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Comparison of different cyclin-dependent kinase inhibitors and KI-67 levels on survival and toxicity in breast cancer treatment

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Abstract. – OBJECTIVE: As cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors, which play a crucial role in the cell cycle, palbociclib and ribociclib are two novel drugs that are recently being used in the treatment of breast cancer. Despite targeting the same pathway, these agents have different molecular activities and processes. KI-67 is known to play a significant role in cell proliferation that has been related to prognosis. This study investigated the impact of palbociclib, ribociclib, and KI-67 on toxicity and survival in breast cancer treatment.

PATIENTS AND METHODS: The study included 140 breast cancer patients in total. Patients were divided into groups based on the use of different CDK inhibitors and KI-67 values. Mortality, progression, treatment response rates, frequency, and severity of adverse events were assessed retrospectively.

RESULTS: The patients in our study had an average age of 53.62±12.71 years, and 62.9% of them were diagnosed at an early stage. 34.3% (n=48) of the patients progressed after receiving treatment, while 19.3% (n=27) of the patients died. The median follow-up time was 576 days, the maximum follow-up time was 1,471 days, and the median time to progression was 301 days (min=28-max=713). Mortality, progression, and treatment response rate between two different CDK inhibitors or KI-67 groups revealed no statistically significant differences.

CONCLUSIONS: Our data show a comparison between the effectiveness of palbociclib and ribociclib, and no noticeable difference is found in breast cancer patients' survival, progression, or severity of adverse effects. Likewise, there is no meaningful difference in KI-67 expression subgroups between progression and survival following treatment.

Key Words:
Breast cancer, CDK inhibitors, KI-67.

Introduction

Breast cancer is a very common cancer and is one of the main causes of death for women. Breast cancer is a heterogeneous disease that can be divided into several subgroups based on histological characteristics and molecular behavior[1,2].

Understanding molecular processes lead the way for the discovery of several novel therapeutic strategies, as well as chemotherapy, hormonal therapy, and monoclonal antibodies in breast cancer[3,4]. The rising of these alternative approaches indicated the development of precision medicine. Precision medicine studies the molecular characteristics, which will affect the selection of type of therapy[5,6]. Important regulators of transcription and cell cycle are cyclin-dependent kinases (CDKs), and inhibiting kinase activity is one of the therapeutic approaches[7].

Progesterone receptor (PgR) and estrogen receptor (ER) are important biomarkers which were discovered by using molecular techniques, and their clinical impact has been remarkable in individuals with malignancies that overexpress human epidermal growth factor 2 (HER2). Reliable biomarkers can be used to identify patients who could benefit from targeted treatments. New biomarker-based tools can ensure that each patient would receive a personalized treatment[8,9].

Selective therapies classified as CDK 4/6 inhibitors are novel approaches. CDK4/6 inhibitors target the CDK-RB1-E2F pathway, which is important for the control of cell proliferation and disruption in most malignancies[10,11]. Clinical studies have demonstrated the mechanism of action of palbociclib. Palbociclib is an agent designed to prevent cell proliferation by inhibiting CDK4 and CDK6, which is crucial to control

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the G1-S transition of the cell cycle. The drug has been studied[12,13] in a variety of tumors and its usage is approved for the treatment of breast cancer. Ribociclib is another CDK4/6 selective inhibitor that prevents the phosphorylation of the retinoblastoma (Rb) protein during the G1 phase of the cell cycle. Although palbociclib and ribociclib are chemically similar and have comparable efficacy evidence, there may be variations in their safety and tolerability[14]. Clinical studies[15,16] have shown that the use of these treatments in combination with endocrine therapy can affect progression-free survival.

Neutropenia, fatigue, diarrhea, nausea, and thrombopenia are prevalent CDK side effects. Palbociclib and ribociclib have similar adverse effects, whereas ribociclib also has cardiotoxic side effects. There may be a dose-dependent prolongation of the QT interval[17,18].

The prognosis for breast cancer depends on a variety of factors. Tumor diameter, axillary lymph node status, histological type of tumor, patient's age, ploidy, and p53 positive are some of the most important prognostic factors for breast cancer[19-21]. One of the cell proliferation markers, KI-67, is used to estimate prognosis and treatment response, using a predetermined 20% cut-off. Based on some studies[22,23], KI-67 expression is correlated with tumor size, histological grade and vascular invasion.

This study compared the effect of two CDK inhibitors, palbociclib and ribociclib, on side effects and survival in breast cancer patients. KI-67 was also used for assessment.

Patients and Methods

This study was conducted in the Department of Oncology at the Faculty of Medicine of Cukurova University, in Turkey. Breast cancer patients who had received treatment with palbociclib or ribociclib between March 2015 and March 2018 were included in this retrospective study.

Groups

The study involved 140 patients who underwent thorough physical examinations. Demographics, clinical characteristics, and treatment patterns were noted. Patients were separated into groups receiving different CDK inhibitors. 86 patients received palbociclib, whereas 54 received ribociclib.

The primary effectiveness variable was survival. A safety assessment was done to determine the severity of the side effects, including the KI-67 percentage assessment for treatment.

The Scientific Research and Publication Ethics Committee of Cukurova University in the Field of Health Sciences approved the study, and each participant signed an informed consent form after being informed in detail.

Statistical Analysis

SPSS 22 program (IBM Corp., Armonk, NY, USA) was used for the analysis of the data and Kolmogorov-Smirnov test was used as the normal distribution test. The data is presented by using arithmetic means, standard deviations, numbers, percentages, medians, and interquartile ranges (IQR). Kaplan-Meier survival analysis, Log-rank, Cox regression analysis, Mann-Whitney, and Chi-square tests were also utilized in the analyzes. A p-value <0.05 was considered statistically significant.

Results

The mean age of the 140 participants (female breast cancer patients) was 53.62±12.71 (min=29-max=86). At the time of diagnosis, 62.9% of patients were at an early stage. After treatment, 34.3% (n=48) of the patients progressed and 19.3% (n=27) of the patients died. The average follow-up time of the patients was 576 days (min=32-max=1,471), and the mean duration for progression was 301 days (min=28-max=713) (Table I).

When mortality, progression, and treatment response rates were compared in patients receiving different CDK inhibitors or separated according to KI-67, there were no statistically significant differences (Figure 1, Table II).

When comparing the frequency and severity of side effects of drugs, increased AST/ALT ratio and QT prolongation in the ribociclib group, diarrhea, and anemia in the palbociclib group were found to be substantially higher than those in the other group. Conversely, there was no significant difference in the severity of side effects between drugs (Table III).

When the frequency and severity of side effects were compared according to the KI-67 level, neutropenia in the >20% group and headache in the ≤20% group were considerably higher (Table IV).

Table I. Sociodemographic and disease characteristics.

Variables	N (%) or $\bar{x}$ ± S.D.
Age	53.62 ± 12.71
Average follow-up time (days)	576.13 ± 226.03
Average progression time (days)	301.59 ± 169.91
CDK groups	
Palbociclib	86 (61.4)
Ribociclib	54 (38.6)
De novo disease	
No	88 (62.9)
Yes	52 (37.1)
Previous chemotherapy (before CDK)	
Yes	40 (27.1)
No	102 (72.9)
Previous endocrine therapy (before CDK)	
No	83 (59.3)
Yes	57 (40.7)
KI67 group	
< 20	78 (55.7)
≥ 20	62 (44.3)
Menopause status	
No (pre and perimenopause)	29 (20.7)
Yes (postmenopause)	111 (79.3)
Treatment response	
Complete	19 (13.6)
Partial	96 (68.6)
Stable	17 (12.1)
Progression	8 (5.7)
Comorbidity	
No	82 (58.6)
Yes	58 (41.4)
ECOG performance	
0	100 (71.4)
1	40 (28.6)
HER2	
Negative	91 (65.0)
1+	14 (10.0)
2+	27 (19.3)
3+	8 (5.7)
Metastasis sites (Before CDK)	
Only bone	45 (32.1)
Only visceral	6 (4.3)
Bone and visceral	89 (63.6)
CSS metastasis	
No	135 (96.4)
Yes	5 (3.6)
Liver metastasis	
No	103 (73.6)
Yes	37 (26.4)
Lung metastasis	
No	79 (56.4)
Yes	61 (43.6)
Progression (at the CDK treatment)	
No	92 (65.7)
Yes	48 (34.3)
Life status	
Survive	113 (80.7)
Ex	27 (19.3)

The mean progression time for palbociclib was 303 days, and the mean survival time was 850 days, while the mean progression time for ribociclib was 306 days, and the mean survival time was 1,156 days. No significant difference was detected between them (Figure 1, Table V).

When the progression time and survival time were compared, according to the KI-67 level, the mean progression time for >20% group was 321 days, and the mean survival time was 1,155 days, while the mean progression time for the < 20% group was 292 days, and the mean survival time was 802 days, with no significant difference between them (Table VI).

The Cox regression model designed to predict mortality was found to be statistically significant (p=0.001). The correction was made in the model according to the CDK inhibitors. The independent variables of the model were KI-67 (ref≤20, risk>20), progression status (ref=-no, risk=yes), and comorbidity status (ref=no, risk=yes). In both treatment groups, the risk of mortality increased: HR=6.05 times in patients with progression and HR=2.18 times in patients with any comorbidities. The percentage of KI-67 at the time of diagnosis was not statistically significant in terms of mortality, according to both drugs (Table VII, Figure 2).

Discussion

Breast cancer is one of the most prevalent forms of cancer, often diagnosed after metastasis, and this cause a challenging situation in breast cancer treatment. Despite novel therapies have significantly improved prognosis, patients might not benefit from them because there are additional subtypes that affect therapeutic efficacy[6,8]. There is a need for comparison of different patient groups and parameters since novel and more effective treatments are being developed to reduce mortality and toxicity.

Cell cycle transitions are regulated by the essential regulatory enzymes known as cyclin-dependent kinases (CDKs), whose function must be controlled to provide cell division[14]. Novel selective drugs called cyclin-dependent kinase (CDK) 4/6 inhibitors represent approved tolerable treatments. Inhibitors of CDK4/6 disrupt the cell cycle in the G1 phase, which may restrict tumor growth. Palbociclib, ribociclib, and abemaciclib

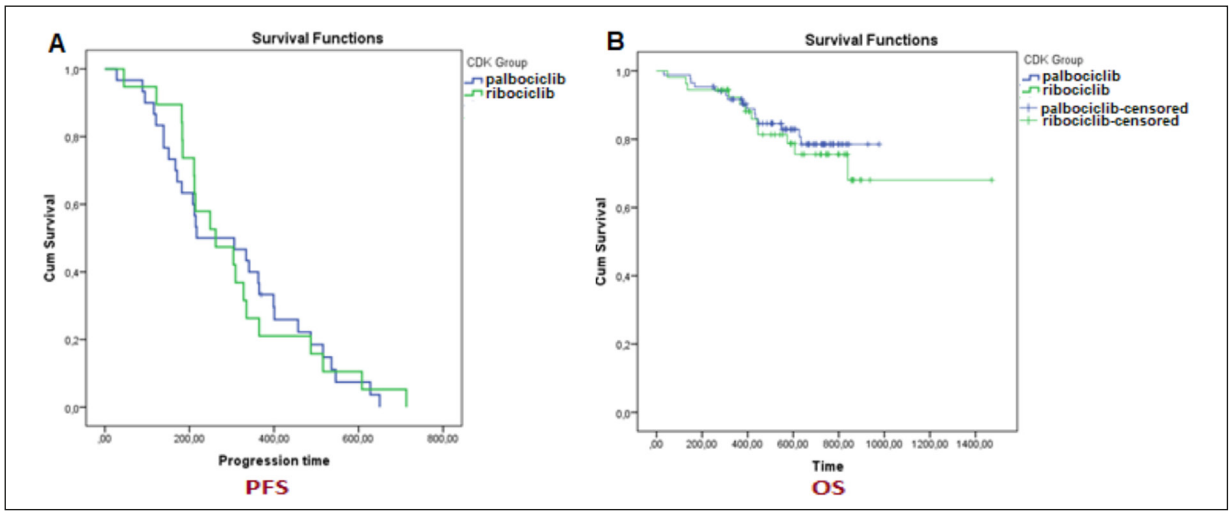

Figure 1. Comparison of progression-free survival (PFS) (**A**), and overall survival (OS) time (**B**).

are the three CDK4/6 inhibitors that are currently approved[24,25], and this study evaluated ribociclib and palbociclib which are accessible for our patients.

CDK inhibitors are orally administered and have similar mechanisms of action, but they can differ in terms of their physical and chemical characteristics, selectivity and efficacy in inhibiting CDK4/6, pharmacokinetics, and pharmacodynamics[25,26]. They have different molecular weights, but ribociclib has a long elimination half-life compared to palbociclib and abemac-

Table II. Comparison of effectiveness according to CDK inhibitors and KI-67 levels.

	CDKi		
	Palbociclib (n = 86)	**Ribociclib (n = 54)**	***p***
Mortality			0.633
No	71 (82.6)	42 (77.8)	
Yes	15 (17.4)	12 (22.2)	
Progression			1.000
No	57 (66.3)	35 (64.8)	
Yes	29 (33.7)	19 (35.2)	
Overall response			0.664
Complete response	13 (15.1)	6 (11.1)	
Partial response	57 (66.3)	39 (72.2)	
Stable disease	12 (14.0)	5 (9.3)	
Progression	4 (4.7)	4 (7.4)	
	KI-67%		
Mortality	≤ 20	> 20	1.000
No	63 (80.8)	50 (80.6)	
Yes	15 (19.2)	12 (19.4)	
Progression			0.786
No	50 (64.1)	42 (67.7)	
Yes	28 (35.9)	20 (32.3)	
Overall response			0.249
Complete response	11 (14.2)	8 (12.9)	
Partial response	55 (70.5)	41 (66.1)	
Stable disease	6 (7.7)	11 (17.7)	
Progression	6 (7.7)	2 (3.2)	

Table III. Comparison of frequency and severity of side effects.

		CDKi n (%) or Median (IQR)		
		Palbociclib (n = 86)	Ribociclib (n = 54)	p
Neutropenia	Yes	53 (61.6)	28 (51.9)	0.335*
	No	33 (38.4)	26 (48.1)	
	Grade$^{\varphi}$	2 (2)	2 (2)	0.421**
Febrile neutropenia	Yes	5 (5.8)	5 (9.3)	0.508*
	No	81 (94.2)	49 (90.7)	
	Grade$^{\varphi}$	2 (1)	1 (2)	0.548**
Infection	Yes	3 (3.5)	2 (3.7)	1.000*
	No	83 (96.5)	52 (96.3)	
	Grade$^{\varphi}$	3 (-)	3 (-)	1.000**
Increased AST/ALT	Yes	14 (16.3)	18 (33.3)	0.033*
	No	72 (83.7)	36 (66.7)	
	Grade$^{\varphi}$	1 (1)	1 (0)	0.722**
Nausea	Yes	27 (31.4)	15 (27.8)	0.791*
	No	59 (68.6)	39 (72.2)	
	Grade$^{\varphi}$	1 (1)	1 (1)	0.959**
Diarrhea	Yes	22 (25.6)	5 (9.3)	0.031*
	No	64 (74.4)	49 (90.7)	
	Grade$^{\varphi}$	1 (0)	1 (0)	0.880**
Fatigue	Yes	35 (40.7)	24 (44.4)	0.794*
	No	51 (59.3)	30 (55.6)	
	Grade$^{\varphi}$	1 (0)	1 (0)	0.138**
Headache	Yes	4 (4.7)	7 (13)	0.106*
	No	82 (95.3)	47 (87)	
	Grade$^{\varphi}$	1 (1)	1 (0)	0.788**
Rash	Yes	4 (4.7)	2 (3.7)	1.000*
	No	82 (95.3)	52 (96.3)	
	Grade$^{\varphi}$	1 (0)	1 (0)	1.000**
Anorexia	Yes	12 (14)	10 (18.5)	0.628*
	No	74 (86)	44 (81.5)	
	Grade$^{\varphi}$	1 (1)	1.50 (1)	0.346**
Anemia	Yes	57 (66.3)	22 (40.7)	0.005*
	No	29 (33.7)	32 (59.3)	
	Grade$^{\varphi}$	1 (1)	1 (1)	0.371**
QT prolongation	Yes	16 (18.8)	28 (51.9)	<0.001*
	No	69 (81.2)	26 (48.1)	
	Grade$^{\varphi}$	1 (0)	1 (1)	0.042**

*Chi-Squared Test, **Mann-Whitney U Test, $^{\varphi}$Median (IQR).

iclib (30-55, 24-34, 17-38 hours, respectively), so different dose levels are required. Suggested dose for palbociclib is 125 mg daily (for 3 weeks) or 200 mg daily (for 2 weeks), for ribociclib it is 600 mg daily (for 3 weeks), and for abemaciclib it is 150 mg daily. The kinase selectivity of palbociclib, ribociclib, and abemaciclib differs from one another. The half maximal inhibitory concentrations are (CDK4:CDK6) 1:1.5, 1:4, 1:5, respectively. These molecules are mostly metabolized by CYP3A4[27,28].

Different CDK inhibitors do not have effect on survival in this study: our analysis shows no statistically significant difference. Both drugs' toxicities were in line with those shown in previous research and clinical trials[15,29,30]. Palbociclib's main toxic side effect that limits dosage is neutropenia, comparable levels, and patterns of hematological toxicity are seen with both palbociclib and ribociclib. There was no difference in the severity of side effects between the two drugs. In our study, the increased AST/ALT ratio and QT prolongation in the ribociclib group, diarrhea, and anemia in the palbociclib group were discovered to be substantially higher. The drug-induced modulation of gene expression may be responsible for the QT interval prolongation seen in ribociclib-treated patients[31]. Although we

Table IV. Comparison of side effects according to the KI-67 levels.

		KI-67 n (%) or Median (IQR)		p
		≤ 20% (n = 78)	> 20% (n = 62)	
Neutropenia	Yes	26 (33.3)	33 (53.2)	0.018*
	No	52 (66.7)	29 (46.8)	
	Grade$^{\varphi}$	2 (2)	2 (2)	0.570**
Febrile neutropenia	Yes	72 (92.3)	58 (93.5)	1.000*
	No	6 (7.7)	4 (6.5)	
	Grade$^{\varphi}$	2 (1)	1.5 (1)	1.000**
Infection	Yes	75 (96.2)	60 (96.8)	1.000*
	No	3 (3.8)	2 (3.2)	
	Grade$^{\varphi}$	2 (-)	3.5 (-)	0.600**
Increased AST or ALT	Yes	64 (82.1)	44 (71.0)	0.177*
	No	14 (17.9)	18 (29.0)	
	Grade$^{\varphi}$	1 (1)	1 (0)	0.292**
Nausea	Yes	52 (66.7)	46 (74.2)	0.436*
	No	26 (33.3)	16 (25.8)	
	Grade$^{\varphi}$	1 (1)	1 (0)	0.485**
Diarrhea	Yes	64 (82.1)	49 (79.0)	0.815*
	No	14 (17.9)	13 (21.0)	
	Grade$^{\varphi}$	1 (0)	1 (0)	1.000**
Fatigue	Yes	48 (61.5)	33 (53.2)	0.322*
	No	30 (38.5)	29 (46.8)	
	Grade$^{\varphi}$	1 (0)	1 (1)	1.000**
Headache	Yes	75 (96.2)	54 (87.1)	0.048*
	No	3 (3.8)	8 (12.9)	
	Grade$^{\varphi}$	1 (-)	1 (0)	0.491**
Rash	Yes	76 (97.4)	58 (93.5)	0.406*
	No	2 (2.6)	4 (6.5)	
	Grade$^{\varphi}$	1 (0)	1 (0)	-
Anorexia	Yes	63 (80.8)	55 (88.7)	0.246*
	No	15 (19.2)	7 (11.3)	
	Grade$^{\varphi}$	1 (1)	1 (1)	1.000**
Anemia	Yes	31 (39.7)	30 (48.4)	0.306*
	No	47 (60.3)	32 (51.6)	
	Grade$^{\varphi}$	1 (1)	1 (1)	0.224**
QT prolongation	Yes	55 (71.4)	40 (64.5)	0.492*
	No	22 (28.6)	22 (35.5)	
	Grade$^{\varphi}$	1 (1)	1 (0)	0.280**

*Chi-Squared Test, **Mann-Whitney U Test, $^{\varphi}$Median (IQR).

Table V. Means and medians for survival time according to CDKi.

	Mean for progression				
			95% Confidence Interval		
CDKi	Estimate	Std. Error	Lower Bound	Upper Bound	p
Palbociclib	303.078	32.586	239.210	366.945	0.925*
Ribociclib	306.789	38.895	230.554	383.025	
Overall	304.942	24.849	256.238	353.646	
CDKi	**Mean for mortality**				
Palbociclib	850.143	29.745	791.844	908.443	0.640*
Ribociclib	1156.171	80.838	997.728	1314.613	
Overall	1187.298	54.822	1079.847	1294.750	

*Kaplan-Meier.

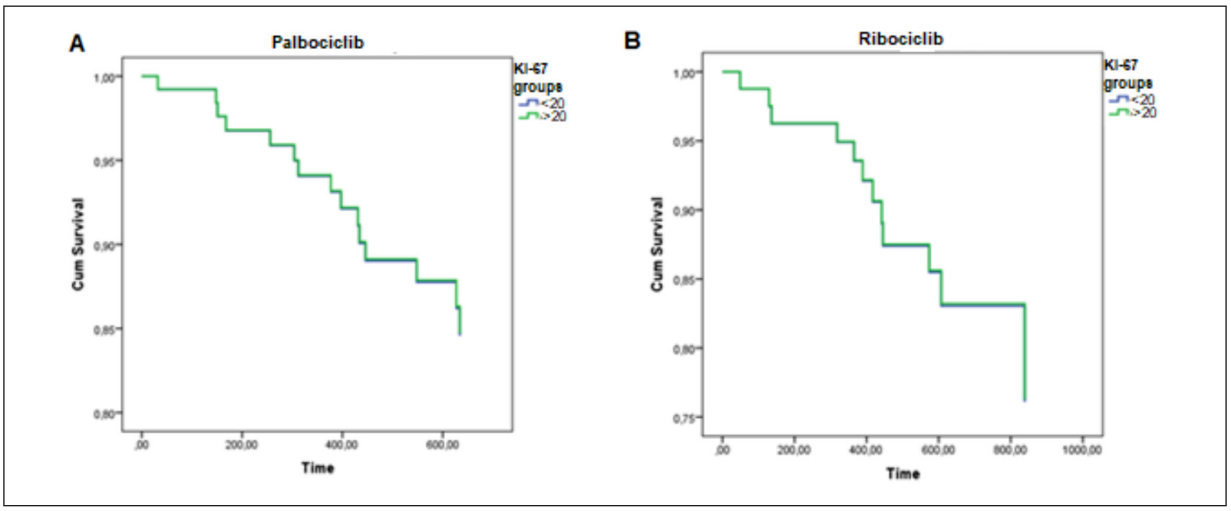

Figure 2. Survival curve according to CDK group: palbociclib (**A**), ribociclib (**B**).

Table VI. Means and medians for survival time according to KI-67%.

KI-67%	Mean for progression				p
			95% Confidence Interval		
	Estimate	Std. Error	Lower Bound	Upper Bound	
< 20% ≥ 20% Overall	292.857 321.913 304.942	29.826 43.247 24.849	234.398 237.148 256.238	351.316 406.677 353.646	0.313
KI-67%	**Mean for mortality**				
< 20 > 20 Overall	802.754 1155.016 1187.298	29.194 88.414 54.822	745.535 981.725 1079.847	859.974 1328.307 1294.750	0.985

Table VII. Cox regression analysis

	B	p	HR	95% CI for HR	
				Lower	Upper
KI-67% Progression Comorbidity	-0.010 1.801 0.780	0.980 < 0.001 0.049	0.990 6.056 2.180	0.461 2.520 1.002	2.126 14.557 4.745

had these data, CDK4/6 inhibitors were chosen according to the experience of physicians, costs, and differences in toxicity profiles[27].

In our study, the choice of CDK inhibitor was based on the physician's preference and the patient's tolerability of drug. Recently, phase studies[32,33] in larger patient populations have demonstrated a statistically significant benefit of ribociclib on overall survival. These findings indicate that future research should prefer ribociclib rather than palbociclib. Further research is needed to compare the CDK4/6 inhibitors and in the treatment of breast cancer.

Due to the diversity of the clinical course of

breast cancers, studies[34,35] have been conducted to find reliable and reproducible prognostic factors. KI-67 is a simple and reliable marker for assessing cell proliferation and is used widely in cancer research. In this study, progression, and treatment response rates were compared in patients separated according to KI-67 levels, detecting no statistically significant differences. Determining different markers would be important for the screening of responsive patients and the improvement of a patient's treatment response.

Limitations

Patients from a single ethnic group participated in the study. The sample size was different for each drug. Despite these limitations, this study represents one of the most comprehensive investigations in literatureon palbociclib and ribociclib, offering important insights regarding the usage of both therapies.

Abemaciclib, another CDK inhibitor, could not be used in our study because it was not in the scope of reimbursement due to health policies.

Conclusions

The new therapies based on palbociclib and ribociclib were compared in this research to reveal more about their efficacy and safety. Both palbociclib and ribociclib were well tolerated, whereas minor variations in their side-effect were observed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

None.

Ethics Approval

The study was approved by Ethical Committee for Non-Interventional Studies of the Faculty of Medicine, Cukurova University, Adana, Turkey (June 3, 2022, Decree No.:123).

Informed Consent

All participants signed informed consent for inclusion.

Availability of Data and Materials

The data of the study are available from the first and corresponding author.

Authors' Contribution

Ertugrul Bayram; conception and design of the study, acquisition of data, analysis and interpretation of data; drafting the article, making critical revisions. Semra Paydas; conception and design of the study, acquisition of data. Burak Mete; conception and design of the study, acquisition of data, analysis, making critical revisions. Tolga Koseci; conception and design of the study. Oguzhan Selvi; conception and design of the study, acquisition of data. Sendag Yaslıkaya; acquisition of data.

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