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LETTER TO THE EDITOR

The Open Issues Regarding Cyclin-Dependent Kinase 4/6 Inhibitors in the Management of Advanced Breast Cancer

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To the Editor,

Since the new cyclin-dependent kinase 4/6 (CDK4/6) inhibitor drug class has steadily entered into the clinical practice following the PALOMA, MONALEESA, and MONARCH seminal trials [1], the therapeutic panorama of metastatic breast cancer (mBC) has been further enriched and complicated. While these trials have provided solid and reliable data that support the entry of these drugs into clinical practice, some issues remain.

Many of the current international guidelines, such as those from the National Comprehensive Cancer Network (NCCN) [2] and European Society for Medical Oncology (ESMO) [3], suggest the use of CDK4/6 inhibitors for first-line treatment in postmenopausal patients with luminal mBC, except in case of visceral crisis. However, when CDK4/6 inhibitors are introduced after progression on endocrine therapy (ET) as monotherapy, it is not yet well established whether it is possible to maintain the same ET in conjunction with CDK4/6 inhibitors. Preliminary evidence suggests that CDK4/6 inhibition therapy may have the potential to reverse endocrine resistance [4], and this combination regimen would take advantage of this feature.

Some preclinical evidence suggests that there is no cross-resistance among CDK4/6 inhibitors [5]. Therefore, maintaining CDK4/6 inhibition beyond progression by modifying the ET backbone may represent a future approach, but to date there are no clinical data. This issue may be addressed once results are known from the MAINTAIN (NCT02632045) [6] and TRINITI-1 (NCT02732119) [7] trials, which involve patients whose disease progressed on CDK4/6 therapy. MAINTAIN trial mandates a switch to a new ET (fulvestrant) for all patients and either additional ribociclib or placebo. The primary endpoint is progression-free survival (PFS) at 24 weeks from study entry, with a secondary endpoint of overall response rate in patients who continue CDK4/6 therapy. TRINITI-1 is a phase I/II, single-arm study of ribociclib in combination with everolimus and exemestane in patients after previous progression on a CDK4/6 inhibitor therapy. The phase II portion of this study will evaluate the clinical benefit rate at 24 weeks as a primary endpoint, and PFS as a secondary endpoint. Notably, TRINITI-1 has included men as a part of its eligible study population, thus contributing invaluable data for this particular group in whom CDK4/6 inhibitor efficacy is not well understood.

One feature related to long-term exposure to CDK4/6 inhibitor treatment is activation of the Akt/mammalian target of rapamycin (mTOR) pathway [8]. As such, the combination of mTOR inhibitors, such as everolimus, and CDK4/6 inhibitors is of some interest in order to overcome potential resistance. However, this approach may be limited by toxicity caused by such combinations. Should the results of the TRINITI-1 trial [7] indicate efficacy of this combination in the context of patients at high risk of rapid progression, this treatment could be adopted as first-line treatment and potentially be trialled against upfront induction chemotherapy.

International guidelines issued by the NCCN [2] and ESMO [3] currently recommend ET plus a CDK4/6 inhibitor as the preferred first-line treatment option in postmenopausal women with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HER2–) mBC, excluding those patients in whom it is necessary to induce rapid disease control. However, a direct comparison between ET plus CDK4/6 inhibitors and chemotherapy has never been performed. This comparison is of considerable importance, particularly in patients with poor prognostic factors (such as an

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absence of progesterone receptor, aggressive disease, and so forth) and those with a short interval between the end of adjuvant ET and subsequent relapse. In postmenopausal women with luminal HER2– mBC who had not previously received systemic treatment for advanced disease, expanded analysis emerging from the PALOMA-1 trial demonstrated the achievement of good clinical benefit rate (over 75%) and a reduction in the risk of progression by 45% in those patients classified as having the worst prognosis according to clinical factors [9]. This group may be regarded as a surrogate for the clinical group in whom upfront chemotherapy is recommended. Furthermore, if combined ET plus CDK4/6 inhibition enters the adjuvant setting over time, a direct comparison between chemotherapy and ET plus CDK4/6 inhibitors will become increasingly critical.

The recent BOLERO-4 trial [10] demonstrated that ET (letrozole) plus everolimus is an effective regimen in first-line management of luminal HER2– mBC, with the investigators concluding that retaining everolimus beyond first-line progression, while switching the ET to exemestane in the second line, can be an effective option, although these conclusions are limited because of the small patient subpopulation. These findings have further enriched and complicated the therapeutic landscape of luminal HER2– mBC, and future trials should focus on head-to-head comparisons between the two approaches (mTOR inhibitors and CDK4/6 inhibitors) in the early-line setting.

In order to better understand the place of CDK4/6 inhibitors in the complex therapeutic landscape of luminal/HER2– mBC, it is increasingly necessary to differentiate patients who would benefit from this treatment from those who would be exposed to only greater toxicity without deriving significant advantages. For this identification a contribution from translational research is necessary, but although preclinical evidence suggests *CCND1* amplification or *CDK2N2A* loss as predictive markers of response [11], to date no specific biomarker has yet been identified from exploratory analysis of the PALOMA trials. Perhaps rather than searching for a single biomarker, increased understanding of the complex molecular network that underlies neoplastic progression will help us to instead identify a panel of biomarkers useful to tailor treatment. This could also help us to understand the correct place for CDK4/6 inhibitors in the increasingly complex therapeutic algorithm of this breast cancer subgroup. While waiting for these data, it would probably be wise to reserve these drugs for patients with the highest risk of progression, administering ET alone in the most indolent clinical situations.

The observation that overexpression of cyclin D1 could be used to promote resistance to anti-HER2 agents has encouraged the use of CDK4/6 inhibitors in estrogen receptor-positive/HER2-positive mBC in order to resensitize tumor cells [12]. This has also driven the design of some clinical studies, such as the NA-PHER2 and PATRICIA trials, that aim to evaluate this innovative approach. The preclinical background is very encouraging, and CDK4/6 inhibitors represent a promising approach in this setting, but further data are required.

CDK4/6 inhibitors are the most promising drugs in the last 10 years of breast cancer therapy, but the journey is still long and we still have a lot to discover about their potential and limitations.

CONFLICT OF INTEREST

The author declares that he has no competing interests.

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