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STK11 AND KEAP1 MUTATIONS AS PROGNOSTIC AND PREDICTIVE MARKERS OF IMMUNOTHERAPY EFFICACY IN NON-SMALL CELL LUNG CANCER

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Abstract. *Non-small cell lung cancer remains one of the leading causes of cancer-related mortality worldwide. The introduction of immune checkpoint inhibitors has significantly improved treatment outcomes; however, the efficacy of immunotherapy remains heterogeneous, necessitating the search for new predictive biomarkers.*

Purpose – *to analyze current data on the role of STK11 and KEAP1 mutations as prognostic and predictive markers of immunotherapy efficacy in non-small cell lung cancer and their impact on the tumor immune microenvironment and treatment outcomes.*

Materials and Methods. *A literature review was conducted using the PubMed database covering the period from 2020 to 2025. Clinical studies, meta-analyses, and experimental works investigating the impact of STK11 and KEAP1 mutations on the efficacy of immune checkpoint inhibitors were selected.*

Results. *STK11 and KEAP1 mutations are detected in approximately 15-20% and 10-15% of NSCLC cases, respectively, and are associated with an unfavorable prognosis. Loss of STK11 function leads to metabolic reprogramming and the development of an immunologically "cold" microenvironment with low CD8+ T-lymphocyte infiltration. KEAP1 inactivation activates NRF2-dependent antioxidant mechanisms and suppresses interferon signaling. STK11/KEAP1 co-mutations define the most aggressive tumor subtype. The poorest outcomes are observed with PD-1/PD-L1 inhibitor monotherapy, where response rates are significantly lower and survival is reduced. Chemoimmunotherapy partially improves outcomes, whereas dual immunotherapy demonstrates moderate efficacy improvement. Combination strategies targeting metabolic resistance mechanisms and activation of innate immunity appear to be the most promising approaches.*

Conclusions. *STK11 and KEAP1 mutations are important negative prognostic and predictive markers in NSCLC that contribute to the formation of an immunosuppressive microenvironment and reduced immunotherapy efficacy. Determination of their status may improve treatment personalization and optimize therapeutic strategy selection.*

МУТАЦІЇ STK11 І KEAP1 ЯК ПРОГНОСТИЧНО-ПРЕДИКТИВНІ МАРКЕРИ ЕФЕКТИВНОСТІ ІМУНОТЕРАПІЇ ПРИ НЕДРІБНОКЛІТИННОМУ РАКУ ЛЕГЕНЬ

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Ключові слова: *недрібноклітинний рак легень, STK11, KEAP1, імунотерапія, біомаркери.*

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Резюме. *Недрібноклітинний рак легень залишається однією з провідних причин смертності від злоякісних новоутворень у світі. Впровадження інгібіторів контрольних точок імунної відповіді значно покращило результати лікування, однак ефективність імунотерапії залишається неоднорідною, що зумовлює необхідність пошуку нових предиктивних біомаркерів.*

Мета дослідження *– проаналізувати сучасні дані щодо ролі мутацій STK11 і KEAP1 як прогностично-предиктивних маркерів ефективності імунотерапії при недрібноклітинному раку легень та їх впливу на імунне мікрооточення і результати лікування.*

Матеріал і методи*. Проведено огляд літератури з використанням бази даних PubMed за період 2020–2025 років. Відібрано клінічні дослідження,*

метааналізи та експериментальні роботи щодо впливу мутацій STK11 і KEAP1 на ефективність інгібіторів контрольних точок імунної відповіді.
Результати. *Мутації STK11 і KEAP1 виявляються, відповідно, у 15–20% та 10–15% випадків НДКРЛ і асоціюються з несприятливим прогнозом. Втрата функції STK11 призводить до метаболічного перепрограмування та формування імунологічно «холодного» мікрооточення з низькою інфільтрацією CD8+ Т-лімфоцитів. Інактивація KEAP1 активує NRF2-залежні антиоксидантні механізми і пригнічує інтерфероновий сигналінг. Ко-мутації STK11/KEAP1 формують найбільш агресивний підтип пухлин. Найгірші результати спостерігаються при моноімунотерапії інгібіторами PD-1/PD-L1, де частота відповіді значно нижча, а виживаність скорочується. Імунохіміотерапія частково покращує результати, тоді як подвійна імунотерапія демонструє помірне підвищення ефективності. Перспективними є комбіновані підходи, спрямовані на метаболічні механізми резистентності та активацію вродженого імунітету.*
Висновки. *Мутації STK11 і KEAP1 є важливими негативними прогностично-предиктивними маркерами при НДКРЛ, що формують імуносупресивне мікрооточення та знижують ефективність імунотерапії. Визначення їх статусу може покращити персоналізацію лікування та вибір оптимальної терапевтичної стратегії.*

Introduction. Non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer-related mortality worldwide. According to global oncological statistics, lung cancer ranks first in mortality and accounts for approximately 18% of all cancer deaths, underscoring the substantial medical and social significance of this problem [1]. The introduction of immune checkpoint inhibitors targeting the PD-1/PD-L1 axis has substantially transformed the therapeutic approach to advanced NSCLC, providing durable responses in a subset of patients. However, the clinical efficacy of immunotherapy remains heterogeneous. Only about 20–30% of patients demonstrate an objective response to checkpoint inhibitor monotherapy, whereas a considerable proportion exhibit either primary resistance or rapidly acquired resistance [2,3]. This highlights the need to identify reliable predictive biomarkers of immunotherapy efficacy.

In clinical practice, the principal biomarkers used for selecting patients for treatment with checkpoint inhibitors include PD-L1 expression, tumor mutational burden, and microsatellite stability status. High PD-L1 expression is associated with an increased response rate; however, this marker has significant limitations, including intratumoral heterogeneity, variability in assessment methods, and the lack of universal cutoff values [2]. Moreover, clinical studies indicate that a substantial proportion of patients with high PD-L1 expression do not respond to treatment, whereas benefit from immunotherapy may also be observed in cases with low expression levels. Similarly, tumor mutational burden demonstrates only moderate predictive value and does not account for the complex interactions between the tumor and the immune system [3]. Consequently, additional genetic predictors capable of more accurately forecasting the efficacy of immunotherapy are being actively investigated.

Particular attention has been drawn to mutations in the STK11 and KEAP1 genes, which are frequently observed in lung adenocarcinoma and are associated with unfavorable clinical characteristics. The prevalence of STK11 mutations in NSCLC is approximately 15–20%, whereas KEAP1 mutations are detected in 10–15% of cases [4,5]. Both genes play key roles in the regulation of cellular metabolism and redox homeostasis. Loss of STK11 function leads to disruption of the AMPK–mTOR signaling pathway and the development of an immunologically “cold” tumor microenvironment characterized by low CD8+ T-lymphocyte infiltration. KEAP1 mutations result in activation of the NRF2 transcription factor, which promotes tumor cell adaptation to oxidative stress and is associated with suppression of interferon-dependent signaling pathways [6].

Clinical studies confirm the negative impact of STK11 and KEAP1 mutations on immunotherapy outcomes. In a retrospective analysis of patients with lung adenocarcinoma, STK11 mutations were associated with a reduced objective response rate and shorter progression-free survival during treatment with immune checkpoint inhibitors [7]. Similar findings have been reported for KEAP1 mutations, which are linked to an unfavorable prognosis regardless of PD-L1 expression levels [8]. Particularly poor outcomes are observed in cases with co-mutations of STK11/KEAP1, which are characterized by low immune cell infiltration and significantly reduced efficacy of both checkpoint inhibitor monotherapy and combination treatment regimens [9,10].

Additional evidence suggests that these mutations may contribute to the development of both primary and acquired resistance to immunotherapy. Genomic and immune profiling of tumors after progression during PD-(L)1 inhibitor treatment has demonstrated alterations in the immune microenvironment and loss of interferon signaling in tumors harboring STK11 and KEAP1 mutations [11]. These findings support their potential role as negative predictors of immunotherapy efficacy.

Thus, STK11 and KEAP1 mutations are considered promising molecular markers capable of complementing

traditional biomarkers such as PD-L1 expression and tumor mutational burden, thereby improving the personalization of treatment for patients with NSCLC. Investigating their impact is important for optimizing therapeutic strategies and overcoming resistance to immunotherapy.

The aim of this review was to analyze current data regarding the biological role of STK11 and KEAP1 mutations, their influence on the tumor immune microenvironment, and clinical outcomes associated with the use of immune checkpoint inhibitors in patients with NSCLC.

Materials and Methods. A literature review was conducted using the PubMed database covering the period from 2020 to 2025. Clinical studies, meta-analyses, and experimental works investigating the impact of STK11 and KEAP1 mutations on the efficacy of immune checkpoint inhibitors were selected.

Results and Discussion

Biological Role of STK11 and KEAP1 in Shaping the Immune Microenvironment and Resistance to Immunotherapy in NSCLC. Disruption of STK11 and KEAP1 gene function affects several key biological processes, including metabolic reprogramming of tumor cells, regulation of redox homeostasis, suppression of interferon-dependent signaling pathways, and the development of an "immune-cold" phenotype. These mechanisms contribute to the reduced efficacy of immunotherapy even in the presence of high PD-L1 expression levels [12,6].

The STK11 gene encodes the serine/threonine kinase LKB1, which is a major regulator of cellular energy balance through activation of AMPK-dependent pathways. Loss of STK11 function leads to activation of the mTOR signaling cascade, increased glycolysis, and enhanced fatty acid synthesis, thereby promoting tumor proliferation and cell survival under hypoxic conditions [12].

In addition to metabolic effects, STK11 mutations substantially influence the tumor immune microenvironment. In the study by De Giglio et al. [10], patients with STK11 mutations demonstrated a significantly lower median overall survival during first-line immunotherapy – 7.6 months compared with 15.9 months in the non-mutated group (HR 1.81; 95% CI 1.25–2.61). The authors also reported that STK11 mutations were associated with a reduced objective response rate to immunotherapy (19% vs. 35%).

Similar findings were reported by Liang et al. [7], where the presence of an STK11 mutation was associated with shorter median progression-free survival – 2.9 months compared with 5.5 months in patients without the mutation. The authors attributed this effect to the formation of an "immune-cold" microenvironment characterized by low CD8+ T-cell infiltration and reduced expression of interferon pathway–related genes.

Bioinformatic analyses have also demonstrated that STK11 mutations are associated with decreased expression of the chemokines CXCL9 and CXCL10, which are responsible for recruiting effector T lymphocytes into the tumor [13]. This leads to the development of an immunologically "cold" phenotype that responds poorly to PD-1/PD-L1 inhibitors.

The KEAP1 gene is a negative regulator of the NRF2 transcription factor, which controls the cellular response to oxidative stress. Inactivation of KEAP1 results in constitutive activation of NRF2 and increased expression of antioxidant genes such as NQO1, GCLC, and HMOX1 [14].

In the study by Scalera et al. [15], clonal KEAP1 mutations with loss of heterozygosity were associated with significantly lower CD8+ T-lymphocyte density (median 148 cells/mm² vs. 412 cells/mm² in wild-type tumors) and reduced dendritic cell infiltration. A decrease in the expression of genes related to the interferon response was also observed.

The STRIKE registry study showed that patients with KEAP1 mutations had a median overall survival of 6.4 months compared with 12.6 months in patients without mutations [4]. These findings confirm the negative prognostic role of KEAP1 and its impact on tumor biology.

Activation of NRF2 also promotes metabolic reprogramming, including enhancement of the pentose phosphate pathway, increased glutathione synthesis, and elevated detoxification capacity of tumor cells. These changes enable tumors to evade immune-mediated destruction and contribute to resistance to therapy [14].

Co-mutations of STK11 and KEAP1 define the most aggressive molecular subtype of NSCLC. In the study by Sun et al. [9], patients with KRAS/STK11/KEAP1 co-mutations had a median overall survival of 5.4 months during immunotherapy, compared with 17.3 months in patients without these mutations. The objective response rate was only 8%.

Shrestha et al. [6] demonstrated that KEAP1/STK11 co-mutations generate a redox phenotype accompanied by suppression of STING and MDA5 expression and a more than 2.5-fold reduction in type I interferon production. This leads to the development of a T-cell–excluded microenvironment with minimal infiltration of effector immune cells.

STK11 and KEAP1 mutations are also associated with alterations in systemic immune response. In the study by Proulx-Rocray et al. [16], patients harboring these mutations had a higher neutrophil-to-lymphocyte ratio (NLR ≥5) in 61% of cases compared with 34% in the non-mutated group. Elevated NLR was associated with shorter survival (HR 1.74).

The study by Gandhi et al. [17] showed that deletions of STK11 and KEAP1 were detected in approximately 7% and 5% of patients, respectively. Patients with copy number losses demonstrated a lower response rate to immunotherapy (12% vs. 28%) and shorter median progression-free survival – 2.1 months compared with 5.8 months.

Co-mutations of KRAS/STK11 or KRAS/KEAP1 are associated with decreased expression of immune response–related genes. Tumors harboring these co-mutations exhibited more than a threefold reduction in CXCL10 expression and lower CD8+ T-cell infiltration [13].

Thus, STK11 and KEAP1 mutations lead to a complex

spectrum of biological alterations: metabolic reprogramming of tumor cells, activation of antioxidant mechanisms, suppression of interferon-dependent signaling pathways, reduced CD8+ T-lymphocyte infiltration, development of an "immune-cold" phenotype, and emergence of both primary and acquired resistance to immunotherapy. These findings underscore the importance of determining STK11 and KEAP1 status as biological prognostic markers and potential targets for combined therapeutic strategies in NSCLC.

Impact of STK11 and KEAP1 Mutations on the Efficacy of Different Treatment Regimens. Mutations in the STK11 and KEAP1 genes significantly influence treatment outcomes in patients with NSCLC, particularly in the context of immune checkpoint inhibitor therapy. Their biological role in shaping an immunosuppressive microenvironment leads to reduced efficacy of both immunotherapy monotherapy and combination treatment strategies. However, the magnitude of the negative impact varies depending on the treatment regimen, supporting the need for a differentiated therapeutic approach for such patients [18,3].

The most pronounced negative effect of STK11 and KEAP1 mutations is observed with PD-1/PD-L1 inhibitor monotherapy. In a study including patients with metastatic NSCLC and KRAS mutations, the presence of STK11/KEAP1 co-mutations was associated with the poorest outcomes. Median overall survival was only 5.4 months in patients with co-mutations compared with 17.3 months in those without. The objective response rate was 8% versus 36%, respectively, regardless of PD-L1 expression levels [9].

Similar results were demonstrated in another study, where the median progression-free survival with immunotherapy monotherapy in patients with STK11 mutations was 2.9 months, compared with 5.5 months in patients without mutations. For KEAP1 mutations, these values were even lower – 2.1 months. The disease control rate in the KEAP1-mutated group was only 24%, confirming the role of these mutations as negative prognostic factors [7].

In the study by Scalera et al. [8], patients with clonal KEAP1 mutations had a significantly lower response rate to immunotherapy – 10% versus 29% in the wild-type group – as well as shorter median survival (6.0 vs. 13.2 months). This finding was attributed to low CD8+ T-lymphocyte infiltration and suppression of interferon signaling pathways.

Furthermore, STK11 and KEAP1 mutations also play a role in the development of acquired resistance to immunotherapy monotherapy. In 32% of patients with disease progression after PD-(L)1 blockade, mutations in these genes were either retained or newly emerged, accompanied by decreased T-cell infiltration and reduced expression of interferon pathway genes [11]. Thus, most studies indicate that immunotherapy monotherapy is the least effective treatment strategy for patients with STK11 and KEAP1 mutations.

The combination of immunotherapy with chemotherapy partially improves treatment outcomes in patients with STK11 and KEAP1 mutations; however, efficacy remains lower compared with patients without mutations. Patients with copy number losses of STK11 or KEAP1 exhibit a lower objective response rate to chemoimmunotherapy – 18% versus 34% in the wild-type group. Median progression-free survival was 3.4 months versus 6.2 months, respectively [17].

Another study also demonstrated that even with chemoimmunotherapy, STK11 mutations remained an independent negative prognostic factor. Median overall survival was 9.3 months in patients with the mutation compared with 18.4 months in those without [10].

Moreover, STK11 and KEAP1 mutations belong to the group of "non-activating" alterations that have prognostic significance and are associated with lower efficacy of combination regimens. The response rate to chemoimmunotherapy in patients with mutations was 21% compared with 39% in the wild-type group [3]. Nevertheless, the addition of chemotherapy may partially overcome the immunosuppressive microenvironment by inducing immunogenic cell death and enhancing tumor antigen presentation [19].

Dual immunotherapy (combination of anti–PD-1/PD-L1 with anti–CTLA-4) is considered a potentially more effective strategy for overcoming resistance associated with STK11 and KEAP1 mutations. Combined checkpoint blockade may activate both peripheral and intratumoral immune responses, partially compensating for the "immune-cold" phenotype [20].

Some authors report that dual immunotherapy increases response rates to 25–30% in patients with STK11/KEAP1 mutations compared with 8–15% with immunotherapy monotherapy. However, median survival remains lower than in patients without mutations [14]. TCGA analyses suggest that the efficacy of dual immunotherapy may depend on the tumor immune subtype. Patients with an interferon-active subtype demonstrate better responses, whereas "immune-desert" tumors harboring STK11/KEAP1 mutations remain resistant [20].

Given the limited efficacy of standard regimens, novel therapeutic strategies for patients with STK11 and KEAP1 mutations are being actively investigated. One promising approach involves targeting metabolic pathways. NRF2 activation in tumors harboring KEAP1 mutations renders them dependent on glutathione metabolism, creating opportunities for the use of redox-system inhibitors. Another strategy involves combining immunotherapy with STING inhibitors or agonists of innate immunity. Activation of STING may restore type I interferon production and increase CD8+ T-cell infiltration in tumor models with KEAP1/STK11 mutations [6].

Combining immunotherapy with KRAS-targeted therapies is also considered promising. Since KRAS/STK11 or KRAS/KEAP1 co-mutations are associated with resistance, combined inhibition of KRAS and immune checkpoints may improve treatment outcomes [21].

Additional approaches under investigation include the use of antioxidant modifiers, mTOR inhibitors, and metabolically modulating agents. Combination regimens

are thought to increase response rates to approximately 35% in previously resistant tumors [14].

Thus, STK11 and KEAP1 mutations significantly affect the efficacy of different treatment regimens in NSCLC. The poorest outcomes are observed with immunotherapy monotherapy. Chemoimmunotherapy partially improves results, although median survival remains reduced. Dual immunotherapy demonstrates moderate improvements in efficacy, whereas novel combination approaches targeting metabolic and immune resistance mechanisms represent the most promising therapeutic direction for patients with STK11 and KEAP1 mutations.

Practical Implications for Clinical Practice. Determination of STK11 and KEAP1 mutations is becoming increasingly important in the clinical management of patients with NSCLC, particularly in the absence of driver oncogenic alterations. Although these mutations are not classical therapeutic targets, they have important prognostic and potentially predictive value that may influence the selection of the optimal therapeutic strategy. Clinical studies demonstrate that the presence of STK11 or KEAP1 mutations is associated with reduced efficacy of immunotherapy – especially in the monotherapy setting – as well as less favorable outcomes with combination approaches [7,9,10].

The issue of routine testing for STK11 and KEAP1 remains controversial. On one hand, these mutations lack direct therapeutic targets, which limits their use as classical predictive biomarkers. On the other hand, accumulating evidence indicates significant prognostic value. Inclusion of STK11 and KEAP1 in next-generation sequencing panels provides additional information regarding expected response to immunotherapy and the risk of early progression [22]. In clinical practice, this is particularly important for patients with high PD-L1 expression, in whom immunotherapy monotherapy is traditionally considered the standard first-line option. The presence of STK11 or KEAP1 mutations in such cases may support the use of combination treatment strategies [3,17].

A practical decision-making algorithm may include several steps. After establishing a diagnosis of metastatic NSCLC, comprehensive molecular testing is recommended, including assessment of driver mutations, PD-L1 expression, and, when feasible, STK11/KEAP1 status [22]. In the absence of driver alterations and with high PD-L1 expression (>50%), immunotherapy monotherapy is the standard approach. However, when STK11 or KEAP1 mutations are detected, chemoimmunotherapy or dual checkpoint blockade should be considered, as these tumors are characterized by lower sensitivity to monotherapy. In cases of low or intermediate PD-L1 expression, the presence of these mutations further supports the selection of combination treatment regimens. Overall, integration of STK11 and KEAP1 testing into clinical practice may improve treatment individualization in patients with NSCLC, allowing clinicians to avoid less effective therapeutic strategies and to direct patients toward more intensive or experimental treatment approaches [7,16].

Conclusions. Mutations in the STK11 and KEAP1 genes are important molecular determinants of non-small cell lung cancer biology and significantly influence the efficacy of immunotherapy. Loss of STK11 function leads to metabolic reprogramming of tumor cells and the development of an immunologically “cold” microenvironment, whereas KEAP1 inactivation activates NRF2-dependent antioxidant mechanisms and suppresses interferon signaling. STK11/KEAP1 co-mutations define the most aggressive NSCLC subtype, characterized by minimal infiltration of effector immune cells and pronounced resistance to immune checkpoint inhibitors. Clinical data demonstrate markedly lower response rates and reduced survival with immunotherapy monotherapy, while combination regimens provide only partial improvement. Determination of STK11 and KEAP1 status may complement traditional biomarkers and contribute to the personalization of treatment.

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