

GYNAECOLOGICAL CANCERS

9930 OCTOPUS: A randomised, multi-centre phase II umbrella trial of weekly paclitaxel +/- novel agents in platinum-resistant ovarian cancer: Vistusertib

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Background: OCTOPUS, an NCRI investigator-initiated umbrella phase II trial, tests the addition of targeted agents to weekly paclitaxel (wP) in recurrent platinum-resistant/refractory ovarian cancer. The first agent tested is the dual mTORC1/mTORC2 inhibitor vistusertib (V). Preclinical studies support targeting PI3K/AKT/mTOR signalling. The combination of V and wP showed activity in ovarian high grade serous carcinoma (HGSC) in phase I. This is the first randomised trial of wP and dual mTORC1/2 inhibition in ovarian cancer.

Methods: In this double-blind trial, patients with platinum-resistant/refractory HGSC were randomised 1:1 to wP (80mg/m² D1, D8, D15 of 28 day cycle) + oral V (50mg BD) or placebo (P) (D1-3, D8-10, D15-17). The primary endpoint is progression-free survival (PFS) (RECIST v1.1/GCIG CA125 criteria) and response is a key secondary end-point. A mandatory pre-treatment biopsy (if technically feasible), archival tumour tissue and serial blood samples were collected. The study uses a 3-outcome approach: significance at 10% (1-sided) for PFS indicates activity, significance at 20% also requires evidence of an improvement in response. The study has 90% power to detect a hazard ratio (HR) of 0.67.

Results: 140 patients were randomised; median age 63 (range: 36-86); 18% platinum-refractory; 54% had ≥3 prior therapy; 7% had prior taxane in previous 6 months (m); 66% had an image-guided biopsy at study entry. Median PFS was 4.5 vs 4.2m (HR 0.84; 80% CI 0.67 to 1.07; 1-sided p = 0.18); median OS was 9.7 vs 11.1m (HR 1.21, 80% CI 0.91 to 1.60; p = 0.80); RR (RECIST/GCIG CA125: CR+PR) was 53% vs 56% for wP+V vs wP+P respectively. Grade 3/4 adverse events were 24 vs 25%. There was significantly more gastro-oesophageal reflux (grd 1/2 10 v 0%), rash (grd 2/3 9 v 0%) and lymphopenia (grd 2/3/4 47 v 31%) on wP+V. Ongoing translational research exploring the influence of PI3K/mTOR signalling on platinum resistance and response to wP will be presented.

Conclusions: There was modest evidence of improvement in PFS with the addition of V, but this was not supported by response or OS. Translational research and subgroup analyses are ongoing.

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