REVIEW

By prof.Nikolay Vladimirov Conev, MD, PhD

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On the dissertation on:

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

Author: Dr.Tanya Lyubomirova Zlatanova

Research supervisors: Assoc. Prof. Jeliazko Iliev Arabadjiev, MD, Phd

According to Order ***№ 15-05-92, Sofia, 11.07.2024*** *г. of the Executive Director of Acibadem City Clinic UMHAT "Tokuda" and based on Article 4 of Law on the development of the academic staff in the Republic of Bulgaria, Article 31 of the Rules for implementation of the Law on the development of the academic staff in the Republic of Bulgaria, Article 29 of The regulations for the development of the academic staffof Acibadem City Clinic UMHAT "Tokuda" and Decision of the scientific council (Protocol number 53/26.06.2024 г.) I was elected as a member of the Scientific Jury under the acquisition procedure for acquiring the educational and scientific degree "Doctor" in the field of higher education 7. Health and sports, professional field 7.1 Medicine, Doctoral Program "Ïnternal Medicine."*

Biographical reference of the candidate:

Education:

- 30.09.2022 – Started a PhD Degree training at Medical Oncology Clinic, Acibadem City Clinic UMHAT "Tokuda"

- 01.07.2013 – 01.07.2016 – Specialization/ Residency/ in Medical Oncology, successfully passed the Board Examination in December 2016, Diploma Serial number AC № 015675/02.02.2017; registration number № 020470

- 01.05. 2002 - 01.05. 2007 – Specialization in Internal Medicine, Diploma Serial Number, AC №011798; registration number № 013024 held in the Military Medical Academy-Sofia, under the supervision of the Medical University in Sofia, Bulgaria

- 04.10.2004 - 12.03.2005- Specialization in Health Management – „Neofit Rilsky" Southwest University – Blagoevgrad Serial Number JZU – 2005 №2450, registration number № 106267

- 1999 – 2001 – graduated from the Medical University – Sofia – acquired a MSc degree in Medicine - Medical Doctor Diploma Serial Number, MUS № 011402

- 1995 – 1998 Medical University – Pleven

- 1990 – 1995 – Language High School – Vratsa, English Language

Work experience:

- 19 March 2012 – till present - Medical Oncology Clinic, Acibadem City Clinic Tokuda Hospital, Sofia

- 01 September 2009 – 18 March 2012 –Tokuda Hospice

- 01September 2004 – 01 September 2009 - Ihtiman State Hospital, Internal Medicine Department

- 01 May 2002- 01 May 2007-Military Medical Academy-Residency in Internal Medicine

Professional Cousres and International Meetings:

- Participated in 6th Annual SITC Women in Cancer Immunotherapy Network (WIN) Leadership Institute, 28-29 September 2023, Chicago, USA
- Participated in Masterclass in Lung Cancer, 5-6 October 2022, at the School of Cancer Sciences, Gustave Roussy – France
- Participated in the ESMO Virtual Advanced Course on KRAS Targeting in NSCLC 13-14 October 2021
- 16 – 17 February 2018, Amsterdam, Netherlands - Participated in the ESMO Advanced Course on Unsolved Questions in Immuno- Oncology
- 10/11/2017 – 11/11/2017 – participated in the prIME Masterclass in Neuroendocrine Tumors, in Amsterdam, Netherlands
- 05.09.2016 – 30.09.2016 - CECOG Targeted Drug Fellowship at the Department of Medicine I, Clinical Division of Oncology, Comprehensive Cancer Center Vienna, Medical University of Vienna

- 04.07.2016 – 05.07.2016 – participated in the ESMO Preceptorship on Immuno – Oncology- From the essentials of tumor immunology to clinical application in Sienna, Italy
- 16.11.2015 – 18.11.2015 – Advanced course in Diagnosis and Treatment of NETs, Uppsala, Sweden
- 03.07.2015 – 08.07.2015 – 2nd ESO – ESMO Eastern Europe and Balkan Region Masterclass in Medical Oncology in Bratislava, Slovakia
- 21.11.2014 – 22.11.2014 – attended the ESMO Sypmosium on Immuno – Oncology in Geneva, Switzerland
- 19.11.2014 – 20.11.2014 – attended the ESMO Preceptorship on Immunotherapy of cancer in Lausanne, Switzerland
- 27.06.2014 – 02.07.2014 – attended the ESO – ESMO Eastern Europe and Balkan Region Masterclass in Medical Oncology in Brdo, Slovenia;
- 22.05.2014 - 23.05.2014 – attended the ESMO Preceptorship on Colorectal Cancer, in Prague, Czech Republic
- 05.04.2014 - Attended the "Expert Practice in Gastrointestinal Malignancies meeting" in Vienna, Austria – a prIME Oncology venue;
- 29.11.2013 – 30.11.2013 – attended the course Molecular Diagnostics in Clinical Oncology in Viareggio, Italy

Dr. Tanya Lyubomirova Zlatanova is a part-time teacher of third-year medical students in the Propaedeutics of Internal Diseases at Sofia University and is also the head of medical oncology trainees.

She has made several appearances as a speaker at local and international scientific events.

He authorizes over 30 full-text scientific publications in Bulgarian and international scientific publications.

Dr. Tanya Lyubomirova Zlatanova speaks English, German, and Russian.

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

Characteristics of the presented dissertation work:

The dissertation has a classic structure.

The dissertation contains 132 standard pages with the following sections: Introduction- 1 page. *Chapter one.* Literature review - 42 pages, *Chapter two.* Methodology: Purpose and tasks - 1 page. Materials and methods - 10 pages, *Chapter three.* Results - 43 pages *Chapter four.* Discussion and analysis of results - 13 pages. *Chapter five.* Conclusions and recommendations - 2 pages. *Bibliography* - 16 pages. *Application* - 1 page.

The work is illustrated with tables and figures of high quality and informativeness. The literature reference includes 198 literary sources. The dissertation has a balanced structure, the proportions between the individual sections are respected and meet the requirements of the Law on the Development of Scientific Staff of the Republic of Bulgaria.

The dissertation student has chosen a critical topic in the field of oncology, researched it in detail, and presented it thoroughly in her thesis. Lung cancer ranks first in morbidity and mortality among all cancers worldwide with more than 2.4 million cases. The available data show that most of the patients are diagnosed at an advanced stage and have a relatively short survival. Despite the significant progress in drug treatment of lung carcinoma in recent decades, the 5-year survival rate for patients with advanced and metastatic disease remains too low - below 5-10%, with variations in different regions of the world (including the Bulgarian population).

In recent years, there has been increasing interest in the discovery of new biomarkers to predict and monitor response to treatment. Initial stratification of patients according to prognosis would help to design an individualized treatment strategy. Candidates for such markers are the Systemic immune inflammation index (SII), the Advanced lung cancer inflammation index (ALI) and the Khorana score (KS), which make them "scientifically attractive" for more in-depth analysis and evaluation.

In her **Literature Review**, Dr. Tanya Lyubomirova Zlatanova has presented in detail the main points in the etiology, epidemiology, pathogenesis, staging, diagnosis and treatment of lung cancer. An exceptional impression is made by the broad information presented by the dissertation student, the precise use of scientific terminology and the correct citation of the authors of scientific publications in the field. Dr. Tanya Lyubomirova Zlatanova's expert presentation of the essence of the aforementioned indices (markers) is extremely important. The dissertation thoroughly and precisely presents the scientific logic and studies that have proven the primary expediency for the use of markers.

The summarization of the presented data in the point "**Conclusions from the Literature review**" also makes a good impression.

The main goal that Dr. Tanya Lyubomirova Zlatanova sets for herself is focused on a current and key problem in patients with lung cancer, namely to establish the prognostic potential of the Systemic Immune Inflammation Index (SII), Khorana score (KS), modified Khorana score (mKS) and Advanced Lung Cancer Index(ALI) in relation to therapeutic response and survival during first-line immunotherapy or chemoimmunotherapy in patients with metastatic non-small cell lung cancer.

The realization of this goal is related to the fulfillment of the **main tasks** that the dissertation student has set herself, namely:

- To investigate and analyze the clinical and laboratory characteristics of patients with metastatic NSCLC treated with 1st line immunotherapy or combined chemoimmunotherapy;

- To look for a correlation between the systemic immune inflammation index SII, Khorana score, ALI score and modified Khorana score;

- To determine the prognostic potential of the systemic immune inflammation index SII, Khorana score, ALI score and modified Khorana score, examined before the start of treatment, in terms of tumor response, progression-free survival and overall survival in patients who underwent mono-immunotherapy, compared to patients on combined chemoimmunotherapy;

- To study the role of Khorana score, modified Khorana score and SII score as prognostic markers for the occurrence of thrombosis;

- To analyze the frequency and type of immune-mediated toxicities;

- To look for an association between markers of systemic inflammation (KS, mKS, SII and ALI) and early death (within 6 months of initiation of systemic therapy) in patients with metastatic NSCLC;

The assigned tasks are clearly and accurately formulated and correspond to the set goal, which shows the good theoretical preparation and mastery of the problem by the dissertation student.

Materials and research methods are well selected and comprehensively explained. The analysis of the collected data was carried out by applying the methods of medical-statistical data processing.

The dissertation is based on an observational ambispective study: with a retrospective and a prospective part. Patients who meet pre-defined inclusion and exclusion criteria, treated from 12.05.2017 to 12.05.2023 at the Medical Oncology Clinic of "Adjibadem City Clinic UMBAL Tokuda" EAD are included. Patients were divided into two groups: Retrospective observation group (retrospective group - RG) and Prospective observation group (prospective group - PG). The retrospective observation group includes patients who started first-line immunotherapy or chemoimmunotherapy after 12.05.2017, followed up to 12.05.2023. The prospective observation group includes patients who started first-line immunotherapy or chemoimmunotherapy after 01.07.2022, followed up until 12.05.2023.

Own results are presented in detail on 43 pages and illustrated with statistically processed numerical tables and graphs. Presented in Sections:

1. Clinical and laboratory characteristics of the examined patients;

2. Levels of SII, KS, ALI and mKS before initiation of systemic therapy;

3. Prognostic potential of SII and KS (retrospective group), SII, KS, mKS, ALI (prospective group) studied before the start of treatment, in terms of tumor response, progression-free survival and overall survival;

4. Role of Khorana score, modified Khorana score and SII score as prognostic markers for occurrence of thrombosis;

5. The frequency and type of immune-mediated toxicities;

6. Relationship between markers of systemic inflammation (KS, mKS, SII and ALI) and early death (within 6 months of initiation of systemic therapy) in patients with advanced and metastatic NSCLC;

In the section "**Discussion and analysis of the results**" (discussion), Dr. Tanya Lyubomirova Zlatanova compares the results of her research with similar studies worldwide, thus emphasizing the innovativeness and relevance of the conducted research, and also identifying some design flaws.

In the section "**Conclusions and recommendations**" the conclusions are described in detail in ten points.

The **abstract**, which is in a volume of 86 pages, is a summary of the main points of the dissertation - materials and methods, aim and tasks, results, discussion, contributions and conclusions of the dissertation. A list of the publications of Dr. Tanya Lubomirova Zlatanova, which are related to the dissertation work, is presented. The main contributions of the scientific work are also presented here:

Scientific contributions of an original nature:

1. For the first time in the world, the role of mKS and SII as a factor in the occurrence of early death (within 6 months of initiation of monoimmunotherapy or combined chemoimmunotherapy) in patients with metastatic NSCLC was investigated.

2. For the first time in Bulgaria, the role of systemic inflammation markers SII, KS, mKS and ALI as prognostic factors for PFS, OS and tumor response in patients with metastatic NSCLC who received 1st line monoimmunotherapy or combined chemoimmunotherapy was studied.

3. For the first time in Bulgaria, the role of SII, KS, mKS and ALI in relation to the risk of thrombosis was investigated.

4. For the first time in Bulgaria, a study is being conducted with prospective observation of patients with metastatic NSCLC with serum albumin and D-dimer testing, before starting systemic therapy, which is possible to become routine in practice, with the aim of evaluating cancer cachexia and determining the risk of thrombosis.

5. For the first time in Bulgaria, the frequency and type of immune-mediated toxicities during first-line monoimmunotherapy or combined chemoimmunotherapy in patients with NSCLC are studied and described.

Contributions of a scientific and practical nature

1. The negative prognostic role of the increase in KS and mKS with respect to OS among patients with metastatic NSCLC treated with monoimmunotherapy could serve to select patients with high expression of PD-L1≥50% in whom the appointment of combined chemoimmunotherapy is appropriate in order to optimize therapeutic results.

2. The negative prognostic role of an increase in SII with respect to OS in patients treated with combined chemoimmunotherapy was demonstrated.

3 The reliable role of ALI score in terms of overall survival in patients treated with monoimmunotherapy as well as patients with combined chemoimmunotherapy was demonstrated in prospectively followed patients, with longer overall survival observed in patients with ALI≥18. These results could provide the basis for a larger prospective study to validate this marker in patients with metastatic NSCLC undergoing first-line immunotherapy or chemoimmunotherapy, including the construction of a clinical behavior algorithm.

4. A higher risk of early death within the first 6 months of treatment with monoimmunotherapy or combined chemoimmunotherapy was demonstrated in patients with mKS values of 3 and above, and patients with SII of 2082.5 and above. Therefore, mKS and SII emerge as potential clinical predictors for selecting patients with an unfavorable prognosis, which requires active and strict follow-up with a view to timely therapeutic actions.

Some critical remarks:

In the structure of the dissertation, some minimal hierarchical inaccuracies are noticeable, as well as the use of non-accepted scientific terms. Regarding the figures that are used to visualize the statistical analysis (SPSS generated), it is noticeable that additional processing for better visualization is missing - font enlargement, removal of background and colors of the curves, and also addition of presence data or absence of statistical significance, which would improve their understanding and interpretation. There are also differences in proportions and sizes of logically similar tables and figures. I also recommend that there is no overlap between the main points of the dissertation and the abstract.

Conclusion

The dissertation work of Dr. Tanya Lyubomirova Zlatanova represents a thorough and complex scientific development. The topic is current and extensive. The applied methods are adequate to achieve the formulated goals and tasks, the results are convincing, the conclusions are clearly formulated, the contributions are of significant theoretical and potential practical value.

The dissertation on the topic "MARKERS FOR SYSTEMIC INFLAMMATION AND EFFICACY OF IMMUNOTHERAPY IN PATIENTS WITH METASTATIC NON-SMALL CELL LUNG CANCER" covers the indicators for obtaining the educational and scientific degree "Doctor", meets the requirements of the Law on the development of the academic staff in the Republic of Bulgaria and the Rules for its implementation.

Based on the above, I give a positive assessment of the dissertation work of Dr. Tanya Lyubomirova Zlatanova and propose to the members of the respected Scientific Jury to award her the educational and scientific degree "DOCTOR".

Prof. Nikolay Conev, PhD

14. AUG. 2024