SUPPLEMENTARY

A phase 1 study of veliparib (ABT-888) plus weekly carboplatin and paclitaxel in advanced solid malignancies, with an expansion cohort in triple negative breast cancer (TNBC) (ETCTN 8620)

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Suppl.Table 1. Mean (standard deviation) pharmacokinetic parameters of veliparib at steady-state in the presence of carboplatin and paclitaxel.

Dose (mg) (N)	C_{max} (ng/mL)	C_{max}/Dose (ng/mL / mg)	T_{max} (h)	AUC_{0-12} (µg•h/mL)	AUC_{0-12}/Dose (ng•h/mL / mg)	$T_{1/2}$ (h)	CL/F (L/h)
50 (3)	424 (122)	8.47 (2.43)	1.33 (0.58)	3.10 (1.35)	62.0 (26.9)	7.1 (6.1)	19.9 (11.0)
100 (3)	641 (251)	6.41 (2.51)	3.00 (1.73)	4.88 (0.88)[a]	48.8 (8.9)[a]	3.9 (0.2)[a]	20.8 (3.8)[a]
150 (18)	1,087 (407)	7.25 (2.72)	1.92 (1.13)	6.90 (3.56)[a]	46.0 (23.7)[a]	4.5 (1.5)[a]	25.2 (8.6)[a]
200 (4)	2,403 (717)	12.0 (3.6)	1.50 (0.58)	14.4 (3.9)[b]	71.9 (19.3)[b]	4.4 (1.8)[b]	14.4 (3.9)[b]
All (28)		7.97 (3.17)	1.91 (1.13)		50.4 (23.4)[c]	4.8 (2.4)[c]	23.2 (8.7)[c]

AUC_{0-12} beyond the last time point sampled had a median extrapolated portion of 17.8% (range 1.56-20.7%).

a: 1 patient not available for parameter evaluation due to insufficient time points.

b. 2 patients not available for parameter evaluation due to insufficient time points.

c: 3 patients not available for parameter evaluation due to insufficient time points.

Suppl.Table 2. Carboplatin PK. Mean (standard deviation) pharmacokinetic parameters of ultrafilterable carboplatin (target dose AUC 2) in the presence of veliparib.

Veliparib Dose (mg) (N)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (mg•min/mL)	$T_{1/2}$ (h)
100 (2)	10.1 (0.5)	1.59 (0.36)	1.6 (0.2)
150 (15)	9.03 (3.09)	1.54 (0.43)	1.9 (0.3)
200 (3)	8.41 (0.62)	1.41 (0.22)	1.9 (0.7)
All (20)	9.04 (2.70)	1.52 (0.39)	1.9 (0.3)

Concentrations expressed as carboplatin mass units.

AUC_{0-inf} beyond the last time point sampled had a median extrapolated portion of 7.0% (range 2.7-15%).

Suppl.Table 3. Paclitaxel PK. Mean (standard deviation) C_{max} of paclitaxel (80 mg/m^2) in presence of veliparib.

Veliparib Dose (mg) (N)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg•h/mL)
100 (2)	3.04 (0.91)	5.33 (0.65)
150 (17)	3.05 (0.66)	5.18 (1.10)
200 (4)	3.75 (1.21)	5.78 (2.10)
All (23)	3.17 (0.79)	5.30 (1.25)

Suppl.Table 4. Overview of efficacy signals observed with veliparib as single agent and phase 2 and 3 trials of combination regimens, sorted by phase and increasing veliparib dose.

Phase Size	Treatment	Dose	Disease	Response	Ref
1 N=62	Veliparib	V: 400 mg BID (RP2D)	BRCA1/2$_{mut}$,Pt-refractory ovarian, or basal-like breast cancer BRCA$_{wt}$.	ORR 23% (BRCA$_{mut}$ at all dose levels)	Puhalla NCI-8282
2 N=50	Veliparib	V: 400 mg BID	Recurrent ovarian, fallopian tube, or primary peritoneal cancer with germline BRCA1/2mut	26% ORR	Coleman GOG-0280 [40]
2 N=116	Veliparib +carboplatin +paclitaxel QW	V: 50 mg BID C: AUC=6, QW P: 80 mg/m^2, QW vs P: 80 mg/m^2, QW prior to doxorubicin (A) and cyclophosphamide(C)	Neo-adjuvant TNBC (3 biomarker driven sub-types)	V: 51%; 95%-PI, 36-66% pCR Control: 26%; 95%-PI, 9-43%	Rugo I–SPY 2 [23]
2 N=158	Veliparib +carboplatin +paclitaxel Q3W	V: 120 mg BID, D 1-7 C: AUC=6, D1 P: 200 mg/m^2, D1	1st line NSCLC	V: 32.4% ORR Placebo: 32.1% V: 5.8 months median PFS Placebo: 4.2 months HR, 0.72; 95%-CI 0.45-1.15; (*P*=0.17) V: 11.7 months median OS Placebo: 9.1 months HR, 0.80; 95%-CI 0.54-1.18; (*P*=0.27)	Ramalingam [54]
2 N=284	Veliparib +carboplatin +paclitaxel Q3W	V: 120 mg BID, D 1-7 C: AUC=6, D3 P: 175 mg/m^2, D3	Recurrent/metastatic TNBC with germline *BRCA*1/2$_{mut}$	V: 77.8% ORR Placebo: 61.3% (*P*= 0.027) V: 14.1 months median PFS Placebo: 12.3 months HR 0.789; 95%-CI 0.536–1.162 (*P*= 0.227)	Han BROCADE 2 [55]

2 **N=320**	Veliparib +cisplatin Q3W	V: 300 mg BID, D1-14 Cis: 75 mg/m^2 D1	Biomarker panel informed BRCA-like and non-BRCA-like phenotyped recurrent/metastatic TNBC or germline *BRCA*1/2$_{mut}$,	BRCA-like V: 5.9 months median PFS Placebo: 4.2 months HR 0.57; 95%-CI 0.37-0.88 (P 0.01) *BRCA*1/2$_{mut}$ V: 6.2 months median PFS Placebo: 6.4 months HR 0.79; 95%-CI 0.38-1.67 (P 0.54) Non-BRCA-like V: 4.0 months median PFS Placebo: 3.0 months HR 0.89; 95%-CI 0.60-1.33 (P 0.57)	Rodler S1416 [41]
3 **N=634**	Veliparib in combination with carboplatin and paclitaxel followed by doxorubicin (A) and cyclophosphamide(C)	V: 50 mg BID C: AUC=6, QW P: 80 mg/m^2, QW vs C: AUC=6, QW P: 80 mg/m^2, QW vs P: 80 mg/m^2, QW prior to doxorubicin (A) and cyclophosphamide(C)	Neo-adjuvant TNBC	VCP: 53% pCR CP: 58% P: 31%	Loibl BrightNess [42]
3 **N=509**	Veliparib +carboplatin +paclitaxel QW/3W	V: 120 mg BID, D-2 to 5 C: AUC=6, D1 P: 80 mg/m^2, QW	Recurrent/metastatic TNBC with germline *BRCA*1/2$_{mut}$	V: 75.8% ORR Placebo: 74.1% V: 14.5 months median PFS Placebo:12.6 months HR 0.71; 95%-CI 0.57-0.88 (*P*= 0.0016)	Dieras BROCADE 3 [43]
3 **N=1140**	Veliparib +carboplatin +paclitaxel Q3W/QW	V: 150 mg BID C: AUC=6, Q3W P: 175 mg/m^2, Q3W / P: 80 mg/m^2, QW	1st line stage III or IV high-grade serous ovarian	V: 23.5 months median PFS Placebo: 17.3 months HR 0.68; 95%-CI 0.56-0.83 (*P*< 0.001)	Coleman VELIA/ GOG-3005 [44]

	Veliparib maintenance			V: 84% ORR Placebo: 74%	