SUPPLEMENTARY INFORMATION

This file includes:

Supplementary Material and Methods

Supplementary References

Supplementary Figures and Tables

Supplementary Figure 1. Sensitivity to selective MET inhibitors in liver cancer cell lines is related to MET gene amplification.

Supplementary Figure 2. Tivantinib sensitivity is associated with high expression of genes involved in cell cycle regulation.

Supplementary Table 1. Liver cancer cell lines.

Supplementary Table 2. Clinical features of HCC series.

Supplementary Table 3. List of the 188 genes analyzed by quantitative RT-PCR.

Supplementary Table 4. Mutations and copy number variations identified in 13 genes among the 35 liver cancer cell lines (GRCh37).

Supplementary Table 5. Association between tivantinib sensitivity and mutation status of the 12 most frequently mutated genes in HCC tumors and MET across the panel of 35 liver cancer cell lines.

Supplementary Materials and Methods

Mutation and copy-number analyses

The 35 liver cancer cell lines were analyzed by whole-exome sequencing as previously described (1). Briefly, sequence capture, enrichment and elution of genomic DNA were performed by IntegraGen (Evry, France) using Agilent in-solution enrichment with their biotinylated oligonucleotides probes library (v5+UTRs-75Mb, Agilent technologies) according to manufacturer's instruction. Eluted-enriched DNA sample was sequenced on an Illumina HiSeq 2000 sequencer as paired-end 75b reads as previously described. Image analysis and base-calling was performed using Illumina Real Time Analysis (RTA) Pipeline version 1.14 with default parameters. Whole-exome sequencing pre-analysis was based on the Illumina pipeline (CASAVA1.8.2) with the reference genome (hg19). The alignment algorithm used is ELANDv2. Only the positions included in the bait coordinates were conserved. The targeted regions in each sample were sequenced to an average depth of 68X, with ~98.7% of the targeted regions covered $\geq 1\times$, ~93.9% $\geq 10X$ and ~82.8% $\geq 25X$.

The list of variants was defined compared to hg19 reference genome in coding regions plus consensus splicing sites (± 2 bases) as previously described (1). In addition, mutations in *TERT* promoter and exon 1 of *ARID1A* were screened by Sanger sequencing because of low coverage in exome sequencing data, as previously described (2). Functional evidence of predictive drastic consequences for the single nucleotide variants (SNV) were investigated using PolyPhen-2 v2.2.2. Only variants with loss of function including indels (both in-frame and frameshift), nonsense and predicted 'damaging' missense consequences were considered in further analyses. Known polymorphisms referenced in the 1000 Genomes Project with a minor allele frequency over 2% were excluded as well as silent mutations.

Copy number variation (CNV) detection was obtained from exome sequence data and method used a per-gene coverage across the targeted baits. Namely, mapped reads were extracted from the original 35 bam files. The read count profiles in each gene region were computed using the Bedtools Coverage (version 2.25) function. Gene's regions refered to known refseq genes extracted using the UCSC Table Browser (3). The raw read counts were then rescaled accounting for a median coverage in cells whole exomes, then rescaled values were centered based on per-gene median coverage values from a set of non-tumor liver tissues. The read count ratios of tumor cells toward non-tumor liver tissues were used as the proxy of the copy number ratios. Distance between intervals were measured using the hg19 genomic coordinated from successive per-gene targeted intervals. Pan genomic plots of a logarithmic based 2 'read count ratios' were done.

Homozygous deletion or Focal Amplification were defined as a contiguous interval of less than 3 Mb, which has a logarithmic based 2 'read count ratios' greater than 1.5 or less than - 1.5. Extraction of variant allele frequency (VAF) from our SNV variants list allowed us to assess the CNV profiles and defined additional abnormalities such as loss of heterozygosity or hemizygosity of specific regions.

Supplementary References

1. Schulze K, Imbeaud S, Letouze E, Alexandrov LB, Calderaro J, Rebouissou S, et al. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. Nat Genet 2015;47:505-511.

2. Nault JC, Mallet M, Pilati C, Calderaro J, Bioulac-Sage P, Laurent C, et al. High frequency of telomerase reverse-transcriptase promoter somatic mutations in hepatocellular carcinoma and preneoplastic lesions. Nat Commun 2013;4:2218.

3. Karolchik D, Hinrichs AS, Furey TS, Roskin KM, Sugnet CW, Haussler D, et al. The UCSC Table Browser data retrieval tool. Nucleic Acids Res 2004;32:D493-496.

Supplementary Figure 1



Supplementary Fig. 1. Sensitivity to selective MET inhibitors in liver cancer cell lines is related to *MET* gene amplification. A, (Top, left panel) GI50 values for two selective MET inhibitors (JNJ-38877605 and PHA-665752) are represented for each of the 35 liver cancer cell lines analyzed. Cell lines are ranked according to their sensitivity from the most sensitive to the most resistant. (Bottom, left panel) The heatmaps below represent for each cell line (columns) sensitivity to MET inhibitors using the AUC, and MET status at the mRNA (q-RT-PCR), protein (RPPA) and genomic (copy number analyzed by exome sequencing) levels. AUC of 1 represents no drug response. Copy number, mRNA and protein levels for each cell line are expressed relative to the mean value of normal non-cirrhotic liver tissues. (Right panel) Dose-response curves obtained for the two selective MET inhibitors representing the two most sensitive cell lines (red and orange) and an example of resistant cell line (black), curves were generated from two independent experiments in duplicates. B, Chromosomal aberrations for the two most sensitive cell lines showing a focal amplification and a gain of *MET* gene respectively in MHCC97H and HCC-3 cell line. Border between chromosomes and centromeres are indicated respectively by vertical plain lines and dotted lines.



_	
_	1

Α

Comparison	Spearman r	P-value	Number of XY Pairs	Expression in tivantinib sensitive <i>vs</i> resistant cell lines
Tivantinib AUC vs. CDC20 mRNA	-0.42	0.01	35	overexpressed
Tivantinib AUC vs. RRM2 mRNA	-0.38	0.02	35	overexpressed
Tivantinib AUC vs. TAF9 mRNA	-0.31	0.07	35	overexpressed
Tivantinib AUC vs. GMNN mRNA	-0.36	0.03	35	overexpressed
Tivantinib AUC vs. RAN mRNA	-0.26	0.13	35	overexpressed
Tivantinib AUC vs. ABCG2 mRNA	-0.18	0.30	35	overexpressed
Tivantinib AUC vs. CREBBP mRNA	0.21	0.23	35	underexpressed
Tivantinib AUC vs. HMGB3 mRNA	0.22	0.20	35	underexpressed
Tivantinib AUC vs. BAZ2B mRNA	0.24	0.16	35	underexpressed
Tivantinib AUC vs. FGF3 mRNA	0.37	0.03	35	underexpressed
Tivantinib AUC vs. PTGDS mRNA	0.32	0.06	35	underexpressed
Tivantinib AUC vs. BBC3 mRNA	0.28	0.11	35	underexpressed

Supplementary Fig. 2. Tivantinib sensitivity is associated with high expression of genes involved in cell cycle regulation. A, Correlation matrix depicting patterns of co-expression among the 12 genes differentially expressed between tivantinib sensitive and resistant cell lines. Correlation between pairs of genes were assessed using Spearman's test. Color scale indicates the degree of correlation with red and blue representing respectively a negative and positive correlation. Spearman correlation coefficients are shown only for significant (P<0.05) association between gene pairs. The thick line highlights the major co-expression network invloving genes related to cell cycle control. B, Spearman's correlations between tivantinib sensitivity assessed by the AUC and each of the 12 genes significantly differentially expressed between tivantinib sensitive and resistant cell lines highlighting significant anti-correlation for genes involved in cell cycle regulation.

Supplementary Table 1. Liver cancer cell lines.

Cell line ID	Tumor type	Supplier
Hep3B	Hepatocellular carcinoma	American Type Culture Collection
Huh7	Hepatocellular carcinoma	American Type Culture Collection
HLE	Hepatocellular carcinoma	Health Science Research Resources Bank
HLF	Hepatocellular carcinoma	Health Science Research Resources Bank
SNU182	Hepatocellular carcinoma	American Type Culture Collection
SNU387	Hepatocellular carcinoma	American Type Culture Collection
SNU398	Hepatocellular carcinoma	American Type Culture Collection
SNU423	Hepatocellular carcinoma	American Type Culture Collection
SNU449	Hepatocellular carcinoma	American Type Culture Collection
SNU475	Hepatocellular carcinoma	American Type Culture Collection
PLC/PRF/5	Hepatocellular carcinoma	American Type Culture Collection
Mahlavu	Hepatocellular carcinoma	American Type Culture Collection
Li7	Hepatocellular carcinoma	RIKEN BioResource Center
HuH1	Hepatocellular carcinoma	Japanese Collection of Research Bioresources Cell Bank
JHH1	Hepatocellular carcinoma	Japanese Collection of Research Bioresources Cell Bank
JHH2	Hepatocellular carcinoma	Japanese Collection of Research Bioresources Cell Bank
JHH4	Hepatocellular carcinoma	Japanese Collection of Research Bioresources Cell Bank
JHH5	Hepatocellular carcinoma	Japanese Collection of Research Bioresources Cell Bank
JHH6	Hepatocellular carcinoma	Japanese Collection of Research Bioresources Cell Bank
JHH7	Hepatocellular carcinoma	Japanese Collection of Research Bioresources Cell Bank
SNU354	Hepatocellular carcinoma	Korean Cell Lines Bank
SNU368	Hepatocellular carcinoma	Korean Cell Lines Bank
SNU739	Hepatocellular carcinoma	Korean Cell Lines Bank
SNU761	Hepatocellular carcinoma	Korean Cell Lines Bank
SNU878	Hepatocellular carcinoma	Korean Cell Lines Bank
SNU886	Hepatocellular carcinoma	Korean Cell Lines Bank
MHCC97H	Hepatocellular carcinoma	Woodland Pharmaceuticals
BEL7402	Hepatocellular carcinoma	Woodland Pharmaceuticals
SMMC7721	Hepatocellular carcinoma	Woodland Pharmaceuticals
HCC-3	Hepatocellular carcinoma	A gift from Bettina Grasl-Kraupp (Austria)
B1	Hepatocellular carcinoma	A gift from Bettina Grasl-Kraupp (Austria)
HCC-1.1	Hepatocellular carcinoma	A gift from Bettina Grasl-Kraupp (Austria)
HCC-1.2	Hepatocellular carcinoma	A gift from Bettina Grasl-Kraupp (Austria)
HepG2	Hepatoblastoma	American Type Culture Collection (ATCC)
Huh6	Hepatoblastoma	RIKEN BioResource Center

		Resected HCC (n=281)		Advanced HCC (n	l stage =29)
Age (years)	Median (extremes)	65 (17-90)	n=281	58 (25-88)	n=29
Gondor	Male	228 (81%)	n=281	25 (86%)	n=29
Gender	Female	53 (19%)	n=281	4 (14%)	n=29
	HCV	62 (22%)	n=281	6 (21%)	n=29
	HBV	51 (18%)	n=280	7 (24%)	n=29
Etiology	Alcohol	114 (41%)	n=281	12 (41%)	n=29
Ellology	Metabolic syndrome	45 (16%)	n=281	4 (14%)	n=29
	Hemochromatosis	23 (8%)	n=280	2 (7%)	n=29
	Without etiology	42 (15%)	n=281	3 (10%)	n=29
Tumor size	≤ 5 cm	110 (39%)	n=281	8 (28%)	n=29
Tumor number	Single	212 (75%)	n=281	11 (38%)	n=29
Differenciation	Edmondson I-II	129 (46%)	n=279	13 (46%)	n=28
Differenciation	Edmondson III-IV	150 (54%)	n=279	15 (54%)	n=28
AFP ≤ 20 ng/ml		150 (56%)	n=266	7 (24%)	n=29
	0	10 (4%)	n=281	0 (0%)	n=29
BCI C ataga	A	184 (65%)	n=281	0 (0%)	n=29
DOLO Staye	В	46 (16%)	n=281	12 (41%)	n=29
	С	41 (15%)	n=281	17 (59%)	n=29

Supplementary Table 2. Clinical features of HCC series.

Supplementary Table 3. List of the 188 genes analyzed by quantitative RT-PCR.

TagMan assay ID	Gene Symbol
He03028000 g1	DNA1855:DNA4555 (Poference gone)
He00181605 m1	ADM
Hs00181005_III1	
Hs00173490_III1	
HSU2/80/42_S1	
HS00375822_m1	
HS00169867_m1	ANGP12
HS00221727_m1	ANGPTL7
Hs00473839_g1	ARID1A
Hs01582073_m1	AURKA
Hs00248075_m1	BBC3
Hs00175098_m1	C8A
Hs00255163_m1	CAP2
Hs00174575_m1	CCL5
Hs00990732_m1	CD34
Hs00415851_g1	CDC20
Hs00169953_m1	CDH2
Hs00355782_m1	CDKN1A
Hs00964504_m1	CLTC
Hs04183452_g1	CRP
Hs04260376_m1	CYP2C9
Hs00426361_m1	CYP3A7;CYP3A7-CYP3A51P
Hs00195090_m1	DHRS2
Hs01076078_m1	EGFR
Hs00158980_m1	EPCAM
Hs00178313_m1	EPHA1
Hs01001580_m1	ERBB2
Hs00174860_m1	ESR1
Hs00155026_m1	FABP1
Hs00236330_m1	FAS
Hs00262071_m1	FCRLA
Hs00192780_m1	FGF19
Hs00274783_s1	G0S2
Hs00169255_m1	GADD45A
Hs00544389_m1	GIMAP5;GIMAP1-GIMAP5
Hs00998725_g1	GLS2
Hs00374213_m1	GLUL
Hs00210707_m1	GMNN
Hs00219089_m1	GNMT
Hs00170471_m1	GPC3
Hs00416887_m1	ADGRG3
Hs00157887_m1	HAL
Hs00221783_m1	HAMP
Hs00801334_s1	HMGB3
Hs00602957_m1	HN1
Hs00230853_m1	HNF4A
Hs00359163_s1	HSPA1A
Hs00609566_m1	IGF1R
Hs00171254_m1	IGF2
Hs00559907_g1	IGF2BP3
Hs01082884_m1	IRF2
Hs01051611_gH	KRT19
Hs00165042_m1	LAMA3
Hs00363282_m1	LAPTM4B
Hs00173415_m1	LCAT
Hs00178427_m1	LCK
Hs00173664_m1	LGR5

TagMan assay ID	Gene Symbol
He00272650 m1	
$H_{0}00272039$ m1	
HS01561502_m1	ABCUT
HS01053790_m1	ABCG2
Hs00240568_m1	AGL
Hs00609411_m1	ALB
Hs00946916_m1	ALDH1A1
Hs00964880_m1	ALDH3A1
Hs01562312_m1	PRKAA1
Hs00326029_m1	ARID2
Hs01112326_m1	ATM
Hs00354807 m1	ATR
Hs00394718 m1	AXIN1
Hs01109276 g1	BAP1
Hs00203782 m1	BAZ2A
Hs00203809_m1	BAZ2B
Hs00608023 m1	BCI 2
Hs00236329 m1	BCI 2I 1
Hs00186838_m1	BECN1
Henn153353 m1	BIRC5
$H_{0}0006799 m1$	CONA2
He00277020 m1	
Hs00277039_III1	
HSU1026536_m1	
HS01075861_m1	
HS00233365_m1	
Hs00275663_m1	CFHR1
Hs00747645_m1	CFHR2
Hs00214990_m1	CHD7
Hs00932892_g1	CREBBP
Hs00229023_m1	DICER1
Hs02558036_s1	DNMT1
Hs01027167_g1	DNMT3A
Hs00176538_m1	ERBB3
Hs00173742_m1	FGF3
Hs00173564_m1	FGF4
Hs01106908_m1	FGFR4
Hs00176619 m1	FRK
Hs00242151 m1	GDF1:CERS1
Hs00171132 m1	GDF15
Hs00266783 s1	H2AFX
Hs00818513 sH	HIST1H2BC
Hs00606086_m1	HK2
Hs00985639 m1	11.6
Hs00234567 m1	JAK2
Hs00169663 m1	
Hs00174020 m1	KIT
Hen1125522 m1	ΙΔΤΩΙ
Henna2/306 m1	
Hen10/024080_1111	
Lono212200 m1	
H001076567 ~1	
	IVIAP ILUJA
HSUU414923_m1	
HSUU610538_m1	KM12A
Hs00231606_m1	KM12D
Hs00407034_m1	KMT2C
Hs00207065_m1	KMT2B

TaqMan assay ID	Gene Symbol
Hs00179024_m1	MERTK
Hs01565584_m1	MET
Hs01032443_m1	MKI67
Hs00168547_m1	NQO1
Hs00180035_m1	NRAS
Hs00170554_m1	NRCAM
Hs00175048_m1	NTS
Hs01127120_m1	LOC646214;PAK2
Hs00170171_m1	REG3A
Hs00696863_g1	PCNA
Hs01125822_m1	PIR
Hs00181117_m1	PTCH1
Hs02621230_s1	PTEN
Hs00168748_m1	PTGDS
Hs00366314_gH	RAB1A
Hs00389131_m1	RAMP3
Hs03044733_g1	RAN
Hs00161209_g1	RARRES2
Hs00219308_m1	RBM47
Hs01085479_g1	RHBG
Hs00177936_m1	RPS6KA3
Hs01072069_g1	RRM2
Hs00754237_s1	SAA2
Hs00271440_m1	SAE1
Hs01566038_m1	SDS
Hs00251986_m1	SLCO1B3
Hs00929647_m1	SMAD4
Hs00959010_m1	SPP1
Hs00918279_g1	TAF9;AK6
Hs00972656_m1	TERT
Hs99999911_m1	TFRC
Hs00998133_m1	TGFB1
Hs00610320_m1	TGFBR1
Hs00234253_m1	TGFBR2
Hs00896999_g1	TNNC1
Hs00426592_m1	UGT2B7
Hs00900055_m1	VEGFA

TaqMan assay ID	Gene Symbol
Hs00196955_m1	NCOR2
Hs00975961_g1	NFE2L2
Hs00246589_m1	NOX1
Hs00242302_m1	PARP1
Hs00193931_m1	PARP2
Hs00260004_m1	PHF20L1
Hs00178181_m1	PIK3R2
Hs00987255_m1	PKM
Hs00234592_m1	PPARG
Hs01115510_m1	PPARG
Hs00427274_m1	PRKACA
Hs00179161_m1	PRKDC
Hs01009250_m1	PROM1
Hs00153108_m1	RB1
Hs00198830_m1	RBP4
Hs00153294_m1	RELA
Hs00169407_m1	RIPK1
Hs01011177_g1	RIPK3
Hs00177228_m1	ROS1
Hs00360675_m1	SALL4
Hs00383442_m1	SETD2
Hs00216962_m1	SETD5
Hs00610060_m1	SFRP1
Hs00536164_m1	SLX4
Hs00161922_m1	SMARCA1
Hs01030846_m1	SMARCA2
Hs00271322_m1	SMC3
Hs00198472_m1	SRCAP
Hs00169491_m1	STK3
Hs00178979_m1	STK4
Hs00794094_m1	TAZ
Hs00174816_m1	THY1
Hs00921974_m1	TNFSF10
Hs00153340_m1	TP53
Hs00918956_m1	TRPM7
Hs01020387_m1	TSC2
Hs00745222 s1	XIAP

Supplementary Table 4. Mutations and copy number variations identified in 13 genes among the 35 liver cancer cell lines (GRCh37).

Cell line	Gene	Genomic change; (nucleotide		
name	Symbol	change from the ATG start site)	Protein change	Coding Effect
HenG2	TERT	chr5; a 1295228G>A; (-124G>A)		Promoter Mutation
		chr5:g 1205228C>A; (124C>A)		Promotor Mutation
	TERT	chr5:g 1295228G>A; (-124G>A)		Promoter_Mutation
		chr5:g 12052200-A; (-1240-A)		Promotor Mutation
SNI 1397	TEDT	chr5:g 1205228G>A; (-124G>A)		Promoter_Mutation
SNU307		chilo.g. 129522667A, (-12467A)		Promoter_Mutation
SINU 390		chilo.g. 129522662A, (-12462A)		Promoter_Mutation
SINU423		CIII5.g. 129522662A, (-12462A)		Promoter_Mutation
SINU475	TERI	CHI5.g. 1295226GPA, (-124GPA		Promoter_Mutation
Hun7	TERI	Chr5:g. 1295228G>A; (-124G>A)		Promoter_Mutation
Ivianiavu		Chr5:g. 1295250G>A; (-146G>A)		Promoter_Mutation
	TERI	CIII5.g. 1295226GPA, (-124GPA)		Promoter_Mutation
		CIII5.g. 129522662A, (-12462A)		Promoter_Mutation
		chilo.g. 129522662A, (-12462A)		Promoter_Mutation
	TERI	CIII5.g. 1295226GPA, (-124GPA)		Promoter_Mutation
		Chr5:g. 1295228G>A; (-124G>A)		Promoter_Mutation
ЛННЭ	TERI	Chr5:g. 1295228G>A; (-124G>A)		Promoter_Mutation
ЈННО		Chr5:g. 1295228G>A; (-124G>A)		Promoter_Mutation
	TERI	Chr5:g. 1295228G>A; (-124G>A)		Promoter_Mutation
SNU354	TERI	CNF5:g.1295228G>A; (-124G>A)		Promoter_Mutation
SNU368	TERI	chr5:g.1295228G>A; (-124G>A)		Promoter_Mutation
5NU739	IERI	cnr5:g.1295228G>A; (-124G>A)		Promoter_Wutation
SNU878	IERI	chr5:g.1295228G>A; (-124G>A)		Promoter_Mutation
SNU886	TERI	chr5:g.1295228G>A; (-124G>A)		Promoter_Mutation
JHH6	<i>TP53</i>	chr1/:g./5/4009_/5/4019del	p.Glu336AspfsX7	Frame_Shift_Del
Li7	TP53	chr17:g.7576572A>C	p.Leu336Val	Missense_Mutation
SNU761	TP53	chr17:g.7576878_7576909del	p.Ser313GlyfsX13	Frame_Shift_Del
JHH7	TP53	chr17:g.7577138C>G	p.Arg267Pro	Missense_Mutation
SNU475	TP53	chr17:g.7577153C>T	p.Gly262Asp	Missense_Mutation
SNU878	TP53	chr17:g.7577529A>T	p.lle251Asn	Missense_Mutation
Mahlavu	TP53	chr17:g.7577534C>A	p.Arg249Ser	Missense_Mutation
PLC/PRF5	TP53	chr17:g.7577534C>A	p.Arg249Ser	Missense_Mutation
JHH4	TP53	chr17:g.7577534C>A	p.Arg249Ser	Missense_Mutation
MHCC97H	TP53	chr17:g.7577534C>A	p.Arg249Ser	Missense_Mutation
HCC-1.2	TP53	chr17:g.7577548C>T	p.Gly245Ser	Missense_Mutation
HLE	TP53	chr17:g.7577550C>G	p.Gly244Ala	Missense_Mutation
HLF	TP53	chr17:g.7577550C>G	p.Gly244Ala	Missense_Mutation
SNU475	TP53	chr17:g.7577566T>C	p.Asn239Asp	Missense_Mutation
HCC-1.1	TP53	chr17:g.7578177C>G	p.Glu224Asp (Splice)	Missense_Mutation;Splice_Site
Huh7	TP53	chr17:g.7578190T>C	p.Tyr220Cys	Missense_Mutation
SNU886	TP53	chr17:g.7578192_7578193del	p.Pro219LeufsX2	Frame_Shift_Del
SNU739	TP53	chr17:g.7578204A>C	p.Ser215Arg	Missense_Mutation
SNU182	TP53	chr17:g.7578205C>A	p.Ser215lle	Missense_Mutation
JHH5	TP53	chr17:g.7578269_7578280del	p.Pro190_His193del	In_Frame_Del
SNU387	TP53	chr17:g.7578440T>A	p.Lys164X	Nonsense_Mutation
SNU449	TP53	chr17:g.7578449C>T	p.Ala161Thr	Missense_Mutation
B1	TP53	chr17:g.7578475G>A	p.Pro152Leu	Missense_Mutation
HCC-3	17P53	chr1/:g.7578475dup	p.Pro153AlatsX28	Frame_Shift_Dup
SNU423	1P53	chr1/:g.7578556T>C	p.Y126_splice	Splice_Site
SNU354	TP53	chr17:g.7579495dup	p.Arg65GInfsX84	Frame_Shift_Dup
Hep3B	17P53	chr1/:g.Homozygous deletion		
MHCC97H	TP53	chr17:g.7579536C>A	p.Glu51X	Nonsense_Mutation
HepG2	CTNNB1	chr3:g.41265568_41266630del	p.Ala5_GIn143del	In_Frame_Del
MHCC97H	CTNNB1	chr3:g.41266101_41266358del	p.Ser33_Asp81delinsTyr	In_Frame_Del;Splice_Site
MHCC97H	CTNNB1	chr3:g.g.41275334_41275335ins45	p.Pro501_Leu781delins10X	In_Frame_Ins;stopgain SNV
Huh6	CTNNB1	chr3:g.41266104G>T	p.Gly34Val	Missense_Mutation
SNU398	CTNNB1	chr3:g.41266113C>G	p.Ser37Cys	Missense_Mutation
B1	CTNNB1	chr3:g.41266124A>G	p.Thr41Ala	Missense_Mutation
SNU423	ARID1A	chr1:g.27059230G>T	p.Gly623X	Nonsense_Mutation
SNU449	ARID1A	chr1:g.27100182_27100183insGCA	p.Pro1326_Gln1327insAla	In_Frame_Ins
SNU368	ARID1A	chr1:g.27101535dup	p.Leu1390ProfsX41	Frame_Shift_Dup
SNU449	ARID1A	chr1:g.27107136dup	p.Glu2033ArgfsX28	Frame_Shift_Dup
SNU387	ARID1A	chr1:g.27023923_27023937del	p.Ala345_Ala349del	
PLC/PRF5	ARID1A	chr1:g.27023020_27023022dup	p.Ala45dup	
Huh1	ARID1A	chr1:g.Homozygous deletion		
SNU354	AXIN1	chr16:g.347963T>A	p.Lys515X	Nonsense_Mutation
SNU423	AXIN1	chr16:g.360044 360056del	p.Pro345ValfsX65	Frame Shift Del

Supplementary Table 4. Mutations and copy number variations identified in 13 genes among the 35 liver cancer cell lines (GRCh37).

Cell line	Gene	Genomic change; (nucleotide	Dustain shanna	O a diam Effect		
name	Symbol	change from the ATG start site)	Protein change	Coding Effect		
Huh1	AXIN1	chr16:g.364656_364668del	p.Glu299ProfsX111	Frame_Shift_Del		
Huh1	AXIN1	chr16:g.364669C>A	p.Arg298Leu	Missense_Mutation		
SNU368	AXIN1	chr16:g.396476G>A	p.Gln184X	Nonsense_Mutation		
Hep3B	AXIN1	chr16:g.396590G>A	p.Arg146X	Nonsense_Mutation		
JHH7	AXIN1	chr16:g.396700_396744del	p.Asp94_GIn108del	In_Frame_Del		
JHH5	AXIN1	chr16:g.397008_397009del	p.GIn6ArgfsX22	Frame_Shift_Del		
JHH6	AXIN1	chr16:g.397010G>A	p.GIn6X	Nonsense_Mutation		
HCC-3	AXIN1	chr16:g.Homozyous ex5del				
SNU475	AXIN1	chr16:g.Homozyous ex1-2del				
HCC-1.1	AXIN1	chr16:g.Homozyous ex2-10del				
PLC/PRF5	AXIN1	chr16:g.Homozyous ex5del				
PLC/PRF5	CDKN2A	chr9:g.21971024G>C	p.Arg112Gly	Missense_Mutation		
SNU368	CDKN2A	chr9:g.21971203A>C	p.Met52Arg	Missense_Mutation		
HCC-1.2	CDKN2A	chr9:g.Homozygous deletion				
SNU387	CDKN2A	chr9:g.Homozygous deletion				
SNU449	CDKN2A	chr9:g.Homozygous deletion				
Li7	CDKN2A	chr9:g.Homozygous deletion				
Hep3B	RPS6KA3	chrX:g.Homozygous deletion				
SNU449	ARID2	chr12:g.46231138A>C	p.His353Pro	Missense_Mutation		
SNU354	ARID2	chr12:g.46245173dup	p.Ala1090CysfsX5	Frame_Shift_Dup		
SNU354	ARID2	chr12:g.46246177del	p.Gly1424ValfsX5	Frame_Shift_Del		
JHH7	ARID2	chr12:g.46298776C>G	p.Ser1808Cys	Missense_Mutation		
SNU886	NFE2L2	chr2:g.178095985C>T	p.Arg426His	Missense_Mutation		
MHCC97H	KEAP1	chr19:g.10600521del	p.Pro445GInfsX13	Frame_Shift_Del		
Huh1	KEAP1	chr19:g.10602338T>A	p.Asn414Tyr p.Asn414Tyr	Missense_Mutation		
SNU475	KEAP1	chr19:g.10610421T>A	p.Lys97X	Nonsense_Mutation		
JHH5	KEAP1	chr19:g.10610511T>C	p.Met67Val	Missense_Mutation		
SNU761	ALB	chr4:g.g.chr4:74274527_74274530del	p.K161_splice	Del;Splice_Site		
HCC-1.1	ALB	chr4:g.g.chr4:74275137_74275138dup	p.Arg184LysfsX58	Frame_Shift_Dup		
B1	ALB	chr4:g.g.chr4:74282008_74282009del	p.Asn410PhefsX7	Frame_Shift_Del		
Huh7	APOB	chr2:g.21232437_21232445del	p.Tyr2432_Gln2434del	In_Frame_Del		
SNU878	APOB	chr2:g.21233189T>C	p.Tyr2184Cys	Missense_Mutation		
JHH1	APOB	chr2:g.21246444C>A	p.Val853Phe	Missense_Mutation		
SNU354	APOB	chr2:g.21247843G>T	p.Leu800Met	Missense_Mutation		
B1	APOB	chr2:g.21249840A>T	p.?	Splice_Site		
SNU368	APOB	chr2:g.21251362C>G	p.Asp556His	Missense_Mutation		
SNU423	APOB	chr2:g.21260084G>A	p.Thr194Met	Missense_Mutation		
PLC/PRF5	MET	chr7:g.116340086A>G	p.Ile316Met	Missense_Mutation		
MHCC97H	MET	chr7:g.Focal amplification				

Supplementary Table 5. Association between tivantinib sensitivity and mutation status of the 12 most frequently mutated genes in HCC tumors and MET across the panel of 35 liver cancer cell lines.

	Tivantinib GI50					Tivantinib AUC				
	N	Ν	NM		P-value	М		NM		P-value
Gene	Mean	Mean SD		SD	M vs NM	Mean	SD	Mean	SD	M vs NM
<i>TERT</i> - M=23(66%) NM=12(34%)	2.196	3.31	5.183	4.5	0.066	0.74	0.14	0.785	0.079	0.073
CTNNB1 - M=5(14%) NM=30(86%)	2.663	4.106	3.313	4.004	0.722	0.799	0.16	0.748	0.119	0.688
TP53 - M=26(74%) NM=9(26%)	2.621	3.535	4.949	4.817	0.239	0.735	0.11	0.814	0.145	0.157
ARID1A - M=6(20%) NM=29(80%)	5.368	5.368 3.906		3.894	0.020	0.794	0.05	0.747	0.134	0.110
AXIN1 - M=12(34%) NM=23(66%)	2.558 3.583		3.565	4.183	0.916	0.731	0.09	0.768	0.138	0.808
CDKN2A - M=6(17%) NM=29(83%)	5.285	4.017	2.793	3.885	0.053	0.833	0.13	0.739	0.12	0.076
ARID2 - M=3(9%) NM=32(91%)	3.65	5.501	3.18	3.906	0.790	0.747	0.09	0.756	0.128	0.930
RPS6KA3 - M=1(3%) NM=34(97%)	10	0	3.021	3.841	0.179	0.83	0	0.753	0.126	0.373
NFE2L2 - M=1(3%) NM=34(97%)	0.5	0	3.3	3.995	0.319	0.64	0	0.759	0.125	0.235
KEAP1 - M=4(11%) NM=31(89%)	3.101 4.608		3.235	3.96	0.774	0.738	0.07	0.758	0.132	0.917
ALB - M=3(9%) NM=32(91%)	3.627 5.53		3.182	3.904	0.790	0.698	0.17	0.761	0.121	0.814
APOB - M=7(20%) NM=28(80%)	2.168 3.507		3.483	4.086	0.724	0.735	0.1	0.761	0.131	0.853
<i>MET</i> - M=2(6%) NM=33(94%)	2.128	1.715	3.286	4.065	0.567	0.76	0.05	0.755	0.128	0.749

M: mutated; NM: non-mutated. The *P*-value column shows the significance of comparison between tivantinib sensitivity assessed either by the GI50 or the AUC in mutated and non-mutated cell lines. Statistical significance was assessed using a Mann-Whitney test.