

**TO
THE CHAIRMAN
OF THE SCIENTIFIC JURY,
DETERMINED BY ORDER No. R-109-96/ 12.02.2026
OF THE RECTOR OF THE MEDICAL UNIVERSITY
"PROF. DR. PARASKEV STOYANOV" - VARNA
PROF. DR. DIMITAR RAIKOV, MD, D.M.Sc.**

REVIEW

By: Prof. Dr. Zdravka Vasileva-Valerianova, MD, PhD

Head of the Department "Management and Coordination of Programs and Projects"

USHATO "Prof. Ivan Chernozemsky" EAD, Sofia

Subject: Conducting a procedure for the defense of Dr. Radostina Bozhidarova Gencheva MD, PhD student in an independent form of study in the doctoral program "Oncology" of a dissertation on the topic: "FREQUENCY OF PIK3CA-MUTATIONS AND THE RESPONSE TO FIRST-LINE ENDOCRINE THERAPY IN THE POPULATION OF BULGARIAN PATIENTS WITH HR (+) HER2(-) METASTASISED BREAST CANCER", for the award of the educational and scientific degree "Doctor" in the field of higher education 7. "Health and Sports", professional direction 7.1. "Medicine", enrolled by order No. R-109-210/ 17.07.2024.

Scientific supervisor of the dissertation: Assoc. Prof. Eleonora Georgieva Dimitrova - Gospodinova, MD, PhD

Dear Mr. Chairman of the Scientific Jury,

Dear Members of the Scientific Jury,

Dr. Radostina Bozhidarova Gencheva, MD was born on June 13, 1982. In 2002, she graduated from the National High School of Natural Sciences and Mathematics, majoring in Chemistry. In 2008, she graduated as a master's degree from the Medical University, Sofia. Dr. Gencheva began her work experience in 2015-2018 at the Evangelist Hospital in Hamm, Germany. During the period 2015-2018, she was a resident in the Clinic of Gastroenterology, Oncology and Internal Medicine at the City Hospital of Solingen, Germany. From May 2018 to December 2021, she was a resident in the Clinic of Oncology, Nadezhda Hospital, Sofia, and subsequently from 2022 to the present, she is a specialist physician in the same hospital. In 2022, she acquired the specialty "Oncology" at the Medical University of Sofia. In 2025 successfully passed the exam at the European Society for Medical Oncology, and in 2021 acquired a GCP certificate. He has

experience in clinical trials of: Lung – III phase-3, Breast – III phase-10, Ovary I phase-1, III phase-4 and Colorectum - III phase1.

He speaks fluently German and at a good level English.

He is a member of ESMO, BAMO, Bulgarian and German Medical Associations.

The dissertation of Dr. Radostina Bozhidarova Gencheva, MD submitted to me for Review contains 115 typewritten pages, including 29 figures and 6 tables. The main text contains: Abbreviations used – 1 page; Introduction - 2 pages; Literature Review - 49 pages; Goal and Objectives – 1 page; Material and Methods - 9 pages; Results - 14 pages; Discussion – 3 pages; Conclusions - 1 page, Contributions – 1 page; Scientific Publications and Participation in congresses, conferences, etc., related to the dissertation – 2 pages; bibliography - 27 pages.

The dissertation is formatted in accordance with the requirements adopted in the country, enshrined in the Act on the Development of the Academic Staff in the Republic of Bulgaria. At the beginning, the Abbreviations used in the scientific work and the table of contents are listed, which facilitates the reading of the included material.

The Introduction is short and clear, and contains the main aspects underlying the presentation of the individual chapters of the dissertation and logically points to the essence of the scientific work and a Review of the Literary sources relevant to the results and their discussion.

In the literature Review of the dissertation submitted to me for Review, the studies of other authors and coauthors on the frequency of PIK3CA mutation in hormone-positive HER2-negative metastatic breast cancer were analyzed. The progression-free survival and overall survival were examined, depending on the PIK3CA mutation status of patients treated with first-line endocrine therapy (ET), as monotherapy or in combination with a CDK4/6 inhibitor. The conclusions drawn from the Literature Review point to the essence of the scientific work.

The goal and additional goal are correctly formulated and correspond to the topic of the dissertation. The objectives are 6 in number, short and in accordance with the set goal.

The Material includes a sample of 250 patients with de novo metastatic hormone-positive, HER2-negative breast cancer or those that progressed after being initially diagnosed at an early stage of the disease. All patients were treated with first-line endocrine therapy in 3 centers in Sofia and Varna. The entire sample underwent initial staging with imaging – CT +/- CCS or PET/CT.

The individual characteristics of the patients included in the study were examined – gender, tumor type, type of metastases, histological verification, TNM staging, TNM classification, genetic and pathomorphological data, etc.

A group of statistical methods were used to analyze the research material – descriptive analysis, Mann Whitney U-test and χ^2 -test, Kaplan-Meyer method and log-rank test for survival assessment, Propensity matching score analysis, Cox proportional hazard model. The data were processed using specialized software SPSS version 23 and EZR.

The Material and the Methods used allow to formulate precise and specific conclusions and to outline the contributions of the dissertation.

The analysis of the results of the scientific study is in the context of the tasks set. The data were compared in the groups of patients with: neoadjuvant and adjuvant chemotherapy; type of adjuvant endocrine therapy; disease progression compared to the adjuvant endocrine therapy performed, etc. It was found that the frequency of the PIK3CA mutation in the scientific study among Bulgarian patients was 29.2%, which is consistent with some international studies. The difference in the median progression-free survival (PFS) on first-line ET ± CDK4/6 inhibitor between patients with a proven PIK3CA mutation and those without a mutation was statistically significant. A similar result was obtained in terms of overall survival. Comparable to the results of the present scientific study are those reported after the subgroup analysis of the MONARCH2 study. It is assumed that the presence of the mutation probably did not play a role in the development of therapeutic resistance in patients who received a CDK4/6 inhibitor plus ET. It was concluded that the presence of a PIK3CA mutation is associated with a more advanced stage of the disease at diagnosis, suggesting a more aggressive course in the presence of the mutation. Another important conclusion is that the presence of PIK3CA has no relation to prognosis and response to first-line endocrine therapy, as the study was retrospective and non-randomized with a relatively small number of included patients.

I accept the 7 conclusions drawn as a result of the dissertation, as well as its contributions.

In connection with the dissertation, 7 publications and participation in scientific forums have been made in Bulgarian and international scientific journals and forums. All of them are related to the developed scientific work.

The abstract contains 51 pages and includes all the main chapters of the dissertation work.

The scientific activity of Dr. Radostina Gencheva, MD meets the criteria for evaluation in the defense of the educational and scientific degree "Doctor" of the Medical University, Varna.

Conclusion: the scientific work presented to me for Review "FREQUENCY OF PIK3CA-MUTATIONS AND RESPONSE TO FIRST-LINE ENDOCRINE THERAPY IN THE POPULATION OF BULGARIAN PATIENTS WITH HR (+) HER2(-) METASTASIRAL BREAST CANCER" possesses all the necessary qualities of a dissertation and meets the requirements of the Act on the Development of Academic Staff in the Republic of Bulgaria and its Implementing Regulations. The topic is dissertable, the methods used are adequate to achieve the set goals and objectives, the results and contributions are well reflected.

I positively evaluate my proposals for a dissertation thesis and propose to the esteemed members of the Scientific Jury to vote for awarding the educational and scientific degree "Doctor" to Dr. Radostina Bozhidarova Gencheva, MD.

Заличено на основание чл. 5,
§1, б. „В“ от Регламент (ЕС)
2016/679

09.04.2026

Prof. Dr. Zdr. Valerianova, MD, PhD.