Editorial Commentary

Predicting clinical benefit from continuation of cyclin dependent kinase (CDK) 4/6 inhibitors beyond progression

Julia Foldi, Adam Brufsky

Division of Hematology and Medical Oncology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Correspondence to: Adam Brufsky, MD, PhD. Breast Medical Oncology, Magee Women's Hospital, University of Pittsburgh Medical Center, 300 Halket Street, Pittsburgh, PA 15213, USA. Email: brufskyam@upmc.edu.

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The introduction of cyclin dependent kinase (CDK) 4 and 6 inhibitors (CDK4/6i) into the armamentarium of cancer-directed therapies has rapidly changed the treatment landscape of metastatic hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancers. Based on significantly improved median progression-free survival (mPFS) in several phase III clinical trials [PALOMA-2 (1), MONALEESA-2 (2) and MONARCH-3 (3)], all three members of the CDK4/6i family have been approved in combination with endocrine therapy (ET) and have become the standard first-line treatment regimen for $HR^+/HER2^-$ metastatic breast cancer (mBC). Most patients eventually develop resistance to this endocrine based combination within 12–36 months of initiating treatment. A major clinical challenge is the selection of optimal second line (2L) therapy after progression on CDK4/6i plus ET. In current practice, sequential endocrine monotherapy or combination therapies are employed until no further endocrine-based options exist or endocrine resistance is demonstrated, followed by sequential single-agent chemotherapies.

The substantial improvement in survival in the 1L setting in $HR^+/HER2^-$ mBC has not been paralleled by results achieved in subsequent lines of therapy. In current routine clinical practice, selection of 2L ET after progression on CDK4/6i plus ET is guided by mutational analysis of the tumor: patients with *PIK3CA*-mutated tumors are eligible to receive the α-selective PI3K inhibitor, alpelisib, in combination with fulvestrant, based on the SOLAR-1 trial (NCT02437318) (4), while those whose tumors harbor an *ESR1* mutation can receive the oral selective estrogen receptor degrader (SERD), elacestrant, based on the EMERALD trial (NCT03778931) (5). 2L ET options for patients whose tumors do not harbor *PIK3CA* or *ESR1* mutations includes the mammalian target of rapamycin (mTOR) inhibitor, everolimus, combined with exemestane, based on the BOLERO-2 trial (NCT00863655) (6), or endocrine monotherapy with fulvestrant and other anti-estrogens. Additional promising new agents include the oral SERD, camizestrant (7), the AKT inhibitor, capivasertib (8), and the proteolysis-targeting chimera (PROTAC®) ER degrader, ARV-471 (9), all with recent phase 2/3 data presentations but no Food and Drug Administration (FDA) approvals yet. Patients on most 2L ET regimens achieve mPFS on the order of 7–8 months, leaving room for significant improvement. Given that all patients eventually develop resistance to endocrine combinations, there have been attempts to combine drugs targeting multiple pathways in order to overcome resistance. Examples of this approach include the phase 1/2 TRINITI-1 trial (NCT02732119) investigating the addition of ribociclib to everolimus plus exemestane (10) and the triplet combination of the PI3K inhibitor, taselisib, with palbociclib and fulvestrant (NCT02389842) (11). The high rates of grade 3/4 and serious adverse events on these combination trials raise questions regarding the toxicity and tolerability of

triplet regimens.

One curious observation in many 2L+ trials of endocrine agents is the sharp drop in PFS seen in approximately 30–50% of participants within the first 2–3 months on treatment. This phenomenon is regardless of duration of prior CDK4/6i therapy, as seen in the EMERALD trial (12), in which subset analysis of patients receiving 1L CDK4/6i's for at least 18 months, signifying endocrine sensitivity, also showed rapid progression within 3 months of randomization in approximately 50% of patients on the standard of care and 40% on the elacestrant arms (12). This drop is less pronounced in the *ESR1*-mutated population treated with elacestrant, consistent with activity of novel SERDs in this subset of patients. However, patients with *ESR1*-mutated tumors randomized to the standard of care arm experienced even more dramatic early progression, even if they were thought to have endocrine sensitive tumors based on clinical benefit on 1L CDK4/6i for at least 18 months. This suggests that a significant proportion of patients who progress on 1L CDK4/6i already developed endocrine resistance at the time of progression. Which patients are likely to progress early versus derive lasting benefit from 2L+ ET combinations remain important unanswered questions in the field.

An alternative strategy to switching or discontinuing targeted therapy at the time of progression on 1L CDK4/6i is continuation with a change in the endocrine partner. Whether this strategy would lead to sustained clinical benefit and for whom has been an open clinical question. Recent observational data (13) suggests potential benefit of continuing CDK4/6 blockade beyond progression on CDK4/6i therapy. In the January 1st, 2023 issue of *Clinical Cancer Research*, Albanell *et al.* (14) reported data from the phase 2 BioPER trial, which had the co-primary objectives of estimating clinical benefit from continuation of palbociclib beyond progression as well as exploring potential biomarkers of clinical benefit. This small single arm study included 33 patients with $ER^+/HER2^-$ mBC who progressed on immediately prior palbociclib plus ET after having achieved clinical benefit on it (response or stable disease ≥24 weeks). While clinical benefit was modest—clinical benefit rate (CBR) of 34.4% and mPFS of 2.6 months [95% confidence interval (CI): 1.8–6.7] in the overall population and 3.2 months (95% CI: 1.8–7.5) among the 24 patients who received study treatment as 2L regimen—the biomarker endpoints provided some clues to patterns of resistance. Patients whose tumors lost retinoblastoma (Rb) protein expression at baseline did not achieve clinical benefit. High expression of cyclin E1 was also associated with lack of clinical benefit and shorter PFS. PAM50 intrinsic subtype was numerically associated with PFS although not in a statistically significant manner: the two patients with luminal A tumors had the longest mPFS at 5.2 months, followed by those with luminal B tumors (3.0 months) and finally the six patients with HER2-enriched subtype had the lowest numerical mPFS at 2.7 months. Circulating tumor DNA (ctDNA) was detected in 21 out of 25 patients with available plasma samples; mutations in 25 genes were identified at baseline with the most commonly altered genes being *ESR1*, *TP53*, *ERBB2*, *MET*, *PIK3CA* and *PTEN*. Higher number of mutations within a tumor was associated with inferior CBR (P=0.033). *ESR1* mutations were present in baseline plasma samples of 13/25 (52.0%) patients and those patients with *ESR1*-mutated tumors showed inferior clinical benefit and shorter mPFS than patients with wild-type (WT) *ESR1* tumors (1.8 versus 5.4 months, respectively, P=0.0054). Finally, in an exploratory analysis, the authors created a signature of therapeutic resistance including low Rb score, high cyclin E1 score, and the presence of *ESR1* mutation. This signature was independently associated with shorter mPFS: 1.9 months (95% CI: 1.7–3.6) in patients whose tumors were positive for the composite biomarker signature versus 6.7 months [95% CI: 4.1–not applicable (NA)] in those with signature-negative tumors. While a signature such as the one identified by the authors needs to be validated in an independent and larger cohort of patients, it is beginning to give us some clues on why certain patients may not derive benefit from continuation of palbociclib beyond first progression.

Other recent trials have investigated CDK4/6i's in the 2L+ setting in patients who had progressed on either the same or a different CDK4/6i during prior lines of treatment. The phase 2 MAINTAIN trial (NCT02632045) compared ribociclib versus placebo plus switching ET after progression on a CDK4/6i plus ET (15). The study included 120 patients; notably, the majority of patients on both arms (86% on placebo and 87% on ribociclib) received palbociclib as 1L CDK4/6i. mPFS was 5.29 in the ribociclib + ET and 2.76 in the placebo + ET arm, hazard ratio 0.57 (95% CI: 0.39–0.95). The phase 2 PACE study (NCT03147287) was designed to explore the activity of continuing CDK4/6 inhibition with palbociclib beyond progression, with a change of ET to fulvestrant, and to explore the addition of an immune checkpoint inhibitor, avelumab (16), to ET. Two hundred and twenty patients were randomized 1:2:1 to fulvestrant alone, fulvestrant plus palbociclib or fulvestrant plus palbociclib plus avelumab

with the primary objective of comparing PFS between the fulvestrant plus palbociclib versus fulvestrant alone arms. All patients progressed on prior CDK4/6i plus ET and 90.9% of the overall population received prior palbociclib as 1L CDK4/6i. The trial did not meet its primary endpoint of showing superior PFS with continuation of palbociclib post-progression: mPFS was 4.6 months in the fulvestrant plus palbociclib versus 4.8 months in the fulvestrant alone arm (hazard ratio 1.11; 90% CI: 0.74–1.66).

Signatures based on known mechanisms of resistance to CDK4/6i plus ET have been developed in the past. For example, the RBsig gene expression signature of Rb loss-of-function was developed to identify cancer cell lines resistant to palbociclib (17). The tumor suppressor Rb protein is a direct target of cyclin-CDKs that control the G1 to S phase transition of the cell cycle, through binding to the E2F family of transcription factors. Rb is inactivated either by hyperphosphorylation or mutation, which is thought to facilitate cell cycle progression [reviewed in (18)]. RBsig consists of 87 E2F regulated genes, and was found to be prognostic in patients with early-stage HR^+ breast cancers in the METABRIC dataset: patients whose tumors expressed high RBsig had significantly worse recurrence free survival than those with RBsig low tumors (17). RBsig has not been validated in mBC; however, Rb loss of function has been associated with resistance to CDK4/6i plus ET in a small case series of three patients with $HR^+/HER2^-$ mBC who were found to have somatic mutations in Rb by ctDNA analysis at the time of progression (19). However, in the PALOMA-2 and -3 randomized trials, tumor mutational analyses failed to show an association between Rb expression (either at the mRNA or protein level) and resistance to CDK4/6i (20,21). Increased activity of cyclin E has also been implicated in endocrine resistance, including in preclinical cell line models (22) and in some clinical trials [PALOMA-3 (20)] but not others [PALOMA-2 (21), MONALEESA-2 (23)], that evaluated CDK4/6i's as first line treatment for $HR^+/HER2^-$ mBC, suggesting that cyclin E level may be a potential biomarker of resistance only in mBC patients previously treated with ET, which is consistent with the findings of the current study from Albanell *et al.* (14).

ESR1 mutations are frequently acquired (25–40%) in $HR^+/HER2^-$ mBC during ET, particularly in those treated with aromatase inhibitors (AIs) (24). While *ESR1* mutations are thought to be subclonal in resistant breast cancer cells, their effect on response to therapy is not clear. In PALOMA-3, the presence of plasma *ESR1* mutated ctDNA at baseline or 15 days into treatment did not predict clinical outcome (25). In the PACE trial, while the numbers are low, palbociclib continuation beyond progression seemed to have a detrimental effect in patients whose tumors were found to have WT *ESR1* (16). Conversely, in the MAINTAIN trial, the benefit of ribociclib as 2L CDK4/6i seemed limited to *ESR1* WT tumors (15). These conflicting data may reflect the small sample sizes in these trials, the presence of additional pathway alterations such as cyclin D and/or the fibroblast growth factor receptor (FGFR) pathway, as well as different CDK4/6i's being used in 2L setting. In the current study, patients with tumors harboring *ESR1* mutations showed inferior clinical benefit and mPFS compared to *ESR1* WT tumors. Overall, the predictive value of *ESR1* mutations remains unclear in the context of CDK4/6i continuation beyond progression.

Taken together, it remains unanswered whether there is clinical benefit to continuing CDK4/6 inhibition beyond progression and which patients may benefit from this approach. While the MAINTAIN trial showed a small but statistically significant improvement in mPFS with the addition of ribociclib as 2L CDK4/6i, given the heterogenous patient population included in that study with most patients having received palbociclib as 1L CDK4/6i, it is difficult to elucidate whether it was switching CDK4/6i or switching ET that led to a clinical benefit. Exploratory biomarker analyses including *ESR1* mutations and their ability to predict clinical benefit is limited by small numbers and are purely hypothesis generating. So far, there is no evidence that continuing palbociclib with a change in ET after progression on 1L palbociclib provides clinical benefit. While the BioPER study was a single arm trial not designed to show superiority, and cross-trial comparisons should be taken with a grain of salt, the mPFS seen here (3.2 months) is comparable to control arms (fulvestrant alone) of other 2L ET trials (5,7,8). Similarly, the PACE study (16) was not able to show superiority of the continuation of palbociclib beyond first progression (versus fulvestrant alone), raising the possibility that patients progressing on 1L palbociclib may have developed resistance to the drug, although in PACE, there was a suggestion that patients with tumors harboring *ESR1* mutations may continue to derive some benefit from palbociclib, again limited by the small numbers, and in direct conflict with the resistance signature presented in the current article (14). The larger, randomized phase 2 PALMIRA trial (NCT03809988) will try to answer the question of clinical benefit of continuing palbociclib in 198 patients who have progressed on palbociclib plus an AI after deriving clinical benefit from it.

Development of reliable molecular signatures to predict response and resistance to ET combinations is clinically invaluable and could inform selection of agents in second and subsequent line settings in $HR^+/HER2^-$ mBC. The proposed signature presented in Albanell *et al.* represents one such attempt, combining three known markers of endocrine resistance, namely loss of Rb, cyclin E activation and *ESR1* mutations, which will require validation in larger, independent cohorts of patients. Whether their signature predicts clinical benefit in the 2L+ ET setting beyond CDK4/6i combinations remains to be seen; retrospective biomarker analyses of existing biospecimens from ongoing and recently completed trials discussed in this commentary could be used for hypothesis generating and validation purposes. Finally, the signature could be further developed and optimized based on current understanding of resistance mechanisms by including additional parameters know to contribute to endocrine resistance such as those related to PI3K/mTOR/AKT and/or FGFR pathway activation.

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