

REVIEW

by Assoc. Prof. Maya Petrova Radeva-Ilieva, MScPharm, PhD

Head of Department of Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy,
Medical University "Prof. Dr. Paraskev Stoyanov" – Varna

regarding

procedure for defending a dissertation work 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 – doctoral student in independent training at the Department of
Pharmacology, Toxicology and Pharmacotherapy, Faculty of Pharmacy at MU-Varna

on the topic

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

scientific supervisors

prof. Kaloyan Dobrinov Georgiev, MScPharm, PhD, DSc

prof. Evgeni Evgeniev Grigorov, MScPharm, PhD

On the basis of Order No. P-109-116/05.02.2025 of the Rector of Medical University –
Varna I was elected as a member of the Scientific Jury, and on the basis of Protocol No.
1/14.02.2025, I was appointed to prepare a review on the procedure for acquiring the educational
and scientific degree "Doctor" by Ivanka Minkova Mutafova.

The present review is prepared in accordance with the requirements of the Law on the
Development of the Academic Staff in the Republic of Bulgaria (LDASRB), as well as the
Regulations for the Implementation of the LDASRB (RILDASRB) and the Regulations for the
Development of the Academic Staff (RDAS) at MU – Varna. The documents submitted by the
candidate meet the specified requirements and are precisely prepared.

I declare that I have no joint scientific works with the doctoral student.

Data on the procedure

According to order No. P-109-12/07.01.2021 Dr. Ivanka Minkova Mutafova was enrolled as a doctoral 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. During the study period, she successfully passed the exams for a doctoral minimum in the specialty "Pharmacology" and in a foreign language. After successfully completing all tasks and activities set out in the individual curriculum, she was enrolled with the right to defense according to order No. P-109-116/05.02.2025 of the Rector of MU-Varna.

Biographical data of the candidate

Ivanka Minkova Mutafova was born on January 16, 1976 in Troyan. Ivanka Mutafova obtained the Master's degree in Medicine from the Medical University of Pleven in 1999. In 2007, she obtained a specialization in Internal Medicine from the Medical University of Sofia. She is currently studying for a specialty in Pharmacology at the Medical University of Sofia, having successfully completed theoretical and practical training by August 31, 2024 and is about to take the state exam. During the period 2000 - 2002, she worked as a doctor at the University Hospital "Dr. Georgi Stranski", Pleven. From 2007 to the present, she has worked in several pharmaceutical companies, mainly in the field of clinical trials and drug safety. Her current position is "Medical Expert in Drug Safety" at Pharmaceutical Research Associates Bulgaria EOOD, Sofia. In the period 2007 – 2015 she worked as a doctor, specialist in Internal Medicine at Vita Hospital, Sofia. She is fluent in English and Russian, has excellent computer skills and digital competencies. She is a member of the Bulgarian Medical Association.

Relevance of the dissertation topic

Nowadays, treatment of oncological diseases is an extremely big challenge, despite the significant progress of medicine and pharmacy in recent decades. In particular, lung cancer is one of the fastest progressing tumor diseases with a relatively short life expectancy. Modern targeted therapy for non-small cell lung cancer, the most frequently diagnosed lung cancer, provides significant advantages over classical chemotherapy in terms of effectiveness, safety and patient survival. However, potential drug-drug interactions can compromise treatment results or lead to the occurrence of serious adverse drug reactions. Therefore, drug-drug interactions usually lead to adverse consequences for the patient. Thus, methods for their study and prediction, including information processing from various databases, are extremely important for the prevention of severe

adverse reactions, especially in patients who have concomitant diseases and take other drugs simultaneously with the drug therapy for non-small cell lung cancer.

Based on the above, I believe that the present dissertation paper addresses a current and significant topic related to the study of potential drug-drug interactions due to the therapy of non-small cell lung cancer with EGFR-inhibitors. Additionally, the results obtained will contribute to increasing the safety of patients during therapy with EGFR-inhibitors.

Structure of the dissertation work

The dissertation work of Ivanka Mutafova is very well structured and has been prepared in accordance with the requirements for obtaining the educational and scientific degree "Doctor". The dissertation work contains a total of 182 pages, divided into the following mandatory sections:

- I. Introduction – 1 p.;
- II. Literature review – 69 p.;
- III. Aim and tasks – 1 p.;
- IV. Materials and methods – 6 p.;
- V. Results and discussion – 52 p.;
- VI. Conclusions – 2 p.;
- VII. Scientific contributions – 1 p.;
- VIII. Bibliography – 10 p.;
- IX. List of scientific publications related to the dissertation work – 1 p.

The dissertation is illustrated with 50 figures and 56 tables. 2 appendices are also included. The literary sources used are a total of 219, of which 17 are in Bulgarian and the remaining 202 - in English.

The literature review is systematically presented and contains a sufficient volume of summarized and analyzed scientific material. It is divided into several parts, which sequentially examine: non-small cell lung cancer (epidemiology, diagnosis, typing, driver mutations, therapy); drug-drug interactions and adverse drug reactions (general review); drug-drug interactions in patients with oncological diseases; pharmacokinetic features of EGFR-inhibitors and drug-drug interactions; pharmacogenetic aspects in the treatment of non-small cell lung cancer with EGFR-inhibitors; medicinal use of EGFR-inhibitors in Bulgaria. At the end of the section, the doctoral student presented his conclusion from the prepared literature review, which is directly related to the formulated goal. The prepared literature review shows very good knowledge of the subject and the ability to analyze and systematize a large volume of scientific information.

The aim and tasks of the present dissertation work are logically related to the prepared literature review. **The aim** of the dissertation is precisely and clearly formulated and is focused on

identifying and analyzing potential drug-drug interactions through a specialized digital platform and reported adverse drug reactions using specialized online databases in patients on EGFR-inhibitor therapy. A secondary aim of the dissertation is to assess the relationship between reported adverse reactions and potential drug-drug interactions. **The tasks** are 7 in total and arise from the set purpose. They are precisely formulated and logically justified, and their implementation enables the achievement of the defined purpose.

The materials and methods used are appropriately selected with regard to the tasks set and their implementation. Numerous analyses of a large volume of information were conducted for the realization of the dissertation work. For the purposes of the analysis, information from the European database of reported suspected adverse drug reactions EudraVigilance and from the digital platform for drug interactions – UpToDate® Lexidrug™ was used. The information chosen according to initially set criteria was subsequently analyzed and selected for the purposes of the dissertation work. The huge number of analyzed reports according to different criteria is impressive, which shows the high scientific value of the presented dissertation work. The experimental work performed is presented in detail.

The results and discussion are combined into one section. They are well structured and follow the tasks set. The identified and analyzed drug-drug interactions are presented separately for each EGFR-inhibitor, followed by the reported interactions between EGFR-inhibitors and other concomitant medications. A comprehensive analysis of the potential adverse reactions associated with the use of EGFR-inhibitors that are reported in EudraVigilance has been prepared, as well as an assessment of the relationship between the adverse drug reactions reported in EudraVigilance and the drug-drug interactions identified through the UpToDate® Lexidrug™ digital platform (risk category X and/or D). The presented results are discussed accordingly. The results are accompanied by numerous figures and tables. I believe that the results obtained are original and reliable, obtained on the basis of a large volume of analyzed and summarized scientific data. The consistency shown in the work of the doctoral student in preparing the dissertation work is impressive.

As a result of the research conducted, specific **conclusions** have been formulated that have a practical focus and are in accordance with the collected and analyzed data. I believe that all conclusions drawn objectively reflect the results obtained by the doctoral student.

The scientific contributions of the dissertation work are well formulated and are divided into those of an original and of an applied and practical nature:

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.

I accept the contributions and believe that they are the personal work of the doctoral student and correctly reflect the results obtained.

Summary of the dissertation work

The summary of the dissertation work has been prepared according to the requirements and contains a total of 80 pages. It is structured correctly and presents important figures and tables.

The candidate's scientific activity related to the dissertation work

Three publications in scientific journals have been presented, in which the doctoral student is the first author. One of the publications is in a journal that is refereed and indexed in world-renowned databases. The doctoral student also presents two participations in national scientific conferences related to the topic of the dissertation.

CONCLUSION

The dissertation work of Ivanka Minkova Mutafova on the topic "**Study of potential drug interactions of epidermal growth factor receptor inhibitors (EGFR inhibitors) in the**

"treatment of non-small cell lung cancer" fully complies with the requirements of LDASRB, RILDASRB and RDAS of MU-Varna. The dissertation work is dedicated to a current topic. Appropriate methods of analysis were used and significant results were obtained, which represent an original contribution to pharmaceutical science and practice.

The present dissertation work demonstrates that Ivanka Mutafova possesses in-depth theoretical knowledge, has mastered modern methods for analyzing potential drug-drug interactions and has gained significant practical experience in this area of pharmacology. The doctoral student demonstrates qualities and abilities for conducting an independent scientific research, including analyzing and systematizing scientific information.

Based on the above, I give my **POSITIVE ASSESSMENT** of the present dissertation work and propose to the esteemed Scientific Jury to award the educational and scientific degree "**Doctor**" in the field of higher education 7. Health and Sport, professional field 7.3. Pharmacy, doctoral program "Pharmacology (incl. pharmacokinetics and chemotherapy)" to **IVANKA MINKOVA MUTAFOVA**.

09.04.2025

Varna

Prepared by: ..

(Assoc. Prof. Maya Radeva-Ilieva, PhD)

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