VIA MEDICA

ORIGINAL ARTICLE

Emilia Barańska-Bała[1], Paulina Małachowska[1], Agnieszka Koper[2, 3], Sławomir Wileński[1, 4], Krzysztof Koper[3, 5]

[1]Central Cytostatic Drug Department, Hospital Pharmacy, The F. Lukaszczyk Oncology Centre, Bydgoszcz, Poland
[2]Department of Oncology, Nicolaus Copernicus University in Torun, Ludwik Rydygier *Collegium Medicum*, Bydgoszcz, Poland
[3]Department of Oncology, Franciszek Lukaszczyk Oncology Centre, Bydgoszcz, Poland
[4]Department of Pharmacy Technology, Nicolaus Copernicus University Ludwik Rydygier *Collegium Medicum*, Bydgoszcz, Poland
[5]Department of Clinical Oncology, and Nursing, Department of Oncological Surgery, Nicolaus Copernicus University in Torun, Ludwik Rydygier *Collegium Medicum*, Bydgoszcz, Poland

The impact of primary radical treatment on the effectiveness and safety of systemic treatment with ribociclib in female patients with advanced breast cancer

Corresponding author:

Sławomir Wileński
Department of Pharmacy Technology,
Nicolaus Copernicus University
Ludwik Rydygier Collegium Medicum,
Jagiellońska 15 St., 85–067 Bydgoszcz,
Poland
e-mail: slawomir.wilenski@cm.umk.pl

Medical Research Journal 2023;
Volume 8, Number 4, 292–299
10.5603/mrj.97119

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Aim of the study: To assess the impact of primary radical treatment on the effectiveness and safety of systemic treatment with ribociclib in patients with advanced breast cancer.

Material and methods: Retrospective data analysis of 180 patients with advanced breast cancer undergoing systemic treatment with ribociclib. The study included a retrospective analysis of data from 180 patients with advanced breast cancer undergoing systemic treatment with ribociclib. The study group included 106 (59%) patients who underwent radical treatment at earlier stages. The control group consisted of 74 patients (41%) diagnosed at an advanced stage.

Results: The analysis showed that progression-free survival is longer in patients with primary advanced disease compared to patients with a history of radical treatment. The median PFS is 21.91 months for patients with a history of radical treatment, while for primary patients it is longer than the total observation time ($p = 0.049$). The median overall survival time did not reach statistical significance and was longer than the time of observation for both groups. In this study, it was observed that the most common adverse event was haematological complications. Neutropenia of any grade was observed in 82.78% of all patients, including G3/G4 neutropenia in 43.89% of patients. Anaemia of any degree was observed in 62.78% of patients, including G3/G4 anaemia in 1.67% of patients. Thrombocytopenia of any degree was observed in 62.78%. For the above complications, no statistically significant differences were observed between the study group and the control group.

Conclusions: A higher benefit (expressed in PFS) from the use of ribociclib will be achieved by patients whose treatment was initiated at a locally advanced or metastatic stage compared to patients with a history of radical treatment of breast cancer. A history of primary radical treatment has no impact on either overall survival or the safety profile of ribociclib treatment.

Keywords: ribociclib, breast cancer, systemic therapy

Med Res J 2023; 8 (4): 292–299

Introduction

Breast cancer is still one of the most commonly diagnosed malignancies worldwide, accounting for 1 in 8 cancer diagnoses. In 2020, 2.3 million new cases of breast cancer were registered among both sexes [1]. Advanced or metastatic breast cancer (MBC) expressing oestrogen receptor (ER+) and epidermal growth factor receptor 2 (HER2–) negative expression is the most common type of metastatic breast cancer. This molecular subtype accounts for 60–70% of all MBCs, that are oestrogen-dependent for development and metastasis. A high level of this hormone is a factor inducing the proliferation of cancer cells and inhibiting their apoptosis [2, 3].

Determination of the expression of receptors, including oestrogen (ER), progesterone (PR) and epidermal growth factor receptor (HER2) is a diagnostic standard, is a predictive and prognostic factor in breast cancer, and enables the selection of optimal therapy. According to the ASCO recommendations, hormone therapy (HT) is an integral part of the treatment of patients with advanced or metastatic luminal type A or HER2-negative luminal type B breast cancer. The type of HT depends on the patient's menopausal status [4, 5].

The purpose of using HT is to eliminate the effect of oestrogens on cancer cells, which is achieved through the use of drugs acting in different mechanisms. The selection of the optimal method depends on many factors, including the risk of disease recurrence, the patient's age, comorbidities and patient preferences [6–11]. Complementary hormone therapy is initially highly effective, reducing the relative risk of recurrence of the disease by about 40%, but in some patients, progression occurs and the need to start another line of treatment. A significant role in increasing the effectiveness and minimizing the risk of recurrence is played by chemotherapy, both perioperatively and used in patients with ER+/HER2– metastatic breast cancer. It should be noted, however, that ER+/HER2– tumours are less susceptible to neoadjuvant chemotherapy than other biological subtypes [12].

A breakthrough in the treatment of advanced ER+/HER2– breast cancer were CDK4/6 inhibitors, including ribociclib, which was registered in 2017 by the FDA based on MONALEESA clinical trials (3, 5 and 7, respectively). These studies showed a statistically significant advantage of ribociclib over placebo. The advantage was related to prolongation of disease progression-free survival, regardless of the line of treatment, prolongation of disease progression-free survival, prolongation of overall survival and overall response to treatment [14–16].

Ribociclib is a selective inhibitor of CDK 4/6, i.e. cyclin-dependent kinases 4 and 6, and cyclin D. Ribociclib shows synergism with endocrine therapy, which results in increased expression of cyclin D and overactivation of CDKs 4 and 6. The inhibition of the cyclin D activation pathway by hormone therapy ultimately reduces the expression of CDK 4/6 kinases and increases the effectiveness of ribociclib [17–19].

Ribociclib is indicated for the treatment of hormone receptor-positive (HR) negative locally advanced, inoperable or metastatic breast cancer without overexpression of human epidermal growth factor 2 (HER2) in combination with an aromatase inhibitor or fulvestrant as first-line endocrine therapy or women who had previously received hormonal treatment [20]. Among the patients treated with ribociclib, some patients started breast cancer treatment from the stage of radical treatment, as well as patients with primary metastases, i.e. patients who start treatment already at the stage of disease with distant metastases. There is a noticeable lack of studies evaluating the effectiveness and safety of ribociclib in specific situations, such as the presence of comorbidities or a history of anticancer treatment. Thus, the results of the available studies on ribociclib do not currently allow for an unambiguous assessment of the impact of treatment of a history of radical breast cancer on the effectiveness and safety of treatment of the disease in the metastatic stage.

One can distinguish haematological and non-haematological adverse events of ribociclib. The most commonly reported haematological adverse reactions during ribociclib therapy include neutropenia, leukopenia and anaemia, while neutropenia, leukopenia and lymphopenia were the most common at G3/4 according to CTCAE (Common Terminology Criteria for Adverse Events). The most common non-haematological adverse reactions were nausea, infections and fatigue. On the other hand, in the G3/G4 according to CTCAE, the most common were: increased ALAT and AST activity and infections [14].

Management of severe or intolerable adverse reactions may require temporary drug interruption, dose reduction, or discontinuation of ribociclib. The starting dose is 600 mg/day. The first dose reduction is 400 mg/day, the second dose reduction is 200 mg/day. If further dose reduction to less than 200 mg/day is required, treatment should be permanently discontinued [20].

Aim of the study

The implementation of the proposed study is aimed at supplementing the knowledge on treatment with ribociclib by comparing the effectiveness and safety profile of this drug in patients previously undergoing radical treatment (study group) *vs.* patients with primary metastasis (control group).

Material and methods

The study is a retrospective analysis in which electronic medical records of patients treated at the Oncology Centre in Bydgoszcz in the years 2017–2022 were used. 180 female patients were included in the study (study group: 106 persons, control group: 74 persons). Data obtained from electronic medical

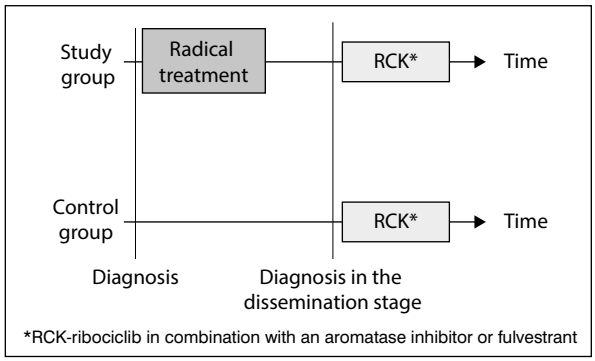

Figure 1. Division into the study group and the control group

records of treated patients include age at the time of starting ribociclib treatment, ECOG performance-status score, previous chemotherapy (for patients from the study group), previous hormone therapy, location of metastases, side effects during ribociclib use, dose reduction of ribociclib, duration of treatment with ribociclib.

The analysis of quantitative variables was performed by calculating the mean, standard deviation, median and quartiles. Qualitative variables were analysed by calculating the number and percentage of occurrences of each value. Comparison of the values of qualitative variables in groups was performed using the chi-square test (with Yates' correction for 2 × 2 tables) or Fisher's exact test. The comparison of quantitative variables in the two groups was performed using the Mann–Whitney test. Kaplan–Meier curves were compared using the LR (long-rank) test. The analysis adopted a significance level of 0.05. The analysis was performed in the R program, version 4.2.2.

Characteristics of the study and control groups

The study involved 180 patients aged 32 to 84 with invasive breast cancer expressing oestrogen receptor (ER+) and epidermal growth factor receptor 2 (HER2–) negative. All patients were treated with ribociclib from January 2017 to December 2022 (Fig. 1).

The study group included 106 (59%) patients who underwent radical treatment at earlier stages, i.e. surgical treatment with possible adjuvant treatment. 67 patients (63.21%) study group received perioperative chemotherapy and 75 patients (75%) perioperative hormone therapy. All patients in the study group exhibited the disseminated stage of the disease and started treatment with ribociclib.

The control group consisted of 74 patients (41%) diagnosed with the disease at the dissemination stage. Out of these patients, 14 patients (18.92%) in the first line of systemic therapy of disseminated disease received chemotherapy, and 18 patients in the control group (24.32%) received hormone therapy. All patients in the control group eventually started treatment with ribociclib. Detailed data are presented in Table 1.

There were no statistically significant differences in the age of patients, ECOG performance-status score or the location of metastases. Among patients previously treated radically, a larger percentage received chemotherapy (63.21%) and hormone therapy (70.75%) than in the control group (respectively: 18.92% and 24.32%).

Results

Progression-free time

The conducted test allows you to assess progression-free survival (PFS) in the horizon 6, 12 and 24 months and its median. In the study group, the survival free of progression in the 6 months was 80.38%. For 12 months, PFS was 62.98%, and for 24 months 44.86%. For the control group, PFS amounted to 92.9%, 78.12% and 68.32%, respectively for 6, 12 and 24 months (Tab. 2). The PFS median is greater than the maximum observation time. PFS curves differ significantly ($p = 0.049$) (Fig. 2).

Overall survival

The conducted test allows for an assessment of overall survival (OS) in the horizon 6, 12 and 24 months. In the study group, total survival in the 6 months was 87.29%. For 12 months, OS was 76.15%, and for 24 months 43.66%. For the control group, the OS amounted to 87.29%, 75.48%, and 49.78%, for 6, 12, and 24 months, respectively (Tab. 3). Curves of survival do not differ significantly (Fig. 3.).

Safety profile

The most common adverse reactions were haematological complications. Neutropenia was observed in 82.78% of all patients, with 84,91% in the study group, and in the control group 79.73%. Neutropenia in the G3 and G4 according to CTCAE occurred in 43.89% of all patients (46.23% study group *vs.* 40.54% control group), but it was not even once a cause of treatment termination. Anaemia occurred in 62.78%

Table 1. Detailed patient characteristics

Parameter		Study group (N = 106)	Control group (N = 74)	Total (N = 180)	P-value
Age	65 years and more	40 (37.74%)	34 (45.95%)	74 (41.11%)	p = 0.343
	Up to 65 years	66 (62.26%)	40 (54.05%)	106 (58.89%)	
ECOG performance-status score	0	69 (65.09%)	49 (66.21%)	118 (65.55%)	p = 0.425
	1	37 (34.90%)	25 (33.78%)	62 (34.44%)	
Earlier chemotherapy	Yes	67 (63.21%)	14 (18.92%)	81 (45.00%)	p < 0.001*
	No	39 (36.79%)	60 (81.08%)	99 (55.00%)	
Earlier HR	Yes	75 (70.75%)	18 (24.32%)	93 (51.67%)	p < 0.001*
	No	31 (29.25%)	56 (75.68%)	87 (48.33%)	
Lung metastasis	Yes	21 (19.81%)	17 (22.97%)	38 (21.11%)	p = 0.745
	No	85 (80.19%)	57 (77.03%)	142 (78.89%)	
Bone metastasis	Yes	58 (54.72%)	33 (44.59%)	91 (50.56%)	p = 0.236
	No	48 (45.28%)	41 (55.41%)	89 (49.44%)	
Other metastases	Yes	32 (30.19%)	24 (32.43%)	56 (31.11%)	p = 0.876
	No	74 (69.81%)	50 (67.57%)	124 (68.89%)	
Combined treatment	IA/lh-rh/gosereline	58 (54.72%)	54 (72.97%)	112 (62.22%)	p = 0.008*
	Fulvestrant	48 (45.28%)	19 (25.68%)	67 (37.22%)	
	None	0 (0.00%)	1 (1.35%)	1 (0.56%)	

p — test chi-squared or accurate Fisher test; *statistically relevant difference (p < 0.05)

Table 2. PFS in 6, 12, 24 months

Group	Number of patients	Event number	Progress-free survival				P-value
			6 months	12 months	24 months	Median [months]	
Study group	106	41	80.38%	62.98%	44.86%	21.91	p =0.049*
Control group	74	13	92.90%	78.12%	68.32%	> max obs.	

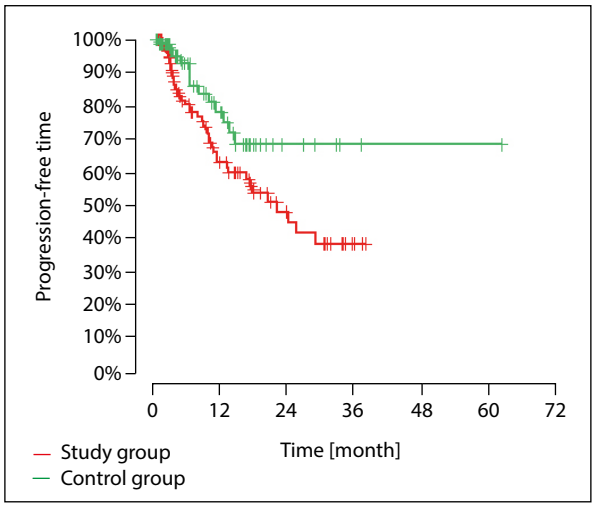

Figure 2. Kaplan–Meier curve for PFS

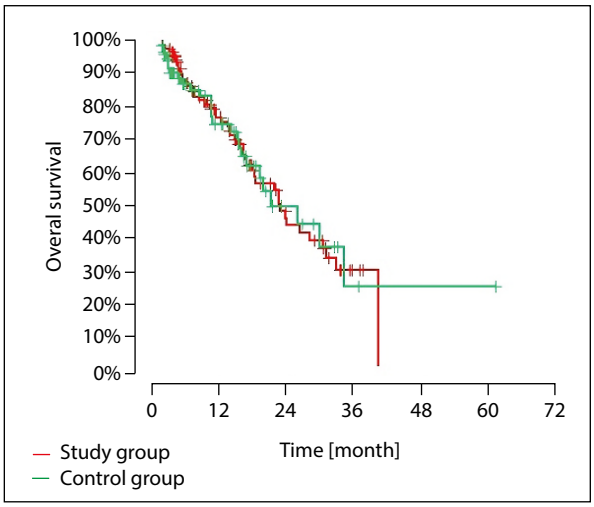

Figure 3. Kaplan–Meier curve for OS

Table 3. OS in 6, 12, 24 months

Group	Number of patients	Number of deaths	Overall survival				P-value
			6 months	12 months	24 months	Median [months]	
Study group	106	45	87.29%	76.15%	43.66%	> max obs.	p = 0.975
Control group	74	25	87.98%	75.48%	49.78%	> max obs.	

Table 4. List of the side effects of ribociclib

Parameter		Study group (N = 106)	Control group (N = 74)	Total (N = 180)	P-value
Neutropenia of any stage	Yes	90 (84.91%)	59 (79.73%)	149 (82.78%)	p = 0.481
	No	16 (15.09%)	15 (20.27%)	31 (17.22%)	
Neutropenia G3 or G4	Yes	49 (46.23%)	30 (40.54%)	79 (43.89%)	p = 0.546
	No	57 (53.77%)	44 (59.46%)	101 (56.11%)	
Anaemia of any stage	Yes	71 (66.98%)	42 (56.76%)	113 (62.78%)	p = 0.215
	No	35 (33.02%)	32 (43.24%)	67 (37.22%)	
Anaemia G3 or G4	Yes	2 (1.89%)	1 (1.35%)	3 (1.67%)	p = 1
	No	104 (98.11%)	73 (98.65%)	177 (98.33%)	
Thrombocytopenia of any stage	Yes	71 (66.98%)	42 (56.76%)	113 (62.78%)	p = 0.215
	No	35 (33.02%)	32 (43.24%)	67 (37.22%)	
Hipertransaminasemia of any stage	Yes	3 (2.83%)	3 (4.05%)	6 (3.33%)	p = 0.691
	No	103 (97.17%)	71 (95.95%)	174 (96.67%)	
Fatigue of any stage	Yes	16 (15.09%)	14 (18.91%)	30 (16.67%)	p = 0.764
	No	90 (84.91%)	60 (81.08%)	150 (83.33%)	
Infections of any stage	Yes	2 (1.88%)	1 (1.35%)	3 (1.67%)	p = 0.975
	No	104 (98.11%)	73 (98.64%)	177 (98.33%)	

of patients. It concerned 66.98% of patients from the study group (1.89% in the G3 and G4 according to CTCAE) and 56.76% of the control group patients (1.1, 35% in G3 and G4 according to CTCAE). Recurrent anaemia requiring blood transfusion was the reason for the termination of treatment in one patient from the study group. Thrombocytopenia occurred in 62.78% of patients. It affected 66.98% of patients from the study group and 56.76% of the control group patients. Thrombocytopenia was not observed in the G3 and G4 according to CTCAE. In none of the analysed cases, thrombocytopenia was the reason for the termination of treatment. Fatigue occurred in 16.67% of patients. It affected 15.09% of patients from the study group and 18,91% of the control group. Infectious occurred in 1.67% of patients. It affected 1.88% of patients from the study group and 1.35% of the control group (Tab. 4).

In the study group, the first-degree reduction occurred in 47 (44.34%) of the respondents, and in the control group in 22 (29.73%). The second-degree reduction concerned 8 (7.55%) patients in the study group and 4 (5.41%) in the control group (Tab. 5).

Discussion

According to the National Comprehensive Cancer Network (NCCN) guidelines, ribociclib (in combination with IA) is recommended as the preferred CDK4/6 inhibitor in the treatment of ER+/HER2 advanced breast cancer [24]. In addition, the second phase of RIGHT Choice showed that ribociclib, combined with hormone therapy, extends PFS compared to associated chemotherapy in patients with aggressive advanced HR+/HER2– breast cancer that had not previously

Table 5. Drug dose reduction

Parameter		Study group (N = 106)	Control group (N = 74)	Total (N = 180)	P-value
1st degree dose reduction	Yes	47 (44.34%)	22 (29.73%)	69 (38.33%)	p = 0.068
	No	59 (55.66%)	52 (70.27%)	111 (61.67%)	
2nd degree dose reduction	Yes	8 (7.55%)	4 (5.41%)	12 (6.67%)	p = 0.764
	No	98 (92.45%)	70 (94.59%)	168 (93.33%)	

been treated systemically. Pre-registration studies have shown that the use of CDK4/6 inhibitors is associated with less toxicity and probably greater efficiency than chemotherapy [25, 26].

In this work, the study group was patients for whom ribociclib, in combination with hormone therapy, was the first or subsequent line of treatment for the advanced disease. Originally, they were patients who were subjected to radical treatment, which included surgery, and possibly, depending on the indications, perioperative chemotherapy and hormone therapy. The control group consisted of patients who began treatment for breast cancer based on the diagnosis of the disease already in a locally advanced or metastatic stage.

The tolerance of ribociclib treatment in both groups was similar. Statistically significant differences in the quantity and degree of side effects were not observed. The most common adverse events in both groups were haematological complications: neutropenia (84.91% *vs.* 79.73%, study group *vs.* control group, respectively), anaemia (66.98% *vs.* 56.76%) and thrombocytopenia (66.98% *vs.* 56.76%). Side effects in the 3rd and 4th according to CTCAE concerned neutropenia (46.23% *vs.* 40.54%) and anaemia (1.89% *vs.* 1.35%). Comparing the above data with the results of the clinical trial of Monalees-2, the convergence of the frequency of haematological complications is noteworthy. Neutropenia (all degrees: 74%, degree 3/4: 60%) and anaemia (all degrees: 19%, degree 3/4: 3%) were the most common side effects reported in this study. In the MONALEESA-2 study, it was also proved that neutropenia ≥ 2nd degree was the most common complication of ribociclib treatment and was the cause of the termination of therapy in less than 1% of patients [27, 28]. In own study, haematological side effects were the cause of termination of treatment in one patient from the study group (1.35%). The reason was recurrent anaemia in st. G3/G4 requiring blood transfusion. In the study group, 44.34% of patients required the first degree of reduction, and in the control group 29.73%. The second degree of reduction concerned 7.55% of patients in the study group and 5.41% in the control group. Severe and difficult-to-tolerate side effects associated with the use of ribociclib result in temporary withdrawal of the drug or dose modification. Initially, patients take 3 tablets of 200 mg of ribociclib, once, for 21 days, followed by 7 days break. In the case of 3rd stage neutropenia, the product should be suspended to return to the rank ≤ 2. and resume the product administration from the same dose. If toxicity in level 3. converts: stop treatment until you return to the degree ≤ 2. Then resume administration and reduce the dose by 1 level (200 mg). In the case of neutropenia, the product is suspended until returns to the rank of ≤ 2. and then administered in a reduced dose by 1 level [29].

In registration tests of ribociclib, 68.5% of patients required dose reduction. In the research conducted so far on ribcyclib, it has not been proven that there are features of patients that would predispose to the increased risk of the occurrence of data from adverse effects. It is worth noting that dose reductions, among others due to neutropenia or any other side effects, were lower in the research of MONALEESA-3 and -7 compared to the previous study of MONALEESA-2, which may be due to greater experience in the field of managing related side effects related with ribciclib. Based on the results from the obtained research, it can be concluded that ribociclib has a predictable, controlling security profile [30, 31].

Progression-free survival differs significantly in both groups. PFS in the 24-month horizon is 44.86 % for the study group, while for the control group 68.32%. The PFS median for the study group is 21.91 months, and for the control group is greater than the observation time. Patients from the control group obtained better results in the field of PFS compared to the study group. It should be emphasized, however, that the examination did not take into account the impact of a number of important elements, e.g. the histological characteristics of the tumour, the degree of malignancy, the presence of lymphatic infiltrates or the presence of vascular invasion, which is known to be factors affecting the response to the therapy and prognosis of patients [35]. Overall survival does not differ significantly in both groups. OS

in the 24-month horizon is 43.66% for the study group and 49.78% for the control group.

The assessment of the effectiveness and safety profile of the use of ribciclib in patients after radical treatment to some extent also fits into the currently developed trend of research on the possibility of using CKD 4/6 inhibitors in the treatment of neoadjuvant or adjuvant breast cancer [36]. Regardless of this concept, it seems significant to develop research on the effectiveness and safety of ribciclib in special groups of patients whose goal would be to separate patients' groups related to the highest benefit from the treatment with ribociclib.

Conclusions

A higher benefit (expressed in PFS) from the use of ribociclib will be achieved by patients whose treatment was initiated at a locally advanced or metastatic stage compared to patients with a history of radical treatment of breast cancer. A history of primary radical treatment has no impact on either overall survival or the safety profile of ribociclib treatment.

Article information

Data availability statement: *The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.*

Ethics statement: *The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.*

Author contributions: *Conceptualization: EBB, SW and KK; methodology: EBB and AK; software: EBB, PM and KK; validation: EBB, PM and KK; formal analysis EBB and AK; investigation EBB and PM; resources, EBB and SW; data curation: EBB and PM; writing — original draft preparation: EBB and SW; writing — review and editing: EBB, PM and AK; visualization: EBB and SW; supervision: EBB, PM SW and KK; project administration: KK. All authors have read and agreed to the published version of the manuscript.*

Funding: *None.*

Acknowledgements: *None.*

Conflict of interest: *None.*

Supplementary material: *None.*

References

1. Arnold M., Morgan E., Rumgay H., et al.; Current and future burden of breast cancer: global statistics for 2020 and 2040, Breast. 2022;66:15-23.
2. Kohler BA., Sherman RL., Howlader N., et al.; Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State, J Natl Cancer Inst. 2015;107(6).
3. Twelves C., Bartsch R., Ben-Baruch NE., et al.; The Place of Chemotherapy in The Evolving Treatment Landscape for Patients With HR-positive/HER2-negative MBC, Clinical Breast Cancer. 2022;22(3):223-34.
4. Araki K., Miyoshi Y.; Mechanism of resistance to endocrine therapy in breast cancer: the important role of PI3K/Akt/mTOR in estrogen receptor-positive, HER2-negative breast cancer, Breast Cancer. 2018;25(4):392-01.
5. García-Becerra R., Santos N., Díaz L., et al.; Mechanisms of Resistance to Endocrine Therapy in Breast Cancer: Focus on Signaling Pathways, miRNAs and Genetically Based Resistance, Int. J. Mol. Sci. 2013;14(1):108-45.
6. Kay C,, Martínez-Pérez C.,, Meehan J., et al., Current trends in the treatment of HR+/HER2+ breast cancer, Future Oncol. 2021;17(13):1665-81.
7. Wysocki PJ., Potemski P., Krzemieniecki K., i wsp.; Nowe możliwości leczenia hormonozależnego raka piersi w stadium zaawansowanym, Onkol. Prak. Klin. 2012; 8(3):85-90.
8. Francis PA., Pagani O., Fleming GF., et al.; Tailoring adjuvant endocrine therapy for premenopausal breast cancer, N Engl J Med. 2018;379(2):122–37.
9. Larissa A. Korde, Mark R. Somerfield, Lisa A., et al.; Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline Hershman, J Clin Oncol. 2021;39(13):1485-05.
10. Santen R.J.; Menopausal hormone therapy and breast cancer, J Steroid Biochem Mol Biol. 2014;142:52-61.
11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, et al.; Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials, Lancet 2011;378(9793):771–84.
12. http://onkologia.zalecenia.med.pl/pdf/zalecenia_PTOK_tom1_05_Rak%20piersi_20201014.pdf data wejścia: 4.02.2023.
13. https://www.cancer.gov/types/breast/breast-hormone-therapy-fact-sheet#how-is-hormone-therapy-used-to-treat-breast-cancer data wejścia 17.02.2023.
14. Hortobagyi GN, Stemmer S M, Burris H A; Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer, Ann Oncol. 2018;29(7):1541-47.
15. http://bipold.aotm.gov.pl/assets/files/zlecenia_mz/2019/288/REK/RP_6_2020_Kisqali_MKP_zaczerniona.pdf.
16. Bayraktar S, Batoo S, Al-Hattab E, Basu S, Okuno S, Glück S. Future perspectives and challenges with CDK4/6 inhibitors in hormone receptor-positive metastatic breast cancer. Future Oncol. 2020; 16(32):2661-2672.
17. Dubiański R, Jagiełło-Gruszfeld A, Nowecki Z.; Cyclin-dependent kinase 4/6 inhibitors in the treatment of advanced estrogen receptor--positive breast cancer, Oncol Clin Pract. 2016;12: 209–14.
18. Dębska-Szmich S, Potemski P.; Clinical use of cyclin-dependent kinase (CDK) 4/6 inhibitors in patients with breast cancer — literature review, Oncol Clin Pract. 2017;13:281–94.
19. C. Louwrens Braal.; Elisabeth M. Jongbloed; Saskia M. Wilting; Inhibiting CDK4/6 in Breast Cancer with Palbociclib, Ribociclib and Abemaciclib: Similarities and Differences, Drugs. 2021;81:317–31.
20. https://www.ema.europa.eu/en/documents/product-information/kisqali-epar-product-information_pl.pdf.
21. Jassem J, Krzakowski M, Bobek-Billewicz B.; Breast cancer, Oncol Clin Pract 2020;16.
22. Dębska-Szmich S.; Potemski P.; Indications for CDK 4/6 inhibitors combined with palliative hormonotherapy and for pertuzumab com-

bined with trastuzumab and neoadjuvant chemotherapy in treatment of breast cancer patients and practical aspects of their reinburstment in Poland, Onkol Prakt Klin Edu 2020;6,2:88–104.
23. Denise A Yardley; MONALEESA clinical program: a review of ribociclib use in different clinical settings, Future Oncol. 2019;15(23):2673-86.
24. https://www.novartis.com/us-en/news/media-releases/novartis-r-ibociclib-kisqali-only-category-1-preferred-first-line-treatment-option-hrher2-mbc-combination-ai-updated-nccn-clinical-practice-guidelines--oncology-nccn-guidelines data wejścia 16.04.2023.
25. Lu YS, Mahidin EIBM, et al. Primary results from the randomized Phase II RIGHT Choice trial of premenopausal patients with aggressive HR+/HER2– advanced breast cancer treated with ribociclib + endocrine therapy vs physician's choice combination chemotherapy. Presented at the 2022 San Antonio Breast Cancer Symposium (SABCS). December 6-10, 2022. Abstract # GS1-10.
26. Gennari A., André F., Barrios C.H.;ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer, Ann Oncol 2021;32:1475-95.
27. Gabriel N. Hortobagyi, M.D., Salomon M. Stemmer, M.D.; Overall Survival with Ribociclib plus Letrozole in Advanced Breast Cancer, N Engl J Med 2022;386:942-50.
28. S.-A. Im, Y.-S. Lu, A. Bardia,; Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer, N Engl J Med 2019;381:307-16.
29. Curigliano G, Gómez Pardo P, Meric-Bernstam F, et al. Ribociclib plus letrozole in early breast cancer: A presurgical, window-of-opportunity study. Breast. 2016; 28: 191–198.
30. Tripathy D., Im S.,Colleoni M.; Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial, Lancet Oncol 2018; 19: 904–15.
31. Burris H., Chan A.,Bardia A.; Safety and impact of dose reductions on efficacy in the randomised MONALEESA-2, -3 and -7 trials in hormone receptor-positive, HER2-negative advanced breast cancer, Br. J. Cancer 2021;125:679–86.
32. Chen T., Bedard P.; Personalized medicine for metastatic breast cancer, Curr. Opin. Oncol. 2013; 25: 615–624.
33. Doraczyńska-Kowalik A., Janus-Szymańska G., Matkowski R.; Genetyka i onkologia (część 2.) Podstawy medycyny personalizowanej w leczeniu rakapiersi i raka jajnika, Biuletyn Polskiego Towarzystwa Onkologicznego Nowotwory 2020; 5:255–72.
34. Nowecki Z., Jagiełło-Gruszfeld A., Pogoda K.; Leczenie przedoperacyjne chorych na raka piersi i jego wpływ na postępowanie operacyjne oraz radioterapeutyczne (część 1.), Biuletyn Polskiego Towarzystwa Onkologicznego Nowotwory 2021;6:17–25.
35. Chajewska–Ciekańska M.; Ocena wpływu wybranych czynników histopatologicznych i klinicznych na skuteczność przedoperacyjnej chemioterapii u pacjentek z rakiem piersi, 2015.
36. Prat A., Cristina Saura C.,Pascual T.;Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor--positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial, Lancet Oncol 2020;21:33-43.