Editorial Commentary

Adjuvant use of CDK4/6 inhibitors, ovarian function and fertility in premenopausal women: insights from the PENELOPE-B trial

Yael Berner-Wygoda^, Eitan Amir^

Division of Medical Oncology and Hematology, Department of Medicine, Princess Margaret Cancer Centre and the University of Toronto, Toronto, ON, Canada

Correspondence to: Eitan Amir, MD, PhD. Division of Medical Oncology and Hematology, Department of Medicine, Princess Margaret Cancer Centre and the University of Toronto, 610 University Ave, 700U, 7-721, Toronto, ON, Canada. Email: eitan.amir@uhn.ca.

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Numerous clinical trials have evaluated the role of adjuvant CDK4/6 inhibitors in high-risk hormone receptor-positive breast cancer, using three different agents over varying timeframes (1-4). These trials have yielded mixed results (5). While the MonarchE and NATALEE trials (using abemaciclib and ribociclib, respectively) showed positive outcomes, the PALLAS and PENELOPE-B trials failed to demonstrate consistent benefit with adjuvant palbociclib. Notably, premenopausal women made up a significant proportion of the participants in all four trials, ranging from 43% to 49%, highlighting the importance of addressing this high-risk group's specific needs.

In their article, Marmé *et al.* (6) provide an exploratory subgroup analysis of the PENELOPE-B trial which aimed to explore the impact of adding 1 year of palbociclib to endocrine therapy in premenopausal women. The specific objectives of this exploratory analysis were to explore the effect of palbociclib both on breast cancer outcomes, but importantly also on ovarian function and reserve as measured using assays of estradiol, follicle-stimulating hormone (FSH), and anti-Müllerian hormone (AMH).

One of the challenges in including premenopausal women in clinical trials is accurately assessing menopausal status, particularly after chemotherapy. It has been well-recognized that ovarian function can resume months or even years after chemotherapy-induced amenorrhea. Smith *et al.* (7) demonstrated that up to 27% of women with chemotherapy-induced amenorrhea regain ovarian function between 3 to 59 months post-chemotherapy. Similarly, Ingle *et al.* (8) found increased estrogen levels over time compared to baseline in women receiving anastrozole, highlighting the importance of serial testing in this population as exposure to aromatase inhibitors (AIs) in women with ovarian reserve can lead to stimulation of ovarian function including ovulation (9). Moreover, stratifying patients based on menopausal status at randomization may not accurately reflect the true nature of the groups analyzed, as ovarian function could resume after randomization, especially in younger women.

In the adjuvant CDK4/6 trials, various approaches were used to define premenopausal women. In the MonarchE menopausal status was determined by the investigator at initial diagnosis (10). Similarly, in the PALLAS trial, all women were stratified according to their menopausal prior to chemotherapy (2,3). In contrast, in both the PENELOPE-B and the NATALEE trials all women under the age of 60 were tested for estradiol and FSH levels after chemotherapy and before randomization. In the NATALEE

^ ORCID: Yael Berner-Wygoda, 0000-0001-8291-5578; Eitan Amir, 0000-0002-3706-525X.

trial, women who experienced chemotherapy-induced amenorrhea were required to confirm postmenopausal status with serial estradiol and FSH tests. This variability in defining menopausal status introduces significant heterogeneity within trial populations, complicating the interpretation of results, particularly for premenopausal subgroups.

A notable distinction among these trials is the type of endocrine therapy provided to premenopausal women. While postmenopausal women received AIs predominantly, premenopausal women were treated with various endocrine therapy regimens, including tamoxifen alone, tamoxifen plus ovarian function suppression (OFS), and AIs plus OFS. In the PALLAS, MonarchE, and PENELOPE-B trials, choice of endocrine therapy was left to the physician's discretion (2,6,10). This almost certainly would have resulted in some confounding by indication. Specifically, patients at highest risk would have been more likely to receive an AI. This difference may have contributed in part to the observed effect. Of note, in the NATALEE trial, treatment was standardized, requiring all pre-menopausal women to receive OFS and AI (3). While standardization enhances the interpretability of the trial treatment effect it also raises concerns about potential overtreatment for lower risk sub-populations in whom OFS may not provide meaningful additional survival benefit (11). This is important not only because the toxicity from the combined treatments can be significant for younger women, but also because the toxicity profile of each treatment component varies considerably. Therefore, a clearer understanding of the relative contribution of each treatment component is valuable.

Among pre-menopausal women in the PENELOPE-B trial, 66% of participants received tamoxifen, 19% tamoxifen with OFS, and 13% an AI with OFS (6). Although the analysis was exploratory and unplanned, there was a numerically greater benefit observed with the addition of palbociclib to endocrine therapy in the subgroup treated with tamoxifen plus OFS. In the MonarchE trial, while no statistical interaction was found between treatment effect and type of endocrine therapy, there were numerically more recurrences with tamoxifen (10). This may explain why patients treated with tamoxifen plus abemaciclib experienced a greater reduction in invasive disease-free survival events (~48% relative reduction) compared to those receiving an AI (~32% relative reduction).

Fertility and ovarian function are important issues in premenopausal women. Understanding the influence of various therapies on ovarian function can guide treatment decisions, pre-treatment fertility preservation strategies, and post-treatment recommendations. Although the effect of chemotherapy on ovarian function has been studied extensively, little is known about the impact of CDK4/6 inhibitors. Moreover, as ongoing trials such as ADAPT cycle (12) investigate omitting chemotherapy in high-risk premenopausal, the impact of CDK4/6 inhibitors on ovarian function needs to be explored further. Beyond fertility itself, another important consideration is the safety of pregnancy after CDK4/6 inhibitor treatment, including determining the appropriate washout period before attempting conception. The younger women in this group (<40 years) are of particular interest, as they are the group with greater natural fertility potential. The PENELOPE-B trial aimed to address the questions of ovarian function and fertility by consecutively measuring estradiol, FSH, and AMH at three-time points: baseline, cycle 7 of palbociclib, and 30 days post-treatment (i.e., around 13 months after randomization) (6). Among the premenopausal group, 4.1% were under 30 years (expected to have the highest natural fertility and thereby AMH levels), 27% were between 30 and 40 years, 59% fell within the 40 to 50 years age range, and 10% were between 50 and 60 years. Overall, the rate of non-fertile AMH levels at baseline was high (92.7%) and remained consistent throughout the study (94.6% at the end of treatment). There were no significant differences in the rate of non-fertile AMH levels between treatment arms or subgroups at any time point. Among patients under 40, 28.1% in the palbociclib arm and 24.7% in the placebo arm had postmenopausal hormone levels at baseline, reaching 27.4% versus 14.5% by the end of treatment. While these differences were not statistically significant, the sample size was low and therefore statistical power was suboptimal. However, quantitatively, a greater that 10% absolute decrease in AMH levels in the infertile range is likely meaningful. These are intriguing results for a number of reasons. First, they show that a sizable proportion of such patients resume ovarian function if not exposed to palbociclib. This has implications on the choice of endocrine therapy such as avoidance of AI in the absence of OFS. Second, it suggests that palbociclib may have an impact on ovarian function in a group of women for whom the probability of resumption of ovarian function is meaningful. Interestingly, the rate of non-fertile AMH levels among patients under 40 was high at baseline (79.4%) and remained stable throughout the study (83.1% at end of treatment), with no significant impact of palbociclib. This

finding is somewhat surprising in light of the POSITIVE trial, where 74% of premenopausal women with previous breast cancer successfully achieved pregnancy, and 63% had at least one live birth, even with 63% having been exposed to chemotherapy (13). Even after accounting for the selection bias that would be inherent between these studies, these differences seem marked. Several factors could explain this discrepancy. First, all patients in PENELOPE-B received chemotherapy. Second, the timing of the last measurement of estradiol, FSH, and AMH was relatively early in follow-up and resumption of ovarian function may occur at a later stage thus requiring longer follow-up. Finally, AMH may only be a suboptimal surrogate for actual fertility. Specifically, while AMH levels remain low, it may not fully capture the ovarian function and reproductive potential of these women.

In summary, the analysis reported by Marmé *et al.* provides some provocative data on impact of palbociclib on cancer outcomes and ovarian function in pre-menopausal women. While the headline results are that palbociclib did not improve cancer outcomes, in a small subgroup of women treated with tamoxifen rather than AIs, there was a signal for some benefit. While this may well be a false discovery, attempts to validate this result in a larger dataset such as the PALLAS trial are warranted. Similarly, despite no significant impact on ovarian function overall, in women age less than 40 years, there may be an adverse effect of palbociclib on ovarian function. While these changes may not be of a magnitude large enough to impact fertility, the effect of resumption of ovarian function on quality of life, bone and cardiac health may be more meaningful. This may be important in guiding treatment decisions, pre-treatment fertility preservation strategies, and post-treatment recommendations. Validation of these data in larger cohorts is warranted especially evaluating whether the effect on ovarian function is a class-effect or palbociclib-specific.

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Footnote

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