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EDITORIAL

Do all patients with early breast cancer meeting the NATALEE criteria benefit from adjuvant ribociclib?

Breast cancer is the leading cause of cancer-related morbidity and mortality in women worldwide.[1] Among patients with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative early breast cancer, the risk of recurrence persists beyond the completion of adjuvant treatments and can approach 50% after 5 years in those with high-risk disease.[2] In this setting, (neo)adjuvant chemotherapy, endocrine therapy, and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have all been shown to improve clinical outcomes, reducing the incidence of invasive and distant recurrences.[1,3,4] The extent of benefit, however, depends on adherence to therapy, which is strongly influenced by treatment-related adverse events and their impact on quality of life.[5,6]

Given the long-lasting risk of recurrence, well-tolerated treatments with a carryover effect (extending beyond treatment discontinuation) are needed to further improve outcomes and ultimately survival. In this context, the CDK4/6 inhibitors abemaciclib and ribociclib reshaped adjuvant therapy for this breast cancer subtype, although long-term data respectively from the monarchE and NATALEE trials remain essential to confirm their long-term benefit.[3,4]

In the phase III, open-label NATALEE trial, 5101 patients with HR-positive/HER2-negative resected early breast cancer at intermediate or high risk of recurrence were randomly assigned to receive adjuvant therapy with a nonsteroidal aromatase inhibitor (NSAI) for 5 years, either alone or combined with 3 years of ribociclib.[4] The primary endpoint was the invasive disease-free survival (iDFS).

In the current report (ref), Crown et al[7] present efficacy outcomes and updated overall survival after a median follow-up of 55.4 months. Ribociclib plus an NSAI continued to show a significant advantage over NSAI alone in terms of iDFS [hazard ratio (HR) for iDFS 0.72, 95% confidence interval (CI) 0.62-0.83, nominal one-sided $P < 0.0001$]. The absolute improvement in iDFS at 5 years was 4.5%, with evidence of a carryover effect beyond the 3-year course of ribociclib. The safety profile remained consistent with prior reports, and one in five patients discontinued ribociclib because of adverse events.

Overall survival (OS) data are still immature (HR 0.80, 95% CI 0.64-1.00, nominal $P = 0.026$). However, the carryover effect in the iDFS curve was evident and the majority of prevented events were distant recurrences (11% versus 8%), underscoring the potential for the observed iDFS advantage to translate into a survival benefit, as follow-up continues to mature.[8] Both features have also been evident in the monarchE trial, where a recent press release reported that adjuvant abemaciclib improved OS in patients with high-risk disease.[9]

In the monarchE trial, concerns were raised about possible imbalances in censoring between treatment groups that could have led to overestimation of survival.[10,11] In contrast, the present NATALEE report includes a detailed assessment of censoring patterns, showing that censoring was noninformative and largely due to early dropout in the control arm. Thus, any missing events in the control group would likely bias the results toward the null hypothesis, suggesting that the true benefit of adjuvant ribociclib may, if anything, be underestimated.

Patients with an intermediate risk of recurrence, who were eligible for NATALEE but not for monarchE ('discordant eligibility criteria'), comprised two groups (Figure 1): (i) those with node-negative disease and additional high-risk features (i.e. pT3-4, high Ki-67, grade 2-3, or high genomic risk as based on several tools of clinical practice) and (ii) those with pN1 disease without other high-risk features (pT1-2 and grade 1-2).

Efficacy results were reported only for the node-negative 'discordant subgroup', which included 614 (12%) patients. In this subgroup, the HR for iDFS was 0.60, with plausible values (95% CI) ranging from 0.37 to 0.99, as compared with 0.74 (95% CI 0.63-0.86) in the pN1-3 subgroup. At 5 years, the absolute iDFS benefit was 5.7% in the node-negative and 4.4% in the pN1-3 subgroup, corresponding to numbers needed to treat (NNT) of 19 and 31, respectively.

Instead, no data are currently available for the 'discordant subgroup' with pN1 disease without other high-risk features (namely, pT3-4 or grade 3), in terms of prevalence, baseline risk, and relative benefit of adjuvant ribociclib. In this population, the 5-year iDFS rate without ribociclib is estimated to be ~90%, according to a *post hoc* analysis of three randomized clinical trials by Arecco and colleagues that included 1346 patients with discordant eligibility criteria (90% of whom had pN1 disease), and consistent with results from the RxPONDER trial, including patients with pN1 disease and low genomic risk.[12,13] When considered alongside data from NATALEE and monarchE, this 5-year iDFS rate of 90% is higher than the rate observed in patients meeting the monarchE criteria (75% at 5 years in the control arm), but also higher than the 85%

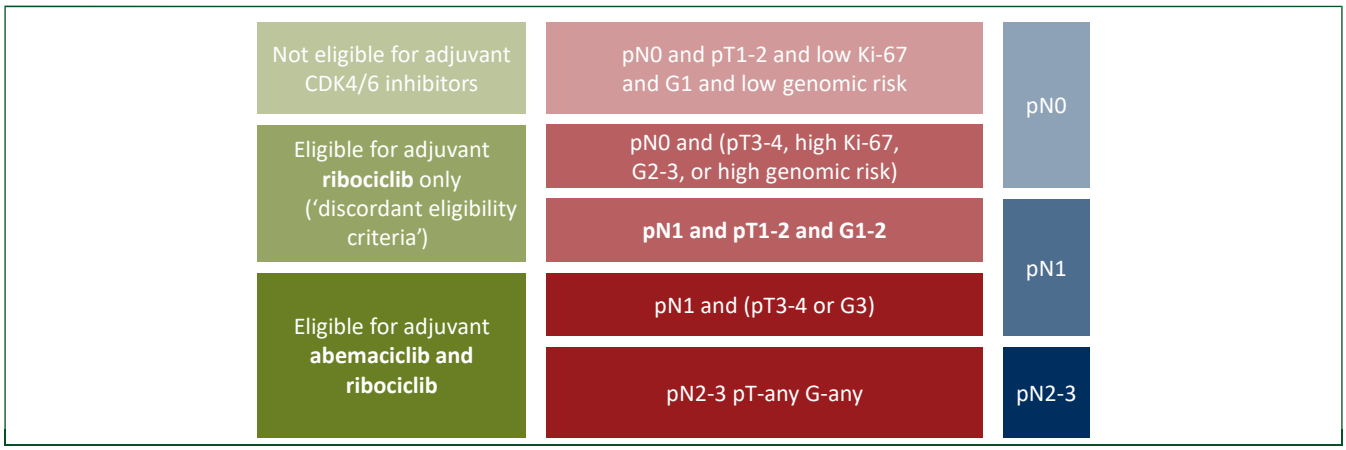

Figure 1. Eligibility criteria for adjuvant ribociclib and abemaciclib.
CDK4/6, cyclin-dependent kinase 4/6.

5-year iDFS rate reported in the control arm of the NATALEE node-negative subgroup. Instead, it is comparable with the 92% rate in patients not eligible for either CDK4/6 inhibitors.[3,13]

Therefore, the +4.4% absolute improvement in the 5-year DFS rate and the NNT of 31 observed in the node-positive cohort of NATALEE may have been diluted by the inclusion of patients with pN1 disease without other high-risk features. In this subgroup, assuming a baseline 5-year iDFS rate of 90%, a hazard ratio of 0.75 (as in the overall node-positive cohort), and proportional hazards, the expected absolute benefit would be speculatively of about +2.5%, corresponding to an NNT of 40 to prevent one invasive recurrence and to eight patients discontinuing ribociclib because of adverse events. These findings suggest that patients with node-negative tumors and additional high-risk features may derive greater benefit from adjuvant ribociclib than those with pN1 disease without other high-risk features.

In our view, this subgroup warrants a dedicated *post hoc* sensitivity and full adjusted analysis of ribociclib efficacy; until such data are available, treatment decisions for patients with pN1 disease without other high-risk features should be individualized, weighing the expected benefits against potential harms, and guided by shared decision making with the patient.

In terms of future perspectives, these data raise two main issues. Firstly, biomarkers for patient selection are needed to optimize the therapeutic benefit, particularly among patients with intermediate-risk disease who may derive only a modest absolute benefit from adjuvant CDK4/6 inhibition.[8] Liquid biopsy detection of minimal residual disease (MRD) through circulating tumor DNA represents a promising strategy that may inform the risk in addition to anatomical and genomic classifiers, and several trials are ongoing. Of note, only 13% of patients in the monarchE trial were MRD-positive in one translational analysis, underscoring the need for defined timing for testing, and the use of ultrasensitive assays.[14]

In parallel, the phase III WSG-ADAPTcycle trial (NCT04055493) is evaluating dynamic changes in Ki67 combined with the 21-gene recurrence score to further dissect the risk of patients with intermediate-risk disease and to test whether 2 years of adjuvant ribociclib may offer benefit compared with adjuvant chemotherapy.[15] In a prior study, for example, the combination of anatomical risk, refined with an early metric of tumor endocrine responsiveness (Ki67 change) and OncotypeDX, was shown to improve prognostication in the intermediate-risk group with node-positive early breast cancer.[16]

A second central issue is whether adjuvant CDK4/6 inhibitors can replace chemotherapy, at least for patients with an intermediate risk of recurrence, even in the context of extended or intensified endocrine therapy with more potent agents such as oral selective estrogen receptor degraders.[8] Ongoing clinical trials are expected to address this issue and may ultimately reshape the treatment landscape for patients with HR-positive/HER2-negative early breast cancer.

In conclusion, with longer follow-up, the NATALEE trial confirmed the benefit of 3 years of adjuvant ribociclib in reducing the risk of invasive breast cancer recurrence, particularly among patients with node-negative disease and high-risk features, and those who met the monarchE criteria. Residual uncertainty regarding node-positive, biologically favorable early breast cancer remains an area of active investigation and is being addressed in ongoing clinical trials, including those evaluating adjuvant ribociclib.

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