Review for obtaining educational and scientific degree "Doctor"

REVIEW OF DISSERTATION
by
PROF. ILKO NIKOLAEV GETOV, PhD
MEDICAL UNIVERSITY, SOFIA
for obtaining educational and scientific degree "DOCTOR"

Field of Higher Education: 7. Healthcare and Sports
Professional Field: 7.3. Pharmacy
Doctoral program "PHARMACOLOGY, incl. PHARMACOKINETICS AND CHEMOTHERAPY"

Author: IVANKA MINKOVA MUTAFOVA
Form of doctoral study: SELF-STUDY
Department: Pharmacology, Toxicology and Pharmacotherapy
Faculty of PHARMACY, Medical University "Prof. Dr. Paraskev Stoyanov", Varna

DOCTORAL THESES:

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 Georgiev, PhD, DSc
Prof. Evgeni Grigorov, PhD

1. General presentation of the procedure and the doctoral student

According to the present procedure, I have been provided with a set of materials in electronic and paper format in accordance with Article 69 of the Regulations for the Development of the Academic Staff of MU-Varna, which includes the required documents:

- Dissertation
- Abstract
- List of scientific publications
- Autobiography, diplomas, orders, protocols, etc

The doctoral student has submitted 3 (three) full-text publications in Bulgarian language, published in Bulgarian refereed scientific journals.

Dr. Ivanka Mutafova is enrolled as a doctoral student for independent training with Order No. P-109-12/07.01.2021 of the Rector of MU-Varna in the doctoral program: PHARMACOLOGY, Professional field 7.3 Pharmacy. After a ONE-year interruption and resumption of training, at a meeting of the Department Council of the Department of Pharmacology, Toxicology and Pharmacotherapy and by Decision of the Faculty Council of the Faculty of Pharmacy of MU-Varna, the doctoral student is enrolled with the right to defense, effective from 05.02.2025.

The set of documents meets the requirements and after having become acquainted in detail with the procedure for the development, presentation and development of the training under the doctoral program, I believe that they meet the requirements of the regulatory framework. The submitted documents prove the legality and completeness of the conducted training and procedure, and the minimum national requirements for acquiring the educational and scientific degree "Doctor" in Professional Field 7.3 Pharmacy are met.

2. Brief biographical data about the doctoral student

Dr. Ivanka Minkova Mutafova has a Master's degree in Medicine from MU-Pleven and completed postgraduate specializations in Internal Medicine and in Pharmacology from MU-Sofia.

The career and professional experience Dr. Mutafova began in 2000 in clinical medicine and after that - in the pharmaceutical industry. The doctoral student has successively held positions in university clinics and local divisions of foreign pharmaceutical companies for clinical research and drug safety. She has successively passed successively through resident physician, specialist physician, clinical trial monitoring specialist, supervisor and drug safety physician, etc..

Dr. Mutafova has excellent computer skills in working with specialized software. She is fluent in English and Russian.

She is a member of the Bulgarian Medical Union.

3. Relevance of the topic and appropriateness of the set goals and objectives

The dissertation work proposed for discussion, developed as a doctoral study of independent preparation for acquiring the educational and scientific degree "doctor" by Dr. Ivanka Minkova Mutafova, with the title: *Study of Potential Drug Interactions of Epidermal Growth Factor Receptor Inhibitors (EGFR inhibitors) in the Treatment of Non-Small Cell Lung Cancer*, has the characteristics of an in-depth interdisciplinary study on the possibilities for identifying, analyzing and evaluating drug-drug interactions in clinical practice, which are of essential importance for the therapeutic process and its outcome. The detection, analysis and evaluation of pharmaceutical, pharmacokinetic and pharmacodynamic drug interactions are important at every stage of new drug development. In the digital age, computer models and simulations can explore hypotheses and predict possible mechanisms related to drug action, drug interactions and adverse effects. The application of these models leads to a significant reduction in development time and reduces costs for pharmaceutical companies. In clinical practice, the identification and assessment of potential drug interactions is of great importance, since the simultaneous use of several drugs often leads to an increased risk of adverse reactions and can compromise treatment. The widespread introduction of targeted therapy poses new challenges for medical professionals.

The content, volume, the conducted own research and the conclusions drawn are comprehensive, have the necessary balance between the individual elements, as well as the applicability of the formulated conclusions and contributions.

4. Knowledge of the topic

The doctoral student demonstrates with this thesis a very good level of knowledge and mastery of the studied subject. The dissertation is based on the understanding that by accessing and summarizing the information obtained and available from the use of online platforms for detecting drug interactions and publicly available databases for reporting adverse drug reactio[illegible] of drug

interactions in the treatment of non-small cell lung cancer with epidermal growth factor receptor inhibitors (EGFR inhibitors) can be significantly enriched.

Based on the solid literature review on the topic of the dissertation, Dr. Mutafova has comprehensively presented the state of the topics of interest to her for non-small cell lung cancer - epidemiology, definition, molecular-pathological typing, oncogenic driver mutations, targeted therapy; drug interactions and adverse drug reactions and available software programs used for drug interaction analysis; drug interactions in patients with oncological diseases; pharmacokinetics, pharmacogenetic aspects, drug interactions and the drug use of epidermal growth factor receptor inhibitors (EGFR inhibitors) in patients with NSCLC.

The literature review has a significant part in the volume of the dissertation work, and the literature used is predominantly from the last 10 years, in English and sources of high scientific value.

5. Research methodology

The section with materials and methodology of the conducted studies is presented on a total of 6 pages and includes a description of the steps and stages of the development. An illustration of the data sources used is presented -- Line Listing Report, Individual Case Safety Report Form, a diagram of the design for selecting the population of reported cases for conducting the study. I accept as justified and reasonably selected the approach for detailed presentation of the study design. A total of 8169 cases reported in EudraVigilance were selected and reviewed as follows: 656 cases for erlotinib, 692 cases for gefitinib, 778 cases for afatinib, 276 cases for dacomitinib and 5767 cases for osimertinib over a three-year period – 2021, 2022 and 2023.

The UpToDate® digital platform and its Lexicomp® Drug Interactions application (Wolters Kluwer, Hudson, OH, USA) were used to analyze potential drug-drug interactions.

The research methods, data sources, materials and statistical techniques used, where appropriate, according to the chapters of the dissertation, are correctly selected. The sources of information are described in detail, justifying the representativeness and significance of the results and the conclusions drawn.

Statistical techniques can be classified as descriptive statistics and the data are presented in numerical values, percentages, averages, standard deviations, coefficient of variation, Pearson's contingency coefficient for measuring the strength of the association between two variables (gender and age). The programs used for statistical processing – Excel 2010 (Microsoft Office) and GraphPad Prism version 8.0.1 (GraphPad Software, USA). The visualization of the results of the statistical analysis was achieved with graphical images such as area charts, line charts, structural images.

I consider that the methodological apparatus used is sufficiently comprehensive, allows achieving the set goals and implementing the research tasks. In order to achieve the completion of the dissertation work, the goals and tasks have been categorically met. As a result of the research conducted, I assume that Dr. Mutafova has mastered the basic scientific methods and techniques for conducting medical-pharmacological-clinical studies.

6. Characteristics and assessment of the dissertation work

The dissertation is structured in a classical form - introduction, literature review, aim and objectives, materials and methods, results and discussion, conclusions, contributions, literature and appendices - a total of 182 pages. The clinical characteristics of NSCLC, drug interactions, adverse drug reactions, pharmacokinetics, pharmacogenetic aspects and the use of EGFR inhibitors are comprehensively reviewed and commented. Conclusions are drawn based on the literature review that significant progress has been achieved in treatment, in the concept of personalized medicine and targeted therapy,

new classes of cancer medications have been introduced. The benefits of treatment and overall survival raise questions about safe administration, checking for possible drug-drug interactions, and reporting adverse drug reactions. The reviewed publications are presented thematically and systematically, with a critical reading and analysis of the data, approaches, and recommendations of different authors, factors, and perspectives.

All leading contemporary foreign and Bulgarian authors are cited because the topic is diverse, studied in different aspects and over a long period of time.

In a separate section, the objectives and SEVEN research tasks completed within the framework of the dissertation are presented. Working hypothesis has not been formulated.

The own research is presented in a separate chapter "Results and Discussion" with SEVEN sections with sub-items that correspond to the tasks set. The results of the study are presented in detail on:

- Analysis of patients demographics;
- Identification of potential EGFR inhibitor - drug and drug - drug interactions using the digital platform UpToDate® Lexidrug™
- Selected drug interactions of the EGFR inhibitor - drug combination falling into risk categories X and/or D with determination of the relative share of the severity of drug interaction cases to the total number of cases reported in EudraVigilance
- Analysis and evaluation of some drugs frequently used in clinical practice and with a risk of drug interactions when used concomitantly with EGFR inhibitors
- Evaluation of the relationship between the number of drugs in the combination therapy, the age and gender of the patients and the potential drug interactions to risk categories X/D
- Analysis of potential ADRs reported in EudraVigilance with the use of EGFR inhibitors
- Evaluation of the relationship between the cases of adverse drug reactions reported in EudraVigilance and the identified drug interactions risk category X/D.

It is very impressive the in-depth analysis of the collected raw registry data and the discussion, which is not presented in a separate section. The study systematically shows the identification of potential interactions, adverse reactions, the possibilities for influencing, through digital tools, and the importance for clinical practice, for each drug from the group of EGFR inhibitors and many other frequently and very frequently used in combination medicinal products.

The presented dissertation contains 7 relevant conclusions to the research tasks, which demonstrate the importance of the research and the potential impact on clinical and regulatory practice.

7. Contributions and significance of the development for science and practice

I consider that the evaluated dissertation work is significant with the results achieved and contributions in an extremely sensitive and interdisciplinary field, which presents a serious challenge from both a clinical and regulatory perspective. Contributions are defined as contributions of an original nature and contributions of an applied-practical nature. I consider that the author could also have made scientific and methodological contributions, in view of the studied application of modern software solutions for the analysis of large databases and the comprehensive systematization of drug interactions.

8. Assessment of publications related to the dissertation

The presented full-text publications on the topic of the dissertation in Bulgarian refereed scientific journals are THREE. In two of the publications the doctoral student is the first author in teams, the third is independent. The publications are only in Bulgarian language, reflect the conducted studies, results and analyses of the dissertation work to a significant extent.

Participation in scientific forums in Bulgaria is with posters - a total of 2, in 2022 and 2024.

The analysis of the submitted documents shows that the doctoral candidate has the required scientific activity. I accept and evaluate the scientific production on its merits, but I also recommend publications in international journals printed in English language as a prerequisite for visibility and citation of the results by the scientific community.

9. Personal involvement of the doctoral student

The personal involvement of the doctoral student in the research conducted, formulation of the goals, tasks, results obtained, recommendations and contributions made, is present. I accept as personal achievement the overall scientific production and the declaration of originality. An obvious fact is the in-depth understanding of the specific subject matter of the dissertation work, the ability to present and describe scientific results, as well as the support of the team of scientific supervisors, in view of their scientific orientation and specialization.

10. Critical observations and recommendations

I have no significant critical remarks and recommendations regarding the reviewed dissertation. I can note minor terminological omissions, spelling and punctuation errors, discrepancies in the technical layout of the tables, and repetitions, which of course do not diminish the scientific value, significance, and scient metrics of the dissertation.

The main omission is the lack of information on the classification of studies and compliance with relevant international guidelines. Per my opinion, the studies are predominantly observational and compliance with STROBE or RECORD requirements for reporting results would be paramount.

CONCLUSION

The dissertation contains original results, conclusions and contributions, and it fully meets the requirements of the Development of Academic Staff in the Republic of Bulgaria Act, the Regulations for Application of the Act on. Development of the Academic Staff in the Republic of Bulgaria and the Regulations for the Development of the Academic Staff of MU-Varna.

Following the above, I give my POSITIVE assessment of the conducted research, presented as a dissertation, abstract, achieved results, conclusions, contributions and publications and I propose to the Scientific Jury TO AWARD the educational and scientific degree "doctor" to Dr. IVANKA MINKOVA MUTAFOVA in the doctoral program "PHARMACOLOGY (incl. Pharmacokinetics and Chemotherapy)" for the development of the topic: ***STUDY OF POTENTIAL DRUG INTERACTIONS OF EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS (EGFR INHIBITORS) IN THE TREATMENT OF NON- SMALL CELL LUNG CANCER***

Reviewe

Prof. Ilko Nikolaev Getov, PhD

Sofia, 24.3.2025