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PROGNOSTIC SIGNIFICANCE OF TP53 AND PD-L1 DEPENDING ON THE TYPE OF ADJUVANT THERAPY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Key words: *non-small cell lung cancer, p53, PD-L1, adjuvant therapy, survival.*

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Abstract. *Non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related mortality despite the widespread implementation of adjuvant chemotherapy and immunotherapy. The identification of molecular biomarkers capable of predicting treatment efficacy is critical for developing a personalized therapeutic approach. TP53, one of the most frequently mutated genes in NSCLC, may influence immunotherapy response through modulation of PD-L1 expression.*

Objective. *To evaluate the prognostic significance of p53 status in surgically treated NSCLC patients, considering PD-L1 expression and type of adjuvant therapy.*

Material and methods. *This retrospective single-center study included 42 patients with stage IA–IIIB NSCLC who received adjuvant platinum-based chemotherapy (n=27) or combined chemoimmunotherapy with atezolizumab (n=15). Immunohistochemical analysis was performed to assess p53 and PD-L1 protein expression in tumor tissues. Mutant p53 was defined as either negative or overexpressed staining. PD-L1 expression was considered positive when ≥1% of tumor cells were stained; <1% was regarded as negative. Statistical analysis was conducted using the χ^2 test, log-rank test, and Kaplan–Meier method in Stata V.19.5. A p-value <0.05 was considered statistically significant.*

Results. *The mean age of patients in the chemoimmunotherapy group was 59.7 ± 5.18 years, while in the chemotherapy group it was 57.7 ± 9.86 years. All patients (100.0%) in the chemoimmunotherapy group demonstrated positive PD-L1 expression, whereas only 55.6% of patients in the chemotherapy group were PD-L1 positive (p = 0.003). A significant difference in progression-free survival (Log-rank p = 0.0293) was observed exclusively among PD-L1-positive patients receiving chemoimmunotherapy: those with mutant p53 had a median PFS of 93.8 months, compared to 9.1 months in patients with wild-type p53. Overall survival was higher in patients with mutant p53, although the difference did not reach statistical significance. No such differences were observed in PD-L1-negative patients or in those who did not receive immunotherapy.*

Conclusions. *TP53 mutations are associated with improved progression-free survival in PD-L1-positive surgically treated NSCLC patients receiving adjuvant chemoimmunotherapy, supporting the prognostic value of p53 and the rationale for its routine evaluation.*

ПРОГНОСТИЧНЕ ЗНАЧЕННЯ TP53 ТА PD-L1 ЗАЛЕЖНО ВІД ТИПУ АД'ЮВАНТНОЇ ТЕРАПІЇ У ХВОРИХ НА НЕДРІБНОКЛІТИННИЙ РАК ЛЕГЕНЬ

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Ключові слова*: недрібноклітинний рак легень, p53, PD-L1, ад'ювантна терапія, виживаність.*

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Резюме. *Недрібноклітинний рак легень (НДКРЛ) залишається провідною причиною онкологічної смертності, попри активне впровадження ад'ювантної хіміо- та імунотерапії. Виявлення молекулярних біомаркерів, що можуть прогнозувати ефективність лікування, має ключове значення для персоналізованого підходу. Ген TP53, один із найчастіше мутованих при НДКРЛ, потенційно впливає на відповідь на імунотерапію через модуляцію експресії PD-L1.*

Мета дослідження - *оцінити прогностичне значення типу p53 у хірургічно пролікованих пацієнтів із НДКРЛ залежно від експресії PD-L1 та виду медикаментозної терапії.*

Матеріал і методи. *У ретроспективне одноцентрове дослідження*

включено 42 пацієнти з IA–IIIB стадією НДКРЛ, які отримували ад'ювантну хіміотерапію (n=27) або комбіновану хіміоімунотерапію з атезолізумабом (n=15). Імуногістохімічно оцінювали експресію білків p53 та PD-L1 у тканині пухлини. Мутантний тип p53 визначали на підставі негативної або гіперекспресії. Позитивним вважали PD-L1 забарвлення 1% та більше пухлинних клітин, негативним – менше 1%. Статистичний аналіз проводили з використанням χ^2-тесту, логарифмічного рангового тесту та методу Каплана-Майєра у програмі Stata V.19.5. Порогом статистичної значущості було p <0,05.

Результати. *Середній вік пацієнтів у групі хіміоімунотерапії становив (59,7±5,18) років, у той час як у групі хіміотерапії – (57,7±9,86) років. У групі хіміоімунотерапії усі пацієнти (100,0%) мали позитивну експресію PD-L1, тоді як у групі хіміотерапії лише 55,6% пацієнтів (p = 0,003). Суттєва різниця у виживаності без прогресування (Log-rank p=0,0293) виявлена лише у PD-L1-позитивних пацієнтів, які отримували хіміоімунотерапію: при мутантному p53 медіана ВБП становила 93,8 міс. проти 9,1 міс. у пацієнтів із диким типом p53. Загальна виживаність була вищою у пацієнтів із мутантним p53, але без статистичної значущості. У PD-L1-негативних хворих і в групі без імунотерапії таких відмінностей не спостерігалось.*

Висновки. *Мутації TP53 асоціюються з кращою виживаністю без прогресування при ад'ювантній хіміоімунотерапії у PD-L1-позитивних хірургічно пролікованих хворих на НДКРЛ, що підтверджує прогностичну значущість p53 та необхідність його рутинної оцінки.*

Introduction. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and is associated with high mortality rates and frequent recurrences, even after radical surgical intervention [1]. Postoperative pharmacological treatment remains a key component of the therapeutic strategy; however, individual responses to chemotherapy and immunotherapy vary significantly, highlighting the need for molecular predictors of treatment efficacy [2].

Recent studies have identified TP53, one of the most frequently mutated genes in NSCLC, as a promising biomarker for immune response and survival. Some findings suggest that TP53 mutations are associated with improved survival in male patients receiving immunotherapy, although this effect appears to be sex-specific and not universal [3]. Similar conclusions were drawn in another study showing that co-mutations of TP53 and ZFHX3 correlated with increased overall survival when immune checkpoint inhibitors (ICIs) were used [4].

TP53 is involved not only in apoptosis regulation but also in modulating PD-L1 expression, a key immune checkpoint that influences tumor sensitivity to ICIs. Liu et al. [5] demonstrated a correlation between TP53 mutations and elevated PD-L1 expression in patients without EGFR/ALK mutations, potentially enhancing immunotherapy response. Likewise, a large cohort analysis involving 1,586 lung adenocarcinoma patients indicated a link between PD-L1 expression, tumor microenvironment characteristics, and genetic mutations, including TP53 [6]. However, Kim et al. [7] reported that TP53 mutations were associated with poorer response to ICIs in patients with metastatic solid tumors, including NSCLC, emphasizing the context-dependence of this biomarker's effect.

Mathiot et al. [8] found that TP53 mutations predicted unfavorable survival in patients with metastatic non-squamous NSCLC, regardless of therapy line. Conversely, Assoun et al. [9] reported longer survival associated with TP53 mutations in patients treated with ICIs, further illustrating the contradictory nature of current data.

In this context, a study by Olivares-Hernández et al. [10] demonstrated that immunohistochemical (IHC) evaluation of the p53 protein could serve as a clinically feasible alternative to molecular TP53 testing, enabling stratification of patients based on prognosis and immunotherapy sensitivity. The study highlighted that specific IHC expression patterns of p53 closely correlated with TP53 mutational status and carried prognostic significance in NSCLC. Given that IHC is widely available and routinely applied in clinical practice, it can be readily incorporated into postoperative pathological evaluation, making it particularly suitable for clinical use [11].

Despite the growing body of evidence regarding the prognostic relevance of TP53 mutations in NSCLC patients undergoing immunotherapy, most studies focus on metastatic cases [12, 13]. Data on surgically treated patients who may receive adjuvant immunotherapy based on PD-L1 expression and p53 status remain limited.

Objective. This study aimed to evaluate the impact of p53 status on disease-free and overall survival in surgically treated NSCLC patients, in the context of PD-L1 expression and the type of pharmacological therapy. The research seeks to fill the existing gap in the literature and provide further justification for a personalized approach to adjuvant NSCLC treatment.

Material and methods. Study design. A total of 42 surgically treated NSCLC patients were included in this retrospective study: 27 received platinum-based adjuvant chemotherapy, and 15 received chemoimmunotherapy

with atezolizumab. The pilot, single-center nature of the study resulted in heterogeneous patient group compositions. Inclusion criteria comprised histologically confirmed NSCLC, stage IA–IIIB disease, age ≥18 years, and the availability of high-quality archived tumor tissue. Patients were followed for at least six years. Final evaluation of progression-free survival and overall survival was performed on June 1, 2025. Death data were retrieved from the Sumy Regional Clinical Oncology Center cancer registry. The study was approved by the Bioethics Committee of Sumy State University (protocol No. 3/12 dated December 17, 2024). Informed consent was obtained from all surviving participants.

Immunohistochemical analysis. Serial 4-μm sections of NSCLC tissue were mounted on SuperFrost adhesive slides (Thermo Scientific, USA) and dried at 60°C for 18 hours. Following deparaffinization, sections underwent antigen retrieval in 0.1 M citrate buffer (pH 6.0) at 95°C. After rinsing in distilled water and cooling for 20 minutes, endogenous peroxidase activity was blocked using MAD-021540Q-125. Monoclonal antibodies were incubated for 10 minutes. Ultra V Block was used to prevent background staining. Primary antibodies included anti–PD-L1 (clone Cal-10, 1:50 dilution) and anti-p53 (clone SP5, 1:50 dilution), both from Master Diagnostica. Reactions were visualized using the In Vitro detection system (Master Diagnostica, Spain).

PD-L1 positivity was defined as distinct membranous staining in ≥1% of tumor cells, with or without partial cytoplasmic staining. Staining limited to cytoplasm or observed in tumor microenvironment cells (macrophages, lymphocytes) was excluded from evaluation.

For p53 evaluation, six tumor regions (1 mm² each) with the most intensely stained nuclei were selected per sample. The immunohistochemical score was calculated by multiplying the percentage of stained nuclei (scored from 0 to 4) by the staining intensity (0–3). A total score of 0 or ≥4 was considered indicative of mutant-type p53.

Statistical analysis. Statistical analysis was conducted using Stata V.19.5 (StataCorp, Texas, USA; https://www.stata.com, 2025). Clinical and pathological characteristics were presented as absolute numbers and percentages. Age was described using mean, standard deviation, and 95% confidence intervals (CIs). A p-value <0.05 was considered statistically significant. The Pearson χ^2 test and Fisher's exact test were used to assess associations between variables and treatment types. Progression-free survival and overall survival were estimated using the Kaplan–Meier method, and survival differences were assessed using the log-rank test.

Results. Patient characteristics. The study included 42 surgically treated NSCLC patients who received either chemotherapy alone (n=27; 64.3%) or combined chemoimmunotherapy (n=15; 35.7%). The mean age of patients in the chemoimmunotherapy group was 59.7 ± 5.18 years (95% CI: 56.8–62.6), compared to 57.7 ± 9.86 years (95% CI: 53.8–61.6) in the chemotherapy group; the difference was not statistically significant. Most patients in both groups were male and had a history of smoking. There were no significant differences in tumor histology or disease stage. Mutant-type p53 was more frequently observed in the chemoimmunotherapy group (60.0%), whereas wild-type p53 predominated in the chemotherapy group (63.0%); however, the difference was not statistically significant. The most notable difference was observed in PD-L1 expression: all patients in the chemoimmunotherapy group (100.0%) were PD-L1 positive, compared to only 55.6% in the chemotherapy group (p = 0.003; Table 1).

Survival analysis. The total follow-up period for the patients was 9.5 years. During this time, disease recurrence was observed in 9 of 15 patients (60%) who received chemoimmunotherapy and in 17 of 27 patients (63%) treated with chemotherapy alone. Median progression-free survival and overall survival were analyzed in subgroups of surgically treated NSCLC patients according to p53 status, PD-L1 expression, and treatment modality (Table 2).

Among PD-L1-negative patients treated with chemotherapy alone, no statistically significant differences were found in either progression-free survival or overall survival. In PD-L1-positive patients who received chemotherapy without immunotherapy, both survival outcomes remained low for those with either wild-type or mutant p53, without meaningful differences.

The most pronounced difference was observed in the PD-L1-positive subgroup receiving combined chemoimmunotherapy. In this group, patients with mutant-type p53 showed a significantly higher median progression-free survival of 93.8 months, compared to only 9.1 months in those with wild-type p53 (p = 0.0293). This was the only subgroup with a statistically significant survival difference (Fig. 1).

Meanwhile, overall survival in the same subgroup was also higher in patients with mutant p53 but did not reach statistical significance: the median overall survival for patients with wild-type p53 was 36.4 months, whereas the median was not reached for those with mutant p53, suggesting a potential survival benefit from ICI in patients harboring TP53 mutations (Fig. 2).

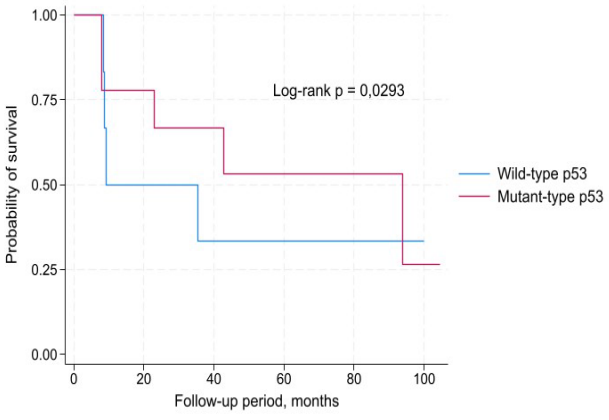

Fig. 1. Progression-free survival in PD-L1-positive surgically treated NSCLC patients receiving combined chemoimmunotherapy

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Table 1

Baseline clinicopathological characteristics of surgically treated NSCLC patients

Variables	Chemoimmunotherapy group 15 (35,7%)	Chemotherapy group 27 (64,3%)	P-value
Age:			0,927
Median	59,7±1,33	57,7±1,89	
95% CI	56,8–62,6	53,8–61,6	
< 60	8 (53,3)	14 (51,9)	
≥ 60	7 (46,7)	13 (48,1)	
Sex:			0,689
Female	2 (13,3)	6 (22,2)	
Male	13 (86,7)	21 (77,8)	
Stage:			0,506
IA-IIA	4 (26,7)	11 (40,7)	
IIB-IIIB	11 (73,3)	16 (59,3)	
Histology:			0,461
Adenocarcinoma	6 (40,0)	14 (51,9)	
Squamous cell carcinoma	9 (60,0)	13 (48,1)	
Smoking:			0,689
Never smokers	2 (13,3)	6 (22,2)	
Current or former smokers	13 (86,7)	21 (77,8)	
p53:			0,152
Wild-type	6 (40,0)	17 (63,0)	
Mutant-type	9 (60,0)	10 (37,0)	
PD-L expression:			0,003
Negative	0 (0,0)	12 (44,4)	
Positive	15 (100,0)	15 (55,6)	

Table 2

Median survival in surgically treated NSCLC patients stratified by p53 status, PD-L1 expression, and treatment type

Subgroups of patients	Wild-type p53, months	Mutant-type p53, months	Log-rank p
Progression-free survival			
PD-L-negative patients, used chemotherapy, n=12	109,4	98,8	0,3595
PD-L-positive patients, used chemotherapy, n=15	7,4	5,7	0,3935
PD-L-positive patients, used chemoimmunotherapy, n=15	9,1	93,8	0,0293
Overall survival			
PD-L-negative patients, used chemotherapy, n=12	114,5	103,8	0,3189
PD-L-positive patients, used chemotherapy, n=15	14,3	19,1	0,2629
PD-L-positive patients, used chemoimmunotherapy, n=15	36,4	median was not reached	0,4923

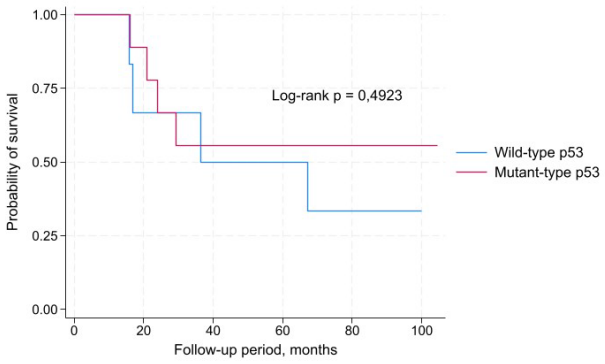

Fig. 2. Overall survival in PD-L1-positive surgically treated NSCLC patients receiving combined chemoimmunotherapy

Discussion. This study demonstrated that TP53 mutations, assessed immunohistochemically, have predictive value for progression-free survival in surgically treated NSCLC patients undergoing adjuvant chemoimmunotherapy. The statistically significant improvement in progression-free survival among PD-L1-positive patients with mutant p53 (93.8 vs. 9.1 months; p = 0.0293) may reflect a potential synergy between disrupted TP53-dependent signaling pathways and the mechanism of action of ICIs.

Our findings align with the study by Huang et al. [15], which showed that patients with TP53 mutations treated with chemoimmunotherapy had better disease control than those with driver mutations alone (e.g., EGFR or ALK). The role of TP53 is increasingly recognized as context-

dependent, as its mutations can contribute to PD-L1 upregulation and promote an immune-permissive tumor microenvironment.

Complementary data from Liu et al. [16] suggest that in patients with driver gene mutations and positive PD-L1 expression, combining ICIs with chemotherapy may enhance treatment efficacy, supporting the clinical relevance of a multimodal approach.

Conversely, some reports indicate that somatic TP53 mutations may be associated with poorer overall survival during immunotherapy, reflecting the complexity of interpreting this biomarker in a heterogeneous immune context [17].

Our study specifically focused on surgically treated patients with early or locally advanced NSCLC, a population for which data on the interplay between TP53 and PD-L1 in the adjuvant setting remain scarce. Notably, the NEOMUN neoadjuvant trial (stage II/IIIA) found no benefit from pembrolizumab in TP53-mutant subgroups [18], suggesting that the predictive value of TP53 may be contingent upon sufficient PD-L1-driven immune activation.

Moreover, Saleh et al. [19] highlighted that the prognostic impact of TP53 varies by disease stage: in localized NSCLC, KEAP1 and TP53 mutations had a lesser negative effect on survival than in advanced stages, reinforcing the importance of subgroup analyses.

The relationship between TP53 and PD-L1 expression has also been confirmed in several studies showing that TP53 mutations correlate with elevated PD-L1 levels in NSCLC regardless of histological subtype, which may enhance responsiveness to ICIs [20]. It is also crucial to consider that not only TP53 status but its co-mutations (e.g., with STK11 or KEAP1) can define distinct immune phenotypes that critically affect immunotherapy outcomes [21].

In our study, no significant survival differences were found in the PD-L1-negative cohort treated with chemotherapy alone, regardless of TP53 status. This supports the notion that the impact of TP53 mutations is realized only in the context of an activated PD-L1-mediated immune response.

Overall, the results of our study contribute to the current understanding of TP53 as a predictive biomarker in NSCLC and, for the first time, demonstrate its clinical relevance in surgically treated patients undergoing adjuvant chemoimmunotherapy. The observed interaction between TP53 mutation and PD-L1 positivity warrants further prospective validation in larger, multicenter cohorts.

While the findings are limited by the small sample size, retrospective nature, and single-center design, they reveal a consistent trend aligned with existing knowledge on the role of TP53 in shaping the tumor immune phenotype. These results should be validated in future prospective multicenter studies.

Conclusions. In surgically treated NSCLC patients with positive PD-L1 expression, TP53 mutations identified through immunohistochemistry are associated with significantly improved progression-free survival following adjuvant chemoimmunotherapy. This association was not observed in PD-L1-negative patients, highlighting the significance of the TP53–PD-L1 interaction as a potential predictor of immunotherapy response. These findings support the integration of p53 assessment into personalized postoperative treatment strategies for NSCLC.

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Conflict of interest. The authors declare no conflict of interest.

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