Supplementary Table 1. Demographics of enrolled patients and PDO-growth associations with clinical variables

	All patients		Patients with successful *ex vivo* growth		Patients with unsuccessful *ex vivo* growth			
	n **= 132**		***n*** **= 102**		***n*** **= 30**			
Variable	**n (range)**	**%**	**n (range)**	**%**	**n (range)**	**%**	**p-value**	**Stat test**
Age at surgery	64 (24-83)	-	63 (24-83)	-	66 (43-79)	-	0.5	Wilcoxon Rank Sum Test
Gender							0,3	Pearson's Chi-squared test
female	47	36%	34	34%	13	43%		
male	84	64%	67	66%	17	57%		
Primary tumor site in colon							>0.9	Pearson's Chi-squared test
left and rectum	94	73%	72	73%	22	73%		
right	34	27%	26	27%	8	27%		
Primary tumor differentiation							0,3	Fisher's exact test
high	11	9%	7	8%	4	15%		
low	14	12%	11	12%	3	11%		
moderate	67	56%	51	55%	16	59%		
mucinous	2	2%	1	1%	1	4%		
unknown	26	22%	23	25%	3	11%		
Nodal status primary tumor							0,4	Fisher's exact test
N0	32	25%	28	29%	4	14%		
N1	53	42%	38	39%	15	52%		
N2	31	25%	23	24%	8	28%		
unknown	10	8%	8	8%	2	7%		
Surgery of primary tumor before CRLM	98	77%	73	74%	25	83%	0,3	Pearson's Chi-squared test
Number of CRLMs detected before surgery[a]	4 (1-31)	-	5 (1-31)	-	3 (1-30)	-	0.12	Wilcoxon Rank Sum Test
Size largest CRLM in mm	27 (6-180)	-	27 (6-180)	-	29 (7-101)	-	0,6	Wilcoxon Rank Sum Test
Number of CRLMs per patient processed							0,7	Fisher's exact test
1	22	17%	15	15%	7	23%		
2	67	51%	54	53%	13	43%		
3	20	15%	15	15%	5	17%		
4	12	9%	10	10%	2	7%		
5	9	7%	7	7%	2	7%		
6	2	2%	1	1%	1	3%		
KRAS							0,11	Pearson's Chi-squared test
mutated	50	40%	37	36%	13	54%		
wild type	76	60%	65	64%	11	46%		
NRAS							0,6	Fisher's exact test
mutated	8	7%	8	8%	0	0%		
wild type	110	93%	94	92%	16	100%		
BRAF							>0.9	Fisher's exact test
mutated	8	7%	7	7%	1	6%		
wild type	110	93%	95	93%	15	94%		
RAS and BRAF							0,5	Pearson's Chi-squared test
mutated	65	52%	51	50%	14	58%		
wild type	60	48%	50	50%	10	42%		
Neoadjuvant systemic treatment	100	78%	77	78%	23	77%	0,9	Pearson's Chi-squared test
Number of cycles of first line chemotherapy	4 (0-20)	-	4 (0-15)	-	4 (4-20)	-	0.5	Wilcoxon Rank Sum Test
Neoadjuvant first line chemotherapy							0,4	Fisher's exact test
FLV	5	4%	5	5%	0	0%		
FOLFIRI	33	26%	23	23%	10	33%		
FOLFOX	57	44%	46	46%	11	37%		
FOLFOXIRI	5	4%	3	3%	2	7%		
Untreated	29	22%	22	22%	7	23%		
Neoadjuvant targeted therapy							0,069	Fisher's exact test
anti-EGFR[b]	17	13%	11	11%	6	21%		
anti-VEGF[b]	10	8%	6	6%	4	14%		
Second line of neoadjuvant chemotherapy							0,2	Fisher's exact test
FOLFIRI	19	15%	17	17%	2	7%		
FOLFOX	7	5%	5	5%	2	7%		
Lonsurf	1	1%	0	0%	1	3%		
Untreated	103	79%	78	78%	25	83%		
Second line of neoadjuvant treatment with targeted drugs							0,8	Fisher's exact test
anti-EGFR[b]	2	2%	2	2%	0	0%		
anti-VEGF[b]	11	9%	8	8%	3	10%		
Third line of neoadjuvant chemotherapy							>0.9	Fisher's exact test
Capecitabin	1	1%	1	1%	0	0%		
FLOX	1	1%	1	1%	0	0%		
FLV	2	2%	2	2%	0	0%		
Untreated	127	97%	97	96%	30	100%		
Third line of neoadjuvant treatment with targeted drugs							>0.9	Fisher's exact test
anti-VEGF[b]	2	2%	2	2%	0	0%		
ASA score							0,6	Fisher's exact test
0	1	1%	1	1%	0	0%		
2	54	44%	40	42%	14	50%		
3	69	56%	55	57%	14	50%		
Surgical access							0,5	Fisher's exact test
L incision	61	47%	48	48%	13	43%		
Laparoscopy	51	40%	40	40%	11	37%		
midline incision	17	13%	11	11%	6	20%		
Syrgery type							0,7	Fisher's exact test
resection	109	83%	82	81%	27	90%		
PVE[c]	15	11%	13	13%	2	7%		
ALPPS[d]	7	5%	6	6%	1	3%		
Radiofrequency ablation	36	27%	31	31%	5	17%	0,13	Pearson's Chi-squared test
Resection margin liver							0,8	Pearson's Chi-squared test
R0 - resection	26	20%	19	19%	7	24%		
R1 - resection	66	51%	51	51%	15	52%		
R2 and/or residual lesions	37	29%	30	30%	7	24%		
Synchronous extrahepatic disease							>0.9	Pearson's Chi-squared test
Yes	34	26%	26	26%	8	27%		
none	96	74%	74	74%	22	73%		
Adjuvant systemic therapy	44	36%	32	35%	12	40%	0.6	Pearson's Chi-squared test
Survival status at 50 months follow-up[e]							0,052	Pearson's Chi-squared test
alive	63	48%	44	43%	19	63%		
dead	69	52%	58	57%	11	37%		

[a] On radiologic imaging before treatment

[b] Given in combination with other conventional chemotherapies

[c] Portal vein embolization

[d] Associating liver partition and portal vein ligation for staged hepatectomy

[e] Not all patients were followed for 50 months (censored earlier).

Supplementary Table 2. Resemblance of histopathology features in PDOs as compared to paired CRLMs (n=46)

	CRLM	PDO	CRLM	PDO	CRLM	PDO	CRLM	PDO	CRLM	PDO	CRLM	PDO	
Sample Name	**Glands/acinar**		**Glands/cystic**		**Cribriform/complex**		**Solid**		**Single cells**		**Vacuoles**		**Resemblance**
Pt50.2_t1	positive	positive	positive	negative	positive	positive	negative	negative	negative	positive	negative	positive	**yes**
Pt106_t1	positive	positive	positive	positive	negative	negative	negative	negative	negative	positive	negative	negative	**yes**
Pt106_t2	positive	positive	positive	positive	positive	negative	negative	negative	positive	positive	negative	negative	**yes**
Pt109_t1	positive	positive	positive	positive	negative	negative	positive	negative	positive	positive	positive	negative	**yes**
Pt109_t2	positive	positive	positive	positive	positive	negative	positive	negative	positive	negative	positive	negative	**yes**
Pt111_t1	positive	positive	positive	negative	positive	positive	negative	positive	negative	positive	negative	negative	**yes**
Pt111_t2	positive	positive	positive	positive	positive	positive	negative	positive	negative	positive	negative	negative	**yes**
Pt112_t2	positive	positive	positive	negative	positive	positive	negative	negative	positive	positive	positive	positive	**yes**
Pt114_t1	positive	positive	positive	positive	positive	positive	negative	negative	negative	negative	negative	negative	**yes**
Pt116_t1	positive	positive	positive	negative	positive	positive	negative	negative	negative	positive	positive	positive	**yes**
Pt119_t1	positive	positive	positive	positive	positive	positive	positive	negative	positive	positive	positive	negative	**yes**
Pt119_t3	positive	positive	positive	positive	positive	positive	positive	negative	positive	negative	positive	negative	**yes**
Pt120_t1	positive	positive	positive	positive	negative	positive	negative	negative	negative	negative	negative	negative	**yes**
Pt120_t2	positive	positive	positive	positive	negative	positive	negative	negative	negative	negative	negative	positive	**yes**
Pt121_t1	positive	positive	positive	positive	negative	negative	negative	negative	negative	negative	negative	positive	**yes**
Pt121_t2	positive	positive	positive	positive	positive	positive	negative	negative	negative	negative	negative	positive	**yes**
Pt121_t3	positive	positive	positive	positive	positive	positive	negative	negative	negative	negative	negative	positive	**yes**
Pt123_t1	positive	positive	positive	positive	negative	positive	negative	negative	negative	positive	negative	negative	**yes**
Pt124_t1	positive	positive	positive	positive	positive	positive	positive	positive	positive	positive	negative	negative	**yes**
Pt124_t2	positive	positive	positive	positive	positive	negative	negative	negative	negative	negative	negative	negative	**yes**
Pt125_t1	positive	positive	positive	positive	positive	negative	negative	negative	positive	negative	positive	negative	**yes**
Pt125_t3	positive	positive	positive	positive	positive	positive	negative	negative	positive	positive	positive	negative	**yes**
Pt126_t1	positive	positive	positive	positive	positive	positive	positive	negative	negative	positive	negative	negative	**yes**
Pt126_t2	positive	negative	positive	positive	positive	positive	NA	negative	positive	negative	negative	negative	**yes**
Pt127_t1	positive	positive	positive	negative	positive	negative	negative	positive	negative	positive	negative	negative	**yes**
Pt128_t1	positive	positive	positive	positive	positive	positive	positive	positive	positive	positive	negative	negative	**yes**
Pt128_t2	positive	positive	positive	negative	positive	positive	positive	positive	positive	negative	negative	negative	**yes**
Pt129_t1	positive	positive	positive	positive	positive	negative	negative	negative	negative	positive	negative	positive	**yes**
Pt129_t2	positive	positive	positive	positive	positive	positive	negative	negative	negative	positive	negative	negative	**yes**
Pt134_t1	positive	positive	positive	negative	positive	negative	positive	negative	negative	positive	negative	negative	**yes**
Pt134_t2	positive	positive	positive	negative	positive	negative	positive	negative	negative	negative	negative	negative	**yes**
Pt134_t4	positive	positive	positive	positive	negative	positive	negative	negative	positive	positive	negative	negative	**yes**
Pt134_t5	positive	positive	positive	positive	positive	negative	positive	negative	positive	positive	positive	positive	**yes**
Pt137_t3	positive	positive	positive	negative	positive	positive	positive	negative	negative	negative	negative	negative	**yes**
Pt137_t5	positive	positive	positive	positive	positive	negative	negative	negative	positive	positive	negative	negative	**yes**
Pt144_t2	positive	positive	positive	positive	negative	positive	negative	positive	negative	positive	negative	positive	**yes**
Pt148_t2	positive	positive	positive	positive	positive	positive	negative	negative	negative	negative	negative	negative	**yes**
Pt151_t1	positive	positive	positive	positive	negative	negative	negative	negative	negative	positive	negative	negative	**yes**
Pt151_t2	positive	positive	positive	positive	positive	negative	negative	positive	negative	positive	negative	negative	**yes**
Pt110_t1	positive	positive	positive	negative	positive	positive	negative	positive	negative	positive	negative	positive	**no**
Pt116_t2	positive	negative	positive	negative	positive	negative	negative	negative	negative	positive	negative	negative	**no**
Pt117_t1	positive	positive	positive	negative	negative	negative	negative	negative	negative	negative	negative	negative	**no**
Pt122_t2	positive	negative	positive	negative	positive	negative	negative	positive	positive	negative	positive	negative	**no**
Pt143_t1	positive	positive	positive	negative	positive	negative	negative	positive	negative	positive	negative	negative	**no**
Pt143_t2	positive	negative	positive	negative	positive	negative	negative	positive	negative	positive	negative	negative	**no**
Pt144_t1	positive	negative	positive	negative	positive	negative	negative	positive	negative	positive	negative	negative	**no**

Supplementary Table 3. Association of molecular and phenotypic traits of PDOs with their resemblance to corresponding tissues.

	Histopathological resemblance between CRLMs and PDOs[1]		
Variable	**no**, N = 7[2]	**yes**, N = 39[2]	**p-value**[3]
***RAS/BRAF*^{V600E}**			>0.9
mut	3 (60%)	17 (57%)	
other	2 (40%)	13 (43%)	
KRAS			0.6
mut	1 (20%)	11 (37%)	
wt	4 (80%)	19 (63%)	
NRAS			0.3
mut	1 (20%)	1 (3.3%)	
wt	4 (80%)	29 (97%)	
BRAF			>0.9
mut	1 (20%)	5 (17%)	
wt	4 (80%)	25 (83%)	
TP53			0.2
TP53 mut	3 (60%)	26 (87%)	
wt	2 (40%)	4 (13%)	
iCMS			0.4
iCMS2	1 (17%)	16 (42%)	
iCMS3	3 (50%)	10 (26%)	
unclassified	2 (33%)	12 (32%)	
PDO morphology			0.3
cystic	0 (0%)	11 (28%)	
mixed	1 (17%)	7 (18%)	
solid	6 (86%)	21 (54%)	
PDO growth speed			0.6
fast	0 (0%)	8 (20%)	
slow	2 (33%)	8 (20%)	
standard	5 (71%)	23 (59%)	

[1] Samples with histopathological resemblance were dichotomized based on Supplementary Table 2.
[2] n (%)
[3] Fisher's exact test

Supplementary Table 4. List of drugs of the library 1 (lib1) and library 2 (lib2).

compound_name	library	min_conc	max_conc	mode_of_action	regimen_type	class	approval_status	supplier	class_id	lib1_lib2	max_dss_lib1	Emax_lib1	mean_R2_lib1	max_dss2_lib2	Emax_lib2	mean_R2_lib2	Excluded	Comment
2-methoxyestradiol	lib1	1 nM	10000 nM	Angiogenesis inhibitor	single drug	Other	Phase 2	Cayman Chemical Company	X.		38,56	0,05	0,67				1	drug lot variability
Disulfiram+Cu	lib1	0 nM	65000 nM	Antabuse	single drug	Metabolic modifier	approved (non-oncology)	Selleck	H.		13,38	0,02	0,18				1	drug lot variability
Crizotinib	lib1	0.1 nM	1000 nM	ALK, c-Met inhibitor	single drug	Kinase inhibitor	approved	Selleck	B.		20,37	0,69	0,07				1	no activity
Tretinoin	lib1	1 nM	10000 nM	Retinoic acid receptor agonist	single drug	Differentiating/ epigenetic modifier	approved	Medchem Express	E.		8,60	0,53	0,15				1	no activity
Vitamin C	lib1	1 nM	10000 nM	metabolite	single drug	Metabolic modifier	approved (non-oncology)	Selleck	H.		13,86	0,73	-0,02				1	no activity
Alectinib	lib2	0.3 nM	1000 nM	ALK inhibitor	single drug	Kinase inhibitor	approved	ChemieTek	B.					2,48	0,62	-0,02	1	no activity
Larotrectinib	lib2	0.3 nM	1000 nM	TRK inhibitor	single drug	Kinase inhibitor	approved	Medchem Express	B.					0,27	0,80	-0,31	1	no activity
Savolitinib	lib2	3 nM	10000 nM	MET inhibitor	single drug	Kinase inhibitor	Phase 3	Medchem Express	B.					0,47	0,76	-0,11	1	no activity
Cetuximab	lib1	35 nM	350 nM	EGFR inhibitor	single antibody drug	Receptor tyrosine kinase inhibitor	approved	Selleck	D.	overlap	NA	NA	NA				1	technical variability
Cetuximab	lib2	0.68 nM	3430 nM	EGFR inhibitor	single antibody drug	Receptor tyrosine kinase inhibitor	approved	Selleck	D.	overlap				31,13	0,21	0,40	1	technical variability
Erastin	lib1	1 nM	10000 nM	VDAC2/3 (ferroptotic)	single drug	Other	pre-clinical	Medchem Express	X.		6,83	0,24	0,33				1	technical variability
Idelalisib	lib2	10 nM	1e+05 nM	PI3K inhibitor	single drug	Kinase inhibitor	approved	ChemieTek	B.					8,23	0,09	0,74	1	technical variability
Oxaliplatin	lib1	0.2 nM	1e+05 nM	RNA translation	single drug	Conv. Chemo	approved	Selleck	A.	overlap	16,61	0,14	0,73				0	
5-FU	lib1	1 nM	10000 nM	anti-metabolite; nucleoside analog	single drug	Conv. Chemo	approved	Medchem Express	A.	overlap	23,31	0,02	0,72				0	
Afatinib	lib1	0.1 nM	1000 nM	EGFR inhibitor	single drug	Kinase inhibitor	approved	Selleck	B.	overlap	25,52	0,06	0,78				0	
Alisertib	lib1	1 nM	10000 nM	Aurora inhibitor	single drug	Kinase inhibitor	Phase 3	Medchem Express	B.	overlap	28,11	0,03	0,77				0	
Atorvastatin	lib1	1 nM	10000 nM	HMG CoA reductase inhibitor	single drug	Metabolic modifier	approved (non-oncology)	ChemieTek	H.	overlap	35,65	0,01	0,82				0	
AZD7762	lib1	0.1 nM	1000 nM	CHEK1 inhibitor	single drug	Kinase inhibitor	Phase 1	Axon Medchem	B.	overlap	27,05	0,00	0,86				0	
Bemcentinib	lib1	1 nM	10000 nM	AXL/MERTK/TYRO3 kinase inhibitor	single drug	Kinase inhibitor	Phase 2	Medchem Express	B.	overlap	17,93	0,00	0,87				0	
Encorafenib	lib1	0.1 nM	1000 nM	BRAF V600E inhibitor	single drug	Kinase inhibitor	approved	Selleck	B.	overlap	5,02	0,27	0,20				0	
Gedatolisib	lib1	0.1 nM	1000 nM	PI3K/mTOR inhibitor	single drug	Kinase inhibitor	Phase 3	Selleck	B.	overlap	28,28	0,01	0,72				0	
Gemcitabine	lib1	0.1 nM	3000 nM	anti-metabolite; nucleoside analog	single drug	Conv. Chemo	approved	Medchem Express	A.	overlap	28,22	0,03	0,89				0	
Idasanutlin	lib1	1 nM	10000 nM	p53-MDM2 inhibitor	single drug	Apoptotic modulator	Phase 3	Medchem Express	G.	overlap	29,75	0,01	0,39				0	
Lapatinib	lib1	0.1 nM	1000 nM	HER2, EGFR inhibitor	single drug	Kinase inhibitor	approved	LC Laboratories	B.	overlap	29,82	0,00	0,64				0	
LCL161	lib1	2.5 nM	25000 nM	IAPs, SMAC mimetic	single drug	Apoptotic modulator	Phase 2	ChemieTek	G.	overlap	34,55	0,06	0,75				0	
LGK974	lib1	1 nM	10000 nM	PORCN inhibitor	single drug	Other	Phase 2	Selleck	X.	overlap	10,00	0,26	0,60				0	
Luminespib	lib1	0.1 nM	1000 nM	HSP90 inhibitor	single drug	HSP inhibitor	Phase 2	ChemieTek	K.	overlap	30,52	0,00	0,95				0	
Methotrexate	lib1	0.5 nM	5000 nM	antimetabolite; anti-folate	single drug	Metabolic modifier	approved	Selleck	H.	overlap	29,23	0,05	0,54				0	
Napabucasin	lib1	2 nM	20000 nM	CSC inhibitor	single drug	Other	Phase 3	Medchem Express	X.	overlap	24,39	0,00	0,94				0	
Palbociclib	lib1	1 nM	10000 nM	CDK4/6 inhibitor	single drug	Kinase inhibitor	approved	Selleck	B.	overlap	22,95	0,02	0,64				0	
Panobinostat	lib1	0.1 nM	1000 nM	pan-HDAC inhibitor	single drug	Differentiating/ epigenetic modifier	approved	LC Laboratories	E.	overlap	34,96	0,00	0,95				0	
Pevonedistat	lib1	1 nM	10000 nM	NEDD8-activing enzyme inhibitor	single drug	Metabolic modifier	Phase 3	ChemieTek	H.	overlap	25,97	0,01	0,88				0	
Regorafenib	lib1	1 nM	10000 nM	multi-kinase	single drug	Kinase inhibitor	approved	Medchem Express	B.	overlap	24,97	0,00	0,80				0	
SN-38	lib1	1 nM	10000 nM	topoisomerase inhibitor	single drug	Conv. Chemo	approved	ChemieTek	A.	overlap	42,99	0,01	0,96				0	
TAS-102	lib1	1 nM	10000 nM	anti-metabolite; nucleoside analog	single drug	Conv. Chemo	approved	Medchem Express	A.	overlap	18,82	0,01	0,31				0	
Trametinib	lib1	0.025 nM	250 nM	MEK1/2 inhibitor	single drug	Kinase inhibitor	approved	ChemieTek	B.	overlap	30,74	0,05	0,91				0	
Volasertib	lib1	0.1 nM	1000 nM	PLK1 inhibitor	single drug	Kinase inhibitor	Phase 3	ChemieTek	B.	overlap	28,56	0,02	0,93				0	
5-FU	lib2	30 nM	1e+05 nM	anti-metabolite; nucleoside analog	single drug	Conv. Chemo	approved	Medchem Express	A.	overlap				26,89	0,08	0,85	0	
Afatinib	lib2	0.3 nM	1000 nM	EGFR inhibitor	single drug	Kinase inhibitor	approved	Selleck	B.	overlap				29,57	0,05	0,77	0	
Alisertib	lib2	3 nM	10000 nM	Aurora inhibitor	single drug	Kinase inhibitor	Phase 3	Medchem Express	B.	overlap				31,19	0,02	0,71	0	
Atorvastatin	lib2	10 nM	1e+05 nM	HMG CoA reductase inhibitor	single drug	Metabolic modifier	approved (non-oncology)	ChemieTek	H.	overlap				34,86	0,00	0,93	0	
AZD7762	lib2	3 nM	10000 nM	CHEK1 inhibitor	single drug	Kinase inhibitor	Phase 1	Axon Medchem	B.	overlap				31,28	0,00	0,95	0	
Bemcentinib	lib2	10 nM	30000 nM	AXL/MERTK/TYRO3 kinase inhibitor	single drug	Kinase inhibitor	Phase 2	Medchem Express	B.	overlap				18,02	0,00	0,94	0	
Encorafenib	lib2	0.3 nM	1000 nM	BRAF V600E inhibitor	single drug	Kinase inhibitor	approved	Selleck	B.	overlap				18,41	0,26	0,10	0	
Gedatolisib	lib2	2.5 nM	7500 nM	PI3K/mTOR inhibitor	single drug	Kinase inhibitor	Phase 3	Selleck	B.	overlap				29,42	0,01	0,87	0	
Gemcitabine	lib2	0.3 nM	1000 nM	anti-metabolite; nucleoside analog	single drug	Conv. Chemo	approved	Medchem Express	A.	overlap				32,97	0,03	0,90	0	
Idasanutlin	lib2	3 nM	10000 nM	p53-MDM2 inhibitor	single drug	Apoptotic modulator	Phase 3	Medchem Express	G.	overlap				31,38	0,08	0,03	0	
Lapatinib	lib2	3 nM	10000 nM	HER2, EGFR inhibitor	single drug	Kinase inhibitor	approved	LC Laboratories	B.	overlap				30,49	0,03	0,88	0	
LCL161	lib2	7.5 nM	25000 nM	IAPs, SMAC mimetic	single drug	Apoptotic modulator	Phase 2	ChemieTek	G.	overlap				41,37	0,07	0,81	0	
LGK974	lib2	3 nM	10000 nM	PORCN inhibitor	single drug	Other	Phase 2	Selleck	X.	overlap				13,00	0,20	0,50	0	
Luminespib	lib2	0.3 nM	1000 nM	HSP90 inhibitor	single drug	HSP inhibitor	Phase 2	ChemieTek	K.	overlap				31,15	0,00	0,96	0	
Methotrexate	lib2	1.5 nM	5000 nM	antimetabolite; anti-folate	single drug	Metabolic modifier	approved	Selleck	H.	overlap				30,61	0,07	0,71	0	
Napabucasin	lib2	6 nM	20000 nM	CSC inhibitor	single drug	Other	Phase 3	Medchem Express	X.	overlap				24,27	0,00	0,94	0	
Oxaliplatin	lib2	30 nM	1e+05 nM	DNA inhibitor	single drug	Conv. Chemo	approved	Selleck	A.	overlap				19,52	0,08	0,79	0	
Palbociclib	lib2	15 nM	50000 nM	CDK4/6 inhibitor	single drug	Kinase inhibitor	approved	Selleck	B.	overlap				26,40	0,00	0,91	0	
Panobinostat	lib2	0.3 nM	10000 nM	pan-HDAC inhibitor	single drug	Differentiating/ epigenetic modifier	approved	LC Laboratories	E.	overlap				36,92	0,00	0,96	0	
Pevonedistat	lib2	3 nM	10000 nM	NEDD8-activing enzyme inhibitor	single drug	Metabolic modifier	Phase 3	ChemieTek	H.	overlap				25,79	0,02	0,90	0	
Regorafenib	lib2	10 nM	1e+05 nM	multi-kinase	single drug	Kinase inhibitor	approved	Medchem Express	B.	overlap				25,38	0,01	0,92	0	
SN-38	lib2	0.3125 nM	10000 nM	topoisomerase inhibitor	single drug	Conv. Chemo	approved	ChemieTek	A.	overlap				38,83	0,03	0,95	0	
TAS-102	lib2	30 nM	1e+05 nM	anti-metabolite; nucleoside analog	single drug	Conv. Chemo	approved	Medchem Express	A.	overlap				19,77	0,05	0,87	0	
Trametinib	lib2	0.075 nM	250 nM	MEK1/2 inhibitor	single drug	Kinase inhibitor	approved	ChemieTek	B.	overlap				29,97	0,08	0,89	0	
Volasertib	lib2	0.3 nM	1000 nM	PLK1 inhibitor	single drug	Kinase inhibitor	Phase 3	ChemieTek	B.	overlap				28,75	0,02	0,92	0	
5-FU/Gemcitabine	lib1	1/1 nM	1000/1000 nM	anti-metabolite/nucleoside analog	drug combination	Conv. Chemo	approved	Medchem Express/Medchem Express	A.		29,01	0,03	0,83				0	
Binimetinib	lib1	0.1 nM	1000 nM	MEK1/2 inhibitor	single drug	Kinase inhibitor	approved	ChemieTek	B.		17,90	0,17	0,75				0	
Eltanexor	lib1	1 nM	10000 nM	XPO1 inhibitor	single drug	Apoptotic modulator	Phase 2	Medchem Express	G.		21,95	0,00	0,92				0	
Erlotinib	lib1	1 nM	10000 nM	EGFR inhibitor	single drug	Kinase inhibitor	approved	Medchem Express	B.		25,67	0,05	0,85				0	
Ipatasertib	lib1	1 nM	10000 nM	AKT inhibitor	single drug	Kinase inhibitor	Phase 3	ChemieTek	B.		36,79	0,10	0,54				0	
Linsitinib	lib1	1 nM	10000 nM	IGF1R, IR inhibitor	single drug	Kinase inhibitor	Phase 3	ChemieTek	B.		20,24	0,12	0,50				0	
Navitoclax	lib1	1 nM	10000 nM	Bcl-2/Bcl-xL inhibitor	single drug	Apoptotic modulator	Phase 2	Selleck	G.		29,63	0,00	0,94				0	
Olaparib	lib1	1 nM	10000 nM	PARP inhibitor	single drug	Differentiating/ epigenetic modifier	approved	LC Laboratories	E.		11,35	0,03	0,37				0	
Sirolimus	lib1	0.01 nM	100 nM	binds FKBP12, causes inhibition of mTORC1	single drug	Rapalog	approved	LC Laboratories	C.		9,14	0,10	0,20				0	
5-FU/Folinic acid (FLV)	lib2	30/10000 nM	30000/10000 nM	nucleoside analog/5-FU enhancer	drug combination	Conv. Chemo	approved	Medchem Express/Sigma-Aldrich	A.					23,97	0,15	0,81	0	
5-FU/Folinic acid/Oxaliplatin (FLOX)	lib2	30/10000/30 nM	30000/10000/30000 nM	nucleoside analog/5-FU enhancer/DNA inhibitor	drug combination	Conv. Chemo	approved	Medchem Express/Sigma-Aldrich/Selleck	A.					21,80	0,14	0,70	0	
5-FU/Folinic acid/SN-38 (FLIRI)	lib2	30/10000/1 nM	30000/10000/300 nM	nucleoside analog/5-FU enhancer/toposiomerase inhibitor	drug combination	Conv. Chemo	approved	Medchem Express/Sigma-Aldrich/ChemieTek	A.					36,96	0,03	0,91	0	
Adavosertib	lib2	3 nM	10000 nM	Wee1 inhibitor	single drug	Kinase inhibitor	Phase 2	ChemieTek	B.					27,96	0,02	0,94	0	
Afatinib/Encorafenib/Trametinib (MAPK-3x)	lib2	0.3/0.3/0.075 nM	300/300/75 nM	MAP pathway inhibitors	drug combination	Kinase inhibitor	Phase 3	Selleck/Selleck/ChemieTek	B.					34,87	0,01	0,92	0	
AZD5991	lib2	3 nM	10000 nM	MCL1 inhibitor	single drug	Other	Phase 2	ChemieTek	X.					30,70	0,03	0,59	0	
BMS-754807	lib2	1 nM	30000 nM	IGF1R inhibitor	single drug	Kinase inhibitor	Phase 2	Medchem Express	B.					31,21	0,00	0,93	0	
Carfilzomib	lib2	0.15 nM	500 nM	20S proteasome inhibitor	single drug	Conv. Chemo	approved	ChemieTek	A.					36,58	0,00	0,97	0	
Ceralasertib	lib2	7.5 nM	25000 nM	ATR inihibitor	single drug	Kinase inhibitor	Phase 3	Medchem Express	B.					26,75	0,02	0,93	0	
Dasatinib	lib2	0.1 nM	10000 nM	SRC family kinases	single drug	Kinase inhibitor	approved	LC Laboratories	B.					26,80	0,01	0,88	0	
Everolimus	lib2	0.03 nM	300 nM	binds FKBP12, causes inhibition of mTORC1	single drug	Rapalog	approved	LC Laboratories	C.					16,39	0,51	0,03	0	
Selinexor	lib2	3 nM	10000 nM	XPO1 inhibitor	single drug	Apoptotic modulator	approved	Selleck	G.					27,54	0,04	0,93	0	
Silmitasertib	lib2	10 nM	1e+05 nM	CSNK2A1 inhibitor	single drug	Kinase inhibitor	Phase 2	Selleck	B.					18,09	0,00	0,95	0	
Sotorasib	lib2	3 nM	10000 nM	KRAS G12C inhibitor	single drug	Kinase inhibitor	approved	Selleck	B.					27,91	0,28	0,03	0	
Talazoparib	lib2	2.5 nM	7500 nM	PARP1/2 inhibitor	single drug	Differentiating/ epigenetic modifier	approved	Medchem Express	E.					39,34	0,02	0,77	0	
Venetoclax	lib2	10 nM	1e+05 nM	Bcl-2-selective inhibitor	single drug	Apoptotic modulator	approved	ChemieTek	G.					21,10	0,02	0,68	0	
Volasertib/SN38	lib2	0.3/0.3 nM	300/300 nM	PLK1 inhibotor/toposiomerase inhibitor	drug combination	Kinase inhibitor/Conv. Chemo	Phase 2	ChemieTek/ChemieTek	X.					36,15	0,04	0,93	0	

maxDSS: Maximum DSS score across samples. Higher numbers indicate higher activity.
Emax: The maximum effect of the drug accross samples. Lower numbers indicate higher activity.
R2: The goodness of fit for the dose-response models. A higher R2 value generally means a better fit.

Supplementary Table 5. Association of drug activities with co-mutated genes

co_mut	drug	n_co.mut	n_other	Wilcoxon_p_value	deltaDSS	Adjusted_p_value (Benjamini-Hochberg)	sig
APC_RAS_BRAFV600E	Lapatinib	68	81	1,6953E-17	-11,227831	1,33081E-14	***
APC_RAS_BRAFV600E	Afatinib	68	81	4,0071E-15	-9,5301657	1,57279E-12	***
TP53_RAS_BRAFV600E	Lapatinib	52	97	4,63836E-14	-9,4274897	1,2137E-11	***
TP53_K_NRAS	Lapatinib	44	105	1,98744E-12	-8,9856754	3,90036E-10	***
APC_K_NRAS	Lapatinib	55	94	5,71145E-12	-9,1090608	8,96698E-10	***
TP53_RAS_BRAFV600E	Afatinib	52	97	2,22126E-11	-10,47959	2,90615E-09	***
APC_K_NRAS	Afatinib	55	94	4,24387E-10	-7,5853159	4,7592E-08	***
TP53_KRAS	Lapatinib	37	112	4,17069E-09	-8,3381658	4,09249E-07	***
TP53_K_NRAS	Afatinib	44	105	4,89293E-09	-9,1583274	4,26772E-07	***
APC_KRAS	Lapatinib	45	104	3,19349E-08	-8,2914162	2,50689E-06	***
APC_RAS_BRAFV600E	Erlotinib	37	40	1,31876E-07	-9,0283159	9,41118E-06	***
APC_TP53	Idasanutlin	115	34	1,9631E-07	-4,9544989	1,28432E-05	***
APC_KRAS	Afatinib	45	104	1,48986E-06	-6,7157554	8,35384E-05	***
TP53_K_NRAS	Erlotinib	25	52	1,40254E-06	-10,459427	8,35384E-05	***
TP53_KRAS	Afatinib	37	112	1,65601E-06	-7,3904693	8,66643E-05	***
APC_K_NRAS	Erlotinib	32	45	2,25824E-06	-8,4484009	0,000110795	***
TP53_K_NRAS	meanDSS_24drugs	44	105	2,99729E-06	-2,6657211	0,000138404	***
TP53_RAS_BRAFV600E	Erlotinib	28	49	3,60739E-06	-9,5843444	0,000157322	***
TP53_RAS_BRAFV600E	meanDSS_24drugs	52	97	7,66421E-06	-2,4829921	0,000316652	***
APC_BRAF	BMS.754807	10	76	1,23348E-05	-10,985428	0,000484141	***
APC_BRAF	Encorafenib	16	133	3,31196E-05	0,9346166	0,001238041	**
TP53_K_NRAS	Volasertib	44	105	5,77428E-05	-4,801115	0,002060369	**
APC_TP53	5-FU	115	34	8,38851E-05	-5,4048963	0,002863035	**
APC_RAS_BRAFV600E	Atorvastatin	68	81	0,000103778	-4,1803404	0,003394406	**
TP53_RAS_BRAFV600E	Atorvastatin	52	97	0,000130663	-4,0315448	0,004102812	**
TP53_RAS_BRAFV600E	Pevonedistat	52	97	0,000139374	-3,4404635	0,004106295	**
APC_RAS_BRAFV600E	Dasatinib	42	44	0,000146467	-3,4431042	0,004106295	**
APC_TP53	TAS-102	115	34	0,000145346	-3,6788395	0,004106295	**
TP53_KRAS	meanDSS_24drugs	37	112	0,000173717	-1,7551904	0,004702349	**
TP53_RAS_BRAFV600E	Volasertib	52	97	0,000191765	-4,1911872	0,005017838	**
APC_TP53	Gemcitabine	115	34	0,000283467	-6,0894381	0,007076659	**
APC_TP53	SN-38	115	34	0,000288475	-6,4089358	0,007076659	**
TP53_KRAS	Erlotinib	19	58	0,000320892	-9,2195926	0,00763333	**
APC_RAS_BRAFV600E	Pevonedistat	68	81	0,000374198	-3,4290957	0,008639562	**
TP53_KRAS	Volasertib	37	112	0,00038824	-4,755352	0,008707668	**
APC_K_NRAS	Volasertib	55	94	0,000473919	-2,8025405	0,010334072	*
APC_ARID1A	Venetoclax	10	76	0,000686179	-6,6934894	0,014175018	*
TP53_ARID1A	Venetoclax	10	76	0,000686179	-6,6934894	0,014175018	*
APC_RAS_BRAFV600E	Volasertib	68	81	0,000718729	-2,8913185	0,014466726	*
TP53_KRAS	Venetoclax	24	62	0,000738902	-4,1207617	0,014500954	*
APC_RAS_BRAFV600E	meanDSS_24drugs	68	81	0,000770228	-1,7475732	0,01474705	*
TP53_K_NRAS	Pevonedistat	44	105	0,000802624	-3,2712589	0,015001418	*
APC_RAS_BRAFV600E	Regorafenib	68	81	0,000871653	0,9452739	0,015551075	*
APC_TP53	Alisertib	115	34	0,000864004	-6,9006275	0,015551075	*
TP53_K_NRAS	5-FU	44	105	0,001129223	-3,5958079	0,019698667	*
TP53_KRAS	Pevonedistat	37	112	0,001212194	-2,8954722	0,020686357	*
APC_TP53	meanDSS_24drugs	115	34	0,001269174	-2,0742133	0,021197911	*
APC_BRAF	Everolimus	10	76	0,001577567	4,5905685	0,025488373	*
APC_TP53	Encorafenib	115	34	0,001590994	-0,203278	0,025488373	*
APC_RAS_BRAFV600E	Panobinostat	68	81	0,001933142	-1,7202664	0,029183009	*
APC_KRAS	Venetoclax	28	58	0,001926741	-4,2915419	0,029183009	*
APC_BRAF	Afatinib	16	133	0,00191885	-9,5888836	0,029183009	*
TP53_K_NRAS	Venetoclax	28	58	0,002114579	-3,9502252	0,030840277	*
APC_TP53	5-FU + Gemcitabine	57	20	0,002121497	-6,1788264	0,030840277	*
APC_KRAS	Erlotinib	24	53	0,002192439	-4,8950103	0,031292079	*
APC_KRAS	Volasertib	45	104	0,002391169	-2,688071	0,032931016	*
TP53_RAS_BRAFV600E	5-FU	52	97	0,002360677	-3,2059498	0,032931016	*
APC_K_NRAS	Pevonedistat	55	94	0,002470172	-3,1672517	0,033432496	*
APC_BRAF	Dasatinib	10	76	0,002722345	-3,9333353	0,036221035	*
PIK3CA_K_NRAS	FLIRI	10	76	0,003105974	9,5371298	0,039970315	*
APC_KRAS	Pevonedistat	45	104	0,003094128	-2,9700138	0,039970315	*
TP53_ARID1A	Pevonedistat	12	137	0,00320587	-4,4626645	0,040590448	*
APC_PIK3CA	BMS.754807	14	72	0,003516321	-4,0690231	0,043814472	*
TP53_K_NRAS	AZD7762	44	105	0,003955776	-2,1062577	0,048520069	*
TP53_K_NRAS	Atorvastatin	44	105	0,004569773	-3,1882017	0,055188797	ns
APC_KRAS	Regorafenib	45	104	0,004900215	0,8880891	0,057412967	ns
TP53_KRAS	5-FU	37	112	0,004889949	-3,4202042	0,057412967	ns
APC_BRAF	Lapatinib	16	133	0,005025139	-5,2832108	0,0580108	ns
TP53_RAS_BRAFV600E	TAS-102	52	97	0,005159867	-2,8542041	0,058702834	ns
APC_K_NRAS	meanDSS_24drugs	55	94	0,005319573	-1,3224246	0,058814999	ns
PIK3CA_RAS_BRAFV600E	Lapatinib	14	135	0,005301414	-5,4484414	0,058814999	ns
TP53_RAS_BRAFV600E	Dasatinib	34	52	0,005471801	-2,8499981	0,058840604	ns
TP53_RAS_BRAFV600E	Gemcitabine	52	97	0,005406052	-3,9395521	0,058840604	ns
TP53_RAS_BRAFV600E	Alisertib	52	97	0,00664573	-4,5327101	0,07049821	ns
APC_TP53	Pevonedistat	115	34	0,006972475	-3,1766886	0,07241623	ns
APC_PIK3CA	MAPK.3x	14	72	0,007010998	-5,1249463	0,07241623	ns
TP53_K_NRAS	Gedatolisib	44	105	0,007139656	-1,8808458	0,072787402	ns
TP53_RAS_BRAFV600E	AZD7762	52	97	0,007489458	-1,9381158	0,075374671	ns
TP53_KRAS	Atorvastatin	37	112	0,007703229	-3,2735056	0,076544741	ns
APC_K_NRAS	Methotrexate	55	94	0,007850172	-4,7380666	0,077029812	ns
APC_K_NRAS	Regorafenib	55	94	0,007971575	0,5908865	0,077255384	ns
TP53_K_NRAS	Gemcitabine	44	105	0,008488591	-3,4692297	0,081262727	ns
TP53_RAS_BRAFV600E	Panobinostat	52	97	0,009145716	-1,3891795	0,086417488	ns
APC_BRAF	SN-38	16	133	0,009247222	-4,5462959	0,086417488	ns
APC_K_NRAS	Venetoclax	33	53	0,009508181	-3,9424715	0,087810851	ns
PIK3CA_K_NRAS	LCL161	13	136	0,010082623	8,4629486	0,089941577	ns
TP53_PIK3CA	Regorafenib	16	133	0,009930186	-1,3538424	0,089941577	ns
KRAS_PIK3CA	Lapatinib	11	138	0,010059215	-5,4210458	0,089941577	ns
TP53_K_NRAS	Alisertib	44	105	0,010554931	-4,4111151	0,092156294	ns
APC_ARID1A	Talazoparib	10	76	0,010683086	-5,61605	0,092156294	ns
TP53_ARID1A	Talazoparib	10	76	0,010683086	-5,61605	0,092156294	ns
APC_K_NRAS	Atorvastatin	55	94	0,011491269	-3,0604438	0,098050502	ns
TP53_KRAS	AZD7762	37	112	0,011889046	-1,9390071	0,099076841	ns
APC_RAS_BRAFV600E	Venetoclax	42	44	0,01178615	-3,825081	0,099076841	ns
APC_ARID1A	Pevonedistat	13	136	0,011990191	-4,4472245	0,099076841	ns
PIK3CA_K_NRAS	Lapatinib	13	136	0,01221129	-5,3828066	0,099852739	ns
TP53_KRAS	Gedatolisib	37	112	0,01234073	-1,7579237	0,099870855	ns
APC_BRAF	FLIRI	10	76	0,016791726	-7,7591667	0,13450515	ns
APC_TP53	Navitoclax	57	20	0,017517616	-5,5645955	0,137513284	ns
APC_TP53	Talazoparib	71	15	0,017383412	-5,9375566	0,137513284	ns
APC_SMAD4	Eltanexor	12	65	0,017959972	3,3452173	0,139589882	ns
APC_RAS_BRAFV600E	Adavosertib	33	42	0,019139219	-3,5694034	0,14729693	ns
APC_RAS_BRAFV600E	Ceralasertib	42	44	0,019896224	-1,9599555	0,151636267	ns
APC_TP53	Volasertib	115	34	0,021187426	-1,2741434	0,159924318	ns
APC_KRAS	Atorvastatin	45	104	0,021400432	-2,8163809	0,159993705	ns
PIK3CA_RAS_BRAFV600E	FLIRI	11	75	0,022100338	9,4386659	0,163667595	ns
APC_BRAF	Gedatolisib	16	133	0,02273725	4,8053854	0,164231413	ns
TP53_PIK3CA	Everolimus	12	74	0,022804107	3,1916469	0,164231413	ns
TP53_K_NRAS	Methotrexate	44	105	0,022546166	-4,5023455	0,164231413	ns
TP53_PIK3CA	LGK974	16	133	0,024037791	-0,7830805	0,169054155	ns
TP53_K_NRAS	Ceralasertib	28	58	0,024240949	-1,6120252	0,169054155	ns
TP53_KRAS	Gemcitabine	37	112	0,024335184	-3,1053173	0,169054155	ns
TP53_PIK3CA	BMS.754807	12	74	0,023694654	-3,417628	0,169054155	ns
TP53_RAS_BRAFV600E	Regorafenib	52	97	0,026673032	0,5947744	0,182072435	ns
TP53_KRAS	Idasanutlin	37	112	0,026661978	-0,0008777	0,182072435	ns
TP53_PIK3CA	5-FU	16	133	0,027941658	-2,9706335	0,189087942	ns
APC_KRAS	Panobinostat	45	104	0,028882941	-1,19955	0,192144986	ns
TP53_RAS_BRAFV600E	Ceralasertib	34	52	0,028810114	-1,555414	0,192144986	ns
TP53_KRAS	Ceralasertib	24	62	0,029925031	-1,6884221	0,195759577	ns
TP53_ARID1A	Gemcitabine	12	137	0,029783175	-5,3066085	0,195759577	ns
PIK3CA_RAS_BRAFV600E	LCL161	14	135	0,031025384	7,1956428	0,197020723	ns
APC_RAS_BRAFV600E	FLV	42	44	0,031121745	-1,2308016	0,197020723	ns
APC_RAS_BRAFV600E	BMS.754807	42	44	0,031121745	-2,4398792	0,197020723	ns
TP53_RAS_BRAFV600E	Oxaliplatin	19	31	0,030881417	-3,0457824	0,197020723	ns
APC_K_NRAS	Trametinib	55	94	0,035504659	2,0882621	0,201908002	ns
APC_RAS_BRAFV600E	Encorafenib	68	81	0,032816638	0,0325177	0,201908002	ns
TP53_K_NRAS	Idasanutlin	44	105	0,033842731	-0,0017554	0,201908002	ns
TP53_KRAS	Panobinostat	37	112	0,035517358	-1,0902607	0,201908002	ns
APC_PIK3CA	Silmitasertib	14	72	0,035751863	-1,1572232	0,201908002	ns
TP53_K_NRAS	Panobinostat	44	105	0,035420798	-1,2759715	0,201908002	ns
APC_PIK3CA	Regorafenib	19	130	0,033062918	-1,2794697	0,201908002	ns
APC_KRAS	Gedatolisib	45	104	0,034096011	-1,7320946	0,201908002	ns
APC_TP53	Eltanexor	57	20	0,034990313	-2,5289002	0,201908002	ns
APC_BRAF	Napabucasin	16	133	0,032614712	-2,8584681	0,201908002	ns
APC_BRAF	Luminespib	16	133	0,034663724	-3,2304784	0,201908002	ns
TP53_RAS_BRAFV600E	Venetoclax	34	52	0,034386176	-3,3080439	0,201908002	ns
TP53_PIK3CA	MAPK.3x	12	74	0,033590711	-4,0877177	0,201908002	ns
TP53_KRAS	Alisertib	37	112	0,03327259	-4,1384521	0,201908002	ns
SMAD4_RAS_BRAFV600E	Lapatinib	11	138	0,03250317	-4,3933128	0,201908002	ns
APC_RAS_BRAFV600E	AZD5991	33	42	0,037890934	-1,6291024	0,212459881	ns
TP53_RAS_BRAFV600E	SN-38	52	97	0,039689193	-3,1090141	0,220964653	ns
APC_KRAS	Methotrexate	45	104	0,040054567	-4,1818957	0,221428415	ns
APC_TP53	Regorafenib	115	34	0,040677823	-0,7423167	0,221443615	ns
APC_KRAS	meanDSS_24drugs	45	104	0,040903598	-0,9512138	0,221443615	ns
APC_TP53	AZD7762	115	34	0,040677823	-1,9558965	0,221443615	ns
TP53_SMAD4	BMS.754807	13	73	0,041606078	2,8141729	0,223703914	ns
APC_K_NRAS	Gedatolisib	55	94	0,042178329	-1,482878	0,225238017	ns
TP53_PIK3CA	Idasanutlin	16	133	0,042518467	0	0,225520248	ns
APC_K_NRAS	Ceralasertib	33	53	0,042893266	-1,505668	0,225981301	ns
APC_BRAF	Panobinostat	16	133	0,043352698	-2,3849389	0,22687912	ns
APC_K_NRAS	Dasatinib	33	53	0,043813849	-2,477282	0,227773985	ns
KRAS_PIK3CA	Afatinib	11	138	0,044719747	-4,9274543	0,230953956	ns
TP53_KRAS	Eltanexor	19	58	0,045206364	-2,3808271	0,23194115	ns
TP53_KRAS	Methotrexate	37	112	0,046286316	-4,4750643	0,235939985	ns
APC_PIK3CA	Trametinib	19	130	0,047328379	-2,1542861	0,23969534	ns
TP53_RAS_BRAFV600E	Idasanutlin	52	97	0,047878381	-0,0017554	0,24092647	ns
APC_ARID1A	Gemcitabine	13	136	0,048348249	-4,1507765	0,241741244	ns
APC_KRAS	Napabucasin	45	104	0,04978349	1,7299344	0,243688257	ns
APC_ARID1A	Carfilzomib	10	76	0,049979375	1,6177482	0,243688257	ns
TP53_ARID1A	Carfilzomib	10	76	0,049979375	1,6177482	0,243688257	ns
APC_RAS_BRAFV600E	Methotrexate	68	81	0,049405232	-3,941071	0,243688257	ns

Supplementary Table 6. Association of drug activities with the primary tumor location

Drug	group1	group2	n1	n2	statistic	Wilcoxon p	p.adj	p.adj.signif (Benjamini-Hochberg)	mean_Left	mean_Right	higher_mean_group
Lapatinib	**Left**	**Right**	**160**	**44**	**5091**	**5,93E-06**	**0,0001**	***	**13,06522**	**7,319388**	**Left**
Afatinib	**Left**	**Right**	**160**	**44**	**4745**	**0,000414**	**0,0052**	**	**12,7612**	**8,14728**	**Left**
Panobinostat	**Left**	**Right**	**160**	**44**	**4530**	**0,0036**	**0,023**	*	**14,86548**	**13,39674**	**Left**
SN-38	**Left**	**Right**	**160**	**44**	**2511**	**0,00364**	**0,023**	*	**28,93043**	**32,77223**	**Right**
TAS-102	**Left**	**Right**	**160**	**44**	**2551**	**0,00519**	**0,026**	*	**6,097738**	**8,544385**	**Right**
Regorafenib	**Left**	**Right**	**160**	**44**	**2633**	**0,0106**	**0,044**	*	**8,703669**	**10,06289**	**Right**
5-FU	Left	Right	160	44	2760	0,029	0,089	ns	10,80552	12,79649	Right
Encorafenib	Left	Right	160	44	2781	0,025	0,089	ns	0,749084	0,477196	Left
Gemcitabine	Left	Right	160	44	2812	0,041	0,103	ns	13,33796	15,63882	Right
Methotrexate	Left	Right	160	44	2805	0,039	0,103	ns	10,75962	13,88649	Right
Idasanutlin	Left	Right	160	44	2911	0,058	0,131	ns	1,878736	7,155347	Right
Luminespib	Left	Right	160	44	2874	0,063	0,131	ns	20,74822	22,30133	Right
Bemcentinib	Left	Right	160	44	3082	0,207	0,398	ns	11,4438	12,21688	Right
AZD7762	Left	Right	160	44	3886	0,292	0,406	ns	19,51256	18,71708	Left
Alisertib	Left	Right	160	44	3145	0,280	0,406	ns	13,91602	15,20912	Right
LGK974	Left	Right	160	44	3901	0,273	0,406	ns	2,303094	2,259266	Left
Napabucasin	Left	Right	160	44	3133	0,264	0,406	ns	16,71614	17,04325	Right
meanDSS_24drugs	Left	Right	160	44	3104	0,231	0,406	ns	12,74492	13,27341	Right
LCL161	Left	Right	160	44	3176	0,322	0,424	ns	9,718157	12,20551	Right
Atorvastatin	Left	Right	160	44	3257	0,449	0,561	ns	14,97121	16,01842	Right
Gedatolisib	Left	Right	160	44	3737	0,533	0,635	ns	12,84916	11,8152	Left
Palbociclib	Left	Right	160	44	3669	0,668	0,759	ns	13,02697	12,54437	Left
Pevonedistat	Left	Right	160	44	3469	0,884	0,921	ns	13,24741	13,18158	Left
Volasertib	Left	Right	160	44	3587	0,848	0,921	ns	19,1398	18,49662	Left
Trametinib	Left	Right	160	44	3500	0,955	0,955	ns	16,33088	16,356	Right

Supplementary Table 7. Correlation of patient age with drug activities (DSS)

Drug	Spearman cor	p_value	adj_p_value (Benjamini-Hochberg)	n
5-FU	**0,284**	**0,001**	**0,024**	**132**
Gemcitabine	0,214	0,014	0,128	132
SN-38	0,205	0,018	0,128	132
Volasertib	0,202	0,021	0,128	132
TAS-102	0,186	0,033	0,149	132
Luminespib	0,183	0,036	0,149	132
AZD7762	0,167	0,055	0,179	132
Alisertib	0,166	0,057	0,179	132
meanDSS_24drugs	0,148	0,090	0,231	132
Lapatinib	-0,147	0,093	0,231	132
Afatinib	-0,143	0,102	0,231	132
Trametinib	0,125	0,155	0,322	132
Regorafenib	0,113	0,197	0,379	132
Bemcentinib	-0,104	0,234	0,418	132
Napabucasin	0,100	0,255	0,426	132
Panobinostat	0,094	0,283	0,437	132
Pevonedistat	0,091	0,297	0,437	132
LGK974	-0,059	0,503	0,666	132
Palbociclib	-0,058	0,506	0,666	132
Atorvastatin	-0,045	0,608	0,760	132
Methotrexate	-0,041	0,640	0,762	132
Encorafenib	0,033	0,710	0,774	132
Gedatolisib	0,033	0,712	0,774	132
LCL161	-0,025	0,773	0,805	132
Idasanutlin	0,012	0,889	0,889	132

Supplementary Table 8. Correlation between the number of liver metastases before surgery and drug activity (DSS)

Drug	Spearman cor	p_value	adj_p_value (Benjamini-Hochberg)	n
SN-38	**-0,2354**	**0,0007**	**0,017**	**205**
Idasanutlin	**-0,2039**	**0,0034**	**0,042**	**205**
TAS-102	-0,1739	0,0126	0,0904	205
Luminespib	-0,1706	0,0145	0,0904	205
Regorafenib	-0,1454	0,0375	0,1877	205
Encorafenib	-0,1342	0,0551	0,1962	205
meanDSS_24drugs	-0,1332	0,0569	0,1962	205
Methotrexate	-0,1253	0,0735	0,1962	205
5-FU	-0,1233	0,0781	0,1962	205
Alisertib	-0,1181	0,0916	0,1962	205
Trametinib	-0,1179	0,0922	0,1962	205
Gemcitabine	-0,1172	0,0942	0,1962	205
Lapatinib	0,0682	0,331	0,5663	205
Panobinostat	0,0678	0,3339	0,5663	205
Volasertib	-0,067	0,3398	0,5663	205
LCL161	-0,0436	0,5349	0,8068	205
Atorvastatin	0,0421	0,5486	0,8068	205
LGK974	-0,0318	0,6511	0,9043	205
Palbociclib	0,0278	0,6922	0,9108	205
Afatinib	0,0145	0,837	0,9979	205
Gedatolisib	-0,0117	0,8679	0,9979	205
Bemcentinib	-0,0081	0,9086	0,9979	205
Pevonedistat	0,0057	0,9355	0,9979	205
AZD7762	-0,0037	0,958	0,9979	205
Napabucasin	-0,0002	0,9982	0,9982	205

Supplementary Table 9. Cox proportional hazard tests of 24 overlapping drugs with overall survival post-liver surgery

Drug DSS	HR	HR 95% CI	p.value	n	nevent	wald.test	adjusted_p.value (Benjamini-Hochberg)
Atorvastatin	**0,92**	(0.87, 0.97)	**0,002**	102	58	9,52	**0,028**
Bemcentinib	**0,87**	(0.80, 0.95)	**0,002**	102	58	9,33	**0,028**
Afatinib	**0,94**	(0.91, 0.98)	**0,003**	102	58	8,6	**0,028**
Lapatinib	**0,96**	(0.92, 0.99)	**0,024**	102	58	5,09	0,134
mean_DSS_24drugs	0,91	(0.82, 1.00)	0,068	102	58	3,34	0,338
Encorafenib	1,13	(0.97, 1.31)	0,113	102	58	2,51	0,433
Regorafenib	1,07	(0.97, 1.18)	0,156	102	58	2,01	0,433
Napabucasin	0,94	(0.87, 1.02)	0,163	102	58	1,94	0,433
SN-38	0,97	(0.93, 1.01)	0,172	102	58	1,86	0,433
Gedatolisib	0,97	(0.93, 1.01)	0,201	102	58	1,63	0,433
Volasertib	0,96	(0.90, 1.02)	0,205	102	58	1,61	0,433
Gemcitabine	0,97	(0.93, 1.02)	0,208	102	58	1,59	0,433
5-FU	0,97	(0.91, 1.03)	0,275	102	58	1,19	0,455
Alisertib	0,98	(0.95, 1.02)	0,286	102	58	1,14	0,455
Panobinostat	0,95	(0.85, 1.05)	0,288	102	58	1,13	0,455
Luminespib	0,97	(0.92, 1.03)	0,302	102	58	1,07	0,455
LGK974	0,93	(0.81, 1.07)	0,321	102	58	0,99	0,455
AZD7762	0,97	(0.92, 1.03)	0,328	102	58	0,96	0,455
Methotrexate	1,02	(0.98, 1.06)	0,354	102	58	0,86	0,466
Pevonedistat	0,98	(0.93, 1.04)	0,489	102	58	0,48	0,605
Palbociclib	0,98	(0.94, 1.03)	0,508	102	58	0,44	0,605
TAS-102	0,99	(0.93, 1.05)	0,738	102	58	0,11	0,839
Trametinib	1,01	(0.96, 1.06)	0,809	102	58	0,06	0,880
LCL161	1,00	(0.97, 1.04)	0,850	102	58	0,04	0,885
Idasanutlin	1,00	(0.97, 1.03)	0,935	102	58	0,01	0,935

median DSS of drugs used for multi-lesion PDOs
HR - Hazard Ratio
CI - Confidence Intervals

Supplementary Table 10: Wilcoxon tests of PDO morphologies with drug sensitivities

Drug	group1	group2	n1	n2	statistic	df	p	p.adj (Benjamini-Hochberg)	#p.adj.signif
Lapatinib	cystic	rest	59	152	5,20	112,41	9,1E-07	2,3E-05	****
Afatinib	cystic	rest	59	152	3,58	114,09	5,0E-04	2,8E-03	**
Alisertib	cystic	rest	59	152	3,55	110,75	5,7E-04	2,8E-03	**
TAS-102	cystic	rest	59	152	3,66	92,05	4,2E-04	2,8E-03	**
mean_DSS_24drugs	cystic	rest	59	152	3,60	101,97	4,9E-04	2,8E-03	**
Volasertib	cystic	rest	59	152	3,18	121,25	1,9E-03	7,8E-03	**
5-FU	cystic	rest	59	152	3,15	90,23	2,2E-03	7,8E-03	**
Gemcitabine	cystic	rest	59	152	3,01	99,05	3,3E-03	1,0E-02	*
SN-38	cystic	rest	59	152	2,68	119,68	8,5E-03	2,4E-02	*
Panobinostat	cystic	rest	59	152	2,27	111,53	2,5E-02	6,4E-02	ns
Pevonedistat	cystic	rest	59	152	2,21	116,16	2,9E-02	6,5E-02	ns
AZD7762	cystic	rest	59	152	1,87	114,08	6,4E-02	1,3E-01	ns
LCL161	cystic	rest	59	152	-1,83	123,34	7,0E-02	1,3E-01	ns
Atorvastatin	cystic	rest	59	152	1,74	102,87	8,4E-02	1,5E-01	ns
Gedatolisib	cystic	rest	59	152	1,69	97,69	9,4E-02	1,6E-01	ns
Encorafenib	cystic	rest	59	152	-1,32	192,13	1,9E-01	2,8E-01	ns
Luminespib	cystic	rest	59	152	1,31	98,19	1,9E-01	2,8E-01	ns
Bemcentinib	cystic	rest	59	152	-1,17	88,97	2,5E-01	3,4E-01	ns
Idasanutlin	cystic	rest	59	152	1,09	84,36	2,8E-01	3,7E-01	ns
Methotrexate	cystic	rest	59	152	0,89	119,76	3,8E-01	4,7E-01	ns
Napabucasin	cystic	rest	59	152	0,50	127,15	6,2E-01	7,4E-01	ns
Palbociclib	cystic	rest	59	152	0,43	100,77	6,7E-01	7,6E-01	ns
LGK974	cystic	rest	59	152	-0,08	93,90	9,4E-01	9,8E-01	ns
Trametinib	cystic	rest	59	152	-0,09	106,25	9,3E-01	9,8E-01	ns
Regorafenib	cystic	rest	59	152	-0,01	104,40	9,9E-01	9,9E-01	ns
Lapatinib	rest	solid	132	79	4,98	173,99	1,6E-06	3,9E-05	****
5-FU	rest	solid	132	79	4,55	185,88	9,7E-06	1,2E-04	***
mean_DSS_24drugs	rest	solid	132	79	4,47	168,79	1,4E-05	1,2E-04	***
Volasertib	rest	solid	132	79	4,26	158,23	3,5E-05	2,2E-04	***
Afatinib	rest	solid	132	79	3,81	164,52	2,0E-04	9,8E-04	***
Alisertib	rest	solid	132	79	3,51	172,86	5,8E-04	2,4E-03	**
TAS-102	rest	solid	132	79	3,31	183,82	1,1E-03	4,1E-03	**
Methotrexate	rest	solid	132	79	3,05	147,44	2,7E-03	8,5E-03	**
Pevonedistat	rest	solid	132	79	3,01	139,56	3,1E-03	8,5E-03	**
LGK974	rest	solid	132	79	2,95	196,89	3,5E-03	8,9E-03	**
Atorvastatin	rest	solid	132	79	2,75	160,67	6,7E-03	1,5E-02	*
Idasanutlin	rest	solid	132	79	2,70	208,93	7,6E-03	1,6E-02	*
Gemcitabine	rest	solid	132	79	2,30	172,48	2,3E-02	4,4E-02	*
SN-38	rest	solid	132	79	2,21	154,79	2,8E-02	5,1E-02	ns
Panobinostat	rest	solid	132	79	2,15	146,98	3,3E-02	5,6E-02	ns
Luminespib	rest	solid	132	79	1,73	179,80	8,6E-02	1,3E-01	ns
AZD7762	rest	solid	132	79	1,67	160,46	9,8E-02	1,4E-01	ns
Encorafenib	rest	solid	132	79	-1,65	87,62	1,0E-01	1,4E-01	ns
Bemcentinib	rest	solid	132	79	-1,37	196,98	1,7E-01	2,3E-01	ns
LCL161	rest	solid	132	79	-1,21	165,40	2,3E-01	2,9E-01	ns
Gedatolisib	rest	solid	132	79	1,02	159,59	3,1E-01	3,7E-01	ns
Napabucasin	rest	solid	132	79	0,64	153,66	5,3E-01	6,0E-01	ns
Trametinib	rest	solid	132	79	0,41	154,14	6,9E-01	7,4E-01	ns
Palbociclib	rest	solid	132	79	-0,33	171,82	7,4E-01	7,7E-01	ns
Regorafenib	rest	solid	132	79	0,03	133,07	9,8E-01	9,8E-01	ns
LGK974	mixed	rest	73	138	2,82	136,78	5,5E-03	1,4E-01	ns
Methotrexate	mixed	rest	73	138	2,42	155,22	1,7E-02	2,1E-01	ns
5-FU	mixed	rest	73	138	1,14	162,81	2,6E-01	8,0E-01	ns
Atorvastatin	mixed	rest	73	138	1,14	157,96	2,6E-01	8,0E-01	ns
Encorafenib	mixed	rest	73	138	-1,47	208,76	1,4E-01	8,0E-01	ns
Idasanutlin	mixed	rest	73	138	1,19	130,85	2,4E-01	8,0E-01	ns
Pevonedistat	mixed	rest	73	138	1,24	170,25	2,2E-01	8,0E-01	ns
Volasertib	mixed	rest	73	138	1,46	148,26	1,5E-01	8,0E-01	ns
mean_DSS_24drugs	mixed	rest	73	138	0,99	160,75	3,2E-01	9,0E-01	ns
AZD7762	mixed	rest	73	138	0,01	143,31	9,9E-01	9,9E-01	ns
Afatinib	mixed	rest	73	138	0,58	148,16	5,6E-01	9,9E-01	ns
Alisertib	mixed	rest	73	138	0,23	142,72	8,2E-01	9,9E-01	ns
Bemcentinib	mixed	rest	73	138	-0,09	140,56	9,3E-01	9,9E-01	ns
Gedatolisib	mixed	rest	73	138	-0,62	164,65	5,3E-01	9,9E-01	ns
Gemcitabine	mixed	rest	73	138	-0,61	153,39	5,5E-01	9,9E-01	ns
LCL161	mixed	rest	73	138	0,36	131,39	7,2E-01	9,9E-01	ns
Lapatinib	mixed	rest	73	138	0,21	151,22	8,3E-01	9,9E-01	ns
Luminespib	mixed	rest	73	138	0,41	142,39	6,8E-01	9,9E-01	ns
Napabucasin	mixed	rest	73	138	0,22	137,50	8,2E-01	9,9E-01	ns
Palbociclib	mixed	rest	73	138	-0,74	144,53	4,6E-01	9,9E-01	ns
Panobinostat	mixed	rest	73	138	0,18	163,17	8,5E-01	9,9E-01	ns
Regorafenib	mixed	rest	73	138	0,04	189,49	9,7E-01	9,9E-01	ns
SN-38	mixed	rest	73	138	-0,08	146,85	9,4E-01	9,9E-01	ns
TAS-102	mixed	rest	73	138	-0,43	158,58	6,7E-01	9,9E-01	ns
Trametinib	mixed	rest	73	138	0,51	155,93	6,1E-01	9,9E-01	ns

Supplementary Table 11. max DSS inter metastatic heterogeneity based on Euclidean distance in assotioation with clinical variables

Variable	Test	Software	Package	Version	Significance	P test	n events analyzed
Overall survival after liver surgery	Cox proportional hazard	R 4.2.1	survival	3.5-5	p=0.39	Log rank and Wald test	62
Sex	Wilxocon rank sum test	R 4.2.1	gtsummary	1.7.0	p=0.25	two-tailed	64
Neoadjuvant systemic therapy	Wilxocon rank sum test	R 4.2.1	gtsummary	1.7.0	p=0.25	two-tailed	62
Neoadjuvant systemic therapy cycles (dichotomized ad >4 or <4)	Wilxocon rank sum test	R 4.2.1	gtsummary	1.7.0	p=0.27	two-tailed	52
Primary tumor location right or left colon	Wilxocon rank sum test	R 4.2.1	gtsummary	1.7.0	p=0.08	two-tailed	62
Primary tumor differentiation	Kruskal-Wallis	R 4.2.1	gtsummary	1.7.0	p=0.38	two-tailed	55
Patient age	Spearman correlation	R 4.2.1	base	R 4.2.1	p=0.63	two-tailed	38
Number of lesions before liver surgery	Spearman correlation	R 4.2.1	base	R 4.2.1	p=0.4	two-tailed	63
Size of the largest metastasis before liver surgery	Spearman correlation	R 4.2.1	base	R 4.2.1	p=0.88	two-tailed	63

Supplementary Table 12. Customized gene panel for DNA sequencing

Gene	Coverage	Mutation types analyzed
APC	All coding regions	SNVs, indels
ARID1A	All coding regions	SNVs, indels
BRAF	All coding regions	SNVs, indels
CCND2	All coding regions, selected intronic	SNVs, indels, amplifications
CTNNB1	All coding regions	SNVs, indels
EGFR	All coding regions, selected intronic	SNVs, indels, amplifications
ERBB2	All coding regions, selected intronic	SNVs, indels, amplifications
FBXW7	All coding regions	SNVs, indels
JAK1	All coding regions	SNVs, indels
KRAS	All coding regions	SNVs, indels
MDM2	All coding regions, selected intronic	SNVs, indels, amplifications
MYC	All coding regions, selected intronic	SNVs, indels, amplifications
NF1	All coding regions	SNVs, indels
NRAS	All coding regions	SNVs, indels
PIK3CA	All coding regions	SNVs, indels
POLE	Mutation hotspots (S459F; A456P; M444K; P436R; L424I; V411L; D368Y; F367S; S297F; M295R, P286R)	SNVs, indels
PTEN	All coding regions	SNVs, indels
SMAD2	All coding regions	SNVs, indels
SMAD4	All coding regions	SNVs, indels
TP53	All coding regions	SNVs, indels

Supplementary Table 13. Immunohistochemistry staining procedure

	Deparaffinization/ Antigen retrieval	Ab 1 / Fluor	Ab-removal	Ab 2 / Fluor	Ab-removal	Ab 3 / Fluor	Ab-removal	Ab 4 / Fluor	Ab-removal
Stain 1	3-in-1 high pH buffer (DAKO)	Anti-KRT20 1:1000, Opal 520 1:100	High pH buffer (Akoya)	Anti-CDX2 1:400, Opal 570 1:100	High pH buffer (Akoya)	Anti-KRT7 1:400, Opal 620 1:150	Low pH buffer (Akoya)	Anti-CDH1 1:10000, Opal 690 1:100	Low pH buffer (Akoya)
Stain 2	3-in-1 high pH buffer (DAKO)	Anti-KRT20 1:400, Opal 620 1:100	High pH buffer (Akoya)	Anti-UGT1A 1:300, Opal 690 1:100	High pH buffer (Akoya)	Anti-ABCG2 1:50, Opal 520 1:75	High pH buffer (Akoya)	-	-
Stain 3	3-in-1 high pH buffer (DAKO)	Anti-KI67 undiluted, Opal 520 1:100	High pH buffer (Akoya)	Anti-UGT1A 1:500, Opal 620 1:125	High pH buffer (Akoya)	Anti-HSF1 1:100, Opal 690 1:100	High pH buffer (Akoya)	-	-
Stain 4	3-in-1 high pH buffer (DAKO)	Anti-RIPK1 1:50, Opal 520 1:75	High pH buffer (Akoya)	Anti-RCC2 1:100, Opal 570 1:100	High pH buffer (Akoya)	Anti-TP53 1:12, Opal 690 1:100	High pH buffer (Akoya)	-	-
Stain 5	3-in-1 high pH buffer (DAKO)	Anti-CFTR 1:2000, Opal 620 1:100	High pH buffer (Akoya)	Anti-ABCB1 1:100, Opal 690 1:100	High pH buffer (Akoya)	Anti-ERBB2 1:500, Opal 520 1:100	High pH buffer (Akoya)	-	-