## Phase II trial of the PI3 kinase inhibitor buparlisib (BKM-120) with or without enzalutamide in men with metastatic castration resistant prostate cancer

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**Background:** Phosphatidylinositol-3-kinase (PI3K) and androgen receptor pathway activation is common in metastatic castration resistant prostate cancer (mCRPC). Buparlisib is an oral, pan-class I PI3 kinase inhibitor.

**Methods:** This was a multisite single arm phase II trial of buparlisib 100 mg ± enzalutamide daily in men with mCRPC whose disease progressed on or who were not candidates for docetaxel. The primary end-point was the rate of radiographic/clinical progression-free survival (PFS) at 6 months.

**Results:** Thirty men were accrued: 67% post-docetaxel; median prostate specific antigen (PSA) was 70 ng/dl, 83% had ≥4 prior therapies for mCRPC; 43% received concurrent enzalutamide. The final 6 month PFS rate was estimated to be 10% (95% confidence interval 2.5–23.6%). Median PFS was 1.9 months and was 3.5 months with concurrent enzalutamide. Median overall survival was 10.6 months. Concurrent enzalutamide led to a five-fold reduction in buparlisib concentrations. PSA declines were observed in 23%; no patients achieved a ≥50% decline, and no radiographic responses were observed. Severe adverse events occurred in four men including respiratory infection and multi-organ failure, urinary tract obstruction, confusion and one seizure in the setting of a new central nervous system (CNS) metastasis. Grade III adverse events were seen in 43% of patients; common toxicities included grade I–II weight loss, diarrhoea, nausea, fatigue, anorexia, rash, hyperglycemia and anxiety/mood disorders.

**Conclusions:** Buparlisib did not demonstrate significant activity in men with mCRPC, suggesting that PI3K inhibition is not sufficient to reverse resistant mCRPC progression. Future studies of PI3K pathway inhibitors with concurrent enzalutamide should develop optimal dosing and focus on selected patients more likely to benefit.