REVIEW

By Prof. Dr. Milena Staneva Staneva, PhD
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Regarding: a dissertation thesis for the acquisition of the educational and scientific degree in the field of higher education 7. Health and Sports, professional field 7.1. Medicine, PhD program "Internal Medicine".

Author: Dr. Tanya Lyubomirova Zlatanova

Form of PhD: Independent preparation

Structural Unit: Clinic of Internal Medicine

Topic: " MARKERS FOR SYSTEMIC INFLAMMATION AND EFFICACY OF IMMUNOTHERAPY IN PATIENTS WITH METASTATIC NON-SMALL CELL CANCER "

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

1. General Overview of the Procedure and the Doctoral Candidate

In the preparation of the dissertation thesis, all procedural requirements have been adhered to, including the selection of the topic, internal defense, and the selection of a Scientific Jury.

Dr. Tanya Zlatanova was enrolled as a doctoral candidate for independent preparation by order No. 15-05-139 / 30.09.2022, issued by the Executive Director and Procurator of "Acibadem City Clinic Tokuda University Hospital" EAD. She has completed her individual doctoral plan and successfully passed the PhD examination. On 11.06.2024, the completed dissertation was presented and successfully defended before an extended Scientific Collegium of the Clinic of Internal Medicine, after which the Doctoral Council (Protocol 53/26.06.2024) discharged the candidate with the right to public defense. By order No. 15-05-92 dated 11.07.2024, of the Executive Director and Procurator of the hospital, I was appointed as an internal member of the Scientific Jury concerning Dr. Tanya Lyubomirova Zlatanova's dissertation thesis. At the first absentee meeting of the Scientific Jury, I was designated to prepare a review. The materials provided by the doctoral candidate, including the dissertation, abstract, and related documents and materials for the official defense, fully comply with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of LDASRB and the Regulations of "Acibadem City Clinic UMHAT Tokuda" EAD.

I declare that I have no conflict of interest with the author of the dissertation.

Dr. Tanya Zlatanova graduated from the Medical University of Sofia in 2001. From 01.05.2002 to 01.05.2007, she specialized in Internal Medicine at the Military Medical Academy (MMA) in Sofia. From 01.09.2004 to 01.09.2009, she worked at the General Hospital "Ihtiman" EOOD in the Internal Medicine Department, and from 01.09.2009 to 18.03.2012, at Tokuda Hospice in Sofia. Since 19.03.2012, she has been a physician at the Medical Oncology Clinic of "ASC Tokuda University Hospital" EAD. Since October 2019, she has been a part-time assistant in the Department of Propedeutics of Internal Medicine (English Language Medicine Program) at the Faculty of Medicine, Sofia University "St. Kliment Ohridski."

She obtained her specialty in Internal Medicine in 2008 and Medical Oncology in 2017 from the Medical University of Sofia. In 2005, she also acquired a professional qualification in Health Management from the South-West University "Neofit Rilski" in Blagoevgrad. From 05.09.2016 to 30.09.2016, she completed a CECOG Targeted Drug Fellowship in the Department of Medicine I, Oncology Division, Comprehensive Cancer Center, Vienna Medical University, Austria.

Dr. Zlatanova has participated in numerous national and international oncology training courses, including as a lecturer.

2. Relevance of the Topic

Lung cancer (LC) ranks first in morbidity and mortality among all oncological diseases worldwide. The majority of cases are classified as non-small cell lung cancer (NSCLC). The disease is aggressive, characterized by rapid growth and early metastasis, leading to most patients being diagnosed at an advanced stage and having relatively short survival times. This underscores the need to establish well-defined prognostic and predictive factors to determine the most appropriate treatment for each patient. In recent years, several prognostic indices and scores have been studied, including the Systemic Immune-Inflammation Index (SII), the Advanced Lung Cancer Inflammation Index (ALI), and the Khorana Score (KS). These indices have shown potential as prognostic biomarkers in patients with advanced NSCLC, but there are still controversies, and they have not yet been universally validated. The search for new, easily accessible prognostic and predictive biomarkers to individualize treatment is a highly relevant issue in oncology, given the social significance and poor prognosis of these patients. The topic of the dissertation is well-chosen and very current.

3. Understanding of the Problem

The doctoral candidate demonstrates in-depth knowledge of the topic and creatively engages with the literature.

4. Structure and Content of the Dissertation

Dr. Zlatanova's dissertation consists of 132 pages, illustrated with 39 figures and 60 tables. It is properly structured and includes: *List of abbreviations and symbols* – 2 pages; *"Introduction"* – 1 page; *Chapter One:* "Literature Review" – 42 pages; *Chapter Two:* "Research Methodology": Objectives and tasks – 1 page, Materials and methods – 10 pages; *Chapter Three:* "Study Results" – 43 pages; *Chapter Four:* "Discussion and Analysis of Results" – 13 pages; *Chapter Five:* "Conclusions and Recommendations" – 2 pages; *Bibliography* – 16 pages ; *Appendices* – 1 page.

The bibliography includes 198 sources, all in Latin script, emphasizing the relevance and scientific foundation of the dissertation. Over 30% of the cited sources were published in the last five years. Each chapter is well-justified and logically connected with the previous ones, allowing the research objectives and tasks to be clearly followed.

Introduction

The introduction is well-formulated, presenting the problem and justifying the aim of the dissertation. A general overview of lung cancer (LC) is presented, which is among the leading causes of cancer-related mortality worldwide. The importance of immunotherapy as a treatment is emphasized, along with the need for prognostic and predictive markers to determine the effectiveness of therapy.

Literature Review

The literature review is competently written, demonstrating a good understanding of the various aspects of the topic. It covers the epidemiology of lung cancer, presenting data on the incidence and mortality of LC globally and in Bulgaria. The pathogenesis, etiology, and risk factors are discussed, including smoking and occupational exposures. Methods for the diagnosis and staging of LC, including the TNM classification, are described. Predictive biomarkers and the role of targetable mutations are reviewed. Prognostic indices and scores used for risk assessment and prognosis in LC patients are also discussed.

Research Methodology

The methodology section includes the objectives, tasks, materials, and methods.

The aim of the dissertation is clearly formulated, aligning with the topic and literature review. Dr. Zlatanova aims to establish the prognostic potential of the Systemic Immune-Inflammation Index (SII), Khorana Score (KS), modified Khorana Score (mKS), and Advanced Lung Cancer Inflammation Index (ALI) in terms of therapeutic response and survival during first-line immunotherapy or chemoimmunotherapy in patients with metastatic non-small cell lung cancer.

Six clearly defined and achievable *tasks* have been set to accomplish this aim.

Materials and Methods

An observational ambispective study with both retrospective and prospective components was conducted. The study details 188 patients treated between 12.05.2017 and 12.05.2023 at the Medical Oncology Clinic of "Acibadem City Clinic Tokuda University Hospital" EAD, which is sufficient to meet the objectives and tasks. The patients were divided into two groups: retrospective and prospective. The prognostic markers SII, KS, mKS, and ALI were studied concerning tumor response, progression-free survival, and overall survival.

Appropriate methods and specialized statistical software (IBM SPSS version 22) were used for data processing, ensuring the reliability of the results.

Results

Dr. Zlatanova's dissertation is distinguished by clarity, accuracy, and specificity. The obtained results are well-illustrated with statistically processed tables and graphs and align with the research objectives. The clinical and laboratory characteristics of the patients before the start of therapy are described.

- The levels of SII, KS, ALI, and mKS before therapy initiation are studied.
- The prognostic potential of various markers regarding tumor response, progression-free survival, and overall survival is analyzed.
- The relationship between prognostic indices and thrombosis risk is examined.
- The frequency of immune-mediated toxicities in different therapeutic regimens is studied.
- The relationship between systemic inflammation and early mortality in patients with metastatic NSCLC is also investigated.

Discussion and Analysis of Results

In *Chapter Four*, the results are discussed and analyzed in the context of the existing literature and data. A critical review of the results and their significance for clinical practice is provided.

Chapter five : Conclusions and Recommendations

Based on the obtained results, Dr. Zlatanova logically draws 10 conclusions and makes recommendations for the clinical application of her findings, which correspond to the research tasks. The emphasis is placed on the role of prognostic markers in optimizing the treatment of patients with metastatic NSCLC.

5. Main Scientific Contributions

The dissertation's main scientific contributions include **nine** *points, five* of which are *original* and *four* are of a *scientific-practical nature*. The most important are:

- ***The role of inflammatory markers in predicting early mortality***: The role of mKS and SII as factors for early mortality in patients with metastatic NSCLC is studied for the first time worldwide.

- *Validation of prognostic biomarkers:* The role of SII and mKS as prognostic factors for survival and therapeutic response in patients with metastatic NSCLC is studied for the first time in Bulgaria.
- *Study of thrombotic risk:* The relationship between KS, mKS, and SII and the risk of thrombosis is examined, contributing to a better understanding of complications in the treatment of NSCLC. It is emphasized that clinicians should actively search for symptoms of DVT and PE, and patients should be educated to recognize them.
- *Summarization of data on immune-related toxicity* observed in patients with NSCLC treated with first-line immunotherapy or chemoimmunotherapy.

6. **The abstract** is 86 pages long and reflects the contents of the dissertation. According to the requirements, the contributions and existing publications by the candidate on the presented topic are included in the abstract.

7. **Evaluation of Publications and Personal Contribution of the Doctoral Candidate**

The candidate has submitted four publications in national journals and eight scientific communications at national and international scientific forums, one of which has an Impact Factor. In two of the submitted publications, Dr. Zlatanova is the first author, and in all scientific communications, she is the sole author. This scientific activity is sufficient to demonstrate that the candidate is consistent in her scientific endeavors and meets the national minimum requirements for the educational and scientific degree of "PhD"

8. **Critical Remarks and Recommendations**

The following remarks can be made without diminishing the value of the scientific work:
- In the statistical figures, there is a lack of additional processing for better visualization of the results.
- Foreign terms are used in the text.
- In the bibliography, the year of publication for some sources is not written according to the accepted format at ASC Tokuda University Hospital, where the year should follow the journal's name.
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CONCLUSION

I highly appreciate Dr. Tanya Lyubomirova Zlatanova's dissertation thesis for the relevance and timeliness of the research conducted, particularly in addressing a crucial issue – the identification of easily measurable biomarkers for predicting therapeutic response and survival in patients with NSCLC treated with immunotherapy or combined chemoimmunotherapy, aiming to individualize treatment. The presented research results and the developed dissertation contribute to the Bulgarian scientific literature. The work is scientifically grounded, methodologically sound, and practically applicable. It is written in a strictly scientific style and meets all the requirements of. The presented materials and dissertation results fully comply with the specific requirements of the Law

on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of LDASRB and the Regulations of "Acibadem City Clinic UMHAT Tokuda" EAD. There are demonstrated qualities and skills for conducting independent scientific research.

Dr. Tanya Zlatanova is an established clinician and physician with extensive experience in internal medicine and medical oncology, with proven theoretical knowledge and professional skills, as confirmed by the presented dissertation.

For the reasons stated above, I confidently give my positive assessment and strongly recommend that the members of the Scientific Jury positively evaluate the dissertation thesis " MARKERS FOR SYSTEMIC INFLAMMATION AND EFFICACY OF IMMUNOTHERAPY IN PATIENTS WITH METASTATIC NON-SMALL CELL CANCER " and award Dr. Tanya Lyubomirova Zlatanova the scientific and educational degree "PhD" in the field of Higher Education 7. Health and Sports, professional field 7.1. Medicine, doctoral program "Internal Medicine."

02.09.2024,
Sofia

Prepared by:

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