

Figure S1. Heatmap matrices 10x10 from the 21 selected synergistic combinations. The combinations that were further validated *in vivo* are highlighted in orange.

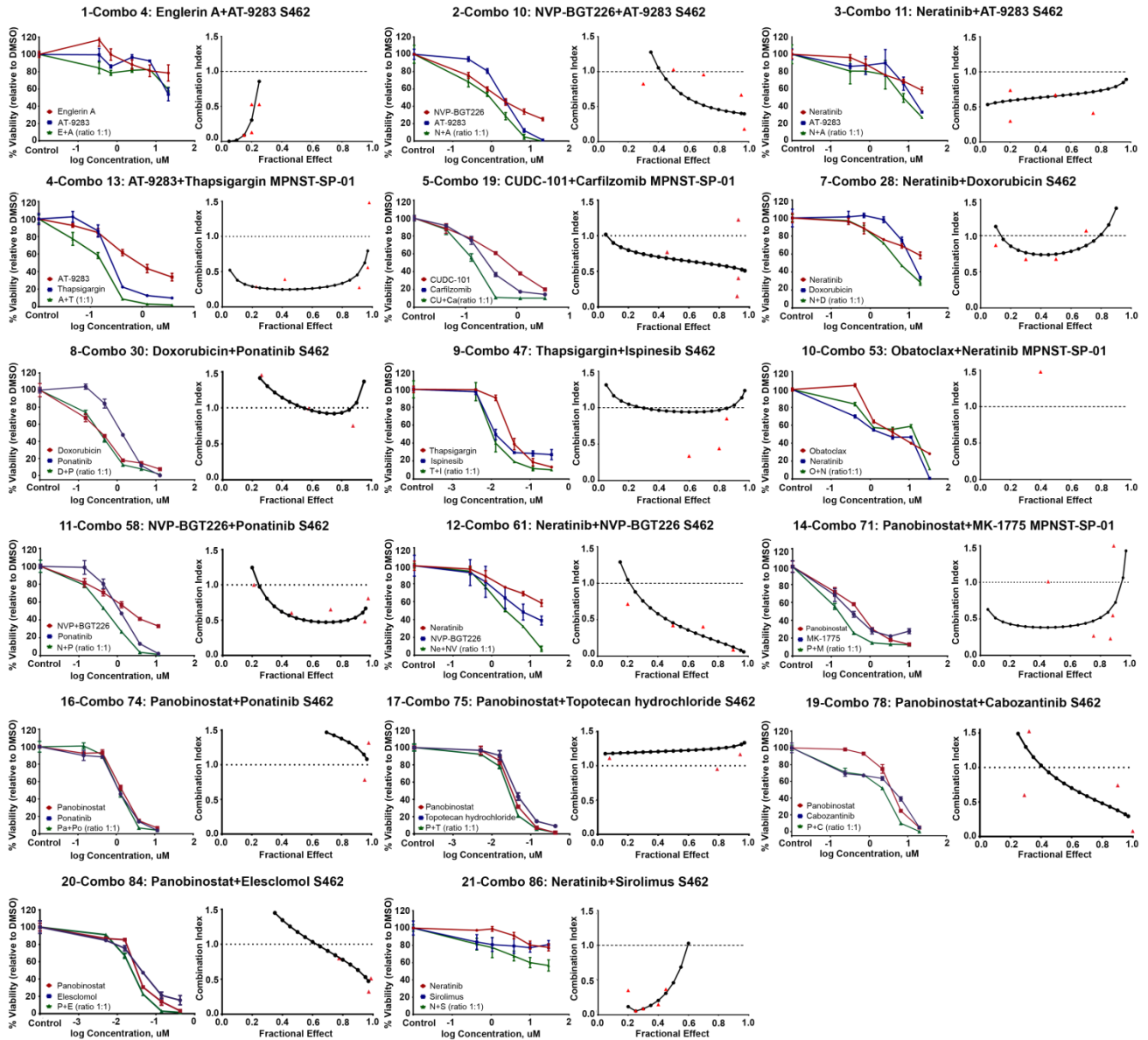


Figure S2. Single-agent and combined responses from the 17 selected synergistic combinations that were not validated *in vivo* in terms of dose-response on cell viability (left) and Combination Index values (right).

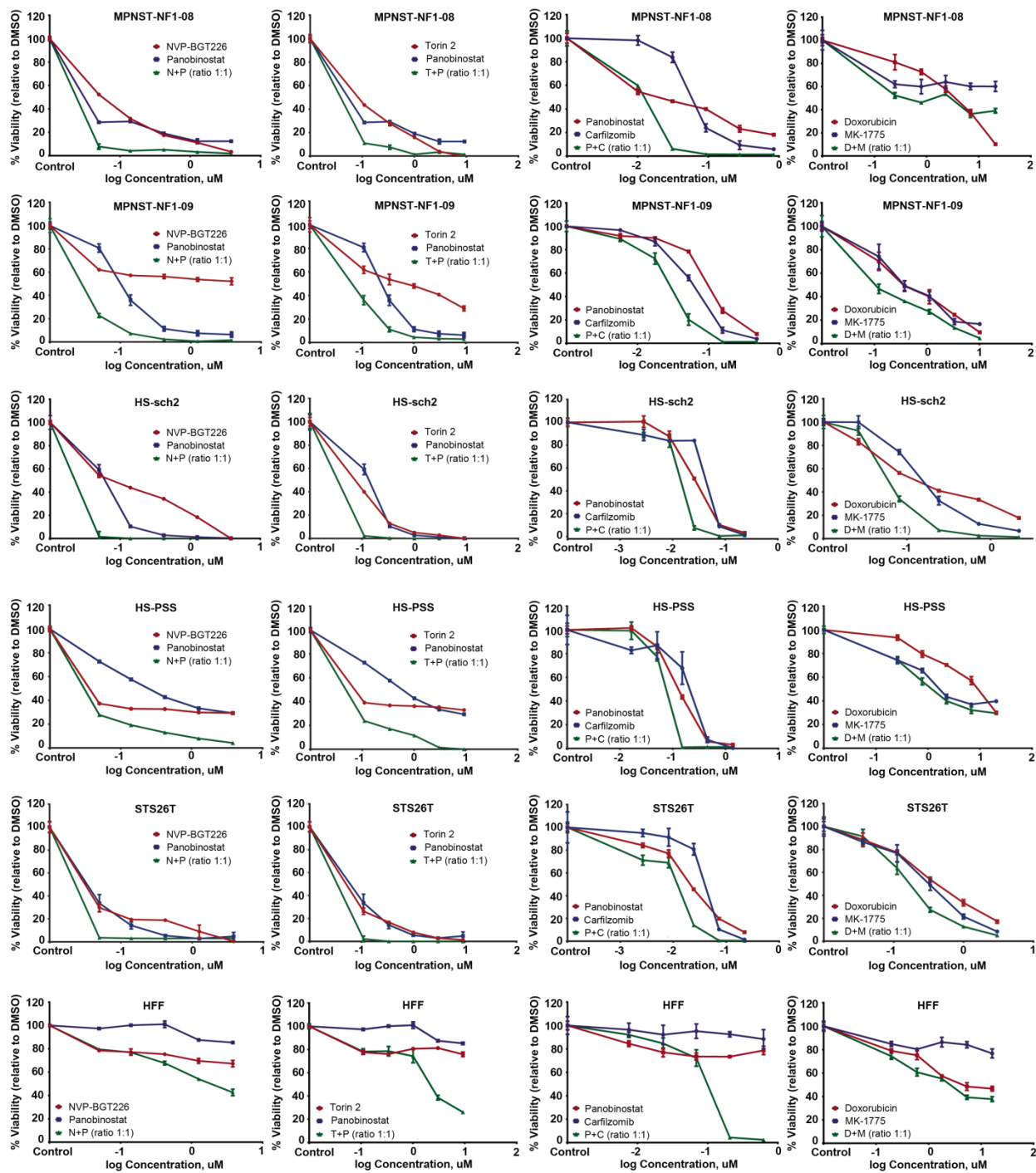


Figure S3. Single-agent and combined responses on cell viability of six MPNST cell lines and a non-tumor fibroblastic cell line (Human Foreskin Fibroblast) from the four most synergistic combinations, which are further validated *in vivo*.

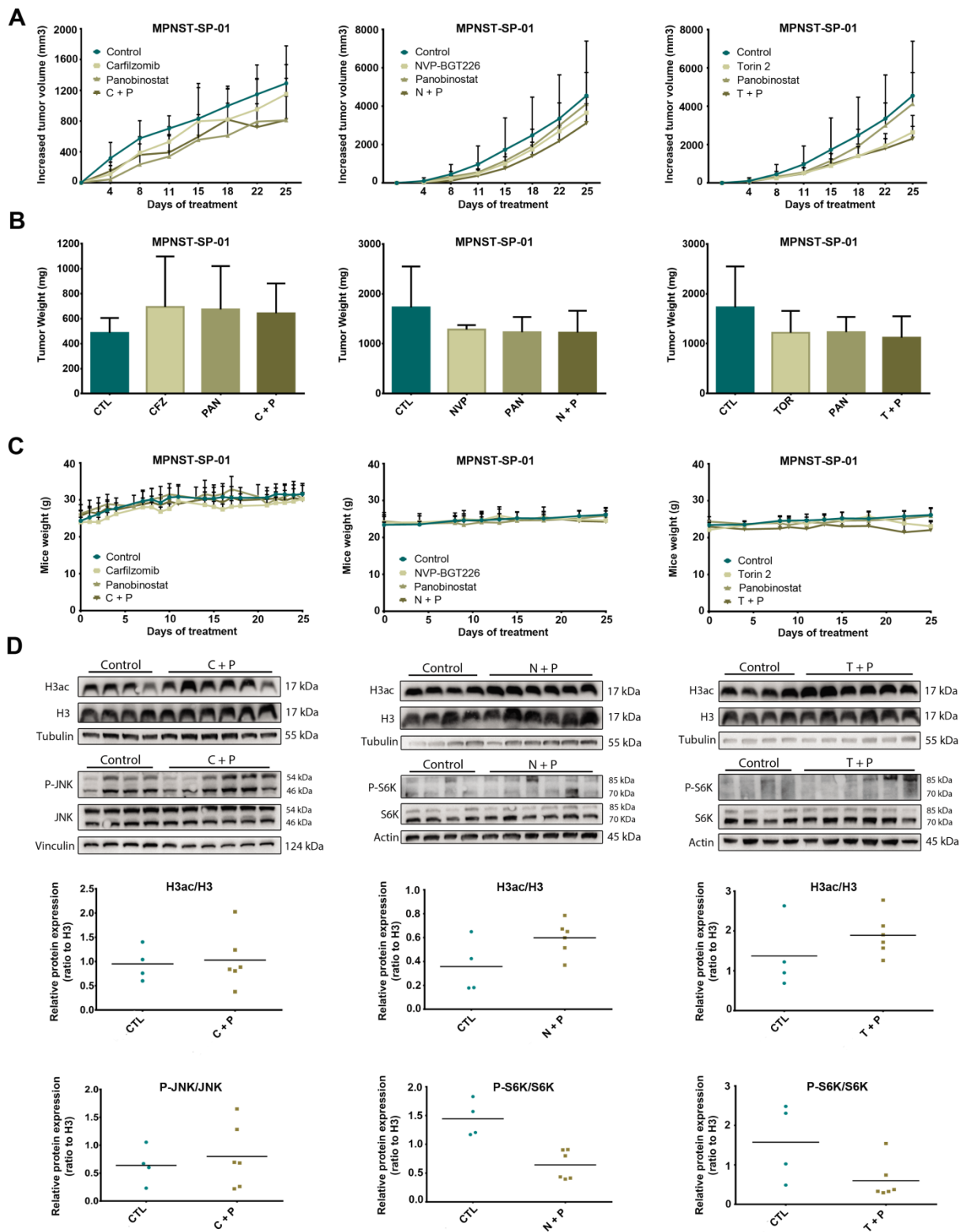


Figure S4. Combination treatments including Panobinostat (with Carfilzomib/Torin 2/NVP-BGT226) in MPNST-SP-01 PDOX model. **A.** Increased tumor volume during treatment with single-agents and combinations. **B.** Mean tumor weight after 25 days of single-agent and combined treatments. **C.** Mouse weight evolution during treatments. **D.** Protein expression analyses by Western blot for the main drug molecular targets in control tumors (n=4) and tumors treated with combinations (n=6). CTL: mice treated with vehicle, BGT226: mice treated with NVP-BGT226, PAN: mice treated with Panobinostat, CFZ: mice treated with Carfilzomib, CFZ+PAN: mice treated with the combination Carfilzomib and Panobinostat, BGT226+PAN: mice treated with the combination NVP-BGT226 + Panobinostat, H3ac: acetylation of Histone 3, P-JNK: phosphorylation of JNK, P-S6K: phosphorylation of S6K.

Table S1. Clinical and molecular data of patients and tumors used to isolate the MPNST-SP-01, MPNST-NF1-08, and MPNST-NF1-09 cell lines.

Tumor ID	Age	Sex	Ethnicity	NF1/ sporadic	Tumor grade	Location	NF1		CDK2NA	PRC2			H3K27 staining	TP53
							Germline	Somatic		SUZ12	EED	EZH1		
MPNST-SP-01	88	M	EU(Spain)	Sporadic	IV	Latero cervical	-	NM_000267.2: c.3520C>T p.(Gln1174*)	-	-	-	NM_001991.3: c.196C>T (p.(Q72X))	Negative	NM_001126115.2: c.553C>T + LOH
MPNST-NF1-08	28	M	EU(Spain)	NF1	III	Dorsal	NM_000267.2: c.701_730+10del (intronic)	LOH	chr9:g.20290684_24186926del (HD by inversions and translocations)	NM_015355.2: c.1235_1240del + LOH	-	-	Negative	-
MPNST-NF1-09	35	F	EU(Spain)	NF1	III	Sciatic nerve	NM_000267.2: c.6792C>A p.(Tyr2264*)	NM_000267.2: c.1186-5_1186-1delATAG (intronic)	chr9:g.21953930_22196588del (HD by inversions)	-	-	-	Positive	NM_001126115.2: c.448C>T + LOH

Table S2. Dosage toxicity and administration schedule tests for the four combinations that were tested in our PDOX models.

	Compound 1	Dose (mg/kg)	Schedule (days a week)	Administration route	Compound 2	Dose (mg/kg)	Schedule (days a week)	Administration route	Weight reduction	Mortality
1	NVP-BGT226	5	5	ip	Panobinostat	5	5	ip	>20%	60%
2	NVP-BGT226	5	3	ip	Panobinostat	5	3	ip	>10%	-
3	NVP-BGT226	2.5	3	ip	Panobinostat	5	3	ip	<10%	-
4	NVP-BGT226	2.5	5	ip	Panobinostat	5	5	ip	>10%	-
5	Torin 2	20	3	ip	Panobinostat	5	3	ip	>20%	90%
6	Torin 2	10	2	ip	Panobinostat	5	2	ip	<10%	-
7	Torin 2	10	3	ip	Panobinostat	5	3	ip	<10%	-
8	Torin 2	10	5	ip	Panobinostat	5	5	ip	>10%	-
9	Torin 2	5	3	ip	Panobinostat	5	3	ip	<10%	-
10	MK-1775	20	5	oral	Doxorubicin	8	Once at beginning	ip	<10%	-
11	MK-1775	50	5	oral	Doxorubicin	8	Once at beginning	ip	<10%	-
12	Carfilzomib	2	2	iv	Panobinostat	5	5	ip	0%	-
13 ¹	Carfilzomib	2	2	iv	Panobinostat	10	5	ip	<10%	-
14	Carfilzomib	2	2	iv	Panobinostat	10	3	ip	<10%	-
15	Carfilzomib	5	2	iv	Panobinostat	5	5	ip	10%	-
16	Carfilzomib	5	2	iv	Panobinostat	10	5	ip	-	100%
17	Carfilzomib	5	2	iv	Panobinostat	10	3	ip	-	100%

¹The doses and administration schedules for Carfilzomib and Panobinostat were further used in our PDOX model, but high mortality occurred in the first week of treatment.

iv: intravenous

ip: intraperitoneal

Table S3. Dosages, solvents, and schedule of administration for the compounds used in the *in vivo* experiments.

Compound	Administration route	Dose (mg/Kg)	Solvent	Schedule	Days of administration per week
Panobinostat	ip	5	98% Dextrose (5%) in water+2% DMSO	TIW	Day 1, 3, 5
NVP-BGT226	ip	2.5	90% Saline+10% DMSO	TIW	Day 1, 3, 5
Torin 2	ip	10	80% water+10% Khollipor+10% DMSO	TIW	Day 1, 3, 5
Carfilzomib	iv	2	Saline 5% Glucose	BW	Day 1, 2
MK-1775	oral	50	Methylcellulose 0.5% in saline	5 Day On, 2 Day Off	Day 1, 2, 3, 4, 5
Doxorubicin	ip	8	Saline	1 dose in the 1 st day	-

TIW: three times a week, BW: twice a week.

iv: intravenous

ip: intraperitoneal