Is There Still a Role for First-Line Single Agent Endocrine Therapy in HR+ and HER2– Advanced Breast Cancer?

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The management of patients with hormone receptor positive, HER2 negative (HR+ HER2–) metastatic breast cancer (MBC) has historically been based on endocrine therapy (ET) [1] Endocrine resistance, both de novo and acquired, has impeded the clinical use of ET over decades, stimulating an exceptional effort in understanding mechanisms of resistance at a cellular and molecular level [2]. The development of targeted agents has recently changed the management paradigm of HR+ HER2– MBC. Such agents currently include the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors palbociclib, ribociclib and abemaciclib, as well as everolimus, which targets the phosphatidylinositol 3-kinase (PI3K)-Akt mammalian target of rapamycin (mTOR). All these agents have been shown to improve patient outcomes in combination with ET as compared to single-agent ET. The PALOMA-2, MONALEESA-2, and MONARCH-3 phase III trials demonstrated improvements in progression-free survival (PFS) in the front-line setting when a CDK4/6 inhibitor was used in combination with a non-steroidal aromatase inhibitor (nsAI) as compared to a single-agent nsAI [3–5]. These studies accepted patients with ‘de novo’ MBC and those who experienced relapse following a long disease-free interval (DFI) (>12 months) after the completion of adjuvant ET, therefore, representing a group with potentially high endocrine sensitivity.

Both palbociclib and abemaciclib have also shown significant prolongation of PFS when used in combination with fulvestrant in the PALOMA-3 [6] and MONARCH-2 phase III trials [7], respectively. In these studies, patients were permitted to receive study regimens as first-line therapy only if they had recurred during adjuvant ET or experienced a short DFI (<1 year) after adjuvant ET.

In all studies, the added toxicity of the combination with CDK4/6 inhibitors seemed manageable and did not result in significant rates of treatment discontinuation [4, 7–9].

Limited to the setting of nsAI pre-treated disease, the BOLERO-2 trial demonstrated the superiority of everolimus in combination with exemestane, compared with exemestane alone in women with HR+ MBC after progression on an nsAI [10]. In this study, similar to PALOMA-3 and MONARCH-2 trials, patients with prior exposure to nsAI in the adjuvant setting and those who either had metastatic disease relapse during adjuvant HT or experienced a short DFI could be admitted to receive the study drugs as first-line therapy. Although efficacious in this combination, everolimus demonstrated a characteristic safety profile which requires appropriate management strategies to minimize the occurrence and severity of adverse events such as stomatitis, hyperglycemia, and pneumonitis [11].

Based on this data, combinations of ET and biologic agents are certainly an option for first-line therapy of those patients with HR+ HER2– MBC who have relapsed during adjuvant HT or have experienced a short DFI after adjuvant therapy with an nsAI and who are deemed suitable for ET. For these patients, appropriate regimens may be either a CDK4/6 inhibitor in combination with fulvestrant or everolimus in combination with exemestane, with the choice ultimately made according to individual preferences and clinical context.

However, the scenario of ‘de novo’ metastatic disease and of ‘nsAI-naive’ patients merits additional consideration. Using single-agent hormonal therapy, a significant proportion (~50%) of patients can achieve disease responses lasting more than 12 months, with minimal side effects [12–14]. In this group of patients with high sensitivity to ET, any potential additional benefit bestowed by combinations incorporating a CDK4/6 inhibitor must be carefully weighed, taking into account additional toxicity and costs. In this context, identifying which subgroup of patients is most likely to benefit from the combination of ET and CDK4/6 inhibitors is therefore of critical importance in defining the most appropriate use of these compounds.

Unfortunately, despite many efforts in pre-clinical and translational studies, to date no tested biomarker has succeeded in distinguishing between those patients more likely to benefit from combination therapy with a CDK4/6 inhibitor, and those who may be...
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References


4 Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, quierek confirmation in a larger study.

5 Recently, however, as this hypothesis derives from a single study with a relatively low number of patients assigned to these subgroups, these data require confirmation in a larger study. In conclusion, targeted combination of agents and ET is revolutionizing the approach to the management of HR+ HER2- MBC. Clinical data currently support a scenario wherein most patients with an indication for front-line ET should receive a targeted agent. It is, however, possible to speculate that for selected patients with clinical characteristics suggestive of indolent, endocrine-sensitive disease, front-line treatment with single-agent hormonal treatment may still play a role. Clearly, more research is needed in this field to obtain solid biomarkers that may aid in patient selection.

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In conclusion, the combination of targeted agents and ET is revolutionizing the approach to the management of HR+ HER2-