

## OPINION

by Assoc. Prof. Maria Atanasova Radanova, PhD,

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*Regarding:* Defense of a dissertation titled: "*Cytogenetic and molecular-cytogenetic markers in patients with multiple myeloma - prognostic significance*" by **Dr. Valentina Dimirova Miteva**, a full-time doctoral student at the Department of Medical Genetics, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, for the awarding of the educational and scientific degree "Doctor" in the Doctoral program "*Genetics*" in the field of higher education 4. *Natural sciences, Mathematics and Informatics*, professional direction: 4.3. *Biological Sciences*. As per the Order of the Rector of the MU - Varna No. R-109-347/07/18/07/2023, I have been included as a member of the Scientific Jury under the procedure according to the Academic Staff Development Act in the Republic of Bulgaria and the Regulations on the Implementation of the Law for awarding the ESD „Doctor“.

### ***Procedure***

Dr. Valentina Dimirova Miteva was enrolled as a full-time doctoral student in Doctoral program "Genetics" at the Department of Medical Genetics, at the Medical University of Varna, under Order No. R-109-429/16.07.2018. Initially, she was supervised by Prof. Dr. Lyudmila Angelova, and later developed her dissertation work under the guidance of Prof. Dr. Ilina Micheva, and Assoc. Prof. Dr. Trifon Chervenkov. She successfully passed exams for a doctoral minimum in the specialty on 07/23/2021, and for a doctoral minimum in a foreign language on 06/24/2021. Based on a report by Prof. Dr. Lyudmila Angelova, MD, Head of the Department of Medical Genetics, and the decision of the Faculty Council of the Faculty of Medicine at the Medical University of Varna, she was granted the right to dissertation defense by Rector's Order No. R-109-347/07/18/2023. The requirements of the Academic Staff Development Act in the Republic of Bulgaria and the Regulations on the Implementation of the Law and the Rules of the Medical University - Varna for awarding of ESD „Doctor“ have been complied with, and all submitted documents are complete and prepared correctly.

### ***Relevance of the Dissertation Topic***

Dr. Miteva's dissertation focuses on studying the frequency and prognostic significance of chromosomal abnormalities in patients with multiple myeloma. Multiple myeloma is a disease that poses a significant health challenge for the aging population in Bulgaria and globally. Patients with elevated serum lactate dehydrogenase and  $\beta$ 2-microglobulin levels, reduced serum albumin levels, and the presence of one of three cytogenetic disorders (del(17p), t(4;14), t(14;16)) are identified as having a poor prognosis and are at risk of early relapse. Therefore, the development of methods for early detection of chromosomal disorders is crucial for diagnosis

and assessment of disease progression. In her dissertation, Dr. Miteva conducts a comparative evaluation of the application of conventional cytogenetics and the more sensitive method, Fluorescence In Situ Hybridization (FISH), in identifying high-risk patients with multiple myeloma. Given this, I assess the topic of her dissertation as both current and relevant from a scientific and clinical perspective.

### ***Characterization and Evaluation of the Dissertation Work***

The presented dissertation adheres to the requirements of the Academic Staff Development Act in the Republic of Bulgaria and the Rules of the Medical University - Varna, and is structured according to the generally accepted format. It comprises 123 standard pages, illustrated with 39 figures and 12 tables. The bibliography includes 206 references. However, the individual sections in the dissertation are not evenly balanced. A significant portion of the dissertation, approximately 46 pages (37%), is dedicated to the literature review, while the results, discussion, and conclusions collectively make up only 25 pages (20%).

The literature review is logically structured, initially detailing the prevalence of multiple myeloma in Europe and globally, compared to the data for Bulgaria. This is followed by a focus on the disease's etiology, genetic predisposition, clinical manifestations, and staging. The role of individual chromosomal disorders in the disease's development is thoroughly presented. The literature review concludes with an overview of markers used for diagnosing and prognosing multiple myeloma. However, it lacks a comparative analysis of methods for evaluating these markers.

The literature review concludes without a conclusion and hypothesis of the study, which would lead to the aim of dissertation work - *to identify and analyze the type, frequency, and prognostic significance of chromosomal disorders in newly diagnosed patients with a clinical diagnosis of multiple myeloma*. The tasks that the doctoral student set for herself are specifically defined and directly related to the aim.

The analysis methods used were standard karyotyping and locus-specific FISH, which are presented in great detail in the Materials and Methods section.

The results obtained were analyzed using statistical analysis methods and programs, and are graphically represented with 10 figures and 3 tables.

The main results in the dissertation are related to the determination of the frequency and structure of chromosomal disorders in newly diagnosed patients with multiple myeloma, using both conventional cytogenetic methods and locus-specific FISH. The percentage of patients with detected chromosomal abnormalities via the FISH assay was 1.8 times higher compared to the cytogenetic method, with all 9 patients exhibiting del(17)(p13). A statistically significant difference was observed in the median overall survival based on cytogenetic findings, with patients having a normal karyotype surviving for 34 months, compared to those with an abnormal karyotype who survived for 8 months.

The conclusions in the dissertation logically stem from the results obtained and summarize the most significant aspects of the analyses conducted.

Contributions are categorized into confirmatory and applied contributions. One of the key contributions of the dissertation, which is not explicitly stated in the text, is the implementation of a new method for the Laboratory of Medical Genetics.

***Publications Related to the Dissertation Topic***

The publications presented in relation to the dissertation total seven, with five in full text and two in abstract. In four of these publications, Dr. Miteva is the first and leading author, which serves as an indicator of the doctoral student's personal contribution to the research, analysis of the obtained results, and preparation of the manuscripts for publication.

***Abstract***

An abstract is prepared according to the requirements and accurately reflects the presented main results and the content of the dissertation work.

***Conclusion***

In conclusion, I am of the opinion that Dr. Valentina Dimirova Miteva's dissertation embodies a completed work of good scientific quality, notwithstanding a few critiques pertaining to the text's structure. The dissertation satisfies the requirements for obtaining the ESD "Doctor" degree, as outlined by the Academic Staff Development Act in the Republic of Bulgaria and the Rules of the Medical University - Varna. I express a positive opinion on awarding the educational and scientific degree "Doctor" to Dr. Valentina Miteva.

Date:  
09/15/2023

Signature:   
(Assoc. Prof. M. Radanova, PhD)