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Recommendations of the Expert Panel and the Polish Lung Cancer Study Group on the use of chemotherapy in combination with osimertinib for treatment of non-small cell lung cancer patients with pathogenic variants of the *EGFR* gene

Introduction

Non-small cell lung cancers (NSCLC) account for approximately 85% of primary lung cancers, and about 15% of patients are diagnosed with small cell lung cancer (SCLC) [1, 2]. The division into NSCLC and SCLC has a prognostic significance due to the different clinical courses and outcomes.

The management of NSCLC patients depends mainly on the clinical stage of the disease. The most effective treatment method is still lung parenchyma resection; however, only 15–20% of patients in Poland are eligible for surgery. In other cases, the decision-making process about therapy should additionally involve considering the histological type of the cancer and the patient's performance status (PS) [3, 4].

The emergence of new treatment methods, primarily the introduction of molecularly targeted drugs and immune checkpoint inhibitors (ICIs), has significantly changed the principles of pathomorphological, molecular, and immunological diagnostics and influenced treatment of NSCLC patients [5, 6].

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Pathomorphological diagnostics in qualification for treatment with EGFR tyrosine kinase inhibitors in combination with chemotherapy in NSCLC patients

The main factors that determine the choice of a diagnostic path remain the morphological type of the cancer and the clinical stage of the disease.

The diagnostic algorithm in advanced and inoperable NSCLC requires defining the type histological of cancer and — depending on the diagnosis — performing predictive immunohistochemical tests. In addition, the material should be secured for further molecular assays to determine predictive factors, allowing optimal treatment choice [4, 6, 7].

The most common type of NSCLC is adenocarcinoma, which currently accounts for about 50% of cases; the second most common type is squamous cell carcinoma, diagnosed in about 20% of patients [7]. The histological classification of both types is based on strictly defined morphological criteria in standard hematoxylin-eosin (H+E) staining during microscopic examination. The criterion for diagnosing adenocarcinomas is the presence of lobular, papillary, and micropapillary structures or detection of mucus in cancer cells in an additional histochemical examination [periodic acid-Schiff (PAS) with diastase and mucicarmine], while for squamous cell carcinoma — the presence of keratinization and/or so-called intercellular bridges [4, 6, 7].

The vast majority of NSCLC cases are diagnosed based on a small amount of oligobiopsy material collected during videobronchofiberoscopy using (in 40%) additional techniques, such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of mediastinal lymph nodes or pulmonary mass [3, 4, 6, 7]. Another method is transthoracic needle biopsy guided by computed tomography (CT) or ultrasonography (USG). Due to the need to establish a pathomorphological diagnosis, determine the morphological type of cancer, and secure material for predictive tests, cytological material is fixed and prepared similarly to tissue material and in the form of so-called cytoblocks.

In order to establish a comprehensive diagnosis, it is recommended to perform immunohistochemical assays using TTF-1 and p40, i.e. markers indicating the glandular and squamous subtypes, respectively [6–8].

In cases with negative reactions with anti-TTF-1 and anti-p40 antibodies, tumor is classified as NSCLC not otherwise specified (NOS). The percentage of patients diagnosed with NSCLC-NOS should not exceed 10% of all diagnosed cases [6–9]. The recommended validated fixative for pathological material is a 10% buffered formalin solution with neutral pH (7.2–7.4). Oligobiopsy samples and cytoblocks should be fixed for 6 to 48 hours, and large postoperative material for 6 to 72 hours. Due to the need to prepare collected material, especially after surgical procedures, it should be sent for pathological diagnostics before the maximum required time, preferably within 24 hours [3, 9].

The term “large cell carcinoma” should not be used in the pathology report from oligobiopsy and cytological material evaluation, as it is a morphological form of NSCLC reserved for cases diagnosed on the basis of postoperative material.

Similarly, the term “ non-squamous non-small cell carcinoma” is not a pathological diagnosis.

In patients with adenocarcinoma or NSCLC-NOS, molecular testing is required to assess the occurrence of gene variants (primarily *EGFR*, *ALK*, *ROS1*, *KRAS*, *NTRK*) [4, 6, 9–11].

Diagnostics of *EGFR* gene variants in qualification for treatment with EGFR tyrosine kinase inhibitors (TKIs)

The *EGFR* gene is located on the short arm of chromosome 7, and its exons 18 to 21 encode a tyrosine kinase located in the intracellular part of the receptor. The tyrosine kinase is responsible for phosphorylation of subsequent signaling proteins in the intracellular pathway, which leads to cell activation and proliferation. Pathogenic variants in exons 18–21 lead to excessive tyrosine kinase activity and tumor development. In addition, a therapeutic target is emerging, which is blocking the binding of adenosine triphosphate (ATP) to *EGFR* tyrosine kinase by small-molecule EGFR tyrosine kinase inhibitors (TKIs) [12–14].

Exon 19 deletions and p.Leu858Arg (L858R) substitution occur in 45–50% and 35–40% of NSCLC patients with *EGFR* gene mutations, respectively. Rare *EGFR* variants include exon 20 insertions and substitutions in codons 719 and 768 of exon 18, as well as in codon 861 of exon 21. The p.Thr790Met (T790M) mutation in exon 20 most frequently occurs in patients with progression during treatment with first- or second-generation EGFR TKIs. The frequency of *EGFR* gene pathogenic variants in Caucasian patients with lung adenocarcinoma ranges from 8 to 15% [13, 14].

A decision to perform molecular tests is made after determining the number and percentage of cancer cells. Testing performed in materials containing 5% or less of cancer cells is usually unreliable.

The introduction of sensitive methods to molecular diagnostics, e.g., droplet digital polymerase chain reaction (ddPCR), has enabled the testing of *EGFR* gene variants in liquid biopsy (peripheral blood, pleural fluid, and other body fluids). A negative result of liquid biopsy should be confirmed in tissue material. Liquid biopsy testing is the most commonly used in detecting p.Thr-790Met mutation in patients with resistance to EGFR TKI therapy [13, 15].

There are two standard methods for diagnosing *EGFR* variants, and their choice depends on the quality and quantity of sampled material, time required for diagnostics, and availability of appropriate equipment.

The real-time polymerase chain reaction (rt-PCR) is still quite commonly used in Poland to diagnose *EGFR* variants. It uses molecular probes complementary to the changed and unchanged gene fragment, and the amplification of the mentioned fragments is confirmed by an increase in fluorescence intensity observed in real time on the computer screen. However, this method has many disadvantages. Molecular probes are complementary to precisely selected gene fragments in which the most common mutations occur. Therefore, the rt-PCR technology identifies only the known and most common variants. There are many more pathogenic variants in the *EGFR* gene, and PCR tests may not detect rare exon 19 deletions, and exon 20 insertions or substitutions. In addition, rt-PCR allows for testing for mutations in only one gene. Other abnormalities (e.g., *ALK* and *ROS1* or *KRAS* and *NTRK* variants) must be diagnosed in separate tests, which leads to a reduction in the amount of available tissue material. Moreover, the rt-PCR method does not detect variants in other genes that may also qualify for molecularly targeted therapy [15, 16].

The next-generation sequencing (NGS) method is currently becoming the standard in molecular diagnostics of NSCLC. This technology is designed to simultaneously detect multiple molecular markers. NGS is used to evaluate from a dozen to several dozen or several hundred genes (target sequencing, comprehensive genomic profiling); it is even possible to evaluate the entire exome of coding sequences [whole exome sequencing (WES)] or the genome [whole genome sequencing (WGS)]. This method allows for the detection of point changes, deletions, insertions, amplifications, and gene fusions, as well as genomic signatures (microsatellite instability, assessment of homologous recombination deficiency, and tumor mutational burden). It is also possible to simultaneously amplify millions of gene fragments in one series, which ensures huge test throughput. The NGS method also offers the detection of new or rare genetic variants [15, 16].

Next-generation sequencing technology in NSCLC diagnostics enables fast (turnaround time is about 2 weeks) and simultaneous qualification of patients for various molecularly targeted therapies. The aforementioned test should be supplemented by assessing the programmed death-ligand 1 (PD-L1) expression using the immunohistochemical (IHC) method. However, NGS technology also has some limitations. First of all, it requires very good quality of tested material. Bioinformatic analysis is extremely important. NGS can detect pathogenic variants of the tested genes, but also variants without mutagenic effects or variants of uncertain significance (VUS). Only an experienced team of diagnosticians can use NGS in the diagnosis of abnormalities in patients with NSCLC [15, 16].

Diagnostics of molecular variants in NSCLC patients in Poland — according to drug program B.6 — must be performed in a laboratory with an external quality control certificate for a given test.

In the FLAURA2 study discussed later, *EGFR* gene variants were assessed in the local laboratories of each center using NGS or rt-PCR.

Analysis of the FLAURA study

The results of the FLAURA study confirmed the value of osimertinib in the first-line treatment of patients with advanced non-squamous NSCLC with exon 19 deletion or L858R mutation in exon 21 of the *EGFR* gene and determined the place of this drug in the therapy algorithm of this patient population [17]. The FLAURA 2 study aimed to assess the value of combining osimertinib with platinum-based chemotherapy compared to osimertinib alone [18]. The study included 557 patients with stage IIIB–IVB non-squamous NSCLC, previously not receiving systemic treatment for advanced disease. Patients with prior radical-intent treatment were also eligible if at least 12 months had passed from documented relapse of the disease. Patients were randomly assigned to the control arm, which received osimertinib at a dose of 80 mg/day, or the experimental arm, which received osimertinib at a dose of 80 mg/day and 4 cycles of chemotherapy [cisplatin at a dose of 75 mg/m^2 or carboplatin at a dose calculated based on the area under the curve (AUC) of 5 (AUC = 5)] in combination with pemetrexed 500 mg/m^2, followed by maintenance pemetrexed plus osimertinib). In both arms, treatment was continued until disease progression or unacceptable toxicity. A summary of the characteristics of the study group is presented in Table 1 [18].

Table 1. Characteristics of the FLAURA 2 study population [18]

	Osimertinib plus chemotherapy (n = 279)	Osimertinib (n = 278)
Age, median (range)	61 (26–83)	62 (30–85)
Sex, n (%)		
Male	106 (38)	109 (39)
Female	173 (62)	169 (61)
Ethnicity, n (%)		
Asian	179 (64)	176 (63)
Caucasian	74 (27)	83 (30)
Other	26 (10)	19 (7)
WHO performance status		
0	104 (37)	102 (37)
1	174 (62)	176 (63
2	1 (< 1)	0
EGFR gene variants		
Del19	169 (61)	168 (60)
p.Leu858Arg (L858R)	106 (38)	107 (38)
CNS metastases	116 (42)	110 (40)
Liver metastases	43 (15)	66 (24)
Bone metastases	132 (47)	142 (51)

CNS — central nervous system; Del — deletion; WHO — World Health Organization

The primary endpoint of the study was progression-free survival (PFS). At the time of the first data analysis, the median follow-up in the experimental arm was 19.5 months compared to 16 months in the control arm. The combination treatment was shown to be superior in terms of the primary endpoint. In patients receiving osimertinib with chemotherapy, median PFS was 25.5 months, while in the control group, it was 16.7 months [hazard ratio (HR) = 0.62; 95% confidence interval (CI) 0.49–0.79; p < 0.001] [18]. The authors also observed a higher percentage of patients remaining progression-free after 24 months from treatment initiation (57% *vs.* 41%, respectively). The subgroup analysis showed a greater reduction in the risk of disease progression in patients with central nervous system (CNS) metastases at the time of enrollment who received osimertinib in combination with chemotherapy. The PFS benefit was observed in patients with both exon 19 deletion and exon 21 substitution in the *EGFR* gene. In patients with exon 19 deletion, the median PFS rate was 27.9 months in the osimertinib plus chemotherapy group and 19.4 months in the arm receiving osimertinib monotherapy. In patients with the L858R mutation, it was 24.7 and 13.9 months, respectively [18]. In patients with CNS metastases at baseline, the median PFS rate was 24.9 months in the group receiving osimertinib with chemotherapy and only 13.8 months in the control group (HR = 0.47; 95% CI 0.33–0.66). In patients without CNS metastases, the median PFS rate was 27.6 and 21.0 months, respectively (HR = 0.75; 95% CI 0.55–1.03) [18]. Objective response (complete or partial) was observed in 83% of patients in the group receiving osimertinib with chemotherapy and 76% of patients in the group treated with osimertinib alone. The median duration of response was 24.0 (95% CI 20.9–27.8) and 15.3 months (95% CI 12.7–19.4), respectively [18].

It should be noted that in the FLAURA 2 study, CNS magnetic resonance imaging was mandatory in the screening period and during the treatment phase. Patients with clinical and/or radiological features of spinal cord compression were not enrolled. Patients with local treatment for symptomatic CNS metastases before qualification for the FLAURA 2 study could be included provided they had stable neurological status and had not taken glucocorticosteroids for at least 14 days. Patients with asymptomatic CNS metastases did not require initial local treatment. CNS metastases were confirmed in 40% of patients in the entire study population. In patients with at least one measurable lesion in the CNS (14% of patients in both arms), a significant reduction in the risk of intracranial progression was demonstrated in the group receiving combined treatment (HR = 0.40; 95% CI 0.19–0.84) [19]. The 24-month intracranial PFS rate was 65% and 37%,

Table 2. Treatment-related adverse events [18]

Adverse event	Osimertinib + chemotherapy		Osimertinib	
	Total number (%)	≥ G3 number (%)	Total number (%)	≥ G3 number (%)
Anemia	128 (46)	55 (20)	22 (8)	1 (< 1)
Diarrhea	120 (43)	8 (3)	112 (41)	1 (< 1)
Nausea	119 (43)	4 (1)	28 (10)	–
Rash	78 (28)	1 (< 1)	57 (21)	–
Fatigue	76 (28)	8 (3)	26 (9)	1 (< 1)
Vomiting	73 (26)	3 (1)	17 (6)	–
Stomatitis	68 (25)	1 (< 1)	50 (18)	1 (< 1)
Neutropenia	68 (25)	30 (11)	9 (3)	2 (1)
ALT increase	56 (20)	4 (1)	21 (8)	1 (< 1)
Thrombocytopenia	51 (18)	16 (6)	12 (4)	3 (1)
AST increase	48 (17)	1 (< 1)	13 (5)	1 (< 1)

ALT — alanine transaminase; AST — aspartate aminotransferase; G — grade

respectively. In the entire group of patients with secondary CNS lesions (measurable and non-measurable), a non-significant reduction in the risk of intracranial progression was observed in the arm receiving osimertinib in combination with chemotherapy (HR = 0.58; 95% CI 0.33–1.01) [18].

Treatment-related adverse event (TRAE) rate was higher in patients receiving osimertinib in combination with chemotherapy. The percentage of patients with grade 3 or higher complications was 64% (combination therapy) and 27% (monotherapy). Serious adverse events occurred in 38% and 19% of patients, respectively. Discontinuation of one of the drugs due to adverse events was necessary in 48% and 6% of patients, respectively. The adverse events reported in the study are presented in Table 2 [18].

At the time of analysis, median overall survival (OS) was not reached in the experimental or control arms. In the combination arm, 100% of patients survived at 12 months, whereas in the osimertinib-only arm, the 12-month OS rate was 89%. No difference in the reduction of the risk of death has been observed between the arms to date (HR = 0.90; 95% CI 0.65–1.24; p = 0.52) [18].

Guidelines and recommendations for qualification and treatment

Osimertinib used as monotherapy has remained a valuable treatment option for several years in patients with advanced NSCLC with activating variants in the *EGFR* gene. The results of the FLAURA 2 study justify individualization of treatment depending on the location of secondary lesions and disease burden and dynamics. The combination of osimertinib with platinum-based chemotherapy may be considered in patients in advanced disease stages with the presence of multi-organ lesions (also in patients with CNS metastases) if they are in good general condition, have good performance status, with functional parameters within the normal range [20]. The eligibility criteria include good performance status [0–1 according to the Eastern Cooperative Oncology Group (ECOG) score] and satisfactory organ function parameters, as well as confirmed presence of a pathogenic *EGFR* variant (only exon 19 deletions or exon 21 substitution).

The treatment regimen, according to the FLAURA 2 study protocol, assumes the use of 4 cycles of platinum-based chemotherapy (cisplatin or carboplatin is used according to the toxicity profile and individual clinical characteristics) followed by maintenance therapy with pemetrexed. Osimertinib is used at a dose of 80 mg/day from the first day of the 1st cycle of chemotherapy. Assessment of therapeutic efficacy should be performed every 6 weeks during the initial treatment phase and every 12 weeks thereafter. Imaging should include the chest with assessment of the upper abdominal structures and CNS, and the remaining areas should be assessed according to the patient's situation.

Due to a higher risk of neutropenia (grade 3/4), primary prophylaxis with granulopoiesis-stimulating factors should be considered in patients receiving platinum-based chemotherapy and osimertinib. It is recommended

to use long-acting granulopoietins (pegylated) within 24 to 48 hours after chemotherapy cessation. Prophylaxis of febrile neutropenia during maintenance therapy with pemetrexed is not recommended [21].

Oligometastatic disease

The use of radiotherapy in patients with stage IV NSCLC has evolved over the last few years, especially in the oligometastatic form. Oligometastatic disease is a generalized disease with the presence of up to 5 metastatic lesions located in up to three organs, in addition to the primary lesion that can be effectively treated locally [22]. Consolidating local treatment in NSCLC patients with up to 3 metastatic lesions without progression after first-line systemic treatment extended PFS almost 3-fold (median — 4.4 *vs.* 14.2 months) and OS (median — 17.0 *vs.* 41.2 months) [23]. The recently published results of the phase III CURB study indicate that stereotactic body radiation therapy (SBRT) of lesions associated with oligoprogression in NSCLC patients undergoing systemic treatment leads to extended PFS (2.2 *vs.* 10.0 months) with an acceptable side-effect profile [24]. Grade 2 or higher toxicity associated with SBRT occurred in 16% of patients [24].

The benefit of adding local treatment may be particularly visible in NSCLC patients with *EGFR*-activating variants [25, 26]. The results of the SINDA study support the use of SBRT for all disease sites before treatment with first-generation EGFR TKIs [27]. The use of SBRT in 5 fractions up to a total dose of 25–40 Gy (depending on the location and volume of lesions) has prolonged PFS (median — 12.5 *vs.* 20.2 months) and OS (median — 17.4 *vs.* 25.5 months), with acceptable toxicity (grade 3/4 pneumonitis according to the Common Toxicity Criteria for Adverse Events [CTCAE] classification in 6% of patients) [27]. The use of consolidating local treatment (surgery or radiotherapy) after 6–12 weeks of osimertinib treatment is currently being evaluated in the prospective NORTHSTAR study [25]. Due to the possibility of achieving regression after systemic anti-EGFR treatment and limiting the toxicity of SBRT, associated with a smaller volume of irradiated lesions, it is reasonable to use SBRT after 2–6 months from TKI treatment initiation [28]. The above-mentioned strategy is consistent with the protocols of numerous ongoing studies on oligometastatic disease [28]. Additionally, SBRT of bone lesions more often leads to complete pain relief compared to standard palliative radiotherapy [29].

The use and sequencing of fractionated SBRT in anti-EGFR therapy in patients with brain metastases is still under discussion [28, 30, 31]. In patients with asymptomatic and small CNS metastases who are receiving anti-EGFR therapy with high CNS penetration, fractionated SBRT may be deferred [30]. Although there is no consensus on the optimal way to combine SBRT with anti-EGFR drugs, most experts do not recommend administering them on the same day; a weekly interval is most commonly suggested [31].

Conclusions

The combination of osimertinib with platinum-based chemotherapy (cisplatin or carboplatin) and pemetrexed is a new option for first-line treatment in patients with metastatic NSCLC with a pathogenic *EGFR* variant (exon 19 deletions or exon 21 substitution). Patients who benefit from this therapy also include those with CNS metastases (asymptomatic or after local treatment), high disease dynamics, and a higher number of metastases. A very good or good performance status is an absolute prerequisite for starting treatment. Due to the risk of at least grade 3 neutropenia, primary prophylaxis with granulopoietin is recommended during platinum-based chemotherapy. In the case of adverse events that prevent the use of chemotherapy, it is possible to continue treatment with osimertinib in monotherapy.

Article Information and Declarations

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Supplementary materials

None.

References

1. Houston KA, Mitchell KA, King J, et al. Histologic Lung Cancer Incidence Rates and Trends Vary by Race/Ethnicity and Residential County. J Thorac Oncol. 2018; 13(4): 497–509, doi: 10.1016/j.jtho.2017.12.010, indexed in Pubmed: 29360512.
2. Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer staging project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eight edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016; 11: 300–311.
3. Postmus PE, Kerr KM, Oudkerk M, et al. ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 28(suppl_4): iv1–iv21, doi: 10.1093/annonc/mdx222, indexed in Pubmed: 28881918.
4. Planchard D, Popat S, Kerr K, et al. ESMO Guidelines Committee. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29(Suppl 4): iv192–iv237, doi: 10.1093/annonc/mdy275, indexed in Pubmed: 30285222.
5. Lindeman N, Cagle P, Aisner D, et al. Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors. J Thorac Oncol. 2018; 13(3): 323–358, doi: 10.1016/j.jtho.2017.12.001.
6. Nicholson AG, Tsao MS, Beasley MB, et al. The 2021 WHO Classification of Lung Tumors: Impact of Advances Since 2015. J Thorac Oncol. 2022; 17(3): 362–387, doi: 10.1016/j.jtho.2021.11.003, indexed in Pubmed: 34808341.
7. WHO Classification of Tumours Editorial Board. Thoracic Tumours. WHO classification of tumours series, 5th ed.; vol. 5. International Agency for Research on Cancer, Lyon 2021.
8. Yatabe Y, Dacic S, Borczuk AC, et al. Best Practices Recommendations for Diagnostic Immunohistochemistry in Lung Cancer. J Thorac Oncol. 2019; 14(3): 377–407, doi: 10.1016/j.jtho.2018.12.005, indexed in Pubmed: 30572031.
9. Sholl LM, Cooper WA, Kerr KM, et al. IASLC Atlas of Molecular Testing for Targeted Therapy in Lung Cancer. IASLC Office, Denver 2023.
10. Langfort R, Szołkowska M. Ocena ekspresji białka PD-L1 w kwalifikacji do leczenia chorych z niedrobnokomórkowym rakiem płuca. Pol J Pathol. 2024; 7(1): 8–12.
11. Tsao MS, Hirsch FR, Yatabe Y. IASLC Atlas of ALK and ROS1 testing in lung cancer. Editorial Rx Press, North Fort Myers, FL 2016.
12. Tan AC, Tan DSW. Targeted Therapies for Lung Cancer Patients With Oncogenic Driver Molecular Alterations. J Clin Oncol. 2022; 40(6): 611–625, doi: 10.1200/JCO.21.01626, indexed in Pubmed: 34985916.
13. Tsubata Y, Tanino R, Isobe T. Current Therapeutic Strategies and Prospects for EGFR Mutation-Positive Lung Cancer Based on the Mechanisms Underlying Drug Resistance. Cells. 2021; 10(11), doi: 10.3390/cells10113192, indexed in Pubmed: 34831415.
14. Pretelli G, Spagnolo CC, Ciappina G, et al. Overview on Therapeutic Options in Uncommon EGFR Mutant Non-Small Cell Lung Cancer (NSCLC): New Lights for an Unmet Medical Need. Int J Mol Sci. 2023; 24(10), doi: 10.3390/ijms24108878, indexed in Pubmed: 37240224.
15. Palacín-Aliana I, García-Romero N, Asensi-Puig A, et al. Clinical Utility of Liquid Biopsy-Based Actionable Mutations Detected via ddPCR. Biomedicines. 2021; 9(8), doi: 10.3390/biomedicines9080906, indexed in Pubmed: 34440110.
16. Passiglia F, Bironzo P, Bertaglia V, et al. Optimizing the clinical management of -mutant advanced non-small cell lung cancer: a literature review. Transl Lung Cancer Res. 2022; 11(5): 935–949, doi: 10.21037/tlcr-22-1, indexed in Pubmed: 35693274.
17. Ramalingam S, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC. N Engl J Med. 2020; 382(1): 41–50, doi: 10.1056/nejmoa1913662.
18. Planchard D, Jänne P, Cheng Y, et al. Osimertinib with or without Chemotherapy in *EGFR* -Mutated Advanced NSCLC. N Engl J Med. 2023; 389(21): 1935–1948, doi: 10.1056/nejmoa2306434.
19. Jänne P, Planchard D, Kobayashi K, et al. CNS Efficacy of Osimertinib With or Without Chemotherapy in Epidermal Growth Factor Receptor–Mutated Advanced Non–Small-Cell Lung Cancer. J Clin Oncol. 2024; 42(7): 808–820, doi: 10.1200/jco.23.02219.
20. Connor Wells J, Mullin MM, Ho C, et al. Outcomes of patients with advanced epithelial growth factor receptor mutant lung cancer treated with first-line osimertinib who would not have met the eligibility criteria for the FLAURA clinical trial. Lung Cancer. 2024; 190: 107529, doi: 10.1016/j.lungcan.2024.107529, indexed in Pubmed: 38452600.
21. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008; 26(21): 3543–3551, doi: 10.1200/JCO.2007.15.0375, indexed in Pubmed: 18506025.
22. Dingemans AMC, Hendriks LEL, Berghmans T, et al. Definition of Synchronous Oligometastatic Non-Small Cell Lung Cancer-A Consensus Report. J Thorac Oncol. 2019; 14(12): 2109–2119, doi: 10.1016/j.jtho.2019.07.025, indexed in Pubmed: 31398540.
23. Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol. 2019; 37(18): 1558–1565, doi: 10.1200/JCO.19.00201, indexed in Pubmed: 31067138.
24. Tsai CJ, Yang JT, Shaverdian N, et al. Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (consolidative use of radiotherapy to block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study. Lancet. 2024; 403(10422): 171–182.
25. M.D. Anderson Cancer Center. Randomized Phase II Trial of Osimertinib With or Without Local Consolidation Therapy (LCT) for Patients With EGFR-Mutant Metastatic NSCLC (NORTHSTAR) [Internet]. clinicaltrials.gov; 2022 Sep [cited 2022 Nov 3]. Report No.: NCT03410043. https://clinicaltrials.gov/ct2/show/NCT03410043.
26. Khan TM, Verbus EA, Gandhi S, et al. Osimertinib, Surgery, and Radiation Therapy in Treating Patients with Stage IIIB or IV Non-Small Cell Lung Cancer with EGFR Mutations (NORTHSTAR). Ann Surg Oncol. 2022; 29(8): 4688–4689, doi: 10.1245/s10434-022-11627-9, indexed in Pubmed: 35527328.
27. Amini A, Rusthoven CG. Ablative Radiation Therapy for Oligometastatic EGFR-Mutated Non-small Cell Lung Cancer: Who, Why, When, and How? Int J Radiat Oncol Biol Phys. 2023; 116(3): 481, doi: 10.1016/j.ijrobp.2023.02.011, indexed in Pubmed: 37270243.
28. Bindels BJJ, Mercier C, Gal R, et al. Stereotactic Body and Conventional Radiotherapy for Painful Bone Metastases: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2024; 7(2): e2355409, doi: 10.1001/jamanetworkopen.2023.55409, indexed in Pubmed: 38345820.
29. Thomas NJ, Myall NJ, Sun F, et al. Brain Metastases in EGFR- and ALK-Positive NSCLC: Outcomes of Central Nervous System-Penetrant Tyrosine Kinase Inhibitors Alone Versus in Combination With Radiation. J Thorac Oncol. 2022; 17(1): 116–129, doi: 10.1016/j.jtho.2021.08.009, indexed in Pubmed: 34455066.
30. Fong CH, Meti N, Kruser T, et al. Recommended first-line management of asymptomatic brain metastases from EGFR mutant and ALK positive non-small cell lung cancer varies significantly according to specialty: an international survey of clinical practice. J Thorac Dis. 2023; 15(8): 4367–4378, doi: 10.21037/jtd-22-697, indexed in Pubmed: 37691657.
31. Kroeze SGC, Pavic M, Stellamans K, et al. Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC-ESTRO OligoCare consortium. Lancet Oncol. 2023; 24(3): e121–e132, doi: 10.1016/S1470-2045(22)00752-5, indexed in Pubmed: 36858728.