PARALLEL PHASE I STUDIES OF TWO SCHEDULES OF BKM120 PLUS CARBOPLATIN AND PACLITAXEL FOR PATIENTS WITH ADVANCED SOLID TUMORS

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Aim: Carboptatin and paclitaxel are mainstays of treatment for metastatic solid tumors, and the PI3K/mTOR pathway is one of the most commonly dysregulated in cancers. The combination of PI3K inhibition and platinum-based chemotherapy may enhance anti-cancer effect.

Methods: Patients with metastatic solid tumors were treated with two regimens: Group 1 received carboplatin AUC 5 and paclitaxel 175mg/m², on day 1 of a 21 day cycle with pegylgrastim support; Group 2 received carboplatin AUC 5 (day 1) and paclitaxel 80mg/m² (days 1, 8 and 15) on a 28-day cycle without growth factor support. In both groups, the pan-PI3K inhibitor buparlisib (BKM120) was administered daily with dose escalation of 50, 80 or 100mg/day, with optional continuation of BKM120 until progression, after cessation of chemotherapy following Cycle 6. The primary endpoint was Recommended Phase II Dose (RP2D).

Results: Between 5 Apr 2011 and 28 Jan 2013, 30 subjects were enrolled. Median age was 53 (range 23-71). The most common tumor types were non-small cell lung cancer (N = 5) and ovarian cancer (N = 5). 16 patients were treated in Group 1 and 14 in Group 2. The median number of cycles was 4.5 (Group 1) or 6 (Group 2). Dose reductions and treatment delays during all cycles were more common in Group 2. The most common adverse events (AE) of any grade in Group 1 were fatigue, hyperglycemia, alopecia, arthralgias, alkaline phosphatase elevation and thrombocytopenia. In Group 2, the most common AEs were hyperglycemia, leucopenia, neutropenia, thrombocytopenia, fatigue and alopecia. The DLTs were elevated alkaline phosphatase (N = 1) and uncomplicated neutropenia (N = 2). The MTD for BKM120 was 100mg/d in Group 1 and 80mg/day in Group 2. Among 25 patients with measurable disease, the objective response rate was 28% (1CR, 4 PR, 2uPR). 5 patients with evaluable disease (not measurable by RECIST) experienced clinical benefit (clinical stability with no new radiographic lesions) for ≥ 10 cycles. Correlative studies in process include analysis of PIK3CA mutation status and PTEN expression status in pre-treatment tumor samples, and pharmacokinetic analysis of BKM120.

Conclusions: BKM120 at 100 mg/d + carboplatin AUC 5 + paclitaxel 175mg/m², both on day 1 of a 21 day cycle with growth factor support, is a well-tolerated regimen with promising activity in advanced solid tumors.

Disclosure: M. Fury: MGF has served on an advisory board for Novartis within the last 12 months. All other authors have declared no conflicts of interest.