10–20% of patients, dysphagia continues to worsen leading to a progressive decline in quality of life.[9,10]

Sixth, because the ORATOR study was of modest sample size, confirmatory trials would be welcome. The ORATOR-2 trial (NCT03210103) has been launched in patients with HPV-driven early tumours to compare deintensified post-operative radiotherapy to deintensified IMRT. The European Organisation for Research and Treatment of Cancer started a trial in early-stage pharyngeal squamous cell carcinoma to compare TORS to IMRT. In these two studies, the endpoint is the patient-reported swallowing function over the first year using the MDADI score.

In conclusion, the trial of Nichols and colleagues showed that radiotherapy (with or without concomitant chemotherapy) is functionally better than TORS (with or without adjuvant concomitant chemoradiotherapy) for the treatment of OPSCC. This finding suggests the utmost importance of appropriate patient selection for minimally invasive surgery to avoid the use of adjuvant treatment modality.

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CDK4/6 inhibitors: taking the place of chemotherapy?

The treatment landscape for advanced breast cancer has shifted dramatically over the past decade with the successive approvals of a multitude of targeted therapies. Specifically, CDK4/6 inhibitors have introduced a new treatment framework in the management of postmenopausal patients with hormone-receptor-positive, HER2-negative disease, who comprise the majority of patients with breast cancer. Clinical practice patterns have begun to veer away from a single-agent chemotherapy approach in the metastatic setting and towards upfront combination therapies with targeted agents in addition to endocrine therapy. Clearly delineating evidence, however, is needed to guide selection of one regimen over another in many cases.

In *The Lancet Oncology*, Mario Giuliano and colleagues[1] report the results of a comprehensive assessment of phase 2 and 3 randomised controlled trials comparing outcomes of postmenopausal patients with hormone-receptor-positive, HER2-negative metastatic breast cancer across a range of regimens based on endocrine therapy versus chemotherapy with and without incorporation of targeted therapies.

Comparing the findings across 140 randomised controlled trials pooled for the network meta-analysis, which includes data from a respectable 50 029 patients, chemotherapy-inclusive regimens were consistently found to be better than hormone monotherapy, albeit with significantly more toxicity. The more relevant finding supported by this study, however, was the inability to establish the effectiveness of chemotherapy-based regimens over the common comparator of palbociclib plus letrozole. In turn, the combination of a CDK4/6 inhibitor and endocrine therapy was


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similarly found to be better than hormone-directed monotherapy. This finding is in line with the results of the PALOMA-2, MONARCH 3, and MONALEESA-2 trials, which served as the basis for the approval by the US Food and Drug Administration of CDK4/6 inhibitors[2–4] in advanced breast cancer.

The unique implementation of a network meta-analysis design in this study allows readers to perhaps unintentionally answer a more pressing question. No meaningful differences in outcomes were noted between comparable regimens containing palbociclib, ribociclib, or abemaciclib, which are the currently approved CDK4/6 inhibitors. Although the quality of this inference does not parallel direct head-to-head comparisons, it might obviate the need for large-scale, cost-prohibitive studies that are unlikely to be done in lieu of more consequential trials investigating novel targeted therapies.

In general practice, the choice of CDK4/6 inhibitor is frequently made on the basis of the slightly variable side-effect profile of each agent. Despite the absence of a clear front-runner based on these findings, questions remain about individual resistance mechanisms. With few exceptions restricted to specific subgroups, overall survival has not yet been clearly demonstrated with the use of CDK4/6 inhibitors, thus bringing into question whether the duration of response to subsequent lines of therapy is affected. The addition of palbociclib to fulvestrant in patients with advanced breast cancer with progression after previous endocrine therapy did not translate to improved overall survival in all patients, although median survival was prolonged by roughly 7 months in a subgroup analysis of postmenopausal patients with previous response to endocrine therapy.[5] More recently, the MONALEESA-7 study reported an overall survival of 70·2% (95% CI 63·5–76·0) with the addition of ribociclib versus 46·0% (32·0–58·9) with placebo at 42 months in premenopausal and perimenopausal women receiving goserelin and letrozole, anastrozole, or tamoxifen.[6]

This meta-analysis solidifies an increasingly accepted role for CDK4/6 inhibitors in the upfront treatment of post-menopausal women with hormone-receptor-positive, HER2-negative metastatic breast cancer. CDK4/6 inhibition is rapidly becoming a cornerstone of treatment in addition to classical mechanisms targeting hormone receptors. These agents are starting to displace more toxic chemotherapy agents as front-line treatments for oestrogen-receptor-positive metastatic breast cancer in general practice because of, to some extent, their similar efficacy with substantially more favourable side-effect profiles.

Certainly, chemotherapy remains widely used in the management of this incurable disease, finding its place more frequently in later lines of therapy and still in the upfront treatment of visceral crisis. Notably, paclitaxel plus bevacizumab showed a better overall response in comparison with palbociclib plus letrozole. Aside from likely differences in enrolled patient populations, this result was not as consistently found with other CDK4/6 inhibitors. Future studies are needed to identify the appropriate setting and sequence for chemotherapy in these patients.

With the ever-increasing range of targeted therapies gaining approval for metastatic breast cancer, the clinical and research community continues to move further away from a monotherapy approach. Trials are currently in progress evaluating the role of inhibitors of PI3K, mTOR, and MEK, among others. How these agents will compare to previously front-line chemotherapy, and whether we will gain more success with the combinations of these targeted therapies in addition to CDK4/6 inhibitors remains to be seen.

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