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Supplementary appendix

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Analysis of circulating DNA and protein biomarkers to predict the clinical activity of regorafenib and assess prognosis in patients with metastatic colorectal cancer: a retrospective, exploratory analysis of the CORRECT trial

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Supplementary appendix

Supplementary Table 1. Hot-spot mutations analysed by BEAMing in CORRECT

Gene	Nucleotide change	Amino acid change
KRAS	G34A	G12S
	G34C	G12R
	G34T	G12C
	G35A	G12D
	G35C	G12A
	G35T	G12V
	G38A	G13D
	A183C	Q61H
	G436A	A146T
PIK3CA	G1624A	E542K
	G1633A	E545K
	A1634G	E545G
	C3139T	H1047Y
	A3140G	H1047R
	A3140T	H1047L
BRAF	T1799A	V600E

Supplementary Table 2. *KRAS* mutations detected by plasma DNA BEAMing in patients in the CORRECT trial whose tumours were determined to be *KRAS* wild type by genotyping of archival tumour tissue DNA

***KRAS* status by tumour tissue DNA BEAMing**	***KRAS* status by plasma DNA BEAMing**		**Prior EGFR therapy**
	Hot-spot mutation	**Mutant allele frequency (%)**	
Patient 1	G12A + Q61H	0·53 + 0·21	Panitumumab
Patient 2*	Q61H	1·05	Cetuximab
Patient 3*	G12C	0·38	Cetuximab
Patient 4	G12R + Q61H	0·09 + 0·03	Cetuximab, panitumumab
Patient 5	G12C + G12D + G12A + G12V + G12R	0·16 + 1·35 + 0·24 + 1·07 + 0·06	Cetuximab
Patient 6	Q61H	14·56	Cetuximab
Patient 7	G12C + G12A	0·04 + 0·17	Cetuximab
Patient 8	Q61H + G12C	0·03 + 0·03	Cetuximab
Patient 9*	Q61H + G12C + G12A + G13D	5·64 + 0·34 + 0·32 + 0·09	Cetuximab
Patient 10*	G12A + G12V + Q61H	0·06 + 0·07 + 0·04	Cetuximab
Patient 11*	G12V	0·05	Panitumumab
Patient 12*	G12A	1·13	Panitumumab
Patient 13*	G12A + Q61H	0·03 + 0·31	Cetuximab
Patient 14*	Q61H + G12A	0·05 + 0·09	Cetuximab
Patient 15*	G12A + Q61H	0·02 + 0·42	Cetuximab
Patient 16*	Q61H + G12A + G13D	5·82 + 0·44 + 1·16	Cetuximab
Patient 17*	G12A + Q61H	22·31 + 0·02	Cetuximab, panitumumab
Patient 18*	Q61H	0·04	Cetuximab
Patient 19*	Q61H + G12S + G12D + G13D	1·58 + 0·20 + 0·13 + 0·07	Panitumumab
Patient 20	Q61H + G12A	0·43 + 0·05	Cetuximab
Patient 21*	Q61H + G12R + G12V	0·05 + 0·11 + 0·03	Panitumumab
Patient 22*	Q61H + G12D + G13D	0·05 + 0·05 + 0·06	Cetuximab
Patient 23*	G12V + G13D	0·05 + 0·03	Cetuximab
Patient 24	Q61H + G12D	0·15 + 0·05	Cetuximab, panitumumab
Patient 25*	G12D	0·20	Cetuximab
Patient 26*	G13D	2·26	Cetuximab
Patient 27	Q61H + G12C + G13D	0·07+ 0·04 + 0·03	Panitumumab
Patient 28*	Q61H	0·20	Cetuximab, panitumumab
Patient 29	Q61H	0·14	Cetuximab
Patient 30	G12R + G12D	0·09 + 0·07	Panitumumab

Historical *KRAS* mutation data were generated before the start of the CORRECT trial using unknown testing technology and reported to the study sponsor at the time of enrolment.
*Specimens in which *KRAS*-wild-type status was also confirmed by next-generation sequencing. Because of the limited amount of tissue available for testing, next-generation sequencing was not performed on all samples.

Supplementary Table 3. *KRAS* and *PIK3CA* mutations in patients in the CORRECT trial in whom mutations were detected via BEAMing in patient-matched plasma DNA and tumour tissue DNA samples

	Plasma DNA BEAMing		Tumour tissue DNA BEAMing
Gene	**Hot-spot mutation**	**Mutant allele frequency (%)**	**Hot-spot mutation**
KRAS	G12D	32·67	G12D
KRAS	G12D	47·65	G12D
KRAS	G12D	5·96	G12D
KRAS	G12D	1·01	G12D
KRAS	G12D	18·06	G12D
KRAS	G12D	18·01	G12D
KRAS	G12D	0·06	G12D
KRAS	G12D	1·40	G12D
KRAS	G12D	9·90	G12D
KRAS	G12D	0·16	G12D
KRAS	G12D	1·68	G12D
KRAS	G12D	34·79	G12D
KRAS	G12D	15·82	G12D
KRAS	G12D	5·55	G12D
KRAS	G12D	3·84	G12D
KRAS	G12D	15·60	G12D
KRAS	G12D	11·65	G12A
KRAS	G12D	1·34	G12D
KRAS	G12D	5·42	G12D
KRAS	G12D	5·84	G12D
KRAS	G12D	2·87	G12D
KRAS	G12D	0·13	G12D + G13D
KRAS	G12D	0·34	G12D
KRAS	G12D	0·13	G12D
KRAS	G12D	3·53	G12D
KRAS	G12D	3·20	G12D
KRAS	G12D	0·70	G12D
KRAS	G12D	3·55	G12D
KRAS	G12D	17·85	G12D
KRAS	G12D	0·09	G12D
KRAS	G12D	11·09	G12D
KRAS	G12D	11·38	G12D
KRAS	G12D	6·84	G12D
KRAS	G12D	0·21	G12D
KRAS	G12D	0·32	G12D
KRAS	G12D	1·21	G12D
KRAS	G12D	23·71	G12D
KRAS	G12D	23·34	G12D
KRAS	G12D	0·37	G12D

	Plasma DNA BEAMing		Tumour tissue DNA BEAMing
Gene	**Hot-spot mutation**	**Mutant allele frequency (%)**	**Hot-spot mutation**
KRAS	G12D	0·63	G12D
KRAS	G12D	3·63	G12D
KRAS	G12D	0·41	G12D
KRAS	G12D	18·17	G12D
KRAS	G12V + G12S	7·31 + 3·04	G12V + G12S
KRAS	G12V	16·25	G12V
KRAS	G12V	18·85	G12V
KRAS	G12V	22·65	G12V
KRAS	G12V	15·96	G12V
KRAS	G12V	19·20	G12V
KRAS	G12V	17·40	G12V
KRAS	G12V	0·72	G12V
KRAS	G12V	36·14	G12V
KRAS	G12V	7·46	G12V
KRAS	G12V	24·09	G12V
KRAS	G12V	23·99	G12V
KRAS	G12V	15·64	G12V
KRAS	G12V	13·09	G12V
KRAS	G12V	5·05	G12V
KRAS	G12V	13·51	G12V
KRAS	G12V	32·67	G12V
KRAS	G12V	0·03	G12V
KRAS	G12V	1·71	G12V
KRAS	G12V	18·60	G12V
KRAS	G12V	10·66	G12V
KRAS	G12V	0·78	G12V
KRAS	G12V	30·58	G12V
KRAS	G12V	9·58	G12V
KRAS	G13D	20·19	G13D
KRAS	G13D	9·01	G13D
KRAS	G13D	2·65	G13D
KRAS	G13D	6·84	G13D
KRAS	G13D	2·90	G13D
KRAS	G13D	11·97	G13D
KRAS	G13D	1·89	G13D
KRAS	G13D	0·18	G13D
KRAS	G13D	24·34	G13D
KRAS	G13D	7·11	G13D
KRAS	G13D	0·70	G13D
KRAS	G13D	5·86	G13D
KRAS	G13D	0·45	G13D

	Plasma DNA BEAMing		Tumour tissue DNA BEAMing
Gene	**Hot-spot mutation**	**Mutant allele frequency (%)**	**Hot-spot mutation**
KRAS	G13D	0·29	G13D
KRAS	G13D	5·31	G13D
KRAS	G13D	16·21	G13D
KRAS	G13D	3·64	G13D
KRAS	G13D	2·68	G13D
KRAS	G12A	17·96	G12A
KRAS	G12A	0·12	G12A
KRAS	G12A	0·09	G12A
KRAS	G12A	16·58	G12A
KRAS	G12A	0·05	G12A
KRAS	G12S	11·32	G12S
KRAS	G12S	23·82	G12S
KRAS	G12S	0·46	G12S
KRAS	G12S	57·93	G12S
KRAS	G12C	23·62	G12C
KRAS	G12C	19·84	G12C
KRAS	G12C	9·76	G12C
KRAS	G12C	0·86	G12C
KRAS	G12R	17·50	G12R
KRAS	G12R	10·61	G12R
KRAS	G12R	14·11	G12R
KRAS	A146T	26·60	A146T
KRAS	A146T	45·76	A146T
KRAS	A146T	1·64	A146T
KRAS	A146T	34·69	A146T
KRAS	Q61H	0·15	G12D
KRAS	Q61H	1·36	Q61H
KRAS	Q61H	0·89	Q61H
PIK3CA	E542K	5·83	E542K
PIK3CA	E542K	1·77	E542K
PIK3CA	E542K	9·94	E542K
PIK3CA	E542K	2·37	E542K
PIK3CA	E542K + E545G	7·24 + 0·03	E542K
PIK3CA	E542K	7·21	E542K
PIK3CA	E545K	20·51	E545K
PIK3CA	E545K	28·99	E545K
PIK3CA	E545K	0·76	E545K
PIK3CA	E545K	0·16	E545K
PIK3CA	E545K	1·67	E545K
PIK3CA	E545K	0·13	E545K
PIK3CA	E545K	0·24	E545K

	Plasma DNA BEAMing		Tumour tissue DNA BEAMing
Gene	**Hot-spot mutation**	**Mutant allele frequency (%)**	**Hot-spot mutation**
PIK3CA	E545K	24·15	E545K
PIK3CA	H1047L	12·68	H1047L
PIK3CA	H1047R	7·03	H1047R

Supplementary Table 4. Patients in the CORRECT trial classified as *KRAS* mutant by BEAMing analysis of both tumour tissue DNA and plasma DNA, but *KRAS* wild type by historical genotyping of tumour tissue

KRAS* status by historical tumour tissue DNA	***KRAS* tumour tissue DNA BEAMing**		***KRAS* plasma DNA BEAMing**	
	Hot-spot mutation	**Frequency (%)**	**Hot-spot mutation**	**Frequency (%)**
Wild type	G12D†	7·10	G12D	9·90
Wild type	G12V†	7·20	G12V	22·65
Wild type	G13D	10·36	G13D	5·31
Wild type	Q61H†	9·26	Q61H	1·36
Wild type	A146T†	23·85	A146T	26·60
Wild type	A146T	21·81	A146T	45·76
Wild type	A146T	27·82	A146T	34·69
Wild type	A146T†	37·60	A146T	1·64

*Historical *KRAS* mutation data were generated before the start of the CORRECT trial using unknown testing technology and reported to the study sponsor at the time of enrolment.
†Specimens in which *KRAS*-wild-type status was also confirmed by next-generation sequencing. Because of the limited amount of tissue available for testing, next-generation sequencing was not performed on all samples.

Supplementary Table 5. Association of baseline plasma DNA levels with overall survival in placebo patients in the CORRECT trial

Quartile	Patients, n	Mean DNA per ml of plasma*	Median OS (days)
1	41	2,633	192
2	42	7,701	159
3	42	18,873	131
4	41	120,213	73

*Mean DNA in genomic equivalents per ml of plasma obtained at enrolment.

Supplementary Table 6. Association of *KRAS*-mutant allele frequency detected in plasma DNA with overall survival in placebo patients in the CORRECT trial

Tertile	**Patients, n**	**Mean *KRAS* mutation frequency***	**Median OS (days)**
1	39	0·44	185
2	38	11	138
3	38	25	82

*Baseline plasma samples from placebo patients obtained at enrolment.

Supplementary Table 7. Association of *KRAS*-mutant molecules detected per ml of plasma with overall survival in placebo-treated patients in the CORRECT trial

Tertile	Patients, n	Mutant molecules per ml of plasma*	Median OS (days)
1	39	28	189
2	38	739	137
3	38	27,831	79

*Determined by multiplying the amount of DNA per ml of plasma by the mutant allele frequency and dividing by 100.

Supplementary Table 8. Clinical activity of regorafenib versus placebo in patients in the CORRECT trial with high or low plasma protein levels

			Overall survival			Progression-free survival		
Protein	**Cutoff Method**	**Protein level***	***n* (events)**	**HR (95% CI)**	**Interaction *P* value†**	***n* (events)**	**HR (95% CI)**	**Interaction *P* value†**
ANG-2	Median	Low	305 (137)	0·71 (0·50–1·00)	0·577	305 (263)	0·47 (0·36–0·61)	0·336
		High	306 (201)	0·67 (0·50–0·89)		306 (274)	0·47 (0·36–0·61)	
	Best fit	Low	488 (239)	0·74 (0·57–0·96)	0·600	447 (386)	0·44 (0·36–0·55)	0·306
		High	123 (99)	0·69 (0·46–1·04)		164 (151)	0·62 (0·44–0·86)	
	ROC Curve	Low	343 (154)	0·72 (0·52–1·00)	0·648	383 (329)	0·46 (0·36–0·58)	0·818
		High	268 (184)	0·68 (0·50–0·92)		228 (208)	0·52 (0·39–0·70)	
BMP-7	Median	Low	528 (295)	0·75 (0·59–0·95)	0·290	528 (467)	0·51 (0·42–0·62)	0·086
		High	83 (43)	0·53 (0·29–0·98)		83 (70)	0·29 (0·16–0·50)	
	Best fit	Low	589 (322)	0·74 (0·59–0·93)	0·061	569 (498)	0·49 (0·40–0·59)	0·487
		High	22 (16)	0·19 (0·05–0·65)		42 (39)	0·39 (0·18–0·83)	
	ROC Curve	Low	589 (322)	0·74 (0·59–0·93)	0·061	569 (498)	0·49 (0·40–0·59)	0·487
		High	22 (16)	0·19 (0·05–0·65)		42 (39)	0·39 (0·18–0·83)	
VWF	Median	Low	305 (151)	0·62 (0·45–0·86)	0·339	305 (261)	0·39 (0·30–0·51)	0·020
		High	306 (187)	0·80 (0·59–1·09)		306 (276)	0·60 (0·46–0·78)	
	Best fit	Low	193 (86)	0·53 (0·34–0·82)	0·145	193 (159)	0·41 (0·29–0·58)	0·267
		High	418 (252)	0·81 (0·63–1·05)		418 (378)	0·52 (0·41–0·64)	
	ROC Curve	Low	254 (119)	0·58 (0·40–0·83)	0·226	182 (149)	0·41 (0·29–0·58)	0·261
		High	357 (219)	0·80 (0·60–1·06)		429 (388)	0·50 (0·40–0·63)	
IL6	Median	Low	305 (129)	0·69 (0·48–0·99)	0·921	305 (268)	0·45 (0·35–0·59)	0·962
		High	306 (209)	0·73 (0·55–0·98)		306 (269)	0·52 (0·40–0·68)	
	Best fit	Low	379 (168)	0·68 (0·50–0·94)	0·597	443 (380)	0·46 (0·37–0·58)	0·639
		High	232 (170)	0·80 (0·58–1·09)		168 (157)	0·54 (0·38-0·75)	
	ROC Curve	Low	270 (106)	0·70 (0·47–1·03)	0·980	442 (379)	0·47 (0·37–0·58)	0·614
		High	341 (232)	0·72 (0·55–0·95)		169 (158)	0·53 (0·38–0·74)	

			Overall survival			Progression-free survival		
Protein	**Cutoff Method**	**Protein level***	***n* (events)**	**HR (95% CI)**	**Interaction *P* value†**	***n* (events)**	**HR (95% CI)**	**Interaction *P* value†**
IL8	Median	Low	305 (119)	0·68 (0·47–0·97)	0·442	305 (260)	0·45 (0·35–0·58)	0·840
		High	306 (219)	0·58 (0·43–0·77)		306 (277)	0·46 (0·36–0·61)	
	Best fit	Low	352 (145)	0·65 (0·47–0·91)	0·941	528 (457)	0·48 (0·39–0·58)	0·63
		High	259 (193)	0·68 (0·50–0·92)		83 (80)	0·57 (0·36–0·91)	
	ROC Curve	Low	290 (107)	0·70 (0·48-1·04)	0·422	361 (306)	0·44 (0·34–0·56)	0·566
		High	321 (231)	0·59 (0·45–0·78)		250 (321)	0·52 (0·39–0·70)	
MCSF	Median	Low	304 (146)	0·67 (0·48–0·93)	0·648	304 (274)	0·41 (0·32–0·53)	0·123
		High	307 (192)	0·74 (0·55–1·00)		307 (263)	0·57 (0·44–0·74)	
	Best fit	Low	334 (159)	0·76 (0·55–1·05)	0·592	284 (257)	0·44 (0·34–0·57)	0·404
		High	277 (179)	0·66 (0·48–0·90)		327 (280)	0·53 (0·41–0·68)	
	ROC Curve	Low	334 (159)	0·76 (0·55–1·05)	0·592	552 (483)	0·47 (0·39–0·57)	0·671
		High	277 (179)	0·66 (0·48–0·90)		59 (54)	0·56 (0·31–1·02)	
PlGF	Median	Low	304 (155)	0·92 (0·64–1·31)	0·095	304 (265)	0·46 (0·35–0·61)	0·862
		High	307 (183)	0·62 (0·46–0·83)		307 (272)	0·49 (0·38–0·63)	
	Best fit	Low	339 (169)	0·85 (0·61–1·18)	0·260	512 (445)	0·47 (0·39–0·58)	0·407
		High	272 (169)	0·65 (0·48–0·88)		99 (92)	0·55 (0·36–0·85)	
	ROC Curve	Low	339 (169)	0·85 (0·61–1·18)	0·260	419 (360)	0·45 (0·36–0·57)	0·146
		High	272 (169)	0·65 (0·48–0·88)		192 (177)	0·56 (0·41–0·77)	
SCDF1	Median	Low	305 (171)	0·77 (0·56–1·06)	0·508	305 (265)	0·52 (0·40–0·67)	0·237
		High	306 (167)	0·68 (0·49–0·92)		306 (272)	0·45 (0·35–0·59)	
	Best fit	Low	46 (18)	0·42 (0·17-1·07)	0·240	233 (201)	0·50 (0·37–0·68)	0·549
		High	565 (320)	0·74 (0·59–0·93)		378 (336)	0·47 (0·38–0·60)	
	ROC Curve	Low	170 (84)	0·81 (0·52–1·27)	0·507	293 (253)	0·51 (0·39–0·67)	0·333
		High	441 (254)	0·68 (0·53–0·88)		318 (284)	0·46 (0·36-0·59)	

Protein	Cutoff Method	Protein level*	Overall survival			Progression-free survival		
			n (events)	HR (95% CI)	Interaction *P* value†	*n* (events)	HR (95% CI)	Interaction *P* value†
VEGFR	Median	Low	305 (181)	0·70 (0·51–0·94)	0·784	305 (269)	0·46 (0·35–0·60)	0·622
		High	306 (157)	0·74 (0·54–1·03)		306 (268)	0·50 (0·39–0·65)	
	Best fit	Low	77 (35)	1·03 (0·47–2·29)	0·401	77 (65)	0·43 (0·25–0·75)	0·765
		High	534 (303)	0·70 (0·56–0·89)		534 (472)	0·49 (0·40–0·60)	
	ROC Curve	Low	77 (35)	1·03 (0·47–2·29)	0·401	157 (132)	0·42 (0·29–0·60)	0·229
		High	534 (303)	0·70 (0·56–0·89)		454 (405)	0·50 (0·41–0·62)	
TIE-1	Median	Low	305 (140)	0·83 (0·58–1·18)	0·248	305 (259)	0·52 (0·40–0·67)	0·492
		High	306 (198)	0·65 (0·49–0·87)		306 (278)	0·45 (0·35–0·59)	
	Best fit	Low	377 (172)	0·87 (0·64–1·20)	0·035	595 (523)	0·47 (0·39–0·57)	0·663
		High	234 (166)	0·56 (0·41–0·77)		16 (14)	0·52 (0·15–1·79)	
	ROC Curve	Low	377 (172)	0·87 (0·64–1·20)	0·035	289 (243)	0·49 (0·38–0·65)	0·800
		High	234 (166)	0·56 (0·41–0·77)		322 (294)	0·47 (0·37–0·60)	
TIMP-2	Median	Low	305 (173)	0·74 (0·54–1·00)	0·812	305 (271)	0·52 (0·40–0·67)	0·322
		High	306 (165)	0·70 (0·51–0·97)		306 (266)	0·45 (0·34–0·58)	
	Best fit	Low	299 (173)	0·77 (0·56–1·04)	0·572	299 (267)	0·53 (0·41–0·69)	0·236
		High	312 (165)	0·68 (0·49–0·94)		312 (270)	0·44 (0·34–0·58)	
	ROC Curve	Low	373 (200)	0·67 (0·50–0·89)	0·488	200 (172)	0·53 (0·38–0·72)	0·667
		High	238 (138)	0·79 (0·56–1·14)		411 (365)	0·46 (0·37–0·58)	
VEGF-A	Median	Low	301 (149)	0·66 (0·47–0·92)	0·613	301 (258)	0·42 (0·32–0·55)	0·127
		High	301 (186)	0·75 (0·55–1·02)		301 (272)	0·57 (0·44–0·74)	
	Best fit	Low	492 (253)	0·76 (0·59–0·99)	0·283	410 (355)	0·46 (0·37–0·58)	0·330
		High	110 (82)	0·60 (0·38–0·93)		192 (175)	0·60 (0·43–0·82)	
	ROC Curve	Low	319 (156)	0·67 (0·48–0·92)	0·628	121 (98)	0·35 (0·22–0·56)	0·169
		High	283 (179)	0·75 (0·55–1·02)		481 (432)	0·53 (0·43–0·65)	

			Overall survival			Progression-free survival		
Protein	**Cutoff Method**	**Protein level***	***n* (events)**	**HR (95% CI)**	**Interaction *P* value†**	***n* (events)**	**HR (95% CI)**	**Interaction *P* value†**
VEGF-C	Median	Low	305 (162)	0·77 (0·55–1·07)	0·518	305 (261)	0·51 (0·39–0·66)	0·748
		High	306 (176)	0·66 (0·49–0·90)		306 (276)	0·46 (0·36–0·59)	
	Best fit	Low	29 (11)	4·51 (0·58–35·26)	0·084	76 (60)	0·58 (0·33–1·03)	0·53
		High	582 (327)	0·69 (0·55–0·86)		535 (477)	0·47 (0·38–0·57)	
	ROC Curve	Low	454 (239)	0·74 (0·57-0·97)	0·631	253 (212)	0·55 (0·41–0·73	0·391
		High	157 (99)	0·66 (0·44-0·99)		358 (325)	0·44 (0·35–0·56)	
VEGF-D	Median	Low	305 (150)	0·71 (0·51–0·99)	0·955	305 (261)	0·44 (0·34–0·57)	0·669
		High	306 (188)	0·71 (0·52–0·96)		306 (276)	0·52 (0·40–0·66)	
	Best fit	Low	387 (189)	0·78 (0·58–1·05)	0·232	439 (376)	0·50 (0·40–0·62)	0·284
		High	224 (149)	0·61 (0·44–0·85)		172 (161)	0·41 (0·28–0·58)	
	ROC Curve	Low	382 (186)	0·76 (0·56–1·02)	0·402	396 (336)	0·52 (0·41–0·65)	0·161
		High	229 (152)	0·64 (0·46–0·89)		215 (201)	0·40 (0·30–0·55)	
VEGF-A isoform 121	Median	Low	305 (157)	0·68 (0·49–0·95)	0·762	305 (270)	0·48 (0·37–0·62)	0·939
		High	306 (181)	0·74 (0·54–1·00)		306 (267)	0·48 (0·37–0·62)	
	Best fit	Low	130 (51)	0·55 (0·31–0·97)	0·271	160 (136)	0·40 (0·27–0·59)	0·442
		High	481 (287)	0·77 (0·60–0·98)		451 (401)	0·51 (0·41–0·63)	
	ROC Curve	Low	160 (67)	0·51 (0·31–0·84)	0·093	159 (135)	0·40 (0·27–0·60)	0·5
		High	451 (271)	0·81 (0·63–1·04)		452 (402)	0·51 (0·41–0·63)	

*Protein levels were determined by multiplex immunoassay or enzyme-linked immunosorbent assay in baseline plasma samples obtained from 611 patients enrolled in the CORRECT trial (placebo: *n* = 199; regorafenib: *n* = 412).

†Interaction p value comparing clinical outcomes in the indicated low versus high biomarker subgroups.

ANG-2: Angiopoietin 2; BMP-7: bone morphogenetic protein 7; CI: confidence interval; HR: hazard ratio; IL6: interleukin 6; IL8: interleukin 8; MCSF: macrophage colony stimulating factor; PlGF: placental growth factor; ROC: receiver operating characteristic; SCDF1 stromal cell-derived factor 1; sTIE-1: soluble tyrosine kinase with immunoglobulin-like and epidermal growth factor like-domains 1; TIMP-2: tissue-derived metalloproteinase 2; VEGF: vascular endothelial growht factor: VEGFR: VEGF receptor; VWF: Von Willebrandt Factor.

Supplementary Table 9. Association of plasma protein levels with overall (OS) and progression-free survival (PFS) in placebo patients in the CORRECT trial

		Overall survival		Progression-free survival	
Protein	**Cutoff Method**	**High/low protein levels HR (95% CI)***	**Log-rank p value**	**High/low protein levels HR (95% CI)***	**Log-rank p value**
ANG-2	Median	2·30 (1·60–3·32)	<0·001	1·62 (1·21–2·16)	0·001
	Best fit	3·38 (2·28–5·01)	<0·001	1·37 (1·00–1·88)	0·046
	ROC curve	2·42 (1·68–3·48)	<0·001	1·45 (1·08–1·96)	0·013
BMP-7	Median	1·18 (0·73–1·91)	0·498	1·67 (1·11–2·50)	0·012
	Best fit	2·96 (1·37–6·40)	0·004	1·58 (0·91–2·73)	0·102
	ROC curve	2·96 (1·37–6·40)	0·004	1.58 (0.91–2.73)	0·102
VWF	Median	1·37 (0·96–1·96)	0·083	0·97 (0·73–1·30)	0·838
	Best fit	1·37 (0·92–2·05)	0·122	1·37 (0·99–1·90)	0·060
	ROC curve	1·41 (0·98–2·04)	0·064	1·39 (1·00–1·93)	0·050
IL6	Median	2·21 (1·52–3·22)	<0·001	1·22 (0·91–1·63)	0·175
	Best fit	2·29 (1·60–3·28)	<0·001	1·72 (1·26–2·35)	<0·001
	ROC curve	2·47 (1·67–3·65)	<0·001	1·72 (1·26–2·35)	<0·001
IL8	Median	3·48 (2·39–5·06)	<0·001	1·63 (1·22–2·18)	<0·001
	Best fit	3·19 (2·21–4·60)	<0·001	2·08 (1·43–3·02)	<0·001
	ROC curve	3·83 (2·60–5·66)	<0·001	1·58 (1·18–2·12)	0·002
MCSF	Median	1·50 (1·05–2·15)	0·026	0·89 (0·67–1·19)	0·447
	Best fit	1·83 (1·27–2·63)	<0·001	1·01 (0·76–1·35)	0·945
	ROC curve	1·83 (1·27–2·63)	<0·001	1·11 (0·68–1·81)	0·667
PlGF	Median	1·81 (1·24–2·65)	0·002	1·06 (0·79–1·43)	0·676
	Best fit	1·75 (1·21–2·53)	0·002	1·38 (0·96–1·96)	0·077
	ROC curve	1·75 (1·21–2·53)	0·002	0·96 (0·71–1·29)	0·776
SCDF1	Median	1·12 (0·78–1·59)	0·546	1·27 (0·95–1·70)	0·108
	Best fit	1·22 (0·62–2·41)	0·564	1·21 (0·89–1·64)	0·231
	ROC curve	1·45 (0·96–2·19)	0·076	1·25 (0·93–1·68)	0·134

		Overall survival		Progression-free survival	
Protein	**Cutoff Method**	**High/low protein levels HR (95% CI)***	**Log-rank p value**	**High/low protein levels HR (95% CI)***	**Log-rank p value**
VEGFR	Median	0·86 (0·60–1·23)	0·408	0·95 (0·71–1·27)	0·743
	Best fit	2·03 (0·99–4·18)	0·049	1·23 (0·76–1·98)	0·405
	ROC curve	2·03 (0·99–4·18)	0·049	1·00 (0·72–1·40)	0·993
sTIE-1	Median	1·91 (1·33–2·76)	<0·001	1·22 (0·92–1·63)	0·171
	Best fit	2·72 (1·90–3·90)	<0·001	2·84 (1·04–7·73)	0·032
	ROC curve	2·72 (1·90–3·90)	<0·001	1·22 (0·91–1·63)	0·181
TIMP-2	Median	0·89 (0·62–1·27)	0·515	0·96 (0·72–1·27)	0·757
	Best fit	0·89 (0·62–1·27)	0·515	0·96 (0·72–1·27)	0·757
	ROC curve	0·92 (0·64–1·34)	0·678	0·94 (0·70–1·27)	0·711
VEGF-A	Median	1·27 (0·89–1·82)	0·188	0·98 (0·73–1·31)	0·870
	Best fit	2·40 (1·61–3·57)	<0·001	1·12 (0·83–1·53)	0·457
	ROC curve	1·36 (0·95–1·94)	0·094	0·93 (0·62–1·40)	0·738
VEGF-C	Median	1·14 (0·79–1·63)	0·485	1·05 (0·79–1·40)	0·739
	Best fit	7·41 (1·03–53·05)	0·019	1·35 (0·82–2·24)	0·239
	ROC curve	1·32 (0·90–1·94)	0·152	1·17 (0·87–1·58)	0·287
VEGF-D	Median	1·29 (0·91–1·85)	0·155	1·06 (0·79–1·41)	0·708
	Best fit	1·77 (1·24–2·53)	0·002	1·51 (1·09–2·08)	0·011
	ROC curve	1·64 (1·15–2·35)	0·006	1·49 (1·10–2·01)	0·009
VEGF-A isoform 121	Median	1·19 (0·83–1·70)	0·337	1·08 (0·81–1·44)	0·596
	Best fit	1·38 (0·85–2·26)	0·192	1·14 (0·81–1·62)	0·444
	ROC curve	1·18 (0·75–1·84)	0·473	1·14 (0·81–1·62)	0·444

*Protein levels were determined by multiplex immunoassay in baseline plasma samples obtained from 199 patients enrolled in the placebo arm of CORRECT. A total of 122 OS events and 187 PFS events were reported.. The analysis of VEGF-A levels included data from 195 patients, with a total of 120 OS events and 183 PFS events reported.

ANG-2: Angiopoietin 2; BMP-7: bone morphogenetic protein 7; CI: confidence interval; HR: hazard ratio; IL6: interleukin 6; IL8: interleukin 8; MCSF: macrophage colony stimulating factor; PlGF: placental growth factor; ROC: receiver operating characteristic; SCDF1 stromal cell-derived factor 1; sTIE-1: soluble tyrosine kinase with immunoglobulin-like and epidermal growth factor like-domains 1; TIMP-2: tissue-derived metalloproteinase 2; VEGF: vascular endothelial growht factor: VEGFR: VEGF receptor; VWF: Von Willebrandt Factor.