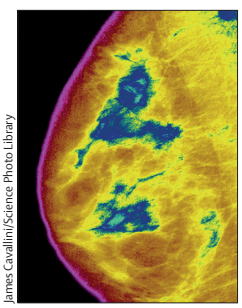
Endocrine-based therapy versus chemotherapy in advanced breast cancer



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Approximately 70% of metastatic breast cancers are oestrogen receptor-positive and HER2-negative. International guidelines recommend endocrine therapy as a preferred first-line treatment for oestrogen receptor-positive, HER2-negative metastatic breast cancer, "even in the presence of visceral disease, unless there is a visceral crisis or concern or proof of endocrine resistance".[1] However, several studies have reported that 35–60% of patients in Europe and North America receive chemotherapy as first-line treatment,[2,3] especially younger patients and those with visceral disease,[4] even though a retrospective study suggested worse outcomes for patients treated with chemotherapy than those treated with endocrine therapy.[3] Several reasons potentially explain low adherence to international guidelines, but one major reason has been the absence of evidence from randomised trials comparing endocrine treatment with chemotherapy in the first-line setting.

In *The Lancet Oncology*, Yeon Hee Park and colleagues[5] report results from the KCSG-BR15-10 trial, a multicentre, open-label, randomised, phase 2 trial done in 189 premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that had relapsed or progressed during or after previous tamoxifen therapy. 184 eligible patients were randomly assigned (1:1) to either palbociclib plus exemestane with a gonadotropin-releasing hormone agonist (n=92) or capecitabine (n=92). 91 (50%) of 178 patients who received their assigned treatment and were included in the safety and efficacy analyses had received no previous treatment for metastatic breast cancer, 153 (86%) patients relapsed while on tamoxifen or within 12 months after completion of adjuvant tamoxifen, and 88 (49%) patients had visceral disease.[5] Median progression-free-survival was longer with palbociclib plus endocrine therapy than with capecitabine (20·1 months [95% CI 14·2–21·8] *vs* 14·4 months [12·1–17·0]; hazard ratio 0·659 [95% CI 0·437–0·994], one-sided p=0·0235). A higher proportion of patients had asymptomatic grade 3–4 neutropenia in the palbociclib plus endocrine therapy group than in the capecitabine group (69 [75%] *vs* 14 [16%] patients), whereas several other any-grade symptomatic adverse events were more common with capecitabine than with palbociclib plus endocrine therapy, including nausea (31 [34%] *vs* 11 [12%] patients), diarrhoea (36 [39%] *vs* 13 [14%]), and hand-foot syndrome (86 [100%] *vs* one [1%] patient). No treatment-related deaths were reported, and adverse events led to discontinuation of the treatment for two patients in the capecitabine group and one patient in the palbociclib plus endocrine therapy group. The results of this study contrast with those of the BOLERO6 study,[6] which did not show improved outcome with exemestane plus everolimus compared with capecitabine.

Although this is the first prospective randomised trial to directly compare treatment with endocrine therapy plus a CDK4/6 inhibitor and chemotherapy, and to demonstrate improved outcome with endocrine-based therapy, these findings should be interpreted in the context of the study design. This is a relatively small phase 2 trial, and moreover the open-label design and the absence of blinded central imaging review for progression-free survival might have introduced bias. The dose intensity for palbociclib in this study was also relatively low (78% of the expected dose), probably reflecting the higher incidence of neutropenia with palbociclib in Asian women, as demonstrated by a previous study.[7]

Several recent reports have demonstrated that CDK4/6 inhibitors improve overall survival, including the MONALEESA-7,[8] MONARCH 2,[9] and MONALEESA-3[10] trials. Across all studies with CDK4/6 inhibitors, a consistent benefit for CDK4/6 inhibitors has been seen in patients with visceral disease.[8–10] All of these findings, combined with the KCSG-BR15-10 results reported by Park and colleagues, confirm that CDK4/6 inhibitors in combination with endocrine therapy should now be the standard of care in first-line treatment for oestrogen receptor-positive, HER2-negative breast cancers, even in young women and in patients with visceral disease for whom evidence from real-world clinical practice has suggested a reluctance by some physicians to follow endocrine-based strategies. The one remaining area of clinical uncertainty remains patients with

visceral crisis, for whom optimal management is still unclear: should these patients receive chemotherapy followed by CDK4/6 inhibitors plus endocrine therapy in maintenance, or should chemotherapy be continued until disease progression, or could endocrine and CDK4/6 inhibitor combinations also supplant chemotherapy for these patients? Ongoing studies will address the optimal management in this remaining small group of patients.

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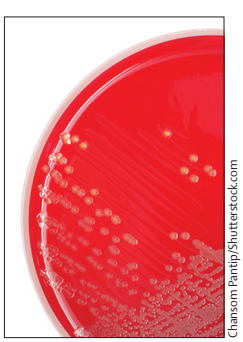
1 Cardoso F, Senkus E, Costa A, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). *Ann Oncol* 2018; **29:** 1634–57.
2 Caldeira R, Scazafave M. Real-world treatment patterns for hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer in Europe and the United States. *Oncol Ther* 2016; **4:** 189–97.
3 Lobbezoo DJA, van Kampen RJ, Voogd AC, et al. In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium. *Ann Oncol* 2016; **27:** 256–62.
4 Bonotto M, Gerratana L, Di Maio M, et al. Chemotherapy versus endocrine therapy as first-line treatment in patients with luminal-like HER2-negative metastatic breast cancer: a propensity score analysis. *Breast* 2017; **31:** 114–20.
5 Park YH, Kim T-Y, Kim GM, et al. Palbociclib plus exemestane with gonadotropin-releasing hormone agonist versus capecitabine in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer (KCSG-BR15-10): a multicentre, open-label, randomised, phase 2 trial. *Lancet Oncol* 2019; published online Oct 24. https://doi.org/10.1016/S1470-2045(19)30565-0.
6 Jerusalem G, de Boer RH, Hurvitz S, et al. Everolimus plus exemestane vs everolimus or capecitabine monotherapy for estrogen receptor-positive, HER2-negative advanced breast cancer: the BOLERO-6 randomized clinical trial. *JAMA Oncol* 2018; **4:** 1367–74.
7 Im S-A, Mukai H, Park IH, et al. Palbociclib plus letrozole as first-line therapy in postmenopausal Asian women with metastatic breast cancer: results from the phase III, randomized PALOMA-2 study. *J Glob Oncol* 2019; **5:** 1–19.
8 Im S-A, Lu YS, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med* 2019; **381:** 307–16.
9 Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy—MONARCH 2: a randomized clinical trial. *JAMA Oncol* 2019; published online Sept 29. DOI:10.1001/jamaoncol.2019.4782.
10 Slamon D, Neven P, Chiaet S, et al. Overall survival results of the phase III MONALEESA-3 trial of postmenopausal patients with hormone receptor-positive, human epidermal growth factor 2-negative advanced breast cancer treated with fulvestrant + ribociclib. ESMO Congress 2019; Barcelona, Spain; Sept 27–Oct 1, 2019 (LBA7_PR).

Reducing infection-related morbidity and mortality in patients with myeloma

Myeloma survival has substantially improved in the past 10 years.[1] Although most myeloma deaths are accountable to progressive disease, a substantial proportion of early deaths and deaths in remission are due to infections.[2] Febrile infections induce considerable morbidity and frequently lead to drug interruption or drug discontinuation. Drug discontinuation can lead to inferior treatment responses, translating to poorer survival outcomes.

Agents with new mechanisms of action and drug combinations dominate current clinical investigations in myeloma. We commend researchers for drawing our focus to an area of supportive care in myeloma. Myeloma is a disease of the elderly, with 40% of newly diagnosed patients in the UK older than 75 years. In their Article in *The Lancet Oncology*, Mark Drayson and colleagues[3] present findings that showed that 12 weeks of fixed-duration levofloxacin prophylaxis reduced the occurrence of febrile episodes and deaths (95 [19%] febrile episodes or deaths in 489 patients in the levofloxacin group *vs* 134 [27%] in 488 patients in the placebo group; hazard ratio [HR] 0·66, 95% CI 0·51–0·86; p=0·0018). Independent to levofloxacin, use of prophylactic low dose co-trimoxazole significantly reduced febrile infections and death. Additionally, use of levofloxacin for a fixed duration was not associated with an increase in adverse events; 597 serious adverse events were reported up to 16 weeks from the start of trial treatment—308 (52%) of which were in the levofloxacin group versus 289 (48%) in the placebo group).

The results of this trial[3] provide a good basis for considering fixed-duration quinolone prophylaxis for newly diagnosed patients with myeloma starting therapy, but several questions remain. Although the primary endpoint of the study was met, there were no differences in overall survival at end of 1 year.[3] This result could be partly explained by the high number of patients who had poorly controlled myeloma in this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