



# CDK4/6 Inhibition in the Metastatic Setting: Where Are We Headed?

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## Opinion statement

Hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER-2-) metastatic breast cancer (MBC) is the most common subtype of breast cancer. Due to therapeutic advances with molecularly targeted therapies, the prognosis for patients with metastatic disease has improved significantly. The advent of CDK4/6 inhibitors (CDK4/6i) has changed the treatment paradigm for patients with HR+HER2-MBC. CDK4/6i allowed for marked improvement in overall survival, delaying the time to chemotherapy initiation, and improved quality of life for our patients. Efforts are now focused on the best approach(es) for patients after progression on CDK4/6i. Can we further harness the benefit of CDK4/6i in novel combinations at the time of progression? Should we continue CDK4/6i or proceed other novel agents or endocrine therapies? As we advance our treatment strategies for HR+HER2-MBC, there is no longer a one-size-fits-all model, but instead a multifaceted and personalized approach leading to improved outcomes for our patients.

## Introduction: CDK4/6 inhibition in metastatic hormone receptor positive breast cancer

Due to therapeutic advances with molecularly targeted therapies, the prognosis for patients with HR+HER2-MBC has improved significantly, due in large part to the approval of CDK4/6i [1]. The landmark, phase III trials leading to the FDA approval of CDK4/6i demonstrated a striking OS benefit of 60 months or more in postmenopausal women and men [2•, 3, 674•, 5•, 8•]. The trials showed a similar improvement in PFS from 14 to 25–30 months when used in combination with ET, rather than ET alone [9–13, 14]. Likewise, CDK4/6i demonstrated PFS improvement in the second line with fulvestrant in patients who progressed on an AI alone or had metastatic relapse on adjuvant AI within 12 months or more [12, 14–16, 17] (Table 1).

In premenopausal women, the efficacy of CDK4/6i has been studied in a randomized fashion in the front-line setting in the MONALEESA-7 study where ribociclib was used in combination with goserelin and tamoxifen or an AI. The improvement in PFS seen in the ribociclib arm was similar to that seen in postmenopausal women in MONALEESA-2; therefore, ribociclib is the CDK4/6i of choice in the first line for premenopausal women [29]. In the second line setting, palbociclib and fulvestrant are approved irrespective of menopausal status, based on PALOMA-3 which included premenopausal women who received goserelin [30]. Abemaciclib can also be used in premenopausal patients in the second line setting with fulvestrant based on data with 72 pre/perimenopausal patients in combination with a GnRH agonist with a significantly improved PFS and overall response rate (ORR) with a generally tolerable safety profile [3].

In patients with brain metastasis or leptomeningeal involvement, clinicians often preferentially turn to abemaciclib as the CDK4/6i of choice based on data from Tolaney et al., in which abemaciclib was found to have an intracranial clinical benefit rate of 24% in patients with heavily pretreated HR+MBC. Abemaciclib was proven to cross the blood brain barrier, achieving therapeutic concentrations in brain tissue [31]. Both palbociclib and ribociclib may have CNS activity; however, these agents have not been specifically studied in this population.

Even in patients with aggressive, life-threatening disease, the practice of giving chemotherapy rather than CDK4/6i in the first line, is quickly changing with results of the phase II RIGHT Choice trial. For patients treated with ribociclib plus ET in visceral crisis, a 1-year improvement in PFS was seen when compared with combination chemotherapy (24 months ribociclib vs. 12.3 months chemotherapy). Additionally, ribociclib with ET had a similar median time to treatment response as compared to combination chemotherapy (4.9 months ribociclib vs. 3.2 months chemotherapy), moving CDK4/6i to the forefront as the preferred, front-line therapy, even for this patient population with aggressive disease [32•].

Preclinical and clinical efforts are ongoing to better understand resistance mechanisms to CDK4/6i. Investigators are evaluating novel strategies with targeted combinations to inhibit crosstalk between pathways of resistance. Approaches include combining CDK4/6i with SERDs, FGFR3, ERK, AKT, CDK2, and mTOR/PI3K inhibitors, with the goal of improving outcomes for our patients on CDK4/6i.

**Table 1. Clinical trials demonstrating the benefit of CDK4/6 inhibition in the metastatic setting: first line, second line, and beyond**

CDK4/6 in the front line setting		CDK4/6 in the metastatic setting: first line, second line, and beyond						
CDK4/6 inhibitor	Dosing schedule	Side effects	Clinical trial	Intervention	Population	PFS Δ (months)	OS Δ (months)	Statistical significance
Ribociclib (Kisqali)	600 mg daily	Neutropenia QTc prolongation Creatinine increase ALT increase Fatigue	MONALEESA-2 [18]	Ribociclib + AI	Postmenopausal	9	12.5	Yes
Palbociclib (Ibrance)	3 weeks on 1 week off	Neutropenia ALT Increase Fatigue	MONALEESA-3 [3, 19, 20]	Ribociclib + Fulvestrant	Postmenopausal and men	15	NR*	Yes
	125 mg daily		MONALEESA-7 [21]	Ribo + AI/Tam + OS	Premenopausal	10	11	Yes
Abemaciclib (Verzenio)	3 weeks on 1 week off	Grade 3 Diarrhea Neutropenia Creatinine increase ALT increase Fatigue	PALOMA-2 [8••]	Palbociclib + AI	Postmenopausal	10	3	No
	150 mg twice daily		MONARCH-3 [4••]	Abemaciclib + AI	Postmenopausal	28/15	12	Trend. Additional follow-up
CDK4/6 in the second line setting		Intervention						
Clinical trial		Primary endocrine resistance <sup>†</sup>						
MONALEESA-3 [3, 19, 20]		Ribociclib + Fulvestrant			Post CDK4/6i (%)	PFS Δ (months)	OS Δ (months)	Statistical significance
MONARCH-2 [22]		Abemaciclib + Fulvestrant			14 vs. 30	5.5	6	Yes
PALOMA-3 <sup>#</sup> [23]		Palbociclib + Fulvestrant			7.9 vs. 20.2	7.6	8.5	Yes
					7.5 vs. 22.7	4.9	6.9	No

**Table 1.** (continued)

Continuation of CDK4/6i at time of progression						
Clinical trial	Intervention	Phase	Prior CDK4/6i exposure	PFS (months) OS (months)	Statistical significance	
PACE [24*]	Fulvestrant vs Palbo + Fulv vs Palbo + Fulv + Avelumab	Phase II	90.9% palbociclib 4.5% ribociclib 4.1% abemaciclib	4.8 vs N/A 4.6 vs 8.1	Yes	
MAINTAIN [25*]	Ribo + Exemestane/Fulv vs. Placebo + ET	Phase II	84% palbociclib 11% ribociclib 2% abemaciclib	5.29 vs N/A 2.76	Yes	
postMONARCH [26]^	Abema + Fulv vs Placebo + Fulv	Phase III	Prior CDK4/6i + AI in front-line metastatic setting or adjuvant setting	N/A	N/A	
ELEVATE [27]^	Arm A: Elacestrant + Alpelisib Arm B: Elacestrant + Everolimus Arm C: Elacestrant + Abema or Ribo Arm D: Elacestrant + Palbo, Abema, or Ribo	Phase I/II	Arm C: Patients must have had prior CDK4/6i + ET in metastatic setting, CDK4/6i on trial must be different than frontline CDK4/6i received Arm D: No prior CDK4/6i, only 1–2 prior ETs in metastatic setting allowed	N/A	N/A	
EMBER-3 [28]^	Imlunestrant vs Exemestane or Fulv vs Imlunestrant + Abema	Phase III	Prior CDK4/6i + AI or AI alone in front-line metastatic setting or adjuvant setting	N/A	N/A	

The table shows pharmacologic differences between the CDK4/6 inhibitors ribociclib, palbociclib, and abemaciclib and their respective randomized, phase III trials demonstrating a PFS and OS benefit of CDK4/6 inhibitors plus ET in the first line and second line settings for the treatment of HR+HER-MBC. Further randomized trials are described evaluating continuation of CDK4/6 inhibition after progression on prior CDK4/6 inhibitor + ET

\*ESMO 2022 update with 70.8 mo follow-up for 1st line where OS not yet reached in first line patients. An exploratory analysis of first line ribociclib+fulvestrant reports mOS of 67.7 months

†Sensitivity to previous endocrine therapy was defined as either a documented clinical benefit (complete response, partial response, or stable disease for >24 weeks) from at least one previous endocrine therapy regimen in the context of metastatic disease or the receipt of at least 24 months of adjuvant endocrine therapy before recurrence

#Beyond second line

^Studies with ongoing recruitment: postMONARCH, EMBER-3, ELEVATE

## The great debate: overall survival differences between CDK4/6 inhibitors in the frontline

Despite different designs for the landmark trials evaluating CDK4/6i with ET, the hazard ratios for PFS are strikingly similar (HR 0.54–0.58) (Table 1). As OS data for the randomized trials matured, however, there are apparent differences among the studies, causing clinicians to question which CDK4/6i is the best first line choice for postmenopausal women or men with HR+HER2-MBC.

The randomized, phase III studies involving ribociclib and abemaciclib for use in the frontline have demonstrated an OS benefit compared to ET alone (MONALEESA-2, MONALEESA-3, MONALEESA-7, and MONARCH-3). Palbociclib, alternatively, did not demonstrate an OS benefit in PALOMA-2 where the mOS was numerically longer in the experimental arm (53.9 months with palbociclib and 51.2 months with placebo), but not statistically significant overall (HR 0.956 [95% CI, 0.777–1.777]  $p=0.3378$ ) [6].

The difference in OS data in PALOMA-2 could be attributed to a number of factors. Follow-up was not available on notable proportion of patients (21% in placebo arm versus 13% in the palbociclib arm). Due to the regulatory approval of palbociclib during the conduct of PALOMA-2, patients likely withdrew consent to receive commercial CDK4/6i outside of the trial. A post hoc sensitivity analysis, which excluded the patients lost to follow-up, resulted in a mOS of 51.6 months for palbociclib versus 44.6 months for placebo (HR 0.869 [95% CI, 0.706–1.069] [6].

As these studies did not directly compare ribociclib and palbociclib, the results from each trial could truly reflect a difference in efficacy. Many clinicians offer ribociclib as the frontline CDK4/6i of choice, given the mature, statistically significant OS data. Despite abemaciclib demonstrating a consistent OS benefit in randomized phase III trials, ribociclib currently remains the preferred CDK4/6i due to less gastrointestinal issues compared to abemaciclib. Further head-to-head comparison trials are needed to answer the debate as to which CDK4/6i is best in the frontline. This study design will be pursued in the HARMONIA trial, which will randomize patients to receive either palbociclib or ribociclib and address the question of which CDK4/6i is best in the frontline in HER2-enriched patients (NCT05207709).

## Continuing a CDK 4/6 inhibitor at the time of progression

Identifying best treatment options following progression on CDK4/6i remains an unmet medical need. One strategy is sequential CDK4/6i after progression. Two phase II randomized trials have been reported evaluating this approach: PACE (evaluating continuation of palbociclib with a change in ET backbone and/or with immunotherapy) and MAINTAIN (changing the CDK4/6i and ET backbone) (Table 1).

The PACE trial is a multicenter, phase II study, in which patients who progressed on prior CDK 4/6i were randomized 1:2:1 to fulvestrant plus palbociclib, fulvestrant alone, fulvestrant plus palbociclib, and avelumab. Palbociclib was the most prevalent CDK4/6i used in the frontline (90.9%), with a minority of patients receiving ribociclib (4.5%) and abemaciclib (4.1%). After a median follow-up of 23.6 months, mPFS was 4.6 months in the fulvestrant + palbociclib arm, 4.8 months in the fulvestrant arm, and 8.1 months in the triplet arm with avelumab. The OS was longer in the avelumab arm than in the other two arms (24.6 vs. 27.5 vs. 42.5 months, respectively). The PACE trial was powered to evaluate the treatment effect of palbociclib with fulvestrant; therefore, data from the avelumab arm is exploratory in nature and has not led to a change in the standard of care. The continued use of palbociclib after progression with adjustment of the ET backbone did not provide a clinical benefit and is therefore not recommended as a treatment strategy at this time [24•].

The phase II MAINTAIN trial evaluated the efficacy of fulvestrant or exemestane +/– ribociclib in patients who had progressed on prior CDK 4/6i (84% palbociclib, 11% ribociclib, 2% abemaciclib). The fulvestrant or exemestane + ribociclib arm had a statistically significant improvement in PFS at 5.33 months versus 2.76 months in the placebo arm (HR = 0.56 (95% CI: 0.37–0.83),  $p = 0.004$ ). At 6 months, 42% in the ribociclib arm versus 24% on the placebo arm had not progressed. While at 12 months, 25% in the ribociclib arm versus 7% on the placebo arm had not progressed [25•]. These data are now mentioned in NCCN guidelines. It is important to reiterate that MAINTAIN was not a registration trial and did not lead to a change in the label; however, this offers initial evidence that patients benefit from treatment with ribociclib in combination with a switch in their ET backbone after progression on prior CDK4/6i and ET. The hazard ratio for patients who received prior ribociclib was similar to those who received prior palbociclib; however, only 14/199 evaluable patients received prior ribociclib.

The postMONARCH phase III, global, randomized study aims to evaluate whether continuation of abemaciclib with a switch in the ET after progression on a prior CDK4/6i may provide benefit. Eligible patients are randomized 1:1 to receive abemaciclib or placebo plus fulvestrant. Patients who experience a metastatic recurrence on or after treatment with CDK4/6i in the adjuvant setting are also eligible, making this the first study to evaluate this cohort of patients. Completion of accrual is anticipated in summer 2023. We are hopeful the results will guide the optimal therapy following metastatic relapse now that CDK4/6i are deployed in the adjuvant setting and yield another treatment option for our patients [26] (Table 1).

## Mechanisms of resistance to CDK4/6 inhibitors

Due to the numerous resistance mechanisms, even the best responders have decreased efficacy of CDK4/6i overtime; however, patients who develop acquired resistance still demonstrate durable clinical benefit

typically exceeding 6 months. Many driver events are implicated in resistance to CDK4/6i impacting both intrinsic and acquired resistance from changes in *RB1*, *AURKA*, *CCNE1/2*, *CDK2*, *AKT/mTOR*, *RAS/MAPK*, *FGFR1/2*, and *ERRB2* (Table 2). We will briefly highlight the biologic mechanisms proposed to cause resistance to CDK4/6i and the ongoing efforts to address these pathways of resistance and improve clinical outcomes for patients.

### Loss of retinoblastoma protein (Rb1)

The tumor suppressor protein *Rb1* is a key checkpoint in the cell cycle. Constitutive activation of the cell cycle can occur when there are mutations in *Rb* via activation of E2F and cycle-CDK2 axis. With loss of *Rb1*, there is no longer dependence on CDK4/6. In PALOMA-3, ctDNA was enriched with *Rb1* mutations in patients who progressed on palbociclib (1/127 versus 0/68 in placebo arm) [33]. Clinical and preclinical data show *Rb1* loss can cause de novo resistance to CDK4/6i. Loss of function mutations in *Rb1* found in CDK4/6 naive tumors portend a worse prognosis with decreased PFS [34, 35]. Breast cancer cell lines with acquired resistance to CDK4/6i with *Rb1* loss had enhanced sensitivity to the novel AURKA inhibitor (Aurora Kinase A), a serine/threonine kinase that contributes to the regulation of cell cycle progression [36]. A phase Ib trial with erbumine (AURKA inhibitor) after progression on a CDK4/6i is underway. In this early phase trial, a patient with MBC treated with erbumine derived a clinical benefit for 11 months after progression on prior CDK4/6i [36]. Future studies are needed to evaluate if AURKA inhibitors with CDK4/6i could prevent the development of acquired resistance to CDK4/6i.

### CCNE1/2 and CDK2 amplification

Cyclin E-CDK2 phosphorylates *Rb1*, allowing release of E2F, causing progression of the cell cycle of G1 to S phase. *CCNE1* encodes cyclin E and, when overexpressed, causes resistance to CDK4/6i [35, 37]. Some CDK4/6i-resistant cells in preclinical studies lose dependence on cyclin D1-CDK4/6 signaling and use the MAPK-AKT signaling cascade or bypass through the PI3K/AKT/mTOR pathway. In preclinical studies, the CDK2 inhibitor roscovitine allowed evasion of resistance to CDK4/6i in *CCNE1*-amplified cells [35]. There is an ongoing phase I/II trial evaluating the CDK2 inhibitor, PF-07104091, with and without palbociclib and letrozole to evaluate if inhibition of cyclin E-CDK2 may be a successful strategy to overcome resistance (NCT04553233).

Notably, when *CHK1* regulates CDK2 activity in breast cancer cells, the cells do not tolerate activity in S-phase [38]. In applying this knowledge,

CCNE2-amplified breast cancer cells were sensitive to *CHK1* inhibition with prexasertib [36], proposing *CHK1* inhibition as another way to combat resistance to CDK4/6i. Prexasertib is currently being evaluated in combination with chemotherapy in several advanced cancers, including breast cancer (NCT02124148).

## FGFR1/2 activation

Fibroblast growth factor receptor (FGFR) signaling pathways are key players in cell differentiation and survival [39] and are responsible for resistance to CDK4/6i and ET [40, 41]. *FGFR1* activates the RAS/MEK/ERK and PI3K/AKT pathways in endocrine-resistant breast cancer [39]. In preclinical models, *FGFR1* activation causes resistance to palbociclib with fulvestrant [42]. Furthermore, *FGFR1* signaling via *FGFR2* promotes endocrine resistance and CDK4/6i resistance [39]. Through ctDNA analysis from PALOMA-3, acquired *FGFR2* mutations or amplification events were present in 4/195 patients at the time of disease progression and were associated with worse PFS [33, 43]. Similarly, in analysis of ctDNA from the MONALEESA-2 study, patients with *FGFR1* amplification events had inferior PFS (10.61 months vs. 24.84 months  $p = 0.075$ ). The higher the level of *FGFR1* expression, the shorter the PFS [44].

Researchers have found *FGFR1/2* amplified breast cancer cells with resistance to CDK4/6i can be re-sensitized to CDK4/6i through treatment with FGFR inhibitors such as lucitanib and erdafitinib [44, 45]. A phase Ib trial, with erdafitinib, an FGFR inhibitor, is being given with palbociclib and fulvestrant in patients with FGFR-amplified tumors that progressed on prior CDK4/6i (NCT03238196). The correlative objectives of this study will be important in determining the therapeutic predictive role of *FGFR1-4*, *CCND1-2*, *CDK4*, and *CDK6* amplifications, *Rb1* and *ESR1* mutations on clinical outcomes. *FGFR1* amplification levels will also be evaluated as an early surrogate of response. In parallel, a phase II trial is recruiting patients to investigate activity of TAS-120, an FGFR inhibitor currently approved for the treatment of cholangiocarcinoma, with fulvestrant in patients treated with a prior CDK4/6i (NCT04024436).

Another possible strategy to target *FGFR1/2* upregulation is through downstream targets via the MAPK or AKT/mTOR pathways, as key players in these pathways are overexpressed in *FGFR1/2* amplified cells [45]. To this end, *FGFR1/2* amplified cells have been sensitive to treatment with meiotic chromosome-axis-associated kinase (MEK) inhibitors and SH2 containing protein tyrosine phosphatase-2 (SHP2) inhibitors [45]. A randomized phase II trial evaluated the efficacy of selumetinib, a MEK inhibitor, with fulvestrant in patients with HR+MBC who progressed on prior AI therapy. This trial stopped accrual early as the experimental arm did not reach the pre-specified disease control rate (DCR). DCR was 23% with selumetinib + fulvestrant and 50% with placebo ( $n = 46$ ). The addition of selumetinib to fulvestrant may have deteriorated the efficacy of ET in some patients [46]. Alternatively, a



**Table 2. Common mechanisms of resistance to CDK4/6 inhibition, potential targets, and clinical investigations underway to target patterns of resistance**

Mechanism of resistance	Potential target	Investigational agent	Clinical trials
Loss of Rb1	Inhibition of cycle E-CDK2 axis	PF-07104091	Phase I/II CDK2 inhibitor (PF-07104091) with and without palbociclib and letrozole (NCT04553133)
	AURKA inhibition	Erbumine (LY3295668)	Phase I/II erbumine in metastatic solid tumors (NCT03092934) Phase Ib erbumine with or without ET after progression on CDK4/6i (NCT0395939)
		Alisertib	Phase II alisertib with or without fulvestrant in endocrine-resistant advanced breast cancer (NCT02860000)
CCNE1/2 CDK2 amplification	CDK2 inhibition	Roscovitine PF-07104091	Phase I/II CDK2 inhibitor (PF-07104091) with and without palbociclib and letrozole (NCT04553133)
	CHK1/2 inhibition	Prexasertib (LY2606368)	Phase Ib trial of prexasertib with chemotherapy in advanced cancers (NCT02124148)
FGFR1/2 upregulation	FGFR inhibition	<i>Lucitanib</i> <sup>*</sup> <i>Erdafitinib</i> <sup>*</sup> Futibatinib (TAS-120)	Phase II trial of futibatinib plus fulvestrant in patients with advanced, HR+breast cancer with FGFR amplification (NCT04024436)
	MEK1/2 inhibition	Selumetinib	Phase II trial of MEK1/2 inhibitor selumetinib, with and without fulvestrant in HR+advanced breast cancer after progression on AI therapy (NCT01160718)
	SHP inhibition	JAB3312	Phase I trial of JAB3312, SHP2 inhibitor, in advanced breast cancer (NCT04045496)
AKT/mTOR RAS/MAPK activation	AKT inhibition	Ipatasertib	TAKTIC: Phase Ib trial evaluating combination of AKT inhibitor, ipatasertib with fulvestrant, AI, or triple combination with fulvestrant+palbociclib (NCT03959891)
	ERK inhibition	LY3214996	Phase I study of ERK inhibitor, LY3214996, with and without abemaciclib in advanced HR+ breast cancer (NCT02857270)
ERBB2 activation	HER2 blockade	Neratinib	SUMMIT trial: neratinib+fulvestrant+trastuzumab for HR+, HER2 negative, HER2 mutant metastatic breast cancer (NCT01953926) NEREA trial: targeting EGFR/ERBB2 with neratinib in HR+/HER2-negative, HER2-enriched ABC (terminated early due to lack of funding)

<sup>\*</sup>Investigational agents evaluated in preclinical setting

first-in-human phase I study of JAB-3312, an SHP inhibitor, is underway in patients with MBC (NCT04045496) and may potentially prove a more effective method to prevent the upregulation of *FGFR1/2* and in turn CDK4/6i resistance.

### RAS/MAPK and AKT/mTOR activation

Activating mutations in *RAS* oncogenes are identified in tumor biopsy specimens from patients resistant to CDK4/6i. Efforts to overcome these mechanisms of resistance are ongoing through the evaluation of the ERK1/2 inhibitor, LY321499 in phase I study with and without abemaciclib in HR+MBC (NCT02857270).

AKT inhibition has proven an effective method to treat HR+HER2-tumors with resistance to ET through the promising phase III CAPItello-291 trial with capivasertib. Capivasertib plus fulvestrant doubled the PFS compared to placebo with fulvestrant in patients who had progressed on prior AI [47]. The TAKTIC trial evaluates the additional efficacy of combining AKT inhibition with CDK4/6i in patients who have progressed on prior CDK4/6i. The AKT1 inhibitor, ipatasertib, was given in the phase Ib/II setting with an AI, fulvestrant, or triplet combination (fulvestrant + ipatasertib + palbociclib). Eighty-four percent of patients enrolled were treated with a prior CDK4/6i. The clinical benefit rate (CBR), defined as the percentage of patients who achieved a partial response or stable disease for 6 months or more, was 48% across the study with a 57% benefit in those who were on triplet therapy. The triplet cohort had a mPFS of 5.5 months and mOS of 24.5 months ( $n = 77$ ) [48] and was generally well tolerated overall, suggesting the addition of AKT inhibition to a CDK4/6i may be helpful to prolong the efficacy of continued CDK4/6i in the second line.

### ERBB2 activation

Beyond *ERBB2*'s known involvement in oncogenic signaling causing endocrine resistance, preclinical work has determined *ERBB2* activation mutations bestow resistance to CDK4/6i [49, 50]. Wander et al. found *ERBB2* mutations in 5 of 41 patients with resistance to CDK4/6i. *ERBB2* mutant cell lines activate downstream signaling pathways such as MAPK and AKT/mTOR, further highlighting the importance of crosstalk between multiple mechanisms of resistance to CDK4/6i [36].

In preclinical models, cells with *ERBB2* activating mutations were sensitive to HER2 kinase inhibition with neratinib [50]. These data prompted the phase II SUMMIT trial which evaluated the combination of fulvestrant + neratinib + trastuzumab in patients with prior exposure to CDK4/6i with metastatic HER2 mutant breast cancer. In patients receiving triple therapy ( $n = 45$ ), objective response rate was 38%, with a CBR of 21 months, median duration of response of 14.4 months, and mPFS of 8.2 months [51] (NCT01953926).

## Novel combinations carrying CDK4/6 inhibitors into the future

Novel combination studies are being investigated to seek creative ways to prolong the clinical benefit of CDK4/6i. Ongoing innovative combinations with SERDs and mTOR/PI3K inhibitors are key areas of interest.

### CDK4/6 inhibitors plus SERD

Important progress has been made in the investigation of novel ER degraders and antagonists to address the challenge of endocrine resistance [52]. Orally bioavailable SERDs, which bind the estrogen receptor causing degradation and downregulation, have shown promising activity, especially in patients with ESR1 mutations. In January 2023, the FDA approved the first oral SERD, elacestrant, for use by postmenopausal women and men with ESR1 mutated tumors, who have progressed on at least one prior ET, including a CDK4/6i [53]. Data from the EMERALD trial revealed the duration of prior treatment with CDK4/6i impacted the PFS benefit of elacestrant, regardless of ESR1 status. Specifically, for those with ESR1 mutations, 6, 12, and 18 months of prior CDK4/6i treatment, correlated with a PFS of 4.14, 8.61, and 8.61 months, respectively [54]. Based on the extended PFS benefit, elacestrant is being explored with other targeted agents (alpelisib, everolimus, CDK4/6i) with ET in the phase Ib/II ELEVATE trial in patients who have received prior AI and CDK4/6i. The design of the ELEVATE trial will also shed light on the utility of continued CDK4/6i after progression. While one of the study arms utilizing CDK4/6i in combination allows for prior CDK4/6i exposure, the other CDK4/6i combination arm will enroll patients treated only with ET, not prior CDK4/6i (Table 1) [27].

The next-generation oral SERD, camizestrant, also improved PFS when compared with fulvestrant in the phase II SERENA-2 trial in patients who progressed on at least one ET. Randomization is stratified so 50% of patients had prior CDK4/6i exposure. Camizestrant improved outcomes in patients with ESR1 mutated tumors, with a PFS benefit of 9.2 months (150 mg) vs. 2.2 months with fulvestrant [55]. Early results led to the phase III SERENA-6 trial assessing the combination of camizestrant with palbociclib or abemaciclib vs. AI plus CDK4/6i in patients with ESR1 mutations. In this trial, ctDNA is checked every 8–12 weeks, while patients are treated with CDK4/6i and AI. If an ESR1 mutation develops, patients are randomized to continue their current therapy or switch to camizestrant with CDK4/6i. This trial will answer several important questions: whether combining an oral SERD with CDK4/6i at the first indication of endocrine resistance will improve outcomes and whether ctDNA can tell us how well therapy is working in real time [28]. By addressing these unmet needs, SERENA-6 was granted fast track designation by the FDA. SERENA-4 is also investigating camizestrant plus palbociclib for use in the first line setting [56].

Imlunestrant, another next generation oral SERD, is being studied in combination with abemaciclib with or without ET in the EMBER phase I study. No safety signals or dose-limiting toxicities were identified in phase I. The majority of treatment-related adverse events (TrAEs) included grade 1 nausea (33.3%), fatigue (27.5%), and diarrhea (23.2%) [57], which are similar to the TrAEs seen with abemaciclib alone. EMBER-3, is a phase III, randomized study comparing imlunestrant versus exemestane or fulvestrant in patients who progressed on prior AI or CDK4/6i. One arm will include imlunestrant plus abemaciclib with the primary endpoint of PFS. Key secondary endpoints are OS and ORR [58] (Table 1).

### CDK4/6 plus mTOR/PI3K inhibitor

Further trials are underway to investigate triplet therapy with CDK4/6i, ET, and a third additional therapeutic, targeting the mTOR or PI3K pathways. The TRINITY-1 phase I/II trial explored the triplet combination of ribociclib, everolimus, and exemestane in patients who progressed on prior CDK4/6i. At week 24, the CBR was 41.1% (95% CI 31.1–51.6%), which met the primary endpoint; however, due to drug-drug interactions with everolimus and ribociclib, this triplet combination is not moving forward into development [59].

A separate, multicenter, phase Ib study evaluating a different triplet combination with ribociclib, fulvestrant, and a PI3K inhibitor (buparlisib or alpelisib) stopped enrollment early due to unexpected toxicity, further demonstrating the difficulty of establishing safe and tolerable triplet therapy regimens in this setting [60].

A larger, phase II/III trial is recruiting 400 participants to study the efficacy and safety of palbociclib, fulvestrant, and inavolisib, a PI3K alpha-inhibitor, versus palbociclib, fulvestrant, and placebo in patients who progressed during treatment or within 12 months of completing adjuvant ET and have not received systemic therapy for metastatic disease (NCT04191499). Data from this trial will highlight whether bringing a PI3K inhibitor forward in combination with CDK4/6i earlier in the metastatic setting will be important for our patients with PI3KCA mutations.

A first-in-class pan-PI3K/mTOR inhibitor, gedatolisib, is being investigated in combination with palbociclib and ET. Gedatolisib has unique pharmacokinetic properties different from other currently approved therapies that target PI3K or mTOR alone [61]. In this phase Ib trial, arm A received gedatolisib plus palbociclib/letrozole first line; arm B received gedatolisib plus palbociclib/fulvestrant (CKD 4/6i naïve); arm C & D had previous treatment with CKD4/6i and received gedatolisib plus palbociclib/fulvestrant. In arm C, gedatolisib was dosed weekly, and in arm D, gedatolisib was dosed 3-weeks-on and 1-week-off. The most common grade 3 or 4 adverse events included stomatitis, neutropenia, and fatigue. Overall, the favorable safety profile and antitumor activity supports the use of the 3-weeks-on, 1-week-off dosing schedule with triplet therapy.

Based on these results, the phase III VIKTORIA-1 trial is further evaluating the efficacy of gedatolisib plus fulvestrant with or without palbociclib vs. standard of care following progression on CDK4/6i (NCT05501886). The primary

outcome is OS, and key secondary outcomes include ORR, and duration of response in PIK3CA wild type and PIK3CA mutated breast cancers. Treatment arms are randomized according to PIK3CA mutational status. The trial began enrolling patients in fall 2022 with expected primary completion in 2024.

These studies exemplify the devotion to significant efforts aimed at overcoming resistance and evasion to ET, further employing the profound effect of CDK 4/6i for our patients with HR + HER2-MBC. Results from these trials will inform clinical decisions regarding CDK4/6i in later-line treatments and better elucidate a strategy for utilizing continued CDK4/6i after disease progression in the first line. In summary, these novel combination strategies will continue to shape our treatment paradigm for later-line treatment options for HR + HER2-MBC.

## Conclusions

CDK4/6i as the recommended, standard, first-line treatment for patients with HR + HER2-MBC continues to make a meaningful impact in the lives of our patients. Ribociclib has become the CDK4/6i of choice in the first line due to OS data and more tolerable side effect profile, even in patients with visceral crisis. Efforts focused on the best approaches for patients after progression on CDK4/6i have shown benefit when switching from palbociclib to ribociclib with a new ET backbone such as exemestane or fulvestrant. Triplet regimens with SERDs and targeted therapies with ET and/or CDK4/6i are underway in hopes to delay resistance to CDK4/6i. Many questions remain. After progression on CDK4/6i, should we use a single agent or combination? Should the combination involve another CDK4/6i? How do we best sequence various agents or combinations? Ultimately, multifaceted treatment options involving CDK4/6i will exist, allowing us to take a personalized approach to the treatment of patients with HR + HER2-MBC.

## Compliance with Ethical Standards

### Conflict of Interest

Elizabeth Sakach declares she has no conflict of interest. Merve Keskinilic declares she has no conflict of interest. Sarah Wood declares she has no conflict of interest. Madison Canning declares she has no conflict of interest. Kevin Kalinsky reports advising/consulting for Genentech/Roche, Immunomedics, Seattle Genetics, Oncosec, 4D pharma, Daicichi Saknyo, Puma Biotechnology, Mersna, Menarini Silicon Biosystems, Myovant Sciences, Takeda. His spouse is currently an employee at EQRX.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human and animals subjects performed by any of the authors.

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- Of importance
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