VIA MEDICA

ORIGINAL ARTICLE

Burcu Gulbagci[1], Ayşe Demirci[2], Abdüssamet Çelebi[3], Sedat Tarık Fırat[4], İvo Gökmen[5], İrem Uğurlu[2], Huri Tilla İlçe[6], Emre Çakır[2], İlhan Hacıbekiroğlu[2]

[1]Tekirdag Dr Ismail Fehmi Cumalioglu City Hospital, Tekirdag, Türkiye
[2]Department of Medical Oncology, Sakarya University, Sakarya, Türkiye
[3]Division of Medical Oncology, Department of Internal Medicine, Marmara University School of Medicine, Istanbul, Türkiye
[4]Division of Medical Oncology, Erciyes University, Kayseri, Türkiye
[5]Division of Medical Oncology, Trakya University, Edirne, Türkiye
[6]Department of Nuclear Medicine, Sakarya University, Sakarya, Türkiye

Does toxicity of cyclin-dependent kinase 4/6 inhibitor predict treatment response in metastatic hormone-positive breast cancer patients?

Address for correspondence:
Burcu Gulbagci, MD
Tekirdag Dr Ismail Fehmi Cumalioglu City Hospital, Suleymanpasa
Tekirdag, Türkiye
e-mail: burcubln@gmail.com

Oncology in Clinical Practice
DOI: 10.5603/ocp.101970

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. In hormone receptor-positive metastatic breast cancer without human epidermal growth factor receptor 2 overexpression (HR+/HER2−), a significant progression-free survival benefit has been obtained with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors in the first-line treatment. We mainly aimed to investigate whether the toxicities of CDK 4/6 inhibitors predict treatment response.

Material and methods. This study was designed retrospectively. A total of 191 patients diagnosed with metastatic HR+/HER2– breast cancer were treated with CDK 4/6 inhibitors in four centers in Türkiye included in our study.

Results. One hundred and six patients received ribociclib, and 85 patients received palbociclib. The most common adverse event in both groups was neutropenia. In this study, we found that toxicities did not predict response rates. Additionally, the response rates (RR) in patients with albumin levels above 4.1 g/dl were better than that in patients with albumin levels of 4.1 g/dl and below in multivariate analysis when all patients were considered (OR = 4.76; 95% CI 1.30–17.46; p = 0.018).

Conclusions. Toxicities of CDK4/6-inhibitors did not predict RRs. However, pretreatment albumin level may predict response to ribociclib.

Keywords: cyclin-dependent kinase, neutropenia, metastatic breast cancer, palbociclib, ribociclib
Oncol Clin Pract

Introduction

Breast cancer is the most common malignancy and the leading cause of death in women worldwide [1]. Approximately 75% of stage IV breast cancer patients have estrogen and/or progesterone receptor expression [hormone receptor (HR)-positive] without human epidermal growth factor receptor 2 (HER2) overexpression ($HR^+/HER2^-$). In $HR^+/HER2^-$ metastatic breast cancer, a significant progression-free survival (PFS) benefit has been obtained with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor and endocrine therapy (ET) combinations in the first-line treatment [2, 3].

The most common side effects of CDK 4/6 inhibitors (ribociclib, palbociclib, and abemaciclib) are cytopenias due to bone marrow suppression and gastrointestinal toxicities, such as nausea, vomiting, diarrhea, mucositis, elevated liver enzymes, and QT prolongation of unknown mechanism [4, 5]. It has been observed that hypertension due to sunitinib, a multikinase inhibitor,

Received: 06.08.2024 Accepted: 12.01.2025 Early publication: 13.02.2025

may be a predictive factor in treating metastatic renal cell carcinoma [6]. We aimed to investigate whether the toxicities of CDK 4/6 inhibitors predict treatment response.

Material and methods

This study was designed retrospectively. A total of 191 patients diagnosed with metastatic $HR^+/HER2^-$ breast cancer were treated with CDK 4/6 inhibitors plus endocrine between January 1, 2019, and December 31, 2021, in four centers included in our study. All participating centers were from Türkiye and included Sakarya University Training and Research Hospital, Trakya University Medical Faculty Hospital, Marmara University Pendik Training and Research Hospital, and Erciyes University Medical Faculty Hospital.

Inclusion criteria:

1) above 18 years of age;
2) ER and/or PR-positive, HER2-negative;
3) HER2-negative;
4) metastatic breast cancer patients who were treated with CDK 4/6 inhibitors in any line.

Exclusion criteria:

1) patients switched between CDK 4/6 inhibitors due to allergy, tolerability, or drug availability;
2) male patients with breast cancers;
3) treatment response assessment not done yet.

In this retrospective study, patient data were collected from the Medical Oncology Outpatient Clinic records, patient files, and computer records.

Clinical assessment

Whole blood biochemical parameters were collected at baseline and on days 10 and 28 of treatment as well as the patients' demographic, clinicopathologic, and outcome data, baseline and treatment response evaluation, carcinoembryonic antigens (CEA) and carbohydrate antigens 15-3 (CA15-3), and toxicity profiles from medical records.

Patients received either oral ribociclib or palbociclib. Both groups received an ET intramuscular fulvestrant, an aromatase inhibitor, or tamoxifen. Tumor response was assessed locally as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 at screening, every 12 weeks after initiation of therapy with palbociclib/ribociclib. Response rate (RR) was defined as complete response, partial response, or stable disease of 24-week duration or longer. Adverse events were monitored and graded according to the Common Terminology Criteria for Adverse Events (version 5.0) [7]. Patients were assigned to groups according to the type of CDK 4/6 inhibitors received at any line. Progression-free survival (PFS) was defined as the time from the date of initiation of ribociclib or palbociclib until the date of radiological progression. Patients were regularly followed up at 12-week intervals using thorax and abdomen computed tomography or fluorodeoxyglucose-18 positron emission tomography examinations. Overall survival (OS) was defined as the time from the date of initiation of ribociclib or palbociclib to the date of death from any cause.

Statistical analyses

The IBM Statistical Package for Social Science Statistics for Windows, version 22.0, was used to conduct statistical analyses (IBM Corp., Armonk, MY). The Kolmogorov-Smirnov test was used to determine whether the variables were regularly distributed. The mean and standard deviation (for normally distributed variables) or the median and interquartile range (IQR) were used to express the continuous variables (for not normally distributed variables). The proportions in the two groups were compared using the Chi^2 test or Fisher's exact test. Multivariate logistic regression was performed to determine the factors affecting RR. The Mann-Whitney *U* test was used to compare the variables that were not normally distributed.

On the other hand, Student's *t*-test was used to compare the variables with normal distribution. Categorical features and relationships between groups were assessed using an appropriate Chi-square test. The Kaplan-Meier test for survival analysis was used. The effects of some variables on OS and PFS were analyzed using the log-rank test. A two-tailed p-value < 0.05 was considered statistically significant.

Results

A total of 191 patients were included in this study. One hundred and six patients received ribociclib, and 85 patients received palbociclib. The median age at the start of treatment with CDK 4/6 inhibitors was 57 years (24–85). The histopathological and clinical characteristics of patients are summarized in Table 1. Toxicity profiles were similar between the two groups. The most common adverse event in both groups was neutropenia (grade 3 /4 neutropenia on day 10 was 17.3% for palbociclib and 15.5% for ribociclib). In addition, no statistically significant difference was observed between the two groups regarding dose reduction and treatment delay due to toxicity ($p = 0.073$ and $p = 0.280$, respectively; Tab. 2).

The RR was 77.4% for ribociclib and 83.5% for palbociclib ($p = 0.288$). Objective RR was 60.4% for ribociclib, and 58.8% ($p = 0.317$) for palbociclib (Tab. 3). PFS was the same in both groups, i.e., 14 months ($p = 0.523$). OS was not reached in the palbociclib arm, whereas it was 26 months for ribociclib ($p = 0.720$).

Table 1. Patient and disease characteristics between treatment groups

	All patients n = 191	Ribociclib n = 106	Palbociclib n = 85	p value
Age [years]	56.4 ± 12.1	54.4 ± 11.7	58.9 ± 12.1	**0.011**
Tumor localization [%]				
Right	90 (47.1)	50 (47.2)	40 (47.1)	
Left	98 (51.3)	53 (50)	45 (52.9)	0.289
Right + left	3 (1.6)	3 (2.8)	0	
Menopause status [%]				
Premenopause	68 (35.6)	47 (44.3)	21 (24.7)	**0.006**
Postmenopause	123 (64.4)	59 (55.7)	64 (75.3)	
Histology				
IDC	151 (79)	84 (79.2)	67 (78.8)	
ILC	21 (11)	11 (10.4)	10 (11.8)	0.930
IDC + ILC	4 (2.1)	3 (2.8)	1 (1.2)	
NOS	15 (7.9)	8 (7.6)	7 (8.2)	
Grade				
Grade 1	21 (11)	17 (16)	4 (4.7)	
Grade 2	91 (47.6)	41 (38.7)	50 (58.8)	**0.012**
Grade 3	41 (21.5)	22 (20.8)	19 (22.4)	
Unknown	38 (19.9)	26 (24.5)	12 (14.1)	
Ki-67 [%]				
1–10	44 (23)	22 (20.8)	22 (25.9)	
11–50	100 (53.4)	54 (50.9)	46 (54.1)	0.302
>50	3 (1.6)	3 (2.8)	0	
Unknown	44 (23)	27 (25.5)	17 (20)	
Stage at diagnosis				
Stage 1	3 (1.6)	1 (0.9)	2 (2.4)	
Stage 2	44 (23)	26 (24.5)	18 (21.2)	0.403
Stage 3	55 (28.8)	26 (24.5)	29 (34.1)	
Stage 4	89 (46.6)	53 (50)	36 (42.4)	
Operation of primer tumor				
Yes	120 (62.8)	65 (61.3)	55 (64.7)	0.654
No	71 (37.2)	41 (38.7)	30 (35.3)	
Endocrine therapy				
Letrozole	87 (45.5)	50 (47.2)	37 (43.5)	
Fulvestrant	95 (49.7)	52 (49.1)	43 (50.6)	0.739
Others (anastrazole, exemestane, and tamoxifen)	9 (4.7)	4 (3.8)	5 (5.9)	
Treatment line				
First	92 (48.2)	44 (41.5)	48 (56.5)	
Second	58 (30.4)	39 (36.8)	19 (22.4)	0.066
Third or higher	41 (21.6)	23 (21.7)	18 (21.1)	
Median (IQR*) NLR				
NLR0	2.53 (1.77–3.30)	2.53 (1.73–3.52)	2.51 (1.81–3.25)	0.564
NLR10	1.54 (1.05–2.33)	1.71 (1.22–2.37)	1.4 (0.9–2.2)	0.070
NLR28	1.21 (0.73–1.90)	1.25 (0.75–2.12)	1.1 (0.7–1.9)	0.559
Median (IQR*) PLR				
PLR0	154.59 (116.20–220.00)	153.5 (120.8–238.6)	155.6 (113.3–205.7)	0.707
PLR10	168.57 (125.50–236.10)	184.0 (128.0–238.8)	162.5 (120.6–216.2)	0.171
PLR28	170.84 (121.20–250.44)	174.2 (124.8–254.8)	169.3 (118.1–243.1)	0.176

→

Table 1 cont. Patient and disease characteristics between treatment groups

	All patients n = 191	Ribociclib n = 106	Palbociclib n = 85	p value
Median (IQR*) CRP (mg/L)	5.60 (2.60–16.07)	6.3 (2.5–17.4)	5.3 (2.9–16.0)	0.838
Median (IQR*) Albumin (g/dl)	4.10 (3.89–4.32)	4.2 (3.9–4.3)	4.1 (3.7–4.5)	0.922
Median (IQR*) CEA (U/ml)	5.30 (2.30–21.60)	4.9 (1.7–22.0)	7.6 (2.5–19.9)	0.401
Median (IQR*) CA15-3 (U/ml)	51.20 (23.85–128.0)	47.9 (19.6–147.0)	53.6 (29.9–124.0)	0.297

Descriptive results for continuous variables are expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution. Statistically significant p values are written in bold; CA 15-3 — carbohydrate antigen 15-3; CEA — carcinoembryonic antigen; CRP — C-reactive protein; IDC — invasive ductal carcinoma; ILC — invasive lobular carcinoma; IQR — interquartile range; NLR — neutrophile lymphocyte ratio; NOS — not otherwise specified; PLR — platelet lymphocyte ratio

Table 2. Toxicity profile of the treatment groups

	Ribociclib (n =106)		Palbociclib (n = 85)		
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	p value
Day 10					
Anemia, n (%)	62 (63.3)	1 (1.0)	53 (65.4)	0	0.645
Neutropenia, n (%)	38 (39.2)	15 (15.5)	37 (45.7)	14 (17.3)	0.530
Thrombocytopenia, n (%)	20 (20.6)	1 (1.0)	23 (28.4)	0	0.332
Transaminitis, n (%)	18 (18.8)	4 (4.2)	14 (17.3)	2 (2.5)	0.786
Day 28					
Anemia, n (%)	68 (67.3)	2 (2.0)	59 (72.8)	0	0.369
Neutropenia, n (%)	58 (58.0)	17 (17.0)	39 (48.8)	20 (25.0)	0.347
Thrombocytopenia, n (%)	18 (18)	1 (1)	20 (24.7)	2 (2.5)	0.382
Transaminitis, n (%)	19 (19.6)	4 (4.1)	14(17.7)	1 (1.3)	0.483
QT prolongation, n (%)					
Yes	4 (3.8)		3 (3.5)		0.929
No	102 (96.2)		82 (96.5)		
Mucositis, n (%)					
Yes	6 (5.7)		4 (4.7)		0.769
No	100 (94.3)		81 (95.3)		
Diarrhea, n (%)					
Yes	8 (7.5)		13 (15.3)		0.089
No	98 (92.5)		72 (84.7)		
Dose reduction, n (%)					
Yes	26 (24.5)		31 (36.5)		0.073
No	80 (75.5)		54 (63.5)		
Dose delaying, n (%)					
Yes	38 (35.8)		37 (43.5)		0.280
No	68 (64.2)		48 (56.5)		

Univariate data analysis of the effects of toxicity profiles on PFS and OS was performed for ribociclib and palbociclib treatments. Transaminitis 10th and 28th, QT prolongation, mucositis, and diarrhea were associated with shorter OS in the palbociclib arm ($p < 0.001$, $p < 0.001$, $p < 0.001$, and $p = 0.047$, respectively). Similarly, transaminitis 10th and 28th, QT prolongation, mucositis, and diarrhea were associated with shorter PFS in the palbociclib arm ($p < 0.001$, $p = 0.011$, $p = 0.001$, and $p = 0.023$, respectively). None of the parameters were associated with OS in ribociclib treatment. Only transaminitis on day 10 was associated with shorter PFS ($p = 0.014$).

Table 3. Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors response rates (RR) and survival results

	Ribociclib (n = 106)	Palbociclib (n = 8 5)	p value
Response rates, n [%]			
Complete	10 (9.4)	11 (12.9)	0.383
Partial	54 (50.9)	39 (45.9)	
Stable	18 (17.0)	21 (24.7)	
Progression	24 (22.6)	14 (16.5)	
RR	82 (77.4)	71 (83.5)	0.288
ORR	64 (60.4)	50 (58.8)	0.317
Follow-up (months)	9 (6–13)	10 (6–13)	0.900
PFS, months ± *SE* (95% CI)	14 ± 2 (10.0–18.0)	14 ± 1 (12.0–16.0)	0.523
OS, months ± *SE* (95% CI)	26 ± 4 (21.7–39.0)	NR	0.720

CI — confidence interval; NR — not reached; ORR — objective response rate; OS — overall survival; PFS — progression-free survival; SE — standard error

Table 4. Multivariate analysis affecting response rate (RR) in all patient populations

	Multivariate analysis of RR		
	OR	**95% CI (lower–upper)**	**p value**
Age (≤ 35 yr *vs.* > 35 yr)	9.15	0.45–184.69	0.149
Grade			
1			0.543
2	0.43	0.08–2.31	0.327
3	0.36	0.05–2.28	0.279
Treatment line			
First			0.143
Second	0.70	0.19–2.60	0.604
Third or higher	0.25	0.06–1.00	0.051
Metastatic region (only bone *vs.* others)	0.00	0.00–NR	0.997
Transaminitis, any grade, day 10 (no *vs.* yes)	1.69	0.37–7.75	0.494
Neutropenia, any grade, day 28 (no *vs.* yes)	2.05	0.55–7.56	0.280
Transaminitis, any grade, day 28 (no *vs.* yes)	0.29	0.07–1.23	0.094
QT prolongation (no *vs.* yes)	0.17	0.01–2.62	0.205
Diarrhea (no *vs.* yes)	2.10	0.40–11.01	0.380
Mucositis (no *vs.* yes)	0.47	0.01–12.06	0.651
Albumin (≤ 4.1 g/dL *vs.* > 4.1 g/dL)	4.76	1.30–17.46	0.018
PLR0 (≤ 154 *vs.* > 154)	0.66	0.21–2.07	0.480

Values in bold indicate statistically significant results. Statistically significant p values are written in bold; CI — confidence interval; NR — not reached; OR — odds ratio; PLR0 — platelet lymphocyte ratio 0

In the multivariate analysis, in which all the factors affecting the RR in all patients were evaluated, it was found that the RR decreased as the number of treatment lines increased [odds ratio (OR) = 0.25; 95% confidence interval 95% (CI) 0.06–1.00; p = 0.051]. In the analysis performed separately for ribociclib and palbociclib, significance was obtained in ribociclib (OR = 0.00–0.37; 95% CI 0.00–0.37; p = 0.008), whereas the RR for palbociclib did not differ according to the treatment line (OR = 0.00; 95% CI 0.00–NR; p = 1.00). In the multivariate analysis, the RR in patients with albumin levels ≥ 4.1 g/dL was better than in patients with albumin levels < 4.1 g/dL (OR = 4.76; 95% CI 1.30–17.46; p = 0.018). When the multivariate analysis was performed separately in ribociclib and palbociclib areas, it was seen that this difference was due to ribociclib (OR = 49.89; 95% CI 2.49–999.16; p = 0.011; Tab. 4).

Albumin level significantly affected PFS (p < 0.001, log-rank test), it was included in the multivariate analysis with other possible influencing factors and toxicities.

The factors that negatively affected PFS in ribociclib recipients were the number of treatment steps ≥ 3 (p = 0.027), albumin level ≤ 4.1 g/dL (p = 0.002), and transaminitis on day 10 (p = 0.010). In contrast, only the number of treatment steps ≥ 3 significantly affected OS (p = 0.008). In the palbociclib group, any degree of transaminitis (p = 0.042) and mucositis (p = 0.026) on day 10 had a negative effect on PFS, whereas diarrhea (p = 0.045) had a negative effect on OS. Neutropenia of any degree on day 28 significantly positively affected OS in palbociclib recipients (p = 0.009).

Discussion

In this study, we found that CDK 4/6 inhibitor-related toxicities in metastatic HR+/HER2− breast cancer did not predict RRs. However, the number of treatment steps and albumin level at the beginning of treatment were found to predict response in the ribociclib group.

In MONALEESA-3, the response rate was 32.4% in the entire patient population receiving ribociclib/fulvestrant. In MONALEESA-2, the objective response rate (ORR) was 54.5% in patients receiving ribociclib/letrozole. In PALOMA-3, the ORR was 25%, and PALOMA-2, the ORR was 55.3% [2, 3, 8, 9]. The response rates in our study were similar to those in the MONALEESA and PALOMA studies. Although there was a numerical difference between the two drugs, there was no statistically significant difference.

In a meta-analysis by Onesti et al. [10], hematologic side effects (especially neutropenia) were the most common with ribociclib and palbociclib, whereas gastrointestinal side effects were the most common with abemaciclib. In addition, regardless of the type of CDK inhibitor, the rate of neutropenia was 33%, and in grades 3 and 4, neutropenia was found to be 21%. Considering the toxicity data, in MONALEESA-3, the rate of ribociclib-induced neutropenia was 71.6% (grades 3 and 4, 57.1%), thrombocytopenia was 8.9% (grades 3 and 4, 1.0%), and anemia was 19% (grades 3 and 4, 3.9%). In contrast, the rates of neutropenia were lower in our study. The rates of thrombocytopenia and anemia were higher (Tab. 2). The rate of neutropenia due to palbociclib was 84.1% (grades 3 and 4, 69.6%), thrombocytopenia was 25.5% (grades 3 and 4, 2.9%), anemia was 31.6% (grades 3 and 4, 4.3%), mucositis was 30.1% (grades 3 and 4, 0.9%), diarrhea was 27.2% (grades 3 and 4, 0%) in PALOMA-3, and anemia was higher in our study. Mucositis, diarrhea, and neutropenia were lower, and thrombocytopenia was observed at similar rates (Tab. 2).

In the real-life data of 177 patients receiving palbociclib, as reported by Odan et al. [11], the neutropenia rate was higher than in our study (92.7% in all grades; grades 3 and 4, 72.2%). Similarly, the rates of leukopenia, thrombocytopenia, anemia, and transaminitis were higher than in our study. The need for dose reduction was 36.5% in our patients receiving palbociclib, which is higher than 70% in the study by Odan et al. In our study, 78.9% of the patients received palbociclib in the first and second steps, whereas 73% received palbociclib in the third and higher steps in the study by Odan et al. [11]. The difference in our current toxicity data may be related to the treatment step [11].

In another real-life study by Sun et al. [12], the correlation between neutrophil count and NLR and PFS in patients receiving palbociclib/ET was investigated. Unlike our study, neutrophil levels were recorded at weeks 2, 4, 6, 8, 12, 16, 18, and 24. Lower neutrophil levels were found to be correlated with lower risk of progression [12]. On the contrary, according to the results obtained in our study, the development of neutropenia on days 10 and 28 did not affect the risk of progression in the palbociclib group. However, the development of neutropenia on day 28 positively affected OS.

Contrary to other studies, we examined the cytopenia rates in the hemogram parameters of the patients on days 10 and 28. No statistically significant difference was found between the toxicity rates of the two drugs on days 10 and 28 (Tab. 2). It has been observed that hypertension due to sunitinib, a multikinase inhibitor, may be a predictive marker in treating metastatic renal cell carcinoma [6]. In our study, a similar prediction was not found with CDK 4/6 inhibitor-related toxicities. However, when the factors that may have affected response were evaluated in univariate and multivariate analyses, the RR in patients with albumin levels above 4.1 g/dl was better than that in patients with albumin levels 4.1 g/dl and below in multivariate analysis when all patients were considered (OR = 4.76; 95% CI 1.30–17.46; p = 0.018). This result may be related to the fact that albumin provides information about systemic inflammation and nutritional status.

Study limitations

The main limitations of our study are that it was retrospective, and the patient groups were heterogeneous. The small number of patients, heterogeneity of clinical characteristics of patients (treatment line, endocrine therapies, menopause status, etc.), short follow-up periods, missing data due to retrospective design (comorbidities, performance status, and clinical toxicity data), and lack of post-progression treatment data were other limitations of the study.

Conclusions

In the literature, there are no prospective studies, with similar designs, that compare these two drugs. According to the studies conducted in line with the available data, there are no easily accessible

parameters other than ER/PR positivity that strongly predicts response to CDK 4/6 inhibitors. However, we were interested in whether baseline laboratory parameters and treatment-related toxicities can predict the RR. In this context, our finding about the high RR in patients with high baseline albumin levels for ribociclib will contribute to the literature. There are no data on albumin levels and response rates in the MONALEESA and PALOMA studies. Therefore, we hope our study results will be supported by multicenter real-life data with a larger number of patients and longer follow-up periods.

Article Information and Declarations

Data availability statement

All data are available on reasonable request.

Ethics statement

The study protocol was approved by the ethics committee of Sakarya University Medical Faculty and conducted according to the principles of the Declaration of Helsinki (02.02.2022-71522473-050.01.04-102086-07). Given the retrospective study design, the need for informed consent was waived.

Author contributions

B.G., A.D., H.T.: contributed to the study's conception and design; I.U., A.Ç., I.G., S.T.F.: prepared materials and collected data; B.G., E.Ç., A.D.: analyzed the data; B.G.: wrote the first draft of the manuscript, and all authors commented on subsequent versions.
All authors read and approved the final manuscript.

Funding

None.

Acknowledgments

None of the authors received any financial support that could be considered a potential conflict of interest regarding the manuscript or its submission.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209–249, doi: 10.3322/caac.21660, indexed in Pubmed: 33538338.
2. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016; 375(20): 1925–1936, doi: 10.1056/NEJMoa1607303, indexed in Pubmed: 27959613.
3. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016; 375(18): 1738–1748, doi: 10.1056/NEJMoa1609709, indexed in Pubmed: 27717303.
4. Braal CL, Jongbloed EM, Wilting SM, et al. Inhibiting CDK4/6 in Breast Cancer with Palbociclib, Ribociclib, and Abemaciclib: Similarities and Differences. Drugs. 2021; 81(3): 317–331, doi: 10.1007/s40265-020-01461-2, indexed in Pubmed: 33369721.
5. Sammons SL, Topping DL, Blackwell KL. HR+, HER2- Advanced Breast Cancer and CDK4/6 Inhibitors: Mode of Action, Clinical Activity, and Safety Profiles. Curr Cancer Drug Targets. 2017; 17(7): 637–649, doi: 10.2174/1568009617666170330120452, indexed in Pubmed: 28359238.
6. Bono P, Rautiola J, Utriainen T, et al. Hypertension as predictor of sunitinib treatment outcome in metastatic renal cell carcinoma. Acta Oncol. 2011; 50(4): 569–573, doi: 10.3109/0284186X.2010.543696, indexed in Pubmed: 21208033.
7. - NIH. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. 0 Published: November : 2017.
8. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2020; 382(6): 514–524, doi: 10.1056/NEJMoa1911149, indexed in Pubmed: 31826360.
9. Turner NC, Slamon DJ, Ro J, et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2018; 379(20): 1926–1936, doi: 10.1056/NEJMoa1810527, indexed in Pubmed: 30345905.
10. Onesti CE, Jerusalem G. CDK4/6 inhibitors in breast cancer: differences in toxicity profiles and impact on agent choice. A systematic review and meta-analysis. Expert Rev Anticancer Ther. 2021; 21(3): 283–298, doi: 10.1080/14737140.2021.1852934, indexed in Pubmed: 33233970.
11. Odan N, Kikawa Y, Matsumoto H, et al. Real-World Outcomes of Treating Advanced Breast Cancer Patients With Palbociclib: A Multicenter Retrospective Cohort Study in Japan-The KBCOG-14 Study. Breast Cancer (Auckl). 2020; 14: 1178223420983843, doi: 10.1177/1178223420983843, indexed in Pubmed: 33447040.
12. Sun J, Zhong X, Ma J, et al. Real-world benefit of combination palbociclib and endocrine therapy for metastatic breast cancer and correlation with neutropenia. Cancer Med. 2021; 10(21): 7665–7672, doi: 10.1002/cam4.4295, indexed in Pubmed: 34590788.