SUPPLEMENTAL DATA

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Supplemental material and methods

Patient samples

Pretreatment frozen bone marrow (BM) samples from 54 de novo adult acute myeloid leukemia (AML) patients were obtained from the Cell and tissue bank of the MD Anderson Cancer center. Informed consent was obtained from the patients in accordance with the Declaration of Helsinki to procure and bank the cells for future research according to institutional guidelines. Patient's samples were prepared by Ficoll-Hypaque (Sigma-Aldrich, St Louis, MO) gradient centrifugation, enriched for leukemic cells by CD3/CD19 depletion (MACS; Miltenyi Biotec, Auburn, CA) and cryopreserved. Cytogenetic analyses of the samples were performed at diagnosis using unstimulated short-term (24-,48-, and 72-hour) cultures with or without a direct method and G-banding. The criteria used to describe a cytogenetic clone and description of karyotype followed the recommendations of the International System for Human Cytogenetic Nomenclature.[1] At least 20 bone marrow metaphase cells were analyzed in patients designated as having a normal karyotype. *FLT3* internal tandem duplication (ITD), activation loop D835 mutations and *NPM1* mutations were performed on most of the samples as previously described at the MD Anderson Molecular Diagnostics Laboratory.[2] All the patients were treated with the same regimen of idarubicin 12mg/m^2 daily on days 1-3 and cytarabine 1500 mg/m^2 continuous infusion for 4 days. Induction deaths were excluded from the analysis. Complete remission (CR) was defined as an absolute neutrophil count of ≥1,500/μL, platelet count of ≥100,000/μL, no leukemic blasts in the blood, BM cellularity ≥20% with maturation of all cell lines, no Auer rods, ≤5% BM

blast cells, and no evidence of extramedullary leukemia, all of which had persisted for at least 1 month.[3]

Pretreatment frozen BM samples from 183 de novo older (≥60) CN-AML patients were obtained from the Cancer and Leukemia Group B (CALGB)/ALLIANCE leukemia tissue bank. Informed consent was obtained from the patients in accordance with the Declaration of Helsinki to procure and bank the cells for future research according to institutional guidelines. Patient characteristics are shown in Table S2. Cytogenetic analyses were performed in CALGB/Alliance-approved institutional laboratories and confirmed by central karyotype review, and the diagnosis of normal cytogenetics was based on ≥20 analyzed metaphase cells in bone marrow specimens. Molecular studies shown in table S2 were performed as described.[4] Patients were treated on one of the following intensive cytarabine/daunorubicin-based CALGB frontline treatment protocols: 8525(n=13),[5] 8923(n=11),[6] 9420(n=4),[7] 9720(n=91),[8,9] or 10201(n=64).[10]Among these protocols, CALGB 9420, 9720, and 10201 included investigational agents other than chemotherapy. CALGB 9720[8,9] was initiated as a phase III trial in untreated AML patients ≥60 years evaluating multidrug resistance modulation by valspodar (PSC-833) during induction and consolidation therapy with cytarabine, daunorubicin, and etoposide. The valspodar (PSC-833) arm was closed after randomized assignment of 120 patients because of excessive early deaths. Enrollment on this protocol continued on the chemotherapy-only control arm. CALGB 10201[10] evaluated the *BCL2* antisense, oblimersen sodium (Genasense; G3139) administered with induction and consolidation chemotherapy; preliminary results showed no impact of the antisense on outcome. CALGB 9420[7] and CALGB 9720[8,9] evaluated a subcutaneous IL-2 regimen in older AML

patients as maintenance therapy, which was demonstrated to induce no clear benefit. Per the protocols, patients enrolled on these studies did not receive stem cell transplantation in first CR.

RNA extraction and miRNA microarray experiments

RNA extraction and miRNA microchip experiments were performed as described in detail elsewhere.[11] Five micrograms of total RNA was used for hybridization on the custom miRNA microarray chip (OSU_CCC version 3.0) which contains ~1,100 miRNA probes, including 345 human and 249 mouse miRNA genes, spotted in duplicates.

Microarray data analysis

miRNA microarray images were analyzed using GENEPIX PRO. Average values of the replicate spots of each miRNA were background subtracted; log2 transformed and normalized using Quantiles and the BRB array tools (http://linus.nci.nih.gov/BRB-ArrayTools.html). A filtering step was performed to remove probe sets that did not show significant variation across the samples: a probe was excluded if less than 20% of expression data had at least a 1.5-fold change in either direction from the gene's median value or the percent of data missing or filtered out exceeds 50%. Class comparison within the BRB tools was used to compare pretreatment miRNA expression levels between CR and no-CR patients.

Real-time quantification of miRNAs

The single-tube TaqMan miRNA assays were used to detect and quantify mature miRNAs as previously described[12] using PCR 9700 Thermocycler ABI Prism 7900HT and the sequence detection system (Applied Biosystems, Foster City, CA). Normalization was performed with U44. Comparative real-time (RT)-PCR was performed in triplicate, including no-template controls. Relative expression was calculated using the comparative Ct method.[13]

Statistical analysis. Two-sample t-tests (or Wilcoxon rank sum tests if distributional assumptions did not hold) and chi-square tests were used to compare baseline clinical features and average miRNA expression between groups of patients (e.g. CR vs. no-CR). Graphical analyses such as scatterplots and side-by-side boxplots were used to graphically assess the association of miR-10 family expression and other factors of interest. miR-10a-5p and miR-10b-5p expression was evaluated as a continuous measure as well as a categorical measure based on cutpoints identified through recursive partitioning algorithms in relation to achievement of CR. Univariable and multivariable logistic regression models were analyzed to assess the impact of various clinical factors and biomarkers (e.g. miR-10a-5p expression) on achievement of CR. Any covariates that were found to be statistically significant ($P<0.05$) in the univariable setting were brought forward for evaluation in the multivariable setting. These included *NPM1* mutational status, age, *FLT3*-ITD (present *v* absent), normal karyotype, unfavorable cytogenetics [presence of complex karyotype, defined as ≥3 cytogenetic abnormalities excluding t(15;17), t(8;21) or inv16 cases), -7, -5, t(6;9) and inv3 cases]. In addition, interaction effects were assessed in multivariable logistic regression models. Statistical significance

was declared at $P<0.05$, and all analyses were conducted using the R statistical program for Windows version 3.0.1. Some graphics were performed using GraphPad prism software (www.graphpad.com).

Multivariable logistic regression models for the CALGB/ALLIANCE dataset were constructed to analyze factors related to the probability of achieving CR using a limited backward selection procedure. Variables in addition to miR-10a-5p, miR-10b-5p and *NPM1* (mutated vs. wild-type) that were considered for Univariable analyses for CR were age, sex, race, hemoglobin, platelet count, white blood count (WBC), *FLT3*-ITD (present vs. absent), *FLT3*-TKD (present vs. absent), *CEBPA* (mutated vs. wild-type), *TET2* (mutated vs. wild-type), *ASXL1* (mutated vs. wild-type), *DNMT3A* (mutated vs. wild-type), *RUNX1* (mutated vs. wild-type), *MLL*-PTD (present vs. absent), *IDH1* (mutated vs wild-type), *IDH2* (mutated vs. wild-type), *WT1* (mutated vs. wild-type), *ERG* expression (high vs. low), *BAALC* expression (high vs. low), *miR-181a* expression (high vs. low) and *miR-155* expression (high vs. low). Variables considered for inclusion in the logistic models were those significant at $\alpha=.20$

Cell transfections and functional experiments. K562, KG-1a, OCI-AML3 and Kasumi-1 cell lines were obtained from American tissue culture collection (ATCC). Five millions cells were nucleoporated using Amaxa with a final concentration of 100 nM of synthetic miR-10a-5p precursors/ scrambled or antimiR-10a-5p and anti-scrambled oligonucleotides purchased from Ambion. MiR-10a-5p expression after transfection was assessed by quantitative RT–PCR with the single-tube TaqMan miRNA assays from Applied Biosystems as described above.[12] The miR-10a-5p HIV lentivirus-based

construct (pMIR-10a)/empty vector (pMIR-EV) purchased from Systems Biosciences (SBI) was used to infect Kasumi-1 cells, according to the manufacturer's instructions (SBI) because of difficulty in achieving successful overexpression using nucleoporation methods. $1x10^6$ of Kasumi-1 cells were infected at 5 MOI and cells were harvested at 48 and 72 hours. To measure cell proliferation, cells were counted at 24-hour intervals using a ViCell counter (Beckman Coulter) after transfection/infection. Apoptosis was measured using Annexin V/propidium iodide (PI) staining (BD Pharmingen) by flow cytometry at 24, 48 and 72 hours after transfection/infection. Furthermore, cells were transfected/infected and immediately cultured with 5μM of cytarabine (10μM for K562 because they are more resistant to the drug) for up to 72 hours. Phosphate-buffered saline (PBS) added medium was used as control. To determine whether miR-10a-5p induces granulocytic differentiation was analyzed up to 72h after infection of Kasumi-1 cells using phycoerythrin (PE) protein conjugated mouse anti-human CD11b (BD Pharmingen) and FACS as described.[14] In addition, cytospin preparations and Giemsa stain were performed and the blasts morphology was analyzed using microscopy as described elsewhere.[14] BM samples from four de novo AML patients were obtained from the OSU leukemia tissue bank after getting informed consent according to the OSU Institutional Review Board guidelines. Two patients had normal cytogenetics with wild-type *NPM1* and *FLT3*, whereas the other two patients had normal cytogenetics with wild-type *FLT3* and mutated *NPM1*. Approximately 3×10^6 primary AML blasts were cultured with StemSpan SFEM supplemented with 20% FBS and StemSpan CC100 cytokine cocktail (STEMCELL Technologies) along with transferrin conjugated nanoparticles (NPs) encapsulated with 0.2 μM synthetic miR-10a-5p, antimiR-10a-5p (anti-10a) or

respective scrambled controls. Nanoparticle conjugated miRNAs were used to improve target cell delivery as described in detail.[15] In addition cytarabine (5μM) or control (PBS) was added to the culture media. The expression of the oligonucleotides after transfection was assessed by quantitative RT–PCR as described before. Apoptosis was measured after 48h using Annexin V/PI and flow cytometry as described for cell lines.

References

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Table S1. Patient Characteristics for the Adult de novo AML MD Anderson Cancer Center patient set.

Characteristic	Patients (n=54)
Gender	
Male	32
Female	22
Age (yrs)	
Median (range)	61 (32 – 80)
Prognostic group*	
Intermediate	40
Unfavorable	14
Cytogenetics group	
CN-AML	33
Complex	10
Other	11
Prior chemotherapy?	
No	50
Yes	4
Prior radiotherapy?	
No	52
Yes	2
NPM1 mutation	
Negative	29
Positive	25
FLT3-ITD	
Negative	23
Positive	10
ND/Missing	21
FLT3-TDK 835	
Negative	32
Positive	5
ND/Missing	17
BM blast (%)	
Median (range)	68 (8 – 93)
Baseline WBC ($x10^9$/L)	
Median (range)	32.5 (1.9 – 278.3)

* Intermediate cytogenetic prognostic group defined by the presence of CN-AML and other karyotypes not included in the unfavorable cytogenetic prognostic group. In this group cases with t(15;17), t(8;21) or inv16) were excluded. Unfavorable cytogenetic prognostic group defined by the presence of complex karyotype (≥ 3 cytogenetic abnormalities excluding t(15;17), t(8;21) or inv16 cases), -7, -5, t(6;9) and inv3 cases.

AML: acute myeloid leukemia, **CN-AML:** cytogenetically normal-AML, ***NPM1*:** nucleophosmin, ***FLT3:*** Fms-Like Tyrosine Kinase 3, **ITD:** internal tandem duplication, **TDK**: tyrosine kinase domain, **BM:** bone marrow, **WBC:** white blood count, ND: not done.

Table S2. Patient Characteristics for the Older (≥60yrs) de novo CN-AML CALGB/ALLIANCE patient set.

Characteristic	Patients (n=183)
Gender	
Male	95
Female	88
Age (yrs)	
Median (range)	69 (60 – 83)
Race	
White	170
Non-White	13
NPM1 mutation	
Negative	80
Positive	103
FLT3-ITD	
Negative	125
Positive	58
CEBPA mutation	
Negative	163
Positive	20
ELN Genetic Group*	
Favorable	80
Intermediate	103
FLT3-TDK 835	
Negative	164
Positive	19
WT1 mutation	
Negative	175
Positive	8
TET2 mutation	
Negative	128
Positive	50

ND/Missing	5
MLL-PTD	
Negative	167
Positive	12
ND/Missing	4
IDH1 mutation	
Negative	162
Positive	21
IDH2 mutation	
Negative	138
R140 Positive	36
R172 Positive	9
ASXL1 mutation	
Negative	153
Positive	26
ND/Missing	4
DNMT3A mutation	
Negative	124
R882 Positive	33
Non-R882 Positive	21
ND/Missing	5
RUNX1 mutation	
Negative	140
Positive	33
ND/Missing	10
ERG (median cut)	
Low	56
High	63
ND/Missing	64
BAALC (median cut)	
Low	71
High	74
ND/Missing	38
MN1 (median cut)	
Low	66
High	71
ND/Missing	46
BM blast	
Median (range)	66 (4 – 97)

PB blasts Median (range)	41 (0 – 99)
Baseline WBC (x10^9/L) Median (range)	24.7 (1.0 – 450.0)
Hemoglobin (g/dL) Median (range)	9.4 (5.4 – 15.0)
Platelet count (x10^9/L) Median (range)	67 (11 – 850)

* Favorable is defined by *CEBPA* mutated or *FLT3-ITD* negative and *NPM1* mutated status; Intermediate-I is defined by patients that are not in the favorable category: *CEBPA* wild-type and either *FLT3-ITD* positive and *NPM1* mutated, *FLT3-ITD* negative and *NPM1* wild-type or *FLT3*-ITD positive and *NPM1* wild-type status.

NPM1*:** nucleophosmin, ***FLT3: Fms-Like Tyrosine Kinase 3, **ITD:** internal tandem duplication, **TDK**: tyrosine kinase domain, **ELN:** European LeukemiaNet, ***CEBPA:*** CCAAT/enhancer-binding protein alpha**,** ***WT1*:** Wilms tumor 1**,** ***TET2:*** tet methylcytosine dioxygenase 2, MLL-mixed lineage leukemia, **PTD:** partial tandem duplications, ***IDH1:*** isocitrate dehydrogenase 1, **ASXL1:** Additional Sex Combs Like 1, ***DNMT3A:*** DNA methyltransferases 3A, ***RUNX1:*** Runt-related transcription factor 1, ***ERG:*** ETS-related gene**,** ***BAALC:*** Brain and acute leukemia cytoplasmic, ***MN1:*** meningioma (disrupted in balanced translocation)1, **BM:** bone marrow, **PB:** peripheral blasts, **WBC:** white blood count, ND: not done.

Table S3. miR-10a-5p and miR-10b-5p expression levels according to chemotherapy induction response in the MD Anderson Cancer Center AML patients.

Characteristic	No-CR (n = 26)	CR (n = 28)	*P*-value
Median age (yrs) (range)	65 (32 – 80)	56 (34 – 76)	0.029
Median baseline WBC ($x10^9$/L) (range)	26.7 (1.9 – 278.3)	47.1 (2.5 – 271)	0.024
Median miR-10a-5p (range)	9.1 (5.1 – 13.5)	12.1 (4.2 – 14.2)	0.003
Median miR-10b-5p (range)	8.1 (4.2 – 13.1)	12.2 (4.2 – 13.7)	0.002

AML: acute myeloid leukemia, **CR:** complete remission, **WBC:** white blood count.

Table S4. Pretreatment microRNA expression levels according to chemotherapy induction response in the MD Anderson Cancer Center AML patients.

microRNA	No-CR (n=26) Mean intensities	CR (n=28) Mean intensities	Fold Change	*P*-value
miR-10a-3p	46.8	389.5	8.3	<0.001
miR-10b-5p	260.4	1817.7	6.9	0.001
miR-10a-5p	705.1	2630.2	3.7	0.009
miR-518a-3p	25.0	83.1	3.3	0.000
miR-485-5p	24.4	79.1	3.2	<0.001
miR-16-2-5p	49.7	122.6	2.4	0.004
miR-7	66.3	163.4	2.4	0.023
miR-361-5p	782.0	1897.8	2.4	0.021
miR-135b	146.2	322.2	2.2	0.028

All genes are significant at the nominal 0.05 level of the Univariate test with a fold change >2 (Class comparison, BRB tools).

AML: acute myeloid leukemia, **CR:** complete remission.

Table S5. miR-10a-5p and miR-10b-5p expression levels according to chemotherapy induction response in CALGB/ALLIANCE CN-AML de novo patients.

Characteristic	No-CR (n= 62)	CR (n = 121)	*P*-value*
Median miR-10a-5p (range)	12.1 (3.7 – 14.5)	12.9 (3.7 – 15.3)	0.015
Median miR-10b-5p (range)	11.0 (3.7 – 13.5)	11.4 (3.6 – 12.8)	0.055

AML: acute myeloid leukemia, **CN-AML:** cytogenetically normal-AML, **CR:** complete remission.

Table S6. Univariable analyses for CR, using logistic regression in older (≥60 years) de novo CALGB/ALLIANCE CN-AML patients

Variable	Categories	*P*-value	Odds Ratio (95% CI)	Entered Multivariable Analysis
miR-10a-5p	Continuous	.23	1.06 (0.96, 1.17)	X
miR-10b-5p	Continuous	.18	1.08 (0.97, 1.20)	X
NPM1	Mutated v. Wild-type	**< .001**	3.68 (1.93, 7.01)	X
FLT3-ITD	Mutated v. Wild-type	.43		
CEBPA	Mutated v. Wild-type	.70		
ELN Risk Group	Favorable v. Intermediate	**< .001**	3.64 (1.84, 7.20)	Using markers
FLT3-TKD	TKD v. No TKD	.43		
WT1	Mutated v. Wild-type	.10		X
MLL-PTD	Present v. Absent	.60		
IDH1	Mutated v. Wild-type	.59		
IDH2	R140 or R172 Mutated v. Wild-type	.32		
ASXL1	Mutated v. Wild-type	**.008**	0.32 (0.13, 0.74)	X
DNMT3A	Mutated v. Wild-type	.61		
RUNX1	Mutated v. Wild-type	**.004**	0.32 (0.14, 0.69)	X
ERG expression	High v. Low	.34		
BAALC expression	High v. Low	**< .001**	0.18 (0.08, 0.40)	X
MN1 expression	High v. Low	**< .001**	0.22 (0.10, 0.47)	Too much missing
miR-181a expression	High v. Low	.99		
miR-3151 expression	High v. Low	**.004**	0.32 (0.15, 0.68)	Too much missing
miR-155 expression	High v. Low	**< .001**	0.29 (0.15, 0.57)	X
Hemoglobin	Continuous	.94		
Platelets	Continuous, 50-unit increase	**.03**	0.80 (0.66, 0.98)	X
WBC	Continuous, 50-unit increase	**.01**	0.72 (0.55, 0.94)	X
%PB Blasts	Continuous, 10% increase	.34		
%BM Blasts	Continuous, 10% increase	.18		Not reliable
Age	Continuous, 10-year increase	.06		X
Race	White v. Non-White	.70		
Sex	Male v. Female	.49		
Extramedullary Involvement	Present v. Absent	**.03**	0.46 (0.23, 0.92)	X

An odds ratio >1 (<1) corresponds to a higher (lower) odds of achieving a CR for higher values of continuous variables and the first level listed of a dichotomous variable.

AML: acute myeloid leukemia, **CN-AML:** cytogenetically normal-AML, **CR:** complete remission, ***NPM1*:** nucleophosmin, ***FLT3:*** Fms-Like Tyrosine Kinase 3, **ITD:** internal tandem duplication, **TDK**: tyrosine kinase domain, **ELN:** European LeukemiaNet, ***CEBPA:*** CCAAT/enhancer-binding protein alpha**,** ***WT1*:** Wilms tumor 1**,** ***TET2:*** tet methylcytosine dioxygenase 2, MLL-mixed lineage leukemia, **PTD:** partial tandem duplications, ***IDH1:*** isocitrate dehydrogenase 1, **ASXL1:** Additional Sex Combs Like 1, ***DNMT3A:*** DNA methyltransferases 3A, ***RUNX1:*** Runt-related transcription factor 1, ***ERG:*** ETS-related gene**,** ***BAALC:*** Brain and acute leukemia cytoplasmic, ***MN1:*** meningioma (disrupted in balanced translocation)1, **BM:** bone marrow, **PB:** peripheral blasts, **WBC:** white blood count, CI: confidence interval.

Supplemental Figure Legends

Figure S1. Baseline miR-10a-5p expression levels obtained from microarray data according to *NPM1* mutation status and chemotherapy response (CR vs. no-CR). There appears to be an interaction effect in the multivariable logistic model with *NPM1* mutation status and miR-10a-5p, where *NPM1* mutation status modifies the effect of miR-10a-5p on CR incidence (P=0.033)

Figure S2. MiR-10a-5p expression levels after miR-10a-5p over-expression or silencing in AML cell lines and primary AML samples. **(A)** miR-10a-5p levels in KG-1a and Kasumi-1 cell lines after ectopic transfection or infection with synthetic miR-10a-5p precursors or lentivirus (pMIR-10a) and their respective controls (scrambled and empty vector pMIR-EV). The results are shown as relative expression of the miRNA with respect to the internal control U44. **(B)** miR-10a-5p levels in K562 and OCI-AML-3 cell lines after ectopic transfection with synthetic antimiR-10a-5p precursors (anti-10a) or scrambled oligonucleotides controls. The results are shown as relative expression of the miRNA with respect to the internal control U44. **(C)** Upper panel: miR-10a-5p levels in two primary BM AML patient samples (CN-AML-*FLT3* and *NPM1* wild type) after culture with transferrin conjugated nanoparticle and encapsulated with synthetic miR-10a-5p precursors (0.5 uM) or scrambled oligonucleotides control. The results are shown as fold change of miR-10a-5p with respect to the scrambled control after normalization with U44. Lower panel: miR-10a-5p levels in two primary AML patient samples (CN-AML-*FLT3* wild type and *NPM1* mutated) after culture with transferrin conjugated nanoparticle encapsulated with synthetic anti-10a-5p (0.5 uM) or scrambled

oligonucleotides control. The results are shown as fold change of miR-10a-5p with respect to the scrambled control after normalization with U44.

Figure S1. miR-10a-5p and *NPM1* mutation status in relationship with chemotherapy responses.

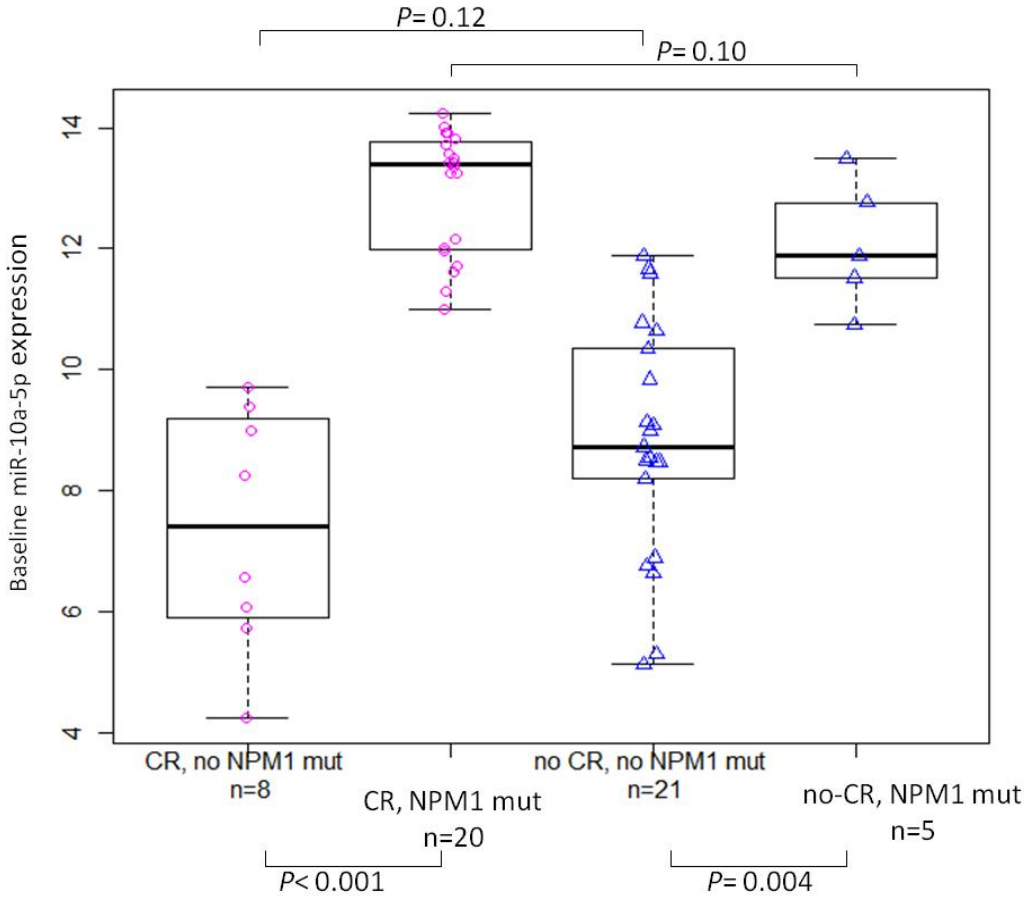
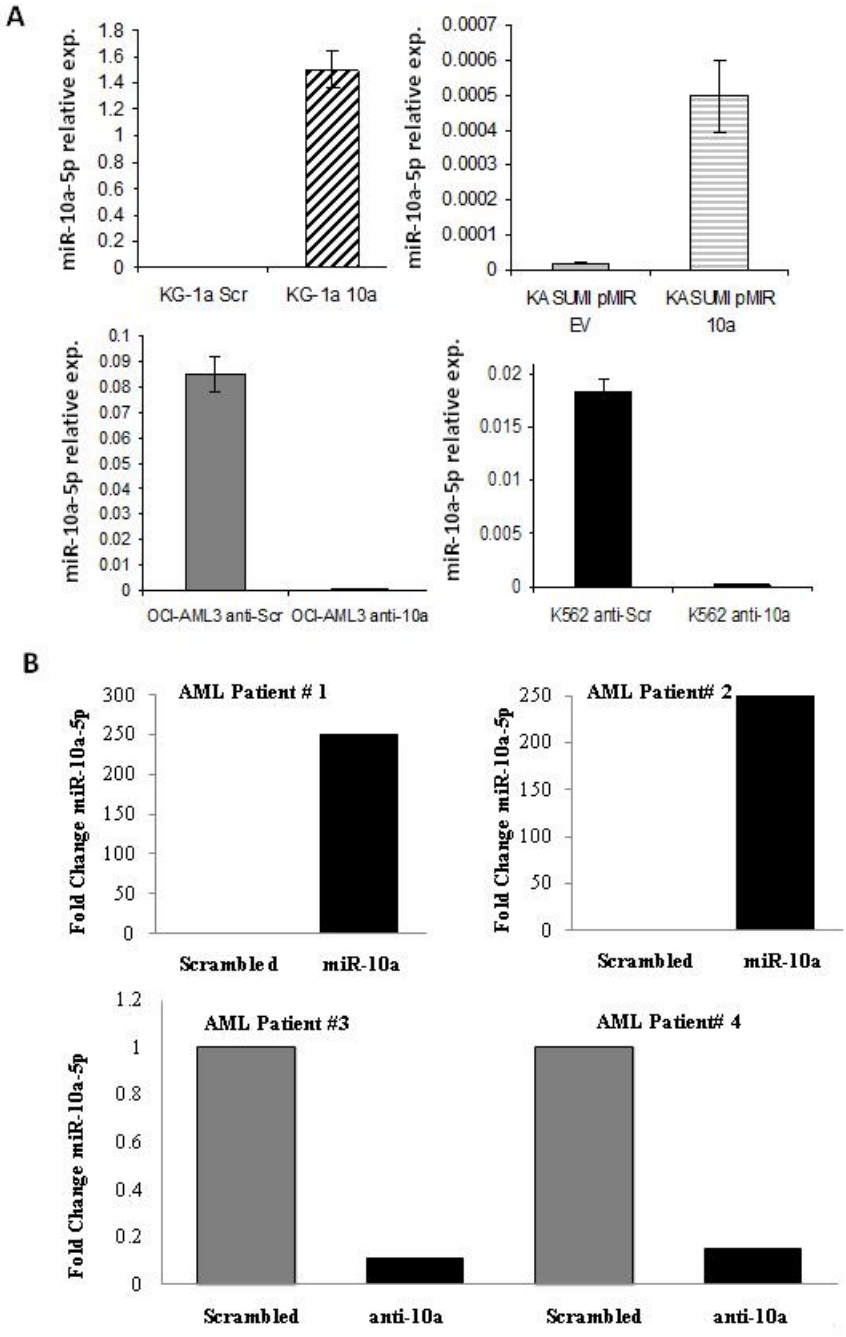


Figure S2.


A
miR-10a-5p relative exp.
KG-1a Scr
KG-1a 10a
KASUMI pMIR EV
KASUMI pMIR 10a
OCI-AML3 anti-Scr
OCI-AML3 anti-10a
K562 anti-Scr
K562 anti-10a
B
AML Patient # 1
AML Patient# 2
AML Patient #3
AML Patient# 4
Fold Change miR-10a-5p
Scrambled
miR-10a
anti-10a