original reports

Pan-AKT Inhibitor Capivasertib With Docetaxel and Prednisolone in Metastatic Castration-Resistant Prostate Cancer: A Randomized, Placebo-Controlled Phase II Trial (ProCAID)

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abstract

PURPOSE Capivasertib is a pan-AKT inhibitor. Preclinical data indicate activity in metastatic castration-resistant prostate cancer (mCRPC) and synergism with docetaxel.

PATIENTS AND METHODS ProCAID was a placebo controlled randomized phase II trial in mCRPC. Patients received up to ten 21-day cycles of docetaxel (75 mg/m^2 intravenous, day 1) and prednisolone (5 mg twice daily, oral, day 1-21) and were randomly assigned (1:1) to oral capivasertib (320 mg twice daily, 4 days on/3 days off, from day 2 each cycle), or placebo, until disease progression. Treatment allocation used minimization factors: bone metastases; visceral metastases; investigational site; and prior abiraterone or enzalutamide. The primary objective, by intention to treat, determined if the addition of capivasertib prolonged a composite progression-free survival (cPFS) end point that included prostate-specific antigen progression events. cPFS and overall survival (OS) were also assessed by composite biomarker subgroup for PI3K/AKT/PTEN pathway activation status.

RESULTS One hundred and fifty patients were enrolled. Median cPFS was 7.03 (95% CI, 6.28 to 8.25) and 6.70 months (95% CI, 5.52 to 7.36) with capivasertib and placebo respectively (hazard ratio [HR], 0.92; 80% CI, 0.73 to 1.16; one-sided $P = .32$). Median OS was 31.15 (95% CI, 20.07 to not reached) and 20.27 months (95% CI, 17.51 to 24.18), respectively (HR, 0.54; 95% CI, 0.34 to 0.88; two-sided $P = .01$). cPFS and OS results were consistent irrespective of PI3K/AKT/PTEN pathway activation status. Grade III-IV adverse events were equivalent between arms (62.2%). The most common adverse events of any grade deemed related to capivasertib were diarrhea, fatigue, nausea, and rash.

CONCLUSION The addition of capivasertib to chemotherapy did not extend cPFS in mCRPC irrespective of PI3K/AKT/PTEN pathway activation status. The observed OS result (a secondary end point) will require prospective validation in future studies to address potential for bias.

J Clin Oncol 39:190-201. © 2020 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on October 20, 2020 and published at ascopubs.org/journal/jco on December 16, 2020: DOI https://doi.org/10.1200/JCO.20.01576

INTRODUCTION

Hormone-sensitive metastatic prostate cancer is usually responsive to androgen-deprivation therapy in docetaxel or hormonal-therapy combinations.[1-3] However subsequent progression to metastatic castration-resistant prostate cancer (mCRPC) is almost inevitable at a median of about one year.[4]

Overall survival (OS) benefit exists for several mCRPC treatment options, including chemotherapy (docetaxel and cabazitaxel), hormonal therapy (abiraterone and enzalutamide), radium-223 and sipuleucel-T.[2] Although docetaxel for mCRPC improves survival, pain, and quality of life, median survival in phase III studies was only 17-19 months.[5,6] No therapy has demonstrated superior efficacy against, or combined with, docetaxel for mCRPC. Most patients develop docetaxel resistance during, or soon after, completion. For example, in a trial of cabazitaxel following prior docetaxel, 28%-30% experienced disease progression during docetaxel and 42%-48% within 3 months.[7]

CONTEXT

Key Objective

To determine if the addition of the AKT inhibitor capivasertib to docetaxel chemotherapy improves progression-free survival in patients with metastatic castration-resistant prostate cancer.

Knowledge Generated

In this phase II trial, the primary end point of progression-free survival was not extended by the addition of capivasertib to chemotherapy, irrespective of biomarker status for the PI3K/AKT/PTEN signaling pathway. We did find that overall survival, which was a secondary end point, was longer in patients who received the combination compared with chemotherapy alone.

Relevance

Based on the primary end point, the addition of capivasertib to chemotherapy was not supported in this trial. The observed overall survival extension would require prospective validation to exclude the potential for bias to have impacted on this finding and the relative data maturity for this end point at the point of this primary analysis.

PI3K/AKT/PTEN pathway activation in prostate cancer is associated with negative clinical outcomes, including castration resistance, chemoresistance or radioresistance, metastasis, and postsurgical recurrence. Approximately half of mCRPCs exhibit functional PTEN loss, and data support PI3K/AKT/PTEN pathway activation as a relevant therapeutic target in virtually all cases.[8-11]

Capivasertib (AZD5363) is an AKT1, 2, and 3 kinase inhibitor. It also inhibits protein kinase A and, with lower potency, Rho-associated protein kinases (ROCK1 and 2). Preclinical data, including prostate cancer models, indicate reduced AKT substrate phosphorylation (PRAS40 and GSK3β) and cell proliferation. Capivasertib also enhanced docetaxel efficacy in breast cancer xenografts.[12,13] Monotherapy trials demonstrated acceptable safety and pharmacodynamic target modulation in tumors. Tumor size reductions occurred in 46% and 56% of *PIK3CA*-mutated breast and gynecological cancers respectively.[14] Clinical activity was also demonstrated in *AKT1*-mutant solid cancers, including estrogen receptor (ER)-positive breast cancer.[15]

The phase Ib part of ProCAID established a recommended phase II dose for capivasertib combined with docetaxel and prednisolone (DP) in mCRPC.[16] Consistent with monotherapy, the most common high-grade, capivasertib-related symptomatic adverse events were rash and diarrhea. Transient hyperglycemia occurred in all patients but was self-limiting. We hypothesized that capivasertib prolongs progression-free survival (PFS) when combined with DP for mCRPC. The phase II part of ProCAID, reported here, tested this.

METHODS

Study Design and Participants

ProCAID was an investigator-initiated, multicenter, randomized, double-blind, phase II, placebo-controlled trial. Patient eligibility criteria (Data Supplement, online only) included ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, suitable for DP and with progressive mCRPC. There were no restrictions on prior hormonal therapies (eg, abiraterone and enzalutamide). Exclusion criteria included previous chemotherapy for mCRPC and diabetes mellitus requiring insulin or ≥ 2 oral hypoglycemic medications. The Protocol (online only) was amended during recruitment to permit prior docetaxel chemotherapy for hormone-sensitive disease.

The study was in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and approved by West London & GTAC Research Ethics Committee (13/LO/1691). All patients provided written informed consent.

Procedures

Patients were randomly assigned (1:1), with a minimization algorithm incorporating a 20% random component, to either capivasertib or matched placebo combined with DP. Stratification occurred for presence of bone metastases, visceral (nonlymph node) disease, prior use of abiraterone or enzalutamide, and investigational site. Capivasertib and placebo were provided by AstraZeneca (Cambridge, United Kingdom).

Patients received up to ten 21-day DP cycles (docetaxel 75 mg/m^2, intravenous, day 1; prednisolone, 5 mg twice daily, or 10 mg once daily, orally, days 1-21) with dexamethasone premedication (8 mg, orally, 12, 3 and 1 hours predocetaxel, or similar) and antiemetic prophylaxis per local practice. Patients also received either capivasertib, or matched placebo, 320 mg orally, twice daily, on a 4 days on/3 days off continuous schedule, commencing cycle one, day 2, until disease progression.[16] Dose modifications and delays were permitted for hematological and nonhematological toxicities within the Protocol.

Patients discontinued study treatment for disease progression by PCWG2 criteria (any of prostate-specific antigen

[PSA] progression, radiological progression, or unequivocal clinical progression) or need for new antiprostate cancer systemic therapy or development of unacceptable toxicities, loss to follow-up, or withdrawal of consent.[17]

PSA level was taken at baseline and every 21 days until disease progression. Radiological disease evaluation was via cross-sectional imaging of the chest, abdomen, and pelvis, and bone scan, at baseline and subsequently as clinically indicated according to local standards of care (rather than prespecified intervals). Archival formalin-fixed paraffin-embedded tumor tissue (diagnostic samples prior to any cancer treatment), and baseline blood samples, were taken for translational end points. Patients were reviewed on day 1 of treatment cycles, and then 6 weekly until disease progression, and then for survival status only.

A composite biomarker for PI3K/AKT/PTEN pathway activation status was prospectively defined for exploratory analysis (Data Supplement). The biomarker population included patients in the intent-to-treat (ITT) population with at least one available result from either tumor tissue or baseline plasma circulating tumor DNA (ctDNA). Patients were biomarker-positive if PTEN deficiency was identified by immunohistochemistry (IHC) of tumor tissue and/or an eligible alteration was detected in *PIK3CA*, *PTEN*, or *AKT1* by next-generation sequencing (NGS) of either tumor tissue or baseline plasma ctDNA.

Outcomes

The primary outcome was investigator-assessed composite PFS, calculated as time from random assignment to disease progression (any of PSA progression [PCWG2[17]], soft tissue disease progression [RECIST v1.1[18]], bone metastases progression [PCWG2[17]], unequivocal clinical progression, and commencement of new antiprostate cancer systemic therapy) or death. Secondary outcomes included OS (time from random assignment to death) PFS excluding PSA progression alone, PSA-based PFS (PSA progression or death counting as events), PSA response (PCWG2[17]), bone pain changes (Brief Pain Inventory), and safety (Common Terminology Criteria for Adverse Events [CTCAE] v4.03).

Statistical Analysis

Statistical analyses were prespecified within an a priori statistical analysis plan. ProCAID was designed to detect 50% improvement in median composite PFS, from 6 (placebo) to 9 months (capivasertib) with 90% power and 20% one-sided level of statistical significance, requiring 111 events in 132 patients with 18-month accrual and 12-month follow-up.[19] To account for patients lost to follow-up or nonevaluable, the Protocol allowed for sample size inflation by 10% to 150 randomly assigned patients. Efficacy analyses (except biomarker analyses) were conducted in the ITT population comprising all randomly assigned patients. The safety population included all randomly assigned patients who received any dose of docetaxel, prednisolone, capivasertib, or placebo.

PFS (primary end point) was compared between study arms by Cox proportional hazards model adjusting for random assignment stratifications. The adjusted *P* value and hazard ratio (HR) with 80% CI was determined with Kaplan-Meier methods to describe the data. Secondary analyses of the primary end point included a test for interaction, to assess whether study arm effect depended on factors in the random assignment stratification (using forest plots), and further subgroup analyses of baseline and demographic characteristics. Sensitivity analyses of the primary end point included unadjusted logrank testing for difference in study arms, post hoc exploratory analysis excluding initiation of new anticancer treatment as events, proportional hazards assumptions checked using log cumulative hazards, Schoenfeld's global test, and time-varying covariate analysis. OS and other PFS time to event end points were analyzed using the same approach as PFS.

Analysis of effect of biomarker status was planned prospectively with subgroup analyses for PFS and OS by PI3K/AKT/PTEN pathway alteration by Cox model using a similar approach to the exploration of minimization factors of the primary end point.

PSA response was compared between arms using logistic regression adjusted for minimization factors, percentage change at 12 weeks, and best response, displayed by waterfall plot. Area under the curve to cycle 5 (Brief Pain Inventory) was used to summarize average bone pain. Worst adverse event grade for each patient was compared between arms by the Mann-Whitney *U* test. Other displays of safety data were by summary and descriptive statistics. Except for the primary analysis described above, all statistical analyses were evaluated with two-sided 95% CIs, *P*-values, and 5% significance. Analyses were performed using STATA (version 16.0; College Station, TX) and SAS (version 9.4; Cary, NC).

This study was overseen by an independent data monitoring committee (IDMC) and registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT02121639).

RESULTS

A total of three hundred ninety-nine patients were screened between September 10, 2015, and January 31, 2019. In October 2018, the IDMC recommended increased recruitment from 132 to 150 randomly assigned patients to address drop out. One hundred and fifty patients from 21 United Kingdom institutions (Data Supplement) were randomly assigned with 75 per arm (ITT population, Fig 1). At data cutoff (December 9, 2019), five patients (3.3%) were still receiving capivasertib or placebo (to date, participants remain blinded and without treatment crossover), with none still receiving DP. Median follow-up, for all patients was 23.7 months (reverse Kaplan-Meier method, interquartile range [IQR], 14.4-31.0; capivasertib arm 22.6

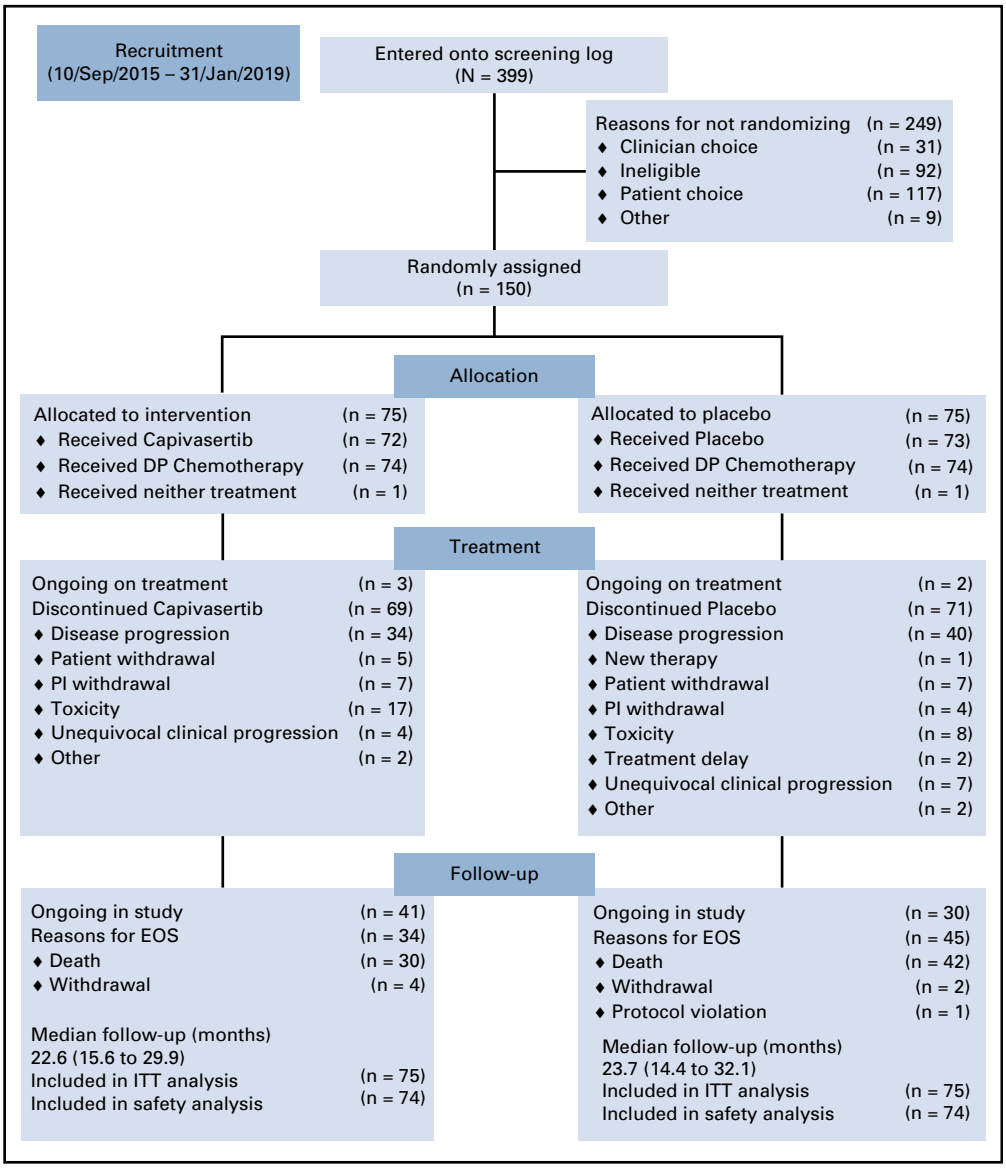

FIG 1. CONSORT diagram. DP, docetaxel and prednisolone; EOS; end of study; ITT, intent to treat.

(IQR, 15.6-29.9); placebo arm 23.7 (IQR, 14.4-32.1); Data Supplement) and for patients still alive was 16.8 months (IQR, 12.0-26.5). Table 1 shows baseline characteristics by treatment allocation.

The safety population comprised 74 patients per arm, with 72 (96.0%) and 73 (97.3%) receiving at least one dose of capivasertib or placebo, respectively. A median of seven (IQR, 5-10) DP treatment cycles were administered with medians of six (IQR, 4-10) in the capivasertib arm and seven (IQR, 5-9) for placebo. Patients received a median of 17.7 weeks (IQR, 6.6-39.3) of capivasertib and 23.7 weeks (IQR, 14.7-36.7) of placebo, with 14 (18.7%) and 13 (17.3%) having at least one dose reduction, respectively. The Data Supplement shows treatment duration, reductions, and delays.

For the primary PFS ITT analysis there were 135 events, with 67 (89.3%) in the capivasertib arm and 68 (90.7%) for placebo. PFS events were by PSA progression in 55 (82.1%) and 55 (80.9%), respectively. Addition of capivasertib to DP did not lower risk of progression or death, with an adjusted HR of 0.92 (80% CI, 0.73 to 1.16, one-sided $P = .32$, Fig 2, Data Supplement). Median PFS was 6.7 months (95% CI, 5.52 to 7.36) in the placebo arm and 7.03 months (95% CI, 6.28 to 8.25) in the capivasertib arm. The 6-month PFS rate was 56% and 62% in the placebo and capivasertib cohorts, respectively.

For the OS secondary end point, there were 72 events (48.0%), with 30 (40.0%) deaths in the capivasertib arm and 42 (56.0%) for placebo. The predominant cause of

TABLE 1. Baseline Characteristics

Characteristic	DP Plus Capivasertib (n = 75)	DP Plus Placebo (n = 75)	Total (N = 150)
Age, years			
Mean (SD)	68.3 (6.79)	70.0 (6.05)	69.2 (6.46)
Median (IQR)	69 (64-67)	70 (66-75)	69 (65-74)
Range	50.0-84.0	55.0-82.0	50.0-84.0
Eastern Cooperative Oncology Group performance status			
0	44 (58.7%)	46 (61.3%)	90 (60.0%)
1	31 (41.3%)	29 (38.7%)	60 (40.0%)
Pain score at baseline[a]			
Range	0-9	0-8	0-9
Median	1	1	1
IQR	0-3	0-3	0-3
Opioid use at baseline			
Yes	17 (22.7%)	19 (25.3%)	36 (24.0%)
No	58 (77.3%)	56 (74.7%)	114 (76.0%)
Time from prostate cancer diagnosis			
Median, years	4.5	4.4	4.4
IQR	2.8-8.5	2.2-8.6	2.6-8.5
Sites of metastatic disease			
Bone	61 (81.3%)	63 (84.0%)	124 (82.7%)
Lymph (pelvic and/or extrapelvic)	37 (49.3%)	32 (42.7%)	69 (46.0%)
Lung	5 (6.7%)	9 (12.0%)	14 (9.3%)
Liver	3 (4.0%)	5 (6.7%)	8 (5.3%)
Other	2 (2.7%)	6 (8.0%)	8 (5.3%)
Visceral (nonlymph node) metastatic disease			
Present	14 (18.7%)	17 (22.7%)	31 (20.7%)
Not present	61 (81.3%)	58 (77.3%)	119 (79.3%)
Prior treatment with abiraterone or enzalutamide			
Enzalutamide only	28 (37.3%)	25 (33.3%)	53 (35.3%)
Abiraterone only	18 (24.0%)	18 (24.0%)	36 (24.0%)
Both	5 (6.7%)	7 (9.3%)	12 (8.0%)
Neither	24 (32.0%)	25 (33.3%)	49 (32.7%)
Prior radical radiotherapy for prostate cancer			
Yes	29 (38.7%)	27 (36.0%)	56 (37.3%)
No	46 (61.3%)	48 (64.0%)	94 (62.7%)
Prior radical prostatectomy			
Yes	13 (17.3%)	7 (9.3%)	20 (13.3%)
No	62 (82.7%)	68 (90.7%)	130 (86.7%)
Gleason score			
7 or less	21 (28.0%)	29 (38.7%)	50 (33.3%)
8-10	51 (68.0%)	40 (53.3%)	91 (60.7%)
Not recorded	3 (4.0%)	6 (8.0%)	9 (6.0%)
PSA, μg/L			
Median (IQR)	37.5 (13.6-93.9)	62.0 (28.0-151.0)	46.5 (16.6-116.0)

(continued on following page)

TABLE 1. Baseline Characteristics (continued)

Characteristic	DP Plus Capivasertib (n = 75)	DP Plus Placebo (n = 75)	Total (N = 150)
Range	3.3-1,405.0	1.2-1,035.0	1.2-1,405.0
Lactate dehydrogenase above ULN	19 (25.3%)	24 (32.0%)	43 (28.7%)
Alkaline phosphate above ULN	28 (37.3%)	33 (44.0%)	61 (40.7%)
Albumin below LLN	7 (9.3%)	9 (12.0%)	16 (10.7%)
Hemoglobin below LLN	41 (54.7%)	46 (61.3%)	87 (58.0%)

Abbreviations: DP, docetaxel and prednisolone; IQR, interquartile range; LLN, lower limit of normal according to the local institutional range; PSA, prostate-specific antigen; SD, standard deviation; ULN, upper limit of normal according to the local institutional range.

[a]Pain in the 24 hours before baseline visit, on a scale from 0-10 (brief pain inventory).

death was prostate cancer in 25 (83.3%) and 38 (90.5%) in the capivasertib and placebo cohorts, respectively. Addition of capivasertib to DP resulted in a 46% reduction in overall risk of death, with an adjusted HR of 0.54 (95% CI, 0.34 to 0.88, two-sided $P = .01$, Fig 2, Data Supplement). A difference in median OS of 10.9 months was shown, from 20.27 months (95% CI, 17.51 to 24.18) in the placebo cohort to 31.15 months (95% CI, 20.07, not reached) in the capivasertib cohort, and 24-month OS rates of 39% versus 56%, respectively.

One hundred and thirty-six (90.7%) of the ITT population were included within the biomarker population analysis. Of these, 98 (72.1%) had an archival tissue biomarker result (IHC and/or NGS); and 130 (95.6%) a baseline ctDNA NGS result. Forty-four (32.4%) were biomarker-positive. Consistent with previous data sets, PTEN alterations were the predominant pathway alteration (36.5% PTEN deficiency by IHC; 24% and 11% alterations by NGS in tissue and plasma, respectively).[20-23] Figure 3 and the Data Supplement show the contribution of the components to biomarker status by patient. PFS and OS results were found to be consistent irrespective of PI3K/AKT/PTEN pathway activation status based on this biomarker (Table 2). Analysis of PFS and OS with respect to individual components of this composite biomarker, and a sensitivity analysis including the ITT population, produced similar results (Data Supplement). Forest plot analysis for stratification factors used in random assignment and baseline characteristics are shown in Figure 4 with respect to PFS and OS.

PSA response rates were not different between treatment arms with 45% (95% CI, 34% to 57%) and 55% (95% CI, 44% to 66%) having a PSA response in the capivasertib and placebo cohorts, respectively (odds ratio, 0.66; 95% CI, 0.35 to 1.26, $P = .207$). Waterfall plots of PSA response to week 12, and to best response, are provided in the Data Supplement. Within the ITT population, PFS excluding PSA progression alone and PSA-based PFS (and exploratory analyses excluding new antiprostate cancer treatment as events) were similar to those for the PFS primary end point with outcomes not different by treatment arm (Supplementary Tables 8-15, online only). No differences were seen between treatment arms for bone pain up to treatment cycle 5.

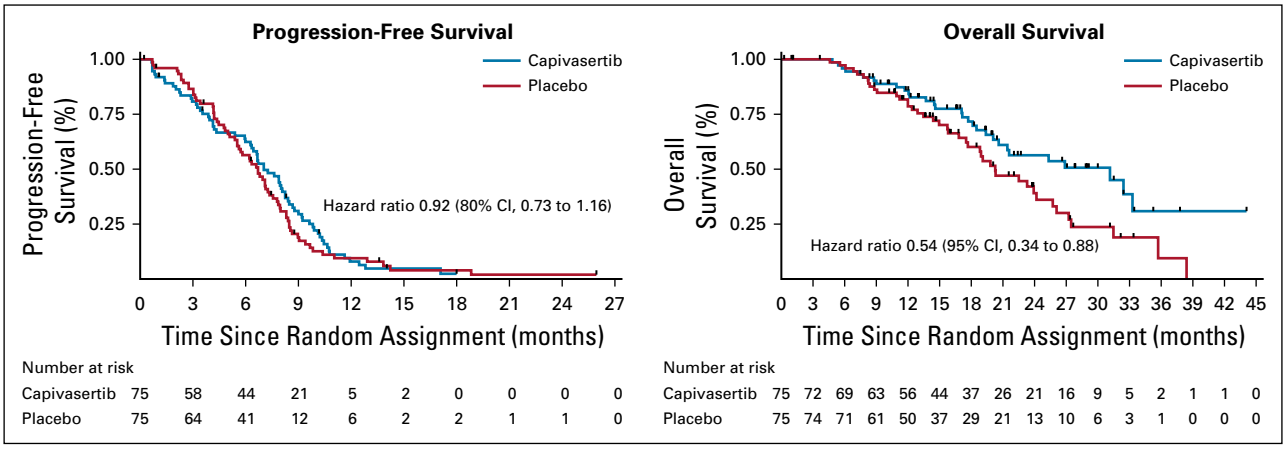

FIG 2. Kaplan-Meier estimates by treatment arm for progression-free survival and overall survival in the intent-to-treat population.

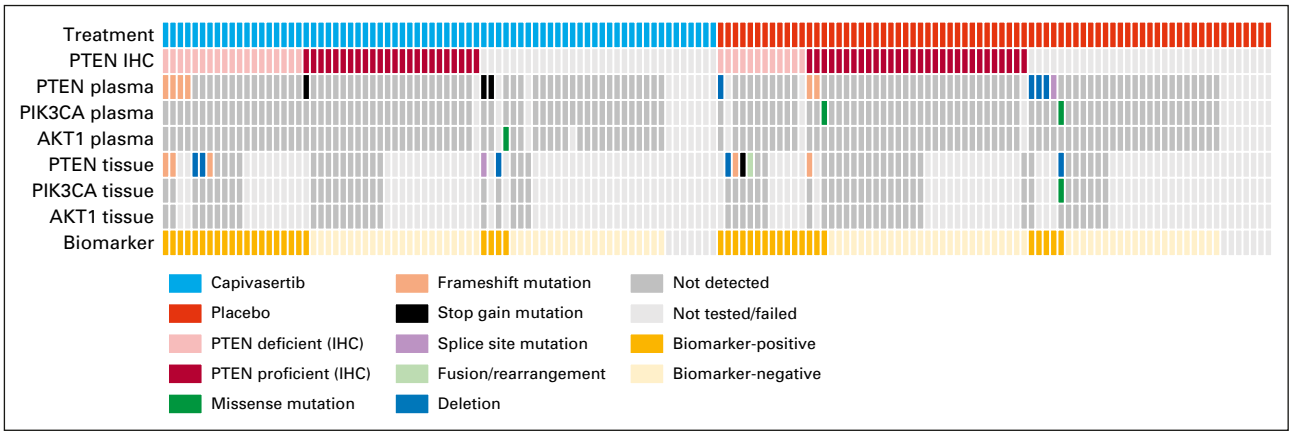

FIG 3. Individual patient status, for the full intent-to-treat population, by treatment arm allocation, for PTEN protein expression in archival tumor tissue and gene alteration for *PIK3CA*, *AKT1*, and *PTEN*, within archival tumor tissue and/or circulating tumor DNA collected at study entry contributing to the biomarker status analysis. IHC, immunohistochemistry.

Within the safety population (74 per arm), every patient had at least one adverse event, and 46 (62.2%) in both arms had at least one grade ≥ 3 adverse event. Adverse events leading to treatment discontinuation occurred in 17 patients (23.0%) in the capivasertib arm and in eight (10.8%) placebo (Data Supplement), with at least one adverse event assessed as related to capivasertib/placebo reported in 60 (81.1%) patients in the capivasertib arm and in 58 (78.4%) in the placebo arm (Data Supplement). There were no grade 5 adverse events, and a Mann-Whitney *U* test exploring the worst CTCAE grade for each patient showed no significant differences between arms ($P = .691$). Table 3 shows adverse events, regardless of causality.

DISCUSSION

To the best of our knowledge, this is the first study to test AKT inhibition combined with chemotherapy in prostate cancer. Addition of capivasertib to DP did not extend the composite primary end point of PFS used in this study in mCRPC.

Intriguingly, however, we have detected a substantial increase in the OS secondary end point. Data from this study do not provide a definitive explanation for why the addition of capivasertib to chemotherapy might extend OS but not PFS. Furthermore, PSA response rates, although not statistically significantly different, favored the placebo arm numerically, and survival outcomes were found to be consistent irrespective of PI3K/AKT/PTEN pathway activation status.

Progression events occurred primarily through PSA progression in > 80% of patients in each arm. PSA level and kinetics are a function of both total androgen receptor (AR) function and disease bulk. One could hypothesize that therapeutic combinations, where neither drug has an AR-directed mechanism, might not impact a PSA-driven PFS end point, at least to the same extent as treatments targeting AR function directly. However, examples of non–AR-directed therapy have previously impacted PSA based end points.[6,7] Preclinical data indicate that reciprocal crosstalk mechanisms exist between PI3K/AKT/PTEN pathway signaling and AR signaling in PTEN-deficient prostate cancer, such that AKT inhibition might potentially increase AR transcriptional activity and thus PSA expression.[24] Potentially, AKT inhibition might alter response to future therapies, or alter patterns of progression rate or metastatic site.

TABLE 2. PFS and Overall Survival With Respect to Primary Biomarker Status

Outcome	Median Capivasertib (Months) (95% CI)	Median Placebo (Months) (95% CI)	HR (95% CI)	*P*
PFS	7.03 (6.28 to 8.25)	6.7 (5.52 to 7.36)	0.92 (0.65 to 1.31)	.32
PFS, biomarker-positive (n = 44)	7.75 (6.44 to 9.63)	7.98 (5.09 to 9.82)	1.17 (0.61 to 2.23)	
PFS, biomarker-negative (n = 92)	7.03 (4.21 to 8.25)	6.34 (4.76 to 7.13)	0.89 (0.57 to 1.37)	
OS	31.15 (20.07 to NR)	20.27 (17.51 to 24.18)	0.54 (0.34 to 0.88)	.01
OS, biomarker-positive	26.87 (14.59 to NR)	20.27 (12.91 to 35.71)	0.62 (0.26 to 1.47)	
OS, biomarker-negative	32.43 (18.5 to NR)	20.30 (16.82 to 24.18)	0.54 (0.30 to 0.99)	

NOTE. PFS (primary end point) has a one-sided *P* value with a corresponding 80% CI for the HR of 0.73-1.16. The *P* value for OS is two-sided.
Abbreviations: HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

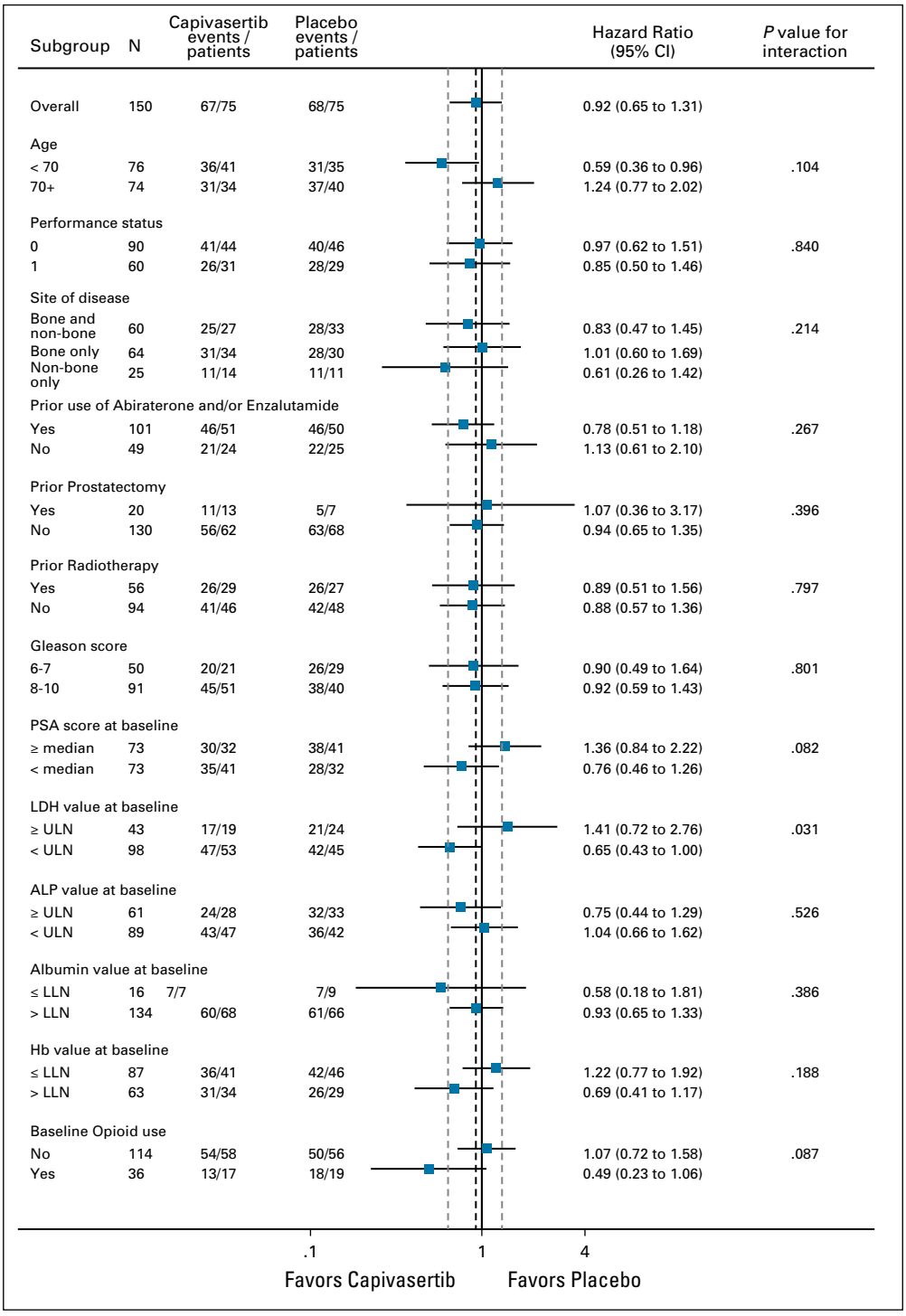

FIG 4. Forest plots for (A) progression-free survival and (B) overall survival. ALP, alkaline phosphatase; LDH, lactate dehydrogenase; LLN, lower limit of normal according to the local institutional range; PSA, prostate-specific antigen; ULN, upper limit of normal according to the local institutional range.

We designed ProCAID at a time when radiographic PFS was a relatively uncommon end point in prostate cancer trials. We recommend future investigation of AKT inhibition should incorporate this end point, excluding PSA from the end point definition.

We acknowledge the possibility that our results, indicating an OS extension despite no PFS impact, might be spurious and are challenging to explain. In addition, the OS data remain relatively immature at this planned primary analysis. Although the size of the OS benefit observed is enticing, the

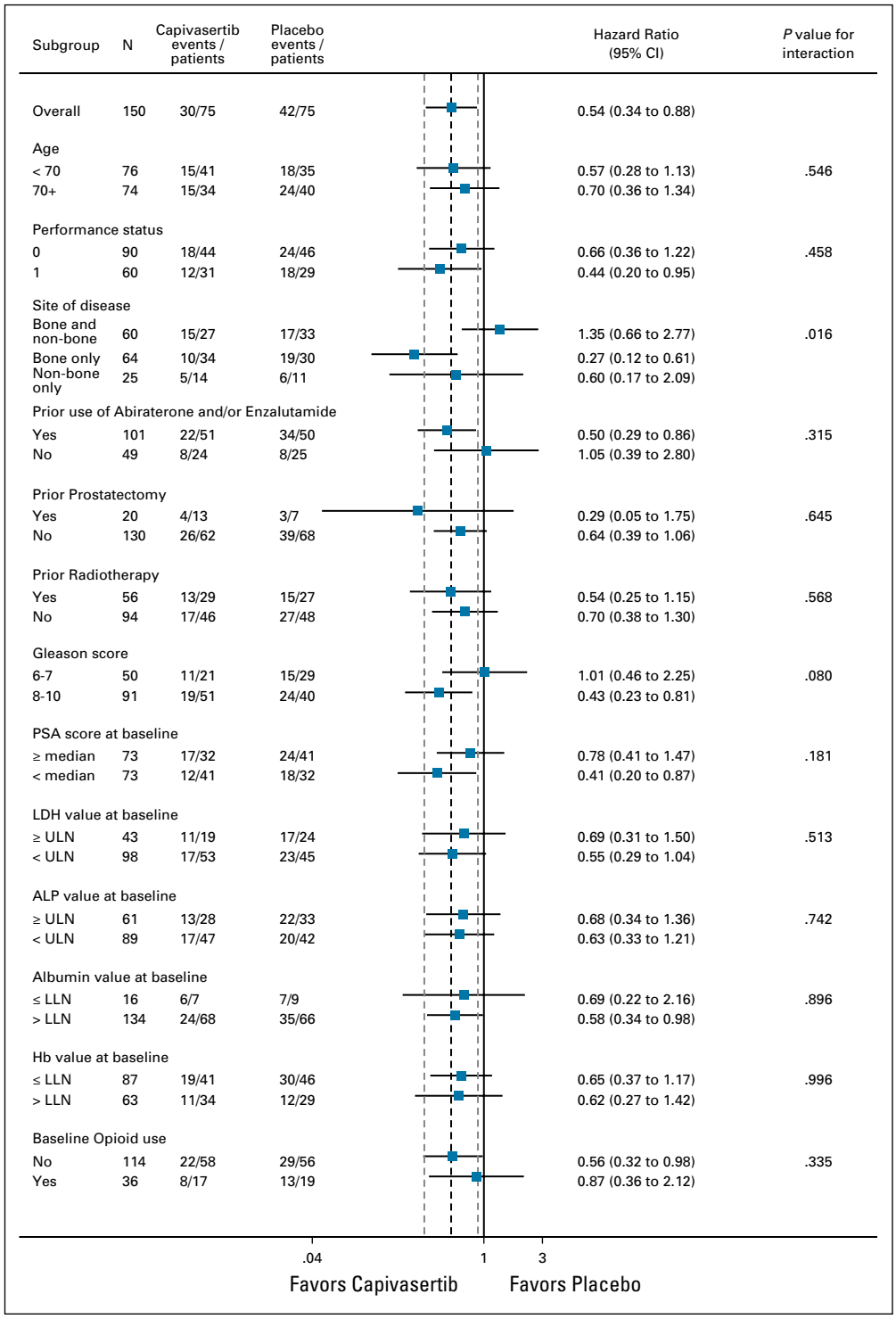

FIG 4. (Continued).

possibility that biases, whether identifiable or not, might have impacted our results should be recognized. Supporting this, we acknowledge some imbalances in baseline patient characteristics that might have favored the capivasertib arm outcome including rates of lung or liver involvement, prior prostatectomy, median PSA, and levels of lactate dehydrogenase, albumin, and alkaline phosphatase (although conversely, good performance status and high Gleason score rates might favor the placebo arm).

TABLE 3. Adverse Events, Irrespective of Causality, Occurring in More Than 10% of Patients in Either Treatment Arm Within the Safety Population

	Capivasertib (n = 74)		Placebo (n = 74)		Total (N = 148)	
Adverse Event	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**
Diarrhea	49 (66.2%)	5 (6.8%)	44 (59.5%)	3 (4.1%)	93 (62.8%)	8 (5.4%)
Fatigue	42 (56.8%)	1 (1.4%)	46 (62.2%)	1 (1.4%)	88 (59.5%)	2 (1.4%)
Nausea	25 (33.8%)	1 (1.4%)	26 (35.1%)	2 (2.7%)	51 (34.5%)	3 (2%)
Alopecia	26 (35.1%)	—	24 (32.4%)	—	50 (33.8%)	—
Neuropathy peripheral	15 (20.3%)	—	29 (39.2%)	2 (2.7%)	44 (29.7%)	2 (1.4%)
Constipation	16 (21.6%)	—	26 (35.1%)	1 (1.4%)	42 (28.4%)	1 (0.7%)
Back pain	19 (25.7%)	5 (6.8%)	23 (31.1%)	2 (2.7%)	42 (28.4%)	7 (4.7%)
Dyspnea	18 (24.3%)	1 (1.4%)	22 (29.7%)	2 (2.7%)	40 (27%)	3 (2%)
Neutropenia	23 (31.1%)	19 (25.7%)	16 (21.6%)	14 (18.9%)	39 (26.4%)	33 (22.3%)
Taste disorder	15 (20.3%)	—	16 (21.6%)	—	31 (20.9%)	—
Cough	16 (21.6%)	—	14 (18.9%)	—	30 (20.3%)	—
Rash[a]	25 (33.8%)	7 (9.5%)	5 (6.8%)	1 (1.4%)	30 (20.3%)	8 (5.4%)
Vomiting	14 (18.9%)	1 (1.4%)	14 (18.9%)	1 (1.4%)	28 (18.9%)	2 (1.4%)
Decreased appetite	13 (17.6%)	—	14 (18.9%)	—	27 (18.2%)	—
Lethargy	14 (18.9%)	2 (2.7%)	13 (17.6%)	1 (1.4%)	27 (18.2%)	3 (2%)
Nail disorder	8 (10.8%)	—	18 (24.3%)	—	26 (17.6%)	—
Edema	12 (16.2%)	—	13 (17.6%)	—	25 (16.9%)	—
Pyrexia	15 (20.3%)	5 (6.8%)	10 (13.5%)	5 (6.8%)	25 (16.9%)	10 (6.8%)
Dysgeusia	10 (13.5%)	—	15 (20.3%)	—	25 (16.9%)	—
Arthralgia	8 (10.8%)	—	15 (20.3%)	1 (1.4%)	23 (15.5%)	1 (0.7%)
Mucosal inflammation	14 (18.9%)	1 (1.4%)	8 (10.8%)	1 (1.4%)	22 (14.9%)	2 (1.4%)
Pain in extremity	9 (12.2%)	—	12 (16.2%)	2 (2.7%)	21 (14.2%)	2 (1.4%)
Anemia	12 (16.2%)	1 (1.4%)	8 (10.8%)	4 (5.4%)	20 (13.5%)	5 (3.4%)
Lower respiratory tract infection	14 (18.9%)	2 (2.7%)	6 (8.1%)	—	20 (13.5%)	2 (1.4%)
Urinary tract infection	7 (9.5%)	—	13 (17.6%)	—	20 (13.5%)	—
Abdominal pain	9 (12.2%)	—	10 (13.5%)	—	19 (12.8%)	—
Insomnia	7 (9.5%)	—	12 (16.2%)	—	19 (12.8%)	—
Febrile neutropenia	11 (14.9%)	11 (14.9%)	6 (8.1%)	5 (6.8%)	17 (11.5%)	16 (10.8%)
Dry skin	9 (12.2%)	—	8 (10.8%)	—	17 (11.5%)	—
Flushing	9 (12.2%)	—	7 (9.5%)	—	16 (10.8%)	—
Dyspepsia	10 (13.5%)	—	5 (6.8%)	—	15 (10.1%)	—
Musculoskeletal pain	8 (10.8%)	—	6 (8.1%)	—	14 (9.5%)	—
Headache	5 (6.8%)	—	8 (10.8%)	—	13 (8.8%)	—
Lacrimation increased	9 (12.2%)	—	2 (2.7%)	—	11 (7.4%)	—
Groin pain	8 (10.8%)	1 (1.4%)	1 (1.4%)	—	9 (6.1%)	1 (0.7%)

NOTE. There were no grade 5 treatment-related adverse events.

[a]Rash is a grouped term for different descriptions of rash.

Prior data, from placebo-controlled phase II studies, support therapeutic targeting of the PI3K/AKT/PTEN pathway in this and other cancers. Heterogeneity exists, however, in patterns of benefit shown for PFS or OS, and outcomes of biomarker subset analysis. In prostate cancer, de Bono et al tested the pan-AKT inhibitor ipatasertib combined with abiraterone versus abiraterone alone. Radiographic PFS was extended in a subset with tumors exhibiting PTEN protein expression loss by IHC. OS was not extended, potentially through data immaturity, in distinction to the result presented here.[25] Capivasertib combinations also have activity in breast cancer. In FAKTION, addition of

capivasertib to fulvestrant extended PFS in ER-positive, HER2-negative, advanced breast cancer. Effect size was not altered by biomarker status for a composite of *PIK3CA* alteration in either tumor or ctDNA, or PTEN protein expression loss in tumor.[26] In PAKT, capivasertib combined with paclitaxel in metastatic triple-negative breast cancer extended both PFS and OS, and this effect was more pronounced for tumors with *PIK3CA*, *AKT1*, or *PTEN* alterations.[27] However, in BEECH, the same combination did not extend PFS in ER-positive, HER2-negative, breast cancer, irrespective of biomarker status for *PIC3CA* alterations. Of note, no concomitant or maintenance endocrine therapy was allowed during this study.[28] The significance of variations across these data sets for disease type, drug combination partner, and biomarker composition remains to be determined and suggest that benefit and the required patient selection approach may be context-dependent. Randomized phase II data for capivasertib combined with the AR antagonist enzalutamide for mCRPC are awaited from the ongoing RE-AKT trial.[29]

Consistent with our prior data, addition of capivasertib to DP resulted in an acceptable toxicity profile.[16] A significant proportion of adverse events recorded were primarily chemotherapy or disease-related. Of those events designated as capivasertib (or placebo)-related, an excess in rash, diarrhea, fatigue, and nausea occurred in the capivasertib arm. These adverse events are expected for capivasertib and common across PI3K and AKT inhibitors and warrant consideration of mitigation strategies in future development of this combination. Prednisolone, as a conventional component of DP for mCRPC, in addition to dexamethasone premedication, did not appear to drive excess of toxicity relating to transient hyperglycemia seen with capivasertib. No cases of hyperglycemia required intervention or triggered protocol defined criteria for use of metformin.

In conclusion, capivasertib did not extend PFS when combined with DP for mCRPC irrespective of PI3K/AKT/PTEN pathway activation status. We found a statistically significant extension in the secondary end point of OS. To address the apparent discordance in this result would require prospective validation studies that should focus on identification of patients most likely to benefit.

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Presented in part at the ASCO 2020 Virtual Annual Meeting, May 29-31, 2020.

SUPPORT

ProCAID was investigator initiated and funded by Cancer Research UK (C9317/A16029, CRUK/12/042). Support from AstraZeneca included provision of capivasertib and placebo, Southampton Clinical Trials Unit running costs, and translational research costs. Simon J. Crabb and Gareth Griffiths had full access to data and final responsibility for submission for publication. Michelle Light and Josh Northey had full access to raw data.

CLINICAL TRIAL INFORMATION

ISRCTN69139368 (ProCAID)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.01576.

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ACKNOWLEDGMENT

ProCAID was undertaken with support from an Investigator-Sponsored Study collaboration between AstraZeneca and the National Cancer Research Network. Funding was from AstraZeneca and Cancer Research United Kingdom. The study was supported by core funding from Cancer Research United Kingdom to Southampton Clinical Trials Unit and Southampton Experimental Cancer Medicine Centre. The authors wish to thank the participants, the investigators, and the site personnel who participated in this study. We thank Stuart Thompson and David Hathorn, our patient research partners. We thank the independent data monitoring committee: John Chester (chair), Janet Brown and Nicholas Counsell.

REFERENCES

1. Chi KN, Agarwal N, Bjartell A, et al: Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 381:13-24, 2019
2. Sartor O, de Bono JS: Metastatic prostate cancer. N Engl J Med 378:1653-1654, 2018
3. Davis ID, Martin AJ, Stockler MR, et al: Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med 381:121-131, 2019
4. James ND, Spears MR, Clarke NW, et al: Survival with newly diagnosed metastatic prostate cancer in the "Docetaxel Era": Data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). Eur Urol 67:1028-1038, 2015
5. Petrylak DP, Tangen CM, Hussain MH, et al: Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 351:1513-1520, 2004
6. Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 351:1502-1512, 2004
7. de Bono JS, Oudard S, Ozguroglu M, et al: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: A randomised open-label trial. Lancet 376:1147-1154, 2010
8. Edwards J, Krishna NS, Witton CJ, et al: Gene amplifications associated with the development of hormone-resistant prostate cancer. Clin Cancer Res 9: 5271-5281, 2003
9. Taylor BS, Schultz N, Hieronymus H, et al: Integrative genomic profiling of human prostate cancer. Cancer Cell 18:11-22, 2010
10. Uzoh CC, Perks CM, Bahl A, et al: PTEN-mediated pathways and their association with treatment-resistant prostate cancer. BJU Int 104:556-561, 2009
11. Vlietstra RJ, van Alewijk DC, Hermans KG, et al: Frequent inactivation of PTEN in prostate cancer cell lines and xenografts. Cancer Res 58:2720-2723, 1998
12. Davies BR, Greenwood H, Dudley P, et al: Preclinical pharmacology of AZD5363, an inhibitor of AKT: Pharmacodynamics, antitumor activity, and correlation of monotherapy activity with genetic background. Mol Cancer Ther 11:873-887, 2012
13. Robertson JFR, Coleman RE, Cheung KL, et al: Proliferation and AKT activity biomarker analyses after capivasertib (AZD5363) treatment of patients with ER(+) invasive breast cancer (STAKT). Clin Cancer Res 26:1574-1585, 2020
14. Banerji U, Dean EJ, Perez-Fidalgo JA, et al: A phase I open-label study to identify a dosing regimen of the Pan-AKT inhibitor AZD5363 for evaluation in solid tumors and in PIK3CA-mutated breast and gynecologic cancers. Clin Cancer Res 24:2050-2059, 2018
15. Hyman DM, Smyth LM, Donoghue MTA, et al: AKT inhibition in solid tumors with AKT1 mutations. J Clin Oncol 35:2251-2259, 2017
16. Crabb SJ, Birtle AJ, Martin K, et al: ProCAID: A phase I clinical trial to combine the AKT inhibitor AZD5363 with docetaxel and prednisolone chemotherapy for metastatic castration resistant prostate cancer. Invest New Drugs 35:599-607, 2017
17. Scher HI, Halabi S, Tannock I, et al: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-1159, 2008
18. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009
19. Royston P, Babiker A: A menu-driven facility for complex sample size calculation in randomized controlled trials with a survival or a binary outcome. Stata J 2: 151-163, 2002
20. Abida W, Armenia J, Gopalan A, et al: Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol 2017:PO.17.00029, 2017
21. Abida W, Cyrta J, Heller G, et al: Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci U S A 116:11428-11436, 2019
22. Ferraldeschi R, Nava Rodrigues D, Riisnaes R, et al: PTEN protein loss and clinical outcome from castration-resistant prostate cancer treated with abiraterone acetate. Eur Urol 67:795-802, 2015
23. Rescigno P, Lorente D, Dolling D, et al: Docetaxel Treatment in PTEN- and ERG-aberrant metastatic prostate cancers. Eur Urol Oncol 1:71-77, 2018
24. Carver BS, Chapinski C, Wongvipat J, et al: Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell 19:575-586, 2011
25. de Bono JS, De Giorgi U, Rodrigues DN, et al: Randomized phase II study evaluating Akt blockade with ipatasertib, in combination with abiraterone, in patients with metastatic prostate cancer with and without PTEN loss. Clin Cancer Res 25:928-936, 2019
26. Jones RH, Casbard A, Carucci M, et al: Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): A multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 21:345-357, 2020
27. Schmid P, Abraham J, Chan S, et al: Capivasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer: The PAKT trial. J Clin Oncol 38:423-433, 2020
28. Turner NC, Alarcon E, Armstrong AC, et al: BEECH: A dose-finding run-in followed by a randomised phase II study assessing the efficacy of AKT inhibitor capivasertib (AZD5363) combined with paclitaxel in patients with estrogen receptor-positive advanced or metastatic breast cancer, and in a PIK3CA mutant sub-population. Ann Oncol 30:774-780, 2019
29. Kolinsky MP, Rescigno P, Bianchini D, et al: A phase I dose-escalation study of enzalutamide in combination with the AKT inhibitor AZD5363 (capivasertib) in patients with metastatic castration-resistant prostate cancer. Ann Oncol 31:619-625, 2020

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Pan-AKT Inhibitor Capivasertib With Docetaxel and Prednisolone in Metastatic Castration-Resistant Prostate Cancer: A Randomized, Placebo-Controlled Phase II Trial (ProCAID)

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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No other potential conflicts of interest were reported.