A Phase I, Open-Label, Dose-Finding Study of GSK2636771, a PI3Kβ inhibitor, Administered with Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer

Debashis Sarker[1], Nancy A Dawson[2], Ana M Aparicio[3], Tanya B Dorff[4], Allan J Pantuck[5], Ulka N Vaishampayan[6], Lynn Henson[7], Lakshmi Vasist[7], Sumita Roy-Ghanta[7], Michele Gorczyca[7], Whitney York[7], Gopinath Ganji[7], Jerry Tolson[8], Johann S de Bono[9]

[1]King's College London and Guy's Hospital, London, UK; [2]Georgetown Lombardi Comprehensive Cancer Center, Washington, DC, USA; [3]MD Anderson Cancer Center, Houston, TX, USA; [4]City of Hope Cancer Center, Duarte, CA, USA; [5]University of California, Los Angeles, CA, USA; [6]University of Michigan, Ann Arbor, MI, USA; [7]GSK, Collegeville, PA, USA; [8]Biogen, Durham, NC, USA; [9]The Institute of Cancer Research and Royal Marsden Hospital, London, UK

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Corresponding author: Johann S de Bono, The Institute of Cancer Research and Royal Marsden Hospital, London, SM2 5NG, UK. Phone: +44-20-8722-4028. E-mail: johann.de-bono@icr.ac.uk

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Statement of translational relevance

Resistance to anti-androgen therapy in metastatic castration-resistant prostate cancer (mCRPC) remains a clinical challenge. Effective treatments are required to inhibit emerging resistance mechanisms while targeting ongoing androgen receptor (AR) signaling. Aberrant signaling of the phosphoinositide 3-kinase (PI3K)/AKT/mechanistic target of rapamycin pathway, as a result of phosphatase and tensin homolog (PTEN) loss, has been identified as a resistance mechanism in mCRPC. The PI3Kβ isoform has been shown to be a key driver of signaling in PTEN-deficient tumors, a common defect in mCRPC. In this study, GSK2636771, a PI3Kβ-selective inhibitor, combined with enzalutamide provided limited antitumor activity in patients with PTEN-deficient mCRPC who had progressed on prior enzalutamide. This may be attributed in part to the nature of this heavily pre-treated population and their advanced disease state. In addition, other resistance pathways and/or genetic alterations may have played a role in diminishing the efficacy observed in this study.

Abstract

Purpose: In patients with metastatic castration-resistant prostate cancer (mCRPC), resistance to androgen receptor (AR) targeted therapies, such as enzalutamide, remains an issue. Inactivation of inhibitory phosphatase and tensin homolog (PTEN) activates phosphoinositide 3-kinase (PI3K)/AKT signaling and contributes to resistance to androgen-deprivation therapy and poor outcomes. Therefore, dual targeting of AR and PI3K/AKT pathways may limit tumor growth and reverse resistance.

Patients and Methods: In this Phase I study (NCT02215096), patients with PTEN-deficient mCRPC, who progressed on prior enzalutamide, received once-daily enzalutamide 160 mg plus PI3Kβ inhibitor GSK2636771 at 300 mg initial dose, with escalation or de-escalation in 100 mg increments, followed by dose expansion. Primary objectives were to evaluate safety/tolerability, determine the recommended Phase II dose (RP2D), and assess the 12-week non-progressive disease (PD) rate.

Results: Overall, 37 patients were enrolled; 36 received ≥1 dose of GSK2636771 (200 mg: n=22, 300 mg: n=12; 400 mg: n=2) plus 160 mg enzalutamide. Dose-limiting toxicities occurred in 5 patients (200 mg: n=1; 300 mg: n=2, 400 mg: n=2). No new or unexpected adverse events nor evidence of drug–drug interaction were observed. At the recommended dose of GSK2636771 (200 mg) plus enzalutamide, the 12-week non-PD rate was 50% (95% CI: 28.2–71.8%, n=22); 1 (3%) patient achieved a radiographic partial response lasting 36 weeks. 4/34 (12%) patients had prostate-specific antigen reduction of ≥50%.

Conclusions: Although there was acceptable safety and tolerability with GSK2636771 plus enzalutamide in patients with PTEN-deficient mCRPC after failing enzalutamide, limited antitumor activity was observed.

Introduction

In men, prostate cancer is the second most frequently diagnosed cancer and is the fifth leading cause of cancer-related deaths worldwide (1). Androgens play a central role in the growth of prostate cancer; as such, androgen deprivation therapy forms the backbone of advanced prostate cancer treatment (2). However, despite the activity of androgen suppression, androgen receptor (AR) signaling recurs and treatment resistance eventually develops; progression to metastatic castration-resistant prostate cancer (mCRPC) is inevitable (2,3). Improvements in outcomes for patients with mCRPC have been achieved by further inhibition of AR signaling with therapies such as enzalutamide and abiraterone but, again, resistance to these treatments ultimately develops in a majority of patients (3). There is a need for interventions that overcome the mechanisms underlying resistance to AR-targeted therapies, and which are also directed at the sustained AR signaling activity that remains in the resistant tumors.

Increased activation of phosphoinositide 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) signaling is associated with resistance to AR-targeted therapies (3,4), with aberrations leading to pathway activation occurring in 70–100% of advanced prostate cancer cases (3). Inactivation of inhibitory phosphatase and tensin homolog (PTEN) is one of the defects that mediates activation of the PI3K/AKT pathway (2), with loss of PTEN protein observed in 40–60% of cases of mCRPC (3,5,6). In addition, *PTEN* genetic alterations are correlated with poor outcomes (5,6). Among the different PI3K isoforms, PI3Kβ drives PI3K activation, cell growth, and survival in PTEN-deficient tumor cells (7).

GSK2636771 is a potent adenosine triphosphate competitive oral inhibitor of PI3Kβ, with an IC_{50} of 5.2 nmol/L against the catalytic subunit, p110β, whilst showing >900-fold selectivity over p110α and p110γ, and >10-fold selectivity over p110δ. This selectivity for PI3Kβ over other Class I PI3K isoforms is postulated to result in fewer on- and off-target toxicities than pan-PI3K inhibitors (8,9). GSK2636771 previously demonstrated antitumor activity in PTEN-deficient preclinical models (7). In a first-time-in-human (FTIH) study, GSK2636771 >200 mg once daily resulted in blood concentrations consistently >0.6 μg/mL (the level predicted to robustly inhibit PI3Kβ in preclinical experiments), with a pharmacodynamic effect demonstrated by inhibition of the downstream target of PI3K, phosphorylated AKT (Ser473), in platelet-rich plasma and tumor biopsies (7). Consistent with these observations, GSK2636771 at the recommended Phase II dose (RP2D) of 400 mg/day demonstrated preliminary activity with a manageable safety profile in patients with PTEN-deficient and/or *PIK3CB*-aberrant advanced solid tumors (7).

Cross-talk exists between PI3K and AR pathways, resulting in reciprocal negative feedback where inhibition of one pathway activates the other, with tumor cells being able to adapt and survive when either pathway is inhibited pharmacologically (10,11). This provides the rationale to combine GSK2636771 with the AR inhibitor, enzalutamide, to inhibit both pathways in mCRPC (2,10,12) and investigate whether the combination therapy can reverse resistance to AR inhibition. Therefore, we performed a Phase I, dose-finding study of GSK2636771 plus enzalutamide in patients with mCRPC who had progressed on prior enzalutamide, prospectively selected for PTEN-deficiency, to assess safety/tolerability, determine the RP2D, and evaluate preliminary antitumor activity of this combination.

Materials and Methods

This was a multicenter, Phase I, open-label, non-randomized, dose-finding study (NCT02215096) of GSK2636771 in combination with enzalutamide in men with PTEN-deficient mCRPC who had progressed on prior enzalutamide. The study was conducted at 7 sites in the USA and the UK.

Study participants

Eligible patients were male, aged ≥18 years, with a histologically or cytologically confirmed diagnosis of prostate adenocarcinoma, surgically castrated or continuously medically castrated (≥8 weeks prior to screening), with PTEN deficiency documented by immunohistochemistry (IHC) [Ventana Medical Systems, Oro Valley, AZ, USA] (Supplementary Methods). Patients had to have completed ≥12 weeks' prior continuous enzalutamide treatment, not been without enzalutamide treatment for >30 days prior to enrolment, and have documented progressive disease (PD) following a run-in period of enzalutamide treatment 160 mg once daily (QD) for 14 days at the time of screening. Other key inclusion criteria were serum testosterone <50 ng/dL (1.7 nM/L), Eastern Cooperative Oncology Group (ECOG) Performance Status 0–1, and adequate organ function. Patients were excluded if they had received anticancer therapy (other than enzalutamide, e.g., chemotherapy with delayed toxicity, immunotherapy, biologic therapy or chemoradiation) within 21 days prior to enrolment, treatment with any PI3K, AKT or mTOR inhibitors, or investigational drug(s) within 30 days or 5 half-lives prior to enrolment. Patients were permitted to continue luteinizing hormone-releasing hormone agonists, AR antagonists (other than enzalutamide, e.g., bicalutamide, flutamide, nilutamide but not abiraterone), growth factors and bisphosphonates during the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Approval from the Institutional Review Boards and ethics

committees was obtained before study start. Written informed consent was obtained from patients prior to enrolment.

Study design and treatment

The study entailed two phases: dose escalation and dose expansion. In the dose-escalation phase, GSK2636771 dosing followed a modified 3+3 dose-escalation procedure to allow safety and pharmacokinetic (PK) analysis of each combination dose level prior to selection of the combination dose(s) for dose expansion. In this procedure, GSK2636771 QD was administered in combination with enzalutamide 160 mg, at a starting dose of 300 mg with escalation or de-escalation in 100 mg increments depending on tolerability. Evaluation of at least 3 patients who had completed 28 days of treatment with the combination was required prior to dose escalation or de-escalation to the next cohort; cohorts could be expanded up to approximately 20 patients per treatment arm.

Patients were enrolled in the dose-expansion phase at doses at or below the maximum tolerated dose (MTD) in the dose-escalation phase. The MTD was defined as the highest dose at which no more than 1 of 6 patients experienced a dose-limiting toxicity (DLT) event during the first 28 days of combination therapy in the dose-escalation phase. A DLT was defined as an event that was attributed to study treatment, occurred within the first 28 days of combination treatment, and met one of the following criteria: 1) Grade 3 or greater non-hematologic toxicity that could not be controlled with routine supportive measures; 2) Grade 4 neutropenia lasting >5 days; 3) febrile neutropenia of any grade or duration as defined by Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0); 4) Grade 4 thrombocytopenia; or 5) alanine aminotransferase (ALT) >3 times upper limit of normal (ULN) with bilirubin >2 times ULN or ALT ≥3 times ULN and ≥1.5 times baseline ALT value, if enrolled with liver metastases/tumor infiltration at baseline, together with bilirubin ≥ 2 times ULN. Any event of Grade 2 or greater (per CTCAE v4.0) that occurred beyond the first 28 days of combination treatment that would be considered dose limiting by the investigator was also considered a DLT. The protocol was amended to allow multiple dose levels to be examined in the dose-expansion phase; up to 20 additional patients per dose level were allowed to enroll, to better characterize the safety profile, PK, and clinical activity of the combination.

Study treatment was permanently discontinued at the time of disease progression, according to Prostate Cancer Working Group 2 (PCWG2) criteria (13) (except for prostate-specific antigen [PSA] progression or non-clinically relevant worsening of an isolated disease site), or due to unacceptable toxicity, substantial protocol deviation, patient withdrawal of consent, investigators discretion, death, loss to follow-up, or study closure.

Outcomes

The primary objectives were: 1) to evaluate the safety and tolerability of GSK2636771 when co-administered with enzalutamide; 2) to evaluate lack of progression in patients treated with the dose-expansion dose by the 12-week non-PD rate (proportion of patients without PD according to PCWG2 criteria, either by Response Evaluation Criteria In Solid Tumors [RECIST] version 1.1, PSA progression, and/or progression in bone(14)); and 3) to determine the RP2D for the treatment combination.

Secondary objectives included objective response rate (ORR; complete or partial response [PR] per RECIST 1.1); time to radiographic progression (per PCWG2 criteria (13), i.e., either by RECIST 1.1 (15), and/or progression in bone (14)); radiographic progression-free survival (rPFS; per RECIST 1.1 and/or bone scans); PSA50 response rate (percentage of patients with ≥50% decrease in PSA from baseline at least 12 weeks after start and confirmed by an additional evaluation after ≥4 weeks); and time to PSA progression (per PCWG2 criteria). PK analysis was also undertaken to assess for drug–drug interactions.

Assessments

All patients receiving at least one dose of GSK2636771 or enzalutamide were assessed for safety through physical examinations, vital signs (blood pressure, temperature, and heart rate) measurements, ECOG performance status, 12-lead electrocardiograms, echocardiogram/multigated acquisition scan, clinical laboratory tests, and monitoring for adverse events (AEs), serious AEs (SAEs), and DLTs.

Bone scans were completed at the screening stage and every 12 weeks after the start of treatment until disease progression, with the first post-treatment bone scan at 12 weeks used as the baseline for evaluating progression (defined as the appearance of at least 2 new lesions as per PCWG2 (14) [Supplementary Table 1]). Per PCWG2 criteria, if progression was observed on the first post-treatment 12-week scan, a confirmatory scan was performed at least 6 weeks later. The date of progression was considered to be the date of the first scan that showed at least 2 new lesions.

Progression was evaluated in the 200 mg dose-expansion cohort according to the PCWG2 guidelines (i.e., either by RECIST 1.1, PSA progression and/or progression in bone (14)) (Supplementary Table 1). ORR was assessed according to RECIST 1.1, PSA values per PCWG2 criteria, and radiographic response per PCGW2 criteria.

Plasma samples were collected for PK analysis of enzalutamide and N-desmethyl enzalutamide from all patients on Day 14 of the enzalutamide run-in period. Blood and plasma samples for analysis of GSK2636771,

enzalutamide, and N-desmethyl enzalutamide were collected on Day 29 of Week 5, and during Weeks 8 and 12 of the dose-escalation phase. A reduced PK sampling strategy was used in the dose-expansion phase, with plasma samples collected on Day 29 of Week 5 and pre-dose plasma samples collected on Day 1 of Weeks 8 and 12.

Statistical considerations and data analyses

It was estimated that 24 patients were required for the dose-escalation phase; the total number of patients was not driven by hypothesis testing, but depended on the number of dose levels, number of patients enrolled at each dose level, and the number of patients enrolled at the recommended dose to robustly evaluate safety. Safety was evaluated in all patients receiving at least one dose of GSK2636771 or enzalutamide. Clinical activity was analyzed in all patients who received at least one dose of GSK2636771 plus enzalutamide (all-treated population); the 12-week non-PD rate was assessed in patients who were treated in the dose-expansion cohort dose (200 mg) and had been on study drug for at least 12 weeks or had discontinued study drug due to disease progression, death or study withdrawal for any reason. To assess whether mCPRC progression could be limited in a clinically meaningful way for at least 12 weeks in the dose expansion phase, the null hypothesis for the 12-week non-PD rate was set to ≤5% and the alternative hypothesis (i.e., the threshold for further development) was ≥30%. The evaluation of futility was based on the predictive probability of success once enrollment reached 10 patients at the 200 mg expansion dose (16).

Results

Study participants

Of 262 patients screened for PTEN loss, 225 were screen failures (178 did not meet inclusion/exclusion criteria, 3 withdrew consent, 43 were lost for other reasons, 1 was missing). In total, 64 (24%) of patients screened were PTEN-deficient; 37 of these patients met all inclusion criteria and were enrolled onto the study, 36 of whom received at least one dose of GSK2636771 in combination with enzalutamide (Figure 1). One patient withdrew during the enzalutamide run-in period prior to receiving GSK2636771 due to a Grade 3 AE of stroke that was considered to be unrelated to treatment. A total of 22 patients received 200 mg GSK2636771 plus 160 mg enzalutamide (n=11 escalation, n=11 expansion); 12 patients received 300 mg GSK2636771 plus 160 mg enzalutamide and 2 patients received 400 mg GSK2636771 plus 160 mg enzalutamide. In all, 30 patients completed the study.

Patient demographics and baseline characteristics are summarized in Table 1**.** All patients had metastatic disease, 8 (22%) had visceral metastases, and 28 (78%) had a history of bone metastases. 14 (39%) had a Gleason score of <8, and 22 (61%) has a score of ≥8. As per the inclusion criteria, all patients had received prior enzalutamide treatment; in addition, 13 (36%) patients had received abiraterone, 9 (25%) had received chemotherapy, 26 (72%) had undergone surgery, and 26 (72%) underwent radiotherapy. Patients had received prior enzalutamide with a median of 329 days (range, 88–2118) on treatment; among the 23 patients with measurable disease at screening, 3 had documented PR, and 7 had documented stable disease (SD), as best responses to prior enzalutamide therapy (Table 1).

Safety and tolerability

Dose escalation was guided by DLTs (Table 2); in the dose escalation cohorts, 7 patients were initially enrolled to escalation Cohort 1 (300 mg GSK2636771 plus enzalutamide) and DLTs were observed in 2 of these patients. As a result, the dose of GSK2636771 was de-escalated to 200 mg for Cohort 2, with the option of escalation back to 300 mg once DLT results from this second cohort were available. Eleven patients were enrolled to escalation Cohort 2 (200 mg GSK2636771 plus enzalutamide), in which 1 DLT occurred and no other safety concerns were observed. After amending the protocol, 5 additional patients were recruited to Cohort 1. Overall, two patients in escalation Cohort 1 (300 mg GSK2636771 plus enzalutamide) were de-escalated to a 200 mg dose of GSK2636771 plus enzalutamide (1 DLT and 1 AE), and after review of data for all patients enrolled in Cohort 1, no new safety concerns were identified and therefore enrolment to escalation Cohort 3 (400 mg GSK2636771 plus enzalutamide) was pursued (n=2). In Cohort 3, DLTs were observed in all patients (n=2) enrolled, exceeding the MTD per protocol; this dose cohort was discontinued. Therefore, 300 mg GSK2636771 was determined as the MTD for this combination regimen. In the dose expansion cohort at 200 mg (n=11), the stopping criteria were not met, allowing for the study to continue as planned.

The observed overall safety and tolerability profile of the combination treatment was favorable and manageable. A total of 4 (11%) patients (all in dose escalation cohorts) had dose reductions of GSK2636771 due to AEs (including hypocalcemia and macular rash). A total of 13 (36%) patients (8 in escalation cohorts, 5 in the expansion cohort) had a dose interruption, mainly due to AEs or non-compliance; the median duration of interruption was 3 days (range 1–72 days).

All 36 patients (100%) in the all-treated population experienced at least one AE of any grade, and 33 (92%) had treatment-related AEs (TRAEs) of any grade (Table 3). Eleven patients (31%) had Grade ≥3 TRAEs; there were no Grade 4 or 5 TRAEs and no Grade 5 AEs. Six patients (17%) had SAEs (Supplementary Table 2). Two patients (6%) had SAEs that the investigator considered to be possibly related to study drugs. Of these patients, one experienced hypocalcemia and acute kidney injury (also a DLT) 7 days after starting GSK2636771 (300 mg) and 21 days after enzalutamide, with the acute renal failure but not the hypocalcemia deemed possibly caused by the combination of GSK2636771 and enzalutamide. The patient discontinued study treatment and the acute renal failure resolved. The second patient (with a history of falls) had a fall requiring hospitalization 16 days after the first dose of GSK2636771 (200 mg) and 30 days after the first dose of enzalutamide, which was considered possibly related to enzalutamide; the patient discontinued study treatment.

One patient in the 400 mg GSK2636771 plus enzalutamide escalation cohort permanently discontinued treatment due to a study-related AE (Grade 3 blood creatinine increased, also a DLT) and one patient in the 300 mg GSK2636771 group with Grade 2 hypocalcemia (possibly study treatment-related or due to co-medication with denosumab) withdrew consent and discontinued the study due to receiving further treatment at a local hospital.

Antitumor activity

The 12-week non-PD rate (primary endpoint) was 50% (95% CI: 28.2%, 71.8%) in the subgroup of 22 patients who received at least one dose of 200 mg GSK2636771 plus enzalutamide (escalation and expansion cohorts). Patient responses and treatment duration observed during the dose escalation and expansion phases are summarized in Figure 2A**.** Investigator-assessed best responses (per RECIST v1.1) for the all-treated population (patients with or without target lesions at baseline) were PR in 1 patient (9%), SD in 12 patients (33%, 9 at the 200 mg, 2 at the 300 mg, and 1 at the 400 mg dose), non-CR/non-PD in 8 (22%) patients and PD in 10 patients (28%). Five patients (14%) were non-evaluable for response. There were no complete responses noted. The patient who achieved PR in the 200 mg GSK2636771 dose-escalation cohort had a confirmed radiographic PR in a lymph node lesion per RECIST v1.1 for 36 weeks (no dose modifications or interruptions; 46% maximum reduction in size from baseline; Supplementary Figure 1), with confirmed responses observed at Weeks 8, 16, 24, and 32, and eventual radiographic progression (new bone lesion) at 36 weeks; the best response to prior enzalutamide treatment was not known for this patient. Among the 12 patients who achieved SD, this was for

>6 months in 8 patients, 3 of whom (2 at the 200 mg dose; 1 at the 400 mg dose) had achieved SD with prior enzalutamide; of the other 5 patients, 1 had PD, 3 had unknown response, and 1 had PR following a first regimen and unknown response following a second regimen of enzalutamide.

Thirty-four patients had baseline and post-baseline PSA measurements; four (12%) had a confirmed PSA ≥50% reduction (PSA50; Figure 2B). In the all-treated group, 25 patients (69%) experienced PSA progression with a median time to PSA progression of 15 weeks (95% CI: 11.3, 19.1; Supplementary Figure 2A). PSA progression and maximum PSA reduction, by treatment group are shown in Supplementary Figure 2B and Figure 2B, respectively. Median rPFS was 34.3 weeks (95% CI: 21.9, 38.4; Figure 3A); rPFS by treatment group is shown in Figure 3B**.**

Pharmacokinetics

The PK for GSK2636771, enzalutamide, and N-desmethyl-enzalutamide was sparsely sampled; individual concentrations of GSK2636771 (in the presence of enzalutamide) by dose are shown in Supplementary Figure 3. When the PK data collected following the 200 mg and 400 mg doses in this study were compared to the PK data from the FTIH study,(7) GSK2636771 concentration values appeared generally higher following co-administration with enzalutamide, although a definitive, model-based assessment could not be made as PK parameters were not estimated due to the sparse sampling.

Discussion

This Phase I, open-label, dose-finding study was designed to test the safety/tolerability, RP2D, and antitumor activity of GSK2636771 in combination with enzalutamide, in patients with PTEN-deficient mCRPC who progressed on prior enzalutamide. The 200 mg dose of GSK2636771 was recommended for cohort expansion based on the overall tolerability profile; the MTD was 300 mg. This dose was lower than the 400 mg GSK2636771 monotherapy dose selected as the R2PD in the FTIH study (7). DLTs were observed in 5 patients overall. Hypocalcemia was the most commonly observed DLT, occurring twice in one patient in escalation Cohort 1 (300 mg GSK2636771 + enzalutamide). Although limited PK data were available to determine the effect of GSK2636771 on enzalutamide and N-desmethyl-enzalutamide PK, there was no evidence to indicate any meaningful drug–drug interaction between the two agents.

Overall, our data indicate that GSK2636771 and enzalutamide in combination had limited antitumor activity in heavily pre-treated patients with mCRPC. However, we observed a 12-week non-PD rate of 50%, which exceeded the clinically meaningful threshold of ≥30% (alternative hypothesis), and 8 (22%) patients in the study achieved durable (>6 months) SD. Interestingly, despite the limited antitumor activity (one PR per RECIST and four patients with a ≥50% reduction in PSA) with the combination, the median rPFS was approximately 8.5 months (34.3 weeks). Therefore, it is possible that the combination may offer a certain degree of tumor response and could reverse AR resistance or delay progression in a sub-population of patients with metastatic disease who failed prior enzalutamide treatment. Additional studies are required to ascertain whether PI3Kβ inhibition merits further evaluation in mCRPC, especially in AR inhibitor-naïve, PTEN-deficient tumors.

While antitumor activity with combination treatment has been previously reported in patients who have progressed on prior enzalutamide therapy, for example with the addition of pembrolizumab (17) and capivasertib (AZD5363) (18), the relatively limited antitumor activity observed with GSK2636771 plus enzalutamide could be partly attributed to the advanced disease state of this heavily pre-treated population. All patients had progressed on prior enzalutamide therapy; concurrent inhibition with the combination may have been more effective if given prior to, rather than after, development of resistance to next generation hormonal agents including enzalutamide or abiraterone, particularly in light of emerging data on AR alterations (e.g., AR splice variants, mutations and amplifications) following treatment with such agents (19). Notably, 36% of patients in this study had received prior treatment with abiraterone. This may have reduced the efficacy of the enzalutamide portion of the combination therapy. Furthermore, PTEN loss occurs in 40–60% of mCRPC cases, often early in tumor development, and is associated with poorer survival and disease recurrence (3,5,6). Recent data presented by de Bono et al have shown that PTEN loss can be a predictor of response to treatments that simultaneously target the PI3K/AKT and AR pathways. In a Phase II study in patients with advanced or mCRPC who had received prior docetaxel and progressed after ≥1 prior hormonal therapy, rPFS was longer with the combination arm of the AKT inhibitor ipatasertib (400 mg) and the AR antagonist abiraterone than abiraterone alone, and was significantly better in patients with PTEN loss (11.5 months vs 4.6 months, respectively) relative to patients with no PTEN loss (7.5 months vs 5.6 months, respectively); no difference was observed in patients with prior enzalutamide treatment (20), although patient numbers were low. This combination was also effective in treatment-naïve patients with mCRPC, where median rPFS was 19.1 vs 14.2 months and ORR was 61% vs 39% for the combination vs abiraterone alone in PTEN-deficient patients (21).

The PI3Kβ isoform drives PI3K activation, cell growth, and survival in PTEN-deficient tumor cells (7). However, PI3Kβ inhibition may only transiently inhibit the PI3K/AKT/mTOR signaling pathway, leading to a rebound in pathway signaling via other isoforms, which may be another reason for limited antitumor activity observed with GSK2636771 plus enzalutamide in this study. Mutations in other PI3K isoforms, such as PI3Kα, can result in hyperactivation of the PI3K/AKT pathway and poorer prognosis (22). In particular, PI3Kα mutations are often associated with PTEN loss and these two factors, when occurring concomitantly, cooperate to drive tumor progression (22). These mechanisms may have contributed to the lower than expected activity observed in this study. Schwartz et al. have reported on the efficacy of enzalutamide in combination with PI3Kα and PI3Kβ inhibitors to overcome feedback activation and suppress both AR and PI3K/AKT pathways effectively compared with the individual agents (12). In our study, analysis of biopsies, including liquid biopsies, at time of progression may have provided insights into resistance mechanisms. Furthermore, *PIK3CB* status, which correlated with monotherapy response in the FTIH study (7), may be associated with a stronger efficacy signal than PTEN. Alternative quantitative approaches to measure PTEN loss, which can provide more accurate stratification (23), were not undertaken in our study. Next-generation sequencing (which was a good predictor of PTEN loss in the ipatasertib plus abiraterone studies (20)) and/or other genomic alterations, may have helped assess the potential association of GSK2636771 plus enzalutamide with response or clinical benefit. Recent reports have also highlighted PTEN as a driver of immune resistance in the tumor microenvironment which might be overcome with different combination approaches (24-26).

In addition to PTEN assessments, measurement of other biomarkers such as AR genetic alterations (e.g., AR mutations, amplifications, splice variants), circulating tumor DNA, or downstream measures of AKT signaling could have been used to define and select patients who are most likely to respond to this combination therapy.

Although there was an acceptable safety profile with the 200 mg GSK2636771 dose in combination with enzalutamide, the limited antitumor activity observed does not support further exploration of this combination in the enzalutamide-failing mCRPC population. However, PI3K/AKT pathway inhibition remains a valid therapeutic approach. PI3K inhibition may also have additional functions relevant to the immune system and antitumor responses, such as breaking immune tolerance, targeting myeloid-derived suppressor cells, and increasing tumor infiltrating T-cells (27). PTEN may also signal through other isoforms including PI3Kα (12) and PI3Kδ (28), indicating the possible clinical utility of other combinations of dual PI3K isoform selective inhibitors (e.g., PI3Kβ plus PI3Kα or PI3Kδ). Targeting the PI3K/AKT pathway is also supported by the results observed with

ipatasertib plus abiraterone in patients with PTEN-deficient, AR inhibitor-naïve mCRPC and those without prior hormonal therapy for their metastatic disease. In addition, the pan-AKT inhibitor capivasertib has shown preliminary clinical activity in combination with enzalutamide in patients with PTEN-deficient mCRPC who have failed on prior abiraterone and/or enzalutamide, and is being assessed in combination with docetaxel in a Phase II trial (18). Potential clinical benefit may be achieved with other GSK2636771 combinations, such as abiraterone, chemotherapy or immunomodulatory therapies (NCT03131908), and/or in selected populations.

Conclusions

In this study, the combination of 200 mg GSK2636771 plus 160 mg enzalutamide had acceptable safety and tolerability with no new or unexpected AEs, but demonstrated limited antitumor activity in patients with PTEN-deficient mCRPC who had failed prior enzalutamide therapy.

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Tables

Table 1. Patient demographics and baseline characteristics.

Characteristic	Patients receiving combination treatment (N=36)
Age, median years (range)	70 (47–85)
Race, n (%)	
White	33 (92)
African American/African	1 (3)
Other	2 (6)
Measurable disease at screening, n (%)	
Yes	23 (64)
No	13 (36)
Non-target lesions at screening, n (%)	
Yes	32 (89)
No	4 (11)
Metastatic disease at screening, n (%)	36 (100)
PTEN status, n (%)	36 (100)
PSA level at baseline, median µg/L (range)	25.90 (0.92–683.70)
Visceral or non-visceral disease, n (%)	
Visceral	8 (22)
Non-visceral	21 (58)
Visceral and non-visceral	7 (19)
Actual time since last recurrence (n=25), median days (range)	180 (9–6578)
History of bone metastases, n (%)	
Yes	28 (78)
No	8 (22)

Gleason score, n (%)	
Patients with Gleason score <8	14 (39)
Patients with Gleason score ≥8	22 (61)
Time on enzalutamide prior to study (n=27), median days (range)	329 (88–2118)
Best response to prior enzalutamide therapy, n (%)	
CR	0
PR	3 (8)
SD	7 (19)
PD	6 (17)
Unknown	16 (44)
N/A	4 (11)
Prior anticancer therapy, n (%)*	
Chemotherapy	9 (25)
Enzalutamide prior to chemotherapy	1 (3)
Enzalutamide following chemotherapy	9 (25)
Any other prior anticancer therapy	36 (100)
Immunotherapy	5 (14)
Abiraterone	13 (36)
Radioactive therapy	4 (11)
Biological therapy	5 (14)
Small-molecule targeted therapy	5 (14)
Surgery	26 (72)
Radiotherapy	26 (72)
Number of radiotherapy regimens received, n (%)	
0	8 (22)
1	18 (50)
2	6 (17)
3	2 (6)

4	2 (6)

*Patients could receive more than one therapy.

CR, complete response; N/A, not applicable; PD, progressive disease; PR, partial response, PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog; SD, stable disease.

Table 2. Summary of dose-limiting toxicities during dose escalation.

	Dose escalation		
	Cohort 1 **300 mg GSK2636771 + enzalutamide** **(N=12)**	**Cohort 2** **200 mg GSK2636771 + enzalutamide** **(N=11)**	**Cohort 3** **400 mg GSK2636771 + enzalutamide** **(N=2)**
Patients with DLTs, n (%)	2 (17)	1 (9)	2 (100)
DLT events, n			
Hypocalcemia	2*	0	0
Blood creatinine increased	0	0	2[§]
Rash	0	1[‡]	0
Acute kidney injury	1[†]	0	0
Macular rash	0	0	1**

DLTs were reported during the first 28 days of combination treatment during the dose-escalation period. All events were Grade 3 except one Grade 2 hypocalcemia event.

*Two events in one patient, the first (Grade 3) resulting in dose reduction to 200 mg, and the second event (Grade 2) resulting in study treatment withdrawal.

[†]Non-fatal Grade 3 event accompanied by increased blood creatinine levels. Resulted in study treatment withdrawal, and resolved.

[‡]Resulted in dose interruption/delay.

[§]Two events in one patient, the first resulting in dose interruption/delay, and the second event resulting in study treatment withdrawal.

**Resulting in two dose reductions: to 300 mg and then 200 mg.

DLT, dose-limiting toxicity.

Table 3. Summary of AEs (occurring in ≥10% patients) and TRAEs by Grade (N=36).

	Any AE		TRAE	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any event	36 (100%)	18 (50%)	33 (92%)	11 (31%)
Diarrhea	23 (64%)	1 (3%)	20 (56%)	1 (3%)
Decreased appetite	11 (31%)	1 (3%)	7 (19%)	1 (3%)
Fatigue	11 (31%)	3 (8%)	8 (22%)	2 (6%)
Anemia	10 (28%)	1 (3%)	2 (6%)	0
Hypocalcemia	9 (25%)	1 (3%)	8 (22%)	1 (3%)
Nausea	8 (22%)	0	6 (17%)	0
Back pain	5 (14%)	0	1 (3%)	0
Hypertension	7 (19%)	4 (11%)	2 (6%)	2 (6%)
Arthralgia	5 (14%)	0	n/a	n/a
Blood creatinine increased	6 (17%)	1 (3%)	6 (17%)	1 (3%)
Blood alkaline phosphatase increased	5 (14%)	0	1 (3%)	0
Constipation	5 (14%)	0	n/a	n/a
Hypermagnesemia	5 (14%)	0	1 (3%)	0
Pain in extremity	5 (14%)	0	1 (3%)	0
Abdominal pain	4 (11%)	1 (3%)	1 (3%)	0
Dizziness	4 (11%)	0	3 (8%)	0
Hot flush	4 (11%)	0	1 (3%)	0

AE, adverse event; TRAE, treatment-related adverse event.

Figures

Figure 1. Study disposition.

*Of the 262 patients with PTEN test, 141 (54%) had PTEN+, 64 (24%) had PTEN-, and 57 (22%) had unknown PTEN status. [†]1 patient had a PTEN unknown status and no other data, and was therefore considered a screen failure with missing reason for failure. [‡]All 37 screened patients were included in the All treated Safety and Biomarker Population. [§]The 36 patients who received combination therapy of GSK2636771 + enzalutamide were included in the All Treated Clinical Activity Population. There were 8 protocol deviations that were considered important in the 200 mg GSK2636771 + enzalutamide dose-escalation cohort, 19 in the 200 mg GSK2636771 + enzalutamide dose-expansion cohort, 5 in the 300 mg GSK2636771 + enzalutamide dose-escalation cohort, and 4 in the 400 mg GSK2636771 + enzalutamide dose-escalation cohort. Most protocol deviations were due to assessments and/or procedures (missed assessments or procedures, informed consent process, and failure to report an SAE within the protocol-specified timeframe).

PTEN, phosphatase and tensin homolog.

Figure 2. Summary of responses and treatment duration (A), and waterfall plot of maximum reduction in PSA values (B), by dose.

Figure 2A: Treatment duration counts time difference between first dosing date and dosing end date without accounting for dose interruptions. Best overall response per RECIST v1.1 criteria is annotated at the end of the bar.

Figure 2B: Best response without confirmation is annotated at the end of the bar (^ indicates confirmed response). Patients were not included in Figure 2B if they had no baseline PSA measure or the PSA values were not assessed post-baseline (patients 24 and 35).

AE, adverse event; CR, complete response; D50, decline ≥50% from baseline; DLT, dose-limiting toxicity; NC, no significant PSA change; NE, not evaluable; PD, progressive disease; PR, partial response; PSA, prostate-specific antigen; PP, increase ≥25% from baseline; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 3. Radiographic progression-free survival (PCWG2 criteria) in A) All Clinical Activity Population (N=36) and B) by dose group.

Figure 3A: Dashed lines represent 95% confidence intervals.

PCWG2, Prostate Cancer Working Group 2.

Figure 1

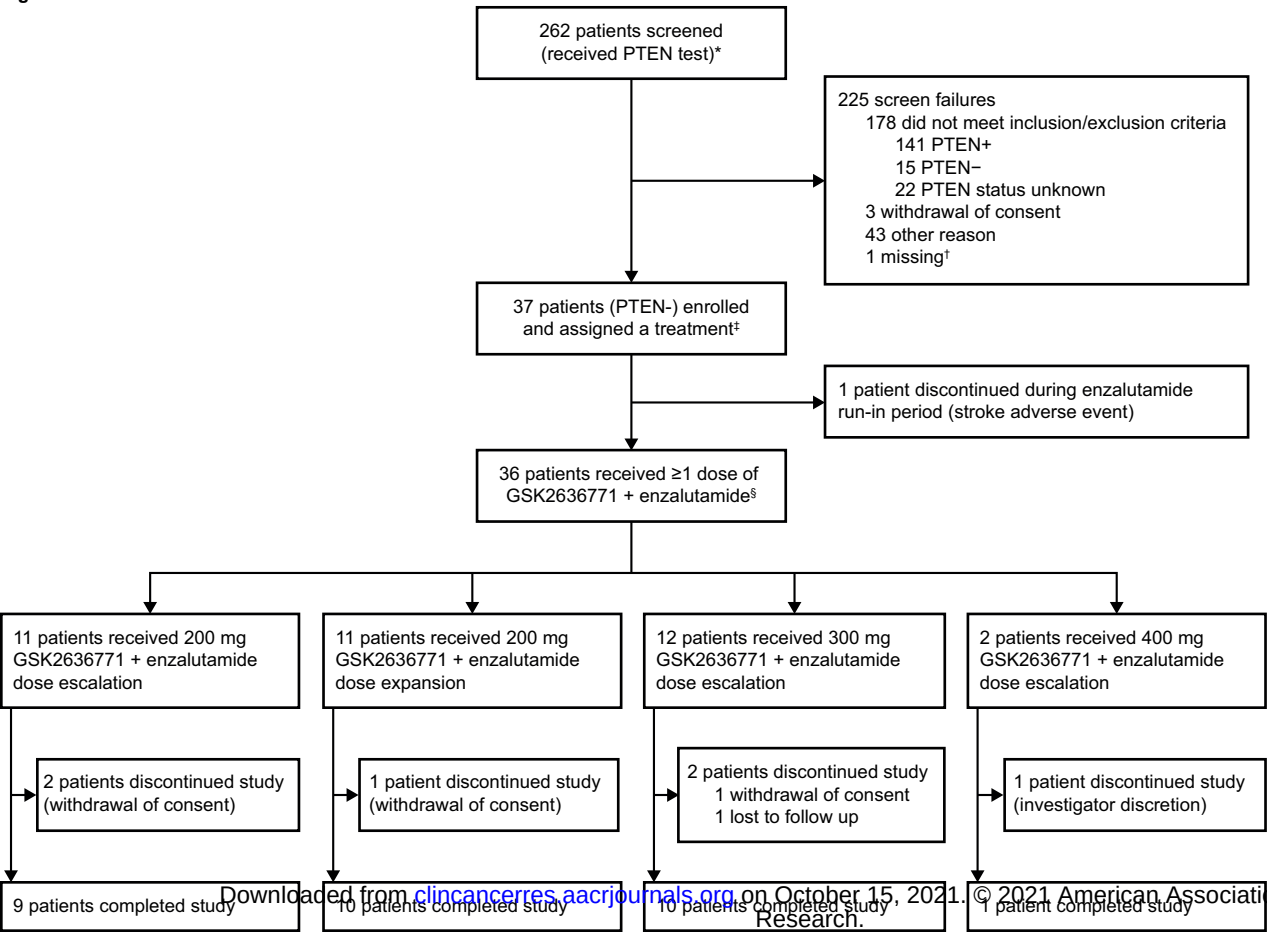


Figure 2

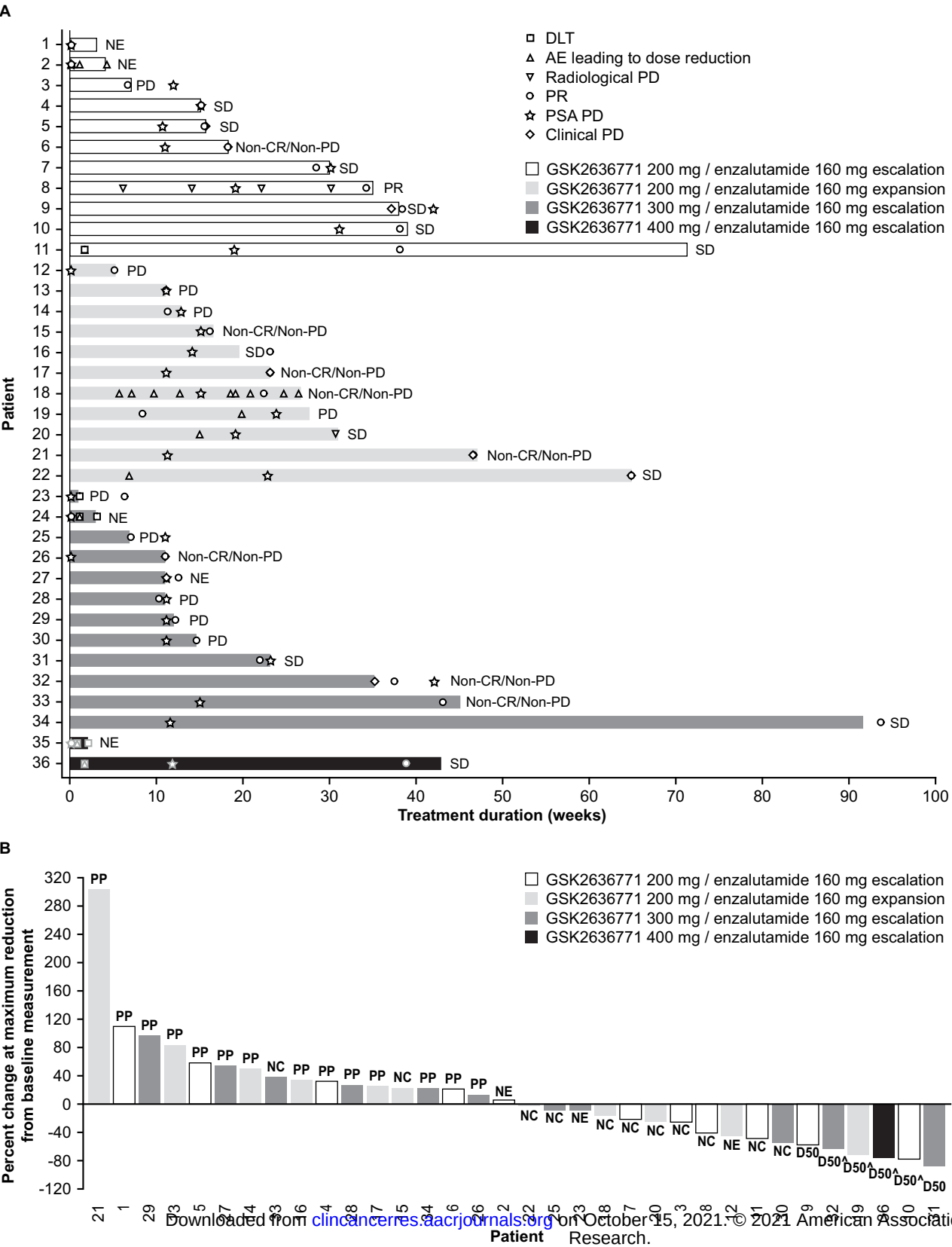
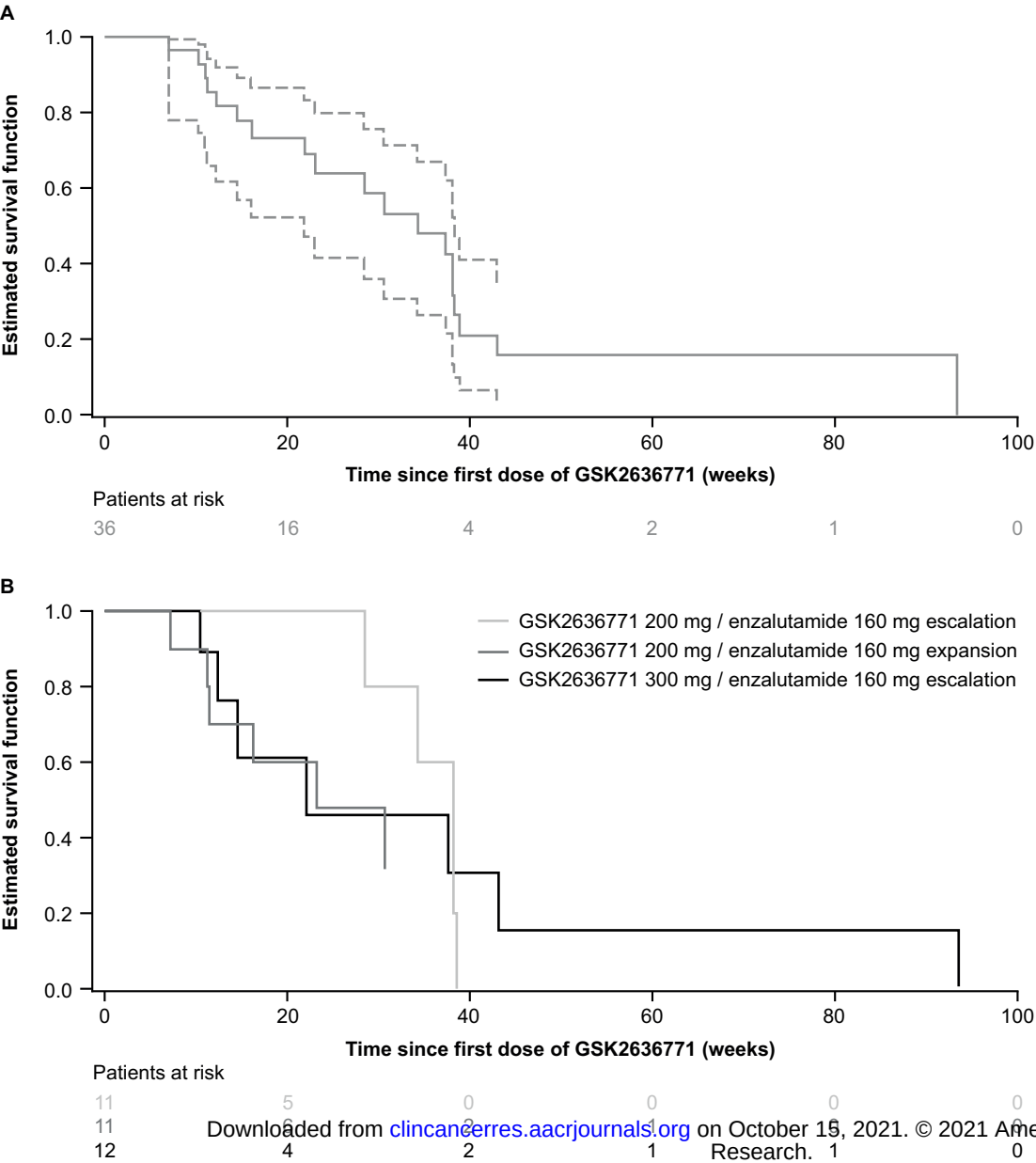


Figure 3



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Clinical Cancer Research

A Phase I, Open-Label, Dose-Finding Study of GSK2636771, a PI3K β inhibitor, Administered with Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer

Debashis Sarker, Nancy A. Dawson, Ana M. Aparicio, et al.

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