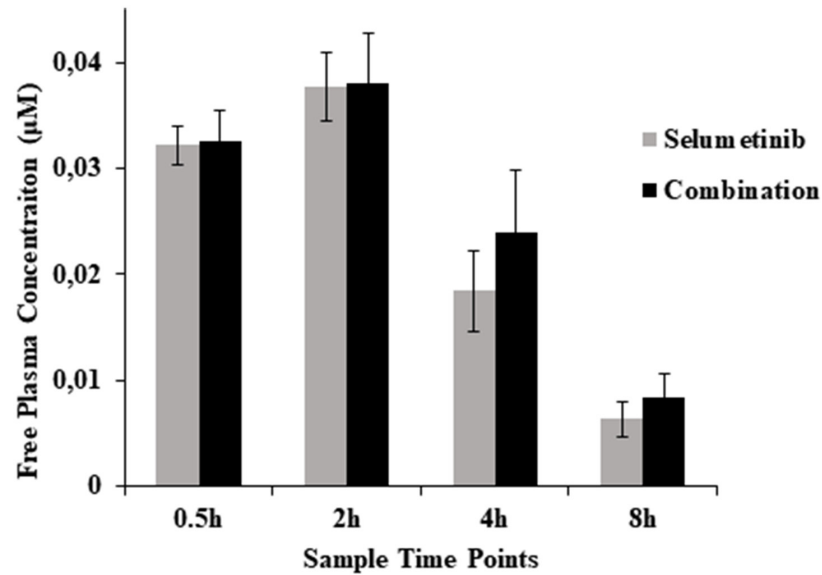
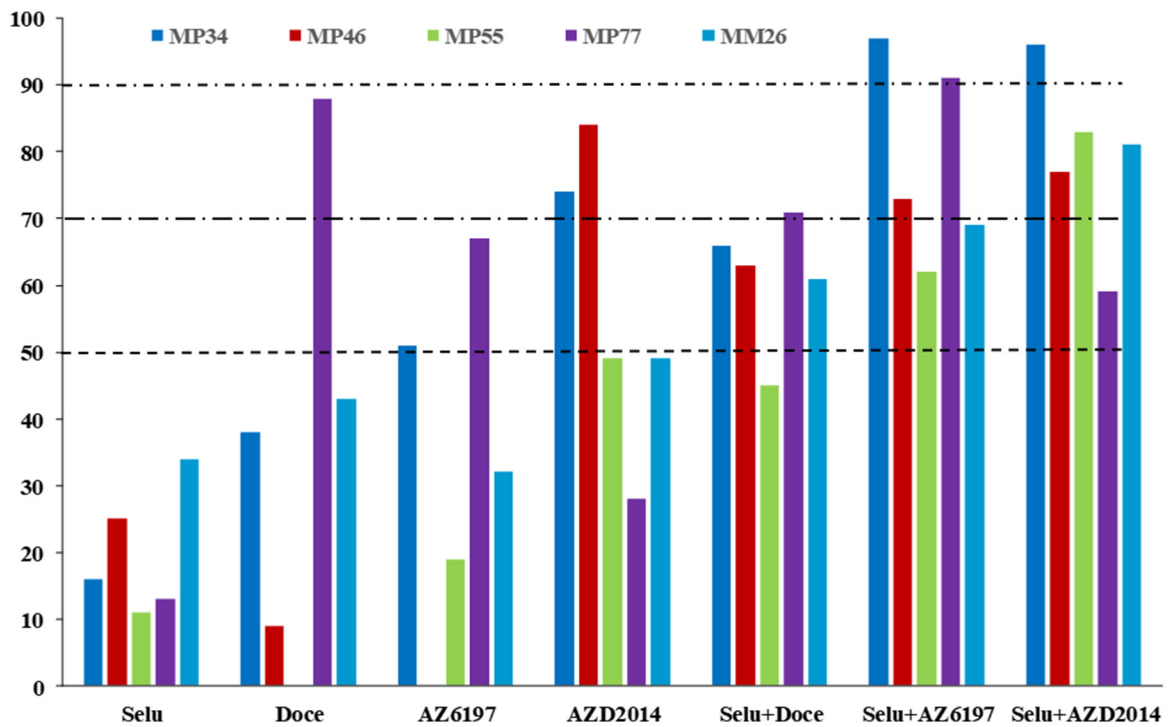


Selumetinib-based therapy in uveal melanoma patient-derived xenografts

SUPPLEMENTARY MATERIALS



Supplementary Figure 1: *In vivo* pharmacokinetics of selumetinib administered alone or in combination with DTIC.



Supplementary Figure 2: Overall responses to new selumetinib-based combinations.

Supplementary Table 1: *In vivo* efficacy of targeted therapies administered alone

All PDXs (%)	Treatments			
	Selumetinib	Docetaxel	AZ6197	AZD2014
RTV ≤ 1	0	0	0	0
ORR ≤ -0.5	0	20	40	40
ORR ≤ -0.75	0	20	0	20
mPFS (days)	11	10	12	23

Abbreviations: RTV, Relative Tumor Volume; ORR, Overall Response Rate; mPFS, median of progression-free survival.

Supplementary Table 2: *In vivo* efficacy score for targeted therapies administered alone or in combinations with Selumetinib

Treatments		MP42	MP46	MP55	MP77	MM26	Total
4 monotherapies (score 1 to 4)	Selumetinib	4	2	3	4	3	16
	Docetaxel	3	4	4	1	2	14
	AZ6197	2	3	2	2	4	13
	AZD2014	1	1	1	3	1	7
3 combinations (score 1 to 3)	S + D	2	3	3	2	3	13
	S + AZ6197	1	2	2	1	2	8
	S + AZD2014	3	1	1	3	1	9
7 treatments (score 1 to 7)	Selumetinib	7	5	6	7	6	31
	Docetaxel	6	6	7	2	5	26
	AZ6197	5	7	5	4	7	28
	AZD2014	2	1	3	6	4	16
	S + D	3	4	4	3	3	17
	S + AZ6197	1	3	2	1	2	9
	S + AZD2014	4	2	1	5	1	13

Abbreviations: S, selumetinib; D, docetaxel.

Supplementary Table 3: *In vivo* efficacy of selumetinib-based combinations

All PDXs (%)	Treatments		
	S + D	S + AZ6197	S + AZD2014
RTV ≤ 1	0	20	0
ORR ≤ -0.5	80	100	100
ORR ≤ -0.75	0	40	60
mPFS (days)	16	22	16

Supplementary Table 4: Characteristics of UM cell lines

Cell lines	Tumor sample origin	Morphology	LOH of chromosome 3	<i>BAP1</i> mutations	<i>BAP1</i> Protein production ³	<i>GNAQ</i> mutations	<i>GNAI1</i> mutations	<i>SF3B1</i> Mutations
MP38	Patient (eye)	S	Yes ¹	Yes	No	Yes	No	No
MP41	PDX (eye)	E	Yes ²	No	Yes	No	Yes	No
MP46	PDX (eye)	M	Yes	No	No	Yes	No	No
MP65	Patient (eye)	S	Yes	Yes	No	No	Yes	No
MM28	PDX (liver)	M	Yes ¹	Yes	No	No	Yes	No
MM66	PDX (liver)	M	No	No	Yes	No	Yes	No

Abbreviations: S, spindle cells; M, mixed cells; E, epithelioid cells.

¹Uniparental disomy of 3q.

² Uniparental disomy of chromosome 3.

³ as determined by Western blotting and Immunohistochemistry.

Supplementary Table 5: Characteristics of UM PDXs

Cell lines	Tumor sample origin	Morphology	LOH of chromosome 3	<i>BAP1</i> mutations	<i>BAP1</i> Protein production ³	<i>GNAQ</i> mutations	<i>GNAI1</i> mutations	<i>SF3B1</i> Mutations
MP34	Eye	E	Yes ¹	No	Yes	No	Yes	Yes
MP46	Eye	M	Yes	No ³	No	Yes	No	No
MP55	Eye	E	Yes	Yes	No	Yes	No	No
MP77	Eye	E	Yes	No	Yes	No	Yes	No
MM26	Liver	E	Yes	No	Yes	Yes	No	Yes

Abbreviations: S, spindle cells; M, mixed cells; E, epithelioid cells.

¹Uniparental disomy of 3q.

² As determined by Western blotting and Immunohistochemistry.

³ Mutation in promoter.

Supplementary Table 6: Density of cell lines in viability tests *in vitro*

Cell lines	number of cells/well
MP38	8000
MP65	8000
xMP41	2000
xMP46	7000
xMM28	5000
xMM66	6000

Supplementary Table 7: Mass Spectrometer and UPLC system parameters

Mass Spectrometer	Waters Xevo TQS		
UPLC system	Water s Acquity i-Class		
Column	Phenomenex Kinetix C18 50 x 2.1 x 1.7 μ m		
Solvent A	95% (v/v) Water, 5% Methanol + 0.1% Formic acid		
Solvent B	95% MeOH, 5% Water + 0.1 % Formic acid		
Elution Gradient	Time (min)	% A	%B
	0	95	5
	0.3	95	5
	2.2	5	95
	2.6	5	95
	2.61	95	5
	2.8	95	5
Flow	0.6 mL/min		
Run time	2.8 min, use a divert valve for initial 0.5 minutes		

Supplementary Table 8: Optimization parameters for mass spectrometry analysis

Compound	Ionization mode	Polarity	Parent ion	Daughter ion	Cone voltage (v)	Collison Energy	Retention Time (min)
Selumetinib	ESI	Positive	459.155	396.846	60	22	1.71
AZ10024306	ESI	Positive	408.064	174.241	60	22	1.53