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REVIEW ARTICLE

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Clinical and economic benefits of using next-generation sequencing (NGS) 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.

Key words: 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).

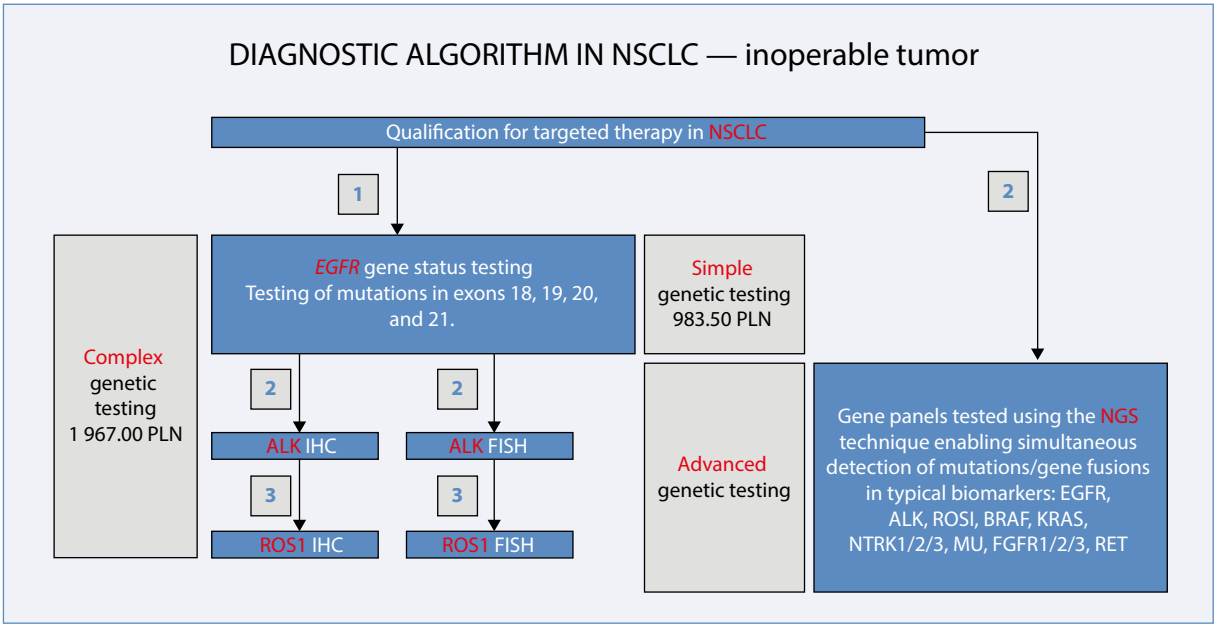

Figure 1. Diagnostic algorithm for patients with inoperable non-small cell lung cancer (NSCLC); NGS — next-generation sequencing

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

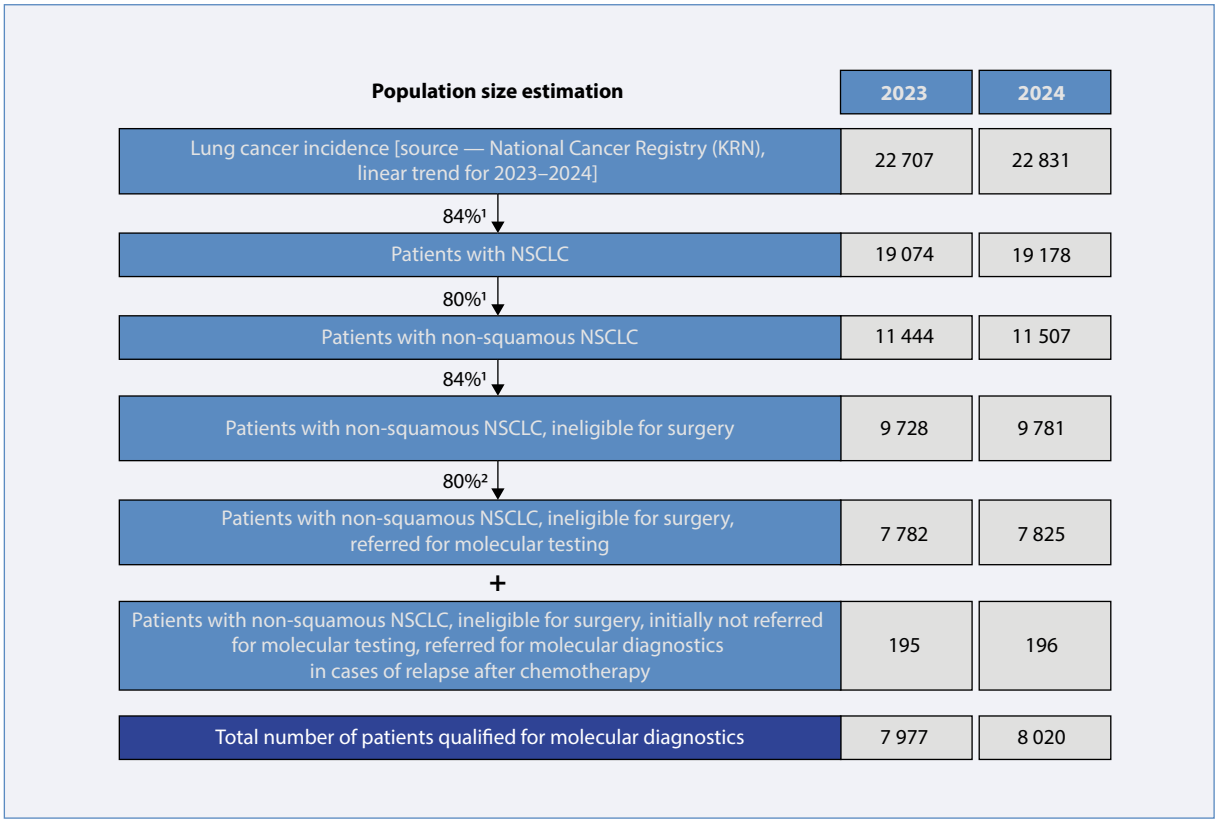

Figure 2. Estimating the size of target population in 2023–2024; 1Based on [17]; 2Data based on clinical expert opinion in Poland; NSCLC — non-small cell lung cancer

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.Dą, 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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