To the Chairman of the Scientific Jury,

As determined by Order No. 1515/30.05.2023

To the Rector of the Medical University of Pleven

Statement

By Associate Professor Dr. Antonio Ivanov Antonov, MD,
Head of the Hematology Clinic,
University Hospital “St. Marina” Pleven,
Professional field: 7. Health and Sports, 7.1 Medicine
Scientific specialty: “Hematology and Blood Transfusion”

of a dissertation work

for awarding the educational and scientific degree of "PhD"

Professional field: 7. Health and Sports, 7.1 Medicine
Scientific specialty: "Hematology and Blood Transfusion"
Author: Dr. Radi Evgeniev Lukanov
Form of doctoral studies: full-time
Scientific organization: Medical University "Prof. Dr. Paraskev Stoyanov" - Varna
Topic: "Biomarkers for a personalized approach in the selection of treatment for patients with Myeloma disease"
Scientific supervisor: Prof. Dr. Ilina Dimitrova Micheva, MD

Brief biographical data:

Dr. Radi Lukanov graduated from High School of Mathematics, and in 2018 from the Medical University "Prof. Dr. Paraskev Stoyanov" Varna with a degree in Medicine.

He started working as a resident in the Hematology Clinic of the University Hospital "St. Marina" Varna.

At the beginning of 2019, he started working as a part-time assistant, and a little later was assigned on full-time.

In 2023, he acquired a specialty in clinical hematology.

He is fluent in several languages and completed an internship in Internal Medicine in Italy.

He takes part in many Bulgarian and international scientific conferences and symposia, presenting rare cases or some cutting-edge research regarding biomarker diagnostics of Multiple Myeloma.

Structure of the dissertation:

The presented dissertation is structured according to generally accepted rules in 11 sections. It is spread over 134 pages with 15 tables and 34 figures. The tables are very well-formed and expressive. The figures clearly visualize the presented results and are accompanied by correct titles.

The bibliography is sufficient, in total it covers 214 titles only in Latin. Most of them are from the last 10 years.

Thematic relevance of the dissertation:

The progress of modern medicine and the introduction of new genetic techniques have formed several basic conclusions about the nature of the malignant hematological diseases.

The main difference from the past is the modern idea of the enormous heterogeneity of the same nosological unit with the formation of many different pathogenetic models at the cellular level. Multiple, interconnected cellular and subcellular disorders were identified. These disorders are expressed by changes in microribonucleic acids. This opens up the possibility of studying the sensitivity and specificity of these as new diagnostic and prognostic markers.

The present work seeks a relationship between selected miRs and classical clinical and prognostic markers to identify more reliable diagnostic biomarkers and possibly monitor the effect of treatment.

The topic is avant-garde, a dissertational subject and evaluates insufficiently studied biomarkers involved in pathobiological and pathophysiological molecular mechanisms for the development and progression of Myeloma disease.

Despite the large literature review, similar thematic studies on hematological pathology are limited worldwide.

There are no developments on this topic in our country.

Literature review:

The presented review covers 44 pages and is illustrated with 7 figures. It presents in detail and in an engaging manner the current concepts of Multiple Myeloma. The principles of risk stratification and prognostic assessment systems are described.
The second part of the review presents initial general data on the synthesis and mechanism of action of MiR. Later, the available data on their role in solid tumors are summarized.
The place of MiR in various aspects of the complex biology of Myeloma disease is examined in detail. A critical interpretation of some dual relationships is made. The place of MiR in treatment and in the development of therapeutic resistance is sought.
Based on these preliminary data, selected circulating MiRs accepted as promising biomarkers are described.
The structure of the review corresponds to the topic of the dissertation. The PhD candidate presents the current concepts on the problem in a complete and systematic manner.

Goal and objectives:

The main goal is formulated specifically and clearly. However, there is no stated reason in the review explaining the fixation of the re-examination of circulating miRs after 6 months. It would be expected that it would be tied to the assessment of the maximum therapeutic response regardless of time of re-examination in the specific patient.
The research tasks are 14 in number and partly overlap each other.
I accept the formulated goal and the research tasks set.

Methodology of the dissertation:

The set goal and objectives of the study require the use of an extensive and diverse methodological panel. It includes routine examinations, laboratory and imaging studies. FISH, RT-PCR and selected statistical processing methods.
The methods are modern, generally accepted, adequate, described in detail and comprehensively.
A total of 56 patients with Myeloma multiplex, diagnosed according to the 2014 IMWG criteria and 12 healthy controls were studied.
The presented methodologies correspond to the set goals and objectives.

Results:

The description of the results follows the order of the research tasks set. They are systematized in detail and illustrated with well-designed figures and tables. The relatively high percentage /43%/ of patients lost to re-examination for reasons beyond the control of the dissertation author is striking.
The presented results are reliable and meet the formulated goals and objectives.

Discussion:

The interpretation of the obtained results is made from the point of view of the main statements in the literature review.
The found significant decrease in miR-126-5p and miR-199a-5p in patients with Multiple Myeloma finds its theoretical basis. They provide grounds for their use as biomarkers for determining the risk and response to therapy. Of interest is the normalization of miR-126-5p levels upon achieving a complete response (CR) or very good partial response (VGPR).
The pathophysiological role of high levels of MiR-214-3p and miR-497-5p as prognostic biomarkers influencing overall survival (OS) and progression-free survival (PFS) is also discussed.
From a theoretical aspect, the theoretical possibilities for modulating miR expression in Multiple Myeloma are also of interest.
The discussion ends with a correct statement of the practical limitations of the study. The conclusion formulates the thesis about the prospective role of circulating miR patterns as biomarkers for diagnosis, prognosis, and response to treatment in Multiple Myeloma.

Conclusions:
The conclusions form the obtained results. They fully correspond to the obtained results.

Contributions of the dissertation work:

The contributions are formed in 2 groups. The first group notes 5 original contributions, presented openly. Here the emphasis is on the innovative approach to the assessment of miR in clinical practice.
Contributions with applied scientific value bring out the practical nature of the dissertation. The scientific work.
In summary, I accept both the contributions formulated by the author and the proposed abstract, which meets the necessary requirements.

Summary:

The dissertation work investigating the search for new biomarkers for improving diagnosis, risk stratification and assessment of treatment effects is an innovative, current and modern development.
It meets the scientometric criteria formulated in the Regulations for Academic Development of the Medical University "Prof. Dr. Paraskev Stoyanov" Varna for awarding the scientific and educational degree "PhD".
I make a recommendation to the Scientific Jury to award the scientific and educational degree "PhD" in the scientific specialty "Hematology and Blood Transfusion" to Dr. Radi Evgeniev Lukanov MD.

Date: 22.05.2025

Assoc. Prof. Dr. A Antonov MD, PhD