EFFORT: EFFicacy Of adavosertib in parp ResisTance: A randomized two-arm non-comparative phase II study of adavosertib with or without olaparib in women with PARP-resistant ovarian cancer.

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Background: Wee1 phosphorylates and inhibits cyclin-dependent kinases 1 and 2 and is involved in regulation of the intra-S and G2/M cell cycle checkpoint arrest for premitotic DNA repair. The Wee1 inhibitor, adavosertib, has demonstrated activity alone and in combination with olaparib in PARP inhibitor (PARPi)-resistant preclinical models. We sought to evaluate efficacy of adavosertib (A) with or without olaparib (O) in a phase II noncomparative study of recurrent PARPi-resistant ovarian cancer. **Methods:** Women with recurrent ovarian, fallopian tube or primary peritoneal cancer with documented progressive disease on a PARPi were eligible. All patients (pts) had measurable disease and adequate end organ function. On the A arm, pts received A 300mg PO daily on days 1-5 and 8-12 of a 21-day cycle. On the A/O arm, pts received A 150mg PO BID on days 1-3 and 8-10 and O 200mg PO BID on days 1-21 of a 21-day cycle. Primary endpoint was objective response per RECIST 1.1 and was assessed every 2 cycles. Clinical benefit rate (CBR) was defined as proportion of pts with objective response or stable disease $>$ 16 weeks. Progression free survival (PFS) was assessed using the Kaplan Meier method and calculated from date of treatment initiation to earliest date of progression, death, or last visit. **Results:** 116 pts were screened with 80 pts enrolled and randomized (A: n=39, A/O: n=41). Median age was 60 years (range 36-76) and the majority of pts had platinum resistant disease (64%) and high grade serous histology (98%). Pts received a median of 4 prior therapies (range 1-11) and 48% had germline or somatic *BRCA* mutations. There were 35 pts evaluable for response in each arm. Table demonstrates efficacy data. On the A arm, Grade 3/4 toxicities occurred in 51% of pts, most commonly neutropenia (13%), thrombocytopenia (10%), and diarrhea (8%). 28 (72%) pts required at least one dose interruption and 20 (51%) required dose reduction. On the A/O arm, Grade 3/4 toxicities occurred in 76% of pts, most commonly thrombocytopenia (20%), neutropenia (15%), diarrhea (12%), fatigue (12%), and anemia (10%). 36 (88%) of pts required at least one dose interruption, 29 (71%) required dose reduction, and 4 (10%) did not restart due to toxicity. **Conclusions:** A given alone and in combination with O demonstrated efficacy in pts with PARPi-resistant ovarian cancer. Although grade 3 and 4 toxicities were observed on both arms, these were generally manageable with supportive care, dose interruptions and dose reductions as needed. Additional translational analyses are ongoing to clarify which pts received clinical benefit. Clinical trial information: NCT03579316. Research Sponsor: AstraZeneca, U.S. National Institutes of Health.

Endpoint	A arm n=35	A/O arm n=35
ORR (90% CI)	23% (12–38)	29% (16–44)
Duration of response, months (95% CI)	5.5 (2.8–NE)	6.4 (2.8–14.6)
CBR (90% CI)	63% (48–76)	89% (76–96)
Median PFS, months (90%CI)	5.5 (3.9–6.9)	6.8 (4.3–8.3)