VELIPARIB WITH TEMOZOLOMIDE IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES: IS THERE A NEED TO ADJUST DOSE?

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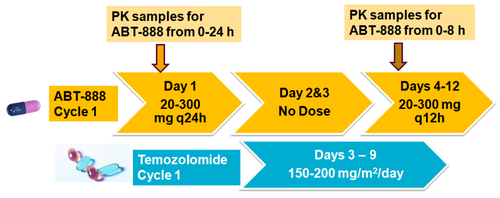
Background & Objective

- Veliparib (ABT-888) is a potent, orally bioavailable poly(ADP-ribose) polymerase (PARP) small molecule inhibitor that is currently in development for the treatment of non-hematologic and hematologic malignancies.
- PARP is a nuclear enzyme that recognizes DNA damage and facilitates DNA repair. PARP inhibitors are expected to sensitize cancer cells to the effects of DNA-damaging agents including alkylators such as temozolomide (TMZ) and radiation therapy.
- Both ABT-888 and TMZ are majorly eliminated by renal route.
- The objective of this analysis was to describe the population pharmacokinetics (PK) of ABT-888 and evaluate the impact of TMZ co-administration on the PK in patients with hematologic malignancies.

Figure 1. Schematic showing Phase-I trial design for ABT-888



Methods

- The analysis dataset included 580 ABT-888 concentration values from 37 patients with hematologic malignancies from phase I study.
- Exploratory analysis and non-compartmental analysis (NCA) were conducted using Rstudio and Phoenix WinNonlin.
- Population PK modeling was performed using Phoenix NLME 1.3. One and two compartment PK models were evaluated.
- Following absorption models were evaluated.
  - Method 1: First order absorption
  - Method 2: First order absorption with lag time (tlag)
  - Method 3: Zero order absorption
  - Method 4: Zero order absorption with first order and lag time and relative bioavailability (RelF)
- Goodness of fit plots and likelihood ratio test was used for comparison of nested models.
- Co-administration with TMZ were evaluated as interoccasion variability (IOV) on CL. Trends of body surface area, age, weight, height, race, sex, creatinine clearance and dose were evaluated.

Results

Table 1. Exposure estimates for ABT-888 from NCA.

Variable	20 mg		80 mg		120 mg		150 mg		200 mg	
	ABT-888 (N=4)	ABT-888 + TMZ (N=4)	ABT-888 (N=2)	ABT-888 + TMZ (N=2)	ABT-888 (N=10)	ABT-888 + TMZ (N=10)	ABT-888 (N=16)	ABT-888 + TMZ (N=13)	ABT-888 (N=4)	ABT-888 + TMZ (N=3)
Linearity factor		1.07		1.65		1.19		1.00		1.00
Accumulation ratio		1.32		1.73		1.40		1.24		1.01
AUC_TAU	0.91	1.2	3.84	6.63	5.5	7.68	7.77	9.65	14.37	14.51
AUCINFpred/Dose	0.06	0.11	0.05	0.11	0.05	0.13	0.06	0.15	0.07	0.09
AUC_TAU/Dose	0.05	0.06	0.05	0.08	0.05	0.06	0.05	0.06	0.07	0.07
AUCINF_pred	1.12	2.28	4.01	8.95	6.45	16.08	9.64	22.6	14.53	17.42
Cmax/Dose	0.005	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02

Figure 2. Dose-exposure trend for ABT-888 with and without TMZ.

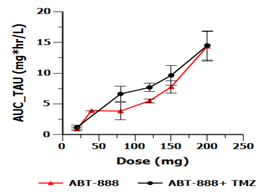


Figure 3. Individual predicted and observed concentrations versus time after dose using model 1 (A) and model 4 (B) for absorption. Filled circles and solid lines represent observed and predicted concentrations, respectively.

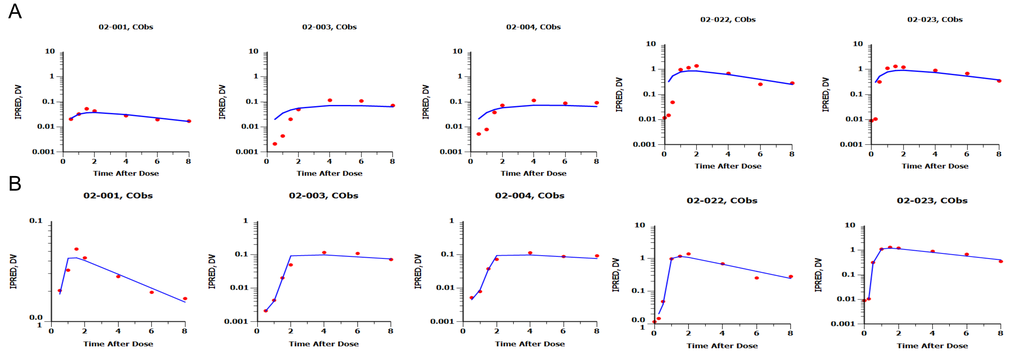


Figure 4. Goodness-of-fit plots for one-compartment PK base model.

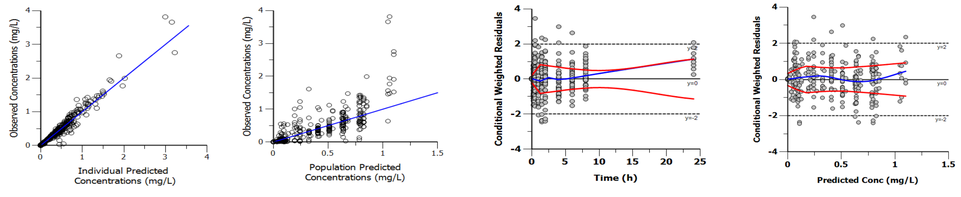


Figure 5. Box plot showing eta CL of ABT-888 with and without TMZ.

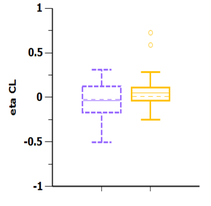


Table 2. Final parameter estimates from base model (left) and IOV on CL. Patient demographics for Phase I clinical trial (right).

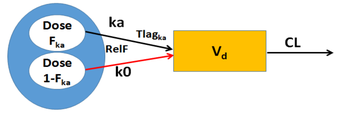
Variable	Estimate (RSE%)	Units	BSV% (RSE%)
V_d/F	190.81 (0.16)	L	41(0.23)
CL/F	15.19 (0.10)	L/h	45 (0.15)
Ka	2.77 (1.19)	1/h	5.3 (1.30)
$Tlag_{ka}$	0.57 (7.86)	h	76 (0.086)
RelF	0.50 (1.06)		173 (0.41)
k0	0.88 (0.47)	h	102 (0.68)
stdev0	0.30 (1.05)		

Variable (unit) N=37	Mean ± SD (range)
Age (years)	66.3 ± 10.4 (31-88)
Body Weight (kg)	80.6 ± 22 (39.2 – 132.8)
Height (cms)	167 ± 8.8 (149.5-184)
BSA (m^2)	1.94 ± 0.3 (1.28-2.69)
CrCL (mL/min)	77.9 ± 34.4 (35.7-186.7)
Ethnicity	Not Hispanic = 36, Unknown = 1
Race	White = 26, Black = 10, Other = 1
Gender	M=18, F=19

Results/Discussion

- NCA analysis revealed linear dose-exposure trend for ABT-888 (Figure 2). Accumulation was observed at steady state (Table 1).
- Summary of patient demographics in the Phase I clinical trial are shown in Table 2.
- A one-compartment model with first-order elimination adequately described ABT-888 PK as shown by goodness-of-fit plots (Figure 4 and 6). Proportional model was used for residual errors and exponential model was used for between subject variability (BSV).
- Zero order absorption followed by first order absorption combined with a lag period and relative bioavailability described the absorption phase well; showing significant improvement over other models (Figure 3).
- CL/F and V_d/F derived from the base model with IOV were 15 L/h and 191 L, respectively (Table 2).
- CL values for ABT-888 did not change in the presence of TMZ administration (Figure 5).

Figure 6: Schematic of final one-compartment PK model.



Ka = First order absorption, $Tlag_{ka}$ = lag time for first order absorption
k0 = Zero order absorption, RelF = relative bioavailability
CL= Clearance, Vd = Volume of distribution

Conclusions

- Dosage adjustment of ABT-888 is not required when TMZ is co-administered in patients with hematologic malignancies.
- The CL/F and V_d/F values in patients with hematological malignancies were similar to those reported in literature for non-hematological malignancies[1].
- Future work will focus on further refinement of the population PK model and validation of the model.

References

1. Salem AH, Giranda VL, Mostafa NM. Population pharmacokinetic modeling of veliparib (ABT-888) in patients with non-hematologic malignancies. Clin Pharmacokinet. 2014 May; 53:479-88