Costs of treatment with cyclin-dependent kinase inhibitors – CDK4/6 in hormone-dependent HER2--negative breast cancer under the B.9 drug programme

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
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Abstract

Background and Study Aim: Breast cancer stands as the most common malignant tumour among women in Poland and worldwide. It is an extremely heterogeneous disease due to the occurrence of mutations and hormonal dependencies. Presently, generalized breast cancer remains incurable; however, innovative therapies offer opportunities for prolonging survival without disease progression and alleviating symptoms. Notably, the utilization of drugs from the CDK4/6 inhibitor group as a supplement and support in the treatment of hormone-dependent breast cancer with HER2/−/ (HR+ HER2/−/) is a breakthrough in the therapy of this type of cancer. This article aims is knowledge about the costs of treating patients with HR+ HER2/−/ breast cancer with CDK4/6 inhibitors, reimbursed in Poland under the drug program.

Material and Methods: The study utilized relevant cost and revenue data pertaining to the treatment of patients diagnosed with HR+ HER2/−/ breast cancer and treated with CDK4/6 inhibitors under the drug programme B.9 'Treatment of Breast Cancer Patients (ICD-10: C-50)' at the regional oncology centre in north-eastern Poland from 2019 to 2023. Financial categories were presented based on the purchasing power parity of PPP / 1 USD inter.

Results: Between 2019 and 2023, the value of the diagnostic lump sum in the B.9 drug programme underwent four changes (the so-called 'quality factor' by the Polish National Health Fund from 2021, increasing the value of the benefit by a multiplier of 1.025, while maintaining the methodology of 1 settlement point = 1 PLN). Subsequent changes in the diagnostic lump sum value stemmed from the increase in the settlement point price: April 2022, 1 point = 1.05 PLN; July 2022, 1 point = 1.37 PLN; July 2023, 1 point = 1.64 PLN.

The value of the benefit for admitting a patient on an outpatient basis increased from 63.66 USD-inter to 101.74 USD-inter in 2023, reflecting a rise of 59.82%. Compared to the average value for 2023 of 93.37 USD-inter, there was an increase in the value of this benefit by 46.67%. The value of drugs administered in 2023 represented about approximately 230% of the therapies delivered in 2020 (the value of stay benefits ranges from 4.30% to 5.20%). In the analysed period, diagnostic costs ranged from 2.30% to 4.10% of the total cost structure.

Conclusions: The utilization of ribociclib and other drugs from the group of CDK4/6 inhibitors as a complement and support to the therapy of hormone-dependent breast cancer with HER2/−/ represents a breakthrough in the treatment of this type of cancer. Ciclibs notably enhance the effectiveness of hormone therapy and improve the prognosis and quality of life of patients with advanced HR+/HER2-negative breast cancer. Moreover, the tablet form of CDK4/6 drugs facilities widespread outpatient treatment while ensuring patient safety. Exclusion of a patient from a drug program due to complications poses a genuine risk of nullifying the financial investments

made for the patient's prior treatment within the program. Underestimation of hospitalization costs similarly poses a tangible risk of financial losses for program implementers, in cases necessitating additional treatment for complications to enable continued therapy.

Keywords: abemaciclib • breast cancer • fight against cancer • hormone therapy • palbociclib • ribociclib

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INTRODUCTION

Among all malignant tumours, breast cancer stands out as the most common among women worldwide (it is estimated that every eighth woman globally will suffer from the disease) [1]. An analysis of incidence rates across different age groups shows a significant rise in the incidence in the 50-69 age group [2]. According to the International Agency for Research on Cancer (IARC), GLOBOCAN statistics covering 185 countries indicate that in 2018 2.3 million cases of breast cancer were recorded, constituting 11.7% of all reported cancer cases, creating with a mortality rate of 6.9. Breast cancer ranks as the second leading cause of death among women, following lung cancer. The highest incidence rate of malignant breast cancer occurs in Europe and North America. Disparities in breast cancer treatment outcomes exist both between and within countries, influenced by various factors spanning the entire cancer care continuum, from prevention to diagnosis, treatment, as well as post-treatment, and palliative care. According to IARC research, the 5-year survival rate for patients with metastatic breast cancer is below 30% worldwide, despite the use of a wide range of systemic treatment options [3].

Poland is among the countries in Central and Eastern Europe with an average incidence of breast cancer. The standardized incidence rate of breast cancer in Poland in 2020 was 26.71 according to the World Standard Population (ASW) rate and 46.68 according to the European Standard Population (ASE), representing 24% of all registered cancers in women. The average 5-year survival rate in Poland is 74% [4]. Since early 1980s, a steady increase in the number of new cases has been observed across all age groups of women in Poland [5], with approximately 17 000 women diagnosed with breast cancer annually, resulting in around 5 000 deaths [4]. In 2020 approximately 100 000 women were living with breast cancer in Poland.

Breast cancer is an extremely heterogeneous disease due to mutations and hormonal dependencies, manifesting in three subtypes: hormone-dependent breast cancer, triple-negative breast cancer, and HER2 breast cancer [6]. Prognostic factors for therapy effectiveness also depend on the specific cancer subtype, as well as other factors such as tumour size, number of lymph nodes involved, stage, and HER2 receptor presence (human epidermal growth factor receptor 2) [7]. Presence of estrogen receptors (estrogen receptor ER) or progestogen receptors (progesterone receptor PR) serves as a positive predictive factor, associated with a less aggressive disease course and better treatment response [8]. Hormone receptor (ER)-positive breast cancer accounts for up to 75% of all invasive breast cancer cases [9], while HER2 receptor overexpression correlates with cancer progression and poorer prognosis. Breast cancers are categorized into HER2-positive and HER2-negative based on the level of HER2 expression in cancer cells [10]. Patients with high HER2 overexpression (3+) or (2+) and presence of HER2 gene amplification have access to targeted therapies using anti-HER2 targeted drugs, such as trastuzumab, pertuzumab, trastuzumab emtansine, or trastuzumab durextecan. For HER2--negative cancer patients (HER2 expression: 2+/no gene amplification, 1+ or 0), other therapies are

Cyclin-dependent kinase 4 and 6 – these kinases are activated upon binding to D-cyclins and play a crucial role in signalling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb). Blocking of retinoblastoma protein (Rb) phosphorylation, inhibits cell cycle progression from the G1 to the S-phase of cell division, leading to suppression of tumour growth.

Abemaciclib – is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), most active against Cyclin D1/CDK4, prevents retinoblastoma protein (Rb) phosphorylation.

Palbociclib – is a selective, reversible inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation.

Ribociclib – is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. In vitro, ribociclib decreased pRb phosphorylation.

Person-day – a unit of measurement used to report medical services by a medical facility for settlement with the payer the Polish National Health Fund. Refers to the patient's stay in an inpatient or day ward. The day of admission of the patient for treatment in the department and the day of its completion are counted as one person-day.

administered. For years, hormone therapy (HT) has been the standard oncological treatment (both in radical and palliative treatment) for patients with HER2-negative hormone-dependent cancer [9]. In the hormonal therapy of breast cancer, tamoxifen remains the most commonly used drug, alongside non-steroidal aromatase inhibitors (such as anastrozole and letrozole) and gonadoliberin analogues [6].

In recent years, a breakthrough in the treatment of HER2-negative breast cancer expressing hormone receptors (HR+) has been cyclin-dependent kinase inhibitors (CDK4/6). Representatives of this group of drugs include: palbociclib, ribociclib and abemaciclib. Palbociclib received approval from the US Food and Drug Administration (FDA) in 2015, followed by ribociclib and abemaciclib in 2017 [10]. CDK4/6 inhibitors are substances that affect the cell cycle, inhibit cancer cell division, and consequently induce their death [11]. Polish patients also have access to CDK4/6 therapy. Palbociclib and ribociclib were included in reimbursement programs from September 2019, followed by abemaciclib from September 2020.

This article aims is knowledge about the costs of treating patients with HR+ HER2/–/ breast cancer with CDK4/6 inhibitors, reimbursed in Poland under the drug programme.

MATERIAL AND METHODS

The study used cost and revenue data related to the treatment of patients with HR+ HER2/–/ breast cancer using CDK4/6 inhibitors within the drug programme B.9 'Treatment of Breast Cancer Patients (ICD-10: C-50)' at regional oncology centre in north-eastern Poland. The analysis spanned from September 2019 to October 2023. The retrospective analysis included financial data on o delivered healthcare services – understood as the set of all elements of the service: health, material, and accompanying elements, provided during a single contact between a patient and a healthcare provider. In the first stage of determining the total costs of treating a patient in the drug programme, direct costs were separated, including drug costs, costs of mandatory diagnostics and hospitalization costs. Fixed costs, defined by general financial and accounting data, constitute the largest cost of each service. Financial and accounting data, along with additional non-financial data, formed the basis for calculating total service cost, including salary and infrastructure costs [12].

Remuneration costs for physicians, nurses and other medical staff constitute the primary component of per-person-day costs i.e., encompassing the patient's hospital ward stay, staffing costs for one-day ward and outpatient care. The number and types of personnel categories engaged in delivering medical services varied according to the specificity of each service. Salary costs were calculated separately for each cost centre (OPK). The cost of one hour of work was determined based on full-time equivalent positions, with one full-time position covering an average of 160 working hours per month. Full-time equivalent positions comprise both regular working hours (resulting from the full-time job) and additional working hours, such as those accrued during medical duties or due to elements affecting real, effective working time, such as absences due to holiday leave. Infrastructure costs (encompassing premises, equipment, and apparatus) were calculated separately for each OPK. To calculate the infrastructure costs per person-day of patient ward stay in the case of inpatient services, fixed costs of non-inpatient services, total infrastructure costs were used, constituting the difference between the total costs of a given OPK and costs associated with salaries, drugs, medical devices, and diagnostic procedures.

The analysis of the collected data facilitated the determination of actual therapy costs for a single patient. In the subsequent part of the analysis, the determined costs borne by the healthcare provider were juxtaposed with the revenues received from the Polish National Health Fund as payment for all services rendered to a patient undergoing treatment with CDK4/6. Settlements with the Polish National Health Fund include reimbursement for medicines issued to the patient, based on purchase invoices from a drug supplier, an annual diagnostic lump sum (settled on a monthly basis as 1/12), and payment for medical services related to patient admission. Due to the fixed-point value of services, according to the tariffs adopted by the public payer, an analysis was conducted on the implementation of the so-called 'quality factor', which was introduced into settlements with oncology hospitals from 2021 [13].

Innovative agonology – is an applied science dedicated to promotion, prevention and therapy related to all dimensions of health and regarding the optimization of activities that increase the ability to survive from micro to macro scales [21, p. 274].

INNOAGON – acronym 'innovative agonology' [22].

The analysis also took into account the variability of the value of the lump sums associated with the Polish National Health Fund's increase in the price of the settlement point. The financial categories were presented by 'USD-inter' currency based on purchasing power parity (PPP) for each year covered by the analysis (2019: 1 USD-inter corresponds to 1.699 PLN; 2020: 1 USD-inter corresponds to 1.698 PLN; 2021: 1 USD-inter corresponds to PLN 1.723; 2022: 1 USD-inter corresponds to 1.787 PLN).

The specificity of this theoretical research means that links to source works appear in the 'Results' section. Some of it constitutes information that in a classic original work should be edited in the 'Material and Methods' section.

No consent from the Bioethics Committee was required. It was a retrospective study on financial and accounting data. Medical records were not analysed.

RESULTS

Currently, three CDK4/6 inhibitors are available in Poland: palbociclib, ribociclib, abemaciclib (Table 1). Reimbursement of combined treatment with CDK4/6 inhibitors is currently being processed under the drug programme B.9 'Treatment of Breast Cancer Patients (ICD-10: C-50)' and is subject to limitations resulting from the criteria of drug programs. Over the years, the B.9 drug program has been modified in terms of the authorization of further drugs and subsequent lines of treatment. The drug program covers the treatment of three subtypes of breast cancer and in this respect differs in inclusion and exclusion criteria, as well as in the tests performed during treatment eligibility and as part of therapy monitoring [14].

In the analysed period, a total of 114 patients with hormone-dependent HER2-negative breast cancer received treatment with CDK4/6 under the B.9 drug programme at this provider (Table 2).

Table 1. Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors covered by reimbursement in Poland under the drug programme B.9 'Treatment of Breast Cancer Patients (ICD-10: C-50)'.

No.	Cyclin-dependent kinase inhibitors CDK4/6	Date of inclusion in the refund
1	palbociclib	01 September 2019
2	ribociclib	01 September 2019
3	abemaciclib	01 September 2020

Source: Own elaboration based on data from the Polish National Health Fund.

Table 2. Number of patients treated with individual CDK4/6 in the period from September 2019 to October 2023.

No.	Cyclin-dependent kinase inhibitors	Year				
		Sep – Dec 2019	2020	2021	2022	Jan – Oct 2023
1	palbociclib	4	19	29	24	21
2	ribociclib	5	15	23	37	50
3	abemaciclib	X	X	X	1	3

Source: own elaboration based on data from the Clinical Hospital of the Ministry of the Internal Affairs and Administration with the Warmia-Mazury Oncology Centre in Olsztyn, Poland.

Diagnostic tests performed when qualifying a patient for a drug programme and related to treatment monitoring – according to the description of a given drug programme, are financed with a lump sum according to the adopted tariff (Table 3).

Between 2019 and 2023, the value of the diagnostic lump sum in the B.9 drug programme underwent four changes. This was due to the implementation of the so-called 'quality factor' by the Polish National Health Fund from 2021, increasing the value of the benefit by a multiplier of 1.025 (while maintaining the methodology of 1 settlement point = 1 PLN). Subsequent changes in the diagnostic lump sum value stemmed from the increase in the settlement point price, as follows: April 2022: 1 point = 1.05 PLN; July 2022: 1 point = 1.37 PLN; July 2023: 1 point = 1.64 PLN. The lump sum values for diagnostics, allocated to the treatment of each of the three subtypes of breast cancer, remained at a similar level, with exception of an anomaly in 2019. Despite the reimbursement of palbociclib and ribociclib from September 2019, the Polish National Health Fund had not introduced the diagnostic lump sum for therapy with these drugs by the end of this year. This circumstance adversely affected the settlement situation for medical services provided using CDK4/6 (Table 4).

Stay medical services related to the patient's treatment in the B.9 drug programme were settled by the Polish National Health Fund according to a fixed-point value, which remained constant throughout the period covered by the analysis. According to the adopted tariff, the number of settlement points per patient-day in both the inpatient ward and the one-day ward was the same. Outpatient services were determined by a lower point value. Changes in the valuation of stay benefits resulted from the introduction of the 'quality factor' and a three-fold increase in the price of the settlement point in 2022 and 2023. The lower lump sum value in the first quarter of 2022 compared to 2021 is a consequence of a decrease in the purchasing power of money (PPP) by 3.58% (1 USD-inter = 1.723 PLN for 2021 vis' 1 USD-inter = 1.787 PLN for 2022). This unfavourable situation was offset by an increase in the price of the settlement point by 5% for the second quarter of 2022, followed by a subsequent increase of 30.48% over the next 12 months. In July 2023, there was another change in the value of stay medical services by 19.70% (Table 5).

Table 3. The value of the lump sum for diagnostics in the B.9 program from 2019 to October 2023 (purchasing power of money in USD-inter).

Year	Benefit name		
	diagnostics in the treatment program for advanced HER+ breast cancer	diagnostics in the neoadjuvant or adjuvant HER+ breast cancer treatment program	diagnostics in a breast cancer treatment program using palbociclib, ribociclib or abemaciclib
2019	1 926.43	1 889.70	X
2020	1 937.83	1 899.81	1 895.17
2021	1 947.08	1 909.65	1 914.36
Jan – Mar 2022	1 877.35	1 841.56	1 845.80
Apr – Jun 2022	1 971.22	1 933.64	1 938.09
Jul 2022 – Jun 2023	2 571.97	2 522.94	2 528.75
Jul – Oct 2023	3 078.85	3 029.16	3 072.12

Source: own elaboration based on data from the Polish National Health Fund.

Table 4. Reimbursement amount for medical stay services of a patient treated under the B.9 drug programme from 2019 to October 2023 (in USD-inter).

Year	Benefit name		
	stay in ward	one-day stay	outpatient stay
2019	286.47	286.47	63.66
2020	286.64	286.64	63.70
2021	289.55	289.55	64.34
Jan – Mar 2022	279.18	279.18	62.04
Apr – Jun 2022	293.13	293.13	65.14
Jul 2022 – Jun 2023	382.47	382.47	84.99
Jul – Oct 2023	457.85	457.85	101.74

Source: own elaboration based on data from the Polish National Health Fund.

Due to several changes in the value of lump sums in 2022 and 2023, the benefits' value from this period was appropriately averaged for the purposes of this analysis. Over the course of five years, the revenue for residential services, in both stationary and one-day modes, increased nominally from 286.47 USD-inter in 2019 to 457.85 USD-inter representing a growth of 59.82% in 2023. The average value of the lump sum for 2023 in the amount of 420.16 USD-inter was 146.67% of the lump sum from 2019, which amounted to 286.47 USD-inter.

The value of the benefit for admitting a patient on an outpatient basis increased from 63.66 USD-inter in September 2019 to 101.74 USD-inter in 2023, reflecting a rise of 59.82%. Compared to the average value for 2023 of 93.37 USD-inter, there was an increase in the value of this benefit by 46.67%. Throughout the entire period covered

Table 5. Revenues and costs per patient treated in B.9 drug programme from September 2019 to October 2023 (in USD-inter).

Year	Stay in ward			One-day stay			Outpatient stay		
	revenue	cost	coverage of costs (%)	revenue	cost	coverage of costs (%)	revenue	cost	coverage of costs (%)
Sep – Dec 2019	286.47	338.03	84.75	286.47	101.20	283.08	63.66	13.91	457.72
2020	286.64	392.99	72.94	286.64	131.92	217.29	63.70	26.67	238.87
2021	289.55	429.22	67.46	289.55	183.91	157.44	64.34	38.85	165.64
2022*	334.31	466.79	71.62	334.31	187.34	178.45	75.97	35.33	215.00
Jan – Oct 2023*	420.16	708.11	59.34	420.16	203.06	206.92	93.37	36.70	254.38

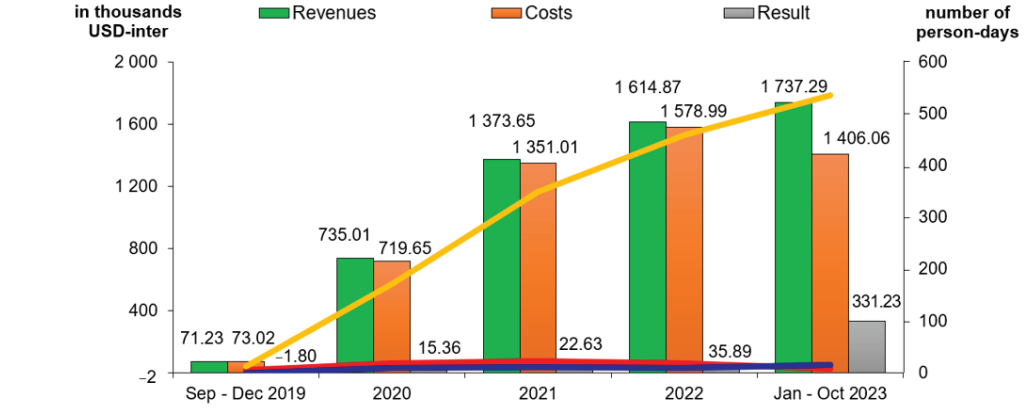
*average value covering price changes during the year

Source: own elaboration based on data from the Clinical Hospital of the Ministry of the Internal Affairs and Administration with the Warmia-Mazury Oncology Centre in Olsztyn, Poland.

by the analysis, the costs of inpatient treatment exceeded the income received from the Polish National Health Fund in this regard. A concerning trend is the permanently decrease in the percentage of costs covered by revenues for stays in the ward, declining from 84.75% in 2019 to 59.34% in 2023. An exception to this trend was a slight improvement in the cost-to-revenue ratio observed in 2022. However, this illusory improvement was swallowed up by cost increases in 2023 by 51.69% compared to the previous year, while revenues increased by only 25.68%. Both the one-day and outpatient modes maintained a positive balance throughout the five-year period. Until 2021, the profitability of providing services in these two modes had been deteriorating due to rising costs alongside relatively stable revenues. The decline in profitability halted in 2022 due to a significant increase in revenues and a slower pace of cost growth. This positive correlation is the result of the distribution of fixed costs of individual OPKs over a larger number of patients treated on a one-day basis and, primarily, on an outpatient basis (Figure 1).

In the initial period of implementing medical services using CDK4/6, a negative financial result was recorded. This was attributed to the inability to settle diagnostic tests due to a delay in the valuation of this service by the Polish National Health Fund and an underestimation of the patient stays in the inpatient unit. In the remaining period covered by the analysis, i.e., from 2020 to 2023, the total costs incurred by the service provider were covered by the revenues obtained, respectively: 2020: 102.12%; 2021: 101.67%; 2022: 102.27%; 2023 123.55%. However, the improvement in profit in 2023 was not significantly influenced by the Polish National Health Fund's increase in the price for medical services provided by healthcare providers, as reflected by the nearly 152% increase in costs with a 126% increase in revenues. The increase in the positive financial result is undoubtedly the result of the increasing use of outpatient treatment, which was characterized by high profitability. This conclusion is confirmed by the growing curve of outpatient person-days.

The tablet form of drugs from the CDK4/6 group facilitates widespread use of outpatient treatment while ensuring patient safety. However, in case of health deterioration and/or complications, hospitalization becomes necessary. This is related to address complications to facilitate the continuation of drug therapy and maximizing



	Sep - Dec 2019	2020	2021	2022	Jan - Oct 2023
Stay in ward	15.0	61.0	76.0	61.0	25.0
One-day stay	0.0	33.0	37.0	30.0	52.0
Outpatient stay	13.0	171.0	349.0	459.0	535.0

Figure 1. Revenues, costs, financial result of therapy using CDK4/6 in the period from September 2019 to October 2023 (in thousands USD-inter) along with the number of person-days in individual treatment modes.

Source: own elaboration based on data from the Clinical Hospital of the Ministry of the Internal Affairs and Administration with the Warmia-Mazury Oncology Centre in Olsztyn, Poland.

health benefits for the patient. Nevertheless, due to the underestimated and constantly increasing costs of hospitalization, any resulting financial loss is borne by the drug program implementer. In this case, the 'eternal dilemma of the profit-and-loss calculus' lies in choosing between the risk of potential individual financial loss and the real loss of effects resulting from the financial outlays for the patient's treatment in the drug program if the patient is excluded from it.

Due to the high costs of innovative drugs used in drug programmes, drug expenses constitute the largest share of the cost structure of drug therapies. This is also the case with CDK4/6 therapy. The nominal value of drugs is noticeably increasing, reflecting the increase in the number of patients treated under this programme. The value of drugs administered in 2023 represented about approximately 230% of the therapies delivered in 2020. In the cost breakdown, the value of stay benefits ranges from 4.30% to 5.20%. The level stay-related costs in implementing the drug programme depends on the mode of service delivery. The small percentage of stay-related costs in the total therapy costs results from the possibility of the widespread use of a less expensive outpatient treatment mode. This is related to the tablet form of the drug. In the analysed period, diagnostic costs ranged from 2.30% to 4.10% of the total cost structure. The increase in diagnostic costs corresponds to the growing number of patients enrolled in the programme and continuing therapy with CDK4/6 (Figure 2).

DISCUSSION

The standard oncological management for patients with hormone-dependent HER2-negative cancer, encompassing both radical and palliative treatment, involves hormone therapy (HT). For hormone-dependent breast cancer diagnosed at early stages, therapeutic management is concerned with reducing the high risk of recurrence (in 30-60% of women with stage II and III breast cancer). In some situations (mainly with lymph node involvement), the duration of hormone therapy is extended up to 10 years. In menopausal patients (whether natural or drug-induced), hormone therapy may be combined with bisphosphonates, which improve prognosis, and also reduce the risk of bone metastases and protect against osteoporosis. The most serious limitation of hormone therapy is hormone resistance, which may develop with the duration hormonal treatment [7].

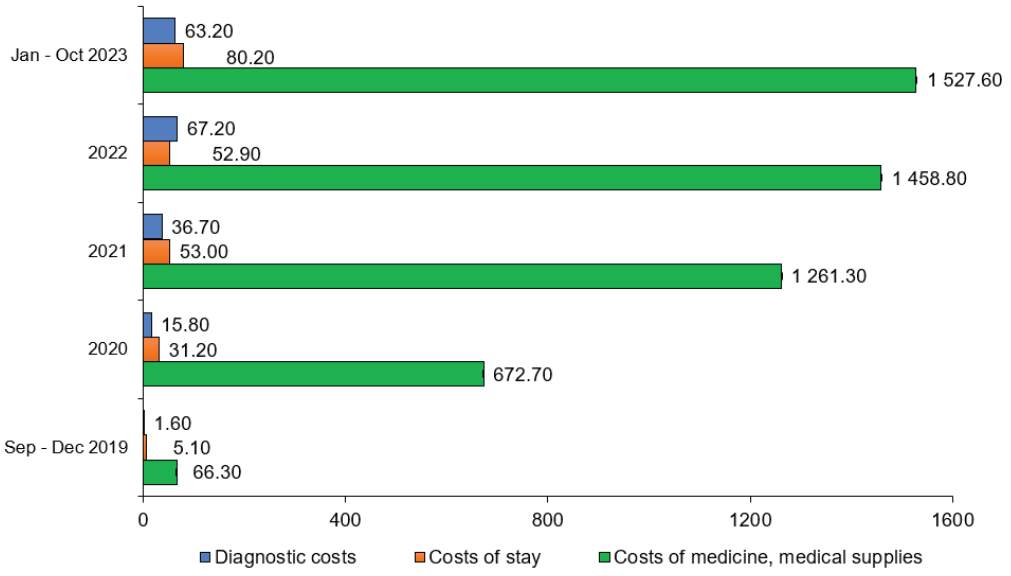


Figure 2. Structure of the costs of providing services in the B.9 drug programme from September 2019 to October 2023 (in thousands USD-inter).

Source: own elaboration based on data from the Clinical Hospital of the Ministry of the Internal Affairs and Administration with the Warmia-Mazury Oncology Centre in Olsztyn, Poland.

Resistance to hormone therapy may be primary or secondary. Primary resistance refers to recurrence within the first 2 years of primary HT. Secondary resistance is defined as tumour recurrence after 2 years of postoperative HT or 12 months after its completion, and in advanced breast cancer, progression later than within the first 6 months of HT. Patients resistant to HT are treated with chemotherapy [15], which is more aggressive and toxic than hormone therapy. Therefore, if we think about the patient's quality of life, the goal of therapeutic treatment should be to defer chemotherapy. The choice of therapy depends on many factors, including: the presence of hormone receptors, the stage of the disease, the patient's age and general condition, the presence of comorbidities, the availability and cost of therapy, and patients' preferences [6].

The indication for chemotherapy in hormone-dependent cancer and with the HER2/–/ feature, the most common is rapid disease progression and life-threatening massive parenchymal organ involvement (so-called 'visceral crisis'). According to the analysis of the European Breast Cancer Triasists' Collaborative Group (EBCTG), approximately 15% of patients experience relapse during complementary hormone therapy, after 10 years as many as 25% of patients, and after 15 years over 33% [7].

The inclusion of drugs from the group of CDK4/6 inhibitors in combination with hormone therapy is extremely helpful in combating the problem of hormone resistance and significantly improves the outcome of hormone-dependent and HER2-negative breast cancer [9]. Drugs from this group show statistically significant prolongation of progression-free survival (PFS) regardless of the line of treatment, prolongation of overall survival (OS), and increased overall response to treatment [6]. A meta-analysis pooling data from all clinical trials with CDK4/6 inhibitors found similar effectiveness of each of the three drugs in terms of PFS and response rates but showed differences in side effects. In terms of OS, ribociclib and abrmaciclib showed significant improvement [12]. A risk has been defined for the entire class of cyclin kinase 4/6 (CDK4/6) dependent drugs, according to which these drugs used to treat some patients with advanced breast cancer may cause a rare but severe pneumonia. The most common side effect of CDK4/6 inhibitors is neutropenia [16].

Patients undergoing ribociclib therapy may develop liver toxicity (increased AST, ALAT and bilirubin levels) and QTc interval prolongation. Whereas abemaciclib-treated patients may experience diarrhoea, creatinine elevation and thromboembolic events. However, the overall benefit of CDK4/6 inhibitors still outweighs the risk of side effects [10, 3]. Among the numerous advantages of using CDK4/6 inhibitors, in addition to the extension of progression-free survival (PFS) and overall survival (OS), there are: acceptable toxicity that resolves quickly after drug discontinuation, few side effects, good tolerance, and easy administration in tablet form – patients can take the medicine themselves at home. All this allows patients to lead an active life and enjoy significantly better well-being. The side effects of treatment with CDK4/6 inhibitors have been well studied and defined. This has identified individuals at risk and their treatment regimens. In most cases, the occurrence of side effects allows the implementation of additional treatment and the continuation of therapy [17].

Breast cancer is the most common malignant tumour among women in Poland. The incidence of breast cancer among men in Poland averages 144 per year, which is the mean from the last 5 years. With the increase in incidence, there is also a simultaneous decrease in the mortality rate in the age group of women 20-49 and its stabilization in the next age group (50-69 years). Older women (over 70) continue to experience high mortality from breast cancer [18]. Prognosis depends primarily on early detection of the cancer, its type and stage. Almost 85% of recurrence occur within 5 years after treatment. 5-year survival, depending on stage, is I: 95%, II: 50%, III: 25%, IV: over 5% [5]. The lower mortality rate is associated with a change in the structure of advancement of detected and registered breast cancers (early-stage cancers are increasingly detected). A major influence on the decreasing mortality rate is the availability of innovative drugs [19].

Generalized breast cancer remains an incurable disease; however, innovative therapies offer various benefits, including prolonging progression-free survival and alleviating disease-related discomfort. This approach is close to the idea of including in the process of therapy and treatment of cancer in each of the known varieties (i.e., fighting against cancer) certain rules and even methods offered either

by narrowly understood science about struggle – agonology [20] or, much more broadly, innovative agonology [21, 22]. This is not a new idea, because the findings of researchers of these phenomena indicate the use of the INNOAGON language (specifically the term 'self-defense' in the titles of scientific publications from various disciplines [23]) long earlier (since 1902) before Tadeusz Kotarbiński published 1938 the general theory of struggle, or agonology [24]. The common property of these publications is that they refer to phenomena that constitute a difficult cognitive or application challenge (when it comes to saving life or health). Hence, the prospect of using the complementary research methodology [25], the basic INNOAGON method, when solving the most difficult issues traditionally associated with medical sciences and medical practice is particularly optimistic.

CONCLUSIONS

The utilization of ribociclib and other drugs from the group of CDK4/6 inhibitors as a complement and support to the therapy of hormone-dependent breast cancer with HER2/−/ represents a breakthrough in the treatment of this type of cancer. Cyclibs notably enhance the effectiveness of hormone therapy and improve the prognosis and quality of life of patients with advanced HR+/HER2-negative breast cancer. Moreover, the tablet form of CDK4/6 drugs facilities widespread outpatient treatment while ensuring patient safety. Exclusion of a patient from a drug programme due to complications poses a genuine risk of nullifying the financial investments made for the patient's prior treatment within the programme. Underestimation of hospitalization costs similarly poses a tangible risk of financial losses for programme implementers, in cases necessitating additional treatment for complications to enable continued therapy.

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