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ORIGINAL ARTICLE

Tolerability and Efficacy of Palbociclib and Ribociclib in Breast Cancer in Hong Kong: A Single-Centre Study

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ABSTRACT

Introduction: *This study aimed to analyse the safety, tolerability, and other potential factors affecting the treatment outcome of advanced breast cancer (including inoperable stage III or stage IV, as per the eighth edition of the American Joint Committee on Cancer staging manual) treated with palbociclib or ribociclib at a single institution in Hong Kong.*

Methods: *The medical records of all breast cancer patients receiving palbociclib or ribociclib at a hospital in Hong Kong during the period of July 2016 to February 2022 were reviewed. Data regarding baseline demographics, treatment-related adverse events, need for dose reduction, and disease progression were collected.*

Results: *A total of 211 patients were included in the study, where 88.6% received palbociclib and 11.4% received ribociclib. Among the patients started on full doses (91.4% for palbociclib and 91.7% for ribociclib), 48.5% and 54.5% required dose reduction, respectively, most often due to neutropenia. No statistically significant factor could be identified for predicting the severity of neutropenia in this cohort. In patients on first-line treatment, dose reduction, treatment delay, high levels of oestrogen receptor and progesterone receptor were associated with longer progression-free survival, with respective p values of < 0.001, 0.010, 0.002, and 0.001.*

Conclusion: *Palbociclib and ribociclib were safe and well-tolerated in a predominantly Asian population in real-life clinical practice, with comparable treatment outcomes to those quoted in international clinical trials. Dose reduction did not compromise the treatment efficacy.*

Key Words: *Asian; Breast neoplasms; Drug tolerance; Hong Kong*

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Ethics Approval: This research was approved by the Hong Kong East Cluster Research Ethics Committee of Hospital Authority, Hong Kong (Ref No.: HKECREC-2022-67). The requirement for informed patient consent was waived by the Committee due to the retrospective nature of the study.

Supplementary Material: The supplementary material was provided by the authors and some information may not have been peer reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong College of Radiologists. The Hong Kong College of Radiologists disclaims all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkjr2317720).

中文摘要

在香港使用帕博西尼及瑞博西尼治療乳癌的耐受性及效用：單一中心研究

孔朗程、宋崧

簡介：本研究旨在分析在香港某所醫院使用帕博西尼及瑞博西尼治療晚期乳癌（包括根據美國癌症聯合委員會癌症分期系統第8版分類的無法進行手術的第III期或第IV期）的安全性、耐受性及影響治療結果的其他潛在因素。

方法：我們回顧了2016年7月至2022年2月期間所有在香港某所醫院接受帕博西尼或瑞博西尼治療的乳癌患者的醫療紀錄，收集的資料包括基線人口特徵、與治療相關的不良事件、減少劑量的需要及病情惡化情況。

結果：本研究共包括211名患者，當中88.6%使用帕博西尼，11.4%使用瑞博西尼。在開始時使用全劑量的患者中（91.4%使用帕博西尼的患者及91.7%使用瑞博西尼的患者），分別有48.5%及54.5%需要減少劑量，大多由嗜中性白血球減少症引致。在預測本隊列的嗜中性白血球減少症的嚴重程度方面，我們找不到具統計學意義的因素。在接受一線治療的患者中，減少劑量、延遲治療、雌激素受體及孕酮受體水平偏高與較長的疾病無惡化存活相關，p值分別為< 0.001、0.010、0.002及0.001。

結論：在以亞裔人口為主的真實臨床診療情況中，帕博西尼及瑞博西尼是安全及具耐受性的藥物，其治療結果與多個國際臨床試驗所引述的相若。減少劑量並無降低治療效用。

INTRODUCTION

Breast cancer is the leading type of female cancer in Hong Kong, accounting for 27.4% of female cancers diagnosed in 2019,[1] of which approximately 70% to 80% exhibit oestrogen receptor (ER) and/or progesterone receptor (PR) positivity.[2]

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have been established as the standard of care in hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer not at risk of imminent visceral compromise,[3] based on their superior treatment effect in landmark registration trials (i.e., the clinical trials that led the drugs to their approval by the United States Food and Drug Administration [FDA]).[4-12]

Palbociclib, ribociclib, and abemaciclib are the three CDK4/6 inhibitors currently available in Hong Kong.[13-15] Abemaciclib was not made available in the Hospital Authority Drug Formulary until 11 July 2020.[16]

We hereby present our data in a real-life cohort of patients from an institution in Hong Kong. We aimed to analyse the safety and tolerability of palbociclib and ribociclib in our centre. We sought to evaluate for any association between various clinicopathological and treatment-related factors such as dose reduction or occurrences of dose delay and treatment outcome, and whether the treatment outcomes demonstrated in international trials were reproducible in Asians.

METHODS

Data Collection

All patients who received palbociclib or ribociclib for treating advanced breast cancer (including inoperable stage III or stage IV, as per the eighth edition of the American Joint Committee on Cancer staging manual) during the period from July 2016 to February 2022 at Pamela Youde Nethersole Eastern Hospital were included in the study. Medical records were reviewed for data collection.

Study Objectives

The primary objective of this study was the safety and tolerability of treatment, as measured by the frequencies of adverse events (AEs) and need for dose reductions. Toxicities were charted based on patients' self-reported symptoms and the regular review of laboratory results before each cycle. AEs were graded according to the Common Terminology Criteria for Adverse Events version 5.0.

The secondary objective was the treatment outcome as reflected by the progression-free survival (PFS), which is defined as the time from treatment commencement until the date of clinical or radiological progression of measurable disease or death due to any cause. Disease was assessed by physical examination at each visit and regular imaging, including computed tomography or positron emission tomography–computed tomography scan that was usually performed at 4- to 6-month intervals. Patients were followed up from date of CDK4/6 inhibitor commencement till date of disease progression or death.

Patients without evidence of disease progression at the time of data cut-off (on 30 November 2022) or those who defaulted follow-up were censored. Those who developed disease progression or expired due to any cause during treatment were defined as having had an event.

Statistical Analysis

Statistical analysis was conducted by SPSS (Windows version 26.0; IBM Corp, Armonk [NY], United States). Continuous variables were analysed by independent sample *t* tests. Categorical variables were analysed by Pearson's Chi squared test or Fisher's exact test. The Kaplan–Meier method was used for estimation of the PFS, with comparison made via the log-rank test. The effects of multiple patient factors and of clinicopathological and treatment-related factors on the PFS were studied by the Cox proportional hazard model. Factors deemed statistically significant (with a p value < 0.05) on univariate analysis were further analysed by multivariable analysis.

This manuscript was prepared in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

RESULTS

Patient Demographics

Patient demographics are detailed in Table 1. A total of 211 female patients with a median age of 61 years (range, 36-89) were included in the study, of which 96.7% were Chinese, 2.8% were other Asians, and 0.5% were Caucasians. A total of 77.7% had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0-1 at the start of treatment, and 11.4% and 10.9% were of ECOG PS score of 2 or 3, respectively. A total of 88.6% received palbociclib and 11.4% received ribociclib, with 57.3% receiving palbociclib or ribociclib as first-line therapy and 18.0% and 24.6% receiving one of the drugs for second-line, third-line, or beyond. The median duration of follow-up was 387 days (range, 5-2024).

Primary Outcome: Treatment Safety and Tolerability

Occurrence of Adverse Events

The occurrence of AEs (by toxicity grades) and onset time (in weeks) are displayed in Table 2. The most commonly observed AE of all grades was neutropenia (96.2%), followed by anaemia (80.6%) and thrombocytopaenia (66.4%). In all, 72.5% experienced Grade ≥ 3 neutropenia, though the overall incidence of febrile neutropenia was low (3.3%). Of note, one patient (0.5%) experienced grade 5 hyperbilirubinaemia and grade 4 thrombocytopaenia after 5.72 months of ribociclib, dying of liver failure.

Occurrence of Dose Adjustments

In all, 171 out of 187 patients (91.4%) on palbociclib and 22 out of 24 patients (91.7%) on ribociclib were started on the standard dose (Table 1). The remaining patients were started on a reduced dose due to advanced age or poor ECOG PS upon their physician's discretion.

Among the patients on the standard starting dose, 48.5% on palbociclib and 54.5% on ribociclib required dose reduction, most commonly due to neutropenia. The pattern and cause of dose reduction among patients on standard starting doses are shown in Figures 1 and 2, respectively. Dose reduction was largely adherent to the recommended dosing levels of the FDA. Other dose reductions included five weekly cycles or '2 weeks on 2 weeks off' regimens.

Patient Factors on the Presentation of Neutropenia

We analysed the association of multiple patient factors on the grade of neutropenia, including age, ECOG PS score, presence of bone metastasis, first-line vs. later treatment, and prior chemotherapy exposure. No statistically significant predicting factors could be identified. The results are detailed in Table 3.

Secondary Outcome: Treatment Outcome

At the time of data cut-off, 59% (n = 125) patients experienced an event of which 56% (n = 119) experienced disease progression and 3% (n = 6) died due to causes unrelated to oncological illness. A total of 40% (n = 84) patients did not experience disease progression. A total of 1% of patients (n = 2) were censored due to lack of follow-up.

Table 1. Patient demographics (n = 211).*

	Subgroup	No. (%)
Median age, y		61 (range, 36-89)
Age-group, y	≤ 40	7 (3.3%)
	41-60	95 (45.0%)
	61-75	89 (42.2%)
	≥ 76	20 (9.5%)
Eastern Cooperative Oncology Group performance status score	0	4 (1.9%)
	1	160 (75.8%)
	2	24 (11.4%)
	3	23 (10.9%)
Race	Chinese	204 (96.7%)
	Other Asians	6 (2.8%)
	Caucasians	1 (0.5%)
Allred score–oestrogen receptor	0-2	0
	3-5	7 (3.3%)
	6-8	190 (90.1%)
	Missing	14 (6.6%)
Allred score–progestogen receptor	0-2	35 (16.6%)
	3-5	50 (23.7%)
	6-8	112 (53.1%)
	Missing	14 (6.6%)
Disease-free interval	*De novo*	89 (42.2%)
	≤12 mo	6 (2.8%)
	13-24 mo	10 (4.7%)
	>24 mo	106 (50.2%)
No. of metastatic sites	0	2 (0.9%)
	1	69 (32.7%)
	2	42 (19.9%)
	3	45 (21.3%)
	4	29 (13.7%)
	5	17 (8.1%)
	≥ 6	7 (3.3%)
Distribution of metastatic sites	Bone	153 (72.5%)
		Bone only: 35 (16.6%)†
	DLN	119 (56.4%)
		DLN only: 14 (6.6%)†
	Lung	103 (48.8%)
		Lung only: 13 (6.2%)†
	Liver	60 (28.4%)
		Liver only: 4 (1.9%)†
	Brain	7 (3.3%)
	Others	39 (18.5%)
Upfront treatment used in advanced breast cancer	Tamoxifen	5 (2.4%)
	Aromatase inhibitors	24 (11.4%)
	Aromatase inhibitors + ovarian ablation	2 (0.9%)
	Chemotherapy	46 (21.8%)
	CDK4/6 inhibitors	121 (57.3%)
	Others	13 (6.2%)
Series of treatments	First-line	121 (57.3%)
	Second-line	38 (18.0%)
	Third-line or beyond	52 (24.6%)
Hormone used with CDK4/6 inhibitor	Letrozole	126 (59.7%)
	Exemestane	14 (6.6%)
	Anastrozole	5 (2.4%)
	Fulvestrant	64 (30.3%)
	Others‡	2 (0.9%)
CDK4/6 inhibitor used	Palbociclib	187 (88.6%)
	Ribociclib	24 (11.4%)
Starting dose–palbociclib, mg daily (n = 187)	125	171 (91.4%)
	100	13 (7.0%)
	75	3 (1.6%)
Starting dose–ribociclib, mg daily (n = 24)	600	22 (91.7%)
	400	1 (4.2%)
	200	1 (4.2%)
Local ablative therapy before or during CDK4/6 inhibitor treatment	Yes	46 (21.8%)§
	No	165 (78.2%)

Abbreviations: CDK4/6 = cyclin-dependent kinase 4 and 6; DLN = distant lymph node.

* Data are shown as No. (%), unless otherwise specified.

† Patients only had metastasis over the corresponding sites without other metastatic involvement.

‡ One patient was under study, and one patient was initially started on fulvestrant then switched to exemestane as the patient was unfit to continue with injections.

§ Twelve patients (26.1%) during CDK4/6 inhibitor treatment and 34 patients (73.9%) before CDK4/6 inhibitor treatment.

Table 2. Occurrence of common adverse events (by toxicity grades) and onset time (in weeks).*

	All patients (n = 211)	Palbociclib only (n = 187)	Ribociclib only (n = 24)
Neutropenia			
Any grade	203 (96.2%)	181 (96.8%)	22 (91.7%)
Grade ≥ 3	153 (72.5%)	136 (72.7%)	17 (70.8%)
Onset time	3 (1-90)	3 (1-90)	3.5 (2-84)
Anaemia			
Any grade	170 (80.6%)	153 (81.8%)	17 (70.8%)
Grade ≥ 3	27 (12.8%)	25 (13.4%)	2 (8.3%)
Onset time	4 (1-213)	4 (1-213)	4 (2-188)
Thrombocytopaenia			
Any grade	140 (66.4%)	126 (67.4%)	14 (58.3%)
Grade ≥ 3	13 (6.2%)	11 (5.9%)	2 (8.3%)
Onset time	3 (1-97)	3 (1-97)	8.5 (2-45)
Febrile neutropenia			
Yes	7 (3.3%)	7 (3.7%)	0
No	204 (96.7%)	180 (96.3%)	24 (100%)
Onset time	3 (2-88)	3 (2-88)	N/A
Diarrhoea			
Any grade	35 (16.6%)	31 (16.6%)	4 (16.7%)
Grade ≥ 3	1 (0.5%)	1 (0.5%)	0
Onset time	8 (1-84)	8 (1-84)	12.5 (5-47)
Fatigue			
Any grade	46 (21.8%)	43 (23.0%)	3 (12.5%)
Grade ≥ 3	6 (2.8%)	5 (2.7%)	1 (4.2%)
Onset time	5 (1-75)	5 (1-75)	20 (2-24)
Nausea			
Any grade	24 (11.4%)	21 (11.2%)	3 (12.5%)
Grade ≥ 3	1 (0.5%)	1 (0.5%)	0
Onset time	7 (1-26)	7 (1-26)	2 (2-21)
ALT elevation			
Any grade	43 (20.4%)	36 (19.3%)	7 (29.2%)
Grade ≥ 3	1 (0.5%)	1 (0.5%)	0
Onset time	11 (1-178)	9 (1-178)	14 (1-150)
Prolonged QTc interval			
Any grade	22/94 (23.4%)	13/71 (18.3%)	9/23 (39.1%)
Grade ≥ 3	4/94 (4.3%)	2/71 (2.8%)	2/23 (8.7%)
Missing (excluded from the percentage)	117	116	1
Onset time	4 (1-54)	4 (1-54)	2 (1-32)
Non-neutropenic infection requiring hospitalisation			
Yes	17 (8.1%)	16 (8.6%)	1 (4.2%)
No	194 (91.9%)	171 (91.4%)	23 (95.8%)
Onset time	9.5 (3-233)	10 (4-233)	3
Mucositis			
Any grade	62 (29.4%)	55 (29.4%)	7 (29.2%)
Grade ≥ 3	1 (0.5%)	0	1 (4.2%)
Onset time	9 (1-93)	8 (1-93)	21 (4-86)
Rash			
Any grade	17 (8.1%)	13 (7.0%)	4 (16.7%)
Grade ≥ 3	0	0	0
Onset time	5 (1-39)	6 (1-39)	4 (2-20)
Hand/foot syndrome			
Any grade	4 (1.9%)	4 (2.1%)	0
Grade ≥ 3	1 (0.5%)	1 (0.5%)	0
Onset time	19 (2-79)	19 (2-79)	N/A
Peripheral neuropathy			
Any grade	5 (2.4%)	5 (2.7%)	0
Grade ≥ 3	0	0	0
Onset time	6 (3-48)	6 (3-48)	N/A
Alopecia			
Any grade	4 (1.9%)	4 (2.1%)	0
Grade ≥ 3	0	0	0
Onset time	6 (4-16)	6 (4-16)	N/A

Abbreviations: ALT = alanine aminotransferase; N/A = not available.
* Data are shown as No. (%) or median (range), unless otherwise specified.

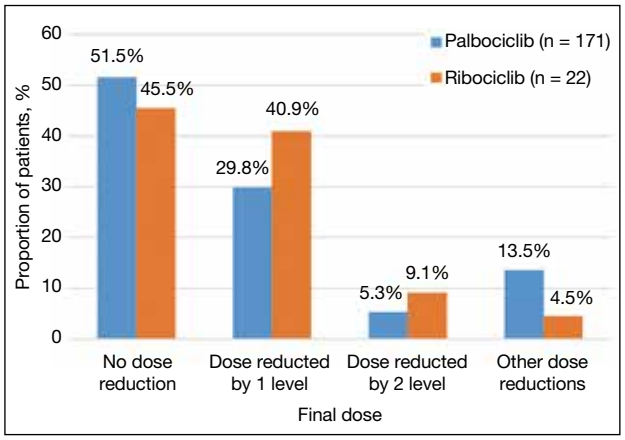

Figure 1. Pattern of dose reduction in patients on standard starting dose.

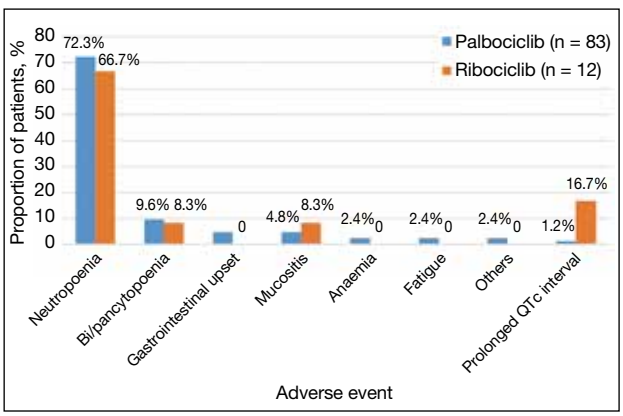

Figure 2. Adverse events necessitating dose reduction.

Patients who received palbociclib or ribociclib as first-line therapy enjoyed longer PFS than those at later lines. Median PFS for first-, second-, and third-line and beyond were 35 months, 20.6 months, and 6.2 months, respectively (Figure 3).

Potential Factors Affecting Treatment Outcome in Patients on First-Line Treatment

Dose reduction, treatment delay (defined by any delay between cycles of ≥ 2 weeks), and high ER and PR levels (with Allred score of 6-8) were each associated with longer PFS, with p values of < 0.001, 0.010, 0.002, and 0.001, respectively. The absence of visceral involvement was not statistically significant (p = 0.352). There was no statistically significant difference in PFS between younger and older age-groups (defined by cut-off at 60 years old), nor between those with ECOG PS scores of 0-1 and 2-3. Subsequent multivariable analysis illustrated that dose reduction and strong PR levels were predictors of longer PFS. ER levels and treatment delay were significant factors in univariate analysis, but such statistical significance was lost upon multivariable analysis. Results are detailed in Table 4 and online supplementary Figure.

Pattern of Dose Reduction on the Treatment Outcome

Amongst the patients started on standard dose regimens who subsequently required dose reductions (n = 95),

Table 3. Patient factors and the grade of neutropenia (n = 211).*

	Grade 0-2 neutropenia (n = 58)	Grade 3-4 neutropenia (n = 153)	p Value
Age, y	61.05 ± 10.54	60.59 ± 11.14	0.787
CDK4/6 inhibitor used			
Palbociclib	51 (87.9%)	136 (88.9%)	
Ribociclib	7 (12.1%)	17 (11.1%)	
Eastern Cooperative Oncology			0.694
Group performance status score			
0	2 (3.4%)	2 (1.3%)	
1	42 (72.4%)	118 (77.1%)	
2	8 (13.8%)	16 (10.5%)	
3	6 (10.3%)	17 (11.1%)	
Presence of bone metastasis			0.291
No	19 (32.8%)	39 (25.5%)	
Yes	39 (67.2%)	114 (74.5%)	
Line of treatment			0.373
First	35 (60.3%)	86 (56.2%)	
Second	7 (12.1%)	31 (20.3%)	
Third	16 (27.6%)	36 (23.5%)	
Prior chemotherapy exposure			0.940
No	25 (43.1%)	74 (48.4%)	
Yes	33 (56.9%)	79 (51.6%)	

Abbreviation: CDK4/6 = cyclin-dependent kinase 4 and 6.
* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified.

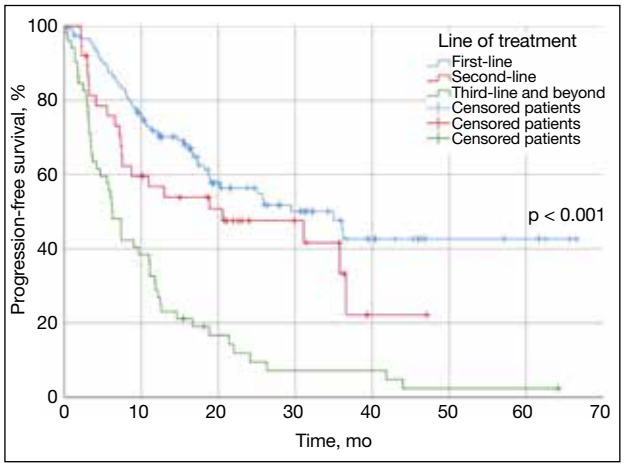

Figure 3. Progression-free survival of patients with different treatment histories.

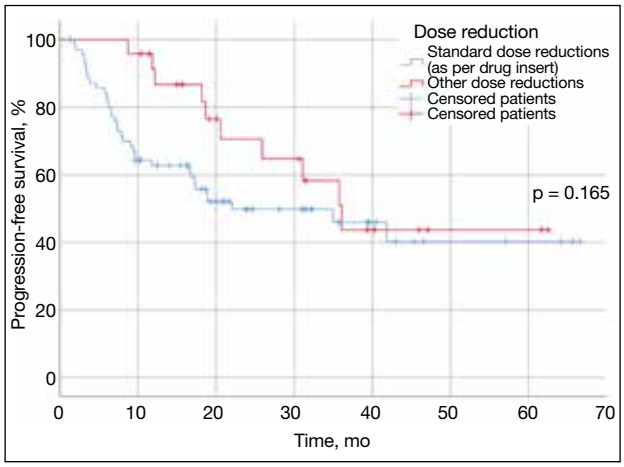

Figure 4. Pattern of dose reduction and treatment outcome shown by progression-free survival in patients on palbociclib or ribociclib who experienced standard dose reductions and other dose reductions.

Table 4. Potential factors affecting treatment outcome in patients on first-line treatment.

	HR (95% CI)	All patients (n = 211)	Patients on palbociclib (n = 104)	Patients on ribociclib (n = 17)
		p Value	p Value	p Value
Dose reduction: no (reference) vs. yes	0.365 (0.209-0.639)	< 0.001	< 0.001	0.277
Treatment delay: no (reference) vs. yes	0.405 (0.204-0.806)	0.010	0.018	0.411
ER level: Allred score 3-5 (reference) vs. 6-8	0.256 (0.107-0.612)	0.002	0.004	0.346
PR level: Allred score 0-5 (reference) vs. 6-8	0.357 (0.198-0.643)	0.001	0.001	0.532
Visceral metastases: present (reference) vs. absent	0.743 (0.397-1.389)	0.352	0.357	0.825
No. of metastatic sites: 0-2 (reference) vs. ≥ 3	1.226 (0.716-2.097)	0.458	0.334	0.750
Age-group: ≤ 60 y (reference) vs. > 60 y	0.949 (0.552-1.631)	0.849	0.734	0.878
ECOG PS: score 0-1 (reference) vs. 2-3	1.167 (0.614-2.218)	0.638	0.971	0.292
Disease status: recurrent disease (reference) vs. *De novo* metastatic disease	0.889 (0.507-1.559)	0.683	0.948	0.304
Starting dose: reduced dose (reference) vs. full dose	2.103 (0.512-8.638)	0.302	0.319	0.721
Multivariable analysis				
Dose reduction: no (reference) vs. yes	0.405 (0.222-0.739)	0.003	0.002	N/A
Treatment delay: no (reference) vs. yes	0.550 (0.262-1.157)	0.115	0.146	N/A
ER level: Allred score 3-5 (reference) vs. 6-8	0.527 (0.211-1.314)	0.169	0.182	N/A
PR level: Allred score 0-5 (reference) vs. 6-8	0.421 (0.228-0.779)	0.006	0.002	N/A

Abbreviations: 95% CI = 95% confidence interval; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor; HR = hazard ratio; N/A = not applicable; PR = progesterone receptor; PS = performance status.

no statistically significant differences in PFS could be observed between those who underwent dose reductions adherent to the FDA drug insert, and those who received dose reductions of other dosing regimens (Figure 4).

DISCUSSION

The treatment landscape of advanced hormone-responsive, HER2-negative breast cancer has transformed dramatically since the emergence of CDK4/6 inhibitors. Palbociclib demonstrated a median PFS of 24.8 and 11.2 months as first- or second-line treatment in PALOMA-2[4] and 3[5] studies, respectively. Ribociclib exhibited consistent PFS advantage in first- and second-line treatment, and in premenopausal women in MONALEESA-2,[6,7] 3,[8] and 7[9] studies (median PFS = 20.5-25.3 months), with updated results revealing a 12.5-month overall survival benefit in first-line therapy.[10] First-line abemaciclib also showed a superior PFS of

28.2 months compared to aromatase inhibitors alone in MONARCH-3 trial.[11,12]

However, Asian patients are often underrepresented in such clinical trials, with only 14.6% and 20% included in PALOMA-2[4] and 3[5] studies, respectively, and 8.4%, 9.3%, and 30% included in MONALESSA-2,[6,7] 3,[8] and 7[9] studies, respectively. There are various cohorts reporting clinical outcomes of CDK4/6 inhibitors around Asia.[17-22] While the recently published PALOMA-4 trial recruited patients from 52 centres across Asia, patients were all of ECOG PS score of 0-1,[21] which was different from the average patients we encounter in our daily clinical practice.

Spanning the dates from July 2016 to February 2022, our study population was predominantly on palbociclib with nearly a quarter of patients not being exposed to CDK4/6 inhibitors unless on third-line therapy or beyond. Such practice was largely influenced by drug availability in our locality. Palbociclib, ribociclib, and abemaciclib were registered in Hong Kong on 2 December 2016,[13] 26 January 2018,[14] and 18 December 2019,[15] respectively. Before their corresponding inclusion into the Hospital Authority Drug Formulary on 14 July 2018,[23] 13 October 2018,[24] and 11 July 2020,[16] patients had to receive such treatment on a named patient basis. The monthly treatment cost of HKD$18,000 to $23,100 precluded its initial accessibility within our public hospital setting, with more widespread use of palbociclib and ribociclib observed since their coverage under the Community Care Fund on 12 January 2019[25] and 13 July 2019,[26] respectively. Abemaciclib was not covered by the Fund till 9 January 2021,[27] and none of our patients in this study received it.

Table 5 displays the median PFS, dose reduction rate, and frequency of toxicities reported in landmark clinical trials and other regional cohorts, compared with our experience. The longer median PFS in first- and second-line treatment in our cohort as compared to those reported in landmark clinical trials could be due to the less unified timing of response assessment in the real-world setting and the relatively short median follow-up time of 12.6 months. While acknowledging that direct comparisons of the PFS with landmark clinical trials are hindered by our heterogeneous patient group, the overall pattern of treatment outcome remains comparable to international standards.

Our dose reduction rates were higher than those of the PALOMA-2 study[4] but similar to those reported in the MONALEESA-2 study[6,7] and other regional Asian cohorts.

Higher rates of grade ≥ 3 haematological toxicities were seen in our cohort than in PALOMA-2 or 3 and MONALEESA-2, 3, or 7 studies, but they were similar to those in PALOMA-4 study and other regional Asian cohorts. This echoes the reports of a higher incidence of grade ≥ 3 neutropenia in Asians, which can be up to 92%.[28] Febrile neutropenia remained low.

Consistent with other international cohorts,[18,19,28-31] dose reduction did not compromise the treatment efficacy.

In a detailed safety analysis of the PALOMA-2 study, Diéras et al[29] conducted a landmark analysis of dose reduction on treatment efficacy at 3, 6, and 9 months in the palbociclib arm. It showed similar PFS in patients who experienced dose reduction and those who did not.[29] Similarly, a pooled safety analysis of MONALEESA-2, 3 and 7 studies showed similar median PFS of 24.8 to 29.6 months across patients on various dose intensities that ranged from ≤ 71% to 100%, which reaffirmed that the PFS, overall response rate, and clinical benefit rate were maintained regardless of dose modifications.[30] One suggestion made by the authors was that variations in drug metabolism and pharmacodynamic effects were present such that patients who experienced more treatment-related AEs, hence requiring dose modifications, were also subjected to enhanced drug exposure leading to an enhanced therapeutic effect.[30] Further studies are warranted to explore the reasons behind this.

Interestingly, we reproduced the same observations noted in a multicentre study from the United Kingdom,[31] in which dose reduction and delays were associated with longer PFS. Owing to the retrospective nature of our study consisting of a relatively small and heterogeneous population, we do not aim to conclude superiority of such dose alterations over the standard dose. Nonetheless, this could be a reassurance that de-escalation of palbociclib or ribociclib dose can be considered in patients when deemed clinically necessary without compromising the treatment outcome.

High PR levels were identified as a statistically significant predictor of longer PFS. High ER levels trended towards statistically significant longer PFS only on univariate but not multivariate analysis. This could be limited by the small number of low–ER level patients (3.3%, n =

Table 5. Published clinical studies on cyclin-dependent kinase 4 and 6 inhibitors for metastatic breast cancer.

	Setting	mPFS, mo	Dose reduction rate	Grade ≥ 3 neutropoenia	Grade ≥ 3 anaemia	Grade ≥ 3 thrombocytopoenia	Febrile neutropoenia	Fatigue	ALT/AST rise	Diarrhoea
PALOMA-2[4]	1L palbociclib + letrozole	24.8	36%	66.5%	5.4%	1.6%	1.8%	37.4%	ALT: 0.23%	26.1%
PALOMA-3[5]	2L palbociclib + fulvestrant	11.2	N/A	69.6%	4.3%	2.9%	1%	44.1%	AST: 11.6%	27.2%
PALOMA-4[21]	1L palbociclib + letrozole in Asians	21.5	28.6%	84.5%	4.8%	6.5%	2.4%	10.1%	ALT: 33.3% AST: 34.5%	10.7%
Lee et al[17]	Palbociclib + letrozole or fulvestrant in Koreans (1L-3L)	25.6 (letrozole) 6.37 (fulvestrant)	32.1%	85.8%	6.5%	8.3%	N/A	27.2%	N/A	3.6%
Shangguan et al[18]	Palbociclib in Chinese	12.8	27.5%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Shen et al[19]	Palbociclib in Chinese	1L: 21 2L: 14 3L: 7	11.1%	30%	32.6% (all grades)	22.1% (all grades)	4.2%	48.4%	N/A	7.9%
MONALEESA-2[6,7]	1L ribociclib + letrozole	25.3	53.9%	59.3%	1.2%	N/A (all grades < 15%)	1.5%	36.5%	ALT: 15.6% AST: 15%	35% (Grade 3: 1.2%)
MONALEESA-3[8]	1L/2L pibociclib + fulvestrant	20.5	37.9%	53.4%	3.1%	1%	1%	31.5%	23.6%	29%
MONALESSA-7[9]	1L ribociclib in pre menopausal patients	23.8	35%	61%	3%	1%	2%	22%	ALT: 7% AST: 8%	19%
Low et al[20]	Palbociclib or ribociclib in Singapore (1L-4L)	1L: 28.2 2L: 18.4 3L: 7.7 ≥ 4L: 9.4	48%	N/A	N/A	N/A	2%	1%	N/A	N/A
MONALEESASIA[22]	Ribociclib + letrozole in Asians	ORR: 56.5%	52.2%	73.9%	N/A	N/A	N/A	N/A	17.4%	N/A
MONARCH-3[11]	1L abemaciclib + aromatase inhibitor	28.2	43.4%	21.1%	5.8%	1.9%	0.3%	40.1%	15.6%	81.3%
The current study	Palbociclib and ribociclib	1L: 35 2L: 20.6 ≥ 3L: 6.2	49.2%	72.5%	12.8%	6.2%	3.3%	21.8%	20.4%	16.6%

Abbreviations: 1L = first-line treatment; 2L = second-line treatment; 3L = third-line treatment; 4L = fourth-line treatment; ALT = alanine aminotransferase; AST = aspartate aminotransferase; mPFS = median progression-free survival; N/A = not available; ORR = overall response rate.

7) in our cohort, precluding analysis. Nevertheless, this mirrored with the observation of PR levels—the other surrogate marker for endocrine responsiveness—and resonates with the exploratory analysis results of the PADA-1 trial presented at the European Society for Medical Oncology Breast Cancer Congress 2022.[32] ER and PR immunohistochemistry scores were shown to have significant impact on PFS achieved with first-line palbociclib, with each 10% gain in ER level being associated with a 10% reduced risk of PFS events (hazard ratio = 0.90; p = 0.002), and each 10% gain in PR level being associated with a 8% risk of PFS events (hazard ratio = 0.92; p < 0.001).[32] This could be a potential area for future studies, aiming to elucidate whether patients with higher ER and PR levels could benefit from a tailor-made reduced dose while still achieving similar therapeutic effect.

Limitations

Limited by its retrospective nature, our clinical study was inevitably influenced by environmental factors such as the varying availability of the drugs due to time and

cost constraints, deviation from standard dose reduction protocol, and underreporting of non-haematological toxicities leading to minor deviations from international cohorts. Nonetheless, the clinical outcomes and safety profile of palbociclib and ribociclib in our centre largely mirrored that seen in drug registration clinical trials and other regional Asian cohorts.

CONCLUSION

To our knowledge, this is the largest cohort of its kind reported locally in Hong Kong. The treatment outcomes and safety profiles of palbociclib and ribociclib demonstrated in our institution, with a predominantly Asian population with ECOG PS scores ranging from 0 to 3, were comparable to those quoted in international clinical trials and other regional Asian cohorts. Dose reduction could be considered when deemed clinically necessary, in hopes of maximising patients' tolerance to treatment and maintaining patients' quality of life, either upon treatment commencement in perhaps older and frailer patients, or in face of AEs, as it did not compromise the treatment efficacy.

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