Medical University “Prof. Dr. Paraskev Stoyanov” – Varna

Faculty of Pharmacy

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Study of Potential Drug Interactions of Epidermal Growth Factor Receptor Inhibitors (EGFR inhibitors) in the Treatment of Non-Small Cell Lung Cancer

Abstract of a dissertation

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The public defense of the dissertation work will take place online on 29.04.2024 at 11.00 a.m. in the Faculty of Pharmacy at an open meeting of the Scientific Jury.
The defense materials are published on the website of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna.

CONTENTS:

Abbreviations used:

LC	Lung cancer
NSCLC	Non-small cell lung cancer
PK	Pharmacokinetics
PD	Pharmacodynamics
ADR	Adverse drug reaction
TKI	Tyrosine kinase inhibitor
SPC	Short product characteristics
EGFR	Epidermal growth factor receptor
CNS	Central Nervous system
GIT	Gastro-intestinal trackt
DDI	Drug-drug interaction
pDDI	Potential drug-drug interaction
P-gp	P-glycoprotein
CYP	Cytochromes P450
BCRP	Breast Cancer resistance protein
PPI	Proton pomp inhibitor
PCAB	Potassium competitive acid blocker
NSAIDs	Non-steroid antiinflamatory drugs
OATP	Organic anion transporting polypeptide
OAT	Organic anion transporter
OCT	Organic cation transporter

I Introduction

The treatment of cancer is the great challenge facing medicine and pharmacy in the 21st century. Lung cancer (LC) is a malignant disease originating from lung tissue and is the leading cause of cancer-related death worldwide. In recent years, with advances in molecular diagnostics, the development of the concept of personalized antitumor therapy, and the increasingly widespread application of targeted and immunotherapy in clinical practice, significant progress has been made in the treatment of cancer, including LC.

The discovery, analysis and evaluation of pharmaceutical, pharmacokinetic and pharmacodynamic drug interactions is of utmost importance at every stage of the development of new drugs. Nowadays, more and more attention is paid to computerized models and simulations that can test 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 evaluation 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. With the introduction of targeted therapy in oncology, medical specialists faced new challenges. On the one hand, these are drugs that have been relatively recently introduced into clinical practice and are not well known to medical specialists in terms of their mechanism of action, contraindications, drug interactions, and adverse reactions. On the other hand, patients with oncological diseases have disorders of almost all organs and functions, such as reduced body weight, anemia, abnormalities in liver function and kidney function, development of depressive states, and pain syndrome. Very often, patients also have other concomitant diseases - cardiovascular, pulmonary, endocrine, etc., which leads to the simultaneous use of a large number of drugs - polypharmacy and additional intake of special foods, nutritional supplements, and herbal products that patients prescribe themselves without the knowledge of medical specialists.

The factors listed above make the recognition of clinically relevant drug-drug interactions one of the major challenges for physicians and pharmacists in clinical practice. The primary goal is to minimize adverse events associated with drug interactions and maximize clinical efficacy leading to increased overall survival and improved quality of life.

This thesis aims to summarize the available and obtained information from the use of online drug interaction detection platforms and publicly available adverse drug reaction reporting databases to enrich the knowledge in the field of drug interactions in the treatment of non-small cell lung cancer with epidermal growth factor receptor (EGFR) inhibitors.

II Objectives and tasks

1. Objectives

- 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 epidermal growth factor receptor inhibitors (EGFR inhibitors) for the treatment of non-small cell lung cancer (NSCLC).
- A secondary objective of the dissertation is to assess the relationship between reported ADRs and potential drug interactions (pDDIs).

2. Tasks

To achieve the goal, the following tasks were set for implementation:

1. To study and analyze the epidemiology, molecular pathological typing, including oncogenic driver mutations in patients receiving targeted therapy for the treatment of NSCLC.

2. To identify potential EGFR inhibitor-drug and drug-drug interactions using the UpToDate® Lexidrug™ digital platform.

3. To select those drug-drug interactions of the EGFR-inhibitor-drug combination falling into risk categories D and/or X and to determine the relative severity of drug-drug interaction cases to the total number of ADRs reported in EudraVigilance.

4. To analyse drugs commonly used in clinical practice with a risk of drug-drug interactions when used concomitantly with EGFR-inhibitors.

5. To assess the relationship between the number of drugs, age and sex of patients and potential drug interactions falling into risk categories D and/or X.

6. To analyse the potential ADRs reported in EudraVigilance when using an EGFR inhibitor:

- ✓ to the total number of ADR cases reported in EudraVigilance
- ✓ to the number of ADRs in cases with EGFR inhibitor use only;
- ✓ to the number of ADRs in cases of EGFR-inhibitor-drug combinations when there are identified EGFR inhibitor-drug interactions of risk rating D and/or X.

7. To detect and investigate possible correlation between identified potential drug interactions and reported ADRs.

III Materials and methods

The identification, analysis and evaluation of drug-drug interactions in clinical practice is essential for the therapeutic process and its outcome. The search for desirable drug-drug interactions and, on the other hand, the avoidance of the development of adverse drug reactions, toxicity and even loss of therapeutic effect, is part of the daily work of medical professionals in the treatment of patients with oncological diseases with a view to achieving the set goals, namely cure, remission or adequate palliative care to improve quality of life. For the evaluation of drug-drug interactions, several specialized digital platforms are available online and contain reliable databases. The object of the study is the information collected, summarised and analysed from the European database of reported suspected adverse drug reactions EudraVigilance. A predefined time period was defined, which refers only to authorised and clinically available drugs targeting the epidermal growth factor receptor (EGFR) in patients with non-small cell lung cancer (NSCLC). We assessed the likelihood of interactions using one of the most commonly used digital drug interaction platforms, UpToDate® Lexidrug™, and evaluated whether there was a possible correlation between reported adverse drug reactions and identified ones.

Sources of scientific pharmacological information used

1.1 Digital platform for drug-drug interaction analysis

The UpToDate® digital platform and its Lexicomp® Drug Interactions application (Wolters Kluwer, Hudson, OH, USA) [available at: http://www.uptodate.com] were used for the identification and analysis of potential drug-drug interactions after purchasing a one-year access license. The program classifies drug interactions into the following groups:

- According to the degree of risk, potential drug-drug interactions are classified into the following categories:
  - rating A (no known interactions)
  - rating B (no action required)
  - rating C (need for therapy monitoring)
  - rating D (require review and change the therapy)
  - rating X (avoid the combination)

- According to the severity of the interaction, potential drug-drug interactions are classified as:
  - major
  - moderate
  - minor
  - lack of classification in previous groups

1.2 Database for Adverse Drug Reaction (ADR) established and managed by the European Medicines Agency (EMA)

EudraVigilance is the system for monitoring, managing and analysing information on suspected adverse reactions to medicines that are authorised or under investigation in clinical trials in the European Economic Area (EEA). It is set up and managed by the EMA. In the development of the thesis, Line Listings Reports from the open access public resource EudraVigilance were used. (Fig.

1) Each Line Listing Report contains information on the population of cases of reported suspected ADRs over a selected time period. The submitted report has an individual number in the system and a date of initial generation. For each case, information is collected on the reporter, either a health professional or a non-health professional, and whether the case is from the European Economic Area. If information is available, the reporter may also cite a literature source related to the reported ADR. The Line Listing Report contains minimal demographic information about the patient, such as gender and indication of age group, and the reporter may not provide this information. All suspected adverse drug reactions are reported, with duration, outcome and severity reported where information is available and the reporter is willing to provide it. The therapy the patient is receiving shall be reported, indicating for each drug the indication, duration of treatment, dosage regimen, pharmaceutical form, route of administration, action taken with respect to the drug. For each reported case, a so-called "Individual Case Safety Report Form" (Fig. 2) is generated which contains all reported information.
In the development of this dissertation, Line Listing Reports for a three-year period (2021 to 2023) for suspected adverse drug reactions to five (5) different EGFR inhibitors (erlotinib, gefitinib, afatinib, dacomitinib, osimertinib) were retrospectively reviewed and studied.

Line Listing Report
Time run: 13/01/2025 21:32:57

EU Local Number	EV Gateway Receipt Date	Report Type	Primary Source Qualification	Primary Source Country for Regulatory Purposes	Literature Reference	Patient Age Group	Patient Age Group (as per reporter)	Patient Sex	Parent Child Report	Reaction List PT (Duration – Outcome - Seriousness Criteria)	Suspect/interacting Drug List (Drug Char - Indication PT - Action taken - [Duration - Dose - Route])	Concomitant/Not Administered Drug List (Drug Char - Indication PT - Action taken - [Duration - Dose - Route])	ICSR Form
EU-EC-10018597230	27/12/2024	Spontaneous	Non Healthcare Professional	Non European Economic Area	Not available	18-64 Years	Not Specified	Female	No	Mucocutaneous disorder (n/a - Unknown -), Mucosal inflammation (n/a - Unknown -), Neuropathy peripheral (n/a - Unknown - Other Medically Important Condition), Paronychia (n/a - Unknown -), Skin disorder (n/a - Unknown -)	DACOMITINIB [DACOMITINIB] (S - Lung adenocarcinoma - Drug withdrawn - [n/a - 15mg - Oral use - More in ICSR])	[MEGESTROL ACETATE] (C - n/a - n/a - [n/a - 160mg - n/a])	ICSR

Fig. 1. Example of one case reported with suspected ADRs to dacomitinib and concomitant therapy in EudraVigilance

EVPM ICSR(s) **Individual Case Safety Report Form** EudraVigilance

General Information

EudraVigilance Local Report Number	EU-EC-10018597230
Sender Type	Health professional
Sender's Organisation	PFIZER S.R.L.
Type of Report	Spontaneous
Primary source country	Non-European Economic Area
Reporter's qualification	Non-Healthcare Professional
Case serious?	Yes

Patient

Age Group	Age Group (as per reporter)	Sex
18-64 Years		Female

Reaction / Event

MedDRA LLT	Duration	Outcome	Seriousness[1]
Mucocutaneous disorder		Unknown	
Mucositis		Unknown	
Skin disorder		Unknown	
Paronychia		Unknown	
Chemotherapy induced peripheral neuropathy		Unknown	other

Drug Information

Role[2]	Drug	Duration	Dose	Units in Interval	Action taken
S	DACOMITINIB - DACOMITINIB		15.0 mg	Days	Drug withdrawn
S	DACOMITINIB - DACOMITINIB		30.0 mg	Days	Drug withdrawn
C	- MEGESTROL ACETATE		160.0 mg		

Drug Information *(cont.)*

Info[3]	Drug	Indication	Pharm. Form	Route of Admin.
	DACOMITINIB - DACOMITINIB	Lung adenocarcinoma	Tablet	Oral use
	DACOMITINIB - DACOMITINIB	Lung adenocarcinoma	Tablet	Oral use
	- MEGESTROL ACETATE	N/A		

Fig. 2. Individual Case Safety Report Form

2. *Study design*

A total of 8169 reported cases were identified and reviewed in EudraVigilance 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.
In order to fulfil tasks 5 and 6, all 8169 cases were divided into 3 (three) groups according to the total number of drugs taken and according to all reported cases of suspected adverse reactions as follows: 1) less than 5 drugs taken; 2) between 5 and 7 drugs taken; 3) more than 7 drugs taken. For each case, the number of reported suspected adverse drug reactions is listed.
Of all 8169 cases reported to Eudravigilance, the following reports were removed from the analysis:

- Where EGFR inhibitors were taken for an indication other than lung cancer or the indication was not specified (n=1,772)
- Where EGFR inhibitors were administered in combination with conventional chemotherapy or in combination with immunotherapy (n = 862)
- All cases where concomitant use of 2 or more EGFR inhibitors was reported (n = 415)

In the digital platform UpToDate® Lexidrug™ , after the selection, 5120 cases were finally analyzed (reports).
After processing the data and establishing drug-drug interactions of EGFR inhibitors in the digital platform, the following cases were removed from the analysis:

- Cases with no drug-drug interactions (n = 344)

- The drug combination cannot be analyzed in the UpToDate® Lexidrug™ digital platform because information is missing for one or more drugs in the combination, including those of plant or animal origin (n = 105)
- The drug combination of 2 or more tyrosine kinase inhibitors TKI (EGFR-inhibitor from the group and/or another type of TKI)* (n = 108)

A total of 4563 cases were analyzed and assigned to groups. In two of these groups, no drug interactions involving the EGFR inhibitor were observed, but were used for comparative analysis as follows:

- All cases where the reported therapy was represented by only one EGFR inhibitor** (n = 3,755) These cases are included in the analysis for the number of reported ADRs (Task 6)
- All cases of drug-drug interactions of other drugs in the combination but no EGFR inhibitor interactions*** (n = 163). These cases entered the analysis to identify potential EGFR inhibitor-drug and drug-drug interactions using the UpToDate® Lexidrug™ digital platform. (Task 2)

The other cases were split into 2 groups:

- All cases of EGFR inhibitor-other drug interactions (n = 240)
- All cases of concurrently observed EGFR inhibitor-other drug interactions and drug-drug interactions of other drugs in the combination (n=405)

From these two groups, all cases with only one observed EGFR inhibitor-other drug interaction with risk rating X and/or D (n = 125) and all cases with more than one observed EGFR inhibitor-other drug interaction with risk rating X and/or D (n = 19) were separated for analysis, i.e. 144 cases with observed EGFR inhibitor-other drug interactions with risk rating X and/or D were selected for analysis.

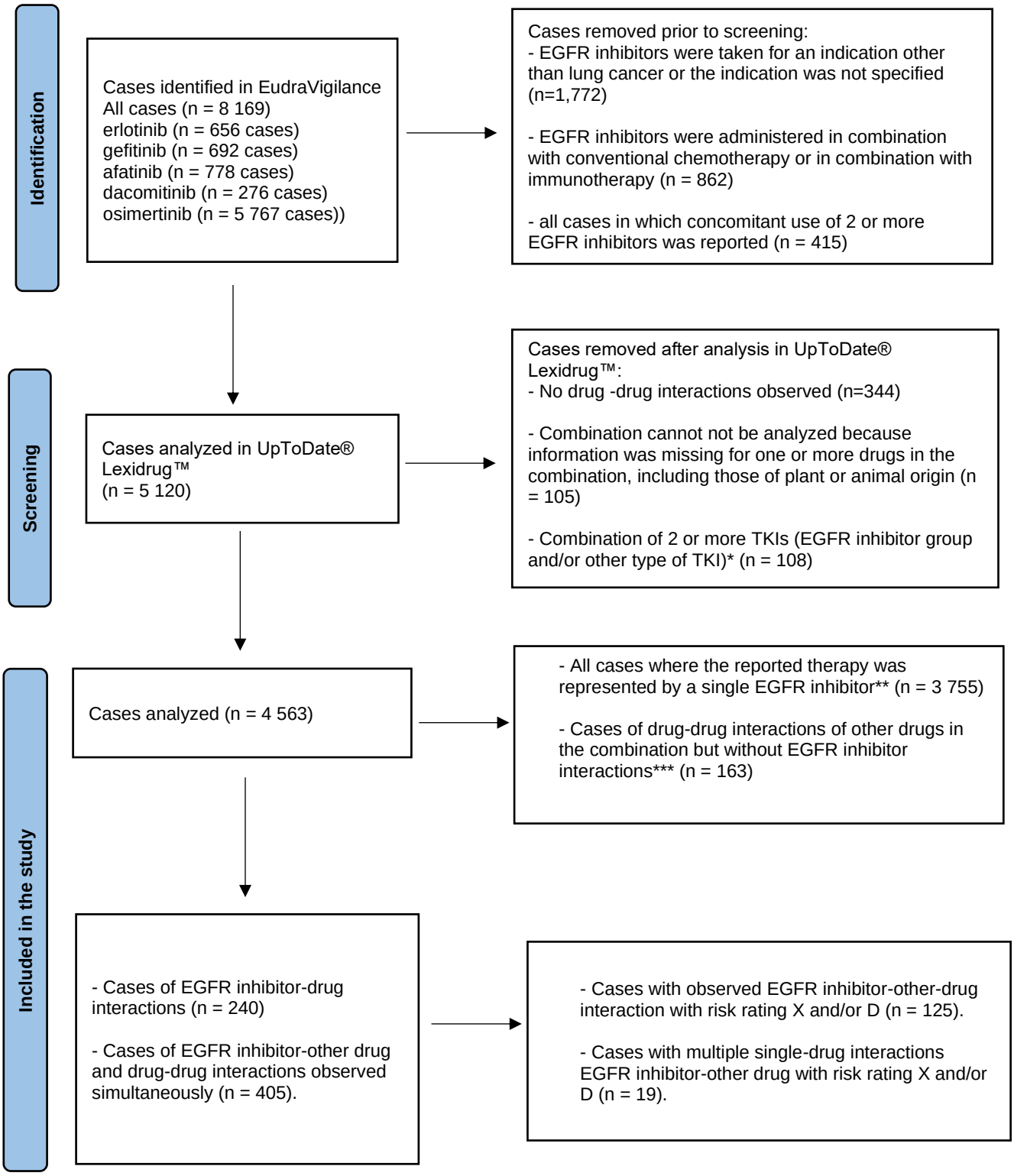

Fig. 3. Selection of the population of reported cases for conducting the study
** Cases with a second neoplasm other than lung cancer and treated with TKI were analyzed.*
*** All cases where the reported therapy was represented by only one EGFR inhibitor were included in the analysis for the average number of reported ADRs.*
**** Cases of drug interactions of other drugs in the combination, but without interactions of the EGFR inhibitor, are included in the analysis to identify potential EGFR inhibitor-drug and drug-drug interactions using the UpToDate® Lexidrug™ digital platform.*

Statistical design and data analysis

Descriptive statistical research was used to analyze the data. Descriptive (situational) statistical research characterizes the state of the research object, with a view to revealing existing problems and contradictions. The data are presented in absolute terms (as a number) and in percentages, the results as average values, standard deviation, coefficient of variation (%). Pearson's correlation coefficient was calculated to measure the strength of association between two variables (gender and age).

To visually present the results of the statistical analysis, graphical images such as area charts, line charts, and structural images were used. The programs used for statistical processing were Excel 2010 (Microsoft Office, USA) and GraphPad Prism version 8.0.1 (GraphPad Software, USA).

IV Results and discussion

1. Demographic characteristics of patients

The demographic characteristics of the patients for the studied period of time (2021 – 2023) show similar characteristics - in all three years the female gender predominates, the most numerous age group for both genders is 65 – 85 years and the average age of the patients is similar. (Table 1)
The demographic characteristics of the selected patients for 2021 show a gender distribution of 1:1.7 men to women. According to age, the majority of patients are in the elderly group (between 65 and 85 years old) – 952 (37.75%), and the number of those over 85 years old is 116 (4.36%). The average age of the patients is 62.7 years.

Table 1. Demographic characteristics of patients

Demographic characteristics of patients	**Number, relative frequency (%) 2021 г. (n = 2663)**	**Number, relative frequency (%) 2022 г. (n = 2669)**	**Number, relative frequency (%) 2023 г. (n = 2837)**
Gender			
Male	903 (33.91 %)	835 (31.29 %)	932 (32.85 %)
Female	1559 (58.55 %)	1586 (59.42 %)	1641 (57.84 %)
Age			
18-64	711 (26.70%)	759 (28.44%)	724 (25.52%)
65-85	952 (35.75%)	972 (36.42%)	1054 (37.15%)
> 85	116 (4.36 %)	97 (3.63%)	90 (3.17%)
Average age (years)	62.7	61.9	62.8

The demographic characteristics of the selected patients for 2022 show an almost identical distribution of indicators as in 2021. In terms of gender, the ratio of men to women is 1:1.89. According to age, the majority of patients are in the elderly group (between 65 and 85 years old) – 972 (36.42%), and the number of those over 85 years old is 97 (3.63%). The average age of the patients is 61.9 years old
The demographic characteristics of the selected patients for 2023 show an almost identical distribution of indicators as in 2021 and 2022. In terms of gender, the ratio of men to women is 1:1.76. By age, the majority of patients are in the elderly group (between 65 and 85 years old) - 1054 (37.15%), and the number of those over 85 years old is 90 (3.17%).
When analyzing the demographic data in EudraVigilance, it turned out that age was not reported in a significantly large percentage of patients: 820 (30.79%) for 2021, 840 (31.47%) for 2022 and 961 (33.87%) for 2023. Gender was not reported in 201 (7.54%) patients for 2021, 249 (9.33%) patients for 2022, and 262 (9.24%) patients for 2023.
The demographic characteristics of the patients for the studied time period (2021 – 2023) show similar characteristics - in all three years the female gender predominated, the most numerous age group for both genders was 65 – 85 years and the average age of the patients was similar – 62 years.
A total of 8169 cases reported over three years (2021, 2022 and 2023) in EudraVigilance for suspected adverse drug reactions to an EGFR inhibitor were reviewed (Table 2 Fig. 4)

Table 2 Number of reported cases for the respective EGFR inhibitor and total number of cases reported in EudraVigilance for the period considered 2021 – 2023. The most cases were reported with the use of the third-generation EGFR inhibitor – osimertinib, and the fewest cases – with dacomitinib, a second-generation EGFR inhibitor.

EGFR-inhibitor	Year			Total number of reported cases
	2021	2022	2023	
Erlotinib	248	217	191	658
Gefitinib	270	220	202	692
Afatinib	395	185	198	778
Dacomitinib	68	108	100	276
Osimertinib	1682	1939	2146	5767
				8169

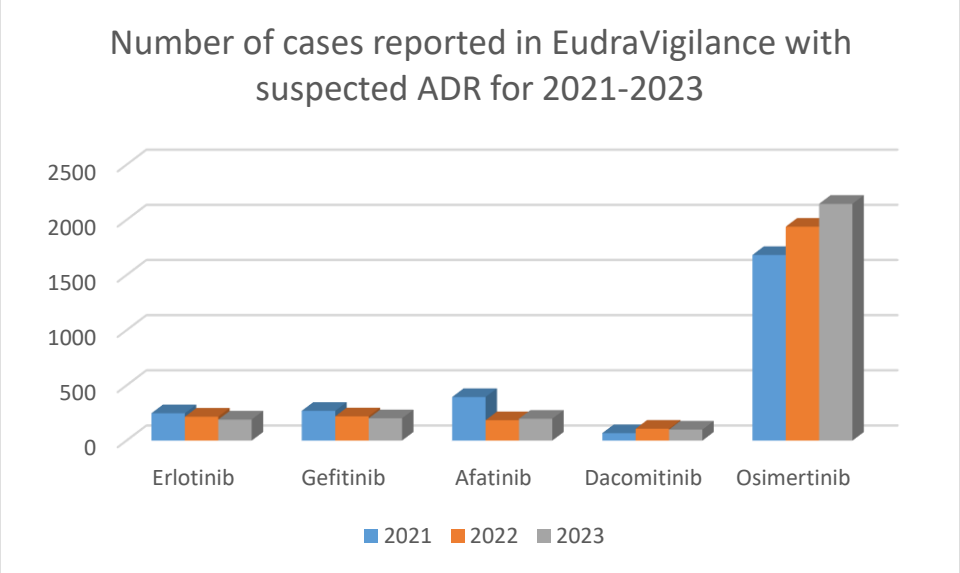

Fig. 4. Number of cases with suspected ADR reported for the respective EGFR inhibitors in EudraVigilance for the period 2021 – 2023.

For the observed period, the most cases were reported for osimertinib – a total of 5767, and the least cases – for dacomitinib, a total of 276. For the first-generation EGFR inhibitors, the following were reported – 658 cases for erlotinib and 692 cases for gefitinib. For afatinib (a second-generation EGFR inhibitor), a total of 778 cases were reported.

When analyzing the number of reported cases, it is noted that for osimertinib, the number of reported cases is increasing, with the least cases reported in 2021 – 1682, with an increase in 2022 -1939 and the most cases reported in 2023 – 2146 cases. At the same time, there has been a decrease in reported cases for first-generation EGFR inhibitors and afatinib (a second-generation EGFR inhibitor), for example, for erlotinib, 248 cases were reported in 2021 and 191 cases in 2023; for gefitinib, 270 cases were reported in 2021 and 202 cases in 2023.

2. Identification of potential EGFR-inhibitor-drug and drug-drug interactions using the UpToDate® Lexidrug™ digital platform rating

One of the functionalities of the UpToDate® Lexidrug™ digital platform is to display a list of interaction results for a single drug. Each of the drugs analyzed was screened for potential drug-drug

interactions with other drugs and the corresponding interaction was classified by risk level into one of five risk categories (X, D, C, B, and A). Table 3

Of the EGFR inhibitors studied, dacomitinib and osimertinib showed the most potential drug interactions with risk rating X (avoid the combination) - when combined with 17 drugs, while afatinib and gefitinib had drug interactions with risk rating X with 4 and 1 drug, respectively.

With risk rating D (require review and change the therapy), drug combinations are observed most often with erlotinib - with simultaneous use with 84 drugs, while for afatinib this number of drugs is 70, and for osimertinib - 58 drugs.

The most potential drug interactions are observed with risk rating C (need for therapy monitoring), as for osimertinib, drug interactions of risk rating C are possible with 122 drugs when used in combination, for dacomitinib - with simultaneous use with 63 drugs, while a significantly smaller number - 30 drugs, lead to risk rating C when used simultaneously with afatinib.

The highest number of drugs with which drug interactions can occur when coadministered with osimertinib – a total of 365 drugs when combined with osimertinib can lead to drug-drug interactions of a different rating. The first-generation EGFR inhibitors - erlotinib and gefitinib, can have drug interactions with a total of 156 and 125 drugs, respectively. The second-generation EGFR inhibitors afatinib and dacomitinib – with a total of 104 and 112 drugs, respectively.

Table 3: Number of drugs with possible drug interactions with EGFR inhibitors distributed by risk rating according to UpToDate® Lexidrug™. No information on drug interactions rating A

	Number of drugs with possible drug-drug interactions with EGFR inhibitors assigned to risk categories according to UpToDate® Lexidrug™				
EGFR - inhibitor	**Rating X**	**Rating D**	**Rating C**	**Rating B**	**Total**
Erlotinib	13	84	55	4	156
Gefitinib	1	41	59	24	125
Afatinib	4	70	30	0	104
Dacomitinib	17	22	63	10	112
Osimertinib	17	58	122	168	365

2.1 Potential drug interactions of erlotinib identified using the UpToDate® Lexidrug™ digital platform

A total of 658 cases of suspected adverse drug reactions were reported for erlotinib in EudraVigilance, distributed over 3 years as follows: for 2021 – 248 cases, for 2022 – 217 cases and 2023 – 191 cases. Of these, all cases where there were drug interactions erlotinib – drug were selected (cases in which the drug therapy included drugs used for chemotherapy, immunotherapy or a tyrosine kinase inhibitor for another type of receptor were excluded) and all cases where there were observed drug interactions of other drugs in the combination therapy with erlotinib, but no drug interactions involving erlotinib were observed.

It should be noted that in most selected cases, more than one drug interaction of different risk categories and with different severity is observed.

For the observed period, 25 potential drug interactions for erlotinib were identified according to risk rating X criteria (avoid the combination), as follows: 10 drug interactions for 2021, 5 for 2022 and 10 for 2023 and 26 potential drug interactions assessed as risk rating D (require review and change the therapy) as follows: 8 potential drug interactions for 2021, 7 for 2022 and 11 for 2023, respectively. A relatively small number of potential erlotinib-drug interactions have been identified with risk rating C (need for therapy monitoring) – 4 for 2021, 2 for 2022 and 3 for 2023. Only 1 erlotinib - drug interaction with risk rating B was noted (2021).

The UpToDate® Lexidrug™ digital platform classifies drug interactions based on the severity of the interaction as severe, moderate, minor, and unclassified. Based on this classification, a total of 45 potential erlotinib-drug interactions were in the major group and 20 observed interactions were the most in 2023, while a total of 15 potential erlotinib-drug interactions were assessed as moderate in severity (Table 4, Fig. 5).

Tab. 4 Potential erlotinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk and drug interaction severity

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI erlotinib – drug	2021	10	8	4	1	0	14	8	1	0
	2022	5	7	2	0	0	11	3	0	0
	2023	10	11	3	0	0	20	4	0	0

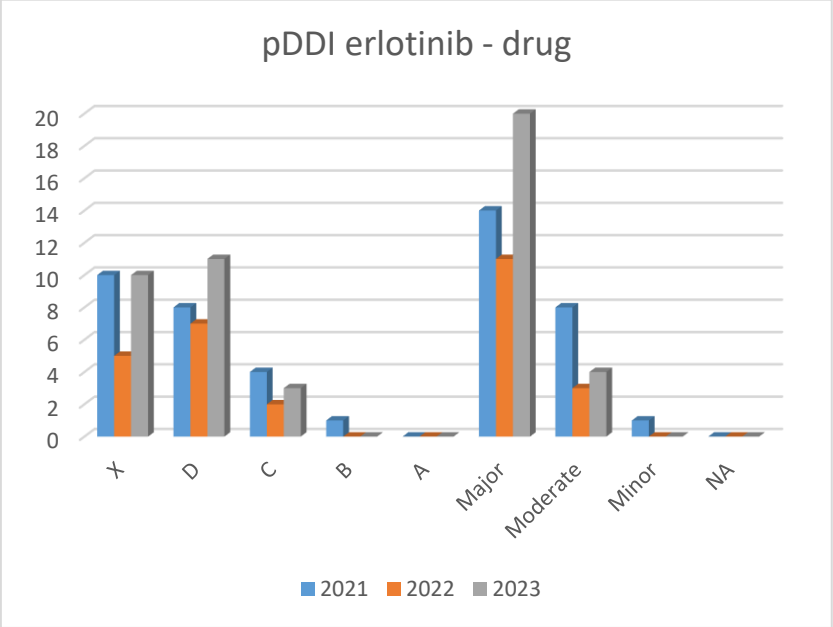

Fig. 5 Potential erlotinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk and drug interaction severity

When analyzing the potential drug - drug interactions between other drugs in the combination therapy of erlotinib, but not involved erlotinib – drug interactions, it is striking that more drug interactions with a risk level of rating C (need for therapy monitoring) and rating B (no action required) are observed. In terms of the severity of the drug interaction, the most ofter are moderate in severity, a total of 187 with the largest number observed in 2023 – 69 cases, while in total 29 major potential drug-drug interactions were observed (9 for 2021, 10 for 2022 and 10 for 2023). (Table 5, Fig. 6)

Table 6 Identified potential drug-drug interactions of drugs in the combined therapy of erlotinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI in other drugs than erlotinib	2021	0	14	55	18	1	9	62	16	1
	2022	4	13	44	14	3	10	56	9	3
	2023	2	10	66	18	0	10	69	17	0

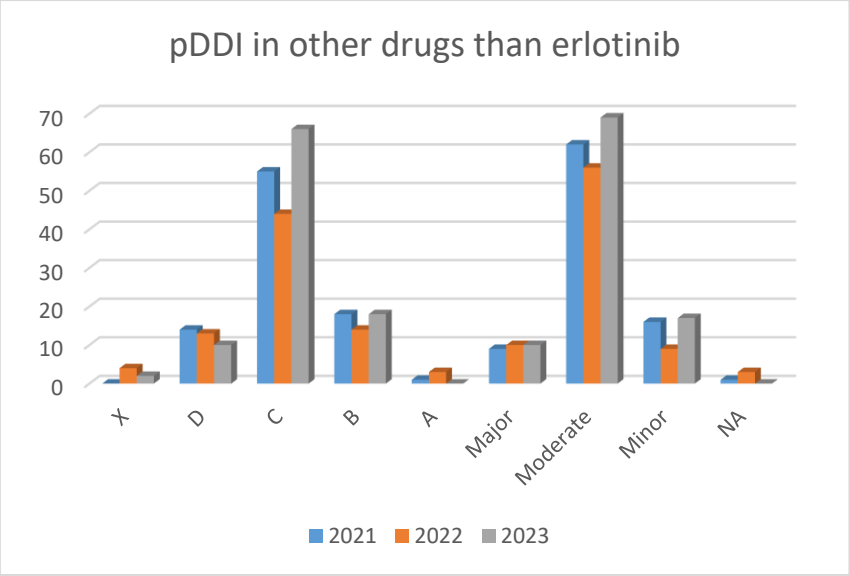

Fig. 6 Identified potential drug-drug interactions of drugs in the combined therapy of erlotinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

2.2 Potential drug interactions of gefitinib identified using the UpToDate® Lexidrug™ digital platform

For gefitinib, a total of 692 cases with suspected adverse drug reactions have been reported to EudraVigilance, spread over 3 years as follows: for 2021 - 270 cases, for 2022 - 220 cases and for 2023 - 202 cases. Of these, all cases where there were gefitinib-drug interactions were selected (excluding cases where the drug therapy included drugs used for chemotherapy, immunotherapy, or a tyrosine kinase inhibitor for another type of receptor) and all cases where there were observed drug-drug interactions of other drugs in the combination therapy with gefitinib, but no drug-drug interactions involving gefitinib were observed (Table 6, Fig. 7).

Compared to erlotinib, no drug-drug interactions risk rating X (avoid the combination) were identified in the gefitinib cases. For the period under review, 32 potential gefitinib-drug interactions were assessed as risk rating D (require review and change the therapy) as follows: 15 potential drug interactions in 2021, 7 potential drug interactions in 2022 and respectively - 10 potential drug interactions in 2023. A relatively small number of potential gefitinib-drug interactions with risk rating C (need for therapy monitoring) were identified - a total of 13 for the entire period and distributed by year as follows: 9 for 2021, 2 for 2022 and 2 for 2023. For the period under review, 4 potential drug interactions with gefitinib of risk rating B were identified.

In terms of drug interaction severity rating, the moderate potential EGFR inhibitor-drug interactions totaled 23 (13 for 2021, 4 for 2022, and 6 for 2023), while the major potential gefitinib-drug interactions totaled 22 (11 for 2021, 5 for 2022, and 6 for 2023).

Table 6 Potential gefitinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI gefitinib - drug	2021	0	15	9	1	0	11	13	1	0
	2022	0	7	2	1	0	5	4	1	0
	2023	0	10	2	2	0	6	6	2	0

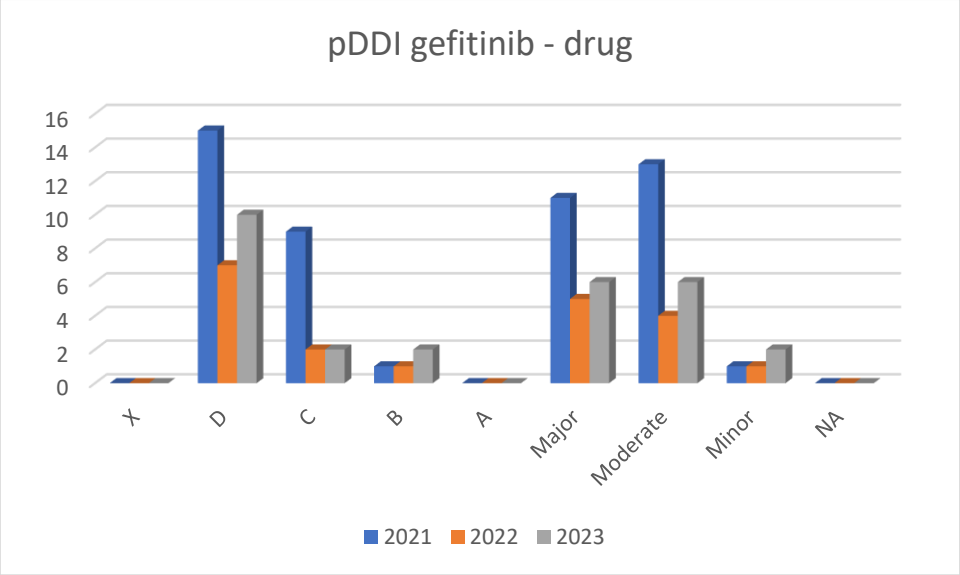

Fig. 7 Potential gefitinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

When analyzing potential drug interactions between other drugs in the combination therapy of gefitinib, but without the gefitinib-drug interactions, the most drug-drug interactions with risk rating C (need for therapy monitoring) were identified – a total of 96 for the entire period and distributed by year as follows: 55 for 2021, 29 for 2022 and 12 for 2023. Only 5 potential drug-drug interactions with risk rating X (avoid the combination) were identified. With risk rating D (require review and change the therapy) – a total of 37 were identified for the entire period and distributed by year as follows: 17 for 2021, 13 for 2022. and 7 for 2023. In terms of the severity of drug interactions, a total of 29 major potential drug-drug interactions were identified: 12 for 2021, 13 for 2022 and 4 for 2023. The moderate ones totaled 105 for the three years considered. (Table 7, Fig. 8)

Table 7 Identified potential drug-drug interactions of drugs in the combined therapy of gefitinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI in other drugs than gefitinib	2021	3	17	55	18	1	12	62	19	1
	2022	2	13	29	9	0	13	30	10	0
	2023	0	7	12	8	0	4	13	10	0

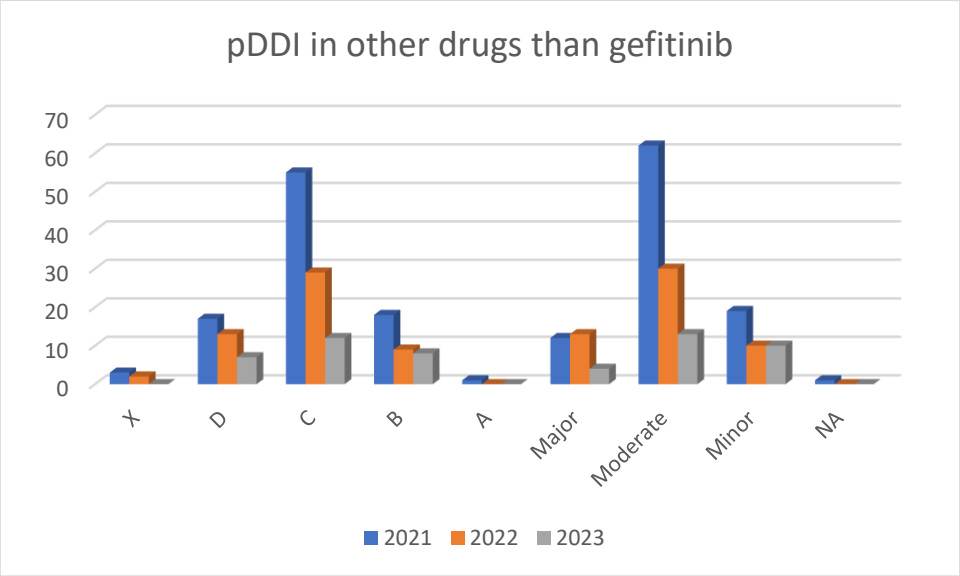

Fig. 8 Identified potential drug-drug interactions of drugs in the combined therapy of gefitinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

2.3 Potential drug interactions of afatinib identified using the UpToDate® Lexidrug™ digital platform

A total of 778 cases of suspected adverse drug reactions with afatinib were reported in EudraVigilance, distributed over 3 years as follows: for 2021 – 395 cases, for 2022 – 185 cases and for 2023 – 198 cases.

Cases with observed potential drug interactions during concomitant use of afatinib with another drug were selected (cases where the drug therapy included drugs used for chemotherapy, immunotherapy or a tyrosine kinase inhibitor targeted against another type of receptor were excluded) and all cases where there were observed potential drug interactions of other drugs in combination therapy with gefitinib, but no drug interactions involving gefitinib were observed. (Table 8, Fig. 9)

No potential drug interactions involving afatinib were identified and with risk rating X were identified (avoid the combination). For the three-year period under review, 8 potential afatinib-drug interactions with risk rating D (require review and change the therapy) were identified as follows: 3 potential drug interactions for 2021, 1 for 2022 and 5 potential drug interactions for 2023, respectively. A relatively larger number of potential afatinib-drug interactions were identified from risk rating C (need for therapy monitoring) – 22 for 2021, 11 for 2022 and 12 for 2023 (total 45 for the 3-year period under review). For the study period, only 3 drug interactions with afatinib from risk rating B were identified.

Table 8 Potential afatinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI afatinib – drug	2021	0	3	22	2	0	0	25	2	0
	2022	0	1	11	0	0	0	12	0	0
	2023	0	5	12	1	0	0	18	0	0

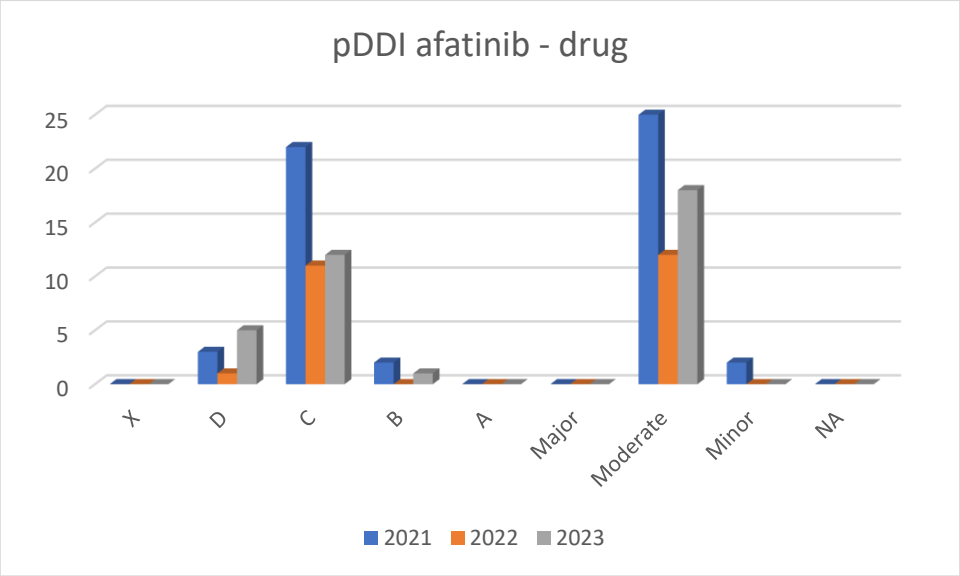

Fig. 9. Potential afatinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

In terms of severity assessment, almost all (55) potential afatinib-drug interactions were rated as moderate, while no severe potential afatinib-drug interactions were observed.
When analyzing potential drug interactions between other drugs in the combination therapy of afatinib, but without afatinib-drug interactions, 13 potential drug-drug interactions of risk rating X were observed with a recommendation to avoid the combination, as follows: 6 for for 2021 and for 2023 and only 1 for 2022. The most observed potential drug interactions were with risk rating C (need for therapy monitoring) – 205. A relatively smaller number of potential drug-drug interactions were assessed as risk rating D (require review and change the therapy) as follows – the total number for the three observed years was 77: 29 drug-drug interactions for 2021, 17 for 2022 and 31 drug-drug interactions for 2023, respectively. In terms of severity assessment, almost all potential drug-drug interactions were assessed as moderate (in 254 cases), while major potential drug-drug interactions were observed in 51 cases. (Table 9, Fig. 10)

Table 9 Identified potential drug-drug interactions of drugs in the combined therapy of afatinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI in other drugs than afatinib	2021	6	29	103	39	0	17	121	39	0
	2022	1	17	47	26	0	13	60	18	0
	2023	6	31	55	19	0	21	73	17	0

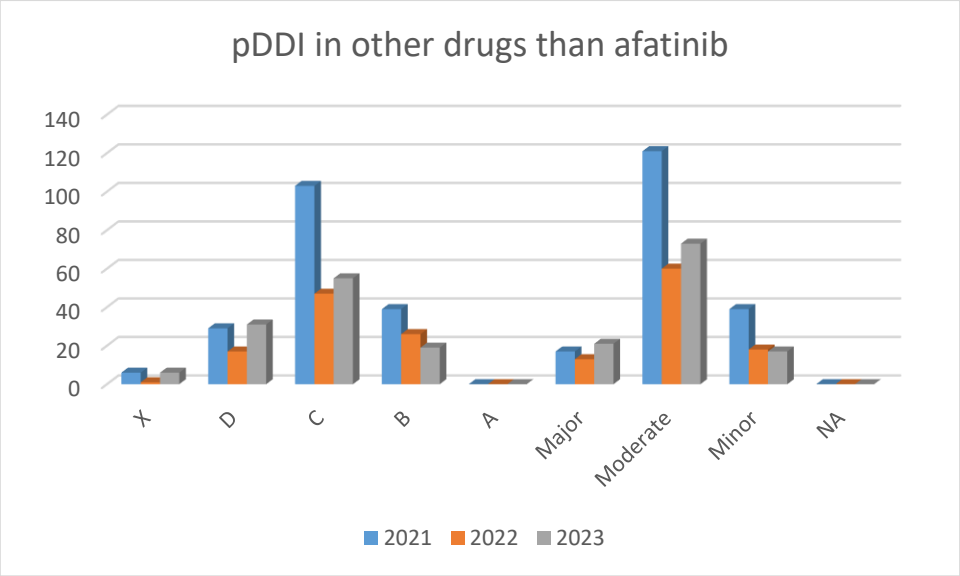

Fig. 10 Identified potential drug-drug interactions of drugs in the combined therapy of afatinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

2.4 Potential drug interactions of dacomitinib identified using the UpToDate® Lexidrug™ digital platform

A total of 276 cases of suspected adverse drug reactions were reported in EudraVigilance for dacomitinib, distributed over 3 years as follows: for 2021 – 68 cases, for 2022 – 108 cases and for 2023 – 100 cases.

In the selected cases where potential drug interactions were observed with the simultaneous use of dacomitinib with another drug (cases in which the drug therapy included drugs used for chemotherapy, immunotherapy or a tyrosine kinase inhibitor targeted against another type of receptor were excluded), a total of 6 potential dacomitinib - drug interactions were identified for the observed period in terms of risk assessment of rating X (avoid the combination), distributed by year as follows: 1 drug-drug interaction for 2021, 2 for 2022 and 3 drug-drug interactions for 2023 respectively. 20 potential drug interactions with dacomitinib were with a risk level of rating D (require review and change the therapy) as follows: 4 drug interactions for 2021, 7 for 2022 and 9 for 2023 respectively. Risk level rating C 27 dacomitinib-drug interactions were identified – 5 for 2021, 12 for 2022, and 10 for 2023.

Table 10 Potential dacomitinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI dacomitinib - drug	2021	1	4	5	2	0	1	10	1	0
	2022	2	7	12	2	0	2	19	2	0
	2023	3	9	10	0	0	3	17	2	0

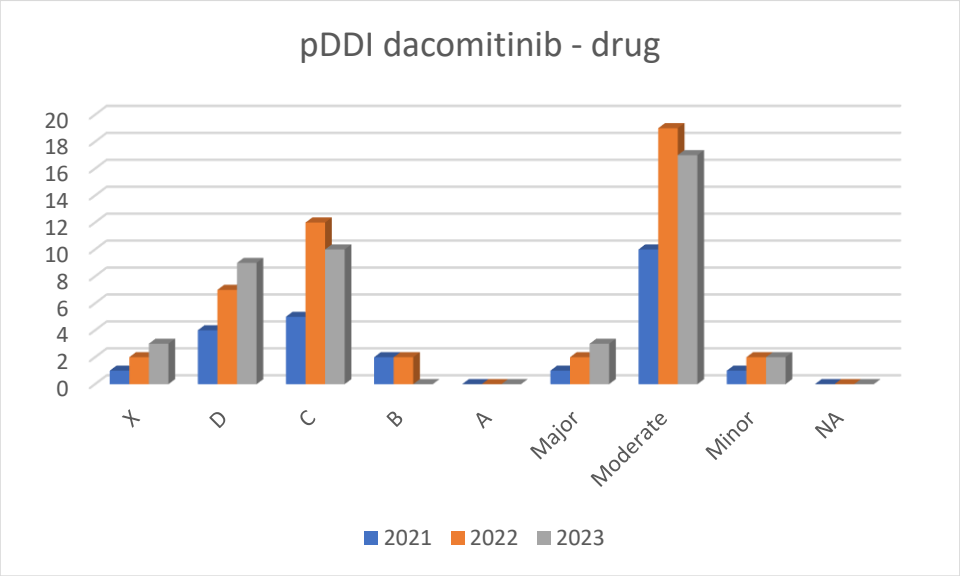

Fig. 11. Potential dacomitinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

In terms of severity rating, almost all potential dacomitinib drug-drug interactions were rated as moderate (46 in total), and 6 potential dacomitinib drug-drug interactions were rated as major. (Table 10, Fig. 11)

In cases where drug interactions of other drugs were observed in the combination therapy with dacomitinib, but without dacomitinib – drug interactions, 2 potential drug-drug interactions with risk rating X were observed with a recommendation to avoid the combination. The most were potential drug interactions with risk rating C (monitoring the therapy) – a total of 69 for the entire observed period. A relatively smaller number of potential drug-drug interactions with risk rating D (require review and change the therapy) were observed as follows: 12 drug interactions for 2021, 6 for 2022 and 18 for 2023 respectively (total 36). In terms of severity assessment, almost all potential drug-drug interactions were assessed as moderate - a total of 82 for the observed period, while the observed major potential drug-drug interactions were a total of 27 for the observed period. (Table 11 Fig. 12)

Table 11 Identified potential drug-drug interactions of drugs in the combined therapy of dacomitinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI in other drugs than dacomitinib	2021	0	12	31	12	0	10	34	11	0
	2022	2	6	25	8	0	6	27	8	0
	2023	0	18	13	16	0	11	21	15	0

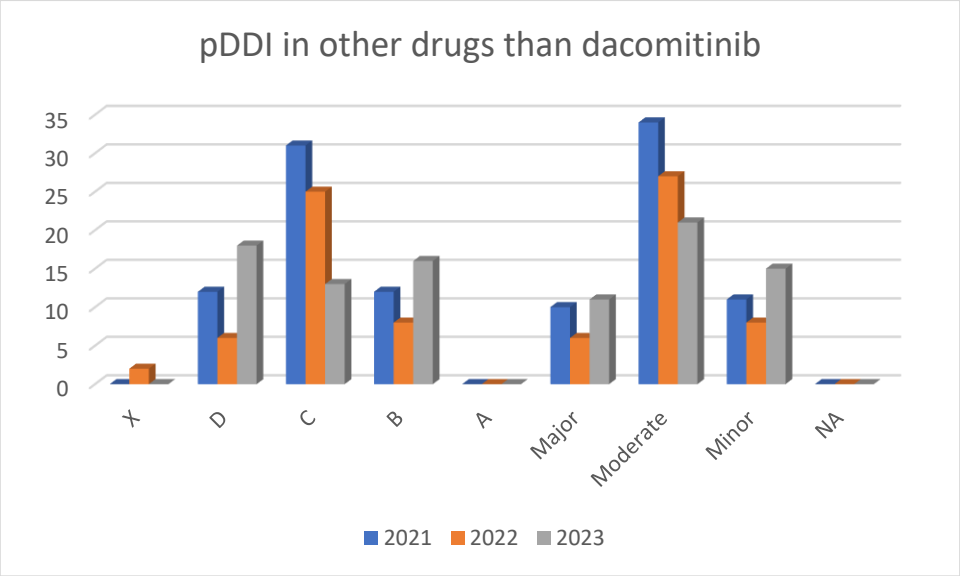

Fig 12 Identified potential drug-drug interactions of drugs in the combined therapy of dacomitinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

2.5 Potential drug interactions of osimertinib identified using the UpToDate® Lexidrug™ digital platform

A total of 5767 cases of suspected adverse drug reactions were reported for osimertinib in EudraVigilance, distributed over 3 years as follows: for 2021 – 1682 cases, for 2022 – 1939 cases and 2023 – 2146 cases.

In the selected cases where there were drug interactions with the simultaneous use of osimertinib with another drug (cases in which the drug therapy included drugs used for chemotherapy, immunotherapy or a tyrosine kinase inhibitor targeted against another type of receptor were excluded), a total of 7 osimertinib-drug interactions were identified in terms of risk assessment of rating X (avoid the combination): 4 for 2021, 1 for 2022 and 2 for 2023. A total of 39 potential osimertinib-drug interactions were assessed as risk grade rating D (require review and change the therapy), as follows: 5 drug interactions for 2021, 14 for 2022 and 20 for 2023, respectively. A total of 266 osimertinib-drug interactions with risk rating C (monitoring the therapy) were identified - 90 for 2021, 74 for 2022, and 103 for 2023. For the study period, 549 osimertinib drug interactions with risk rating B were identified.

Table 12 Potential osimertinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI osimertinib - drug	2021	4	5	90	186	0	5	113	167	0
	2022	1	14	74	153	0	8	91	141	0
	2023	2	20	103	210	0	12	139	184	0

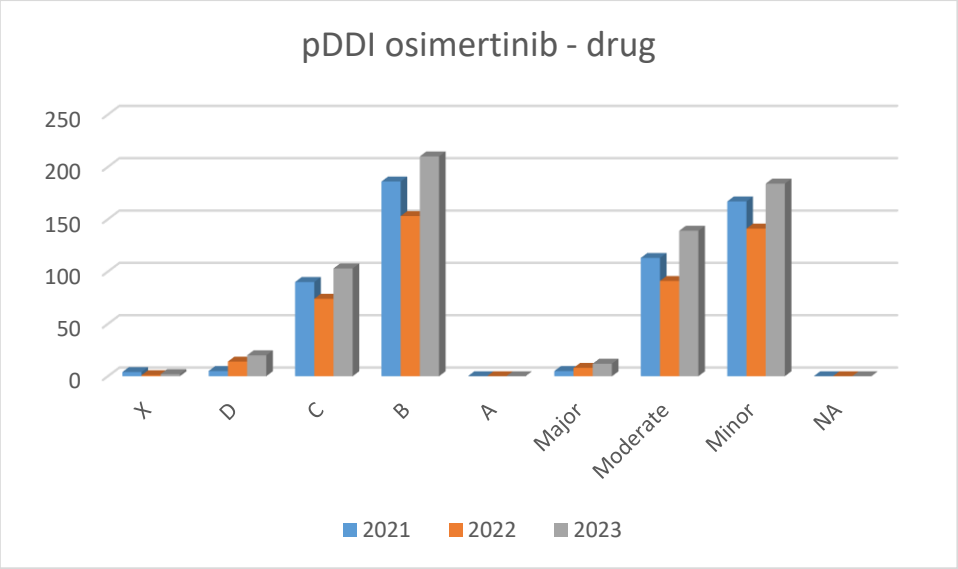

Fig. 13. Potential osimertinib - drug interactions identified using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

In regards of severity assessment, the most osimertinib-drug interactions were assessed as minor (492 drug interactions), the moderate drug interactions were 343, and 25 potential osimertinib-drug interactions were assessed as major. (Table 12, Fig. 13)

In cases where potential drug interactions of other drugs were observed in the combination therapy with osimertinib, but without osimertinib-drug interactions, 42 potential drug-drug interactions of risk rating X were observed with a recommendation to avoid the combination, as follows: 22 drug interactions for 2021, 7 for 2022 and 13 for 2023 respectively. The most potential drug interactions are risk rating C (monitoring the therapy) – 1307 and relatively fewer were assessed with a risk level of rating D (require review and change the therapy) as follows: 151 drug interactions for 2021, 77 for 2022 and 124 for 2023 respectively (total 352). (Table 13, Fig. 14).

Regarding the severity assessment, for the period under consideration 2021 -2023 266 potential drug-drug interactions were rated as major, 1460 were rated as moderate, and 328 potential drug-drug interactions were rated as minor.

Table 13 Identified potential drug-drug interactions of drugs in the combined therapy of osimertinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

Drug	year	X	D	C	B	A	Major	Moderate	Minor	NA
pDDI in other drugs than osimertinib	2021	22	151	388	106	3	104	465	110	3
	2022	7	77	329	85	1	59	369	70	1
	2023	13	124	590	150	3	103	626	148	3

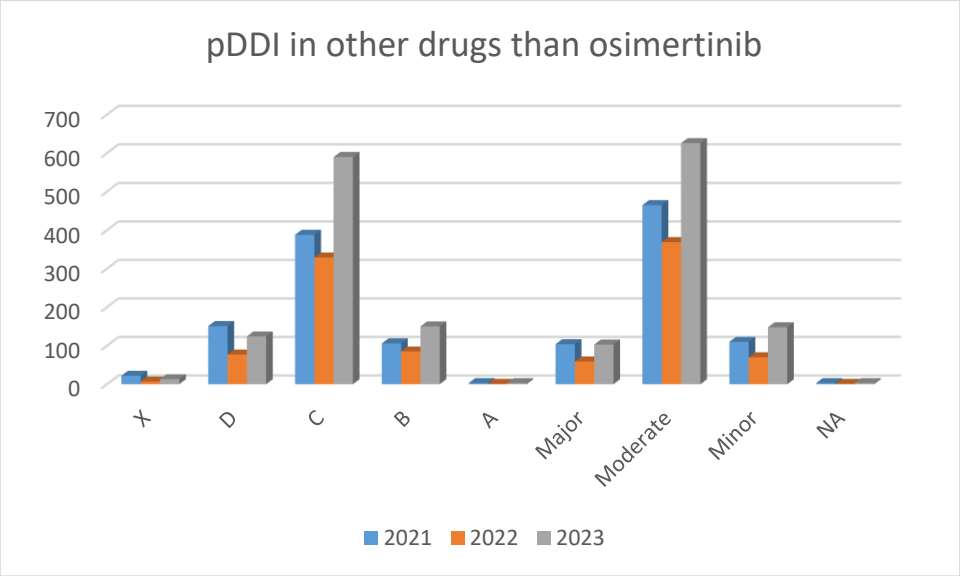

Fig 14 Identified potential drug-drug interactions of drugs in the combined therapy of osimertinib using the UpToDate® Lexidrug™ digital platform and stratified by risk level and severity of the drug interaction

After analyzing drug combinations for potential drug interactions using the UpToDate® Lexidrug™ digital platform, all drug interactions involving an EGFR inhibitor and all drug interactions between other drugs administered concomitantly with an EGFR inhibitor were identified. When comparing the identified potential EGFR inhibitor-drug interactions in terms of severity and degree of risk of the drug interaction, for erlotinib most potential drug interactions were with risk category X and D and were classified as severe according to the severity of the interaction. For gefitinib, most potential drug interactions were observed with risk category D, and according to the severity of the interaction, there was a slight predominance of severe over moderate in severity. For the second-generation EGFR inhibitors afatinib and dacomitinib, mainly drug interactions with risk category C were observed and were classified as moderate according to the severity of the interaction. For osimertinib, most identified potential drug interactions were of risk category B, and according to the severity of the interaction, there was a slight preponderance of those with minor severity over those with moderate severity.
When analyzing potential drug interactions between other drugs used in combination, most drug interactions were moderate in severity and of risk category C.

3. Selection of drug interactions of the EGFR-inhibitor-drug combination falling into risk categories X and/or D and to determine the relative proportion of the severity of the drug interaction cases to the total number of cases reported in EudraVigilance

After reviewing the database, identifying potential drug interactions, and assessing the risk rating using the UpToDate® Lexidrug™ digital platform, drug combinations of EGFR-inhibitor with other drugs were selected, where at least one case of drug interaction of the combination EGFR-inhibitor - drug with risk rating X and/or D was observed.
A total of 144 cases with observed potential drug interactions of risk rating X and/or D of an EGFR inhibitor with another drug were identified for the period 2021 – 2023 (Table 14). The most cases for the period were observed for erlotinib – a total of 44 cases, distributed by year as follows: 16 cases for 2021, 10 cases for 2022 and 18 cases for 2023. The same number (44) were also identified for osimertinib, respectively 9 cases for 2021, 15 cases for 2022 and 20 cases for 2023. The fewest cases

were identified for afatinib – a total of 9 cases for the three years: 3 cases for 2021, 1 case for 2022 and 5 cases for 2023 (Fig. 15)

In 124 of the cases, only one EGFR-inhibitor - drug interaction was observed with risk rating X or D, and in 20 of the cases, more than one drug interaction with risk rating X and/or D was identified. (Table 26) The most cases with more than one potential drug interaction were observed for erlotinib (7 cases) and gefitinib (8 cases), while no cases were identified for afatinib.

Table 14 Total number of cases with observed potential drug interactions with risk rating X and/or D for the period 2021 – 2023.

EGFR-inhibitor	year			Total number of cases with observed pDDI with risk rating X and/or D for the period 2021-2023
	2021	2022	2023	
Erlotinib	16	10	18	44
Gefitinib	11	6	7	24
Afatinib	3	1	5	9
Dacomitinib	4	7	12	23
Osimertinib	9	15	20	44
				144

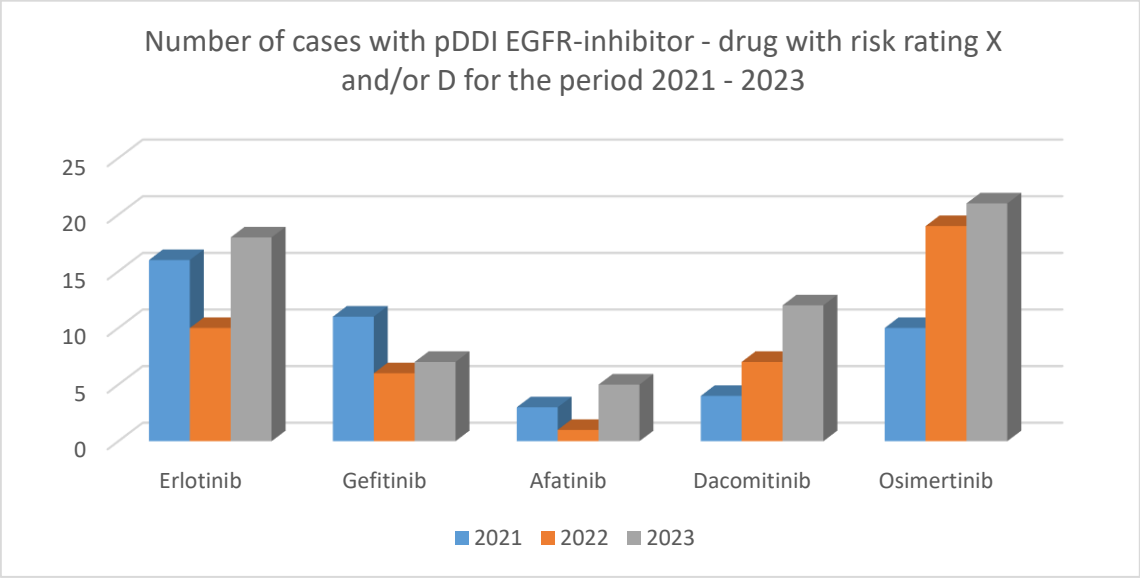

Fig. 15 Number of observed cases with potential drug interactions EGFR inhibitor – drug with risk rating X and/or D for the period 2021 – 2023

Table 15 Number of cases with observed drug interactions with risk rating X and/or D

EGFR – inhibitor	Number of cases with only one observed pDDI with risk rating X or D in the drug combination for the period 2021-2023	Number of cases with more than one pDDI with risk rating X and/or D in the drug combination in the period 2021-2023	Total number of cases with observed drug interactions with risk rating X and/or D in the period 2021-2023
Erlotinib	37	7	44
Gefitinib	16	8	24
Afatinib	9	0	9
Dacomitinib	20	3	23
Osimertinib	42	2	44
Total	124	20	144

When calculating the relative share of severity of cases of observed drug interactions with risk rating X and/or D compared to the total number of cases of suspected adverse drug reactions reported in EudraVigilance, it turned out that the second-generation EGFR inhibitor dacomitinib (8.33) had the highest relative share, followed by erlotinib (6.71) and gefitinib (3.47), and the lowest relative share was afatinib (1.16) and osimertinib (0.76). (Table 16)

Although an equal number of observed drug interactions with risk category X and/or D were identified for erlotinib and osimertinib, the relative severity ratio of potential drug interactions for erlotinib was greater than that for osimertinib, as follows - 6.71 for erlotinib versus 0.76 for osimertinib. Also, with an almost equal number of observed drug interactions with risk category X and/or D for gefitinib and dacomitinib, the relative severity ratio of potential drug interactions for dacomitinib was 8.33 and 3.47 for gefitinib.

Table 16 Relative share of severity of cases of observed drug interactions with risk rating X and/or D compared to the total number of cases reported in EudraVigilance

EGFR – inhibitor	Total number of ADR cases reported in EudraVigilance for the period 2021 - 2023	Severity of pDDI from groups X and D for the period 2021 - 2023	Relative share of pDDI burden to total number of EudraVigilance cases
Erlotinib	656	44	6.71
Gefitinib	692	24	3.47
Afatinib	778	9	1.16
Dacomitinib	276	23	8.33
Osimertinib	5767	44	0.76

4 Analysis and evaluation of some drugs commonly used in clinical practice and with a risk of drug interactions when used concomitantly with EGFR inhibitors

A review of the EudraVigilance database for the period 2021 - 2023 identified drugs that are commonly used in clinical practice and that, when administered in combination with an EGFR inhibitor, may lead to clinically significant drug interactions. For two of the observed EGFR inhibitors

- gefitinib and afatinib, no drug interactions involving the EGFR inhibitor belonging to risk rating X were observed. A complete list of all identified potential drug interactions of EGFR inhibitors with an assessment of risk and severity and possible mechanisms of drug interactions observed for the period 2021 - 2023 is given in Appendix 1.

4.1 H2-receptor blockers, antacids, proton pump inhibitors (PPIs) and potassium-competitive acid blockers (PCABs)

Proton pump inhibitors (PPIs) are among the most commonly used drugs for conditions such as gastro-esophageal reflux disease, esophagitis, gastritis, gastric and duodenal ulcers, as well as for prophylaxis in treatment with drugs with ulcerogenic risk. A major drug interaction, belonging to risk rating X, involving erlotinib, is the simultaneous use of PPIs and PCABs. 24 interactions with PPIs and 2 interactions with PCABs were detected. PPIs and PCABs can reduce the serum concentration of erlotinib due to their mediated increase in gastric pH and, accordingly, a decrease in the solubility of erlotinib in the upper GIT. It is known that the solubility of erlotinib is inversely proportional to gastric pH (i.e. solubility decreases with increasing pH). The same pharmacokinetic mechanism is observed when erlotinib is used concomitantly with H2-receptor blockers and antacids. When erlotinib is used concomitantly with H2-receptor blockers, the severity of the reaction is classified as major, while in terms of risk it is in rating D, while for antacids, the severity of the reaction is classified as moderate, while in terms of risk it is also rating D. However, according to the EudraVigilance data, more patients took PPIs and PCABs than H2-receptor blockers and antacids.

Compare to erlotinib, for gefitinib the drug interactions with H2-receptor blockers (4 cases observed), PPIs (11 cases observed) and PCABs (7 cases observed) belong to risk rating D and the severity of the reaction is classified as major. In a retrospective study of 15 patients treated with gefitinib, the AUC and Cmax of gefitinib were 35% lower in patients who received concomitant PPI therapy compared to 24 patients who received gefitinib alone. The mechanism of the gefitinib-H2 blocker/PPIs/PCABs drug interaction is uncertain, but it has been shown that the aqueous solubility of gefitinib decreases with increasing gastric pH and may reduce the absorption of gefitinib. The drug interaction with concomitant use of gefitinib with antacids is moderate in severity and belongs to risk rating C.

The digital drug interaction assessment platform – UpToDate® Lexidrug™ classifies drug interactions between afatinib and PPIs and PCABs as moderate in severity and belonging to risk rating C. Concomitant use with PPIs was observed in 45 cases and with PCABs in 2 cases. The afatinib-PPI drug interaction has never been studied in humans. G D Marijn Veerman et al. conducted a randomized crossover study of afatinib with esomeprazole to evaluate AUC 0-24. In 18 patients, concomitant use of 40 mg esomeprazole reduced steady-state AUC 0-24 of afatinib by 10.2% (95% CI -29.2 to +14.0%; p = 0.564) compared with afatinib without a PPI. Taking esomeprazole three hours before afatinib did not significantly affect AUC 0-24 of afatinib (-0.6%; 95% CI -14.9 to +16.1%; p = 1.0). The authors concluded that esomeprazole did not alter afatinib exposure and, as there was no clinically significant drug interaction, esomeprazole can be safely co-administered with afatinib. In contrast, in a retrospective study of 1418 patients newly diagnosed with NSCLC who initiated afatinib, those who received concomitant PPIs had reduced overall survival compared with patients who received afatinib without a PPI (HR 1.29 [95% CI, 1.05 to 1.59]).

H2-antagonists, PPIs and PCABs may decrease the serum concentration of dacomitinib. The likely mechanism for this interaction is reduced absorption of dacomitinib due to increased pH. The drug interaction was rated as major and risk rating X (PPIs) and moderate and risk rating D (H2-receptor antagonists). Six drug interacions dacomitinib-PPIs were identified.

Unlike other EGFR inhibitors, drug interactions of osimertinib with PPIs and with PCABs are classified as minor in severity and belong to risk rating B.

4.2 Antiarrhythmic agents

Amiodarone may increase the serum concentration of erlotinib. The potential mechanism of this interaction is unclear but may be due to amiodarone-mediated inhibition of P-glycoprotein (P-gp), leading to increased concentrations of erlotinib. The drug interaction of amiodarone and erlotinib is classified as moderate in severity and belongs to risk rating C.

Moderate drug interactions and risk rating D involving afatinib are concomitant use with P-gp/ABCB1 inhibitors, which may increase serum concentrations of afatinib. Two cases of concomitant use of afatinib with amiodarone were identified. The suspected primary mechanism of these interactions is inhibition by P-gp/ABCB1 inhibitors of P-gp-mediated efflux of afatinib.

Several cases of concomitant use of dacomitinib with antiarrhythmics were observed in EudraVigilance: one case with flecainide (class IC) and six cases with the beta-blocker metoprolol (class II). These drug interactions were assessed as moderate in severity and risk rating C. As a potent CYP2D6 inhibitor, dacomitinib may increase serum concentrations of flecainide and metoprolol. Patients should be monitored for increased effects and toxicity of flecainide (e.g. QTc prolongation) and for excessive response to metoprolol (e.g. bradycardia, prolonged PR interval, hypotension), which may require a reduction in the dose of metoprolol.

All class IA and III antiarrhythmics are associated with a high risk of QT prolongation. Amiodarone is metabolised by CYP3A4 and CYP2C8. Osimertinib is an in vitro inhibitor of CYP3A4 and may increase serum concentrations of amiodarone. Osimertinib does not inhibit or induce CYP2C8, and the major metabolite of amiodarone, desethylamiodarone, is a weak inhibitor of CYP3A4 and CYP2C19, a moderate inhibitor of CYP2C9, CYP2D6 and CYP2B6, and a strong inhibitor of CYP1A1 and P-gp. Osimertinib is metabolised by CYP3A4 and is an in vitro substrate of P-gp and concentrations may be increased due to inhibition by desethylamiodarone. No clinically relevant effect on osimertinib exposure is expected due to inhibition of CYP3A4 and P-gp. However, co-administration of osimertinib and amiodarone could potentially lead to QTc prolongation. Pharmacokinetic/ pharmacodynamic analysis suggests a concentration-dependent prolongation of the QTc interval. Therefore, co-administration with other QT-prolonging medicinal products such as amiodarone should be approached with caution. Due to the long half-life of amiodarone, interactions may be observed several months after discontinuation of amiodarone.

Flecainide is primarily metabolised by CYP2D6, with approximately 30% of the parent drug eliminated unchanged via the kidneys. Osimertinib does not inhibit or induce CYP2D6 and is unlikely to affect this elimination pathway. However, co-administration of osimertinib and flecainide has the potential to cause QTc prolongation.

In EudraVigilance, co-administration of osimertinib with amiodarone was observed in 13 cases and with sotalol in one case. Co-administration of osimertinib with class IC antiarrhythmics was observed in 5 cases. The severity of the drug interaction reaction of osimertinib with class III antiarrhythmics (amiodarone and sotalol) is classified as major and risk rating D.

4.3 Cardiac glycosides

Moderate drug interactions and belonging to risk rating D involving osimertinib, is the concomitant use with digoxin. Digoxin is eliminated by the kidneys via the renal transporters OATP4C1 and P-gp. P-gp/ABCB1 inhibitors (osimertinib) may increase the serum concentration of digoxin. The mechanism of this interaction is pharmacokinetic and is due to inhibition of P-gp. A total of 8 cases of osimertinib-digoxin drug interactions were observed in Eudravigilance.

4.4 Beta- and alpha-adrenergic blockers

Carvedilol undergoes glucuronidation by UGTs 1A1, 2B4 and 2B7 and further metabolism by CYP2D6 and to a lesser extent CYPs 2C9 and 1A2. Afatinib does not inhibit or induce CYP or UGTs. Carvedilol is also a P-gp inhibitor and may increase afatinib concentrations by inhibiting P-gp-mediated efflux of afatinib by P-gp/ABCB1 inhibitors. However, the clinical significance of P-gp inhibition by carvedilol is unknown. Monitoring for afatinib toxicity and, if possible, measurement of afatinib concentrations may be necessary. The afatinib-carvedilol drug interaction is moderate in severity and belongs to risk rating D.

4.5 HMG-CoA reductase inhibitors (statins)

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have complex pharmacokinetic characteristics that include the involvement of uptake transporters (OATP1B1), biotransformation by cytochrome enzymes (CYP3A4 for simvastatin, lovastatin and atorvastatin, while fluvastatin is mainly metabolised by CYP2C9) and efflux pumps (e.g. MDR1). The EGFR inhibitor-statin drug interactions we observed were moderate in severity and belong to risk rating C with the exception of the simvastatin-osimertinib interaction (mild in severity and risk rating B).

4.6 Anticoagulants

Oral anticoagulants are widely used in clinical practice, but the risk of ADRs is high. Clinically significant interactions with warfarin include drugs that modify CYP2C9, CYP3A4, or both enzymes. Drugs that modify P-gp can interact with all direct oral anticoagulants, and CYP3A4 modifiers can interact with rivaroxaban and apixaban.

Potential drug interactions were identified between warfarin and erlotinib (1 case) and warfarin – gefitinib (3 cases), which were classified as moderate in severity and belong to risk rating C. Warfarin is a mixture of enantiomers that are metabolized by different cytochromes. R-warfarin is metabolized primarily by CYP1A2 and CYP3A4. Concentrations may be increased due to moderate inhibition of CYP3A4 by erlotinib. S-warfarin (more potent) is metabolized by CYP2C9. Erlotinib does not inhibit or induce CYP2C9. However, the interaction of erlotinib with coumarin anticoagulants has been shown to result in increased ADRs associated with bleeding and an increase in international normalized ratio (INR). The mechanism of this interaction is unknown, but it is thought that it may involve displacement of transport proteins, impaired vitamin K absorption due to erlotinib-induced diarrhea, or competition or inhibition of CYP enzymes responsible for warfarin metabolism. Gefitinib may also potentiate the anticoagulant effect of vitamin K antagonists, necessitating careful monitoring of INR and adjustment of warfarin dosage when necessary.

4.7 Analgesics

Concomitant use of the non-opioid analgesic metamizole (a moderate CYP3A4 inducer) with erlotinib was observed in one patient and with gefitinib in three patients. The drug interaction is moderate in severity and belongs to risk rating C.

There are no recommendations for the use of gefitinib with moderate CYP3A4 inducers, but observation of reduced efficacy of the EGFR inhibitor when combined with metamizole is warranted. The likely mechanism for this interaction is increased CYP3A4-mediated metabolism of erlotinib/gefitinib.

Tramadol is metabolized by CYP3A4, 2B6, and 2D6. The metabolite M1 is responsible for the majority of the analgesic effect and is formed by metabolism of CYP2D6, which is inhibited by dacomitinib. Inhibition of CYP2D6 by dacomitinib reduces exposure to M1 and may lead to reduced efficacy of tramadol. Close monitoring of tramadol efficacy is recommended. Related studies comparing patients or healthy volunteers with a genetic mutation resulting in a lack or significant reduction of functional CYP2D6 (i.e., poor metabolizers) with those with genetically “normal”

CYP2D6 (i.e., extensive metabolizers) have generally found similar results, with poor metabolizers showing significantly altered tramadol/M1 concentrations, greater tramadol consumption, and at least partial interference with clinical response compared with extensive metabolizers.
The drug interaction between afatinib and cannabidiol is moderate in strength and risk rating D. As a P-glycoprotein/ABCB1 inhibitor, cannabidiol may increase the serum concentration of afatinib. The suspected primary mechanism of this interaction is pharmacokinetic, through inhibition by cannabidiol of P-gp-mediated efflux of afatinib.
There were 8 cases of concomitant use of osimertinib and metamizole and 22 cases of concomitant use of osimertinib and morphine. Both drug interactions are moderate in severity and have a risk rating C, but occur via a different pharmacokinetic mechanism.
Morphine is glucuronidated primarily to morphine-3-glucuronide (UGT2B7>UGT1A1) and to a lesser extent to the pharmacologically active morphine-6-glucuronide (UGT2B7>UGT1A1). Morphine is also a substrate of P-gp. Osimertinib is an inhibitor of UGT1A1 (in vitro) and P-gp and may increase morphine concentrations. Metamizole, a moderate CYP3A4 inducer, may decrease the serum concentration of osimertinib. The osimertinib SmPC does not recommend dose adjustment when osimertinib is combined with moderate CYP3A4 inducers, but patients should be monitored for reduced effects of osimertinib when these agents are combined.

4.8 Antibiotics

In one case, concomitant use of erlotinib with clarithromycin, a strong CYP3A4 inhibitor, was observed. Strong CYP3A4 inhibitors may increase serum concentrations of erlotinib by a pharmacokinetic mechanism by reducing CYP3A4-mediated metabolism of erlotinib.
Erythromycin is an inhibitor of CYP3A4 and P-gp and may increase serum concentrations of afatinib. According to the afatinib SmPC, if a P-gp inhibitor is required but concomitant use of afatinib and P-gp inhibitors is not tolerated, the daily dose of afatinib should be reduced by 10 mg. The afatinib–erythromycin drug interaction is moderate in severity and risk rating D. Concomitant use of osimertinib with fluorinated quinolones was observed: 7 cases with levofloxacin and 8 cases with moxifloxacin (moderate in severity, risk rating C). Levofloxacin is eliminated renally primarily by glomerular filtration and active secretion (likely OCT2). Osimertinib is unlikely to affect this elimination pathway and does not inhibit or induce OCT. However, co-administration of osimertinib and levofloxacin could potentially cause QTc prolongation. Moxifloxacin is primarily glucuronidated by UGT1A1. Osimertinib is an in vitro inhibitor of UGT1A1 and may increase moxifloxacin concentrations. Pharmacokinetic/pharmacodynamic analysis suggests a concentration-dependent prolongation of the QTc interval. Concomitant use of osimertinib with clarithromycin was observed in 5 cases (moderate severity, risk rating D). Clarithromycin is a strong inhibitor of CYP3A4 and co-administration of osimertinib and clarithromycin may cause QTc prolongation. Pharmacokinetic/pharmacodynamic analysis suggests a concentration-dependent prolongation of the QTc interval. A major and risk rating D drug interaction with rifampicin (a strong CYP3A4 inducer) was reported in 4 cases in EudraVigilance. Strong CYP3A4 inducers may decrease the serum concentration of osimertinib. In a pharmacokinetic study in 35 patients, the strong CYP3A4 inducer rifampin (600 mg daily for 21 days) decreased the AUC and Cmax of osimertinib (80 mg daily) by 78% and 73%, respectively.

4.9 Antifungals

In a pharmacokinetic study in 12 healthy volunteers, the strong CYP3A4 inhibitor ketoconazole increased the AUC and Cmax of erlotinib by 69% and 52%, respectively.
The drug-drug interaction between the strong CYP3A4 inhibitor itraconazole and gefitinib (observed in two cases in EudraVigilance) is moderate and belongs to risk rating C. Strong CYP3A4 inhibitors

may increase the serum concentration of gefitinib, with the likely mechanism for this interaction being inhibition of the CYP3A4-mediated metabolism of gefitinib, which is metabolized primarily by CYP3A4 and to a lesser extent by CYP2D6.
Concomitant use of osimertinib with fluconazole (a QT-prolonging moderate CYP3A4 inhibitor) is moderate in severity and risk rating C. Moderate CYP3A4 inhibitors may increase serum concentrations of osimertinib and may therefore potentiate the QT-prolonging effect, as both drugs can prolong the QTc interval. Although itraconazole is a strong CYP3A4 inhibitor, in a pharmacokinetic study in 36 patients, itraconazole (200 mg twice daily for 5 days) increased the AUC of osimertinib (80 mg single dose) by 24% and decreased the Cmax of osimertinib by 20%.

4.10 Antidepressants

Moderate in severity, risk rating C is the interaction of gefitinib with the strong CYP2D6 inhibitor fluoxetine. The effect of drugs that inhibit CYP2D6 on the PK of gefitinib has not been evaluated. However, in healthy CYP2D6 poor metabolizers, the concentration of O-desmethyl-gefitinib was not measurable and the mean exposure to gefitinib was 2-fold higher compared to that measured in CYP2D6 extensive metabolizers. Dacomitinib, as a strong CYP2D6 inhibitor, may inhibit the metabolism of duloxetine (metabolized by CYP2D6 and CYP1A2) and increased serum concentrations of the antidepressant may be observed. The drug interaction is moderate in severity and risk rating C.
Dacomitinib, as a strong inhibitor of CYP2D6, may inhibit the metabolism of duloxetine (metabolized by CYP2D6 and CYP1A2) and increased serum concentrations of the antidepressant may be observed. The drug interaction is moderate in severity and risk rating C. The drug interaction osimertinib – quetiapine is major in severity and risk rating D, reported in 6 cases in EudraVigilance. Quetiapine is primarily metabolized by CYP3A4, and osimertinib is an inhibitor of CYP3A4 and may increase quetiapine concentrations. The combined use of drugs that prolong the QTc interval may further increase the risk of serious toxic effects.

4.11 Antiepileptic medications

Concomitant use of gefitinib with phenytoin (a strong inducer of CYP3A4, UGT and P-gp) was observed in one patient. This drug interaction may result in decreased serum concentrations of gefitinib and it is recommended that, in the absence of severe ADRs, the dose of gefitinib be increased to 500 mg/day during the co-administration period and that the standard dose of 250 mg/day be resumed 7 days after discontinuation of the strong CYP3A4 inducer. The proposed mechanism of this interaction is induction of CYP3A4-mediated metabolism of gefitinib, leading to reduced systemic exposure, although induction of other gefitinib metabolic pathways (e.g. CYP1A2, CYP2C9) may also play a role.
The drug interactions osimertinib-phenytoin and osimertinib-carbamazepine are major and belong to risk rating D. Phenytoin is metabolized primarily by CYP2C9 and to a lesser extent by CYP2C19. Osimertinib does not inhibit or induce CYP2C9 or CYP2C19. Phenytoin is a potent inducer of CYP3A4, UGT and P-gp. Osimertinib is metabolized by CYP3A4 and is a substrate of P-gp and its concentrations may decrease due to enzyme induction by phenytoin. Decreased exposure may lead to reduced efficacy of osimertinib. Carbamazepine is metabolized primarily by CYP3A4 and to a lesser extent by CYP2C8. Osimertinib is an in vitro inhibitor of CYP3A4 and may increase carbamazepine concentrations. In addition, carbamazepine is an inducer of CYP2C8 (strong), CYP2C9 (strong), CYP3A4 (strong), CYP1A2 (weak), CYP2B6, P-gp (moderate) and UGT1A1. Osimertinib is metabolised by CYP3A4 and is a substrate of P-gp and its concentrations may be decreased due to induction of metabolising enzymes by carbamazepine. The osimertinib SmPC informs that the concomitant use of osimertinib and strong CYP3A4 inducers should be avoided

whenever possible. If concomitant use is unavoidable, the osimertinib dose should be increased to 160 mg daily. The osimertinib dose should be reduced to 80 mg daily 3 weeks after discontinuation of the strong CYP3A4 inducer.

4.12 Prokinetics/antiemetics

Dacomitinib is a strong inhibitor of CYP2D6 and as such may affect the metabolism of a number of drugs that are primarily metabolized by CYP2D6. Co-administration of dacomitinib and dextromethorphan, a CYP2D6 test substrate, increased the Cmax and AUC0 of dextromethorphan by 973% and 362%, respectively. A similar effect may occur after co-administration with metoclopramide. The drug interaction between dacomitinib and metoclopramide is categorized as moderate in severity and belongs to risk rating D. 5 cases of this drug combination were identified. Patients should be monitored for increased metoclopramide toxicity, including extrapyramidal symptoms, neuroleptic malignant syndrome, and possibly serotonin syndrome/serotonin toxicity (SS/ST), when these drugs are combined. Concomitant use of osimertinib with domperidone was observed in 5 cases in EudraVigilance. The osimertinib–domperidone drug interaction is categorized as moderate in severity and belongs to risk rating X. Domperidone is primarily metabolized by CYP3A4. Osimertinib is an in vitro inhibitor of CYP3A4 and may increase serum concentrations of domperidone. QT-prolonging drugs (osimertinib) may potentiate the QTc-prolonging effect of domperidone. There is considerable evidence that these drugs can cause QTc prolongation or torsades de pointes (TdP). In a case-control study, domperidone use was associated with an increased risk of sudden cardiac death (OR 3.7, [95% CI, 1.7 to 8.1]).

The concomitant use of osimertinib with ondansetron is categorized as moderate in severity and belongs to risk rating C and was observed in 13 cases. Ondansetron is metabolized primarily by CYP1A2 and CYP3A4 and to a lesser extent by CYP2D6. Ondansetron is also a substrate of P-gp. Osimertinib is an in vitro inhibitor of CYP3A4 and P-gp and may increase serum concentrations of ondansetron. There is evidence that ondansetron (particularly ondansetron administered intravenously) and kinase inhibitors may cause QTc prolongation or TdP.

4.13 Immunosuppressants

A major drug interaction, belonging to risk rating D, involving erlotinib is the concomitant use with teriflunomide (a moderate CYP1A2 inducer), an immunomodulatory agent used to treat relapsing-remitting multiple sclerosis. Although erlotinib is primarily metabolized by CYP3A4 and to a lesser extent by CYP1A2, inducers of CYP1A2 may reduce the serum concentration of erlotinib and hence its efficacy. Concomitant use of tacrolimus with erlotinib, afatinib and osimertinib has been observed. In all three cases, the drug interactions occurred via a PK mechanism, but involving different enzyme systems: CYP3A4 (erlotinib), P-gp (afatinib) and together P-gp/ ABCB1 and CYP3A4 (osimertinib). All three cases were moderate in severity, rating C. The tacrolimus SmPC recommends caution and increased monitoring when tacrolimus is used with a weak or moderate CYP3A4 inducer (erlotinib), as tacrolimus is primarily metabolised by CYP3A enzymes. Concomitant use of CYP3A4 inducers may increase the metabolism of tacrolimus, resulting in lower trough concentrations and a greater risk of rejection. Erlotinib is metabolized by CYP3A4 (~70%) and concentrations may be increased due to inhibition by tacrolimus. Erlotinib is dosed at/near the maximum tolerated dose (MTD) and thus any increase in erlotinib exposure may result in toxicity. Tacrolimus may increase serum concentrations of afatinib. The proposed mechanism of this interaction is inhibition of P-gp-mediated efflux of afatinib and patients should be monitored for toxic effects of afatinib and possibly a dose reduction of afatinib. P-gp/ABCB1 inhibitors (osimertinib) may increase serum concentrations of tacrolimus. The mechanism of this interaction is likely inhibition of P-gp, the transporter responsible for the distribution of tacrolimus. Tacrolimus is also a substrate of CYP3A4, but these studies

included drugs that inhibit P-gp alone or only weakly inhibit CYP3A4, suggesting that modulation of P-gp may have clinically important effects on tacrolimus exposure.
A moderate drug interaction and risk rating D involving afatinib is the concomitant use with cyclosporine (P-gp/ABCB1 inhibitor), as cyclosporine may increase the serum concentration of afatinib. However, when osimertinib is used concomitantly with cyclosporine, the P-gp inhibitor (osimertinib) may increase the concentration of cyclosporine. The mechanism of this interaction is due to inhibition of P-gp, the transporter responsible for the distribution of cyclosporine. Inhibition of CYP3A4 may also be relevant.
Co-administration of osimertinib with methotrexate (a BCRP/ABCG2 substrate) was observed in six cases. According to the osimertinib SmPC, co-administration with a BCRP substrate may result in increased exposure to the BCRP substrate, i.e. plasma concentrations of methotrexate may increase.

4.14 Concomitant use of EGFR inhibitors with other tyrosine kinase inhibitors (TKIs)

The concomitant use of an EGFR inhibitor with another tyrosine kinase inhibitor for the treatment of a second cancer was reported in EudraVigilance. Moderate in severity and risk rating C is the concomitant use of imatinib and gefitinib (observed in 4 cases) and the concomitant use of osimertinib and midostaurin (1 case). The concomitant use of osimertinib with lenvatinib is risk rating D because they may potentiate the prolongation of the QTc interval.

4.15 Other medications

Antihistamines

The concomitant use of osimertinib with bilastine is moderate in severity and belongs to risk rating X. We observed this combination in 2 cases. Osimertinib (a P-gp/ABCB1 inhibitor) may increase the serum concentration of bilastine, and this interaction may be even more severe in patients with moderate to severe renal insufficiency. Increased plasma concentrations of bilastine may increase the risk of QTc prolongation. Bilastine is not metabolized in the liver and the possible mechanism is pharmacokinetic - inhibition of the P-gp transporter responsible for the distribution of bilastine.

Capillary and venotonic drugs

Diosmin improves the elasticity and tone of the venous walls and maintains the good condition of the veins. It is available in the form of dietary supplements or medications, often available over the counter. As a P-gp/ABCB1 inhibitor, its simultaneous use with afatinib may increase the serum concentration of the afatinib. The drug interaction between afatinib and diosmin is classified as moderate in severity and belongs to risk group D by pharmacokinetic mechanism. The SmPC of afatinib recommends that the dose of afatinib be reduced when combined with a P-gp/ABCB1 inhibitor.

Androgen receptor antagonists

Enzalutamide is a nonsteroidal antiandrogen used in advanced prostate cancer. Enzalutamide is a moderate to strong inducer of multiple cytochrome P450 enzymes, including CYP3A4 (strong), CYP2C9 (moderate), and CYP2C19 (moderate), and therefore has a high potential for clinically significant drug interactions. As a strong inducer of CYP3A4, enzalutamide may decrease the serum concentration of osimertinib. The drug interaction between osimertinib and enzalutamide is major and belongs to risk rating D. Enzalutamide concentrations may be altered by inhibitors and inducers of CYP2C8 and CYP3A4 and should be avoided if possible.

In the analysis and evaluation of commonly used drugs in clinical practice, it was found that drugs affecting gastric acidity have a risk of drug interactions category X and/or D when used simultaneously with first-generation EGFR inhibitors and second-generation dacomitinib. As a result,

it is possible that the plasma concentration of the EGFR inhibitor may be affected and a reduced efficacy of the EGFR inhibitor may be observed. Unlike other EGFR inhibitors, drug interactions of osimertinib with PPIs and PCABs are classified as minor in severity and belong to risk category B. The observed drug interactions of EGFR inhibitors were most often by pharmacokinetic mechanism involving CYP enzymes. For the second-generation EGFR inhibitor afatinib, moderate in severity drug interactions and belong to risk category D were observed when used simultaneously with P-gp/ABCB1 inhibitors, which may increase the serum concentration of afatinib. In contrast, cases were identified where osimertinib as a P-gp/ABCB1 inhibitor altered the serum concentrations of drugs that are primarily eliminated by P-gp/ABCB1. For osimertinib, the most drug interactions were observed with drugs with the potential to prolong the QT interval, with some cases identifying the concomitant use of 3 or more drugs with such properties. Concomitant use of strong CYP3A4 inducers (carbamazepine, phenytoin, rifampicin) with gefitinib and osimertinib has been observed. Strong CYP3A4 inducers may decrease the serum concentrations of gefitinib and osimertinib and lead to reduced efficacy. Concomitant use of strong CYP3A4 inhibitors (clarithromycin, antifungals) with osimertinib has been observed, which likely increase the serum concentrations of osimertinib by inhibiting CYP3A4-mediated metabolism.

5. Assessment of the relationship between the number of drugs in the combination therapy, the age and gender of the patients and potential drug interactions falling into risk categories X and/or D

5.1 Ratio and odds of number of drugs in combination therapy (under 5 drugs, between 5 and 7 drugs, and over 7 drugs) against risk rating X and D. The ADR cases identified in EudraVigilance in which potential drug interactions were observed between an EGFR inhibitor and a drug in the combination therapy with risk rating X and D were divided into 3 groups according to the number of drugs in the combination: concomitant use of less than 5 drugs, concomitant use of between 5 and 7 drugs and concomitant use of more than 7 drugs.

5.1.1 Erlotinib For the period 2021-2023, a total of 44 cases of ADRs with potential drug interactions with erlotinib - drug with a risk rating X and/or D in the therapy - were reported in EudraVigilance. Distributed by year, 16 cases were reported in 2021, 10 cases in 2022 and 18 cases in 2023. (Table 17, Fig. 16, 17)

Table 17 Relative share and distribution of cases with potential drug interactions erlotinib – drug to the number of drugs in the therapy with risk rating X and/or D

Number of drugs in the therapy	2021	2022	2023	total	relative proportion (%)
• less than 5 drugs	4	2	4	10	22.73
• between 5 and 7 drugs	7	5	8	20	45.45
• more than 7 drugs	5	3	6	14	31.82
Number of observed cases of pDDI erlotinib – drug risk rating X and/or D	16	10	18	44	

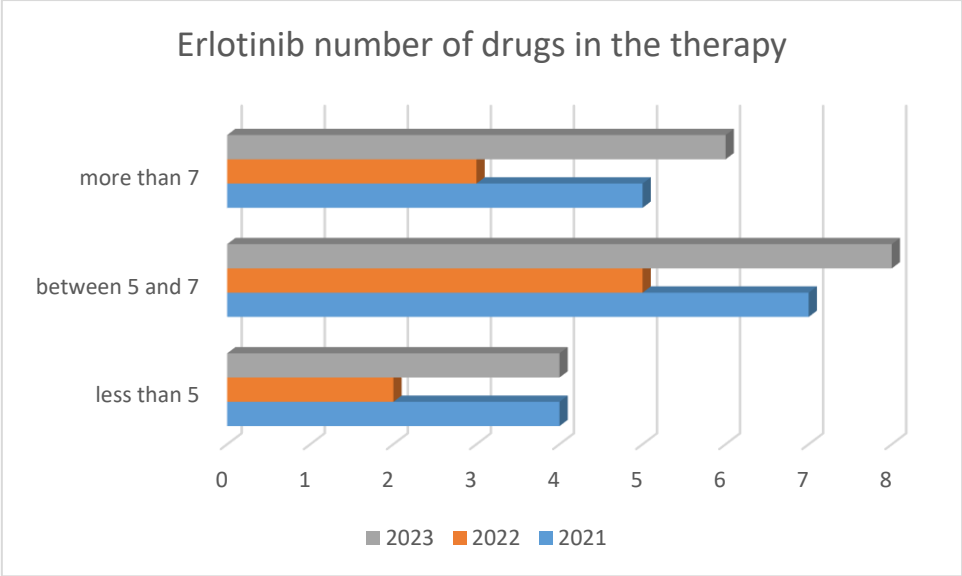

Fig. 16 Distribution of cases with potential erlotinib - drug interactions by years by number of drugs in the therapy

Of the 44 cases of reported suspected adverse drug reactions for erlotinib with drug interactions with risk rating X and/or D of erlotinib with one or more drugs from the reported therapy, the most cases with potential drug interactions (20) were observed when patients were taking between 5 and 7 drugs together, and the fewest cases when the therapy was less than 5 drugs.

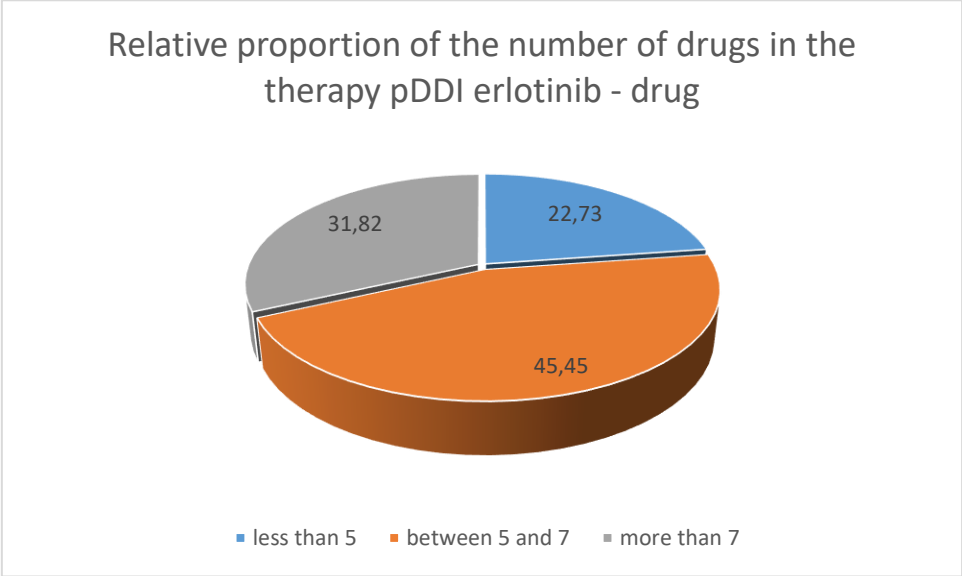

Fig. 17. Relative proportion (%) of the number of drugs in combination therapy to the total number of cases of potential drug interactions erlotinib – drug with risk rating X and/or D

5.1.2 Gefitinib For the period 2021-2023, a total of 24 cases of ADRs with potential drug interactions gefitinib - drug with risk rating X and/or D in the therapy were reported in EudraVigilance. Distributed by year, 11 cases were reported in 2021, 6 cases in 2022 and 7 cases in 2023. (Table 18, Fig. 18, 19)

Table 18 Relative share and distribution of cases with potential drug interactions gefitinib – drug to the number of drugs in the therapy with risk rating X and/or D

Number of drugs in the therapy	2021	2022	2023	total	relative proportion (%)
• less than 5 drugs	4	1	1	6	25,00
• between 5 and 7 drugs	4	4	3	11	45,83
• more than 7 drugs	3	1	3	7	29,17
Number of observed cases of pDDI gefitinib – drug risk rating X and/or D	11	6	7	24	

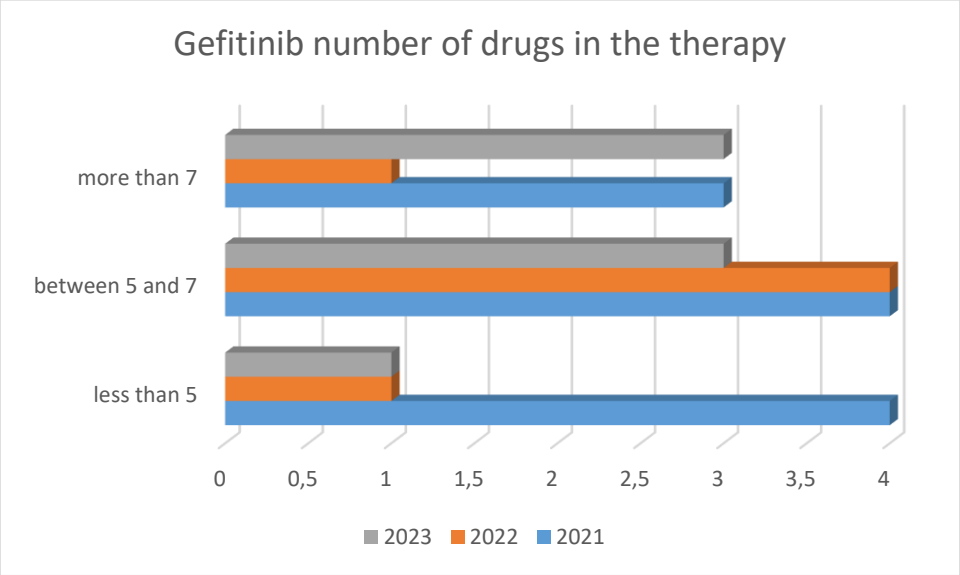

Fig. 18 Distribution of cases with potential gefitinib - drug interactions by years by number of drugs in the therapy

Of the 24 reported suspected adverse drug reactions for gefitinib with drug interactions with risk rating X and/or D of gefitinib with one or more drugs from the reported therapy, the most cases of drug interactions (11) were observed when patients were taking between 5 and 7 drugs together, and the fewest cases when the therapy was less than 5 drugs.

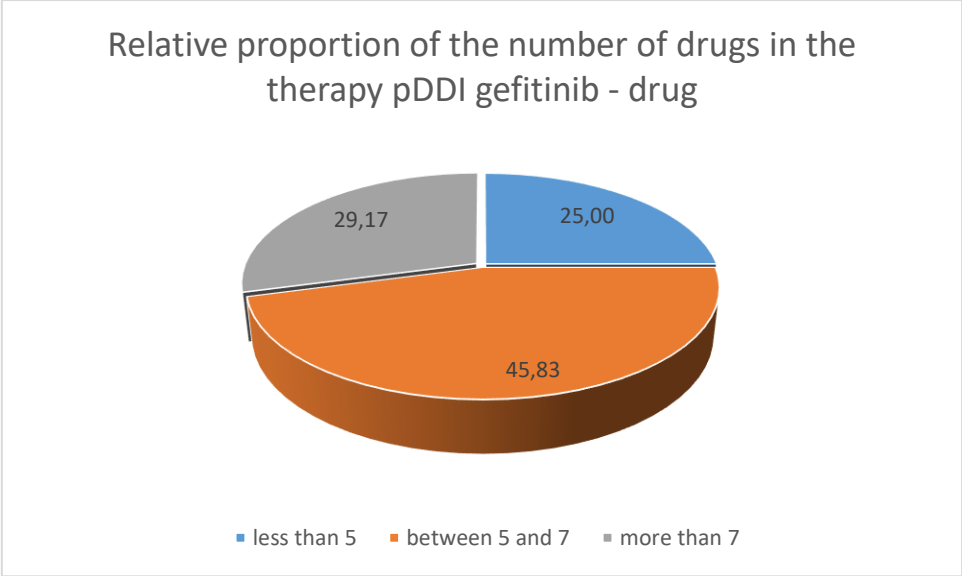

Fig. 19. Relative proportion (%) of the number of drugs in combination therapy to the total number of cases of potential drug interactions gefitinib – drug with risk rating X and/or D

5.1.3 Afatinib For the period 2021 - 2023, a total of 9 cases of ADRs with potential drug interactions with afatinib - drug with a risk rating X and/or D in the therapy - were reported in EudraVigilance. Distributed by year, 3 cases were reported in 2021, 1 case in 2022 and 5 cases in 2023. (Table 19, Fig. 20, 21)

Table 19 Relative share and distribution of cases with potential drug interactions afatinib – drug to the number of drugs in the therapy with risk rating X and/or D

Number of drugs in the therapy	2021	2022	2023	total	relative proportion (%)
• less than 5 drugs	0	0	1	1	11,11
• between 5 and 7 drugs	1	0	1	2	22,22
• more than 7 drugs	2	1	3	6	66,67
Number of observed cases of pDDI afatinib – drug risk rating X and/or D	3	1	5	9	

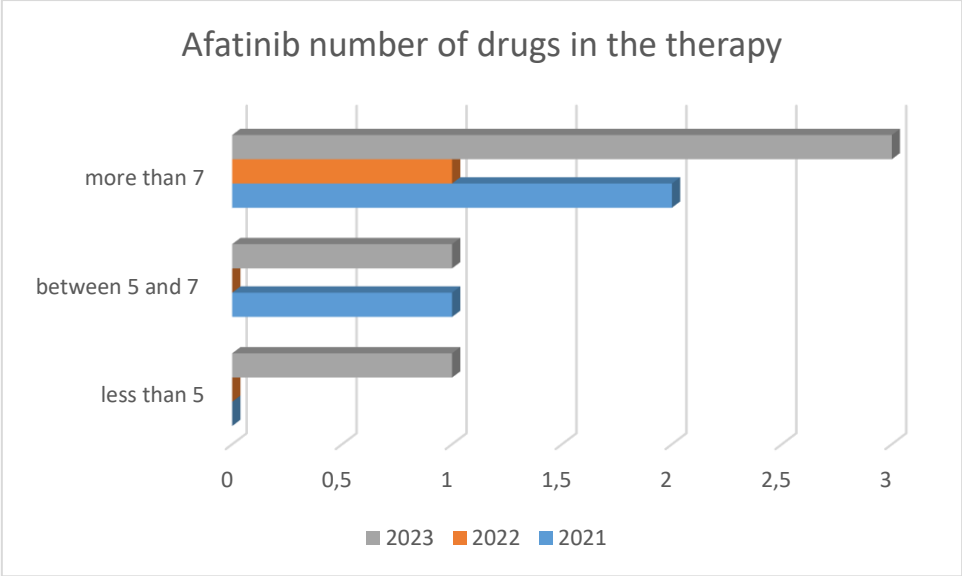

Fig. 20 Distribution of cases with potential afatinib - drug interactions by years by number of drugs in the therapy

Of the 9 cases of reported suspected adverse drug reactions for afatinib with drug interactions with risk rating X and/or D of afatinib with one or more drugs from the reported therapy, the most cases of drug interactions (6) were observed when patients were taking more than 7 drugs together, and the fewest cases when the therapy was less than 5 drugs.

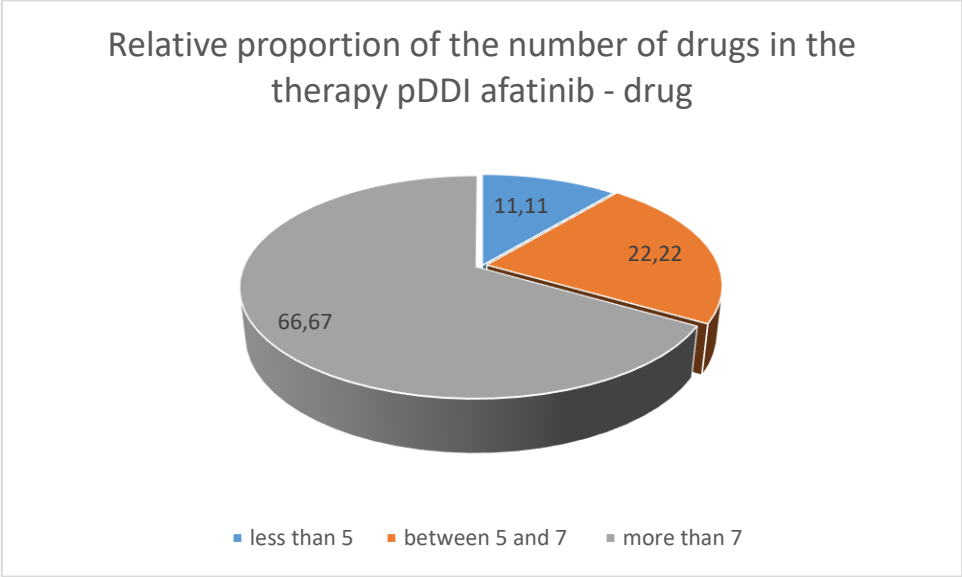

Fig. 21. Relative proportion (%) of the number of drugs in combination therapy to the total number of cases of potential drug interactions afatinib – drug with risk rating X and/or D

5.1.4 Dacomitinib For the period 2021-2023, a total of 23 cases of ADRs with potential drug interactions dacomitinib - a drug with risk rating X and/or D in the therapy - were reported in

EudraVigilance. Distributed by year, 4 cases were reported in 2021, 7 cases in 2022 and 12 cases in 2023. (Table 20, Fig. 22, 23)

Table 20 Relative share and distribution of cases with potential drug interactions dacomitinib – drug to the number of drugs in the therapy with risk rating X and/or D

Number of drugs in the therapy	2021	2022	2023	total	relative proportion (%)
• less than 5 drugs	0	2	2	4	17.39
• between 5 and 7 drugs	0	2	2	4	17.39
• more than 7 drugs	4	3	8	15	65.22
Number of observed cases of pDDI dacomitinib – drug risk rating X and/or D	4	7	12	23	

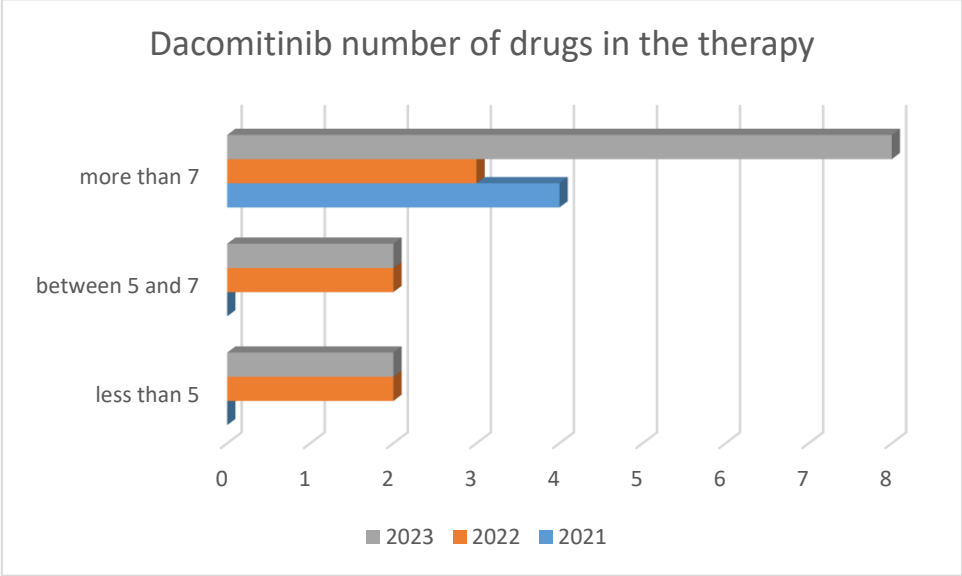

Fig. 22 Distribution of cases with potential dacomitinib - drug interactions by years by number of drugs in the therapy

Of the 23 reported suspected adverse drug reactions for dacomitinib with drug interactions of risk rating X and/or D of dacomitinib with one or more drugs from the reported therapy, the most drug interaction cases (15) were observed when patients were taking more than 7 drugs together.

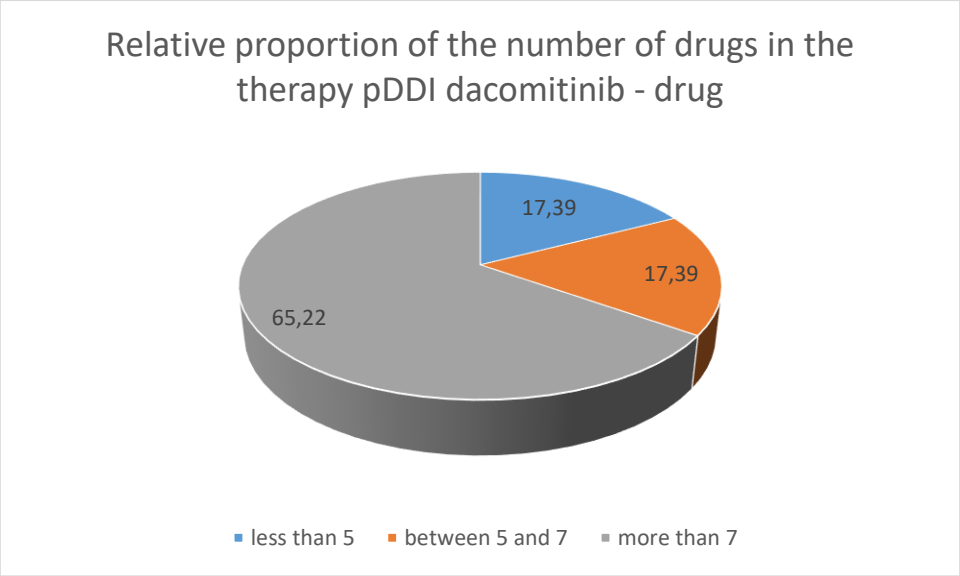

Fig. 23. Relative proportion (%) of the number of drugs in combination therapy to the total number of cases of potential drug interactions dacomitinib – drug with risk rating X and/or D

5.1.5 Osimertinib For the period 2021-2023, a total of 44 cases of ADRs with potential drug interactions with osimertinib - a drug with a risk rating X and/or D in therapy - were reported in EudraVigilance. Distributed by year, 9 cases were reported in 2021, 15 cases in 2022 and 20 cases in 2023. (Table 21, Fig. 24, 25)

Table 21 Relative share and distribution of cases with potential drug interactions osimertinib – drug to the number of drugs in the therapy with risk rating X and/or D

Number of drugs in the therapy	2021	2022	2023	total	relative proportion (%)
• less than 5 drugs	0	2	6	8	18.18
• between 5 and 7 drugs	4	6	3	13	29.55
• mor ethan 7 drugs	5	7	11	23	52.27
Number of observed cases of pDDI osimertinib – drug risk rating X and/or D	9	15	20	44	

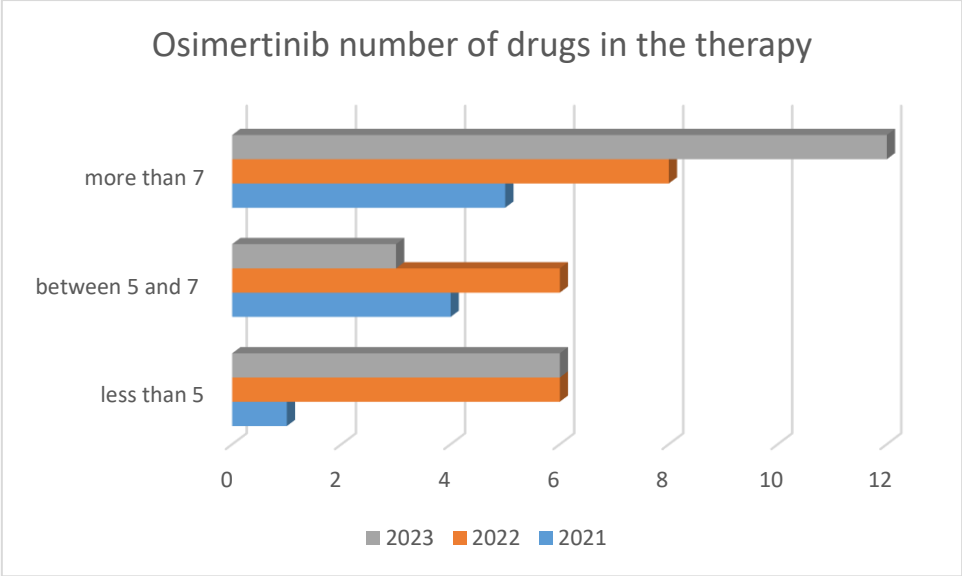

Fig. 24 Distribution of cases with potential osimertinib drug interactions by years by number of drugs in the therapy

Of the 44 cases of reported suspected adverse drug reactions for osimertinib with drug interactions with risk rating X and/or D of osimertinib with one or more drugs from the reported therapy, the most cases of drug interactions (23) were observed when patients were taking more than 7 drugs together, and the fewest cases when the therapy was less than 5 drugs.

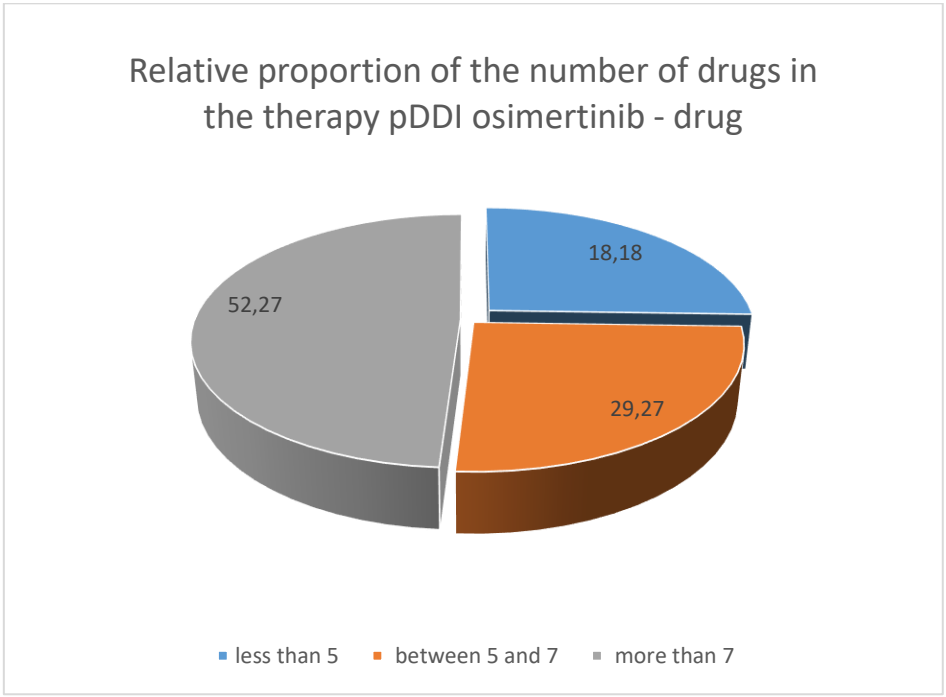

Fig. 25. Relative persentage (%) of the number of drugs in combination therapy to the total number of cases of potential drug interactions osimertinib – drug with risk rating X and/or D

When evaluating the odds ratio and number of drugs in the combination therapy (under 5 drugs, between 5 and 7 drugs and over 7 drugs) against observed drug interactions risk category X and D, it was found that for erlotinib and gefitinib, the most cases with potential drug interactions were observed when patients were taking between 5 and 7 drugs simultaneously, while for the other EGFR inhibitors, the most cases with potential drug interactions were observed when patients were taking more than 7 drugs simultaneously.

5.2 Assessment of the relationship between patient age and gender and potential drug interactions falling into risk categories X and/or D

5.2.1 Erlotinib For the period under review 2021-2023, 44 cases of potential drug interactions erlotinib – drug of risk rating X and D were identified.

In 19 of the cases, only potential drug interactions belonging to risk rating D were observed, in 19 of the cases, only potential drug interactions belonging to risk rating X were observed, and in 6 of the cases, potential drug interactions from both groups X and D were observed simultaneously. (Tables 22, 23, 24 Fig. 26, 27, 28)

Table 22 Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Erlotinib pDDI risk rating D									
	2021		2022		2023		total		
	m	f	m	f	m	f	m	f	sum
≤ 64 year	0	0	0	2	0	1	0	3	3
> 65 year	4	1	3	0	5	3	12	4	16
total	4	1	3	2	5	4	12	7	19

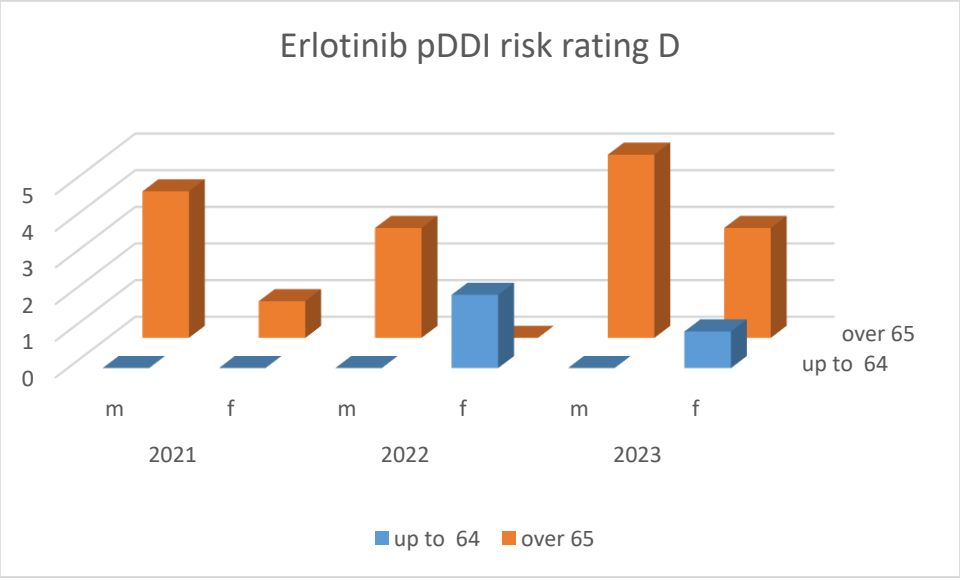

Fig. 26. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Table 23 Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating X

Erlotinib pDDI risk rating X									
	2021		2022		2023		total		sum
	m	f	m	f	m	f	m	f	
≤ 64 year	0	1	0	1	1	1	1	3	4
> 65 year	0	8	2	0	3	1	5	9	14
total	0	9	2	1	4	2	6	12	18
					1 unspecified gender				

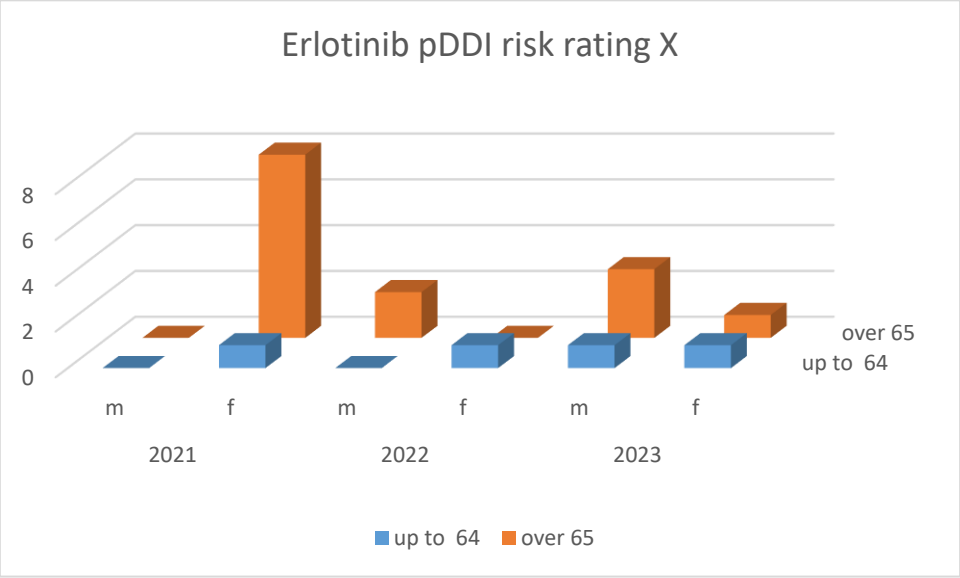

Fig. 27 Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating X

Table 24 Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating X and D

Erlotinib pDDI risk rating X and D									
	2021		2022		2023		total		sum
	m	f	m	f	m	f	m	f	
≤ 64 year	0	0	0	0	0	0	0	0	0
> 65 year	0	1	2	0	3	0	5	1	6
total	0	1	2	0	3	0	5	1	6

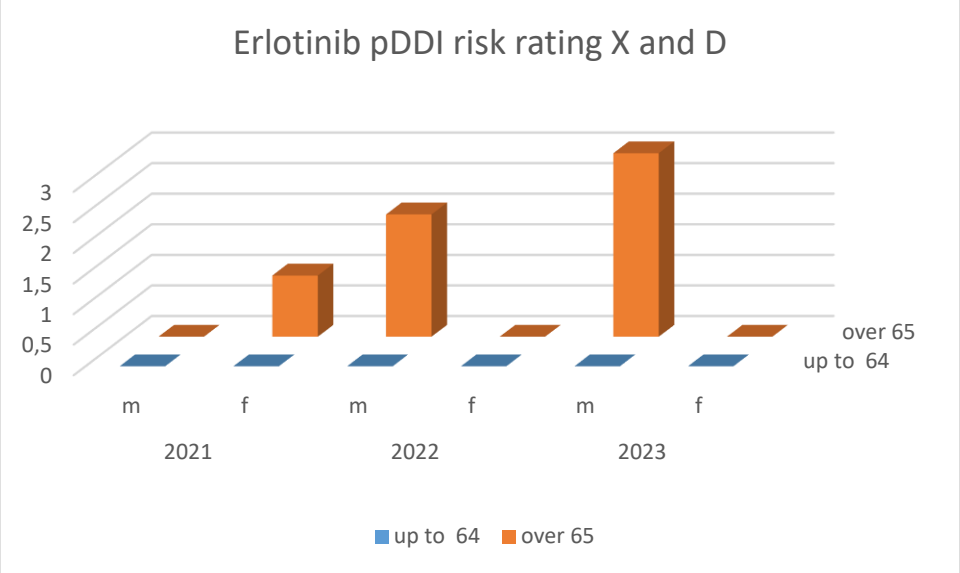

Fig. 28 Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating X and D

Distributed by age, patients ≤ 64 years had a total of 7 cases with potential drug interactions, and those over 65 years had 36 cases with potential drug interactions (1 case was excluded because the patient's gender was not specified). Distributed by gender, there was a slight male predominance - cases in men were 23, and in women - 20. (Table 25)

Table 25 Distribution of patients by age and gender with reported potential drug interactions

Erlotinib pDDI			
	m	f	
18-64 year	1	6	7
> 65 year	22	14	36
	23	20	43

When calculating the Pearson correlation coefficient the result was 0.3276 - a moderate correlation

5.2.2 Gefitinib For the period under review 2021 - 2023, 24 cases of potential drug interactions of risk rating D were identified for gefitinib. No potential drug interactions of risk rating X were observed (Table 26, Fig. 29)

Table 26 Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Gefitinib pDDI risk rating D									
	2021		2022		2023		total		
	m	f	m	f	m	f	m	f	sum
≤ 64 year	0	1	0	1	0	0	0	2	2
> 65 year	2	2	1	3	3	5	6	10	16
age not specified	1	1	1	0	1	2	3	3	6
total	3	4	2	4	4	7	9	15	24

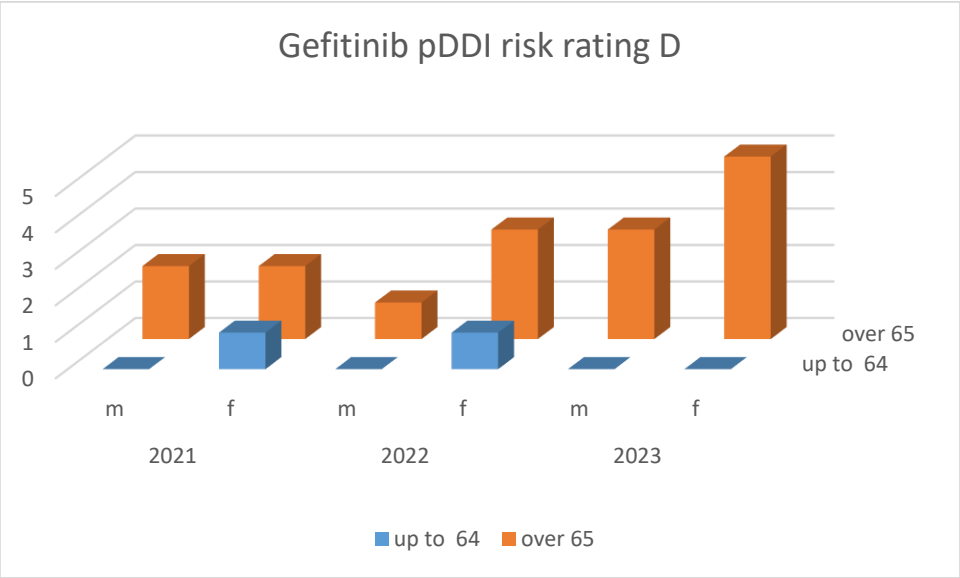

Fig. 29 Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Distributed by gender, females predominate - cases in men are 9, and in women - 15. Distributed by age, patients ≤ 64 years have a total of 2 cases with reported potential drug interactions, and those over 65 years - 16 cases with reported potential drug interactions. In 6 of the reported cases, the age of the patients was not specified, as a result of which the number of cases by gender was adjusted - adjusted cases in men are 6 and 12 in women. (Table 27)

Table 27. Distribution of patients by age and gender with reported potential drug interactions

Gefitinib pDDI			
	m	f	
18-64 year	0	2	2
> 65 year	6	10	16
	6	12	18

When calculating the Pearson correlation coefficient the result was 0.2424 - a weak correlation

5.2.3 Afatinib As with gefitinib, no potential drug interactions were observed for afatinib with an EGFR inhibitor - a drug of risk rating X. For the period under review 2021 - 2023, 9 cases with potential drug interactions of risk rating D were identified for afatinib. (Table 28, Fig. 30)

Table 28. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Afatinib pDDI risk rating D									
	2021		2022		2023		total		
	m	f	m	f	m	f	m	f	sum
≤ 64 year	0	0	0	0	2	1	2	1	3
> 65 year	2	1	0	0	0	1	2	2	4
age not specified	0	0	0	1	0	1	0	2	2
total	2	1	0	1	2	3	4	5	9

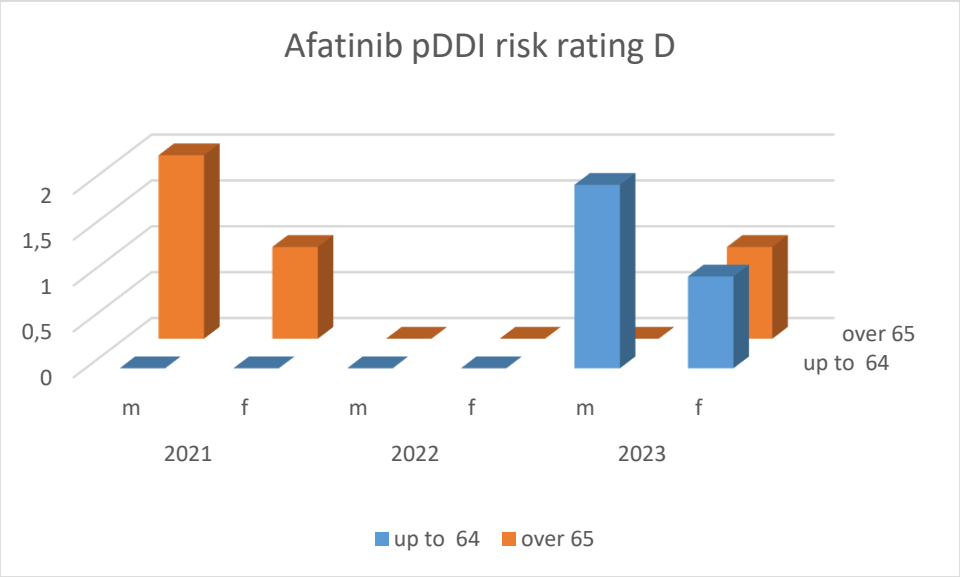

Fig. 30. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Distributed by gender, the female gender predominates - the cases in men are 4 and in women - 5. Distributed by age, patients ≤ 64 years have a total of 3 cases with potential drug interactions, and those over 65 years - 4 cases with potential drug interactions. In 2 of the reported cases, the age of the patients was not specified, as a result of which the number of cases by gender was adjusted - adjusted cases in men are 4 and 3 in women. (Table 29)

Table 29. Distribution of patients by age and gender with reported potential drug interactions

Afatinib pDDI			
	m	f	
≤ 64 year	2	1	3
> 65 year	2	2	4
	4	3	7

When calculating the Pearson correlation coefficient the result was 0.1642 - a weak correlation

5.2.4 Dacomitinib For the period under review 2021 - 2023, 23 cases were identified for dacomitinib with potential drug interactions of risk rating X and D.

In 17 of the cases, only potential drug interactions belonging to risk rating D were observed, in 4 of the cases only potential drug interactions belonging to risk rating X were observed, and in 2 of the cases, potential drug interactions from both risk rating X and D were observed on the same time (Tables 30, 31, 32 Fig. 31, 32, 33)

Table 30 Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Dacomitinib pDDI risk rating D									
	2021		2022		2023		total		
	m	f	m	f	m	f	m	f	sum
≤ 64 year	0	3	1	2	1	8	2	13	15
> 65 year	0	0	2	0	0	0	2	0	2
total	0	3	3	2	1	8	4	13	17

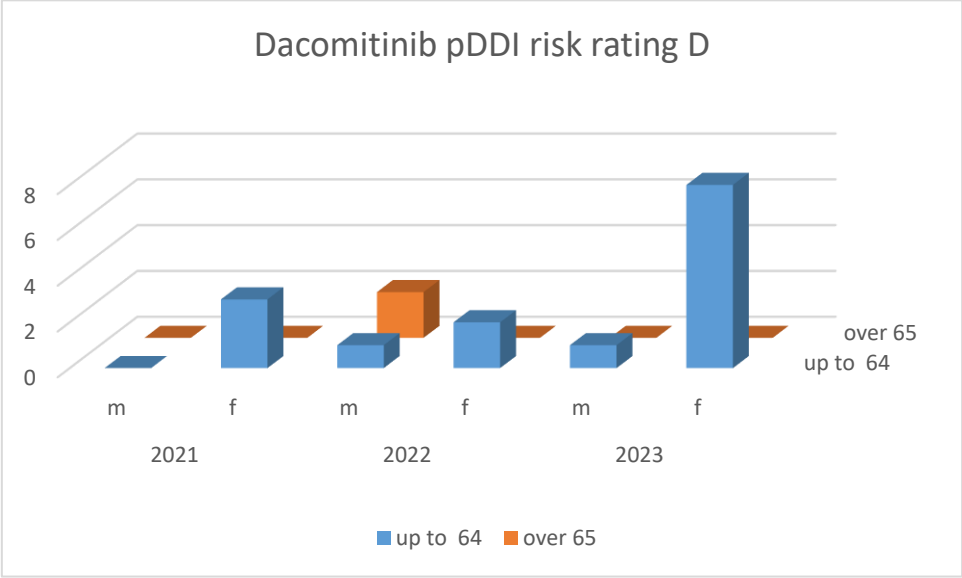

Fig. 31. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Table 31. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating X

Dacomitinib pDDI risk rating X									
	2021		2022		2023		общо		
	m	f	m	f	m	f	m	f	sum
≤ 64 year	0	0	0	0	0	2	0	2	2
> 65 year	0	0	1	0	0	1	1	1	2
total	0	0	1	0	0	3	1	3	4

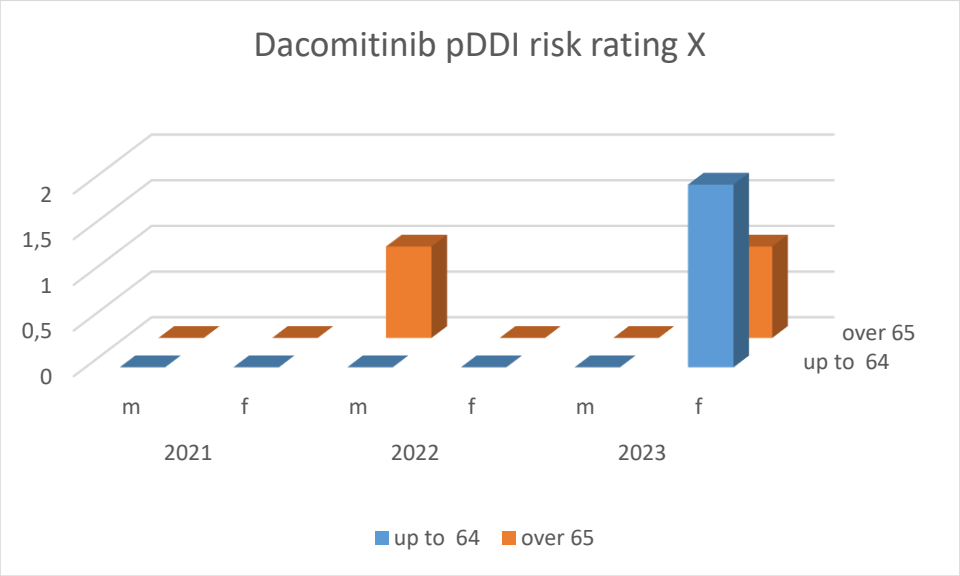

Fig. 32. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating X

Table 32. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating X and risk rating D

Dacomitinib pDDI risk rating X and D									
	2021		2022		2023		total		
	m	f	m	f	m	f	m	f	sum
≤ 64 year	0	0	1	0	0	0	1	0	1
> 65 year	1	0	0	0	0	0	1	0	1
total	1	0	1	0	0	0	2	0	2

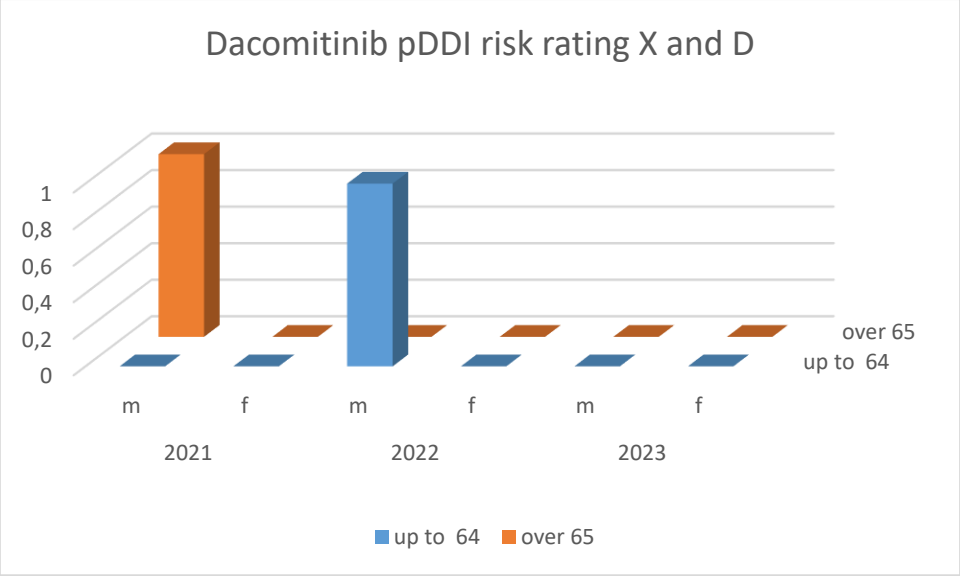

Fig. 33. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D and risk rating X

Distributed by age, patients ≤ 64 years had a total of 18 cases with potential drug interactions, and those over 65 years – 5 cases with potential drug interactions. Distributed by gender, there is a predominance of females - cases in men are 7, and in women – 16. (Table 33)

Table 33. Distribution of patients by age and gender with reported potential drug interactions

Dacomitinib pDDI			
	m	f	
18-64 year	3	15	18
> 65 year	4	1	5
	7	16	23

When calculating the Pearson correlation coefficient the result was 0.4937 - a moderate correlation

5.2.5 Osimertinib For the period under review 2021-2023, 44 cases were identified for osimertinib in which potential drug interactions of risk rating X and D were reported.

In 37 of the cases, only potential drug interactions belonging to risk category D were observed, and in 7 of the cases, only reported potential drug interactions belonging to risk rating X were observed. (Tables 34, 35 Fig. 34, 35)

Table 34. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Osimertinib pDDI risk rating D									
	2021		2022		2023		total		
	m	f	m	f	m	f	m	f	sum
≤ 64 year	0	0	0	3	0	0	0	3	3
> 65 year	2	3	2	8	8	8	12	19	31
age not specified	0	0	0	1	0	2	0	3	3
total	2	3	2	12	8	10	12	25	37

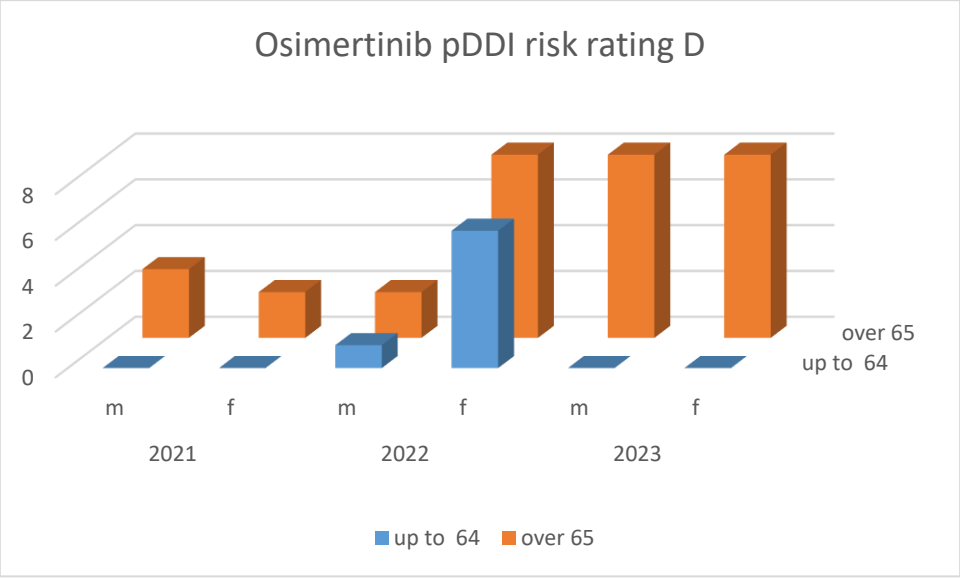

Fig. 34. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating D

Table 35. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating X

Osimertinib pDDI risk rating X									
	2021		2022		2023		total		
	m	f	m	f	m	f	m	f	sum
≤ 64 year	0	0	0	0	0	0	0	0	0
> 65 year	0	3	0	0	0	1	0	4	4
age not specified	0	1	0	1	0	0	0	2	2
total	0	4	0	1	0	1	0	6	6
1 age and gender not specified total patients:									7

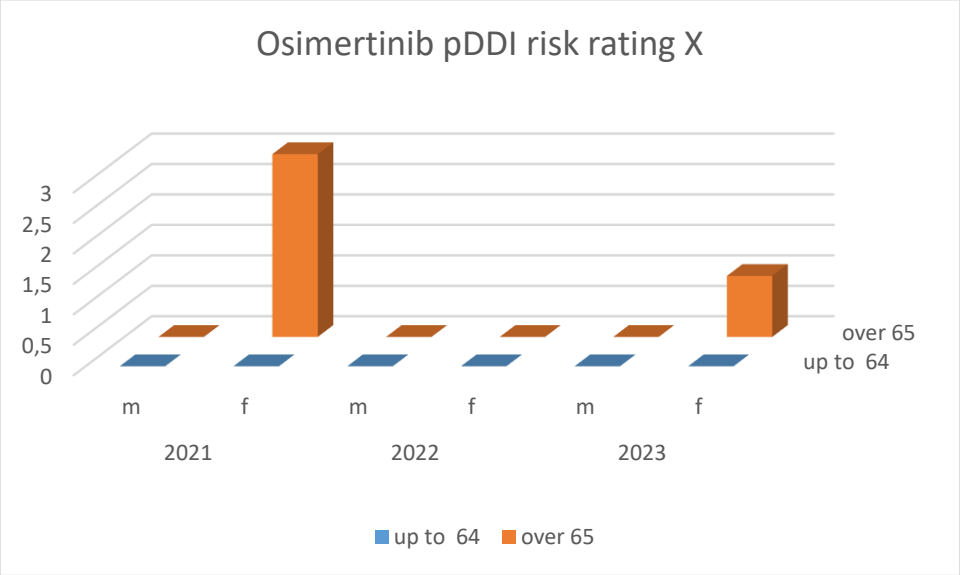

Fig. 35. Distribution of patients by age and gender with reported potential drug interactions belonging to risk rating X

Distributed by age, patients ≤ 64 years have a total of 7 cases with potential drug interactions, and those over 65 years – 35 cases with potential drug interactions (8 cases were excluded because the gender or age of the patient was not specified). Distributed by gender, there is a predominance of the female sex - cases in men are 14, and in women – 28. (Fig. 36)

Table 36 Distribution of patients by age and gender with reported potential drug interactions

Osimertinib pDDI			
	m	f	
18-64 year	0	3	3
> 65 year	12	23	35
	12	26	38

When calculating the Pearson correlation coefficient the result was 0.1952 - weak correlation

The association between patient age and gender and potential drug interactions falling into risk categories X and/or D was assessed by calculating the Pearson correlation coefficient. A moderate association was observed for erlotinib and dacomitinib, and a weak association was observed for gefitinib, afatinib, and osimertinib.

6. Analysis of potential ADRs reported in EudraVigilance with EGFR inhibitor use:

- **to the total number of ADR cases reported in EudraVigilance**
- **to the number of ADRs in cases with EGFR inhibitor use only**
- **to the number of ADRs in cases of EGFR inhibitor - drug combinations, when there are identified EGFR inhibitor - drug interactions of risk rating D and/or X.**

When comparing the estimated average number of reported suspected ADRs across all reported cases in EudraVigilance, the highest average number of ADRs were reported in cases of dacomitinib therapy (3.09 in 2021, 3.97 in 2022 and 6.99 in 2023) and gefitinib (3.43 in 2021, 3.42 in 2022 and 3.21 in 2023), and the lowest average number of suspected ADRs in cases of osimertinib therapy (2.39 in 2021, 2.10 in 2022 and 2.23 in 2023). (Table 37)

Table 37. Average number of suspected ADRs reported per case in EudraVigilance

EGFR - inhibitor	2021			2022			2023		
	average number	standard deviation	coefficient of variation (%)	average number	standard deviation	coefficient of variation (%)	average number	standard deviation	coefficient of variation (%)
Erlotinib	2,94	2,59	88,3	2,77	2,75	99,34	2,46	2,00	81,35
Gefitinib	3,43	4,19	122,07	3,42	2,83	82,63	3,21	2,20	68,55
Afatinib	2,90	2,73	94,21	2,98	2,94	98,59	2,99	3,08	102,91
Dacomitinib	3,09	3,33	107,93	3,97	5,53	139,28	6,99	6,73	96,28
Osimertinib	2,39	2,33	97,73	2,10	2,01	95,85	2,23	2,17	97,93

In cases where only one EGFR inhibitor was used, the highest average number of suspected ADRs was reported for dacomitinib – 2.74 for 2021, 3.2 for 2022 and 4.65 for 2023, and the lowest average number of suspected ADRs was reported for osimertinib – 2.02 for 2021, 1.86 for 2022 and 1.94 for 2023. Cases with the use of erlotinib alone also showed a low average number of reported suspected ADRs – 2.23 for 2021, 2.14 for 2022 and 2.12 for 2023 (Table 38)

Table 38 Average number of ADRs reported in cases where there is treatment with only one EGFR inhibitor

EGFR - inhibitor	2021			2022			2023		
	average number	standard deviation	coefficient of variation (%)	average number	standard deviation	coefficient of variation (%)	average number	standard deviation	coefficient of variation (%)
Erlotinib	2,23	1,74	78,07	2,14	1,39	64,79	2,12	1,38	65,22
Gefitinib	2,42	1,87	77,21	2,47	1,65	66,78	2,72	2,2	80,85
Afatinib	2,74	2,17	79,07	2,87	3,03	105,86	2,58	2,32	90,15
Dacomitinib	2,74	2,91	105,93	3,2	2,44	76,03	4,65	3,95	84,88
Osimertinib	2,02	2,1	103,93	1,86	1,81	97,33	1,94	1,92	98,95

When investigating cases of drug combinations where a drug interaction is observed EGFR-inhibitor - a drug with risk rating X and/or D, it is seen that the number of reported suspected ADRs is

increasing. The highest average number of ADRs was reported for cases with the use of dacomitinib - 11.25 for 2021, 9.29 for 2022 and 15.67 for 2023. After dacomitinib, the next drug with a high average number of reported suspected ADRs is gefitinib - 9.73 for 2021 and 7.33 for 2022, and for 2023 - for afatinib an average of 6.73 suspected ADRs were reported. With the lowest average number of reported suspected ADRs for 2021 and 2022 is afatinib – 1.67 and 1.00 respectively, and for 2023 – erlotinib with 2.67 average number of reported suspected ADRs. (Table 39)

Table 39. Average number of reported ADRs in cases of drug combinations where a drug interaction EGFR-inhibitor – drug with risk rating X and/or D was observed

EGFR -inhibitor	2021			2022			2023		
	average number	standard deviation	coefficient of variation (%)	average number	standard deviation	coefficient of variation (%)	average number	standard deviation	coefficient of variation (%)
Erlotinib	4,00	2,18	54,49	4,70	6,94	147,73	2,67	2,62	98,43
Gefitinib	9,73	14,02	144,13	7,33	8,14	110,97	3,29	2,19	66,51
Afatinib	1,67	0,47	28,28	1,00	0,00	0,00	6,80	6,27	92,26
Dacomitinib	11,25	3,03	26,94	9,29	5,01	53,91	15,67	9,58	61,13
Osimertinib	5,10	5,87	115,15	3,20	2,91	90,89	3,86	2,93	76,02

When comparing the average number of reported suspected ADRs when using only one EGFR inhibitor with the average number of all cases with reported ADRs of the same EGFR inhibitor and with the average number of ADRs when an EGFR inhibitor-drug interaction with risk rating X and/or D is observed, it is seen that, with the exception of the results for afatinib in 2021 and 2022, for all other EGFR inhibitors an increase in the average number of reported suspected ADRs when there is an EGFR inhibitor-drug interaction with risk rating X and/or D is observed. (Fig. 36)

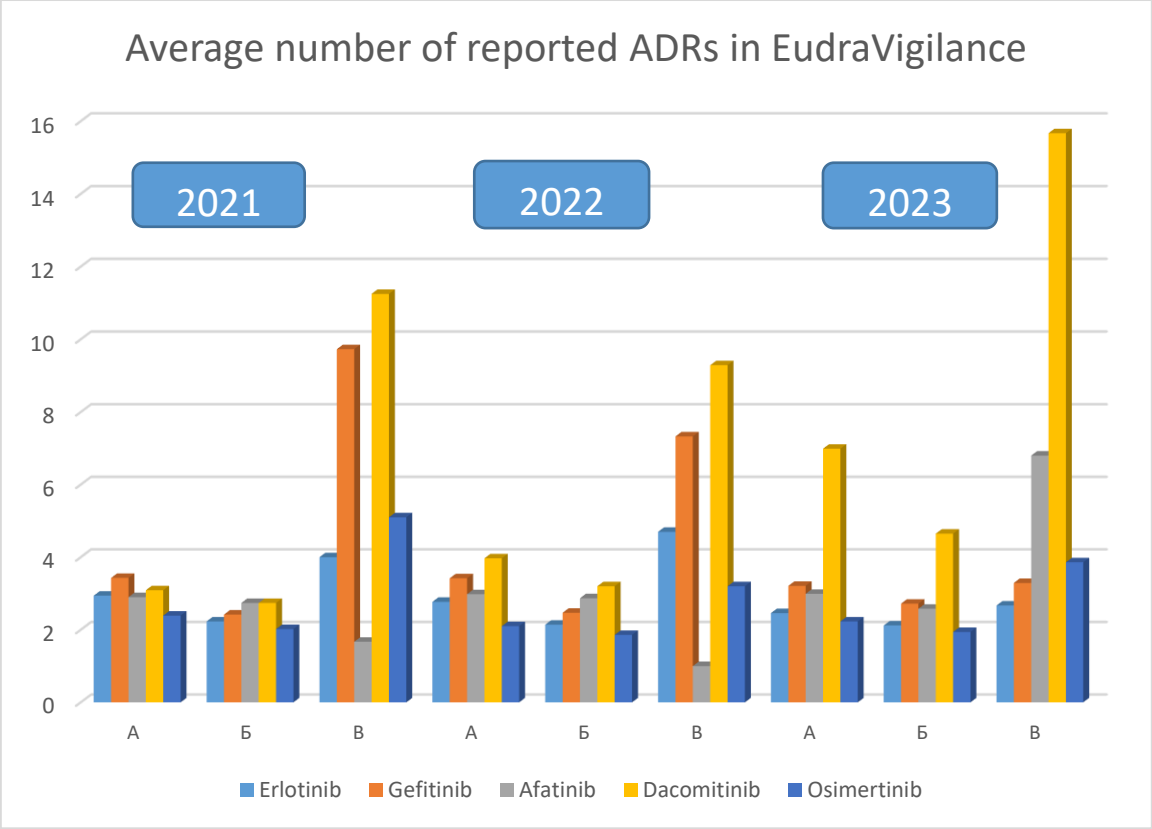

Fig. 36. Average number of reported suspected ADRs in EudraVigilance distributed as average number of reported suspected ADRs in all reported cases in EudraVigilance (A), average number of ADRs when using only one EGFR inhibitor (Б) and average number of reported ADRs when a drug interaction of the EGFR inhibitor with risk category X and/or D is observed (B) for the period 2021 – 2023.

With erlotinib, an increase in the average number of reported suspected ADRs was observed as follows:

- in 2021 – the average number of reported ADRs was 2.23 when only erlotinib is used in the therapy compared to 4.00 average number of reported ADRs when a drug interaction of erlotinib with risk rating X and/or D is observed;
- in 2022 the increase is respectively from 2.14 average number of reported suspected ADRs when only erlotinib is used in the therapy to 4.70 average number of reported ADRs when a drug interaction of erlotinib with risk rating X and/or D is observed
- in 2023 - the average number of reported ADRs was 2.12 when only erlotinib is used in the therapy, compared to 2.67 average number of reported ADRs when a drug interaction of erlotinib with risk rating X and/or D is observed.

An increase in the average number of ADRs reported with gefitinib was observed as follows:

- in 2021 – the average number of reported ADRs was 2.42 when only gefitinib is used in the therapy compared to 9.73 average number of reported ADRs when a drug interaction gefitinib - drug with risk rating X and/or D is observed
- in 2022, the increase is respectively from 2.47 average number of reported suspected ADRs when only gefitinib is used in the therapy to 7.33 average number of reported ADRs when a drug interaction of gefitinib with risk rating X and/or D is observed
- in 2023 - 2.72 average number of reported ADRs when only gefitinib is used in therapy compared to 3.29 average number of reported ADRs when a drug interaction of gefitinib with risk rating X and/or D is observed.

Regarding afatinib, a decrease in the average number of reported ADRs was observed when a drug interaction afatinib - drug with risk ratingX and/or D was observed for 2021 (2.74 to 1.67 average number of reported ADRs) and for 2022 (2.87 to 1.00 average number of reported ADRs), but in 2023 an increase in the average number of reported ADRs was observed 2.58 average number of reported ADRs. when afatinib alone is used in the therapy compared to 6.80 average number of reported ADRs when a drug interaction afatinib - drug with risk rating X and/or D was observed.

Dacomitinib had the highest average number of reported ADRs in both groups, but also an increase in the average number of reported ADRs when a dacomitinib-drug interaction with a risk category X and/or D was observed, as follows:

- for 2021 - 2.74 average number of reported ADRs when only dacomitinib is used in the therapy compared to 11.25 average number of reported ADRs when a drug interaction dacomitinib - a drug with risk category X and/or D is observed;
- for 2022, the increase is respectively from 3.2 average number of reported ADRs when only dacomitinib is used in the therapy to 9.29 average number of reported ADRs when a drug interaction is observed dacomitinib - a drug with risk category X and/or D and
- for 2023 - 4.65 average number of reported ADRs when only dacomitinib is used in the therapy to 15.67 average number of reported ADRs when a drug interaction dacomitinib - a drug with risk category X and/or D is observed.

Regarding osimertinib, an increase in the average number of reported ADRs was observed as follows:

- for 2021 - 2.02 average number of reported ADRs when only osimertinib is used in the therapy compared to 5.10 average number of reported ADRs when a drug interaction osimertinib - a drug with risk category X and/or D is observed;

- for 2022, the increase is respectively from 1.86 average number of reported ADRs when only osimertinib is used in the therapy to 3.2 average number of reported ADRs when a drug interaction is observed osimertinib - a drug with risk category X and/or D and
- for 2023 - 1.94 average number of reported ADRs when only osimertinib is used in the therapy to 3.86 average number of reported ADRs when a drug interaction osimertinib - drug with risk category X and/or D is observed. (Fig. 37, 38, 39)

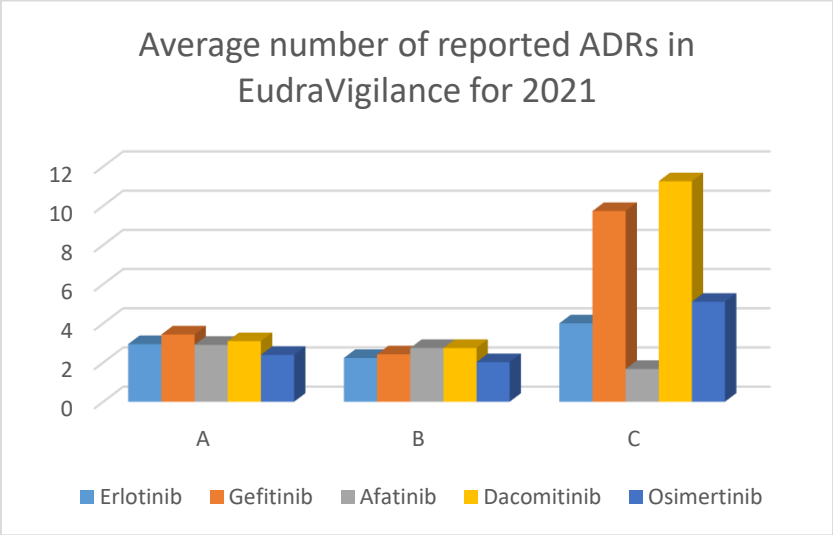

Fig. 37. Average number of reported suspected ADRs in EudraVigilance distributed as average number of reported suspected ADRs in all reported cases in EudraVigilance (A), average number of ADRs when using only one EGFR inhibitor (B) and average number of reported ADRs when a drug interaction of the EGFR inhibitor with risk category X and/or D is observed (C) for 2021.

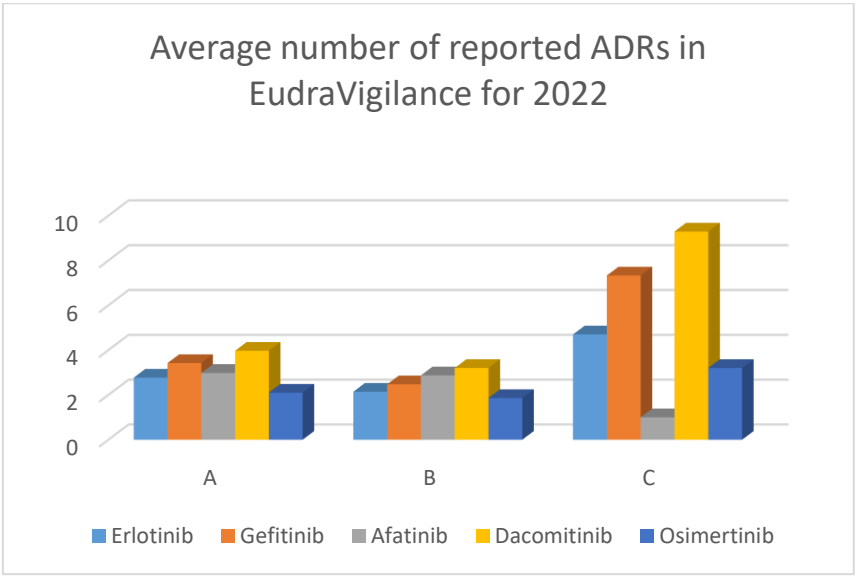

Fig. 38. Average number of reported suspected ADRs in EudraVigilance distributed as average number of reported suspected ADRs in all reported cases in EudraVigilance (A), average number of ADRs when using only one EGFR inhibitor (B) and average number of reported ADRs when a drug interaction of the EGFR inhibitor with risk category X and/or D is observed (C) for 2022.

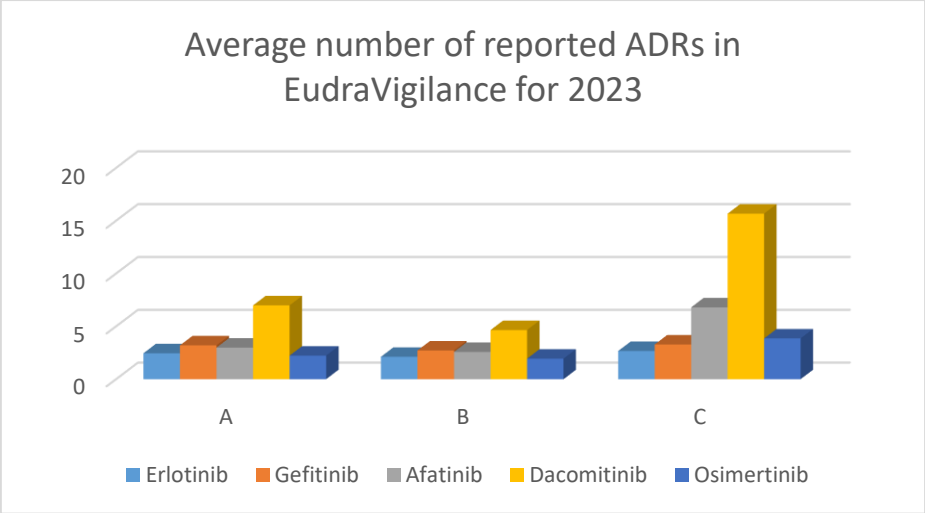

Fig. 39. Average number of reported suspected ADRs in EudraVigilance distributed as average number of reported suspected ADRs in all reported cases in EudraVigilance (A), average number of ADRs when using only one EGFR inhibitor (B) and average number of reported ADRs when a drug interaction of the EGFR inhibitor with risk category X and/or D is observed (C) for 2023.

7. Assessment of the relationship between adverse drug reaction cases reported in EudraVigilance and identified drug interactions risk category X and/or D

From the cases reported in EudraVigilance with suspected adverse drug reactions to the EGFR inhibitors erlotinib, gefitinib, afatinib, dacomitinib and osimertinib, all cases in which drug interactions between an EGFR inhibitor and another drug belonging to risk category X and/or D were observed, were selected 144 cases and these were distributed into 5 groups according to the EGFR inhibitor.

For each case, the following information was taken from EudraVigilance: age group, gender of the patient, all reported suspected ADRs, list of drugs. To the drug interactions EGFR-inhibitor - drug risk category X and/or D already identified through the digital platform UpToDate® Lexidrug™, drug interactions EGFR-inhibitor - drug risk category C were also added, if they were observed for the specific case. Drug interactions EGFR-inhibitor - drug risk category B were not analyzed because, although the indicated drugs may interact with each other, there is little or no evidence of clinical effects as a result of their concomitant use and, accordingly, no measures such as monitoring or change in therapy are necessary in the case of their concomitant use.

Based on the information on the pharmacological properties of EGFR inhibitors and the drugs that were reported as being taken concomitantly, a comment was made on the mechanisms of possible drug interactions and whether some or all of the listed adverse drug reactions were already reported in the SmPC of the drugs involved in the interaction. Depending on whether the drug interaction involving the EGFR inhibitor affected the pharmacological properties and effects of the EGFR inhibitor itself and/or another drug, a relationship was assumed and the cases were divided into two groups: *Group 1. The drug interaction involving the EGFR inhibitor could not cause any of the reported ADRs* or *Group 2. The drug interaction involving the EGFR inhibitor could cause at least one of the reported ADRs.* Since many of the cases also had drug interactions EGFR inhibitor - drug risk category C, group 2 was divided into 2.1 when the risk category was X and/or D and 2.2 when the risk category was C. Based on the analysis, cases were identified in which a drug interaction involving the EGFR inhibitor may have been the cause of a reported adverse drug reaction. Recommendations were made for clinical practice to avoid the drug interaction.

7.1 Erlotinib For erlotinib, 44 cases were identified with a drug interaction involving erlotinib, of which 32 cases had only one drug interaction involving the EGFR inhibitor and 12 cases had two drug interactions involving the EGFR inhibitor. In 38 cases (86.36%), the drug interaction involving erlotinib could not be the cause of any of the reported ADRs. In 7 cases (15.90%), the ADRs reported in EudraVigilance could be a consequence of a drug interaction, with 5 of these cases being the result of a drug interaction with risk category X and/or D. (Table 40)

Table 40 Relationship between reported suspected ADRs and identified drug interactions erlotinib – drug risk category X and/or D (2.1) and risk category C (2.2)

Erlotinib	Could not cause any of the reported ADRs (1)	Can cause:			Total cases	Relative proportion (%)	
		at least one of the reported ADRs (2.1) X, D	*at least one of the reported ADRs (2.2) C*	total		Could not cause any of the reported ADRs (1)	Can cause
1	*2*	*3*	*4*	*5=3+4*	*6=2+5*	*7*	*8*
Drug interactions involving the EGFR inhibitor, including:	38	5	2	7	44	86,36	15,90
One pDDI EGFR-inhibitor drug	29	3	0	3	32	90,62	9,37
Two pDDI EGFR-inhibitor drug	9	2	1	3	12	75,00	25,00

7.2 Gefitinib For gefitinib, 24 cases were identified in which there was a drug interaction involving gefitinib, with 14 of the cases having only one drug interaction involving gefitinib, 9 of the cases having two drug interactions involving gefitinib and 1 case having 3 drug interactions, each involving gefitinib. In 16 of the cases (66.66%), the drug interaction could not be the cause of any of the reported suspected ADRs. However, in 8 of the cases (33.33%), the ADRs reported in EudraVigilance could be the consequence of a drug interaction, with 6 of these cases being the result of a drug interaction with risk category X and/or D, and in two of the cases being the result of a drug interaction with risk category C. (Table 41)

Table 41. Relationship between reported suspected ADRs and identified drug interactions gefitinib – drug risk category X and/or D (2.1) and risk category C (2.2)

Gefitinib	Could not cause any of the reported ADRs (1)	Can cause:			Total cases:	Relative proportion (%)	
		at least one of the reported ADRs (2.1) X, D	*at least one of the reported ADRs (2.2) C*	total		Could not cause any of the reported ADRs (1)	Can cause
1	*2*	*3*	*4*	*5=3+4*	*6=2+5*	*7*	*8*
Drug interactions involving the EGFR inhibitor, including:	16	6	2	8	24	66,66	33,33
One pDDI EGFR-inhibitor drug	10	4	0	4	14	71,42	28,57
Two pDDI EGFR-inhibitor drug	6	2	1	3	9	66,66	33,33
Three pDDI EGFR-inhibitor drug	0	0	1	1	1	0	100

7.3 Afatinib For afatinib, 9 cases were identified where there was a drug interaction involving afatinib, with 2 of the cases having only one drug interaction involving afatinib and 7 of the cases having two drug interactions involving afatinib. In 1 case (11.1%), the drug interaction could not be the cause of any of the reported suspected ADRs. In 8 of the cases (88.9%), the ADRs reported in EudraVigilance could be a consequence of a drug interaction, with all cases resulting from drug interactions with risk category X and/or D. (Table 42)

Table 42 Relationship between reported suspected ADRs and identified drug interactions afatinib – drug risk category X and/or D (2.1) and risk category C (2.2)

Afatinib	Could not cause any of the reported ADRs (1)	Can cause:			Total cases:	Relative proportion (%)	
		at least one of the reported ADRs (2.1) X, D	*at least one of the reported ADRs (2.2) C*	total		Could not cause any of the reported ADRs (1)	Can cause
1	2	3	4	5=3+4	6=2+5	7	8
Drug interactions involving the EGFR inhibitor, including:	1	8	0	8	9	11,11	88,88
One pDDI EGFR-inhibitor drug	0	2	0	2	2	0	100
Two pDDI EGFR-inhibitor drug	1	6	0	6	7	14,28	85,71

7.4 Dacomitinib In EudraVigilance, 23 cases were identified with a potential drug interaction involving dacomitinib, of which 13 cases had only one drug interaction involving dacomitinib, 5 cases had two drug interactions involving dacomitinib, 1 case had 3 drug interactions identified, 3 cases had 4 drug interactions and 1 case had 6 drug interactions, each involving dacomitinib. In 5 cases (21.73%), the drug interaction involving dacomitinib could not be the cause of any of the reported ADRs. However, in 18 cases (78.26%), the suspected ADRs reported in EudraVigilance could be the result of a drug interaction, with 17 of these cases resulting from a drug interaction with risk category X and/or D and only 1 case from a drug interaction with risk category C. (Table 43)

Table 43. Relationship between reported suspected ADRs and identified drug interactions dacomitinib – drug risk category X and/or D (2.1) and risk category C (2.2)

Dacomitinib	Could not cause any of the reported ADRs (1)	Can cause:			Total cases:	Relative proportion (%)	
		at least one of the reported ADRs (2.1) X, D	*at least one of the reported ADRs (2.2) C*	total		Could not cause any of the reported ADRs (1)	Can cause
1	*2*	*3*	*4*	*5=3+4*	*6=2+5*	*7*	*8*
Drug interactions involving the EGFR inhibitor, including:	5	17	1	18	23	21,73	78,2609
One pDDI EGFR-inhibitor drug	5	8	0	8	13	38,46	61,53
Two pDDI EGFR-inhibitor drug	0	5	0	5	5	0	100
Three pDDI EGFR-inhibitor drug	0	1	0	1	1	0	100
Four pDDI EGFR-inhibitor drug	0	2	1	3	3	0	100
Six pDDI EGFR-inhibitor drug	0	1	0	1	1	0	100

7.5 Osimertinib 44 cases were identified with a potential drug interaction involving osimertinib, of which 28 cases had only one drug interaction involving osimertinib, 12 cases had two drug interactions involving osimertinib, 2 cases had 3 drug interactions, 1 case had 4 drug interactions, and 1 case had 5 drug interactions, each involving osimertinib. In 25 cases (56.81%), the drug interaction could not be the cause of any of the reported ADRs. However, in 19 cases (43.18%), the suspected ADRs reported in EudraVigilance could be a consequence of a drug interaction, with 12 of these cases being the result of a drug interaction with risk category X and/or D, in 2 of the cases – of a drug interaction with risk category C, and in 5 of the cases – the reported ADRs may be the result of a simultaneous drug interaction with risk category X and/or D and risk category C. (Table 44)

Table 44 Relationship between reported suspected ADRs and identified drug interactions osimertinib – drug risk category X and/or D (2.1), risk category C (2.2) and with concomitantly observed drug interactions of risk category X and/or D and risk category C

Osimertinib	Could not cause any of the reported ADRs (1)	Can cause:				Total cases:	Relative proportion (%)	
		at least one of the reported ADRs (2.1) X, D	*at least one of the reported ADRs (2.2) C*	*pDDIs may cause at least one of the reported ADRs (2.1) X, D and (2.2) C*	total		Could not cause any of the reported ADRs (1)	Can cause
1	*2*	*3*	*4*	*5*	*6=3+4+5*	*7=2+6*	*8*	*9*
Drug interactions involving the EGFR inhibitor, including:	25	12	2	5	19	44	56,81	43,18
One pDDI EGFR-inhibitor drug	19	9	0	0	9	28	67,85	32,14
Two pDDI EGFR-inhibitor drug	5	3	1	3	7	12	41,66	58,33
Three pDDI EGFR-inhibitor drug	1	0	1	0	1	2	50	50
Four pDDI EGFR-inhibitor drug	0	0	0	1	1	1	0	100
Five pDDI EGFR-inhibitor drug	0	0	0	1	1	1	0	100

Of the 144 cases identified and analysed with a potential drug interaction involving the EGFR inhibitor and belonging to risk category X and/or D, 63 of them may have a possible relationship with the suspected ADRs reported in EudraVigilance. The highest relative proportion of possible relationship between drug interaction and reported ADRs were afatinib (88.88%) and dacomitinib (78.26%). For osimertinib, 43.18% of the reported suspected ADRs could be due to a drug interaction with osimertinib. In 63 cases, drug interactions could be the cause of at least 1 observed ADR. In absolute terms, the most cases were identified with osmertinib (19) and dacomitinib (18), but in relative terms, with erlotinib and gefitinib, the potential drug interactions that can cause ADRs have the lowest relative proportion – with erlotinib 20.45% and gefitinib – 37.5%, and with osimertinib the relative proportion is 43.18% (Table 45). As a result, by optimizing drug therapy, drug interactions can be avoided and, hence, adverse drug reactions can be reduced.

Table 45. Relationship between reported suspected ADRs and identified drug interactions EGFR - inhibitor - drug risk category X and/or D (2.1), risk category C (2.2) and with concomitantly observed drug interactions of risk category X and/or D and risk category C

EGFR - inhibitor	Could not cause any of the reported ADRs (1)	Can cause:				Total cases:	Relative proportion (%)	
		at least one of the reported ADRs (2.1) X, D	*at least one of the reported ADRs (2.2) C*	*pDDIs may cause at least one of the reported ADRs (2.1) X, D and (2.2) C*	total		Could not cause any of the reported ADRs (1)	Can cause
1	*2*	*3*	*4*	*5*	*6=3+4+5*	*7=2+6*	*8*	*9*
Erlotinib	35	7	2	0	9	44	79,54	20,45
Gefitinib	15	6	3	0	9	24	62,50	37,50
Afatinib	1	8	0	0	8	9	11,11	88,88
Dacomitinib	5	17	1	0	18	23	21,73	78,26
Osimertinib	25	12	2	5	19	44	56,81	43,18
	Total:				63	144		

For the first-generation EGFR inhibitors erlotinib and gefitinib and the second-generation EGFR inhibitor dacomitinib, drug interactions of risk category X and/or D were most frequently identified when used concomitantly with H2-receptor blockers, antacids, proton pump inhibitors (PPIs) and potassium-competitive acid blockers (PCABs). The concomitant use of both classes of drugs leads to a pharmacokinetic interaction at the level of absorption - the change in the acidity of the upper GIT due to the use of H2-blockers, antacids, PPIs and PCABs leads to reduced absorption of the EGFR inhibitor and, respectively, reduced bioavailability. Several cases of reported ADRs were observed. Progression of the oncological disease and the concomitant use of erlotinib, gefitinib and dacomitinib. A reported lack of drug effect has been reported with the concomitant use of erlotinib and teriflunomide (a moderate CYP1A2 inducer). As a result of this interaction, reduced bioavailability of erlotinib may be observed due to induction of the CYP1A2 enzyme responsible for erlotinib metabolism.

P-gp inhibitors may increase the serum concentration of afatinib and lead to the occurrence of adverse drug reactions characteristic of afatinib. This pharmacokinetic mechanism was mainly observed in the identified drug interactions with afatinib. Although a small number of drug interactions involving afatinib were identified (9 cases), in 8 of them the drug interaction was a result of P-gp inhibition and the observed suspected ADRs were reported in the afatinib SmPC (diarrhoea, rash, nausea and vomiting). In one case report with afatinib, the following ADRs were reported: *Alopecia, Dermatitis acneiform, Diarrhea, Dizziness, Drug intolerance, Dry eye, Dry skin, Dysgeusia, Abnormal sensation, Hypoesthesia, Inappropriate dosing schedule, Insomnia, Malignant disease progression, CNS metastases, Seizures, Skin exfoliation, Transient ischemic attack, Non-adherence to treatment, Urinary tract infection*. In this case, 2 potential drug interactions of afatinib were identified – with cyclosporine (risk category D) and with omeprazole (risk category C). Some of the listed suspected ADRs, for example: Dermatitis acneiform, Diarrhea, Dry eye, Dry skin, Skin exfoliation have been reported with the use of afatinib. Concomitant use of afatinib with cyclosporine (a P-gp/ABCB1

inhibitor) may increase the serum concentration of afatinib. Therefore, a relationship between these ADRs and a drug-drug interaction afatinib - cyclosporine cannot be excluded.
Proton pump inhibitors (PPIs) may reduce the therapeutic effect of afatinib when used together. Although proton pump inhibitors (PPIs) do not appear to alter the pharmacokinetics of afatinib, retrospective studies have concluded that they may reduce survival in patients with NSCLC, i.e. a relationship between cancer progression and afatinib-PPI drug-drug interaction cannot be excluded. After analysis, it was assumed that drug interactions involving the EGFR inhibitor may cause at least one of the reported ADRs.
When analyzing one case of dacomitinib use in drug therapy with reported concomitant administration of 19 drugs, four potential drug interactions involving dacomitinib were identified: one with risk category X, one with risk category D, and two with risk category C. Of the listed ADRs, the following have been reported with the use of dacomitinib: *Asthenia, Diarrhea, Stomatitis.* The reported ADRs should not be a result of dacomitinib-PPI and dacomitinib-H2 antagonist drug interactions, as the solubility of dacomitinib decreases with increasing upper GI pH, thereby reducing dacomitinib absorption and hence its bioavailability. Therefore, there should be no relationship between the reported ADRs and the concomitant use of dacomitinib-PPI and dacomitinib-H2 antagonist. Since it was stipulated that all possible pharmacological interactions of the EGFR inhibitor would be analyzed for the reported suspected ADRs, the drug interactions dacomitinib-tramadol and dacomitinib-tamsulosin (risk category C) were also considered. Dacomitinib, as a strong inhibitor of CYP2D6, may decrease serum concentrations of the active metabolite(s) of tramadol and increase serum concentrations of tramadol and tamsulosin, resulting in ADRs characteristic of tramadol (increased blood pressure, respiratory distress) and tamsulosin (asthenia, dizziness), respectively. Therefore, a relationship between the reported ADRs characteristic of tramadol and tamsulosin and their concomitant use with dacomitinib cannot be excluded.
The following suspected ADRs have been reported in EudraVigilance with concomitant use of osimertinib with amiodarone (risk category D) and moxifloxacin (risk category C): *Cardiac disease, Torsade de pointes.* QTc prolongation may lead to an increased risk of ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. QTc prolongation is an uncommon ADR (≥1/1,000 to <1/100) reported with the use of osimertinib. Medicinal products with the highest risk of QT prolongation (e.g. amiodarone) may potentiate the QTc prolonging effect of osimertinib. Quinolone antibiotics that prolong the QT interval may also potentiate the QTc prolonging effect of kinase inhibitors. Therefore, a relationship between the concomitant use of osimertinib, amiodarone and moxifloxacin and the reported ADR Torsade de pointes cannot be excluded.
Concomitant use of rifampicin and osimertinib was reported in 4 cases. Rifampicin, as a potent inducer of CYP3A4, may decrease serum concentrations of osimertinib. The drug interaction between rifampicin and osimertinib is a risk category D. Of the 4 cases observed, a possible relationship between the concomitant use of both drugs and the reported suspected ADRs was found in 2. In the first case, the ADR reported was the presence of CNS metastases as a manifestation of disease progression. Therefore, a relationship between the concomitant use of osimertinib and rifampicin and the reported potential ADR cannot be excluded. In the second case, the ADRs Asthenia, Drug interaction, Insomnia, Malignant disease progression were reported. In this case, concomitant use of Osimertinib with Rifampicin (CYP3A4 strong inducer, risk category D) and Osimertinib with Metamizole (CYP3A4 moderate inducer, risk category C) was reported. Concomitant use of rifampicin (strong CYP3A4 inducer) with osimertinib and metamizole (moderate CYP3A4 inducer) with osimertinib may lead to decreased serum concentrations of the EGFR inhibitor. Therefore, a relationship between the concomitant use of osimertinib with rifampicin and osimertinib with metamizole and the reported ADR Malignant disease progression cannot be excluded.

An analysis of the possible relationship between the identified potential drug interactions and the ADRs reported in EudraVigilance was performed for all 144 cases and is included in Appendix 2.
Of the 144 cases identified and analyzed in which there was a drug interaction involving the EGFR inhibitor and belonging to risk category X and/or D, 63 of them may have a relationship with the potential ADRs reported in EudraVigilance. The highest relative share of possible relationship between drug interaction and reported ADRs were afatinib (88.88%) and dacomitinib (78.26%). For osimertinib, 43.18% of reported ADRs may be due to a drug interaction with osimertinib. In 63 cases, drug interactions may be the cause of at least 1 (one) observed adverse drug reaction. In absolute terms, the most cases were identified with osmertinib and dacomitinib therapy, but in relative terms, erlotinib and gefitinib had the lowest relative proportion of potential drug interactions that could cause ADRs. Optimizing drug therapy with a preliminary analysis of potential drug interactions may reduce adverse drug reactions and increase the effectiveness of targeted therapy and adherence to targeted therapy.

V Conclusions

1. Lung cancer is the most common cancer in men and the second most common (after breast cancer) in women in 2022, with a trend of increasing cases in the coming years. Non-small cell lung cancer accounts for about 85% of all NSCLC cases. The development of molecular analyses has led to the identification of new therapeutic targets and the creation of new drugs. Targeted therapy is recommended as standard treatment for advanced stage IV NSCLC with positive results from molecular tests (i.e. with proven oncogenic mutations).

2. First-generation EGFR inhibitors (erlotinib, gefitinib) show a smaller number of potential drug interactions with other drugs, but the degree of risk and severity of drug interactions is greater compared to third-generation EGFR inhibitors (osimertinib).

- When comparing EGFR inhibitors in regards of severity and degree of risk of drug interactions, for erlotinib most drug interactions are of risk category X and D and according to the severity of the interaction, are classified as severe, for gefitinib - most drug interactions are of risk category D and according to the severity of the interaction, there is a slight predominance of severe over moderate in severity, for afatinib and dacomitinib most drug interactions are of risk category C and according to the severity of the interaction, are classified as moderate, for osimertinib - most drug interactions are of risk category B and according to the severity of the interaction, there is a slight predominance of those with minor over moderate.

- When analyzing potential drug interactions between other drugs without the involvement of an EGFR inhibitor, most drug interactions were moderate in severity and risk category C.

3. The relative proportion of drug interaction cases severity to the total number of cases reported in EudraVigilance was lowest for osimertinib and highest for dacomitinib and erlotinib

4. When EGFR inhibitors are used concomitantly with drugs commonly used in clinical practice, the most frequently observed drug interactions are with PK mechanisms, at the level of absorption, metabolism (CYP3A4, CYP1A2, CYP2C9, P-gp/ ABCB1) and with PD mechanisms (QT prolongation).

5. For first-generation EGFR inhibitors (erlotinib and gefitinib), no association was observed between the number of medications taken and potential drug interactions falling into risk categories D and/or X. Such an association was observed for second- and third-generation EGFR inhibitors. Regarding the association between patient age and gender and potential drug interactions falling into risk categories D and/or X, a moderate association was observed for erlotinib and dacomitinib, and a weak association was observed for gefitinib, afatinib, and osimertinib.

6. The number of suspected ADRs reported in EudraVigilance is higher when there is an identified drug interaction between an EGFR inhibitor and a drug of risk category D and X compared to the number of ADRs reported when using an EGFR inhibitor alone and compared to the total number of ADRs when using EGFR in combination with other drugs.

7. A possible relationship between the identified potential drug interactions and the reported ADRs was observed in 63 cases. In absolute numbers, the most cases were identified with osmertinib (19) and dacomitinib (18). In relative terms, for erlotinib and gefitinib, the potential drug interactions that could cause ADRs had the lowest relative proportion for erlotinib 20.45% and gefitinib – 37.5%, while for osimertinib the relative proportion was 43.18%. The highest relative proportion was observed for dacomitinib 78.26% and afatinib 88.88%.

Inferences

The discovery of genetic mutations in NSCLC has led to the creation of a new class of drugs targeting different oncogenic mutations. Treatment with these drugs has resulted in prolongation of overall survival (OS) and progression-free survival (PFS) in patients. However, to improve safety and ensure a better quality of life, it is necessary for patients to be screened for potential drug interactions before prescribing pharmacotherapy. If such are identified, they should be avoided accordingly. The professional responsibility of healthcare professionals is to minimize the risk of adverse drug interactions. Reporting potential ADRs in EudraVigilance leads to continuous monitoring of the safety of medicines and analysis of the benefit-risk ratio of their use. A disadvantage of all currently available online platforms for detecting drug interactions is that they lack information on genetic mutations in NSCLC. This is due to the fact that such data are not currently collected and therefore cannot be analyzed by the system.

VI Scientific 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.

VII List of scientific publications and reports related to the dissertation

Publications related to the dissertation:

Risk for QT prolongation in patients with oncology diseases
I. Mutafova, E. Grigorov, K. Georgiev, V. Belcheva, M. Eneva; Cardiovascular diseases, 2022, 53, № 1, 18-30

Targeted therapy for Non-small cell lung cancer (NSCLC) with KRAS mutations
Ivanka Mutafova, Teodora Handjieva-Darlenska, Kaloyan Georgiev, Evgeni Grigorov, Velko Minchev Thoracic Medicine, Official Journal of the Bulgarian Respiratory Society Volume XIII / 2024 / Issue 2, 12-27

Pharmacotherapy of Non-Small Cell Lung Cancer with EGFR Activating Mutations Using Tyrosine Kinase Inhibitors: The Role of Hospital Pharmacists in Preventing Drug-Drug Interactions in This Class of Medicines
Ivanka Mutafova
Annual for hospital pharmacy, 2024, Volume 10, №1, 72-89.

Participation in scientific forums on the topic:

The Eighth Pharmaceutical Business Forum with a Scientific and Practical Conference "Pharmacists and doctors - united in patient support" 28-29 October 2022
Poster: **NOVEL MEDICINES FOR NON-SMALL CELL LUNG CANCER (NSCLC) APPROVED BY FDA AND TARGETING EGFR EXON 20 INSERTION MUTATIONS – A PHARMACOLOGY PROSPECTIVE**
Ivanka Mutafova, Evgeni Grigorov, Kaloyan Georgiev, Svetoslav Tsenov

The Eighth Pharmaceutical Business Forum with a Scientific and Practical Conference “New horizons in cooperation between science and business” 07-09 November 2024
Poster: **MANAGEMENT OF EGFR THERAPY TO REDUCE POTENTIAL DRUG-DRUG INTERACTIONS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER**
Ivanka Mutafova, Alexander Zlatanov

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