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KSR2 is a novel oncogene in *TAL1* subtype of T-cell acute lymphoblastic leukemia with potential clinical and prognostic implications

Running title: *KSR2* is a novel oncogene in TAL1 subtype of T-ALL

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Author contributions

MDŚ was responsible for conceptualization, formal analysis, funding acquisition, investigation, methodology, visualization, writing original draft, manuscript review and editing. NMM was responsible for formal analysis, funding acquisition, investigation, methodology, and visualization. RJ was responsible for data curation, formal analysis, software and visualization. IF was responsible for investigation, visualization and manuscript review and editing. MK was responsible for investigation and methodology. JC was responsible for investigation, funding acquisition and contributed to writing of the original draft. ML and KD were responsible for resources (clinical data). ŁS, TS and AP were responsible for resources (samples). TS and MW were responsible for funding acquisition. PN was responsible for conceptualization, manuscript review and editing and funding acquisition. MD was responsible for conceptualization, funding acquisition, methodology, project administration, supervision, writing original draft, manuscript review and editing and overall direction.

Data Availability Statement:

The datasets generated during the current study are available in ArrayExpress repository under accession number E-MTAB-11759 and E-MTAB-14919 (RNA sequencing data in T-ALL patients), GEO repository under accession number GSE286430 (RNA sequencing data

in T-ALL cell line) and in Zenodo repository (Supplementary Materials - https://doi.org/10.5281/zenodo.21492388; and raw experimental data - https://doi.org/10.5281/zenodo.21511142, https://doi.org/10.5281/zenodo.21511461).

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Competing interests:

The authors declare that two national patent applications have been filed based on the results described in this manuscript (Patent Office of the Republic of Poland, patent applications no. P.454125 and P.454126).

The identification of molecular subtypes in T-cell acute lymphoblastic leukemia (T-ALL) provides invaluable biological insights, yet for many years their clinical relevance remained unestablished. Recently, comprehensive genomic and transcriptomic analysis of ~1000 pediatric T-ALL cases revealed 15 subtypes, characterized by divergent outcomes[1]. However, routine genome- and transcriptome-wide profiling is not feasible in most clinical settings. Therefore, identifying simple and accessible biomarkers is crucial for the early identification of patients at risk of relapse or drug resistance (~20% pediatric cases), for whom the prognosis remains poor[1,2]. DNA methylation has been associated with T-ALL biology[3] and prognosis[4]. Leukemias with global DNA hypomethylation, referred to as CpG island methylator phenotype negative (CIMP-), have been linked to inferior outcomes compared to hypermethylated cases (CIMP+)[4], a finding we previously confirmed in a cohort of 109 Polish pediatric T-ALL patients[5]. The hypomethylation phenotype is considered a consequence of intensive proliferation rather than a primary driver, underscoring the need to identify molecular determinants associated with these subgroups[5]. Here, we report that *KSR2* gene is ectopically expressed in a subset of CIMP- T-ALL, linked to the TAL1 subtype, and associated with adverse outcome. Using integrated transcriptomic and methylation data, we identify a regulatory mechanism involving DNA demethylation-dependent TAL1 binding and demonstrate that *KSR2* has functional, prognostic and potentially therapeutic relevance in T-ALL.

The detailed descriptions of materials, methods and raw experimental data are available at Zenodo (https://doi.org/10.5281/zenodo.21492388, https://doi.org/10.5281/zenodo.21511142, https://doi.org/10.5281/zenodo.21511461). Characteristics of the analyzed patient cohort are shown in Supplementary Table 1. Samples were collected at the centers of Polish Pediatric Leukemia and Lymphoma Study Group, with informed consent of the patients/legal guards, in accordance with the Declaration of Helsinki. To investigate transcriptomic differences between methylation-defined subgroups, we analyzed 45 Polish pediatric T-ALL patients with published EPIC DNA methylation array data[5] and available mRNA-seq data, alongside 6 normal thymocyte samples (3 CD4+_CD8+ and 3

CD34+)[6], deposited in ArrayExpress (E-MTAB-11759 and E-MTAB-14919). *KSR2* emerged as significantly upregulated in CIMP- compared to CIMP+ cases and was not expressed in normal thymocytes (Fig. 1A). *KSR2* has been described as a putative oncogene in solid tumors, implicated in the regulation of RAS/RAF/MEK/ERK and AMPK signaling pathways[7–10]. To explore its role, we analyzed RNA-seq data from 88 Polish pediatric patients (45 previously mentioned and 43 additional) and stratified them based on the bimodal distribution of *KSR2* expression values (cutoff 100 normalized reads). Principal component analysis (PCA) revealed clustering of most *KSR2*-positive cases within a group enriched for TAL1-driven leukemias, classified based on ectopic expression and/or gene fusions involving *TAL1*. Indeed, 18/24 *KSR2*-positive patients were TAL1-positive (Fig. 1B, Supplementary Table 1). *KSR2* expression was higher in TAL1-T-ALL compared to other subtypes, where it was largely absent (Fig. 1C). This association was validated in an independent cohort of 1014 pediatric patients[1], confirming significantly higher *KSR2* expression in TAL1-positive cases. The majority of *KSR2*-positive patients belonged to the recently identified TAL1αβ-like subtype (Fig. 1D)[1].

Since TAL1 is a transcription factor, we hypothesized that it may directly regulate *KSR2* expression. TFLink database analysis identified *KSR2* as a validated TAL1 target. Examination of published TAL1 ChIP-seq data from the JURKAT cell line[11] using GTRD[12] revealed TAL1 binding within an intronic region of *KSR2*, a putative regulatory element located ~100 kbp from the transcription start site (Fig. 1E). Functional validation using shRNA-mediated *TAL1* knockdown in JURKAT resulted in a ~60% reduction in *KSR2* expression (Fig. 1F), supporting a regulatory interaction. However, not all TAL1-positive cases expressed *KSR2*, suggesting that TAL1 presence alone is not sufficient to induce *KSR2* expression. Further analysis of 45 T-ALL patients with matched methylation and RNA-seq data showed an inverse correlation between promoter methylation and *KSR2* expression (Supplementary Fig. 1A). While all *KSR2*-positive cases exhibited low promoter methylation, the hypomethylation was also observed in normal thymocytes lacking *KSR2* expression,

indicating that promoter methylation status does not determine gene activation (Supplementary Fig. 1B). Thus, we next analysed the methylation in the *KSR2* intronic regulatory region, targeted by TAL1. This region includes CpG sites recognized by 6 array probes, 3 of which showed significantly lower methylation in *KSR2*-positive compared to *KSR2*-negative patients and normal thymocytes (Supplementary Fig. 1C). Methylation at these sites distinguished *KSR2*-positive from *KSR2*-negative cases within the TAL1 subgroup (Supplementary Fig. 1D). We targeted the identified regulatory region using a CRISPR interference (CRISPRi) with dCas9-KRAB in JURKAT cells, characterized by *KSR2*-positivity. Blocking this locus led to a significant reduction in *KSR2* expression (Supplementary Fig. 1E), supporting the model in which focal DNA demethylation modulates chromatin accessibility and enables TAL1 binding and transcriptional activation.

We evaluated the clinical relevance of *KSR2*. In the Polish cohort (88 cases) *KSR2* status was not associated with outcome. However, within the TAL1 subgroup (35 cases), *KSR2*-positive patients exhibited worse overall and relapse-free survival, (OS and RFS) with all relapses and deaths occurring in *KSR2*-positive cases (Fig. 2A, 2B). In an independent cohort of 1014 patients, *KSR2* expression was associated with inferior survival irrespective of genetic subtype (Fig. 2C, 2D). Furthermore, *KSR2*-positive cases with positive measurable residual disease (MRD) represent a subgroup at particularly high risk, while MRD-negative *KSR2*-positive patients have OS similar to MRD-positive *KSR2*-negative cases (Fig. 2E, 2F), pointing to the potential of *KSR2* evaluation to improve the MRD-based risk stratification.

To assess the functional role of *KSR2*, we performed CRISPRi-mediated repression in *KSR2*-positive JURKAT and RPMI-8402 cell lines. Efficient downregulation at mRNA and protein level (Fig. 3A, 3B) resulted in a loss of growth advantage in competition assays, supporting a pro-survival role for *KSR2* in T-ALL (Fig. 3C). We next evaluated the therapeutic potential of targeting *KSR2* using APS-2-79, a small-molecule inhibitor[13]. Treatment reduced viability of *KSR2*-positive cell lines in a dose-dependent manner (IC50 11–14 µM), while *KSR2*-negative cell lines were insensitive, indicating specificity of the effect (Fig. 3D). RNA-seq profiling of

JURKAT cells treated with APS-2-79, deposited in GEO (GSE286430), identified widespread transcriptomic changes, with enrichment of pathways related to metabolism, DNA replication, RNA processing, and cell cycle regulation (Supplementary Fig. 2A). Gene set enrichment analysis (GSEA) revealed activation of lipid and oligosaccharide biosynthesis pathways and suppression of processes associated with DNA conformational changes, suggesting impaired proliferation. These findings pointed toward a role of *KSR2* in metabolic regulation (Fig. 3E). Given prior reports linking *KSR2* to AMPK signaling[7], we hypothesized that its oncogenic activity in T-ALL may be mediated through this pathway. To test this, we assessed AMPK activation in *KSR2*-silenced JURKAT cells under glucose starvation. *KSR2* inhibition resulted in a decreased ratio of phosphorylated to total AMPKα, indicating reduced pathway activation (Supplementary Fig. 2B). In line, GSEA analysis of the Polish cohort revealed upregulation of genes involved in AMPK pathway in KSR2-positive patients compared to KSR2-negative, possibly balancing higher proliferative activity and energy expenditure (Fig. 3F, Supplementary Fig. 2C). This supports a model in which *KSR2* promotes leukemic cell survival through positive regulation of AMPK signaling.

We identify *KSR2* as a novel oncogenic factor in T-ALL, closely linked to the TAL1 molecular subtype, and provide evidence for its epigenetically regulated activation. We demonstrate that *KSR2* expression is driven by TAL1 binding to an intronic regulatory region, with focal DNA demethylation facilitating transcription factor recruitment. This mechanism connects aberrant transcriptional activation with the hypomethylated (CIMP-) phenotype, previously associated with high proliferation and worse outcome in T-ALL. Functionally, both genetic and pharmacological inhibition of KSR2 impaired the growth of *KSR2*-positive T-ALL cells, indicating a pro-survival role. Our results suggest that this effect is mediated primarily through AMPK signaling. Although AMPK is often considered tumor-suppressive, its role appears context-dependent[14]. In T-ALL, AMPK activity may support leukemic cell survival under metabolic stress, a condition associated with rapid proliferation[14,15]. Consistently, *KSR2* expression was largely restricted to CIMP- cases, supporting the hypothesis that KSR2

contributes to metabolic adaptation and survival advantage in aggressive, highly proliferative leukemias.

While *KSR2* has not previously been studied in hematologic malignancies, its relevance has been reported in solid tumors, including hepatocellular and endometrial cancers, where it promotes proliferation and is associated with inferior outcomes[8,9]. In lung cancer *KSR2* was associated with resistance to anti-PD-1 therapy via metabolic reprogramming[10]. These observations are consistent with our findings and support its broader role in cancer biology.

KSR2 represents both a potential prognostic biomarker and a therapeutic target. We show that *KSR2* expression identifies a subgroup of patients with poor outcome. Importantly, the survival of MRD-negative *KSR2*-positive patients was comparable to that of MRD-positive *KSR2*-negative cases, indicating that *KSR2* expression may capture clinically relevant risk not identified by MRD assessment alone.

Pharmacological KSR2 inhibition using APS-2-79 reduced viability of *KSR2*-positive T-ALL cells, although the observed potency suggests that combination strategies will be required for clinical application. Our data indicate that *KSR2* inhibition affects metabolic pathways and AMPK signaling, revealing a mechanism distinct from its previously described role in RAS pathway modulation in other cancers[13].

Our findings position *KSR2* as a biologically relevant and clinically actionable factor in T-ALL, linking epigenetic deregulation with oncogenic signaling and metabolic adaptation. Its potential as a biomarker and a therapeutic target warrants further investigation.

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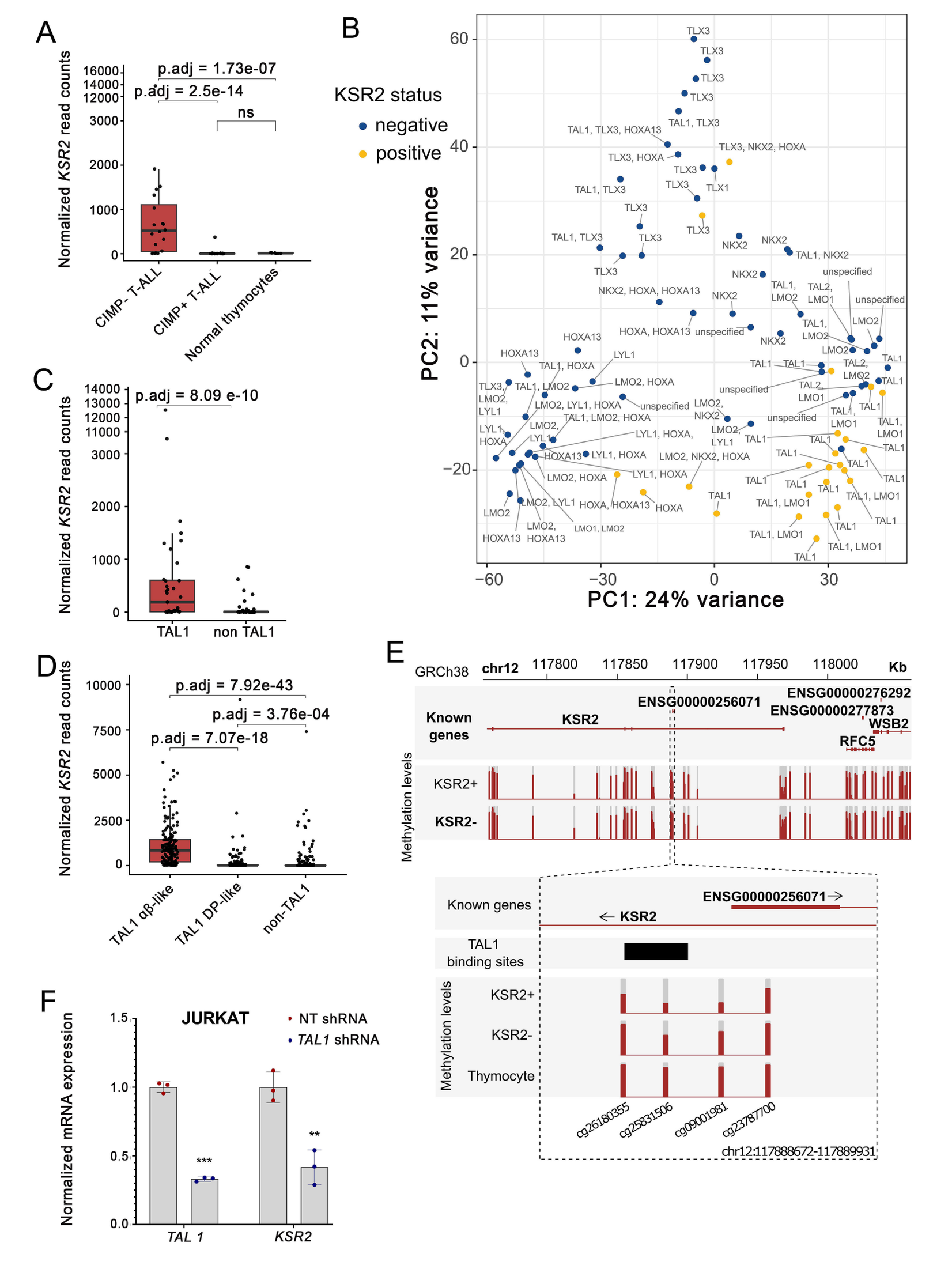
Figure legends

Figure 1. *KSR2* expression in T-cell acute lymphoblastic leukemia. A. Expression of *KSR2* in 45 Polish T-ALL patients (with available CIMP phenotype information) compared to normal thymocytes, analyzed using Wald test. **B.** Principal component analysis (PCA) of 88 Polish T-ALL patients based on RNA-seq. The labels indicate genetic T-ALL subtype. The color of dots indicate the status of *KSR2* expression. **C.** Comparison of *KSR2* expression in 88 Polish T-ALL patients depending on TAL1 subtype status, analyzed using Wald test. **D.** Comparison of *KSR2* expression in 1026 T-ALL patients from KidsFirst cohort depending on TAL1 subtype status, analyzed using Wald test. **E.** Visualization of a fragment of KSR2 gene including promoter region and first exons. The upper methylation level panel shows average β-values for CpG sites recognized by EPIC methylation array probes in *KSR2*-positive and *KSR2*-negative Polish T-ALL patients. The lower panel shows a zoom to potential TAL1 binding site identified in JURKAT cell line and the average β-values for 6 CpG sites located in its proximity in *KSR2*-positive, *KSR2*-negative T-ALL patients and normal thymocytes. **F.** Relative expression of TAL1 and KSR2 mRNA measured by RT-qPCR in reference to GAPDH and ACTB in JURKAT T-ALL cell lines transduced with negative control (NT) or anti-TAL1 shRNA vector, analyzed using unpaired two-tailed t-test. *p< 0.05; **p<0.01; ***p<0.001; ns – not significant.

Figure 2. Prognostic relevance of *KSR2* expression in T-cell acute lymphoblastic leukemia. A., B. The comparison of overall survival (**A**) and relapse-free survival (**B**) in 35 Polish TAL1 T-ALL patients depending on *KSR2* expression status. **C., D.** The comparison of overall survival (**C**) and relapse-free survival (**D**) in 1014 KidsFirst T-ALL patients depending on *KSR2* expression status. **E., F.** The comparison of overall survival (**E**) and relapse-free survival (**F**) in 1007 KidsFirst T-ALL patients depending on *KSR2* expression and MRD status defined by the threshold of 10^{-4} (0.01%) MRD. Relapse free survival (RFS) and Overall free survival (OS) was analyzed using Cox proportional hazards regression. Pairwise comparisons between groups were performed using Wald test on marginal means derived from Cox model, with Benjamini-Hochberg correction for multiple testing.

Figure 3. Functional analysis of *KSR2* function in T-cell acute lymphoblastic leukemia. A., B. Relative expression of *KSR2* on mRNA (RT-qPCR) and protein (immunoblot) level upon CRISPRi-mediated repression of KSR2 in JURKAT (**A**) and RPMI-8402 (**B**) cell lines upon the use of 2 sgRNAs targeting KSR2 transcription start site locus compared to non-targeting (NT) sgRNA. **C**. GFP growth competition assay upon KSR2 repression in JURKAT and RPMI-8402 T-ALL cell lines. The GFP percentage for each time point was calculated in reference to the GFP percentage at the first day of measurement (Day 4 after transduction) and analyzed by two-way ANOVA. **D.** Normalized cell viability upon the use of a range of APS-2-79 concentrations (5-15 μM) compared to control (vehicle only) in KSR2-positive (JURKAT, RPMI-8402, PF-382) and KSR2-negative (ALL-SIL, HPB-ALL) T-ALL cell lines. **E.** Selected activated and suppressed processes based on Gene Set Enrichment Analysis (GSEA), involving genes differentially expressed in JURKAT cell line upon 24h treatment with 11 μM (IC50 dose) of APS-2-79 KSR2 inhibitor compared to vehicle treated (0.5% DMSO) control. **F.** GSEA showing significant enrichment of genes involved in the activation of AMPK pathway in *KSR2*-positive vs *KSR2*-negative T-ALL patients from Polish cohort (88 cases), as indicated

by a positive normalized enrichment score (NES) that remained significant after multiple-testing correction. ***p< 0.001; **p<0.01; *-p<0.05.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CIMP+ T-ALL
Normal thymocytes
B
KSR2 status
negative
positive
PC2: 11% variance
PC1: 24% variance
C
Normalized KSR2 read counts
p.adj = 8.09 e-10
TAL1
non TAL1
D
Normalized KSR2 read counts
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p.adj = 3.76e-04
p.adj = 7.07e-18
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TAL1 DP-like
non-TAL1
E
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chr12
Kb
Known genes
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RFC5
Methylation levels
KSR2+
KSR2-
TAL1 binding sites
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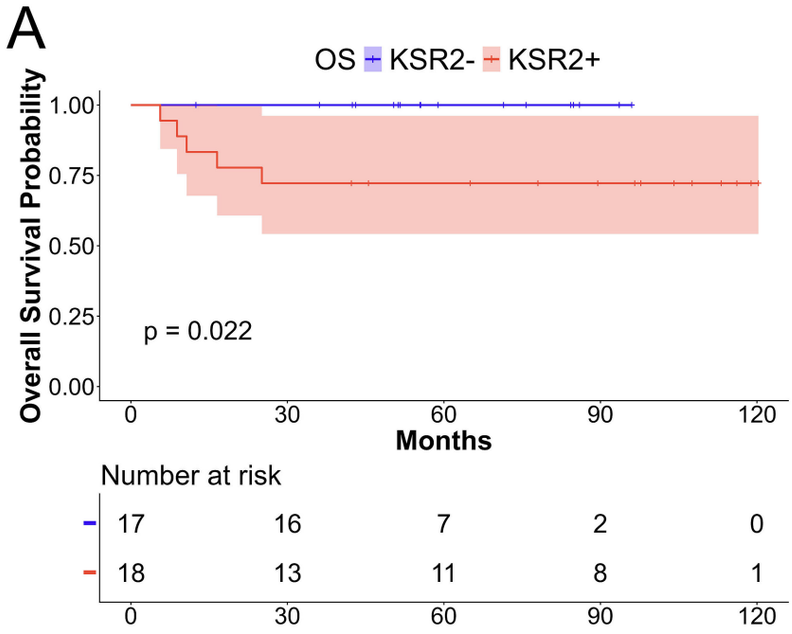
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90
120
Months
Number at risk
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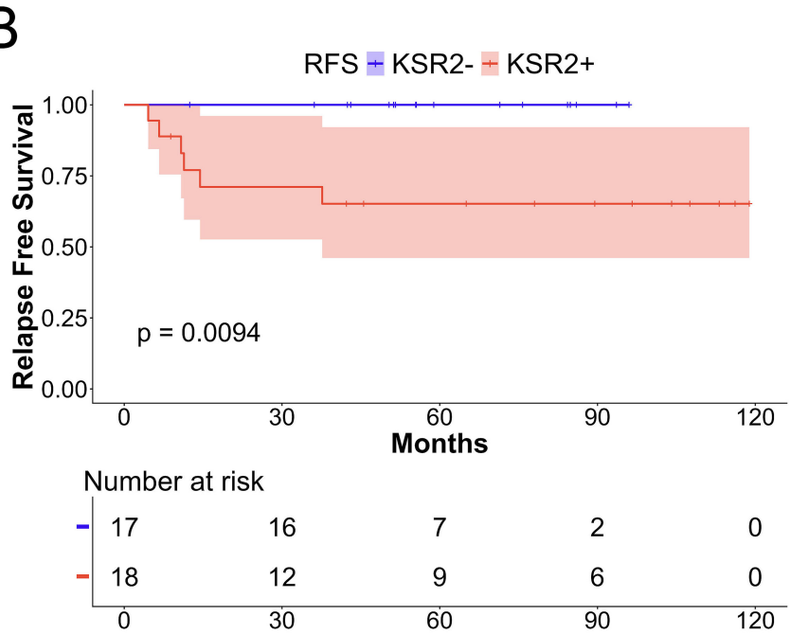
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Relapse Free Survival
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0.75
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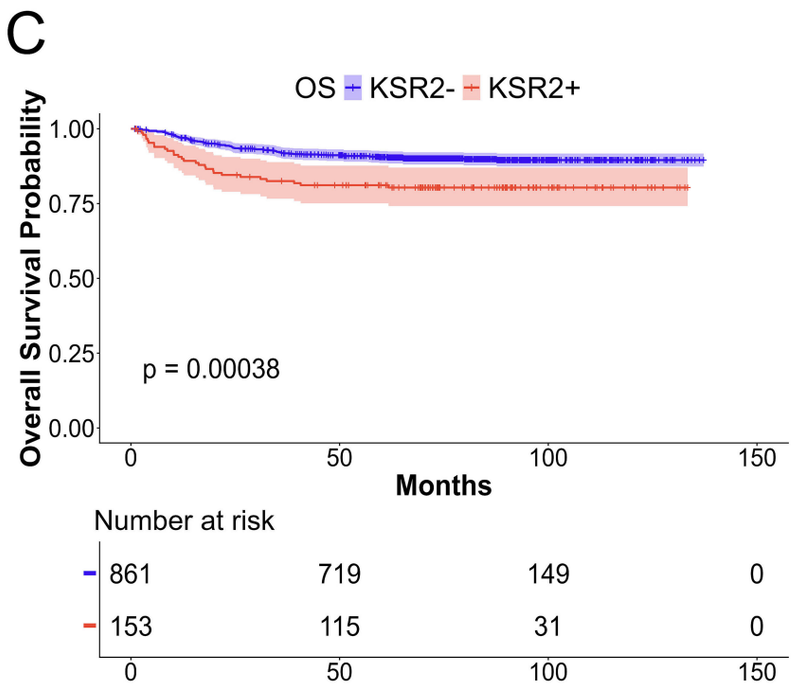
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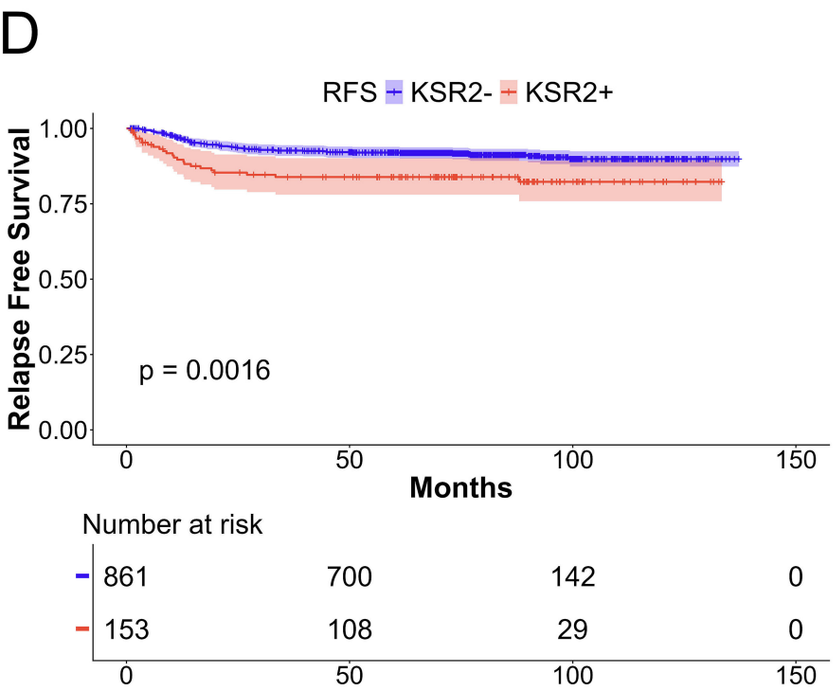
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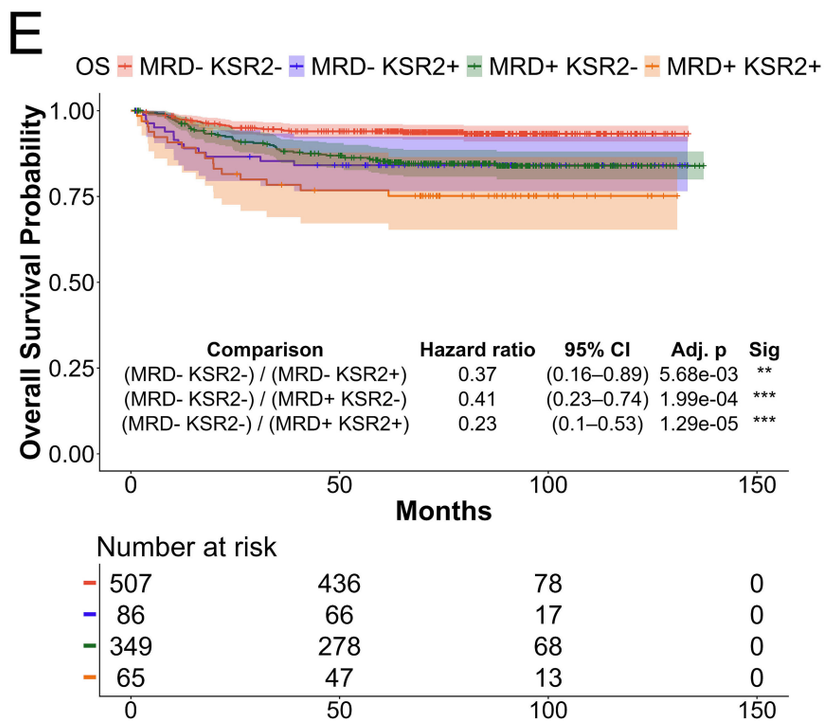
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1.00
0.75
0.50
0.25
0.00
Comparison Hazard ratio 95% CI Adj. p Sig
(MRD- KSR2-) / (MRD- KSR2+) 0.37 (0.16–0.89) 5.68e-03 **
(MRD- KSR2-) / (MRD+ KSR2-) 0.41 (0.23–0.74) 1.99e-04 ***
(MRD- KSR2-) / (MRD+ KSR2+) 0.23 (0.1–0.53) 1.29e-05 ***
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50
100
150
Months
Number at risk
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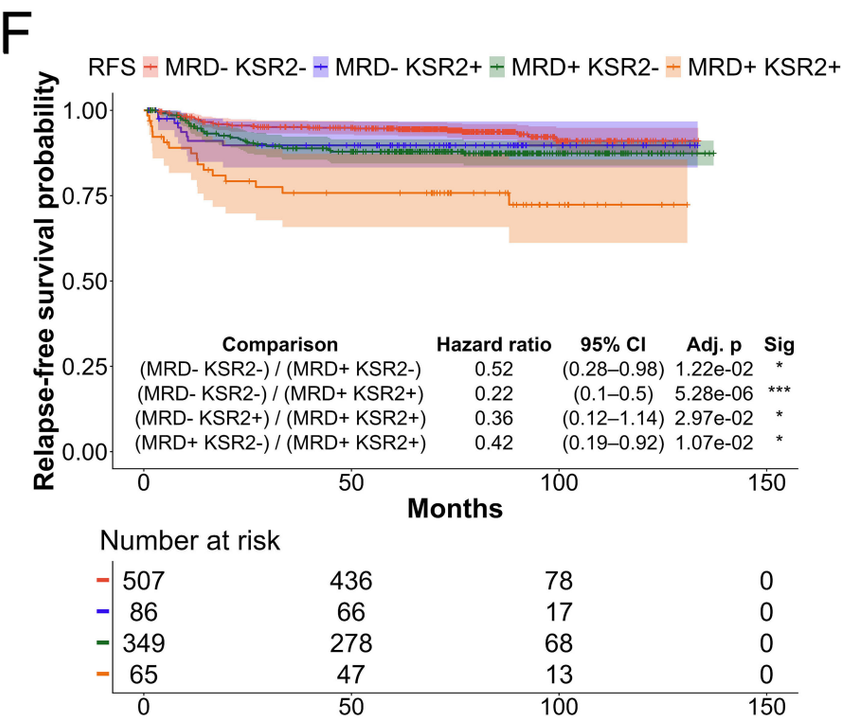
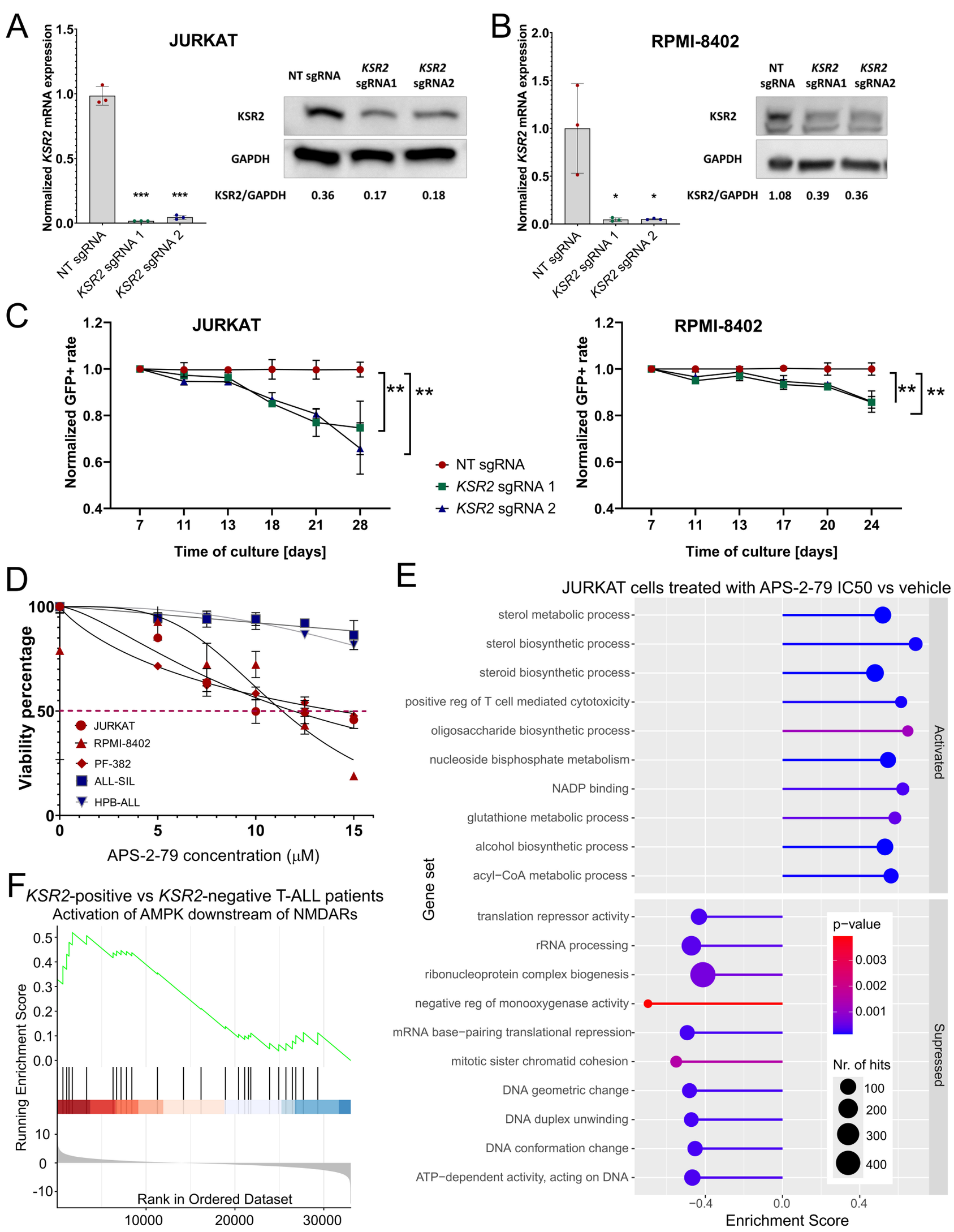
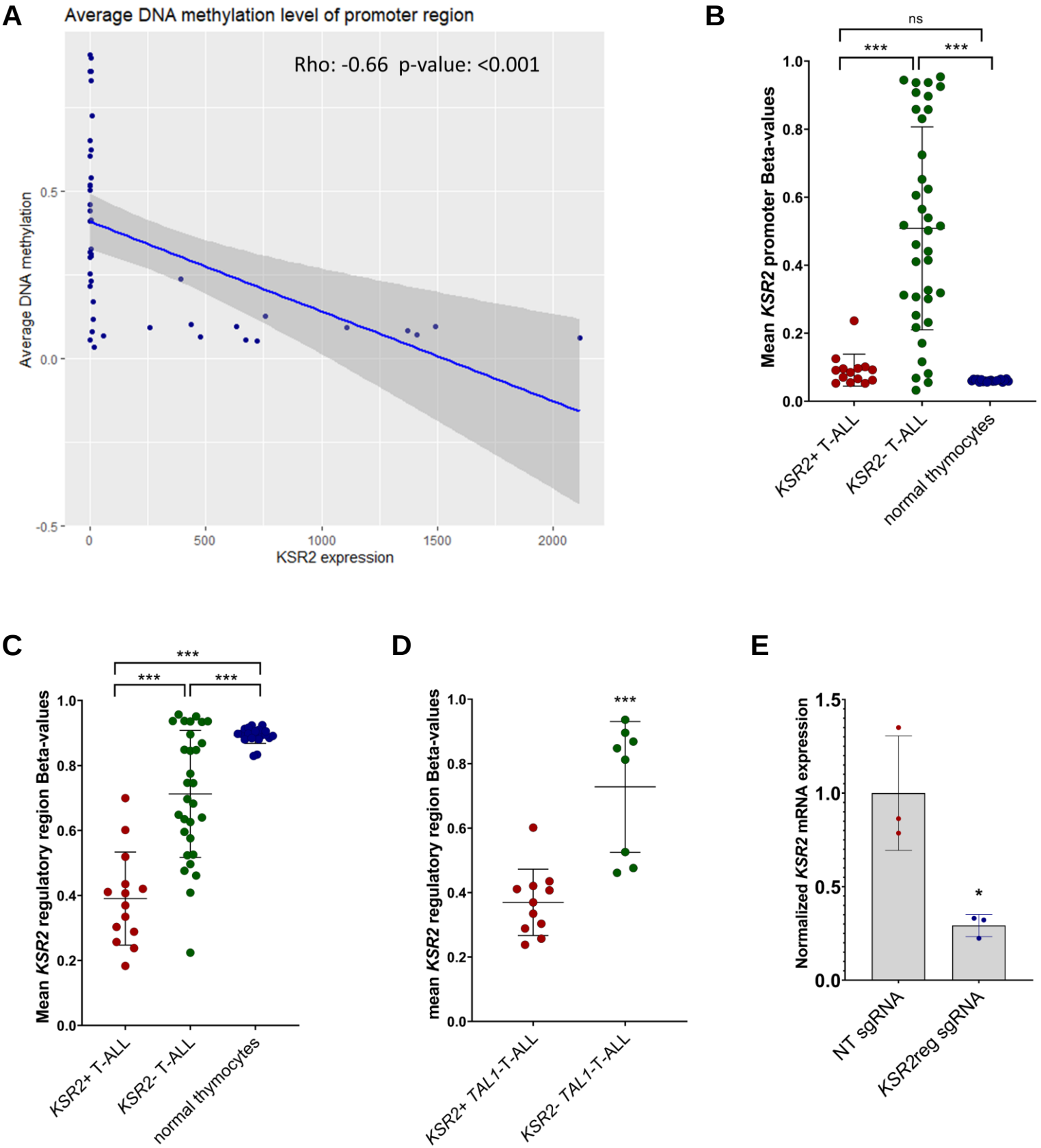

F
RFS MRD- KSR2- MRD- KSR2+ MRD+ KSR2- MRD+ KSR2+
Relapse-free survival probability
1.00
0.75
0.50
0.25
0.00
Comparison Hazard ratio 95% CI Adj. p Sig
(MRD- KSR2-) / (MRD+ KSR2-) 0.52 (0.28–0.98) 1.22e-02 *
(MRD- KSR2-) / (MRD+ KSR2+) 0.22 (0.1–0.5) 5.28e-06 ***
(MRD- KSR2+) / (MRD+ KSR2+) 0.36 (0.12–1.14) 2.97e-02 *
(MRD+ KSR2-) / (MRD+ KSR2+) 0.42 (0.19–0.92) 1.07e-02 *
0
50
100
150
Months
Number at risk
507 436 78 0
86 66 17 0
349 278 68 0
65 47 13 0
0 50 100 150

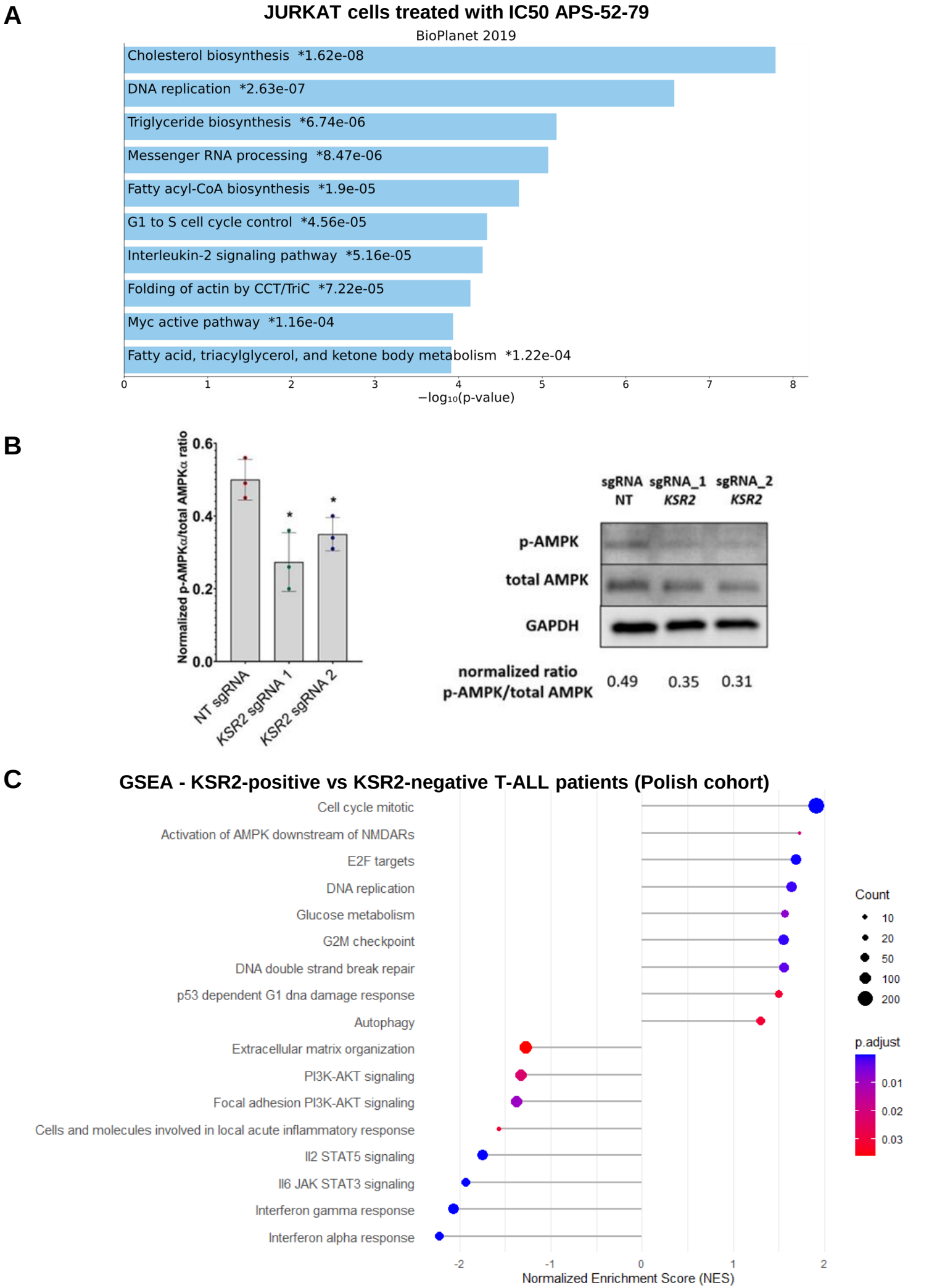

A
JURKAT
Normalized KSR2 mRNA expression
NT sgRNA
KSR2 sgRNA 1
KSR2 sgRNA 2
***
***
NT sgRNA
KSR2 sgRNA1
KSR2 sgRNA2
KSR2
GAPDH
KSR2/GAPDH 0.36 0.17 0.18
B
RPMI-8402
Normalized KSR2 mRNA expression
*
*
KSR2/GAPDH 1.08 0.39 0.36
C
JURKAT
RPMI-8402
Normalized GFP+ rate
Time of culture [days]
NT sgRNA
KSR2 sgRNA 1
KSR2 sgRNA 2
D
Viability percentage
APS-2-79 concentration (μM)
JURKAT
RPMI-8402
PF-382
ALL-SIL
HPB-ALL
E
JURKAT cells treated with APS-2-79 IC50 vs vehicle
sterol metabolic process
sterol biosynthetic process
steroid biosynthetic process
positive reg of T cell mediated cytotoxicity
oligosaccharide biosynthetic process
nucleoside bisphosphate metabolism
NADP binding
glutathione metabolic process
alcohol biosynthetic process
acyl−CoA metabolic process
translation repressor activity
rRNA processing
ribonucleoprotein complex biogenesis
negative reg of monooxygenase activity
mRNA base−pairing translational repression
mitotic sister chromatid cohesion
DNA geometric change
DNA duplex unwinding
DNA conformation change
ATP−dependent activity, acting on DNA
Gene set
Activated
Supressed
p−value
Nr. of hits
Enrichment Score
F
KSR2-positive vs KSR2-negative T-ALL patients
Activation of AMPK downstream of NMDARs
Running Enrichment Score
Rank in Ordered Dataset

Supplementary Figure 1



Supplementary Figure 1. A. Spearman's correlation with Benjamini and Hochberg correction between *KSR2* expression (evaluated by RNA-seq) and mean DNA methylation of 11 CpG sites located in close proximity to *KSR2* promoter (evaluated by EPIC methylation array) in 45 Polish pediatric T-ALL patients. **B.** The comparison of mean promoter DNA methylation level of *KSR2* gene between *KSR2*-positive, *KSR2*-negative T-ALL patients and normal thymocyte subsets, calculated with one-way ANOVA with post-hoc Tukey's test. **C.** The comparison of mean DNA methylation level of 3 CpG sites located *KSR2* regulatory intronic region between *KSR2*-positive, *KSR2*-negative T-ALL patients and normal thymocyte subsets, calculated with one-way ANOVA with post-hoc Tukey's test. **D.** The comparison of mean DNA methylation level of 3 CpG sites located *KSR2* regulatory intronic region between *KSR2*-positive and *KSR2*-negative T-ALL patients with TAL1 subtype, calculated with Wilcoxon test. **E.** Evaluation of *KSR2* expression on mRNA level in KSR2-positive JURKAT cell line expressing dCas9-KRAB, transduced with non-targeting (NT) sgRNA or sgRNA targeting *KSR2* intronic regulatory region (*KSR2*reg), analyzed with unpaired two-tailed t-test. * - $p<0.05$; *** - $p<0.001$.

Supplementary Figure 2



Supplementary Figure 2. A. Overrepresentation analysis of genes differentially expressed in JURKAT cells upon 24h treatment with IC50 dose of APS-2-79 (11 μM) compared to cells treated with vehicle (0.5% DMSO) analyzed using EnrichR tool and BioPlanet database. The top 10 enriched terms for the input gene set are displayed based on the -log10(p-value), with the actual p-value shown next to each term. The term at the top has the most significant overlap with the input query gene set. **B.** Relative ratio of phospho-AMPKα Thr172 to total AMPKα protein normalized by GAPDH in JURKAT cell line upon CRISPRi-mediated repression of KSR2 cultured in glucose-starvation conditions. Exemplary immunoblot shows protein bands of phospho-AMPKα Thr172, total AMPKα and GAPDH. The experiment was performed in three biological replicates. The results were analyzed with unpaired two-tailed t-test. **C.** Selected activated and suppressed processes based on Gene Set Enrichment Analysis, involving genes differentially expressed between *KSR2*-positive vs. *KSR2*-negative T-ALL patients from Polish cohort (88 cases).
* - $p<0.05$.

Supplementary Table 1. Data for 88 Polish pediatric T-ALL patients

Patient ID	Sex	Age at diagnosis (years)	Genetic subtype	Fusion genes	Genomic alterations	TAL1 status	KSR2 status	CIMP status	Relapse	Dead/Alive	Treatment protocol	Risk group
1357	male	13	LYL1, HOXA		WT1	non TAL1	negative	CIMP+	yes	dead	ALL IC BFM 2009	HR
1389	male	1	TAL1	STIL::TAL1	TAL1, PTENdel, CDKN2A/B, LEF1	TAL1	positive	CIMP-	yes	alive	ALL IC BFM 2009	HR
1393	male	16	LMO1, LMO2		WT1, SUZ12del	non TAL1	negative	CIMP-	no	alive	ALL IC BFM 2009	HR
1414	female	8	TLX3, LMO2, LYL1	TLX3::TRBC1	nd	non TAL1	negative	nd	no	alive	EsPhALL	HR
1422	male	9	LYL1, HOXA		WT1, EEDdel	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
1428	male	14	TAL1	STIL::TAL1	TAL1, CDKN2A/B	TAL1	positive	CIMP-	no	alive	ALL IC BFM 2009	HR
1472	male	1	NKX2	NKX2-1::TCRD	NKX2-1, PTENdel, CDKN2A/B, LEF1	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	IR
1489	male	10	TAL1, LMO1	STIL::TAL1	TAL1, LEF1	TAL1	positive	CIMP-	no	alive	ALL IC BFM 2009	IR
1490	male	5	TLX3, NKX2, HOXA	TLX3::TRBC1	TLX3, CDKN2A/B	non TAL1	positive	CIMP+	no	alive	ALL IC BFM 2009	HR
1538	male	12	TAL1	STIL::TAL1	nd	TAL1	negative	nd	no	alive	ALL IC BFM 2009	IR
1583	male	4	TAL1		del6q	TAL1	positive	CIMP-	no	alive	ALL IC BFM 2009	HR
1606	male	1	LMO2, LYL1	STAG2::LMO2		non TAL1	negative	CIMP-	no	alive	ALL IC BFM 2009	HR
1633	male	2	TAL1		CDKN2A/B, del6q	TAL1	positive	CIMP-	yes	alive	ALL IC BFM 2009	HR
1654	male	6	TAL1	STIL::TAL1	TAL1, PTENmut, CDKN2A/B	TAL1	positive	CIMP-	no	alive	ALL IC BFM 2009	IR
1660	male	3	TAL1, LMO1	LMO1::TRBC2	PTENmut, CDKN2A/B, del6q	TAL1	positive	CIMP-	yes	dead	ALL IC BFM 2009	HR
1701	male	16	TLX3		WT1, CDKN2A/B	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
1702	female	9	LYL1		EEDdel, del6q	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2002	HR
1743	male	3	TAL2, LMO2	TAL2::TRBC2	CDKN2A/B, EZH2mut	non TAL1	negative	CIMP-	no	dead	ALL IC BFM 2009	IR
1829	male	3	TAL1	STIL::TAL1	TAL1, CDKN2A/B	TAL1	positive	CIMP-	yes	dead	ALL IC BFM 2009	HR
1853	male	3	NKX2		CDKN2A/B	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
1886	male	14	HOXA		CDKN2A/B, CTCF, EEDdel, del5q	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2002	IR
1895	male	4	TLX3		TLX3, CDKN2A/B, CTCF	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	IR
1909	female	4	TLX3	TLX3::LOC105370656	TLX3, CDKN2A/B	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	IR
1939	female	3	TAL1	STIL::TAL1	TAL1, CDKN2A/B, EZH2dup, del6q	TAL1	positive	CIMP-	yes	dead	ALL IC BFM 2009	HR
1994	female	8	LMO2, LYL1, HOXA		HOXA	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
2000	male	3	TAL1		del6q	TAL1	positive	CIMP-	no	alive	ALL IC BFM 2009	IR
2003	male	9	TLX3		TLX3, CTCF, SUZ12del, del5q	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
2007	female	5	TLX1	TLX1::TCRB	nd	non TAL1	negative	nd	no	alive	ALL IC BFM 2009	IR
2049	male	13	LMO2			non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
2095	male	17	NKX2, HOXA		NKX2-1, CDKN2A/B	non TAL1	negative	CIMP+	yes	dead	ALL IC BFM 2009	HR
2101	female	3	TAL1, LMO1		PTENmut	TAL1	positive	CIMP-	no	alive	ALL IC BFM 2009	HR
2155	male	4	TAL1, LMO1	STIL::TAL1, RIC3-DT::LMO1	TAL1, PTENmut, CDKN2A/B	TAL1	positive	CIMP-	no	alive	ALL IC BFM 2009	HR
2156	male	10	LMO2, NKX2			non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
2177	male	10	TAL1, LMO1, LMO2, LYL1			TAL1	negative	CIMP-	no	alive	ALL IC BFM 2009	HR
2205	male	10	TLX3, HOXA		TLX3, PTENmut, CDKN2A/B	non TAL1	negative	CIMP+	yes	dead	ALL IC BFM 2009	IR
2221	female	5	TAL1, TLX3		TLX3, CDKN2A/B	TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
2223	male	15	TAL1, TLX3		TLX3, CDKN2A/B	TAL1	negative	nd	no	alive	ALL IC BFM 2009	HR
2237	male	7	TAL1		CDKN2A/B	TAL1	positive	CIMP-	no	alive	ALL IC BFM 2009	HR
2245	male	16	TLX3		TLX3, CDKN2A/B	non TAL1	negative	CIMP+	yes	dead	ALL IC BFM 2009	HR
2301	male	3	unspecified		nd	non TAL1	negative	nd	no	alive	ALL IC BFM 2009	IR
2328	male	2	TAL1	STIL::TAL1	TAL1, CDKN2A/B, del6q	TAL1	positive	CIMP-	no	alive	ALL IC BFM 2009	HR
2341	male	3	TAL1		CDKN2A/B	TAL1	negative	CIMP-	no	alive	ALL IC BFM 2009	HR
2362	male	12	LMO2, HOXA		HOXA	non TAL1	negative	CIMP+	yes	dead	ALL IC BFM 2009	HR
2373	male	7	unspecified		CDKN2A/B	non TAL1	negative	CIMP-	yes	dead	ALL IC BFM 2009	IR
2408	male	13	TLX3		TLX3, WT1	non TAL1	negative	CIMP+	no	dead	ALL IC BFM 2009	HR
2409	male	16	LMO2, HOXA		nd	non TAL1	negative	nd	yes	dead	ALL IC BFM 2009	HR
2413	male	7	TAL2, LMO1	TAL2::TRBC2	nd	non TAL1	negative	nd	no	alive	ALL IC BFM 2009	IR
2425	male	6	TAL1, TLX3		TLX3, CDKN2A/B, CTCF	TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
2428	female	5	TAL1, TLX3		TLX3, CDKN2A/B	TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	IR
2495	male	12	TAL1, LMO2, HOXA			TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	HR
2513	male	10	TAL1, LMO2		CDKN2A/B	TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	IR

2515	male	14	LMO2, LYL1		nd	non TAL1	negative	nd	no	alive	ALL IC BFM 2009	HR
2523	male	4	TLX3		TLX3, CDKN2A/B	non TAL1	negative	CIMP+	no	alive	ALL IC BFM 2009	IR
E01468	male	17	TAL1, LMO1		nd	TAL1	positive	nd	no	dead	ALL IC BFM 2009	SR
E01830	male	8	TAL1		nd	TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
E02221	male	14	TAL1, LMO1		nd	TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
E02841	male	15	TLX3		nd	non TAL1	negative	nd	yes	alive	AIEOP BFM 2017	SR
E02867	male	17	unspecified		nd	non TAL1	negative	nd	no	alive	no data	nd
E02946	male	16	TAL1	STIL::TAL1	nd	TAL1	positive	nd	no	alive	AIEOP BFM 2017	HR
E02968	male	3	LMO2		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
E03137	female	16	NKX2-5		nd	non TAL1	negative	nd	yes	alive	AIEOP BFM 2017	nonSR
E03248	female	9	LMO2		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
E03463	male	10	LMO2, NKX2		nd	non TAL1	positive	nd	no	alive	AIEOP BFM 2017	HR
E03493	male	1	TAL1		nd	TAL1	negative	nd	no	alive	AIEOP BFM 2017	HR
Y01588	male	10	HOXA	PICALM:MLLT10	nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
Y01849	female	17	TAL1, HOXA		nd	TAL1	negative	nd	no	alive	AIEOP BFM 2017	HR
Y01966	female	9	NKX2	NKX2-1::TRGV10	nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
Y01980	male	13	HOXA		nd	non TAL1	positive	nd	no	alive	AIEOP BFM 2017	HR
Y02335	female	7	TAL1, LMO2		nd	TAL1	negative	nd	no	alive	AIEOP BFM 2017	HR
Y02479	female	11	unspecified		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
Y02780	female	7	HOXA	KMT2A::MLLT1	nd	non TAL1	negative	nd	yes	dead	AIEOP BFM 2017	HR
Y03008	male	7	TAL1, LMO2		nd	TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
Y03082	female	4	TLX3		nd	non TAL1	positive	nd	no	alive	AIEOP BFM 2017	nonSR
Y03088	male	1	NKX2	NKX2-LOC112268189	nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
Y03130	male	6	TAL1		nd	TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
Y03492	male	6	HOXA		nd	non TAL1	negative	nd	no	dead	AIEOP BFM 2017	HR
Y03593	male	6	TLX3		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
Y03860	male	6	TAL1		nd	TAL1	positive	nd	no	alive	AIEOP BFM 2017	nonSR
Y04021	male	17	TAL1, LMO1		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	SR
Y04181	female	14	HOXA		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	HR
Y04262	female	4	TAL1	STIL::TAL1	nd	TAL1	negative	nd	no	alive	AIEOP BFM 2017	HR
Y04382	female	11	HOXA		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	nonSR
Y04518	male	15	LMO2		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	nd
Y04543	female	10	unspecified		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	nd
Y04758	male	12	unspecified		nd	non TAL1	positive	nd	no	alive	AIEOP BFM 2017	SR
Y05108	male	14	TAL1		nd	TAL1	positive	nd	yes	dead	AIEOP BFM 2017	SR
Y05114	male	4	HOXA		nd	non TAL1	positive	nd	no	alive	AIEOP BFM 2017	HR
Y05183	female	12	unspecified		nd	non TAL1	negative	nd	no	alive	AIEOP BFM 2017	HR

*nd - not determined

SR - standard risk; IR - intermediate risk; HR - high risk, nonSR - nonstandard risk