OPINION STATEMENT

By Prof. Gueorgui Nikolaevitch Balatzenko, MD, PhD
Head of the Consultative and Diagnostic Unit
Specialized Hospital for Active Treatment of Hematological Diseases - EAD, Sofia

Regarding: Competition for the academic position of Professor in the field of higher education "7. Health and Sport", professional field "7.1 Medicine", scientific specialty "Clinical Hematology" for the needs of the Medical University - Varna, Second Department of Internal Medicine, Faculty of Medicine, and Clinic "Clinical Hematology" at the University Hospital "St. Marina" EAD - Varna, announced in the State Gazette No. 102 of 23/12/2022.

Only one candidate submitted documents for participation in the competition: **ASSOC. PROF. ILINA DIMITROVA MICHEVA**, MD, PhD - Head of the Clinic of Clinical Hematology at the University Hospital "St. Marina" – Varna.

By order No. P-109-144/23.02.2023 of the Rector of the Medical University (MU) "Prof. Dr. Paraskev Stoyanov" - Varna, Prof. Dr. Valentin Ignatov, PhD, I have been appointed as an external member of the Scientific Jury, at the first meeting of which I have been selected to prepare an opinion.

I. ANALYSIS OF THE APPLICANT'S CAREER PROFILE, EDUCATION AND QUALIFICATIONS

ASSOC. PROF. DR. ILINA MICHEVA graduated from the Medical University (MU) - Varna in 1993 (Diploma of Higher Education - Series A 92000379 Reg. №5476/28.11.1993 – with a Master's degree along with the professional qualification "physician"- Doctor of Medicine. She is board certified in Internal Medicine (Diploma Reg. №003523/20.02.1999) and in Clinical Hematology (Reg. № 012038/31.01.2007 - series MUV-2007 №1457). She also holds a master's degree in public health and health Management (Diploma Series MUS No. 049821/12.12.2022).
During the period 2000-2005 she was a full-time PhD student at the University of Patras, Department of Internal Medicine, Division of Hematology - Greece, where she successfully defended her PhD thesis entitled "The role of dendritic cells in the hematopoietic defects in patients with Myelodysplastic Syndrome", and the Higher Attestation Committee with the decision №1809-BAK/07.11.2007 confirmed her educational and scientific degree "Doctor" in the scientific specialty 03.01.39 Hematology and blood transfusion.

PROFESSIONAL DEVELOPMENT AND SPECIALIZATIONS

The professional career of Assoc. Prof. Ilina Micheva started as a resident physician at the Medical University of Varna (1994), after which she worked as a doctor at the company "Alissa 33" in Varna (06.1994-07.1998). Since 01.2006 she has been working at the Hospital "Sveta Marina" EAD - Varna, where she works at present, initially as a physician (2006), after which she was appointed as a doctor-hematologist at the Clinic of Clinical Hematology. Afterwards she was appointed as Head of the Stem Cell Transplantation Unit at the Clinic of Hematology (12.2014-04.2019), Head of the Clinic of Clinical Hematology and Head of the Stem Cell Transplantation Unit (04.2019-09.2022), and finally from 10.2022 onward – as Head of the Clinic of Clinical Hematology.
At the time of submission of application documents (05.01.2023), Assoc. Prof. Ilina Micheva had a total work experience as doctor of 20 years, 11 months, and 26 days.

She has undergone a number of courses and specific training on various problems in hematology, including: a one-year course in free elective "Clinical Cytology" at MU-Varna (1993-1994); long-term specialization at Patras University, Department of Internal Medicine, Department of Hematology, Greece (2000-2005); various training courses at home and abroad related to hematopoietic stem cell transplantation (HSCT) - European School of Hematology - ESH (2016); at the Medical University of Hannover, Germany (2017); Erasmus training at the University of Ljubljana, Clinic of Hematology, Transplantation Unit (2018). She has also obtained additional qualifications related to working principles and technical proficiency in flow cytometry and fluorescence-activated cell sorting, maintenance, and operation of a fluorescence-activated cell sorting system; cell and molecular biology methods, including cell culture, Western blotting, PCR, fluorescence in situ hybridization (FISH), ELISA, etc. She has also undergone pedagogical training for educators from medical institutions (2014).

TEACHING EXPERIENCE

Assoc. Prof. Ilina Micheva successively held the positions of Assistant Professor (2008-2010) and Chief Assistant Professor (2010-2015) at the Medical University - Varna, Department of Internal Medicine, Department of Hematology. In 2015, after competing with her thesis, she was elected for the academic position of Associate Professor at MU-Varna, Department of Internal Medicine, UNH of Hematology (Diploma № 117/20.05.2015), and subsequently she was appointed as Head of the Board of Hematology.
According to the submitted documentation, Assoc. Prof. Ilina Micheva has a total of teaching experience of 14 years and 10 months, including 2 years and 1 month as an assistant, 5 years and 1 month as a senior assistant, and 7 years as an Associate Professor.

GENERAL DESCRIPTION OF THE COMPETITION SUBMISSIONS

The submitted documents by Assoc. Prof. Ilina Micheva are complete, neatly arranged, and fully meet the legal requirements of the Act on Development of the Academic Staff in the Republic of Bulgaria and the Rules for its implementation, as well as those set forth in Art. 138 (1) of the Regulations for the Development of Academic Staff at MU "Prof. P. Stoyanov" – Varna. The presented documents provide comprehensive information concerning her professional development, research and publication activities, and teaching experience. All necessary evidence and source documentation are available.

II. GENERAL CHARACTERISTICS OF SCIENTIFIC PRODUCTION AND ASSESSMENT OF THE SCIENTIFIC METRICS FOR COMPLIANCE WITH THE MINIMUM REQUIREMENTS FOR THE ACADEMIC POSITION OF PROFESSOR

The submitted list of all scientific works by Assoc. Prof. Ilina Micheva includes a total of seventy-four publications, ninety-seven scientific communications, and one textbook. Of these, beyond those submitted during the development of the dissertation and habilitation, a total of forty-three scientific papers, representing 58.1% of the total scientific output, and fifty-three scientific communications have been submitted for participation in this competition. Of the forty-three total papers submitted, two of the titles are e-posters [#24;#25] presented at a scientific meeting and are not subject to peer review, regardless of their scientific significance. The remaining 41 include: 23 original full-text articles (56.1%) [#1-#5;#7;#8;#10;#11;#14; #19;#20;#23;#26;#29;#31;#34;#37;#39-#43]; 13 literature reviews (31.7%) [#13;#15-#18;#21;#22;#27;#28;#30;#32;#36;#38], and 5 rare cases from the clinical practice [#6;#9;#12;#33;#35] (12.2%). In addition, forty-five [#a44-#a88] scientific communications

with published abstracts are also attached, including twenty-five presented in international forums, most of them with abstracts presented in prestigious high IF journals, and twenty presented in national scientific forums. Besides, other eight papers were presented at alternative scientific forums.

INDICATOR GROUP [A1]. Dissertation for the Award of an Educational and Scientific Degree "Doctor"

ASSOC. PROF. ILINA MICHEVA has successfully defended her dissertation work for the acquisition of the educational and scientific degree "Doctor" on the topic: "The role of dendritic cells in the hematopoietic defects in patients with myelodysplastic syndrome." in MU - Patras, Greece, in scientific specialty 03.01.39 "Hematology and blood transfusion" (official note issued by the Higher Attestation Commission, which by decision No. 1809-BAK/07.11.2007).

CONCLUSION: The candidate fulfills the required indicator (50 points out of the 50 required).

INDICATOR GROUP [B4]. Habilitation work: scientific publications (not less than 10), equivalent to or replacing published monographic work, in publications that are refereed and indexed in world-known databases of scientific information.

ASSOC. PROF. ILINA MICHEVA submitted 10 publications (#1-#10), including 2 rare clinical cases (#6;#9) of which 4 are in Bulgarian (#1-#3;#5) and 6 in English (#4;#6-#10). Three of the papers are indexed in the international database Scopus (#1;#2;#4), another three – in Web of Science (CABI) (#3;#5;#9), and 4 – In both databases (#6-#8;#10). Three of the publications are in scientific journals with an impact factor (IF) and impact rank (SJR) - *Acta Medica Bulgarica* [#4 (2022) -IF 0.204/ SJR 0.120, Q4]; *Folia Medica* [#7 (2021) IF-0.84/SJR 0. 203, Q4); *Nuclear Medicine Review* [#9 (2016) - IF 0.55/SJR 0.217, Q4); and 2 – in an impact rank only journal – *J IMAB* [#8 (2016) - SJR 0.225; #10 (2016) - SJR 0.225]. In three of the articles, Assoc. Prof. Ilina MICHEVA was the first author [#1;#6;#10]; in 3 – the second author [#4;#5;#9], and in 3 – the last author [#2;#7;#8].

CONCLUSION: The candidate meets the required benchmark of 156.02 points out of the100 required.

INDICATOR GROUP [G7]. Publications and reports published in scientific journals, refereed and indexed in world-known databases with scientific information

ASSOC. PROF. ILINA MICHEVA has presented 15 papers (including 3 in press): 5 original full-text articles; 7 literature reviews; 1 case-report; and 2 scientific communications in the form of e-posters that are not peer-reviewed [#24;#25].

Of the remaining thirteen papers, two are refereed in both Scopus and Web of Science databases [# 13#20]; 7 in Scopus [#11;#12;#14;#15;#17;#18;#23] and 3 in Web of Science [#16;#19; #21]. Five of the articles were published in scientific journals with an IF [#20 – *New England Journal of Medicine* (2020) - IF-91,245; #12 – *European Review for Medical & Pharmacological Sciences* (2023) – IF-3,14; *Rom. J. Intern. Med* (2022) – IF-1,703; #11 – *Cytology & Genetics* (2021) – IF 0.643; #14 *Archives of Hellenic Medicine* (2023) – IF-0.2]. In 4 articles, ASSOC. PROF. ILINA MICHEVA is a co-author (#16;#17;#18;#21); in 1 – second author (#22); in 5 – subsequent author (#13;#15#19;#20;#23) and in 3 – the last one (#12;#14;#19).

Total number of points in the indicator – 231.45

INDICATOR GROUP [G8]. Publications and papers published in non-refereed peer-reviewed journals or published in edited collective volumes

ASSOC. PROF. ILINA MICHEVA has submitted 18 papers (including 3 in print), of which: 10 original articles in full text [#26;#29;#31;#34;#37;#39-#43]; 6 – literature reviews [#27;#28 #30;#32;#36;#38] and 2 – case-reports from the practice [#33;#35]. She was the first author

[#32; #36;#43] or co-author [#28;#33;#37-#39;#41] in 9 papers, the second author [#26] in 1 the subsequent author in 4 [#29;#30;#34;#42] and the last author in 2 [#31;#40]
Total number of points in the indicator: 231.45
CONCLUSION: In total for the two indicators of group G, ASSOC. PROF. ILINA MICHEVA has - 231.45 points [G7] + 215.75 points [G8] = 447.2 points, with the required minimum number of 200.

INDICATORS GROUP [D]. Citations or reviews in scientific journals, refereed and indexed in world-known databases with scientific information or in monographs and collective volumes [D10]; citations in monographs and collective volumes with scientific peer review [D11] and citations or reviews in non-refereed journals with scientific peer review [D12].
From the submitted references, it is evident that ASSOC. PROF. ILINA MICHEVA has a total of 188 citations, of which 165 are in [D10] scientific publications, refereed and indexed in world-known databases with scientific information or in monographs and collective volumes [2475 items]; 7 – in [D11] monographs and collective volumes with scientific peer review [70 points] and 16 – in [D12] in non-refereed journals with scientific peer review [80 points].
CONCLUSION: Overall, for the indicators of group [D], ASSOC. PROF. ILINA MICHEVA has 2625 points, with 100 points required.

INDICATOR GROUP [E14]. Supervision of a successfully defended PhD student
Under the supervision of ASSOC. PROF. ILINA MICHEVA four dissertations for the acquisition of the educational and scientific degree "Doctor" have been successfully defended: (1) Dr. M. Ephraim: "Clinical-biological and genetic markers in risk stratification in patients with myelodysplastic syndrome" (2021) [40 points]; (2) Dr. S. Dimitrova: "Primary, posteritremic, and postthrombocythemic myelofibrosis – the involvement of inflammatory cytokines (interleukin 6, interleukin 8) and the regulators of iron metabolism (hepcidin) in the pathogenesis of the anemic syndrome" (2021) [40 points]; (3) Dr. D. Niyazi: "Study on bacteremias and invasive mycotic infections in patients after autologous and allogeneic hematopoietic stem cell transplantation" (2022) [supervisor together with Prof. T. Stoeva - 20 points] . In addition, currently ASSOC. PROF. ILINA MICHEVA is a scientific supervisor of seven other PhD students whose dissertations are in progress.

Total number of points in the indicator – 100.

INDICATOR GROUP [E15]. Acquired medical specialty
ASSOC. PROF. ILINA MICHEVA has two acquired medical specialties: Internal Medicine (Diploma Reg. No. 003523/20.02.1999) [40 pts.] and Clinical Hematology (Reg. No. 012038/31.01.2007, series MUV-2007 No. 1457) [40 pts.].
Total number of points in the indicator – 80.

INDICATORS GROUP [E16-E19]. Participation in a national scientific or educational project
ASSOC. PROF. ILINA MICHEVA has participated in the realization of eight scientific research projects that have been successfully finalized, as well as in nine other projects that are in the process of development:

- [E16] PARTICIPATION IN A NATIONAL SCIENTIFIC OR EDUCATIONAL PROJECT (n=4): (1) Clinical aspects of intercellular adhesions in pleural inflammation and tumor metastasis – Funding LC442/94 with the Research Fund of the Ministry of Science and Technology – 1994-1996 [15 points]; (2) Invasive bacterial infections in patients after

autologous and allogeneic bone marrow transplantation: etiologic spectrum and resistance to strategic beta-lactam and glycopeptide antibiotics (No. 19019). Funding: Science Fund at MU - Varna (2019-2022) [15 points]; (3) Scientific approaches to complementary and alternative medicine (CAM)-concept, context, quality of life. Funding: The Science Fund at MU - Varna (2020-2022) [15 points]; (4) NNP "Creation of a database of blood donors in the Republic of Bulgaria for markers of transmissible infections", funded by the National Research Fund – Ministry of Education and Science (2020-2022) [15 points].

Total number of points in the indicator – 60.

- [E17] PARTICIPATION IN AN INTERNATIONAL SCIENTIFIC OR EDUCATIONAL PROJECT (N=3): (1) Academic project of AGMT, jointly with Bulgaria: "MABTENANCE: International, multicenter, randomized phase III study with Rituximab as maintenance therapy versus observation in patients with chronic lymphocytic leukemia" – conducted in the Clinic of Clinical Hematology, MBAL Hospital "St. Marina" EAD Varna, together with the Austrian group AGMT. Sub-investigator – 2009-2019 https://clinicaltrials.gov/ct2/show /NCT01118234 [20 points]; (2) In vitro dendritic cell generation and peripheral dendritic cell subsets in patients treated with purine nucleoside analogs, Implementation report of NATO EAP.RIG project 982938. Return fellow - 2007-2010 [20 points]; (3) A study of reactive oxygen species biological effects in the pathogenesis of myelodysplastic syndrome. Project of Hematology Division, Department of internal medicine, Patras University Medical School, Patras, Greece, and Hematology division. Department of Internal Medicine, Medical University, Varna, Bulgaria. Laboratory coordinator - 2007-2009 [20 points]

Total number of points in the indicator – 60.

- [E18]. MANAGEMENT OF NATIONAL SCIENTIFIC OR EDUCATIONAL PROJECT (n=1). Dr. St. S. Dimitrova, full-time postgraduate student with a supervisor Assoc. Prof. Dr. Ilina Micheva, Ph. Scientific Research Project of Young Doctors up to 35 years of age, postgraduate and doctoral students at the BMA (Contract No. 5/29.08.2019). - 2019-2021
Total number of points in the indicator – 30.

INDICATOR GROUP [E21]. Published university textbook or textbook used in the school network

Babacheva V, Balatsenko G, Varbanov H, Ganeva P, Genova M, Gercheva L, Goranov S, Goranova-Marinova V, Grudeva-Popova J, Ignatova K, Kaleva V, Milcheva K, **Micheva I**, Nenova I, Petrov Y, Raynov Y, Rachev R, Sapunarova K, Simeonov S, Spasov B, Spasov E, Stoeva V, Hadzhiev E, Tsvetkova G, Shemelekova L. "Guide to the diagnosis and treatment of hematological diseases". 2018. Varna: Art Trace. 544 p. ISBN: 978-619-7094-39-8
Total number of points in the indicator – 1.6.

INDICATOR GROUP [E22]. Training of interns, postgraduate students, and PhD students (seminars and practical classes)

The spectrum of teaching activities of the Assoc. Prof. Ilina Micheva includes a variety of activities: practical exercises and lectures on clinical hematology with medical students in their fifth year, including English-speaking students, supervision of postgraduate students in the Clinic of Hematology. She was or is the supervisor of five clinical hematology postgraduate students: Dr. St. Dimitrova (2014-2018); Dr. D. Ribov (2019-2021); Dr. Al. Todorova (2019-2023); Dr. N. Daskalova (2022-2026) and Dr. R. Lukanov (2018-2022)
Total number of points in the indicator – 30.
Conclusion: Overall, for the indicators of group [E], Assoc. Prof. Ilina Micheva has 361.6

points with 100 points required.

III. SCIENTIFIC ACTIVITIES AND CONTRIBUTIONS

The diverse scientific interests of Assoc. Prof. Ilina Micheva are outlined in the presented references and the attached publications. All scientific contributions were obtained because of joint developments in a team with other researchers determined by the specific goals and objectives, therefore I accept that the contributions of Assoc. Prof. Ilina Micheva are equal to those of the other members of the respective authors' collectives. In general, the contributions can be summarized in the following main areas:

Myelodysplastic syndromes (MDS): The clinical features and the disease course in patients with chronic myelomonocytic leukemia were studied and it was found that the prognosis of the disease is unfavorable with an average survival of 21.4 months and in a significant proportion of cases the disease transforms into acute myeloid leukemia (AML) within an average of 13.1 months and an average survival 2.5 months after the transformation [#10]. Based on a study of 219 patients with MDS, a significant difference in survival was found for individual subtypes according to the FAB and WHO (2016) classifications, age, and sex, as well as depending on the prognostic group determined by the established risk stratification scales (IPSS, IPSS -R, WPSS), with IPSS-R [#37] being the most accurate for the forecast. For the first time in the country, the importance of comorbidity indices [Charlson comorbidity index, HCT-comorbidity index (HCT-CI), MDS-specific comorbidity index (MDS-CI), Comorbidity Evaluation-27 (ACE-27)] and the degree of [Clinical Frailty Scale (CFS)] for MDS outcome, finding a significant difference in median survival according to comorbid indices and CFS, independent of IPSS-R, IPSS, and WPSS, adding additional prognostic information to established prognostic systems [#a53,#a77]. Application of the MDS-CI index to WPSS subgroups has been found to allow refinement of prognostic assessment in MDS patients [#39].

Myelofibrosis (MF): The level of one of the main regulators of iron metabolism, hepcidin, has been studied in patients with different forms and stages of MF. Patients with newly diagnosed MF were found to have higher levels of hepcidin compared to those with long evolution. Differences in hepcidin levels associated with patients' transfusion dependence, the conduct of cytogenetic or targeted therapy, leukocytosis, age, ferritin level, serum iron, and IL-6 were found [#25;#a40;#a68;#a83]. High hepcidin levels were also found to correlate with high risk by DIPSS, JAK2 V617F mutation status, and WHO (2016) fibrotic phase, with no correlation with survival [#a41]. Serum levels of IL-6 and their relationship with clinical-laboratory characteristics of patients with MF were analyzed, and it was found that the mean levels of IL-6 in all MF patients were significantly higher in comparison to those in healthy controls, with the highest values being observed in patients with grade 3 fibrosis. A significant association between the level of IL-6 and the number of blood transfusions was also observed [#5;#a51;#a74]. A 3-year experience of several centers in the country with ruxolitinib treatment of patients with primary MF was summarized [#a84]. The influence of impaired iron homeostasis on the pathogenesis of anemia in MF was studied and a significant correlation was found between the levels of hemoglobin, serum ferritin and total iron-binding capacity. The change in serum ferritin level is an indirect indicator of the significance of hepcidin and interleukin levels for the severity of PMF anemia [#8].

Acute leukemia: A retrospective study was conducted on the frequency and spectrum of chromosomal aberrations at the time of diagnosis in adult patients with AML and an abnormal karyotype was found in 46% of cases. Based on karyotyping data, patients were stratified into a favorable (9.5%), intermediate (69.8%) and unfavorable risk (20.6%) groups, with 2-year overall survival rates of 64%, 24%, and 10%, respectively, in the individual groups [#a47,#a66,

#a73]. The efficacy of azacitidine treatment in patients with MDS and AML has been studied. It has been found that at 18 months, 60% of MDS patients were alive, compared to 41.7% in AML cases. Median overall survival was 12.6 months in patients with MDS, and 5.4 months in those with AML [#43;#a90]. Some rare cases from the clinical practice are also described – a patient with previous mammary gland and ovarian carcinoma, who developed therapy related (t-)MDS with a complex karyotype, and high risk according to IPSS, who within two months progressed to t-AML, high risk and rapid fatal outcome [#33]; as well as a rare case of a patient with Ph(+) acute lymphoblastic leukemia with an ABL1 T315I mutation who, after an early relapse, was successfully treated with inotuzumab+ponatinib followed by allogeneic transplantation of hematopoietic stem cells and maintenance with ponatinib [#6].

Multiple Myeloma (MM): A retrospective analysis of the cytogenetic profile of newly diagnosed MM patients, assessed by conventional cytogenetic analysis and fluorescence in situ hybridization (FISH), was performed, and an abnormal karyotype was found in 16% of patients, in most cases in the form of a complex karyotype. By FISH, del(17p13) was demonstrated in 23% of cases. The established cytogenetic profile was significantly associated with all prognostic variables, including overall survival [#3;#14;#19,#a52]. Experience with Bortezomib maintenance therapy in patients with MM after achieving a complete response (CR) or very good partial response (VGPR) is presented, with the finding that at a median follow-up of 31.8 months, none of these patients' progression was recorded, whereas in most of the observation patients it occurred within a median period of 24.17 months [#a62]. Within the framework of the PORT study (NCT04412707), the pharmacokinetic characteristics of central [central venous catheter (CVC)] and peripheral administration of melflufen were compared, and the local tolerability of the peripheral administration of the preparation was also evaluated. It was established, that the differences in pharmacokinetic parameters related to the method of administration of the preparation have no clinical consequences, since their duration of plasma exposure is short. No local reactions have been found after peripheral administration of melflufen [#a49;#a50]. The role of 18F-FDG PET/CT in determining the extent of bone disease and extramedullary involvement and staging of newly diagnosed MM patients was evaluated. 18F-FDG PET/CT has been found to have higher specificity and sensitivity compared to other imaging approaches and has key prognostic value in MM [#a60;#a61]. Pathogenetic mechanisms with established or suspected significance for the development of myeloma-induced bone disease were investigated. Serum levels of periostin, sRANKL, and osteoptin have been found to gradually increase during the clinical evolution from MGUS to more advanced multiple myeloma, reflecting the severity of bone destruction [#64]. Correlations with the severity of bone disease have also been demonstrated in serum levels of inhibitors of the canonical Wnt signaling pathway – sclerostin and DKK-1, which are responsible for osteoblast differentiation [#65].

Infectious complications in hematological malignancies: The spectrum and antibiotic resistance of bacterial pathogens associated with blood infections in patients with hematological malignancies were studied. It was found that a dominance of Gram(-) bacteria, a persistently high level of ESBL-producing members of the Enterobacteriaceae family and multi-resistant Enterococcus faecium, and a high proportion of carbapenem-resistant Acinetobacter baumannii and methicillin-resistant Coagulase(-) staphylococci (CoNS), as well as the appearance of invasive carbapenem-resistant isolates from the Enterobactericeae family [#2]. Slime production was studied in isolates of Staphylococcus spp. in bacteremia in post-THSC patients, determining the relationship between slime production and carriage of ica genes, as well as the correlation between ica and methicillin resistance [#4]. Assessed the clinical significance of the Aspergillus Galactomannan antigen (GM) test in the diagnosis of invasive pulmonary aspergillosis in patients with hematological neoplasia, including after HSCT when examining

blood samples and bronchoalveolar lavage samples [#7,#a83]. The species diversity of clinically relevant Staphylococcus spp. was analyzed. Isolates were obtained from blood cultures of patients with a central venous catheter (CVC) after THC, and their drug susceptibilities were determined. CoNS were found to be the most common cause of catheter-related infections, with S. epidermidis being the predominant species. All CoNS isolates were resistant to methicillin and had reduced susceptibility to other antimicrobials [#26]. The incidence and spectrum of multidrug-resistant (MDR) intestinal colonizers were investigated. Genes associated with treatment resistance were identified, e.g. - blaSHV, blaCTX-M, blaTEM with third generation cephalosporins, blaVIM - with carbapenem, vanA - with glycopeptide resistance. [#a46]. The in vitro activity of ceftazidime-avibactam (CZA) against extended-spectrum beta-lactamase-producing (ESBL) and carbapenem-resistant Gram(-) bacteria recovered from blood and fecal samples of patients after hematopoietic stem cells transplantation (HSCT) was analyzed and CZA was found to have pronounced activity against ESBL producers, but its effect is limited against carbapenemase producers [#a63]. The species diversity and profile of resistance to antimycotic drugs of Candida spp. isolates obtained from clinical materials of patients after HSCT were analyzed [#a71].

Hematopoietic stem cell transplantation: The results of the clinical application of autologous HSCT in patients with MM were analyzed, and the obtained results confirmed the efficacy and safety of the therapeutic procedure, noting that the achievement of CR+VGPR before transplantation was a factor for prolonged overall survival (OS) and progression free survival (PFS). [#1,#a76]. The results from the application of haploidentical HSCT were evaluated, using, in 81.8% of the cases a myeloablative conditioning regimen, and in the remaining patients – conditioning with a reduced intensity. As part of GvHD prophylaxis, cyclophosphamide was administered after transplantation in all except one, who received an anti-thymocyte globulin. 72.2% of patients were found to be alive after transplantation, with 45.5% achieving remission and 27.3% having relapsed [#a45;#a75]. The results of salvage autologous HSCT in patients with refractory non-Hodgkin's lymphomas (NHL) and Hodgkin's disease were evaluated, and it was found that complete or partial remission was achieved in 39% and 61% of patients, respectively, at the 3rd month after transplantation, and 39% - progressed within 6 months. The estimated 5-year survival rate was 78% [#a54]. The results of the application of different chemo-G-CSF protocols (DHAP;CY;IGEV, ICE,CHOEP,VTD-PACE) for the purpose of peripheral stem cell mobilization in patients with lymphomas who received autologous HSCT were compared. The mean yield of successfully mobilized cells was found to be 8.44x106/kg, with different chemo-G-CSFs having comparable efficacy with acceptable toxicity and being superior to CY-G-CSF for stem cell mobilization [#a57]. A case of successful desensitization in a patient with AML and donor-specific antibodies before haploidentical allogeneic HSCT is presented [#a72].

Lymphoproliferative neoplasia: In the first multicenter retrospective study in the country, the results from treatment with Brentuximab Vedotin (BV) in patients with refractory or relapsed Hodgkin's lymphoma after autologous HSCH, who received 2 to 5 lines of therapy were analyzed, and an improvement in the therapeutic response, prolongation of time to progression, and increased overall survival were observed. It was found that the only significant prognostic factor determining a longer remission was the achieved response: in the CR+PR group, up to the time of analysis, the PFS had not being reached, while in the patients with stable disease or progression, it was 7 months. The number of courses performed with BV is an independent factor influencing OS and PFS [#23,#a55, #a56,#a58,#a81]. VEGF expression was investigated in newly diagnosed patients with aggressive and indolent NHL; significantly higher levels of VEGF were found in patients versus healthy controls, in indolent versus aggressive lymphomas, and in high versus normal LDH values. Patients at intermediate and high risk and with elevated VEGF levels have a poor prognosis and short overall survival [#31]. The level of platelet-

neutrophil complexes (PNC) in patients with indolent and aggressive NHL was investigated, and significantly higher levels of PNC were found in patients with NHL compared to healthy controls, as well as in aggressive vs. indolent NHL. An inverse relationship between PNC and hemoglobin values has also been reported. [#34]. The efficacy and safety of TruximaTM treatment combined with different chemotherapy regimens [CHOP, Bendamustin, FC, MINE,ACVBP,COP,ICE,Leukeran] in patients with NHL and chronic lymphocytic leukemia. (CLL) were studied. A complete response was achieved in 30% of patients, a partial response in 56.7%, stable disease in 13.3%, and progression was observed in only one case. No unexpected side effects were reported [#a59]. Rare clinical cases were presented outlining some important aspects of clinical practice: the advantages of 18F-FDG PET/CT in the diagnosis and follow-up of a patient with generalized NHL with multiple extranodal lesions, especially for detecting diffuse organ-infiltrating lesions [#9]; a rare case of a patient with severe myasthenia gravis, possibly associated with relapsed CLL, who was started on combined targeted and immunotherapy, with an acceptable tolerability [#12]. A rare case of a young woman with Langerhans histiocytosis with multisystem involvement, including the bone, orbit, pulmonary system, and central nervous system has also been reported. After undergoing chemotherapy for 6 months with a partial response achieved and a PET/CT positive lesion in the right iliac bone, and disease progression occurred one year later [#35].

Other topics: A 10-year experience in the study of chromosomal aberrations in patients with hematological malignancies was summarized, determining the relative proportion of samples with karyotype abnormalities and the spectrum of the most common chromosomal aberrations in different entities [#11;#29]. In a multicenter, randomized, double-blind, phase 3 study, best maintenance treatment plus luspatercept versus placebo in adult patients with transfusion-dependent β-thalassemia were compared and it was found that luspatercept reduces the transfusion requirements. The results of this study led to the approval of the medication and its inclusion in the therapeutic guidelines [#20]. In another multicenter study, TCR-dependent interactions between blasts and T-cells were investigated in an experimental model after in vitro incubation of CD4xCD123 bispecific antibodies (BsAbs) with bone marrow cells from patients with AML. It has been found that direct contact between T-cells and blasts by BsAb can in some cases directly reactivate preexisting tumor-specific T-cells, and this secondary T-cell response requires cross-presentation from classical APCs or blasts directly, independent of BsAb, which can be blocked by anti HLA or TCR antibodies [#24]. The potential role of HLA-II alleles in the development of myeloproliferative neoplasms has been investigated, with the finding that HLA class II can limit JAK2 V617F and CALR mutation-associated oncogenesis [#a44]. "Incidental findings not related to the specific disease" identified during karyotyping of patients with hematological diseases, which allowed the diagnosis of an unsuspected chromosomal disorder or required genetic counseling in at-risk first-degree relatives with a possible further impact on their reproduction, were analyzed. [#a48]. A number of clinical cases are presented, that enrich the knowledge of the heterogeneity of hematological diseases and contribute to the practical diagnostic-therapeutic behavior of conditions that do not correspond to the classical ideas of symptomatology, laboratory changes, and clinical course [#a86, #87,#a91, # a92, #a93, #a94].

IV. OTHER SCIENTIFIC AND PROFESSIONAL ACTIVITIES

Assoc. Prof. Ilina Micheva, is a Vice-Chair of the Board of the Bulgarian Society of Hematology and is Chair of the Scientific Group "Myeloproliferative Neoplasms and Myelodysplastic Syndromes", as well as a member of the Working Group on "Hematopoietic Stem Cell Transplantation" of the Society. She is a member of the "Expert Council on Clinical Hematology" at the Ministry of Health and is also the chair of the

working committees for health technology assessment at the National Council on Drug Prices and Reimbursement (NCPR). She is also an expert on the Programme Committee of the European Commission and in the "AML Community of excellence".
She is a member of the editorial board of the journals "Hematology" and "Pro medica", and has been a reviewer for leading international journals in the field of hematology (British Journal of Haematology, Asian Haematology Research Journal, Turkish Journal of Hematology, etc.). She has reviewed research projects for the Research Fund of the Ministry of Education and Science and for the Research Fund of the Medical University of Plovdiv. In addition, she has been a member of scientific juries for the academic positions of "Professor", "Associate Professor", "Senior Assistant Professor" and for the degree of "Doctor" at MU-Varna, MU-Pleven, MU-Plovdiv, MMA-Sofia.

V. ASSESSMENT TABLE OF THE APPLICANT'S CONFORMITY WITH THE MINIMUM SCIENTIFIC-METRIC INDICATORS AND CRITERIA REQUIRED FOR THE ACADEMIC POSITION OF PROFESSOR

GROUP	INDICATORS	NUMBER OF POINTS NEEDED FOR A PROFESSOR	Points of Assoc. Prof. Ilina Micheva
A	1. Thesis for the award of the educational and scientific degree "Doctor"	50	50
V	4. Habilitation work - scientific publications (not less than 10), equivalent to/replacing a published monographic work, in publications that are referred and indexed in world-known databases of scientific information	100	156.02
G	7. Publications and reports published in scientific journals, referred, and indexed in world-renowned databases of scientific information	200	231.45
	8. Publications and papers published in non-refereed peer-reviewed journals or published in edited collective volumes		215.75
	Total G7+G8	200	447.2
D	10. Citations or reviews in scientific journals referenced and indexed in world-renowned databases of scientific information or in monographs and collective volumes	100	2475
	11. Citations in monographs and peer-reviewed collective volumes		70
	12. Citations or reviews in non-refereed peer-reviewed journals		80
	Total D11+D12+D13		2625
E	14. Supervision of a successfully defended PhD student (n is the number of supervisors of the respective PhD student)	100	100
	15. Board certified in recognized medical specialties		80
	16. Participation in national scientific or		60

	educational projects		
	17. Participation in international scientific or educational projects		60
	18. Leadership of national scientific project team		30
	21. Published university handbook or handbook used in the school		1.6
	22. Training of interns, postgraduate students, and PhD students (seminars and practical classes)		30
	Total E14+E15+E16+E17+E18+E21+E22	100	361.6
	Total:	**550**	**3599.82**

CONCLUSION

The presented documents, scientific production, citations, as well as the volume of teaching and learning activities reflect the teaching experience, versatile scientific interests, achievements, and contributions of **ASSOC. PROF. DR. ILINA DIMITROVA MICHEVA, MD, PHD** and outline her as an established professional with authority in the field of clinical hematology and an established teacher. The evaluation of her scientific-metric indicators exceeds the criteria and conditions for holding the academic position of "Professor", regulated in the Law on the Development of Academic Staff in the Republic of Bulgaria and its Implementing Regulations, as well as the Regulations for the Development of Academic Staff at MU - Varna. All this gives me grounds to have a positive opinion regarding the candidature of **ASSOC. PROF. DR. ILINA DIMITROVA MICHEVA, MD, PHD,** and to confidently recommend the members of the esteemed Scientific Jury to vote positively for her election to the academic position of "Professor" in the field of higher education 7. Health and Sport, professional field 7.1. Medicine, scientific specialty "Hematology" for the needs of MU - Varna

Sofia

18.04.2023

Prof. Gueorgui Balatzenko, MD, PhD