

Supplementary Tables

Supplementary Table 1. Targeted drug screen candidates for PI3K/Akt combination treatments and respective inhibited pathways.

Inhibitor	Target	Inhibitor	Target
Omipalisib	PI3K α / β / δ / γ	Mebendazole	Tubulin depolymerization
		Ibrutinib	Brutons tyrosine kinase BTK & ITK
		Crizotinib	Multi-tyrosine kinase, c-MET
		PF-3758309	PAK4
		KPT-9274	PAK4 and NAMPT
		(-)- β -Hydrastine	PAK4
Pictilisib	PI3K α / δ	PF-3758309	PAK4
Buparlisib	PI3K α / β / δ / γ	Danuserib	Aurora-A/B/C Kinase
		Nintedamib	WGFR-1/2/3
		Crizotinib	Multi-tyrosine kinase, c-MET
		PF-3758309	PAK4
		KPT-9274	PAK4 and NAMPT
		(-)- β -Hydrastine	PAK4

Supplementary Table 2. EC50 drug concentrations for human (HS01, HS02/HS03) and mouse (MS01) MD-SC lines when drugs are delivered as monotherapies.

Inhibitor	EC50 HS01	EC50 HS02/HS03	EC50 MS01
Omipalisib	2.02 nM	26.8 nM	7.01 nM
Pictilisib	> 10 μ M	> 10 μ M	1462 nM
Buparlisib	1905 nM	2098 nM	870 nM
Mebendazole	2068 nM	774 nM	195 nM
Ibrutinib	7812 nM	11.7 μ M	7045 nM
Crizotinib	1536 nM	621 nM	
PF-3758309	2009 nM	1765 nM	207 nM
KPT-9274	> 10 μ M	691 nM	
(-)- β -Hydrastine	> 10 μ M	384 nM	
Danuserib	1527 nM	15.6 μ M	9071 nM
Nintedamib	5352 nM	> 10 μ M	3121 nM

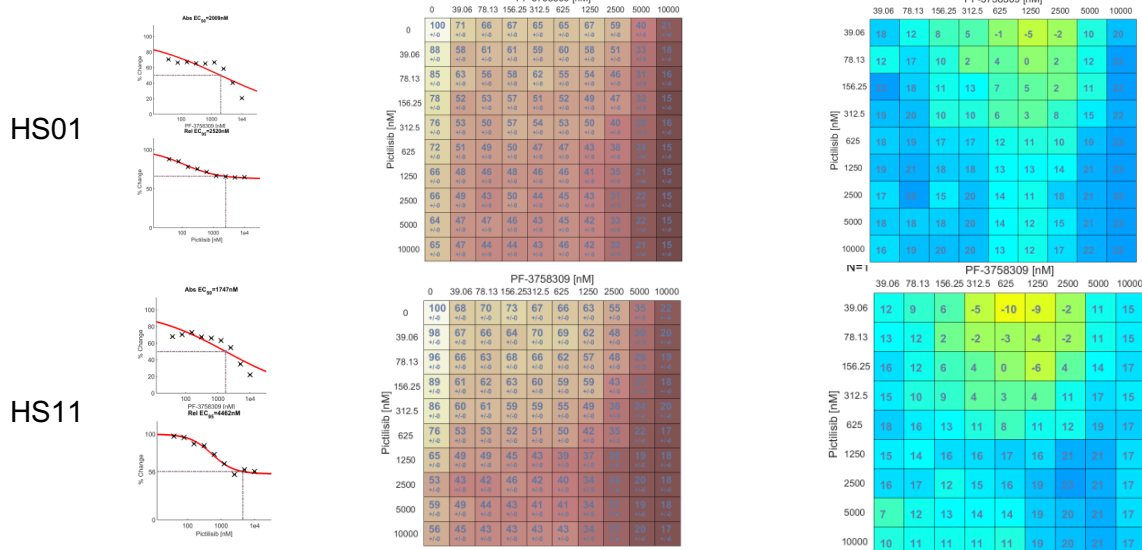
Supplementary Table 3. Loewe synergy scores (sum_syn_ant) for drug combinations in human MD-SC lines (HS01, HS03) and mouse MD-SC lines (MS01). Drugs were tested in 10x10 combination matrices.

Inhibitor	Inhibitor	Loewe Synergy Score (HS01)	Loewe Synergy Score (HS03)	Loewe Synergy Score (MS01)
Omipalisib	Mebendazole	16.49	3.25	2.53
	Ibrutinib	12.65	1.02	3.27
	Crizotinib	12.12	7.02	
	PF-3758309	73.55	12.12	
	KPT-9274	1.00	6.89	
	(-)- β -Hydrastine	8.42	43.60	
Pictilisib	PF-3758309	79.75	58.85	93.12
Buparlisib	Danusertib	28.4	12.06	1.99
	Nintedanib	4.27	43.69	7.76
	Crizotinib	9.44	4.79	
	PF-3758309	36.66	9.44	
	KPT-9274	33.47	28.06	
	(-)- β -Hydrastine	1.46	9.44	

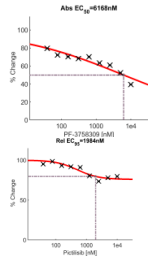
Supplementary Figures

Supplementary Figure S1

Pictilisib vs. PF-3758309

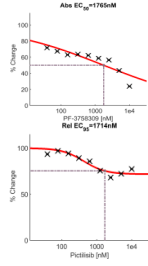


HS04.3



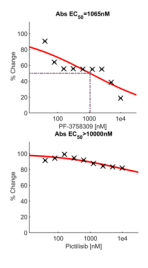
		PF-3758309 [nM]											
		0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000		
Pictilisib [nM]	0	100	80	72	70	68	71	63	61	51	52	37	19
	39.06	95	75	71	73	73	71	68	64	54	47	37	20
	78.13	98	80	73	72	69	69	61	61	49	39	30	20
	156.25	93	78	71	71	67	62	64	59	45	35	26	16
	312.5	92	72	67	64	67	63	59	59	44	34	25	16
	625	91	68	66	62	64	62	59	53	43	38	28	18
	1250	80	63	61	62	61	58	58	52	47	41	31	21
	2500	73	60	60	60	58	59	57	50	44	38	28	18
	5000	78	64	61	57	59	57	54	50	42	42	32	22
	10000	80	63	63	58	59	60	58	54	43	41	31	21

HS03



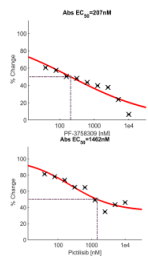
		PF-3758309 [nM]											
		0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000		
Pictilisib [nM]	0	100	72	67	63	64	62	59	56	44	36	26	16
	39.06	93	67	62	62	62	58	62	54	41	35	25	15
	78.13	97	66	61	60	58	57	55	51	39	35	25	15
	156.25	94	62	59	58	56	55	52	46	36	28	18	8
	312.5	89	59	55	53	54	52	50	45	34	25	17	7
	625	86	55	52	52	51	51	48	42	32	24	16	6
	1250	76	52	50	49	48	48	44	42	31	23	15	5
	2500	68	48	45	48	44	44	43	37	27	19	12	5
	5000	72	51	48	48	48	47	45	38	30	21	13	5
	10000	77	50	47	47	48	48	45	41	31	24	15	5

HS12



		PF-3758309 [nM]											
		0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000		
Pictilisib [nM]	0	100	90	64	56	56	55	55	55	39	19	10	5
	39.06	91	62	57	59	56	56	52	53	35	18	8	4
	78.13	94	59	57	55	53	51	50	50	31	16	7	4
	156.25	99	57	54	48	45	51	50	45	25	11	5	3
	312.5	94	57	59	49	42	43	36	36	16	16	8	4
	625	92	57	57	49	44	49	41	37	28	17	10	5
	1250	88	55	51	49	45	42	40	37	27	17	10	5
	2500	84	53	51	55	55	43	44	35	25	18	10	5
	5000	83	51	41	46	40	39	38	36	25	18	10	5
	10000	82	49	47	48	46	45	37	33	21	19	10	5

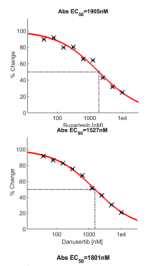
MS01



		PF-3758309 [nM]											
		0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000		
Pictilisib [nM]	0	100	61	57	50	48	43	46	38	28	7	5	4
	39.06	91	48	49	44	44	44	41	31	19	6	4	3
	78.13	78	42	38	40	36	34	31	21	14	6	4	3
	156.25	74	38	35	35	30	28	28	12	5	3	2	1
	312.5	85	35	31	31	25	22	20	9	5	3	2	1
	625	85	35	31	31	22	20	16	7	5	3	2	1
	1250	69	30	28	22	20	18	12	6	5	3	2	1
	2500	63	25	23	19	20	19	15	10	6	6	4	3
	5000	63	25	21	21	21	18	13	7	6	4	3	2
	10000	63	23	20	20	21	21	18	13	6	5	4	3

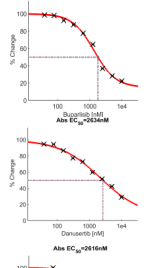
Buparlisib vs. Danusertib

HS01



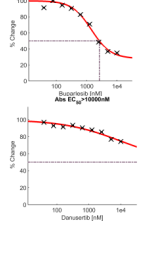
		Danusertib [nM]											
		0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000		
Buparlisib [nM]	0	100	91	87	83	76	67	51	43	31	21	14	8
	39.06	90	85	83	77	74	63	53	45	30	20	14	8
	78.13	92	87	84	76	65	53	48	39	25	15	9	5
	156.25	80	81	75	69	62	55	47	40	28	19	11	6
	312.5	80	73	74	65	56	49	43	39	27	18	10	6
	625	66	65	64	56	53	46	39	31	23	16	9	5
	1250	64	59	49	49	47	40	34	28	19	14	8	5
	2500	45	37	41	41	38	34	31	25	15	12	7	4
	5000	34	30	28	28	26	23	20	13	11	7	4	3
	10000	31	28	28	28	27	25	20	15	11	11	7	4

HS11

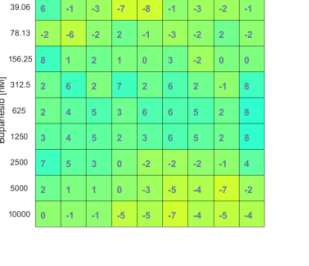
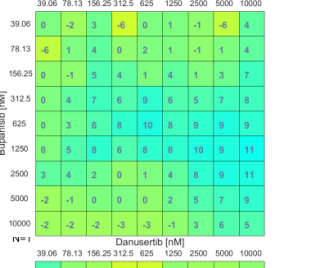
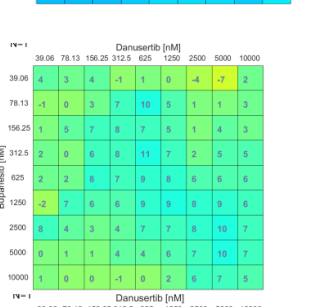
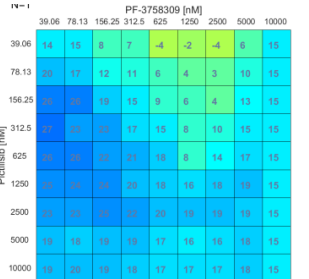
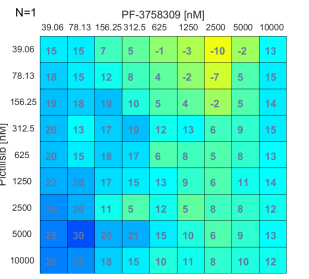
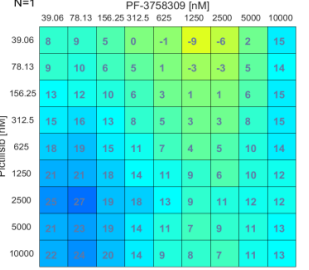
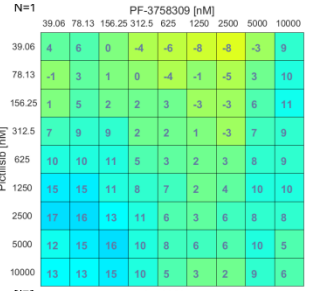


		Danusertib [nM]											
		0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000		
Buparlisib [nM]	0	100	95	94	87	77	73	60	52	37	25	16	9
	39.06	99	93	92	83	86	71	60	51	45	27	16	9
	78.13	98	98	89	81	79	69	60	51	38	25	16	9
	156.25	92	91	89	78	74	68	56	49	36	23	13	8
	312.5	87	85	79	72	68	58	52	43	30	22	13	8
	625	78	75	71	65	59	51	48	43	31	23	13	8
	1250	65	59	53	49	50	44	39	35	23	16	9	5
	2500	53	48	43	39	41	36	33	28	20	14	8	5
	5000	43	39	35	31	30	27	23	21	17	13	8	5
	10000	40	35	32	28	28	24	21	18	14	14	8	5

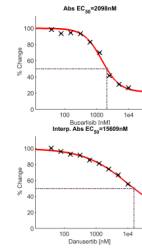
HS04.3



		Danusertib [nM]											
		0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000		
Buparlisib [nM]	0	100	97	93	91	93	90	88	85	77	74	61	41
	39.06	91	91	97	96	99	97	87	85	81	76	61	41
	78.13	100	98	100	95	89	89	89	84	76	76	61	41
	156.25	95	87	83	90	89	88	88	83	76	74	61	41
	312.5	90	88	84	88	81	83	77	77	78	65	51	31
	625	78	75	71	65	59	51	48	43	31	23	13	8
	1250	71	64	64	63	65	63	61	61	63	55	41	21
	2500	46	44	46	46	50	53	53	52	52	47	31	21
	5000	37	37	35	35	32	32	44	43	46	41	26	16
	10000	35	33	33	33	32	32	40	37	38	31	21	16

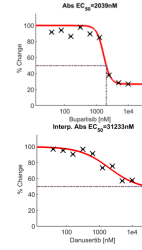


HS03



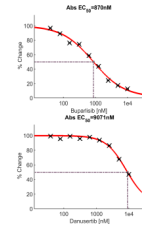
Buparlisib [nM]	Danuserib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	100	100	96	93	91	85	81	74	67	55	40
39.06	98	96	91	96	97	87	80	74	66	56	40
78.13	94	97	96	96	83	77	71	65	56	45	30
156.25	95	89	85	85	88	81	71	67	60	52	35
312.5	93	92	89	84	83	73	70	67	58	47	30
625	83	83	79	74	76	70	63	61	52	41	25
1250	70	68	59	57	68	57	55	54	48	38	20
2500	42	42	43	44	40	47	46	43	37	27	15
5000	12	10	14	14	16	16	15	13	11	9	5
10000	1	1	1	1	1	1	1	1	1	1	1

HS12



Buparlisib [nM]	Danuserib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	100	97	95	91	97	91	73	76	67	58	40
39.06	92	92	85	86	87	75	71	64	48	35	20
78.13	94	99	96	88	79	76	71	68	53	50	30
156.25	87	79	79	78	88	71	69	64	52	43	25
312.5	98	87	82	86	75	70	77	57	52	43	25
625	90	80	69	71	67	74	69	56	45	40	20
1250	85	68	65	60	53	54	61	49	39	33	15
2500	59	52	55	42	46	49	47	41	35	25	10
5000	18	15	13	13	13	13	13	11	9	7	5
10000	1	1	1	1	1	1	1	1	1	1	1

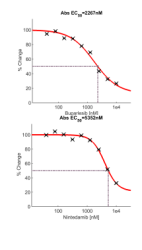
MS01



Buparlisib [nM]	Danuserib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	100	99	96	99	96	98	94	86	68	47	25
39.06	97	93	92	100	97	104	92	81	74	48	25
78.13	89	92	92	90	92	93	84	74	65	48	25
156.25	76	72	77	78	89	91	84	76	61	46	20
312.5	74	75	78	75	77	87	81	68	48	37	15
625	59	60	55	62	64	61	61	49	45	30	10
1250	44	43	39	37	39	39	38	31	27	19	5
2500	18	15	15	12	14	15	15	10	14	10	5
5000	11	10	10	10	10	15	15	15	13	13	5
10000	1	1	1	1	1	1	1	1	1	1	1

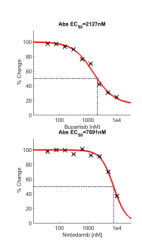
Buparlisib vs. Nintedanib

HS01



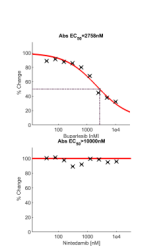
Buparlisib [nM]	Nintedanib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	100	100	100	100	93	99	92	79	52	26	10
39.06	95	104	96	98	95	92	83	47	31	20	10
78.13	98	95	99	94	87	91	87	78	42	26	10
156.25	89	90	95	98	89	94	80	76	61	38	15
312.5	88	91	82	85	84	84	79	73	50	30	10
625	78	81	77	73	71	70	69	65	51	30	10
1250	69	67	64	61	61	60	60	51	41	21	10
2500	43	46	41	45	46	56	41	37	13	13	5
5000	18	18	13	13	13	13	13	13	14	14	5
10000	1	1	1	1	1	1	1	1	1	1	1

HS11



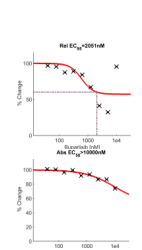
Buparlisib [nM]	Nintedanib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	100	98	100	100	94	101	93	91	70	37	10
39.06	98	94	98	100	96	94	90	86	63	36	10
78.13	97	97	98	96	98	94	89	83	63	31	10
156.25	93	99	96	97	94	94	85	75	68	38	10
312.5	90	93	89	88	85	83	82	74	50	31	10
625	76	80	84	77	72	73	66	56	49	30	10
1250	70	65	65	66	61	60	50	36	31	21	10
2500	42	41	40	41	40	58	31	29	18	15	5
5000	18	17	15	15	15	15	15	15	15	15	5
10000	1	1	1	1	1	1	1	1	1	1	1

HS04.3



Buparlisib [nM]	Nintedanib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	100	100	102	98	89	92	100	99	95	96	10
39.06	89	92	91	96	99	101	95	94	93	83	10
78.13	91	93	96	98	99	95	97	93	92	96	10
156.25	88	88	93	90	94	93	96	90	93	90	10
312.5	86	86	89	93	90	88	90	89	90	88	10
625	80	83	79	81	80	80	81	81	81	76	10
1250	68	71	71	72	66	70	68	67	69	63	10
2500	45	49	47	46	47	58	47	40	51	46	10
5000	18	18	18	17	17	17	18	18	18	18	10
10000	1	1	1	1	1	1	1	1	1	1	1

HS03



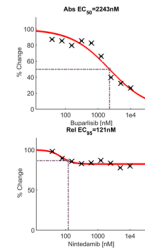
Buparlisib [nM]	Nintedanib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	100	101	100	96	100	92	94	87	87	74	10
39.06	97	93	95	97	94	96	92	90	83	66	10
78.13	96	96	95	97	89	94	93	89	82	72	10
156.25	87	89	94	91	90	91	89	84	85	71	10
312.5	89	92	88	93	89	86	85	80	75	66	10
625	84	86	84	83	80	81	77	76	73	61	10
1250	67	66	67	69	67	66	63	60	57	49	10
2500	41	42	44	43	41	44	41	41	40	36	10
5000	18	18	18	18	18	18	18	18	18	18	10
10000	1	1	1	1	1	1	1	1	1	1	1

Buparlisib [nM]	Danuserib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	1	4	-2	-7	-1	0	-1	-1	0	0	0
39.06	1	-1	3	1	3	3	2	2	1	1	0
78.13	6	8	6	0	3	8	5	4	3	3	0
156.25	0	2	4	3	9	7	3	4	6	6	0
312.5	6	3	6	3	5	6	5	7	16	16	0
625	-2	6	6	3	5	5	2	4	7	7	0
1250	3	2	1	-1	-2	-2	0	1	8	8	0
2500	-1	-1	-2	-3	-4	-4	-2	0	4	4	0
5000	2	-3	-4	-3	-6	-2	-3	-3	3	3	0

Buparlisib [nM]	Danuserib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	7	6	11	6	0	3	-1	-2	8	8	0
39.06	0	1	7	13	10	7	2	8	6	6	0
78.13	19	16	17	3	14	9	6	9	12	12	0
156.25	11	15	9	15	16	-1	11	8	12	12	0
312.5	15	7	20	16	6	3	9	13	13	13	0
625	10	14	16	20	14	2	8	16	16	16	0
1250	5	0	-3	-7	-10	-7	-2	3	8	8	0
2500	-4	-5	-2	-5	-6	-5	-4	1	2	2	0
5000	2	1	-3	2	1	2	2	3	4	4	0
10000	-3	-2	-2	-2	-3	-1	-1	0	1	1	0

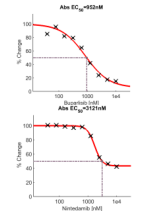
Buparlisib [nM]	Danuserib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	10000
0	1	2	-6	-4	-13	-4	-1	-8	0	0	0
39.06	-2	-3	-1	-4	-7	-1	2	-2	5	5	0
78.13	10	5	3	-7	-10	-4	-4	3	5	5	0
156.25	-4	-7	-4	-7	-2	5	4	6	8	8	0
312.5	-3	2	-6	-7	-6	-8	1	-1	7	7	0
625	-1	3	6	2	2	4	7	7	9		

HS12



	Nintedanib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	98	89	86	83	84	87	83	78	80	
39.06	87	96	94	88	84	93	99	93	87	81	
78.13	85	85	85	85	85	86	88	82	77	79	
156.25	80	99	96	89	83	84	87	84	83	75	
312.5	85	85	86	83	83	81	79	76	75	70	
625	83	90	86	79	82	81	88	79	72	63	
1250	66	66	66	64	64	64	64	63	61	61	
2500	40	45	42	40	33	40	37	41	42	39	
5000	15	15	15	15	15	15	15	15	15	15	
10000	10	10	10	10	10	10	10	10	10	10	

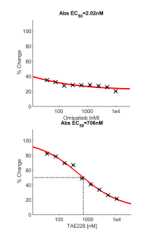
MS01



	Nintedanib [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	101	101	99	97	98	86	55	46	42	
39.06	85	103	97	93	89	89	64	52	49	43	
78.13	96	99	100	92	90	89	75	55	47	43	
156.25	82	92	84	86	89	83	69	57	46	39	
312.5	79	84	78	75	70	66	56	45	38	50	
625	65	65	64	61	52	55	56	41	35	31	
1250	42	38	39	37	42	39	39	30	23	24	
2500	22	22	22	20	20	21	16	17	17	17	
5000	18	16	16	16	15	14	14	12	12	10	
10000	15	16	15	13	13	12	11	10	9	7	

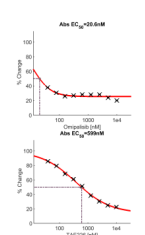
Ompalisib vs. TAE226

HS01



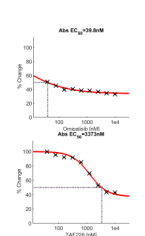
	TAE226 [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	82	79	70	67	49	41	34	26	22	
39.06	81	74	70	65	55	45	33	21	17	15	
78.13	81	69	65	55	45	35	24	12	11	11	
156.25	71	59	54	45	35	25	22	21	18	15	
312.5	60	56	50	42	35	25	20	15	13	15	
625	38	47	40	30	25	20	13	11	14	14	
1250	30	35	30	25	20	15	12	14	14	14	
2500	17	24	20	15	15	12	10	14	12	13	
5000	10	22	21	21	20	16	14	13	13	13	
10000	10	15	17	15	15	15	14	14	14	14	

HS11



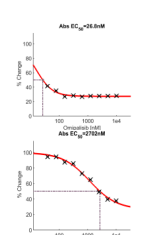
	TAE226 [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	86	79	68	61	51	38	26	16	15	
39.06	81	74	65	55	45	35	24	12	11	11	
78.13	81	69	65	55	45	35	24	12	11	11	
156.25	69	59	54	45	35	25	22	21	22	17	
312.5	57	49	45	35	25	20	15	13	15	15	
625	38	47	40	30	25	20	13	11	14	14	
1250	30	35	30	25	20	15	12	14	14	14	
2500	17	24	20	15	15	12	10	14	12	13	
5000	10	22	21	21	20	16	14	13	13	13	
10000	10	15	17	15	15	15	14	14	14	14	

HS04.3



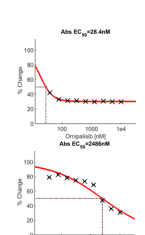
	TAE226 [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	100	95	92	85	70	53	43	43	43	
39.06	81	89	89	89	87	84	42	32	37	37	
78.13	86	40	45	47	42	43	39	39	40	40	
156.25	80	41	43	42	38	37	31	36	35	37	
312.5	61	39	40	38	38	37	37	36	36	36	
625	39	37	37	37	37	37	34	34	34	34	
1250	30	30	31	30	30	30	28	28	28	28	
2500	27	30	30	31	30	30	28	28	28	28	
5000	28	30	30	30	30	30	28	28	28	28	
10000	30	30	30	30	30	30	28	28	28	28	

HS03

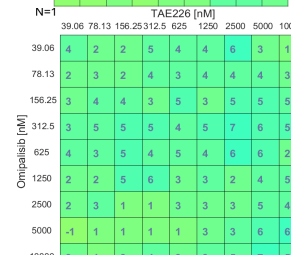
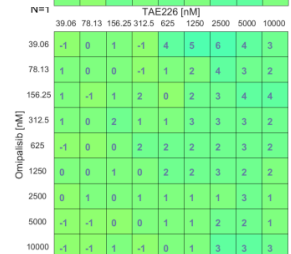
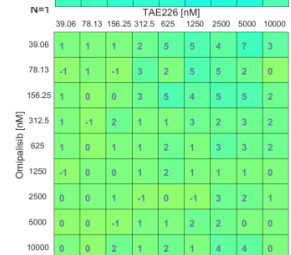
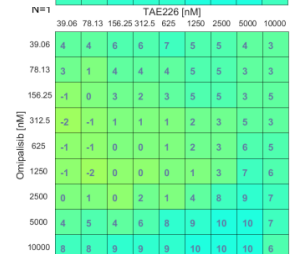
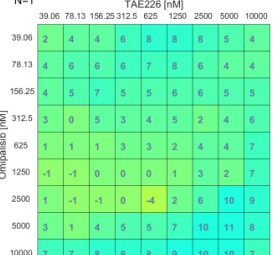
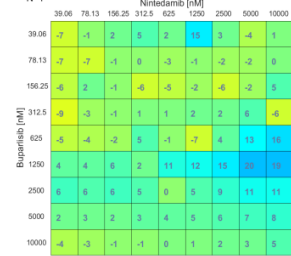
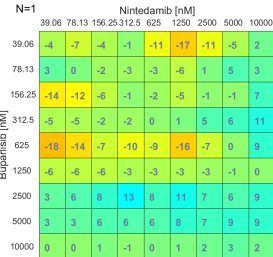


	TAE226 [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	95	95	87	86	73	65	49	46	39	
39.06	85	42	41	40	42	38	35	31	31	31	
78.13	81	32	31	31	34	31	31	30	30	30	
156.25	76	30	30	30	30	30	28	28	28	28	
312.5	61	30	30	30	30	30	28	28	28	28	
625	39	37	37	37	37	37	34	34	34	34	
1250	30	30	30	30	30	30	28	28	28	28	
2500	28	30	30	31	30	30	28	28	28	28	
5000	28	30	30	30	30	30	28	28	28	28	
10000	30	30	30	30	30	30	28	28	28	28	

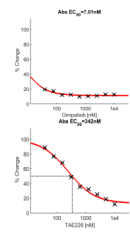
HS12



	TAE226 [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	79	83	78	75	73	69	47	30	25	
39.06	82	30	30	30	30	30	30	28	28	28	
78.13	81	30	30	30	30	30	30	28	28	28	
156.25	67	30	30	30	30	30	30	28	28	28	
312.5	61	30	30	30	30	30	30	28	28	28	
625	39	37	37	37	37	37	34	34	34	34	
1250	30	30	30	30	30	30	28	28	28	28	
2500	27	30	30	30	30	30	28	28	28	28	
5000	28	30	30	30	30	30	28	28	28	28	
10000	30	30	30	30	30	30	28	28	28	28	



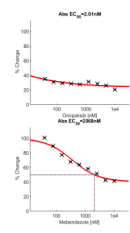
MS01



Ompalsib [nM]	TAE226 [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	89	77	68	49	38	33	33	19	12	
39.06	77	15	14	13	12	12	11	10	10	8	
78.13	52	11	11	10	10	9	10	9	8	7	
156.25	42	11	11	10	10	9	9	9	8	7	
312.5	33	11	11	10	10	9	9	9	8	7	
625	10	9	9	8	8	8	8	7	7	7	
1250	11	11	10	10	10	10	10	9	8	8	
2500	11	10	10	10	10	9	11	10	9	7	
5000	10	13	12	12	12	13	13	12	11	9	
10000	13	12	12	12	13	12	13	11	10	9	

Ompalsib [nM]	TAE226 [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	2	4	5	5	5	5	5	7			
39.06	1	2	3	3	3	4	5	4	6		
78.13	3	3	3	3	4	4	5	5	6		
156.25	2	2	3	2	3	3	3	4	5		
312.5	3	3	3	4	4	4	4	4	5		
625	1	2	2	1	1	2	3	3	4		
1250	1	1	1	1	1	1	1	2	4		
2500	-2	-1	-1	-1	-2	-1	-1	1	2		
5000	-2	-1	0	-2	0	-1	1	1	3		
10000	-1	-1	0	-2	0	-1	1	1	3		

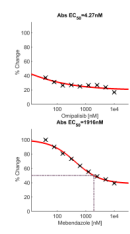
HS01



Ompalsib [nM]	Mebendazole [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	101	89	77	68	54	55	49	45	41	
39.06	77	77	68	54	54	49	45	45	41	37	
78.13	52	49	49	44	44	44	44	44	44	41	
156.25	42	49	49	44	44	44	44	44	44	41	
312.5	33	49	49	44	44	44	44	44	44	41	
625	10	49	49	44	44	44	44	44	44	41	
1250	11	49	49	44	44	44	44	44	44	41	
2500	11	49	49	44	44	44	44	44	44	41	
5000	10	49	49	44	44	44	44	44	44	41	
10000	13	49	49	44	44	44	44	44	44	41	

Ompalsib [nM]	Mebendazole [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	-1	-1	0	1	2	4	6	5	7		
39.06	2	3	2	4	4	4	5	5	5		
78.13	4	1	1	1	1	2	4	1	4		
156.25	-1	1	2	1	0	2	3	2	3		
312.5	-2	0	-2	0	1	0	1	3	3		
625	-4	-3	0	0	2	4	5	6	6		
1250	-2	0	0	3	4	5	6	7	7		
2500	1	1	4	3	5	6	8	8	8		
5000	5	6	6	7	7	8	9	10	10		
10000	6	6	6	7	7	8	9	10	10		

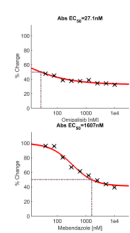
HS11



Ompalsib [nM]	Mebendazole [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	100	90	81	73	64	55	49	45	39	
39.06	77	77	68	54	54	49	45	45	41	37	
78.13	52	49	49	44	44	44	44	44	44	41	
156.25	42	49	49	44	44	44	44	44	44	41	
312.5	33	49	49	44	44	44	44	44	44	41	
625	10	49	49	44	44	44	44	44	44	41	
1250	11	49	49	44	44	44	44	44	44	41	
2500	11	49	49	44	44	44	44	44	44	41	
5000	10	49	49	44	44	44	44	44	44	41	
10000	13	49	49	44	44	44	44	44	44	41	

Ompalsib [nM]	Mebendazole [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	-1	-1	0	-4	5	10	11	10	13		
39.06	3	1	3	4	6	7	8	9	9		
78.13	4	3	3	3	5	5	6	7	10		
156.25	1	1	2	1	2	3	4	4	5		
312.5	-1	-1	-1	0	0	1	3	4	4		
625	-3	-2	-2	-2	2	1	2	3	4		
1250	-3	-2	-1	0	1	3	3	4	3		
2500	0	1	3	1	3	5	6	6	6		
5000	4	5	4	4	5	6	7	6	6		
10000	4	5	4	4	5	6	7	6	6		

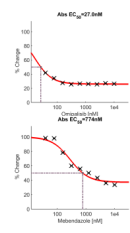
HS04.3



Ompalsib [nM]	Mebendazole [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	96	96	80	67	61	56	49	44	39	
39.06	77	77	68	54	54	49	45	45	41	37	
78.13	52	49	49	44	44	44	44	44	44	41	
156.25	42	49	49	44	44	44	44	44	44	41	
312.5	33	49	49	44	44	44	44	44	44	41	
625	10	49	49	44	44	44	44	44	44	41	
1250	11	49	49	44	44	44	44	44	44	41	
2500	11	49	49	44	44	44	44	44	44	41	
5000	10	49	49	44	44	44	44	44	44	41	
10000	13	49	49	44	44	44	44	44	44	41	

Ompalsib [nM]	Mebendazole [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	-5	-3	-1	-2	2	6	6	5	8		
39.06	-3	-4	1	0	5	6	6	8	8		
78.13	1	2	3	1	3	4	6	7			
156.25	-1	-2	-1	2	2	3	2	3	5		
312.5	1	0	1	0	0	-1	2	4			
625	-1	-1	-3	-2	-1	-1	-1	-3	0		
1250	-1	0	-2	-2	-1	-2	-3	-2	-2		
2500	-1	0	-1	0	-1	-3	-3	-1	0		
5000	2	2	0	0	-2	-2	0	0	2		
10000	2	2	0	0	-2	-2	0	0	2		

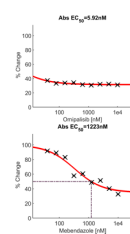
HS03



Ompalsib [nM]	Mebendazole [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	98	96	78	60	56	50	43	39	34	
39.06	77	77	68	54	54	49	45	45	41	37	
78.13	52	49	49	44	44	44	44	44	44	41	
156.25	42	49	49	44	44	44	44	44	44	41	
312.5	33	49	49	44	44	44	44	44	44	41	
625	10	49	49	44	44	44	44	44	44	41	
1250	11	49	49	44	44	44	44	44	44	41	
2500	11	49	49	44	44	44	44	44	44	41	
5000	10	49	49	44	44	44	44	44	44	41	
10000	13	49	49	44	44	44	44	44	44	41	

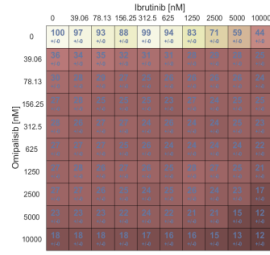
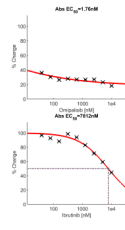
Ompalsib [nM]	Mebendazole [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	1	-1	3	-1	3	7	7	8	12		
39.06	-1	0	1	2	3	3	4	6	7		
78.13	0	1	1	1	3	2	3	3	5		
156.25	1	0	1	1	0	2	1	2	3		
312.5	1	1	0	-1	0	1	0	2			
625	-1	0	-1	-1	-1	-1	-1	-2	2		
1250	1	0	-1	-3	-2	-2	-1	0	0		
2500	-1	-1	-1	-3	-3	-3	-1	-2	0		
5000	0	1	-1	-2	-1	-2	-1	-1	1		
10000	0	1	-1	-2	-1	-2	-1	-1	1		

HS12

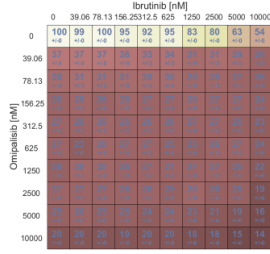
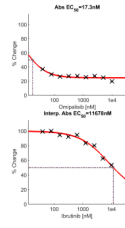


Ompalsib [nM]	Mebendazole [nM]										
	0	39.06	78.13	156.25	312.5	625	1250	2500	5000	10000	
0	100	92	89	83	58	61	49	51	40	34	
39.06	77	77	68	54	54						

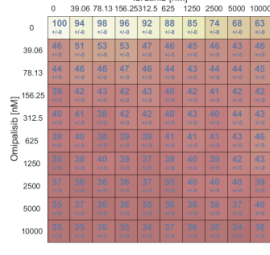
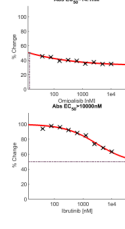
HS01



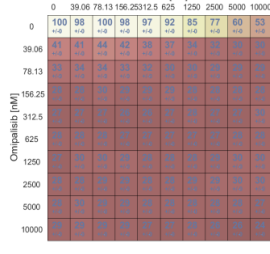
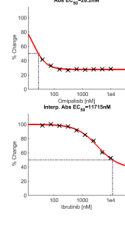
HS11



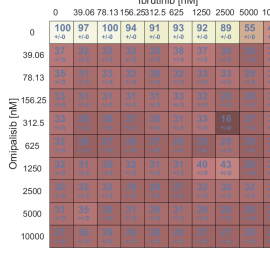
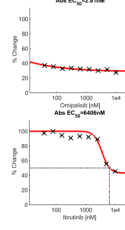
HS04.3



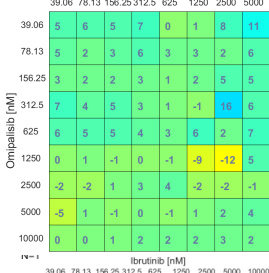
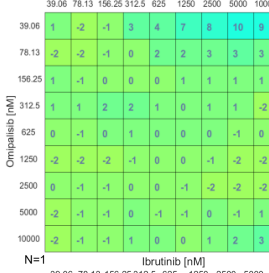
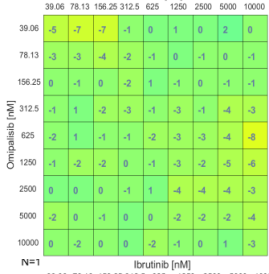
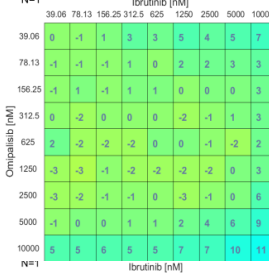
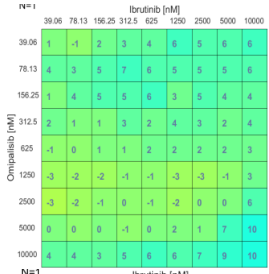
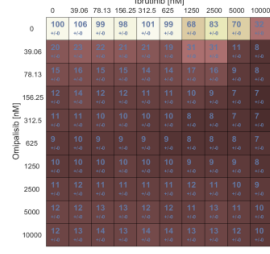
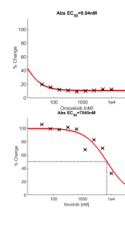
HS03



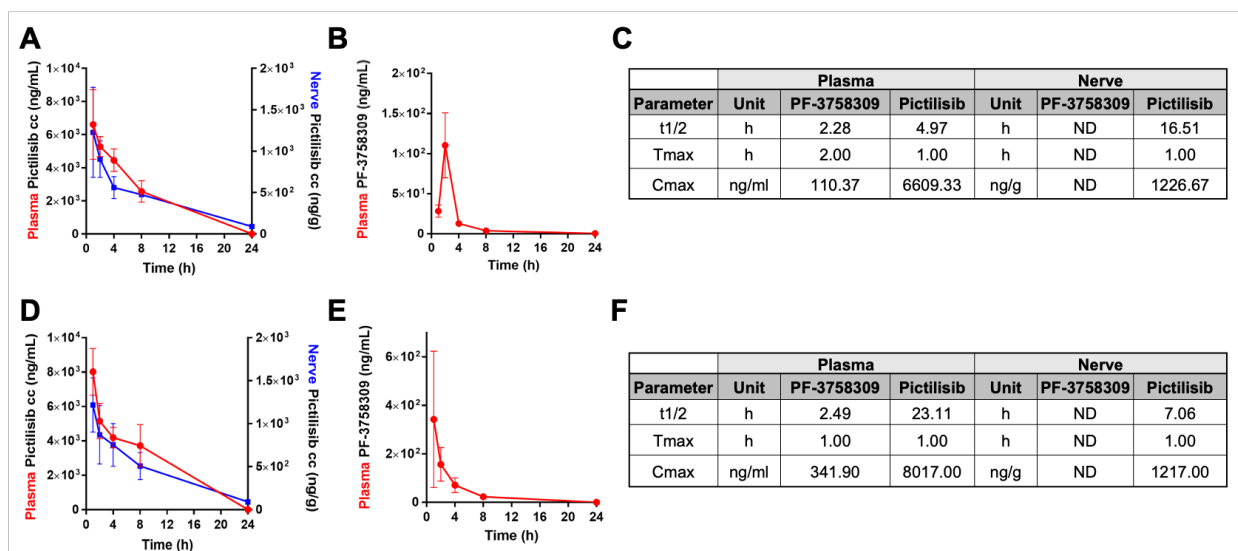
HS12



MS01

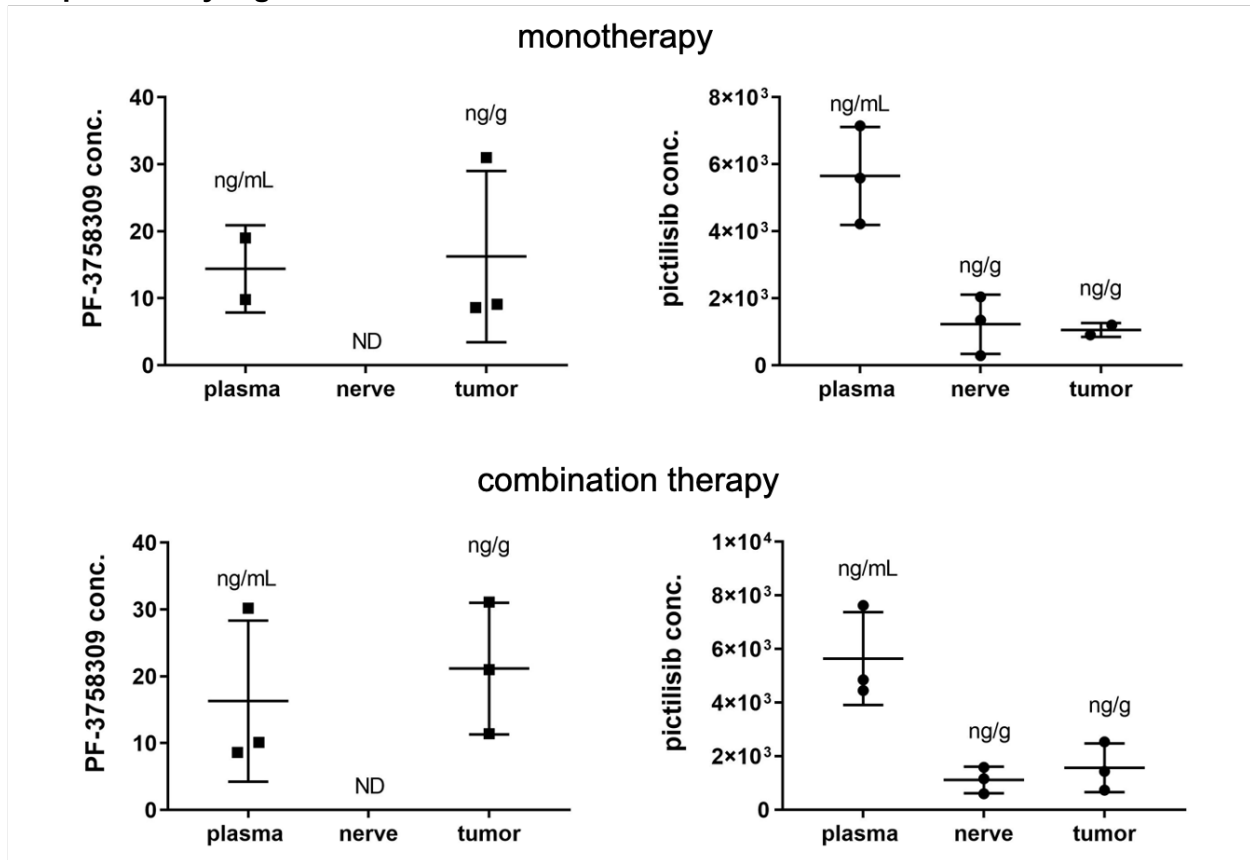


Supplementary Figure S2



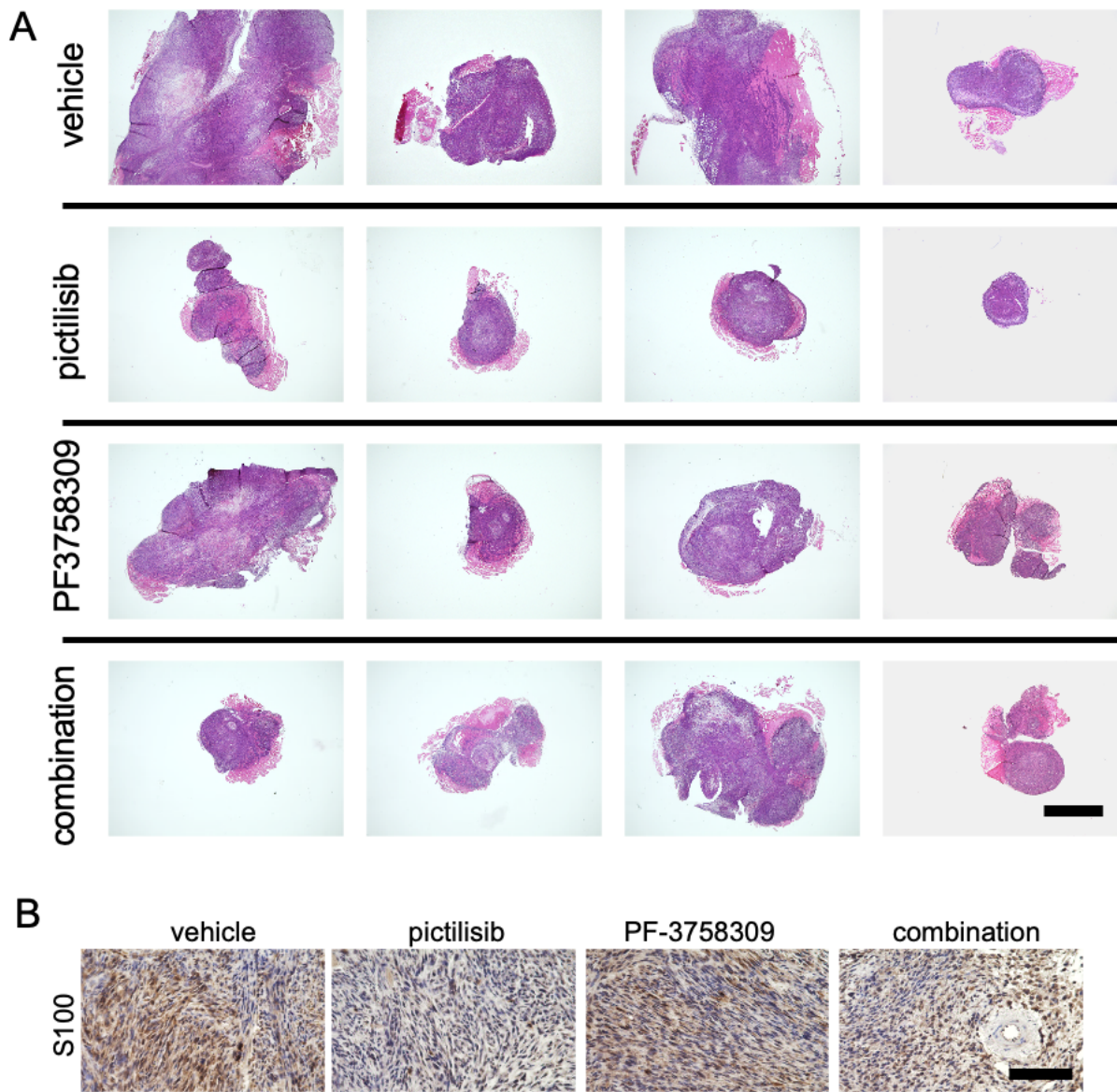
Supplementary Figure S2. Pharmacokinetic analysis of pictilisib and PF-3758309 as monotherapies and in combination after a single dose. (A) Plot of monotherapeutic pictilisib concentration as a function of time (plasma shown in red, nerve shown in blue). (B) Plot of monotherapeutic PF-3758309 concentration in plasma as a function of time (not detected in nerve). (C) Pictilisib and PF-3758309 pharmacokinetic parameters when delivered as monotherapeutics. (D) Plot of pictilisib concentration in the presence of PF-3758309 as a function of time (plasma shown in red, nerve shown in blue). (E) Plot of PF-3758309 concentration in plasma in the presence of pictilisib as a function of time (not detected in nerve). (F) Pictilisib and PF-3758309 pharmacokinetic parameters when delivered in combination. Data in graphs shown as mean±SEM. t1/2: plasma/nerve half-life; Tmax: time to maximum plasma/nerve concentration; Cmax: peak plasma/nerve concentration

Suupplementary Figure S3



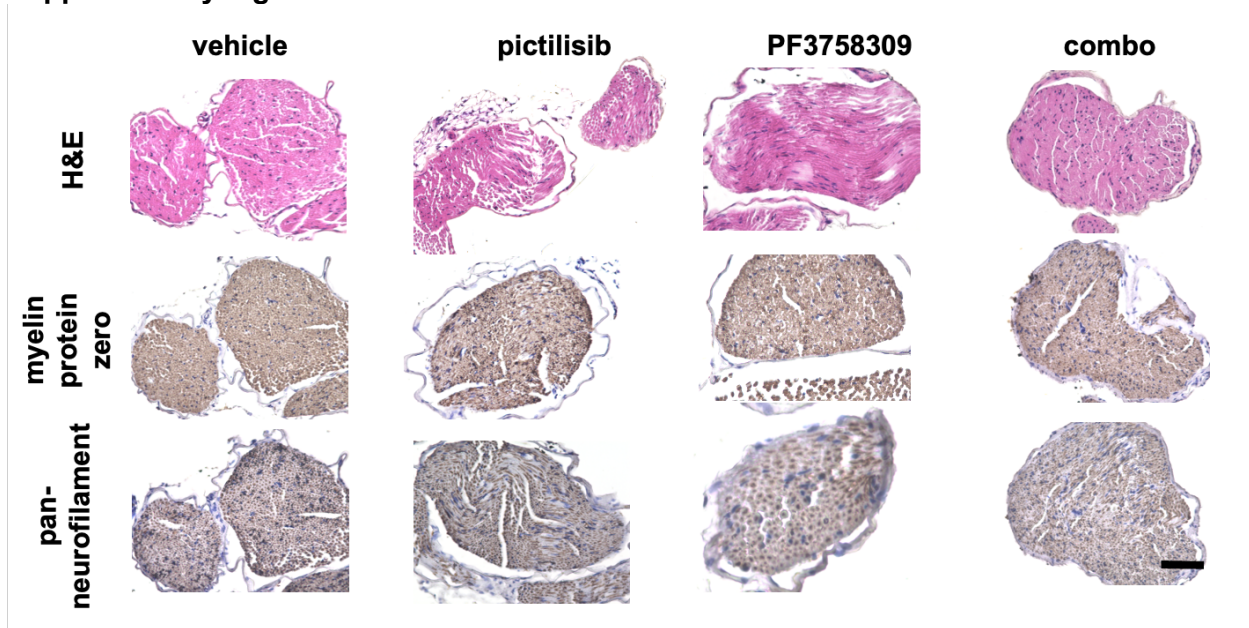
Suupplementary Figure S3. Pharmacokinetic analysis of pictilisib and PF-3758309 as monotherapies and in combination after two weeks of daily dosing. PF-3758309, although not detected in naïve nerve, was detected in tumor, revealing disruption of the blood-nerve barrier in nerves grafted with the merlin-deficient Schwann cells and the possibility of reduced clearance rate from the tumors for PF-3758309. PF-3758309 was detected at similar levels in plasma and tumor when delivered alone and with pictilisib. Pictilisib was observed in the plasma, normal nerve and tumors of all mice treated as single or combination therapy.

Supplementary Figure S4



Supplementary Figure S4. Representative images of graft samples processed for histology (n=4/group) and (A) stained with hematoxylin and eosin imaged at 50x and (B) stained for S100 expression and imaged at 400x. Scale bar in A represents 1.5 mm. Scale bar in B represents 200 μ m.

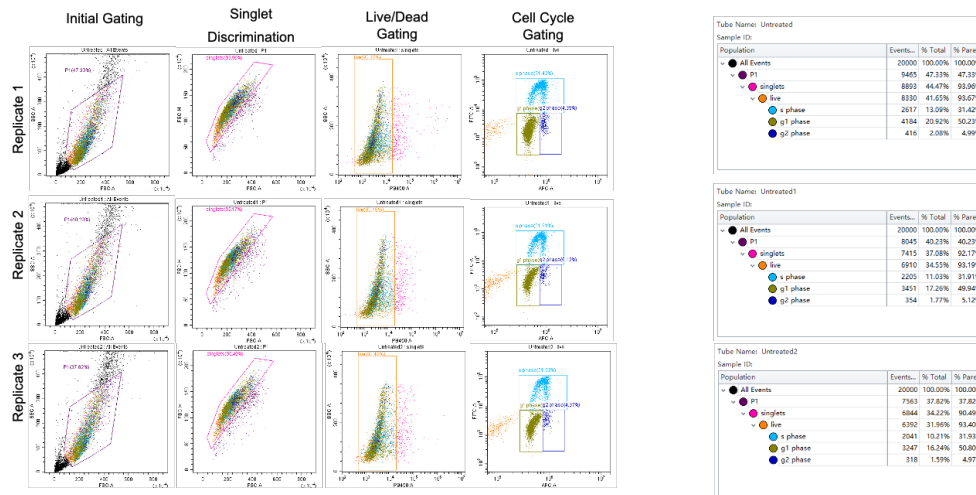
Supplementary Figure S5



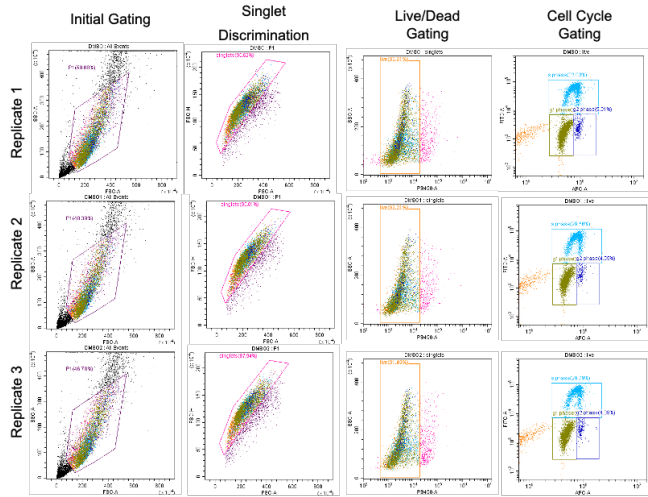
Supplementary Figure S5. Representative 100x images of contralateral control sciatic nerve samples processed for histology and stained with hematoxylin and eosin, myelin protein zero, and pan-neurofilament. There are no clear differences between groups in nerve morphology or Schwann cell-specific protein expression. Scale bar represents 400 μm .

Supplementary Figure S6

Untreated cells



DMSO treated cells



Tube Name: DMSO

Sample ID:

Population	Events	% Total	% Para...
All Events	20000	100.00%	100.00%
P1	11816	59.08%	59.08%
singlets	10708	53.54%	90.62%
live	10024	50.12%	93.61%
s phase	3211	16.06%	32.09%
g1 phase	5214	26.07%	52.02%
g2 phase	502	2.51%	5.01%

Tube Name: DMSO1

Sample ID:

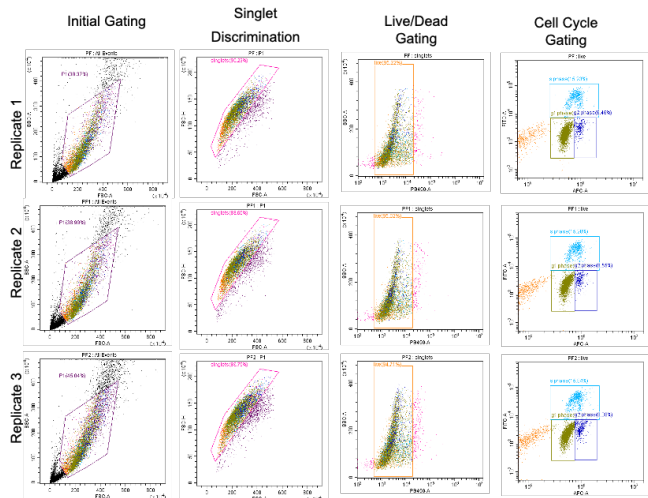
Population	Events	% Total	% Para...
All Events	20000	100.00%	100.00%
P1	9677	48.39%	48.39%
singlets	8710	43.55%	90.01%
live	8101	40.51%	93.01%
s phase	2395	11.98%	29.56%
g1 phase	4255	21.43%	53.02%
g2 phase	369	1.85%	4.55%

Tube Name: DMSO2

Sample ID:

Population	Events	% Total	% Para...
All Events	20000	100.00%	100.00%
P1	9355	46.78%	46.78%
singlets	8227	41.14%	87.84%
live	7527	37.64%	91.49%
s phase	2242	11.21%	29.79%
g1 phase	3979	19.90%	52.80%
g2 phase	306	1.53%	4.89%

PF-3758309 treated cells



Tube Name: PF

Sample ID:

Population	Events	% Total	% Para...
All Events	20000	100.00%	100.00%
P1	7613	38.07%	38.07%
singlets	6923	34.62%	90.21%
live	6592	32.96%	85.22%
s phase	1004	5.02%	15.23%
g1 phase	3871	19.36%	58.72%
g2 phase	436	2.13%	6.46%

Tube Name: PF1

Sample ID:

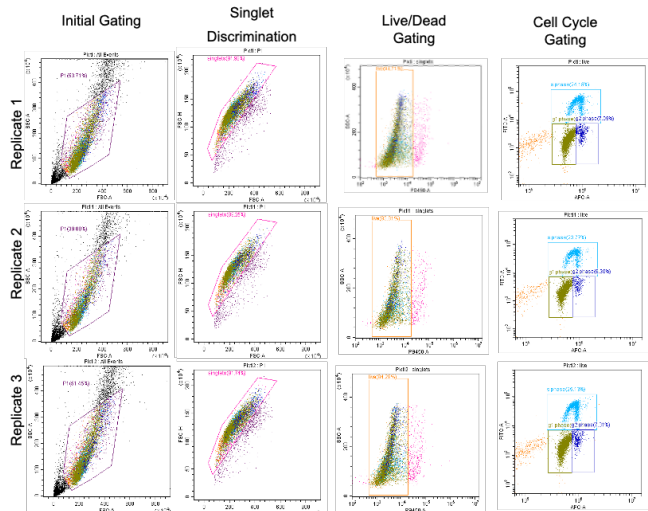
Population	Events	% Total	% Para...
All Events	20000	100.00%	100.00%
P1	7790	38.95%	38.95%
singlets	6909	34.55%	88.60%
live	6565	32.83%	95.02%
s phase	958	4.79%	15.20%
g1 phase	3644	18.22%	60.08%
g2 phase	430	2.15%	6.55%

Tube Name: PF2

Sample ID:

Population	Events	% Total	% Para...
All Events	20000	100.00%	100.00%
P1	9007	45.04%	45.04%
singlets	7814	39.07%	86.75%
live	7401	37.01%	94.71%
s phase	1122	5.61%	15.86%
g1 phase	4584	22.92%	62.07%
g2 phase	620	3.10%	8.38%

Pictilisib



Tube Name: Pic1

Sample ID:

Population	Events	% Total	% Para...
All Events	20000	100.00%	100.00%
P1	10741	53.71%	53.71%
singlets	9880	49.40%	91.98%
live	9227	46.14%	94.71%
s phase	2260	11.30%	24.51%
g1 phase	5828	29.14%	62.88%
g2 phase	663	3.32%	7.09%

Tube Name: Pic11

Sample ID:

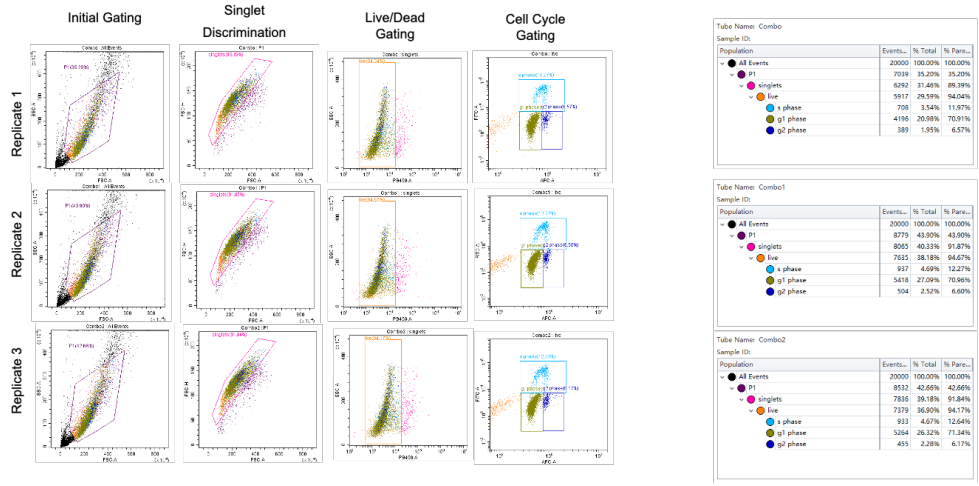
Population	Events	% Total	% Para...
All Events	20000	100.00%	100.00%
P1	7815	39.08%	39.08%
singlets	6975	34.88%	89.25%
live	6543	32.72%	93.81%
s phase	1555	7.78%	23.77%
g1 phase	4284	21.42%	62.42%
g2 phase	412	2.06%	6.30%

Tube Name: Pic12

Sample ID:

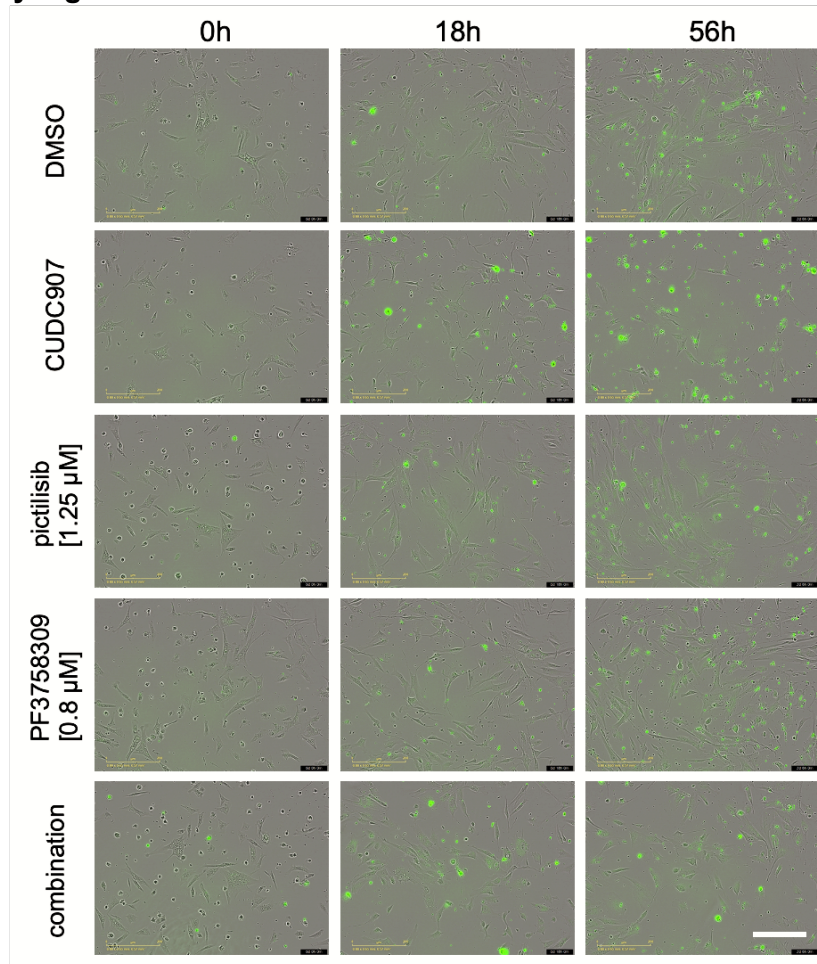
Population	Events	% Total	% Para...
All Events	20000	100.00%	100.00%
P1	10290	51.45%	51.45%
singlets	9440	47.20%	91.74%
live	8931	44.66%	94.29%
s phase	2227	11.14%	25.13%
g1 phase	5420	27.10%	60.89%
g2 phase	651	3.26%	7.31%

Combination treated cells



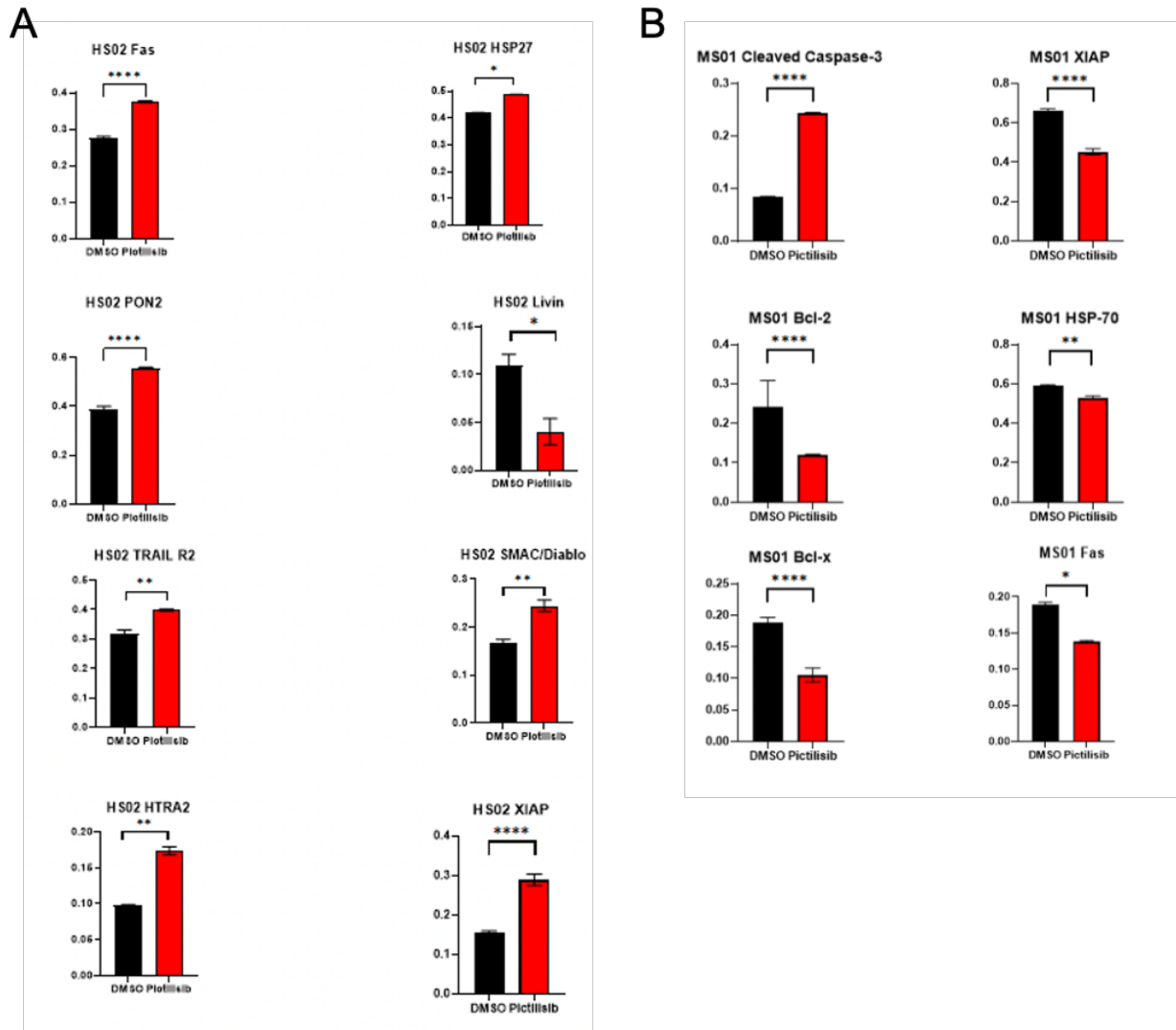
Supplementary Figure S6. Flow analysis of cell cycle in treated and untreated HS01 cells.

Supplementary Figure S7



Supplementary Figure S7. Representative images of cleaved caspase3/7+ (green) cells imaged at 0h, 18h, and 54h of cultures with indicated treatments.

Supplementary Figure S8.



Supplementary Figure S8. All significant differences in protein levels detected by human (A) and mouse (B) Apoptosis Proteome Profiles arrays. * $p < 0.05$; ** $p < 0.01$, **** $p < 0.0001$ by Šídák's multiple comparisons test.