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ORIGINAL ARTICLE

A phase I dose-escalation study of enzalutamide in combination with the AKT inhibitor AZD5363 (capivasertib) in patients with metastatic castration-resistant prostate cancer

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Background: Activation of the PI3K/AKT/mTOR pathway through loss of phosphatase and tensin homolog (PTEN) occurs in approximately 50% of patients with metastatic castration-resistant prostate cancer (mCRPC). Recent evidence suggests that combined inhibition of the androgen receptor (AR) and AKT may be beneficial in mCRPC with PTEN loss.

Patients and methods: mCRPC patients who previously failed abiraterone and/or enzalutamide, received escalating doses of AZD5363 (capivasertib) starting at 320 mg twice daily (b.i.d.) given 4 days on and 3 days off, in combination with enzalutamide 160 mg daily. The co-primary endpoints were safety/tolerability and determining the maximum tolerated dose and recommended phase II dose; pharmacokinetics, antitumour activity, and exploratory biomarker analysis were also evaluated.

Results: Sixteen patients were enrolled, 15 received study treatment and 13 were assessable for dose-limiting toxicities (DLTs). Patients were treated at 320, 400, and 480 mg b.i.d. dose levels of capivasertib. The recommended phase II dose identified for capivasertib was 400 mg b.i.d. with 1/6 patients experiencing a DLT (maculopapular rash) at this level. The most common grade $\geq$3 adverse events were hyperglycemia (26.7%) and rash (20%). Concomitant administration of enzalutamide significantly decreased plasma exposure of capivasertib, though this did not appear to impact pharmacodynamics. Three patients met the criteria for response (defined as prostate-specific antigen decline $\geq$50%, circulating tumour cell conversion, and/or radiological response). Responses were seen in patients with PTEN loss or activating mutations in AKT, low or absent AR-V7 expression, as well as those with an increase in phosphorylated extracellular signal-regulated kinase (pERK) in post-exposure samples.

Conclusions: The combination of capivasertib and enzalutamide is tolerable and has antitumour activity, with all responding patients harbouring aberrations in the PI3K/AKT/mTOR pathway.

Clinical Trial Number: NCT02525068

Key words: prostate cancer, AZD5363, capivasertib, AKT inhibitor, enzalutamide, biomarkers

INTRODUCTION

Systemic therapy for advanced prostate cancer has largely focused on targeting the androgen receptor (AR). Even in castration-resistant prostate cancer (CRPC) the AR remains an important target as has been unequivocally proven by the clinical success of AR pathway targeting therapies such as abiraterone and enzalutamide.[1–3] Despite the success of AR pathway targeted therapies resistance inevitably develops and CRPC remains an incurable, lethal disease.

Activation of the PI3K/AKT/mTOR pathway is one of the most common aberrations in human cancers and is associated with tumour growth, survival, and drug resistance.[4] Approximately 50% of CRPC patients have activation of this pathway predominately due to loss of phosphatase and tensin homolog (PTEN).[5] Preclinical prostate cancer models with PTEN loss have demonstrated that a reciprocal relationship exists between the AR and PI3K/AKT/mTOR pathways such that

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inhibition of one leads to up-regulation of the other.[6] Furthermore, combined inhibition of both pathways results in synergistic antitumour activity in PTEN loss models with similar results seen in some PTEN wildtype models.[7,8]

AZD5363 (capivasertib) is a highly selective pan-AKT inhibitor that is undergoing investigation in a number of malignancies. Two separate phase I trials in Western and Japanese populations found 480 mg b.i.d. 4 days on and 3 days off every week (4/7) to be the single-agent recommended phase II dose (RP2D).[9,10] We initiated a phase I/II trial to investigate the combination of enzalutamide and capivasertib in patients with metastatic CRPC. Here we present the results of the phase I trial.

METHODS

Patients

Patients aged ≥18 years with histologically confirmed metastatic CRPC and Eastern Cooperative Oncology Group (ECOG) performance status 0–2[11] with disease progression on or after one to two lines of taxane-based chemotherapy and ≥12 weeks of either abiraterone or enzalutamide were eligible. Initially, prior treatment with abiraterone was mandated; however, this was amended to allow either enzalutamide or abiraterone due to slow accrual. Inclusion criteria are in the supplementary Material, available at *Annals of Oncology* online.

Trial oversight

This investigator-initiated trial was supported by a grant from AstraZeneca, endorsed by Cancer Research UK, and co-sponsored by the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research. It received ethical approval from the NRES Committee London, Surrey Borders. The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU), London had responsibility for all aspects of trial management and statistical analysis. The Trial Management Group oversaw day-to-day trial conduct with strategic oversight provided by an independent trial steering committee. Safety data were reviewed and dose-escalation decisions made by the Safety Review Committee.

Study objectives

The co-primary objectives of this study were the safety and tolerability of capivasertib in combination with enzalutamide and the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of this combination. Secondary objectives were antitumour activity and the pharmacokinetic (PK) effect of enzalutamide on capivasertib. Exploratory objectives were pharmacodynamics (PD) and biomarker analyses.

Study design and treatment

This was a phase I, open-label, single-centre dose-escalation study with a 3+3 design.[12] Based on prior studies,[9,10] capivasertib was given b.i.d. on a 4/7 schedule starting at 320 mg with a predefined dose-escalation/de-escalation schedule (supplementary Material, available at *Annals of Oncology* online). Patients initially received a single dose of capivasertib on cycle 0 day 1 (C0D1) at their respective dose level followed by PK and PD sampling. Patients started enzalutamide at a fixed dose of 160 mg daily and capivasertib at C1D1 (supplementary Figure S1, available at *Annals of Oncology* online). All cycles were 28 days in length except cycle 0, which was 7 days. Dose escalation continued until dose-limiting toxicity (DLT) occurred in ≥2/6 patients in a cohort at which point the tolerable dose would have been exceeded. The MTD and RP2D were the highest dose level with a minimum of six patients and fewer than one third experiencing DLT. DLT criteria are in the supplementary Material, available at *Annals of Oncology* online.

Assessments

Safety and tolerability were assessed using adverse event (AE) reporting according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. AE reporting occurred from the time of first dose of study treatment to 30 days after treatment discontinuation. Response assessments used prostate-specific antigen (PSA), bone scan, objective soft tissue assessments (RECIST v1.1), and circulating tumour cell (CTC) counts. Patients were considered to have responded if (in the absence of contradictory evidence) any one of the following occurred: confirmed PSA decline ≥50% from baseline or objective response according to RECIST v1.1 or CTC count conversion from ≥5/7.5 ml blood at baseline to <5/7.5 ml blood.

Statistical analysis of clinical data

Statistical analysis was descriptive. AEs were tabulated and the proportion of patients with grade 3/4 toxicities and the number and type of serious adverse events (SAEs) were reported. Patients receiving any study treatment were included in the safety analysis. Patients who received at least 12 weeks of combination treatment or discontinued before 12 weeks due to progression were included in response analysis. Response rates by each criterion and overall were calculated with a 95% confidence interval (CI).

Research sample collection and analysis

Venous blood samples for PK of capivasertib were taken sequentially up to 48 hours after dosing on C0D1, C2D1, C2D4, and C2D11. PK parameters analyzed included maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and area under the plasma concentration time curve (AUC_{8h}). Geometric means of dose normalized C_{max} and AUC_{8h} on cycle 2 (combination with enzalutamide) were compared with that of cycle 0 (capivasertib alone). Platelet-rich plasma (PRP) and hair follicles were taken for PD analysis of biomarkers of AKT inhibition including phosphorylated (p) Ser9 and total GSK3β and pThr246 and total PRAS40. Statistical analysis of PD samples used one-way ANOVA with Kruskal–Wallis *post hoc* test and Dunnett's

multiple comparison test, with a *P* value of <0.05 meeting significance. Samples were taken at screening, on treatment, and at progression for biomarker analysis including next-generation sequencing (NGS), PTEN immunohistochemistry (IHC), androgen receptor splice variant 7 (ARv7) IHC, ARv7 CTC mRNA quantification, and phosphorylated extracellular signal-regulated kinases (pERK) IHC (see supplementary Material, available at *Annals of Oncology* online).

RESULTS

Patients

Sixteen patients were recruited from December 2014 to May 2016 with 15 receiving study treatment. Two patients were not assessable for dose-escalation decisions, one withdrew consent before completing the DLT window without experiencing a DLT, and one had dose delays during the DLT window for non-drug related AEs. At the time of data cut-off (10 March 2017) all patients had discontinued treatment: 12 due to progressive disease, 1 due to AE, and 2 withdrawing consent without experiencing disease progression. Baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics

		Total $n = 16$
Age	Median (IQR)	70.4 (68.0% to 72.6)
Ethnicity	Caucasian	15 (93.8%)
	African-Caribbean	1 (6.3%)
Gleason score at diagnosis	<8	4 (25%)
	≥ 8	9 (56.3%)
	Not available	3 (18.8%)
Metastatic disease at diagnosis	Yes	8 (50%)
	No	7 (43.8%)
	Not available	1 (6.3%)
Location of metastatic disease	Lymph nodes only	3 (18.8%)
	Bone only	7 (43.8%)
	Bone and lymph nodes	3 (18.8%)
	Visceral and bone	2 (12.5%)
	Visceral, bone, and lymph nodes	1 (6.3%)
Prior systemic therapy	Abiraterone	14 (87.5%)
	Cabazitaxel	8 (50%)
	Docetaxel	16 (100%)
	Enzalutamide	8 (50%)
Prior local treatment	Surgery[a]	3 (18.8%)
	Radiotherapy	6 (37.5%)
	Surgery[a] and radiotherapy	2 (12.5%)
ECOG performance status	0	2 (12.5%)
	1	14 (87.5%)
Hemoglobin	Median (range)	115 (97–146) g/l
Alkaline phosphatase	Median (range)	148 (57–1606) U/l
Albumin	Median (range)	34.5 (31–41) g/l
Lactate dehydrogenase	Median (range)	226.5 (106–729) U/l
PSA	Median (range)	361 (55–11 329) µg/l

PSA, prostate-specific antigen.
[a] Surgery includes radical prostatectomy and transurethral resection of prostate (TURP).

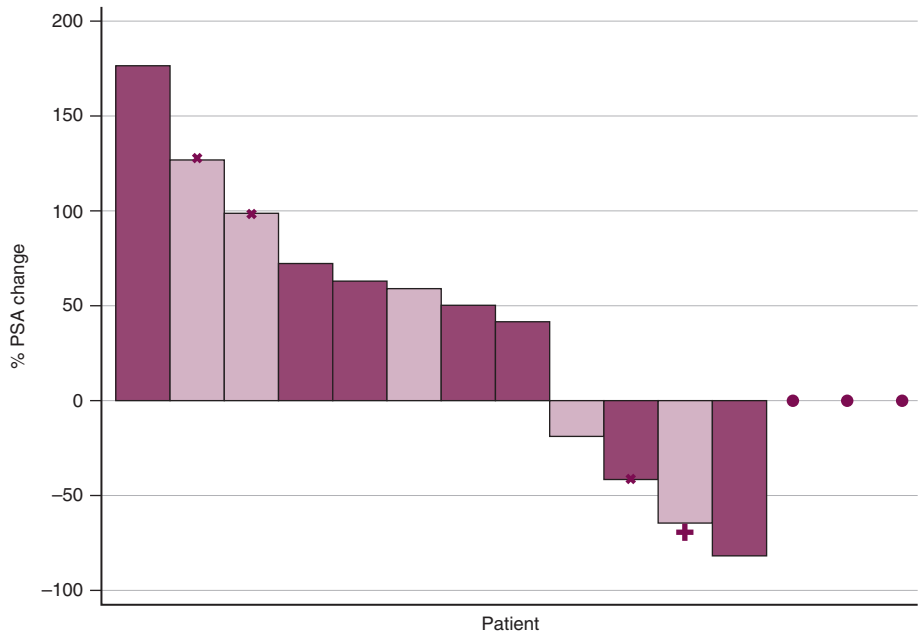
Safety and tolerability

At the capivasertib 320 mg dose level, three patients were treated without experiencing DLT (supplementary Table S1, available at *Annals of Oncology* online). Dose escalation to 480 mg occurred with five patients treated, four of whom were evaluable for dose-escalation decisions. Two patients experienced DLT of grade 3 maculopapular rash with the first occurring at C1D13 and with capivasertib held the rash resolved at C1D21; capivasertib was re-challenged first at 480 mg on C1D22 then 320 mg on C2D1, both times resulting in recurrent grade-2 rash followed by a 2-week interruption with the patient eventually tolerating 240 mg starting C2D15. The second DLT occurred at C1D10 and with capivasertib held the rash resolved at C1D17; capivasertib was restarted at 400 mg for 3 days then decreased to 360 mg due to drug supply issues with no recurrence of rash. Dose de-escalation to an intermediate dose of 400 mg occurred. Seven patients were treated with six evaluable for DLT. One patient experienced a DLT of grade 3 maculopapular rash at C1D10 that resolved at C1D27 after capivasertib was held and the patient was able to restart capivasertib at a 320-mg dose without recurrence of rash. Based on this data, capivasertib 400 mg b.i.d. 4/7 was selected as the MTD and RP2D (supplementary Figure S2, available at *Annals of Oncology* online).

In the safety population, 259 AEs were reported with 42.5% of those judged to be treatment-related. All patients experienced at least one treatment-related AE (supplementary Table S2, available at *Annals of Oncology* online). Grade ≥ 3 treatment-related AE occurred in eight patients (53.5%) with hyperglycemia and maculopapular rash being the most frequent. During the DLT period nine patients (60%) had a dosing interruption or reduction in enzalutamide, capivasertib, or both; five of these (55.6%) were due to AEs. Fourteen patients continued treatment beyond cycle 1; of these, six patients (42.9%) had a dosing interruption or reduction. Three patients remained on treatment for at least 24 weeks. Twelve SAEs occurred in seven patients with four considered to be related to the study drug and expected: hyperglycemia (dose level 480 mg); hyperglycemia and elevated creatinine (dose level 400 mg); maculopapular rash (dose level 480 mg); and nausea, anorexia, and pain (dose level 320 mg). One suspected unexpected serious adverse reaction (SUSAR) occurred at dose level of 480 mg: systemic inflammatory response syndrome (grade 2) that was felt to be probably related to capivasertib and resolved after drug interruption and did not recur upon re-challenge. There were no fatal SAEs.

Antitumour activity

Ten patients completed 12-weeks of study treatment and two patients discontinued before week 12 due to progressive disease (Figure 1, supplementary Table S3, available at *Annals of Oncology* online). Therefore, 12 patients were considered assessable for response (supplementary Table S4, available at *Annals of Oncology* online). Of the



Patient	7	5	6	12	15	11	3	9	8	10	1	16	2	13	14
Dose level	480	480	480	400	400	400	320	480	480	400	320	400	320	400	400
PTEN	N	N	L	N	N	N	L	N	L	N	L	N	N	L	N
ARV7	+	+	−	−	+	−	+	NA	+	+	−	−	NA	+	+
pERK	−	−	+	−	−	−	NA	−	−	−	+	+	NA	NA	−
NGS	−	+	−	−	−	−	−	−	−	−	−	+	−	−	−
PSA-r	No	No	No	No	No	No	No	No	No	N/E	Yes	Yes	N/E	N/E	N/E
RECIST-r	No	No	No	N/E	No	No	N/E	No	No	N/E	Yes	N/E	No	N/E	N/E
CTC-r	No	N/E	No	No	N/E	N/E	Yes	No	No	N/E	Yes†	Yes†	N/E	N/E	N/E
Overall-r	No	No	No	No	No	No	Yes	No	No	N/E	Yes	Yes	No	N/E	N/E
Time on treatment (weeks)	13.9	12.1	7.3	13.0	24.9	13.0	12.7	12.9	26.4	3.6	24.9	22.1	8.9	7.7	11.1
Reason for discontinuation	PD	PD	PD	PD	PD	PD	PD	PD	PD	PC	PD	PD	PD	AE	PC

Figure 1. Percent change in prostate-specific antigen (PSA) at 12 weeks relative to baseline PSA.
Each bar represents an individual patient. Light colour indicates the patient previously received treatment with both abiraterone and enzalutamide; dark colour indicates prior treatment with only abiraterone and not enzalutamide. Patients indicated with × discontinued before 12 weeks but safety follow-up results are available; in these patients, the percent change of PSA at discontinuation relative to baseline is presented. The patient indicated with + also met response criteria for RECIST and circulating tumour cell (CTC) conversion. Patients indicated with a dot discontinued treatment before 12 weeks with no post-treatment PSA values obtained. Dose level refers to the dosage of capivasertib the patient received in mg. Phosphate and tensin homolog (PTEN) status refers to immunohistochemistry (IHC) expression with N representing normal and L representing loss. ARV7 status refers to pre-treatment tumour biopsy baseline AR-V7 expression by IHC with + indicating an H-score of >10 and − indicating ≤10. Phosphorylated extracellular signal-related kinases (pERK) refers to increased expression by IHC on post-treatment tumour biopsy samples relative to baseline indicated by +, whereas − indicates no increase. NGS refers to next-generation sequencing with + representing known or likely deleterious mutations in PI3K/AKT/mTOR pathway genes and − representing an absence of such mutations. NA indicates not available. Patients meeting response criteria assessed by PSA, soft tissue objective response by RECIST, CTC conversions, and overall [indicated by (-r) respectively] are indicated by (Yes), with non-responders indicated by (No), and (N/E) indicating non-evaluable. † indicates non-confirmed CTC conversions. Reasons for discontinuation included progressive disease (PD), patient choice (PC), and AE.

12 assessable patients, 11 were assessable by PSA, 9 by RECIST v1.1, and 8 by CTC enumeration. Three patients met at least one response criteria with only one showing conflicting response criteria (conversion of CTC count to <5/7.5 ml whole blood but a rising PSA). One of these patients who previously had progressive disease on both abiraterone and enzalutamide met all three response criteria and remained on treatment for 25 weeks. Additionally, one patient who withdrew consent before completing the first cycle of combination therapy had a 41.4% PSA reduction at 4 weeks.

Pharmacokinetics and pharmacodynamics

Administration of enzalutamide decreased both C_{max} and AUC of capivasertib in 11 out of 13 patients when compared with capivasertib monotherapy (approximate mean 40% decrease at cycle 2 compared with cycle 0) (supplementary

Tables S5 and S6, Figure S3A and B, available at *Annals of Oncology* online). Following dose normalization to 320 mg the geometric means were significantly different (based on 90% CI). It should be noted that the overall inhibition of capivasertib by enzalutamide is greater than 40% given the accumulation that occurs over 4 weeks of administration. Noticeably, the predose levels on cycle 2 day 1 ranged from 51 to 483 ng/ml (data not shown). The administration of ADZ5363 with and without enzalutamide resulted in variable but notable decrease in pGSK3β in PRP at all dose levels at 4 h after dose [percentage decrease at C0D1 (without enzalutamide) and C2D1 (with enzalutamide), respectively: at 320 mg 61% to 96% and 63% to 82%; at 400 mg 20% to 70% and 5% to 65%; and at 480 mg 42% to 73% and 14% to 78%; no significant difference $P = 0.3880$ one-way ANOVA with Kruskal-Wallis post hoc test] (supplementary Figure S4A, available at *Annals of Oncology* online). In patients treated with 400 mg a significant reduction of $>$20% was observed in pGSK3β at 2 h (mean decrease 56%) and 4 h (44%) after dose compared with baseline when AZD5363 was administered alone (cycle 0) ($P = 0.0086$ one-way repeated measures ANOVA with Dunnett's multiple comparison test) though pGSK3β returned to baseline at 8 h after the dose (mean decrease 22%) and beyond (supplementary Figure S4B, available at *Annals of Oncology* online). Furthermore, decreases in pPRAS40 from hair follicle samples were also measured at cycles 0 and 2 [percentage decrease at 320 mg without enzalutamide (−) 31% to 46% with enzalutamide (+) −101% to 33%, 400 mg −6% to 53%, +19% to 61%, 480 mg −18% to 52%, + −19% to 59%; not significant $P = 0.8647$ one-way ANOVA with Kruskal–Wallis *post hoc* test] (supplementary Figure S5, available at *Annals of Oncology* online). Despite the decreased exposure of AZD5363 in the presence of enzalutamide, the inhibition of GSK3β and PRAS40 phosphorylation was not significantly lower than that observed with AZD5363 alone. For example, mean percentage reduction in PRAS40 is 38%, 26%, and 23% without enzalutamide and −34%, 40%, and 22% with enzalutamide for doses 320, 480, 400 mg, respectively.

Exploratory endpoints

PTEN loss was found in 6 of 16 patients while targeted NGS identified pathogenic mutations in PI3K/AKT/mTOR pathway genes in 2 of 15 (Figure 1 and supplementary Table S5, available at *Annals of Oncology* online). In the three responders, two had PTEN loss by IHC with the third PTEN normal and harbouring an activating *AKT* E17K mutation (supplementary Table S5, available at *Annals of Oncology* online). Another patient who had a $\geq$30% PSA response at 4 weeks but withdrew from the trial before completing the 35-day DLT window was found to be PTEN normal and to have a *PIK3CA* I391M single-nucleotide aberration of uncertain significance (Genomic alteration identified are summarized in supplementary Table S7).

AR-V7 status by IHC was available for 14 patients at baseline and 13 after treatment. AR-V7 mRNA expression in CTCs by AdnaTest was available for 14 patients at baseline and 6 post-treatment. CTCs were present in 10 of 14 patients at baseline (supplementary Figure S6, available at *Annals of Oncology* online). All patients who were negative for AR-V7 expression by IHC at baseline were either negative for AR-V7 mRNA expression in CTCs by AdnaTest or CTC negative. Similarly, all patients with detectable AR-V7 mRNA in CTCs at baseline were positive for AR-V7 by IHC; however, the absence of AR-V7 mRNA in CTCs was not predictive of the absence of AR-V7 expression by IHC (supplementary Material, available at *Annals of Oncology* online). The AdnaTest for AR-V7 was positive in three patients all of whom were non-responders. In responding patients at baseline 2, they had detectable CTCs with no detection of AR-V7 and one had no CTCs detected. AR-V7 expression at baseline appeared to predict lack of benefit, with IHC for AR-V7 positive in one responder though at very low levels (supplementary Figures S7 and S8, available at *Annals of Oncology* online). After treatment, CTCs were detected in three patients who were CTC negative at baseline, with AR-V7 detected in two of these patients. pERK expression by IHC was low or absent in all but two patients at baseline and increased after treatment in three patients including two of the responders (supplementary Figure S8, Table S8, available at *Annals of Oncology* online).

DISCUSSION

Clinically validated biomarkers have yet to be introduced in mCRPC though several candidates appear poised to change this paradigm, with early studies showing AR-V7 associating with poor outcome to AR targeted therapies[13] and DNA damage response (DDR) gene and mismatch repair (MMR) defects predicting response to PARP inhibitors[14] and immunotherapy, respectively.[15,16] Activation of the PI3K/AKT/mTOR pathway through PTEN loss is one of the most common molecular events in CRPC and has been proposed as a mechanism of resistance to AR targeted therapies[4,6,17–19] with preclinical studies showing synergistic antitumour activity with combined AR and PI3K/AKT/mTOR pathway inhibition.[6–8]

Here we demonstrate the safety and tolerability of co-targeting AR and AKT signalling with enzalutamide and capivasertib in mCRPC patients. While enzalutamide significantly lowered plasma concentrations of capivasertib this did not appear to compromise the PD effect with similar albeit variable modulation of GSK3β and PRAS40 phosphorylation both in the presence and absence of enzalutamide. Furthermore, the AEs typical of capivasertib such as maculopapular rash, hyperglycemia, and diarrhea occurred frequently with the RP2D found in this study of 400 mg b.i.d. 4/7 being in fact lower than that found in two separate single-agent phase I studies of this compound,[9,10] though the same as when combined with paclitaxel.[20]

We identified antitumour activity in this heavily pretreated population. All patients meeting response criteria had pathogenic events within the PI3K/AKT/mTOR pathway. Baseline AR-V7 expression by AdnaTest and IHC appeared to predict resistance to this combination, similar to what has been demonstrated with AR-targeted therapy

alone.[13,21] Another putative predictive biomarker of AKT inhibition may be extracellular signal-regulated kinase (ERK).[22,23] AKT negatively regulates ERK activation through the phosphorylation of N-terminus inhibitory sites of Raf.[24–27] Therefore inhibition of AKT releases cross-inhibition of Raf and increases phosphorylation of ERK. We found that among patients with evaluable pre- and post-treatment biopsies, IHC pERK score substantially increased in responders.

Interestingly, a recent randomized phase II trial of abiraterone with or without the AKT inhibitor ipatasertib provides additional support for co-targeting the AR and AKT. This study demonstrated improved rPFS in the overall population though subgroup analysis demonstrated a marked benefit for PTEN loss patients relative to PTEN normal.[28] Of note, ipatasertib was given continuously whereas in the current study capivasertib was given on a 4/7 intermittent schedule based on the single-agent phase I study demonstrating favourable tolerability, PK profile, and target engagement compared with other schedules[9] and supported by preclinical PK-PD efficacy mathematical modelling.[29] Whether this results in clinically relevant differences in antitumour activity is not known. Co-targeting of the AR and AKT may be a viable strategy in PTEN loss mCRPC though further validation is required.

In conclusion, co-targeting of the AR and AKT with enzalutamide and capivasertib is safe with preliminary evidence of antitumour activity supporting the ongoing phase II portion of this trial. All responding patients in this study had aberrations in the PI3K/AKT/mTOR pathway and absent or low AR-V7 expression at baseline, with two of the three responders showing an increase in pERK expression after treatment. However, due to the small sample size further study is required to determine the potential value of these as predictive biomarkers for this combination.

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DISCLOSURES

MK has accepted honoraria and/or consulting fees from Janssen, Ipsen, Astellas, BMS, Merck, AstraZeneca, Bayer, and travel support from Novartis. JM has participated in advisory boards for AstraZeneca, Roche, Janssen and has participated as a speaker in events sponsored by Astellas and Sanofi. JDB has accepted honoraria and consulting fees from AstraZeneca, Astellas, Janssen, Merck Serono, MSD, GSK, Daiichi Sankyo, Genentech-Roche, Boehringer Ingelheim, Pfizer Oncology, and Bayer. All remaining authors have declared no conflicts of interest.

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