**Table S1.** Selected miRNAs for further validation, by individual qRT-PCR. Selected miRNAs for further validation, by individual qRT–PCR, in serum samples of patients included in the study. miRNA accession numbers and absolute values of the log of fold change are presented**.**

| **miRNA ID** | **Accesion number** | **Fold change** | ***p* value** |
|---|---|---|---|
| miR-126-3p | MIMAT0000445 | –3.671 | 0.013 |
| miR-126-5p | MIMAT0000444 | –3.174 | 0.018 |
| miR-139-5p | MIMAT0000250 | –5.631 | 0.012 |
| miR-140-3p | MIMAT0004597 | 2.075 | 0.021 |
| miR-143-5p | MIMAT0004599 | 2.21 | 0.021 |
| miR-152-3p | MIMAT0000438 | –1.695 | 0.021 |
| miR-185-5p | MIMAT0000455 | –3.056 | 0.022 |
| miR-28-3p | MIMAT0004502 | –2.434 | 0.039 |
| miR-338-3p | MIMAT0000763 | 2.227 | 0.059 |
| miR-362-3p | MIMAT0004683 | –3.424 | 0.049 |
| miR-551a | MIMAT0003214 | 3.78 | 0.009 |
| miR-582-5p | MIMAT0003247 | 6.756 | 0.029 |

**Table S2.** Panel of miRNAs selected for further validation in paraffin embedded primary tumor biopsies. Panel of miRNAs selected for further validation in paraffin embedded primary tumor biopsies. The previously reported miRNAs associated with CRC histopathological and clinical features, including our data, were also determined in this study by qRT–PCR and listed here. miRNA accession numbers are presented.

| **miRNA ID** | **Accesion Number** |
|---|---|
| hsa-miR-1-3p | MIMAT0000416 |
| hsa-miR-10a-5p | MIMAT0000253 |
| hsa-miR-16-5p | MIMAT0000069 |
| hsa-miR-19a-3p | MIMAT0000073 |
| hsa-miR-19a-5p | MIMAT0004490 |
| hsa-miR-20a-3p | MIMAT0004493 |
| hsa-miR-20a-5p | MIMAT0000075 |
| hsa-miR-23b-3p | MIMAT0000418 |
| hsa-miR-24-3p | MIMAT0000080 |
| hsa-miR-27b-3p | MIMAT0000419 |
| hsa-miR-29c-3p | MIMAT0000681 |
| hsa-miR-92a-1-5p | MIMAT0004507 |
| hsa-miR-99a-5p | MIMAT0000097 |
| hsa-miR-143-3p | MIMAT0000435 |
| hsa-miR-145-5p | MIMAT0000437 |
| hsa-miR-193b-5p | MIMAT0004767 |
| hsa-miR-320a | MIMAT0000510 |
| hsa-miR-326 | MIMAT0000756 |
| hsa-miR-642b-3p | MIMAT0018444 |
| hsa-Let7a-5p | MIMAT0000062 |

**Table S3.** SNPs could have added value to patient clinical variables.

**a) Data from the Fishers Exact analysis correlating SNPs with histopathological and clinical variables that showed statistical significance**

| Gene | Probe (rs) | Genotype | Resp (SD+PR+CR) vs. NResp | Survival | PFS (days) | T (T1–T4) | N (N0–N2) | M (M0–M1) | Histological grade (G1–3) | Disease location (colon/rectum/colorectal) | Locoregional | Surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **VEGFA** | rs699947 | _2578AA | NS | 0.07 | **0.07** | NS | **0.08** | **0.07** | NS | NS | **0.03** | NS |
| **VEGFA** | rs1570360 | _1154A | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **IL8** | rs4073 | _25T | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFA** | rs2010963 | _634GG | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **ICAM1** | rs5498 | 469T/C | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **CXCR2** | rs2230054 | 785CC | NS | NS | **0.05** | NS | NS | **0.05** | NS | NS | NS | **0.01** |
| **VEGFA** | rs3025039 | 936CT | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFR1** | rs9582036 |  | **0.07** | 0.08 | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFR1** | rs7993418 |  | **0.03** | 0.03 | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFR2** | rs2305948 | val273Ile | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |

**b) Data from the Fishers Exact analysis correlating SNPs with other clinical variables and toxicity (these analyses were non–significant)**

| Gene | Probe (rs) | Genotype | Metastasis (Mets) | Liver Mets | Lung Mets | Peritoneal Mets | Distant Mets | Toxicity (Grade 3 and 4) | Asthenia | Hypertension | Diarrhea | Palma–plantar erythrodysesthesia syndrome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **VEGFA** | rs699947 | _2578AA | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFA** | rs1570360 | _1154A | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **IL8** | rs4073 | _25T | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFA** | rs2010963 | _634GG | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **ICAM1** | rs5498 | 469T/C | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **CXCR2** | rs2230054 | 785CC | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFA** | rs3025039 | 936CT | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFR1** | rs9582036 |  | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFR1** | rs7993418 |  | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| **VEGFR2** | rs2305948 | val273Ile | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |

**Table S4.** SNPs correlates with patient clinical features. A logistic regression model was performed with the clinical variables and then adding the genotypes one by one. In this model, the SNP location is used and the p–values are calculated. These values were used to construct the area under the curve (AUC) with the corresponding confidence intervals.

| Gene | SNP (rs) | 2.5% | 97.5% | *p*-value |
|---|---|---|---|---|
| **VEGFA** | rs699947 | 0.021 | 0.966 | 0.060 |
| **VEGFA** | rs1570360 | 0.007 | 1.400 | 0.143 |
| **VEGFA** | rs2010963 | 0.186 | 6.808 | 0.941 |
| **VEGFA** | rs3025039 | 0.152 | 4.015 | 0.746 |
| **VEGFR1** | rs9582036 | 0.880 | 30.069 | 0.084 |
| **VEGFR1** | rs7993418 | 1.066 | 44.348 | **0.049** |
| **VEGFR2** | rs2305948 | 0.152 | 5.545 | 0.881 |
| **ICAM1** | rs5498 | 0.025 | 1.128 | 0.086 |
| **CXCR2** | rs2230054 | 0.152 | 5.545 | 0.881 |

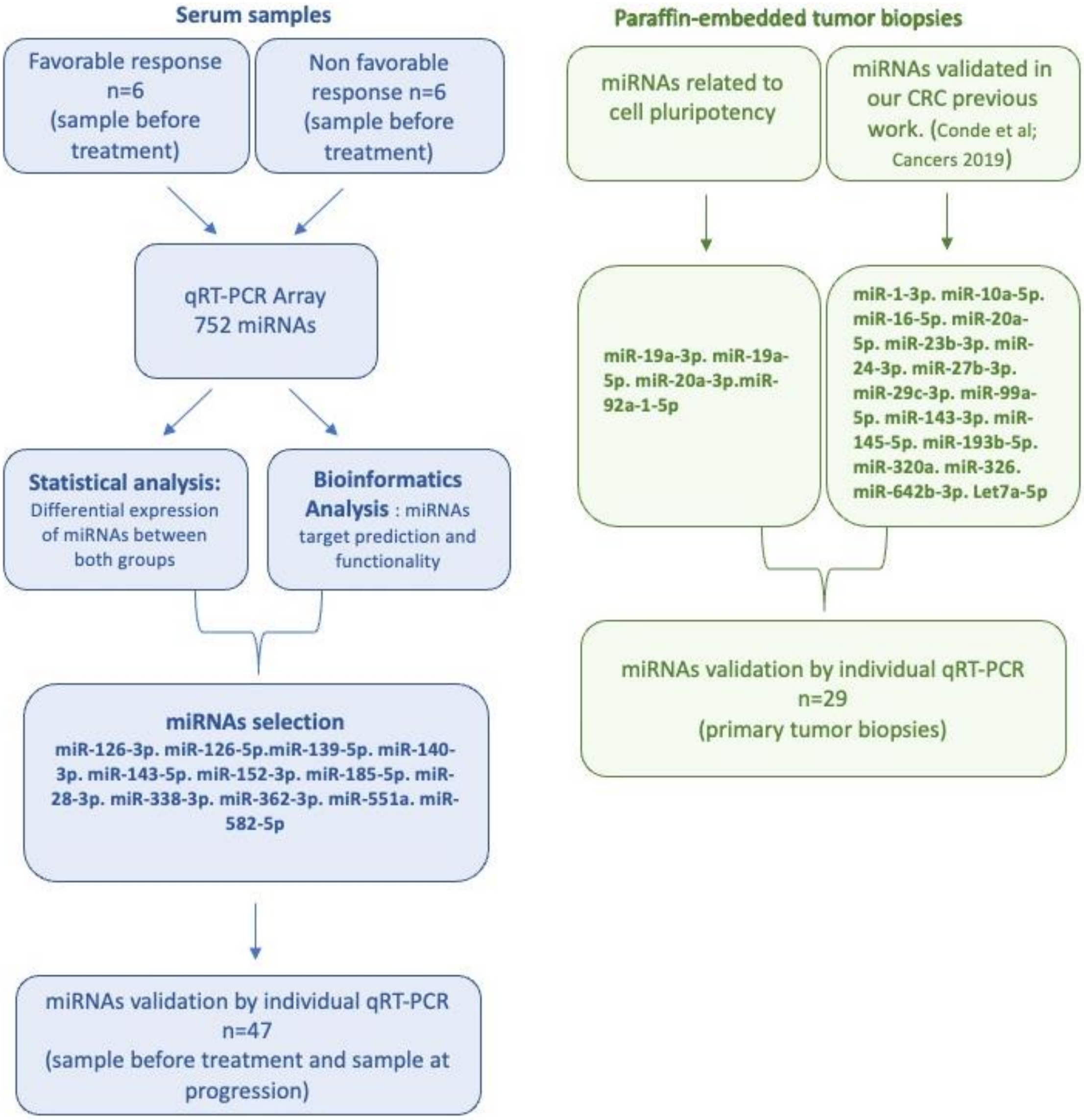

**Figure S1.** miRNAs studies workflow.

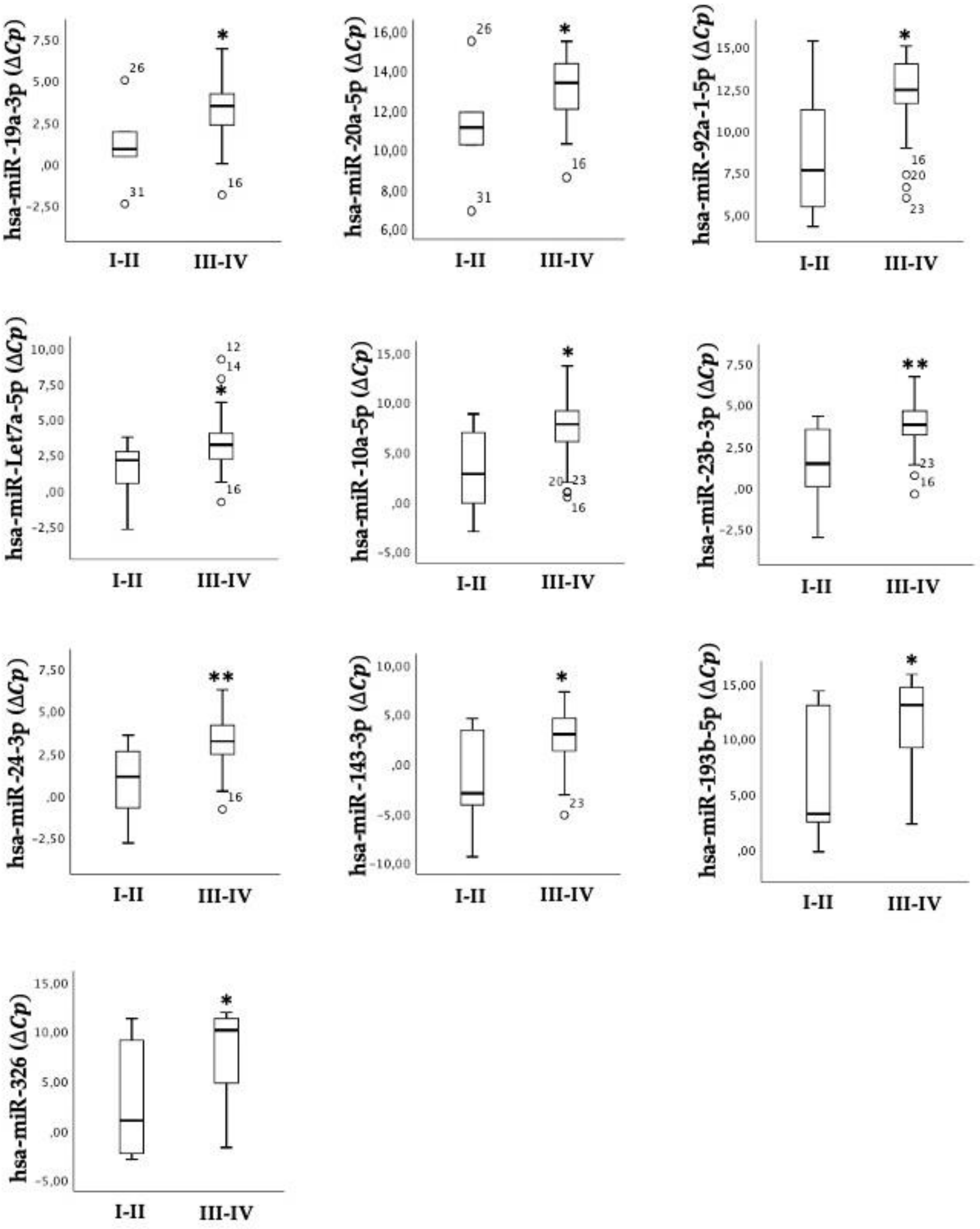

**Figure S2.** miRNAs determined in primary tumors correlates with tumor stage. Statistical association of selected tissue miRNAs with tumor staging. miRNA levels are expressed as delta-crossing threshold (DCT), the mean of miR-103a-3p Cq and miR-30c-5p Cq was used as a normalizer Cq. Only miRNAs showing a statistically significant association are shown. Data are presented as median and interquartile range with: * $p < 0.05$, ** $p < 0.01$.

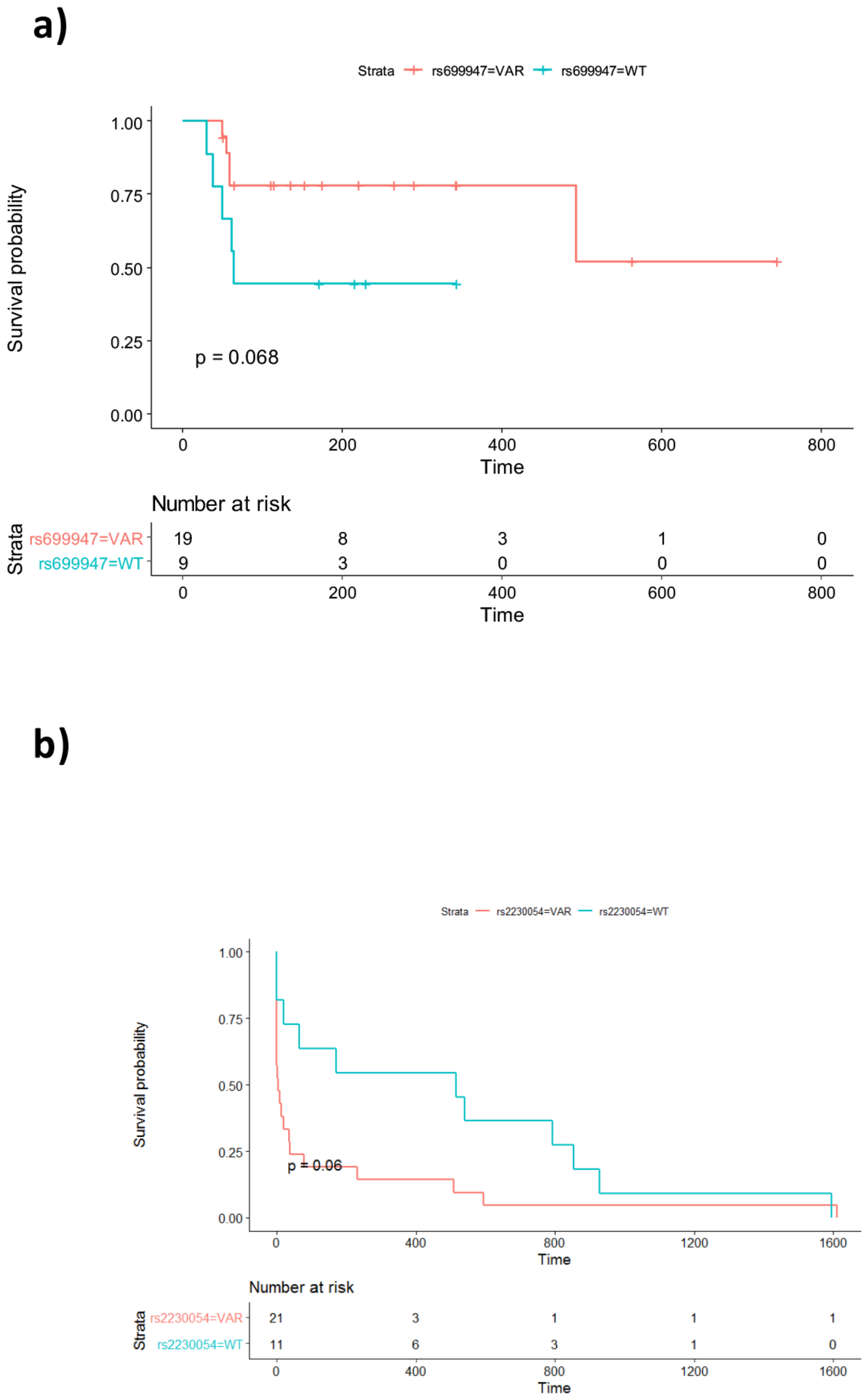

**Figure S3.** SNPS correlates with tumor progression upon Regorafenib treatment. Kaplan Meier plots of the association with disease free progression time of SNPs (**a**) rs699947 and (**b**) rs2230054.