to 1.27, p=0.002) predicted OS. We found an increase of 9% of diameter as the best threshold for discriminating OS (HR 2.64, 95% CI 1.61 to 4.34, p <0.001). In the multivariate analysis, baseline and week 8 cavitation remained significant PFS predictors. Baseline cavitation, RECIST 1.1 and ΔSTL remained predictors of OS in exploratory multivariable models. Assessment of liver metastases density did not predict clinical outcome.

Conclusions RECIST 1.1 and ΔSTL predict favourable outcome to regorafenib. In contrast to liver metastases density that failed to be a predictor, lung metastases

Key questions

What is already known about this subject?

- Presently, no molecular markers of sensitivity or resistance to regorafenib are validated in clinical practice. Since a rapidly growing body of knowledge suggests that tumour response to multikinase inhibitors may not be adequately described by RECIST, we investigated whether new radiological parameters can predict outcomes to regorafenib in metastatic colorectal carcinoma (mCRC).

What does this study add?

- The RadioCORRECT study showed that RECIST 1.1 and change in the sum of target lesion diameters (ΔSTL) assessed by week 8 contrast-enhanced CT predict overall survival (OS) to regorafenib in mCRC. The evaluation of liver metastases density failed to predict clinical outcome, while the presence of lung metastases cavitation is associated with favourable outcome to regorafenib.

How might this impact on clinical practice?

- RECIST 1.1 remains an adequate method to assess response to regorafenib since it is associated with OS. The evaluation of tumour size as a continuous variable, expressed as ΔSTL, supports continuation of treatment in those patients with stable disease, without any tumour shrinkage. We identify lung metastases cavitation as a new imaging marker, which deserves consideration.

cavitation represents a novel radiological marker of favourable outcome that deserves consideration.

INTRODUCTION

Regorafenib prolongs progression-free survival (PFS) and overall survival (OS) in patients with pretreated metastatic colorectal carcinoma (mCRC).[1 2] The multikinase activity of regorafenib makes it difficult to identify molecular markers of sensitivity or resistance.[3] In the era of targeted therapies, a rapidly growing body of knowledge has generated criticisms regarding timing and parameters for cancer response evaluation. Preliminary studies suggest that radiological assessment of early tumour shrinkage and changes in tumour density are potential predictive markers to targeted agents.[4–6] Regorafenib induces tumour shrinkage, although commonly not reaching partial response (PR) by RECIST. We also noticed that regorafenib causes reduction in tumour density of liver metastases and cavitation of pulmonary metastases; the latter appears to be associated with a reduced risk of progressive disease (PD).[7–9] Based on these observations, we hypothesised that these radiological changes likely mirror a biological effect that parallels clinical outcome. Therefore, we tested whether changes in tumour characteristics detected by contrast-enhanced CT (CECT) would be a radiological imaging marker predicting clinical outcomes.

PATIENTS AND METHODS

RadioCORRECT is an investigator-initiated post hoc analysis of patients from the phase III placebo-controlled CORRECT trial (NCT 01103323), which enrolled 760 patients with refractory mCRC randomly assigned (2:1) to receive regorafenib (n=505) or placebo (n=255).[1] The RadioCORRECT study was approved by the Institutional Review Board at the coordinating centre (Grande Ospedale Metropolitano Niguarda, Milan, Italy) and at participating institutions, and was conducted in accordance with Declaration of Helsinki. Patients were collected from the 13 highest recruiting institutions (four Italy, four France, three Belgium, one Spain, one the USA) and were included whether they had their first post-treatment evaluation by CECT at week 8.

Primary and secondary objectives were to develop univariable and multivariable models for patients treated with regorafenib by testing the following early radiological parameters for prediction of OS and PFS, respectively: response by RECIST 1.1 at week 8; change in the sum of target lesion diameters (ΔSTL) at week 8; cavitation of lung metastases at baseline and at week 8; tumour density of liver metastases at baseline and at week 8.

RADIOLOGICAL METHODS

Participating institutions provided baseline and week 8 CECT images of the chest, abdomen and pelvis. Tumour response by RECIST 1.1, sum of target lesion diameters (STL), PFS and OS were retrieved from the CORRECT database. The cut-off of this data was 21 July 2011 as reported in the final analysis of the CORRECT trial.[1] Cavitation of lung metastases and tumour density of liver metastases were analysed at the coordinating centre by two experienced radiologists who were blinded to patient treatment and outcomes. Cavitation was assessed in a consensus reading session. At baseline CECT, cavitation was defined as the presence of an air-filled cavity ≥10% of the maximum diameter in one or more lung metastasis ≥10 mm, while at week 8 CECT as de novo onset or as an increase of a pre-existent cavitation. Tumour density of liver metastases was evaluated in two separate reading sessions and expressed in Hounsfield units (HU) with SD (σ). Measurements were assessed in the portal venous phase by drawing a region of interest (ROI) around the margins of the lesions, excluding necrotic areas. These ROIs were then analysed by week 8 CECT to detect any variation in density. We considered each one of the lesions reported in the CORRECT trial. Tumour density (μ) and σ were analysed separately. When two liver metastases were present, μ and σ were summarised by the mean value. The percentage change from baseline at week 8 in μ (Δμ) and σ (Δσ) was calculated as follows: [(week 8 value - baseline value) / baseline value] × 100.

STATISTICAL METHODS

The Cox regression model was the unique statistical tool used for the development of PFS and OS predictive models; the HR was used as the population parameter.[10–12] For analysis of continuous parameters, the ratio between week 8 and baseline values (Ra) was computed for each patient; the ratio between Ra for regorafenib and placebo (RR) was estimated by fitting a linear regression model to observed Ra values on a log scale. The t-statistic was used to test H_0: log RR=0. For categorical parameters, Fisher's exact test was used.

Survival functions were estimated using the Kaplan-Meier method. Baseline covariate distributions, radiological parameters and clinical outcomes were summarised using descriptive statistics (median, IQR and range for continuous variables, absolute and percentage frequencies for categorical variables).

Sequential analytical procedures applied for predictive models

Step I: screening predictors

For each predictor, a main effect was mandatory; the Wald test statistic was used to test H_0: log HR=0; all statistical tests were two-sided and statistical significance was detected at the 5% probability level; a p-value >0.05 stopped further research on the predictor.

Step II: assessment of model fit and development of univariable PFS predictive models

IIa. In order to test the linearity assumption for a continuous predictor, a restricted cubic spline function was added to each model successfully evaluated in step I;

knots were defined considering the percentile distribution respectively of the predictor; Akaike's information criterion (AIC) was used for a data-based choice of the number of knots; a formal test (refer to R function anova() inside the R rms package) was performed at the 0.05 significance level to detect deviation from linearity.
IIb. In order to test graphically the proportional hazard (PH) assumption and to determine a functional form yielding linearity, the log HR function (and 95% confidence band) was plotted; logarithmic and polynomials were considered as interesting transformations; the model maximizing AIC was the best 'for the money'; the Grambsch-Therneau test was performed in order to test formally the PH assumption.
IIc. In order to identify the best thresholds for a continuous predictor, the CART methodology was applied to each model successfully evaluated in step I; the regression trees were generated through the R rpart package; each tree was pruned back in order to avoid data overfitting; the tree size that minimised the cross-validated error was chosen; at least one threshold was mandatory.

Step III: developing multivariable predictive models

All identified predictors, time-interaction terms, non-linear terms and linear interactions were introduced in a full model; a backward elimination Cox regression procedure at 0.20 level was run to identify the strongest predictors.

Step IV: performance of predictive models

The discriminatory ability of the identified univariable and multivariable Cox regression models was assessed by the Harrell's C-index. Apart from backward selection, predictive models were developed using the R software, version 3.2.3. Backward selection for the multivariable Cox regression models was performed using the SAS software (SAS Institute, Cary, NC, USA), version 9.2.

RESULTS

Overall, 202 patients were analysed (see online supplementary figure S1). Patient characteristics are reported in table 1. At baseline, the STL was 91.5 mm (range 10–344) for regorafenib and 88 mm (range 10–237) for placebo. At a median follow-up of 8.8 months for regorafenib (IQR 7.2–10.6) and 8.2 months for placebo (IQR 6.3–9.4), the median PFS was 3.2 months (95% CI 1.9 to 3.5, IQR 1.8–5.5) and 1.7 months (95% CI 1.7 to 1.8, IQR 1.6–1.9), respectively (HR 0.43, 95% CI 0.31 to 0.59, p <0.001). Median OS was 9.5 months (95% CI 7.2 to 10.8, IQR 4.9–NR) and 6.6 months (95% CI 5.4 to 7.8, IQR 3.7–NR) for regorafenib and placebo (HR 0.67, 95% CI 0.45 to 1.01, p=0.05). At the time of the analysis, PFS and OS events were reached in 119/134 (88.8%) and 65/134 (48.5%) patients in the regorafenib group and in 65/68 (95.6%) and 39/68 (57.3%) patients in the placebo group.

ASSESSMENT OF RADIOLOGICAL PARAMETERS IN THE OVERALL POPULATION

RECIST 1.1 and ΔSTL

Among the 199 patients evaluable for dimensional response, the disease control rate (DCR) was 53.4% (70/131) and 20.6% (14/68) in patients treated with regorafenib and placebo (p <0.001). No PR to regorafenib was reported. Median ΔSTL was 4% (IQR −3.8 to 16.4) and 21% (IQR 5.1–40.4%) in the regorafenib and placebo groups (RR 0.89, 95% CI 0.84 to 0.95, p <0.001), respectively (see online supplementary figure S2).

Cavitation of lung metastases

At baseline, cavitation was found in 18/88 (20.4%) and in 3/43 (6.9%) patients treated with regorafenib and placebo (p=0.07). Some examples of cavitation are displayed in figure 1. At week 8, cavitation was found in 36/88 (40.9%) and 0/43 (0%) patients treated with regorafenib and placebo, respectively (p <0.001). Overall, 24/70 (34.3%) patients had de novo cavitation and 12/18 (66.7%) had an increase of a pre-existing cavitation (p=0.002). Week 8 cavitation was associated with RECIST 1.1 response. In the regorafenib group, DCR was 69.7% (23/33) and 42.3% (22/52) in patients with and without cavitation at week 8 (p=0.01) and 66.7% (12/18) versus 49.2% (33/67) in patients with and without baseline cavitation (p=0.29). In the subgroup with baseline cavitation, the DCR was 91.7% (11/12) and 16.7% (1/6) in patients with or without cavitation increase at week 8 (p=0.004). However, the small number of patients with cavitated metastases at baseline limits the interpretation of data. In the subgroup without baseline cavitation, the DCR was 57.1% (12/21) and 45.6% (21/46) in patients with or without cavitation onset at week 8 (p=0.44).

Density of liver metastases

At baseline, median μ for regorafenib and placebo was 59 HU (range 19–108) and 51 HU (range 26–92) versus 58 HU (range 24–110) and 52 HU (range 22–88) as assessed by radiologists A and B, respectively. Median σ for regorafenib and placebo was 17 HU (range 9–38) and 18 HU (range 7–27) versus 18 HU (range 9–40) and 19 HU (range 9–30) according to radiologists A and B, respectively. At week 8, the Δμ for regorafenib and placebo was −33% (IQR −44 to −20) and −15% (IQR −21.8 to 0.3) as assessed by radiologist A (RR 0.79, 95% CI 0.71 to 0.88, p <0.001) versus −29% (IQR 41 to −19) and −12% (IQR −19 to −2) as assessed by radiologist B (RR 0.78, 95% CI 0.70 to 0.86, p <0.001). The Δσ for regorafenib and placebo was −11% (IQR −21 to −5) and 7% (IQR −7.1 to 32.3) according to radiologist A (RR 0.81, 95% CI 0.73 to 0.90, p <0.001) versus −11% (IQR −21 to −4) and 6% (IQR −9 to −31) according to radiologist B (RR 0.85, 95% CI 0.79 to 0.92, p <0.001). Bland-Altman plots showed good inter-observer agreement (see online supplementary figure S3).

SURVIVAL IN PATIENTS TREATED WITH REGORAFENIB

Progression-free survival

Table 2 summarises the results of univariate analysis. RECIST response and ΔSTL were excluded from this analysis because they define PFS. Baseline cavitation (HR 0.50, 95% CI 0.27 to 0.92, p=0.03; Harrell's C-index, 0.54) and week 8 cavitation (HR 0.58, 95% CI 0.36 to 0.93,

Table 1 Patient characteristics

	Treatment N (%)	
	Placebo	**Regorafenib**
All cases	68 (33.7)	134 (66.3)
Age, median, years	63.6	59.6
Sex		
Male	44 (64.7)	76 (56.7)
Female	24 (35.3)	58 (43.3)
ECOG performance status		
0	38 (55.9)	82 (61.2)
1	30 (44.1)	52 (38.8)
KRAS status		
Wild type	25 (38)	59 (48)
Mutated	41 (62)	65 (52)
Missing	2 (3)	10 (7)
Previous treatment with bevacizumab		
Yes	68 (100.0)	134 (100.0)
More than three lines before randomisation		
No	36 (52.9)	57 (42.5)
Yes	32 (47.1)	77 (57.5)
Time from M1 diagnosis to randomisation		
Median, years	2.3	2.7
Q1	1.5	1.7
Q3	3.8	3.8
Site of target lesions		
Liver	38 (55.9)	92 (68.7)
Target lesions, no.		
1	14 (37.8)	30 (33.0)
2	23 (62.2)	61 (67.0)
Missing	1 (2.6)	1 (1.1)
Lung	43 (63.2)	88 (65.7)
Target lesions, no.		
1	19 (45.2)	28 (32.2)
2	23 (54.8)	59 (67.8)
Missing	1 (2.3)	1 (1.1)
Other sites		
Lymphnode	8 (30.8)	20 (41.7)
Abdominal cavity/pelvis	8 (30.8)	10 (20.8)
Peritoneum	5 (19.2)	14 (29.2)
Adrenal gland	4 (15.4)	2 (4.2)
Intestine/rectum	0 (0.0)	2 (4.2)
Other sites	11 (42.3)	11 (22.9)

ECOG, Eastern Cooperative Oncology Group.

p=0.02; Harrell's C-index, 0.57) predicted PFS. Median PFS was 3.5 months (95% CI 2.8 to 5.7) and 1.9 months (95% CI 1.8 to 3.4) in patients with and without cavitation at week 8 versus 3.4 months (95% CI 1.9 to 7.8) and 2 months (95% CI 1.8 to 3.5) in those with and without cavitation at baseline, respectively (figure 2). In a

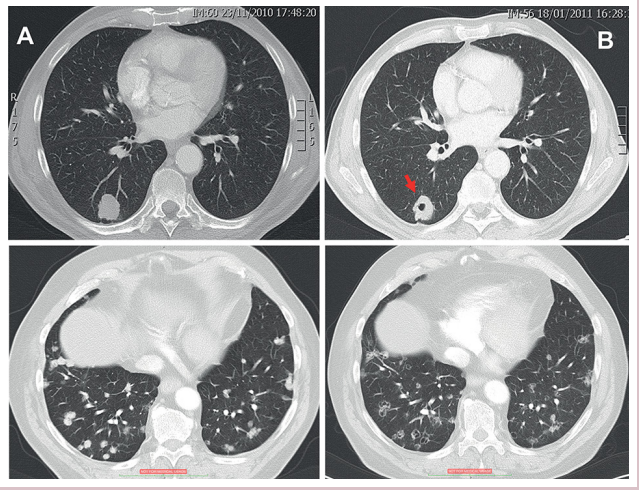

Figure 1 Baseline (A) and week 8 (B) CT displaying the onset of cavitation at week 8 in two patients treated with regorafenib. Upper: the arrow highlights single tumour metastases with cavitation. Lower: cavitation in multiple lung metastases.

multivariable model that included all radiological and clinical predictors identified by the univariate analysis, both baseline and week 8 cavitation remained significant predictors of PFS (see online supplementary table S1). An interaction analysis showed that patients with baseline cavitation had a median PFS of 7.4 months (95% CI 2.8 to NR) if they had an increase of cavitation at week 8 versus 1.8 months (95% CI 1.0 to 3.4) if they did not (HR 0.10, 95% CI 0.02 to 0.42, p=0.002; Harrell's C-index, 0.72) (figure 2). Conversely, the PFS of patients without baseline cavitation was not affected by de novo onset of cavitation at week 8 (HR 0.96, 95% CI 0.57 to 1.63, p=0.88; Harrell's C-index 0.52, interaction p=0.001) (figure 2).

Overall survival

At univariate analysis, the radiological variables predicting OS were baseline cavitation (HR 0.23, 95% CI 0.08 to 0.66, p=0.007; Harrell's C-index 0.60), RECIST 1.1 (HR 0.23, 95% CI 0.14 to 0.4, p <0.001; Harrell's C-index 0.70) and ΔSTL (HR 1.16, 95% CI 1.06 to 1.27, p=0.002; Harrell's C-index, 0.63) (table 2). By applying CART methodology, we found an increase of 9% of diameter in tumour size as the best threshold for discriminating OS. Patients with STL increase ≥9% had a median OS of 5.8 months (95% CI 4.7 to 7.3); instead patients with a variation <9% had a median OS of 10.8 months (95% CI 9.0 to NR) (HR 2.64, 95% CI 1.61 to 4.34, p <0.001) (figure 3). Median OS for patients with and without baseline cavitation was 11.8 (95% CI 10.8 to NR) and 8.7 months (95% CI 5.7 to 10.4), respectively (figure 3). The OS of patients with baseline cavitation was not affected by cavitation onset at week 8 (interaction, p=0.74). Patients with DCR and PD had a median OS of 11.5 months (95% CI 9.8 to NR) and 5.5 months (95% CI 4.4 to 6), respectively (figure 3). In an exploratory analysis, multivariable Cox models showed that cavitation at baseline, RECIST 1.1 and ΔSTL were predictors of OS (see online supplementary table S2). We reported the Harrell's C-index for each predictor statistically associated to PFS and OS. Since no comparison between different predictors was planned by study design, we reported this discriminatory measure only with a descriptive purpose.

DISCUSSION

The RadioCORRECT study showed that an early radiological evaluation of tumour response is helpful to predict clinical outcome to regorafenib in mCRC. We found that RECIST 1.1 and ΔSTL are predictors of OS. Moreover, our findings suggest that slowing tumour progression down by limiting the increase in STL to 9%, even without tumour shrinkage, was sufficient to predict a prolongation of OS. Since response to multikinase inhibitors may not be adequately described by dimensional criteria, we evaluated if other radiological markers could be identified, such as cavitation of lung metastases and density of liver metastases.[5 13–16] Literature data indicate that cavitation in lung metastases may occur spontaneously or, more frequently, may be induced by cancer therapy, especially by anti-angiogenetic agents.[17–21] It has been postulated that the appearance of an air-filled cavity is a consequence of central necrosis due to an insufficient blood supply after inhibition of angiogenesis or caused by arterial thrombosis. In 2013, we described for the first time the onset of cavitation of lung metastases in a small cohort of patients with mCRC treated with regorafenib and subsequently found an association with DCR.[7 9] The present study confirms our preliminary observations. We hypothesise that cavitation induced by regorafenib might depend on its broad multikinase inhibitory activity on tumour microenvironment, angiogenesis and tumour growth. The absence of onset of cavitation in patients receiving placebo corroborate this remark. In patients treated with regorafenib, we found that the presence of cavitation in lung metastases at week-8 was associated with DCR and PFS. More than 20% of patients treated with regorafenib showed cavitation at baseline CECT. These patients are more likely to develop an increase of cavitation at week-8 and they achieved greater PFS and OS when compared with those without baseline cavitation. These findings have significant implications and might be helpful for therapeutic choice before treatment begins. Our data appear in agreement with the proposal of other authors to consider tumour cavitation as a new radiological biomarker.[22 23] Recently, Lim *et al* evaluated lung metastases cavitation in 53 mCRC patients treated with regorafenib.[24] Although 32.1% of these patients developed cavitation, no significant association with clinical outcome was reported. These results are in contrast with those of the present study, but the small number of patients may have underpowered the statistical analysis. Indeed, patients with cavitary changes showed a non-significant prolongation of PFS and a greater DCR (82.4% vs 63.9%). Furthermore, these authors analysed

Table 2 Univariate analysis of progression-free survival (PFS) and overall survival (OS) in patients receiving regorafenib

		PFS				OS			
	Category	HR	95% CI	Chi²	p Value	HR	95% CI	Chi²	p Value
Radiological predictors at baseline CECT									
Cavitation	No	1	-	4.948	0.03	1	-	7.320	0.007
	Yes	0.50	0.27–0.92			0.23	0.08–0.66		
Density of liver metastases									
Radiologist A									
μ (unit:10 HU)	-	1.02	0.89–1.16	0.079	0.78	0.97	0.81–1.17	0.080	0.78
σ (unit:10 HU)	-	0.76	0.51–1.13	1.821	0.18	1.35	0.84–2.18	1.552	0.21
Radiologist B									
μ (unit:10 HU)	-	1.02	0.89–1.16	0.056	0.81	0.99	0.82–1.20	0.005	0.94
σ (unit:10 HU)	-	0.92	0.62–1.38	0.151	0.70	1.84	1.10–3.06	5.489	0.02
Sum of target lesions (unit: 1 cm)	-	0.99	0.96–1.02	0.394	0.53	1.05	1.02–1.09	9.964	0.002
Radiological predictors at week 8 CECT									
Cavitation	No	1	-	5.211	0.02	1	-	1.105	0.30
	Yes	0.58	0.36–0.93			0.71	0.38–1.34		
Density of liver metastases									
Radiologist A									
μ (unit:10 HU)	-	0.91	0.81–1.01	3.178	0.07	0.94	0.82–1.07	0.946	0.33
σ (unit:10 HU)	-	1.01	0.90–1.13	0.009	0.92	0.90	0.78–1.03	2.346	0.13
Radiologist B									
μ (unit:10 HU)	-	0.94	0.83–1.06	0.965	0.33	0.99	0.86–1.15	0.011	0.91
σ (unit:10 HU)	-	0.95	0.85–1.07	0.784	0.38	0.98	0.85–1.14	0.049	0.82
ΔSTL (unit:10%)	-	-	-	-	-	1.16	1.06–1.27	9.809	0.002
RECIST 1.1	PD	-	-	-	-	1	-		
	DCR	-	-	-	-	0.23	0.14–0.40	28.339	<0.001
Other predictors									
Age (years) at random (unit: 10 years)	-	1.01	0.83–1.22	0.003	0.96	0.87	0.66–1.14	0.975	0.32
Sex	Male	1	-	6.749	0.009	1	-	3.702	0.05
	Female	1.63	1.13–2.36			1.62	0.99–2.66		
ECOG	0	1	-	1.665	0.20	1	-	5.801	0.02
	1	1.28	0.88–1.85			1.83	1.12–2.98		
KRAS mutation	No	1	-	0.394	0.53	1	-	0.310	0.58
	Yes	0.89	0.61–1.29			0.86	0.52–1.44		
More than three lines before regorafenib	No	1	-	0.326	0.57	1	-	0.013	0.91
	Yes	0.90	0.62–1.30			0.97	0.60–1.59		
Time from M1 diagnosis to randomisation (years)	-	0.90	0.78–1.03	2.552	0.11	0.92	0.76–1.10	0.873	0.35

Continued

Table 2 Continued

		PFS				OS			
	Category	HR	95% CI	Chi²	p Value	HR	95% CI	Chi²	p Value
Liver target lesions	No	1	-	4.478	0.03	1	-	10.554	0.001
	Yes	1.55	1.03–2.33			3.06	1.56–6.00		
Lung target lesions	No	1	-	0.350	0.55	1	-	0.915	0.34
	Yes	0.89	0.61–1.30			0.78	0.46–1.30		

CECT, contrast-enhanced computed tomography; ECOG, Eastern Cooperative Oncology Group; HU, Hounsfield unit; RECIST, Response Evaluation Criteria in Solid Tumors; μ = tumour density in HU; σ = standard deviation; ΔSTL = change in the sum of the target lesions diameters.

all metastatic lesions, including non-target metastases (<1 cm), and only 66% of patients had measurable lesions, making it difficult to compare data from these two different studies. Since the occurrence of cavitation of lung metastases can be of clinical concern in terms of risk of pulmonary haemorrhage,[21 25] we reviewed the occurrence of grade 3 and 4 pulmonary adverse events in our cohort based on matched reporting from the CORRECT Trial. In our study, among the 36 patients who had cavitation of lung metastases, we found only one respiratory grade 4 adverse event (pulmonary embolism) that has been judged as not related to regorafenib.

Measurement of pretreatment and on-treatment tumour density of liver metastases has been widely investigated in solid tumour assessments.[5 26] In xenograft models, regorafenib led to an early reduction of tumour perfusion and vascularity, assessable by radiological imaging.[27–29] In our study, regorafenib induced a decrease in tumour density in most of the patients. However, neither a reduction of tumour density at week 8 nor baseline values were useful for predicting outcomes. This finding is supported by a recent study in patients with gastrointestinal stromal tumours treated with regorafenib, in which CHOI criteria, which include tumour

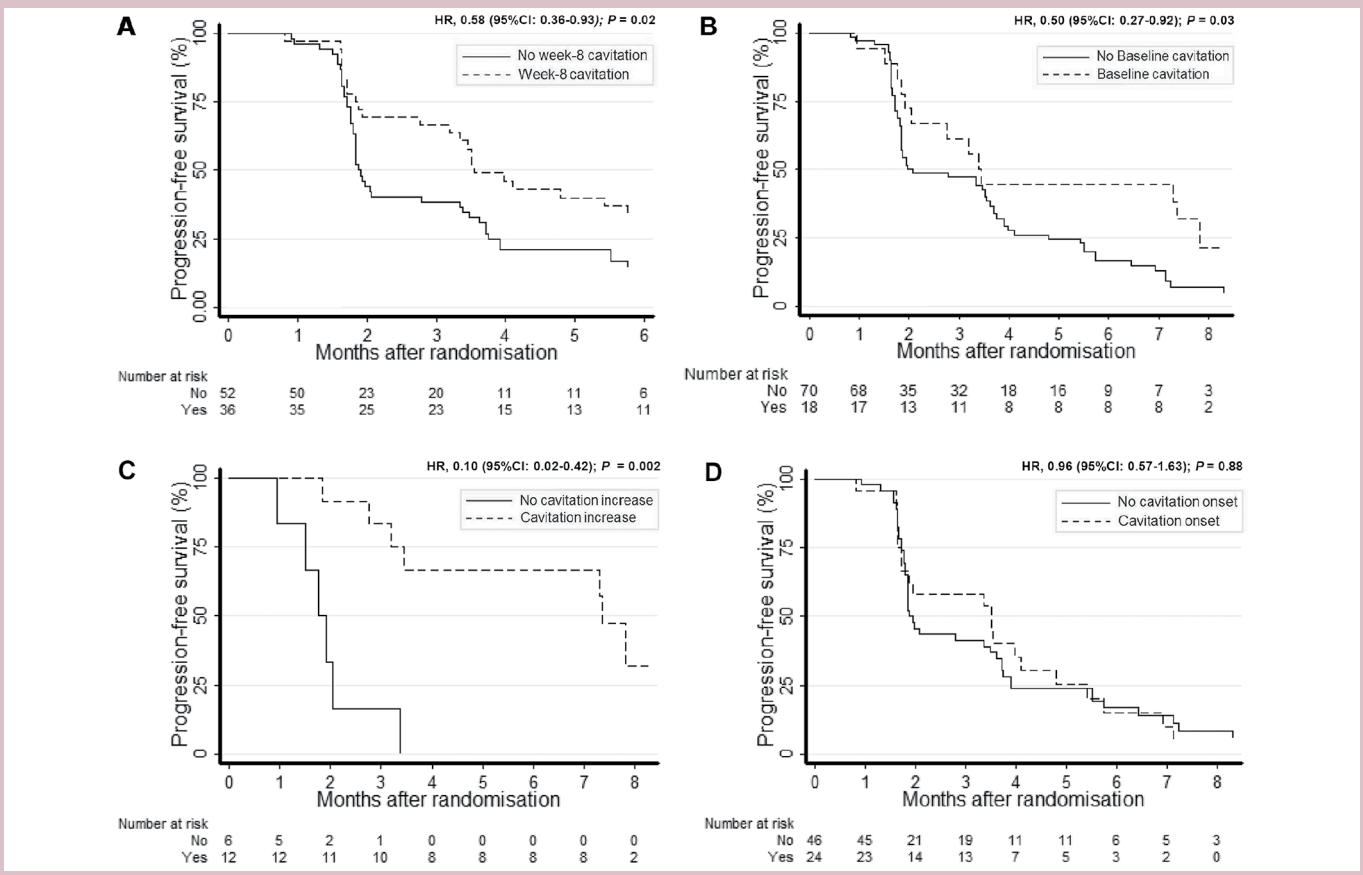

Figure 2 Kaplan-Meier estimates of progression-free survival (PFS) in patients treated with regorafenib. (A) PFS according to the presence of cavitation at week 8. (B) PFS according to the presence of baseline cavitation. (C) Subgroup analysis of PFS in patients with baseline cavitation, according to its increase at week 8. (D) Subgroup analysis of PFS in patients without baseline cavitation, according to its onset at week 8.

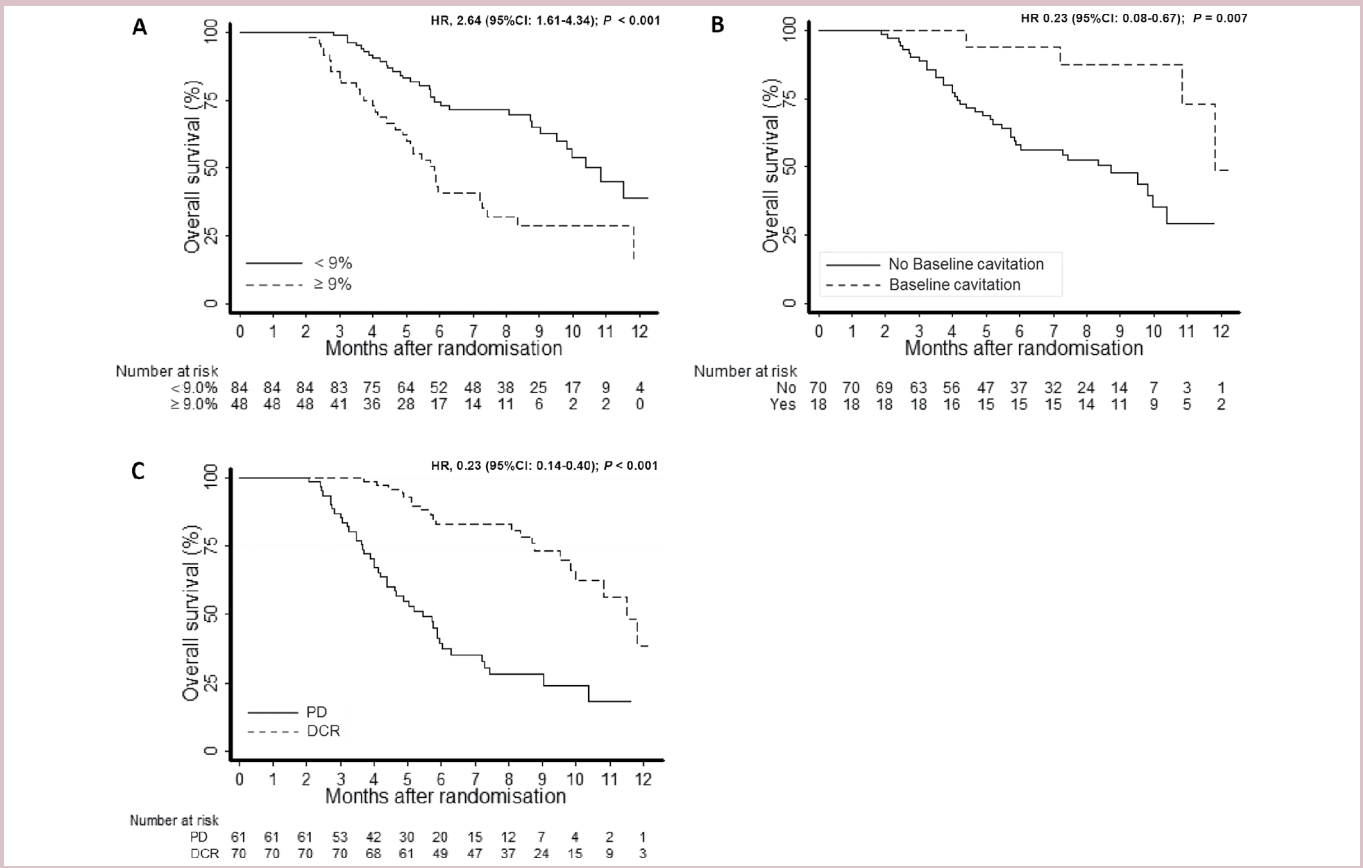

Figure 3 Kaplan-Meier estimates of overall survival in patients treated with regorafenib. (A) Survival according to change in the sum of the target lesion diameters (ΔSTL) (≥9% vs. <9%). (B) Survival according to the presence of baseline cavitation. (C) Survival according to Response Evaluation Criteria in Solid Tumors (RECIST) response. All patients achieved disease control rate (DCR) had stable disease (SD) as best response because no partial response (PR) or complete response (CR) were reported. PD, progressive disease.

density variation besides dimensional changes, had a less favourable concordance between PFS and OS prediction when compared with RECIST 1.1 or WHO criteria.[30] In mCRC patients treated with regorafenib, Lim *et al* found a tumour density decrease in most of cases, but the magnitude of change was not associated with clinical outcomes.[24]

Our study has several limitations. First, it is a post hoc analysis of patients enrolled in a prospective, placebo-controlled phase III trial. A priori power statistical analysis was not performed and the number of patients evaluated limits the interpretation of the results.

Second, we found both baseline and week-8 cavitation are associated with a favourable outcome to regorafenib. Unfortunately, the imbalance of baseline cavitation between regorafenib and placebo group did not allow to evaluate clinical outcomes in patients treated with placebo. This hamper to clarify whether baseline cavitation affects the natural history of disease regardless of treatment received. For this reason, the role of cavitation as predictive rather than prognostic marker should be further investigated in larger series and across other studies. Third, density was assessed in the same liver metastases identified in the CORRECT study. Morphological features such as the presence of necrotic area may have affected the analysis of density. Finally, since we included only patients that underwent the first post-treatment CECT, planned at week 8, we cannot rule out a selection bias by excluding patients with more aggressive or primary resistant tumours. It remains to be assessed how fast cavitation occurs and if an earlier evaluation by CECT would be capable of capturing the same radiological signals of efficacy.

CONCLUSIONS

Our findings showed that an early radiological assessment of tumoural response to regorafenib is useful for driving clinical decisions. RECIST 1.1 remains an adequate method to assess therapeutic response, being associated with OS. The evaluation of tumour size as a continuous variable, expressed as ΔSTL, supports continuation of treatment in those patients achieving stable disease without any tumour shrinkage. Our data also indicate that the evaluation of liver metastases density does not provide complementary information to traditional dimensional-based criteria. Conversely, we identify lung metastases cavitation as a novel imaging predictor of

favourable clinical outcome to regorafenib that deserves consideration.

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Acknowledgements The authors thank the patients, their families and the study investigators, Alessandra Gambaro and Giovanna Marrapese of Niguarda Cancer Center for data management, in the CORRECT study. The corresponding author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its licensees to permit this article (if accepted) to be published in ESMO Open editions and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence.

Funding This study was supported by a research grant from Bayer HealthCare Pharmaceuticals and partly by Fondazione Oncologia Niguarda Onlus. Bayer HealthCare Pharmaceuticals had no role in the design and conduct of the study, management, analysis and interpretation of data. Bayer HealthCare Pharmaceuticals reviewed this manuscript before the submission for publication and the authors retained editorial control over the content. Bayer HealthCare Pharmaceuticals had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data. Bayer HealthCare Pharmaceuticals reviewed this manuscript before the submission for publication and the authors retained editorial control over the content. This project has received funding from the European Union Horizon 2020 research and innovation programme under grant agreement No 635342 (MoTriColor grant to SS)

Competing interests The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are: RR reports grants from Bayer, during the conduct of the study, personal fees from Bayer (Consultancies, Speaker) outside the present work; AV reports grants from Bayer, during the conduct of the study; SG reports grants from Bayer, during the conduct of the study; AG reports grants and other from Bayer, during the conduct of the study; grants and other from Genentech, other from Taiho, outside the submitted work; AF reports grants and personal fees from Amgen, grants and personal fees from Merck, grants and personal fees from Roche, grants and personal fees from Bayer, personal fees from Lilly and personal fees from Sevier, outside the submitted work; MY reports personal fees from BAYER, personal fees from ROCHE, personal fees from AMGEN, outside the submitted work; CB reports personal fees from Bayer, outside the submitted work; OB reports personal fees from ROCHE, personal fees from MERCK SERENO, personal fees from NOVARTIS, personal fees from LILLY, personal fees from AMGEN, from null, outside the submitted work; MP reports grants from Bayer, during the conduct of the study, personal fees from Amgen, Sanofi, Servier outside the submitted work; YH reports other from Bayer Pharma, during the conduct of the study; LM reports honorarium charges displacement of Congress; JT reports other from Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Symphogen, Taiho, and Takeda, outside the submitted work; TM reports grants from ROCHE, personal fees from SANOFI, personal fees and non-financial support from AMGEN, outside the submitted work; DR reports grants from Bayer, during the conduct of the study; KB reports grants from Bayer, during the conduct of the study; CF reports grants from Bayer, during the conduct of the study; AA reports personal fees from Amgen, personal fees from Bayer, personal fees from Lilly, outside the submitted work; AS-B participated at advisory boards for Amgen, Bayer and Lilly. AV reports grants from Bayer, during the conduct of the study; SS reports grants from Bayer, during the conduct of the study, participated at advisory boards for Amgen, Bayer, Lilly, Merck, Roche and Sanofi.

Provenance and peer review Not commissioned; internally peer reviewed.

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