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PRESS RELEASE

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

Munich, Germany, 20 October 2018 - 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 (1).

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 (2).

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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Notes to Editors

Please make sure to use the official name of the meeting in your reports: ESMO 2018 Congress

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References

1. Abstract 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 ' will be presented by Massimo Cristofanilli during Presidential Symposium 1 on Saturday, 20 October, 16:30 to 18:20 (CET) in Hall A2 – Room 18. *Annals of Oncology*, Volume 29 Supplement 8 October 2018
2. Cristofanilli M, Turner NC, Bondarenko I et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncology 2016; 17: 425-439

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.

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.

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.
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