**Abstract S2-05: Efficacy and tolerability of veliparib (V; ABT-888) in combination with carboplatin (C) and paclitaxel (P) vs placebo (Plc)+C/P in patients (pts) with *BRCA1* or *BRCA2* mutations and metastatic breast cancer: A randomized, phase 2 study**

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**Abstract**

**Background:** Poly(ADP-ribose) polymerase (PARP) inhibitors block DNA damage repair and may thereby enhance the clinical activity of DNA-damaging chemotherapy. Homologous recombination is defective in *BRCA1/2*-mutated tumors, leading to more error-prone mechanisms of DNA repair and increased sensitivity to PARP inhibition. V is a potent PARP inhibitor that enhances the antitumor activity of platinum agents in preclinical models. This phase 2 trial ([NCT01506609](#)) investigated the safety and efficacy of V+C/P or V+ temozolomide (TMZ) vs Plc+C/P in pts with locally recurrent or metastatic breast cancer harboring a *BRCA1* or *BRCA2* mutation. Results of the V+C/P and Plc+C/P arms are presented; V+TMZ results will be presented separately.

**Methods:** Pts ≥18 years with histologically confirmed locally recurrent or metastatic breast cancer were randomized 1:1:1 to: 1) V 40 mg BID D1–7+TMZ, 28-D cycle; 2) V 120 mg BID D1–7+C AUC 6, D3 and P 175 mg/m$^2$, D3, 21-D cycle; or 3) Plc BID D1–7+C/P. Key eligibility criteria included deleterious *BRCA1/2* mutation, ≤2 prior chemotherapies for metastatic disease, no prior platinum agent, and no CNS metastases. Randomization was stratified by hormone receptor status, prior cytotoxic therapy, and ECOG PS. The primary endpoint was progression-free survival (PFS) per RECIST 1.1 of each V arm vs Plc+C/P by independent review. Primary analysis occurred at the 112th PFS event in the V+C/P and Plc+C/P arms. Overall survival (OS), objective response rate (ORR), tolerability, and quality of life were also evaluated.

**Results:** A total of 196 pts (193 *BRCA+* per central lab) were randomized to receive double-blinded V+C/P (n=97) or Plc+C/P (n=99). Baseline demographics and disease characteristics were balanced across all treatment arms. Median study drug exposure was 10 cycles for Plc+C/P and 12 cycles for V+C/P. The V+C/P arm demonstrated numeric improvements for both PFS and OS compared to the Plc+C/P arm; improvement in ORR was statistically significant (Table 1). There was no meaningful increase of toxicity with addition of V. The most common treatment-emergent adverse events (AEs) with Plc+C/P or V+C/P were neutropenia (74%/74%), thrombocytopenia (70%/71%), and nausea (58%/71%). Grade ≥3 AEs in ≥30% of pts were neutropenia (55%/56%) and thrombocytopenia (26%/31%), respectively. There was no difference in the use of G-CSF with addition of V. Significant improvements in fatigue, pain, and insomnia (all *P*<0.05) were observed with V+C/P vs Plc+C/P.

**Conclusions:** This is the first randomized phase 2 trial of a PARP inhibitor in combination with platinum-based therapy for treatment of *BRCA1/2*-mutated advanced breast cancer. V+C/P demonstrated significantly higher ORR and symptom improvement compared to Plc+C/P, with nonsignificant trends for improved OS and PFS. Phase 3 trials are ongoing.

| Efficacy (ITT population – BRCA mutation) | Plc+C/P, n=98 | V+C/P, n=95 | HR (95% CI); P value |
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| PFS(mo, 95% CI) | 12.3 (9.3–14.5) 14.1 (11.5–16.2) | 0.789 (0.536–1.162); 0.231 |
| OS (mo, 95% CI) | 25.0 (18.1–34.8) | 28.5 (22.4–NR) 0.725 (0.468–1.121); 0.148 |
| ORR, % (95% CI) | 61.3 (49.7–71.9) | 77.8 (66.4–86.7) P=0.027 |

Table 1

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