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Research Article

PALBOCICLIB RESPONSE IN IRAQI PATIENTS WITH METASTATIC BREAST CANCER, CLINICAL PRACTICE

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ABSTRACT

Objectives: To evaluate palbociclib, a novel small molecule inhibitor of cyclin-dependent kinases 4 and 6, in the treatment of hormone receptor-positive/human epidermal growth factor receptor 2 (HR+/HER2−) advanced breast cancer (CA) Iraqi patients.

Methods: One hundred forty female patients with advanced breast CA were enrolled in this prospective cohort study, treated with palbociclib in combination with endocrine therapy.

Results: The mean age of the patients analyzed was 53.51 years (range 23–70). 72.1% were postmenopausal women and 27.9% premenopausal. 56.4% had visceral metastasis, whereas 21.4% of patients had bone-only disease. An overall objective response rate of 36.4% was detected, with 22.9% complete responses and 13.6% partial responses. Stable disease was achieved by 28 patients (20%) with an overall clinical benefit rate (CBR) of 56.4%. There was a difference among biological and clinical demographic characteristics parameters among the treatment response groups that is statistically insignificant, with the exception of the hormonal status parameter, which shows statistical significant difference.

Conclusion: The response to palbociclib treatment in Iraqi patients with HR+/HER2− metastatic breast CA in the form of CBRs, an overall response rate, as well as the factors affecting this treatment, was comparable to that reached by studies in the world (PALOMA-2 and PALOMA-3).

Keywords: Metastatic breast cancer, Hormone receptor positive, Palbociclib, Real-world evidence, Cyclin-dependent kinases 4 / 6 inhibitor.

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INTRODUCTION

Breast cancer (CA) is the most commonly diagnosed CA among women in the world and in Iraq [1]. It represents 21% of all newly diagnosed CA cases in the population and 35% of CA cases in females in 2023, according to the CA registry annual report announced by the Iraqi Ministry of Health [2]. Hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) breast CA subtypes account for approximately 75% of all breast CA cases. These tumors rely heavily on active estrogen receptor signaling for growth and survival [3].

While women with early-stage breast CA typically have a favorable prognosis, those diagnosed with distant metastases face significantly poorer outcomes with a 5-year relative survival rate of just 27% [4].

Cell-cycle signaling has emerged as a key area of research in understanding both the development of breast CA and resistance to endocrine therapy (ET). Disruptions in cell cycle checkpoints regulation due to molecular alterations drive uncontrolled cellular proliferation and are considered a hallmark of CA [5].

The mammalian cell cycle is regulated by a network of cyclins and their associated cyclin-dependent kinases (CDKs). Deregulations of the cyclin-CDK pathway are a defining feature of CA. Among these, D-type cyclins and their associated kinases, including CDK4 and CDK6, are essential for promoting G1 to S phase transition by phosphorylating and inactivating the retinoblastoma protein (RB), the crucial constituent of cell cycle machinery. Evidence has shown that uncontrolled formation of cyclin D1 and CDK 4 / 6 complexes plays a crucial role in both the initiation and progression of CA and may contribute to endocrine resistance [6].

CDK 4 / 6 inhibitors have transformed the treatment landscape for patients with HR+/HER2− metastatic breast CA and have recently demonstrated clinically meaningful efficacy with a favorable tolerability profile in those patients [7].

Palbociclib, a first-in-class orally bioavailable potent and highly selective CDK4 / 6 inhibitor, was approved by the Food and Drug Administration in 2017 for the targeted treatment of metastatic breast CA, inducing cell cycle arrest with synergetic effects when combined with ET [8].

Human cells must cross a checkpoint called the restriction point in the G1 phase of the cell cycle to divide and finish the cell cycle. Phosphorylation of the RB permits the cell to overcome the restriction point and results in cell division. Palbociclib prevents the cyclin D-CDK4 / 6 complex from helping phosphorylating RB, that is loss of RB phosphorylation by blocking CDK4 and CDK6. This prevents the cell from continuing to complete the cell cycle by preventing overcoming the restriction point and escaping the G1 phase of the cell cycle [9,10].

Findings from the PALOMA I and II trials led to the approval of palbociclib for the treatment of patients with HR+/HER2− metastatic breast CA in combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women or with fulvestrant for those who experienced disease progression following prior ET [11,12].

The response evaluation criteria in solid tumors (RECIST), including version 1.0 and 1.1, have been widely recognized and adopted as the standard for assessing treatment response, remaining stable or progressing following treatment [13,14].

A surrogate endpoint of treatment success and morphologic change of tumor size, as calculated by RECIST, is frequently associated with

survival extent. Dynamic changes in tumor diameters as determined by imaging are used to evaluate treatment response in solid tumors [15]. Currently, the most effective techniques for measuring objective lesions for response evaluation are magnetic resonance imaging, computed tomography, and positron emission tomography scan. A chief component of the clinical evaluation of CA treatments is the measurement of the alteration in tumor burden, including both disease progression and tumor shrinkage (objective response) [16].

ET continues to serve as the cornerstone of treatment for women with HR+/HER2− advanced breast CA [17]. Although the effectiveness of ET is often compromised by both intrinsic and acquired resistance, with up to 50% of HR+ patients with metastatic breast CA developing mechanisms of resistance to the therapy they receive [18].

To help to prevent or delay the development of resistance to ET, additional strategies and novel classes of agents targeting alternative growth pathways have been developed [3]. Outside of randomized clinical trials, treatment patterns and clinical effectiveness of palbociclib in patients with metastatic breast CA have not been broadly evaluated in real-world settings. This prospective cohort study represents the first evaluation of palbociclib in real-world clinical practice among Iraqi patients diagnosed with HR+/HER2− advanced breast CA.

This study aimed to evaluate the treatment response for palbociclib in combination with ET in-patients with metastatic breast CA and examine potential predictive factors for disease outcome.

METHODS

Study design

One hundred forty patients were enrolled in a prospective cohort study that spanned from the period of December 2023 to December 2024. This study was carried out in the Middle Euphrates Oncology Center in Al-Najaf governorate. Informed consent was obtained from all individual participants included in the study, and it was approved by the Ethical Committee in the Faculty of Medicine/University of Kufa (No. 41 on November 20, 2023). The research was performed in accordance with the Declaration of Helsinki and the ethical principles.

Study population

All involved patients had advanced metastatic histologically proven (HR+/HER2−) breast CA. They were eligible for enrollment if:

- They had not received prior systemic therapy for advanced disease that had been diagnosed with metastatic disease without prior ET or had relapsed or progressed after endocrine-based therapy
- Pre- and postmenopausal women
- Adequate organ function, hepatic and renal
- Eastern Cooperative Oncology Group (ECOG) performance status of 0–1
- Presence of measurable or evaluable lesions, age at the study entry, disease characteristics, metastatic sites, and number of metastases, as well as tumor biology, were considered and included
- Eligible patients were required to have follow-up data and to have received treatment for 6 months duration, and data collection began with the administration of the first dose of palbociclib.

Treatment plan and procedures

Patients were administered palbociclib (Ibrance®, Pfizer) capsules orally at a dose of 125 mg/day following a 4-week cycle consisting of 3 weeks on treatment and 1 week off and combined either with aromatase inhibitors (letrozole [Femara®] tablets 2.5 mg/day or anastrozole [Armidex®] tablets 1 mg/day continuously), or fulvestrant, (Faslodex®) injection 500 mg intramuscular injection on days 1, 15, 29 and then once every month. Pre/perimenopausal women should be combined with luteinizing hormone-releasing hormone agonists, goserelin (ZOLADEX®) 3.6 mg once monthly subcutaneous injection according to current clinical practice standards. Before the initiation of each treatment cycle, a complete blood count and assessments of organ function were performed. The tumor assessment was conducted at baseline and approximately 6 months later, in accordance with clinical practice and the physician's approach. Median time to response of palbociclib was 6 months (range 4–8) [19].

Treatment was continued until documented disease progression, the occurrence of unacceptable toxicity, or patient refusal.

Treatment efficacy was estimated using RECIST version 1.1. RECIST guideline defined complete response (CR) as the disappearance of all target lesions, partial response (PR) was defined as a decrease of at least 30% in the sum of diameters of target lesions, compared to the baseline sum of diameters, progressive disease (PD) was defined as a rise of at least 20% in the total diameters of target lesions or the emergence of new lesions, stable disease (SD) was defined as a state in which the tumor size did not decrease enough to meet the criteria for PR, nor increase sufficiently to meet the criteria for PD [16].

Statistical analysis

The Statistical Package for the Social Sciences software, version 26.0, was used for statistical analysis. All data were considered statistically significant with $p < 0.05$. Pearson's Chi-square test was used for the assessment of discrete variables, whereas a one way analysis of variance test was used to assess the continuous data across outcome treatment groups.

RESULTS

Over the study period, 140 patients with HR+/HER2− metastatic breast CA patients were enrolled, treated, evaluated, and considered for data analysis.

The demographic physical baseline characteristics of the whole population are demonstrated in Table 1. The age of the patients analyzed was 23–70 years. 82.9% of the patients were aged 65 years or less, whereas 17.1% of patients were more than 65 years. Their height was range 139–198 cm. The weight of the participants was range 39–95. Their body mass index and body surface area were in the range 12.04–45.92 kg/m^2 and 1.34–2.00 m^2, respectively.

Treatment activity and efficacy

All patients received six cycles of palbociclib-based therapy. According to their treatment, 32 (22.9%) showed CR, and 19 (13.6%) displays PR SD was achieved by 28 patients (20%), and 61 patients (43.6%) experienced PD during treatment (Fig. 1).

As a whole response, 51 patients (36.4%) developed an objective response rate (ORR) that was equal to (CR+PR) (Fig. 2).

Regarding clinical benefit rate (CBR), which is equal to (ORR+SD), that was attained in 79 patients (56.4%) (Fig. 3).

Comparison of biological and clinical demographic characteristics parameters among the response groups

Comparison among the response groups according to the patients' menopausal status

As shown in the study, the majority of patients were postmenopausal 72.1% and the SD group showed the highest percentage 82.1%, whereas those of the CR, PR, and PD groups were 65.6%, 68.4%, and 72.1%,

Table 1: Baseline physical demographic characteristics of participants with breast cancer: (n=140)

Characteristic	Minimum	Maximum	Mean	SD
Age	23	70	53.51	10.104
Height	139	198	164.17	13.8
Weight	39	95	68.90	12.5
BMI	12.04	45.92	26.1320	6.6
Body surface area	1.34	2.00	1.7345	0.16

SD: Standard deviation, BMI: Body mass index

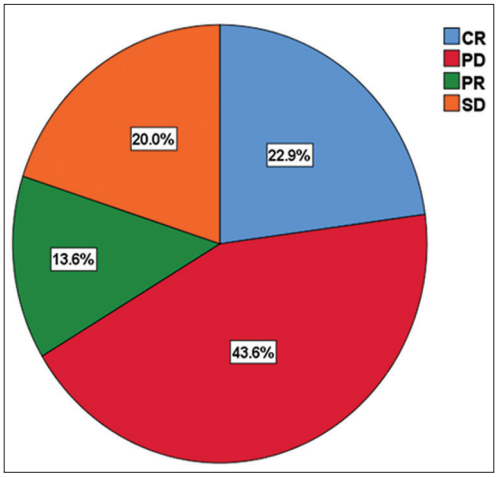

Fig. 1: Distribution of best overall response according to response evaluation criteria in solid tumors 1.1

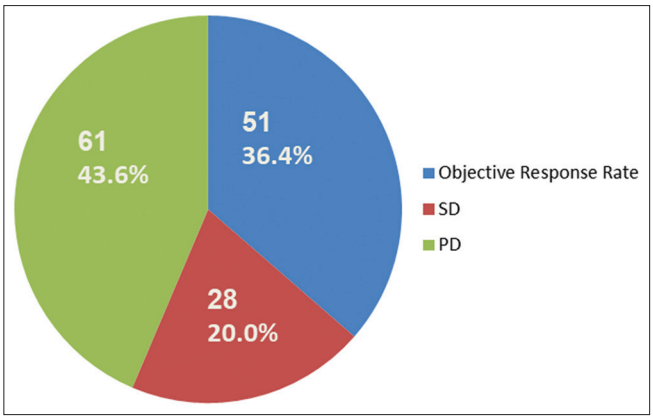

Fig. 2: Objective response rate according to response evaluation criteria in solid tumors 1.1

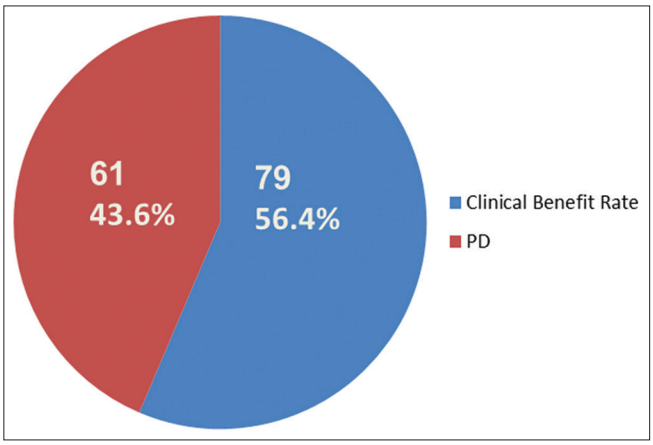

Fig. 3: Clinical benefit rate according to response evaluation criteria in solid tumors 1.1

respectively. Among those in the premenopausal parameter, the main percentage was in the CR group 34.4% and the least in the SD group, 17.9%, whereas those in the PD and PR groups were 27.9% and 31.6%, respectively. Hence, there was a difference in the menopausal status parameter and among response group patients, which is statistically non-significant with *P* = 0.532 (Table 2).

Comparison among the response groups according to the patients' age

As shown in the study, the majority of patients were ≤65 (82.9%), with 86.9% those in the PD group, whereas 84.4%, 84.2%, and 71.4% in the CR, PR, and SD groups, respectively.

While 17.1% of the patients with age >65 and present mainly in the SD group, 28.6%, whereas those in the CR, DP, and PR occur with lower percentages, with 15.6%, 13.1%, and 15.8%, respectively. Hence, there was a difference in the age parameter and among response group patients that is statistically insignificant with *P* = 0.341 (Table 2).

Comparison among the response groups according to the patients' ECOG performance score

As shown in the study, the majority of participants were in ECOG performance status of score 1 (58.6%), with 65.6% in the CR group, whereas 50.8%, 63.2%, and 64.3% those in the PD, PR, and SD groups, respectively.

Those with an ECOG performance status score of 0 was 41.4% and present mainly in the PD group, 49.2%, whereas those in the CR, PR, and SD groups expressed as 34.4%, 36.8%, and 35.7%, respectively. Hence, there was a difference in the ECOG performance status parameter and among response group patients, which is statistically insignificant with *P* = 0.439 (Table 2).

Comparison of pathological demographic characteristics parameters among the response groups

Comparison among the response groups according to the patients' histopathological types

The present study shows that 75% of the histopathological subtypes were invasive ductal carcinoma and expressed mainly in the PR group, with a percentage of 78.9%, whereas those in CR, PD, and SD present as 71.9%, 75.4%, and 75.0%, respectively.

Invasive lobular carcinoma was expressed as 25% and occurred mainly in the CR group with 28.1%, whereas present as 24.6%, 21.1%, and 25.0% in the PD, PR, and SD groups, respectively. Hence, there was a difference in the histopathological subtypes parameter and among response group patients, which is statistically insignificant with p = 0.99 (Table 3).

Comparison among the response groups according to the patients' hormonal status

As revealed in the study, 65% of patients were estrogen receptor positive/progesterone receptor positive (ER+/PR+), and 100% were in the CR group, whereas those in the PD, PR, and SD give a number of 47.5%, 47.4%, and 75%, respectively. The 2nd most common presenting hormonal status was ER−/PR+, which was mainly expressed in the PD group (27.9%), whereas represent as 0%, 26.3%, and 14.3% in the CR, PR, and SD groups, respectively. The least represented hormonal status was ER+/PR−, which was shown mainly in the PR group (26.3%) and expressed as 0%, 24.6%, and 10.7% in CR, PD, and SD groups, respectively. Hence, there was a difference in the hormonal status parameter and among response group patients that is statistically significant with p = 0.0001 (Table 3).

Comparison among the response groups according to the patients' tumor grade

As described in the present study, the majority of tumor grade was Grade 1 (42.9%) and mainly present in the group of PR 52.6%, with the group of CR, PD, and SD expressed as 40.6%, 44.3%, and 35.7%, respectively.

Grade 2 expressed as 35.0% and mainly present in the SD group, 53.6%, whereas those of CR, PD, and PR groups present as 28.1%, 32.8%, and 26.3%, respectively.

Table 2: Comparison of biological and clinical demographic characteristics parameters among the response groups

Parameters	Response				Total	p
	CR (n=32) (%)	PD (n=61) (%)	PR (n=19) (%)	SD (n=28) (%)		
Menopausal status						
Premenopausal	11 (34.4)	17 (27.9)	6 (31.6)	5 (17.9)	39 (27.9)	0.532
Postmenopausal	21 (65.6)	44 (72.1)	13 (68.4)	23 (82.1)	101 (72.1)	
Age/years (Mean±SD)	51.97±9.8	53.15±9.1	54.79±11.1	55.18±11.9		0.6
Age group (years)						
≤65	27 (84.4)	53 (86.9)	16 (84.2)	20 (71.4)	116 (82.9)	0.341
>65	5 (15.6)	8 (13.1)	3 (15.8)	8 (28.6)	24 (17.1)	
ECOG performance score						
0	11 (34.4)	30 (49.2)	7 (36.8)	10 (35.7)	58 (41.4)	0.439
1	21 (65.6)	31 (50.8)	12 (63.2)	18 (64.3)	82 (58.6)	

PR: Partial response, CR: Complete response, PD: Progressive disease, SD: Standard deviation, ECOG: Eastern Cooperative Oncology Group

Table 3: Comparison of pathological demographic characteristics parameters among the response groups

Parameters	Response				Total	p
	CR (n=32) (%)	PD (n=61) (%)	PR (n=19) (%)	SD (n=28) (%)		
ER/PR						
ER+/PR+	32 (100)	29 (47.5)	9 (47.4)	21 (75)	91 (65)	0.0001
ER+/PR−	0 (0)	15 (24.6)	5 (26.3)	3 (10.7)	23 (16.4)	
ER−/PR+	0 (0)	17 (27.9)	5 (26.3)	4 (14.3)	26 (18.6)	
TYPE						
Invasive ductal carcinoma	23 (71.9)	46 (75.4)	15 (78.9)	21 (75.0)	105 (75)	0.99
Invasive lobular carcinoma	9 (28.1)	15 (24.6)	4 (21.1)	7 (25.0)	35 (25)	
Grade						
Grade 1	13 (40.6)	27 (44.3)	10 (52.6)	10 (35.7)	60 (42.9)	0.287
Grade 2	9 (28.1)	20 (32.8)	5 (26.3)	15 (53.6)	49 (35.0)	
Grade 3	10 (31.3)	14 (23.0)	4 (21.1)	3 (10.7)	31 (22.1)	

PR+: Progesterone receptor positive, ER+: Estrogen receptor positive, CR: Complete response, PD: Progressive disease, SD: Standard deviation

On the other hand, tumor Grade 3 presents as 22.1% and primarily presents in the CR group with a percentage of 31.3%, but those in the PD, PR, and SD groups expressed as 23.0%, 21.1%, and 10.7%, respectively. Hence, there was a difference in the tumor grade parameter and among response group patients, which is statistically insignificant with p = 0.287 (Table 3).

Comparison of clinical and metastatic disease demographic characteristics parameters among the response groups

Comparison among the response groups according to the patient's visceral metastasis

According to study results, the majority of patients had visceral metastasis 56.4% with the highest percentage present in the PD group, 62.3%, whereas those of CR, PR, and SD occur with 46.9%, 57.9%, and 53.6%, respectively. Non-visceral metastasis present with a low percentage 43.6% and mainly in the CR group 53.1% but 37.7%, 42.1%, and 46.4% occur in PD. PR and SD group, respectively.

There was a difference in the visceral metastasis parameter and among response group patients, which is statistically insignificant with p = 0.542 (Table 4).

Comparison among the response groups according to the patients' bone-only metastasis

As shown in the study, the minority of patients had bone-only metastasis 21.4% and expressed mainly in the PR group, 26.3%, though those of CR, PD, and SD presented with 21.9%, 19.7%, and 21.4%, respectively. Those participants who had no bone only metastasis were present as 78.6% and expressed mainly in the PD group with a percentage of 80.3%, although those of CR, PR, and SD were present as 78.1% 73.7%, and 78.6%, respectively. There was a difference in the bone-only metastasis parameter and among response group patients, but it is statistically insignificant with *P* = 0.943 (Table 4).

Comparison among the response groups according to the number of metastatic sites

The majority of patients had metastases involving two organs (42.9%) and primarily expressed in the CR and SD groups (50%), whereas those of the PD and PR groups presented as 34.4% and 47.4%. Although 29.3% of the population had only one site of metastases, mainly occurring in the PD group, 32.8% followed by 25%, 26.3%, and 28.6% in the CR, PR, and SD groups, respectively. In addition to that, 20.7% of the participants had three organs of metastatic sites, and mainly found in the PR group, 26.3%, whereas those in the CR, PD, and SD groups expressed as 21.9%, 19.7%, and 17.9%, respectively.

6.4%, and 0.7% of participants had four and five organs of metastatic sites, respectively, and mainly present in the PD group, 11.5% and 1.6%, respectively.

There was a difference in the number of metastasis sites parameter and among response group patients, but it is statistically insignificant with p = 0.735 (Table 4).

Comparison among the response groups according to organs involved by metastatic disease

As shown in the current study, patients present mainly with bone metastasis and represent the highest percentage 79.3% and are primarily expressed in the CR group, 84.4%, whereas those of PD, PR, and SD are expressed as 77%, 73.7%, and 82.1%, respectively. On the other hand, those patients who had no bone metastasis present as 20.7%. Moreover, mainly present in the PR group.

There was a difference in the bone metastatic site parameter and among response group patients, but it is statistically insignificant with p = 0.755 (Table 4).

Table 4: Comparison of clinical and metastatic disease demographic characteristics parameters among the response groups

Parameters	Response				Total	p
	CR (n=32) (%)	PD (n=61) (%)	PR (n=19) (%)	SD (n=28) (%)		
Visceral metastasis						
No	17 (53.1)	23 (37.7)	8 (42.1)	13 (46.4)	61 (43.6)	0.542
Yes	15 (46.9)	38 (62.3)	11 (57.9)	15 (53.6)	79 (56.4)	
Bone only metastasis						
No	25 (78.1)	49 (80.3)	14 (73.7)	22 (78.6)	110 (78.6)	0.943
Yes	7 (21.9)	12 (19.7)	5 (26.3)	6 (21.4)	30 (21.4)	
No. of metastatic sites						
1	8 (25)	20 (32.8)	5 (26.3)	8 (28.6)	41 (29.3)	0.735
2	16 (50)	21 (34.4)	9 (47.4)	14 (50.0)	60 (42.9)	
3	7 (21.9)	12 (19.7)	5 (26.3)	5 (17.9)	29 (20.7)	
4	1 (3.1)	7 (11.5)	0 (0)	1 (3.6)	9 (6.4)	
5	0 (0)	1 (1.6)	0 (0)	0 (0)	1 (0.7)	
Lymph node metastasis						
No	14 (43.8)	32 (52.5)	10 (52.6)	18 (64.3)	74 (52.9)	0.469
Yes	18 (56.3)	29 (47.5)	9 (47.4	10 (35.7)	66 (47.1)	
Lung metastasis						
No	23 (71.9)	38 (62.3)	11 (57.9)	16 (57.1)	88 (62.9)	0.634
Yes	9 (28.1)	23 (37.7)	8 (42.1)	12 (42.9)	52 (37.1)	
Bone metastasis						
No	5 (15.6)	14 (23)	5 (26.3)	5 (17.9)	29 (20.7)	0.755
Yes	27 (84.4)	47 (77)	14 (73.7)	23 (82.1)	111 (79.3)	
Brain metastasis						
No	31 (96.9)	54 (88.5)	19 (100)	26 (92.9)	130 (92.9)	0.265
Yes	1 (3.1)	7 (11.5)	0 (0.0)	2 (7.1)	10 (7.1)	
Liver metastasis						
No	22 (68.8)	36 (59)	12 (63.2)	20 (71.4)	90 (64.3)	0.649
Yes	10 (31.3)	25 (41)	7 (36.8)	8 (28.6)	50 (35.7)	

PR: Partial response, CR: Complete response, PD: Progressive disease, SD: Standard deviation

Lymph node metastatic site was expressed as 47.1% with the highest percentage in the CR group, 56.3%, whereas those with 47.5%, 47.4%, and 35.7% were occur in the PD, PR, and SD, respectively. Those patients with no lymph node metastasis represent as 52.9% and are mainly found in the SD group, 64.3%.

There was a difference in the lymph node metastatic site parameter and among response group patients, but it is statistically insignificant with p = 0.469 (Table 4).

On the other hand, lung metastasis was expressed as 37.1%. Moreover, the primary existing in the SD group 42.9%, whereas those of CR, PD, and PR present as 28.1%, 37.7%, and 42.1%, respectively. Meanwhile, those patients without lung metastasis present as 62.9% and mainly expressed in the PD 62.3%.

There was a difference in the lung metastatic site parameter and among response group patients, but it is statistically insignificant with p = 0.634 (Table 4).

Liver metastasis occurred in the patients with percentage of 35.7% and mainly presented in the PD group 41%, whereas those in the CR, PR, and SD present as 31.3%, 36.8%, and 28.6%, respectively. On the other hand, those participants with no liver metastasis expressed as 64.3%, and present generally in the SD group, 71.4%.

There was a difference in the liver metastatic site parameter and among response group patients, but it is statistically insignificant with p = 0.649 (Table 4).

The least metastatic site was brain metastasis, and present as 7.1% and chiefly expressed as 11.5% in the PD group, whereas those in the CR, PR, and SD group present as 3.1%, 0.0%, and 7.1%, respectively.

Those patients who had no brain metastasis presented as 92.9%, mainly in the PR group, with a percentage of 100%.

There was a difference in the brain metastatic site parameter and among response group patients, but it is statistically insignificant with p = 0.265 (Table 4).

DISCUSSION

Breast CA is now the most commonly diagnosed CA globally and remains the leading cause of CA-related death among women. Its incidence is closely linked to levels of human development, with higher rates observed in more developed regions [20].

The combination of ET with selective CDK4 / 6 inhibitors, palbociclib, has emerged as the new standard of care for women with HR+/HER2− metastatic breast CA. CDK4 / 6 selective inhibitors have demonstrated improved response rates in randomized phase III trials in both first and second line settings [21-23].

As shown in our study, the mean age of the patients analyzed was 53 years (range 23–70). 82.9% of the patients were aged 65 years or less, whereas 17.1% of patients were more than 65 years. All randomized controlled trials used age cutoffs of ≥65 years to define the older population. This was comparable to Palumbo *et al*., in which the median age in the whole population was 62 years (range 47–79), 51.6% of the patients were aged 65 years or less [19]. As reached by the results of the study, there was no effect of age on the palbociclib response, and this was reached by Brain *et al*. Palbociclib revealed similar benefits regardless of age, and palbociclib treatment in older patients in real-world settings demonstrated comparable clinical benefits. Likewise, our data suggest that palbociclib-based regimens were similarly effective in older and younger patients [24].

The majority of the patients were postmenopausal, and this was consistent with the study of Loi *et al*. that evaluated palbociclib in postmenopausal women [25], whereas Loibl *et al*. and DeMichele *et al*. analyzed palbociclibin premenopausal women and also included postmenopausal women in their study [26,27]. As analyzed by the results of our study, there was no effect of menopausal status on the

palbociclib response outcome, and this was confirmed by the PALOMA-3 trial, which included both pre/perimenopausal and postmenopausal patients, demonstrating that palbociclib plus ET improves outcome regardless of menopausal status [28].

The histopathological subtypes in our study included primarily invasive ductal carcinoma and, to a lesser extent, invasive lobular carcinoma. This was comparable to previous studies, which revealed that invasive ductal carcinoma is the most common type of breast CA and represents around 80% of all breast CAs followed by invasive lobular carcinoma [29].

We reached the fact that the histopathological subtypes of carcinoma of the breast do not affect the response to palbociclib treatment. The study done by Finn *et al*. [27] and the PALOMA-3 Trial did not specifically analyze outcomes by histology, invasive ductal versus lobular carcinoma [28].

As described in the present study, the majority of tumor grade was grade 1. This was inconsistent with that reached by the Badowska-Kozakiewicz *et al*., the largest percentage of tumors being classified as Grade 2. Tumor grade describes how much the CA cells resemble normal breast cells. It plays an important role in predicting how fast the CA might grow and spread [30]. As presented in this research, there was no effect of tumor grade on the palbociclib response. Hence, palbociclib is used regardless of tumor grade.

More patients treated with palbociclib plus ET had an ECOG performance status of 0 and 1, with percentages of 41.4% and 58.6%, respectively, and this was similar to Rugo *et al*., who display that participants treated with palbociclib had an ECOG performance status of 0 [31]. Ourresults demonstrated that the response to palbociclib treatment was not affected by the performance status of the patients.

Regarding hormonal status, our study shows that the most common type of hormonal receptor status was ER+/PR+. About 70–80% of breast CAs test positive for these receptors, making ER+ the most prevalent hormone receptor status. Among these ER+ breast CAs, more than 50% also test PR+ [32].

In the present study, the palbociclib response in breast CA was affected by hormonal receptor status, and this was similar to what was reported by Turner *et al*., which revealed that hormonal receptor status plays a crucial role in predicting the response to palbociclib, which is mainly effective in HR+, HER2− breast CA. Clinical trials have demonstrated that the addition of palbociclib to ET shows significant improvement in progression-free survival for patients with this specific subtype [12].

Visceral metastases were present in more than half of cases in this study, 79 cases (56.4%) comparing with 49% in PALOMA-2 [11] and 60% in PALOMA-3 [26], respectively, and this what we reached by the fact that, many women with HR+, human epidermal growth factor receptor 2 negative metastatic breast CA have visceral metastases, which are mostly associated with poorer prognosis compared to those without visceral involvement [33] and this was similar to Finn *et al*. who shows that visceral metastases was presented in most of the cases [29].

Our study demonstrated that, patients with breast CA present with bone only metastasis in a percentage of 21.4% comparing with 38% in PALOMA-2 [11], and 25% in PALOMA-3 [26], respectively, and this explained by the point that bone only metastasis is a common pattern of breast CA spread and it can occur in a substantial proportion of patients with metastatic breast CA, often associated with a favorable prognosis compared to metastasis involving other organs such as the lung or liver [34].

Concerning the number of metastatic sites and regarding patient profile, in our study, the majority of patients had metastases involving two organs (42.9%), whereas 29.3% of the population had only one site of metastasis, whereas other participants had three, four, and five organs of metastatic sites. The number of metastatic sites differs widely among patients with advanced breast CA; some may present with one site, and others have several. For instance, one study reported that 29.4% of patients had three or fewer metastatic sites, 38.6% had between four and five, and 32.0% had between six and thirteen sites [35].

Regarding organs involved by metastatic disease and concerning patient profile, in our study, the most common site of metastases primarily in the bone (79.3%) followed by lung then the liver with non-regional lymph nodes and brain metastases occur with a lesser extent and this was consistent to what we revealed by Kastytis Sidlauskas *et al*., who shows that the most common sites for metastases are commonly involve bone (30–62.5%), lung (11–34%), liver (7.3–32%), and brain (2–16%) [36].

According to their treatment with palbociclib, 22.9% of patients show CR and 13.6% displays PR. SD was achieved by 20% of participants, and 43.6% experienced PD during treatment. This finding was reached according to RECIST, which stands for RECIST, a standardized method for evaluating how solid tumors respond to CA therapy [37]. This was consistent with what we reached by DeMichele *et al*., who assessed the efficacy of palbociclib in combination with ET in women with metastatic breast CA [27]. Mycock *et al*., who studied and supported the use of palbociclib in a broad range of patient populations encountered in real-world clinical practice. This IRIS study program has delivered comprehensive real-world evidence on treatment patterns and clinical outcomes linked to palbociclib across several countries [38].

Again, in certain patients, palbociclib may result in a PR, which is characterized by a reduction in the size of the tumor but does not completely disappear, and this is a significant finding because it indicates that the treatment slows the CA progression and reduces tumor size. Real-world data, such as analysis from Flatiron Health database, displays that palbociclib, when combined with ET, yields a higher overall tumor response rate (complete+PR) 59.8% compared to ET alone [27]. Therapy outcomes can be influenced by factors such as the CA's stage, prior therapies, and the patient's overall health status [39]. In addition to that, palbociclib can lead to an SD in which the CA does not significantly shrink or grow but stays at a consistent size for a certain period. It can leads a SD as a response, and adherence to the treatment regimen is crucial for achieving positive outcomes and optimal results, as was reached by Jadallah *et al*. [40].

In our study, the ORR was 36.4%, and the CBR was 56.4 %, results which show favorable comparison to the data from the PALOMA-2 study (ORR, 42%, CBR, 67%) [11] and similarly, the results are comparable to the efficacy data from PALOMA-3 (ORR, 19%; CBR 67%) [28]. Although the studies are not directly comparable owing to design differences and the number of study populations.

In our study research, although palbociclib improves CBRs, disease progression may still occur in some patients while on treatment, and this was comparable to Maurer, who reported the activity of palbociclib in combination with any ET, in which PD 68.4%. Palbociclib is not a chemotherapy agent and does not kill CA cells; rather, it slows their growth. Although it can be effective in controlling the disease, it is not a cure, and the benefits are not indefinite; some patients may still experience disease progression [41]. Although palbociclib can help overcome resistance to ET, CA cells may eventually adapt and become resistant, leading to PD [42-45].

The study has certain limitations that should be taken into account, including the fact that the follow-up period of the study was relatively short and the sample size was limited compared to some clinical trials.

It represented the first real-world study that offered valuable insights into the demographic, treatment pattern, and clinical characteristics and outcome of patients in Iraq treated with palbociclib in routine

clinical practice. We recommend future studies with a large sample size, multicenter, and a longer period of follow-up.

CONCLUSION

The response to palbociclib treatment in Iraqi patients with HR+/HER2− metastatic breast CA in the form of CBRs, an overall response rate, as well as the factors affecting this treatment, was comparable to that reached by studies in the world (PALOMA-2 and PALOMA-3).

AUTHOR'S CONTRIBUTION

Ammar Rasoul Mohammad, Introduction and discussion (50%); Sarmad Nory Gany, Statistical analyst and Concept (30%), Thekra A Al-Kashwan, Results and Discussion (20%).

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

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