

# OPINION

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Regarding: Dissertation titled: "Markers for Systemic Inflammation and Efficacy of Immunotherapy in Patients with Metastatic Non-Small Cell Lung Cancer"

Author: Dr. Tanya Lyubomirova Zlatanova

Scientific Supervisor: Assoc. Prof. Dr. Jeliazko Arabadjiev, MD.

Following the meeting of the Scientific Council of "ACIBADEM CITY CLINIC UMHAT TOKUDA" on June 26, 2024 (Protocol No. 53/26.06.2024) and in accordance with Order No. 15-05-92/11.07.2024 of the Executive Director and Procurator of "Acibadem City Clinic UMHAT Tokuda", I have been selected as a member of the Scientific Jury and assigned to prepare an opinion on the procedure for awarding the educational and scientific degree of "Doctor" in the area of higher education 7. Healthcare and Sports, professional field 7.1. Medicine, doctoral program "Internal Diseases."

## **1. Brief Information About the Candidate**

Dr. Tanya Zlatanova was born on December 14, 1976. In 1995, she graduated from the "Yoan Ekzarh" Language High School in Vratsa with a profile in English. In 2001, she graduated as a physician from the Medical University of Sofia. In 2005, she acquired a professional qualification in "Health Management," in 2008, she specialized in Internal Diseases, and in 2017, she specialized in Medical Oncology.

From 2004 to 2009, she worked in the Internal Medicine Department of MBAL "Ihtiman" Ltd., from 2009 to 2012, she worked at Tokuda Hospice - Sofia, and since 2012, she has been working at the Medical Oncology Clinic of "ACC UMHAT Tokuda" JSC.

Dr. Tanya Zlatanova has numerous participations, including as a lecturer at various national and international scientific forums.

She is an adjunct lecturer for third-year medical students in the discipline of Internal Medicine Propedeutics at Sofia University.

She participates in the training of residents in Medical Oncology at the Medical Oncology Clinic, and since March 2022, she has been the supervisor of the residency of Dr. Vladimir Milov.

She is a member of the Clinical Committee on Chemotherapy at Acibadem City Clinic - Tokuda Hospital.

Dr. Tanya Zlatanova is proficient in English and German and has studied Russian.

She is a member of ESMO, ASCO, IASLC, ESCO, and BSSIO.

A list of 34 scientific publications is presented, of which Dr. Zlatanova is part of the author collective, and in 17 of them, she is the first author.

## **2. Relevance of the Dissertation and the Importance of the Problem**

Lung cancer is among the socially significant diseases in modern society. The high incidence and mortality from lung cancer, frequent diagnosis in advanced stages, and short survival rates for patients make this disease one of the serious challenges in modern oncology practice.

Despite the advancements in diagnostic methods, improved capabilities for characterizing tumor biology, and the introduction of new drugs and personalized therapeutic approaches, the 5-year survival rate for patients with advanced and metastatic disease remains low - under 5-10%. This underscores the need to identify and implement more clearly defined prognostic and predictive markers in clinical practice to ensure the most appropriate

treatment for each patient. Indices and scales introduced in recent years, such as the Systemic Immune-Inflammation Index (SII), the Advanced Lung Cancer Inflammation Index (ALI), and the Khorana score (KS), have been discussed as potential prognostic biomarkers in patients with advanced NSCLC. However, due to conflicting data, they have not been validated.

### **3. Structure of the Dissertation**

The dissertation consists of 132 pages, with the following sections:

"Introduction" - 1 page, "Literature Review" - 42 pages, "Research Methodology - Aims and Objectives" - 1 page, "Materials and Methods" - 10 pages, "Research Results" - 43 pages, "Discussion and Analysis of Results" - 13 pages, "Conclusions and Recommendations" - 2 pages, "Bibliography" - 16 pages, and "Appendix" - 1 page.

The work is illustrated with 39 figures, 60 tables, and 1 appendix.

The bibliography includes 198 references, all in Latin script.

The research aim is clearly and specifically defined, providing the primary directions for the research work - to determine the prognostic potential of the Systemic Immune-Inflammation Index (SII), Khorana score (KS), modified Khorana score (mKS), and Advanced Lung Cancer Inflammation Index (ALI) concerning therapeutic response and survival during first-line immunotherapy or chemoimmunotherapy in patients with metastatic non-small cell lung cancer.

To achieve the stated objective, six tasks have been clearly and precisely formulated:

- To investigate and analyze the clinical and laboratory characteristics of patients with metastatic NSCLC treated with first-line immunotherapy or combined chemoimmunotherapy.
- To explore the correlation between the Systemic Immune-Inflammation Index (SII), Khorana score, ALI score, and modified Khorana score (mKS).
- To determine the prognostic potential of SII, Khorana score, ALI score, and mKS, assessed before the initiation of treatment, in relation to tumor response, progression-free survival, and overall survival in patients who received monotherapy compared to those who received combined chemoimmunotherapy.



- To examine the role of KS, mKS, and SII as prognostic markers for the occurrence of thrombosis.
- To analyze the frequency and type of immune-mediated toxicities.
- To investigate the relationship between markers of systemic inflammation (KS, mKS, SII, ALI) and early mortality (within 6 months of initiating systemic therapy) in patients with metastatic NSCLC.

The structure of the dissertation is well-balanced and organized. The individual sections follow a logical sequence and have comprehensive content. The research work meets the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria.

#### **4. Literature Awareness**

The doctoral candidate presents a thorough analysis of a large volume of scientific information. Data are presented on the medical and social significance of the problem-advanced and metastatic NSCLC, the high frequency of thromboembolic events, and the high mortality among these patients.

Markers of systemic inflammation, in the form of scales and indices that have been studied in small retrospective studies among patients treated with chemotherapy or targeted therapy before the widespread introduction of immunotherapy into clinical practice, are described, as is the need for the validation of simple, easy-to-calculate scales and indices to identify patients at high risk of thrombosis and death, and if necessary, optimize therapeutic approaches.

#### **5. Research Design and Methodology**

An observational ambispective study was conducted—retrospective for the period from May 12, 2017, to May 12, 2023, and prospective for the period from July 1, 2022, to May 12, 2023. All 188 patients included meet the inclusion criteria and do not meet the exclusion criteria; they were treated in the Medical Oncology Clinic at Acibadem City Clinic UMHAT Tokuda JSC from May 12, 2017, to May 12, 2023. Patients were divided into two groups—retrospective group (RG) and prospective group (PG). They received first-line immunotherapy or chemoimmunotherapy.



The methods used to assess the predetermined and retrospectively processed parameters for study and follow-up are described in detail, and the specific methods of the study are presented: for the retrospective group—SII and KS, and for the prospective group—SII, KS, ALI, and mKS, as well as the method of their calculation. The therapeutic regimens used, the patient follow-up methods, the imaging methods applied, and the criteria for assessing therapeutic response are described. The methods used for data processing, including descriptive and analytical statistics, are described, with the specialized statistical package IBM SPSS version 22 employed.

## **6. Consistency Between Aim, Results, and Conclusions**

There is consistency between the stated aim, the formulated objectives, and the results obtained, as summarized in the discussion and conclusions.

The research results are thoroughly described by the doctoral candidate and are illustrated with tables and figures. Based on the representative data obtained, a detailed discussion is developed, and the corresponding conclusions are formulated:

- The similar distribution of patients in both groups by the main specified characteristics reduces the likelihood of bias in data analysis.
- A positive correlation is found between SII and Khorana score, as well as between SII and mKS. The relationship between them supports the hypothesis of an association between inflammation and thrombotic risk.
- A negative correlation is found between ALI and the other markers (KS, mKS, SII); an increase in ALI (with improvement in BMI and correction of hypoalbuminemia) and a decrease in SII, KS, mKS may lead to a reduction in thrombotic risk.
- No statistically significant correlation is found between the studied scales and the response to first-line therapy, both in the retrospective and prospective groups. Therefore, it is not recommended to use markers of systemic inflammation as a predictive factor for response to first-line treatment.
- KS and mKS show potential as prognostic factors for OS in patients treated with first-line monotherapy in the prospective group.

- SII could be used as a prognostic factor for OS in patients receiving first-line chemoimmunotherapy.
- ALI has the potential to be a reliable prognostic factor for OS in patients with NSCLC.
- KS, mKS, SII, ALI do not have prognostic value for the occurrence of venous thromboembolism in the studied patient population.
- The observed immune-mediated toxicities in patients treated with monotherapy and those treated with combined chemoimmunotherapy are similar in frequency and type.
- Using mKS and SII, patients at increased risk of death in the first 6 months can be identified, guiding certain therapeutic approaches.

## **7. Analysis of Contributions**

Based on the analyzed data, specific conclusions and contributions are formulated.

Major contributions with original character:

- For the first time globally, the role of mKS and SII as factors for early death in patients with metastatic NSCLC has been studied.
- For the first time in Bulgaria, the role of certain markers of systemic inflammation as prognostic factors for tumor response, PFS, and OS in patients with NSCLC treated with first-line monotherapy or combined chemoimmunotherapy has been studied.
- For the first time in Bulgaria, the role of SII, KS, mKS, ALI regarding the risk of thrombosis has been studied.
- For the first time in Bulgaria, a prospective study among patients with metastatic NSCLC has been conducted, examining albumin and D-dimer to assess cancer cachexia and thrombotic risk.
- For the first time in Bulgaria, the type and frequency of immune-mediated toxicities arising during first-line therapy in patients with metastatic NSCLC have been described.

Major contributions with scientific and practical character:

- The negative prognostic role of increasing SII on OS in patients treated with chemoimmunotherapy is demonstrated.
- The role of the ALI score regarding OS in patients from the prospective group is demonstrated.
- mKS and SII have the potential as clinical predictors for selecting patients with poor prognosis.

## Conclusion

The dissertation developed by Dr. Tanya Lyubomirova Zlatanova, titled "Markers for Systemic Inflammation and Efficacy of Immunotherapy in Patients with Metastatic Non-Small Cell Lung Cancer" meets and exceeds the necessary scientometric requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria and the Rules for the Development of the Academic Staff at Acibadem City Clinic UMHAT Tokuda JSC for acquiring the educational and scientific degree of "Doctor." This, along with the presented scientific production, provides a strong basis for me to confidently give my positive evaluation and to recommend to the members of the esteemed Scientific Jury to award the educational and scientific degree of "Doctor" to Dr. Tanya Lyubomirova Zlatanova.

12 SEP 2024

Prepared by:



/Assoc. Prof. Dr. Eleonora Georgieva Dimitrova-Gospodinova /

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