

STATEMENT

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of dissertation work
**"THE NATURE OF PIK3CA MUTATIONS AND THE RESPONSE
TO
FIRST LINE ENDOCRINE THERAPY IN
THE POPULATION OF BULGARIAN PATIENTS WITH HR(+)
HER2(-) METASTASIFIED BREAST CANCER"**

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the scientific specialty "Oncology" (code 03.01.46)

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The dissertation work has been discussed and approved for public official defense by the Department Council of the Department of Medical Oncology, Medical University - Varna with a report of the Department Council, entry No. 1 / 24.02.2026 and in accordance with Order R- 109-96 / 12.02.2026 of the Rector of the Medical University - Varna.

The topic of the dissertation is contemporary and dissertable. Breast cancer is a leading oncological disease of great social significance, which is characterized by significant biological heterogeneity. Despite progress in early diagnosis and screening programs, a significant proportion of cases are still detected or progress to a metastatic stage, which requires refinement of therapeutic approaches. One of the key modern markers is the mutation in the PIK3CA gene, which functions both as a prognostic and predictive factor in patients with a hormone-positive (HR+),

HER2-negative tumor profile. The present study is the first of its kind, aimed at systematically determining the frequency of these mutations in the specific population of Bulgarian patients and comparing them with global databases. By using high-tech methods for genetic analysis (RT-PCR), the work analyzes the relationship between mutational status and the effectiveness of first-line endocrine therapy, as well as its impact on progression-free survival. The results emphasize the need for routine genetic testing in Bulgarian clinical practice to ensure personalized and maximally effective treatment of this disease.

The dissertation is presented in a volume of 115 pages and contains 6 tables and 29 figures.

The presentation of **the literature review** has very good cognitive value in an optimal volume and is focused on the following topics: Risk factors for the development of breast cancer; Prognostic biomarkers in breast cancer; Predictive factors in breast cancer; Diagnosis of breast cancer; Treatment of RG.

The dissertation sets a clearly formulated **goal**, namely: to determine the frequency of *the PIK3CA* mutation in the population of Bulgarian patients with hormone-positive HER2 negative metastatic breast cancer and to compare it with the frequency of its distribution worldwide, as well as to study and compare PFS and OS according to the *PIK3CA* mutation status of patients treated with first-line ET, as monotherapy or in combination with a CDK4/6 inhibitor. As an additional goal, the establishment of a relationship between the main clinicopathological characteristics and *PIK3CA* status is also set. In order to fulfill this goal, the following tasks must be completed:

1. Selection of patients in metastatic stage with hormone-positive HER2-negative breast cancer
2. To determine the frequency of *PIK3CA* mutation among selected patients by examining tumor tissue from the primary tumor or metastasis.

Comparison of results with those from The Cancer Genome AtlasUSA database.

3. To investigate the correlation between mutational status and clinicopathological characteristics such as age, menopausal status, type of metastases, type of adjuvant ET, and type of material examined.
4. To analyze the relationship between the presence of a *PIK3CA* mutation and the diagnosis of patients at a more advanced stage at diagnosis.
5. To determine whether there is a relationship between the presence of a *PIK3CA* mutation and the development of primary endocrine resistance to ET administered as first-line therapy for metastatic disease.
6. To analyze whether the presence of a *PIK3CA* mutation affects the effectiveness of endocrine therapy administered as 1st line and whether it has a relationship to overall survival.

Dr. Gencheva's study is retrospective, multicenter. **It was implemented in** the structures of three Oncology Clinics in Bulgaria - MHAT "Nadezhda" - Sofia, UMHTA "St. Marina" - Varna, Acibadem City Clinic MHAT Tokuda - Sofia and covers the period from 01.2016 to 11.2022. The patient population includes **250 patients**.

To solve the tasks set, Dr. Gencheva applied a number of **methods** on the patients included in her study, which emphasizes the scientific merits of the work. Clinical, imaging, genetic, pathomorphological and statistical methods are included.

The results are presented comprehensively, in detail illustrated and illustrated with graphs, tables and figures. Dr. Gencheva examined demographic and clinical characteristics of the patients, as well as their genetic profiles - *PIK3CA* gene, p.C420R (exon 7), p.E542K, p.E545A, p.E545D [c.1635G > only T], p.E545G, p.E545K, p.Q546E and p.Q546R (exon 9) and p.H1047L, p.H1047R and p.H1047Y (exon 20). She analyzed key prognostic indicators such as progression-free survival (PFS) and overall survival (OS) in patients with metastatic breast cancer. Of great importance is the comparative analysis between the presence of *PIK3CA* mutations

and various clinicopathological characteristics, including menopausal status and type of metastases. Of important clinical importance is the study of therapeutic efficacy by monitoring the response to first-line endocrine therapy, administered alone or in combination with modern inhibitors.

The discussion demonstrates the author's in-depth approach to the research problem and the ability of Dr. Gencheva to analyze her own results in the context of global data. It is logical to conclude that the frequency of *PIK3CA* mutations among Bulgarian patients (29.2%) is comparable to international levels, which confirms the representativeness of the studied group. The analysis proves the significance of mutational status as a key prognostic factor influencing progression-free survival and overall survival in women with metastatic breast cancer. The data emphasize the critical need for routine genetic testing and an individualized therapeutic approach, including targeted inhibitors, in order to optimize clinical outcome and overcome endocrine resistance.

conclusions in number and they arise from the results obtained - they reliably summarize the results of the study.

As **contributions** of the dissertation, I can acknowledge:

- For the first time in Bulgaria, the frequency of *the PIK3CA* mutation among patients with metastatic hormone-positive, HER2(-) breast cancer is being studied.
- *the PIK3CA* mutation and progression-free survival in relation to the first-line endocrine therapy applied is being studied .
- *PIK3CA* mutation and overall survival is analyzed .
- *PIK3CA* mutation and the development of endocrine resistance to first-line therapy is being investigated .

Dr. Radostina Gencheva has established herself as a highly competent and promising specialist in the field of medical oncology. The presented dissertation has significant scientific and practical value, as it is the first in Bulgaria to systematize data on the frequency and clinical impact of *PIK3CA* mutations in patients with metastatic breast cancer. The study proves the role of these genetic markers in

refining endocrine therapy and optimizing therapeutic strategies in oncological practice. The achieved results and the contributions made give full grounds for the esteemed Scientific Jury to award Dr. Radostina Gencheva the educational and scientific degree "**DOCTOR**".

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