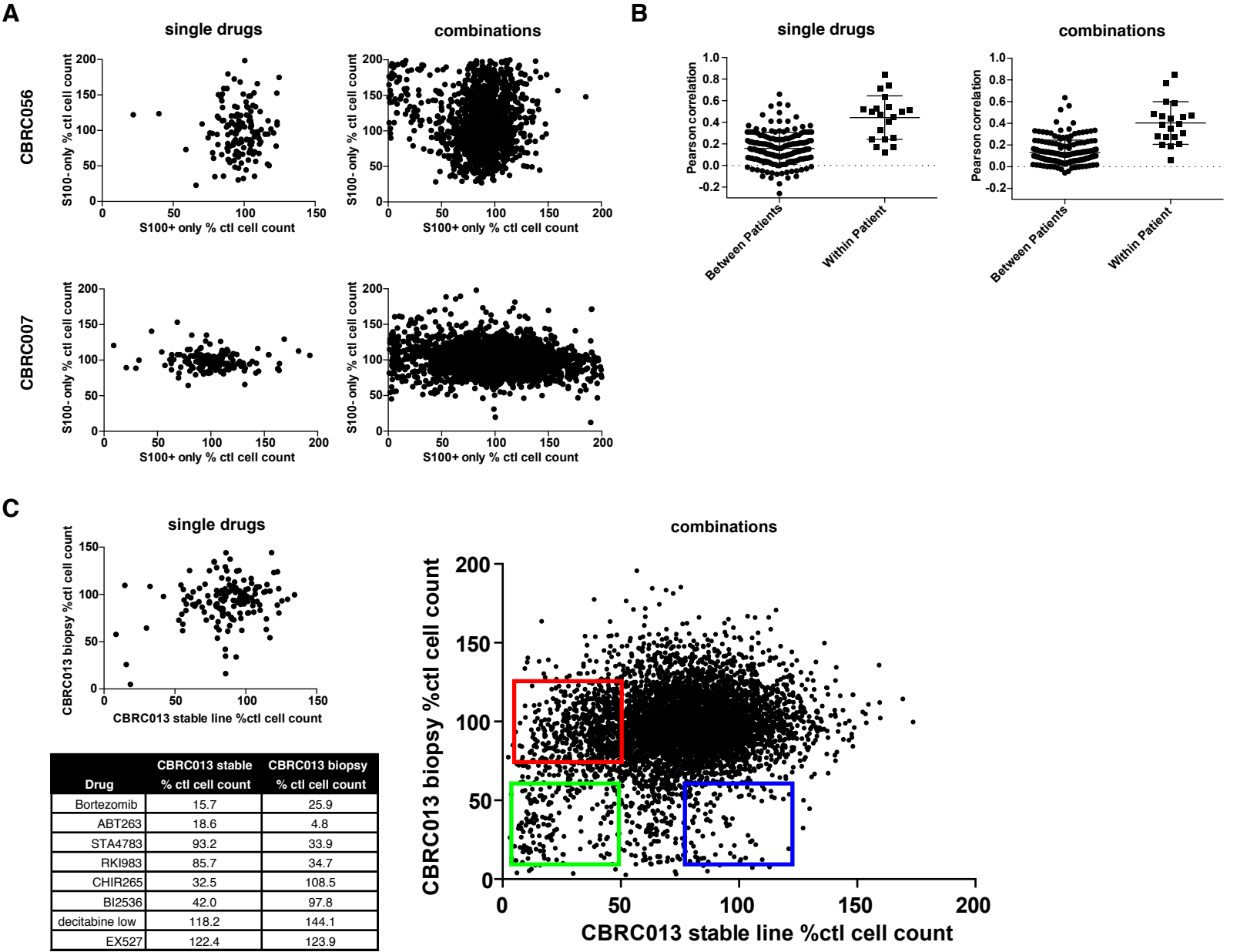


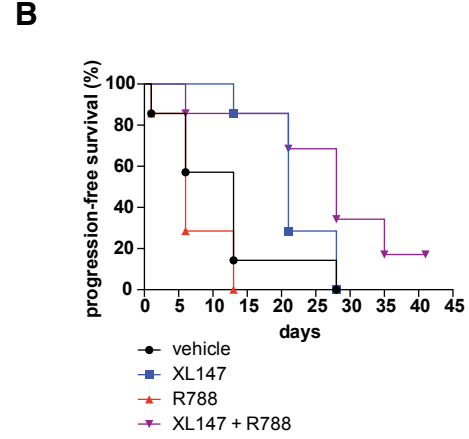
Supplementary Information



Supplementary Figure 1. A, Comparison of single (left) and combination (right) drug effects in two primary patient biopsies, CBRC056 (top) and CBRC007 (bottom). No correlation was seen between effects in the melanoma population (S100+) and non-melanoma stroma population (S100-). B, Pearson correlation coefficients for single (left) or combinatorial (right) drug effects between different patient samples or within patient samples when replicates were technically possible. C, Comparison of drug effects in a stable short-term culture derived from patient biopsy CBRC013 around passage 10 compared to the primary patient biopsy. Single drug effects are shown at left and in table below, showing some drugs had similar effects in both the biopsy and stable cell-line but others diverged. Similarly, for combination drugs (plot at right), combinations either affected both primary and stable cells (green box), only the primary biopsy (blue box), or only the stable cell line (red box).

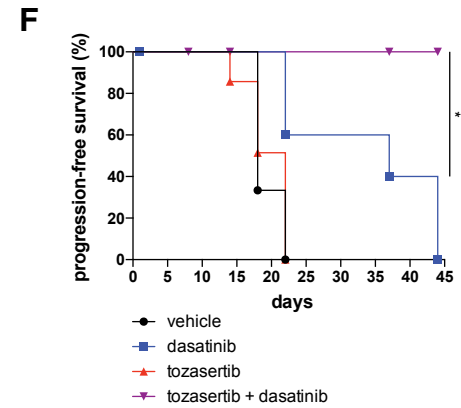
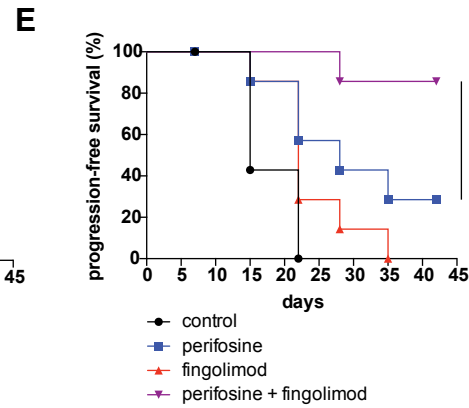
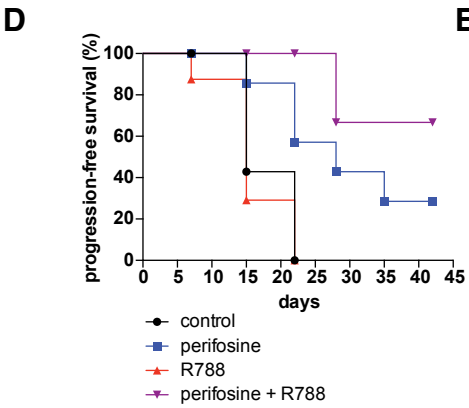
A

Rank	Drug 1	Drug 2
1	STA4783	Tamatinib/R406
2	vorinostat/SAHA	STA4783
3	sunitinib	STA4783
4	STA4783	IPA3
5	STA4783	fingolimid
6	Bortezomib	BMS536924
7	STA4783	Veliparib/ABT888
8	Tamatinib/R406	fingolimid
9	STA4783	CX4945
10	STA4783	everolimus
11	NVP-BEZ235	BMS536924
12	fingolimid	Bortezomib
13	XL147	Tamatinib/R406
14	STA4783	NVP-BEZ235
15	sorafenib	bivanib/BI2536
16	sunitinib	Bortezomib
17	STA4783	Dovitinib/CHIR-258
18	OSI906	fingolimid
19	sunitinib	Tamatinib/R406
20	Tideglusib/TZDZ-8	STA4783



C

Rank	Drug 1	Drug 2
1	Tamatinib/R406	Perifosine
2	Tozasertib/VX680	dasatanib
3	Perifosine	fingolimid
4	FK866	cisplatin
5	sorafenib	decitabine
6	Tozasertib/VX680	sorafenib
7	OSI906	cisplatin
8	STA4783	Perifosine
9	IMD0354	cisplatin
10	MK2206	FK866
11	JNK5a	STA4783
12	nilutamide	FK866
13	FK866	Bortezomib
14	decitabine	Bortezomib
15	PF562271	SNS-032
16	STA4783	PF04217903
17	decitabine	dasatanib
18	decitabine	ABT263
19	sorafenib	SNS-032
20	IMD0354	ENMD2076



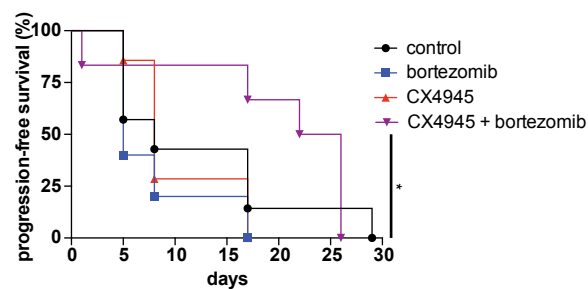
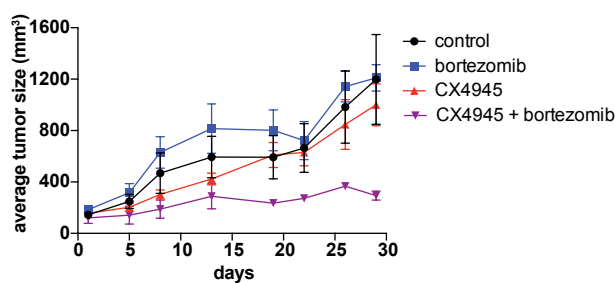
Supplementary Figure 2. A, Biopsy CBRC013 top 20 drug combinations by *ex vivo* screening algorithm. B, Progression (growth beyond 300mm³) free survival of CBRC013 xenografts showed a trend towards increased PFS with the R788 and XL147 combination compared to XL147 alone ($P = 0.1$, log-rank test). C, Biopsy CBRC029 top 20 drug combinations by *ex vivo* screening algorithm. D, Progression (growth beyond 1000mm³) free survival of CBRC029 xenografts showed a trend towards increased PFS of the perifosine and R788 combination-treated animals compared to only perifosine-treated animals ($P = 0.2$, log-rank test). E, Progression (growth beyond 1000mm³) free survival of CBRC029 xenografts. F, Progression (growth beyond 1500mm³) free survival of CBRC029 xenografts.

A

Rank	Drug 1	Drug 2
1	vatalanib/PTK787	Bortezomib
2	PF562271	Bortezomib
3	FK866	ABT263
4	decitabine	Bortezomib
5	palbociclib/PD332991	erlotinib
6	Midostaurin/PKC412	Perifosine
7	vorinostat/SAHA	Enzastaurin
8	NVP-BEZ235	everolimus
9	VX702	vorinostat/SAHA
10	OSI906	dasatanib
11	Tideglusib/TZDZ-8	ABT263
12	YM155	STA4783
13	JNK5a	dasatanib
14	MK2206	everolimus
15	Indole-3-carbinol	ABT263
16	Midostaurin/PKC412	OSI906
17	vorinostat/SAHA	everolimus
18	PF04217903	Perifosine
19	vincristine	dasatanib
20	STA4783	Darinaparsin

B

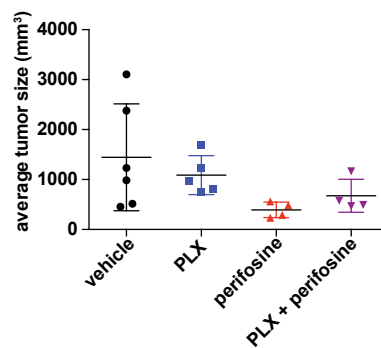
Rank	Drug 1	Drug 2
1	FK866	ABT263
2	Bortezomib	CX4945
3	Bortezomib	vatalanib/PTK787
4	FK866	decitabine
5	Bortezomib	temozolomide
6	Perifosine	PF04217903
7	Perifosine	Tamatinib/R406
8	FK866	RK1983
9	NVP-BEZ235	Bortezomib
10	FK866	ENMD2076
11	FK866	Midostaurin/PKC412
12	Bortezomib	decitabine
13	Perifosine	Midostaurin/PKC412
14	Perifosine	nilutamide
15	Bortezomib	SNS-032
16	FK866	PF562271
17	Bortezomib	Tanespimycin/17-AAG
18	ruxolitinib	FK866
19	FK866	SNS-032
20	FK866	Dovitinib/CHIR-258



C

Rank	Drug 1	Drug 2
1	YM155	STA4783
2	ruxolitinib	FK866
3	STA4783	BI78D3
4	Tozasertib/VX680	BI78D3
5	FK866	SNS-032
6	STA4783	palbociclib/PD332991
7	OSU03012	gemcitabine
8	YM155	SNS314
9	OSI906	BI78D3
10	ingolimod	FK866
11	Tozasertib/VX680	dasatanib
12	YM155	lapatinib
13	FK866	cisplatin
14	YM155	Perifosine
15	YM155	PF04217903
16	Indole-3-carbinol	ruxolitinib
17	ZM336372	BI78D3
18	FK866	ABT263
19	gemcitabine	BI78D3
20	RK1983	FK866

Rank	Drug 1	Drug 2
349	PLX4720	YM155
681	PLX4720	etoposide
690	PLX4720	Dovitinib/CHIR-258
697	PLX4720	JNK5a
719	PLX4720	Perifosine
848	PLX4720	Crizotinib/PF2341066
853	PLX4720	ABT263
873	PLX4720	PF04217903

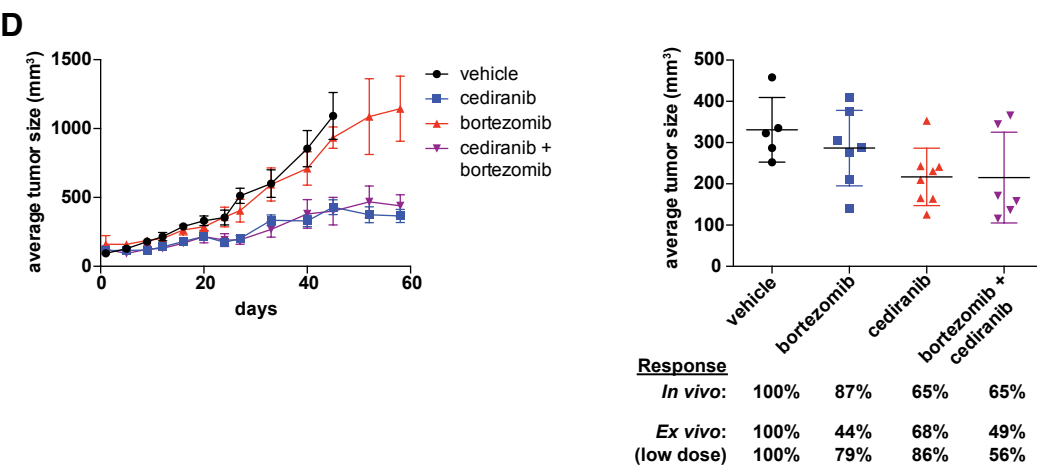
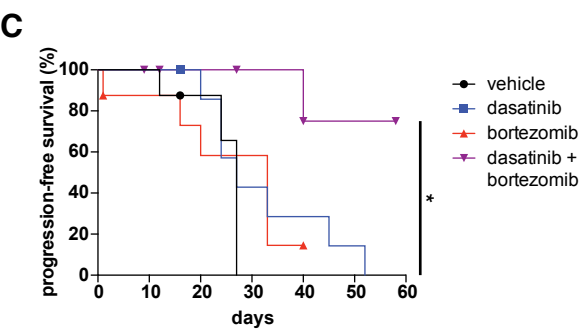
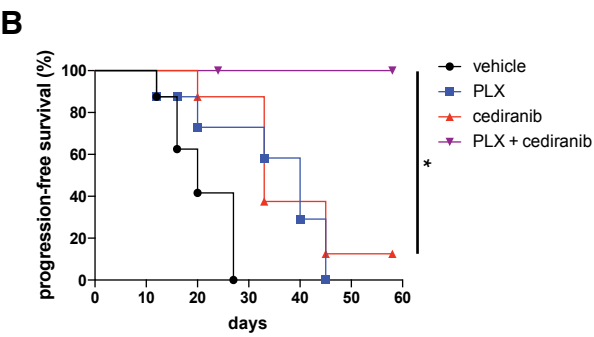
**Response**

In vivo:	100%	75%	27%	47%
Ex vivo:	100%	57%	119%	71%
(low dose)	100%	59%	130%	73%

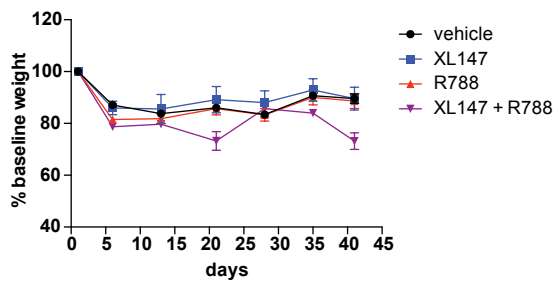
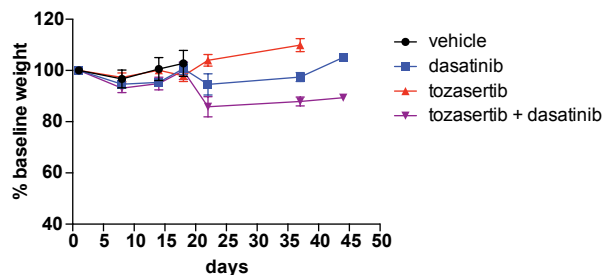
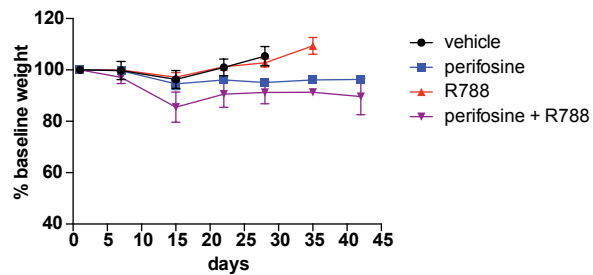
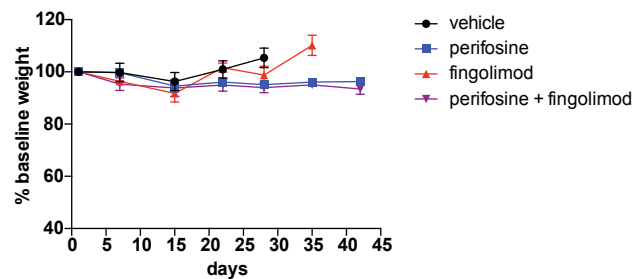
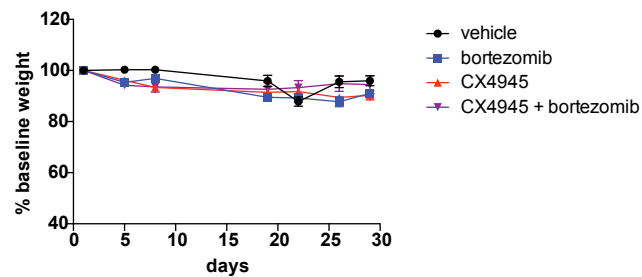
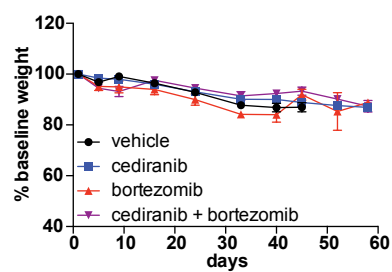
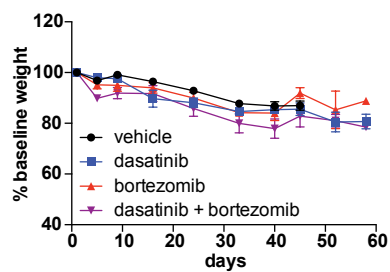
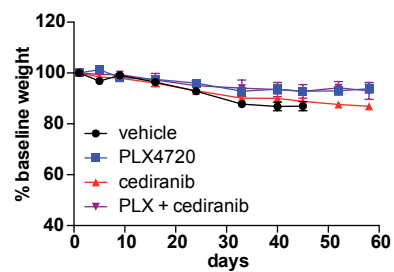
Supplementary Figure 3. A, Biopsy CBRC056 top 20 drug combinations by *ex vivo* screening algorithm. B, (left) Biopsy CBRC056 top 20 drug combinations by alternate screening algorithm. (middle) Average CBRC056 tumor sizes in animals treated with bortezomib, CX4945, or both ($N = 8$). Values are shown as mean \pm S.E.M. ranges. (right) Progression (growth beyond 300mm^3) free survival of CBRC056 xenografts. C, (left) Biopsy CBRC058 top 20 drug combinations by *ex vivo* screening algorithm. (right) CBRC058 PDX tumor sizes after four weeks of treatment. There was no significant difference in tumor sizes between animals treated with perifosine alone or perifosine in combination with PLX4720. (bottom) Top drug combinations containing PLX4720 by *ex vivo* screening algorithm.

A

Rank	Drug 1	Drug 2
1	BI78D3	CX4945
2	Bortezomib	dasatinib
3	BI78D3	decitabine
4	BI78D3	EX527
5	fingolimod	Tanespimycin/17-AAG
6	fingolimod	AZD7762
7	fingolimod	SNS-032
8	IPA3	CP690550
9	Indole-3-carbinol	IPA3
10	fingolimod	lenalidomide
11	BI78D3	NVP-BEZ235
12	BI78D3	OSI906
13	Perifosine	nilutamide
14	PLX4720	cediranib/AZD2171
15	RK1983	PF04217903
16	BI78D3	STA4783
17	CX4945	STA4783
18	BI78D3	JNK5a
19	Bortezomib	JNK5a
20	BI78D3	Tideglusib/TZDZ-8



Supplementary Figure 4. A, Biopsy CBRC026 top 20 drug combinations by *ex vivo* screening algorithm. B, Progression (growth beyond 300mm³) free survival of animals with CBRC026 xenografts. C, Progression (growth beyond 350mm³) free survival of animals with CBRC026 xenografts. D, Effects of cediranib and bortezomib combination on PDX tumor size. (left) Average tumor sizes in animals treated with cediranib, bortezomib, or both (*N* = 7-8). Values are shown as mean +/- S.E.M. ranges. (right) CBRC026 PDX tumor sizes after three weeks of treatment.

A**B****C****D****E**

Supplementary Figure 5. A, Weights for animals bearing CBRC013 xenografts. XL147 and R788 combination decreased animal weight by three weeks of continuous dosing compared to R788 alone (Two-way ANOVA with repeated measures, with Tukey's correction). B, Weights for animals bearing CBRC029 xenografts. (left) Co-dosing perifosine and R788 decreased animal weights compared to perifosine alone after four weeks of continuous treatment (Two-way ANOVA with repeated measures, with Tukey's correction). (Right) The combination of tozasertib and dasatinib resulted in decreased animal weights compared to dasatinib alone after five weeks of continuous dosing (Two-way ANOVA with repeated measures, with Tukey's correction). C, Addition of fingolimod to perifosine did not further decrease weights of CBRC029 xenograft bearing animals. D, Weights for animals bearing CBRC056 xenografts. There was no significant difference in animal weights between treatment groups. E, Weights for animals bearing CBRC026 xenografts. There was no significant difference in animal weights between treatment groups in all three experiments. Values are shown as mean +/- S.E.M. ranges.

Supplementary Table 1. Screening results for drug combinations, expressed as percent of control (DMSO-treated) values.