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LBA4

IPATential150: Phase III study of ipatasertib (ipat) plus abiraterone (abi) vs placebo (pbo) plus abi in metastatic castration-resistant prostate cancer (mCRPC)

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Background

PI3K/AKT and androgen receptor (AR) signalling are dysregulated in mCRPC. PTEN loss (40%-50% of mCRPC) results in activation of AKT, the ipat target, and worse outcomes. Preclinically, dual pathway inhibition has greater antitumor activity than AR inhibition. IPATential150 is a phase III, randomised, double-blind study evaluating the efficacy and safety of adding ipat to abi in asymptomatic or mildly symptomatic pts previously untreated for mCRPC.

Methods

Pts with mCRPC were randomised 1:1 to receive ipat (400 mg/d) + abi (1000 mg/d) + prednisone (5 mg bid) or pbo + abi + prednisone. Coprimary endpoints were investigator-assessed radiographic (r) PFS by PCWG3 criteria in pts with PTEN-loss tumours by immunohistochemistry (IHC; PTEN-loss in ≥ 50% of tumour cells) and in the overall ITT. Secondary endpoints included time to PSA progression, PSA response rate, confirmed ORR (per RECIST 1.1 + PCWG3) in ITT pts and pts with PTEN-loss tumours by IHC, and rPFS in pts with PTEN-loss tumours by next-generation sequencing (NGS).

Results

1101 pts were randomised: 547 to ipat + abi and 554 to pbo + abi. Median follow-up was 19 mo. In PTEN loss by IHC pts, median rPFS was 18.5 mo (95% CI: 16.3, 22.1) with ipat and 16.5 mo (95% CI: 13.9, 17.0) with pbo (HR: 0.77; 95% CI: 0.61, 0.98; P = 0.0335); in ITT pts, rPFS was 19.2 mo (95% CI: 16.5, 22.3) with ipat and 16.6 mo (95% CI: 15.6, 19.1) with pbo (HR: 0.84; 95% CI: 0.71, 0.99; P = 0.0431). Secondary endpoints favoured the combination arm (Table). Serious adverse events (AEs) occurred in 40% and 23% of ipat and pbo pts, respectively; AEs leading to discontinuation of ipat/pbo occurred in 21% and 5%.

Conclusions

In this primary endpoint analysis, ipat + abi as first-line treatment for mCRPC resulted in significantly improved rPFS and antitumor activity vs pbo + abi in pts with PTEN-loss mCRPC, but not in the ITT. The safety profile was in line with known and potential risks.Table: LBA4

	PTEN Loss by IHC n = 521		ITTN = 1101	
	Pbo + abi	Ipat + abi	Pbo + abi	Ipat + abi
Time to PSA progression, n	261	260	554	547
Median (95% CI), mo	7.6 (6.4, 9.3)	12.6 (10.2, 15.3)	8.4 (7.4, 9.3)	12.9 (10.3, 15.1)
Stratified HR (95% CI)	0.69 (0.55, 0.87)	0.73 (0.62, 0.85)		
PSA response, n/N, %	187/261, 72	217/260, 84	418/554, 76	444/546, 81

	PTEN Loss by IHC n = 521		ITTN = 1101	
	Pbo + abi	Ipat + abi	Pbo + abi	Ipat + abi
P	0.0012[a]	0.0183[a]		
Time to pain progression, n/N, %	95/261, 36	73/260, 28	187/554, 34	156/547, 29
HR (95% CI)	0.77 (0.56, 1.04)	0.87 (0.70, 1.08)		
Confirmed ORR, n/N	37/96	60/99	98/225	122/201
%	39	61	44	61
Difference (95% CI), %	22 (7, 37)	17 (7, 27)		
rPFS in PTEN loss by NGS, n	103	105		
Median (95% CI), mo	14.2 (10.9, 18.7)	19.1 (13.9, NE)		
HR (95% CI)	0.65 (0.45, 0.95)			

NE, not evaluable. [a] Descriptive.

Clinical trial identification

NCT03072238.

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