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# developmental therapeutics

## 375P A phase Ib dose-finding study of alpelisib (ALP; BYL719) and paclitaxel (PTX) in advanced solid tumors (aST)

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**Background:** Aberrant activation of the phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin pathway due to alterations in *PIK3CA* (encoding PI3Kα) frequently occurs in aST. We report safety findings from an ongoing, phase Ib dose-escalation study of ALP (PI3Kα inhibitor) + PTX (NCT02051751).

**Methods:** Patients (pts) aged ≥18 years with aST (not amenable to resection/progressed on standard therapy), ECOG performance status ≤2, adequate bone marrow/organ function, and no prior treatment with PI3K or AKT inhibitors were recruited. The primary objective was to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose of ALP + PTX based on dose-limiting toxicities (DLTs) in Cycle 1. Dose escalation of ALP was guided by an adaptive Bayesian logistic regression model with escalation with overdose control principle.

**Results:** As of Dec 7, 2015, 19 pts received oral ALP (300 mg [n = 6], 250 mg [n = 4], or 150 mg [n = 9] once daily [QD]) and IV PTX (80 mg/m$^2$ once weekly [QW]). The most common primary sites of cancer were breast (n = 5) and rectum (n = 3). Treatment was discontinued in 18/19 pts due to disease progression (n = 12, 63%), pt decision (n = 3, 16%), adverse events (AEs; n = 2, 11%; 1 pt for grade [G]3 dehydration, G3 hyperglycemia, and G3 acute kidney injury; 1 pt for G4 neutropenia and G4 γ-glutamyltransferase increase), and physician decision (n = 1, 5%). DLTs occurred in 5/12 pts in the dose-determining set: 1/1 (100%) pt at 300 mg QD, 2/3 (67%) pts at 250 mg QD, and 2/8 (25%) pts at 150 mg QD. Six DLTs were reported: G2 hyperglycemia (n = 3), G4 hyperglycemia, G4 leukopenia, and G3 acute kidney injury (each n = 1). The MTD of ALP + PTX (80 mg/m$^2$ QW) was declared as 150 mg QD. All 19 pts had ≥1 treatment-emergent AE. Grade 3/4 AEs occurred in 11 (58%) pts, the most frequent being hyperglycemia (n = 6, 32%), diarrhea, anemia, lymphopenia, neutropenia, and leukopenia (each n = 2, 11%).

**Conclusions:** In pts with aST, the MTD of ALP + PTX (80 mg/m$^2$ QW) was 150 mg QD. Due to the challenging safety profile of the combination and lack of available data confirming the pharmacodynamics and/or clinical activity of ALP at 150 mg QD, planned dose expansion in pts with breast cancer and head and neck squamous cell carcinoma will not go forward.

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