

STATEMENT

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According ordinance No. **P-109-263/ 21.07.2020 r.** from the Rector of Medical University – Varna, I was appointed to prepare a statement for the dissertation thesis of Jeliazko Iliev Arabadjiev, MD

Concerning dissertation thesis entitled:

Dissertation thesis and author's abstract entitled "PREDICTIVE AND PROGNOSTIC VALUE OF TUMOR-INFILTRATING LYMPHOCYTES IN WOMEN WITH BREAST CANCER" for acquisition of the educational and scientific degree "Doctor" scientific specialty of "Oncology" code 03.01.46, in the field of higher education "Public health and sports", professional direction 7.1 "Medicine"

Author: Jeliazko Iliev Arabadjiev, MD

1. Significance of the problem and formulation of the goal and tasks:

Breast cancer (BC) is characterized by the highest incidence of all cancers in women and leads to the highest mortality. Despite significant advances in the diagnosis and treatment of breast cancer in recent decades, these indicators are increasing. Stratification of risk categories in patients with breast cancer is a long-standing practice. This stratification has historically started with TNM, continued with the addition of biological markers such as ER, PR and HER2, to the point of using even multigenic signatures. At present, there are no routinely used prognostic markers in clinical practice to differentiate aggressive cases with short survival from cases with slower and more favorable survival.

Tumor infiltrating lymphocytes (TILs) are a heterogeneous population of cells that play different roles in the body's immune response. They can stimulate the immune response against tumor cells or inhibit it and thus provide a suitable environment for neoplastic proliferation. Over the last decade, TILs have been the subject of extensive research to elucidate their role as a prognostic and predictive biomarker in carcinomas of different histogenesis. A more detailed study and typing of TILs would contribute not only to clarify their role in immune surveillance in breast cancer and to determine their prognostic and predictive value, but also to discover new signaling pathways and create new therapeutic approaches. Thus, in the foreign literature there is no one-way generalized data on the prognostic and predictive role of TILs in breast cancer. Data are scarce and contradictory on this issue.

For these reasons, the dissertation thesis of Dr. Arabadjiev is of current importance, both from a theoretical and practical point of view and has a contribution to the strategy in the diagnosis and therapy of breast cancer.

2. Structure of the dissertation thesis:

The dissertation thesis has a classical structure. It is written on 118 pages and contains the following sections: literature review 54 pages, purpose and tasks 1 page, material and

methods 5 pages, own results 23 pages, discussion 3 pages, conclusions 1 page, contributions 1 page and three appendices, bibliography. The dissertation thesis contains 31 figures, 21 tables. The literature reference includes 246 literary sources, of which 1 in Cyrillic and 245 in Latin. The structure of the dissertation thesis is well balanced, the proportions between the separate sections are observed and meets the requirements of the Law for development of the scientific staff in the Republic of Bulgaria.

3. Literature acknowledgement of the author:

The literature review is written with skill. The epidemiology, etiology, genetic predisposition, diagnosis, staging and treatment of breast cancer at the current level are considered. The main place is given to the predictive and prognostic factors and markers, the role of the immune system and especially of TILs in breast cancer. The scientific publications on the topic are approached critically and the main problems and unresolved issues in this direction are presented.

The wide information handled by the author, the correct use of the scientific terminology and the full and correct citation of the authors of the scientific publications in the field are impressive. It is worth noting the strict focus of the review on the problem under consideration, which presents Dr. Arabadjiev as a multifaceted excellently prepared researcher. The bibliography includes 246 literature sources. I would like to draw attention to the topicality of the literature used, as 65% of the sources are from the last 10 years.

The aim of the dissertation thesis is a logical continuation of the literature review, namely: to study the degree of TILs in patients with breast cancer in order to establish their prognostic and predictive value and the possibility of specific application in practice.

There are six main tasks, which are formulated clearly and precisely, they are specific, well-planned and correspond to the set goal, which shows the good theoretical preparation and mastery of the problem by the author.

4. Methodological level and design of scientific research:

The section Material and methods presents the patients included in the scientific work with correctly defined inclusion criteria and description of the used methods. The dissertation thesis is based on a retrospective analysis of 118 patients with early and recurrent / metastatic breast cancer.

5. Correspondence between the goal, the results and the conclusions:

There is a logical correspondence between the set goal, the obtained results, the discussion and the conclusions made. The own results are presented on 26 pages, following the course of the set tasks and are presented in detail, illustrated with statistically processed digital tables and graphs.

Correlations of the degree of TILs are indicated in detail and consistently in the following respects: (1) to survival (general and no event), (2) to disease characteristics; (3) to the natural evolution of the disease; (4) to the type of drug therapy; (5) to adjuvant radiotherapy; (6) to tumor immunohistochemistry and (7) to disease-free survival. The results are the subject of analytical discussion in relation to literary references, creative hypotheses are formulated.

6. Analysis of the conclusions and contributions:

Based on the obtained results, the author synthesizes 9 conclusions, which are written specifically and clearly and are relevant to the goal and the tasks developed.

The findings substantiate the prognostic and predictive correlations of the degree of TILs: (1) with respect to the three categories of therapeutic stages of the disease - without significant differences; (2) in relation to the primary tumor localizations and the groups in the development of the disease - without significant differences; (3) relative to overall survival in adjuvant systemic therapy - tendency for reciprocal relation; (4) relative to overall survival in hormone-receptor-positive, HER2-negative immunohistochemistry - significant reciprocal relation; (5) relative survival in patients treated with adjuvant chemotherapy / endocrine therapy - significant reciprocal relation; (6) relative to overall survival in those treated with chemotherapy alone - significant positive relation; (7) relative to overall survival in radiotherapy-treated patients - without significant difference; (8) relative to disease-free survival - significant reciprocal relation.

I accept the presented contributions of the author, which can be defined as theoretical and scientific-applied.

For the first time in national clinical oncology, data on the relationship between TILs and survival according to the immunohistochemical status of breast cancer have been reported. The interpretations of the predictive value of this indicator for the different therapeutic choices - endocrine therapy, radiotherapy and chemotherapy are also original.

An original hypothesis for a possible function of TILs as a marker for de-escalation of treatment approaches is proposed.

In connection with the dissertation thesis Dr. Arabadjiev has 6 real publications in which he is the first author, all related to the topic of the dissertation.

The dissertation thesis is written clearly and concisely, in good literary Bulgarian.

The abstract is written concisely and adequately reflects the content of the dissertation thesis.

Conclusion:

The dissertation thesis of Dr. Jeliazgo Ilijev Arabadjiev is an in-depth and precisely conducted scientific development.

The dissertation thesis is a contemporary work with scientific and applied value. The goal and tasks are precisely set, the results obtained are convincing, the conclusions are clearly formulated and comprehensive. The contributions have theoretical and practical value and are the basis for future research. The dissertation covers the quantitative indicators for acquiring the educational and scientific degree "Doctor" and fully meets the requirements of the Law and the Regulations for its implementation.

When taking into consideration all of the above, I give a positive assessment of the dissertation thesis of Dr. Jeliazgo Arabadjiev and recommend to the esteemed Scientific Jury to award him the scientific and educational degree "DOCTOR".

Prof. Antonia Conevska, MD, PhD

