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REVIEW

Addressing physician barriers to administering cyclin-dependent kinases 4 and 6 inhibitors in first-line treatment of hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer

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Abstract: Combination therapy with a cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor and an aromatase inhibitor (AI) for first-line treatment of postmenopausal women with advanced breast cancer (ABC) has demonstrated improvement in progression-free survival (PFS) over AI monotherapy without adding substantial toxicity. However, CDK4/6 inhibitor plus AI therapy is not uniformly used as first-line therapy for ABC, indicating that barriers to CDK4/6 inhibitor use exist. Such barriers may include the following perceptions: patients with bone-only metastases, with a long disease-free interval, or who are older may respond to AI monotherapy and may not benefit from a CDK4/6 inhibitor; tumor response rates may be lower and delayed with CDK4/6 inhibitor plus AI therapy than chemotherapy; the increased incidence of adverse events with CDK4/6 inhibitor plus AI therapy outweighs benefits; and the cost of CDK4/6 inhibitors may be prohibitive. Some of these barriers are addressed with data from follow-up analyses of CDK4/6 inhibitor trials, which have shown a PFS benefit of combination therapy in all subgroups assessed, including older patients, those with bone-only metastatic disease, and those with a long disease-free interval. Tumor response rates with CDK4/6 inhibitor plus AI therapy are comparable to those with first-line cytotoxic chemotherapy. Finally, adverse events associated with CDK4/6 inhibitor plus AI therapy are manageable and occur with decreasing severity during treatment, with similar reports of quality of life to those with AI monotherapy. These data support CDK4/6 inhibitor plus AI therapy as the standard of care in first-line treatment of ABC.

Keywords: aromatase inhibitor, ribociclib, palbociclib, abemaciclib

Introduction

Breast cancer is the most frequently diagnosed cancer and a leading cause of cancer deaths in women in the United States, with an estimated 266,120 new cases and 40,920 deaths in 2018.[1] Approximately 71% of breast cancer cases are hormone receptor–positive (HR+; estrogen receptor–positive [ER+] or progesterone receptor–positive) and human epidermal growth factor receptor 2–negative (HER2−).[2] In HR+, HER2− advanced postmenopausal breast cancer, aromatase inhibitor (AI) monotherapy is the standard-of-care treatment.[3] However, progression is inevitable in the advanced setting, with most patients progressing on AI monotherapy within 13–16 months of treatment, as demonstrated in published studies.[4,5] Thus, providing a first-line therapy that extends

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the duration of response to treatment while maintaining quality of life (QoL) is critical for this population of patients with advanced breast cancer (ABC).

Five randomized Phase II or III trials of the cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors palbociclib, ribociclib, and abemaciclib in combination with an AI have provided evidence of prolonged progression-free survival (PFS) with combination therapy compared with AI monotherapy.[6–10] CDK4/6 inhibitors have been approved for use since palbociclib was approved in 2015 on the basis of PALOMA-1 trial results.[11–13] However, many physicians continue to prescribe AI monotherapy or chemotherapy to patients with HR+, HER2− metastatic breast cancer in the first-line setting.[14,15] Here, we briefly review the overall findings from clinical trials of CDK4/6 inhibitors in the first-line setting, present physician barriers to use of CDK4/6 inhibitor combination therapy in the first-line setting, and review current data that address these barriers.

Addressing barriers to use of CDK4/6 inhibitor combination therapy in the first-line setting

Five clinical trials, including four Phase III trials, have investigated the use of CDK4/6 inhibitors in combination with an AI in first-line treatment of HR+, HER2− ABC.[6–10,16] Although these trials enrolled similar patient populations overall, with some notable exceptions (the MONALEESA-7 trial [ribociclib] included only premenopausal women), there are certain patient characteristics that were represented to a greater extent in some trials than others. For example, there were more Asian patients in the MONARCH 3 trial (abemaciclib) and MONALEESA-7 trial (ribociclib) than other trials (Table 1).[7,8,10,16] Thus, caution is advised when comparing individual trial efficacy and safety because conclusions from such comparisons are limited by differences in trial design and patient population.

The overall efficacy and safety of CDK4/6 inhibitors in combination with AIs in the first-line setting are summarized in Tables 2 and 3. As of the latest interim data cutoff dates for the Phase III trials, the median PFS in patients receiving a CDK4/6 inhibitor in combination with an AI ranged from 25.3 to 27.6 months (the median PFS was not reached at a median follow-up of 17.8 months in the MONARCH 3 trial).[8–10,17] Median PFS for the AI control group ranged from 13.0 to 16.0 months.[8–10,17] Combination therapy with CDK4/6 inhibitors was associated with an increased rate of asymptomatic neutropenia vs AI monotherapy, as well as other hematologic adverse events (AEs), nausea, diarrhea, fatigue, and alopecia (Table 3).[7–10]

Table 1 Baseline characteristics of patients enrolled in trials of CDK4/6 inhibitors plus an AI for first-line treatment of HR+, HER2– ABC

	MONALEESA-2[16]		MONALEESA-7[10]		MONARCH 3[8]		PALOMA-2[7]	
	RIB + LET (n=334)	PBO + LET (n=334)	RIB + TAM or NSAI (n=335)	PBO + TAM or NSAI (n=337)	ABE + NSAI (n=328)	PBO + NSAI (n=165)	PAL + LET (n=444)	PBO + LET (n=222)
Median age, years	62	63	43	45	63	63	62	61
ECOG PS, %								
0	61	60	73	76	58	63	58	46
1	39	40	26	23	42	37	40	53
2	0	0	0	<1	0	0	2	1
Race, %								
White	81	84	56	60	57	62	77	78
Asian	8	7	30	29	31	27	15	14
Other or unknown	11	9	15	11	3	4	8	9
Visceral disease, %	59	59	58	56	52	54	48	50
Bone-only disease, %	21	23	24	23	21	24	23	22
De novo metastatic disease, %	34	34	41	40	41	37	38	36
Prior (neo)adjuvant ET, %	52	51	38	42	46	48	56	57
Prior TAM, %	42	43	Not reported	Not reported	Not reported	Not reported	47[a]	44[a]
Prior CT, %	44[b]	43[b]	41[b]	41[b]	38	40	48[b]	49[b]

Notes: [a]In the adjuvant setting only. [b]In the neoadjuvant or adjuvant setting.

Abbreviations: ABC, advanced breast cancer; ABE, abemaciclib; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinases 4 and 6; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; LET, letrozole; NR, not reported; NSAI, nonsteroidal aromatase inhibitor; PAL, palbociclib; PBO, placebo; RIB, ribociclib; TAM, tamoxifen.

Table 2 Overall efficacy reported in trials of CDK4/6 inhibitors plus an AI for first-line treatment of HR+, HER2– ABC

	MONALEESA-2[9]		MONALEESA-7[10]		MONARCH 3[8]		PALOMA-2[7]	
	RIB + LET (n=334)	PBO + LET (n=334)	RIB + TAM or NSAI (n=335)	PBO + TAM or NSAI (n=337)	ABE + NSAI (n=328)	PBO + NSAI (n=165)	PAL + LET (n=444)	PBO + LET (n=222)
Median PFS, months	25.3	16.0	23.8	13.0	Not reached	14.7	24.8	14.5
Hazard ratio (95% CI)	0.57 (0.46–0.70)		0.55 (0.44–0.69)		0.54 (0.41–0.72)		0.58 (0.46–0.72)	
P-value	9.63×10^{-8}		<0.0001		2.1×10^{-5}		<0.001	
CBR, %	79.9[a]	73.1[a]	79.1	69.7	78.0[b]	71.5[b]	84.9[c]	70.3[c]
ORR, %[d]	42.5	28.7	40.9	29.7	48.2	34.5	42.1	34.7

Notes: [a]CBR = CR + PR + SD for ≥24 weeks + NCRNPD for ≥24 weeks. [b]CBR = CR + PR + SD for ≥6 months. [c]CBR = CR + PR + SD for ≥24 weeks. [d]ORR = CR + PR.
Abbreviations: ABC, advanced breast cancer; ABE, abemaciclib; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinases 4 and 6; CR, complete response; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; LET, letrozole; NCRNPD, neither complete response nor progressive disease; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; PAL, palbociclib; PBO, placebo; PFS, progression-free survival; PR, partial response; RIB, ribociclib; SD, stable disease; TAM, tamoxifen.

Table 3 Overall safety reported in trials of CDK4/6 inhibitors plus an AI for first-line treatment of HR+, HER2– ABC

Adverse events, any grade, in ≥30% of patients in any treatment group, %	MONALEESA-2[9]		MONALEESA-7[10]		MONARCH 3[8]		PALOMA-2[7]	
	RIB + LET (n=334)	PBO + LET (n=330)	RIB + TAM or NSAI (n=335)	PBO + TAM or NSAI (n=337)	ABE + NSAI (n=327)	PBO + NSAI (n=161)	PAL + LET (n=444)	PBO + LET (n=222)
Neutropenia[a]	77	6	76	8	41	2	80	6
Nausea	53	31	32	20	39	20	35	26
Infections (pooled)	50[16]	42[16]	Not reported	Not reported	39	29	60[12]	42[12]
Fatigue	41	32	24	25	40	32	37	27
Diarrhea	38	25	20	19	81	30	26	19
Vomiting	34	17	19	17	28	12	16	17
Alopecia	34	16	19	12	27	11	33	16
Leukopenia[b]	33	5	31	6	21	2	39	2
Arthralgia	33	33	30	27	Not reported	Not reported	33	34
Hot flush[c]	25	25	34	34	Not reported	Not reported	21	31
Anemia[d]	21	6	21	10	28	5	24	9

Notes: [a]In the MONALEESA-2 trial, neutropenia also included granulocytopenia and decreased neutrophil count. In the PALOMA-2 trial, neutropenia also included decreased neutrophil count. [b]In the PALOMA-2 and MONALEESA-2 trials, leukopenia also included decreased white blood cell count. [c]In the MONALEESA-7 and MONALEESA-2 trials, hot flash was reported. [d]In the MONALEESA-2 trial, anemia also included decreased hemoglobin and macrocytic anemia. Superscripted numbers represent reference citations.
Abbreviations: ABC, advanced breast cancer; ABE, abemaciclib; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinases 4 and 6; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; PAL, palbociclib; PBO, placebo; RIB, ribociclib; TAM, tamoxifen.

Abemaciclib therapy was associated with a lower incidence of neutropenia (41%) compared to ribociclib (77%) and palbociclib (80%) therapy, but also a higher incidence of diarrhea (81%) compared to palbociclib (26%) and ribociclib (38%) therapy.[7–9] Ribociclib therapy was associated with a higher incidence of nausea (53%) compared to palbociclib (35%) and abemaciclib (39%) therapy.[7–9] Any decision regarding cancer therapy should be made considering the potential risks and benefits of a given regimen with respect to the individual patient. Below, we address important points physicians should consider regarding use of CDK4/6 inhibitor plus AI therapy.

Prolonged response to AI monotherapy

Physician barrier: certain patients may respond well to AI monotherapy and may not benefit enough from the addition of a CDK4/6 inhibitor to outweigh safety concerns

It is important to consider individual patient characteristics when treating ABC. In older patients, those who have bone-only metastatic disease or those who have a long disease-free interval after completion of adjuvant therapy, AI monotherapy

may be highly efficacious, with median PFS responses greater than the previously mentioned 13.8–16.0 months demonstrated in first-line AI monotherapy studies. However, results from randomized trials indicate that CDK4/6 inhibitor combination therapy provides greater benefit than AI monotherapy in each of these subgroups, with similar safety profiles in older and younger patients (Table 4).

Older patients

In a pooled analysis of the PALOMA-1 and PALOMA-2 trials, the median PFS in patients in the placebo plus letrozole group was longer in patients aged 65–74 years (21.8 months; n=94) than that in patients aged <65 years (12.3 months; n=183); although, in patients aged ≥75 years in the placebo plus letrozole group (n=26), the median PFS was only 10.9 months.[18] Nevertheless, palbociclib plus letrozole therapy resulted in a 69% (median PFS, not reached) and 34% (median PFS, 27.5 months) reduction in risk of disease progression in patients aged ≥75 years or aged 65–74 years, respectively, compared to letrozole monotherapy. Hematologic AEs, infections, and decreased appetite were more commonly observed in patients ≥65 years old than <65 years old.[18]

A subgroup analysis in patients aged ≥65 years in the MONARCH 3 trial, after a median follow-up of 17.8 months, reported a 43% reduction in risk of progression with abemaciclib plus nonsteroidal AI (NSAI) therapy compared to placebo plus NSAI therapy, consistent with findings in the overall population.[8]

In a subgroup analysis in patients aged ≥65 years in the MONALEESA-2 trial, after a median follow-up of 15.3 months, the median PFS in older patients in the placebo plus letrozole group (18.4 months; n=145) was longer than that in younger (aged <65 years) patients (13.0 months; n=189).[16,19] However, older patients exhibited a 39% reduction in risk of progression with ribociclib plus letrozole therapy (median PFS, not reached) compared to placebo plus letrozole therapy (median PFS, 18.4 months), consistent with findings in the overall population.[19] Rates of AEs, including neutropenia, were similar in older and younger patients.[19]

Finally, a pooled retrospective subgroup analysis of the registration studies that led to approval of the three CDK4/6 inhibitors in older and younger patients conducted by the US Food and Drug Administration confirmed a PFS benefit of CDK4/6 inhibitor plus AI therapy in older patients across trial populations.[20] Therefore, there are no data to support withholding CDK4/6 inhibitor plus AI therapy based solely on age.

Patients with bone-only disease

The overall prevalence of bone-only metastases in patients with ABC in the first-line setting ranges from ~15% to 35%, according to a retrospective review of medical records and

Table 4 Efficacy reported in subgroups from trials of CDK4/6 inhibitors plus an AI for first-line treatment of HR+, HER2– ABC

	MONALEESA-2[16,19,26,73]		MONARCH 3[8]		PALOMA-2[18,27,46]	
	RIB + LET	PBO + LET	ABE + NSAI	PBO + NSAI	PAL + LET	PBO + LET
Older patients, cutoff (n)	≥65 years (150)	≥65 years (145)	≥65 years (not reported)	≥65 years (not reported)	≥65 and <75 years (162)[a]	≥65 and<75 years (94)[a]
Median follow-up, months	15.3		17.8		Not reported	
Median PFS, months	Not reached	18.4	Not reported	Not reported	27.5[a]	21.8[a]
Hazard ratio (95% CI)	0.608 (0.394–0.937)		0.57 (0.36–0.90)		0.66[a] (0.45–0.97)	
P-value	Not reported		Not reported		<0.016[a]	
Patients with bone-only disease, n	69	78	70	39	103	48
Median follow-up, months	15.3		17.8		23	
Median PFS, months	Not reached	15.3	Not reached	Not reached	Not reached	11.2
Hazard ratio (95% CI)	0.690 (0.381–1.249)		0.58 (0.27–1.25)		0.36 (0.22–0.59)	
P-value	Not reported		Not reported		<0.0001	
Patients with long disease-free interval, cutoff (n)	>48 months (54)	>48 months (49)	≥36 months (94)	≥36 months (40)	>12 months (178)	>12 months (93)
Median follow-up, months	26.4		17.8		23	
Median PFS, months	29.6	19.2	Not reached	Not reached	25.4	13.8
Hazard ratio (95% CI)	0.496 (0.274–0.898)		0.83 (0.46–1.52)		0.52 (0.37–0.73)	
P-value	Not reported		Not reported		<0.0001	

Notes: [a]Results in older patients reported from a pooled analysis of PALOMA-1 and PALOMA-2 trial participants.

Abbreviations: ABC, advanced breast cancer; ABE, abemaciclib; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinases 4 and 6; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; LET, letrozole; NSAI, nonsteroidal AI; PAL, palbociclib; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

a prospective tumor registry study.[21,22] In Phase III trials of CDK4/6 inhibitors in combination with fulvestrant in the second-line setting, 24%–27% of patients had bone-only metastases.[23,24] Patients enrolled in the MONARCH 2 trial with bone-only metastases experienced a benefit from addition of abemaciclib after a median follow-up of 19.5 months (median PFS, 24.0 months [abemaciclib] vs 16.6 months [placebo]; hazard ratio, 0.544 [95% CI, 0.355–0.834]).[23,25] Similarly, in the PALOMA-3 trial, patients with bone-only metastases demonstrated a PFS benefit with the addition of palbociclib (median PFS, 14.3 months [palbociclib plus fulvestrant] vs 9.2 months [placebo plus fulvestrant]; $P<0.05$).[24] In Phase III clinical trials of CDK4/6 inhibitors in combination with AIs in the first-line setting, a similar proportion of participants had enrolled with bone-only metastatic disease (range, 21%–24%).[7,8,10,16] These trials reported hazard ratios favoring combination therapy in patients with bone-only disease, reporting between 31% and 64% reduction in risk of disease progression (Table 4).[8,26,27]

Although all pivotal trials lack long-term follow-up, preliminary data for patients with bone-only disease are promising and consistent in favoring CDK4/6 inhibitor plus AI therapy over AI monotherapy. The median PFS was not reached in the CDK4/6 inhibitor plus AI treatment groups of the PALOMA-2, MONARCH 3, and MONALEESA-2 trials at the current data cutoffs for these analyses (median follow-up lengths of 23 months, 17.8 months, and 15.3 months, respectively), restricting any numerical comparisons of PFS between treatment groups.[8,16,26,27] However, the lower limit of the 95% CI of median PFS in patients on palbociclib plus letrozole combination therapy in the PALOMA-2 trial suggests that the true median PFS will likely be >24.8 months in these patients. Comparatively, the median PFS in the letrozole plus placebo group of the PALOMA-2 trial was 11.2 months (95% CI, 8.2–22.0 months).[27] Results from the MONALEESA-2 (ribociclib) and MONARCH 3 (abemaciclib) trials are still immature.[8,26] Given the consistent PFS benefit of CDK4/6 inhibitor plus AI therapy demonstrated in patients with bone-only disease, it is reasonable to consider combination therapy for these patients.

Patients with a long disease-free interval after neoadjuvant or adjuvant therapy

Patients with a long disease-free interval after completion of adjuvant therapy can experience a longer median PFS with AI monotherapy in first-line ABC compared to patients with a short disease-free interval.[27,28] In the PALOMA-2, MONALEESA-2, and MONARCH 3 trials, disease-free interval was calculated as the time from the end of the last neoadjuvant or adjuvant therapy received to randomization.[8,27,28] In patients receiving AI monotherapy, the median PFS was greater in patients with a long disease-free interval vs those with a short disease-free interval in the MONALEESA-2 trial (>48 months vs ≤48 months; 8.3-month difference) and PALOMA-2 trial (>12 months vs ≤12 months; 2.8-month difference).[27,28] However, even in these patients, a PFS benefit of CDK4/6 inhibitor plus AI therapy was observed.

In the MONALEESA-2 trial, after a median follow-up of 26.4 months, an exploratory subgroup analysis of 298 patients with prior neoadjuvant or adjuvant endocrine therapy (ET) demonstrated benefit of ribociclib plus letrozole combination therapy over letrozole monotherapy in patients with a treatment-free interval of >24, >36, or >48 months (54.5%, 49.3%, and 50.4% reduction in risk of disease progression or death with ribociclib, respectively).[28]

In the PALOMA-2 trial, results from a subgroup analysis of patients with a disease-free interval of >12 months at a median follow-up of 23 months reported the median PFS in the palbociclib plus letrozole group as 25.4 months (95% CI, 22.2 months – not reached; n=178) vs 13.8 months (95% CI, 9.6–18.2 months; n=93) in the placebo plus letrozole group, a 48% reduction in risk of progression.[27] A similar analysis of the MONALEESA-7 trial at a median follow-up of 19.2 months demonstrated a 25% reduction in risk of progression with ribociclib plus NSAI/tamoxifen combination therapy compared to NSAI/tamoxifen in 25 premenopausal women with a disease-free interval of >12 months.[10]

In contrast, the MONARCH 3 trial reported an exploratory subgroup analysis of 134 patients with a disease-free interval of ≥36 months at a median follow-up of 17.8 months.[8] This analysis did not demonstrate a difference between groups, with the median PFS not reached in either group, thus highlighting the need for longer follow-up to demonstrate a PFS benefit of abemaciclib plus AI combination therapy in this group of patients.[8]

All these analyses report results at interim data cutoffs, often with limited sample sizes. Final analyses with longer follow-up may more clearly define differences in efficacy between CDK4/6 inhibitor plus AI therapy and AI monotherapy in these patients.

Tumor response rates with chemotherapy and CDK4/6 inhibitor combination therapy

Physician barrier: tumor response rates with chemotherapy may be higher than with CDK4/6 inhibitors in the first-line setting

National guidelines recommend use of ET over chemotherapy in the first-line setting unless the disease is immediately life-threatening or patients have rapid visceral recurrence during adjuvant ET.[3] Tumor response rates were reported in Phase III trials of CDK4/6 inhibitor plus AI therapy; however, except in the MONALEESA-7 trial, these trials excluded patients who progressed within 12 months after adjuvant NSAI therapy.[7,8,10,16] Patients with immediately life-threatening disease were also excluded in the MONALEESA-7, MONARCH 3, and PALOMA-2 trials, and patients with inflammatory breast cancer were excluded in the MONALEESA-2, MONALEESA-7, and MONARCH 3 trials.[7,8,10,16,29] Interpretation of tumor response rates should take into consideration these trial characteristics.

In postmenopausal women with HER2– ABC in the first-line setting, overall response rates (ORRs) for single-agent docetaxel or *nab*-paclitaxel ranged from 35% to 49%, while ORRs in Phase III trials of CDK4/6 inhibitors ranged from 29% to 35% for AI monotherapy and from 42% to 48% for CDK4/6 inhibitor plus AI therapy.[4,7–9,30,31] In these same trials, CBRs ranged from 58% to 80% for single-agent docetaxel or *nab*-paclitaxel, 70% to 73% for AI monotherapy, and 78% to 85% for CDK4/6 inhibitor plus AI therapy.[4,7–9,30,31]

Tumor responses with single-agent docetaxel or paclitaxel have been reported to occur within the first 6–12 weeks of treatment in patients with ABC.[32,33] Tumor response to CDK4/6 inhibitor-based therapy also tends to occur within the first few months of treatment. In the MONALEESA-2 trial, an improvement in tumor response with ribociclib plus letrozole combination therapy compared to AI monotherapy was observed at 8 weeks.[28] In the PALOMA-3 trial, which assessed palbociclib plus fulvestrant as second-line therapy, the median time to response was 16 weeks.[34]

Patients with visceral metastases were enrolled in all four Phase III clinical trials of first-line CDK4/6 inhibitor plus AI therapy (PALOMA-2: 73%; MONALEESA-2: 59%; MONARCH 3: 53%; MONALEESA-7: 57%) and in the FALCON trial, which assessed first-line fulvestrant monotherapy vs anastrozole monotherapy in ET-naive postmenopausal patients with HR+ ABC.[7,8,10,16,35] Subgroup analyses have shown a PFS benefit with CDK4/6 inhibitor plus AI therapy over AI monotherapy in patients with visceral metastases. In the PALOMA-2 trial, after a median follow-up of 23 months, palbociclib plus letrozole combination therapy demonstrated a 6.4-month greater median PFS in patients with visceral disease compared to letrozole monotherapy.[27] Data from the MONALEESA-2 and MONARCH 3 trials are either immature or not inclusive of all visceral metastases, but both support similar trends as those observed in the PALOMA-2 trial.[8,25,26]

Among ET-naive patients in the FALCON trial, those with visceral metastases had similar PFS benefit with fulvestrant or anastrozole monotherapy. Among patients without visceral metastases in the FALCON trial, those administered fulvestrant had a longer median PFS compared to those administered anastrozole (fulvestrant: 22.3 months; anastrozole: 13.8 months).[35] All of these data to date support the use of hormonal therapy as first-line therapy in patients with visceral metastases that are not immediately life-threatening.

Tolerability and QoL with CDK4/6 inhibitors

Physician barrier: CDK4/6 inhibitor combination therapy is associated with increased AEs that may limit tolerability, negatively affect QoL, or outweigh efficacy benefits compared with endocrine monotherapy

Neutropenia is the most common Grade 3/4 AE observed with palbociclib and ribociclib in combination with letrozole. Neutropenia is also observed with abemaciclib in combination with letrozole, although to a lesser extent (Table 3). Neutropenia associated with CDK4/6 inhibitor combination therapy is rarely associated with fever and is thought to be mechanistically different from neutropenia associated with chemotherapy.[36] CDK4/6 inhibitors induce cell-cycle arrest rather than apoptotic cell death in hematopoietic stem cells.[36] The maintenance of these hematopoietic progenitor cell populations under CDK4/6 inhibition is hypothesized to allow for the rapid resolution of neutropenia associated with CDK4/6 inhibitors in clinical trials.[36] Use of growth factors is not recommended with CDK4/6 inhibitor-induced neutropenia, except in the case of concurrent fever.[37] Dose reductions and interruptions due to neutropenia occurred in the PALOMA-2 trial (24.3% and 54.7% of patients, respectively) and MONALEESA-2 trial (31.1% and 49.7% of patients, respectively).[38,39] However, discontinuation due to neutropenia was low in both the MONALEESA-2

and PALOMA-2 trials (0.9% and 1.1% of patients, respectively), indicating that neutropenia was manageable.[38,39] An analysis of patients who underwent dose modification in the palbociclib group of the PALOMA-2 trial suggests that dose modification does not negatively affect PFS.[38] CDK4/6 inhibitor-induced neutropenia typically occurs early during treatment and is reversible.[8,39,40] Rates of Grade 3/4 neutropenia in the MONALEESA-2 trial decreased from 60.2% in the ribociclib plus letrozole group within the first 12 months of treatment to 16.8% after 18 months of treatment.[39] In the MONARCH 3 trial, Grade 3/4 neutropenia was less commonly observed after the first two cycles of therapy, with incidences of <5% in any given cycle.[8]

Among nonhematologic toxicities, diarrhea is the most common with abemaciclib combination therapy and is observed to a lesser extent with ribociclib or palbociclib combination therapy (Table 3). Diarrhea observed with CDK4/6 inhibitors is predominantly Grade 1 or 2.[7–10] A high rate of Grade 3 diarrhea is observed with abemaciclib therapy, but this can be managed with antidiarrheal medications.[8,41]

In addition to diarrhea, CDK4/6 inhibitor combination therapy is associated with nausea and vomiting, fatigue, infections, and alopecia (Table 3). These AEs are predominantly Grade 1 or 2.[7–10] Fatigue was reported in 24%–40% of patients with CDK4/6 inhibitor plus AI therapy vs 25%–32% with AI monotherapy. Alopecia is observed in 19%–34% of patients receiving CDK4/6 inhibitor plus AI therapy vs 11%–16% of patients receiving AI monotherapy.[7–10] Grade 1 alopecia is defined as <50% of the patient's hair falling out, with effects not noticeable from a distance.[42] A small proportion of patients (<3%) receiving palbociclib plus letrozole in the PALOMA-2 trial or receiving abemaciclib plus NSAI in the MONARCH 3 trial reported experiencing Grade 2 alopecia, where ≥50% of the patient's hair has fallen out, and a wig or other head covering is necessary to camouflage the hair loss.[7,8,42] The MONALEESA-2 trial had a similar proportion of patients who experienced any grade of alopecia as the PALOMA-2 and MONARCH 3 trials.[9]

All approved CDK4/6 inhibitors are associated with laboratory abnormalities.[8,11,12] In addition to being associated with decreased cell counts related to hematologic AEs, all CDK4/6 inhibitors are associated with increases in alanine aminotransferase (range, 33%–48%) and aspartate aminotransferase (range, 37%–52%), although liver function tests are currently only recommended with ribociclib and abemaciclib.[8,11,12,41] Increases in liver aminotransferases are manageable with dose modification.[8,16] Abemaciclib in combination with an NSAI is associated with increased creatinine compared to NSAI monotherapy, although this is not associated with impaired renal function.[8]

Prolongation of the QT interval has been reported with palbociclib and ribociclib in the PALOMA-2, MONALEESA-2, and MONALEESA-7 trial populations, and biweekly electrocardiogram monitoring is recommended through the beginning of the second month of ribociclib use.[11] Because the QT interval can be altered by resting heart rate, the electrocardiogram reading must be corrected by heart rate for accurate interpretation.[43] The QT interval can vary from beat to beat, so multiple readings should be performed to accurately assess the presence of QT interval prolongation.[44] Fridericia's formula was used to correct the QT interval reading in the MONALEESA-2 and MONALEESA-7 trials and is recommended to be used when assessing the QT interval in patients who are initiating ribociclib therapy.[11,16] In both the MONALEESA-2 and PALOMA-2 trials, the reported rate of QT interval prolongation was low, with only one patient in either trial experiencing a corrected QT interval (Fridericia's formula) of ≥500 ms.[39,45] In the MONALEESA-7 trial, five patients (1%) in the ribociclib combination therapy group experienced a corrected QT interval (Fridericia's formula) of >500 milliseconds.[10] Data on the effect of abemaciclib on QT interval prolongation have not yet been reported in the MONARCH 3 trial population.[8]

Patient reports of QoL in the PALOMA and MONALEESA trials suggest that QoL is not negatively affected by the above toxicities. In the PALOMA-2 trial, there was no difference in global health status, as measured by the EuroQol 5-domain questionnaire and visual analog scale.[46] In the PALOMA-1/TRIO-18 trial, an analysis of pain from the Brief Pain Inventory tool found that pain severity and pain interference scores remained stable with a slight improvement in pain in both treatment groups and no overall differences between treatment groups.[47]

In the MONALEESA-2 and MONALEESA-7 trials, patient-reported outcomes were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.[10,48] In the MONALEESA-2 trial, no differences between groups were seen in global health-related QoL or symptom scales, and patients in the ribociclib group exhibited similar or greater reduction in pain than patients in the placebo group.[48] In the MONALEESA-7 trial in premenopausal women, time to definitive deterioration of ≥10% in global health status/QoL score was improved with ribociclib plus ovarian suppression in combination with either an NSAI or tamoxifen compared to ovarian suppression with

an NSAI or tamoxifen without ribociclib, and improvement in pain score from baseline was observed in the ribociclib group at 8 weeks.[10] As of the development of this review, abemaciclib QoL data are not currently publicly available.

Costs associated with CDK4/6 inhibitors

Physician barrier: prescribing CDK4/6 inhibitors with AI therapy may add prohibitive costs to treatment

The starting dose of all three CDK4/6 inhibitors are priced at >$11,000 per monthly dose without considering discounts or insurance.[49–51] A cost-effectiveness analysis of palbociclib therapy in the United States based on wholesale acquisition cost pricing on January 2016 reported lifetime patient costs of palbociclib plus letrozole combination therapy to be $372,761 while providing 2.13 quality-adjusted life years.[52] The lifetime patient costs of letrozole monotherapy were $128,435 while providing an average of 1.82 quality-adjusted life years.[52] Thus, palbociclib plus letrozole therapy at prices in January 2016 cost $768,498 more per quality-adjusted life year than letrozole monotherapy.[52]

Two years later, with two more CDK4/6 inhibitors on the market, costs have only increased.[49–51,53] To offset these costs, all three pharmaceutical companies have established programs to reduce patient costs from wholesale acquisition costs. Palbociclib and ribociclib are both attainable to some uninsured or low-income patients at costs ranging from $0 to $10 per month.[53–55] Commercially insured patients can qualify for savings of up to $25,000 per year with palbociclib or abemaciclib. Ribociclib offers a co-pack of ribociclib and letrozole tablets at the same cost as ribociclib alone, with some commercially insured patients qualifying for savings of up to $15,000 per product per year.[54] Palbociclib is supplied at three doses of 125, 100, and 75 mg, while abemaciclib is supplied at four doses of 200, 150, 100, and 50 mg, with a 1-month supply priced the same regardless of dose level.[49,51] When dose reductions are needed for either of these, patients may need to discard part of their expensive monthly supply and order the next lower dose bottle.[12,41] Ribociclib is formulated in 200 mg tablets with dose reduction requiring taking one fewer tablet per day.[11] Thus, 400 and 200 mg dose packs are priced proportionally lower than the starting 600 mg dose, which could result in reduced costs for some patients.[50] Currently, the only support for patients on Medicare and Medicaid insurance is conditional support for palbociclib if no charitable support is available.[54–56] Taking eligibility for price reductions into account, financial costs should be considered alongside efficacy and safety when prescribing CDK4/6 inhibitor plus AI therapies.

Predictive biomarkers

The barriers in this review have likely limited the use of CDK4/6 inhibitors in first- and second-line treatment of HR+, HER2− ABC more than might be anticipated given the favorable Phase III data available. In addition to these barriers, the current lack of readily available predictive biomarkers to identify marked sensitivity or resistance to these compounds is an impediment to their use. Preclinical studies in tumor cell models have suggested that breast tumors may be resistant to CDK4/6 inhibitor therapy if they contain certain mutations in the cell-cycle pathway, such as changes in cyclin D1 or cyclin E1 expression or loss of retinoblastoma protein (Rb).[57–60] Genetic loss of Rb occurs in only 2% of breast cancer cases, and Phase III trials of CDK4/6 inhibitors have not reported results in this patient subgroup.[61] Clinical trial analyses have investigated the effect of baseline mutations on the efficacy of CDK4/6 inhibitors; however, these results may be limited by the small number of enrolled patients in some subgroups and duration of follow-up.[62–64] Additionally, no diagnostic tools are available to clinicians to assess these biomarkers in the real-world setting, restricting the ability of clinicians to apply results to clinical practice. Nevertheless, CDK4/6 inhibitor plus AI therapy has demonstrated improved PFS over AI monotherapy in many patient subgroups split by baseline biomarker phenotypes enrolled in the PALOMA-1, PALOMA-2, and MONALEESA-2 trials.

From the PALOMA-1 and PALOMA-2 trials, PFS benefit of palbociclib plus letrozole was observed in patients irrespective of *CCND1*, *CDK4*, *CDK6*, *RB1*, *CDKN2A*, *CCNE1*, *CCNE2*, *CDK2*, *CCND3*, *ESR1*, or *AR* gene expression or Ki67 or ER protein expression.[62,65,66] This benefit was also observed in patients with high gene expression of *PDCD1*, high protein expression of Rb, p16, or cyclin D1, or irrespective of Rb localization or p16 nuclear expression levels.[62,65,66] Small sample sizes restrict conclusions made about efficacy in tumors with low p16, Rb, or cyclin D1 protein expression.[45,62]

From the MONALEESA-2 trial, PFS benefit of ribociclib plus letrozole combination therapy was observed in patients irrespective of p16 protein expression or *PIK3CA* mutation status and in patients with high gene expression of *ESR1*, low gene expression of *CDKN2A* or *CCND1*, and high protein expression of Rb or Ki67.[64] However, small sample sizes and

limited follow-up restricted conclusions made from analyses of other expression levels of these proteins and genes.[64]

Even in patients with baseline genetic changes that promote resistance to CDK4/6 inhibitor plus AI therapy, patients may achieve a PFS benefit with CDK4/6 inhibitor plus AI therapy over AI monotherapy. For example, baseline mutations in *TP53*, which encodes the tumor suppressor protein p53, have been associated with resistance to abemaciclib and early progression on palbociclib and ribociclib.[63,67,68] However, in the MONALEESA-2 trial in patients with mutant *TP53,* a PFS benefit was observed with ribociclib plus letrozole combination therapy over letrozole monotherapy.[63]

Evidence from ongoing trials suggests that CDK4/6 inhibitor–based combination therapy can provide benefit to patients who have resistance to prior therapies. The TREnd trial reported that patients whose disease had progressed after >6 months of ET in the advanced setting demonstrated a significant improvement in median PFS with palbociclib plus the same ET vs palbociclib alone (11.5 months vs 6.5 months, P=0.02).[69,70] Furthermore, the Phase I/II TRINITI-1 trial reported that patients whose disease had progressed after CDK4/6 inhibitor-based therapy experienced a benefit of ribociclib in combination with everolimus and exemestane.[71] A similar Phase II trial, BioPER, is recruiting patients with metastatic breast cancer who had experienced clinical benefit with palbociclib plus ET and had progressed on the treatment 3–8 weeks before study entry.[72] While no results have yet been reported, the trial will assess biomarkers of resistance and clinical benefit of palbociclib plus ET in the post-palbociclib setting. These trials begin to address questions of sequencing after resistance to CDK4/6 inhibitor therapy occurs.

Conclusion

Despite the gains in efficacy, some physicians are still reluctant to use CDK4/6 inhibitors in combination with an AI as first-line treatment in postmenopausal women with HR+, HER2− ABC because of concerns about efficacy, safety, and cost. However, our review of the data indicates that CDK4/6 inhibitors improve PFS in all eligible patients, with comparable response rates to first-line chemotherapy. CDK4/6 inhibitors in combination with AIs result in a greater number of AEs compared to AI monotherapy; however, patient-reported QoL is similar between treatment groups, suggesting that AEs are manageable with recommended monitoring. Patient costs remain a barrier with three CDK4/6 inhibitors on the market, but patient support programs may greatly reduce these costs for some patients, and assessment of this barrier should be on a case-by-case basis alongside desired efficacy and safety concerns.

While no changes in mRNA or protein expression that predict resistance to CDK4/6 inhibitors in the clinical setting have been found, further research is needed to identify mechanisms of resistance to CDK4/6 inhibitor plus AI therapy. Ongoing trials may provide valuable insights into continued use of CDK4/6 inhibitors after resistance to first-line combination therapy develops. As the breadth of studies of CDK4/6 inhibitors continues to expand, physicians should ensure that they consider current clinical trial data alongside individual patient needs in their treatment decisions.

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Author contributions

Dr Mahtani and Dr Vogel conceived of and designed the review, revised it critically for important intellectual content, and approved the final version to be published. Both authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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