it must be accompanied by improved diagnostic and treatment facilities with universal access. International collaboration will be an essential component of the necessary capacity building.[9] It is to be hoped that the present study will help to stimulate the necessary improvements, and future iterations can monitor their success.

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I declare no competing interests. The author alone is responsible for the views expressed in this Comment and they do not necessarily represent the decisions, policy, or views of Public Health England.

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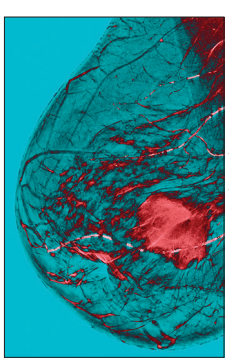
Overcoming endocrine resistance in neoadjuvant endocrine therapy for early breast cancer

Endocrine therapy is the mainstay of treatment for oestrogen receptor-positive breast cancer, now classified as either the luminal A (HER2-negative with low levels of Ki67) or luminal B (HER2 positive or negative, with high levels of Ki67) phenotype. Historically, endocrine therapy has included the approach of targeting the oestrogen receptor itself, either by means of selective oestrogen receptor modulators such as tamoxifen, or fulvestrant, a selective oestrogen receptor degrader. Another mode of action is the inhibition of oestrogen production so that no ligand is available to activate the receptor. This is the mode of action of aromatase inhibitors, which block the aromatase enzyme and lower oestrogen levels in postmenopausal women; whereas in premenopausal women, luteinising hormone-releasing hormone agonists reduce oestrogen production in the ovaries by interacting via the regulatory axis from the pituitary gland to the ovary. Since the 1990s, data have suggested that aromatase inhibitors might be the optimal neoadjuvant endocrine therapy treatment approach in postmenopausal women with breast cancer, resulting in better overall responses, improved pathological complete responses, and increased breast conservation at surgery.[1] More empirically, a 3-month period for neoadjuvant endocrine therapy was introduced as the standard of care in postmenopausal women with breast cancer in the mid-1990s. However, compared with neoadjuvant chemotherapy, neoadjuvant endocrine therapy has always yielded inferior results in terms of pathological complete responses.[2] Once introduced in the metastatic breast cancer setting, combinations of endocrine therapy plus mTOR inhibitors or CDK4/6 inhibitors instantly changed the standard treatment approach. However, resistance and disease progression while on treatment have occurred in both the adjuvant and metastatic settings.[3]

Apart from oestrogen expression, receptor levels, and to some extent a decrease in Ki67 levels, no biomarker has been identified as a prognostic marker for the benefit of neoadjuvant endocrine therapy. The phosphatidylinositol 3-kinase (PI3K) pathway is frequently altered in oestrogen receptor-positive breast cancer and has been implicated in resistance to endocrine therapies.[4] Furthermore, *PIK3CA*, which encodes the PI3K p110α isoform, is mutated in approximately 40% of oestrogen receptor-positive breast cancers.[5] Oestrogen-independent breast cancer cell growth can be inhibited by adding PI3K inhibitors to anti-oestrogens.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The PI3K isoform-selective, orally available inhibitors alpelisib and taselisib have shown promising anti-tumour activity in vitro and in vivo by inhibiting the p110α subunit more potently than the p110β subunit. Taselisib also inhibits the PI3K-δ and PI3K-γ isoforms. In heavily pretreated, oestrogen receptor-positive, HER2-negative, *PIK3CA*-mutant, metastatic breast cancer, the combination of taselisib and letrozole or fulvestrant has led to some promising outcomes, including breast cancer remissions.[8,10]

In the multicentre, randomised, double-blind, phase 2 LORELEI trial in *The Lancet Oncology*, Cristina Saura and colleagues evaluated letrozole (2·5 mg/day, continuously) and taselisib (4 mg; in a 5 days on, 2 days off schedule) versus letrozole plus placebo in the neoadjuvant endocrine therapy setting for a period of 16 weeks before surgery in 334 postmenopausal women with early-stage (stage I–III) breast cancer.[7] The investigators evaluated the presence of *PIK3CA* mutations as a biomarker for response. The coprimary endpoints were the proportion of patients who achieved an objective response by MRI or a pathological complete response in the breast and axilla (ypT0/pTis, ypN0) at the time of surgery in the whole patient population and in patients with *PIK3CA*-mutated tumours. Notably, both of these endpoints were reviewed independently from the local sites. Secondary endpoints included the proportion of patients with *PIK3CA* wild-type tumours who achieved an objective response and pathological complete response. *PIK3CA* mutations were detected in 152 (46%) of 334 patients. In summary, the study met only one of the predefined coprimary endpoints, with a significant improvement in the proportion of patients who achieved an objective response by MRI for the combination of letrozole and taselisib versus letrozole plus placebo in both the overall population (odds ratio [OR] 1·55, 95% CI 1·00–2·38) p=0·049) and the *PIK3CA*-mutant population (OR 2·03, 95% CI 1·06–3·88; p=0·033). However, pathological complete responses were low in both the overall population (three patients [2%] for the combination *vs* one [1%] in the placebo group) in the *PIK3CA*-mutant cohort (one patient [1%] *vs* none, respectively).

The results of the LORELEI trial are in principle in line with the previous report on the combination of taselisib and fulvestrant in metastatic breast cancer as presented in the SANDPIPER trial.[8] In both trials, adherence to the combination in terms of maintaining the critical dose over the treatment period might be a crucial issue to consider when analysing the reasons why the effects are not so pronounced in the group carrying the mutation compared with the group with no mutation.

Clearly, the effect of the combination therapy of taselisib and letrozole in a treatment-naive setting such as neoadjuvant endocrine therapy differs to the results seen in metastatic breast cancer. The safety profile is manageable in both settings. Considering the LORELEI outcome data, the effect of the combination therapy on objective responses according to MRI imaging might be an interesting observation, the lack of a clear decrease in presurgical Ki67 levels and the very low number of pathological complete responses reported suggest that this combination is not a breakthrough neoadjuvant endocrine treatment, even if the authors speculate on the somewhat short duration of the neoadjuvant endocrine therapy. The NEO-ORB trial[9] evaluated burpalesib or taselisib in combination with letrozole given for 24 weeks before surgery in a rather similar patient population. The trial reported negative results objective responses and pathological complete responses in both cohorts (ie, both *PIK3CA* wild-type and *PIK3CA*-mutant patients). The results are almost identical to those of LORELEI and, taken together, the results of the two trials are unable to demonstrate a benefit with either drug combination for *PIK3CA*-mutant patients. Notably, only 52% of the randomised patients in the NEO-ORB trial were able to complete the full course of 24 weeks of neoadjuvant endocrine therapy.[9] By contrast, in a phase 2 trial evaluating taselisib in combination with fulvestrant in second-line postmenopausal metastatic breast cancer, the median duration of treatment was almost 6 months, resulting in pathological complete responses in 38·5% of patients.[10]

The neoadjuvant approach is the only option to evaluate new combinations in a treatment-naive setting and therefore remains the best option to evaluate predictive factors in the tissue as well as blood-borne markers such as circulating tumour cell DNA. In future studies, it might be important to increase the relative total dose intensity of the combination therapy to be tested in order to evaluate the effect on toxicity.

Cross-trial comparisons with studies of neoadjuvant endocrine therapy in metastatic breast cancer are unlikely to provide further insight, but the takeaway message is based on the data discussed here that the efficacy of such treatment approaches is different in metastatic breast cancer, compared with the small effect on objective responses and pathological complete responses in neoadjuvant endocrine therapy for early breast cancer. The good news, however, is that taselisib might offer an improved therapeutic index with a more favourable toxicity profile than pan-PI3K inhibitors.

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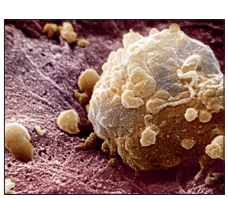
5-year results for pembrolizumab treatment of advanced melanoma

Current standard practice is to use checkpoint inhibitors for the treatment of patients with metastatic melanoma. The cytotoxic T-lymphocyte-associated antigen-4 (CTLA4) antibody ipilimumab was the first drug that was shown to improve the survival of patients with metastatic melanoma.[1] Although the proportions of patients who achieved a response were low (only 10–20%), approximately 20% of patients achieved long-term tumour control.[2] These findings gave rise to hopes of being able to even cure patients with advanced melanoma. The KEYNOTE-006 randomised phase 3 trial, reported by Caroline Robert and colleagues[3] in *The Lancet Oncology*, has shown that the PD-1 antibody pembrolizumab is more effective than ipilimumab, with 235 (42%) of 556 patients assigned to pembrolizumab achieving an objective response versus 46 (17%) of 278 patients assigned to ipilimumab, median progression-free survival of 8·4 months versus 3·4 months, and overall survival of 32·7 months versus 15·9 months, respectively. These results for pembrolizumab are similar to those recorded for patients on nivolumab monotherapy; however, the combination of ipilimumab and nivolumab currently seems to be the most effective immunotherapy for melanoma, especially among distinct subgroups of patients with a PD-L1-negative tumour, high tumour load, or brain metastases.[4–7] Additionally, BRAF or MEK inhibition is a possible alternative for patients with *BRAF*-mutant melanoma. Hence, an individualised first-line treatment decision should be made for every patient based on their clinical situation.

The 5-year follow-up results for the KEYNOTE-006 study showed 5-year overall survival of 38·7% for pembrolizumab and 31·0% for ipilimumab, thus showing that pembrolizumab has a clear advantage over ipilimumab. However, only 23% of patients assigned to pembrolizumab remained progression free at 4 years. Today, the key question is how long patients should be treated with a PD-1 antibody. In KEYNOTE-006, 103 (19%) of 556 patients completed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