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

Andrew J. Armstrong a,*, Susan Halabi b, Patrick Healy b, Joshi J. Alumkal c, Carolyn Winters a, Julie Kephart a, Rhonda L. Bitting d, Carey Hobbs a, Colleen F. Soleau e, Tomasz M. Beer c, Rachel Slottke c, Kelly Mundy a, Evan Y. Yu e, Daniel J. George a

a Duke University Departments of Medicine, Surgery, and Pharmacology and Cancer Biology, Division of Medical Oncology, The Duke Cancer Institute, Durham, NC, USA
b Duke University Department of Biostatistics, USA
c Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA
d Wake Forest University, Winston-Salem, NC, USA
e University of Washington, Seattle, WA, USA

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Abstract 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.
1. Introduction

Despite immunotherapy, chemotherapy and novel androgen receptor (AR) directed therapies, men with metastatic castration resistant prostate cancer (mCRPC) develop resistant disease progression within months to a few years [1–6]. Thus, there is an urgent need to develop more effective treatments.

A key oncogenic pathway implicated in CRPC progression is the phosphatidylinositol-3-kinase (PI3K) pathway, which is activated in the majority of metastatic human prostate cancer (PC) samples, often through PTEN loss [7,8]. The PI3K pathway has been shown to promote castration and chemotherapy resistance, stemness, cell growth and differentiation, as well as AR signalling, key hallmarks of CRPC lethality and progression [9–12]. Clinical trials of mammalian target of rapamycin (mTOR; TORC1) inhibitors in men with PC have not demonstrated sufficient clinical activity, suggesting alternative pathways such as PI3 kinase and AR signalling may contribute to resistance [13–17].

Buparlisib (BKM-120) is an orally bioavailable pan-class I PI3K inhibitor [18]. In preclinical models, growth inhibition was observed in tumours with PIK3CA mutations preferentially, and in PTEN null models [18]. The recommended phase II dose of buparlisib is 100 mg once daily, with significant toxicities including mood disturbances (neuropsychiatric), hyperglycaemia, and rash and target inhibition was demonstrated [19]. Pharmacodynamic inhibition of phospho-S6, a downstream biomarker of PI3K/mTOR pathway activity, was observed in 80% of patients at this dose level, along with concurrent increases in insulin and blood glucose, consistent with pathway inhibition. Partial response or stable disease was observed in over 50% of patients, including colorectal and breast carcinoma [19].

Reciprocal feedback inhibition of AR by PI3K signalling in PC has been noted, in which inhibition of PI3K leads to re-repression and activation of AR target genes, and inhibition of AR leads to reciprocal PI3K pathway activation in PC models [20,21]. On the other hand, comitant suppression of both PI3K and AR pathways led to tumour regressions [20]. Given that PI3K pathway activation is common in men with mCRPC, we conducted a phase II efficacy trial of buparlisib, with and without the potent AR inhibitor enzalutamide [1], in men with progressive mCRPC that progressed after multiple lines of standard therapy. The amendment permitting concurrent AR inhibition with enzalutamide was based on emerging data suggesting that combined PI3K and AR pathway inhibition could overcome reciprocal feedback AR pathway activation by PI3K single agent inhibition [20,21].

2. Methods

2.1. Eligibility

Men with mCRPC were eligible if they were 18 years of age or older, had a Karnofsky performance status ≥70 and a life expectancy of at least 3 months. Patients were required to have histologically confirmed PC, metastatic disease and progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST 1.1) [22] or Prostate Cancer Working Group 2 (PCWG2) prostate specific antigen (PSA) or radiographic progression (computed tomography [CT]/bone scan) criteria [23]. We amended the study after 17 subjects were enrolled to permit patients who were progressing on enzalutamide continue enzalutamide with the addition of buparlisib therapy (see CONSORT diagram, Supplementary Fig. 1). All men were continued on androgen deprivation therapy in order to maintain a castrate level of testosterone (<50 ng/dl), and bone anti-resorptive therapy if bone metastases were present. Men were required to have had at least one prior systemic taxane-based chemotherapy for PC unless the patient refused or did not tolerate chemotherapy.

Exclusion criteria included untreated brain metastases, chronic liver disease or active infection, significant mood disorders (anxiety, depression, bipolar disorder, psychosis, homicidality or suicidality), or uncontrolled cardiac conditions, diabetes and a fasting blood glucose ≥120, and concurrent use of strong inhibitors/inducers of CYP3A4. Full details are available on clinicaltrials.gov (NCT01385293). All patients provided informed consent under an institutional review board (IRB)-approved consent form.

2.2. Trial design and study treatment

This was a prospective, open-label single arm investigator-initiated trial conducted across 3 sites within the
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