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A phase III study of capivasertib (capi) + abiraterone (abi) vs placebo (pbo) + abi in patients (pts) with PTEN deficient de novo metastatic hormone-sensitive prostate cancer (mHSPC): CAPItello-281

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Background

In HSPC tumours, PTEN deficiency is associated with dysregulation of PI3K/AKT and androgen receptor (AR) signalling resulting in reduced benefit from AR pathway inhibition and shorter time to progression. An unmet need exists for a targeted treatment for PTEN deficient mHSPC. CAPItello-281 (NCT04493853) is a randomised, double-blind, phase 3 study evaluating capi + abi in pts with PTEN deficient *de novo* mHSPC.

Methods

Pts aged ≥18 years with PTEN deficient tumours (defined as ≥90% of viable malignant cells with no specific cytoplasmic staining by immunohistochemistry) and ECOG 0-1 received capi or matched pbo (1:1) in combination with abi + prednisone/prednisolone and androgen deprivation therapy. Primary endpoint was investigator-assessed radiographic progression-free survival (rPFS); overall survival (OS) was a key secondary endpoint. rPFS in post hoc exploratory subgroups at more stringent PTEN cutoffs was also assessed.

Results

1012 pts received capi + abi (n=507) or pbo + abi (n=505). Baseline characteristics were generally balanced between arms. A statistically significant improvement in rPFS was observed with capi + abi vs pbo + abi (HR 0.81, *P*=0.034; Table). rPFS HRs at increasing PTEN deficiency cutoffs (≥95%, n=814 to 100%, n=331) ranged from 0.75 to 0.68. Interim OS analysis numerically favoured capi + abi. 18.3% of pts discontinued capi due to an AE vs 4.8% pbo (9.5 vs 5.4% abi).Table: 23830

Overall population (≥90% PTEN deficiency)	Capi + abi (n=507)	Pbo + abi (n=505)
rPFS (39.3% maturity)		
Median, months (95% CI)	33.2 (25.8, 44.2)	25.7 (22.0, 29.9)
HR (95% CI)	0.81 (0.66, 0.98)	
P-value	0.034	
OS (26.4% maturity)		
Median, months (95% CI)	NC (42.5, NC)	NC (NC, NC)
HR (95% CI)	0.90 (0.71, 1.15)	
P-value	0.401	

Dosage: capi 400 mg twice daily, 4 days on, 3 days off; abi, 1000 mg once daily; prednisone/prednisolone 5 mg once daily. 19% and 55% of

Dosage: capi 400 mg twice daily, 4 days on, 3 days off, abi, 1000 mg once daily, prednisone/prednisolone 5 mg once daily. 15% and 35% of pts had high volume disease with and without visceral metastases, respectively; 25% had low volume disease. Data cutoff 07 October 2024. CI, confidence interval; HR, hazard ratio; NC, not calculable.

Conclusions

CAPItello-281 met its primary objective showing a statistically significant rPFS benefit with capi + abi vs pbo + abi in pts with PTEN deficient *de novo* mHSPC. Increasing benefit was observed in subgroups selected using progressively more stringent PTEN cutoffs. The safety profile was broadly consistent with the known profiles of capi and abi. Capi in combination with abi represents a potential first-in-class targeted treatment for this poor prognosis population with high unmet need.

Clinical trial identification

NCT04493853.

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Legal entity responsible for the study

AstraZeneca.

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Disclosure

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