Peer Review

by Prof. Krasimir Ivanov, MD, PhD, DSc

Medical University "Paraskev Stoyanov", Varna

The competition was announced in SG No. 83 / 03.10.2023 for the academic position of "Professor" in the field of higher education 7. Health care and sports, professional direction 7.1. Medicine and scientific specialty "Oncology" for the needs of the "Oncology" Department, Faculty of "Medicine" at MU-Varna.

I. Brief biographical data

Associate Professor Nikolay Vladimirov Conev graduated secondary education from PMG "St. Kliment Ohridski" - Silistra with a Biology profile. In 2002, he graduated from the University of Economics - Varna - Bachelor of Economics, specialty in Commodities Science. In 2009, he graduated as a medical doctor at the Medical University of Varna, specialty in Medicine.

In 2010, he started working (as an oncology fellow) at the Medical Oncology Clinic, UMHAT "St. Marina" - Varna. For the period 2010/2015, he worked as an oncology fellow – at Medical Oncology Clinic, UMHAT St. Marina. In 2015, he acquired a medical specialty "Medical Oncology". Since 2016, he has been an oncologist at the Medical Oncology Clinic, UMHAT St. Marina. Since 2018, he has been the head of the Medical Oncology Clinic, and since 2019, he has been the head of the "Oncology Clinics Direction" at UMHAT Saint Marina.

In 2013, he was appointed as a part-time assistant in the Department of "Propaedeutics of Internal Diseases" at the Medical University - Varna, since 2017 he was a full-time assistant at the Medical University - Varna, and since 2018 he has been a chief assistant, and in the same year (2018) - Associate Professor at the Department of "Propaedeutics of Internal Diseases". Since

2020, he has been an Associate Professor at the Department of Oncology. Since 2019, he has been the head of the "Oncology and Rare Diseases" department at the Research Institute of the MU - Varna.

In 2016, he acquired a PhD in the scientific specialty of Medical Oncology on the topic: "Microribonucleic acids miR-17, miR-21, miR-29a and miR-92 as potential markers for assessing the risk of relapse after adjuvant chemotherapy in patients with colon cancer".

Associate Professor Nikolay Conev has participations in various master courses of the European School of Oncology (ESO), as well as continuing medical education courses at ESMO, among which are the Qualification Course/Seminar on Organization, management and conduct of a clinical trial, November 2012, Specialized course on Antiangiogenesis treatment, Belgium (2014), Antiangiogenic therapy in recurrent platinum-sensitive ovarian carcinoma and Masterclass in Molecular Oncology, Prague, Czech Republic in 2015.

He is a member of ESMO (European Society for Medical Oncology), and ASCO (American Society of Clinical Oncology) and is an indexed author of J-Stage (Japan science and technology information aggregator).

He presents scientific work at over 50 international scientific forums.

II. Analysis of the materials provided for the competition

Associate Professor Nikolay Conev participates in the competition with the following scientific work:

1. Provides a diploma for an acquired PhD in the relevant specialty.
2. Provides a diploma for acquired medical specialty "Oncology".
3. Provides a diploma for the acquired position of "Associate Professor" in the relevant specialty.
4. Provides 12 full-text publications equivalent to a monographic work, which are referenced and indexed in world-renowned databases of scientific information.
5. Provides a total of 33 publications and reports that have been published in scientific journals, referenced and indexed in world-renowned databases of scientific information.

6. Provides a total of 12 publications and reports published in non-referenced peer-reviewed journals or published in reviewed collective volumes.

7. Participation in international and national scientific congresses with presentation of own research - 56 participations, the most significant of which are:

-   "Levels of miR-17, miR-21, miR-29a and miR-92 as recurrence markers after adjuvant chemotherapy in Nx lymph node status colon cancer patients", ESMO, Copenhagen, Denmark, 2016;

-   "Time perception as a novel ultra-short screening tool for distress in cancer patients", ASCO, Chicago, USA, 2018;

-   "Unexpected discordance in 5-year OS rates between Nx colon cancer patients and those in stages II plus III", ESMO, Barcelona, 2018;

-   "Evaluation of genetic variants in miR-146-a, miR-618, and miR-181b as risk factors of colorectal cancer in Bulgarian patients".
    ESMO, 2020;

-   "Regorafenib and trifluridine/tipiracil efficacy and safety in chemorefractory metastatic colorectal cancer patients: A single Bulgarian center retrospective study".
    ESMO, Barcelona, 2020;

-   "Plasma levels of hsa_circ_0001445 and hsa_circ_0007915 may indicate the presence of metastatic disease in patients with colorectal cancer".
    ESMO, 2021;

-   "Higher muscle mass is associated with better response to concurrent neoadjuvant chemoradiotherapy in rectal cancer patients".
    ESMO, 2021;

-   "Impact of travel burden on overall survival in patients with lung cancer".
    ASCO, Chicago, USA, 2022;

-   "Translationally controlled tumor protein as a prognostic marker in metastatic colon cancer".
    ASCO, Chicago, USA, 2023;

-   "PI3KCA mutation prevalence and outcome among patients with metastatic breast cancer in Bulgaria treated with first-line endocrine therapy".
    ASCO, Chicago, USA, 2023;

8. Participation in significant scientific projects - "Investigation of single nucleotide polymorphisms in non-coding RNAs in patients with colorectal cancer with the aim of identifying new diagnostic, prognostic and predictive biomarkers for the Bulgarian population", Fund "Nauka", Position: Expert, "Research on the impact of specific carboxylesterase inhibitors on the efficacy of Capecitabine chemotherapy'. Period: 19.12.2019 – 20.12.2021. Organization: MU-Varna. Position: Expert, Investigation of expression levels of immunohistochemical markers of necroptosis in breast cancer. Period: 19.12.2019 – 20.12.2021. Organization: MU-Varna. Position: **Scientific supervisor.**

9. Supervision of successfully defended PhD students - three.

10. IF reference - total 1276.168.

III.   Dissertation analysis

Topic: "Microribonucleic acids miR-17, miR-21, miR-29a, and miR-92 as potential markers for assessing recurrence risk after adjuvant chemotherapy in patients with colon cancer".

The prognosis for patients with colon cancer who underwent radical surgery and adjuvant chemotherapy varies from patient to patient and depends on a number of factors. Currently, the "gold standard" is the TNM clinicopathological classification and disease stages determined by this system. However, the prognosis in different patients at the same stage is not the same, and other clinical, histopathological and biomolecular markers can also provide further stratification of groups according to prognosis. Over the past two decades, a large number of protein, biomolecular and genetic markers have been the subject of intensive research. So far, although there are many published recommendations for the inclusion of new prognostic markers, no clear consensus has been reached for most of the new markers studied and they are very slow to enter daily practice.

Microribonucleic acids (miRNAs) are small RNA molecules made up of about 21-25 nucleotides that do not code for proteins but have an important function in regulating gene expression, with the first reports of miRNAs dating back to 1993, and they possess some features, which make them suitable for biomarker use.

Among the most significant contributions of the work are:

- For the first time in Bulgaria and the in world, the plasma levels of miR-17, miR-21, miR-29a and miR-92 were investigated as potential biomarkers to predict recurrence up to one year after adjuvant chemotherapy in radically operated patients with cancer of the colon.
- For the first time worldwide, it is reported that the expression levels of miR-17, miR-21 and miR-92 in the group of Nx patients are statistically significant and can be considered as a non-invasive diagnostic biomarker for relapse after adjuvant chemotherapy in patients with colon cancer.

IV. Contributions of more significant scientific works:

1. Circulating Histones to Detect and Monitor the Progression of Cancer. Int J Mol Sci. 2023

Liquid biopsies are a minimally invasive cancer detection and monitoring method that can identify cancer-related changes at the level of nucleosomes or histones as well as modifications in blood, saliva and urine. Histones, the core component of the nucleosome, are essential for compacting chromatin and modulating gene expression. Increasing evidence suggests that circulating histones and histone complexes, which are released upon cell death or by immune cell activation, may act as promising biomarkers for cancer detection and treatment.

2. Impact of travel burden on clinical outcomes in lung cancer. Support Care Cancer. 2022, Jun;30(6):5381 7.

A retrospective study found significant differences in the overall survival of lung cancer patients depending on the distance and travel time to an oncology facility. Despite similar clinical and pathologic characteristics (sex, stage at initial diagnosis, histologic subtype), median overall survival was significantly lower in these subgroups of patients with higher travel burden.

3. Single Nucleotide Polymorphisms in microRNA Genes and Colorectal Cancer Risk and Prognosis. Biomedicines. 2022;10(1):156.

There is a growing interest in single nucleotide polymorphisms SNPs in microRNA miRNA genes that may be associated with the development of colorectal cancer, as they may elucidate disease prognosis and/or predict response to treatment. Furthermore, these miRNAs SNPs may serve as novel, non-invasive biomarkers.

4. New Circulating Circular RNAs with Diagnostic and Prognostic Potential in Advanced Colorectal Cancer. Int J Mol Sci. 2021 Dec;22(24):13283.

Circular RNAs circRNAs are a group of special endogenous long non-coding RNAs that are stable in the circulation and therefore suitable as novel biomarkers for colorectal cancer. Prognostic significance of hsa_circ_ 0001445 was found in patients with metastatic CRC.

5. One minute time interval estimation as a novel potent indicator of emotional concerns in cancer patients prior to starting chemotherapy. Curr Psychol. 2021, Aug;40(8):3997 4003.

The study investigated the potential relationship between time perception assessment and distressing problems in cancer patients before starting chemotherapy. Time estimation was determined prospectively in 375 chemonaive patients with solid tumors by subjective assessment by the patients of how quickly one minute passed compared to the actual time. An easy-to-administer, time-saving, non-intrusive, ultrashort screening tool has been developed that is suitable even for patients who do not wish to reveal their emotional state through direct questionnaires.

6. Circulating miR 618 Has Prognostic Significance in Patients with Metastatic Colon Cancer. Curr Oncol. 2021, Apr;28(2):1204 15.

The study evaluated the prognostic role of circulating miRNA 618 in patients with metastatic colon cancer (mCC) and whether miR 618 gene rs 2682818 (single nucleotide polymorphisms (SNP)) was associated with colon cancer susceptibility and with the expression levels of mature a miR 618 . 104 patients with mCC were studied before the start of chemotherapy. The data suggest that circulating miRNA 618 may be useful as a prognostic biomarker in mCC. Patients with the AC rs 2682818 genotype had a reduced risk of colon cancer compared to patients with the CC and AA genotypes.

7. Sarcopenia and high NLR are associated with the development of hyperprogressive disease after second line pembrolizumab in patients with non-small cell lung cancer. Clinical and Experimental Immunology. 2020 Dec 1;202(3):353

A retrospective study to assess the incidence of hyperprogressive disease (HPD) after second-line treatment with pembrolizumab in patients (n 167) with metastatic non-small cell lung cancer whose tumors express Programmed cell death ligand 1. The study also investigates hematological

and imaging biomarkers associated with its development. Data suggest that high NLR 2 before immunotherapy and the presence of sarcopenia are potential risk factors for the development of HPD.

8. Fast time perception is associated with high levels of anxiety in cancer patients prior to starting chemotherapy. BioSci Trends. 2020 Feb;14(1):35.

Diagnosing anxiety is known to be challenging due to the lack of objective biomarkers and diagnosis based on symptoms alone. The study suggests a potential marker for anxiety for the first time, and further studies are needed to confirm the results.

9. Neutrophil to lymphocyte ratio as a potential predictive marker for treatment with pembrolizumab as a second line treatment in patients with non-small cell lung cancer. BioSci Trends. 2020 Feb;14(1):48 55.

The aim of this multicenter retrospective study was to evaluate the predictive and prognostic value of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio and their dynamics in patients with non-small cell lung cancer treated with second-line pembrolizumab. The data suggest that NLR is a potential predictive marker that may identify patients suitable for immunotherapy as a second-line treatment.

10. One minute time interval estimation as a novel ultrashort tool for distress screening. Support Care Cancer. 2019 Jun;27(6):2031 7.

Time perception assessment is a new powerful tool for the investigation of high levels of distress in cancer patients. This test is an easy-to-administer, time-saving and non-intrusive ultrashort screening tool that is suitable even for patients who do not wish to disclose their level of distress through direct questionnaires.

V. Educational and teaching activity - since 2013 Associate Professor Nikolay Conev has led the practical seminars in the specialty "Propaedeutics of Internal Diseases" at the Medical University - Varna with a total workload of 180 hours per year. Since 2023, he has been conducting lecture courses and practical seminars in Oncology.

The provided scientific materials, participation in scientific forums, and references for the teaching activity of Associate Professor Nikolay Vladimirov Conev fully meet the requirements for acquiring the academic position "Professor ", defined in the regulations for the development of the academic staff at the Medical University "Prof. P. Stoyanov" - Varna.   Due to the above, I give my positive assessment, suggesting to the honorable scientific jury to vote positively for his election to the academic position of "Professor".

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/Prof. Krasimir Ivanov, MD, PhD, DSc/