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Liste des abréviations

AINS : Anti Inflammatoires Non Stéroïdiens
ALD : Affection Longue Durée
ALK : Activin receptor-Like Kinase
AMM : Autorisation de Mise sur le Marché
ATC : Anatomique, Thérapeutique et Chimique
ATP : Adénosine TriPhosphate
BCMD : Base de Causes Médicales de Décès
CépiDC : Centre d'épidémiologie sur les causes médicales de DéCès
CBPC : Cancer Bronchique à Petites Cellules
CBNPC : Cancer Bronchique Non à Petites Cellules
CIP : Code Identifiant de Présentation
CTLA-4 : Cytotoxic T-Lymphocyte-Associated protein 4
DCIR : Datamart de Consommation Inter Régime
DDD : doses quotidiennes définies, Defined Daily Dose
DLCO : Capacité de Diffusion du Monoxyde de Carbone,
EC : Essai Clinique
EGFR : Epidermal Growth Factor Receptor
EI : Effet Indésirable
EMA : European Medicines Agency
FDA : Food and Drug Administration
GHM : Groupes Homogènes Maladies
HAD : Hospitalisation A Domicile
IPK : Inhibiteur de Protéines Kinases
IPP : Inhibiteur de Pompe à Proton
MCO : Médecine Chirurgie Obstrétrie
MDPH : Maisons Départementales des Personnes Handicapées
MEK : Mitogen Activated Protein Kinase Kinase
MPR : Ratio de Possession de Médicament
PD 1 : Programmed Death 1
PD-L1 : Programmed Death-Ligant 1
PMSI : Programme de Médicalisation des Systèmes d'Information
RGO : Reflux Gastro-Oesophagien
RSA : Résumé de Séjours Anonymisés
RSI : Régime Social des Indépendants

SNDS : Système National des Données de Santé

SNIIRAM : Système National d'Information Inter-Régimes de l'Assurance Maladie

SSR : Soins de Suite et de Réadaptation

TEP : Tomographie par Emission de Positons

VEGF : Vascular Endothelial Growth Factor

VEMS : Volume Expiratoire Maximal par Seconde

Introduction

Le cancer du poumon est un des cancers les plus fréquents et représente en France la première cause de décès par cancer. C'est une pathologie à prédominance masculine. Cependant, du fait que la prévalence de consommation du tabac augmente chez les femmes, l'incidence de ce type de cancer chez ces dernières augmente graduellement d'année en année. Il est distingué deux types de cancer du poumon : le Cancer Bronchique Non à Petites Cellules (CBNPC), le plus fréquent, et le cancer bronchique à petites cellules (CBPC). Historiquement, la prise en charge de ce cancer repose sur la chirurgie, l'immunochimiothérapie et la radiothérapie. Cependant, depuis les années 2000, une médecine dite de précision, qui tente de cibler plus spécifiquement les cellules cancéreuses a été développée en oncologie. Ces nouvelles thérapies sont l'immunothérapie et les Inhibiteurs de Protéines Kinases (IPKs).

Dans ce travail, nous avons étudié les IPKs indiqués dans les tumeurs des CBNPC présentant un récepteur Epidermal Growth Factor Receptor (EGFR) muté. Actuellement, cinq IPKs ont l'Autorisation de Mise sur le Marché (AMM) au sein de l'Union Européenne : l'erlotinib, le géfitinib, l'afatinib, le dacomitinib et l'osimertinib. La Partie III du présent manuscrit fait l'état des lieux des connaissances scientifiques actuelles sur ces médicaments. Dans cette partie sont aussi présentés les Effets Indésirables (EIs) rapportés dans les Essais Cliniques (ECs) et dans la base mondiale de pharmacovigilance VigiBase®, pour ces cinq médicaments.

Puis, nous avons évalué le potentiel impact d'une interaction pharmacologique entre les Inhibiteurs de Pompe à Proton (IPPs) et ces IPKs d'intérêt. Certaines études réalisées en vie réelle de soins ont mis en évidence une interaction résultant en une diminution de l'efficacité des IPKs quand ils sont associés avec les IPPs. Les IPPs en bloquant la pompe à proton au niveau de l'estomac pourraient diminuer l'absorption des IPKs et de ce fait leur efficacité. La prévalence de l'exposition aux IPPs des patients atteints de cancer et pris en charge par des IPKs serait supérieure à 20 %. Ce type d'interaction a été mis en évidence dans quelques études pour l'erlotinib, le géfitinib et l'afatinib mais pas pour l'osimertinib. Dans ce travail, nous présentons les résultats d'une étude conduite à partir des données du Système National des Données de Santé (SNDS), qui a pour objectif d'évaluer l'impact de la prise concomitante d'IPKs (erlotinib, géfitinib, afatinib et osimertinib) et d'IPPs sur la survie globale des patients (partie V).

PARTIE 1 : Les inhibiteurs de protéines kinases indiqués dans le cancer du poumon

A) Epidémiologie du cancer du poumon

En France, le cancer du poumon est le quatrième cancer le plus fréquent et la première cause de décès par cancer. L'incidence annuelle est d'environ 49 000 nouveaux cas et nous comptabilisons 29 000 décès. La survie à 5 ans, après le diagnostic de ce cancer, est de 14 % (13 % chez les hommes et 18 % chez les femmes) [1].

Ce type de cancer est à prédominance masculine [2]. Chez les hommes, c'est le deuxième cancer le plus fréquent après celui de la prostate et avant celui du colon. Chez les femmes, c'est le troisième cancer le plus fréquent après celui du colon et du sein. Depuis les années 1960, la prévalence du tabagisme a augmenté chez les femmes, conduisant à une augmentation du nombre de cancer du poumon dépisté chez les femmes. L'âge moyen de diagnostic de ce type de cancer est de 66 ans [1].

B) Facteurs de risque

Le tabagisme est le principal facteur de risque identifié. Il est directement lié à la survenue de 90 % des cancers du poumon chez les femmes et 79 % chez les hommes [3]. Le risque de survenue d'un cancer du poumon est aussi augmenté chez les personnes exposées à un tabagisme passif. Le tabagisme passif causerait 16 % des cancers bronchiques pulmonaires chez les patients non-fumeurs [4].

Une exposition à l'amiante, au radon, à l'arsenic, au chrome, au cobalt, aux produits issus du charbon, aux carburants, aux microparticules, aux poêles à bois ou au chlorure de vinyle constitue aussi un facteur de risque de survenue de ce type de cancer [1,5]. Enfin, l'exposition aux radiations ionisantes est aussi un facteur de risque [6].

Certaines pathologies pulmonaires chroniques sont également reconnues comme pouvant augmenter le risque de cancer du poumon : la bronchopneumopathie obstructive chronique, la fibrose pulmonaire idiopathique ou encore la tuberculose. De même, les patients avec une

tumeur bénigne pré existante située au poumon ont un risque plus élevé de développer ce type de cancer [7-9].

C) Présentation clinique

Environ 90 % des cancers du poumon sont diagnostiqués chez des patients symptomatiques [10]. Les patients peuvent consulter pour des symptômes non spécifiques comme une fatigue, une anorexie ou des signes liés à la tumeur primaire ou à son extension au niveau intra ou extra thoracique [11].

Les symptômes les plus couramment associés à la tumeur primaire sont une gêne thoracique, une dyspnée, une toux ou une hémoptysie.

Cependant, 40 % des patients peuvent avoir des symptômes résultant d'une atteinte intrathoracique comme une altération de la voix due à une paralysie du nerf laryngé, une élévation de l'hémidiaphragme ou encore un épanchement pleural [11].

Ensuite, près d'un tiers des patients vont avoir des symptômes liés à l'extension extra-thoracique de la tumeur. Les principaux sites métastatiques sont les os, le foie, les glandes surrénales, les ganglions lymphatiques, le cerveau et la moelle épinière [11].

Enfin, environ 10 % des patients atteints de ces types de cancers vont présenter des symptômes d'atteintes paranéoplasiques [11].

D) Classification des cancers du poumon

Les cancers du poumon se distinguent selon l'aspect microscopique des cellules cancéreuses.

1) Cancer bronchique à petites cellules

Ils représentent environ 15 % des cancers du poumon et ont une évolution rapide. Ce type de cancer présente un pronostic des plus défavorables parmi les types de cancer du poumon, car il est fréquemment diagnostiqué à un stade très avancé. Il se caractérise en général par une atteinte centrale du poumon et s'étend au niveau du médiastin. Il est associé à la survenue de métastases extra-thoraciques précoces ou de symptômes paranéoplasiques [12].

2) Cancer bronchique non à petites cellules

Ils représentent 85 % des cancers du poumon et ont une évolution plus lente et donc un pronostic plus favorable que l'entité à petites cellules [12]. Les trois principaux types de CBNPC sont les suivants : les adénocarcinomes, les carcinomes épidermoïdes et les carcinomes à grandes cellules indifférenciées. Les adénocarcinomes représentent 40 % de ce type de cancer, les carcinomes épidermoïdes 25 % et les carcinomes à grandes cellules indifférenciées 10 % [11].

Les adénocarcinomes pulmonaires sont caractérisés par des masses hétérogènes périphériques avec un potentiel élevé de formation précoce de métastases. Ils se développent souvent chez des patients présentant une maladie pulmonaire sous-jacente [11].

Les carcinomes épidermoïdes sont caractérisés par des masses endobronchiques centrées qui peuvent se manifester par une hémoptysie, une pneumopathie post-obstructive ou un collapsus du lobe pulmonaire. Contrairement aux adénocarcinomes et aux carcinomes à grandes cellules peu différenciées, ces types de cancers forment des métastases plus tardivement [11].

Les carcinomes à grandes cellules indifférenciées se caractérisent par de larges tumeurs situées en périphérie et par l'apparition de métastases précoces [11].

E) Outil de diagnostic

En cas de suspicion d'un cancer bronchique, un examen clinique est à réaliser. Le diagnostic de ce cancer va reposer sur des explorations d'imagerie avec une radiographie des poumons et / ou un scanner du thorax, de l'abdomen ou de l'ensemble du corps si la présence de métastases est soupçonnée [14].

Puis, une confirmation anatomo-pathologique est nécessaire. Une biopsie de la tumeur est indiquée pour caractériser son aspect histologique. Celle-ci pourra être réalisée par thoracotomie si le patient est éligible à une prise en charge par chirurgie. Sinon, elle devra être réalisée par la méthode la plus pratique et la moins invasive possible. Différentes méthodes de prélèvement peuvent être proposées comme la bronchoscopie souple, la ponction transpariétale sous guidage scanographique et / ou un prélèvement sur site métastatique (N+ / M+) [14].

Enfin, un bilan d'extension avec d'autres examens comme la Tomographie par Emission de Positon (TEP) ou la tomodensitométrie peut être indiquée [14].

Une évaluation de la fonction respiratoire des patients doit être réalisée. Il peut être estimé le Volume Expiratoire Maximal par Seconde (VEMS) et la Capacité de Diffusion du Monoxyde de Carbone (DLCO). Ces paramètres peuvent être de bons indicateurs de la morbidité et de la mortalité des patients bénéficiant d'une résection pulmonaire [15].

F) Stade du cancer

Il est défini des stades de ces cancers par une classification TNM qui prend en compte la taille de la tumeur primitive (T), la présence éventuelle de métastases ganglionnaires régionales (N) ou de métastases à distance (M) [16].

1) Cancer à petites cellules

Deux stades sont définis pour ce type de cancer. Le premier stade est caractérisé par une atteinte limitée à l'hémithorax. Le second est caractérisé par une maladie avec des métastases étendues au-delà de l'hémithorax ipsilatéral [11].

2) Cancer non à petites cellules

a) Local

Le stade Ia (T1N0M0) est caractérisé par une tumeur de taille inférieure ou égale à 3 cm, entourée par le poumon et la plèvre et qui n'envahit pas la bronche principale. Dans le stade Ib (T2N0M0), la tumeur mesure plus de 3 cm, peut envahir la plèvre et s'étendre dans la bronche principale mais reste à 2 cm ou plus de la carène. A ce stade, il peut y avoir une pneumopathie segmentaire ou une atélectasie. Enfin, le stade IIa (T1N1M0) sera caractérisé par une atteinte des ganglions péribronchiques ou hiliaires ipsilatéraux et des ganglions intrapulmonaires [11].

b) Localement avancé

Le stade IIb (T2N1M0 et T3N0M0) est caractérisé par une invasion de la paroi thoracique, du diaphragme, de la plèvre, de la bronche principale distale moins de 2 cm par rapport à la

carène. Au cours de ce stade, il peut y avoir une atélectasie distale de la carène ou de l'entièreté du poumon. Le stade IIIa (T1N2M0, T2N2M0, T3N1M0, et T3N2M0) est caractérisé par une atteinte des ganglions médiastinaux ou subcarinaux ipsilatéraux. Le stade IIIb (T4N1-3M0) est caractérisé par une invasion du médiastin, du cœur, des gros vaisseaux, de la trachée, de l'œsophage, du corps vertébral et de la carène. Les nodules tumoraux sont séparés. Un épanchement pleural malin est possible [11].

c) Avancé

Le stade IV (T1-4N1-3M1) de cette maladie est caractérisé par la présence de métastases à distance [11].

G) Stratégie thérapeutique

La stratégie thérapeutique de prise en charge des cancers bronchiques dépendra principalement du stade et des caractéristiques histologiques de la tumeur.

Le traitement de choix est la résection chirurgicale. Si elle ne peut être réalisée de manière complète, un traitement par radiothérapie et/ou chimiothérapie est proposé. La chimiothérapie adjuvante peut être proposée. Si le patient a un bon état général, une association de deux produits cytotoxiques sera proposée. Un médicament à base de platine tel que la carboplatine ou le cisplatine pourra être associé aux taxanes (paclitaxel ou docétaxel), aux anti-métabolites (gemcitabine ou permetrexed), ou aux vinca-alcaloides (vinblastine) [17-21].

Une immunothérapie peut être proposée comme les inhibiteurs de Programmed Death-Ligant 1 (PD-L1) (atezoluzumab, durvalumab), de Programmed Death 1 (PD1) (nivolumab, pembrolizumab) du Vascular Endothelial Growth Factor (VEGF) (bévacizumab) ou du Cytotoxic T-Lymphocyte-Associated protein 4 (CTLA-4) (ipilimumab) dans le CBNPC [22, 23].

Depuis ces 20 dernières années, différents IPKs peuvent être indiqués pour le traitement du CBNPC [24].

H) Les inhibiteurs de protéines kinases

1) Intérêt des inhibiteurs de protéines kinases

Dans la littérature, il a été mis en évidence une amélioration de la survie globale et de la survie sans progression des patients atteints d'un CBNPC pris en charge avec des IPKs par rapport à la chimiothérapie. Par exemple, un EC a mis en évidence une amélioration de la survie sans progression des patients exposés à l'association gemcitabine-erlotinib en comparaison à la gemcitabine seule [25] (figure 1).

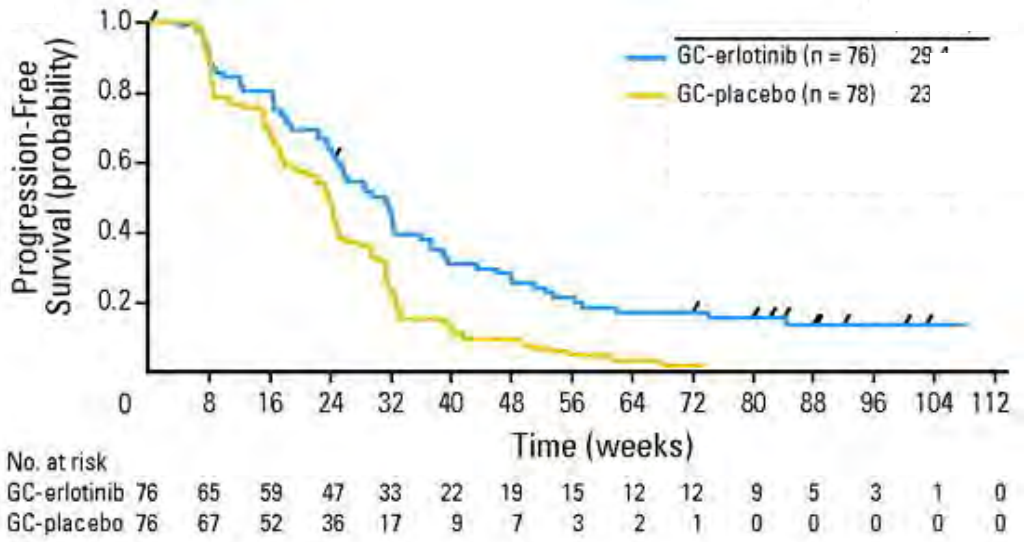

Figure 1 : comparaison des courbes de survie sans progression des patients atteints d'un CBNPC pris en charge par gemcitabine associée à de l'erlotinib vs gemcitabine seule [25].

Cette amélioration de la survie sans progression a aussi été mise en évidence plus récemment chez des patients exposés à de l'osimertinib par rapport à l'association composée de sels de platine et de permetrexed (figure 2) chez des patients atteints d'un CBNPC [26].

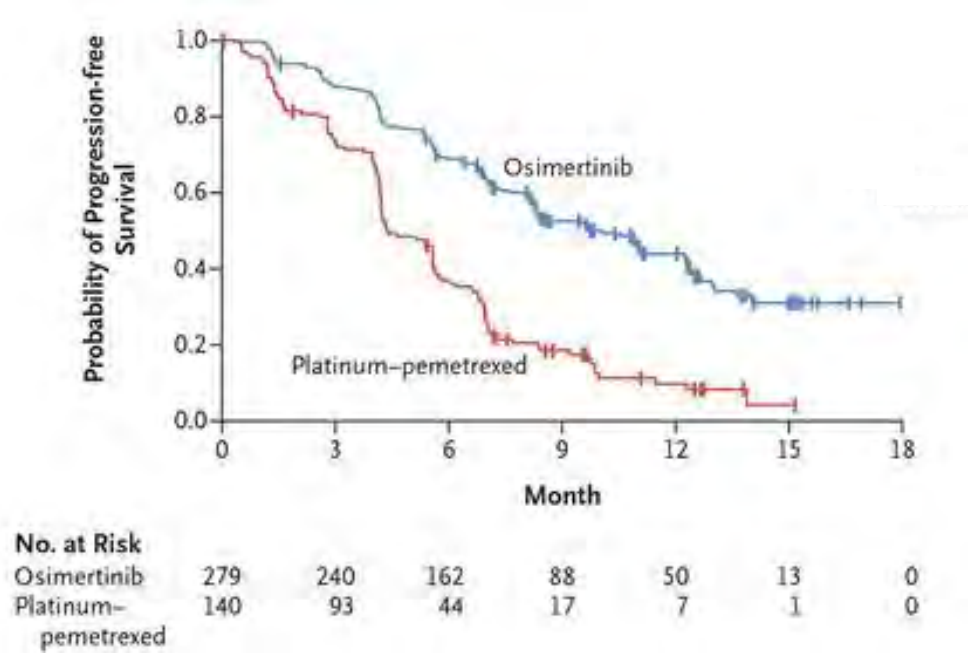

Figure 2 : comparaison des courbes de survie sans progression des patients atteints d'un CBNPC pris en charge par osimertinib vs l'association entre les sels de platine et le permetrexed [26].

2) Mécanismes d'action des inhibiteurs de protéines kinases

Chez l'homme, plus de 500 kinases ont été identifiées. L'ensemble des kinases identifiées peuvent être représentées sous la forme d'un kinome (figure 3) [27]. Le rôle principal des kinases est de permettre la transduction intracellulaire des signaux notamment pour la régulation des cycles cellulaire. Dans certaines pathologies oncologiques et de rhumatologie, le fonctionnement de ces kinases peut être altéré [27].

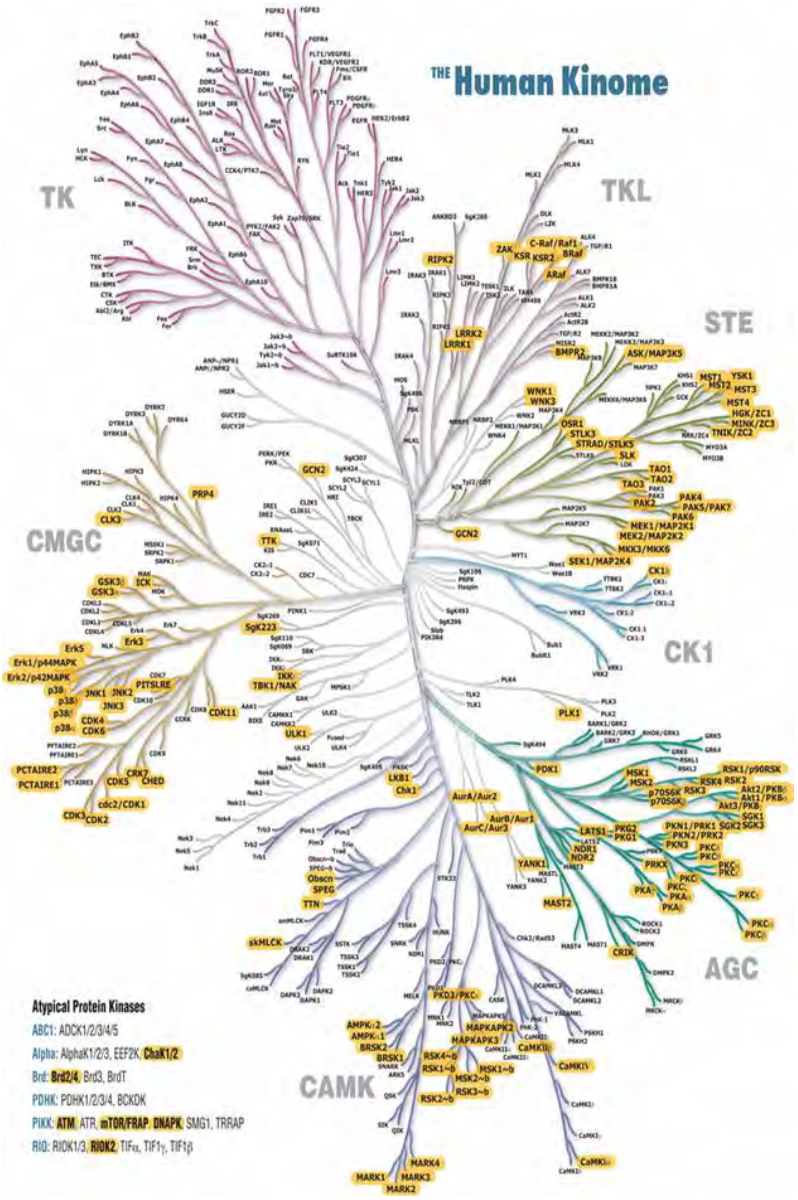

Figure 3 : représentation du kinome humain [27].

Les protéines kinases vont phosphoryler une enzyme cible très souvent elle-même kinase entrainant son inhibition ou son activation. Les kinases sont classées en fonction de l'acide aminé (sérine, thréonine ou tyrosine) portant une fonction alcool qui est le lieu de la fixation du groupement phosphate. L'action de l'IPK peut être réversible ou irréversible et sur ou à distance du site catalytique de l'Adénosine TriPhosphate (ATP) [27].

3) Différents types de protéines kinases indiqués pour le cancer bronchique non à petites cellules

Les principales cibles moléculaires identifiées pour la prise en charge du CBNPC sont les suivantes : EGFR, Activin receptor-Like Kinase (ALK), Mitogen Activated Protein Kinase Kinase (MEK) et BRAF. En cas de mutation du récepteur EGFR, une prise en charge par l'erlotinib, le géfitinib, l'afatinib, le dacomitinib et l'osimertinib peut être indiquée. En cas de mutation des récepteurs ALK, il peut être proposé des inhibiteurs de ces récepteurs comme le lorlatinib, le brigatinib, le ceritinib, le crizotinib et l'alectinib. Des inhibiteurs des récepteurs MEK-1 et MEK-2 ou de BRAF (tramétinib ou dabrafénib) peuvent être indiqués [28, 29].

PARTIE 2 : Revue de la littérature sur les inhibiteurs de protéines kinases ciblant l'epidermal growth factor receptor muté

L'erlotinib, le géfitinib, l'afatinib, le dacomitinib et l'osimertinib sont des IPKs ciblant le récepteur EGFR muté dans le CBNPC, ayant eu une AMM par la Food and Drug Administration (FDA) puis par l'European Medicine Agency (EMA). L'erlotinib et le géfitinib appartiennent à la première génération de ces médicaments. La seconde génération regroupe l'afatinib et le dacomitinib. Enfin, l'osimertinib correspond à la troisième génération de cette classe médicamenteuse. Ces médicaments sont indiqués pour la prise en charge du CBNPC localement avancé ou métastatique avec une mutation activatrice sur le récepteur EGFR.

L'article présenté ci-après a été rédigé afin de regrouper l'ensemble des informations disponibles à ce jour sur ces médicaments. Des notions telles que la pharmacodynamie, la pharmacocinétique, les mécanismes de résistance, les essais cliniques ou encore les effets indésirables, seront abordées en utilisant la base de données bibliographiques PubMed ainsi que la base mondiale de pharmacovigilance VigiBase®.

Cet article a été soumis dans le journal « Thérapie » le 9 juillet 2023.

Therapies

Protein kinase inhibitors indicated for lung cancer: pharmacodynamics, pharmacokinetics, adverse drug reactions and evaluation in clinical trials

--Projet de manuscrit--

Numéro du manuscrit:	
Type d'article:	Article original / Original Article
Second titre complet:	
Mots-clés:	lung cancer; EGFR inhibitor; protein kinase inhibitor; clinical trials; adverse event; adverse drug reaction
Mots-clés secondaires:	
Auteur correspondant:	Fabien DESPAS TOULOUSE, FRANCE
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	Julien MAZIERES
	Fabien DESPAS
Résumé:	Objective This review summarises the information available to date on the first anti-EGFRs granted market authorisation: erlotinib TARCEVA®, gefitinib IRESSA®, afatinib GIOTRIF®, dacomitinib VIZIMPRO® and osimertinib TAGRISSO®. Methods A literature search was conducted in the PubMed database including studies published in English using the terms gefitinib, erlotinib, afatinib, osimertinib and dacomitinib. Furthermore, bibliographies of selected references were also studied for relevant articles. Clinical trial (CT) data were extracted from clinicaltrials.gov (ongoing trials, adverse events [AEs]). Assessment of AEs for these drugs was conducted using global pharmacovigilance data from VigiBase®. Results Erlotinib and gefitinib are first generation anti-EGFR drugs, able to bind competitively and reversibly to the ATP-binding site of the EGFR exon 19 and exon 21 mutations. Afatinib and dacomitinib are second generation anti-EGFRs able to bind covalently and irreversibly to the ATP site and inhibit EGFR and HER such as HER2 and HER4 enzyme activity. Osimertinib is a third generation PKI and overcomes the EGFR T790M gatekeeper mutation through covalent binding at the ATP site. Medical interactions with these drugs were reported, notably with cytochrome P450 inducers or inhibitors. The most reported AEs in CTs were cutaneous reactions and gastro-intestinal disorders. The occurrence of cutaneous reactions and severe diarrhoea are less reported with third generation than with first and second generation anti-EGFR drugs. These results are consistent with the results from the VigiBase® global pharmacovigilance database. Conclusion This review summarises current knowledge regarding five anti-EGFRs in the literature. The current aim of medical research is to develop other anti-EGFR drugs to overcome the resistance profiles reported for previous generations.

Résumé secondaire:	
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A) List of abbreviations

ABC: ATP-binding cassette
AE: Adverse event
ATP: Adenosine triphosphate
AUC: Area under the curve
ALK: Activin receptor-like kinase
BCRP: Breast cancer resistant protein
CL: Clearance
Cmax: Peak concentration
CYP: Cytochrome P450
EGFR: Epidermal growth factor receptor
EMA: European medicines agency
FDA: Food and drug administration
GABA: Gamma-aminobutyric acid
HER2: Human epidermal growth factor receptor 2
HER3: Human epidermal growth factor receptor 3
HER4: Human epidermal growth factor receptor 4
HGF: Hepatocyte growth factor
ILD: Interstitial lung disease
INR: International normalised ratio
JAK/STAT: Janus kinase/signal transducer and transcription activator
KRAS: Kirsten rat sarcoma viral oncogene homologue
MAPK: Mitogen-activated protein kinase
NSCLC: Non-small cell lung cancer
P-gp: P-glycoprotein
PI3K: Phosphatidylinositol 3-kinase
PKI: Protein kinase inhibitor
SOCs: System organ classes
T1/2: Half-life
Tmax: Time to peak drug concentration
UDP: Uridine diphosphate
UGT: UDP glucuronosyltransferase
USA: United States of America
VEGF: Vascular endothelial growth factor
Vz: Volume of distribution

B) Introduction

Lung cancer has been one of the most commonly diagnosed deadly cancers in the last several decades [1]. Approximatively 2.1 million lung cancers were diagnosed in 2018. The incidence of this disease is lower for women than men because the consumption of tobacco differs according to sex [1]. In 2018, this cancer was associated with 1.8 million deaths worldwide. There are two different types of lung cancer: NSCLC and small cell lung cancer which are reported in 85% and 15% of patients respectively [2]. In addition to tobacco consumption, other reported risk factors were asbestos, radon, arsenic, chromium, nickel and vinyl chloride exposure, and also particulate matter 2.5 (PM2.5) [3]. Different treatment types exist, including surgery, radiotherapy, immunotherapy and targeted therapy [4]. However, even though the drugs under discussion are preselected as targeted therapies, the mechanism of action of such drugs is not lung-tumour-specific. Therefore, in practice these drugs have a profile of sometimes complex AEs associated with their ability to bind to proteins of interest (On-target) and also to other proteins (Off-target) [5,6]. The current aim of medical research is to develop personalised medicine. In oncology, the objective is to bring to market target therapies to decrease the occurrence of AEs. Several PKIs have been developed. In the last twenty years, around 450 PKIs have been studied in clinical trials [7]. Various PKIs are indicated for the treatment of lung cancer and target ALK or EGFR receptors in particular. The physiological pathway that appears to be the most promising is EGFR inhibition [8]. Five EGFR receptor targeting PKIs (erlotinib, gefitinib, afatinib, dacomitinib and osimertinib) have received marketing authorisation from the EMA and the FDA [9,10]. Globally, the most frequent resistance mechanism with first generation PKIs is the onset of 790 mutation on exon 20 [11,12]. Therefore, a second generation was developed to target this mutation. However, during clinical trials, this generation of drugs was not fully active against these mutations. Therefore, a third generation was developed to overcome EGFR receptors with T790M mutation [13,14]. In clinical trials, these drugs are associated with better outcomes than standard therapy [15].

These drugs have been studied in various clinical trials and a number of studies have been published. Our aim in this review is to collate and summarise the information available on these five EGFR inhibitors.

C) Material and methods

A literature search was conducted in the PubMed database, for the years 1993-2021, on English language studies published that contain any of the following terms: erlotinib, gefitinib, afatinib, dacomitinib and osimertinib. The bibliography of the articles in question was also studied. The studies included in this review were limited to those providing the most recent available human data.

Clinical trials relative to the five PKIs of interest were identified from the ClinicalTrials website: www.clinicaltrials.gov. For each clinical trial, several data points were collected such as: clinical development phase, clinical trial status (active not yet recruiting, completed, recruiting, suspended, terminated or unknown), results availability, estimated number of enrolled patients and cancer location. We selected six clinical trials which compared the efficacy of PKIs and presented their results. We also examined AEs reported in these clinical trials with for all PKIs combined: afatinib, dacomitinib and osimertinib. We chose to identify AEs in ClinicalTrials because they are all referenced with a MedDRA classification. In our AE analysis, a distinction was made between severity levels. Serious AEs were events such as death, life-threatening events and/or events requiring patient hospitalisation or extension of current hospitalisation. AEs resulting in significant incapacity, a substantial interference with normal living, or those associated with a congenital malformation were also classed as serious. AEs not associated with death or that were not life–threatening or did not require hospitalisation were classed as serious AEs if the patient was at risk of or actually required surgical intervention to prevent one of the results listed above [16]. We listed the twenty most frequent non-serious and serious AEs identified in the six clinical trials selected. When presenting the AEs reported in the clinical trial, we added the patient number for whom an AE was reported in each drug arm. For the three drug arms, we calculated the proportion of patients for whom each AE was reported out of all patients receiving the drug (expressed as a percentage).

Then, we identified AEs reported in VigiBase®, which is the global pharmacovigilance database, of the five PKIs of interest in our study. This database contains data such as patient data (age, sex, and medical history), reporter, country, suspect and the use of concomitant drugs (name, dosage, drug start and stop dates) and AEs (description, severity). The ten most common SOCs were presented for each PKI.

D) Drug composition

The empirical formula of erlotinib is C22H23N3O4 and the molecular weight is 393.4. The chemical name is N-(3-ethylnylphenyl)-6,7-bis(2-methoxyethoxy) quinazolin-4-amine. Previous names were OSI-774 and CP-358774 [17].

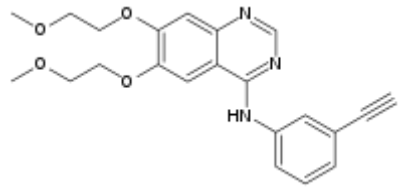
The empirical formula of gefitinib is C22H24ClFN4O3. The molecular weight is 446.9. The chemical name is N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine. Previous names were 184475-35-2, ZD1839 or 184475-35-2 [17].

The empirical formula of afatinib is C24H25ClFN5O3. The molecular weight is 485.9. The chemical name is N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide. Previous names were 439081-18-2, BIBW-2992 and 439081-18-2 [17].

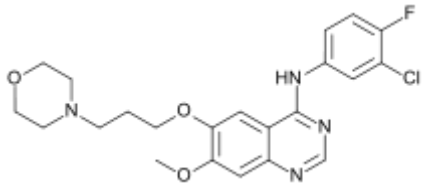
The empirical formula of dacomitinib is C24H25ClFN5O2. The molecular weight is 469.9. The chemical name is (E)-N-(4-((3-chloro-4-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)-4-(piperidin-1-yl)but-2-enamide. Previous names were 1110813-31-4 and PF-00299804 [17].

The empirical formula of osimertinib is C28H33N7O2. The molecular weight is 499.6. The chemical name is N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide. Its previous name was AZD-9291 [17].

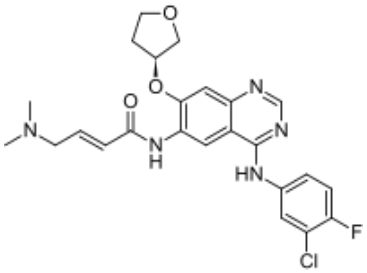
The formulae for these drugs are presented in figure 1.



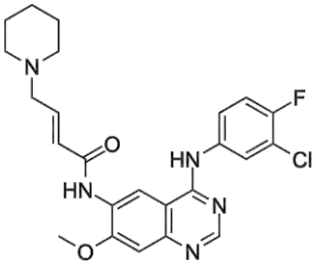
Erlotinib



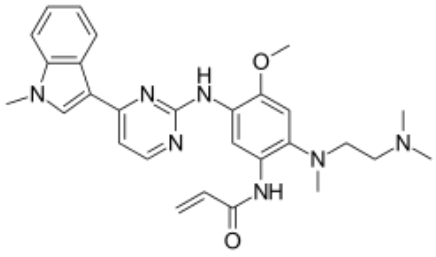
Gefitinib



Afatinib



Dacomitinib

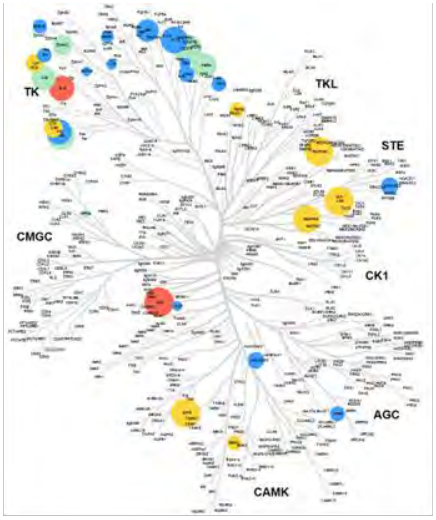


Osimertinib

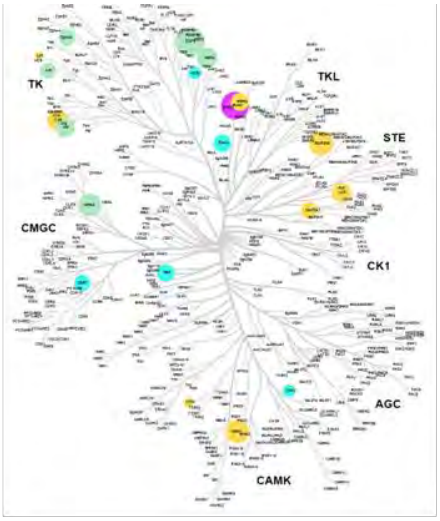
Figure 1: chemical structure depiction of erlotinib, gefitinib, afatinib, dacomitinib and osimertinib.

E) Pharmacological action

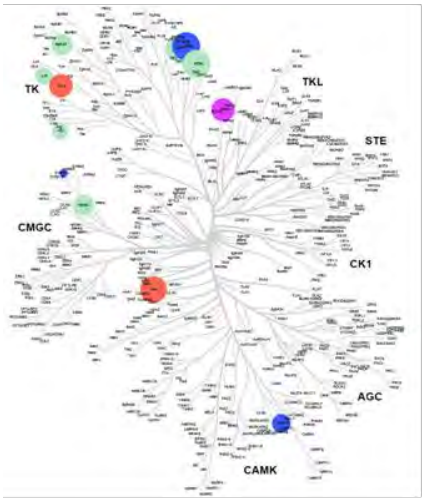
EGFR is in the ERBB group, which are tyrosine kinase receptors. In the ERBB group there are four receptor EGFR (ERBB1), HER2 (ERBB2), HER3 (ERBB3) and HER4 (ERBB4). They are present in different signalling pathways. They regulate cell growth, survival, adhesion, migration and differentiation. The physiological pathways of the mechanism of action are RASRAF, MAPK, PI3K/AKT and JAK/STAT [18]. Affinity profiles for protein kinases differ for erlotinib, gefitinib and afatinib (figure 2). Little data on protein kinases are available for dacomitinib and osimertinib.



Erlotinib



Gefitinib



Afatinib

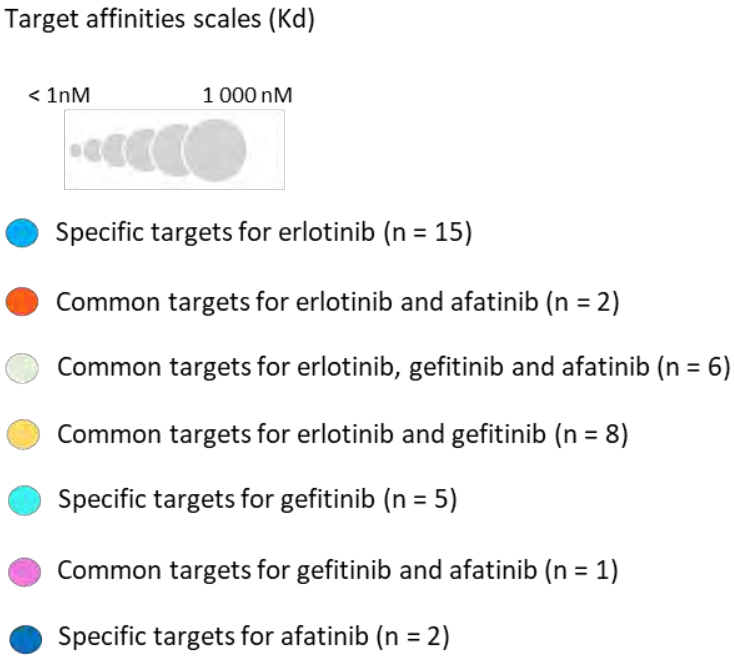


Figure 2: kinome phylogenetic dendrogram representing the target profiles of erlotinib, gefitinib and afatinib. Each circle for each protein kinase represents the interactions observed for the two kinase inhibitors based on IUPHAR data [119]. Only affinities less than 1000 nM are shown. Larger circles indicate higher affinity for the kinase. This kinase dendrogram were created from the interactive web application CORAL. For recent commercialised PKI as dacomitinib and osimertinib kinase affinity profile was few studied.

The proportion of EGFR mutation differs according to ethnicity. In the South-East Asian population, this mutation is present for 40-60% patients with NSCLC but concerns only 10 to 15% of Caucasian patients [11,19,20]. The mutation is located between the 18 to 21 exons which encode for the ATP binding pocket in the intracellular protein kinase domain [18]. The mutation/deletion is mainly located on exon 19 in 60% of patients [7]. It can also be located on exon 21 (30% of patients). This mutation permits the stimulation of tyrosine residues that give rise to a tumour profile that is dependent on EGFR activity for its development. EGFR inhibition is associated with tumour cell division decrease and death of cells overexpressing EGFR [18]. The overexpression of EGFR can also lead to the development of other types of cancer including head and neck, prostate, breast, ovarian and colon [21].

The anti-EGFR treatments can be categorised according to their generations. Erlotinib and gefitinib are first generation anti-EGFR drugs. The first PKI generation drugs bind competitively and reversibly to the ATP-binding site [22]. Afatinib and dacomitinib are second generation anti-EGFRs. This second PKI generation binds covalently and irreversibly to the ATP site and inhibits EGFR and HER such as HER2 and HER4 enzyme activity [23,24]. Osimertinib is a third generation PKI [18]. This generation overcomes EGFR with T790M mutation and inhibition is irreversible on the ATP site [13,14]. This generation is also 200-fold less potent in inhibiting wild type EGFR.

F) Resistance mechanism

1) First PKI generation: erlotinib and gefitinib

The first-generation PKIs are active on the EGFR exon 19 deletion and on EGFR L858R mutation. The sensitivity of first generation anti-EGFR treatments is around 70% for patients with EGFR mutation. However, within 1 or 2 years these patients will develop an acquired resistance [18,25].

There are three resistance mechanisms: target modification, signalling pathway bypass and histological modification of the tumour [13,26]. For target modification, two resistance mechanisms have been reported. These are defined as primary and secondary mutations.
Primary resistance is reported for 10-20% of NSCLC patients. Several primary resistance mechanisms have been reported such as T790 exon 20 mutation, HGF overexpression, T854A exon 21 mutation and D761Y and L747S exon 19 mutation. Other resistance mechanisms have been reported including de novo HER2 and MET amplification [11].

Overall, the most frequent resistance mechanism (49% of patients) is the onset of 790 mutation on exon 20 [11,12]. It is the substitution between threonine to methionine. The side chain becomes bulky. Thus, EGFR therapy cannot interact with the ATP site [22]. The second most frequent resistance mechanism is MET amplification. This concerns 20% of patients who receive a first generation PKI. A first PKI generation may be proposed in combination with a c-Met inhibitor [12].

2) Second generation PKIs: afatinib and dacomitinib

This generation was initially developed to inhibit EGFR with T790 or T854 mutations and HER2 amplification. However, during clinical studies, this type of drug was not fully active against these mutations. The majority of patients developed a resistance to this treatment, with around 50-60% presenting T790 mutation. Other mutations have been reported such as HER2 and MET amplification, and also phenotypic and genotypic lung cancer modifications [12,27]. C797S, TP53, PTEN and PKHD1 mutations have also been reported [28,29].

3) Third generation PKI: osimertinib

Osimertinib resistance can occur for example due to EGFR exon 20 C797S mutation. Other EGFR mutations can occur such as I796, L792, L718, L844, and G719. Resistance mechanisms can be of EGFR-independent such as MET amplification, HER2 amplification and PI3K activation. Other resistance processes involved in NSCLC have been reported: cell cycle alteration, oncogenic fusion and histologic and phenotypic modification of the cancer [13,30–33]. This type of mutation may be associated with the emergence of other mutations such as KRAS or Met amplification. For mutations such as L718Q, or L844V in the absence of T790M mutation, treatment with gefitinib and afatinib is possible [13].

G) Pharmacokinetics

Pharmacokinetic parameters differed for each of the PKIs of interest (table 1).

Table 1: pharmacokinetics characteristics of PKI such as erlotinib, gefitinib, afatinib, dacomitinib and osimertinib [9, 35, 51, 118].

Pharmacokinetic parameters and units	Erlotinib	Gefitinib	Afatinib	Dacomitinib	Osimertinib
Bioavailability	59	50	NA	80	70
AUC_t	27 (ng/h/mL)	258 (ng/h/mL)	631 (ng/h/mL)	1171 (ng/h/mL)	9 570 (nmol/h/L)
C_{max}	1 521 (ng/mL)	101 (ng/mL)	38.0 (ng/mL)	21.51 (ng/mL)	550.4 (nmol/L)
$T_{max\ (h)}$	4	4	3	8	4
$T1/2_{(h)}$	36	52	37	63	48.6
CL/F (L/H)	4.5	46	1070	27.06	17.7
V_z/F (L)	232	1 700	2 870	2 415	1 216
Protein binding (%)	95	90	95	98	95

1) Absorption

Erlotinib, gefitinib and osimertinib absolute bioavailability is estimated to be 59, 50 and 70 percent, respectively. For the PKIs of interest, Tmax is between 3 and 4 hours. However, Tmax for dacomitinib was estimated to be 8 hours. Cmax differed with each drug. For example, this parameter was estimated to be 1 521 ng/mL for erlotinib. However, for gefitinib it was 101 ng/mL [9]. The absolute bioavailability of dacomitinib is around 80%, ranging between 65% and 100% [34]. The absolute bioavailability of afatinib is unknown.

2) Distribution

The distribution volume differed according to the PKI. Afatinib has a high distribution volume of approximately 2 870 L. For gefitinib and osimertinib, the distribution volume is estimated to be around 1 216 and 1 700 L, respectively. Finally, for erlotinib the distribution volume is around 232 L. Dacomitinib distribution volume was estimated to be 3 310 L [35]. Protein binding was estimated to be between 90 and 95% for the PKIs of interest [9].

3) Elimination

Erlotinib is principally eliminated in feces (83%) and in low amounts in urine (8%) [36]. The elimination half-life for the drug is around 36 hours. The elimination half-life for gefitinib is 52 hours. This drug is mainly eliminated in feces and in low amounts in urine (7%) [37]. The elimination half-life for afatinib is estimated to be around 37 hours. The elimination half-life for osimertinib is estimated to be 48.6 hours and is eliminated in feces (68%) and in urine (14%) [38]. Dacomitinib is mainly eliminated in feces and a small percentage (5%) in urine [39]. The elimination half-life for dacomitinib is estimated to be 63 hours [40].

4) Variation factors

Erlotinib and afatinib absorption can be affected when administered with food. Food can delay gastric emptying and modify the bioavailability of erlotinib and osimertinib. These drugs can be administered one hour before meals or two hours after eating [9, 41].

The pharmacokinetics of gefitinib, dacomitinib and osimertinib are not affected when administered with food [9, 42].

The anti-EGFRs of interest are metabolised by CYP2D6 [43, 44]. As a result, metabolisation may be modified if the patient is a poor CYP2D6 metaboliser. The proportion of poor CYP2D6 metabolisers is around 5 to 10% in the Caucasian population and is a rarity for Asian people. For Sub-Saharan African and Afro-American patients, this proportion is variable. For CYP 2D6 intermediate metabolisers, the proportion is around 10 to 15% for Caucasians, over 50% for Asians and around 30% for Sub-Saharan African and African-American populations [45]. For CYP 2D6 ultra-rapid metabolisers, the proportion is around 6.4% for Caucasians, around 2% for Asians and less than 1% for Sub-Saharan African and African-American populations [46,47]. Other patients are considered extensive metabolisers.

The AUC of gefitinib was higher for poor versus extensive metabolisers (3060 vs 1430 ng. h/mL). However, dosage adjustment is not required in this case [48]. The AUC of gefitinib metabolites was higher for intermediate vs extensive metabolisers (1460 vs 12 523 ng. h/mL). However, this decreased AUC was not associated with any increases in adverse reactions [49]. The AUC of gefitinib was around 39% lower for ultra-rapid versus extensive metabolisers. However, the clinical consequence of this decrease is limited [50]. Similar pharmacokinetics parameters were reported for patients with different CYP2D6 metabolisation profiles for

dacomitinib. However, for its metabolite PF-05199265, the AUC and peak exposure were higher for extensive versus intermediate CYP2D6 metabolisers [51]. Few other studies have been conducted to assess the effect of differences in CYP2D6 metabolisation on the pharmacokinetic parameters of PKIs.

H) Drug interactions

Anti-EGFR PKIs can be affected by concomitant antacid administration, such as Proton Pump Inhibitors (PPI) and histamine H2-receptor antagonists [52]. This can affect the solubility of anti-EGFRs with a pKa value of less than 4-5. The concomitant administration of these drugs can lead to a decrease in anti-EGFR bioavailability [45]. This interaction was particularly demonstrated for erlotinib and gefitinib. In the case of concomitant administration with gefitinib, PPI and H2-receptor antagonists must be taken 12 and 6 hours respectively before or after PKI administration. For erlotinib, the use of a PPI should also be avoided. In the case of concomitant administration of an H2-receptor antagonist and a PKI, erlotinib must be taken at least 2 hours before or 6 hours after antacid drugs. Afatinib is soluble at a pH of between 1 and 7.5. As a result, no interaction between antacids is to be expected with this PKI [45,53]. Dacomitinib bioavailability is decreased by the concomitant administration of a PPI [42,54,55]. Therefore, the concomitant administration of dacomitinib and a PPI must be avoided. In the case of co-administration of an H2-receptor antagonist with a PKI, dacomitinib must be taken at least 2 hours before or 10 hours after antacids [34]. Finally, for osimertinib, several studies have reported an absence of any interaction with antacids [41,56].

Interactions between anti-EGFR drugs and other medications can be explained by inducer and inhibitor cytochrome metabolism (table 2). The cytochrome metabolisation profile varied with different anti-EGFRs [45,57,58].

Table 2: cytochrome involved in the pharmacological mechanism of anti-EGFR PKIs.

	3A4	3A5	2D6	1A1	1A2	1B1	2C8	2C9	2C19	2E1	May inhibit	May induce
Erlotinib	+++	+++	+	+	++	+	+	+	-	-	CYP3A4 CYP2C8 CYP1A1	CYP1A1 CYP1A2
Gefitinib	+++	++	+++	++	+	-	-	-	-	-	CYP2C19 CYP2D6	-
Afatinib	-	-	-	-	-	-	-	-	-	-	-	-
Dacomitinib	+	-	+++	-	-	-	-	+	-	-	CYP1A2 CYP2B6 CYP2C8 CYP2C9 CYP2C19 CYP3A4 CYP3A5	CYP1A2, CYP2B6 CYP3A4
Osimertinib	+++	+++	-	-	-	-	-	-	-	-	-	CYP3A4

Erlotinib metabolism is mainly mediated by CYP3A4 and 3A5. Thus, erlotinib metabolism can be increased by co-administering a CYP3A4 inducer. For example, erlotinib exposure was around 69% for rifampicin. Co-administration of ketoconazole and ciprofloxacin increase erlotinib metabolism by 86 and 39% respectively. If the co-administration of a potent CYP3A4 inhibitor is unavoidable and if AEs occur the erlotinib dosage can be decreased to 50 mg. Erlotinib also inhibits CYP3A4, CYP2C8 and CYP1A1. More cases of AEs were reported when erlotinib is co-administered with CYP3A4 and CYP2C8 substrates such as phenytoin and simvastatin [45,59–61].

Gefitinib is mainly metabolised by CYP3A4 and CYP2D6 [45] and less by CYP3A5, CYP1A1 and CYP1A2. However, it is metabolised more by CYP3A4 than by CYP2D6. Thus, gefitinib metabolisation is influenced by a CYP3A4 inducer or inhibitor. For example, the co-administration of itraconazole with this PKI is characterised by an increase in the AUC of around 78%. Also, gefitinib administration with rifampicin or phenytoin decrease the PKI AUC to 83% and 47% respectively. When gefitinib is administered with a CYP3A4 inducer the PKI dosage can be increased to 500 mg per day. The administration of a CYP2D6 inducer can also inhibit gefitinib metabolisation. However, this interaction was less studied. Finally, gefitinib can increase the exposure of drugs metabolised by CYP 2D6. For example, in the case of metoprolol and gefitinib co-administration, exposure is increased by around 35% [37,45,48].

Afatinib is metabolised less by cytochromes. Consequently, its exposure is not influenced by concomitant administration of cytochrome inhibiting and inducing drugs [45].

Dacomitinib is mainly metabolised by CYP 2D6. This drug is also less metabolised by other cytochromes such as CYP 3A4 and CYP 2C9. In vitro, dacomitinib is a minor inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5. It is also a minor CYP1A2, CYP2B6 and CYP3A4 inducer [34]. In the case of concomitant administration with dacomitinib, the AUC of a CYP 2D6 substrate may increase. For example, compared with dextromethorphan alone, the AUC of dextromethorphan co-administered with dacomitinib increased by around 955% [62]. Similarly, in the case of concomitant administration of dacomitinib and trazodone, exposure to both drugs increased [63].

Finally, osimertinib is mainly metabolised by CYP3A4 and CYP3A5 and may induce CYP3A4. In pharmacokinetic studies, no clinically significant interaction was demonstrated between osimertinib and itraconazole, a potent CYP3A4 inhibitor. However, osimertinib absorption at around 2 hours was higher and AUC PKI was increased. Finally, with the co-administration of rifampicin, a potent CYP3A4 inducer, the AUC of the PKI decreased by around 78%. The co-administration of a cytochrome inducer with osimertinib must be avoided if possible. If co-administration is unavoidable, osimertinib dosage should be increased to 160 mg per day, and a standard dosage (80 mg/day) may be prescribed only 3 weeks after the end of cytochrome inducer treatment [45].

Another interaction mechanism concerns UGT1A1 (Uridine-diphosphate (UDP)-glucuronosyltransferase). This catalyses glucuronic acid conjugation to endogenous and exogenous substances. UGT1A1 is responsible for bilirubin elimination and prevents its accumulation. The co-administration of a different UGT inhibitor can cause AEs such as hyperbilirubinemia and hepatotoxicity. Erlotinib is also a potent UGT1A1 inhibitor. Patients with low UGT1A1 expression can develop a high bilirubin serum concentration [45,64]. Gefitinib is a UGT inhibitor, particularly of UGT1A1, UGT1A7, UGT1A9 and UGT2B7. However, this drug is unlikely to cause clinically significant drug interactions. Dacomitinib is also a minor inhibitor of UGT1A4, UGT1A6, UGT1A9, UGT2B7 and UGT2B15 [34].

Drug interactions can occur with PKI transport in blood circulation. Different transporters participate in PKI metabolism, notably efflux transporters such as P-gp and ABC sub-family B. Erlotinib is a potent inhibitor of BCRP and P-gp. Interaction can occur with co-administration of a P-gp inhibitor such as cyclosporine or verapamil. Gefitinib inhibits P-gp activity. As a result, gefitinib can inhibit transporter activity and cause clinically significant drug interactions. Afatinib

is a substrate and a P-gp inhibitor. As a result, afatinib metabolism can increase with the co-administration of a P-gp inhibitor such as ritonavir. Conversely, in the case of co-administration with a potent P-gp inducer, afatinib exposure can decrease. For example, rifampicin co-administration decreases afatinib exposure by around 34%. With P-gp inhibitor co-administration, afatinib dosage can be reduced by 10 mg. If afatinib is co-administered with a P-gp inducer, its dosage can be increased by 10 mg. Afatinib is also a substrate and a BCRP inhibitor. It can increase the bioavailability of BCRP substrates such as rosuvastatin and sulfasalazine [45]. Dacomitinib is also a minor P-gp and BCRP inhibitor [34]. Finally, osimertinib is a potent BCRP inhibitor and can increase exposure to its substrates. For example, it increases the AUC of rosuvastatin by around 35% [45].

Other significant drug interactions have been reported. For example, an increase in INR is reported with erlotinib and gefitinib when co-administered with warfarin [65–67].

I) Dosage adjustment and methods of administration

One of the advantages of these anti EGFR PKIs is that they can be orally administered [68].

The recommended daily dose of erlotinib is 150 mg. No change in dose is recommended in the event of mild or moderate renal or hepatic failure. However, erlotinib prescription is not recommended for patients with severe renal or hepatic failure [68].

The recommended daily dosage for gefitinib is 250 mg. No change in dose is recommended for mild or moderate renal or hepatic failure [69].

The recommended daily dose of afatinib is 40 mg. An increase of this dose to 50 mg is possible if the patient does not present any AEs. No change in dose is recommended for patients with renal failure. Again, no change in dose is recommended in the case of mild or moderate hepatic failure. However, afatinib prescription is not recommended in the case of severe hepatic failure. Nevertheless, under FDA recommendations, afatinib may be prescribed for patients with severe hepatic failure [70,71].

The recommended daily dose of dacomitinib is 45 mg. Dacomitinib can be administered to patients with mild and moderate renal or hepatic failure. For patients with severe hepatic failure a dose of 30 mg per day is recommended [34,72]. No change in dose is recommended for

patients with mild or moderate renal failure. Limited data are available for patients with severe renal failure [34].

The daily dose of osimertinib is 80 mg. No change in dose is recommended for patients with renal failure. Also, no change in dose is recommended for patients with mild or moderate hepatic failure. The administration of osimertinib is not recommended in cases of severe hepatic failure. However, in the literature, a minimal correlation has been suggested between renal osimertinib clearance and renal function [73].

Several cases reported the safe administration of the PKIs of interest for patients undergoing dialysis [74–77].

Anti-EGFR PKI efficacy can be decreased by being a smoker and can cause treatment resistance. Smoking increases oxidative stress with an imbalance in reactive oxygen species and is linked to abnormal EGFR activation. Cigarette smoke can also induce CYP1A1 and 1A2 and increase erlotinib catabolism and clearance. For smokers, erlotinib clearance can increase by around 24% in comparison with non-smokers. Moreover, smokers required a dose of 300 mg to obtain the same area under the curve value obtained with the recommended dose administered to non-smokers. According to the FDA, erlotinib dosage should be increased to 300 mg per day. This interaction was less studied for gefitinib, afatinib dacomitinib and osimertinib [78–80].

J) Clinical development of anti-EGFR treatment

Information concerning ongoing clinical trials with the PKIs of interest are summarised in the tables below (tables 3, 4, 5, 6, 7).

The different results of clinical trials evaluating erlotinib, gefitinib, afatinib, dacomitinib and osimertinib are presented in Table 8. Clinical trials are referenced with varying degrees of progress (extracted in January 2023 from clinicaltrials.gov).

In this review, the main clinical trials comparing these drugs are presented. The LUX-Lung 7 (phase 2) and LUX-lung 8 (phase 3) clinical trials compared the efficacy of afatinib with that of erlotinib and gefitinib. The AURA 2 clinical trial (phase 2) presented the efficacy of osimertinib following treatment with erlotinib and gefitinib. The progression free survival rate increased with afatinib in comparison with erlotinib. Also, overall survival significantly increased with

afatinib compared with first-generation anti-EGFRs. In the case of dacomitinib, the overall survival rate increased significantly compared with erlotinib in recent phase III clinical trials. However, the increase in the overall survival rate was not significant when dacomitinib was compared with erlotinib. In clinical trials, the overall survival rate also increased with osimertinib. In the AURA 2 clinical trial, following progression with first line anti-EGFR treatment, the median progression survival with osimertinib was 8.6 months CI95% [8.28; 9.72]. Recently, a phase III study demonstrated an increase in the overall survival rate compared with first generation anti-EGFR PKIs [81]. Several other indications have been studied in the literature for this anti-EGFR PKI of interest such as pancreatic, breast, head and neck cancer. However, only erlotinib is indicated for other cancers.

Table 3: all ongoing clinical trials on clinicaltrials.gov for erlotinib. Information in table is presented as: number of clinical trials and expected number of patients included.

Phase (number of clinical trials, expected number of patients included)	Status (number of clinical trials, expected number of patients included)	Study results (number of clinical trials, expected number of patients included)	Condition (number of clinical trials, expected number of patients included)
Early phase 1 (3, 52) **Phase 1** (170, 9 138) **Phase 1 / 2** (79, 4 593) **Phase 2** (444, 38 711) **Phase 2/3** (11, 1 793) **Phase 3** (89, 42 891) **Phase 4** (20, 8 774) **Unknown** (101, 35 287)	**Not recruiting** (4, 648) **Recruiting** (31, 19 679) **Approved for marketing.** (1, 0) **Active, not recruiting.** (37, 8 892) **Terminated** (132, 7 237) **Completed** (552, 84 236) **Suspended** (4, 644) **Unknown status** (125, 19 903) **Withdrawn** (30, 0) **Temporarily not available** (1, 0)	**Results** (344, 58 660) **No results** (573, 82 579)	**Lung cancer** (536, 103 290) **Renal cancer** (19, 1199) **Head and neck cancer** (59, 2974) **Oesophageal cancer** (15, 768) **Brain cancer** (50, 5 155) **Hepatic cancer** (19, 1497) **Gastrointestinal cancer** (147, 14 274) **Haematological cancer** (9, 904) **Skin Cell Cancer** (2, 10) **Breast cancer** (30, 1686) **Thyroid neoplasm** (1, 13) **Pancreatic neoplasm** (89, 9003) **Urogenital cancer** (41, 2 984)

Table 4: all ongoing clinical trials on clinicaltrials.gov for gefitinib. Information in table is presented as: number of clinical trials and expected number of patients included.

Phase (number of clinical trials, expected number of patients included)	Status (number of clinical trials, expected number of patients included)	Study results (number of clinical trials, expected number of patients included)	Condition (number of clinical trials, expected number of patients included)
Phase 1 (46, 1 769) **Phase 1 / 2** (36, 2 308) **Phase 2** (229, 16 449) **Phase 2/3** (10, 1 922) **Phase 3** (62, 22 750) **Phase 4** (11, 2 827) **Unknown** (54, 27 903)	**Not recruiting** (5, 1 706) **Recruiting** (15, 5 684) **Approved for marketing.** (3, 0) **Active, not recruiting** (16, 3 905) **Terminated** (41, 3 574) **Completed** (246, 42 774) **Suspended** (2, 122) **Unknown status** (118, 17 885) **Withdrawn** (12, 278)	**Results** (73, 16 917) **No results** (385, 59 011)	**Lung cancer** (297, 58 810) **Healthy volunteers** (3, 160) **Renal cancer** (6, 144) **Head and neck cancer** (44, 3194) **Oesophageal cancer** (12, 882) **Brain cancer** (18, 2130) **Haematological cancer** (2, 74) **Gastrointestinal cancer** (37, 2088) **Hepatic cancer** (3, 129) **Skin Cell Cancer** (3, 79) **Breast cancer** (26, 2082) **Thyroid neoplasm** (2, 67) **Pancreatic neoplasm** (3, 212) **Urogenital cancer** (25, 1168)

Table 5: all ongoing clinical trials on clinicaltrials.gov for afatinib. Information in the table is presented as: number of clinical trials and expected number of patients included.

Phase (number of clinical trials, expected number of patients included)	Status (number of clinical trials, expected number of patients included)	Study results (number of clinical trials, expected number of patients included)	Condition (number of clinical trials, expected number of patients included)
Early phase 1 (1, 10) **Phase 1** (50, 1 712) **Phase 1 / 2** (10, 2 681) **Phase 2** (101, 18 026) **Phase 2/3** (1, 174) **Phase 3** (17, 6 780) **Phase 4** (7, 277) **Unknown** (39, 15 496)	**Not recruiting** (10, 288) **Recruiting** (31, 12 486) **Enrolling by invitation** (1, 48) **Approved for marketing** (3, 0) **Active, not recruiting** (15, 9 740) **Terminated** (22, 1 519) **Completed** (109, 13 992) **Suspended** (1, 38) **Unknown status** (27, 7 045) **Withdrawn** (6, 0) **No longer available** (1, 0)	**Results** (76, 12 271) **No results** (150, 32 885)	**Lung cancer** (112, 29 417) **Healthy volunteers** (7, 181) **Renal cancer** (1, 6452) **Head and neck cancer** (26, 9066) **Oesophageal cancer** (9, 6753) **Brain cancer** (5, 264) **Haematological cancer** (4, 10 773) **Gastrointestinal cancer** (20, 7981) **Hepatic cancer** (1, 6452) **Skin Cell Cancer** (2, 6477) **Breast cancer** (18, 7556) **Thyroid neoplasm** (1, 6452) **Pancreatic neoplasm** (7, 7806) **Urogenital cancer** (6, 6795)

Table 6: all ongoing clinical trials on clinicaltrials.gov for dacomitinib. Information in the table is presented as: number of clinical trials and expected number of patients included.

Phase (number of clinical trials, expected number of patients included)	Status (number of clinical trials, expected number of patients included)	Study results (number of clinical trials, expected number of patients included)	Condition (number of clinical trials, expected number of patients included)
Early phase 1 (1, 17) **Phase 1** (21, 684) **Phase 1 / 2** (3, 188) **Phase 2** (26, 3 993) **Phase 3** (3, 2 050) **Phase 4** (1, 101) **Unknown** (6, 4 560)	**Not recruiting** (3, 960) **Recruiting** (10, 4390) **Enrolling by invitation** (1, 1200) **Active, not recruiting** (3, 1045) **Terminated** (4, 51) **Completed** (36, 3790) **Unknown status** (4, 157)	**Results** (18, 3101) **No results** (43, 8492)	**Lung cancer** (35, 8323) **Healthy volunteers** (9, 159) **Severe hepatic impairment** (2, 41) **Head and neck cancer** (9, 380) **Brain cancer** (4, 133) **Haematological cancer** (1, 40) **Gastrointestinal cancer** (6, 230) **Skin Squamous Cell Cancer** (1, 43) **Breast cancer** (2, 150) **Urogenital cancer** (1, 32) **Oesophageal cancer** (3, 127) **Pancreatic neoplasm** (1, 40)

Table 7: all ongoing clinical trials on clinicaltrials.gov for osimertinib. Information in the table is presented as: number of clinical trials and expected number of patients included.

Phase (number of clinical trials, expected number of patients included)	Status (number of clinical trials, expected number of patients included)	Study results (number of clinical trials, expected number of patients included)	Condition (number of clinical trials, expected number of patients included)
Early phase 1 (3, 40) **Phase 1** (48, 3 374) **Phase 1 / 2** (27, 2 847) **Phase 2** (88, 14 725) **Phase 2/3** (2, 197) **Phase 3** (29, 13 625) **Phase 4** (5, 1160) **Unknown** (51, 21 449)	**Not recruiting** (25, 2 359) **Recruiting** (92, 17 995) **Enrolling by invitation** (3, 380) **Active, not recruiting** (52, 17 811) **Terminated** (5, 538) **Completed** (44, 10 330) **Suspended** (1, 58) **Unknown status** (27, 7 948) **Withdrawn** (3, 0) **No longer available** (1, 0)	**Results** (23, 7090) **No results** (230, 50 327)	**Lung cancer** (236, 52 071) **Healthy volunteers** (4, 194) **Renal cancer** (2, 6482) **Head and neck cancer** (3, 6945) **Oesophageal cancer** (3, 6945) **Brain cancer** (18, 1301) **Haematological cancer** (1, 6452) **Gastrointestinal cancer** (2, 6832) **Hepatic cancer** (1, 6452) **Skin Cell Cancer** (1, 6452) **Breast cancer** (1, 6452) **Thyroid neoplasm** (1, 6452) **Pancreatic neoplasm** (2, 6565) **Urogenital cancer** (2, 6482)

Table 8: outcomes in six principal clinical trials with the PKIs of interest.

Name of clinical trial	LUX-Lung 8 (NCT01523587)	LUX-Lung 7 (NCT01466660)	AURA2 (NCT02094261)	ARCHER 1050 (NCT01774721)	ARCHER 1009 (NCT01360554)
Design	Phase 3 trial Open label Randomly assigned with a 1:1 ratio	Phase 2 trial Open label Randomly assigned with a 1:1 ratio	Phase 2 trial Open label Single arm study	Phase 3 trial Open label Randomly assigned with a 1:1 ratio	Phase 3 trial Double blind Randomly assigned with a 1:1 ratio
Pathology	NSCLC	Lung adenocarcinoma	NSCLC patients failing with Previous EGFR PKI Therapy	Advanced NSCLC	NSCLC
Population concerned	18 years of age or older	18 years of age or older	Between 18 and 130 years old	Between 18 and 99 years old	18 years of age or older
Dose	40 mg once daily for the first 28-day, then 50 mg	40 mg once daily for the first 28-day, then 50 mg	80 mg once daily	48 mg once daily	45 mg once daily
Treatment	Afatinib vs Erlotinib	Afatinib vs Gefitinib	Osimertinib	Dacomitinib vs Gefitinib	Dacomitinib vs Erlotinib
Number of patients	398 vs 397	160 vs 159	210	227 vs 225	439 vs 439
Progression free survival	2.6 versus 1.9 months (HR: 0.8; 95% CI: [0.3; 1.0], p = 0.01)	12.8 versus 11.2 months (HR: 0.8; 95% CI: [0.7; 1.0], p = 0.09)	8.6 months, 95% CI [8.3; 9.7]	14.7 versus 9.2 months (HR: 0.6; 95% CI: [0.5; 0.7], p < 0.0001)	2.6 versus 2.5 months (HR: 0.9; 95% CI: [0.8; 1.1], p = 0.20)
Overall survival	7.82 versus 6.77 months (HR: 0.8; 95% CI: [0.7; 0.97], p = 0.02)	27.9 versus 24.5 months (HR: 0.9; 95% CI: [0.7; 1.1], p = 0.02)	NA	NA	7.9 versus 8.3 months (HR: 1.0; 95% CI: [0.9; 1.2], p = 0.64)
Number of participants with objective response	22 versus 11 (HR: 2.1; 95% CI: [1.0; 4.3], p = 0.0551)	79.4% versus 74.8% (HR: 1.3; 95% CI: [0.8; 2.2], p = 0.32)	70.9%, CI95% [64.0; 77.1]	74.9% versus 71.6 (p = 0.19)	NA

K) Principal AEs

In the clinical trials under study, 831 patients were included in the erlotinib arm, 363 in the gefitinib arm, 552 in the afatinib arm, 663 in the dacomitinib arm and 210 in the osimertinib arm.

Only serious AEs with a frequency greater than 1% (all trials combined) are presented in table 9.

Table 10 sets out the overall AEs (serious and non-serious) reported in the three clinical trials on clinicaltrials.gov. Only AEs with a frequency of more than 10% (all trials combined) are presented.

Table 9: serious adverse events for erlotinib, gefitinib, afatinib, dacomitinib and osimertinib in five clinical trials.

	TOTAL erlotinib N = 831 patients (%)	TOTAL Gefitinib N = 383 patients (%)	TOTAL afatinib N = 552 patients (%)	TOTAL dacomitinib N = 663 patients (%)	TOTAL osimertinib N = 210 patients (%)
Disease progression	48 (5.8)	11 (2.9)	0 (0.0)	61 (9.2)	0 (0.0)
Pneumonia	31 (3.7)	7 (1.8)	34 (6.2)	17 (2.6)	4 (1.9)
Malignant neoplasm progression	17 (2.1)	2 (0,5)	30 (5.4)	0 (0.0)	0 (0.0)
Diarrhoea	14 (1.7)	2 (0.5)	29 (5.3)	25 (3.8)	0 (0.0)
Dyspnoea	38 (4.6)	9 (2.4)	14 (2.5)	9 (1.4)	1 (0.5)
Pulmonary embolism	8 (1.0)	5 (1.3)	16 (2.9)	5 (0.8)	8 (3.8)
Dehydration	10 (1.2)	1 (0.3)	15 (2.7)	14 (2.1)	1 (0.5)
General physical health deterioration	16 (1.9)	4 (1.0)	12 (2.2)	4 (0.6)	0 (0.0)
Pleural effusion	8 (1.0)	4 (1.0)	12 (2.2)	7 (1.1)	0 (0.0)
Respiratory failure	17 (2.1)	1 (0.3)	3 (0.5)	6 (0.9)	0 (0.0)
Asthenia	5 (0.6)	1 (0.3)	10 (1.8)	3 (0.5)	0 (0.0)
Sepsis	5 (0.6)	4 (1.0)	10 (1.8)	2 (0.3)	1 (0.5)
Renal failure acute	1 (0.1)	0 (0.0)	9 (1.6)	0 (0.0)	0 (0.0)
Dizziness	5 (0.6)	6 (1.6)	3 (0.5)	1 (0.2)	0 (0.0)
Haemoptysis	11 (1.3)	2 (0.5)	5 (0.9)	7 (1.1)	0 (0.0)
Interstitial lung disease	4 (0.5)	5 (1.3)	5 (0.9)	3 (0.5)	2 (1.0)
Anaemia	10 (1.2)	1 (0.3)	5 (0.9)	3 (0.5)	1 (0.5)
Chronic obstructive pulmonary disease	5 (0.6)	0 (0.0)	6 (1.1)	1 (0.2)	0 (0.0)
Back pain	1 (0.1)	3 (0.8)	6 (1.1)	1 (0.2)	0 (0.0)
Bronchitis	9 (1.1)	0 (0.0)	3 (0.5)	1 (0.2)	0 (0.0)

Table 10: serious and non-serious adverse events for erlotinib, gefitinib, afatinib, dacomitinib and osimertinib in five clinical trials.

	TOTAL erlotinib N = 831 patients (%)	TOTAL Gefitinib N = 383 patients (%)	TOTAL afatinib N = 552 patients (%)	TOTAL dacomitinib N =663 patients (%)	TOTAL osimertinib N = 210 patients (%)
Diarrhoea	389 (46.8)	229 (59.8)	456 (82.6)	545 (82.2)	81(38.6)
Rash	392 (47.2)	111 (29.0)	296 (53.6)	259 (39.1)	49 (23.3)
Paronychia	62 (7,5)	73 (19,1)	130 (23.6)	234 (35.3)	32 (15.2)
Alanine aminotransferase increased	23 (2.8)	133 (34.7)	20 (3.6)	52 (7.8)	15 (7.1)
Decreased appetite	226 (27.2)	96 (25.1)	142 (25.7)	211 (31.8)	29 (13.8)
Aspartate aminotransferase increased	22 (2.7)	120 (31.3)	16 (2.9)	52 (7.8)	12 (5.7)
Dermatitis acneiform	144 (17.3)	98 (25.6)	73 (13.2)	193 (29.1)	16 (7.6)
Stomatitis	74 (8.9)	58 (15.1)	121 (21.9)	183 (27.2)	22 (10.5)
Dry skin	131 (15.8)	101 (26.4)	88 (15.9)	149 (22.5)	52 (24.8)
Nausea	150 (18.1)	95 (24.8)	126 (22.8)	137 (20.7)	34 (16.2)
Cough	143 (17.2)	89 (23.2)	116 (21.0)	102 (15.4)	25 (11.9)
Dyspnoea	188 (22.6)	63 (16.5)	116 (21.0)	114 (17.2)	15 (7.2)
Fatigue	165 (19.9)	50 (13.1)	100 (18.1)	100 (15.1)	32 (15.2)
Pruritus	106 (12.8)	72 (18.8)	78 (14.1)	94 (14.2)	32 (15.2)
Weight decreased	90 (10.8)	47 (12.3)	56 (10.1)	122 (18.4)	0 (0.0)
Back pain	56 (6.7)	69 (18.0)	50 (9.1)	54 (8.1)	25 (11.9)
Asthenia	112 (13.5)	52 (13.6)	92 (16.7)	97 (14.6)	11 (5.2)
Constipation	103 (12.4)	55 (14.4)	74 (13.4)	74 (11.2)	32 (15.2)
Mucosal inflammation	43 (5.2)	27 (7.1)	84 (15.2)	89 (13.4)	0 (0.0)
Vomiting	116 (14.0)	51 (13.3)	84 (15.2)	97 (14.6)	16 (7.6)
Alopecia	18 (2.2)	55 (14.4)	19 (3.4)	67 (10.1)	0 (0.0)
Chest pain	64 (7.7)	51 (13.3)	35 (6.3)	43 (6.5)	0 (0.0)
Upper respiratory tract infection	12 (1.4)	48 (12.5)	19 (3.4)	41 (6.2)	12 (5.7)
Musculoskeletal pain	40 (4.8)	47 (12.3)	35 (6.3)	48 (7.2)	15 (7.1)
Headache	20 (2.4)	44 (11.5)	15 (2.7)	32 (4.8)	21 (10.0)
Anaemia	95 (11.4)	22 (5.7)	50 (9.1)	60 (9.1)	20 (9.5)
Insomnia	42 (5.1)	42 (11.0)	33 (6.0)	38 (5.7)	11 (5.2)
Conjunctivitis	14 (1.7)	19 (5.0)	14 (2.5)	72 (10.9)	0 (0.0)
Dizziness	51 (6.1)	41 (10.7)	27 (4.9)	39 (5.9)	11 (5.2)
Pyrexia	75 (9.0)	27 (7.1)	58 (10.5)	66 (10.0)	1 (0.5)
Haemoptysis	87 (10.5)	23 (6.3)	54 (9.8)	40 (6.0)	0 (0.0)

Epistaxis	33 (5.0)	19 (5.0)	57 (10.3)	58 (8.8)	0 (0.0)
Nasopharyngitis	21 (2.5)	30 (7.8)	11 (2.0)	40 (6.0)	21 (10.0)

1) Cutaneous reactions

Cutaneous reactions have been reported for all anti-EGFR PKIs. However, third generation drugs are less linked to such reactions than first and second generation drugs. This can be explained by the more selective profile of third generation PKIs. This cutaneous AE is rarely serious or fatal, but it is frequent. Severe cutaneous reaction may require dosage modification or discontinuation of the PKI [82].

Several studies have reported a relationship between tumour response and overall survival and rash occurrence [83–85].

a) First and second-generation anti EGFR treatments

Within the first two weeks following PKI initiation, rashes or pruritus can appear. This is characterised by acneiform eruptions together with inflamed papules and pustules. Furthermore, serious and/or haemorrhagic crusting have been reported. After the first one or two months of treatment, the occurrence of dry skin/pruritus, fissures, stomatitis and mucositis, facial hirsutism, and eyelash trichomegaly have been reported. After 6 to 8 weeks, nail changes are a possible AE. Finally, after two or three months, the occurrence of alopecia has been reported in the literature [82,86].

First and second generation drugs inhibit wild-type EGFR. However, this receptor type is expressed in epidermal basal cells in hair follicles, and the sweat and sebaceous glands, and also in periungual tissue. These drug types inhibit proliferation, migration and differentiation of these cells, and consequently are associated with impaired skin integrity with an inflammatory mechanism [82,87].

b) Third generation anti-EGFR treatments

In clinical trials, among patients exposed to osimertinib, different cutaneous AEs have been reported: rash, dry skin, and paronychia. Few reactions were reported with a severity grade greater than or equal to 3. For dry skin and paronychia, no reactions with a severity grade greater than or equal to 3 were reported [82].

c) Management of cutaneous AEs

In the case of rash, pruritus or paronychia, treatment such as a topical corticosteroid lotion or solution or anti-inflammatory drugs, can be prescribed. For pruritus, oral antihistamines or GABA agonists can be prescribed. To treat xerosis or dry skin, moisturising creams or lotions containing urea, colloidal oatmeal, zinc oxide and salicylic acid and exfoliants can be administered to the patient [87]. Minocycline and doxycycline can be prescribed in the event of cutaneous reactions with PKIs [88–91]. If the patient has an intolerable or severe reaction, the PKI can be discontinued, or the dosage can be decreased. If the reaction is evaluated as grade 4 severity, the drug must be immediately discontinued without trying dosage reduction [82].

2) Interstitial lung disease

This is a rare but a severe and potentially fatal AE associated with anti-EGFR PKIs [92,93]. It occurred in approximately 1-3% of patients treated with an anti-EGFR PKI. The occurrence of this AE is higher for osimertinib than gefitinib. However, the proportion of Interstitial lung disease (ILD] with a grade superior or equal to 3 was the same [94]. Different risk factors are associated with this AE occurrence: male sex, smoking, a clinical history of pulmonary fibrosis, poor performance status, previous radiotherapy and treatment with a PD-1 inhibitor. Also, a clinical history of interstitial pneumonia is a risk factor for developing this AE [95].

This AE is managed by the prescription of high dosage and prolonged administration of corticosteroid or immunosuppressive drugs. The anti-EGFR must be discontinued. However, some case studies reported a possible rechallenging with the same or another anti EGFR after this AE [96–98].

The pharmacological mechanism for this AE is unknown. However, the anti-EGFR can decrease EGFR phosphorylation and regenerative epithelial proliferation. It can lead to the development of pulmonary fibrosis. As a result, the risk of ILD can be exacerbated [93].

3) Gastro-intestinal disease

Different gastro-intestinal diseases have been reported in the literature with these drugs. Diarrhoea is the most frequent AE with anti-EGFRs [99,100]. However, few cases of rare but severe gastro-intestinal perforations have been reported [101,102].

a) Diarrhoea

Diarrhoea frequency varied according to the anti-EGFR PKI. In several studies, for erlotinib and gefitinib, it was estimated respectively at around 27-69% and 18-68%. For afatinib, between 87 and 95% patients had this AE. For osimertinib, diarrhoea prevalence was estimated to be 41% [99]. The prevalence of a grade 3 diarrhoea reaction was estimated for erlotinib, gefitinib, afatinib and osimertinib respectively to be around 1-25%, 1-12%, 5-17% and 1% [99]. For dacomitinib, diarrhoea occurrence was observed in 97.5% of patients but only 12.5% had grade 3 or 4 reactions [103]. The prevalence of grade 3 and 4 diarrhoea was lower with osimertinib than with erlotinib, gefitinib or afatinib. This AE mainly occurred in the first weeks following initiation of PKI treatment [99,104].

The pharmacological mechanism of this AE is unknown. EGFR receptors are also located in the basolateral membranes of gastrointestinal trac epithelial cells. They regulate ion transport. EGFRs also play a role in intestinal epithelial chloride secretion, which is linked to passive water movement. Because EGFR inhibition can dysregulate ion transport, chloride secretion can increase and cause secretory diarrhoea [99]. For grade 1 and 2 diarrhoea, drugs such as loperamide and racecadotril can be prescribed. For grades greater than or equal to 3, symptomatic treatments for associated AEs such as nausea/vomiting, fever, neutropenia and septicaemia must be prescribed. Drug discontinuation or dosage reduction are possible [99].

b) Gastro-intestinal perforation

Some cases of gastro-intestinal perforation have been reported with erlotinib. Risk factors associated with this AE occurrence are concomitant administration of anti-angiogenic agents, corticosteroids, nonsteroidal anti-inflammatory drugs, and taxane-based chemotherapy. Prior peptic ulceration or diverticular disease are also risk factors for developing this AE. The pharmacological mechanism is unknown. However, anti EGFR PKIs can reduce VEGF expression and have an anti-angiogenic effect. This can cause local ischemia and inadequate vascular perfusion of the gastro-intestinal tract. The treatment for this AE is surgical, but in most of the case reported in the literature, this AE resulted in death [102,105].

L) AEs in VigiBase®, the global pharmacovigilance database

Data were extracted from VigiBase® on 11 January 2023. There were 76 891 cases and 145 120 AEs reported with the PKIs of interest. Among them 41 448, 9 243, 11 354, 504 and 14 162 patients respectively received erlotinib, gefitinib, afatinib, dacomitinib and osimertinib. There were 78 854 reported AEs with erlotinib, 15 606 with gefitinib, 26 353 with afatinib, ,078 with dacomitinib and 22 549 with osimertinib (figures 3, 4, 5, 6, 7).

Overall, for the PKIs of interest for our study, the male female distribution was 54.3 – 40.1% (with 5.6% no data). For erlotinib, gefitinib, afatinib and osimertinib the median age was between 65 and 74 years. For dacomitinib, the median age was between 45 and 64 years. For erlotinib, the male female distribution was 50.2 – 45.1% (with 4.7% no data). For gefitinib, the male female distribution was 59.6 – 35.3% (with 5.0% no data). For afatinib, the male female distribution was 59.0 – 37.6% (with 3.5% no data). For dacomitinib, the male female distribution was 43.1 – 49.4% (with 7.5% no data). For osimertinib, the male female distribution was 59.3 – 30.0% (with 10.7% no data). Figures represent the 10 most represented SOCs for AEs. Percentages are for the number of SOC AEs out of the total number of AEs.

These results are consistent with those found in the clinical trials. Gastro-intestinal, cutaneous and subcutaneous tissue adverse events were more frequently reported than other AEs as is the case in the clinical trials. It is noteworthy that cutaneous and subcutaneous reactions are among the three most reported adverse reactions to osimertinib, as in the clinical trials. This type of reaction,

such as the occurrence of a rash or acneiform dermatitis, was less reported with third generation PKIs in clinical trials.

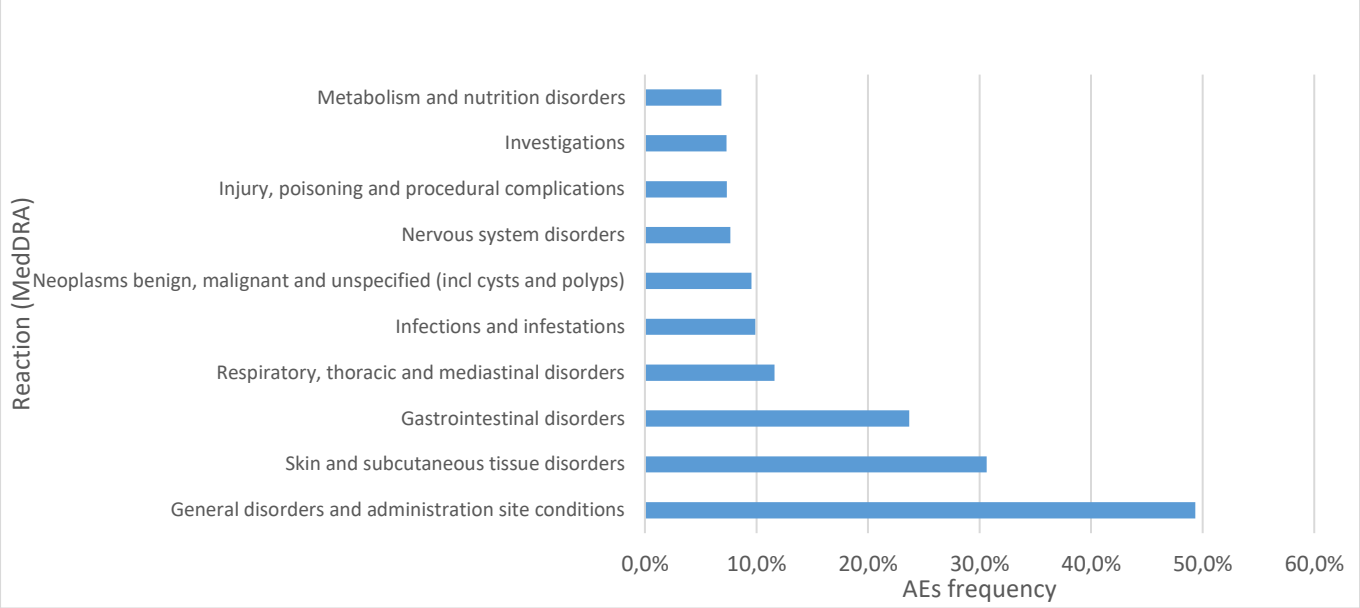


Figure 3: the 10 most frequent SOCs found in VigiBase® for erlotinib.

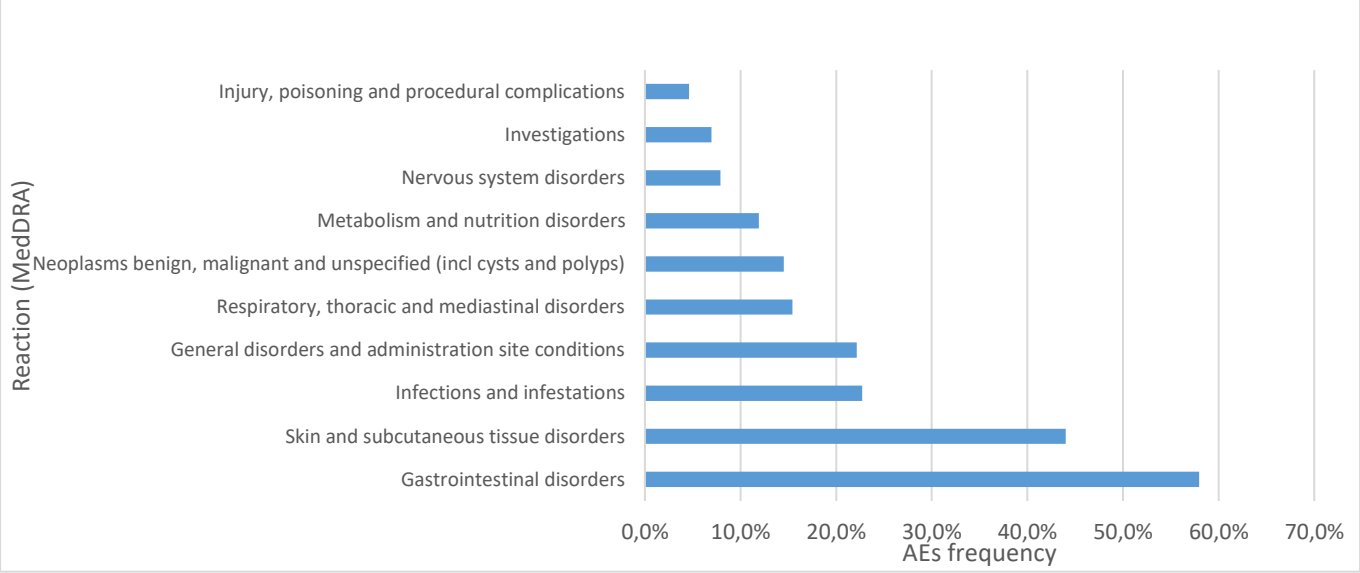


Figure 4: the 10 most frequent SOCs found in VigiBase® for gefitinib.

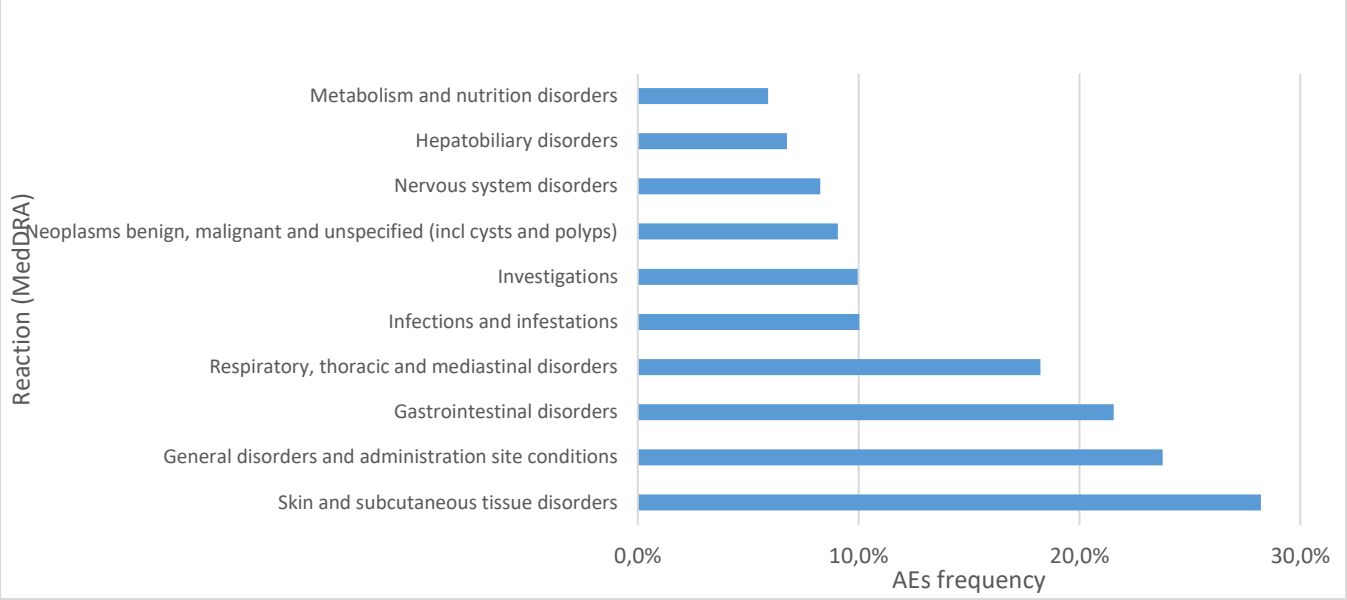


Figure 5: the 10 most frequent SOCs found in VigiBase® for afatinib.

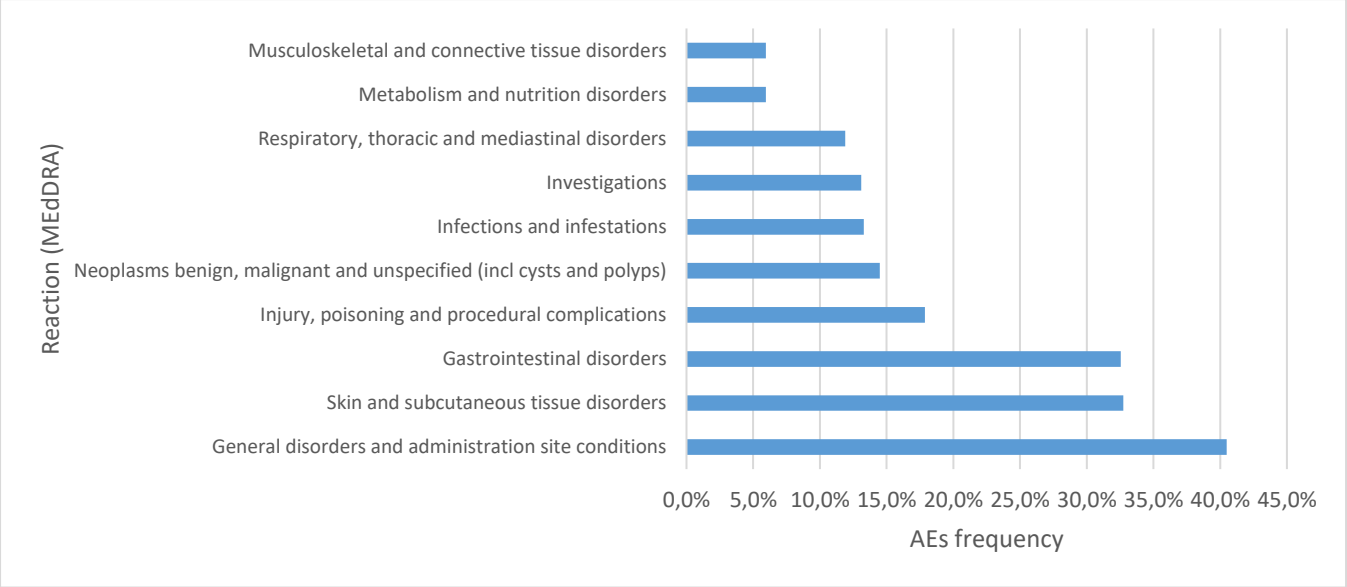


Figure 6: the 10 most frequent SOCs found in VigiBase® for dacomitinib.

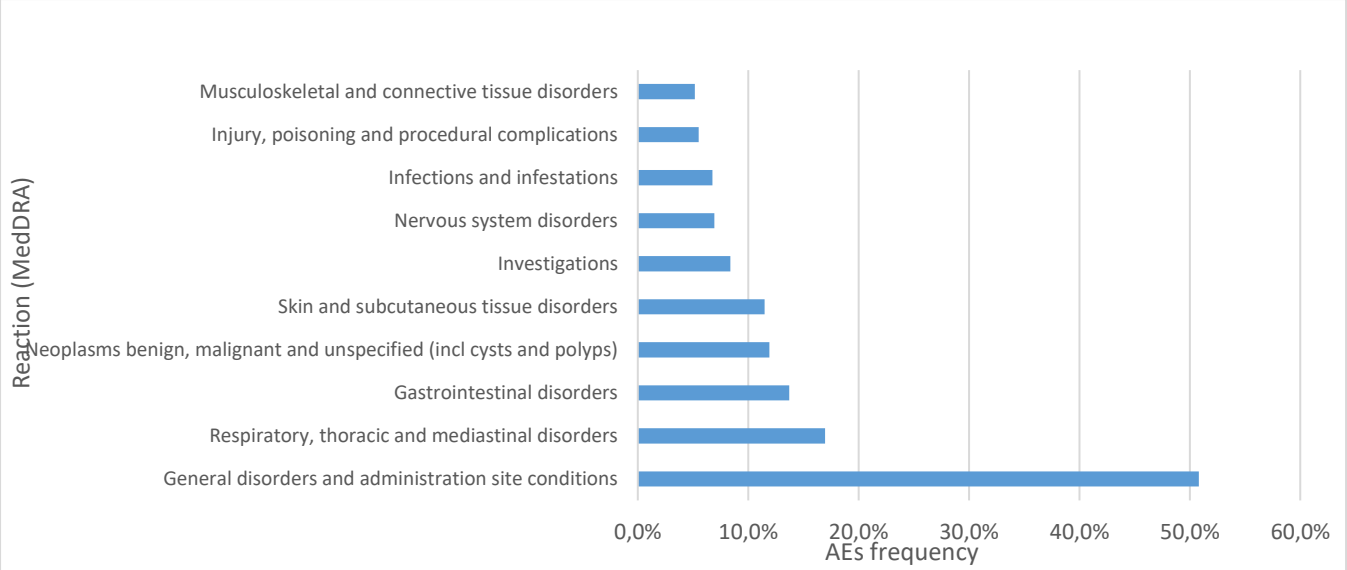


Figure 7: the 10 most frequent SOCs found in VigiBase® for osimertinib.

M) Regulatory status of anti-EGFR PKIs

Erlotinib was approved by the FDA on 18 November, 2004, and by the EMA on 19 September, 2005. The brand name is TARCEVA® [106,107].

Gefitinib was approved by the FDA on 5 May, 2003, and by the EMA on 24 June, 2009. The brand name is IRESSA® [108,109].

Afatinib was approved by the FDA on 12 July, 2013, and by the EMA on September 25, 2013. The brand name is GIOTRIF® [110,111].

Dacomitinib was approved by the FDA on 27 September, 2018, and by the EMA on April 2, 2019. The brand name is VIZIMPRO®[23,34].

Osimertinib was approved by the FDA on 13 November, 2015, and by the EMA on 2 February, 2016. The brand name is TAGRISSO® [112].

N) Indications

These drugs are indicated for the treatment of NSCLC, with EGFR mutation. They are indicated as a first line treatment for advanced and metastatic NSCLC [9]. Erlotinib is indicated for maintenance treatment for patients with stable disease following first-line chemotherapy. Erlotinib is also indicated for locally advanced and metastatic lung cancer, following the failure of first-line chemotherapy [113]. Erlotinib is also indicated for pancreatic cancer [114].

Gefitinib is indicated for the treatment of locally advanced and metastatic lung cancer [115].

Afatinib is indicated for the treatment of locally advanced and metastatic lung cancer. Afatinib is also indicated for epidermoid cancer for the treatment of locally advanced and metastatic lung cancer that has progressed during or following treatment with platinum chemotherapy [116].

Dacomitinib is indicated as a monotherapy for the treatment of locally advanced or metastatic NSCLC with EGFR mutations [34].

Osimertinib is indicated as an adjuvant treatment following complete tumour resection in stage IB – IIIA NSCLC. It is also indicated for the treatment of locally advanced and metastatic lung cancer with or without the EGFR T790 mutation [116].

O) Conclusion

EGFR receptor inhibitors are an alternative for the treatment of lung cancer having this mutation instead of standard chemotherapy. These drugs have a better profile in terms of safety and AEs. The development of other ErBB receptor protein kinase inhibitors such as poziotinib, furmonertinib and sunvozertinib is currently being studied [117]. The principal limitation of this treatment type is the emergence of resistance.

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PARTIE 3 : Les inhibiteurs de la pompe à proton

A) Généralités

La dénomination de ces médicaments renseigne sur leur cible pharmacologique car ils bloquent la pompe à proton afin de limiter la production d'acidité au niveau gastrique.

Actuellement, cinq IPPs (l'ésoméprazole, l'oméprazole, le lansoprazole, le pantoprazole et le rabéprazole) sont commercialisés en France.

Au sein de la population française, des données estiment que la proportion de patients exposés aux IPPs est de 29,8 % [30].

B) Composition

Le premier IPP à avoir été commercialisé est l'oméprazole. Les différent IPPs ont une structure chimique commune (figure 4). Ce sont des dérivés du benzimidazole. Ils sont constitués d'une molécule hétérocyclique avec une fraction pyridine et benzimidazole qui vont être reliés par un groupe méthylsulfinyle [31].

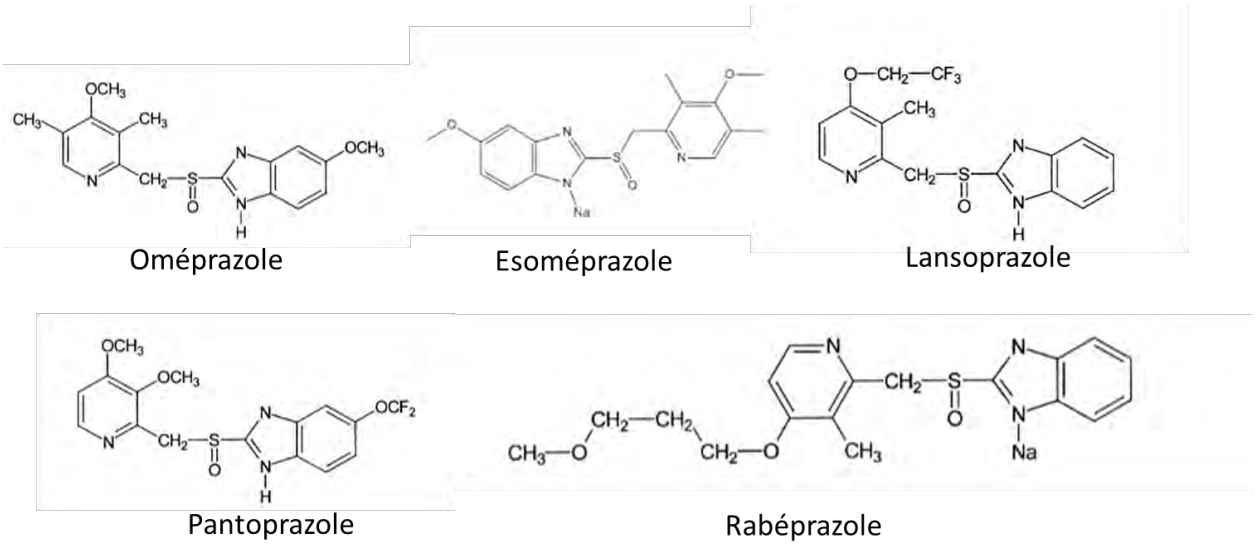

Figure 4 : structure chimique des IPPs commercialisés en France [32, 33].

Deux composés stéréo-isomères ont été développés l'ésoméprazole et le dexlansoprazole [34, 35].

C) Pharmacodynamie

Ce sont des médicaments à visée systémique qui doivent être absorbés, atteindre la circulation générale et diffuser jusqu'aux cellules pariétales de l'estomac pour pouvoir interagir avec leur cible pharmacologique. En se concentrant au niveau des canalicules acides, l'IPP est clivé d'une liaison sulfoxyde chirale, en acide sulfénique acide et/ou en sulfamide. Ce clivage ne sera pas réalisé pour les stéréo-isomères. L'IPP va ensuite se lier au niveau des résidus de cystéine des pompes H+/K+ ATPase et provoquer son effet inhibiteur de la sécrétion acide jusqu'à ce que des nouvelles pompes de remplacement soient synthétisées (environ 24 à 48 heures) [36-38].

Pour que l'IPP puisse se fixer sur sa cible, il faut que les pompes H+/K+ soient actives, ce qui ne va se produire que pendant le repas. Au cours d'un seul repas, seulement les deux tiers des pompes H+/K+ ATPase vont être inhibées par une prise d'IPP [38].

Les IPPs ont une efficacité supérieure aux antagonistes des récepteurs histamine de type 2 car ils permettent de maintenir un pH supérieur à 4, pendant une durée comprise entre 15 à 21 heures par jour, contre 8 heures pour les antagonistes des récepteurs histamine de type 2. De même, l'effet des IPPs peut être maintenu à long terme sans qu'une augmentation de dose ne soit nécessaire [39].

D) Pharmacocinétique

Les IPPs ont des propriétés pharmacocinétiques similaires mais celles-ci peuvent différer un peu selon les différents principes actifs (table 1). Globalement ces principes actifs ont une assez bonne biodisponibilité mais une importante liaison aux protéines plasmatiques. Le temps d'apparition du pic plasmatique se situe entre 1 à 5 heures. Ces médicaments sont principalement métabolisés par le CYP2C19 et ont une excrétion principalement hépatique. Ils sont caractérisés par une demi-vie courte. Leurs temps de demi-vie sont inférieurs à 2 heures. Après la métabolisation hépatique, la plupart des IPPs sont éliminés par voie rénale hormis le lansoprazole qui a une élimination plus biliaire.

Table 1 : propriétés pharmacocinétiques des IPPs [39, 40].

	Oméprazole	Esoméprazole	Lansoprazole	Pantoprazole	Rabéprazole
Biodisponibilité (%)	30 - 40	64 - 90	80 - 85	77	52
Temps jusqu'au pic plasmatique (tmax, en heure)	0,5 - 3,5	1,5	1,7	2 - 3	2 - 5
Liaisons aux protéines, %	95	97	97	98	96,3
Demi-vie (en heure)	0,5 - 1	1 – 1,5	1,6	1 - 1,9	1 - 2
Excrétion primaire	Hépatique	Hépatique	Hépatique	Hépatique	Hépatique
Principal métabolisme hépatique	CYP 2C19	CYP 2C19	CYP 2C19 CYP 3A4	CYP 2C19 CYP3A4	CYP 2C19 CYP 3A4

L'oméprazole et son dérivé l'ésoméprazole sont quasiment exclusivement métabolisés par le CYP 2C19 et sont donc plus à risque d'interactions significatives que le lansoprazole et le rabéprazole qui sont plutôt métabolisés par le CYP 3A4.

E) Voie d'administration et posologie

1) Formulation

Les IPPs sont des pro-médicaments, de structures chimiques bases faibles et sont transformés lorsque le pH est proche de 2 en composés actifs sulfénamides. Ils peuvent donc être dégradées avant leur absorption par l'acidité gastrique intraluminale [41]. Afin d'être préservé de ces conditions, des formulations galéniques dites gastrorésistantes ont été mises au point, permettant leurs libérations dans les fractions proximales de l'intestin grêle. Les IPPs peuvent être présentés sous forme de comprimés ou de gélules composées de gélatine contenant des microganules gastro-résistantes. De même, les IPPs peuvent se présenter sous forme de granules gastro résistantes à diluer dans un verre d'eau. Ces formes sont dites à libération prolongée [42].

Une libération immédiate est possible de l'IPP en ajoutant du bicarbonate de sodium à sa formulation. L'IPP sera administré avant le coucher. Le bicarbonate de sodium aurait une

capacité à activer la sécrétion de la gastrine qui pourrait activer les pompes à proton. L'absorption et la biodisponibilité de l'IPP seraient ainsi augmentées [41].

D'autres formes galéniques ont été développées pour augmenter la durée d'action des IPPs avec par exemple une formule où deux pics de libération sont observés. Une première quantité de principe actif est libérée 1 à 2 heures après la prise et un second pic peut être observé 4 à 5 heures après l'administration du médicament. Ce type de formulation est à prendre au cours du repas du soir [43].

L'IPP peut être aussi administré par voie intraveineuse, ce qui permet de limiter les contraintes lors de cette phase d'absorption par voie orale.

2) Formes commercialisées en France

En France, 5 IPPs administrés par voie orale sont commercialisés :

- Oméprazole MOPRAL®, ZOLTUM® (10, 20 mg). Une association de kétoprofène / oméprazole (200 / 20 mg) est aussi commercialisée.
- Esoméprazole INEXIUM®, NEXIUM CONTROL® (10, 20, 40 mg)
- Pantoprazole EUPANTOL®, INIPEPSIA®, INIPOMP® (20, 40 mg)
- Lansoprazole LANZOR®, OGASTORO®, OGAST® (15, 30 mg)
- Rabéprazole PARIET® (10, 20 mg)

En France, l'ésoméprazole INEXIUM® (40 mg) administré par voie intraveineuse est également disponible.

La dose pleine de l'ésoméprazole et du pantoprazole est de 40 mg. Celle de l'oméprazole et du rabéprazole est de 20 mg. La dose pleine du lansoprazole est de 30 mg.

3) Indication et posologie

a) Reflux gastro-oesophagien et oesophagite

Pour le traitement symptomatique du Reflux Gastro-Oesophagien (RGO) sans œsophagite, tous les IPPs commercialisés en France sont indiqués. Le lansoprazole peut être prescrit à demi ou à pleine dose pendant une durée de 4 à 6 semaines. L'oméprazole peut être prescrit à demi ou à pleine dose pour une durée de 4 semaines. L'ésoméprazole, le rabéprazole et le

pantoprazole peuvent être prescrits à demi-dose pendant 4 semaines, puis à la demande jusqu'à disparition des symptômes [44].

Pour la prise en charge de la cicatrisation de l'œsophagite associée à un RGO, tous les IPPs commercialisés en France sont indiqués. Le lansoprazole, l'ésoméprazole, l'oméprazole et le rabéprazole peuvent être prescrits à dose pleine pendant 4 à 8 semaines. Pour l'oméprazole, en cas d'œsophagite résistante au bout de 4 semaines de prescription à pleine dose, il est recommandé une administration à double dose pendant les 4 semaines suivantes. Le pantoprazole peut être prescrit à demi-dose pendant 4 à 8 semaines. En cas de résistance aux autres IPPs, le pantoprazole peut être prescrit à pleine dose [44].

Pour prévenir les récidives d'œsophagite par RGO, tous les IPPs commercialisés en France sont indiqués. Le lansoprazole, le rabéprazole et le pantoprazole peuvent être indiqués à pleine ou à demi-dose. La pleine dose pour le pantoprazole est indiquée en cas de récidive. L'ésoméprazole peut être prescrit à demi-dose. L'oméprazole peut être indiqué à demi-dose, pleine-dose ou à double dose [44].

Les IPPs n'ont pas l'AMM pour le soulagement des manifestations extradigestives non liées au RGO [45, 46].

b) Lésions gastroduodénales dues aux anti inflammatoires non stéroïdiens

Pour la prévention des lésions dues aux Anti Inflammatoires Non Stéroïdiens (AINS), le lansoprazole, le pantoprazole, l'oméprazole et l'ésoméprazole peuvent être prescrits. Le pantoprazole et l'ésoméprazole sont à prescrire à demi-dose. L'oméprazole est à prescrire à pleine dose. Le lansoprazole est à prescrire à demi-dose. Cependant, en cas d'échec antérieur, il peut être prescrit à pleine dose. La prévention de ce type de lésion n'est à faire que chez les patients à risque c'est-à-dire avec un âge supérieur à 65 ans, qui ont eu un antécédent d'ulcère gastro duodénal ou qui prennent les médicaments suivants : des anti-agrégants plaquettaires, des anticoagulants ou des corticoïdes [44].

Pour le traitement des lésions dues aux AINS, seul le lansoprazole, l'ésoméprazole et l'oméprazole sont à privilégier. Le lansoprazole et l'oméprazole sont à prescrire à pleine dose pendant 4 à 8 semaines. L'ésoméprazole est à prescrire à demi-dose pendant 4 à 8 semaines [44].

c) Ulcère gastrique et duodénal

Pour la prise en charge de ce type d'ulcère associé à une infection à Helicobacter Pylori, tous les IPPs commercialisés en France peuvent être prescrits. Le lansoprazole, l'oméprazole, le pantoprazole et le rabéprazole sont à prescrire à pleine dose, 2 fois par jour pendant 7 jours. L'ésoméprazole est à prescrire à demi-dose 2 fois par jour pendant 7 jours [44].

Pour la prise en charge de l'ulcère gastrique ou duodénal, les IPPs suivants sont à privilégier le lansoprazole, l'oméprazole, le pantoprazole et le rabéprazole. L'ésoméprazole n'a pas cette indication. Pour la prise en charge de l'ulcère duodénal, le traitement à pleine dose est recommandé pendant 4 à 8 semaines pour le rabéprazole et le pantoprazole. Le lansoprazole et l'oméprazole sont indiqués pour la prise en charge de cette pathologie mais pendant une durée de 2 à 4 semaines. Pour la prise en charge de l'ulcère gastrique, l'oméprazole, le lansoprazole et le pantoprazole sont indiqués à pleine dose pendant une durée de 4 à 8 semaines. Le rabéprazole est indiqué à pleine dose pendant une durée de 6 à 12 semaines pour la prise en charge de la cette pathologie [44].

Le traitement d'entretien de l'ulcère duodénal consiste en une prise en charge par oméprazole à demi-dose ou à pleine dose ou lansoprazole à pleine dose [44].

d) Syndrome de Zollinger-Ellison

Les IPPs suivants, l'oméprazole, l'ésoméprazole, le pantoprazole, le lansoprazole, le rabéprazole sont indiqués pour la prise en charge de cette indication. La posologie initiale de l'ésoméprazole est de deux prises de 40 mg par jour. La posologie initiale de l'oméprazole, du rabéprazole et du lansoprazole est de 60 mg/j. La posologie initiale de pantoprazole recommandée est de 80 mg/j [44-46].

4) Adaptation de dose

a) Chez le sujet avec une insuffisance hépatique

Pour le lansoprazole, chez les sujets atteints de maladies sévères hépatiques ou modérées, une réduction de la dose journalière de 50 % est recommandée [45].

Pour le pantoprazole et l'ésoméprazole, chez les sujets atteints de pathologies sévères hépatiques, la dose journalière de 20 mg ne doit pas être dépassée [45].

b) Chez le sujet âgé

Pour le lansoprazole, une dose journalière supérieure à 30 mg ne doit pas être dépassée, sauf s'il existe des indications cliniques pertinentes [45].

F) Effets indésirables

1) Diminution vitamine B12

La prise d'IPP serait associée à une malabsorption de la vitamine B12, par la diminution de la sécrétion d'acide gastrique [47].

2) Hypomagnésémie

Une diminution du taux de magnésium est possible lors d'un traitement par IPP. Le mécanisme pharmacologique à l'origine de cet EI est peu connu. Cependant, les IPPs pourraient provoquer une malabsorption de cet ion et interférer avec son élimination [48].

3) Infection tube digestif

Du fait de la modification du pH par les IPPs, la croissance de certains micro-organismes au sein du tube digestif peut être augmentée. De ce fait, une augmentation du risque d'avoir une infection à Clostridium Difficile a été mise en évidence avec l'exposition aux IPPs au long cours. Une prise au long cours de ces médicaments pourrait être aussi associée à une augmentation du risque de récidive de l'infection [49].

Par un mécanisme pharmacologique similaire, il a été mis en évidence que la prise d'IPP pourrait être associée à une augmentation du risque de survenue d'infection à Salmonella ou à Campylobacter [50].

4) Pneumopathie aigue communautaire

Certaines études ont mis en évidence une association entre la prise d'IPP et la survenue de pneumopathie aigue communautaire. Par leurs actions sur l'acidité gastrique, les IPPs pourraient favoriser la prolifération de micro-organismes au sein de l'appareil gastrique. Ils pourraient ensuite migrer et aller vers les poumons [51].

5) Insuffisance rénale

La prise d'IPP peut être associée à une augmentation du risque de néphrite interstitielle aigue. Bien que le mécanisme pharmacologique ne soit pas clairement identifié, les IPPs et leurs métabolites pourraient se déposer sur les tubules interstitiels et provoquer un processus auto-immun. Ceci pourrait conduire à une diminution du débit de filtration glomérulaire ou une néphrite interstitielle chronique en cas d'usage au long cours [51].

6) Polypes gastriques

Il a été mis en évidence que l'exposition aux IPPs était associée à une augmentation du risque de développer des polypes gastriques. Ces polypes pourraient se développer du fait de l'hypergastrinémie provoquée par les IPPs [51].

7) Cancers gastriques et du colon

Différentes études ont mis en évidence une association entre la prise d'IPP au long cours et la survenue de cancers gastriques. Les IPPs peuvent être responsables d'une hypergastrinémie et d'une hypochlorhydrie rendant favorable la prolifération de la muqueuse gastrique. De même, ces médicaments pourraient être associés à une augmentation du risque de développement de tumeurs carcinoïdes.

Cependant, il a été mis en évidence que la prise d'IPP pourrait augmenter la sensibilité d'une tumeur solide aux médicaments cytotoxiques en diminuant la chimiorésistance via leur action sur les pompes ATPase. De plus, les IPPs pourraient inhiber la migration cellulaire et l'invasion des tumeurs gastriques [51].

8) Fracture et ostéoporose

Il a été mis en évidence, que la prise d'IPP au long cours et à forte dose était associée à une augmentation du risque d'avoir des fractures au niveau de la hanche, du poignet et de la colonne vertébrale. Les IPPs entraineraient une hypochlorhydrie qui engendrerait une diminution de l'absorption intestinale du calcium et de la densité minérale osseuse [51].

9) Démence

Quelques études ont mis en évidence que les IPPs pourraient être associés à une augmentation du risque de démence. Il a été mis en évidence chez l'animal que ces médicaments augmenteraient le taux de β amyloïdes, ce qui est un mécanisme physiologique similaire à celui mis en évidence dans la maladie d'Alzheimer. De même, par la diminution du taux de vitamine B12, les IPPs pourraient être associés à une démence [51].

G) Interaction

1) Par leurs propriétés pharmacodynamiques

En augmentant le pH intra gastrique, les IPPs peuvent modifier la solubilité de certains principes actifs et donc leurs biodisponibilités. Par exemple, l'absorption de certains antifongiques (kétoconazole, itraconazole), antirétroviraux (nelfinavir, rilpivirine), médicaments permettant de prendre en charge l'hépatite C (ledipasvir, sofosbuvir), anticancéreux (géfitinib, erlotinib) pourrait être diminuée. A contrario, du fait de l'influence des IPPs sur le pH gastrique, certains médicaments pourraient avoir une meilleure absorption et biodisponibilité comme la digoxine, la nifédipine ou encore l'alendronate [52, 53].

De même, la prise d'IPP peut interagir avec la lévothyroxine orale. En effet, cette dernière nécessite un pH acide pour se dissoudre et atteindre l'intestin pour être absorbée. Une diminution du pH est susceptible d'entrainer une diminution de l'absorption et de la biodisponibilité de la lévothyroxine [54].

2) Par leurs propriétés pharmacocinétiques

Du fait de leur métabolisation par le cytochrome P450 et notamment le CYP2C19, certaines interactions médicamenteuses sont attendues. Le clopidogrel peut lors d'une prise

concomitante avec les IPPs (oméprazole et ésoméprazole), avoir une transformation en métabolite actif diminuée. Des inducteurs du CYP3A4 peuvent augmenter l'exposition aux IPPs comme le voriconazole ou la clarithromycine [55].

Une interaction entre le méthotrexate et les IPPs est possible. Il a été montré que les IPPs pouvaient inhiber la pompe H+/K+ située au niveau rénal. Or, le méthotrexate est éliminé par le rein. Dans la littérature, il a été décrit que l'interaction entre les IPPs et le méthotrexate pouvait conduire à une augmentation de la toxicité de ce dernier [40].

H) Utilisation en cancérologie

Aux Etats Unis, la prévalence d'exposition à des médicaments pouvant modifier l'acidité gastrique chez les patients atteints d'un cancer a été estimée entre 20 et 33 %. La majorité de ces médicaments étaient des IPPs ou des antagonistes des récepteurs histamine de type 2. Cette prévalence variait en fonction du type de cancer traité. Pour les patients ayant un cancer gastro intestinal, la prévalence a été estimée entre 50 et 67 %. Pour ceux avec une atteinte pancréatique elle a été estimée entre 39 et 55 %, avec un glioblastome autour de 35 et 53 % et avec un cancer du poumon autour de 33 et 46 % [55].

En France, parmi les patients atteints d'un cancer, la prévalence d'exposition aux IPPs a été estimée à 26,3 % [56]. La prévalence des patients recevant des IPKs et exposés de façon concomitante aux IPPs a été estimée à 22,7 % [57].

Cette importante proportion de patients atteints de cancer et exposés aux médicaments inhibant l'acidité gastrique peut être expliquée par les troubles gastro intestinaux, induits par le cancer selon sa localisation mais aussi par les traitements anticancéreux administrés. La prise d'IPK est associée à la survenue d'atteintes gastro intestinales. De ce fait, les IPPs peuvent davantage être prescrits chez les patients traités par IPKs [55].

I) Situation usage inapproprié

Seulement, en France, il a été mis en évidence que l'utilisation des IPPs n'était pas toujours en conformité avec les recommandations françaises, avec une constatation de prise au long cours sans reconsidération systématique de la déprescription.

Parmi les patients exposés aux IPPs en France, il a été estimé que 53,4 % avaient une prescription concomitante d'AINS, mais une large majorité d'entre eux n'avait pas de facteurs de risque justifiant l'instauration d'un traitement par IPP systématique. Il a été estimé que pour 32,4 % des patients ayant eu au moins une délivrance d'IPP, il n'avait pas pu être identifié l'indication du médicament [30].

PARTIE 4 : Description du système national des données de santé

Les bases médico-administratives permettent de reconstituer de façon longitudinale le parcours de soin d'une population cible. De ce fait, elles peuvent être utilisées pour suivre les dépenses nationales dans le domaine de santé mais aussi mener des études épidémiologiques à l'aide de données issues de la vie réelle. Ces bases peuvent permettre de faire des comparaisons internationales [58].

A) Le système de santé en France

Le système français de santé consiste en une couverture universelle de la santé par la sécurité sociale. Ce système permet de rembourser chaque individu pour la plupart des dépenses de santé réalisées dans les établissements publics et privés. Les remboursements des frais hospitaliers sont réalisés selon la tarification à l'activité en se basant sur les Groupes Homogènes Maladies (GHM). Les médicaments et les dispositifs médicaux onéreux sont remboursés en dehors du forfait hospitalier c'est-à-dire en « sus du GHM ».

Le SNDS rassemble et met à disposition des informations de santé exhaustives, pseudonymisées et individuelles. Il couvre l'essentiel des assurés sociaux en France soit environ 66 millions de personnes et 99 % de la population. Dans le SNDS, les bénéficiaires sont affectés à un régime parmi une douzaine, selon leur statut professionnel. Le principal régime de l'assurance maladie est celui général. Ensuite, il y a le Régime Social des Indépendant (RSI) et celui de la mutualité sociale agricole.

Le SNDS est constitué et permet de lier trois bases déjà existantes : les données du Système National d'Information Inter-Régimes de l'Assurance Maladie (SNIIRAM), du Programme de Médicalisation des Systèmes d'Information (PMSI) et la Base de Causes Médicales de Décès (BCMD). Ces bases sont reliables à l'aide d'un identifiant unique pour chaque bénéficiaire. Actuellement dans le SNDS, il n'y a pas encore d'informations dans le SNDS sur les Maisons Départementales des Personnes Handicapées (MDPH) ni sur les organismes complémentaires de l'assurance maladie [58].

1) Le datamart de consommation inter régime

Le Datamart de Consommation Inter Régime (DCIR) contient des informations sociodémographiques relatives aux bénéficiaires. Cette base de données regroupe aussi les informations issues des remboursements effectués, pour les soins du secteur libéral et les établissements de santé privé. Elle contient des informations concernant les comorbidités des bénéficiaires identifiables par les Affections Longue Durée (ALD) et les médicaments remboursés en ville (nom, nombre de boite, dosage et conditionnement). A l'aide du DCIR, il peut être identifié les médicaments remboursés en sus, par les établissements privés et les médicaments rétrocédés. Des informations concernant les actes médicaux, les examens biologiques réalisés et les dispositifs médicaux délivrés sont identifiables dans le SNDS. Enfin, des données concernant les visites médicales des patients sont disponibles avec notamment la date de visite médicale et la spécialité du prescripteur [59].

2) Le programme de médicalisation des systèmes d'information

Le PMSI regroupe des informations concernant les séjours et les activités externes des établissements privés ou publics. Il contient les informations des services de Médecine Chirurgie Obstrétrie (MCO), de psychiatrie, de Soins de Suite ou de Réadaptation (SSR), et des Hospitalisation A Domicile (HAD). Ces données sont centralisées sous la forme d'un Résumé de Séjour Anonymisé (RSA). Chaque RSA regroupe des informations concernant le séjour (date d'entrée, durée, type d'unité), les diagnostics posés (principaux, relatifs et associés), les médicaments délivrés en sus et les actes médicaux réalisés [58, 59].

3) La base de causes médicales de décès

La BCMD contient des informations sur chaque décès survenu en France. Elle regroupe des informations concernant les caractéristiques démographiques du défunt, la cause et les facteurs ayant pu contribuer à son décès. Le service du Centre d'Epidémiologie sur les causes médicales de DéCès (CépiDC) est chargé de sa gestion [60].

B) Forces du système national des données de santé

L'un des avantages de cette base est d'être exhaustive en couvrant plus de 66 millions d'habitants en France. C'est la plus grande base de données relative à la santé des individus en Europe et l'une des plus grandes à l'échelle mondiale. Dans les études réalisées à l'aide

de cette base, le biais de sélection est diminué et la puissance statistique des analyses est augmentée. L'utilisation de cette base permet aussi de diminuer le biais d'attrition. Enfin, la prévalence et l'incidence de maladies rares peuvent être estimées dans cette base et l'état de santé des sujets atteints peut être suivi.

Enfin le SNDS, permet d'identifier de façon précise les médicaments remboursés, par un Code Identifiant de Présentation (CIP) unique, le conditionnement et le nombre de boites délivrées. De même, il peut être identifié la date de délivrance et de prescription et certaines informations concernant le prescripteur. Ces éléments permettent pour chaque délivrance d'estimer le cycle et la durée de traitement d'un patient, le nombre de Doses Quotidiennes Définies (DDD) ou encore de Ratio de Possession de Médicament (MPR). La DDD est définie en fonction de la classification Anatomical Therapeutic Chemical (ATC) et de la voie d'administration. Il correspond à la dose d'entretien supposée prise journalièrement par le patient en fonction de l'indication principale du médicament. La MPR correspond au ratio entre le nombre de jour de traitement délivré et le nombre de jour pendant lequel le patient a été en possession de son médicament. Le SNDS permet donc de mettre à disposition des informations concernant l'exposition des patients aux médicaments en limitant certains biais d'information [61].

C) Limites du système national des données de santé

Le SNDS est constitué de tables médico-administratives qui ont comme seul but d'assurer la gestion des remboursements de soins, dans le cadre de la sécurité sociale nationale. Ainsi leurs utilisations à des fins de recherche peuvent être limitées du fait de l'indisponibilité de certaines données. Une première limite est l'absence des résultats des actes réalisés pour la pose d'un diagnostic (examens biologiques, imagerie …). De même, des informations relatives à certains variables de confusion comme le mode de vie des patients sont difficilement identifiables dans le SNDS. Cependant, celles-ci peuvent être identifiables par des proxys construits à l'aide des ALD, des diagnostics médicaux ou encore des actes réalisés.

Ensuite, certains médicaments délivrés aux patients ne sont pas identifiables dans le SNDS, comme ceux en vente libre ce qui peut entrainer un biais de classement des patients. La dose prescrite n'est pas identifiable. Seuls le nombre d'unités délivrées et leurs dosages le sont. Enfin, le SNDS a comme limite de ne pas donner d'informations concernant l'observance du patient pour son médicament.

PARTIE 5 : Cancer bronchique non à petites cellules traité par inhibiteurs de protéines kinases : réduction d'efficacité par interaction avec des inhibiteurs de la pompe à proton analyse à partir des données françaises du système national des données de santé

A) Précédentes études

Une potentielle interaction entre l'exposition concomitante aux IPPs et à certains IPKs (géfitinib et erlotinib) a été mise en évidence dans des études de pharmacocinétiques [62, 63]. La biodisponibilité de ces IPKs serait diminuée en cas d'association avec des IPPs. Cependant, une des limites de ce type d'étude est qu'elles sont réalisées avec un faible échantillon de patients souvent sains. Cette interaction a aussi été étudiée dans des études en vie réelle. Certaines ont mis en évidence une interaction entre les IPKs suivants (géfitinib, erlotinib et afatinib) et la prise concomitante d'IPP qui conduirait à une diminution de la survie globale des patients [64-69]. Néanmoins, d'autres ne sont pas parvenues à mettre en évidence cette interaction [70-73]. A notre connaissance, aucune étude n'a été publiée en prenant en compte l'ensemble des IPKs d'intérêt commercialisés en France (erlotinib, géfitinib, afatinib et osimertinib).

B) Mécanisme de l'interaction

1) Le calcul du pH sanguin

Le calcul du pH sanguin est régi par l'équation d'Henderson Hasselbach qui l'estime par une réaction acido-basique entre l'acide carbonique (HCO_3^-) et le bicarbonate (H_2CO_3). L'acide carbonique va recevoir un proton pour former le bicarbonate (figure 5) [74].

$$HCO_3^- + H^+ \rightleftharpoons H_2CO_3$$

$$pH\ sang = pKa + \log_{10}([HCO_3^-]_{sang}/[H_2CO_3]_{sang})$$

$$= 6,1 + \log_{10}([HCO_3^-]_{sang}/[H_2CO_3]_{sang})$$

Figure 5 : réaction d'Henderson Hasselbach.

Les valeurs normales du pH sanguin sont comprises entre 7,35 et 7,45 [75].

2) Influence du pH sur l'absorption d'un médicament

L'absorption d'un médicament dépend du pH de l'organe dans lequel il va être absorbé et de son pKa. Si le pKa du médicament est inférieur au pH de cet organe, la forme non ionisée du médicament prédominera et l'absorption du médicament sera bonne. Si le pKa du médicament est supérieur au pH de cet organe, la forme ionisée du médicament prédominera et donc son absorption sera moins bonne (figure 6) [76].

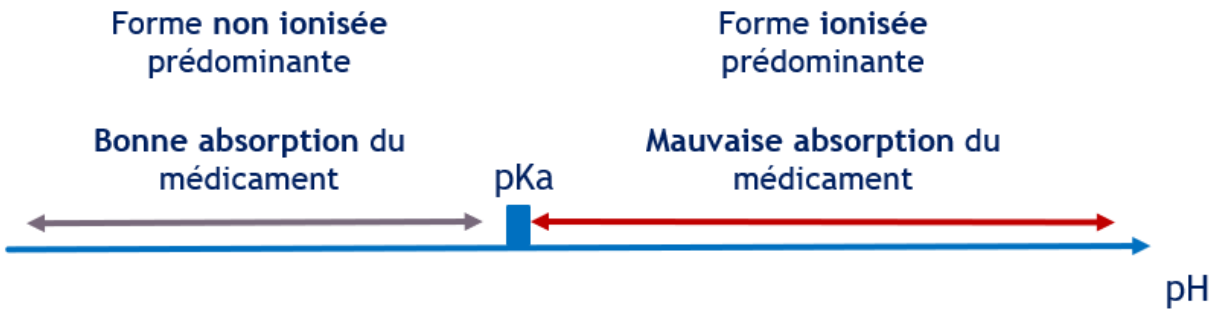

Figure 6 : influence du pH sur l'absorption du médicament.

3) Mécanisme pharmacologique de l'interaction

Les IPKs d'intérêts ont un Tmax (temps à partir de l'administration où la concentration du médicament sanguine est maximale) assez faible qui varie entre 3 et 4 heures. De ce fait, leurs principes actifs sont absorbés dans l'estomac [77].

Le pH de l'estomac est autour de 1 à 3 [76]. Les pKa de l'erlotinib, de l'afatinib et de l'osimertinib sont respectivement autour de 5,5, 8,2 et 9,2 [78]. Le pKa du géfitinib est entre 5,4 et 7,2 [79]. De ce fait, les pKa des IPKs d'intérêts sont supérieurs au pH de l'estomac, ainsi leurs principes actifs seront majoritairement absorbés sous forme non ionisée.

Cependant, une interaction est possible entre ces IPKs et les IPPs. En effet, les IPPs en bloquant la pompe H+/K+ ATPase vont entrainer une diminution de la concentration en protons au niveau gastrique conduisant à une augmentation du pH dans cet organe, qui peut devenir être supérieur ou égale à 6 [33]. Ainsi, associé aux IPPs, les valeurs de pH dans les fractions proximales du tube digestif peuvent être modifiées et la proportion de principe actif des IPKs sous forme non ionisée et la biodisponibilité de ces médicaments peut être diminuée, concourant vraisemblablement à une diminution d'efficacité des IPKs.

C) Objectifs et hypothèses

Dans cette partie du manuscrit, nous présentons une étude conduite à partir des données de l'assurance maladie qui a pour objectif d'évaluer l'impact sur la survie globale de la prise concomitante d'IPP avec des IPKs (erlotinib, géfitinib, afatinib et osimertinib).
Nous formulons l'hypothèse que pris de façon concomitante avec les IPPs, l'efficacité des IPKs serait diminuée. La survie globale des patients exposés à cette interaction serait plus faible que ceux qui n'y étaient pas exposés.

D) Article: pharmacological interaction of proton pump inhibitors on protein kinase inhibitors indicated in non-small cell lung cancer decreased survival: real life data.

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1) Summary

INTRODUCTION: The concomitant use of protein kinase inhibitors (PKI) and proton pump inhibitors (PPI) on risk of death has been identified in a few studies already published in the literature. However, the effect of this interaction is controversial. The objective of our study was to identify the impact on overall survival due to the pharmacological interaction between PPI and PKI indicated for lung cancer in the French health insurance database.

MATERIAL AND METHODS: This study was conducted using the French national health care insurance system database. We identified patients with (i) an age superior or equal to 18 years, (ii) lung cancer and (iii) at least one reimbursement for one of the following medications: erlotinib, gefitinib, afatinib and osimertinib. The index date was defined as the first reimbursement for a PKI of interest and the point date was defined as December 31, 2021 or date of death. The cumulative exposure to PPI duration during PKI treatment was defined as the ratio between the number of concomitant exposure days to PPI/PKI and the number of exposure days to PKI. For all different cumulative exposure duration levels (0.10, 0.20, 0.40, 0.60, 0.80), patients exposed to a cumulative duration superior or equal to the cut-off were considered as exposed and the others were viewed as not exposed. A Cox model was then conducted to assess risk of death following interaction caused by PPI and PKI exposure.

RESULTS: 34 048 patients received at least one reimbursement for the PKIs of interest while 26 133 (76.8%) were exposed to erlotinib, 3 142 (9.2%) to gefitinib, 1 417 (4.2%) to afatinib and 3 356 (9.9%) to osimertinib. In the main analysis, patients with concomitant exposure to PPI and PKI superior or equal to 20% during PKI treatment demonstrated an increased risk of death (HR, 1.60 [95% CI, 1.57–1.64]) compared to other patients. The risk of death increased with expanded cumulative PPI exposure during PKI treatment. This interaction type was identified for all the PKIs of interest.

DISCUSSION/CONCLUSION: In literature, an increased risk of death was observed with the interaction between PPI and PKI for erlotinib, gefitinib and afatinib. However, to our knowledge this type of interaction was not estimated for osimertinib in previous studies. Finally, we were able to identify a dose-dependent effect for this interaction which might be a factor favoring causality.

Key words: Protein kinase inhibitor, Proton pump inhibitor, Interaction, Lung cancer.

2) List of abbreviations

ALK: Activin Receptor-Like Kinase
ATC: Anatomic Therapeutic Chemical
CI: Confidence Interval
DCIR: Données de Consommation Inter-Régimes
DDD: Defined Daily Dosage
EGFR: Epidermal Growth Factor Receptor
EMA: European Medicine Agency
HR: Hazard Ratio
ICD-10: International Classification of Diseases, 10th edition
IQR: InterQuartile Range
LTD: Long-Term Disease
NSCLC: Non-Small Cell Lung Cancer
PKI: Protein Kinase Inhibitor
PMSI: Programme de Médicalisation des Systèmes d'Information
PPI: Proton Pump Inhibitor
SD: Standard Deviation
SNDS: Système National des Données de Santé

3) Introduction

Lung cancer has been one of the most diagnosed deadly cancers over the last several decades [1]. There are two different types of this cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer which have been reported in 85% and 15% of patients respectively [2]. The principal risk factor is tobacco consumption. Different forms of treatment exist including surgery, radiotherapy, immunotherapy and targeted therapy [3].

Various PKIs are indicated for the treatment of NSCLC and target Activin receptor-like kinase (ALK) or epidermal growth factor receptor (EGFR) receptors in particular. The physiological pathway that appears most promising is EGFR inhibition [4]. Five EGFR receptors targeting PKIs (erlotinib, gefitinib, afatinib, dacomitinib and osimertinib) have received marketing authorization from the European Medicine Agency (EMA) [5]. In clinical trials, these drugs were more effective on progression-free-survival in the treatment of this cancer compared to standard therapies such as chemotherapy [6].

Furthermore, several studies have identified high exposure to anti-acid drugs notably PPIs, accounting for around 20 and 33% for patients with cancer [7]. For those prescribed PKI, PPI exposure prevalence was estimated at around 22.7% [8]. However, an interaction between PPI and anti-EGFR therapies was identified in pharmacokinetic studies. The PPI increased gastric pH which can lead to decreased bioavailability and efficacy of PKI [9-11]. The principal limitation of these pharmacokinetic studies was the inclusion of a few samples from often healthy subjects.

Few epidemiological studies have described this type of interaction [12-19] and it has been identified with erlotinib, gefitinib as well as afatinib. However, the main limitation of these studies was the inclusion of a small sample of patients [17, 19]. Finally, some studies failed to detect this type of interaction [20-23]. To our knowledge, none of the studies compared the effect of this interaction between the four principal different PKIs.

The main objective of our study was to identify the impact on overall survival due to the pharmacological interaction between PPI and PKI indicated for lung cancer in the French health insurance database. For the purposes of studying this aim, interaction exposure was defined as PKI and PPI concomitant reimbursement duration superior or equal to 20% of the total PKI reimbursement duration.

The secondary objectives were:

- to identify the impact on overall survival due to the pharmacological interaction between PPI and PKI indicated for lung cancer in the French health insurance database with exposure definition variations. Interaction exposure was defined as PKI and PPI concomitant reimbursement duration superior or equal to 10%, 40%, 60% and 80% of the total PKI reimbursement duration.
- to identify the impact of the interaction on overall survival for each distinct PKI indicated for lung cancer in the French health insurance database. Interaction exposure was

defined as PKI and PPI concomitant reimbursement duration superior or equal to 10%, 20%, 40%, 60% and 80% of the total PKI reimbursement duration.

4) Material and methods

a) Database

We used a cancer pulmonary cohort built from the SNDS database that contains exhaustive, pseudonymized individual health care data systematically collected by the French national health care insurance system (*SNDS*, *Système National des Données de Santé*) [24]. The SNDS covers approximately 66 million people, corresponding to 99% of the French population. It includes data from the French national outpatient claims database (*Données de Consommation Inter-Régimes, DCIR*) and the French national hospital discharge database (*Programme de Médicalisation des Systèmes d'Information, PMSI*). (See Supplemental Appendix A: Methods) [24].

The SNDS is a database adapted to conduct epidemiology studies [25, 26].

b) Study population

Inclusion criteria were defined as:

- diagnosis of lung cancer identified between January 1, 2011 and December 31, 2021 (Appendix S1).
- at least one or more reimbursements for a single PKI of interest among erlotinib, gefitinib, afatinib and osimertinib (Appendix S2) between January 1, 2011 and December 31, 2021.

Non-inclusion criteria were defined as:

- beneficiaries with an age inferior to 18 years and/or a provisional registration.
- patients with a delay between death and the first reimbursement of PKI inferior to 30 days.
- patients with reimbursements for two or more PKIs of interest during follow-up among erlotinib, gefitinib, afatinib and osimertinib.

A lung cancer diagnosis was identified by:

- a principal or related diagnosis of lung cancer in the hospital reimbursement database OR
- a long-term disease (LTD) related to the lung cancer [27] (Appendix S1).

c) Exposure definition

To define duration of exposure to PKI and PPI, we used the Defined Daily Dosage (DDD). The DDD corresponds to the maintenance dosage per day for each drug in terms of its main indication for adult patients. The DDD is calculated for adult patients weighing 70 kg. The DDD measurement is defined by the World Health Organization Collaborative Center for Drug Statistics Methodology [28]. The DDD-PPI/DDD-PKI interaction exposure for each patient was established by the cumulative exposure duration to PPI during PKI treatment. For each patient, the ratio between the number of concomitant exposure days to PPI/PKI and the number of exposure days to PKIs was calculated. Several cumulative exposure thresholds were defined (0.10, 0.20, 0.40, 0.60, 0.80). For all the different levels, patients with a cumulative duration of exposure superior or equal to the cut-off were considered as exposed and the others were viewed as not exposed (Figure 1).

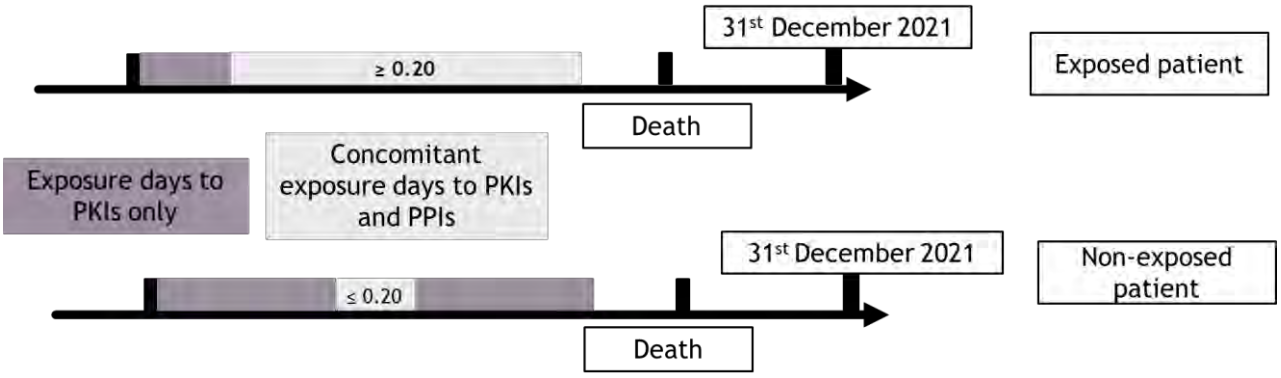

Figure 1: Exposure definition with the cut-off 0.20.

d) Outcomes

The outcome was defined as a death identified in the out of hospital reimbursement and In hospital reimbursement databases. If the date of death differed between these two databases, the first death date was considered.

e) Date definitions

The index date was defined as the first reimbursement of a PKI of interest and the point date was defined as December 31, 2021 or date of death.

f) Covariables

For each cohort of patients, several forms of information were identified. Socio-demographic, lung cancer and comorbidities characteristics were collected. In addition, reimbursement of several concomitant treatments considered as potential confounding factors was recorded.

Socio-demographic characteristics were identified in the out of hospital database. Sex, age, department of residence and social disadvantage index were recorded.

Characteristics related to lung cancer were identified in the hospital reimbursement database. Lung surgery procedures before the index date were noted as well as lung cancer treatment (radiotherapy, chemotherapy and immunotherapy) reimbursed prior to the index date. A diagnosis of metastasis before the index date was also logged (Appendix S1). The ratio between the number of days of hospitalization for a principal or related diagnosis of lung cancer or metastasis and the number of follow-up days (Appendix S1) were also noted. Hospitalization stays which lasted less than 24 hours were excluded.

The Charlson index score was estimated for each patient and it was identified a medical history of obesity at the inclusion [27, 29] (Appendix S1, S2, S3, S4, S5).

Exposure to antiplatelet aggregators and anticoagulants, antihypertensive drugs and/or lipid-lowering drugs with at least 3 reimbursements the year before the index date (Appendix S2) was also recorded. Finally, at least one reimbursement for non-steroidal anti-inflammatory drugs was identified during follow-up (Appendix S2).

g) Statistical analysis

Firstly, a descriptive analysis of the patients identified in the cohort following the first PKI reimbursement and different PPI exposure definitions was conducted.

Quantitative data were described with mean, standard deviation, median, interquartile range. Qualitative data were presented using effectives and percentages.

Secondly, we conducted a Cox model to compare incidence of death following PPI exposure. For continuous and qualitative variables, the linearity hypothesis and proportional risk hypothesis were assessed respectively. If linearity was not maintained, the variable was recoded in class intervals. If the proportional risk hypothesis was not respected, the variables

were considered as time dependent for PPI and non-steroidal anti-inflammatory drug exposure. Several overlaps between duration of PKI and PPI concomitant exposure and total PKI exposure duration were considered: 0.10, 0.20, 0.40, 0.60 and 0.80. Subgroup analyses were conducted following exposure to PKI.

All analysis were performed using SAS, version 9.4 software (SAS Institute, Inc).

5) Results

The study population is presented in Figure 2.

In our study, 480 275 patients with pulmonary cancer were identified. Among them, 34 048 received at least one reimbursement for the PKIs of interest. 26 133 (76.8%) patients were exposed to erlotinib, 3 142 (9.2%) to gefitinib, 1 417 (4.2%) to afatinib and 3 356 (9.9%) to osimertinib (Figure 2).

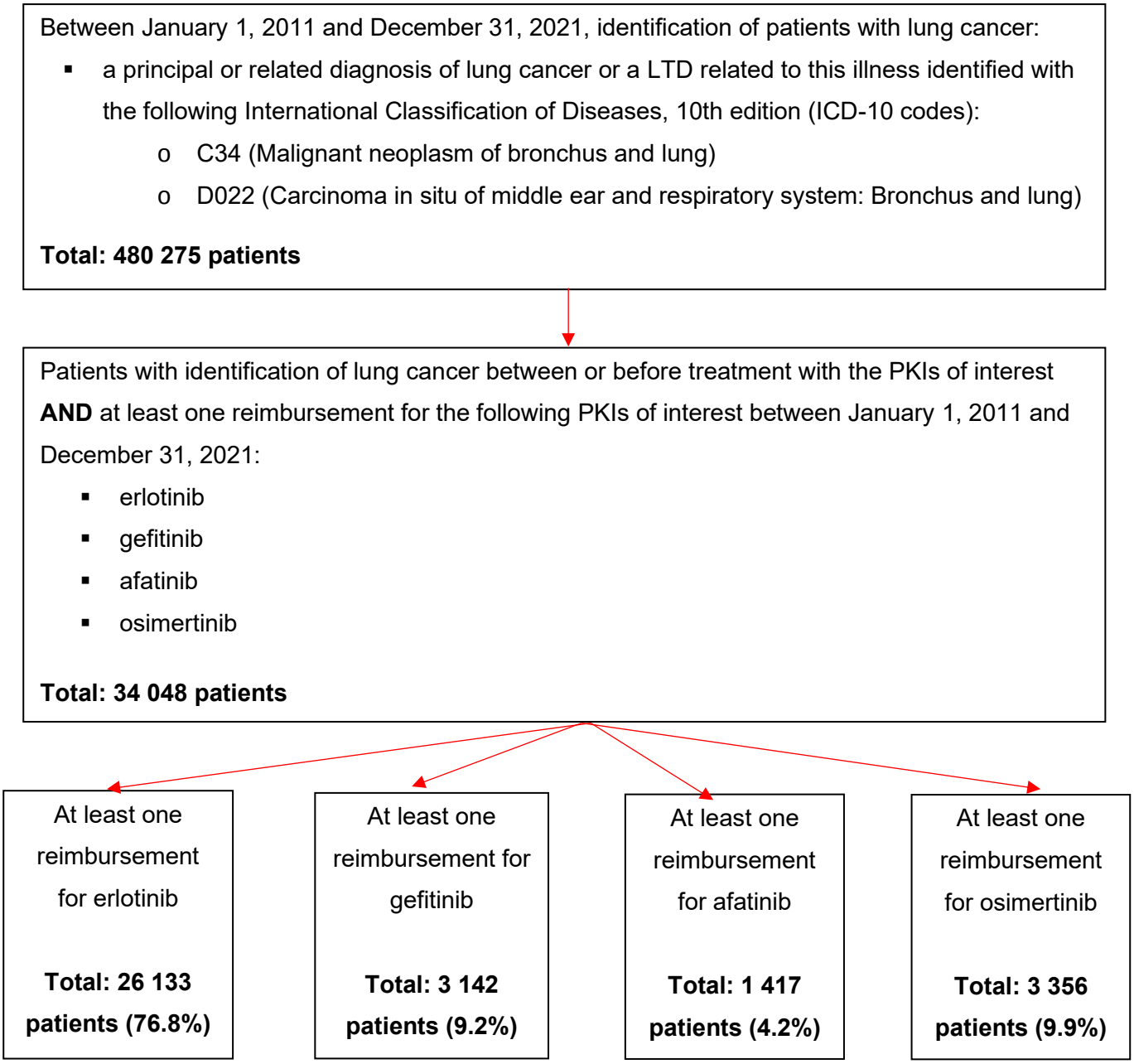

Figure 2: flow chart, study population selection.

Patient characteristics at inclusion are presented in Table 1. Overall, the mean age for patients was 67.1 ± 11.0 years. In terms of gender, there were more males than females (58.8% vs. 41.2%). For the most part, patients included in this cohort demonstrated a deprivation score equal to 5 (6 918, 21.5%) and had mainly undergone chemotherapy and immunochemotherapy (25 049, 73.6%) treatment. However, a few patients received surgical treatment before the index date (5 554, 16.3%). The overall mean Charlson score was 7.3 ± 3.0 points. By and large, patients had metastasized cancer at the index date (24 516, 72.0%).

In terms of patients exposed to erlotinib, the overall mean age was 66.2 ± 10.7 years and there was a predominantly male (66.4%). Anticoagulant and antithrombotic drug exposure was higher (44.5%) compared to the overall population (41.2%). The distribution of the other variables was comparable to characteristics of the total population.

For patients exposed to gefitinib who were predominantly female (65.4%), the overall mean age was 71.4 ± 11.6 years. The Charlson score was lower with a mean of 6.9 ± 3.0 compared to the overall population at 7.3 ± 3.0. Anticoagulant and antithrombotic drug exposure was inferior (32.3%) compared to the overall population (41.2%). Antihypertensive exposure was higher (55.4%) compared to the overall population (51.4%).

Patients exposed to afatinib had an overall mean age of 67.9 ± 10.9 years and were predominantly female (68.6%). The Charlson score was lower with a mean of 6.9 ± 3.0 compared to the overall population at 7.3 ± 3.0.

Regarding patients exposed to osimertinib, their overall mean age was 69.1 ± 11.8 years and they were predominantly female (70.6%). Compared to the overall population (16.3%), more patients had undergone lung surgery (21.3%). The Charlson score was lower with a mean of 6.3 ± 3.2 compared to the overall population at 7.3 ± 3.0. Anticoagulant and antithrombotic drug exposure was inferior (27.2%) compared to the overall population (41.2%). Lipid-lowering drug exposure was more limited (24.3%) compared to the overall population (31.4%).

Characteristics during follow-up are depicted in Table 2. In the overall population, few patients were exposed to non-steroidal anti-inflammatory drugs during follow-up (535, 1.6%). In the overall population, the proportion of patients with a high risk of DDD-PPI/DDD-PKI interaction defined with a cut-off ≥ 0.20 was 50.2%. For the different drug groups, the percentage of patients with a high risk of DDD-PPI/DDD-PKI interaction varied between 36.6% for osimertinib to 52.7% for erlotinib while the gefitinib and afatinib groups recorded levels of 46.5% and 45.6% respectively. The median exposure days to PPIs during PKI treatment appeared to be higher

for gefitinib (29) medication than the overall population (19). From January 1, 2011 to December 31, 2021, a total of 29 426 (86.4%) patients died. Patient deaths varied by group with the osimertinib group presenting the lowest proportion at 34.6% and erlotinib group the highest at 93.6%.

Characteristics of patients included in the cohort following PPI exposure are presented in Table 3. Male patients seemed to be more exposed to the DDD-PPI/DDD-PKI interaction than females. Overall, patients with higher PPI exposure during their PKI treatment had a greater number of comorbidities and higher Charlson scores than other patients. They were also more likely to have undergone chemotherapy or immunotherapy and be more exposed to antihypertensive, lipid-lowering agents as well and anticoagulant/antithrombotic drugs.

The association between several of the patient characteristics and risk of death are presented in Supplementary Table S1.

The correlation between several patient PPI exposure definitions and risk of death are presented in Table 4.

In the main analysis, patients with concomitant exposure duration to PPI and PKI superior or equal to 20% of PKI treatment duration had an increased risk of death (HR, 1.60 [95% CI, 1.57–1.64]) compared to other patients.

This risk increased as the period of concomitant exposure to PKI and PPI expanded. For example, when exposure to PPI and PKI was defined as an overlap of concomitant reimbursement duration superior or equal to 10% of PKI treatment duration, the estimated HR was 1.46 [95% CI, 1.43–1.50]. For an overlap superior or equal to 80% of PKI duration, the estimated HR was 2.19 [95% CI, 2.12–2.25].

In terms of erlotinib, patients with concomitant exposure duration to PPI and PKI superior or equal to 20% of PKI treatment duration had an increased risk of death (HR, 1.49 [95% CI, 1.45–1.53]) compared to other patients. When the exposure was defined with an overlap superior or equal to 10%, the estimated HR was 1.36 [95% CI, 1.33–1.40]). For an overlap superior or equal to 80%, the estimated HR was 2.04 [95% CI, 1.98–2.11]).

For gefitinib, patients exposed to a combination of PKI and PPI during at least 20% of the PKI treatment duration demonstrated an increased risk of death (HR, 1.85 [95% CI, 1.71–2.18]) compared to patients without this exposure. When the exposure overlap definition varied

between 10% to 80%, HRs were estimated to 1.68 [95% CI, 1.55–1.81] and 2.71 [95% CI, 2.41–3.04] respectively.

Regarding afatinib, patients with concomitant exposure to PPI and PKI duration superior or equal to 20% of the PKI treatment experienced an increased risk of death (HR, 1.87 [95% CI, 1.64–1.53]) compared to other patients. When exposure was defined with an overlap superior or equal to 10% and 80%, the estimated HRs were 1.65 [95% CI, 1.46–1.87] and 2.71 [95% CI, 2.27–3.23] respectively.

For osimertinib, patients with a concomitant exposure to PPI and PKI during at least 20% of PKI treatment duration had an increased risk of death (HR, 2.14 [95% CI, 1.89–2.41]) compared to non-exposed patients. When the PKI and PPI exposure overlap varied between 10% to 80%, the estimated HRs were 1.94 [95% CI, 1.71–2.19] and 4.07 [95% CI, 3.40–4.88] respectively.

Analysis stratified in terms of metastases diagnosis at inclusion are presented in Tables S2 and S3.

Table 1: patient characteristics at inclusion related to socio-demographic characteristics, lung cancer and comorbidities.

	Overall patients, n **34 048**	**Erlotinib, n (%)** **26 133 (76.8)**	**Gefitinib, n (%)** **3 142 (9.2)**	**Afatinib, n (%)** **1 417 (4.2)**	**Osimertinib, n (%)** **3 356 (9.9)**
Age categories (in years), n (%)					
< 60	9 146 (26.9)	7 538 (28.8)	545 (17.4)	326 (23.0)	737 (22.0)
[60; 70]	11 108 (32.6)	8 979 (24.2)	759 (24.2)	466 (32.9)	904 (26.9)
> 70	13 794 (40.5)	1 838 (58.5)	1 838 (58.5)	625 (44.1)	1 715 (51.1)
Mean ± SD	67.1 ± 11.0	66.2 ± 10.7	71.4 ± 11.6	67.9 ± 10.9	69.1 ± 11.8
Median [IQR]	67.1 [59.4; 75.4]	66.0 [58.8; 74.2]	72.7 [63.7; 80.2]	68.4 [60.7; 75.8]	70.3 [61.3; 77.6]
Male, n (%)	20 021 (58.8%)	17 361 (66.4)	1 087 (34.6)	586 (41.4)	987 (29.4)
Social deprivation index, n (%)					
1	5 807 (18.1)	4 197 (17.0)	573 (19.6)	257 (19.0)	780 (24.8)
2	6 058 (18.9)	4 588 (18.6)	576 (19.8)	265 (19.6)	629 (20.0)
3	6 751 (21.0)	5 169 (20.9)	645 (22.1)	259 (19.2)	678 (21.5)
4	6 593 (20.5)	5 163 (20.9)	584 (20.0)	276 (20.4)	570 (18.1)
5	6 918 (21.5)	5 591 (22.6)	539 (18.5)	294 (21.8)	494 (15.7)
Anterior lung cancer treatment					
Surgery	5 554 (16.3)	4 083 (15.6)	511 (16.3)	247 (17.4)	713 (21.3)
Radiotherapy	9 428 (27.7)	7 861 (30.1)	577 (18.4)	357 (25.2)	633 (18.9)
Chemotherapy and immunotherapy	25 049 (73.6)	21 955 (84.0)	1 213 (38.6)	648 (45.7)	1 233 (36.7)
Metastatic cancer, n (%)	24 516 (72.0)	19 361 (74.1)	2 159 (68.7)	978 (69.0)	2 018 (60.1)
Charlson score, n (%)					
< 7	9 323 (27.4)	6 606 (25.3)	965 (30.7)	432 (30.5)	1 320 (39.3)
[7; 8]	11 202 (32.9)	8 332 (31.9)	1 187 (37.8)	531 (37.5)	1 152 (34.3)
> 8	13 523 (39.7)	11 195 (42.8)	990 (31.5)	454 (32.0)	884 (26.4)
Mean ± SD	7.3 ± 3.0	7.5 ± 2.9	6.9 ± 3.0	6.9 ± 3.0	6.3 ± 3.2
Median [IQR]	8.0 [4.0; 9.0]	8.0 [6.0; 9.0]	8.0 [3.0; 9.0]	8.0 [3.0; 9.0]	8.0 [2.0; 9.0]
Antihypertensive drug exposure, n (%)	17 503 (51.4)	13 518 (51.7)	1 741 (55.4)	685 (48.3)	1 559 (46.5)
Obesity, n (%)	2 621 (7.7)	2 113 (8.1)	195 (6.2)	110 (7.8)	203 (6.0)
Lipid-lowering drugs exposure, n (%)	10 688 (31.4)	8 475 (32.4)	979 (31.2)	420 (29.6)	814 (24.3)
Anticoagulant and antithrombotic drugs exposure, n (%)	14 037 (41.2)	11 627 (44.5)	1 014 (32.3)	482 (34.0)	914 (27.2)

Table 2: patient characteristics during follow-up.

	Overall patients, n **34 048**	**Erlotinib, n (%)** **26 133 (76.8)**	**Gefitinib, n (%)** **3 142 (9.2)**	**Afatinib, n (%)** **1 417 (4.2)**	**Osimertinib, n (%)** **3 356 (9.9)**
Ratio between the number of days of hospital stay and the number of days of follow-up, (%)					
< 5%	18 458 (54.2)	12 676 (48.5)	2 137 (68.0)	881 (62.2)	2 764 (82.4)
≥ 5%	15 590 (45.8)	13 457 (51.5)	1 005 (32.0)	536 (37.8)	592 (17.6)
Hospital stays (in days)					
Mean ± SD	20.7 ± 40.1	21.3 ± 40.9	24.5 ± 43.8	23.6 ± 42.8	10.8 ± 24.4
Median [IQR]	6 [2; 21]	7 [2; 22]	8 [2; 27]	8 [2; 25]	2 [0; 8]
Non-steroidal anti-inflammatory drugs, n (%)	535 (1.6)	447 (1.7)	52 (1.7)	14 (1.0)	22 (0.7)
Exposure to DDD-PPI/DDD-PKI interaction, n (%)					
[0; 0.10[	14 856 (43.6)	10 901 (41.7)	1 421 (45.2)	666 (47.0)	1 868 (55.7)
[0.10; 0.20 [	2 068 (6.1)	1 446 (5.5)	260 (8.3)	105 (7.4)	257 (7.7)
[0.20; 0.40 [	3 347 (9.8)	2 523 (9.7)	339 (10.8)	156 (11.0)	329 (9.8)
[0.40; 0.60 [	3 760 (11.0)	2 929 (11.2)	369 (11.7)	152 (10.7)	310 (9.2)
[0.60; 0.80 [	3 909 (11.5)	3 147 (12.0)	363 (11.6)	137 (9.7)	262 (7.8)
[0.80; 1.00 [	6 108 (17.9)	5 187 (19.8)	390 (12.4)	201 (14.2)	330 (9.8)
Interaction exposure duration (in days)					
Mean ± SD	51.8 ± 117.5	44.0 ± 99.3	97.6 ± 195.3	80.0 ± 176.4	58.3 ± 107.5
Median [IQR]	19 [0; 54]	19 [0; 50]	29 [0; 105]	22 [0; 71]	14 [0; 65]
Death, n (%)	29 426 (86.4)	24 453 (93.6)	2 723 (86.7)	1 089 (76.9)	1 161 (34.6)

Table 3: characteristics of patients according to level of exposure to the DDD-PPI/DDD-PKI interaction.

	[0; 0.10] DDD-PPI/DDD-PKI interaction exposure, n (%)	**[0.10; 0.20] DDD-PPI/DDD-PKI interaction exposure, n (%)**	**[0.20; 0.40] DDD-PPI/DDD-PKI interaction exposure, n (%)**	**[0.40; 0.60] DDD-PPI/DDD-PKI interaction exposure, n (%)**	**[0.60; 0.80] DDD-PPI/DDD-PKI interaction exposure, n (%)**	**[0.80; 1.00] DDD-PPI/DDD-PKI interaction exposure, n (%)**
	14 856 (43.6)	**2 068 (6.1)**	**3 347 (9.8)**	**3 760 (11.0)**	**3 909 (11.5)**	**6 108 (17.9)**
Age categories (in years), n (%)						
< 60	3 969 (26.7)	579 (28.0)	921 (27.5)	955 (25.4)	1 055 (27.0)	1167 (27.3)
[60; 70]	4 802 (32.3)	674 (32.6)	1 124 (33.6)	1 292 (34.4)	1 189 (30.4)	2 027 (33.2)
> 70	6 085 (41.0)	815 (39.4)	1 302 (38.9)	1 513 (40.2)	1 665 (42.6)	2 414 (39.5)
Male, n (%)	8 490 (57.2)	1 095 (53.0)	1 921 (57.4)	2 271 (60.4)	2 317 (59.3)	3 927 (64.3)
Social deprivation index, n (%)						
[1; 2]	5 211 (37.3)	743 (38.1)	1 193 (37.9)	1 297 (36.6)	1 340 (36.2)	2 081 (35.8)
[3; 5]	8 759 (62.7)	1 205 (61.9)	1 955 (62.1)	2 252 (63.5)	2 364 (63.8)	3 727 (64.2)
Anterior lung cancer treatment, n (%)						
Surgery	2 363 (15.9)	376 (18.2)	539 (16.1)	619 (16.5)	622 (15.9)	1 035 (16.9)
Radiotherapy	3 669 (24.7)	537 (26.0)	971 (29.0)	1 125 (29.9)	1 201 (30.7)	1 925 (31.5)
Chemotherapy and immunotherapy	10 536 (24.7)	1 418 (68.6)	2 507 (74.9)	2 841 (75.6)	2 944 (75.3)	4 803 (78.6)
Metastasized cancer, n (%)	10 130 (68.2)	1 445 (69.9)	2 492 (74.5)	2 821 (75.0)	2 998 (76.7)	4 630 (75.8)
Ratio between the number of days of hospital stay and the number of days of follow-up, n (%)						
< 5%	10 329 (69.5)	1 059 (51.2)	1 474 (44.0)	1 620 (43.1)	1 642 (42.0)	2 334 (38.2)
≥ 5%	4 527 (30.5)	1 009 (48.8)	1 873 (56.0)	2 140 (56.9)	2 267 (58.0)	3 774 (61.8)
Charlson score, n (%)						
< 7	4 648 (31.3)	618 (29.9)	837 (25.0)	914 (24.3)	879 (22.5)	1 427 (23.4)
[7; 8]	5 113 (34.4)	729 (35.3)	1 154 (34.5)	1 222 (32.5)	1 218 (31.2)	1 766 (28.9)
> 8	5 095 (34.3)	721 (34.9)	1 356 (40.5)	1 624 (43.2)	1 812 (46.4)	2 915 (47.7)
Antihypertensive drug exposure, n (%)	7 087 (47.7)	949 (45.9)	1 672 (50.0)	2 032 (54.0)	2 241 (57.3)	3 522 (57.7)
Obesity, n (%)	1 003 (6.8)	126 (6.1)	237 (7.1)	313 (8.3)	335 (8.6)	607 (9.9)
Lipid-lowering drugs exposure, n (%)	4 062 (27.3)	585 (27.3)	1 024 (30.6)	1 333 (35.5)	1 419 (36.3)	2 285 (37.4)
Anticoagulant and antithrombotic drug exposure, n (%)	5 378 (36.2)	714 (34.5)	1 360 (40.6)	1 667 (44.3)	1 877 (48.0)	3 041 (49.8)
Non-steroidal anti-inflammatory drugs, n (%)	264 (1.8)	46 (2.2)	49 (1.5)	63 (1.7)	53 (1.4)	60 (1.0)

Table 4: Association between DDD-PPI/DDD-PKI interaction exposure and risk of death.

	Event/total	Crude HR	Adjusted HR*
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	12 268 / 14 856	-	-
≥ 0.10	17 158 / 19 192	1.70 (1.66-1.74)	1.46 (1.43-1.50)
≥ 0.20	15 426 / 17 124	1.88 (1.83-1.92)	1.60 (1.57-1.64)
≥ 0.40	12 491 / 13 777	2.21 (2.16-2.26)	1.89 (1.85-1.94)
≥ 0.60	9 133 / 10 017	2.40 (2.34-2.46)	2.06 (2.00-2.11)
≥ 0.80	5 600 / 6108	2.59 (2.51-2.67)	2.19 (2.12-2.25)
Erlotinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	10 062 / 10 901	-	-
≥ 0.10	14 391 / 15 232	1.50 (1.46-1.54)	1.36 (1.33-1.40)
≥ 0.20	13 058 / 13 786	1.63 (1.59-1.68)	1.49 (1.45-1.53)
≥ 0.40	10 692 / 11 263	1.91 (1.86-1.96)	1.75 (1.70-1.79)
≥ 0.60	7 930 / 8 334	2.08 (2.03-2.14)	1.91 (1.86-1.97)
≥ 0.80	4 939 / 5 187	2.23 (2.16-2.30)	2.04 (1.98-2.11)
Gefitinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	1 200 / 1 421	-	-
≥ 0.10	1 523 / 1 701	1.83 (1.70-1.98)	1.68 (1.55-1.81)
≥ 0.20	1 305 / 1 461	2.04 (1.89-2.20)	1.85 (1.71-2.00)
≥ 0.40	1 000 / 1 122	2.44 (2.25-2.64)	2.22 (2.05-2.41)
≥ 0.60	665 / 753	2.57 (2.35-2.80)	2.33 (2.12-2.55)
≥ 0.80	349 / 390	3.04 (2.71-3.41)	2.71 (2.41-3.04)
Afatinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	472 / 666	-	-
≥ 0.10	617 / 751	2.04 (1.81-2.30)	1.65 (1.46-1.87)
≥ 0.20	534 / 646	2.35 (2.08-2.64)	1.87 (1.64-2.12)
≥ 0.40	402 / 490	2.80 (2.47-3.17)	2.22 (1.94-2.53)
≥ 0.60	277 / 338	3.12 (2.72-3.58)	2.44 (2.11-2.83)
≥ 0.80	166 / 201	3.48 (2.95-4.11)	2.71 (2.27-3.23)
Osimertinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	534 / 1 868	-	-
≥ 0.10	627 / 1 488	2.47 (2.20-2.77)	1.94 (1.71-2.19)
≥ 0.20	529 / 1 231	2.74 (2.43-3.07)	2.14 (1.89-2.41)
≥ 0.40	397 / 902	3.53 (3.12-3.99)	2.76 (2.43-3.14)
≥ 0.60	261 / 592	4.26 (3.70-4.90)	3.35 (2.89-3.87)
≥ 0.80	146 / 330	5.36 (4.49-6.38)	4.07 (3.40-4.88)

*Adjusted for age, sex, metastasis, cancer treatment, hospitalization stays for lung cancer or metastasis diagnosis, Charlson score, obesity, antihypertensive drug exposure, lipid-lowering drug exposure, anticoagulant and antithrombotic drug exposure and non-steroidal anti-inflammatory drug exposure.

6) Discussion

In our study, we identified a strong association between risk of death and concomitant exposure to the DDD-PPI/DDD-PKI pharmacological interaction. An overlap between PPI and PKI superior or equal to 20% was linked to an increased risk of death (HR, 1.60 [95% CI, 1.57–1.64]). This correlation was identified for all the PKIs of interest in our study. Overall, when the overlap varied from 0.10 to 0.80, the estimated HRs were 1.46 [95% CI, 1.43–1.50] and 2.19 [95% CI, 2.12–2.25] respectively. Our study suggests a potential dose-dependent effect of this interaction for all PKIs of interest which might be considered a factor favoring causality.

Our results were similar to those identified in literature for erlotinib and gefitinib exposure, notably a study with a closer exposure definition than our main objective [16]. It identified an association between PPI/PKI exposure duration superior or equal to 20% of PKI treatment and death with gefitinib and erlotinib with HR estimated at 1.58 [95% CI, 1.42–1.76]) and 1.54 [95% CI, 1.30–1.82] respectively. In this study, authors also defined other levels of overlap and showed a potential dose-dependent effect for this interaction. When the overlap varied between 20% to 30%, the risk of death was higher. The HR difference compared to our results can be explained by an adjustment in terms of other variables to consider confusion bias. The authors collected information such as smoking status and lung cancer characteristics including lung stage at inclusion but did not take into consideration the cancer treatment. Furthermore, another study observed an increased risk of death for patients exposed to a concomitant association of gefitinib and PPI compared to patients exposed to gefitinib alone [13]. When they compared the risk of death between PPI users and non-PPI users, they estimated an HR of around 1.65 [95% CI, 1.15–2.36]. However, they defined PPI users as patients with at least one PPI dose identified during the gefitinib treatment.

Another study also identified an increased risk of death in case of concomitant afatinib and PPI exposure (HR = 1.29 [95% CI, 1.05–1.59] [15]. In this study, exposure was defined as at least one PPI prescription after the PKI initiation. Estimated HR in this study was lower than that of our study for patients exposed to afatinib with an exposure definition corresponding an overlap superior or equal to 10%.

Our study also detected a strong association between risk of death and concomitant exposure to the DDD-PPI/DDD-PKI pharmacological interaction for osimertinib. To our knowledge, a link between risk of death and concomitant exposure to osimertinib and PPI has not been identified in pharmaco-epidemiology studies although decreased osimertinib bioavailability and rabeprazole exposure was observed in pharmacokinetic studies [30]. In our study, a strong

link between concomitant osimertinib and PPI use was observed compared to the other PKIs. Osimertinib was approved in 2016 by the EMA. We therefore found a smaller number of patients exposed to this medication than the other PKIs in our database which could explain why osimertinib demonstrated the strongest association.

This interaction can be explained by increased gastric pH due to PPI use. Gastric pH can be superior or equal to 6 after exposure to this type of medication [31]. The PKIs of interest are absorbed by the stomach. The pka for erlotinib, afatinib and osimertinib are around 5.5, 8.2 and 9.2 respectively [32]. Gefitinib pka is around 5.4 and 7.2 [33]. Therefore, an increase in gastric pH can lead to elevation in the ionized form of the active substance which could decrease PKI bioavailability and drug efficacy.

In our study, several already known factors associated with death have been identified such as being of female sex [34]. We also noted a decreased risk of death for patients aged under 60 years compared to others. In literature it is controversial that younger patients have better overall survival than older patients [35, 36].

The principal advantage of our study was access to the French health insurance database which contains information relating to more than 99% percent of the French population, covering 66 million beneficiaries. Therefore, the use of this database limits selection and attrition bias [37].

However, some clinical information such as biological or imaging results are not available in the SNDS database meaning that lung cancer severity cannot be identified precisely. We cannot therefore exclude potential residual confusion bias. Nevertheless, we tried to consider the severity of lung cancer by adjusting the ratio between the number of days of hospitalization stays and the number of days of follow-up. However, drug prescription cannot be identified in the SNDS database although we tried to estimate PPI and PKI exposure with DDD which has been endorsed in pharmaco-epidemiology studies [38]. The use of DDD to estimate PPI exposure in health reimbursement databases has already been validated [39]. Finally, all PPI delivery is not reimbursed in France. Thus, some potential PPI exposure periods cannot be identified in the SNDS database, leading to classification bias. However, patients with lung cancer regularly consult physicians and we therefore estimated that this type of bias is limited for this population.

7) Conclusion

In this study, we identified a strong link between risk of death and concomitant PKI/PPI exposure. This association was observed in the four anti-EGFR studied. In literature, the correlation seems less strong with H2 antagonists [16] and PKI treatment could be prescribed with H2 antagonists instead of PPIs if necessary.

This type of interaction was also detected with other PKIs indicated for breath cancer such as palbociclib or ribociclib [40]. Further studies would be needed to confirm our results and identify other medication-based interactions with this recently commercialized drug class.

8) Supplementary files

APPENDIX A:

The DCIR essentially provides data on all reimbursed out-patient healthcare consumption, notably all reimbursed drugs (name, dosage, pharmaceutical form) identified with the anatomic therapeutic chemical (ATC) classification. It also includes information about severe and costly LTD patients who are coded using ICD-10. Patient information such as sex, age, vital status, department and region of residence, social deprivation index (ranging from 1 to 5, defined according to the proportion of employed, unemployed and graduates aged 15-64 years and average household tax income in the area of residence) are recorded in the DCIR.

For acute-care facilities, PMSI data includes all hospitalization discharge summaries and covers all hospital stays in publicly funded and private institutions including acute-care units. For each stay, it contains the diagnoses classified using ICD-10-codes as principal diagnosis, related diagnosis and significant associated diagnosis. Additional information on hospital stays is available such as entry and exit date, admission source, hospital discharge or medical procedures.

Appendix S1: ICD-10 codes used for the covariables definition.

Covariables	ICD-10 codes inclusion
Lung cancer	C34, D022
Metastatic tumor	C77-C80
Chemotherapy administration	Z511
Radiotherapy	Z510
Obesity	E66 excluding E66.03, E66.13, E66.83, E66.93

Appendix S2: ATC codes used for the covariables definition.

Drugs	ATC codes used
PKIs of interest	L01EX03, L01XE02, L01XE13, L01XE35
Immunotherapy	L01XC11, L01XC17, L01XC18, L01XC28, L01XC32
PPI	A02BC
Lipid-lowering drugs	C10
Antihypertensive drugs	C02AB02, C02AC01, C02AC02, C02AC05, C02AC06, C02CA01, C02CA06, C02DC01, C02LA01, C03AA01, C03AA03, C03BA04, C03BA10, C03BA11, C03BX03, C03CA01, C03CA02, C03CA03, C03DA01, C03DB01, C03EA, C03EA01, C03EA04, C07AA02, C07AA03, C07AA05, C07AA06, C07AA12, C07AA15, C07AA16, C07AA23, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB08, C07AB12, C07AG01, C07BA02, C07BB02, C07BB03, C07BB07, C07BB12, C07CA03, C07DA06, C07FB02, C07FB03, C08CA01, C08CA02, C08CA03, C08CA04, C08CA05, C08CA08, C08CA09, C08CA11, C08CA13, C08CX01, C08DA01, C08DB01, C08GA02, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA10, C09AA13, C09AA15, C09AA16, C09BA01, C09BA02, C09BA03, C09BA04, C09BA05, C09BA06, C09BA07, C09BA09, C09BA15, C09BB02, C09BB04, C09BB07, C09BB10, C09BX02, C09CA01, C09CA02, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08, C09DA01, C09DA02, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C09DB01, C09DB02, C09DB04, C09XA02, C09XA52, C10BX03
Anticoagulant and antithrombotic drugs	B01
Non-steroidal anti-inflammatory drugs	M01A
HIV-AIDS	J05AE01, J05AE02, J05AE03, J05AE04, J05AE05, J05AE07, J05AE08, J05AE09, J05AE10, J05AF01, J05AF02, J05AF03, J05AF04, J05AF06, J05AG01, J05AG03, J05AG04, J05AG05, J05AG06, J05AJ01, J05AJ03, J05AR01, J05AR02, J05AR04, J05AR06, J05AR08, J05AR09, J05AR10, J05AR13, J05AR18, J05AR19, J05AR20, J05AR21, J05AR24, J05AR25, J05AX07, J05AX09
Oral antidiabetic agents, insulin	A10B, A10A
Bronchodilator drugs	R03
Drugs indicated for dementia	N06DA, N06DX01

Appendix S3: Medical act codes used for the covariables definition.

Procedures	Medical act codes used
Lung surgery	GECA001, GEFA011, GELE002, GELE004, GELE005, GELE007, GELE008, GELE009, GELE133, GELE308, GEMA001, GEME121, GENE001, GENE002, GENE003, GENE004, GENE005, GENE006, GENE008, GFFA001, GFFA002, GFFA003, GFFA004, GFFA005, GFFA006, GFFA007, GFFA008, GFFA009, GFFA010, GFFA011, GFFA012, GFFA013, GFFA014, GFFA015, GFFA016, GFFA017, GFFA018, GFFA019, GFFA021, GFFA022, GFFA023, GFFA024, GFFA025, GFFA026, GFFA027, GFFA028, GFFA029, GFFA030, GFFA031, GFFA032, GFFA033, GFFA034, GFFA035, GFFC002, GFFC003, GFFC004, GFFC005, GFFC006, GFNH174, GFNH214, GGCA001, GGFA001, GGFA003, GGNA001, GGNC001, GGPA001, GHFA001, GHFA002, GHFA003, GHFA004
Dialysis	JVJB001, JVJB002, JVJF002, JVJF003, JVJF004, JVJF005, JVJF006, JVJF007, JVJF008, JVRP004, JVRP007 JVRP008, JVRP007, JVRP008
Laser surgery	DGAF007, DGLF003, ECAF004, ECLF004, ECPF005, EBAF010, EBAF011, EBAF001, EBAF006, EBAF014, EAAF002, EAAF900, ECAF001, ECLF003, ECPF001, ECPF002, DGAF005, EDAF003, DGPF002, EDPF009, DGLF001, DGLF002, DGLF005, EDLF004, EDLF005, EDAF005, EDPF004, EDLF006, EDLF008, EDAF001, EDAF010, EDPF005, EDLF013, EDAF006, EDPF001, EDLF007, EEAF002, EEAF004, EEAF006, EEPF001, ENAF001
Peripheral vascular stenting	DGAF007, DGLF003, ECAF004, ECLF004, ECPF005, EBAF010, EBAF011, EBAF001, EBAF006, EBAF014, EAAF002, EAAF900, ECAF001, ECLF003, ECPF001, ECPF002, DGAF005, EDAF003, DGPF002, EDPF009, DGLF001, DGLF002, DGLF005, EDLF004,EDLF005, EDAF005, EDPF004, EDLF006, EDLF008, EDAF001, EDAF010, EDPF005, EDLF013, EDAF006, EDPF001, EDLF007, EEAF002, EEAF004, EEAF006, EEPF001, ENAF001
Bariatric surgery	HFCA001, HFCC003, HFFA001, HFFA011, HFFC004, HFFC018, HFGC900, HFKA001, HFKA002, HFKC001, HFMA009, HFMA010, HFMA011, HFMC006, HFMC007, HFMC008, HGCA009, HGCC027

Appendix S4: Identification of Charlson comorbidities.

Covariables	ICD 10 codes	Procedures	Drugs
Myocardial infarction	I200+0, I21 - I24		
Congestive heart failure	I110, I130, I132, I139, K761 (exclusion for LTD identification), J81 (exclusion for LTD identification), I50		
Peripheral vascular disease	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959	Peripheral vascular stenting	
Cerebrovascular disease	G45, G46, H340, I6		
Alzheimer and other dementia	F00-F03 (exclusion F023, F024), F051, G30		At least 3 reimbursements for anti-Alzheimer drugs
Chronic pulmonary disease	J40-J47, J60-J67 (exclusion for LTD identification), J96 (exclusion of J96.0 and J96.9 for hospital diagnosis), J98		At least 3 reimbursements for bronchodilator drugs
Connective tissue disease	M05, M06, M315, M32, M33, M34, M351, M353, M360		
Ulcer disease	K25-K28		
Mild liver disease	B18, K700-K703, K709, K713 - K715, K717, K73, K74, K760, K762-K764, K768, K769, Z944		
Diabetes	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128-E131, E136, E138-E141, E146, E148, E149		At least 3 reimbursements (or at least 2 in case of large pack sizes) for oral antidiabetic agents and/or insulin
Hemiplegia	G041, G114, G801, G802, G81, G82, G830 - G834, G839		
Moderate or severe renal disease	I120, I131, N032-N037, N052-N057, N18, N19, N250, Z490, Z491, Z492, Z940, Z992	Dialysis	
Diabetes with end-organ damage	E102-E105, E107, E112-E115, E117, E122-E125, E127, E132-E135, E137, E142-E145, E147	Laser surgery for diabetic retinopathy	
Moderate or severe liver disease	I850, I859, I864, I982, K704, K711, K721, K729, K765-K767		
Metastatic solid tumor	C77-C80		
HIV-AIDS	B20-B24, F024, Z21	Biological tests related to HIV-AIDS pathology monitoring	At least 3 reimbursements for HIV-AIDS drugs

Appendix S5: Biological test codes used for the covariables definition.

Procedures	Biological test codes used
HIV-AIDS	0805, 0806, 1691, 4117, 4122

Table S1: Association between different patient characteristics and risk of death.

	Event/total	Crude HR (CI95%)	P value
Age categories (in years), n (%)			
< 60	8 134 / 9 146	1	< 0.0001
[60; 70]	9 714 / 11 108	0.92 (0.89-0.94)	
> 70	11 578 / 13 794	0.83 (0.81-0.85)	
Male, n (%)	18 249 / 20 021	1.43 (1.40-1.47)	< 0.0001
Social deprivation index, n (%)			
[1; 2]	10 088 / 11 865	1	< 0.0001
[3; 5]	17 804 / 20 262	1.07 (1.05-1.10)	
Anterior lung cancer treatment			
Surgery	4 564 / 5 554	0.87 (0.84-0.89)	< 0.0001
Radiotherapy	8 450 / 9 428	1.21 (1.18-1.24)	< 0.0001
Chemotherapy and immunotherapy	22 931 / 25 049	1.68 (1.63-1.72)	< 0.0001
Metastasized cancer, n (%)	21 758 / 24 516	1.39 (1.35-1.42)	< 0.0001
Charlson score, n (%)			
< 7	7 474 / 9 323	1	
[7; 8]	9 694 / 11 202	1.26 (1.23-1.30)	
> 8	12 258 / 13 523	1.53 (1.48-1.57)	< 0.0001
Interaction DDD-PPI/DDD-PKI exposure, n (%)			
< 5%	14 104 / 18 458	1	
≥ 5%	15 322 / 15 590	3.19 (3.12-3.27)	< 0.0001
Antihypertensive drugs exposure, n (%)	15 318 / 17 503	1.05 (1.03-1.07)	< 0.0001
Obesity, n (%)	2 313 / 2 621	1.02 (0.98-1.06)	0.3950
Lipid-lowering drugs exposure, n (%)	9 516 / 10 688	1.07 (1.05-1.10)	< 0.0001
Anticoagulant and antithrombotic drugs exposure, n (%)	12 614 / 14 037	1.24 (1.22-1.27)	< 0.0001
Non-steroidal anti-inflammatory drugs, n (%)	464 / 535	1.18 (1.08-1.29)	0.0005

Table S2: Association between DDD-PPI/DDD-PKI interaction exposure and risk of death for patients with a diagnosis of metastases identified on the index date.

	Event/total	Crude HR	Adjusted HR*
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	8 680 / 10 130	-	-
≥ 0.10	13 078 / 14 386	1.66 (1.62-1.71)	1.45 (1.41-1.49)
≥ 0.20	11 831 / 12 941	1.85 (1.80-1.90)	1.60 (1.55-1.64)
≥ 0.40	9 614 / 10 449	2.19 (2.13-2.25)	1.90 (1.84-1.95)
≥ 0.60	7 061 / 7 628	2.39 (2.33-2.46)	2.08 (2.02-2.14)
≥ 0.80	4 311 / 4 630	2.59 (2.50-2.67)	2.21 (2.14-2.29)
Erlotinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	7 155 / 7 713	-	-
≥ 0.10	11 043 / 11 648	1.50 (1.45-1.54)	1.36 (1.32-1.41)
≥ 0.20	10 078 / 10 607	1.64 (1.59-1.69)	1.49 (1.45-1.54)
≥ 0.40	8 289 / 8 702	1.92 (1.87-1.98)	1.76 (1.71-1.81)
≥ 0.60	6 169 / 6 460	2.11 (2.05-2.18)	1.95 (1.89-2.01)
≥ 0.80	3 828 / 4 009	2.27 (2.19-2.35)	2.08 (2.00-2.16)
Gefitinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	804 / 924	-	-
≥ 0.10	1 106 / 1 235	1.81 (1.65-1.99)	1.67 (1.52-1.84)
≥ 0.20	950 / 1 055	2.01 (1.83-2.20)	1.84 (1.68-2.02)
≥ 0.40	718 / 804	2.36 (2.15-2.60)	2.17 (1.97-2.40)
≥ 0.60	486 / 548	2.56 (2.30-2.84)	2.35 (2.10-2.61)
≥ 0.80	249 / 276	3.01 (2.63-3.45)	2.72 (2.37-3.12)
Afatinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	347 / 443	-	-
≥ 0.10	461 / 535	1.94 (1.69-2.23)	1.60 (1.38-1.86)
≥ 0.20	400 / 462	2.25 (1.96-2.58)	1.83 (1.58-2.13)
≥ 0.40	300 / 348	2.75 (2.38-3.17)	2.23 (1.91-2.60)
≥ 0.60	204 / 237	3.03 (2.58-3.55)	2.38 (2.01-2.83)
≥ 0.80	118/ 136	3.51 (2.89-4.27)	2.59 (2.09-3.21)
Osimertinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	374 / 1 050	-	-
≥ 0.10	468 / 968	2.29 (1.99-2.62)	1.88 (1.63-2.16)
≥ 0.20	403 / 817	2.62 (2.29-3.01)	2.16 (1.88-2.49)
≥ 0.40	307 / 595	3.54 (3.07-4.09)	2.89 (2.49-3.36)
≥ 0.60	202 / 383	4.40 (3.75-5.17)	3.58 (3.03-4.23)
≥ 0.80	116 / 209	5.91 (4.85-7.20)	4.57 (3.73-5.61)

*Adjusted for age, sex, cancer treatment, hospitalization stays for lung cancer or metastasis diagnosis, Charlson score, obesity, antihypertensive drug exposure, lipid-lowering drug exposure, anticoagulant and antithrombotic drug exposure and non-steroidal anti-inflammatory drug exposure.

Table S3: Association between DDD-PPI/DDD-PKI interaction exposure and risk of death for patients without a diagnosis of metastases identified on the index date.

	Event/total	Crude HR	Adjusted HR*
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	3 588 / 4 726	-	-
≥ 0.10	4 080 / 4 806	1.66 (1.58-1.73)	1.49 (1.42-1.56)
≥ 0.20	3 595 / 4 183	1.81 (1.73-1.89)	1.61 (1.53-1.68)
≥ 0.40	2 877 / 3 328	2.11 (2.02-2.21)	1.87 (1.79-1.97)
≥ 0.60	2 072 / 2 389	2.25 (2.14-2.37)	1.97 (1.87-2.08)
≥ 0.80	1 289 / 1 478	2.43 (2.29-2.58)	2.10 (1.97-2.23)
Erlotinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	2 907 / 3 188	-	-
≥ 0.10	3 348 / 3 584	1.43 (1.36-1.50)	1.36 (1.29-1.43)
≥ 0.20	2 980 / 3 179	1.53 (1.46-1.61)	1.46 (1.38-1.53)
≥ 0.40	2 403 / 2 561	1.77 (1.68-1.86)	1.68 (1.60-1.78)
≥ 0.60	1 761 / 1 874	1.89 (1.79-2.00)	1.79 (1.69-1.90)
≥ 0.80	1 111 / 1 178	2.03 (1.90-2.17)	1.91 (1.79-2.05)
Gefitinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	396 / 497	-	-
≥ 0.10	417 / 486	1.77 (1.54-2.03)	1.69 (1.46-1.95)
≥ 0.20	355 / 406	1.99 (1.73-2.29)	1.91 (1.65-2.21)
≥ 0.40	282 / 318	2.51 (2.17-2.91)	2.42 (2.08-2.82)
≥ 0.60	179 / 205	2.44 (2.06-2.89)	2.32 (1.95-2.76)
≥ 0.80	100 / 114	2.96 (2.40-3.66)	2.72 (2.19-3.39)
Afatinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	125/ 223	-	-
≥ 0.10	156 / 216	2.08 (1.64-2.64)	1.95 (1.53-2.50)
≥ 0.20	134 / 184	2.35 (1.86-2.98)	2.16 (1.69-2.76)
≥ 0.40	102 / 142	2.71 (2.11-3.47)	2.39 (1.85-3.10)
≥ 0.60	73 / 101	3.11 (2.37-4.09)	2.73 (2.06-3.63)
≥ 0.80	48 / 65	3.46 (2.52-4.74)	3.22 (2.31-4.49)
Osimertinib group			
DDD-PPI/DDD-PKI interaction exposure, n (%)			
< 0.10	160 / 818	-	-
≥ 0.10	159 / 520	2.59 (2.08-3.23)	2.09 (1.65-2.63)
≥ 0.20	126 / 414	2.68 (2.14-3.36)	2.08 (1.63-2.66)
≥ 0.40	90 / 307	3.09 (2.42-3.95)	2.43 (1.86-3.15)
≥ 0.60	59 / 209	3.54 (2.66-4.71)	2.73 (2.01-3.71)
≥ 0.80	30 / 121	3.81 (2.60-5.57)	2.79 (1.86-4.17)

*Adjusted for age, sex, cancer treatment, hospitalization stays for lung cancer or metastasis diagnosis, Charlson score, obesity, antihypertensive drug exposure, lipid-lowering drug exposure, anticoagulant and antithrombotic drug exposure and non-steroidal anti-inflammatory drug exposure

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Conclusion et perspectives

Au cours de ces dernières décennies, les progrès en termes de suivi dans le CBNPC sont incontestablement impressionnants. Les médicaments IPKs ont apportés de réels bénéfices pour les patients et ont totalement modifiés les habitudes de prise en soins avec des administrations par voie orale au long cours pour des patients ambulatoires. Néanmoins, la revue de la littérature exposée dans ce manuscrit montre que ces médicaments sont complexes tant par leurs propriétés pharmacodynamiques que pharmacocinétiques. Leur profil d'EIs doit encore être étudié par la conduite d'études de pharmacovigilance et de pharmaco-épidémiologique. Cependant, comme tout médicament les IPKs peuvent présenter des interactions médicamenteuses. Ce manuscrit présente une étude conduite en vie réelle dans la base de données de l'assurance maladie qui est parvenue à mettre en évidence une augmentation du risque de décès chez les patients qui étaient exposés à la prise concomitante des IPKs d'intérêt et d'IPPs par rapport à ceux n'ayant pas été exposés à cette interaction. Ces résultats restent encore à confirmer par d'autres études mais ce signal doit être pris au sérieux.

Enfin, au-delà des IPKs indiqués dans le CBNPC, ce travail de thèse pose cette problématique pour d'autres IPKs qui pourraient présenter une interaction pharmacologique significative avec des IPPs. Des études précédemment publiées ont mis en évidence une interaction potentielle entre les IPPs et certains autres IPKs indiqués pour le cancer du sein ou la leucémie myéloïde chronique comme le palbociclib ou l'imatinib [80-82]. En adaptant les modalités d'analyse suivant les caractéristiques des patientes de leur prise en soins, l'utilisation du SNDS pourrait permettre de répondre à ces interrogations.

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NON-SMALL CELL LUNG CANCER: IMPACT OF PHARMACOLOGICAL INTERACTION BETWEEN PROTON PUMP INHIBITORS AND PROTEIN KINASE INHIBITORS ON SURVIVAL IN FRANCE

Over the last 20 years, medicine has become increasingly personalized and tailored to individual patients. In the area of oncology, so-called "targeted" therapies that attempt to target cancerous tumors more specifically have been developed, in particular Protein Kinase Inhibitors (PKIs). PKIs targeting the Epidermal Growth Factor Receptor (EGFR) are indicated for the treatment of Non-Small Cell Lung Cancer (NSCLC). These drugs are associated with better progression-free and overall survival than chemotherapy, which is one of the standard treatments for this type of cancer. These new therapies are very complex in view of their pharmacodynamic, and pharmacokinetic properties and the various resistance mechanisms associated with their prescription. Their Adverse Reaction (AR) profile is becoming clearer, as a result of the clinical trials conducted on these drugs and the worldwide pharmacovigilance database. However, the drug interaction profile of these recent drugs has yet to be studied. This manuscript presents, in particular, the results of a study conducted using health insurance data, which identified that the overall survival of patients who were exposed to the concomitant use of Proton Pump Inhibitors (PPIs) and EGFR-targeting PKIs indicated for NSCLC was reduced compared with those who were not exposed to this association. Further studies should be conducted to confirm the increased risk of death when exposed to this interaction. In addition, the impact of this interaction should be investigated by considering other PKIs indicated for the treatment of breast cancer or chronic myeloid leukemia, for example.

KEY-WORDS: Protein Kinase Inhibitors (PKI), Epidermal Growth Factor Receptor (EGFR), Non-Small Cell Lung Cancer (NSCLC), Proton Pump Inhibitor (PPI)

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TITRE : CANCER BRONCHIQUE NON A PETITES CELLULES : IMPACT SUR LA SURVIE EN FRANCE DE L'INTERACTION PHARMACOLOGIQUE ENTRE LES INHIBITEURS DE LA POMPE A PROTON ET LES INHIBITEURS DE PROTEINES KINASES

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LIEU ET DATE DE SOUTENANCE :
Université Toulouse III – Paul Sabatier UFR de santé, Département des Sciences Pharmaceutiques, le 8 septembre 2023

RESUME en français :
Depuis ces 20 dernières années, la médecine se veut de plus en plus personnalisée et adaptée individuellement au patient. Dans le domaine de la cancérologie, des thérapies dites « ciblées » qui tente d'agir plus spécifiquement sur les tumeurs cancéreuses ont été développées, notamment les Inhibiteurs de Protéine Kinase (IPKs). Des IPKs ciblant l'Epidermal Growth Factor Receptor (EGFR) sont indiquées pour la prise en charge du Cancer Bronchique Non à Petites Cellules (CBNPC). Ces médicaments sont associés à une survie globale et sans progression plus élevée par rapport à la chimiothérapie, qui consiste en une des prises en charge standard de ce type de cancer. Ces nouvelles thérapies sont complexes par leurs propriétés pharmacodynamiques et pharmacocinétiques et les différents mécanismes de résistance associés à leur utilisation. Leur profil d'effet indésirable commence à être identifié grâce aux essais cliniques relatifs à ces médicaments et à la base mondiale de pharmacovigilance. Cependant, le profil d'interaction médicamenteuse de ces nouveaux médicaments doit encore être étudié. Ce manuscrit présente, notamment, les résultats d'une étude réalisée avec les données de l'assurance maladie qui a mis en évidence que la survie globale des patients qui étaient exposés à la prise concomitante d'Inhibiteurs de la Pompe à Proton (IPPs) et d'IPKs ciblant l'EGFR et indiqués pour le CBNPC était diminuée par rapport à ceux qui n'étaient pas exposés à cette association. D'autres études devront être conduites pour confirmer l'augmentation du risque de décès en cas d'exposition à cette interaction. De plus, il devrait être investigué l'impact de cette interaction en prenant en compte d'autres IPKs indiqués pour la prise en charge du cancer du sein ou de la leucémie myéloïde chronique par exemple.

DISCIPLINE administrative : Pharmacologie

MOTS-CLES : Inhibiteur de Protéines Kinase (IPK), Epidermal Growth Factor Receptor (EGFR), Cancer Bronchique Non à Petites Cellules (CBNPC), Inhibiteur de la Pompe à Proton (IPP)

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