Supplementary Information

Supplementary Materials & Methods

Patient samples

All patients were enrolled in multicenter pediatric ALL trials (AIEOP-BFM ALL, CoALL, ALL-SCT BFM, ALL-REZ BFM 2002) and the ALL-REZ BFM registry. The treatment studies, the registry and the concomitant research were all approved by the respective institutional review boards and informed consent was obtained from all patients and/or their legal guardians. Patients with frank hematologic post-allo-SCT relapse were identified in the database of the ALL-SCT-BFM 2003 trial, after treatment of primary disease or first relapse in either the ALL-BFM, CoALL, or ALL-REZ-BFM trial, respectively. Bone marrow specimens representing pre- and post-allo-SCT relapse, as well as leukemia-free patient and donor germline were obtained from the ALL-REZ-BFM biobank, with missing samples provided by the frontline ALL trials and/or local treatment centers.

Primer sequences for Sanger sequencing

TP53-f1 TCCCCTGCCCTCAACAAG, TP53-r1 GCACCACCACACTATGTCG, TP53-f2 TGTGTTATCTCCTAGGTTGGC, TP53-r2 AGTGTGCAGGGTGGCAAG, NT5C2-f1 AATGTCAACCTCCTGGAGTG, NT5C2-r1 CTGTAAAATGAAGTCCCACTTC, NT5C2-f2 TGATTTTCTGTCTGGACGGAG, NT5C2-r2 GAGGCTAAAGGTTCTCTGTAC, NOTCH1-f TGCCTCACCATGTCCTGAC, NOTCH1-r CACACTTACTCTGCACGGC

Amplicon sequencing

For deep sequencing of *NT5C2* and *TP53* mutations, Illumina TruSeq Adapters were used with the following product-specific primers: NT5C2 K26E forward: AATGTCAACCTCCTGGAGTG, reverse: CTGTAAAATGAAGTCCCACTTC; NT5C2 D113N forward: TGATTTTCTGTCTGGACGGAG, reverse: GAGGCTAAAGGTTCTCTGTAC; NT5C2 R367Q forward: TCTGATACGATCTGTGACCTG, reverse: ACTCTTGTCAGTCCAGACATG; TP53 V173M/R181H/R196* forward: ATCTACAAGCAGTCACAGCAC, reverse: GCACCACCACACTATGTCG; TP53 G245S/R248P/R248Q forward: TGTGTTATCTCCTAGGTTGGC, reverse: AGTGTGCAGGGTGGCAAG. In a total volume of 25 µl, 20 ng DNA were amplified with 0.5 µl 10 µM each forward and reverse primers, 0.5 µl 10 mM each dNTPs (QIAGEN, Hilden, Germany), 2.5 µl 10x PCR Buffer (QIAGEN), and 0.1 µl Taq Polymerase (QIAGEN). PCR conditions were as follows: 2 min initial denaturation at 94°C, ten cycles of 94°C, 65°C-1°C per cycle, 72°C, 25 cycles of 94°C, 55°C, and 72°C. The PCR products were separated on an agarose gel, cut from it, and clean up was performed

with the QIAquick Gel Extraction Kit (QIAGEN). The extracted DNA was measured on a Bioanalyzer 2100 (Agilent, Santa Clara, USA) and brought to a concentration of 2 nM prior to sequencing. Sequencing was carried out on an Illumina HiSeq 2500.

Deep sequencing analysis

After extraction of the sequencing reads (see "data processing") and alignment to the genomic target regions of the studied TP53 and NT5C2 SNVs, we assessed the background error rate and thus defined the individual sensitivity for SNV detection in each sequenced sample. To achieve this goal, we calculated the mean and standard deviation of the specific variant allele frequency at the five nearest genomic loci with the identified reference base as in the genomic position of the SNV under study. Variant allele frequencies at the locus of analysis were considered "truly positive" if exceeding the mean plus three standard deviations (i.e. representing the upper limit of the 95% confidence interval) of the background error rate as defined above. Values below this threshold were considered "negative" and are reported as <0.2% or <0.1% in the figures and the respective Supplementary Tables depending on the sequencing depth reached.

Computation of oncogenomes

Oncogenomes were computed from the variant calls combining MuTect[1] and VarScan2[2] tools. SNVs were kept for further analysis only if they met the following criteria: region covered at least 10x in all samples of a patient set; had a general minor allele frequency (GMAF) of less than 1%; and were mapped to canonical transcripts. The datasets were compiled and analyzed using R. Genes associated with DNA repair, DNA Polymerase function and Fanconi anemia were extracted from the gene families 'Fanconi anemia complementation groups (FANC)' and 'DNA polymerases (POL)' from HGNC database [HGNC].

Supplementary Tables

Supplementary Table 1: Detailed patient characteristics

Patient ID	107	202	316	318	337	514	590	660	685	735
Sex	f	f	m	m	m	m	f	m	f	m
Age at first diagnosis of disease (in years)	0.3	5.7	1.0	5.3	2.8	2.5	7.3	5.1	5.7	10.2
Immunophenotype at first disease	common ALL	common ALL	common ALL	common ALL	common ALL	common ALL	common ALL	cortical T	pro-T	pB-ALL
CNS disease / status at first disease	TLP+	CNS negative	TLP+	CNS negative	CNS negative	CNS positive	CNS negative	TLP+	CNS positive	CNS negative
treatment protocol at first disease	Interfant 06	CoALL	ALL-BFM	ALL-BFM	CoALL	CoALL	ALL-BFM	ALL-BFM	ALL-BFM	CoALL
risk category at first disease	HR	LR intensified	HR	HR	HR	HR-S	MR	HR	HR	HR
Age at relapse (in years)	no relapse prior to SCT	7.5	3.3	7.7	5.9	5.0	10.7	6.4	6.8	12.3
Type of relapse (BM, CNS, other extramedullary)	no relapse prior to SCT	BM	BM	KM	BM	BM	BM	BM	BM	BM
Treatment protocol at relapse	no relapse prior to SCT	ALL-REZ BFM 2002	ALL-REZ BFM 2002	ALL-REZ BFM 2002	ALL-REZ BFM 2002	ALL-REZ BFM 2002	ALL-REZ BFM 2002	ALL-REZ BFM 2002	ALL-REZ BFM 2002	ALL-REZ BFM 2002
Immunophenotype at relapse	no relapse prior to SCT	common ALL	common ALL	common ALL	common ALL	pre-B	common	mature T	mature T	pB-ALL
Age at SCT (in years)	0.8	8.1	3.9	8.0	6.3	5.5	11.2	6.7	7.0	12.8
Study for transplant	ALL-SCT	ALL-SCT	ALL-SCT	ALL-SCT	TCRalpha/beta-Haplo2010	ALL-SCT	ALL-SCT	ALL-SCT	ALL-SCT	ALL-SCT
MRD before SCT	$<1x10^{-4}$	$<1x10^{-3}$-$1x10^{-4}$	$1x10^{-6}$	$1x10^{-4}$	$<1x10^{-4}$	$<1x10^{-4}$	$<1x10^{-5}$	$<1x10^{-4}$	$1x10^{-3}$-$1x10^{-4}$	$<1x10^{-4}$
Type of SCT performed (MD, MSD, haploidentical)	MUD, 9/10 HLA-ident	MD	MSD	MD	haplo (mother)	MD	MD	MSD	MD	MD
Type of conditioning regimen	Flu/Treo/Thio/ ATG	VP16, ATG, TBI	TBI/VP 16	Flu/Thio/Treo/ATG	Flu/Thio/Mel/ATG	Bu, Cy, VP16, ATG	TBI, VP16/ATG	TBI, VP16	TBI, VP 16, ATG	TBI, VP16, ATG
Time to relapse (in years) after SCT	0.3	0.7	0.4	1.7	1.2	0.3	1.2	0.6	0.2	0.2
Type of relapse (BM, CNS, other) after SCT	BM	BM	BM	BM	BM	BM	BM	BM	BM	BM
Immunophenotype at relapse after SCT	common ALL	common ALL	unknown	common ALL	common ALL	pre-B	not done	T-ALL	n/a	B-lineage ALL
Survival status	alive	dead	dead	alive	dead	dead	dead	dead	dead	dead

M, male; f, female; BM, bone marrow; CNS, central nervous system; TLP +, traumatic lumbar puncture; n/a, not available; SCT, stem cell transplant; MRD, minimal residual disease

Supplementary Table 2: Blast counts and remission status of all analyzed samples.

Patient ID	INIT (blasts in %)	REMI (MRD)	RLPS (blasts in %)	TREMI (MRD / chimerism)		TRLPS (blasts in %)
107	81%	neg	no relapse	neg	full donor	99%
202	n/a	neg	98%	neg	full donor	59%
316	95%	neg	91%	neg	full donor	78%
318	n/a	neg	95%	neg	full donor	96%
337	97%	neg	90%	neg	full donor	70%
514	95%	neg	86%	neg	full donor	81%
590	84%	neg	97%	neg	full donor	85%
660	92%	neg	98%	neg	full donor	80%
685	93%	neg	97%	neg	full donor	94%
735	n/a	neg	89%	neg	full donor	35%

n/a, sample not available; MRD, minimal residual disease, neg, MRD $<1x10^{-3}$

Supplementary Table 3: Whole exome sequencing statistics

	INIT		RLPS		REMI		TREMI		TRLPS	
	read count	% covered 30x	read count	% covered 30x	read count	% covered 30x	read count	% covered 30x	read count	% covered 30x
107	139,603,701	94.9	n/a	n/a	127,279,651	93.0	149,352,096	95.7	115,455,476	84.4
202	n/a	n/a	172,195,218	94.6	139,618,835	93.1	52,157,900	62.0	139,562,229	94.6
316	135,391,847	95.3	65,600,377	69.0	150,844,390	95.7	131,771,856	95.4	133,598,060	88.1
318	152,623,113	96.8	127,394,801	93.7	94,577,465	89.8	137,865,191	96.1	139,201,091	93.4
337	98,063,793	88.2	102,757,062	89.1	97,302,749	87.7	82,025,664	82.7	88,562,638	90.8
514	208,040,678	97.0	128,929,690	93.2	120,757,360	93.2	118,582,817	93.2	106,380,210	90.0
590	266,588,232	98.1	117,749,322	92.2	112,131,000	91.2	81,311,366	82.1	127,828,704	92.4
660	248,115,931	98.3	144,639,413	84.5	219,746,232	88.4	116,411,930	89.2	147,344,415	89.1
685	122,669,504	92.0	248,667,768	93.2	225,072,750	88.4	272,233,107	95.1	251,048,560	96.5
735	n/a	n/a	138,821,273	84.9	127,827,416	92.9	120,773,821	88.9	250,460,753	92.9

n/a, sample not available

Supplementary Table 4: Full list of all identified genes carrying SNVs.

See separate file. Gene symbols are indicated.

Supplementary Table 5: SNVs in DNA repair pathways in the large oncogenomes

patient	oncogenome	chr	gen.pos.	ref	alt	gene	AA alt
590	OG1	13	32906593	C	A	BRCA2	S326R
590	OG1	5	74877232	G	A	POLK	R298H
590	OG1	9	97912259	G	C	FANCC	P211R
514	OG2	2	86267597	C	T	POLR1A	G1220R
514	OG2	10	79784800	C	T	POLR3A	R140Q
514	OG2	2	86254613	C	T	POLR1A	C1699Y
514	OG2	11	67120788	A	G	POLD4	L28P
514	OG2	19	50902310	G	A	POLD1	G69R
316	OG2	4	120981424	T	C	MAD2L1	Y156C
514	OG3	16	22320292	G	A	POLR3E	R71H
514	OG3	16	22325015	G	A	POLR3E	A147T
514	OG3	17	7400822	C	T	POLR2A	P323S
514	OG3	17	7401078	G	A	POLR2A	R364H
735	OG3	3	121206244	C	T	POLQ	R1981Q
735	OG3	17	59821817	C	T	BRIP1	A745T
735	OG3	12	106889850	G	A	POLR3B	V911I
735	OG3	14	45645568	G	A	FANCM	R1204H
735	OG3	19	50918754	G	A	POLD1	R875H
735	OG3	22	41940089	T	C	POLR3H	E6G

chr indicates chromosome; gen.pos., genomic position (hg19); ref/alt, reference/alternative, AA alt, alteration in the amino acid sequence (positions are always stated for the longest transcript variant)

Supplementary Table 6: Recurrent SNVs in OG2 in detail

gene	107	202	316	318	337	514	590	660	685	735
ADAMTS15	0	1	1	0	0	0	0	0	0	0
ADRBK2	0	0	0	0	0	1	0	0	0	1
ALMS1	0	0	0	0	0	1	1	0	0	0
ANKRD62	0	1	1	0	0	0	0	0	0	0
BMP5	0	0	0	0	1	0	0	1	0	0
C1QL1	0	0	1	0	0	0	0	0	0	1
CBR1	0	0	1	0	0	0	0	0	0	1
CCDC171	0	0	0	1	0	1	0	0	0	0
CCNYL2	0	0	0	0	0	0	1	0	1	0
CEP128	0	1	0	0	0	1	0	0	0	0
CHD7	0	0	0	1	0	1	0	0	0	0
CLSTN3	0	1	1	0	0	0	0	0	0	0
CPA1	0	0	1	0	0	0	0	0	1	0
CPSF1	0	0	0	1	0	0	0	1	0	0
CSF3R	0	0	0	1	0	1	0	0	0	0
CTBP2	0	0	1	0	0	0	1	0	1	0
DACH2	0	0	0	0	0	1	0	0	0	1
DCHS1	0	0	1	1	0	0	0	0	0	0
DEF8	0	1	0	0	0	1	0	0	0	0
DGKA	0	1	1	0	0	0	0	0	0	0
DPP9	0	0	0	0	0	1	0	0	0	1
EIF4G1	0	0	1	0	0	0	0	0	0	1
ELMSAN1	0	0	1	1	0	0	0	0	0	0
FAM160A2	0	1	0	1	0	0	0	0	0	1
FAT1	0	0	0	0	0	1	0	1	0	0
FBN1	0	0	1	1	0	0	0	0	0	0
FCGBP	0	0	0	0	0	1	0	1	0	0
FICD	0	0	1	1	0	0	0	0	0	0
FMN2	0	0	0	0	0	1	0	0	1	0
FMNL2	0	0	0	1	0	1	0	0	0	0
GPR50	0	0	0	0	1	1	0	0	0	0
HEATR8	0	0	1	0	0	0	0	0	1	0
HS3ST5	0	0	0	1	0	0	0	0	0	1
IGSF22	0	0	0	1	0	1	0	0	0	0
IKZF1	0	0	1	0	0	1	0	1	0	0
INTS1	0	0	1	0	1	0	0	0	0	0
INTS2	0	0	0	1	0	1	0	0	0	0
KIAA0895	0	0	0	1	0	1	0	0	0	0
KIAA1549L	0	0	0	1	0	1	0	0	0	0
KIR2DL4	0	0	1	0	0	0	0	1	0	0
LRRC8E	0	0	1	1	0	0	0	0	0	0
MACF1	0	0	0	1	0	1	0	0	0	0
MAP3K6	0	0	1	0	0	0	0	0	0	1
MIB2	0	0	1	1	0	0	0	0	0	0
MTCH2	0	0	1	1	0	0	0	0	0	0
MUC16	0	0	1	1	0	0	0	0	1	0
MUC6	0	0	0	1	0	0	0	0	0	1
NOTCH1	0	0	1	0	0	0	0	1	1	0
NRAS	0	1	1	1	0	0	0	0	0	0
NT5C2	0	0	0	0	0	1	0	0	1	1

OR1E1	0	0	1	1	0	0	0	0	0	0
OR1S2	0	1	0	0	0	0	0	1	0	0
OR3A1	0	0	1	0	0	0	0	0	0	1
PALD1	0	0	1	1	0	0	0	0	0	0
PDE3A	0	0	1	1	0	0	0	0	0	0
PDIA2	0	0	1	1	0	0	0	0	0	0
PPRC1	0	0	1	1	0	0	0	0	0	0
PTPN14	0	0	0	0	1	1	0	0	0	0
PYGB	0	0	1	1	0	0	0	0	0	0
RBM12B	0	0	0	0	0	1	0	0	0	1
RBMXL3	0	0	0	0	0	1	0	0	0	1
RELN	0	0	0	1	0	1	0	0	0	0
ROBO3	0	0	1	1	0	0	0	0	0	0
RYR2	0	0	0	0	0	1	0	0	1	0
SELENBP1	0	0	1	0	0	0	0	0	1	0
SEMA6D	0	0	0	0	0	1	0	0	1	0
SLC12A9	0	0	1	0	0	0	0	1	0	0
SORBS2	0	0	0	0	0	1	0	0	1	0
SPON2	0	0	0	1	0	1	0	0	0	0
SSC5D	0	0	0	1	0	1	0	0	0	0
STOML3	0	0	0	0	1	1	0	0	0	0
SYTL2	0	0	0	1	0	0	0	0	0	1
TCHH	0	0	0	0	0	1	0	0	0	1
TECTA	0	0	0	0	0	1	1	0	0	0
TOP2A	0	0	0	0	0	1	0	0	1	0
TP53	0	0	0	0	0	1	0	0	0	1
TRBV5-7	0	0	0	0	0	0	0	1	0	1
TTN	0	1	0	0	0	1	0	0	0	0
TUBGCP6	0	0	1	0	0	0	0	0	1	0
TYRO3	0	0	1	0	0	0	1	0	0	0
VPS13B	0	0	0	0	0	1	0	0	0	1
WDR35	0	0	0	0	0	1	0	1	0	0
ZDBF2	0	0	0	0	0	1	0	0	1	0
ZNF460	0	0	0	0	0	1	0	0	0	1
ZNF462	0	0	0	0	1	1	0	0	0	0
ZNF717	0	1	0	0	0	0	0	1	0	0

Gene names and patient IDs are indicated; 0, no SNV in the respective gene; 1, at least one SNV present in the respective gene; only those genes are given in the above list, which are not only affected in the large oncogenomes of patients 316 and 514.

Supplementary Table 7: Recurrent SNVs in OG3 in detail

gene	107	202	316	318	337	514	590	660	685	735
ABCA8	0	0	1	0	0	1	0	0	0	1
ACAP1	0	0	0	1	0	1	0	0	0	1
ADRB1	0	0	0	0	0	0	0	0	1	1
APC2	0	0	0	0	1	0	0	0	0	1
ATP2B2	0	0	0	0	0	1	0	1	0	0
BIRC6	0	1	0	0	0	1	0	0	0	0
BMP5	0	0	0	0	1	0	0	1	0	0
CDC27	1	0	0	0	0	1	0	0	0	0
CLASP1	0	0	0	0	1	1	0	1	0	0
COL6A1	0	0	0	0	0	0	0	1	1	1
CREBBP	0	1	0	0	0	1	0	0	0	0
CSMD3	0	0	0	0	0	1	1	0	0	0
DDC	0	0	0	0	0	1	1	0	0	0
DYNC2H1	0	0	0	0	0	0	0	0	1	1
FAM84A	1	0	0	0	0	0	0	0	0	1
FILIP1	0	0	0	0	1	1	0	0	0	0
FLT4	1	0	0	0	0	1	0	0	0	1
FREM2	0	0	0	0	0	0	0	0	1	1
GPR179	0	1	1	0	0	0	0	0	0	0
GRIN2B	0	0	0	0	0	1	0	0	1	0
HECTD4	0	1	0	1	0	0	0	0	0	0
HMCN1	0	0	0	0	0	1	0	1	0	0
INTS1	0	0	0	0	1	1	0	0	0	0
KDM4E	0	0	1	0	0	0	0	0	0	1
KIAA0368	1	0	0	0	0	1	0	0	0	0
KRAS	1	0	0	0	0	0	0	1	0	0
LAMB4	0	0	0	0	1	0	0	0	0	1
LURAP1L	0	1	0	0	0	1	0	0	0	0
MED12	0	1	0	0	0	1	0	0	0	0
MEGF10	0	1	0	0	0	0	0	0	0	1
MYOCD	0	1	0	0	0	1	0	0	0	0
MYOM2	0	0	1	0	0	1	0	0	0	0
NMRAL1	0	0	0	0	1	0	0	0	0	1
NOTCH1	0	0	0	0	0	0	0	1	1	0
NR0B1	0	0	0	0	0	0	0	0	1	1
NRAS	0	1	1	1	0	0	0	0	0	0
NUP153	0	0	0	0	0	1	0	0	1	0
OBSCN	0	0	0	0	0	1	0	0	1	1
PAK7	0	0	0	1	0	0	0	0	0	1
PI4KA	0	1	0	0	0	1	0	0	0	0
PLCB1	0	0	0	0	1	0	0	1	0	0
PLXNA4	0	1	0	0	0	1	0	0	0	0
RADIL	0	0	0	0	0	1	0	0	1	0
RBM47	0	0	0	0	0	0	1	0	0	1
RHPN2	1	0	0	0	0	0	0	0	0	1
SH3BP4	0	0	0	0	1	0	0	0	0	1
SLCO3A1	0	0	0	0	0	1	1	0	0	0
SORBS2	0	0	0	0	0	0	0	0	1	1
SPTBN5	0	1	0	0	0	0	0	0	0	1
TBC1D29	0	0	1	0	0	0	0	0	0	1
TOP2A	0	0	0	0	0	1	0	0	1	0
TP53	0	0	0	0	0	1	0	1	1	0
TRAM1L1	0	0	0	0	0	1	0	0	1	0
TTN	0	1	0	0	0	0	0	1	1	1
URB1	0	0	0	0	0	1	1	0	0	0
VWA5B1	0	1	0	0	0	0	0	0	0	1
WWC3	0	0	1	0	0	1	0	0	0	1
ZDBF2	0	1	0	0	1	0	0	0	1	0

Gene names and patient IDs are indicated; 0, no SNV in the respective gene; 1, at least one SNV present in the respective gene; only those genes are given in the above list, which are not only affected in the large oncogenomes of patients 514 and 735.

Supplementary Table 8: Core mutation sets across those seven patients with all three oncogenomes available

UPN	gene name	found in	cancer gene
316	ATP13A1	OG1+OG2+OG3	No
316	BCL6	OG1+OG2+OG3	Yes
316	CUX1	OG1+OG2+OG3	Yes
316	NRAS	OG1+OG2+OG3	Yes
318	DST	OG1+OG2+OG3	No
318	ERG	OG1+OG2+OG3	Yes
318	FAM214A	OG1+OG2+OG3	No
318	KCNK2	OG1+OG2+OG3	No
318	OR1E1	OG1+OG2+OG3	No
318	TMTC1	OG1+OG2+OG3	No
337	INTS1	OG1+OG2+OG3	No
337	LAMB4	OG1+OG2+OG3	No
337	MDGA2	OG1+OG2+OG3	No
337	MET	OG1+OG2+OG3	Yes
337	TRAF3IP2	OG1+OG2+OG3	No
514	EEF2	OG1+OG2+OG3	No
514	UNK	OG1+OG2+OG3	No
590	ADARB2	OG1+OG2+OG3	No
590	ALMS1	OG1+OG2+OG3	No
590	CACNA1I	OG1+OG2+OG3	No
590	CAPN13	OG1+OG2+OG3	No
590	CCDC82	OG1+OG2+OG3	No
590	COL10A1	OG1+OG2+OG3	No
590	CSMD3	OG1+OG2+OG3	Yes
590	DDC	OG1+OG2+OG3	No
590	GPIHBP1	OG1+OG2+OG3	No
590	HILPDA	OG1+OG2+OG3	No
590	OR2A2	OG1+OG2+OG3	No
590	OR5K4	OG1+OG2+OG3	No
590	PCDH10	OG1+OG2+OG3	No
590	PGBD2	OG1+OG2+OG3	No
590	PLEKHA7	OG1+OG2+OG3	No

590	RB1	OG1+OG2+OG3	Yes
590	TMX3	OG1+OG2+OG3	No
590	URB1	OG1+OG2+OG3	No
660	BMP5	OG1+OG2+OG3	Yes
660	EWSR1	OG1+OG2+OG3	Yes
660	FBXW7	OG1+OG2+OG3	Yes
660	KRAS	OG1+OG2+OG3	Yes
660	NOTCH1	OG1+OG2+OG3	Yes
660	SLC12A9	OG1+OG2+OG3	No
685	NOTCH1	OG1+OG2+OG3	Yes
685	SAP130	OG1+OG2+OG3	No
685	SERPINB9	OG1+OG2+OG3	No
685	SORBS2	OG1+OG2+OG3	No
685	SPTB	OG1+OG2+OG3	No
685	TUBGCP6	OG1+OG2+OG3	No
685	WHSC1	OG1+OG2+OG3	Yes
685	ZDBF2	OG1+OG2+OG3	No
685	ZNF600	OG1+OG2+OG3	No

UPN, unique patient identifier; oncogenomes, in which the respective mutations were found, are indicated. Cancer genes are highlighted in yellow.

Supplementary Table 9: TCR/IgH markers

Patient ID	Number of TCR/IG markers in total	Number of **stable** markers before/afteSCT	Number of **gained** markers after SCT	Number of **lost** markers after SCT
107	no data			
202	no data			
316	3	3		
318	3	2	1	
337	no data			
514	4	2	2	
590	2	2		
660	1	1		
685	5	4	1	
735	3	2		1

Patient IDs are indicated. Also indicated are numbers of stable/gained/lost markers in the post alloSCT relapse.

Supplementary Table 10: NT5C2 mutations

Gene	AA change	NM_012229	exon	prediction	OG1/WES	OG1/AS	OG2/WES	OG2/AS	OG3/WES	OG3/AS
NT5C2	D113N	c.C337T	4	deleterious	not detected	n.d.	25.61%	n.d.	not detected	0.28%
NT5C2	K26E	c.T76C	1	tolerated	not detected	< 0.2%	37.47%	n.d.	not detected	< 0.2%
NT5C2	R367Q	c.C1100T	13	deleterious	not detected	< 0.1%	6.40%	n.d.	not detected	< 0.1%
NT5C2	R367Q	c.C1100T	13	deleterious	n/a	n/a	9.42%	n.d.	not detected	< 0.2%

chr indicates chromosome; AA, amino acid; WES, whole exome sequencing; AS, amplicon sequencing; prediction of functional consequences was performed using PolyPhen2[3] and SIFT[4]; n.d., not done; INIT, initial leukemia; RLPS, first relapse; REMI, remission prior to SCT; TREMI, remission post SCT; TRLPS, post-allo-SCT relapse; BAFs of the respective SNV are indicated in percentages; samples, in which the SNVs were detected by WES are highlighted in blue; those, in which neither WES nor AS detected an SNV in green and those, in which only AS detected the SNV in yellow

Supplementary Table 11: TP53 mutations

Patient	Gene	AA change	gen.pos.	ref	alt	prediction	OG1/WES	OG1/AS	OG2/WES	OG2/AS	OG3/WES	OG3/AS
514	**TP53**	R248Q	chr17:7577538	C	T	deleterious	not detected	n.d.	40.48%	n.d.	not detected	0.79%
514	**TP53**	R181H	chr17:7578388	C	T	deleterious	not detected	n.d.	not detected	0.10%	48.72%	n.d.
590	**TP53**	V173M	chr17:7578413	C	T	deleterious	64.00%	n.d.	88.00%	n.d.	46.00%	n.d.
660	**TP53**	R248P	chr17:7577538	C	G	deleterious	not detected	< 0.1%	0.00%	0.09%	18.33%	n.d.
685	**TP53**	G245S	chr17:7577548	C	T	deleterious	not detected	< 0.1%	not detected	< 0.1%	46.88%	n.d.
685	**TP53**	R248Q	chr17:7577538	C	T	deleterious	not detected	< 0.1%	not detected	< 0.1%	6.67%	n.d.
685	**TP53**	R196*	chr17:7578263	G	A	premature st	not detected	< 0.2%	not detected	< 0.1%	22.22%	n.d.
735	**TP53**	R248Q	chr17:7577538	C	T	deleterious	n/a	n/a	6.76%	n.d.	not detected	< 0.1%

chr indicates chromosome; gen.pos., genomic position (hg19); ref/alt, reference/alternative; AA, amino acid; AA, amino acid; WES, whole exome sequencing; AS, amplicon sequencing; n.d., not done; prediction of functional consequences was performed using PolyPhen2[3] and SIFT[4]; BAFs of the respective SNV are indicated in percentages; samples, in which the SNVs were detected by WES are highlighted in blue; those, in which neither WES nor AS detected an SNV in green and those, in which only AS detected the SNV in yellow

Supplementary Table 12: Core mutation sets across all oncogenomes

UPN	gene name	found in	cancer gene
107	OR5F1	OG1+OG2	no
107	SLITRK3	OG1+OG2	no
202	AGPAT1	OG2+OG3	no
202	C7	OG2+OG3	no
202	CEP128	OG2+OG3	no
202	CKMT1B	OG2+OG3	no
202	CLSTN3	OG2+OG3	no
202	CREBBP	OG2+OG3	yes
202	DGKA	OG2+OG3	no
202	DHRS7C	OG2+OG3	no
202	LURAP1L	OG2+OG3	no

202	MEGF10	OG2+OG3	no
202	MXRA5	OG2+OG3	no
202	NRAS	OG2+OG3	yes
202	OCLN	OG2+OG3	no
202	OMG	OG2+OG3	no
202	PCDH19	OG2+OG3	no
202	PDZD3	OG2+OG3	no
202	PLAC1	OG2+OG3	no
202	SCN9A	OG2+OG3	no
202	SHC3	OG2+OG3	no
202	SLC35G2	OG2+OG3	no
202	TAX1BP1	OG2+OG3	no
202	TTN	OG2+OG3	no
202	VWA5B1	OG2+OG3	no
316	ATP13A1	OG1+OG2+OG3	no
316	BCL6	OG1+OG2+OG3	yes
316	CUX1	OG1+OG2+OG3	yes
316	NRAS	OG1+OG2+OG3	yes
318	DST	OG1+OG2+OG3	no
318	ERG	OG1+OG2+OG3	yes
318	FAM214A	OG1+OG2+OG3	no
318	KCNK2	OG1+OG2+OG3	no
318	OR1E1	OG1+OG2+OG3	no
318	TMTC1	OG1+OG2+OG3	no
337	INTS1	OG1+OG2+OG3	no
337	LAMB4	OG1+OG2+OG3	no
337	MDGA2	OG1+OG2+OG3	no
337	MET	OG1+OG2+OG3	yes
337	TRAF3IP2	OG1+OG2+OG3	no
514	EEF2	OG1+OG2+OG3	no
514	UNK	OG1+OG2+OG3	no
590	ADARB2	OG1+OG2+OG3	no
590	ALMS1	OG1+OG2+OG3	no
590	CACNA1I	OG1+OG2+OG3	no
590	CAPN13	OG1+OG2+OG3	no
590	CCDC82	OG1+OG2+OG3	no
590	COL10A1	OG1+OG2+OG3	no
590	CSMD3	OG1+OG2+OG3	yes
590	DDC	OG1+OG2+OG3	no
590	GPIHBP1	OG1+OG2+OG3	no
590	HILPDA	OG1+OG2+OG3	no
590	OR2A2	OG1+OG2+OG3	no
590	OR5K4	OG1+OG2+OG3	no
590	PCDH10	OG1+OG2+OG3	no

590	PGBD2	OG1+OG2+OG3	no
590	PLEKHA7	OG1+OG2+OG3	no
590	RB1	OG1+OG2+OG3	yes
590	TMX3	OG1+OG2+OG3	no
590	URB1	OG1+OG2+OG3	no
660	BMP5	OG1+OG2+OG3	yes
660	EWSR1	OG1+OG2+OG3	yes
660	FBXW7	OG1+OG2+OG3	yes
660	KRAS	OG1+OG2+OG3	yes
660	NOTCH1	OG1+OG2+OG3	yes
660	SLC12A9	OG1+OG2+OG3	no
685	NOTCH1	OG1+OG2+OG3	yes
685	SAP130	OG1+OG2+OG3	no
685	SERPINB9	OG1+OG2+OG3	no
685	SORBS2	OG1+OG2+OG3	no
685	SPTB	OG1+OG2+OG3	no
685	TUBGCP6	OG1+OG2+OG3	no
685	WHSC1	OG1+OG2+OG3	yes
685	ZDBF2	OG1+OG2+OG3	no
685	ZNF600	OG1+OG2+OG3	no
735	CBR1	OG2+OG3	no
735	DACH2	OG2+OG3	no
735	DOT1L	OG2+OG3	no
735	EIF4G1	OG2+OG3	no
735	FGFR4	OG2+OG3	yes
735	FOXI2	OG2+OG3	no
735	HECA	OG2+OG3	no
735	HS3ST5	OG2+OG3	no
735	KCNC2	OG2+OG3	no
735	KCNJ3	OG2+OG3	no
735	MAML1	OG2+OG3	no
735	MASP2	OG2+OG3	no
735	NR1H2	OG2+OG3	no
735	OTP	OG2+OG3	no
735	PKD2L1	OG2+OG3	no
735	RHPN2	OG2+OG3	no
735	SLC11A1	OG2+OG3	no
735	SYTL2	OG2+OG3	no
735	VPS13B	OG2+OG3	no
735	WWC3	OG2+OG3	no

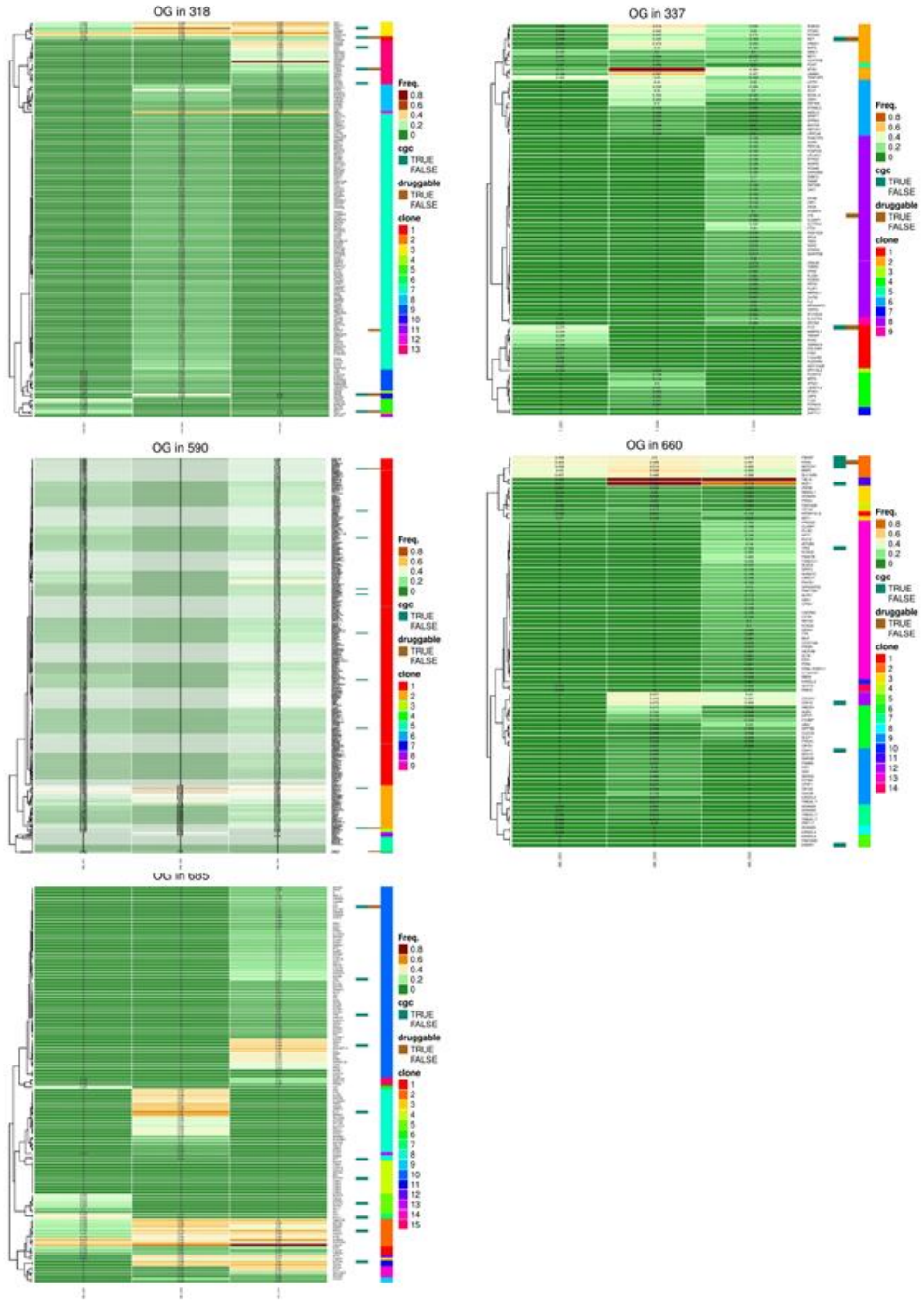
UPN, unique patient identifier; oncogenomes, in which the respective mutations were found, are indicated. Cancer genes are highlighted in yellow.

Supplementary Table 13: Targetable SNVs in detail

gene	chr	gen.pos.	ref	alt	AA pos	ref	alt	patient	drugs	sift	polyphen	consequence
FLT4	5	180046074	C	A	933	G	C	107	axitinib, cabozantinib, nintedanib	deleterious	probably_damaging	missense_variant
FLT4	5	180046074	C	A	933	G	C	107	axitinib, cabozantinib, nintedanib	deleterious	probably_damaging	missense_variant
FLT4	5	180046074	C	A	933	G	C	107	axitinib, cabozantinib, nintedanib	deleterious	probably_damaging	missense_variant
KRAS	12	25398284	C	A	12	G	V	107	trametinib	deleterious	probably_damaging	missense_variant
KRAS	12	25398284	C	A	12	G	V	107	trametinib	deleterious	probably_damaging	missense_variant
KRAS	12	25398284	C	A	12	G	V	107	trametinib	deleterious	probably_damaging	missense_variant
MST1R	3	49940448	C	T	199	V	M	202	cabozantinib, crizotinib	deleterious	probably_damaging	missense_variant
NRAS	1	115258747	C	G	12	G	A	202	trametinib	deleterious	possibly_damaging	missense_variant
NRAS	1	115258744	C	T	13	G	D	316	trametinib	deleterious	benign	missense_variant
NRAS	1	115256528	T	G	61	Q	H	318	trametinib	deleterious	benign	missense_variant
NRAS	1	115258747	C	T	12	G	D	318	trametinib	deleterious	possibly_damaging	missense_variant
LYN	8	56864575	A	G	180	I	V	337	bosutinib, dasatinib	tolerated	benign	missense_variant
LYN	8	56864575	A	G	180	I	V	337	bosutinib, dasatinib	tolerated	benign	missense_variant
MET	7	116339926	C	T	263	T	M	337	cabozantinib, crizotinib	deleterious	probably_damaging	missense_variant
MET	7	116339926	C	T	263	T	M	337	cabozantinib, crizotinib	deleterious	probably_damaging	missense_variant
MET	7	116339926	C	T	263	T	M	337	cabozantinib, crizotinib	deleterious	probably_damaging	missense_variant
MET	7	116339926	C	T	263	T	M	337	cabozantinib, crizotinib	deleterious	probably_damaging	missense_variant
EGFR	7	55273278	G	A	1201	A	T	514	afatinib, cetuximab, erlotinib, gefitinib, lapatinib, panitumumab, vandetanib	tolerated	benign	missense_variant
EGFR	7	55273278	G	A	1201	A	T	514	afatinib, cetuximab, erlotinib, gefitinib, lapatinib, panitumumab, vandetanib	tolerated	benign	missense_variant
EGFR	7	55273278	G	A	1201	A	T	514	afatinib, cetuximab, erlotinib, gefitinib, lapatinib, panitumumab, vandetanib	tolerated	benign	missense_variant
EGFR	7	55273278	G	A	1201	A	T	514	afatinib, cetuximab, erlotinib, gefitinib, lapatinib, panitumumab, vandetanib	tolerated	benign	missense_variant
EGFR	7	55273278	G	A	1201	A	T	514	afatinib, cetuximab, erlotinib, gefitinib, lapatinib, panitumumab, vandetanib	tolerated	benign	missense_variant
EGFR	7	55273278	G	A	1201	A	T	514	afatinib, cetuximab, erlotinib, gefitinib, lapatinib, panitumumab, vandetanib	tolerated	benign	missense_variant
FLT4	5	180046343	G	A	891	R	C	514	axitinib, cabozantinib, nintedanib	deleterious	probably_damaging	missense_variant
FLT4	5	180046343	G	A	891	R	C	514	axitinib, cabozantinib, nintedanib	deleterious	probably_damaging	missense_variant
FLT4	5	180046343	G	A	891	R	C	514	axitinib, cabozantinib, nintedanib	deleterious	probably_damaging	missense_variant
IL1B	2	113591101	G	A	51	R	*	514	canakinumab	NA	NA	stop_gained
KIT	4	55569972	C	T	280	A	V	514	axitinib, cabozantinib, dasatinib, imatinib, nilotinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib	tolerated	benign	missense_variant
KIT	4	55569972	C	T	280	A	V	514	axitinib, cabozantinib, dasatinib, imatinib, nilotinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib	tolerated	benign	missense_variant
PARP1	1	226549680	G	C	985	L	V	514	olaparib	deleterious	probably_damaging	missense_variant
PRKCD	3	53217145	G	A	875	A	T	514	trametinib	tolerated	probably_damaging	missense_variant
PRKCD	3	53217145	G	A	194	A	T	514	trametinib	tolerated	probably_damaging	missense_variant
PRKCE	2	46203640	G	A	194	A	T	514	trametinib	tolerated	probably_damaging	missense_variant
KRAS	12	25398284	C	A	12	G	V	660	trametinib	deleterious	probably_damaging	missense_variant
KRAS	12	25398284	C	A	12	G	V	660	trametinib	deleterious	probably_damaging	missense_variant
KRAS	12	25398284	C	A	12	G	V	660	trametinib	deleterious	probably_damaging	missense_variant
KDR	4	55955112	C	G	1145	G	R	685	axitinib, cabozantinib, nintedanib, pazopanib, ponatinib, ramucirumab, regorafenib, sorafenib, sunitinib, vandetanib	deleterious	benign	missense_variant
DNMT3A	2	25469632	C	T	379	R	H	735	azacitidine, decitabine	deleterious	benign	missense_variant
DNMT3A	2	25469632	C	T	379	R	H	735	azacitidine, decitabine	deleterious	benign	missense_variant
DNMT3A	2	25469632	C	T	379	R	H	735	azacitidine, decitabine	deleterious	benign	missense_variant
DNMT3A	2	25469632	C	T	379	R	H	735	azacitidine, decitabine	deleterious	benign	missense_variant
DNMT3A	2	25469632	C	T	379	R	H	735	azacitidine, decitabine	deleterious	benign	missense_variant
FGFR3	4	1803564	C	T	248	R	C	735	nintedanib, pazopanib, ponatinib	deleterious	probably_damaging	missense_variant
FGFR3	4	1803564	C	T	248	R	C	735	nintedanib, pazopanib, ponatinib	deleterious	probably_damaging	missense_variant
FGFR3	4	1803564	C	T	248	R	C	735	nintedanib, pazopanib, ponatinib	deleterious	probably_damaging	missense_variant
FGFR3	4	1803564	C	T	248	R	C	735	nintedanib, pazopanib, ponatinib	deleterious	probably_damaging	missense_variant
FGFR4	5	176519774	C	T	461	T	M	735	nintedanib, ponatinib	deleterious	probably_damaging	missense_variant
FGFR4	5	176519774	C	T	461	T	M	735	nintedanib, ponatinib	deleterious	probably_damaging	missense_variant
FGFR4	5	176519774	C	T	461	T	M	735	nintedanib, ponatinib	deleterious	probably_damaging	missense_variant
FGFR4	5	176519774	C	T	461	T	M	735	nintedanib, ponatinib	deleterious	probably_damaging	missense_variant
FGR	1	27939583	G	A	478	P	S	735	bosutinib, dasatinib, ibrutinib	deleterious	benign	missense_variant
FGR	1	27939583	G	A	478	P	S	735	bosutinib, dasatinib, ibrutinib	deleterious	benign	missense_variant
FLT4	5	180045859	C	T	971	R	Q	735	axitinib, cabozantinib, nintedanib	tolerated	benign	missense_variant
FLT4	5	180045859	C	T	971	R	Q	735	axitinib, cabozantinib, nintedanib	tolerated	benign	missense_variant
FLT4	5	180045859	C	T	971	R	Q	735	axitinib, cabozantinib, nintedanib	tolerated	benign	missense_variant
GAK	4	843694	C	T	1274	V	M	735	bosutinib, dasatinib, erlotinib, gefitinib	deleterious	probably_damaging	missense_variant
GAK	4	843694	C	T	1274	V	M	735	bosutinib, dasatinib, erlotinib, gefitinib	deleterious	probably_damaging	missense_variant
GAK	4	843694	C	T	1274	V	M	735	bosutinib, dasatinib, erlotinib, gefitinib	deleterious	probably_damaging	missense_variant
IGF1R	15	99456467	G	A	595	R	H	735	ceritinib	tolerated	benign	missense_variant
IGF1R	15	99456467	G	A	595	R	H	735	ceritinib	tolerated	benign	missense_variant
IGF1R	15	99456467	G	A	595	R	H	735	ceritinib	tolerated	benign	missense_variant
MERTK	2	112722824	G	A	272	V	M	735	bosutinib, crizotinib, sunitinib	deleterious	probably_damaging	missense_variant
MERTK	2	112722824	G	A	272	V	M	735	bosutinib, crizotinib, sunitinib	deleterious	probably_damaging	missense_variant
MERTK	2	112722824	G	A	272	V	M	735	bosutinib, crizotinib, sunitinib	deleterious	probably_damaging	missense_variant
NRG3	10	84745302	C	T	702	R	*	735	afatinib, emtansine, lapatinib, pertuzumab, trastuzumab	NA	NA	stop_gained
NRG3	10	84745302	C	T	702	R	*	735	afatinib, emtansine, lapatinib, pertuzumab, trastuzumab	NA	NA	stop_gained
NRG3	10	84745302	C	T	702	R	*	735	afatinib, emtansine, lapatinib, pertuzumab, trastuzumab	NA	NA	stop_gained
NRG3	10	84745302	C	T	702	R	*	735	afatinib, emtansine, lapatinib, pertuzumab, trastuzumab	NA	NA	stop_gained
NRG3	10	84745302	C	T	702	R	*	735	afatinib, emtansine, lapatinib, pertuzumab, trastuzumab	NA	NA	stop_gained
NRG3	10	84745302	C	T	702	R	*	735	afatinib, emtansine, lapatinib, pertuzumab, trastuzumab	NA	NA	stop_gained
NRG3	10	84745302	C	T	702	R	*	735	afatinib, emtansine, lapatinib, pertuzumab, trastuzumab	NA	NA	stop_gained
PDGFRA	4	55138618	C	T	432	T	M	735	axitinib, dasatinib, imatinib, nintedanib, pazopanib, ponatinib, sorafenib	tolerated	benign	missense_variant
PDGFRA	4	55138618	C	T	432	T	M	735	axitinib, dasatinib, imatinib, nintedanib, pazopanib, ponatinib, sorafenib	tolerated	benign	missense_variant
PDGFRA	4	55138618	C	T	432	T	M	735	axitinib, dasatinib, imatinib, nintedanib, pazopanib, ponatinib, sorafenib	tolerated	benign	missense_variant
PHLPP2	16	71686887	C	T	432	T	M	735	Bosutinib, Gefitinib, Idelalisib, Lapatinib, Nintedanib, Pertuzumab, Ponatinib, Siltuximab, Tocilizumab, Trastuzumab	deleterious	probably_damaging	missense_variant
PHLPP2	16	71686887	C	T	875	A	T	735	Bosutinib, Gefitinib, Idelalisib, Lapatinib, Nintedanib, Pertuzumab, Ponatinib, Siltuximab, Tocilizumab, Trastuzumab	deleterious	probably_damaging	missense_variant
PHLPP2	16	71686887	C	T	875	A	T	735	Bosutinib, Gefitinib, Idelalisib, Lapatinib, Nintedanib, Pertuzumab, Ponatinib, Siltuximab, Tocilizumab, Trastuzumab	deleterious	probably_damaging	missense_variant
PRKCE	2	46411917	G	A	162	R	H	735	trametinib	tolerated	benign	missense_variant
SHH	7	155595695	C	T	704	R	Q	735	vismodegib	tolerated	NA	missense_variant
SHH	7	155595695	C	T	430	A	T	735	vismodegib	tolerated	NA	missense_variant
SHH	7	155595695	C	T	430	A	T	735	vismodegib	tolerated	NA	missense_variant
SHH	7	155595695	C	T	430	A	T	735	vismodegib	tolerated	NA	missense_variant

chr indicates chromosome; gen.pos., genomic position (hg19); ref/alt, reference/alternative; AA pos, amino acid position; prediction of functional consequences was performed using PolyPhen2[3] and SIFT[4]; oncogenomes, in which the respective alterations are present, are highlighted in bold text; in case of several ensemble transcripts ID, the respective SNV is mapped to all available transcripts (see e.g. DNM T3A). Please refer to Suppl. Table 9 for the AA positions of the TP53 mutations.

Supplementary Figures



Supplementary Figure 1: Heatmaps of mutational clusters.

Shown are the seven patients for whom information on all three oncogenomes was available. Different mutational patterns can be observed, both within as well as across the patients. Genes are displayed as heatmaps, in which the observed mutational frequencies dictate the position in the cluster tree. Shades from green to yellow to brown refer to the observed mutational frequencies. The colors to the right of the heatmap

indicate the individual mutational clusters (termed “clones” in the figure), which are also displayed in Supplementary Figure 2. Green / brown bars indicate, whether a particular genes is part of the cancer gene census or is a druggable gene, respectively.

Supplementary References

1. Cibulskis K, Lawrence MS, Carter SL, et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. *Nat Biotechnol*. 2013;31(3):213-219.
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4. Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat Protoc*. 2009;4(7):1073-1081.