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Spotlight

Optimizing hormone therapy for breast cancer: Translating gains to the early-stage setting

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First-line CDK4/6 inhibitor ribociclib plus letrozole improves survival in the metastatic setting, but lack of accrual of African American women is a shortcoming. Predicting benefit in the early-stage setting and diverse enrollment in trials need to be priorities.[1]

Hormonal therapies have proven to be among the most effective and widely prescribed targeted therapies in breast cancer treatment. However, intrinsic and acquired resistance to endocrine therapies have continued to limit our ability to eradicate the disease for all patients. The cyclin-dependent kinases (CDKs), specifically the cyclin D1-CDK4/6-RB1 complex, are major mediators of cellular proliferation. Inhibitors of CDK4/6 have transformed the treatment landscape for nearly all patients with hormone receptor-positive (HR+) HER2-negative metastatic breast cancer. There are three CDK4/6 inhibitors approved for HR+ HER2-breast cancer: palbociclib, abemaciclib, and ribociclib. These three agents were developed in parallel and have each been tested in first-line setting and later-line settings; there were near identical improvements in progression-free survival (PFS) in all three pivotal first-line trials.[2–4] In the March 10, 2022 issue of the *New England Journal of Medicine*, Hortobagyi et al. showed improvement in overall survival (OS) from the phase 3 MONALEESA-2 trial testing front-line letrozole in combination with ribociclib versus placebo in postmenopausal women.[1] With a median 6.6-year follow-up, authors report a 24% improvement in OS in the combination arm (63.9 versus 51.4 months in the placebo group). This benefit was seen despite a third of patients in the placebo arm receiving CDK4/6 inhibitor after progression. MONALEESA-2 definitively shows that CDK4/6 inhibitors should be used as first-line treatment as they improve survival and delay time to chemotherapy by nearly one year.

The survival benefit seen with ribociclib in MONALEESA-2 was similar across all clinical subgroups. As CDK4/6 inhibitors move into the early-stage setting where the balance between efficacy and toxicity is critical, predictive biomarkers of response and resistance will be critical, especially as many women will be cured with an AI alone, and not all patients will be rescued by CDK4/6 inhibitors. Abemaciclib was recently approved in the adjuvant setting for patients with high-risk node-positive HR+ HER2-early-stage breast cancer with Ki67 $\geq$ 20% based on significant improvement in invasive disease-free survival (iDFS) in the Monarch E trial.[5] Overall survival data are still immature. In contrast, the adjuvant palbociclib trials PALLAS and Penelope-B have not demonstrated the same benefit in any clinical subgroup. Whether ribociclib will have a role in the adjuvant setting depends on results from the ongoing NATALEE trial. Abemaciclib is the first adjuvant approval specifically for patients with HR+ HER2-early breast cancer since the approval of exemestane more than 16 years ago. However, even within this clinically defined high-risk group, not everyone will benefit. The task at hand is to determine whose benefit is sufficient to justify the physical and financial toxicity associated with 2 years of CDK4/6 inhibitors to prevent metastatic disease.

Treating patients in the neoadjuvant setting (before surgery) and assessing treatment response at the time of surgery is the best hope for determining which populations will benefit. In molecularly high-risk disease, pathologic complete response (pCR) after neoadjuvant chemotherapy is highly prognostic for long-term outcome and therapy benefit.[6] One of the major challenges in testing hormone-based strategies in the neoadjuvant setting is the lack of a robust, validated short-term surrogate endpoint for DFS and OS, like pCR and residual cancer burden (RCB) are for neoadjuvant chemotherapy in molecularly high-risk tumors. Short-term changes of cell proliferation markers are the best validated surrogate endpoints for efficacy;[7] however, they lack reproducibility and are difficult to interpret for CDK4/6 inhibitors, which cause cell-cycle arrest. All three CDK4/6 inhibitors have been studied in the neoadjuvant setting. Conclusions have been limited by the lack of a robust primary efficacy endpoint. The I-SPY2 Endocrine Optimization Protocol (EOP) is a pilot sub-study within the I-SPY2 TRIAL that tests novel hormone-based strategies in patients with molecularly lower-risk but clinically high-risk disease. The objective of the I-SPY2 EOP trial is to evaluate a number of potential surrogate efficacy endpoints including, but not limited to, blood-based markers (including circulating tumor DNA), change in breast MRI functional volume and background enhancement, Fluroestradiol

(FES) mammiPET, and RCB. These types of studies are essential to accelerate learning about who is at risk of recurrence despite standard endocrine therapy and who will benefit from new therapies such as CDK4/6 inhibitors.

Non-Hispanic Black women have a 40% higher mortality rate from breast cancer and higher incidence rates under the age of 40[8] compared with White women. Mortality disparity has been, in part, attributed to the disproportionate number of triple negative breast cancers (TNBCs) among Black women. Recent findings from our analysis of clinical outcomes by patient self-identified race in the I-SPY2 TRIAL suggest there may be other factors.[9] In the context of the I-SPY2 TRIAL, where women with high-risk stage 2/3 breast cancers receive neoadjuvant therapies tailored to their tumor profiles, there are no significant differences in DFS among White, Black, or Asian patients when pCR is achieved. However, when pCR is not achieved, outcomes are significantly worse among the HR+ HER2-molecular subtype for Black women compared with White women. This difference in outcome in the HR+ HER2-subtype among Black women is consistent with work from Olopade et al.[10] These important observations were possible because in I-SPY2, 12% of patients self-identified as Black or African American (reflecting the racial demographic population of the US with 13%–14% African Americans). Our findings of differential outcomes by race in DFS among non-responders with the HR+ HER2-subtype were not observed among non-responders with TNBC. Our findings underscore the importance of broadening access and inclusion of underrepresented women in clinical trials. Black women remain persistently underrepresented in landmark breast cancer clinical trials such as the MONALEESA-2 trial, where there was less than 2.5% participation by African or African American women. Despite the groundbreaking findings presented from this trial, we are inevitably left to question whether ribociclib will benefit Black women with HR+ HER2-breast cancers, especially with the known heterogeneity within this subtype. It is critical that we examine enrollment in clinical trials and develop effective strategies to increase enrollment of underrepresented patient populations. If patient demographics are not reflective of the patient population with breast cancers, we will fail to understand and reduce inequities in breast cancer mortality.

DECLARATION OF INTERESTS

The authors declare no competing interests. I-SPY2 Trial and EOP is sponsored by the not for profit Quantum Leap Healthcare Collaborative (QLHC). Dr. Esserman is an unpaid board member of QLHC.

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