REVIEW

on a dissertation on the topic:

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"PREVALENCE OF PIK3CA-MUTATIONS AND RESPONSE TO FIRST-LINE ENDOCRINE THERAPY IN A POPULATION OF BULGARIAN PATIENTS WITH HR(+) HER2(-) METASTATIC BREAST CANCER"

for the award of the academic and scientific degree "PhD"
PhD Program: "Oncology"
Field of higher education: 7. Health Care and Sports
Professional field: 7.1 Medicine

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Supervisor:	assoc. prof. dr. Eleonora Dimitrova-Gospodinova, MD
Reviewer:	prof. Savina Petrova Hadzhidekova, MD

I. General presentation of the procedure and the PhD student

This review was prepared in accordance with Order R-109-96/12.02.2026 of the Rector of Medical University – Varna and Minutes 1/24.02.2026 of the Departmental Council.

The set of materials submitted for the defense complies with the Procedure for Awarding the Academic Degree of "PhD" at MU-Varna.

In preparing this review, the requirements of the Law on Academic Degrees and Academic Titles and the Regulations for its implementation have been observed, as well as the specific Criteria for holding academic positions and acquiring academic degrees at MU-Varna.

II. Brief information from the candidate's professional and creative biography.

Radoslava Bozhidarova Gencheva is a physician with significant professional experience and a clear focus in the field of medical oncology. She completed her secondary education at the National Natural Sciences and Mathematics High School, majoring in "Chemistry," after which

she continued her studies at the Medical University of Sofia, where she earned a Master's degree in Medicine in 2008.

Her professional career began with work and specialization in the fields of hematology and oncology, including at the National Specialized Hospital for Active Treatment of Hematological Diseases in Sofia. She later gained international experience in Germany, where she worked in clinics specializing in gastroenterology, oncology, and internal medicine, as well as in oncology departments, where she completed various stages of specialization.

Since 2018, she has been affiliated with Nadezhda Hospital in Sofia, where she initially specialized in medical oncology and subsequently worked as a specialist physician. In 2022, she obtained a specialty in "Oncology" and successfully passed the exam administered by the European Society for Medical Oncology (ESMO), confirming her high professional standing.

Her research focuses on current issues in oncology, including molecular markers, prognostic factors, and the effects of therapeutic approaches for various oncological diseases. She is the author of numerous scientific publications and has participated in international forums, including studies related to PIK3CA mutations in breast cancer, microbiome changes, and the effects of immunotherapy in oncology patients.

Gencheva also possesses practical experience in clinical trials, including participation in Phase I–III trials, as well as a certificate in Good Clinical Practice (GCP). She is fluent in German and has a good command of English, which further supports her international professional development.

Her overall professional profile is characterized by consistent development, international experience, and active scientific work in the field of medical oncology.

III. Relevance and Significance of the Study.

This dissertation addresses an extremely relevant and socially significant issue in modern oncology—the molecular-genetic characteristics and therapeutic prognosis of metastatic hormone-positive HER2-negative breast cancer. The incidence of breast cancer remains the leading cause of cancer in the female population worldwide; despite advances in diagnosis and treatment, the metastatic form continues to be associated with an unfavorable prognosis and limited survival.

In this context, the assessment of *PIK3CA* mutation status is of significant importance because: it represents an important predictive and prognostic biomarker and is associated with resistance

to endocrine therapy; it determines the feasibility of targeted PI3K inhibitor therapy; it supports a personalized therapeutic approach.

The study is particularly significant because it presents data on the Bulgarian population, which are limited in the literature. This lends scientific novelty and practical applicability to the results.

IV. Review on the structure and content of the dissertation

Literature review

The literature review is comprehensive, systematic, and well-structured. It covers: the epidemiology of breast cancer, risk factors, histological and molecular subtypes, prognostic and predictive biomarkers; diagnostic approaches; current therapeutic options, the role of *PIK3CA* mutations in tumorigenesis and therapeutic response. The author demonstrates in-depth knowledge of the current scientific literature, utilizing up-to-date international sources and clinical guidelines. A critical analysis is provided, rather than merely a descriptive presentation.

Objective and Tasks

The objective is clearly formulated—to investigate the frequency and prognostic significance of the PIK3CA mutation in Bulgarian female patients with metastatic HR(+)/HER2(–) breast cancer treated with first-line endocrine therapy.

The objectives are logically derived and include: determining the frequency of the mutation; analyzing the clinical and pathological characteristics; assessing the association with progression-free survival and overall survival; and conducting a comparative analysis with international databases.

Methods

The methodological approach is appropriate for the stated objective. The following were used: clinical and demographic analyses; imaging methods for assessing therapeutic response; genetic and pathomorphological studies; statistical methods for survival and correlation analysis. The methods are modern, validated, and ensure the reliability of the results.

Materials

The study was conducted on a real patient population, describing: the study setting; inclusion and exclusion criteria; demographic indicators; clinical and oncological characteristics. The selection is appropriate and allows for statistical validity.

Study design. The study design is retrospective-prospective (or as described in the paper), with clearly defined endpoints—PFS and OS. The organization of data collection and processing is methodologically sound.

Results and Discussion

The results are presented systematically through tables, graphs, and statistical analyses. The following are analyzed: the frequency of the *PIK3CA* mutation; the association with clinical-pathological indicators; the impact on survival; and comparisons with TCGA and other international data. The discussion is in-depth, with the results compared to leading global studies. Similarities, differences, and possible reasons for them are noted.

The first subsection, **"Characteristics of the Study Population,"** provides a detailed clinical and demographic profile of the included patients. Indicators such as age, menopausal status, location and type of metastases, prior treatment, type of endocrine therapy administered, and stage at diagnosis were analyzed. This characterization provides a reliable basis for subsequent comparative and prognostic analyses. The population is representative of real-world clinical practice, which enhances the practical value of the results.

Frequency of the *PIK3CA* mutation. The frequency of the *PIK3CA* mutation was determined in the studied Bulgarian population, with a comparison to international databases (e.g., TCGA). It was found that the frequency is comparable to global data; no significant population differences were identified; the results confirm the universal nature of the mutation spectrum. This is of great importance as it validates the applicability of international therapeutic algorithms to the Bulgarian population as well.

Association between mutation status and clinical-pathological characteristics. A correlation analysis was performed between the presence of a PIK3CA mutation and a number of clinical indicators. No statistically significant association was found with: age, menopausal status, type of metastasis, type of adjuvant endocrine therapy, or type of tissue sample. This result is consistent with some international studies, , according to which PIK3CA mutations are a molecular rather than a clinically determined factor. A correlation with a more advanced stage at diagnosis has been established. This points to a possible role of the mutation in tumor progression and biological aggressiveness, which is adequately discussed by the author.

Impact on progression-free survival (PFS). The effect of mutation status on progression-free survival in first-line endocrine therapy was analyzed. Key results show that no significant shortening of PFS is observed in mutation carriers; the mutation does not lead to a poorer

therapeutic response. These data are particularly important, as there are conflicting results in the literature regarding the prognostic value of *PIK3CA*.

Impact on overall survival (OS). A Kaplan-Meier analysis and comparative assessment between mutation-positive and mutation-negative groups **were** performed. No statistically significant difference in overall survival was found; mutation status is not an independent negative prognostic factor. This is a significant scientific finding that contributes to the debate regarding the prognostic significance of *PIK3CA* mutations.

Association with endocrine resistance. The association between the mutation and the development of primary endocrine resistance was investigated. The results show no association between the PIK3CA mutation and primary resistance. This has important clinical implications, as it does not necessitate a change in the first-line endocrine strategy based solely on mutation status and supports the use of standard therapy in this patient group.

Comparison with therapeutic guidelines. The analysis shows that Bulgarian patients are treated in accordance with European and global standards; there is no difference in the therapeutic approach compared to leading oncology centers. This confirms the external validity of the results.

Conclusions.

The conclusions are logically formulated, derived from the results, and address the research objectives. They have both scientific and clinical value, particularly regarding personalized therapy.

Contributions

These can be summarized as: determining the frequency of the PIK3CA mutation in the Bulgarian population; analyzing its prognostic value; demonstrating a link to therapeutic response ( ); and contributing to personalized oncology in Bulgaria. There are scientific and applied contributions with a practical focus.

Bibliography

The bibliography accompanying the dissertation is extensive, thematically relevant, and adequately reflects the current state of scientific knowledge on the subject matter. The bibliography presented includes a significant number of literature sources (266 references) covering both fundamental and clinical-applied aspects of breast cancer.

V. Publications on the topic of the dissertation

In connection with the dissertation, the PhD student presents four full-text publications, three of which she is the first author.

1. Gencheva R. et al. Prevalence and prognosis of PIK3CA mutations in Bulgarian patients with metastatic breast cancer receiving endocrine therapy in a first-line setting. Cancer Reports. 2024;7:e1966.

2. Gencheva R., Dimitrova E. Endocrine resistance in metastatic hormone-positive HER2-negative breast cancer—mechanisms of development.

MedicPlus, VII, pp. 5–9, October 2025.

3. Ivanova A., Gencheva R. Abemaciclib – a modern treatment for metastatic hormone-positive HER2-negative breast cancer. MedicPlus, pp. 14–18, No. 09/2021.

4. Gencheva R. et al. The PIK3CA mutation in breast cancer as a prognostic and predictive factor. MedicPlus, pp. 28–30, No. 03/2025.

The candidate also presents an abstract from her participation in the international scientific forum *"PIK3CA* mutation prevalence and outcome among patients with metastatic breast cancer in Bulgaria treated with first-line endocrine therapy." Abstract, ASCO Annual Meeting 2023, e13005. She has participated twice in national scientific forums – "The prevalence of the PIK3CA mutation among the population of Bulgarian female patients with HR(+), HER2(–) metastatic breast cancer." from the 9th Annual Scientific Conference of the Bulgarian Association of Medical Oncology (BAMO), June 17–19, 2022, and "What Do We Need to Know When Treating Patients with Solid Tumors Aged Over 75?" from the 10th Annual Scientific Conference of the Bulgarian Association of Medical Oncology (BAMO), May 12–14, 2023

VI. Abstract

The abstract has been prepared in accordance with the established academic requirements for structure and content. All mandatory sections are included—introduction, aim and objectives, materials and methods, results, discussion, conclusions, scientific contributions, and publications—presented in a concise and clear manner. There is consistency between the abstract and the dissertation in terms of scope, methodology, and scientific results.

VII. Conclusion

Dr. Radoslava Gencheva's dissertation represents a complete, independent scientific study with a clearly formulated objective, sound methodology, and significant scientific and applied contributions.

The topic is timely, the results are original for Bulgarian medical practice, and they have the potential for implementation in clinical oncology, especially in the context of personalized treatment of metastatic breast cancer.

The scope, structure, scientific content, and publication record meet the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria.

Based on the foregoing, I give a positive evaluation and propose that the esteemed scientific jury award Dr. Radoslava Bozhidarova Gencheva the academic and scientific degree of "PhD."

April 14, 2026

Sofia

Review prepared by

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Prof. Savina Hadzhidekova, MD