Editorial Commentary

Adjuvant CDK4/6 inhibitors: can they improve clinical outcomes in hormone receptor-positive (HR+) early breast cancer?

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Breast cancer is the most common malignancy in women worldwide, with 70% of tumors being hormone-receptor-positive (HR+) (1). The majority of patients with early-stage HR+ disease are cured by loco-regional surgery, radiotherapy and chemotherapy if indicated, followed by adjuvant endocrine therapy taken for between 5–10 years (2). The anti-estrogen tamoxifen was introduced over 35 years ago as targeted adjuvant endocrine therapy for HR+ early breast cancer, and 5 years of tamoxifen compared to no endocrine therapy reduces risk of recurrence by 40% and improves overall survival by 30% (3). For post-menopausal women, further incremental gains in preventing recurrences followed the introduction of aromatase inhibitors 20 years ago (4), together with extended adjuvant therapy taken for 10 years in higher risk patients (5). However, there remains an ongoing risk of both early and late recurrence in HR+ breast cancer (6), and this risk correlates with both anatomical stage (tumor size and nodal involvement) and biological intrinsic subtype (determined by histologic grade, proliferation rate, and tumor genomic signature) (2). As such, despite progress made with current loco-regional therapy, systemic chemotherapy and endocrine-based treatment for HR+ early breast cancer, one fifth of patients may still relapse during the first 10 years (4,5).

Given the ongoing risk of recurrence for some patients, better strategies are needed to enhance the chance of cure. Following a deeper biological understating of HR+ breast cancer, several clinical studies have investigated adding targeted therapies to endocrine treatments. In HR+ breast cancers, estrogen receptor signaling regulates a number of genes, including various proteins that regulate cell cycle progression such as cyclins and cyclin-dependent kinases (CDKs). Signaling in the G1 part of the cell cycle results in D-type cyclin expression with activation of the kinases CDK4 and CDK6, and cyclin/CDK complexes phosphorylate retinoblastoma-associated protein 1 (Rb1) which releases E2F transcription factors and allows cell cycle progression (7). The CDK 4/6 inhibitors prevent phosphorylation of Rb, resulting in G1 cell cycle arrest and ultimately cell death (apoptosis) (7). Preclinical studies showed that CDK 4/6 inhibitors such as P0332991 (palbociclib) were especially active in HR+ breast cancer including those resistant to endocrine therapies (8,9). Subsequently three orally active and highly potent specific inhibitors of CDK4 and CDK6 (palbociclib, abemaciclib, and ribociclib) were developed in HR+ breast cancer, each showing enhanced clinical efficacy when given with endocrine therapy in advanced breast cancer (10).

Palbociclib was the first oral CDK 4/6 inhibitor to improve objective response rates and progression-free survival in advanced HR+ breast cancer when combined with endocrine therapy (11), and subsequently became an approved combination both with an aromatase inhibitor in the 1st-line setting, and with fulvestrant as 2nd-line

therapy based on randomized phase III trials (12,13). The main additional side-effect from palbociclib is reversible neutropenia without associated risk of fever or infection, and this is managed in clinical practice in advanced disease by dose holds and/or dose reductions. Similar gains in efficacy were demonstrated in phase III studies in advanced HR+ breast cancer for both ribociclib (14,15) and abemaciclib (16,17), and as such CDK 4/6 inhibitors are now integrated into updated international consensus guidelines as standard of care for the management of HR+ advanced breast cancer (18). Given this significant advance in HR+ breast cancer, it became logical to determine whether the addition of CDK 4/6 inhibitors to adjuvant endocrine therapy could improve clinical outcomes in HR+ early breast cancer.

The first adjuvant CDK 4/6 inhibitor study to start recruitment in September 2015 was the phase III PAlbociclib CoLLaborative Adjuvant Study (PALLAS), the final results of which were published recently by Gnant *et al.* (19) in the Journal of Clinical Oncology. This was a prospective, randomized, open-label phase III trial conducted in 406 centers in 21 countries worldwide, that recruited stage II or III HR+ early breast cancer patients in whom staging investigations at diagnosis had confirmed no evidence of metastatic disease. Prior to randomisation, patients completed their definitive breast surgery and (neo) adjuvant chemotherapy and/or radiotherapy if indicated. Enrolment into the PALLAS trial occurred within 6 months of starting adjuvant endocrine therapy. Eligible patients were then randomised to Palbociclib for 2 years (starting at standard dose of 125 mg once daily, days 1–21 followed by 7 days off in a 28-day cycle) in addition to standard endocrine therapy, or standard endocrine therapy alone. Palbociclib dose reductions and interruptions were defined in the protocol, with discontinuations for repeated grade 3 or higher neutropenia. Patients were stratified by anatomic stage, prior adjuvant or neoadjuvant chemotherapy, age (≤ or >50 years) and geographic region. Patients were followed clinically every 3 months for the first 2 years, and then 6-monthly to year 5, and annually thereafter to year 10. Any imaging was symptom directed as per international guidelines for the follow-up of early-stage breast cancer. The primary time-to event end point of the trial was invasive disease-free survival (iDFS). The original required sample size was 4,600 patients, but in 2018 was increased to 5,600 patients based on lower event rate in comparable trials.

At the second pre-defined interim analysis in May 2020 when 67% of the planned events had occurred, the futility boundary was crossed and those few patients (approximately 350) still taking palbociclib were recommended to stop taking the drug. The analysis showed that after a median follow-up of 23.7 months, the PALLAS study failed to meet its primary endpoint of improved iDFS [3-year iDFS of 88.2% for palbociclib + endocrine therapy *vs.* 88.5% for endocrine therapy alone, hazard ratio (HR) 0.93; P=0.51] (20). In the final analysis reported by Gnant *et al.*, with a median follow-up of 31 months, similar results remained between the two treatments (4-year iDFS of 84.2% *vs.* 84.5%, HR 0.96; P=0.65) (19). No significant differences were observed for secondary endpoints of distant recurrence-free survival and overall survival, and subgroup analysis did not show any differences in efficacy based on low or high-risk patients. A total of 44.9% of patients discontinued palbociclib prematurely, 27.1% due to an adverse event (AE), with 55.2% and 33.4% of patients requiring palbociclib dose reductions to 100 and 75 mg, respectively (19). Grade 3/4 AEs observed most often in the palbociclib arm included neutropenia (61.3%), leukopenia (30.2%), and fatigue (2.1%).

For breast cancer clinicians, given the proven efficacy of palbociclib in the advanced breast cancer setting (11-13), the completely negative results from the large adjuvant PALLAS trial at both the interim (20) and final (19) analysis were both disappointing and surprising. Potential explanations included the high discontinuation rate (44%) suggesting sub-optimal drug exposure as a possible reason for the negative results. The protocol was very strict regarding dose holds and dose reductions for grade 3 neutropenia (with discontinuation for repeated events), whereas in clinical practice in advanced disease palbociclib treatment often continues in these situations given the low levels of infective complications even with recurrent grade 3 neutropenia. Gnant *et al.* refute suboptimal drug exposure as an explanation for the negative results, as subsequent 24-month landmark analysis in the PALLAS trial compared patients who did receive the complete pre-planned treatment versus those who stopped palbociclib and showed no difference in the lack of iDFS benefit (19). Indeed, in a second smaller trial PENELOPE-B that investigated palbociclib for 1 year only vs placebo in high-risk disease defined as residual disease following neo-adjuvant chemotherapy where there were far fewer discontinuations (only 17.5%), likewise there was no iDFS benefit [HR 0.93, 95% confidence interval (CI): 0.74–1.17] observed for palbociclib after a median follow-up of 42.8 months (21).

Another potential explanation is that the population

treated in PALLAS had a lower risk of recurrence than expected, such that any treatment effect in the early years could not be observed due to a low event rate. The trial population was heterogeneous with a number of lower risk patients with 18% T1 (<2 cm tumor size), 13% node-negative, 67% grade 1 or 2 disease, and 17.5% not receiving adjuvant or neoadjuvant chemotherapy (19). Event rate is dependent on level of risk, and the more heterogenous the population in the trial, the more likely that treatment effect could be diluted. However, even in the high-risk patients (defined as either >4 nodes, or if 1–3 nodes either grade 3 and/or large tumor size T3 or T4) who made up 59% of the patients in PALLAS, there was no benefit seen for the addition of palbociclib (HR =0.89, 95% CI: 0.70–1.13) compared to low-risk patients (HR = 0.93, 95% CI: 0.61–1.43) (20).

Do the negative results from the PALLAS trial mean the end for adjuvant CDK 4/6 inhibitor therapy? The other large global phase III adjuvant study (monarchE) investigated the CDK 4/6 inhibitor abemaciclib in combination with adjuvant endocrine therapy, and subsequently reported positive results at the pre-planned interim analysis in April 2020 (22). MonarchE enrolled 5,637 patients with HR+, HER2-negative early breast cancer who were all node-positive and were also defined as having high-risk disease (i.e., ≥4 nodes, or if 1 to 3 nodes then either grade 3 tumor, tumor size ≥5 cm, or high proliferation rate determined by Ki67 level ≥20%). Patients were treated with standard endocrine therapy with/without 2 years of abemaciclib (initial dose of 150 mg twice daily), which unlike palbociclib or ribociclib is given by continuous dosing due a lower haematological toxicity profile. After a median follow-up of 15.5 months at the second interim analysis, the addition of abemaciclib significantly increased 2-year iDFS compared to endocrine therapy alone (92.2% *vs.* 88.7%, HR 0.75, 95% CI: 0.60–0.93). Consistent benefit occurred across patient subgroups, and abemaciclib reduced the risk of distant recurrence by 28% (22). At the subsequent updated analysis performed at the request of regulatory authorities after a median follow-up of 27 months, after events in 565 patients the iDFS HR had strengthened to 0.70 (95% CI: 0.59–0.82), and in high-risk node-positive patients who were also defined by high tumor cell proliferation (central Ki-67% >20%) the reduction in risk of recurrence was 37% (23). The most common AEs with abemaciclib were gastrointestinal events (diarrhea, nausea, abdominal pain), fatigue, and cytopenias (22,23), with most frequent grade 3/4 events being neutropenia (19.1%), diarrhea (7.7%), and fatigue (2.8%). Thromboembolic events and interstitial lung disease occurred in 2.4% and 2.9% of abemaciclib treated patients, respectively. AEs tend to start early and were managed by therapy interruption and/or dose reduction allowing patients to remain on therapy. Discontinuation of abemaciclib for any reason occurred in 27.7% patients, with only 17.2% discontinuing due to an AE (22,23). Patient-reported outcomes and health-related quality of life were similar between the 2 treatment arms (24).

The positive results in the monarchE trial led to the global approval of adjuvant abemaciclib in combination with endocrine in high-risk node-positive HR+ early breast cancer, with in some countries such as USA & China restriction to those who also have high Ki-67 (25), albeit ASCO guidelines have endorsed it for all high-risk node-positive patients as per the monarchE trial population (26). However, the discordant results from PALLAS and monarchE have been debated in the respective publications by both Gnant *et al.* (19) and Harbeck *et al.* (23), leaving unanswered questions as to why both drugs work equally well in the advanced breast cancer setting, yet palbociclib failed in 2 large adjuvant studies while abemaciclib had positive results. Potential explanations include either inherent differences between the drugs in potency or target inhibition, or differences in the dosing scheduling (intermittent *vs.* continuous) that may be more critical in the early breast cancer setting than in advance disease. Palbociclib has equivalent CDK4/cyclin D3 and CDK6/cyclin D1 potency, whereas abemaciclib has stronger inhibitory capacity for CDK4 with a higher CDK4:CDK6 inhibition ratio (27). The lower relative CDK6 inhibition with abemaciclib versus palbociclib explains less frequent myelosuppression which allows continuous instead of intermittent administration of abemaciclib versus intermittent dosing (3 weeks on, 1 week off) for palbociclib (28). In addition, abemaciclib has a broader CDK inhibitory profile than other CDK4/6 inhibitors, more profoundly inhibiting kinases beyond CDK4 and 6 with secondary targets including CDK1/cyclin B and CDK2/cyclin A/E complexes (29) that are involved in S to G2 phase transition. While the clinical impact of inhibiting other kinases remains largely unknown, it could be an explanation for the differences between agents in both toxicity profile and clinical activity in the early breast cancer setting.

The impact of CDK 4/6 inhibitor dosing schedule (intermittent vs continuous) on clinical efficacy seems to be irrelevant in the advanced breast cancer setting given

similar results between palbociclib and abemaciclib in improving response rates and progression-free survival in the respective phase III trials (12,13,16,17). In established secondary (metastatic) tumor deposits with many thousands of cancer cells in each tumor, complete responses (i.e., elimination of all disease in patients) are rare, and most endocrine based therapies reduce tumor volume and maintain stable disease which is accomplished much better and for longer by the addition of CDK 4/6 inhibitors to standard endocrine therapy. However, in an early breast cancer setting when trying to eradicate a few residual microscopic cancer cells (the ultimate source for recurrences in high-risk patients), it is conceivable that dosing schedule may have a very different impact. In this setting the chance of elimination of residual cancer cells may be much higher if effective anti-proliferative drugs are dosed continuously rather than intermittently, especially if stopping therapy allows re-growth of growth-suppressed cells.

In the neoadjuvant setting in HR+ early breast cancer evidence exists that both abemaciclib (30) and palbociclib (31) inhibit cell proliferation (as determined by reduction in Ki67 expression) and induce complete cell cycle arrest (CCCA) to a much greater extent that endocrine therapy alone, but that if either drug is withdrawn after 4–9 days cell growth as determined by Ki-67 rapidly rebounds. In the phase 2 neoMONARCH trial, abemaciclib (with or without anastrozole) was associated with significantly greater Ki-67 suppression and CCCA than anastrozole alone, but exploratory analyses revealed Ki-67 rebound in 69% of patients who discontinued treatment >4 days before biopsy compared with only 11% who discontinued treatment 1–4 days before biopsy (30). Similarly, in the randomized phase 2 PALLET trial (31), CCCA was observed at week 14 in 90% of patients receiving palbociclib plus letrozole versus 58% receiving letrozole alone. However, after palbociclib withdrawal cell growth rebound was indicated by rapid Ki-67 increase in a timeframe (5–9 days) similar to the week off palbociclib that occurs in the standard intermittent schedule (21 days on, 7 days off every 28 days) (32). These consistent findings in both the PALLET and neoMONARCH trials suggest that in the neoadjuvant (and possibly adjuvant) settings suppression of cancer cell growth may require ongoing continuous rather than intermittent drug exposure.

As such, dosing schedule is a viable hypothesis to explain the negative results in the PALLAS trial as reported by Gnant *et al.* (19), yet positive results in the monarchE trial (23). Follow up of both trials is ongoing to assess long term maturity of the data and any impact on ultimate overall survival, together with large associated translational research programs aimed at understanding the biology of response/resistance to CDK 4/6 inhibitor based endocrine therapies. A third adjuvant study of ribociclib (NATALEE) is still unreported, and while that drug is also given in an intermittent schedule, the dose used is lower than in advanced disease (maybe resulting is fewer discontinuations), and overall duration of therapy is longer at 3 years (33). Other phase III trials are ongoing aimed at targeting adjuvant CDK 4/6 inhibitors at those patients who show a poor anti-proliferative pre-operative response to short-term endocrine therapy (34).

To conclude, can we say that CDK 4/6 inhibitors improve clinical outcomes in early breast cancer? While the neo-adjuvant studies have demonstrated that both palbociclib and abemaciclib induce greater inhibition of cell proliferation and higher CCCA over a 14-week period prior to surgery (30,31), in neither study has this been correlated with clinical outcome as determined by relapse-free survival. In the adjuvant setting palbociclib did not improve clinical outcome as shown in the PALLAS trial (19), and the various reasons for this have been discussed above. However, for patients with HR+ high-risk node-positive early breast cancer, the approval of abemaciclib based on the monarchE trial does offer those patients at greatest risk of recurrence a treatment that can improve their outcome (23), and ongoing research will further refine those patients who benefit most from this approach, and whether CDK 4/6 inhibitors may have any other roles in HR+ early-stage disease.

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Footnote

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