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6100

Final overall survival (OS) analysis of PROfound: Olaparib vs physician's choice of enzalutamide or abiraterone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene alterations

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Background

The phase 3 randomized, open-label PROfound trial (NCT02987543) met its primary endpoint of significantly prolonged radiographic progression-free survival with olaparib vs physician's choice of enzalutamide or abiraterone (control arm) in pts with mCRPC with progression on prior therapy and alterations in *BRCA1*, *BRCA2* or *ATM* (Cohort A), and in the overall population (Cohorts A+B) with alterations in any of 15 prespecified genes with a direct or indirect role in HRR. Final OS data are reported.

Methods

Men with mCRPC and disease progression on a prior new hormonal agent (eg enzalutamide or abiraterone) were randomized 2:1 to olaparib or control treatment. Pts could crossover to olaparib upon radiographic disease progression. A prespecified key secondary endpoint was OS in Cohort A, analysed by alpha-controlled stratified log-rank test.

Results

At data cut-off (20 March 2020), median final OS in Cohort A was significantly longer with olaparib than with physician's choice of enzalutamide or abiraterone (HR 0.69; 95% CI 0.50, 0.97; *P*=0.0175), with a trend towards improvement in the overall population (HR 0.79; 95% CI 0.61, 1.03; nominal *P*=0.0515). Of pts in the control arm, 56 (67%) in Cohort A and 86 (66%) in the overall population crossed over to olaparib. Longer follow-up yielded no new safety signals.Table: 6100

	Cohort A		Overall population	
	Olaparib n=162	Control n=83	Olaparib n=256	Control n=131
Events, n (%)	91 (56)	57 (69)	160 (63)	88 (67)
Median (95% CI) OS (months)	19.1 (17.4, 23.4)	14.7 (11.9, 18.8)	17.3 (15.5, 18.6)	14.0 (11.5, 17.1)
HR (95% CI)	0.69 (0.50, 0.97)	0.79 (0.61, 1.03)		
P value (2-sided)	0.0175*	0.0515†		
OS rate (%)				
12-month	73	61	67	56
18-month	54	42	47	39
Median follow-up (months)‡	21.9	21.0	20.7	20.5

*0.047 alpha spent at final OS analysis; †Nominal; ‡Censored pts. CI, confidence interval; HR, hazard ratio; OS overall survival

Conclusions

PROfound is the first phase 3 trial to show a PARP inhibitor benefit in alpha-controlled OS analyses. Despite extensive crossover from the control arm, olaparib conferred a statistically significant and clinically meaningful prolongation of OS vs sequential therapy with enzalutamide or abiraterone in men with mCRPC with progression on prior therapy and alterations in *BRCA1*, *BRCA2* or *ATM*, with a 31% reduction in the risk for death.

Clinical trial identification

NCT02987543.

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