Aim: Activation of the PI3 kinase-AKT-mTOR pathway is hypothesized to contribute to resistance to chemotherapy and targeted agents in many cancers. Enhanced PI3 kinase pathway signaling has been shown in ovarian cancer cell lines and ascitic cells from pts showing chemoresistance. In a previous phase I trial the maximum tolerated dose (MTD) of the dual mTORC1/2 inhibitor AZD2014 (A) as monotherapy was defined as 50 mg bd 7/7. Preclinically, when A is combined with P, additive apoptosis is observed. Therefore, the combination of A and P was evaluated in a multicentre Phase I trial in patients with solid tumours (EudraCT 2012-003896-20). Study aims were to determine the MTD and recommended dose for the combination of fixed dose weekly P with two intermittent schedules of A, based on safety, tolerability, pharmacokinetics (PK) profile, pharmacodynamics (PD) and antitumour activity.

Methods: A was administered orally bd either 3 days on 4 days off (3/7 schedule) or 2 days on 5 days off (2/7 schedule) starting on the same day as fixed dose weekly intravenous P 80mg/m². A cycle comprised 6 weekly treatments every 49 days. A 3 + 3 dose escalation design was employed.

Results: 17 pts have been treated in the study so far. On the 3/7 schedule (12 treated), 2 pts had dose-limiting toxicities (DLT) of grade (Gr) 3 fatigue and mucositis at 75 mg bd of A. On the 2/7 schedule (5 treated), 2 pts had DLT of Gr 3 rash at 100mg bd of A. Frequently observed adverse events of any grade were fatigue, diarrhoea, anaemia, mucositis and anorexia. PK and PD data for the 2 schedules will be presented. To date, 3/5 pts with taxane-pretreated ovarian cancer have achieved RECIST and/or GCIG CA125 partial response (PR). 2/2 pts with taxane-pretreated squamous NSCLC and 1/2 pts with EGFR-mutant lung adenocarcinoma have shown significant necrosis of their tumours and PR by RECIST.

Conclusions: The MTD for the 3/7 schedule is P 80 mg/m² plus A 50 mg bd. For the 2/7 schedule, 100mg bd A + weekly P is declared non-tolerated, based on 2 DLTs of Gr 3 rash. Expansions in relapsed ovarian cancer and squamous cell lung cancer are now planned. The study is supported by AstraZeneca, Cancer Research UK, Experimental Cancer Medicine Centre and NIHR Biomedical Research Centre Initiatives. It is co-sponsored by the Institute of Cancer Research/Royal Marsden NHS Foundation Trust.

Disclosure: S. Banerjee, S.B. Kaye and J.S. De Bono: Served on Advisory Board for AstraZeneca. All other authors have declared no conflicts of interest.