Effect of palbociclib as single agent or in combination with the endocrine therapy received before disease progression for estrogen receptor-positive, HER2-negative metastatic breast cancer

Palbociclib is a selective, potent and orally available inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) [1] that prevents cell proliferation by blocking cell cycle progression from the G1 to the S phase [2], and synergistic with endocrine therapy (ET) [3,4] .
Some trials have shown that combining palbociclib with ET approximately doubles progression-free survival (PFS) rates when compared to ET plus placebo in estrogen receptor-positive, human epidermal grown factor receptor 2 (HER2)-negative advanced breast cancer (ABC) patients in both the setting of first-line treatment [5] .This proven activity in the setting of endocrine resistance is of particular interest, given the existence of previous preclinical evidence that suggests adding palbociclib to ET may partially reverse resistance to the particular agent to which resistance has been acquired [4] . Resistance to ET is considered an eventual inevitability in the treatment of hormone receptor-positive ABC [6] , therefore, strategies that may ameliorate resistance (thereby postponing the need to progress to potentially more toxic lines of cytotoxic treatment) are important and remains an unmet clinical need.To date, the activity of palbociclib as a single agent has not been extensively studied, with the only available clinical data in this context limited to heavily pre-treated patients [7].

Recent randomized, open-label phase II trial published in 1 June 2018, and was performed at eight Italian centres aimed to test the activity and safety of palbociclib as a single agent in a moderately pre-treated population of women with estrogen receptor-positive ABC, as well as in combination with the same ET as was received at the time of disease progression.
Between October 2012 and July 2016, a total 115 women who agreed to participate in the study and met the selection criteria were included in the study randomized 1: 1 with assuming activity as a clinical benefit rate (CBR) 40% and measure (PFS) . Those in the monotherapy arm received single-agent oral palbociclib 125 mg once daily, for 3 weeks, followed by 1 week off (28-day cycle). Those allocated to the combination arm received palbociclib at the same dose and regimen, plus continuation of the prior ET taken before progression (oral anastrozole 1 mg/day or letrozole 2.5 mg/day or exemestane 25 mg/day, or intramuscular fulvestrant 500 mg every 4 weeks). All ET was given continuously.
Dose interruptions and reductions were allowed as required. The assigned study treatment was continued until disease progression, unacceptable toxicity or consent withdrawal.
Randomization was stratified according to: number of previous ET lines (1 versus 2), duration of prior-line ET (6 months versus >6 months), metastatic disease site (visceral versus nonvisceral) and treating center then response was assessed locally at baseline, after cycle 3, and every 12 weeks thereafter [8].

The results were generally well-balanced between the two arms. CBR was 54% (95% CI: 41.5–63.7) in the palbociclib plus ET arm, and 60% (95% CI: 47.8–72.9) in the palbociclib monotherapy arm (exploratory P-value for the difference =0.52), this might suggest that in spite of the similar (CBR) between the two treatment arms, and when analysed Median PFS it was 10.8 months (95% CI: 5.6–12.7) for combination therapy, and 6.5 months (95% CI:

5.4–8.5) for monotherapy (95% CI: 0.4–1.1, exploratory P-value=0.12), this revealed the PFS advantage for combination therapy was seen in the subgroup of patients who received prior ET for >6 months (95% CI: 0.3–0.9, exploratory P-value =0.02), but not in those who received prior ET for 6 months [8].

In conclusion the study showed that Palbociclib has clinical activity as a single agent in women with moderately pre-treated, oestrogen receptor- positive, HER2-negative advanced breast cancer. Palbociclib may have potential to reverse endocrine resistance in patients with a history of previous durable response to ET. Our data collectively may merit further studies in a selected population of patients who obtained prolonged benefit during their prior line of ET.

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