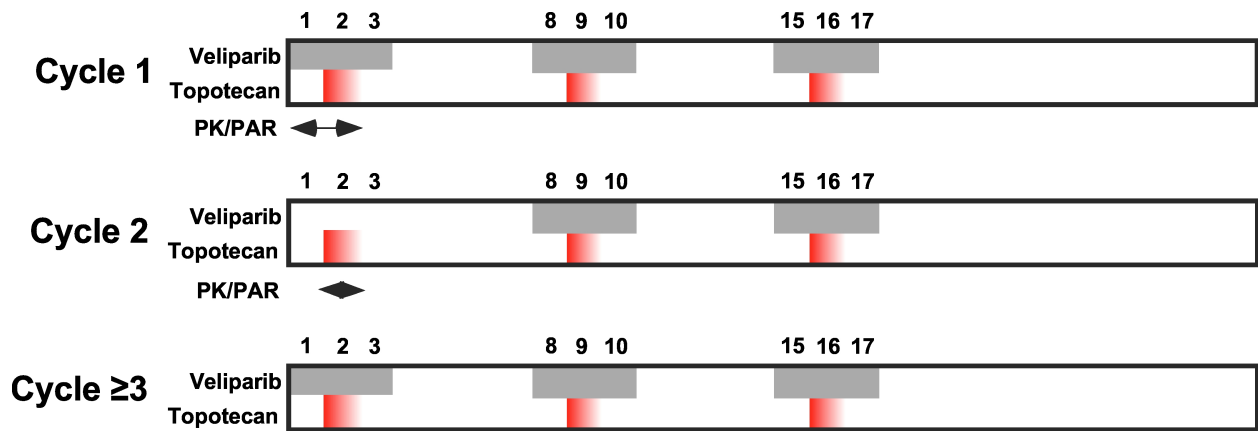


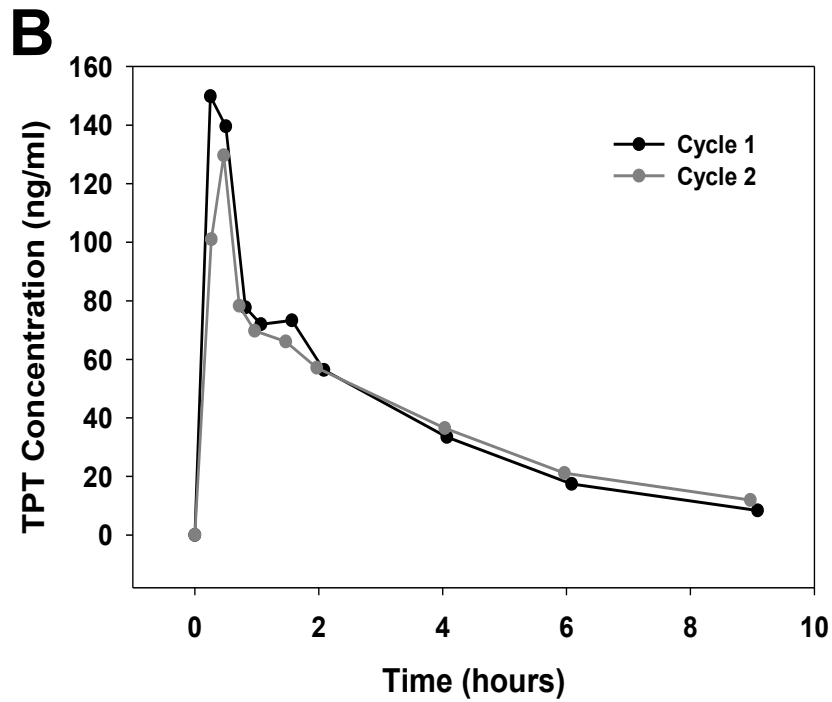
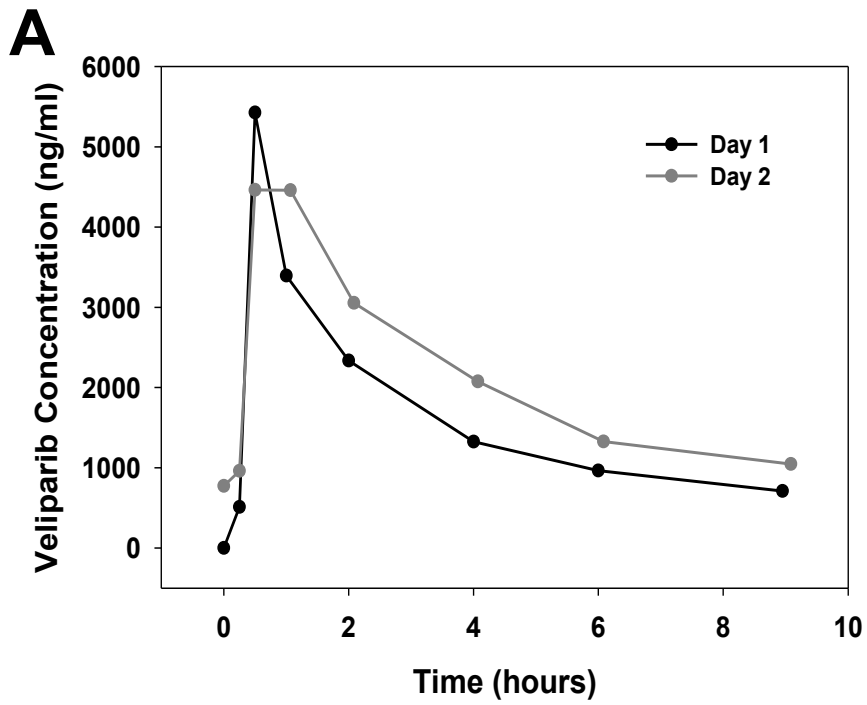
**Supplementary Material to**

**A Phase I Clinical Trial of the Poly(ADP-ribose) Polymerase Inhibitor Veliparib and  
Weekly Topotecan in Patients with Solid Tumors**

Andrea E. Wahner Hendrickson, Michael E. Menefee Lynn C. Hartmann,  
Harry J. Long, Donald W. Northfelt, Joel M. Reid, Felix Boakye-Agyeman,  
Olumide Kayode, Karen S. Flatten, Maria I. Harrell, Elizabeth M. Swisher,  
Guy G. Poirer, Daniel Satele, Jake Allred, Janet L. Lensing Alice Chen, Jiuping Ji,  
Yiping Zang, Charles Erlichman, Paul Haluska, and Scott H. Kaufmann

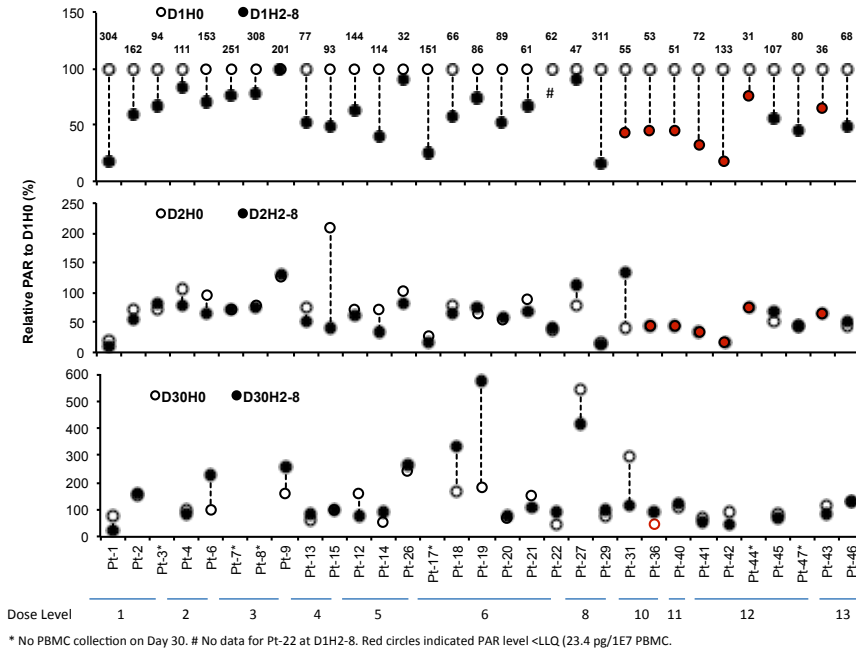


**Figure S1. Trial schema.** Patients received veliparib once or twice daily on days 1-3, 8-10 and 15-17 along with topotecan on days 2, 9 and 16 as indicated in Table 2. The timing of pharmacokinetic (PK) and pharmacodynamic studies (PAR assays) is indicated. To permit pharmacokinetic and PAR assays after topotecan alone, veliparib was omitted on Days 1-3 of Cycle 2 only.



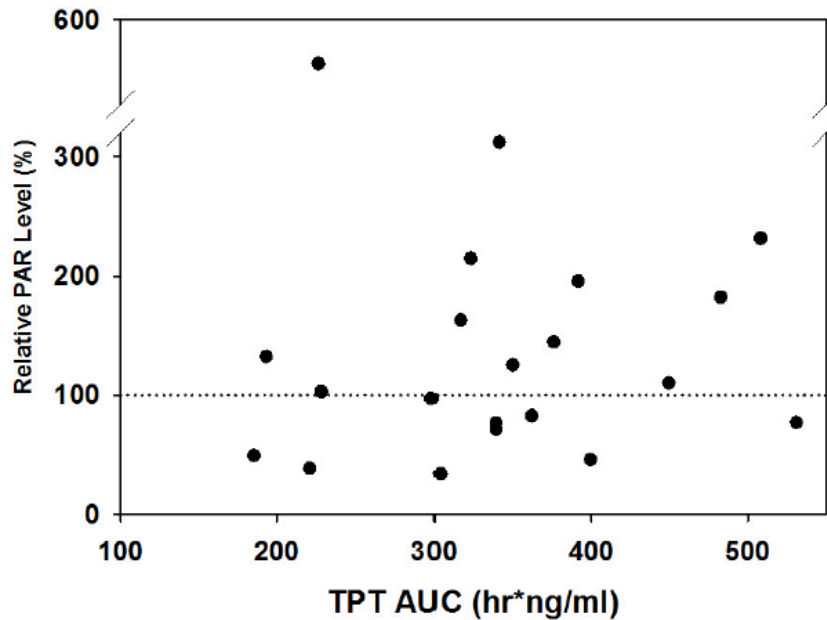
**Supplementary Figure 2.** Representative plasma concentration-time profiles for one patient treated with 200 mg veliparib (**A**) and 3 mg/m<sup>2</sup> topotecan (**B**).

# A Relative PAR Level to Pre-dose at D1H0 (%)



\* No PBMC collection on Day 30. # No data for Pt-22 at D1H2-8. Red circles indicated PAR level <LLQ (23.4 pg/1E7 PBMC).

# B



**Supplementary Figure 3. Effect of treatments on PAR levels.** A, PMBC PAR levels before treatment (open circles) and with largest change from before treatment level (closed circles) on days 1 (top), 2 (middle) and 30 (bottom) expressed as a % of baseline (Day 1, 0 hour) levels. **Numbers at top** indicate pretreatment PAR level in each patient's PBMCs in  $\text{pg}/10^7$  cells. **Red circles** indicate that samples on Day 1, hours 2-8 (upper panel) or Day 2, hours 0-8 (middle panel) were below the lower limit of quantitation, which is indicated by placement of the circle. Where only one red circle is present, all values on that day were below the limit of quantitation. \* **behind the patient number at bottom of figure** indicates no PBMC collection on Day 30. # indicates no

data for patient 22 on Day 1, hours 2-8. **B**, Relative PAR levels on Day 30 after topotecan (TPT) treatment as a function of TPT exposure. Shown are the mean values between 2 and 8 hours after TPT ÷ value at 0 h on day 30.

### Supplementary Table 1

#### Topotecan and Veliparib Pharmacokinetics Following Administration Alone and in Combination

Dose Level Veliparib (mg)/ Topotecan (mg/m <sup>2</sup> )	n	Veliparib				Topotecan*			
			Veliparib alone	Veliparib + TPT	Ratio	n	TPT alone	Veliparib + TPT	Ratio
1 10/2	3	C <sub>max</sub> <sup>a</sup>	92±36	69±6	0.82±0.29	3/2	135±61	211, 74	0.98, 1.42
		AUC <sub>0-9h</sub>	351±69	382±48	1.11±0.22		328±134	304, 228	1.59, 1.07
		Half-life	6.4±1.0	6.1±1.3	0.95±0.05		3.2±0.9	3.2, 4.1	1.24, 0.86
2 20/2	3	C <sub>max</sub>	141±51	165±15	1.24±0.31	3/2	96±28	99, 113	0.90, 1.12
		AUC <sub>0-9h</sub>	717±77	854±60	1.20±0.07		316±156	257, 508	0.83, 0.97
		Half-life	5.2±0.5	5.6±0.4	1.09±0.16		3.1±0.4	2.9, 4.1	1.04, 0.86
3 10/3	3	C <sub>max</sub>	120±71	133±94	1.07±0.11	1	137±54	123	1.00
		AUC <sub>0-9h</sub>	510±234	551±203	1.12±0.20		366±97	316	0.96
		Half-life	6.5±2.4	6.9±1.9	1.09±0.12		2.9±0.6	2.3	1.01
4 20/3	3	C <sub>max</sub>	133±32	156±33	1.18±0.07	3/3	130±12	145±68	1.02±0.41
		AUC <sub>0-9h</sub>	616±118	740±177	1.19±0.06		310±86	403±278	0.94±0.46
		Half-life	7.4±3.4	6.4±2.8	0.88±0.15		2.3±0.3	2.7±0.8	0.89±0.21
5 20/4	6	C <sub>max</sub>	145±24	147±29	1.04±0.22	6/5	133±52	90±26	1.64±0.57
		AUC <sub>0-9h</sub>	607±56	760±213	1.25±0.35		464±196	365±128	1.05±0.05
		Half-life	9.4±5.1	7.5±2.6	0.96±0.46		2.8±0.6	3.0±0.7	0.92±0.04
6 30/4	7	C <sub>max</sub>	191±57	227±72	1.22±0.39	5/4	116±37	125±38	1.01±0.10
		AUC <sub>0-9h</sub>	966±255	1040±350	1.06±0.13		309±68	294±70	1.09±0.08
		Half-life	5.9±1.4	6.9±1.9	1.15±0.09		2.6±0.5	2.6±0.2	0.93±0.04
7 * 30/3	2	C <sub>max</sub>	178, 330	250, 232	1.40, 0.70	3/3	135±53	101±49	1.39±0.32
		AUC <sub>0-9h</sub>	965, 998	1217, 1064	1.26, 1.07		255±69	222±53	1.13±0.04
		Half-life	10.0, 6.1	10.6, 6.2	1.06, 1.02		2.0±0.2	2.2±0.5	0.94±0.12
8 * 50/3	3	C <sub>max</sub>	300±73	303±48	1.03±0.16	3/3	114±48	137±61	0.85±0.18
		AUC <sub>0-9h</sub>	1402±190	1581±106	1.13±0.10		277±74	320±18	0.87±0.25
		Half-life	4.2±1.9	5.3±3.2	1.24±0.19		2.3±0.2	2.3±0.5	1.04±0.17
9 * 100/3	3	C <sub>max</sub>	560±173	559±171	1.00±0.00	2/2	206, 104	211, 112	0.98, 0.93
		AUC <sub>0-9h</sub>	3001±370	3169±449	1.06±0.06		358, 395	348, 332	0.99, 1.12
		Half-life	5.0±1.9	5.3±1.5	1.10±0.24		2.6, 2.2	2.9, 2.4	0.88, 0.92
10 * 150/3	6	C <sub>max</sub>	1293±330	1573±345	1.23±0.12	5/4	120±21	103±16	1.10±0.08
		AUC <sub>0-9h</sub>	6502±1287	8449±1246	1.32±0.17		341±70	271±70	1.20±0.17
		Half-life	4.5±1.4	6.4±2.1	1.49±0.50		2.3±0.3	2.4±0.3	0.93±0.04
11 * 200/3	5	C <sub>max</sub>	1599±240	1638±280	1.02±0.07	4/1	138±12	148	1.04
		AUC <sub>0-9h</sub>	9040±1270	10557±1561	1.17±0.14		348±70	276	1.13
		Half-life	5.8±3.2	19.3±25.7	2.51±1.93		2.7±0.6	2.7	0.81

12 *	4	C <sub>max</sub>	3203±1556	3359±750	1.15±0.30	4/2	184±34	177, 130	1.04, 1.16
		AUC <sub>0-9h</sub>	15031±3094	18903±1175	1.29±0.24		370±106	328, 348	1.00, 0.97
		Half-life	5.1±1.1	7.2±3.2	1.45±0.73		2.7±0.5	2.7, 3.0	0.94, 0.81
13 *	1	C <sub>max</sub>	5872	5569	0.95	1	134	109	1.22
		AUC <sub>0-9h</sub>	33939	28421	0.84		536	434	1.14
		Half-life	5.3	12.8	2.40		2.7	3.6	0.76

\* Veliparib was administered twice daily

<sup>a</sup>Units: C<sub>max</sub>, ng/ml; AUC<sub>0-9h</sub>, ng/ml x h; Half-life, hours, number of patients treated with topotecan alone in Cycle 2. Individual values are reported when PK were available for < 3 patients in a dose level.