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LEARN & APPLY

Population PK/PD from a Phase I Study of the Single-Agent PARP Inhibitor, Veliparib (ABT-888) in Patients with Cancer

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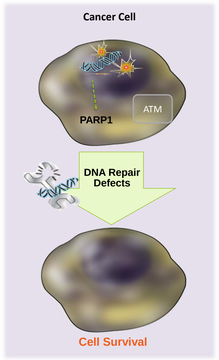
We thank the patients and their families

Background

- Poly ADP ribose polymerase (PARP) is an enzyme activated during DNA damage response and repair.
- Because of the role PARP plays during signaling and repair of DNA damage[1], PARP inhibitors have been developed to increase the efficacy of DNA damaging agents.
- In-vitro studies have shown that inhibitors of PARP are cytotoxic in cell-lines deficient for *BRCA1* and *BRCA2*[2].
- Veliparib (ABT-888) is a PARP inhibitor that has been studied as both a single agent and in combination with chemotherapy, and is currently in phase III trials.
- This study examines single-agent therapy.

Figure 1. PARP1 Cellular Repair Schema



Objective

- The objectives of these analyses were to evaluate veliparib population PK by assessing typical parameter values, random inter-individual and residual variabilities, the effect of covariates (e.g. demographics or disease state) and to determine if the product of PARP is activated through PAR measurements.

Methods

- 73 evaluable patients (Table 1)
- BID dosing of veliparib after Day 1 (QD on Day 1).
- Dose escalations to determine maximum tolerated doses (MTD) of veliparib studied at 50, 100/50, 100, 150/100, 150, 200, 300, 400 and 500 mg (split am/pm dosing).
- PK assessed on Cycle 1 Day 1 and Day 15 at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 & 24 hours post dose.
- PBMCs collected to measure PAR activity (PD endpoint) on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 4 Day 1 at predose, 2, 4, 8 & 24 hours post dose.
- Bioanalysis conducted for veliparib and metabolite (M8), however, the sparse data from the inactive metabolite (M8) was excluded from analyses.

Patient Characteristics

Table 1. Baseline Patient Characteristics (n=67)*

Median Age (years)		53.8
Gender (female:male)		65:2
Performance Status (ECOG Scores)	0	N=45
	1	N=22
	2	N=6

*Only 67 of the 73 patients had PK results and 41 of them had PD results.
4 patients did not have PK results but had PD results.

Results/Discussion

- Phoenix NLME Version 1.3 used for data analyses.
- The data was visually inspected using concentration-time plots (Figure 1), scatterplots versus dose, and scatterplots and boxplots of covariates.
- NCA conducted to generate initial estimates (Table 2).

Figure 2. Veliparib (ABT-888) and PAR Concentrations vs Time Plots

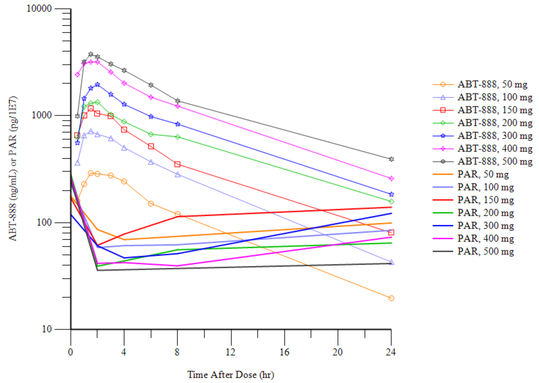


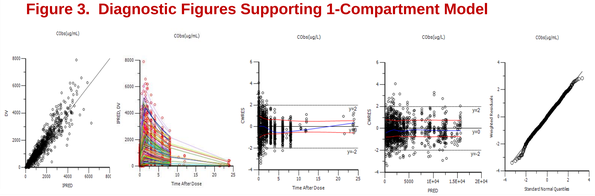
Table 2. Mean ABT-888 NCA Parameters

		Cycle 1, Day 1					Cycle 1, Day 15				
Dose (mg)	N	C_{max} (ug/L)	T_{max} (h)	Vz/F (L)	CL/F (L/h)	N	C_{max} (ug/L)	T_{max} (h)	Vz/F (L)	CL/F (L/h)
50	9	399 (161)	1.58 (0.500 - 4.05)	168 (67.0)	19.6 (8.15)	8-9	490 (206)	2.00 (1.00 – 4.00)	310 (269)	13.7 (5.88)
100	9	839 (223)	1.50 (1.00 - 3.00)	136 (28.4)	15.6 (3.47)	6-7	997 (230)	1.00 (1.00 – 4.00)	232 (80.2)	12.1 (4.10)
150	12	1260 (370)	1.75 (0.500 - 3.13)	144 (38.8)	17.0 (5.05)	12	1480 (358)	2.00 (1.00 – 3.00)	316 (189)	14.6 (4.75)
200	6	1550 (586)	1.27 (0.500 - 2.00)	197 (116)	14.4 (9.02)	6	1980 (486)	2.00 (1.00 – 3.00)	338 (79.1)	10.4 (3.28)
300	8	2070 (223)	2.00 (1.00 - 2.02)	149 (40.6)	15.8 (4.24)	6-8	2660 (616)	2.00 (1.00 – 5.00)	268 (84.8)	11.5 (3.92)
400	16	3810 (920)	1.50 (0.500 - 3.00)	136 (49.7)	15.5 (6.59)	10	4160 (1550)	2.00 (1.00 – 3.00)	397 (212)	14.4 (6.14)
500	6-7	4230 (1810)	1.50 (1.00 - 2.00)	137 (74.0)	15.5 (8.14)	5	5030 (1270)	2.00 (1.00 – 3.00)	520 (379)	11.6 (3.70)

Data Presented as Mean (SD) with exception to T_{max} which is median (min – max)
Vz/F follows one-compartment model estimations

- Both 1- and 2-compartment models were assessed[3]: (Figure 3). Although appearing biphasic, PK was best described with a 1-compartment model.

Figure 3. Diagnostic Figures Supporting 1-Compartment Model



- Residual error models were assessed (Table 3).

Table 3. Goodness of fit Table for Residual Error Model Selection

Population Model Name	n	-2LL	AIC	BIC	Eps Shrinkage
2 C PK Model with Proportional error	73	20587.73	20609.73	20666.28	0.64
1 C PK Model with Mixed error	73	18832.04	18848.04	18889.04	0.03
1 C PK Model with log-additive error	73	2235.929	2249.9287	2285.912	0.07
1 C PK Model with additive error	73	18973.31	18987.317	19023.3	0.05
1 C PK Model with proportional error	73	17821.67	17835.67	17871.54	0.07
1 C PK Model with prop error & T_{lag}	73	18689.85	18707.85	18753.97	-39.17

- C_{max} was underestimated & initial absorption phase was not well characterized by 1-stage model (bimodal distribution observed).
- Individual plots showed both zero order and first order absorption (Figure 4), therefore, a 2-stage model approach was assessed for fit (Table 4).
- T_{lag} did not significantly improve fit (for first order observations) and was not incorporated in the final structural model PK parameter estimates (Table 5).

Figure 4. (Top) 1-Stage model underestimated fits and (Bottom) 2-Stage model shows better estimation

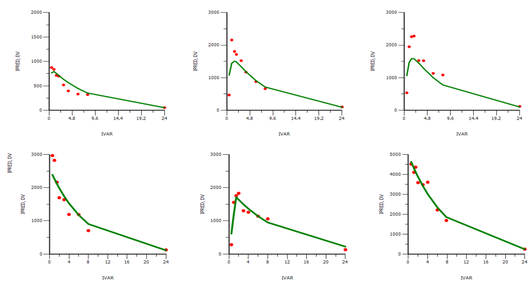


Table 4. Goodness of fit for 2-Stage model with and without t_{lag}

	Model Eval 1C k0 prop 2stg				Model Eval 1C tlag k0 prop 2stg			
Variable	N	Mean	SD	CV Percent	N	Mean	SD	CV Percent
-2LL	71	217.56	75.17	34.55	71	213.88	74.58	34.87
AIC	71	**225.56**	75.17	33.33	71	**223.88**	74.58	33.31
BIC	67	241.85	55.22	22.83	67	240.78	55.52	23.06
LogLik	71	-108.78	37.59	-34.55	71	-106.94	37.29	-34.87
nObs	71	16.39	5.30	32.32	71	16.39	5.30	32.32
nParm	71	4	0	0	71	5	0	0

Table 5. Parameter Estimates from the 2-Stage model without t_{lag}

	1C k0 prop 2stg			
Parameter	tvCl	tvV	tvK0	stdev
Estimate	16.6	141	1.14	0.255
Error (CV%)	33.5	32.7	59.3	39.7

- Covariates vs Clearance (CL), Volume (V) and absorption (k0) were assessed for correlations (Figures 5, 6, and 7).

Results/Discussion

Figure 5. Clearance versus covariates

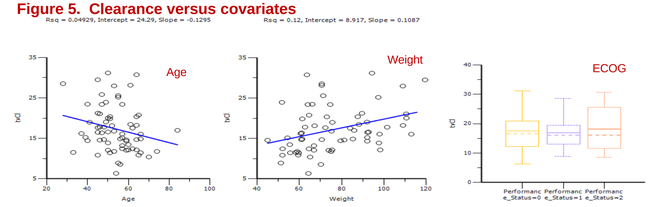


Figure 6. Volume versus covariates

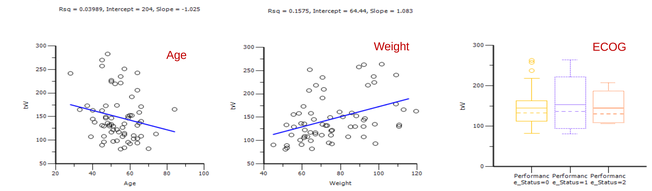
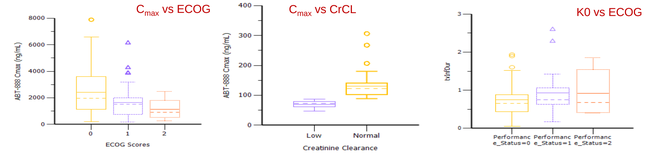


Figure 7. C_{max} and Absorption k0 versus ECOG



- Weight and Age versus CL and V were obvious covariates.
- Although variable, C_{max} values were greater with ECOG of 0.
- C_{max} values were lower with impaired (low) renal function.
- ECOG of 0 tended to absorb veliparib faster than ECOG scores of 1 or 2.

Conclusions

- Veliparib PK can be described by a one-compartment model using a 2-stage approach to best described zero and first order absorption
- Weight and Age somewhat alters PK.
- ECOG seems to correlate with drug absorption (k0) – healthier patients absorb ABT-888 at a faster rate (C_{max} ↑ in patients with ↓ ECOG)
- C_{max} ↓ with impaired ↓ renal function.
- Initial assessments of PK/PD relationships show exposure response correlations.

References

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