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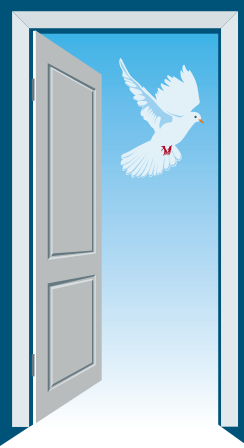

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BREAST CANCER

PALOMA-2 — hope beyond the threshold

Resistance to endocrine therapy, the standard of care for patients with hormone-receptor-positive (HR+) breast cancer, is common. The cyclin-D–cyclin-dependent kinase 4/6 (CDK4/6)–Rb pathway is a promising therapeutic target in HR+ cancer, which account for 60–65% of all malignant breast neoplasms. Indeed, gene alterations affecting cell-cycle regulation have been identified in this subset of tumours, and a role of these aberrations in resistance to endocrine therapy has been proposed. Results of PALOMA-2, a trial led by Richard Finn, have now been published, and show that the small-molecule CDK4/6 inhibitor palbociclib confers a progression-free survival (PFS) advantage to patients with advanced-stage HR+ breast cancer.

Over the past decade, Finn and colleagues have conducted extensive research on palbociclib. In preclinical studies, they characterized the growth-inhibitory effect of this agent on oestrogen-receptor-positive (ER+) breast cancer cell lines, as well as its synergistic effects with tamoxifen. These observations formed the basis for PALOMA-1, a randomized phase II trial comparing palbociclib plus letrozole with letrozole alone in women with advanced-stage ER+/HER2– breast cancer. As Finn explains, the results of this trial were "remarkable, with a >10-month improvement in PFS [with palbocilcib], and thus PALOMA-1 supported the accelerated FDA approval of palbociclib as first-line treatment for these patients".

> "This is the first time that a treatment strategy… crosses over this 2-year threshold"

PALOMA-2, a randomized phase III trial, was designed to confirm the observations from PALOMA-1. In this study, 666 women were randomly assigned in a 2:1 ratio to receive either palbociclib and letrozole or placebo and letrozole. Approximately 50% of participants had received neoadjuvant or adjuvant chemotherapy, and 56% had received prior adjuvant endocrine therapy. The median PFS was 24.8 months with palbociclib–letrozole versus 14.5 months with placebo–letrozole. Subgroup analyses confirmed a consistent benefit across all the subgroups defined. The clinical benefit rate (confirmed complete or partial response, or stable disease for ≥24 weeks) was 84.9% with palbociclib–letrozole and 70.3% with placebo–letrozole.

Haematological adverse events of any grade were more frequent among patients receiving palbociclib–letrozole than in those receiving placebo–letrozole, and included neutropenia (79.5% versus 6.3%), leukopenia (39% versus 2.3%), anaemia (24.1% versus 9%) and thrombocytopenia (15.5% versus 1.4%); serious adverse events of any type occurred in 19.6% and 12.6% of patients, respectively.

Regarding the relevance of these results, Finn comments "this study confirms our earlier findings that palbocilib and letrozole is a very active combination in women with advanced-stage ER+ breast cancer. The observed improvement in PFS is clinically very meaningful. In addition, the safety profile was favourable". Nicholas Turner, an investigator not involved in this study, considers that "the size of improvement in disease control was substantial. A combination regimen has been identified that is well-tolerated and is associated with an average response duration of over 2 years. This is the first time that a treatment strategy for patients with metastatic breast cancer that crosses over this 2-year threshold has been identified".

These results are in line with those of other phase III trials of CDK4/6 inhibitors in patients with HR+ breast cancer: in MONALEESA-2, the median PFS was significantly longer in patients treated with the CDK4/6 inhibitor ribociclib and letrozole than in those receiving letrozole alone (not reached versus 14.7 months; $P<0.001$). Indeed, Turner points out that "these phase III studies place CDK4/6 inhibitors as a major new advance in the treatment of patients with ER+ breast cancer."

Finn concludes, "the degree of benefit and very manageable adverse-events profile should make the combination of palbociclib and letrozole a first-choice option for most women with ER+ breast cancer."

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FURTHER READING Finn, R. S. *et al.* The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol.* **16,** 25–35 (2015)