LBA2_PR

Overall survival (OS) with palbociclib plus fulvestrant in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC): Analyses from PALOMA-3

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Background: Endocrine therapy (ET)–resistant ABC is dependent on cyclin dependent kinase (CDK) 4/6. In the prospective, randomized, double-blind, phase 3 PALOMA-3 study, the CDK4/6 inhibitor PAL in combination with FUL significantly improved progression-free survival (PFS) vs placebo (PBO)+FUL (median PFS, 11.2 vs 4.6 mo; absolute difference, 6.6 mo; hazard ratio [HR] 0.50 [95% CI, 0.40–0.62]; P < 0.000001). Here, we report OS analysis with a median follow up of 44.8 mo.

Methods: HR+/HER2– ABC (N = 521) patients (pts) who had relapsed or progressed on prior ET were randomized 2:1 to PAL (125 mg/d orally, schedule 3/1) + FUL (500 mg per standard of care) or PBO+FUL. Primary endpoint was investigator-assessed PFS. A key secondary endpoint was OS. OS analysis occurred when approximately 60% (n≈310) of the 521 pts died.

Results: Median OS improved with PAL+FUL vs PBO+FUL by an absolute difference of 6.9 mo (Table). In pts with sensitivity to prior ET, the absolute improvement in median OS was 10.0 mo with PAL+FUL vs PBO+FUL. In pts without visceral disease, median OS significantly improved with PAL+FUL vs PBO+FUL (11.5 mo). Time to end of the next-line treatment was 18.8 (PAL+FUL) and 14.1 (PBO+FUL) mo (HR 0.68 [95% CI, 0.56–0.84]; P < 0.0001). Improvements in median OS, although not statistically significant at the prespecified level, were shown with PAL+FUL vs PBO+FUL regardless of ESR1 mutation status or prior lines of therapy. Median time on subsequent therapy was similar in both arms; median time to chemotherapy was 17.5 (PAL+FUL) and 8.8 (PBO+FUL) mo (HR 0.58; P < 0.000001). No new safety signals were observed with longer follow-up.

Conclusions: In HR+/HER2– ABC pts, PAL+FUL showed a clinically meaningful improvement in OS (6.9 mo vs PBO+FUL), especially in pts with sensitivity to prior ET. The absolute difference of PFS gain was maintained in OS.

Clinical trial identification: NCT01942135.

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Table: LBA2_PR OS in the ITT population and by subgroup

Subgroup	n (%)	HR (95% CI)	PAL+FUL median OS (95% CI)	PBO+FUL median OS (95% CI)	1-sided P value	Interaction P value
ITT, stratified	521 (100)	0.81 (0.64–1.03)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	0.043	–
ITT, unstratified	521 (100)	0.79 (0.63–1.00)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	0.025	
Sensitivity to previous endocrine therapy						
Endocrine sensitive	410 (78.7)	0.72 (0.55–0.94)	39.7 (34.8–45.7)	29.7 (23.8–37.9)	–	0.124
Endocrine resistant	111 (21.3)	1.14 (0.71–1.84)	20.2 (17.2–26.4)	26.2 (17.5–31.8)	–	
Site of metastatic disease						
Visceral disease	311 (59.7)	0.85 (0.64–1.13)	27.6 (24.4–31.2)	24.7 (20.8–31.8)	–	0.442
Nonvisceral disease	210 (40.3)	0.69 (0.46–1.04)	46.9 (39.3–NE)	35.4 (24.6–NE)	–	
Menopausal status at study entry						
Postmenopausal	413 (79.3)	0.73 (0.57–0.95)	34.8 (28.8–40.1)	27.1 (22.8–32.1)	–	0.251
Pre/perimenopausal	108 (20.7)	1.07 (0.61–1.86)	38.0 (24.4–NE)	38.0 (22.2–NE)	–	

FUL=fulvestrant; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; OS=overall survival; PAL=palbociclib; PBO=placebo.