

Supplemental Table S1: Patient characteristics

Patient	Gender	Age	Isotype	Treatment	patient status	RASSF4 expression (Log2)	RAS status
#1	M	65	IgG λ	High dose melphalan + autograft	relapse	7.959108807	NRAS mutation
#2	F	47	IgG κ	VRD + High dose melphalan + autograft	diagnosis	7.572650968	no mutation
#3	F	79	IgA κ	MPV - experiment made at diagnosis	diagnosis	6.584070609	no mutation
#4	M	72	BJ λ	VD + High dose melphalan + autograft	relapse	ND	ND
#5	M	64	IgG λ	VRD + High dose melphalan + autograft	relapse	7.572650968	no mutation
#6	M	61	IgG κ	VRD + High dose melphalan + autograft	diagnosis	6.350846033	KRAS and NRAS mutation
#7	M	72	IgG λ	newly diagnosed	diagnosis	7.827214388	ND
#8	F	63	BJ κ	VRD + High dose melphalan + autograft	diagnosis	6.883851717	KRAS mutation
#9	M	51	IgG λ	VD + High dose melphalan + autograft	relapse	9.807791529	no mutation
#10	F	56	IgA κ	newly diagnosed	diagnosis	8.805949542	ND

λ: lambda, κ: kappa, VRD: Velcade-Revlimid-Dexamethasone , MPV: Melphalan-Prednisone-Velcade, VD; Velcade-dexamethasone, ND: non determined.

Supplemental Table S4: kinases differentially phosphorylated in RASSF4 overexpressing cells treated with trametinib compared to parental cells treated with trametinib and/or RASSF4 overexpressing cells.

	T	Dox	T + Dox
UP			
p27 (T198)	0.99	1.61	1.42
c-JUN (S63)	0.86	1.78	2.06
DOWN			
Akt 1/2/3 (T308)	0.64	0.57	0.55
STAT5a/b (Y694/Y699)	0.70	0.58	0.54
STAT5a (Y694)	0.70	0.64	0.58
FAK (Y397)	0.50	0.46	0.39
PRAS40 (T246)	0.80	0.80	0.70
beta-catenin	0.74	0.76	0.66
TOR (S2448)	0.90	0.92	0.77
AMPKa1 (T183)	0.73	0.65	0.45
Akt 1/2/3 (S473)	0.89	1.00	0.77
MSK1/2 (S376/S360)	0.81	0.92	0.68
p70 S6 kinase (T421/S424)	0.63	0.81	0.56
HSP60	0.72	0.83	0.56
GSK-3 alpha/beta (S21/9)	0.68	0.81	0.51
WNK1 (T60)	0.42	0.72	0.32
STAT3 (S727)	0.69	1.02	0.59
ERK1/2 (T202/Y204, T185/Y187)	0.11	0.90	0.09

Supplemental table S4: Kinases differentially phosphorylated in RASSF4 overexpressing cells treated with trametinib compared to parental cells treated with trametinib and/or RASSF4 overexpressing cells. AMO-1-RF4 cells were treated with 50nM trametinib, 3 days after adding dox, for an additional 24h. Samples were collected to perform a phospho-kinase array according to manufacturer's protocol.

Supplemental Table S5: Statistical analysis and combination index (CI) values

XG-7	Trimatinib	Quisinostat	s	CI
	50	2.5	***	0.18
	50	5	***	0.29
	50	10	***	0.32
	100	2.5	***	0.18
	100	5	***	0.25
	100	10	***	0.31
	200	2.5	***	0.16
	200	5	***	0.23
	200	10	***	0.3

XG-7	Trimatinib	Panobinostat	s	CI
	50	5	***	0.45
	50	10	***	0.54
	50	15	ns	0.68
	100	5	***	0.44
	100	10	***	0.54
	100	15	ns	0.74
	200	5	***	0.43
	200	10	**	0.63
	200	15	ns	0.7

AMO-1	Trimatinib	Quisinostat	s	CI
	50	2.5	**	0.08
	50	5	***	0.02
	50	10	***	<0.01
	100	2.5	***	0.03
	100	5	***	<0.01
	100	10	***	<0.01
	200	2.5	***	0.01
	200	5	***	<0.01
	200	10	***	<0.01

AMO-1	Trimatinib	Panobinostat	s	CI
	50	5	ns	0.22
	50	10	***	0.12
	50	15	***	0.11
	100	5	*	0.18
	100	10	***	0.08
	100	15	***	0.08
	200	5	**	0.14
	200	10	***	0.07
	200	15	***	0.07

MM1S	Trimatinib	Panobinostat	s	CI
	50	5	ns	0.62
	50	10	***	0.38
	50	15	***	0.15
	100	5	ns	0.63
	100	10	***	0.38
	100	15	***	0.16
	200	5	ns	0.66
	200	10	***	0.38
	200	15	***	0.16

JJN3	Trimatinib	Quisinostat	s	CI
	50	2.5	***	<0.01
	50	5	***	<0.01
	50	10	***	<0.01
	100	2.5	***	<0.01
	100	5	***	<0.01
	100	10	***	<0.01
	200	2.5	***	<0.01
	200	5	***	<0.01
	200	10	***	<0.01

JJN3	Trimatinib	Panobinostat	s	CI
	50	5	ns	0.55
	50	10	ns	0.46
	50	15	***	0.32
	100	5	ns	0.54
	100	10	ns	0.41
	100	15	***	0.3
	200	5	ns	0.53
	200	10	ns	0.41
	200	15	***	0.25

OPM-2	Trimatinib	Panobinostat	s	CI
	50	2.5	***	0.69
	50	5	***	0.55
	50	7.5	***	0.35
	100	2.5	***	0.56
	100	5	***	0.49
	100	7.5	***	0.34
	200	2.5	***	0.47
	200	5	***	0.44
	200	7.5	***	0.34

Supplemental table S5: Significance and combination index (CI) values calculated for the different drug concentrations. Statistical significance was evaluated with an one-way ANOVA test using GraphPad Prism 5.0 software. ns = not significant, * p<0.05, ** p<0.01, *** p<0.001 when compared to both single agents. CI values were calculated by the Chou and Thalalay method using CompuSyn 1.0 software (nd = not determined, CI ≤ 1 = synergistic).