SUPPLEMENTARY INFORMATION

Parameter		Number (%)
Age	<65.8	28 (35)
	≥65.8	52 (65)
Gender	female	30 (38)
	male	50 (63)
Tumor site	right colon (right colon and transverse)	34 (43)
	left colon (left colon and sigmoid colon)	29 (36)
	rectum	13 (16)
	unknown	1 (1)
Grading	G1	4 (5)
	G2	60 (75)
	G3	9 (11)
	undefined	7 (9)
Progression (RECIST CRITERIA)	Not Progressed	35 (44)
	Progressed	45 (56)
Overall Survival	Alive	30 (38)
	Dead	50 (63)
Best Response (RECIST CRITERIA)	Complete Response	9 (11)
	Partial Response	18 (23)
	Stable disease	31 (39)
	Progression	16 (20)
	Unknown	6 (7)
***KRAS* status**	Wild type	26 (32)
	Mutated	47 (59)
	undefined	7 (9)

Table S1. Distribution of clinicopathological and molecular characteristics. Absolute values and percentages are indicated. All the clinical data were collected by medical oncologists of the hospitals involved in the study.

| MARKER	NEGATIVE/INACTIVE SAMPLE	POSITIVE/ACTIVE SAMPLE	References
hERG1	0-49%	≥50%	Lastraioli et al, 2012
B1-Integrin	0-49%	≥50%	N/A
pAKT	0-10%	≥10%	N/A
NFkB	0-100% cytoplasm 0% nucleus	1-100% nucleus	N/A
HIF-1α	0-100% cytoplasm 0% nucleus	1-100% nucleus	N/A
HIF-2α	0-100% cytoplasm 0% nucleus	1-100% nucleus	N/A
p53	0-10%	>10%	Lastraioli et al, 2012
VEGF-A	0-10%	>10%	Lastraioli et al, 2012
GLUT-1	0-10%	>10%	Lastraioli et al, 2012
CA-IX	0-10%	>10%	Lastraioli et al, 2012

Table S2. Scoring system. The applied scoring system for each marker is reported, it is indicated the percentage and/or the localization of labelled tumour cells.

|	Log-Rank test Pr>Chi square	Comparison	Pr>Chi square	Hazard Ratio	95% Wald Confidence
hERG1-pAKT	0.032	+- vs --	0.023	0.277	0.092-0.835
		++ vs --	0.012	0.259	0.100-0.702
hERG1-NFkB	0.021	+- vs --	0.015	0.347	0.149-0.807
		++ vs --	0.001	0.270	0.112-0.649
hERG1-HIF-1α	0.011	+- vs --	0.022	0.305	0.113-0.819
		++ vs --	0.013	0.297	0.114-0.769
hERG1-HIF-2α	0.012	++ vs --	0.001	0.235	0.090-0.613
hERG1-VEGF-A	0.001	++ vs --	0.044	0.358	0.135-0.947
KRAS-hERG1	0.008	-+ vs +-	0.021	0.310	0.113-0-850
		++ vs +-	0.001	0.210	0.080-0.551

Table S3. PFS analysis of combined markers expression. Only statistically significant results are reported in the table. Negative/inactive marker is indicated with – and positive/active marker with +. For *KRAS* status, - indicates Wild type *KRAS* and + identifies mutated *KRAS* samples.

	Number In	P Value
hERG1	0	**<u>0.002</u>**
HIF-2α	1	0.219
GLUT-1	2	0.265
KRAS status	3	0.238
NFkB	4	0.365
β1-Integrin	5	0.481
HIF-1α	6	0.527
pAKT	7	0.547
VEGF-A	8	0.718
p53	9	0.838
CA-IX	10	0.974

Table S4. Multivariate PFS analysis. Significant P values are in bold. A) Multivariate PFS analysis with all markers of proangiogenic pathway and *KRAS* status. Multivariate analysis was performed as described in Materials and Methods section. P values of Log Rank test, Median PFS: 11.2 months. Significant P values are in bold and underlined.
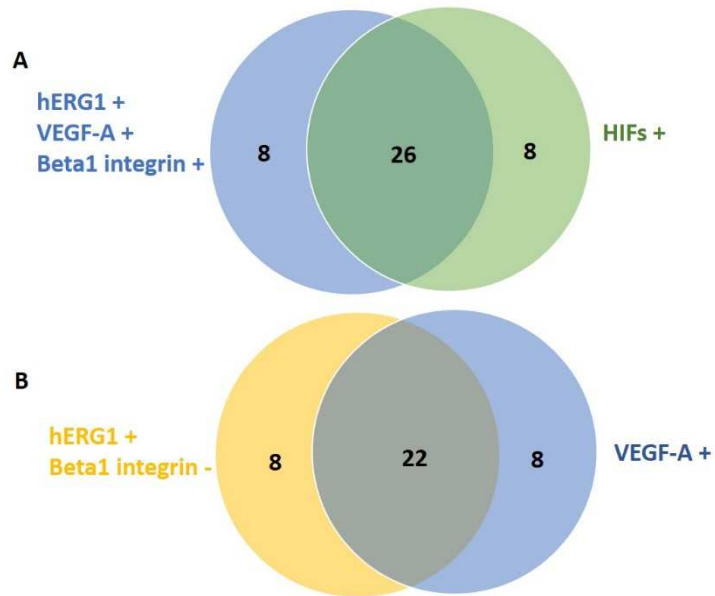
Figure S1. Venn diagram showing the distribution and overlapping of some of the markers evaluated in the patients enrolled in the study. **A)** Patients expressing hERG1, β1-integrin and VEGF-A (34/80) were positive also for aHIF-1α and/or aHIF-2α (26/34). **B)** 30/80 samples were positive for hERG1 and negative for β1-Integrin, 22/30 of them were positive also for VEGF-A.
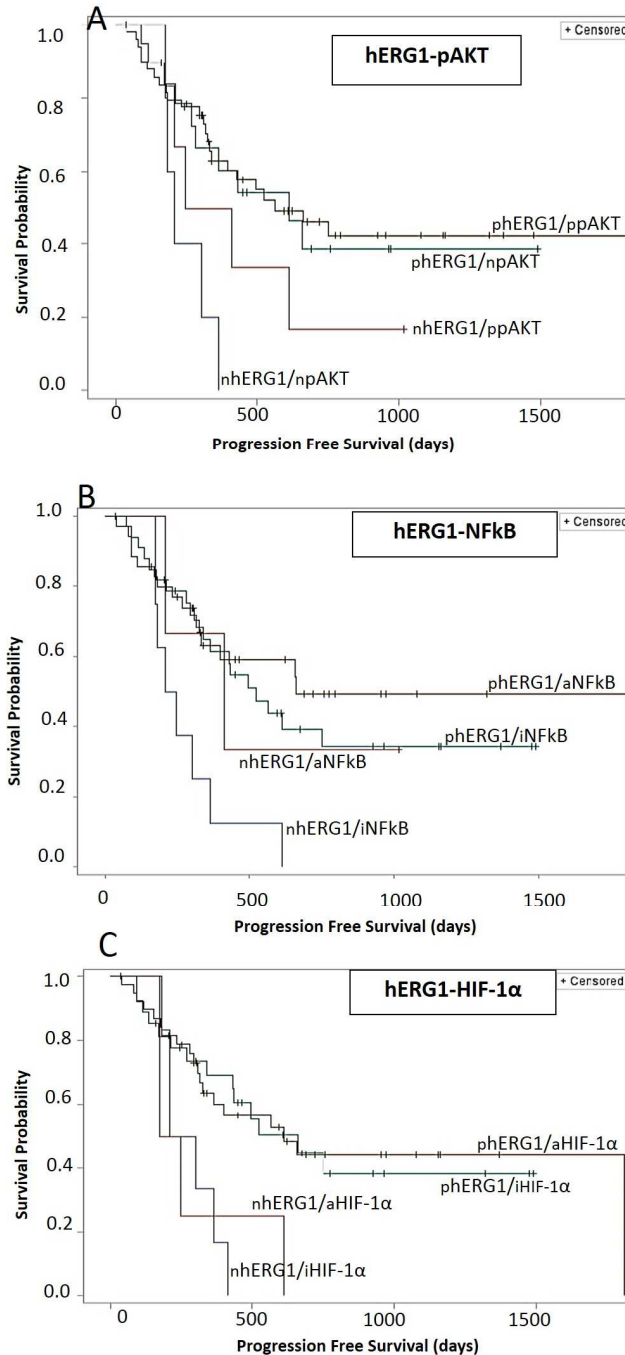
Figure S2. Kaplan-Meier curves of significant progression free survival obtained from the risk analysis with combined markers. A) hERG1 and pAKT combination; **B)** hERG1 and NFkB; **C)** hERG1 and HIF-1α. Combinations are defined as follows: 00: hERG1 negative- other marker negative/inactive; 01: hERG1 negative- other marker positive/active; 10: hERG1 positive-other marker negative/inactive; 11: both hERG1 and other marker positive/active. Number of patients: hERG1 and pAKT (00: 5, 10: 20); (00: 5, 11: 49); hERG1 and NFkB (00: 8, 10: 34); (00: 8, 11: 35); hERG1 and HIF-1α (00: 6, 10: 27); (00: 6, 11: 39). Only statistically significant curves are reported. "n": Negative samples; "p": positive samples; "a": samples with active protein; "I": samples with inactive protein.