New option for women with advanced breast cancer resistant to hormone therapy

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Table. 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.

Treatment with the cyclin dependent kinase (CDK) 4/6 inhibitor palbociclib achieves a clinically meaningful improvement in overall survival in patients with hormone receptor positive (HR+) human epidermal growth factor receptor-2 negative (HER2-) advanced breast cancer that has relapsed or progressed on hormonal therapy, according to the final analysis of overall survival results from the PALOMA-3 study reported at ESMO 2018. Credit: © European Society for Medical Oncology

Treatment with the cyclin dependent kinase (CDK) 4/6 inhibitor

palbociclib achieves a clinically meaningful improvement in overall survival in patients with hormone receptor positive (HR+) human epidermal growth factor receptor-2 negative (HER2-) advanced breast cancer that has relapsed or progressed on hormonal therapy, according to the final analysis of overall survival results from the PALOMA-3 study reported at ESMO 2018.

Most patients with HR+ breast cancer become resistant to hormonal therapies over time and inhibiting CDK4/6 has been identified as a target for overcoming or delaying resistance to hormonal therapy in advanced HR+/HER2-breast cancer. The prospective, randomised phase 3 PALOMA-3 trial showed that the first-in-class CDK 4/6 inhibitor palbociclib in combination with fulvestrant significantly improved progression-free survival (PFS) in 521 women with HR+/HER2- metastatic breast cancer that had progressed on previous hormonal therapy.

The new analysis assessed overall survival (OS), a key secondary endpoint of PALOMA-3, after a median follow-up of 44.8 months in 521 patients with HR+/HER2- advanced breast cancer. The patients had relapsed or progressed on prior endocrine therapy before being randomised to palbociclib (125mg/day orally, schedule 3/1) plus fulvestrant (500mg per standard of care) or placebo plus fulvestrant. Researchers carried out the OS analysis when approximately 60% (n?310) of the 521 patients in the study had died.

Results showed that median overall survival improved by 6.9 months with palbociclib plus fulvestrant (median OS 34.9 months, 95% confidence interval [CI] 28.8-40.0) compared to placebo plus fulvestrant (median OS 28.0 months, 95% CI 23.6-34.6, p=0.043).

The improvement was even greater in patients with sensitivity to prior endocrine therapy, with an absolute improvement in median OS of 10.0

months. Median OS improved significantly by 11.5 months in patients without visceral disease. No new safety signals were observed with longer follow-up.

"Here, we present the first-ever overall survival results from a phase 3 study for a CDK4/6 inhibitor in a pre-planned analysis of the PALOMA-3 trial. Importantly, this is the first report demonstrating that the absolute gain in survival is similar to the absolute gain in progression-free survival in the whole population. Moreover, this prolongation of life is of a large magnitude in patients with prior sensitivity to endocrine therapy, "said lead author Massimo Cristofanilli, Professor of Medicine, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Feinberg School of Medicine, Chicago, USA.

"This is very important for patients, as it shows that the improvement in PFS observed in previous studies may have a positive impact on overall survival, an ultimate goal of treatment, therefore improving the chance for a long-term life in spite of advanced disease," said Cristofanilli. He added: "The demonstration of a positive impact on OS also provides additional confidence to clinicians and patients as to the benefits of this combination as an appropriate and effective treatment approach."

Commenting on the findings for ESMO, Dr. Carmen Criscitiello, European Institute of Oncology Milan, Italy, said: "These data were much awaited, as the clinical benefit obtained with CDK 4/6 inhibitors was incontestable, but there was the hot question whether the PFS benefit translates into OS benefit. This randomised Phase III trial shows for the first time an improvement in OS with a CDK4/6 inhibitor in the metastatic setting for ER+/HER2- breast cancer." However, she added: "The study was unpowered for OS so the data should be cautiously interpreted. Although the results strongly suggest that the PFS benefit may translate into OS benefit, the other trials conducted with CDK4/6 inhibitors will contribute to confirm the estimate of the OS benefit

observed in this study."

Dr. Matteo Lambertini, ESMO fellow at the Institut Jules Bordet, Brussels, Belgium, agreed: "Collecting mature OS data at longer follow-up from randomised trials that investigated the combination of endocrine therapy and CDK 4/6 inhibitors is crucial to have a clearer understanding on the benefit of these expensive agents. The limited OS data that we had so far from these trials are now supported by the PALOMA-3 updated results, which strongly suggest that this treatment should become widely available for women with advanced HR+/HER2- disease." He said: "Further research is needed to better understand how to optimise the sequencing of the available treatment options in this setting as well as to identify patients who may benefit from endocrine therapy alone."

Looking to the future, Cristofanilli said: "The significant impact of CDK 4/6 inhibitors on disease-free and overall survival in metastatic disease lead us to be excited about the potential of this class of agents in early-stage breast cancer, where our goal is to improve the cure rate. On that front, two large randomised adjuvant trials of palbociclib in early stage breast cancer, PENELOPE-B and PALLAS, are ongoing."

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