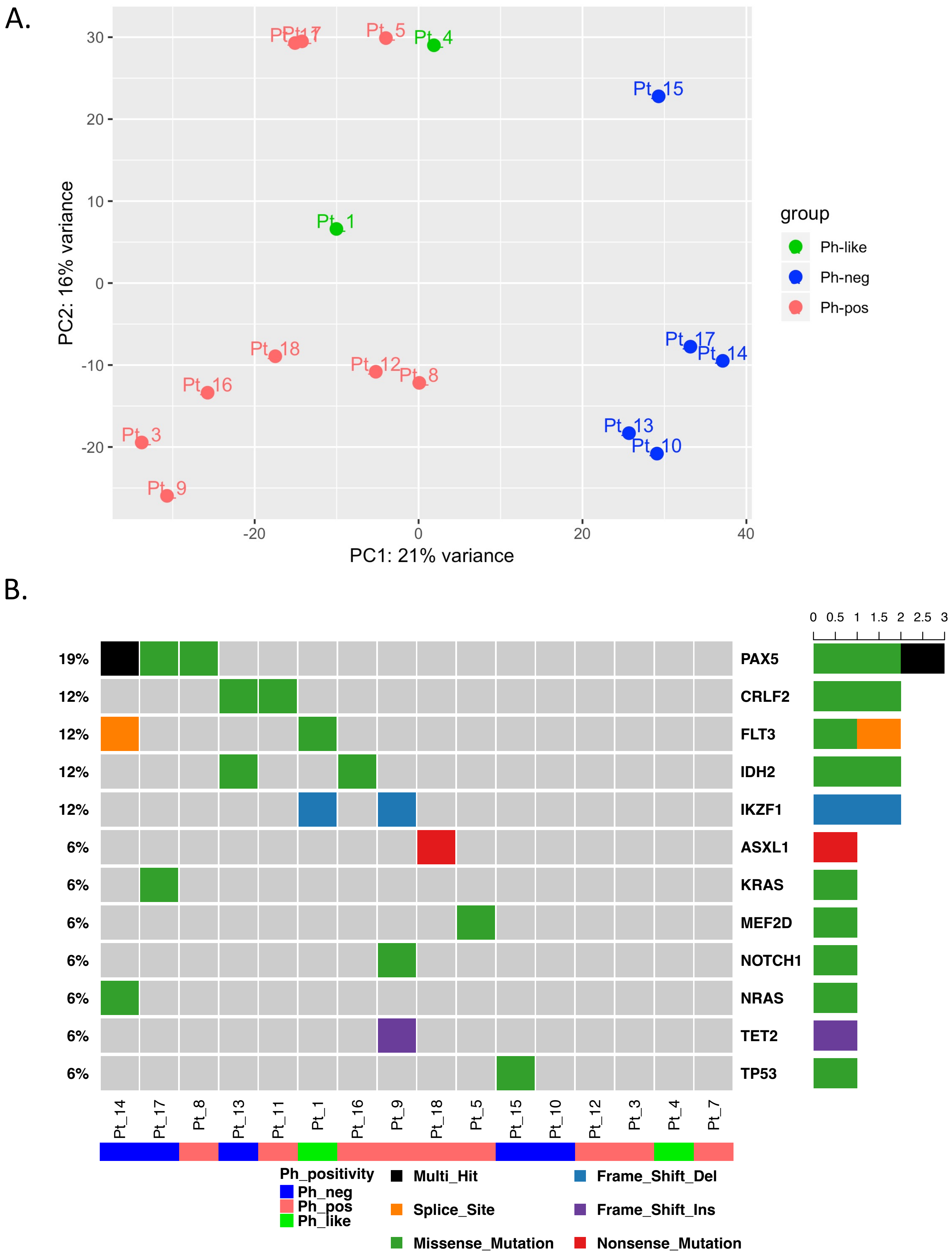
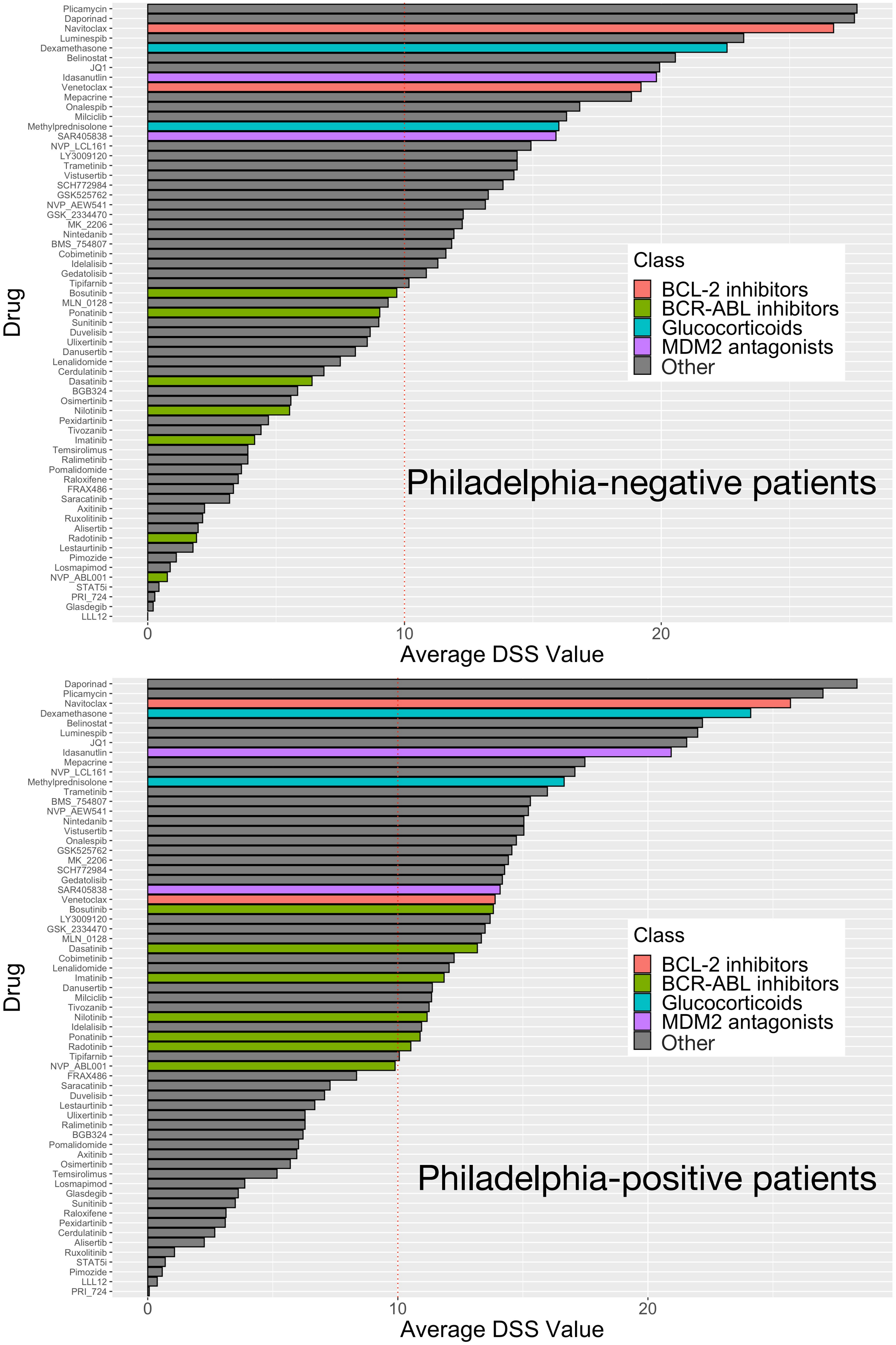
Supplementary Figure S1.

A) PCA plot from RNAseq data (DESeq2). B) Variants found from RNAseq in commonly mutated genes in leukemia.



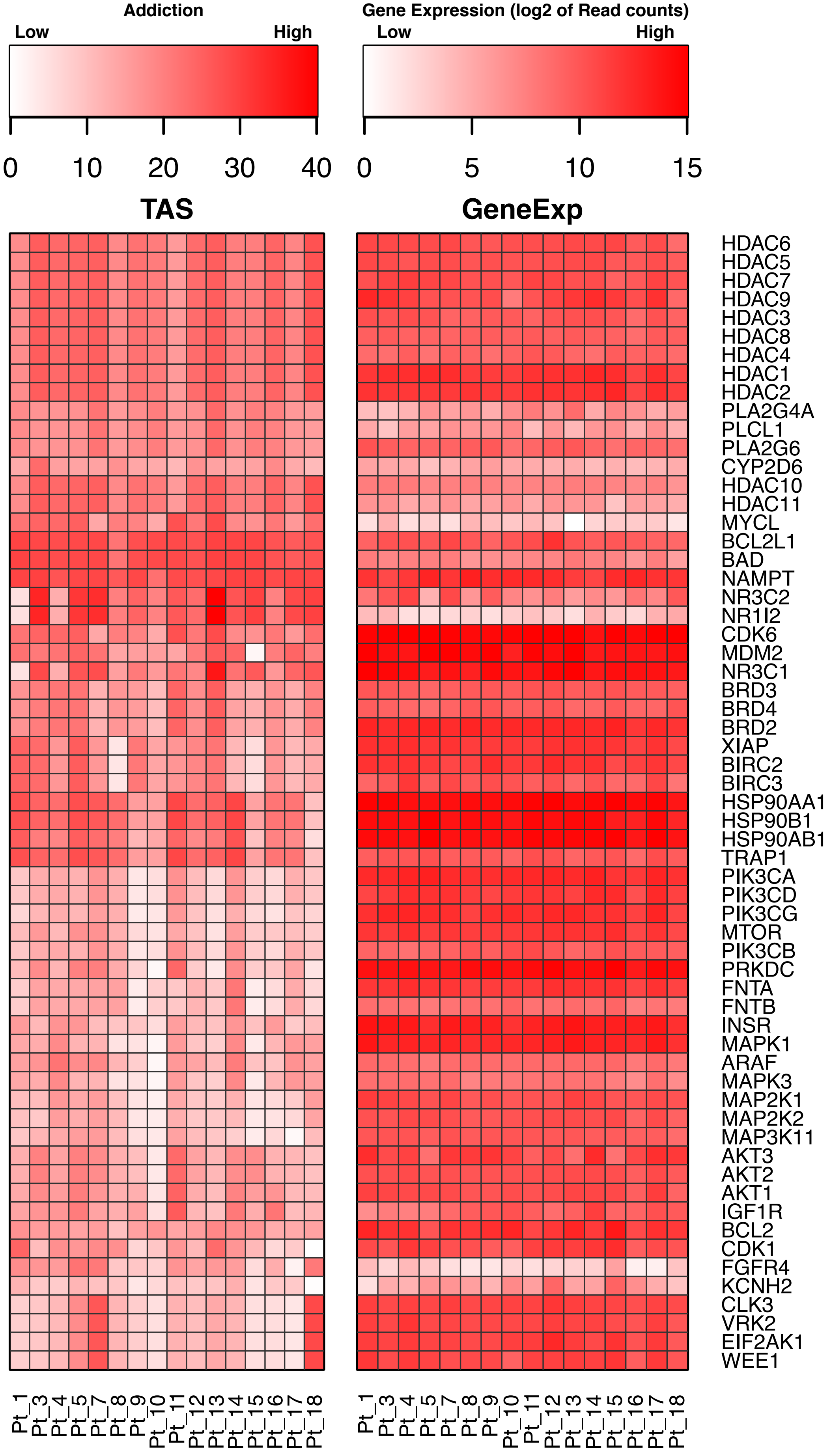
Supplementary Figure S2.

Average drug sensitivity score (DSS) values of all tested drugs in Philadelphia-positive (n=10) and negative (n=8) ALL patients. Philadelphia-like patients are included in the Ph-negative group.



Supplementary Figure S3.

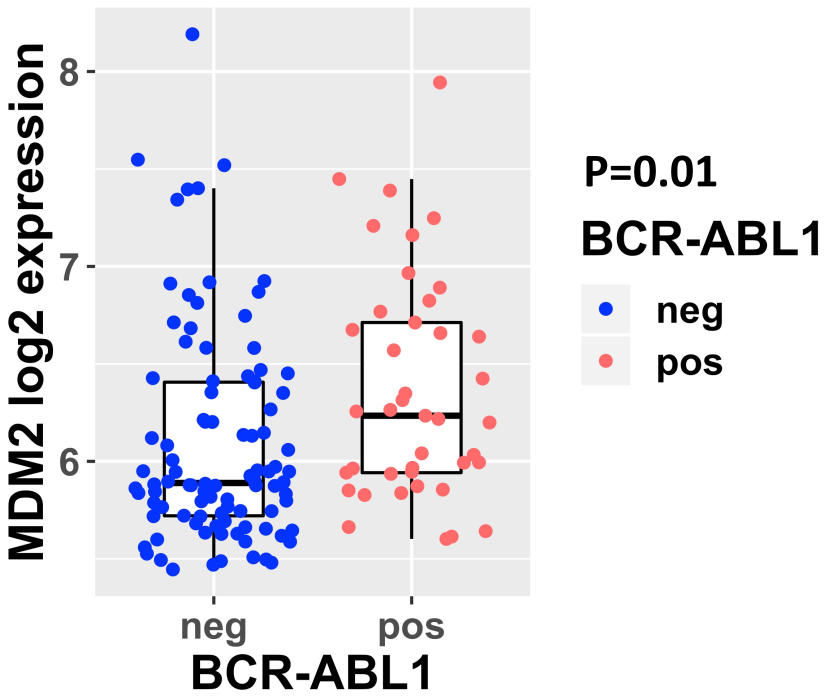
Addicted drug targets in the custom drug panel recognized by target addiction scoring (TAS) and gene expression of the same targets in whole transcriptome sequencing.



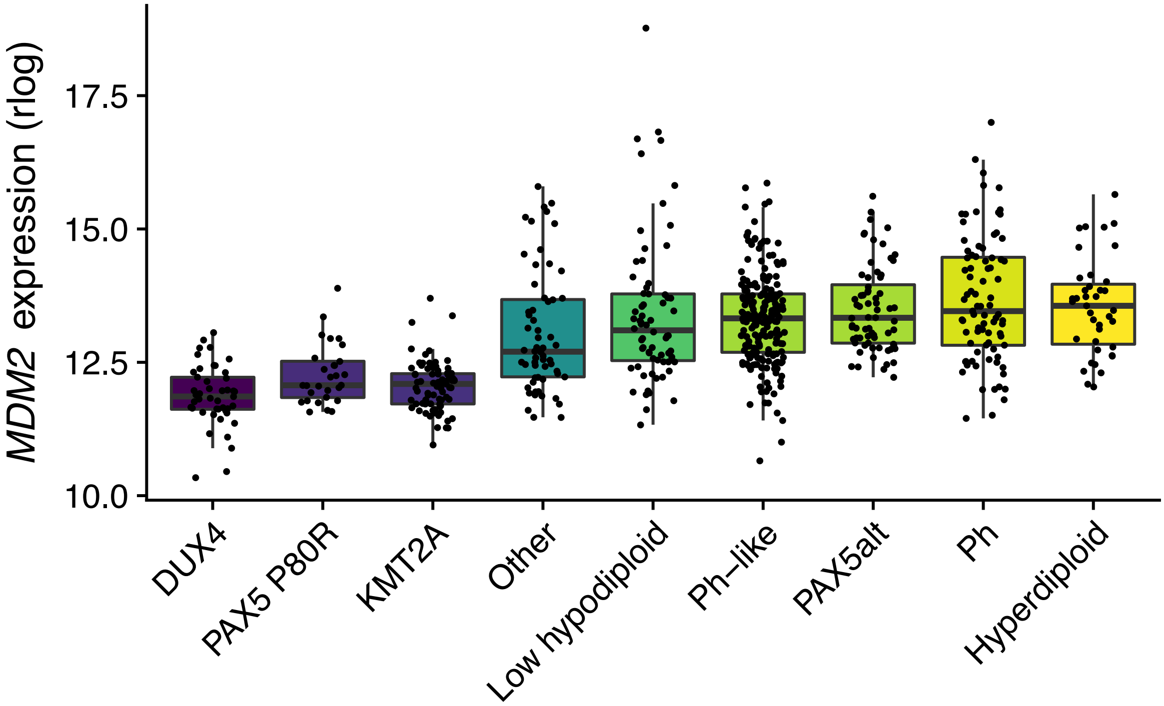
Supplementary Figure S4.

The expression of *MDM2* in the A) E-MTAB-5035 cohort and in the B) B ALL 1988 cohort. Group differences tested with Mann-Whitney U test.

A.



B.

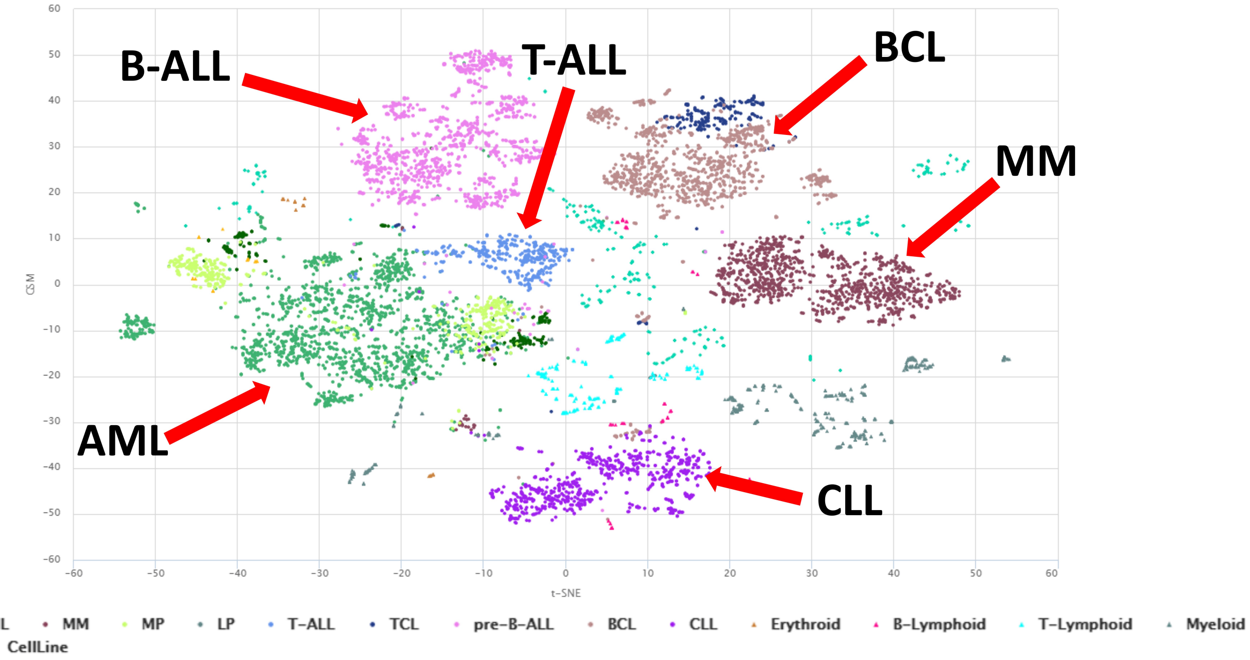


Supplementary Figure S5.

A) An overview of all HEMAP samples. B) *MDM2* e-staining of HEMAP samples. *MDM2* is highly expressed in a majority of B-ALL samples. B-ALL, pre B-cell acute lymphoblastic leukemia; T-ALL, T-cell acute lymphoblastic leukemia; BCL, B-cell lymphoma; MM, multiple myeloma; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia.

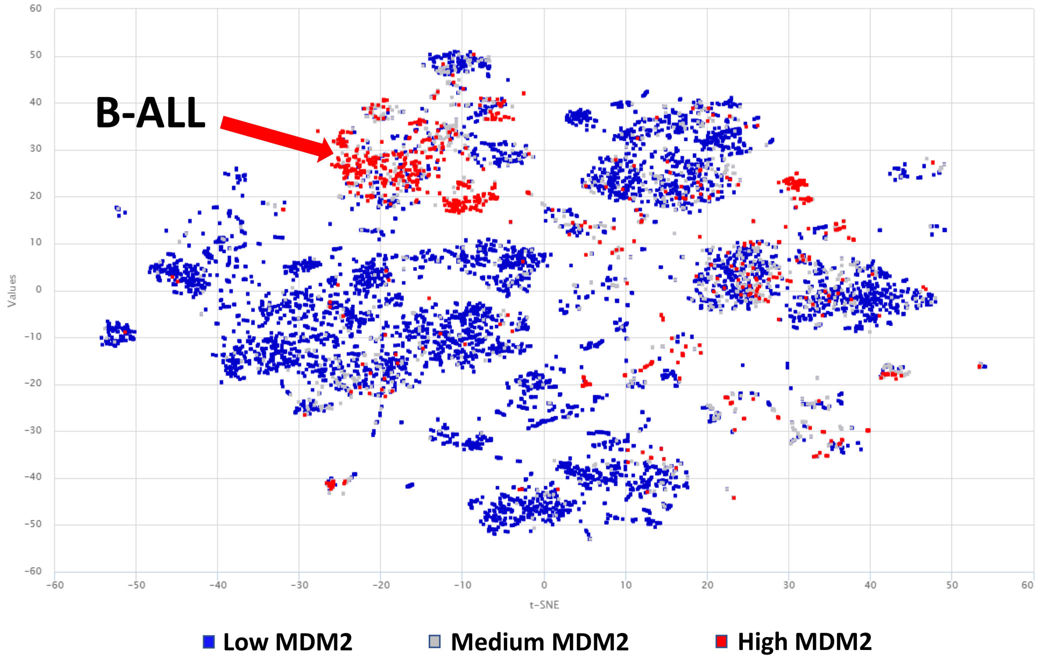
A.

HEMAP samples



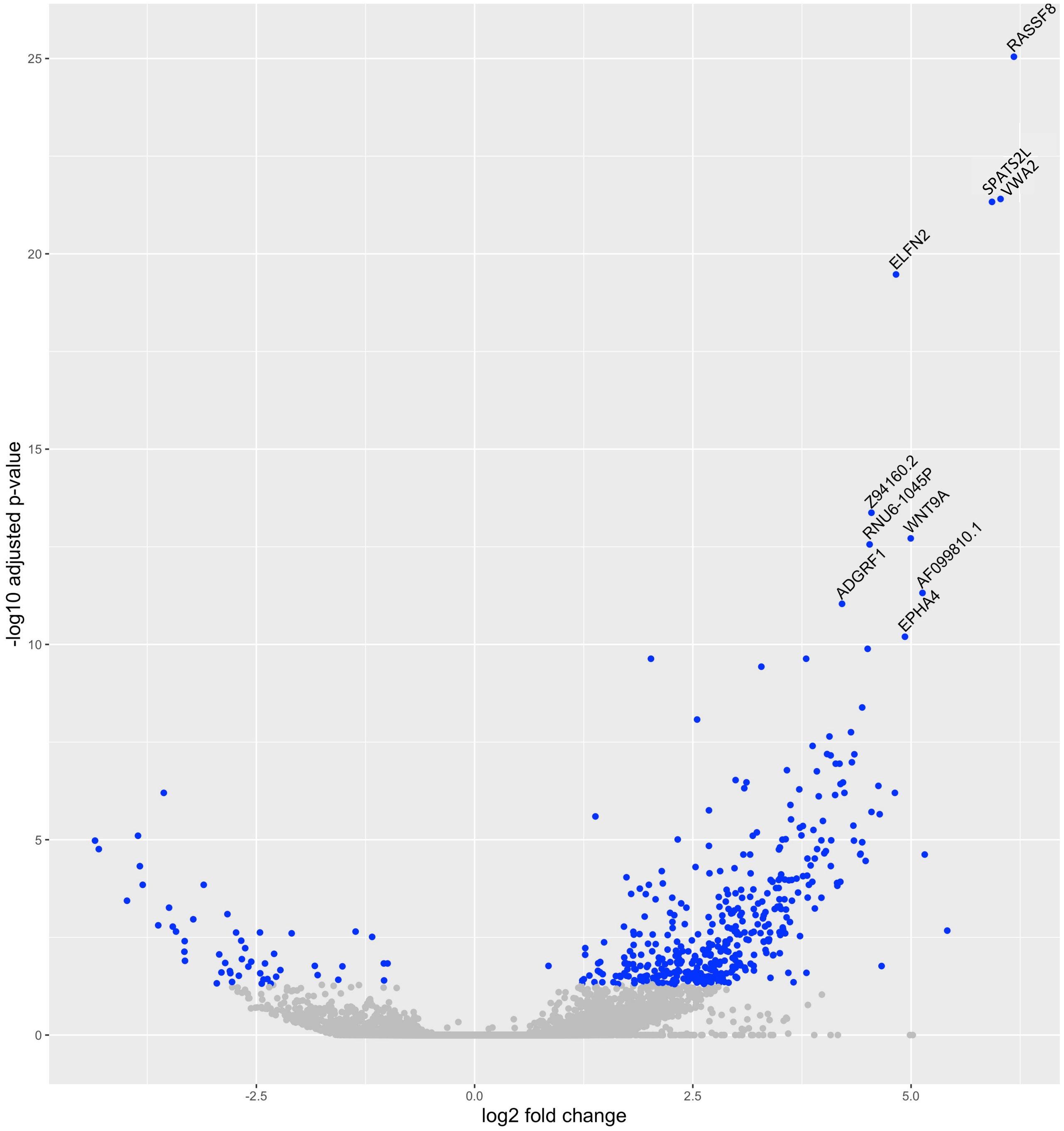
B.

MDM2 e-staining HEMAP samples

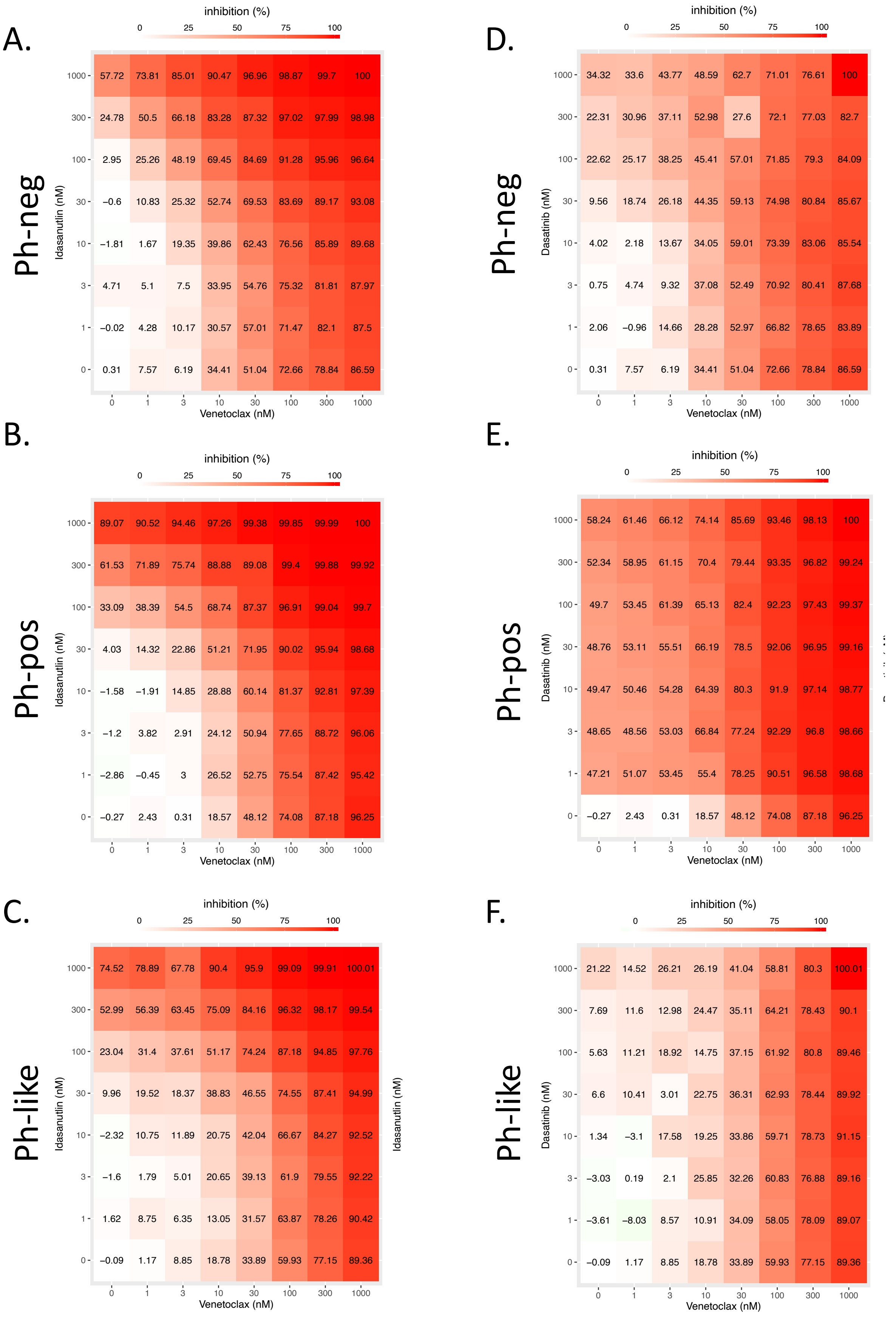


Supplementary Figure S6.

Volcano plot of differentially expressed (DE) genes (Philadelphia positive versus negative) in whole transcriptome sequencing. P-values adjusted with Benjamini-Hochberg method, and significantly ($q<0.05$) DE genes ($n=242$) are annotated in blue. DESeq2 used for DE analysis with log2FC threshold 0.32. Ph-like patients were kept in the analysis, but the comparison was made between Philadelphia-positive and true negative patients.



Supplementary Figure S7.
Combination score matrix of venetoclax – idasanutlin drug combination in A) Kasumi-2, B) NALM-21, and C) MHH-CALL-4 cell lines, and combination score matrix of venetoclax – dasatinib drug combination in D) Kasumi-2, E) NALM-21, and F) MHH-CALL-4 cell lines.



A.

	0	1	3	10	30	100	300	1000
1000	57.72	73.81	85.01	90.47	96.96	98.87	99.7	100
300	24.78	50.5	66.18	83.28	87.32	97.02	97.99	98.98
100	2.95	25.26	48.19	69.45	84.69	91.28	95.96	96.64
30	−0.6	10.83	25.32	52.74	69.53	83.69	89.17	93.08
10	−1.81	1.67	19.35	39.86	62.43	76.56	85.89	89.68
3	4.71	5.1	7.5	33.95	54.76	75.32	81.81	87.97
1	−0.02	4.28	10.17	30.57	57.01	71.47	82.1	87.5
0	0.31	7.57	6.19	34.41	51.04	72.66	78.84	86.59

D.

	0	1	3	10	30	100	300	1000
1000	34.32	33.6	43.77	48.59	62.7	71.01	76.61	100
300	22.31	30.96	37.11	52.98	27.6	72.1	77.03	82.7
100	22.62	25.17	38.25	45.41	57.01	71.85	79.3	84.09
30	9.56	18.74	26.18	44.35	59.13	74.98	80.84	85.67
10	4.02	2.18	13.67	34.05	59.01	73.39	83.06	85.54
3	0.75	4.74	9.32	37.08	52.49	70.92	80.41	87.68
1	2.06	−0.96	14.66	28.28	52.97	66.82	78.65	83.89
0	0.31	7.57	6.19	34.41	51.04	72.66	78.84	86.59

B.

	0	1	3	10	30	100	300	1000
1000	89.07	90.52	94.46	97.26	99.38	99.85	99.99	100
300	61.53	71.89	75.74	88.88	89.08	99.4	99.88	99.92
100	33.09	38.39	54.5	68.74	87.37	96.91	99.04	99.7
30	4.03	14.32	22.86	51.21	71.95	90.02	95.94	98.68
10	−1.58	−1.91	14.85	28.88	60.14	81.37	92.81	97.39
3	−1.2	3.82	2.91	24.12	50.94	77.65	88.72	96.06
1	−2.86	−0.45	3	26.52	52.75	75.54	87.42	95.42
0	−0.27	2.43	0.31	18.57	48.12	74.08	87.18	96.25

E.

	0	1	3	10	30	100	300	1000
1000	58.24	61.46	66.12	74.14	85.69	93.46	98.13	100
300	52.34	58.95	61.15	70.4	79.44	93.35	96.82	99.24
100	49.7	53.45	61.39	65.13	82.4	92.23	97.43	99.37
30	48.76	53.11	55.51	66.19	78.5	92.06	96.95	99.16
10	49.47	50.46	54.28	64.39	80.3	91.9	97.14	98.77
3	48.65	48.56	53.03	66.84	77.24	92.29	96.8	98.66
1	47.21	51.07	53.45	55.4	78.25	90.51	96.58	98.68
0	−0.27	2.43	0.31	18.57	48.12	74.08	87.18	96.25

C.

	0	1	3	10	30	100	300	1000
1000	74.52	78.89	67.78	90.4	95.9	99.09	99.91	100.01
300	52.99	56.39	63.45	75.09	84.16	96.32	98.17	99.54
100	23.04	31.4	37.61	51.17	74.24	87.18	94.85	97.76
30	9.96	19.52	18.37	38.83	46.55	74.55	87.41	94.99
10	−2.32	10.75	11.89	20.75	42.04	66.67	84.27	92.52
3	−1.6	1.79	5.01	20.65	39.13	61.9	79.55	92.22
1	1.62	8.75	6.35	13.05	31.57	63.87	78.26	90.42
0	−0.09	1.17	8.85	18.78	33.89	59.93	77.15	89.36

F.

	0	1	3	10	30	100	300	1000
1000	21.22	14.52	26.21	26.19	41.04	58.81	80.3	100.01
300	7.69	11.6	12.98	24.47	35.11	64.21	78.43	90.1
100	5.63	11.21	18.92	14.75	37.15	61.92	80.8	89.46
30	6.6	10.41	3.01	22.75	36.31	62.93	78.44	89.92
10	1.34	−3.1	17.58	19.25	33.86	59.71	78.73	91.15
3	−3.03	0.19	2.1	25.85	32.26	60.83	76.88	89.16
1	−3.61	−8.03	8.57	10.91	34.09	58.05	78.09	89.07
0	−0.09	1.17	8.85	18.78	33.89	59.93	77.15	89.36