

# REVIEW

**FROM PROF. KRASIMIR IVANOV, MD, PhD, DSc.**

**MEMBER OF THE SCIENTIFIC JURY**

**ELECTED BY ORDER NUMBER P-109-567/19.12.2023**

**OF THE RECTOR OF THE MEDICAL UNIVERSITY - VARNA**

**About:** The dissertation thesis of Maria Ivanova Penkova-Ivanova, MD, for the award of the Education and Scientific degree „Doctor“ at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, specialty - Oncology, dissertation thesis "Expression of markers of tumor reversion in colorectal cancer" with scientific supervisor Assoc. Prof. Eleonora Georgieva Dimitrova-Gospodinova, MD, PhD

## **Biography:**

Dr. Maria Ivanova Penkova-Ivanova graduated from Natural and Mathematical High School – Sliven with a degree in Biology, Chemistry and German. In 2016 she graduated with excellent grades in medicine from Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. After graduation she worked in an outpatient clinic for primary outpatient care and was a visiting assistant at the Second Department of Internal Medicine, UNU - Gastroenterology, Hepatology and Nutrition. Since October 2015 she has been working as a specialist physician at the Clinic of Medical Oncology of the University Hospital "St. Marina" - Varna and is a regular assistant professor at the Department of Propaedeutics of Internal Medicine at the Medical University - Varna, English-speaking training. From 2020 she was reassigned to the newly formed Department of Oncology, and in the same year she was enrolled as a full-time PhD student at the Department. She speaks English and German. Dr. Penkova is a member of the European Society of Medical Oncology (ESMO).

**Globally, colorectal cancer (CRC)** ranks third among human malignancies and accounts for approximately 10% of all malignant solid tumors. Despite advances in its treatment over the past decade, the 5-year survival rate for patients in clinical stage IV still does not exceed 10%.

The development of CRC is a multistep process that is influenced by a number of endogenous and exogenous factors. Studying the pathogenesis of malignant solid tumors raises the question of studying its opposite process - tumor reversion. Tumor reversion is a complex biological process in which some neoplastic cells lose their partially or completely malignant phenotype.

One of the major players in the process of tumor reversion is the **Translationaly controlled tumor protein (TCTP)**.

In Dr. Penkova's dissertation the correlation between the expression levels of the tumor reversion marker TCTP in the primary tumor of patients with histologically verified CRC and some clinicopathological characteristics of the studied group of patients - gender, age, tumor differentiation grade, RAS mutation status, as well as with progression-free survival and overall survival was sought.

### **Characteristics of the dissertation submitted for review:**

The dissertation is presented in a volume of 117 pages and is illustrated with 18 tables and 17 figures. The scientific work has the following structure: "Introduction" - 2 pages, "Literature review" - 58 pages, "Aim and objectives of the study" - 1 page, "Patient population and study methods" - 11 pages, "Results" - 12 pages, "Discussion" - 4 pages, "Conclusion" - 1 page, "Conclusions" - 1 page, "Contributions of the dissertation" - 1 page, "Scientific publications and communications related to the dissertation" - 2 pages (5 scientific publications are presented, of which 3 are published in international journals). The literature review contains 273 Latin and 1 Cyrillic titles.

In the **literature review**, Dr. Penkova has presented up-to-date data regarding the epidemiology of CRC, both for Bulgaria and the entire world. She has prepared an in-depth analysis of the etiology, pathogenesis of CRC, the study of predictive and prognostic factors, and new approaches in the treatment of CRC. The process of tumor reversion is discussed in detail and systematically, presenting the most important players in the process and their influences in the development of not only CRC but also other malignant solid tumors. Particular attention is paid to the introduction of the main mediator in the process of reversion in particular - TCTP. Its structure, biological function and its role in the processes of carcinogenesis and tumor reversion are presented in detail.

**The aim of** this thesis is clearly and precisely formulated - to identify the potential value of TCTP as a novel prognostic biomarker in patients with histologically verified colorectal cancer. To realize the set aim, the PhD student has set the following **tasks**:

1. Selection of patients with histologically verified colorectal cancer before initiation of systemic drug therapy.
2. To collect the main clinicopathological characteristics of the patients and their response to the systemic drug therapy.
3. Quantify nuclear and cytoplasmic expression levels of TCTP in primary tumor cells.
4. Analyze correlations between nuclear and cytoplasmic TCTP expression levels and various clinicopathological characteristics of patients.

5. To analyze the prognostic potential of nuclear and cytoplasmic expression of TCTP in terms of relapse-free survival, progression-free survival and overall survival.

6. Comparison of the data obtained in the studied patient population with the accumulated data from the world literature.

### **Results:**

This thesis presents the results of a retrospective single-centre clinical trial in which 74 patients with histologically verified CRC were selected and followed up for one year - January 2015 to December 2015. The PhD student has synthesized and well illustrated with tables and figures the distribution of the selected patients according to their clinicopathological characteristics: gender, age, performance status, RAS mutation status, localization and tumor differentiation grade.

Analysis of test results found no correlation between TCTP expression levels in the primary tumor and sex, age, performance status, primary tumor location, and stage at diagnosis. In the course of the study, a significant difference in progression-free survival was found for the low nuclear TCTP expression group compared with the high nuclear TCTP expression group. A significant difference was also reported in terms of overall survival in the two groups, with significantly longer overall survival in the low nuclear expression group compared with the high nuclear expression TCTP group. The systematic results of this study suggest that high nuclear TCTP expression levels are an independent prognostic factor for worse progression-free survival and overall survival.

**The discussion** on the analysed results highlights their significance. A comparison is made between the results obtained and results from other similar trials worldwide. The dissertation takes a self-critical approach, pointing out some limitations in the present study and providing directions for future developments.

**Conclusions:** 7 clearly formulated conclusions are synthesized, which accurately and concisely summarize the results of the dissertation and fully meet the set goals and objectives. The dissertation contributions have been pointed out not only in Bulgaria but also worldwide.

**The abstract** presents a concise summary of the main points of the thesis - materials and methods, aim and objectives, results, discussion, contributions and conclusions of the thesis. The scientific publications and communications related to the dissertation are also attached.

### **Brief notes and recommendations:**

In the present trial, the dissertator selected a relatively small group of patients (74), and this in turn requires further studies. However, the results analyzed herein strongly suggest that the level of TCTP expression in the primary tumor is a novel prognostic biomarker in patients with histologically verified colorectal cancer. I believe that the dissertation will have the opportunity to add to and expand the knowledge and contributions in the field of the topic under consideration in the coming years.

**Conclusion:**

The dissertation work of Dr. Maria Penkova-Ivanova entitled: "Expression of tumor reversion markers in colorectal cancer" presents results and conclusions with an original contribution to science and meets all the requirements of the Academic Staff Development Act of the Republic of Bulgaria (ASDA), the Implementing Regulations of ASDA and the Regulations of MU-Varna.

The dissertation shows that the dissertant Dr. Maria Penkova-Ivanova has acquired in-depth theoretical knowledge and demonstrates qualities and skills for independent scientific research.

Because of the above, I cogently give my positive evaluation of the dissertation.

**I propose to the highly respected Scientific Jury to award to Dr. Maria Penkova-Ivanova the educational and scientific degree "DOCTOR".**

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Prof. Krasimir Ivanov, MD, PhD, DSc.