

Synergistic Activity of PARP Inhibition by Talazoparib (BMN 673) with Temozolomide in Pediatric Cancer Models in the Pediatric Preclinical Testing Program

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Supplemental Figure 1. Kaplan-Meier estimates for Event-Free Survival in Ewing sarcoma xenograft models.

Supplemental Figure 2. Quantification of total (cleaved + uncleaved) PARP, and cleaved PARP following 5 days treatment of TC-71R tumors with talazoparib, temozolomide or the combination. Relative levels of total and cleaved PARP are shown for parental TC-71 xenografts.

Supplemental Table I: Topotecan in vitro activity in the presence and absence of talazoparib (10 nM)

Cell Line	Histotype	Topotecan rIC ₅₀ (nM)	Topotecan + Talazoparib rIC ₅₀ (nM)	Potential	Topotecan Relative I/O% (Observed Ymin) ³	Topotecan + Talazoparib Relative I/O% (Observed Ymin) ³
RD	Rhabdomyosarcoma	1.7	7.2	4.3	37%	38%
Rh41	Rhabdomyosarcoma	20.4	12.9	0.6	-22%	-31%
Rh18	Rhabdomyosarcoma	3.9	10.8	2.8	-11%	-34%
Rh30	Rhabdomyosarcoma	4.1	11.3	2.7	-23%	-50%
BT-12	Rhabdoid	7.1	20.1	2.8	14%	12%
CHLA-266	Rhabdoid	8.9	20.6	2.3	2%	-7%
TC-71	Ewing sarcoma	NE	4.3	NA	-98%	-99%
CHLA-9	Ewing sarcoma	1.2	2.1	1.8	-94%	-94%
CHLA-10	Ewing sarcoma	3.2	10.8	3.3	-82%	-85%
CHLA-258	Ewing sarcoma	4.9	10.7	2.2	-75%	-80%
GBM2	Glioblastoma	2.9	9.0	3.1	-61%	-66%
NB-1643	Neuroblastoma	2.6	6.7	2.6	-87%	-88%
NB-EBc1	Neuroblastoma	5.6	12.5	2.2	-91%	-93%
CHLA-90	Neuroblastoma	5.5	NE	NA	29%	32%
CHLA-136	Neuroblastoma	4.2	14.1	3.4	-46%	-50%
NALM-6	ALL	3.5	11.6	3.3	-99%	-99%
COG-LL-317	ALL	0.8	3.3	4.0	-98%	-99%
RS4;11	ALL	4.3	12.5	2.9	-96%	-97%
MOLT-4	ALL	1.3	5.2	3.9	-100%	-100%
CCRF-CEM (1)	ALL	4.0	9.6	2.4	-97%	-97%
Kasumi-1	AML	6.4	13.5	2.1	-63%	-77%
Karpas-299	ALCL	8.0	21.2	2.7	0%	-51%
Ramos-RA1	NHL	2.1	8.3	4.1	-89%	-87%
Median		4.1	10.8	2.8	-75%	-80%
Minimum		0.8	2.1	0.6	-100%	-100%
Maximum		20.4	21.2	4.3	37%	38%

¹ Ratio of topotecan rIC₅₀ in absence and presence talazoparib (10 nM)

² Ymin (observed) for topotecan in the presence of 10 nM talazoparib. See Materials and Methods for definition.

³ Relative In/Out% (observed Ymin) for topotecan or topotecan or topotecan in the presence of 10 nM talazoparib. See Materials and Methods for definition.

NE = not evaluable. NA = not applicable.

Supplemental Table II. Efficacy of PPTP Single agents and combinations in Xenograft Models

Study Information		Animal Counts/Status						EFS Evaluation			Tumor Volume Evaluation					Response Evaluation							Overall Group Response	
Cell Line	Line Description	Group ¹	N1 ²	Nd ³	No ⁴	Na ⁵	No. ev ⁶	KM med. ⁷	Log-Rank P-value	EFS T/C	Med. RTV ⁸	Avg. RTV ⁹	T/C (Day)	Wilc. P ¹⁰	PD	PD1	PD2	SD	PR	CR	MCR	Median Score		
A2	KT-10	A ¹	10	0	0	10	10	17.6			>4	2.74	.	.	10	0	0	0	0	0	0	0	0.0	PD
		B ²	10	0	0	10	10	21.8	0.084	1.2	>4	1.74	0.64	14	0.043	0	4	1	0	2	3	0	4.0	SD
		C ²	10	0	0	10	5	.	<0.001	>5.2	>4	0.02	0.01	14	<0.001	0	0	0	0	0	8	2	8.0	CR
		D ²	10	0	0	10	0	.	<0.001	>5.2	0.0	0.02	0.01	14	<0.001	0	0	0	0	0	0	10	10.0	MCR
		E ²	10	0	0	10	0	.	<0.001	>5.2	0.0	0.00	0.00	14	<0.001	0	0	0	0	0	0	10	10.0	MCR
		D v E							1.000															
A6	SK-NEP-1	A	9	0	0	9	9	10.5			>4	2.92	.	.	9	0	0	0	0	0	0	0	0.0	PD
		B	9	0	0	9	9	8.9	0.389	0.8	>4	3.09	1.06	7	0.666	0	9	0	0	0	0	0	0.0	PD1
		C	9	0	0	9	9	10.1	0.916	1.0	>4	2.78	0.95	7	0.666	0	8	1	0	0	0	0	0.0	PD1
		D	9	0	0	9	8	32.3	<0.001	3.1	>4	0.28	0.09	7	<0.001	0	0	0	0	5	4	0	6.0	PR
		E	10	0	0	10	0	.	<0.001	>8.6	0.0	0.23	0.08	7	<0.001	0	0	0	0	0	0	10	10.0	MCR
		D v E							<0.001															
B2	EW5	A	9	0	0	9	9	8.8			>4	3.17	.	.	9	0	0	0	0	0	0	0	0.0	PD
		B	10	0	0	10	10	9.9	0.507	1.1	>4	2.41	0.76	7	0.035	0	10	0	0	0	0	0	0.0	PD1
		C	10	0	0	10	10	8.9	0.941	1.0	>4	3.05	0.96	7	0.720	0	10	0	0	0	0	0	0.0	PD1
		D	10	0	0	10	10	28.6	<0.001	3.3	>4	0.61	0.19	7	<0.001	0	0	3	0	3	4	0	6.0	PR
		E	10	0	0	10	10	24.0	<0.001	2.7	>4	0.60	0.19	7	<0.001	0	0	4	0	0	6	0	8.0	CR
		D v E							0.055															
B3	EW8	A	10	0	0	10	10	6.8			>4	4.13	.	.	10	0	0	0	0	0	0	0	0.0	PD
		B	10	0	0	10	10	9.1	0.005	1.3	>4	2.94	0.71	7	<0.001	0	9	1	0	0	0	0	0.0	PD1
		C	10	0	0	10	10	13.4	<0.001	2.0	>4	1.61	0.39	7	<0.001	0	1	9	0	0	0	0	2.0	PD2
		D	10	0	0	10	10	15.7	<0.001	2.3	>4	1.83	0.44	7	<0.001	0	1	9	0	0	0	0	2.0	PD2
		E	10	0	0	10	10	12.6	<0.001	1.9	>4	2.28	0.55	7	<0.001	0	3	7	0	0	0	0	2.0	PD2
		D v E							0.361															
B11	TC-71	A	9	0	0	9	9	10.4			>4	6.07	.	.	9	0	0	0	0	0	0	0	0.0	PD
		B	10	0	0	10	10	10.7	0.368	1.0	>4	6.98	1.15	14	0.315	0	10	0	0	0	0	0	0.0	PD1
		C	10	0	0	10	10	12.2	0.016	1.2	>4	4.95	0.82	14	0.113	0	9	1	0	0	0	0	0.0	PD1
		D	10	0	0	10	3	.	<0.001	>8.8	0.0	0.04	0.01	14	<0.001	0	0	0	0	0	3	7	10.0	MCR
		E	10	0	0	10	4	.	<0.001	>8.8	0.0	0.06	0.01	14	<0.001	0	0	0	0	0	4	6	10.0	MCR
		D v E							0.833															
B12	CHLA258	A	10	0	0	10	10	9.5			>4	8.66	.	.	10	0	0	0	0	0	0	0	0.0	PD
		B	10	0	0	10	10	10.2	0.242	1.1	>4	7.20	0.83	7	0.211	0	9	1	0	0	0	0	0.0	PD1

Study Information		Animal Counts/Status					EFS Evaluation			Tumor Volume Evaluation					Response Evaluation							Overall Group Response				
Cell Line	Line Description	Group ¹	N1 ²	Nd ³	No ⁴	Na ⁵	No. ev ⁶	KM med. ⁷	Log-Rank P-value	EFS T/C	Med. RTV ⁸	Avg. RTV ⁹	T/C (Day)	Wilc. P ¹⁰	PD	PD1	PD2	SD	PR	CR	MCR	Median Score				
B15	ES6	C	10	0	0	10	10	11.8	0.034	1.2	>4	5.88	0.68	14	0.029	0	8	2	0	0	0	0	0.0	PD1		
		D	10	0	0	10	0	.	<0.001	>9.6	0.0	0.07	0.01	14	<0.001	0	0	0	0	0	0	10	10.0	MCR		
		E	10	0	0	10	5	.	<0.001	>9.6	>4	0.05	0.01	14	<0.001	0	0	0	0	0	8	2	8.0	CR		
		D v E		0.033																						
		A	10	0	0	10	10	19.1				>4	2.93	.	.		10	0	0	0	0	0	0	0.0	PD	
		B	10	0	0	10	10	25.1	0.039	1.3	>4	2.22	0.76	14	0.105	0	7	3	0	0	0	0	0	0.0	PD1	
		C	10	0	0	10	10	20.6	0.845	1.1	>4	2.68	0.92	14	0.393	0	10	0	0	0	0	0	0	0.0	PD1	
B6	Rh28	D	10	0	0	10	10	35.9	<0.001	1.9	>4	0.93	0.32	14	<0.001	0	1	6	0	1	2	0	2.0	PD2		
		E	10	0	0	10	10	31.6	<0.001	1.7	>4	1.37	0.47	14	<0.001	0	3	7	0	0	0	0	2.0	PD2		
		D v E		0.162																						
		A	9	0	0	9	9	30.0				>4	2.46	.	.		9	0	0	0	0	0	0	0.0	PD	
		B	10	0	0	10	3	.	<0.001	>3.0	0.0	1.17	0.48	14	<0.001	0	0	0	0	0	3	7	10.0	MCR		
		C	10	0	0	10	10	13.7	0.003	0.5	>4	3.83	1.56	7	0.017	0	10	0	0	0	0	0	0	0.0	PD1	
		D	10	0	0	10	1	.	<0.001	>3.0	0.0	0.56	0.23	14	<0.001	0	0	0	0	0	1	9	10.0	MCR		
B7	Rh30	E	10	0	0	10	0	.	<0.001	>3.0	0.0	0.03	0.01	14	<0.001	0	0	0	0	0	0	10	10.0	MCR		
		D v E		1.000																						
		A	10	0	0	10	10	15.4				>4	3.93	.	.		10	0	0	0	0	0	0	0.0	PD	
		B	10	0	0	10	10	16.8	0.799	1.1	>4	3.60	0.91	14	0.739	0	10	0	0	0	0	0	0	0.0	PD1	
		C	10	0	0	10	10	15.0	0.624	1.0	>4	3.74	0.95	14	0.796	0	8	2	0	0	0	0	0	0.0	PD1	
		D	10	0	0	10	10	50.0	<0.001	3.2	>4	0.34	0.09	14	<0.001	0	0	0	0	4	6	0	8.0	CR		
		E	10	0	0	10	10	37.3	<0.001	2.4	>4	0.58	0.15	14	<0.001	0	0	5	0	3	2	0	4.0	SD		
B8	Rh41	D v E		<0.001																						
		A	10	0	0	10	10	12.8				>4	4.75	.	.		10	0	0	0	0	0	0	0.0	PD	
		B	10	0	0	10	10	11.8	0.176	0.9	>4	5.18	1.09	14	0.247	0	10	0	0	0	0	0	0	0.0	PD1	
		C	10	0	0	10	10	11.1	0.090	0.9	>4	5.41	1.14	14	0.143	0	10	0	0	0	0	0	0	0.0	PD1	
		D	10	0	0	10	10	11.3	0.072	0.9	>4	5.11	1.08	14	0.247	0	10	0	0	0	0	0	0	0.0	PD1	
		E	10	0	0	10	10	13.9	0.061	1.1	>4	3.35	0.70	14	0.089	0	7	3	0	0	0	0	0	0.0	PD1	
		D v E		0.009																						
B16	ES-4	A	10	0	0	10	10	11.4				>4	5.56	.	.		10	0	0	0	0	0	0	0.0	PD	
		B	10	0	0	10	10	15.8	0.001	1.4	>4	3.73	0.67	14	0.005	0	8	2	0	0	0	0	0.0	PD1		
		C	10	0	0	10	10	14.3	0.032	1.3	>4	4.67	0.84	14	0.089	0	9	1	0	0	0	0	0.0	PD1		
		D	10	0	0	10	8	81.5	<0.001	7.1	>4	0.01	0.00	14	<0.001	0	0	0	0	0	9	1	8.0	CR		
		E	10	0	0	10	7	77.4	<0.001	6.8	>4	0.00	0.00	14	<0.001	0	0	0	0	0	9	1	8.0	CR		
		D v E		0.814																						
		B29	ES-2	A	9	0	0	9	9	11.8				>4	5.25	.	.		9	0	0	0	0	0	0	0.0
B	9			0	0	9	9	12.7	0.567	1.1	>4	5.75	1.10	14	0.730	0	9	0	0	0	0	0	0	0.0	PD1	

Study Information		Animal Counts/Status					EFS Evaluation			Tumor Volume Evaluation					Response Evaluation							Overall Group Response			
Cell Line	Line Description	Group ¹	N1 ²	Nd ³	No ⁴	Na ⁵	No. ev ⁶	KM med. ⁷	Log-Rank P-value	EFS T/C	Med. RTV ⁸	Avg. RTV ⁹	T/C	T/C Time (Day)	Wilc. P ¹⁰	PD	PD1	PD2	SD	PR	CR	MCR	Median Score		
B30	ES-3	C	9	0	0	9	9	14.0	0.712	1.2	>4	4.44	0.85	14	0.297	0	9	0	0	0	0	0	0.0	PD1	
		D	10	0	0	10	10	19.2	0.002	1.6	>4	2.20	0.42	14	0.002	0	3	7	0	0	0	0	2.0	PD2	
		E	10	0	0	10	10	30.3	<0.001	2.6	>4	0.84	0.16	14	<0.001	0	0	4	0	0	6	0	8.0	CR	
		D v E		0.019																					
		A	9	0	0	9	9	8.9			>4	8.93	.	.		9	0	0	0	0	0	0	0.0	PD	
		B	10	0	0	10	10	10.3	0.007	1.2	>4	6.69	0.75	14	0.013	0	9	1	0	0	0	0	0.0	PD1	
		C	10	0	0	10	10	10.7	0.011	1.2	>4	6.57	0.74	14	0.013	0	10	0	0	0	0	0	0.0	PD1	
		D	10	0	0	10	10	26.0	<0.001	2.9	>4	0.95	0.11	14	<0.001	0	0	0	0	2	8	0	8.0	CR	
		E	10	0	0	10	10	18.3	<0.001	2.1	>4	2.51	0.28	14	<0.001	0	0	2	0	2	6	0	8.0	CR	
		D v E		0.001																					
B31	ES-7	A	9	0	0	9	9	11.6			>4	5.37	.	.		9	0	0	0	0	0	0.0	PD		
		B	10	0	0	10	10	18.3	0.003	1.6	>4	2.95	0.55	14	0.006	0	3	7	0	0	0	0	2.0	PD2	
		C	9	0	0	9	9	15.7	0.021	1.4	>4	3.69	0.69	14	0.024	0	6	3	0	0	0	0.0	PD1		
		D	9	0	0	9	0	.	<0.001	>7.8	0.0	0.06	0.01	14	<0.001	0	0	0	0	0	0	9	10.0	MCR	
		E	9	0	0	9	0	.	<0.001	>7.8	0.0	0.02	0.00	14	<0.001	0	0	0	0	0	0	9	10.0	MCR	
		D v E		1.000																					
B32	ES-8	A	10	0	0	10	10	5.7			>4	5.20	.	.		10	0	0	0	0	0	0.0	PD		
		B	10	0	0	10	10	7.1	0.110	1.2	>4	4.18	0.80	7	0.063	0	8	2	0	0	0	0.0	PD1		
		C	10	0	0	10	10	10.7	<0.001	1.9	>4	2.23	0.43	7	<0.001	0	2	8	0	0	0	2.0	PD2		
		D	10	0	0	10	7	38.7	<0.001	6.7	>4	0.16	0.03	7	<0.001	0	0	0	0	0	7	3	8.0	CR	
		E	10	0	0	10	6	33.4	<0.001	5.8	>4	0.15	0.03	7	<0.001	0	0	0	0	0	6	4	8.0	CR	
		D v E		0.797																					
D1	GBM2	A	10	0	0	10	10	6.5			>4	4.17	.	.		10	0	0	0	0	0	0.0	PD		
		B	10	0	0	10	10	35.3	<0.001	5.4	>4	0.87	0.21	7	<0.001	0	0	0	0	0	10	0	8.0	CR	
		C	10	0	0	10	10	8.0	0.295	1.2	>4	3.68	0.88	7	0.529	0	8	2	0	0	0	0.0	PD1		
		D	10	0	0	10	6	83.2	<0.001	12.8	>4	0.60	0.14	7	<0.001	0	0	0	0	0	6	4	8.0	CR	
		E	10	0	0	10	3	.	<0.001	>14.0	0.0	0.48	0.12	7	<0.001	0	0	0	0	0	3	7	10.0	MCR	
D v E		0.298																							

¹ A: Control; B, TMZ 30 mg/kg daily x 5; C; talazoparib 0.25 mg/kg BID x 5; D; TMZ 30 mg/kg x 5 + talazoparib 0.1 mg/kg BID x 5 (Combination A); E, TMZ 12 mg/kg x 5 + talazoparib 0.25 mg/kg BID x 5 (Combination B).

² N1 – number of mice in group; ⁴ Nd – number of mice that experienced toxic deaths; ⁵ No – number of additional mice excluded; ⁶ Na – number of mice analyzed; ⁷ Number of events. An event was defined as a quadrupling of tumor volume from the initial volume for solid tumor cell lines and reaching $\geq 25\%$ hCD45 cells for ALL cell lines; ⁸ Kaplan-Meier estimate of median days to event. Time to event was estimated using interpolation; ⁹ For solid tumor cell lines, this column is the median relative tumor volume at the end of the study; for ALL cell lines, this is the median hCD45% at the end of the study; ¹⁰ For solid tumor cell lines, this column is the average relative tumor volume at the day T/C

was assessed (day 21 or before); ¹¹ P-value testing the relative tumor volumes between treatment and control groups at the day T/C was assessed (day 21 or before) (the exact Wilcoxon rank-sum test was used). Note: Studies where the EFS was significantly (or marginally) different between control and treatment groups ($p < 0.10$) and where the median EFS in the control group was longer than the median EFS in the treatment group are highlighted in yellow.

Supplemental Table III. Efficacy of Combination B against PPTP Xenograft Models

Study Information			Animal Counts/Status					EFS Evaluation			Tumor Volume Evaluation					Response Evaluation							Overall Group Response	
Cell Line	Line Description	Group	N1 ³	Nd ⁴	No ⁵	Na ⁶	No. ev ⁷	KM med. ⁸	Log-Rank P-value	EFS T/C	Med. RTV ⁹	Avg. RTV ¹⁰	T/C	T/C Time (Day)	Wilc. P ¹¹	PD	PD1	PD2	SD	PR	CR	MCR	Median Score	
D1	GBM2	A ¹	10	0	0	10	10	11.2			>4	2.73	.	7		10	0	0	0	0	0	0	0.0	PD
		B ²	10	5	0	5	0	.	<0.001	> 3.7	0.0	0.00	0.00	7	<0.001	0	0	0	0	0	0	5	10.0	MCR
D2	BT-39	A	10	0	0	10	10	5.4			>4	6.00	.	7		10	0	0	0	0	0	0	0.0	PD
		B	10	4	0	6	6	12.4	<0.001	2.3	>4	3.29	0.55	7	<0.001	0	1	5	0	0	0	0	2.0	PD2
D3	D645	A	10	0	0	10	10	8.7			>4	3.35	.	7		10	0	0	0	0	0	0	0.0	PD
		B	10	2	0	8	0	.	<0.001	> 4.8	0.0	0.40	0.12	7	<0.001	0	0	0	0	0	0	8	10.0	MCR
E1	NB-SD	A	10	0	0	10	10	6.5			>4	4.35	.	7		10	0	0	0	0	0	0	0.0	PD
		B	10	0	1	9	8	38.6	<0.001	5.9	>4	2.47	0.57	7	<0.001	0	0	9	0	0	0	0	2.0	PD2
E3	NB-1691	A	10	0	0	10	10	5.5			>4	5.76	.	7		10	0	0	0	0	0	0	0.0	PD
		B	10	0	0	10	10	15.1	<0.001	2.8	>4	1.43	0.25	7	<0.001	0	0	10	0	0	0	0	2.0	PD2
E4	NB-EBc1	A	10	0	0	10	10	4.0			>4	11.29	.	7		10	0	0	0	0	0	0	0.0	PD
		B	10	0	0	10	10	10.7	<0.001	2.7	>4	2.07	0.18	7	<0.001	0	0	10	0	0	0	0	2.0	PD2
E5	CHLA-79	A	8	0	0	8	8	6.2			>4	4.64	.	7		8	0	0	0	0	0	0	0.0	PD
		B	10	0	0	10	9	32.1	<0.001	5.2	>4	0.75	0.16	7	<0.001	0	0	2	0	1	7	0	8.0	CR
E6	NB-1643	A	10	0	0	10	10	6.2			>4	5.04	.	7		10	0	0	0	0	0	0	0.0	PD
		B	10	0	0	10	10	19.7	<0.001	3.2	>4	1.48	0.29	7	<0.001	0	0	9	0	1	0	0	2.0	PD2
F1	OS-1	A	10	0	0	10	10	22.5			>4	3.68	.	21		10	0	0	0	0	0	0	0.0	PD
		B	10	1	0	9	9	33.1	<0.001	1.5	>4	2.34	0.64	21	<0.001	0	5	4	0	0	0	0	0.0	PD1
F2	OS-2	A	10	0	0	10	10	24.7			>4	2.91	.	21		10	0	0	0	0	0	0	0.0	PD
		B	10	2	0	8	0	.	<0.001	> 1.7	2.7	1.22	0.42	21	<0.001	0	0	8	0	0	0	0	2.0	PD2
F3	OS-17	A	10	0	0	10	10	20.1			>4	4.21	.	21		10	0	0	0	0	0	0	0.0	PD
		B	10	0	0	10	10	29.7	<0.001	1.5	>4	2.63	0.63	21	<0.001	0	6	4	0	0	0	0	0.0	PD1
F11	OS-31	A	10	0	0	10	10	21.6			>4	3.75	.	21		10	0	0	0	0	0	0	0.0	PD
		B	10	2	0	8	5	38.5	<0.001	1.8	>4	1.47	0.39	21	<0.001	0	0	8	0	0	0	0	2.0	PD2
G1	ALL-2	A	9	0	0	9	9	8.3			>25	.	.	.		9	0	0	0	0	0	0	0.0	PD
		B	9	1	0	8	8	17.7	0.050	2.1	>25	.	.	.		0	3	5	0	0	0	0	2.0	PD2
G3	ALL-4	A	9	0	1	8	8	6.0			>25	.	.	.		8	0	0	0	0	0	0	0.0	PD
		B	9	4	0	5	5	12.0	0.009	2.0	>25	.	.	.		0	0	4	0	1	0	0	2.0	PD2
G4	ALL-7	A	9	0	0	9	9	6.0			>25	.	.	.		9	0	0	0	0	0	0	0.0	PD
		B	9	5	0	4	4	11.8	0.001	2.0	>25	.	.	.		0	0	4	0	0	0	0	2.0	PD2
G5	ALL-8	A	9	0	0	9	9	6.0			>25	.	.	.		9	0	0	0	0	0	0	0.0	PD
		B	9	4	0	5	5	22.0	<0.001	3.7	>25	.	.	.		0	0	4	0	1	0	0	2.0	PD2
G7	ALL-17	A	9	0	0	9	8	6.2			>25	.	.	.		8	0	0	0	1	0	0	0.0	PD
		B	9	7	0	2	2	21.7	0.182	3.5	>25	.	.	.		0	0	2	0	0	0	0	2.0	PD2

Study Information		Animal Counts/Status						EFS Evaluation		Tumor Volume Evaluation					Response Evaluation						Overall Group Response		
Cell Line	Line Description	Group	N1 ³	Nd ⁴	No ⁵	Na ⁶	No. ev ⁷	KM med. ⁸	Log-Rank P-value	EFS T/C	Med. RTV ⁹	Avg. RTV ¹⁰	T/C (Day)	Wilc. P ¹¹	PD	PD1	PD2	SD	PR	CR	MCR	Median Score	
G8	ALL-19	A	9	0	0	9	8	4.1			>25	.	.	.	8	0	0	0	1	0	0	0.0	PD
		B	9	5	0	4	4	11.9	0.540	2.9	>25	.	.	.	0	0	4	0	0	0	0	2.0	PD2
G14	ALL-31	A	9	0	0	9	9	10.0			>25	.	.	.	9	0	0	0	0	0	0	0.0	PD
		B	9	4	0	5	5	9.1	0.390	0.9	>25	.	.	.	0	3	2	0	0	0	0	0.0	PD1
G15	MLL-7	A	9	0	0	9	8	9.1			>25	.	.	.	8	0	0	1	0	0	0	0.0	PD
		B	9	6	0	3	3	26.5	0.327	2.9	>25	.	.	.	0	0	0	0	2	1	0	6.0	PR

¹ A: Control; ² B: Treated (temozolomide 12 mg/kg Dx5, talazoparib 0.25 mg/kg BID x5); ³ N1 – number of mice in group; ⁴ Nd – number of mice that experienced toxic deaths; ⁵ No – number of additional mice excluded; ⁶ Na – number of mice analyzed; ⁷ Number of events. An event was defined as a quadrupling of tumor volume from the initial volume for solid tumor cell lines and reaching $\geq 25\%$ hCD45 cells for ALL cell lines; ⁸ Kaplan-Meier estimate of median days to event. Time to event was estimated using interpolation; ⁹ For solid tumor cell lines, this column is the median relative tumor volume at the end of the study; for ALL cell lines, this is the median hCD45% at the end of the study; ¹⁰ For solid tumor cell lines, this column is the average relative tumor volume at the day T/C was assessed (day 21 or before); ¹¹ P-value testing the relative tumor volumes between treatment and control groups at the day T/C was assessed (day 21 or before) (the exact Wilcoxon rank-sum test was used).

Supplemental Table IV: Therapeutic Enhancement in vivo.

Cell Line	Xenograft	TMZ ¹ (group B) T-C	TAL ² (group C) T-C	Combo A (group D) T-C	P-value [combination D vs. 0904]	P-value [combination D vs. 1206]	Therapeutic Enhancement
A2	KT-10	4.17	>73.41	>73.41	0.000011	0.032508	NO
A6	SK-NEP-1	-1.61	-0.43	21.79	0.000041	0.000041	YES
B2	EW5	1.11	0.10	19.85	0.000011	0.000011	YES
B3	EW8	2.35	6.64	8.93	0.000065	0.659843	NO
B11	TC-71	0.31	1.84	>80.62	0.000011	0.000011	YES
B12	CHLA258	0.68	2.37	>81.52	0.000011	0.000011	YES
B15	ES6	6.00	1.46	16.79	0.008833	0.000011	YES
B6	Rh28	>61.02	-16.29	>61.02	0.210526	0.000011	NO
B7	Rh30	1.38	-0.42	34.60	0.000011	0.000011	YES
B8	Rh41	-0.95	-1.69	-1.45	0.62267	0.769664	NO
B16	ES4	4.41	2.88	70.07	0.000011	0.000011	YES
B29	ES2	0.85	2.16	7.40	0.001331	0.002219	YES
B30	ES3	1.46	1.83	17.10	0.000011	0.000011	YES
B31	ES7	6.74	4.10	>79.40	0.000011	0.000041	YES
B32	ES8	1.33	4.93	32.99	0.000011	0.000011	YES
D1	GBM2	28.82	1.54	76.72	0.000011	0.000011	YES
		TMZ(group B) T-C	TAL (group C) T-C	Combo B (group E) T-C	P-value [combination E vs. 0904]	P-value [combination E vs. 1206]	Therapeutic Enhancement
A2	KT-10	4.17	>73.41	>73.41	0.000011	0.032508	NO
A6	SK-NEP-1	-1.61	-0.43	>80.46	0.000011	0.000011	YES
B2	EW5	1.11	0.10	15.17	0.000011	0.000011	YES
B3	EW8	2.35	6.64	5.80	0.006495	0.335729	NO
B11	TC-71	0.31	1.84	>80.62	0.000011	0.000011	YES
B12	CHLA258	0.68	2.37	>81.52	0.000011	0.000011	YES
B15	ES6	6.00	1.46	12.44	0.116207	0.000022	NO
B6	Rh28	>61.02	-16.29	>61.02	0.210526	0.000011	NO
B7	Rh30	1.38	-0.42	21.88	0.000011	0.000011	YES
B8	Rh41	-0.95	-1.69	1.09	0.006971	0.003204	YES
B16	ES4	4.41	2.88	65.92	0.000011	0.000011	YES
B29	ES2	0.85	2.16	18.44	0.000054	0.000054	YES
B30	ES3	1.46	1.83	9.43	0.000011	0.000011	YES
B31	ES7	6.74	4.10	>79.40	0.000011	0.000041	YES
B32	ES8	1.33	4.93	27.69	0.000011	0.000011	YES
D1	GBM2	28.82	1.54	>84.50	0.000022	0.000011	YES

¹ TMZ, temozolomide; ² TAL, talazoparib.

Supplemental Table V. Responses to Tumor Models to Combination B (talazoparib plus low-dose temozolomide)

Line	Tumor Type	Median Time to Event	P-value ²	EFS T/C ³	Median RTV/CD45 at End of Study ⁴	Group Response ⁵
D645*	Glioblastoma	> EP	<0.001	> 4.8	0.0	MCR
NB-SD	Neuroblastoma	38.6	<0.001	5.9	>4	PD2
NB-1691	Neuroblastoma	15.1	<0.001	2.8	>4	PD2
NB-EBc1	Neuroblastoma	10.7	<0.001	2.7	>4	PD2
CHLA-79*	Neuroblastoma	32.1	<0.001	5.2	>4	CR
NB-1643*	Neuroblastoma	19.7	<0.001	3.2	>4	PD2
OS-1	Osteosarcoma	33.1	<0.001	1.5	>4	PD1
OS-2	Osteosarcoma	> EP	<0.001	> 1.7	2.7	PD2
OS-17	Osteosarcoma	29.7	<0.001	1.5	>4	PD1
OS-31	Osteosarcoma	38.5	<0.001	1.8	>4	PD2
ALL-2	ALL B-precursor	17.7	0.050	2.1	>25	PD2

¹ Temozolomide 12 mg/kg x 5 + talazoparib 0.25 mg/kg BID x 5

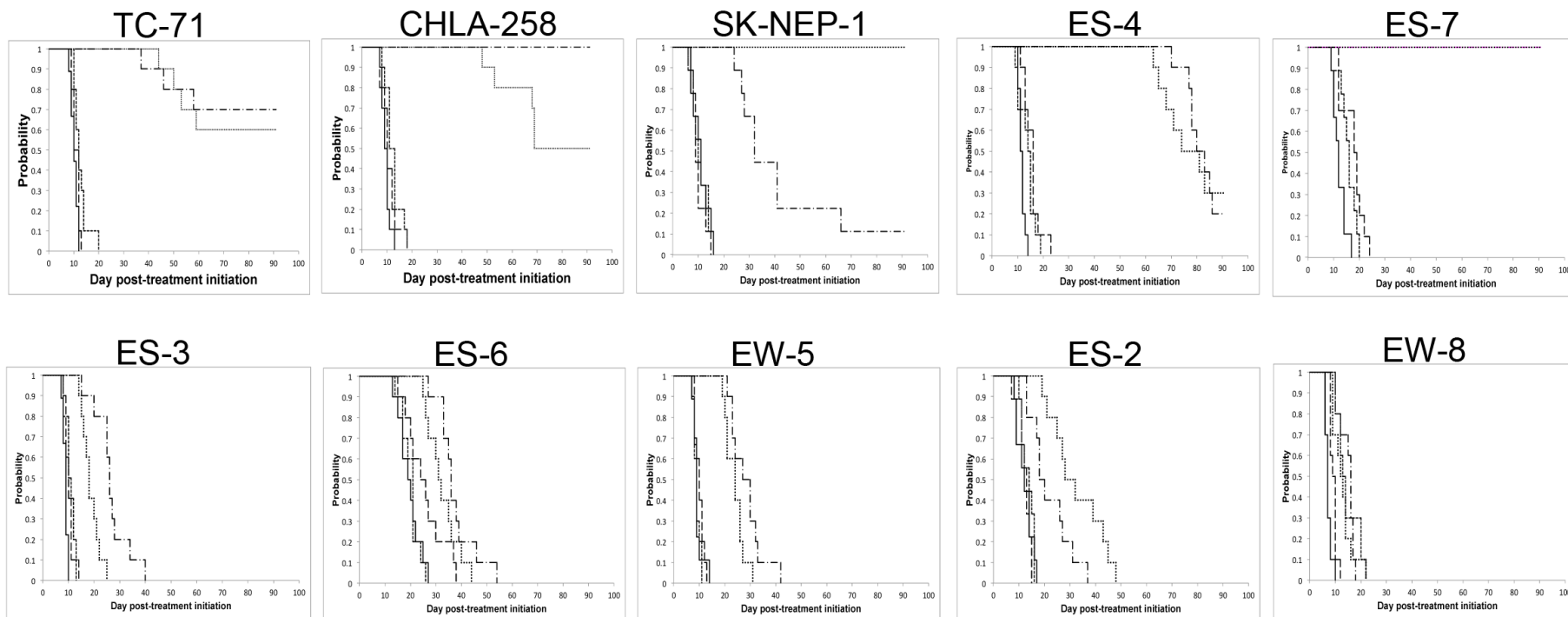
² P-value comparing EFS distribution of treated and control groups.

³ EFS T/C: ratio of event-free survival (median time to event) for treated and control groups

⁴ RTV: ratio of median relative tumor volume at end of observation period for treated to control groups

⁵ See Materials and Methods section for definitions of Progressive Disease 1 (PD1), Progressive Disease 2 (PD2), Stable Disease (SD), Partial Response (PR), Complete Response (CR), and Maintained Complete Response (MCR)

*Low MGMT-expressing xenograft lines.

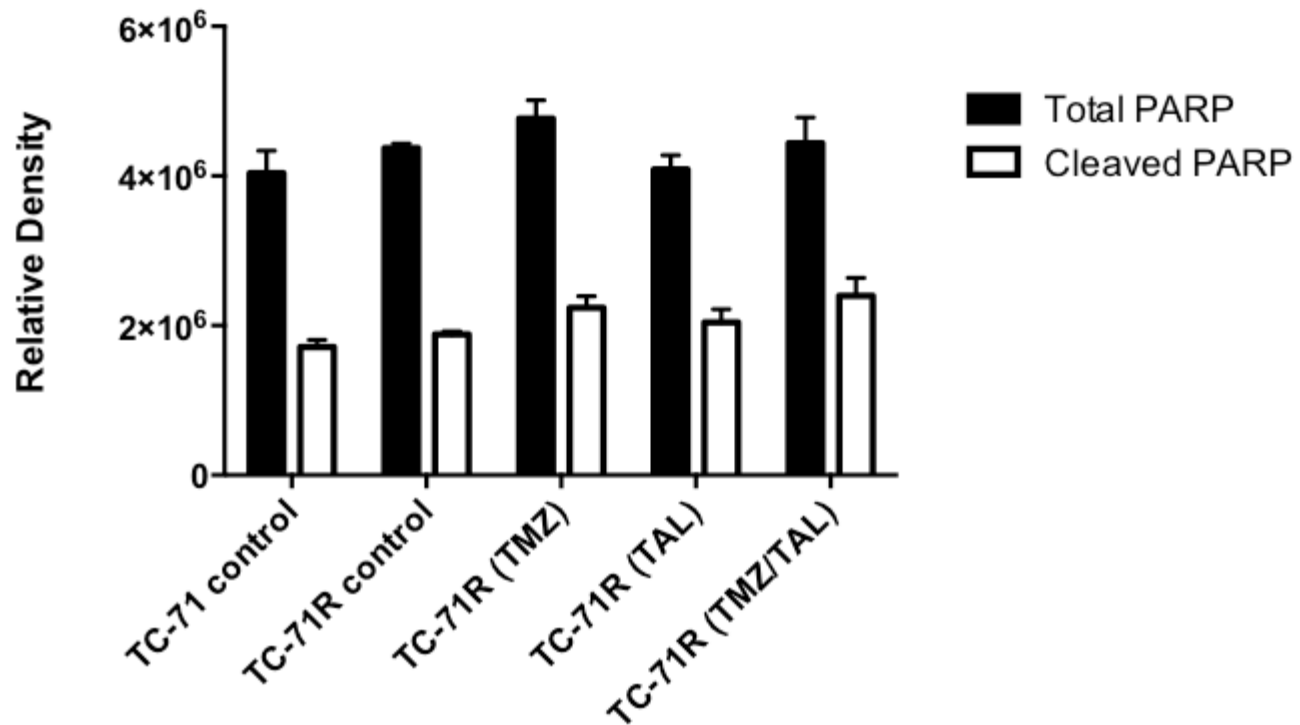


Supplemental Figure 1. Kaplan-Meier estimates for Event-Free Survival in Ewing sarcoma xenograft models.

Treatment Group

A
 B
 C
 D
 E

- A: Control;
- B, TMZ 30 mg/kg daily x 5;
- C; talazoparib 0.25 mg/kg BID x 5;
- D; TMZ 30 mg/kg x 5 + talazoparib 0.1 mg/kg BID x 5 (Combination A);
- E, TMZ 12 mg/kg x 5 + talazoparib 0.25 mg/kg BID x 5 (Combination B).



Supplemental Figure 2. Quantification of total (cleaved + uncleaved) PARP, and cleaved PARP following 5 days treatment of TC-71R tumors with talazoparib, temozolomide or the combination, from Figure 4F. Relative levels of total and cleaved PARP are shown for parental TC-71 xenografts.