

LETTERS TO THE EDITOR

Is adjuvant ribociclib ready for prime time?



In 2021, data from the monarchE trial led to U.S. Food and Drug Administration approval of adjuvant abemaciclib in combination with endocrine therapy (ET) for patients with high-risk hormone receptor-positive (HR+) early breast cancer (EBC).¹ Recent data from the NATALEE trial has led to a broad FDA approval for adjuvant ribociclib in combination with an aromatase inhibitor for stage II and III HR+ EBC, including those with high-risk node-negative disease.² This data leaves us with the question: how do we incorporate ribociclib in routine clinical practice?

In the NATALEE trial, patients with anatomic stage II and III disease were randomized to 3 years of ribociclib at 400 mg for 3 weeks on/1 week off with ET or ET alone. In contrast to monarchE, which only included high-risk node-positive patients, NATALEE allowed for a limited number of higher risk node-negative patients (T3/T4 or T2 with high risk features such as grade 3 or grade 2 with Ki-67 \geq 20% or high genomic risk score). At the final invasive disease-free survival (iDFS) analysis, with 33.3 months of follow-up, 20.7% of patients were still receiving ribociclib, and there was a significant 3.1% absolute improvement (iDFS 90.7% versus 87.6%). Now with longer follow up (and all patients off ribociclib), at 4 years there continues to be a deepening of benefit with a 4.9% absolute improvement in iDFS (88.5% versus 83.6%, hazard ratio 0.715),³ with 20.0% discontinuing ribociclib due to adverse events, with the most common cause being liver related toxicity.⁴

In the monarchE trial, there was a 2.8% absolute iDFS benefit at 2 years which deepened to 5.9% at 4 years, and 7.6% at 5 years of follow-up, suggestive of a carry-over effect.⁵⁻⁷ In monarchE early discontinuation due to adverse events for abemaciclib was 18.5%, similar to what was seen in the NATALEE trial.⁸ Given that both ribociclib and abemaciclib have demonstrated survival benefits in the metastatic setting, one could hypothesize that the early benefit seen with adjuvant ribociclib will continue to grow, just as it did with longer follow-up with adjuvant abemaciclib.

Of particular relevance is the efficacy of ribociclib in node-negative patients, which represents a limited subset of the NATALEE trial population (12% of patients were pathologically node-negative at the time of surgery). Although a 5.1% absolute difference (92.1% versus 87.0%) suggests benefit in this population, there were only 15 events separating the two arms (23/285 [8.1%] versus 38/328 [11.6%]). While the hazard ratio in this subset is 0.67, there are wide confidence intervals crossing one (0.40-1.12) due to the small sample size, and this raises uncertainty regarding the true benefit in this population at this point in time.⁹ It will be critical to ascertain the benefit in the node-negative population with longer follow-up as broadly utilizing ribociclib in all patients who meet eligibility criteria for the trial will have tremendous

implications for patient toxicity and health care spending. The number needed to treat (NNT) to prevent one event is 20 (100/4.9), and the NNT to prevent one distant recurrence is 22 (100/4.5) for ribociclib. While the NNT is likely to decrease with longer follow-up, at present, with an estimated cost of ~\$400,000 for 3 years of therapy for one individual patient, the cost to prevent one distant disease-free recurrence is \$8.8 million. Given that adjuvant cyclin-dependent kinase 4/6 (CDK4/6) inhibition will likely represent the bulk of early-stage breast cancer cost of care, careful understanding of benefit, potential toxicity for 3 years of therapy, and cost should be considered as we expand its use routinely in this node-negative population.

At present, there are two options for adjuvant CDK4/6 inhibition. Adjuvant abemaciclib remains the CDK4/6 inhibitor of choice for high-risk HR+ EBC given the longer follow up, deepening benefit after completion of treatment, and shorter treatment duration. In patients with high-risk node-positive disease who did not meet criteria for monarchE, adjuvant ribociclib is recommended. Although the NATALEE data are promising in the overall study population, and suggest continued benefit even after patients have discontinued ribociclib, further follow-up is necessary before routinely recommending adjuvant ribociclib to those with node-negative disease, particularly those with smaller T2 tumors, and longer follow-up will be critical in this subset of patients.

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Unlocking methodological insights on oncology efficacy endpoints: from statistical to clinical and vice versa. Letter to the editor regarding 'Abemaciclib plus a nonsteroidal aromatase inhibitor as initial therapy for HR+, HER2- advanced breast cancer: final overall survival results of MONARCH 3' by M. P. Goetz et al



We read with interest the final overall survival (OS) analysis from the MONARCH-3 trial.¹ At a median follow-up of 8.1 years, the game-changing result of a sustained increase in progression-free survival (PFS) is confirmed [hazard ratio (HR) 0.54, 95% confidence interval 0.43-0.67; nominal $P < 0.0001$], reinforcing the evidence for using endocrine therapy plus a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (CDK4/6i) as a first-line treatment in hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-)

disease.² Abemaciclib, combined with a nonsteroidal aromatase inhibitor (NSAI), resulted in longer OS compared with NSAI alone, with a median improvement of 13.1 months, but statistical significance was not achieved ($P = 0.0664$).

However, the null hypothesis that abemaciclib offers no OS benefit assumes that the striking PFS gain (13.4 months) would be followed by a worse postprogression survival (PPS) in the abemaciclib arm, an assumption not supported by the comparison of the OS curves: the difference in median OS is 13.1 months, almost identical to the difference in median PFS.^{3,4} Alternatively, one might speculate that PPS is independent of the first-line therapy, and the benefit from delaying progression is maintained in OS. Yet, even if this alternative hypothesis holds, the type and size of the effect of abemaciclib on OS differ from those on PFS, due to the long PPS (median 38-39 months, estimated by the difference between the median OS and the median PFS, which is similar in the two arms: $53.7-14.8 = 38.9$ and $66.8-28.2 = 38.6$, respectively). No data on the distribution of PPS times nor on the causes of death in both arms have been provided, but this long PPS has three consequences:

- no beneficial effect of abemaciclib on OS can be expected in the first period following randomization (months or even years, depending on the presence and extent of the correlation between PFS and PPS at the individual level);
- the relative effect of abemaciclib on OS is bound to be less than that on PFS; OS, in each individual, is equal to $PFS + PPS$: if PFS is almost doubled (HR 0.54) but PPS is almost three times as long, and it is the same in the two arms, the resulting relative increase in OS will be smaller than that in PFS (if the PFS in the control arm is considered equal to 1, then PFS in the abemaciclib arm should be assumed to be equal to 1.84 ($1/0.54$), and postprogression free equal to 2.6 ($38.7/13$). OS in the placebo and in the abemaciclib arm will then become $1 + 2.7 = 3.7$ and $1.8 + 2.7 = 4.5$, respectively);
- the effect of abemaciclib on OS cannot be adequately described by the HR, due to the lack of constant proportionality in the hazards.

The observed effect of abemaciclib on OS in the MONARCH-3 trial aligns with the predictions based on the assumption of equal PPS in both arms, without invoking a CDK4/6i postprogression effect. However, because CDK4/6is were used differentially in the two arms after progression (see Table 1 on postdiscontinuation therapy¹), a postprogression beneficial effect of first-line CDK4/6i treatment might be hypothesized.

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