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Platinum Priority – Brief Correspondence

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Overall Survival Update for Patients with Metastatic Castration-resistant Prostate Cancer Treated with Capivasertib and Docetaxel in the Phase 2 ProCAID Clinical Trial

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Abstract

The PI3K/AKT/PTEN pathway is frequently deregulated in metastatic castration-resistant prostate cancer (mCRPC). ProCAID was a phase 2 trial assessing addition of the AKT1/2/3 inhibitor capivasertib to docetaxel for patients with mCRPC. We previously reported that capivasertib did not extend a composite progression-free survival primary endpoint but did significantly improve the secondary endpoint of overall survival (OS). Here we present OS data after 66% of events had occurred in the intent-to-treat population ($n = 150$). Median OS was 25.3 mo for capivasertib plus docetaxel versus 20.3 mo for placebo plus docetaxel (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.47–1.05; nominal $p = 0.09$). Receipt of subsequent life-extending treatments was balanced between the treatment arms. The OS benefit associated with capivasertib was maintained in a subset of patients previously treated with abiraterone and/or enzalutamide (median OS 25.0 vs 17.6 mo; HR 0.57, 95% CI 0.36–0.91; nominal $p = 0.02$) but not in abiraterone/enzalutamide-naïve patients (median OS 31.1 mo vs not reached; HR 1.43, 95% CI 0.63–3.23). We conclude that OS may be extended by addition of capivasertib to docetaxel. Exploratory analysis revealed that the OS benefit was maintained in a subset of patients previously exposed to androgen receptor–targeted agents, which should be evaluated in prospective trials.

Patient summary: The ProCAID study examined whether adding the AKT inhibitor drug capivasertib to docetaxel chemotherapy improves outcomes for patients with advanced prostate cancer. Initial analysis of the ProCAID results suggested that capivasertib improved overall survival benefit. This follow-up analysis suggests that capivasertib addition may be particularly beneficial for patients whose cancer was previously treated with drugs that target the androgen receptor.

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Several therapies improve the overall survival (OS) of patients with metastatic castration-resistant prostate cancer (mCRPC), including docetaxel as first-line chemotherapy [1]. However, median survival from the point of mCRPC remains less than 3 yr, and most patients develop chemotherapy resistance [2,3]. The PI3K/AKT/PTEN pathway is commonly aberrantly activated in prostate cancer and has been associated with the development of resistance to taxane chemotherapy in cell lines [4,5].

Capivasertib is a potent selective inhibitor of all three AKT isoforms (AKT1/2/3). Preclinical, phase 1 and phase 2 studies have demonstrated capivasertib target engagement and preliminary signs of clinical efficacy for several cancer types [4,6]. Phase 1 of the ProCAID trial (NCT02121639) established a recommended dose for capivasertib in combination with docetaxel for patients with mCRPC [7]. Phase 2 of ProCAID then examined whether addition of capivasertib to docetaxel chemotherapy improved clinical outcomes [8]. Although the primary analysis found no difference in the primary endpoint (composite progression-free survival; cPFS), the prespecified secondary endpoint of OS was extended in the capivasertib plus docetaxel arm in comparison to placebo plus docetaxel (median 31.2 vs 20.3 mo; hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.34–0.88; p = 0.01) [8]. The OS data were relatively immature at the time of the primary analysis (72 deaths in the intent-to-treat [ITT] population of 150 patients). Here we report an updated OS analysis after extended follow-up in the ITT population, as well as a subgroup analysis.

The design, methods, and primary analysis findings from ProCAID have previously been reported [8]. In brief, the study recruited 150 patients with progressive mCRPC (Supplementary Table 1). Prior hormonal therapies were permitted but not prior chemotherapy for mCRPC. Patients received docetaxel and prednisolone according to local practice. Patients were randomly assigned 1:1 to receive either capivasertib 320 mg or matched placebo orally twice daily using an intermittent dosing schedule (4 d on, 3 d off) until disease progression according to Prostate Cancer Working Group-2 criteria, need for new systemic therapy for prostate cancer, development of unacceptable toxicities, loss to follow-up, or withdrawal of consent. Patients and investigators remained blinded to treatment allocation at the point of this extended OS analysis, which was preplanned to occur after ≥65% OS events. OS was assessed as the time from random assignment to death (with last patient contact used as the censoring date). Analysis of the ITT population was undertaken according to a Cox proportional hazards model adjusted for minimisation factors (presence of bone metastases, presence of visceral metastases, investigational site, and prior treatment with an androgen receptor–targeted agent [ARTA; abiraterone and/or enzalutamide]).

At the time of this updated analysis, 99 patients in the ProCAID ITT population (n = 150) had died (49 treated with capivasertib, 50 treated with placebo), with 88 of these deaths due to prostate cancer (Supplementary Table 2). Median follow-up (obtained using the reverse Kaplan-Meier method applied to the full patient cohort) was 35.0 mo for the capivasertib group and 32.0 mo for the placebo group. One patient (0.67%) remained on the study treatment. Median OS in this follow-up analysis was 25.3 mo for the capivasertib plus docetaxel group versus 20.3 mo for the placebo plus docetaxel group (apparent difference in OS between the treatment arms 5.0 mo; HR 0.70, 95% CI 0.47–1.05; nominal p = 0.09; Fig. 1A and Table 1). In total,

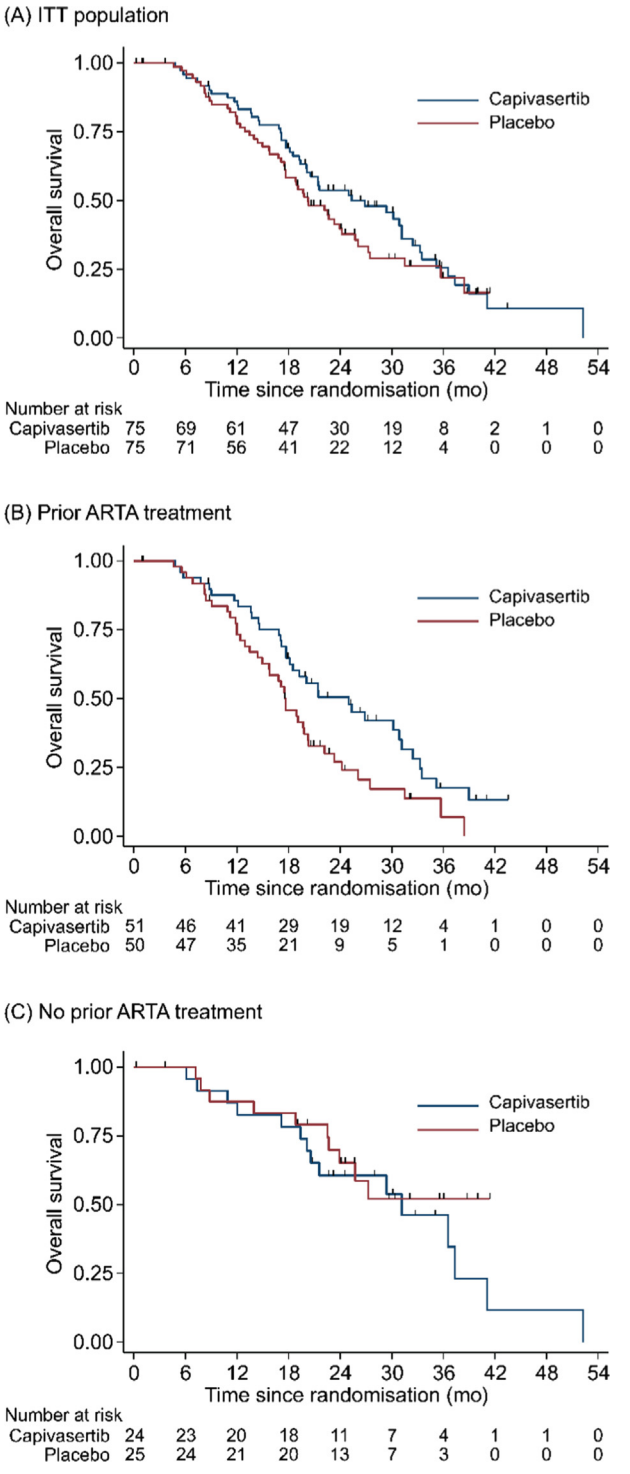

Fig. 1 – Kaplan-Meier estimates of overall survival by treatment arm allocation for (A) the ITT population, (B) the subgroup that received prior ARTA (abiraterone and/or enzalutamide) before entering ProCAID, and (C) the subgroup that had not received prior ARTA therapy. Tick marks denote censored patients. ARTA = androgen receptor-targeting agent; ITT = intent-to-treat.

Table 1 – Updated OS and subsequent treatments in the ITT population and subgroups who received and did not receive prior ARTA therapy before entering the ProCAID study

	ITT population		Prior ARTA therapy		No prior ARTA therapy	
	DOC + CAP (n = 75)	DOC + placebo (n = 75)	DOC + CAP (n = 51)	DOC + placebo (n = 50)	DOC + CAP (n = 24)	DOC + placebo (n = 25)
24-mo OS probability (95% CI)	0.54 (0.41–0.65)	0.40 (0.28–0.51)	0.51 (0.35–0.64)	0.27 (0.15–0.41)	0.61 (0.38–0.77)	0.65 (0.42–0.81)
36-mo OS probability (95% CI)	0.26 (0.14–0.39)	0.22 (0.11–0.35)	0.18 (0.07–0.32)	0.07 (0.01–0.23)	0.46 (0.23–0.67)	0.52 (0.28–0.72)
Median OS, mo (95% CI)	25.3 (20.1–31.2)	20.3 (17.5–24.2)	25.0 (17.7–31.1)	17.6 (14.4–20.3)	31.1 (20.1–41.1)	NR (22.7–NR)
Subsequent LETs, n (%)						
Yes (at least one treatment)	51 (68)	48 (64)				
Abiraterone	8 (11)	7 (9.3)				
Enzalutamide	21 (28)	14 (19)				
Cabazitaxel	24 (32)	19 (25)				
Radium-223	19 (25)	15 (20)				
No	22 (29)	25 (33)				
Unknown[a]	2 (2.7)	2 (2.7)				
Subsequent treatments, n (%)						
None/unknown	24 (32)	27 (36)				
1 treatment	33 (44)	41 (55)				
2 treatments	15 (20)	7 (9.3)				
3 treatments	3 (4.0)	0 (0.0)				
4 treatments	0 (0.0)	0 (0.0)				

ARTA = androgen receptor–targeted agent; CAP = capivasertib; DOC = docetaxel; CI = confidence interval; ITT = intent-to-treat; LETs = life-extending treatments; NR = not reached; OS = overall survival.
[a] Information was not reported for four patients (two in each arm) because of withdrawal from the study.

99 patients (66%; 68% of the capivasertib arm, 64% of the placebo arm) had received at least one life-extending therapy (an ARTA, cabazitaxel, or radium-223) after discontinuing the study treatment and the proportions were balanced between the treatment arms (Table 1). No clinically significant differences from the previously reported safety outcomes were seen on extended follow-up [8].

Current treatment paradigms have evolved such that most patients with mCRPC would now have received an ARTA before docetaxel chemotherapy, typically while their disease was hormone-sensitive [9,10]. As an exploratory analysis, we therefore investigated OS outcomes for the subgroup of 101 patients (67% of the ITT population) who had received an ARTA before entering the ProCAID study (Supplementary Tables 1 and 3), which had been included as a minimisation factor within the trial design. The median OS benefit associated with capivasertib plus docetaxel versus placebo plus docetaxel was 7.4 mo for the ARTA-pretreated subgroup (median 25.0 vs 17.6 mo; HR 0.57, 95% CI 0.36–0.91; p = 0.02; Fig. 1B and Table 1); the two arms had similar baseline characteristics and similar frequencies of life-extending treatments (Supplementary Tables 1 and 4). By contrast, in the subgroup of 49 patients (accepting that this analysis is underpowered) who had not received prior ARTA treatment, there was no difference in OS between the capivasertib and placebo cohorts (median 31.1 mo vs not reached; HR 1.43, 95% CI 0.63–3.23; Fig. 1C and Table 1). OS also appeared to be longer in this group than in the group with prior ARTA exposure, regardless of treatment (Fig. 1C and Table 1).

In conclusion, this updated OS analysis provides further evidence that addition of capivasertib to docetaxel chemotherapy improves survival for patients with mCRPC in comparison to treatment with docetaxel alone. The difference in median OS between treatment arms in the ITT population had narrowed in comparison to that demonstrated by the primary analysis, and an exploratory analysis indicated that the OS benefit associated with capivasertib addition was confined to the subgroup of patients who had previously received an ARTA. We had previously shown that there was no evident relationship between OS and biomarker status for PI3K/AKT/PTEN pathway activation [8]. This update demonstrates that the apparent OS benefit associated with capivasertib does not appear to be explained by imbalance in subsequent therapies. It remains unclear why the addition of capivasertib to chemotherapy improved OS but not the primary ProCAID endpoint of cPFS [8]. Larger trials are required to resolve this question and to confirm the OS benefit detected in ProCAID. The phase 3 CAPItello-280 trial (NCT05348577) examining capivasertib plus docetaxel for patients with mCRPC who have previously received an ARTA is positioned to provide these answers.

Author contributions: Simon J. Crabb had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Crabb, Birtle, Khoo, Jones.
Acquisition of data: Crabb, Griffiths, Dunkley, Radford, Ellis, Downs, Birtle, Khoo, Jones.
Analysis and interpretation of data: Crabb, Griffiths, Light, Northey, Whitehead, Wilding, Birtle, Khoo, Jones.
Drafting of the manuscript: Crabb, Griffiths, Dunkley, Downs, Ellis, Radford, Light, Northey, Whitehead, Wilding, Birtle, Khoo, Jones.
Critical revision of the manuscript for important intellectual content: Crabb, Griffiths, Birtle, Khoo, Jones.
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***Data sharing statement*:** Individual participant data can be made available, after deidentification, to investigators who provide a written request in accordance with General Data Protection Regulation and following authorisation from the sponsor organisation, starting immediately and ending 3 yr after publication. Data sharing requests should be directed to Simon J. Crabb and Gareth Griffiths. The Southampton Clinical Trials Unit (SCTU; University of Southampton, Southampton, UK) is committed to the responsible sharing of clinical trial data and trial samples with the wider research community. Data access is administered through the SCTU Data Release Committee. Requests for data access and sharing for SCTU trials should be e-mailed to the SCTU Data Release Committee Coordinator at ctu@soton.ac.uk.

Peer Review Summary

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2022.05.019.

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