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SUPPLEMENT ARTICLE

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Hormone receptor positive, HER2 negative metastatic breast cancer: Impact of CDK4/6 inhibitors on the current treatment paradigm

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Abstract

Resistance to endocrine therapy is a significant therapeutic challenge in the treatment of women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2–) advanced breast cancer. Cyclin-dependent kinase (CDK)4/6 inhibitors in combination with endocrine therapy have been shown to improve progression free survival, overall response rate and clinical benefit rate in women with HR+ HER2– metastatic breast cancer compared with endocrine therapy alone. This review examines the clinical evidence to support the use of CDK4/6 inhibitors in first and second line settings. Practical guidance is provided for the use of CDK4/6 inhibitors, including tolerability data, monitoring requirements and management of key toxicities for each of the available agents.

KEYWORDS

CDK4/6 inhibitor, endocrine therapy, metastatic breast cancer

1 | INTRODUCTION

Hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2–) breast cancer is the most common subtype of breast cancer accounting for more than 70% of cases.[1] It is well established that endocrine therapy improves outcomes for patients with early and metastatic HR+, HER2– breast cancer. Endocrine therapies block estrogen-driven tumor growth through a number of different mechanisms providing an array of opportunities for resistance to develop. De novo or acquired resistance to endocrine therapy results in treatment failure, which limits survival and prevents cure in patients with metastatic disease. With advances in understanding of tumor biology, these mechanisms may potentially be overcome by specific inhibitors against molecules upregulated or mutated in resistant cells. Cyclin-dependent kinase (CDK)4/6, a downstream target of estrogen receptor (ER) signaling that regulates cell entry into the cell cycle, represents such a mechanism that may be activated by alternative routes in this setting. Cyclin-CDK complexes regulate proliferation in breast cancer cells through phosphorylation and inactivation of the retinoblastoma tumor suppressor protein (Rb).[2] Hyperphosphorylation of Rb leads to increased DNA replication within the tumor cell and subsequent driving of the cell cycle. Tumor cells are able to avoid senescence through mechanisms such as CDK4 amplification. Consequently, inhibition of CDK4 can lead to senescence. Furthermore, CDK6

inhibition appears to have an independent antiangiogenic role in tumor therapy.[2]

Three CDK4/6 inhibitors, ribociclib, palbociclib and abemaciclib, are either approved or in late stage clinical trials. All three drugs in combination with endocrine therapy have been shown to improve progression free survival (PFS) in HR+ HER2− metastatic breast cancer compared with endocrine therapy alone in the first and second line settings, leading to a significant shift in patterns of care.[3–11] Although clinical data is very similar for the three agents, molecular and functional profiling suggest there may be some subtle differences in activity.[12]

Ribociclib has been listed for reimbursement with the Pharmaceutical Benefits Scheme (PBS) in Australia since July 1, 2018. Palbociclib is Therapeutic Goods Administration (TGA) approved for first and second line use in combination with endocrine therapy.[13,14] Abemaciclib is not currently approved for use in Australia. All three CDK4/6 inhibitors are also currently being evaluated in clinical trials for high risk early breast cancer patients (NCT02831530, NCT02513394, NCT03078751).

We conducted a search of the literature for Phase II to IV clinical trials using CDK4/6 inhibitors palbociclib, ribociclib and abemaciclib in women with HR+ HER2− metastatic breast cancer. The Cochrane Library, PubMed, Embase, Medline, Medline Daily and In-Process, PreMedline, American Society of Clinical Oncology and San Antonio Breast Cancer Symposium meeting abstracts were appraised. In this review, we have included phase II and III randomized controlled clinical trials of CDK4/6 inhibitors reporting efficacy, safety and/or quality of life outcomes in women with HR+ HER2− metastatic breast cancer.

We review the clinical evidence to support the use of CDK4/6 inhibitors, assess tolerability and provide practical guidance for the use of CDK4/6 inhibitors in clinical practice.

2 | CLINICAL TRIAL DATA: EFFICACY

2.1 | First line in postmenopausal women

The efficacy data for CDK4/6 inhibitors in combination with a nonsteroidal aromatase inhibitor (NSAI) for first line treatment of HR+ HER2− metastatic breast cancer in postmenopausal women is derived from three phase III double-blind randomized controlled trials (MONARCH-3[6], PALOMA-2[15] and MONALEESA-2[8]) and one phase II study (PALOMA-1[5]) (Table 1). In addition, the MONALEESA-3 study compared ribociclib in combination with the selective estrogen receptor degrader (SERD) fulvestrant to fulvestrant plus placebo and included patients who had received one prior line of therapy as well as treatment-naïve patients.[16]

First line CDK4/6 inhibitors in combination with a NSAI improved PFS compared to a NSAI plus placebo (HR between 0.49 and 0.58 in postmenopausal women with HR+, HER2− metastatic breast cancer).[6,8,15] Considering the combination arms, median PFS in the PALOMA-2 study for palbociclib with letrozole was 24.8 months (95% CI 22.1 to not estimable (NE))[15] and in MONALEESA-2, for ribociclib plus letrozole median PFS was 25.3 months (95% CI 23.0 to 30.3).[17] In the MONARCH-3 study, PFS for abemaciclib and letrozole was not reached in the abemaciclib combination arm after a median follow-up of 17.8 months.[6] The median PFS for a NSAI alone in the three studies ranged from 10.2 to 16 months in keeping with previous studies of NSAIs.[18] Median PFS was not reached in the sub-group of patients receiving first line ribociclib plus fulvestrant in MONALEESA-3; in the fulvestrant alone arm median PFS was 18.3 months (hazard ratio (HR) 0.58; 95% CI, 0.42 to 0.80) (Figure 1).[10]

Overall response rates (ORR) for CDK4/6 inhibitors in combination with a NSAI, ranged between 42.1% and 48.2%, compared to 28.7% to 34.7% for an NSAI with placebo. The clinical benefit rate (CBR) for patients receiving both a CDK4/6 inhibitor and a NSAI ranged from 78% to 84.9% compared to 58% to 72.8% in those receiving the NSAI plus placebo. The PALOMA-2 study reported 22.5 months median duration of response for the combination arm compared to 16.8 months for the control arm. In the MONARCH-3 study, median duration of response was not reached for the active arm and was 14.1 months in the control arm. After a median follow-up period of 15.3 months in the MONALEESA-2 study, median duration of response was not reached in either arm.[19]

Overall survival (OS) in the PALOMA-3 study showed a positive trend in the hazard ratio favoring palbociclib, similar in absolute terms to the improvement in median PFS, although this trend did not reach statistical significance.[20] Similarly, results from the PALOMA-1 phase II study showed a non-significant trend toward an improvement in median OS with palbociclib plus letrozole compared with letrozole alone (37.5 months vs. 34.5 months; HR 0.90; 95% CI 0.62 to 1.29).[21] In the MONALEESA-2 study, the overall survival data was not yet mature for analysis. At a median follow-up duration of 26.4 months, there were 116 deaths reported including 50 deaths in the ribociclib arm and 66 deaths in the placebo arm (HR: 0.75; 95% CI 0.52 to 1.08).[17] Data for OS were not yet mature for MONARCH-3 at the time of writing. All of these trials are likely to be underpowered for survival outcomes, particularly considering that patients have many options for post-progression treatment open to them.

2.2 | Second or later lines in postmenopausal women

Each of the three CDK4/6 inhibitors, in combination with the SERD fulvestrant, also improved PFS in second or later lines of therapy. The phase III studies MONALEESA-3, MONARCH-2 and PALOMA-3 demonstrated a median PFS of 20.5 months (first and second line combined), 16.4 months and 9.5 months in the combination arms compared with the fulvestrant monotherapy arms of 12.8, 9.3 and 4.6 months respectively, with similar HR to those seen in the first line studies.[3,10,11] In the sub-group of patients receiving second line ribociclib plus fulvestrant in the MONALEESA-3 study, median PFS was 14.6 months compared to 9.1 months in the fulvestrant alone arm (HR 0.57; 95% CI, 0.43 to 0.74).[10,16]

2.3 | Premenopausal women

MONARCH-2 and PALOMA-3 included some premenopausal women (with a Luteinising Hormone Releasing Hormone (LHRH) agonist) and demonstrated similar efficacy to postmenopausal women. In the

TABLE 1 Clinical Trials of CDK4/6 inhibitors in HR+ HER2- metastatic breast cancer

Study name First author (Publication year)	Phase	Line of Therapy	Experimental Regimen (n)	Control Regimen (n)	Primary Endpoint	Median follow-up months (95% CI)	PFS Experimental Arm months (95% CI)	PFS Control Arm months (95% CI)	PFS Hazard Ratio (95% CI)	ORR Experimental Arm % (95% CI)	ORR Control Arm % (95% CI)	CBR Experimental Arm (months)	CBR Control Arm (months)
MONARCH-3[6] Goetz (2017)	III	First	Abemaciclib + anastrozole or letrozole ($n = 328$)	Anastrozole or letrozole ($n = 165$)	PFS	17.8 (NR)	NE	14.7 (–)	0.54 (0.41–0.72; $P < 0.0001$)	48.2 (42.8–53.6)	34.5 (27.3–41.8; $P = 0.002$)	78 (73.6–82.5)	71.5 (64.6–78.4; $P = 0.101$)
PALOMA-2[15] Finn 2016	III	First	Palbociclib + letrozole ($n = 444$)	Letrozole ($n = 222$)	PFS	23 (NR)	24.8 (22.1–NE)	14.5 (12.9–17.1)	0.58 (0.46–0.72; $P < 0.001$)	42.1 (37.5–46.9)	34.7 (28.4–41.3; $P = 0.06$)	84.9 (81.2–88.1)	70.3 (63.8–76.2; $P < 0.001$)
MONALEESA-2[8,17] Hortobagyi (2016/2018)	III	First	Ribociclib + letrozole ($n = 334$)	Letrozole ($n = 334$)	PFS	26.4 (NR)	25.3 (23.0–30.3)	16.0 (13.4–18.2)	0.56 (0.43–0.72; $P < 0.0001$)	42.5 (NR)	28.7 (NR)	79.6 (75.3–84.0)	72.8 (68.0–77.5)
PALOMA-1[5] Finn (2015)	II	First	Palbociclib + letrozole ($n = 84$)	Letrozole ($n = 81$)	PFS	29.6 (27.9–36.0) experimental arm) 27.9 (25.5–31.1) (control arm)	20.2 (13.8–27.5)	10.2 (5.7–12.6)	0.49 (0.32–0.75; $P = 0.0004$)	43 (32 – 54)	33 (23–45; $P = 0.13$)	81 (71–89)	58 (47–69; $P = 0.0009$)
MONALEESA-7[a,7,47] Harbeck (2018)	III	First	Ribociclib + goserelin + tamoxifen/NSAI ($n = 335$)	Placebo + goserelin + tamoxifen/NSAI ($n = 337$)	PFS	15.1 (experimental arm) 11.4 (control arm)	23.8 (19.2–NE)	13.0 (11.0–16.4)	0.55 (0.44–0.69; $P < 0.0001$)	40.9 (NR)	29.7 (NR; $P = 0.001$)	79.1 (NR)	69.7 (NR; $P = 0.002$)
MONALEESA-3[16] Slamon (2018)	III	First or Second	Ribociclib + fulvestrant ($n = 484$)	Placebo + fulvestrant ($n = 242$)	PFS	12.7 (experimental arm) 11.1 (control arm)	20.5 (18.5–23.5)	12.8 (10.9–16.3)	0.59 (0.48–0.73; $P < 0.0001$)	32.4 (NR)	21.5 (NR; $P = 0.0009$)	70.2 (NR)	62.8 (NR; $P = 0.002$)
MONARCH-2[11,23] Sledge (2017)	III	First or Second	Abemaciclib + fulvestrant ($n = 446$)	Fulvestrant ($n = 223$)	PFS	19.5 (NR)	16.4(NR)	9.3 (NR; $P < 0.0001$)	0.55 (0.45–0.68; p < 0.001)	35.2 (30.8–39.6)	16.1 (11.3–21.0)	72.2 (68.0–76.4)	56.1 (49.5–62.6; p < 0.001))
PALOMA-3[3] Cristofanelli (2016)	III	Second or later	Palbociclib + fulvestrant ($n = 347$)	Fulvestrant ($n = 174$)	PFS	8.9 (IQR 8.7–9.2)	9.5 (9.2–11.0)	4.6 (3.5–5.6)	0.46 (0.36–0.59; $P < 0.0001$)	NR	NR	67 (61.3–71.5)	40 (32.3–47.3)
TREnd[9] Malorni (2017)	II	Second or later	Palbociclib + aromatase inhibitor or fulvestrant ($n = 57$)	Palbociclib ($n = 58$)	CBR	NR	10.8 (5.6–12.7)	6.5 (5.4–8.5)	0.69 (0.4–1.1)	11 (3–19)	7 (0.4–13)	54 (42 – 67)	60 (48–73)

NR, not reported; PFS, progression free survival; CBR, clinical benefit rate; ORR, overall response rate; IQR, median H score.

[a] Premenopausal women.

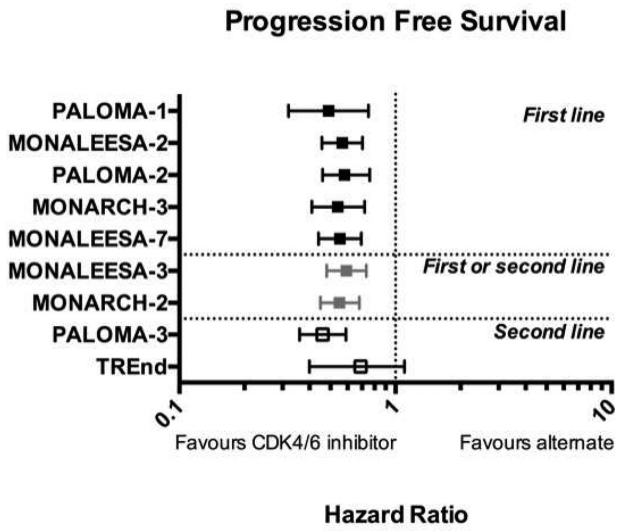

FIGURE 1 Progression free survival in phase III first line studies. Solid squares represent first line studies, grey squares represent first and second line studies, and white squares represent second line studies

subgroup analysis of 108 premenopausal women (21%) in the PALOMA-3 study, median PFS was 9.5 months for patients who received combination therapy compared with 5.6 months for patients who received fulvestrant alone (HR 0.50; 95% CI 0.29 to 0.87).[22]

In the subgroup of 114 pre/peri-menopausal women in the MONARCH-2 study, the median PFS was not reached in the abemaciclib arm ($n = 72$) after a median follow-up of 20.4 months, compared to 10.5 months in the placebo arm ($n = 42$) after a median follow-up of 19.6 months (HR 0.45; 95% CI, 0.264 to 0.754; $P = 0.002$).[23]

In the phase III first line MONALEESA-7 study, which only included premenopausal women, patients receiving first line ribociclib with standard endocrine therapy had significantly improved PFS compared with endocrine therapy alone (23.8 months [95% CI 19.2 to not reached (NR)] vs. 13.0 months [95% CI 11.0 to 16.4; HR 0.55; 95% CI 0.44 to 0.69; $p \leq 0.0001$]).[24]

2.4 | Other subgroups

Comparable efficacy has also been demonstrated in the sub-group with de novo advanced breast cancer in the MONALEESA-2 study. The median PFS was not reached in the ribociclib plus letrozole arm compared with 16.4 months with letrozole (HR 0.45; 95% CI 0.27 to 0.75).[25] In addition, ribociclib plus a NSAI also had clinical activity in patients with high burden of disease, and was associated with a lower rate of treatment discontinuation in patients with three or more metastatic sites compared to placebo (45% vs. 60%).[26]

There were no sub-groups that did not appear to benefit from the addition of CDK4/6 inhibitors to a NSAI across all trials. The most prominent benefit differential appeared to be between Asian and Caucasian patients with Asian patients obtaining a larger relative benefit in PFS in all studies but one (MONARCH-3: HR 0.30; 95% CI 0.17 to 0.52; PALOMA-2: HR 0.48, 95% CI 0.27 to 0.87; MONALEESA-2: HR 0.39, 95% CI 0.17 to 0.91; PALOMA-1: HR not reported).[5,6,8,15] The other trend is that patients with a tumor expressing only estrogen or progesterone receptors rather than both, appear to derive more benefit from the addition of a CDK4/6 inhibitor (MONALEESA-2: HR 0.396, 95% CI 0.20 to 0.65).[8] This raises the question as to whether studies of grade, metastatic site, Ki67 or luminal A relative to luminal B tumors would also show differentials.

2.5 | Monotherapy

While the majority of trials in HR+, HER2– breast cancer have evaluated CDK4/6 inhibitors in combination with endocrine therapy, there are some data for CDK4/6 inhibitors demonstrating single agent activity in the second line or later setting (Table 1). In the phase II TREnd study comparing palbociclib plus an AI to palbociclib alone, the primary endpoint of CBR was 60% (95% CI, 48% to 73%) in the combination arm compared to 54% (95% CI, 42% to 67%) with palbociclib alone.[9]

Single agent abemaciclib demonstrated clinical activity in the refractory setting. MONARCH-1 was a phase II single arm study of abemaciclib at a higher dose of 200 mg twice daily and was associated with an overall response rate of 19.7% (95% CI, 13.3% to 27.5%).[27]

2.6 | Quality of life

Health related Quality of Life questionnaires (HRQoL) were included in the MONALEESA-2 and PALOMA-3 studies.[28–30] In the first line setting, the addition of ribociclib to letrozole maintained quality of life (HR 0.89; 95% CI 0.67 to 1.18).[30] Clinically meaningful reduction in pain was also observed as early as week 8 and maintained for at least 15 cycles.[31] In the second or later lines, the addition of palbociclib to fulvestrant significantly improved overall global HRQoL scores relative to endocrine therapy alone (66.1; 95% CI 64.5 to 67.7 vs. 63.0 95% CI 60.6 to 65.3; $P = 0.0313$).[28] In addition, palbociclib plus fulvestrant significantly improved EuroQoL-5D scores.[29]

3 | BIOMARKERS FOR RESPONSE

A number of biomarker hypotheses have been explored in attempts to identify patients that will obtain the most benefit from CDK4/6 inhibition in combination with standard anti-estrogen therapy. This is partly driven by the cost effectiveness, the efficacy of anti-estrogens alone in some patients and the potential toxicity of this class of compounds. This is especially relevant should this class of compound move into the adjuvant space, which constitutes a larger patient population. Studies have included the analysis of pretreatment tumor samples, correlations of efficacy with toxicity, and the tracking of tumor mutational status through circulating tumor DNA (ctDNA), but none have gained any traction to date.

The PALOMA-1 study included an unselected cohort and one that demonstrated amplification of cyclin D1 (CCND1), loss of p16 (INK4A or CDKN2A), or both in the pretreatment tumor sample. Efficacy was not found to be superior in the biomarker selected group. The PALOMA-2 and MONALEESA-2 studies analyzed a similar series of biomarkers as predictors of response to CDK4/6 inhibitors, including

TABLE 2 Grade 3 or 4 adverse events of clinical interest in phase III studies of first line CDK4/6 inhibitors

	MONARCH-3[6] (*n* = 493)		PALOMA-2[15] (*n* = 666)		MONALEESA-2[8] (*n* = 668)	
Adverse Event	**Abemaciclib *n* (%)**	**Placebo *n* (%)**	**Palbociclib *n* (%)**	**Placebo *n* (%)**	**Ribociclib *n* (%)**	**Placebo *n* (%)**
Neutropenia	69 (21.1)	2 (1.2)	295 (66.4)	3 (1.4)	198 (59.3)	3 (0.9)
Leukopenia	25 (7.6)	1 (0.6)	110 (24.8)	0 (0)	70 (21.0)	2 (0.6)
Anemia	19 (5.8)	2 (1.2)	24 (5.4)	4 (1.8)	4 (1.2)	4 (1.2)
ALT increased	20 (6.1)	3 (1.9)	NR	NR	31 (9.3)	4 (1.2)
AST increased	NR	NR	NR	NR	19 (5.7)	4 (1.2)
Fatigue	6 (1.8)	0 (0)	8 (1.8)	1 (0.5)	8 (2.4)	3 (0.9)
Diarrhea	31 (9.5)	2 (1.2)	6 (1.4)	3 (1.4)	4 (1.2)	3 (0.9)
Vomiting	4 (1.2)	3 (1.9)	2 (0.5)	3 (1.4)	12 (3.6)	3 (0.9)

NR, not reported; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

ER, Rb, p16, cyclin D1 (CCND1) and Ki67.[32,33] Only ER showed predictive value for response to CDK4/6 inhibitors. Of note the majority of studies were carried out on the primary tumor.

With regard to links between efficacy and toxicity, in PALOMA-3 no correlation with efficacy was seen for either degree of neutropenia, nor for dose adjustments made on account of neutropenia.[34] No studies to date have confirmed this lack of association for other toxicities or other agents.

Turning to the monitoring of potential sub-clones during therapy using blood-based DNA analysis, initial assessment of 52 patients from the PALOMA-3 study showed that PFS was significantly longer with fulvestrant and palbociclib in patients with relatively larger reductions in circulating PiK3CA ctDNA over the first 15 days of therapy suggesting that relative clonal proportions may influence eventual outcomes.[35]

4 | TOLERABILITY

Table 2 provides an overview of NCI-CTCAE grade 3 or 4 adverse events of special interest reported in the first line phase III studies of CDK4/6 inhibitors. Dose reductions due to adverse events were reported in 36% to 51% of patients receiving a CDK4/6 inhibitor compared with between 0% and 19% for those receiving placebo.[6,8,15]

4.1 | Hematological adverse events

In first line phase III clinical trials of a CDK4/6 inhibitor, 66.4%, 59.3% and 21.1% of patients receiving palbociclib, ribociclib and abemaciclib experienced grade 3 or 4 neutropenia and 24.8%, 21.0% and 7.6% experienced grade 3 or 4 leukopenia, respectively (Table 2).[8,15,36] Neutropenia associated with ribociclib occurred mainly in the first four weeks of treatment. Five (1.5%) patients receiving ribociclib in the MONALEESA-2 study and eight (1.8%) patients receiving palbociclib in the PALOMA-2 study experienced febrile neutropenia. One patient receiving abemaciclib in the MONARCH-3 study experienced non-serious febrile neutropenia associated with a grade 2 urinary tract infection.[6] Anemia was uncommon, being observed in up to 5.8% of patients receiving abemaciclib and palbociclib and in 1.2% of patients receiving ribociclib.

The rate of neutropenia with palbociclib in the second line setting was similar to the first line setting. Grade 3 or 4 neutropenia was reported in 65% of patients receiving palbociclib in combination with fulvestrant.[34] Grade 3 or 4 leukopenia was reported in 42.7%, anemia in 2.9% and thrombocytopenia in 3.0%. Of the patients experiencing grade 3 or 4 neutropenia, 3.2% had concurrent grade 3 or 4 anemia and 3.2% had concurrent grade 3 or 4 thrombocytopenia. In this study, patients with Asian ethnicity were at greater risk for developing grade 3 or 4 neutropenia compared to non-Asian patients (92% vs. 57%; $P < 0.0001$). Prior chemotherapy, age, ECOG performance status and number of disease sites did not significantly increase the risk of developing grade 3 or 4 neutropenia. The median time for the development of any grade of neutropenia from the first dose of palbociclib was 15 days (range 13–140). The median duration of grade 3 or 4 neutropenia was 7.0 days (range 1–98). Granulocyte-colony stimulating factor (G-CSF) was administered to 11% of patients receiving palbociclib.

Despite the very common occurrence of neutropenia in these studies, low grade infection rates were only modestly increased and severe infection rates were uniformly low. In the MONALEESA 2 and MONARCH 3 studies, 50.3% and 39.1% of patients experienced infections, and 4.3% and 4.9% experienced grade 3 or 4 infections with ribociclib and abemaciclib, respectively, most of which were urinary tract infections and upper respiratory tract infections.[6,8] This compared to 42.4% and 28.6% experiencing infections, and 2.4%, and 3.1% with grade 3 or 4 infections with endocrine therapy alone. Similarly, the PALOMA 2 study reported no increase in the rate of grade 3 or 4 infections on addition of palbociclib. Further, in the PALOMA 3 study only 0.9% of patients experienced febrile neutropenia in the palbociclib arm and 0.6% in the placebo arm, with a rate of concurrent grade 3 or 4 infection of < 2%.

As with palbociclib, the phase III MONARCH-2 study that included patients receiving first or second line abemaciclib with fulvestrant showed similar rates of grade 3 or 4 hematological toxicity to the first line MONARCH-3 study.[11]

4.2 | QTc prolongation

In the MONALEESA-2 study, 3.3% ($n = 11$) of patients receiving ribociclib experienced prolongation of QTc interval to more than 480 ms.[8] Nine patients (2.7%) had an increase of more than 60 ms from

baseline. Changes in QTc interval occurred mostly in the first 4 weeks of treatment. Most patients with QT prolongation continued treatment with 600 mg ribociclib without interruption. Patients with high risk of QTc prolongation were excluded from the trial, and concomitant medications with this propensity were carefully screened for. In a single reported case of sudden death, a patient who had taken a prohibited concomitant medication with a known risk for QT prolongation (methadone) developed prolonged QTcF interval and hypokalemia during cycle 2.[8] Palbociclib and abemaciclib on the other hand have not been shown to prolong the QTc interval.[37] No other cardiac abnormalities have been reported for the CDK4/6 inhibitors.

4.3 | Other adverse events

Grade 3 or 4 increases in alanine and aspartate transaminase levels have been observed with CDK4/6 inhibitors (Table 2).[6,8,15] These are generally asymptomatic and reversible with dose adjustment (Table 4).[13,14]

In the first line phase III studies, grade 3 or 4 diarrhea was more commonly reported in patients receiving abemaciclib (9.5%) compared with palbociclib (1.4%) or ribociclib (1.2%).[6,8,15] In the single agent abemaciclib study, which was administered at a higher dose (MONARCH 1), diarrhea rather than neutropenia was the dose limiting toxicity. A study with neoadjuvant abemaciclib using aggressive prophylactic loperamide therapy is currently underway.

In MONARCH 2 and MONARCH 3, a higher incidence of venous thromboembolic events was observed in the abemaciclib arm.[6,11] In MONARCH 3, the majority of patients who experienced these events did not discontinue abemaciclib.[6]

Rates of grade 3 or 4 fatigue were similar for all CDK4/6 inhibitors (approximately 2%) across the same studies.[6,8,15] However, fatigue of any grade was reported between 36.5% and 40.1% of patients receiving a CDK4/6 inhibitor compared with 27.5% to 31.7% of those receiving an AI alone.

NSAIs have been described previously to cause both male and female pattern hair loss and this appears to be exacerbated by the addition of a CDK inhibitor.[38] There were no reports of grade 3 or 4 alopecia across the first line phase III studies, however alopecia of any grade in the experimental arm was reported in 26.6% of patients in the MONARCH-3 study, 32.9% in PALOMA-2 and 33.2% in the MONALEESA-2 study, compared with10.6%, 15.8% and 15.5% in the placebo group respectively.[6,8,15]

5 | PATIENT MANAGEMENT

Selection of patients for treatment with a CDK4/6 inhibitor requires consideration of a number of key factors: comorbidities, hepatic function, hematological status, concomitant medications and timing with respect to surgery, prior radiotherapy and chemotherapy. When considering ribociclib, cardiac history and comorbidities should be determined, especially conditions that cause baseline prolongation of QT interval. Similarly, medication history should include assessment for concomitant use of drugs known to prolong the QT interval.[39] Drugs associated with a high risk of QT prolongation and torsades de pointes include some antidepressants, antihistamines, antimicrobials, antipsychotics and cardiac drugs as well as cisapride, methadone, ondansetron and chloroquine.[39] ECG monitoring is recommended in the first 2 cycles of ribociclib treatment (Table 3).

TABLE 3 On treatment monitoring for adverse events associated with palbociclib and ribociclib[13,14]

Timepoint	Full Blood Count	Serum Electrolytes	Liver Function Tests	ECG (ribociclib)
Prior to initiation of therapy	X		X	X
Cycle 1 Day 1[a]	X	X	X	
Cycle 1 Day 15	X		X	X
Cycle 2 Day 1[a]	X	X	X	X
Cycle 2 Day 15	X		X	As clinically indicated
Cycle 3 Day 1[a]	X	X	X	As clinically indicated
Cycle 4 Day 1[a]	X	X	X	As clinically indicated
Cycle 5 Day 1[a]	X	X	X	As clinically indicated
Cycle 6 Day 1[a]	X	X	X	As clinically indicated

See local prescribing information for specific instructions for palbociclib or ribociclib, prescribing information for abemaciclib is not available in Australia.

[a]Prior to starting treatment.

CDK4/6 inhibitor dose adjustments for neutropenia require close monitoring in the first few cycles particularly, until a stable dose is established (Table 3 and Table 4). Neutrophil recovery tends to be rapid on cessation of therapy. Palbociclib and ribociclib are dosed for 21 days followed by 7 days' rest during each 28-day cycle to allow for recovery of neutrophils. Abemaciclib, with its lower propensity for neutropenia is dosed continuously.[40]

Patients receiving abemaciclib should be provided with loperamide and instructed to commence it at the first sign of loose stools. The dose can be interrupted or reduced if diarrhea fails to settle, escalates to grade 3, or there is persistent grade 2 diarrhea for more than 7 days (Table 4).

CDK4/6 inhibitors are metabolized by CYP3A, therefore drugs that inhibit or induce CYP3A including several antifungals and antivirals or non-prescription drugs such as cannabis, should be avoided in combination with CDK4/6 inhibitors.[41,42] If necessary to use the treatments concomitantly, the dose of the CDK4/6 inhibitor may be adjusted and neutrophil count monitored closely. Grapefruit juice and pomegranate juice should also be avoided.

For patients scheduled for surgery, it is suggested that CDK4/6 inhibitor therapy is interrupted for 7 days prior to surgery and for 3 weeks after surgery to avoid neutropenia during wound healing and recovery time.[41]

For radiotherapy, there is preclinical data suggesting both potential prevention of radiation-induced toxicity, presumptively by induction of cellular quiescence in normal proliferating tissues,[43] as well as synergy of anticancer effect through direct reactivation of Rb suppression[44] and inhibition of DNA repair by CDK4/6 inhibitors.[45] However, controlled clinical studies are required before considering combining

TABLE 4 Summary table of dose modifications for toxicity related to treatment with palbociclib or ribociclib[13,14]

Adverse Event	Grade/value	Interrupt therapy until	Restart at the same dose	Reduce to next dose level	Discontinue
Neutropenia -first event	3	Grade ≤ 2	X		
Neutropenia -recurring event	3	Grade ≤ 2		X	
Neutropenia	4	Grade ≤ 2		X	
Febrile Neutropenia	3	Grade ≤ 2		X	
AST and/or ALT change from baseline – first event	2	Return to baseline	X		
AST and/or ALT change from baseline – recurring event	2	Return to baseline		X	
AST and/or ALT change from baseline – first event	3	Return to baseline		X	
AST and/or ALT change from baseline – recurring event	3	X			X
AST and/or ALT > 3 x ULN					
plus total bilirubin > 2 x ULN	-	X			X
Diarrhea – first event	3	Grade 1	X		
Diarrhea – recurring event	3	Grade 1		X	
Diarrhea	4	Permanently			X
QT interval – first event[a]	**>480 ms**	<481 ms	X		
QT interval – recurring event[a]	**>480 ms**	<481 ms		X	
QT interval[a,b]	**>500 ms**	<481 ms		X	

See local prescribing information for dosing levels and specific instructions for palbociclib or ribociclib, prescribing information for abemaciclib is not available in Australia.
[a]Ribociclib only.
[b]QT interval is > 500 ms on 2 separate ECGs on the same day.

radiation and CDK4/6 treatment routinely, and cessation of CDK4/6 inhibition during radiotherapy is currently recommended.

6 | DISCUSSION

Comparable efficacy has been demonstrated for the CDK4/6 inhibitors whether given first or second line, and regardless of the choice of backbone endocrine therapy. PFS, ORR and CBR data for CDK4/6 inhibitors show consistent improvement compared to endocrine therapy alone. While the PFS data is extremely encouraging, data for OS remains immature. A key reason for the lack of mature OS data is the significant prolongation of PFS by CDK4/6 inhibitors compared to endocrine therapy alone such that there are insufficient deaths within the prespecified follow-up periods of the phase III trials to accurately report OS. PFS as a surrogate for OS has therefore played a critical role in the approval of these agents.

While CDK4/6 inhibitors are associated with an increased risk of hematological adverse events, these events are predictable and manageable. Furthermore, a meta-analysis of phase II and III clinical trials showed that the rate of febrile neutropenia is not increased compared to endocrine therapy.[46] Monitoring of patients for potential toxicity is required prior to and through the early stages of treatment. The more commonly reported adverse events can be managed by dose modification.

Limitations of this review include that it was not conducted as a registered systematic review or meta-analysis. There are limited numbers of studies included in this review.

7 | CONCLUSIONS

CDK4/6 inhibitors in combination with endocrine therapy represent a significant advance in the treatment of patients with HR+, HER2– metastatic breast cancer. Timely, consistent access to CDK4/6 inhibitors is therefore critical to improve clinical outcomes for patients in Australia.

While current evidence shows a clear role for CDK4/6 inhibitors with endocrine therapy for the first or second line treatment of HR+, HER2– metastatic breast cancer, there is scope for better understanding of their broader role within the clinic. In our accompanying review, we explore the use of CDK4/6 inhibitors in different regimens, combinations and dosing schedules. We consider their role for treating patients with CNS metastases or HR+, HER2+ metastatic breast cancer. Additionally, we look at treatment options for patients with progression of disease after a CDK4/6 inhibitor, including mechanisms of resistance and the role of biomarkers.

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DISCLOSURES

F.B. has served as an investigator on CDK inhibitor trials, and on advisory boards for Pfizer, Novartis, Eli Lilly, Astra Zeneca and Roche. N.W.

has been an investigator on CDK inhibitor trials, owns stock in CSL, has participated in advisory boards for Roche and Novartis and has provided editorial support to Pfizer. R.H. has participated in advisory boards for Novartis, Merck Sharp and Dohme, AstraZeneca, Roche, Bristol Myer Squibb, and Pfizer and has received speaker honoraria from Novartis, Merck Sharp and Dohme, AstraZeneca, Roche, Bristol Myer Squibb, and Boehringer Ingelheim. J.B. has participated in advisory boards for Pfizer, Novartis, Eli Lilly and Roche. R.D.B. served as an investigator on CDK inhibitor trials, is a member of advisory boards for Novartis and Roche and has received speaker honorariums from Novartis, Roche, Amgen and Genomic Health. A.R. has been an investigator on CDK inhibitor trials, and participated on advisory boards for Pfizer, Novartis, Roche, and Eisai. E.L. has received research funding from Novartis and Bayer Pharmaceuticals, and has participated in advisory boards for Pfizer, Novartis, Roche, Eisai and Lilly. N.M.C. has been an investigator on CDK inhibitor trials and participated in advisory boards for Pfizer, Novartis, Roche and Astra Zeneca.

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