SUPPLEMENTAL MATERIALS AND METHODS

Quantitative RT-PCR

Quantitative RT-PCR analysis was performed using the Universal miRCURY LNA™ microRNA PCR System (Exiqon), following the manufacturer's instructions. In brief, 10ng of total RNA was reversely transcribed, using the miRCURY LNA™ Universal RT microRNA PCR kit (Exiqon). The resulting cDNA was diluted and PCR reactions were carried out using ExiLENT SYBR® Green Master Mix kit (Exiqon) and LNA™-enhanced microRNA PCR primer sets (Exiqon). MiRNA expression was quantified using the QuantStudio™ 6-7 Flex Real-Time PCR System (Applied Biosystems, Foster City, California). Stably expressed endogenous control 5s RNA was used for data normalization. Three samples with a low expression of the 5s RNA were excluded from the analysis. Expression of each miRNA was calculated using the comparative Ct method using the Ct value of the endogenous control to normalize the data. Negative controls were present in all PCR series and assays were carried out in quadruplicates.

Data analysis

Data analysis was performed in R version 3.1.2. From the initial 2576 miRNAs those that had a normalized count value below 15 in 95% of the samples were considered to be of low expression and were filtered out, reducing the initial number to 374. Differential expression between tumors with PD as best response to TKI treatment and those with other responses were assessed using the exact negative binomial test from the edgeR package [26]. P values were corrected for multiple hypotheses testing using Benjamini & Hochberg False Discovery Rate (FDR) adjustment [27].

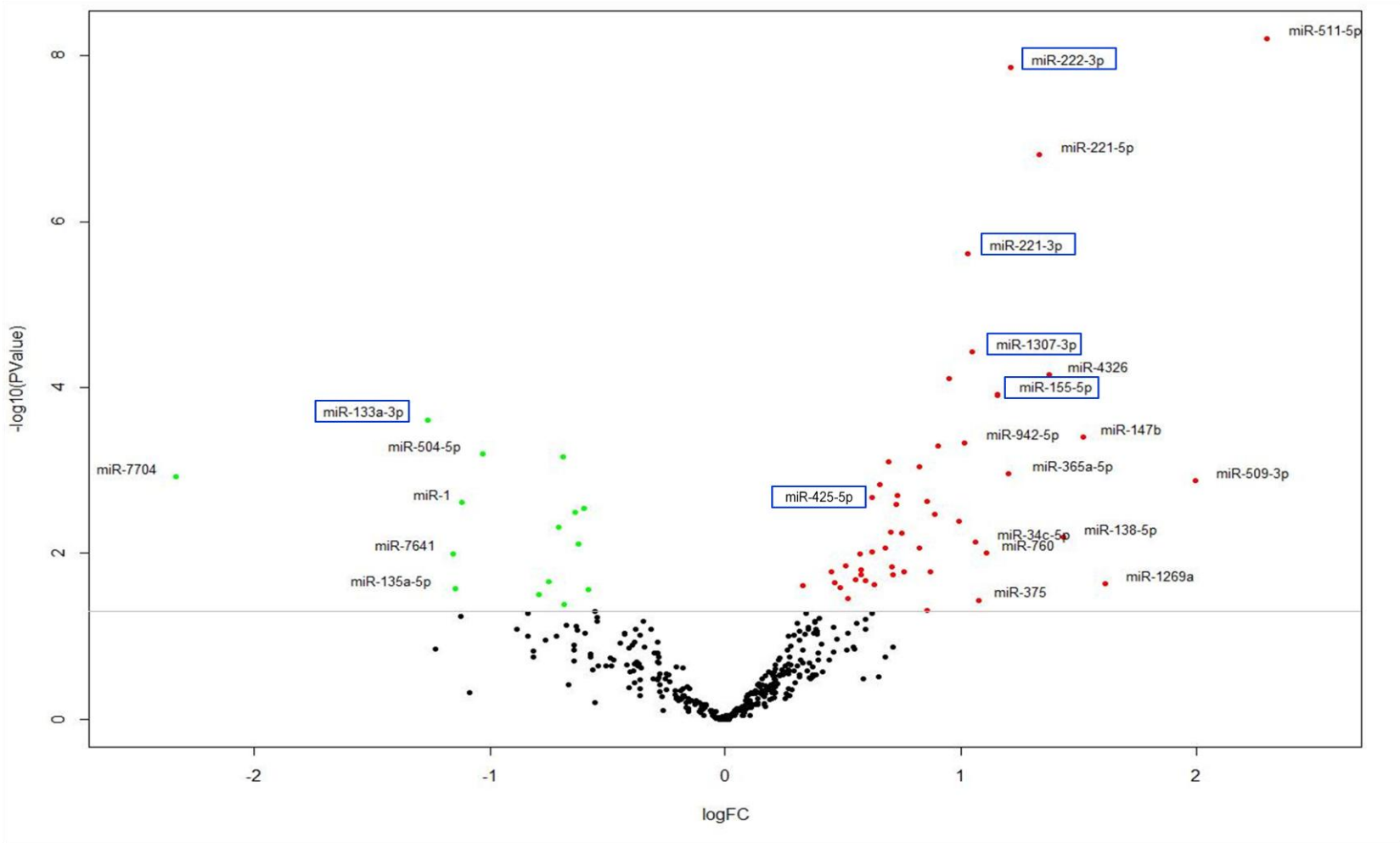
Models correlating TKI response and miRNAs expression were constructed using step-wise conditional logistic regression analysis with the total population. To combine the data, the

expression of the miRNAs was expressed as a dichotomous variable using as threshold in each series the median miRNA expression. To avoid a possible series' effect, a binary variable that identified each series was included in the analysis.

For PFS and OS analysis, we defined PFS as the time between the first day of treatment with sunitinib and the date of radiological or clinical PD or clear clinical evidence of PD. We defined disease specific OS as the time between the first day of treatment with sunitinib and patient death due to disease. Patients who were lost to follow-up or had not progressed (for PFS analysis)/ were alive (OS analysis) at the time of the study were treated as censored events. To have comparable miRNA effect magnitudes in the survival analyses, the expression of each miRNA was divided by its median expression value.

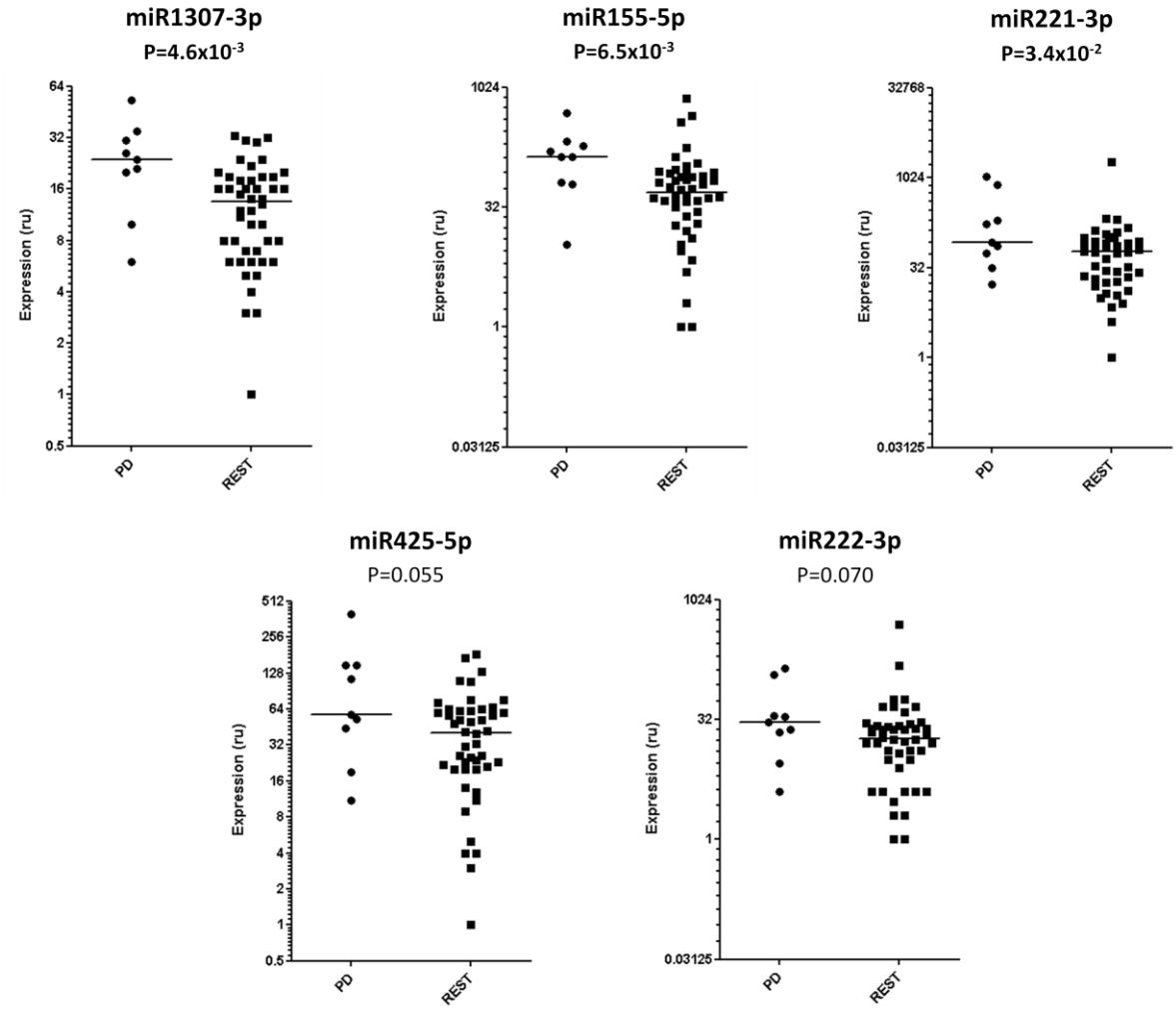
To identify the target pathways of the miRNAs associated with TKI refractoriness, PFS and OS we used the DIANA miRPath software, using experimentally validated miRNA interactions derived from DIANA-TarBase v6.0 predictions.

SUPPLEMENTARY FIGURE 1



Supplementary Figure 1. **Volcano plot of miRNAs in the NGS discovery series.** The x-axis shows the miRNAs' expression log2 fold-change, whereas the y-axis shows the −log10 of the P value for each miRNA. MiRNAs with P<0.05 are marked: in red those up-regulated in tumors with PD as best response; in green those down-regulated in tumors with PD as best response. MiRNAs selected for validation are indicated by a rectangle.

SUPPLEMENTARY FIGURE 2



Supplementary Figure 2. Expression of miRNAs in the validation series. Expression of miR-1307-3p, miR-155-5p, miR-221-3p, miR-425-5p and miR-222-3p in patients with PD as best tumor response and in patients with at least stable disease (REST). P values correspond to one-sided nonparametric Mann-Whitney test comparing the two groups.

SUPPLEMENTARY TABLES

Supplementary Table 1. Characteristics of the 64 primary tumor ccRCCs cases treated with first-line sunitinib in the validation set.

Characteristic	Nr.	%
Age at sunitinib (y)		
Median	66	
Min-Max (IQR)	46-82 (54-72)	
Gender		
Male	42	66
Female	22	34
ECOG		
0	18	28
1	37	58
2	4	6
Missing	5	8
Nr. of metastatic sites at sunitinib		
1	17	27
2	33	52
3	11	17
4	3	5
MSKCC risk factors		
0 (favorable)	36	56
1-2 (intermediate)	27	42
3 (poor)	1	2
Objective Response		
CR	0	0
PR	30	47
SD	19	30
PD	9	14
Unknown	6	9

Supplementary Table 2. Full list of miRNAs differentially expressed (P<0.05) in tumors progressing under TKI therapy compared to tumors showing at least stable disease

miRNA[a]	FC	Expression in PD	P value	FDR	Ref. [b]
miR-511-5p	4.9	Up	$6.3x10^{-9}$	**$2.3x10^{-6}$**	
miR-222-3p	2.3	Up	$1.4x10^{-8}$	**$2.6x10^{-6}$**	[17] (s)
miR-221-5p	2.5	Up	$1.6x10^{-7}$	**$2.0x10^{-5}$**	[17] (s)
miR-221-3p	2.0	Up	$2.4x10^{-6}$	**$2.2x10^{-4}$**	[17] (s)
miR-1307-3p	2.1	Up	$3.7x10^{-5}$	**$2.8x10^{-3}$**	
miR-4326	2.6	Up	$6.9x10^{-5}$	**$4.1x10^{-3}$**	
miR-130b-5p	1.9	Up	$7.7x10^{-5}$	**$4.1x10^{-3}$**	
miR-155-5p	2.2	Up	$1.2x10^{-4}$	**$5.7x10^{-3}$**	[18] (s)
miR-133a-3p	0.4	Down	$2.5x10^{-4}$	**$1.0x10^{-2}$**	[19] (s/i)
miR-147b	2.9	Up	$4.0x10^{-4}$	**$1.4x10^{-2}$**	
miR-4497	0.1	Down	$4.3x10^{-4}$	**$1.4x10^{-2}$**	
miR-942-5p	2.0	Up	$4.7x10^{-4}$	**$1.5x10^{-2}$**	[19] (s)
miR-149-5p	1.9	Up	$5.1x10^{-4}$	**$1.5x10^{-2}$**	
miR-504-5p	0.5	Down	$6.4x10^{-4}$	**$1.7x10^{-2}$**	
miR-143-5p	0.6	Down	$7.0x10^{-4}$	**$1.8x10^{-2}$**	
miR-941	1.6	Up	$7.9x10^{-4}$	**$1.9x10^{-2}$**	
miR-132-5p	1.8	Up	$9.2x10^{-4}$	**$2.0x10^{-2}$**	
miR-365a-5p	2.3	Up	$1.1x10^{-3}$	**$2.3x10^{-2}$**	
miR-7704	0.2	Down	$1.2x10^{-3}$	**$2.4x10^{-2}$**	
miR-509-3p	4.0	Up	$1.3x10^{-3}$	**$2.5x10^{-2}$**	
miR-1301-3p	1.6	Up	$1.5x10^{-3}$	**$2.7x10^{-2}$**	
miR-18a-5p	1.7	Up	$2.0x10^{-3}$	**$3.5x10^{-2}$**	
miR-425-5p	1.5	Up	$2.2x10^{-3}$	**$3.5x10^{-2}$**	[17] (s)
miR-146b-5p	1.8	Up	$2.4x10^{-3}$	**$3.7x10^{-2}$**	
miR-1	0.5	Down	$2.5x10^{-3}$	**$3.7x10^{-2}$**	
miR-340-3p	1.7	Up	$2.6x10^{-3}$	**$3.7x10^{-2}$**	
miR-10b-5p	0.7	Down	$2.9x10^{-3}$	**$4.0x10^{-2}$**	
miR-145-3p	0.6	Down	$3.2x10^{-3}$	**$4.3x10^{-2}$**	
miR-223-5p	1.9	Up	$3.4x10^{-3}$	**$4.4x10^{-2}$**	
miR-199b-5p	2.0	Up	$4.2x10^{-3}$	$5.2x10^{-2}$	
miR-143-3p	0.6	Down	$4.9x10^{-3}$	$5.9x10^{-2}$	
miR-130b-3p	1.6	Up	$5.7x10^{-3}$	$6.4x10^{-2}$	
miR-150-5p	1.7	Up	$5.7x10^{-3}$	$6.4x10^{-2}$	
miR-138-5p	2.7	Up	$6.4x10^{-3}$	$7.0x10^{-2}$	
miR-34c-5p	2.1	Up	$7.4x10^{-3}$	$7.9x10^{-2}$	
miR-10b-3p	0.7	Down	$7.7x10^{-3}$	$8.0x10^{-2}$	
miR-708-5p	1.6	Up	$8.7x10^{-3}$	$8.6x10^{-2}$	
miR-3615	1.8	Up	$8.7x10^{-3}$	$8.6x10^{-2}$	
miR-142-5p	1.5	Up	$9.7x10^{-3}$	$9.1x10^{-2}$	
miR-760	2.2	Up	$9.9x10^{-3}$	$9.1x10^{-2}$	
miR-7641	0.4	Down	$1.0x10^{-2}$	$9.1x10^{-2}$	
miR-21-5p	1.5	Up	$1.0x10^{-2}$	$9.1x10^{-2}$	
miR-362-5p	1.4	Up	$1.4x10^{-2}$	$1.2x10^{-1}$	

miR-7-5p	1.6	Up	$1.5x10^{-2}$	$1.2x10^{-1}$	
miR-548k	1.5	Up	$1.6x10^{-2}$	$1.3x10^{-1}$	
miR-193b-3p	1.7	Up	$1.7x10^{-2}$	$1.3x10^{-1}$	
miR-193b-5p	1.8	Up	$1.7x10^{-2}$	$1.3x10^{-1}$	
miR-185-5p	1.4	Up	$1.7x10^{-2}$	$1.3x10^{-1}$	
miR-330-5p	1.5	Up	$1.8x10^{-2}$	$1.4x10^{-1}$	
miR-142-3p	1.6	Up	$1.8x10^{-2}$	$1.4x10^{-1}$	
miR-500b-5p	1.5	Up	$2.1x10^{-2}$	$1.5x10^{-1}$	
miR-128-3p	1.5	Up	$2.2x10^{-2}$	$1.5x10^{-1}$	
miR-194-5p	0.6	Down	$2.2x10^{-2}$	$1.6x10^{-1}$	
miR-421	1.4	Up	$2.2x10^{-2}$	$1.6x10^{-1}$	
miR-1269a	3.1	Up	$2.3x10^{-2}$	$1.6x10^{-1}$	
miR-502-5p	1.6	Up	$2.4x10^{-2}$	$1.6x10^{-1}$	
miR-98-5p	1.3	Up	$2.4x10^{-2}$	$1.6x10^{-1}$	
miR-17-3p	1.4	Up	$2.6x10^{-2}$	$1.7x10^{-1}$	
miR-135a-5p	0.5	Down	$2.7x10^{-2}$	$1.7x10^{-1}$	
miR-145-5p	0.7	Down	$2.8x10^{-2}$	$1.7x10^{-1}$	
miR-139-3p	0.6	Down	$3.1x10^{-2}$	$1.9x10^{-1}$	
miR-224-5p	1.4	Up	$3.5x10^{-2}$	$2.1x10^{-1}$	
miR-375	2.1	Up	$3.7x10^{-2}$	$2.2x10^{-1}$	
miR-192-5p	0.6	Down	$4.2x10^{-2}$	$2.5x10^{-1}$	
miR-31-5p	1.8	Up	$4.9x10^{-2}$	$2.8x10^{-1}$	

[a] All miRNAs with a P value <0.05 are listed. In bold miRNAs with a FDR<0.05.

[b] Evidences in literature and direction (risk/ protection) of the association in current and referenced study: same direction of association (s); inverse direction of association (i).

Supplementary Table 3. Full list of microRNAs associated with PFS.

miRNA [a]	Univariate			Multivariable [b]		Ref. [c]
	HR (95% CI)	P value	FDR	HR (95% CI)	p value	
miR-221-3p	2.25 (1.67-3.02)	$6.8x10^{-8}$	**$2.5x10^{-5}$**	2.07 (1.52-2.81)	$3.8x10^{-6}$	[17] (s)
miR-222-3p	2.02 (1.51-2.71)	$2.3x10^{-6}$	**$4.3x10^{-4}$**	1.89 (1.41-2.54)	$2.0x10^{-5}$	[17] (s)
miR-221-5p	1.60 (1.30-1.98)	$1.0x10^{-5}$	**$1.3x10^{-3}$**	1.68 (1.29-2.17)	$9.8x10^{-5}$	[17] (s)
miR-425-5p	1.72 (1.32-2.25)	$6.2x10^{-5}$	**$5.7x10^{-3}$**	1.63 (1.21-2.18)	$1.1x10^{-3}$	[17] (s)
miR-4326	1.37 (1.16-1.62)	$1.5x10^{-4}$	**$1.1x10^{-2}$**	1.33 (1.11-1.59)	$1.7x10^{-3}$	
miR-365a-5p	1.15 (1.07-1.24)	$2.5x10^{-4}$	**$1.5x10^{-2}$**	1.15 (1.06-1.25)	$5.7x10^{-4}$	
miR-193b-3p	1.18 (1.08-1.29)	$3.5x10^{-4}$	**$1.8x10^{-2}$**	1.14 (1.03-1.26)	$9.3x10^{-3}$	
miR-130b-5p	1.60 (1.23-2.09)	$5.2x10^{-4}$	**$2.0x10^{-2}$**	1.52 (1.16-1.98)	$2.4x10^{-3}$	
miR-185-5p	1.65 (1.24-2.19)	$5.9x10^{-4}$	**$2.0x10^{-2}$**	1.48 (1.09-2.01)	$1.1x10^{-2}$	
miR-193b-5p	1.12 (1.05-1.20)	$6.1x10^{-4}$	**$2.0x10^{-2}$**	1.09 (1.02-1.17)	$9.4x10^{-3}$	
miR-375	1.06 (1.03-1.10)	$4.4x10^{-4}$	**$2.0x10^{-2}$**	1.05 (1.01-1.09)	$1.3x10^{-2}$	
miR-7-5p	1.25 (1.09-1.43)	$1.3x10^{-3}$	**$4.0x10^{-2}$**	1.21 (1.06-1.39)	$4.8x10^{-3}$	
miR-1269a	1.01 (1.00-1.02)	$2.1x10^{-3}$	$5.6x10^{-2}$	1.01 (1.00-1.01)	$1.9x10^{-2}$	
miR-149-5p	1.29 (1.10-1.51)	$2.1x10^{-3}$	$5.6x10^{-2}$	1.20 (1.02-1.42)	$3.2x10^{-2}$	
miR-147b	1.08 (1.03-1.14)	$2.4x10^{-3}$	$5.8x10^{-2}$	1.06 (1.01-1.12)	$3.0x10^{-2}$	
miR-511-5p	1.05 (1.02-1.09)	$2.6x10^{-3}$	$6.0x10^{-2}$	1.05 (1.01-1.08)	$8.3x10^{-3}$	
miR-150-5p	1.46 (1.14-1.86)	$2.9x10^{-3}$	$6.3x10^{-2}$	1.40 (1.08-1.80)	$1.1x10^{-2}$	
miR-223-5p	1.16 (1.05-1.28)	$3.8x10^{-3}$	$7.6x10^{-2}$	1.16 (1.04-1.29)	$6.0x10^{-3}$	
miR-589-5p	1.86 (1.22-2.85)	$4.0x10^{-3}$	$7.6x10^{-2}$	1.67 (1.09-2.55)	$1.7x10^{-2}$	
miR-548k	1.59 (1.15-2.19)	$4.7x10^{-3}$	$8.6x10^{-2}$	1.54 (1.14-2.10)	$5.4x10^{-3}$	
miR-652-3p	1.34 (1.09-1.65)	$5.2x10^{-3}$	$9.0x10^{-2}$	1.22 (0.98-1.52)	$7.0x10^{-2}$	
miR-130b-3p	1.61 (1.15-2.25)	$5.5x10^{-3}$	$9.2x10^{-2}$	1.72 (1.21-2.44)	$2.4x10^{-3}$	
miR-204-5p	0.68 (0.52-0.9)	$5.8x10^{-3}$	$9.2x10^{-2}$	0.68 (0.52-0.90)	$6.7x10^{-3}$	
miR-18a-5p	1.63 (1.15-2.32)	$6.3x10^{-3}$	$9.3x10^{-2}$	1.65 (1.14-2.38)	$7.4x10^{-3}$	
miR-629-5p	1.39 (1.10-1.75)	$6.1x10^{-3}$	$9.3x10^{-2}$	1.27 (1.00-1.61)	$4.8x10^{-2}$	
miR-941	1.78 (1.17-2.71)	$6.9x10^{-3}$	$9.6x10^{-2}$	1.58 (1.02-2.46)	$4.2x10^{-2}$	
miR-134-5p	1.11 (1.03-1.20)	$7.5x10^{-3}$	$9.9x10^{-2}$	1.07 (0.99-1.16)	$9.6x10^{-2}$	
miR-345-5p	2.07 (1.21-3.52)	$7.6x10^{-3}$	$9.9x10^{-2}$	2.03 (1.20-3.43)	$8.3x10^{-3}$	
miR-1301-3p	1.32 (1.07-1.63)	$9.2x10^{-3}$	$1.1x10^{-1}$	1.22 (0.99-1.52)	$6.3x10^{-2}$	
miR-421	2.24 (1.22-4.09)	$9.1x10^{-3}$	$1.1x10^{-1}$	2.10 (1.14-3.89)	$1.8x10^{-2}$	
let-7b-3p	0.39 (0.19-0.79)	$9.6x10^{-3}$	$1.1x10^{-1}$	0.50 (0.25-1.02)	$5.8x10^{-2}$	
miR-5100	0.77 (0.63-0.94)	$1.0x10^{-2}$	$1.2x10^{-1}$	0.83 (0.67-1.02)	$7.2x10^{-2}$	
miR-99a-3p	0.53 (0.33-0.86)	$1.1x10^{-2}$	$1.2x10^{-1}$	0.50 (0.29-0.86)	$1.2x10^{-2}$	
miR-146b-5p	1.23 (1.05-1.44)	$1.2x10^{-2}$	$1.3x10^{-1}$	1.13 (0.96-1.34)	$1.5x10^{-1}$	
miR-362-5p	1.52 (1.09-2.10)	$1.2x10^{-2}$	$1.3x10^{-1}$	1.30 (0.91-1.85)	$1.5x10^{-1}$	
miR-342-5p	1.21 (1.04-1.40)	$1.3x10^{-2}$	$1.4x10^{-1}$	1.14 (0.98-1.33)	$8.2x10^{-2}$	
miR-127-5p	1.06 (1.01-1.12)	$1.5x10^{-2}$	$1.4x10^{-1}$	1.04 (0.99-1.10)	$1.3x10^{-1}$	
miR-1307-3p	1.16 (1.03-1.31)	$1.4x10^{-2}$	$1.4x10^{-1}$	1.12 (0.99-1.26)	$6.7x10^{-2}$	
miR-342-3p	2.14 (1.16-3.93)	$1.4x10^{-2}$	$1.4x10^{-1}$	2.13 (1.11-4.06)	$2.2x10^{-2}$	
miR-199b-5p	1.21 (1.04-1.40)	$1.5x10^{-2}$	$1.4x10^{-1}$	1.18 (0.99-1.41)	$7.2x10^{-2}$	
miR-942-5p	1.24 (1.04-1.49)	$1.6x10^{-2}$	$1.4x10^{-1}$	1.27 (1.06-1.51)	$7.7x10^{-3}$	[19] (s)

miR-30a-3p	0.61 (0.40-0.92)	$1.9x10^{-2}$	$1.6x10^{-1}$	0.64 (0.40-1.00)	$5.0x10^{-2}$	
let-7c-5p	0.55 (0.33-0.93)	$2.6x10^{-2}$	$1.7x10^{-1}$	0.57 (0.34-0.96)	$3.3x10^{-2}$	
let-7i-5p	1.63 (1.06-2.51)	$2.5x10^{-2}$	$1.7x10^{-1}$	1.46 (0.94-2.25)	$9.1x10^{-2}$	
miR-125b-1-3p	1.19 (1.03-1.39)	$2.1x10^{-2}$	$1.7x10^{-1}$	1.14 (0.98-1.32)	$9.2x10^{-2}$	
miR-142-5p	1.35 (1.04-1.77)	$2.5x10^{-2}$	$1.7x10^{-1}$	1.31 (1.01-1.71)	$4.3x10^{-2}$	
miR-197-3p	2.11 (1.11-4.00)	$2.3x10^{-2}$	$1.7x10^{-1}$	1.80 (0.93-3.48)	$8.3x10^{-2}$	
miR-21-3p	1.55 (1.06-2.26)	$2.3x10^{-2}$	$1.7x10^{-1}$	1.33 (0.89-1.98)	$1.7x10^{-1}$	
miR-26b-5p	0.40 (0.18-0.88)	$2.4x10^{-2}$	$1.7x10^{-1}$	0.44 (0.19-1.01)	$5.2x10^{-2}$	
miR-27b-3p	0.53 (0.31-0.92)	$2.4x10^{-2}$	$1.7x10^{-1}$	0.61 (0.36-1.05)	$7.4x10^{-2}$	
miR-324-5p	1.53 (1.07-2.19)	$2.1x10^{-2}$	$1.7x10^{-1}$	1.24 (0.82-1.88)	$3.1x10^{-1}$	
miR-326	1.10 (1.01-1.18)	$2.3x10^{-2}$	$1.7x10^{-1}$	1.06 (0.98-1.15)	$1.4x10^{-1}$	
miR-330-5p	1.31 (1.03-1.66)	$2.5x10^{-2}$	$1.7x10^{-1}$	1.19 (0.94-1.52)	$1.5x10^{-1}$	
miR-3607-5p	0.75 (0.59-0.96)	$2.2x10^{-2}$	$1.7x10^{-1}$	0.77 (0.61-0.97)	$2.8x10^{-2}$	
miR-377-3p	1.14 (1.02-1.27)	$2.4x10^{-2}$	$1.7x10^{-1}$	1.11 (0.99-1.25)	$8.1x10^{-2}$	
miR-432-5p	1.24 (1.03-1.48)	$2.4x10^{-2}$	$1.7x10^{-1}$	1.14 (0.94-1.39)	$1.7x10^{-1}$	
miR-487b-3p	1.19 (1.02-1.39)	$2.7x10^{-2}$	$1.7x10^{-1}$	1.16 (0.99-1.37)	$6.3x10^{-2}$	
miR-664b-3p	0.67 (0.47-0.95)	$2.6x10^{-2}$	$1.7x10^{-1}$	0.67 (0.46-0.98)	$3.8x10^{-2}$	
miR-9-5p	1.04 (1.00-1.07)	$2.6x10^{-2}$	$1.7x10^{-1}$	1.04 (1.01-1.08)	$6.9x10^{-3}$	
miR-17-3p	1.51 (1.04-2.19)	$2.9x10^{-2}$	$1.7x10^{-1}$	1.43 (0.96-2.12)	$7.7x10^{-2}$	
miR-3607-3p	0.76 (0.60-0.97)	$2.9x10^{-2}$	$1.7x10^{-1}$	0.78 (0.61-0.99)	$3.8x10^{-2}$	
miR-423-5p	1.16 (1.02-1.33)	$2.9x10^{-2}$	$1.7x10^{-1}$	1.09 (0.94-1.26)	$2.3x10^{-1}$	
miR-106b-3p	1.47 (1.02-2.1)	$3.7x10^{-2}$	$1.9x10^{-1}$	1.38 (0.96-1.97)	$8.3x10^{-2}$	
miR-10b-5p	0.51 (0.28-0.95)	$3.4x10^{-2}$	$1.9x10^{-1}$	0.66 (0.35-1.23)	$1.9x10^{-1}$	
miR-146b-3p	1.16 (1.01-1.33)	$3.7x10^{-2}$	$1.9x10^{-1}$	1.10 (0.95-1.27)	$2.0x10^{-1}$	
miR-15b-3p	1.45 (1.03-2.04)	$3.5x10^{-2}$	$1.9x10^{-1}$	1.35 (0.94-1.94)	$1.1x10^{-1}$	
miR-187-3p	0.86 (0.74-0.99)	$3.3x10^{-2}$	$1.9x10^{-1}$	0.85 (0.74-0.98)	$2.7x10^{-2}$	
miR-196a-5p	0.54 (0.30-0.95)	$3.4x10^{-2}$	$1.9x10^{-1}$	0.66 (0.38-1.15)	$1.4x10^{-1}$	
miR-494-3p	1.22 (1.01-1.48)	$3.6x10^{-2}$	$1.9x10^{-1}$	1.20 (0.99-1.47)	$6.7x10^{-2}$	
miR-502-5p	1.30 (1.02-1.65)	$3.5x10^{-2}$	$1.9x10^{-1}$	1.25 (0.99-1.58)	$5.9x10^{-2}$	
miR-155-5p	1.15 (1.01-1.31)	$3.8x10^{-2}$	$2.0x10^{-1}$	1.13 (0.99-1.28)	$7.4x10^{-2}$	[18] (s)
miR-499a-5p	0.66 (0.45-0.98)	$3.9x10^{-2}$	$2.0x10^{-1}$	0.70 (0.46-1.05)	$8.7x10^{-2}$	
miR-18a-3p	1.20 (1.01-1.42)	$4.0x10^{-2}$	$2.0x10^{-1}$	1.10 (0.92-1.33)	$2.9x10^{-1}$	
miR-148a-5p	1.34 (1.01-1.77)	$4.3x10^{-2}$	$2.1x10^{-1}$	1.28 (0.96-1.72)	$9.6x10^{-2}$	
miR-223-3p	1.20 (1.01-1.42)	$4.3x10^{-2}$	$2.1x10^{-1}$	1.17 (0.96-1.43)	$1.1x10^{-1}$	
miR-369-3p	1.13 (1.00-1.28)	$4.6x10^{-2}$	$2.2x10^{-1}$	1.08 (0.95-1.23)	$2.5x10^{-1}$	
miR-452-3p	1.23 (1.00-1.52)	$4.6x10^{-2}$	$2.2x10^{-1}$	1.09 (0.87-1.36)	$4.4x10^{-1}$	
miR-411-5p	1.20 (1.00-1.44)	$4.7x10^{-2}$	$2.2x10^{-1}$	1.17 (0.97-1.41)	$9.2x10^{-2}$	
miR-4485	0.85 (0.72-1.00)	$5.0x10^{-2}$	$2.3x10^{-1}$	0.89 (0.74-1.07)	$2.2x10^{-1}$	

[a] All miRNAs with a P value <0.05 in univariate analysis are listed. In bold miRNAs with a FDR<0.05.

[b] Multivariable analysis including as covariates age, MSKCC prognostic classification and time from nephrectomy to TKI treatment.

[c] Evidences in literature and direction (risk/ protection) of the association in current and referenced study: same direction of association (s); inverse direction of association (i).

Supplementary Table 4. Full list of microRNAs associated with OS.

miRNA [a]	Univariate			Multivariable [b]		Ref. [b]
	HR (95% CI)	P value	FDR	HR (95% CI)	P value	
miR-222-3p	1.77 (1.41-2.22)	$7.8x10^{-7}$	**$1.5x10^{-4}$**	1.60 (1.25-2.05)	$1.7x10^{-4}$	[15](s)
miR-375	1.10 (1.06-1.14)	$9.7x10^{-7}$	**$1.5x10^{-4}$**	1.08 (1.03-1.12)	$9.6x10^{-4}$	
miR-193b-5p	1.21 (1.12-1.30)	$1.2x10^{-6}$	**$1.5x10^{-4}$**	1.17 (1.08-1.26)	$1.1x10^{-4}$	
miR-185-5p	2.13 (1.54-2.94)	$4.7x10^{-6}$	**$4.3x10^{-4}$**	1.79 (1.27-2.53)	$8.2x10^{-4}$	
miR-193b-3p	1.25 (1.13-1.38)	$8.1x10^{-6}$	**$4.7x10^{-4}$**	1.19 (1.07-1.33)	$1.2x10^{-3}$	
miR-365a-5p	1.20 (1.11-1.30)	$8.6x10^{-6}$	**$4.7x10^{-4}$**	1.21 (1.11-1.32)	$2.3x10^{-5}$	[10](s)
miR-221-3p	1.71 (1.35-2.16)	$8.9x10^{-6}$	**$4.7x10^{-4}$**	1.53 (1.19-1.98)	$1.1x10^{-3}$	[15](s)
miR-1301-3p	1.65 (1.31-2.08)	2.4x10-5	**$1.1x10^{-3}$**	1.47 (1.16-1.86)	$1.6x10^{-3}$	
miR-4326	1.37 (1.18-1.60)	5.6x10-5	**$2.3x10^{-3}$**	1.29 (1.09-1.54)	$3.6x10^{-3}$	
miR-652-3p	1.59 (1.26-2.00)	9.5x10-5	**$3.5x10^{-3}$**	1.42 (1.12-1.80)	$4.1x10^{-3}$	
miR-425-5p	1.63 (1.27-2.09)	$1.4x10^{-4}$	**$4.5x10^{-3}$**	1.62 (1.21-2.18)	$1.2x10^{-3}$	
miR-7-5p	1.31 (1.14-1.52)	$2.6x10^{-4}$	**$7.6x10^{-3}$**	1.31 (1.13-1.53)	$4.1x10^{-4}$	
miR-134-5p	1.18 (1.08-1.29)	$2.7x10^{-4}$	**$7.6x10^{-3}$**	1.12 (1.02-1.23)	$1.4x10^{-2}$	
miR-223-5p	1.22 (1.09-1.36)	$3.3x10^{-4}$	**$8.6x10^{-3}$**	1.26 (1.11-1.42)	$2.1x10^{-4}$	[10](s)
miR-221-5p	1.23 (1.10-1.37)	$3.7x10^{-4}$	**$8.7x10^{-3}$**	1.18 (1.05-1.33)	$6.0x10^{-3}$	
miR-149-5p	1.39 (1.16-1.67)	$3.8x10^{-4}$	**$8.7x10^{-3}$**	1.27 (1.05-1.53)	$1.3x10^{-2}$	[10](s)
miR-423-5p	1.30 (1.12-1.50)	$4.5x10^{-4}$	**$9.4x10^{-3}$**	1.18 (1.01-1.38)	$3.7x10^{-2}$	
miR-342-5p	1.35 (1.14-1.60)	$4.8x10^{-4}$	**$9.4x10^{-3}$**	1.25 (1.05-1.49)	$1.1x10^{-2}$	
miR-326	1.17 (1.07-1.27)	$4.9x10^{-4}$	**$9.4x10^{-3}$**	1.12 (1.02-1.22)	$1.6x10^{-2}$	
miR-629-5p	1.62 (1.23-2.12)	$5.3x10^{-4}$	**$9.8x10^{-3}$**	1.45 (1.11-1.89)	$6.8x10^{-3}$	
miR-127-5p	1.10 (1.04-1.16)	$6.2x10^{-4}$	**$1.1x10^{-2}$**	1.07 (1.01-1.14)	$1.4x10^{-2}$	
miR-17-3p	1.87 (1.27-2.74)	$1.4x10^{-3}$	**$2.4x10^{-2}$**	1.79 (1.17-2.72)	$7.0x10^{-3}$	
miR-193a-5p	1.31 (1.11-1.55)	$1.6x10^{-3}$	**$2.5x10^{-2}$**	1.22 (1.03-1.45)	$2.1x10^{-2}$	
miR-18a-5p	1.76 (1.23-2.54)	$2.2x10^{-3}$	**$3.4x10^{-2}$**	1.93 (1.31-2.83)	$7.9x10^{-4}$	[10](s)
miR-330-5p	1.49 (1.15-1.92)	$2.3x10^{-3}$	**$3.4x10^{-2}$**	1.32 (1.02-1.70)	$3.6x10^{-2}$	
miR-941	1.86 (1.24-2.79)	$2.5x10^{-3}$	**$3.5x10^{-2}$**	1.68 (1.10-2.55)	$1.5x10^{-2}$	
miR-1307-5p	1.11 (1.04-1.19)	$2.8x10^{-3}$	**$3.5x10^{-2}$**	1.07 (1.00-1.15)	$5.6x10^{-2}$	
miR-147b	1.07 (1.02-1.12)	$3.0x10^{-3}$	**$3.5x10^{-2}$**	1.05 (1.00-1.10)	$5.3x10^{-2}$	
miR-671-5p	1.07 (1.02-1.12)	$3.0x10^{-3}$	**$3.5x10^{-2}$**	1.04 (0.99-1.09)	$1.3x10^{-1}$	
miR-22-3p	1.34 (1.10-1.62)	$3.0x10^{-3}$	**$3.5x10^{-2}$**	1.20 (0.98-1.46)	$7.1x10^{-2}$	
miR-324-5p	1.90 (1.24-2.89)	$3.0x10^{-3}$	**$3.5x10^{-2}$**	1.41 (0.86-2.31)	$1.7x10^{-1}$	
miR-1307-3p	1.18 (1.06-1.32)	$3.3x10^{-3}$	**$3.6x10^{-2}$**	1.13 (1.01-1.27)	$3.0x10^{-2}$	
miR-21-3p	1.86 (1.23-2.81)	$3.4x10^{-3}$	**$3.6x10^{-2}$**	1.64 (1.06-2.54)	$2.7x10^{-2}$	[10,11,14](s)
miR-185-3p	1.10 (1.03-1.17)	$3.5x10^{-3}$	**$3.6x10^{-2}$**	1.07 (1.00-1.14)	$4.3x10^{-2}$	
miR-99a-3p	0.43 (0.25-0.76)	$3.6x10^{-3}$	**$3.6x10^{-2}$**	0.41 (0.23-0.76)	$4.3x10^{-3}$	
miR-432-5p	1.37 (1.11-1.69)	$3.6x10^{-3}$	**$3.6x10^{-2}$**	1.26 (1.01-1.57)	$3.6x10^{-2}$	
miR-501-5p	1.15 (1.05-1.27)	$3.7x10^{-3}$	**$3.6x10^{-2}$**	1.09 (0.99-1.22)	$9.2x10^{-2}$	[12](s)
miR-331-3p	1.57 (1.16-2.12)	$3.7x10^{-3}$	**$3.6x10^{-2}$**	1.23 (0.86-1.74)	$2.5x10^{-1}$	
miR-146b-3p	1.26 (1.08-1.49)	$4.2x10^{-3}$	**$4.0x10^{-2}$**	1.18 (1.00-1.38)	$5.0x10^{-2}$	[10,19](s)
miR-146b-5p	1.31 (1.09-1.59)	$4.8x10^{-3}$	**$4.3x10^{-2}$**	1.18 (0.96-1.44)	$1.1x10^{-1}$	

miR-425-3p	1.16 (1.05-1.30)	$4.8x10^{-3}$	**$4.3x10^{-2}$**	1.10 (0.98-1.24)	$9.1x10^{-2}$	
miR-130b-5p	1.43 (1.11-1.84)	$5.3x10^{-3}$	**$4.5x10^{-2}$**	1.29 (0.98-1.68)	$6.5x10^{-2}$	[10](s)
miR-26b-5p	0.27 (0.11-0.68)	$5.3x10^{-3}$	**$4.5x10^{-2}$**	0.32 (0.12-0.83)	$1.9x10^{-2}$	
miR-148a-5p	1.52 (1.13-2.06)	$5.9x10^{-3}$	**$4.9x10^{-2}$**	1.57 (1.14-2.16)	$5.2x10^{-3}$	
miR-320d	1.06 (1.02-1.11)	$7.2x10^{-3}$	$5.9x10^{-2}$	1.04 (0.99-1.09)	$8.9x10^{-2}$	
miR-127-3p	1.08 (1.02-1.14)	$7.6x10^{-3}$	$6.0x10^{-2}$	1.06 (1.00-1.12)	$5.9x10^{-2}$	
miR-125b-1-3p	1.28 (1.06-1.53)	$8.3x10^{-3}$	$6.4x10^{-2}$	1.22 (1.02-1.46)	$2.7x10^{-2}$	[13](s)
miR-320a	1.07 (1.02-1.13)	$8.4x10^{-3}$	$6.4x10^{-2}$	1.05 (0.99-1.11)	$1.2x10^{-1}$	
miR-2110	1.14 (1.03-1.25)	$9.0x10^{-3}$	$6.7x10^{-2}$	1.08 (0.98-1.20)	$1.3x10^{-1}$	
let-7e-3p	0.50 (0.30-0.84)	$9.3x10^{-3}$	$6.8x10^{-2}$	0.53 (0.31-0.91)	$2.2x10^{-2}$	
miR-589-5p	1.84 (1.16-2.93)	$9.6x10^{-3}$	$6.9x10^{-2}$	1.71 (1.08-2.72)	$2.3x10^{-2}$	
miR-370-3p	1.03 (1.01-1.05)	$1.1x10^{-2}$	$7.5x10^{-2}$	1.02 (1.00-1.04)	$9.0x10^{-2}$	
miR-204-5p	0.65 (0.47-0.91)	$1.1x10^{-2}$	$7.5x10^{-2}$	0.66 (0.46-0.93)	$1.8x10^{-2}$	[10](s)
miR-382-5p	1.07 (1.02-1.13)	$1.1x10^{-2}$	$7.5x10^{-2}$	1.05 (0.99-1.11)	$1.2x10^{-1}$	
miR-130b-3p	1.60 (1.11-2.29)	$1.1x10^{-2}$	$7.5x10^{-2}$	1.56 (1.09-2.25)	$1.6x10^{-2}$	
miR-146a-5p	1.10 (1.02-1.18)	$1.2x10^{-2}$	$7.5x10^{-2}$	1.06 (0.98-1.15)	$1.4x10^{-1}$	
miR-320b	1.10 (1.02-1.19)	$1.2x10^{-2}$	$7.6x10^{-2}$	1.06 (0.97-1.15)	$2.1x10^{-1}$	
miR-409-3p	1.07 (1.01-1.13)	$1.2x10^{-2}$	$7.6x10^{-2}$	1.04 (0.99-1.10)	$1.2x10^{-1}$	
miR-10b-3p	0.45 (0.24-0.84)	$1.2x10^{-2}$	$7.6x10^{-2}$	0.53 (0.27-1.05)	$7.0x10^{-2}$	[10,11](s)
miR-18a-3p	1.30 (1.06-1.61)	$1.3x10^{-2}$	$7.6x10^{-2}$	1.19 (0.96-1.47)	$1.2x10^{-1}$	
miR-548k	1.60 (1.11-2.32)	$1.3x10^{-2}$	$7.6x10^{-2}$	1.56 (1.09-2.23)	$1.5x10^{-2}$	
miR-199b-5p	1.22 (1.04-1.44)	$1.3x10^{-2}$	$7.8x10^{-2}$	1.23 (1.00-1.50)	$4.5x10^{-2}$	
miR-106b-3p	1.58 (1.10-2.27)	$1.3x10^{-2}$	$7.8x10^{-2}$	1.62 (1.11-2.37)	$1.2x10^{-2}$	
miR-196a-5p	0.43 (0.22-0.84)	$1.4x10^{-2}$	$8.1x10^{-2}$	0.59 (0.31-1.13)	$1.1x10^{-1}$	
miR-223-3p	1.26 (1.05-1.52)	$1.5x10^{-2}$	$8.1x10^{-2}$	1.24 (1.00-1.54)	$5.2x10^{-2}$	
let-7c-5p	0.46 (0.25-0.86)	$1.5x10^{-2}$	$8.1x10^{-2}$	0.50 (0.27-0.91)	$2.5x10^{-2}$	
miR-1269a	1.01 (1.00-1.02)	$1.5x10^{-2}$	$8.1x10^{-2}$	1.01 (1.00-1.01)	$5.9x10^{-2}$	
miR-942-5p	1.21 (1.04-1.40)	$1.5x10^{-2}$	$8.2x10^{-2}$	1.19 (1.02-1.37)	$2.2x10^{-2}$	[19](s)
miR-10b-5p	0.40 (0.19-0.84)	$1.6x10^{-2}$	$8.3x10^{-2}$	0.58 (0.28-1.20)	$1.4x10^{-1}$	
miR-150-5p	1.33 (1.05-1.67)	$1.6x10^{-2}$	$8.3x10^{-2}$	1.26 (0.99-1.60)	$5.9x10^{-2}$	
miR-320c	1.07 (1.01-1.13)	$1.6x10^{-2}$	$8.4x10^{-2}$	1.04 (0.98-1.10)	$1.7x10^{-1}$	
miR-138-5p	1.02 (1.00-1.04)	$1.7x10^{-2}$	$8.5x10^{-2}$	1.01 (0.99-1.03)	$3.2x10^{-1}$	
miR-27a-5p	1.19 (1.03-1.38)	$1.7x10^{-2}$	$8.7x10^{-2}$	1.23 (1.05-1.45)	$1.1x10^{-2}$	[10](i)
let-7i-3p	1.58 (1.08-2.32)	$1.9x10^{-2}$	$9.3x10^{-2}$	1.28 (0.87-1.90)	$2.1x10^{-1}$	
miR-362-5p	1.40 (1.06-1.86)	$1.9x10^{-2}$	$9.5x10^{-2}$	1.22 (0.90-1.65)	$2.1x10^{-1}$	
miR-887-3p	1.06 (1.01-1.12)	$2.0x10^{-2}$	$9.5x10^{-2}$	1.03 (0.98-1.09)	$2.2x10^{-1}$	
miR-511-3p	1.21 (1.03-1.42)	$2.1x10^{-2}$	$9.8x10^{-2}$	1.23 (1.05-1.44)	$1.1x10^{-2}$	
miR-342-3p	2.16 (1.11-4.17)	$2.3x10^{-2}$	$1.1x10^{-1}$	2.30 (1.09-4.87)	$3.0x10^{-2}$	
miR-504-5p	0.60 (0.38-0.94)	$2.7x10^{-2}$	$1.2x10^{-1}$	0.77 (0.48-1.22)	$2.6x10^{-1}$	
let-7i-5p	1.75 (1.07-2.86)	$2.7x10^{-2}$	$1.2x10^{-1}$	1.63 (0.98-2.71)	$6.0x10^{-2}$	
miR-197-3p	2.17 (1.08-4.33)	$2.9x10^{-2}$	$1.3x10^{-1}$	1.88 (0.93-3.80)	$8.0x10^{-2}$	
let-7b-3p	0.40 (0.18-0.92)	$3.0x10^{-2}$	$1.3x10^{-1}$	0.51 (0.23-1.14)	$1.0x10^{-1}$	
miR-200c-3p	0.90 (0.82-0.99)	$3.1x10^{-2}$	$1.4x10^{-1}$	0.91 (0.83-1.01)	$6.5x10^{-2}$	
miR-142-5p	1.34 (1.03-1.75)	$3.2x10^{-2}$	$1.4x10^{-1}$	1.30 (0.99-1.71)	$5.9x10^{-2}$	
let-7f-2-3p	0.57 (0.35-0.95)	$3.2x10^{-2}$	$1.4x10^{-1}$	0.64 (0.37-1.12)	$1.2x10^{-1}$	

miR-411-5p	1.24 (1.02-1.50)	$3.3x10^{-2}$	$1.4x10^{-1}$	1.23 (1.00-1.50)	$4.6x10^{-2}$	
miR-1270	0.70 (0.50-0.97)	$3.5x10^{-2}$	$1.4x10^{-1}$	0.81 (0.58-1.14)	$2.2x10^{-1}$	
miR-126-5p	0.50 (0.26-0.95)	$3.5x10^{-2}$	$1.4x10^{-1}$	0.62 (0.32-1.21)	$1.6x10^{-1}$	[14](s)
miR-324-3p	1.41 (1.02-1.93)	$3.5x10^{-2}$	$1.4x10^{-1}$	1.18 (0.83-1.67)	$3.6x10^{-1}$	
miR-27b-3p	0.50 (0.26-0.96)	$3.6x10^{-2}$	$1.5x10^{-1}$	0.65 (0.36-1.18)	$1.6x10^{-1}$	
miR-30a-3p	0.60 (0.37-0.97)	$3.7x10^{-2}$	$1.5x10^{-1}$	0.68 (0.40-1.17)	$1.7x10^{-1}$	
miR-26a-5p	0.36 (0.14-0.94)	$3.8x10^{-2}$	$1.5x10^{-1}$	0.42 (0.15-1.15)	$9.2x10^{-2}$	
miR-30c-5p	0.48 (0.24-0.96)	$3.8x10^{-2}$	$1.5x10^{-1}$	0.50 (0.23-1.07)	$7.5x10^{-2}$	
miR-769-5p	1.14 (1.01-1.30)	$4.1x10^{-2}$	$1.6x10^{-1}$	1.08 (0.94-1.23)	$2.8x10^{-1}$	[10](i)
miR-503-5p	1.52 (1.02-2.29)	$4.1x10^{-2}$	$1.6x10^{-1}$	1.54 (0.98-2.43)	$6.2x10^{-2}$	
miR-365a-3p	1.33 (1.01-1.75)	$4.2x10^{-2}$	$1.6x10^{-1}$	1.17 (0.89-1.55)	$2.5x10^{-1}$	
miR-377-3p	1.13 (1.00-1.27)	$4.2x10^{-2}$	$1.6x10^{-1}$	1.12 (0.99-1.27)	$8.2x10^{-2}$	
miR-125a-5p	0.44 (0.20-0.97)	$4.3x10^{-2}$	$1.6x10^{-1}$	0.49 (0.21-1.14)	$9.6x10^{-2}$	
miR-421	1.82 (1.02-3.27)	$4.4x10^{-2}$	$1.6x10^{-1}$	1.68 (0.96-2.93)	$6.9x10^{-2}$	
miR-30d-3p	0.59 (0.36-0.99)	$4.5x10^{-2}$	$1.6x10^{-1}$	0.49 (0.25-0.95)	$3.5x10^{-2}$	
miR-511-5p	1.03 (1.00-1.06)	$4.5x10^{-2}$	$1.6x10^{-1}$	1.02 (0.99-1.06)	$1.3x10^{-1}$	
miR-3613-5p	1.51 (1.01-2.26)	$4.5x10^{-2}$	$1.6x10^{-1}$	1.20 (0.78-1.83)	$4.1x10^{-1}$	
miR-34a-5p	1.88 (1.00-3.51)	$4.9x10^{-2}$	$1.7x10^{-1}$	1.48 (0.79-2.78)	$2.2x10^{-1}$	

[a] All miRNAs with a P value <0.05 in univariate analysis are listed. In bold miRNAs with a FDR<0.05.
[b] Multivariable analysis including as covariates age, MSKCC prognostic classification and time from nephrectomy to TKI treatment.
[c] Evidences in literature and direction (risk/ protection) of the association in current and referenced study: same direction of association (s); inverse direction of association (i).

Supplementary Table 5. Pathways predicted to be deregulated by miRNAs. DIANA miRPath software[a] was used to perform pathway analysis using experimentally validated miRNA interactions derived from DIANA-TarBase v6.0predictions.

PD as best TKI response [b]		PFS [b]		OS [b]	
KEGG pathway [c]	FDR	KEGG pathway	FDR	KEGG pathway	FDR
Pathways in cancer	$1.78x10^{-16}$	**DNA replication**	$1.17x10^{-19}$	**DNA replication**	$8.48x10^{-18}$
Colorectal cancer	$1.24x10^{-13}$	Prion diseases	$9.09x10^{-19}$	Hepatitis B	$1.90x10^{-13}$
		Prostate cancer	$7.01x10^{-15}$	**Prostate cancer**	$3.04x10^{-13}$
		Hepatitis B	$1.73x10^{-14}$	**p53 signaling pathway**	$3.83x10^{-13}$
		Non-small cell lung cancer	$2.71x10^{-14}$	**Small cell lung cancer**	$7.51x10^{-13}$
		Colorectal cancer	$6.27x10^{-13}$	**Pathways in cancer**	$8.02x10^{-13}$
		Cell cycle	$2.34x10^{-12}$	Prion diseases	$3.36x10^{-12}$
		Endometrial cancer	$5.46x10^{-12}$		
		Pathways in cancer	$6.50x10^{-11}$		

[a] Vlachos *et al.* Nucleic Acids Res. 2012 Jul;40(Web Server issue):W498-504.
[b] MiRNAs associated with PD as best TKI response, PFS and OS with an FDR<0.05 were used for the analysis.
[c] Pathways with an associated FDR $<1x10^{-10}$ are shown; those related with cancer processes are shown in bold.