

OPINION

by Assoc. Prof. Nadezhda Rumenova Karkkeselyan, MScPharm, PhD

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regarding

procedure for defending a PhD thesis for the acquisition of an educational and scientific degree

"Doctor" in the field of higher education 7. Healthcare and sport, professional field 7.3.

Pharmacy, doctoral program "Pharmacology (incl. pharmacokinetics and chemotherapy)"

of

Ivanka Minkova Mutafova – PhD student in an independent form of study at the Department of
Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy at MU-Varna

on the topic ***"Study of potential drug interactions when using epidermal growth factor receptor
inhibitors (EGFR- inhibitors) in the treatment of non-small cell lung cancer "***

with scientific supervisors Prof. Kaloyan Dobrinov Georgiev, PhD, DSc and Prof. Evgeni
Evgeniev Grigorov , PhD.

By order of the Rector of MU-Varna No. P-109-116 dated 05.02.2025, I was elected as a member of the Scientific Jury, and on the basis of Protocol No. 1 dated 14.02.2025, I was appointed to prepare an opinion on the procedure for acquiring the educational and scientific degree "Doctor" by Ivanka Minkova Mutafova.

The documents submitted for the competition by Ivanka Minkova Mutafova are in accordance with the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of the LDASRB (RILDASRB) and the Regulations for the Development of the Academic Staff (RDAS) at MU – Varna and are formatted correctly according to the Procedure for Acquiring the educational and scientific degree "Doctor" at the Medical University - Varna.

Candidate biographical data

Dr. Ivanka Mutafova graduated from the Medical University of Pleven in 1999. She acquired a specialty in Internal Medicine in 2007, and in 2024 - a specialty in Pharmacology at the Medical University of Sofia. In the period 2000 - 2002 she worked as a doctor at the University Hospital Dr.

Georgi Stranski, Pleven. Since 2007 she has been actively working in the field of clinical trials as a Clinical Trials Specialist, and currently holds the position of Physician-Expert in Pharmacovigilance at the company Pharmaceutical. Research Associates Bulgaria EOOD, Sofia. In the period 2007 – 2015 she also worked as a doctor, specialist in Internal Medicine at Vita Hospital. She teaches external exercises “Clinical Cases in Pulmonology” to students, specialty “Pharmacy” at MU – Varna. Dr. Mutafova is a co-author in writing 8 scientific publications and has participated in two scientific forums. She has also participated in projects for the development of new drugs. She is fluent in English and Russian, has excellent computer skills and digital competencies. She is a member of the Bulgarian Medical Union.

Dr. Mutafova was enrolled by order No. R-109-12/07.01.2021 at the end of 2021 as a PhD student in an independent form of study in the doctoral program "Pharmacology (incl. pharmacokinetics and chemotherapy)" at the Department of "Pharmacology, Toxicology and Pharmacotherapy" of the Faculty of Pharmacy at MU-Varna. She completed all tasks and activities set out in the individual curriculum on time. She successfully passed the doctoral minimum exam.

Relevance of the dissertation topic

Lung cancer is the leading cause of cancer-related death worldwide. With the introduction of targeted therapies in oncology, physicians and pharmacists are faced with new challenges related to poorly understood drugs and complex patients with multiple comorbidities and polypharmacy, which increases the risk of adverse reactions and treatment compromise. Therefore, it is critical to recognize clinically relevant drug interactions to minimize adverse events and increase clinical efficacy, leading to improved quality of life and increased patient survival. The application of computerized models and simulations related to drug action, drug interactions, and adverse effects can help achieve better disease control and minimize the risk of potential adverse reactions resulting from drug interactions.

Based on the above, I believe that the presented PhD thesis addresses a relevant and important topic related to enriching the knowledge in the field of treatment of non-small cell lung cancer with epidermal growth factor receptor inhibitors (EGFR inhibitors).

Structure of the PhD thesis

Ivanka Mutafova's dissertation includes a total of 182 pages and is structured in accordance with the requirements for acquiring the educational and scientific degree "Doctor". The structure of the work includes all mandatory sections, which are precisely formatted and balanced in volume, as follows: Introduction - 1 page, Literature review - 69 pages, Aim and objectives - 1 page, Materials and methods - 6 pages, Results and discussion - 52 pages, Conclusions - 2 pages, Contributions - 1

page, References - 10 pages, List of scientific publications and contributions related to the dissertation - 1 page.

The dissertation is illustrated with 50 figures, 56 tables and 2 appendices. The bibliography includes 219 sources, of which 17 are in Cyrillic and 202 in Latin.

The literature review is presented with the necessary depth and includes an extensive analysis of the available scientific data on the topic to date. The information contained is comprehensive and clearly demonstrates the deep theoretical knowledge of Dr. Mutafova on the issues considered in the dissertation. The review is divided into several parts, which sequentially address: non-small cell lung cancer with its epidemiology, diagnosis and treatment, an overview of drug interactions and adverse drug reactions, software programs used for drug interaction analysis, drug interactions in patients with oncological diseases, pharmacokinetics, drug interactions and pharmacogenetic aspects of treatment with epidermal growth factor receptor inhibitors (EGFR-inhibitors) in patients with NSCLC, as well as the medicinal use of EGFR-inhibitors in Bulgaria.

The main aim of the presented dissertation is to identify and analyze potential drug interactions through a specialized digital platform and to establish reported adverse drug reactions (ADRs) using specialized online databases, in the clinical practice of using EGFR inhibitors for the treatment of NSCLC. The doctoral student has also formulated a secondary objective of the dissertation to assess the relationship between reported ADRs and potential drug interactions.

The tasks are 7 in total and arise from the defined aim. They are formulated correctly and are adequate for its achievement.

The materials and methods are appropriately selected according to the specifics of the study and the implementation of the tasks set. The methods included in the study are described in detail and discussed in detail. The study design is appropriately selected and precisely illustrated with 3 figures. Numerous studies have been conducted related to the assessment of a potential relationship between the reported adverse drug reactions in the EudraVigilance ADR database and those identified from the UpToDate® platform and its Lexicomp® Drug Interactions application. The in-depth knowledge and skillful use of modern digital platforms and databases by the doctoral student is impressive.

The results and discussion are combined into one section. They are well structured and follow the tasks set, with each presented result being presented with a discussion regarding its meaning and interpretation. It is noticeable that every statement or assumption is supported and justified with scientific information. Numerous figures and tables contribute to the visualization of the obtained results. I believe that the obtained results are original and reliable, supported by a large volume of analyzed and summarized scientific material. **The contributions** of the dissertation are

well formulated and are divided into those of an original and scientific-practical nature. The more important results and contributions could be summarized as follows:

- EudraVigilance were purposefully analyzed, containing information on drug combinations for which potential drug interactions in the use of EGFR inhibitors in the treatment of NSCLC were identified;
- Data on the most common drug interactions when using the different generations of EGFR inhibitors were 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 with the use of EGFR inhibitors have been determined, as well as their relationship with the number of drugs taken, the age and gender of the patients.
- For the first time, an attempt has been made to investigate and discover a possible correlation 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.

Based on the analyses performed, specific **conclusions** with a practical focus have been drawn, which would be useful for specialists in the field of pharmacology and clinical pharmacology, as well as for physicians. Given the results of the analyses conducted, it is quite reasonable to argue that such an original approach to research and detect a possible relationship between reported cases of suspected ADRs and potential drug interactions, when using EGFR inhibitors, would be particularly useful for other drug groups, with the possibility of their prevention.

I think that the synthesized **Conclusions** correspond to the collected and analyzed data and objectively reflect the results obtained by the doctoral student.

Summary of the PhD thesis

The summary of the dissertation is comprehensive, well illustrated and sufficient in volume of 80 pages to present the essence of the work. It has been prepared in accordance with the requirements of the Regulations for the Development of the Academic Staff of the Medical University of Varna.

The candidate's scientific activity related to the PhD thesis

Dr. Ivanka Mutafova has presented three full-text publications related to the dissertation, thus fulfilling the requirements for obtaining the educational and scientific degree "Doctor". In addition, some of the results related to the topic of the dissertation have been presented at two national forums.

CONCLUSION

The dissertation thesis of Ivanka Minkova Mutafova on the topic "Study of potential drug interactions when using epidermal growth factor receptor inhibitors (EGFR- inhibitors) in the

treatment of non-small cell lung carcinoma" fully complies with the requirements of LDASRB, RILDASRB and RDAS of MU-Varna.

Based on the above, I confidently give my **POSITIVE ASSESSMENT** of the presented PhD thesis and propose to the members of the esteemed Scientific Jury to vote for awarding the educational and scientific degree " **Doctor** " in the field of higher education 7. Health and Sports, professional field 7.3. Pharmacy, doctoral program "Pharmacology (incl. pharmacokinetics and chemotherapy)" to **IVANKA MINKOVA MUTAFOVA**.

20.03.2025

Varna

Prepared by:

(Assoc. Prof. Nadezhda Karkkeselyan, PhD)

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