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Management of melanoma central nervous system metastases

Introduction

Melanoma is the third most frequent malignancy (after breast and lung cancers) that causes metastases in the central nervous system (CNS). It is one of the 20 most common human cancers, and its incidence is steadily increasing by about 3–7% per year. It is estimated that in about 50–60% of patients with advanced melanoma, the disease will disseminate in the CNS (of whom about 75% of patients will develop multiple metastases often asymptomatic at baseline). Central nervous system metastases are found in 7% of melanoma patients at diagnosis and about 75% on autopsy. The primary tumor cannot be found in 3% of patients diagnosed with melanoma metastasis in the CNS. Of note is that only 8–46% of melanoma patients are diagnosed with CNS metastases. In 94% of them, brain metastases are the direct cause of death. In the latest 8th edition of the American Joint Committee on Cancer (AJCC) staging system, the presence of CNS metastases was distinguished as a separate, last category in stage IV (M1d) [1]. The risk of metastases in the CNS increases with the disease stage [2]. Central nervous system metastases occur in 37% of patients with stage IV melanoma [3]. Currently, there are no known factors identified that predict the risk of CNS metastases in melanoma patients. Nevertheless, it is known that certain factors are associated with a higher risk of metastases in the CNS (primary lesion within the head and neck, elevated lactate dehydrogenase (LDH) activity, ulceration in the primary lesion, mutations in the *BRAF*, *NRAS,* and *PTEN* genes) [4]. The detection of lesions in the CNS is associated with poor prognosis. Central nervous system metastases lead to death in 20–50% of patients, and symptomatic lesions are the immediate cause of death in about 90% of patients. According to historical data, median overall survival (OS) after CNS metastasis diagnosis was 5 to 7 months. However, in symptomatic patients undergoing whole brain radiotherapy (WBRT), which is now rarely used, median OS was 2–5 months, and in patients undergoing surgery or stereotactic radiotherapy — twice as long [5].

This summary study aims to present multidisciplinary guidelines on diagnostic and therapeutic management of melanoma patients with CNS metastases, which is currently the greatest challenge in the care of patients with advanced melanoma.

New treatment methods introduced into daily clinical practice have resulted in a significant change in therapeutic management compared to those used 5 years ago. Central nervous system metastases are increasingly diagnosed at the asymptomatic stage using routine magnetic resonance imaging (MRI) and/or computed tomography (CT) of the brain as part of the follow-up or qualification of patients for systemic treatment. Advanced techniques of stereotactic radiotherapy have become the main therapeutic option used in local treatment. In the last 10 years, 11 new drugs for patients with advanced melanoma have been registered in Europe [vemurafenib, dabrafenib, trametinib, cobimetinib,

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binimetinib, encorafenib, ipilimumab, nivolumab, pembrolizumab and relatlimab in combination with nivolumab and talimogene laherparepvec (T-VEC)]. In Poland, 6 of the new therapies are currently available under drug programs (vemurafenib with cobimetinib, dabrafenib with trametinib, encorafenib with binimetinib, ipilimumab with nivolumab, pembrolizumab, and nivolumab). Based on data from clinical trials median OS in the entire group of patients with *BRAF* mutant metastatic melanoma treated with pembrolizumab/ /nivolumab and a combination of BRAF (BRAFi) and MEK (MEKi) inhibitors is now approximately 2 years (approximately 4 times longer than 5 years ago). So far, the best results have been achieved with dual immunotherapy (anti-CTLA-4 and anti-PD-1). The combination of anti-PD-L1 therapy with BRAFi and MEKi (e.g. atezolizumab plus vemurafenib and cobimetinib) also allows for obtaining some benefits. Perhaps using other methods of combined treatment, for example, anti-PD-1/anti-PD-L1 with anti-LAG3 and/or TIM3 will allow further improvement. In each case of confirmed CNS metastases, it is mandatory to examine the status of the *BRAF* gene in the fixed material (if it has not been previously assessed) [6, 7]. According to the current National Comprehensive Cancer Network (NCCN) and European Society of Clinical Oncology (ESMO) guidelines, in patients with *BRAF*-mutated melanoma and metastases in the CNS (especially asymptomatic and less than 3 cm in size), dual immunotherapy is recommended if no contraindicated. However, depending on the clinical setting, the use of BRAFi and MEKi in the first line of treatment should be considered.

Even in the treatment of multiple metastatic lesions, the use of modern radiotherapy techniques has become much more common, replacing WBRT in many clinical situations. Stereotactic radiotherapy involves delivering a biologically high dose of radiation to a precisely defined small volume with a significant decrease in the dispersed dose in healthy tissues outside the target volume. Treatment can be done with a single fractional dose [stereotactic radiosurgery (SRS)] or 3–5 fractions (fractionated stereotactic radiosurgery, fSRS).

Therapeutic decisions should be individualized, taking into consideration treatment goals (short-term *versus* long-term benefits) and based on clinical picture (LDH level, other organs involvement, tumor mass, patient performance status, course of the disease, comorbidities and their treatment, and patient preferences) [8]. The basic and applicable rule in the case of melanoma metastases in the CNS should be optimizing the management by multidisciplinary teams whose members are experienced in the diagnosis and treatment of patients with melanoma. The team should include at least a neurosurgeon, a radiation oncologist, and a clinical oncologist [9].

Diagnostics

Signs and symptoms of CNS metastases may be mild and difficult to recognize. They depend, among other things, on the number, size, and location of metastases. Metastases most often occur in the telencephalon; in about 15% of cases they occur in the cerebrum and about 5% in the brainstem. The most common symptoms include headache (sometimes accompanied by nausea and/or vomiting), seizures, speech, comprehension, and vision disorders, numbness, and movement disorders. The presence of clinical symptoms of CNS metastases is associated with poorer treatment outcomes. Patients with stages I and II melanoma have a lower risk of developing metastases in the CNS compared to patients with stages III and IV [10]. In younger patients, the risk of late metastases in the CNS is higher in thicker melanomas [11]. Based on the data from a retrospective analysis of the large multicenter S0008 study, the risk of CNS metastases at stage IIIB and IIIC was 15%, and metastases were mainly diagnosed within the first 3 years after surgery [12]. The time from treatment of the primary lesion may be relatively long and may even be 3–4 years (median) [13].

Therefore, in patients with stage III and IV melanoma, the detection of CNS metastases based on follow-up imaging tests in the absence of clinical symptoms is of great importance. The prognosis in asymptomatic patients and the efficacy of treatment are definitely better compared to patients with symptoms resulting from CNS metastases. The risk of developing CNS metastses in patients with stage IV melanoma is very high and reaches almost 40%. Performing an MRI of the CNS during the disease staging after the diagnosis of stage IV melanoma is the standard of care. In stage III, the risk of developing metastases in the CNS is also high and ranges from 18.5 to 23.5% [14, 15]. In asymptomatic patients with melanoma stage IIIC and higher, CT or MRI of the CNS should be considered [7]. The results of the analysis of 202 patients done by Derks et al. indicate that routine MRI in patients after radical resection of stage III melanoma before starting adjuvant treatment is not recommended [3, 16]. Performing periodic MRI examinations for up to 3 years after treatment cessation is indicated to detect asymptomatic CNS metastases (especially in high-risk patients — i.e. stage IIIC or higher, in whom no CNS metastases have been detected so far). Patients with successful treatment of CNS metastases in the past require regular follow-up with MRI. In patients with signs and/or symptoms (including even mild symptoms) indicating the possibility of CNS lesions, an MRI examination is recommended [17]. MRI is the most sensitive imaging for detecting CNS metastases and has an advantage over contrast-enhanced CT. It should be emphasized

Table 1. Recursive Partitioning Analysis (RPA) prognostic scale (n = 1200) [19]

	Class I	Class II	Class III
KPS [points]	≥ 70	≥ 70	< 70
Primary tumor	Cured	Active	Active
Age	< 65 years	> 65 years	Any
Non-CNS lesions	No	Present	Present
Prevalence	15%	65%	20%
Median survival [months]	7.1	4.2	2.3

CNS — central nervous system; KPS — Karnofsky performance status

Table 2. Prognostic assessment of survival in melanoma patients with brain metastases: Diagnosis Specific — Graded Prognostic Assessment (DS-GPA) scale [20]

KPS [points]	< 70	70–80	90–100	
Number of CNS metastases	> 3	2–3	1	
Points		1	2	
Based on the sum of points assigned according to KPS and the number of metastases				
DS-GPA	0–1.0	1.5–2.0	2.5–3.0	3.5–4.0
Median survival [months]	3.4	4.7	8.8	13.2

CNS — central nervous system; KPS — Karnofsky performance status

that melanoma CNS metastases are usually multifocal and hemorrhagic [18].

Therapeutic management

Therapeutic management depends on the clinical setting and includes systemic, local (radiotherapy and/or surgery), and/or symptomatic treatment. In addition to clinical symptoms, there are numerous disease- and patient-related parameters playing an important role in the treatment of melanoma patients with CNS metastases (number, size, and location of metastases, presence and control of lesions outside the CNS, previous treatment for melanoma and the outcome, *BRAF* gene mutation status, general condition, and age, comorbidities and their treatment). In symptomatic treatment, anti-edematous drugs (mainly glucocorticosteroids) are used. In the case of seizure, antiepileptic treatment should be initiated, but interactions with other drugs used by the patient (including glucocorticoids) should be taken into consideration.

Tables 1 [19] and 2 [20] present prognostic scales in patients with CNS metastases; Recursive Partitioning Analysis — Radiation Therapy Oncology Group (RPA-RTOG) scale applies to all cancers, and Diagnosis Specific — Graded Prognostic Assessment (DS-GPA) scale applies only to patients with melanoma. However, it should be remembered that the aforementioned scales were developed before the introduction of new methods of systemic treatment of patients with metastatic melanomas. The median OS in all melanoma patients

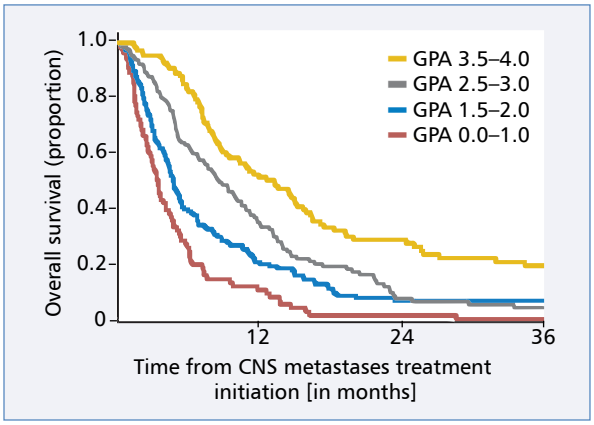

Figure 1. Kaplan-Meier survival curves for individual groups in the Graded Prognostic Assessment (GPA) scale [20]; CNS — central nervous system

was 6.74 months (range: 3.38 to 13.32 months, number of patients n = 481) (Fig. 1).

The management algorithm in melanoma patients with CNS metastases is presented in Figure 2.

Local treatment of melanoma patients with CNS metastases

The expected survival in untreated melanoma patients with symptomatic CNS metastases is 2–3 months, and only 13% of patients have OS longer than a year (prognosis is more favorable in patients below 65 years of age and performance status > 70 according to

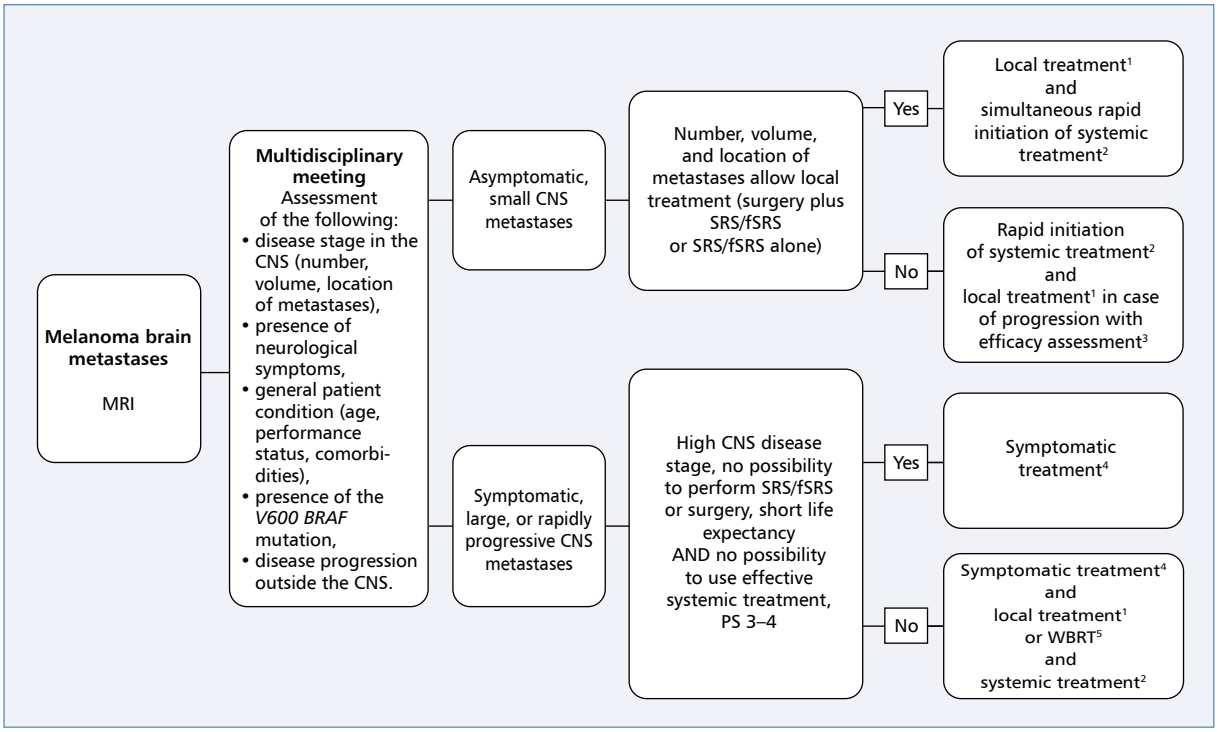

Figure 2. Algorithm of management in melanoma patients with metastases in the central nervous system (CNS); SRS/fSRS — radiosurgery, fractionated radiosurgery (stereotactic radiotherapy); WBRT — whole brain radiotherapy; [1]Local treatment is understood as standalone or combined use of surgical methods and techniques of stereotactic radiotherapy, available options include metastasectomy plus adjuvant SRS/fSRS, hybrid treatment (metastasectomy plus adjuvant SRS/fSRS to postoperative bed plus radical SRS/fSRS of other metastases) or only SRS/fSRS. Hybrid treatment may bring particular benefits in the case of multiple metastases available for SRS/fSRS, among which some lesions give neurological symptoms or are associated with expected lower efficacy of SRS/fSRS (large, bleeding lesions, with a fluid component) and are available for surgical treatment; [2]Available options include immunotherapy (combination of nivolumab with ipilimumab as a combination effective in the CNS) or BRAF inhibitors with MEK inhibitors in patients with a confirmed *BRAF* mutation. The preferred treatment option is dual immunotherapy, regardless of *BRAF* mutation status. In the presence of high-volume disease and clinical symptoms, treatment with BRAF inhibitors with MEK inhibitors in patients with a known *BRAF* mutation should be considered as an alternative. Single-agent immunotherapy does not provide adequate CNS response rates; [3]This management requires close observation of the CNS with the use of contrast-enhanced magnetic resonance imaging (MRI) and comparative assessment. Baseline MRI should be performed at treatment initiation, then in a month, and then every 2–3 months; [4]Anti-oedematous and/or anti-epileptic treatment, if necessary; [5]In the case of leptomeningeal metastases or if SRS/fSRS/metastasectomy is not possible

the Karnofsky scale). Resection or radiotherapy of all metastatic lesions influences the prognosis. In the situation of leaving one of several lesions, the prognosis is identical as in untreated patients [20]. In the case of multiple asymptomatic and non-life-threatening metastases in the CNS, the priority is to start systemic combined treatment with proven value in the CNS (especially — nivolumab and ipilimumab) with the possibility of postponing local treatment until the first assessment of systemic therapy efficacy (especially when WBRT is the only possible procedure due to the multiplicity of metastatic lesions or unavailability of techniques for simultaneous radiotherapy of multiple metastases). In the case of a limited number of metastases available for local treatment techniques, the preferred method of management is a combination of radiotherapy with immunotherapy or molecularly targeted treatment during the first 2–3 months from systemic treatment initiation, instead of radiotherapy as part of salvage treatment [8].

There are still no unequivocal predictors of the occurrence of melanoma metastases in the CNS. However, certain factors are known to be associated with increased risk, including:

— primary lesion within the head and neck;
— increased LDH level;
— ulceration in the primary lesion;
— mutations in the *BRAF*, *NRAS,* and *PTEN* genes [4].

In total 24–58% of patients with CNS metastases have *BRAF* mutation, and 23% of patients have *NRAS* mutation.

Surgical treatment

Eligibility criteria for surgical treatment of melanoma patients with CNS metastases (EBM, 2010, level 1) include:

— newly diagnosed single lesions (up to 4 in total);
— size over 3 cm;
— location of lesions surgically accessible;
— symptomatic lesions:
— lesions causing neurological deficit and/or symptoms of increased intracranial pressure due to their volume and/or associated hemorrhagic focus and/or secondary to fluid tract obstruction leading to hydrocephalus (lesions located in the posterior cranial fossa);
— Karnofsky performance status (KPS) > 70, age < 65 years;
— progression after previous radiosurgery, fractionated radiosurgery (stereotactic radiotherapy) (SRS/fSRS).

The goals of surgical treatment include:
— histological verification;
— radical removal of all lesions, which affects OS (no justification for biopsy); in multiple tumors, it is possible to use hybrid therapy, involving resection of large and surgically accessible lesions in combination with SRS/fSRS for smaller lesions located in deep brain structures;
— improvement or stabilization of neurological status (occurrence of new neurological deficits shortens OS by 4 months);
— enabling further oncological treatment;
— resection of symptomatic lesions of radiation necrosis after SRS/fSRS.

Radiotherapy

Stereotactic radiotherapy

Radiosurgery, fractionated radiosurgery (stereotactic radiotherapy) can be performed with use of dedicated equipment (GammaKnife, CyberKnife, Edge) or conventional linear accelerators equipped with a high-definition multi-leaf collimator (HD-MLC). The total dose and fractionation depend on the location and size of metastatic lesions. In order to achieve local control, it is recommended to provide biologically effective dose higher than 100 Gy. The efficacy of SRS/fSRS in the treatment of small CNS melanoma metastases has been confirmed in many studies and is similar to surgical resection. Appropriate qualification of patients for treatment, which should be conducted by multidisciplinary teams, is very important.

Inclusion criteria for SRS/fSRS are:
— performance status 0–2 according to the World Health Organization (WHO) scale;
— single metastasis < 3 cm in diameter;
— a number of metastases > 1, when the total volume of the healthy brain irradiated with a dose of 12 Gy does not exceed 10 cm^3 (for single-fraction SRS);
— no progression outside the CNS or when potentially effective systemic treatment is available;
— indications for radiotherapy of postoperative bed [8, 21, 22];
— indications for possible repeated local irradiation when progression is confirmed;
— life expectancy > 6 months.

Radiosurgery, fractionated radiosurgery (stereotactic radiotherapy) was originally reserved for patients with fewer than 3 metastases; however, indications for this method have been recently extended [7]. According to them, the number of metastases is less important, and SRS is limited by the total volume of all lesions and brain volume, which receives a total dose of 12 Gy [23, 24]. It has been demonstrated that the volume of healthy brain tissue receiving a single dose of 12 Gy, which is greater than 10 cm^3, is associated with high risk of radiation necrosis. In this case, a reduction in the therapeutic dose or fSRS should be considered [25]. With proper qualification, the local efficacy of SRS/fSRS (no progression in the irradiated volume) is achieved in 90–95% of melanoma patients [26, 27]. A radiologically significant tumor response is observed in half of patients [26]. Local efficacy is closely related to the location of metastatic lesions and their size.

According to the ESMO recommendations, SRS/fSRS is the preferred method of adjuvant treatment after resection of melanoma metastases in the CNS [8].

Whole brain radiotherapy (WBRT)

Melanoma is considered to be radioresistant and sensitive only to higher doses per fraction. The fractionation regimens used for WBRT (5 × 4 Gy or 10 × 3 Gy) do not provide an adequate biological dose for long-term CNS disease control. Whole brain radiotherapy is associated with neurological toxicity. The deterioration in patient quality of life is mainly caused by the impairment of cognitive functions [28, 29]. Modern high-conformal radiotherapy techniques enable single isocenter SRS/fSRS for multiple brain metastases (hypothetically without a limited number of lesions if the criteria organs at risk are met, which also limits the use of WBRT) [30, 31].

In addition, the results of a phase III study published in 2019 indicate that WBRT should not be used as adjuvant treatment after resection of 1–3 melanoma metastases in the CNS [32].

Whole brain irradiation should only be reserved for the following patients:
— not eligible for surgery and SRS/fSRS;
— with rapid progression of metastases and inability or lack of efficacy of systemic treatment with proven value in the CNS;
— with leptomeningeal metastases (LMs) in good general condition.

Patients in poor general condition (WHO performance status 4) and with short life expectancy should be disqualified from any form of radiotherapy. The treatment of choice is best supportive care (BSC) (effective

anti-edematous and anti-convulsant treatment as well as alleviating symptoms that often accompany progression in the CNS).

Systemic treatment

Systemic treatment is the backbone therapy in patients with metastatic melanoma (including the CNS). Similar to molecularly targeted agents (BRAFi and MEKi), the use of immunotherapy (including anti-CTLA4, anti-PD1, and anti-PD-L1 drugs) significantly improves the prognosis of melanoma patients with CNS metastases. Currently, in the treatment of advanced disease, anti-PD-1 therapy combined with anti-LAG3 (nivolumab with relatlimab) is also used, although data on the use of this combination in patients with brain metastases are limited. Additionally, long-term remissions in immunotherapy responders are increasingly frequently observed, and drugs introduced into systemic therapy — both immunotherapy and molecularly targeted therapy — allowed for a significant extension of median OS [33]. The choice of appropriate systemic therapy should be determined by previously used treatment, presence of the V600 *BRAF* mutation, patient's condition, and clinical setting. In most patients, this therapy should be supplemented with local treatment. In the case of few and minor metastases in the CNS, only systemic treatment remains an option.

Molecularly targeted therapy

The efficacy of molecularly targeted drugs (BRAFi and MEKi) in patients with skin melanoma with CNS metastases has been shown in several prospective clinical trials. The first clinical trials conducted exclusively in this group of patients evaluated the efficacy of BRAFi in monotherapy. The largest study — involving 172 patients with asymptomatic CNS metastases — assessed the efficacy of dabrafenib (phase II BREAK-MB study). Patients included in this study were assigned into 2 groups depending on previous local treatment of CNS metastases (patients without prior local treatment *vs.* patients with progression after previous local treatment). The intracranial response rate was 39.2% and 30.8%, respectively. Median OS in both groups was over 8 months [2]. In a similar phase II clinical trial of vemurafenib in 146 patients with CNS metastatic skin melanoma, the intracranial response rate was 18%, regardless of previous local treatment. Median OS was approximately 9 months [34]. In the assessment of the response by an independent review committee (IRC), the intracranial response rates in both studies were very similar (approximately 18%). Both studies showed a high disease control rate (approximately 70–80%). In most patients, a reduction in CNS metastatic lesions was observed, but only in some patients, it met partial response criteria.

Symptomatic metastases in the CNS are associated with particularly poor prognosis (median OS — 3–4 months), and this is challenging. A clinical trial involving only patients with symptomatic metastases evaluated the use of vemurafenib in monotherapy [35]. This small study involved 24 patients who were ineligible for neurosurgical treatment after prior treatment of CNS metastases and required glucocorticoids for symptom control. The intracranial response rate was 16% and median OS was 5.3 months. During the treatment, pain relief, an improvement in patient performance status, and a decrease in the need for glucocorticoids were observed. Unfortunately, the treatment effect was short-term, and the disease progressed rapidly.

Combination of BRAFi with MEKi improved the results of targeted treatment. The phase II COMBI-MB study using dabrafenib with trametinib was the first prospective clinical trial evaluating the activity of this treatment in patients with CNS metastases [36]. The study included 125 patients with performance status 0–2 with or without prior local treatment for CNS metastases. Intracranial response rates were 56–59% regardless of previous local treatment and the presence of symptomatic metastases. Duration of response (DoR) was the longest in patients with asymptomatic CNS metastases. However, the median duration of response was much shorter than that observed in phase III clinical trials without the participation of patients with CNS metastases (approximately 6 months versus 12–14 months) [37–39]. However, there were no significant differences in treatment tolerance, with fever and gastrointestinal disorders being the most common. The efficacy of BRAFi/MEKi has also been confirmed in clinical practice, including in patients pretreated with these drugs. In a retrospective analysis of 24 patients with CNS metastatic *BRAF* mutant melanoma treated with encorafenib and binimetinib, the CNS objective response rate (ORR) was 33%, and the disease control rate (DCR) was 63%. In patients previously treated with BRAFi/MEKi, the ORR and DCR were 24% and 57%, respectively [40].

The results of these studies confirm the activity of the BRAFi/MEKi combination in patients with CNS metastases. The response to treatment is rapid, with most patients achieving tumor reduction. This effect significantly contributes to OS improvement in the group of patients with poor prognosis and quality of life, particularly in patients with symptomatic CNS metastases. Unfortunately, the above data also indicate a short-term therapeutic effect of this targeted therapy. Resistance develops faster than in patients without CNS metastases. Therefore, attempts to combine BRAFi/MEKi with other kinase inhibitors or immunotherapy to improve treatment outcomes are ongoing.

Table 3. Studies evaluating the efficacy of molecularly targeted therapy in the treatment of melanoma patients with metastases in the central nervous system (CNS)

Study	Patient characteristics	Number of patients	Median PFS [months]	Median OS [months]
Phase II study [34]	CNS metastases previously untreated	90	3.7	8.9
(NCT01378975)	CNS metastases after prior treatment	56	4.0	9.6
Vemurafenib				
Pilot study [35]	Previously treated, symptomatic CNS metastases	24	3.9	5.3
(NCT01253564)				
Vemurafenib				
Phase II study	CNS metastases without prior treatment of CNS metastases	89	~4[a]	~8[a]
BREAK-MB [2]				
(NCT01266967)	Progression after previous local treatment	83	~4[a]	~8[a]
Dabrafenib				
Phase II study	Asymptomatic CNS metastases without previous local treatment	76	5.6	10.8
COMBI-MB [36]	ECOG PS 0–1			
(NCT02039947)	Asymptomatic CNS metastases	16	7.2	24.3
Dabrafenib + trametinib	Prior local treatment			
	ECOG PS 0–1			
	Asymptomatic with/without prior local treatment	16	4.2	10.1
	ECOG PS 0–1			
	Symptomatic with/without prior local treatment	17	5.5	11.5
	ECOG PS 0–2			
GEM1802/EBRAIN-MEL [41, 42]	Asymptomatic CNS metastases	14	7.1	NA
(NCT03898908)	Symptomatic CNS metastases	15	9.3	18.4
Encorafenib and binimetinib in combination with radiotherapy				

[a]median applies to patients with the *BRAF* V600E mutation; ECOG — Eastern Cooperative Oncology Group; NA — data not available

The results of studies using BRAFi/MEKi in melanoma patients with CNS metastases are presented in Table 3 [2, 34–36, 41, 42].

Radiotherapy in combination with targeted treatment

High BRAFi/MEKi initial activity in melanoma patients with CNS metastases slightly changed the approach to using radiotherapy. Increasing use of SRS enables a high local control rate. Therefore, radiotherapy is often used only during BRAFi/MEKi treatment. Data on combining BRAFi drugs with concomitant radiotherapy are contradictory. On the one hand, there are potential benefits in terms of sensitization of melanoma cells to radiotherapy after BRAFi administration, which was described in *in vitro* studies [43]. On the other hand, the radiosensitizing effect of BRAFi can lead to increased side effects, which has been confirmed by several dozen case reports of significant skin toxicity with simultaneous use of irradiation (including WBRT) and BRAFi. It is worth mentioning, however, that these data refer only to older-generation BRAFi, currently replaced with newer molecules. New reports indicate that there is no need to interrupt treatment with newer-generation inhibitors. The data from the analysis of a small group of patients (GEM1802/EBRAINMEL study with encorafenib and binimetinib) indicate the possibility of improving treatment outcomes with new BRAFi/MEKs combined with radiotherapy [41, 42, 44, 45]. However, these findings were not reflected in the recommendations (as of 2023). There is no unequivocal evidence of an increased risk of neurotoxicity, hemorrhage, or radiation-related brain necrosis in the case of a combination of targeted treatment with radiotherapy [46–48]. In the case of conventional radiotherapy, the most common side effect is skin toxicity (more severe with vemurafenib) [49]. Currently, it is recommended to discontinue BRAFi/MEKi at least 3 days before the start of WBRT and to restart the drugs 3 days after completion of radiotherapy at the earliest. Withdrawal of molecularly targeted therapy is not justified when using SRS/fSRS [8].

Immunotherapy

Immunotherapy is the basic treatment option in melanoma patients with CNS metastases without V600 *BRAF* mutation. In patients with a mutation in the *BRAF* gene, the use of immunotherapy or BRAFi/MEKi treatment depends on the clinical situation.

In the open-label phase II study of ipilimumab (NCT00623766), the highest response rates were observed in asymptomatic patients not receiving glucocorticoids. Based on criteria for the immune-related response (IRR), median PFS in patients with CNS lesions was 1.9 months in the asymptomatic group *vs.* 1.2 months in the group requiring symptomatic treatment with glucocorticoids, and median OS was 7.0 *vs.* 3.7 months, respectively [50]. In the CheckMate 204 study (NCT02320058) with nivolumab and ipilimumab in glucocorticosteroids-naïve patients with at least one CNS lesion, the composite primary endpoint was the intracranial clinical benefit rate (CBR), consisting of objective responses and disease stabilization lasting more than 6 months. The CNS control rate was 55%, and the complete response rate reached 21%. Non-CNS responses were similar to those seen in the CNS, with a 6-month PFS rate of 67%. The results of the study confirm that, similar to the treatment of extracranial lesions, in patients with CNS metastases, it is possible to obtain a similar response to treatment for CNS lesions [51].

In 2019, updated results of the CheckMate 204 study in cohort A (patients with asymptomatic metastases in the CNS, e.g. without neurological symptoms and not taking glucocorticoids) and cohort B (patients with neurological symptoms regardless of glucocorticoid use) were presented. Patients in both groups received nivolumab at a dose of 1 mg/kg body weight (bw) and ipilimumab at a dose of 3 mg/kg bw every 3 weeks (4 administrations), and then only nivolumab at a dose of 3 mg/kg bw every 2 weeks until disease progression or treatment toxicity. In cohort A, after a follow-up of 20.6 months, the CBR was 58.4%, and in cohort B, after a follow-up of 5.2 months, it was 22.2%. Grade 3 and 4 treatment-related adverse events were observed in 54% of patients in cohort A and 56% of patients in cohort B. Grade 3 and 4 treatment-related neurologic adverse events occurred in 7% and 17% of patients, respectively [52, 53]. Similarly, the Australian ABC study (NCT02374242), which compared nivolumab versus nivolumab with ipilimumab in 79 melanoma patients with CNS metastases, demonstrated the efficacy of immunotherapy (including the advantage of doublet therapy in melanoma patients with asymptomatic CNS metastases). In the ABC study, patients were assigned to 3 cohorts: A (asymptomatic patients not treated locally due to CNS metastases receiving ipilimumab with nivolumab; n = 36), B (asymptomatic patients not treated locally due to CNS metastases and receiving nivolumab; n = 27) and C (patients after failure of local treatment of CNS metastases, or symptomatic patients with CNS metastases, and patients with LM and receiving nivolumab; n = 16). Complete responses to treatment were observed in 17% of patients in cohort A and 12% of patients in cohort B (cohort C — no response) [54, 55].

In the CheckMate 204 study and ABC study, grade 3 and 4 treatment-related adverse events occurred in 52% and 54% of patients receiving doublet therapy, respectively.

In asymptomatic patients, the presented clinical trials demonstrated the efficacy and good tolerance of immunotherapy. With ipilimumab, the response rate was as high as 16%, and with nivolumab and pembrolizumab it was approximately 20%. In studies on the combination of anti-PD-1 and anti-CTLA-4 agents in the group of asymptomatic patients, further significant improvement in treatment results was obtained. In patients with symptomatic metastases, the intracranial clinical response rate was also significant and amounted to 16.7%. With the availability of anti-PD-1 and anti-CTLA-4 combination therapy (nivolumab with ipilimumab — regardless of *BRAF* gene mutation status) and anti-BRAF and anti-MEK therapy in patients with mutation in the *BRAF* gene and good performance status, it is the treatment of choice, especially in the case of asymptomatic metastases in the brain, with the option of postponing local treatment until disease progression in patients receiving combined therapy.

Overall, the safety profile of immunotherapy in the aforementioned studies was consistent with that for patients without brain metastases. Moreover, intracranial and extracranial responses were largely consistent, which was confirmed by the results of a meta-analysis published by Rulli et al. in 2019 [56].

The choice of systemic therapy after diagnosis of CNS metastases remains an important issue.

The authors of an analysis published in 2023 retrospectively assessed the results of treatment in patients after first-line therapy due to generalized melanoma without CNS metastases (n = 1704), with and without the *BRAF* mutation. In patients with *BRAF* mutation-positive melanoma undergoing first-line anti-PD1 and anti-CTLA4 immunotherapy, brain metastases occurred less frequently and later as compared to BRAFi and MEKi therapy. In addition, the use of doublet immunotherapy was associated with longer OS. Interestingly, no differences in terms of OS were found between dual immunotherapy and anti-PD-1 monotherapy in melanoma patients without the *BRAF* mutations [57].

Derks et al. [58] published 2023 an analysis of melanoma patients with CNS metastases treated in daily

Table 4. Studies evaluating the efficacy of immunotherapy in the treatment of melanoma patients with metastases in the central nervous system (CNS)

Treatment	Patients	Patient characteristics	IC DCR	IC ORR	IC DOR [months]	mPFS [months]	mOS [months]
Ipilimumab	51 (A)	Asymptomatic	24%	16%	–	1.4	7.0
CA184-042 [50]	21 (B)	Symptomatic	10%	5%		1.2	3.7
Ipilimumab + fotemustine: NIBIT-M1 [59]	20	Asymptomatic	50%	40%	30.3	4.5	12.7
Pembrolizumab: (NCT02085070) [60, 61]	23	Untreated or progressive brain metastases	–	26%	–	2	17
Nivolumab: ABC; CA209-170 [54] (NCT02374242)	27 (B)	Asymptomatic, no local treatment (B)	20%	20%	NR	2.5	18.5
	16 (C)	previously treated or symptomatic (C)	19%	6%	NR	2.3	5.1
Nivolumab + ipilimumab: ABC; CA209-170	36 (A)	Asymptomatic, no local treatment (A)	57%	46%	NR	NR	NR
Nivolumab + ipilimumab: CheckMate 204 [52, 53] (NCT02320058)	75	Asymptomatic, previously treated, ≤ 3 metastases	60%	55%	NR	NR	–

IC DCR — intracranial diseases controls rate; IC DOR — intracranial duration of response; IC ORR — intracranial objective response rate; NR — not reached; OS — overall survival; PFS — progression-free survival

clinical practice in Rotterdam from 2005 to 2021, comparing the period before and after the introduction of new treatment methods (cut-off point 2015). In total, 430 patients were analyzed, and OS was assessed before and after 2015 when checkpoint inhibitors and molecularly targeted therapy began to be used much more frequently. The analysis included 152 melanoma patients with CNS metastases before 2015 and 278 treated after 2015. Median OS in patients treated after 2015 was significantly longer compared to patients treated before 2015 (6.9 *vs.* 4.4 months, hazard ratio 0.67, $p < 0.001$). Median OS was shorter in patients who received systemic treatment before the diagnosis of CNS metastases. The use of immunotherapy immediately after the diagnosis of CNS metastases was associated with an increase in median OS from 4.2 months to 21.5 months ($p < 0.001$). BRAF and MEK inhibitors can cause a rapid response to treatment and have been frequently administered (> 70%) in patients with symptomatic metastases and poor performance status [58].

Studies have also been conducted to evaluate sequential and combination therapy with BRAF and MEK inhibitors and immunotherapy in melanoma patients with CNS metastases. The combined use of atezolizumab plus vemurafenib and cobimetinib resulted in an intracranial response rate of 42% and median OS of 13.7 months. In some situations, the above regimen may be an option in subsequent treatment lines, but currently, the combination of BRAF and MEK inhibitors with immunotherapy is not a standard of care.

The results of studies using immunotherapy in melanoma patients with CNS metastases are summarized in Table 4 [50, 52–54, 59–61] while the results of studies evaluating the efficacy of molecularly targeted therapy combined with immunotherapy are presented in Table 5 [62–65].

Combining radiotherapy with immunotherapy

There are more and more reports related to the beneficial effect of combining radiotherapy with immunotherapy. The studies published so far have shown a significant increase in the percentage of abscopal effect phenomenon (response of untreated lesions to local treatment of another lesion) after adding radiotherapy to immunotherapy [66, 67]. The effect is explained by local stimulation of the immune system and intensification of antigenic effect, where dendritic cells probably play an important role. Currently, many clinical trials are conducted in which radiotherapy and immunotherapy are combined. There are no contraindications to combining radiotherapy with immunotherapy, and this decision should be made at a multidisciplinary meeting individually for each patient [8]. Attention should be paid to the prophylactic anti-edematous treatment administered during radiotherapy in the form of high doses of glucocorticosteroids, which may reduce immunotherapy efficacy. According to the current recommendations, indications for the use of glucocorticosteroids as part of anti-edematous treatment during SRS/fSRS are significantly limited.

Table 5. Studies evaluating the efficacy of molecularly targeted therapy combined with immunotherapy in melanoma patients with the *BRAF* mutation and metastases in the central nervous system (CNS)

Study	Study phase	Treatment	Number of patients	IC ORR % (CR + PR)	mPFS [month]	mOS [month]
TRIDENT [62] Patients with anti-PD1 resistance (n = 17) or previous or current brain metastases, including active metastases, asymptomatic metastases, or mild symptoms/requiring corticosteroids (n = 10)	II	Nivolumab + + dabrafenib + + trametinib	10	4/7 patients (57%)	8.0	NR
IMSpire 150 [63, 64] Exploratory analysis	III	Vemurafenib + + cobimetinib + + atezolizumab *versus* vemurafenib + + cobimetinib	244 *versus* 247	Cumulative incidence of brain metastasis as the first site of progression: after 12 months: 16% *vs.* 19% after 24 months: 24% *vs.* 26% after 36 months: 25% *vs.* 28% after 48 months: 28% *vs.* 29% Stratified HR = 0.91; 95% CI 0.64–1.29		
TRICOTEL [65] (Cohort 1: *BRAF* V600 positive melanoma patients with brain metastases; n = 15; Cohort 2: *BRAF* V600 negative melanoma patients with brain metastases)	II	Atezolizumab + + vemurafenib + + cobimetinib	65	42 IRC-assessed (51 investigator-assessed)	5.3 IRC-assessed (5.8 investigator-assessed)	13.7

CI — confidence interval; CR — complete response; HR — hazard ratio; IC ORR — intracranial objective response rate; ICR — independent review committee; NR — not reached; OS — overall survival; PFS — progression-free survival; PR — partial response

The combination of immunotherapy or molecularly targeted therapy with SRS/fSRS seems to be generally well tolerated, as demonstrated by studies and analyses conducted so far. In 2016, the results of a retrospective analysis conducted in a subgroup of patients participating in two prospective studies with nivolumab due to unresectable or metastatic disease were published [68]. Twenty-six patients treated for melanoma and undergoing SRS/fSRS due to CNS metastases were analyzed, including patients with CNS metastases diagnosed and treated with SRS within 6 months of nivolumab treatment (before, after, or during immunotherapy). A total of 73 lesions in the CNS were identified in this group of patients. The primary endpoint was treatment tolerance, while the secondary endpoints included control of CNS disease, lesions outside the CNS, and OS. Most metastatic patients were treated with SRS, and only 12 CNS lesions underwent fSRS. Grade 2 headache was observed in one patient, which resolved after using glucocorticoids. No other treatment-related neurological complications were observed. In 8 CNS lesions (11%), treatment failure was observed in the form of an increase in lesion volume of at least 20%. Local control rates at 6 and 12 months were 91% and 85%, respectively. Median OS was 12.0 months from initiation of nivolumab treatment and 11.8 months from SRS/ fSRS.

In 2017, a systematic review was published to assess the tolerance of the combination of immunotherapy or targeted therapy with SRS/fSRS. The review included 6 retrospective studies and 2 case reports on patients treated with SRS/fSRS and ipilimumab. Based on this analysis, it can be concluded that the combination of ipilimumab and SRS/fSRS for intracranial lesions is a safe treatment option [69].

New methods of systemic treatment in melanoma patients with CNS metastases

Due to often short-term or insufficient response to immunotherapy or molecularly targeted therapy in melanoma patients with CNS metastases, attempts are currently being made to combine BRAF/MEK inhibitors with other kinase inhibitors or immunotherapy to improve the outcomes. An example is the TRIDeNT study with the use of nivolumab in combination with dabrafenib and/or trametinib, involving melanoma patients with CNS and leptomeningeal metastases (NCT02910700) [62]. Another interesting trial is

the NCT05704933 study with the perioperative use of nivolumab in combination with ipilimumab or relatlimab in patients with resectable melanoma metastases in the CNS [70]. Strategies based on systemic therapy combined with radiotherapy are also being evaluated. An example is the phase II BEPCOME-MB study, in which binimetinib with encorafenib and pembrolizumab are used together with SRS/fSRS in patients with *BRAF* mutation-positive melanoma and CNS metastases (NCT04074096) [71].

Monitoring of patients after local treatment due to CNS metastases and management in case of progression

The melanoma brain metastases occurrence is associated with an increased risk of new brain metastases. This justifies the regular brain MRI in all patients treated due to melanoma with CNS dissemination [7]. In approximately 50% of patients, new metastatic lesions or progression of previously treated metastases (recurrence in the postoperative bed, progression after SRS/fSRS/WBRT) will be detected [72]. The first MRI is recommended within a month after neurosurgery or SRS, and every 2–3 months afterwards. The results of imaging tests should be interpreted with caution, especially in patients receiving immunotherapy due to the risk of pseudoprogression and/or posttreatment lesions that may be difficult to distinguish from real disease progression. Despite the introduction of modern neuroimaging techniques, it is difficult to determine the nature of the detected changes (progression of an active neoplastic process or radiation necrosis). In doubtful situations, resection should be the treatment of choice, because — apart from oncological indications — removal of necrotic tissues reduces brain edema. In order to differentiate between radiation necrosis and disease recurrence, magnetic resonance spectroscopy (MRS) may be considered [73]. It is helpful to use structured assessment methods, such as the RANO (Response Assessment in Neuro-Oncology) criteria [74].

In the case of CNS progression, it is usually possible to use one of the local salvage treatments (resection, SRS/fSRS, WBRT) after discussing the patient's case at a multidisciplinary meeting [75–78]. There are possible two different scenarios. If progression is found outside the irradiated volume, it is usually possible to use SRS/fSRS or WBRT. In the case of progression within the irradiated volume, emergency surgical treatment remains the method of choice, with maintaining the previously described qualification criteria for neurosurgical treatment.

Leptomeningeal metastases

The prognosis of patients with leptomeningeal metastases is poor and survival usually does not exceed a few weeks. Data on the efficacy of modern systemic therapies in patients with meningeal involvement are limited, and evidence-based standards of management are missing. The results of recently published retrospective analyzes indicate that molecularly targeted therapy and immunotherapy may improve the prognosis in these patients [79, 80]. A phase I clinical trial (NCT03025256) is currently conducted with the use of systemic and intrathecal nivolumab in patients with leptomeningeal disease.

Data on systemic use of interleukin-2 (IL-2) are encouraging — 1-, 2-, and 5-year survival rates in the group of 43 patients were 36%, 26%, and 13%, respectively. However, due to increased toxicity, the use of IL-2 is not a standard procedure [81].

Radiotherapy in the form of WBRT involving the meninges up to level C2 is a palliative treatment and should be used only in a selected group of patients (good general condition, active systemic treatment).

Summary

The basic and applicable rule in the management of melanoma metastases in the CNS should be a multidisciplinary approach involving, at least, a neurosurgeon, radiation oncologist and clinical oncologist experienced in the treatment of melanoma patients with CNS metastases. There are no clear risk factors for melanoma brain metastases. The detection of CNS metastases is associated with poor prognosis; they are the cause of death in 20–50% of patients, and symptomatic tumors are the immediate cause of death in about 90% of patients. Historical data indicated a median OS of 5–7 months after the diagnosis of CNS metastasis. Currently, more and more CNS metastases are diagnosed at the asymptomatic stage using routine brain imaging during the follow-up or qualification for systemic treatment. Treatment of melanoma with CNS metastases includes, depending on the clinical situation, local and/or systemic therapy and symptomatic treatment. In local treatment, advanced techniques of stereotactic radiotherapy are the most valuable. During the last 10 years, 11 new drugs have been registered in Europe for the treatment of patients with advanced melanoma. Due to the introduction of modern systemic therapies, median OS is now about 2 years, based on data from clinical trials. Anti-PD1 and anti-CTLA-4 dual therapy (nivolumab with ipilimumab), when available, can be the choice in patients with CNS metastasis up to 3 cm in diameter and with good performance status. BRAF

inhibitors and MEKi can be the upfront treatment in patients with *BRAF* mutation and asymptomatic metastases.

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VIA MEDICA

ORIGINAL ARTICLE

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Predictive factors of hepatotoxicity in immunotherapy with checkpoint inhibitors in patients treated for melanoma and kidney cancer

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ABSTRACT

Introduction. Checkpoint inhibitors immunotherapy (CPI) is widely used in the treatment of malignant tumors and has a positive effect on patient prognosis. CPI treatment is associated with various immunological adverse events (AEs), including a rare one — immunological hepatitis.

Material and methods. This study aims to analyze hepatic AEs in patients undergoing CPI therapy and to attempt to determine hepatotoxicity predictors. A retrospective statistical analysis of medical records of 223 CPI patients treated in the years 2014–2021 in Lower Silesian Oncology, Pulmonology and Hematology Center in Wrocław was performed.

Results. Toxicity grade 1–4 according to the Common Terminology Criteria for Adverse Events (CTCAE) occurred in 26% of patients, of which 6% were grade 3–4. An increased risk of hepatotoxicity was found in the group of patients ≤ 60 years of age compared to the > 60-year-old group (34.1% *vs*. 21.7%, p = 0.0418). It has also been confirmed that the occurrence of hepatic AEs during first-line immunotherapy increases the risk of toxicity recurrence during second-line immunotherapy (58.3% *vs*. 15.4%, p = 0.0199). No significantly increased risk of hepatic AEs has been demonstrated in patients with liver metastases, hepatic steatosis, or other chronic liver disease, or in patients after chemotherapy, with elevated baseline levels of lactate dehydrogenase (LDH), or increased body mass index (BMI).

Conclusions. The hepatotoxicity of CPI immunotherapy poses a significant diagnostic and therapeutic challenge. Its early detection and treatment according to the recommended algorithms increases patient safety for patients and sometimes allows the continuation of treatment.

Keywords: hepatotoxicity, immunotherapy, immune checkpoint inhibitors, melanoma, renal cell carcinoma

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Introduction

Immunotherapy with anti-cytotoxic T-cell antigen 4 (anti-CTLA4), anti-programmed cell death protein 1 (anti-PD-1), and anti-programmed cell death ligand 1 (anti-PD-L1) is widely used in the treatment of malignant tumors and has a positive effect on patient prognosis. It has been demonstrated to be effective in improving both progression-free survival (PFS) and overall survival (OS) in the treatment of many cancers, inclu ding melanoma and renal cell carcinoma [1, 2].

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At the same time, the treatment is associated with the occurrence of immunological toxicities, such as dermatological, endocrinological, pulmonary, or gastroenterological [3, 4]. These include immune-mediated hepatitis (IMH) induced by immune checkpoint inhibitors, which is relatively rare (1–5% depending on the criteria). It most often appears around the 2nd month of therapy and initially is usually asymptomatic, revealing abnormalities only in laboratory tests. However, it can also lead to serious liver damage, including acute failure [5, 6]. Therefore, it is necessary to monitor the patient's condition and laboratory parameters. If abnormalities are detected in tests evaluating liver function, the management recommended by oncological societies depends on the severity of adverse events (AEs) according to the Common Terminology Criteria for Adverse Events (CTCAE). The main treatment is high-dose glucocorticosteroid (CS) therapy, and if steroids fail, non-steroidal immunosuppressants. For grade 1 immune-related liver injury, monitoring of liver enzymes every 1–2 weeks is recommended, with no need to suspend Checkpoint inhibitors immunotherapy (CPI) therapy. For grade 2 immune-related liver injury, temporarily withholding CPI therapy is suggested, with monitoring of transaminases and bilirubin twice weekly. Initiation of CS therapy, preferably (methyl)prednisolone 0.5–1 mg/kg/day should be considered. For patients with grade 3 or 4 immune-related liver injury, hospitalization, and initiation of CS therapy, with (methyl) prednisolone 1–2 mg/kg/day is recommended. If there is no response to CS therapy within 2–3 days, alternative immunosuppressive therapy should be considered, such as mycophenolate mofetil (1000 mg twice daily), tocilizumab (8 mg/kg), tacrolimus, azathioprine, cyclosporine, or anti-thymocyte globulin. Immunosuppressants should be continued until full improvement is achieved, and CS therapy should be maintained for at least several weeks after normalization; dose reduction should be cautious [7–9]. In each case, other causes of liver damage should be excluded, such as viral hepatitis, other hepatotoxic substances/drugs, or disease progression in the liver; however, differential diagnosis is not always conclusive [10]. In the literature on hepatic AEs of CPI, it is difficult to clearly distinguish between IMH-type inflammation and similar liver dysfunction (idiopathic autoimmune hepatitis, drug-induced autoimmune hepatitis), and the differentiation should always take into account malignant liver damage, e.g. hyper progression, especially in patients with liver metastases [11].

Material and methods

A total of 223 patients were analyzed, including 208 diagnosed with melanoma and 15 with kidney cancer, who were treated in the years 2014–2021 in the Lower Silesian Oncology, Pulmonology and Hematology Center with immunotherapy, i.e. anti-PD-1 antibodies (nivolumab, pembrolizumab) and/or anti-CTLA4 (ipilimumab). In the entire population, 47% of patients received nivolumab, 36% of patients received pembrolizumab, 34% of patients received ipilimumab, and in the subgroup of patients diagnosed with melanoma, 18% received sequentially one of the anti-PD-1 drugs and ipilimumab. In the group of patients with melanoma, patients with advanced disease were analyzed (96%), but also 4% of patients treated with radical intent (adjuvant therapy after optimal surgical treatment).

Clinical data were collected, such as sex (females: 84, males: 139), age (26–92 years, median 65), body mass index (BMI), some comorbidities, baseline lactate dehydrogenase (LDH) (above normal in 26%), presence of liver metastases at the time of therapy initiation (in 27%), previous use of cytostatic chemotherapy for any oncological indication (in 15%), hepatic AEs in previous pharmacotherapy, and for the group treated with anti-PD-1, an increased baseline dose of the drug understood as 480 mg of nivolumab or 400 mg of pembrolizumab from first administration (15%). Before the first analyzed CPI treatment, 44% of patients had previously received first-line systemic treatment for melanoma/kidney cancer, including anti-BRAF +/– MEK (56%), chemotherapy (30%), and tyrosine kinase inhibitors (15%). The study did not include patients treated with combined anti-PD-1 + anti-CTLA-4 immunotherapy due to the limited patient population (the combination was reimbursed in Poland for the treatment of melanoma in 2021), and the difficulty in clearly comparing subgroups. Detailed patient characteristics are presented in Table 1.

The values of selected parameters as predictors of hepatotoxicity were assessed. A retrospective, statistical analysis of the documentation was performed. Correlations between several clinical factors and hepatotoxicity were analyzed by the Chi-square test.

Archival data obtained for the project were anonymized, and ethics approval for the study was granted by the Bioethics Committee in Hirszfeld Institute of Immunology and Experimental Therapy, the Polish Academy of Sciences in Wrocław (No. KB — 4/2023).

Results

In the analyzed cohort, immunotherapy, in general, was associated with hepatotoxicity, defined as an increase in transaminase values above the normal limit and/or hyperbilirubinemia: CTCAE grade 1–4 in 26% of patients, and CTCAE grade 3–4 in 6% of patients. The

Table 1. Patient characteristics

Characteristics	n	[%]
Enrolled	223	100
Sex		
Male	139	62
Female	84	38
Age [years], median (range)	65 (26–92)	
ECOG performance status		
0	28	13
1	191	86
2	4	2
Neoplasm		
Melanoma	208	93
— Stage IV	199	89
— Stage III (adjuvant)	9	4
Renal cell carcinoma (RCC)	15	7
Type of CPI immunotherapy		
Anti-PD-1	34	19
— Nivolumab	105	47
— Pembrolizumab	81	36
Anti-CTLA4 - ipilimumab	75	34
Anti-PD-1 followed by anti-CTLA-4	38	17
Previous systemic treatment due to any oncological disease		
Any	109	49
Chemotherapy	35	15
Previous systemic treatment due to melanoma/RCC		
Any	98	44
BRAF +/– MEK inhibitors	55	25
Chemotherapy	29	13
Other tyrosine kinase inhibitors	15	7
Other immunotherapy (clinical trials)	4	2
Increased starting dose of the drug		
Nivolumab 480 mg	26	12
Pembrolizumab 400 mg	2	< 1
Site of metastasis		
Lymph node	169	76
Lung	136	61
Skin	105	47
Liver	59	26
Brain	42	19
Other	100	45
Pre-existing liver disease		
Hepatic steatosis	42	19
Liver dysfunction on any previous cancer pharmacotherapy	35	16
Viral hepatitis	6	3
Other	6	3
Baseline blood abnormalities		
LDH > ULN	58	26
ALT > ULN	22	10
AST > ULN	15	7
Hypoalbuminemia	12	5
Bilirubin > ULN	6	3
BMI median (range) [kg/m^2]	27 (17–47)	
> 25	141	63
≤ 25	82	37

ALT — alanine aminotransferase; AST — aspartate aminotransferase; BMI — body mass index; BRAF — type B rapidly accelerated fibrosarcoma; ECOG — Eastern Cooperative Oncology Group; LDH — lactate dehydrogenase; MEK — mitogen-activated extracellular signal-regulated kinase; ULN — upper limit of normal

median time to the first liver function disorder on anti-PD-1 therapy was 2.3 months, and 1.4 m on anti-CTLA4 therapy. AEs grade 3–4 according to the CTCAE in patients treated with anti-CTLA4 occurred twice as often as in the group treated with anti-PD-1 (12% and 6%, respectively).

In the analysis of predictive factors of hepatotoxicity of any grade during immunotherapy, a statistically significant difference in the frequency of hepatic AEs of the therapy depending on age was demonstrated. The age of 60 was established as a cutoff criterion for old age. An increased risk of hepatotoxicity was found in the group of patients ≤ 60 years of age compared to the group > 60 years of age (34.1% *vs*. 21.7%, respectively, p = 0.0418). Therefore, hepatotoxicity occurred in every third patient up to 60 years of age, and in every fifth patient over 60 years of age.

In the subgroup of 38 patients with melanoma treated with sequential immunotherapy (anti-PD-1 followed by anti-CTLA-4), the occurrence of any grade of hepatotoxicity during first-line immunotherapy significantly increased the risk of its recurrence during second-line immunotherapy (58.3% *vs*. 15.4%, p = 0.0199).

There was no statistically significant effect on the occurrence of hepatotoxicity of any degree for such parameters as liver dysfunction during previous cancer pharmacotherapy (p = 0.4677), presence of liver metastases [not significant (NS)], hepatic steatosis (NS), increased baseline BMI (NS), sex (p = 0.3124), elevated LDH levels (NS), or prior use of any cytostatic chemotherapy (p = 0.3456). In the group treated with anti-PD-1, no association with an increased starting dose of the drug was found (p = 0.5539). Detailed univariate analysis of hepatotoxicity predictors is provided in Table 2.

Table 2. Univariate analysis of hepatotoxicity predictive factors

Covariate	n (%)	Incidence of hepatotoxicity [%]	Chi-square	p value
Liver dysfunction during any previous cancer pharmacotherapy				
Yes	35 (16%)	31.4	0.5273	0.4677
No	188 (84%)	25.5		
Liver metastases				
Present	59 (26%)	27.4	Not tested	NS
Absent	164 (74%)	27.1		
Hepatic steatosis				
Present	60 (27%)	20.0	Not tested	NS
Absent	163 (73%)	17.8		
Baseline BMI				
Increased (> 25)	141 (63%)	27.0	Not tested	NS
Normal (≤ 25)	82 (37%)	25.6		
Sex				
Male	139 (62%)	28.8	1.0204	0.3124
Female	84 (38%)	22.6		
Baseline lactate dehydrogenase				
Increased	58 (26%)	25.9	Not tested	NS
Normal	165 (74%)	26.7		
Age				
≤ 60 years	85 (38%)	36	4.1423	0.0418
> 60 years	138 (62%)	21		
Prior use of any chemotherapy				
Yes	35 (16%)	20,0	0,8897	0.3456
No	188 (84%)	27.7		
Increased starting dose of the drug				
Yes	28 (15%)	21.4	0.3504	0.5539
No	157 (85%)	26.8		
(anti-PD-1 subgroup only n = 185)				
Any hepatotoxicity during the anti-PD-1 therapy				
Yes	12 (32%)	58.3	5.4234*	0.0199
No	26 (68%)	15.4		
(melanoma sequential therapy anti-PD-1 followed by anti-CTLA-4 subgroup only n = 38)				

*Chi-square with Yates correction; BMI — body mass index; NS — non significant

Discussion

There is no consistent definition of hepatotoxicity in the literature, as in some studies, this complication was reported as a single category while in others, it was categorized depending on deviations of various biochemical parameters, such as alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGTP), or bilirubin. Some clinical trials, even those with registration, did not report such AEs in publications at all. For our analysis, we adopted hepatotoxicity defined as an increase of ALT and/or AST and/or bilirubin above the upper limit of normal (ULN) according to the CTCAE, divided by severity: all (grade 1–4) and severe (grade 3–4) or an increase of one or more grades of an initially present disorder. Table 3. presents detailed hepatic adverse event grading according to the CTCAE (version 5.0).

Due to a significant clinical problem such as liver dysfunction during immunotherapy, risk factors for its occurrence are researched. It has been shown that the risk of hepatotoxicity increases when a similar AE occurs during previous immunotherapy treatment and is higher when using CTLA-4 inhibitors compared to treatment

Table 3. Hepatic adverse events grading according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0)

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	> ULN — 3.0 × ULN if baseline was normal; 1.5–3.0 × baseline if baseline was abnormal	> 3.0–5.0 × ULN if baseline was normal; > 3.0–5.0 × baseline if baseline was abnormal	> 5.0–20.0 × ULN if baseline was normal; > 5.0–20.0 × baseline if baseline was abnormal	> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal	–
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen					
Aspartate aminotransferase increased	> ULN — 3.0 × ULN if baseline was normal; 1.5–3.0 × baseline if baseline was abnormal	> 3.0–5.0 × ULN if baseline was normal; > 3.0–5.0 × baseline if baseline was abnormal	> 5.0–20.0 × ULN if baseline was normal; > 5.0–20.0 × baseline if baseline was abnormal	> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal	–
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in the blood specimen					
Blood bilirubin increased	> ULN — 1.5 × ULN if baseline was normal; > 1.0–1.5 × baseline if baseline was abnormal	> 1.5–3.0 × ULN if baseline was normal; > 1.5–3.0 × baseline if baseline was abnormal	> 3.0–10.0 × ULN if baseline was normal; > 3.0–10.0 × baseline if baseline was abnormal	> 10.0 × ULN if baseline was normal; > 10.0 × baseline if baseline was abnormal	–
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess of bilirubin is associated with jaundice					

ALT/SGPT — alanine transaminase; AST/SGOT — aspartate transaminase; ULN — upper limit of normal

based on PD-1 inhibitors. At the same time, there are reports of an increased risk of hepatic AEs when using anti-PD-1 immunotherapy at an increased initial dose [12], which is inconsistent with our results. There is no definite link between chronic liver disease or the presence of liver metastases and an increased risk of toxicity [13]. Interestingly, CPI therapy in melanoma is associated with higher risk of hepatotoxicity than in other cancers — odds ratio 5.66 *vs*. 2.71 [14], which may be caused by the relatively frequent presence of liver metastases, as well as the originally registered "high" dose of ipilimumab (3 mg/kg). The positive correlation between the risk of hepatotoxicity and the younger age of patients, as demonstrated, has not been mentioned in the literature and needs to be confirmed in further studies.

The main limitation of this study is a relatively small population, and consequently a small percentage of patients with higher-grade hepatotoxicity according to the CTCAE. All non-baseline serum ALT, AST, or total bilirubin elevations during immunotherapy were included in the analysis. Of 59 patients, 32 (54%) had only grade 1 toxicity.

Conclusions

Immune hepatitis is a potentially serious complication of immunotherapy. This toxicity is more likely to occur with CTLA-4 inhibitors alone than with PD-L1 inhibitors. Earlier occurrence of hepatic AEs, during first-line immunotherapy, predisposes to the occurrence of this complication also during subsequent immunotherapy. Patients younger than 60 years of age may be at higher risk of immunotherapy-induced hepatotoxicity. There was no evidence of an increased risk of hepatic AEs in patients with chronic liver disease, hepatic steatosis, liver metastases, prior chemotherapy, elevated LDH, or BMI.

Article Information and Declarations

Data availability statement

The data that support the findings of this study are available from the corresponding author, M.M., upon reasonable request.

Ethics statement

The publication of the results was approved by the Bioethics Committee in Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences in Wrocław.

Author contributions

M.M.: conceptualization and design, investigation, data curation and original draft preparation; Z.C.: investigation, data curation and original draft preparation;

N.K.-K.: investigation; J.B.: formal analysis and execution of the data; E.F.-C.: supervision.

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Conflict of interest

M. Malik report potential conflict of interest in the context of the published results — travel/accommodation/expenses from Bristol-Myers Squibb; no potential competing interest was reported by other living co-authors.

Supplementary material

None.

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ORIGINAL ARTICLE

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Non-drug related costs of treatment with pertuzumab and trastuzumab in HER2-positive breast cancer patients in Poland

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ABSTRACT

Introduction. HER2-positive breast cancer represents 10–20% of all breast tumors. This study aimed to create a model-based cost-minimization analysis that compared non-drug related costs of different therapies used in the treatment of HER2-positive breast cancer in Poland: pertuzumab SC plus trastuzumab SC (Pert/TrasSC) *vs.* pertuzumab IV plus trastuzumab IV (PertIV + TrasIV) *vs.* pertuzumab IV plus trastuzumab SC (PertIV + TrasSC).

Material and methods. The cost-minimization analysis was based on the results of a questionnaire addressed to leading oncology centers in Poland. The model was broken down into three categories of cost savings: reduced labor costs of nurses, pharmacists and non-drug related consumables, and from two categories of treatment time reduction: occupation of infusion chair and duration of hospital stay. Data on resources used and costs were collected in the first half of 2022.

Results. Data were obtained from four oncology centers. The savings generated per patient from healthcare personnel's work and from non-drug consumables for the Pert/TrasSC arm were 178 PLN compared to PertIV + TrasIV and 168 PLN compared to PertIV + TrasSC. Full adaptation of Pert/TrasSC was estimated to result in average 8-fold higher savings in healthcare personnel workload per patient and in a treatment capacity increase of 241 patients.

Conclusions. Our model shows that Pert/TrasSC treatment is associated with significantly lower labor costs for nurses and pharmacists and lower costs of non-drug consumables compared to the other treatment options. Moreover, it reduced patients' chair time due to shorter administration/observation time and released capacity in chemotherapy infusion sites.

Keywords: non-drug costs, HER2-positive breast cancer, pertuzumab, trastuzumab, subcutaneous, PH FDC SC, pharmacoeconomics

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Introduction

Breast cancer (BC) is the most common malignant neoplasm in women, both in Poland (25.3%) and in the European Union (28.7%) [1]. According to the data from the National Cancer Register, in 2017 over 19.6 thousand people were newly diagnosed with BC in Poland, while in 2008 there were almost 4 thousand fewer new cases, which illustrates the constant growth of the population suffering from this disease [2]. The incidence rate of BC (standardized by age) was 119.1 per 100,000 people in Poland in 2020, and the European average (EU-27) was 142.8 [3].

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In Europe, breast cancer (16.5%) is the most common cause of death in women with neoplastic diseases, while in Poland it is the second (16.4%) most common cause of death after lung cancer [1]. The standardized mortality rate in Poland in 2020 was estimated at 41.8 per 100 000, which was one of the worst results in Europe [3]. According to the Eurostat data, this cancer was responsible for more than a quarter (26.5%) of all deaths from curable diseases in women [4].

A properly selected path of diagnosis and treatment for each patient with BC has a significant impact on their prognosis, survival, and quality of life. Therefore, comprehensive care for BC patients should take place in centers with a team of experienced specialists in various fields, including oncological surgeons experienced in breast reconstructive surgery, clinical oncologists, radiotherapists and radiologists, psycho-oncologists, and physiotherapists [3]. In Poland, only 9 centers were accredited to meet the Breast Cancer Unit (BCU) requirements, and 10 hospitals provide oncological care in the KON-Piers system (1 of them has BCU status) [3].

HER2-positive BC represents 10% to 20% of all breast tumors and has more aggressive behavior [5]. These tumors grow faster and metastasize more frequently beyond the breast compared to HER2-negative breast cancers. HER2-positive BC can be treated with anti-HER2 targeted agents that stop uncontrolled tumor growth [1].

In recent years, significant progress has been made in the development of diagnostic and therapeutic methods in BC management [3]. With a variety of HER2-targeted therapies approved and implemented in clinical practice, the historically adverse prognosis of HER2-positive breast cancer has improved significantly. Dual HER2 blockade with trastuzumab and pertuzumab combined with cytotoxic agents is the treatment of choice in both the neoadjuvant and metastatic setting [6, 7].

On June 29, 2020, the Food and Drug Administration (FDA) approved a new method of treatment for patients with HER2-positive BC with pertuzumab, trastuzumab, and hyaluronidase-zzxf combined in a single formulation (PH FDC SC) [8]. This treatment provides a *subcutaneous* (SC) route of administration for pertuzumab and trastuzumab over 5 to 8 minutes, every 3 weeks, offering breast cancer patients an alternative to *intravenous* (IV) pertuzumab and intravenous trastuzumab [9]. Patients treated with PH FDC SC must have HER2-positive tumor status, defined as a score of 3 + by immunohistochemistry and/or a ratio of ≥ 2.0 by in situ hybridization, assessed by a validated test [10]. The FDA approval was based on the results of a non-inferiority phase III study (FeDeriCa) that demonstrated equivalent efficacy and safety compared to an intravenous combination of trastuzumab and pertuzumab [11, 12].

The presented analysis aimed to estimate non-drug related cost differences between treatment with pertuzumab and trastuzumab in HER2-positive breast cancer in Poland.

Material and methods

A model-based cost-minimization analysis was performed to compare non-drug-related costs of three different therapies: pertuzumab SC plus trastuzumab SC (Pert/TrasSC; PH FDC SC), pertuzumab IV plus trastuzumab IV (PertIV + TrasIV) and pertuzumab IV plus trastuzumab SC (PertIV + TrasSC) used in the treatment of HER2-positive BC in Poland. Cost-minimization analysis was based on the results of a questionnaire sent to eight leading oncology centers located in Warsaw, Cracow (two hospitals), Szczecin, Gdansk, Lodz, Bydgoszcz, and Kielce. Data were obtained from four centers (Warsaw, two from Cracow, Szczecin). The remaining centers refused to participate in the questionnaire due to lack of time or difficulty in collecting data for the questionnaire. The answers were based on the data of patients with HER2-positive BC treated in selected centers in 2021. Data on resources used and costs were collected in the first half of 2022.

The survey consisted of questions about:

— number of patients treated in oncology centers (treated with each of the aforementioned pertuzumab plus trastuzumab regimens);
— organization of work in the chemotherapy room (the number of working doctors/nurses and working hours/days per day/week);
— parameters related to chemotherapy sessions: chair time (time between entry and exit of the patient using the infusion chair), observation time (time of hospital stay of the patient after the end of chemotherapy);
— information on working hours of healthcare personnel (HCP) involved in preparation/administration of drugs — active HCP: mean time spent on preparation of drugs by pharmacists, mean time spent on a patient by medical staff during chemotherapy session/after the end of chemotherapy session;
— the amount and total costs of medical supplies (consumables) used in each therapy,
— average hourly working rate of nurses and pharmacists.

The survey results worked as the input data for the model estimating the non-drug cost difference between Pert/TrasSC, PertIV + TrasIV, and PertIV + TrasSC. The model was broken down into

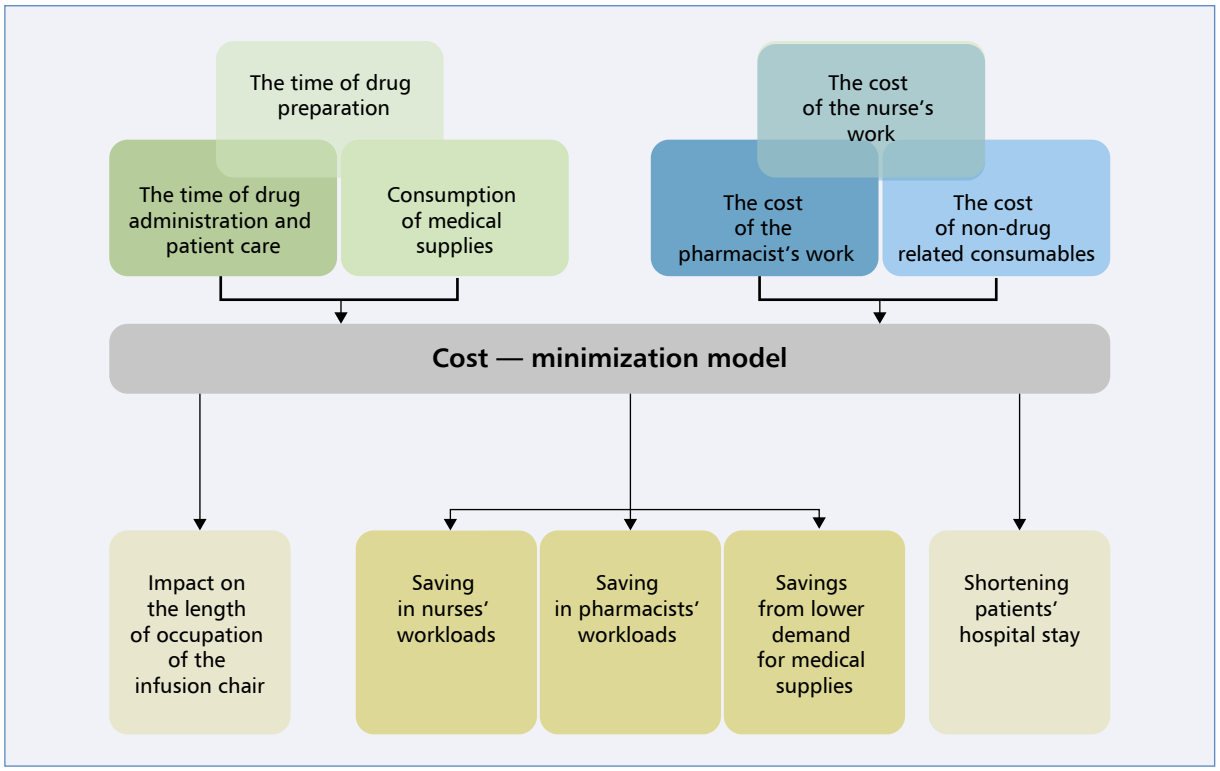

Figure 1. Model overview

three categories of cost savings generated by decreasing nurses'/pharmacists' workloads and demand for non-drug related consumables, and two categories of time savings: shorter occupation of the infusion chair and shorter duration of the hospital stay, which is displayed in Figure 1.

Results

Results of the questionnaire

Of all participating oncology centers, only one hospital treated patients with HER2-positive BC using all three regimens, including Pert/TrasSC therapy. Therefore, in the model, the data from this facility were used to calculate cost differences in other hospital centers. In total, 240 patients were treated with PertIV + TrasIV, 200 patients with PertIV + TrasSC, and 6 patients with Pert/TrasSC, which is summarized in Table 1.

Apart from one facility that worked 6 days a week, 12 hours a day, the others worked from Monday to Friday, 8 or 11 hours, which is presented in Table 2.

On average, 2 to 4 doctors and 2 to 5 nurses worked during a shift, as displayed in Table 3.

In Pert/TrasSC, the time between the patient's entry to and exit from the infusion chair was more than twice shorter than in the PertIV + TrasSC regimen and even 4-fold shorter compared to full IV administration. The time of hospital stay of the patient after the end of chemotherapy was much shorter in the full SC regimen compared to the other treatment regimens, as summarized in Table 4.

The average time spent on Pert/TrasSC preparation by the pharmacist was estimated at 2 minutes and was much shorter compared to other treatment options: 27 minutes with PertIV + TrasIV and 20 minutes with PertIV + TrasSC, which is presented in Table 5. The average time spent by nurses during a chemotherapy session with one patient was: 35 minutes with PertIV + TrasIV, 30 minutes with PertIV + TrasSC, and 25 minutes with Pert/TrasSC. There was also a large difference in the average time nurses spent on a patient after a chemotherapy session between Pert/TrasSC and the other treatments — 15 minutes *vs.* 120 minutes, which is displayed in Table 6. The time reduction achieved by Pert/TrasSC in active HCP time was driven by fewer tasks being performed in the drug preparation area and less time spent by HCP observing patients after chemotherapy sessions.

Table 1. Number of treated patients in participating oncology centers

	PertIV + TrasIV	PertIV + TrasSC	Pert/TrasSC	Summary
Oncology center 1	10	129	0	**139**
Oncology center 2	122	54	6	**182**
Oncology center 3	40	15	0	**55**
Oncology center 4	68	2	0	**70**
Summary	**240**	**200**	**6**	**446**

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 2. Working hours per week in the chemotherapy room

	Working days per week	Working hours per day	Working hours per week
Oncology center 1	5	11	55
Oncology center 2	5	11	55
Oncology center 3	5	8	40
Oncology center 4	6	12	72
Average	**5.25**	**10.5**	**55.5**

Table 3. Medical staff in the chemotherapy room

	Average number of doctors	Average number of nurses	Summary
Oncology center 1	3.0	5.0	**8.0**
Oncology center 2	2.0	2.0	**4.0**
Oncology center 3	2.0	3.0	**5.0**
Oncology center 4	4.0	4.5	**8.5**
Average	**2.8**	**3.6**	**6.4**

Table 4. Average chair time and observation time patients

	PertIV + TrasIV		PertIV + TrasSC		Pert/TrasSC	
	Chair time [min.]	Observational time [min.]	Chair time [min.]	Observational time [min.]	Chair time [min.]	Observational time [min.]
Oncology center 1	90	120	60	120	–	–
Oncology center 2	80	120	50	120	25	15
Oncology center 3	120	120	60	120	–	–
Oncology center 4	120	120	60	120	–	–
Average	**102.5**	**120**	**57.5**	**120**	**25**	**15**

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Due to incomplete data on the average time physicians spent on a patient during a chemotherapy session, this parameter was not analyzed. Only two facilities reported the time that physicians dedicate to patients while administering chemotherapy, and the other two, including Oncology center 2, which was the only facility that treated patients with the Pert/TrasSC regimen, indicated that they were unable to estimate it. Therefore, we assumed that labor costs of the physicians were the same in each treatment regimen, and they did not influence our analysis.

The average cost of non-drug consumables used in PertIV + TrasIV and PertIV + TrasSC was 51.79 PLN or 59.67 PLN (depending on infusion device) per

Table 5. Average time spent on drug preparation by pharmacist (in minutes)

	PertIV + TrasIV	PertIV + TrasSC	Pert/TrasSC
Oncology center 2	20	20	2
Oncology center 3	30	20	0
Oncology center 4	30	20	0
Average	**26.7**	**20**	**2**

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 6. Average time spent on a patient by nursing staff during/after chemotherapy (chemo) session (in minutes)

	PertIV + TrasIV		PertIV + TrasSC		Pert/TrasSC	
	During chemo	After chemo	During chemo	After chemo	During chemo	After chemo
Oncology center 1	20	120	15	120	–	–
Oncology center 2	40	120	35	120	25	15
Oncology center 3	40	120	35	120	–	–
Oncology center 4	40	120	35	120	–	–
Average	**35**	**120**	**30**	**120**	**25**	**15**

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 7. Average costs of non-drug consumables used in each therapy per patient

Medical supplies	PertIV + TrasIV	PertIV + TrasSC	Pert/TrasSC
Intravenous cannula or Vascuport needle	2.27 PLN or 9.99 PLN	2.27 PLN or 9.99 PLN	–
Needle	–	–	0.03 PLN
Opaque infusion giving set	37.37 PLN	37.37 PLN	–
Syringe	0.16 PLN (or 0.32 PLN if Vascuport)	0.16 PLN (or 0.32 PLN if Vascuport)	0.16 PLN
Sodium chloride	1.67 PLN	1.67 PLN	–
Luer Lock plug	0.30 PLN	0.30 PLN	–
Seal for infusion bag	2.27 PLN	2.27 PLN	–
Sterile swabs	0.10 PLN	0.10 PLN	0.10 PLN
Sterile hand gloves	1.60 PLN	1.60 PLN	–
Non-sterile hand gloves	0.90 PLN	0.90 PLN	0.30 PLN
Sterile bandage for puncture	2.07 PLN	2.07 PLN	0.30 PLN
Securing tape	2.93 PLN	2.93 PLN	0.00 PLN
Fabric plasters	0.15 PLN	0.15 PLN	0.15 PLN
Summary	**51.79 PLN** (*intravenous* cannula) or **59.67 PLN** (Vascuport)	**51.79 PLN** (*intravenous* cannula) or **59.67 PLN** (Vascuport)	**1.04 PLN**

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

patient, whereas in Pert/TrasSC it was only 1.04 PLN, which is presented in Table 7. These savings resulted mainly from the lack of costs of the opaque infusion set and intravenous line in Pert/TrasSC treatment.

Based on results from the questionnaire the average hourly working rate of a nurse is 50.00 PLN and of a pharmacist 54.00 PLN. These data were used as input data to estimate the non-drug cost difference between

Pert/TrasSC and IV administration generated from nurses' and pharmacists' work.

Results of the cost-minimization model

In the cost-minimization model, the following assumptions were made:

— for each oncology center, the same number of patients was assumed for each method of treatment;
— the time of Pert/TrasSC administration was adopted for all centers on the basis of the data from the only facility (participating in the questionnaire) treating patients with this regimen today;
— savings in nursing time were the most important component of hospital costs;
— according to the information provided by the cancer centers, the model assumed that the drugs were prepared by pharmacists.

Simulation using input data from questionnaires showed that depending on the oncology center, patients using Pert/TrasSC treatment would occupy from 0.4 to almost 1.4 infusion sites per week, which was a large reduction compared to other treatments — 1.0 to 4.4 (Fig. 2).

Taking this into account, we can assume that if we replaced existing treatment regimens with trastuzumab and pertuzumab by Pert/TrasSC, an average of 241 additional patients could be treated in all participating oncology centers (Tab. 8).

The model showed that if all patients in all participating oncology centers were treated with Pert/TrasSC, the hospitals would save 8-fold more hours (3 345 *vs.* 26 760 hours) compared to the other regimens (Tab. 9).

The cost minimization model showed that the average savings (per patient) generated by the reduced workload of nurses using Pert/TrasSC treatment amounted to nearly 96 PLN compared to PertIV + TrasIV and 92 PLN for PertIV + TrasSC. The average savings (per patient) generated by the reduced workload of pharmacists for Pert/TrasSC were 22 PLN and 16 PLN compared to PertIV + TrasIV and PertIV + TrasSC, respectively (Tab. 10). The model showed that the costs of non-drug consumables for Pert/TrasSC treatment were significantly lower than in the case of the other existing treatment regimens — the savings (per patient) were 60 PLN.

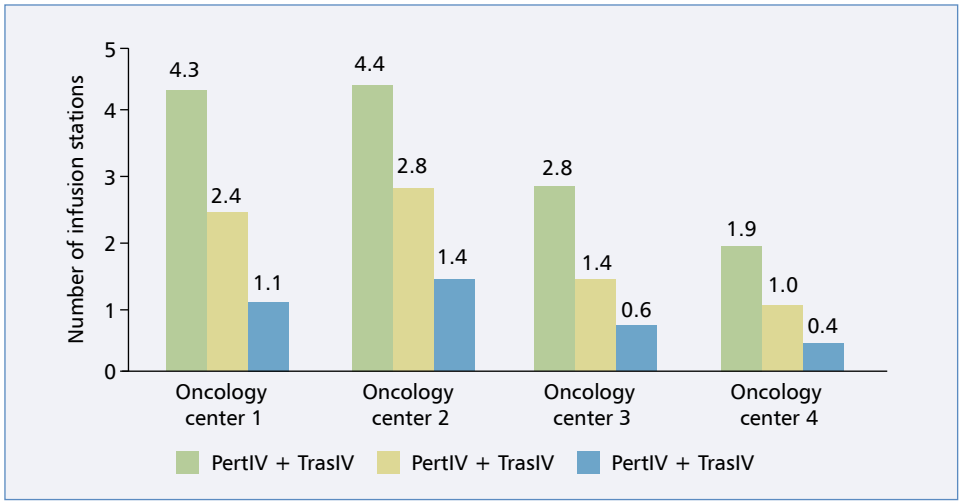

Figure 2. Number of infusion stations occupied by patients for all treatment regimens based on the model assumptions

Table 8. Number of additional patients who could receive treatment in the studied facilities if the existing regimens were replaced with *pertuzumab subcutaneous plus trastuzumab* subcutaneous (Pert/TrasSC)

	PertIV + TrasIV	PertIV + TrasSC	Summary
Oncology center 1	26	181	**207**
Oncology center 2	268	54	**322**
Oncology center 3	152	21	**173**
Oncology center 4	258	3	**261**
Average			**241**

PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 9. Time spent in the hospital by patients (post-chemotherapy observation time in hours)

	PertIV + TrasIV	PertIV + TrasSC	Pert/TrasSC
Oncology center 1	8 340	8 340	1 043
Oncology center 2	10 920	10 920	1 365
Oncology center 3	3 300	3 300	413
Oncology center 4	4 200	4 200	525
Summary	**26 760**	**26 760**	**3 345**

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 10. Labor cost of nurses/pharmacists work, and non-drug consumables per patient for each treatment option

Total cost per patient of:	**PertIV + TrasIV**	**PertIV + TrasSC**	**Pert/TrasSC**	**Savings: Pert/TrasSC *vs.* PertIV + TrasIV**	**Savings: Pert/TrasSC *vs.* PertIV + TrasSC**
Nurse labor cost	129.17 PLN	125.00 PLN	33.33 PLN	95.83 PLN	91.67 PLN
pharmacist's labor cost	24.00 PLN	18.00 PLN	1.80 PLN	22.20 PLN	16.20 PLN
medical supplies	59.67 PLN	59.67 PLN	1.04 PLN	58.63 PLN	58.63 PLN
Summary	**212.84 PLN**	**202.67 PLN**	**36.17 PLN**	**176.66 PLN**	**166.50 PLN**

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

The largest savings for Pert/TrasSC came from the reduced labor costs of nurses: 54–55% of total savings compared to other regimens. The model showed that Pert/TrasSC treatment was associated with significantly lower labor costs for nurses and pharmacists, and lower costs of non-drug consumables, generating total savings of nearly 177 PLN compared to PertIV + TrasIV and 167 PLN compared to PertIV + TrasSC (Tab. 10).

Discussion

Clinical Practice Guidelines in Oncology issued by the National Comprehensive Cancer Network (NCCN) state that pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use may be substituted in patients who receive IV pertuzumab plus trastuzumab as part of systemic therapy for HER2--positive BC [13]. This improved formulation of the cornerstone therapy for HER2-positive BC can have positive effects on patients and the healthcare system. The presented cost-minimization analysis aimed to estimate potential cost differences between Pert/TrasSC, PertIV + TrasIV, and PertIV + TrasSC. The model was based on a questionnaire sent to eight leading oncology centers; however, only 50% of the hospitals answered the survey. Total savings generated from reduced workloads of nurses/pharmacists and reduced costs of non-drug consumables in the treatment of HER2-positive BC in Poland using trastuzumab and pertuzumab regimens were calculated. This analysis also studied the impact of different therapies on occupation of infusion sites during chemotherapy sessions and duration of patient hospital stay.

The model demonstrated that Pert/TrasSC treatment was associated with savings in each analyzed cost category. These savings were largely driven by shorter patient chair time, less active HCP time, and reduced non-drug consumable costs. Our findings were consistent with the literature. There are several studies demonstrating that switching from intravenous pertuzumab and trastuzumab to Pert/TrasSC resulted in reduced non-drug costs for healthcare providers mainly through time savings and improved patient satisfaction [14 –17]. Notably, the feasibility of the Pert/TrasSC administration in patients' homes was also reported, which has the potential to further optimize HCP workload and patients' quality of life [18, 19].

Reduction in nurses' workload not only brought savings for the hospital budget but was also associated with a positive influence on organizational and systemic aspects. According to the OECD report Health at a Glance 2021 [20], Poland, with a small number of professionally active nurses (an average of 5.1 per 1 000 inhabitants) is in the penultimate place in the EU, with Lithuania in the last place. By comparison, countries such as Switzerland and Norway have an average of 18 nurses per 1000 inhabitants. Due to drastic shortages of nursing staff that

hospitals must deal with, the difference in active HCP time of more than 100 minutes per treatment session is a very important factor for hospitals supporting the use of Pert/TrasSC. Our simulation showed that if we replaced the other treatment regimens with Pert/TrasSC, additional 241 patients, in all participating oncology centers, could be treated. Occupation of infusion stations in chemotherapy sessions is a significant organizational and cost-effectiveness parameter because places occupied by patients represent the lost opportunity cost (not analyzed in this study), which prevents the optimal use of hospital infrastructure and does not allow it to generate additional income. In the study PHranceSCa [15], a randomized, open-label phase II study, the authors indicated that due to the reduced observation time for Pert/TrasSC, hospitals may avoid having too many patients in the hospital at the same time. This was an important factor in the COVID-19 pandemic as it reduced the risk of infection associated with visiting hospitals.

Our model also showed that with Pert/TrasSC, all patients in all participating oncology centers would spend a total of 3,345 hours in these hospitals, which is 8-fold shorter compared to the other regimens. Shortening the administration and observation time could significantly affect the quality of patients' lives. In a study by Jackisch C. et al. [14] patients preferred the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection into intravenous pertuzumab and trastuzumab due to time savings that had a positive impact on their daily life. The authors [14] also confirmed that Pert/TrasSC generated cost savings released capacity in chemotherapy units and significantly reduced intravenous compounding costs and waste. In PHranceSCa [12], patients preferred Pert/TrasSC because of the savings in time and feeling more comfortable during administration.

The main limitation of our study was the number of oncology centers participating in the questionnaire and the fact that only one hospital treated patients with all possible treatment regimens.

Conclusions

In our study, we created a model-based cost-minimization analysis to estimate non-drug-related costs differences between treatment with pertuzumab and trastuzumab in HER2-positive breast cancer in Poland. The model shows that Pert/TrasSC treatment was associated with significantly lower labor costs for nurses and pharmacists and lower costs of non-drug consumables. In addition, it reduced the length of hospital stay due to shorter administration and observation times, which directly improved patients' quality of life. This benefit also released capacity at chemotherapy infusion sites, allowing more patients to be treated in the hospital. Our analysis showed that the non-drug cost differences between Pert/TrasSC, PertIV + TrasIV, and PertIV + TrasSC were always in favor of Pert/TrasSC.

Article Information and Declarations

Data availability statement

Original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

The method of data collection for the model (survey) eliminates the need for an ethical assessment of the published results.

Author contributions

M.S.: conceptualization, survey conducting, planned the cost minimalization model and drafted the manuscript, writing, all work coordinator; T.B.: resources, data curation, collecting data, critical revision of data, support in clinical aspects; J.A.: participated in the design of the model, critical revision of data; A.L.: writing, review and editing the manuscript, critical revision of data; P.M.P.: participated in the critical revision of the manuscript, support in clinical aspects

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Conflict of interest

M.S.: owner of a consulting company implementing pharmacoeconomic projects for Roche.
P.M.P.: travel grants, speaker fees, clinical trials for Roche.
Other authors declare no conflict of interest.

Supplementary material

None.

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VIA MEDICA

ORIGINAL ARTICLE

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Systemic treatment of patients with advanced pancreatic cancer — is there still a place for gemcitabine in the first-line setting? Experience of Polish oncology centers

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ABSTRACT

Introduction. Despite some progress in the treatment of patients with pancreatic cancer, it is still a malignancy with a poor prognosis, which results from its rapid local growth with a tendency to infiltrate surrounding tissues and metastasize, and late diagnosis at the advanced stage. The use of multi-drug regimens and modern targeted therapies did not completely eliminate the use of gemcitabine in monotherapy, which is a therapeutic option mainly in patients with poor performance status, ineligible for more advanced therapies.

This study aimed to evaluate the results of treatment with single-agent gemcitabine in everyday clinical practice in Poland and to attempt to identify the predictors of obtaining long-term responses resulting from this treatment.

Material and methods. A retrospective analysis of 167 patients with advanced pancreatic cancer treated with single-agent gemcitabine in five oncology centers in Poland in the years 2017–2022 was conducted. Gemcitabine was used as monotherapy at an initial dose of 1000 mg/m^2 of body surface area (BSA) weekly, 7 times in an 8-week cycle, then 3 times in a 4-week cycle.

Results. Median overall survival (OS) in the entire group of patients was 6.1 months (range — 0.2–32.3 months), and median progression-free survival (PFS) was 4.2 months (range — 0.2–31.3 months). A group of 60 patients was identified as "long responders" (LR), with a response of at least 6 months and a group of 107 as "short responders" (SR). Median PFS in the LR group was 9.15 months (range — 6.0–31.3 months) and in the SR group, it was 3.2 months (range — 0.2–5.8 months). Median OS was 11.6 months (range — 5.9–30.8) and 3.8 months (range — 0.2–32.3 months), respectively. In multivariate analysis, the likelihood of achieving at least a 6-month response (LR) was assessed using a logistic regression model. The model takes into account four variables: the neutrophil/lymphocyte (NLR) ratio, liver metastases, sex, and Hb level.

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Conclusions. The obtained results confirm that gemcitabine monotherapy is still useful in the first-line treatment of patients with advanced and metastatic pancreatic adenocarcinoma. An appropriate selection of patients for this treatment may improve the results while maintaining lower toxicity compared to combined treatment.
Keywords: advanced pancreatic cancer, gemcitabine, overall survival, progression-free survival
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Introduction

Pancreatic cancer is one of the cancers with the fastest increasing incidence. It is the 7th most common malignancy in Europe [1]. Over the last 3 decades, the incidence rate has more than doubled worldwide. It is believed that the burden of this disease will increase along with life expectancy because the incidence increases with age, and most patients are diagnosed at the age of over 65 [2].

Even more disturbing are the data on mortality, which is also increasing. Pancreatic cancer is 4th most common cancer-related cause of death in the world [3]. In Poland, pancreatic cancer is the 5th most common cause of cancer-related deaths among women and 6th among men, which accounts for 5% of all cancer-related deaths in 2020 [4].

The prognosis in pancreatic cancer patients remains unfavorable. It is a high-grade tumor characterized by rapid local growth, with a tendency to infiltrate surrounding tissues and metastasize — primarily in the peritoneum, lymph nodes, and liver. In most patients, pancreatic cancer is diagnosed at a locally advanced or metastatic stage, and only 10–15% of patients are diagnosed at an early stage [5–7]. In the latter group, radical surgical treatment is possible, but 80% of patients undergoing surgery experience a recurrence within 2 years [8].

Diagnosis at a late stage (in more than half of cases in the dissemination stage) and limited treatment options for advanced disease result in an unfavorable prognosis [9, 10]. Median overall survival (OS) in patients with metastatic pancreatic cancer ranges from 3 to 6 months, and the 5-year survival rates have been in single digits for years [3, 5].

Due to clinical characteristics of pancreatic cancer, most patients require systemic treatment at various stages of the disease. The treatment of patients with advanced pancreatic cancer involves chemotherapy using single drugs or multidrug regimens with gemcitabine, fluoropyrimidine, nab-paclitaxel (nab-P), or irinotecan. A choice of the first-line treatment regimen should be adapted to the patient's performance status (PS) [7, 11–13]. According to the recommendations of the European Society of Medical Oncology (ESMO), multidrug regimens (FOLFIRINOX and nab-P with gemcitabine) should be used in patients in good or very good condition, e.g. with PS 1 or 0 according to the Eastern Cooperative Oncology Group (ECOG) scale. Patients with poorer performance status (ECOG PS 2) should receive gemcitabine monotherapy. A performance status of 3–4 on the ECOG scale, and the presence of comorbidities is an indication for the best supportive care (BSC) [14]. The National Comprehensive Cancer Network (NCCN) guidelines also recommend combination therapy (FOLFIRINOX, nab-P with gemcitabine, and other regimens, e.g. gemcitabine with erlotinib) in patients with good PS, while monotherapy (gemcitabine, capecitabine, or fluorouracil) is recommended in patients with poor performance status [15].

For several years, attempts have been made to use molecularly targeted therapies (olaparib, larotrectinib, entrectinib) [16, 17] and immunotherapy (pembrolizumab) [18]. The study results indicate some advantages of these drugs over classical chemotherapy, which was the basis for the registration and introduction of new drugs into clinical practice (e.g. olaparib is currently available under the B.85 drug program). However, these drugs can only be used in selected patients with specific molecular targets (*BRCA1/2* gene mutation, *NTRK* gene fusion, mismatch repair deficiency, and microsatellite instability, respectively). Such patients constitute a small percentage of the whole population of patients with advanced pancreatic cancer.

Despite progress in the treatment of pancreatic cancer, including the use of multidrug regimens and modern compounds, there is still a place for gemcitabine, which was introduced into clinical practice in 1997 after Burris et al. demonstrated its advantages over fluorouracil [19]. The PRODIGE-4 and Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) studies showed the superiority of the FOLFIRINOX regimen and nab-paclitaxel with gemcitabine, respectively, over gemcitabine alone; however, at the cost of increased toxicity [12, 13].

Therefore, a question arose about the criteria for qualifying patients for particular methods of systemic treatment. It seems that patients with ECOG PS 2 and patients with relative contraindications to the use of

oxaliplatin, irinotecan, or long-term fluorouracil infusions could be natural candidates for chemotherapy with nab-paclitaxel and gemcitabine. Such patients constituted less than 10% of the MPACT study population; therefore, it is difficult to clearly comment on the effectiveness of the treatment compared to gemcitabine alone.

Our study aimed to evaluate the results of gemcitabine monotherapy in daily clinical practice in Poland. An attempt was also made to determine predictors of long-term responses to such a therapy.

Material and methods

We performed a retrospective analysis of 167 patients with advanced pancreatic cancer treated with gemcitabine monotherapy in five oncology centers in Poland (Oncology Center in Opole, Oncology Clinic of the Jagiellonian University in Kraków, Oncology Center in Białystok, West Pomeranian Oncology Center in Szczecin, Oncology and Radiotherapy Clinic in Gdańsk).

Patients treated between 2017 and 2022 were included in the analysis. Demographic and clinical data extracted from medical records were anonymized before analysis. We obtained approval from the Bioethics Committee of the District Medical Chamber in Opole (resolution no. 347/2023).

All patients received gemcitabine monotherapy in first-line treatment. In each participating site, treatment with nab-P patients in combination with gemcitabine was available as part of the B.85 drug program. The majority of patients (68%) eligible for gemcitabine treatment did not meet the inclusion criteria for the drug program (primarily due to the absence of metastases or ECOG PS > 1).

The analysis included variables related to the patient's profile, disease biology and stage, and complete blood count (CBC). Follow-up was completed on December 1, 2022. Due to the retrospective nature of the analysis, the causes of death were not determined. Overall survival was defined as the time from the treatment initiation to death due to any cause, and PFS was defined as the time from treatment initiation to disease progression or death due to any cause, whichever occurred first. Response to treatment was defined as no clinical and/or radiological evidence of disease progression.

The Mann-Whitney and Wilcoxon tests were used for continuous data and Fisher's and χ^2 tests for categorical data. The Shapiro-Wilk test was used to evaluate the normality hypotheses. A logistic regression model was used in multivariate analysis. For appropriate selection of variables, a model with all variables, models with each variable analyzed individually, and a model using the stepwise method selected in the R program, in accordance with the Akaike information criterion (AIC), were taken into account. Tests based on Wald statistics were used to assess the significance of parameters in the logistic regression equation. Moreover, the model selected using the AIC criterion was tested with a likelihood ratio test, comparing the model with one variable and adding further variables until four selected variables were obtained.

Results

Clinical characteristics

The median age was 71 years, and almost 60% of patients were female. More than half of patients had a normal body mass index (BMI), and one-third were overweight or obese. Almost all patients had good (61%) or moderate (30%) PS (Tab. 1). Only one patient underwent genetic consultation and *BRCA1/2* gene status determination.

More than half of patients were in clinical stage IV, and the liver was the most common location of metastases (42.5%). Histological differentiation grade was not analyzed due to missing data in two-thirds of patients. In most patients (71%), the CA19-9 serum level at the time of treatment initiation was above the upper limit of normal (ULN) (median — 675, range 0–5657311 U/mL).

At the time of treatment initiation, more than 60% of patients had anemia, mainly grade 1, according to the Common Terminology Criteria for Adverse Events (CTCAE), v. 5.0 (Tab. 1). Parameters of CBC allowed for assessment of white blood cell fraction disorders and calculation of the absolute neutrophils to absolute lymphocytes ratio [neutrophils/lymphocytes ratio (NLR)] and the absolute platelets to absolute lymphocytes ratio [platelets/lymphocytes ratio (PLR)] in peripheral blood. The median NLR was 2.69 (range — 0.3–36.65) and PLR — 146.54 (range — 18.53–1118.57).

Gemcitabine treatment course

Gemcitabine was used as monotherapy at an initial dose of 1000 mg/m^2 of BSA every week, 7 times in an 8-week cycle, then 3 times in a 4-week cycle. The treatment was well tolerated; grade 3 and 4 adverse events (AEs) were reported in 20% of patients (the most common — thrombocytopenia and neutropenia; Tab. 2).

Table 1. Patient characteristics

Characteristic	Number of patients = 167 (%)
Age at diagnosis [years]	
Median	71.24
Range	(47.44–85.87)
Sex	
Women	97 (58.08%)
Men	70 (41.92%)
BMI at treatment initiation	
Median	22.84
Range	(14.88–34.11)
Underweight	22 (13.17%)
Standard	92 (55.09%)
Overweight and obesity	53 (31.74%)
ECOG PS at treatment initiation	
0	7 (4.19%)
1	102 (61.08%)
2	50 (29.94%)
3	7 (4.19%)
No data	1 (0.60%)
Baseline clinical stage according to the TNM classification	
III	59 (35.33%)
IV	95 (56.89%)
No data	13 (7.78%)
Location of the primary tumor	
Head of the pancreas	81 (48.50%)
Pancreatic body	42 (25.15%)
Tail of the pancreas	19 (11.38%)
Multiple locations	12 (7.19%)
No data	13 (7.78%)
Location of metastases at treatment initiation	
Liver and possibly other locations	71 (42.51%)
Other locations excluding the liver	36 (21.56%)
No metastases	60 (35.93%)
CA19-9 serum level at treatment initiation [U/mL]	
Median	675
Range	(0–5657311)
Within normal range	22 (13.17%)
Above ULN	119 (71.26%)
No data	26 (15.57%)
Hemoglobin level at treatment initiation [g/dL]	
Median	12.05
Range	(6.4–14.8)
Below LLN	108 (64.67%)
Within normal range	58 (34.73%)
No data	1 (0.60%)
Leukocyte count at treatment initiation [G/L]	
Within normal range and below LLN	119 (71.26%)
Above ULN	48 (28.74%)
NLR at treatment initiation	
Median	2.69
Range	(0.5–36.65)
Platelet count at treatment initiation [G/L]	
Within normal range and below LLN	134 (80.24%)
Above ULN	33 (19.76%)
PLR at treatment initiation	
Median	146.54
Range	(18.53–1118.57)

BMI — body mass index; ECOG — Eastern Cooperative Oncology Group; LLN — lower limit of normal; NLR — neutrophil/lymphocyte ratio; PLR — platelet/lymphocyte ratio; PS — performance status; ULN — upper limit of normal

Table 2. Gemcitabine treatment course

Characteristic	Number of patients = 167 (%)
Reduction in initial body weight during treatment by > 10%	
Yes	19 (11.38%)
No	147 (88.02%)
No data	1 (0.60%)
Toxicity ≥ 3 grade	
No	132 (79.04%)
Yes	35 (20.96%)
Reason for treatment discontinuation:	
Radiological disease progression	73 (43.71%)
PS deterioration without progression	59 (35.33%)
Toxicity	8 (4.79%)
Other	25 (14.97%)
Treatment continuation	2 (1.20%)
Further systemic treatment	
None	118 (71.52%)
FU/LV	4 (2.42%)
FOLFOX	20 (12.12%)
NALIRI	2 (1.21%)
FOLFIRI	2 (1.21%)
Other (e.g. clinical trial)	18 (11.52%)

FOLFIRI — fluorouracil, leucovorin, irinotecan; FOLFOX — fluorouracil, leucovorin, oxaliplatin; FU/LV — fluorouracil/leucovorin; NALIRI — lysosomal irinotecan

A reduction in initial body weight by > 10% during treatment was observed in 11% of patients. The most common reason for treatment discontinuation (44%) was disease progression (radiological or clinical) detected by the treating physician and deterioration of performance status without objective signs of progression (35%); in only 5% of patients, treatment was discontinued due to toxicity (most often persistently recurring thrombocytopenia). Next-line systemic treatment was used in only 30% of patients — the most frequent was the FOLFOX regimen (12% of all patients), and other regimens were occasionally used (exceptionally, treatment as part of clinical trials).

Treatment results

Median OS in the entire group of patients was 6.1 months (range — 0.2–32.3 months), and median PFS reached 4.2 months (range — 0.2–31.3 months) (Fig. 1 and 2). The 1-year survival rate was 24.5%.

For this analysis, we identified a group of 60 patients who achieved a response lasting at least 6 months [long responders (LR)], and the remaining 107 patients achieved a shorter response [short responders (SR)].

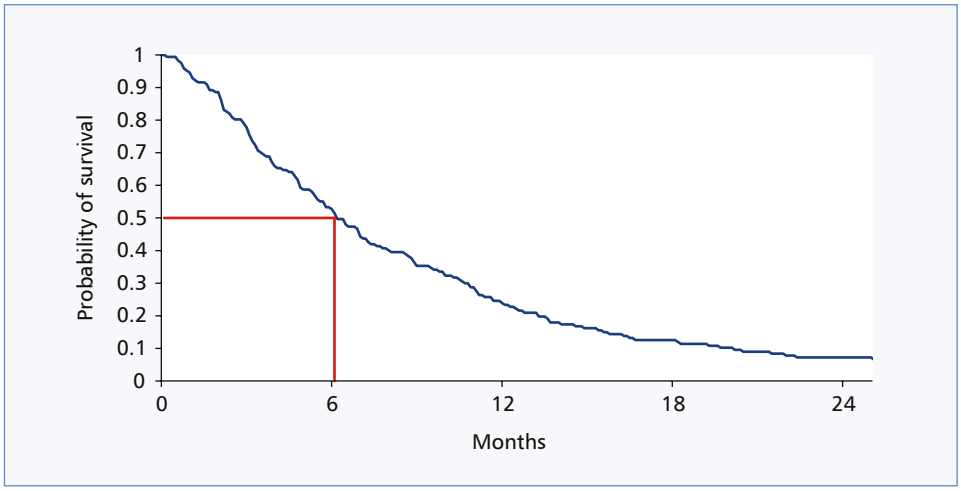

Figure 1. Overall survival in the entire study group

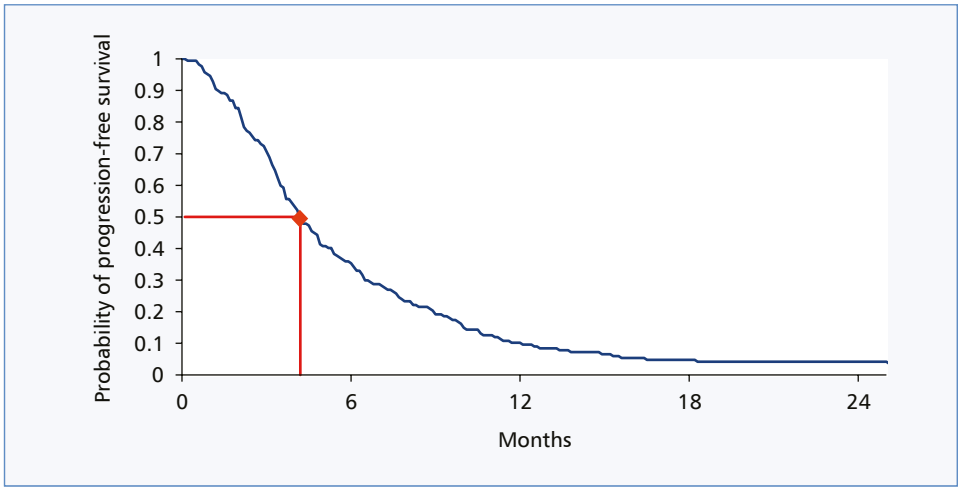

Figure 2. Progression-free survival in the entire study group

The time criterion was established based on median PFS obtained in patients receiving first-line treatment with gemcitabine in combination with nab-paclitaxel in MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial), which was 5.5 months. Median PFS in the LR group was 9.15 months (range — 6.0–31.3 months) while in the SR group — 3.2 months (range — 0.2––5.8 months). Differences were also noted in terms of OS, whose median was three times longer in the LR group compared to SR [11.6 months (range — 5.9–30.8) and 3.8 months (range 0.2–32.3), respectively] (Fig. 3).

In order to determine the factors that influence the likelihood of achieving a long-term response, individual clinical features were compared in the SR and LR groups (Tab. 3).

Among the analyzed factors, the following had a significant impact on achieving a long-term response (LR): initial clinical stage, presence of liver metastases, leukocyte count, NLR, and the occurrence of grade 3 and/or 4 toxicity during gemcitabine treatment.

In multivariate analysis, the probability of achieving at least a 6-month treatment response (LR) was assessed using a logistic regression model. Variables for creating the model were selected based on data from the literature and histoclinical characteristics of the study group and included: age, BMI, NLR, sex, initial clinical stage according to the TNM classification, location of the primary tumor, location of metastases, ECOG PS, leukocyte count, hemoglobin level (in terms of a categorical variable). Models with one of the above-mentioned

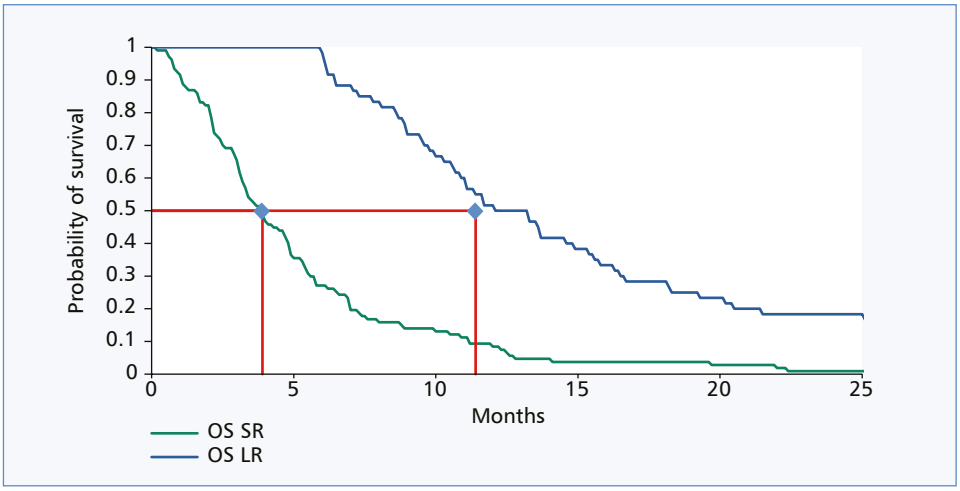

Figure 3. Overall survival (OS) in short (SR) and long-response (LR) subgroups

variables were analyzed successively. Significance tests were performed for all models, and additionally, for models with one variable, log odds plots against this variable were analyzed. On this basis, a model was selected that takes into account 4 variables: the NLR (continuous variable), liver metastases (yes or no), sex, and hemoglobin level (within normal range or below LLN).

The relationships between the logarithm of the odds and the values for individual variables are presented in Figure 4. The graphs present the differences in the chance of achieving a long-term response depending on patient characteristics, for the variables that were selected for the model. A woman with anemia and liver metastases was less likely to achieve a long-term response compared to a man with normal hemoglobin levels and no liver metastases.

As the NLR increased, the chance of achieving a long-lasting response decreased. The coefficient for the NLR variable is exp (–0.1905) = 0.83, so with an increase in the NLR by one unit, the chance that the patient would be in the LR group decreased by 17%, with other parameters unchanged. The absence of liver metastases increased the chance of achieving a long-term response [exp(1.5427) = 4.68], which means that the chance in a patient without liver metastases increased by 368%, compared to a patient with liver metastases, with other parameters unchanged. The chance of obtaining a long-term response for a patient with a normal hemoglobin level was 112% higher than for a patient with a hemoglobin level below the norm, with other parameters unchanged [exp(0.7531) = 2.12]. Men were 89% more likely to achieve a long-lasting response than women with all other parameters equal [exp(0.6348) = 1.89]. The following formula can be used to predict the probability that a patient will be in the LR group:

$$\ln \frac{P(\times)}{1\text{-}P(\times)} = -1.5117 - 0.1905 \times \text{NLR} - 1.5427 \times \text{metastases} + 0.6348 \times \text{sex} + 0.7531 \times \text{Hg},$$

where:

$$\text{metastases} = \begin{cases} 0, \text{ when patient has liver metastases,} \\ 1, \text{ when patient has no liver metastases;} \end{cases}$$

$$\text{sex} = \begin{cases} 0, \text{ when patient is female,} \\ 1, \text{ when patient is male;} \end{cases}$$

$$\text{Hg} = \begin{cases} 0, \text{ when patient has hemoglobin level below LLN,} \\ 1, \text{ when patient has hemoglobin level within normal range} \end{cases}$$

and the NLR takes the value calculated for a given patient. The relationship between the variables included in the model and the odds ratio of achieving a response to treatment lasting at least 6 months is shown in Figure 5.

With the assumed significance level of 0.05, not all variables turned out to be statistically significant in the adopted model. However, this is not the only criterion for selecting variables for the model [20]. The model with these variables is statistically significant, which means that it best explains the studied phenomenon — achieving a treatment response lasting at least 6 months — compared to the other models considered. This model was the best, taking into account the AIC criterion and using the likelihood ratio test for the selected model, the p-value was 0.00001154285.

Examples of predictions for patients with a favorable and unfavorable profile are presented in Table 4.

Table 3. Clinical features with significantly different presentations in the short response (SR) and long response (LR) subgroups

Characteristic	Patient percentage		
	SR group (n = 107)	LR group (n = 60)	p value
Age at diagnosis [years]			
Median	71.0	72.5	0.583
Range	47.4–85.5	48.8–85.9	
Sex			
Women	65	32	0.442
Men	42	28	
BMI at treatment initiation			
Median	22.5	23.5	0.108
Range	14.9–33.6	15.4–34.1	
ECOG PS at treatment initiation			
0	3	4	0.371
1	64	38	
2	36	14	
3	4	3	
No data	0	1	
Baseline clinical stage according to the TNM classification			
III	30	25	**0.007**
IV	70	29	
No data	7	6	
Location of the primary tumor			
Head of the pancreas	48	33	0.116
Pancreatic body	27	15	
Tail of the pancreas	16	3	
Multiple locations	10	2	
No data	6	7	
Presence of liver metastases			
Yes	60	11	**< 0.001**
No	47	49	
Hemoglobin level at treatment initiation [g/dL]			
Median	12.0	12.1	0.4155
Range	8.4–14.5	6.4–14.8	
Below LLN	71	36	
Within normal range	35	23	
No data	1	1	
Leukocyte count at treatment initiation [G/L]			
Within normal range and below LLN	69	50	**0.016**
Above ULN	38	10	
NLR at treatment initiation			
Median	3.02	2.25	**< 0.001**
Range	0.5–36.7	0.525–7.56	
Grade 3 and 4 toxicity			
Yes	17	18	**0.046**
No	90	42	

BMI — body mass index; ECOG — Eastern Cooperative Oncology Group; LLN — lower limit of normal; NLR — neutrophil/lymphocyte ratio; PS — performance status; ULN — upper limit of normal

Discussion

Pancreatic adenocarcinoma is characterized by constantly increasing incidence and mortality [1–4] and has a consistently poor prognosis due to the aggressive disease biology and diagnosis occurring at the advanced stage [5–8]. The basis of treatment in patients with advanced pancreatic cancer is chemotherapy. For the last decade, some progress has been observed in this field, which was mainly related to the introduction of the

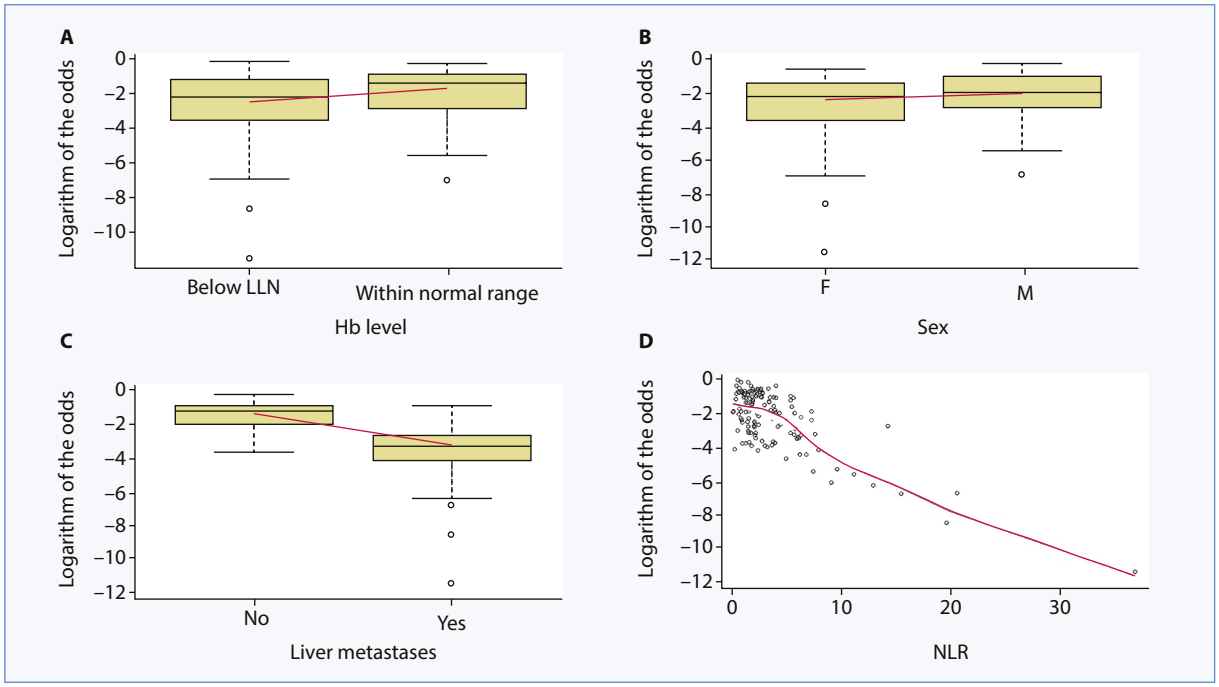

Figure 4. Box plots of logarithms of the odds depending on individual variables: hemoglobin (Hb) level (**A**), sex (**B**), presence of liver metastases (**C**) (median logarithms of the odds for individual values are connected by segments), and a plot of the dependence of the logarithm of the odds on the neutrophil/lymphocyte ratio (NLR) (**D**) (with locally weighted regression curve highlighted); F — female; LLN — lower limit of normal; M — male

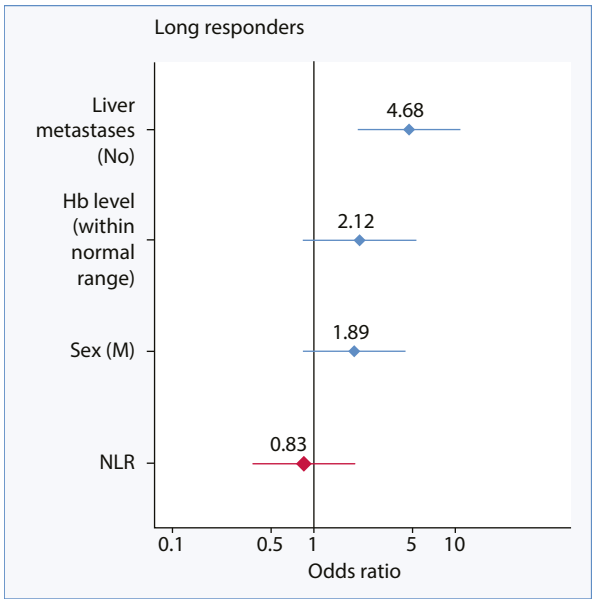

Figure 5. Forest plot for the selected model; Hb — hemoglobin; M — male; NLR — neutrophil/lymphocyte ratio

multi-drug regimen FOLFIRINOX and nab-P [7, 11–13] and immunotherapy and PARP inhibitors in selected patient populations [16, 18]. Despite the introduction of new therapeutic options, gemcitabine monotherapy still has an important place in treatment algorithms. The benefits of this treatment were demonstrated a quarter of a century ago, showing the advantage of gemcitabine monotherapy over fluorouracil [19], and this agent is still included in the guidelines of ESMO, NCCN [14, 15], and the Polish Society of Clinical Oncology [21]. The ESMO recommends the use of gemcitabine monotherapy in patients with poor performance status (ECOG PS 2) or with bilirubin level exceeding 1.5 times the upper limit of normal, and the NCCN recommends gemcitabine monotherapy in patients with poor performance status. This is related to the results of the PRODIGE-4 and MPACT trials, in which the FOLFIRINOX and nab-P with gemcitabine were superior to gemcitabine monotherapy, but at the cost of increased toxicity [12, 13].

However, following the above-mentioned guidelines has a certain limitation in Poland, which is due to drug reimbursement. Firstly, in Poland, treatment of patients with advanced pancreatic cancer with a combination of nab-P and gemcitabine is possible within the so-called Drug Program, whose inclusion criteria are metastatic disease, ECOG PS 0 or 1, and ineligibility to use of FOLFIRINOX chemotherapy. It has to be mentioned that in the MPACT study, such a patient population represented less than 10% of the overall patient population. In this study, there were 57% patients with metastatic

Table 4. Examples of predictions for achieving at least 6 months of progression-free survival [long responders (LR) patient]

Patient profile	Clinical features	LR probability	Interpretation
Favorable	NLR = 2.5 Male sex Liver metastases: NO Hb level within normal range	0.7196345	LR chance equal to 2.57, i.e. approximately 257:100; We predict that of 357 patients with these characteristics, 257 will achieve LR
Unfavorable	NLR = 8 Female sex Liver metastases: YES Hb level below LLN	0.04585096	LR chance equal to 0.048, i.e. approximately 48:1000; We predict that of 1048 patients with these characteristics, 48 will achieve LR

Hb — hemoglobin; LLN — lower limit of normal; NLR — neutrophil/lymphocyte ratio

disease, and 57% and 66% patients with a performance status of 0 or 1, respectively. This means that arbitrarily adopted reimbursement criteria may limit access to the treatment for which patients would be eligible when only clinical criteria were applied. Secondly, in patients treated with gemcitabine monotherapy, a very wide range of individual values is observed. In the presented analysis, median OS in the entire group was 6.1 months (range — 0.2–32.3 months) and median PFS was 4.2 months (range — 0.2–31.3 months).

Among 1174 patients with locally advanced unresectable or metastatic pancreatic ductal adenocarcinoma included in the German TPK registry (*Tumorregister Pankreaskarznom*), 23% were treated with gemcitabine monotherapy in the first line [22]. This group included mainly elderly patients (median age — 78 years) with poorer performance status (73% of patients with ECOG PS ≥ 1). Median PFS in this group was 4.6 months, median OS was 6.8 months, the 6-month survival rate was 58%, and the disease control rate (DCR) was 30%. In patients receiving gemcitabine monotherapy in the PRODIGE-4 trial, median OS was 6.8 months, median PFS was 3.3 months, and the overall response rate (ORR) was 9.4% [12]. In turn, in the MPACT trial, median OS, median PFS, and 1- and 2-year survival rates were 3.7 months, 6.7 months, 22%, and 4%, respectively. The authors of these studies drew attention to the similarity of the results obtained in the group treated with gemcitabine to the results obtained in the study by Cunnigham et al. and in other phase III studies with this drug [23]. The results of our study also show many similarities although of course a direct comparison and conclusions would be unjustified. Nevertheless, the wide range of survival parameters encourages the search for patients who could particularly benefit from gemcitabine monotherapy.

In this analysis, an attempt was made to determine predictors of long-term responses in patients receiving gemcitabine monotherapy. The criterion for such a benefit was obtaining a response of at least 6 months. Various models were initially evaluated, and a model taking into account NLR, presence of liver metastases, sex, and hemoglobin level was selected for the final analysis. These factors differ from the parameters of better response to combined treatment established in the ESMO recommendations, NCCN recommendations, and the PRODIGE-4 and MPACT studies, which mainly included the clinical disease stage, ECOG performance status 3–4, age, and the presence of comorbidities. This is especially true for the NLR. In recent years, many researchers have paid attention to the prognostic value of this indicator in cancer and other diseases (e.g., cardiovascular and infectious diseases) [24]. In our analysis, the median NLR was 2.69 (range — 0.5–36.65). The wide range of values and the inclusion of this indicator in the model assessing the chances of obtaining a long-term response indicate that the NLR may have prognostic significance.

Many studies have attempted to define a prognostic model enabling determination of the prognosis in patients with advanced pancreatic cancer. One of the most frequently assessed is the NLR. A high NLR is associated with worsened OS in many solid tumors and is an easily available and inexpensive biomarker [25]. Many studies have confirmed these observations in patients with pancreatic cancer [26, 27] as well as meta-analyses assessing the prognostic significance of the NLR in patients with pancreatic cancer [28, 29].

Other studies have shown a significant impact of preoperative CA19-9 and CA125 levels on long-term survival of patients with pancreatic cancer [30], as well as the PLR, whose high values also indicate an unfavorable prognosis in terms of OS and PFS in patients with advanced pancreatic cancer [31, 32].

However, the authors of the mentioned publications draw attention to the need to take into account additional data in prognostic models (e.g. chemotherapy regimen or comorbidities).

Conclusions

The obtained results confirm that gemcitabine monotherapy is still used in the first-line treatment of patients with advanced and metastatic pancreatic adenocarcinoma. It seems that an appropriate selection of patients for this treatment may improve results while maintaining lower toxicity compared to combined treatment. The model assessing the chances of obtaining a long-term response indicated in our analysis may be the basis for proper patient qualification although it requires confirmation in further prospective studies with a larger number of patients involved.

Article Information and Declarations

Data availability statement

All analyzed data are included in this article. Further inquiries may be directed to the corresponding author.

Ethics statement

Approval of the Bioethics Committee of the District Medical Chamber in Opole was obtained (resolution no. 347/2023).

Author contributions

I.R.: should be considered the main author, author of the concepts, methods, research, data analysis, literature review, original manuscript; data collection, and the author giving final approval of the article; P.Z.: data collection; statistical analysis, and final approval of the article; A.S.: statistical analysis, final approval of the article; J.S., B.Cz.-A., A.Ch.-B., M.T., K.W., A.S., W.R., M.J.: data collection, final approval of the article; B.R.: should be considered the senior author, author of the concepts, methods, research, data analysis, literature review, original manuscript; data collection, and the author giving final approval of the article.

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Conflict of interest

All authors declare no conflict of interest in connection with this article.

Supplementary material

None.

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REVIEW ARTICLE

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Clinical and economic benefits of using next-generation sequencing in the diagnostics of patients with non-small cell lung cancer with rare mutations

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ABSTRACT

Molecular diagnostics are necessary to make therapeutic decisions in patients with non-small cell lung cancer (NSCLC), especially regarding targeted therapies. They include the analysis of PD-L1 expression and mutations or rearrangements in the *EGFR*, *KRAS*, *BRAF*, *ALK*, *ROS1*, *NTRK1/2/3,* and *RET* genes. In Poland, it is recommended to perform analyses for point mutations in exons 18, 19, 20, and 21 of the *EGFR* gene and rearrangements of the *ALK* and *ROS1* genes. Due to the turnaround time, costs, and availability of biological material, the benefits of routine use of NGS in NSCLC patients are increasingly highlighted compared to performing multiple tests of individual genes. Pharmacoeconomic analyzes were conducted to assess the impact of the use of next-generation sequencing (NGS) in clinical practice on the budget of the public payer in Poland in comparison with the current practice. They demonstrated a decrease in incremental expenses of the public payer related to molecular diagnostics with NGS in all eligible patients by approx. 3.4 million PLN in 2023 and 2024 and a reduction in diagnostic costs per patient by 1 695 (21%) PLN. This article presents the efficacy and safety of amivantamab in NSCLC patients with an insertion in exon 20 of the *EGFR* gene. In conclusion, NGS should be the preferred diagnostic method in patients with advanced NSCLC.

Keywords: non-small cell lung cancer, molecular diagnostics, next-generation sequencing, amivantamab

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Introduction

Lung cancer is the most frequently diagnosed malignant tumor and the most common cause of cancer-related deaths in Poland and worldwide. In 2020, in Poland 18 814 new cases of lung cancer were recorded (11 518 in men and 7 296 in women), and the number of deaths due to lung cancer was 22 213 (14 211 in men and 8 002 in women) [1]. Approximately 80–85% of cases are non-small cell lung cancer (NSCLC), which affects over 1.5 million people worldwide annually [2].

Increasingly better knowledge regarding genetic determinants of NSCLC allows for more accurate characterization of the disease, which leads to more detailed classifications of NSCLC, depending on detected molecular abnormalities [3]. Identification of molecular disorders that are possible therapeutic targets permits using more effective treatments (especially targeted therapies), which significantly improves outcomes. However, the growing number of identifiable molecular markers (including the so-called rare mutations) and targeted therapies requires careful planning

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of diagnostics to use the most appropriate management in subsequent treatment lines.

According to the European Society for Medical Oncology (ESMO) guidelines, analysis of specific biomarkers is necessary to make therapeutic decisions in patients with advanced NSCLC [4].

The European Medicines Agency (EMA) has approved targeted therapies for NSCLC patients which require identification of variants in as many as seven different genes and, additionally, analysis of the programmed death-ligand 1 (PD-L1) expression [5]. In order to choose the optimal treatment regimen, it is necessary to perform molecular tests to detect variants in exons 18, 19, and 21 of the *EGFR* gene, substitutions p.G12C and p.V600E in the *KRAS* and *BRAF* genes, respectively, and rearrangements of the *ALK*, *ROS1*, *NTRK1/2/3,* and *RET* genes [5]. Considering the dynamic development of personalized medicine and the currently conducted clinical trials, it should be expected that precise detection of exon 20 insertions and duplications in the *EGFR* gene, exon 14 skipping mutations and amplification in the *MET* gene, point variants and amplification of the *ERBB2* or *NRG1* gene rearrangement will be required in the near future. In addition, increasing attention is being paid to the need to determine mutation status in the *STK11*, *KEAP1*, and *TP53* genes and the value of genomic signature analysis, for example, tumor mutation burden (TMB) [6].

In Poland, in NSCLC patients, it is recommended to perform molecular analyses including the identification of point variants in exons 18, 19, 20, and 21 of the *EGFR* gene and rearrangement of the *ALK*, *ROS1,* and *NTRK1-3* genes [7]. The tests are conducted sequentially or in parallel using polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH) methods, respectively. However, due to an increase in the number of assessable biomarkers, conducting many individual tests is becoming increasingly time- and cost-consuming. Another problem is the limited amount of tissue material available for routine molecular diagnostics, which may even make it impossible to perform many individual tests. Therefore, the need to introduce next-generation sequencing (NGS) is commonly indicated, which should be routinely used in the diagnostics of patients with advanced NSCLC. The NGS method allows for simultaneous analysis of different variants in multiple genes using a limited amount of tissue material [5, 6]. According to the latest ESMO guidelines, the NGS method is the preferred tool for molecular diagnostics not only in lung cancer but also in ovarian cancer, prostate cancer, or cholangiocarcinoma [6].

Due to the aforementioned need to analyze several different genes, it has been shown that the NGS method is more cost-effective than sequential or parallel analysis of single genes [8]. The turnaround time in the case of NGS analysis of a single gene may be longer compared to single-gene tests (14–17 *vs.* 7–11 days). However, it should be remembered that with the sequential analysis of three different genes, it would take approximately 21–33 days to perform a full diagnosis using single-gene tests [9, 10].

The limited amount of tissue that can be used for diagnostics in NSCLC patients is another important aspect. In the vast majority of cases, the analyzed tissue is a biopsy material. In Yu et al. study [10], it was found that when four or more biomarkers need to be assessed, the use of NGS increases the chance of starting and, even more importantly, completing diagnostics using less tissue compared to single-gene tests.

The use of diagnostic methods based on high-throughput methods allows the identification of a higher number of variants in the examined genes in NSCLC patients [11, 12]. The analysis of a large number of samples showed that the PCR method did not allow for the identification of about 50% of insertions and duplications in exon 20 of the *EGFR* gene otherwise detected by NGS [13]. The use of the NGS method allows for the appropriate diagnostics, which may have a positive impact on the prognosis of patients with advanced NSCLC [14]. This method permits the identification of not only point mutations, deletions, and insertions, but also gene fusions. Moreover, the presence of gene fusions — for example, *ALK*, *ROS1*, *NTRK1/2/3,* or *RET* — determines the sensitivity of cancer cells to appropriate tyrosine kinase inhibitors [5, 15]. Due to the possibility of detecting gene fusion, it is recommended to perform NGS with the use of RNA, which allows for the effective identification of gene rearrangements in NSCLC patients. It is also possible to conduct an analysis using DNA and RNA [15].

Method and assumptions adopted in the financial analysis

An analysis was conducted to estimate *the financial consequences of adopting* the NGS method in clinical practice in Poland for the public payer (budget impact).

The target scenario assuming the use of the NGS method in all NSCLC patients requiring molecular diagnostics was compared with the current situation based on sequential genetic testing in the majority of patients. It has been assumed that in the current scenario, 90% of patients undergo sequential diagnostics, e.g. step-by-step searching for mutations in the *EGFR* gene by PCR and possibly resistance mutations (step 1), rearrangement of the *ALK* gene by IHC or FISH (step 2), and rearrangement of the *ROS1* gene by FISH (step 3). In that scenario, the NGS method is used in only 10% of patients (step 4) (Fig. 1).

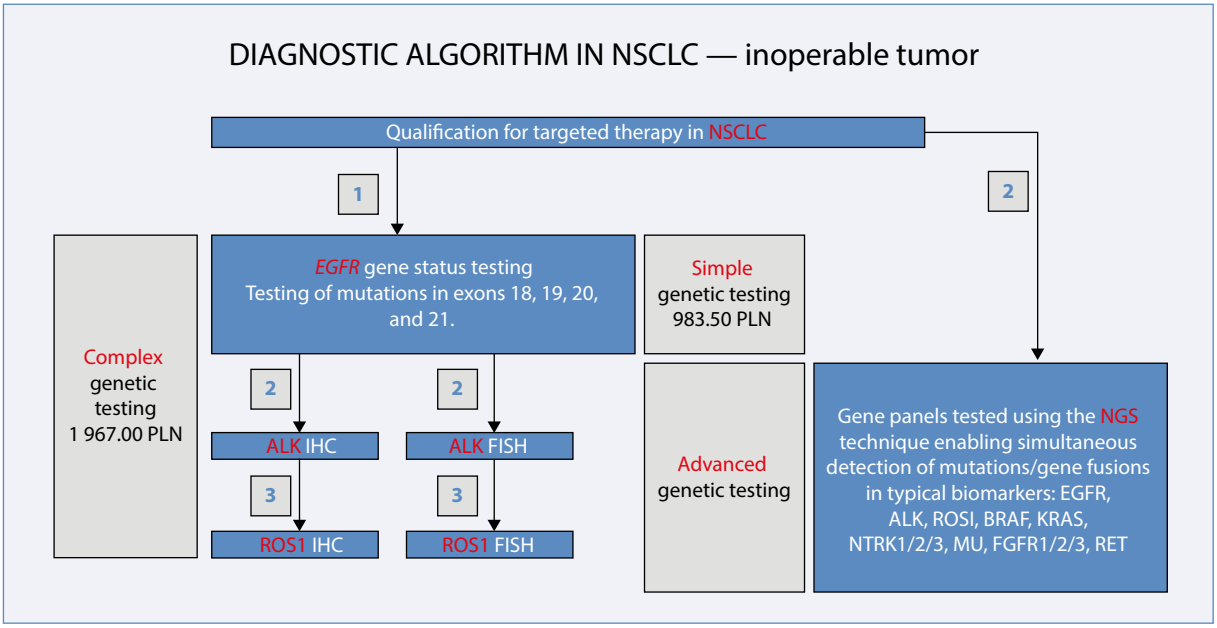

Figure 1. Diagnostic algorithm for patients with inoperable non-small cell lung cancer (NSCLC); NGS — next-generation sequencing

Based on data from the National Cancer Registry (annual incidence of lung cancer: ICD-10 C.34), it was assumed that the data for the years 1999–2019 were historical, while the data for the years 2023–2024 were projected using a linear trend. Based on these estimates, it was assumed that 7 977 and 8 020 patients would be qualified for molecular diagnosis of lung cancer in 2023 and 2024, respectively (Fig. 2 [17]).

The calculations assumed that genetic tests would be ordered and settled under the contract with the National Health Fund regarding hospital service as billing products: simple genetic testing in cancer (code 5.53.01.0005001), complex genetic testing in cancer (code 5.53.01.0005002), and advanced genetic testing in cancer (code 5.53.01.0005003).

Results

In the baseline scenario of the financial analysis, it was assumed that currently 90% of molecular tests are performed using classical methods, and only 10% using the NGS method. Taking into account sensitivity and specificity of the diagnostic methods used, a mutation/rearrangement in the *EGFR*, *ALK,* or *ROS1* genes would be detected in 1275 patients in 2023 and 1282 patients in 2024 (Tab. 1). The cost of the diagnostic procedure would be 17.4 million PLN and 17.5 million PLN in 2023 and 2024, respectively. The cost of detecting mutations in the *EGFR*, *ALK,* or *ROS1* genes per one diagnosed patient would be 13 665 PLN. On the other hand, if molecular diagnostics based on NGS were used in 100% of patients, the number of patients with a detected mutation/rearrangement in the *EGFR*, *ALK,* or *ROS1* genes and with mutations in the *KRAS* and *BRAF* genes, for whom targeted therapies had not yet been reimbursed, would amount to 4 507 in 2023 and 4 531 in 2024. The cost of this diagnostic procedure would amount to 29.4 million PLN and 29.6 million PLN in 2023 and 2024, respectively. The cost of such a procedure would amount to 6 527 PLN per one diagnosed patient. The difference between the considered diagnostic strategies indicates an increase by approximately 12.0 million PLN in 2023 and 12.1 million PLN in 2024 in the expenditure of the public payer related to molecular diagnostics of all eligible patients using the NGS method. Nevertheless, the number of detected mutations would significantly increase while reducing the cost of diagnostics per patient by 7 139 PLN (reduction by approx. 52%).

The results of the financial analysis in the baseline scenario are summarized in Table 1.

In one of the alternative scenarios of the sequential genetic testing process, it was assumed that at the initial stage, tests for mutations in the *EGFR* gene would be performed using the PCR method, and then — in patients with a negative result — a multi-gene panel using the NGS method. For the analysis, it was assumed that the above procedure would be used in 90% of patients, and the NGS method only in 10% of patients. The number of patients with a detected mutation or rearrangement in the *EGFR*, *ALK,* and *ROS1* genes as well as in the *KRAS* and *BRAF* genes would then be 3 987 in 2023 and 4 009 in 2024. The cost of this diagnostic

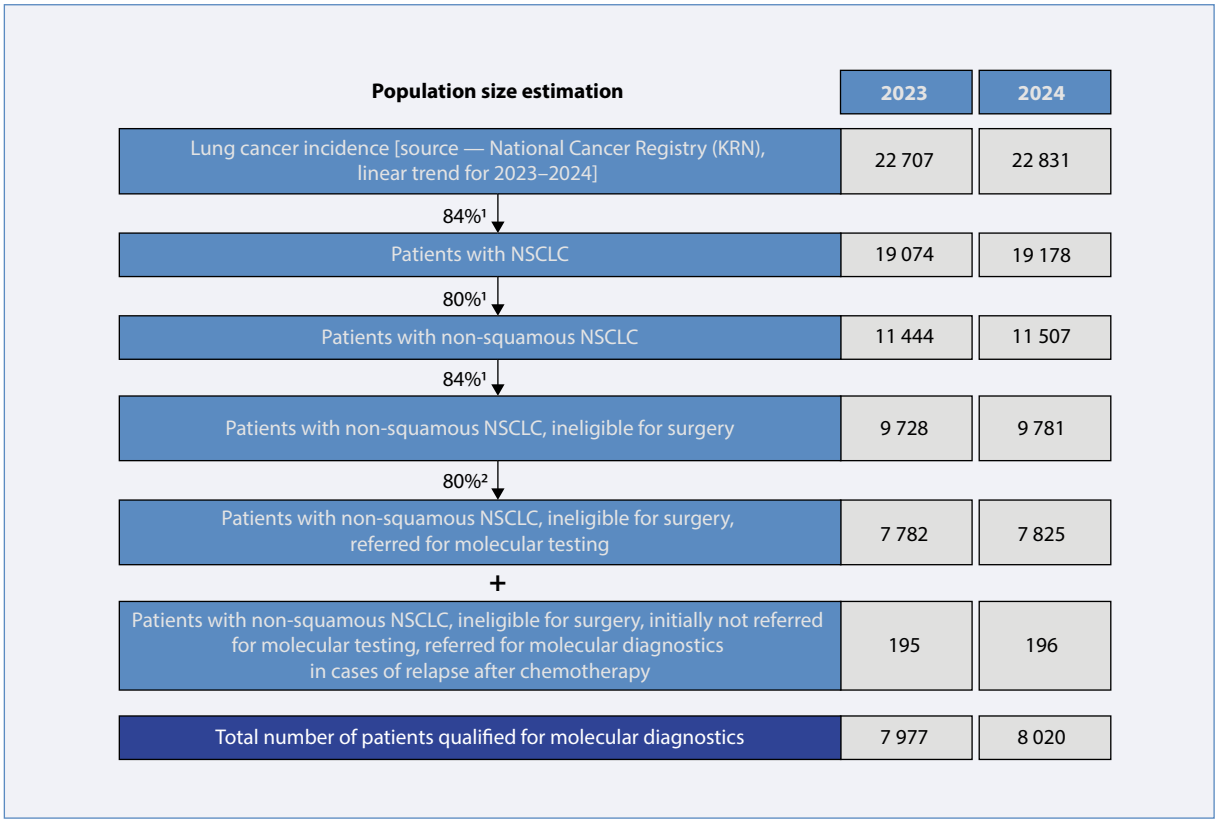

Figure 2. Estimating the size of target population in 2023–2024; [1]Based on [17]; [2]Data based on clinical expert opinion in Poland; NSCLC — non-small cell lung cancer

Table 1. Results of baseline scenario analysis (PLN)

Number of diagnosed patients		Diagnostics costs		Cost per patient
2023	2024	2023	2024	–
Sequential method EGFR => ALK => ROS1 90%; NGS 10%				
1275	1282	17.4 million PLN	17.5 million PLN	13665 PLN
Sequential method 0%; NGS 100%				
4507	4531	29.4 million PLN	29.6 million PLN	6527 PLN
Difference in the number of diagnosed patients		**Incremental costs**		**Difference in cost per patient**
3232	3250	12.0 million PLN	12.1 million PLN	–7 139 PLN

NGS — next-generation sequencing

procedure would be 32.8 million PLN and 32.9 million PLN in 2023 and 2024, respectively. After conversion, the cost per diagnosed patient would be 8 222 PLN. If 100% of patients were immediately diagnosed with the use of the NGS method, the number of patients with detected mutations or rearrangements in the *EGFR*, *ALK*, and *ROS1* genes and with mutations in the *KRAS* and *BRAF* genes would be 4 507 in 2023 and 4 531 in 2024. The cost of the diagnostic procedure would then amount to 29.4 million PLN and 29.6 million PLN in 2023 and 2024, respectively. After conversion per one diagnosed patient, the cost of the procedure would be 6 527 PLN.

The analysis of the alternative scenario indicates a decrease in the public payer's expenses related to molecular diagnostics of all eligible patients using the NGS method by approximately 3.4 million PLN in both 2023 and 2024. The cost of diagnostics per patient will be significantly reduced — it would amount to PLN 1 695 (reduction by approximately 21%).

The results of the financial analysis in this alternative scenario are summarized in Table 2.

Table 2. Results of alternative scenario analysis (PLN)

Number of diagnosed patients		Diagnostics costs		Cost per patient
2023	2024	2023	2024	–
Sequential method EGFR => NGS 90%; NGS 10%				
3987	4009	32.8 million PLN	32.9 million PLN	8222 PLN
Sequential method EGFR => NGS 0%; NGS 10%				
4507	4531	29.4 million PLN	29.6 million PLN	6527 PLN
Difference in the number of diagnosed patients		**Incremental costs**		**Difference in cost per patient**
520	523	–3.4 million PLN	–3.4 million PLN	–1695 PLN

NGS — next-generation sequencing

Conclusions from the financial analysis

The presented analyses show that the replacement of the currently used sequential diagnostic process with the NGS method would be associated with an increase in the total expenditure of the public payer. However, such a procedure would significantly increase the effectiveness of the diagnostic process, due to the greater number of detected mutations, and consequently the possibility of using optimal modern targeted therapeutic options, which can be seen as extremely rational management of the public payer's budget. The cost per diagnosed patient would be significantly lower than in the case of using sequential methods, and the number of comprehensively diagnosed patients would be incomparably higher.

The role of amivantamab in the treatment of patients with *EGFR* exon 20 insertion

Insertions in exon 20 are the third most frequent molecular disorder in the epidermal growth factor receptor (*EGFR*) gene and account for fewer than 12% of *EGFR* gene disorders. *EGFR* exon 20 insertions constitute a heterogeneous group of mutations in the vicinity of the C-helix of the kinase domain, which affects approximately 1% of NSCLC patients [17, 18]. The prognosis in this group of patients is particularly unfavorable, and the response rates to registered EGFR tyrosine kinase inhibitors (EGFR TKIs) are low and range between 0 and 9%. Platinum-based chemotherapy has remained the standard of treatment so far. In patients treated with chemotherapy, median overall survival (OS) is 16 months and is significantly shorter than in patients with activating mutations in the *EGFR* gene, which are sensitive to EGFR TKIs [19–21].

Amivantamab is a fully human bispecific antibody directed against the epidermal growth factor (EGF) and mesenchymal-epidermal transition (MET) receptors. Amivantamab disrupts EGFR and MET signaling functions by blocking ligand binding and induces antibody-dependent cellular cytotoxicity involving natural killer (NK) cells [22, 23].

The efficacy and safety of amivantamab in NSCLC patients as monotherapy and in combination with other drugs were evaluated in the multi-cohort single-arm phase I CHRYSALIS study. During the first part of the study with dose-escalation, the recommended dose for evaluation in the second part was established. The recommended dose of amivantamab in patients weighing less than 80 kg is 1050 mg, and in patients weighing 80 kg or more, the dose is 1400 mg. The drug is given once a week for the first 4 weeks and then every 2 weeks from week 5 onwards. The primary endpoints in the dose escalation and expansion parts were dose-limiting toxicity (DLT) and overall response rate (ORR). Key secondary endpoints included duration of response (DoR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS). Cohort D of the study population enrolled patients with unresectable or metastatic NSCLC with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, with the *EGFR* exon 20 insertion, and disease progression during or after platinum-based chemotherapy. The median number of prior treatment lines was 2 (range 1 to 7). In 22% of patients, metastases were found in the central nervous system, which had previously been treated locally. After a median follow-up of 9.7 months, the ORR in patients treated with amivantamab was 40% by an independent blinded committee and 36% by the investigator, while the CBR was 74%. The median DoR, PFS, and OS were 11.2 months, 8.3 months, and 22.8 months, respectively [24]. At the European Lung Cancer Congress (ELCC 2023), the updated results of the CHRYSALIS clinical trial were presented after a median follow-up of 19.2 months (study results are presented in Tab. 3). Long-term clinical benefit from amivantamab treatment (≥ 12 cycles) was reported in 42% of patients. Univariate analysis showed a statistically significant association between ECOG 0 performance status and long-term treatment response ($p = 0.021$) and a trend towards

Table 3. Results of the CHRYSALIS study [24]; median follow-up period — 19.2 months

mPFS		mOS	
6.9 months (95% CI 5.6-8.8)		23 months (95% CI 18.5-29.5)	
1-year PFS	2-year PFS	1-year OS	2-year OS
35.4%	13.7%	73.3%	47.2%

CI — confidence interval; mOS — median overall survival; mPFS — median progression-free survival); OS — overall survival; PFS — progression-free survival

shorter treatment duration (< 12 cycles) in underweight patients (BMI < 18.5 kg/m^2) [25].

Adverse events reported during amivantamab treatment are characteristic of EGFR and MET inhibition and include rash (86% of patients), paronychia (45%), stomatitis (21%), pruritus (17%), diarrhea (12%), hypoalbuminemia (27%). and peripheral edema (18%). Among the most common side effects of amivantamab are infusion-related reactions, which occur in 66% of patients, mainly during the first infusion. In order to reduce this type of complications, the first dose of amivantamab is divided into 2 days, the rate of infusion should be lower for the first 2 hours of drug administration, and premedication is recommended before each dose of amivantamab, including antihistamines, antipyretics, and optionally glucocorticosteroids (obligatory during the first infusion). Due to side effects, dose reduction was required in 13% of patients included in cohort D of the CHRYSALIS study, but only 4% discontinued treatment due to adverse events [24]. Amivantamab was registered by the US Food and Drug Administration (FDA) on May 21, 2021, and by the EMA on December 9, 2021, for the treatment of adult NSCLC patients with activating *EGFR* exon 20 insertion mutations after failure of platinum-based chemotherapy.

Data from clinical practice on Canadian patients with *EGFR* gene mutations confirm that exon 20 insertion significantly worsens prognosis as compared to patients with the so-called frequent mutations. After failure of platinum-based therapy, most patients received chemotherapy with or without platinum. Median OS was 11.2 months in patients with exon 20 insertion *vs.* 20.8 months in patients with exon 19 deletion and 15.7 months in patients with *EGFR* exon 21 L858R substitution. The median time to the next treatment line was 4.1 months, 8.2 months, and 9.6 months, respectively, for the first-line treatment and 5 months, 7.1 months, and 6.4 months, respectively, for the second-line treatment [26]. Currently, the standard of care in patients with exon 20 insertion is platinum-based chemotherapy. The results of a retrospective cohort study show that there is no standardized approach to follow-up treatment. Of 3701 analyzed patients, *EGFR* exon 20 insertion was found in 5% of patients (n = 177). In the first-line treatment, platinum-based chemotherapy was used in 66% of patients. Patients with disease progression after first-line treatment were qualified for immunotherapy (26%) or again for platinum-based chemotherapy (26%), while in the third-line treatment, 28% and 23% of patients, respectively, were qualified for immunotherapy and chemotherapy [27].

Real-world treatment outcomes of *amivantamab* in a pre-approval access (PAA) program confirmed the results of the CHRYSALIS study. In total, 210 program participants with *EGFR* exon 20 insertion received amivantamab after failure of platinum-based chemotherapy. A partial response was achieved in 31.2% of patients, while the proportion of patients with confirmed clinical benefit was 75.3%, and it was independent of the region of the *EGFR* gene where the insertion was found [28].

Since the CHRYSALIS study is a non-randomized and single-arm trial, the real-world evidence (RWE) is of great importance in assessing the effectiveness of amivantamab, as well as other therapies, in patients with *EGFR* exon 20 insertion after failure of platinum-based chemotherapy. The published data on 125 patients from three databases (Concert, COTA, and Flatiron) show that non-platinum chemotherapy (25.1%), immunotherapy (24.2%), EGFR TKIs (16.3%), and platinum-based chemotherapy (16.3%) were the most frequent regimes used in this population. However, the pooled analysis showed, that compared to patients treated with amivantamab in the CHRYSALIS study, patients receiving other therapies were less likely to respond to treatment (ORR 40% and 16% for amivantamab and other therapies, respectively), had shorter PFS (median 8.3 *vs.* 2.9 months for amivantamab and other therapies, respectively), shorter time to next therapy (TNT) (14.8 *vs.* 4.8 months, respectively), and shorter OS (median 22.8 months *vs.* 12.8 months) [29]. Similar analysis was performed comparing the data of patients from the CHRYSALIS study and 383 patients meeting the inclusion criteria for cohort D, treated in Europe and the United States (EGFR TKIs — 69 patients, immunotherapy — 91 patients, non-platinum chemotherapy — 87 patients, vascular endothelial growth factor in combination with chemotherapy — 57 patients, other methods — 79 patients). A statistically and clinically significant benefit of amivantamab has been demonstrated in terms of OS, PFS, ORR, and TNT compared to other treatments used in routine clinical practice [30].

Currently, the phase III PAPILLON study is being conducted to assess the efficacy and safety of first-line treatment with amivantamab in combination with carboplatin-pemetrexed chemotherapy *vs.* chemotherapy alone in NSCLC patients with *EGFR* exon 20 insertion (NCT04538664) [31]. The efficacy and safety of amivantamab is also assessed in first-line treatment of patients with *EGFR* exon 19 deletion or exon 21 L858R substitution in the MARIPOSA study (NCT04487080) (amivantamab in combination with lazertinib *vs.* osimertinib *vs.* lazertinib), in second-line treatment of patients with frequent mutations after osimertinib failure in the MARIPOSA-2 study (NCT04988295) (amivantamab in combination with lazertinib and chemotherapy *vs.* standard platinum-based chemotherapy), and in subcutaneous form in the PALOMA study (NCT04606381) [31].

The second drug registered by the FDA for the treatment of patients with *EGFR* exon 20 insertion is mobocertinib (TAK-788), a small-molecule and irreversible EGFR tyrosine kinase inhibitor, specifically designed to selectively target *EGFR* and *HER2* insertions. The efficacy and safety of mobocertinib in previously treated patients was evaluated in the EXCLAIM study. In total, 28 patients were included in part II of this study. The primary endpoint, ORR was 43%, while the disease control rate (DCR) was twice as high and amounted to 86%. The median DoR was 13.9 months, median PFS was 7.3 months, while median OS reached 24 months. The safety of treatment was assessed in a group of 72 patients receiving mobocertinib at a dose of 160 mg daily. Adverse events were typical of EGFR tyrosine kinase inhibitors and include diarrhea (82%), nausea (39%), vomiting (36%), and acneiform rash, occurring in 46% of patients [32].

Conclusions

The introduction of new diagnostic methods with NGS results in a higher rate of *EGFR*-mutated NSCLC diagnosis, with more frequent detection of other disorders than the so-called frequent mutations (e.g. exon 20 insertion). The NGS method is an effective alternative to single-gene testing. It enables qualifying a larger number of NSCLC patients for systemic treatment with registered new drugs (e.g. amivantamab), which in turn contributes to better prognosis in this population. Financial analyses indicate that using NGS in all lung cancer patients will provide the following benefits:

— the diagnostic process will be significantly shorter;
— the number of patients receiving targeted therapies, according to their actual diagnosis, will be optimized;
— the number of undiagnosed and ineffectively treated patients will be reduced to a minimum;
— the public payer's budget will be spent in a very rational manner;
— it will be possible to conduct comprehensive molecular diagnostics and detect all mutations in lung cancer patients.

Considering the increasing number of therapies, for which it is necessary to identify targetable biomarkers, NGS should be the preferred diagnostic method in patients with advanced NSCLC.

Article Information and Declarations

Author contributions

K.S., B.W., C.P.: concept, substantive input, content editing; K.D, P.K., K.Dz, M.B.: substantive input, content editing; M.K.: substantive supervision, content editing.

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Conflict of interest

The authors report no conflict of interest.

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REVIEW ARTICLE

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Pembrolizumab in combination with chemotherapy in patients with advanced squamous cell lung cancer — clinical trials and real-world data

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ABSTRACT

Advanced squamous-cell lung carcinoma remains a disease with an unfavorable prognosis. Until recently, chemotherapy was used in systemic treatment, and its effectiveness was limited. Implementation of immune check-point inhibitors allowed for an improvement in treatment results. The KEYNOTE-407 study included patients with squamous-cell lung cancer who received 4 immunochemotherapy cycles followed by maintenance treatment with pembrolizumab. Median overall survival of 17.2 months versus 11.6 months for chemotherapy was obtained (risk of death reduction by 29%) while the percentage of patients remaining in follow-up was 18%. Analysis of patients with good performance status treated in clinical practice confirms the results from the registration study and emphasizes the importance of taking into consideration clinical factors while qualifying patients for treatment.
Keywords: squamous-cell lung cancer; pembrolizumab, immunochemotherapy, prognostic and predictive factors

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Introduction

There are about 23000 newly diagnosed patients with non-small cell lung cancer (NSCLC) in Poland each year [1]. The therapy of choice in patients with generalized stage remains systemic treatment, and the therapeutic aim is to extend overall survival (OS) and improve quality of life (QoL). During qualification for treatment, apart from the patient's performance status (PS), comorbidities, results of laboratory tests, and status of biomarkers are also taken into account.

In patients with a documented presence of molecular disorders in the EGFR, *ALK* and *ROS1* genes, the management is based on use of molecularly targeted drugs. In other cases, chemotherapy, immunotherapy, or a combination of chemotherapy and immune checkpoint inhibitors (ICIs) may be considered. Immunotherapy mainly uses programmed death receptor type 1 (PD-1) inhibitors [2]. The biomarker that is decisive in qualifying for immunotherapy is the expression level of programmed death ligand 1 (PD-L1) on tumor cells (TCs) assessed by a validated immunohistochemical (IHC) assay. If PD-L1 expression is positive in ≥ 50% of cells, pembrolizumab, atezolizumab, or cemiplimab monotherapy should be considered. On the other hand, if the TC is < 50%, it is possible to use immunochemotherapy. Currently, regimens based on pembrolizumab and nivolumab combined with ipilimumab are available in Poland. Both regimens can be used regardless of the histological cancer type.

It is estimated that the incidence of squamous cell lung cancer (SCLC), among all types of NSCLC, is

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Table 1. Characteristics of the KEYNOTE-407 study population (based on [6])

	Pembrolizumab and chemotherapy (278 patients)	Placebo and chemotherapy (281 patients)
Median age (range) [years]	65 (29–87)	65 (36–88)
Patients > 65 years of age	54.6%	54.8%
Male sex	79.1%	83.6%
Asian race	19.4%	18.5%
ECOG performance status		
0	26.3%	32.0%
1	73.7%	68.0%
Non-smokers	7.9%	6.8%
Brain metastases	7.2%	8.5%
PD-L1 expression		
< 1%	34.2%	35.2%
1–49%	37.0%	30.0%
≥ 50%	26.3%	26.0%
Not assessed	2.5%	1.8%

ECOG — Eastern Cooperative Oncology Group; PD-L1 — programmed death ligand 1

currently 30–40% [3–5]. This study summarizes data from pivotal studies and observations from daily clinical practice (RWE) regarding SCLC patients qualified for immunochemotherapy with pembrolizumab.

Efficacy of immunochemotherapy — pivotal study results

The KEYNOTE-407 study enrolled patients diagnosed with SCLC who had not previously received systemic treatment due to generalized disease [6]. Patients receiving previous neoadjuvant or adjuvant treatment were still eligible for the study provided that the time between treatment cessation and disease dissemination was at least 12 months. Patients previously treated with pembrolizumab or other immune checkpoint inhibitors were not eligible for the study. In total, 559 patients were qualified for treatment, regardless of PD-L1 expression level (0–100%). The characteristics of the study population are presented in Table 1. Patients were randomly assigned to the chemotherapy arm [carboplatin for AUC 6 and paclitaxel 200 mg/m^2 every 21 days or nab-paclitaxel (nab-P) 100 mg/m^2 on days 1, 8, and 15] or to pembrolizumab-based immunochemotherapy. The treatment consisted of four cycles of immunochemotherapy or chemotherapy followed by maintenance treatment with pembrolizumab or placebo for a total of 35 cycles (2 years of treatment) [6]. After an initial follow-up period (with a median of 7.8 months), an advantage was observed in favor of pembrolizumab in combination with chemotherapy. Median OS for immunochemotherapy and chemotherapy were 15.9 and 11.3 months, respectively [hazard ratio (HR) was 0.64; 95% confidence interval (CI) 0.49–0.85; $p < 0.001$], and median PFS was 6.4 and 4.8 months, respectively (HR = 0.56; 95% CI 0.45–0.70; $p < 0.001$) [6]. The clinical benefit was independent of sex, age, PD-L1 expression level, and taxanes used (paclitaxel *vs*. nab-P) [6]. In the following years, updated data on the efficacy and safety of treatment were published (selected information is presented in Tab. 2) [7, 8]. It should be emphasized that in the experimental arm, 109 patients (39.2%) received systemic treatment after disease progression (including immunotherapy in 33 patients) while in the control arm, treatment was administered to 172 patients (61.4%), including 143 patients receiving immunotherapy. In the group of patients initially qualified for immunochemotherapy, 19.8% of patients completed the entire treatment planned and received 35 cycles of pembrolizumab [8]. In this subgroup, after another three years of follow-up, 60% of patients were still progression-free.

A special subgroup in this population included patients with a PD-L1 expression < 1%, who accounted for 35.2% of all patients included in the analysis in the KEYNOTE-407 study. The initially published results indicated that PD-L1 expression level does not significantly affect the likelihood of clinical benefit (HR = 0.61; 95% CI 0.38–0.98), but later analyses documented a limited advantage of immunochemotherapy over chemotherapy in the subgroup (HR = 0.79; 95% CI 0.56–1.11). However, it is worth noting the relatively high activity of chemotherapy used in the control arm in patients with a PD-L1 expression < 1% (median OS — 11 months). The percentage of patients

Table 2. Efficacy of treatment in the KEYNOTE-407 study (data for the general study population, based on the results of studies [6–8])

	ORR [%]	Median PFS [months]	PFS [%]	Median OS [months]	OS [%]
Paz-Ares (2018)	57.9 *vs.* 38.4	6.4 *vs.* 4.8 HR = 0.56; 95% CI 0.45–0.70; p < 0.001	–	15.9 *vs.* 11.3 HR = 0.64; 95% CI 0.49–0.85; p < 0.001	–
Paz-Ares (2020)	62.6 *vs.* 38.4	8 *vs.* 5.1 HR = 0.56; 95% CI 0.45–0.70; p < 0.001	After 12 months: 35.8 *vs.* 17.7	17.1 *vs.* 11.6 HR = 0.71; 95% CI 0.58–0.88; p < 0.001	After 12 months: 64.7 *vs.* 49.6
Novello (2023)	62.2 *vs.* 38.8	8 *vs.* 5.1 HR = 0.62; 95% CI 0.52–0.74	After 60 months: 10.8 *vs.* 3.5	17.2 *vs.* 11.6 HR = 0.71; 95% CI 0.59–0.85	After 60 months: 18.4 *vs.* 9.7

CI — confidence interval; HR — hazard ratio; ORR — objective response rate; OS — overall survival; PFS — progression-free survival

Table 3. Efficacy of pembrolizumab in combination with chemotherapy by PD-L1 expression level (based on study results [6–8])

	Median PFS [months] HR (95% CI)			Median OS [months] HR (95% CI)		
	< 1%	1–49%	≥ 50%	< 1%	1–49%	≥ 50%
Paz-Ares (2018)	0.68 (0.47–0.98)	0.56 (0.39–0.80)	0.37 (0.24–0.58)	0.61 (0.38–0.98)	0.57 (0.36–0.90)	0.64 (0.37–1.10)
Paz-Ares (2020)	0.67 (0.49–0.91)	0.50 (0.39–0.63)		0.79 (0.56–1.11)	0.67 (0.51–0.87)	
Novello (2023)	0.7 (0.52–0.95	0.6 (0.45–0.81)	0.48 (0.33–0.69)	0.83 (0.61–1.13)	0.61 (0.45–0.83)	0.68 (0.47–0.97)

CI — confidence interval; HR — hazard ratio; OS — overall survival; PFS — progression-free survival

with a PD-L1 expression < 1% remaining in follow-up after 5 years was 10.7% in the experimental arm and 13.1% in the control arm. A summary of treatment efficacy data in subgroups determined by PD-L1 expression level is presented in Table 3.

Efficacy of immunochemotherapy — real-world data

For a few years, immunochemotherapy based on pembrolizumab has been the standard of care in the first-line treatment of patients with advanced SCLC and PD-L1 expression levels < 50%. In Poland, this regimen has been financed since January 2021. Real-world data can establish the real value of immunochemotherapy and help identify subgroups of patients who benefit most from this treatment. Several reports concerning this clinical setting have been published recently.

Waterhouse et al. [9] analyzed a group of 4 271 patients, including 814 diagnosed with SCLC, who received immunochemotherapy (almost all patients were treated with pembrolizumab in combination with chemotherapy). Median OS was 10.6 months (95% CI 9.3–11.8). After 12 and 24 months of follow-up, 45.1% and 24.5% of patients were alive, respectively. Performance status had a significantly negative prognostic value. In patients with good performance status [0–1 according to the Eastern Cooperative Oncology Group (ECOG) scale], median OS was 11.6 months (95% CI 10.1–14.3), and in patients in average general condition (ECOG PS 2), OS was 8 months (95% CI 5.6–11.2). At the same time, significant differences were observed between the percentage of patients remaining in follow-up after 12 months (49.5% *vs.* 32.5%). An additional negative prognostic factor is the presence of brain metastases during qualification for treatment. Median OS for patients with and without brain metastases was 6.7 and 1.1 months, respectively, and the percentage of patients remaining in follow-up after 12 months was 32.1% and 45.9%, respectively [9].

In 364 patients diagnosed with SCLC, long-term clinical benefit after pembrolizumab-based immunochemotherapy was obtained in approximately 35% of

Table 4. Efficacy of pembrolizumab in combination with chemotherapy in squamous cell lung cancer patients — real-world data

	Number of patients		Median PFS [months] (95% CI)		Median OS [months] (95% CI)		OS at 12 months
	Total	PD-L1 < 1%	Total	PD-L1 < 1%	Total	PD-L1 < 1%	
Waterhouse (2021)	814	209 (35.9%)	ND		10.6 (9.3–11.8)	8.7 (7.7–12.4)	Total: 45.1% PD-L1 < 1%: 42.3% PD-L1 1–49%: 43.3% PD-L1 ≥ 50%: 50.9%
Liu (2022)	364	94 (35.3%)	6.5 (5.6–7.6)	5.8 (4.6–8.3)	15.3 (11.7–18.6)	17.2 (10.8–20.6)	Total: 54.9% PD-L1 < 1%: 57.0% PD-L1 1–49%: 56.0%
Wagenius (2023)	62	ND	ND	ND	18.9 (14.1, NE)	ND	71.3%

CI — confidence interval; HR — hazard ratio; ND — no date; NE — not estimable; OS — overall survival; PD-L1 — programmed death ligand 1; PFS — progression-free survival

patients (37% of patients remained in follow-up after 24 months) [10]. Median OS was 15.3 months (95% CI 11.7–18.6), and there were no differences related to PD-L1 expression level. In patients with a PD-L1 expression ≥ 1% and < 1%, median OS was 16.2 months (95% CI 10.3–20.6) and 17.2 months (95% CI 10.8––20.6), respectively [10]. The impact of other clinical and morphological factors on the prognosis in this group of patients was not assessed.

The SPINNAKER study included in the analysis a group of 308 patients (including 17% of patients diagnosed with SCLC) receiving pembrolizumab-based immunochemotherapy [11]. Median PFS for the general population was 8 months (95% CI 7.1–8.8), and median OS was 12.7 months (95% CI 10.2–15.2). The percentage of patients remaining in follow-up after 12 months was 52.2%. Detailed data on the SCLC patient subgroup were not presented. However, a multivariate analysis showed that a diagnosis of SCLC, presence of metastases in 3 or more sites, and a high value of the Systemic Inflammatory Index (SII) calculated based on platelet count and neutrophil-to-lymphocyte ratio (NLR) are negative prognostic factors for both PFS and OS. The performance status of patients also had a significant impact (ECOG: 0 *vs*. 1; HR = 1.46; 95% CI 1.06–2.02; p < 0.022) [11]. Selected real-world data regarding treatment efficacy are summarized in Table 4 [9, 10, 12].

Safety profile

A different mechanism of action of immune checkpoint inhibitors (including pembrolizumab) leads to the occurrence of immune-related adverse events (irAEs), which result from the activation of the immune system. In addition, due to the combined nature of the treatment, these patients also experience typical side effects of chemotherapy. In the KEYNOTE-407 study, adverse events were reported in 98.6% (74.8% grades 3–5), and irAEs were reported in 95.7% of patients (57.2% grades 3–5). Side effects led to discontinuation of one of the drugs in 28.8% of patients (in 17% of patients both immunotherapy and chemotherapy were discontinued). Complications of systemic treatment were considered the cause of death in 11% of patients. The frequency of adverse events is presented in Tables 5 and 6.

Table 5. Adverse events of pembrolizumab in combination with chemotherapy (based on the results of the KEYNOTE-407 study [8])

	Any grade [%]	Grade 3–5 [%]
Total	98.6	74.8
Anemia	54.7	15.8
Neutropenia	37.8	23.0
Nausea	36.3	1.4
Diarrhea	33.5	4.3
Thrombocytopenia	30.9	8.3
Loss of appetite	27.7	2.5
Joint pain	25.5	1.8
Asthenia	24.5	7.7
Peripheral neuropathy	21.9	1.1
Rash	18.7	0.7
Pruritus	18.3	0.4
Vomiting	18.3	0.4
Cough	17.6	0.7
Increased body temperature	15.1	0.7

In the aforementioned retrospective SPINNAKER study, irAEs of any grade were observed in 43% of patients (including 43 patients with grade 3 or 4).

Table 6. Immune-related adverse events (based on the results of the KEYNOTE-407 study [8])

	Any grade [%]	Grade 3–5 [%]
Total	35.6	13.3
Hypothyroidism	12.2	0.4
Pneumonitis	8.3	3.3
Hyperthyroidism	7.6	0.4
Infusion-related reaction	5.4	1.8
Colitis	3.5	2.5
Pituitary insufficiency	1.4	0.8

The occurrence of irAEs was a favorable prognostic factor — median OS was 17.5 months versus 10.1 months ($p < 0.001$) in the group of patients without adverse events [13].

Conclusions

Advanced SCLC is still associated with unfavorable prognosis, resulting from, among others, limited effectiveness of chemotherapy. Implementation of immune checkpoint inhibitors in the treatment of NSCLC patients, initially after chemotherapy failure, allowed for prolonged OS in some patients (long-term clinical benefit was observed in about 20% of cases) [14, 15]. Immunochemotherapy based on pembrolizumab is currently one of possible treatment options in this group of patients already in the first line of systemic treatment. The available data indicate the possibility of obtaining an objective treatment response in about 60% of patients and median OS of about 17 months [6–8]. In the KEYNOTE-407 study, 18.4% of patients in the immunochemotherapy arm remained in follow-up after 5 years from treatment initiation (*vs*. 9.7% in the chemotherapy arm).

However, it should be emphasized that the profile of patients who qualified for the pivotal study — consistent with inclusion criteria in the Drug Program in Poland — included good performance status (ECOG PS 0–1), absence of active brain metastases or molecular abnormalities in the *EGFR* and *ALK* genes. Publications based on real-world data confirm that performance status is an important prognostic factor. It seems reasonable to take into account other predictive and prognostic factors, which are discussed in the literature on immune checkpoint inhibitors in NSCLC patients. The presence of metastases in the skeletal system and liver, advanced stage of the disease, significant weight loss before treatment commencement, high activity of lactate dehydrogenase (LDH), elevated NLR and hypoalbuminemia may have a negative impact on the prognosis in patients undergoing immunochemotherapy [16–20]. In addition, the importance safety profile should be emphasized — in the KEYNOTE-407 study, approximately 30% of patients required treatment discontinuation due to adverse events.

Rational qualification for treatment of SCLC patients allows for their optimal selection and gives a chance for long-term clinical benefit.

Article information and declarations

Author contributions

M.K-W.: review of the literature, writing a preliminary version manuscript.
D.M.K.: verification and supervision.

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Conflict of interest

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Supplementary material

None.

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REVIEW ARTICLE

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Sotorasib for non-small cell lung cancer — current options and perspectives

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ABSTRACT

KRAS regulates several cellular processes, such as cell proliferation, cell cycle regulation, metabolic changes, cell survival, and cell differentiation. Abnormalities in the *KRAS* gene are found in approximately 30% of patients with non-small cell lung cancer, usually in patients diagnosed with nonsquamous cancer and more often in Caucasian patients, women, and smokers. The p.G12C variant is most frequently found in KRAS-positive patients. Sotorasib is the first drug approved for this population. The superiority of sotorasib over docetaxel after failure of immunochemotherapy was demonstrated in the CodeBreak 200 phase III study for the primary endpoint — median progression-free survival was 5.6 months [95% confidence interval (CI) 4.3–7.8] *vs*. 4.5 months (3.0–5.7); hazard ratio = 0.66 (95% CI 0.51–0.86; p = 0.0017), while the 12-month progression-free survival rate was 24.8% for sotorasib and 10.1% for docetaxel. Currently, sotorasib monotherapy, at an initial dose of 960 mg/day, is indicated for use in adults with advanced non-small cell lung cancer with the *KRAS* p.G12C mutation who have experienced disease progression after at least one previous line of systemic treatment. More randomized trials are needed to determine the optimal place of sotorasib in the systemic treatment sequence in this patient population.

Keywords: non-small cell lung cancer, *KRAS* gene, sotorasib

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Introduction

Patients diagnosed with advanced non-small cell lung cancer (NSCLC) represent a heterogeneous population. Currently, the choice of optimal systemic therapy is determined not only by the patient's clinical and morphological characteristics (performance status, comorbidities, or histological type) but also by the immunohistochemical (IHC) and molecular profile of the disease [1, 2]. In daily practice, next-generation sequencing (NGS) is increasingly used to diagnose molecular characteristics of lung cancer, allowing simultaneous assessment of multiple molecular abnormalities. Abnormalities in the Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene are essential from a practical point of view since they are detected in approximately 30% of patients, usually in individuals diagnosed with nonsquamous NSCLC and more often in Caucasians, women, and smokers [3]. The p.G12C variant is found most frequently and accounts for approximately 50% of patients with *KRAS* gene abnormalities [1]. Despite the high prevalence of these molecular abnormalities, attempts to develop targeted therapies have been unsuccessful for years. It was not until 2021 that the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved sotorasib, which is the first

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selective small-molecule KRAS inhibitor [4, 5]. This article summarizes the current understanding of the role of the KRAS pathway in oncogenesis, mutational analysis of the *KRAS* gene, and the efficacy and safety profile of sotorasib, including data from clinical trials and real-world experience.

The role of the KRAS pathway

The *KRAS* gene is located on the short arm of chromosome 12 (12p11.1–12p12.1) [6]. *KRAS* encodes six exons, resulting in two splice variants, KRAS4A and KRAS4B. There is a difference in the C-terminal sequence between these two variants. KRAS4A is expressed in a tissue-specific and developmentally restricted fashion, while KRAS4B is ubiquitously expressed and dominant [7]. Together with Harvey rat sarcoma viral oncogene (*HRAS*) and neuroblastoma rat sarcoma viral oncogene (*NRAS*), they encode proteins belonging to the RAS family [8]. The KRAS protein consists of several domains, each with a specific function. The G domain is responsible for binding to guanosine triphosphate (GTP) and guanosine diphosphate (GDP) and hydrolyzing GTP to GDP [9]. The G domain is critical for the switching between active (GTP-bound) and inactive (GDP-bound) states of the protein. In addition, KRAS has a flexible C-terminal structural element, also known as the hypervariable region, responsible for membrane anchoring and localization of KRAS to the cell membrane [10]. Other critical functional elements of KRAS are the switch regions, which are crucial for conformational changes during GTP binding and hydrolysis. The switch-I and switch-II regions undergo structural changes that influence the interaction of KRAS with downstream effectors [11]. Only in the GTP-bound state, turned on by extracellular stimuli, can KRAS bind and activate its effector proteins [12]. Key effector pathways downstream of oncogenic KRAS include mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K), and Ras-like (Ral) GEF (RalGEF). Therefore, activated KRAS regulates several cellular processes, such as cell proliferation, cell cycle regulation, metabolic changes, cell survival, and cell differentiation. Activating *KRAS* mutations results in the high-affinity binding of GTP and loss of GTPase activity, resulting in the deregulation of RAS-dependent signaling pathways [13]. *KRAS* mutations are commonly found in various types of tumors, most often in pancreatic (88%), colorectal (45–50%), and lung cancer (31––35%) [14]. Most mutations in *KRAS* affect codons 12, 13, 61, and 146. However, mutations of codon 146 occur in colorectal cancers and hematological malignancies, while they are relatively rare in NSCLC. The most frequent *KRAS* mutations in NSCLC are p.G12C, p.G12V, and p.G12D [15]. Therefore, lung cancer cells express mutations in KRAS4A and KRAS4B splice variants [7].

Detection of *KRAS* mutations

In 1981, point mutations in the *KRAS* gene resulting in single amino acid changes in specific codons (G12, G13, and G61) were detected in lung cancer cells [16]. This finding started the era of molecular diagnostics in oncology. Today, *KRAS* is a well-characterized protooncogene, whose activating mutations are frequently detected in various tumors [14]. *KRAS* alterations are among the most frequent genetic variants detected in NSCLC [17]. *KRAS* alterations are detected in approximately 20–40% and 5% of patients with adenocarcinoma and squamous NSCLC, respectively [18]. The vast majority of *KRAS* mutations (> 95%) occur primarily at codon 12, with the most frequent alteration resulting in a substitution of glycine for cysteine at codon 12 (p.G12C) [15]. This variant is identified in approximately 40% of NSCLC patients with *KRAS* mutations. Other frequent *KRAS* substitutions are p.G12V, p.G12D, and p.G12A, detected in 21%, 17%, and 7% of NSCLC patients, respectively [19].

The emergence of targeted therapies for specific mutations, such as *KRAS* p.G12C, highlights the importance of molecular testing in guiding treatment decisions. Identifying the presence of the *KRAS* p.G12C mutation in a patient's tumor helps to select the most appropriate treatment options, and improves the chances of a favorable response. The EMA has approved molecularly targeted therapies for NSCLC patients who require the identification of variants in many different genes [20]. To administer an optimal treatment regimen in these patients, it is necessary to perform molecular tests that allow the precise detection of not only point mutations in *EGFR*, *KRAS, BRAF,* and *ERBB2* genes but also fusions of *ALK*, *ROS1, NTRK1/2/3, MET,* and *RET* genes [20]. In addition, increasing attention is being paid to the need to determine the presence of mutations in the *STK11, KEAAP1,* and *TP53* genes or the analysis of genomic signatures, such as tumor mutational burden (TMB) [21]. Therefore, according to the current guidelines of the European Society for Medical Oncology (ESMO), NGS is a method that should be routinely used to diagnose patients with advanced NSCLC [21]. In addition, numerous studies conducted on patients with advanced lung cancer have shown that the simultaneous

analysis of biomarkers is more effective than the sequential use of single-gene tests [22–25]. One of these studies found that sequential testing results in more false positives (3.3%) than simultaneous analysis of several genes (1.4%), as each additional test increases the likelihood of a false positive result. At the same time, it was found that the sequential use of single-gene tests also increases the number of nondiagnostic results (sequential tests — 6.9% *vs*. NGS — 2.7%) [22]. Studies have also shown that diagnostics conducted with sequential tests have a negative impact on the total turn-around time (TAT) or diagnostic costs [22–24]. In addition, using multiple tests also increases the risk of material exhaustion before the end of the diagnostic process in individual patients [22, 24].

Effectiveness of sotorasib — data from clinical trials

Initially, the value of sotorasib was assessed in CodeBreaK100, a multicohort dose-escalation study in patients with various solid tumors [26–28]. A total of 427 patients with the *KRAS* p.G12C mutation were enrolled. The updated results of this trial have been published on a group of 174 patients diagnosed with NSCLC, in which 52% of participants were women, 23% had brain metastases, and all individuals had received at least one line of systemic treatment (25% — three lines) [28]. Most patients had received chemotherapy and immunotherapy before qualifying for sotorasib (83%). The objective response rate (ORR) was 41% [95% confidence interval (CI) 33.3–48.4], and the disease control rate (DCR) was 84% (95% CI 77.3–88.9). In the group of patients who achieved an objective response at 12 months, 50.6% remained progression-free. Median progression-free survival (PFS) was 6.3 months with a 95% CI of 5.3–8.2, and median overall survival (OS) was 12.5 months (95% CI 10.0–17.8). The proportions of patients still alive at 12 and 24 months were 51% and 33%, respectively. Intracranial control was documented in 88% of the patients (14 of 16).

The phase III CodeBreak200 trial aimed to compare the value of sotorasib to second-line standard chemotherapy with docetaxel in patients who had failed immunochemotherapy (treatment with chemotherapy and immune checkpoint inhibitor could be concurrent or sequential) [29]. Patients were eligible if they had good performance status, had no active brain metastases, and had not previously received docetaxel for advanced disease. Patients were randomly assigned to receive sotorasib (960 mg/day) or docetaxel (75 mg/m^2). Patients were treated until disease progression, significant adverse events, or death. Crossover was allowed in this trial. In the sotorasib arm, 98% of the patients had nonsquamous NSCLC, 33% had brain metastases, and 17% had liver metastases. Before qualifying for sotorasib, 45% of the patients had received one line of therapy, and the rest had received two or more. The primary endpoint of the CodeBreak200 trial was PFS assessment.

The superiority of sotorasib over docetaxel was demonstrated for the primary endpoint: median PFS was 5.6 months (95% CI 4.3–7.8) *vs.* 4.5 months (95% CI 3.0–5.7); hazard ratio (HR) = 0.66 (95% CI 0.51–0.86; p = 0.0017), the 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel [29]. There was also a superiority of sotorasib in terms of the ORR 28.1% (95% CI 21.5–35.4) *vs.* 13.2% (8.6–19.2); p < 0.001. Clinical benefit was observed in the overall population, including patients with brain metastases. Additionally, the benefit in quality-of-life parameters was documented. The time to deterioration in global health status, physical functioning, and cancer-related symptoms (dyspnea and cough) was delayed with sotorasib. However, there were no differences in OS between groups (HR = 1.01; 95% CI 0.77–1.33), probably due to the crossover between the arms. At the time of analysis (median study follow-up 17.7 months), in both subgroups, approximately 40% of patients received systemic treatment after disease progression. Of the patients initially treated with docetaxel, 143 discontinued treatment (95 due to disease progression), and 49 patients subsequently received sotorasib [29]. It is also worth noting that in previous clinical trials (with immune checkpoint inhibitors in the second-line setting with docetaxel as a comparator), mPFS for docetaxel was approximately 3–4 months, with a 12-month PFS rate estimated at 6–8% and mOS of approximately 9 months [30–33]. In the current study, the clinical benefit was more significant in this arm. Table 1 summarizes the treatment efficacy data from CodeBreak200.

Safety profile of sotorasib

In the CodeBreak200 trial, adverse effects were observed in almost all patients from both groups. Treatment-identified adverse effects were more common in docetaxel-treated patients (86% *vs*. 70%) and similarly treatment-related severe adverse effects (23% *vs*. 11%). Fifteen percent of patients treated with sotorasib required a dose reduction and 10% required treatment discontinuation. For sotorasib, diarrhea and an increase in aminotransferase activity were observed most frequently. For docetaxel, neutropenia and fatigue

Table 1. Treatment efficacy of sotorasib in the CodeBreak200 study [29]

	Sotorasib (171)	Docetaxel (174)	HR (95% CI)	p
ORR [%]	28.1	13.2		< 0.001
DCR [%]	82.5	60.3		
mPFS [months]; 95% CI	5.6 (4.3–7.8)	4.5 (3.0–5.7)	0.66 (0.51–0.86)	0.0017
mOS [months]; 95% CI	10.6 (8.9–14.0)	11.3 (9.0–14.9)	1.01 (0.77–1.33)	0.53
12-months PFS	24.1	10.1		

CI — confidence interval; DCR — disease control ratio; HR — hazard ratio; m — median; ORR — overall response ratio; OS — overall survival; PFS — progression-free survival

Table 2. The most common adverse events of sotorasib and docetaxel in the CodeBreak200 study

	Sotorasib		Docetaxel	
	Any grade [%]	Grade ≥ 3 [%]	Any grade [%]	Grade ≥ 3 [%]
Diarrhea	34	12	19	2
Fatigue	7	1	25	6
Nausea	14	1	21	0
Anemia	3	1	18	3
Stomatitis	1	0	11	1
Alanine aminotransferase increase	10	8	0	0
Aspartate aminotransferase increase	10	5	0	0
Neutropenia	1	0	13	12
Edema peripheral	0	0	9	1
Febrile neutropenia	0	0	5	5

were the most frequently reported. Details of the safety profile are presented in Table 2.

Effectiveness of sotorasib — real-world data

The availability of sotorasib is limited in many countries. In Poland, sotorasib was reimbursed for use in patients diagnosed with advanced NSCLC and a confirmed *KRAS* p.G12C mutation after the failure of at least one line of chemotherapy and/or immunotherapy in September 2023. As a result, data from the literature documenting the value of sotorasib in daily practice are limited. Several congress abstracts have been presented recently, and these are briefly discussed below.

At the 2022 ESMO Congress, Awad et al. [34] presented the results of an international analysis of patients treated with sotorasib as part of the Expanded Access Programme (EAP). Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were eligible for the EAP. A total of 137 patients were included in the analysis; approximately 90% had previously received platinum-based immunotherapy and chemotherapy, and 26% had brain metastases (in most cases, after previous local treatment). Median PFS in the whole analyzed population was 6.4 months. No significant differences were found in the subgroups of patients with brain metastases or ECOG 2. Treatment-related grade ≥ 3 adverse effects occurred in 23% of patients; the most common was aminotransferase elevation levels (5%). Dose reduction was required in 25% of patients [34]. The updated results of this study were presented during the European Lung Cancer Congress (ELCC) in 2023, where the results of a group of 147 patients were summarized [35]. With a median follow-up of 13.6 (95% CI 11.1–14.6) months, median OS was 9.5 (95% CI 8.6–12.0) months. The median OS rate was similar in patients with and without a history of CNS metastases. However, clinical factors such as performance status (ECOG 2), number of previous lines of treatment (> 2), and smoking status (never smokers) may have negatively influenced OS [35]. Some additional safety data were reported.

Cadranel et al. [36] presented the results of an analysis of a group of 651 patients after failure of chemotherapy, with or without immunotherapy. Fifty-one percent of patients received sotorasib immediately after failure of

immunotherapy. Due to reimbursement procedures in France, the results were presented for two cohorts of patients. The median duration of treatment with sotorasib was 7.5 (1.5–11.3) months for patients in the first group (121/130) and 3.5 (0.2–5.7) months for patients in the second group (152/549) [36].

In the 105 patients described by Thummalapali et al. [37], sotorasib treatment resulted in the ORR in 28% of patients, with median PFS and OS of 5.3 months and 12.6 months, respectively. The potential predictive value of coexisting molecular abnormalities was also demonstrated: for *KEAP1* mutations, the differences were statistically significant (for PFS HR = 3.19; p = 0.004; for OS HR = 4.10; p = 0.003). No effect on survival parameters was observed for coexisting abnormalities in the *TP53* and *STK11* genes. Furthermore, patients previously treated with immune checkpoint inhibitors had a higher incidence of adverse events. The most common was hepatic toxicity [37]. The coexistence of *KRAS* p.G12C variant with *KEAP1, SMARCA4*, and *CDKN2A* variants may limit the efficacy of sotorasib (as well as another KRAS inhibitor, adagrasib) in this patient population. However, extensive molecular profiling is not routinely performed when qualifying patients for treatment [38].

Conclusions

Currently, sotorasib monotherapy, at an initial dose of 960 mg/day, is indicated for use in adult patients with advanced NSCLC with *KRAS* p.G12C mutation who have experienced disease progression after at least one prior line of systemic treatment [39]. In the CodeBreak 200 trial, most patients received platinum-based chemotherapy and immune checkpoint inhibitors before the initiation of sotorasib. Considering the relatively high prevalence of the variant p.G12C, it is reasonable to routinely perform molecular assessment, including the *KRAS* gene, with concurrent evaluation of all clinically relevant abnormalities in NSCLC by NGS. Currently, immunotherapy or immunochemotherapy, depending on the level of PD-L1 expression, remains the standard of care for the first-line treatment of NSCLC. This also applies to patients with the p.G12C mutation in the *KRAS* gene, in whom the efficacy of immune checkpoint inhibitors is comparable to that in other patients [40–45]. Clinical trials are underway to evaluate the value of sotorasib in combination with other cancer drugs in first-line treatment (NCT05920356, NCT04933695) [46, 47]. More randomized trials are needed to determine the optimal place of sotorasib in the systemic treatment sequence in this patient population. It is important to remark on the relatively good safety profile of sotorasib, with diarrhea and liver dysfunction as the most common adverse events. At the same time, the higher risk of liver toxicity reported in the literature in patients who received immunotherapy shortly before starting sotorasib treatment should be noted [48].

In conclusion, sotorasib is the first drug to prolong PFS and significantly increase the proportion of patients who remain progression-free at 12 months in patients diagnosed with advanced *KRAS* p.G12C-mutated NSCLC after failure of systemic therapy.

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Author contributions

M.K.-W., B.W.: conceptualization, literature review, writing of draft manuscript.
Both authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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Supplementary material

None.

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REVIEW ARTICLE

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Diagnosis and treatment of patients with breast cancer and mutation in the *BRCA1/2* genes

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ABSTRACT

Breast cancer is the most common cancer among women in Poland and worldwide, second only to lung cancer in terms of mortality. Germline mutations account for approximately 5–10% of all breast cancer cases, with mutations in the *BRCA1/2* genes being the most frequently identified. The presence of pathogenic variants in the *BRCA1/2* genes is associated with a more than 60% risk of developing breast cancer, a 40–60% risk of ovarian cancer in women with a *BRCA1* mutation, and a 13–30% risk in women with a *BRCA2* variant. Breast cancer is often diagnosed at a younger age in *BRCA1/2* mutation carriers. The prevalence and increased accessibility of genetic testing, especially next-generation sequencing, lead to a higher number of diagnosed individuals and healthy family members. Identifying a pathogenic variant in the *BRCA1/2* genes, analyzing a family history, and genetic counseling enables the development of individual recommendations for further management. This article aims to present the diagnostic and therapeutic approach in breast cancer patients with a pathogenic variant in the *BRCA1/2* genes.

Keywords: breast cancer, pathogenic variant, *BRCA1*, *BRCA2*, next-generation sequencing

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Introduction

Breast cancer is the most common cancer in women in Poland and worldwide and the second cause of cancer-related deaths after lung cancer. In Poland, there is a constant increase in the incidence of breast cancer, which is mainly associated with lifestyle changes and environmental factors. The most important risk factors include sex, older age, presence of mutations in the *BRCA1/2* genes, family history of breast cancer (especially at a young age), early menstruation, late menopause, late birth of the first child, long-term hormone replacement therapy (HRT), mainly based on estrogens and gestagens, long-term contraception (to a small extent), obesity in the postmenopausal period, and radiotherapy to the chest area at a young age. Breast cancers associated with hereditary mutations account for 5–10% of all cases, with most commonly diagnosed mutations in the *BRCA1/2* genes [1].

The presence of pathogenic variants in the *BRCA1* and *BRCA2* genes is associated with greater than 60% risk of breast cancer, as well as 40–60% risk of ovarian cancer in women with a mutation in the *BRCA1* gene and 13–30% risk in women with a variant in the *BRCA2* gene. In addition, there is an increased risk of melanoma, prostate, and pancreatic cancer. Breast cancer is more often diagnosed at a young age. In women with a mutation in the *BRCA1* gene, the greatest risk is noted between 30 and 40 years of age, and in the case of a variant in the *BRCA2* gene — between 40 and 50 years of age; then the risk declines and reaches a plateau until the age of 80. The risk of contralateral breast cancer is higher than in the general population (26% and 40% in women with a mutation in the *BRCA1* and *BRCA2* genes, respectively). In patients with mutations in *BRCA1/2* genes, tumors with a high histological grade (G3) that do not express estrogen (ER) and progesterone receptors (PR) and with no *HER2* gene amplification occur more often than in the general population [2].

Women with mutations in the *BRCA1/2* genes are a special group of patients, due to the presence of the following factors: need for cascade diagnostics in

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family members, possibility of implementing procedures reducing cancer risk, possibility of appropriate surgical treatment, availability of targeted systemic therapy, applicability of methods securing fertility, which can be used before oncological treatment or before bilateral risk-reducing salpingo-oophorectomy (RRSO) and the use of *in vitro* fertilization combined with preimplantation genetic diagnosis.

The multidisciplinary team conducting the treatment of breast cancer consists of a clinical oncologist, surgical oncologist, radiotherapist, gynecologist, reproductive medicine specialist, geneticist, psychologist, and senology nurse. The strategy planned and conducted by the aforementioned team ensures safety and effectiveness of treatment as well as a holistic approach. Dissemination and increasing access to genetic testing — especially next-generation sequencing (NGS) — increases the number of diagnosed patients and healthy family members. Diagnosis of a pathogenic variant in the *BRCA1/2* genes, pedigree analysis, and genetic consultation enable the development of individual recommendations for further management.

This article aims to present diagnostic and therapeutic procedures in breast cancer patients with a pathogenic mutation in the *BRCA1/2* genes.

Mutations in the *BRCA1/2* genes

The relationship between the presence of mutations in the *BRCA1/2* genes and an increased risk of breast and ovarian cancers was described in 1994 [3]. Screening tests to detect mutations in the *BRCA1/2* genes were introduced to clinical practice as early as 1996 [4]. The prevalence of variants in the *BRCA1* and *BRCA2* genes in Western populations ranges from 1 in 400 to 1 in 500 [5]. In addition to *BRCA1/2*, variants in other genes, such as *TP53* (Li Fraumeni syndrome), *PTEN* (Cowden syndrome), *CDH1*, *STK11* (Peutz-Jeghers syndrome), and *MLH1, MSH2, MSH6,* and *PMS2* (Lynch syndrome) are also known to increase the risk of developing breast or ovarian cancer [6].

So far, almost 5000 sequence variants have been described in the *BRCA1/2* genes, most of which are deletions or insertions changing the reading frame and substitutions leading to premature termination of translation and the formation of a shortened protein product [7]. Some abnormalities in the *BRCA1/2* genes may constitute large rearrangements (LRs), whose occurrence varies in individual populations. In the Dutch, Irish, Czech, and German populations, these variants accounted for 27–36%, 11%, 6%, and 3%, respectively [8–11]. In the population of Polish patients with breast and/or ovarian cancer, large *BRCA1/2* gene rearrangements accounted for 2.1–5% [12, 13].

The variable frequency of specific mutations is due to the occurrence of a strong founder effect in some isolated populations or ethnic groups. The clearest relationship concerns the Ashkenazi Jews population, in whom three mutations with a total frequency of 1/40 are identified: c.68_69delAG, c.5266dupC in the *BRCA1* gene and c.5946delT in the *BRCA2* gene [14]. In the Polish population, founder mutations in the *BRCA1* gene are c.5266dupC, c.181T>G, and c.4035del [15]. These variants account for 64–84% of all lesions detected in the Polish population [12, 16, 17].

However, due to the large variety of abnormalities detected in the *BRCA1/2* genes in breast cancer patients, in the case of negative results of the targeted analysis (e.g. no pathogenic variant identified), it is necessary to analyze the entire coding sequence of these genes [6].

The *BRCA1* and *BRCA2* genes play an important role in maintaining the integrity of the genome — when they are disrupted, cells become more sensitive to DNA damaging agents (deoxyribonucleic acid), which causes chromosomal aberrations [18–20]. Both genes are involved in DNA damage repair processes by homologous recombination (HR).

Molecular diagnostics

Currently, only the detection of germline variants in the *BRCA1/2* (*gBRCA1/2*) genes has an impact on the diagnostic and therapeutic management in breast cancer patients. Genetic material isolated from peripheral blood cells should be used in routine molecular tests [21–23]. It is also possible to use fixed tissue material for tests aimed at detecting mutations in the *BRCA1/2* genes. However, there are some limitations regarding use of tissue material [6].

First, if a genetic variant is detected in tissue sample, it is necessary to perform additional analysis using DNA isolated from peripheral blood. This allows for determining whether the detected variant in the *BRCA1/2* genes is germline and can be the basis for further diagnostic and therapeutic procedures.

Second, performing molecular analysis using DNA isolated from tumor tissue may prevent the detection of approximately 10% of terminal variants (deletions or duplications).

Third, the classification of somatic and germline variants is based on a different methodology. Therefore, it is possible that a lesion that would be considered a germline pathogenic or possibly pathogenic variant based on peripheral blood testing may be classified as a variant of unknown or no clinical significance.

Due to the large variety of variants in the *BRCA1/2* genes, molecular diagnostics in breast cancer patients should be performed using the NGS method [6, 21]. This method

should make it possible to detect point variants and large rearrangements, deletions, and duplications. If the test does not allow for the identification of the above aberrations, it is advisable to perform a supplementary analysis using the multiplex ligation-dependent probe amplification (MLPA).

Currently, as part of hospital services, it is possible to order molecular diagnostics in patients diagnosed with breast cancer based on the list of genetic tests in cancer [24]. In this group of patients, advanced genetic tests should be ordered because only within the framework of the aforementioned service is it possible to finance tests using the NGS technique. Tests can be performed using fresh material collected from patients for diagnostic purposes or from archival material. The current rules for ordering advanced genetic testing by the National Health Fund (NHF) indicate that fresh material, i.e. peripheral blood, can only be settled during the patient's hospitalization. This generates additional procedures and costs for the payer. Therefore, fixed tissue material, which can be settled on an outpatient basis, is often used for molecular diagnostics. Then, when fixed tissue material is used for molecular diagnostics, the methodological limitations presented above should be considered.

As part of outpatient specialist care, all patients with breast cancer are entitled to genetic counseling and molecular diagnostics [25]. It should be noted, however, that the tests offered in genetic outpatient clinic in the first stage allow only the detection of the most common mutations in the Polish population in the *BRCA1* (c.5266dupC; c.181T>G; c.4035delA; c.66_67delAG; c.3700_3704 del GTAAA), *PALB2* (c.509_510 delGA; c. 172_175 del TTGT) and *CHEK2* (1100del C; IVS+1G>A; del 5395; I157T) genes. The diagnostic effectiveness of this test will therefore be limited, and it does not allow excluding of other variants in the *BRCA1/2* genes.

Only at the next stage, it is possible to perform molecular diagnostics for mutations in the *BRCA1/2*, *PALB2,* and *CHEK2* genes using the NGS method in women in whom none of the above mutations were detected and diagnosed with breast cancer, e.g.:

— before the age of 45, regardless of family history;
— with triple-negative receptor status (no expression of estrogen and progesterone receptors, no *HER2* gene amplification);
— simultaneously or sequentially diagnosed with ovarian cancer or bilateral breast cancer;
— and ≥ 1 first- or second-degree relative was diagnosed with breast cancer (male breast cancer), or ≥ 1 first- or second-degree relative was diagnosed with ovarian cancer;
— and ≥ 1 first- or second-degree relative was diagnosed with breast cancer, including at least one diagnosis below 50 years of age;
— and ≥ 2 maternal or paternal first- or second-degree relatives were diagnosed with breast cancer, regardless of age at diagnosis;
— molecular diagnostics for mutations in the *BRCA1/2*, *PALB2,* and *CHEK2* genes using the NGS method can be also used in men diagnosed with breast cancer. Only NGS testing allows for the exclusion of the presence of variants in the *BRCA1/2* genes, provided that the analysis allows the detection of point variants and large rearrangements (deletions and duplications) [5]. This information should be included in the test report.

Following the above two-step diagnostic scheme significantly increases the turnaround time to obtain a comprehensive genetic result. Attention should also be paid to the limited availability of genetic outpatient clinics in Poland, which also contributes to prolongation of this diagnostic path.

Cascade diagnostics

In first- or second-degree relatives of a breast cancer patient diagnosed with a germline variant in the *BRCA1/2* genes, it is possible to conduct genetic counseling and perform predictive testing for a known familial mutation (so-called cascade diagnostics) [25]. These tasks are conducted as part of a program of care for families with a high and hereditary risk of breast or ovarian cancer, financed by the NHF. According to the assumptions of this program, genetic counseling and molecular diagnostics may also be performed in relatives of women diagnosed with ovarian cancer. It is possible to perform cascade diagnostics aimed at detecting variants not only in the *BRCA1/2* genes but also *in PALB2* and *CHEK2* genes.

In conclusion, the optimal diagnostic algorithm should include the possibility of performing molecular analysis in breast cancer patients on outpatient basis. This test should enable the detection of all germline variants in the *BRCA1/2* genes; therefore it should be performed using DNA isolated from peripheral blood using the NGS technique. Due to the potential impact of the molecular test result on decisions regarding the scope of surgery, it should be available before the procedure. According to this, such a test should be ordered at the earliest possible stage by a clinician, not a genetic clinic. However, each patient with confirmed germline variant in the *BRCA1/2* should be subject to genetic counseling.

Procedures reducing the risk of developing cancer

In women with a mutation in the *BRCA1/2* genes, breast cancer does not preclude the possibility of developing contralateral breast cancer, ovarian cancer, primary peritoneal cancer, or pancreatic cancer. The implementation of procedures reducing the risk of cancer is, therefore, of particular importance.

Bilateral risk-reducing mastectomy (RRM) reduces the risk of breast cancer by about 90%. Mastectomy in patients already diagnosed with cancer reduces the risk of cancer of the other breast. The impact of these procedures on overall survival (OS) is ambiguous. Young patients diagnosed with early breast cancer (stages I and II) seem to benefit the most. Due to the young age, the risk of developing cancer in the other breast is higher than the risk of recurrence and spread of the primary tumor. Simultaneous reconstruction seems to be a safe procedure, and this prophylactic procedure does not require sentinel node surgery due to the low risk (below 5%) of diagnosis of breast cancer [26].

Risk-reducing salpingo-oophorectomy not only reduces the risk of ovarian cancer by about 90% but also reduces the all-cause mortality and breast/ovarian cancer related deaths in some patients (especially in women with a mutation in the *BRCA1* gene). The protective effect in the case of mutations in the *BRCA2* gene is less certain, which is mainly due to the small patient cohorts in clinical trials [27].

The time of performing RRM and RRSO depends, among others, on the patient's cancer history, family history, procreation plans, and patient's preferences. RRSO is recommended between 35 and 40 years of age in women with a mutation in the *BRCA1* gene and between 40 and 45 years of age in women with a varian in the *BRCA2* gene, which is related to ovarian cancer being delayed by 8–10 years compared to the risk in women with a mutation in the *BRCA1* gene [28].

In a phase II study in women with a mutation in the *BRCA1/2* genes who underwent treatment for breast cancer, irradiation of the other breast reduced the risk of developing cancer; however, the procedure is not generally recommended [29].

Systemic treatment

BRCA1/2 genes are involved in the repair of DNA strand breaks based on the homologous recombination mechanism. In the presence of mutations, alternative pathways protect the cell from irreversible double helix damage. Poly-ADP-ribose polymerase (PARP) is a great target for PARP inhibitors (PARPi) leading to irreversible damage to cancer cells.

The effectiveness of PARPi was first proven in patients with advanced disease in the first and subsequent treatment lines. The OlympiAD and EMBRACA trials showed a benefit in terms of extending the time to cancer progression and improving the quality of life compared to systemic treatment of investigator's choice [7.0 *vs.* 4.2 months; hazard ratio (HR) = 0.58; 95% confidence interval (CI) 0.43–0.8; $p < 0.001$] and (8.6 *vs*. 5.6 months; HR = 0.4; 95% CI 0.41–0.71; $p < 0.001$), respectively. No increase in overall survival was observed [30, 31].

In patients with early breast cancer with high recurrence risk, any intervention that improves prognosis is of great importance. The OlympiA study compared one-year therapy with olaparib in combination with hormone therapy and zoledronic acid with placebo in patients after surgery and completion of perioperative treatment (chemotherapy, radiotherapy). There was a statistically significant reduction in the risk of death of approximately 30% (HR = 0.68; 98.5% CI 0.47–0.97; $p = 0.009$), an improvement in the 4-year invasive disease-free survival rate [82.7% *vs.* 75.4% (Δ 7.3%; 95% CI 3.0–11.5%)] and the 4-year metastasis-free survival rate [86.5% *vs.* 79.1% (Δ 7.4%; 95% CI 3.6–11.3%)] [32].

Platinum derivatives in combination with chemotherapy based on anthracyclines and taxanes in HER2-negative breast cancer patients in stages II and III and with mutations in *BRCA1/2* genes are the standard of care in neoadjuvant treatment, regardless of the mutation status in these genes. Achieving a complete response confirmed by pathomorphological examination was associated with a reduction in recurrence risk, also regardless of the patient's genetic burden [33].

The effectiveness of platinum derivatives in patients with advanced breast cancer is similar to that of docetaxel, which is one of the most active drugs in breast cancer. The results of the TNT study confirm that women with mutations in the *BRCA1/2* genes are particularly platinum-sensitive, with an objective response rate (ORR) 2-fold higher than with docetaxel (68% *vs*. 33%; $p = 0.01$). The time to cancer progression was also longer in patients receiving carboplatin (6.8 *vs.* 4.4 months; $p = 0.002$) but without OS prolongation [34].

Contraception

Family planning is one of the elements of care for women with a mutation in the *BRCA1/2* genes and applies to healthy people and those diagnosed with cancer. Removal of the ovaries should be planned after the pedigree analysis, but also after the completion of procreation plans. Patients with ovarian cancer at a young age should consider early motherhood, and cooperation among a gynecologist, oncologist, geneticist, and reproductive medicine specialist is extremely important in their case [35].

Hormonal contraception reduces the risk of ovarian cancer, but its protective effect is not comparable to the effect of RRSO. Data on the impact of hormonal contraception on breast cancer risk are ambiguous — it seems that this risk be higher if it is used before the age of 20 or if the patient develops cancer at a young age [36].

In women with mutations in the *BRCA1/2* genes who developed breast cancer, hormonal contraception is not

recommended regardless of cancer biological subtype, which also applies to patients diagnosed with triple-negative breast cancer. A safe option is hormone-free or barrier contraception (condom, cervical cap, hormone-free intrauterine device) used during treatment and for a certain period after treatment (depending on the therapy used, e.g. for 12 months after chemotherapy, 7 months after trastuzumab, 3 months after hormone therapy, and 5 months after immunotherapy).

Fertility protection

Pregnancy after breast cancer treatment is possible and safe, regardless of the biological subtype of cancer or presence of mutations in the *BRCA1/2* genes. In cancer patients, however, it requires appropriate planning in relation to the treatment, the risk of cancer recurrence, and the patient's age and preferences. Some reports indicate a better prognosis for patients who become pregnant after anti-cancer treatment; this has been called the "healthy mother effect" [37].

The first data from the POSITIVE trial indicate the safety of discontinuing adjuvant hormone therapy to realize maternity plans. Most of the patients participating in the study were diagnosed with early-stage breast cancer (I–II). Patients who gave birth within a planned interval had a lower risk of recurrence than those who did not become pregnant. The treatment interruption itself, which was a maximum of 2 years, did not reduce the effectiveness of therapy. Some patients benefited from assisted reproductive methods. Observations are certainly promising, but patients require further follow-up [38].

It should be remembered that cancer treatment may lead to permanent or reversible infertility. The gonadotoxic effect of chemotherapy depends on the treatment used, patient's age, and initial ovarian reserve. In patients with estrogen-dependent cancer, adjuvant hormone therapy is used for 5–10 years. Treatment alone does not increase the risk of premature ovarian failure, but it postpones the possibility of becoming pregnant, which in some patients over 30 years of age may preclude motherhood. In the treatment of patients with early triple-negative breast cancer in certain stages, in addition to chemotherapy, perioperative immunotherapy is also used. Immune checkpoint inhibitors can lead to primary or secondary hypogonadism and infertility. Some patients may experience late effects of immunotherapy. Currently, there are no known factors that would allow oncologists to select a group of patients who will develop infertility caused by immunotherapy.

Some studies indicate worse ovarian reserve at baseline in women with mutations in the *BRCA1/2* genes, which is an additional argument for the need to consult patients with a reproductive medicine specialist before starting anticancer treatment. Fertility protection gives patients a chance for motherhood after treatment completion [39].

The basic method of fertility preservation in women with mutations in the *BRCA1/2* genes is cryopreservation of oocytes or embryos, which requires hormonal stimulation. The whole process lasts from 2 to 3 weeks, which slightly postpones the start of anti-cancer treatment. During the stimulation, tamoxifen or an aromatase inhibitor is used, effectively lowering the level of endogenous estrogens. If the patient has a partner, it is possible to fertilize eggs with sperm and then cryopreserve embryos. Preimplantation diagnostic techniques allow for the examination of embryos before implantation into the uterine cavity and selecting only those that are free of mutations in *BRCA1/2* genes. The availability of this procedure in Poland is very limited, but the test itself is an important option for women with mutations in the *BRCA1/2* genes [40].

Another fertility preservation procedure is excision of ovarian tissue and its freezing, followed by ortho- or heterotopic reimplantation after treatment. The advantage of this method is the possibility of natural pregnancy and return of hormonal activity. Cryopreservation of ovarian tissue is rarely chosen in women with *BRCA1/2* gene mutations who are at high risk of developing ovarian cancer. Despite performing appropriate diagnostic tests before tissue freezing, there is a risk of reimplantation of cancer cells with ovarian tissue. Therefore, the method can be considered when it is not possible to use the freezing of oocytes or embryos [41].

An important option to supplement the basic methods of fertility preservation is using gonadoliberin analogs during perioperative chemotherapy, which reduces the risk of premature ovarian failure and increases the chance of pregnancy after treatment [42].

Conclusions

In the population of Polish breast cancer patients, mutations in the *BRCA1/2* genes are most often germline variants. Genetic diagnosis at an early stage of cancer is of great importance for the patient and her family. The implementation of an appropriate surgical treatment, which most often consists of bilateral mastectomy with or without reconstruction and systemic therapy in the case of early or advanced disease, is associated with an improvement in patients' prognosis. Appropriate treatment, procedures reducing the risk of cancer, planning children, and contraception require proper preparation of several specialists engaged in the care of a patient with a mutation in the *BRCA1/2* genes, regardless of her previous cancer history. It is essential

to conduct molecular diagnostics in strictly defined populations of patients, in whom the risk of mutations in *BRCA1/2* genes is relatively high. Appropriate methodology used for molecular tests, correct qualification of genetic variants detected in *BRCA1/2* genes, as well as consultation with a clinical geneticist while deciding further procedures are equally important.

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