

To  
The Chairman of the Scientific Jury  
In Accordance with Order №P-109-303/16.07.21  
Of the Rector of Medical University – Varna

## **PEER REVIEW**

From

**Prof. Dr. Julian Raynov, Ph.D.**

**Clinic of Haematology -Military Academy Hospital– Sofia**

Of the dissertation for acquiring academic degree doctor

Area of education: **7. Healthcare and Sports**

Professional Area: **7.1 Medicine**

Doctoral program for awarding educational and scientific degree **“Haematology and blood transfusion” – cipher 03.09.39.**

Author: **Assistant Doctor Merlin Erol Efraim**

Form of doctoral studies: **self-study doctoral student**

Scientific Organisation: **Department of Internal Diseases II**

Subject: **Clinical-biological and genetic markers in risk stratification in patients with myelodysplastic syndrome**

Scientific Supervisor: **Assoc. Prof. Dr. Ilina Dimitrova Micheva, Ph.D**

Chairman of the Scientific Jury: **Prof. Dr. Valeria Kaleva, Ph.D.**

Honourable Mrs Chairman,

### **1. General Presentation of the procedure and the doctoral student**

The submitted package of documents for defence of the dissertation is in accordance with the requirements for awarding educational and scientific degree “Doctor” of Medical University – Varna accompanied with an authenticity declaration. Assistant Doctor Merlin Efraim has been registered as a self-study doctoral student in the Department of Internal Diseases II, Faculty of Medicine, Medical University – Varna with order of the rector: № P-109-128/01.04.2019. Exam

of doctoral minimum was taken on 25.09.2020. Internal defence in front of department committee was performed on 22.06.2021. On this date proposal for the scientific jury was also submitted.

Application to the Rector for initiating the procedure of defence was made on 26.07.2021. The scientific jury has been appointed with the order of the Rector with reference (№P-109-303/16.07.21) and on its first meeting (protocol №1/21.07.21) I have been appointed to prepare a review and the second meeting of the scientific jury has been scheduled for 10th September 2021 for the official defence. The procedure is progressing in accordance with the new regulations of Medical University – Varna where the scientific supervisor and doctoral student do not participate in the scientific jury. Taking into account the whole administrative process in accordance with regulations for the state requirements for registering and education of doctoral students, renewed in the State Newspaper 78/7.09.2004 as well as in accordance with the regulation of the development of academic staff of the Republic of Bulgaria, regulation of its application and regulation for registering and education of doctoral students in Medical University Varna, all administrative requirements and rules have been adhered to.

Three scientific publications of the doctoral student have also been included in the application documents.

## **2. Brief biographic information for the doctoral student**

D-r Merlin Efraim graduated from Nancho Popovich Mathematics and Science High School in Shumen in 2002 and medicine in Prof D-r Paraskev Stoyanov Medical University – Varna. She worked in the emergency department of the hospital at the town of Provadia as a doctor. From 2010 she started her specialization of clinical haematology in the clinic of haematology of the Sveta Marina University Hospital – Varna, where in 2015 acquired specialty in clinical haematology. In the same year she has been appointed as an assistant. In April 2019 she was registered as a self-study doctoral student and since then conducts research in the area of **Clinical-biological and genetic markers in risk stratification in patients with myelodysplastic syndrome** which is the subject of her dissertation. After successful procedures of approbation and deduction her official defence date has been scheduled for the 10th September 2021. Assistant D-r Merlin Efraim speaks English, Turkish and Russian languages. She is a member of the Bulgarian Haematology Association, Bulgarian Doctors' Association and some international haematology associations.

## **3. Relevance of the chosen topic and expediency of the proposed aims and tasks**

The topic chosen by D-r Merlin Efraim is relevant. It reflects accurately on the essence of the issue which is exposed in the contents of the scientific work. The dissertation is dedicated to diseases which are very often met in clinical practice, unified and known as myelodysplastic syndrome. This heterogeneous group of clonal diseases of the pluripotent hematopoietic stem cell is characterised with one or more cytopenias in the peripheral blood. Their clinical development includes a series of cytogenetic events and the acquisition of additional genetic anomalies in

some of the patients leads to transformation into acute myeloid leukemia. The clonal mutation can be a result of genetic predisposition or damage to the hematopoietic stem cells caused by an exposition. The frequency of MDS is increasing which is linked to the aging population and enhanced diagnostics. MDS poses considerable challenges with regards to diagnostics, risk stratification, clinical course and as well as in the treatment of the disease. The determination of risk is done by using approved scales of prognostic scoring systems. The complex assessment of the different prognostic and predictive factors allows the creation of precise diagnosis and adequate treatment. The relevance of the topic is indisputable and D-r Merlin Efraim has chosen to research and analyse the clinical-biological characteristics of the disease outside the proven and determined classifications and scales for risk stratification and assess their application in clinical practice on patients with MDS. This allows to conclude that scientific and scientifically applicable problems can be successfully discussed and resolved. In this regard the dissertation is useful for different groups of specialists from overlapping specialties and is an important source of contemporary knowledge.

#### **4. Knowledge of the issue**

The title of the dissertation is connected with the topic, the aim is clear, specific and feasible. The literature review is scientifically oriented and makes connection between theory and practice. It is in-depth and thorough, it also successfully provides the necessary information and the comparison between the obtained results from the doctoral student and those from the cited authors. Assistant D-r Merlin Efraim is familiar with the problem and works on it, her dissertation has analytical, correct and accurate approach which demonstrates that during her scientific work she has accumulated comprehensive knowledge and skills. Declaration for 'originality' in accordance with 27 (2) from the regulations for the development of academic staff has been submitted, which certifies that the written thesis is the own work of the doctoral student.

#### **5. Methodology of the research**

The chosen methodology of the research allows the achievement of the aim and obtaining adequate answers for the tasks which are examined and resolved in the dissertation. The dissertation has mixed methodology and uses different scientific areas – clinical haematology, medical genetics, pathology and others. All methods used for the research have been described in detail. In my opinion the chosen methods are sensitive and specific enough and that they correspond to the tasks and provide results comparable with other similar research topics. The volume of this section is not regulated, but usually it is 10-15% of the total volume of the dissertation. The statistical analysis allow precise processing of the obtained materials, their perception and their reproduction in future.

#### **6. Structure and assessment of the dissertation**

The structure of the dissertation is in accordance with 27(2) from the regulations for the development of academic staff of the Republic of Bulgaria. It includes all the compulsory chapter for a dissertation and the analytical review reveals correct distribution of the volume. The

required numbering of the chapters and sectors has been complied with. The dissertation is richly illustrated with 28 tables and 82 figures which demonstrates professionalism and aesthetics. The work presented for review consists of 211 pages which slightly exceeds the recommended standard volume of (130-180 pages) for the educational and scientific degree 'doctor'. There is a clear logical connection between the different parts of the dissertation.

The *introduction* points the importance of the investigated and analysed problem. It outlines the motives for the choice of the topic, the justification for the essence of the unsolved problems which reflects on the contents of the scientific work. The subject of the research shows clearly the aspect of the problem, what is known so far in the scientific literature and what will be researched, analysed and discussed. The introduction gives us a brief enlightenment of the main problems in this topic. The conclusions from it are logical and convincing, and outline the important and unsolved problems of the topic of the dissertation.

The *literature review* consists of 58 pages (27.49 %) and is within the recommended volume of (25-30%). It is detailed and points the importance of the chosen topic, it has a clear and analytical approach and demonstrates the comprehensive knowledge accumulated in the process of preparing the dissertation. It is scientifically oriented to the topic and makes connection between theory and practice. The literature review discusses the contemporary concepts which are used for diagnostics, the prognosis and treatment of heterogeneous group of MDS. The problem is covered in detail with the presentation of up-to-date literature data regarding investigations of different teams for the specific disease. Historical review has been done of the epidemiological data, detailed review of the pathogenesis, the characteristic dysplastic changes and the risk factors with MDS. The well-known classifications of the disease (FAB, WHO) and the scales for risk stratification (IPSS, IPSS-R, WPSS, MDAPSS) have been mentioned and their clinical application and consideration. The Clinical frailty scale (CFS) of the patient and scales for determining the comorbidity index have been reviewed in detail. Different prognostic factors connected with the disease such as clinical-laboratory, cytogenetic and molecular have also been discussed. In my opinion the discussion of the FLT3, JAK2V617F mutations in the literature review is controversial.

The literature review points the scientific achievements in the chosen topic in the context of the dissertation's aim and tasks. It demonstrates understanding of the essence of the problem from theoretical point of view and shows that the doctoral student has in-depth and comprehensive knowledge of the published references of the most important theoretical and methodological questions. The literature review motivates the choice of the topic and the methods of the research in the context of the actual scientific realities. The reason for choice of the topic and its development into dissertation has been well presented and ends with formulating a clear scientific hypothesis which has a logical transition to the aim of the dissertation.

**Aim and Tasks** – the title of the dissertation is relevant to the chosen topic. The topic is clear, specific and feasible. The aim of the current dissertation is to research and analyse the impact of the factors connected with this disease (clinical-biological and genetic) and with the patient (age,

ECOG, comorbidities), the risk stratification, survival and the risk of transformation of MDS into AML. The chosen tasks for the performance of the aim are clearly formulated and their solutions are in sync with the used scientific methods and means, allowing the achievement of the aim. They are in total 6, ancillary to the aim and discuss and analyse the following: characteristics of patients with MDS; the survival assessed by using the scales for comorbidities and frailty, comparison with the classification systems and scales for risk stratification. There is a task to analyse the transformation of MDS to AML and factors for the favourable and unfavourable prognosis of the survival. The tasks determine the direction of the planned investigations and are benchmarks in the section 'results'.

**Materials and Methods** – this section consists of 6 pages (2.84%). 219 patients above the age of 18 with MDS are included in the research. The patients have been diagnosed and treated in the clinics of clinical haematology of Sveta Marina University Hospital – Varna for a period of 10 years (May 2010 – May 2020). Retrospective analysis has been performed on the demographic, clinical-biological and genetic markers, systems for classification and risk stratification, frailty scale and comorbidity scales or patients with MDS which is in close connection with the aims and tasks. The choice of patients have been performed in accordance with the determined criteria for the diagnostics of MDS (IWCG). Different approved methods have been used in the retrospective analysis described in detail in the relevant chapter. The statistical analysis has been performed professionally by using the statistical programme package SPSS Statistics v.20.0 for Window.

Hypothesis check is done by using dispersion analysis (ANOVA), variation analysis – for researching the differences between the investigated factors, correlation analysis – for researching the extent of dependence between different markers, regression analysis – for assessment of the causal dependences of more than two variables.

**Results** – this chapter follows the sequence of the tasks and 78 pages of the dissertation are dedicated to it (36.97%). The results are correctly presented with adequate statistical assessment and very well illustrated with plenty of tables and figures. The latter have been described according to the rules, briefly, accurately and correctly. The obtained results correspond to the requirements of the tasks. They are generated and archived in specially prepared individual patient cards (Appendix №1), containing all the researched and analysed markers. From total of 219 patients, 205 (93.6%) are with 'de novo' MDS and only 14 (6.4%) have secondary MDS. Significant difference is determined in the distribution depending on the type of MDS. In the group of patients with 'de novo' MDS males prevail (61%) while in the group with secondary MDS women prevail (64.3%) ( $p = 0.048$ ). The obtained results consist 1/3 of the volume of the dissertation and allow for the smooth entry into the dissertation, namely the discussion of the results.

**Discussion** – it is a 'mirror' of the qualities of each doctoral student. The discussion is 23 pages and its volume is 10.90% which is within the standard structural requirements (10-15%) of the total volume of the dissertation. In this chapter the author competently compares the data of her

research with the analogous data of different research teams, scientifically justifies it and seeks the reasons for differences in the results if there are any. Successful connection has been made in the chapter between own results and those described in the literature review. The question arises whether each planned result analysis is designed as a scientific question incorporated in the aim, tasks and then successfully in the dissertation. In my opinion the answer is positive, as here the contributions of the dissertation are seen.

**Conclusions** – there are 11 conclusions in total, which logically derive from the tasks of the dissertation. For each task corresponds one or more conclusions, and the successful solution of each task can be discussed as scientific, scientifically-practical and practical contribution of the doctoral student. The conclusions are brief, clear and categorical and something important – they do not include part of the results.

The presented final conclusion by D-r Merlin Efraim includes synthesis of the results, discussion and conclusions. It is confirmed that the outcome of the disease varies according to the risk group determined by the approved scales of risk stratification. Age is the main prognostic factor with negative impact on the survival. The role of the systems for classification and risk stratification has been taken into account for determining the survival and the risk transformation into AML. Of the utmost importance determining the course of the disease have factors such as age, myeloblasts in bone marrow, extent of dysplasia, diversions from the peripheral blood count, some biochemical markers and cytogenetic abnormalities. The comorbidity as a frequent accompanying factor has a significant impact on the outcome of the disease. It combined with the extent of frailty play a role in determining the survival of patients. Defining the risk by using the scales for stratification of the risky comorbidity indices significantly improves the prognosis assessment. Their combination allows for the more precise risk stratification, determining the prognosis and therapeutic course.

**References** – this chapter consists of 35 pages with 243 titles. Authors are well chosen and scientific articles published in the last 10 years are 88 (35.92%). Authors in the reference section are numbered and arranged in alphabetic order, something which is not complied with in the literature review and violates the connection between these two parts of the dissertation. The compulsory condition of quoting in Cyrillic known Bulgarian authors who worked on this topic.

At the end of the dissertation as an *appendix* the clinical card used for the research has been added.

## **7. Contributions of the Dissertation for the Science and Practice**

The characteristic and the assessment of the authenticity of the dissertation allow for the implication of contributions. The main achievement of the dissertation is the large-scale research of a group with high number of patients with MDS and the utilisation of a complex approach and the defined constellations with diagnostic significance. The contributions implicated in the dissertation can be divided into two groups: with original (fundamental character) – 4 and the same number with affirmative character. The relatively low number of dissertations on this topic

is now enriched with this large-scale scientifically sustained research which clinical haematology and other related specialties will use.

The significance of the dissertation for science and practice is based on the fact that there hasn't been such a large-scale analysis of patients with MDS so far, which can be considered as a future register of these group of patients in Bulgaria. The analysed parameters in the dissertation do not detect significant deviations in the Bulgarian population of what has been discovered for the rest of the world. Scientific contribution of the dissertation is the use of scales of comorbidity and frailty in combination with the risk scales. The defining of the risk group of patients by using approved scales in combination with comorbidities has been affirmed as a factor, which has to be taken into account to determine the therapeutic approach and the risk of transformation.

#### **8. Assessment of the publications of the dissertation work**

Assistant D-r Merlin Efraim has presented 3 publications in relation to the dissertation. In 2 of them she is the first author. Publications are original articles, published in their full volume and they fully comply with the requirements for structure and elements of the scientific article. The doctoral student meets the necessary criteria for publication activity.

#### **9. Personal Participation of the Doctoral Student**

The doctoral student has personal participation in the dissertation work and the obtained results, conclusions and contributions are as well her own merit. The style of the author is featured with certain positive characteristics in relation to the scientific awareness, accessibility and efficiency of the chosen wording, with accuracy and academicity of the expression.

#### **10. Abstract**

The presented abstract of 100 pages slightly exceeds the recommended volume of 45-88 pages. It is a summary of the dissertation work and it is its shortened version. It is structured correctly and its contents complies with that of the dissertation and contains all its chapters.

#### **11. Critical Remarks and Recommendations**

My critical remarks are pointed in the different sections of the dissertation. I recommend the results established by the doctoral student, conclusions and recommendations to find place in the periodic haematology magazine published in Bulgaria.

#### **12. Personal Impressions**

By observing the professional qualities of assistant D-r Merlin Efraim throughout the years and her participation in scientific forums of clinical haematology, my personal impressions are excellent.

## Conclusion

My overall assessment for the work presented by assistant D-r Merlin Efraim is that it complies with the requirements for the elaboration of dissertation work: structure; knowledge of the issue; analysis of the results; presentation and defence of the main thesis of the author as well as a successful attempt to propose her own concept. She has conducted successful, independent, long-standing scientific research and has presented the obtained results in an understandable and logical way. In D-r Merlin Efraim's dissertation the scientific problem, solutions, aim and tasks, conclusions and contributions have been stated correctly. Each section demonstrates something significant and the results are reliably proven with a certain scientific, practical and contributory character. The dissertation work of D-r Merlin Efraim complied with all the requirements of the Rules for Development of the Academic Staff of the Republic of Bulgaria, the regulations of its application and the regulations of Medical University – Varna.

**My positive assessment** is based on the contents of the dissertation in which the doctoral student proves that she has mastered the methodology of the scientific research and is in position to apply it for solving important for the practice tasks. With conviction I propose to the Honourable Jury to award with the educational and scientific degree 'doctor' assistant D-r Merlin Efraim in the doctoral program 'Haematology and Blood Transfusion'.

10<sup>th</sup> August 2021

Review Prepared By:

Prof. Dr. Julian Raynov, MD, Ph.D.

