WRITTEN STATEMENT

from Assoc. Prof. Valentina Yovcheva Belcheva, PhD,
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(Internal member of the Scientific Jury, approved by Order No. P-109-116/05.02.2025 of the Rector of MU-Varna)

Subject: Procedure for the defense of a dissertation for obtaining educational and scientific degree "Doctor", FHE 7. Healthcare and sports, PF 7.3. Pharmacy, in the doctoral program " Pharmacology /incl. pharmacokinetics and chemotherapy/".

Topic of the dissertation:
"Study of Potential Drug Interactions of Epidermal Growth Factor Receptor Inhibitors (EGFR inhibitors) in the Treatment of Non-Small Cell Lung Cancer"
Author of the dissertation:
Dr. IVANKA MINKOVA MUTAFOVA- PhD student in self-study form of education at the Medical University-Varna.
Scientific supervisors:
Prof. Kaloyan Dobrinov Georgiev, MScPharm, PhD, DSc
Prof. Evgeni Evgeniev Grigorov, MScPharm, PhD

Significance of the topic: In recent years, the development of the concept of personalized antitumor therapy and the increasing clinical application of targeted and immunotherapy in clinical practice, significant progress has been made in the treatment of non-small cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) inhibitors have led to prolonged survival of NSCLC patients who have a mutation in the epidermal growth factor receptor (EGFR) gene. However, very often, patients with NSCLC have concomitant diseases, which necessitates treatment with medications from different therapeutic classes, including off-label or over-the-counter drugs. The concomitant use of EGFR inhibitors with other medications may lead to the occurrence of pharmacokinetic and/or pharmacodynamic drug-drug interactions. This may lead to the development of adverse drug reactions, toxicity and even loss of therapeutic effect.
Relevance of the developed topic: The dissertation work of Dr. Ivanka Mutafova is dedicated to the study of potential drug-drug interactions between the various representatives of the group of EGFR-inhibitors and drugs of different therapeutic classes. As is known, the incidence of NSCLC is increasing worldwide and the number of patients with EGFR mutations receiving treatment with

EGFR inhibitors is increasing. Although they are classified in the same ATC group (L01EB Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors), the individual agents have different pharmacokinetic characteristics, which means that a drug can be administered without the risk of drug interactions with one of the EGFR inhibitors, while the simultaneous use of the same drug with another EGFR inhibitor may have the risk of clinically significant drug interactions requiring a change in therapy. It is the professional responsibility of medical professionals to minimize the risk of adverse drug-drug interactions. The use of digital platforms for identifying potential drug interactions can significantly facilitate this task. After doing a review of numerous scientific publications on the problem, the current data indicated by the doctoral student unequivocally prove that the topic being developed is in a direction that is actively developing scientifically and with extremely practical application in daily clinical practice. The doctoral student was able to summarize the more significant interactions observed between EGFR inhibitors and commonly used medicinal products for pharmacotherapy.

The implementation of studies to assess potential interactions between EGFR inhibitors in the treatment of NSCLC and conventional drugs can significantly reduce the frequency of adverse drug reactions due to drug-drug interactions, increase the safety of the drug combinations taken and influence the course of the disease.

Structure of the dissertation: The dissertation work of Dr. Ivanka Mutafova is very well formed and structured in terms of its main parts and fully complies with the Regulations for Development of the Academic Staff of MU-Varna. It contains the following sections:

- Introduction
- Literature review;
- Aim and objectives;
- Materials and methods;
- Results and discussion;
- Conclusions;
- Contributions;

Then the bibliography is placed. The dissertation covers a total of 182 standard typewritten pages, including 50 figures, 56 tables and 2 applications. 219 literary sources are cited, of which, however, only 17 are in Bulgarian.

The literature review contains a sufficient amount of summarized and analyzed scientific material, which reflects a lot of data and information about research on the topic so far. It is systematically presented and reveals a very good knowledge of the subject related to drug interactions and justifies the choice of topic for the dissertation. The literature review is divided into several parts, in which

consequently are discussed: epidemiology, molecular pathological typing, oncogenic mutations and targeted therapy in NSCLC; general overview of the types of drug interactions and adverse drug reactions; software programs used for drug interaction analysis; drug interactions in patients with oncological diseases; pharmacokinetics and drug interactions in the treatment of NSCLC with EGFR inhibitors; pharmacogenetic aspects in the treatment of NSCLC with EGFR inhibitors; medicinal use of EGFR inhibitors in Bulgaria.

The main objective of the dissertation is to identify and analyze potential the drug interactions through a specialized digital platform and to establish reported adverse drug reactions (ADRs) using specialized online databases, in the clinical practice of EGFR inhibitors for the treatment of NSCLC. A secondary objective of the dissertation is to assess the possible correlation between reported ADRs and potential drug interactions (pDDIs).

The tasks are 7 in total and result from the set primary and secondary objectives. They are formulated precisely and are logically justified, so their implementation allows the author to achieve the defined objectives

The object of the study: The study was conducted using information collected, summarized and analyzed from the European database of reported suspected adverse drug reactions EudraVigilance over a three-year period. The likelihood of interactions was assessed using a digital drug-drug interaction platform – UpToDate® Lexidrug™ and whether there was a possible correlation between the reported adverse drug reactions and the identified drug-drug interactions.

The research methods used are:

General methods:

- Documentary method: A thorough review of clinical trial results, regulatory documents and the product characteristics of the studied drugs was conducted;
- Tabular-graphical method: Tabular illustration of the study results and their graphical representation;
- Comparative analysis: Comparison and comparison of several selected indicators (number of drug interactions according to risk categories and risk severity, number of adverse drug reactions, number of drugs in therapy, age and gender of patients) in order to reveal relationships and dependencies;
- A method for systematizing information to provide the most important facts, in accordance with the objectives of the research in the dissertation;
- Internet reference and review of the content of official websites listed in the literature used;

Specific methods:

- Database analysis: A retrospective analysis of a database from the European Medicines Agency regarding reported potential adverse drug reactions (EudraVigilance) was conducted
- Statistical methods – descriptive and analytical

The overall design of the study is evidence of the in-depth knowledge and mastery of the PhD student of modern methodological approaches in pharmacology. It makes a good impression that the methods used are diverse and in different directions.

The results obtained are clearly presented and well-structured for each aspect of the study, accompanied by numerous figures and tables. The more important results is that the number of suspected ADRs reported in EudraVigilance is higher when there is an identified drug-drug interaction EGFR-inhibitor-drug of risk category D and X compared to the number of ADRs reported when using EGFR-inhibitor alone and compared to the total number of ADRs when using EGFR-inhibitor in combination with other drugs. Another significant result is the indication of a possible correlation between the identified potential drug-drug interactions and the ADRs reported in the European database EudraVigilance. This suggests that prior analysis of drug combinations may prevent adverse drug reactions and thus change the course of the disease.

The obtained results are original and reliable, supported by a large volume of analyzed and summarized scientific material.

The discussion is well structured as the PhD student consistently and in detail discusses each of the results obtained in the research. It makes a very good impression that every statement or assumption is supported and substantiated by scientific information.

Conclusions. Specific conclusions from the conducted research have been formulated, which have a practical orientation and are in accordance with the collected and analyzed data. Given the results of the analyses conducted, it is reasonable to argue that there is a risk of drug interactions when using EGFR inhibitors with some widely used drugs in medical practice.

I believe that all the conclusions made objectively reflect the results obtained by the PhD student.

Contributions of the dissertation

ORIGINAL CONTRIBUTIONS:

- *For the first time, information specifically extracted from EudraVigilance regarding reported cases of suspected ADRs in treatment with EGFR inhibitors for a 3-year period (2021-2023) has been summarized;*
- *In a pilot study for Bulgaria, data reported in EudraVigilance containing information on drug combinations for which potential drug interactions in the use of EGFR inhibitors in the treatment of NSCLC have been purposefully analyzed;*
- *Data on the most common drug interactions in the use of individual generations of EGFR inhibitors have been summarized and analyzed and compared with each other in terms of number and degree of risk and severity, using a specialized online platform for this purpose;*
- *The main PK and PD mechanisms responsible for potential drug interactions in the use of EGFR inhibitors have been determined, as well as their relationship with the number of drugs taken, age and gender of patients.*

CONTRIBUTIONS OF AN APPLIED AND PRACTICAL NATURE:

- *For the first time, an attempt has been made to investigate and detect a possible relationship between reported cases of suspected ADRs and potential drug interactions in the use of EGFR inhibitors, using an original methodology developed by the doctoral student.*
- *Such an approach would be particularly useful for clarifying the relationship between observed ADRs and drug interactions, not only with EGFR inhibitors, but also with other drug groups, providing an opportunity for their prevention.*

The presented contributions are divided into those of original and applied-practical nature, which is in line with established practice in this scientific field.

Abstract and publications. The abstract is prepared in accordance with the requirements of the Regulations for the Development of the Academic Staff of the Medical University of Varna and correctly reflects the results obtained and the scientific contributions of the dissertation. Three publications in scientific journals and two participations in scientific conferences related to the topic of the dissertation are presented. In all articles the PhD student is the first author, which shows his personal participation in the development, discussion and presentation of the results.

Conclusion. I positively evaluate the dissertation work of Dr. Ivanka Mutafova and I believe that in terms of content and scientific contributions it fully meets the requirements of Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the Development of the Academic Staff of MU-Varna. The good methodological preparation, the in-depth theoretical knowledge and the accumulated practical experience of the PhD student in the field of Pharmacology are an excellent prerequisite for his future successful development as a scientist. All this gives me reason to convincingly recommend to the members of the respected Scientific Jury to award **IVANKA MINKOVA MUTAFOVA** the educational and scientific degree "**Doctor**".

Stara Zagora
06 March 2025

Member of the Scientific Jury:.....

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

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(Assoc. Prof. Valentina Belcheva, PhD)

By signing here, I declare that I am not related to the doctoral student, and that I have no private interest that could affect the impartial and objective implementation of the opinion in the current procedure for acquiring ESD "Doctor".